Synthesis of Novel Piperidine Building Blocks and their Use for the Preparation of Donepezil Analogues

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Synthesis of Novel Piperidine Building Blocks and their Use for the Preparation of Donepezil Analogues

by

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Abstract

The piperidine moiety is found in a vast number of bioactive natural products as well as numerous marketed drugs and is therefore an interesting target for synthetic modifications. Synthetic piperidines currently in the clinic are predominantly limited to 1,4-disubstitution on the piperidine ring, hence it is important to develop strategies to access new drug candidates with diverse substitution configurations on the ring. For this purpose, the *aza*-Michael reaction can be used as an atom-efficient method to access biologically important piperidines.

An initial study into the utility of divinyl ketone as the substrate for a double *aza*-Michael addition has led to the development of a facile, manganese dioxide mediated, one-pot oxidation-cyclisation method for the preparation of a diverse range of *N*-substituted 4-piperidones in moderate to good yield over two steps. Substituted divinyl ketones were prepared from their corresponding alcohols and used in a subsequent *aza*-Michael cyclisation with benzylamine for the synthesis of racemic, aromatically and aliphatically 2-substituted *N*-benzylic 4-piperidones. Employing S-α-phenylethylamine as the primary amine substrate in this protocol afforded separable, diastereomeric 4-piperidone products with resolved stereochemistry in position 2 on the piperidine ring.

The suitability of such 2-substituted 4-piperidones for the synthesis of biologically relevant compounds was demonstrated by employing these building blocks in the synthesis of analogues of the acetylcholinesterase inhibiting drug donepezil. Access to the important 4-formyl piperidines was accomplished through a concise and high yielding route *via* a Wittig reaction followed by acidic hydrolysis to the desired aldehydes. Further synthetic steps afforded the final donepezil analogues as inseparable diastereomeric mixtures with resolved stereochemistry in position two on the piperidine ring. Evaluating the acetylcholinesterase inhibiting potency of these analogues compared to donepezil provided information about the sensitivity of donepezil's piperidine moiety towards stereoselective substitution in position two on the ring.

A detailed investigation of the manganese dioxide mediated side reaction, which is observed in the one-pot oxidation-cyclisation reaction, led to the finding that under the same reaction conditions the oxidation of primary benzylic amines proceeds smoothly to the corresponding amides. The interconversion of all intermediates in this process was demonstrated experimentally and the vital role of both manganese dioxide and the molecular sieves explored. A range of benzylic amides was prepared in good to excellent yield using the developed methodology.

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Abbreviations and Acronyms

$[\alpha]$	specific optical rotation
δ	chemical shift
Å	angstrom(s)
a.u.	arbitrary unit
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
APCI	atmospheric-pressure chemical ionization
aqu.	aqueous
Ar	aryl
ATCI	acetylthiocholine
atm	atmosphere(s)
ax	axial
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
BSA	bovine serum albumin
Bu, *n*-Bu	normal butyl
t-Bu	*tert*-butyl
BuChE	butyrylcholinesterase
Bz	benzoyl
°C	degree Celsius
c	concentration
^{13}C-NMR	carbon nuclear magnetic resonance

calcd	calculated
cat.	catalytic
Cbz	benzyloxycarbonyl
Ch	choline
CNS	central nervous system
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet (spectroscopic) or day(s)
DBA	dibenzylideneacetone
dd	doublet of doublet
ddd	doublet of doublets of doublets
de	diastereomeric excess
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
DTNB	dithiobisnitrobenzoate
ee	enantiomeric excess
***ee*AChE**	electric eel acetylcholinesterase
eq	equatorial
equiv	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
EWG	electron withdrawing group
h	hour(s)
***h*AChE**	human acetylcholinesterase
^{1}H-NMR	proton nuclear magnetic resonance
HFA	hexafluoroacetone

HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	2-iodoxybenzoic acid
***i*-Pr**	isopropyl
IR	infrared
J	NMR coupling constant
KO*t*-Bu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
M	molar
m	multiplet (spectroscopic) or milli
m/z	mass to charge ratio
M+	parent molecular ion
MCI	mild cognitive impairment
Me	methyl
MeCN	acetonitrile
MHz	megahertz
min	minute(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	mesyl or methanesulfonyl
MS	molecular sieves or mass spectrometry
MW	molecular weight
n-	normal
NMDA	*N*-methyl-*D*-aspartate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

NSI	nano electrospray ionisation
Nu	nucleophile
OMS-2	octrahedral molecular sieves
OTf	trifluoromethanesulfonate (triflate)
Ph	phenyl
ppm	part(s) per million
Pr	propyl
q	quartet
R$_f$	retention factor
rt	room temperature
s	singlet (spectroscopic) or second(s)
SAR	structure-activity relationship
sat.	saturated
SD	standard deviation
t-	*tert-*
t	triplet
Et	ethyl
TBAB	tetrabutylammonium bromide
***t*-BuOK**	potassium *t*-butoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl or tetramethylsilane
TNB	5-thio-2-nitrobenzoic acid
TRIS	tris(hydroxymethyl)aminomethane
Ts	*p*-toluenesulfonyl or tosyl
UV-Vis	ultraviolet visible
WHO	World Health Organization

Chapter 1

Introduction

1.1   Introduction to Biologically Important Piperidines

The piperidine moiety **1** (Figure 1.1) is found in a vast number of natural products and is often associated with their distinct pharmacological or toxic properties.[1] Naturally occurring piperidine compounds constitute an important group of alkaloids originating from both plants and animals with new structures of pharmacological interest still being isolated.[2,3]
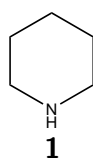
Figure 1.1: The piperidine structural motif.

Due to their bioactive nature, many natural products have the potential to function as templates for synthetically prepared analogues for the development of new pharmaceuticals.[4,5]

Natural Piperidine Products

Examples from the pool of natural piperidines originating from plants, illustrated in Figure 1.2, demonstrate the high pharmacological potential of the simple piperidine

ring structure. The bioactive alkaloid piperine **2** was isolated from black pepper (*Piper nigrum*) by Hans Christian Ørsted in 1820. The French chemist Auguste Cahours further investigated piperine and found that upon treatment with aqueous alkali, a basic product was formed. Due to its origin, he named this unknown compound piperidine. The cyclic structure of piperidine was only resolved much later, in 1883.[6]
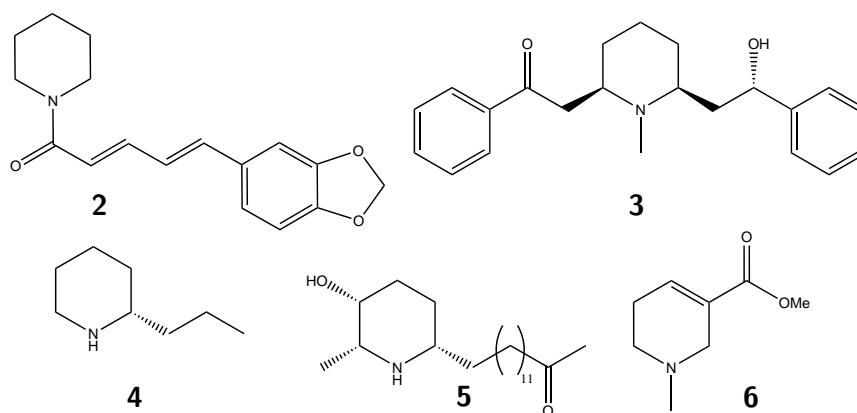
Figure 1.2: Biologically active piperidine alkaloids originating from plants.

Today it is known that the piperidine containing alkaloid piperine **2** possesses several pharmacologically important properties. Not only is it responsible for the spiciness of black pepper, but it has been shown to positively influence the bioavailability of many other substances, for example curcumin,[7] theophylline and propranolol.[8] *In vitro* and *in vivo* studies have shown that piperine **2** inhibits a range of drug-metabolizing enzymes, such as the arylhydrocarbon hydroxylase and the ethylmorphine-*N*-demethylase[9] and enhances the activity of multiple enzymes involved in digestive processes, such as trypsin, lipases and disaccharidases.[10,11] Another pharmaceutically interesting piperidine alkaloid is lobeline **3** (Figure 1.2), which is isolated from the Indian Tabacco (*Lobelia inflata*).[12] Due to its stimulating effects on the respiratory system it has been successfully used to support the treatment of conditions including bronchitis, asthma and pneumonia.[13] Lobeline acts as an antagonist at nicotinic acetylcholine receptors in the central nervous system (CNS) and as this ultimately results in lowered concentrations of dopamine in the synaptic cleft, it has also been investigated for the treatment of psychostimulant abuse.[14]

Coniine **4** (Figure 1.2), a simple piperidine molecule and potent neurotoxin, is the chief alkaloid isolated from hemlock (*Conium maculatum*). It can cause death by respiratory

failure and has been used as a poison for centuries.[15] (-)-Spectaline **5**, an alkaloid from *Cassia leptophylla*, bears a more complex substitution pattern on the piperidine ring, possessing stereocentres at position 2, 5 and 6. This natural product has been found to exhibit anticancer potential based on a yeast assay[16] and antinociceptive effects in mice.[17] The major alkaloid found in the betel nut (*Areca catechu*) is arecoline **6** and is responsible for the stimulating and addictive effects evoked when chewing the nut and leaves of this plant.[18] The tradition of chewing parts of the betel nut has spread widely across the globe and has been associated with various types or pharyngeal and oral cancer[19] and neurotoxicity *via* the increased formation of reactive oxygen species.[20]

Pharmaceuticals Bearing a Piperidine Substructure

In addition to being encountered in naturally occurring compounds, the piperidine ring is also an important substructure found in many pharmaceuticals (Figure 1.3). The piperidine moiety is one of the most common nitrogen heterocycles in synthetic drugs and is often relevant for their pharmacokinetic and pharmacodynamic profile.[21]

Piperidine containing pharmaceuticals cover a wide range of indications and are currently used extensively in the clinic. Most of these drugs are limited to a simple 1,4-disubstitution on the piperidine ring, for example the antidiarrheal loperamide **7**. This drug is a strong μ-receptor agonist, acting exclusively peripherally,[22] and has been listed on the *WHO Model List of Essential Medicines*.[23] Sertindole **8**, risperidone **9** as well as its active metabolite **10** are classified as atypical antipsychotics and are used in the treatment of schizophrenia and bipolar disorders with the therapeutic advantage of causing less extrapyramidal side effects than other available drugs.[24]

Another widely used piperidine containing pharmaceutical is raloxifene **11**, a selective estrogen receptor modulator. By acting as an estrogen receptor agonist in bones it reduces the risk of fractures in postmenopausal women with osteoporosis.[25] Simultaneously raloxifene acts as an estrogen receptor antagonist in the uterus and breast and is therefore an important drug in the prevention of breast cancer in postmenopausal women.[26] Donepezil **12**, used in the treatment of Alzheimer's disease, is an acetylcholinesterase inhibitor which prevents the degradation of the important neurotransmitter acetylcholine
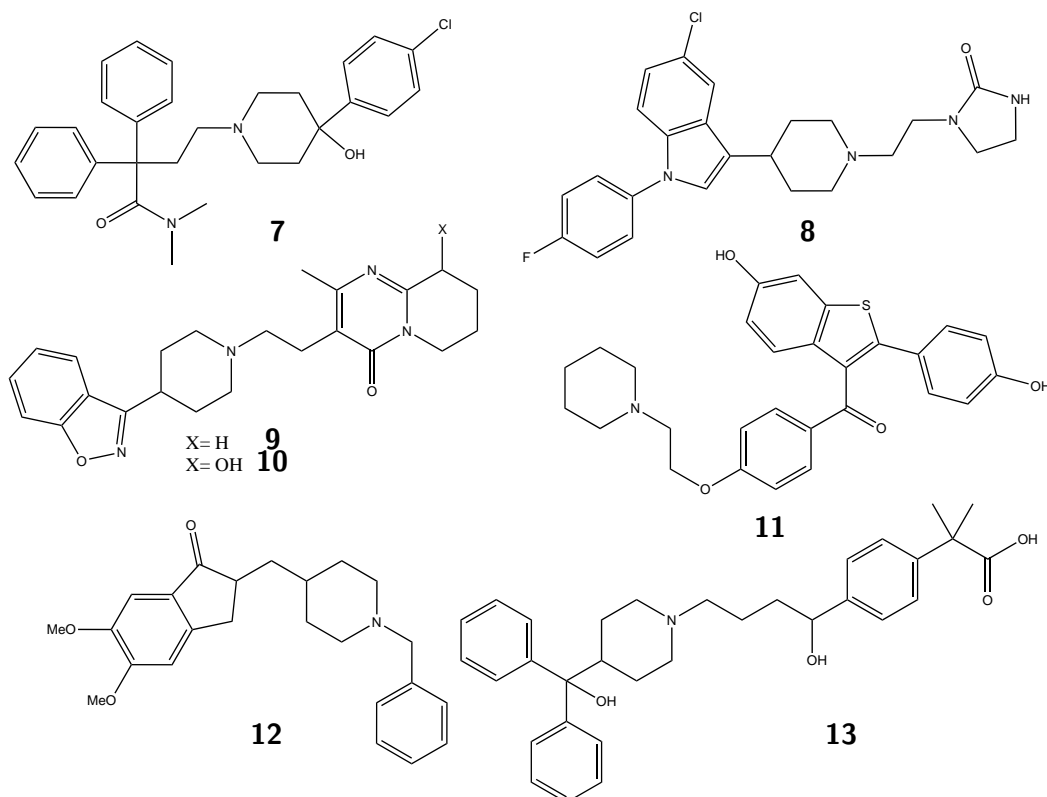
Figure 1.3: A selection of important pharmaceutical agents bearing the piperidine ring substructure.

in the brain.[27] The selective histamine H_1 receptor antagonist fexofenadine **13** is used for the treatment of allergic symptoms, such as allergic rhinitis and idiopathic urticaria. As it does not cross the brain-barrier like most first-generation antihistamines, it causes reduced drowsiness in patients.[28]

Modifications on the Piperidine Ring

Another example of a drug which possesses the classical 1,4-disubstitution pattern on the piperidine ring is the selective μ-receptor agonist fentanyl **14** (Figure 1.4). This drug is widely used for pain management and as anaesthetic and is about 100 times more potent than morphine.[29] Despite the fact that fentanyl and other μ-opiates are used extensively in the clinic and their pharmacological properties are well explored, it is not fully understood which of their structural features are responsible for the ligand recognition that results in such high-affinity binding. Until recently[30] the crystal

structure of the complex membrane-bound μ-receptor was not available and models on a molecular level were difficult to establish.

During structure-activity relationship (SAR) studies it has been shown that substitution on the fentanyl piperidine ring can have a significant impact on the drug's activity profile.[31–33] Analogues possessing an additional methoxymethyl group **15** or a methyl ester **16** in position 4[33] as well as analogues bearing a methyl group in position 3 on the ring, such as derivative **17**,[31,32] lead to an increased activity at the μ-receptor (Figure 1.4).
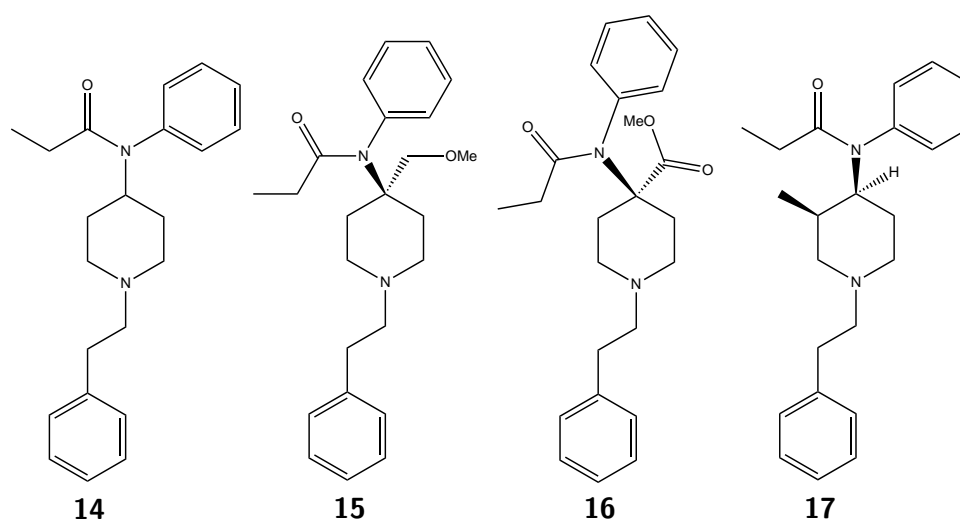
Figure 1.4: Analogues of fentanyl **14**.

In vivo studies in mice and rats have shown that the four possible methyl substituted stereoisomers **17-20** exhibit different activities (Figure 1.5). $3R,4S$-*cis*-3-Methylfentanyl **17** has been found to be approximately 20 times more potent than fentanyl, while its enantiomer **18** is approximately 5 times less potent.[31,32]

In an attempt to explain the different activities of these close fentanyl analogues, Dosen-Micovic[34] conducted a detailed molecular modelling study. The binding pocket for fentanyl **14** within the receptor was shown to lie close to the extracellular region and between two transmembrane helices (TM3 and TM7) (Figure 1.6). The fentanyl-ligand's N-phenylpropanamide group protrudes towards the extracellular side of this pocket while the N-phenethyl group is buried inside the cavity. Fentanyl is protonated and maintains a stable salt-bridge to an aspartate residue in close proximity. While the
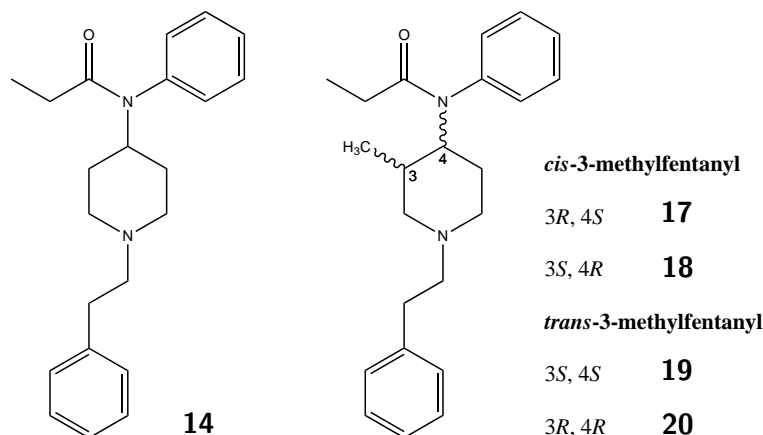
Figure 1.5: Fentanyl **14** and its 3-methyl-substituted analogues **17-20**.

geometries of the methyl-substituted analogues **18-20** are similar to the best fentanyl orientation, the position and orientation of the more potent analogue **17** is different. This analogue occupies the same binding pocket and maintains the salt bridge as the other isomers, but is rotated and shifted in a way that the methyl group points into a small hydrophobic pocket of the cavity (Figure 1.6). Through this difference in overall orientation it connects the surrounding transmembrane helices TM3 and TM6 and reaches a closer proximity to TM7, ultimately resulting in a higher binding affinity.[34]
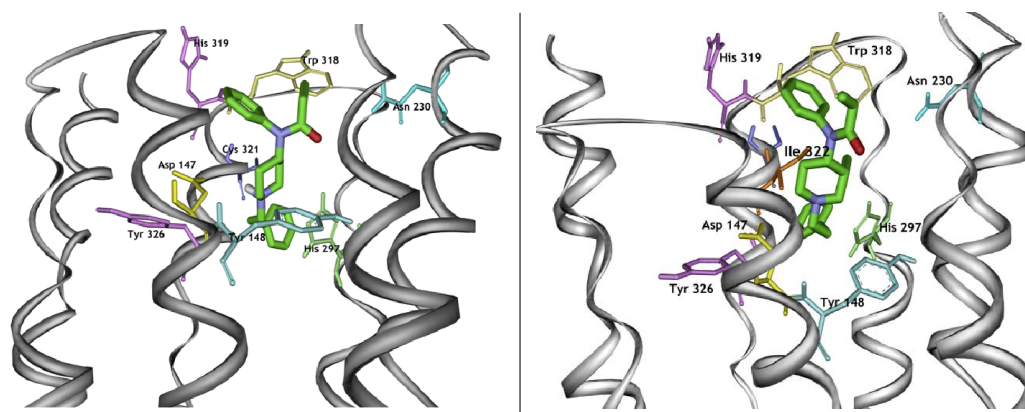
Figure 1.6: *On the Left:* Fentanyl **14** in its best orientation in the binding pocket. *On the Right:* 3R,4S-analogue **17** in the binding pocket.

This example demonstrates how a small additional substituent on the 1,4-disubstituted piperidine moiety of a drug can have a significant influence on binding behaviour and activity. SAR studies of this type are rarely reported in the literature, possibly due to the increased number of synthetic steps and the complication of purification and separation caused by the introduction of additional stereocentres.

1.2 Methods for the Synthesis of 1,2,4-Trisubstituted Piperidines

Since substituted piperidines ring systems are found in a diverse range of bioactive natural products, the pharmaceutical industry has developed great interest in obtaining such compounds in a stereoselective manner. Currently, the $N(1),C(4)$-disubstitution pattern prevails amongst drugs in the clinic and therefore the easy access to steroselectively substituted piperidines, such as $N(1),C(2),C(4)$-trisubstituted building blocks, is highly desirable in order to gain further structure-activity related information on existing and new pharmaceuticals.

Many different approaches towards the synthesis of a multi-substituted piperidine core exist, and review literature illustrates the current interest in this important area of organic chemistry.[35–40] Out of this large amount of different strategies available for the synthesis of substituted piperidines, examples specifically for the stereoselective synthesis of 1,2,4-trisubstituted piperidines will be presented in the following section, emphasising the key steps of these routes.

Nucleophilic 1,4-Addition to Dihydropyridones

Shintani reported an enantioselective preparation of 2-aryl-substituted 4-piperidones *via* rhodium catalysis (Scheme 1.1).[41] Nucleophilic 1,4-addition of aromatic organozinc reagents **22** to 2,3-dihydro-4-pyridone **21** utilising [RhCl(R-binap)]$_2$ as a catalyst leads to the target compounds. The reaction proceeds under mild conditions and furnishes 2-substituted 4-piperidones **23** with excellent enantioselectivity (>99% ee) and in high yields (87-100%).
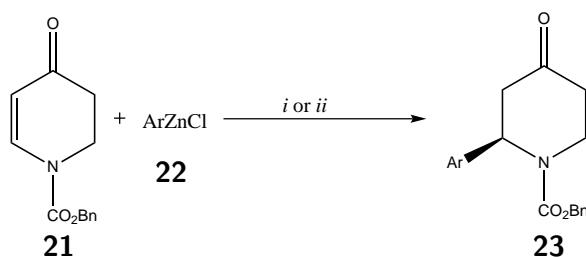
i) Ar= Ph, 4-Ph-C$_6$H$_4$, 4-F-C$_6$H$_4$ **91-97%**
ii) Ar= 4-MeO-C$_6$H$_4$, 3,5-Me$_2$-C$_6$H$_3$, 2-Me-C$_6$H$_4$ **87-100%**

Scheme 1.1: Reaction conditions: *i)* **22** (1.5 equiv.), 3 mol% [RhCl(R-binap)]$_2$, THF, 20 °C, 2 h, then H$_2$O quench; *ii)* **22** (3.0 equiv.), 6 mol% [RhCl(R-binap)]$_2$, THF, 20 °C, 2 h, then H$_2$O quench.

This protocol was applied to the synthesis of piperidone **26**, an important interme-diate for the further synthesis of potent tachykinin NK1 receptor antagonist **27**[42] (Scheme 1.2). In the first step, the rhodium catalysed 1,4-addition yielded desired 2-aryl substituted **25**, which was hydrogenated over a palladium catalyst to remove the benzyloxycarbonyl moiety and obtain building block R-**26** in high yield and stereoselectivity (73% for two steps, 97% ee).[41]
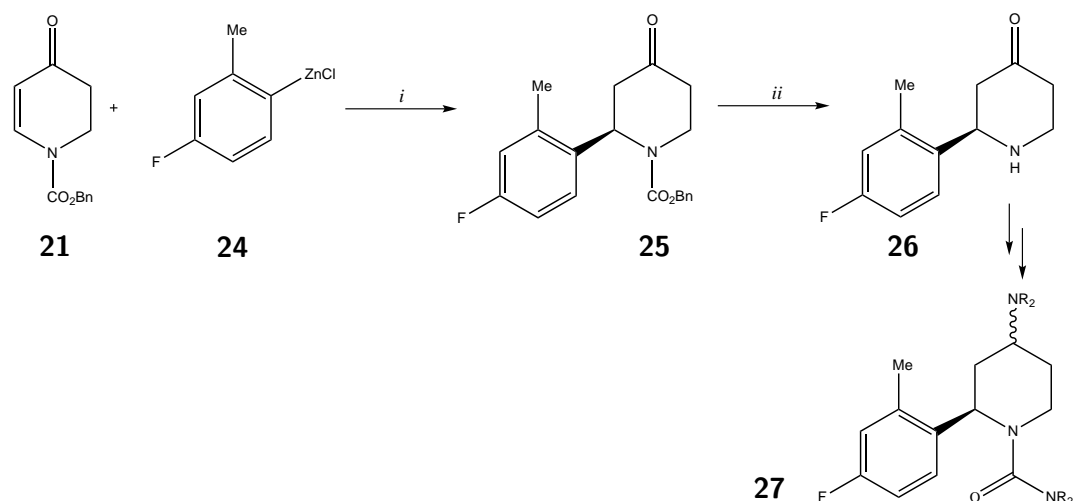
Scheme 1.2: Reaction conditions: *i)* 8 mol% [RhCl(R-binap)]$_2$, THF, 20 °C, 9 h, then H$_2$O quench; *ii)* 9 mol% Pd/C, H$_2$, 1 atm, MeOH, 20 °C, 4 h.

Nucleophilic Addition to *N*-Acylpyridinium Salts

Starting from simple, commercially available 4-methoxypyridine **28**, Comins achieved the diastereoselective synthesis of 2-aryl substituted dihydropyridones (Scheme 1.3).[43] Chiral chloroformate **32**, derived from (-)-menthol, was utilised to generate optically active 1-acylpyridinium salt **29** *in situ*. A subsequent Grignard addition and aqueous workup provided the diastereomeric dihydropyridone products **30** and **31** in a combined yield of 79% and a diastereomeric excess (de) of 34% (with **30** being the major product).
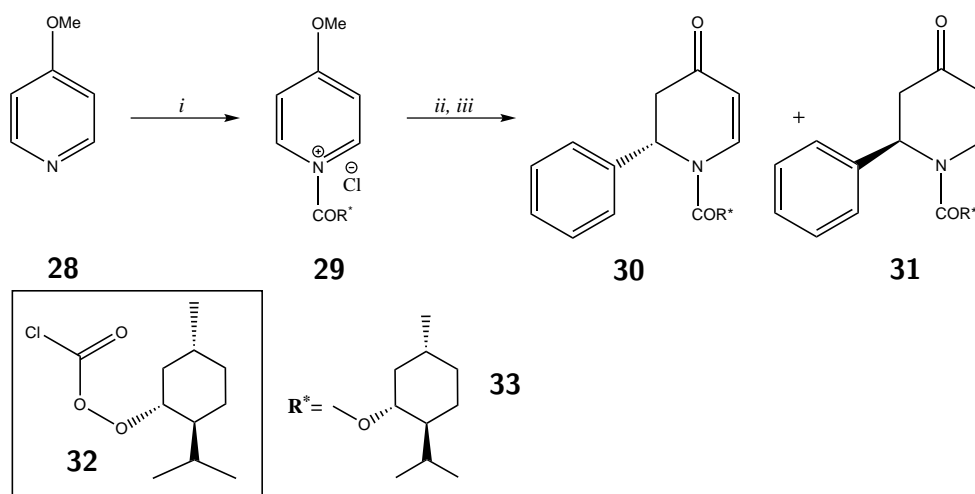
Scheme 1.3: Reaction conditions: *i)* **32**, toluene, -23 °C, 15 min; *ii)* PhMgCl, toluene/THF (24:1), -78 °C, 1 h; *iii)* 10% HCl (aqu.), 23 °C, 10 min.

A similar route towards the diastereoselective synthesis of 2-substituted 4-piperidones *via* nucleophilic addition to an *N*-acylpyridinium salt was described by Watson (Scheme 1.4).[44] The origin of the diastereoselectivity in this synthetic approach is due to the unique properties of *N*-acylpiperidine **34** (Figure 1.7).
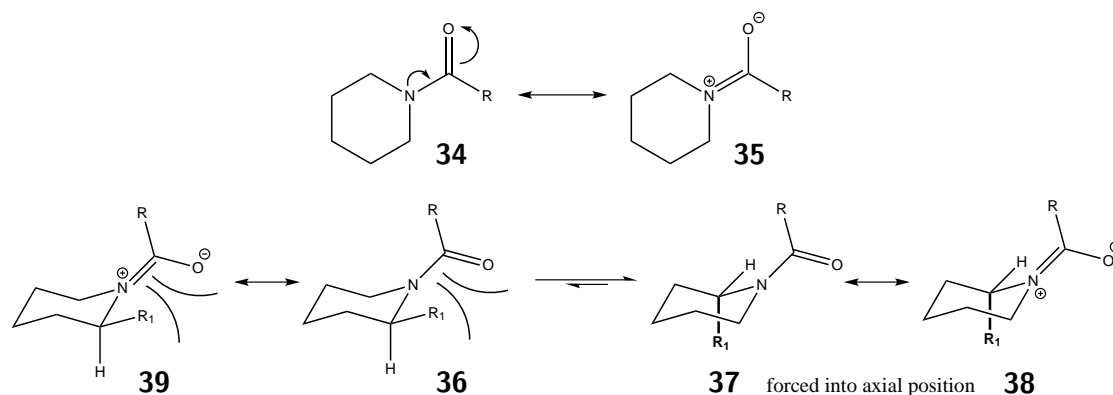
Figure 1.7: *N*-Acylpiperidines and their resonance hybrids.

Resonance hybrids **34** and **35** exist due to the delocalisation of the nitrogen's lone pair of electrons. The result is a pseudo-allylic system which causes an $A^{1,3}$-strain on the C2 carbon of the piperidine ring. If a substituent in position 2 on the ring is large enough, it is forced into an axial position (**37** and **38**) due to minimized steric hindrance. As the conformation where the substituent adopts an equatorial position (**36** and **39**) is disfavoured because of steric interference, it becomes possible to influence the diastereoselectivity of the reaction.

In the first step of Watson's synthesis,[44] 4-methoxypyridine **28** is reacted with phenyl chloroformate to give an *N*-acylpyridinium salt as the intermediate (Scheme 1.4). The Grignard reagent is then added to position two on the ring and generates the unstable intermediate **40**. Acidic aqueous workup yields dihydropyridone **41**[45] which is subsequently subjected to a deprotection and reprotection step to obtain Boc protected dihydropyridone **42** in a yield of 41-73% over three steps. Reduction of **42** to 2-substituted piperidone **43** is followed by a Wittig olefination to provide styrene **44** in high overall yield (89-95%). Reduction of the double bond and deprotection on the nitrogen afforded piperidine **45** in good diastereoselectivity (*trans:cis* 88:1 for **45a**, 4:1 for **45b** and 18:1 for **45c**) in yields of 97-100%.
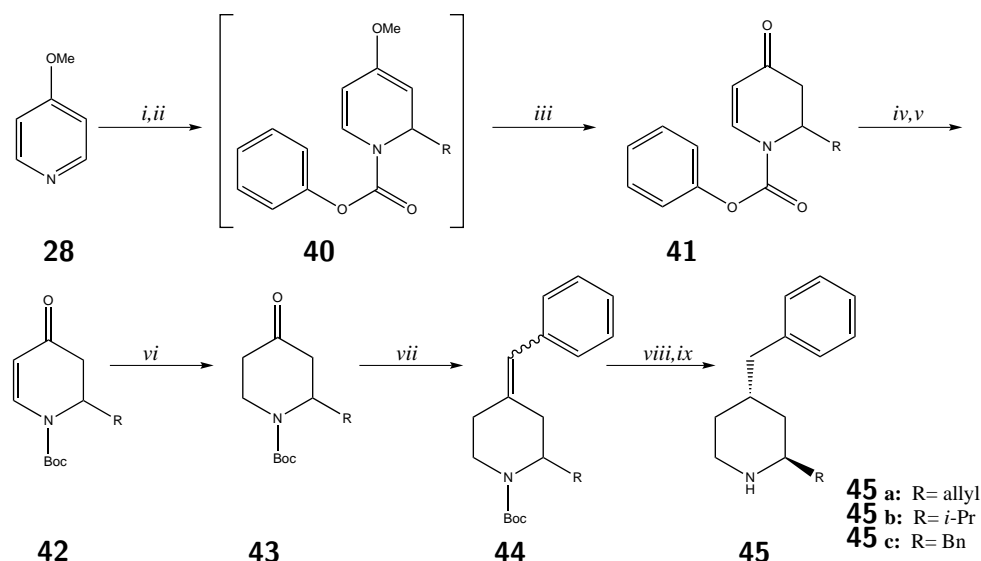
Scheme 1.4: Reaction conditions: *i)* PhOC(O)Cl, THF, -20 °C, 15 min; *ii)* RMgCl, -78 °C, 1 h; *iii)* 10% HCl (aqu.), 23 °C, 10 min; *iv)* NaOMe, MeOH, 23 °C, 2 h; *v)* Boc$_2$O, DMAP, MeCN, 23 °C, 12 h; *vi)* Zn, HOAc, 50 °C, 12 h; *vii)* t-BuOK, PhCH$_2$P(Ph)$_3$Cl, THF, 23 °C, 24 h; *viii)* Li, NH$_3$, THF, -78 °C, to -28 °C, 1 h; *ix)* 75% TFA/CH$_2$Cl$_2$, 2 h.

Imino Diels-Alder Reactions

The imino Diels-Alder reaction has been frequently employed as a convenient approach to access substituted piperidines in an asymmetric manner.[46,47] Typically, an electron rich diene, for example Danishefsky's diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene), reacts with an electrophilic imine and affords the desired piperidone with good enantioselectivity.

Mancheño applied this methodolody to the synthesis of *N*-sulfonyl 2,3-dihydropyridone **48** as part of the formal synthesis of the quinolizidine alkaloid (+)-lasubine I **49** (Scheme 1.5).[48] Danishefsky's diene **46**, catalysed by copper-fesulphos bromo dimer catalyst **50**,[49] reacts with *N*-tosyl aldimine **47** to afford 2*R*-aryl-substituted piperidone **48** in good yield (71%) and excellent enantioselectivity (94% ee). Dihydropyridone **48** is then converted to (+)-lasubine I **49** in a further 5 steps.

46 **47** **48** **49**

(+)-Lasubine I

copper complex of
phosphino sulfenyl ferrocene

50
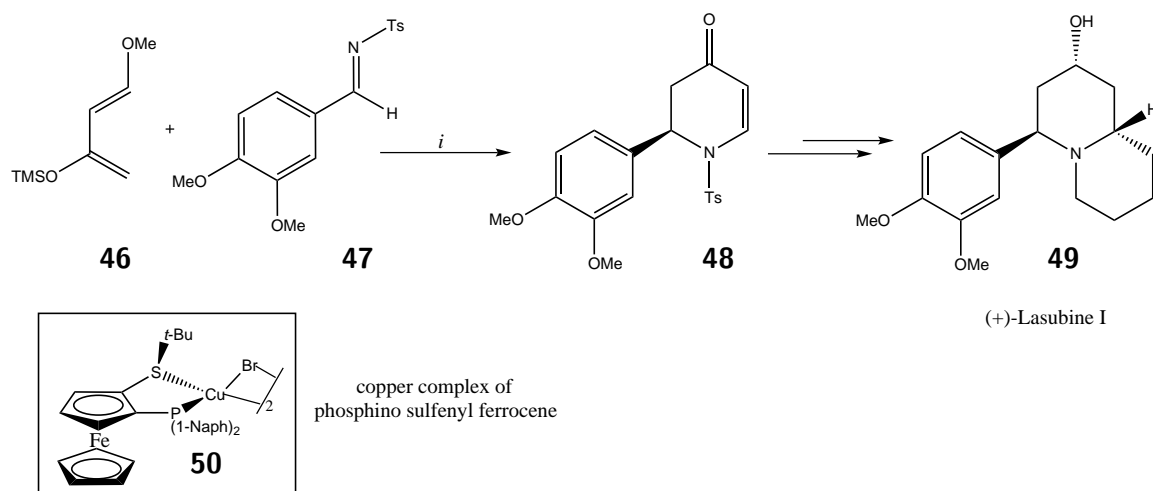
Scheme 1.5: Reaction conditions: *i)* 5.1 mol% **50**, 10 mol% AgClO$_4$, then TFA, CH$_2$Cl$_2$, -20°C, 12 h.

Bailey also explored the *aza*-Diels-Alder reaction for the synthesis of 2,4-substituted piperidines (Scheme 1.6).[50] Imine **52**, a dienophile with a tethered chiral auxiliary, was prepared by the condensation of *R*-phenylethylamine and ethyl glyoxylate.

51 **52** **53** **54** **55**
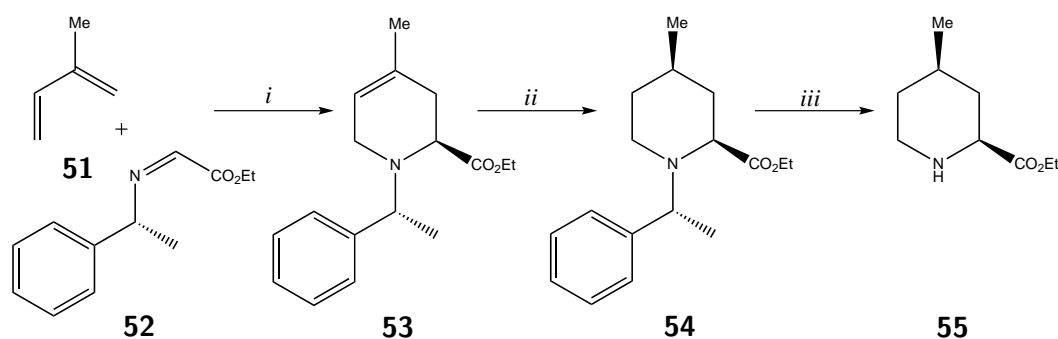
Scheme 1.6: Reaction conditions: *i)* DMF/TFA (6:1), H$_2$O (cat.), rt, 30 h; *ii)* H$_2$, 3% Pt-C, EtOAc, rt, 16 h; *iii)* H$_2$, Pd(OH)$_2$, EtOH, rt, 8 h.

A catalytic amount of water was found to greatly improve the yield of the reaction and suggested that there is hydrogen bond formation taking place between imine **52** and water (Figure 1.8). This cyclic intermediate promotes the reaction, as it helps to stabilise the 6-membered transition state of the subsequent *aza*-Diels-Alder reaction. In their model, the use of *R*-phenylethylamine as chiral auxiliary leads to an *endo* attack of diene **51** on the *si* face of imine **52**, resulting in a major product bearing *S*-chirality in position 2 on the ring.
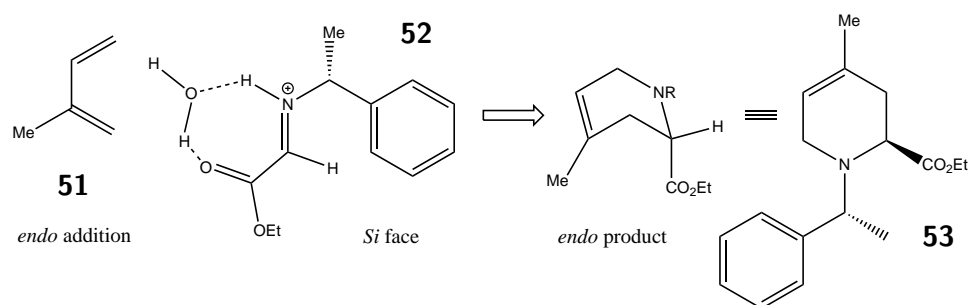
Figure 1.8: Water coordinating chiral imine intermediate **52** leading to an *endo* product bearing *S*-chirality in position 2 on the ring.

Chiral imine **52** reacts with diene **51** to give 2*S*-**53** as the major product and 2*R*-**53** as the minor product (2*S*:2*R* 81:19). The diastereomers can be conveniently separated by flash chromatography and when 2*S*-**53** is subjected to reduction over a platinum catalyst, *cis* disubstituted **54** is obtained as the major product (*cis:trans* 88:12). In a second reduction step removal of the chiral auxiliary is achieved using Pearlman's catalyst to give deprotected piperidine **55** as final product in 72% yield.

Aza-Prins-Type Reactions

Murty's approach shows an example for the stereoselective preparation of 2,4-substituted piperidines *via* an *aza*-Prins type reaction (Scheme 1.7).[51] Reacting *N*-tosyl protected amine **56** in the presence of bismuth(III) chloride with various aliphatic or aromatic epoxides **57** delivers *N*-tosyl protected 2-substituted 4-chloropiperidines **58** in high yields (80-93%) and good diastereoselectivity (*trans:cis* 9:1 for R= Ph).

R= Ph, Me, 4-MeO-C$_6$H$_4$, *i*-Pr
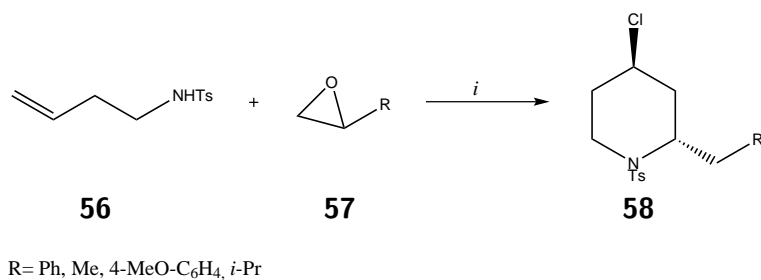
Scheme 1.7: Reaction conditions: *i)* BiCl$_3$, CH$_2$Cl$_2$, 0 °C-rt, 30 min.

This *aza*-Prins cyclisation reaction is promoted by bismuth(III) chloride, which is acting as a Lewis acid and facilitates the ring-opening of the epoxide substrate **59** to **60**

(Figure 1.9). A hydride shift gives intermediate **61** which is subsequently attacked by nucleophilic amine **56**. The resulting iminium ion **64** is stabilised by the tosyl protecting group and cyclises to piperidine **66**. The addition of chloride to the carbocation results in the formation of *trans*-substituted piperidine **67**.
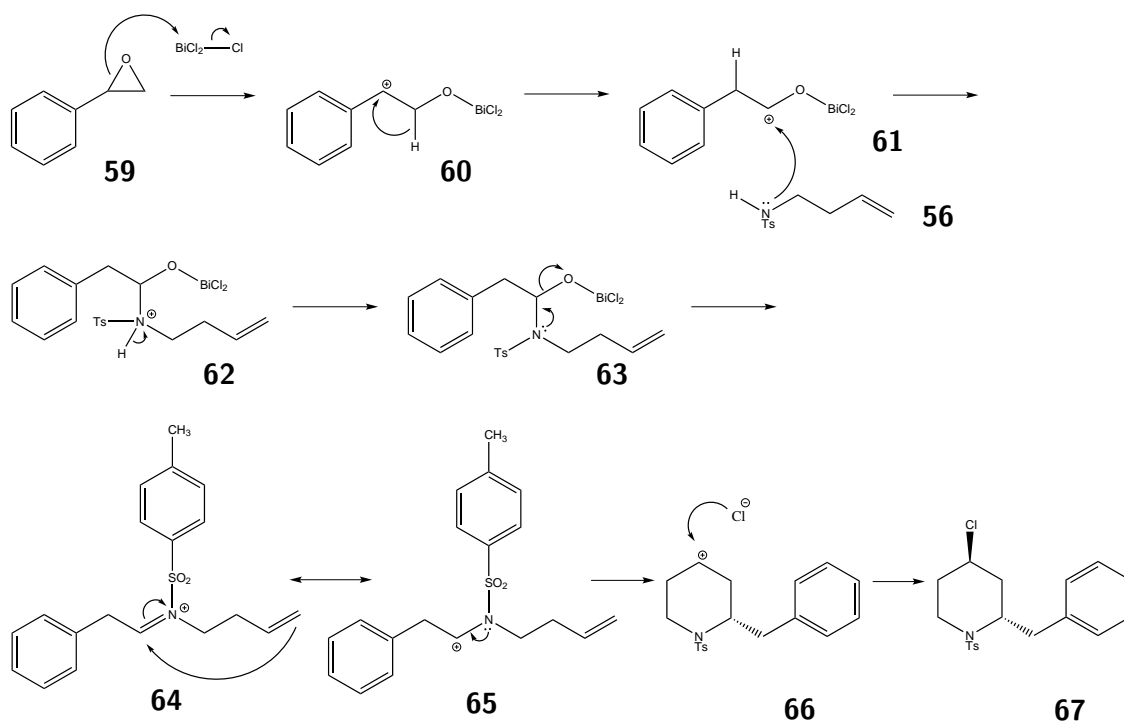
Figure 1.9: Reaction pathway for the *aza*-Prins type reaction.

An *aza*-Prins type cyclisation reaction can furthermore be employed for the construction of heterotricycles, such as shown in the protocol described by Reddy (Scheme 1.8).[52] Benzo[*f*]isoquinoline products **72** are dopamine congeners[53] and can be decorated with aromatic or aliphatic substituents adjacent to the nitrogen on the ring. In this reaction the Brønsted acid *p*-toluenesulfonic acid and the Lewis acid $Sc(OTf)_3$ act synerigistically and achieve an initial addition of the tosyl-protected amine substrate **68** to aldehyde **69**, followed by the formation of iminium intermediate **71**. The nucleophilic aryl-moiety of **71** then attacks the resulting carbocation equatorially and thereby furnishes exclusively the *trans*-diastereomeric product **72**. This *aza*-Prins/Friedel-Crafts reaction proceeds with good yield (75-88%) and allows easy access to potential dopamine analogues **73** *via* a simple deprotection.

i) R= *i*-Pr, 4-Me-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$, -C$_7$H$_{15}$
ii) R= *i*-Pr
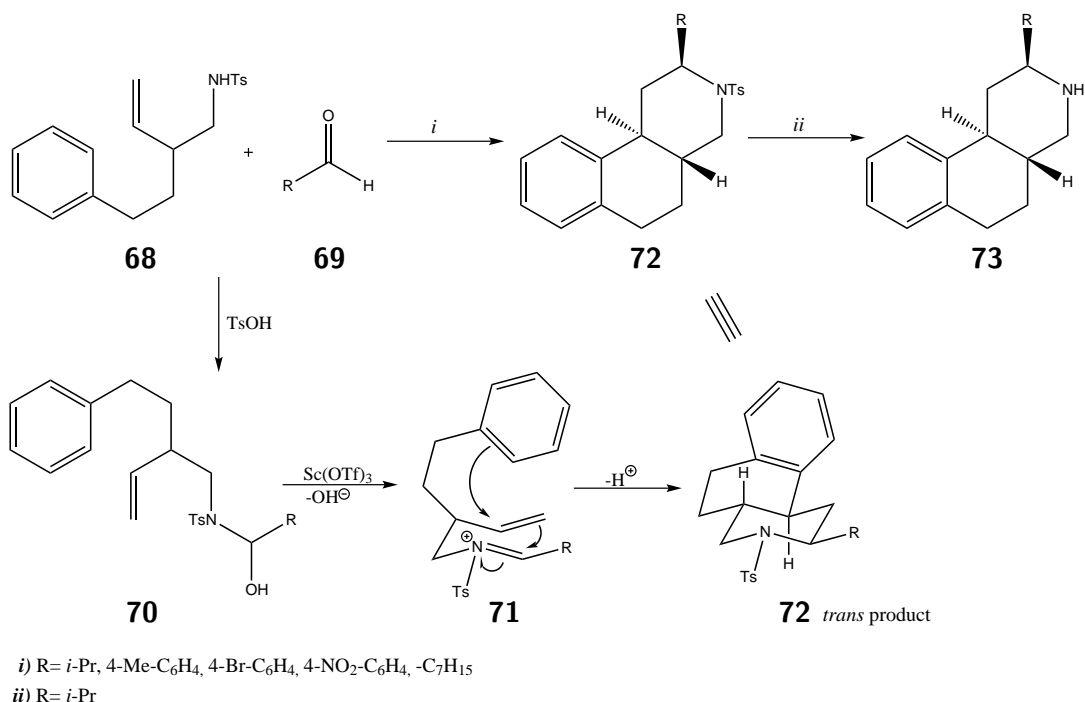
Scheme 1.8: Reaction conditions: *i)* TsOH, $Sc(OTf)_3$, CH_2Cl_2, 80 °C, 4-8 h; *ii)* Li/naphthalene, THF, 40 °C, 30 min.

Rutjes developed a protocol for the synthesis of 2,4-disubstituted pipecolic acid derivative **80**, using non-natural amino acids as starting material (Scheme 1.9).[54] Enantiopure amino acid derivatives such as **74** are prepared using enzymatic resolution of the corresponding amino acid amides and subsequent protection. In the presence of the Lewis acid $SnCl_4$ and 1,3,5-trioxane, a source of C_1, *N*-acyliminium **77** is generated. This

intermediate cyclises readily to give secondary carbocation **78**, which can be trapped by chloride from the less hindered equatorial position to yield the *trans* product. Another possibility is that the ester group stabilises the positive charge and leads to the formation of dioxycarbenium ion intermediate **79**, which can be further hydrolysed during workup to yield the *cis* product. In this reaction, the 4-hydroxy-*cis*-isomer **76** is obtained as major product in a yield of 73% and can be used as building block for the further synthesis of **80**.
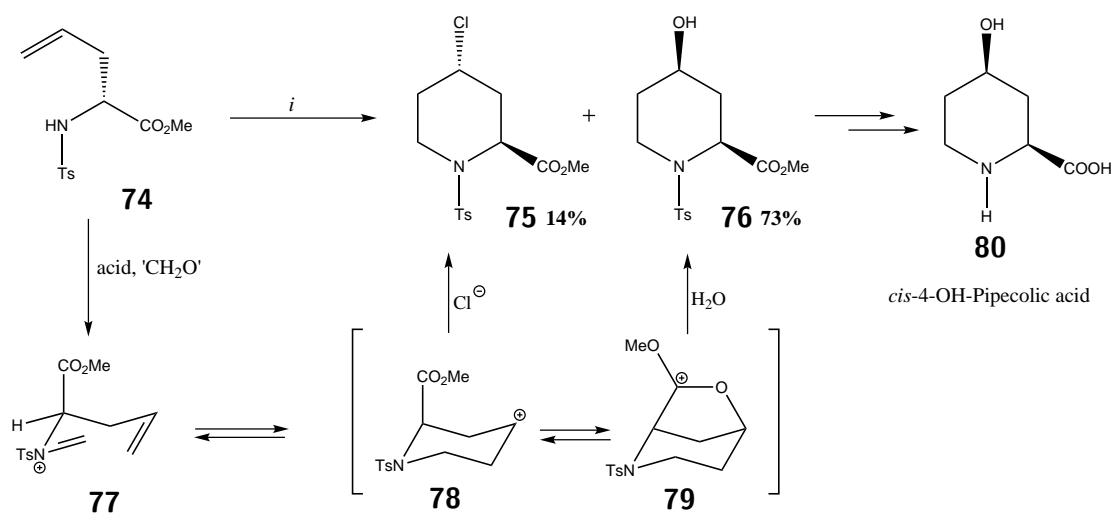
Scheme 1.9: Reaction conditions: *i)* 1,3,5-trioxane, $SnCl_4$, CH_2Cl_2, rt, 20 h.

1.3 The *Aza*-Michael Addition for the Construction of Substituted Piperidines

The *Aza*-Michael Reaction

The classical carbon Michael addition involves the base-catalysed attack of a nucleophilic enolate (Michael donor) to an activated, α,β-unsaturated carbonyl compound (Michael acceptor).[55] An example therefore is the reaction of ethyl acetoacetate **81**, a Michael donor, with methyl acrylate **84**, a Michael acceptor (Figure 1.10).[55] Upon deprotonation of acetoacetate **81**, a nucleophilic enolate anion is formed. This anion reacts with the double bond of acrylate **84** and forms a new carbon-carbon bond. The carbonyl group of the Michael acceptor stabilises the resulting anion **85** until protonation occurs. The addition of enolate anion **81** to the alkene is the rate determining step. According to the strength of the base, the concentration of enolate ions and therefore also the rate of the reaction vary.
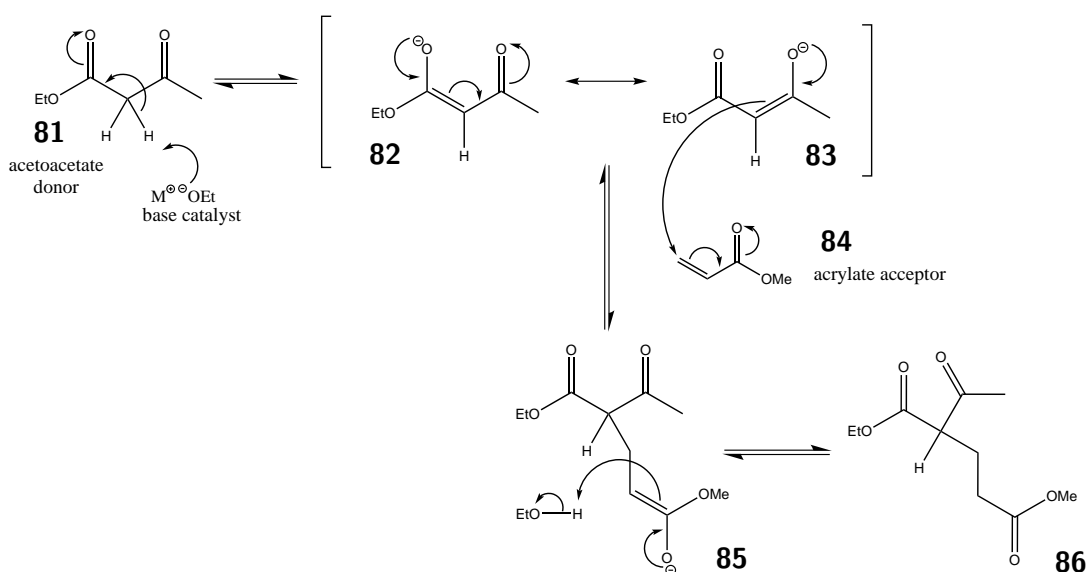
Figure 1.10: Mechanism for the addition of ethyl acetoacetate to methyl acrylate.[55]

If the nucleophile in the reaction is not a carbanion, but a heteroatom, the reaction is called a *hetero*-Michael addition (Scheme 1.10). Those heteroatom-nucleophiles, such as amines,[39,56] thiols and alcohols[57] can react with activated electrophilic olefins in a Michael-like manner. As it is the case in the carbon-Michael addition, it is important

that the alkene bears an electron-withdrawing substituent in order to facilitate the nucleophilic attack on the β-carbon of the Michael acceptor. If the nucleophile is a primary or secondary amine, the reaction is called an *aza*-Michael addition.

EWG= CO$_2$R, C(O)NR$_2$, C(O)R, CN, SO$_2$R, P(O)R$_2$
Nu= NHR, NR$_2$, PR$_2$, OR, SR (R= Alk, Ar)
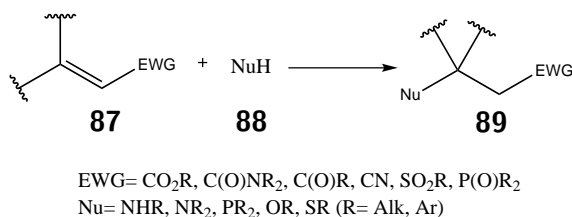
Scheme 1.10: Schematic depiction of a hetero-Michael addition.[56]

Sokoloff and Latschinoff[58] were the first to describe such a reaction when they observed the addition of ammonia **91** to mesityl oxide **90** (Scheme 1.11). The *aza*-Michael addition is a powerful tool for the formation of new C-N bonds and widely used for accessing nitrogen-containing, biologically active molecules.[59–61]
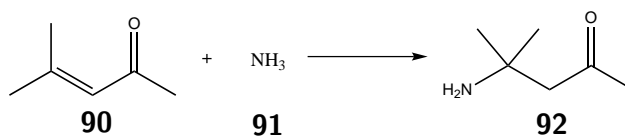
Scheme 1.11: Formation of diacetonamine **92**.

Since amines are both nucleophilic and basic, there is in general no need for additional base catalysis to achieve the addition to an activated olefin. The higher the nucleophilicity of the amine and the more electrophilic and sterically accessible the Michael acceptor, the more efficient the reaction will be. Secondary amines, especially if they are cyclic, are more nucleophilic and therefore react readily and in high yield with simple Michael acceptors. Conversely, primary amines are less reactive towards nucleophilic attack and often require harsher reaction conditions, such as increased temperatures and long reaction times.[56]

The choice of solvent for a Michael reaction depends on the solubility of the reagents and the chemical sensitivity of other functional groups present. In general, polar protic solvents including methanol, ethanol, and water and polar aprotic solvents including

acetonitrile and dichloromethane are preferred. These solvents can stabilise the charged reaction intermediates and in the case of protic solvents also facilitate proton transfer.[55]

In water, an aliphatic, secondary amine such as piperidine **93** reacts with ethyl acrylate **94** without the need for any further catalyst and affords addition product **95** in high yield (85%) (Scheme 1.12),[62] whereas a primary amine substrate like benzylamine **96** gives a mixture of mono- and di-substituted products **97** and **98** in low yield (20%) when reacting with methyl acrylate Michael acceptor **94** (Scheme 1.13).[63] This contrast in reactivity of piperidine and benzylamine towards an activated Michael acceptor can be explained by their differences in nucleophilicity. A secondary amine, such as piperidine is more nucleophilic in water than benzylamine, hence reacting with a Michael acceptor at a faster rate, resulting in higher yields.[64]
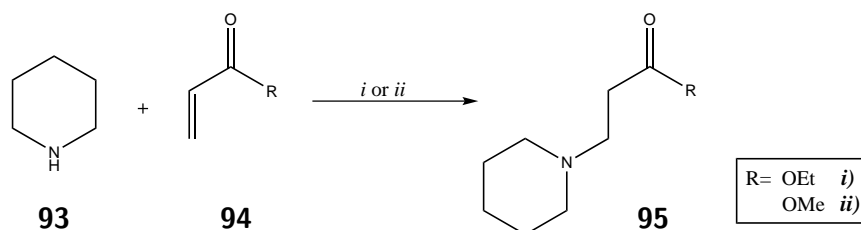
Scheme 1.12: Reaction conditions: *i)* H_2O, rt, 14 h, 85%; *ii)* MeCN, rt, 20 h, 40%.
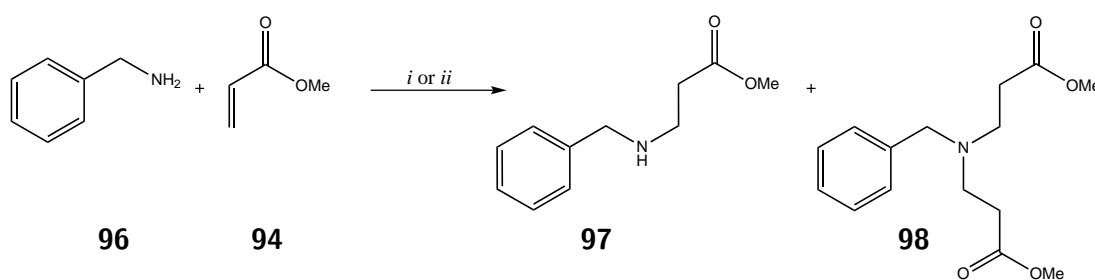
Scheme 1.13: Reaction conditions: *i)* H_2O, rt, 6 h, 20% (**97**:**98** 35:65); *ii)* MeCN, rt, 48 h, 70% (**97**:**98** 100:0).

Although the addition of benzylamine **96** to methyl acrylate **94** in water is low yielding, these conditions promote the mono-subsituted product **97** to ungergo a second *aza*-Michael addition, therefore forming disubstituted product **98** as the major product. Acetonitrile facilitates the addition of benzylamine **96** to the Michael acceptor and increases the yield to 70%, but gives exclusively the mono-substituted product **97**

(Scheme 1.13).[65] On the contrary, piperidine **93** is less reactive in acetonitrile and gives **95** in only 40% yield (Scheme 1.12).[65] These observations suggest that using acetonitrile as the solvent promotes the reaction of a primary amine with an acitivated Michael acceptor, but is less suitable for *aza*-Michael additions with secondary amine substrates.

Less reactive *aza*-Michael substrates can be activated using a range of catalysts.[38,66] Catalysts enhance either the nucleophilicity of the amine or the electrophilicity of the Michael acceptor. In cases where sterically hindered, α or β-substituted olefins or less reactive primary amines are involved, Lewis acid catalysts have been successfully employed. Lewis acids such as copper and nickel salts, triflates[67] and transition and main-group metal chlorides[63,66,68] have been shown to improve the yields for various *aza*-Michael reactions (Scheme 1.14, Table 1.1). Commonly, 5-20 mol%[56] of these catalysts are used to accelerate the reaction by coordination to the carbonyl function of the Michael acceptor, which is thereby activated towards nucleophilic attack.[55]
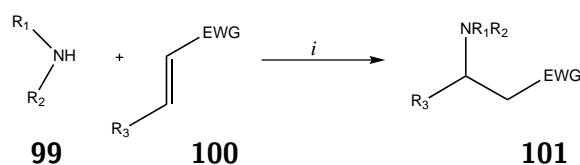
Scheme 1.14: Lewis-acid catalysed conjugate additions. Reagents and conditions: *i)* various.

Table 1.1: Lewis-acid catalysed conjugate addition of various aliphatic amines **99**.

Entry	Catalyst	R_3	EWG	Amine **99**	Solvent	Yield of **101** (%)
1	$CdCl_2$[a]	H	CO_2Et	$BnNH_2$	CH_2Cl_2	93[68]
2	$CdCl_2$[a]	H	CO_2Et	$BnCH_2NH_2$	CH_2Cl_2	87[68]
3	-	Me	CO_2Et	$BnNH_2$	THF	0[67]
4	$Yb(OTf)_3$[b]	Me	CO_2Et	$BnNH_2$	THF	92[67]
5	$Yb(OTf)_3$[b]	Me	CO_2Et	pyrrolidine	THF	95[67]
6	$InCl_3$[a]	Me	CO_2Me	$BnNH_2$	H_2O	70[c,63]
7	$InCl_3$[a]	Me	CO_2Me	Me_2NH	H_2O	85[63]

[a] 20 mol% of catalyst used.
[b] 10 mol% of catalyst used.
[c] Ratio of mono-substituted to disubstituted product 33:67.

Many more catalytic systems, such as Brønsted acids,[57] silica gel[69] and lipases[70] have been developed for enhancing the reactivity of the *aza*-Michael components and it should

be noted that their application can be highly specific. However, the results obtained depend on the steric properties of the reactants as well as the solvent system and other reaction conditions.

Intramolecular *Aza*-Michael Additions

An asymmetric synthesis of 4-oxo-*L*-pipecolic acid **106a**, starting from *L*-aspartic acid, has been developed by Golubev (Scheme 1.15).[71] The uncommon amino acid **106a** is a structural component of the cyclic peptide virginiamycin S_1 which has been shown to possess antibiotic properties.[72] Protected amino acid **102** was prepared by the reaction of *L*-aspartic acid with hexafluoroacetone (HFA). Acid chloride formation yields **103** and is followed by Stille coupling using vinyltrimethyltin and a palladium catalyst to give enone **104a**. A Lewis acid catalysed intramolecular *aza*-Michael addition leads to the formation of protected piperidone **105a** in a yield of 50-55%. 4-Oxo-*L*-pipecolic acid **106a** is obtained following deprotection.
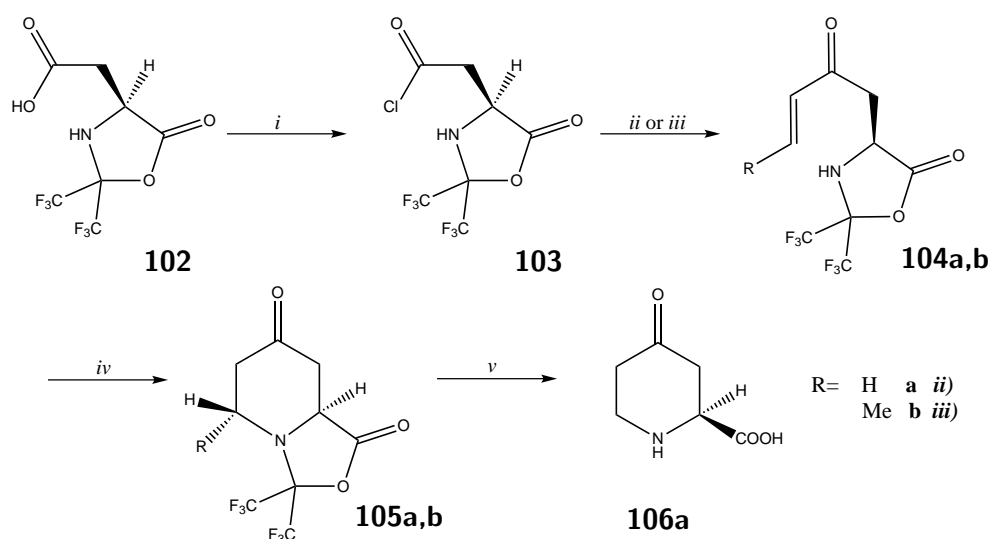
Scheme 1.15: Reaction conditions: *i)* $SOCl_2$, reflux; *ii)* $CH_2=CH-SnMe_3$, $PhCH_2Pd(PPh_3)_2Cl$, dimethoxyethane; *iii)* $Me-CH=CH-Sn(n-Bu)_3$, $Pd_2(DBA)_3$, toluene; *iv)* $BF_3 \cdot OEt_2$, benzene, reflux; *v)* H_2O/i-PrOH.

When *trans*-methyl-substituted enone **104b** is subjected to the same *aza*-Michael addition conditions, the cyclisation yields 30% of *trans*-6-methyl-4-oxo-*L*-pipecolic acid derivative **105b**. According to their observations, no Michael products were formed when dimethyl, methoxycarbonyl or phenyl substituted enones were reacted under similar conditions. It seems plausible that the increased steric hindrance at these substituted

enones combined with their reduced electrophilicity make them less active towards an intramolecular nucleophilic addition, thereby not giving the desired cyclisation products under the tested reaction conditions.

Due to the interesting biological properties of Diospongins,[73] a tetrahydropyran-derived class of natural products isolated from *Dioscorea spongiosa*, Chandrasekhar developed an asymmetric route towards an unnatural, piperidin-based analogue of a diospongin, namely *aza*-(-)-diospongin A **110** (Scheme 1.16).[74] Amino alcohol **107** is prepared in 6 steps and used as the starting point for the synthesis. Employing Grubbs catalyst **111**, enone product **109** is prepared by cross-metathesis of **107** with phenyl vinyl ketone **108**. In the final step, a one-pot Boc-group deprotection and intramolecular *aza*-Michael cyclisation give the desired diospongin analogue **110** in excellent yield (96%) and 99% optical purity.
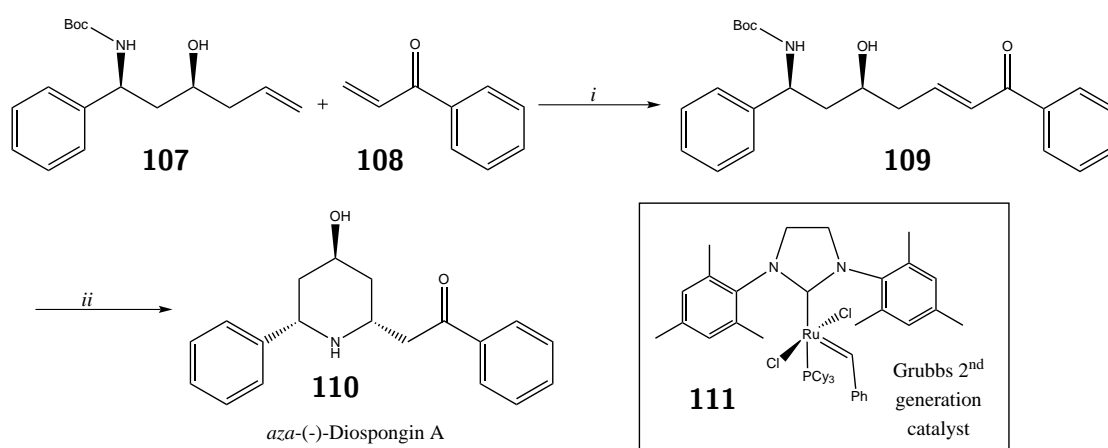
Scheme 1.16: Reaction conditions: *i)* 20 mol% **111**, CH_2Cl_2, rt, 1 h; *ii)* TFA, CH_2Cl_2, 0 °C, 5 h.

Exploring the synthetic versatility of the new sulfone building block **112**, Barco developed a route towards 2-substituted 4-piperidones, which makes use of an intramolecular tandem Michael reaction (Scheme 1.17).[75] Building block **112** possesses a stabilised ylide moiety on one side of the molecule and a sulfone functionality on the other and can be conveniently prepared in three steps. The reaction of **112** with aldehyde **113** proceeds smoothly to yield enone **114**.

