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Step-Efficient Asymmetric Approaches to Saturated Nitrogen Heterocycles

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Doctor of Philosophy

September 2012

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Step-Efficient Asymmetric Approaches to Saturated Nitrogen Heterocycles

by Amanda Clare Cutter

An imino-aldol reaction between phenyl chlorovalerate and a variety of (*S*)-*tert* butylsulfinimines was developed which gave consistently high diastereoselectivites of up to 95:5:0:0 dr and yields of up to 87%. In several cases, single crystal X-ray crystallography confirmed the stereochemistry of the major products to be *syn*. Successful isolation of these *syn* imino-aldol products allowed them to be converted to a variety of enantiopure saturated nitrogen heterocycles. Natural products (–)-epilupinine (**(–)-1.71**) and (–)-tashiromine (**(–)-1.72**) were successfully synthesised in enantiopure form in 6 steps from chloroalkanoic acid phenyl esters *via* this highly stereoselective imino-aldol reaction with 19 and 12% overall yield respectively. Absolute stereochemical determination of the minor *anti* imino-aldol product was possible through its use in the synthesis of (+)-lupinine (**(+)-1.70**).

A new synthetic route towards the synthesis of (+)-allomatrine (**(+)-1.121**) was devised and investigated. The key imino-aldol step was not very selective however, as such this approach was abandoned and was not investigated further due to time constraints.

Finally a range of piperidine analogues was synthesised from a variety of imino-aldol products produced using our reaction conditions. These confirmed the stereochemistry of the major diastereomers as being *syn*, demonstrating both the reliability of these reaction conditions, and the effectiveness of using the imino-aldol reaction as the key step in this short route to enantiopure saturated nitrogen heterocycles.

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DECLARATION

I declare that this thesis is of my own composition from work wholly performed by myself while in candidature at this university for the degree of Doctor of Philosophy, except where it is clearly marked otherwise. No part has been submitted for a degree or other qualification.

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Amanda Clare Cutter
September 2012

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All X-ray crystallography data included in this thesis was collected and processed by Mark Light, thank you.

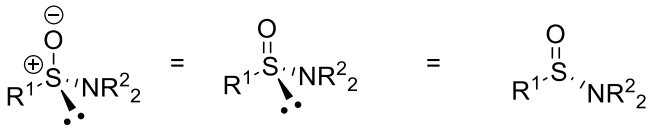
There were many times when the kind words and support of my dear friends Ben and Jon helped me through this long process. Thank you. Ben, thank you also for your patient proof reading efforts and trying to teach me spelling and grammar!

Finally, I would like to thank the School of Chemistry at the University of Southampton, Prosidion(OSI) and the EPSRC for funding.

ABBREVIATIONS & DEFINITIONS

→	to
Ac	Acetyl
Aq	Aqueous
Ar	Aryl
Atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyl carbonate
Bt	1,2,3-Benzotriazol-1-yl
Bu	Butyl
BuLi	Normal butyl lithium (*n*BuLi)
CAN	Ceric ammonium nitrate
cat	Catalyst
Cp	Cyclopentadienyl ring
CPME	Cyclopentylmethyl ether
DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DIBAL-H	Diisobutyl aluminium hydride
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E+	Electrophile
ee	Enantiomeric excess
EI	Electron impact ionisation
equiv	Equivalents
ESI-	Electrospray ionisation (negative ion)
ESI+	Electrospray ionisation (positive ion)
Et	Ethyl
GC	Gas chromatography
H	Hour
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
HRMS	High resonance mass spectroscopy
IR	Infrared spectroscopy
LD50	The median lethal dose of a substance, or the amount required to kill 50% of a given test population
LDA	Lithium di*iso*propylamide
LRMS	Low resonance mass spectroscopy
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
min	minute
MP	Melting point
MS	Molecular sieves
Ms	Mesyl
MTPA	α-Methoxy-α-(trifluoromethyl)phenylacetic acid
NMR	Nuclear magnetic resonance spectroscopy
p	para
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*p*-Methoxybenzyl ether

PMP	*p*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluene sulfonate
Pr	Propyl
quant.	Quantitative
RCM	Ring closing metathesis
rt	Room temperature
sat.	Saturated
SCX	Strong cation exchange
SMP	(S)-2-Methoxymethylpyrrolidine
SPE	Solid phase extraction
t	tert
TBS	*tert*-Butyl dimethyl silyl
TBSA	*tert*-Butylsulfinamide
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TMS	Trimethylsilyl
Ts	*para*-Toluene sulfonyl
w/w	Weight for weight
xs	Excess
Δ	Reflux



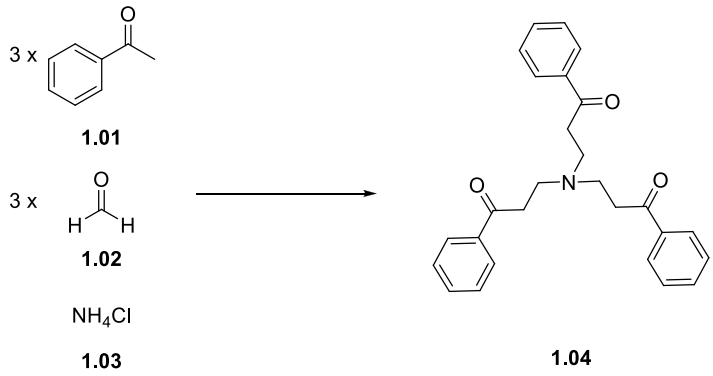
For clarity, sulfur oxygen bond will be represented as a double bond and the lone pair of electrons on the sulfur atom of sulfinamines and related compounds will not be included in figures and schemes.

1. Introduction

1.1. Mannich reaction

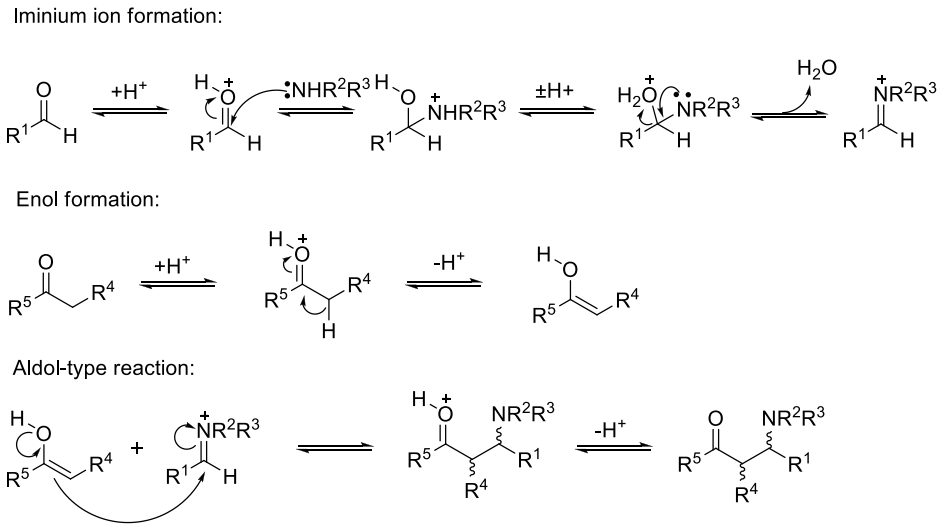
1.1.1. Background

The first reported “Mannich” reaction was carried out by Tollens and von Marle,[1] when they reacted acetophenone **1.01** with formaldehyde **1.02** and ammonium chloride **1.03** to form tertiary amine **1.04** (**Scheme 1.1.1**).



Scheme 1.1.1: First reported Mannich reaction

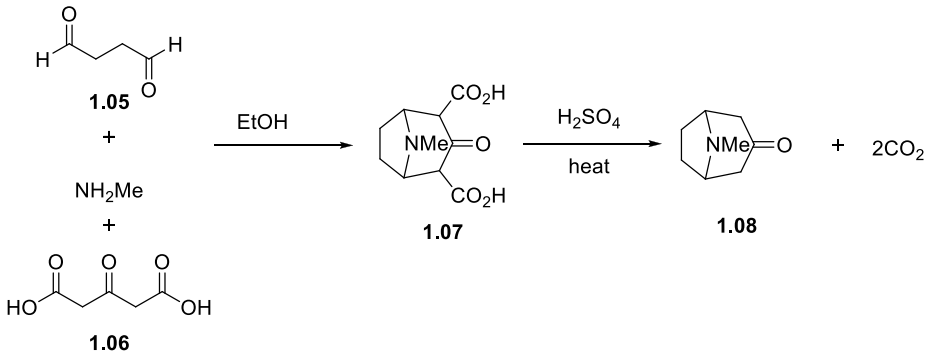
The generality of the reaction was later realised by Carl Mannich in 1917.[2] The reaction, which subsequently became known as the Mannich reaction, is a 3 component condensation of an aldehyde, ammonia (or amine) and a carbonyl with an α-proton. It is related to the aldol condensation and is sometimes performed with a preformed imine and in these cases often referred to as an imino-aldol reaction (although some flexibility between the two terms is applied in the literature). The main focus of the research described in this thesis is reactions involving a preformed imine, and these will be referred to as imino-aldol reactions, for clarity.



Scheme 1.1.2: Proposed mechanism for the acid catalysed Mannich reaction

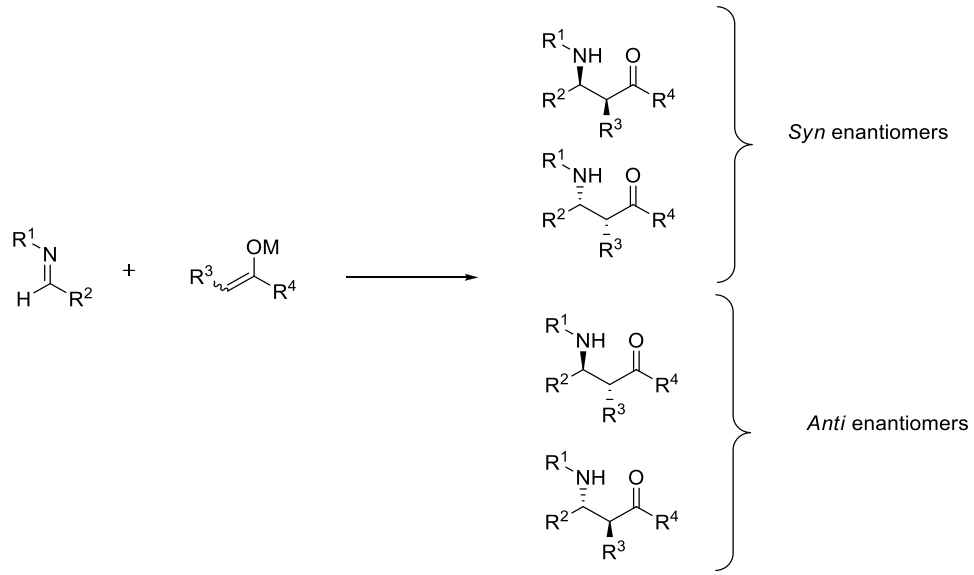
The Mannich reaction can occur under both basic and acidic conditions, although more commonly acidic conditions are employed. The Mannich reaction occurs in three stages (**Scheme 1.1.2**). The first stage is the condensation of the amine (or ammonia) onto the electrophilic aldehyde with the loss of water resulting in the formation of the iminium ion. Separately, the enolisable carbonyl forms the enol, which is then ready for the final stage: the aldol-type attack onto the iminium ion and then the loss of a proton gives the Mannich base.

An early classic example of the Mannich reaction being put to use is in Robinson's synthesis of the alkaloid tropinone (**1.08**) published in 1917.[3] Although synthesised previously by Willstatter,[4] Robinson's biomimetic approach significantly shortened the synthesis and the overall yield of the reaction. Robinson's synthesis used succinaldehyde (**1.05**), methylamine and acetonedicarboxylic acid (**1.06**) (or acetone, which gave a lower yield). It employed a double Mannich reaction to cyclise and to form the bicyclic alkaloid **1.07** in one step. Subsequent double decarboxylation yielded tropinone (**1.08**) (**Scheme 1.1.3**).



Scheme 1.1.3: Robinson's tropinone synthesis

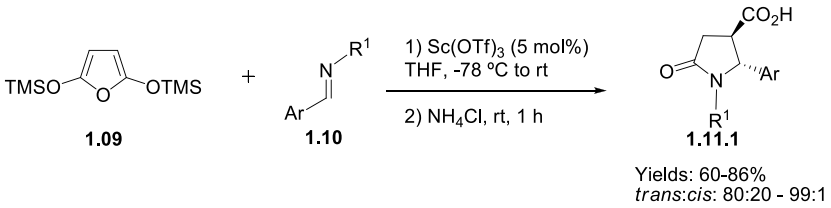
More recently, research involving Mannich type reactions has focused on gaining the desired products stereoselectively. As with the classic aldol reaction, up to two new chiral centres may be created in the resulting products, giving two *syn* products and two *anti* products (**Scheme 1.1.4**).



Scheme 1.1.4: Imino-aldol reaction and the resultant products

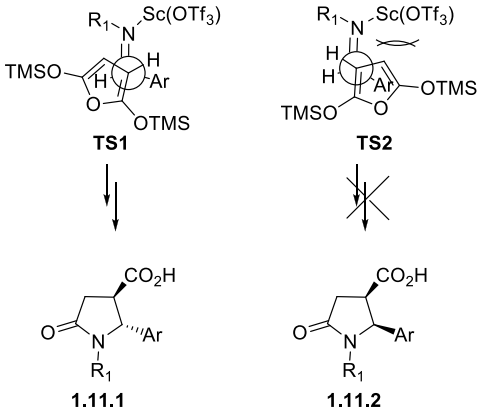
1.1.2. Stereocontrol in imino-aldol reactions

Various approaches have been taken to direct the selectivity of the Mannich and imino-aldol reactions.[5,6,7] A Mukaiyama-aldol type reaction has been used to give diastereoselectivities of up to 99:1 dr in the synthesis of γ-lactams (**Scheme 1.1.5**).[8]



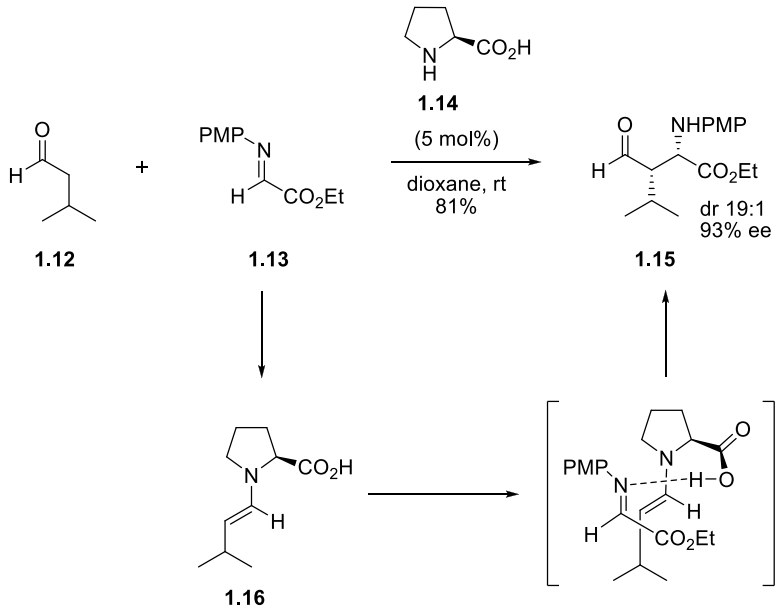
Scheme 1.1.5: Example of Mukaiyama reaction [8]

The selectivity is thought to arise from steric interactions in the transition state between the coordinating scandium(III) triflate and the cyclic anhydride with a preference for TS1 over TS2 (**Scheme 1.1.6**). After acidic deprotection, the new amine functionality opens the lactone to allow formation of the γ-lactam products **1.11.1**.



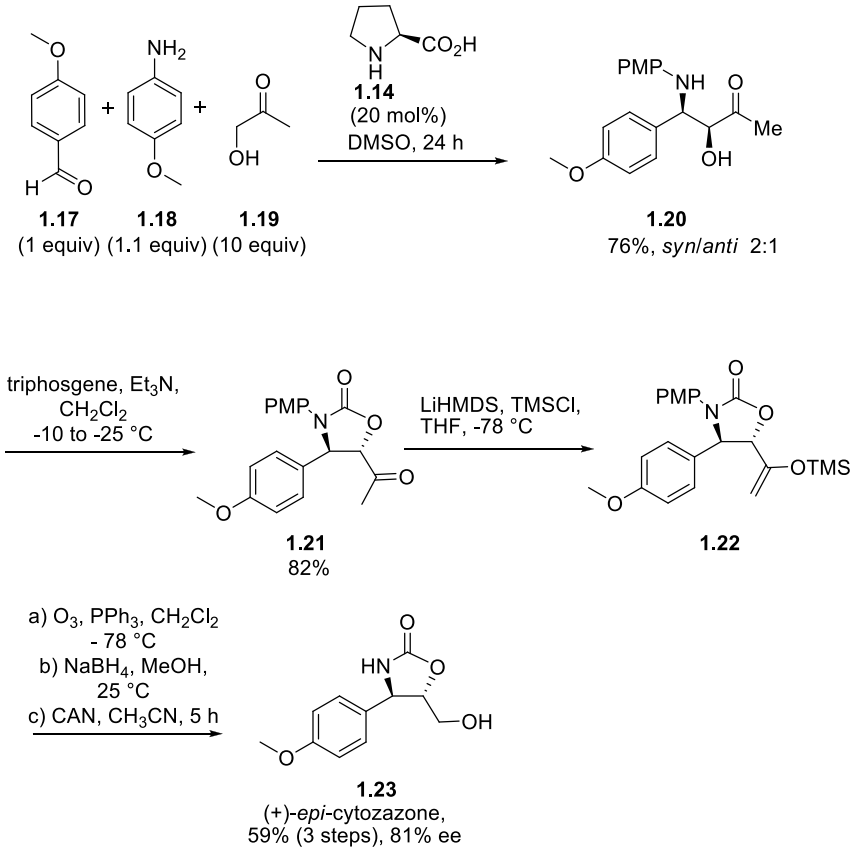
Scheme 1.1.6: Transition states for Mukaiyama reaction[8]

The area of organocatalysis has been expanded greatly in the last decade or so, especially with the greater emphasis on green, metal-free chemistry.[9] Organocatalysis has been successfully applied to the Mannich and imino-aldol reactions. Initial work using L-proline (**1.14**) as a catalyst formed the *syn* diastereomers exclusively.[10] Reaction of L-proline (**1.14**) with unmodified aldehydes (**1.12**) forms the enamine in its *anti* conformation (**1.16**), due to steric hindrance with the carboxylic group (**Scheme 1.1.7**). Hydrogen bonding with the lone pair of electrons on the imine to the carboxylic proton is then thought to influence the transition state to give the *syn* product **1.15**.



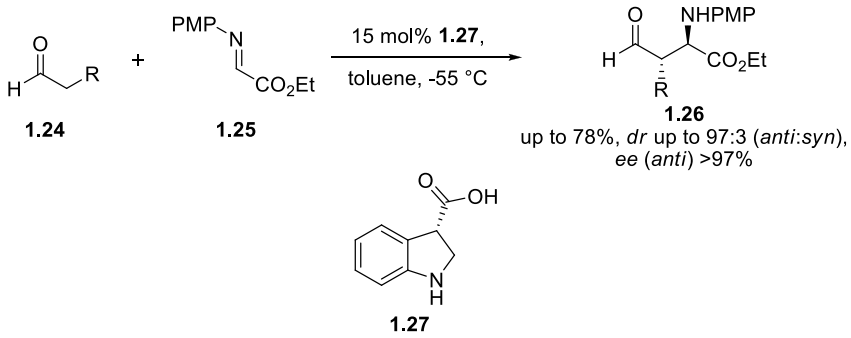
Scheme 1.1.7: Organocatalysis of the imino-aldol reaction

This approach has been successfully applied to the total synthesis of (+)-*epi*-cytoxazone which was synthesised in 6 steps from *p*-anisaldehyde *via* an L-proline catalysed Mannich reaction (**Scheme 1.1.8**).[11] *p*-Methoxybenzaldehyde (**1.17**) was condensed with *p*-methoxyaniline (**1.18**) and hydroxyacetone (**1.19**) in the presence of 20 mol% of L-proline (**1.14**) in DMSO to form the imino-aldol product **1.20** with a *syn*/*anti* ratio of 2:1. The major diastereomer was isolated by column chromatography and then reacted with triphosgene to form oxazolidinone **1.21** in 82% yield. The silyl enol ether **1.22** was formed and then subjected to *in situ* ozonolysis followed by a reductive work up and PMP deprotection to yield (+)-*epi*-cytoxazone (**1.23**) in 59% yield and 81% ee.



Scheme 1.1.8: Example of a Mannich reaction used in the total synthesis of (+)-epi-cytozazone.[11]

Anti imino-aldol products can be obtained by using alternative organocatalysts. Usually modified proline catalysts are employed.[12] These proline analogues can be tricky to synthesise. However, work carried out by Pietruszuka[13] and Simon applied an enzymatically synthesised catalyst to form *anti* imino-aldol products. They reacted *N*-PMP-protected α-imino ethyl glyoxylate (**1.25**) with a series of alkyl aldehydes (**1.24**) to form the *anti* imino-aldol products **1.26** in yields up to 78% with dr of up to 97:3 (*anti*:*syn*) and ee (*anti*) of >97%. Selectivity was achieved by using (*S*)-indoline-3-carboxylic acid **1.27** as a chiral organocatalyst (**Scheme 1.1.9**).

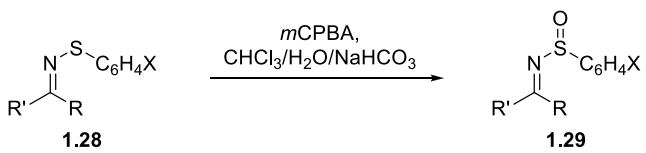


Scheme 1.1.9: Example of imino-aldol reaction using organocatalysis to impart stereoselectivity[13]

This type of catalysis could be thought of as using an *in situ* formed chiral aldehyde derivative as the nucleophile. Organocatalysis works by activating unmodified aldehydes and improving their nucleophilicity. A wide range of aldehydes can therefore be employed. The choice of imine, however, is limited, with only those that have been activated towards electrophilic attack by the inclusion of electron withdrawing groups, being suitable for organocatalysis.

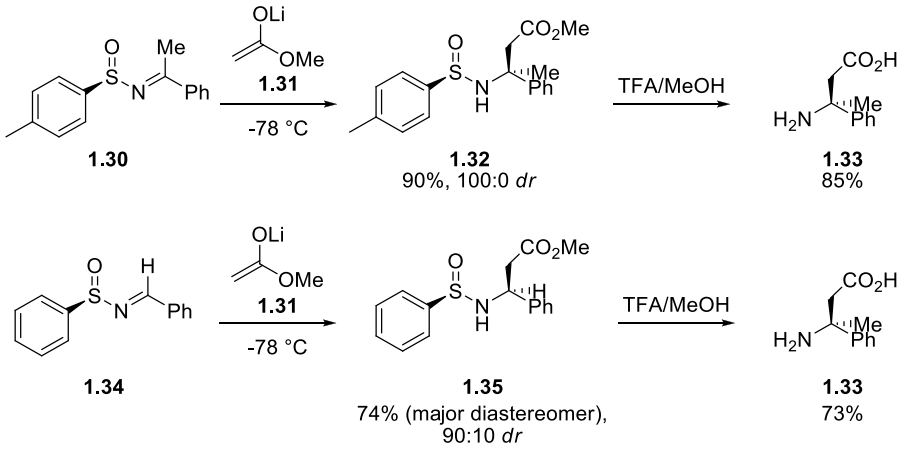
1.1.2.1. Sulfinimines

Another way to activate imines and to induce stereocontrol, which has been developed and widely used since the mid-late 1990s, is the application of non-racemic *N*-sulfinimines.[14] These can act as *N*-protecting groups as well as activating the C=N bond towards 1,2-addition. In addition, the chirality of the sulfinyl group can be used to induce stereocontrol in many processes. Extensive work into the use of sulfinyl groups was carried out by F.A. Davis, who, in 1974, achieved his first synthesis of racemic sulfinimines by the *m*CPBA oxidation of the sulfenimines (**Scheme 1.1.10**).[15] Later syntheses of enantiomerically pure sulfinimines allowed their exploitation as chiral directing groups.



Scheme 1.1.10: Davis's oxidation of sulfenimine to furnish sulfinimide[15]

One way in which Davis exemplified the utility of the enantiomerically pure sulfinimines was by the addition of enolates to synthesise β-amino acids.[16] The lithium enolate of methyl acetate was reacted with sulfinimines **1.30** and **1.34** to yield sulfinamides **1.32** and **1.35** in 90 and 74% yields respectively (**Scheme 1.1.11**). Where the *p*-tolyl sulfinyl auxiliary was applied, complete facial selectivity was achieved, while use of the phenyl sulfinyl auxiliary provided a slight drop in stereocontrol with 90:10 dr.



Scheme 1.1.11: Enolate addition to sulfinimines.[16]

While Davis's work has focused on variously substituted phenyl groups on sulfur, with his *p*-tolyl sulfinimine being the most successful, other groups have used a variety of different *S*-substitutions (**Figure 1.1**). These have included including *t*-butyl sulfinimines popularised by Ellman (A),[17] as well as sulfinimines used for more targeted applications including those reported by Wills (B),[18] Kawecki (C),[19] and Senaryak (D and E).[20]

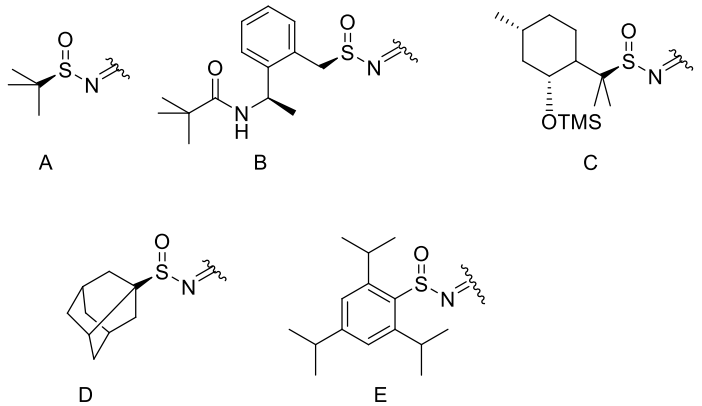
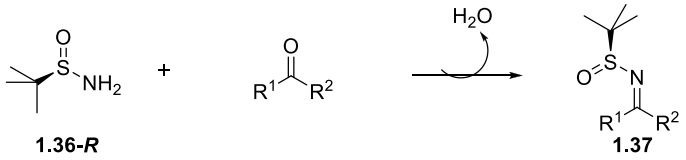


Figure 1.1: Examples of sulfinimines.

1.1.2.1.1. tert-Butyl Sulfinimines

tert-Butyl sulfinimines were first synthesised in enantiopure form by Ruano *et al*. to be used in asymmetric aziridination reactions.[21] Later extensive work by Ellman greatly expanded the interest in this sulfinyl auxiliary, largely thanks to new simplified synthetic routes to both enantiomers of *tert*-butyl sulfinamide (**1.36**, TBSA), both of which are now commercially available.[22-24] Ellman and his collaborators have exploited non-racemic TBSA to form a variety of asymmetric sulfinimines **1.37** by simple condensation with aldehydes and ketones (**Scheme 1.1.12**).[25]



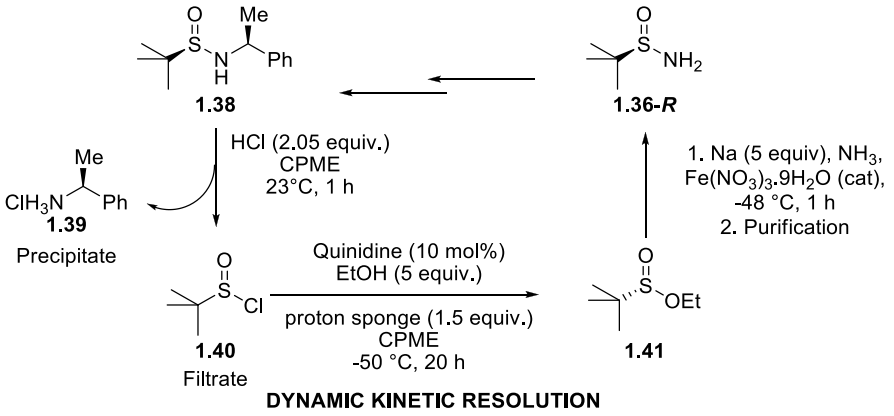
1.36-*R* **1.37**

Scheme 1.1.12: Condensation of TBSA with ketone to form *tert*-butyl sulfinimine

In part, the versatility of this chiral group is derived from the ease of cleavage by acid, whilst it is stable to base, making it a Boc equivalent protecting group. Another advantage of *tert*-butyl sulfinyl aldimines is that they have been shown to consistently adopt an *E* configuration, mainly enforced by the large steric hindrance between the *tert*-butyl group and the R group. Two recent reviews by Ellman[26] and Chelma[27] highlight the synthesis and some of the applications of TBSA published in the literature.

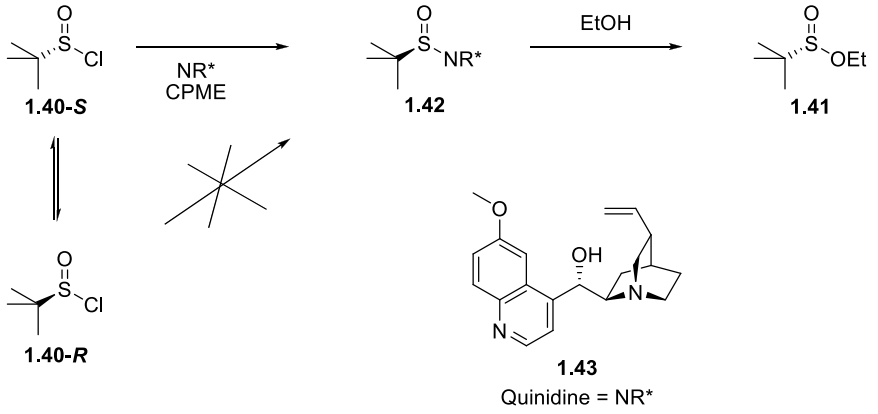
A recent advance in the use of *tert*-butyl sulfinimines is the development of methodology allowing the recycling of the TBSA in up to 65% yield with 99% ee (**Scheme 1.1.13**).[28] This was achieved by using dynamic kinetic resolution. Ellman and Wakayama deprotected sulfinamide **1.38** with HCl in aprotic cyclopentylmethyl ether (CPME) which afforded the hydrochloric salt of the amine (**1.39**) as a precipitate whilst the racemic sulfinyl chloride **1.40** remained in solution. The isolated sulfinyl chloride was then subjected to dynamic catalytic resolution to eventually form the *S*-ethanolic ester **1.41**. This was then

converted to the sulfinamide **1.36** using sodium in ammonia *via* another S_N2 reaction, thus restoring the original *R* configuration.



Scheme 1.1.13: Use of dynamic kinetic resolution to recycle TBSA

Dynamic catalytic resolution is possible when the starting material can racemise under the reaction conditions. Thus, as the desired enantiomer is removed from the system by an irreversible reaction, this drives the equilibrium of racemisation further towards the desired enantiomer. This leads to the possibility of full conversion as opposed to a maximum 50% conversion with conventional resolution (**Scheme 1.1.14**).

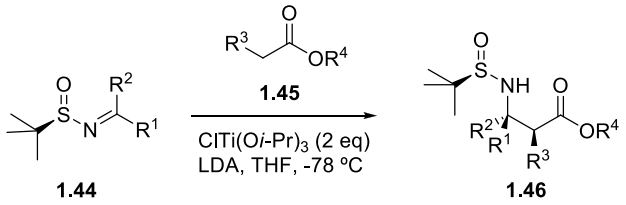


Scheme 1.1.14: Dynamic kinetic resolution

In this example, one of the sulfinyl chloride enantiomers (**1.40-*S***) reacts selectively with the chiral amine quinolidine **1.43**, which then acts as a leaving group and activates the sulfinyl towards attack by ethanol to form the ethanolic

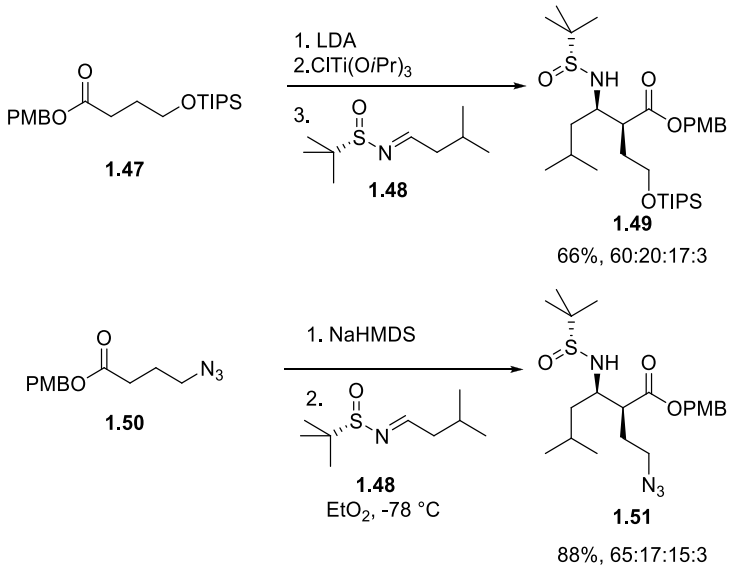
ester **1.41**. Thus, *via* 3 successive S_N2 reactions, the desired *R*-enantiomer of the sulfinamide can be obtained and the sulfinyl group recycled.

One application of the *tert*-butyl sulfinimines that Ellman has focused on has been towards developing a stereoselective imino-aldol reaction.[23,29-31] Using this chiral directing group together with titanium enolates, imino-aldol products **1.46** were formed in yields of 65% to 96%, together with high diastereoselectivities (up to 96:4) (**Scheme 1.1.15**).



Scheme 1.1.15: Ellman's imino-aldol system[32]

The scope of the ester enolates (**1.45**) employed was limited to examples where R^3 was either a methyl group or a benzyl derivative. When longer chain lengths were introduced, together with further functionality (azide, **1.50**, and TIPS protected alcohol, **1.47**), modified reaction conditions were required and the selectivities were reduced (**Scheme 1.1.16**).[29]



Scheme 1.1.16: Imino-aldol reactions of esters containing functionalised chains[29]

A large area for the application of sulfinamides specifically and Mannich type reactions in general is in the synthesis of saturated nitrogen heterocycles, which will be discussed in the following section.

1.1.3. Synthesis of Saturated Nitrogen Heterocycles

Saturated nitrogen heterocycles are widely found in nature and both natural and synthetic molecules are of great interest to the pharmaceutical and agrichemical industries, as they are often key components of active compounds. This is particularly true of compounds that contain piperidine and pyrrolidine rings, of which biologically active examples abound (**Figure 1.2**).[33]

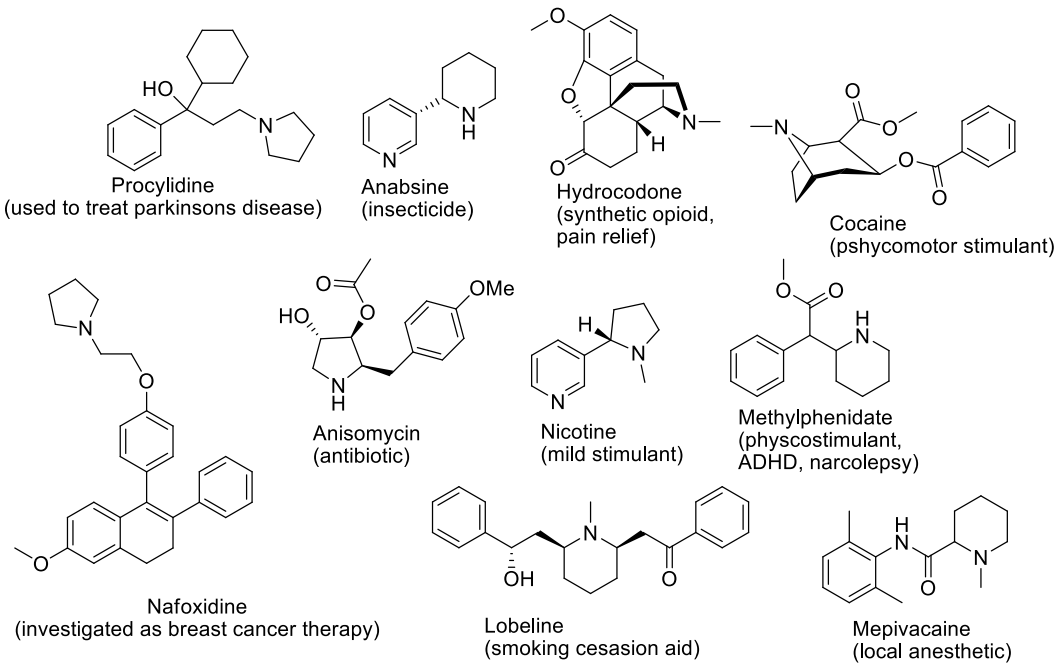
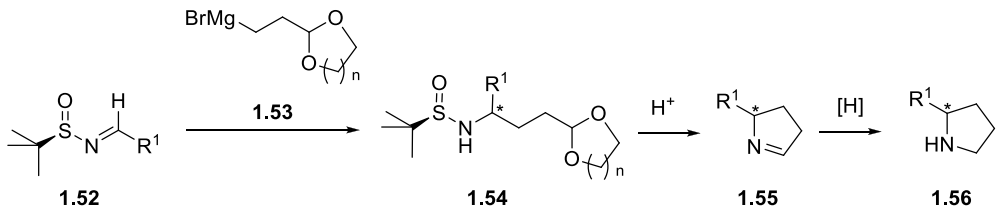


Figure 1.2: Examples of bioactive piperidine and pyrrolidine containing compounds.

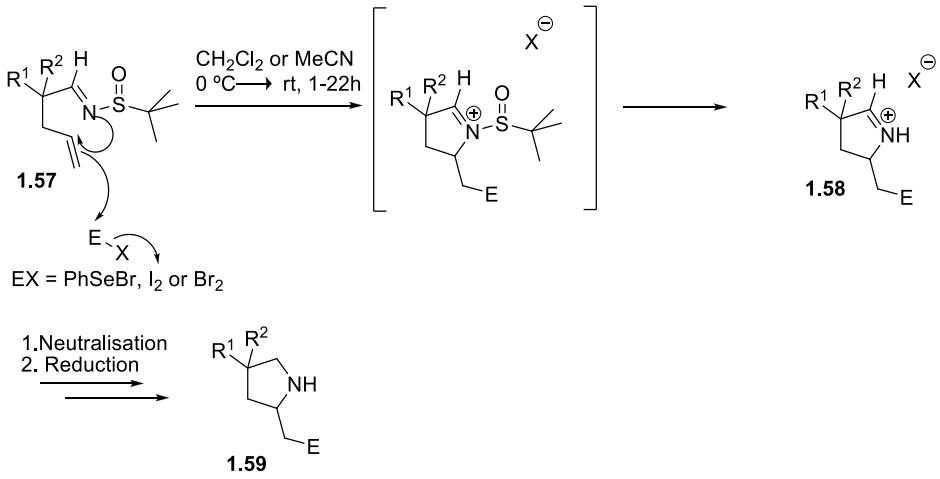
Specific examples where *tert*-butyl sulfinimines are key in the synthesis of saturated nitrogen heterocycles include Ellman and Brinner's synthesis of 2-substituted pyrrolidines (**Scheme 1.1.17**).[34] This is achieved *via* a 1,2-nucleophilic attack of an acetal functionalised Grignard reagent **1.53** onto the *tert*-butyl sulfinimine **1.52**. The resulting sulfinamides **1.54** were formed in 86 - 100% yield with a dr of up to 9:1. Deprotection of both the acetal and

sulfinamide was carried out in a 95:5 mixture of TFA:H_2O. After 30 minutes of stirring, Et_3SiH was added to the reaction mixture to complete the final reduction, yielding the desired 2-substituted pyrrolidine **1.56** in up to 92% yield and 99% ee.



Scheme 1.1.17: General synthesis of 2-substituted pyrrolidines[34]

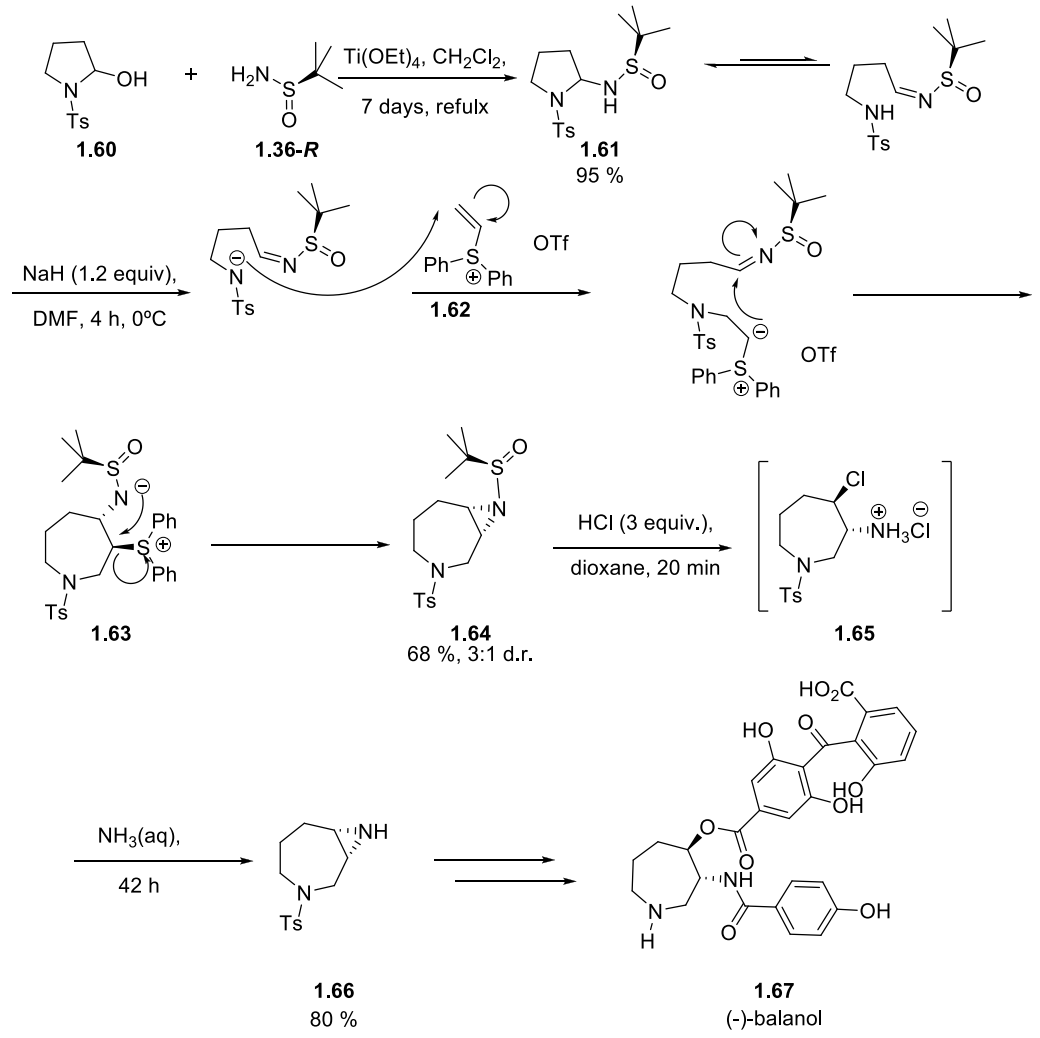
De Kimpe and Dondas used *tert*-butyl sulfinimines to form substituted pyrrolidines (**Scheme 1.1.18**).[35] They took unsaturated sulfinimines **1.57** and slowly warmed them from 0 ºC to room temperature in the presence of phenylselenium bromide, iodine or bromine, which then induced cyclisation in a 5-endo-trig fashion. These formed the iminium salts which were deprotected in the same step by further stirring at room temperature to form **1.58**. Subsequent neutralisation and reduction afforded a variety of pyrrolidines **1.59** in 44 - 87% overall yield from the unsaturated aldehydes. Efforts towards developing a chiral cyclisation resulted in 20% ee at best and therefore were not pursued.



Scheme 1.1.18: Electrophile induced cyclisation to synthesise pyrrolidines[35]

Aggarwal *et al.*[36] completed the formal synthesis of (–)-balanol (**1.67**) by forming the key aziridine precursor **1.63** (**Scheme 1.1.19**). The *tert*-butyl sulfinimine

protected aminal **1.61** was formed by condensation of hemiaminal **1.60** with *tert*-butyl sulfinamide (**1.36**) in 95%. This exists in both the ring closed aminal and the open form. This was then reacted with diphenylsulfonium salt **1.62** and cyclised onto the sulfinimine before forming the azide by elimination of diphenyl sulfide. This yielded the protected aziridine, **1.64**, in 68% yield with a dr of 3:1. The two diastereomers were separated by column chromatography and the stereochemistry of the major diastereomer was deduced after X-ray analysis of the minor diastereomer. The major diastereomer was deprotected in acid to form the intermediate salt **1.65**. After treatment with aqueous ammonia, ring closure formed the unprotected aziridine **1.66** in 80% over 2 steps. This completed the formal synthesis of (–)-balanol (**1.67**).



Scheme 1.1.19: Formal synthesis of (–)-balanol[36]

1.2. Lupin Alkaloids

The lupin alkaloids are a family of saturated nitrogen heterocycles that have long been of interest to synthetic chemists wanting to find efficient routes to synthesise them. These bitter tasting compounds are mildly toxic which helps plants to avoid being eaten by herbivores, as well as providing a bactericidal effect.[37] The basic core of lupin alkaloids consists of a quinolizidine. Below is a selection of members of the lupin family (**Figure 1.3**).

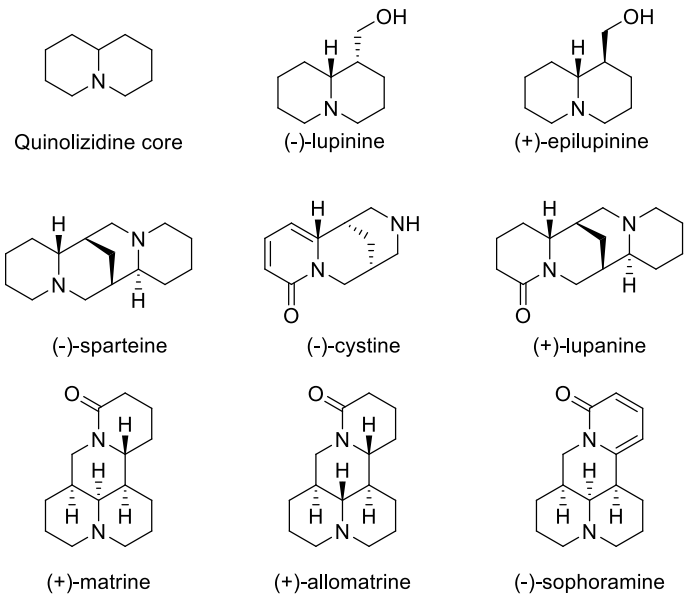
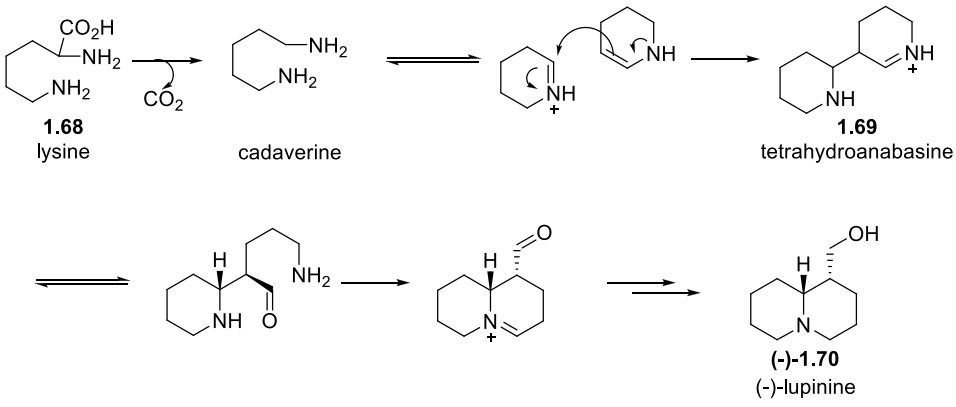


Figure 1.3: Various lupin alkaloids

These alkaloids are formed biosynthetically from L-lysine (**1.68**) *via* tetrahydroanabasine (**1.69**) (**Scheme 1.2.1**).[38]



Scheme 1.2.1: Biosynthetic origins of the lupin family of alkaloids

The following two sections will focus on the background and synthesis of 3 alkaloids of relevance to the research described in this thesis: epilupinine (**1.71**) and its homologue tashiromine (**1.72**), followed by allomatrine (**1.121**).

1.2.1. Epilupinine and Tashiromine

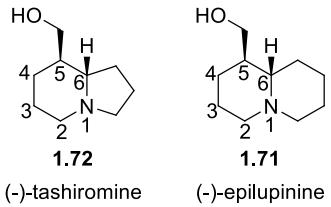


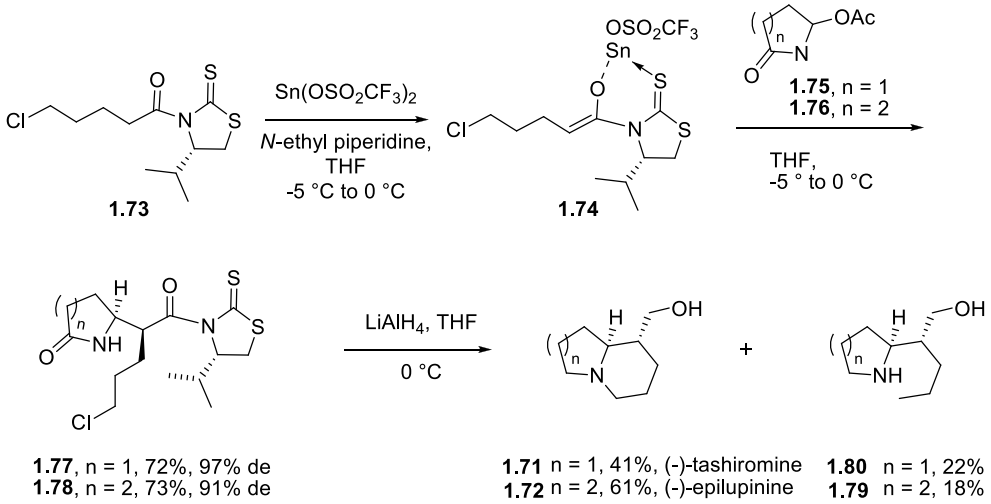
Figure 1.4: Natural products tashiromine and epilupinine

Epilupinine (**1.71**) and tashiromine (**1.72**) are two alkaloids with common stereochemistry at the C-5 and C-6 centres (**Figure 1.4**). The indolizidine tashiromine (**1.72**) was first isolated in 1990 from *Maackia tashiroi* collected in Kumamoto, Japan.[39] *Maackia tashiroi* is a deciduous shrub which grows widely in subtropical Asia. Before its isolation from nature it had been synthesised separately by Nagao[40] and Beckwith.[41] Epilupinine (**1.72**) (also known as *iso*lupinine in older references due to its first synthesis by isomerisation of the already known lupinine, **1.70**)[42] was first isolated from *Lupinus consetinii* seeds and leaves in 1951 in its (+)-form[43] (*Lupinus consetinii* has also been known as *L. pilosus*, *L. varius* and *L. digitatus*).[44] Lupinine (**1.70**) and epilupinine (**1.71**) are members of the lupin family of alkaloids. Although *Lupinus consetinii* is of Mediterranean origin, the samples used in the first isolations were from plants naturalised along the south western coastal plains of Australia.[45] The absolute configuration of (–)-lupinine (**(–)-1.70**) (and as such also that of (+)-epilupinine, **(+)-1.71**) was later determined by Cookson.[46] Efforts towards the synthesis of lupinine (**1.70**) (and its epimer) can be dated back to at least 1931.[47] (+)-Epilupinine (**(+)-1.71**) has been shown to exhibit *in vitro* inhibition against Leukaemia P-388 (LD_{50} = 25 mg/mL) and lymphocytic Leukaemia L1210 (LD_{50} = 28 mg/mL) cells.[48]

1.2.1.1. Asymmetric Syntheses of Epilupinine and Tashiromine

Since the initial syntheses of epilupinine (**1.71**) and tashiromine (**1.72**), there have been numerous routes published in the literature. The popularity of these alkaloids as targets arises from their relatively simple structure and their usefulness in helping to demonstrate new methodology or to determine the stereochemical outcome of new reactions. The number of asymmetric syntheses has grown, with 7 different approaches to one or other enantiomer of epilupinine (**1.71**)[40,48-53] and 7 approaches to the tashiromine (**1.72**) enantiomers[40,54-59] being published. Interestingly, only 4 of these 13 differing routes (Nagao's route was applied to both alkaloids) involve the insertion of both stereocentres in one step. As many of these routes have been previously reviewed,[60] here we will review those where the adjacent stereocentres are introduced in one step along with more recent additions to the asymmetric syntheses of these alkaloids.

The first asymmetric synthesis of either alkaloid was achieved by Nagao in 1988.[40] (This was 2 years before tashiromine (**1.72**) was first isolated from *Maackia tashiroi* and gained its common name.)[39]

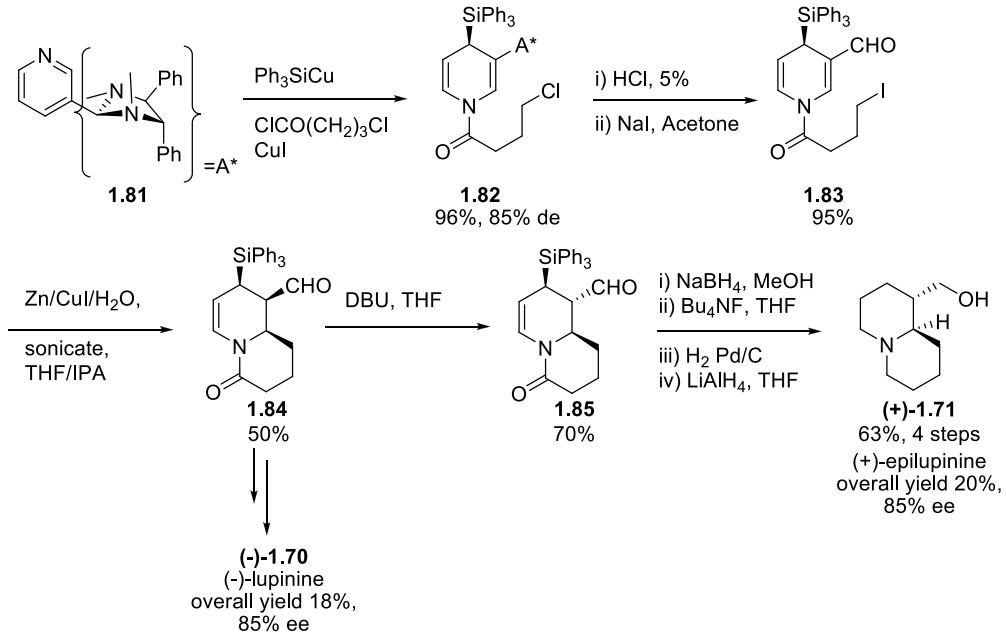


Scheme 1.2.2: Nagao's route to (–)-epilupinine and (–)-tashiromine[40,61]

Nagao's approach involved the use of both enantiomers of chiral auxiliary isopropyl-1,3-thiazolidine-2-thione. This was *N*-acylated to give **1.73** and then

the tin enolates, **1.74**, were formed to be reacted with either 5-acetoxy-2-pyrrolidinone (**1.75)** or 6-acetoxy-2-piperidine (**1.76)** (or α,β-unsaturated aldehydes). The influence of the chiral auxiliary, working together with the chelating tin Lewis acid, afforded the 2 adjacent stereocentres in 91 - 98% de and 57 - 92% yield for various enolates, and both 5 and 6 membered rings (**1.77** and **1.78**). The major alkylation products were isolated by column chromatography and then final reduction of the amide and reductive annulation steps were both neatly achieved by employing $LiAlH_4$, affording the desired products (–)-tashiromine (**(–)-1.72**) in 41%, (–)-epilupinine (**(–)-1.72**) in 61% and (+)-epilupinine in 59%. Also isolated were the over reduced by-products **1.79** and **1.80** in yields of 18 - 22%.

