UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

CHEMISTRY

Towards the total synthesis of (−)-sparteine and other lupin alkaloids
&
New chiral catalysts for asymmetric epoxidations

by

Ionut-Alexandru Pop

Thesis for the degree of Doctor of Philosophy

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Abstract

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TOWARDS THE TOTAL SYNTHESIS OF (−)-SPARTEINE AND OTHER LUPIN ALKALOIDS

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NEW CHIRAL CATALYSTS FOR ASYMMETRIC EPOXIDATIONS

Ionut-Alexandru Pop

Two synthetic routes towards the total synthesis of (−)-sparteine (**1.1**) have been investigated. An imino-aldol reaction between different ester enolates and chiral sulfinimines was explored to install two of the stereogenic centres. An *N*-acylimnium precursor was introduced from a selective imide reduction with $LiEt_3BH$ and several cyclisation strategies were investigated to install the two remaining stereocenters. Total synthesis of the bicyclic lupin alkaloid (−)-lamprolobine (**1.107**) has been completed in 21% yield over 12 steps as part of the synthetic studies towards **1.1**. The target molecule was assembled using a diastereoselective imino-aldol reaction and radical deoxygenation as key transformations in the synthesis. The stereochemistry of the major *syn* product of the imino-aldol reaction was confirmed by single crystal X-ray crystallography.

In addition to this, several chiral acyclic α-ketoamides and cyclic α-ketoamides have been synthesised and evaluated in ketone mediated epoxidation of olefins. Despite the modest enantiomeric excesses (ee < 10%) achieved, it was shown that these *α*-ketocarboxylic acid derivatives are capable of efficient epoxidation at low catalyst loadings.

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Declaration of authorship

I, Ionut-Alexandru Pop

declare that the thesis entitled

Towards the total synthesis of (−)-sparteine and other lupin alkaloids & New chiral catalysts for asymmetric epoxidations.

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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Abbreviations

Ac	Acetyl
AIBN	2,2′-Azobis(2-methylpropionitrile)
aq.	Aqueous
ATMS	Allyltrimethylsilane
Boc_2O	Di-*tert*-butyl dicarbonate
Bu	Butyl
BtH	1*H*-Benzotriazole
Cbz	Benzyloxycarbonyl
CM	Cross-metathesis
ca.	Circa
conc.	Concentrated
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DIAD	Di-*iso*-propyl azodicarboxylate
DIBAL-H	Di-*iso*-butyl aluminium hydride
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMM	Dimethoxymethane
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
dr	Diastereomeric ratio
DTR	Dynamic thermodynamic resolution
EDAC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
equiv.	Equivalents
Et	Ethyl
EX	Electrophile
ES^+	Electrospray ionisation (positive ion)
ES^-	Electrospray ionisation (negative ion)
FT	Fourier transform
g	Gram(s)
h	Hour(s)
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
i	*Iso*
IPA	*Iso*-propylalcohol
IR	Infra-red
K	Kelvin
L	Ligand
LC-MS	Liquid chromatography mass spectroscopy
LDA	Lithium di-*iso*-propylamide
LiHMDS	Lithium hexamethyldisilazide
LRMS	Low resolution mass spectroscopy
M	Molar
Me	Methyl
mg	Milligram(s)

MHz	Megahertz
min	Minute(s)
mL	Millilitre
mmol	Millimole
M.p.	Melting point
Ms	Methanesulfonyl
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
Oxone®	Potassium peroxymonosulfate
p	*para*
Ph	Phenyl
Pr	Propyl
psi	Pound-force per square inch
Py	Pyridine
RCM	Ring-closing metathesis
R_f	Retention factor
rt	Room temperature
sat.	Saturated
t(tert)	Tertiary
T	Temperature
T_3P	Propylphosphonic anhydride
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TBSA	*tert*-Butylsulfinamide
Tf	Trifluromethanesulfonyl
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin-layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPPP	Tetraphenylphosphonium monoperoxysulfate
TsOH	*para*-Toluenesulfonic acid
TTMSS	1,1,1,3,3,3-Hexamethyl-2-trimethylsilyl-trisilane
UV	Ultra-violet
Δ	Heating

Chapter 1: (−)-Sparteine and other lupin alkaloids

1.1 Introduction

1.1.1 Lupin alkaloids

The lupin alkaloids are a large family of structurally diverse natural products based on quinolizidine and indolizidine moieties (sparteine, leontidine).[1] The alkaloids are isolated by extraction from a plethora of *Lupinus* or *Sophora* genus of plants. Lupin beans are used as food in Latin America but are generally toxic and require a special leaching process prior to consumption. The lupin alkaloids can be divided into three main groups: bicycle alkaloids (epilupinine type), tricycle alkaloids (cytisine type) and the tetracyclic alkaloids (sparteine, matrine type) (**Figure 1.01**).

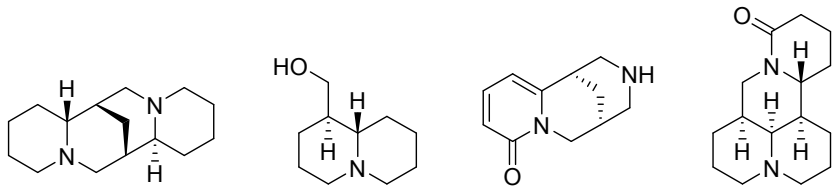


Figure 1.01 Representative examples of lupin alkaloids.

1.1.2 (−)-Sparteine

(−)-Sparteine is a naturally occurring lupin alkaloid, isolated by extraction from certain papilionaceous plants (e.g. *Cytius scoparisus*). The original isolation and determination of the molecular formula of sparteine was described by Stenhouse in 1851,[2] and the sparteine-type structure of the carbon skeleton was established by Clemo *et al*. in 1933.[3] The absolute stereochemistry of sparteine was clarified by Marion *et al*. in 1951[4] and *Okuda et al.* published an extensive work on the determination of the absolute configuration of the lupin alkaloids in 1965.[5]

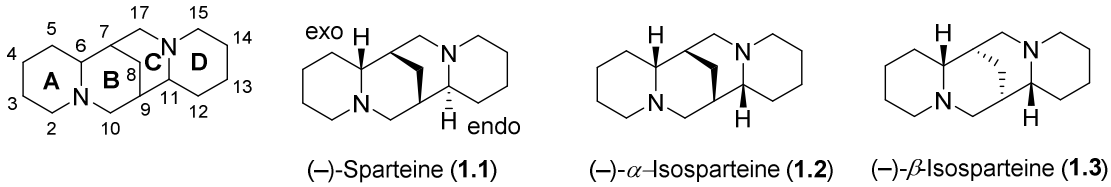


Figure 1.02 Lupin alkaloids of the sparteine subgroup: (−)-sparteine, (−)-α-isosparteine, (−)-β-isosparteine.

The remaining two levorotatory lupin alkaloids of the sparteine type, (−)-α-isosparteine (**1.2**) (−)-β-isosparteine (**1.3**) are C_2-symmetric and related to (−)-sparteine in reference to the relative stereochemistry across the C6-C7 and C9-C11 bonds.

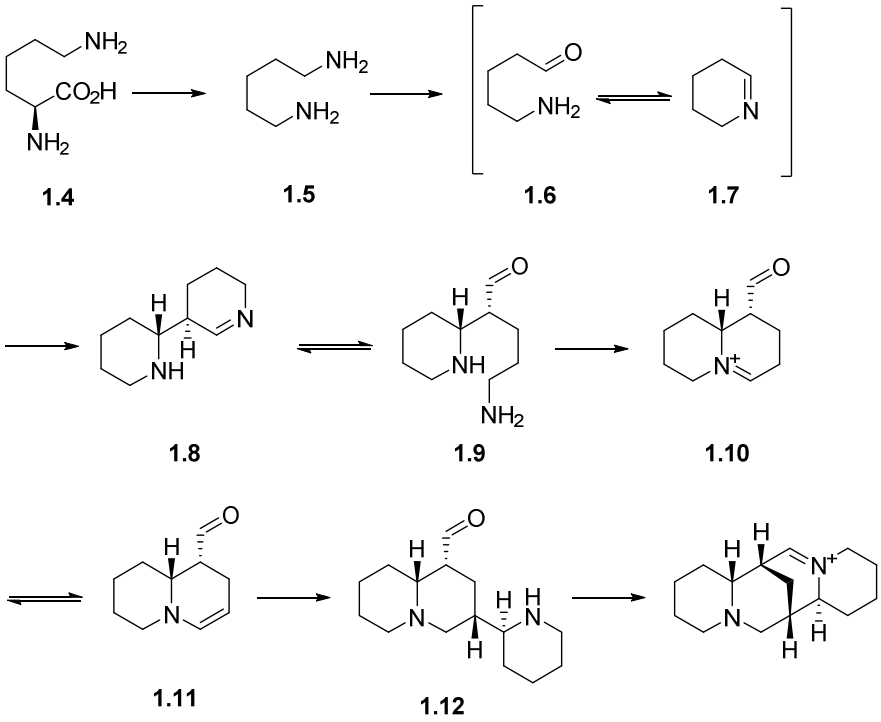
(−)-α-Isosparteine (**1.2**) was first isolated from *Lupinus caudatus* by Marion *et al*. in 1951,[6] but prior to its isolation, (−)-α-isosparteine was obtained *via* a semi-synthesis from (−)-sparteine in 1934.[7] (−)-β-Isosparteine (**1.3**) was isolated from *Lupinus sericeus* by Carmack *et al*. in 1955.[8] The dextrorotatory enantiomer of sparteine, (+)-sparteine is obtained by extraction from *Cytisus caucasicus*[9] or from the resolution of (±)-lupanine followed by reduction of (−)-lupanine.[10]

Sparteine have been demonstrated to display antiarrhythmic activity in guinea pigs through action on the membrane potential and contraction of the mammalian heart muscles.[11,12] Administration of the natural product results in a blockage of the Na^+ and K^+ channels which reduces the arrhythmias.[13]

1.1.3 The biosynthesis of sparteine type alkaloids

The biosynthesis of the sparteine-type alkaloids was first proposed by Ritchie *et al.* in 1950, but it was discredited few years later due to an abnormal conformation in one of the intermediates.[14-16] The exact mechanism of biosynthesis is still disputed but it is accepted that degradation of L-lysine (**1.4**) to cadaverine **1.5** is the source of carbon and nitrogen present in the lupin alkaloids.[17,18] Golebiewski *et al*. proposed a sequence for the biosynthesis of sparteine-type alkaloids where three molecules of L-lysine are necessary to build the backbone (**Scheme 1.01**).[19-21] The first step of the biosynthesis is the decarboxylation of L-lysine (**1.4**) to give cadaverine **1.5**. Oxidative deamination of

cadaverine gives dehydropiperidine **1.7** which readily dimerises to furnish tetrahydroanabasine (**1.8)**. Hydrolysis of the imine followed by oxidative deamination and intramolecular cyclisation secures iminium **1.10** and its tautomer enamine **1.11**. Quinolizidine derivative **1.11** then combines with another molecule of **1.7** to furnish the saturated tricycle **1.12** which undergoes intramolecular condensation to form the tetracyclic backbone of the sparteine-type alkaloids.