112 + **113** → **114**

114 + **115** → [**116** → **117**] → **118**
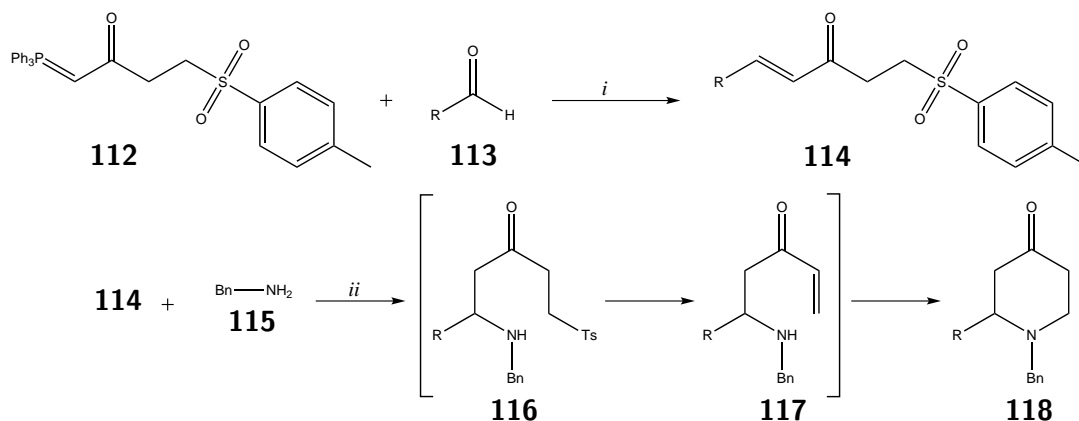
R= 3-pyridyl, 4-chloro-3-pyridyl, Me, CH₂-(CH₂)₇Me

Scheme 1.17: Reaction conditions: *i)* heating in benzene or toluene for varying reaction times (3-12 h); *ii)* THF, 25 °C, 15-20 h.

Barco demonstrated that upon reaction with benzylamine **115**, racemic piperidone **118** can be accessed in yields of 50-76%. In this step the initial Michael adduct **116** is formed, followed by basic elimination of *p*-toluenesulfinic acid in order to generate a double bond which can act as a new Michael acceptor (**117**). Reaction of **114** with chiral *S*-(-)-phenylethylamine as the nucleophilic partner under the same conditions affords a separable mixture of diastereomers **119** and **120** in a 3:1 ratio and a combined yield of 70% (Scheme 1.18). The major diastereomer **119** was subjected to two reductive steps to be converted to (-)-anabasine **121**.

114 → **119** + **120**

119 → **121** (-)-Anabasine
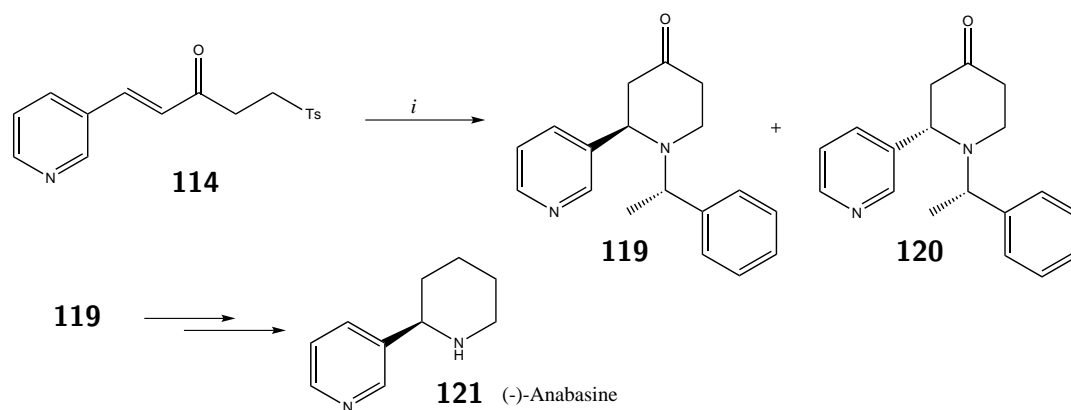
Scheme 1.18: Reaction conditions: *i)* *S*-(-)-phenylethylamine, THF, 25 °C, 15-20 h.

An interesting example for an organocatalysed intramolecular *aza*-Michael reaction is the addition of enone carbamates for the enantioselective synthesis of functionalized 2-substituted piperidines described by Liu (Scheme 1.19).[76]
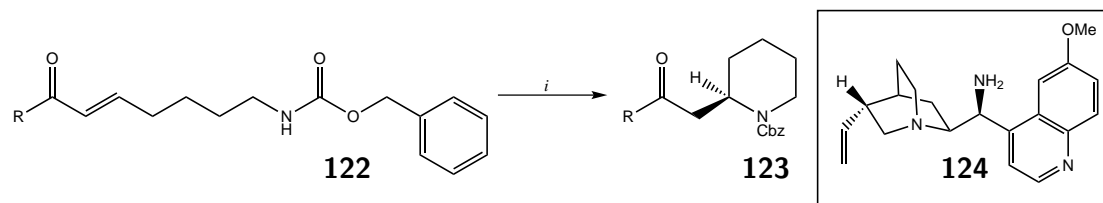
Scheme 1.19: Reaction conditions: *i)* 20 mol% **124**, TFA, THF, 25 °C, 8-120 h.

Employing chiral, *Cinchona*-derived catalyst **124** in combination with the Brønsted acid TFA, a highly efficient and stereocontrolled conversion of enone carbamates **122** to piperidines **123** has been developed (Scheme 1.19, Table 1.2). Alkyl and aryl-substitued enone substrates **122** react to corresponding 2*R*-substituted piperidine products **123** in yields of 75-95% and excellent optical purity (ee 96-98%). The reaction time for alkyl substituted enone starting materials **122a** and **b** is 8-10 h, whereas aryl substituted enones **122c** and **d** have prolonged reaction times of 24 and 120 h respectively, which can be explained by steric hindrance and decreased electrophilicity of the Michael acceptor moiety (Table 1.2). Using the highly electron-enriched *para*-methoxy-phenyl substituted enone **122e** as substrate, piperidine **123e** is only obtained in traces after a reaction time of 5 days.

Table 1.2: Organocatalysed asymmetric synthesis of piperidines **123**.

Entry	Substrate	R	Product	t (h)	Yield (%)	Ee (%)[a]
1	**122a**	Me	**123a**	8	95	98
2	**122b**	Et	**123b**	10	94	96
3	**122c**	Ph	**123c**	24	95	96
4	**122d**	4-Me-C$_6$H$_4$	**123d**	120	75	96
5	**122e**	4-MeO-C$_6$H$_4$	**123e**	120	trace	-

[a] Determined by chiral HPLC.

In the presence of TFA, catalyst **124** and enone **122** form iminium intermediate **125**, which gives rise to two possible transition states, **125a** and **125b** (Figure 1.11). Transition state **125a** is preferred due to decreased steric hindrance, therefore nucleophilic attack of the Michael donor carbamate on the iminium moiety occurs almost exclusively

on the *Re* face, resulting in high *R*-enantioselectivity in position 2 of piperidine product **123**.
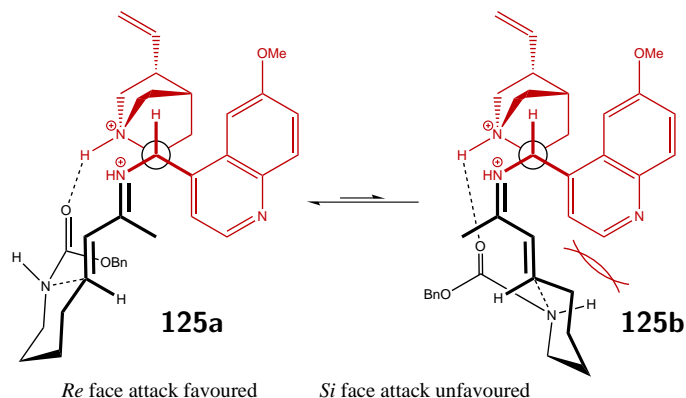
Figure 1.11: Transition states of iminium intermediate **125**.

For the construction of similar 2-substituted piperidine building blocks, Carlson also made use of a chiral amine catalyst for the promotion of an intramolecular *aza*-Michael cyclisation (Scheme 1.20).[77] In this case, the starting material is enal carbamate **126** and when Jørgensen's trifluoromethyl-aryl derivative **131**[78] is added, the intramolecular cyclisation proceeds with high enantioselectivity.
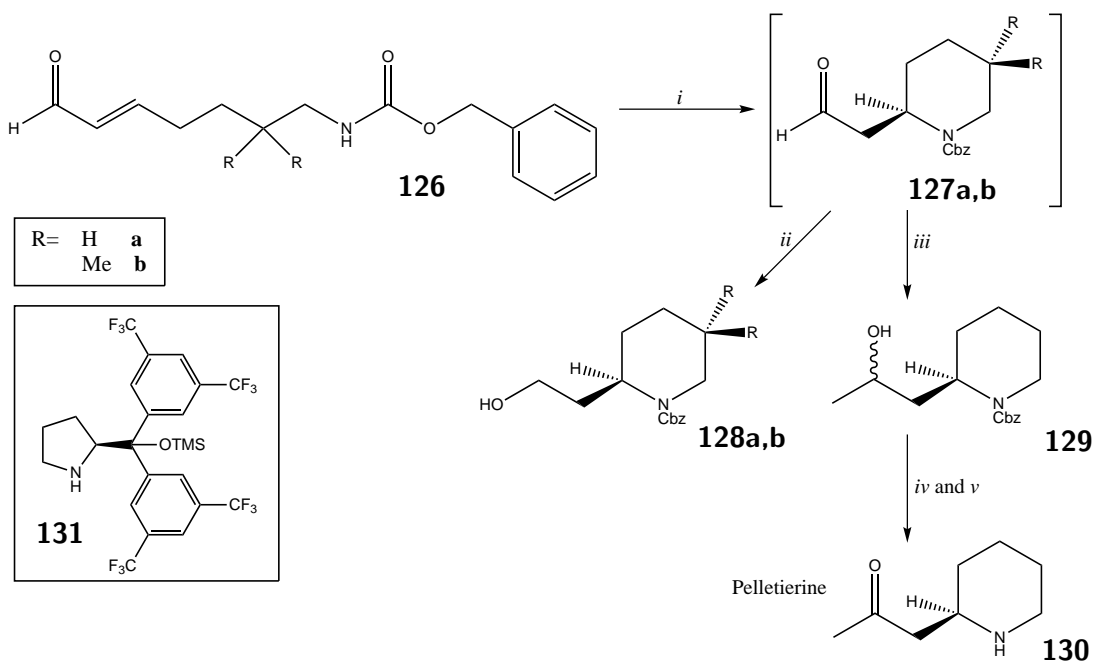
Scheme 1.20: Reaction conditions: *i)* 20 mol% **131**, MeOH/dichloroethane 1:1, -25 °C, 2-3 d; *ii)* NaBH$_4$, 0 °C, 2 h; *iii)* **127a**, MeMgBr, Et$_2$O/THF, -78 °C to rt, 4 h; *iv)* Dess-Martin periodane (DMP), NaHCO$_3$, CH$_2$Cl$_2$, 4 h; *v)* 10% Pd/C, H$_2$, EtOAc, 2 h.

Due to stability issues, aldehyde **127** is immediately converted to the corresponding stable alcohol **128**. With this protocol, 2*R*-substituted piperidine **128a** is obtained in a yield of 70% and an ee of 95%, whereas the analogue with a dimethyl-substitution **128b** is prepared in a yield of 63% and an ee of 95%. Aldehyde intermediate **127a** can be further used for the synthesis of the alkaloid pelletierine **130**, which is achieved *via* a Grignard addition to furnish diastereomeric alcohols **129**, followed by an oxidation and deprotection step.

During their effort to prepare tricyclic guadinium compound **134** as building block for the total synthesis of the natural product cylindrospermin, McAlpine and Armstrong utilised an intramolecular *aza*-Michael addition as the key reaction for the formation of the important precursor **133** (Scheme 1.21).[79] Chiral enone **132** was prepared in 11 steps from a commercially available derivative of aspartic acid and then refluxed in benzene with catalytic tosylic acid to give the highly-substituted piperidine **133** as a single diastereomer in a yield of 74%.
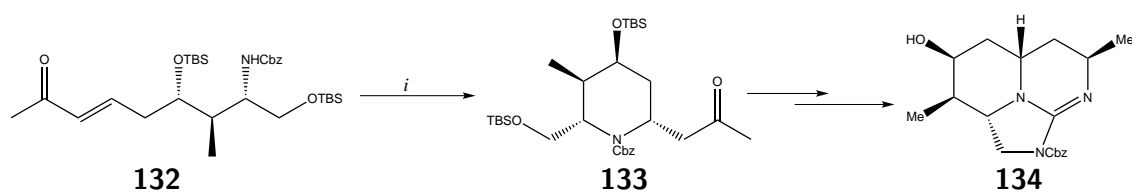
Scheme 1.21: Reaction conditions: *i)* cat. tosylic acid, benzene, reflux.

Ying developed a protocol for the stereoselective synthesis of 2,6-disubstituted piperidines **136** and **137** *via* an intramolecular *aza*-Michael addition to access both of (+)-myrtine **138** and (-)-epimyrtine **139** (Scheme 1.22).[80] Alcohol **135** is oxidised and the crude ketone subjected to an amine-catalysed Michael addition in a separate step. When the conjugate Michael acceptor moiety is activated by the addition of 20 mol% of the pyrrolidine derivative **S-140**, piperidine products **136** and **137** are obtained in high combined yield (Table 1.3).
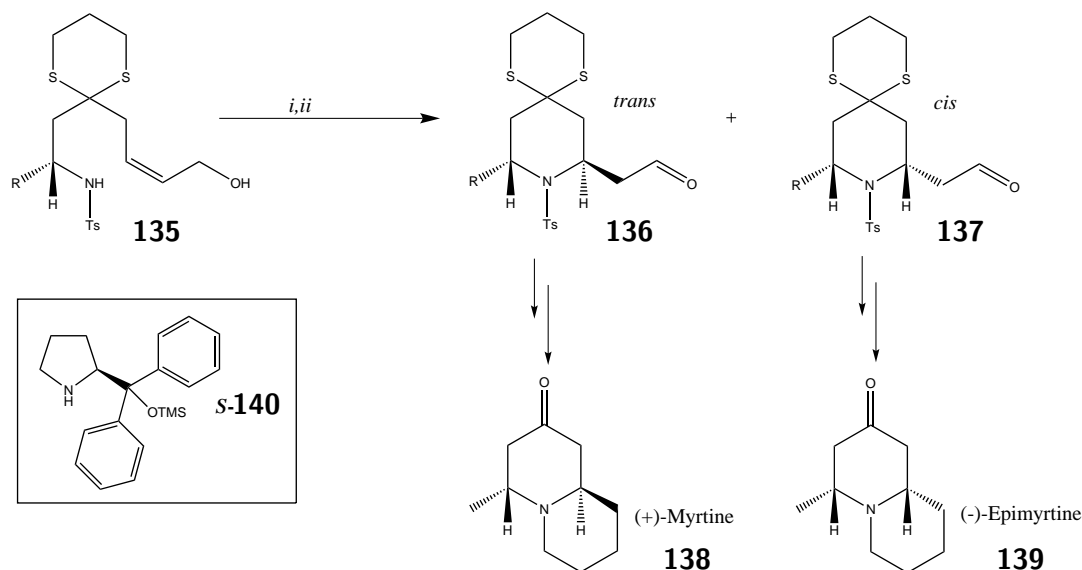
Scheme 1.22: Reaction conditions: *i)* MnO$_2$, CH$_2$Cl$_2$, 25°C, 3 h; *ii)* 20 mol% **140**, CH$_2$Cl$_2$, 0°C, 7-10 h.

Utilising **S-140**, in all cases *cis* piperidine **137** is obtained as the major product. Reacting the precursor for the natural products **135a** in the presence of **R-140**, gives *trans* piperidine **136a** as the major product, however, the observed diastereoselectivity is considerably lower (Table 1.3, entry 1).

Table 1.3: Organocatalysed formation of piperidines **136** and **137**.

Entry	R		Yield	dr (**136:137**)	Catalyst
1	Me	**a**	90%	1:15	*S*-**140**
			75%	2:1	*R*-**140**
2	CH$_2$OBn	**b**	91%	1:11	*S*-**140**
3	*i*-Pr	**c**	78%	1:10	*S*-**140**

For the synthesis of 2-substituted piperidines **142** and **143**, Fustero explored the utility of *N*-sulfinyl enone **141** as starting material for an intramolecular *aza*-Michael addition (Scheme 1.23).[60] The *N*-sulfinyl amine moiety of **141** can function as both nitrogen-centred nucleophilic Michael donor and chiral auxiliary. The influence of different bases, solvents and temperatures on stereoselectivity and yield were investigated and it was found that 2*R*-piperidine **143** can be obtained as a single diastereoisomer in a yield of 85% when potassium *tert*-butoxide is used in tetrahydrofuran at room temperature. The high degree of stereoselectivity is explained by the π-stacking interaction between the *p*-tolyl group of the sulfinyl moiety and the Michael acceptor enone (**144**).
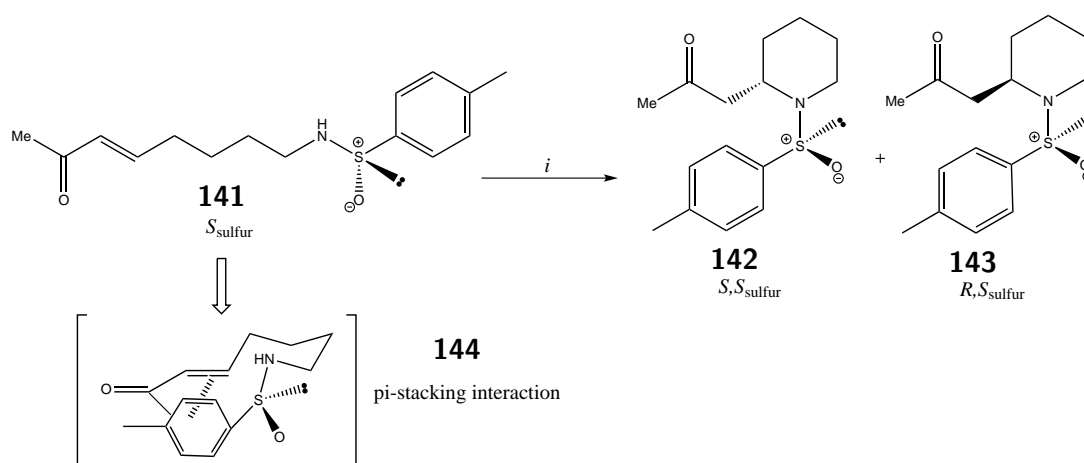
Scheme 1.23: Reaction conditions: *i)* *t*-BuOK, THF, rt, 30 min.

Intermolecular Double *Aza*-Michael Additions

In a double *aza*-Michael reaction a primary amine adds twice to a double Michael acceptor in succession. An example of such a double Michael acceptor is divinyl ketone **149** (Scheme 1.24), which is an important precursor used for the preparation of (-)-lentiginosine **153** (Scheme 1.25).[61]

The synthetic approach for the synthesis of Michael acceptor **149** starts from dienediol **145**, which is initially protected as a silyl ether, followed by a cross metathesis with acrolein to give aldehyde **146**. Upon protection of the second hydroxy group, resulting in **147**, the addition of vinyl Grignard reagent affords alcohol **148**. This divinyl alcohol is ultimately oxidised to give desired divinyl ketone **149**.
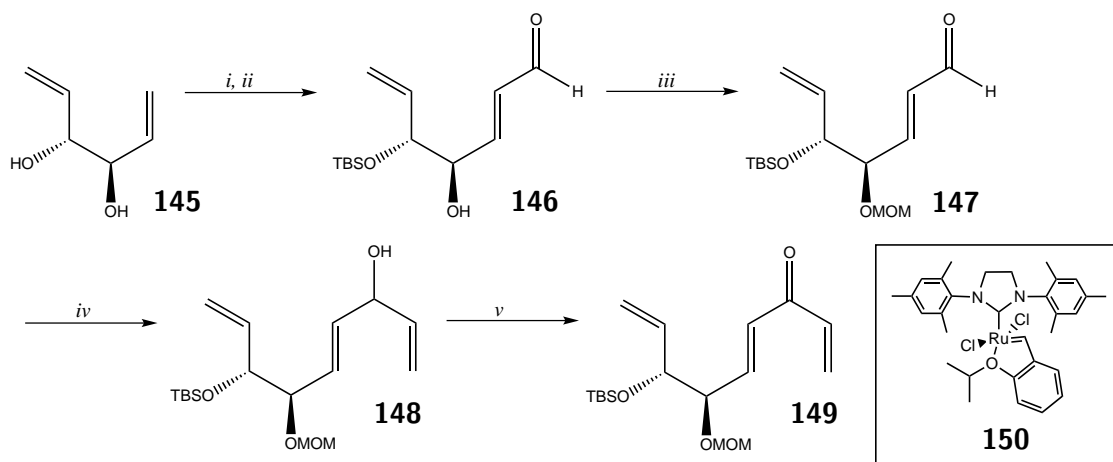
Scheme 1.24: Reaction conditions: *i)* TBSCl, imidazole, CH$_2$Cl$_2$, 0-45 °C, 16 h; *ii)* 3 mol% Hoveyda-Grubbs catalyst **150**, acrolein, CH$_2$Cl$_2$, rt, 48 h; *iii)* MOMCl, DIPEA, CH$_2$Cl$_2$, 0-45 °C, 16 h; *iv)* H$_2$C=CHMgBr, THF, 0 °C, 2 h; *v)* DDQ, dioxane, rt, 48 h.

Double Michael acceptor **149** then undergoes a cyclisation process with benzylamine to yield separable, diastereomeric 2-substituted 4-piperidone products **151** and **152** (Scheme 1.25). The piperidones were obtained in a diastereomeric ratio of 3:1, with the major product being **151**, in a combined yield of 54%. Different solvent systems, reaction times and changing the reaction temperature does not significantly affect the diastereomeric ratio. Adding 10 mol% TFA to the reaction mixture in CH$_2$Cl$_2$ increases the yield to 75%, however the diastereomeric ratio drops to 2:1. Major piperidone product **151** can be subjected to further synthetic modifications to gain access to the natural product (-)-lentiginosine **153**.
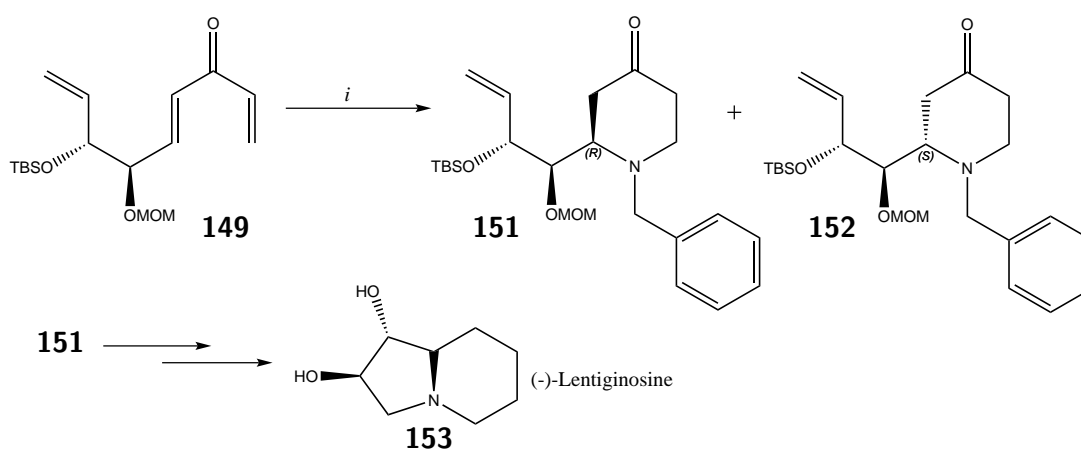
Scheme 1.25: Reaction conditions: *i)* benzylamine, MeCN, rt, 16 h.

Rosiak[81] has developed a route for the synthesis of 3-phenyl substituted 4-piperidones by employing an intermolecular double *aza*-Michael cyclisation as the key step (Scheme 1.26). The highly reactive and unstable divinyl ketone **156** is prepared in two steps. Starting from a Shapiro reaction between 2,4,6-triisopropyl-phenyl-sulfonyl-hydrazone **154** and acrolein, stable allylic alcohol **155** is obtained in a yield of 82%. Oxidation with an excess of MnO_2 under mild conditions affords crude ketone **156** (90%).
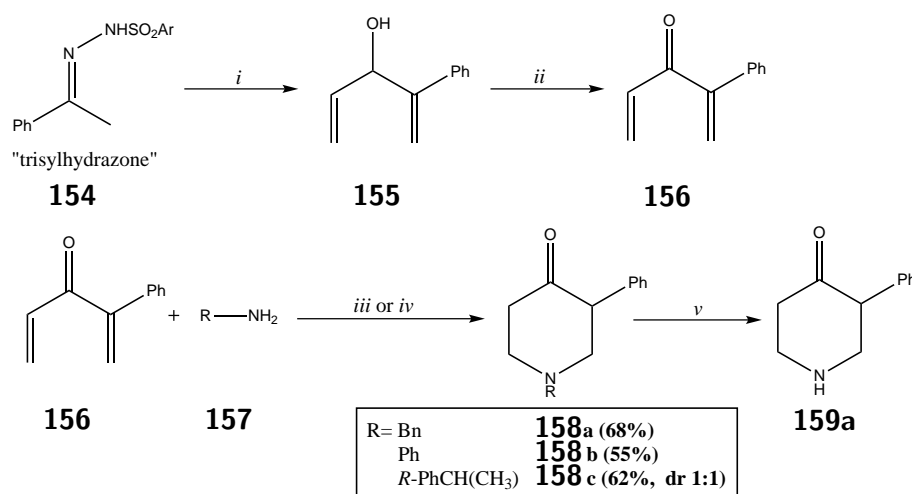
Scheme 1.26: Reaction conditions: *i)* *n*-BuLi, acrolein, THF, -78 °C-0 °C, 2 h; *ii)* MnO_2, CH_2Cl_2, 23 °C, 20 min; *iii)* **157a**, MeCN, 80°C, 1.5 h; *iv)* **157b+c**, MeCN, 80 °C, 3 h, then 23 °C, 16 h; *v)* **158a**, Pd/C, H_2, cat. HCl, *i*-PrOH, 23 °C, 16 h.

Optimised reaction conditions for the subsequent *aza*-Michael addition lead to 3-substituted piperidone **158** in good yields (55-68%). When chiral amine **157c** is used for this cyclisation process, the ratio of diastereomeric piperidones **158c** is 1:1, with no chiral induction being observed. Unprotected piperidone **159a** is further obtained by hydrogenation of **158a** over a palladium catalyst.

1.4 Acetylcholinesterase Inhibitors for the Treatment of Alzheimer's Disease

Alzheimer's Disease: A Short Overview

Alzheimer's disease (AD) is the most common form of dementia and can be described as a progressive, degenerative and incurable neurological brain disease that causes deterioration of neurons and is ultimately fatal.[82] Dementia has a global prevalence of 5-7% amongst the population aged ≥60 years and affected 35.6 million people worldwide in 2010. This number is expected to double every 20 years, resulting in an estimated 65.7 million people suffering from dementia in 2030 and 115.4 million in 2050.[83] AD accounts for 60-80% of dementia cases and as it causes high health care costs, it also has a large economic impact.[84,85]

Although current research provided an insight into the changes that occur in the brain of an AD patient, the ultimate causes of the disease remain unknown. It is the current understanding of AD that an interplay of different pathological factors causes a number of brain changes which start taking place years before the clinical onset of the disease.[86,87] The most relevant developments in the brain include the aggregation of of the β-amyloid (Aβ) protein, also called Aβ plaques, outside neurons. Plaque formation interferes with the neurons' synaptic communication processes and contributes to cellular decline.[88,89] Another pathological process is the self-assembly of abnormal hyperphosphorylated tau proteins into so-called neurofibrillary tangles. As a consequence the neurons' transport system, being composed of microtubules stabilised by normal tau protein, collapses and the transfer of nutrients along neurons is disrupted, thereby further contributing to cell death.[90,91] On a global level, the increasing neuronal loss leads to extreme shrinkage of the brain, especially in the hippocampus and cortex and to enlargement of the ventricles.[92]

People age ≥60 suffering from mild cognitive impairment (MCI) experience slight memory difficulties, but are not clinically demented or affected in their daily activities.[93] Almost half of those patients develop AD later on in their lives, therefore MCI is sometimes referred to as "prodromal AD".[82,84] At a later stage, which is termed "dementia due to AD", daily living is severely affected and symptoms include memory loss, problems with speaking and writing, disorientation, behaviour changes and

difficulties with walking and swallowing. It is usually only in this phase that AD is diagnosed clinically and pharmacological treatment is started.[84] Since neuronal loss starts long before the symptomatic onset of AD, current efforts are being made to improve clinical tools, such as identifying biomarkers[94] and developing imaging techniques[95] to facilitate earlier diagnosis and treatment.

So far, no disease-modifying treatment has been found and all currently prescribed drugs merely address the symptomatic aspects of AD. At present, many therapeutic targets, such as the Aβ-accumulation,[96–98] the tau hyperphosphorylation,[99] inflammation,[100] oxidative stress[101] and preventative measures[102] are being investigated as potential new starting points for finding a cure for AD.

Acetylcholinesterase Inhibitors and the Cholinergic Hypothesis

The cholinergic hypothesis is based on the observation that the brains of AD patients exhibit decreased cholinergic activity in combination with a progressive loss in cognitive function.[103,104]

Acetylcholine **160** (ACh) (Scheme 1.27) is produced in cholinergic neurons in the brain and is an important neuromodulator, which has been found to be involved in complex processes, such as memory, learning and circadian rhythmicity.[105–107] A major aggregation of cholinergic neurons is located in the basal forebrain, which also constitutes the main source of ACh for the cerebral cortex.[108]
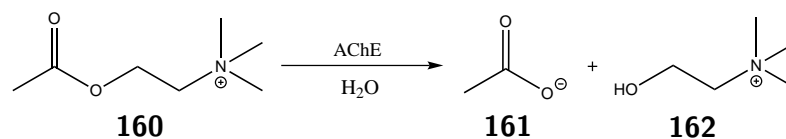
Scheme 1.27: Enzymatic hydrolysis of acetylcholine to acetate and choline.

The concentration of ACh in the synaptic cleft of cholinergic neurons is regulated by the enzyme acetylcholinesterase (AChE), which degrades the neurotransmitter into acetate **161** and choline **162** (Scheme 1.27), thereby inactivating it and inhibiting further neuronal transmission (Figure 1.12). Early discoveries found the anticholinergic tropane alkaloid scopolamine to cause memory impairment in rhesus monkeys, which could

be reversed by the administration of the acetylcholinesterase inhibitor (AChI) alkaloid physostigmine.[109]
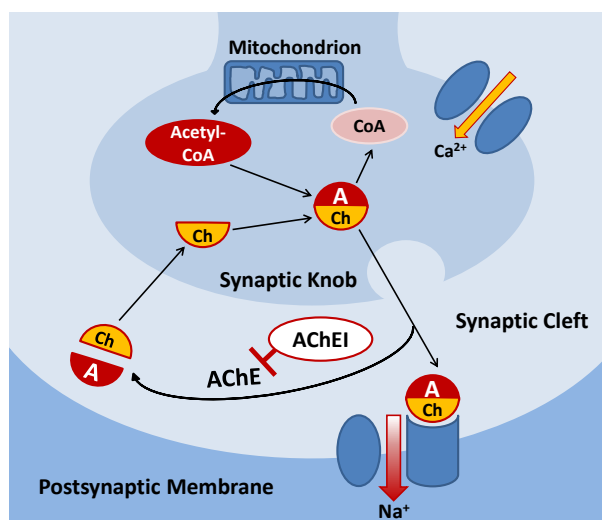
Figure 1.12: Schematic depiction of a cholinergic synapse: Acetylcholinesterase (AChE) degrades acetylcholine (ACh) into acetate (A) and choline (Ch) - a process which is inhibited by acetylcholinesterase inhibitors (AChEI).

Following these observations it was anticipated that inhibition of AChE and the increased availability of synaptic ACh could be beneficial for AD patients (Figure 1.12). The first drug to be approved by the U.S. Food and Drug Administration for the treatment of mild to moderate AD was tacrine **163** in 1993 (Figure 1.13). AChEIs such as tacrine, although leading to improvements in cognitive function, could not stop the overall progression of the disease for the long term.[110] Due to the increased risk for hepatotoxic side effects and the necessity for close patient monitoring[111] tacrine is no longer prescribed.

The only four drugs that are currently approved for the treatment of various stages of AD are the AChEIs rivastigmine **164**, galantamine **165** and donepezil **12** and the *N*-methyl-*D*-aspartate (NMDA) glutamate receptor antagonist memantine **166** (Figure 1.14). Rivastigmine **164** is a derivative of the alkaloid physostigmine which inhibits both AChE and butyrylcholinesterase and is used widely in all stages of AD.[112] Furthermore it is used in the treatment of Parkinson's disease dementia.[113,114] Galantamine **165** is an alkaloid isolated from *Galanthus nivalis* and before being identified as a potential AChE inhibitor, it has been used in traditional medicine in Eastern Europe for the treatment of neurological problems.[115,116] In addition to the AChE enzyme inhibiting properties, galantamine also possesses an allosteric sensitising effect on nicotinic receptors for the

binding of ACh in the synaptic cleft, thereby possibly further increasing the therapeutic utility of this drug.[117] Memantine **166** is the only approved drug for the treatment of AD which does not act as an AChEI. It is classified as a centrally acting low to medium affinity NMDA receptor receptor antagonist. The level of glutamate, another important neurotransmitter in the brain, is pathologically increased in AD and leads to an overstimulation of NMDA receptors, which subsequently causes excitotoxicity and cell death. Memantine was found to block the NMDA receptor and thereby prevent hyperpolarisation of the neurons,[118] a mode of action which renders this drug useful in the treatment of moderate to severe AD.[119]
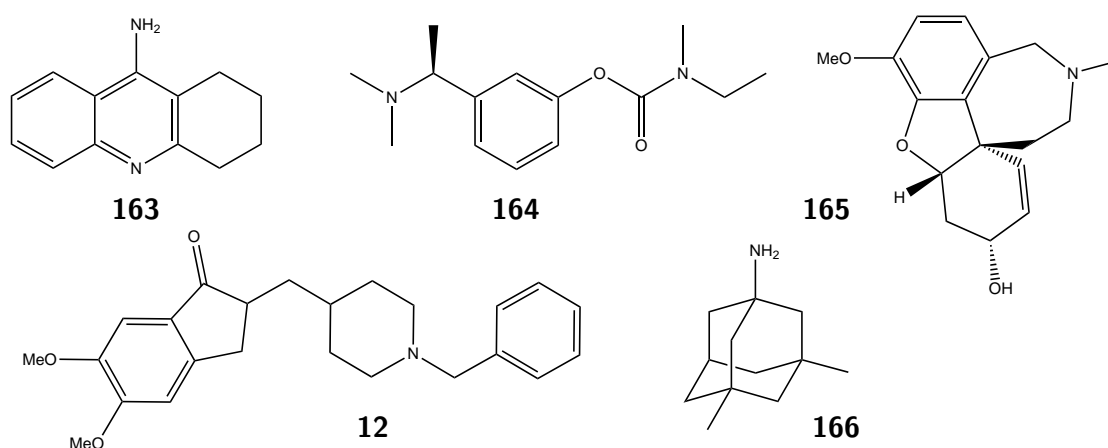
Figure 1.13: Drugs for the treatment of Alzheimer's disease.

Donepezil

Donepezil was developed by the Japanese company Eisai[120] and since its approval in the U.S. in 1996 and shortly after worldwide, has been marketed as Aricept® for the treatment of mild to moderate AD.

Discovery of Donepezil

Esai's initial research into the development of a novel class of acetylcholinesterase inhibitors started in 1983,[121,122] when a blind screening process afforded *N*-benzylpiperazine **167** as a potential candidate (Figure 1.14). The *in vitro* AChE inhibitory activity of **167** was found to be 12.6 μM at IC$_{50}$ and, albeit its moderate activity, it was used as a template for the synthesis of approximately 700 analogues. An important step to improve

the biological properties of **167** was the replacement of the piperazine moiety with a piperidine ring. Compound **168** possessed a significantly increased AChE inhibition activity of 340 nM at IC_{50}. The replacement of the ether group with an amide moiety and the removal of the nitro substituent gave piperidine compound **169**, which had a slightly decreased inhibitory activity of 560 nM at IC_{50}. It was further shown that the biological activity was maintained when the amide moiety was replaced with a ketone function (**170**). An intermediate bearing an indanone substructure, such as **171**, showed a further increase in potency with an IC_{50} of 230 nM. Replacement of the ethylene linker unit by a methylene group gave compound **172**, possessing an IC_{50} value of 150 nM.[120,121,123,124]
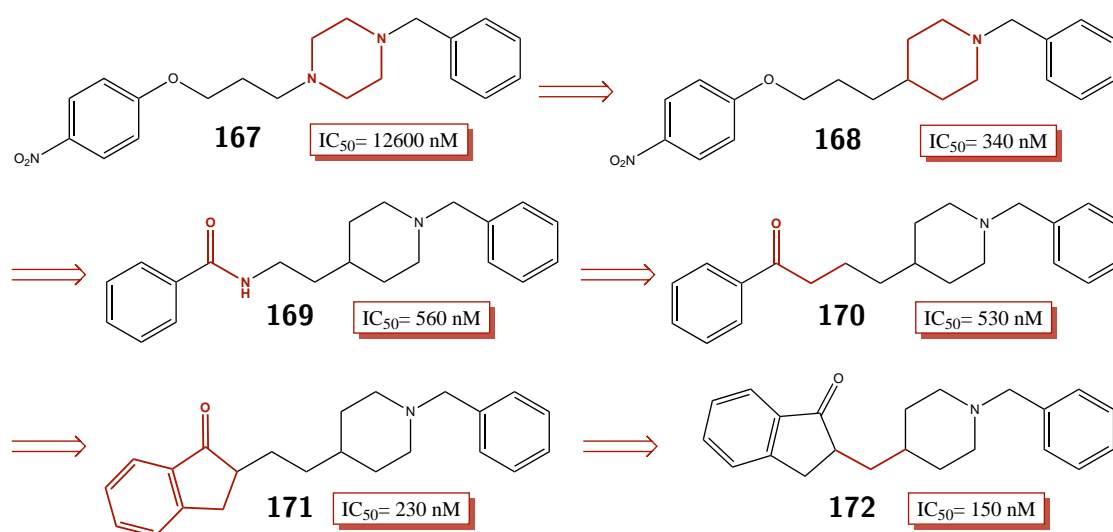
Figure 1.14: Lead compounds towards the discovery of donepezil

Structure Activity Relationships

Analogue **172** was chosen as a lead compound for further synthetic modification in the indanone series.[120] Structure-activity relationship studies were undertaken and the *in vitro* AChE inhibition of the synthesised derivatives evaluated according to a protocol by Ellman.[125] Lead structure **172** can be divided into four parts, the indanone moiety **A**, a linker unit **B**, the piperidine moiety **C** and the benzyl moiety **D** (Figure 1.15).

Modifications on component **A** were shown to dramatically influence the inhibition potencies of the analogues (Table 1.4). Expansion of the indanone ring (**173**) or the removal of the carbonyl function as in indene derivative **174** led to deactivation, while
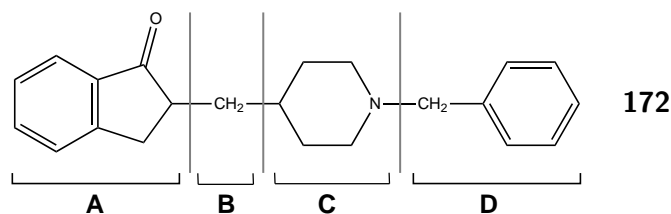
Figure 1.15: Four subunits of the lead compound.

the introduction of a methoxy group on the indanone (**175**) greatly improved the activity. Donepezil **12** bears two methoxy groups on the aromatic indanone part and was found to be a potent inhibitor of AChE with an IC_{50} of 5.7 nM. When the chain length of linker unit **B** was modified (Figure 1.15), the activity was also affected and it was found that complete removal of the bridging unit was particularly disadvantageous in terms of potency, leading to an analogue with an IC_{50} of 3300 nM.[120]

Table 1.4: Inhibitory activity of compounds with modifications on subunit **A**.

Entry	Compound	Part **A**	IC_{50} [nM][a]
1	**172**		150
2	**173**		2100
3	**174**		4400
4	**175**		81
5	**12**		5.7

[a] Inhibition of AChE *in vitro*.

The position of the nitrogen on the ring proved to be be extremely important, as the replacement of piperidine with piperazine, as in **176**, and to an even greater extent, an analogue with the piperidine ring reversed, as in **177**, led to decreased inhibitory activity (Table 1.5). Many derivatives bearing modifications on part **D** (Figure 1.15) have been synthesised and it was found that complete removal of the benzyl group as well as the introduction of a benzoyl or 2-naphthyl group drastically decreased the activity. It was

concluded that both the basicity of the nitrogen as well as its distance to the indanone carbonyl function are crucial for the inhibitory effects of such analogues.[120,126]

Table 1.5: Inhibitory activity of compounds with modifications on subunit **C**.
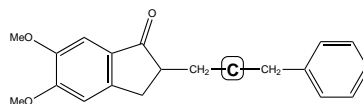
Entry	Compound	Part **C**	IC$_{50}$ [nM]^a
1	**176**		94
2	**177**		480
3	**12**		5.7

^{a} Inhibition of AChE *in vitro*.

Due to the presence of an asymmetric carbon on the indanone part of the molecule, all of the evaluated analogues were racemic mixtures. Under physiological conditions, the two enantiomers of indanone-compounds like donepezil **12** interconvert quickly because of keto-enol tautomerism,[127] which is the main reason why donepezil was developed and commercialised as a racemic mixture.[126]

Pharmacology and Clinical Studies

Although donepezil has been classified as a mixed competitive-noncompetitive inhibitor of AChE, the noncompetitive mode of action predominates.[128,129] In initial *in vitro* experiments,[125] the inhibitory activity of donepezil towards AChE and butyryl-cholinesterase (BuChE), a non-specific cholinesterase occurring especially in the liver, was measured in comparison with tacrine and physostigmine.[120] The concentration of donepezil needed for inhibiting 50% of AChE (from rat brain homogenate) was found to be 5.7 nM, whereas the IC$_{50}$ for the inhibition of BuChE (from rat plasma) was much higher (7138 nM), therefore demonstrating a strong selectivity towards AChE as opposed to BuChE. Both physostigmine and tacrine express a much higher selectivity for BuChE,[130] which also associates these compounds with a higher occurrence of peripheral side effects. *In vivo* experiments using rats further demonstrated that donepezil can enhance the extracellular concentration of ACh in the cerebral cortex of rats at lower doses than other AChE inhibitors, indicating that it possesses a selectivity towards the

central cholinergic system.[131] Compared to other common AChE inhibitors, the half-life of donepezil is significantly longer (70-80 h)[132] and patient compliance is improved by only requiring one dose per day.[133]

To date many clinical trials for the use of donepezil in AD have been conducted and have shown that donepezil is beneficial for AD patients in terms of slowing the progressive cognitive impairment. A study which focussed on the effects of donepezil in patients in the early stage of AD concluded that an improvement of daily cognitive functions was achieved over the course of 24 weeks.[134] Similar results were found in a study with patients suffering from mild to moderate AD, as donepezil was well-tolerated and improved global function and cognition.[135] The long term efficacy and safety of donepezil in patients with mild to moderately severe AD was assessed in a multi-centre open-label study and it was found that donepezil was effective and well tolerated as a symptomatic treatment over a period of up to 4.9 years.[136]

Acetylcholinesterase in Complex with Donepezil

The acetylcholinesterase enzyme is vital for correct signal transmission at neuronal and neuromuscular synapses, degrading the neurotransmitter acetylcholine and thereby controlling its concentration in the synaptic cleft.[137] The enzyme is classified as a serine hydrolase because its catalytic site, the "catalytic triad", consists of a serine, histidine and glutamate residue and hydrolyses acetylcholine to acetate and choline.[138] The first crystal structure of the enzyme was solved for the electric ray (*Torpedo californica*). This made it possible to locate the catalytic triad at the bottom of a narrow gorge which protrudes deep into the enzyme.[139]

The first crystal structure of a complex of donepezil with the *Torpedo californica* AChE (*Tc*AChE) was published by Kryger and allowed detailed insight into the orientation and positioning of donepezil within the enzyme and its interactions with the amino acid residues of the active-site.[140] Even though donepezil was designed on the basis of quantitative structure-activity relationship (QSAR) models,[141,142] many of these previous findings could be confirmed by analysis of the donepezil-*Tc*AChE complex. Only recently the structure of recombinant human AChE (*rh*AChE) in complex with donepezil has been described and provides further understanding of donepezil's binding behaviour.[143]

Figure 1.16 depicts donepezil in complex with rhAChE and is described as being situated along the narrow active-site gorge, spanning from the anionic site at the bottom of the gorge to the upper peripheral anionic site.[140] In this complex donepezil does not obstruct or interfere directly with the catalytic triad, which is supported by the observation of a binding-simulation where donepezil apparently inhibits both the acylated and the free enzyme.[144] Tyrosine Y337 has been described as a "swinging gate" which moves upon donepezil binding, allowing entrance into the active-site gorge (Figure 1.16).[140,143] In rhAChE, π-π-stacking interactions are observed between the benzyl ring and tryptophan W86 as well as between the indanone moiety and tryptophan W286. A water molecule is held by forming hydrogen bonds to the nitrogen on the piperidine ring of donepezil and to residues Y341 and Y337.[143]
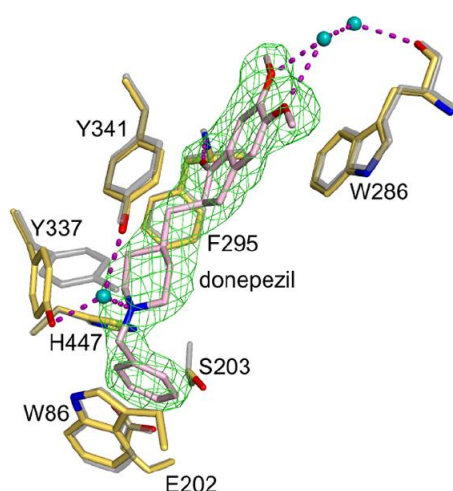
Figure 1.16: Donepezil bound in the active site gorge of rhAChE.[143] The carbons of donepezil are coloured pink an the carbons of the residues are coloured yellow. Oxygen and nitrogen atoms are coloured red and blue. Water molecules are light blue spheres and hydrogen bonds are represented by pink dashes.

Both Kryger[140] and Cheung[143] conclude that additional substituents on the piperidine ring of donepezil could be accommodated in the binding pocket and thereby lead to an improvement of the drug's pharmacological profile. Interestingly, such substituted analogues of donepezil have not been described in the literature, despite the realisation of extensive SAR studies and the early finding that the insertion of a piperidine into the structure led to analogues possessing a much higher biological activity.[120,123]

1.5 Aim of the Project

The piperidine ring is an important moiety in pharmaceutical research and is a ubiquitous structural motif encountered in countless natural products.[1,5] At present, the 1,4-disubstitution pattern on the piperidine ring prevails amongst pharmaceuticals due to shorter synthetic routes from commercial precursors and the absence of stereochemical complications. However, it has been shown that additional substituents on the piperidine and can result in compounds with increased biological activity.[31,32] The facile preparation of chiral, versatile piperidine building blocks for the synthesis of biologically active compounds is therefore of current interest.

A double *aza*-Michael addition of a primary amine to a divinyl ketone is an atom-efficient approach to the synthesis of substituted 4-piperidones. The initial aim of this project will be to evaluate the utility of unsubstituted ketone **178** as the electrophile in an *aza*-Michael cyclisation reaction to obtain a range of *N*-substituted 4-piperidones **179** (Figure 1.17).
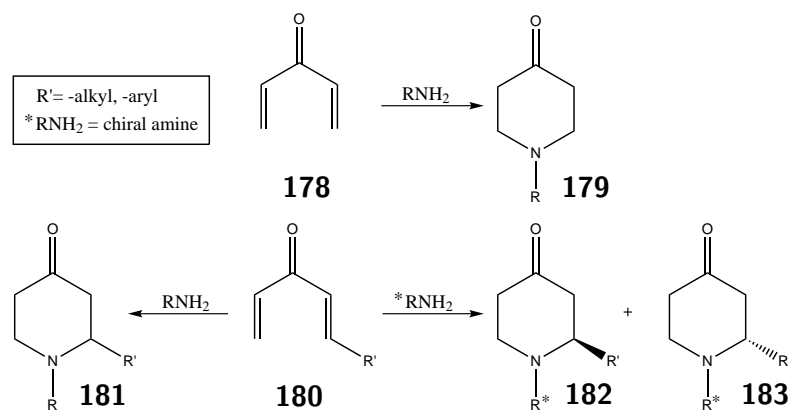
Figure 1.17: Synthesis of *N*-substituted piperidone **179**, racemic 2-substituted piperidone **181** or diastereomeric piperidones **182** and **183**.

Furthermore it is intended to achieve the synthesis of substituted divinyl ketones **180** and to cyclise them using the previously developed method to access racemic 2-substituted 4-piperidones **181** (Figure 1.17). By employing a suitable chiral amine for the *aza*-Michael cyclisation with substituted ketones **180**, it is envisioned that it will be possible to prepare separable, diastereomeric 2-substituted 4-piperidones **182** and **183** (Figure 1.17).

The utility of the methodology will then be demonstrated by using the 2-substituted 4-piperidones **182** and **183** as building blocks for the synthesis of piperidine ring 2-substituted analogues **185** of the acetylcholinesterase inhibiting drug donepezil **12** (Figure 1.18). The stereoselective synthesis of piperidine-substituted donepezil analogues has not been reported, despite the fact that early structure-activity relationship studies [126] showed the importance of the piperidine ring moiety for the biological activity of this drug.
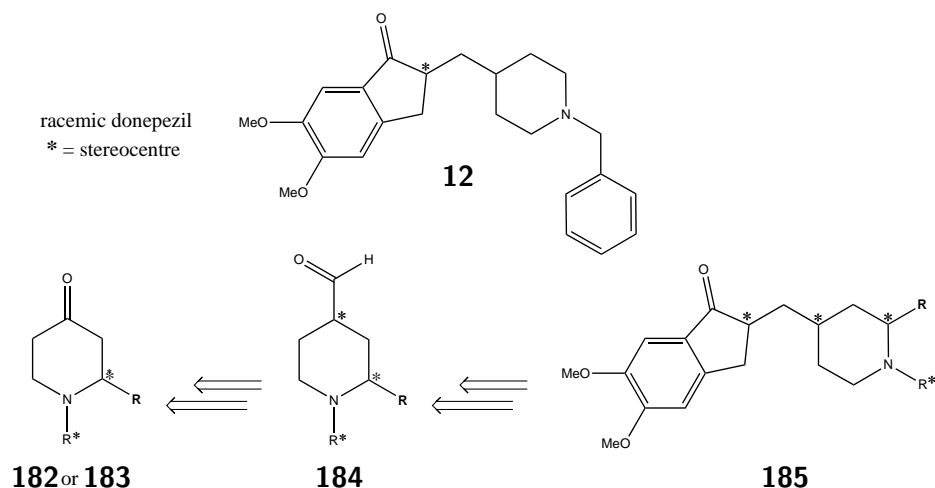
Figure 1.18: Donepezil **379** and stereoselectively piperidine 2-substituted analogue **185**.

Donepezil analogues **185** are envisioned to be accessible *via* the transformation of diastereomeric piperidones **182** and **183** into aldehydes **184**, which will serve as key precursors for the synthesis of the target compounds (Figure 1.18). The evaluation of the biological activity of these analogues will provide information on how donepezil's inhibitory potency is affected by stereoselective substitution on the piperidine ring.

Chapter 2

Results and Discussion

2.1 Studies Into the Synthesis of Novel Piperidines

2.1.1 Synthesis of *N*-Substituted 4-Piperidones

For the synthesis of simple *N*-substituted 4-piperidones **187**, divinyl ketone **178** was chosen as the key building-block (Figure 2.1). As this dienone is unsubstituted and therefore sterically accessible towards nucleophilc attack, it was envisioned that it would be an ideal double Michael acceptor for an *aza*-Michael addition/cyclisation reaction. Facile access to this reactive and unstable[145] ketone was believed possible *via* the oxidation of commercially available divinylcarbinol **186**.
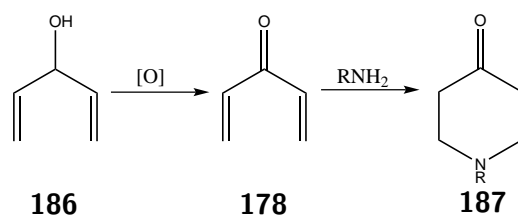
Figure 2.1: Synthesis of *N*-substituted 4-piperidones **187** in two steps.

Having achieved the preparation of ketone **178**, the next step would be the investigation of a double *aza*-Michael addition involving various aromatic and aliphatic amines.

Preparation of the Divinyl Ketone Building Block

Due to the unstable nature of divinyl ketone **178** it was necessary to achieve an efficient and particularly mild oxidation of divinyl alcohol **186** (Figure 2.2). For this purpose, 2-iodoxybenzoic acid (IBX) was the oxidant of initial choice, as it is known to smoothly and efficiently convert primary and secondary alcohols to the corresponding aldehyde or ketone.[146]
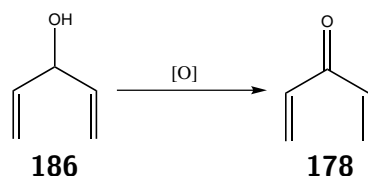
Figure 2.2: Oxidation of divinylcarbinol **186**.

IBX **189** was prepared from 2-iodobenzoic acid **188** following the procedure of Santagostino[147] in a yield of 85% (Scheme 2.1). The advantage of this method over other reported preparations[148] is the use of less toxic and environmentally benign reagents.
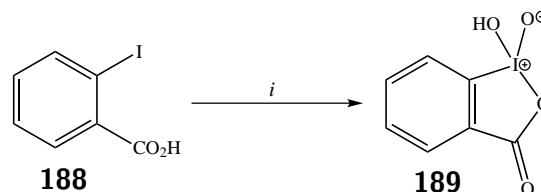
Scheme 2.1: Reaction conditions: *i)* Oxone, H_2O, 70°C, 3 h.

Initial attempts to oxidise divinylcarbinol **186** with IBX were carried out using the procedure of Rao[149] (Scheme 2.2). This method involves the oxidation of alcohols at room temperature using IBX in a water/acetone mixture containing β-cyclodextrin as a supramolecular catalyst.
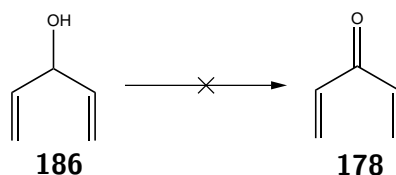
Scheme 2.2: Reaction conditions: *i)* IBX, β-cyclodextrin, H_2O/acetone 7.5:1.0, rt, 48 h, 50°C, 5 h; *ii)* IBX, DMSO, rt, 18 h.

When the reaction was performed according to this protocol, thin layer chromatography (TLC) analysis revealed that no product formed after 48 hours of stirring at room

temperature. After heating to 50 °C for 5 hours, ^{1}H-NMR analysis of the crude residue revealed that while no product was formed, considerable starting material remained, accompanied by side-products that could not be identified. When the oxidation with IBX was carried out under nitrogen using dimethyl sulfoxide (DMSO) as a solvent, no formation of ketone **178** was observed.

Due to the lack of conversion of alcohol **186** to ketone **178** under the IBX-mediated conditions, another oxidant, MnO_2, was investigated for this conversion. MnO_2 is a mild and widely used oxidant especially for the selective transformation of benzylic and allylic alcohols to the corresponding ketone or aldehyde.[150–152] The oxidising power of MnO_2 is variable and depends on the origin of the reagent as well as on its structure, and standardised protocols for the preparation of active MnO_2 have been reported.[153,154]

When Reed[145] described the MnO_2 oxidation of divinylcarbinol **186** to divinyl ketone **178** in 1962, he identified that the type of MnO_2 oxidant employed for this conversion was crucial for both the yield and the rate of the reaction (Figure 2.3). He compared the commercially available reagent to MnO_2 prepared according to the protocols of Attenburrow[153] and Harfenist[154] and observed varying yields for ketone **178**, not only depending on the type of oxidant but also on the ratio of divinylcarbinol to MnO_2.[145]
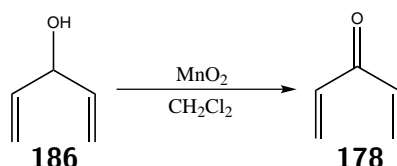
Figure 2.3: Oxidation of divinylcarbinol **186** with MnO_2.

Reed observed that when reacting divinylcarbinol **186** in the presence of Attenburrow's MnO_2 at room temperature for 24 h with the ratio of alcohol to oxidant being 1:15, upon distillation of crude ketone **178**, the maximum yield obtained was 50%. However, he showed that when the divinyl ketone was isolated as its 2,4-dinitrophenylhydrazone, a yield of 96% was obtained, indicating that a significant amount of product was lost upon distillation.

For the purpose of oxidising divinylcarbinol **186**, we decided to initially use commercially available, technical grade activated MnO_2 as received from the vendor (*Alfa Aesar*). The alcohol was stirred at room temperature with a suspension of MnO_2 (15 equivalents)

in CH_2Cl_2 (Figure 2.3, Table 2.1, entry1). After the reaction mixture had been filtered through a pad of *Celite*®, washed with acetone and dichloromethane and carefully reduced *in vacuo*, ^{1}H-NMR analysis of the crude product showed that only 26% had been converted to divinyl ketone **178**, while the rest of the starting material remained unreacted.

Table 2.1: Optimisation study on the oxidation of divinylcarbinol **186** employing MnO_2.

Entry	MnO_2 (equiv.)	Type of MnO_2[b]	Conditions	Conversion to **178**[a](%)
1	15	untreated	22 h, rt	26
2	20	treated:untreated 1:1	22 h, rt	52
3	30	treated	20 h, 40 °C	68
4	30	treated, 4 Å MS	20 h, 40 °C	100

[a] Conversion was determined by ^{1}H-NMR analysis of the crude spectra.
[b] Untreated MnO_2: Reagent used as received from vendor (*Alfa Aesar*); Treated MnO_2: Washed with nitric acid (10%) and water, dried at 105 °C for two days.

As unreacted starting material remained when untreated, purchased MnO_2 was employed for the oxidation, we concluded that further activation was required to achieve full conversion to the desired ketone. Harfenist[154] reported an increased oxidising activity of MnO_2 when it was washed with nitric acid followed by drying. Following this protocol, MnO_2 was treated with diluted nitric acid (10%) and extensively washed with water until the filtrate was neutral. The powder was then dried at 105 °C for two days and the brittle, caked black solid was finely ground with mortar and pestle.

The oxidation of divinylcarbinol **186** was repeated with a mixture of untreated and acid-washed MnO_2 (1:1) which led to an improvement of the conversion rate to 52% (Table 2.1, entry 2). The yield of the ketone was further increased to 68% by using only acid-washed MnO_2 at an elevated reaction temperature (Table 2.1, entry 3). Full conversion by NMR to the desired divinyl ketone **178** was finally achieved when 4 Å molecular sieves (MS) were added to the reaction mixture (Table 2.1, entry 4). We believe that the molecular sieves capture water, which is generated during the oxidative process with MnO_2. The removal of water prevents the inactivation of the surface of MnO_2 and maintains the rate of oxidation,[155] thereby leading to the observed improvements in the conversion to ketone **178**.
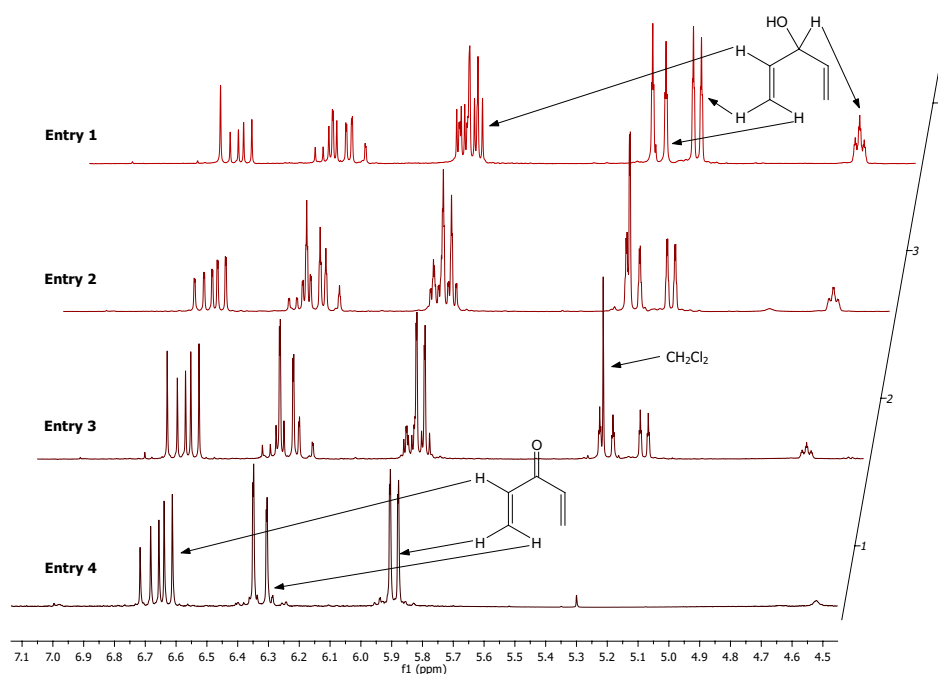
Figure 2.4: Crude ^{1}H-NMR spectra (7.1-4.5 ppm) of the experiments in Table 2.1.

Figure 2.4 depicts the crude ^{1}H-NMR spectra for the oxidation of divinylcarbinol **186**, which were obtained by carrying out the reactions according to the protocols described in Table 2.1. In entry 1-3, the conversion of alcohol **186** to ketone **178** was incomplete, wherefore starting material was visible in the otherwise clean crude spectra (Figure 2.4). In the spectrum that was obtained under the conditions of entry 4 in Table 2.1, ketone **178** was clean and no undesired side-products or remaining starting material were observed. It was hence decided to use this crude ketone without further purification for the next synthetic step. In order to prevent polymerisation of the ketone during isolation, the filtrate was carefully concentrated at temperatures below 40 °C.

Having accessed the divinyl ketone building block, the next step towards the synthesis of piperidones, a double *aza*-Michael cyclisation, could be targeted.

Synthesis of 4-Piperidones *via* Double *Aza*-Michael Cyclisation

A double *aza*-Michael reaction consists of two conjugate additions which take place in the same molecule. For our substrate, initially an intermolecular conjugate addition takes place between the nucleophilic primary amine **190** and divinyl ketone **178** (Figure 2.5). This results in the formation of intermediate enone **193**, which is also a Michael acceptor. Subsequent intramolecular conjugate addition occurs to yield the target six-membered, *N*-substituted 4-piperidone **187**.
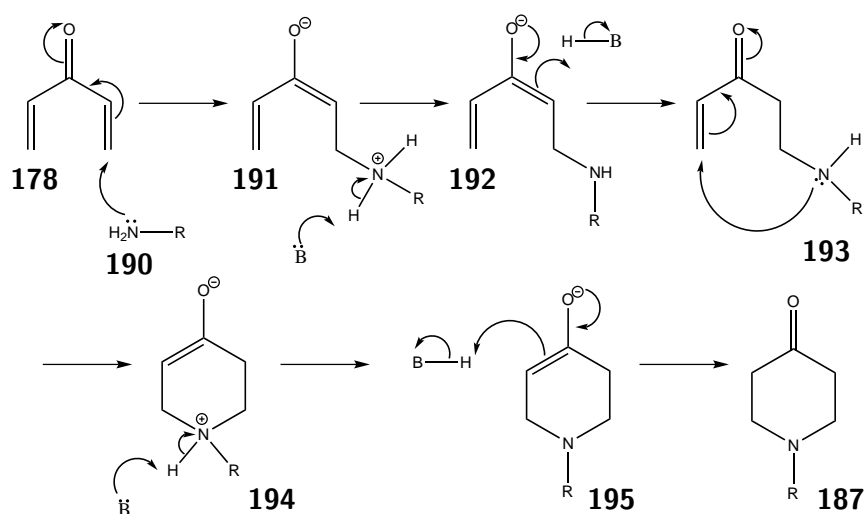
Figure 2.5: Mechanism of the double *aza*-Michael cyclisation giving *N*-substituted 4-piperidones.

Benzylamine was chosen as a test-substrate for the role of the nucleophilic primary amine in this double Michael addition. The aromaticity of benzylamine would make the product detectable by TLC and the prominent signal of the methylene group in the ^{1}H-NMR spectrum would enable the progress of the reaction to be conveniently monitored.

Cyclisation in Two Steps

From related examples in the literature[61,81] it has been shown that acetonitrile can act as a suitable solvent for this type of *aza*-Michael cyclisations. Liu[61] describes a double *aza*-Michael reaction for the synthesis of piperidones **197** and **198** in acetonitrile in a combined yield of 54% (Scheme 2.3), whereas Rosiak[81] achieved the cyclisation

of an α-substituted divinyl ketone with benzylamine in acetonitrile in a yield of 68%
(Scheme 2.4). The first attempt to synthesise a *N*-substituted 4-piperidone from
benzylamine and divinyl ketone would therefore be carried out using acetonitrile as
the solvent.
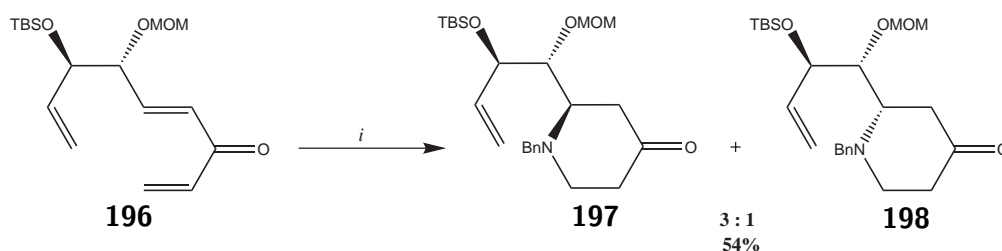
Scheme 2.3: Reaction conditions: *i)* BnNH$_2$, CH$_3$CN, 25°C, 16 h.
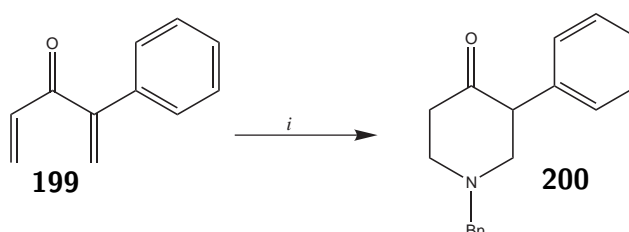
Scheme 2.4: Reaction conditions: *i)* BnNH$_2$, CH$_3$CN, 80°C, 1.5 h.

Initially crude divinyl ketone **178** and benzylamine were refluxed in acetonitrile for 4
hours (Scheme 2.5). After workup, target piperidone **201** was obtained in poor yield
(11% over two steps). It was observed that due to its instability, dienone **178** had to be
used for the following cyclisation reaction directly after its isolation.
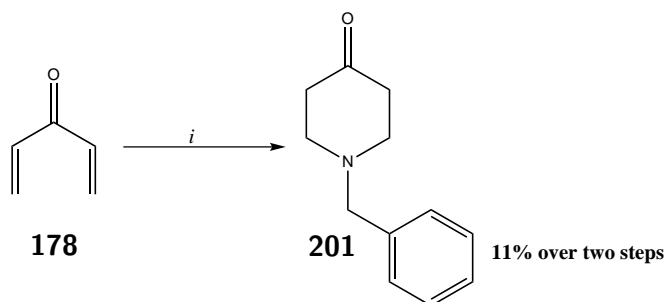
Scheme 2.5: Reaction conditions: *i)* Crude **178**, BnNH$_2$, CH$_3$CN, reflux, 4 h.

A subsequent investigation with a shorter reaction time of 1.5 hours gave a comparable
yield over two steps (12%). When the crude ketone was reacted with benzylamine
in acetonitrile at room temperature for 24 hours, only traces of product were found

in the crude ^{1}H-NMR spectrum. To minimise loss and degradation of ketone **178**, the solvent from the previous step was not completely evaporated. The ketone in residual dichloromethane was therefore added directly to a solution of acetonitrile and benzylamine using the same conditions as previously (Scheme 2.5). Nevertheless, these measurements did not improve the overall yield significantly (14% over two steps).

Cyclisation in a One-pot Approach

We envisioned that, due to the instability of divinyl ketone, an *in-situ* oxidation of carbinol **186** followed by subsequent cyclisation in a one-pot approach could lead to a higher yield of piperidone **201**. A reaction of this type (Figure 2.6) would achieve both the oxidation and the Michael cyclisation without the need to handle the intermediate ketone.
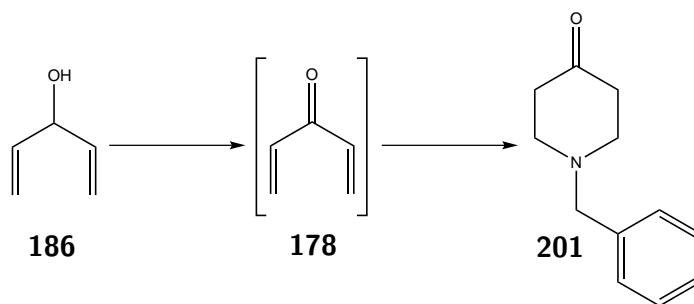
Figure 2.6: One-pot preparation of *N*-benzyl-4-piperidone **201** in CH_2Cl_2 using benzylamine as the primary amine.

In a stepwise one-pot process, divinylcarbinol **186** was first fully oxidised using the previously optimised conditions, before benzylamine was added to the reaction mixture (Table 2.2, entry 1). Stirring was continued for 24 hours and upon work-up and isolation piperidone **201** was afforded in 34% yield over two steps. Although the yield for this reaction was improved, the overall result was still unsatisfactory.

In further optimisation experiments, a simultaneous one-pot approach was investigated. For these experiments benzylamine was added to the reaction mixture at the same time as the MnO_2. It was found that while only 1.4 equivalents of benzylamine were used, the addition of the reagents in a simultaneous manner led to an improved isolated yield of the desired piperidone product (entry 2). Further adjustments of the reaction conditions

Table 2.2: Optimisation reactions for the synthesis of *N*-benzyl-4-piperidone **201**.