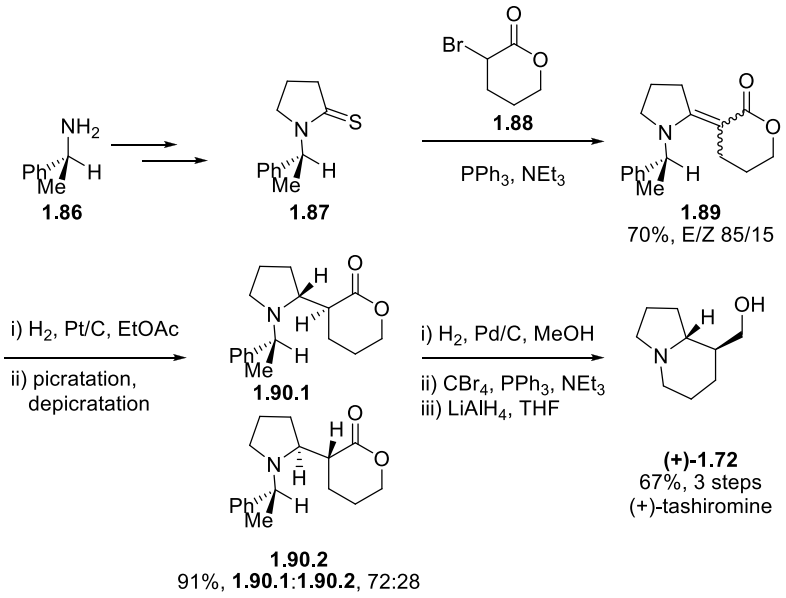
Mangeney *et al.* published a synthesis of (+)-epilupinine (**(+)-1.71**) and (–)-lupinine (**(–)-1.70**), where the two stereocentres are inserted with reasonable stereocontrol (85% de), directed by a chiral silyl group, chosen for its lability (**Scheme 1.2.3**). The authors assert that the cyclisation is *via* a radical pathway, however a substitution reaction would seem to be the more obvious explanation.



Scheme 1.2.3: Total synthesis of (+)-epilupinine and (–)-lupinine by Mangeney[50]

Cyclisation precursor **1.82** was prepared from chiral aminal **1.81**, chlorobutanoyl chloride and Ph_3SiCu with CuI in THF. The chloro-aminal derivative was then transformed into the iodo-aldehyde derivative **1.83** in two steps. First the aminal was hydrolysed in HCl and then refluxed with NaI in acetone to yield **1.83**. This was sonicated with a mixture of Zn metal and CuI in a water/*iso*propanol/THF mix to effect the cyclisation. This selectively gave the *cis* diastereomer **1.84** as the sole product in 50% (which itself was taken through to give (–)-lupinine, **(–)-1.70**). Bicycle **1.84** was epimerised under basic conditions to **1.85**, followed by cleavage of the silyl group. Subsequent hydrogenation and reduction gave (+)-epilupinine, **(+)-1.71**, in 20% yield from **1.81** and an ee of 85%.

Lhommet *et al.* have synthesised (+)-tashiromine (**(+)-1.72**) twice, using variations on the same route (**Scheme 1.2.4**).[56,62]

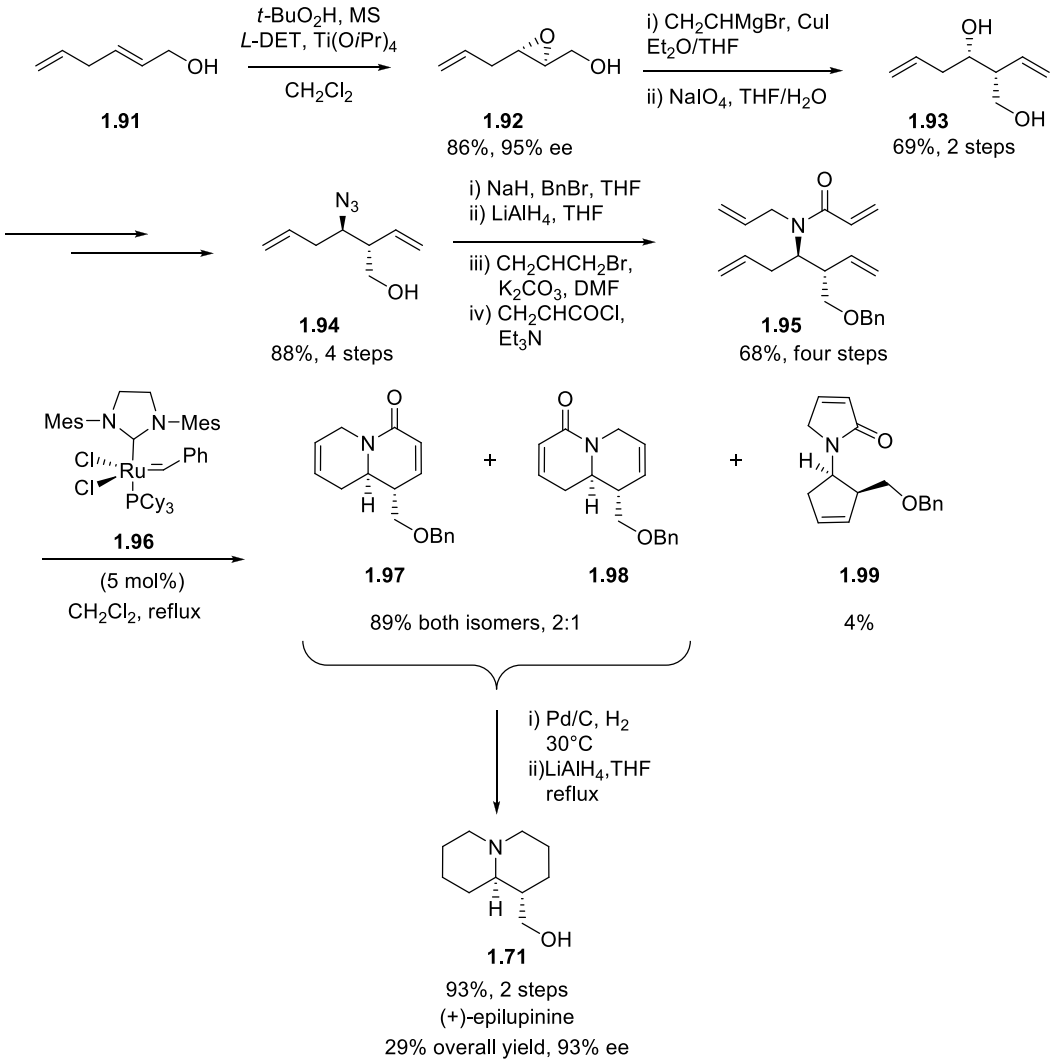


Scheme 1.2.4: Lhommet's route to (+)-tashiromine[62]

This route involves the use of (*S*)-α-methylbenzylamine (**1.86**) to influence the stereoselective reduction of chiral β-enamino lactone **1.89**. Use of Pt/C (5%) and $H_{2(g)}$ in EtOAc, gave the two *anti* diastereomers of **1.90** in a ratio of 72:28 (**1.90.1:1.90.2**) and 91% yield. The two diastereomers were separated by formation of the picrate salts, recrystallisation and then depicratation, to give the main diastereomer **1.90.1**. Hydrogenolysis, with Pd/C, H_2 in methanol, removed the chiral α-methylbenzyl group and also opened the lactone ring. The second

ring was then closed by reaction with PPh_3/CBr_4 to form the bromide, which reacted to give the amine in the presence of triethylamine and gave the indolizidine core. A final reduction of the methyl ester by $LiAlH_4$ completed the synthesis of (+)-tashiromine (**(+)-1.72**).

Ma *et al*. published a synthesis of all four diastereomers of the epilupinine/lupinine series in 2004.[51] Their synthesis was focused on using a double ring-closing metathesis reaction on nitrogen tetraenes to construct the bicyclic framework (**Scheme 1.2.5**). They employed Sharpless's asymmetric epoxidation methodology to gain selective access to the required stereocentres. The construction of the nitrogen tetraenes commenced with an epoxidation step whereby the combining of the relevant *E* or *Z* 2,5-hexadienol **1.91** together with either D- or L-diethyl tartrate meant that the adjacent stereocentres were selectively installed for all four diastereomers of **1.92** with 86 to 93% ee (as determined from the Mosher's esters).

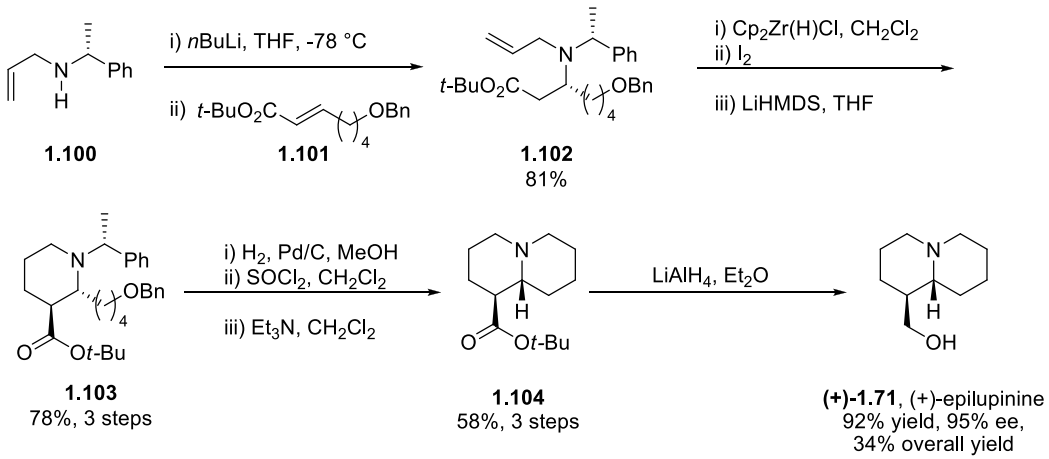


Scheme 1.2.5: Ma's synthesis of epilupinine[51]

Further manipulation of the epoxides (**Scheme 1.2.5**) allowed access to the nitrogen tetraenes **1.95** which were then subjected to the ring closing metathesis conditions, with second generation Grubbs' catalyst leading to a mixture of three products: **1.97**, **1.98** and **1.99**. The hydrogenolysis/hydrogenation and reduction of structural isomers **1.97** and **1.98**, where the carbonyl group of the lactam were in different positions, both led to the formation of (+)-epilupinine (**(+)-1.71**).

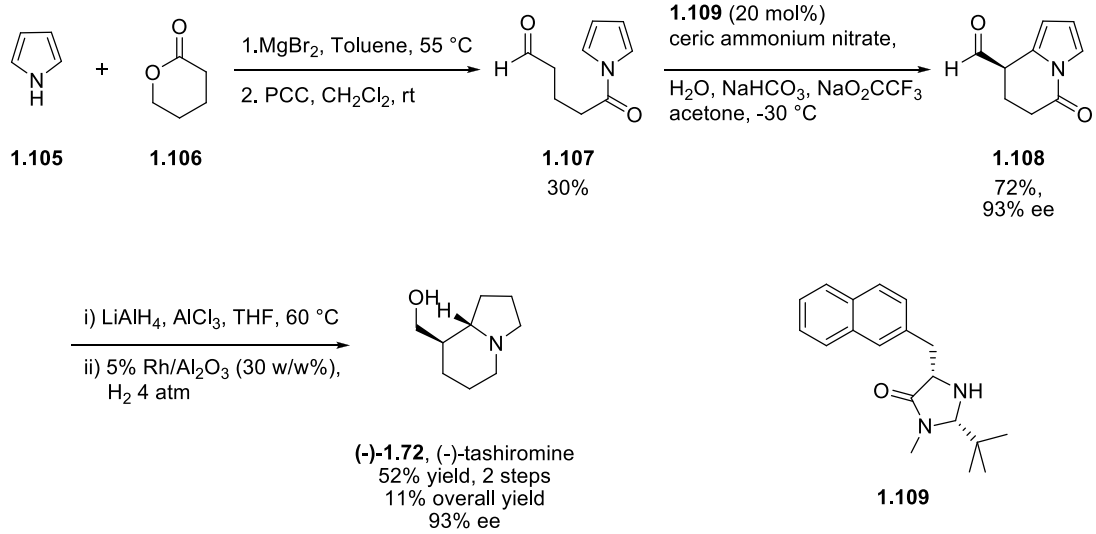
Szymoniak *et al*. published a synthesis of (+)-epilupinine (**(+)-1.71**) in 2008 (**Scheme 1.2.6**).[52] This synthesis used a chiral amine **1.100** to direct a stereoselective Davis 1,4-addition and then a diastereoselective annulation to give the second stereocentre. Alkylation of chiral amine **1.100** with α,β-unsaturated ester **1.101** proceeded with complete stereocontrol to yield **1.102**.

Tertiary amine **1.102** was then reacted under Szymoniak's hydrozirconation iodination sequence, followed by the final stereocontrolled ring closure using LiHMDS. Deprotection of the amine and the alcohol using Pd/C under H_2 followed by chlorination of the alcohol group and subsequent ring closure to form the quinolizidine **1.104**, were completed with 58% yield. The final reduction of the ester to give (+)-epilupinine (**(+)-1.71**) was effected using $LiAlH_4$.



Scheme 1.2.6: Synthesis of (+)-epilupinine[52] by Szymoniak *et al*.

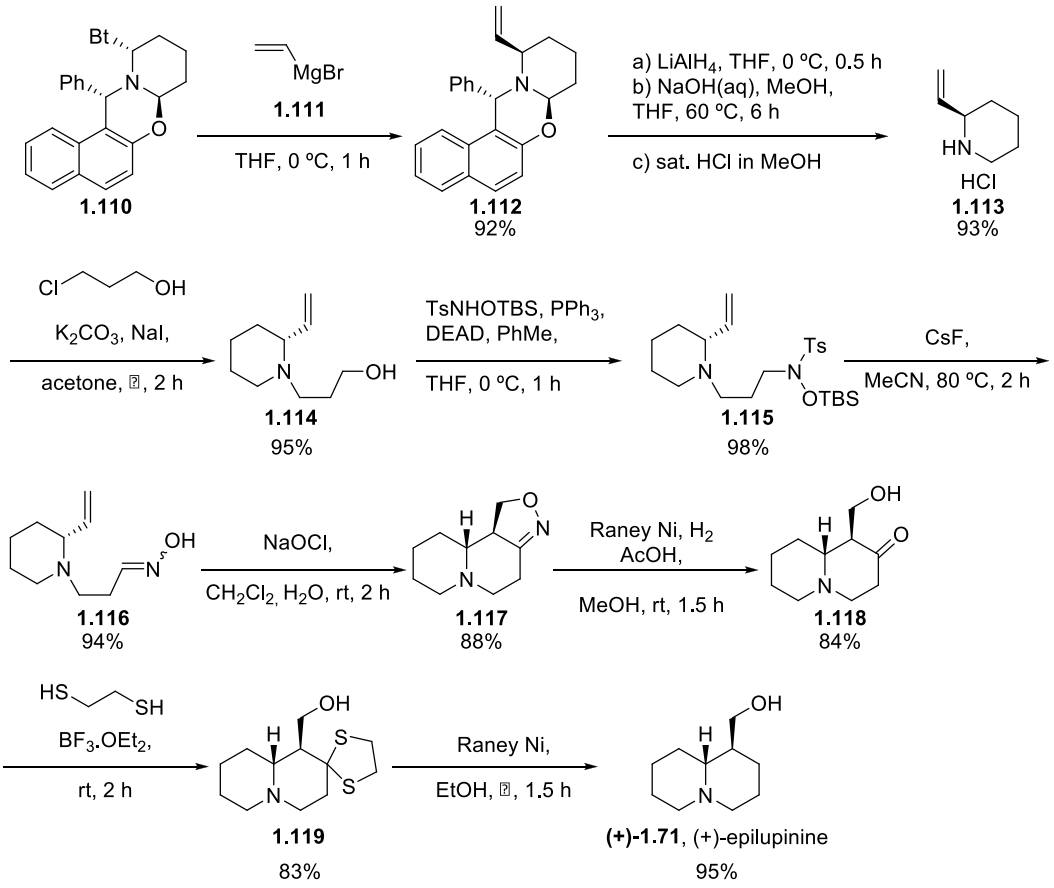
A short four step synthesis of (–)-tashiromine (**(–)-1.72)**) was published by MacMillan *et al*. in 2009,[59] starting from pyrrole which was reacted with γ-valerolactone (**1.106**) and then oxidised to form aldehyde **1.107** in 30% yield (**Scheme 1.2.7**).



Scheme 1.2.7: MacMillan's route to (–)-tashiromine[59]

The first stereocentre was then put in place by an enantioselective α-arylation reaction using 20 mol% of imidazolidinone **1.109** to impart chirality on the resulting bicycle **1.108** with 93% ee. Reduction of the carbonyl groups was carried out using $LiAlH_4$ and $AlCl_3$ in THF. The final stereoselective hydrogenation of the pyrrole used rhodium on aluminium as a catalyst to yield (–)-tashiromine (**(–)-1.72**) in 11% overall yield from pyrrole with 93% ee.

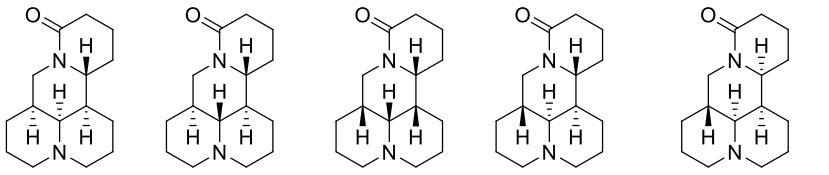
A long, but high yielding synthesis of (+)-epilupinine (**(+)-1.71**) was published by Wang *et al.* (**Scheme 1.2.8**).[53] They started from the aminobenzylnapthol (Betti base) derivative **1.110** which was alkylated by ethyl Grignard (**1.111**) to give **1.112** as a single diastereomer in 92% installing the first stereocentre. One pot cleavage of the C-O bond using $LiAlH_4$, followed by *N*-debenzylation, yielded amine **1.113** as its hydrochloric salt in 93%. *N*-Alkylation, followed by Fukuyama's 2 step oxime synthesis formed **1.116**, the key intermediate for the nitrile oxide-alkene cycloaddition. This route avoided the troublesome aldehyde which was found to undergo intramolecular E1cB elimination. The cyclisation was successfully carried out when oxime **1.116** was oxidised with 10% NaOCl (aq) in CH_2Cl_2 at room temperature over 2 hours to yield 4,5-dihydroisoxazole **1.117** in 88% yield, selectively installing the second stereocentre to form a single diastereomer. Hydrogenolysis of the 4,5-dihydroisoxaze (**1.117**) using Raney nickel cleaved the O-N bond and subsequent hydrolysis afforded ketone **1.118**. Removal of the ketone *via* the *S*,*S*-ketal formation and subsequent desulfurisation yielded (+)-epilupinine **(+)-1.71** in 48% overall yield over 9 steps.



Scheme 1.2.8 Synthesis of (+)-epilupinine *via* an intramolecular nitrile oxide-alkene cycloaddition reported by Wang *et al*.[53]

1.2.2. Allomatrine

The matrine stereoisomers, are a group of tetracyclic lupin alkaloids with 2 fused quinolizidine cores (**Scheme 1.2.9**).

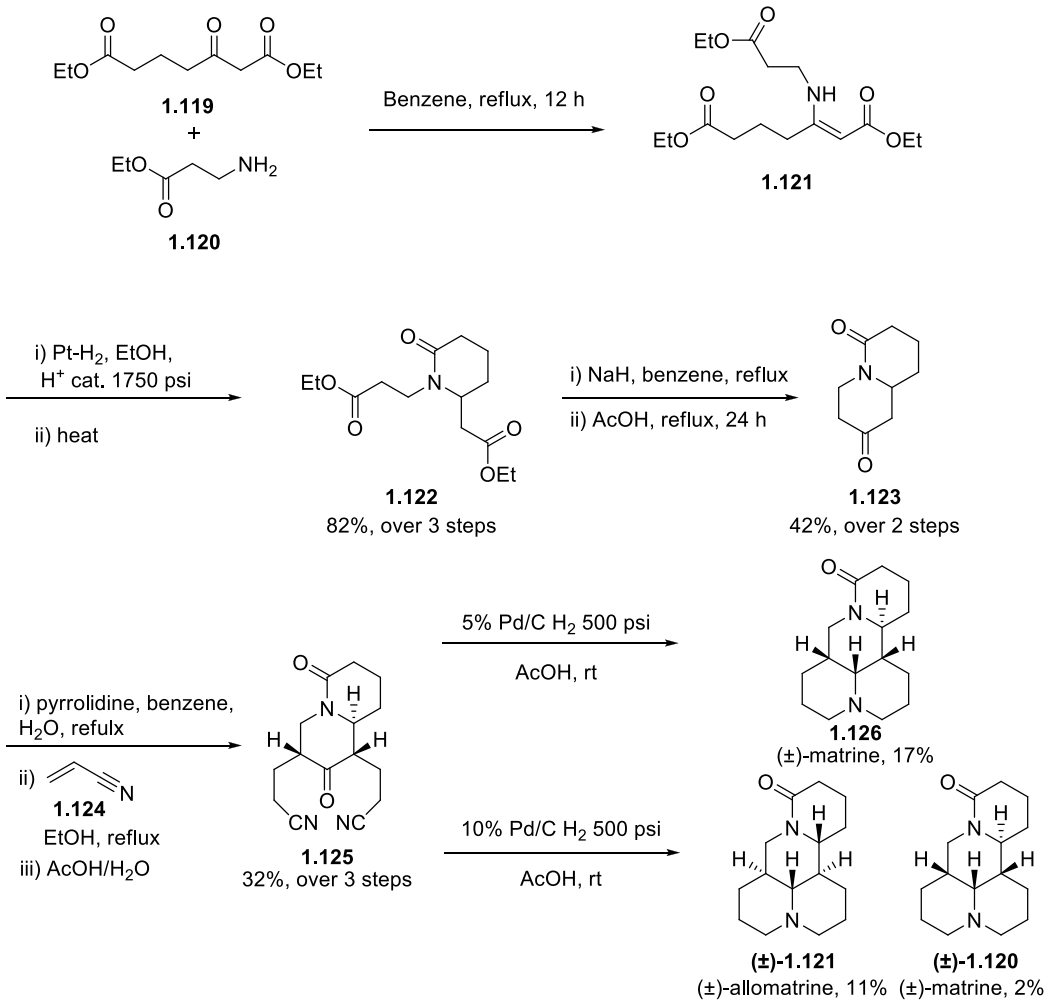


Scheme 1.2.9: Matrine alkaloids

Alkaloid **1.121** is known in its racemic and (+)-form as allomatrine and in the (–)-form originally as isoleontine and later leontine. To save confusion, the alkaloid **1.121** shall be referred to as (+) or (–)-allomatrine here, together with its optical

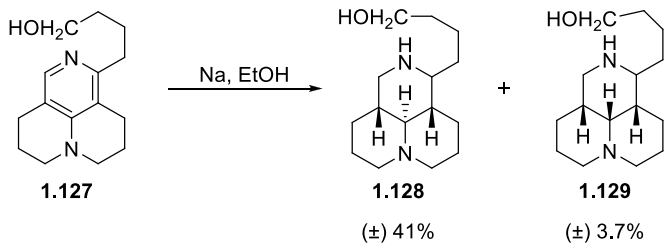
rotation where necessary. Allomatrine (**1.121**) was first isolated in 1953[44] in the (–)-form from *Leontice eversmanni*, a herbaceous perennial which is found in the Middle East.

The first total syntheses of (±)-allomatrine (**(+)-1.121**) and (±)-matrine, (**(+)-1.120**) were reported by Freeman *et al.* (**Scheme 1.2.10**).[63] The synthesis started with the condensation of diethyl 3-oxopimelate (**1.119**) and ethyl β-alaninate (**1.120**). The triester product **1.121** was then reduced, cyclised and decarboxylated to furnish quinolizidinone **1.123**. Bisalkylation with acrylonitrile (**1.124**) yielded **1.125** containing the carbon framework for the matrine series. Finally reductive cyclisation with palladium on charcoal catalyst gave (±)-matrine (**1.120**) when 5% catalyst was used. The isomerisation of (±)-matrine (**1.120**) to (±)-allomatrine (**1.121**) was achieved when more catalyst was used, with 10% palladium on carbon giving a mixture of predominantly (±)-allomatrine (**1.121**) with (±)-matrine (**1.120**).



Scheme 1.2.10: Synthesis of (±)-matrine and (±)-allomatrine.[63]

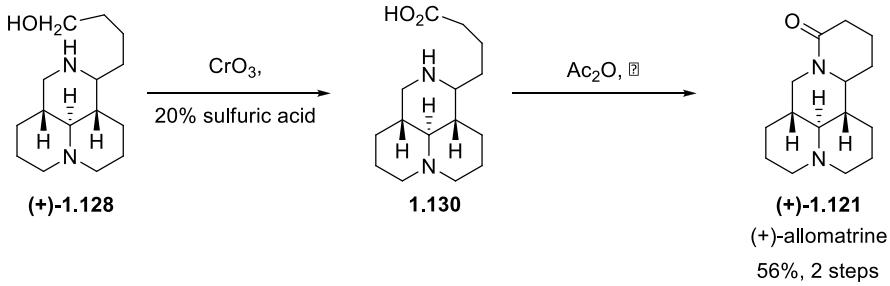
Shortly after Freeman's publication, the synthesis of (+)-allomatrine (**(+)-1.121**) by optical resolution was published by Okuda *et al.*[64]



Scheme 1.2.11: Reduction of didehyromatrine **1.127**

This synthesis started from didehydromatrine **1.127**, which had been previously synthesised by Tsuda *et al*.[65] This was reduced by refluxing with sodium in ethanol to yield (±)-allomatrinol **1.128** (41%) and (±)-matrinol **1.129** (3.7%) (**Scheme 1.2.11**). The optical resolution of (±)-allomatrinol **1.128** was achieved by formation and then selective crystallisation of the dibenzoyl-(+)-tartaric acid

salt. (+)-Allomatrinol **1.128** was released by basic treatment with K_2CO_3 and recrystallised. Oxidation of (+)-allomatrinol using the Jones reagent gave the amino acid **1.130**. The subsequent cyclisation was then performed in acetic anhydride at reflux to yield (+)-allomatrine **1.121** (**Scheme 1.2.12**).



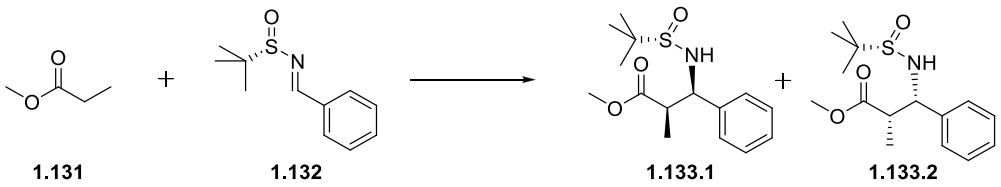
Scheme 1.2.12: Synthesis of (+)-allomatrine

To the best of our knowledge there have been no other reports of further synthetic methods towards either enantiomer of allomatrine. Additionally we have found no other reports of asymmetric syntheses of the matrine alkaloids.

1.3. Previous work in the Brown group

Within the Brown group we are interested in developing new methodology to synthesise natural products and biologically active compounds.[66-70] Part of this research has been directed towards developing a stereoselective imino-aldol reaction to be used in the synthesis of alkaloids and other saturated nitrogen heterocycles.[60]

Previous attempts to optimise the imino-aldol reaction using (*S*)-*tert*-butyl sulfinamide as an auxiliary gave disappointing results. When the conditions employed by Ellman (LDA, $TiCl(O\textit{i}Pr)_3$, –78 °C, THF) were repeated in our laboratory, it was found that not only were the high diastereoselectivities (up to 96:4:0:0 dr) not reproduced but a reversal of selectivity, favouring the other *syn* diastereomer to that noted by Ellman, was observed (**Scheme 1.3.1**).

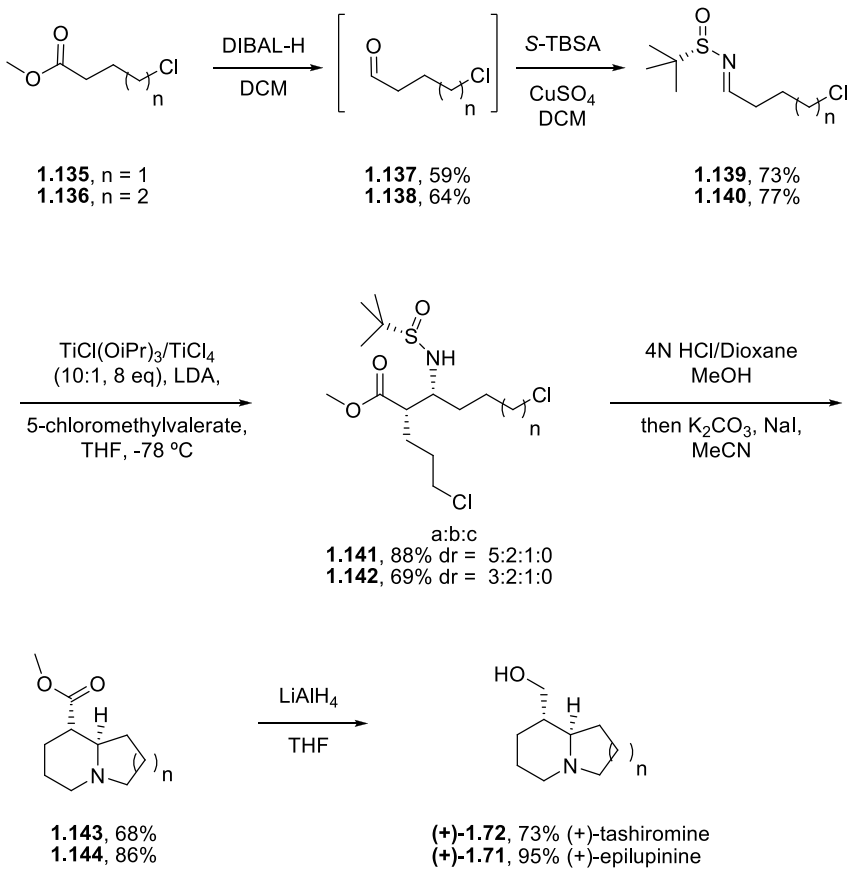


Lewis Acid		dr
$TiCl(OEt)_3$	Ellman[29]	24:1
$TiCl(OEt)_3$	Brown and Miller[60]	1:2
$TiCl(OEt)_3/TiCl_4$	Brown and Miller[60]	10:1

Scheme 1.3.1: Model imino-aldol reaction

The failure to reproduce the published results led Miller and Brown to investigate the influence of the Lewis acid upon the diastereoselectivity of the imino-aldol reaction, based on the hypothesis that halide impurities could affect the composition of the titanium Lewis acid employed. Investigation of this reaction using a model system led to the development of modified reaction conditions, which resulted in some improvement in the stereoselectivity observed. This consisted of using an alternative Lewis acid composition by doping $TiCl(O\textit{i}Pr)_3$ with a small amount of $TiCl_4$ (thereby effectively altering the stoichiometry of $TiCl(O\textit{i}Pr)_3$). In the model system this was found to return the sense of the diastereoselectivity to that originally observed by Ellman although the very high selectivities reported were never achieved (**Scheme 1.3.1**).

With modified imino-aldol reaction conditions returning satisfactory levels of diastereocontrol, application to the synthesis of the alkaloids tashiromine (**1.72**) and epilupinine (**1.71**) afforded the natural products in 5-steps and allowed confirmation of the stereochemistry obtained in the key imino-aldol reaction (**Scheme 1.3.2**).

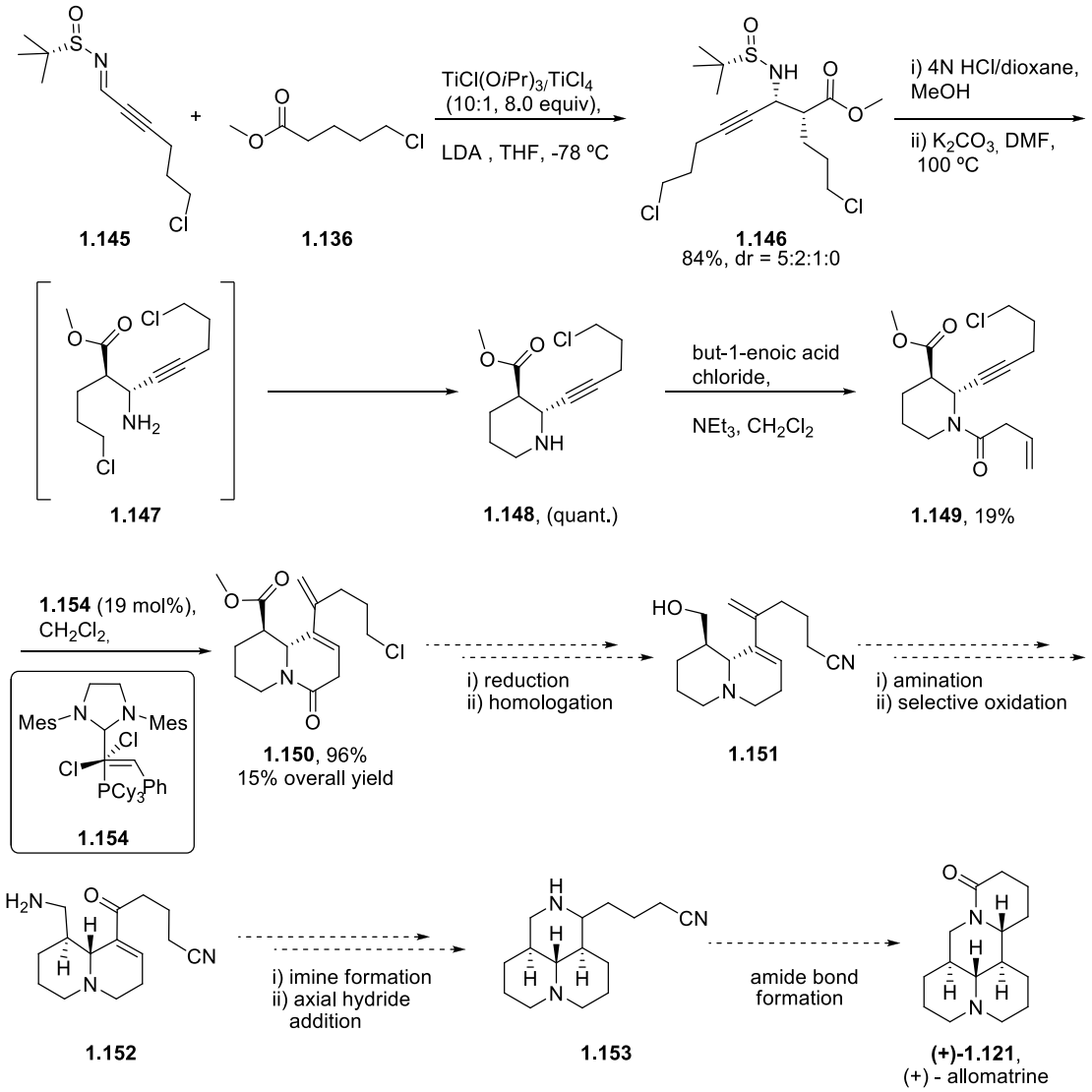


Scheme 1.3.2: Route to enantiomerically enriched (+)-tashiromine and (+)-epilupinine.[60] (N.B. compounds **1.141** and **1.142** were taken through to the natural products as a mixture of the two *syn* diastereomers)

Unfortunately, when the imino-aldol reaction was applied to the epilupinine and tashiromine precursors, there were a number of unforeseen problems (**Scheme 1.3.2**). First, there was a reduction in stereoselectivities for the tashiromine and epilupinine series compared to the model system (5:2:1:0 or 3:2:1:0 respectively; *c.f.* 10:1 for **1.133**). Secondly, isolation of the pure major diastereomer proved elusive in Miller's hands, with another diastereomer always present. And thirdly, and of most concern, when the major diastereomer (together with the inseparable minor diastereomer) were taken through to the enantiomerically enriched natural products, it was found that the major diastereomers were the (+)-enantiomers when the (–)-enantiomers were expected based on the model studies. This change in orientation was completely unexpected when all of the reaction conditions had remained consistent. As a consequence, the general application of these conditions in

synthesising imino-aldol products of specific orientation from any set of substrates is unreliable. The unpredictable sense and levels of diastereocontrol observed for these imino-aldol reactions, together with a complicated practical procedure and high stoichiometric use of the titanium Lewis acid and the ester, were less than ideal.

Subsequent research by Miller and Brown towards the total synthesis of (+)-allomatrine (**1.121**) applied the imino-aldol reaction towards the synthesis of this more complex tetracyclic matrine alkaloid (**Scheme 1.3.3**).



Scheme 1.3.3: Synthetic route towards (+)-allomatrine [60]

The key steps in this route were the imino-aldol reaction to form amine **1.146** which would impart the desired stereochemistry at C5 and C6, and the ring-closing metathesis (RCM) step to form quinolizidine **1.150**. The synthesis of the intermediate **1.150** was successfully achieved in 4 steps with an overall yield of 15%. There were, however, problems with the synthesis, including the low diastereoselectivity of the imino-aldol step under the modified Lewis acidic conditions of $TiCl(O\textit{i}Pr)_3/TiCl_4$ 10:1, giving a dr of only 5:2:1. The relative and absolute stereochemistry of the diastereomers of **1.150** was not determined, but was tentatively assigned based on previous results obtained by Miller.

The aim of the research described in this thesis was to develop an imino-aldol reaction that works in a reliable manner to give high diastereoselectivities on a range of substrates containing functionality suitable for further manipulation, in particular for a step-efficient route to saturated nitrogen heterocycles. Chapter 2 discusses the development of a versatile imino-aldol reaction and Chapter 3 covers the synthesis of a variety of asymmetric piperidines including the natural products (–)-tashiromine (**(–)-1.72**) and (–)-epilupinine (**(–)-1.71**).

2. The Imino-Aldol Reaction

In this chapter the development of new methodology for the imino-aldol reaction will be described. First, the synthesis of the key sulfinimines and esters was achieved and these were then used in the subsequent reactions to develop the methodology. Initial investigations focused on varying the Lewis acid employed, starting with titanium based acids and then moving to lithium Lewis acids. Our strategy was then to investigate the effect of different carboxylic acid derivatives on the imino-aldol reaction. These included esters and amides, which were successfully synthesised and reacted. The stereochemistry of the resultant imino-aldol products was then determined, and the effect of the functionality of the alkyl chains on the reaction was also investigated.

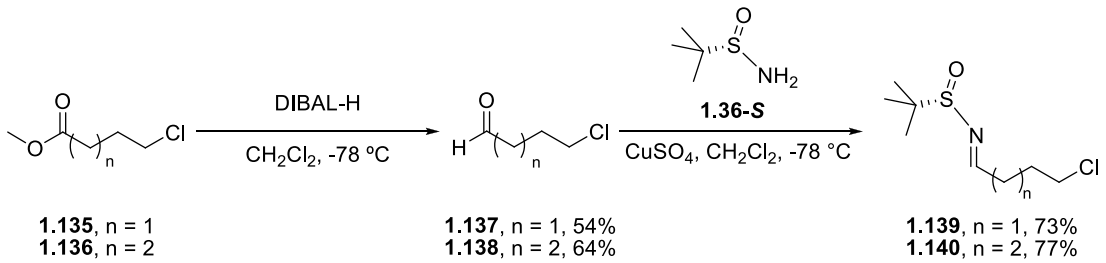
2.1. Investigation of the Influence of Lewis Acid on the Imino-Aldol Reactions

Our investigations into the imino-aldol reaction focused initially on the role of the Lewis acid in the reaction. Results gained previously in our group on the imino-aldol reaction had shown that the Lewis acid composition could affect the diastereoselectivity (see **Section 1.3**). We had also seen that results with simple model systems (sulfinimines obtained from benzaldehyde) were not representative of those achieved with the precursors of epilupinine (**1.71**) and tashiromine (**1.72**). Therefore, the natural product precursors **1.139** or **1.140** with **1.136** from our synthetic route were used in further investigatory work.

2.1.1. Synthesis of sulfinimines

The sulfinimines were synthesised in two steps from commercially available methyl 5-chloropentanoate (**1.136**) and methyl 4-chlorobutyrate (**1.135**) (**Scheme 2.1.1**). DIBAL-H mediated reductions yielded 5-chloropentanal (**1.138**) in 54% and 4-chlorobutanal (**1.137**) in 64% yield, which were not purified due to the difficulty in handling these volatile liquids. The crude aldehydes were then condensed with commercially available (*S*)-2-methylpropane-2-sulfinamide

(**1.36-*S***) in the presence of anhydrous $CuSO_4$, which yielded sulfinimines **1.139** and **1.140** in 77% and 73% respectively.



Scheme 2.1.1: Synthesis of sulfinimines **1.139** and **1.140**

The conditions under which the sulfinimines are stored proved to be very important and it was found that these sulfinimines underwent some decomposition at room temperature over several weeks and were therefore stored in the freezer. We were able to isolate a by-product by column chromatography, obtaining a white crystalline compound which was identified by X-ray crystallography (**Figure 2.5**). Curiously, the by-product obtained was an interesting mixed valence di-sulfur compound (**2.01**).

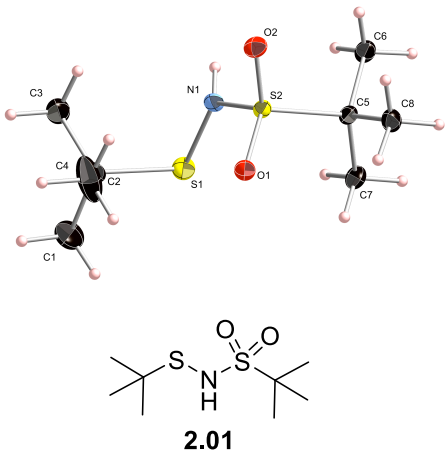
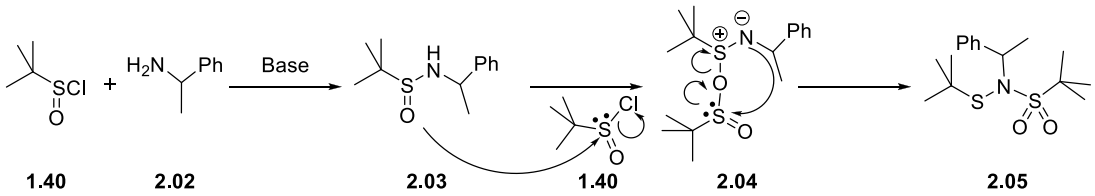


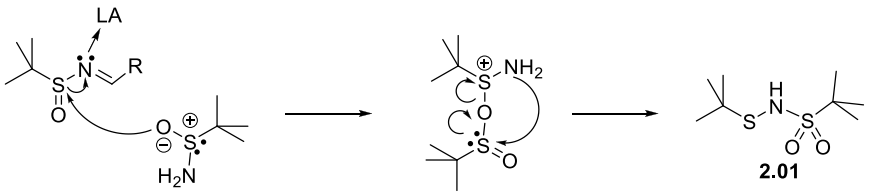
Figure 2.5: X-ray of divalent sulfur side product (**2.01**)

The synthesis of *N*-sulfonyl sulfenamide compounds has been reported by Drabowicz, who also initially observed it as an unexpected side product, **2.05**. Drabowicz proposed the following mechanism for the rearrangement under basic conditions (**Scheme 2.1.2**).[71]



Scheme 2.1.2: Rearrangement mechanism from literature[71]

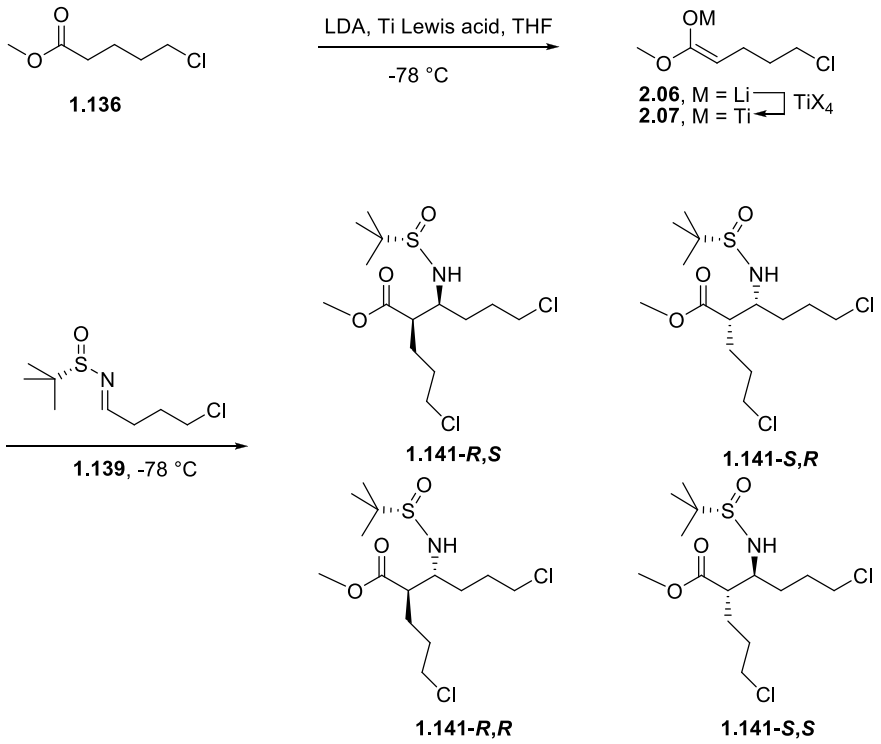
In our case, the reaction is probably accelerated by slightly acidic or Lewis acidic conditions resulting from residual $CuSO_4$ or silica gel used in chromatographic purification. A proposed mechanism to account for the by-product **2.01** is presented in **Scheme 2.1.3**. It is conceivable that the mechanism of formation of our side product is similar to that previously suggested (**Scheme 2.1.3**). The impurity was not observed when imines were stored below – 5 °C.



Scheme 2.1.3: Proposed mechanism for the formation of *N*-sulfonyl sulfenamide **2.01** under acidic conditions.

2.1.2. Reactions of Titanium Enolates

Following investigation of the sulfinimines, we moved on to look at the effect of the Lewis acid on the imino-aldol reaction with the tashiromine precursor **1.139**. Commercially available methyl 5-chloropentanoate (**1.136**) was deprotonated with LDA at –78 °C in THF to form the lithium enolate. It was then transmetallated to the titanium enolate by addition of titanium Lewis acid solution, before being reacted with sulfinimine **1.139** for around 30 minutes (**Scheme 2.1.4**).



Scheme 2.1.4: Imino-aldol reaction

Previous syntheses of natural products (+)-tashiromine (**(+)-1.72**) and (+)-5-epi-tashiromine[a] in the Brown group *via* imino-aldol products **1.141-*S*,*R*** and **1.141-*S*,*S*** allowed the assignment of one of the *syn* and one of the *anti* diastereomers by comparison of the optical rotation with literature values (this allowed the stereochemical assignment of the remaining *syn* and *anti* diastereomers **1.141-*R*,*S*** and **1.141-*R*,*R***). The diastereomers were known to have distinctive 1H doublet peaks for the NH proton in the 1H NMR spectra the integration of these peaks was used to measure the relative ratios of the diastereomers. Unless stated otherwise, all diastereomeric ratios quoted in this work were measured from ^{1}H NMR spectra of the crude reaction material prior to purification.

[a] The absolute stereochemistry of 5-epi-tashiromine was made by analogy to the assignment of the homologous *anti* imino-aldol product of **1.141-*S*,*S*** in the phenyl ester series (**2.19-*S*,*S***) which was converted to (+)-lupinine **(+)-1.70** (see **Section 3.1.3**).

Entry	Transmetallation conditions (equiv)	Equiv ester	Yield [a] (%)	dr[d] (*R*,*S*:*S*,*S*:*S*,*R*:*R*,*R*)
1	$TiCl(OiPr)_3$ (4)	1.4	43[b]	72:17:11:0
2[e]	$TiCl(OiPr)_3$:$TiCl_4$, 9:1 (8)	4	80[c]	24:11:65:0
3	$TiCl(OiPr)_3$:$TiCl_4$, 10:1 (4)	2	54[b]	69:16:15:0

[a] Combined yield of diastereomers.
[b] Unoptimised yield.
[c] Optimised yield.
[d] Estimated by integration of NH doublets in crude ^{1}H NMR at 4.21:4.48:3.20 ppm (***R*,*S***:***S*,*S***:***S*,*R***).
[e] Result taken from work carried out by Iain Miller.[60]

Table 2.1.1: Effect of Lewis-acid composition on diastereoselectivity

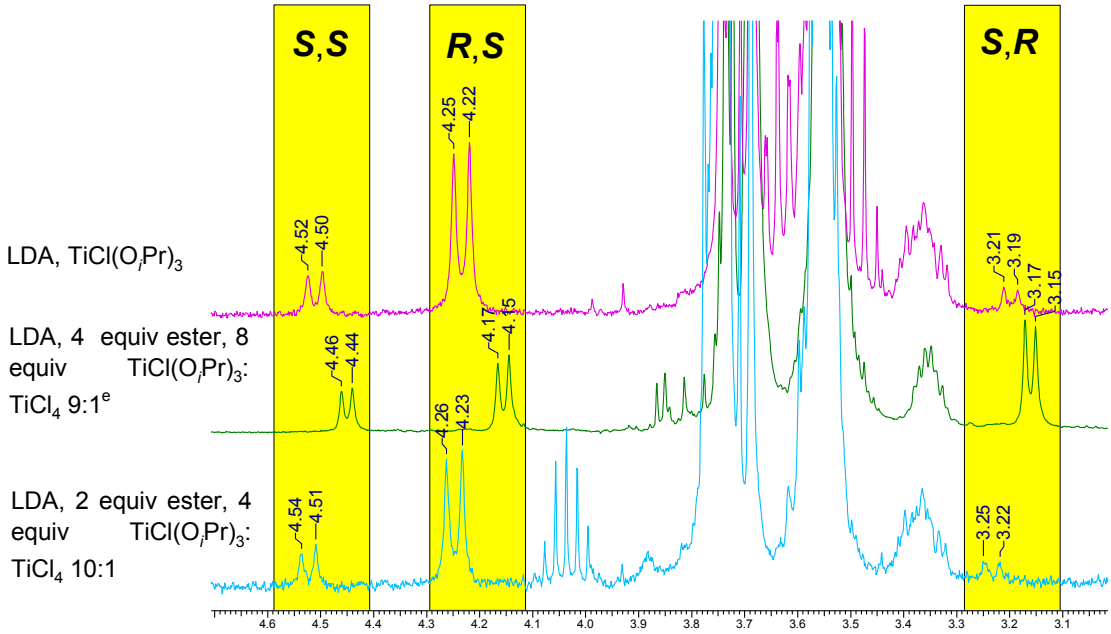


Figure 2.6: Comparison of NH doublets in ^{1}H NMR spectra of crude reaction material from Ti enolate reaction conditions between methyl ester **1.136** and sulfinimine **1.139**.

Selectivities resulting from using different Lewis acid mixtures to form the titanium enolates were compared (**Table 2.1.1**, **Figure 2.6**).

First we repeated Ellman's favoured conditions using 4 equivalents of $TiCl(OiPr)_3$ (**Entry 1**, **Table 2.1.1**). Analysis of the crude ^{1}H NMR data showed that the diastereomers had formed in 72:17:11:0 dr (***R*,*S*:*S*,*S*:*S*,*R*:*R*,*R***), favouring the Ellman *syn* diastereomer. Isolation of the mixture of diastereomers gave a combined yield of 43%. As had been found previously, complete

separation of *syn* diastereomers ***R,S*** and ***S,R*** from each other was challenging by flash column chromatography as well as preparative HPLC.

Next we reviewed the results obtained by Miller on model systems which had shown a reversal in facial selectivity when the Lewis acid was doped with $TiCl_4$ by using 4 equivalents of the enolate with 8 equivalents of a 9:1 mixture of $TiCl(O\textit{i}Pr)_3$: $TiCl_4$ (**Entry 2**, **Table 2.1.1**). This furnished three diastereomers in 80% yield and 24:11:65:0 dr (***R,S*:*S,S*:*S,R*:*R,R***). Interestingly this adjustment in the Lewis acid composition significantly altered the stereoselectivity, favouring the other "non-Ellman" *syn* diastereomer, ***S,R***, as opposed to diastereomer ***R,S*** which was favoured previously.

Attempts were made in the current work to reduce the amount of ester and Lewis acid used in the reaction by using 2 equivalents of enolate with 4 equivalents of a solution of 10:1 $TiCl(O\textit{i}Pr)_3$:$TiCl_4$ (**Entry 3**, **Table 2.1.1**). Intriguingly, in the present work under these conditions the selectivity of the reaction reverted to favour the "Ellman" ***R,S*** *syn* diastereomer, giving a modest selectivity that was very similar to that observed under Ellman's favoured conditions, with 69:16:15:0 dr.

From this series of reactions it seems that the stoichiometry of titanium enolate has a significant effect on the facial selectivity of the reaction (**Table 2.1.1**, **Figure 2.6**). This is exhibited by the reversal of facial selectivity when 8 equivalents of titanium Lewis acid, combined with 4 equivalents of the enolate were used (**Entry 2**, **Table 2.1.1**) compared to results with lower stoichiometry of enolate and Lewis acid species (**Entries 1** and **3**, **Table 2.1.1**). We hypothesise that where there was a large excess of coordinating species the Zimmerman-Traxler type transition state (**Figure 2.7**) may have been disrupted and caused an open transition state to predominate, resulting in the switch-over in facial selectivity observed.

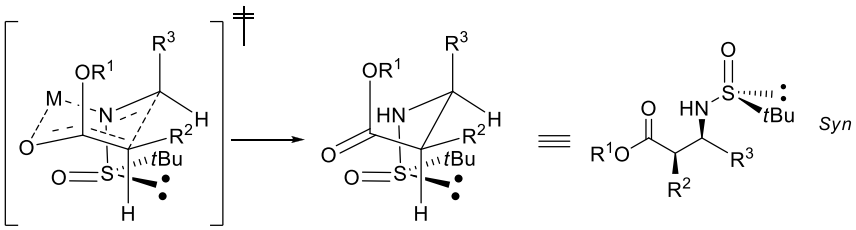
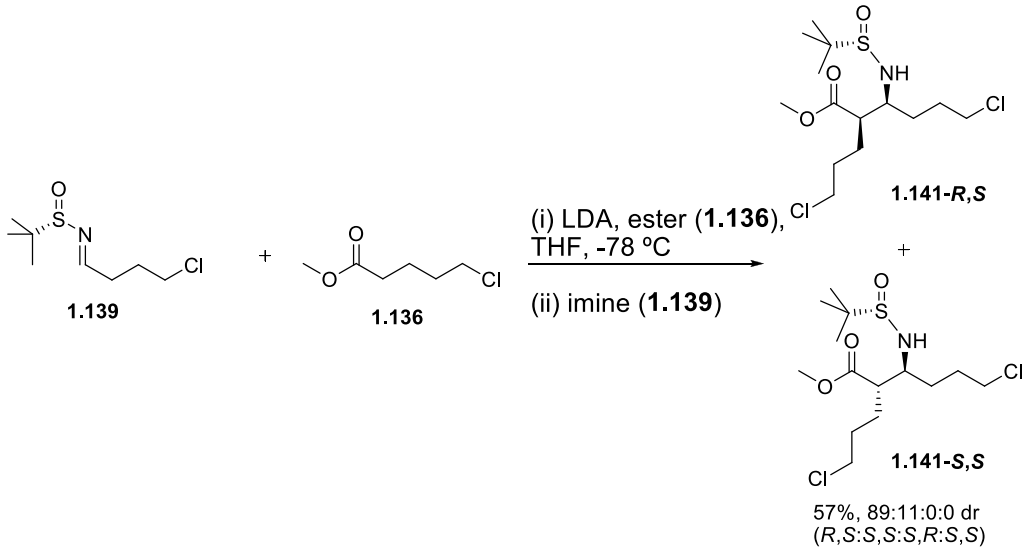


Figure 2.7: Proposed Zimmerman-Traxler transition state for standard imino-aldol reaction

2.1.3. Reactions of Lithium Enolates

Since the imino-aldol reaction seemed to be very sensitive to the titanium enolate stoichiometry and Lewis acid composition, it was decided to react the lithium enolate directly with the sulfinimine to see what effect this might have on the reaction selectivity (**Scheme 2.1.5**). Indeed, Ellman had reported the use of both Li and Na enolates with the imino-aldol reaction, although these proved less selective on his systems than the Ti enolate with 67:33 to 96:4 dr, whilst titanium enolates gave up to 99:1 dr.[31]



Scheme 2.1.5: Imino-aldol reaction with lithium enolate

The reaction of the lithium enolate of **1.136** worked well, further increasing the diastereoselectivity to 89:11:0:0 dr (***R,S***:***S,S***) with an unoptimised yield of 57% (**Scheme 2.1.5**). This improved the diastereoselectivity and simplified the reaction procedure by eliminating the transesterification step. It also eliminated

the formation of the second (***S,R***)-*syn* diastereomer. This improvement in reaction procedure gave only *syn* diastereomer ***R,S*** and *anti* diastereomer ***S,S***.