Scheme 1.01 Golebiewski biosynthesis of sparteine.[21]

1.1.4 Applications of sparteine as a chiral ligand in enantioselective reactions

Introduction of the concept “umpolung reactivity” by Seebach *et al.* encouraged scientists to search for new building blocks in synthetic chemistry.[22-24] A major focus was on reagents for carbanionic synthons which provided new reactivity and selectivity.[25-28] Organolithiums contain a lithium-carbanion pair, where the metal tends to exist in a tetrahedral coordination at higher aggregates; suitable solvents and ligands could generate chirality at the carbanionic centre. It was shown by theoretical calculations that (−)-sparteine could behave as a bidentate ligand in the *chair-chair*

conformation, with the metal ion encapsulated between the two nitrogens resulting in a dissymmetric coordination (**Figure 1.03**).[29] The major interest of sparteine in recent years has been in applications as a chiral ligand in organolithium chemistry for a wide range of highly enantioselective transformations.[30-33]

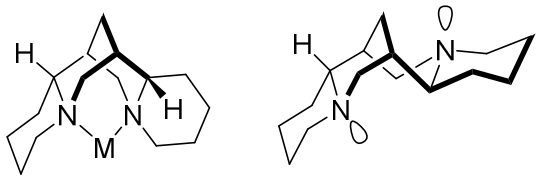
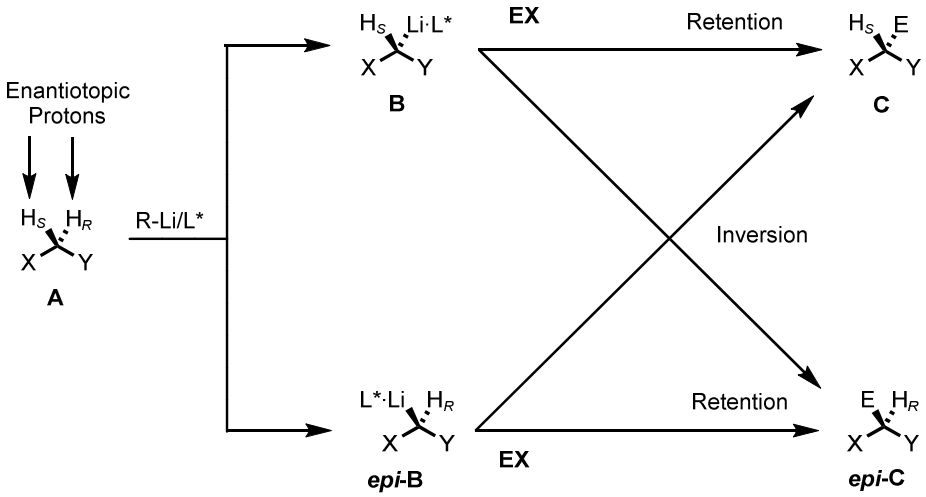


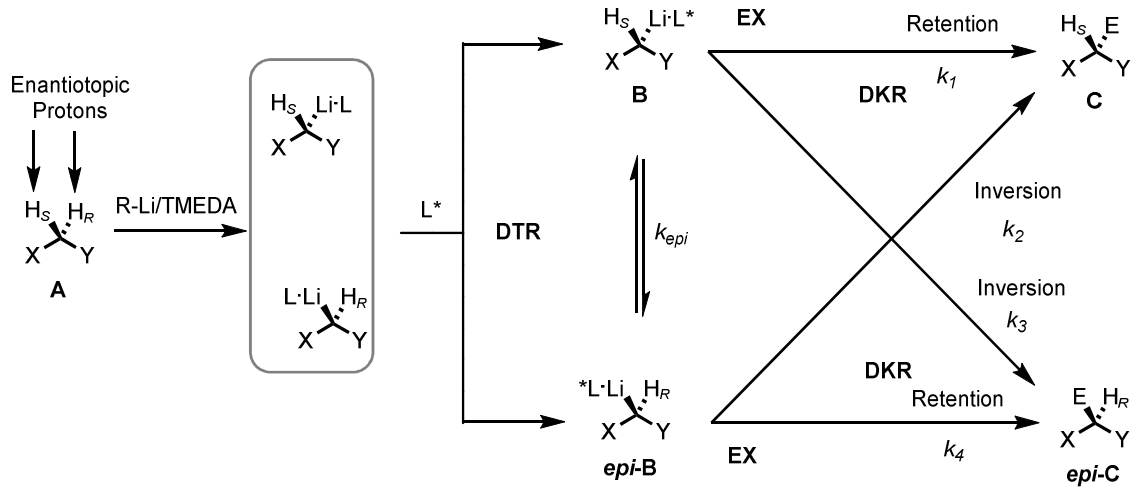
Figure 1.03 Conformations of sparteine.

The successful application of chiral non-racemic organolithium reagents in synthesis relies on two fundamental processes: asymmetric deprotonation and asymmetric substitution. The stereoselectivity of these transformations are dependent on the following factors: the selective conversion of a *pro*-chiral molecule **A** into two enantiomers **B** and ***epi*-B**, the rate of epimerisation between **B** and ***epi*-B** and the stereo-outcome of the electrophilic substitution (**Scheme 1.02, Scheme 1.03**).[33]



Scheme 1.02 Asymmetric deprotonation of *pro*-chiral molecules.

Asymmetric deprotonation and asymmetric substitution are distinct methods for asymmetric induction.[34] In asymmetric deprotonation, the chiral base extracts preferentially one enantiotopic and/or diastereotopic proton resulting in the formation of one epimer dominantly. The organolithium must be configurationally stable in order to avoid loss of the enantiopurity, and transformation is usually achieved at −78 °C. The quench with an electrophile occurs with retention or inversion of configuration in a stereospecific fashion. Asymmetric substitution can be achieved using resolution processes such as: dynamic thermodynamic resolution (DTR), dynamic kinetic resolution (DKR) and crystallisation induced dynamic control.[34] In a resolution the organolithium must be configurationally labile under the influence of ligand, resulting in different stability and reactivity of the organolithium chiral ligand complexes.

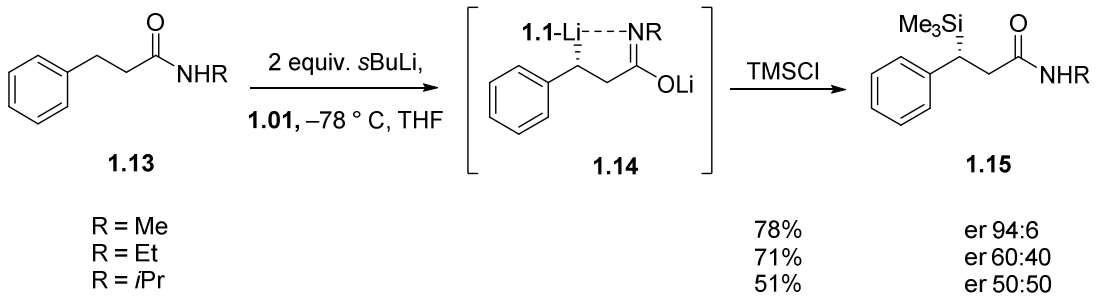


Scheme 1.03 Dynamic resolutions.

In the case of the dynamic thermodynamic resolution, the conversion between the epimers of chiral organolithium is relatively slow compared with the rate of substitution ($k_{1–4} > k_{epi}$) (**Scheme 1.03**). These transformations are dependent on the temperature and by cooling and warming the reaction prior to the electrophile quench an equilibration occurs between the stereoisomers such that the rate of interconversion is relatively slow. Dynamic kinetic resolution proceeds under thermodynamic control with equilibration of the epimers such that the process does not suffer from decay in the enantiomer ratio. The conversion between the epimers of chiral organolithium is fast compared with the

rate of substitution ($k_{epi} > k_{1-4}$). The crystallisation induced dynamic control relies on the crystallisation of organolithium complex in the presence of chiral ligand. To achieve an effective resolution studies regarding the concentration, solvent, temperature and chiral ligand need to be optimised. The first examples of highly selective asymmetric transformations were reported by Beak *et al.*[35-37]

Double deprotonation of **1.13** in presence of (−)-sparteine (**1.1**) afforded the chiral organolithium **1.14** which undergoes TMSCl trapping to give amide **1.15** with high selectivity (R = Me) (**Scheme 1.04**). For bulkier amides (R = Et, *i*Pr), poor or no selectivity was observed and this can be explained by the steric interactions of the substituents which prevented coordination of **1.1** with the organolithium. Mechanistic studies have shown that this reaction follows a dynamic thermodynamic resolution with the organolithium chiral complex thermodynamically stable at −105 °C.[36]



Scheme 1.04 Dynamic thermodynamic resolution of benzylic carbanions.

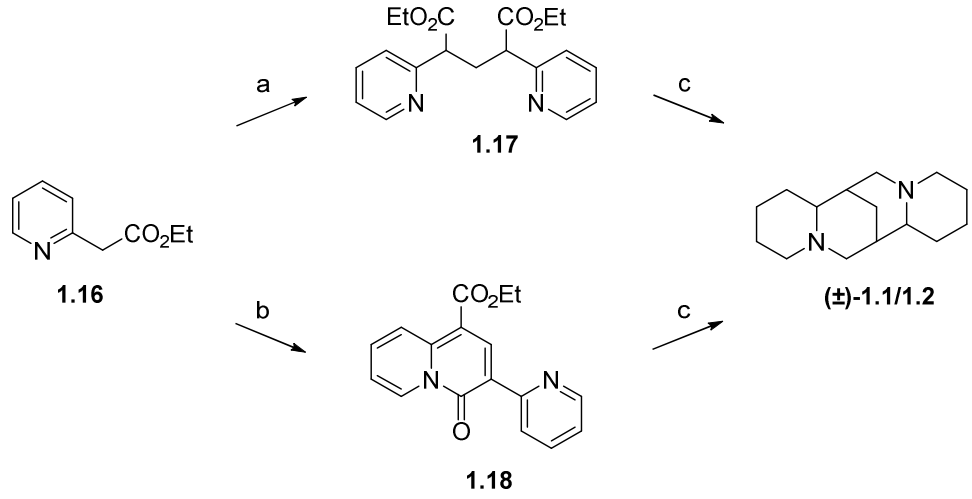
In recent years there has been a shortage of (−)-sparteine (**1.1**). O'Brien and co-workers synthesised a (+)-sparteine (**1.1**) surrogate which provided similar enantioselectivity to **1.1** in many reactions.[38] Due to the employment of sparteine in a plethora of enantioselective reactions, combined with our ongoing interest in the synthesis of lupin alkaloids, we consider this natural product to be an attractive target for total synthesis.

1.2 Previous syntheses of sparteine

Synthesis of sparteine has been attempted several times to determine the absolute and relative configuration of the natural products and for the preparation of enantiomerically pure material. There have been over ten total syntheses of sparteine-type alkaloids; an overview of the synthetic work is documented bellow in chronological order. The syntheses performed by Aube *et al*. and by O'Brien *et al*. represent the only two total syntheses of (+)/(−)-sparteine documented to date.

1.2.1 Leonard's synthesis of (±)-sparteine and (±)-*α*-isosparteine

The first total synthesis of (±)-sparteine was published in 1948 by Leonard *et al.*[39] Leonard and co-workers developed a methodology for the synthesis of (±)-sparteine (**1.1**), (±)-*α*-isosparteine (**1.2**) from ethyl 2-pyridyl-acetate (**1.16**).[40] (±)-Sparteine (**1.1**) and (±)-*α*-isosparteine (**1.2**) were synthesised as a racemic mixture in two linear steps (**Scheme 1.05**). The synthesis requires a one-step condensation and reductive cyclisation of either pyridyl intermediates **1.17** or **1.18** to furnish sparteine from two different precursors.



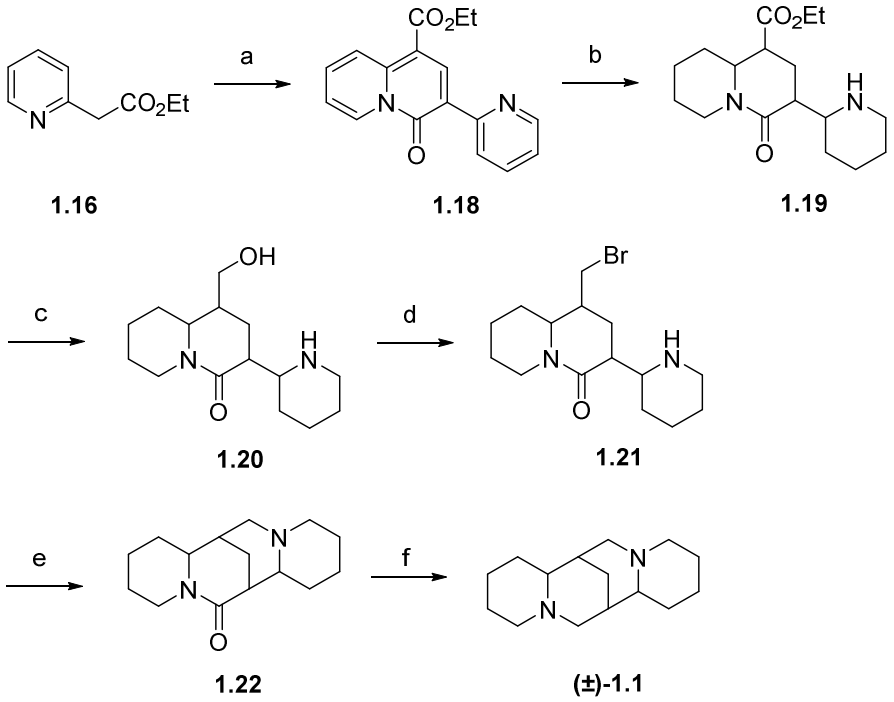
Scheme 1.05 *Reagents and conditions:* a) Paraformaldehyde, piperidine, Δ. b) ethyl orthoformate, Ac_2O, Δ. c) H_2, copper chromite, dioxane, 350 atm, Δ.