Entry	BnNH$_2$	BnNH$_2$ addition	MnO$_2$	Conditions	Yield^a of **201** (%)
1	2.1 equiv	stepwise	30 equiv	20 h, 24 h^b	34
2	1.4 equiv	simultaneous	30 equiv	18 h, 50 °C	45
3	1.5 equiv	simultaneous	25 equiv	18 h, 50 °C	55
4	1.5 equiv	simultaneous	25 equiv	18 h, 50 °C, 20 mol% TFA	51

^{a} Isolated yields.
^{b} Oxidation of **186** to **178** at 45 °C for 20 h, followed by the addition of benzylamine and subsequent cyclisation at 50 °C for 24 h

gave an improved isolated yield of 55% (entry 3). When this experiment was repeated using a shorter reaction time of 6 hours, the yield was found to be significantly lowered (30% as determined by the analysis of the crude ^{1}H-NMR spectrum).

Liu[61] reported reduced side-product formation and an increased yield for the product of a similar double *aza*-Michael addition in the presence of 10 mol% trifluoroacetic acid. However, under our one-pot oxidation-cyclisation conditions, neither the addition of 10 mol%, nor the addition of 20 mol% trifluoroacetic acid further increased the yield of piperidone **201** (Figure 2.6, entry 4).
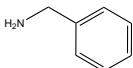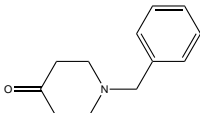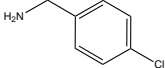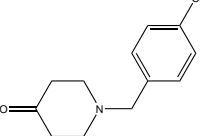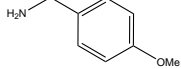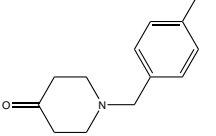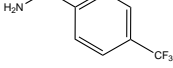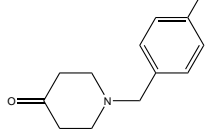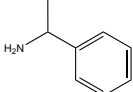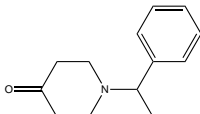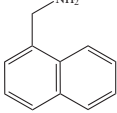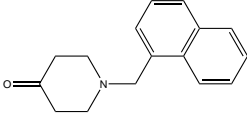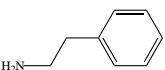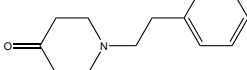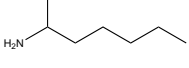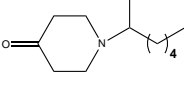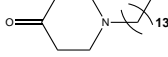
Having improved the yield over two steps of piperidone **201** from 12% in acetonitrile to 55% in dichloromethane, we decided to apply this protocol to the synthesis of further piperidone derivatives to explore the scope of the methodology.

Synthesis of Piperidone Analogues

Table 2.3 summarises the piperidone derivatives synthesised according to the previously established protocol. The *in-situ* oxidation-cyclisation reaction of dienone **178** with benzylamine derivatives (entry 1-4) led to the formation of piperidones **201**, **204**, **206** and **208** and yields for these substrates ranged from 45 to 55% over two steps. Amine **205**, bearing a methoxy group in *para* position of the benzyl ring (entry 3) resulted in a slightly lower yield of piperidone **206** of 45%. We believe that due to the polar methoxy substituent, amine **205** is adsorbed to the surface of the surface of MnO_2 to a higher extent than the other benzylamines and is thus less available for the cyclisation reaction with divinyl ketone **178**.

Using α-phenylethylamine **209** as substrate for the double *aza*-Michael reaction gave piperidone **210** in a yield of 49% (entry 5), therefore indicating that the additional methyl group on the benzyl moiety does not have a sterically detrimental effect on the cyclisation reaction. Amine **211** (Table 2.3, entry 6) gave a low yield of piperidone **212** (28%) which could be explained by the steric bulk of the amine that possibly hinders the intramolecular addition step in the cyclisation process. Employing phenylethylamine **213** as substrate (entry 7), piperidone **214** was obtained in a higher yield of 58%. When aliphatic amines were used as substrates for the double *aza*-Michael reaction (entry 8 and 9), yields for the isolated products **216** and **218** were 60 and 61% over two steps.

Table 2.3: *In-situ* oxidation-cyclisation giving various *N*-substituted 4-piperidones.

Entry	Amine	Product	Yield[a](%)
1	**202**	**201**	55
2	**203**	**204**	53
3	**205**	**206**	45
4	**207**	**208**	53
5	**209**	**210**	49
6	**211**	**212**	28
7	**213**	**214**	58
8	**215**	**216**	60
9	**217**	**218**	61

[a] Isolated yield over two steps.

The main byproducts of the one-pot oxidation/cyclisation reaction with benzylamine were isolated and identified as benzyl alkylimine **220** and benzaldehyde **221** based on the analysis of their ^{1}H-NMR spectrum (Figure 2.7). From the crude ^{1}H-NMR spectra of the optimisation experiments (Table 2.2, entry 2-4) it was found that approximately 60% of the benzylamine used was converted to benzyl alkylimine **220** and benzaldehyde **221**. The ratio of the aldehyde to the imine was determined from the crude ^{1}H-NMR spectra and observed to be slightly variable, ranging from 1.0:1.6 to 1.0:4.9 for **221**:**220**.
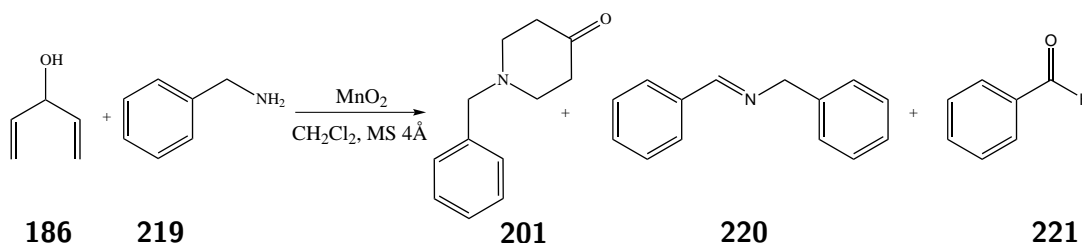
Figure 2.7: Identified byproducts **220** and **221**.

We believe that, in the presence of MnO$_2$, benzylamine **219** undergoes an oxidation to unstable imine **222**, which is further hydrolysed to aldehyde **221** (Figure 2.8).[156] The aldehyde then reacts with a molecule of benzylamine **219** to give alkylimine **220**. This side-reaction, which is due to the reactivity of benzylamine derivatives towards MnO$_2$, consequently leads to a lowered availability of the amine substrate for the participation in the double *aza*-Michael cyclisation with ketone **178**.
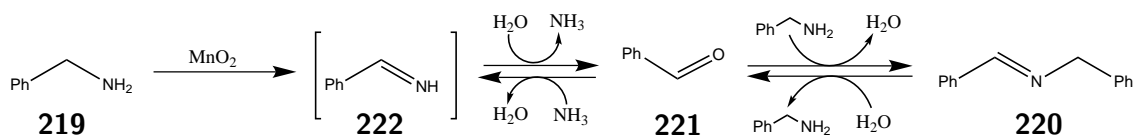
Figure 2.8: Proposed pathway for the formation of byproducts **221** and **220**.

Side products as shown in Figure 2.7 were not observed when using aliphatic amine substrates, which explains the higher yields that were obtained for the corresponding *N*-alkyl piperidones in comparison to the *N*-benzylic piperidones.

2.1.2   Preparation of Substituted Divinyl Ketones

As the previously developed one-pot oxidation/cyclisation protocol proved successful for the synthesis of a range of N-substituted 4-piperidones, it was envisioned that when using a substituted divinyl alcohol **223**, the same method could be applied to the preparation of 2-substituted N-protected 4-piperidones (Figure 2.9).
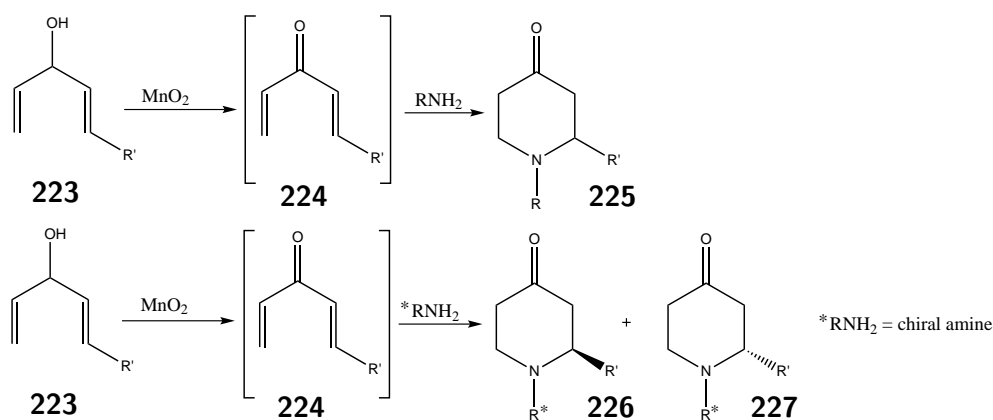
Figure 2.9: Schematic route towards the synthesis of racemic piperidone **225** or diastereomeric piperidones **226** and **227**.
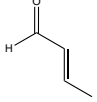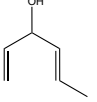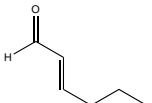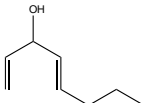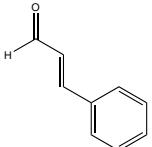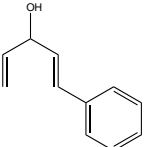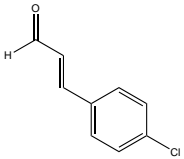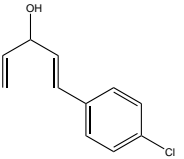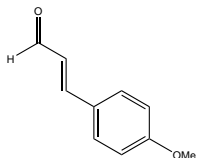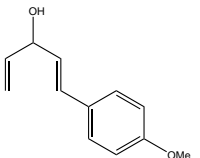
Synthesis of mono-substituted divinyl alcohols

For the synthesis of substituted divinyl alcohols **233**-**237**, the corresponding vinyl aldehydes **228**-**232** were subjected to a Grignard reaction utilising commercially available vinylmagnesium bromide (Scheme 2.6). The dienols were obtained in high yield and were of sufficient purity to be used in the next synthetic step without further purification (Table 2.4).

R	Aldehyde	Alcohol
—CH$_3$	**228**	**233**
⌒CH$_3$	**229**	**234**
phenyl	**230**	**235**
phenyl—Cl	**231**	**236**
phenyl—OMe	**232**	**237**
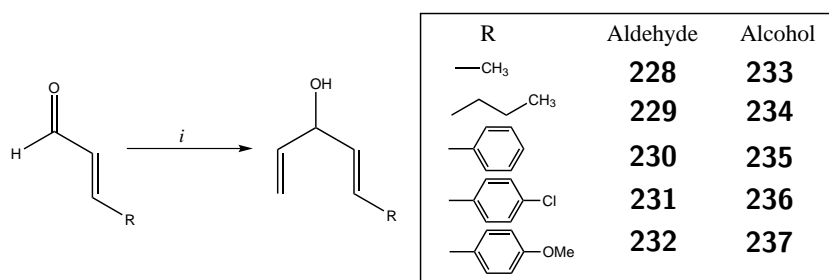
Scheme 2.6: Reaction conditions: *i)* CH$_2$=CHMgBr, THF, 0 °C (dropwise), then rt, 1 h.

Table 2.4: Grignard reaction giving mono-substituted divinyl alcohols.

Entry	Aldehyde	Product[a]	Yield (%)[b]
1	**228**	**233**	99 (82)
2	**229**	**234**	99
3	**230**	**235**	98 (86)
4	**231**	**236**	100
5	**232**	**237**	98

[a] Standard reaction conditions: Aldehyde, $CH_2=CHMgBr$, THF, 0 °C

(dropwise), then rt, 1 h.

[b] Crude yield. Isolated yield in parentheses.

The synthesised divinyl alcohols (Table 2.4) can be stored in the fridge (4 °C) for several weeks without observed degradation as judged by ^{1}H-NMR analysis and are therefore practical precursors for the synthesis of substituted piperidones.

Substituted Divinyl Alcohols in the One-pot Double *Aza*-Michael Reaction

With the mono-substituted dienols in hand, their utility as substrates for the one-pot oxidation/*aza*-Michael reaction could be investigated. Subjecting alcohols **233** and **235** to the same reaction conditions as previously described, using benzylamine as the amine component, gave racemic 2-substituted piperidones **241** and **242** in low yields over two steps (17% and 21% respectively, Scheme 2.7).

233 (R=Me)	**238** (R=Me)	**241** 17% (R=Me) *i*
235 (R=Ph)	**239** (R=Ph)	**242** 21% (R=Ph) *i*
234 (R=Pr)	**240** (R=Pr)	**243** 22% (R=Pr) *ii,iii*
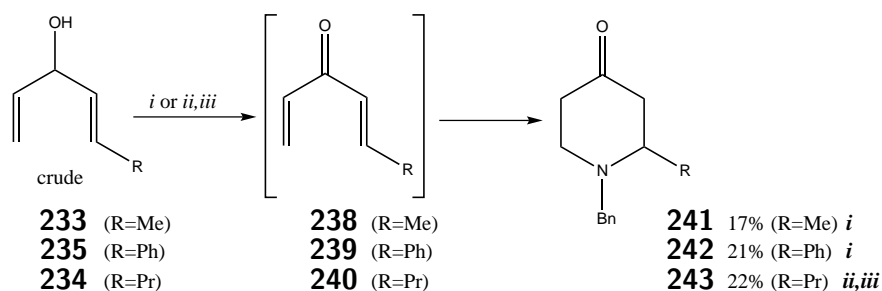
Scheme 2.7: Reaction conditions: *i)* BnNH$_2$, MnO$_2$, 4 Å MS, CH$_2$Cl$_2$, 50 °C, 18 h; *ii)* MnO$_2$, 4 Å MS, CH$_2$Cl$_2$, 45 °C, 3 h, microwave irradiation; *iii)* BnNH$_2$, 45 °C, 1 h, microwave irradiation.

We believe that in comparison to unsubstituted divinyl ketone **178**, substituted dienones, such as **238**, **240** and **239**, possess a lowered reactivity towards the subsequent double Michael reaction with benzylamine. A substituent β to the carbonyl function decreases the electrophilicity of the Michael acceptor and leads to steric hindrance during the cyclisation process with benzylamine. The piperidone formation takes place at a slower rate and consequently more time is allowed for the previously described MnO$_2$ mediated side reaction to occur, which is further contributing to a decreased yield by resulting in a reduced availability of benzylamine over time.

Investigating the effects of microwave irradiation on this type of reaction, propyl alcohol **234** was oxidised to its ketone **240** in the presence of only 10 equivalents of MnO$_2$ within a reaction time of three hours. Addition of benzylamine to the reaction mixture and microwave irradiation for another hour gave piperidone **243** in a yield of 22%. This shows that a stepwise reaction sequence under the influence of microwave irradiation did not significantly promote the formation of the piperidone product.

As these preliminary results were not satisfactory, we decided to first oxidise the substituted divinyl alcohols to their corresponding ketones before using them in the *aza*-Michael addition. In this way it would be easier to evaluate the utility of a substituted dienone as a double Michael acceptor.

Oxidation of Mono-substituted Dienols

A MnO_2 mediated oxidation of crude divinyl alcohol **233** gave corresponding ketone **238** in a crude yield of 71% (Scheme 2.8). Monitoring the reaction by TLC showed that the conversion took place faster (3 h) than previously observed for unsubstituted divinylcarbinol **186** (20 h). However, when employing MnO_2 as the oxidant, phenyl-substituted alcohol **235** was not converted to its corresponding ketone. Despite complete consumption of the starting material, no formation of ketone **239** was observed even after a prolonged reaction time. Analysis of the crude ^{1}H-NMR spectrum showed a complex mixture of products.
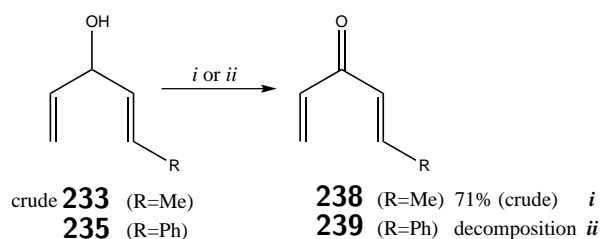
Scheme 2.8: Reaction conditions: *i)* MnO_2, 4 Å MS, CH_2Cl_2, 50 °C, 3 h; *ii)* MnO_2, 4 Å MS, CH_2Cl_2, 50 °C, 18 h.

The phenyl-substituted ketone **239** must have formed during the one-pot reaction with benzylamine (Scheme 2.7), since the final piperidone product was not only observed but also isolated. Therefore we can deduce that dienol **235** is oxidised to ketone **239** and then, in the absence of a primary amine and promoted by MnO_2, undergoes an immediate polymerisation/degradation process.

As dienone **239** was not stable under the previous reaction conditions employing MnO_2 and as no product could be isolated, another reagent suitable for oxidising allylic and benzylic alcohols, 2,3-dichloro-5,6-dicyano-*p*-quinone (DDQ),[157,158] was investigated. DDQ is a powerful oxidant at room temperature and upon conversion of the alcohol substrate it conveniently precipitates from a suitable solvent as its hydroquinone.[155] Scheme 2.9 shows the results of DDQ-mediated oxidation with the methyl, propyl and phenyl substituted allylic alcohols **233**, **234** and **235**.

All substrates were smoothly converted to their corresponding ketones and due to the DDQ hydroquinone's low solubility in dioxane, we were able to filter this off at the end of the reaction (Scheme 2.9). Analysis of the crude products by ^{1}H-NMR showed clean spectra, however, an intense red colour of the dienone residues remained. This suggests that the crude products still contained traces of the reagent, which might be detrimental in subsequent synthetic steps.

R	Solvent	Crude Yield (%)	Isolated Yield (%)
Me	dioxane (*i*)	95	0
Pr	CH$_2$Cl$_2$ (*ii*)	97	18
Ph	dioxane (*i*)	98	74
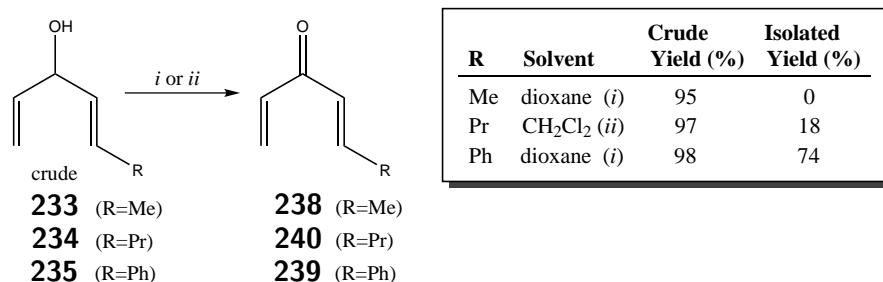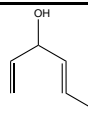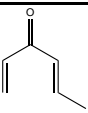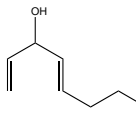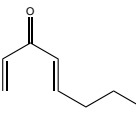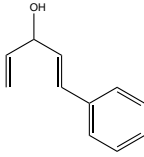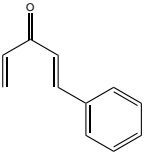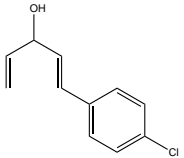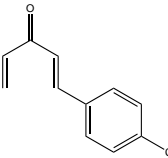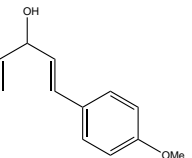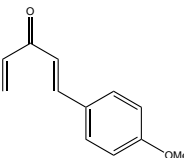
Scheme 2.9: Reaction conditions: *i)* DDQ, dioxane, rt, 18 h; *ii)* DDQ, 4 Å MS, CH$_2$Cl$_2$, rt, 18 h.

To investigate the effect of solvents on this oxidation, propyl dienol **234** was reacted in dichloromethane instead of dioxane (Scheme 2.9). DDQ hydroquinone has a lower solubility in dichloromethane compared to dioxane[157] and has the additional advantage of being highly volatile, thereby facilitating complete removal of the solvent under milder conditions. Nevertheless, the red colour remained regardless of the choice of solvent.

In the case of phenyl dienone **239**, column chromatography could be applied and pure product was obtained in a yield of 74%. In contrast, crude crotyl dienone **238** is highly unstable and degraded completely upon attempts of purification by column chromatography. Pure propyl divinyl ketone **240** was obtained in a significantly diminished yield of 18% when subjected to column chromatography on silica. In addition to not tolerating column chromatography conditions, it was necessary to use dienones **238** and **240** shortly after their isolation, in order to avoid further loss of material. A similar observation concerning the instability of **238** is reported by Han and Krische[159] and comments about the capricious nature of similar divinyl ketones have been made in the literature.[81,160,161]

Table 2.5 depicts a summary of all synthesised divinyl ketones. When aliphatically substituted ketones **238** and **240** were synthesised from their corresponding alcohols by

Table 2.5: Summary of prepared divinyl ketones employing MnO_2 or DDQ as the oxidant.

Entry	Alcohol[a]	Product[b]	Yield (%)[c]
1	**233**	**238**	71[d]
2	**234**	**240**	62[d]
3	**235**	**239**	74
4	**236**	**244**	56
5	**237**	**245**	53

[a] Crude starting materials.
[b] *Reaction conditions for entry 1 and 2:* Alcohol, MnO_2, 4 Å MS, CH_2Cl_2, 50 °C 3 h; *Reaction conditions for entry 3-5:* Alcohol, DDQ, dioxane, rt, 18 h.
[c] Isolated yield unless otherwise stated.
[d] Crude yield.

oxidation with DDQ, a purification by column chromatography was necessary because traces of the reagent were present in the crude residues. However, ketones **238** and **240** are instable on silica, wherefore we chose to synthesise them from their corresponding alcohols by oxidation with MnO_2, thereby ensuring complete removal of the reagent by simple filtration. The crudes of ketones **238** and **240** were of sufficient purity to be used in the next synthetic step without further purification. As dienone products **239**, **244** and **245** were stable on silica, the DDQ-facilitated oxidation was chosen for aromatically substituted dienols and pure products were obtained in moderate to good isolated yields over two steps.

2.1.3 Synthesis of 2-Substituted 4-Piperidones

Since the synthesis of 2-substituted 4-piperidones using a one-pot oxidation/cyclisation approach starting from mono-substituted divinyl alcohols did not give satisfactory results, a stepwise oxidation and double *aza*-Michael cyclisation was investigated.

As the stability of phenyl dienone **239** allows purification on silica, this ketone substrate was selected for the exploration of suitable reaction conditions for the conversion to piperidone **242** from cyclisation with benzylamine (Figure 2.10). It was believed that the excess of MnO_2 in the one-pot method was limiting the availability of benzylamine in the *aza*-Michael reaction due to its previously described conversion to an imine and an aldehyde byproduct. Therefore an experiment was carried out under the same one-pot reaction conditions, but in the absence of the MnO_2 oxidant (Table 2.6, entry 1). The reaction time ranged from 3-24 h, but only traces of piperidone **242** were observed in the crude ^{1}H-NMR spectrum. Phenyl dienone **239** was completely consumed and besides unreacted benzylamine, a complex mixture of products was observed.
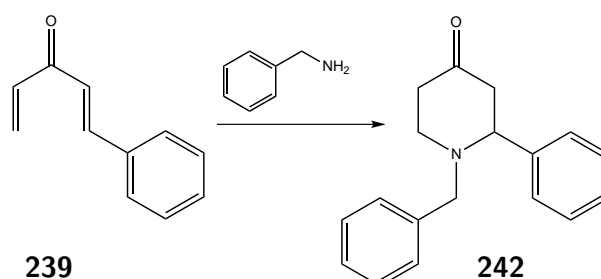
Figure 2.10: Reaction conditions and yields for the synthesis of **242** detailed in Table 2.6.

Microwave irradiation has the potential to shorten reaction times and has been successfully employed in *aza*-Michael reactions,[162–164] therefore microwave heating was investigated in promoting the cyclisation of ketone **239** in dichloromethane (entry 2). However, under these conditions only traces of product were formed, despite complete consumption of the starting ketone.

Both dichloromethane[59,74,80] and acetonitrile[61,81] are commonly used solvents for *aza*-Michael reactions, hence acetonitrile was also investigated in an attempt to synthesise **242** (entry 3). The reaction was followed by TLC over the course of 4 days, but analysis

Table 2.6: Tested reaction conditions for the synthesis of **242** (see Figure 2.10).

Entry	Solvent	Conditions	Reagents/Catalysts	Yield (%)
1	CH_2Cl_2	50 °C, 3-24 h	-	traces[a,c]
2	CH_2Cl_2	75 °C, 2 h	microwave irradiation	traces[a,c]
3	CH_3CN	rt, 4 d	-	no product
4	CH_2Cl_2	rt, 48 h	-	11[b]
5	CH_2Cl_2	rt, 18 h	TFA (0.1 equiv)	9[b]
6	CH_3CN/H_2O[d]	16-95 °C, 1.5 h	$NaHCO_3$ (3.75 equiv)	79[b]

[a] Traces of product found in crude ^{1}H-NMR spectrum. Isolation of the product was not possible.
[b] Isolated yield.
[c] 4 Å MS added to the reaction mixture.
[d] Ratio of CH_3CN/H_2O: 3:1. Addition of the ketone at 16 °C over 40 min followed by reflux at 95 °C for 1.5 h.

of the crude ^{1}H-NMR spectrum showed no piperidone formation and a only complex mixture of products that was not further investigated.

When **239** was reacted with benzylamine in dichloromethane at room temperature without added molecular sieves (entry 4), 11% of piperidone product **242** could be isolated. We believe that the trace water, which is present in the absence of molecular sieves, leads to an improved yield by acting as a proton shuttle and thereby facilitates the cyclisation process of ketone **239**. Adding a catalytic amount of trifluoroacetic acid to increase the electrophilicity of **239** (entry 5) did not significantly influence the obtained yield under these conditions.

The patent literature described a procedure for the synthesis of 2-methyl substituted *N*-benzyl 4-piperidone **241**, using crotyl dienone **238** for the cyclisation with benzylamine (Scheme 2.10).[165–167] In the procedure outlined by Guzzo,[167] benzylamine was added to a mixture of acetonitrile and 1.8 M aqueous sodium bicarbonate. At a temperature of 16 °C, crude divinyl ketone **238** was slowly added over a period of 40 min and the mixture refluxed for one hour. The yield of isolated piperidone product **241**, as reported by Guzzo, was 54% (Scheme 2.10). When reacting phenyl dienone **239** with benzylamine under these reaction conditions, the yield of the 2-phenyl substituted piperidone **242** was 79% (Table 2.6, entry 6), which is a considerable improvement over what had been achieved in previous attempts.

238 **241**
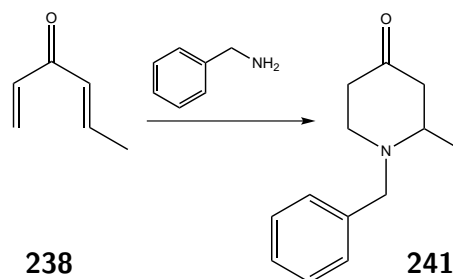
Scheme 2.10: Reaction conditions: benzylamine, $NaHCO_3$, CH_3CN/H_2O 3:1, 16 °C 40 min., then reflux 1 h.[167]

Since the earlier experiment in acetonitrile (Table 2.6, entry 3) had not led to any product formation, it was surprising to see such a significant improvement when using acetonitrile/water as a mixed solvent system. In the literature a report was identified about the rate accelerating effect of water on the *aza*-Michael reaction.[168] The addition of a broad range of cyclic and acyclic aliphatic primary amines and benzylamine to Michael acceptors in pure water at room temperature is described by Ranu.[168] It was shown that benzylamine reacts much faster with Michael acceptor **246** and results in a higher yield of product **251** in water than in organic solvents, such as tetrahydrofuran and dichloromethane (Figure 2.11, Table 2.7).

Table 2.7: Effect of different solvents on the yield and reaction time of product **251**.

Entry	Solvent	Time (h)	Yield of **251** (%)
1	THF	15	30
2	CH_2Cl_2	15	50
3	H_2O	0.8	85

The rationale for the promotion of the reaction is that water increases not only the electrophilicity of the Michael acceptor through the formation of a hydrogen bond with the carbonyl moiety, but also the nucleophilicity of the primary amine by forming another hydrogen bond between the water molecule's oxygen atom and the amine hydrogen atom (Figure 2.11).[168]

Recently, Tang reported the reaction of aniline derivatives with ethyl acrylate at 50 °C in aqueous sodium carbonate (Figure 2.12).[169] While in pure water at room temperature the yield of addition product **254** was less than 10% when using aniline as the substrate,
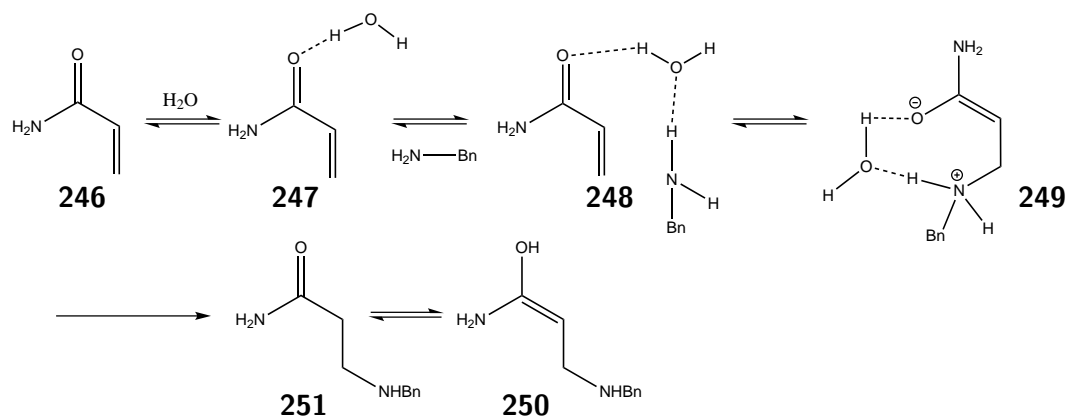
Figure 2.11: Rationale for the rate accelerating effect of water in the *aza*-Michael reaction.

it could be improved to 90% in the presence of sodium carbonate and at an elevated temperature of 50 °C. Water is again forming a hydrogen bond to the carbonyl oxygen to enhance the Michael acceptor's electrophilic character. In addition, carbonate is present in the activated complex **253**, acting as a proton shuttle by supporting the proton transfer from the nitrogen atom to the oxygen atom.
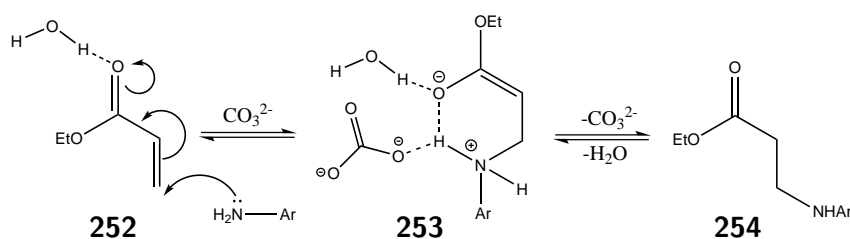
Figure 2.12: Rationale for the rate accelerating effect of aqueous sodium carbonate in the *aza*-Michael reaction.[169]
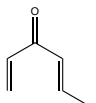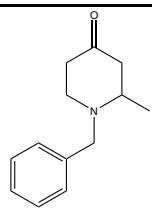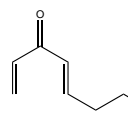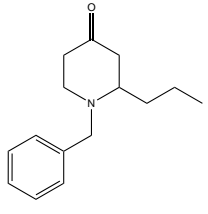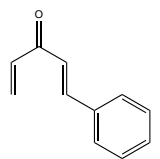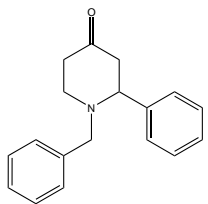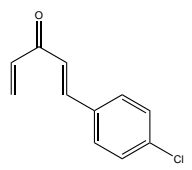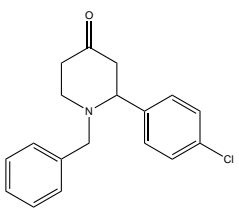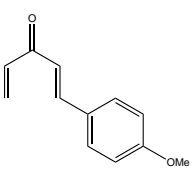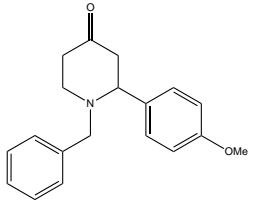
We believe that under the reaction conditions used in entry 6 (Table 2.6), the water and sodium bicarbonate act together and facilitate the double *aza*-Michael addition to form the piperidone product. As seen previously, neat acetonitrile is unsuitable as a solvent for this reaction. However, because of its ability to solubilise both starting materials and products and its miscibility with aqueous sodium bicarbonate, the combination with water becomes an active solvent system, where the solvent is participating in the reaction.

Synthesis of Further Analogues

Utilising the protocol employing acetonitrile and aqueous sodium bicarbonate, a diverse range of aliphatically and aromatically substituted piperidones have been prepared (Table 2.8). As expected, the yields for the methyl and propyl substituted piperidones **241** and **243** (entry 1 and 2) were lower due to the unstable nature of the crude starting ketones **238** and **240**. When purified, aromatically substituted dienones **239**, **244** and **245** were used for the cyclisation with benzylamine (entry 3-5), the desired piperidones **242**, **255** and **256** were obtained in high yield (79-84%).

The obtained products possess only a single stereocentre in position two of the piperidine ring and are therefore inseparable enantiomeric mixtures that cannot be distinguished by NMR analysis. Although these piperidones are interesting building blocks for further synthetic modifications, they are only of limited use when incorporated into more complex biologically active molecules, as they will not give easily interpretable results in stereosensitive SAR studies. In order to gain clear insight into the structural activity related to piperidine compounds it would be necessary to evaluate compounds that have resolved stereochemistry on the ring moiety, thereby facilitating an unambiguous determination of the influence of a piperidine ring substituent on a compound's biological activity.

Table 2.8: Synthesis of 2-substituted *N*-benzylic 4-piperidones.

Entry	Substrate	Product[a]	Yield (%)[b]
1	**238**	**241**	42[c]
2	**240**	**243**	36[c]
3	**239**	**242**	79
4	**244**	**255**	84
5	**245**	**256**	84

[a] Standard reaction conditions: Ketone, benzylamine, $NaHCO_3$, CH_3CN/H_2O

   3:1, 16 °C, 40 min, 95 °C, 1.5 h.

[b] Isolated yield.

[c] Crude ketone from MnO_2 oxidation used as starting material.

The Synthesis of Diastereomeric 2-Substituted *N*-α-Phenylethyl-4-piperidones

In order to obtain diastereomeric, potentially separable 2-substituted 4-piperidones, chiral *S*-α-phenylethylamine **257** was chosen as a suitable primary amine for the *aza*-Michael cyclisation (Figure 2.13). *S*-α-phenylethylamine is both a nucleophile and a potential chiral auxiliary,[170–172] besides being commercially available and cheap. Furthermore it possesses similar chemical properties as the previously employed benzylamine and can be easily removed by hydrogenolysis over a palladium catalyst.
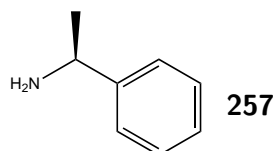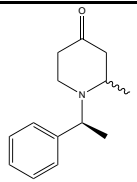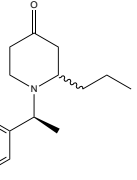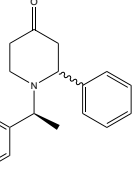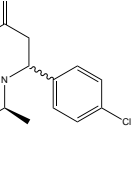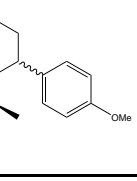
Figure 2.13: *S*-α-Phenylethylamine.

Table 2.9 records the combined yields and product ratios of the diastereomeric piperidones that were synthesised according to the previously developed method using aqueous sodium bicarbonate. Since dienones **238** and **240** were used as crude for this cyclisation reaction, the combined yields for the aliphatically substituted crotyl and propyl piperidones were lower (27-37%, entry 1 and 2). The isolation of **258** and **259** as well as **260** and **261** was straight forward due to good separation of the respective distereomers under silica column chromatography conditions. Aromatically substituted piperidones (entry 3-5) were obtained in good (61-68%), albeit lower combined yields as when compared to the cyclisation with benzylamine (Table 2.8). Due to their comparable R_f values, the separation of the aryl substituted diastereomeric pairs proved more difficult. In order to obtain the diastereomer bearing the lower R_f value in a pure form, it was necessary to repeat the column chromatography. In this way complete removal of traces of the diastereomer with the higher R_f value could be achieved.

Table 2.9: Synthesis of diastereomeric 2-substituted *N*-α-phenylethyl-4-piperidones.

Entry	Ketone	Products[a]	Yield (%)[b]	Major:Minor Product[c]
1	**238**[d]	**258+259**	37	1.06:1.00
2	**240**[d]	**260+261**	27	1.45:1.00
3	**239**	**262+263**	63	2.94:1.00
4	**244**	**264+265**	68	2.78:1.00
5	**245**	**266+267**	57	3.69:1.00

[a] Standard reaction conditions: Ketone, *S*-α-phenylethylamine, NaHCO$_3$, CH$_3$CN/H$_2$O 3:1, 16 °C, 40 min, 95 °C, 1.5 h.

[b] Isolated combined yield.

[c] Ratio of isolated products.

[d] Crude ketone used for reaction.

Assignment of the Correct Stereochemistry

The 2-methyl substituted diastereomeric piperidones **258** and **259** are known com-pounds[173,174] with their stereochemistry having been confirmed by X-ray analysis.[175] In order to assign the stereochemistry of the other diastereomeric pairs of piperidones correctly, their spectroscopic data was analysed.

It can be seen in Table 2.10, entry 1, that the experimentally obtained signal for the methyl group on the α-phenylethyl substituent in the ^{13}C-NMR is shifted upfield by approximately 5.5 ppm in *S,S*-methyl diastereomer **258** when compared to the same

Table 2.10: Experimental ^{13}C-NMR shifts of 2-substituted 1-α-phenylethyl-4-piperidones.

Entry	2-Substituent[a]	Product	δ, ppm			
			CH$_3$[b]	CH[b]	C=O	2-CH$_3$[c]
1	Me	*S,S*-**258**	16.47	57.76	210.54	16.33
		R,S-**259**	21.93	58.84	210.54	14.78
2	Pr	Major	19.30	58.19	210.89	14.34
		Minor	22.50	58.71	210.79	14.11
3	Ph	Major	9.52	54.97	209.15	
		Minor	19.56	56.63	208.83	
4	4-Cl-Ph	Major	9.83	55.16	208.61	
		Minor	19.52	56.87	208.22	
5	4-MeO-Ph	Major	9.57	54.85	209.34	
		Minor	19.65	56.45	209.50	

[a] Referring to the substituent in position two on the piperidine ring.
[b] Referring to the α-phenylethyl substituent in position one on the ring.
[c] Referring to the methyl group-substituent in position two on the ring.

signal in *R,S*-**259**. Besides that, a small upfield shift of 1.1 ppm for the α-phenylethyl-CH signal and a small downfield shift in the methyl group in position two on the piperidine ring is observed in **258**. The carbonyl signals of **258** and **259** are identical.

The chemical shifts of the propyl-substituted analogues were investigated (Table 2.10, entry 2) and the signals for the major and the minor diastereomer were in accordance with the pattern that had been observed for compound *S,S*-**258** in respect to *R,S*-**259**. In addition, the carbonyl peak belonging to the major and firstly eluting product was also the one that was shifted slightly downfield in the spectrum.

For the 2-phenyl diastereomeric piperidones (Table 2.10, entry 3), the major product possessed the higher R$_f$ value and presented the same ^{13}C-NMR signal pattern as *S,S*-**258**. In this case, the major product's α-phenylethyl methyl signal is shifted 10.0 ppm upfield in comparison to the same carbon signal in its minor diastereomer. The same pattern of difference in chemical shifts in the ^{13}C-NMR spectra between the two

diastereomers was observed in the 4-chloro- and the 4-methoxy-phenyl 2-substituted piperidone compounds (Table 2.10, entry 4 and 5).

Leshcheva[176] conducted a similar analysis of the ^{13}C-NMR spectra of methyl piperidones **258** and **259** and used the difference in chemical shifts to elucidate the configuration of the substituents on the piperidine ring. The molecular models developed were established based on the assumption that the nitrogen inversion equilibrium is completely shifted towards the equatorial position of the N-alkyl substituent. Figure 2.14 shows the most favoured rotamers with respect to the N-α-phenylethyl moiety for both diastereomers in their conformational equilibria.
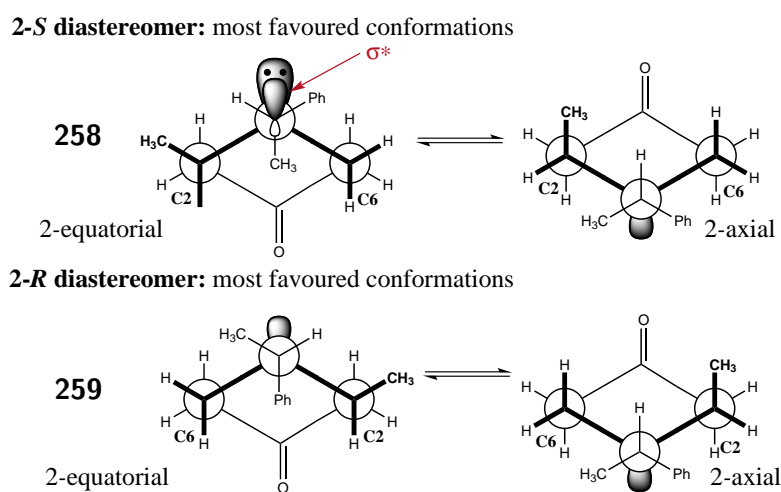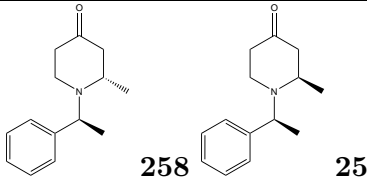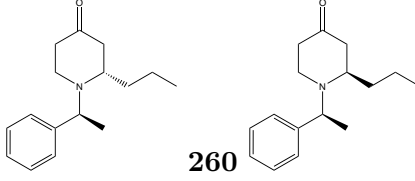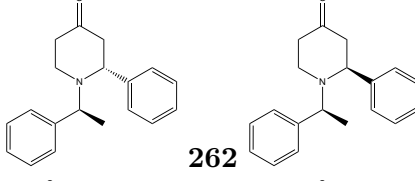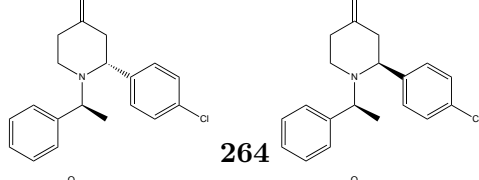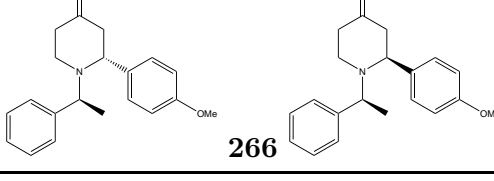
Figure 2.14: Most favourable rotamers of the equatorial conformers of $2S$-**258** and $2R$-**259** in their conformational equilibria.[176]

According to this analysis, the large upfield shift in the methyl group on the α-phenylethyl substituent of one diastereomer is caused by a hyperconjugation effect which is due to the methyl group's axial orientation in relation to the nitrogen lone pair of electrons. Only in this conformation can the nitrogen lone pair be donated into to the σ^* orbital of the adjacent C-C bond and cause the observed upfield shift of the CH$_3$ group. As shown in Figure 2.14, such an axial position of the methyl group is only found in the $2S$ diastereomer, therefore the correct configuration of the two diastereomers can be readily assigned.[176]

According to this rationale, the major propyl-substituted diastereomer with the higher R$_f$ value was assigned as S,S-**260** and subsequently the minor one with the lower R$_f$

value as *R,S*-**261** (Table 2.11, entry 2).

Table 2.11: Summarising table of the diastereomeric piperidones with their assigned stereochemistry.

Entry	Products		Ratio[a]
1	**258**	**259**	*S,S*-**258**:*R,S*-**259** 1.06:1.00
2	**260**	**261**	*S,S*-**260**:*R,S*-**261** 1.45:1.00
3	**262**	**263**	*R,S*-**262**:*S,S*-**263** 2.94:1.00
4	**264**	**265**	*R,S*-**264**:*S,S*-**265** 2.78:1.00
5	**266**	**267**	*R,S*-**266**:*S,S*-**267** 3.69:1.00

[a] Ratio of isolated products.

The phenyl-substituted diastereomer **262**, bearing the same configuration as the the methyl and propyl substituted *S,S*-**258** and *S,S*-**260**, is hence labelled with *R*-chirality in position two on the ring (Figure 2.15).

In conclusion, the major phenyl-diastereomer was assigned as *R,S*-**262** and subsequently the minor product as *S,S*-**263** (Table 2.11, entry 3). According to this rationale, the other aryl-piperidones were assigned in analogy as *R,S*-**264**, *S,S*-**265**, *R,S*-**266** and *S,S*-**267** concerning their configuration in position two on the piperidine ring (Table 2.11, entry 4 and 5).
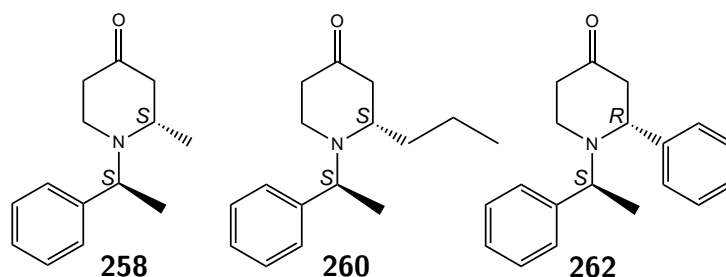
Figure 2.15: Major piperidones *S,S*-**258**, *S,S*-**260** and *R,S*-**262**.

Investigation of the diastereomeric piperidone products by Nuclear Overhauser effect spectroscopy (NOESY) was not possible in most cases, due to overlapping signals that prevented an unambiguous analysis. However, in one of the synthesised piperidones, 2*S*-phenyl substituted **263**, the analysis of the NOESY spectrum was conclusive (Figure 2.16). The signal of H_{ax}-1 in the ^{1}H-NMR spectrum was observed at 3.67 ppm as a dd with coupling constants of *J* 9.4 and 4.5 Hz, but unfortunately the couplings of the H_{ax}-2, H_{eq}-2 and H_{ax}-5 could not be determined due to overlapping signals. Nevertheless the observed coupling constants for H_{ax}-1 indicate an axial position for this proton, a suggestion which is further supported by the observed NOE correlation to H_{ax}-5. H_{ax}-5 has a chemical shift of 2.20-2.24 ppm and is therefore much further upfield than its geminal H_{eq}-5 that appears as ddd at 3.34 ppm (*J* 12.0, 5.7 and 3.8 Hz).
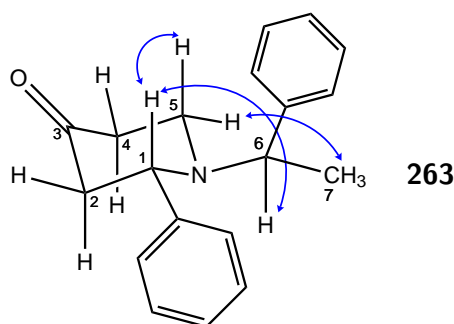
Figure 2.16: Observed NOESY interactions for *S,S*-diastereomer **263**.

Diastereoselectivity of the Reaction

As derived from the ratios of the isolated piperidones, a certain degree of diastereoselectivity was observed in this double *aza*-Michael cyclisation depending on the substituent in position two on the ring (Table 2.11).

The isolated yields of 2-methyl piperidones **258** and **259** suggest a roughly equal product distribution. The crude ^{1}H-NMR spectrum was too complex to allow an accurate analysis of the product distribution, therefore it could not be unambiguously determined whether chiral induction had taken place during the formation of **258** and **259**. For the propyl substituted analogues **260** and **261**, the ratio of diastereomers could be derived from the crude ^{1}H-NMR and was found to be 1.37:1.00, respectively. This is in accordance with the isolated product ratio of 1.45:1.00 and suggests a small diastereoselective effect due to the increased chain length of the substituent on the ring. In the case of phenyl-substituted **262** and **263**, a higher degree of chiral induction was observed. A ratio of 2.55:1.00 was deducted from the crude ^{1}H-NMR spectrum and a ratio of 2.94:1.00 was obtained from the isolated product yields.
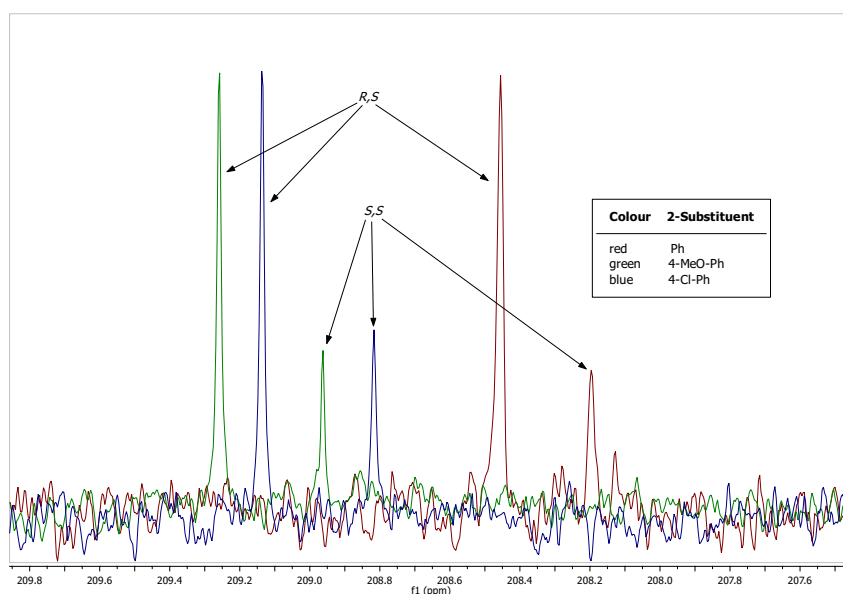
Figure 2.17: Expanded, overlaid, crude ^{13}C-NMR spectra of 2-aryl 1-α-phenylethyl-4-piperidones.

Determination of the diastereoselectivity of the reaction of 4-methoxy- and 4-chloro-phenyl substituted piperidone products was not possible from the crude ^{1}H-NMR spectra, but their isolated product ratios suggest a similar extent of chiral induction as what had been observed with the phenyl substituted piperidones (Table 2.11, entry 3-5). The comparable product distribution for the aromatically substituted piperidones was further visualised by overlaying the crude ^{13}C-NMR spectra. In Figure 2.17 the superimposed spectra are expanded to the ketone region and show that the carbonyl signals of the major *R,S*-diastereomers **262**, **266** and **264** are shifted downfield when compared to their corresponding minor *S,S*-diastereomers **263**, **267** and **265**.

The stereochemical outcome of the double *aza*-Michael cyclisation is determined during the second addition process, where the amine nucleophile intramolecularly attacks the sterically more hindered double bond bearing a substituent. We believe that in accordance with the conformational analysis by Leshcheva[176] (Figure 2.14), the hyperconjugation effect that leads to the significant difference in chemical shift of the methyl groups in the two diastereomers, is also responsible for the observed diastereoselectivity in this reaction (Figure 2.18). The favoured transition state is the one that leads to a cyclisation product in which the two orbitals can interact. As this is the only possible in diastereomer **268**, it is also the major product of the reaction.
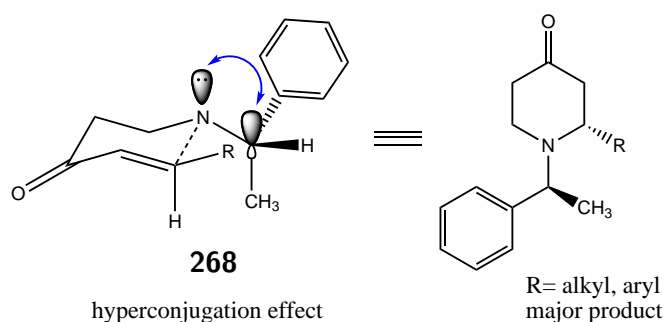
Figure 2.18: Rationale for the observed diastereoselectivity.

2.2 A Facile Method For The Oxidation of Benzylic Primary Amines

Manganese Dioxide in Organic Chemistry

Manganese has three oxidation states (+II, +III, +IV), giving rise to a diverse range of stable mineral oxides that are used extensively in pigments, in batteries and as catalysts.[177] There are various types of manganese dioxides, including α-MnO_2 (cryptomelane), β-MnO_2 (pyrolusite), γ-MnO_2 (nsutite) and δ-MnO_2 (birnessite), but all consist of MnO_6 octahedral building blocks (Figure 2.19).[177]
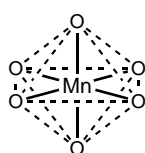
Figure 2.19: A MnO_6 octahedron.

Depending on the type of MnO_2, these octahedra can be arranged in either a tunnel/chain structure or a layered structure (Figure 2.20) and can contain different cations and water.[178,179]
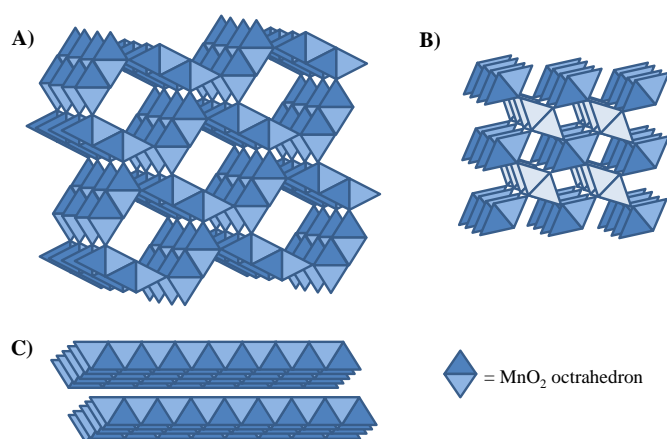
Figure 2.20: Structure representation of MnO_2 frameworks: *A)* cryptomelane *B)* pyrolusite *C)* birnessite.

Manganese dioxide is used extensively in organic synthesis and is a versatile and selective oxidising agent.[155] The observation that MnO_2 can act as an oxidant if suspended in

organic solvents was first made by Ball[180] in 1948. He showed that MnO_2 was able to efficiently oxidise vitamin A **269** and thereby convert it to retinene **270** (Scheme 2.11). Attenburrow[153] also explored the properties of this oxidant during his work on vitamin A and furthermore described the preparation of activated MnO_2 from manganese sulphate and potassium permanganate under basic reaction conditions.
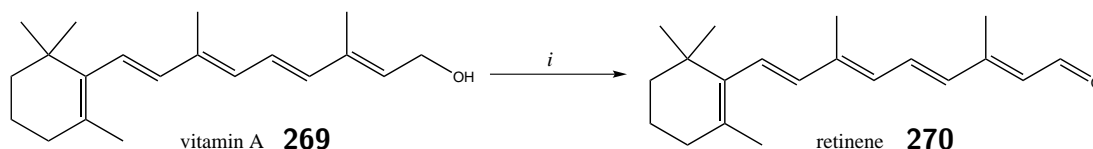
Scheme 2.11: Reaction conditions: *i)* MnO_2, petroleum ether, rt, 6-10 d.

MnO_2 has become a widely used oxidant for the selective transformation of benzylic and allylic alcohols into their corresponding aldehydes and ketones.[150–152,181] This is particularly useful for the oxidation of allylic alcohols in the presence of aliphatic alcohols and other oxidant-sensitive functional groups (Scheme 2.12).[182] The secondary benzylic alcohol of **271** is selectively oxidised, while the phenol and aliphatic primary alcohol remain unchanged.
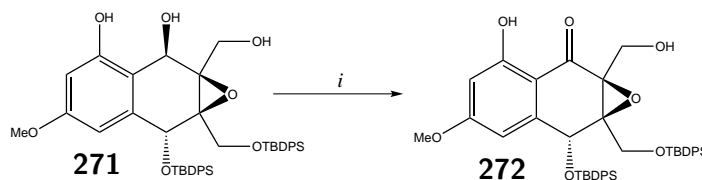
Scheme 2.12: Reaction conditions: *i)* MnO_2, acetone, rt.

MnO_2 can also be employed in tandem oxidation processes. The important natural product building block **275** can be prepared by either a stepwise approach or a MnO_2-mediated tandem oxidation process (Scheme 2.13). Various oxidants have been investigated for their use to access the highly unstable aldehyde **274**, but upon treatment with (carboxyethoxymethylene)triphenylphosphorane, the product of the Wittig olefination **275** is obtained only in poor overall yield (10-30%).[183] When the reaction was modified to a one-pot method employing MnO_2 as the oxidant, the handling of the labile intermediate **274** can be avoided and dienoate **275** isolated in a yield of 78% over two steps.[184]
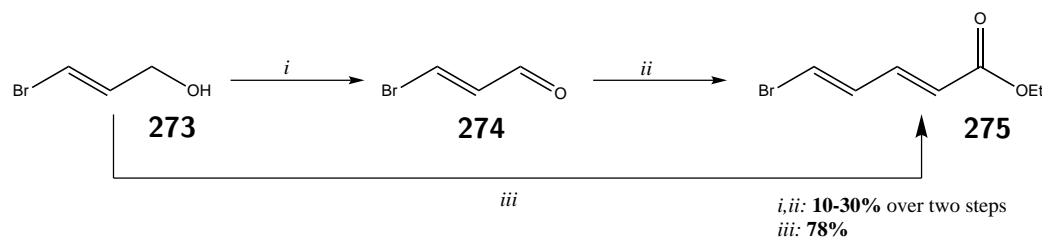
Scheme 2.13: Reaction conditions: *i)* various oxidants *ii)* Ph$_3$P=CHCO$_2$Et *iii)* MnO$_2$, Ph$_3$P=CHCO$_2$Et, CH$_2$Cl$_2$, rt, 24 h.

In reactions employing MnO$_2$, the choice of solvents plays a crucial role in the success of the oxidation. Polar solvents and alcohols can adsorb to the surface of MnO$_2$ and compete with the substrate's hydroxyl group, thus leading to a decreased activity of the oxidant.[155] Furthermore it is important to use dry solvents, because additional water, other than the water that is bound to the surface of the metal oxide, can deactivate MnO$_2$.[155]

A Manganese Dioxide Mediated Oxidation of Benzylic Primary Amines

During the synthesis of *N*-benzyl-4-piperidone **201**, aromatic byproducts were formed (Figure 2.21). The side-products were identified as alkylimine **220** and aldehyde **221**. As the reactivity of benzylamine towards MnO$_2$ was lowering the yield of the piperidone product, we decided to further investigate this side-reaction.
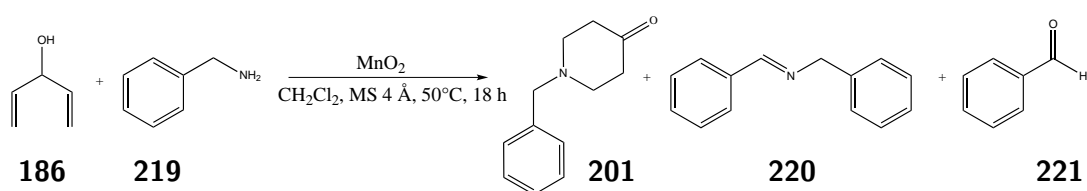
Figure 2.21: Aromatic byproducts **220** and **221** in the one-pot oxidation/*aza*-Michael reaction.

Under the same conditions as in the synthesis of piperidone **201** (Figure 2.21), benzylamine **219** alone was reacted with MnO$_2$ (Scheme 2.14). In the absence of divinylcarbinol **186**, benzamide **276** was obtained in a yield of 98%.
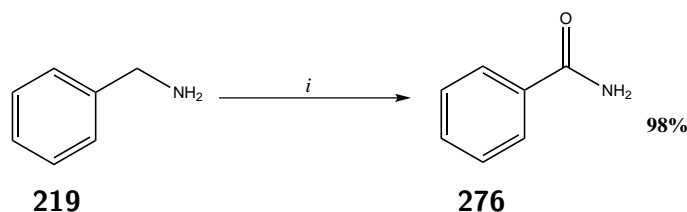
Scheme 2.14: Reaction conditions: *i)* MnO_2, 4 Å MS, CH_2Cl_2, 40 °C, 24 h.

The direct oxidative transformation of primary amines to their corresponding amides is difficult to achieve and has not been extensively explored in the literature. Yoshifuji[185] previously reported a procedure which employs *in-situ* generated RuO_4 as oxidant, but requires prior *tert*-butoxycarbonyl (Boc) protection of the amino group (Scheme 2.15).
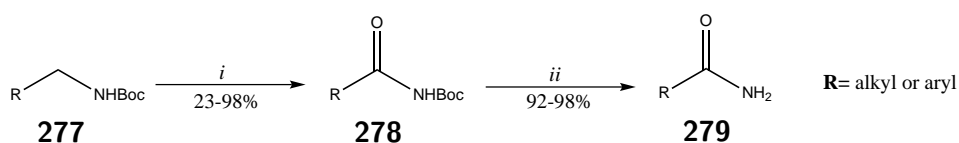
Scheme 2.15: Reaction conditions: *i)* $RuO_2 \cdot xH_2O$, $NaIO_4$ aqu., EtOAc, rt, 0.25-15 h; *ii)* TFA/CH_2Cl_2 1:1, rt, 1 h.

Nishinaga's procedure[186] involves the condensation of arylmethylamines **280** with 2,6-di-*tert*-butyl-*p*-benzoquinone **281** followed by base catalysed oxygenation to yield the corresponding amides **283** in moderate to good yields (36-85%) (Scheme 2.16).
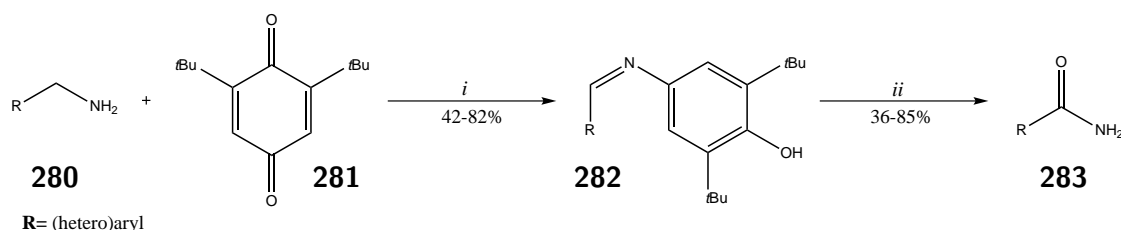
Scheme 2.16: Reaction conditions: *i)* reflux in EtOH; *ii)* *t*-BuOK, *t*-BuOH, O_2, 25 °C, 2-6 h.

More recently, two systems have been reported for a dehydrogenation-hydration sequence which achieves the conversion of primary amines to their corresponding amide in a one pot reaction (Scheme 2.17, Scheme 2.18).[156,187] Kim's procedure[187] allows the conversion of primary amines into their corresponding amides in good to excellent yield (77-98%),

employing an alumina supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$, in water (Scheme 2.17).
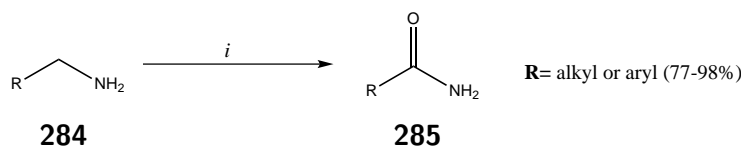
Scheme 2.17: Reaction conditions: *i)* $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%), H_2O, 130-160°C, 5 atm air, 10-24 h, sealed teflon vessel.

Wang[156] recently reported the amide formation from benzylamine derivatives in excellent yields, utilizing manganese oxide based octahedral molecular sieves (OMS-2) and aqueous ammonia (Scheme 2.18). The OMS-2 catalyst used in this method is a cryptomelane-type MnO_2 consisting of a tunnel framework (Figure 2.20) and is prepared from manganese sulphate and potassium permanganate.[188]
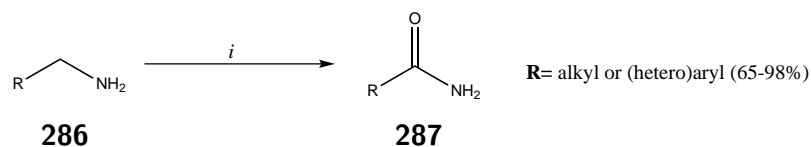
Scheme 2.18: Reaction conditions: *i)* OMS-2, NH_3 aqu., 1,4-dioxane, 130-160°C, 6 atm air, 3 h, sealed teflon vessel.

The drawbacks of both Kim's and Wang's procedure are the forcing conditions which involve reaction temperatures of 130-160°C, the application of 5-6 atmospheres of air and the necessity of an explosion-proof Teflon apparatus. These reactions can not be carried out in a standard laboratory and are therefore impractical to use. In comparison to these methods, our oxidation (Scheme 2.14) possesses several advantages. Firstly, we are able to use commercially available, cheap, pyrolusite-type[189,190] manganese dioxide (*Alfa Aesar*), which only requires activation by treatment with 10% nitric acid and drying at 105 °C for 48 h. Furthermore, there is no need for the addition of aqueous ammonia or other reagents. As conversion to the amide proceeds smoothly under mild conditions, at a reaction temperature of 40 °C and at atmospheric pressure, the reaction can be carried out in standard glassware.

Figure 2.22 shows the mechanism for the OMS-2 mediated transformation of primary amines to primary amides as proposed by Wang.[156] An OMS-2 catalysed oxidative

dehydrogenation first transforms the primary amine into unstable aldimine **287** and successively into nitrile **288**. Subsequently, the nitrile is hydrated and leads to the formation of primary amide **289**. If the unstable imine hydrolyses to aldehyde **290**, it can subsequently react with starting material and give alkylimine **291**.

Under Wang's experimental conditions, the addition of aqueous ammonia was crucial for a successful hydration of the nitrile to the amide. In the absence of ammonia, alkylimine **291** formed as the major product in a yield of 75%.
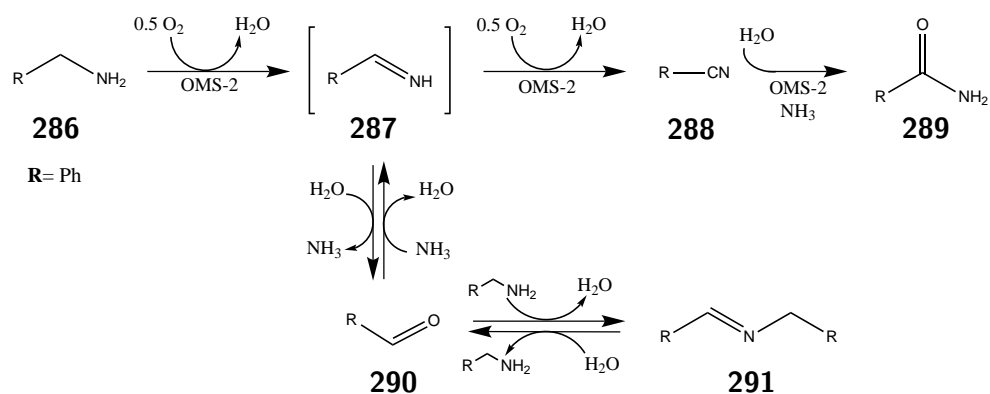
Figure 2.22: Reaction pathway for the transformation to the primary amide proposed by Wang.[156]

For our initial investigations into this reaction pathway, 4-chlorobenzylamine **292** was selected as the starting amine. It gives an easily distinguishable pair of doublets in the aromatic region of the ^{1}H-NMR-spectrum and therefore facilitates the assignment and identification of the resulting products. When 4-chlorobenzylamine **292** was evaluated under the same conditions (Scheme 2.19), the corresponding amide **293** formed in quantitative yield. The product was obtained by filtration and washing with hot (60 °C) methanol without the need of further purification.
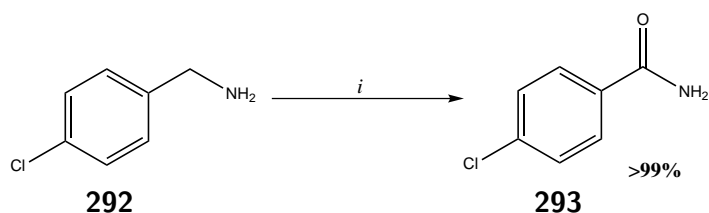
Scheme 2.19: Reaction conditions: *i)* MnO_2, 4 Å MS, CH_2Cl_2, 40 °C, 24 h.