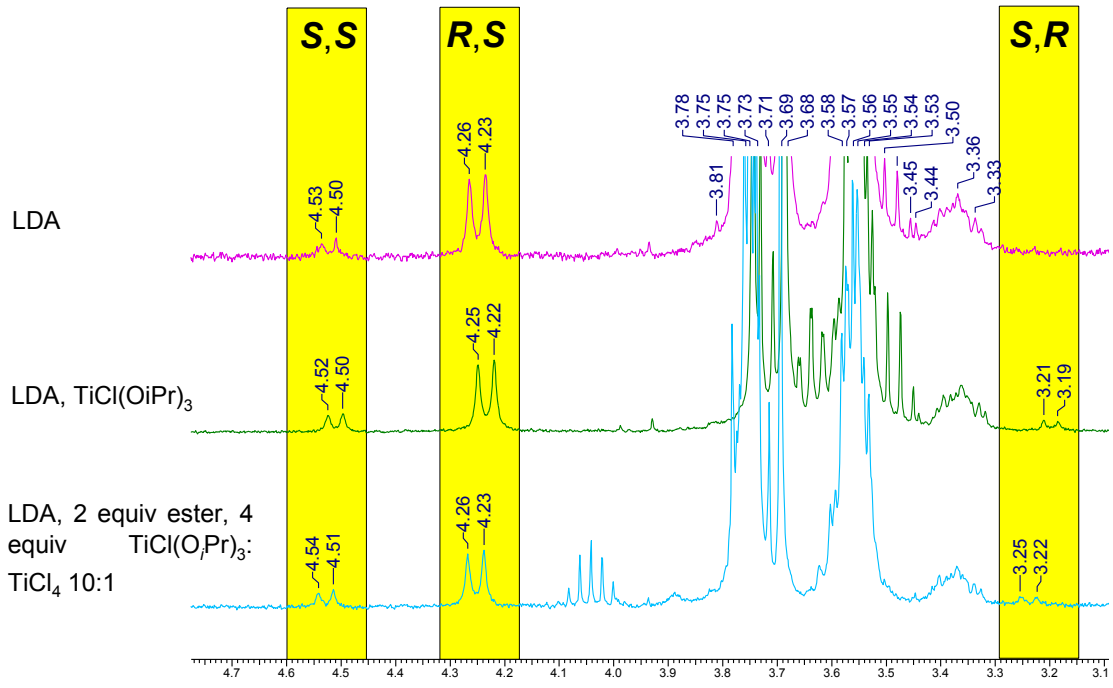


Figure 2.8: ^{1}H NMR spectra of crude reaction material from imino-aldol reactions of lithium and titanium enolates of methyl ester **1.136** and sulfinimine **1.139** showing varying diastereoselectivities.

Comparison of the NH doublets of the crude ^{1}H NMR spectra for the different reaction conditions clearly illustrates the increase in selectivity for the ***R,S*** diastereomer obtained by reacting the lithium enolate, compared to the various titanium enolate conditions (**Figure 2.8**).

The doublet at 3.2 ppm corresponds to the NH peak for *syn* diastereomer ***S,R***, and this can be seen to have disappeared under the LDA reaction conditions, whilst the doublet at 4.2 ppm for the other *syn* diastereomer ***R,S*** predominates over the minor *anti* diastereomer ***S,S*** with its doublet at 4.5 ppm.

The reaction with the lithium enolate offered us significant advantages over the titanium enolates. These included complete facial selectivity as well as simplified and cheaper reaction conditions. The diastereoselectivity had improved but we felt that further improvements could be made. We therefore

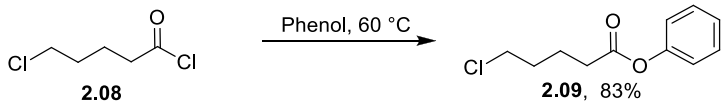
used the lithium enolates as we continued to explore the imino-aldol reaction and attempted to further increase the diastereoselectivity.

2.2. The Effect of Different Carboxylic Acid Derivatives on Diastereoselectivity

Just as the choice of metal enolate greatly affected the diastereocontrol in the imino-aldol reaction, we postulated that the choice of carboxylic acid derivative may also provide a means to enhance diastereoselectivity. Furthermore, use of different carboxylic acid derivatives may allow for easier separation of the diastereomers. As our proposed synthetic route to epilupinine (**1.71**) and tashiromine (**1.72**) involved the reduction of a carboxylic acid derivative to an alcohol, these changes could be easily incorporated into the synthetic strategy without changing the outcome. Four carboxylic acid derivatives were chosen for investigation. These were: 5-chloropentanoic acid phenyl ester (**2.09**), 2,6-dimethylphenyl 5-chloropentanoate (**2.11**), 5-chloro-1-piperidin-1-yl pentan-1-one (**2.15**) and 3-(5-chloro-pentanoyl) oxazolidin-2-one (**2.13**).

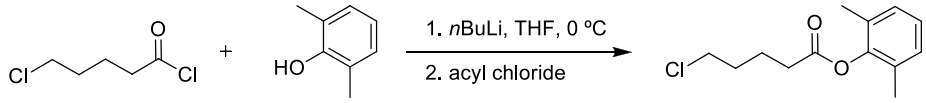
2.2.1. Synthesis of carboxylic acid derivatives

5-Chloropentanoic acid phenyl ester (**2.09**) was synthesised from commercially available 5-chloropentanoic acid chloride (**2.08**) and phenol to give the ester in 83% yield (**Scheme 2.2.1**).



Scheme 2.2.1: Synthesis of ester **2.09**

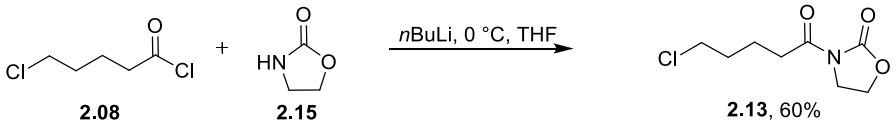
2,6-Dimethylphenyl 5-chloropentanoate (**2.11**) was formed in 48% by reacting the lithium salt of 2,6-dimethylphenol (**2.10**) with 5-chloropentanoic acid chloride (**2.08**) (**Scheme 2.2.2**).



2.08 **2.10** **2.11**, 48%

Scheme 2.2.2: Synthesis of ester **2.11**

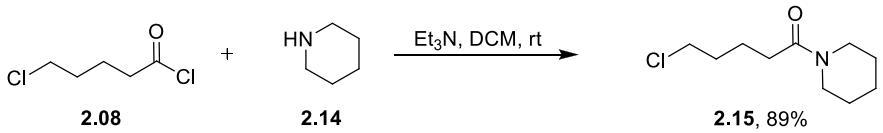
Deprotonated oxazolidinone (**2.12**) was reacted in a similar fashion with the acid chloride **2.08** to yield 3-(5-chloropentanoyl)oxazolidin-2-one (**2.13**) in 60% yield (**Scheme 2.2.3**).



2.08 **2.15** **2.13**, 60%

Scheme 2.2.3: Synthesis of *N*-acyl oxazolidinone **2.13**

Finally piperidine (**2.14**) was reacted with acid chloride **2.08** to yield 5-chloro-1-piperidin-1-yl-pentan-1-one (**2.15**) in 89% yield (**Scheme 2.2.4**).

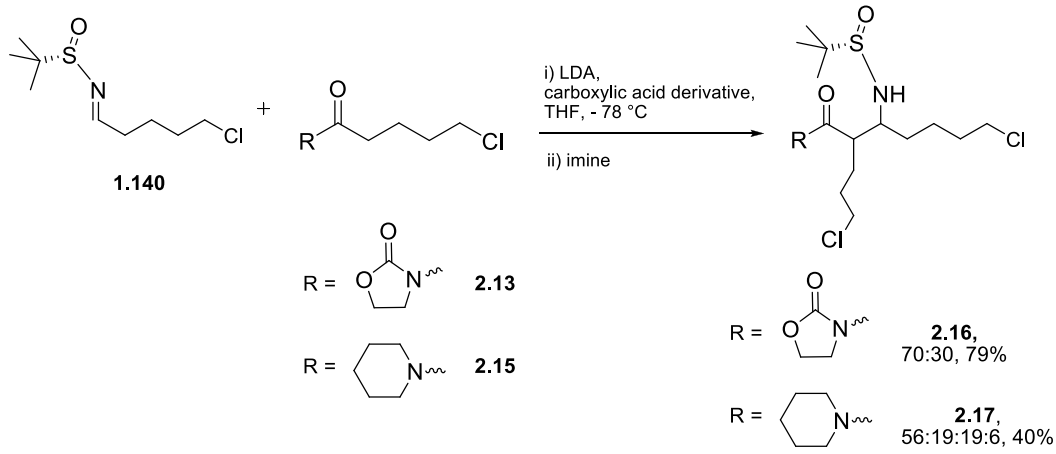


2.08 **2.14** **2.15**, 89%

Scheme 2.2.4: Synthesis of amide **2.15**

2.2.2. Imino-aldol reactions with different carboxylic acid derivatives.

With these four carboxylic acid derivatives in hand the lithium enolates were formed and then reacted with sulfinimine **1.140** to give the respective imino-aldol products.

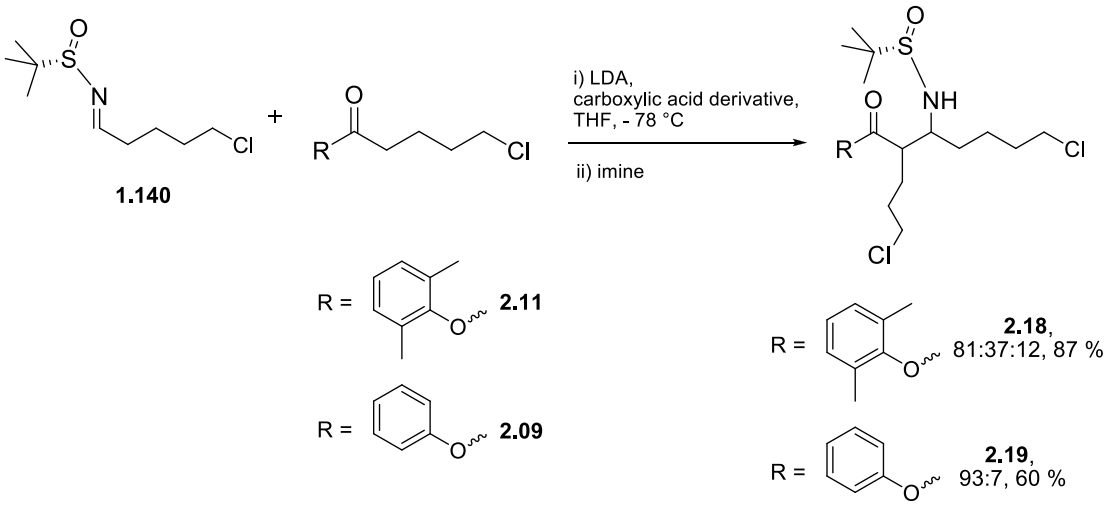


Scheme 2.2.5: Imino-aldol reaction with *N*-acyl oxazolidinone and piperidinyl derivatives.

As with previous reactions, distinctive signals from the NH protons were apparent in the ^{1}H NMR spectra for the imino-aldol products, allowing for estimation of the diastereoselectivity. Piperidinyl **2.15** reacted to give a mixture of all four possible diastereomers (**2.17**) in a poor selectivity (56:19:19:6 dr) [a] and in 40% yield[b] (**Scheme 2.2.5**). When *N*-acyl oxazolidinone (**2.13**) was reacted in the imino-aldol reaction, only 2 diastereomers were formed (**2.16**) in 70:30 dr[c] and 79% yield[b]. Furthermore, these two diastereomers were separable, which was encouraging. The diastereoselectivity, however, was still worse than that obtained in the imino-aldol reaction with the lithium enolate of the methyl ester (**Scheme 2.1.5**).

We next we turned our attention to the phenyl esters prepared. The imino-aldol reaction between 2,6-dimethylphenyl ester **2.11** and sulfinimine **1.140** gave a mixture of 3 diastereomers in 51:37:12[a] dr and 87%[b] yield (**Scheme 2.2.6**).

[a] dr calculated from integration of crude ^{1}H NMR spectra. The stereochemistry of individual diastereomers was not determined (except for **2.19**, see **Section 2.2.3** below). dr listed in order of majority. Where they are not listed other diastereomers were not identified.
[b] Unoptimised yield of isolated mixture of diastereomers.
[c] dr calculated from ratio of isolated diastereomers.



Scheme 2.2.6: Imino-aldol reaction with phenyl esters

Isolation of a small sample of the second most abundant diastereomer was achieved by crystallisation. However, the other two diastereomers were inseparable. The most promising results came when phenyl ester **2.09** was reacted with sulfinimine **1.140** to give a mixture of two diastereomers in 93:7[a] dr in 60%[b], where the other 2 possible diastereomers were not observed.

2.2.3. Stereochemical Determination

Isolation of the two diastereomers of **2.19** was achieved by column chromatography. Pleasingly, the major diastereomer was found to be crystalline, whilst the minor was an oil. This enabled optimisation of the purification procedure, including use of crystallisation, as well as the opportunity to analyse the major diastereomer by single crystal X-ray crystallography.

[a] dr calculated from integration of crude ^{1}H NMR spectra. The stereochemistry of individual diastereomers was not determined (except for **2.19**, see **Section 2.2.3** below). dr listed in order of majority. Where they are not listed other diastereomers were not identified.
[b] Optimised yield of isolated mixture of diastereomers.

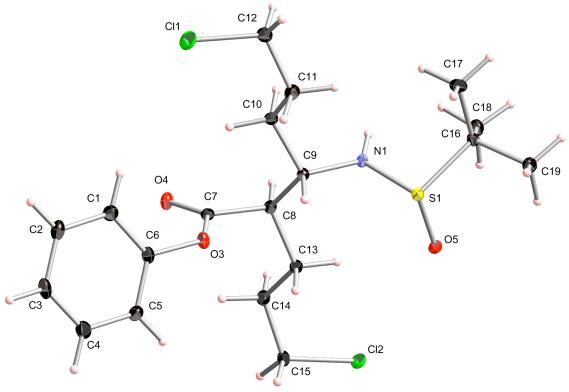


Figure 2.9: X-ray of **2.19-*R*,*S*** with thermal ellipsoids drawn at the 35% probability level

From the X-ray (**Figure 2.9**) it was possible to determine the absolute stereochemistry of the imino-aldol product. It was assigned as *R* at C-8 and *S* at C-9, with the chiral auxiliary retaining its *S* configuration. This stereoselectivity is consistent with the original reports from the Ellman group.[31] It is however, the other *syn* diastereomer to that reported previously by Miller and Brown in the course of their syntheses of (+)-epilupinine (**(+)-1.71**) and (+)-tashiromine (**(+)-1.72**).

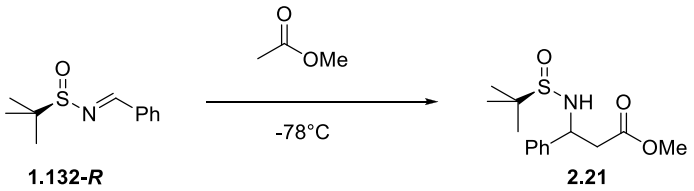
2.3. Further investigations

In this next section of work we wanted to test the boundaries of the reaction further to see if improvements could be made to the reaction itself, as well as investigating the versatility of this imino-aldol reaction. First we looked at the effect of different carboxylic acid derivatives on the imino-aldol reaction. The stereochemistry of the resultant imino-aldol products was then determined, and the effect of the functionality of the alkyl chains on the reaction was investigated. Finally, the optimum reaction stoichiometry was found.

2.3.1. Titanium and lithium enolate imino-aldol reactions on phenyl esters

The results published by Ellman and co-workers showed that titanium enolates gave superior selectivities compared to those with lithium enolates (**Table 2.3.1**).[29] They found that when comparing lithium enolates to both sodium and titanium based enolates, the results gained with the titanium enolates were

superior in terms of diastereoselectivity, and that the yields given matched the best yields gained with other enolates.



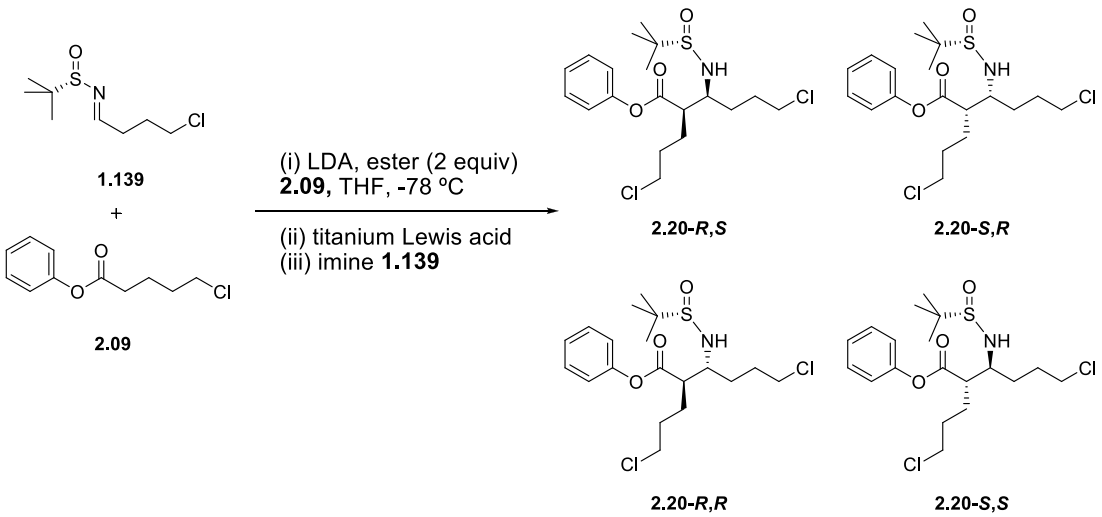
1.132-*R* **2.21**

Entry	Base	Solvent	Yield (%)	dr[a]
1	LDA	THF	76	83:17
2	LDA	Et_2O	91	67:33
3	NaHMDS	THF	89	75:25
4	NaHMDS	Et_2O	78	96:4
5	LDA/1 equiv of $TiCl(O_iPr)_3$	THF	90	87:13
6	LDA/2 equiv of $TiCl(O_iPr)_3$	THF	90	98:2
7	LDA/3 equiv of $TiCl(O_iPr)_3$	THF	90	99:1
8	LDA/4 equiv of $TiCl(O_iPr)_3$	THF	90	99:1

Table 2.3.1: Results published by Ellman showing effects of changing enolisation base, Lewis acid and solvents.[29]

(a) Diastereomeric ratios determined through peak integration from HPLC analysis of MTPA amide derivatives prepared from crude reaction mixtures.

We therefore felt that it was logical to examine the effect of transmetallation of the phenyl esters to the titanium enolate on the imino-aldol reactions (**Scheme 2.3.1**, **Table 2.3.2**).



Scheme 2.3.1: Imino-aldol reaction of phenyl ester **2.09** under different Lewis acid conditions

Entry	Titanium Lewis acid (equiv)	Yield (%)	dr[b] (*R*,*S*:*S*,*S*:*S*,*R*:*R*,*R*)
1	-	70	96:4:0:0
2	$TiCl(O_iPr)_3$ (4)	56[a]	72:11:0:17
3	$TiCl(O_iPr)_3$:$TiCl_4$, 10:1 (4)	55[a]	82:18:0:0

[a] Unoptimised yield of combined diastereomers.
[b] Estimated by integration of NH peaks in crude ^{1}H NMR.

Table 2.3.2: Imino-aldol reaction with methyl and phenyl esters and a variety of Lewis acid conditions

In contrast to the literature results, the titanium enolates gave lower diastereoselectivites than that obtained with the corresponding lithium enolates. Using $TiCl(OiPr)_3$ to transmetallate, a yield of 56% was achieved with 72:11:0:17 dr (***R***,***S***:***S***,***S***:***S***,***R***:***R***,***R***) (**Entry 2**, **Table 2.3.2**). While the diastereoselectivity improved when the doped mixture of $TiCl(OiPr)_3$ and $TiCl_4$ was employed to 82:18:0:0 dr (***R***,***S***:***S***,***S***:***S***,***R***:***R***,***R***) (**Entry 3**, **Table 2.3.2**), this was still inferior to the result using the lithium enolate (**Entry 1**, **Table 2.3.2**). Interestingly, while the results with the phenyl ester are superior to those with the methyl ester (**Table 2.1.1**), the diastereoselectivities of the two sets of reactions under the various Lewis acid conditions follow similar patterns.

Overall, the use of phenyl ester **2.09** has proved to be superior over methyl ester **1.136** in terms of both diastereoselectivity and ease of isolation of the major ***R,S*** diastereomer. Similarly the reaction procedure using the lithium enolate is simpler, less costly, and returns higher levels of diastereocontrol than any of the titanium enolate conditions tested. The improvement in

diastereoselectivity of the imino-aldol reaction with the phenyl ester **2.09** when using the lithium enolate compared to the titanium conditions, can be seen in the crude ^{1}H NMR spectra (**Figure 2.10**). Inspection of the NH doublets for the two diastereomers ***R,S*** and ***S,S*** at 4.25 and 4.50 ppm respectively shows a clear difference depending on the reaction conditions.

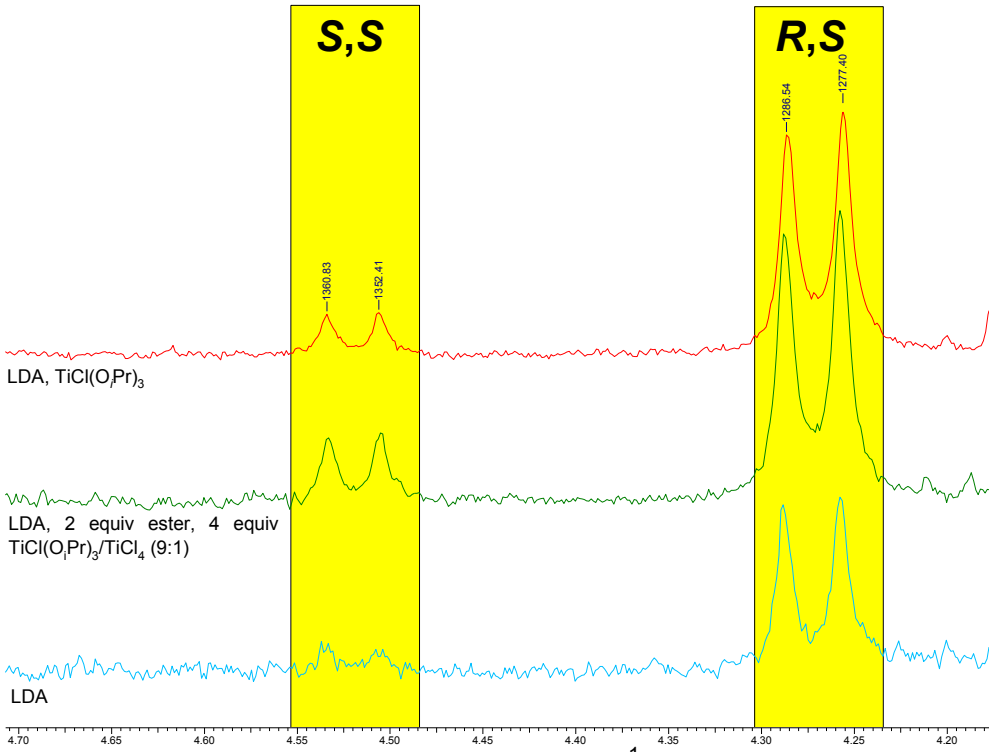


Figure 2.10: Comparison NH doublets in crude ^{1}H NMR spectra for the three sets of reaction conditions between phenyl ester **2.09** and sulfinimine **1.139**.

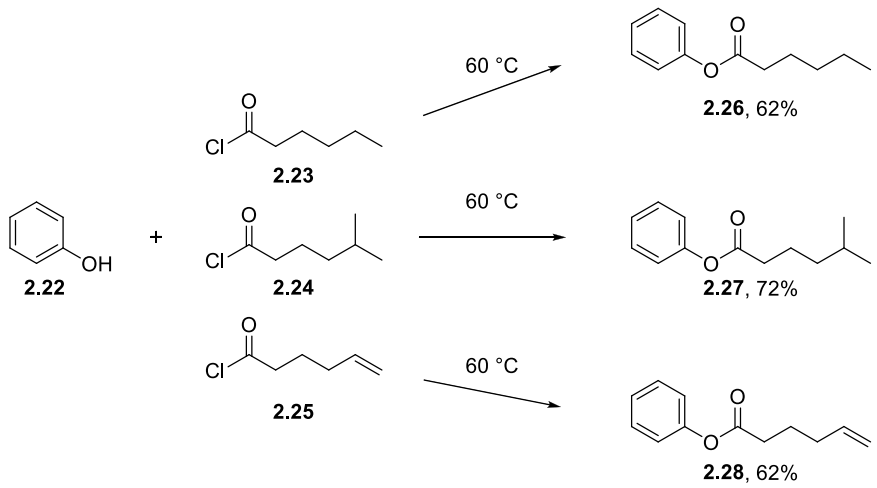
2.3.2. Tolerance of the imino-aldol reaction to variations in the alkyl chain functionality

In order to more fully understand this imino-aldol reaction and its versatility we wanted to examine the effect of the functionality of the alkyl chains on the reaction outcomes. Un-functionalised sulfinimine **2.30** and ester **2.26** analogues were therefore synthesised, as well as phenyl 5-methylhexanoate (**2.27**) and phenyl hex-5-enoate (**2.28**).

2.3.2.1. Synthesis of sulfinimine and ester analogues

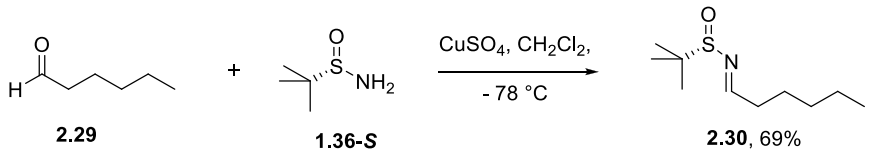
The required esters were formed by taking the respective acid chlorides (formed by reacting the corresponding carboxylic acids with oxalyl chloride in the presence of DMF) and heating these directly with phenol. These reactions

proceeded smoothly to furnish the phenyl esters in yields from 62% to 72% after purification (**Scheme 2.3.2**).



Scheme 2.3.2: Synthesis of phenyl ester analogues

The simple alkyl sulfinimine **2.30** was formed by the same condensation procedure described above with (*S*)-*tert*-butyl sulfinamide (**1.36-*S***) and commercial 1-hexanal (**2.29**) in the presence of anhydrous $CuSO_4$. The desired sulfinimine **2.30** was obtained in 69% yield after purification (**Scheme 2.3.3**).

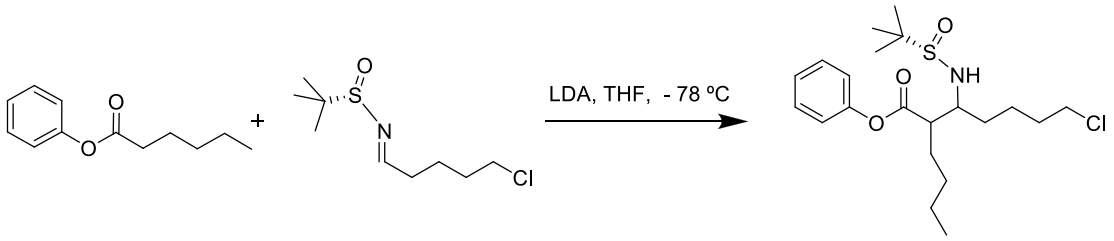


Scheme 2.3.3: Synthesis of sulfinimine **2.30**

2.3.3. Imino-aldol reactions with different sulfinimines and esters

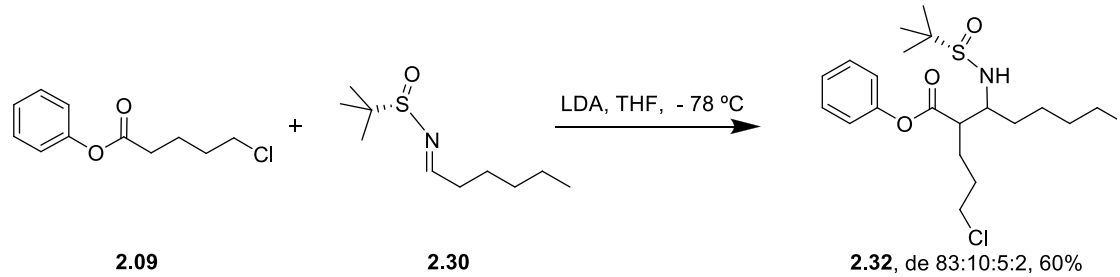
In the first imino-aldol reaction, phenyl hexanoate **2.26** was reacted with chloroalkyl sulfinimine **1.140**, to yield 4 diastereomers of **2.31** (**Scheme 2.3.4**). The yield of all of the diastereomers was 64% with 90:4:4:2 dr. From the formation of all 4 diastereomers we can deduce that the facial selectivity has been slightly eroded (compare with **Entry 1**, **Table 2.3.2**). This indicates that the presence of the chlorine on the ester portion of the chain is important for

complete facial selectivity of the reaction, although the origin of this effect is not obvious.



Scheme 2.3.4: Imino-aldol reaction with straight alkyl chain on ester portion [a]

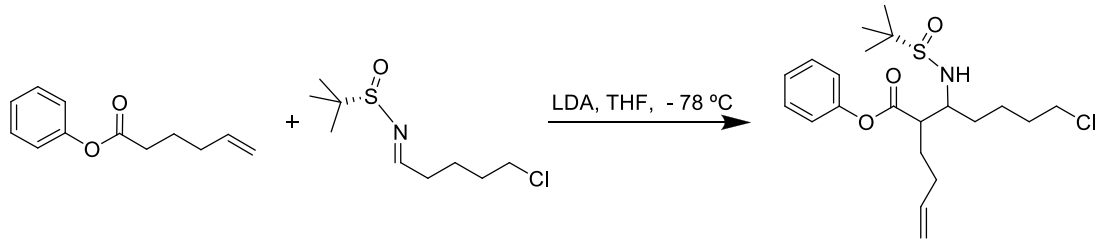
Subsequently, the chlorinated ester **2.09**, was reacted with unfunctionalised sulfinimine **2.30** to form all 4 possible diastereomers of **2.32** (**Scheme 2.3.5**). Not only was the facial selectivity eroded, but the diastereoselectivity seems to also have been eroded slightly with a *syn*:*anti* ratio of 88:12[b]. This suggests that the chlorine atom on the end of the alkyl chain of the sulfinimine helps to increase the diastereoselectivity as well as the facial selectivity.



Scheme 2.3.5: Imino-aldol reaction with straight alkyl chain on sulfinimine portion [a]

The imino-aldol reaction was then carried out between sulfinimine **1.140** and ester **2.25** containing a terminal alkene (**Scheme 2.3.6**).

[a] dr is estimated from integration of ^{1}H NMR of the crude reaction material. Diastereomers were not identified and are listed in order of yield.
[b] Diastereomers were tentatively assigned as *syn* or *anti* by analogy with chemical shifts of NH peaks in [1] for the **2.20** series of diastereomers.

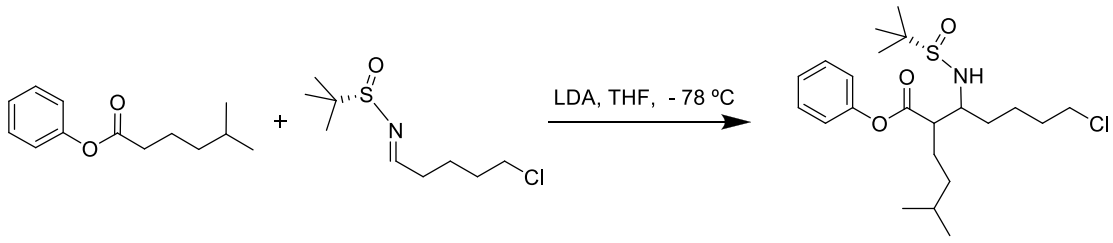


2.25 **1.140** **2.33**, 88:6:4:2, 58%

Scheme 2.3.6: Imino-aldol reaction to form **2.33**[a]

The major diastereomer, **2.33.1**, was isolated as a while crystalline solid. All 3 of the other diastereomers were distinguished by ^{1}H and ^{13}C NMR, but were not isolated. The total yield for all diastereomers was 58%, which is comparable to other unoptimised imino-aldol reactions, although the selectivity was reduced marginally compared to previously, with 88:6:4:2 dr.

The *iso*propyl ester **2.24**, was successfully reacted with **1.140** and the major diastereomer (**2.34.1**) was isolated as a white solid (**Scheme 2.3.7**).



2.24 **1.140** **2.34**, 91:5:2:2, 56%

Scheme 2.3.7: Imino-aldol reaction to form **2.34**[a]

Once again, all 4 diastereomers were distinguishable in the crude reaction mixture, with a total yield of all 4 diastereomers of 56%. The selectivity seen (91:5:2:2 dr) varied little from that previously observed for phenyl hexanoate (**2.26**). Similarly, a slight drop in facial selectivity compared to chloro-ester **2.09**, was seen again.

From all of these results it can be seen that the inclusion of the chloroalkyl group is important in obtaining very high facial selectivity in the imino-aldol reactions. Interestingly, the chlorine on the sulfinimine reagent appears to have a more pronounced effect on the diastereoselectivity of the reaction than that on

[a] dr is estimated from integration of crude ^{1}H NMR. Diastereomers were not identified and are listed in order of yield.

the ester. These results have confirmed that the inclusion of chlorine on both the sulfinimine and ester portions appears to be important for very high facial selectivity and a diastereoselectivity of 96:4:0:0 dr.

2.3.4. Equivalents of ester

Previously, 2.0 equivalents of the ester had been used in all of the reactions. However, it was desirable to increase the efficiency of the reaction by reducing the ester stoichiometry. As such, two parallel reactions were set up using 1.0 and 1.3 equivalents of ester respectively. Both reactions proceeded smoothly to give imino-aldol products. Where 1.0 equivalent of ester was used, 15% of the sulfinimine was left unreacted (estimated by integration of crude ^{1}H NMR). This compared to 2% when 1.3 equivalents was employed. Altering the stoichiometry of the ester did not affect the diastereoselectivity of the imino-aldol reaction. As such it was decided to use 1.3 equivalents of ester to balance efficiency of conversion and economy of Lewis acid use.

2.4. Conclusions

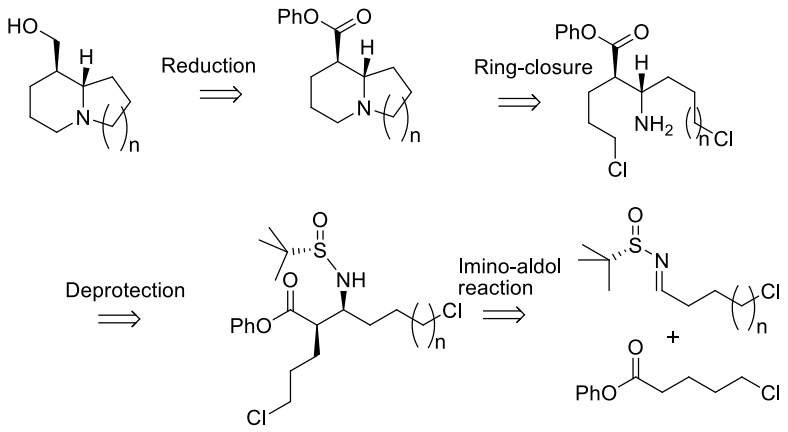
Our investigations into the imino-aldol reaction found that the best conditions for tashiromine (**1.72**) and epilupinine (**1.71**) precursors **1.140** and **1.139** involved using LDA to deprotonate 1.3 equivalents of phenyl ester **2.09** in THF at –78 °C and then subsequent reaction of the enolate with 1 equivalent of sulfinimine **1.139** or **1.140.** This formed imino-aldol products **2.19** and **2.20** in 60% and 78% respectively with 93:7:0:0 and 94:6:0:0 dr. A selection of other aliphatic esters and sulfinimines were synthesised and used in the imino-aldol reaction to determine the tolerance of the reaction to different functionality. These were found to give reduced diastereoselectivities compared to the use of alkyl chains with terminal chlorine atoms. With these optimised reaction conditions having been developed, the next stage was to apply them to the synthesis of natural products epilupinine and tashiromine, as well as other cyclic amines which will be discussed in Chapter 3.

3. Synthesis of saturated nitrogen heterocycles

3.1. Epilupinine and Tashiromine

3.1.1. Retrosynthetic analysis of epilupinine and tashiromine

Previously in the Brown group, enantiomerically enriched natural products (+)-epilupinine (**(+)-1.71**) and (+)-tashiromine (**(+)-1.72**) have been synthesised.[60] However, both were prepared with unsatisfactory levels of stereocontrol in the key imino-aldol reaction, ultimately leading to the natural products with moderate enantiopurity (50% ee and 66% ee respectively). With the optimisation of the imino-aldol reaction conditions giving imino-aldol products with very high selectivity, we were in a position to complete a stereocontrolled synthesis of (–)-epilupinine (**(–)-1.71**) and (–)-tashiromine (**(–)-1.72**).

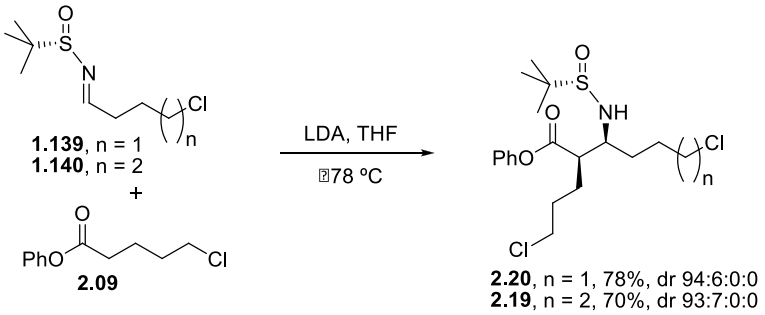


Scheme 3.1.1: Proposed retrosynthesis of (–)-epilupinine and (–)-tashiromine

Our retrosynthetic analysis of the alkaloids identified an *N*-protected β-amino acid as a suitable advanced intermediate (**Scheme 3.1.1**). This amino acid could be formed by the stereoselective imino-aldol reaction that had been optimised between *tert*butyl sulfinimine and a phenyl ester in conjunction with chloro- substituents to enable simple cyclisation at a later stage.[72]

3.1.2. Synthesis of epilupinine and tashiromine

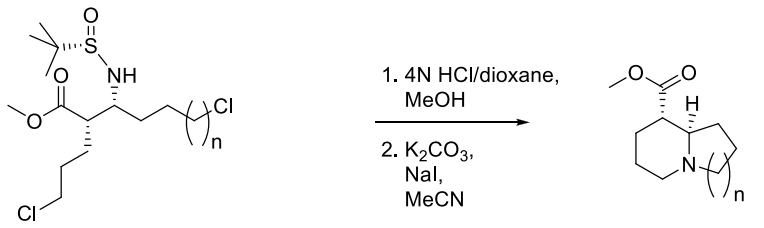
The first stage of the synthesis of epilupinine and tashiromine involved scaling up the optimised imino-aldol reaction on both chain lengths of the sulfinimine (**Scheme 3.1.2**) to produce sufficient quantities of the imino-aldol products to carry through the synthesis.



Scheme 3.1.2: Imino-aldol reaction on epilupinine and tashiromine precursors

Where previous reactions had been carried out with around 1 mmol of sulfinimines **1.139** and **1.140** (reactions on smaller scales than this proved capricious), the scaling up to 12 mmol was achieved with ease. The selectivities remained consistent at 96:4 and 93:7 dr for **2.19** and **2.20**. The pure major ***R,S*** diastereomers were isolated away from the other diastereomers in yields of 78 and 70% respectively by a combination of crystallisation and column chromatography.

With sufficient material from the imino-aldol reactions in hand, the deprotection-cyclisation reactions were performed. In the previous Brown group synthesis this was carried out in a one-pot procedure (**Scheme 3.1.3**).[60] The *tert*butyl sulfinyl group was removed under acidic conditions using a solution of conc. HCl(aq) in 1,4-dioxane and methanol followed by evaporation of the solvents and cyclisation under basic conditions (K_2CO_3 and NaI in acetonitrile) to furnish the bicyclic amines **1.143** and **1.144**.

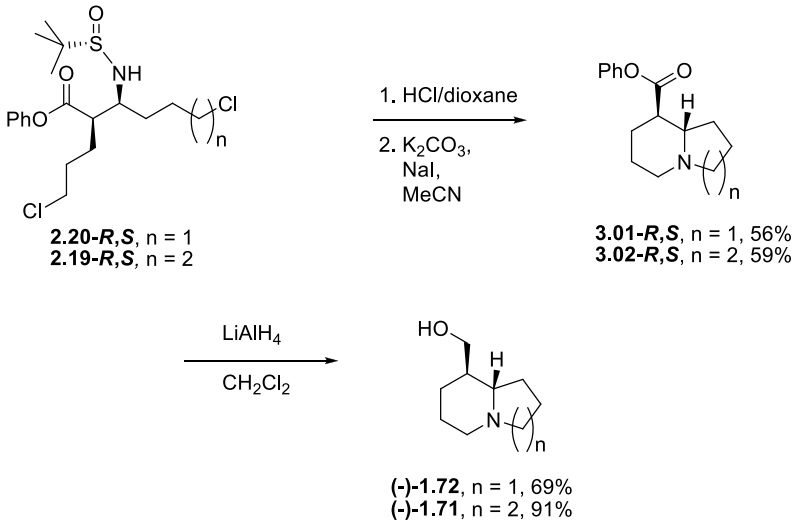


1.141, n = 1
1.142, n = 2

1.143, n = 1, 68%
1.144, n = 2, 86%

Scheme 3.1.3: Deprotection and cyclisation with methyl ester system[60]

However, in this work we found that when the methyl ester **1.136** was replaced by the more labile phenyl ester **2.09**, partial transesterification to the methyl ester **1.136** was observed under these acidic deprotection conditions. Fortunately, the imino-aldol products were soluble in 1,4-dioxane alone, making the mixture with methanol unnecessary. When the reactions were carried out with conc. HCl(aq) in 1,4-dioxane, followed by basic cyclisation, the reactions proceeded smoothly to yield the bicyclic amines **3.01** and **3.02**. Purification of these tertiary amines was carried out by column chromatography on Brockmann grade III basic alumina gel to give the esters in 56 and 59% yields respectively (**Scheme 3.1.4**).



2.20-*R*,*S*, n = 1
2.19-*R*,*S*, n = 2

3.01-*R*,*S*, n = 1, 56%
3.02-*R*,*S*, n = 2, 59%

(-)-1.72, n = 1, 69%
(-)-1.71, n = 2, 91%

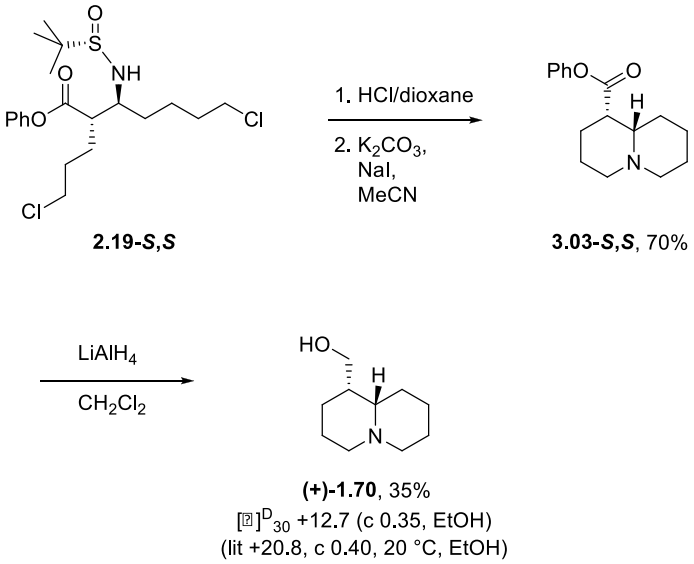
Scheme 3.1.4: Completion of the total synthesis of (–)-epilupinine and (–)-tashiromine

The final step in the synthesis was the reduction of the ester to the primary alcohol. We had anticipated that the more reactive phenyl ester may be reduced under mild conditions in the presence of $NaBH_4$. However, attempts at using $NaBH_4$ in MeOH to reduce the phenyl ester led only to the transesterification to

the methyl ester, which was not reduced under these conditions. Gratifyingly when the phenyl esters **3.01** and **3.02** were reduced with $LiAlH_4$, the reaction yielded the natural products (–)-epilupinine (**(–)-1.71**) and (–)-tashiromine (**(–)-1.72**) (**Scheme 3.1.4**). Purification of these amines away from the phenol proved difficult by conventional column chromatography. However, use of strong cation exchange solid phase extraction cartridges (Biotage SCX-2 SPE cartridges were used) yielded the natural products in yields of 69 and 91% respectively. The spectrographic data for the synthetic material closely matched those reported for the natural products. Both natural products synthesised had the expected negative values for their optical rotation (epilupinine, **1.71**, $[\alpha]_D^{26}$ – 29.2 (*c* 1.00, EtOH), lit.[51] $[\alpha]_D^{20}$ – 33.0 (*c* 0.72, EtOH); tashiromine, **1.72**, $[\alpha]_D^{26}$ – 43.6 (*c* 1.02, EtOH), lit.[62] (+)-enantiomer $[\alpha]_D^{20}$ + 44.8 (*c* 1.58, EtOH)). Thus the total synthesis of the two natural products (–)-epilupinine and (–)-tashiromine was completed in 6 steps with 19 and 12% overall yield respectively.

3.1.3. Stereochemistry of minor diastereomers

After the success of synthesising (–)-epilupinine (**(–)-1.71**) and (–)-tashiromine, (**(–)-1.72**) we wanted to determine the stereochemistry of the minor diastereomer obtained from the imino-aldol reactions (**Scheme 3.1.2**). In order to do this we took the purified minor diastereomer **2.19-*S,S*** and followed the same synthetic route as used previously, to synthesise lupinine and confirm the stereochemistry by comparison of optical rotation of our synthetic product with literature values for the natural product (**Scheme 3.1.5**).



Scheme 3.1.5: (+)-Lupinine synthesis

The deprotection and cyclisation of the minor imino-aldol product **2.19-*S,S*** gave the cyclised amine **3.03-*S,S*** in 70% yield. The NMR spectrum for this product was different to that for the cyclised major diastereomer **2.19-*R,S***, proving that it is one of the *anti* diastereomers rather than the (+)-enantiomer of the *syn* product already formed. Reduction by $LiAlH_4$ yielded the *anti* product **1.70**, which gave spectroscopic data consistent with lupinine. Furthermore, it was shown to be the (+)-enantiomer by measuring the optical rotation. (+)-Lupinine is the unnatural enantiomer of (–)-lupinine. (–)-Lupinine has been isolated from a variety of sources including *Anabasis aphylla*, *Lupinus luteus* and *L. palmeri.*[44] Both enantiomers have been synthesised previously and are well characterised in the literature.

3.1.4. Stereochemical determination

In previous publications it has been suggested that the imino-aldol reaction with *tert*-butyl sulfinimines might proceed *via* a closed transition state.[31] When considering these reactive pathways it is assumed that the bulky *tert*-butyl group is not positioned underneath the six-membered ring of the proposed cyclic transition state but pointing away from it to minimise steric interactions with the reacting enolate. Thus, there are four different approaches to consider for the reactants, depending on if there is *Re* or *Si* faced attack on the

sulfinimine and whether the *E* or *Z* enolates are involved. The stereochemistry of the minor diastereomer indicates very high facial selectivity with use of lithium enolates.

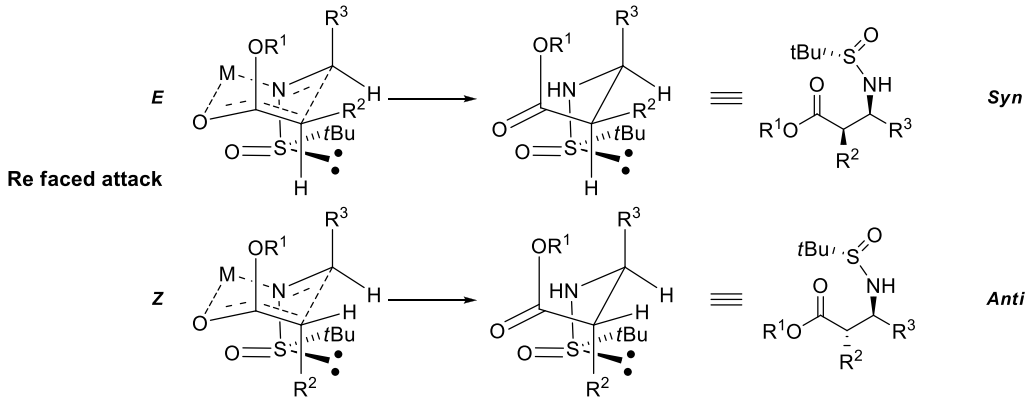


Figure 3.11: *Re* faced attack on sulfinimine

Both the major and minor products we observed can be formed by *Re* faced attack of the enolate on the sulfinimine (**Figure 3.11**). In the closed Zimmerman-Traxler type transition state the oxygen on the sulfur is positioned below the coordinating metal species and this could be said to be stabilised in this position. When the *E* enolate is formed, the major *syn* diastereomer will be formed, and from the *Z* enolate the *anti* diastereomer is formed.

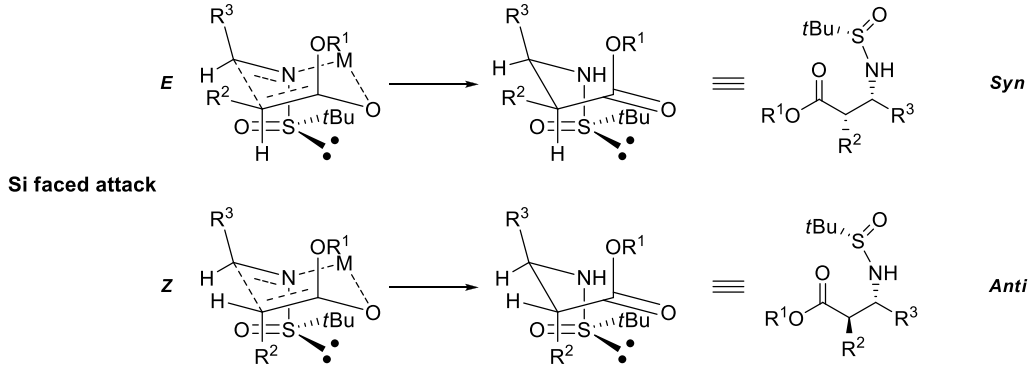


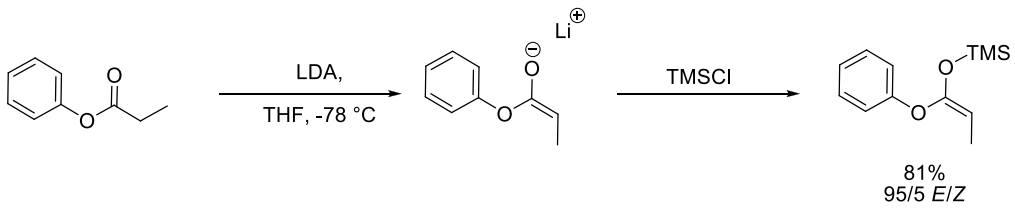
Figure 3.12: Closed transition state *Si* faced attack on sulfinimine

Conversely if the *Si* face were to be attacked, the oxygen now cannot coordinate to the metal, if we are to avoid the *tert*-butyl group being positioned beneath the ring (**Figure 3.12**). The exclusive formation of products derived from *Re* face attack in the tashiromine and epilupinine synthesis suggests that the coordination of the oxygen is an important factor in determining the facial

selectivity. If this model is true then the *syn*/*anti* ratio is determined by the *E*/*Z* ratio of the enolate. Ester enolates are known to favour the *E* conformation and so preference of the *syn* product results.[73] However, these arguments are not readily reconciled with the variation in diastereoselectivites observed with apparently minor changes to the structures of ester and sulfinimine reported above. Although the model broadly accounts for the observed results, more subtle factors must also be involved.

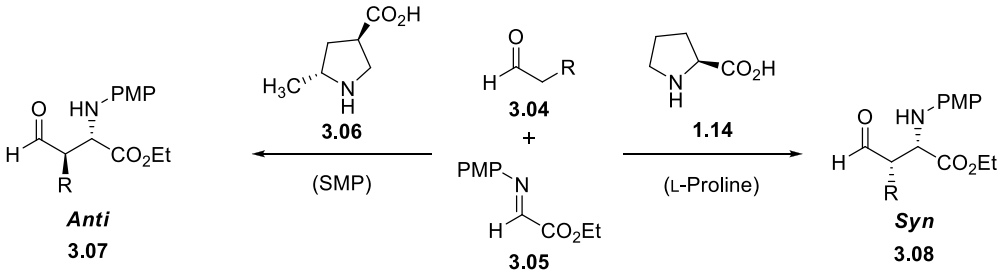
3.1.5. Attempted synthesis of minor *anti* diastereomer

After determining the stereochemistry of the minor diastereomer it was decided to investigate the possibility of directing the selectivity of the imino-aldol reaction to favour this *anti* diastereomer. Initial attempts were made to understand the role of the enolate stereochemistry in the reaction by trapping the enolates with various silyl groups, but these attempts failed. There are relatively few examples in the literature where phenyl esters have been trapped, and the few that have been reported are for simpler compounds (**Scheme 3.1.6**).[74]



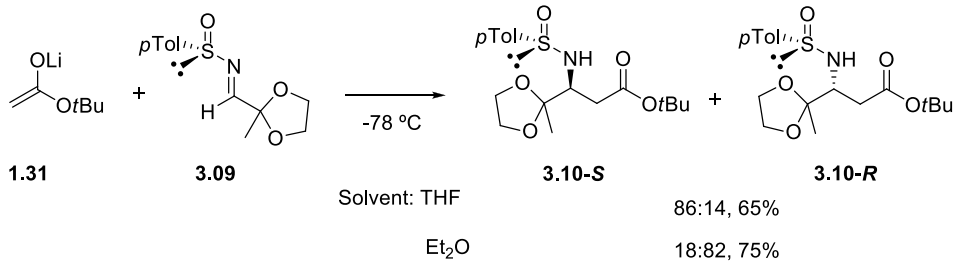
Scheme 3.1.6: Formation of phenoxy-1-(trimethylsiloxy)propene[74]

We then examined the literature for examples of imino-aldol reactions that enabled a switch in the stereochemical outcome. Most of the examples relied upon the use of differing imine protecting groups to favour either the *syn* or *anti* products. Organocatalysis allows for a switchover in selectivity through selection of different catalysts. L-Proline (**1.14**), the most widely used catalyst, typically yields the *syn* diastereomer. Barbas has developed the use of a range of organocatalysts that have been applied to an imino-aldol type reaction (**Scheme 3.1.7**). This includes *anti* selective (*S*)-2-methoxymethylpyrrolidine **3.06** (SMP)[12] which gives the *anti* diastereomer **3.07,** whereas when *syn* selective L-Proline **1.14** is employed *syn* diastereomer **3.08** results.[75]



Scheme 3.1.7: Example of varying the organocatalyst to give either *anti* or *syn* products

Fujisawa[76] *et al*. induced a switchover in diastereoinduction with different reaction conditions, both by changing the solvent and by changnig the metal species and additives used (**Scheme 3.1.8**). One of their findings was that by switching solvents from THF to diethyl ether for the imino-aldol reactions, a switchover in diastereofacial selectivity was observed.

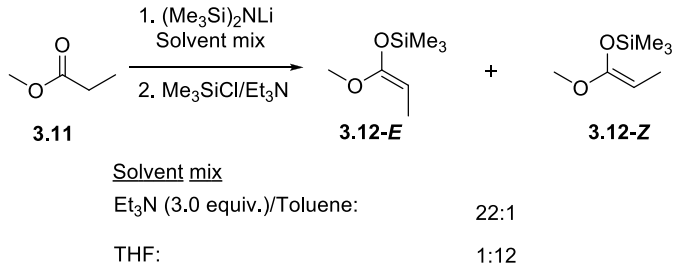


Scheme 3.1.8: Switchover in selectivity with solvent recorded by Fujisawa *et al*.[76,77]

Parellel reactions were carried out on our imino-aldol reaction using THF and diethyl ether. Disappointingly, these both gave the same stereoselectivity favouring the same *syn* diastereomer. The reaction with diethyl ether showed a slight drop in selectivity with 90:10 dr compared to 93:7 dr for THF, and also a drop in yield, with 56% of isolated diastereomers.

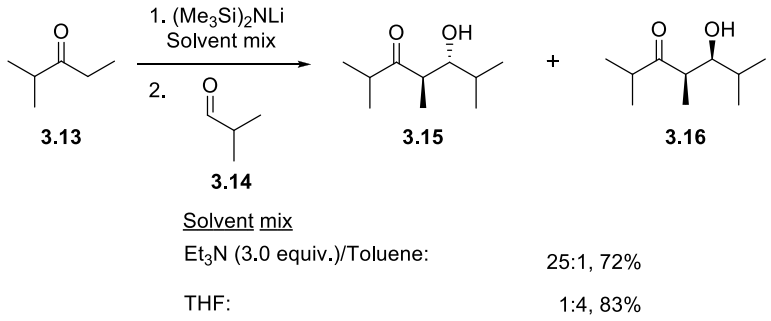
Our literature search then broadened to include the classic aldol reaction including work carried out in the Collum group, where diastereoselectivities were altered by changing the amount of coordinating species in the reaction mixture.[78] Their investigations focused on altering reaction conditions to alter

the *E*/*Z* ratios. It was found that by using LiHMDS as a base together with Et_3N as an additive in toluene, the formation of *E* enolates is favoured, whilst LiHMDS in THF favours *Z* enolate formation (**Scheme 3.1.9**). It should be noted that the reported studies focused on methyl esters rather than phenyl esters.