l-Carbethoxy-4-keto-3-(2'-pyridyl)-pyridocoline (**1.18**) was accessed using chemistry reported by Clemo *et al.* (**Scheme 1.05**).[41] Condensation of ethyl pyridyl-2-acetate (**1.16**) with ethyl orthoformate in refluxing Ac_2O and subsequent recrystallisation from petroleum ether gave pure pyridocoline **1.18**. Reductive cyclisation of **1.18** in dioxane at 250 °C and 250–350 atm over copper chromite catalyst led to the formation of two pure bases: (±)-sparteine (**1.1**) and (±)-*α*-isosparteine (**1.2**). The identity of the samples was confirmed by comparision of the monoperchlorate and dipicrate salt which had been previously reported.[42]

Using chemistry reported by Sorn *et al.*,[42] ethyl pyridyl-2-acetate (**1.16**) was condensed with paraformaldehyde to access glutarate **1.17** in 58% yield (**Scheme 1.05**). In the synthesis a by-product was isolated which corresponded to pyridocoline **1.18**. Reductive cyclisation of **1.17** in dioxane at 250 °C and 250–350 atm over copper chromite catalyst led to the formation of an equimolar mixture of isomers: (±)-sparteine (**1.1**) and (±)-*α*-isosparteine (**1.2**) which were separated chromatographically. Resolution of racemic sparteine using either enantiomer of *β*-camphorsulfonic acid in EtOH, followed by recrystallisation from acetone, led to the isolation of either (+)-sparteine or (−)-sparteine.[43]

1.2.2 Clemo's synthesis of (±)-sparteine

A total synthesis of (±)-sparteine was reported in 1949 by Clemo *et al.*[44] Initial efforts towards the synthesis of (±)-sparteine led to the formation of 17-oxosparteine (**1.22**) in 1936 which was later converted to (±)-sparteine, since at the time of the original work, no suitable reducing agents were available (**Scheme 1.06**).[41]

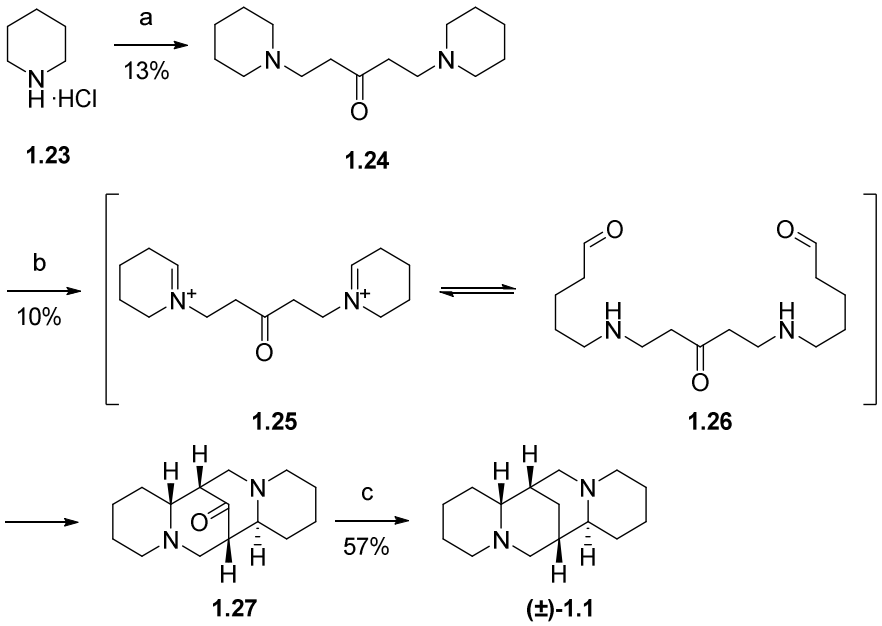


Scheme 1.06 *Reagents and conditions:* a) Ethyl orthoformate, Ac_2O, Δ. b) H_2, PtO_2, AcOH. c) Na, EtOH, Δ. d) PBr_5, C_6H_6, Δ. e) K_2CO_3, Δ. f) $LiAlH_4$, Et_2O, rt.

Condensation between ethyl pyridyl-2-acetate (**1.16**) and ethyl orthoformate in refluxing Ac_2O led to the formation of pyridocoline **1.18** which was subsequently converted into quinolizidine **1.19** *via* catalytic hydrogenation in AcOH over PtO_2. Bouveault reduction of ester **1.19** accessed alcohol **1.20** and the formation of bromide **1.21** was completed by heating with PBr_5 in refluxing benzene. Final cyclisation was achieved by heating the saturated tricycle **1.21** with K_2CO_3 in a sealed tube over a steam bath to furnish 17-oxosparteine (**1.22**). The synthesis of (±)-sparteine (**1.1**) was completed 13 years later in 1949 when **1.22** was reduced with $LiAlH_4$.[44]

1.2.3 Tamelen's synthesis of (±)-sparteine

A total synthesis of (±)-sparteine was performed by Tamelen *et al.* in 1960 using a biogenetic type synthesis (**Scheme 1.07**).[45] Tamelen and co-workers developed a methodology for the synthesis of (±)-epilupinine, (±)-lupinine and sparteine using a similar Mannich type cyclisation.[46]

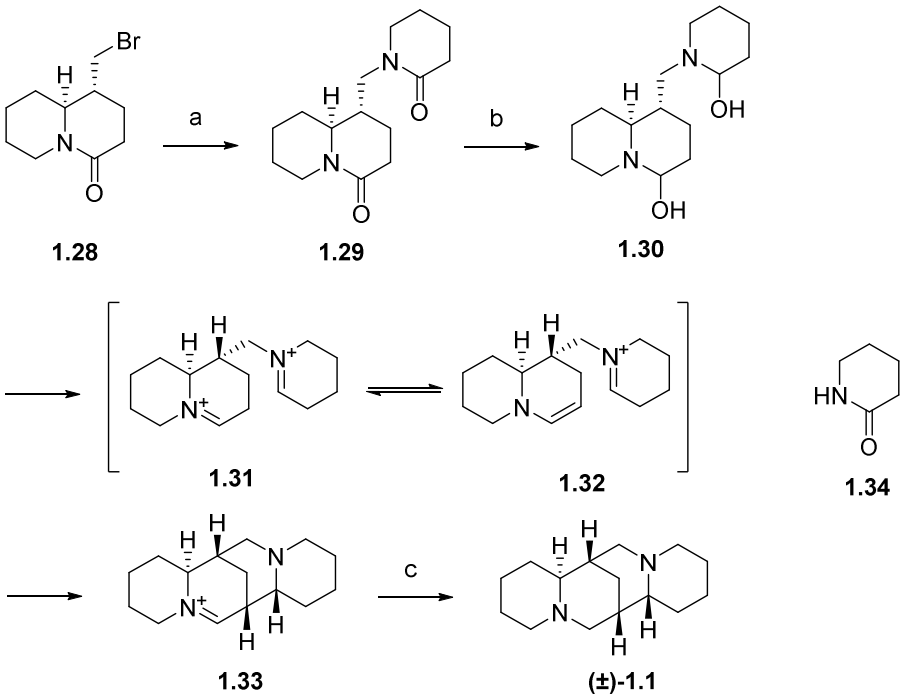


Scheme 1.07 *Reagents and conditions:* a) Paraformaldehyde, acetone, AcOH, Δ. b) i) $Hg(OAc)_2$, 5% AcOH, Δ. ii) H_2S, K_2CO_3. c) 85% NaOH, diethylene glycol, hydrazine, Δ.

The bispiperidine **1.24** was prepared by a symmetrical bis-Mannich condensation of piperidine hydrochloride (**1.23**), formaldehyde and acetone in AcOH in 13% yield. Treatment of the free base **1.24** with an excess $Hg(OAc)_2$ in 5% AcOH gave intermediate **1.26** *via* iminium hydrolysis of **1.25** which was subsequently converted into 8-oxosparteine (**1.27**). Reduction of the **1.27** was performed using the Huang-Minlon modification of the Wolf-Kishner reduction to furnish (±)-sparteine (**1.1**). The identity of the samples was confirmed by comparision of the monoperchlorate and dipicrate salt reported previously by Leonard.[40]

1.2.4 Bohlmann's synthesis of (±)-sparteine

The synthesis of (±)-sparteine was reported in 1973 by Bohlmann *et al.* using lactam reduction and cyclisation to tetracyclic adduct **1.33** as key steps in the synthesis (**Scheme 1.08**).[47]

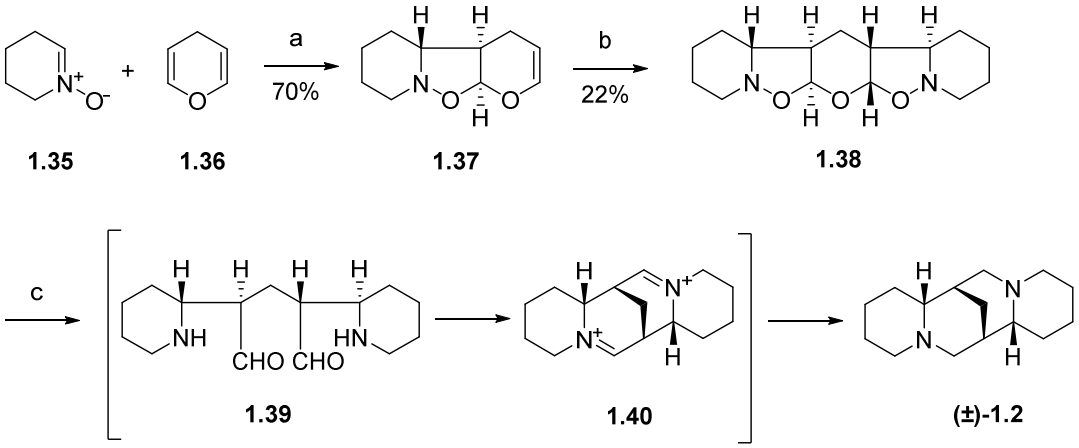


Scheme 1.08 *Reagents and conditions:* a) NaH, piperidinone **1.34**, C_6H_6/$PhCH_3$, rt. b) i) DIBAL-H, $PhCH_3$, –50 °C to −20 °C. ii) HCl, −20 °C to rt. c) $NaBH_4$, EtOH, rt.

Piperidinone **1.34** was deprotonated using NaH in benzene and alkylated with bromide derivative **1.28** to give bisamide **1.29**. Treatment of **1.29** with DIBAL-H at −78 °C led to the formation of amidal **1.30** upon treatment with aq. HCl. The amidal **1.30** was dehydrated in acidic conditions furnishing the iminium ion **1.31** and its tautomer enamine **1.32**, which subsequently underwent intramolecular cyclisation to tetracyclic adduct **1.33**. The final reduction was achieved using $NaBH_4$ in ethanol to furnish (±)-sparteine (**1.1**).