As the reaction does not need to be carried out in a sealed vessel, the reaction mixture could be sampled at any time point during the reaction to monitor the progress of the amide formation by ^{1}H-NMR analysis. After a reaction time of one hour, all the major intermediate products proposed by Wang[156] could be identified in the ^{1}H-NMR spectrum (Figure 2.23). Aldehyde **296** was only visible in traces whereas the other intermediates, alkylimine **295** and nitrile **294**, were observed as intense signals.
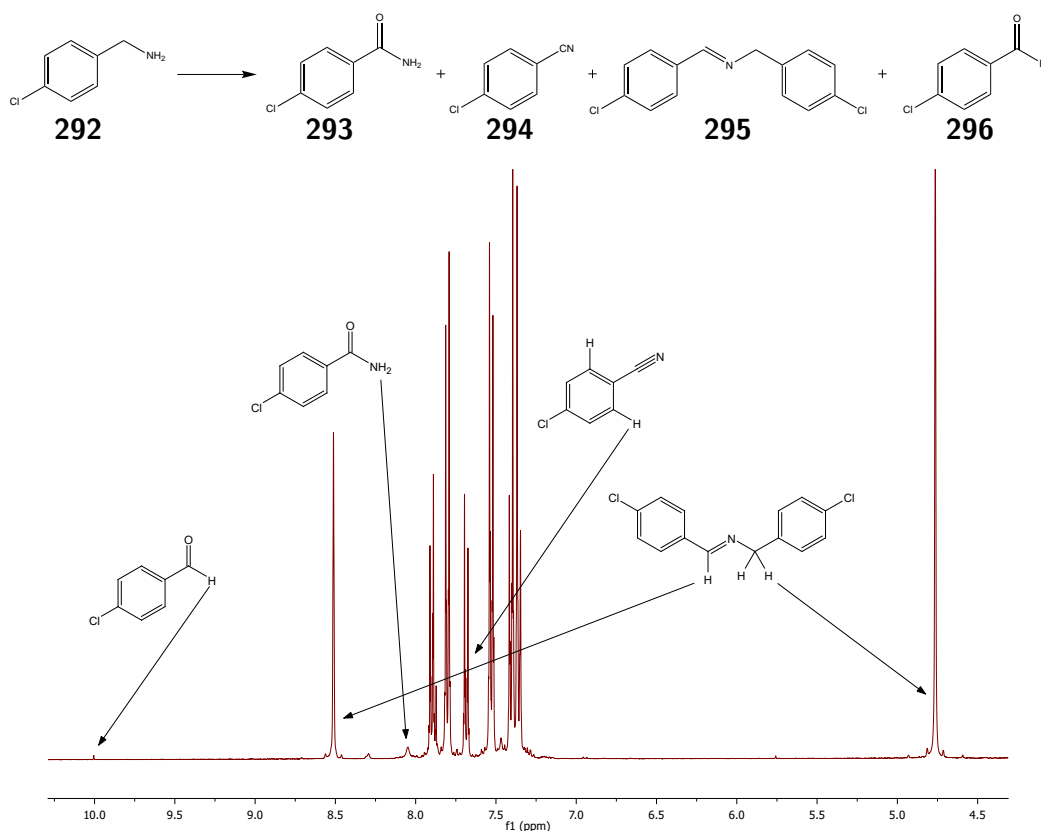
Figure 2.23: Intermediate products in the oxidation of 4-chlorobenzylamine to 4-chlorobenzamide after a reaction time of one hour.

To follow the conversion of these intermediates to the amide, samples were taken at further time points (Figure 2.24). After one hour, a small amount of amide **293** had formed and it increased gradually as the signals for alkylimine **295** decreased (the methylene protons of the alkylimine appear at 4.76 ppm, Figure 2.23). Nitrile **294** could only be detected in the first spectrum after one hour, suggesting that its hydration to the amide happens rapidly. After a reaction time of 24 h, a complete conversion to amide **293** had taken place and no signals of the intermediate products were observed.
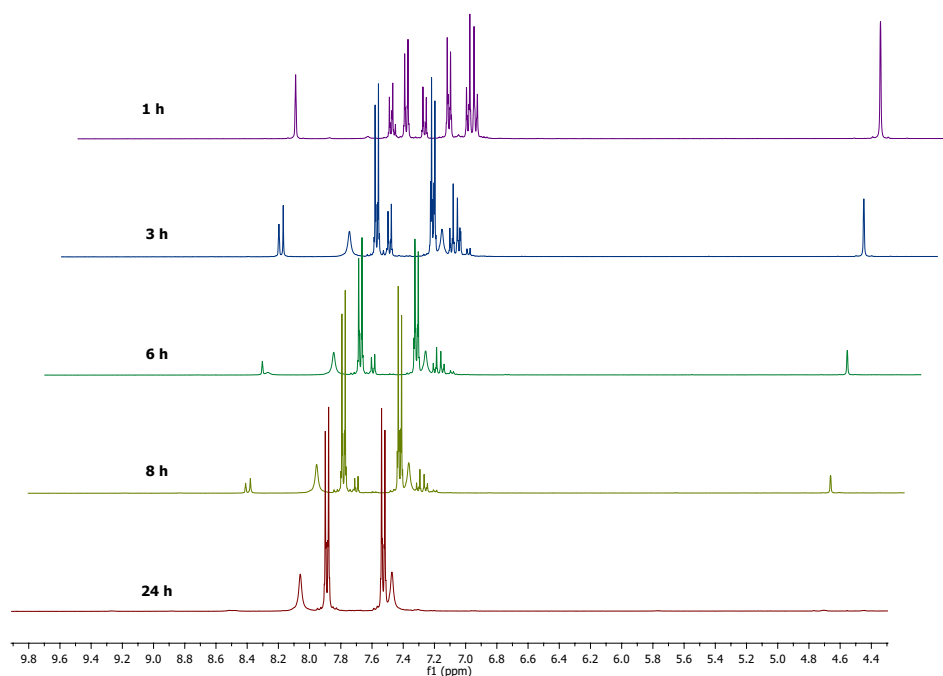
Figure 2.24: NMR-investigation experiment for the transformation of amine **292** to amide **293**.

To further probe the mechanism of the MnO_2 mediated amide formation, a range of reaction conditions was investigated (Figure 2.25, Table 2.12). Under the standard reaction conditions, 4-chlorobenzylamine **292** was quantitatively converted to its corresponding amide **293** (Table 2.12, entry 1). It is noteworthy that not only MnO_2 from *Alfa Aesar*, but also the acid-treated MnO_2 from *Sigma Aldrich* achieved a quantitative conversion to the amide.
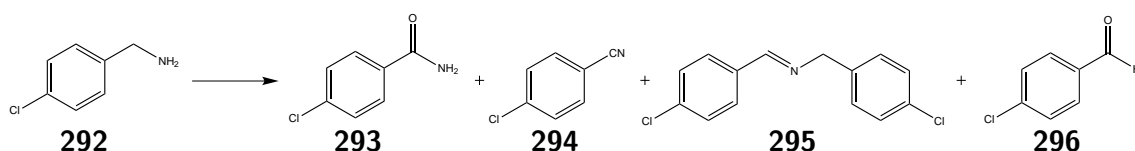
Figure 2.25: Oxidation of 4-chloro-benzylamine **292** using MnO_2.

In order to investigate the role of the molecular sieves, the reaction was carried out in their absence (Table 2.12, entry 2). The yield of the amide obtained under these conditions was low (44%), with considerable nitrile **294** (16%) and alkylimine **295** (36%) formation. We believe that the molecular sieves play a crucial role in the reaction

by preventing the inactivation of the manganese dioxide's surface due to its ability to capture excess water from the reaction mixture. Without the molecular sieves, the MnO_2 mediated oxidative conversion of the unstable aldimine to nitrile **294** is less efficient, which is demonstrated by the formation of alkylimine **295**. Obtaining nitrile **294** as product further means that without the added molecular sieves, the hydration to the amide product is incomplete.

Employing untreated MnO_2, which was used as received from the vendor, resulted in a drop yield of the desired amide **293** to 63% (Table 2.12, entry 3). This demonstrates that pre-treatment of the oxidant is vital for the performance of MnO_2 as an oxidant in this reaction. Decreasing the amount of MnO_2 in the reaction to 12.5 equivalents also resulted in a significantly reduced amide formation, with nitrile **294** and alkylimine **295** having formed as well (entry 4). Hereby it is shown that when less MnO_2 is present, the hydration of nitrile **294** can not proceed to completion. Furthermore, under these conditions the unstable aldimine is not fully converted to nitrile **294** and is hydrolysed to aldehyde **296**, ultimately leading to the formation of alkylimine **295**.

Table 2.12: Summarising table for the effects of various reaction conditions on the MnO_2-mediated transformation of **292** to **293**.

Entry	Conditions[b]	Yield (%)[a]			
		293	**294**	**295**	**296**
1	Standard conditions	99	≤1	≤1	≤1
2	No molecular sieves	44	16	36	3
3	Untreated MnO_2	63	≤1	37	≤1
4	12.5 equiv. MnO_2	56	17	24	3
5	Under N_2 atmosphere	71	≤1	29	≤1
6	Recycled MnO_2	73	≤1	27	≤1
7	Aqu. NH_3, untreated MnO_2	66	≤1	33	≤1
8	NH_3 in THF, untreated MnO_2	70	24	5	≤1
9	NH_3 in THF, no molecular sieves	77	23	≤1	≤1

[a] Yields were determined by ^{1}H-NMR analysis.
[b] Standard reaction conditions: amine **292** (0.5 mmol), acid-washed MnO_2 (25 equiv), 4 Å molecular sieves, CH_2Cl_2 (3.5 mL), 40°C, 24 h

Carrying out the reaction under an inert nitrogen atmosphere (Table 2.12, entry 5), resulted in amide **293** being formed in a yield of 71%, indicating that it is not oxygen coming from the air, but rather oxygen bound to the surface of MnO_2 which achieves the

oxidation.[151] Although employing recycled MnO_2 in this reaction resulted in a reduced yield of amide **293** (entry 6), the distribution of products was simpler compared to when a smaller amount of MnO_2 was used (entry 4). Only a trace of nitrile **294**, but a considerable amount of alkylimine **295** was formed. This means that although the recycled MnO_2 achieves a complete hydration of nitrile **294** to the amide, a lack in oxygen on the surface of MnO_2 prevents a complete conversion of the the unstable aldimine to nitrile **294**. The aldimine is therefore hydrolysed to aldehyde **296** and consequently converted to alkylimine **295**.

The addition of aqueous ammonia in combination with untreated MnO_2 did not significantly improve the yield of the amide (entry 7), compared to when untreated MnO_2 was used (entry 3). This is in contrast to the results obtained by Wang, who reported that without the addition of aqueous ammonia, alkylimine **295** was obtained as the major product.[156] Under our reaction conditions, the addition of aqueous ammonia results in a biphasic solvent system, due to the immiscibility of dichloromethane with water. The ammonia molecules are therefore highly solvated in the aqueous phase which means that the ammonia is not able to transfer to the organic phase and participate in the reaction.

To avoid these shortcomings, the experiment was repeated using a 0.5 M solution of ammonia in tetrahydrofuran (entry 8). The yield for amide **293** was only modestly increased (70%), in addition to a change in the product distribution. While alkylimine **295** was the major intermediate product observed in the presence of aqueous ammonia (entry 7), nitrile **294** was favourably formed when using 0.5 M ammonia in tetrahydrofuran (entry 8). The ammonia in the reaction mixture is competing with amine **292** to react with aldehyde **296**. If an excess of ammonia is present, the aldehyde is more likely to react to nitrile **294** *via* the unstable aldimine than to alkylimine **295**, which also explains the considerable amount of nitrile which was observed in this experiment (entry 8). When aqueous ammonia is used in the reaction (entry 7), no such excess of ammonia is available, therefore aldehyde **296** rather reacts with amine **292**, leading to the observed formation of alkylimine **295**.

A similar product distribution was also obtained when the experiment was repeated

with 0.5 M ammonia in tetrahydrofuran using activated MnO_2 without added molecular sieves (entry 9). As there was also a considerable amount of nitrile **294** formed in this experiment, we believe that the excess of ammonia in this reaction interacts with the MnO_2 in a way that reduces its ability to hydrate the nitrile.

Conversion of the Reaction Intermediates to the Amide

In order to further investigate the MnO_2 mediated oxidation process, the intermediates alkylimine **295** and **220** were synthesised in quantitative yield by condensation of their corresponding amine and aldehyde (Scheme 2.20).
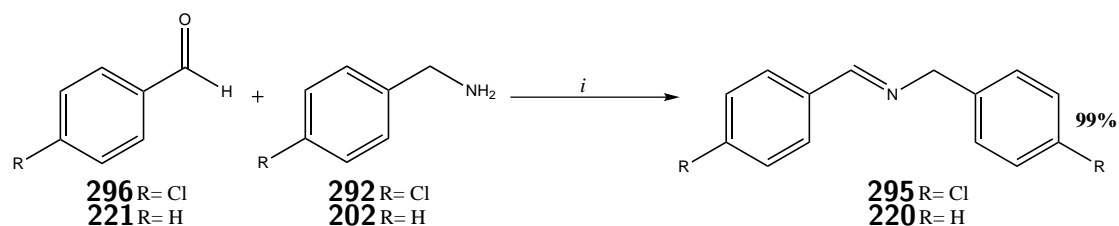
Scheme 2.20: Reaction conditions: *i)* 4 Å MS, CH_2Cl_2, 40 °C, 1.5 h.

Alkylimine **295** was reacted with MnO_2 under the standard reaction conditions and amide **293** was obtained in a yield of 95% (Scheme 2.21), thereby demonstrating that alkyminine **295** can be hydrolysed back to amine **292** and aldehyde **296**, rendering it possible for the amine to undergo the MnO_2 facilitated oxidation to the amide. Unlike Wang's observations, where additional ammonia was required to convert the alkylimine to the amide,[156] in our experiment no external source of ammonia was needed to achieve this conversion.
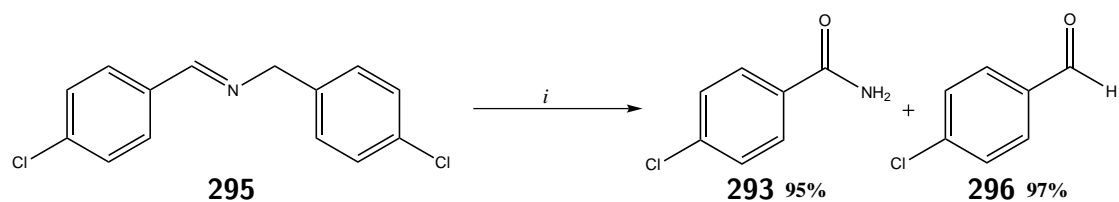
Scheme 2.21: Reaction conditions: *i)* MnO_2, 4 Å MS, CH_2Cl_2, 40 °C, 24 h.

In a further experiment (Scheme 2.22), nitrile **294** was reacted under the same conditions and afforded amide **293** in quantitative yield within only two hours. This result supports

the data that was obtained from the NMR-investigation experiment earlier (Figure 2.24) and shows that nitrile **294** is rapidly converted to the final amide. Wang reported a yield of 70% for the amide when reacting the nitrile in the presence of aqueous ammonia under their standard reaction conditions. However, adding pure water to this reaction instead of the aqueous ammonia decreased the yield of the amide to 36%.[156]
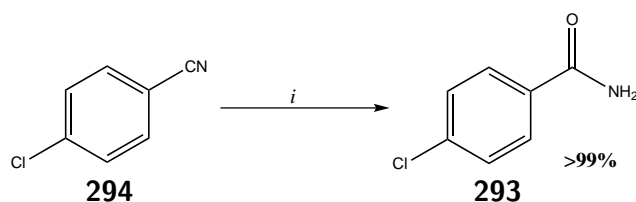
Scheme 2.22: Reaction conditions: *i)* MnO_2, 4 Å MS, CH_2Cl_2, 40 °C, 2 h.

An interesting observation in this context is that even though the conversion from the nitrile to the amide happens *via* hydration, the addition of water-scavenging molecular sieves used in our standard reaction conditions seems to be important for complete conversion to amide **293** (Table 2.12, entry 2). We believe that the water necessary for the hydration of the nitrile is not provided by the solvent, but by MnO_2. The molecular sieves capture water from the solvent environment and therefore prevent deactivation of the MnO_2. On the contrary, water bound to the surface of MnO_2 is not affected by added molecular sieves and can thus still take part in the hydration process.[155]

Reacting aldehyde **296** with activated MnO_2 and ammonia (0.5 M in THF, 1.5 equiv) gave amide **293** in quantitative yield both in the presence and absence of molecular sieves (Scheme 2.23) thereby showing that an external source of ammonia can be used to convert the aldehyde back to amide **293**.
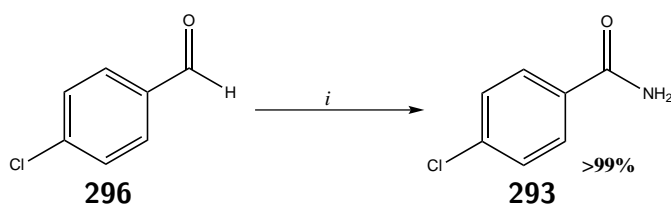
Scheme 2.23: Reaction conditions: *i)* MnO_2, NH_3, CH_2Cl_2/THF (1.7:1), 40 °C, 24 h.

The Dual Role of Manganese Dioxide

From the previous experiments we concluded that MnO_2 not only acts as a catalyst in the oxidation processes, but also serves as a source of water during the reaction. As the molecular sieves remove water from the reaction mixture, it is the water bound to the surface of the MnO_2[151] which facilitates the hydrolysis of alkylimine **295** to the aldehyde **296** and consequently the hydration of the nitrile **294** to the final amide product. Furthermore, if only oxygen from the air was used to achieve the oxidative dehydration of amine **292** to nitrile **294** *via* the unstable aldimine, no amide formation would be observed in a reaction under an inert nitrogen atmosphere (Table 2.12, entry 5).This indicates that the oxygen consumed during the reaction is originating from the surface of activated MnO_2. If there is insufficient oxygen available, for example when reused MnO_2 is employed (Table 2.12, entry 6), the remaining aldehyde intermediate is locked away as the easily formed alkylimine.

The Role of the Molecular Sieves

The 4 Å molecular sieves used in this reaction are microporous alumino-silicate zeolites bearing Brønsted acidic sites.[191] In addition to water, other molecules with a diameter smaller than 4 Å can be adsorbed within the pores of this material. Ammonia is known to be adsorbed on the surface of these zeolites as the ammonium ion NH_4^+.[192,193]

When ammonia is released upon the formation of aldehyde **296** from the unstable aldimine, ultimately leading to the formation of alkylimine **295**, it must be available for the reaction back as well, otherwise quantitative formation of amide **293** would not be observed. We believe that the molecular sieves play a crucial role in this process and prevent the loss of ammonia from the reaction mixture by acting as a storage and making the ammonia available for the reaction with the aldehyde back to nitrile **294**. Hence, through a dual mode of action, the molecular sieves render the ammonia available throughout the reaction process and furthermore retain excess water to prevent the inactivation of the MnO_2 surface.

When an excess of ammonia was added to the reaction with aldehyde **296**, the amide product was obtained in quantitative yield both in the presence and absence of molecular sieves (Scheme 2.23). We believe that in this case the molecular sieves are not vital for a complete conversion to the amide, since with the increased availability of ammonia in the reaction mixture, there is no need for its storage throughout the reaction process.
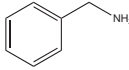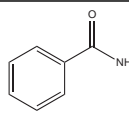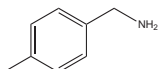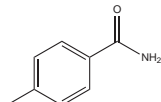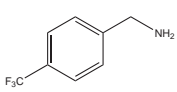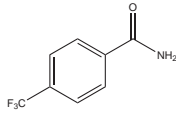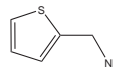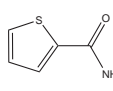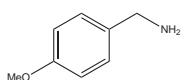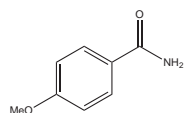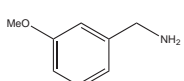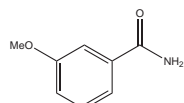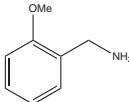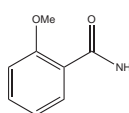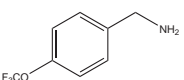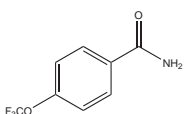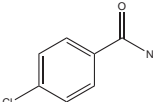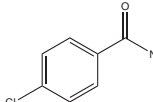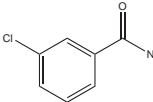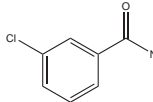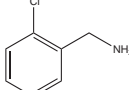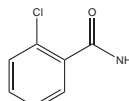
Synthesis of Further Analogues

A diverse range of amides has been synthesised according to our protocol (Table 2.13). The products were obtained after filtration of the reaction mixture with hot methanol followed by evaporation of the solvent. In some cases it was not necessary to further purify the crude residue since pure product was obtained. If small amounts of by-products were present, it was sufficient to wash the crude residue with a few millilitres of hexane. The amide products are practically insoluble in hexane, which allows a selective dissolution of the nitrile, alkylimine and aldehyde by-products. In only a few cases was column-chromatography required.

For most amide products the yields are good to excellent. When benzylic amines with a methoxy substituent were used in this reaction (entry 5-7), lower yields of the corresponding amides were obtained compared to when substrates with a chloro substituent on the benzyl moiety were employed (entry 9-11). The lowest yield was obtained when the methoxy substituent was placed in the *ortho* position on the aromatic ring (entry 7). In this case, 2-methoxybenzonitrile was also isolated in a 28% yield. We believe that the hydration of this particular nitrile substrate takes place more slowly due to steric hindrance and therefore causes the comparatively lower yield of amide **308** after 24 hours. When the aliphatic amine octylamine was subjected to these reaction conditions, no amide product was formed.

When the reaction was carried out on a larger scale, using 19 mmol of benzylamine **202**, the yield of the amide product was not significantly affected. Benzamide **276** was obtained in a yield of 96% as compared to a yield of 98% on a 1 mmol scale, thereby further demonstrating the synthetic utility of this protocol.

Table 2.13: Summarising table for the transformation of primary benzylic amines to primary amides.

Entry	Substrate	Product[a]	Yield (%)[b]
1	**202**	**276**	98
2	**297**	**298**	98
3	**299**	**300**	87
4	**301**	**302**	98
5	**303**	**304**	93
6	**305**	**306**	83
7	**307**	**308**	69
8	**309**	**310**	89
9	**292**	**293**	99
10	**311**	**312**	92
11	**313**	**314**	83

[a] Standard reaction conditions: amine substrate, acid-washed MnO_2, 4 Å molecular sieves, CH_2Cl_2, 40°C, 24 h

[b] Isolated yield.

2.3 Studies Towards the Synthesis of Donepezil Analogues

Having prepared aliphatically and aromatically 2-substituted, diastereomeric 1-α-phenylethyl-4-piperidones **315**, we set about incorporating these building blocks into the AChE inhibitor donepezil **12** to obtain analogues **316** with modified biological activity (Figure 2.26). Initially, experiments would utilise both diastereomers of the methyl as well as the phenyl substituted piperidone **315** and the AChE inhibition potency of analogues **316** would be evaluated relative to donepezil.
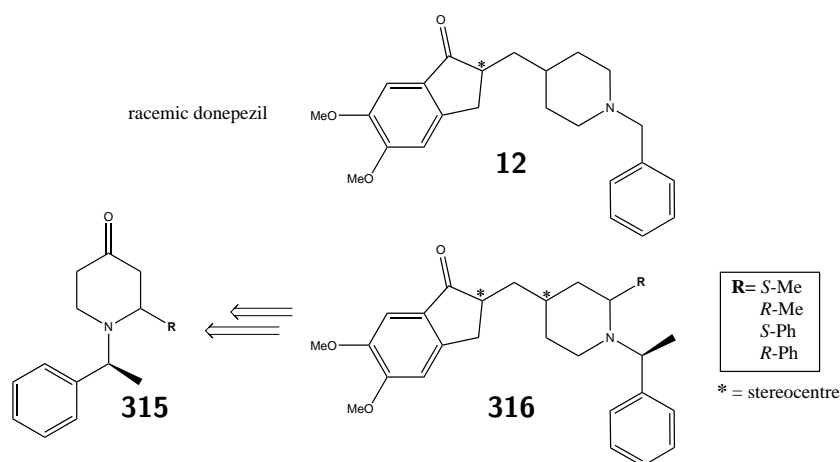
Figure 2.26: Incorporation of chiral piperidones **315** into donepezil **12** for the synthesis of analogues **316**.

1-Benzyl-4-formyl-piperidine **319** is an important building block in the synthesis of donepezil. This aldehyde is unstable, therefore its easy and clean preparation is particularly relevant for the overall cost-efficient synthesis of donepezil. Sugimoto[194] described the synthesis of this vital reagent from commercially available 1-benzyl-4-piperidone **317** (Scheme 2.24). The piperidone is subjected to a Wittig reaction to give methoxymethylene intermediate **318**, followed by hydrolysis under acidic conditions to desired aldehyde **319**.
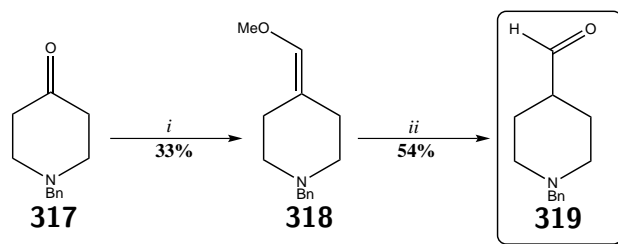
Scheme 2.24: Reaction conditions: *i)* $((Ph_3)PCH_2OCH_3)Cl$, *n*-BuLi, Et_2O, rt→0 °C→rt, 3 h; *ii)* MeOH/1 M HCl 1:1, reflux, 3 h.

An alternative route to aldehyde **319** was described by Niphade[195] (Scheme 2.25). Commercially available carboxylic ester **320** is firstly benzylated to give **321**, followed by a reduction with the organoaluminium compound Vitride® to alcohol **322**. A final Swern oxidative step leads to the formation of the target aldehyde in an overall yield of 67%.
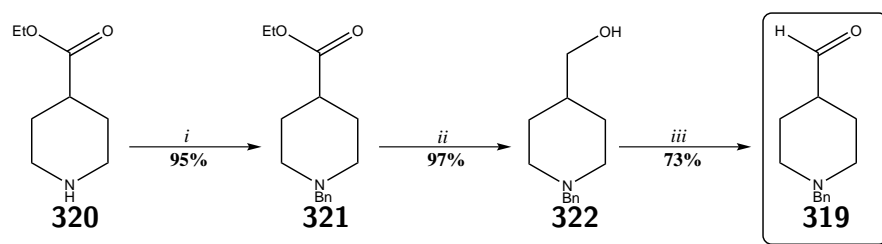
Scheme 2.25: Reaction conditions: *i)* BnCl, TEA, toluene, 75 °C, 7 h; *ii)* Vitride®, toluene, 15 °C, 3 h; *iii)* $(CO_2)Cl_2$/DMSO, TEA, CH_2Cl_2, -60 °C→-70 °C, 5 h.

Sheng and Hu[196] reported a route consisting of only two steps and a high overall yield of 82% (Scheme 2.26). Again, 1-benzyl-4-piperidone **317** is used as starting material and transformed to epoxide **323** *via* a Corey-Chaykovsky reaction, followed by a Meinwald rearrangement of the epoxide to give the desired aldehyde.
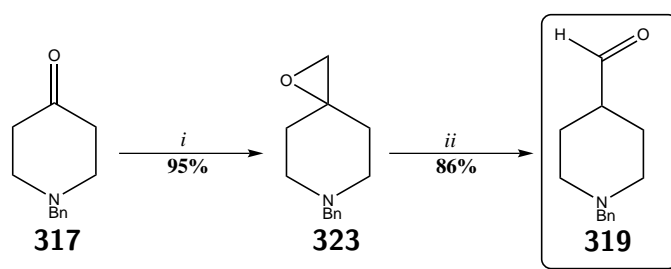
Scheme 2.26: Reaction conditions: *i)* TBAB, $(CH_3)_3S^+OI^-$, NaOH, toluene/water 3.3:1, 80 °C, 4 h; *ii)* $MgBr_2 \cdot OEt_2$, toluene, 40 °C, 20 min.

It was envisioned that when following either Sugimoto's[194] or Sheng's[196] route (Scheme 2.24, Scheme 2.26), not only *N*-benzyl-4-piperidinone **317**, but also 2-substituted piperidones **315** could be converted into their corresponding aldehydes to serve as building blocks for the synthesis of donepezil analogues **316** (Figure 2.26).

The synthesis of donepezil was first reported by Sugimoto[120,194] (Scheme 2.27). Aldol condensation of 5,6-dimethoxy-1-indanone **324** and aldehyde **319** gives enone **325** (62%), hydrogenation of which over a palladium catalyst yields racemic donepezil as its hydrochloride salt **326** (86%).
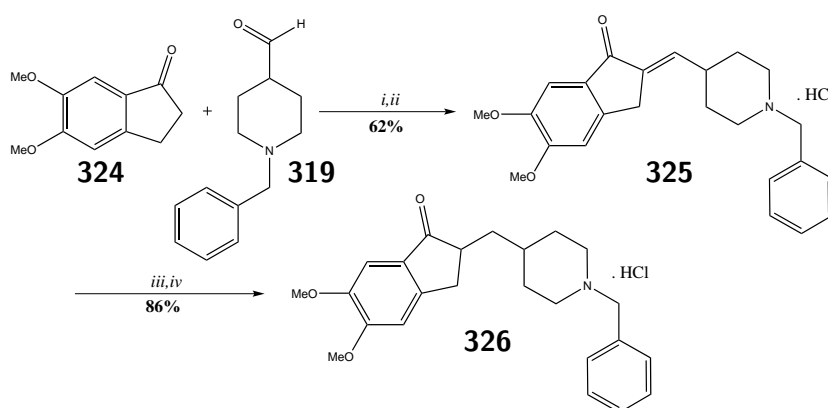
Scheme 2.27: Reaction conditions: *i)* *n*-BuLi/THF/hexamethylphosphoric triamide (HMPA), -78 °C to rt, 2 h; *ii)* 10% HCl-EtOAc; *iii)* 10% Pd-C, H$_2$, THF, rt, 6 h; *iv)* 10% HCl-EtOAc.

2.3.1 Access to Aldehyde Building Blocks *via* Epoxidation and Rearrangement of 4-Piperidones

The initial efforts towards the synthesis of chiral 2-substituted 1-benzyl-4-formyl-piperidine building blocks were undertaken following Sheng's[196] route, as it consists of only two steps in high overall yield (Scheme 2.26).

Epoxidation of 4-Piperidones

The first step in the synthesis is a Corey-Chaykovsky epoxidation,[197] where a methylide nucleophile **329** is generated by the deprotonation of trimethylsulfoxonium iodide **327** by a base (Figure 2.27).
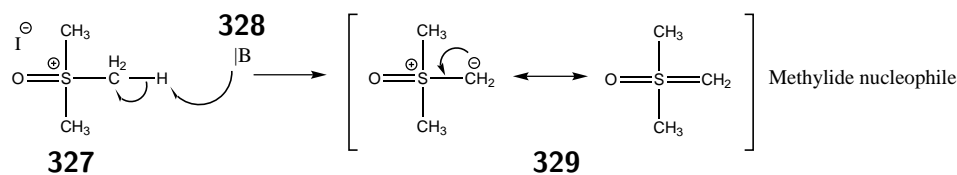
Figure 2.27: Formation of methylide nucleophile **329**.

In Sheng's procedure, which uses a mixture of toluene and aqueous NaOH, a phase transfer catalyst facilitates the deprotonation step. Dropwise addition of the aqueous NaOH is necessary to achieve a better dispersion of the aqueous droplets, thereby ensuring a gradual TBAB aided transfer of the base to the organic phase.

When piperidone **317** was subjected to these conditions, analysis of the crude ^{1}H-NMR spectrum showed that after 4 h, 90% of product **323** had formed while 10% of the starting material remained (Scheme 2.28). Not only to further improve the conversion rate, but also because the dropwise addition of aqueous NaOH was found impractical, the literature was searched for an alternative procedure.
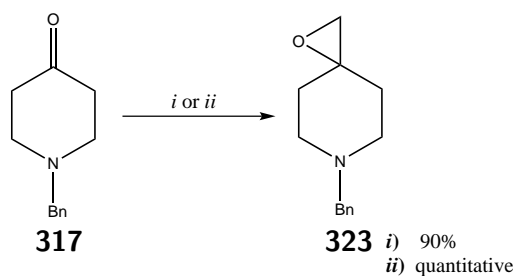
Scheme 2.28: Reaction conditions: *i)* TBAB, $(CH_3)_3S^+OI^-$, NaOH, toluene/water 3.3:1, 80 °C, 4 h; *ii)* $(CH_3)_3S^+OI^-$ and *t*-BuOK premixed (1:1), DMSO, 55 °C, 50 min.

Ciaccio[198] reported the epoxidation of various ketones and aldehydes in high yields using a modified version of the standard Corey-Chaykovsky reaction procedure which employs potassium *t*-butoxide as the base. *t*-Butoxide is a solid and can be conveniently pre-mixed with the trimethylsulfoxonium iodide salt and then stored for prolonged periods of time without loss of activity.[198] When **317** was reacted with this mixture at 55 °C in DMSO, a complete conversion to epoxide **323** was observed within 50 minutes (Scheme 2.28). Since this protocol required a lower reaction temperature, a shorter reaction time and was overall more practical, we decided to apply this method to the preparation of 2-substituted epoxide analogues. The 2-methyl and 2-phenyl substituted

enantiomeric piperidones **241** and **242** were epoxidised and obtained as inseparable mixtures of stereoisomers in 68% and 65% isolated yield, respectively (Scheme 2.29).
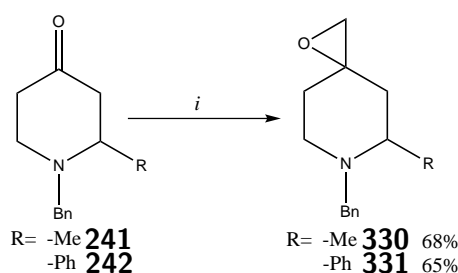
Scheme 2.29: Reaction conditions: *i)* $(CH_3)_3S^+OI^-$ and *t*-BuOK premixed (1:1), DMSO, 55 °C, 50 min.

When diastereomer 2*R*-**259** was subjected to these epoxidation conditions, the formation of a minor and a major epoxide product was observed (Scheme 2.30). From the analysis of the crude ^{1}H-NMR spectrum the diastereomeric mixture was a 1:3 ratio of **332**:**333**. The two epoxides **332** and **333** could be separated by column chromatography and were obtained in 11% and 47% yield, respectively.
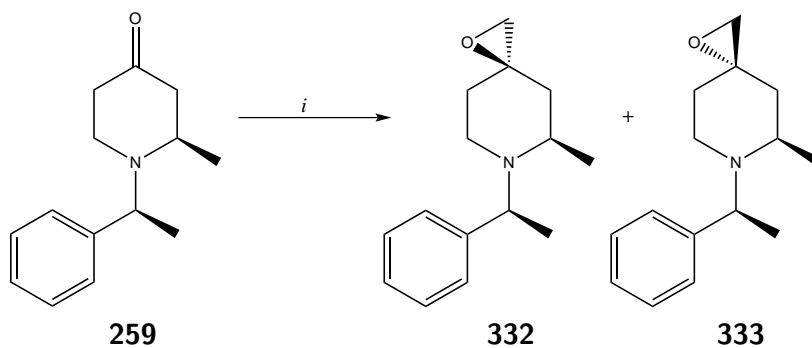
Scheme 2.30: Reaction conditions: *i)* $(CH_3)_3S^+OI^-$ and *t*-BuOK premixed (1:1), DMSO, 55 °C, 60 min.

The rationale for the assignment of the correct stereochemistry of epoxide products **332** and **333** is depicted in Figure 2.28. An attack at the carbonyl group of piperidone **334** is possible from both faces, but due to 1,3-diaxial interactions, axial addition of a large nucleophile such as the methylide is less favoured. An equatorial attack is less hindered and results in the formation of epoxide 2*R*,4*S*-**338** as the major product. The chirality of the stereocenter in position 4 on the piperidine ring of epoxides **332** and **333** (Scheme 2.30) was assigned in analogy to this model.
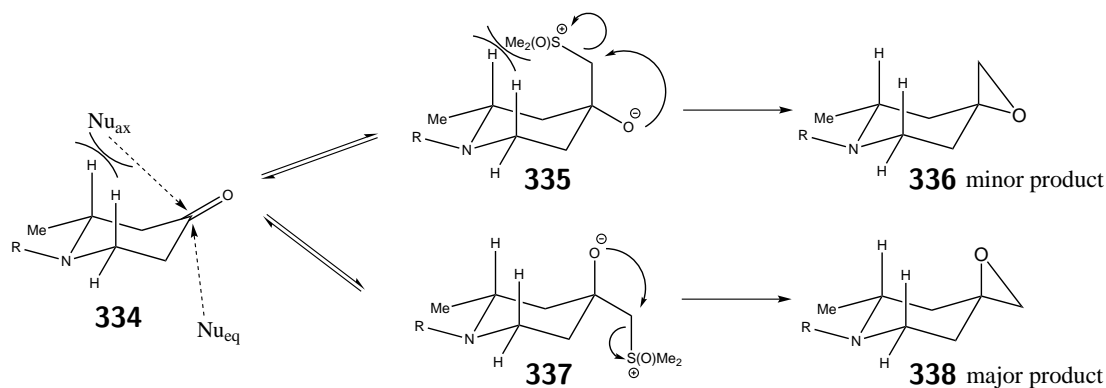
Figure 2.28: Rationale for the preferred equatorial attack of methylide **329**.

Having achieved the epoxidation of simple 1-benzyl-4-piperidone as well as chiral 2-methyl and 2-phenyl substituted piperidones, the next step in the synthesis, a Meinwald rearrangement, was investigated.

Meinwald Rearrangement of Epoxides to Aldehydes

A Meinwald rearrangement is a Lewis acid catalysed reaction in which an epoxide is converted to an aldehyde or ketone.[199] The proposed mechanism of this rearrangement process involves Lewis acid activation of **339**, the epoxide ring opening of **340** and the formation of intermediate **341**, which bears a tertiary carbocation in position 4 on the piperidine ring (Figure 2.29). A subsequent 1,2-hydride shift, followed by aqueous work-up yields aldehyde product **343**.
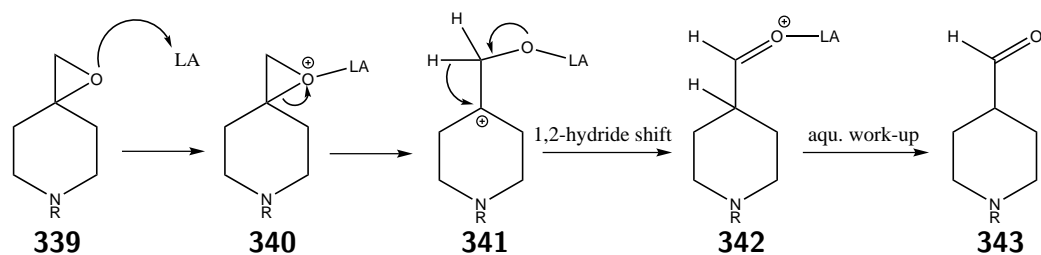
Figure 2.29: Mechanism for the Meinwald rearrangement of epoxide **339** to aldehyde **343**.

Sheng[196] reacted epoxide **323** in the presence of the Lewis acid magnesium bromide etherate and upon distillation of the crude reaction mixture, obtained the rearranged *N*-benzyl-4-formyl-piperidine **319** in a yield of 83% (Scheme 2.31). Repeating Sheng's

rearrangement protocol of epoxide **323**, analysis of the crude ^{1}H-NMR spectrum showed that approximately 40% of the epoxide had been converted to the aldehyde, while there was still unreacted starting material present (18%), in addition to two unidentified byproducts (18% and 25%) (Scheme 2.31). While the separation of the epoxide starting material by column chromatography was possible, aldehyde **319** was only obtained in a yield of 27% due its instability on silica.
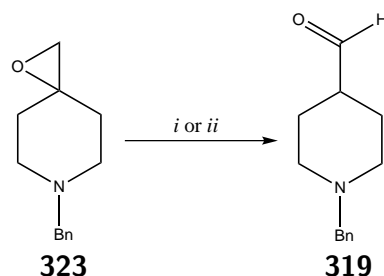
Scheme 2.31: Reaction conditions: *i)* $MgBr_2 \cdot OEt_2$, toluene, 40 °C, 20 min; *ii)* $MgBr_2 \cdot OEt_2$, toluene, 40 °C, 4 Å MS, N_2, 30 min.

When the reaction was carried out under an atmosphere of nitrogen in the presence of molecular sieves, epoxide **323** was found to be completely consumed as determined by TLC. Analysis of the crude ^{1}H-NMR spectrum showed that an improved 59% of aldehyde **319** were present, accompanied by the same two unknown byproducts that were observed under the previous reaction conditions. Upon reduced pressure distillation of the crude material, due to the decomposition of the unstable aldehyde **319**, only 19% of pure product could be isolated.

When this procedure was applied to 2-methyl and phenyl substituted epoxides **330** and **331**, the formation of the corresponding aldehydes did not occur (Scheme 2.32). The crude ^{1}H-NMR spectra showed only traces of the characteristic aldehyde proton and considerable starting material remained alongside an unidentified byproduct. When **330** was subjected to the rearrangement conditions for an extended reaction time of 4 h, all epoxide starting material was consumed, but only traces of aldehyde **344** were found in the crude spectrum. The same reaction at room temperature gave a similar result, with unreacted starting material present in the crude mixture. Although the byproduct observed in these experiments was not isolated, we believe that epoxide **330**

was hydrolysed under the acidic conditions, possibly leading to the formation of the corresponding diol.[200,201]

R= -Me **330**
 -Ph **331**

R= -Me **344**
 -Ph **345**
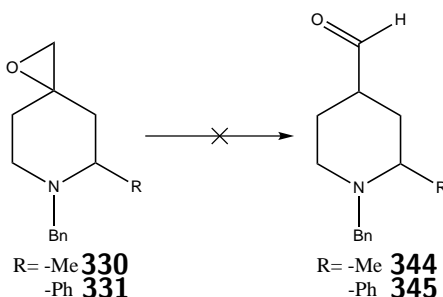
Scheme 2.32: Attempted synthesis of aldehydes **344** and **345**.

To identify whether the formation of the unidentified byproduct also occured in the presence of a different Lewis acid catalyst, boron trifluoride etherate was investigated for its utility in this rearrangement reaction. Although the use of boron trifluoride etherate has been reported in similar epoxide-opening reactions,[202,203] it was not effective for the rearrangement of epoxide **330** in dichloromethane both at 0 °C and at room temperature. Analysis of the ^{1}H-NMR spectra of the crude residues showed a complex mixture of products, while the byproduct which had been observed earlier, when using magnesium bromide etherate, was not detected under these conditions.

Despite the successful synthesis of 1-benzyl-4-formyl-piperidine **319** according to Sheng's protocol, the same methodology was found unsuitable for the rearrangement of 2-substituted epoxides under various tested conditions. It was therefore decided that another route should be investigated in order to achieve the synthesis of the desired aldehyde intermediates for the further synthesis of donepezil analogues.

2.3.2 Access to Aldehyde Building Blocks from 4-Piperidones *via* Wittig Reaction and Enol Ether Hydrolysis

Sugimoto[194] describes an alternative route towards the synthesis of 1-benzyl-4-formyl-piperidine **319** from 1-benzyl-4-piperidone **317** *via* a Wittig reaction and acidic deprotection (Scheme 2.33). The reported yields for these transformations are low to moderate (33% and 54%) and purification by column chromatography of aldehyde **319** is necessary to obtain pure product.
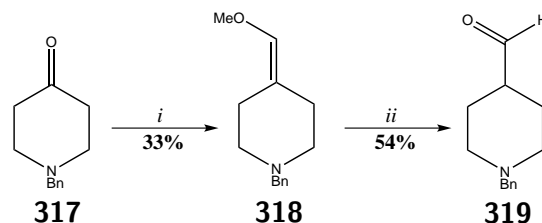
Scheme 2.33: Reaction conditions: *i)* $((Ph_3)PCH_2OCH_3)Cl$, *n*-BuLi, diethyl ether, rt→0 °C→rt, 3 h; *ii)* MeOH/1 M HCl 1:1, reflux, 3 h.

Meyer[204] subjected cyclohexanone derivative **346** to a Wittig-Horner reaction using the phosphine oxide methoxymethyldiphenylphosphine to give intermediate **347**; treatment with trifluoroacetic acid in water and tetrahydrofuran yielded aldehyde **348** (Scheme 2.34). Although the yield for the first synthetic step is high (72%), the method uses the comparatively more expensive methoxymethyldiphenylphosphine as well as carcinogenic HMPA as a co-solvent.
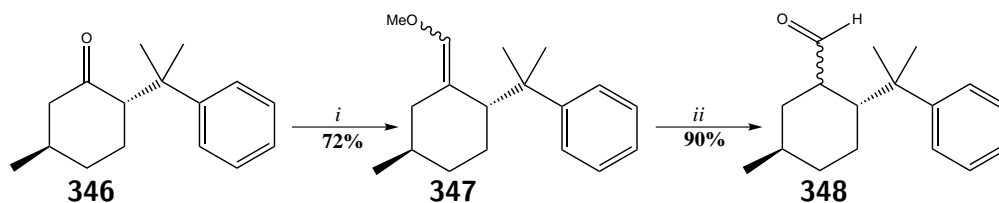
Scheme 2.34: Reaction conditions: *i)* $(Ph)_2P(O)CH_2OCH_3$, LDA, HMPA, THF, 0 °C→rt→reflux, 2 h; *ii)* TFA, THF/water 50:1, reflux, 15 h.

In another example a similar Wittig conversion of piperidone **349** to intermediate **350** is achieved in 57% yield and after acidic deprotection under mild conditions, aldehyde **351** is obtained in quantitative yield (Scheme 2.35).[205]
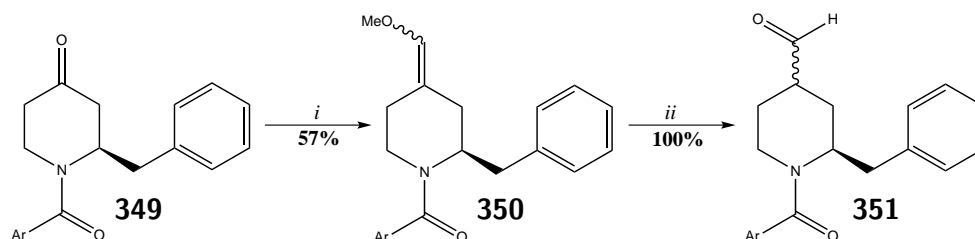
Scheme 2.35: Reaction conditions: *i)* $((Ph_3)PCH_2OCH_3)Cl$, LDA, THF, rt→-25 °C→rt, overnight; *ii)* 1.6 M HCl, H_2O/THF 1:1, 40 °C, 1 h.

Wittig Reaction of 4-Piperidones to 4-Methoxymethylene-piperidines

To prepare methoxymethylene piperidine **318**, piperidone **317** was subjected to a Wittig reaction using methoxymethylene triphenylphosphonium chloride and lithium diisopropylamide (Scheme 2.36). Analysis of the crude ^{1}H-NMR spectrum showed that the Wittig product had formed, but only in low yield (41%), while the rest of the mixture contained unreacted piperidone. In this experiment the characteristic color change, indicating a successful ylide formation, was not observed and we believe that this was due to the low temperatures which had been maintained throughout the reaction.
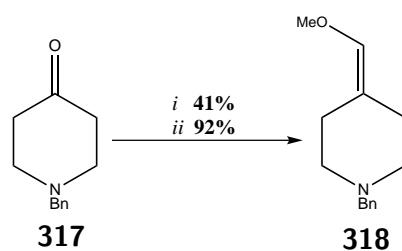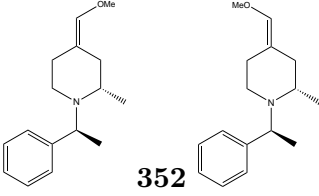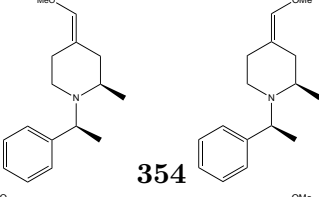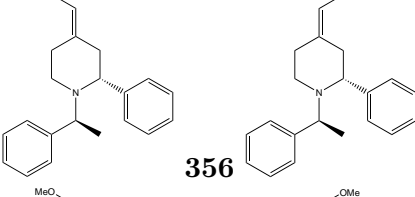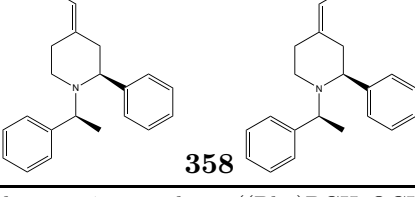
Scheme 2.36: Reaction conditions: *i)* $((Ph_3)PCH_2OCH_3)Cl$, LDA, THF, -78 °C→0 °C, 1 h; *ii)* $((Ph_3)PCH_2OCH_3)Cl$, LDA, 4 Å MS, THF, -78 °C→rt→-20 °C→rt, 16 h.

In an example from the literature[205] (Scheme 2.35) the reaction was allowed to warm to room temperature after the addition of lithium diisopropylamide to the Wittig salt had been completed. Repeating the experiment, upon warming the ylide salt from -78 °C to room temperature, we observed the development of the characteristic red color (Scheme 2.36). A slight excess of the phosphonium salt and the base was used (1.5 equiv) to provide a sufficient amount of yilde, moreover molecular sieves were added to ensure anhydrous conditions. During the subsequent addition of piperidone substrate **317**, the mixture was cooled to -20 °C and then warmed to room temperature. The addition of the piperidone resulted in a gradual discolouration of the mixture and stirring for a prolonged period of time (16 h) afforded the desired Wittig product **318** in an isolated yield of 92%.

This protocol was also used for the synthesis of chiral methoxymethylene products, bearing a methyl or phenyl substituent on the piperidine ring (Table 2.14). The *cis* and *trans* products were obtained in good to excellent combined yields (75-97%) and it was possible to partially separate the stereoisomers by column chromatography in all cases.

Table 2.14: Combined yields and product ratios for the synthesised methoxymethylene piperidines.

Entry	Substrate	Products[a]		Yield (%)[b]	Ratio[c]
1	2S-**258**	**352**	**353**	90	***Z:E*** 1.21:1.00
2	2R-**259**	**354**	**355**	75	***Z:E*** 1.23:1.00
3	2R-**262**	**356**	**357**	97	***Z:E*** 1.00:1.03
4	2S-**263**	**358**	**359**	78	***Z:E*** 1.06:1.00

[a] Standard reaction conditions: 4-piperidone, $((Ph_3)PCH_2OCH_3)Cl$, LDA, 4 Å MS, THF, -78 °C→rt→-20 °C→rt, 16 h.

[b] Isolated combined yield.

[c] *Entry 1-3:* Ratio of products was determined by analysis of the crude ^{1}H-NMR spectra. *Entry 4:* Ratio was determined by isolation of the products.

The obtained product ratios were determined by analysis of the crude ^{1}H-NMR spectra, with a slight preference towards the formation of *cis*-isomers being observed for the methyl substituted products (entry 1 and 2), while the phenyl substituted products formed without preference (entry 3 and 4). The partial separation of the two isomers of all substrates allowed the unambiguous determination of their correct stereochemistry thanks to distinct NOE correlations found in all isolated products (Figure 2.30).
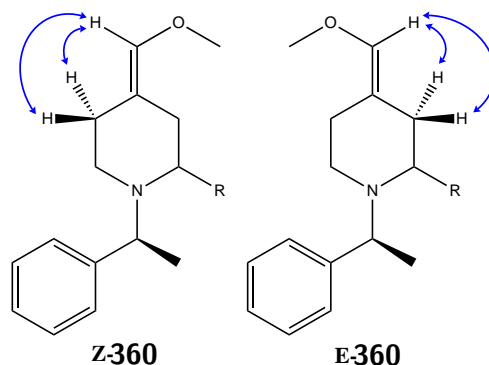
Figure 2.30: Observed NOESY interactions in chiral methoxymethylene Z/E isomers.

Deprotection of 4-Methoxymethylene-piperidines to Aldehydes

As Sugimoto's originally reported conditions[194] for the acidic hydrolysis of methoxymethylene intermediate **318** to 1-benzyl-4-formyl-pipereridine **319** resulted in a moderate yield of 54%, due to the necessity for purification of the product by column chromatography, we decided to follow a different protocol.[205]
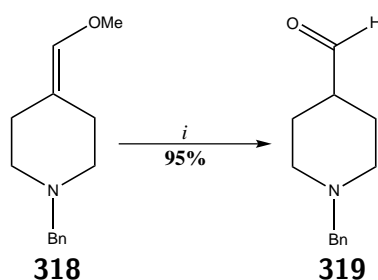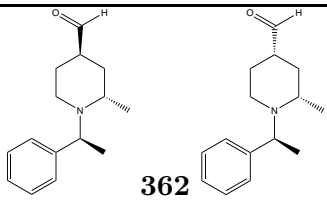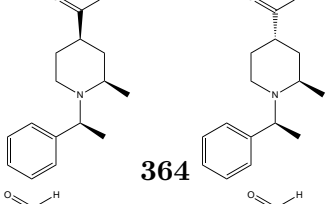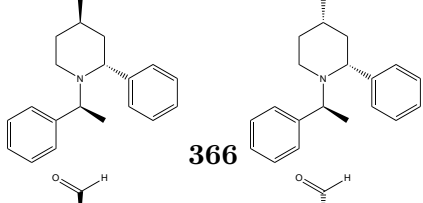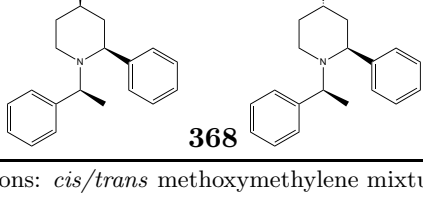
Scheme 2.37: Reaction conditions: *i)* THF/1.6 M HCl 1:1, 45 °C, 2 h.

A mild hydrolysis to aldehyde **319** was achieved by treating enol ether **318** with a 1:1 mixture of tetrahydrofuran and 1.6 M aqueous HCl at 45 °C. Aldehyde **319** was obtained in a crude yield of 95% with the starting material completely converted and the product being pure by NMR analysis. It was observed that storage of the aldehyde at low temperatures (-20 °C) was necessary in order to prevent degradation over time.

When the *cis/trans* mixtures of chiral enol ethers were subjected to the hydrolysis conditions, mixtures of the corresponding diastereomeric aldehydes were obtained in excellent yields (97-100%) and purity (Table 2.15).

Table 2.15: Combined yields and product ratios for the synthesised aldehydes.

No.	Substrates	Products[a]		Yield[b](%)	Ratio[c]
1	*Z*-**352**:*E*-**353** 1.00:1.70	**362**	**363**	97	**362:363** 1.00:1.29
2	*Z*-**355**:*E*-**354** 1.16:1.00	**364**	**365**	100	**364:365** 1.85:1.00
3	*Z*-**357**:*E*-**356** 1.32:1.00	**366**	**367**	100	**366:367** 1.00:1.33
4	*Z*-**359**:*E*-**358** 1.10:1.00	**368**	**369**	100	**368:369** 2.04:1.00

[a] Standard reaction conditions: *cis/trans* methoxymethylene mixtures, THF/1.6 M HCl 1:1, 45 °C, 2-3 h.
[b] Crude combined yield.
[c] Ratio of products was determined by analysis of the crude ^{1}H-NMR spectra.

It was possible to determine the diastereomeric ratio by analysis of the crude ^{1}H-NMR spectra and to assign the chirality of the 4-formyl moiety in all products from the observed NOESY correlations. Figure 2.31 shows the detected NOESY interactions for 2*R*-methyl substituted aldehydes **364** and **365**. In aldehyde **364** correlations were observed between H_{ax}-2 and and the proton in position 4. This suggests an axial position for H-4 and hence *R*-chirality for the stereocenter. In diastereomer **365**, no such NOESY correlation between H_{ax}-2 and the proton in position 4 was found, instead an interaction between the protons of the methyl group in position 2 and H_{eq}-4, confirming *S*-chirality for this piperidine.
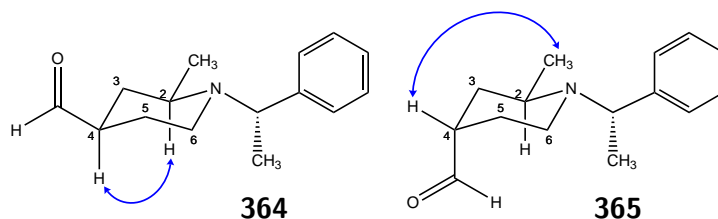
Figure 2.31: Observed NOESY correlations in diastereomeric aldehydes **364** and **365**.

Furthermore, single *cis* and *trans* methoxymethylene stereoisomers were subjected to the hydrolysis conditions to investigate whether this would result in the exclusive formation of a *syn* or *anti* product (Scheme 2.38). If a single aldehyde diastereomer had formed in this reaction, its use in the subsequent aldol condensation step would have led to only one product. However, when *Z*-**352** or *E*-**356** were used, in both cases diastereomeric mixtures were obtained.
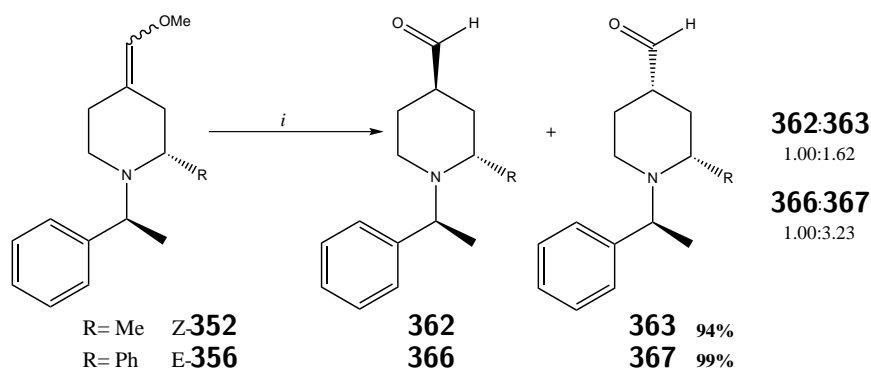
Scheme 2.38: Reaction conditions: *i)* THF/1.6 M HCl 1:1, 45 °C, 2 h.

2.3.3 Synthesis of Donepezil Analogues

Having achieved the preparation of diastereomeric mixtures of 2-methyl and 2-phenyl 4-formyl-piperidines, these building blocks could be used as substrates for the next step in the synthetic route towards donepezil analogues.

Aldol Condensation of 4-Formyl-piperidines and 5,6-Dimethoxy-1-indanone

For the synthesis of donepezil precursor **370**, aldehyde **319** and 5,6-dimethoxy-1-indanone **324** were subjected to an aldol condensation reaction (Scheme 2.39). The
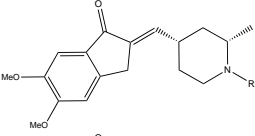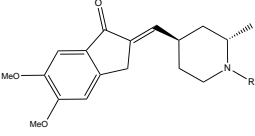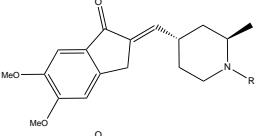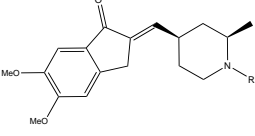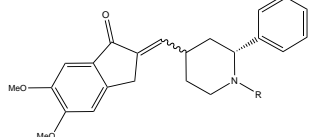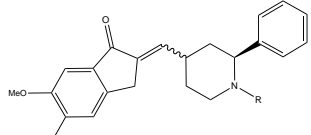
protocol used for this conversion was similar to the one described by Imai[206] and avoided the low temperatures (-78 °C) and toxic solvents (HMPA) reported by Sugimoto.[120,194] The base catalysed nucleophilic enolate addition of **324** to the carbonyl function of aldehyde **319** was achieved by reacting the substrates in the presence of sodium methoxide in methanol. Upon dehydratation of the aldol product at reflux, donepezil-precursor **370** was obtained in good yield (84%) after isolation by column chromatography. An increased yield (91%) could be achieved by precipitating the product from the reaction by slowly cooling the hot reaction mixture to 0 °C.
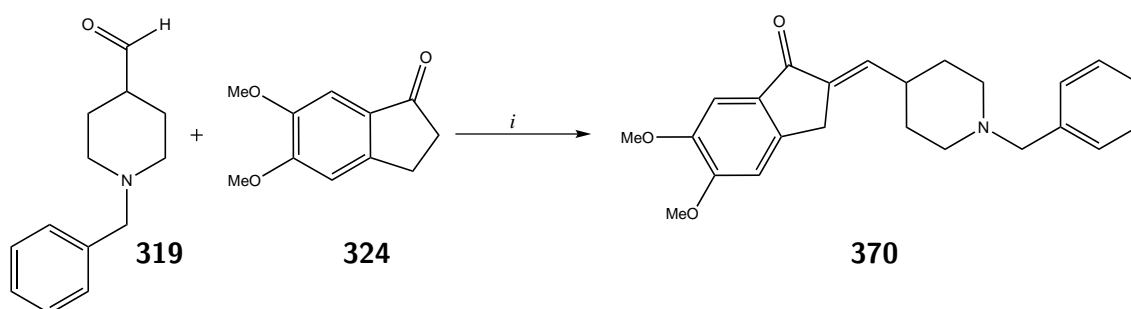
Scheme 2.39: Reaction conditions: *i)* **319**, **324**, NaOMe, MeOH, 80 °C, 75 min.

When a mixture of the 2*S*-methyl substituted aldehydes **362** and **363** was subjected to the aldol condensation with indanone derivative **324**, two diastereomeric products were obtained in a combined yield of 87% (Table 2.16, entry 1). The different R_f values of the two products allowed the partial separation of indanones **371** and **372** by column chromatography. Similarly, 2*R*-methyl substituted aldehydes **364** and **365** were subjected to the aldol condensation and the diastereomeric products were again partially separated (Table 2.16, entry 2). In this case the yield was lower due to loss of material upon isolation by column chromatography, caused by closely running minor impurities. The diastereomeric ratios for both methyl-substituted diastereomeric product pairs (entry 1 and 2) were determined by analysis of the signals for the olefinic protons in the crude ^{1}H-NMR spectra.

Table 2.16: Combined yields and product ratios for the aldol condensation products.

Entry	Aldehydes	Products[a]	Yield[b](%)	Ratio[c]
1	4R-**362**:4S-**363** 1.00:1.42	**371** **372**	87	**371**:**372** 1.63:1.00
2	4R-**364**:4S-**365** 2.00:1.00	**373** **374**	64	**373**:**374** 1.00:1.68
3	4R-**366**:4S-**367** 1.00:1.33	**375**+**376**	64	ND
4	4R-**368**:4S-**369** 2.04:1.00	**377**+**378**	59	ND

[a] R= -S-α-phenylethyl. Standard reaction conditions: aldehyde mixture, **324**, NaOMe, MeOH, 80 °C, 1.5-2 h.
[b] Combined isolated yield.
[c] Ratio of products was determined by analysis of the crude ¹H-NMR spectra. ND= not determined.

Figure 2.32 shows the observed NOESY correlations in the diastereomeric products **371** and **372**. In the product with the higher R_f value, a correlation is observed between the proton on C-4 and H_{ax}-2, therefore indicating an equatorial position for the indanone-substituent in position 4 on the ring. Conversely, no such correlation is observed in the product with the lower R_f value and an interaction between the protons of the methyl group in position 2 and the proton on C4 confirmed the axial position of the indanone-moiety in this diastereomer. Hence, the chirality for the aldol products was assigned as 4S and 4R for **371** and **372**, respectively.
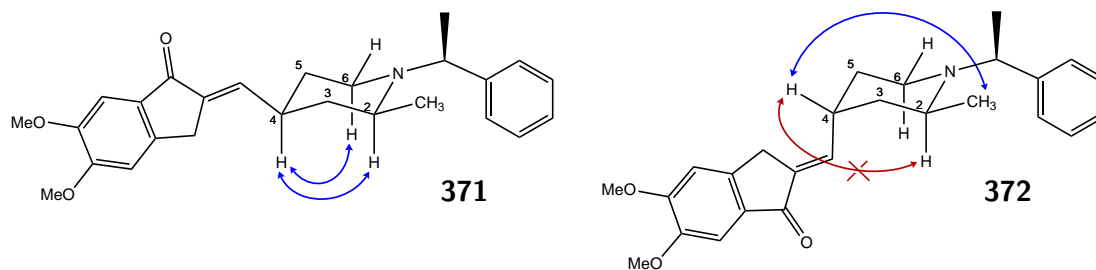
Figure 2.32: Observed NOESY correlations in diastereomeric aldol products **371** and **372**.

For both 2-phenyl substituted aldehyde mixtures, 4*R*-**366**+4*S*-**367** and 4*R*-**368**+4*S*-**369** (entry 3 and 4), the corresponding aldol products were obtained as inseparable mixtures. It was neither possible to determine a diastereomeric ratio from the NMR spectra of the crude nor of the isolated product mixtures. The signals in the ^{13}C-NMR were identical for both diastereomers and also in the ^{1}H-NMR spectra most signals were identical and overlapping, complicating a determination of the product ratio.

Having successfully prepared the diastereomeric aldol condensation products with methyl and phenyl substituents in position 2 on the piperidine ring in good to high yields (59-87%), the next step was a hydrogenation of the double bond to give the target donepezil analogues.

Reduction to Donepezil Analogues

Hydrogenation of alkene **370** using palladium on activated carbon was investigated according to a protocol by Sugimoto[120] (Scheme 2.40). After shaking **370** in the presence of 1 atm of hydrogen gas at room temperature in tetrahydrofuran for 6 hours, racemic donepezil **379** was obtained in a yield of 84% after purification by column chromatography.
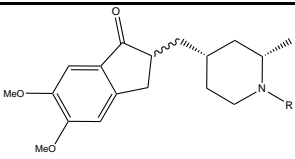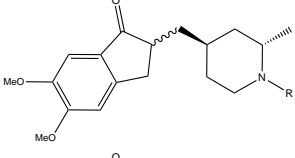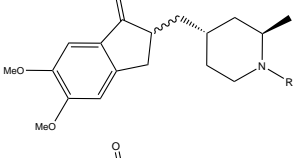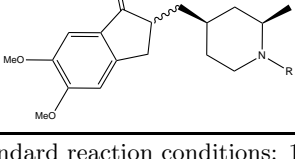
When the diastereomeric 2*S* or 2*R*-methyl substituted aldol condensation products **371**-**374** were individually subjected to these hydrogenation conditions, the methyl-substituted donepezil analogues were obtained as inseparable, diastereomeric mixtures (Table 2.17, entry 1-4). The low isolated yields for the product mixtures in entry 2
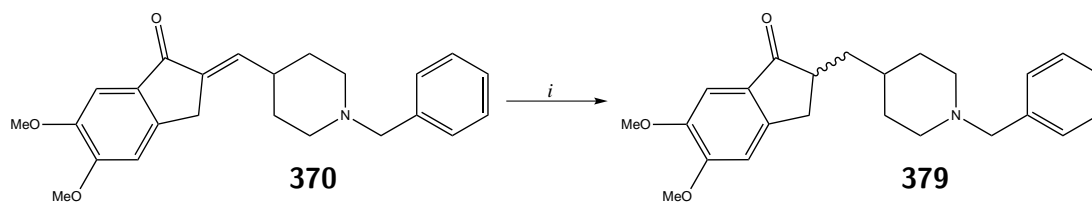
Scheme 2.40: Reaction conditions: *i)* 10% Pd/C, 1 atm H$_2$, THF, rt, 6 h.

and 3 are explained by a complicated purification by column chromatography, caused by closely eluting and streaking minor byproducts.

Table 2.17: Combined yields for the synthesised donepezil analogues bearing a methyl substituent on the piperidine ring.
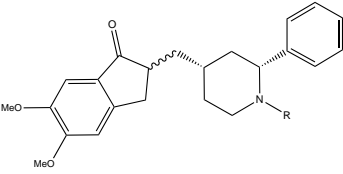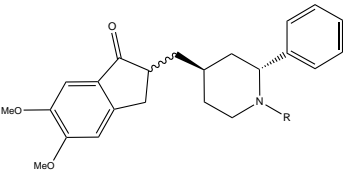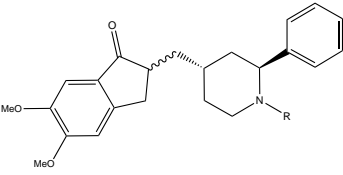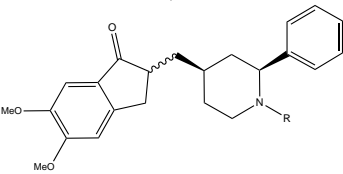
Entry	Substrates	Products[a]	Yield[b](%)
1	4*S*-**371**	**380+381**	68
2	4*R*-**372**	**382+383**	35
3	4*S*-**373**	**384+385**	42
4	4*R*-**374**	**386+387**	67

[a] R= -*S*-α-phenylethyl. Standard reaction conditions: 10% Pd/C, 1 atm H$_2$, THF, rt, 7-9 h.
[b] Combined isolated yield.

The synthesised donepezil analogues with 2*R* or 2*S* phenyl substituents in position 2 of the piperidine ring are shown in Table 2.18. As the starting materials in these hydrogenation reactions were diastereomeric mixtures due to the unresolved stereocentres in position 4 on the piperidine ring, the reduced products were obtained as mixtures of 4 diastereomers in yields of 77-84%.

Table 2.18: Combined yields for the synthesised donepezil analogues bearing a phenyl substituent on the piperidine ring.

Entry	Substrates	Products[a]	Yield[b](%)
		389+390 **391+392**	
1	4*S*-**375**+4*R*-**388**	**391+392**	77
		394+395 **396+397**	
2	4*S*-**377**+4*R*-**393**	**396+397**	84

[a] R= -*S*-α-phenylethyl. Standard reaction conditions: 10% Pd/C, 1 atm H$_2$, THF, rt, 8-10 h.
[b] Combined isolated yield.

It has been reported that the R and S enantiomers of donepezil interconvert in an aqueous solution at 37 °C with a racemisation half-life of 78 h due to ketoenol-tautomerism.[127] A similar racemisation behaviour of the stereocentre on the indanone moiety is also anticipated for the synthesised donepezil analogues. Therefore, in order to avoid the time of separating the diastereomeric pairs by chiral preparative high-performance liquid chromatography (HPLC), it was decided to take these analogues forward as mixtures when evaluating their AChE inhibitory activity.