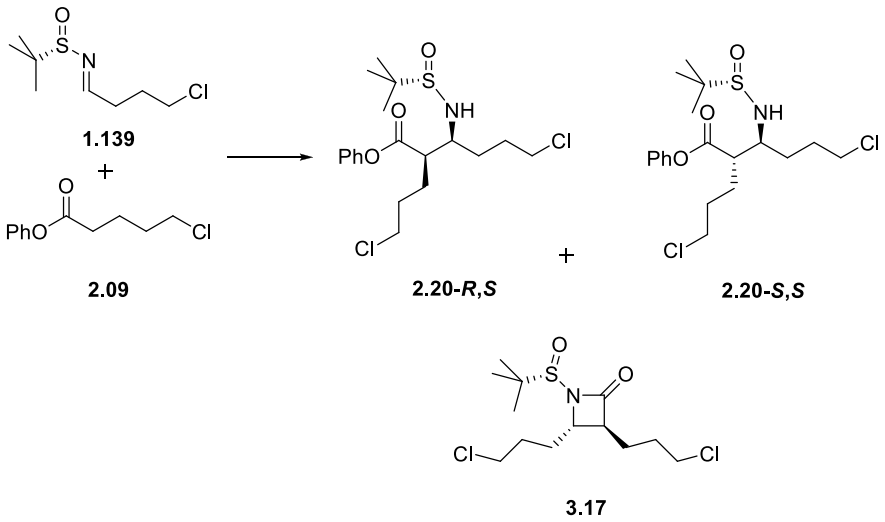
Scheme 3.1.9: Change of solvent conditions was found to alter E/Z ratio in Collum's work[78]

They applied these reaction conditions to a few aldol reactions using various ketones to demonstrate its utility, and found that the switchover in *E*/*Z* selectivity translated to a switch in *syn*/*anti* ratio (**Scheme 3.1.10**).



Scheme 3.1.10: Reversal of simple diastereoselection in aldol reactions with different enolisation conditions[78]

With the potential influence of enolate geometry on the imino-aldol reaction, where a closed transition state is involved, we wanted to investigate whether altering the enolate geometry would affect diastereoselectivty. We therefore applied these conditions to our system (**Scheme 3.1.11**). At first glance our results seemed to show a variation of the diastereoselectivity depending on the reaction conditions, despite the fact that a switchover from *syn* to *anti* diastereoselectivity is not observed.



Scheme 3.1.11: Products formed in imino-aldol reactions under modified conditions.

When LiHMDS/toluene/Et_3N conditions (favours *E* enolate) were used, the ratio of the major ***R,S*** and minor ***S,S*** diastereomers in the crude reacation material by ^1H NMR was observed to be 97:3 dr respectivley. However, when LiHMDS in THF (favours *Z* enolate) was used, an increase in the amount of the minor diastereomer was observed, with 78:22 dr (***R,S***:***S,S***). However, closer inspection of the fractions isolated by column chromatography revealed that a crystaline side-product had also formed. Characterisation by X-ray crystallography revealed that the structure of the side product was β-lactam **3.17** with *anti* stereochemistry at C-5 and C-10 centres (**Figure 3.13**).

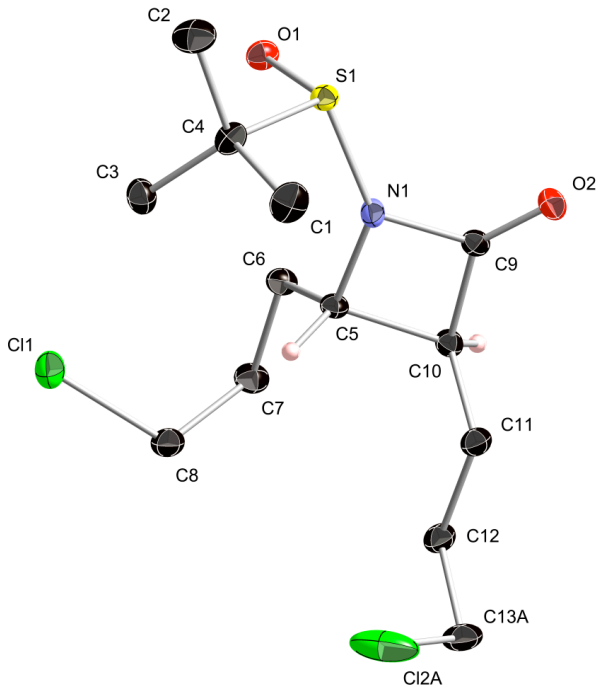
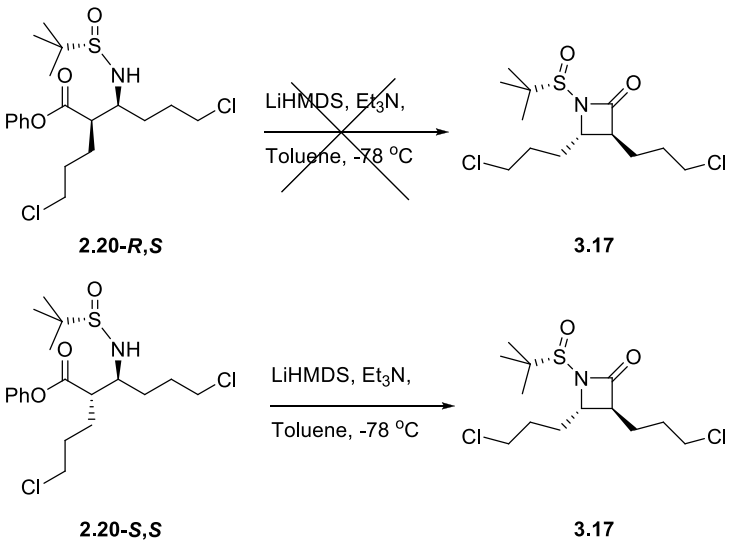


Figure 3.13: X-ray crystallography structure of **3.17**. Thermal ellipsoids drawn at the 35% probability level. (Selected hydrogens and disorder omitted for clarity.)

The synthesis of β-lactams *via* the condensation of enolates and sulfinimines has been established since the first discovery in 1943,[79,80] as has the cyclisation of β-amino esters to form the β-lactams.[80] In the light of our X-ray structure, this would imply that only the minor *anti* diastereomer of the β-amino ester was cyclising.

In order to test whether this β-lactam could be formed from the imino-aldol product, the *syn* and *anti* diastereomers were separately subjected to LiHMDS and Et_3N in toluene (**Scheme 3.1.12**). With the *syn* diastereomer under these conditions, the cyclised product was not formed. However, when the *anti* diastereomer was reacted, the β-lactam was formed. These confirmed that where we appeared to have near complete conversion to the major *syn* diastereomer, we were simply seeing the formation of the β-lactam side product from the minor diastereomer. After the event, it is clear that cyclisation of the *anti* stereoisomer is more facile due to the reduced steric interactions encountered during the closure of the *trans*-disubstituted system.



2.20-*R*,*S* **3.17**

2.20-*S*,*S* **3.17**

Scheme 3.1.12: Synthesis of β-lactam **3.17**

Although some modest increase in the levels of *anti* selectivity was achieved (observed by isolation of both the *anti* diastereomer and the *anti* β-lactam), Collum's conditions did not offer a complete reversal in selectivity. Other approaches to favouring the *anti* diastereomer and preventing cyclisation to the β-lactam were not investigated, as our focus switched instead to the synthesis of the more complex tetra-cyclic alkaloid allomatrine (**1.121**), which is described in the following section.

3.2. A Revised Approach Towards (+)-Allomatrine

The lupin alkaloid allomatrine (**Figure 3.14**, **(+)-1.121**) has the same *syn* stereochemistry as epilupinine (**1.71**) and tashiromine (**1.72**) at the C5, C6 centres, so it was envisaged that the imino-aldol chemistry already developed could be used as a basis for the synthesis of this natural product.

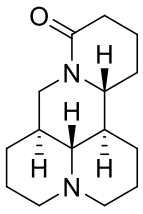
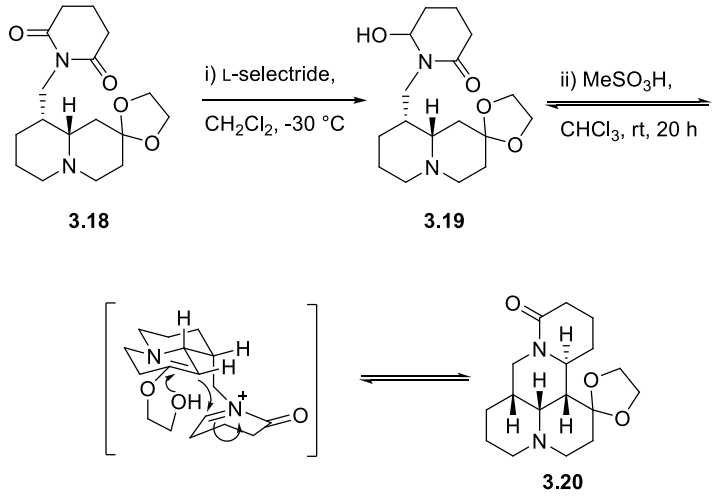


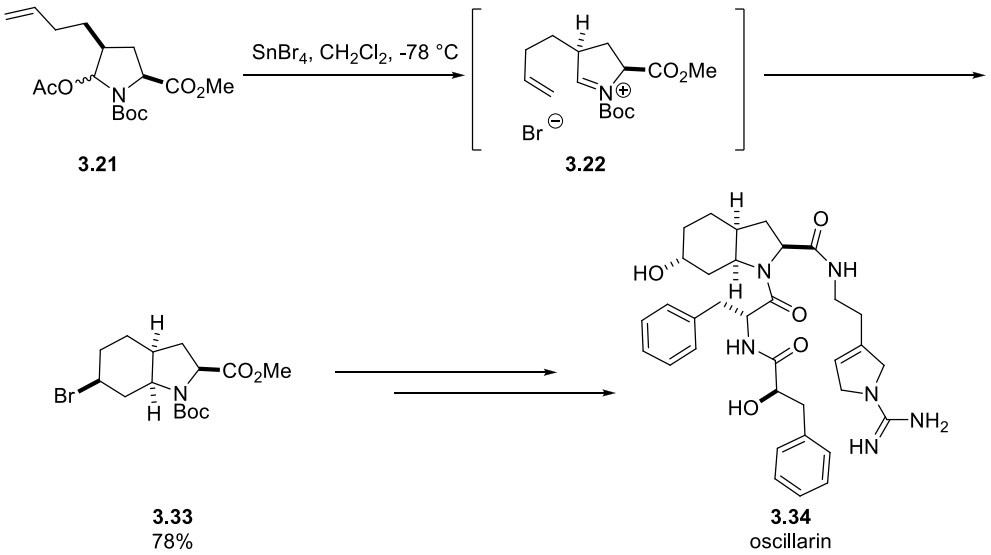
Figure 3.14: (+)-Allomatrine, **(+)-1.121**

An interesting synthesis of matrine (**1.120**) (of which allomatrine, **1.121**, is a stereoisomer) by Chen *et al.* was published in 1986.[81] In their synthesis the final cyclisation was carried out by the intra-molecular reaction of an acetal-quinolizidinone onto an iminium ion (**Scheme 3.1.2**). The enol intermediate is activated towards nucleophilic attack by the presence of the oxygen, allowing successful attack onto the electrophilic iminium ion. The reaction is believed to be reversible and so equilibrates to give the most thermodynamically stable product, **3.20** precursor to (±)-matrine **1.120**.



Scheme 3.2.1: Key steps in Chen's synthesis of (±)-matrine.[81]

The related aza-Prins reaction offers examples of nucleophilic attack of unactivated olefins onto iminium ions. In their synthesis of the marine natural product oscillarin (**3.34**), Hanessian *et al*. applied an *N*-acyloxyminium ion aza-Prins carbocyclisation which yielded octahydroindole **3.33** (**Scheme 3.2.2**).[82] The tin bromide mediated reaction of a tethered unfunctionalised alkene onto an *N*-Boc acyliminium selectively inserted two stereocentres. Further investigations by Hanessian *et al*. revealed that analogous results, although slightly less selective, could be achieved using $SnCl_4$ or by cyclisation onto 6-acetoxy-*L*-pipecolic acid analogues. They did note the apparent importance of an antiperiplanar alignment of the olefin and the iminium ion as well as minimal $A^{1,2}$ strain in determining the stereochemical outcome.



Scheme 3.2.2: Example of aza-Prins reaction in synthesis of oscillarin

Application of a related cyclisation approach to the synthesis of (+)-allomatrine (**(+)-1.121**) is anticipated to lead to the thermodynamic product: namely the *trans*-decalin type all-chair conformation of the (+)-allomatrine precursor **3.36** under equilibrating conditions (**Figure 3.15**).

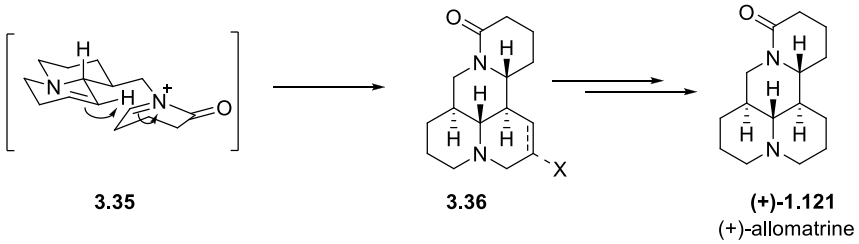
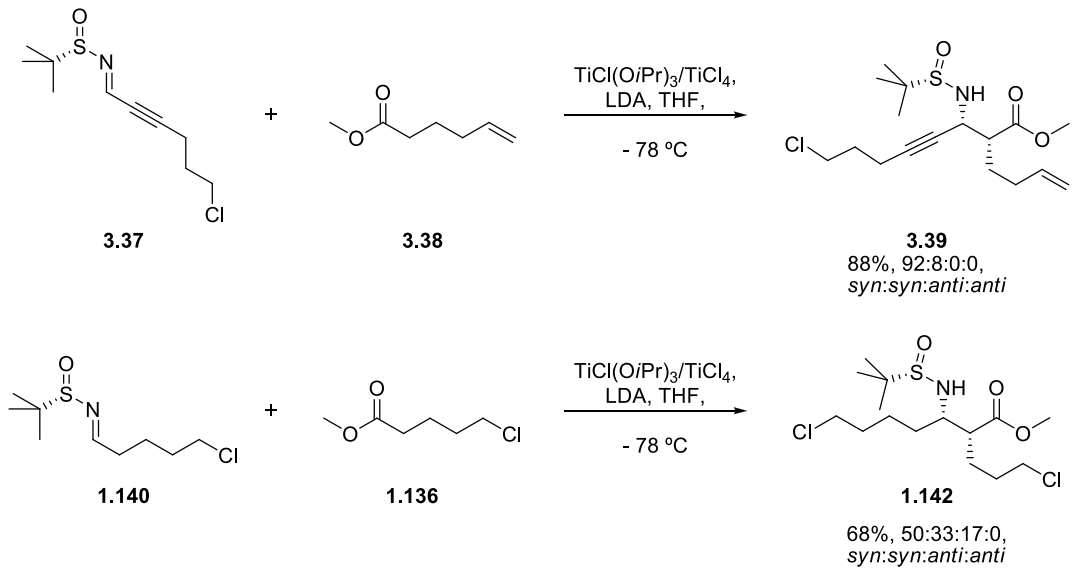


Figure 3.15: Proposed synthesis of (+)-allomatrine

In order to include the required alkene for the cyclisation it was necessary to include the unsaturation from the start of the synthesis in the sulfinimine. It was decided to do this by incorporating the α,β-alkynyl functionality into the sulfinimine (**3.46**). This would have two advantages over use of the alkene; first the potential for increased selectivity with the imino-aldol reaction, and secondly the possibility of later functionalisation to encourage the final cyclisation, should the unfunctionalised alkene fail to cyclise.

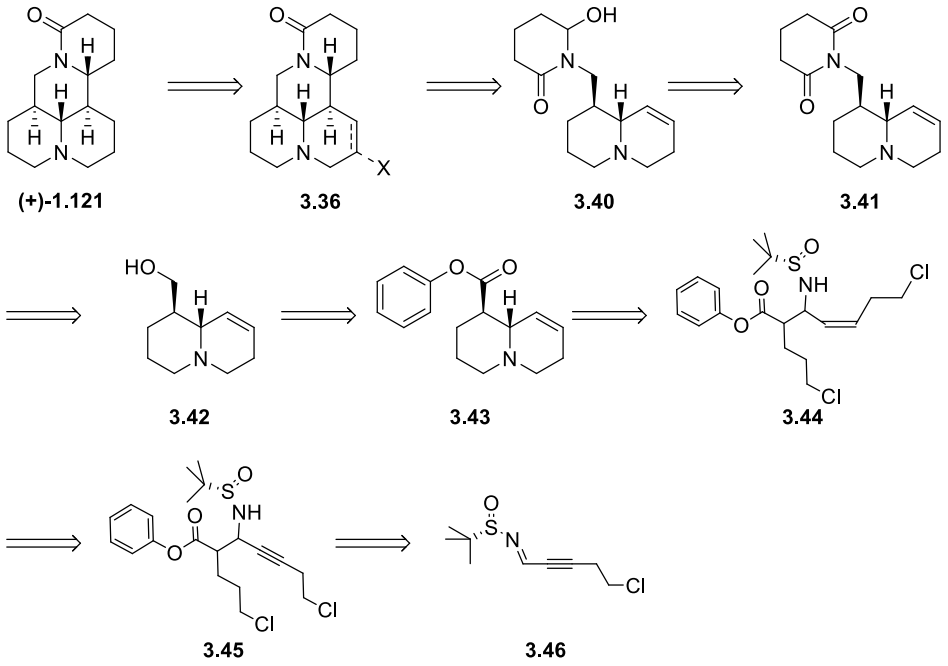
We anticipated an increase in selectivity of the imino-aldol reaction could arise as a result of a more favourable transition state. As discussed earlier (**Section**

3.1.4), the proposed Zimmerman-Traxler transition state is thought to involve the coordination of the oxygen of the sulfinyl to the Lewis-acid metal as deduced by the observation of exclusive *Re* face attack. Since the sulfinimines preferentially adopt the *E* configuration this would force the larger substituent on the sulfinimine into the usually unfavourable pseudo-axial position. We hoped that by including the relatively compact alkynyl functionality in the sulfinimine, unfavourable $A^{1,3}$ strain interactions in this pseudo-axial position would be minimised, and consequently, diastereoselectivity would increase. Indeed, previous work carried out in our own group had found that incorporation of alkyne functionalities could increase diastereoselectivity (**Scheme 3.2.3**). Previous reactions between alkynyl sulfinimine **3.37** and methyl ester **3.38** gave a stereoselectivity of 92:8:0:0, whilst a similar reaction with chloro-alkyl sulfinimine **1.140** and methyl ester **1.136** had a much poorer selectivity of only 50:33:17:0.[60]



Scheme 3.2.3: Miller's results for imino-aldol reactions of alkynyl and alkyl sulfinimines.[60]

By combining our newly established imino-aldol reaction conditions with an aza-Prins type cyclisation strategy and the alkynyl functionality, a new short retrosynthesis of (+)-allomatrine (**(+)-1.121**) was proposed (**Scheme 3.2.4**).

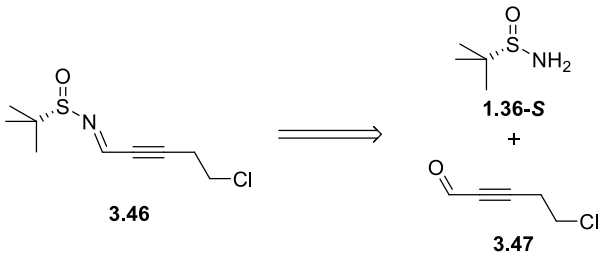


Scheme 3.2.4: Proposed retrosynthesis of allomatrine

Starting from alkyne **3.46**, an imino-aldol reaction would furnish β-amino ester **3.45**. Selective reduction to the *Z* alkene, followed by cyclisation and reduction would yield alcohol **3.42**. Mitsinobu reaction with glutarimide would introduce the third ring. Selective reduction and subsequent acid-catalysed aza-Prins type reaction would insert the final two stereocentres and close the final ring. Further manipulations, dependent on the exact cyclisation product, could then be carried out to furnish the desired (+)-allomatrine (**(+)-1.121**). It was hoped that this short synthesis would neatly provide the first synthesis of enantiomerically pure allomatrine (**1.121**).

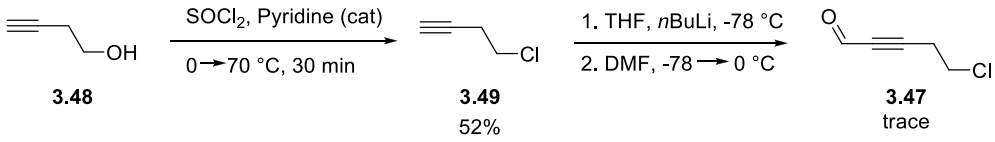
3.2.1. Attempted Synthesis of Allomatrine

The first stage in the synthesis was the preparation of sulfinimine **3.46** from aldehyde **3.47**, which in turn could be synthesised from 4-butyn-1-ol (**3.48**).



Scheme 3.2.5: Retrosynthesis of sulfinimine **3.46**

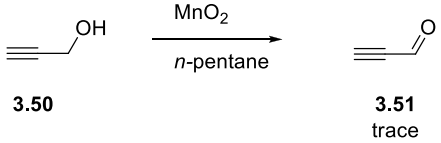
4-Butyne-1-ol (**3.48**) was chlorinated with one equivalent of thionyl chloride and catalytic pyridine. Distillation gave the desired product in 52% yield (**Scheme 3.2.6**).



Scheme 3.2.6: Attempted synthesis of 5-chloropent-2-ynal

The formylation of 4-chlorobutyne (**3.49**) was attempted by reacting the lithiated chlorobutyne with DMF. Unfortunately only a trace amount of aldehyde **3.47** was observed by ^{1}H NMR after work up and distillation of the solvent.

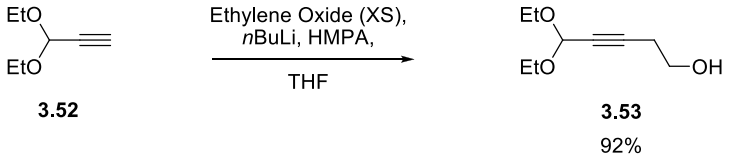
Our attention then switched to the introduction of the aldehyde prior to the chloroalkyl chain. The oxidation of propargyl alcohol (**3.50**) by manganese(IV) oxide was carried out in *n*-pentane. Distillation of the solvent left a mixture of products including some aldehyde (**3.51**), that we were unable to isolate due to its low boiling point (**Scheme 3.2.7**).



Scheme 3.2.7: Attempted oxidation of propargyl alcohol

Since the isolation of volatile aldehyde **3.51** was proving tricky, the protected aldehyde diethoxypropyne, **3.52** (which is commercially available) was used. Initial attempts at the alkylation of diethoxypropyne (**3.52**) with 1-bromo-2-chloroethane failed, and so an alternative approach was sought. Using literature

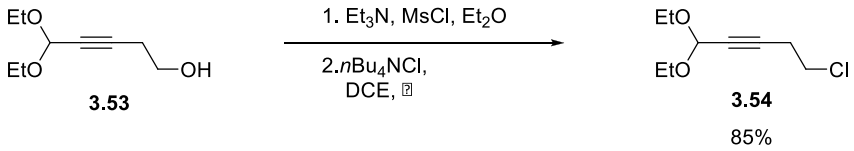
precedent diethoxypropyne (**3.52**) was deprotonated by *n*BuLi in THF with HMPA as an additive.[83] This was then heated at reflux with an excess of ethylene oxide to furnish alcohol **3.53** in 92% yield (**Scheme 3.2.8**).



3.52 **3.53** 92%

Scheme 3.2.8: Synthesis of alcohol **3.53**

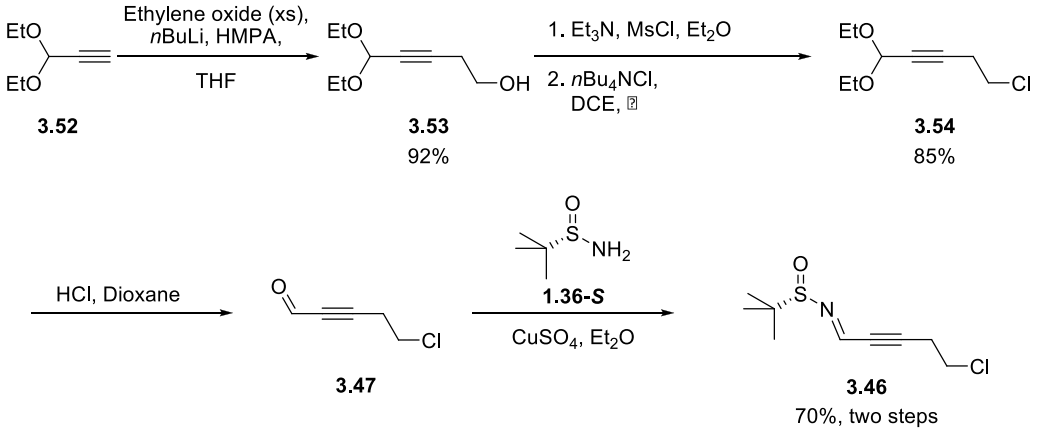
A one step mesylation-chlorination procedure using 2,6-lutidine, LiCl and methyl chloride in DMF gave the desired haloalkyne **3.54** in 26%. Also isolated in lower yields were the mesylated product and the eliminated product. To obtain improved yields, a literature procedure was applied where the pre-formed mesylate was chlorinated using nBu$_4$NCl, returning the desired product, **3.54**, in 85% (**Scheme 3.2.9**).[84]



3.53 **3.54** 85%

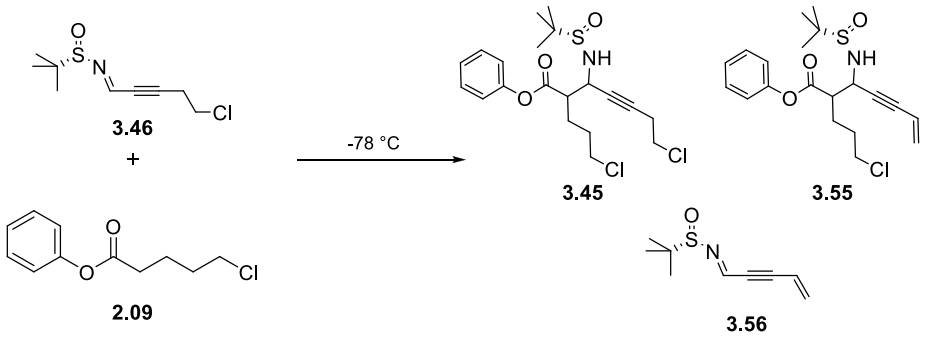
Scheme 3.2.9: Mesylation and chlorination.

In order to avoid having to handle the volatile aldehyde, the direct formation of the sulfinimine (**3.46**) from the acetal (**3.54**) was attempted. Ellman *et al.* used PPTS and Ti(O*i*Pr)$_4$ as well as $CuSO_4$ for the formation of sulfinimines from aldehydes and ketones,[3] and both of these two acidic procedures were attempted on our acetal with the anticipation that they would both deprotect the acetal and condense with the sulfinamide. Both reactions, however, failed to yield the desired product. This approach was abandoned and the acetal was deprotected and reacted in two steps. We found that the best analytical method for following the acetal deprotection was by GC, which allowed us to determine when the hydrolysis had gone to completion accurately. In order to avoid losing the volatile aldehyde upon concentration, the crude reaction mixture was extracted into Et_2O and used without purification as a solution in the sulfinimine formation.



Scheme 3.2.10: Synthesis of alkynyl sulfinimines

With the sulfinimine **3.46** in hand, the imino-aldol reaction was investigated by applying our optimised conditions (LDA in dry THF). Under these conditions it was found that the imino-aldol product **3.45** was formed in a yield of 51%. It was also found however, that another 17% of the imino-aldol product had undergone elimination of the chloride under these conditions to give the conjugated enyne **3.55**. Additionally, the diastereoselectivity of **3.45** was rather disappointing at 50:30:20 dr of the three observed diastereomers (stereochemical determination was not carried out).



Scheme 3.2.11: Imino-Aldol reaction under various conditions

This imino-aldol reaction was then carried out under three different reaction conditions used previously, to attempt to reduce the undesired elimination side reaction and improve the diastereoselectivity. First, the imino-aldol reaction was carried out with LiHMDS, Et_3N and toluene. This resulted in none of the desired imino-aldol product **3.45**, or the eliminated imino-aldol product **3.55**. Instead, the major product observed was the eliminated sulfinimine **3.56** (30%), which was

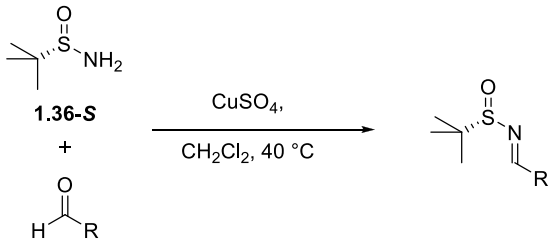
present along with starting materials. When the reaction was carried out using LDA to form the enolate, followed by transmetallation to $TiCl(O\textit{i}Pr)_3$, a complex mixture of the desired (**3.46**) and eliminated (**3.55**) imino-aldol products was observed, together with unreacted sulfinimine resulted (again, some eliminated sulfinimine **3.56** was present). When the modified titanium mixture (10:1, $TiCl(O\textit{i}Pr_3)$:$TiCl_4$) was used for the transmetallation, none of the eliminated product (**3.55**) was observed, however the conversion from the starting materials was low resulting in a disappointing yield of 19%. The diastereoselectivity (67:21:12) showed a small improvement on that seen using the lithium enolate in THF. It was found, however, that the major diastereomer could not be isolated from the other diastereomers.

3.2.2. Conclusion

As this imino-aldol reaction was not giving satisfactory outcomes in terms of yield and selectivity, this approach was abandoned. Unfortunately, due to time constraints, it was not possible to investigate alternative routes towards allomatrine (**1.121**). Our attention did however turn to synthesising a range of different enantioenriched piperidine analogues using the imino-aldol methodology.

3.3. Synthesis of cyclic amines

The synthesis of various cyclic amines was undertaken by applying the imino-aldol methodology developed for the synthesis of epilupinine (**1.71**) and tashiromine (**1.72**). A range of commercial aldehydes were selected with both electron withdrawing and electron donating groups.



Scheme 3.3.1: Synthesis of sulfinimines

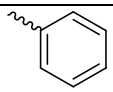
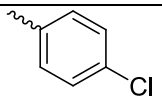
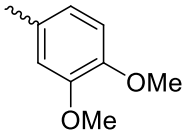
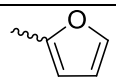
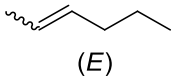
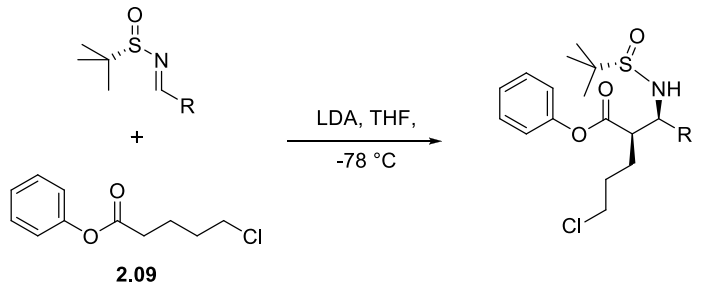
Entry	R	Product	Yield (%)
1		**3.57**	68
2		**3.58**	47
3		**3.59**	36
4		**3.60**	59
5		**3.61**	77

Table 3.3.1: Synthesis of sulfinimines

The synthesis of the sulfinimines (**Scheme 3.3.1**) by condensation of the relevant aldehyde with (*S*)-*tert*-butyl sulfinamide (**1.36-*S***) proceeded smoothly to provide the sulfinimines in average to good yields (**Table 3.3.1**). The synthesis of the more electron-rich sulfinimines proceeded in lower yields, with 36% for **3.59** (Entry 3) and 59% for **3.60** (Entry 4). Alternative reaction conditions for the synthesis of sulfinimines employed by Ellman include the use of $Ti(OEt)_4$ in THF at room temperature, which was higher yielding for some sulfinimines.[25] Due to time considerations alternative reaction conditions were not explored here.

With the sulfinimines in hand, it was possible to carry out the imino-aldol reactions with phenyl ester **2.09**. For these reactions, the optimised reaction conditions were followed, forming the lithium enolate of the ester using LDA at - 78 °C in dry THF and then reacting this with the sulfinimine (**Scheme 3.3.2**).



Scheme 3.3.2: Synthesis of a range of chiral monocyclic amines

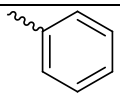
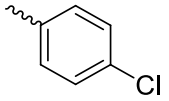
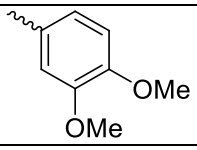
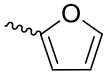
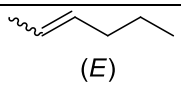
Entry	sulfinimine	R	Product	Yield (%)	dr
1	**3.57**		**3.62**	73[b]	73:23:4[a, g]
2	**3.58**		**3.63**	69[b]	76:15:9[c, g]
3	**3.59**		**3.64**	68[d]	95:5[a, g]
4	**3.60**		**3.65**	87[f]	85:11:4[a, e]
5	**3.61**		**3.66**	63[d]	89:11[c, g]

Table 3.3.2: Results from imino-aldol reactions.

[a] By integration of crude ^{1}H NMR, see experimental section for details.
[b] Yield of mixture of diastereomers.
[c] Calculated from yields of isolated diastereomers.
[d] Isolated yield of major diastereomer.
[e] The fourth diastereomer was not observed in the crude spectrum. However, a fraction containing a mixture of two minor diastereomers (4.4 mg, 0.01 mmol, 1%, in ratio 27:73 respectively) was isolated.
[f] Yield of isolated mixture of two major diastereomers.
[g] Other diastereomers were not observed.

These reactions all gave the diastereomers in good yields of 63 - 87%. The diastereoselectivities for these reactions were variable. Imino-aldol product **3.62** showed 3 diastereomers in the crude NMR spectra (**Entry 1, Table 3.3.2**) with integration of the *tert*-butyl singlets giving 73:23:4 dr. The major diastereomer was isolated by column chromatography as a white solid (64%), with the other two diastereomers being isolated as a mixture (9%). As with most of the imino-aldol reactions the isolated yield was lower than that estimated from the crude ^{1}H NMR, in which no sulfinimine was observed and only product and excess ester were visible. Imino-aldol product **3.64** was formed in 68% (**Entry 3, Table 3.3.2**). Two diastereomers were visible from the ^{1}H NMR of the crude reaction mixture in 95:5 dr. The major diastereomer was separated from the minor. In

the ^{1}H NMR spectrum of the crude reaction material of imino-aldol products **3.66**, the signals for the major and minor diastereomers were not resolved (**Entry 5, Table 3.3.2**). Purification by column chromatography yielded the major diastereomer as a yellow oil (259 mg, 0.63 mmol, 63%). A minor diastereomer was also isolated as a yellow oil (35 mg, 0.08 mmol, 8%). The calculated diastereoselectivity of the isolated diastereomers was 89:11 dr. The synthesis of imino-aldol product **3.63** yielded the major diastereomer (**3.63.1**) as a white crystalline solid (53%) after sequential chromatography and crystallisation (**Entry 2, Table 3.3.2**). Also isolated were two minor diastereomers (**3.63.2**, 2% and **3.63.3**, 6%), as well as a fraction containing a mixture of diastereomers **3.63.2** and **3.63.3** in a ratio of 53:47 respectively (9%). Overall this gives the reaction 76:9:15 dr for diastereomers 1:2:3 and a total a yield of 69% for the combined diastereomers. The fourth diastereomer was not observed. Single crystal X-ray crystallography of the major diastereomer (**3.63.1**) proved the stereochemistry of this imino-aldol product was the expected *syn* stereochemistry with C8 *R*, C12, *R* (**Figure 3.16**).

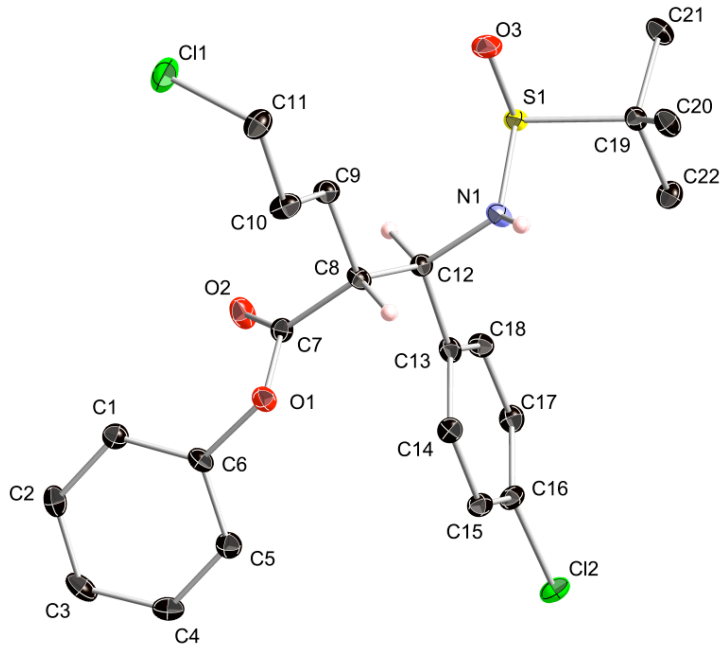


Figure 3.16: Single crystal X-ray of **3.63.1**. Thermal ellipsoids drawn at the 35% probability level, selected hydrogens omitted for clarity.

In the ^{1}H NMR spectrum of the crude product **3.65**, 3 diastereomers were visible 85:4:11 dr (**3.65:1**: **3.65:2**: **3.65:3**, by integration of two NH doublets in **3.65.1** and **3.65.2** and the CHNH double doublet in **3.65.3** respectively, diastereomer **3.65.4** was not observed in the crude spectrum) (**Entry 4, Table 3.3.2**). Purification yielded a mixture of the diastereomers **3.65.1** and **3.65.3** (87%) and a fraction consisting of a mixture of diastereomers **3.65.2** and **3.65.4** (1%, in ratio 27:73 respectively). Crystallisation of the mixture of **3.65.1** and **3.65.3** enabled isolation of the major diastereomer **3.65.1** as white needles which were characterised by single crystal X-ray crystallography. The stereochemistry of this diastereomer was *syn* as expected (*R* C12, *R* C8). Interestingly, this major diastereomer was isolated as a hydrate with a 1:1 ratio. The bonding crystal structure was shown to involve hydrogen bonds between the NH proton, and the water hydrogen and the other hydrogen in the water was in turn bound to the sulfur bound oxygen to give this hydrate (**Figure 3.17** and **Figure 3.18**).

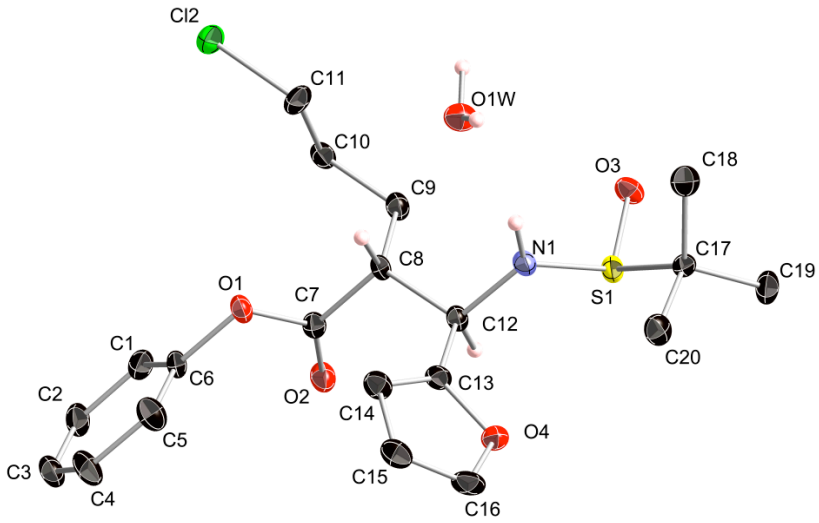


Figure 3.17: Single crystal X-ray for major diastereomer of **3.65.** Thermal ellipsoids drawn at the 35% probability level, selected hydrogens omitted for clarity.

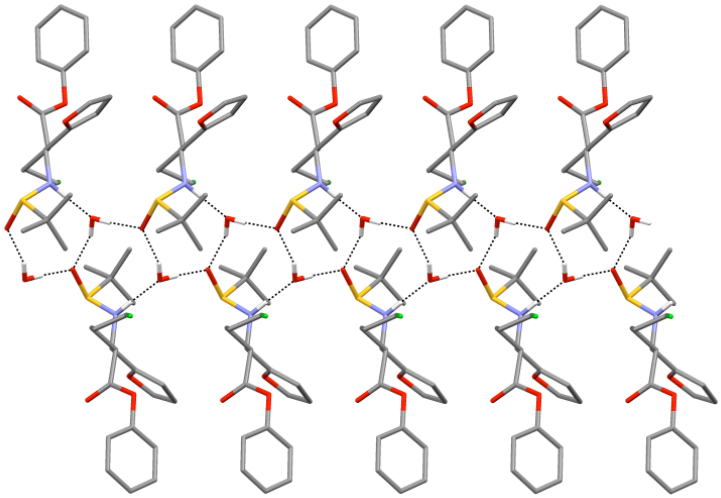
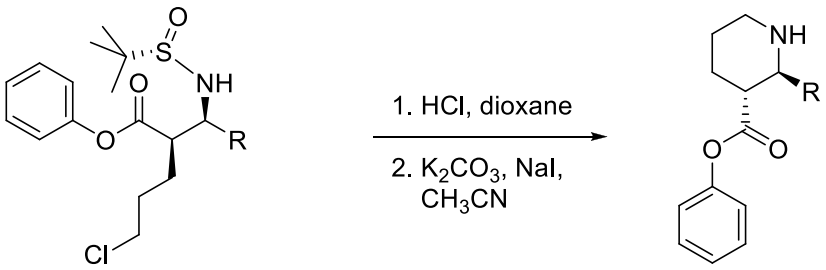
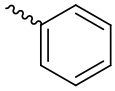
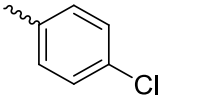


Figure 3.18 The crystal lattice showing the hydrogen bonding of the hydrate of **3.65**. Hydrogen bonded chains extend along the *b* axis.

It should also be noted that the chemical shift for the NH doublets in the ^{1}H NMR of the imino-aldol products seemed to vary by up to 0.1 ppm in some cases, while the coupling constant (and chemical shifts of other signals) were consistent.

Following the successful isolation of all the major diastereomers and of these imino-aldol products, they were individually subjected to the acid deprotection and then base cyclisation conditions. These reactions proceeded smoothly to yield chiral amines **3.67**, **3.68**, **3.69**, **3.70** and **3.71** in good to excellent yields (**Table 3.3.3**).



Entry	Sulfinimine	R	Product	Yield (%)
1	**3.62**		**3.67**	78
2	**3.63**		**3.68**	85

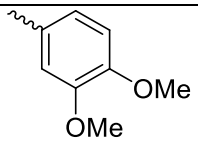
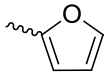
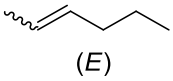
3	**3.64**		**3.69**	55
4	**3.65**		**3.70**	quant.
5	**3.66**		**3.71**	60

Table 3.3.3: Results from deprotection and cyclisation

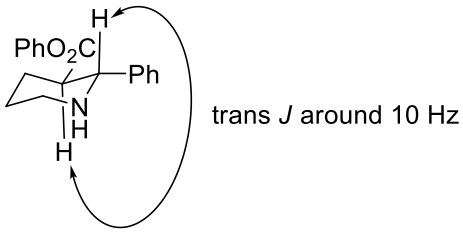


Figure 3.19: Coupling constants in piperidines

Analysis of the ^{1}H NMR coupling constants of the CH signals showed that they had a coupling constant of around 10 Hz for each cyclic amine. This would indicate that the CH protons are *trans* to each other (
Figure 3.19). From the X-ray crystallography results of precursors **3.65** and **3.63** the stereochemistry of these amines **3.70** and **3.68** can be confidently assigned as *R* at both chiral centres. This gives them the same stereochemistry as that of (–)-epilupinine and (–)-tashiromine. By analogy, the stereochemistry of the remaining amines can be assigned with a high level of confidence (**Figure 3.20**).

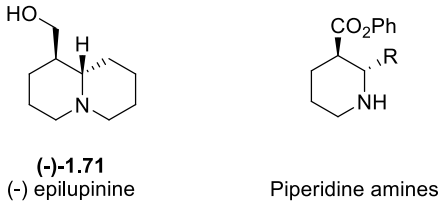


Figure 3.20: Comparison of epilupinine to piperidine amines

The overall yields for the synthesis of this small library of enantiopure chiral piperidines are 13 - 49% over three steps (**Figure 3.21**).

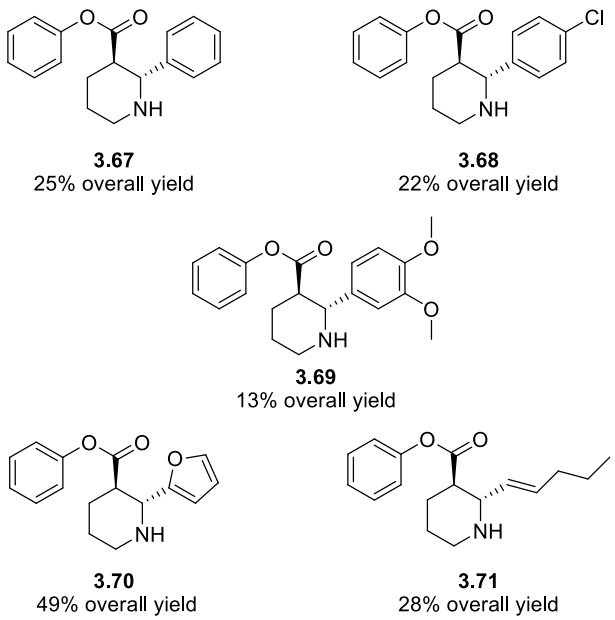


Figure 3.21: Library of chiral piperidines prepared *via* 3-step synthesis

3.4. Conclusions

This thesis details investigations into the imino-aldol reaction and development of an improved reaction procedure which offers advantages in higher diastereoselectivity, simpler reaction procedure and cheaper reagent costs. Our optimum conditions used LDA to form the lithium enolate of phenyl ester **2.09** and then subsequent reaction with chloroalkyl sulfinimines. This formed imino-aldol products in 60% to 78% yield, favouring the *syn* diastereomers with up to 94:6:0:0 dr. The stereochemistry of the major product was confirmed by single crystal X-ray crystallography. A selection of aliphatic esters and sulfinimines were synthesised and used in the imino-aldol reaction to determine the tolerance of the reaction to different functionality. Those consisting of alkyl chains with terminal chlorine atoms were found to give the best diastereoselectivities compared to straight and branched alkyl chains, as well as those with terminal olefin groups.

(–)-Epilupinine (**(–)-1.71**) and (–)-tashiromine (**(–)-1.72**) were successfully synthesised in enantiopure form in 6 steps from chloroalkanoic acid phenyl esters *via* this highly stereoselective imino-aldol reaction with 19 and 12%

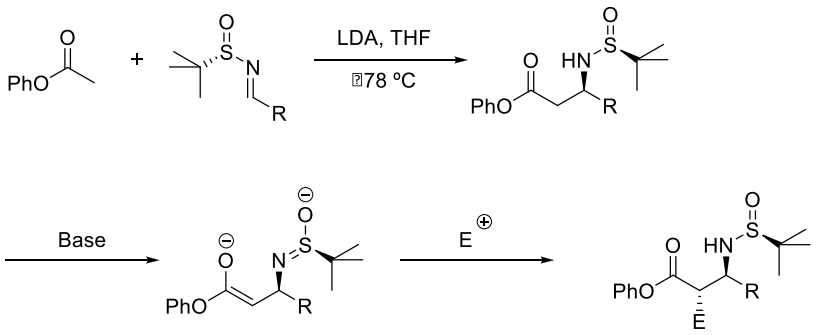
overall yield respectively. Stereochemical determination of the minor imino-aldol product was possible by using it to synthesise (+)-lupinine (**(+)-1.70**) and comparison of the spectrographic data with literature values for the natural product. This led to a discussion of the possible closed transition state for the imino-aldol reaction and apparent selective *Re* face attack.

We then attempted to favour the minor *anti* diastereomer from the imino-aldol reaction. Although a modest increase in the levels of *anti* selectivity was achieved, a change in the reaction conditions resulted in favouring cyclisation of the *anti* imino-aldol product to give the β-lactam. Other approaches to favouring the *anti* diastereomer were not investigated.

A new synthetic route towards the synthesis of (+)-allomatrine (**(+)-1.121**) was devised and investigated. The insertion of the first 2 stereocentres *via* the imino-aldol step was not very selective, however, and had very poor yields under several different reaction conditions. As such this approach was abandoned. Unfortunately, due to time constraints, it was not possible to investigate alternative routes towards allomatrine (**1.121**). Our attention did, however, turn to successfully synthesising a range of different enantiopure piperidine analogues using the imino-aldol methodology. The stereochemical outcome (as determined by X-ray crystallography and by measuring coupling constants in ^{1}H NMR spectra) was consistent with that seen previously for this imino-aldol reaction, further displaying the reliability of these reaction conditions to selectively furnish the *syn* imino-aldol product in good selectivity and yield.

3.5. Future Work

As an extension to this work we would like to investigate a viable route to forming the *anti* imino-aldol products. Our efforts towards varying the reaction conditions did not enable us to favour the *anti* product over the *syn* product (**Section 3.1.5**). As such, we now propose an alternative approach whereby the two stereocentres are formed in separate steps (**Scheme 3.5.1**).



Scheme 3.5.1: Proposed route to formation of *anti* β-amino acids.

First by reacting phenyl acetate with a *tert*-butyl sulfinimine under our optimised conditions we hope to selectively insert our first stereocentre. By subjecting this β-amino acid to basic conditions to affect a double deprotonation and then charging the desired electrophile we expect the *anti* product to predominate with the enolate approaching from the opposite face to the sulfinamide.

Using this method, we hope to find a complementary route to the anti imino-aldol products, which together with the route detailed in the current work, could be applied to the synthesis of a wide range of saturated nitrogen heterocycles.

4. Experimental

4.1. General experimental

Unless otherwise stated reactions were performed under either an argon (Ar) or nitrogen (N_2) atmosphere and all glassware used was oven or flame dried prior to use, where necessary. Dry solvents used were distilled before use; THF was distilled over sodium/benzophenone, toluene was distilled over sodium and CH_2Cl_2 over CaH_2. Other reagents were used as obtained, unless specified otherwise. Thin layer chromatography was carried out on silica gel 60 F254, visualized under UV illumination (254 nm) and stained with potassium permanganate, phosphomolybdic acid or ceric ammonium molybdate solutions. Column chromatography was carried out using silica 60 Å, 35-70 micron or basic aluminum oxide 50-200 micron, deactivated with 6% H_2O to Brockmann III grade, where specified. Melting points were collected on an electrothermal apparatus and are uncorrected. Optical rotations were collected using a polarimeter with a 589 nm light source. ^{1}H NMR spectra were recorded either at 300 MHz or 400 MHz and ^{13}C NMR spectra were recorded either at 75 MHz or 100 MHz in $CDCl_3$ at 300 K. ^{13}C NMR chemical shifts are quoted to 2 decimal places where it is required to distinguish between diastereomers and 1 decimal place otherwise. Chemical shifts for proton and carbon spectra are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^{1}H and 77.00 ppm for ^{13}C). Fourier transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}). All electrospray low resolution mass spectra were recorded on a ZMD quadrupole spectrometer. EI and CI low resolution mass spectroscopic data were collected on a single quadrupole GCMS. Where not stated, stereochemistry was unassigned.

General Procedures

A) General procedure for the synthesis of sulfinimines

Following the procedure described by Ellman *et al*.,[30] (*S*)-2-methylpropane-2-sulfinamide (1.0 equiv) was dissolved in dry solvent before anhydrous $CuSO_4$ (2.2 equiv) was added in one portion followed by the aldehyde (1.0 equiv). The reaction mixture was heated to 40 °C for 18 h then filtered through Celite® and the filter cake was washed with solvent. The solvent was removed *in vacuo* to yield the crude reaction mixture.

B) General procedure for the imino-aldol reaction with LDA

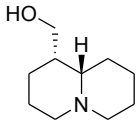
To a solution of LDA (1.37 equiv) in dry THF (0.2 M) at –78 °C, the carboxylic acid derivative (1.30 equiv) was added dropwise as a solution in THF. The reaction mixture was stirred for 30 min before the sulfinimine (1.0 equiv) was added as a solution in THF. The reaction was monitored by TLC. The reaction was quenched by addition of sat. NH_4Cl (aq) and allowed to warm to rt. The aqueous and organic phases were separated. The aqueous phase was extracted into Et_2O (x 3). The combined organic phases were washed with brine, dried ($MgSO_4$), and solvents were removed *in vacuo* to yield the crude product.

C) General procedure for the imino-aldol reaction with $TiCl(O_iPr)_3$: $TiCl_4$ 10:1

To a solution of LDA (1.3 equiv) in dry THF at –78 °C, the ester (1.3 equiv) was then added dropwise as a solution in THF and the reaction mixture was stirred for 30 min before a pre-prepared 10:1 solution of $TiCl(OiPr)_3$:$TiCl_4$ was added. After 30 min the sulfinimine (1.0 equiv) was added. The reaction was monitored by TLC. The reaction was quenched by addition of sat. NH_4Cl (aq) and was allowed to warm to rt. The aqueous and organic phases were separated. The aqueous phase was extracted into EtOAc (x 3). The combined organic phases were washed with brine, dried ($MgSO_4$), and solvents were removed *in vacuo* to yield the crude product.

4.2. Experimental Detail

((+)-1.70) (+)-(1S,9aS)-1-(Octahydro-quinolizin-1-yl)-methanol, (+)-Lupinine

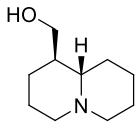


$C_{10}H_{19}NO$, 169.26 g/mol

To a solution of $LiAlH_4$ (23 mg, 0.61 mmol, 4.3 equiv) in THF (0.5 mL) at 0 °C under an inert atmosphere, was added a solution of quinolizine **3.03-*S*,*S*** (36 mg, 0.14 mmol, 1.0 equiv) in THF (0.1 mL). The reaction was left stirring at 0 °C for 10 min before being allowed to warm to rt. The reaction mixture was quenched after 16 h by the sequential addition of H_2O (26 µL), 20% NaOH (aq) (75 µL) and H_2O (26 µL) and then left to stir for 20 min. The reaction mixture was then filtered and washed with CH_2Cl_2 (0.5 mL) before being concentrated *in vacuo* to yield a pale yellow oil. Purification by strong cation exchange solid phase extraction cartridge (Biotage SCX-2 SPE cartridges were used) yielded the title alkaloid as a yellow oil (8.3 mg, 0.05 mmol, 35%). Spectroscopic data were consistent with the literature.[51]

$[\alpha]_D^{30}$ +12.7 (*c* 0.35, EtOH) (lit.[51] **$[\alpha]_D^{20}$** +20.8 (*c* 0.40, EtOH)); **^{1}H NMR** (400 MHz, $CDCl_3$ δ ppm 4.17 (1H, ddd, *J* = 10.7, 4.7, 1.4 Hz, C<u>H</u>HOH), 3.70 (1H, d, *J* = 10.8 Hz, CH<u>H</u>OH), 2.87 - 2.78 (2H, m, 2 x NC<u>H</u>H), 2.25 - 2.09 (2H, m, NC<u>H</u> + O<u>H</u>), 2.03 - 1.96 (1H, m, NC<u>H</u>H), 1.91 - 1.70 (4H, m, NC<u>H</u>H, C<u>H</u>$_2$, and CH<u>H</u>), 1.65 - 1.46 (7H, m, C<u>H</u>CH$_2$OH and C<u>H</u>$_2$ x 3), 1.34 - 1.19 (1H, m, C<u>H</u>H); **^{13}C NMR** (100 MHz, $CDCl_3$ δ ppm 66.0 (<u>C</u>H$_2$OH), 65.1 (N<u>C</u>H), 57.2 (N<u>C</u>H$_2$), 57.1 (N<u>C</u>H$_2$), 38.1 (<u>C</u>HCH$_2$OH), 31.5 (<u>C</u>H$_2$), 29.7 (<u>C</u>H$_2$), 25.6 (<u>C</u>H$_2$), 24.6 (<u>C</u>H$_2$), 22.9 (<u>C</u>H$_2$); **IR** (film) ν_{max}/cm^{-1} 3355 (br), 2934 (s), 2859 (m), 1445 (m), 1028 (s); **LRMS** (ES$^+$) *m/z* 170 ([M + H]$^+$).