1.2.5 Kakisawa's total synthesis of (±)-*α*-isosparteine

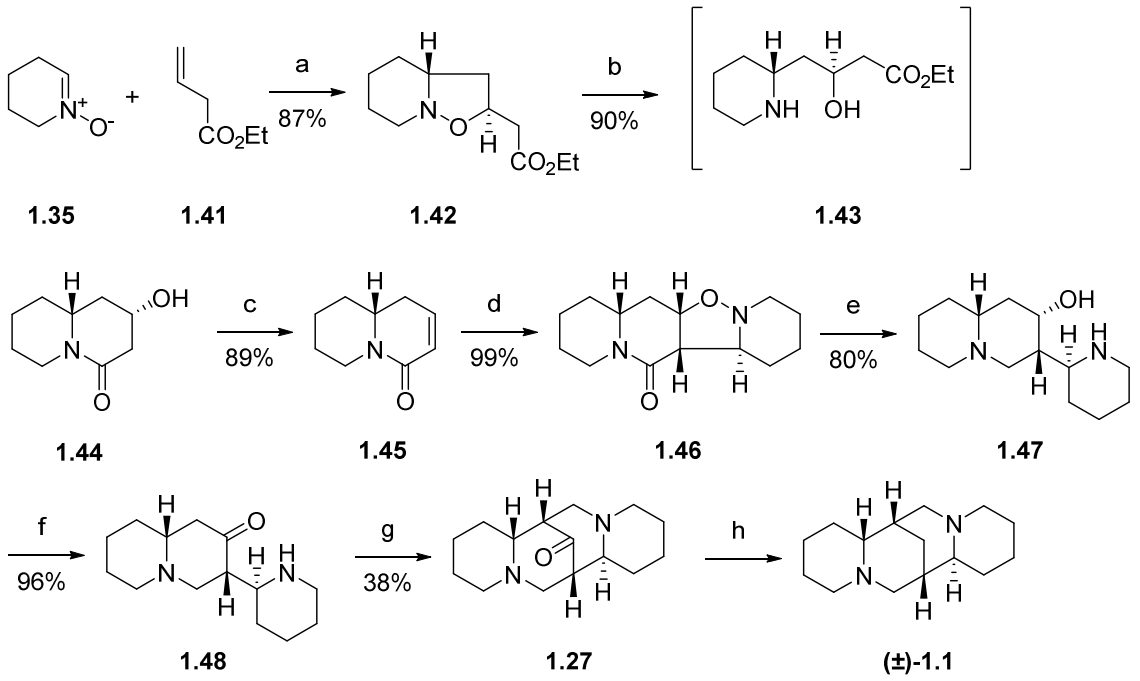
A stereoselective synthesis of (±)-*α*-isosparteine (**1.2**) was reported in 1983 by Kakisawa *et al.* using 1,3-dipolar cycloadditions (**Scheme 1.09**).[48,49] Cycloaddition reaction of nitrone **1.35** and 4*H*-pyran (**1.36**) in refluxing benzene preceded with the formation of adduct **1.37** in 70% yield as 1:1 mixture of regioisomers. A 2nd cycloaddition reaction between **1.37** and nitrone **1.35** secured **1.38** in 22% yield as 2:1 mixture of isomers. Catalytic hydrogenation of **1.38** over $Pd(OH)_2$ in MeOH furnished (±)-*α*-isosparteine (**1.2**). The identity of the sample was confirmed by comparison of physical and ^1H and ^{13}C NMR data with an authentic sample.



Scheme 1.09 *Reagents and conditions:* a) C_6H_6, Δ. b) 4*H*-pyran (**1.36**), Δ. c) H_2, $Pd(OH)_2$, MeOH, rt.

1.2.6 Otomasu's formal synthesis of (±)-sparteine

A formal synthesis of (±)-sparteine was reported in 1987 by Otomasu *et al.* (**Scheme 1.10**).[50] Otomasu and co-workers developed a methodology for the synthesis of (±)-leontiformine and (±)-leontiformidine using a 1,3-dipolar cycloaddition as the key step in the synthesis.[51]



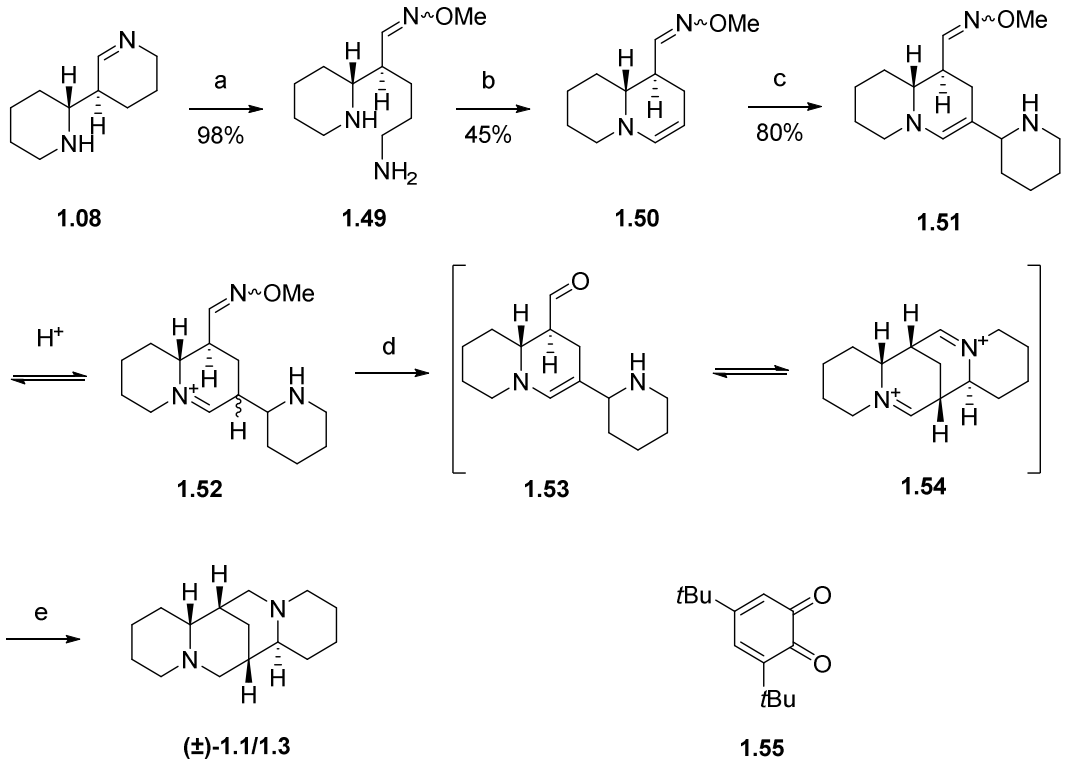
Scheme 1.10 *Reagents and conditions:* a) $PhCH_3$, Δ. b) H_2, Pd/C, EtOH, rt. c) i) MsCl, Et_3N, CH_2Cl_2, rt. ii) DBU, THF, Δ. d) Nitrone **1.35**, $CHCl_3$, Δ. e) i) $LiAlH_4$, Et_2O, Δ. ii) H_2, Pd/C, MeOH, rt. f) Jones oxidation. g) 35% formaldehyde, EtOH, pH 7−8, Δ. h) KOH, hydrazine, $(C_2H_4OH)_2O$, Δ.

Using chemistry reported by Tufariello,[52] 1,3 dipolar cycloaddition reaction of 1-pyrrolidine nitrone (**1.35**) and ethyl 3-butenoate (**1.41**) in refluxing toluene led to the formation of *exo*-adduct **1.42** in 87% yield as a single racemic diastereoisomer. Catalytic hydrogenolysis in EtOH over Pd/C induced reductive N–O bond cleavage to furnish intermediate **1.43**, which was subsequently cyclised to access amide **1.44** in 90% yield as a single isomer. Mesylation of alcohol **1.44** and elimination of the

mesylate intermediate in the presence of DBU proceeded in excellent yield to access enone **1.45**. A second 1,3 dipolar cycloaddition reaction of nitrone **1.35** and enone **1.45** furnished tetracyclic **1.46**. It was reported that an inseparable mixture of regioisomers in ratio of ~ 6:1 was observed due to the *exo*-addition of nitrone **1.35** from both sides of enone **1.45**. Reduction of the amide moiety was performed with $LiAlH_4$ and the formation of quinolizidine derivative **1.47** completed by hydrogenolysis in MeOH over Pd/C. Jones oxidation led to the formation of ketone **1.48**. Mannich reaction of **1.48** with formaldehyde at neutral pH furnished 8-oxosparteine (**1.27**) in 38% yield. A Huang-Minlon modification of the Wolf-Kishner reduction was again employed to complete the synthesis of (±)-sparteine (**1.1**).

1.2.7 Koomen's synthesis of (±)-sparteine and (±)-*β*-isosparteine

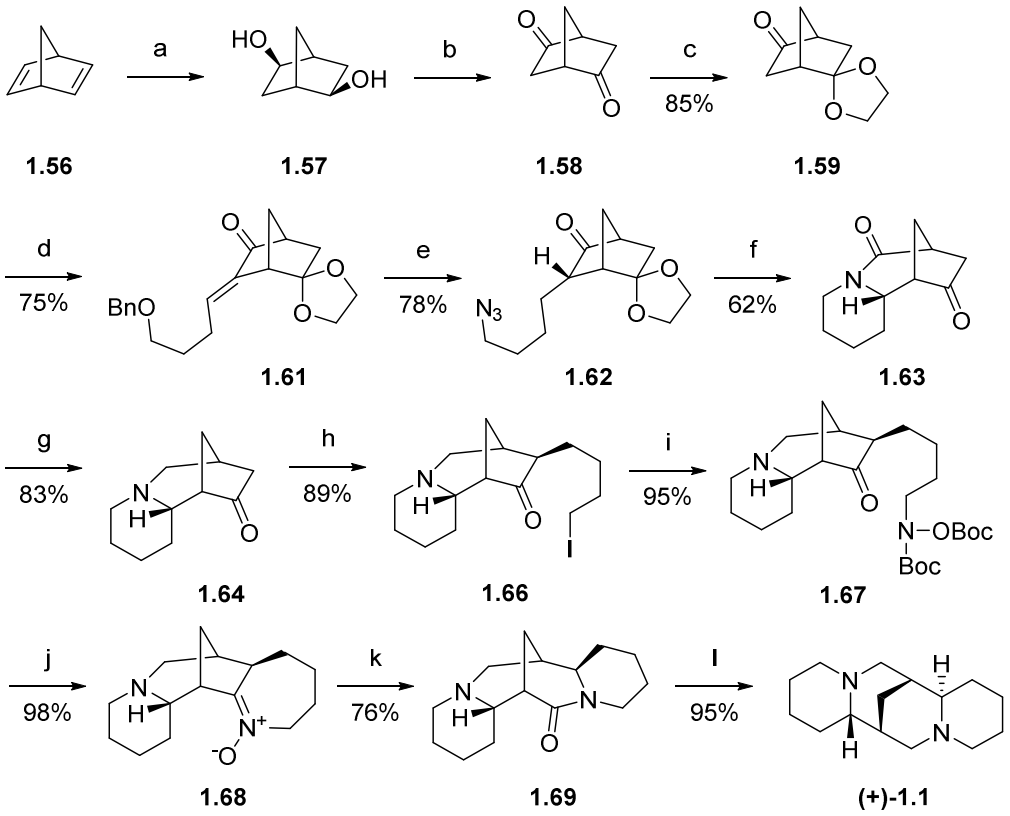
A total synthesis of (±)-sparteine was reported in 1996 by Koomen *et al.* starting from the biogenetic type precursor, (±)-tetrahydroanabasine (**1.8**) (**Scheme 1.11**).[50] Using chemistry reported by Schöpf,[53] tetrahydroanabasine (**1.8**) was treated with methoxyamine in aq. MeOH to furnish oxime **1.49** as a mixture of *syn/anti* adducts. Oxidative deamination of **1.49** using *o*-quinone derivative **1.55** followed by intramolecular cyclisation led to the formation of enamine **1.50** which was subsequently treated with tripiperidine monomer and NaOAc in MeOH to give 3-piperidylquinolizidine **1.51** as a 1:1 mixture of isomers. Oxidative removal of the oxime **1.51** using O_3 in aq. HCl proceeded very slowly to obtain **1.53**. Treatment of this intermediate with NaOAc/AcOH accessed the iminium salt **1.54** which was subsequently reduced with $NaCNBH_3$ to secure the synthesis of (±)-sparteine (**1.1**). Reductive hydrolysis of oxime **1.51** using $TiCl_3$ in aq. HCl and subsequent reduction with $NaCNBH_3$ furnished a mixture of (±)-sparteine (**1.1**) and (±)-*β*-isosparteine (**1.3**).



Scheme 1.11 *Reagents and conditions:* a) NH_2OMe, $MeOH/H_2O$, rt. b) **1.55**, MeOH, rt. c) i) tripiperidine, aq. HCl, rt. ii) NaOAc, MeOH, rt. d) i) O_3, HCl, MeOH, −50 °C ii) Me_2S, −50 °C to rt or $TiCl_3$, aq. HCl, Δ to rt. e) $NaCNBH_3$, aq. HCl, rt.

1.2.8 Aube's synthesis of (+)-sparteine

The first total synthesis of optically pure (+)-sparteine was performed by Jeffrey Aube *et al.* in 2002 (**Scheme 1.12**).[54] Aube and co-workers developed a methodology that can allow access to either sparteine enantiomer using two different nitrogen ring-expansion reactions.[55] (+)-Sparteine (**1.1**) was synthesised in 15 steps and 16% overall yield from 2,5-norbornadiene (**1.56**).