Synthesis of the *N-S-α*-Phenylethyl Donepezil Analogue

To evaluate the influence that substituents in position 2 on the piperidine ring of the *N*-α-phenylethyl diastereomers have on the AChE inhibitory activities in comparison with donepezil, it was necessary to synthesise reference analogues **401**+**402**, which possess the chiral *N*-α-phenylethyl moiety, but no additional substituent on the piperidine ring (Scheme 2.41).
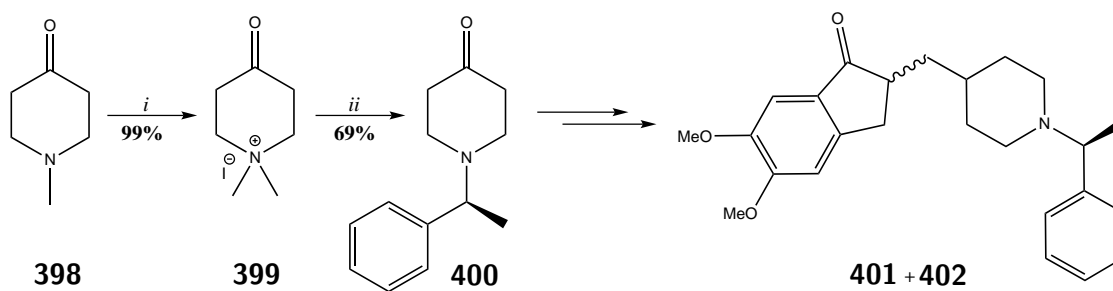
Scheme 2.41: Reaction conditions: *i)* methyl iodide, acetone, 25 °C, 2 h; *ii)* **399**, *S*-α-phenylethylamine, K_2CO_3, ethanol/water 1:1, 95 °C, 30 min.

N-S-α-Phenylethyl-4-piperidone **400** was conveniently prepared from commercially available *N*-methyl-4-piperidone **398** (Scheme 2.41). In the first step methylation with methyl iodide in acetone afforded *N,N*-dimethyl-4-oxopiperidinium iodide **399** in a yield of 99%.[207] Iodide salt **399** was then reacted with *S*-α-phenylethylamine in a substitution reaction under basic conditions[208,209] to give desired piperidone **400** in a yield of 69%.

Mistryukov's[209] proposed mechanism for this exchange reaction is shown in Figure 2.33 and consists of an initial base catalysed conversion of iodide salt **399** to enolate **403**. Primary amine **405** can then add to the β carbon of **404** in a an *aza*-Michael type manner to give the intermediate addition product. Upon protonation of the tertiary amine, the secondary amine in **405** attacks intramolecularly to displace the dimethylamine and gives *N*-substituted piperidone **406**.
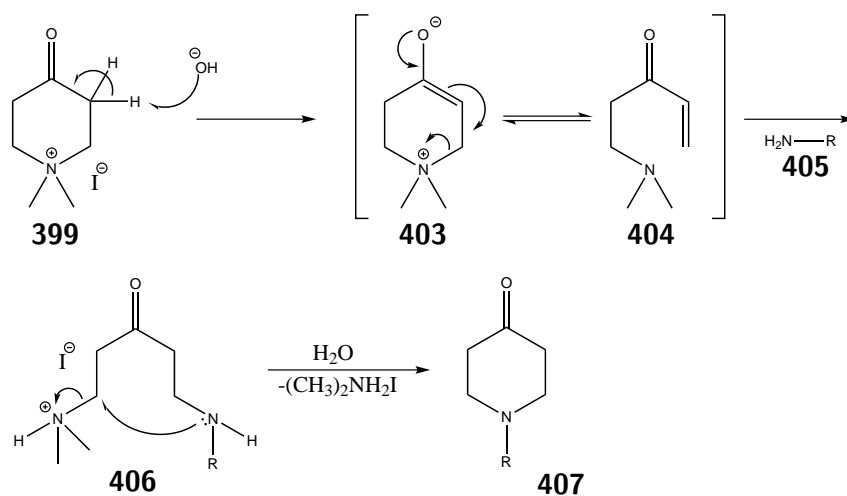
Figure 2.33: Mechanism for the β-elimination/intramolecular cyclisation to yield *N*-substituted piperidone **407**.[209,210]

Scheme 2.42 shows the synthetic route from piperidone **400** to the final donepezil analogues. Following the previously discussed protocols, Wittig product **408** was obtained in a yield of 93% and subsequently hydrolysed to aldehyde **409** in a crude yield of 92%. Aldol condensation with 5,6-dimethoxy-1-indanone gave alkene **410** in a yield of 67%, which was then subjected to a hydrogenation to give an inseparable diastereomeric mixture of the donepezil analogues **401+402** in a yield of 58%.
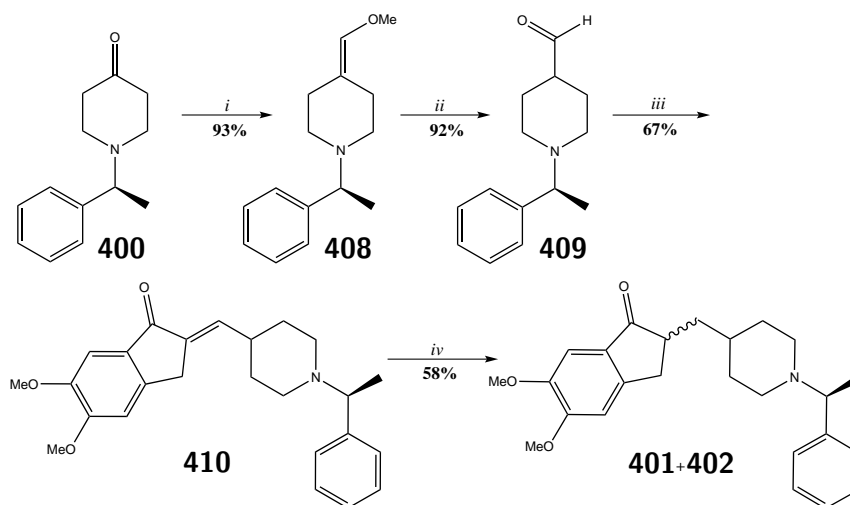
Scheme 2.42: Reaction conditions: *i)* ((Ph$_3$)PCH$_2$OCH$_3$)Cl, LDA, 4 Å MS, THF, -78 °C→rt→-20 °C→rt, 16 h; *ii)* THF/1.6 M HCl 1:1, 45 °C, 2.5 h; *iii)* **409**, 5,6-dimethoxy-1-indanone, NaOMe, MeOH, 80 °C, 75 min; *iv)* 10% Pd/C, 1 atm H$_2$, THF, rt, 8 h.

2.4 Acetylcholinesterase Inhibition Assay

To evaluate the inhibitory activity of the synthesised donepezil analogues, an ultraviolet-visible (UV-Vis) spectrophotometric assay was selected from the range of available methods.[211] The Ellman method[125] is the most widely used protocol to determine both AChE activity and its inhibition and was therefore considered suitable for our purposes.

The principle of this assay involves the enzymatic hydrolysis of the substrate acetylthiocholine (ATCI) **411** into acetate **412** and thiocholine **413**, followed by a colorimetric reaction (Figure 2.34). In this colorimetric step, the Ellman reagent dithiobisnitrobenzoate (DTNB) **414** reacts with hydrolysis product thiocholine **413** to form disulfide **415** and yellow 5-thio-2-nitrobenzoic acid (TNB) **416**. The intensity of the yellow colour is proportional to the enzyme's activity.[125,211]

Enzymatic hydrolysis

Colorimetric reaction
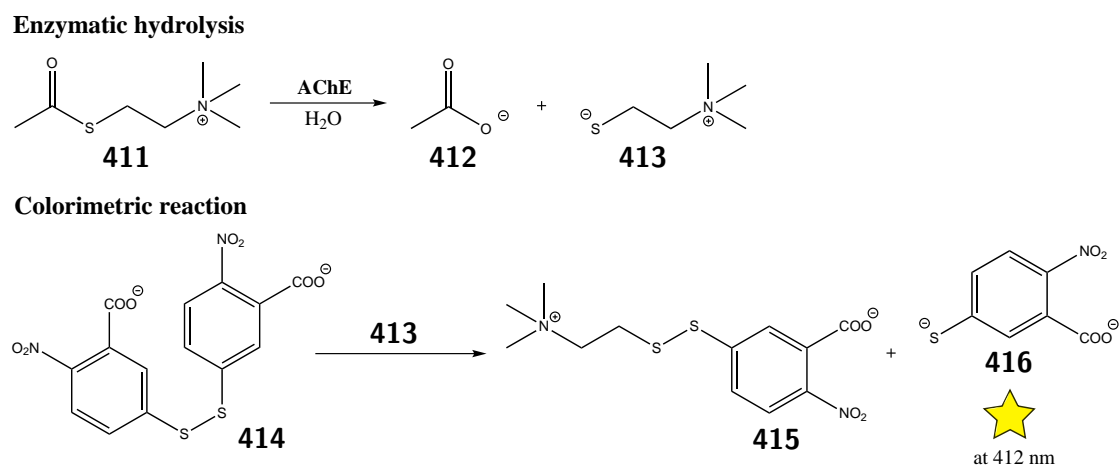
Figure 2.34: The principle of the colorimetric AChE inhibition assay based on Ellman's reagent.

Changes of the original Ellman method have led to modified protocols using microplates, thereby facilitating a simple and reproducible determination of IC_{50} values of AChE inhibitors. According to Järvinen,[212] IC_{50} values for the same inhibitor can vary largely across the literature, because of a lack of consistency in the applied protocol. The IC_{50} value for donepezil towards AChE of the electric eel (*ee*AChE) has been reported as 0.01 μM,[213] 0.04 μM,[214] as well as 0.12 μM.[215,216] Details concerning the sequence of reagent addition, the concentrations of reagents and the buffer systems are frequently omitted,

despite the fact that these factors are known to affect the obtained half-inhibitory concentrations.[212]

The commercially available human AChE is expensive and therefore the significantly cheaper AChE from the electric eel is routinely used in inhibition bioassays.[211] Although donepezil inhibits hAChE at slightly lower concentrations than eeAChE,[215,217] the electric eel enzyme is a useful and inexpensive alternative to obtain initial inhibitory results.

For the analysis of the donepezil analogues, the assay was carried out following a protocol described by Mohamed.[218] In Mohamed's procedure, dilutions of the test compounds were prepared in buffer (pH=8) containing 1% DMSO, with the positive control donepezil giving an IC_{50} value of 0.032 μM against hAChE. When Mohamed's protocol was applied, a half-inhibitory concentration of donepezil for eeAChE of 0.094 μM was obtained, a value which is comparable with those found in the literature (Figure 2.35, **A**).[214,215]
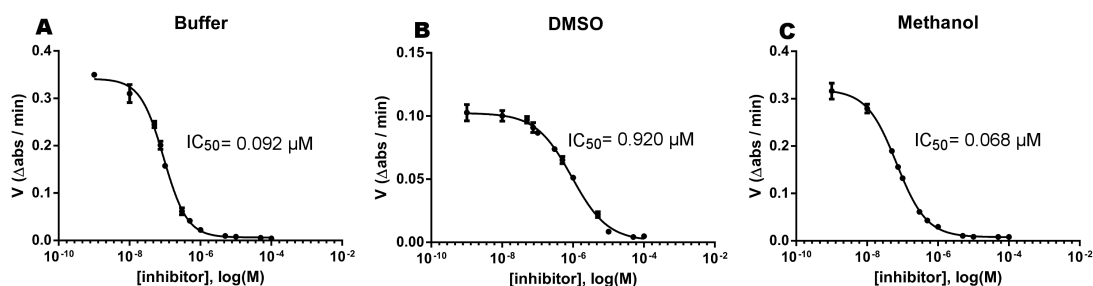
Figure 2.35: The effect of different solvents on the IC_{50} value of donepezil.

As the donepezil derivatives bearing a phenyl ring on the piperidine ring (**389**-**392** and **394**-**397**) were not soluble in buffer containing 1% DMSO, it was necessary to find a more suitable solvent for the test compounds. When the donepezil control dilution series was made up in pure DMSO, the final DMSO concentration in the assay changed from less than 1% to 4%. This increase in the total DMSO concentration resulted in a 10-fold higher IC_{50} of 0.974 μM, caused by a much smaller change of absorption over time (Figure 2.35, **B**). As DMSO severely interfered with the assay, it was deemed to be unsuitable as solvent. Methanol had been previously reported as a suitable solvent for test compounds in the Ellman-based assay[219] and when applied to the current

protocol, an IC_{50} of 0.068 μM was obtained for donepezil (Figure 2.35, **C**). Hence, as the inhibitory activity and the change of absorption over time were not significantly influenced, methanol was chosen for all subsequent analyses.

Another factor known to influence the observed potency of an inhibitor is the order of enzyme and ATCI substrate addition.[212] In our protocol, the inhibitors were preincubated with *ee*AChE for 7 minutes and subsequently the hydrolysis reaction initiated by the addition of ATCI. Following this order of reagent addition, spontaneous hydrolysis of the substrate before the start of the enzyme reaction is avoided.[125,212] Furthermore, the time elapsed between the beginning of the ATCI addition and the start of the spectrophotometric measurement was kept at 2 minutes, again to ensure consistent results. Two measurements at 412 nm were made 5 minutes apart and the IC_{50} values were calculated using GraphPad Prism software applying a nonlinear regression analysis (sigmoidal dose-response fit with a variable slope).
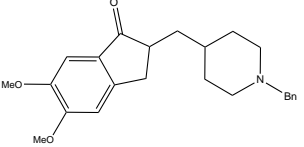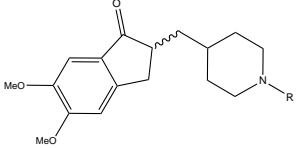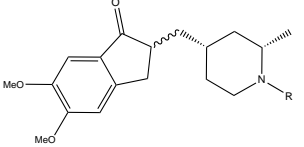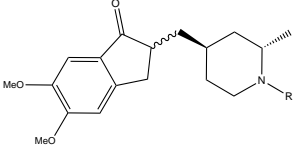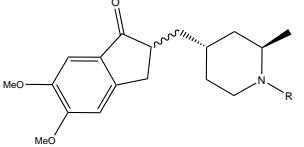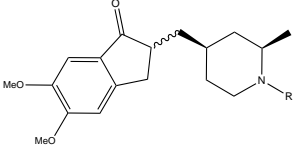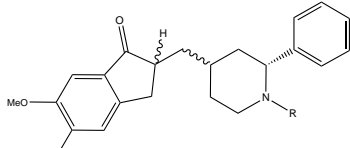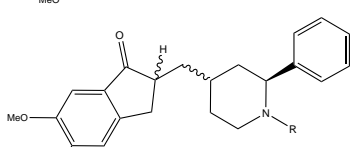
The Inhibitory Activities of Piperidine-Ring Substituted Donepezil Analogues

The half inhibitory concentrations of all compounds possessing a substituent in position 2 on the piperidine ring were evaluated in comparison to the diasteriomeric pair of compounds lacking a substituent on the the piperidine ring, bearing only a N-S-α-phenylethyl moiety (**401**+**402**), and the N-benzyl substituted donepezil reference **379** (Table 2.19).

The mixture of piperidine-ring unsubstituted derivatives **401** and **402** has an IC_{50} of 1.83 μM (entry 2) and is approximately 27 times less active than the donepezil **379** (entry 1), signifying that the additional methyl group has a detrimental effect on the drug's inhibitory activity.

Interestingly, 2S-methyl-4S compounds **380** and **381** possess a lower half-inhibitory concentration of 1.01 μM (entry 3), indicating that the additional methyl group on the piperidine partially compensates for some of the initial drop in activity caused by the N-S-α-phenylethyl moiety in **401** and **402** (entry 2).

Table 2.19: eeAChE IC$_{50}$ values for the synthesised donepezil analogues.

Entry	Compounds[a]	Chirality[b]	IC$_{50}$ [μM][c]
1	Donepezil **379**	-	0.068±0.002[d]
2	**401**+**402**	-	1.83±0.04
3	**380**+**381**	2S,4S	1.01±0.03
4	**382**+**383**	2S,4R	8.82±0.21
5	**384**+**385**	2R,4S	24.32±1.32
6	**386**+**387**	2R,4R	13.07±0.47
7	**389**-**392**	2R,4S/R	n.a.[e]
8	**394**-**397**	2S,4S/R	n.a.[e]

[a] R= -S-α-phenylethyl.
[b] Chirality of the stereocentres on the piperidine ring.
[c] IC$_{50}$ values are the mean of two separate experiments ± standard deviation (SD). Each experiment was carried out in triplicates.
[d] This IC$_{50}$ value is the mean of three separate experiments.
[e] Not active in the tested concentration range.

The 2S-methyl-4R-mixture of **382** and **383** (entry 4) is 9 times less active than the 2S-methyl-4S-mixture (entry 3), suggesting that the stereocentre in position 4 on the piperidine ring is of importance for the overall inhibitory activity.

Both mixtures bearing the 2-methyl group in *R*-chirality demonstrated decreased activities (entry 5 and 6) in comparison to the compounds with the 2-substituent in *S*-chirality (entry 3 and 4). The reduced inhibitory potency of these derivatives signifies that donepezil is sensitive to stereoselective substitution in position 2 on the piperidine ring, possibly caused by significant changes in the overall conformation within the enzyme's binding pocket and therefore also in the binding affinities.

Both mixtures possessing a phenyl ring in position 2 on the ring (entry 7 and 8) showed no activity in the tested concentration range (0.001-100 μM). We believe that the bulky phenyl ring prevents these compounds from entering the narrow, "swinging-gate"-controlled[140,143] entry site to the binding gorge of the enzyme.

When comparing the IC_{50} values of the *syn*-substituted compounds (entry 3, entry 6) to the *anti*-substituted analogues (entry 4, entry 5), in both cases the *syn*-compounds are significantly more active. 2*S*,4*S*-*syn*-Substituted compounds **380** and **381** are approximately 24 times more active than the 2*R*,4*S*-*anti*-substituted analogues **384** and **385** (Figure 2.36), demonstrating that the stereochemistry of the substituent in position 4 relative to the stereochemistry of the substituent in position 2 significantly affects the overall inhibitory activity of the diastereomeric mixtures.
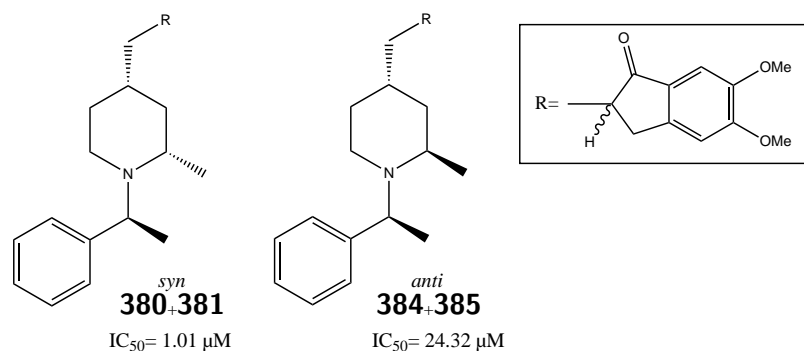
Figure 2.36: Activities of *syn* and *anti*-substituted donepezil analogues.

It can be summarised that, despite the *S*-α-phenylethyl moiety's detrimental effect on the inhibition potency, an additional methyl substituent in position 2 on the piperidine ring leads to compounds with modified activity. We observed that among the 2-methyl substituted analogues, those with 2*S*-chirality are more active than the ones with 2*R*-chirality, furthermore we deduced that a 2,4-*syn*-substitution pattern gives lower IC_{50}

values than a 2,4-*anti*-substitution pattern. These are interesting initial results which encourage further investigations into the search for donepezil analogues with an improved pharmacological profile.

2.5 Overall Summary and Conclusions

In the initial study, a double *aza*-Michael addition of primary amines to divinyl ketone **178** was investigated. A manganese dioxide facilitated one-pot oxidation-cyclisation protocol was developed, generating the unstable ketone *in situ* and allowed a diverse range of aromatically and aliphatically *N*-substituted 4-piperidones to be synthesised in moderate to good yields over two steps (28-61%). The reactivity of benzylamine substrates towards activated manganese dioxide was identified as a side-reaction in this one-pot method.

Aliphatically and aromatically substituted divinyl alcohols were prepared from their corresponding aldehydes and their utility as substrates in the previously developed one-pot oxidation-cyclisation protocol was investigated. Since 2-substituted *N*-benzylic 4-piperidones could not be efficiently prepared using this method, a stepwise approach was investigated. Employing substituted divinyl ketones in an *aza*-Michael cyclisation protocol using aqueous sodium bicarbonate in acetonitrile resulted in high yields of the 2-aryl substituted *N*-benzylic 4-piperidone products (79-84%) and moderate yields for the 2-alkyl substituted piperidones (36-42%). Furthermore, to obtain separable piperidone products with resolved stereochemistry in position 2 on the piperidine ring, *S*-α-phenylethylamine was used as amine substrate in the cyclisation reaction. The stereochemistry of the diastereomeric piperidone products was assigned on the basis of their distinct differences in chemical shifts as observed in their ^{13}C-NMR spectra. In this *aza*-Michael cyclisation, a small degree of diastereoselectivity was observed, which was found to be more significant amongst the aryl-substituted piperidone products investigated. In conclusion, chirally resolved 2-substituted 4-piperidones were prepared from commercially available starting materials in three steps, thereby giving easy access to valuable building blocks for the assembly of new, biologically relevant piperidine scaffolds.

Investigating the manganese dioxide mediated side reaction in the one-pot oxidation-cyclisation protocol, it was discovered that in the absence of a divinyl ketone Michael acceptor, the oxidation of primary benzylic amines proceeded smoothly to the corresponding amides under mild conditions. The intermediates of the reaction pathway

were identified and their interconversion to the amide product followed by ^{1}H-NMR experiments. Varying the reaction conditions allowed the crucial role of both the manganese dioxide and molecular sieves to be elucidated. All intermediates were converted to the amide under the standard reaction conditions and a range of benzylic amides was prepared in good to excellent yield (69-99%).

The 2-methyl and 2-phenyl N-α-phenylethyl 4-piperidones were used as building blocks for the synthesis of donepezil analogues. In order to access the important 4-formyl piperidine compounds, the piperidones were subjected to a Wittig reaction and the methoxymethylene products were obtained in high combined yields (75-97%). Subsequent hydrolysis under acidic conditions gave the desired, inseparable aldehydes in excellent yields (97-100%). There was no need for further purification of the unstable aldehyde building blocks, thereby making this route superior with respect to overall yield and purity in comparison to procedures published earlier.[194–196] Condensation of the aldehydes with an indanone derivative furnished partially separable diastereomeric intermediates, which were subjected to hydrogenation over a palladium catalyst to give the final donepezil analogues as inseparable mixtures of diastereomers. Despite the importance of the piperidine ring for the biological activity of donepezil,[126] the synthesis of analogues of this drug bearing sterically resolved substituents in position 2 on the ring has not yet been reported in the literature.

The AChE inhibitory activity of the synthesised donepezil analogues was evaluated in comparison to donepezil. An UV-Vis spectrophotometric based assay was conducted and the IC_{50} values for the diastereomeric mixtures determined. It was found that while the phenyl substituted donepezil analogues were inactive, the methyl substituted analogues possessed moderate inhibitory activity. The S-methyl substituted analogues were significantly more active than the analogues bearing a methyl group with R-chirality, therefore demonstrating that the stereochemistry of substituents on the piperidine ring plays an important role in the binding behaviour of such compounds within the enzyme's binding pocket.

2.6 Future Work

Having prepared diastereomeric 2-substituted 4-piperidones building blocks for the synthesis of donepezil analogues, scope for further research lies in the optimisation of the double *aza*-Michael cyclisation reaction. The stereoselectivity as well as the yield of this reaction might be improved by the addition of chiral amine catalysts, for example proline-derivative **417**[77,78,80] or cinchona alkaloid derived catalyst **418**[76] (Figure 2.37). These catalysts enhance the electrophilicity of the dienone by the formation of an iminium intermediate, thereby facilitating the nucleophilic attack of the primary amine on the β-carbon of the Michael acceptor. Furthermore, a more diverse range of chiral amine substrates could be investigated to evaluate their utility as nucleophiles in the reaction with substituted divinyl ketones, hence determining the wider scope of the *aza*-Michael cyclisation.
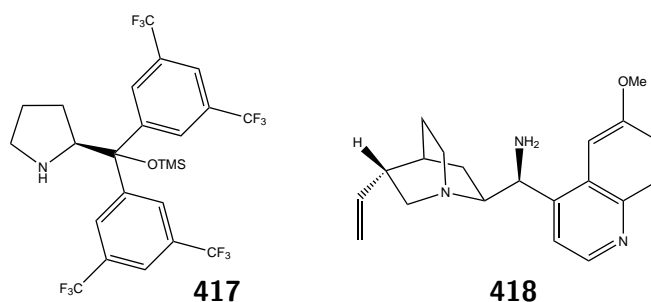
Figure 2.37: Chiral amine catalysts.

The methyl and phenyl substituted donepezil analogues prepared bear a S-α-phenylethyl moiety on the piperidine nitrogen. The initial evaluation of the biological activity of these analogues revealed that the additional methyl group on the N-benzyl substituent has a detrimental effect on the inhibition potency. Thus, the synthesis of further donepezil analogues, bearing a simple N-benzyl substituent, could fully elucidate the biological effects of chiral substituents in position 2 of the drug's piperidine ring. Removal of the nitrogen substituent by hydrogenation of the diastereomeric 2-substituted 4-piperidones **419** over a palladium catalyst,[174] followed by the reaction with benzylbromide[220] gives enantiopure N-benzylic 2-substituted piperidones **421** which could be used as precursors for the preparation of additional donepezil analogues **422** (Figure 2.38).
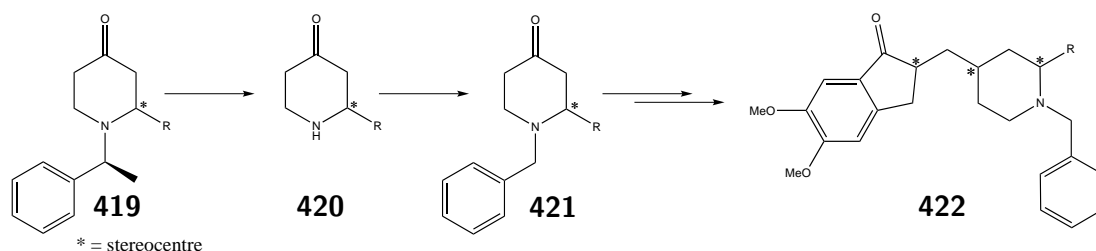
Figure 2.38: Synthesis of donepezil analogues bearing a *N*-benzyl substituent.

Moreover, α-substituted divinyl ketones **423**[81,221,222] could be investigated for their use in a double *aza*-Michael cyclisation to obtain 3-substituted 4-piperidones **424** (Figure 2.39). Although the stereochemistry of the substituent in position 3 will be determined by keto-enol tautomerism and not by chiral induction from the chiral Michael donor amine substrate, piperidone products **424** will be obtained as separable diastereomers. In further synthetic steps, piperidones **424** can be employed for the preparation of donepezil analogues **426**, bearing the substituent in position 3 on the piperidine ring. These analogues will possess modified biological activity and can therefore provide additional information on the sensitivity of the piperidine ring for stereoselective substitution.
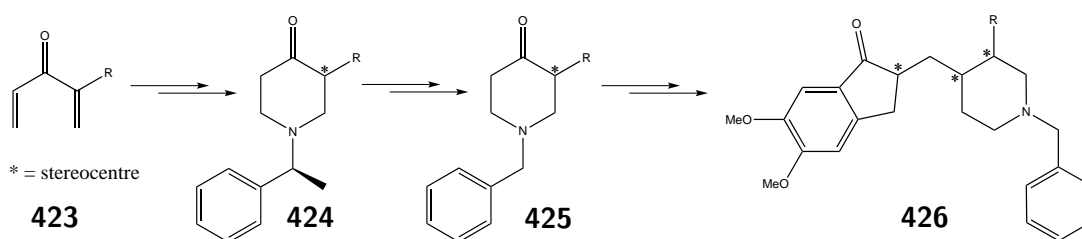
Figure 2.39: Synthesis of donepezil analogues bearing a substituent in position 3 on the piperidine ring.

Scope for further research also remains in the biological evaluation of the synthesised donepezil analogues. As the determination of the biological activity was carried out using the AChE enzyme from the electric eel, the analogues' potency to inhibit the human enzyme could be varied due to structural differences in the binding pockets of the two enzyme species. Furthermore, in order to explain the results obtained, a molecuar dynamics study can be carried out to investigate the analogues' ability to enter the binding pocket. Such a study would shed light on the question whether the entrance

to the binding pocket of 2-phenyl substituted analogues *via* the narrow "swinging"-gate[140] is prevented due to the increased bulkiness of the additional phenyl ring. A docking study of the analogues in their energy minimised conformations would further lead to an understanding of whether the additional piperidine ring substituents protrude into hydrophobic pockets within the binding gorge,[140,143] hence leading to an increased binding affinity.

Chapter 3

Experimental

3.1 General Experimental Procedures

Infrared spectra were obtained on a Perkin Elmer 100 FTIR spectrometer operating in attenuated total reflection (ATR) mode. Only significant absorptions (ν_{max}) are reported and all absorptions are recorded in wavenumbers (cm^{-1}). Melting points were measured with an Electrothermal apparatus and are uncorrected.

Proton magnetic resonance spectra (^{1}H-NMR) were recorded at 400 MHz using a Bruker spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual protonated solvent peak. The order of citation in parentheses is (i) number of equivalent nuclei (by integration), (ii) multiplicity (s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), (iii) coupling constant (J) quoted in Hertz (Hz) to one decimal place, (iv) assignment. Signals on a monosubstituted and a 1,4-disubstituted aromatic ring are described using the terms *ipso*, *ortho*, *meta* and *para*. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded at 100.6 MHz using a Bruker spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. The assignment is quoted in parentheses. Where necessary, assignments were made with the aid of DEPT, COSY, HSQC, HMBC or NOESY correlation experiments.

Low resolution mass spectra (m/z) were recorded using an LCQ DECA XP instrument by electron spray ionization (ESI). Only molecular ions and major fragments of the molecular ions are reported. Accurate masses were determined using a quadrupole time-of-flight mass (QTOF) spectrometer at King's College London or a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Facility in Swansea using nanospray ESI (NSI) and atmospheric pressure chemical ionization (APCI).

Flash Chromatography was carried out using silica gel (Aldrich, 230-400 mesh) as the stationary phase. Thin Layer Chromatography was carried out on aluminium plates pre-coated with silica (Merck silica gel 60 F_{254} on aluminium) which was visualized by the quenching of ultraviolet fluorescence (λ_{max}=254 nm) and/or by staining with potassium permanganate solution followed by heat. All reactions were carried out at atmospheric pressure with stirring unless otherwise stated. All reagents were used as received unless otherwise stated. The fractions of light petroleum ether boiling between 40 and 60 °C are referred to as "hexanes". Optical rotations ($[\alpha]_D^T = \alpha/\text{l.c}$) were measured by a Bellingham and Stanley ADP 220 polarimeter at 589 nm (sodium-D line). Concentration (c) is in g 100 mL^{-1}.

The HPLC analysis was performed on a Hewlett-Packard 1050 system equipped with an autosampler, a reversed-phase HPLC column (Agilent Zorbax 300 Å, C-18, 2.1 mm x 100 mm, particle size 3.5 μm) and a diode-array detector (DAD) set to monitor 281 nm. The flow rate was 0.2 mL/min and the column was eluted using three different linear gradients:

i)   0-90% MeCN in 0.1% (v/v) trifluoroacetic acid aqueous solution in 20 min (t_{R1});

ii)   0-90% MeCN in 0.1% (v/v) trifluoroacetic acid aqueous solution in 30 min (t_{R2});

iii)   0-50% MeCN in 0.1% (v/v) trifluoroacetic acid aqueous solution in 50 min (t_{R3});

3.2   Experimental Procedures

Preparation of activated manganese dioxide

MnO_2 was purchased from *Alfa Aesar* (Cat. No. 014340.22, Manganese(IV) oxide, activated, tech., Mn 58% min, 100 g) and further activated by treatment with dilute nitric acid:

MnO_2 (50 g) was placed on a large Büchner funnel and 10% nitric acid (80 mL) was added slowly. After the addition was completed, the MnO_2 cake was washed with water (2-3 L) until the filtrate was neutral. The MnO_2 was subsequently dried at 105 °C for two days.

Penta-1,4-dien-3-one 178

178
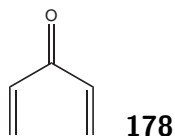
Divinylcarbinol (165 μl, 1.70 mmol, 1.0 equiv) was added to a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (10 mL). MnO_2, which had been previously activated by washing with diluted nitric acid (4.44 g, 51.0 mmol, 30.0 equiv), was added portionwise. The temperature was kept at 40 °C and after 20 h the mixture was filtered through a pad of Celite, followed by washing with acetone (150 mL). The solvent was evaporated *in vacuo* and crude ketone **178** (131 mg, 88%) was obtained as a pale yellow oil. It could be used in the next step without further purification; R_f 0.40 (3:1 hexane:ethyl acetate); ν_{max} (film) 3162, 3062, 1651 (C=O), 1618, 1575, 1448, 1296, 1178, 1141, 1120, 1024, 917; δ_H (400 MHz, $CDCl_3$) 6.58 (2H, dd, *J* 17.5 Hz, 10.6 Hz, 2 x -C$\underline{H}$=CH_2), 6.26 (2H, dd, *J* 17.5 Hz, 1.2 Hz, 2 x -CH=C$\underline{H}_{2\ trans}$), 5.82 (2H, dd, *J* 10.7 Hz, 1.2 Hz, 2 x -CH=C$\underline{H}_{2\ cis}$); δ_C (100.6 MHz, $CDCl_3$) 189.1 (C=O), 133.3 (CH), 128.3 (CH_2). *In agreement with published data.*[145,223]

2-Iodoxybenzoic acid 189

189
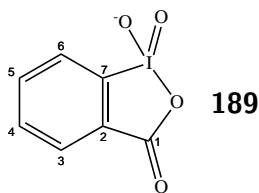
2-Iodobenzoic acid (24.800 g, 100.00 mmol, 1.0 equiv) was added to a solution of Oxone (potassium peroxymonosulfate) (79.920 g, 130.00 mmol, 1.3 equiv.) in deionized water (295 mL, 0.44 M) and stirred at 70 °C for 4 h. The mixture was then cooled to 5 °C and kept stirring at this temperature for 1.5 h. The mixture was filtered and the solid was washed with deionized water and acetone. 2-Iodoxybenzoic acid **189** (23.870 g, 85%) was obtained as white crystals; mp 231-233 °C; δ_H (400 MHz, DMSO-d_6) 8.14 (1H, d, *J* 8.0 Hz, Ar-H-3), 8.06-7.97 (2H, m, Ar-H-5, Ar-H-6), 7.84 (1H, app t, *J* 7.3 Hz, Ar-H-4); δ_C (100.6 MHz, DMSO-d_6) 167.61 (C=O), 146.61 ($Ar_{quart.}$), 133.47 (Ar), 133.03 (Ar), 131.48 ($Ar_{quart.}$), 130.16 (Ar), 125.05 (Ar).
In agreement with published data.[147]

1-Benzylpiperidin-4-one 201
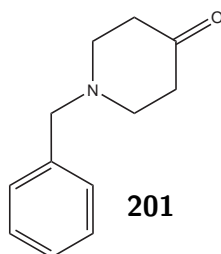
201

To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). Benzylamine (278 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with acetone (250 mL). Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1 with 1% TEA) gave product **201** (164 mg, 51% over two steps) as a pale yellow oil; R_f 0.20 (1:1 ethyl acetate:hexane); ν_{max} (film) 2960, 2910, 2807, 2764, 1718 (C=O), 1599, 1495, 1454, 1349, 1195, 1126, 1072, 1012, 739, 699; δ_H (400 MHz, $CDCl_3$) 7.29-7.19 (5H, m, Ph), 3.55 (2H, s, N-C$\underline{H}_2$-Ph), 2.68 (4H, t, *J* 5.9 Hz, 2 x β-CH_2), 2.39 (4H, t, *J* 6.0 Hz, 2 x α-CH_2); δ_C (100.6 MHz, $CDCl_3$) 208.3 (C=O), 137.1 (*ipso* Ph), 127.9 (*ortho* Ph), 127.4 (*meta* Ph), 126.3 (*para* Ph), 61.0 (N-$\underline{C}H_2$-Ph), 51.9 (β-CH_2), 40.3 (α-CH_2). *In agreement with published data.*[224]

(4-Chloro-benzyl)-piperidin-4-one 204
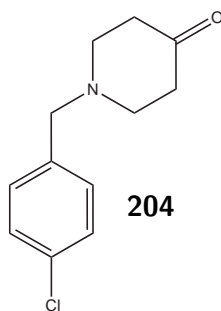
204

To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). 4-Chloro-benzylamine (361 mg, 2.55 mmol, 1.5 equiv.) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a

pad of Celite and washed with acetone and CH_2Cl_2. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1 with 1% TEA) gave product **204** (210 mg, 53% over two steps) as a pale yellow oil; R_f 0.29 (1:1 ethyl acetate:hexane + 1% TEA); ν_{max} (film) 2960, 2910, 1718 (C=O), 1596, 1491, 1348, 1196, 1128, 1087, 1015, 845, 799; δ_H (400 MHz, $CDCl_3$) 7.24 (4H, s, 4 x Ar-H), 3.51 (2H, s, N-C$\underline{H}_2$-Ar), 2.66 (4H, t, J 6.2 Hz, 2 x β-CH_2), 2.38 (4H, t, J 6.0 Hz, 2 x α-CH_2); δ_C (100.6 MHz, $CDCl_3$) 208.1 (C=O), 135.7 (*ipso* Ar), 132.0 (*para* Ar), 129.1 (*ortho* Ar), 127.5 (*meta* Ar), 60.2 (N-$\underline{C}H_2$-Ar), 51.9 (β-CH_2), 40.3 (α-CH_2); m/z (ESI+) 256 [M+H+CH_3OH]$^+$, 224 [M+H]$^+$. *In agreement with published data.*[225]

Phenethylpiperidin-4-one 214
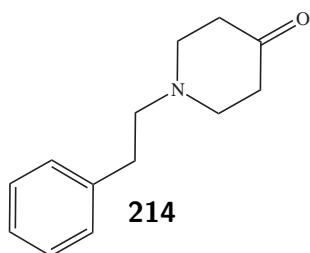
214

To a suspension of 4 Å molecular sieves in (1.00 g) CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). Phenylethylamine (310 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with CH_2Cl_2. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1 with 1% TEA) gave product **214** (186 mg, 58% over two steps) as a yellow solid; mp 59-61 °C; R_f 0.24 (1:5.5 hexane:ethyl acetate); ν_{max} (solid) 3062, 3023, 2972, 2984, 2809, 2772, 1716 (C=O), 1602, 1495, 1457, 1230, 1123, 1009, 752, 707, 699; δ_H (400 MHz, $CDCl_3$) 7.14-7.25 (5H, m, Ph), 2.75-2.8 (6H, m, 2 x β-CH_2, N-C$\underline{H}_2$-CH_2-Ph), 2.64-2.68 (2H, m, N-CH_2-C$\underline{H}_2$-Ph), 2.42 (4H, t, J 6.1 Hz, 2 x α-CH_2); δ_C (100.6 MHz, $CDCl_3$) 208.1 (C=O), 139.0 (*ipso* Ph), 127.7 (*meta* Ph), 127.5 (*ortho* Ph), 125.2 (*para* Ph), 58.3 (N-$\underline{C}H_2$-CH_2-Ph), 52.1 (β-CH_2), 40.3 (α-CH_2), 33.1 (N-CH_2-$\underline{C}H_2$-Ph). *In agreement with published data.*[226]

((Naphthalen-4-yl)methyl)piperidin-4-one 212

212
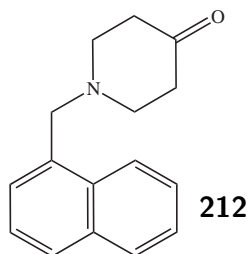
To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (8 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). 2-(Aminomethyl)naphthalene (374 mg, 2.38 mmol, 1.4 equiv) was added and the mixture stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with acetone. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1 with 1% TEA) gave product **212** (113 mg, 28% over two steps) as a pale yellow solid; mp 89-91 °C; R_f 0.39 (1.5:1 hexane:ethyl acetate); ν_{max} (solid) 3046, 2960, 2907, 2809, 1716 (C=O), 1597, 1509, 1472, 1365, 1344, 1233, 1197, 1122, 1018, 796; δ_H (400 MHz, $CDCl_3$) 8.27 (1H, d, *J* 8.2 Hz, Ar-H), 7.79 (1H, dd, *J* 7.5 Hz, 2.4 Hz, Ar-H), 7.73 (1H, dd, *J* 7.2 Hz, 2.4 Hz, Ar-H), 7.41-7.48 (2H, m, 2 x Ar-H), 7.32-7.37 (2H, m, 2 x Ar-H), 3.94 (2H, s, N-C$\underline{H}_2$-Ar), 2.74 (4H, t, *J* 6.0 Hz, 2 x β-CH$_2$), 2.37 (4H, t, *J* 6.1 Hz, α-CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 208.5 (C=O), 132.9 (2 x Ar$_{quart.}$), 131.4 (Ar$_{quart.}$), 127.5 (Ar), 127.3 (Ar), 126.3 (Ar), 124.9 (Ar), 124.7 (Ar), 124.1 (Ar), 123.6 (Ar), 59.2 (N-$\underline{C}$H$_2$-Ar), 52.1 (β-CH$_2$), 40.3 (α-CH$_2$); *m/z* (ESI+) 258 [M+H+H$_2$O]$^+$, 240 [M+H]$^+$, 141; Exact Mass Calcd for $C_{16}H_{17}NO$ [M+H]$^+$ requires *m/z* 240.1383 Found 240.1384 (NSI+)

(4-Methoxy-benzyl)-piperidin-4-one 206
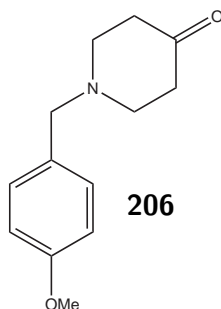
206

OMe

To a suspension of 4 Å molecular sieves in (1.00 g) CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2

(3.69 g, 42.50 mmol, 25.0 equiv). 4-Methoxy-benzylamine (350 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with CH_2Cl_2. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1 with 1% TEA) gave product **206** (169 mg, 45% over two steps) as a yellow oil; R_f 0.27 (1.5:1 ethyl acetate:hexane); ν_{max} (film) 2958, 2910, 2804, 2763, 1717 (C=O), 1612, 1585, 1512, 1463, 1349, 1302, 1246, 1178, 1122, 1084, 1034, 835, 802; δ_H (400 MHz, $CDCl_3$) 7.19 (2H, d, *J* 8.7 Hz, *ortho* Ar-H), 6.81 (2H, d, *J* 8.7 Hz, *meta* Ar-H), 3.74 (3H, s, -OC$\underline{H}_3$), 3.49 (2H, s, N-C$\underline{H}_2$-Ar), 2.66 (4H, t, *J* 6.1 Hz, 2 x β-CH_2), 2.38 (4H, t, *J* 6.2 Hz, 2 x α-CH_2); δ_C (100.6 MHz, $CDCl_3$) 209.43 (C=O), 158.92 (*para* Ar), 130.15 (*ortho* Ar), 130.09 (*ipso* Ar), 113.74 (*meta* Ar), 61.36 (N-$\underline{C}H_2$-Ar, 52.79 (-O$\underline{C}H_3$), 55.29 (β-CH_2), 41.30 (α-CH_2); *m/z* (ESI+) 252 [M+H+CH_3OH]$^+$; 220 [M+H]$^+$. *In agreement with published data.*[227]

1-(Heptan-2-yl)piperidin-4-one 216
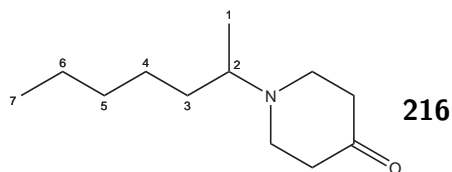
216

To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (11 mL) was added divinylcarbinol (165 μl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). 1-Methyl-hexylamine (0.299 g, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with acetone. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (20% ethyl acetate in hexane) gave product **216** (201 mg, 60% over two steps) as a pale yellow oil; R_f 0.22 (20% ethyl acetate in hexane); ν_{max} (film) 2959, 2929, 2858, 2806, 1720 (C=O), 1589, 1463, 1381, 1346, 1220, 1163, 1076; δ_H (400 MHz, $CDCl_3$) 2.92-2.64 (5H, m, H-2, 2 x β-CH_2), 2.52-2.31 (4H, m, 2 x α-CH_2), 1.59-1.21 (8H, m, 4 x CH_2), 0.98 (3H, d, *J* 6.6 Hz, CH_3-1), 0.90 (3H, t, *J* 7.0 Hz, CH_3-7); δ_C (100.6 MHz, $CDCl_3$) 210.12 (C=O), 58.90 (C2), 48.12 (β-CH_2), 42.13 (α-CH_2), 33.91 (C3), 31.99 (C5), 26.68 (C4), 22.68 (C6), 14.36 (C1), 14.1 (C7); *m/z* (ESI+) 230 [M+H+CH_3OH]$^+$, 198 [M+H]$^+$; Exact Mass Calcd for $C_{12}H_{23}NO$ [M+H]$^+$ requires *m/z* 198.1852 Found 198.1853 (NSI+)

1-Tetradecylpiperidin-4-one 218
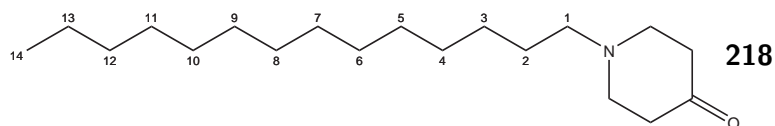
To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). Tetradecylamine (550 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with acetone and ethyl acetate. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (20% ethyl acetate in hexane) gave product **218** (306 mg, 61% over two steps) as a waxy, pale yellow solid; mp 35-37 °C; R_f 0.21 (20% ethyl acetate in hexane); ν_{max} (solid) 2956, 2914, 2847, 2805, 2768, 1728 (C=O), 1475, 1463, 1376, 1350, 1218, 1212, 1129, 1084, 1009, 806, 761, 730, 719; δ_H (400 MHz, $CDCl_3$) 2.67 (4H, t, J 6.1 Hz, 2 x β-CH_2), 2.56-2.22 (6H, m, CH_2-1, 2 x α-CH_2), 1.51-1.06 (24H, m, 12 x CH_2), 0.81 (3H, t, J 6.8 Hz, CH_3-14); δ_C (100.6 MHz, $CDCl_3$) 207.79 (C=O), 55.95 (C1), 51.49 (β-CH_2), 39.57 (α-CH_2), 30.23 (C12), 28.00 (CH_2), 27.99 (CH_2), 27.97 (CH_2), 27.96 (CH_2), 27.93 (CH_2), 27.90 (CH_2), 27.86 (CH_2), 27.67 (CH_2), 25.84 (CH_2), 25.80 (CH_2), 21.00 (C13), 12.44 (C14); m/z (ESI+) 328 $[M+H+CH_3OH]^+$; 296 $[M+H]^+$; Exact Mass Calcd for $C_{19}H_{38}NO$ $[M+H]^+$ requires m/z 296.2948 Found 296.2953 (NSI+)

1-(4-(Trifluoromethyl)benzyl)piperidin-4-one 208
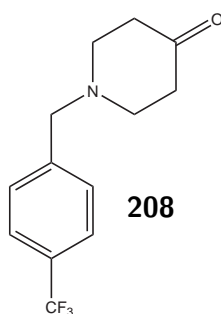
To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (11 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv). 4-Trifluoromethyl-benzylamine (447 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered

through a pad of Celite and washed with CH_2Cl_2. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (20% ethyl acetate in hexane with 1 % TEA) gave product **208** (232 mg, 53% over two steps) as a pale yellow oil; R_f 0.25 (1:1 ethyl acetate:hexane); ν_{max} (film) 2961, 2915, 2807, 2767, 1720 (C=O), 1620, 1418, 1350, 1326, 1240, 1196, 1163, 1124, 1087, 1066, 1019, 850; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, J 8.1 Hz, *meta* Ar-H), 7.43 (2H, d, J 8.0 Hz, *ortho* Ar-H), 3.60 (2H, s, N-CH$_2$-Ar), 2.69 (4H, t, J 6.1 Hz, 2 x β-CH$_2$), 2.40 (4H, t, J 6.2 Hz, 2 x α-CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 207.82 (C=O), 128.62 (q, $^2J_{CF}$ 32 Hz, *para* Ar) 127.95 (*ortho* Ar), 124.35 (q, $^3J_{CF}$ 3.8 Hz, *meta* Ar), 123.15 (q, $^1J_{CF}$ 272 Hz, -CF$_3$), 60.42 (N-CH$_2$-Ar), 51.98 (β-CH$_2$), 40.23 (α-CH$_2$); m/z (ESI+) 290 [M+H+CH$_3$OH]$^+$, 258 [M+H]$^+$; Exact Mass Calcd for $C_{13}H_{15}F_3NO$ [M+H]$^+$ requires m/z 258.1100 Found 258.1103 (NSI+)

1-α-Phenylethyl-4-piperidone 210

210
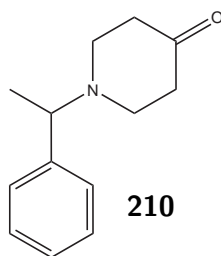
To a suspension of 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (10 mL) was added divinylcarbinol (165 µl, 1.70 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (3.69 g, 42.50 mmol, 25.0 equiv.). 1-Phenyl-ethylamine (309 mg, 2.55 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with acetone and methanol. Concentration of the combined filtrates under reduced pressure and purification by column chromatography (20% ethyl acetate in hexane) gave product **210** (169 mg, 49% over two steps) as a pale yellow oil; R_f 0.29 (1:1 ethyl acetate:hexane); ν_{max} (film) 3028, 2971, 2908, 2806, 2756, 1718 (C=O), 1493, 1454, 1412, 1386, 1342, 1316, 1284, 1220, 1131, 1080, 1011, 767, 703; δ_H (400 MHz, $CDCl_3$) 7.24-7.37 (5H, m, 5 x Ar-H), 3.62 (1H, q, J 6.7 Hz, N-CH<), 2.69-2.80 (4H, m, 2 x β-CH$_2$), 2.42 (4H, t, J 6.2 Hz, 2 x α-CH$_2$), 1.42 (3H, d, J 6.7 Hz, -CH$_3$); δ_C (100.6 MHz, $CDCl_3$) 209.86 (C=O), 143.57 (*ipso* Ar), 128.49 (*meta* Ar), 127.50 (*ortho* Ar), 127.29 (*para* Ar), 63.55 (N-CH<), 50.15 (β-CH$_2$), 41.69 (α-CH$_2$), 19.51 (CH$_3$); m/z (ESI+) 236 [M+H+CH$_3$OH]$^+$, 204 [M+H]$^+$; *In agreement with published data.*[228]

N-Benzylidene benzylamine 220

220
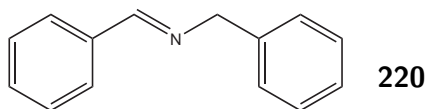
To a suspension of 4 Å molecular sieves (3 g) in dichloromethane (15 mL) was added benzaldehyde (212 mg, 2.0 mmol, 1.0 equiv) and benzylamine (214 mg, 2.0 mmol, 1.0 equiv). The reaction was left to stir at 40 °C for 1.5 h. The molecular sieves were filtered off and washed with some acetone. Concentration under reduced pressure gave product **220** (386 mg, 99%) as a colourless oil; R_f 0.65 (1:1 ethyl acetate:hexane); ν_{max} (film) 3085, 3062, 3028, 2872, 2840, 1702, 1644 (imine), 1601, 1580, 1496, 1452, 1379, 1343, 1311, 1292, 1027, 753, 694; δ_H (400 MHz, CDCl$_3$) 8.41 (1H, s, Ph-C$\underline{H}$=N-), 7.81-7.78 (2H, s, 2 x Ar-H), 7.43-7.26 (8H, m, 8 x Ar-H), 4.84 (2H, s, N-C$\underline{H}_2$-Ph); δ_C (100.6 MHz, CDCl$_3$) 162.15 (Ph-$\underline{C}$H=N-), 139.42 (*ipso* Ph-CH=N-), 136.28 (*ipso* Ph-CH$_2$N), 130.91, 128.74, 128.63, 128.41, 128.12, 127.13, 65.20 (N-$\underline{C}$H$_2$-Ph). *In agreement with published data.*[229,230]

E-1,4-Hexadien-3-ol 233

233
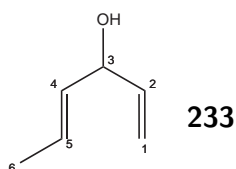
Crotonaldehyde (747 mg, 10.70 mmol, 1.3 equiv) in THF (6 mL) was added dropwise to an ice-cooled solution of vinylmagnesium bromide in THF (8.00 mmol, 1.0 M in THF, 1.0 equiv) under an atmosphere of nitrogen. After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of saturated NH$_4$Cl (10 mL) and ice (10 g) and stirred vigorously for 5 min. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic phases were dried over MgSO$_4$. Concentration of the solvent under reduced pressure and purification by column chromatography (ethylacetate:hexane 1:3) gave alcohol **233** (639 mg, 82%) as a pale yellow oil; R_f 0.17 (5:1 hexane:diethyl ether); ν_{max} (film) 3370, 3296, 2918, 1671, 1634, 1336, 1378, 1074, 990, 967, 924; δ_H (400 MHz, CDCl$_3$) 5.83 (1H, ddd, *J* 17 Hz, 10.4 Hz, 5.9 Hz, H-2), 5.66 (1H, dqd, *J* 15.3 Hz, 6.5 Hz, 0.8 Hz, H-5), 5.46 (1H, ddq, *J* 15.3 Hz, 6.7 Hz, 1.5 Hz, H-4), 5.18 (1H, dt, *J* 17.2 Hz, 1.4 Hz, H-1$_{trans}$), 5.06 (1H, dt, *J* 10.4 Hz 1.2 Hz, H-1$_{cis}$), 4.51 (1H, t, *J* 6.0 Hz, H-3), 1.82-1.74 (3H, m, H-6); δ_C (100.6 MHz, CDCl$_3$) 138.78

(C2), 131.22 (C4), 126.63 (C5), 113.68 (C1), 72.83 (C3), 16.71 (C6). *In agreement with published data.*[231]

E-1,4-Hexadien-3-one 238

238
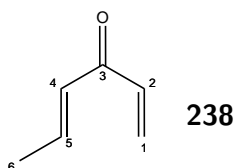
Crude allylic alcohol **233** (167 mg, 1.70 mmol, 1.0 equiv) was added to 4 Å molecular sieves suspended in CH_2Cl_2 (13 mL). MnO_2(3.69 g, 42.50 mmol, 25.0 equiv) was added in portions and the mixture was stirred at 50 °C for 3 h. The mixture was filtered through a pad of Celite, followed by washing with CH_2Cl_2 (150 mL). Concentration of the solvent under reduced pressure gave crude ketone **238** (115 mg, 71%) as a yellow oil; R_f 0.34 (5:1 hexane:ethyl acetate); ν_{max} (film) 2969, 2931, 1713, 1444, 1377, 1256, 1164, 1129, 1086, 970, 735; δ_H (400 MHz, CDCl$_3$) 6.96 (1H, dq, *J* 15.5 Hz, 6.8 Hz, H-5), 6.59 (1H, dd, *J* 17.4 Hz, 10.6 Hz, H-2), 6.39 (1H, dq, *J* 15.6 Hz, 1.6 Hz, H-4), 6.28 (1H, dd, *J* 17.4 Hz, 1.3 Hz, H-1$_{trans}$), 5.81 (1H, dd, *J* 10.6 Hz, 1.3 Hz, H-1$_{cis}$), 1.94 (3H, dd, *J* 6.8 Hz, 1.6 Hz, H-6); δ_C (100.6 MHz, CDCl$_3$) 189.83 (C3), 144.31 (C5), 134.98 (C2), 129.87, 128.51, 18.64 (C6). *In agreement with published data.*[159,232]

E-Octa-1,4-dien-3-ol 234

234
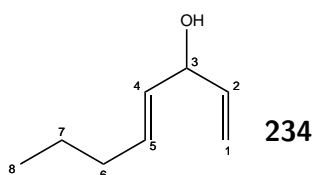
trans-2-Hexenal (1.37 g, 14.00 mmol, 1.0 equiv) in THF (12 mL) was added dropwise to an ice-cooled solution of vinylmagnesium bromide in THF (16.00 mmol, 0.7 M in THF, 1.1 equiv) under an atmosphere of nitrogen. After allowing the flask to warm to room temperature and stirring for 1 h, the reaction mixture was poured into a mixture of saturated NH_4Cl (20 mL) and ice (24 g) and stirred for 10 min. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic phases were washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Crude alcohol **234** (1.74 g, 99%) was obtained

as a yellow oil; R$_f$ 0.40 (3:1 hexane:ethyl acetate); ν_{max} (film) 3392, 3081, 2960, 2930, 2873, 1692, 1639, 1458, 1380, 1262, 1019, 989, 970, 920 δ_{H} (400 MHz, CDCl$_3$) 5.91 (1H, ddd, *J* 16.9 Hz, 10.4 Hz, 5.8 Hz, H-2), 5.64-5.74 (1H, m, H-5), 5.50 (1H, dd, *J* 15.4 Hz, 6.7 Hz, H-4), 5.26 (1H, d, *J* 17.3 Hz, H-1$_{\text{trans}}$), 5.12 (1H, d, *J* 10.5 Hz, H-1$_{\text{cis}}$), 4.59 (1H, t, *J* 5.5 Hz, H-3), 2.03 (2H, app q, *J* 7.1 Hz, H-6), 1.36-1.45 (2H, m, H-7), 0.90 (3H, t, *J* 7.4 Hz, H-8); δ_{C} (100.6 MHz, CDCl$_3$) 140.01 (C2), 132.95 (C5), 131.21 (C4), 114.85 (C1), 74.05 (C3), 34.44 (C6), 22.35 (C7), 13.82 (C8). *In agreement with published data.*[233]

E-Octa-1,4-dien-3-one 240

240
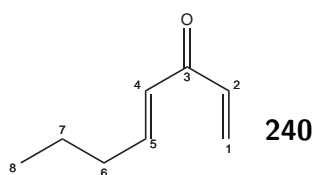
Method A:

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (343 mg, 1.51 mmol, 1.1 equiv) was added to crude allylic alcohol **234** (173 mg, 1.37 mmol, 1.0 equiv.) and 4 Å molecular sieves in CH$_2$Cl$_2$ (4 mL). The mixture was stirred at rt for 18 h, filtered and washed with CH$_2$Cl$_2$ (30 mL). Concentration of the solvent under reduced pressure and purification by column chromatography (hexane:diethyl ether 5:1) gave ketone **240** (30 mg, 18%) as a colourless oil.

Method B:

Crude allylic alcohol **234** (711 mg, 5.64 mmol, 1.0 equiv) was added to 4 Å molecular sieves suspended in CH$_2$Cl$_2$ (30 mL). MnO$_2$ (12.26 g, 141.00 mmol, 25.0 equiv) was added in portions and the mixture was stirred at 50 °C for 3 h. The mixture was filtered through a pad of Celite, followed by washing with CH$_2$Cl$_2$ (400 mL). Concentration of the solvent under reduced pressure gave crude ketone **240** (433 mg, 62%) as a yellow oil; R$_f$ 0.65 (3:2 hexane:ethyl acetate); ν_{max} (film) 2962, 2932, 2874, 1667, 1633, 1612, 1403, 1219, 1100, 1043; δ_{H} (400 MHz, CDCl$_3$) 6.94 (1H, dt, *J* 15.6 Hz, 6.9 Hz, H-5), 6.61 (1H, dd, *J* 17.4 Hz, 10.6 Hz, H-2), 6.36 (1H, dt, *J* 15.7 Hz, 1.5 Hz, H-4), 6.28 (1H, dd, *J* 17.4 Hz, 1.3 Hz, H-1$_{\text{trans}}$), 5.81 (1H, dd, *J* 10.6 Hz, 1.3 Hz, H-1$_{\text{cis}}$), 2.20-2.26 (2H, m, H-6), 1.47-1.57 (2H, m, H-7), 0.94 (3H, t, *J* 7.4 Hz, H-8); δ_{C} (100.6 MHz, CDCl$_3$) 189.99 (C3), 149.06 (C5), 135.04 (C2), 128.45 & 128.44 (C4 & C1), 34.84 (C6), 21.50

(C7), 13.85 (C8); m/z (ESI+) 157 $[M+H+CH_3OH]^+$, 125 $[M+H]^+$; Exact Mass Calcd for $C_8H_{12}O$ $[M+H]^+$ requires m/z 125.0961 Found 125.0959 (APCI+).

4*E*-1-Phenylpenta-1,4-dien-3-ol 235

235
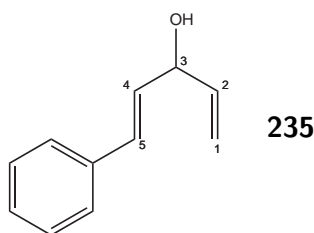
Cinnamaldehyde (925 mg, 10.70 mmol, 1.3 equiv) in THF (6 mL) was added dropwise to an ice-cooled solution of vinylmagnesium bromide in THF (8.00 mmol, 1.0 M in THF, 1.0 equiv) under an atmosphere of nitrogen. After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of saturated NH_4Cl (10 mL) and ice (10 g) and stirred for 5 min. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic phases were dried over $MgSO_4$. Concentration of the solvent under reduced pressure and purification by column chromatography (ethylacetate:hexane 1:8) gave alcohol **235** (1.09 g, 86%) as a pale yellow oil; R_f 0.41 (3:2 hexane:ethyl acetate); ν_{max} (film) 3351, 3027, 1656, 1599, 1494, 1449, 987, 966, 750, 692; δ_H (400 MHz, CDCl$_3$) 7.37-7.11 (5H, m, Ph), 6.55 (1H, d, J 16.0 Hz, H-5), 6.17 (1H, dd, J 15.9 Hz, 6.4 Hz, H-4), 5.91 (1H, ddd, J 17.2 Hz, 10.4 Hz, 5.9 Hz, H-2), 5.28 (1H, dt, J 17.2 Hz, 1.2 Hz, H-1$_{trans}$), 5.13 (1H, dt, J 10.4 Hz, 1.1 Hz, H-1$_{cis}$), 4.75 (1H, t, J 6.0 Hz, H-3); δ_C (100.6 MHz, CDCl$_3$) 138.19 (C2), 135.51 (*ipso* Ph), 129.83 (C4), 129.26 (*para* Ph), 127.56 (*meta* Ph), 126.78, 125.52, 114.45 (C1), 72.84 (C3). *In agreement with published data.*[234,235]

4*E*-1-Phenyl-penta-1,4-dien-3-one 239

239
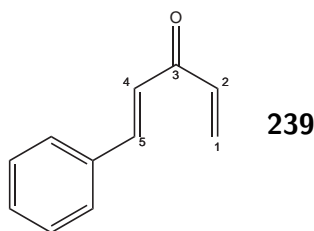
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (674 mg, 2.97 mmol, 1.1 equiv) was added to crude allylic alcohol **235** (436 mg, 2.70 mmol, 1.0 equiv) in 1,4-dioxane (8.5

mL). The mixture was stirred at rt for 18 h, filtered and washed with CH_2Cl_2 (20 mL). Concentration under reduced pressure and purification by column chromatography (ethylacetate:hexane 1:8) afforded ketone **239** (317 mg, 74%) as a yellow oil; R_f 0.54 (3:2 hexane:ethyl acetate); ν_{max} (film) 3048, 1655, 1623, 1592, 1497, 1451, 1404, 1348, 1205, 1104, 984, 875, 691; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 16.0 Hz, H-5), 7.58-7.60 (2H, m, 2 x Ar-H), 7.40-7.42 (3H, m, 3 x Ar-H), 7.02 (1H, d, *J* 16.0 Hz, H-4), 6.72 (1H, dd, *J* 17.4 Hz, 10.6 Hz, H-2), 6.39 (1H, dd, *J* 17.4 Hz 1.2 Hz, H-1$_{trans}$), 5.90 (1H, dd, *J* 10.4 Hz, 1.1 Hz, H-1$_{cis}$); δ_C (100.6 MHz, $CDCl_3$) 189.72 (C3), 144.14 (C5), 135.59, 134.77, 130.76, 129.12, 128.78, 128.54, 124.25 (C4). *In agreement with published data.*[236,237]

E-1-(4-Chlorophenyl)penta-1,4-dien-3-ol 236
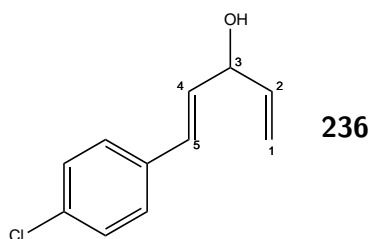
E-4-Chlorocinnamaldehyde (1.000 g, 6.00 mmol, 1.0 equiv) in THF (8 mL) was added dropwise to an ice-cooled solution of vinylmagnesium bromide in THF (7.20 mmol, 0.7 M in THF, 1.1 equiv) under an atmosphere of nitrogen. After allowing the flask to warm to room temperature and stirring for 1 h, the reaction mixture was poured into a mixture of saturated NH_4Cl (10 mL) and ice (12 g) and stirred for 10 min. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic phases were washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Crude alcohol **236** (1.160 g, 100%) was obtained as a yellow oil; R_f 0.14 (1:2.7 diethyl ether:hexane); ν_{max} (film) 3369, 1592, 1491, 1405, 1090, 1013, 967, 926, 807; δ_H (400 MHz, $CDCl_3$) 7.26-7.31 (m, 4 H, *ortho* Ar-H and *meta* Ar-H), 6.56 (dd, 1 H, *J* 16.0 Hz, 1.1 Hz, H-5), 6.20 (dd, 1 H, *J* 15.9 Hz, 6.3 Hz, H-4), 5.96 (ddd, 1 H, *J* 17.1 Hz, 10.3 Hz, 5.9 Hz, H-2), 5.33 (dt, 1 H, *J* 17.1 Hz, 1.3 Hz, H-1$_{trans}$), 5.20 (dt, 1H, *J* 10.3 Hz, 1.3 Hz, H-1$_{cis}$), 4.80 (td, 1 H, *J* 6.2 Hz, 1.3 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) 139.16 (C2), 135.18 (*ipso* Ar), 133.50 (*para* Ar), 131.07 (C5), 129.59 (C4), 128.86 (*ortho* Ar), 127.86 (*meta* Ar), 115.76 (C1), 73.79 (C3); Mass ion not found (ESI+/-) Exact Mass Calcd for $C_{11}H_{11}ClO$ [M-OH]$^+$ requires *m/z* 177.0461 Found 177.0466 (APCI+).

E-1-(4-Chlorophenyl)penta-1,4-dien-3-one 244

244
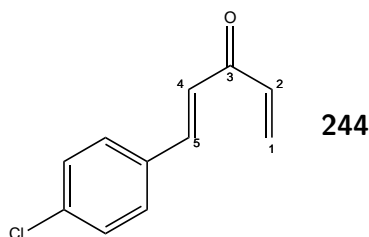
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.45 g, 6.38 mmol, 1.1 equiv) was added to crude allylic alcohol **236** (1.128 g, 5.80 mmol, 1.0 equiv) in dioxane (19 mL). The mixture was stirred at rt for 18 h, filtered and washed with CH_2Cl_2. Concentration of the solvent under reduced pressure and purification by column chromatography (hexane:diethyl ether 3:1) gave ketone **244** (627 mg, 56%) as a yellow solid; mp 178-182 °C; R_f 0.20 (1:2.7 diethyl ether:hexane); ν_{max} (solid) 1656, 1603, 1591, 1566, 1491, 1408, 1382, 1313, 1294, 1260, 1240, 1194, 11779, 1090, 1014, 970, 827; δ_H (400 MHz, CDCl$_3$) 7.61 (1H, d, *J* 16.0 Hz, H-5), 7.50 (2H, d, *J* 8.3 Hz, *ortho* Ar-H), 7.36 (2H, d, *J* 7.4 Hz, *meta* Ar-H), 6.97 (1H, d, *J* 16.0 Hz, H-4), 6.69 (1H, dd, 17.4 Hz, 10.6 Hz, H-2), 6.38 (1H, dd, *J* 17.4 Hz, 1.1 Hz, H-1$_{trans}$), 5.89 (1H, dd, *J* 10.6 Hz, 1.1 Hz, H-1$_{cis}$); δ_C (100.6 MHz, CDCl$_3$) 189.35 (C=O), 142.55 (C5), 136.60 (*para* Ar), 135.56 (C2), 133.23 (*ipso* Ar), 129.63 (*ortho* Ar), 129.36 (*meta* Ar), 128.97 (C1), 124.50 (C4); Mass ion not found (ESI+/-) Exact Mass Calcd for $C_{11}H_9ClO$ [M+H]$^+$ requires *m/z* 193.0413 Found 193.0415 (APCI+).