((–)-1.71) (–)-(1R,9aS)-1-(Octahydro-quinolizin-1-yl)-methanol, (-)-Epilupinine

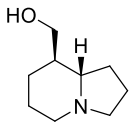


$C_{10}H_{19}NO$, 169.26 g/mol

To a solution of $LiAlH_4$ (117 mg, 3.1 mmol, 4.0 equiv) in THF (3.0 mL) at 0 °C under an inert atmosphere, was added a solution of quinolizine **3.02-*R,S*** (200 mg, 0.77 mmol, 1.0 equiv) in THF (6.0 mL). The reaction was stirred at 0 °C for 10 min before being allowed to warm to rt. The reaction mixture was quenched after 16 h by the sequential addition of H_2O (141 µL), 20% NaOH (411 µL) and H_2O (141 µL) and then left to stir for 20 min. The reaction mixture was then filtered and washed with CH_2Cl_2 (5 mL) before being concentrated *in vacuo* to yield a pale yellow oil (129 mg). Purification by column chromatography (Al_2O_3 gel Brockmann III, eluent gradient 0:20 → 1:19 MeOH/CH_2Cl_2) and strong cation exchange solid phase extraction cartridge (Biotage SCX-2 SPE cartridges were used) yielded the title alkaloid, which crystallised on standing to give a pale yellow crystalline solid (118 mg, 0.70 mmol, 91%). Data were consistent with the literature.[51]

MP 78 - 81°C (lit.[51] 78-79°C); **$[\alpha]_D^{26}$** – 29.2 (*c* 1.00, EtOH) (lit.[51] **$[\alpha]_D^{20}$** – 33.0 (*c* 0.72, EtOH)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 3.62 (1H, dd, *J* = 10.6, 3.5 Hz, C<u>H</u>HOH), 3.50 (1H, dd, *J* = 10.6, 5.8 Hz, CH<u>H</u>OH), 2.84 - 2.70 (2H, m, 2 x NC<u>H</u>H), 2.58 (1H, br. s, O<u>H</u>), 2.06 - 1.92 (2H, m, 2 x NC<u>H</u>H), 1.91 - 1.78 (2H, m, 2 x CH<u>H</u>), 1.77 - 1.70 (1H, m, C<u>H</u>HCH$_2$N), 1.69 - 1.61 (3H, m, NC<u>H</u> and C<u>H</u>$_2$), 1.60 - 1.52 (2H, m, C<u>H</u>$_2$), 1.43 - 1.31 (1H, m, C<u>H</u>CH$_2$OH), 1.29 - 1.09 (3H, m, C<u>H</u>HCH$_2$N and 2 x C<u>H</u>H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 64.5 (N<u>C</u>H), 64.3 (<u>C</u>H$_2$OH), 56.9 (N<u>C</u>H$_2$), 56.6 (N<u>C</u>H$_2$), 43.9 (<u>C</u>HCH$_2$OH), 29.7 (<u>C</u>H$_2$), 28.2 (<u>C</u>H$_2$), 25.5 (<u>C</u>H$_2$), 25.0 (<u>C</u>H$_2$), 24.5 (<u>C</u>H$_2$); **IR** (film) ν_{max}/cm^{-1} 3209 (br), 2923 (s), 2855 (m), 2805 (m), 2805 (m), 2757 (m), 1442 (m), 1295 (m), 1112 (s), 1092 (s), 1069 (s), 1014 (s); **LRMS** (ES^+) *m/z* 170 ($[M + H]^+$); **HRMS** (ES^+) for $C_{10}H_{20}NO$, requires 170.1539, found 170.1539 Da.

((–)-1.72) (–)-(1R,8aS)-1-(Octahydro-indolizin-1-yl)-methanol, (-)-Tashiromine

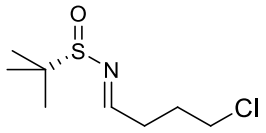


$C_9H_{17}NO$, 155.24 g/mol

To a solution of $LiAlH_4$ (70 mg, 1.84 mmol, 4.0 equiv) in THF (2 mL) at 0 °C under an inert atmosphere, was added a solution of indolizine **3.01-*R,S*** (120 mg, 0.46 mmol, 1.0 equiv) in THF (4.0 mL). The reaction was stirred at 0 °C for 10 min before being allowed to warm to rt. The reaction mixture was quenched after 16 h by the sequential addition of H_2O (84 µL), 20% NaOH (aq) (244 µL) and H_2O (84 µL) and then stirred for 20 min. The reaction mixture was then filtered and washed with CH_2Cl_2 (3 mL) before being concentrated *in vacuo* to yield a pale yellow oil (72 mg). Purification by strong cation exchange solid phase extraction cartridge (Biotage SCX-2 SPE cartridges were used) yielded the title alkaloid which crystallised on standing to give a white crystalline solid (49 mg, 0.32 mmol, 69%). Data were consistent with the literature.[62]

MP 36 - 39 °C (lit.[62] 35 °C); **$[\alpha]_D^{26}$** – 43.6 (*c* 1.02, EtOH) (lit.[62] (+) enantiomer **$[\alpha]_D^{20}$** + 44.8 (*c* 1.58, EtOH)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 3.61 (1H, dd, *J* = 10.7, 4.6 Hz, CH<u>H</u>OH), 3.44 (1H, dd, *J* = 10.7, 6.5 Hz, C<u>H</u>HOH), 3.11 - 2.99 (2H, m, CH<u>H</u>N x 2), 2.24 (1H, br s, O<u>H</u>), 2.05 (1H, q, *J* = 9.1 Hz, CH<u>H</u>N), 1.98 - 1.37 (10H, m, C<u>H</u>N, C<u>H</u>CH_2OH, CH<u>H</u>CHCHN, CH<u>H</u>N, CH_2 x 3), 1.02 (1H, qd, *J* = 12.5, 4.8 Hz, C<u>H</u>HCHCHN); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 66.4 (N<u>C</u>H), 65.5 (<u>C</u>H_2OH), 54.1 (<u>C</u>H_2N), 52.7 (<u>C</u>H_2N), 44.6 (<u>C</u>HCH_2OH), 29.0 (<u>C</u>H_2CHN), 27.6 (<u>C</u>H_2CHCH_2OH), 25.1 (<u>C</u>$H_2$$CH_2$N), 20.7 (<u>C</u>$H_2$$CH_2$N); **IR** (film) ν_{max}/cm^{-1} 3297 (br), 2929 (s), 2872 (m), 2793 (s), 2717 (m), 1444 (m), 1330 (m), 1217 (m), 1164 (m), 1092 (s), 1047 (s); **LRMS** (ES^+) *m/z* 156 ($[M + H]^+$); **HRMS** (ES^+) for $C_9H_{18}NO$, requires 156.1383, found 156.1381 Da.

((+)-1.139) (+)-(S)-N-[(1E)-4-Chlorobutylidene]-2-methylpropane-2-sulfinamide

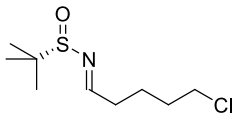


$C_8H_{16}ClNOS$, 209.74 g/mol

Following the procedure described by Witiak *et al.,*[85] methyl 4-chlorobutyrate (**1.135**, 1.8 mL, 14.6 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (40 mL), cooled to –60 °C before being treated with DIBAL-H (16.0 mL of 1M soln. in hexanes, 16.0 mmol, 1.1 equiv) over 10 min. The reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by pouring onto a sat. soln. of NH_4Cl (50 mL). The suspension was filtered through Celite® and extracted with CH_2Cl_2 (20 mL x 3). The combined organic phases were washed with brine (40mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a yellow oil (0.92 g, 8.6 mmol, 54%) which was not purified further. ^{1}H NMR spectroscopic data were consistent with those published for 4-chlorobutan-1-al (**1.137**).[85,86] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.83 (1H, s, C<u>H</u>O), 3.61 (2H, t, *J* = 7.0 Hz, C<u>H</u>$_2$Cl), 2.68 (2H, t, *J* = 7.0 Hz, C<u>H</u>$_2$CHO), 2.12 (2H, tt, *J* = 7.0, 7.0 Hz, C<u>H</u>$_2$). General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.05 g, 8.7 mmol, 1.01 equiv), CH_2Cl_2 (17 mL), $CuSO_4$ (3.03 g, 19.0 mmol, 2.2 equiv) and 4-chlorobutanal (**1.137**, 0.92 g, 8.6 mmol, 1.0 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 3:1 hexane/EtOAc) yielded a pale yellow free flowing oil (1.40 g, 6.7 mmol, 73%). Data were consistent with the literature.[87]

$[\alpha]_D^{24}$ +209.2 (*c* 0.49, $CHCl_3$), (lit. **$[\alpha]_D^{25}$** +229.2 (*c* 1.01, $CHCl_3$))[87]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (1H, t, *J* = 3.9 Hz, NC<u>H</u>), 3.63 (2H, t, *J* = 6.6 Hz, C<u>H</u>$_2$Cl), 2.71 (2H, td, *J* = 7.2, 3.9 Hz, NCHC<u>H</u>$_2$), 2.14 (2H, tt, *J* = 7.2, 6.6 Hz, C<u>H</u>$_2$CH$_2$Cl), 1.20 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (<u>C</u>HN), 56.6 (<u>C</u>(CH$_3$)$_3$, 44.0 (<u>C</u>H$_2$Cl), 33.1 (<u>C</u>H$_2$CHN), 27.9 (<u>C</u>H$_2$CH$_2$Cl), 22.3 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2960 (m), 1624 (s), 1081 (s).

((+)-1.140) (+)-(S)-N-[(1E)-5-Chloropentylidene]-2-methylpropane-2-sulfinamide



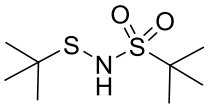
$C_9H_{18}ClNOS$, 223.76 g/mol

Following the procedure described by Witiak *et al.,*[85] methyl 5-chloropentanoate (**1.136**. 1.9 mL, 13.3 mmol, 1 equiv) was dissolved in CH_2Cl_2 (40.0 mL), cooled to –60 °C before being treated with DIBAL-H (14.6 mL of 1 M soln. in hexanes, 14.6 mmol, 1.1 equiv) over 10 min. The reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by pouring onto a sat. soln. of NH_4Cl (50 mL). The suspension was filtered through Celite® and extracted with CH_2Cl_2 (20 mL x 3). The combined organic phases were washed with brine (40 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a yellow oil (1.00 g, 8.3 mmol, 62%), which was not purified further. ^{1}H NMR spectroscopic data are consistent with those published for 5-chloropentanal (**1.138**).[88] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.5 Hz, C<u>H</u>O), 3.62 - 3.53 (2H, m, C<u>H</u>$_2$Cl), 2.60 - 2.44 (2H, m, C<u>H</u>$_2$CHO), 1.90 - 1.75 (4H, m, 2 x C<u>H</u>$_2$). General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.10 g, 9.05 mmol, 1.05 equiv), CH_2Cl_2 (17 mL), $CuSO_4$ (3.00 g, 19.0 mmol, 2.2 equiv) and 5-chloropentanal (**1.138**, 1.00 g, 8.62 mmol, 1.0 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 3:1 hexane/EtOAc) yielded a pale yellow, free flowing oil (1.50 g, 6.7 mmol, 77%). Data were consistent with the literature.[72]

$[\alpha]_D^{26}$ +227 (*c* 1.03, $CHCl_3$) (lit. **$[\alpha]_D^{26}$** +214.0 (*c* 2.13, $CHCl_3$))[72]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (1H, t, *J* = 4.5 Hz, C<u>H</u>N), 3.56 (2H, t, *J* = 6.2 Hz, C<u>H</u>$_2$Cl), 2.56 (2H, td, *J* = 7.0, 4.5 Hz, C<u>H</u>$_2$CHN), 1.94 - 1.72 (4H, m, C<u>H</u>$_2$ x 2), 1.19 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (<u>C</u>HN), 56.6 (<u>C</u>(CH$_3$)$_3$), 44.4

($\underline{C}H_2Cl$), 35.2 ($\underline{C}H_2CHN$), 31.9 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2CH_2Cl$), 22.3 ($C(\underline{C}H_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2958 (m), 1623 (s), 1081 (s).

(2.01) N-(2-Methylpropane-2-sulfanyl)-2-methylpropane-2-sulfonamide

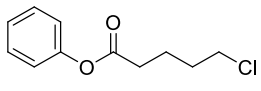


White needles, $C_8H_{19}NO_2S_2$, 225.37 g/mol

By-product obtained as white needles after column chromatography of sulfinimines which had been stored at room temperature for several weeks.

MP 167 - 169 °C (EtOAc); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 5.48 (1H, br s, N$\underline{H}$), 1.42 (9H, s, ($C\underline{H}_3)_3$), 1.30 (9H, s, ($C\underline{H}_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 61.2 ($\underline{C}(CH_3)$), 48.5 ($\underline{C}(CH_3)$), 28.1 ($\underline{C}H_3$ x 3), 24.7 ($\underline{C}H_3$ x 3); **IR** (film) ν_{max}/cm^{-1} 3234 (m), 2962 (m), 1362 (m), 1296 (s), 1123 (s), 885 (s); **LRMS** (ES^-) *m/z* 224 ($[M - H]^-$); **HRMS** (ES^+) for $C_8H_{19}NNaO_2S_2$ + CH_3CN, requires 289.1015, found 289.1018 Da.

(2.09) Phenyl 5-chloropentanoate

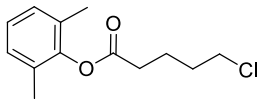


$C_{11}H_{13}ClO_2$, 212.67 g/mol

Adapted from the procedure described by Gilbert *et al.*[89] 5-chloropentanoyl chloride (**2.08**, 6.2 g, 40.0 mmol, 1.00 equiv) was slowly dripped onto phenol (3.78 g, 40.2 mmol, 1.01 equiv) *via* a dropping funnel. After complete addition the dropping funnel was replaced by a condenser and the reaction mixture was heated to 60 °C. After 1 h the reaction mixture was removed from the heat. Separation of the unreacted phenol was achieved by column chromatography (SiO_2 gel, eluent gradient 19:1 → 18:2 → 17:3, hexane/ EtOAc) to yield the title ester as a colourless liquid (7.03 g, 33.1 mmol, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 - 7.32 (2H, m, $\underline{H}_{Ar\ meta}$ x 2), 7.30 - 7.17 (1H, m, $\underline{H}_{Ar\ ortho}$), 7.14 - 7.04 (2H, m, $\underline{H}_{Ar\ para}$ x 2), 3.69 - 3.50 (2H, m, $C\underline{H}_2Cl$), 2.71 - 2.50 (2H, m, $C\underline{H}_2CO_2$), 2.00 - 1.84 (4H, m, $C\underline{H}_2$ x 2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.6 ($\underline{C}O_2Ph$), 150.6 ($\underline{C}_{Ar\ ipso}$), 129.4 ($\underline{C}_{Ar\ meta}$ x 2), 125.8 ($\underline{C}_{Ar\ para}$), 121.4 ($\underline{C}_{Ar\ ortho}$ x 2), 44.3 ($\underline{C}H_2Cl$), 33.4 ($\underline{C}H_2CO_2$), 31.7 ($\underline{C}H_2CH_2Cl$), 22.2 ($\underline{C}H_2CH_2CO_2$); **IR** (film) ν_{max}/cm^{-1} 2958 (w), 1755 (m), 1192 (s), 1161 (s), 1122 (s), 689 (m); **LRMS** (EI) *m*/*z* 212 [$M^{+\bullet}$] (7%), 119 (22%), 121 (8%), 94 (100%), 55 (80%); **HRMS** (EI) for $C_{11}H_{13}ClO_2$, requires 212.06041, found 212.06043 Da.

(2.11) 2,6-Dimethylphenyl 5-chloropentanoate



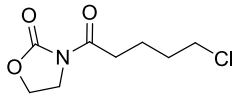
$C_{13}H_{17}ClO_2$, 240.73 g/mol

To a solution of 2,6-dimethylphenol (**2.10**, 2.61 g, 21.4 mmol, 1 equiv) in THF (30 mL) at 0 °C, *n*BuLi (13.4 mL of a 2.5 M soln. in hexanes, 21.4 mmol, 1.0 equiv) was added dropwise over 5 min. After stirring for 10 min 5-chloropentanoyl chloride (**2.08**, 2.5 mL, 21.4 mmol, 1.0 equiv) was added dropwise. After 1 h the reaction was quenched by addition of sat. $NaHCO_3$(aq) (35 mL), and then extracted into EtOAc (2 x 20 mL). The combined organic phases were washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow liquid. Purification by column chromatography (Si_2O gel, CH_2Cl_2) yielded the title ester as a pale yellow liquid (2.48 g, 10.3 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.10 - 7.03 (3H, m, $\underline{H}_{Ar}$ x 3), 3.64 - 3.59 (2H, m, $C\underline{H}_2Cl$), 2.71 - 2.64 (2H, m, $C\underline{H}_2CO$), 2.16 (6H, s, $C\underline{H}_3$ x 2), 2.03 - 1.90 (4H, m, $C\underline{H}_2$ x 2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 170.8 ($\underline{C}O$), 148.1 ($\underline{C}_{Ar\ ipso}$), 123.0 ($\underline{C}_{Ar}CH_3$ x 2), 128.6 ($\underline{C}_{Ar\ meta}$ x 2), 125.8 ($\underline{C}_{Ar\ para}$), 44.4 ($\underline{C}H_2Cl$), 33.1 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 22.4 ($\underline{C}H_2$), 16.4 ($\underline{C}H_3$ x 2); **IR** (film) ν_{max}/cm^{-1} 2955 (w), 1751 (s), 1475 (m), 1220 (s), 1124 (s), 769 (s); **LRMS** (EI) *m*/*z* 240 [$M^{+\bullet}$] (11%), 242

(4%), 121 (100%), 91 (46%), 77 (37%), 54 (49%); **HRMS** (EI) for $C_{13}H_{17}ClO_2$, requires 240.09171, found 240.09135 Da.

(2.13) Oxazolidin-2-one-3-yl-5-chloropentan-1-one

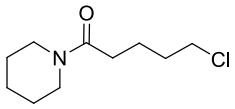


$C_8H_{12}ClNO_3$, 205.64 g/mol

To a solution of 1,3-oxazolidin-2-one (**2.15**, 0.98 g, 11.3 mmol, 1 equiv) in THF (20 mL) at 0 °C, *n*BuLi (4.6 mL of a 2.5 M soln in hexanes, 11.3 mmol, 1.0 equiv) was added dropwise over 5 min. After stirring for 20 min 5-chloropentanoyl chloride (**2.08**, 1.46 mL, 1.75 g, 11.3 mmol, 1.0 equiv) was added dropwise, the reaction mixture turned yellow. The reaction was followed by the disappearance of the N-H (3369 cm^{-1}) stretch by IR analysis. After 30 min the reaction was quenched by addition of sat. $NaHCO_3$(aq) (15 mL), and then extracted into EtOAc (3 x 10 mL). The combined organic phases were washed with 1 M HCl (aq) (2 x 15 mL) and brine (2 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow liquid (1.69 g). Purification by column chromatography (SiO_2 gel, eluent 3:2 EtOAc/hexane) yielded the title oxazolidinone as a pale yellow liquid (1.39 g, 6.8 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 - 4.36 (2H, m, NC$\underline{H}_2$), 4.09 - 3.96 (2H, m, $CO_2C\underline{H}_2$), 3.64 - 3.50 (2H, m, C$\underline{H}_2$Cl), 3.04 - 2.88 (2H, m, C$\underline{H}_2$C(O)N), 1.89 - 1.74 (4H, m, C$\underline{H}_2$ x 2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.8 ($\underline{C}$(O)CH_2), 153.5 (N$\underline{C}$(O)O), 62.0 ($\underline{C}O_2CH_2$), 44.5 ($\underline{C}H_2$Cl), 42.4 ($\underline{C}H_2$OC(O)), 34.3 ($\underline{C}H_2$CO), 31.8 ($\underline{C}H_2CH_2$Cl), 21.5 ($\underline{C}H_2(CH_2)_2$Cl); **IR** (film) ν_{max}/cm^{-1} 2924 (w), 1770 (s), 1693 (s), 1385 (s), 1222 (s); **LRMS** (EI) *m/z* 206 $[M^{\bullet}+H]^+$ (14%), 208 (3.9%), 170 (84%), 142 (100%), 119 (75%), 88 (80%), 55 (95%); **HRMS** (EI) for $C_8H_{13}O_3NCl$, requires 206.0584, found 206.0495 Da.

(2.15) Piperidin-1-yl-5-chloropentan-1-one

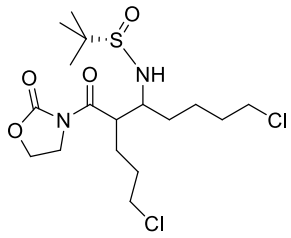


$C_{10}H_{18}ClNO$, 203.71 g/mol

To a solution of piperidine (**2.14**, 1.1 mL, 0.9 g, 11.3 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL), Et_3N (1.0 mL, 0.7 g, 11.3 mmol, 1.0 equiv) was added and stirred for 15 min. 5-Chloropentanoyl chloride (**2.08**, 1.46 mL, 1.8 g, 11.3 mmol, 1.0 equiv) was then added dropwise over 10 min. Analysis by IR after complete addition of the acid chloride indicated that the reaction had gone to completion by the disappearance of the ClC=O stretch at 1794 cm^{-1}, a new peak for NC=O at 1636 cm^{-1} was observed in the spectrum. Water (15 mL) was added to the reaction mixture and the aqueous and organic phases were separated. The aqueous phase was extracted into CH_2Cl_2 (15 mL x 2). The combined organic phases were washed with 1 M HCl (10 mL x 4) and water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (SiO_2 gel, eluent 3:2 EtOAc/hexane) yielded the title amide as a yellow liquid (2.04 g, 10.0 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 - 3.50 (4H, m, $(C\underline{H}_2)_2N$), 3.84 (2H, t, *J* = 5.5 Hz, $C\underline{H}_2Cl$), 2.35 (2H, t, *J* =7.0 Hz, $C\underline{H}_2CON$), 1.91 - 1.70 (4H, m, $C\underline{H}_2(CH_2)_2Cl$ and $CH_2C\underline{H}_2CH_2Cl$), 1.69 - 1.48 (6H, m, $C\underline{H}_2$ x 3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 ($\underline{C}O$), 44.7 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 32.2 ($\underline{C}H_2$), 24.5 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$); **IR** (film) ν_{max}/cm^{-1} 3935 (m), 1635 (s), 1441 (m), 1252 (m), 1224 (m); **LRMS** (ES^+) *m/z* 204 & 206 ($[M+H]^+$), 267 & 269 ($[M+Na+CH_3CN]^+$); **HRMS** (ES^+) for $[2x(C_{10}H_{18}ClNO) + Na]^+$, requires 429.2046 found 429.2049 Da.

(2.16) 3-(7-Chloro-2-(3-chloropropyl)-3-((S)-2-methylpropane-2-sulfinamino)-heptanoyl) oxazolidin-2-one



$C_{17}H_{30}Cl_2N_2O_4S$, 429.40 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (1.25 mL of a 1.68 M soln. in THF, 2.1 mmol, 2.1 equiv), THF (10.0 mL), oxazolidin-2-one **2.13** (411 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **1.140** (224 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 30 min. Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 5:15 → 6:14 → 8:12 → 10:10 → 12:8 → 0:20 EtOAc/hexane) separated two diastereomers of the desired imino-aldol product, major diastereomer **2.16.1** (235 mg, 0.55 mmol, 55%) and minor diastereomer **2.16.2** (103 mg, 0.24 mmol, 24%) giving 70:30 dr by isolated mass. No other diastereomers were observed. Stereochemistry was not assigned.

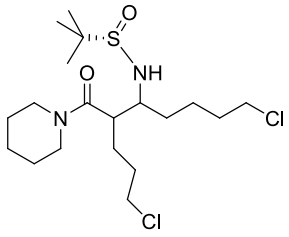
(2.16.1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.09 (1H, ddt, *J* = 14.2, 9.7, 4.0 Hz, C<u>H</u>H), 3.95 (1H, ddd, *J* = 14.2, 7.0, 4.1 Hz, CH<u>H</u>), 3.88 (1H, dt, *J* = 6.3, 4.6 Hz, C<u>H</u>H), 3.67 - 3.54 (3H, m, C<u>H</u>$_2$Cl, CH<u>H</u>), 3.51 (2H, t, *J* = 6.6 Hz, C<u>H</u>$_2$Cl), 2.79 (1H, td, *J* = 7.0, 4.8 Hz, C<u>H</u>), 2.25 - 2.14 (1H, m, C<u>H</u>), 2.09 - 1.40 (10H, m, C<u>H</u>$_2$ x 5), 1.28 (9H, s, C(C<u>H</u>$_3$)$_3$), signal for N<u>H</u> was not observed; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.4 (<u>C</u>(O)CH), 153.5 (O<u>C</u>(N)O), 62.1 (<u>C</u>(CH$_3$)$_3$), 61.1 (<u>C</u>H$_2$), 47.9 (<u>C</u>H), 46.0 (<u>C</u>H), 44.4 (<u>C</u>H$_2$), 44.3 (<u>C</u>H$_2$), 43.0 (<u>C</u>H$_2$), 32.4 (<u>C</u>H$_2$), 30.2 (<u>C</u>H$_2$), 29.9 (<u>C</u>H$_2$), 24.3 (<u>C</u>H$_2$), 23.5 (<u>C</u>H$_2$), 22.3 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3485 (w), 2960 (w), 1712 (m), 1665 (s), 1409 (m), 1068 (s), 751 (s).

(2.16.2)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.53 - 4.36 (2H, m, C$\underline{H}_2$), 4.20 - 4.10 (2H, m, C$\underline{H}_2$), 4.03 (1H, ddd, *J* = 10.9, 9.2, 7.4 Hz, C$\underline{H}$), 3.71 (1H, d, *J* = 5.2 Hz, N$\underline{H}$), 3.64 - 3.49 (5H, m, C$\underline{H}_2$Cl x 2, C$\underline{H}$), 1.97 - 1.62 (10H, m, C$\underline{H}_2$ x 5), 1.22 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.0 (C(O)CH), 153.4 (OC(O)N), 62.2 ($\underline{C}H_2$), 56.0 ($\underline{C}(CH_3)_3$), 55.6 ($\underline{C}H$), 45.9 ($\underline{C}H$), 44.7 ($\underline{C}H_2$), 44.5 ($\underline{C}H_2$), 42.8 ($\underline{C}H_2$), 33.3 ($\underline{C}H_2$), 32.1 ($\underline{C}H_2$), 30.3 ($\underline{C}H_2$), 23.1 ($\underline{C}H_2$), 22.8 ($\underline{C}H_2$), 22.7 ($C(\underline{C}H_3)_3$); **IR** (film) ν_{max}/cm^{-1} 3288 (w), 2957 (w), 1771 (s), 1686 (m), 1386 (s), 1218 (s), 1042 (s), 752 (s); **LRMS** (ES^+) *m/z* 429, 431 & 433 ($[M + H]^+$), 451, 453 & 455 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{17}H_{30}Cl_2N_2NaO_4S$, requires 451.1196, found 451.1186 Da.

(2.17) 7-Chloro-2-(3-chloropropyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-(piperidin-1-yl) heptan-1-one



$C_{19}H_{36}Cl_2N_2O_2S$, 427.47 g/mol

General procedure **B** for imino-aldol reaction was followed using LDA (0.6 mL of a 1.8 M soln. in THF, 1.1 mmol, 1.1 equiv), THF (10.0 mL), piperidinyl **2.15** (208 mg, 1.0 mmol, 1.0 equiv) and sulfinimine **1.140** (228 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 30 min. Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 2:2 → 3:1 → 4:0 EtOAc/hexane) recovered a mixture of diastereomers of the desired imino-aldol product (172 mg, 0.40 mmol, 40%). The dr was estimated to be 56:19:19:6 for diastereomers 1:2:3:4 (by integration of the crude ^{1}H NMR using C$\underline{H}$ peak at 2.90 ppm and N$\underline{H}$ peaks at, 4.81, 4.13 and 5.82 ppm respectively). Stereochemistry was not assigned.

(2.17.1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.65 - 3.36 (10H, m, C$\underline{H}_2$Cl x 2, C$\underline{H}$, C$\underline{H}_2$N x 2, N$\underline{H}$), 2.90 (1H, td, *J* = 8.5, 3.9 Hz, C$\underline{H}$), 1.93 - 1.36 (16H, m, C$\underline{H}_2$ x 8), 1.22 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.5 (C$\underline{O}$), 58.7 (C$\underline{H}$), 56.3 (C$\underline{(CH_3)_3}$), 47.0 (C$\underline{H}_2$NCO x 2), 45.7 (C$\underline{H}$), 44.9 (C$\underline{H}_2$Cl), 44.8 (C$\underline{H}_2$Cl), 42.9 (C$\underline{H}_2$CH$_2$NCO x 2), 32.9 (C$\underline{H}_2$), 32.0 (C$\underline{H}_2$), 30.1 (C$\underline{H}_2$), 26.7 (C$\underline{H}_2$), 25.8 (C$\underline{H}_2$), 24.5 (C$\underline{H}_2$), 22.7 (C(C$\underline{H}_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3236 (w), 2937 (m), 2860 (w), 1736 (w), 1614 (s), 1443 (s), 1244 (m), 1050 (s); **LRMS** (ES$^+$) m/z 427, 429 & 431 ([M + H]$^+$), 449, 451 & 453 ([M + Na]$^+$); **HRMS** (ES$^+$) for $C_{19}H_{37}Cl_2N_2O_2S$, requires 427.1947, found 427.1940 Da.

(2.17.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.81 (1H, d, *J* = 9.0 Hz, N$\underline{H}$)

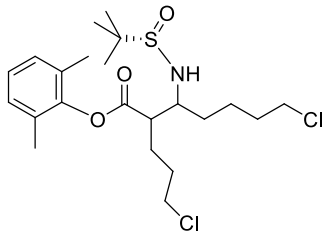
(2.17.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13 (1H, d, *J* = 5.7 Hz, N$\underline{H}$)

(2.17.4)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.82 (1H, d, *J* = 8.0 Hz, N$\underline{H}$), 3.67 - 3.43 (6H, m, C$\underline{H}_2$Cl, C$\underline{H}_2$N x 2), 3.43 - 3.37 (2H, m, C$\underline{H}_2$), 3.28 (1H, m, C$\underline{H}$), 2.87 (1H, td, *J* = 7.0, 3.0 Hz, C$\underline{H}$), 2.40 - 2.31 (2H, m, C$\underline{H}_2$), 2.01 - 1.35 (14H, m, C$\underline{H}_2$ x 7), 1.26 (9H, s, C(C$\underline{H}_3$)$_3$); **LRMS** (ES$^+$) *m/z* 427, 429 & 431 ([M + H]$^+$), 449, 451 & 453 ([M + Na]$^+$).

(2.18) 7-Chloro-2-(3-chloropropyl)-3-((S)-2-methyl propane-2-sulfinamino)-1-(2,6-dimethyl phenyl) heptanoate



$C_{22}H_{35}Cl_2NO_3S$, 464.49 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (1.25 mL of a 1.68 M soln. in THF, 2.1 mmol, 2.1 equiv), THF (10.0 mL), 2,6-dimethylphenyl ester **2.11** (481 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **1.140** (224 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 30 min. Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 3:1 → 2:2 hexane/EtOAc) yielded a mixture of diastereomers of the desired imino-aldol product (in total 405 mg, 0.87 mmol, 87%). The diastereomeric ratio was estimated from the ^{1}H NMR of the crude reaction mixture to be 51:37:12 (by integration of NH peaks at 4.44, 4.02 and 4.66 ppm of diastereomers 1:2:3 respectively). Further purification of a small sample by crystallisation (hexane/EtOAc) enabled isolation of the diastereomer 2 for characterisation. Stereochemistry was not assigned.

(2.18.1) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (3H, s, H_{Ar} x 3), 4.43 (1H, d, *J* = 8.8 Hz, NH), 3.56 (4H, t, *J* = 6.2 Hz, CH_2Cl), 3.33 (1H, dt, *J* = 8.5, 4.3 Hz, CH), 2.17 (6H, s, $C_{Ar}CH_3$ x 2), 1.23 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.9 (CO), 147.9 ($C_{Ar\ ipso}$), 129.8 ($C_{Ar\ ortho}$ x 2), 128.8 ($C_{Ar\ meta}$ x 2), 126.2 ($C_{Ar\ para}$), 58.3 (CH), 56.2 ($C(CH_3)_3$), 49.4 (CH), 44.7 (CH_2Cl), 44.5 (CH_2Cl), 35.2 (CH_2), 32.0 (CH_2), 30.7 (CH_2), 26.2 (CH_2), 23.8 (CH_2), 22.7 ($C(CH_3)_3$), 16.8 ($C_{Ar}CH_3$ x 2).

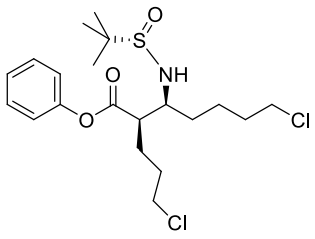
(2.18.2)

MP 87 - 90 ºC (EtOAc/hexane); **$[\alpha]_D^{28}$** +40.0 (c 0.095, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08 (3H, s, $\underline{H}_{Ar}$ x 3), 4.01 (1H, d, *J* = 9.5 Hz, N$\underline{H}$), 3.62 (2H, m, *J* = 6.2 Hz, C$\underline{H}_2$Cl), 3.57 (3H, t, *J* = 6.6 Hz, C$\underline{H}_2$Cl), 3.53 - 3.44 (1H, m, C$\underline{H}$), 3.03 - 2.92 (1H, m, C$\underline{H}$), 2.17 (6H, s, C$\underline{H}_3$ x 2), 2.12 - 1.62 (10H, m, C$\underline{H}_2$ x 5), 1.25 (9H, s, (C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1 (C$\underline{O}$), 129.7 ($\underline{C}_{Ar\ ortho}$ x 2), 128.9 ($\underline{C}_{Ar\ meta}$ x 2), 126.2 ($\underline{C}_{Ar\ para}$), 57.7 (C$\underline{H}$), 56.6 (C$\underline{(CH_3)_3}$), 48.0 (C$\underline{H}$), 44.7 (C$\underline{H}_2$Cl), 44.4 (C$\underline{H}_2$Cl), 34.9 (C$\underline{H}_2$), 32.2 (C$\underline{H}_2$), 30.2 (C$\underline{H}_2$), 26.9 (C$\underline{H}_2$), 23.9 (C$\underline{H}_2$), 22.9 (C(C$\underline{H}_3$)$_3$), 16.8 (CArC$\underline{H}_3$ x 2), $\underline{C}_{Ar\ ipso}$ not seen; **IR** (film) ν_{max}/cm^{-1} 3215(w), 2955(m), 1743 (s), 1474 (m), 1135 (s), 1066 (s); **LRMS** (ES^+) m/z 464, 466 & 468 ($[M + H]^+$), 486, 488 & 490 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{22}H_{35}Cl_2NNaO_3S$, requires 486.1607, found 486.1610 Da.

(2.18.3) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (3H, s, $\underline{H}_{Ar}$ x 3), 4.65 (1H, d, *J* = 8.8 Hz, N$\underline{H}$), 2.99 (1H, m, C$\underline{H}$), 2.17 (6H, s, $C_{Ar}C\underline{H}_3$ x 2), 1.25 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 128.8 ($\underline{C}_{Ar\ meta}$ x 2), 126.2 ($\underline{C}_{Ar\ para}$), 57.3 (C$\underline{H}$), 56.5 (C$\underline{(CH_3)_3}$), 48.4 (C$\underline{H}$), 44.7 (C$\underline{H}_2$Cl), 44.5 (C$\underline{H}_2$Cl), 32.1 (C$\underline{H}_2$), 30.5 (C$\underline{H}_2$), 26.3 (C$\underline{H}_2$), 24.0 (C$\underline{H}_2$), 22.9 (C(C$\underline{H}_3$)$_3$), 16.7 ($C_{Ar}C\underline{H}_3$ x 2).

(2.19) (+)-(2R,3S)-7-Chloro-2-(3-chloropropyl)-3-((S)-2-methylpropane-2-sulfinylamino)-1-phenyl heptanoate



$C_{20}H_{31}Cl_2NO_3S$, 436.44 g/mol

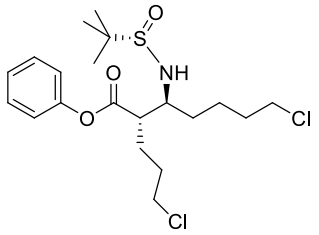
General procedure **B** for the imino-aldol reaction was followed using LDA (13.7 mL of 1.20 M soln. in THF, 16.4 mmol, 1.37 equiv), THF (120 mL), phenyl ester **2.09** (3.32 g, 15.6 mmol, 1.3 equiv) as a solution in THF (3.6 mL) and

sulfinimine **1.140** (2.68 g, 12.0 mmol, 1.0 equiv). The reaction was quenched after 1 h. Work up yielded the crude product as a brown liquid (6.05 g, integration of NH peaks in crude ^{1}H NMR gives dr = 93:7, ***R,S***:***S,S***, diastereomer **2.19-*R,R***, isolated under different reaction conditions, was not observed). Purification of the crude product by column chromatography (SiO_2 gel, eluent 4:1 hexane/EtOAc) yielded the product as a yellow solid (3.13 g, 60%, 98:2 dr by ^{1}H NMR). Recrystallisation from EtOAc/hexane yielded the pure major diastereomer ***R,S*** (2.31 g, 5.3 mmol, 44%). Column chromatography of the combined filtrates (SiO_2 gel, eluent gradient 1:3 → 2:2 EtOAc/hexane) afforded a mixture of diastereomers ***R,S*** and ***S,S*** (1.36 g, 3.1 mmol, 26%). This gives a combined isolated yield of the major diastereomer ***R,S*** of 70%. Further careful chromatography of the mixture of diastereomers enabled isolation of the minor diastereomer ***S,S*** for characterisation purposes. Diastereomer ***R,R*** was not observed under these conditions.

(2.19-R,S)

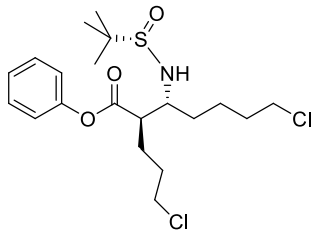
MP 92 - 94 ºC (EtOAc/hexane); **$[\alpha]_D^{27}$** +21.0 (*c* 1.04, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.37 (2H, m, $H_{Ar\ meta}$ x 2), 7.30 - 7.23 (1H, m, $H_{Ar\ para}$), 7.12 - 7.06 (2H, m, $H_{Ar\ ortho}$ x 2), 4.19 (1H, d, *J* = 8.5 Hz, NH), 3.68 - 3.58 (2H, m, CH_2Cl), 3.56 (2H, t, *J* = 6.3 Hz, CH_2Cl), 3.53 - 3.45 (1H, m, NHCH), 3.18 (1H, dt, *J* = 8.8, 4.7 Hz, CO_2CH), 2.09 - 1.50 (10H, m, CH_2 x 5), 1.25 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.24 (CO_2Ph), 150.18 ($C_{Ar\ ipso}$), 129.58 ($C_{Ar\ meta}$ x 2), 126.20 ($C_{Ar\ para}$), 121.42 ($C_{Ar\ ortho}$ x 2), 58.50 (NHCH), 56.25 ($C(CH_3)_3$), 50.07 ($CHCO_2Ph$), 44.72 (CH_2Cl), 44.51 (CH_2Cl), 32.03 (CH_2), 31.48 (CH_2), 30.60 (CH_2), 26.16 (CH_2), 23.66 (CH_2), 22.74 ($C(CH_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2956 (m), 1751 (s), 1492 (m), 1190 (s), 1163 (s), 1128 (s), 1066 (s); **LRMS** (ES^+) *m/z* 458, 460 & 462 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{20}H_{31}Cl_2NNaO_3S$, requires 458.1294, found 458.1284 Da.
See **Appendix 6.1** for X-ray crystallography data.

(2.19-S,S)



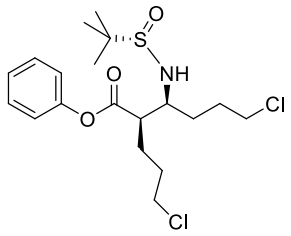
[α]$_D^{27}$ +9.70 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 - 7.36 (2H, m, $\underline{H}_{Ar\ meta}$ x 2), 7.31 - 7.23 (1H, m, $\underline{H}_{Ar\ para}$), 7.12 - 7.03 (2H, m, $\underline{H}_{Ar\ ortho}$ x 2), 4.47 (1H, d, *J* = 8.4 Hz, N$\underline{H}$), 3.68 - 3.59 (2H, m, C$\underline{H}_2$Cl), 3.56 (2H, t, *J* = 6.4 Hz, C$\underline{H}_2$Cl), 3.53 - 3.46 (1H, m, NHC$\underline{H}$), 2.96 - 2.86 (1H, m, $CO_2C\underline{H}$), 2.21 - 1.49 (10H, m, C$\underline{H}_2$ x 5), 1.25 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.41 ($\underline{C}O_2$Ph), 150.10 ($\underline{C}_{Ar\ ipso}$), 129.60 ($\underline{C}_{Ar\ meta}$ x 2), 126.29 ($\underline{C}_{Ar\ para}$), 121.34 ($\underline{C}_{Ar\ ortho}$ x 2), 57.75 (NH$\underline{C}$H), 56.39 ($\underline{C}$(CH$_3$)$_3$), 48.55 ($\underline{C}$HCO$_2$Ph), 44.68 ($\underline{C}$H$_2$Cl), 44.28 ($\underline{C}$H$_2$Cl), 35.08 ($\underline{C}$H$_2$), 32.08 ($\underline{C}$H$_2$), 30.45 ($\underline{C}$H$_2$), 26.76 ($\underline{C}$H$_2$), 23.54 ($\underline{C}$H$_2$), 22.88 (C($\underline{C}$H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2956 (m), 1740 (s), 1189 (s), 1162 (s), 1131 (s), 1063 (s); **LRMS** (ES$^+$) *m/z* 458, 460 & 462 ([M + Na]$^+$).

(2.19-R,R) selected data



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, t, *J* = 7.8 Hz, $\underline{H}_{Ar\ meta}$ x 2), 7.27 (1H, t, *J* = 6.0 Hz, $\underline{H}_{Ar\ para}$), 7.09 (2H, d, *J* = 8.7 Hz, $\underline{H}_{Ar\ ortho}$ x 2), 3.78 (1H, d, *J* = 9.4 Hz, N$\underline{H}$), 3.65 - 3.56 (4H, m, C$\underline{H}_2$Cl x 2), 3.56 - 3.47 (1H, m, NHC$\underline{H}$), 2.92 - 2.85 (1H, m, $CO_2C\underline{H}$), 2.09 - 1.63 (10H, m, C$\underline{H}_2$ x 5), 1.24 (9H, s, C(C$\underline{H}_3$)$_3$).

(2.20-R,S) (+)-(2R,3S)-6-Chloro-2-(3-chloropropyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl hexanoate



$C_{19}H_{29}Cl_2NO_3S$, 422.41 g/mol

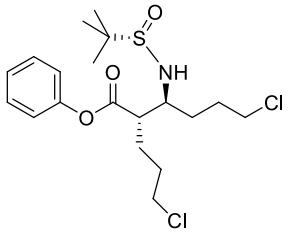
General procedure **B** for imino-aldol reaction was followed using LDA (12.4 mL of 1.32 M soln. in THF, 16.4 mmol, 1.37 equiv), THF (120 mL), phenyl ester **2.09** (3.32 g, 15.6 mmol, 1.3 equiv) and sulfinimine **1.139** (2.51 g, 12.0 mmol, 1.0 equiv) were used. The reaction was stopped after 1 h. Integration of NH peaks in ^{1}H NMR of the crude product gives 94:6 dr, ***R,S***:***S,S***, diastereomers **2.20-*R,R*** and **2.20-*S,R***, isolated under different reaction conditions, was not observed. Purification by column chromatography (SiO_2 gel, eluent gradient 1:3 → 2:2 → 3:1 EtOAc/hexane) yielded the imino-aldol product as a mixture of diastereomers as a yellow liquid (3.96 g, 9.39 mmol, 78%). This was recrystallised (EtOAc/hexane) to yield the major diastereomer as a white crystalline solid (2.02 g, 4.8 mmol, 40%). The filtrates contained more of the major diastereomer which was not isolated.

(2.20-R,S)

MP = 66 - 70 °C; **$[\alpha]_D^{27}$** +5.90 (*c* 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.38 (2H, m, $H_{Ar\ meta}$ x 2), 7.30 - 7.24 (1H, m, $H_{Ar\ para}$), 7.14 - 7.08 (2H, m, $H_{Ar\ ortho}$ x 2), 4.25 (1H, d, *J* = 9.0 Hz, NH), 3.69 - 3.57 (4H, m, CH_2Cl and CH_2Cl), 3.54 - 3.45 (1H, m, CHNH), 3.22 (1H, dt, *J* = 4.7, 8.9 Hz, CO_2CH), 2.14 - 1.63 (8H, m, CH_2 x 4), 1.25 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.11 (CO_2Ph), 150.12 ($C_{Ar\ ipso}$), 129.53 ($C_{Ar\ meta}$ x 2), 126.19 ($C_{Ar\ para}$), 121.40 ($C_{Ar\ ortho}$ x 2), 58.17 (NHCH), 56.27 ($C(CH_3)_3$), 50.15 ($CHCO_2Ph$), 44.43 (CH_2Cl x 2), 30.55 (CH_2), 29.39 (CH_2), 29.26 (CH_2), 26.22 (CH_2), 22.68 (($CH_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2959 (m), 1749 (s), 1492 (m), 1189 (s), 1162 (s), 1128 (s), 1051

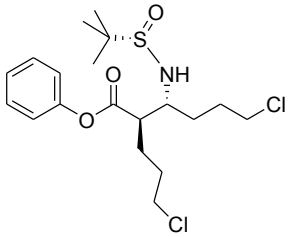
(s); **LRMS** (ES^+) *m/z* 444, 446 & 448 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{19}H_{29}Cl_2NNaO_3S$, requires 444.1137, found 444.1143 Da.
See **Appendix 6.1** for X-ray crystallography data.

(2.20-S,S)



$[\alpha]_D^{23}$ +5.45 (*c* 1.01, $CHCl_3$); **^{1}H NMR** (400 MHz ,$CDCl_3$) δ 7.45 - 7.37 (2H, m, $H_{Ar\ meta}$), 7.30 - 7.24 (1H, m, $H_{Ar\ para}$), 7.12 - 7.06 (2H, m, $H_{Ar\ ortho}$ x 2), 4.50 (1H, d, *J* = 8.5 Hz, NH), 3.70 - 3.61 (2H, m, CH_2Cl), 3.59 (2H, t, *J* = 6.5 Hz, CH_2Cl), 3.56 - 3.50 (1H, m, CH), 2.94 - 2.88 (1H, m, CO_2CH), 2.18 - 1.67 (8H, m, CH_2 x 4), 1.25 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.34 (CO_2Ph), 150.11 ($C_{Ar\ ipso}$), 129.61 ($C_{Ar\ meta}$ x 2), 126.31 ($C_{Ar\ para}$), 121.37 ($C_{Ar\ ortho}$ x 2), 57.41 (NHCH), 56.49 ($C(CH_3)_3$), 48.71 ($CHCO_2Ph$), 44.49 (CH_2Cl), 44.25 (CH_2Cl), 33.08 (CH_2), 30.46 (CH_2), 29.25 (CH_2), 26.72 (CH_2), 22.89 (($CH_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2959 (m), 1743 (s), 1492 (m), 1191 (s), 1163 (s), 1133 (s), 1065 (s); **LRMS** (ES^+) *m/z* 422, 424 & 426 ($[M + H]^+$), 444, 446 & 448 ($[M + Na]^+$).

(2.20-R,R)[a]

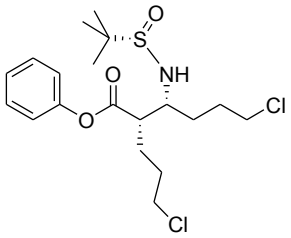


$[\alpha]_D^{24}$ +22.2 (*c* 0.62, $CHCl_3$); **^{1}H NMR** (400 MHz ,$CDCl_3$) δ 7.46 - 7.36 (2H, m, $H_{Ar\ meta}$), 7.30 - 7.23 (1H, m, $H_{Ar\ para}$), 7.13 - 7.04 (2H, m, $H_{Ar\ ortho}$), 3.76 (1H, d, *J* = 9.2 Hz, NH), 3.69 - 3.49 (5H, m, CH_2Cl x 2, CH), 2.90 - 2.83 (1H, m, CO_2CH),

[a] isolated as a mixture with diastereomer ***S,R***.

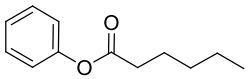
2.19 - 1.74 (8H, m, $C\underline{H}_2$ x 4), 1.24 (9H, s, $C(C\underline{H}_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.52 ($\underline{C}O_2Ph$), 150.23 ($\underline{C}_{Ar\ ipso}$), 129.59 ($\underline{C}_{Ar\ meta}$ x 2), 126.23 ($\underline{C}_{Ar\ para}$), 121.35 ($\underline{C}_{Ar\ ortho}$ x 2), 57.91 (NH$\underline{C}$H), 56.65 ($\underline{C}(CH_3)_3$), 49.60 ($\underline{C}HCO_2Ph$), 44.68 ($\underline{C}H_2Cl$), 44.34 ($\underline{C}H_2Cl$), 32.44 ($\underline{C}H_2$), 30.15 ($\underline{C}H_2$), 28.86 ($\underline{C}H_2$), 27.16 ($\underline{C}H_2$), 22.84 (($\underline{C}H_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2959 (m), 2359 (w), 1751 (s), 1492 (m), 1192 (s), 1163 (s), 1131 (s), 1058 (s); **LRMS** (ES^+) *m/z* 444, 446 & 448 ($[M + Na]^+$).

(2.20-S,R)[a]



^{1}H NMR (400 MHz ,$CDCl_3$) δ 3.29 (1H, d, *J* = 7.7 Hz, N$\underline{H}$), 3.22 (1H, m, $CO_2C\underline{H}$), 1.25 (9H, s, $C(C\underline{H}_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 129.54 ($\underline{C}_{Ar\ meta}$ x 2), 126.11 ($\underline{C}_{Ar\ para}$), 58.03 (NH$\underline{C}$H), 56.46 ($\underline{C}(CH_3)_3$), 51.08 ($\underline{C}HCO_2Ph$), 44.63 ($\underline{C}H_2Cl$), 44.49 ($\underline{C}H_2Cl$), 31.27 ($\underline{C}H_2$), 30.38 ($\underline{C}H_2$), 28.81 ($\underline{C}H_2$), 25.35 ($\underline{C}H_2$), 22.79 (($\underline{C}H_3)_3$).

(2.26) Phenyl hexanoate



$C_{12}H_{16}O_2$, 192.25 g/mol

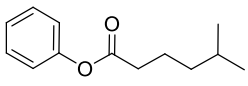
To a dry solution of DMF (1.55 mL, 1.46 g, 20.0 mmol, 1.0 equiv) and hexanoic acid (2.51 mL, 2.32 g, 20.0 mmol, 1.0 equiv) in hexane (40 mL), oxalyl chloride (8.46 mL, 12.69 g, 100 mmol, 5.0 equiv) was carefully added. The reaction mixture was left stirring for 1 h after which the colourless upper layer of the biphasic solution was separated into a dry flask and concentrated *in vacuo* to yield hexanoyl chloride as a yellow liquid (**2.23**). No further purification was

[a] isolated as a mixture with diastereomer ***R*,*R***, other ^{1}H and ^{13}C NMR signals were obscured in the mixed spectrum

attempted. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.89 (2H, t, *J* = 7.4 Hz, C$\underline{H}_2$COCl), 1.73 (2H, quin, *J* = 7.3 Hz, C$\underline{H}_2$CH$_3$), 1.42 - 1.24 (4H, m, C$\underline{H}_2$ x 2), 0.98 - 0.88 (3H, m, C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8 (C$\underline{O}$Cl), 47.1 (C$\underline{H}_2$COCl), 30.5 (C$\underline{H}_2$), 24.7 (C$\underline{H}_2$), 22.1 (C$\underline{H}_2$), 13.8 (C$\underline{H}_3$). Adapted from the procedure described by Gilbert *et al.*[89] to a dry flask charged with phenol (2.89 g, 20.1 mmol, 1.01 equiv) at 0 °C hexanoyl chloride (**2.23**, used unpurified from the previous reaction) was added slowly *via* syringe. The reaction was then heated to 60 °C for 90 min. Purification by column chromatography (SiO_2 gel, eluent gradient 19:1 → 18:2 hexane/EtOAc) yielded the title ester as a colourless liquid (2.38 g, 12.4 mmol, 62%). Data were consistent with the literature.[90]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.34 (2H, m, $\underline{H}_{Ar}$ x 2), 7.26 - 7.19 (1H, m, $\underline{H}_{Ar\ para}$), 7.10 - 7.08 (2H, m, $\underline{H}_{Ar}$ x 2), 2.57 (2H, t, *J* = 7.4 Hz, C$\underline{H}_2$CO$_2$), 1.78 (2H, quin, *J* = 7.4 Hz, C$\underline{H}_2$), 1.47 - 1.33 (4H, m, C$\underline{H}_2$ x 2), 0.93 (3H, t, *J* = 7.0 Hz, C$\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.3 (C$\underline{O}$), 150.8 ($\underline{C}_{Ar\ ipso}$), 129.4 ($\underline{C}_{Ar}$ x 2), 125.7 ($\underline{C}_{Ar\ para}$), 121.6 ($\underline{C}_{Ar}$ x 2), 34.4 (C$\underline{H}_2$), 31.3 (C$\underline{H}_2$), 24.6 (C$\underline{H}_2$), 22.3 (C$\underline{H}_2$), 13.9 (C$\underline{H}_3$); **IR** (film) ν_{max}/cm^{-1} 2957 (m), 2931 (m), 1759 (s), 1493 (m), 1194 (s), 1161 (s), 1139 (s), 1101 (s), 688 (s).

(2.27) Phenyl 5-methylhexanoate



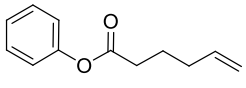
$C_{13}H_{18}O_2$, 206.28 g/mol

To a dry solution of DMF (1.55 mL, 1.46 g, 20.0 mmol, 1.0 equiv) and 5-methylhexanoic acid (2.86 mL, 2.60 g, 20.0 mmol, 1.0 equiv) in hexane (40 mL), oxalyl chloride (8.46 mL, 12.69 g, 100 mmol, 5.0 equiv) was very carefully added portionwise. The reaction mixture was left stirring for 1 h after which the colourless upper layer of the biphasic solution was separated into a dry flask and concentrated *in vacuo* to yield 5-methylhexanoyl chloride (**2.24**) as a yellow liquid. No further purification was attempted. Spectroscopic data were consistent with the literature.[91] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.87 (2H, t, *J* = 7.4

Hz, C$\underline{H}_2$COCl), 1.78 - 1.66 (2H, m, C$\underline{H}_2$), 1.57 (1H, spt, *J* = 6.6 Hz, C$\underline{H}$), 1.29 - 1.18 (2H, m, C$\underline{H}_2$), 0.90 (6H, d, *J* = 6.6 Hz, C$\underline{H}_3$ x 2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8 (C$\underline{O}$Cl), 47.3 (C$\underline{H}_2$COCl), 37.6 (C$\underline{H}_2$), 27.6 (C$\underline{H}$), 23.0 (C$\underline{H}_2$), 22.3 (C$\underline{H}_3$ x 2). Adapted from the procedure described by Gilbert *et al.*[89] to a dry flask charged with phenol (2.89 g, 20.1 mmol, 1.01 equiv) at 0 °C 5-methylhexanoyl chloride (**2.24**, used unpurified from the previous reaction) was added slowly *via* syringe. The reaction was then heated to 60 °C and stirred for 1.5 h. Purification by column chromatography (SiO_2 gel, eluent gradient 19:1 → 18:2 hexane/EtOAc) yielded the title ester as a colourless liquid (2.96 g, 14.4 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 - 7.34 (2H, m, $\underline{H}_{Ar}$ x 2), 7.23 (1H, t, *J* = 7.4 Hz, $\underline{H}_{Ar\ para}$), 7.14 - 7.04 (2H, m, $\underline{H}_{Ar}$ x 2), 2.55 (2H, t, *J* = 7.4 Hz, C$\underline{H}_2$CO$_2$), 1.84 - 1.72 (2H, m, C$\underline{H}_2$), 1.70 - 1.57 (1H, septet, *J* = 6.6 Hz, C$\underline{H}$), 1.38 - 1.24 (2H, m, C$\underline{H}_2$), 0.94 (3H, s, C$\underline{H}_3$), 0.93 (3H, s, C$\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.3 (C$\underline{O}_2$), 150.8 ($\underline{C}_{Ar\ ipso}$), 129.4 ($\underline{C}_{Ar}$ x 2), 125.7 ($\underline{C}_{Ar\ para}$), 121.6 ($\underline{C}_{Ar}$ x 2), 38.3 (C$\underline{H}_2$), 34.6 (C$\underline{H}_2$), 27.8 (C$\underline{H}$), 22.8 (C$\underline{H}_2$), 22.5 (C$\underline{H}_3$ x 2); **IR** (film) ν_{max}/cm^{-1} 2954 (m), 1759 (s), 1493 (m), 1195 (s), 1161 (s), 1142 (s), 1104 (s), 688 (s); **LRMS** (EI) m/z 206 [$M^{+\bullet}$] (32%), 113 (51%), 94 (100%), 69 (53%), 43 (63%); **HRMS** (EI) for $C_{13}H_{18}O_2$, requires 206.13068 found 206.13048 Da.