Scheme 1.12 *Reagents and conditions:* a) i) $HSiCl_3$, $[(Allyl)PdCl]_2$, (–)-*S*-MOP. ii) H_2O_2, KI, $KHCO_3$. b) Swern. c) Ethylene glycol, TsOH, THF, Δ. d) i) LDA, $BnO(CH_2)_3CHO$ **1.60**, THF, −78 °C to 0 °C. ii) MsCl, Et_3N, CH_2Cl_2, 0 °C. iii) DBU, THF, Δ. e) i) H_2, Pd/C, $Pd(OH)_2$, EtOH, 60 psi. ii) $Zn(N_3)_2$·2pyr, DEAD, PPh_3, C_6H_6, rt. f) $TiCl_4$, CH_2Cl_2, 0 °C to rt. g) i) Lawesson's reagent. ii) H_2, Ni/Raney, EtOH, rt. h) i) LDA, $I(CH_2)_4Cl$ **1.65**, THF, −78 °C to 0 °C ii) NaI, acetone, Δ. i) K_2CO_3, BocONHBoc, DMF, rt. j) TFA, CH_2Cl_2, rt. k) hυ (254 nm), C_6H_6. l) $LiAlH_4$, THF, Δ.

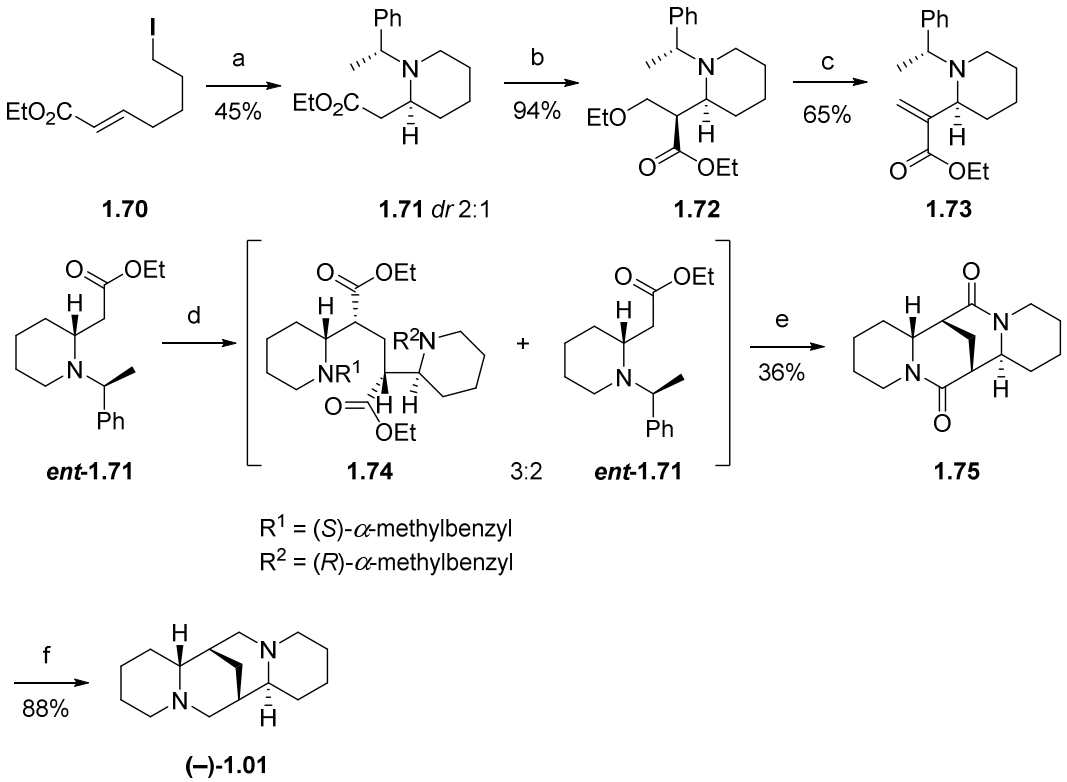
Using chemistry reported by Hayashi, the norbornadiene **1.56** was converted to diol **1.57** with high enantio- and regio-selectivity (**Scheme 1.12**).[56] Swern oxidation led to the formation of C_2-symetrical ketone **1.58** which was subsequently protected to access acetal **1.59**. Treatment of **1.59** with LDA at −78 °C followed by slow addition of aldehyde **1.60** and subsequent mesylation and elimination of the crude product furnished the functionalised enone **1.61**. One-pot reduction with H_2 over Pd/C and $Pd(OH)_2$ removed the benzylic ether protecting group, hydrogenated the *exo* face of the olefin and the formation of the azide **1.62** was completed using a modified Mitsunobu

azidation. Treatment of this intermediate with $TiCl_4$ accessed the functionalised lactam **1.63** *via* an intramolecular Schmidt ring expansion as a single isomer.[57] Thiation of amide **1.63** using Lawesson's reagent and subsequent hydrogenation over Ni/Raney accessed the desired quinolizidine **1.64**. Treatment of this intermediate with LDA at −78 °C and enolate addition to 1-chloro-4-iodobutane (**1.65**) followed by Finkelstein reaction accessed the iodide **1.66** in 74% yield over four steps from amide **1.63**. Displacement of the iodide with BocONHBoc secured the hydroxylamine derivative **1.67** which underwent Boc deprotection using TFA and intramolecular condensation to furnish nitrone **1.68**. Photo-Beckmann rearrangement of **1.68** in benzene afforded 10-oxosparteine (**1.69**).[58] The final reduction of amide **1.69** was achieved using $LiAlH_4$ in quantitative yield, thus completing the synthesis of (+)-sparteine (**1.1**). The identity of the sample was confirmed by comparison of optical rotation with levorotatory material purchased from Aldrich and chiral GC.

1.2.9 O'Brien's synthesis of (−)-sparteine

The first total synthesis of optically pure (−)-sparteine was performed by Peter O'Brien *et al.* in 2004 (**Scheme 1.13**).[59] Using chemistry reported by Hense,[60] ethyl-7-iodohept-2-enoate (**1.70**) was prepared in 82% yield over three steps from 5-chloropentanol. Alkylation of iodide **1.70** with (*R*)-*α*-methylbenzylamine in refluxing EtOH and subsequent intramolecular Michael addition of the amine furnished piperidine **1.71** as a mixture of adducts in a ratio of ~ 2:1. Despite the poor selectivity in the conjugate addition the mixture was readily separable and the major isomer **1.71** was accessed in gram quantities. The treatment of **1.71** with LiHMDS at −78 °C followed by enolate addition to $EtOCH_2Cl$ accessed the functionalised piperidine **1.72** as a single isomer. Ethoxide elimination from **1.72** was accomplished using a modified procedure reported by Sworin and Lin to secure the Michael precursor **1.73**.[61] Kinetic deprotonation of ***ent*-1.71** at −78 °C using LDA and subsequent enolate addition to *α*,*β*-unsaturated amino ester **1.73** led to the formation of the bispiperidine **1.74**. Disappointingly, no pure sample could be isolated. As a result, an inseparable mixture of ***ent*-1.71** and adduct **1.74** in a ratio of 3:2 was submitted to hydrogenation over $Pd(OH)_2/C$, $NH_4^+HCO_2^-$ in

EtOH to furnish 10,17-dioxosparteine (**1.75**) after removal of the α-methylbenzyl ether protecting group and intramolecular cyclisation of the free amine.



1.70 **1.71** *dr* 2:1 **1.72** **1.73**

***ent*-1.71** **1.74** ***ent*-1.71** **1.75**

(–)-1.01

Scheme 1.13 *Reagents and conditions:* a) (*R*)-*α*-Methylbenzylamine, Et_3N, EtOH, Δ. b) i) LiHMDS, THF, −78 °C. ii) $EtOCH_2Cl$, THF −78 °C to rt. c) *t*-BuOK, THF, −78 °C. d) i) LDA, THF, −78 °C ii) Michael acceptor **1.73**, THF, −30 °C. iii) 1 M HCl, rt. e) H_2, $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, Δ. f) $LiAlH_4$, THF, Δ.

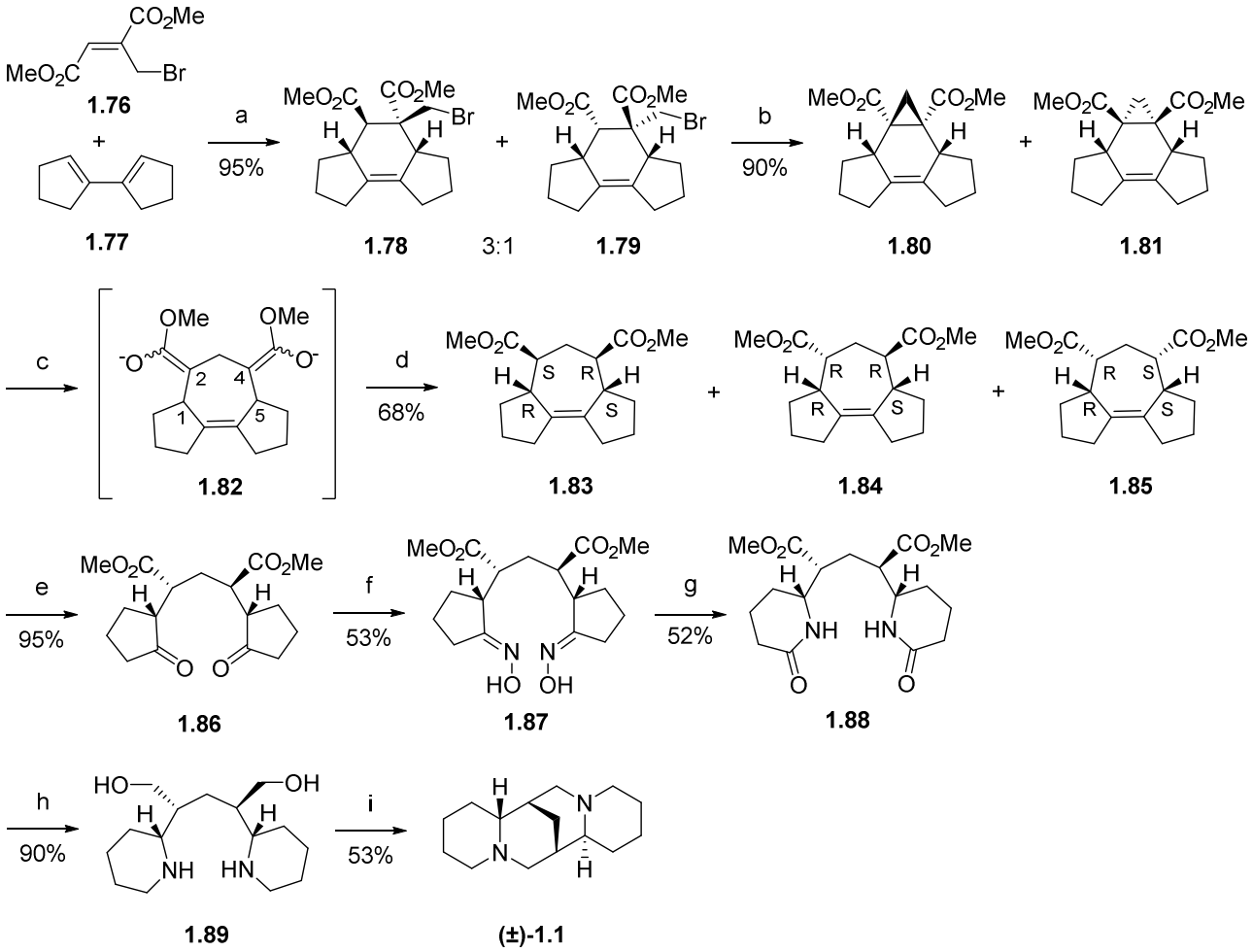
The final reduction of bislactam **1.75** was achieved using $LiAlH_4$ to furnish (−)-sparteine (**1.1**). The identity of the sample was confirmed by comparison of the optical rotation and ^1H and ^{13}C NMR data with an authentic sample.

1.2.10 Fleming's synthesis of (±)-sparteine

A total synthesis of (±)-sparteine was reported by Fleming *et al.* in 2005.[62] Fleming and co-workers developed a synthesis of racemic (±)-sparteine using a Diels-Alder reaction and a Beckman rearrangement as key steps (**Scheme 1.14**).[63]

Diels-Alder reaction between *Z*-diester **1.76** and bromomesaconate **1.77** accessed a mixture of bromides **1.78** and **1.79** in a ratio of 3:1. Treatment of these intermediates with NaOMe in refluxing $PhCH_3$ gave a mixture of cyclopropanes **1.80** and **1.81** in the same ratio. Except to characterise the major isomers, the bromides or the cyclopropanes were not separated prior to use in the next step.