E-1-(4-Methoxyphenyl)penta-1,4-dien-3-ol 237

237
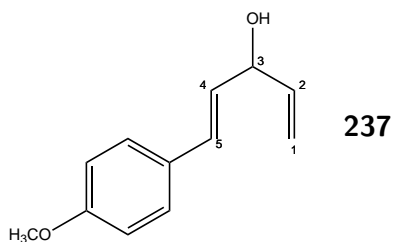
E-4-Methoxycinnamaldehyde (5.000 g, 30.82 mmol, 1.0 equiv) in THF (26 mL) was added dropwise to an ice-cooled solution of vinylmagnesium bromide in THF (35.13 mmol, 0.7 M in THF, 1.1 equiv) under an atmosphere of nitrogen. After allowing the flask to warm to room temperature and stirring for 1 h, the reaction mixture was poured into a mixture of saturated NH_4Cl (45 mL) and ice (54 g) and stirred for 5 min. The

aqueous solution was extracted with ether (3 x 60 mL) and the combined organic phases were washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Crude alcohol **237** (5.740 g, 98%) was obtained as a thick, yellow oil; R_f 0.46 (2:3 ethyl acetate:hexane); ν_{max} (film) 3392, 2961, 2837, 1660, 1606, 1512, 1464, 1422, 1300, 1251, 1175, 1109, 1032, 969, 925, 805; δ_H (400 MHz, $CDCl_3$) 7.26-7.33 (m, 2 H, *ortho* Ar-H), 6.84-6-86 (2H, m, *meta* Ar-H), 6.55 (1H, d, *J* 16.0 Hz, H-5), 6.10 (1H, dd, *J* 15.9 Hz, 6.6 Hz, H-4), 5.98 (1H, ddd, *J* 17.3 Hz, 10.5 Hz, 5.9 Hz, H-2), 5.33 (1H, dt, *J* 17.3 Hz, 1.5 Hz, H-1$_{trans}$), 5.18 (1H, dt, *J* 10.3 Hz, 1.3 Hz, H-1$_{cis}$), 3.80 (3H, s, -OC$\underline{H}_3$); δ_C (100.6 MHz, $CDCl_3$) 159.47 (*para* Ar), 139.56 (C2), 130.59 (C5), 129.42 (*ipso* Ar), 128.26 (C4), 127.87 (*ortho* Ar), 115.32 (C1), 114.11 (*meta* Ar), 74.10 (C3), 55.40 (-OCH_3). *In agreement with published data.*[238]

E-1-(4-Methoxyphenyl)penta-1,4-dien-3-one 245
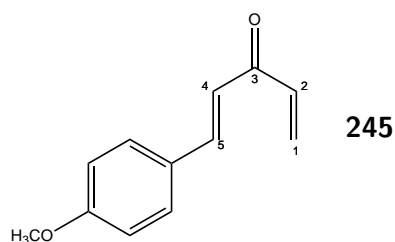
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.85 g, 8.13 mmol, 1.1 equiv) was added to crude allylic alcohol **237** (1.404 g, 7.39 mmol, 1.0 equiv) and in dioxane (27 mL). The mixture was stirred at rt for 18 h, filtered and washed with CH_2Cl_2. Concentration of the solvent under reduced pressure and purification by column chromatography (hexane:diethyl ether 3:1) gave ketone **245** (741 mg, 53%) as a yellow solid; mp 64-67 °C; R_f 0.51 (2:3 ethyl acetate:hexane); ν_{max} (solid) 2936, 2838, 1654, 1601, 1572, 1512, 1463, 1442, 1424, 1404, 1306, 1254, 1222, 1200, 1174, 1103, 1030, 988, 830; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 15.9 Hz, H-5), 7.52-7.55 (2H, m, *ortho* Ar-H), 6.86-6.95 (3H, m, *meta* Ar-H and H-4), 6.70 (1H, dd, *J* 17.4 Hz, 10.6 Hz, H-2), 6.36 (1H, dd, *J* 17.4 Hz, 1.3 Hz, H-1$_{trans}$), 5.84 (1H, dd, *J* 10.6 Hz, 1.3 Hz, H-1$_{cis}$), 3.84 (3H, s, -OC$\underline{H}_3$); δ_C (100.6 MHz, $CDCl_3$) 189.61 (C=O), 161.83 (*para* Ar), 143.93 (C5), 135.65 (C2), 130.28 (*ortho* Ar), 128.23 (C1), 127.44 (*ipso* Ar), 122.12 (C4), 114.55 (*meta* Ar), 55.52 (-OC$\underline{H}_3$). *In agreement with published data.*[159]

1-Benzyl-2-methylpiperidin-4-one 241

241
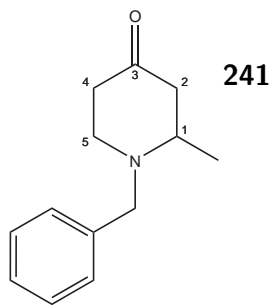
Method A:

To a suspension of 4 Å molecular sieves in CH_2Cl_2 (10.5 mL) was added divinyl alcohol **233** (216 mg, 2.20 mmol, 1.0 equiv), followed by portionwise addition of MnO_2 (4.78 g, 55.00 mmol, 25.0 equiv). Benzylamine (330 mg, 3.08 mmol, 1.4 equiv) was added and the mixture was stirred at 50 °C for 18 h. MnO_2 was filtered through a pad of Celite and washed with a mixture of CH_2Cl_2 and methanol (1:1). Concentration of the combined filtrates under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:4) gave product **241** (76 mg, 17% over three steps) as a pale yellow oil;

Method B:

Benzylamine (2.90 g, 27.06 mmol, 1.3 equiv) was dissolved in acetonitrile (30 mL) and a solution of aqueous $NaHCO_3$ (6.56 g in 17 mL H_2O) was added. The resulting suspension was cooled to 16 °C and crude ketone **238** (2.00 g, 20.83 mmol, 1.0 equiv) in acetonitrile (20 mL) was slowly added over a period of 35 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (60 mL). The solution was stirred for 20 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 60 mL). The organic layers were combined and washed with water (60 mL) and brine (60 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Purification by column-chromatography (ethyl acetate:hexane 1:2 with 1% TEA) afforded product **241** (1.66 g, 39%) as a pale yellow oil; R_f 0.33 (1:1 ethyl acetate:hexane); ν_{max} (film) 2966, 2802, 1720, 1601, 1495, 1453, 1377, 1349, 1332, 1250, 1177, 1137, 1064, 1028, 762, 733; δ_H (400 MHz, $CDCl_3$) 7.25-7.38 (5H, m, 5 x Ar-H), 3.97 (1H, d, *J* 13.4 Hz, 1 x N-C$\underline{H}_2$-Ph) 3.45 (1H, d, *J* 13.5 Hz, 1 x N-C$\underline{H}_2$-Ph), 2.97-3.02 (2H, m, H-1 and 1 x H-5), 2.53-2.56 (2H, m, 1 x H-5 and 1 x H-4), 2.37-2.40 (2H, m, H-2), 2.26-2.31 (1H, m, 1 x H-4), 1.18 (3H, d, *J* 6.4 Hz, -C$\underline{H}_3$); δ_C (100.6 MHz, $CDCl_3$) 209.89 (C=O), 139.13 (*ipso* Ar), 128.80 (Ar), 128.49 (Ar), 127.26 (*para* Ar),

57.18 (N-C$\underline{\text{H}}_2$-Ph) 56.30 (C1), 48.89 and 48.75 (C4 and C5), 41.03 (C2), 17.61 (-C$\underline{\text{H}}_3$). *In agreement with published literature.*[75]

1-Benzyl-2-propylpiperidin-4-one 243
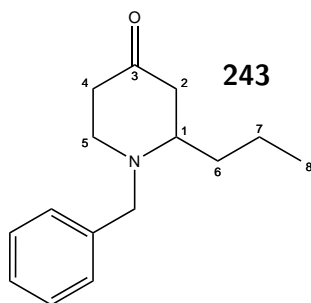
Benzylamine (196 mg, 1.83 mmol, 1.3 equiv) was dissolved in acetonitrile (5 mL) and a solution of aqueous $NaHCO_3$ (454 mg in 3 mL H_2O) was added. The resulting suspension was cooled to 16 °C and crude ketone **240** (179 mg, 1.44 mmol, 1.0 equiv) in acetonitrile (5 mL) was slowly added over a period of 40 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (12 mL). The solution was stirred for 20 min, the layers were separated and the organic layer was washed with water (12 mL) and brine (12 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent and purification by column-chromatography (ethyl acetate:hexane 1:2.95) afforded product **243** (120 mg, 36%) as a pale yellow oil; R_f 0.15 (5:1 hexane:ethyl acetate); ν_{max} (film) 3028, 2958, 2930, 2872, 2807, 1718, 1495, 1454, 1419, 1350, 1264, 1201, 1174, 1139, 1071, 1027, 942, 733; δ_H (400 MHz, CDCl$_3$) 7.25-7.39 (5H, m, 5 x Ar-H), 3.90 (1H, d, *J* 13.5 Hz, 1 x N-C$\underline{\text{H}}_2$-Ph), 3.66 (1H, d, *J* 13.5 Hz, 1 x N-C$\underline{\text{H}}_2$-Ph), 2.97-3.07 (2H, m, H-1 and 1 x H-5), 2.69-2.75 (1H, m, 1 x H-5), 2.57 (1H, ddd, *J* 14.0 Hz, 4.7 Hz, 1.3 Hz, 1 x H-2), 2.38-2.45 (1H, m, 1 x H-4), 2.29-2.35 (2H, m, 1 x H-2 and 1 x H-4), 1.54-1.64 (1H, m, 1 x H-6), 1.28-1.45 (3H, m, 1 x H-6 and 2 x H-7), 0.90 (3H, t, *J* 7.2 Hz, H-8); δ_C (100.6 MHz, CDCl$_3$) 210.28 (C=O), 139.39 (*ipso* Ar), 128.70 (*ortho* Ar), 128.53 (*meta* Ar), 127.30 (*para* Ar), 60.63 (C1), 56.11 (N-C$\underline{\text{H}}_2$-Ph), 48.09 (C5), 44.83 (C2), 39.62 (C4), 33.53 (C6), 19.04 (C7), 14.27 (C8); *m/z* (ESI+) 264 [M+H+CH$_3$OH]$^+$, 232 [M+H]$^+$; Exact Mass Calcd for C$_{16}$H$_{26}$NO [M+H+CH$_3$OH]$^+$ requires *m/z* 264.1958 Found 264.1960 (NSI+)

1-Benzyl-2-phenylpiperidin-4-one 242
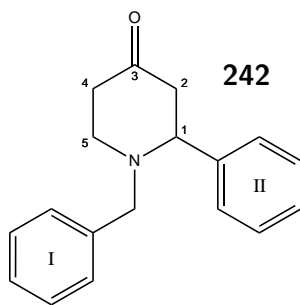
Benzylamine (139 mg, 1.30 mmol, 1.3 equiv) was added to a mixture of acetonitrile (3 mL) and aqueous $NaHCO_3$ (315 mg in 2 mL H_2O). The resulting suspension was cooled to 15 °C and ketone **239** (158 mg, 1.00 mmol, 1.0 equiv) in acetonitrile (3 mL) was slowly added over a period of 25 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (8 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and washed with water (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Purification by column-chromatography (ethyl acetate:hexane 1:7) afforded product **242** (210 mg, 79%) as a pale yellow oil; R_f 0.19 (ethyl acetate:hexane 1:8); ν_{max} (film) 3025, 2797, 1726, 1495, 1454, 1257, 1236, 1160, 1101, 1073, 1023, 907, 823; δ_H (400 MHz, $CDCl_3$) 7.24-7.48 (10H, m, 10 x Ar-H) 3.84 (1H, d, *J* 13.4 Hz, 1 x N-C<u>H</u>$_2$-Ph), 3.59 (1H, dd, *J* 11.0 Hz, 3.7 Hz, H-1), 3.20-3.25 (1H, m, 1 H, 1 x H-5), 2.94 (1H, d, *J* 13.6 Hz, 1 x N-C<u>H</u>$_2$-Ph), 2.62-2.74 (2H, m, 1 x H-2 and 1 x H-4), 2.54 (1H, app dq, *J* 14.6 Hz, 2.5 Hz, 1 x H-2), 2.32-2.39 (2 H, m, 1 x H-4 and 1 x H-5); δ_C (100.6 MHz, $CDCl_3$) 208.68 (C=O), 142.67 (*ipso* ArII), 139.10 (*ipso* ArI), 129.13, 128.66, 128.45, 127.95, 127.46 (*para* ArII), 127.20 (*para* ArI), 68.50 (C1), 58.22 (N-C<u>H</u>$_2$-Ph), 51.33 (C5), 50.45 (C2), 41.62 (C4). *In agreement with published data.*[224]

1-Benzyl-2-(4-chlorophenyl)piperidin-4-one 255
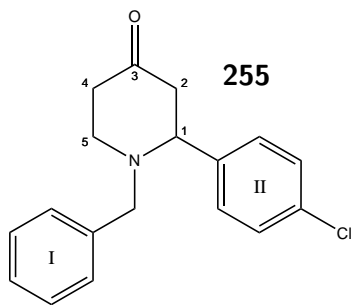
Benzylamine (74 µl, 0.68 mmol, 1.3 equiv) was dissolved in acetonitrile (1.6 mL) and a solution of aqueous $NaHCO_3$ (164 mg in 1 mL H_2O) was added. The resulting suspension was cooled to 16 °C and ketone **244** (99 mg, 0.52 mmol, 1.0 equiv) in acetonitrile (1.6 mL) was slowly added over a period of 30 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (10 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and washed with water (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Purification by column-chromatography (ethyl acetate:hexane 1:5 with 1% TEA) afforded product **255** (131 mg, 84%) as a pale yellow oil; R_f 0.32 (1:4 ethyl acetate:hexane); ν_{max} (film) 2963, 2803, 1721, 1599, 1494, 1453, 1410, 1368, 1326, 1300, 1259, 1240, 1160, 1088, 1015, 836, 736; δ_H (400 MHz, $CDCl_3$) 7.22-7.42 (9H, m, 9 x Ar-H), 3.80 (1H, d, *J* 13.5 Hz, 1 x N-C$\underline{H}_2$-Ph), 3.58 (1H, dd, *J* 10.8 Hz, 3.9 Hz, H-1), 3.19-3.24 (1H, m, 1 x H-5), 2.95 (1H, d, *J* 13.5 Hz, 1 x N-C$\underline{H}_2$-Ph), 2.61-2.69 (2H, m, 1 x H-2, 1 x H-4), 2.52 (1H, ddd, *J* 14.5 Hz, 3.8 Hz, 2.3 Hz, 1 x H-2), 2.32-2.39 (2H, m, 1 x H-5, 1 x H-4); δ_C (100.6 MHz, $CDCl_3$) 208.13 (C=O), 141.20 (*ipso* ArII), 138.72 (*ipso* ArI), 133.59 (*para* ArII), 129.34, 128.78, 128.60, 128.51, 127.33 (*para* ArI), 67.68 (C1), 58.20 (N-C$\underline{H}_2$-Ph), 51.21 (C5), 50.20 (C2), 41.50 (C4); *m/z* (ESI+) 318 $[M+H+H_2O]^+$, 300 $[M+H]^+$, 282, 120, 91; Exact Mass Calcd for $C_{18}H_{18}NO$ $[M+H]^+$ requires *m/z* 300.1150 Found 300.1153 (NSI+)

1-Benzyl-2-(4-methoxyphenyl)piperidin-4-one 256

Benzylamine (409 µl, 3.74 mmol, 1.3 equiv) was dissolved in acetonitrile (9 mL) and a solution of aqueous $NaHCO_3$ (907 mg in 6 mL H_2O) was added. The resulting suspension was cooled to 16 °C and ketone **245** (542 mg, 2.88 mmol, 1.0 equiv) in acetonitrile (9 mL) was slowly added over a period of 35 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (20 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 20 mL). The organic layers were combined and washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Purification by column-chromatography (ethyl acetate:hexane 1:3.2 with 1% TEA) afforded product **256** (712 mg, 84%) as a pale yellow oil; R_f 0.19 (1:5 ethyl acetate:hexane); ν_{max} (film) 3029, 2800, 1720, 1611, 1585, 1512, 1495, 1454, 1367, 1325, 1303, 1248, 1173, 1115, 1032, 837, 816, 770, 738; δ_H (400 MHz, $CDCl_3$) 7.35-7.39 (2H, m, *ortho* ArII-H), 7.21-7.33 (5H, m, 5 x ArI-H), 6.90-6.93 (2H, m, *meta* ArII-H), 3.84 (1H, d, *J* 13.6 Hz, 1 x N-C<u>H</u>$_2$-Ph), 3.81 (3H, s, -OC<u>H</u>$_3$), 3.54 (1H, dd, *J* 10.9 Hz, 3.7 Hz, H-1), 3.21 (1H, ddd, *J* 11.1 Hz, 6.2 Hz, 2.4 Hz, 1 x H-5), 2.92 (1H, d, *J* 13.5 Hz, 1 x N-C<u>H</u>$_2$-Ph), 2.61-2.72 (2H, m, 1 x H-2 and 1 x H-4), 2.52 (1H, ddd, *J* 14.6 Hz, 3.7 Hz, 2.5 Hz, 1 x H-2), 2.30-2.37 (2H, m, 1 x H-4 and 1 x H-5); δ_C (100.6 MHz, $CDCl_3$) 208.84 (C=O), 159.24 (*para* ArII), 139.21 (*ipso* ArI), 134.68 (*ipso* ArII), 128.64, 128.53, 128.41, 127.14 (*para* ArI), 114.41 (*meta* ArII), 67.76 (C1), 58.04 (N-<u>C</u>H$_2$-Ph), 55.42 (-O<u>C</u>H$_3$), 51.25 (C5), 50.51 (C2), 41.61 (C4); *m/z* (ESI+) 314 [M+H+H$_2$O]$^+$, 296 [M+H]$^+$, 177, 120, 91; Exact Mass Calcd for $C_{20}H_{26}NO_2$ [M+H+CH$_3$OH]$^+$ requires *m/z* 328.1907 Found 328.1910 (NSI+).

S-2-Methyl-1-(*S*-1-phenylethyl)piperidin-4-one 258 and *R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-one 259
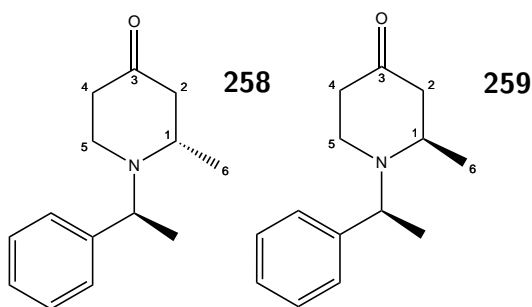
S-α-Phenylethylamine (4.92 g, 40.63 mmol, 1.3 equiv) was dissolved in acetonitrile (30 mL) and a solution of aqueous $NaHCO_3$ (9.85 g in 20 mL H_2O) was added. The resulting suspension was cooled to 16 °C and crude ketone **238** (3.000 g, 31.25 mmol, 1.0 equiv) in acetonitrile (30 mL) was slowly added over a period of 30 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (60 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 60 mL). The organic layers were combined and washed with water (60 mL) and brine (60 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Purification by column-chromatography (ethyl acetate:hexane 1:6 → 1:3) afforded product **258** (1.280 g, 19%) as a pale yellow oil and product **259** (1.220 g, 18%) as a pale red solid;

Product 258, eluting first: $[\alpha]_D^{21}$ -47.7 (*c* 0.30, $CHCl_3$); R_f 0.25 (1:4 ethyl acetate:hexane); ν_{max} (film) 3028, 2969, 2814, 1720, 1601, 1492, 1453, 1380, 1353, 1307, 1262, 1230, 1180, 1140, 766, 70; δ_H (400 MHz, $CDCl_3$) 7.43-7.45 (2H, m, 2 x Ar-H), 7.31-7.35 (2H, m, 2 x Ar-H), 7.23-7.27 (1H, m, 1 x Ar-H), 4.01 (1H, q, *J* 6.7 Hz, -CH̲(CH₃)C₆H₅), 3.34-3.41 (1H, m, H-1), 2.75 (1H, ddd, *J* 12.5 Hz, 7.7 Hz, 4.9 Hz, 1 x H-5), 2.61-2.70 (2H, m, 1 x H-5 and 1 x H-2), 2.29-2.37 (1H, m, 1 x H-4), 2.16-2.24 (2H, m, 1 x H-4 and 1 x H-2), 1.33 (3H, d, *J* 6.8 Hz, -CH(CH̲₃)C₆H₅), 1.14 (3H, d, *J* 6.4 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 210.54 (C=O), 145.32 (*ipso* Ar), 128.46, 127.34, 126.99 (*para* Ar), 57.76 (C̲H(CH₃)C₆H₅), 52.54 (C1), 48.89 (C2), 43.99 (C5), 41.46 (C4), 16.47 (C6), 16.33 (-CH(C̲H₃)C₆H₅). *In agreement with published literature.*[175]

Product 259, eluting second: $[\alpha]_D^{20}$ -40.5 (*c* 0.15, $CHCl_3$); mp 72-75 °C; R_f 0.12 (1:4 ethyl acetate:hexane); ν_{max} (solid) 3027, 2971, 2838, 1719, 1493, 1454, 1418, 1376, 1351, 1285, 1228, 1179, 1122, 1076, 1027, 768, 702; δ_H (400 MHz, $CDCl_3$) 7.30-7.35 (4H, m, 4 x Ar-H), 7.23-7.27 (1H, m, 1 x Ar-H), 3.92 (1H, q, *J* 6.7 Hz, -CH̲(CH₃)C₆H₅),

3.12-3.19 (1H, m, H-1), 2.90-3.00 (2H, m, 2 x H-5), 2.49-2.58 (2H, m, 1 x H-2 and 1 x H-4), 2.28-2.35 (1H, m, 1 x H-4), 2.07-2.12 (1H, m, 1 x H-2), 1.42 (3H, d, J 6.7 Hz, -CH(C$\underline{H}_3$)C$_6$H$_5$), 1.03 (3H, d, J 6.6 Hz, H-6); δ_C (100.6 MHz, CDCl$_3$) 210.54 (C=O), 144.11 (*ipso* Ar), 128.55, 127.35, 127.22 (*para* Ar), 58.84 ($\underline{C}$H(CH$_3$)C$_6$H$_5$), 52.45 (C1), 48.37 (C2), 43.19 (C5), 41.20 (C4), 21.93 (-CH($\underline{C}$H$_3$)C$_6$H$_5$), 14.78 (C6). *In agreement with published literature.*[174]

S-1-(*S*-1-Phenylethyl)-2-propylpiperidin-4-one 260 and
## *R*-1-(*S*-1-phenylethyl)-2-propylpiperidin-4-one 261
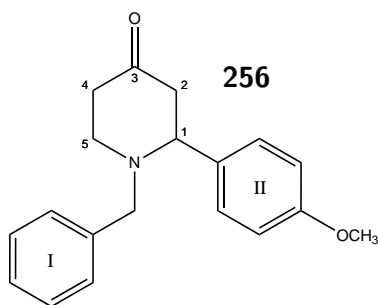

S-α-Phenylethylamine (496 mg, 4.09 mmol, 1.3 equiv) was dissolved in acetonitrile (9 mL) and a solution of aqueous NaHCO$_3$ (1.01 g in 6 mL H$_2$O) was added. The resulting suspension was cooled to 16 °C and crude ketone **240** (400 mg, 3.22 mmol, 1.0 equiv) in acetonitrile (9 mL) was slowly added over a period of 30 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (12 mL). The solution was stirred for 20 min, the layers were separated and the organic layer was washed with water (12 mL) and brine (12 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and filtered. Evaporation of the solvent and purification by column-chromatography (ethyl acetate:hexane 1:5) afforded product **260** (123 mg, 16%) as a pale yellow oil and product **261** (86 mg, 11%) as pale yellow oil;

Product 260, eluting first: $[\alpha]_D^{22}$ -36.4 (*c* 0.52, CHCl$_3$); R$_f$ 0.42 (1:3 ethyl acetate:hexane); ν_{max} (film) 3026, 2959, 2931, 2872, 1716, 1601, 1492, 1454, 1351, 1282, 1219, 1178, 1082, 967, 770; δ_H (400 MHz, CDCl$_3$) 7.40-7.43 (2H, m, 2 x Ar-H), 7.31 (2H, m, 2 x Ar-H), 7.23-7.26 (1H, m, 1 x Ar-H), 4.00 (1H, q, J 6.7 Hz, -C$\underline{H}$(CH$_3$)C$_6$H$_5$), 3.17-3.22 (1H, m, H-1), 2.92-2.98 (1H, m, 1 x H-5), 2.83-2.89 (1H, m, 1 x H-5), 2.65 (1H, ddd, J 13.9 Hz, 5.5 Hz, 0.8 Hz, 1 x H-2), 2.36-2.44 (1H, m, 1 x H-4), 2.24 (1H, ddd, J 14.0 Hz, 4.1 Hz, 2.0 Hz, 1 x H-2), 2.12-2.18 (1H, m, 1 x H-4), 1.45-1.53 (1H, m, 1 x H-6), 1.25-1.37 (6H, m, 3 x -CH(C$\underline{H}_3$)C$_6$H$_5$, 2 x H-7, 1 x H-6), 0.87 (3H, t, J

7.1, H-8); δ_C (100.6 MHz, CDCl$_3$) 210.89 (C=O), 145.80 (*ipso* Ar), 128.55 (*ortho* Ar), 127.30 (*meta* Ar), 127.12 (*para* Ar), 58.19 (-CH(CH$_3$)C$_6$H$_5$), 57.00 (C1), 44.54 (C2), 43.72 (C5), 40.33 (C4), 32.56 (C6), 19.30 and 19.14 (C7 and -CH(CH$_3$)C$_6$H$_5$), 14.34 (C8); *m/z* (ESI+) 264 [M+H+H$_2$O]$^+$, 246 [M+H]$^+$, 142, 105; Exact Mass Calcd for C$_{28}$H$_{26}$NO [M+H+CH$_3$OH]$^+$requires *m/z* 278.2115 Found 278.2118 (NSI+).

Product 261, eluting second: $[\alpha]_D^{21}$ -25.0 (*c* 1.08, CHCl$_3$); R$_f$ 0.23 (1:3 ethyl acetate:hexane); ν_{max} (film) 3027, 2960, 2932, 2872, 1713, 1602, 1492, 1454, 1352, 1281, 1219, 1174, 1083, 967, 770; δ_H (400 MHz, CDCl$_3$) 7.23-7.42 (5H, m, 5 x Ar-H), 3.99 (1H, q, *J* 6.5 Hz, -CH(CH$_3$)C$_6$H$_5$), 3.27-3.32 (1H, m, H-1), 2.88-2.99 (2H, m, H-5), 2.49-2.61 (2H, m, 1 x H-2 and 1 x H-4), 2.11-2.19 (2H, m, 1 x H-2 and 1 x H-4), 1.47-1.58 (1H, m, 1 x H-6), 1.40 (3H, d, *J* 6.5 Hz, 3 x -CH(CH$_3$)C$_6$H$_5$); 1.20-1.37 (3H, m, 2 x H-7, 1 x H-6), 0.88 (3H, t, *J* 7.0 Hz, H-8); δ_C (100.6 MHz, CDCl$_3$) 210.79 (C=O), 145.57 (*ipso* Ar), 128.65 (*ortho* Ar), 127.26 (*meta & para* Ar), 58.71 (-CH(CH$_3$)C$_6$H$_5$), 56.18 (C1), 44.15 (C2), 43.51 (C5), 39.48 (C4), 32.34 (C6), 22.50 (-CH (CH$_3$)C$_6$H$_5$), 19.50(C7), 14.11 (C8); *m/z* (ESI+) 264 [M+H+H$_2$O]$^+$, 246 [M+H]$^+$, 142, 105; Exact Mass Calcd for C$_{16}$H$_{24}$NO [M+H]$^+$requires *m/z* 246.1852 Found 246.1855 (NSI+).

R-2-Phenyl-1-(*S*-1-phenylethyl)piperidin-4-one 262 and *S*-2-phenyl-1-(*S*-1-phenylethyl)piperidin-4-one 263

S-α-Phenylethylamine (291 mg, 2.40 mmol, 1.3 equiv) was dissolved in acetonitrile (6 mL) and a solution of aqueous NaHCO$_3$ (599 mg in 4 mL H$_2$O) was added. The resulting suspension was cooled to 16 °C and ketone **239** (300 mg, 1.90 mmol, 1.0 equiv) in acetonitrile (6 mL) was slowly added over a period of 40 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (12 mL). The solution was stirred for 20 min, the layers were separated and the organic layer was washed with water (12 mL) and brine (12 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$ and filtered. Evaporation of the solvent and purification by column-chromatography (ethyl

acetate:hexane 1:5.5) afforded product **262** (249 mg, 47%) as a pale yellow solid and product **263** (83 mg, 16%) as a pale yellow oil;

Product 262, eluting first: $[\alpha]_D^{21}$ -34.2 (*c* 0.42, CHCl$_3$); mp 87-90 °C; R$_f$ 0.31 (17:3 hexane:ethyl acetate); ν_{max} (solid) 3059, 2972, 2820, 1712, 1600, 1492, 1447, 1421, 1380, 1365, 1331, 1257, 1239, 1168, 1122, 1027, 1011, 805, 785; δ_H (400 MHz, CDCl$_3$) 7.47-7.50 (4H, m, 4 x Ar-H), 7.22-7.40 (6H, m, 6 x Ar-H), 3.90-3.98 (2H, m, 1 x -C$\underline{H}$(CH$_3$)C$_6$H$_5$ and 1 x H-1), 2.88-2.93 (1H, m, 1 x H-5), 2.73 (1H, dd, *J* 14.4 Hz, 10.4 Hz, 1 x H-2), 2.49-2.64 (3H, m, 1 x H-2 and 1 x H-4 and 1 x H-5), 2.29-2.33 (1H, m, 1 x H-4), 1.23 (3H, d, *J* 6.8 Hz, -C$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 209.15 (C=O), 143.93 (*ipso* Ar), 142.30 (*ipso* Ar), 129.13, 128.24, 127.96, 127.57, 127.49, 126.82, 64.90 (C1), 54.97 ($\underline{C}$H(CH$_3$)C$_6$H$_5$), 50.39 (C2), 44.16 (C5), 42.05 (C4), 9.52 ($\underline{C}$H$_3$); *m/z* (ESI+) 312 [M+H+CH$_3$OH]$^+$, 280 [M+H]$^+$, 176, 147, 129; Exact Mass Calcd for C$_{20}$H$_{42}$NO$_2$ [M+H+CH$_3$OH]$^+$ requires *m/z* 312.1958 Found 312.1961 (NSI+)

Product 263, eluting second: $[\alpha]_D^{22}$ -95.1 (*c* 0.28, CHCl$_3$); R$_f$ 0.23 (17:3 hexane:ethyl acetate); ν_{max} (film) 3029, 2971, 2817, 1721, 1601, 1493, 1454, 1363, 1309, 1261, 1241, 1108, 1073, 1030, 759, 702; δ_H (400 MHz, CDCl$_3$) 7.24-7.43 (8H, m, 8 x Ar-H), 7.06-7.09 (2H, m, 2 x Ar-H), 4.03 (1H, q, *J* 7.1 Hz, -C$\underline{H}$(CH$_3$)C$_6$H$_5$), 3.67 (1H, dd, *J* 9.4 Hz, 4.5 Hz, H-1), 3.34 (1H, ddd, *J* 12.0 Hz, 5.7 Hz, 3.8 Hz, 1 x H-5), 2.37-2.68 (4H, m, 2 x H-4 and 2 x H-2), 2.20-2.24 (1H, m, 1 x H-5), 1.44 (3H, d, *J* 7.2 Hz, C$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 208.83 (C=O), 143.10 (*ipso* Ar), 139.01 (*ipso* Ar), 129.12, 128.46, 128.07, 127.67, 127.66, 127.36, 64.63 (C1), 56.63 ($\underline{C}$H(CH$_3$)C$_6$H$_5$), 50.56 (C2), 44.52 (C5), 41.84 (C4), 19.56 ($\underline{C}$H$_3$); *m/z* (ESI+) 312 [M+H+CH$_3$OH]$^+$, 280 [M+H]$^+$, 176, 147, 129; Exact Mass Calcd for C$_{19}$H$_{22}$NO [M+H]$^+$requires *m/z* 280.1696 Found 280.1698 (NSI+).

R-2-(4-Chlorophenyl)-1-(*S*-1-phenylethyl)piperidin-4-one 264 and *S*-2-(4-chlorophenyl)-1-(*S*-1-phenylethyl)piperidin-4-one 265
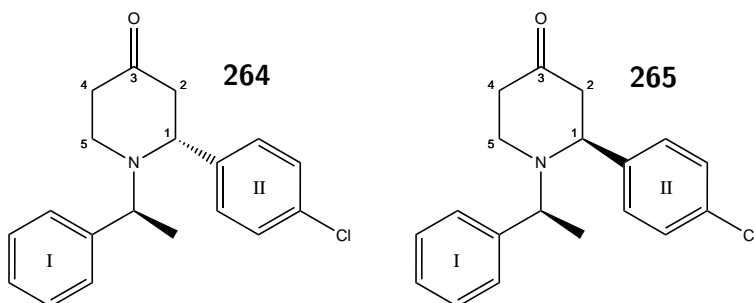
S-α-Phenylethylamine (345 µl, 2.68 mmol, 1.3 equiv) was dissolved in acetonitrile (6.5 mL) and a solution of aqueous NaHCO$_3$ (649 mg in 4.3 mL H$_2$O) was added. The

resulting suspension was cooled to 16 °C and ketone **244** (396 mg, 2.06 mmol, 1.0 equiv) in acetonitrile (6.5 mL) was slowly added over a period of 30 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1.5 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (15 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 15 mL). The organic layers were combined and washed with water (15 mL) and brine (15 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Purification by column-chromatography (ethyl acetate:hexane 1:5.5 with 1.5% TEA) afforded product **264** (270 mg, 42%) as a pale yellow solid and a mixture of product **264** and product **265** (170 mg, 26%) as a pale yellow oil. NMR investigation indicated that the mixed fractions of diastereomers were a 0.47:1 ratio of **264**:**265**. Further purification of this diastereomeric mixture afforded pure **265**.

Product 264, eluting first: $[\alpha]_D^{24}$ -56.0 (*c* 0.38, CHCl$_3$); mp 91-94 °C; R$_f$ 0.39 (1:4 ethyl acetate:hexane); ν_{max} (solid) 2989, 2813, 1719, 1600, 1487, 1447, 1412, 1381, 1366, 1299, 1260, 1239, 1166, 1123, 1088, 1014, 835; δ_H (400 MHz, CDCl$_3$) 7.23-7.46 (9H, m, 9 x Ar-H), 3.89-3.95 (2H, m, -C$\underline{H}$(CH$_3$)C$_6$H$_5$, H-1), 2.90 (1H, ddd, *J* 11.6 Hz, 5.7 Hz, 3.4 Hz, 1 x H-5), 2.47-2.69 (4H, m, 2 x H-2, 1 x H-4, 1 x H-5), 2.32 (1H, ddd, *J* 14.0 Hz, 5.4 Hz, 2.9 Hz, 1 x H-4), 1.23 (3H, d, *J* 6.8 Hz, -C$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 208.61 (C=O), 143.62 (*ipso* ArI), 140.87 (*ipso* ArII), 133.60 (*para* ArII), 129.35, 128.88, 128.34, 127.41, 126.98 (*para* ArI), 64.07 (C1), 55.16 (-$\underline{C}$H(CH$_3$)C$_6$H$_5$), 49.98 (C2), 44.02 (C5), 41.86 (C4), 9.83 (-$\underline{C}$H$_3$); *m/z* (ESI+) 332 [M+H+H$_2$O]$^+$, 314 [M+H]$^+$, 210, 134, 105; Exact Mass Calcd for C$_{19}$H$_{20}$ClNO [M+H+CH$_3$OH]$^+$ requires *m/z* 346.1568 Found 346.1572 (NSI+).

Product 265, eluting second: $[\alpha]_D^{23}$ -116.5 (*c* 0.13, CHCl$_3$); R$_f$ 0.30 (1:4 ethyl acetate:hexane); ν_{max} (film) 2972, 2815, 1720, 1600, 1487, 1453, 1411, 1370, 1278, 1261, 1240, 1167, 1111, 1088, 1014, 834, 768, 734; δ_H (400 MHz, CDCl$_3$) 7.23-7.44 (7H, m, 7 x Ar-H), 7.04-7.06 (2H, m, *ortho* ArI-H), 3.97 (1H, q, *J* 7.1 Hz, -C$\underline{H}$(CH$_3$)C$_6$H$_5$), 3.67 (1H, dd, *J* 8.5 Hz, 5.4 Hz, H-1), 3.33 (1H, ddd, *J* 12.0 Hz, 5.7 Hz, 4.0 Hz, 1 x H-5), 2.37-2.51 (3H, m, 2 x H-2 and 1 x H-4), 2.25 (1H, td, *J* 11.8 Hz, 3.3 Hz, 1 x H-5), 1.44 (3H, d, *J* 7.1 Hz, -C$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 208.35 (C=O), 141.65 (*ipso* ArII), 138.88 (*ipso* ArI), 133.27 (*para* ArII), 129.31, 128.98, 128.36, 128.16, 127.49 (*para* ArI), 63.77 (C1), 56.87 (-$\underline{C}$H(CH$_3$)C$_6$H$_5$), 50.17(C2), 44.39 (C5), 41.70 (C4), 19.63 (-$\underline{C}$H$_3$); *m/z* (ESI+) 332 [M+H+H$_2$O]$^+$, 314 [M+H]$^+$, 210, 134, 105; Exact Mass Calcd for C$_{19}$H$_{21}$ClNO [M+H]$^+$requires *m/z* 314.1306 Found 314.1309 (NSI+).

R-2-(4-Methoxyphenyl)-1-(*S*-1-phenylethyl)piperidin-4-one 266 and *S*-2-(4-methoxyphenyl)-1-(*S*-1-phenylethyl)piperidin-4-one 267
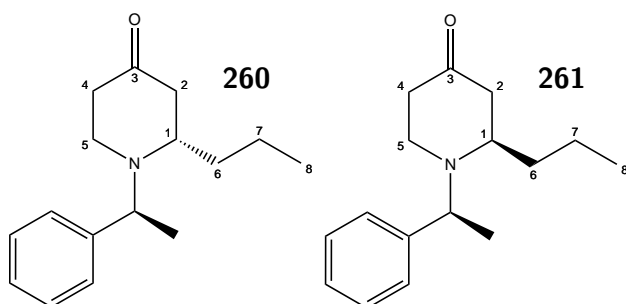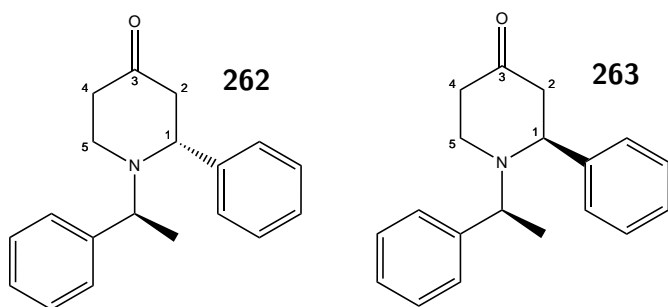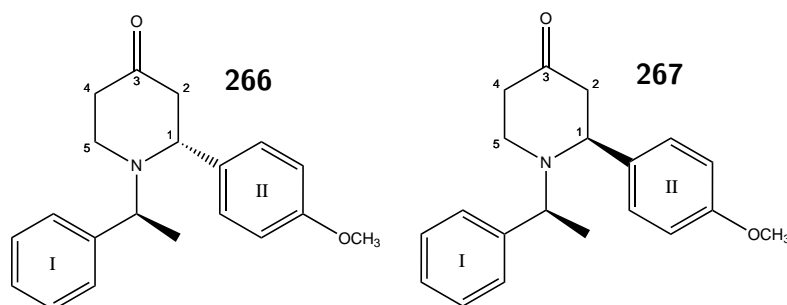

S-α-Phenylethylamine (365 μl, 2.83 mmol, 1.3 equiv) was dissolved in acetonitrile (6 mL) and a solution of aqueous NaHCO$_3$ (687 mg in 4 mL H$_2$O) was added. The resulting suspension was cooled to 16 °C and ketone **245** (410 mg, 2.18 mmol, 1.0 equiv) in acetonitrile (6 mL) was slowly added over a period of 35 minutes. Upon addition of the ketone, the reaction was stirred at reflux for 1 h. Evaporation of acetonitrile *in vacuo* was followed by the addition of ethyl acetate (12 mL). The solution was stirred for 15 min, the layers were separated and the aqueous layer was again extracted with ethyl acetate (2 x 12 mL). The organic layers were combined and washed with water (12 mL) and brine (12 mL). The organic layer was dried with anhydrous Na$_2$SO$_4$, filtered and the solvent was evaporated *in vacuo*. Purification by column-chromatography (ethyl acetate:hexane 1:5.5 with 1.5% TEA) afforded product **266** (284 mg, 42%) as a pale yellow solid and a mixture of product **266** and product **267** (99 mg, 15%) as a pale yellow oil. NMR investigation indicated that the mixed fractions of diastereomers were a 0.34:1 ratio of **266**:**267**. Further purification of this diastereomeric mixture afforded pure **267** as a pale yellow oil.

Product 266, eluting first: $[\alpha]_\mathrm{D}^{21}$ -90.9 (*c* 0.22, CHCl$_3$); mp 76-79 °C; R$_f$ 0.24 (1:6 ethyl acetate:hexane); ν_max (solid) 2968, 2835, 1717, 1611, 1584, 1512, 1446, 1380, 1366, 1302, 1250, 1174, 1031, 835, 773, 724, 699; δ_H (400 MHz, CDCl$_3$) 7.45-7.47 (2H, m, *meta* ArI-H), 7.38-7.41 (2H, m, *ortho* ArII-H), 7.31-7.34 (2H, m, *ortho* ArI-H), 7.21-7.25 (1H, m, *para* ArI-H), 6.89-6.93 (2H, m, *meta* ArII-H), 3.95 (1H, q, *J* 6.7 Hz, -C$\underline{\mathrm{H}}$(CH$_3$)C$_6$H$_5$), 3.86 (1H, dd, *J* 10.3 Hz, 3.7 Hz, H-1), 3.80 (3H, s, -OC$\underline{\mathrm{H}}_3$), 2.87-2.92 (1H, m, 1 x H-5), 2.70 (1H, dd, *J* 14.2 Hz, 10.6 Hz, 1 x H-2), 2.47-2.58 (3H, m, 1 x H-2 and 1 x H-4 and 1 x H-5), 2.27-2.32 (1H, m, 1 x H-4), 1.22 (3H, d, *J* 6.8 Hz, -CH(C$\underline{\mathrm{H}}_3$)C$_6$H$_5$); δ_C (100.6 MHz, CDCl$_3$) 209.34 (C=O), 159.25 (*para* ArII), 144.06 (*ipso* ArI), 134.33 (*ipso* ArII), 128.61 (*ortho* ArII), 128.22 (*ortho* ArI), 127.47 (*meta* ArI), 126.77 (*para* ArI), 114.45 (*meta* ArII), 64.21 (C1), 55.41 (-OC$\underline{\mathrm{H}}_3$), 54.85 (-C$\underline{\mathrm{H}}$(CH$_3$)C$_6$H$_5$), 50.51 (C2), 44.13 (C5), 42.06 (C4), 9.57 (-C$\underline{\mathrm{H}}_3$); *m/z* (ESI+) 328 [M+H+H$_2$O]$^+$, 310 [M+H]$^+$, 206, 177,

134, 105; Exact Mass Calcd for $C_{21}H_{28}NO_2$ [M+H+CH_3OH]$^+$requires m/z 342.2064 Found 342.2067 (NSI+).

Product 267, eluting second: $[\alpha]_D^{22}$ -131.2 (c 0.32, $CHCl_3$); R$_f$ 0.16 (1:6 ethyl acetate:hexane); ν_{max} (film) 3029, 2970, 2835, 1719, 1611, 1585, 1511, 1454, 1365, 1302, 1249, 1173, 1033, 835, 771, 704; δ_H (400 MHz, $CDCl_3$) 7.22-7.35 (5H, m, *ortho* ArII-H and *meta* ArI-H and *para* ArI-H), 7.07-7.09 (2H, m, *ortho* ArI-H), 6.94-6.98 (2H, m, *meta* ArII-H), 4.04 (1H, q, J 7.1 Hz, -C$\underline{H}$(CH_3)C_6H_5), 3.85 (3H, s, -OC$\underline{H}_3$), 3.63 (1H, dd, J 9.1 and 4.5 Hz, H-1), 3,32 (1H, ddd, J 12.0 Hz, 5.7 Hz, 3.9 Hz, 1 x H-5), 2.36-2.66 (4H, m, 2 x H-2 and 2 x H-4), 2.21 (1H, td, J 11.5 Hz, 3.3 Hz, 1 x H-5), 1.43 (3H, d, J 7.1 Hz, -CH(C$\underline{H}_3$)C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 209.01 (C=O), 159.01 (*para* ArII), 139.25 (*ipso* ArI), 135.00 (*ipso* ArII), 128.74 (*ortho* ArII), 128.42 (*ortho* ArI), 128.04 (*meta* ArI), 127.29 (*para* ArI), 114.40 (*meta* ArII), 63.92 (C1), 56.42 (-$\underline{C}$H(CH_3)C_6H_5), 55.42 (-O$\underline{C}H_3$), 50.65 (C2), 44.51 (C5), 41.85 (C4), 19.64 (-$\underline{C}H_3$); m/z (ESI+) 342 [M+H+CH_3OH]$^+$, 310 [M+H]$^+$, 206, 177, 134, 105; Exact Mass Calcd for $C_{20}H_{24}NO_2$ [M+H]$^+$requires m/z 310.1802 Found 310.1804 (NSI+).

Benzamide 276

276
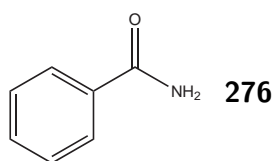
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added benzylamine (107 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave benzamide **276** (119 mg, 98%) as a white solid;

To a suspension of 4 Å molecular sieves (10.0 g) in dichloromethane (130 mL) was added benzylamine (2.00 g, 18.7 mmol, 1.0 equiv). Manganese dioxide (40.57 g, 466.6 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (600 mL). Concentration under reduced pressure and recrystallisation (hexane) gave benzamide **276** (2.18 g, 96%) as a white solid; mp 125-127 °C; R$_f$ 0.13 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3360 (N-H), 3162 (N-H), 3062, 1651 (C=O), 1618, 1575, 1448, 1296, 1178, 1141, 1120, 1024, 917; δ_H (400 MHz, DMSO-d$_6$) 7.99 (1H, s, -CON$\underline{H}_2$),

7.88 (2H, d, *J* 8.4 Hz, *ortho* Ph-H), 7.52 (1H, t, *J* 7.3 Hz, *para* Ph-H), 7.45 (2 H, t, *J* 7.4 Hz, *meta* Ph-H), 7.37 (1 H, s, -CON$\underline{\text{H}}_2$); δ_{C} (100.6 MHz, DMSO-d$_6$) 167.91 (C=O), 134.26 (*ipso* Ph), 131.24 (*para* Ph), 128.23 (*meta* Ph), 127.47 (*ortho* Ph). *In agreement with published data.*[239,240]

4-Methylbenzamide 298

298

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-methyl-benzylamine (121 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure afforded 4-methylbenzamide **298** (132 mg, 98%) as a white solid; mp 159-160 °C; R$_f$ 0.13 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3337 (N-H), 3157 (N-H), 2929, 1666 (C=O), 1613, 1568, 1411, 1395, 1189, 1144, 1123, 1021; δ_{H} (400 MHz, DMSO-d$_6$) 7.89 (1H, s, -CON$\underline{\text{H}}_2$), 7.77 (2 H, d, *J* 8.1 Hz, *ortho* Ar-H), 7.24 (3H, d, *J* 8.0 Hz, *meta* Ar-H and -CON$\underline{\text{H}}_2$), 2.34 (3H, s, C$\underline{\text{H}}_3$); δ_{C} (100.6 MHz, DMSO-d$_6$) 167.78 (C=O), 141.07 (*para* Ar), 131.47 (*ipso* Ar), 128.74 (*meta* Ar), 127.51 (*ortho* Ar), 20.96 (-$\underline{\text{C}}$H$_3$). *In agreement with published data.*[240,241]

4-Trifluoromethylbenzamide 300
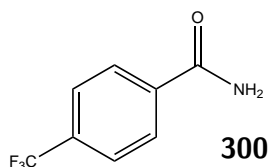
300

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-trifluoromethyl-benzylamine (175 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The filtrate was concentrated under reduced pressure and the crude product was washed with a small amount of hexane (5 mL). 4-Trifluoromethylbenzamide

300 was obtained as a white solid (165 mg, 0.87 mmol) in a yield of 87%; mp 182-184 °C; R_f 0.18 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3375 (N-H), 3177 (N-H), 1655 (C=O), 1627, 1579, 1516, 1418, 1322, 1067, 1016 δ_H (400 MHz, DMSO-d$_6$) 8.21 (1H, s, -CON$\underline{H}_2$), 8.06 (2H, d, *J* 8.1 Hz, *ortho* Ar-H), 7.83 (2H, d, *J* 8.2 Hz, *meta* Ar-H), 7.63 (1H, s, -CON$\underline{H}_2$); δ_C (100.6 MHz, DMSO-d$_6$) 166.73 (C=O), 138.11 (*ipso* Ar), 131.18 (q, $^2J_{CF}$ 32 Hz, *para* Ar), 128.37 (*ortho* Ar), 125.31 (q, $^3J_{CF}$ 3.2 Hz, *meta* Ar), 124.01 (q, $^1J_{CF}$ 272 Hz, -$\underline{C}$F$_3$); ^{19}F-NMR δ (376 MHz, DMSO) -61.30. *In agreement with published data.*[240,242]

Thiophene-2-carboxamide 302
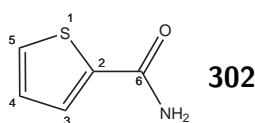
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-(aminomethyl)-thiophene (113 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure afforded thiophene-2-carboxamide **302** (125 mg, 98%) as a white solid; mp 176-178 °C; R_f 0.12 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3356 (N-H), 3164 (N-H), 1650 (C=O), 1601, 1524, 1429, 1392, 1242, 1123, 1096, 1041, 858; δ_H (400 MHz, DMSO-d$_6$) 7.98 (1H, s, -CON$\underline{H}_2$), 7.75-7.73 (2H, m, H-3 and H-5), 7.38 (1H, s, -CON$\underline{H}_2$), 7.12 (1H, t, *J* 4.1 Hz, H-4); δ_C (100.6 MHz, DMSO-d$_6$) 162.90 (C=O), 140.35 (C2), 131.01 (C3), 128.70 (C5), 127.93 (C4). *In agreement with published data.*[243,244]

4-Methoxybenzamide 304
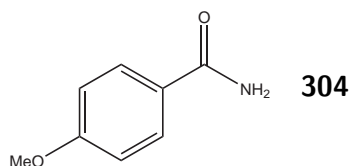
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-methoxy-benzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for

24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column-chromatography (ethyl acetate:hexane, 1:1 → 4:1). 4-Methoxybenzamide **304** (140 mg, 93%) was obtained as a white solid; mp 165-167 °C; R_f 0.08 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3387 (N-H), 3159 (N-H), 2843, 1641 (C=O), 1615, 1572, 1515, 1457, 1421, 1391, 1308, 1249, 1190, 1179, 1145, 1114, 1023, 848; δ_H (400 MHz, DMSO-d_6) 7.84 (2H, d, *J* 8.7 Hz, *ortho* Ar-H), 7.84 (1H, s, -CON$\underline{H}_2$), 7.18 (1H, s, -CON$\underline{H}_2$), 6.97 (2H, d, *J* 8.7 Hz, *meta* Ar-H), 3.79 (3H, s, -OC$\underline{H}_3$); δ_C (100.6 MHz, DMSO-d_6) 167.47 (C=O), 161.61 (*para* Ar), 129.39 (*ortho* Ar), 126.51 (*ipso* Ar), 113.41 (*meta* Ar), 55.35 (-OC$\underline{H}_3$). *In agreement with published data.*[240]

3-Methoxybenzamide 306

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 3-methoxy-benzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column-chromatography (ethyl acetate:hexane, 1:1 → 4:1). 3-Methoxybenzamide **306** (125 mg, 83%) was obtained as a white solid; mp 131-133 °C; R_f 0.16 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3128, 1664 (C=O), 1627, 1581, 1463, 1429, 1330, 1247, 1131, 1030, 902, 877; δ_H (400 MHz, DMSO-d_6) 7.96 (1H, s, -CON$\underline{H}_2$), 7.46-7.33 (4H, m, 3 x Ar-H and -CON$\underline{H}_2$), 7.08 (1H, ddd, *J* 8.1 Hz, 2.6 Hz, 0.8 Hz, H-6), 3.79 (3H, s, -OC$\underline{H}_3$); δ_C (100.6 MHz, DMSO-d_6) 167.64 (C=O), 159.14 (C1), 135.73 (C3), 129.33 (C5), 119.69 (C4), 117.07 (C6), 112.63 (C2), 55.23 (-OC$\underline{H}_3$). *In agreement with published data.*[242]

2-Methoxybenzamide 308 and 2-methoxybenzonitrile 427

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-methoxy-benzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column-chromatography (ethyl acetate:hexane, 1:1 → 3:1). 2-Methoxybenzamide **427** (104 mg, 69%) was obtained as a white solid and 2-methoxybenzonitrile **427** (37 mg, 28%) was obtained as a colorless oil;

2-Methoxybenzamide **308**: mp 126-128 °C; R_f 0.15 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3410 (N-H), 3190 (N-H), 3013, 2980, 2948, 2840, 1623 (C=O), 1597, 1573, 1488, 1462, 1434, 1394, 1274, 1240, 1179, 1106, 1020; δ_H (400 MHz, DMSO-d_6) 7.79 (1H, dd, J 7.7 Hz, 1.8 Hz, H-3), 7.63 (1H, s, -CON$\underline{H}_2$), 7.52 (1H, s, -CON$\underline{H}_2$), 7.47 (1H, ddd, J 8.4 Hz, 7.4 Hz, 1.9 Hz, H-5), 7.12 (1H, d, J 8.2 Hz, H-6), 7.02 (1H, td, J 7.6 Hz, 0.9 Hz, H-4), 3.88 (3H, s, -OC$\underline{H}_3$); δ_C (100.6 MHz, DMSO-d_6) 166.34 (C=O), 157.24 (C1), 132.48 (C5), 130.74 (C3), 122.73 (C4), 120.41 (C2), 111.99 (C6), 55.82 (-O$\underline{C}$H$_3$). *In agreement with published data.*[240,245]

2-Methoxybenzonitrile **427**: R_f 0.64 (1:1 ethyl acetate:hexane); ν_{max} (film) 2975, 2948, 2843, 2228 (CN), 1688, 1599, 1494, 1465, 1290, 1262, 1021, 758; δ_H (400 MHz, CDCl$_3$) 7.72-7.25 (2H, m, H-3 and H-5), 7.16-6.64 (2H, m, H-4 and H-6), 3.87 (3H, m, -OC$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 161.25 (C1), 134.39 (C5), 133.79 (C3), 120.77 (C4), 116.52 (C6), 111.27 (CN), 101.83 (C2), 56.00 (-O$\underline{C}$H$_3$). *In agreement with published data.*[246,247]

4-Trifluoromethoxybenzamide 310

310

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-trifluoromethoxy-benzylamine (191 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column-chromatography (ethyl acetate:hexane, 1:1 → 3:1). 4-Trifluoromethoxybenzamide **310** (181 mg, 88%) was obtained as a white solid; mp 152-154 °C; R_f 0.18 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3372 (N-H), 3172 (N-H), 1652 (C=O), 1622, 1585, 1510, 1419, 1397, 1207, 1153, 1015, 926, 858; δ_H (400 MHz, DMSO-d$_6$) 8.11 (1H, s, -CON$\underline{H}_2$), 8.00 (2H, d, *J* 8.7 Hz, *ortho* Ar-H), 7.51 (1H, s, -CON$\underline{H}_2$), 7.45 (2H, d, *J* 8.3 Hz, *meta* Ar-H); δ_C (100.6 MHz, DMSO-d$_6$) 166.59 (C=O), 150.26 (*para* Ar), 133.37 (*ipso* Ar), 129.75 (*ortho* Ar), 120.50 (*meta* Ar), 119.93 (q, -O$\underline{C}$F$_3$, $^1J_{CF}$ 255 Hz); ^{19}F-NMR δ (376 MHz, DMSO) -56.68. *In agreement with published data.*[248]
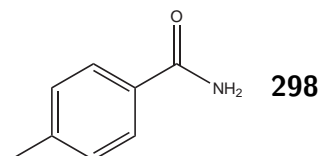
4-Chlorobenzamide 293

293

To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-chloro-benzylamine (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure gave 4-chlorobenzamide **293** (154 mg, 99%) as a white solid;
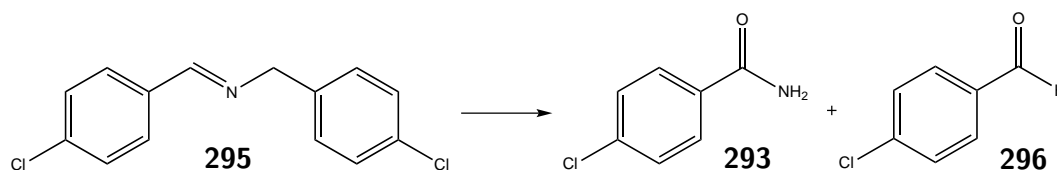
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added *N*-(4-Chlorobenzylidene)-1-(4-chlorophenyl)methanamine **295** (263 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave 4-chlorobenzamide **293** (148 mg, 95%) as a white solid. Concentration of the hexane filtrate under reduced pressure gave 4-chlorobenzaldehyde **296** (0.136 mg, 97%) as a white solid;

4-Chlorobenzamide **293**: mp 176-177 °C; R_f 0.18 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3368 (N-H), 3177 (N-H), 1658 (C=O), 1620, 1568, 1493, 1407, 1388, 1089, 1013; δ_H (400 MHz, DMSO-d$_6$) 8.06 (1H, s, -CON$\underline{H}_2$), 7.89 (2H, d, *J* 8.3 Hz, *ortho* Ar-H), 7.53 (2H, d, *J* 9.6 Hz, *meta* Ar-H), 7.47 (1H, s, -CON$\underline{H}_2$); δ_C (100.6 MHz, DMSO-d$_6$) 166.78 (C=O), 136.04 (*para* Ar), 133.00 (*ipso* Ar), 129.38 (*meta* Ar), 128.28 (*ortho* Ar). *In agreement with published data.*[249,250]

4-Chlorobenzaldehyde **296**: mp 43-46 °C; R_f 0.57 (1:2 ethyl acetate:hexane); ν_{max} (solid) 1690 (C=O), 1575, 1386, 1292, 1206, 1153, 1092, 1011, 838, 813; δ_H (400 MHz, DMSO-d$_6$) 10.00 (1H, s, C$\underline{H}$O), 7.91-7.94 (2H, m, *ortho* Ar-H), 7.65-7.68 (2H, m, *meta* Ar-H); δ_C (100.6 MHz, DMSO-d$_6$) 192.15 ($\underline{C}$HO), 139.40 (*para* Ar), 134.85 (*ipso* Ar), 131.20 (*ortho* Ar), 129.38 (*meta* Ar). *In agreement with published data.*[251]

N-(4-Chlorobenzylidene)-1-(4-chlorophenyl)methanamine 295
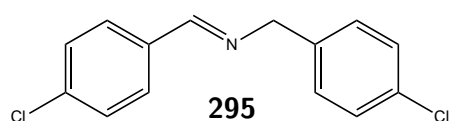
To a suspension of 4 Å molecular sieves (3 g) in dichloromethane (30 mL) was added 4-chlorobenzaldehyde (1.66 g, 11.8 mmol, 1.0 equiv) and 4-chloro-benzylamine (1.67 g, 11.8 mmol, 1.0 equiv). The reaction was left to stir at 40 °C for 1.5 h. The molecular sieves were filtered off and washed with some acetone. Concentration under reduced pressure gave *N*-(4-chlorobenzylidene)-1-(4-chlorophenyl)methanamine **295** (3.051 mg,

99%) as a white solid; mp 62-64 °C; R_f 0.56 (1:2 ethyl acetate:hexane); ν_{max} (solid) 2817, 1642, 1593, 1568, 1489, 1428, 1404, 1372, 1090, 1047, 1013, 862; δ_H (400 MHz, DMSO-d_6) 8.50 (1H, s, Ar-C$\underline{H}$=N-), 7.79 (2H, d, J 8.6 Hz, 1 x Ar-H), 7.52 (2H, d, J 8.4 Hz, 2 x Ar-H), 7.34-7.41 (4H, m, 2 x Ar-H), 4.76 (2H, s, N-C$\underline{H}_2$-Ar); δ_C (100.6 MHz, DMSO-d_6) 161.11, 138.55, 135.48, 134.80, 131.45, 129.72, 129.68, 128.86, 128.36, 62.90. *In agreement with published data.*[252]

3-Chlorobenzamide 312
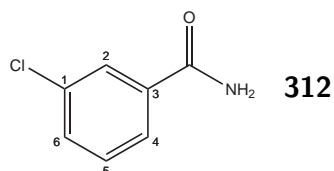
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 3-chloro-benzylamine (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave 3-chlorobenzamide **312** (142 mg, 92%) as a white solid; mp 132-134 °C; R_f 0.26 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3347 (N-H), 3167 (N-H), 1656 (C=O), 1620, 1561, 1426, 1387, 1122, 901; δ_H (400 MHz, DMSO-d_6) 8.11 (1H, s, -CON$\underline{H}_2$), 7.91 (1H, s, H-2), 7.83 (1H, d, J 7.7 Hz, H-4), 7.59 (1H, d, J 8.0 Hz, H-6), 7.54 (1H, s, -CON$\underline{H}_2$), 7.49 (1H, t, J 7.9 Hz, H-5); δ_C (100.6 MHz, DMSO-d_6) 166.44 (C=O), 136.32 (C3), 133.16 (C1), 131.12 (C6), 130.30 (C5), 127.33 (C2), 126.22 (C4). *In agreement with published data.*[250]
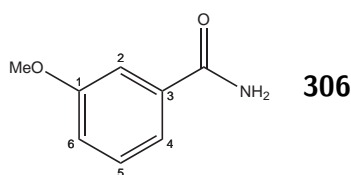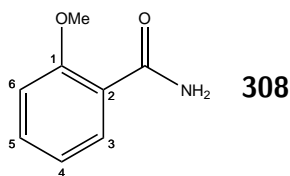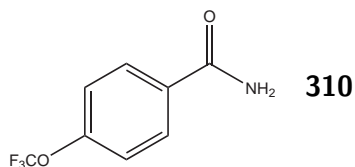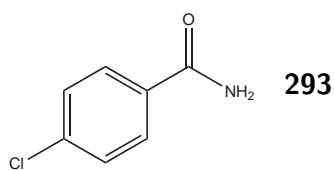
2-Chlorobenzamide 314
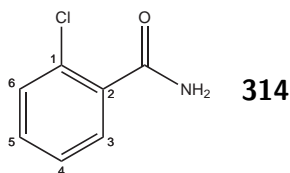
To a suspension of 4 Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-chloro-benzylamine (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40 °C for 24 h.

The reaction mixture was filtered through a pad of Celite and washed with hot (60 °C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column-chromatography (ethyl acetate:hexane, 1:1 → 4:1). 2-Chlorobenzamide **314** (128 mg, 83%) was obtained as a white solid; mp 139-141 °C; R_f 0.19 (1:1 ethyl acetate:hexane); ν_{max} (solid) 3357 (N-H), 3172 (N-H), 1638 (C=O), 1563, 1480, 1432, 1401, 1119, 1047, 953; δ_H (400 MHz, DMSO-d_6) 7.87 (1H, s, -CON$\underline{H}_2$), 7.59 (1H, s, -CON$\underline{H}_2$), 7.47-7.35 (4H, m, 4 x Ar-H); δ_C (100.6 MHz, DMSO-d_6) 168.17 (C=O), 137.17 (C), 130.56 (CH), 129.62 (C), 129.60 (CH), 128.66 (CH), 127.03 (CH). *In agreement with published data.*[241]

1-Benzyl-4-(methoxymethylene)piperidine 318
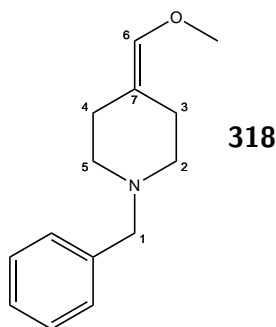
(Methoxymethyl)triphenylphosphonium chloride (1.028 g, 3.00 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (6 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (1.500 mL, 3.00 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -78 °C for 5 min and then allowed to warm to room temperature while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **201** (379 mg, 2.00 mmol, 1.0 equiv) in absolute THF (4 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH$_4$Cl solution (5 mL) and ethyl acetate (10 mL) were added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:ethyl acetate 1:1) afforded **318** (400 mg, 92%) as a colourless oil; ν_{max} (film) 2932, 2898, 2833, 2796, 1692, 1495, 1454, 1358, 1227, 1190, 1125, 1069, 987, 737; δ_H (400 MHz, CDCl$_3$) 7.22-7.33 (5H, m, 5 x Ar-H), 5.78 (1H, s, H-6), 3.54 (3H, s, -OC$\underline{H}_3$), 3.50 (2H, s, H-1), 2.39 (4H, t, J 5.6 Hz, 2 x H-2, 2 x H-5),

2.30 (2H, t, *J* 5.5 Hz, 2 x H-3), 2.06 (2H, t, *J* 5.5 Hz, 2 x H-4); δ_C (100.6 MHz, CDCl$_3$) 139.69 (C6), 138.63 (*ipso* Ar), 129.32 (*ortho* Ar), 128.27 (*meta* Ar), 127.04 (*para* Ar), 114.89 (C7), 63.37 (C1), 59.50 (-OCH$_3$), 55.35 (C5), 54.17 (C2), 29.81 (C4), 25.28 (C3); *m/z* (ESI+) 218 [M+H]$^+$, 186, 91; Exact Mass Calcd for C$_{14}$H$_{20}$NO [M+H]$^+$ requires *m/z* 218.1539 Found 218.1539 (NSI+).

N-Benzyl-4-formyl-piperidine 319
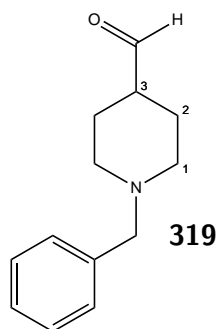
Method A:

1.6 N HCl (1 mL) was added to a solution of **318** (100 mg, 0.46 mmol) in THF (1 mL) and stirred at 45 °C for two hours. THF was evaporated under reduced pressure and the residue was diluted with water (4 mL). The pH was adjusted to 10 by the addition of an aqueous Na$_2$CO$_3$ solution. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 6 mL) and the combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and aldehyde **319** (87 mg, 95%) was obtained as a colourless oil. The product could be used for the next step without the need of further purification.

Method B:

Magnesium bromide etherate (1.867 g, 7.23 mmol, 2.0 equiv) was added to toluene (7.5 mL) and 4 Å molecular sieves and the system was put under an atmosphere of nitrogen and heated to 40 °C. **323** (734 mg, 3.61 mmol, 1.0 equiv) in toluene (1.5 mL) was added to the mixture and the reaction was stirred for 35 min. Water (10 mL) was added to quench the reaction and the creamy mixture was stirred until it became clear. The aqueous mixture was extracted with ethyl acetate (3 x 25 mL), washed with brine and dried over Na$_2$SO$_4$. The solvent was reduced under reduced pressure and the crude was subjected to destillation under reduced pressure at a temperature of 145-149 °C to give product **319** (141 mg, 19%) as a colourless oil.

R_f 0.13 (1:1 ethyl acetate:hexane); ν_{max} (film) 3028, 2941, 2804, 2759, 1723, 1495, 1453, 1394, 1366, 1342, 1311, 1264, 1144, 967, 739; δ_H (400 MHz, CDCl$_3$) 9.64 (1H, d, J 1.1 Hz, -C$\underline{H}$O), 7.23-7.34 (m, 5 H, 5 x Ar-H), 3.50 (2H, s, -N-C$\underline{H}_2$-Ph), 2.82 (2H, dt, J 11.1 Hz, 3.6 Hz, 2 x H-1), 2.20-2.28 (1H, m, H-3), 2.11 (2H, dt, J 11.2 Hz, 2.7 Hz, 2 x H-1), 1.85-1.91 (2H, m, 2 x H-2), 1.64-1.74 (2H, m, 2 x H-2); δ_C (100.6 MHz, CDCl$_3$) 201.24 (C=O); 138.34 (*ipso* Ar), 129.23 (*ortho* Ar), 128.36 (*meta* Ar), 127.19 (*para* Ar), 63.38 (-N-$\underline{C}$H$_2$-Ph), 52.62 (C1), 48.14 (C3), 25.57 (C2); *In agreement with published data.*[196,253]

6-Benzyl-1-oxa-6-azaspiro[2.5]octane 323
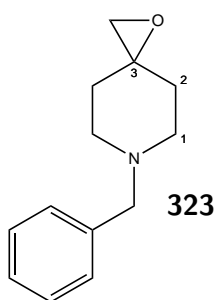
A solution of 1-benzylpiperidin-4-one **201** (185 µl, 1.00 mmol, 1.0 equiv) in anhydrous DMSO (8 mL) was added to a dry mixture of *t*-BuOK (224 mg, 2.00 mmol, 2.0 equiv) and Me$_3$S(O)$^+$I$^-$ (440 mg, 2.00 mmol, 2.0 equiv) under an atmosphere of nitrogen. The resulting solution was stirred at 55 °C for 50 min. The mixture was added with water (50 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL), dried over anhydrous MgSO$_4$, filtered and evaporated *in vacuo* to afford epoxide **323** (201 mg, 99%) as a colourless oil. **323** could be used for the next step without the need of further purification; R_f 0.18 (1:1 ethyl acetate:hexane); ν_{max} (film) 3029, 2948, 2918, 2799, 1495, 1467, 1454, 1366, 1351, 1256, 1130, 1093, 1072, 1012, 920, 791, 739; δ_H (400 MHz, CDCl$_3$) 7.23-7.36 (5H, m, 5 x Ar-H), 3.56 (2H, s, -N-C$\underline{H}_2$-Ph), 2.65 (2H, s, O-CH$_2$-), 2.53-2.62 (4H, m, H-1), 1.80-1.87 (2H, m, 2 x H-2), 1.52-1.58 (2H, m, 2 x H-2); δ_C (100.6 MHz, CDCl$_3$) 138.57 (*ipso* Ar), 129.22 (*ortho* Ar), 128.37 (*meta* Ar), 127.18 (*para* Ar), 63.07 (-N-$\underline{C}$H$_2$-Ph) 57.57 (C3) 53.87 (O-CH$_2$-), 52.03 (C1), 33.16 (C2). *In agreement with published data.*[196]

6-Benzyl-5-methyl-1-oxa-6-azaspiro[2.5]octane 330

330
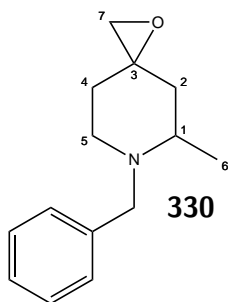
A solution of 1-benzyl-2-methylpiperidin-4-one **241** (300 mg, 1.48 mmol, 1.0 equiv) in anhydrous DMSO (12 mL) was added to a dry mixture of *t*-BuOK (330 mg, 2.95 mmol, 2.0 equiv) and $Me_3S(O)^+I^-$ (649 mg, 2.95 mmol, 2.0 equiv) under an atmosphere of nitrogen. The resulting solution was stirred at 55 °C for 60 min. The mixture was added with water (75 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (ethyl acetate:hexane 1:2→ 1:1) afforded epoxide **330** as a mixture of inseparable stereoisomers (218 mg, 68%) as a colourless oil; R_f 0.21 (1:1 ethyl acetate:hexane); ν_{max} (film) 3029, 2918, 2799, 1599, 1494, 1452, 1377, 1328, 1290, 1150, 1066, 1011, 917, 777, 734; δ_H (400 MHz, $CDCl_3$) 7.22-7.36 (5H, m, 5 x Ar-H), 4.07 (1H, d, *J* 13.5 Hz, 1 x -N-C$\underline{H}_2$-Ph), 3.26 (1H, d, *J* 13.5 Hz, 1 x -N-C$\underline{H}_2$-Ph), 2.80 (1H, td, *J* 11.7 Hz, 4.2 Hz, 1 x H-5), 2.70-2.75 (1H, m, H-1), 2.65 (2H, s, H-7), 2.34 (1H, td, *J* 11.6 Hz, 3.3 Hz, 1 x H-5), 1.95 (1H, ddd, *J* 13.5 Hz, 11.3 Hz, 4.5 Hz, 1 x H-4), 1.85 (1H, dd, *J* 13.5 Hz, 10.1 Hz, 1 x H-2), 1.37-1.42 (1H, m, 1 x H-2), 1.24-1.30 (1H, m, 1 x H-4), 1.20 (3H, d, *J* 6.3 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 19.44 (C6), 32.78 (C4), 41.20 (C2), 49.26 (C5), 53.60 (C7), 54.73 (C1), 57.36 (C3), 57.77 (-N-C$\underline{H}_2$-Ph), 126.97 (*para* Ar), 128.33 (*meta* Ar), 129.13 (*ortho* Ar), 139.39 (*ipso* Ar); *m/z* (ESI+) 218 [M+H]$^+$, 126, 91; Exact Mass Calcd for $C_{14}H_{19}NO$ [M+H]$^+$requires *m/z* 218.1539 Found 218.1539 (NSI+).