(2.28) Phenyl hex-5-enoate



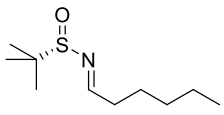
$C_{12}H_{14}O_2$, 190.24 g/mol

To a dry solution of DMF (1.55 mL, 1.46 g, 20.0 mmol, 1.0 equiv) and 5-hexenoic acid (2.37 mL, 2.28 g, 20.0 mmol, 1.0 equiv) in hexane (40 mL), oxalyl chloride (8.46 mL, 12.69 g, 100 mmol, 5.0 equiv) was very carefully added portionwise. The reaction mixture was left stirring for 1 h after which the colourless upper layer of the biphasic solution was separated into a dry flask and concentrated *in vacuo* to yield hex-5-enoyl chloride (**2.25**) as a yellow liquid. No further purification was attempted. Spectroscopic data were

consistent with the literature.[92] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* = 17.0, 10.3, 6.4 Hz, =C<u>H</u>), 5.12 - 5.00 (2H, m, =C<u>H</u>$_2$), 2.91 (2H, t, *J* = 7.0 Hz, C<u>H</u>$_2$COCl), 2.14 (2H, tdt, *J* = 7.4, 6.4, 0.8 Hz, C<u>H</u>$_2$CHCH$_3$) 1.83 (2H, tt, *J* = 7.0, 7.4, C<u>H</u>$_2$CH$_2$CO$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.7 (<u>C</u>OCl), 136.6 (=<u>C</u>H), 116.2 (=<u>C</u>H$_2$), 46.2 (<u>C</u>H$_2$COCl), 32.2 (<u>C</u>H$_2$), 24.1 (<u>C</u>H$_2$). Adapted from the procedure described by Gilbert *et al.*[89] to a dry flask charged with phenol (2.89 g, 20.1 mmol, 1.01 equiv) at 0 °C hex-5-enoyl chloride (**2.25**, used unpurified from the previous reaction) was added slowly *via* syringe. The reaction was then heated to 60 °C for 1.5 h. Purification by column chromatography (SiO_2 gel, eluent gradient 19:1 → 18:2 hexane/EtOAc) yielded the title ester as a colourless liquid (2.38 g, 12.4 mmol, 62%). Data were consistent with the literature.[93]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 - 7.35 (2H, m, <u>H</u>$_{Ar}$ x 2), 7.26 - 7.20 (1H, m, <u>H</u>$_{Ar\ para}$), 7.13 - 7.06 (2H, m, <u>H</u>$_{Ar}$ x 2), 5.95 - 5.71 (1H, m, C<u>H</u>=), 5.14 - 5.01 (2H, m, C<u>H</u>$_2$=), 2.59 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$CO$_2$), 2.26 - 2.16 (2H, m, C<u>H</u>$_2$), 1.88 (2H, quin, *J* = 7.3 Hz, C<u>H</u>$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.1 (<u>C</u>O$_2$), 150.7 (<u>C</u>$_{Ar\ ipso}$), 137.5 (<u>C</u>H), 129.4 (<u>C</u>H$_{Ar}$ x 2), 125.7 (<u>C</u>H$_{Ar\ para}$), 121.5 (<u>C</u>H$_{Ar}$ x 2), 115.6 (<u>C</u>H$_2$), 33.6 (<u>C</u>H$_2$), 33.0 (<u>C</u>$_{Ar}$), 24.0 (<u>C</u>$_{Ar}$); **IR** (film) ν_{max}/cm^{-1} 2935 (w), 1757 (s), 1493 (m), 1193 (s), 1162 (s), 1132 (s), 913 (m), 688 (s).

(2.30) (+)-(S)-N-[(1E)-Hexylidene]-2-methylpropane-2-sulfinamide



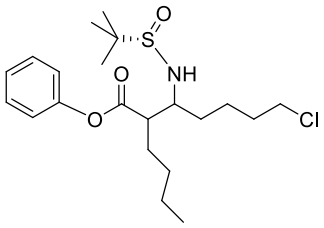
$C_{10}H_{21}NOS$, 203.34 g/mol

General procedure **A** for sulfinimine formation was followed using hexanal (**2.29**, 4.6 mL, 3.76 g, 37 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL), (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 3.03 g, 25 mmol, 1.0 equiv) and $CuSO_4$ (9.98 g, 62.5 mmol, 2.5 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 1:9 EtOAc/hexane) yielded the title sulfinimine as a

colourless liquid (3.48 g, 17 mmol, 69%). Data were consistent with the literature.[94]

$[\alpha]_D^{24}$ +237 (c 0.91, $CHCl_3$) (lit. **$[\alpha]_D$** +240 (c 1.0, $CHCl_3$))[94a]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (1H, t, *J* = 4.8 Hz, C<u>H</u>N), 2.52 (2H, td, *J* = 7.4, 4.8 Hz, C<u>H</u>$_2$CH(N)), 1.70 - 1.57 (2H, m, C<u>H</u>$_2$), 1.40 - 1.31 (4H, m, C<u>H</u>$_2$ x 2), 1.20 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.97 - 0.84 (3H, m, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.8 (<u>C</u>N), 56.5 (<u>C</u>(CH$_3$)$_3$), 36.1 (<u>C</u>H$_2$), 31.4 (<u>C</u>H$_2$), 25.2 (<u>C</u>H$_2$), 22.4 (<u>C</u>H$_2$), 22.4 (C(<u>C</u>H$_3$)$_3$),13.9 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1} 2656 (w), 2928 (w), 1621 (m), 1084 (s).

(2.31) 7-Chloro-2-butyl-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl heptanoate



$C_{21}H_{34}ClNO_3S$, 416.02 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (1.2 mL of a 1.8 M soln. in THF, 2.1 mmol, 2.1 equiv), THF (10.0 mL), phenyl hexanoate **2.26** (384 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **1.140** (224 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. The diastereomeric ratio was estimated from the crude ^{1}H NMR to be 6:94 (by integration of N<u>H</u> peaks at 4.50 and 4.19 ppm respectively) with the N<u>H</u> peaks of the other diastereomers indistinguishable from the baseline. Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 100:0 → 90:10 CH_2Cl_2/EtOAc) isolated the desired imino-aldol products as mixed diastereomers (268 mg, 0.64 mmol, 64%). The diastereomeric ratio estimated from the ^{1}H NMR of the isolated mixture was 90:4:4:2 for diastereomers 1:2:3:4 (by integration of N<u>H</u> peaks at 4.19, 3.84, 4.50 and 3.30 ppm respectively). Further purification by column chromatography (SiO_2 gel, 30:70 EtOAc/hexane)

[a] There is no temperature recorded for the $[\alpha]^D$ measurement in this paper.

of this mixture allowed isolation of a portion of the major diastereomer away from the other minor diastereomers for characterisation. Stereochemistry was not assigned.

(2.31.1)

MP 54 - 59 ºC; **$[\alpha]_D^{27}$** +7.6 (c 0.89, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.36 (2H, m, $\underline{H}_{Ar}$ x 2), 7.29 - 7.22 (1H, m, $\underline{H}_{Ar\ para}$), 7.12 - 7.04 (2H, m, $\underline{H}_{Ar}$ x 2), 4.19 (1H, d, *J* = 8.4 Hz, N$\underline{H}$), 3.56 (2H, t, *J* = 6.2 Hz, C$\underline{H}_2$Cl), 3.51 - 3.44 (1H, m, C$\underline{H}$), 3.17 - 3.11 (1H, m, C$\underline{H}$), 2.01 - 1.31 (12H, m, C$\underline{H}_2$ x 6), 1.24 (9H, s, C(C$\underline{H}_3$)$_3$), 0.98 - 0.91 (3H, m, C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.8 ($\underline{C}$O), 150.3 ($\underline{C}_{Ar\ ipso}$), 129.5 ($\underline{C}_{Ar}$ x 2), 126.1 ($\underline{C}_{Ar\ para}$), 121.5 ($\underline{C}_{Ar}$ x 2), 58.2 ($\underline{C}$H), 56.2 ($\underline{C}$(CH$_3$)$_3$), 50.7 ($\underline{C}$H), 44.7 ($\underline{C}$H$_2$Cl), 32.1 ($\underline{C}$H$_2$), 31.4 ($\underline{C}$H$_2$), 29.9 ($\underline{C}$H$_2$), 28.4 ($\underline{C}$H$_2$), 23.6 ($\underline{C}$H$_2$), 22.7 ($\underline{C}$H$_2$), 22.5 (C($\underline{C}$H$_3$)$_3$), 13.9 ($\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1} 3348 (w), 2955 (m), 1746 (m), 1189 (s), 1160 (m), 1046 (s); **LRMS** (ES^+) m/z 438, 440 & 442 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{21}H_{34}ClNO_3SNa$, requires 438.1840, found 438.1831 Da.

(2.31.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.84 (1H, d, *J* = 9.9 Hz, N$\underline{H}$), 2.84 (1H, ddd, *J* = 8.6, 6.0, 5.1, C$\underline{H}$).

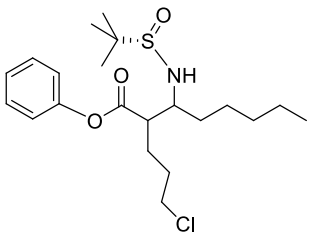
(2.31.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.50 (1H, d, *J* = 8.4 Hz, N$\underline{H}$), 2.86 (1H, m, C$\underline{H}$).

(2.31.4) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.30 (1H, d, *J* = 7.7 Hz, N$\underline{H}$), 2.78 (1H, ddd, *J* = 10.2, 5.8, 4.1, C$\underline{H}$).

(2.32) 2-(3-Chloropropyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl octanoate



$C_{21}H_{34}ClNO_3S$, 416.02 g/mol

General procedure **B** for imino-aldol reaction was followed using LDA (1.2 mL of a 1.8 M soln. in THF, 2.1 mmol, 2.1 equiv), THF (9.4 mL), phenyl ester **2.09** (425 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **2.30** (203 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 70 min. Purification of the crude product by column chromatography (SiO_2 gel, 1:3 EtOAc/hexane) yielded mixtures of diastereomers of the desired imino-aldol product (in total 250 mg, 0.60 mmol, 60%). The diastereomeric ratio was estimated from the ^{1}H NMR of the isolated mixture to be 83:10:5:2 for diastereomers 1:2:3:4 (by integration of NH peaks at 4.17, 4.44, 3.71 and 3.22 ppm respectively). Stereochemistry was not assigned.

(2.32.1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 - 7.38 (2H, m, H_{Ar} x 2), 7.29 - 7.23 (1H, m, $H_{Ar\ para}$), 7.12 - 7.05 (2H, m, H_{Ar} x 2), 4.17 (1H, d, *J* = 8.7 Hz, NH), 3.68 - 3.56 (2H, m, CH_2), 3.49 (1H, ddt, *J* = 8.7, 9.0, 4.3 Hz, NHCH), 3.16 (1H, dt, *J* = 9.0, 4.5 Hz, CO_2CH), 2.10 - 1.76 (4H, m, CH_2 x 2), 1.71 - 1.48 (4H, m, CH_2 x 2), 1.41 - 1.26 (4H, m, CH_2 x 2), 1.24 (9H, s, $C(CH_3)_3$), 0.91 (3H, t, *J* = 6.7 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.4 (CO), 150.2 ($C_{Ar\ ipso}$), 129.6 (C_{Ar} x 2), 126.2 ($C_{Ar\ para}$), 121.5 (C_{Ar} x 2), 58.6 (CHNH), 56.2 ($C(CH_3)_3$), 50.1 ($CHCO_2$), 44.6 (CH_2Cl), 32.2 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 22.7 ($C(CH_3)_3$), 22.5 (CH_2), 14.0 (CH_3); **LRMS** (ES^+) *m/z* 416, 418 & 420 ($[M + H]^+$); **HRMS** (ES^+) for $C_{21}H_{35}ClNO_3S$, requires 416.2021, found 416.2020 Da.

(2.32.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.44 (1H, d, *J* = 8.4 Hz, NH), 2.93 - 2.86 (1H, m, CH).

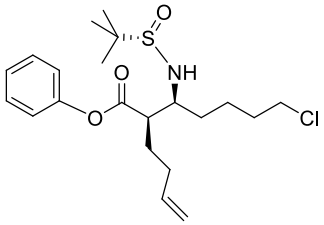
(2.32.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 - 7.35 (2H, m, H_{Ar} x 2), 7.31 - 7.18 (1H, m, H_{Ar}), 7.13 - 6.98 (2H, m, H_{Ar} x 2), 3.71 (1H, d, *J* = 9.4 Hz, NH), 3.65 - 3.56 (2H, m, CH_2), 3.53 - 3.45 (1H, m, NHCH), 2.95 - 2.82 (1H, m, CO_2CH), 2.10 - 1.29 (12H, m, CH_2 x 6), 1.22 (9H, s, $C(CH_3)_3$), 0.97 - 0.82 (3H, m, CH_3); **LRMS** (ES^+) *m*/*z* 416, 418 & 420 ($[M + H]^+$), 438, 440 & 442 ($[M + Na]^+$).

(2.32.4) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.22 (1H, d, *J* = 7.6 Hz, NH), 2.79 (1H, dt, *J* = 8.2, 5.6 Hz, CO_2CH).

(2.33) 7-Chloro-2-(but-3-enyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl heptanoate



$C_{21}H_{32}ClNO_3S$, 414.00 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (1.2 mL of a 1.8 M soln. in THF, 2.1 mmol, 2.1 equiv), dry THF (10.0 mL), phenyl ester **2.28** (380 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **1.140** (224 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. Purification by column chromatography (SiO_2 gel, eluent gradient 100:0 → 90:10 CH_2Cl/EtOAc) yielded a mixture of diastereomers of the desired imino-aldol product (in total 242 mg, 0.58 mmol, 58%). The diastereomeric ratio was estimated from the ^{1}H NMR of the isolated diastereomer mixture to be 88:6:4:2

for diastereomers 1:2:3:4 (by integration of NH peaks at 4.18, 4.51, 3.82 and 3.24 ppm respectively). Further purification by column chromatography (SiO_2 gel, 1:1 hexane/EtOAc) enabled a small portion of diastereomer **2.33.1** to be isolated as a white solid for characterisation. Stereochemistry was not assigned.

(2.33.1)

MP 66 - 68 ºC; **$[\alpha]_D^{24}$** +15.9 (*c* 0.55, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.46 - 7.35 (2H, m, $H_{Ar\ ortho}$ x 2), 7.30 - 7.21 (1H, m, $H_{Ar\ para}$), 7.13 - 7.05 (2H, m, $H_{Ar\ meta}$ x 2), 5.85 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, CH=), 5.17 -5.01 (2H, m, CH_2=), 4.18 (1H, d, *J* = 8.4 Hz, NH), 3.52 (2H, t, *J* = 6.2 Hz, CH_2Cl), 3.48 (1H, ddt, *J* = 9.1, 8.4, 4.5, NHCH), 3.17 (1H, dt, *J* = 9.1, 4.6 Hz, CO_2CH), 2.35 -1.41 (10H, m, CH_2 x 5), 1.24 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.6 (CO_2), 150.3 ($C_{Ar\ ipso}$), 137.2 (CH=), 129.5 ($C_{Ar\ ortho}$ x 2), 126.1 ($C_{Ar\ para}$), 121.5 ($C_{Ar\ meta}$ x 2), 115.9 (CH_2=), 58.2 (NHCH), 56.2 ($C(CH_3)_3$), 49.9 (CO_2CH), 44.7 (CH_2Cl), 32.1 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 28.0 (CH_2), 23.6 (CH_2), 22.7 (CH_3 x 3); **IR** (film) ν_{max}/cm^{-1} 2955 (w), 1742 (m), 1186 (s), 1160 (m), 1049 (s); **LRMS** (ES^+) *m/z* 414 & 416 ($[M + H]^+$) and 436 & 438 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{21}H_{33}ClNO_3S$, requires 414.1864, found 414.1860 Da.

(2.33.2) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.51 (1H, d, *J* = 7.7 Hz, NH), 2.90 (1H, ddd, *J* = 9.0, 5.9, 3.5 Hz, $CHCO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 173.8 (CO_2), 150.2 ($C_{Ar\ ipso}$), 126.2 ($C_{Ar\ para}$), 121.4 ($C_{Ar\ meta}$ x 2), 57.7 (NHCH), 56.3 ($C(CH_3)_3$), 48.1 (CO_2CH), 35.3 (CH_2), 32.1 (CH_2), 29.1 (CH_2), 23.5 (CH_2), 22.9 (CH_3 x 3).

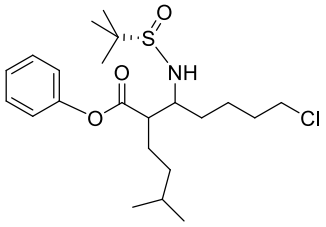
(2.33.3) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.82 (1H, d, *J* = 9.9 Hz, NH), 2.89 (1H, ddd, *J* = 8.4, 6.0, 4.6 Hz, $CHCO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 173.1 (CO_2), 137.0 (CH=), 121.4 ($C_{Ar\ meta}$ x 2), 116.1 (CH_2=), 58.3 (NHCH), 56.6 ($C(CH_3)_3$), 48.4 (CO_2CH), 44.7 (CH_2Cl), 35.0 (CH_2), 32.2 (CH_2), 31.3 (CH_2), 29.2 (CH_2), 23.1 (CH_2), 22.8 (CH_3 x 3).

(2.33.4) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47 - 7.33 (2H, m, H_{Ar} x 2), 7.30 - 7.21 (1H, m, $H_{Ar\ para}$), 7.13 - 7.03 (2H, m, H_{Ar} x 2), 5.83 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, C<u>H</u>=), 5.16 - 5.02 (2H, m, CH_2), 3.73 - 3.63 (1H, m, C<u>H</u>NH), 3.58 (2H, t, *J* = 6.5 Hz, CH_2Cl), 3.24 (1H, d, *J* = 8.0 Hz, N<u>H</u>), 2.86 - 2.78 (1H, m, C<u>H</u>CO_2), 2.34 - 1.62 (10H, m, CH_2 x 5), 1.23 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.1 (CO_2), 137.3 (<u>C</u>H=), 129.5 ($C_{Ar\ ortho}$ x 2), 126.0 ($C_{Ar\ para}$), 121.4 ($C_{Ar\ meta}$ x 2), 116.0 (CH_2=), 58.5 (NH<u>C</u>H), 56.4 ($C(CH_3)_3$), 50.1 (CO_2<u>C</u>H), 44.6 (CH_2Cl), 33.3 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 26.8 (CH_2), 23.2 (CH_2), 22.8 ($C(CH_3)_3$).

(2.34) 7-Chloro-2-(3-methyl butyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl heptanoate



$C_{22}H_{36}ClNO_3S$, 430.04 g/mol

General procedure **B** for imino-aldol reaction was followed using LDA (1.2 mL of a 1.8 M soln. in THF, 2.1 mmol, 2.1 equiv), THF (10.0 mL), phenyl ester **2.27** (412 mg, 2.0 mmol, 2.0 equiv) and sulfinimine **1.140** (224 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. Purification by column chromatography (SiO_2 gel, 10:0 → 9:1 CH_2Cl_2/EtOAc) isolated the desired imino aldol product as a mixture of diastereomers (239 mg, 0.56 mmol, 56%). Further purification by column chromatography (SiO_2 gel, 3:7 EtOAc/hexane) of this mixture enabled isolation of the major diastereomer **2.34.1** (a white solid) for characterisation purposes. Analysis of the isolated mixture of diastereomers by integration of the ^{1}H NMR gives a diastereomeric ratio of 91:5:2:2 for

diastereomers 1:2:3:4 (by integration of NH peaks at 4.19, 4.50, 3.35 and 3.88 ppm respectively). Stereochemistry was not assigned.

(2.34.1)

MP 57 - 61 ºC; **$[\alpha]_D^{27}$** +11.6 (*c* 1.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.46 - 7.35 (2H, m, H_{Ar} x 2), 7.32 - 7.21 (1H, m, $H_{Ar\ para}$), 7.15 - 7.02 (2H, m, H_{Ar} x 2), 4.19 (1H, d, *J* = 8.4 Hz, NH), 3.56 (2H, t, *J* = 6.4 Hz, CH_2Cl), 3.52 - 3.44 (1H, m, CH), 3.15 - 3.08 (1H, m, CH), 1.99 - 1.27 (11H, m, CH_2 x 5, $CH(CH_3)_2$), 1.25 (9H, s, $C(CH_3)_3$), 0.94 (3H, s, CH_3), 0.92 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ pm 172.8 (CO), 150.3 ($C_{Ar\ ipso}$), 129.5 (C_{Ar} x 2), 126.1 ($C_{Ar\ para}$), 121.5 (C_{Ar} x 2), 58.3 (CH), 56.2 ($C(CH_3)_3$), 51.0 (CH), 44.6 (CH_2), 36.8 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 22.5 ($C(CH_3)_3$), 22.4 (CH_3); **IR** (film) ν_{max}/cm^{-1} 2953 (m), 2867 (w), 1756 (m), 1188 (m), 1157 (m), 1109 (m), 1056 (s); **LRMS** (ES^+) *m*/*z* 430 & 432 ($[M + H]^+$), 452 & 454 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{22}H_{37}ClNO_3S$, requires 430.2177, found 430.2182 Da.

(2.34.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.50 (1H, d, *J* = 7.7 Hz, NH)

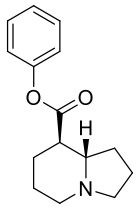
(2.34.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.35 (1H, d, *J* = 7.7 Hz, NH)

(2.34.4) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.88 (1H, d, *J* = 9.8 Hz, NH)

(3.01-R,S) (–)-(8R,8aS)-Phenyl octahydroindolizine-8-carboxylate

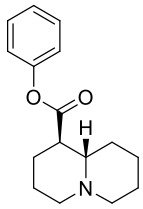


$C_{15}H_{19}NO_2$, 245.32 g/mol

To imino-aldol product **2.20-*R,S*** (75 mg, 0.176 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL), a solution of 4 M HCl(aq) in 1,4-dioxane (0.34 mL) was added and stirred r for 1 h. The reaction mixture was concentrated *in vacuo* to give a yellow oil. This oil was dissolved in MeCN (1.27 mL) then K_2CO_3 (199 mg, 1.44 mmol, 8 equiv) and NaI (3 mg, 0.02 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an orange oil (30 mg). Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:4 EtOAc/hexane) yielded the title indolizidine as a yellow oil (26 mg, 0.106 mmol, 56%).

$[\alpha]_D^{25}$ – 50.6 (*c* 0.74, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.44 - 7.33 (2H, m, $H_{Ar\ ortho}$ x 2), 7.26 - 7.19 (1H, m, $H_{Ar\ para}$), 7.11 - 7.02 (2H, m, $H_{Ar\ meta}$ x 2), 3.19 - 3.05 (2H, m, NCHH and NC'HH), 2.51 (1H, ddd, *J* = 11.9, 9.4, 3.6 Hz, CHCO), 2.25 - 2.02 (5H, m, NCHH, NC'HH, NCH and CH_2), 1.92 - 1.54 (6H, m, CH_2 x 3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.8 (CO), 150.6 ($C_{Ar\ ipso}$), 129.4 ($C_{Ar\ ortho}$ x 2), 125.7 ($C_{Ar\ para}$), 121.5 ($C_{Ar\ meta}$ x 2), 65.1 (NCH), 54.0 (NCH_2), 52.2 (NCH_2), 48.2 (COCH), 29.3 (CH_2), 28.1 (CH_2), 24.8 (CH_2), 20.6 (CH_2); **IR** (film) ν_{max}/cm^{-1} 2938 (m), 2787 (w), 1753 (s), 1493 (m), 1192 (s), 1163 (m), 1114 (s); **LRMS** (ES^+) *m/z* 246 ($[M + H]^+$); **HRMS** (ES^+) for $C_{15}H_{20}NO_2$, requires 246.1489, found 246.1485 Da.

(3.02-R,S) (–)-(1R,9aS)-Phenyl octahydro-1H-quinolizine-1-carboxylate

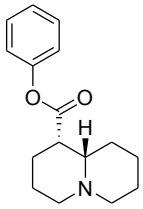


$C_{16}H_{21}NO_2$, 259.34 g/mol

To imino-aldol product **2.19-*R,S*** (51 mg, 0.12 mmol, 1.0 equiv) in 1,4-dioxane (0.65 mL), a solution of 4 M HCl (aq) in 1,4-dioxane (0.22 mL) was added and stirred for 1.25 h. The reaction mixture was concentrated *in vacuo* to give a yellow oil. The oil was dissolved in MeCN (0.83 mL) then K_2CO_3 (130 mg, 0.94 mmol, 8 equiv) and NaI (2 mg, 0.01 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield an orange oil (28 mg). Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:4 EtOAc/hexane) yielded the title quinolizidine as a yellow oil (18 mg, 0.07 mmol, 59%).

$[\alpha]_D^{25}$ +31.6 (*c* 0.86, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.43 - 7.33 (2H, m, $\underline{H}_{Ar\ ortho}$ x 2), 7.28 - 7.19 (1H, m, $\underline{H}_{Ar\ para}$), 7.10 - 7.03 (2H, m, $\underline{H}_{Ar\ meta}$ x 2), 2.86 (2H, m, NC$\underline{H}$H and NC'$\underline{H}$H), 2.52 (1H, ddd, *J* = 12.0, 10.0, 4.0 Hz, C$\underline{H}$CO), 2.21-2.06 (4H, m, NC$\underline{H}$, NCH$\underline{H}$ and C$\underline{H}_2$), 1.88 - 1.59 (7H, m, C$\underline{H}_2$ x 3 and NC'H$\underline{H}$), 1.47 - 1.25 (2H, m, C$\underline{H}_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 173.2 ($\underline{C}O_2$), 150.6 ($\underline{C}_{Ar\ ipso}$), 129.4 ($\underline{C}_{Ar\ ortho}$ x 2), 125.8 ($\underline{C}_{Ar\ para}$), 121.5 ($\underline{C}_{Ar\ meta}$ x 2), 63.5 (N$\underline{C}$H), 56.6 (N$\underline{C}H_2$), 56.0 (N$\underline{C}H_2$), 49.5 (CO$\underline{C}$H), 31.0 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 24.5 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$); **IR** (film) ν_{max}/cm^{-1} 2933 (m), 1750 (s), 1492 (m), 1193 (s), 1179 (s), 1156 (s), 1110 (s); **LRMS** (ES$^+$) *m/z* 260 ([M + H]$^+$); **HRMS** (ES$^+$) for $C_{16}H_{22}NO_2$, requires 260.1645, found 260.1648 Da.

(3.03-S,S) (+)-(1S,9aS)-Phenyl octahydro-1H-quinolizine-1-carboxylate

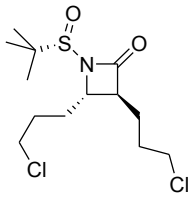


$C_{16}H_{21}NO_2$, 259.34 g/mol

To imino-aldol product **2.20-*S,S*** (88 mg, 0.20 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL), a solution of 4 M HCl(aq) in 1,4-dioxane (0.34 mL) was added and then stirred for 2 h. The reaction mixture was concentrated *in vacuo* to give a yellow oil. The oil was dissolved in MeCN (1.3 mL) then K_2CO_3 (221 mg, 1.6 mmol, 8 equiv) and NaI (3 mg, 0.02 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:4 EtOAc/hexane) yielded the title quinolizidine as a yellow oil (37 mg, 0.14 mmol, 70%).

$[\alpha]_D^{25}$ +22.3 (*c* 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.31 (2H, m, $H_{Ar\ ortho}$), 7.24 - 7.17 (1H, m, $H_{Ar\ para}$), 7.13 - 7.07 (2H, m, $H_{Ar\ meta}$), 3.01 - 2.90 (2H, m, NCHH and NCHH), 2.82 (1H, dd, *J* = 3.9, 8.3 Hz, NCH), 2.34 - 1.96 (5H, m, $CHCO_2$, NCHH, NCHH, CHH and C'HH), 1.87 - 1.50 (7H, m, CH_2 x 3 and CHH), 1.33 (1H, tq, *J* = 4.0, 12.7 Hz, CHH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.8 (CO_2), 150.7 ($C_{Ar\ ipso}$), 129.2 ($C_{Ar\ ortho}$ x 2), 125.5 ($C_{Ar\ para}$), 121.6 ($C_{Ar\ meta}$ x 2), 62.9 (NCH), 57.2 (NCH_2 x 2), 44.6 (COCH), 26.5 (CH_2), 25.1 (CH_2 x 2), 24.6 (CH_2), 22.2 (CH_2); **IR** (film) ν_{max}/cm^{-1} 2931 (m), 1759 (s), 1492 (m), 1196 (s), 1162 (m), 1117 (m), 1101 (s); **LRMS** (ES^+) *m/z* 260 ($[M + H]^+$).

(3.17) (+)-(3S,4S)-3,4-bis(3-Chloropropyl)-1-[(S)-2-methylpropane-2-sulfinyl]azetidin-2-one

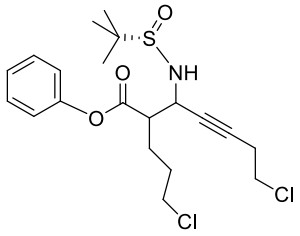


$C_{13}H_{23}Cl_2NO_2S$, 328.30 g/mol

To a solution of the imino-aldol product **2.20-*S,S*** (21 mg, 0.05 mmol, 1.0 equiv) in dry toluene (0.25 mL) at – 78 °C was carefully added LiHMDS (0.14 mL, of 0.71 M soln. in toluene, 0.10 mmol, 2.0 equiv). The reaction was quenched after 1.5 h by addition of sat. NH_4Cl(aq) (2 mL) followed by the addition of Et_2O (2 mL). The aqueous phase was extracted with Et_2O (2 mL x 3). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. Purification by column chromatography (SiO_2 gel, eluent gradient 5:15 → 6:14 EtOAc/hexane) yielded the title β-lactam as a white solid (16.5 mg, 0.05 mmol, 100%).

$[\alpha]_D^{24}$ +35.9 (*c* 1.17, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 3.90 - 3.81 (1H, m, C<u>H</u>), 3.65 - 3.49 (4H, m, C<u>H</u>$_2$Cl x 2), 2.96 (1H, dt, *J* = 2.6, 7.2 Hz, C<u>H</u>), 2.32 - 2.17 (1H, m, C<u>H</u>H), 2.06 - 1.78 (7H, m, C<u>H</u>$_2$ x 3, CH<u>H</u>), 1.34 (9H, s, (C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.2 (<u>C</u>O), 62.6 (<u>C</u>H), 59.1 (<u>C</u>(CH$_3$)$_3$), 56.1 (<u>C</u>H), 44.2 (<u>C</u>H$_2$ x 2), 31.5 (<u>C</u>H$_2$), 29.7 (<u>C</u>H$_2$), 28.7 (<u>C</u>H$_2$), 26.4 (<u>C</u>H$_2$), 23.4 (C(<u>C</u>H$_3$)); **IR** (film) ν_{max}/cm^{-1} 2961 (w), 1760 (s), 1448 (m), 1287 (m), 1157 (s), 1103 (s), 1075 (s), 1033 (s); **LRMS** (ES$^+$) *m/z* 350, 352 & 354 ([M + Na]$^+$).
See **Appendix 6.1** for crystallography data.

(3.45) 7-Chloro-2-(3-chloropropyl)-3-((S)-2-methylpropane sulfinamino)-1-phenyl hept-4-ynoate



$C_{20}H_{27}Cl_2NO_3S$, 432.40 g/mol

LDA

General procedure **B** for the imino-aldol reaction was followed using LDA (0.81 mL of a 1.68 M soln. in THF, 1.36 mmol, 1.36 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.46** (220 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 1.5 h. Purification of the crude product was carried out by column chromatography (SiO_2 gel, eluent gradient 9:1 → 4:6 hexane/EtOAc) to yield inseparable mixtures of diastereomers of the desired imino-aldol product **3.45** and the undesired eliminated product **3.55** (in total 256 mg of the mixture was isolated, with approximately 82% **3.45** and 12%, **3.55** in the mixture). Calculated yield of **3.45** 226 mg, 0.52 mmol, 52%, with 50:30:20 dr for diastereomers **3.45.1**:**3.45.2**:**3.45.3** (by comparison of the integration of NH peaks at 4.29, 3.78 and 4.08 ppm respectively in the different mixtures). The calculated yield of the undesired eliminated product, **3.55**, was 30 mg, 0.08 mmol, 8%, with 3 diastereomers visible by ^{1}H and ^{13}C NMR. However, it was not possible to determine an accurate dr for these. Stereochemistry was not assigned.

$TiCl(O_iPr)_3$: $TiCl_4$, 10:1

General procedure C for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (213 mg, 1.3 mmol, 1.3 equiv) in THF (0.3 mL), a pre-prepared 10:1 solution of $TiCl(O_iPr)_3$:$TiCl_4$ (2.6 mL of a commercial 1 M soln. in THF, 2.6 mmol of $TiCl(O_iPr)_3$; and 0.26 mL of a commercial 1M soln. in CH_2Cl_2, 0.26 mmol, 0.26 equiv of $TiCl_4$) and sulfinimine **3.46** (220 mg, 1.0 mmol, 1.0 equiv) in THF

(0.3 mL). Purification was carried out by column chromatography (SiO_2 gel, eluent gradient 9:1 → 7:3 hexane/EtOAc) to yield an inseparable mixture of diastereomers of the desired imino-aldol product **3.45** (170 mg in total, 0.39 mmol, 39%). The dr was calculated to be 67:21:12 (by comparison of the integration of NH peaks at 4.29, 3.78 and 4.08 ppm respectively in the different mixtures). Unreacted sulfinimine **3.46** (115 mg, 0.52 mmol, 52%) was also recovered.

$TiCl(O_iPr)_3$

To a solution of LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv) in THF (10.0 mL) at –78 °C, phenyl ester **2.09 (**213 mg, 1.3 mmol, 1.3 equiv) was added dropwise as a solution in THF (0.3 mL). The reaction mixture was stirred for 30 min, to this was then added $TiCl(O_iPr)_3$ (2.6 mL of a 1 M soln. in THF, 2.6 mmol, 2.6 equiv). After 30 min sulfinimine **3.46 (**220 mg, 1.0 mmol, 1.0 equiv) was added as a solution in THF (0.3 mL). The reaction was monitored by TLC. The reaction was quenched by addition of sat. NH_4Cl (aq) (10 mL) and allowed to warm to rt. The aqueous and organic phases were separated. The aqueous phase was extracted into EtOAc (5 mL x 3). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and solvents were removed *in vacuo* to yield the crude product. ^{1}H NMR analysis showed the crude product to be a mixture of unreacted imine **3.46**, eliminated imine **3.56**, the desired imino-aldol product **3.45** as well as the undesired eliminated product **3.55**. No further purification was attempted.

(3.45.1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 - 7.35 (2H, m, H_{Ar}), 7.30 - 7.21 (1H, m, $H_{Ar\ para}$), 7.16 - 7.05 (2H, m, H_{Ar}), 4.47 (1H, ddt, *J* = 6.9, 4.6, 2.1 Hz, CH), 4.29 (1H, d, *J* = 6.6 Hz, NH), 3.65 - 3.56 (4H, m, CH_2Cl x 2), 3.13 - 3.05 (1H, m, CH), 2.77 - 2.66 (2H, m, CH_2), 2.18 - 1.88 (4H, m, CH_2 x 2), 1.25 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.3 (CO), 150.2 ($C_{Ar\ ipso}$), 129.5 (C_{Ar} x 2), 126.2 ($C_{Ar\ para}$), 121.4 (C_{Ar} x 2), 83.3 (C≡), 78.5 (≡C), 56.2 ($C(CH_3)_3$), 50.5 (CH), 49.4 (CH), 44.4 (CH_2Cl), 42.0 (CH_2Cl), 30.3 (CH_2), 26.1 (CH_2), 23.1 (CH_2), 22.5 (($CH_3)_3$); **IR** (film) ν_{max}/cm^{-1} 3221 (w), 2964 (w), 1751 (m), 1190 (s), 1162 (s),

1132 (m), 1053 (s), 747 (m), 690 (m); **LRMS** (ES^+) *m/z* 432, 434 & 436 ([M + H]$^+$), 454, 456 & 458 ([M + Na]$^+$); **HRMS** (ES^+) for $C_{20}H_{27}Cl_2NO_3SNa$, requires 454.0981, found 454.0990 Da.

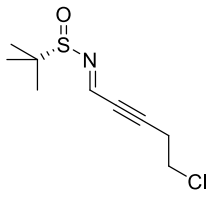
(3.45.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.36 (1H, tt, *J* = 8.5, 2.1 Hz, C<u>H</u>), 3.78 (1H, d, *J* = 8.6 Hz, N<u>H</u>), 1.24 (9H, s, (C<u>H</u>$_3$)$_3$).

(3.45.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.08 (1H, d, *J* = 7.1 Hz, N<u>H</u>), 1.21 (9H, s, (C<u>H</u>$_3$)$_3$).

(3.46) (+)-(S)-N-((1E)-5-Chloropent-2-ynylidene)-2-methylpropane-2-sulfinamide



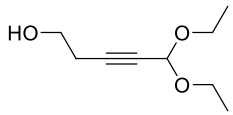
$C_9H_{14}ClNOS$, 219.73 g/mol

Adapted from the procedure described by Szabo *et al.*[95] 5-chloro 1,1-diethoxypent-2-yne **3.54** (1.66 g, 8.7 mmol, 1.0 equiv) in acetone (9.0 mL) was refluxed with 0.2 M HCl (aq) (9.0 mL). The reaction progress was monitored by GC analysis. After 1.5 h, Et_2O (10 mL) was added and the aqueous phase was extracted into Et_2O (10 mL x 2). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The resulting aldehyde (**3.47**) was not concentrated or purified due to its volatility. Selected data for 5-chloropent-2-ynal, **3.47**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.21 (1H, s, C<u>H</u>O), 3.67 (2H, t, *J* = 7.1 Hz, C<u>H</u>$_2$Cl), 2.90 (2H, t, *J* = 7.1 Hz, C<u>H</u>$_2$CH$_2$Cl); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.7 (<u>C</u>HO), 93.4 (<u>C</u>≡C), 82.4 (<u>C</u>≡C), 40.5 (<u>C</u>H$_2$Cl), 23.4 (<u>C</u>H$_2$CH$_2$Cl).

General procedure **A** for sulfinimine formation was adapted using 1-chloro pent-2-ynal (**3.47**) in Et_2O and acetone solution (used crude and un-concentrated from the previous reaction, full conversion assumed: 8.7 mmol, 1.0 equiv), (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.16 g, 9.6 mmol, 1.1 equiv) and $CuSO_4$ (3.05 g, 19.1 mmol, 2.2 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 1:1 EtOAc/hexane) yielded the title imine as a yellow oil (1.33 g, 6.1 mmol, 70% over two steps).

$[\alpha]_D^{27}$ +200.0 (*c* 0.99, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (1H, t, *J* = 1.6 Hz, NC<u>H</u>), 3.66 (2H, t, *J* = 7.1 Hz, C<u>H</u>$_2$Cl), 2.92 (2H, td, *J* = 7.1, 1.6 Hz, C<u>H</u>$_2$CH$_2$Cl), 1.21 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.8 (N<u>C</u>H), 97.8 (<u>C</u>≡C), 79.0 (<u>C</u>≡C), 58.2 (<u>C</u>(CH$_3$)), 40.9 (C<u>H</u>$_2$Cl), 23.9 (C<u>H</u>$_2$CH$_2$Cl), 22.5 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2963 (w), 2347 (w), 2223 (m), 1566 (s), 1364 (m), 1178 (m), 1083 (s); **LRMS** (ES$^+$) *m*/*z* 242 & 244 ([M + Na]$^+$); **HRMS** (ES$^+$) for $C_9H_{14}ClNOSNa$ requires 242.0377 found 242.0381 Da.

(3.53) 5,5-Diethoxypent-3-yn-1-ol

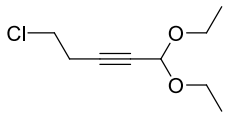


$C_9H_{16}O_3$, 172.22 g/mol

Following the procedure described by Maddaluno *et al.*[83] a dry-ice condenser, thermometer and septum were fitted to a 3 neck flask. Diethoxypropyne (1.0 mL, 894 mg, 7.0 mmol, 1.0 equiv), HMPA (1.22 mL, 1.25 g, 7.0 mmol, 1.0 equiv) and THF (10 mL) were added to the flask *via* syringe. The flask was then cooled to –78 °C before *n*BuLi (3.3 mL of 2.11 M soln. in hexanes, 7.0 mmol, 1.0 equiv) was added. The reaction mixture was stirred for 45 min before a large excess of ethylene oxide solution was added *via* cannula. The reaction was allowed to warm to rt and had gone to completion by TLC analysis after 1 h. It was quenched by the addition of water (10 mL) then Et_2O (5 mL), then the aqueous phase was extracted with EtOAc (5 mL x 7). The combined organic phases were then washed with sat. NH_4Cl (aq) (10 mL x 4), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title alcohol as a dark yellow liquid (1.11 g, 6.47 mmol, 92%), no further purification was required. Data were consistent with literature values.[83]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (1H, t, *J* = 1.5 Hz, C<u>H</u>O_2), 3.72 - 3.64 (4H, m, C<u>H</u>HCH_3 x 2 and CH_2OH), 3.51 (2H, dq, *J* = 9.6, 7.0 Hz, C<u>H</u>HCH_3 x 2), 2.93 (1H, br. s, O<u>H</u>), 2.45 (2H, td, *J* = 7.0, 1.5 Hz, CH_2CH_2OH), 1.17 (6H, t, *J* = 7.0 Hz, CH_3 x 2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 91.2 (≡C<u>C</u>H), 83.1 (≡<u>C</u>CH_2), 77.0 (≡<u>C</u>CH), 60.6 (<u>C</u>H_2CH_3 x 2), 60.4 (<u>C</u>H_2OH), 22.7 (<u>C</u>H_2CH_2OH), 14.8 (<u>C</u>H_3 x 2); **IR** (film) ν_{max}/cm^{-1} 3417 (br. w), 2976 (w), 2242 (w), 1329 (m), 1149 (s), 1044 (s), 1002 (s).

(3.54) 5-Chloro-1,1-diethoxypent-2-yne

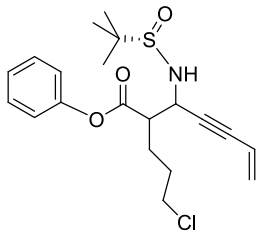


$C_9H_{15}ClO_2$, 190.67 g/mol

Adapted from the procedure described by Caddick *et al.*[84] to a solution of 5,5-diethoxypent-3-yn-1-ol (**3.53**, 5.12 g, 29.8 mmol, 1 equiv) in THF (150 mL), was added Et_3N (12.5 mL, 9.05 g, 89.4 mmol, 3 equiv) *via* syringe. The reaction mixture was cooled to 0 °C before MsCl (2.54 mL, 3.76 g, 32.8 mmol, 1.1 equiv) was slowly added. After 1 h the reaction was quenched with sat. $NaHCO_3$(aq) (20 mL) and the aqueous phase was extracted with Et_2O (30 mL x 3). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the mesylate intermediate. Selected data for mesylate intermediate: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.21 (1H, t, *J* = 1.7 Hz, C<u>H</u>), 4.28 (2H, t, *J* = 6.8 Hz, $S(O)_2OC\underline{H}_2$), 3.70 (2H, dq, *J* = 9.5, 7.0 Hz, C<u>H</u>HCH$_3$ x 2), 3.54 (2H, dq, *J* = 9.5, 7.0 Hz, C<u>H</u>HCH$_3$ x 2), 3.03 (3H, s, $C\underline{H}_3S(O)_2$), 2.70 (2H, td, *J* = 6.8, 1.7 Hz, $C\underline{H}_2C\equiv$), 1.20 (6H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 91.1 (<u>C</u>H), 80.1 ($CH_2\underline{C}\equiv$), 78.3 (≡<u>C</u>CH), 66.8 ($S(O)_2O\underline{C}H_2$), 60.7 ($\underline{C}H_2CH_3$ x 2), 37.6 ($\underline{C}H_3S(O)_2$), 19.8 ($\underline{C}H_2C\equiv$), 14.9 ($\underline{C}H_3CH_2$ x 2). The residue was dissolved in $CH_3CH_2Cl_2$ (60 mL) and refluxed with *n*Bu_4NCl (16.6 g, 59.6 mmol, 2 equiv) for 3 h. Solvents were removed *in vacuo*. The residue was dissolved in Et_2O (20 mL), the aqueous phase was extracted with Et_2O (5 mL x 3). The combined organic phases were washed with H_2O (20 mL), brine (20 mL x 2), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title chloride as a yellow liquid (4.82 g, 25.3 mmol, 85% over two steps). This required no further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, m, C<u>H</u>), 3.80 - 3.64 (2H, m, C<u>H</u>HCH$_3$ x 2), 3.64 - 3.49 (4H, m, C<u>H</u>HCH$_3$ x 2 and $C\underline{H}_2Cl$), 2.71 (2H, td, *J* = 7.2, 1.5 Hz, ≡CC<u>H</u>$_2$), 1.22 (6H, t, *J* = 7.2 Hz, C<u>H</u>$_3$ x 2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 91.2 (<u>C</u>H), 81.8 (≡<u>C</u>CH$_2$), 77.8 (≡<u>C</u>CH), 60.7 ($\underline{C}H_2CH_3$ x 2), 41.6 ($\underline{C}H_2Cl$), 23.0 ($\underline{C}H_2CH_2Cl$), 15.0 ($\underline{C}H_3$ x 2); **IR** (film) ν_{max}/cm^{-1} 2976 (w), 1329 (w), 1146 (m), 1049 (s), 1011 (m); **LRMS** (ES$^+$) *m/z* 213 & 215 ([M + Na]$^+$).

(3.55) 2-(3-Chloropropyl)-3-((S)-2-methylpropane sulfinamino)-1-phenyl hept-6-en-4-ynoate



$C_{20}H_{26}ClNO_3S$, 395.94 g/mol

Side product isolated as a mixture of 3 distinguishable diastereomers from reaction to form sulfinimine **3.45** (see above for experimental detail). Stereochemistry was not assigned.

(3.55.2)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.35 (2H, m, $\underline{H}_{Ar}$ x 2), 7.28 - 7.21 (1H, m, $\underline{H}_{Ar\ para}$), 7.14 - 7.06 (2H, m, $\underline{H}_{Ar}$ x 2), 5.84 (1H, ddd, *J* = 17.4, 11.0, 1.8 Hz, C$\underline{H}$=CH_2), 5.70 (1H, dd, *J* = 17.4, 2.1 Hz, CH=C$\underline{H}_{trans}$H), 5.54 (1H, dd, *J* = 11.0, 2.1 Hz, CH=CH$\underline{H}_{cis}$), 4.49 (1H, ddd, *J* = 8.6, 8.2, 1.8 Hz, C$\underline{H}$NH), 3.87 (1H, d, *J* = 8.6 Hz, N$\underline{H}$), 3.63 (2H, q, *J* = 5.9 Hz, C$\underline{H}_2$Cl), 3.08 - 2.95 (1H, m, C$\underline{H}$$CH_2$), 2.15 - 1.89 (4H, m, C$\underline{H}_2$ x 2), 1.23 (9 H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.5 (C$\underline{O}$), 150.3 ($\underline{C}_{Ar\ ipso}$), 129.5 ($\underline{C}H_{Ar}$ x 2), 128.3 ($\underline{C}H_2$=CH), 126.1 ($\underline{C}H_{Ar\ para}$), 121.3 ($\underline{C}H_{Ar}$ x 2), 116.3 ($\underline{C}H$=CH_2), 86.8 ($\underline{C}$≡C), 85.3 (C≡$\underline{C}$), 56.7 ($\underline{C}$(CH_3)$_3$), 51.4 ($\underline{C}$H), 50.1 ($\underline{C}$H), 44.2 ($\underline{C}H_2$Cl), 29.8 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 22.6 (C($\underline{C}H_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3187 (w), 2960 (w), 1752 (m), 1190 (s), 1162 (s), 1132 (s), 1055 (s); **LRMS** (ES$^+$) *m/z* 396 & 398 ([M + H]$^+$), 418 & 420 ([M + Na]$^+$); **HRMS** (ES$^+$) for $C_{20}H_{26}ClNNaO_3S$, requires 418.1214, found 418.1206 Da.

(3.55.2) selected data

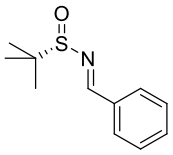
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.84 (1H, ddd, *J* = 17.4, 11.0, 1.8 Hz, C$\underline{H}$=CH_2), 5.70 (1H, dd, *J* = 17.4, 2.1 Hz, CH=C$\underline{H}_{trans}$H), 5.55 (1H, dd, *J* = 11.1, 2.3 Hz, CH=CH$\underline{H}_{cis}$), 4.61 (1H, ddd, *J* = 7.6, 7.6, 1.8 Hz, C$\underline{H}$NH), 4.20 (1H, d, *J*

= 7.6 Hz, NH), 1.25 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.7 (CO), 150.3 ($C_{Ar\ ipso}$), 129.6 (CH_{Ar} x 2), 126.2 ($CH_{Ar\ para}$), 121.4 (CH_{Ar} x 2), 116.2 (CH=CH_2), 86.3 (C≡C), 85.5 (C≡C), 56.3 (C(CH_3)$_3$), 50.9 (CH), 49.9 (CH), 44.2 (CH_2Cl), 29.9 (CH_2), 26.6 (CH_2), 22.5 (C(CH_3)$_3$).

(3.55.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.69 (1H, dd, *J* = 17.7, 2.0 Hz, CH=CH_{trans}H), 3.78 (1H, d, *J* = 7.1 Hz, NH), 1.21 (1H, s, C(CH_3)$_3$);**^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 121.4 (C_{Ar}), 22.6 (C(CH_3)$_3$).

(3.57) (+)-(S)-N-((E)-Benzylidene)2-methylpropane-2-sulfinamide

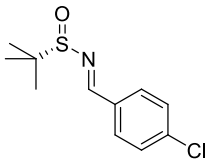


$C_{11}H_{15}NOS$, 209.31 g/mol

General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.00 g, 8.3 mmol, 1 equiv), CH_2Cl_2 (16.5 mL), $CuSO_4$ (2.90 g, 18.2 mmol, 2.2 equiv), and freshly distilled benzaldehyde (0.90 mL, 964 mg, 9.1 mmol, 1.1 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 10:3 EtOAc/hexane) yielded the title imine as a pale yellow oil (1.18 g, 5.7 mmol, 68%). Data were consistent with the literature.[21]

$[\alpha]_D^{27}$ +115 (c 1.03, $CHCl_3$) (lit. **$[\alpha]_D^{20}$** +104 (c 1.00, $CHCl_3$))[21]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.60 (1H, s, NCH), 7.86 (2H, dd, *J* = 7.9, 1.6 Hz, H_{Ar}), 7.57 - 7.44 (3H, m, H_{Ar}), 1.27 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.7 (NCH), 133.9 ($C_{Ar\ ipso}$), 132.4 ($CH_{Ar\ para}$), 129.3 ($CH_{Ar\ ortho}$ x 2), 128.8 ($CH_{Ar\ meta}$ x 2), 57.7 (C(CH_3)$_3$), 22.5 (C(CH_3)$_3$); **IR** (film) ν_{max}/cm^{-1} 2960 (w), 1605 (s), 1572 (s), 1082 (s).

(3.58) (S)-N-((E)-4-Chlorobenzylidine)-2-methylpropane-2-sulfinamide

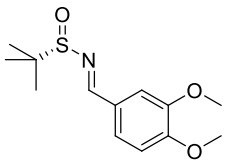


$C_{11}H_{14}ClNOS$, 243.75 g/mol

General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.21 g, 10 mmol, 1.0 equiv), CH_2Cl_2 (20 mL), $CuSO_4$ (4.79 g, 30 mmol, 3.0 equiv) and 4-chlorobenzaldehyde (2.11 g, 15 mmol, 1.5 equiv). Purification of the crude product by column chromatography (SiO_2 gel, 20:0 → 19:1 CH_2Cl/EtOAc) yielded the title imine as a white solid (1.16 g, 4.7 mmol, 47 %). Data were consistent with the literature.[96]

MP 49 - 52 °C (lit.[96] 41 - 42 °C); **$[\alpha]_D^{24}$** +83.8 (*c* 1.11, $CHCl_3$) (lit. **$[\alpha]_D^{25}$** +76 (*c* 1.00, $CHCl_3$))[96]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 (1H, s, NC<u>H</u>), 7.79 (2H, d, *J* = 8.4 Hz, C<u>H</u>$_{Ar}$ x 2), 7.45 (2H, d, *J* = 8.4 Hz, C<u>H</u>$_{Ar}$ x 2), 1.26 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.5 (N<u>C</u>H), 138.6 (NC(H)<u>C</u>$_{Ar}$), 132.5 (<u>C</u>$_{Ar}$Cl), 130.5 (<u>C</u>$_{Ar}$H x 2), 129.3 (<u>C</u>$_{Ar}$H x 2), 57.9 (<u>C</u>(CH$_3$)$_3$), 22.6 ((<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2960 (w), 1608 (w), 1591 (m), 1564 (m), 1080 (s).

(3.59) (S)-(+)-N-((E)-3,4-Dimethoxybenzylidene)-2-methylpropane-2-sulfinamide

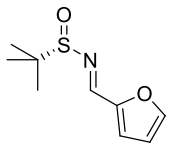


$C_{13}H_{19}NO_3S$, 269.36 g/mol

General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.21 g, 10 mmol, 1.0 equiv), CH_2Cl_2 (20 mL), $CuSO_4$ (4.79 g, 30 mmol, 3.0 equiv) and 3,4-dimethoxy benzaldehyde (2.49 g, 15 mmol, 1.5 equiv). Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 1:99 → 2:98 → 3:99 → 5:95 → 10:90 → 20:80 → 50:50 hexane/EtOAc) yielded the title imine as a white solid (0.96 g, 3.6 mmol, 36%). Data were consistent with the literature.[97]

$[\alpha]_D^{24}$ +42.1 (*c* 1.10, $CHCl_3$) (lit; **$[\alpha]_D^{20}$** +19.8 (*c* 0.57, $CHCl_3$))[97]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (1H, s, NC<u>H</u>), 7.45 (1H, d, *J* = 1.8 Hz, <u>H</u>$_{Ar}$), 7.37 (1H, dd, *J* = 8.4, 1.8 Hz, <u>H</u>$_{Ar}$), 6.94 (1H, d, *J* = 8.4 Hz, <u>H</u>$_{Ar}$), 3.95 (6H, s, OC<u>H</u>$_3$ x 2), 1.26 (9H, s, (C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.0 (N<u>C</u>H), 152.8 (<u>C</u>$_{Ar}$OCH$_3$), 149.4 (<u>C</u>$_{Ar}$OCH$_3$), 127.4 (<u>C</u>$_{Ar}$OCCHN), 125.0 (NC(H)C<u>C</u>$_{Ar}$(H)COCH$_3$), 110.6 (<u>C</u>$_{Ar}$H), 109.7 (<u>C</u>$_{Ar}$H), 57.6 (<u>C</u>(CH$_3$)$_3$), 56.0 (<u>C</u>H$_3$), 55.9 (<u>C</u>H$_3$), 22.6 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2957 (w), 1596 (m), 1572 (m), 1510 (s), 1265 (s), 1077 (s), 1022 (m).

(3.60) (+)-(S)-N-((E)-Furan-2-ylmethylene)-2-methylpropane-2-sulfinamide

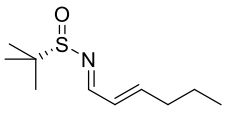


$C_9H_{13}NO_2S$, 199.27 g/mol

General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.21 g, 10 mmol, 1.0 equiv), CH_2Cl_2 (20 mL), $CuSO_4$ (4.79 g, 30 mmol, 3.0 equiv) and 2-furaldehyde (1.24 mL, 1.44 g, 15 mmol, 1.5 equiv). Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 20:0 → 20:1 CH_2Cl/EtOAc) yielded the title imine as a yellow liquid (1.18 g, 5.9 mmol, 59%). Data were consistent with the literature.[98]

$[\alpha]_D^{27}$ +159 (*c* 1.12, $CHCl_3$) (lit. *R* enantiomer, **$[\alpha]_D^{23}$** -168 (*c* 1.00, $CHCl_3$))[98]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.39 (1H, s, NC<u>H</u>), 7.64 (1H, d, *J* = 1.5 Hz, OC<u>H</u>$_{furan}$), 7.01 (1H, d, *J* = 3.4 Hz, OCC<u>H</u>$_{furan}$), 6.57 (1H, dd, *J* = 3.4, 1.5 Hz, OCHC<u>H</u>$_{furan}$), 1.25 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.8 (<u>C</u>$_{furan}$CHN), 149.8 (<u>C</u>HN), 146.8 (O<u>C</u>H$_{furan}$), 118.6 (OCH<u>C</u>H$_{furan}$), 112.5 (OC<u>C</u>H$_{furan}$), 57.8 (<u>C</u>(CH$_3$)$_3$), 22.5 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 2960 (w), 1611(s), 1470(m), 1074 (s), 1017 (m), 757 (m).