The treatment of **1.80** and **1.81** with Li in ammonia accessed an intermediate meso bisenolate **1.82**. In theory, from the protonation of the enolates, three possible diastereomers could be formed, two *meso* isomers **1.83** (*R*,*S*,*R*,*S*) and **1.85** (*R*,*R*,*S*,*S*) and the desired isomer **1.84** (*R*,*R*,*R*,*S*) for the synthesis of sparteine. In practice, only isomers **1.83** and **1.84** were isolated, without any trace of **1.85**. The relative stereochemistry between the two *meso* adducts was ascertained by single crystal X-ray crystallography and the relative stereochemistry between **1.83** and **1.84** was confirmed by ^{1}H NMR since the latter had two methoxy singlets. Different ratios of **1.83** and **1.84** were obtained when enolate **1.82** was quenched with various proton sources. Treatment of **1.82** with NH_4Cl led to the formation of a mixture of **1.83** and **1.84** in a ratio of ~ 3:1. Treatment of **1.82** with NaOMe gave a mixture of **1.83** and **1.84** in a ratio of ~ 1:4.5.

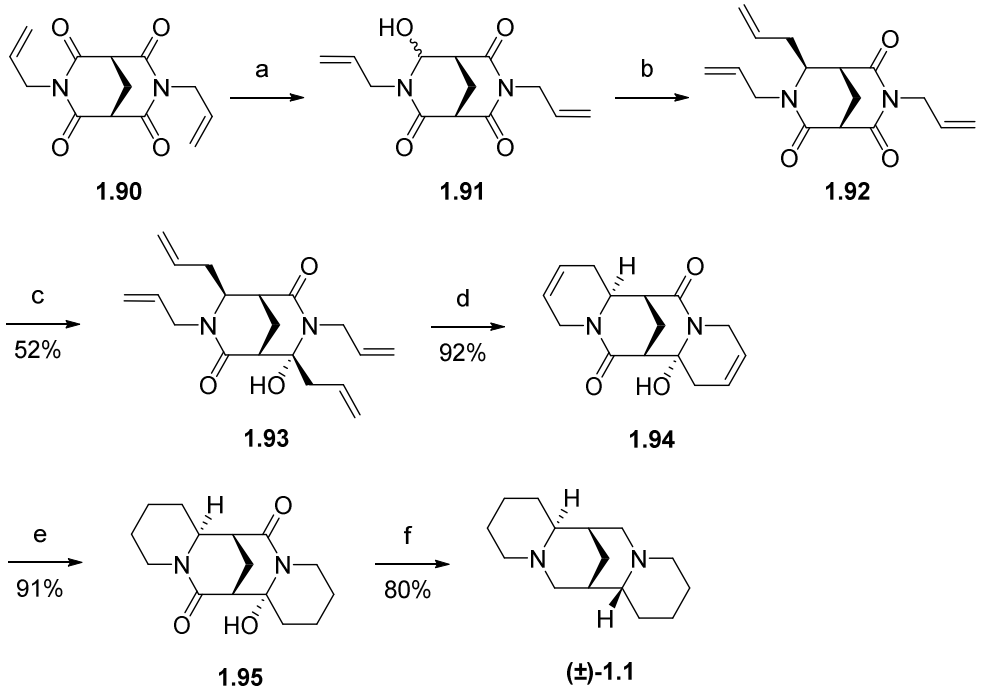


Scheme 1.14 *Reagents and conditions:* a) Me_2AlCl, CH_2Cl_2, −78 °C to rt. b) NaOMe, $PhCH_3$, Δ. c) i) Li, NH_3, Et_2O, −78 °C. ii) isoprene, −78 °C. d) MeOH, Δ. e) O_3, Me_2CO, PPh_3, −78 °C to rt. f) $NH_2OH{\cdot}HCl$, Py, EtOH, 0 °C. g) i) MsCl, Et_3N, −20 °C to rt. ii) THF/H_2O, Δ. h) $LiAlH_4$, THF, Δ. i) CCl_4, PPh_3, Et_3N, rt.

The oxidative cleavage of the alkene **1.84** was performed with O_3 in acetone at −78 °C giving the biscyclopentanone **1.86** in quantitative yield. Treatment of **1.86** with hydroxylamine accessed the bisoxime **1.87**. Beckman rearrangement was facilitated when **1.87** was converted to mesylate with methanesulfonate followed by subsequent heating in aq. THF to furnish bisamide **1.88** in 52% yield over two steps. Reduction of **1.88** with $LiAlH_4$ in refluxing THF accessed diol **1.89** which underwent Appel reaction followed by double cyclisation to secure the synthesis of (±)-sparteine (**1.1**).

1.2.11 Blakemore's synthesis of (±)-sparteine, (±)-*α*-isosparteine and (±)-*β*-isosparteine

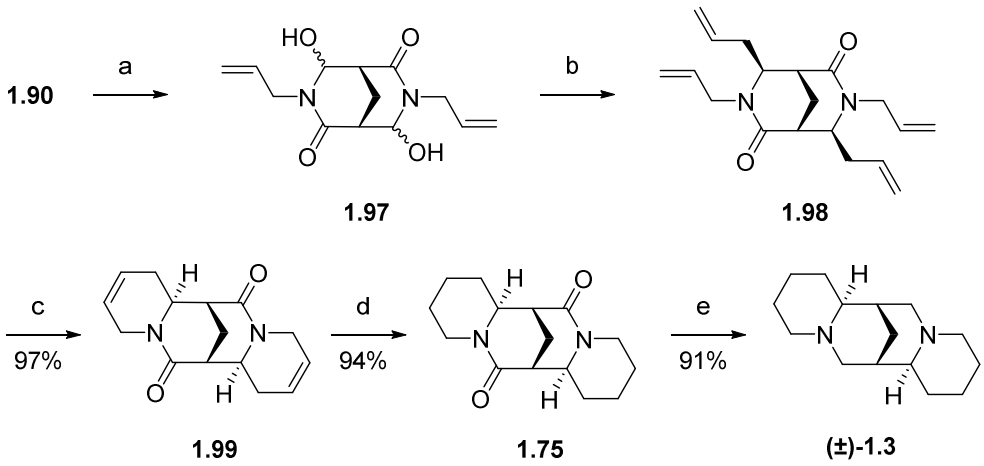
The most recent total synthesis of (±)-sparteine was published in 2008 by Blakemore *et al.* (**Scheme 1.15**).[64] Blakemore and co-workers developed a methodology for the synthesis of (±)-sparteine, (±)-*α*-isosparteine and (±)-*β*-isosparteine from a common tetraoxobispidine intermediate **1.90**.[65,66] Tetraoxobispidine **1.90** was treated with $NaBH_4$ in THF to give hydroxylactam **1.91**. Using chemistry reported by Sakurai, the crude aminol **1.91** was allylated with ATMS in presence of the Lewis acid $BF_3{\cdot}OEt_2$, which induced formation of the *N*-acyliminium ion and subsequent addition of the nucleophile accessed imidolactam **1.92** in 33% yield over two steps. The treatment of **1.92** with allylmagnesium bromide (**1.96**) accessed the functionalised pseudo-C_2-symetrical amide **1.93** as a single stereoisomer.



Scheme 1.15 *Reagents and conditions:* a) $NaBH_4$, THF, 0 °C. b) ATMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt. c) Allylmagnesium bromide (**1.96**), Et_2O/THF, −78 °C. d) Grubbs II, CH_2Cl_2, Δ. e) H_2, Pd/C, MeOH/H_2O, rt. f) $LiAlH_4$, THF, Δ.

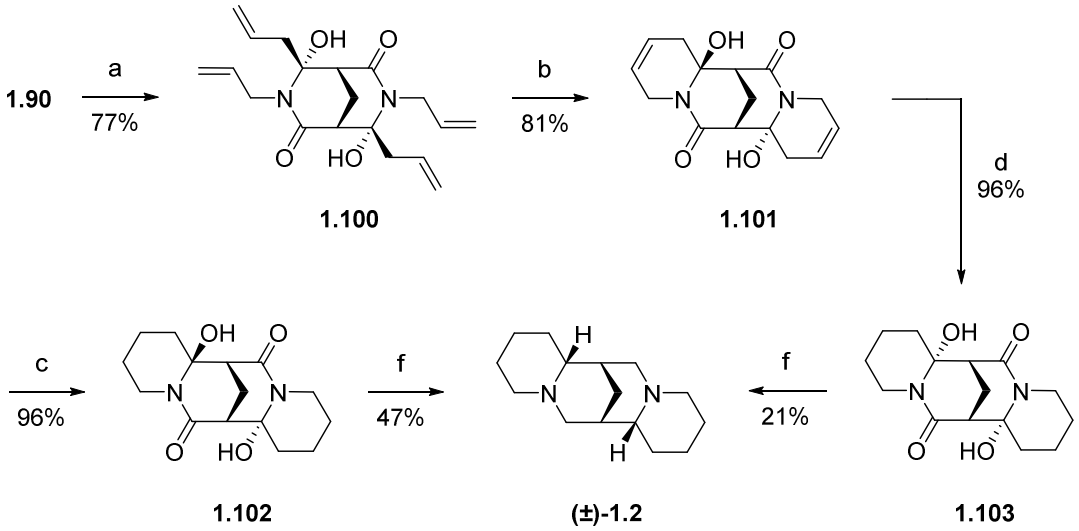
Double RCM was performed using Grubbs II to give the tetracyclic diene **1.94** in 92% (**Scheme 1.15**). Hydrogenation of **1.94** over Pd/C to tetracyclic amide **1.95** followed by $LiAlH_4$ reduction in refluxing THF completed the synthesis of (±)-sparteine (**1.1**) after distillation. The relative stereochemistry of **1.95** was ascertained by single crystal X-ray crystallography. The identity of the sample (±)-sparteine (**1.1**) was confirmed by comparison of infrared and ^{1}H and ^{13}C NMR data with an authentic sample of (−)-sparteine (**1.1**).

A similar approach was used to access (±)-*β*-isosparteine (**1.3**) (**Scheme 1.16**). Tetraoxobispidine **1.90** was treated with $NaBH_4$ in THF to give bishydroxylactam **1.97** which was subsequently converted into tetraene **1.98** in 16% yield over two steps using a double Sakurai-type allylation. Double RCM was performed using Grubbs I to give tetracyclic diene **1.99** in 97%. Hydrogenation of **1.99** over Pd/C to 10,17-dioxosparteine (**1.75**) followed by $LiAlH_4$ completed the synthesis of (±)-*β*-isosparteine (**1.3**).



Scheme 1.16 *Reagents and conditions:* a) $NaBH_4$, THF, 0 °C. b) ATMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt. c) Grubbs I, CH_2Cl_2, rt. d) H_2, Pd/C, $MeOH/H_2O$, rt. f) $LiAlH_4$, THF, Δ.

(±)-*α*-Isosparteine (**1.2**) was prepared using the same tetraoxobispidine intermediate (**Scheme 1.17**). Tetraoxobispidine **1.90** was double alkylated with allylmagnesium bromide (**1.96**) to access bishydroxylactam **1.100**. Double RCM was performed using Grubbs I to secure the tetracyclic diene **1.101** in 81%. Hydrogenation of **1.101** over of Pd/C in a very polar solvent mixture (MeOH–H_2O, 5:1) gave the nonsymmetric bishemiaminal **1.102** as a single isomer while the reduction in a less polar solvent (EtOH–EtOAc, 2:1) accessed the symmetric adduct **1.103**. The final reduction of **1.102** and **1.103** was achieved in a strereocontrolled manner using a large excess of borane tetrahydrofuran complex. The identity of (±)-*α*-isosparteine (**1.2**) was confirmed by comparison of physical and ^{1}H and ^{13}C NMR data with those from natural or synthetic samples of *α*-isosparteine.[49]



Scheme 1.17 *Reagents and conditions:* a) Allylmagnesium bromide (**1.96**), Et_2O/THF, −78 °C. b) Grubbs I, CH_2Cl_2, rt. c) H_2, Pd/C, MeOH/H_2O, rt. d) H_2, Pd/C, EtOH/EtOAc, rt. f) BH_3·THF, THF, 0 °C to rt.

1.3 The Brown group's approach to lupin alkaloids

In recent years Brown and co-workers reported the asymmetric synthesis of three natural products from the lupin family: (−)-epilupinine (**1.104**), (+)-allomatrine (**1.106**) and (−)-lamprolobine (**1.107**) and one indolizidine alkaloid isolated from *Maackia tashiroi*:[67] (−)-tashiromine (**1.105**) (**Figure 1.04**). These natural products have been synthesised using diastereoselective imino-aldol reactions as key steps to install the two adjacent stereocenters at C-5 and C-6, and *N*-acyliminium chemistry to install the remaining two stereocenters in (−)-allomatrine (**1.106**).