6-Benzyl-5-phenyl-1-oxa-6-azaspiro[2.5]octane 331
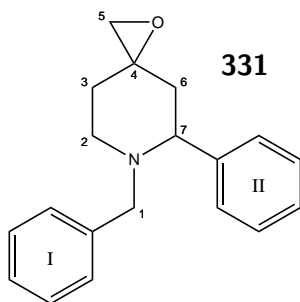
A solution of 1-benzyl-2-phenylpiperidin-4-one **242** (142 mg, 0.54 mmol, 1.0 equiv) in anhydrous DMSO (4 mL) was added to a dry mixture of *t*-BuOK (120 mg, 1.07 mmol, 2.0 equiv) and $Me_3S(O)^+I^-$ (235 mg, 1.07 mmol, 2.0 equiv) under an atmosphere of nitrogen. The resulting solution was stirred at 55 °C for 60 min. The mixture was added with water (15 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (3 x 8 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (ethyl acetate:hexane 1:10 → 1:8) afforded epoxide **331** as a mixture of inseparable stereoisomers (98 mg, 65%) as a white solid; mp 81-84 °C; R_f 0.45 (1:5 ethyl acetate:hexane); ν_{max} (solid) 2941, 2800, 1494, 1451, 1380, 1247, 1117, 1064, 990, 958, 919, 851, 810, 764; δ_H (400 MHz, $CDCl_3$) 7.20-7.49 (10H, m, 10 x Ar-H), 3.82 (1H, d, *J* 13.5 Hz, 1 x H-1), 3.52 (1H, dd, *J* 11.7 Hz, 3.0 Hz, H-7), 2.97-3.01 (1H, m, 1 x H-2), 2.89 (1H, d, *J* 13.5 Hz, 1 x H-1), 2.68 (2H, dd, *J* 13.1 Hz, 4.5 Hz, H-5), 2.20-2.39 (3H, m, 1 x H-2, 1 x H-3, 1 x H-6), 1.37-1.43 (1H, m, 2 x H-6), 1.20 (1H, ddd, *J* 13.4 Hz, 5.0 Hz, 2.4 Hz, 1 x H-3); δ_C (100.6 MHz, $CDCl_3$) 144.35 (*ipso* Ar-II), 139.70 (*ipso* Ar-I), 128.84, 128.77, 128.25, 127.58, 127.41, 126.84, 66.47 (C7), 59.18 (C1), 57.46 (C4), 53.24 (C5), 50.13 (C2), 43.24 (C6), 32.74 (C3); *m/z* (ESI+) 280 [M+H]$^+$, 188, 120, 91; Exact Mass Calcd for $C_{19}H_{21}NO$ [M+H]$^+$requires *m/z* 280.1696 Found 280.1697 (NSI+)

3*S*,5*R*-5-Methyl-6-(*S*-1-phenylethyl)-1-oxa-6-azaspiro[2.5]octane 332 and 3*R*,5*R*-5-methyl-6-(*S*-1-phenylethyl)-1-oxa-6-azaspiro[2.5]octane 333
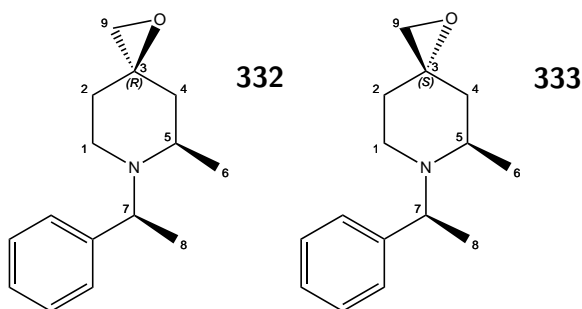
A solution of *R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-one **259** (67 mg, 0.31 mmol, 1.0 equiv) in anhydrous DMSO (2.5 mL) was added to a dry mixture of *t*-BuOK (69 mg, 0.62 mmol, 2.0 equiv) and $Me_3S(O)^+I^-$ (136 mg, 0.62 mmol, 2.0 equiv) under an atmosphere of nitrogen. The resulting solution was stirred at 55 °C for 60 min. The mixture was added with water (10 mL) and extracted with diethyl ether (3 x 6 mL). The combined organic extracts were washed with brine (3 x 5 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (ethyl acetate:hexane 1:1→ 3:1) afforded **332** (8 mg, 11%) as a colourless oil and **333** (34 mg, 47%) as a colourless oil.

Compound 332, eluting first: $[\alpha]_D^{24}$ -71.4 (*c* 0.07, $CHCl_3$); R_f 0.22 (3:2 ethyl acetate:hexane); ν_{max} (film) 3029, 2967, 2928, 2850, 1727, 1492, 1453, 1376, 1279, 1130, 1098, 1076, 1026, 924, 768, 736, 702; δ_H (400 MHz, $CDCl_3$) 7.22-7.34 (5H, m, 5 x Ar-H), 4.02 (1H, q, *J* 6.8 Hz, H-7), 2.98 (1H, ddd, *J* 11.6 Hz, 7.8 Hz, 3.8 Hz, 1 x H-1), 2.62-2.70 (1H, m, H-5), 2.42-2.51 (3H, m, 1 x H-1, H-9), 1.60-1.79 (3H, m, 2 x H-2, 1 x H-4), 1.41-1.46 (4H, m, 1 x H-4, H-8), 1.17 (3H, d, *J* 6.4 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 142.95 (*ipso* Ar), 128.23 (*ortho* Ar), 127.87 (*meta* Ar), 126.94 (*para* Ar), 57.94 (C7), 57.19 (C3), 52.89 (C9), 51.64 (C5), 42.23 (C1), 40.60 (C4), 33.49 (C2), 21.11 (C8), 15.87 (C6); *m/z* (ESI+) 232 [M+H]$^+$, 128, 105; Exact Mass Calcd for $C_{15}H_{21}NO$ [M+H]$^+$ requires *m/z* 232.16959 Found 232.17017 (ESI+)

Compound 333, eluting second: $[\alpha]_D^{23}$ -76.5 (*c* 0.24, $CHCl_3$); R_f 0.15 (3:2 ethyl acetate:hexane); ν_{max} (film) 2971, 2940, 2816, 1728, 1601, 1495, 1453, 1365, 1289, 1280, 1145, 1099, 1076, 1041, 1028, 919, 762, 751, 702; δ_H (400 MHz, $CDCl_3$) 7.21-7.33 (5H, m, 5 x Ar-H), 4.08 (1H, q, *J* 6.9 Hz, H-7), 2.90 (1H, ddd, *J* 11.1 Hz, 6.6 Hz, 4.0 Hz, 1 x H-1), 2.71-2.79 (1H, m, H-5), 2.64 (1H, d, *J* 4.7 Hz, 1 x H-9), 2.60 (1H, d, *J* 4.7 Hz, 1 x H-9), 2.48-2.55 (1H, m, 1 x H-1), 1.76 (1H, ddd, *J* 12.8 Hz, 8.6 Hz, 3.9 Hz, 1 x H-2), 1.55-1.63 (3H, m, 1 x H-2, 2 x H-4), 1.43 (3H, d, *J* 6.9 Hz, H-8), 1.13 (3H, d, *J*

6.4 Hz, H-6); δ_C (100.6 MHz, CDCl$_3$) 142.41 (*ipso* Ar), 128.23 (*ortho* Ar), 127.91 (*meta* Ar), 126.97 (*para* Ar), 57.60 (C7), 57.06 (C3), 54.23 (C9), 51.39 (C5), 42.75 (C1), 41.05 (C4), 33.46 (C2), 20.78 (C8), 16.80 (C6); *m/z* (ESI+) 232 [M+H]$^+$, 128, 105; Exact Mass Calcd for C$_{15}$H$_{21}$NO [M+H]$^+$requires *m/z* 232.1696 Found 232.1697 (NSI+)

S,Z-4-(Methoxymethylene)-2-methyl-1-(*S*-1-phenylethyl)piperidine 352 and *S,E*-4-(methoxymethylene)-2-methyl-1-(*S*-1-phenylethyl)piperidine 353
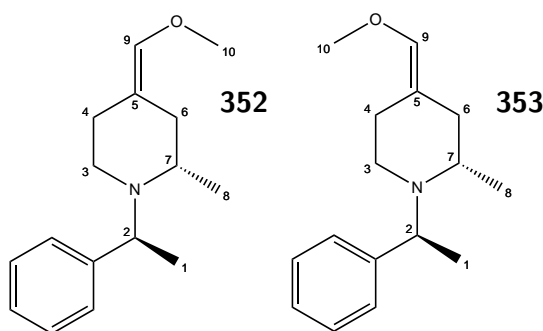
(Methoxymethyl)triphenylphosphonium chloride (1.419 g, 4.14 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (8 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (2.07 mL, 4.14 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -78 °C for 5 min and then allowed to warm to room temperature while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **258** (600 mg, 2.76 mmol, 1.0 equiv) in absolute THF (7 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH$_4$Cl solution (12 mL) and ethyl acetate (25 mL) was added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:ethyl acetate 10:1) afforded **352** and **353** as acolourless oil (607 mg, 2.48 mmol) in a combined yield of 90%. Several pure fractions of **352** and **353** could be obtained and were used for spectral analysis. The other fractions contained a mixture of the two diastereoisomers. NMR investigation of the crude residue indicated that the mixture of diastereoisomers was a 1.21:1 ratio of **352:353**.

Compound 352, eluting first: $[\alpha]_D^{24}$ -51.4 (*c* 0.18, CHCl$_3$); R$_f$ 0.19 (1:10 ethyl acetate:hexane); $\nu_{\max}$ (film) 2968, 2931, 2833, 1689, 1601, 1492, 1454, 1370, 1315, 1228,

1210, 1126, 1029, 977, 766; δ_H (400 MHz, CDCl$_3$) 7.42-7.44 (2H, m, 2 x *ortho* Ar-H), 7.29-7.32 (2H, m, 2 x *meta* Ar-H), 7.19-7.22 (1H, m, *para* Ar-H), 5.80 (1H, s, H-9), 3.94 (1H, q, *J* 6.7 Hz, H-2), 3.53 (3H, s, H-10), 2.93-3.00 (1H, m, H-7), 2.47 (1H, dd, *J* 13.4 Hz, 3.8 Hz, 1 x H-6), 2.37 (1H, ddd, *J* 11.3 Hz, 7.1 Hz, 4.1 Hz, 1 x H-3), 2.22 (1H, ddd, *J* 11.3 Hz, 7.2 Hz, 4.0 Hz, 1 x H-3), 2.11 (1H, dd, *J* 13.4 Hz, 6.8 Hz, 1 x H-6), 1.87-1.93 (1H, m, 1 x H-4), 1.79-1.85 (1H, m, 1 x H-4), 1.26 (3H, d, *J* 6.7 Hz, 3 x H-1), 1.09 (3H, d, *J* 6.3 Hz, 3 x H-8); δ_C (100.6 MHz, CDCl$_3$) 146.23 (*ipso* Ar), 139.97 (C9), 128.17 (*ortho* Ar), 127.64 (*meta* Ar), 126.47 (*para* Ar), 114.97 (C5), 59.48 (C10), 57.68 (C2), 51.53 (C7), 46.07 (C3), 33.36 (C6), 30.06 (C4), 15.54 (C8), 15.09 (C1); *m/z* (ESI+) 246 [M+H]$^+$, 142; Exact Mass Calcd for C$_{16}$H$_{24}$NO [M+H]$^+$ requires *m/z* 246.1852 Found 246.1854 (NSI+).

Compound 353, eluting second: $[\alpha]_D^{24}$ -29.2 (*c* 0.15, CHCl$_3$); R$_f$ 0.13 (1:10 ethyl acetate:hexane); ν_{max} (film) 2968, 2931, 2825, 1692, 1601, 1492, 1453, 1371, 1311, 1265, 1230, 1211, 1186, 1125, 1028, 766; δ_H (400 MHz, CDCl$_3$) 7.42-7.44 (2H, m, 2 x *ortho* Ar-H), 7.29-7.34 (2H, m, 2 x *meta* Ar-H), 7.20-7.24 (1H, m, *para* Ar-H), 5.75 (1H, s, H-9), 3.91 (1H, q, *J* 6.7 Hz, H-2), 3.53 (3H, s, 3 x H-10), 2.92-3.00 (1H, m, H-7), 2.36 (1H, ddd, *J* 11.5 Hz, 7.3 Hz, 4.3 Hz, 1 x H-3), 2.20-2.25 (2H, m, 1 x H-3, 1 x H-6), 2.11-2.17 (1H, m, 1 x H-4), 2.02-2.08 (1H, m, 1 x H-4), 1.85 (1H, dd, *J* 13.2 Hz, 6.5 Hz, 1 x H-6), 1.26 (3H, d, *J* 6.7 Hz, 3 x H-1), 1.06 (3H, d, *J* 6.4 Hz, 3 x H-8); δ_C (100.6 MHz, CDCl$_3$) 146.24 (*ipso* Ar), 139.77 (C9), 128.20 (*ortho* Ar), 127.61 (*meta* Ar), 126.49 (*para* Ar), 114.69 (C5), 59.51 (C10), 57.83 (C2), 52.18 (C7), 44.65 (C3), 37.76 (C6), 25.50 (C4), 15.42 (C1), 15.18 (C8); *m/z* (ESI+) 246 [M+H]$^+$, 142; Exact Mass Calcd for C$_{16}$H$_{24}$NO [M+H]$^+$ requires *m/z* 246.18524 Found 246.18577 (ESI+).

R,E-4-(Methoxymethylene)-2-methyl-1-(*S*-1-phenylethyl)piperidine 354 and *R,Z*-4-(methoxymethylene)-2-methyl-1-(*S*-1-phenylethyl)piperidine 355

(Methoxymethyl)triphenylphosphonium chloride (473 mg, 1.38 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (3 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (690 µl, 1.38 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -78 °C for 5 min and then allowed to warm to room temperature while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **259** (200 mg, 0.92 mmol, 1.0 equiv) in absolute THF (2 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH_4Cl solution (5 mL) and ethyl acetate (10 mL) were added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:ethyl acetate 1.3:1) afforded **354** and **355** as a colourless oil (170 mg, 0.69 mmol) in a combined yield of 75%. Several pure fractions of **354** and **355** could be obtained and were used for spectral analysis, the other fractions contained a mixture of the two diastereoisomers. NMR investigation of the crude residue indicated that the mixture of diastereoisomers was a 1:1.23 ratio of **354:355**.

Product 354, eluting first: $[\alpha]_D^{24}$ -58.4 (*c* 0.29, $CHCl_3$); R_f 0.29 (1:1 ethyl acetate:hexane); ν_{max} (film) 2970, 2931, 2828, 1693, 1492, 1453, 1371, 1230, 1211, 1125, 768; δ_H (400 MHz, $CDCl_3$) 7.20-7.32 (5H, m, Ar-H), 5.67 (1H, s, H-9), 3.90 (1H, q, *J* 6.8 Hz, H-2), 3.51 (3H, s, H-10), 2.69 (1H, ddd, *J* 11.6 Hz, 7.4 Hz, 4.7 Hz, 1 x H-3), 2.56 (1H, dq, *J* 12.2 Hz, 6.1 Hz, H-7), 2.39-2.44 (1H, m, 1 x H-3), 2.28-2.32 (2H, m, 2 x H-4), 2.12 (1H, dd, *J* 13.3 Hz, 4.1 Hz, 1 x H-6), 1.73 (1H, dd, *J* 13.2 Hz, 6.0 Hz, 1 x H-6), 1.38 (1H, d, 3 H, *J* 6.8 Hz, H-1), 1.00 (1H, d, 3 H, *J* 6.3 Hz, H-8); δ_C (100.6 MHz, $CDCl_3$)

143.63 (*ipso* Ar), 139.79 (C9), 128.15 (*ortho* Ar), 127.87 (*meta* Ar), 126.75 (*para* Ar), 113.89 (C5), 59.48 (C10), 58.59 (C2), 52.43 (C7), 43.87 (C3), 37.56 (C6), 25.63 (C4), 21.29 (C1), 14.43 (C8); m/z (ESI+) 246 [M+H]$^+$, 142; Exact Mass Calcd for $C_{16}H_{24}NO$ [M+H]$^+$ requires m/z 246.1852 Found 246.1854 (NSI+).

Product 355, eluting second: $[\alpha]_D^{24}$ -126.05 (*c* 0.12, CHCl$_3$); R$_f$ 0.23 (1:1 ethyl acetate:hexane); ν_{max} (film) 2969, 2929, 2833, 1692, 1492, 1453, 1372, 1229, 1193, 1124, 768; δ_H (400 MHz, CDCl$_3$) 7.20-7.33 (5H, m, Ar-H), 5.79 (1H, s, H-9), 3.95 (1H, q, *J* 6.8 Hz, H-2), 3.49 (s, 3 H, H-10), 2.73 (1H, ddd, *J* 11.4 Hz, 7.7 Hz, 4.0 Hz, 1 x H-3), 2.52-2.59 (1H, m, 1 x H-7), 2.37 (1H, ddd, *J* 11.1 Hz, 6.7 Hz, 4.2 Hz, 1 x H-3), 2.29 (1H, dd, *J* 13.5 Hz, 3.5 Hz, 1 x H-6), 1.98-2.13 (3H, m, 1 x H-6, 2 x H-4), 1.38 (3H, d, *J* 6.8 Hz, H-1), 1.04 (3H, d, *J* 6.3 Hz, H-8); δ_C (100.6 MHz, CDCl$_3$) 143.39 (*ipso* Ar), 140.04 (C9), 128.15 (*ortho* Ar), 127.91 (*meta* Ar), 126.78 (*para* Ar), 114.28 (C5), 59.43 (C10), 58.31 (C2), 51.93 (C7), 45.37 (C3), 33.18 (C6), 30.17 (C4), 21.15 (C1), 15.03 (C8); m/z (ESI+) 246 [M+H]$^+$, 142; Exact Mass Calcd for $C_{16}H_{24}NO$ [M+H]$^+$ requires m/z 246.18524 Found 246.18566 (ESI+).

R,E-4-(Methoxymethylene)-2-phenyl-1-(*S*-1-phenylethyl)piperidine 356 and *R,Z*-4-(methoxymethylene)-2-phenyl-1-(*S*-1-phenylethyl)piperidine 357

(Methoxymethyl)triphenylphosphonium chloride (1.028 g, 3.00 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (6 mL) under an atmosphere of nitrogen. The mixture was cooled to -70 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (1.500 mL, 3.00 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -70 °C for 5 min and then allowed to warm to room temperature while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **262** (558 mg, 2.00 mmol, 1.0 equiv) in absolute THF (4 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH$_4$Cl solution

(8 mL) and ethyl acetate (15 mL) were added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (ethyl acetate:hexane 1:36 $\rightarrow$ 1:28) afforded **356** (128 mg, 21%) as a colourless oil, a mixture of **356** and **357** (392 mg, 64%) as a colourless oil and **357** (72 mg, 12%) as a colourless oil. NMR investigation of the crude residue indicated that the mixture of diastereoisomers was a 1.03:1 ratio of **356:357**.

Product 356, eluting first: $[\alpha]_D^{23}$ -69.8 (*c* 0.94, CHCl$_3$); R$_f$ 0.31 (1:20 ethyl acetate:hexane); ν_{max} (film) 3060, 3027, 2967, 2931, 2901, 2814, 1692, 1493, 1452, 1372, 1228, 1211, 1126, 1029, 761, 732; δ_H (400 MHz, CDCl$_3$) 7.46-7.50 (4H, m, 2 x *meta* ArI-H, 2 x *meta* ArII-H), 7.29-7.36 (4H, m, 2 x *ortho* ArI-H, 2 x *ortho* ArII-H), 7.18-7.27 (2H, m, *para* ArI-H, *para* ArII-H), 5.80 (1H, s, H-9), 3.85 (1H, q, *J* 6.8 Hz, H-2), 3.55 (3H, s, H-10), 3.47 (1H, dd, *J* 10.7 Hz, 3.2 Hz, H-7), 2.60-2.66 (2H, m, 1 x H-3, 1 x H-4), 2.28-2.34 (1H, m, 1 x H-6), 2.19 (1H, td, *J* 11.6 Hz, *J* 3.0 Hz, 1 x H-3), 2.10-2.14 (1H, m, 1 x H-6), 1.86 (1H, td, *J* 13.1 Hz, 4.9 Hz, 1 x H-4), 1.16 (3H, d, *J* 6.8 Hz, H-1); δ_C (100.6 MHz, CDCl$_3$) 144.71 (*ipso* ArI), 144.41 (*ipso* ArII), 139.55 (C9), 128.73, 127.96, 127.69, 127.60, 127.28 (*para* ArI), 126.29 (*para* ArII), 115.95 (C5), 67.01 (C7), 59.58 (C10), 54.96 (C2), 45.16 (C3), 40.69 (C6), 25.83 (C4), 8.50 (C1); *m/z* (ESI+) 308 [M+H]$^+$, 204, 172; Exact Mass Calcd for C$_{21}$H$_{26}$NO [M+H]$^+$requires *m/z* 308.2009 Found 308.2009 (NSI+)

Product 357, eluting second: $[\alpha]_D^{24}$ -149.6 (*c* 0.12, CHCl$_3$); R$_f$ 0.28 (1:20 ethyl acetate:hexane); ν_{max} (film) 2931, 2833, 1692, 1600, 1492, 1451, 1378, 1245, 1225, 1204, 1127, 1029, 975, 774, 758; 7.46-7.52 (4H, m, 2 x *meta* ArI-H, 2 x *meta* ArII-H), 7.28-7.36 (4H, m, 2 x *ortho* ArI-H, 2 x *ortho* ArII-H), 7.18-7.27 (2H, m, *para* ArI-H, *para* ArII-H), 5.81 (1H, t, *J* 1.6 Hz, H-9), 3.87 1H, q, *J* 6.8 Hz, H-2), 3.54 (3H, s, H-10), 3.49 (1H, dd, *J* 10.9 Hz, 3.3 Hz, H-7), 2.86 (1H, ddd, *J* 13.6 Hz, 2.8 Hz, 2.0 Hz, 1 x H-6), 2.65 (1H, ddd, *J* 10.5 Hz, 3.9 Hz, 2.9 Hz, 1 x H-3), 2.19 (1H, "dt", *J* 11.8 Hz, 2.6 Hz, 1 x H-3), 2.04 -2.12 (2H, m, 1 x H-6, 1 x H-4), 1.88-1.93 (1H, m, 1 x H-4), 1.17 (3H, d, *J* 6.8 Hz, H-1); δ_C (100.6 MHz, CDCl$_3$) 144.81 (*ipso* ArI), 144.51 (*ipso* ArII), 128.65, 127.94, 127.75, 127.62, 127.18 (*para* ArI), 126.27 (*para* ArII), 115.72 (C5), 65.41 (C7), 59.52 (C10), 54.98 (C2), 46.37 (C3), 35.81 (C6), 30.11 (C4), 8.63 (C1); *m/z* (ESI+) 308 [M+H]$^+$, 204, 172; Exact Mass Calcd for C$_{21}$H$_{26}$NO [M+H]$^+$requires *m/z* 308.2009 Found 308.2010 (NSI+)

S,E-4-(Methoxymethylene)-2-phenyl-1-(S-1-phenylethyl)piperidine 358 and S,Z-4-(methoxymethylene)-2-phenyl-1-(S-1-phenylethyl)piperidine 359
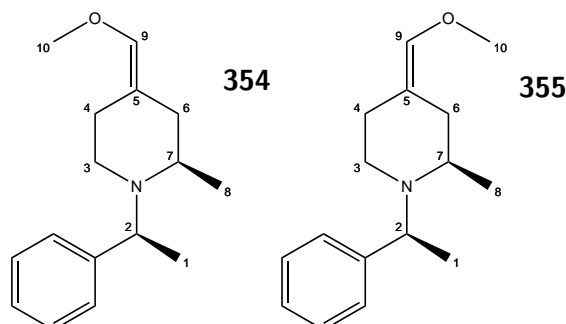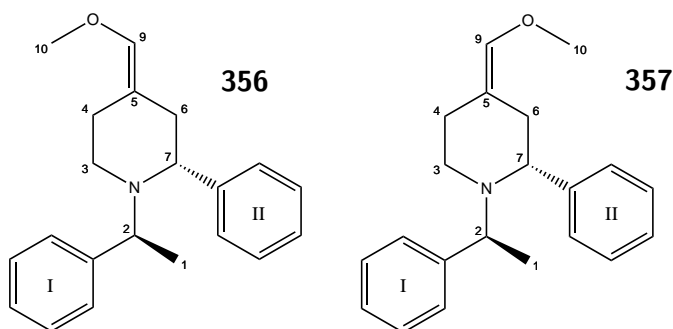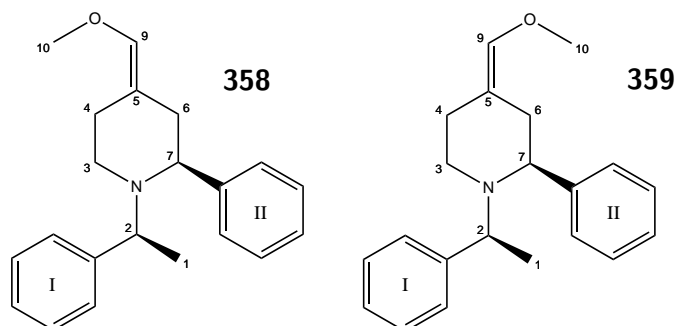

(Methoxymethyl)triphenylphosphonium chloride (922 mg, 2.69 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (6 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (1.345 mL, 2.69 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -78 °C for 5 min and then allowed to warm to room temperature while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **263** (500 mg, 1.79 mmol, 1.0 equiv) in absolute THF (4 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH_4Cl solution (8 mL) and ethyl acetate (15 mL) were added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (ethyl acetate:hexane 1:28 → 1:10) afforded **358** (20 mg, 4%) as colourless oil, a mixture of **358** and **359** (304 mg, 55%, ratio of **358**:**359** 1.62:1) as a colourless oil and **359** (104 mg, 19%) as a colourless oil. NMR investigation of the crude residue indicated that the mixture of diastereoisomers was a 1.06:1 ratio of **359**:**358**.

Product 358, eluting first: $[\alpha]_D^{23}$ -116.4 (c 0.19, $CHCl_3$); R_f 0.42 (1:8 ethyl acetate:hexane); ν_{max} (film) 2823, 1692, 1492, 1453, 1227, 1122, 944, 822, 759, 701; δ_H (400 MHz, $CDCl_3$) 7.19-7.45 (8H, m, 2 x *ortho* ArI, 2 x *meta* ArI, 2 x *meta* ArII, 1 x *para* ArI, 1 x *para* ArII), 7.00-7.02 (2H, m, 2 x *ortho* Ar-II), 5.66 (1H, s, H-9), 3.96 (1H, q, J 7.1 Hz, H-2), 3.47 (3H, s, 3 x H-10), 3.17 (1H, ddd, J 10.9 Hz, 4.4 Hz, 2.9 Hz, 1 x H-3), 3.11 (1H, dd, J 10.5 Hz, 3.5 Hz, H-7), 2.67-2.72 (1H, m, 1 x H-4), 2.09-2.16 (1H, m, 1 x H-6), 1.96-2.04 (2H, m, 1 x H-6, 1 x H-4), 1.75 (1H, td, J 12.2 Hz, 2.9 Hz,

1 x H-3), 1.39 (3H, s, *J* 7.2 Hz, 3 x H-1); δ_C (100.6 MHz, CDCl$_3$) 145.33 (*ipso* ArII), 139.30 (C9), 139.04 (*ipso* ArI), 128.93 (*ortho* ArII), 128.75 (*ortho* ArI), 127.86 (*meta* ArII), 127.64 (*meta* ArI), 127.03 (*para* ArII), 126.85 (*para* ArI), 115.42 (C5), 67.20 (C7), 59.46 (C10), 56.76 (C2), 45.87(C3), 41.47 (C6), 25.93 (C4), 18.98 (C1); *m/z* (ESI+) 308 [M+H]$^+$, 204, 172; Exact Mass Calcd for C$_{21}$H$_{26}$NO [M+H]$^+$requires *m/z* 308.20089 Found 308.20020 (ESI+)

Product 359, eluting second: $[\alpha]_D^{24}$ -148.2 (*c* 0.16, CHCl$_3$); R$_f$ 0.36 (1:8 ethyl acetate:hexane); ν_{max} (film) 2833, 1692, 1492, 1453, 1225, 1196, 1124, 912, 838, 757, 700; δ_H (400 MHz, CDCl$_3$) 7.19-7.48 (8H, m, 2 x *ortho* ArII, 2 x *meta* ArI, 2 x *meta* ArII, 1 x *para* ArI, 1 x *para* ArII), 7.02 (2 H, d, *J* 7.2 Hz, 2 x *ortho* ArI), 5.69 (1H, s, H-9), 3.99 (1H, q, *J* 7.1 Hz, H-2), 3.45 (3H, s, 3 x H-10), 3.13-3.20 (2H, m, 1 x H-3, H-7), 2.70-2.75 (1H, m, 1 x H-6), 2.20 (1H, ddd, *J* 12.8 Hz, 4.1 Hz, 2.3 Hz, 1 x H-4), 1.98-2.03 (1H, m, 1 x H-4), 1.89-1.95 (1H, m, 1 x H-6), 1.74 (1H, td, *J* 11.6 Hz, 2.9 Hz, 1 x H-3), 1.39 (3H, d, *J* 7.1 Hz, 3 x H-1); δ_C (100.6 MHz, CDCl$_3$) 145.41 (*ipso* ArII), 139.24 (C9), 139.13 (*ipso* ArI), 128.90 (*ortho* ArII), 128.69 (*ortho* ArI), 127.90 (*meta* ArII), 127.63 (*meta* ArI), 126.93 (*para* ArII), 126.85 (*para* ArI), 115.19 (C5), 65.63 (C7), 59.40 (C10), 56.67 (C2), 47.08 (C3), 36.59 (C6), 30.15 (C4), 18.98 (C1); *m/z* (ESI+) 308 [M+H]$^+$, 204, 172; Exact Mass Calcd for C$_{21}$H$_{26}$NO [M+H]$^+$requires *m/z* 308.20089 Found 308.20013 (ESI+)

2*S*,4*R*-2-Methyl-1-(*S*-1-phenylethyl)piperidine-4-carbaldehyde 362 and 2*S*,4*S*-2-methyl-1-(*S*-1-phenylethyl)piperidine-4-carbaldehyde 363
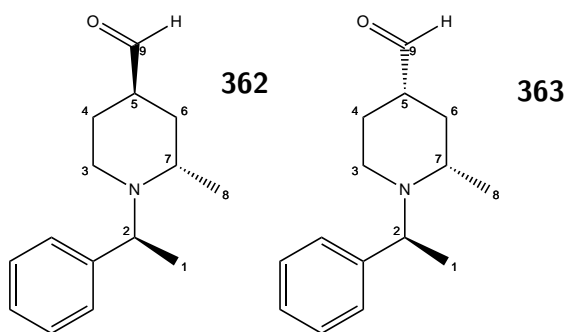
1.6 N HCl (2.4 mL) was added to a solution of a diastereomeric mixture of **352** and **353** (ratio of **352:353** was 1:1.70) (274 mg, 1.12 mmol) in THF (2.4 mL) and stirred at 45 °C for two hours. THF was evaporated under reduced pressure and the residue was diluted with water (10 mL). The pH was adjusted to 10 by the addition of an aqueous Na$_2$CO$_3$ solution. The aqueous phase was extracted with DCM (3 x 15 mL) and the combined organic layers were washed with brine and dried over MgSO$_4$. The solvent

was removed under reduced pressure and crude aldehydes **362** and **363** were obtained as a colourless oil (253 mg, 97%). The products could be used for the next step without the need of further purification.

NMR investigation indicates that the mixture of diastereoisomers is a 1:1.29 ratio of **362**:**363**. NOe analysis suggests that compound **363** is the major product and compound **362** is the minor compound (labelled as $_M$).

Products 362 and 363 as a mixture: Product **362** is labelled as $_M$. R_f 0.08 (1:3 ethyl acetate:hexane); $\nu_{\max}$ (film) 2968, 2935, 2803, 1724, 1601, 1493, 1446, 1376, 1331, 1286, 1267, 1194, 1145, 1073, 912, 782, 765; δ_{H} (400 MHz, CDCl$_3$) 9.65 (1H, d, J 1.2 Hz, H-9$_M$), 9.59 (1H, d, J 1.6 Hz, H-9), 7.44-7.46 (2H, m, 2 x Ar-H), 7.28-7.37 (6H, m, 2 x Ar-H, 4 x Ar-H$_M$), 7.20-7.24 (2H, m, *para* Ar-H, *para* Ar-H$_M$), 4.35 (1H, q, J 6.8 Hz, H-2), 3.71 (1H, q, J 6.6 Hz, H-2$_M$), 3.29-3.37 (1H, m, H-7$_M$), 2.64 (1H, dqd, J 12.4 Hz, 6.2 Hz, 2.6 Hz, H-7), 2.45-2.56 (2H, m, 1 x H-3, 1 x H-5$_M$), 2.22 -2.40 (3H, m, 2 x H-3$_M$), 1 x H-5), 2.12 (1H, "td", J 11.7 Hz, 2.5 Hz, 1 x H-3), 1.87-1.97 (2H, m, 1 x H-6, 1 x H-6$_M$), 1.54-1.76 (4H, m, 1 x H-6$_M$, 1 x H-4, 2 x H-4$_M$), 1.31-1.45 (2H, m, 1 x H-6, 1 x H-4), 1.24-1.27 (9H, m, 3 x H-1, 3 x H-1$_M$, 3 x H-8), 1.09 (3H, d, J 6.6 Hz, 3 x H-8$_M$); δ_{C} (100.6 MHz, CDCl$_3$) 205.15 (C9$_M$), 204.18 (C9), 146.41 (*ipso* Ar$_M$), 144.49 (*ipso* Ar), 128.36 (Ar), 128.04 (Ar), 127.86 (Ar), 127.39 (Ar), 126.72 (*para* Ar$_M$), 126.46 (*para* Ar), 59.43 (C2$_M$), 54.35 (C2), 52.85 (C7), 49.64 (C5), 48.25 (C7$_M$), 44.45 (C5$_M$), 44.00 (C3), 42.48 (C3$_M$), 35.05 (C6), 32.18 (C6$_M$), 26.15 (C4), 25.51 (C4$_M$), 20.70 (C8), 18.43 (C1$_M$), 12.38 (C8$_M$), 8.55 (C1); m/z (ESI+) 264 [M+H+CH$_3$OH]$^+$, 232 [M+H]$^+$, 128, 105; Exact Mass Calcd for C$_{15}$H$_{22}$NO [M+H]$^+$ requires m/z 232.1696 Found 232.17028 (ESI+)

2R,4R-2-Methyl-1-(S-1-phenylethyl)piperidine-4-carbaldehyde 364 and 2R,4S-2-methyl-1-(S-1-phenylethyl)piperidine-4-carbaldehyde 365

1.6 N HCl (850 µl) was added to a solution of a diastereomeric mixture of **354** and **355** (ratio of **354:355** was 1:1.16) (94 mg, 0.38 mmol) in THF (850 µl) and stirred at 45 °C for two hours. THF was evaporated under reduced pressure and the residue was diluted with water (4 mL). The pH was adjusted to 10 by the addition of an aqueous Na$_2$CO$_3$ solution. The aqueous phase was extracted with DCM (3 x 6 mL) and the combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and crude aldehydes **364** and **365** were obtained as a colourless oil (87 mg, 100%). The products could be used for the next step without the need of further purification.

NMR investigation indicates that the mixture of diastereoisomers is a 1:1.85 ratio of **365:364**. NOe analysis suggests that compound **364** is the major product and compound **365** is the minor compound (labelled as $_M$).

Products 364 and 365 as a mixture: Product **365** is labelled as $_M$. R$_f$ 0.10 (2:1 ethyl acetate:hexane); ν_{max} (film) 3027, 2971, 2932, 2805, 2741, 1724, 1493, 1452, 1376, 1278, 1070, 762, 703; δ_H (400 MHz, CDCl$_3$) 9.60 (1H, d, J 1.36 Hz, H-9$_M$), 9.55 (1H, d, J 1.42 Hz, H-9), 7.20-7.35 (10H, m, 5 x Ar-H, 5 x Ar-H$_M$), 4.33 (1H, q, J 7.1 Hz, H-2), 3.72 (1H, q, J 6.5 Hz, H-2$_M$), 3.15 (1H, dt, J 11.5 Hz, 3.7 Hz, 1 x H-3), 2.87-2.94 (1H, m, H-7$_M$), 2.80 (1H, dt, J 11.5 Hz, 4.3 Hz, 1 x H-3$_M$), 2.57 (1H, dt, J 11.7 Hz, 3.0 Hz, 1 x H-3$_M$), 2.42-2.50 (m, 1 H, H-5$_M$), 2.21 (1H, dqd, J 12.0 Hz, 6.0 Hz, 2.9 Hz, H-7), 2.08 (1H, ttd, J 12.2 Hz, 3.9 Hz, 1.5 Hz, H-5), 1.70-1.91 (5H, m, 1 x H-4, 1 x H-6, 1 x H-3, 2 x H-4$_M$, 1 x H-6$_M$), 1.43-1.62 (5H, m, 1 x H-6$_M$, 1 x H-4, 3 x H-1), 1.24-1.41 (7H, m, 1 x H-6, 3 x H-8, 3 x H-1$_M$), 0.97 (3H, d, J 6.6 Hz, H-8$_M$); δ_C (100.6 MHz, CDCl$_3$) 204.97(C9$_M$), 203.86 (C9), 144.90 (*ipso* Ar$_M$), 139.48 (*ipso* Ar), 128.46 (Ar), 128.40 (Ar), 127.94 (Ar), 127.42 (Ar), 127.04 (Ar), 126.89 (Ar), 59.67 (C2$_M$), 55.86 (C2), 52.93 (C7), 48.93 (C7$_M$, C5), 44.95 (C3), 43.89 (C5$_M$), 41.03 (C3$_M$), 34.93 (C6), 32.14 (C6$_M$), 26.20 (C4), 25.76 (C4$_M$), 22.03 (C1$_M$), 21.13 (C8), 19.09 (C1), 11.30

(C8$_M$); *m/z* (ESI+) 264 [M+H+CH$_3$OH]$^+$, 232 [M+H]$^+$, 128, 105; Exact Mass Calcd for C$_{15}$H$_{22}$NO [M+H]$^+$ requires *m/z* 232.1696 Found 232.1696 (NSI+)

2R,4R-2-Phenyl-1-S-1-phenylethyl)piperidine-4-carbaldehyde 366 and 2R,4S-2-phenyl-1-(S-1-phenylethyl)piperidine-4-carbaldehyde 367
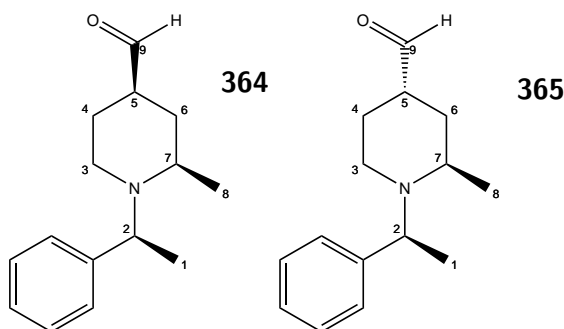

1.6 N HCl (2.8 mL) was added to a solution of a diastereomeric mixture of **356** and **357** (ratio of **356**:**357** was 1:1.32) (365 mg, 1.19 mmol) in THF (2.8 mL) and stirred at 45 °C for three hours. THF was evaporated under reduced pressure and the residue was diluted with water (10 mL). The pH was adjusted to 10 by the addition of an aqueous Na$_2$CO$_3$ solution. The aqueous phase was extracted with DCM (3 x 15 mL) and the combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and crude aldehydes **366** and **367** were obtained as a colourless oil (349 mg, 100%). The products could be used for the next step without the need of further purification.

NMR investigation indicates that the mixture of diastereoisomers is a 1:1.33 ratio of **366**:**367**. NOe analysis indicates that compound **367** is the major product and compound **366** is the minor compound (labelled as $_M$).

Products 366 and 367 as a mixture: Product **366** is labelled as $_M$. R$_f$ 0.13 (1:20 ethyl acetate:hexane); ν_{max} (film) 2968, 2938, 2808, 2712, 1723, 1601, 1492, 1446, 1384, 1365, 1266, 1204, 1129, 1071, 1025, 953, 910, 760; δ_H (400 MHz, CDCl$_3$) 9.82 (1H, s, H-9$_M$), 9.61 (1H, d, *J* 1.5 Hz, H-9), 7.18-7.51 (20H, m, 10 x Ar-H, 10 x Ar-H$_M$), 3.89 (1H, q, *J* 6.8 Hz, H-2), 3.83 (1H, q, *J* 6.9 Hz, H-2$_M$), 3.58-3.63 (2H, m, 1 x H-7, 1 x H-7$_M$), 2.72 (1H, dt, *J* 11.6 Hz, 3.4 Hz, 1 x H-3), 2.60-2.63 (1H, m, H-5$_M$), 2.50 (1H, dt, *J* 12.0 Hz, 3.6 Hz, 1 x H-3$_M$), 2.23-2.43 (4H, m, 1 x H-5, 1 x H-3, 1 x H-6$_M$, 1 x H-3$_M$), 2.09-2.15 (1H, m, 1 x H-4$_M$), 1.95-2.08 (2H, m, 1 x H-6, 1 x H-6$_M$), 1.79-1.89 (2H, m, 1 x H-4, 1 x H-4$_M$), 1.67-1.76 (1H, m, 1 x H-6), 1.48-1.58 (1H, m, 1 x H-4), 1.20 (3H, d, *J* 6.8 Hz, H-1), 1.13 (3H, d, *J* 6.8 Hz, H-1$_M$); δ_C (100.6 MHz, CDCl$_3$) 205.17 (C8$_M$), 203.58 (C8),

144.44 (C$_{quart.M}$), 144.19 (C$_{quart.}$), 144.10 (C$_{quart.M}$), 143.81(C$_{quart.}$), 128.89, 128.81, 128.02, 128.00, 127.64, 127.59, 127.55, 127.39, 126.44, 126.40, 64.48 (C7), 61.89 (C7$_M$), 55.19 (C2$_M$), 54.82 (C2), 49.86 (C5), 46.16 (C5$_M$), 44.01 (C3), 41.86 (C3$_M$), 36.13 (C6), 34.73 (C6$_M$), 26.05 (C4), 24.97(C4$_M$), 8.88 (C1$_M$), 8.20 (C1); *m/z* (ESI+) 326 [M+H+CH$_3$OH]$^+$, 294 [M+H]$^+$, 190; Exact Mass Calcd for C$_{20}$H$_{24}$NO [M+H]$^+$requires *m/z* 294.1852 Found 294.1850 (NSI+).

2*S*,4*R*-2-phenyl-1-*S*-1-Phenylethyl)piperidine-4-carbaldehyde 368 and 2*S*,4*S*-2-phenyl-1-(*S*-1-phenylethyl)piperidine-4-carbaldehyde 369
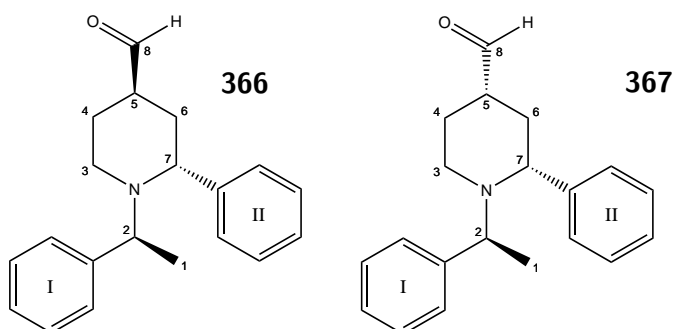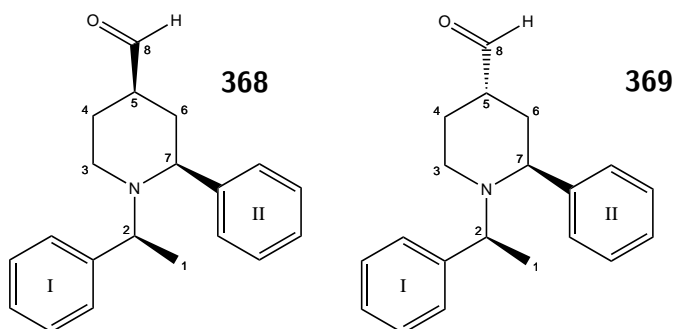

1.6 N HCl (3 mL) was added to a solution of a diastereomeric mixture of **358** and **359** (ratio of **358**:**359** was 1:1.10) (395 mg, 1.29 mmol) in THF (3 mL) and stirred at 45 °C for two hours. THF was evaporated under reduced pressure and the residue was diluted with water (10 mL). The pH was adjusted to 10 by the addition of an aqueous Na$_2$CO$_3$ solution. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and crude aldehydes **368** and **369** were obtained as a colourless oil (379 mg, 100%). The products could be used for the next step without the need of further purification.

NMR investigation indicates that the mixture of diastereoisomers is a 2.04:1 ratio of **368**:**369**. NOe analysis indicates that compound **368** is the major product and compound **369** is the minor compound (labelled as $_M$).

Products 368 and 369 as a mixture: Product **369** is labelled as $_M$. R$_f$ 0.16 (1:8 ethyl acetate:hexane); ν_{max} (film) 2809, 1720, 1492, 1453, 1374, 959, 911, 759, 734, 701; δ_H (400 MHz, CDCl$_3$) 9.62 (1H, s, H-8$_M$), 9.53 (1H, s, H-8), 7.18-7.46 (16 H, m, 2 x *meta* ArI, 1 x *para* ArI, 2 x *ortho* ArII, 2 x *meta* ArII, 1 x *para* ArII, 2 x *meta* ArI$_M$, 1 x *para* ArI$_M$, 2 x *ortho* ArII$_M$, 2 x *meta* ArII$_M$, 1 x *para* ArII$_M$), 7.03 (2H, d, *J* 7.8 Hz, 2 x *ortho* ArI), 6.98 (2H, d, *J* 7.7 Hz, 2 x *ortho* ArI$_M$), 3.99 (1H, q, *J* 7.0 Hz, H-2), 3.93 (1H,

q, *J* 7.0 Hz, H-2$_M$), 3.24-3.31 (2H, m, 1 x H-3, 1 x H-7$_M$), 3.20 (1H, dd, *J* 11.1 Hz, 2.3 Hz, H-7), 3.01 (1H, dt, *J* 11.8 Hz, 3.5 Hz, 1 x H-3$_M$), 2.46-2.50 (1H, m, H-5$_M$), 2.10-2.22 (3H, m, H-5, 1 x H-4$_M$, 1 x H-6$_M$), 1.80-1.97 (6H, m, 1 x H-4$_M$, 1 x H-6$_M$, 1 x H-3$_M$, 1 x H-3, 1 x H-4, 1 x H-6), 1.44-1.66 (2H, m, 1 x H-4, 1 x H-6), 1.38 (3H, d, *J* 7.2 Hz, 3 x H-1), 1.35 (3H, d, *J* 7.1 Hz, 3 x H-1$_M$); δ_C (100.6 MHz, CDCl$_3$) 204.81 (C8$_M$), 203.38 (C8), 144.97 (*ipso* ArI$_M$), 144.85 (*ipso* ArI), 139.13 (*ipso* ArII$_M$), 138.33 (*ipso* ArII), 128.95, 128.93, 128.83, 128.63, 127.83, 127.79, 127.73, 127.35, 127.14, 127.08, 127.04, 64.73 (C7), 62.12 (C7$_M$), 56.87 (C2$_M$), 56.56 (C2), 49.35 (C5), 45.65 (C5$_M$), 44.68 (C3), 42.78 (C3$_M$), 37.14 (C6), 35.36 (C6$_M$), 26.14 (C4), 25.15 (C4$_M$), 19.14 (C1$_M$), 18.66 (C1); *m/z* (ESI+) 326 [M+H+CH$_3$OH]$^+$, 294 [M+H]$^+$, 190; Exact Mass Calcd for C$_{20}$H$_{24}$NO [M+H]$^+$ requires *m/z* 294.18524 Found 294.18498 (ESI+).

E-2-((1-Benzylpiperidin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one 370
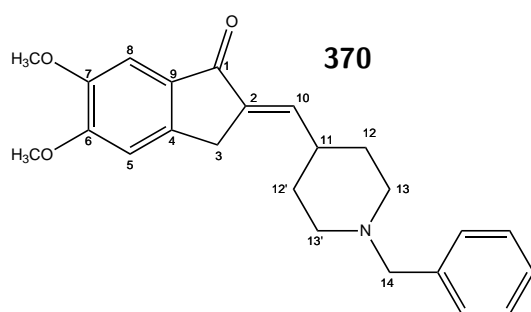
5,6-Dimethoxy-1-indanone (71 mg, 0.37 mmol, 1.0 equiv) was added to a solution of **319** (75 mg, 0.37 mmol, 1.0 equiv) in methanol (2 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 77 μl, 0.44 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 75 min, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (5 mL). Water (3 mL) was added and the phases were separated. The aqueous phase was extracted again with CH$_2$Cl$_2$ (2 x 6 mL), the organic phases were combined and washed with brine and dried over MgSO$_4$. The solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:methanol 19:1.5) afforded product **370** (117 mg, 84%) as a white solid; mp 169-171 °C; R$_f$ 0.16 (100% ethyl acetate); ν_{max} (solid) 1688, 1646, 1602, 1586, 1498, 1458, 1309, 1255, 1240, 1214, 1134, 1119, 1021, 1000, 981, 855, 843, 803, 766; δ_H (400 MHz, CDCl$_3$) 7.23-7.33 (6H, m, H-8, 2 x *ortho* Ph-H, 2 x *meta* Ph-H, *para* Ph-H), 6.89 (1H, s, H-5), 6.66 (1H, d, *J* 9.6 Hz, H-10), 3.97 (3H, s, H$_3$CO-C6), 3.92 (3H, s, H$_3$CO-C7), 3.58-3.59 (2H, m, H-3), 3.53

(2H, s, H-14), 2.92-2.95 (2H, m, 1 x H-13, 1 x H-13'), 2.28-2.38 (1H, m, H-11), 2.04-2.10 (2H, m, 1 x H-13, 1 x H-13'), 1.58-1.71 (4H, m, 4 x H-12); δ_C (100.6 MHz, CDCl$_3$) 192.61(C=O), 155.32 (C6), 149.52 (C7), 144.53 (C9), 139.81 (C10), 138.07 (*ipso* Ph), 135.66 (C4), 131.87 (C2), 129.26 (*ortho* Ph), 128.22 (*meta* Ph), 127.07 (*para* Ph), 107.24 (C5), 105.05 (C8), 63.47 (C14), 56.26 (C6-OCH$_3$), 56.16 (C7-OCH$_3$), 53.04 (C13), 37.24 (C11), 31.17 (C12), 29.51 (C3). *In agreement with published data.*[254]

E-5,6-Dimethoxy-2-((2S,4S-2-methyl-1-(S-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1H-inden-1-one 371 and E-5,6-dimethoxy-2-((2S,4R-2-methyl-1-(S-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1H-inden-1-one 372
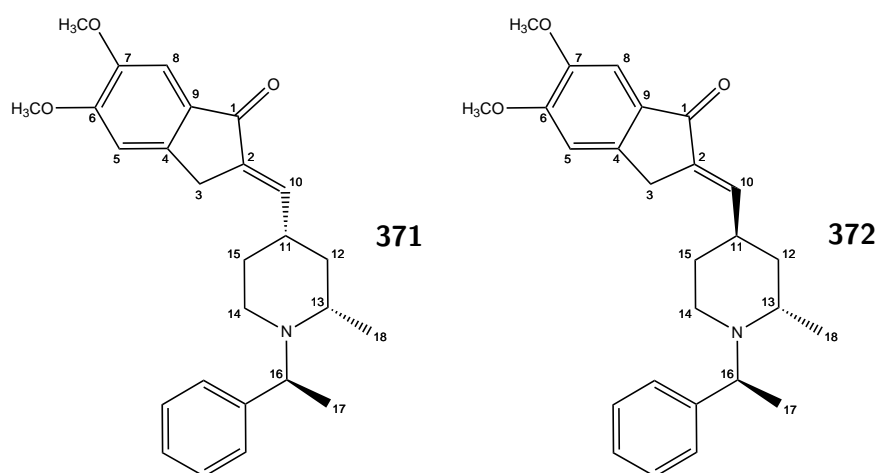
5,6-Dimethoxy-1-indanone (349 mg, 1.82 mmol, 1.0 equiv) was added to a solution of a mixture of **362** and **363** (420 mg, 1.82 mmol, 1.0 equiv, ratio of **362:363** was 1:1.42) in methanol (10 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 382 µl, 2.18 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 90 min, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (25 mL). Water (15 mL) was added and the phases were separated. The aqueous phase was extracted again with CH$_2$Cl$_2$ (2 x 20 mL), the organic phases were combined and washed with brine and dried over MgSO$_4$. The solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:hexane 3:2 → 100% ethyl acetate) afforded product **371** (368 mg, 50%) as white crystals, a mixture of **371** and **372** (129 mg, 18%) as white crystals and **372** (144 mg, 19%) as pale yellow crystals.

NMR analysis of the crude residue indicated that the mixture of diastereomers was a 1.63:1 ratio of **371:372**. NOe analysis of the purified products indicated the correct stereochemistry.

Product 371, eluting first: $[\alpha]_D^{21}$ 11.2 (*c* 0.22, CHCl$_3$); mp 84-87 °C; R$_f$ 0.30 (3:1 ethyl acetate:hexane); ν_{max} (solid) 2911, 1694, 1652, 1606, 1591, 1502, 1427, 1367, 1307, 1251, 1214, 1130, 1071, 997, 802, 761, 720, 697; δ_H (400 MHz, CDCl$_3$) 7.47-7.49 (2H, m, *ortho* Ar-H), 7.20-7.35 (4H, m, 2 x *meta* Ar-H, *para* Ar-H, H-8), 6.90 (1H, s, H-5), 6.60 (1H, dt, *J* 9.6 Hz, 1.8 Hz, H-10), 4.38 (1H, q, *J* 6.8 Hz), 3.97 (3H, s, H$_3$CO-C6), 3.92 (3H, s, H$_3$CO-C7), 3.58 (2H, s, H-3), 2.61-2.69 (1H, m, H-13), 2.49 (1H, dt, *J* 11.4 Hz, 3.3 Hz, 1 x H-14), 2.35-2.39 (1H, m, H-11), 2.17 (1H, dt, *J* 11.7 Hz, 2.2 Hz, 1 x H-14), 1.68 -1.73 (1H, m, 1 x H-12), 1.50-1.56 (1H, m, 1 x H-15), 1.32-1.45 (2H, m, 1 x H-15, 1 x H-12), 1.21-1.29 (6H, m, 3 x H-17, 3 x H-18); δ_C (100.6 MHz, CDCl$_3$) 192.82 (C1), 155.35 (C6), 149.58 (C7), 144.65 & 144.55 (C9 & *ipso* Ar), 140.33 (C10), 135.36 (C$_{quart.}$), 132.03 (C$_{quart.}$), 128.01 & 127.96 (*ortho* Ar & *meta* Ar), 126.41 (*para* Ar), 107.35 (C5), 105.12 (C8), 56.37 (C6-OCH$_3$), 56.27 (C7-OCH$_3$), 54.29 (C16), 53.23 (C13), 44.39 (C14), 41.11 (C12), 38.68 (C11), 31.87(C15), 29.62 (C3), 20.91 (C18), 8.15 (C17); *m/z* (ESI+) 406 [M+H]$^+$, 302; Exact Mass Calcd for C$_{26}$H$_{32}$NO$_3$ [M+H]$^+$ requires *m/z* 406.23767 Found 406.23728 (ESI+); HPLC t_{R1}= 14.1 min, t_{R2} 16.9 min, t_{R3} 31.2 min.

Product 372, eluting second: $[\alpha]_D^{20}$ -95.0 (*c* 0.50, CHCl$_3$); mp 66-69 °C; R$_f$ 0.16 (3:1 ethyl acetate:hexane); ν_{max} (solid) 2927, 1693, 1648, 1604, 1587, 1499, 1454, 1369, 1302, 1253, 1216, 1124, 1084, 996, 913, 801, 763, 727, 700; δ_H (400 MHz, CDCl$_3$) 7.19-7.38 (6H, m, 5 x Ar-H, 1 x H-8), 6.90 (1H, s, H-5), 6.68 (1H, dt, *J* 9.4 Hz, 1.7 Hz, H-10), 3.96 (3H, s, H$_3$CO-C6), 3.92 (3H, s, H$_3$CO-C7), 3.59-3.64 (3H, m, 2 x H-3, 1 x H-16), 3.44-3.51 (1H, m, H-13), 2.59-2.69 (1H, m, H-11), 2.46 (1H, dt, *J* 12.2 Hz, 4.0 Hz, 1 x H-14), 2.33 (1H, dt, *J* 11.7 Hz, 3.0 Hz, 1 x H-14), 1.80-1.87 (1H, m, 1 x H-12), 1.58-1.63 (1H, m, 1 x H-12), 1.50-1.55 (1H, m, 1 x H-15), 1.38-1.48 (1H, m, 1 x H-15), 1.30 (3H, d, *J* 6.6 Hz, H-17), 1.11 (3H, d, *J* 6.6 Hz, H-18); δ_C (100.6 MHz, CDCl$_3$) 192.80 (C1), 155.38 (C6), 149.60 (C7), 144.65 (*ipso* Ar, overlapping C9), 140.56 (C10), 135.61 (C$_{quart.}$), 132.04 (C$_{quart.}$), 128.43 (*ortho* Ar), 127.39 (*meta* Ar), 126.76 (*para* Ar), 107.35 (C5), 105.15 (C8), 60.57 (C16), 56.38 (C6-OCH$_3$), 56.29 (C7-OCH$_3$), 47.94 (C13), 42.96 (C14), 37.59 (C12), 32.35 (C11), 31.28 (C15), 29.62 (C3), 20.28 (C17), 10.99 (C18); *m/z* (ESI+) 406 [M+H]$^+$, 302; Exact Mass Calcd for C$_{26}$H$_{32}$NO$_3$ [M+H]$^+$ requires *m/z* 406.23767 Found 406.23770 (ESI+)

E-5,6-Dimethoxy-2-((2R,4S-2-methyl-1-(S-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1H-inden-1-one 373 and E-5,6-dimethoxy-2-((2R,4R-2-methyl-1-(S-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1H-inden-1-one 374
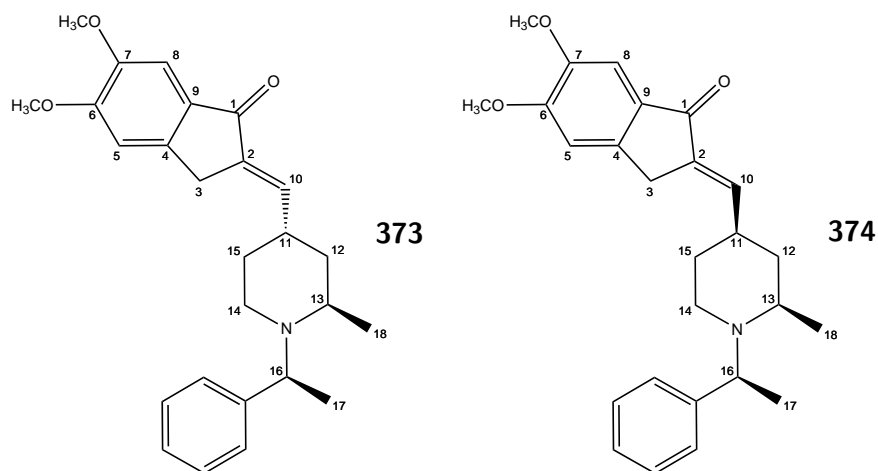

5,6-Dimethoxy-1-indanone (340 mg, 1.77 mmol, 1.0 equiv) was added to a solution of a mixture of **364** and **365** (410 mg, 1.77 mmol, 1.0 equiv, ratio of **364:365** was 2:1) in methanol (10 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 372 µl, 2.12 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 90 min, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (25 mL). Water (15 mL) was added and the phases were separated. The aqueous phase was extracted again with CH_2Cl_2 (2 x 20 mL), the organic phases were combined and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:hexane 6:1 → 100% ethyl acetate) afforded product **373** (64 mg, 9%) as pale yellow crystals, a mixture of **373** and **374** (121 mg, 17%, **373:374** 1.36:1) as white crystals and a mixture of **373** and **374** (274 mg, 38%, **373:374** 1:5.39) as white crystals.

NMR analysis of the crude residue indicated that the mixture of diastereomers was a 1:1.68 ratio of **373:374**. NOe analysis of the purified products indicated the correct stereochemistry.

Product 373, eluting first: $[\alpha]_D^{22}$ -177.6 (c 0.11, CHCl$_3$); mp 66-68 °C; R$_f$ 0.28 (19:1.5 ethyl acetate:methanol); ν_{max} (solid) 1693, 1648, 1605, 1587, 1500, 1454, 1303, 1253, 1217, 1127, 1080, 996, 801, 763; δ_H (400 MHz, CDCl$_3$) 7.21-7.37 (6H, m, H-8, *ortho* Ar-H, *meta* Ar-H, *para* Ar-H), 6.90 (1H, s, H-5), 6.63 (1H, dt, J 9.5 Hz, 2.0 Hz,

H-10), 3.97 (3H, s, H$_3$CO-C6), 3.92 (3H, s, H$_3$CO-C7), 3.58-3.67 (3H, m, H-16, 2 x H-3), 2.93-2.99 (2H, m, H-13, 1 x H-14), 2.52-2.66 (2H, m, H-11, 1 x H-14), 1.64-1.73 (3H, 2 x H-15, 1 x H-12), 1.37-1.51 (1H, m, 1 x H-12), 1.32 (3H, d, *J* 5.8 Hz, H-17), 0.98 (3H, d, *J* 5.9 Hz, H-18); δ_C (100.6 MHz, CDCl$_3$) 192.76 (C=O), 155.36 (C6), 149.58 (C7), 145.66 (C9), 144.63 (*ipso* Ar), 140.69 (C10), 135.55 (C2), 132.02 (C4), 128.45 (*meta* Ar), 127.40 (*ortho* Ar), 126.84 (*para* Ar), 107.34 (C5), 105.13 (C8), 60.36 (C16), 56.37 & 56.28 (C6-OC̲H$_3$, C7-OC̲H$_3$), 48.86 (C13), 41.36 (C14), 37.74 (C12), 31.99 (C11), 31.73 (C15), 29.61 (C3), 22.57 (C17), 10.16 (C18); *m/z* (ESI+) 406 [M+H]$^+$, 302; Exact Mass Calcd for C$_{26}$H$_{32}$NO$_3$ [M+H]$^+$ requires *m/z* 406.2377 Found 406.2376 (NSI+)

Product 374, eluting second: $[\alpha]_D^{22}$ -62.5 (*c* 0.19, CHCl$_3$); mp 76-78 °C; R$_f$ 0.23 (19:1.5 ethyl acetate:methanol); ν_{max} (film) 1693, 1648, 1605, 1588, 1499, 1454, 1302, 1254, 1216, 1129, 1080, 996, 748, 702, 665; δ_H (400 MHz, CDCl$_3$) 7.23-7.37 (6H, m, H-8, *meta* Ar-H, *ortho* Ar-H, *para* Ar-H), 6.84 (1H, s, H-5), 6.56 (1H, dt, *J* 9.7 Hz, 2.0 Hz, H-10), 4.39 (1H, q, *J* 6.7 Hz, H-16), 3.95 (3H, s, H$_3$CO-C6), 3.91 (3H, s, H$_3$CO-C7), 3.47 (2H, d, *J* 1.9 Hz, H-3), 3.15 (1H, app d, *J* 11.3 Hz, 1 x H-14), 2.14-2.23 (2H, m, H.13, H-11), 1.86 (1H, app t, *J* 11.8 Hz, 1 x H-14), 1.37-1.71 (7H, m, 2 x H-12, 2 x H-15, H-17), 1.30 (3H, d, *J* 5.8 Hz, H-18); δ_C (100.6 MHz, CDCl$_3$) 192.71 (C=O), 155.34 (C6), 149.55 (C7), 144.61 (C9), 144.59 (*ipso* Ar), 139.89 (C10), 135.53 (C2), 131.95 (C4), 128.74 (*meta* Ar), 127.86 (*ortho* Ar), 127.04 (*para* Ar), 107.30 (C5), 105.08 (C8), 56.37 & 56.26 (C6-OC̲H$_3$, C7-OC̲H$_3$), 55.72 (C16), 53.31 (C13), 45.29 (C14), 40.91 (C15), 38.01 (C11), 31.85 (C12), 29.59 (C3), 21.36 (C18), 19.00 (C17); *m/z* (ESI+) 406 [M+H]$^+$, 302; Exact Mass Calcd for C$_{26}$H$_{32}$NO$_3$ [M+H]$^+$ requires *m/z* 406.23767 Found 406.23771 (ESI+)

***E*-5,6-Dimethoxy-2-((2*R*,4*S*-2-phenyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1*H*-inden-1-one 375 and *E*-5,6-dimethoxy-2-((2*R*,4*R*-2-phenyl-1-(*S*-1-phenylethyl)piperidin-4-yl)methylene)-2,3-dihydro-1*H*-inden-1-one 388**
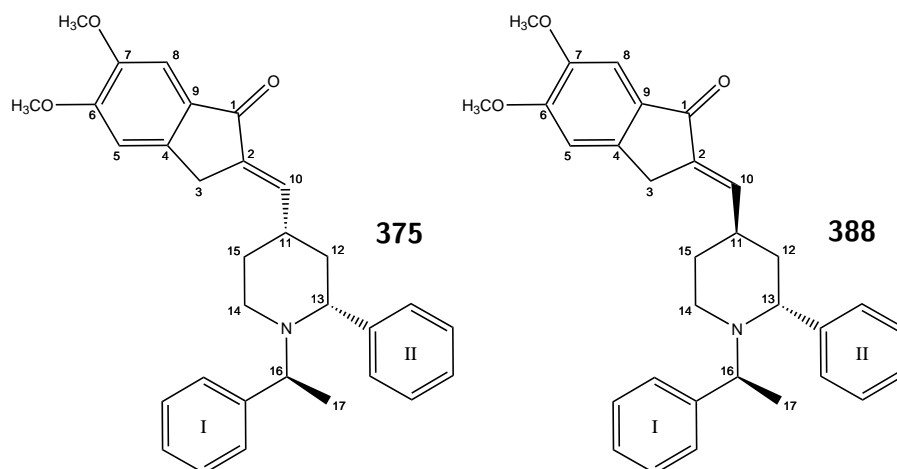
5,6-Dimethoxy-1-indanone (206 mg, 1.07 mmol, 1.0 equiv) was added to a solution of a mixture of **366** and **367** (314 mg, 1.07 mmol, 1.0 equiv, ratio of **366:367** was 1:1.33) in methanol (5 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 225 μl, 1.28 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 2 h, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (25 mL). Water (15 mL) was added and the phases were separated. The aqueous phase was extracted again with CH_2Cl_2 (2 x 20 mL), the organic phases were combined and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:3 with 1% TEA) afforded the inseparable mixture of **375** and **388** (317 mg, 64%) as white crystals;

Products 375 and 388 as a mixture: R_f 0.18 (1:1 ethyl acetate:hexane); ν_{max} (solid) 2930, 1694, 1650, 1604, 1586, 1499, 1453, 1302, 1254, 1214, 1127, 1076, 1029, 998, 801, 759, 699; δ_H (400 MHz, CDCl$_3$) 7.44-7.49 (4H, m, 2 x *meta* ArI-H, 2 x *meta* ArII-H), 7.19-7.36 (7H, m, 2 x *ortho* ArI-H, 2 x *ortho* ArII-H, *para* ArI-H, *para* ArII-H, H-8), 6.90 (1H, s, H-5), 6.62 (1H, dt, *J* 9.4 Hz, 1.8 Hz, H-10), 3.97 (3H, s, H̲$_3$CO-C6), 3.86-3.95 (4H, m, H̲$_3$CO-C7, H-16), 3.56-3.66 (3H, m, 2 x H-3, 1 x H-13), 2.67 (1H, "dt", *J* 11.5 Hz, 3.3 Hz, 1 x H-14), 2.44-2.54 (1H, m, H-11), 2.36 (1H, "td", *J* 11.7 Hz, 2.4 Hz, 1 x H-14), 1.83-1.89 (1H, m, 1 x H-12), 1.72-1.78 (1H, m, 1 x H-12), 1.65-1.69 (1H, m, 1 x H-15), 1.51-1.61 (1H, m, 1 x H-15), 1.21-1.26 (3H, m, H-17); δ_C (100.6 MHz,

CDCl$_3$) 192.68 (C1), 155.38 (C6), 149.59 (C7), 144.60 & 144.33 & 144.13 (*ipso* ArI, *ipso* ArII, C9), 139.65 (C10), 135.60 (C2), 131.97(C4), 128.81, 127.99, 127.64, 127.61, 127.39, 126.37, 107.33 (C5), 105.12 (C8), 64.86 (C13), 56.37 & 56.25 (C6-O$\underline{C}$H$_3$, C7-O$\underline{C}$H$_3$), 54.85 (C16), 44.33 (C14), 41.89 (C12), 38.79 (C11), 31.79 (C15), 29.64 (C3), 8.10 (C17); *m/z* (ESI+) 468 [M+H]$^+$, 381, 363, 293; Exact Mass Calcd for C$_{31}$H$_{34}$NO$_3$ [M+H]$^+$requires *m/z* 468.2533 Found 468.2527 (NSI+); HPLC t_{R1}= 15.8 min, t_{R2} 19.5 min, t_{R3} 38.2 min.