(3.61) (+)-(S)-N-((1E,2E)-Hex-2-en-1-ylidene)-2-methylpropane-2-sulfinamide



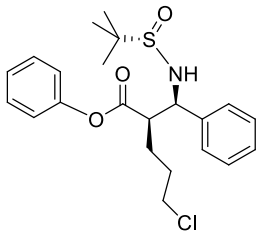
$C_{10}H_{19}NOS$, 201.33 g/mol

General procedure **A** for sulfinimine formation was followed using (*S*)-2-methylpropane-2-sulfinamide (**1.36-*S***, 1.21 g, 10 mmol, 1.0 equiv), CH_2Cl_2

(20 mL), $CuSO_4$ (3.51 g, 22 mmol, 2.2 equiv) and *trans*-2-hexen-1-al (1.16 mL, 0.981 g, 10 mmol, 1.0 equiv). Purification of the crude product by column chromatography (SiO_2 gel, eluent gradient 20:0 → 20:1 CH_2Cl/EtOAc) yielded the title imine as a yellow liquid (1.56 g, 7.7 mmol, 77%).

$[\alpha]_D^{25}$ +493 (c 1.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 9.1 Hz, NC<u>H</u>), 6.55 (1H, dt, *J* = 15.5, 6.6 Hz, $CH_2C\underline{H}$=CH), 6.43 (1H, ddt, *J* = 15.5, 9.1, 1.5 Hz, CH=C<u>H</u>CHN), 2.27 (2H, tdd, *J* = 7.1, 6.6, 1.5 Hz, =C<u>C</u>H_2), 1.53 (2H, qt, *J* = 7.3, 7.1 Hz, <u>C</u>H_2CH_3), 1.21 (9H, s, C(<u>C</u>H_3)$_3$), 0.96 (3H, t, *J* = 7.3 Hz, <u>C</u>H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.2 (<u>C</u>HN), 151.6 (CH_2<u>C</u>H=), 128.8 (CH=<u>C</u>HCHN), 57.1 (<u>C</u>(CH_3)$_3$), 35.0 (<u>C</u>H_2CH=), 22.4 (C(<u>C</u>H_3)$_3$), 21.5 (<u>C</u>H_2CH_3), 13.7 (<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1} 2959 (m), 2929 (w), 1640 (s), 1170 (w), 1579 (s), 1079 (s); **LRMS** (ES$^+$) *m*/*z* 202 ([M + H]$^+$); **HRMS** (ES$^+$) for $C_{10}H_{20}NOS$, requires 202.1260 found 202.1258.

(3.62) (+)-(2R)- 5-Chloro-2-((R)-phenyl ((S)-2-methylpropane-2-sulfinamino)methyl)-1-phenyl pentanoate



$C_{22}H_{28}ClNO_3S$, 421.98 g/mol

General Procedure **B** for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.57** (209 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 30 min. Purification by column chromatography (SiO_2 gel, eluent gradient 1:3 → 2:2 EtOAc/hexane) yielded the major diastereomer **3.62.1-*R,S*** as a white solid (271 mg, 0.64 mmol, 64%). Two other diastereomers were isolated as a mixture (36 mg. 0.09 mmol, 9%). Analysis of the crude mixture by ^{1}H NMR shows 73:23:4 dr for diastereomers **3.62.1**:**3.62.2**:**3.62.3** (by integration of C(<u>C</u>H_3)$_3$ singlets at 1.23, 1.21 and 1.36 ppm respectively). A fourth diastereomer was not observed.

(3.62.1-R,S)

MP 126 - 128 °C; **$[\alpha]_D^{28}$** +62.1 (*c* 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 - 7.36 (5H, m, $\underline{H}_{Ar}$ x 5), 7.36 - 7.29 (2H, m, $\underline{H}_{Ar}$ x 2), 7.23 - 7.17 (1H, m, $\underline{H}_{Ar}$), 6.83 - 6.76 (2H, m, $\underline{H}_{Ar}$ x 2), 4.78 (1H, dd, *J* = 6.6, 3.5 Hz, C$\underline{H}$NH), 4.18 (1H, d, *J* = 3.5 Hz, N$\underline{H}$), 3.63 - 3.56 (2H, m, C$\underline{H}_2$Cl), 3.15 - 3.04 (1H, m, C$\underline{H}CO_2$), 2.05 - 1.83 (4H, m, C$\underline{H}_2$ x 2), 1.23 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7 ($\underline{C}O_2$), 150.1 ($\underline{C}_{Ar}$OCO), 138.9 ($\underline{C}_{Ar}$CHNH), 129.5 ($\underline{C}_{Ar}$ x 2), 128.6 ($\underline{C}_{Ar}$ x 2), 128.3 ($\underline{C}_{Ar\ para}$), 128.1 ($\underline{C}_{Ar}$ x 2), 126.1 ($\underline{C}_{Ar\ para}$), 121.3 ($\underline{C}_{Ar}$ x 2), 60.1 ($\underline{C}$HNH), 56.0 ($\underline{C}(CH_3)_3$), 52.1 ($\underline{C}HCO_2$), 44.2 ($\underline{C}H_2Cl$), 30.3 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 22.6 (C($\underline{C}H_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3309 (w), 2950 (w), 2349 (w), 1752 (s), 1217 (m), 1187 (s), 1047 (s), 1025 (s); **LRMS** (ES^+) *m/z* 444 & 446 ([M + Na]$^+$), 485 & 487 ([M + Na + MeCN]$^+$); **HRMS** (ES^+) for $C_{22}H_{28}ClNNaO_3S$, requires 444.1371, found 444.1369 Da.

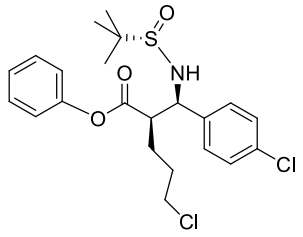
(3.62.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (2H, dd, *J* = 6.1, 5.6 Hz, C$\underline{H}$NH), 4.66 (2H, d, *J* = 5.6 Hz, N$\underline{H}$), 3.10 - 3.01 (1H, m, C$\underline{H}CO_2$), 1.21 (9H, s, C(C$\underline{H}_3$)$_3$).

(3.62.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, d, *J* = 6.6 Hz, N$\underline{H}$), 1.36 (9H, s, C(C$\underline{H}_3$)$_3$).

(3.63) (+)-(2R)-5-Chloro-2-((R)-4-chlorophenyl ((S)-2-methylpropane-2-sulfinamino) methyl)-1-phenyl pentanoate



$C_{22}H_{27}Cl_2NO_3S$, 456.43 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.58** (243 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. Purification by column chromatography (SiO_2 gel, 1:3 EtOAc/hexane) yielded the major diastereomer **3.63.1-*R,S*** as a white solid (265 mg, 0.58 mmol, 58%). This solid was then crystallised (EtOAc/hexane) to yield a white solid (241 mg, 0.53 mmol, 53%). Also isolated were two minor diastereomers (**3.63.2**, 7 mg, 0.02 mmol, 2% and **3.63.3**, 27 mg, 0.06 mmol, 6%), as well as a fraction containing a mixture of **3.63.2** and **3.63.3** in a ratio of 53:47 respectively (42 mg, 0.09 mmol, 9%). Overall this gives the reaction a dr of 76:9:15 for diastereomers 1:2:3 and a total a yield of 317 mg, 0.69 mmol, 69% for the diastereomers combined. A fourth diastereomer was not observed.

(3.63.1-R,S)

MP 119 - 125 ºC (EtOAc/hexane); **$[\alpha]_D^{27}$** +57.5 (*c* 1.03, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 - 7.29 (6H, m, $\underline{H}_{Ar}$ x 6), 7.26 - 7.17 (1H, m, $\underline{H}_{Ar}$), 6.92 - 6.73 (2H, m, $\underline{H}_{Ar}$ x 2), 4.78 (1H, dd, *J* = 6.6, 3.2 Hz, C$\underline{H}$NH), 4.21 (1H, d, *J* = 3.2 Hz, N$\underline{H}$), 3.58 (2H, t, *J* = 5.8 Hz, C$\underline{H}_2$Cl), 3.25 - 2.96 (1H, m, C$\underline{H}CO_2$), 2.07 - 1.78 (4H, m, C$\underline{H}_2$ x 2), 1.23 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5 ($\underline{C}O_2$), 150.0 ($\underline{C}_{Ar}$OCO), 137.3 ($\underline{C}_{Ar}$Cl), 134.2 ($\underline{C}_{Ar}$CHNH), 129.5 ($\underline{C}H_{Ar\ Cl}$ x 4), 128.8 ($\underline{C}H_{Ar\ meta\ to\ ester}$ x 2), 126.2 ($\underline{C}_{Ar\ para\ to\ ester}$), 121.2 ($\underline{C}H_{Ar\ ortho\ to\ ester}$ x 2), 59.2 ($\underline{C}$HNH), 56.0 ($\underline{C}(CH_3)_3$), 51.8 ($\underline{C}HCO_2$), 44.1 ($\underline{C}H_2Cl$), 30.1 ($\underline{C}H_2$), 25.6 ($\underline{C}H_2$), 22.5 (C($\underline{C}H_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3341 (w), 2958 (w), 2360 (w), 1742 (s), 1190

(s), 1060 (s), 1041 (s); **LRMS** (ES^+) *m/z* 478, 480 & 482 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{22}H_{28}Cl_2NO_3S$, requires 456.1161, found 456.1165 Da.
See Appendix 6.1 for X-ray crystallography data.

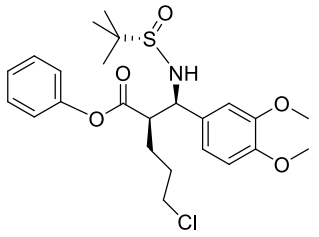
(3.63.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.32 (5H, m, H_{Ar} x 5), 7.29 (2H, d, *J* = 8.4 Hz, H_{Ar} x 2), 6.95 (2H, d, *J* = 8.1 Hz, H_{Ar} x 2), 4.73 - 4.67 (1H, m, CHNH), 4.65 (1H, d, *J* = 4.8 Hz, NH), 3.63 - 3.52 (2H, m, CH_2Cl), 3.01 (1H, dd, *J* = 8.6, 6.4 Hz, $CHCO_2$), 2.07 - 1.74 (4H, m, CH_2 x 2), 1.21 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.4 (CO), 149.7 ($C_{Ar}OCO$), 138.4 ($C_{Ar}Cl$), 133.8 ($C_{Ar}CHNH$), 129.4 (CH_{Ar} x 2), 128.7 (CH_{Ar} x 2), 128.5 (CH_{Ar} x 2), 126.2 ($CH_{Ar\ para\ to\ ester}$), 121.1 ($CH_{Ar\ ortho\ to\ ester}$ x 2), 59.6 (CHNH), 55.8 ($C(CH_3)_3$), 51.4 ($CHCO_2$), 43.8 (CH_2Cl), 29.9 (CH_2), 27.1 (CH_2), 22.4 ($C(CH_3)_3$).

(3.63.3) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.30 (6H, m, H_{Ar} x 6), 7.26 - 7.21 (1H, m, H_{Ar}), 6.96 (2H, d, *J* = 8.1 Hz, H_{Ar}), 4.65 (1H, dd, *J* = 8.0, 9.1 Hz, CHNH), 4.26 (1H, d, *J* = 9.1 Hz, NH), 3.56 (2H, t, *J* = 6.0 Hz, CH_2Cl), 3.10 (1H, td, *J* = 8.0, 4.4 Hz, $CHCO_2$), 1.99 - 1.66 (4H, m, CH_2 x 2), 1.20 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.2 (CO), 150.1 ($C_{Ar}OCO$), 138.6 ($C_{Ar}Cl$), 134.1 ($C_{Ar}CHNH$), 129.5 (CH_{Ar} x 2), 129.1 (CH_{Ar} x 2), 128.5 (CH_{Ar} x 2), 126.2 ($CH_{Ar\ para\ to\ ester}$), 121.2 ($CH_{Ar\ ortho\ to\ ester}$ x 2), 61.0 (CHNH), 56.7 ($C(CH_3)_3$), 51.8 ($CHCO_2$), 44.1 (CH_2Cl), 30.0 (CH_2), 27.4 (CH_2), 22.6 ($C(CH_3)_3$).

(3.64) (+)-(2R)-5-Chloro-2-((R)-(3,4-dimethoxyphenyl) ((S)-2-methylpropane-2-sulfinamino) methyl)-1-phenyl pentanoate



$C_{24}H_{32}ClNO_5S$, 482.03 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.59** (269 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. Purification by column chromatography (SiO_2 gel, 1:3 EtOAc/hexane) yielded a single diastereomer **3.64.1-*R,S*** of the desired product as a white solid (329 mg, 0.68 mmol, 68%), as well as a mixed fraction containing another more minor diastereomer **3.64.2** and the major diastereomer **3.64.1-*R,S*** (40 mg). Analysis of the crude ^{1}H NMR shows a ratio of 95:5 (by integration of NH doublet peaks at 4.25 ppm and 4.56 ppm respectively) for the identifiable major and a minor diastereomers. No other diastereomers where observed. It should also be noted that the chemical shift for the NH doublets in the ^{1}H NMR seemed to vary by up to 0.1 ppm, while the J values and chemical shifts of other signals were consistent.

(3.64.1-R,S)

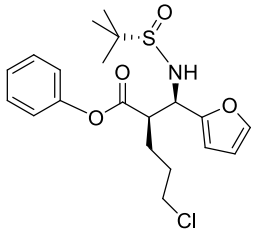
MP 104 - 106 ºC; **$[\alpha]_D^{27}$** +59.5 (*c* 1.02, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.31 (2H, m, $H_{Ar\ meta\ to\ ester}$ x 2), 7.22 (1H, t, *J* = 7.6 Hz, $H_{Ar\ para\ to\ ester}$), 6.95 (1H, dd, *J* = 8.3, 1.7 Hz, $CCH_{Ar}CHCOCH_3$), 6.90 (1H, d, *J* = 1.7 Hz, $CCH_{Ar}COCH_3$), 6.89 (1H, d, *J* = 8.3 Hz, $CCHCH_{Ar}COCH_3$), 6.85 (2H, d, *J* = 7.6 Hz, $H_{Ar\ ortho\ to\ ester}$ x 2), 4.74 (1H, dd, *J* = 6.6, 2.8 Hz, CHNH), 4.15 (1H, d, *J* = 2.8 Hz, NH), 3.90 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.59 (2H, t, *J* = 6.1 Hz, CH_2Cl), 3.07 (1H, dt, *J* = 6.6, 7.1 Hz, $CHCO_2$), 2.05 - 1.80 (4H, m, CH_2 x 2), 1.24 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7 (CO_2), 150.2 ($C_{Ar}OCO$), 149.0 ($C_{Ar}OCH_3$), 149.0 ($C_{Ar}OCH_3$), 131.1 ($C_{Ar}CHNH$), 129.5 ($CH_{Ar\ meta\ to\ ester}$ x 2), 126.2 ($CH_{Ar\ para\ to\ ester}$), 121.3 ($CH_{Ar\ ortho\ to\ ester}$ x 2), 120.7

($C\underline{C}H_{Ar}CHCOCH_3$), 111.2 ($CCH\underline{C}H_{Ar}COCH_3$), 111.0 ($C\underline{C}H_{Ar}COCH_3$), 59.5 ($\underline{C}HNH$), 55.9 ($\underline{C}H_3$ x 2), 55.9 ($\underline{C}(CH_3)_3$), 52.1 ($\underline{C}HCO_2$), 44.3 ($\underline{C}H_2Cl$), 30.2 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 22.6 ($C(\underline{C}H_3)_3$); **IR** (film) ν_{max}/cm^{-1} 2958 (w), 1751 (m), 1516 (m), 1189 (s), 1147 (s), 1045 (s), 1020 (s); **LRMS** (ES^+) *m/z* 504 & 506 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{24}H_{32}ClNNaO_5S$, requires 504.1582, found 504.1570 Da.

(3.64.2) selected data

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.67 (1H, dd, *J* = 7.0, 4.4 Hz, $C\underline{H}NH$), 4.53 (1H, d, *J* = 4.4 Hz, $N\underline{H}$) 1.21 (9H, s, $C(C\underline{H}_3)_3$).

(3.65) (2R)-5-Chloro-2-((R)-furan-2-yl ((S)-2-methylpropane-2-sulfinamino) methyl)-1-phenyl pentanoate



$C_{20}H_{26}ClNO_4S$, 411.94 g/mol

General procedure **B** for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.60** (199 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 60 min. 3 diastereomers were visible in the ^{1}H NMR spectrum, 85:4:11 dr **3.65.1**:**3.65.2**:**3.65.3** (by integration of $N\underline{H}$ doublet at 4.30, 4.61 and $C\underline{H}NH$ double doublet in C at 4.68 ppm respectively, diastereomer **3.65.4** was not observed in the crude spectrum). Purification by column chromatography (SiO_2 gel, 1:3 EtOAc/hexane) yielded a mixture of the diastereomers **3.65.1** and **3.65.3** (358 mg, 0.87 mmol, 87%) as well as a second fraction consisting of a mixture of diastereomers **3.65.2** and **3.65.4** (4.4 mg, 0.01 mmol, 1%, in ratio 27:73 respectively). Crystallisation (EtOAc/hexane) further purified the product to yield the major diastereomer **3.65.1** as white needles for characterisation purposes.

(3.65.1-R,S)

MP 79 - 85 ºC; **$[\alpha]_D^{27}$** +39.6 (c 0.39, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 1.7 Hz, OC<u>H</u>$_{furan}$), 7.37 (2H, t, *J* = 7.8 Hz, C<u>H</u>$_{Ph\ meta}$ x 2), 7.23 (1H, t, *J* = 7.6 Hz, C<u>H</u>$_{Ph\ para}$), 6.98 (2H, d, *J* = 7.6 Hz, C<u>H</u>$_{Ph\ ortho}$ x 2), 6.38 (1H, dd, *J* = 3.4, 1.7 Hz, C<u>H</u>CHO$_{furan}$), 6.34 (1H, d, *J* = 3.4 Hz, OCC<u>H</u>$_{furan}$), 4.83 (1H, dd, *J* = 6.6, 6.6 Hz, C<u>H</u>NH), 4.30 (1H, d, *J* = 6.6 Hz, N<u>H</u>), 3.61 (2H, t, *J* = 5.8 Hz, C<u>H</u>$_2$Cl), 3.29 - 3.21 (1H, m, C<u>H</u>CO_2), 2.09 - 1.87 (4H, m, C<u>H</u>$_2$ x 2), 1.22 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5 (<u>C</u>O_2), 152.2 (<u>C</u>$_{furan\ ipso}$), 150.2 (<u>C</u>$_{Ph\ ipso}$), 142.6 (<u>C</u>(H)O$_{furan}$), 129.5 (<u>C</u>H$_{Ph\ meta}$ x 2), 126.2 (<u>C</u>H$_{Ph\ para}$), 121.4 (<u>C</u>H$_{Ph\ ortho}$ x 2), 110.4 (<u>C</u>HCHO$_{furan}$), 108.5 (<u>C</u>HCO$_{furan}$), 56.3 (<u>C</u>(CH$_3$)$_3$), 55.3 (<u>C</u>HNH), 50.0 (<u>C</u>HCO_2), 44.3 (<u>C</u>H$_2$Cl), 30.4 (<u>C</u>H$_2$), 26.1 (<u>C</u>H$_2$), 22.5 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1} 3477 (s), 3156 (s), 2360 (s), 1749 (m), 1132 (m), 1025 (s); **LRMS** (ES^+) m/z 434 & 436 ($[M + Na]^+$); **HRMS** (ES^+) for $C_{20}H_{27}ClNO_4S$, requires 412.1344, found 412.1348 Da.
See Appendix 6.1 for X-ray crystallography data.

(3.65.2) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.44 (1H, d, *J* = 1.1 Hz, C<u>H</u>O $_{furan}$), 7.39 (2H, t, *J* = 7.3 Hz, <u>H</u>$_{Ph\ meta}$ x 2), 7.28 - 7.22 (1H, m, <u>H</u>$_{Ph\ para}$), 7.02 (1H, d, *J* = 7.7 Hz, <u>H</u>$_{Ph\ ortho}$ x 2), 6.38 (1 H, dd, *J* = 3.3, 1.7 Hz, C<u>H</u>CHO $_{furan}$), 6.33 (1H, d, *J* = 3.3 Hz, <u>H</u>$_{Ar}$, C<u>H</u>CO $_{furan}$), 4.79 (1H, dd, *J* = 6.6, 6.6 Hz, C<u>H</u>NH), 4.61 (1H, d, *J* = 6.6 Hz, N<u>H</u>), 3.68 - 3.51 (3 H, m, C<u>H</u>$_2$Cl), 3.34 - 3.25 (1H, m, CO_2C<u>H</u>), 2.13 - 1.66 (4H, m, C<u>H</u>$_2$ x 2), 1.21 (9H, s, C(C<u>H</u>$_3$)$_3$).

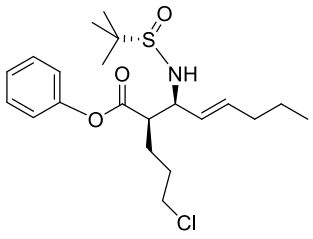
(3.65.3) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.02 (2H, d, *J* = 8.4 Hz, <u>H</u>$_{Ph\ ortho}$ x 2), 6.46 (1H, d, *J* = 3.3 Hz, C<u>H</u>CO$_{furan}$), 4.68 (1 H, dd, *J* = 9.9, 8.1 Hz, CHN<u>H</u>).

(3.65.4) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47 (1H, d, *J* = 1.7 Hz, C<u>H</u>O_{furan}), 7.09 (1H, d, *J* = 8.4 Hz, <u>H</u>$_{Ph\ ortho}$ x 2), 6.50 (1H, d, *J* = 3.3 Hz, C<u>H</u>CO_{furan}), 6.40 (1H, dd, *J* = 3.3, 1.7 Hz, C<u>H</u>CHO_{furan}), 5.21 (1H, d, *J* = 6.2 Hz, N<u>H</u>), 1.32 (9 H, s, C(C<u>H</u>$_3$)$_3$).

(3.66) (+)-(2R, 3S)-2-(3-Chloropropyl)-3-((S)-2-methylpropane-2-sulfinamino)-1-phenyl oct-4E-enoate



$C_{21}H_{32}ClNO_3S$, 414.00 g/mol

General Procedure **B** for the imino-aldol reaction was followed using LDA (0.77 mL of a 1.68 M soln. in THF, 1.3 mmol, 1.3 equiv), THF (10.0 mL), phenyl ester **2.09** (276 mg, 1.3 mmol, 1.3 equiv) and sulfinimine **3.61** (201 mg, 1.0 mmol, 1.0 equiv). The reaction was stopped after 30 min. Only one diastereomer was observed in the ^{1}H NMR of the crude product (**3.66.1-*R,S***). Purification by column chromatography (SiO_2 gel, eluent gradient 1:3 → 2:2 EtOAc/hexane) yielded the major diastereomer **3.66.1-*R,S*** as a yellow oil (259 mg, 0.63 mmol, 63%). A minor diastereomer (**3.66.2**) was also isolated as a yellow oil (35 mg, 0.08 mmol, 8%). The diastereoselectivity of the isolated diastereomers was 89:11 dr for diastereomers **3.66.1-*R,S*** :**3.66.2**.

(3.66.1-R,S)

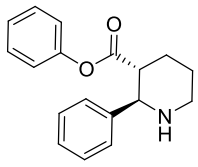
$[\alpha]_D^{27}$ +59.3 (*c* 1.08, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.35 (2H, m, <u>H</u>$_{Ar\ ortho}$ x 2), 7.25 (1H, t, *J* = 7.9 Hz, <u>H</u>$_{Ar\ para}$), 7.06 (2H, d, *J* = 7.6 Hz, <u>H</u>$_{Ar\ meta}$ x 2), 5.81 (1H, dt, *J* = 15.2, 7.1 Hz, CH_2C<u>H</u>=), 5.48 (1H, ddt, 15.2, 8.2, 1.5 Hz, NHCHC<u>H</u>=), 4.12 (1H, dt, *J* = 8.3, 4.4 Hz, C<u>H</u>CO_2), 3.95 (1H, d, *J* = 4.0 Hz, N<u>H</u>), 3.63 - 3.57 (2H, m, C<u>H</u>$_2$Cl), 2.94 (1H, dt, *J* = 9.3, 4.9 Hz, NHC<u>H</u>), 2.09 (2H, dt, *J* = 7.6, 6.6 Hz, C<u>H</u>$_2$CH=), 2.04 - 1.80 (4H, m, C<u>H</u>$_2$ x 2), 1.44 (2H, tq, *J* = 7.8,

7.4 Hz, C$\underline{H}_2$), 1.23 (9H, s, C(C$\underline{H}_3$)$_3$), 0.92 (3H, t, *J* = 7.3 Hz, C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.9 (C$\underline{O}$), 150.3 (C$\underline{C}_{Ar\ ipso}$), 136.4 (=C$\underline{H}$CH$_2$), 129.5 (C$\underline{H}_{Ar\ meta}$ x 2), 126.5 (=C$\underline{H}$CH), 126.1 (C$\underline{H}_{Ar\ para}$), 121.4 (C$\underline{H}_{Ar\ ortho}$ x 2), 58.7 (C$\underline{H}$), 55.6 (C$\underline{C}$(CH$_3$)$_3$), 50.5 (C$\underline{H}$), 44.3 (C$\underline{H}_2$Cl), 34.3 (C$\underline{H}_2$), 30.3 (C$\underline{H}_2$), 25.9 (C$\underline{H}_2$), 22.7 (C$\underline{H}_2$), 22.1 (C(C$\underline{H}_3$)$_3$), 13.6 (C$\underline{H}_3$); **IR** (film) ν_{max}/cm^{-1} 2958 (w), 1752 (m), 1191 (s), 1161 (s), 1128 (m), 1050 (s); **LRMS** (ES$^+$) *m/z* 436 & 438 ([M + Na]$^+$), 477 & 479 ([M + Na + MeCN]$^+$); **HRMS** (ES$^+$) for $C_{21}H_{32}ClNNaO_3S$, requires 436.1684, found 436.1694 Da.

(3.66.2) selected data

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.39 (2H, t, *J* = 7.7 Hz, H$\underline{}_{Ar\ meta}$ x 2), 7.24 (1H, t, *J* = 7.3 Hz, H$\underline{}_{Ar\ para}$), 7.07 (2 H, d, *J* = 8.1 Hz, H$\underline{}_{Ar\ ortho}$ x 2), 5.79 (1H, dt, *J* = 15.0, 7.5 Hz, CH$_2$C$\underline{H}$=), 5.40 (1H, dd, *J* = 15.4, 7.3 Hz, CHC$\underline{H}$=), 4.18 - 4.07 (2H, m, N$\underline{H}$ and C$\underline{H}$), 3.64 - 3.57 (2H, m, C$\underline{H}_2$Cl), 2.87 - 2.78 (1H, m, C$\underline{H}$), 2.13 - 2.05 (2H, m, C$\underline{H}_2$), 1.99 - 1.89 (4H, m, C$\underline{H}_2$ x 2), 1.51 - 1.97 (2H, m, C$\underline{H}_2$), 1.22 (9H, s, C(C$\underline{H}_3$)$_3$), 0.91 (3H, t, *J* = 7.7 Hz, CH$_2$C$\underline{H}_3$).

(3.67) (–)-(2R, 3R)-Phenyl 2-phenylpiperidine-3-carboxylate



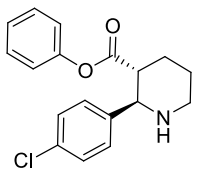
$C_{18}H_{19}NO_2$, 281.35 g/mol

The imino-aldol product **3.62.1-*R,S*** (100 mg, 0.24 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (1.32 mL), to this a solution of 4 M HCl(aq) in 1,4-dioxane (0.45 mL) was added and then stirred for 2 h. The reaction mixture was concentrated *in vacuo* to give a yellow solid. This was dissolved in MeCN (1.70 mL), then K_2CO_3 (265 mg, 1.92 mmol, 8 equiv) and NaI (4 mg, 0.02 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column

chromatography (Al_2O_3 gel Brockmann III, 1:3 EtOAc/hexane) yielded the title piperidine as a yellow oil (53 mg, 0.19 mmol, 78%).

$[\alpha]_D^{25}$ – 32.7 (*c* 0.62, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 - 7.43 (2H, m, C$\underline{H}_{PhCHNH}$ x 2), 7.41 - 7.30 (3H, m, C$\underline{H}_{PhCHNH}$ x 2 and C$\underline{H}_{PhCHNH\ para}$), 7.25 (2H, t, *J* = 7.3 Hz, C$\underline{H}_{PhOCO\ meta}$ x 2), 7.18 - 7.08 (1H, m, C$\underline{H}_{PhOCO\ para}$), 6.59 (2H, d, *J* = 8.1 Hz, C$\underline{H}_{PhOCO\ ortho}$ x 2), 3.88 (1H, d, *J* = 9.9 Hz, C$\underline{H}$NH), 3.23 (1H, dt, *J* = 11.6, 1.7 Hz, CH$\underline{H}$NH), 2.96 - 2.82 (2H, m, C$\underline{H}$HNH and C$\underline{H}CO_2$), 2.35 - 2.22 (1H, m, C$\underline{H}$HCHCO$_2$), 2.00 - 1.62 (4H, m, C$\underline{H}$HCHCO$_2$, C$\underline{H}_2$CH$_2$NH and N$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.5 ($\underline{C}O_2$), 150.3 ($\underline{C}_{PhOCO\ ipso}$), 141.9 ($\underline{C}_{PhCHNH\ ipso}$), 129.2 ($\underline{C}H_{PhOCO\ meta}$ x 2), 128.5 ($\underline{C}H_{PhCHNH}$ x 2), 128.0 ($\underline{C}H_{PhCHNH\ para}$), 127.8 ($\underline{C}H_{PhCHNH}$ x 2), 125.6 ($\underline{C}H_{PhOCO\ para}$), 121.4 ($\underline{C}H_{PhOCO\ ortho}$ x 2), 64.5 ($\underline{C}$HNH), 50.5 ($\underline{C}HCO_2$), 47.1 ($\underline{C}H_2$NH), 28.8 ($\underline{C}H_2CHCO_2$), 25.0 ($\underline{C}H_2CH_2$NH); **IR** (film) ν_{max}/cm^{-1} 2936 (w), 2836 (w), 1750 (s), 1188 (s), 1133 (s), 1115 (s), 760 (s); **LRMS** (ES^+) *m/z* 282 ($[M + H]^+$); **HRMS** (ES^+) for $C_{18}H_{20}NO_2$, requires 282.1489, found 282.1488 Da.

(3.68) (–)-(2R, 3R)-Phenyl 2-(4-chlorophenyl)piperidine-3-carboxylate



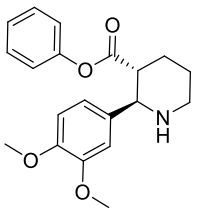
$C_{18}H_{18}ClNO_2$, 315.79 g/mol

The imino-aldol product **3.63.1-*R,S*** (150 mg, 0.33 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (1.86 mL), to this a solution of 4 M HCl(aq) in 1,4-dioxane (0.62 mL) was added and then stirred for 1 h. The reaction mixture was concentrated *in vacuo*. This was dissolved in MeCN (2.37 mL) then K_2CO_3 (364 mg, 2.63 mmol, 8 equiv) and NaI (5 mg, 0.03 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated

in vacuo to yield a white solid. Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:3 EtOAc/hexane) yielded the title piperidine as a yellow oil which became solid with tituration (88 mg, 0.28 mmol, 85%).

MP 64 - 69 ºC; **$[\alpha]_D^{25}$** – 76.1 (*c* 0.62, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 - 7.39 (2H, m, C$\underline{H}_{Ar\ ortho\ to\ Cl}$ x 2), 7.38 - 7.31 (2H, m, C$\underline{H}_{Ar\ meta\ to\ Cl}$ x 2), 7.31 - 7.25 (2H, m, C$\underline{H}_{Ar\ meta\ to\ ester}$ x 2), 7.19 - 7.11 (1H, m, C$\underline{H}_{Ar\ para\ to\ ester}$), 6.70 - 6.62 (2H, m, C$\underline{H}_{Ar\ ortho\ to\ ester}$ x 2), 3.87 (1H, d, *J* = 10.1 Hz, C$\underline{H}$NH), 3.22 (1H, dt, *J* = 11.7, 2.2 Hz, C$\underline{H}$HNH), 2.89 (1H, td, *J* = 11.9, 2.5 Hz, CH$\underline{H}$NH), 2.81 (1H, ddd, *J* = 11.7, 10.1, 3.5 Hz, C$\underline{H}CO_2$), 2.33 - 2.23 (1H, m, C$\underline{H}$HCHCO$_2$), 1.94 - 1.65 (4H, m, C$\underline{H}$HCHCO$_2$, C$\underline{H}_2$HCH$_2$NH and N$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.3 (C$\underline{O}$), 150.2 (C$\underline{_{Ar}}$OCO), 140.5 (C$\underline{_{Ar}}$Cl), 133.6 (C$\underline{_{Ar}}$CHNH), 129.3 (C$\underline{H}_{Ar\ ortho\ to\ Cl}$ x 2), 129.2 (C$\underline{H}_{Ar\ meta\ to\ ester}$ x 2), 128.6 (C$\underline{_{Ar\ meta\ to\ Cl}}$ x 2), 125.8 (C$\underline{H}_{Ar\ para\ to\ ester}$), 121.3 (C$\underline{H}_{Ar\ ortho\ to\ ester}$ x 2), 63.5 (C$\underline{H}$NH), 50.5 (C$\underline{H}CO_2$), 47.0 (C$\underline{H}_2$NH), 28.8 (C$\underline{H}_2$CHCO$_2$), 24.9 (C$\underline{H}_2$CH$_2$NH); **IR** (film) ν_{max}/cm^{-1} 3256 (w), 2954 (w), 2790 (w), 1748 (s), 1190 (m), 1137 (s), 1109 (s); **LRMS** (ES$^+$) *m/z* 316 ([M + H]$^+$); **HRMS** (ES$^+$) for $C_{18}H_{19}ClNO_2$, requires 316.1099, found 316.1096 Da.

(3.69) (–)-(2R, 3R)-Phenyl 2-(3,4-dimethoxyphenyl)piperidine-3-carboxylate



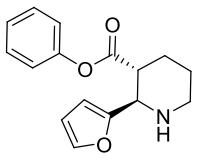
$C_{20}H_{23}NO_4$, 341.40 g/mol

The imino-aldol product **3.64.1-*R,S*** (155 mg, 0.32 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (1.80 mL) to this a solution of 4 M HCl(aq) in 1,4-dioxane (0.60 mL) was added and then stirred for 2 h. The reaction mixture was concentrated *in vacuo* to give a yellow solid. This was dissolved in MeCN (2.30 mL) then K_2CO_3 (354 mg, 2.56 mmol, 8 equiv) and NaI (5 mg, 0.03 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and organic phase was separated.

The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid. Purification by column chromatography (Al_2O_3 gel Brockmann III, eluent gradient 1:3 → 2:2 EtOAc/hexane) yielded the title piperidine as a pale yellow solid (60 mg, 0.18 mmol, 55%).

MP 81 - 84 ºC; **[α]$_D^{27}$** – 66.0 (*c* 0.92, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 - 7.22 (2H, m, $H_{Ar\ meta\ to\ ester}$ x 2), 7.18 - 7.11 (1H, m, $H_{Ar\ para\ to\ ester}$), 7.03 (1 H, d, *J* = 2.0 Hz, $CCH_{Ar}COCH_3$), 6.99 (1H, dd, *J* = 8.1, 2.0 Hz, $CCH_{Ar}CHCOCH_3$), 6.85 (1H, d, *J* = 8.1 Hz, $CCHCH_{Ar}COCH_3$), 6.66 (2H, d, *J* = 7.6 Hz, $CH_{Ar\ ortho\ to\ ester}$ x 2), 3.89 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 3.84 (1H, d, *J* = 10.1 Hz, CHNH), 3.23 (1H, dt, *J* = 11.6, 1.8 Hz, CHHNH), 2.95 - 2.81 (2H, m, CHHNH and $CHCO_2$), 2.27 (1H, dd, *J* = 12.9, 2.8 Hz, $CHHCHCO_2$), 1.96 - 1.80 (3H, m, $CHHCHCO_2$, $CHHCH_2NH$ and NH), 1.71 (1H, qt, *J* = 13.6, 5.1 Hz, $CHHCH_2NH$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.6 (CO), 150.4 ($C_{Ar\ ipso\ to\ ester}$), 149.0 ($C_{Ar}OCH_3$), 148.7 ($C_{Ar}OCH_3$), 134.6 ($C_{Ar}CHNH$), 129.2 ($CH_{Ar\ meta\ to\ ester}$ x 2), 125.7 ($CH_{Ar\ para\ to\ ester}$), 121.4 ($CH_{Ar\ ortho\ to\ ester}$ x 2), 120.0 ($CCH_{Ar}CHCOCH_3$), 110.9 ($CCHCH_{Ar}COCH_3$), 110.7 ($CCH_{Ar}COCH_3$), 64.1 (CHNH), 55.9 (OCH_3), 55.9 (OCH_3), 50.7 ($CHCO_2$), 47.2 (CH_2NH), 28.8 (CH_2CHCO_2), 24.9 (CH_2CH_2NH); **IR** (film) ν_{max}/cm^{-1} 2925 (w), 1744 (s), 1516 (s), 1232 (s), 1185 (s), 1160 (s), 1127 (s); **LRMS** (ES$^+$) *m/z* 342 ([M + H]$^+$); **HRMS** (ES$^+$) for $C_{20}H_{24}NO_4$, requires 342.1700, found 342.1707 Da.

(3.70) (–)-(2R,3R)-Phenyl 2-(furan-2-yl)piperidine-3-carboxylate



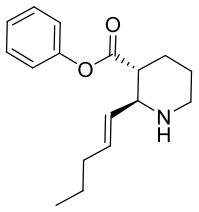
$C_{16}H_{17}NO_3$, 271.31 g/mol

The imino-aldol product **3.65.1-*R,S*** (75 mg, 0.18 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (1.00 mL), to this a solution of 4 M HCl(aq) in 1,4-dioxane (0.34 mL) was added and then stirred for 2 h. The reaction mixture was

concentrated *in vacuo* to give a yellow solid. This was dissolved in MeCN (1.30 mL) then K_2CO_3 (199 mg, 1.44 mmol, 8 equiv) and NaI (3 mg, 0.02 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phases was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:3 EtOAc/hexane) yielded the title piperidine as a yellow solid (48 mg, 0.18 mmol, quant).

MP 78 - 82 ºC; **$[\alpha]_D^{28}$** – 63.5 (*c* 0.49, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (1H, d, *J* = 1.5 Hz, OC$\underline{H}_{furan}$), 7.36 - 7.29 (2H, m, C$\underline{H}_{Ph\ meta}$ x 2), 7.23 - 7.16 (1H, m, C$\underline{H}_{Ph\ para}$), 6.90 - 6.86 (2H, m, C$\underline{H}_{Ph\ ortho}$), 6.35 (1H, dd, *J* = 3.5, 1.5 Hz, C$\underline{H}$CHO$_{furan}$), 6.32 (1H, d, *J* = 3.5 Hz, OCC$\underline{H}_{furan}$), 4.11 (1H, d, *J* = 10.1 Hz, C$\underline{H}$NH), 3.21 (1H, d, *J* = 12.6 Hz, C$\underline{H}$HNH), 2.97 (1H, ddd, *J* = 11.9, 10.4, 4.0 Hz, C$\underline{H}CO_2$), 2.86 (1H, td, *J* = 12.3, 2.8 Hz, CH$\underline{H}$NH), 2.34 - 2.25 (1H, m, C$\underline{H}$HCHCO$_2$), 2.08 (1H, br. s, N$\underline{H}$), 1.89 (1H, qd, *J* = 13.1, 4.0 Hz, CH$\underline{H}$CHCO$_2$), 1.86 - 1.78 (1H, m, C$\underline{H}CH_2NH$), 1.64 (1H, qt, *J* = 12.5, 3.5 Hz, CH$\underline{H}CH_2NH$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 ($\underline{C}O$), 154.6 ($\underline{C}_{furan\ ipso}$), 150.5 ($\underline{C}_{Ph\ ipso}$), 142.1 ($\underline{C}$(H)O$_{furan}$), 129.3 ($\underline{C}H_{Ph\ meta}$ x 2), 125.7 ($\underline{C}H_{Ph\ para}$), 121.4 ($\underline{C}H_{Ph\ ortho}$ x 2), 110.1 ($\underline{C}$HCHO$_{furan}$), 106.5 ($\underline{C}$HCO$_{furan}$), 56.3 ($\underline{C}$HNH), 47.8 ($\underline{C}HCO_2$), 46.2 ($\underline{C}H_2NH$), 28.3 ($\underline{C}H_2CHCO_2$), 24.9 ($\underline{C}H_2CH_2NH$); **IR** (film) ν_{max}/cm^{-1} 3240 (w), 3116 (w), 2940 (w), 2786 (w), 1743 (s), 1184 (s), 1154 (s), 733 (s), 715 (s); **LRMS** (ES$^+$) *m/z* 272 ([M + H]$^+$); **HRMS** (ES$^+$) for $C_{16}H_{18}NO_3$, requires 272.1281, found 272.1284 Da.

(3.71) (–)-(2R, 3S, E) Phenyl-2-(pent-1-enyl)piperidine-3-carboxylate



$C_{17}H_{23}NO_2$, 273.37 g/mol

The imino-aldol product **3.66.1-*R,S*** (193 mg, 0.47 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (2.64 mL) to this a solution of 4 M HCl(aq) in 1,4-dioxane (0.88 mL) was added and then stirred for 1 h. The reaction mixture was concentrated *in vacuo*. This was dissolved in MeCN (3.39 mL) then K_2CO_3 (516 mg, 3.7 mmol, 8 equiv) and NaI (7 mg, 0.05 mmol, 0.1 equiv) were added. The resulting bright yellow solution was stirred for 16 h. H_2O (5 mL) and Et_2O (5 mL) were added and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (5 mL x 2) and then the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid. Purification by column chromatography (Al_2O_3 gel Brockmann III, 1:3 EtOAc/hexane) yielded the title piperidine as a white solid (77 mg, 0.28 mmol, 60%).

MP 99 - 102 ºC; **$[\alpha]_D^{27}$** – 32.6 (*c* 1.03, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (2H, dd, *J* = 8.6, 7.2 Hz, $H_{Ar\ meta}$ x 2), 7.22 (1H, tt, *J* = 7.2, 1.0, $H_{Ar\ para}$), 7.01 (2H, dd, *J* = 8.6, 1.0 Hz, $H_{Ar\ ortho}$ x 2), 5.76 (1H, dt, *J* = 15.3, 6.9 Hz, CH_2CH=CH), 5.51 (1H, ddt, *J* = 15.3, 8.1, 1.0 Hz, CH=CHCH), 3.35 (1H, dd, *J* = 9.8, 8.1 Hz, NHCHC(H)=C), 3.12 (1H, dt, *J* = 12.0, 2.0 Hz, $CHHCHCO_2$), 2.77 (1H, td, *J* = 12.1, 2.5 Hz, $CHHCHCO_2$), 2.50 (1H, ddd, *J* = 12.0, 9.8, 3.8 Hz, $CHCO_2$), 2.24 - 2.12 (1H, m, CHHNH), 2.03 (2H, tdd, *J* = 7.5, 6.9, 1.0 Hz, CH_2C=), 1.85 - 1.70 (2H, m, CHHNH and $CHHCH_2NH$), 1.65 - 1.45 (2H, m, $CHHCH_2NH$ and NH), 1.40 (2H, tq, *J* = 7.5, 7.3 Hz, CH_2CH_3), 0.90 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.8 (CO_2), 150.7 ($C_{Ar\ ipso}$), 133.5 (CH_2CH=CH), 130.7 (CH=CHCH), 129.3 ($CH_{Ar\ meta}$ x 2), 125.7 ($CH_{Ar\ para}$), 121.5 ($CH_{Ar\ ortho}$ x 2), 61.2 (NHCH), 49.3 ($CHCO_2$), 46.2 (CH_2CHCO_2), 34.4 (CH_2C(H)=), 28.1 (CH_2NH),

24.9 (<u>C</u>H_2CH_2NH), 22.3 (<u>C</u>H_2CH_3), 13.7 (<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1} 3236 (w), 2934 (m), 1747 (s), 1190 (s), 1160 (s), 1123 (s); **LRMS** (ES^+) *m/z* 274 ([M + H]$^+$); **HRMS** (ES^+) for $C_{17}H_{24}NO_2$, requires 274.1802, found 274.1808 Da.

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6. Appendices

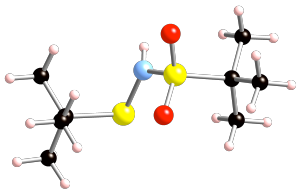
6.1. Appendix A: X-ray crystallography data

All data was collected and calculated by Dr Mark Light at the University of Southampton.

UNIVERSITY OF Southampton
School of Chemistry

Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
Contact: Dr Mark E Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details for **compound 2.01**



Identification code	**2010sot0052**
Empirical formula	$C_8H_{19}NO_2S_2$
Formula weight	225.36
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*Pbca*
Unit cell dimensions	a = 12.7149(2) Å
	b = 10.1500(2) Å
	c = 19.0661(2) Å
Volume	2460.60(7) Å^3
Z	8
Density (calculated)	1.217 Mg / m^3
Absorption coefficient	0.407 mm^{-1}
F(000)	976
Crystal	Block; Colourless
Crystal size	0.40 × 0.22 × 0.20 mm^3
θ range for data collection	3.34 – 27.48°
Index ranges	$-16 \le h \le 16$, $-13 \le k \le 13$, $-24 \le l \le 24$
Reflections collected	17239
Independent reflections	2810 [R_{int} = 0.0442]
Completeness to θ = 27.48°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9230 and 0.8541
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2810 / 0 / 128
Goodness-of-fit on F^2	1.080
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0454, $wR2$ = 0.0887
R indices (all data)	$R1$ = 0.0571, $wR2$ = 0.0950
Largest diff. peak and hole	0.348 and –0.344 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, the NH was located in the difference map and freely refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	2792(1)	2312(1)	5508(1)	29(1)	1
S2	2488(1)	1757(1)	7008(1)	18(1)	1
O1	2175(1)	489(1)	6746(1)	25(1)	1
O2	1849(1)	2382(2)	7533(1)	26(1)	1
N1	2511(1)	2768(2)	6340(1)	22(1)	1
C1	1738(3)	1797(4)	4344(2)	79(1)	1
C2	1500(2)	2321(2)	5074(1)	29(1)	1
C3	1068(3)	3702(3)	5041(2)	60(1)	1
C4	741(3)	1423(4)	5446(2)	72(1)	1
C5	3811(2)	1629(2)	7355(1)	21(1)	1
C6	4164(2)	3001(2)	7589(1)	30(1)	1
C7	4528(2)	1074(2)	6785(1)	32(1)	1
C8	3748(2)	687(2)	7978(1)	31(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–N1	1.6919(18)	C1–C2	1.520(3)
S1–C2	1.839(2)	C2–C4	1.505(4)
S2–O2	1.4351(15)	C2–C3	1.507(3)
S2–O1	1.4368(14)	C5–C7	1.526(3)
S2–N1	1.6357(17)	C5–C8	1.528(3)
S2–C5	1.812(2)	C5–C6	1.530(3)
N1–S1–C2	103.44(10)	C3–C2–C1	111.1(2)
O2–S2–O1	118.77(9)	C4–C2–S1	110.93(17)
O2–S2–N1	106.01(9)	C3–C2–S1	110.41(17)
O1–S2–N1	107.22(9)	C1–C2–S1	103.4(2)
O2–S2–C5	107.65(9)	C7–C5–C8	110.70(18)
O1–S2–C5	108.61(9)	C7–C5–C6	111.62(18)
N1–S2–C5	108.17(10)	C8–C5–C6	110.98(18)
S2–N1–S1	124.24(11)	C7–C5–S2	108.82(14)
C4–C2–C3	110.4(3)	C8–C5–S2	106.26(15)
C4–C2–C1	110.4(3)	C6–C5–S2	108.27(14)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	29(1)	33(1)	25(1)	1(1)	4(1)	2(1)
S2	16(1)	15(1)	23(1)	0(1)	−1(1)	−1(1)
O1	27(1)	14(1)	34(1)	0(1)	−7(1)	−5(1)
O2	21(1)	28(1)	30(1)	−2(1)	5(1)	1(1)
N1	30(1)	12(1)	24(1)	0(1)	−6(1)	−1(1)
C1	98(3)	109(3)	30(2)	−26(2)	−20(2)	46(2)
C2	39(1)	24(1)	23(1)	−4(1)	−8(1)	3(1)
C3	74(2)	35(2)	71(2)	−16(2)	−40(2)	17(2)
C4	55(2)	87(3)	73(2)	33(2)	−41(2)	−38(2)
C5	18(1)	18(1)	29(1)	−2(1)	−4(1)	1(1)
C6	24(1)	21(1)	46(1)	−3(1)	−10(1)	−2(1)
C7	21(1)	38(1)	39(1)	−5(1)	−3(1)	7(1)
C8	39(1)	23(1)	32(1)	2(1)	−13(1)	1(1)

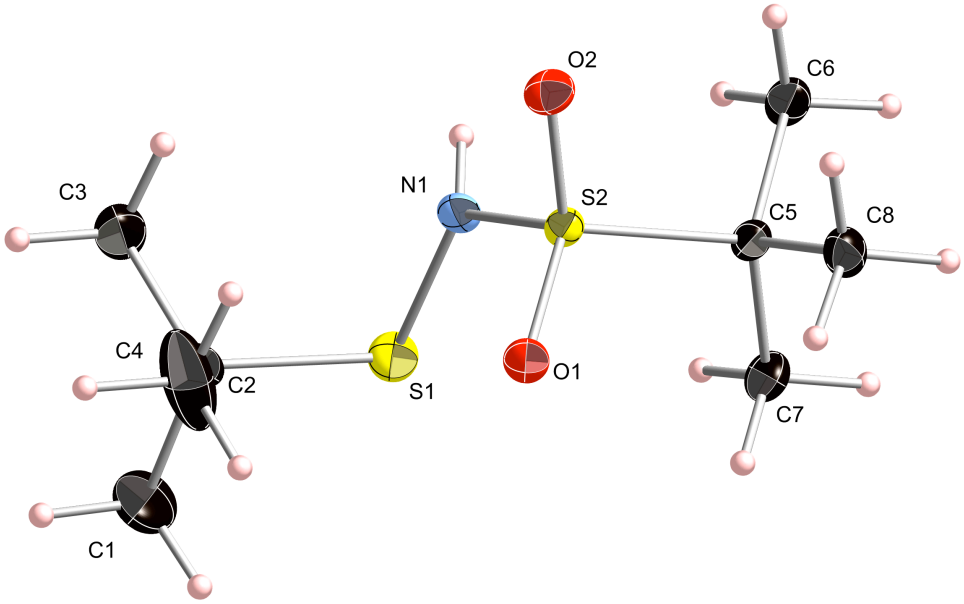
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	2583(19)	3530(30)	6433(12)	24(6)	1
H1A	1089	1777	4067	119	1
H1B	2026	904	4380	119	1
H1C	2253	2372	4115	119	1
H3A	392	3695	4795	90	1
H3B	1563	4270	4790	90	1
H3C	968	4038	5519	90	1
H4A	633	1739	5927	107	1
H4B	1029	528	5458	107	1
H4C	68	1419	5196	107	1
H6A	3680	3334	7947	45	1
H6B	4162	3599	7185	45	1
H6C	4875	2950	7784	45	1
H7A	4518	1660	6377	49	1
H7B	4279	198	6647	49	1
H7C	5248	1007	6966	49	1
H8A	4450	572	8181	47	1
H8B	3479	−168	7820	47	1
H8C	3273	1052	8334	47	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N1–H1···O1^{i}	0.80(3)	2.10(3)	2.896(2)	176(2)

Symmetry transformations used to generate equivalent atoms:
(i) –x+1/2,y+1/2,z



Thermal ellipsoids drawn at the 35% probability level

UNIVERSITY OF Southampton
School of Chemistry

Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
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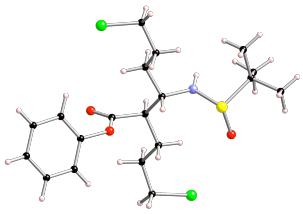
Table 1. Crystal data and structure refinement details for **compound 2.19-*R,S***



Identification code	**2009sot1091**	
Empirical formula	$C_{19}H_{29}Cl_2NO_3S$	
Formula weight	422.39	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*1	
Unit cell dimensions	a = 5.4592(2) Å	α = 115.132(2)°
	b = 10.5364(4) Å	β = 94.071(2)°
	c = 10.8295(4) Å	γ = 104.311(2)°
Volume	535.34(3) Å^3	
Z	1	
Density (calculated)	1.310 Mg / m^3	
Absorption coefficient	0.419 mm^{-1}	
F(000)	224	
Crystal	Block; Colourless	
Crystal size	0.35 × 0.11 × 0.10 mm^3	
θ range for data collection	3.73 – 27.54°	
Index ranges	$-7 \le h \le 7$, $-13 \le k \le 13$, $-14 \le l \le 14$	
Reflections collected	10452	
Independent reflections	4680 [R_{int} = 0.0355]	
Completeness to θ = 27.50°	99.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9593 and 0.8673	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4680 / 3 / 238	
Goodness-of-fit on F^2	1.258	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0324, *wR2* = 0.0747	
R indices (all data)	*R1* = 0.0340, *wR2* = 0.0760	
Absolute structure parameter	0.06(5)	
Largest diff. peak and hole	0.200 and –0.230 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.
Chirality: C8 = R, C9 = S.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Cl1	12819(1)	–825(1)	6409(1)	36(1)	1
Cl2	4738(1)	5752(1)	4228(1)	23(1)	1
S1	4531(1)	78(1)	2205(1)	17(1)	1
O3	8428(3)	3006(2)	7388(2)	20(1)	1
O4	12363(3)	4437(2)	7510(2)	22(1)	1
O5	3344(3)	1168(2)	2098(2)	24(1)	1
N1	7570(3)	818(2)	3027(2)	16(1)	1
C1	10647(4)	3001(3)	9404(2)	24(1)	1
C2	10934(5)	3395(3)	10821(2)	26(1)	1
C3	9463(5)	4203(3)	11616(2)	28(1)	1
C4	7745(5)	4650(3)	11016(2)	28(1)	1
C5	7455(4)	4274(3)	9609(2)	24(1)	1
C6	8913(4)	3451(2)	8834(2)	19(1)	1
C7	10280(4)	3594(2)	6845(2)	15(1)	1
C8	9270(4)	3062(2)	5321(2)	16(1)	1
C9	8272(4)	1359(2)	4535(2)	14(1)	1
C10	10305(4)	702(2)	4852(2)	17(1)	1
C11	9226(4)	–934(2)	4423(2)	21(1)	1
C12	11258(5)	–1618(3)	4616(2)	22(1)	1
C13	7206(4)	3780(2)	5179(2)	17(1)	1
C14	8250(4)	5464(2)	5955(2)	20(1)	1
C15	6241(4)	6220(2)	5963(2)	20(1)	1
C16	5079(4)	–996(2)	445(2)	19(1)	1
C17	6174(5)	–2184(3)	483(3)	26(1)	1
C18	6814(4)	11(3)	–20(2)	24(1)	1
C19	2409(4)	–1723(3)	–508(3)	30(1)	1

Table 3. Bond lengths [Å] and angles [°].