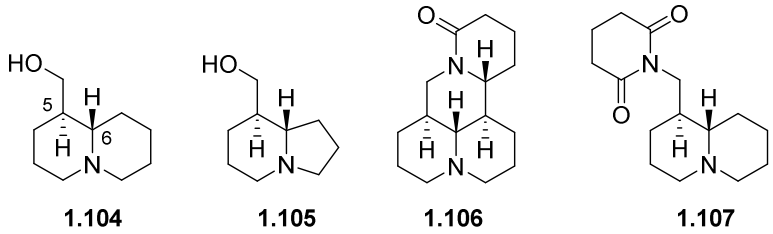
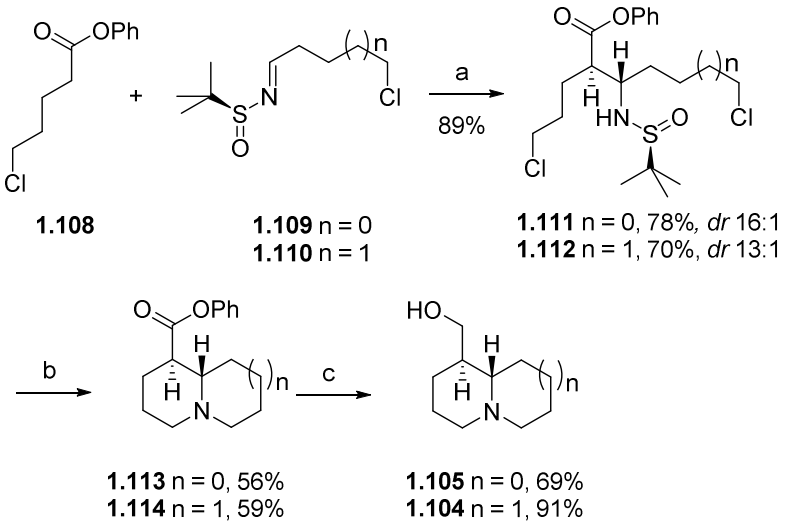


Figure 1.04 Alkaloids synthesised by Brown and co-workers.[68,69]

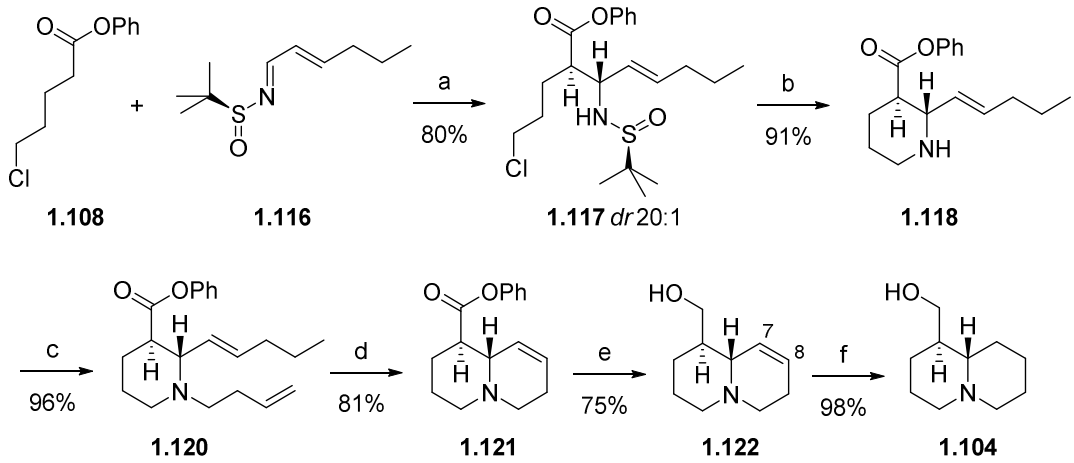
1.3.1 Total syntheses of (−)-epilupinine, (−)-tashiromine

The synthesis of (−)-epilupinine (**1.104**) was performed twice by researchers in the Brown group starting from two different chiral sulfinylimines as functionalised fragments in the imino-aldol reaction. Addition of the lithium enolates derived from phenyl 5-chlorovalerate (**1.108**) to imines **1.109** and **1.110** proceeded smoothly to afford *β*-amino acid derivative **1.111** and **1.112** with high diastereoselectivity, *dr* 16:1 in the case of **1.111** and 13:1 for **1.112** in favour of the expected *syn* products (**Scheme 1.18**). Deprotection of the *N*-sulfinyl protecting group using conc. HCl furnished the primary amine and subsequent treatment with K_2CO_3 and NaI induced double intramolecular cyclisation to furnish either indolizidine **1.113** or quinolizidine **1.114**. Final reduction using $LiAlH_4$ in THF secured the syntheses of (−)-epilupinine (**1.104**) and (−)-tashiromine (**1.105**) in 12% and 15% overall yields respectively.[68]



Scheme 1.18 *Reagents and conditions:* a) LDA, THF, −78 °C, imine **1.109** or **1.110**. b) i) conc. HCl, dioxane, rt. ii) K_2CO_3, NaI, MeCN, rt. c) $LiAlH_4$, THF, 0 °C to rt.

A second approach to (−)-epilupinine involved the addition of lithium enolate derived from phenyl 5-chlorovalerate (**1.108**) to *α,β*-unsaturated imine **1.116** to furnish *β*-amino acid **1.117** in 80% yield with high diastereoselectivity *dr* 20:1 in favour of the *syn* product (**Scheme 1.19**).

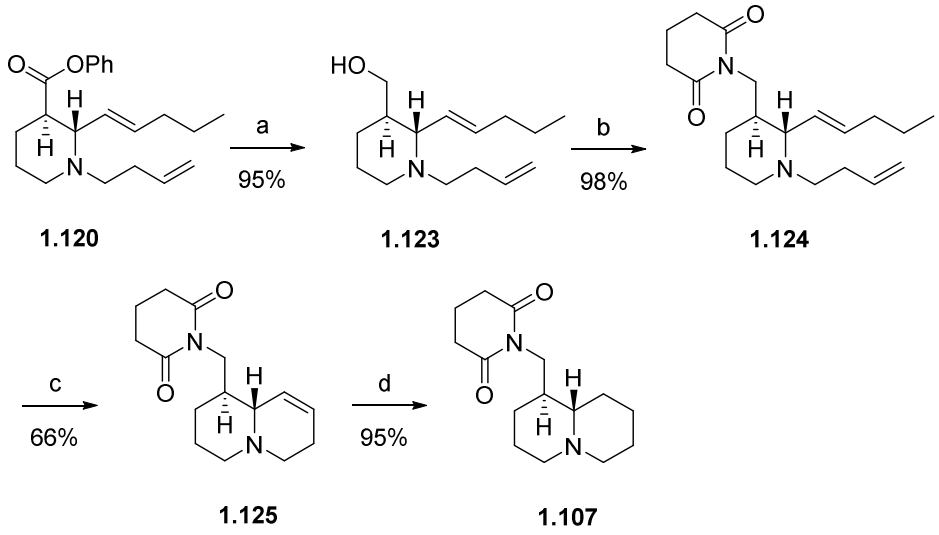


Scheme 1.19 *Reagents and conditions:* a) LDA, THF, −78 °C, imine **1.116**. b) i) conc. HCl, dioxane, rt. ii) K_2CO_3, NaI, MeCN, rt. c) 4-bromo-but-1-ene (**1.119**), K_2CO_3, MeCN, Δ. d) Grubbs I (10 mol %), CH_2Cl_2, Δ. e) $LiAlH_4$, THF, 0 °C to rt. f) H_2, Pd/C, EtOH, rt.

Deprotection of the *N*-sulfinyl protecting group using conc. HCl afforded the primary amine and subsequent treatment with K_2CO_3 and NaI gave piperidine **1.118**. *N*-alkylation of piperidine **1.118** with 4-bromo-1-ene (**1.119**) followed by RCM of diene **1.120** using Grubbs I furnished the quinolizidine derivative **1.121** in 78% yield over the two steps. Reduction of ester **1.121** using $LiAlH_4$ and subsequent hydrogenation of unsaturated quinolizidine **1.122** over Pd/C completed the synthesis of (−)-epilupinine (**1.104**) in seven linear steps and 39% yield. The interest in this longer route was derived from the ability to introduce the 7,8-unsaturation, which was later investigated as a handle to form the tetracyclic alkaloids.

1.3.2 Total synthesis of (−)-lamprolobine

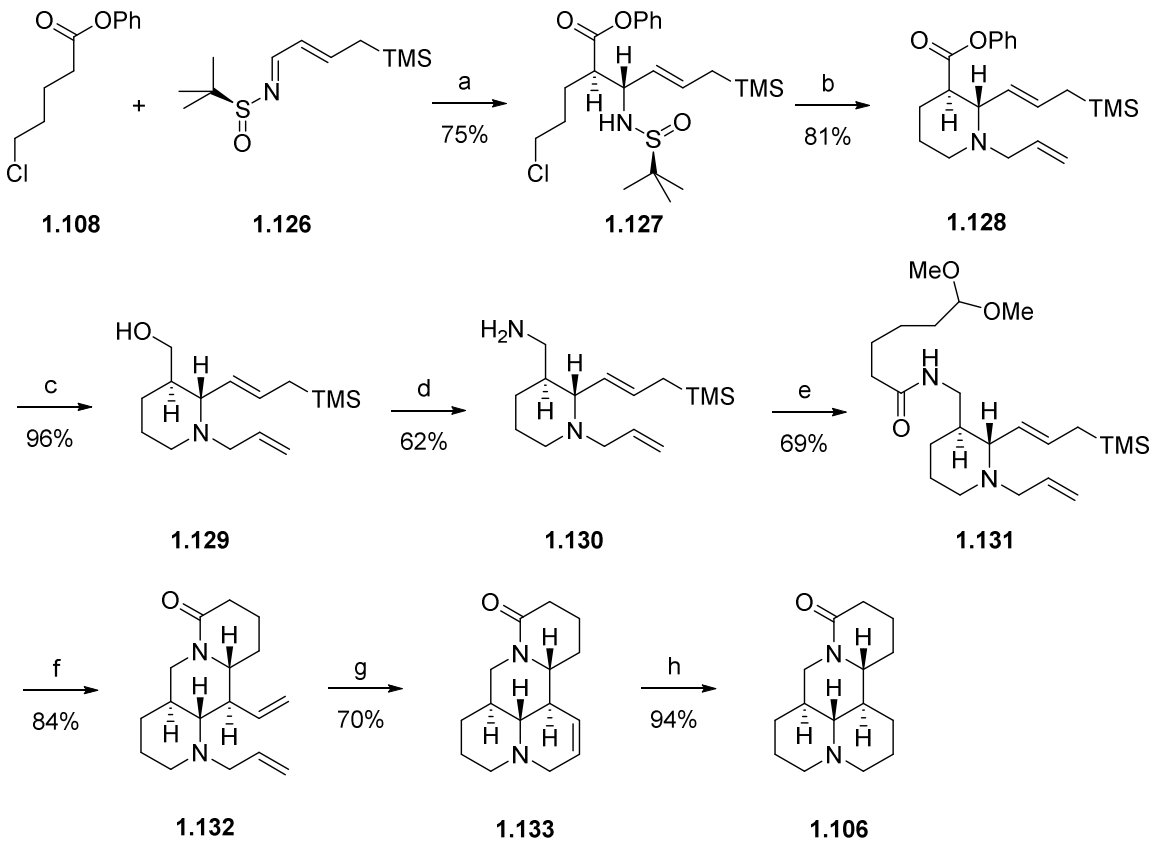
The synthesis of (−)-lamprolobine (**1.107**) was accomplished using as starting point the piperidine **1.120** previously synthesised as an intermediate in the synthesis of (−)-epilupinine (**Scheme 1.20**).[70] Reduction of ester **1.120** using $LiAlH_4$ and subsequent Mitsunobu reaction of alcohol **1.123** with glutarimide accessed the functionalised piperidine **1.124** in 93% yield over the two steps. Quinolizidine derivative **1.125** was furnished *via* RCM of diene **1.124** using Grubbs I and final hydrogenation over Pd/C proceeded smoothly to furnish (−)-lamprolobine (**1.107**) in eight linear steps and 39% yield (**Scheme 1.20**).



Scheme 1.20 *Reagents and conditions:* a) $LiAlH_4$, Et_2O, 0 °C to rt. b) DIAD, PPh_3, glutarimide, THF/CH_2Cl_2, 0 °C to rt. c) Grubbs I (10 mol %), CH_2Cl_2, Δ d) H_2, Pd/C, EtOH, rt.