E-5,6-Dimethoxy-2-((2*S*,4*S*-2-phenyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methylene)-2,3-dihydro-1*H*-inden-1-one 377 and *E*-5,6-dimethoxy-2-((2*S*,4*R*-2-phenyl-1-(*S*-1-phenylethyl)piperidin-4-yl)methylene)-2,3-dihydro-1*H*-inden-1-one 393
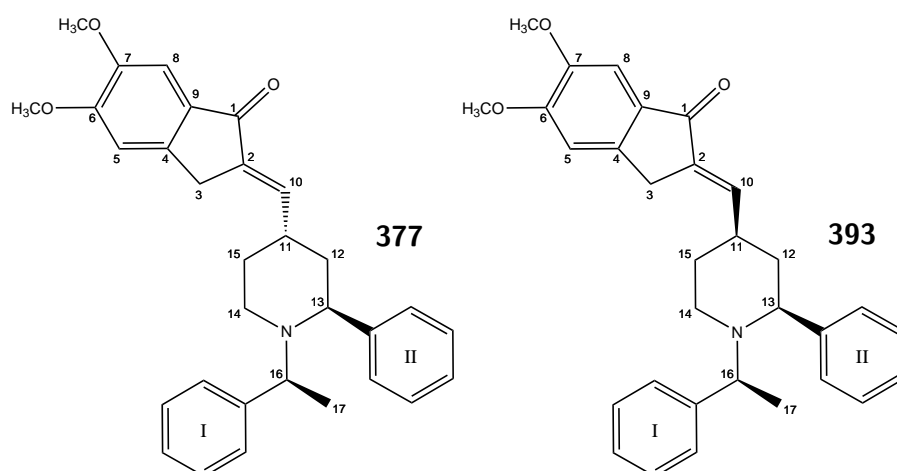
5,6-Dimethoxy-1-indanone (236 mg, 1.23 mmol, 1.0 equiv) was added to a solution of a mixture of **368** and **369** (360 mg, 1.23 mmol, 1.0 equiv, ratio of **368**:**369** was 2.04:1) in methanol (5 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 258 μl, 1.47 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 2 h, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (25 mL). Water (15 mL) was added and the phases were separated. The aqueous phase was extracted again with CH$_2$Cl$_2$ (2 x 20 mL), the organic phases were combined and washed with brine and dried over MgSO$_4$. The solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:3 → 1:1) afforded inseparable product **377** and **393** (335 mg, 59%) as white crystals;

Products 377 and 393 as a mixture: R_f 0.30 (1:2 ethyl acetate:hexane); $\nu_{\max}$ (solid) 2928, 1695, 1649, 1605, 1587, 1499, 1453, 1303, 1253, 1215, 1129, 1976, 802, 760, 702; δ_H (400 MHz, CDCl$_3$) 7.26-7.46 (9H, m, H-8, 2 x *ortho* Ar-II, 4 x *meta* Ar, 2 x *para* Ar), 7.06-7.08 (2H, m, 2 x *ortho* Ar-I), 6.85 (1H, s, H-5), 6.56 (1H, "dt", *J* 9.5 Hz, 1.8 Hz, H-10), 4.02 (1H, q, *J* 7.2 Hz, H-16), 3.96 (3H, s, H$_3$CO-C6), 3.91 (3H, s, H$_3$CO-C7), 3.49-3.50 (2H, d, *J* 1.5 Hz, H-3), 3.22-3.27 (2H, m, 1 x H-14, 1 x H-13), 2.22-2.32 (1H, m, H-11), 1.90 (1H, "dt", *J* 11.8 Hz, 2.3 Hz, 1 x H-14), 1.63-1.80 (3H, m, 2 x H-15, 1 x H-12), 1.52-1.62 (1H, m, 1 x H-12), 1.41 (3H, d, *J* 7.2 Hz, 3 x H.17); δ_C (100.6 MHz, CDCl$_3$) 192.56 (C1), 155.44 (C6), 149.66 (C7), 145.10 (*ipso* ArII), 144.55 (C9), 139.51 (C10), 138.54 (*ipso* ArI), 135.65 (C2), 131.99 (C4), 129.08 (*ortho* Ar), 128.87 (*ortho* Ar), 127.72 (*meta* Ar), 127.65 (*meta* Ar), 127.15 (*para* Ar), 126.98 (*para* Ar), 107.38 (C5), 105.20 (C8), 65.14 (C13), 56.62 (C16), 56.35 & 56.25 (C6-OCH$_3$, C7-OCH$_3$), 45.05 (C14), 42.90 (C12), 38.28 (C11), 31.89 (C15), 29.62 (C3), 18.64 (C17); *m/z* (ESI+) 468 [M+H]$^+$, 381, 363, 293; Exact Mass Calcd for C$_{31}$H$_{34}$NO$_3$ [M+H]$^+$requires *m/z* 468.25332 Found 468.25197 (ESI+); HPLC t_{R1}= 16.1 min, t_{R2} 19.8 min, t_{R3} 39.7 min.

2-((1-Benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (Donepezil) 379
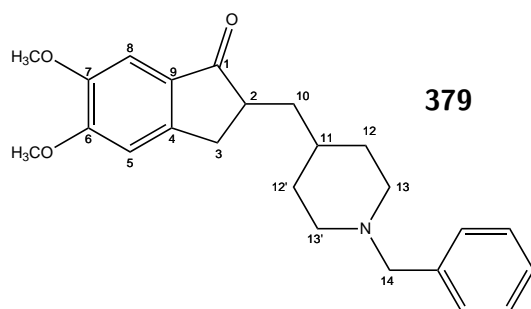
A solution of **370** (52 mg, 0.19 mmol) in THF (4 mL) was hydrogenated over palladium 10% on activated charcoal (5.2 mg) for 6 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$ (10 mL). The solvent was removed under reduced pressure and purification by column chromatography (CHCL$_3$:MeOH 30:1) afforded **379** (62 mg, 84%) as an off-white solid; mp 83-85 °C; R_f 0.20 (18:1.7 ethyl acetate:methanol); $\nu_{\max}$ (solid) 2919, 1692, 1590, 1499, 1438, 1365, 1311, 1262, 1219, 1120, 1036, 973, 862, 803, 786; δ_H (400 MHz, CDCl$_3$) 7.21-7.32 (5H, m, 5 x Ar-H), 7.16 (1H, s, H-8), 6.84 (1H, s, H-5), 3.95 (3H, s, H$_3$CO-C6), 3.89 (3H, s, H$_3$CO-C7), 3.50 (2H, s, H-14), 3.22 (1H, dd, *J* 17.6 Hz, 8.1 Hz, 1 x H-3), 2.87-2.91 (2H, m, 1 x H-13, 1 x H-13'), 2.66-2.71 (2H, m, 1 x H-3, H-2), 1.87-2.00 (3H, 1 x H-13, 1 x H-13', 1 x H-10), 1.63-1.75 (2H, m, 1 x H-12, 1 x H-12'), 1.43-1.54 (1H, m, H-11),

1.24-1.41 (3H, m, 1 x H-12, 1 x H-12', 1 x H-10); δ_C (100.6 MHz, CDCl$_3$) 207.95 (C1), 155.54 (C6), 149.51 (C7), 148.88 (C4), 138.50 (*ipso* Ar), 129.41 (C9), 129.35 (*ortho* Ar), 128.23 (*meta* Ar), 127.02 (*para* Ar), 107.44 (C5), 104.46 (C8), 63.54 (C14), 56.31 & 56.19 (C6-O$\underline{C}$H$_3$, C7-O$\underline{C}$H$_3$), 53.88 & 53.86 (C13, C13'), 45.56 (C2), 38.81 (C10), 34.56 (C11), 33.44 (C3), 33.11 & 31.88 (C12, C12'); Exact Mass Calcd for C$_{24}$H$_{29}$NO$_3$ [M+H]$^+$requires *m/z* 380.2220 Found 380.2220 (NSI+). *In agreement with published data.*[255]

### *R*-5,6-Dimethoxy-2-((2*S*,4*S*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 380 and *S*-5,6-dimethoxy-2-((2*S*,4*S*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 381
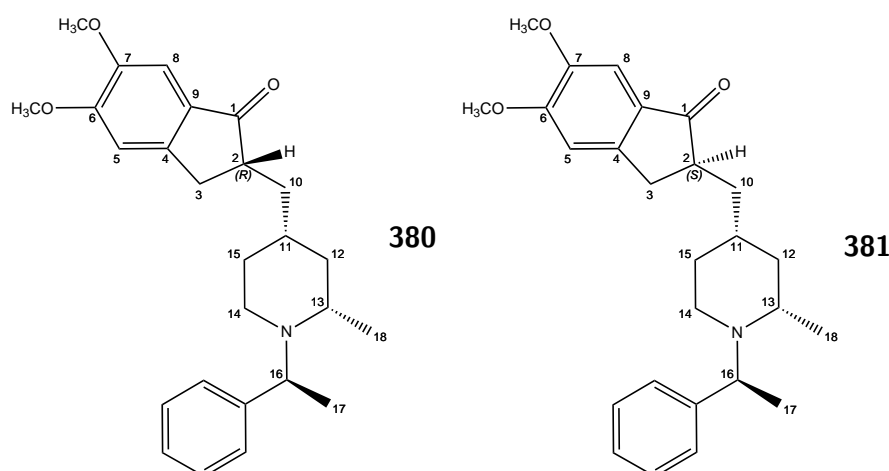
A solution of **371** (150 mg, 0.37 mmol) in THF (15 mL) was hydrogenated over palladium 10% on activated charcoal (25 mg) for 8 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$ (40 mL). The solvent was removed under reduced pressure and purification by column chromatography (ethyl acetate:hexane 2:1 → 100% ethyl acetate) afforded an inseparable mixture of product **380** and product **381** (103 mg, 68%) as a pale yellow solid.

Products 380 and 381 as a mixture: R$_f$ 0.32 (8:1 ethyl acetate:methanol); ν_{max} (solid) 2919, 1693, 1590, 1499, 1454, 1420, 1307, 1262, 1221, 1119, 1034, 764, 721, 698; δ_H (400 MHz, CDCl$_3$) 7.46-7.48 (4H, m, 4 x *ortho* Ar-H), 7.30-7.33 (4H, m, 4 x *meta* Ar-H), 7.19-7.23 (2H, m, 2 x *para* Ar-H), 7.16 (2 H, s, 2 x H-8), 6.84-6.85 (2H, m, 2 x H-5), 4.35 (2H, q, *J* 6.1 Hz, 2 x H-16), 3.96 (6H, s, 6 x $\underline{H}_3$CO-C6), 3.90 (6H, s, 6 x H$_3$CO-C7), 3.23 (2H, dd, *J* 17.5 Hz, 8.1 Hz, 2 x *H*H-3), 2.65-2.71 (4H, m, 2 x H*H*-3, 2 x H-2), 2.53-2.61 (2H, m, 2 x H-13), 2.42-2.47 (2H, m, 2 x *H*H-14), 2.06-2.12 (2H, m, 2

x HH-14), 1.82-1.90 (2H, m, 2 x HH-10), 1.68-1.78 (2H, m, 2 x HH-12), 1.48-1.59 (4H, m, 2 x HH-15, 2 x H-11), 1.02-1.31 (18H, m, 2 x HH-10, 6 x H-17, 6 x H-18, 2 x HH-12, 2 x HH-15); δ_C (100.6 MHz, CDCl$_3$) 208.13 & 208.12 (C1), 155.51 (C6), 149.49 (C7), 148.97 & 148.96 (C4), 144.89 (*ipso* Ar), 129.47 & 129.44 (C9), 127.95 & 127.92 (*ortho* & *meta* Ar), 126.27 (*para* Ar), 56.34 & 56.22 (C6-O$\underline{C}$H$_3$, C7-O$\underline{C}$H$_3$), 54.26 (C16), 53.54 (C13), 45.68 & 45.52 (C2), 44.88 (C14), 43.48 & 42.35 (C12), 39.20 & 39.12 (C10), 35.66 & 35.57 (C11), 33.72 & 32.45 (C15), 33.54 (C3), 21.16 & 21.14 (C18), 8.15 & 8.12 (C17); m/z (ESI+) 408 [M+H]$^+$, 304; Exact Mass Calcd for C$_{26}$H$_{34}$NO$_3$ [M+H]$^+$ requires m/z 408.25332 Found 408.25278 (ESI+); HPLC t_{R1}= 14.2 min, t_{R2} 17.0 min, t_{R3} 31.3 min.

R-5,6-Dimethoxy-2-((2*S*,4*R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 382 and *S*-5,6-dimethoxy-2-((2*S*,4*R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 383

A solution of **372** (72 mg, 0.18 mmol) in THF (7 mL) was hydrogenated over palladium 10% on activated charcoal (10 mg) for 8 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$ (30 mL). The solvent was removed under reduced pressure and purification by column chromatography (100% ethyl acetate → ethyl acetate:methanol 10:1) afforded an inseparable mixture of product **382** and product **383** (26 mg, 35%) as a pale yellow sticky solid.

Products 382 and 383 as a mixture: R$_f$ 0.20 (9:1 ethyl acetate:methanol); ν_{max} (film) 2921, 1693, 1606, 1591, 1500, 1454, 1310, 1263, 1122, 1039, 751, 701, 649; δ_H (400 MHz, CDCl$_3$) 7.35-7.41 (4H, m, 4 x *ortho* Ar-H), 7.28-7.32 (4H, m, 4 x *meta* Ar-H), 7.20-7.23 (2H, m, 2 x *para* Ar-H), 7.16 (2H, s, 2 x H-8), 6.85 (2H, "ds", 2 x H-5), 3.95 (6H, s, 6 x $\underline{H}_3$CO-C6), 3.90 (6H, s, 6 x $\underline{H}_3$CO-C7), 3.45-3.63 (4H, m, 2 x H-16, 2 x H-13),

3.19-3.26 (2H, m, 2 x *H*H-3), 2.65-2.73 (4H, m, 2 x H*H*-3, 2 x H-2), 2.42-2.52 (2H, m, 2 x *H*H-14), 2.28-2.36 (2H, m, 2 x H*H*-14), 1.78-1.92 (4H, m, 2 x H-11, 2 x *H*H-10), 1.48-1.65 (6H, m, 4 x H-12, 2 x *H*H-15), 1.07-1.33 (16H, m, 6 x H-17, 2 x H*H*-10, 2 x H*H*-15, 6 x H-18); δ_C (100.6 MHz, CDCl$_3$) 208.04 (C1), 155.54 & 155.53 (C6), 149.50 (C7), 148.93 (C4), 147.03 (*ipso* Ar), 129.43 & 129.39 (C9), 128.50 (*meta* Ar), 127.48 (*ortho* Ar), 126.93 (*para* Ar), 107.44 (C5), 104.43 & 104.42 (C8), 61.15 (C16), 56.34 & 56.21 (C6-OC̲H$_3$, C7-OC̲H$_3$), 48.68 (C13), 45.64 & 45.39 (C2), 43.87 (C14), 38.95 & 38.89 (C10), 37.77 (C12), 33.54 & 33.48 (C3), 31.42 (C15), 28.97 & 28.67 (C11), 20.94 (C17), 10.64 (C18); *m/z* (ESI+) 408 [M+H]$^+$, 304; Exact Mass Calcd for C$_{26}$H$_{34}$NO$_3$ [M+H]$^+$ requires *m/z* 408.25332 Found 408.25349 (ESI+); HPLC t_{R1}= 14.4 min, t_{R2} 17.4 min, t_{R3} 32.2 min.

R-5,6-Dimethoxy-2-((2*R*,4*S*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 384 and *S*-5,6-dimethoxy-2-((2*R*,4*S*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 385
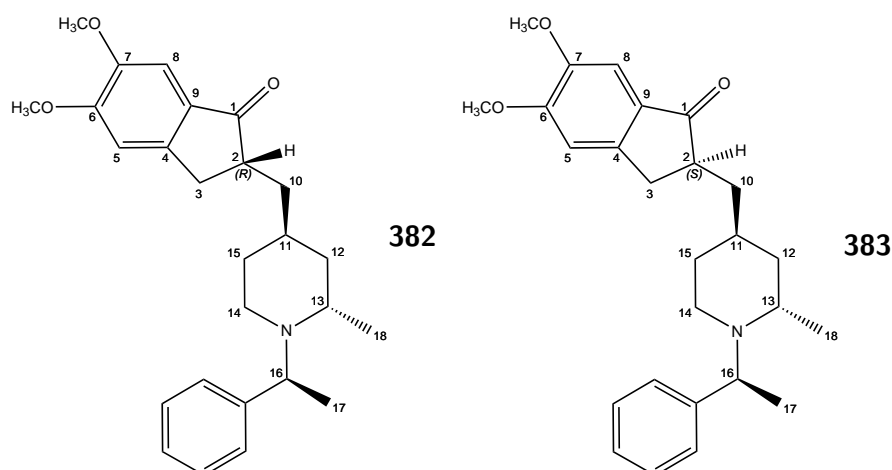

A solution of **373** (72 mg, 0.18 mmol) in THF (8 mL) was hydrogenated over palladium 10% on activated charcoal (14 mg) for 9 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$ (30 mL). The solvent was removed under reduced pressure and purification by column chromatography (ethyl acetate:hexane 8:1 → 100% ethyl acetate → ethyl acetate:methanol 10:1) afforded an inseparable mixture of product **384** and product **385** (31 mg, 42%) as a pale yellow sticky solid.

Products 384 and 385 as a mixture: R$_f$ 0.09 (100% ethyl acetate); ν_{max} (film) 2921, 1692, 1606, 1591, 1499, 1454, 1311, 1263, 1121, 1037, 913, 767, 728, 702, 646; δ_H

(400 MHz, CDCl$_3$) 7.41-7.43 (2H, m, 2 x *meta* Ar-H), 7.32 (2H, t, *J* 7.4 Hz, 2 x *ortho* Ar-H), 7.22-7.26 (1H, m, *para* Ar-H), 7.15 (1H, s, H-8), 6.84-6.85 (1H, 'm', H-5), 3.95 (3H, s, H$_3$CO-C6), 3.89 (3H, s, H$_3$CO-C7), 3.67-3.72 (1H, m, H-16), 3.23 (1H, dd, *J* 17.4 Hz, 8.0 Hz, 1 x H-3), 3.01-3.11 (2H, 1 x H-14, H-13), 2.54-2.71 (3H, m, 1 x H-3, H-2, 1 x H-14), 1.76-1.88 (3H, 1 x H-10, 1 x H-15, H-11), 1.23-1.57 (7H, 1 x H-15, 2 x H-12, H-18, 1 x H-10), 0.98-1.00 (3H, m, 3 x H-18); δ_C (100.6 MHz, CDCl$_3$) 207.93 & 207.91 (C1), 155.58 (C6), 149.54 (C7), 148.91 (C4), 142.64 (*ipso* Ar) 129.40 & 129.37 (C9), 128.61 (*ortho* Ar), 127.60 (*meta* Ar), 127.22 (*para* Ar), 107.46 (C5), 104.43 (C8), 61.12 (C16), 56.33 (C6-OCH$_3$), 56.20 (C7-OCH$_3$), 50.08 (C13), 45.46 & 45.34 (C2), 42.40 (C14), 38.91 & 38.84 (C10), 37.73 (C12), 33.63 & 33.54 (C3), 31.57 (C15), 28.25 & 28.14 (C11), 22.02 (C17), 10.49 (C18); *m/z* (ESI+) 408 [M+H]$^+$, 304; Exact Mass Calcd for C$_{26}$H$_{34}$NO$_3$ [M+H]$^+$requires *m/z* 408.25332 Found 408.25396 (ESI+); HPLC t_{R1}= 14.5 min, t_{R2} 17.6 min, t_{R3} 32.7 min.

R-5,6-Dimethoxy-2-((2*R*,4*R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 386 and *S*-5,6-dimethoxy-2-((2*R*,4*R*-2-methyl-1-(*S*-1-phenylethyl)piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 387
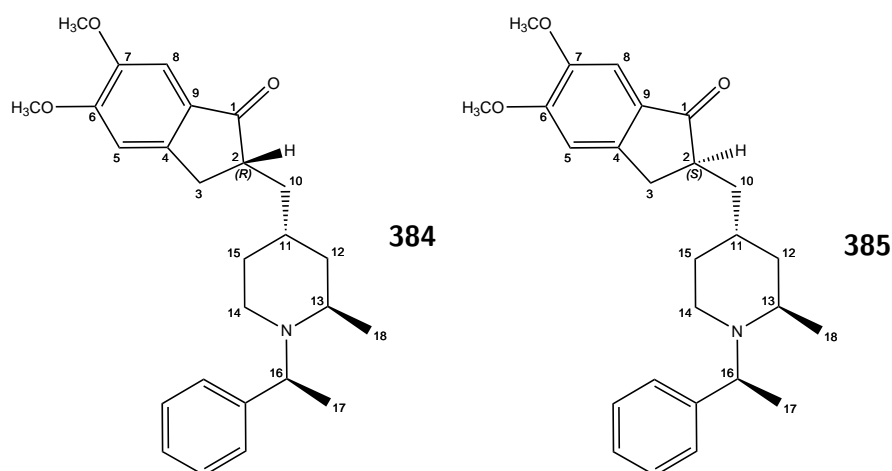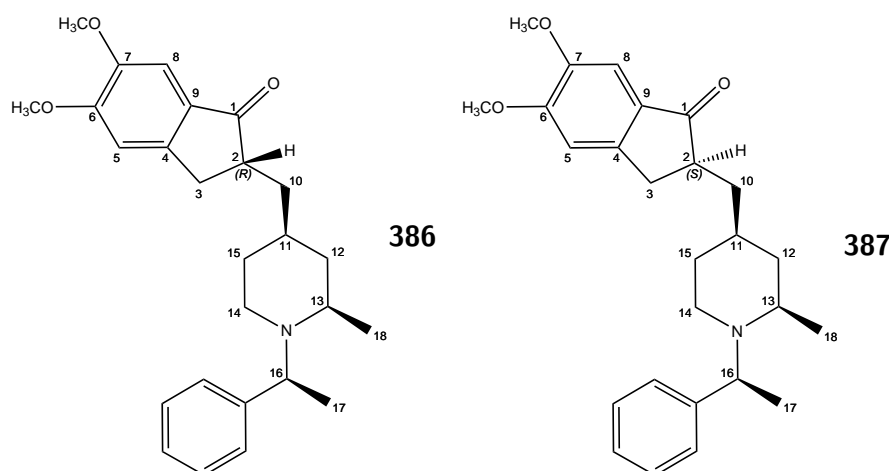

A solution **374** (85 mg, 0.21 mmol) in THF (10 mL) was hydrogenated over palladium 10% on activated charcoal (16 mg) for 7 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$ (40 mL). The solvent was removed under reduced pressure and purification by column chromatography (ethyl acetate:hexane 3:1 → 100% ethyl acetate) afforded the inseparable mixture of product **386** and product **387** (57 mg, 67%) as a pale yellow foamy solid.

Products 386 and 387 as a mixture: R_f 0.25 (9:1 ethyl acetate:methanol); ν_{max} (film) 2918, 1693, 1605, 1590, 1499, 1453,1307, 1262, 1119, 1035, 762, 733, 702, 651; δ_H (400 MHz, CDCl$_3$) 7.23-7.36 (10H, m, 4 x *ortho* Ar-H, 4 x *meta* Ar-H, 2 x *para* Ar-H), 7.14 (2H, s, 2 x H-8), 6.81 (2H, s, 2 x H-5), 4.39 (2H, q, *J* 7.1 Hz, 2 x H-16), 3.94 (6H, s, 6 x $\underline{H}_3$CO-C6), 3.89 (6H, s, 6 x 6 x $\underline{H}_3$CO-C7), 3.12-3.19 (4H, m, 2 x *H*H-14, 2 x *H*H-3), 2.58-2.68 (4H, m, 2 x H-2, 2 x H*H*-3), 2.14-2.17 (2H, m, 2 x H-13), 1.58-1.87 (8H, m, 2 x H*H*-14, 2 x *H*H-10, 2 x *H*H-12, 2 x *H*H-15), 1.50 (6H, d, *J* 7.0 Hz, 6 x H-17), 1.10-1.37 (14 H, 2 x H-11, 6 x H-18, 2 x H*H*-10, 2 x H*H*-15, 2 x H*H*-12); δ_C (100.6 MHz, CDCl$_3$) 207.83 & 207.79 (C1), 155.40 (C6), 149.37 (C7), 148.74 (C4), 138.96 (*ipso* Ar), 129.29 & 129.27 (C9), 128.68 (*meta* Ar), 127.71 (*ortho* Ar), 126.94 (*ipso* Ar), 107.32 (C5), 104.33 (C8), 56.21 & 56.09, (C6-O$\underline{C}$H$_3$, C7-O$\underline{C}$H$_3$), 55.72 & 55.69 (C16), 53.71 (C13), 45.71 (C14), 45.35 & 45.26 (C2), 42.98 & 41.88 (C12), 38.85 & 38.77 (C10), 34.68 (C11), 33.33 (C3, overlapping 1 x C15), 32.09 (1 x C15), 21.34 & 21.29 (C18), 18.88 & 18.87 (C17); *m/z* (ESI+) 408 [M+H]$^+$, 304; Exact Mass Calcd for C$_{26}$H$_{34}$NO$_3$ [M+H]$^+$ requires *m/z* 408.25332 Found 408.25274 (ESI+); HPLC t_{R1}= 14.5 min, t_{R2} 17.6 min, t_{R3} 32.9 min.

R-5,6-Dimethoxy-2-((2*R*,4*S*-2-phenyl-1-(*S*-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 389 and *R*-5,6-dimethoxy-2-((2*R*,4*R*-2-phenyl-1-(*S*-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 391 and *S*-5,6-dimethoxy-2-((2*R*,4*S*-2-phenyl-1-(*S*-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 390 and *S*-5,6-dimethoxy-2-((2*R*,4*R*-2-phenyl-1-(*S*-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1*H*-inden-1-one 392
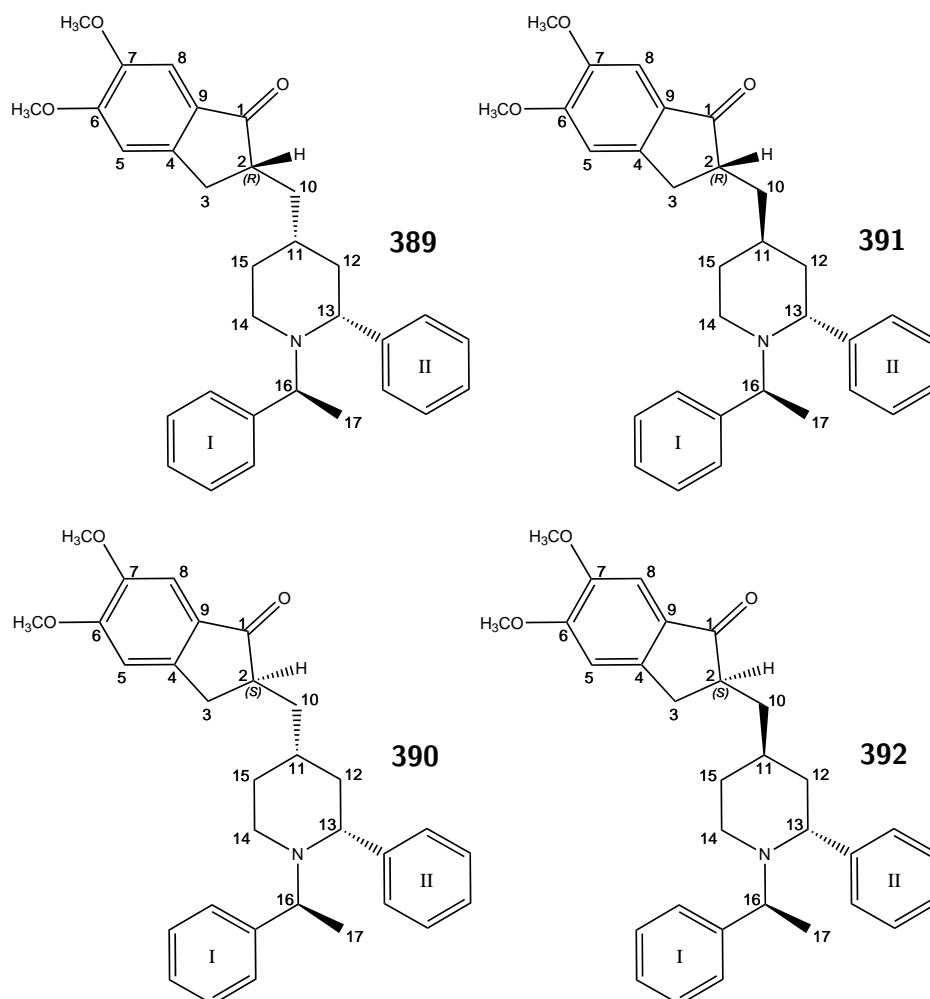
A solution of a mixture of **375** and **388** (139 mg, 0.30 mmol) in THF (13 mL) was hydrogenated over palladium 10% on activated charcoal (14 mg) for 10 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (40 mL). The solvent was removed under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:3.5) afforded an inseparable mixture of products **389**, **391**, **390**, and **392** (108 mg, 77%) as a foamy white solid;

Product 389, 391, 390 and 392 as a mixture: R_f 0.47 (1:1 ethyl acetate:hexane); ν_{max} (solid) 2910, 1693, 1606, 1591, 1499, 1453,1309, 1262, 1120, 1032, 909, 762, 728, 690; δ_H (400 MHz, CDCl$_3$) 7.44-7.50 (4H, m, 4 x Ar-H), 7.16-7.36 (7H, m, 7 x Ar-H), 6.84-6.85 (1H, m, H-5), 3.94-3.95 (3H, m, H$_3$CO-C6), 3.89 (3H, s, H$_3$CO-C7), 3.84-3.92 (1H, m, H-16), 3.55-3.61 (1H, m, H-13), 3.19-3.26 (1H, m, 1 x H-3), 2.59-2.73 (3H, m, H-2, 1 x H-3, 1 x H-14), 2.26-2.32 (1H, m, 1 x H-14), 1.86-1.94 (2H, m, 1 x H-10, 1 x H-12), 1.60-1.74 (2H, m, H-11, 1 x H-15), 1.41-1.53 (1H, m, 1 x H-15), 1.20-1.38 (5H, m, 1 x H-10, 1 x H-15, H-17); δ_C (100.6 MHz, CDCl$_3$) 207.89 & 207.85 (C1), 155.51 & 155.50 (C6), 149.48 (C7), 148.86 & 148.83 (C4), 144.95 & 144.90 (*ipso* ArII), 144.64 (*ipso* ArI), 129.38 (C9), 128.69 (Ar), 127.89 (Ar), 127.63 (Ar), 127.55 (Ar), 127.17 (Ar), 127.13 (Ar), 126.20 (Ar), 107.43 & 107.41 (C5), 104.43 (C8), 65.18 (C13), 56.29 & 56.16 (C6-OCH$_3$, C7-OCH$_3$), 54.79 (C16), 45.45 & 45.38 (C2), 44.69 & 44.67 (C14), 44.42 & 43.31 (C12), 39.12 & 39.03 (C10), 35.85 & 35.63 (C11), 33.69 & 33.43 (C3), 33.38 & 32.32 (C15), 8.12 (C17); *m/z* (ESI+) 470 [M+H]$^+$, 366; Exact Mass Calcd for C$_{31}$H$_{36}$NO$_3$ [M+H]$^+$requires *m/z* 470.26897 Found 470.26805 (ESI+); HPLC t_{R1}= 15.7 min, t_{R2} 19.4 min, t_{R3} 37.8 min.

R-5,6-Dimethoxy-2-((2S,4S-2-phenyl-1-(S-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1H-inden-1-one 394 and R-5,6-dimethoxy-2-((2S,4R-2-phenyl-1-(S-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1H-inden-1-one 396 and S-5,6-dimethoxy-2-((2S,4S-2-phenyl-1-(S-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1H-inden-1-one 395 and S-5,6-dimethoxy-2-((2S,4R-2-phenyl-1-(S-1-phenylethyl)-piperidin-4-yl)-methyl)-2,3-dihydro-1H-inden-1-one 397
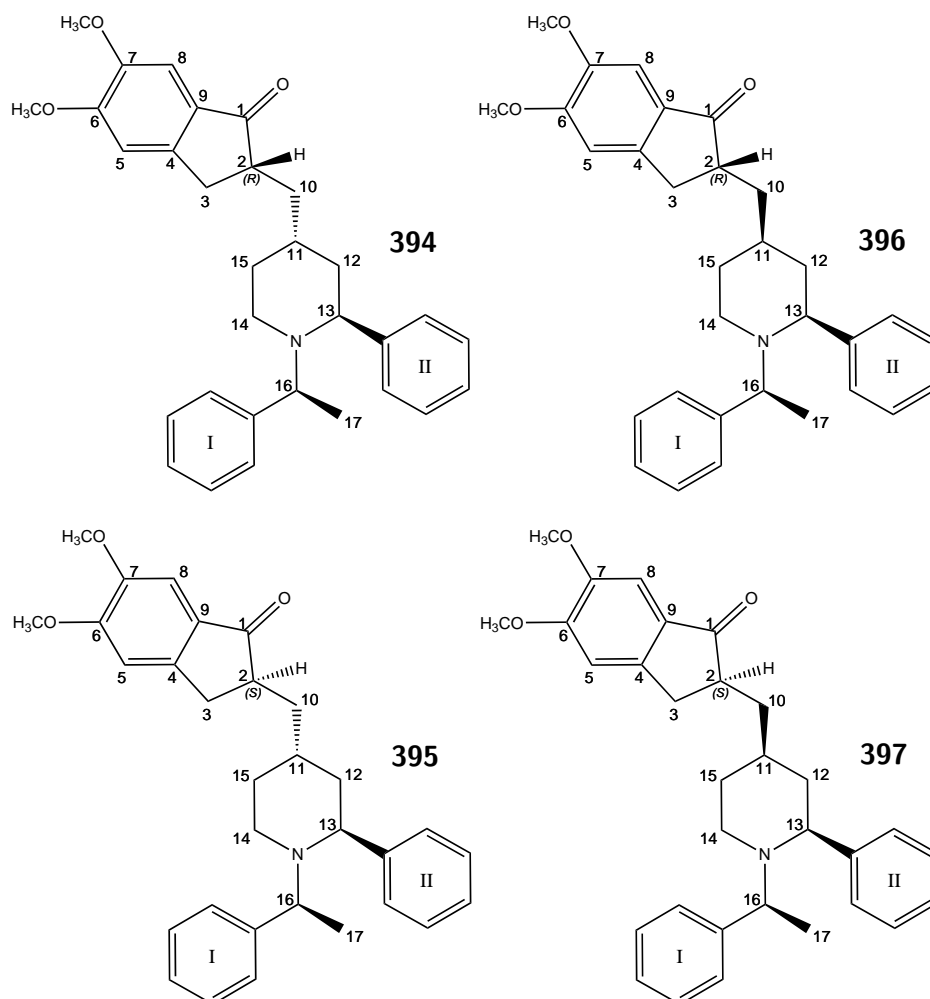
A solution of a mixture of **377** and **393** (200 mg, 0.43 mmol) in THF (16 mL) was hydrogenated over palladium 10% on activated charcoal (26 mg) for 8 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (100 mL). The solvent was removed under reduced pressure and purification by column chromatography (chloroform:methanol 4:0.1) afforded an inseparable mixture of products **394**, **396**, **395**, and **397** (171 mg, 84%) as a colourless solid;

Products 394, 396, 395 and 397 as a mixture: R_f 0.31 (1:2 ethyl acetate:hexane); ν_{max} (film) 2923, 1693, 1591, 1500, 1453, 1311, 1263, 1216, 1119, 1033, 844, 759, 735, 701; δ_H (400 MHz, CDCl$_3$) 7.37-7.45 (4H, m, 4 x Ar-H), 7.22-7.32 (4H, m, 4 x Ar-H), 7.13 (1H, s, H-8), 7.03-7.05 (2H, m, 2 x *ortho* ArI-H), 6.79-6.81 (1H, m, H-5), 3.97 (1H, q, *J* 7.2 Hz, H-16), 3.93-3.94 (3H, s, H$_3$CO-C6), 3.88 (3H, s, H$_3$CO-C7), 3.10-3.21 (3H, m, 1 x H-14, H-13, 1 x H-3), 2.55-2.67 (2H, m, H-2, 1 x H-3), 1.66-1.86 (4H, m, 1 x H-14, 1 x H-10, 1 x H-15, 1 x H-12), 1.26-1.45 (6H, m, H-11, 3 x H-17, 1 x H-15, 1 x H-12), 1.12-1.21 (1H, m, 1 x H-10); δ_C (100.6 MHz, CDCl$_3$) 207.82 & 207.73 (C1), 155.58 & 155.55 (C6), 149.55 (C7), 148.83 & 148.78 (C4), 145.86 & 145.84 (*ipso* ArII), 138.66 (*ipso* ArI), 129.43 (C9), 129.06, 128.78, 127.75, 127.57, 126.95, 126.91, 126.88, 107.49 & 107.47 (C5), 104.52 (C8), 65.56 (C13), 56.62 & 56.60 (C16), 56.31 & 56.20 (C6-OCH$_3$, C7-OCH$_3$), 45.51 & 45.48 (C14, C12), 45.43 & 45.34 (C2), 44.34 (C12'), 38.97 & 38.89 (C10), 35.32 & 35.05 (C11), 33.57 (C3), 33.30 & 32.32 (C15), 18.73 & 18.70 (C17); *m/z* (ESI+) 470 [M+H]$^+$, 366; Exact Mass Calcd for C$_{31}$H$_{36}$NO$_3$ [M+H]$^+$ requires *m/z* 470.26897 Found 470.26726 (ESI+); HPLC t_{R1}= 16.0 min, t_{R2} 20.0 min, t_{R3} 40.0 min.

1,1-Dimethyl-4-oxopiperidin-1-ium iodide 399
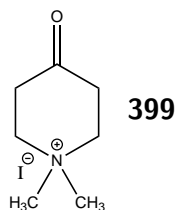
Methyl iodide (4.126 mL, 66.28 mmol, 2.5 equiv) was added to a stirring solution of 1-methyl-4-piperidone (3.261 mL, 26.51 mmol, 1.0 equiv) in acetone (140 mL) at 25 °C. After stirring for 2 h, the precipitate was isolated by filtration and subsequent washing with acetone (40 mL). Product **399** (6.713 g, 99%) was obtained as a pale yellow solid; mp 185-189 °C (decomposition) ; ν_{max} (solid) 1726, 1476, 1386, 1333, 1295, 1169, 1025, 909, 773, 757; δ_H (400 MHz, DMSO-d$_6$) 3.76 (4H, t, *J* 6.6 Hz, 2 x β-CH$_2$), 3.29 (6H, s, 2 x -CH$_3$), 2.71 (4H, t, *J* 6.6 Hz, 2 x α-CH$_2$); δ_C (100.6 MHz, DMSO-d$_6$) 201.66 (C=O), 60.02 (β-CH$_2$), 50.90 (α-CH$_2$), 35.13 (CH$_3$) *In agreement with published data.*[256]

S-1-(1-Phenylethyl)piperidin-4-one 400
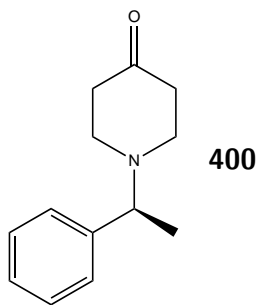
S-α-Phenylethylamine (2.128 mL, 16.50 mmol, 1.0 equiv) was added to a solution of ethanol (25 mL), potassium carbonate (4.790 g, 34.66 mmol, 2.65 equiv) and water (12 mL) and the resulting mixture was heated to 95 °C. **399** (4.210 g, 16.50 mmol, 1.0 equiv) in water (14 mL) was added dropwise to the mixture. The mixture was heated at reflux for another 30 min and then cooled to room temperature. The ethanol was removed under reduced pressure and the aqueous residue was extracted with ether (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, the solvent was evaporated under reduced pressure and purification by column chromatography (ethyl acetate:hexane 1:1) afforded product **400** (2.327 g, 69%) as a yellow oil; R_f 0.29 (1:1 ethyl acetate:hexane); $[\alpha]_D^{23}$ -29.3 (*c* 0.72, CHCl$_3$); $\nu_{\max}$ (film) 3028, 2971, 2908, 2806, 2756, 1718, 1493, 1454, 1412, 1386, 1342, 1316, 1284, 1220, 1131, 1080, 1011, 767, 703; δ_H (400 MHz, CDCl$_3$) 7.24-7.37 (5H, m, 5 x Ar-H), 3.62 (1H, q, *J* 6.7 Hz, N-C$\underline{H}$<), 2.69-2.80 (4H, m, 2 x β-C$\underline{H}_2$), 2.42 (4H, t, *J* 6.2 Hz, 2 x α-C$\underline{H}_2$), 1.42 (3H, d, *J* 6.7 Hz, -C$\underline{H}_3$); δ_C (100.6 MHz, CDCl$_3$) 209.84 (C=O), 143.58 (*ipso* Ar), 128.47 (*meta* Ar), 127.48 (*ortho* Ar), 127.27 (*para* Ar), 63.53 (N-$\underline{C}$H<), 50.14 (β-$\underline{C}$H$_2$), 41.68 (α-$\underline{C}$H$_2$), 19.50 ($\underline{C}$H$_3$). *In agreement with published data.*[208]

R-5,6-Dimethoxy-2-((1-(S-1-phenylethyl)piperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one 401 and S-5,6-dimethoxy-2-((1-(S-1-phenylethyl)piperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one 402
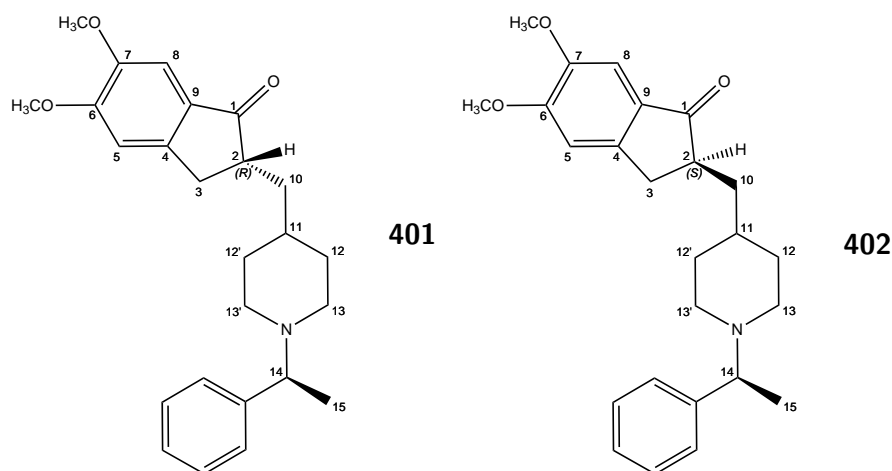
A solution of **410** (300 mg, 0.77 mmol) in THF (29 mL) was hydrogenated over palladium 10% on activated charcoal (48 mg) for 8 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (100 mL). The solvent was removed under reduced pressure and purification by column chromatography (100% ethyl acetate → ethyl acetate:methanol 10:0.5) afforded product **401** and product **402** (176 mg, 58%) as a colourless sticky solid.

Products 401 and 402 as a mixture: R_f 0.23 (19:2.5 ethyl acetate:methanol); ν_{max} (film) 2920, 1693, 1606, 1591, 1499, 1453, 1312, 1262, 1121, 1036, 912, 763, 728, 701, 647; δ_H (400 MHz, CDCl$_3$) 7.22-7.34 (5H, 5 x Ar-H), 7.15 (1H, s, H-8), 6.83 (1H, s, H-5), 3.95 (3H, s, H$_3$CO-C6), 3.89 (1H, s, H$_3$CO-C6), 3.47-3.53 (1H, m, H-14), 3.20 (1H, dd, J 17.6 Hz, 8.1 Hz, 1 x H-3), 3.07-3.11 (1H, m, 1 x HH-13), 2.84-2.90 (1H, m, 1 x HH-13), 2.64-2.71 (2H, 1 x H-3, H-2), 1.95-2.03 (1H, m, 1 x HH-13), 1.84-1.93 (2H, m, 1 x HH-13, 1 x H-10), 1.60-1.77 (2H, m, 2 x HH-12), 1.23-1.46 (7H, m, 1 x H-11, 3 x H-15, 1 x H-10, 2 x HH-12); δ_C (100.6 MHz, CDCl$_3$) 207.91 (C1), 155.57 (C6), 149.55 (C7), 148.87 (C4), 143.07 (*ipso* Ar), 129.44 (C9), 128.27 (*meta* Ar), 128.04 (*ortho* Ar), 127.11 (*para* Ar), 107.47 (C5), 104.50 (C8), 65.02 (C14), 56.34 (C6-OCH$_3$), 56.22 (C7-OCH$_3$), 51.15 & 51.13 (C13), 50.50 (C13), 45.54 & 45.53 (C2), 38.77 (C10), 34.57 (C11), 33.49 & 33.47 (C3), 33.01 (C12), 31.95 & 31.89 (C12), 19.46 & 19.43 (C15); m/z (ESI+) 394 [M+H]$^+$, 290; Exact Mass Calcd for C$_{25}$H$_{32}$NO$_3$ [M+H]$^+$ requires m/z 394.23767 Found 394.23764 (ESI+); HPLC t_{R1}= 14.1 min, t_{R2} 16.9 min, t_{R3} 31.3 min.

S-4-(Methoxymethylene)-1-(1-phenylethyl)piperidine 408
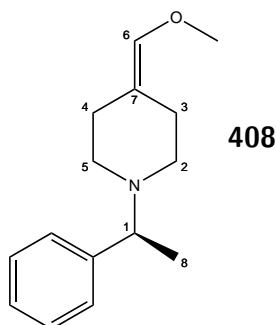
(Methoxymethyl)triphenylphosphonium chloride (2.785 g, 8.12 mmol, 1.5 equiv) and molecular sieves were placed in an oven-dried flask and added with absolute THF (17 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and a 2 M solution of lithium diisopropylamide in THF/heptane/ethylbenzene (4.06 mL, 8.12 mmol, 1.5 equiv) was added slowly. The mixture was stirred at -78 °C for 5 min and then allowed to warm to rt while stirring for another 20 min. The reaction mixture was cooled to -20 °C and a solution of **400** (1.100 g, 5.42 mmol, 1.0 equiv) in absolute THF (12 mL) was added slowly. The mixture was stirred at -20 °C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1 M NH_4Cl solution (25 mL) and ethyl acetate (50 mL) was added and the solution was stirred vigorously for 5 min. The phases were separated and the aqueous phase was again extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:ethyl acetate 3:2) afforded **408** as a colourless oil (1.165 g, 93%); $[\alpha]_D^{23}$ -42.6 (*c* 1.21, $CHCl_3$); R_f 0.25 (1.5:1 ethyl acetate:hexane); ν_{max} (film) 1691, 1452, 1223, 1190, 1121, 1075, 837, 758, 735, 700; δ_H (400 MHz, $CDCl_3$) 7.23-7.37 (5H, m, 5 x Ar-H), 5.77 (1H, s, H-6), 3.54 (3H, s, -OC$\underline{H}_3$), 3.49 (1H, q, *J* 6.9 Hz, H-1), 2.36-2.48 (4H, m, 2 x H-2, 2 x H-5), 2.31 (2H, t, *J* 5.8 Hz, 2 x H-3), 2.06 (2H, t, *J* 5.6 Hz, 2 x H-4), 1.41 (3H, d, *J* 6.8 Hz, H-8); δ_C (100.6 MHz, $CDCl_3$) 143.74 (*ipso* Ar), 139.42 (C6), 128.18 & 127.85 (*meta* & *ortho* Ar), 126.87 (*para* Ar), 115.30 (C7), 64.60 (C1), 59.43 (-OC$\underline{H}_3$), 52.38 (C5), 51.14 (C2), 30.04 (C4), 25.53 (C3), 19.28 (C8); *m/z* (ESI+) 232 [M+H]$^+$, 128; Exact Mass Calcd for $C_{15}H_{22}NO$ [M+H]$^+$ requires *m/z* 232.16959 Found 232.16937 (ESI+)

S-1-(1-Phenylethyl)piperidine-4-carbaldehyde 409

409
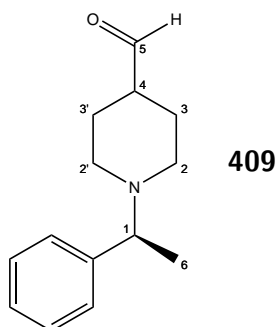
1.6 N HCl (9 mL) was added to a solution of **408** (1.000 g, 4.33 mmol) in THF (9 mL) and stirred at 45 °C for 2.5 hours. THF was evaporated under reduced pressure and the residue was diluted with water (20 mL). The pH was adjusted to 10 by the addition of an aqueous Na_2CO_3 solution. The aqueous phase was extracted with DCM (3 x 40 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and crude aldehyde **409** was obtained as a colourless oil (863 mg, 92%). The product could be used for the next step without the need of further purification; $[\alpha]_D^{24}$ -71.8 (*c* 0.20, $CHCl_3$); R_f 0.23 (1.5:1 ethyl acetate:hexane); ν_{max} (film) 1723, 1492, 1450, 1373, 1147, 1132, 941, 769, 758, 701; δ_H (400 MHz, $CDCl_3$) 9.62 (1H, s, H-5), 7.22-7.35 (5H, 5 x Ar-H), 3.45 (1H, q, *J* 6.7 Hz, H-1), 2.93-2.96 (1H, m, 1 x *H*H-2), 2.73-2.79 (1H, m, 1 x *H*H-2), 2.15-2.22 (1H, m, H-4), 2.03-2.13 (2H, m, 2 x H*H*-2), 1.83-1.91 (2H, m, 2 x *H*H-3), 1.58-1.75 (2H, m, 2 x H*H*-3), 1.38 (3H, d, *J* 6.8 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 204.25 (C5), 143.56 (*ipso* Ar), 128.35 (*meta* Ar), 127.78 (*ortho* Ar), 127.10 (*para* Ar), 64.84 (C1), 49.75 (C2), 49.56 (C2'), 48.24 (C4), 25.75 (C3), 19.31 (C6); *m/z* (ESI+) 236 [M+H+H_2O]$^+$, 218 [M+H]$^+$, 132, 114, 105; Exact Mass Calcd for $C_{14}H_{20}NO$ [M+H]$^+$ requires *m/z* 218.15394 Found 218.15448 (ESI+).

E-5,6-Dimethoxy-2-((1-(S-1-phenylethyl)piperidin-4-yl)methylene)-2,3-dihydro-1H-inden-1-one 410
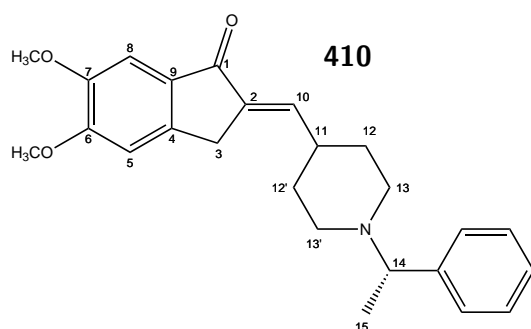
5,6-Dimethoxy-1-indanone (679 mg, 3.53 mmol, 1.0 equiv) was added to a solution of **409** (767 mg, 3.53 mmol, 1.0 equiv) in methanol (18 mL) and the system was put under an atmosphere of nitrogen. The mixture was heated to 80 °C and a sodium methoxide solution (28% in methanol, 740 μl, 4.24 mmol, 1.2 equiv) was added. Stirring under reflux was continued for 75 min, then the reaction was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and purification by column chromatography (100% ethyl acetate → ethyl acetate:methanol 19:1.5) afforded product **410** (926 mg, 67%) as a white foamy solid; $[\alpha]_D^{23}$ -53.5 (c 0.35, CHCl$_3$); mp 76-79 °C; R$_f$ 0.26 (19:1.5 ethyl acetate:methanol); ν_{max} (solid) 1693, 1648, 1605, 1587, 1499, 1453, 1424, 1303, 1253, 1216, 1126, 1075, 984, 802, 762, 731, 701; δ_H (400 MHz, CDCl$_3$) 7.22-7.34 (6H, m, 2 x *meta* Ar-H, 2 x *ipso* Ar-H, *para* Ar-H, H-8), 6.88 (1H, s, H-5), 6.64 (1H, dt, J 9.5 Hz, 1.6 Hz, H-10), 3.96 (3H, s, H$_3$CO-C6), 3.91 (3H, s, H$_3$CO-C7), 3.55 (2H, "d", J 1.4 Hz, H-3), 3.46 (1H, q, J 6.6 Hz, H-14), 3.06-3.10 (1H, m, 1 x HH-13), 2.84-2.89 (1H, m, 1 x HH-13), 2.22-2.32 (1H, m, H-11), 2.02-2.08 (1H, m, 1 x HH-13), 1.93-1.98 (1H, m, 1 x HH-13), 1.50-1.74 (4H, m, 4 x H-12), 1.40 (3H, J 6.8 Hz, H-15); δ_C (100.6 MHz, CDCl$_3$) 192.70 (C1), 155.40 (C6), 149.60 (C7), 144.62 (C9), 143.36 (*ipso* Ar), 139.98 (C10), 135.70 (C4), 131.97 (C2), 128.28 (*meta* Ar), 127.90 (*ortho* Ar), 127.05 (*para* Ar), 107.34 (C5), 105.13 (C8), 65.09 (C14), 56.35 & 56.25 (C6-OCH$_3$ & C7-OCH$_3$), 50.41 & 50.06 (C13 & C13'), 37.53 (C11), 31.49 (C12 & C12'), 29.60 (C3), 19.49 (C15); m/z (ESI+) 392 [M+H]$^+$, 288; Exact Mass Calcd for C$_{25}$H$_{30}$NO$_3$ [M+H]$^+$ requires m/z 392.2220 Found 392.2216 (NSI+); HPLC t_{R1}= 14.1 min, t_{R2} 16.9 min, t_{R3} 31.2 min.

3.2.1 Acetylcholinesterase Inhibition Assay

The inhibitory activity of compounds **380+381**, **382+383**, **384+385**, **386+387**, **401+402**, **389-392** and **394-397** towards AChE (enzyme commission (EC) number 3.1.1.7, type VI-S from *Electrophorus electricus* (electric eel)) was measured using a protocol based on Ellman's reagent.[125] The 96-well plate format of this assay, as described by Mohamed,[218] was further adjusted to result in the following protocol.

The control compound donepezil (Bertin Pharma, Cayman, France) and the test compounds were dissolved in methanol to obtain stock solutions of 10 mM. 12 further dilutions were made of each compound using methanol, resulting in final assay concentrations of 0.001-100 μM. To obtain a 1.5 mM solution, 29.73 mg 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB, Ellman's reagent, Alfa Aesar) were dissolved in 50 mL of 50 mM tris(hydroxymethyl)aminomethane (TRIS)-HCl buffer (pH=8.0) containing 0.1 M NaCl and 0.02 M $MgCl_2 \cdot 6\,H_2O$. A 259 U/mL stock solution of AChE in buffer (50 mM TRIS-HCl, pH=8.0, 0.1% w/v bovine serum albumin (BSA)) was prepared and aliquots of 21 μL were frozen in Eppendorf tubes and stored at -20 °C. Before running the assay, one of these aliquots was diluted with buffer (50 mM TRIS-HCl, pH=8.0, 0.1% w/v BSA) to obtain 25 mL of a solution with an enzyme concentration of 0.22 U/mL. A 15 mM solution of acetylthiocholine iodide (ATCI, Sigma-Aldrich) was prepared by dissolving 108.45 mg in ultrapure water (25 mL). All these solutions were prepared freshly directly before the assay was run.

In 96-well plates, 160 μL of the 1.5 mM DTNB solution were first added, followed by 10 μL of the different concentrations of test compounds. Then the 0.22 U/mL enzyme solution was added (50 μL) and incubated at room temperature for 7 min. The background absorbance was measured at a wavelength of 412 nm on a POLARstar OPTIMA (BMG Labtech) microplate reader. The addition of 30 μL of the 15 mM ATCI solution initiated the enzymatic reaction and the time that passed between the beginning of the pipetting and the first measurement (t=0) was noted and kept consistently at 2 min. Further kinetic measurements were made at different time intervals (t= 1, 2, 3, 4, 5 min) after a short episode of shaking (10 s).

Each experiment was carried out in triplicates. Various control incubations containing 10 μL methanol were run alongside the test compounds on each plate. The IC_{50} values were calculated using GraphPad Prism software (version 6.01) applying a nonlinear regression analysis (sigmoidal dose-response fit with a variable slope).

Chapter 4

Appendix

4.1   HPLC Chromatograms of Biologically Tested Donepezil Analogues

Chromatogram 1: Mixture of 401 and 402

401+402
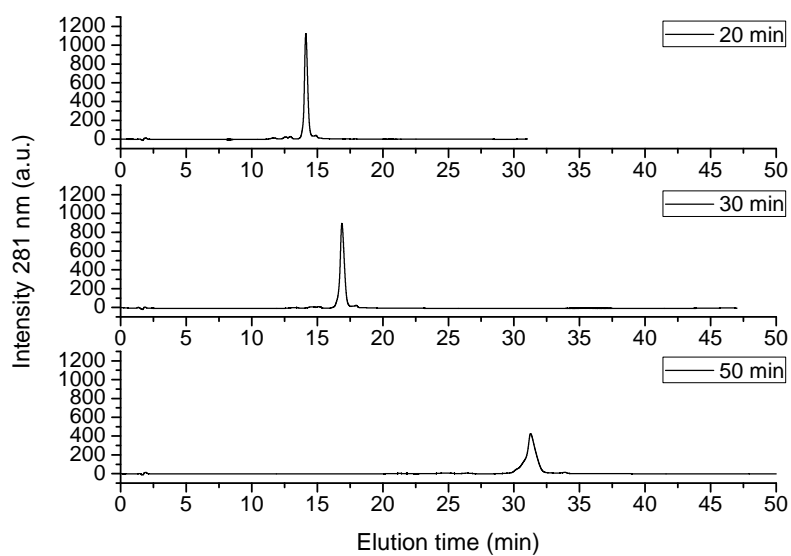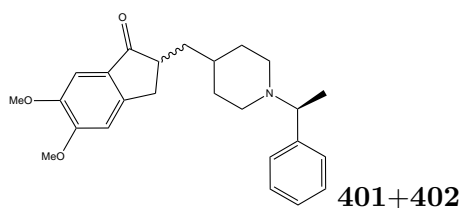
Chromatogram 2: Mixture of 380 and 381

380+381
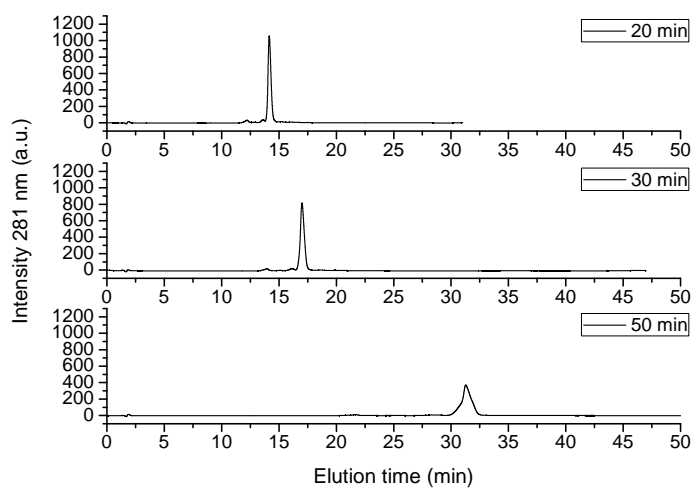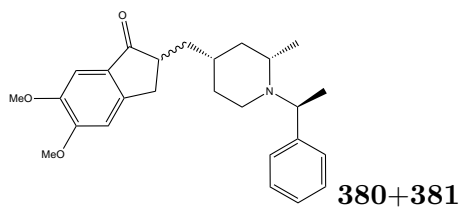
Chromatogram 3: Mixture of 382 and 383

382+383
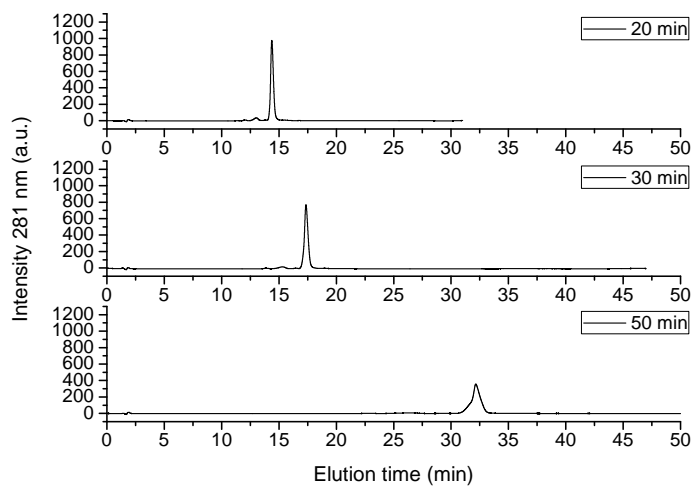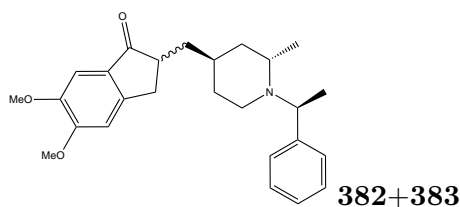
Chromatogram 4: Mixture of 384 and 385

384+385
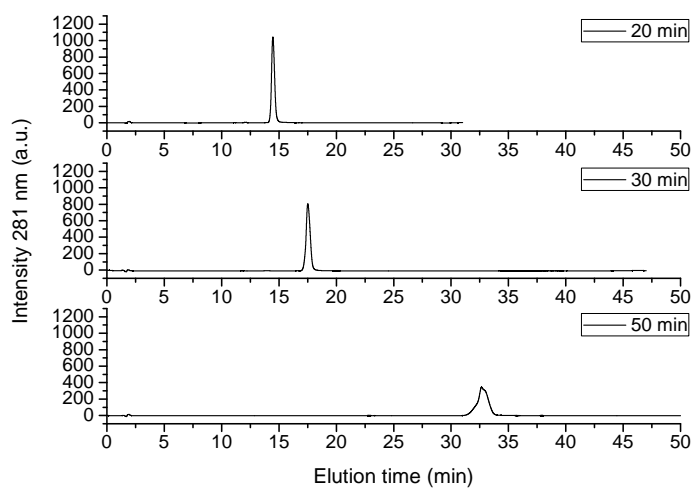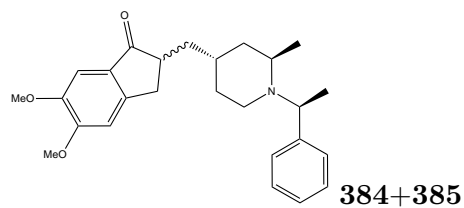
Chromatogram 5: Mixture of 386 and 387

386+387
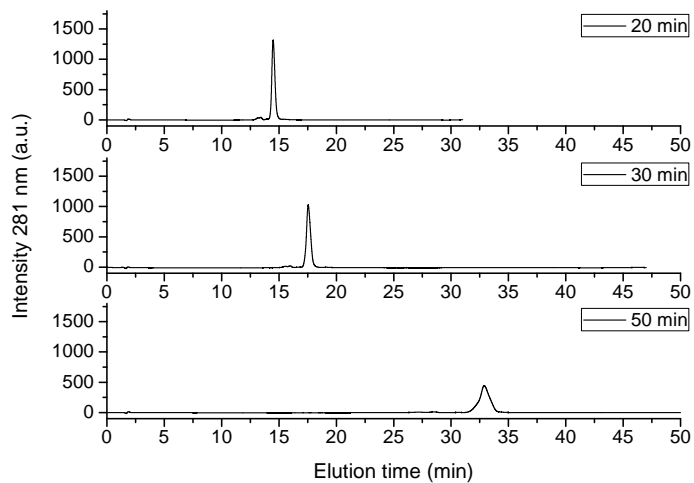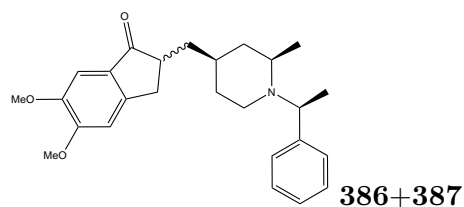
Chromatogram 6: Mixture of 389-392

389+390   **391+392**
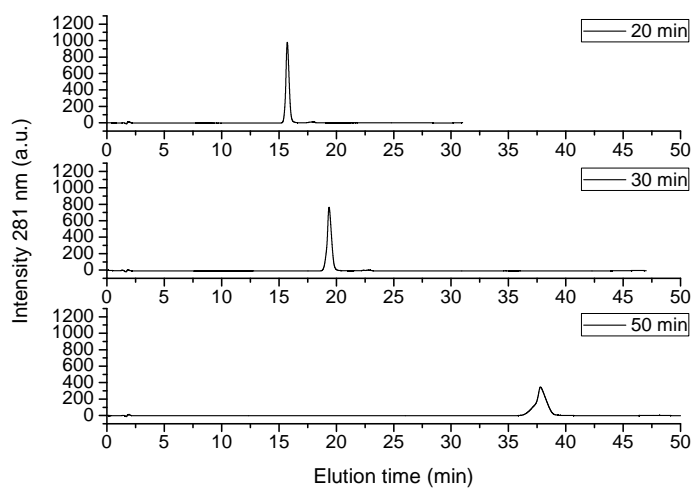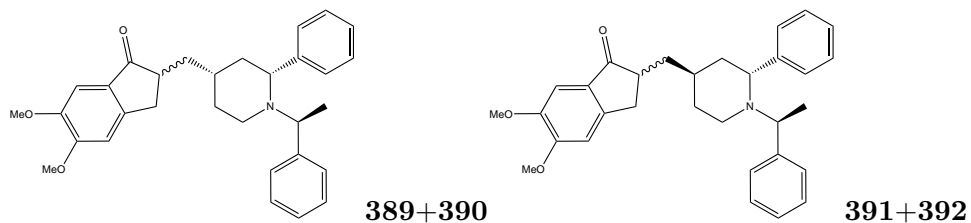
Chromatogram 7: Mixture of 394-397

394+395   **396+397**
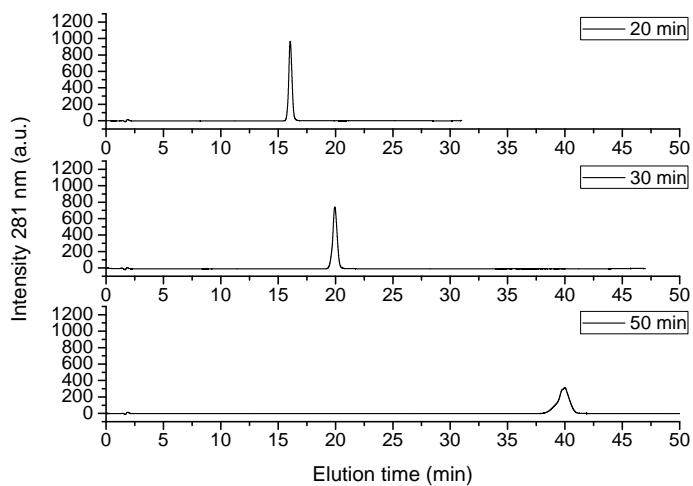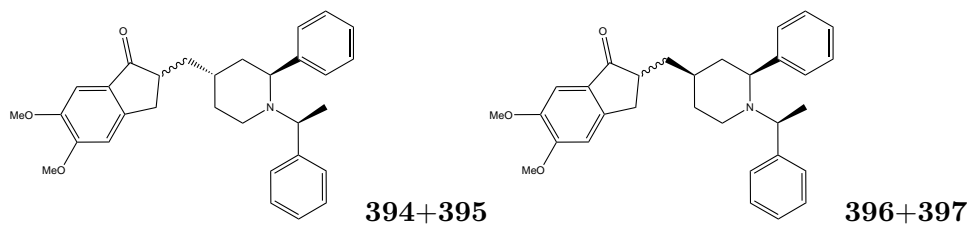
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