Cl1–C12	1.797(2)	C4–C5	1.388(3)
Cl2–C15	1.801(2)	C5–C6	1.382(3)
S1–O5	1.4908(16)	C7–C8	1.509(3)
S1–N1	1.6476(17)	C8–C13	1.537(3)
S1–C16	1.849(2)	C8–C9	1.548(3)
O3–C7	1.355(2)	C9–C10	1.535(3)
O3–C6	1.413(2)	C10–C11	1.521(3)
O4–C7	1.200(3)	C11–C12	1.510(3)
N1–C9	1.467(2)	C13–C14	1.531(3)
C1–C6	1.375(3)	C14–C15	1.506(3)
C1–C2	1.394(3)	C16–C18	1.517(3)
C2–C3	1.387(3)	C16–C17	1.529(3)
C3–C4	1.383(4)	C16–C19	1.530(3)
O5–S1–N1	113.25(9)	C7–C8–C9	110.92(16)
O5–S1–C16	105.80(9)	C13–C8–C9	113.00(17)
N1–S1–C16	97.77(9)	N1–C9–C10	109.71(16)
C7–O3–C6	118.57(16)	N1–C9–C8	111.63(16)
C9–N1–S1	121.23(14)	C10–C9–C8	110.61(16)
C6–C1–C2	118.4(2)	C11–C10–C9	113.17(17)
C3–C2–C1	120.1(2)	C12–C11–C10	113.49(18)
C4–C3–C2	120.3(2)	C11–C12–Cl1	112.20(15)
C3–C4–C5	120.2(2)	C14–C13–C8	111.90(17)
C6–C5–C4	118.5(2)	C15–C14–C13	114.03(18)
C1–C6–C5	122.5(2)	C14–C15–Cl2	111.89(15)
C1–C6–O3	120.73(19)	C18–C16–C17	113.22(18)
C5–C6–O3	116.61(19)	C18–C16–C19	110.02(19)
O4–C7–O3	123.97(19)	C17–C16–C19	109.47(19)
O4–C7–C8	126.56(19)	C18–C16–S1	110.59(15)
O3–C7–C8	109.44(17)	C17–C16–S1	107.75(15)
C7–C8–C13	108.97(16)	C19–C16–S1	105.48(14)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	44(1)	35(1)	30(1)	16(1)	−4(1)	18(1)
Cl2	26(1)	24(1)	23(1)	11(1)	0(1)	11(1)
S1	15(1)	18(1)	14(1)	5(1)	2(1)	5(1)
O3	18(1)	24(1)	14(1)	8(1)	2(1)	2(1)
O4	19(1)	23(1)	19(1)	9(1)	−3(1)	1(1)
O5	24(1)	26(1)	20(1)	7(1)	0(1)	14(1)
N1	14(1)	19(1)	13(1)	6(1)	1(1)	4(1)
C1	22(1)	27(1)	23(1)	12(1)	5(1)	8(1)
C2	22(1)	30(1)	26(1)	17(1)	−3(1)	3(1)
C3	26(1)	35(1)	15(1)	10(1)	2(1)	1(1)
C4	25(1)	34(1)	21(1)	7(1)	7(1)	10(1)
C5	19(1)	30(1)	22(1)	11(1)	2(1)	9(1)
C6	19(1)	20(1)	15(1)	8(1)	2(1)	0(1)
C7	18(1)	16(1)	17(1)	9(1)	4(1)	8(1)
C8	16(1)	16(1)	17(1)	8(1)	3(1)	5(1)
C9	15(1)	13(1)	14(1)	6(1)	2(1)	3(1)
C10	17(1)	16(1)	18(1)	8(1)	4(1)	7(1)
C11	22(1)	15(1)	26(1)	9(1)	1(1)	5(1)
C12	27(1)	21(1)	22(1)	10(1)	6(1)	11(1)
C13	16(1)	15(1)	16(1)	6(1)	1(1)	4(1)
C14	22(1)	14(1)	20(1)	6(1)	−1(1)	5(1)
C15	23(1)	18(1)	16(1)	6(1)	0(1)	6(1)
C16	17(1)	19(1)	14(1)	2(1)	2(1)	6(1)
C17	27(1)	21(1)	27(1)	6(1)	7(1)	12(1)
C18	25(1)	29(1)	17(1)	10(1)	4(1)	8(1)
C19	17(1)	36(1)	21(1)	1(1)	−1(1)	6(1)

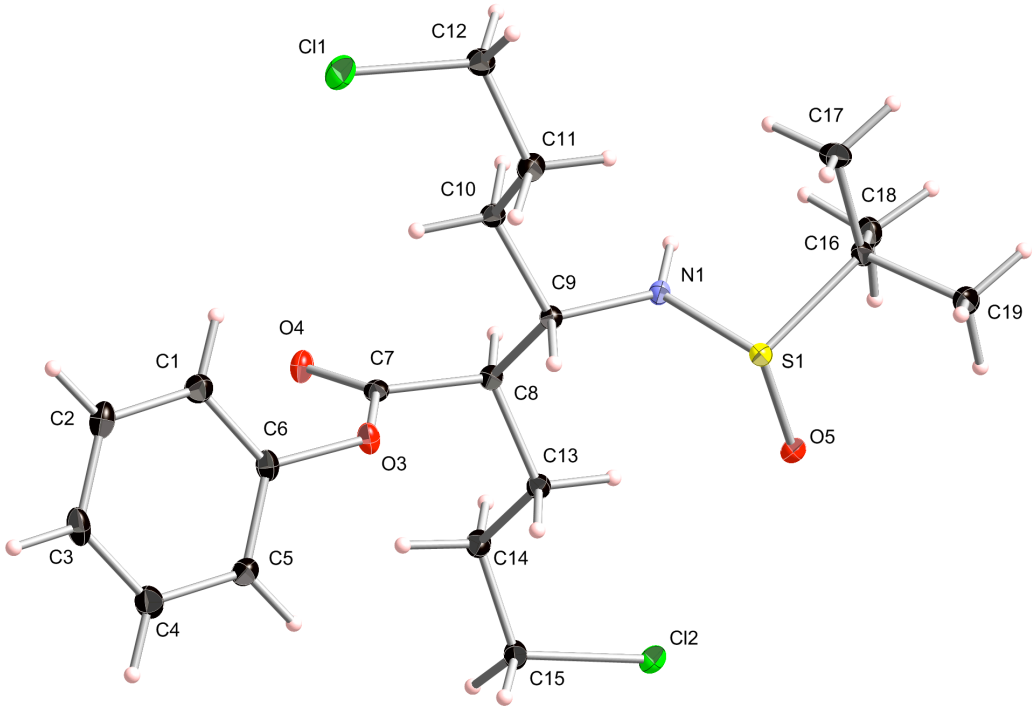
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H901	8796	891	2552	19	1
H1	11625	2436	8847	28	1
H2	12138	3110	11243	31	1
H3	9636	4451	12577	33	1
H4	6761	5215	11569	34	1
H5	6280	4577	9189	29	1
H8	10733	3402	4916	19	1
H9	6695	1017	4866	17	1
H10A	11720	855	4358	20	1
H10B	11044	1235	5863	20	1
H11A	7918	–1077	4979	26	1
H11B	8348	–1455	3432	26	1
H12A	12569	–1479	4060	27	1
H12B	10444	–2689	4263	27	1
H13A	6588	3465	4181	20	1
H13B	5718	3438	5553	20	1
H14A	9032	5766	6929	24	1
H14B	9633	5802	5520	24	1
H15A	7058	7300	6486	24	1
H15B	4904	5933	6448	24	1
H17A	6280	–2847	–462	39	1
H17B	5043	–2748	860	39	1
H17C	7902	–1719	1077	39	1
H18A	6830	–541	–1010	36	1
H18B	8571	384	526	36	1
H18C	6162	839	121	36	1
H19A	1646	–961	–471	45	1
H19B	1299	–2367	–197	45	1
H19C	2571	–2307	–1466	45	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H901···O5^{i}	0.88	2.54	3.357(2)	155.8

Symmetry transformations used to generate equivalent atoms:
(i) x+1,y,z



Thermal ellipsoids drawn at the 35% probability level

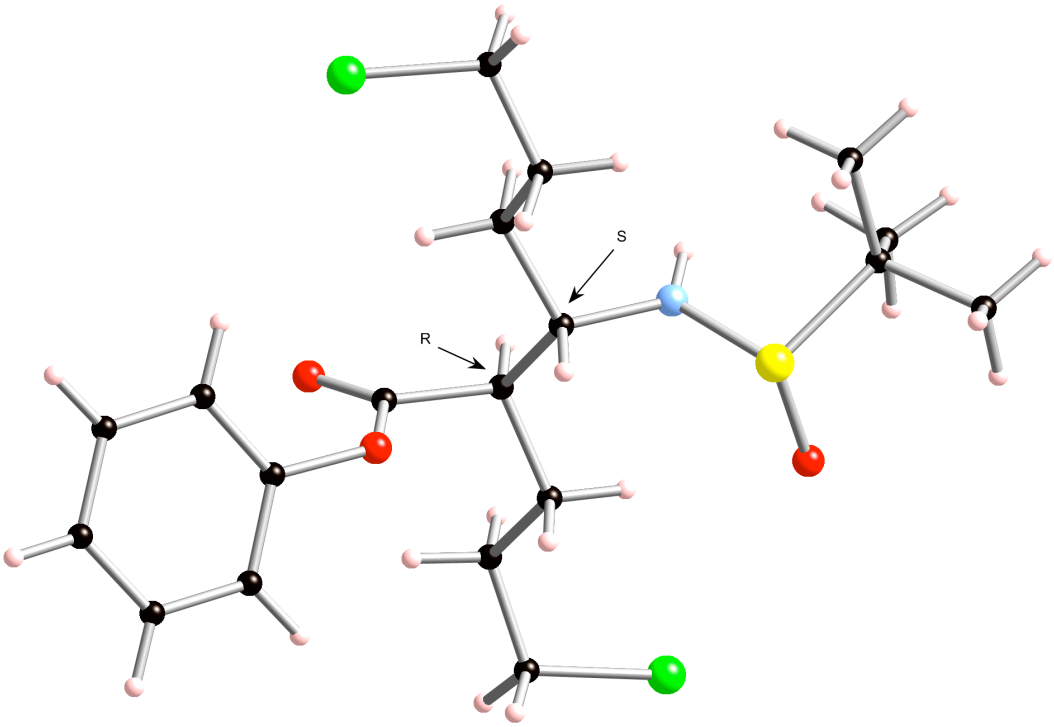


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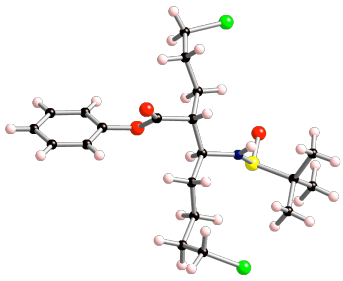
Table 1. Crystal data and structure refinement details for **compound 2.20-*R*,*S***



Identification code	**2008sot1181**
Empirical formula	$C_{20}H_{31}Cl_2NO_3S$
Formula weight	436.42
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.5850(2) Å
	b = 8.2126(3) Å β = 93.2480(10)°
	c = 23.9178(7) Å
Volume	1095.28(6) Å^3
Z	2
Density (calculated)	1.323 Mg / m^3
Absorption coefficient	0.412 mm^{-1}
$F(000)$	464
Crystal	Slab; Colourless
Crystal size	0.3 × 0.2 × 0.04 mm^3
θ range for data collection	3.01 – 27.48°
Index ranges	$-7 \le h \le 7$, $-10 \le k \le 10$, $-30 \le l \le 31$
Reflections collected	12551
Independent reflections	4970 [R_{int} = 0.0227]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9837 and 0.8765
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4970 / 1 / 252
Goodness-of-fit on F^2	1.050
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0270, $wR2$ = 0.0620
R indices (all data)	$R1$ = 0.0284, $wR2$ = 0.0626
Absolute structure parameter	0.45(4)
Largest diff. peak and hole	0.282 and –0.181 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except the NH which was freely refined. The Flack parameter refines to a value of 0.45(4) using the TWIN and BASF SHELX cards. This is interpreted as a partial mix of enantiomers.
Relative chirality: C4 = R, C5 = S.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Cl1	4214(1)	6693(1)	3117(1)	31(1)	1
Cl2	11260(1)	−2985(1)	834(1)	34(1)	1
S1	4490(1)	1417(1)	1519(1)	16(1)	1
O1	7689(2)	88(2)	3536(1)	20(1)	1
O2	11397(2)	1226(2)	3601(1)	22(1)	1
O3	2933(2)	2802(2)	1670(1)	27(1)	1
N1	7175(2)	1500(2)	1838(1)	18(1)	1
C1	5287(3)	5264(2)	3644(1)	23(1)	1
C2	7360(3)	4265(2)	3446(1)	23(1)	1
C3	6631(3)	3121(2)	2961(1)	19(1)	1
C4	8608(3)	1900(2)	2821(1)	16(1)	1
C5	7692(3)	658(2)	2371(1)	16(1)	1
C6	9440(3)	−759(2)	2299(1)	18(1)	1
C7	8293(3)	−2150(2)	1956(1)	19(1)	1
C8	9906(3)	−3628(2)	1897(1)	23(1)	1
C9	12081(3)	−3344(2)	1565(1)	26(1)	1
C10	9481(3)	1049(2)	3356(1)	16(1)	1
C11	8012(3)	−761(2)	4043(1)	17(1)	1
C12	6198(3)	−612(2)	4404(1)	22(1)	1
C13	6331(4)	−1507(3)	4901(1)	30(1)	1
C14	8257(4)	−2530(3)	5023(1)	35(1)	1
C15	10044(4)	−2678(3)	4648(1)	34(1)	1
C16	9938(3)	−1796(2)	4151(1)	23(1)	1
C17	5381(3)	1823(2)	797(1)	16(1)	1
C18	3015(3)	1911(3)	443(1)	24(1)	1
C19	6740(3)	3427(2)	764(1)	20(1)	1
C20	6837(3)	367(2)	620(1)	21(1)	1

Table 3. Bond lengths [Å] and angles [°].

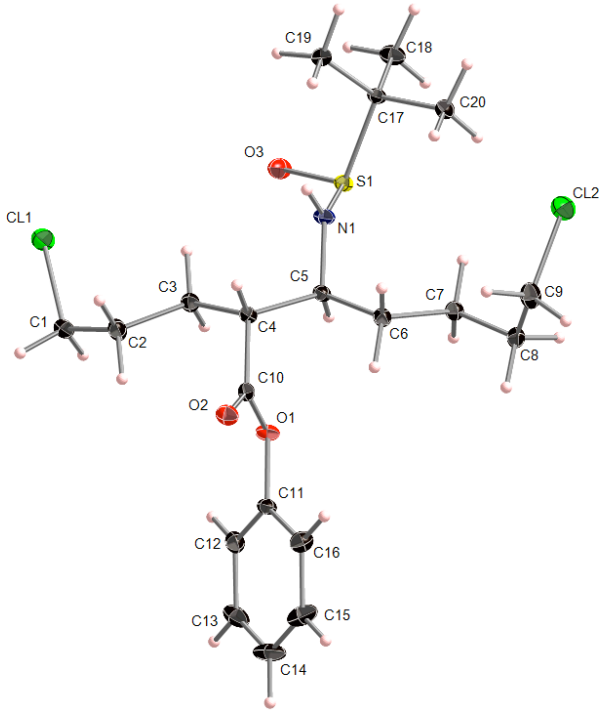
Cl1–C1	1.7985(18)	C5–C6	1.535(2)
Cl2–C9	1.8060(18)	C6–C7	1.526(2)
S1–O3	1.4890(13)	C7–C8	1.523(2)
S1–N1	1.6453(13)	C8–C9	1.507(2)
S1–C17	1.8535(14)	C11–C12	1.374(2)
O1–C10	1.364(2)	C11–C16	1.384(2)
O1–C11	1.4003(19)	C12–C13	1.397(3)
O2–C10	1.1989(19)	C13–C14	1.382(3)
N1–C5	1.465(2)	C14–C15	1.384(3)
C1–C2	1.516(2)	C15–C16	1.391(2)
C2–C3	1.530(2)	C17–C20	1.519(2)
C3–C4	1.543(2)	C17–C19	1.525(2)
C4–C10	1.515(2)	C17–C18	1.530(2)
C4–C5	1.548(2)		
O3–S1–N1	112.64(8)	O2–C10–O1	124.51(14)
O3–S1–C17	106.33(7)	O2–C10–C4	126.33(15)
N1–S1–C17	97.98(7)	O1–C10–C4	109.10(13)
C10–O1–C11	120.06(12)	C12–C11–C16	121.98(16)
C5–N1–S1	120.91(12)	C12–C11–O1	115.87(15)
C2–C1–Cl1	111.37(12)	C16–C11–O1	121.93(15)
C1–C2–C3	113.19(14)	C11–C12–C13	118.90(18)
C2–C3–C4	113.64(13)	C14–C13–C12	120.11(18)
C10–C4–C3	108.43(12)	C13–C14–C15	119.93(17)
C10–C4–C5	111.16(14)	C14–C15–C16	120.68(18)
C3–C4–C5	111.53(12)	C11–C16–C15	118.38(17)
N1–C5–C6	110.82(13)	C20–C17–C19	112.96(13)
N1–C5–C4	109.54(13)	C20–C17–C18	110.03(14)
C6–C5–C4	112.97(13)	C19–C17–C18	110.29(14)
C7–C6–C5	112.18(14)	C20–C17–S1	107.09(11)
C8–C7–C6	114.43(14)	C19–C17–S1	111.37(11)
C9–C8–C7	115.07(15)	C18–C17–S1	104.76(10)
C8–C9–Cl2	111.58(11)		

Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

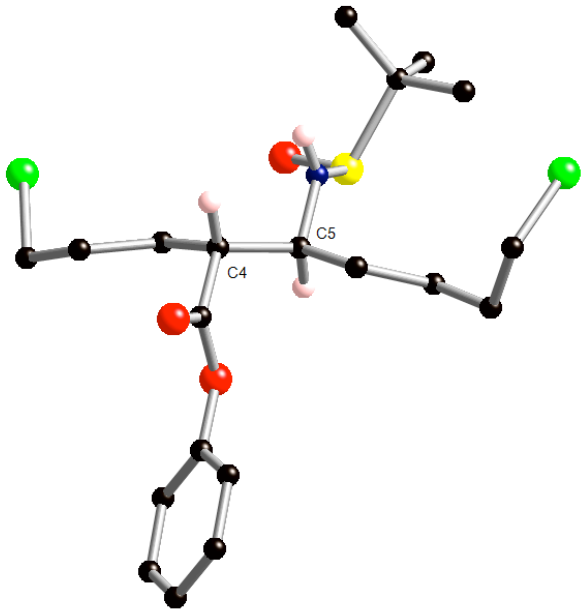
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	39(1)	30(1)	23(1)	1(1)	1(1)	14(1)
Cl2	42(1)	33(1)	27(1)	−1(1)	11(1)	5(1)
S1	17(1)	19(1)	13(1)	2(1)	2(1)	3(1)
O1	19(1)	25(1)	15(1)	7(1)	−2(1)	−2(1)
O2	19(1)	26(1)	19(1)	1(1)	−2(1)	−1(1)
O3	30(1)	30(1)	22(1)	4(1)	8(1)	15(1)
N1	20(1)	22(1)	13(1)	4(1)	0(1)	−4(1)
C1	31(1)	23(1)	15(1)	0(1)	3(1)	3(1)
C2	27(1)	23(1)	19(1)	−5(1)	−3(1)	5(1)
C3	22(1)	18(1)	16(1)	−1(1)	−3(1)	3(1)
C4	20(1)	17(1)	12(1)	0(1)	2(1)	−1(1)
C5	19(1)	17(1)	12(1)	0(1)	0(1)	−1(1)
C6	20(1)	17(1)	16(1)	−1(1)	−1(1)	1(1)
C7	22(1)	18(1)	17(1)	−1(1)	1(1)	−2(1)
C8	32(1)	17(1)	19(1)	−3(1)	−4(1)	2(1)
C9	25(1)	25(1)	29(1)	−7(1)	−2(1)	5(1)
C10	18(1)	15(1)	15(1)	−2(1)	2(1)	1(1)
C11	22(1)	18(1)	12(1)	2(1)	−1(1)	−3(1)
C12	22(1)	23(1)	20(1)	−4(1)	1(1)	−1(1)
C13	33(1)	39(1)	17(1)	−2(1)	6(1)	−14(1)
C14	36(1)	45(1)	22(1)	16(1)	−12(1)	−18(1)
C15	28(1)	32(1)	40(1)	17(1)	−10(1)	−1(1)
C16	20(1)	23(1)	26(1)	4(1)	2(1)	1(1)
C17	18(1)	18(1)	11(1)	2(1)	2(1)	1(1)
C18	20(1)	34(1)	20(1)	6(1)	−2(1)	−3(1)
C19	23(1)	19(1)	18(1)	2(1)	2(1)	0(1)
C20	26(1)	19(1)	17(1)	−1(1)	5(1)	1(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	5816	5861	3988	28	1
H1B	3964	4526	3736	28	1
H2A	8052	3613	3763	28	1
H2B	8623	5013	3325	28	1
H3A	6199	3781	2624	22	1
H3B	5185	2507	3057	22	1
H4	9977	2519	2672	19	1
H5	6152	191	2493	19	1
H6A	10859	–356	2111	21	1
H6B	9996	–1174	2673	21	1
H7A	6818	–2498	2133	23	1
H7B	7812	–1737	1577	23	1
H8A	10450	–4005	2277	28	1
H8B	8944	–4515	1717	28	1
H9A	13148	–4305	1600	32	1
H9B	12980	–2392	1721	32	1
H12	4875	88	4317	26	1
H13	5096	–1414	5157	36	1
H14	8354	–3129	5363	42	1
H15	11357	–3390	4731	41	1
H16	11157	–1901	3892	28	1
H18A	3349	2035	47	37	1
H18B	2081	2846	562	37	1
H18C	2099	909	492	37	1
H19A	8264	3347	986	30	1
H19B	5774	4308	911	30	1
H19C	7055	3657	373	30	1
H20A	7182	477	225	31	1
H20B	5920	–634	673	31	1
H20C	8346	318	850	31	1
H99	8110(30)	2200(20)	1731(7)	10(4)	1



Thermal ellipsoids drawn t the 50% probability level



UNIVERSITY OF Southampton
School of Chemistry

Single Crystal X-Ray Diffraction Service

School of Chemistry - University of Southampton
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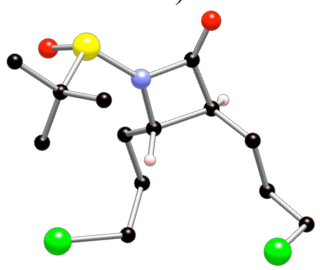
Table 1. Crystal data and structure refinement details for **compound 3.17**



Identification code	**2010sot0812** (ACC/5942/6A2)
Empirical formula	$C_{13}H_{23}Cl_2NO_2S$
Formula weight	328.28
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.7825(2) Å
	b = 8.5273(1) Å β = 100.646(1)°
	c = 11.1250(2) Å
Volume	818.82(3) Å^3
Z	2
Density (calculated)	1.331 Mg / m^3
Absorption coefficient	0.522 mm^{-1}
$F(000)$	348
Crystal	Fragment; Colourless
Crystal size	0.30 × 0.18 × 0.10 mm^3
θ range for data collection	3.27 – 27.48°
Index ranges	$-11 \le h \le 11$, $-10 \le k \le 11$, $-14 \le l \le 14$
Reflections collected	10534
Independent reflections	3662 [R_{int} = 0.0382]
Completeness to θ = 27.48°	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9497 and 0.8592
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3662 / 1 / 179
Goodness-of-fit on F^2	0.993
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0342, $wR2$ = 0.0946
R indices (all data)	$R1$ = 0.0366, $wR2$ = 0.0978
Absolute structure parameter	–0.04(5)
Largest diff. peak and hole	0.246 and –0.422 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. One of the terminal chlorines is modelled as disordered over 2 slightly different positions (ca. 80:20), thermal parameter restraints were used.
Chirality: C5 = S, C10 = S

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	5344(3)	3017(3)	5599(2)	32(1)	1
C2	7403(3)	1145(3)	6617(2)	34(1)	1
C3	4752(2)	1025(3)	7145(2)	25(1)	1
C4	5962(2)	2083(2)	6754(2)	22(1)	1
C5	3561(2)	4466(2)	8280(2)	16(1)	1
C6	3586(2)	3781(2)	9541(2)	19(1)	1
C7	1988(2)	3738(3)	9891(2)	23(1)	1
C8	851(2)	2614(3)	9147(2)	26(1)	1
C9	5023(2)	6268(2)	7820(2)	16(1)	1
C10	3391(2)	6286(2)	8121(2)	18(1)	1
C11	2130(2)	6898(2)	7097(2)	21(1)	1
C12	522(2)	6752(2)	7401(2)	23(1)	1
N1	5131(2)	4646(2)	7940(1)	17(1)	1
O1	6993(2)	2604(2)	9126(1)	21(1)	1
O2	5895(2)	7222(2)	7531(1)	22(1)	1
S1	6711(1)	3509(1)	7968(1)	16(1)	1
Cl1	1545(1)	622(1)	9328(1)	36(1)	1
C13A	−761(3)	7303(3)	6388(2)	31(1)	0.79(3)
Cl2A	−958(4)	5979(11)	5050(3)	62(1)	0.79(3)
C13B	−761(3)	7303(3)	6388(2)	31(1)	0.21(3)
Cl2B	−862(13)	6420(30)	5125(11)	62(1)	0.21(3)

Table 3. Bond lengths [Å] and angles [°].

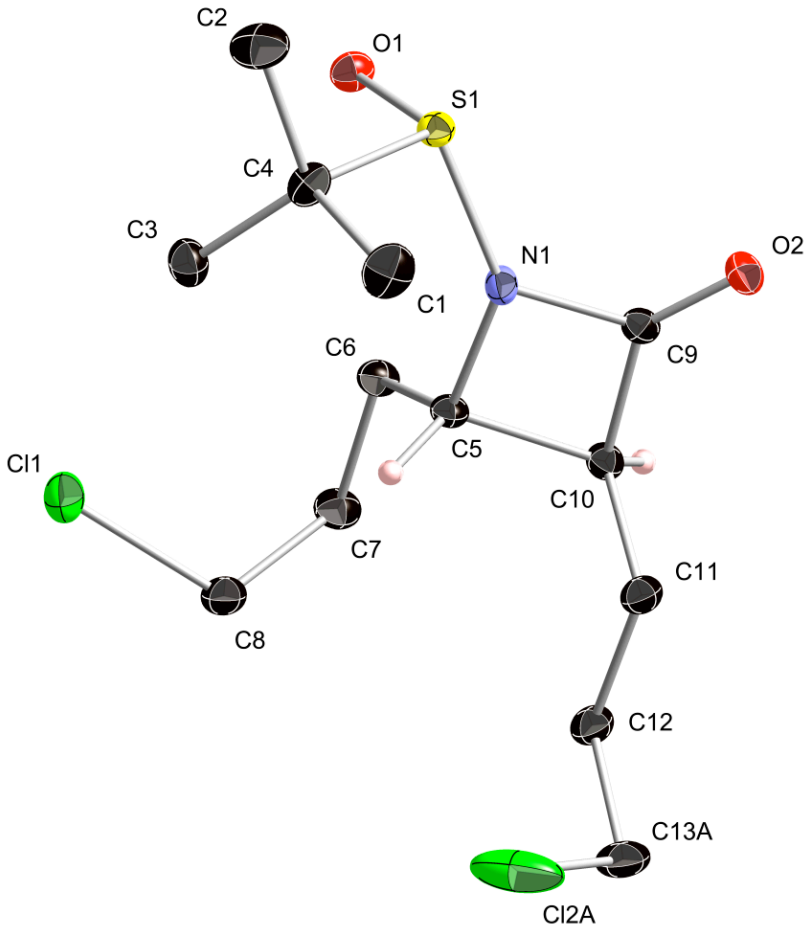
C1–C4	1.524(3)	C9–O2	1.201(2)
C2–C4	1.528(3)	C9–N1	1.392(2)
C3–C4	1.518(3)	C9–C10	1.532(2)
C4–S1	1.846(2)	C10–C11	1.527(3)
C5–N1	1.504(2)	C11–C12	1.517(3)
C5–C6	1.517(2)	C12–C13A	1.514(3)
C5–C10	1.567(3)	N1–S1	1.6879(16)
C6–C7	1.524(3)	O1–S1	1.4828(13)
C7–C8	1.515(3)	C13A–Cl2A	1.850(8)
C8–Cl1	1.804(2)		
C3–C4–C1	113.15(19)	N1–C9–C10	92.22(14)
C3–C4–C2	110.76(18)	C11–C10–C9	114.78(15)
C1–C4–C2	111.23(17)	C11–C10–C5	117.59(16)
C3–C4–S1	110.81(13)	C9–C10–C5	86.63(13)
C1–C4–S1	107.19(14)	C12–C11–C10	112.46(16)
C2–C4–S1	103.18(14)	C13A–C12–C11	113.83(17)
N1–C5–C6	114.48(15)	C9–N1–C5	94.38(14)
N1–C5–C10	86.74(13)	C9–N1–S1	127.88(13)
C6–C5–C10	118.06(15)	C5–N1–S1	136.52(13)
C5–C6–C7	112.88(15)	O1–S1–N1	108.66(8)
C8–C7–C6	114.87(16)	O1–S1–C4	105.82(9)
C7–C8–Cl1	111.07(14)	N1–S1–C4	100.65(9)
O2–C9–N1	131.58(18)	C12–C13A–Cl2A	110.8(2)
O2–C9–C10	136.11(18)		

Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	43(1)	34(1)	18(1)	3(1)	1(1)	2(1)
C2	34(1)	35(1)	33(1)	−12(1)	8(1)	9(1)
C3	29(1)	21(1)	26(1)	−2(1)	3(1)	−3(1)
C4	26(1)	21(1)	18(1)	−1(1)	5(1)	4(1)
C5	12(1)	18(1)	20(1)	−1(1)	5(1)	0(1)
C6	16(1)	23(1)	18(1)	4(1)	3(1)	0(1)
C7	23(1)	25(1)	23(1)	4(1)	9(1)	2(1)
C8	18(1)	27(1)	34(1)	10(1)	6(1)	1(1)
C9	16(1)	17(1)	14(1)	−1(1)	0(1)	−1(1)
C10	16(1)	18(1)	20(1)	−1(1)	5(1)	−1(1)
C11	18(1)	21(1)	23(1)	4(1)	6(1)	3(1)
C12	19(1)	23(1)	29(1)	3(1)	8(1)	4(1)
N1	15(1)	15(1)	23(1)	1(1)	8(1)	−1(1)
O1	21(1)	24(1)	16(1)	3(1)	2(1)	1(1)
O2	22(1)	19(1)	26(1)	2(1)	5(1)	−4(1)
S1	15(1)	17(1)	17(1)	0(1)	4(1)	1(1)
Cl1	30(1)	23(1)	57(1)	6(1)	12(1)	−3(1)
C13A	18(1)	36(1)	40(1)	5(1)	7(1)	7(1)
Cl2A	26(1)	107(3)	48(1)	−41(1)	−4(1)	−2(1)
C13B	18(1)	36(1)	40(1)	5(1)	7(1)	7(1)
Cl2B	26(1)	107(3)	48(1)	−41(1)	−4(1)	−2(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	5046	2296	4910	48	1
H1B	6151	3730	5425	48	1
H1C	4438	3626	5720	48	1
H2A	7851	664	7403	50	1
H2B	8167	1847	6359	50	1
H2C	7117	323	6001	50	1
H3A	4514	158	6562	38	1
H3B	3808	1630	7164	38	1
H3C	5152	604	7962	38	1
H5	2826	3890	7636	20	1
H6A	4290	4414	10152	23	1
H6B	4005	2701	9566	23	1
H7A	2111	3445	10765	28	1
H7B	1541	4807	9801	28	1
H8A	696	2910	8272	32	1
H8B	–162	2691	9413	32	1
H10	3366	6824	8916	21	1
H11A	2338	8014	6941	25	1
H11B	2168	6303	6338	25	1
H12A	335	5640	7585	28	1
H12B	482	7371	8147	28	1
H13A	–530	8379	6138	37	0.79(3)
H13B	–1751	7334	6692	37	0.79(3)
H13C	–616	8437	6253	37	0.21(3)
H13D	–1763	7176	6664	37	0.21(3)



Thermal ellipsoids drawn at the 35% probability level, selected hydrogens and disorder omitted for clarity.

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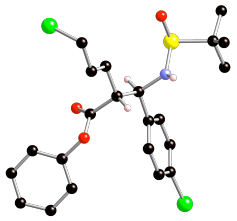
Table 1. Crystal data and structure refinement details for **compound 3.63**



Identification code	**2011SOT0108** (ACC/5942/32B5)
Empirical formula	$C_{22}H_{27}Cl_2NO_3S$
Formula weight	456.41
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	a = 5.80130(10) Å α = 94.3940(10)°
	b = 8.8609(2) Å β = 102.4860(10)°
	c = 11.3222(3) Å γ = 100.7770(10)°
Volume	554.05(2) Å^3
Z	1
Density (calculated)	1.368 Mg / m^3
Absorption coefficient	0.411 mm^{-1}
F(000)	240
Crystal	Rod; Colourless
Crystal size	0.21 × 0.06 × 0.04 mm^3
θ range for data collection	3.17 – 27.48°
Index ranges	$-7 \le h \le 7$, $-11 \le k \le 11$, $-14 \le l \le 14$
Reflections collected	11054
Independent reflections	4884 [R_{int} = 0.0342]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9838 and 0.9187
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4884 / 3 / 269
Goodness-of-fit on F^2	1.056
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0328, *wR2* = 0.0699
R indices (all data)	*R1* = 0.0343, *wR2* = 0.0715
Absolute structure parameter	0.09(4)
Largest diff. peak and hole	0.251 and –0.240 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except that of the NH which was freely refined.
Chirality: C8 = R, C12 = R

Table 2. Atomic coordinates [× 10⁴], equivalent isotropic displacement parameters [Å² × 10³] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Cl1	8053(1)	−1145(1)	12007(1)	33(1)	1
Cl2	−1725(1)	8424(1)	8518(1)	21(1)	1
S1	3910(1)	1604(1)	7041(1)	17(1)	1
O1	2810(3)	3372(2)	12134(1)	17(1)	1
O2	6130(3)	4272(2)	11448(2)	24(1)	1
O3	4777(3)	135(2)	7221(2)	29(1)	1
N1	2150(3)	1915(2)	7960(2)	17(1)	1
C1	5614(4)	4747(3)	13993(2)	19(1)	1
C2	6051(4)	5853(3)	15005(2)	22(1)	1
C3	4367(4)	6742(3)	15128(2)	24(1)	1
C4	2238(4)	6534(3)	14234(2)	22(1)	1
C5	1764(4)	5427(3)	13231(2)	19(1)	1
C6	3469(4)	4552(2)	13135(2)	16(1)	1
C7	4235(4)	3387(2)	11327(2)	16(1)	1
C8	3097(4)	2166(2)	10233(2)	16(1)	1
C9	4461(4)	828(2)	10316(2)	18(1)	1
C10	3786(4)	−203(3)	11260(2)	22(1)	1
C11	4877(4)	−1632(3)	11337(2)	23(1)	1
C12	3193(4)	2986(2)	9085(2)	15(1)	1
C13	1985(4)	4381(2)	9023(2)	16(1)	1
C14	205(4)	4576(2)	9636(2)	16(1)	1
C15	−895(4)	5849(2)	9509(2)	18(1)	1
C16	−229(4)	6899(2)	8738(2)	16(1)	1
C17	1568(4)	6751(3)	8130(2)	19(1)	1
C18	2655(4)	5484(3)	8276(2)	18(1)	1
C19	1616(4)	1190(2)	5582(2)	15(1)	1
C20	−343(4)	−214(3)	5600(2)	21(1)	1
C21	3060(4)	874(3)	4639(2)	20(1)	1
C22	586(4)	2639(3)	5369(2)	21(1)	1

Table 3. Bond lengths [Å] and angles [°].

Cl1–C11	1.790(2)	C7–C8	1.521(3)
Cl2–C16	1.743(2)	C8–C9	1.542(3)
S1–O3	1.4933(17)	C8–C12	1.544(3)
S1–N1	1.6499(18)	C9–C10	1.526(3)
S1–C19	1.846(2)	C10–C11	1.518(3)
O1–C7	1.358(3)	C12–C13	1.529(3)
O1–C6	1.416(2)	C13–C14	1.392(3)
O2–C7	1.199(3)	C13–C18	1.396(3)
N1–C12	1.468(3)	C14–C15	1.398(3)
C1–C6	1.377(3)	C15–C16	1.384(3)
C1–C2	1.395(3)	C16–C17	1.388(3)
C2–C3	1.387(3)	C17–C18	1.390(3)
C3–C4	1.389(3)	C19–C20	1.524(3)
C4–C5	1.386(3)	C19–C22	1.529(3)
C5–C6	1.383(3)	C19–C21	1.532(3)
O3–S1–N1	111.51(10)	C10–C11–Cl1	111.69(16)
O3–S1–C19	105.53(10)	N1–C12–C13	108.99(17)
N1–S1–C19	98.75(9)	N1–C12–C8	111.93(16)
C7–O1–C6	118.67(16)	C13–C12–C8	114.05(17)
C12–N1–S1	118.65(15)	C14–C13–C18	118.61(19)
C6–C1–C2	118.4(2)	C14–C13–C12	123.53(19)
C3–C2–C1	120.5(2)	C18–C13–C12	117.82(19)
C2–C3–C4	119.7(2)	C13–C14–C15	120.89(19)
C5–C4–C3	120.5(2)	C16–C15–C14	118.92(19)
C6–C5–C4	118.5(2)	C15–C16–C17	121.6(2)
C1–C6–C5	122.4(2)	C15–C16–Cl2	118.68(16)
C1–C6–O1	121.68(19)	C17–C16–Cl2	119.75(17)
C5–C6–O1	115.81(19)	C16–C17–C18	118.6(2)
O2–C7–O1	124.3(2)	C17–C18–C13	121.4(2)
O2–C7–C8	124.2(2)	C20–C19–C22	111.95(18)
O1–C7–C8	111.47(17)	C20–C19–C21	111.54(18)
C7–C8–C9	109.39(17)	C22–C19–C21	110.75(18)
C7–C8–C12	106.80(17)	C20–C19–S1	110.62(14)
C9–C8–C12	113.15(17)	C22–C19–S1	108.00(14)
C10–C9–C8	111.18(17)	C21–C19–S1	103.61(14)
C11–C10–C9	115.22(18)		

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	23(1)	43(1)	32(1)	7(1)	0(1)	10(1)
Cl2	20(1)	18(1)	28(1)	8(1)	7(1)	8(1)
S1	17(1)	21(1)	13(1)	2(1)	4(1)	8(1)
O1	18(1)	18(1)	16(1)	−1(1)	6(1)	1(1)
O2	18(1)	32(1)	19(1)	−2(1)	6(1)	−4(1)
O3	41(1)	36(1)	20(1)	5(1)	7(1)	28(1)
N1	17(1)	18(1)	15(1)	−1(1)	6(1)	1(1)
C1	19(1)	19(1)	19(1)	3(1)	6(1)	4(1)
C2	20(1)	25(1)	17(1)	1(1)	0(1)	0(1)
C3	30(1)	18(1)	20(1)	−5(1)	9(1)	−2(1)
C4	25(1)	18(1)	26(1)	1(1)	11(1)	5(1)
C5	20(1)	21(1)	18(1)	4(1)	6(1)	4(1)
C6	20(1)	13(1)	14(1)	1(1)	6(1)	1(1)
C7	18(1)	16(1)	13(1)	3(1)	3(1)	6(1)
C8	19(1)	16(1)	13(1)	−1(1)	5(1)	4(1)
C9	20(1)	19(1)	17(1)	4(1)	7(1)	8(1)
C10	22(1)	23(1)	27(1)	10(1)	11(1)	9(1)
C11	22(1)	20(1)	28(1)	8(1)	4(1)	5(1)
C12	14(1)	14(1)	15(1)	0(1)	3(1)	3(1)
C13	18(1)	14(1)	15(1)	0(1)	2(1)	3(1)
C14	17(1)	15(1)	17(1)	5(1)	6(1)	2(1)
C15	15(1)	20(1)	19(1)	3(1)	5(1)	5(1)
C16	14(1)	13(1)	22(1)	2(1)	1(1)	4(1)
C17	21(1)	19(1)	17(1)	5(1)	4(1)	3(1)
C18	18(1)	21(1)	17(1)	1(1)	6(1)	3(1)
C19	17(1)	16(1)	13(1)	1(1)	3(1)	4(1)
C20	22(1)	20(1)	18(1)	−1(1)	5(1)	0(1)
C21	25(1)	21(1)	15(1)	1(1)	8(1)	3(1)
C22	25(1)	21(1)	20(1)	6(1)	4(1)	8(1)

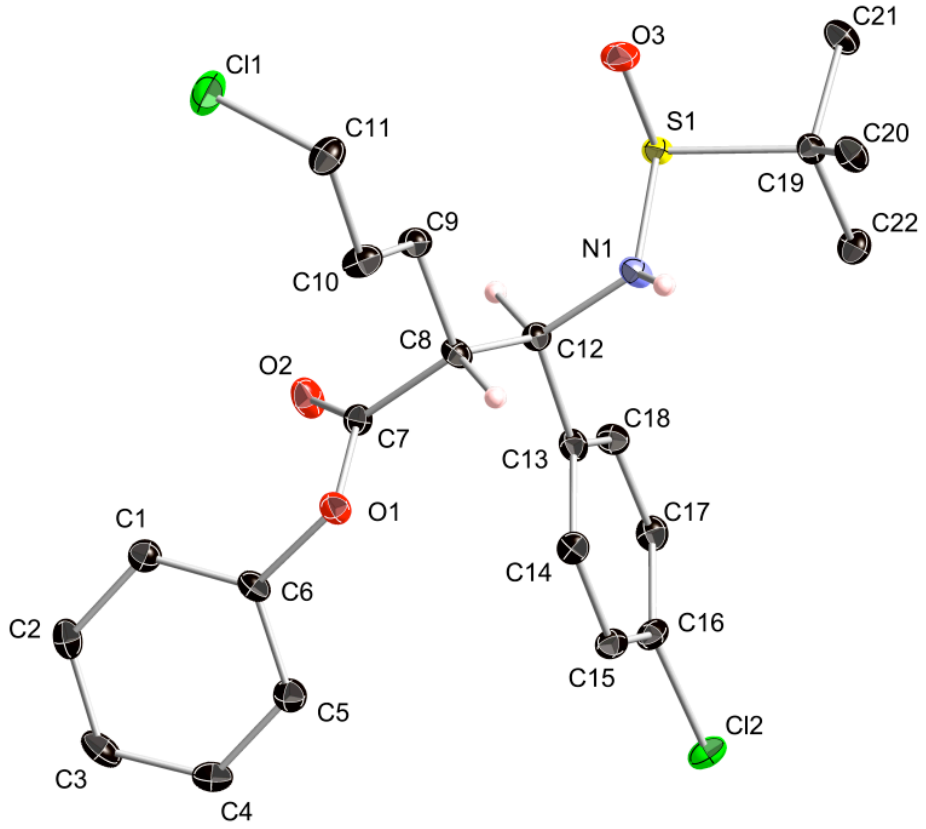
Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H901	940(50)	1280(30)	7930(30)	30(8)	1
H1	6769	4144	13899	22	1
H2	7511	5998	15613	26	1
H3	4670	7491	15820	28	1
H4	1097	7156	14311	27	1
H5	300	5273	12624	23	1
H8	1372	1756	10239	19	1
H9A	4067	200	9509	21	1
H9B	6221	1257	10540	21	1
H10A	4296	422	12071	27	1
H10B	2006	−538	11071	27	1
H11A	4592	−2184	10508	28	1
H11B	4068	−2337	11830	28	1
H12	4935	3377	9104	18	1
H14	−269	3835	10148	19	1
H15	−2081	5990	9945	21	1
H17	2044	7499	7623	23	1
H18	3879	5367	7859	22	1
H20A	−1335	59	6149	31	1
H20B	408	−1063	5886	31	1
H20C	−1363	−540	4775	31	1
H21A	3706	−57	4792	30	1
H21B	4395	1759	4704	30	1
H21C	2001	718	3819	30	1
H22A	−490	2492	4555	32	1
H22B	1911	3532	5435	32	1
H22C	−322	2824	5983	32	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H901···Cl2^{i}	0.80(3)	2.92(3)	3.652(2)	153(3)

Symmetry transformations used to generate equivalent atoms:
(i) x,y−1,z



Thermal ellipsoids drawn at the 35% probability level, selected hydrogens omitted for clarity.

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Table 1. Crystal data and structure refinement details for **compound 3.65**

Identification code	**2011sot0107** (ACC/5942/30B3)
Empirical formula	$C_{20}H_{28}ClNO_5S$
	$C_{20}H_{26}ClNO_4S, H_2O$
Formula weight	429.94
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 12.7350(7) Å
	b = 5.6064(4) Å β = 106.106(4)°
	c = 15.9372(10) Å
Volume	1093.21(12) Å^3
Z	2
Density (calculated)	1.306 Mg / m^3
Absorption coefficient	0.300 mm^{-1}
$F(000)$	456
Crystal	Rod; Colourless
Crystal size	0.22 × 0.04 × 0.02 mm^3
θ range for data collection	3.23 – 25.03°
Index ranges	$-15 \le h \le 15$, $-6 \le k \le 6$, $-18 \le l \le 18$
Reflections collected	12339
Independent reflections	3681 [R_{int} = 0.0793]
Completeness to θ = 25.03°	99.3 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9940 and 0.9369
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3681 / 3 / 265
Goodness-of-fit on F^2	1.220
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0603, $wR2$ = 0.1065
R indices (all data)	$R1$ = 0.0793, $wR2$ = 0.1156
Absolute structure parameter	0.06(11)
Largest diff. peak and hole	0.310 and –0.295 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, those of the NH and water were refined using distance restraints and thermal parameter constraints.
Chirality: C8 = R, C12 = R

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
N1	9307(3)	6603(7)	6771(2)	22(1)	1
O1	12657(2)	5362(6)	8930(2)	24(1)	1
O2	11782(2)	8756(7)	9090(2)	28(1)	1
O3	8760(2)	9779(6)	5561(2)	26(1)	1
O4	8696(2)	5550(7)	8445(2)	28(1)	1
S1	8434(1)	8668(2)	6318(1)	22(1)	1
Cl2	14421(1)	5728(3)	6804(1)	41(1)	1
C1	14035(4)	7296(10)	10101(3)	27(1)	1
C2	14616(4)	7357(10)	10978(3)	33(1)	1
C3	14447(4)	5650(11)	11546(3)	33(1)	1
C4	13700(4)	3827(12)	11245(3)	38(1)	1
C5	13097(4)	3767(12)	10369(3)	33(1)	1
C6	13276(3)	5503(10)	9824(3)	23(1)	1
C7	11882(3)	7082(9)	8653(3)	21(1)	1
C8	11206(3)	6663(9)	7721(3)	19(1)	1
C9	11562(3)	8468(10)	7132(3)	24(1)	1
C10	12770(3)	8294(9)	7159(3)	25(1)	1
C11	13008(3)	5969(11)	6781(3)	33(1)	1
C12	9985(3)	6911(9)	7683(3)	21(1)	1
C13	9674(3)	5137(9)	8270(3)	23(1)	1
C14	10127(4)	3134(9)	8669(3)	28(1)	1
C15	9402(4)	2187(10)	9121(3)	31(1)	1
C16	8544(4)	3704(11)	8958(3)	31(1)	1
C17	7215(3)	6878(9)	5785(3)	23(1)	1
C18	7394(4)	5517(11)	5015(3)	31(1)	1
C19	6291(3)	8692(11)	5496(3)	31(1)	1
C20	6992(4)	5194(10)	6466(3)	30(1)	1
O1W	10354(3)	3392(7)	5834(2)	31(1)	1

Table 3. Bond lengths [Å] and angles [°].

N1–C12	1.480(5)	C4–C5	1.395(6)
N1–S1	1.629(4)	C5–C6	1.364(7)
O1–C7	1.362(5)	C7–C8	1.514(6)
O1–C6	1.426(5)	C8–C9	1.533(7)
O2–C7	1.197(6)	C8–C12	1.545(6)
O3–S1	1.515(3)	C9–C10	1.530(6)
O4–C16	1.365(6)	C10–C11	1.502(7)
O4–C13	1.369(5)	C12–C13	1.492(6)
S1–C17	1.846(5)	C13–C14	1.340(7)
Cl2–C11	1.795(4)	C14–C15	1.422(7)
C1–C6	1.380(7)	C15–C16	1.352(7)
C1–C2	1.388(6)	C17–C18	1.515(6)
C2–C3	1.374(8)	C17–C20	1.523(7)
C3–C4	1.389(8)	C17–C19	1.527(7)

C12–N1–S1	119.5(3)	C9–C8–C12	112.5(3)
C7–O1–C6	115.8(4)	C10–C9–C8	114.0(4)
C16–O4–C13	106.4(4)	C11–C10–C9	110.9(4)
O3–S1–N1	109.97(19)	C10–C11–Cl2	111.7(3)
O3–S1–C17	103.80(19)	N1–C12–C13	110.7(4)
N1–S1–C17	101.6(2)	N1–C12–C8	109.6(4)
C6–C1–C2	118.1(5)	C13–C12–C8	110.8(4)
C3–C2–C1	120.6(5)	C14–C13–O4	109.9(4)
C2–C3–C4	120.2(4)	C14–C13–C12	134.6(4)
C3–C4–C5	119.8(5)	O4–C13–C12	115.4(4)
C6–C5–C4	118.5(5)	C13–C14–C15	107.4(4)
C5–C6–C1	122.8(4)	C16–C15–C14	105.7(5)
C5–C6–O1	116.9(4)	C15–C16–O4	110.5(4)
C1–C6–O1	120.3(4)	C18–C17–C20	111.4(4)
O2–C7–O1	123.4(4)	C18–C17–C19	111.5(4)
O2–C7–C8	124.7(4)	C20–C17–C19	110.4(4)
O1–C7–C8	111.8(4)	C18–C17–S1	110.5(3)
C7–C8–C9	108.3(4)	C20–C17–S1	108.0(3)
C7–C8–C12	108.5(3)	C19–C17–S1	104.9(4)

Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	21(2)	25(3)	17(2)	−2(2)	1(2)	4(2)
O1	21(2)	28(2)	18(2)	1(2)	−1(1)	4(2)
O2	25(2)	29(2)	25(2)	−6(2)	−1(1)	5(2)
O3	28(2)	29(2)	21(2)	5(1)	6(1)	−3(1)
O4	28(2)	34(2)	24(2)	6(2)	12(1)	6(2)
S1	18(1)	24(1)	21(1)	−1(1)	1(1)	1(1)
Cl2	21(1)	69(1)	32(1)	−6(1)	6(1)	4(1)
C1	20(2)	29(3)	32(3)	4(2)	7(2)	1(2)
C2	22(2)	40(3)	30(3)	−3(3)	−2(2)	0(2)
C3	31(3)	42(3)	20(2)	−1(3)	−4(2)	9(3)
C4	47(3)	36(3)	25(2)	12(3)	1(2)	1(3)
C5	32(3)	34(3)	28(2)	3(3)	−1(2)	−3(3)
C6	16(2)	31(3)	18(2)	0(2)	−1(2)	3(2)
C7	19(2)	21(3)	21(2)	2(2)	4(2)	0(2)
C8	19(2)	22(3)	14(2)	−2(2)	0(2)	3(2)
C9	22(2)	25(3)	21(2)	1(2)	1(2)	3(2)
C10	24(2)	32(3)	18(2)	1(2)	2(2)	−3(2)
C11	15(2)	49(4)	35(3)	−6(3)	9(2)	0(2)
C12	19(2)	25(3)	17(2)	0(2)	1(2)	4(2)
C13	21(2)	30(3)	18(2)	−4(2)	4(2)	−1(2)
C14	27(3)	31(4)	24(3)	−1(2)	4(2)	−4(2)
C15	40(3)	26(3)	25(3)	6(2)	9(2)	−2(3)
C16	33(3)	42(3)	23(2)	5(3)	14(2)	−7(3)
C17	18(2)	31(3)	18(2)	−7(2)	4(2)	0(2)
C18	26(2)	34(3)	32(3)	−4(3)	6(2)	−6(3)
C19	20(2)	37(3)	34(3)	4(3)	2(2)	4(3)
C20	22(2)	33(3)	31(3)	2(2)	4(2)	−8(2)
O1W	34(2)	30(2)	30(2)	−5(2)	11(2)	−7(2)

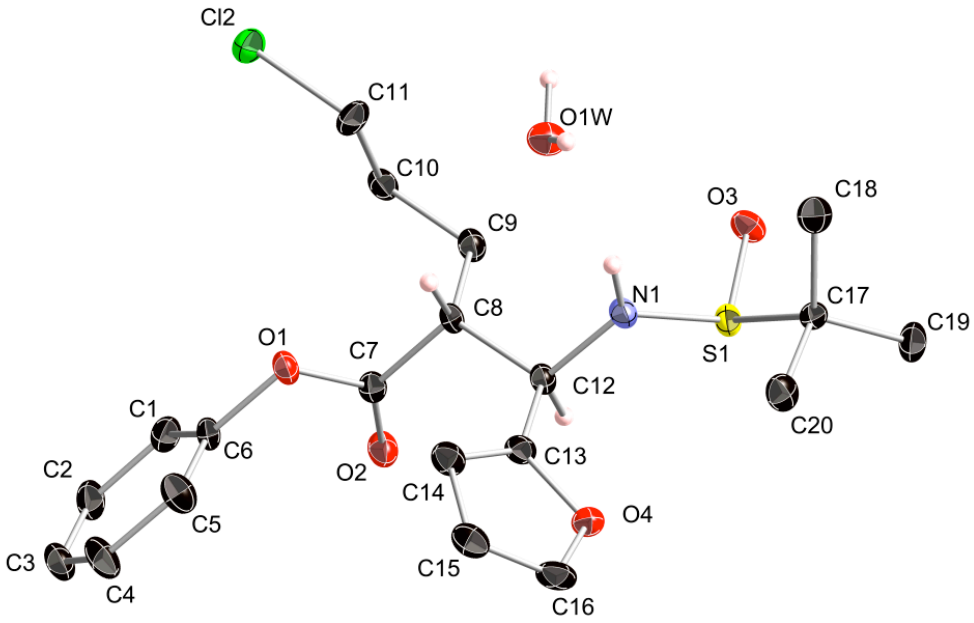
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H901	9450(40)	5540(100)	6450(30)	26	1
H1	14157	8455	9704	32	1
H2	15134	8590	11187	39	1
H3	14843	5718	12146	40	1
H4	13599	2623	11635	46	1
H5	12574	2546	10156	40	1
H8	11345	5012	7540	23	1
H9A	11113	8225	6522	28	1
H9B	11413	10098	7309	28	1
H10A	12962	9631	6824	30	1
H10B	13226	8427	7771	30	1
H11A	12548	5837	6170	39	1
H11B	12814	4635	7117	39	1
H12	9859	8550	7883	26	1
H14	10807	2468	8653	34	1
H15	9500	779	9466	37	1
H16	7922	3513	9170	37	1
H18A	6719	4687	4710	47	1
H18B	7981	4350	5224	47	1
H18C	7597	6634	4614	47	1
H19A	6183	9508	6009	47	1
H19B	5615	7868	5187	47	1
H19C	6480	9863	5105	47	1
H20A	7590	4037	6644	44	1
H20B	6303	4348	6216	44	1
H20C	6941	6113	6976	44	1
H1W	10580(40)	3480(110)	5390(20)	37	1
H2W	9940(40)	2200(60)	5720(30)	37	1

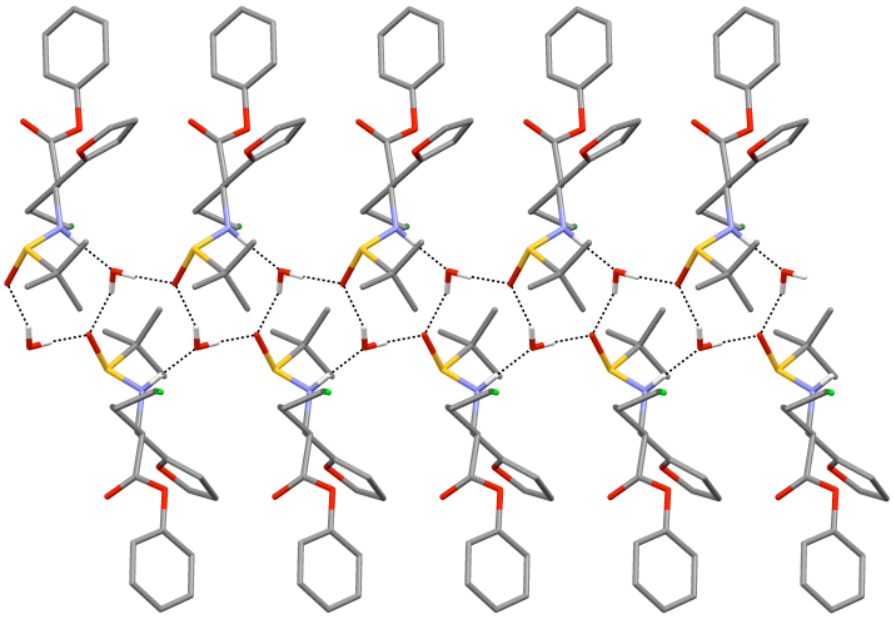
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H901···O1W	0.84(5)	2.08(5)	2.890(5)	160(4)
O1W–H1W···O3^{i}	0.830(19)	2.07(3)	2.866(5)	162(6)
O1W–H2W···O3^{ii}	0.84(2)	1.99(2)	2.814(5)	168(5)

Symmetry transformations used to generate equivalent atoms:
(i) –x+2,y–1/2,–z+1 (ii) x,y–1,z



Thermal ellipsoids drawn at the 35% probability level, selected hydrogens omitted for clarity.



Hydrogen bonded chains extend along the *b* axis.

6.2. Appendix B: Publication

Total Syntheses of (–) Epilupinine and (–)-Tashiromine Using Imino-Aldol Reactions

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