1.3.3 Total synthesis of (+)-allomatrine

The first stereocontrolled total synthesis of (+)-allomatrine (**1.106**) was published in 2013 from this laboratory (**Scheme 1.21**). Based on the imino-aldol chemistry described above,[68] lithium enolate of phenyl 5-chlorovalerate (**1.108**) underwent addition to *α,β*-unsaturated imine **1.126** to furnish *β*-amino acid **1.127** in 75% yield as a single diastereoisomer. Deprotection of the *N*-sulfinyl protecting group using 1.0 equiv. of conc. HCl furnished the primary amine and subsequent treatment with K_2CO_3 and NaI afforded the piperidine intermediate which was *N*-alkylated *in situ* with allyl bromide to access the functionalised piperidine **1.128.** Reduction of ester **1.128** to alcohol **1.129** followed by a modified Mitsunobu reaction to introduce the azide functionality and reduction using $LiAlH_4$ accessed the primary amine **1.130**.

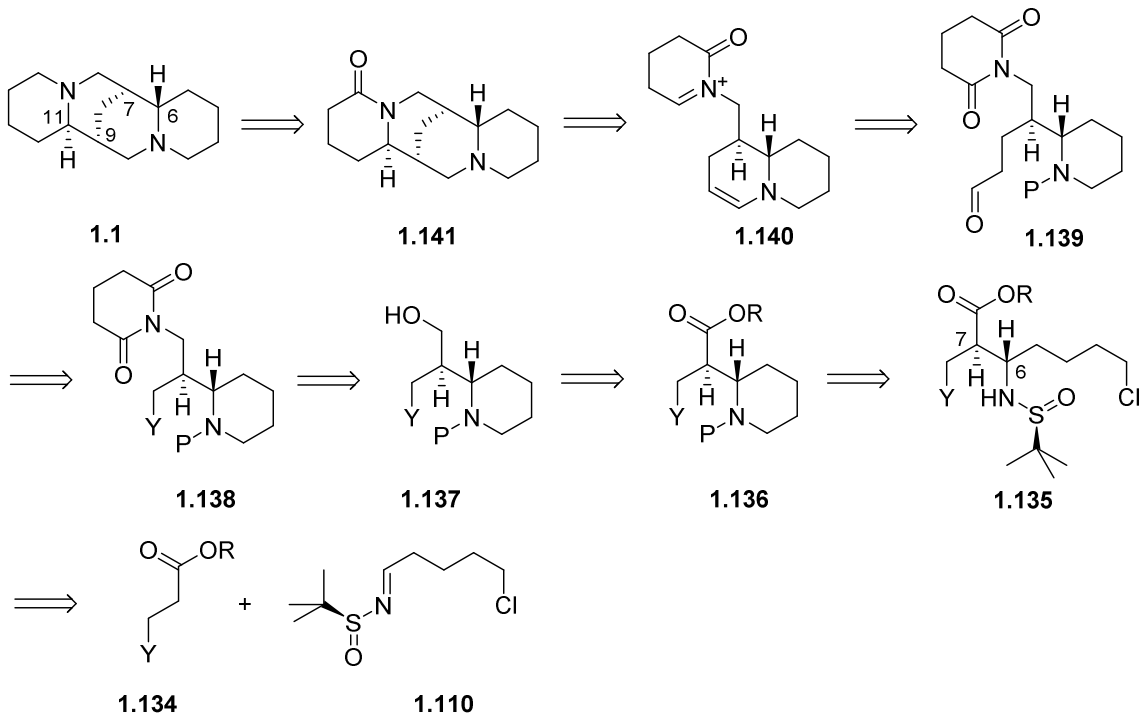


Scheme 1.21 *Reagents and conditions:* a) LDA, THF, −78 °C, imine **1.126**. b) i) 1 equiv. HCl, dioxane, rt. ii) K_2CO_3, NaI, MeCN, rt. iii) ally bromide, K_2CO_3, MeCN, Δ. c) $LiAlH_4$, Et_2O, 0 °C to rt. d) i) DIAD, PPh_3, $(PhO)_2P(O)N_3$, THF, −10 °C to rt. ii) $LiAlH_4$, THF, 0 °C to rt. e) 5,5-Dimethoxypentanoic acid, T_3P, Et_3N, EtOAc, rt. f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt. g) Grubbs II (5 mol %), CH_2Cl_2, Δ. h) H_2, Pd/C, EtOH, rt.

Amidation of **1.130** with 5,5-dimethoxypentanoic acid was performed in the presence of the coupling agent T_3P to secure the cyclisation precursor **1.131**. Treatment of this intermediate with the Lewis acid $BF_3{\cdot}OEt_2$ triggered a sequence of reactions, culminating with the addition of the TMS activated alkene on the *N*-acyliminium ion generated *in situ* to assemble the tricycle adduct **1.132**. RCM of the diene **1.132** using Grubbs II and subsequent hydrogenation of 8,9-dehydroallomatrine (**1.133)** over Pd/C completed the first total synthesis of (+)-allomatrine (**1.106**) in 13 steps and 14% overall yield.

1.4 Retrosynthetic analysis of (–)-sparteine

The strategy employed by Brown *et al.* allowed the synthesis of three lupin alkaloids. We hypothesised that using the same methodology we could rapidly assemble the quinolizidine moiety and a final *N*-acyliminium cyclisation would furnish (+)-lupanine (**1.141**), which can be reduced to sparteine (**Scheme 1.22**).



Scheme 1.22 Retrosynthetic analysis of (−)-sparteine.

The key steps in the retrosynthetic analysis require two highly functionalised fragments which are brought together in a diastereoselective imino-aldol reaction giving control of the absolute stereochemistry at C-6 and C-7 in adduct **1.135**. Sulfinyl deprotection, followed by cyclisation to piperidine intermediate and a suitable protection would allow access to ester **1.136**. Reduction to alcohol **1.137** and subsequent Mitsunobu reaction with glutarimide would allow access to imide **1.138**. Phenyl ester **1.134** requires a side chain containing a latent aldehyde functionality, which at a later stage of the synthesis would allow access to aldehyde **1.139**. Reduction of the imide to the corresponding

hydroxylactam followed by treatment with acid or Lewis acid would undergo one-pot piperidine deprotection, cyclisation to the enamine **1.140** and *N*-acyliminium cyclisation of an this intermediate would lead to (+)-lupanine (**1.141**). Final reduction of the tetracyclic compound would access (−)-sparteine (**1.1**). The following chapter describes efforts to complete a total synthesis of sparteine following this general strategy.

Chapter 2: Efforts towards the total synthesis of (−)-sparteine and other lupin alkaloids

2.1 Designing fragments for the imino-aldol reaction

As outlined in our retrosynthetic analysis, we require two highly functionalised fragments, which are brought together in a diastereoselective imino-aldol reaction to install the desired adjacent stereogenic centres at C-6 and C-7. Our preliminary research focused on designing suitable esters, which bear functionalised side chains to allow access to aldehyde functionality at a later stage in the synthesis (**Figure 2.01**).

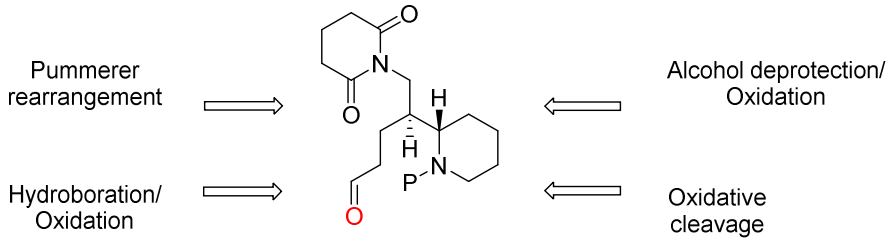
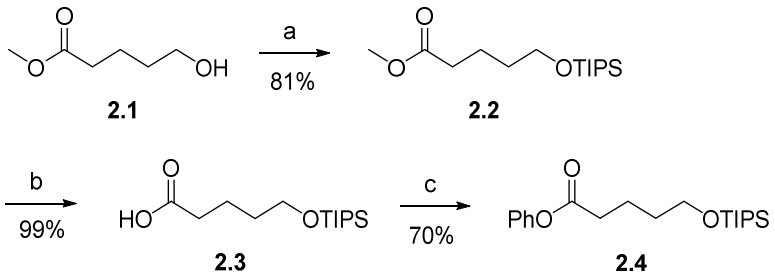


Figure 2.01 Latent aldehyde functionality.

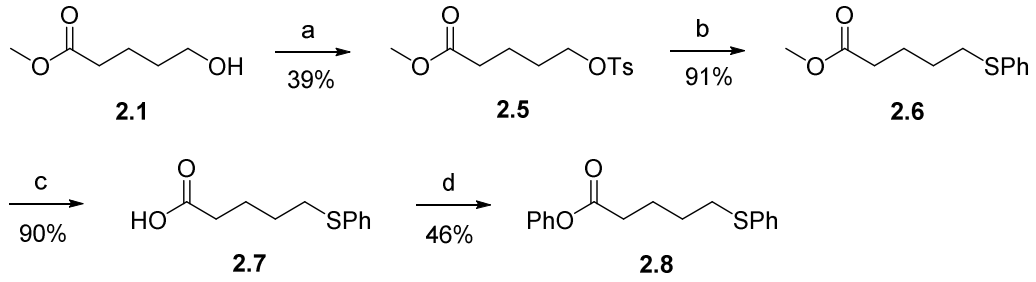
2.1.1 Synthesis of esters

The first approach investigated ester substrates containing a simple protected alcohol functionality in the side-chain. Synthesis of TIPS protected of 5-oxypentanoic acid methyl ester **2.2** was achieved from alcohol **2.1** in 81%. Hydrolysis of ester **2.2** to acid **2.3** and esterification with phenol furnished the ester **2.4** in 56% over three steps (**Scheme 2.01**).

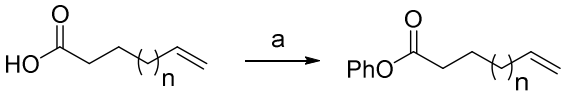


Scheme 2.01 *Reagents and conditions:* a) TIPSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt. b) NaOH, MeOH/THF, Δ. c) PhOH, DMAP, DCC, CH_2Cl_2, rt.

As an alternative latent aldehyde functionality, the use of a phenylthioether was also investigated. The aldehyde would be unmasked by oxidation to the corresponding sulfoxide followed by Pummerer reaction. Synthesis of ester **2.8** started with tosylation of the free alcohol **2.1** to furnish ester **2.5**, which was subsequently alkylated with thiophenol to secure thioether **2.6**. Hydrolysis of ester **2.6** to acid **2.7** and re-esterification with phenol *via* the freshly prepared acid chloride gave the desired ester **2.8** in 15% over five steps (**Scheme 2.02**).



Scheme 2.02 *Reagents and conditions:* a) TsCl, DMAP, Et_3N, CH_2Cl_2, rt. b) *t*-BuOK, TBAB, PhSH, THF, rt. c) NaOH, MeOH/THF, Δ. d) i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt. ii) PhOH, Et_3N, CH_2Cl_2, 0 °C to rt.



2.9 n = 0
2.10 n = 1

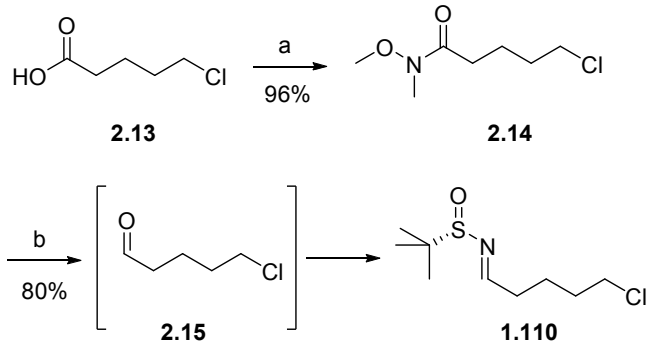
2.11 n = 0, 89%
2.12 n = 1, 97%

Scheme 2.03 *Reagents and conditions:* a) i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt. ii) PhOH, Et_3N, CH_2Cl_2, 0 °C to rt.

Enolate precursors **2.11** and **2.12** bearing terminal alkene functionality were also prepared. 5-Hexenoic acid (**2.10**) and 4-pentenoic acid (**2.9**) were converted to the corresponding acid chlorides using oxalyl chloride and DMF and coupled with phenol to furnish esters **2.11** and **2.12** in near-quantitative yield (**Scheme 2.03**).

2.1.2 Synthesis of sulfinyl imine

Sulfinyl imine **1.110** was synthesised in four steps starting from the commercially available 5-chloropentanoic acid (**2.13**) (**Scheme 2.04**). Acid **2.13** was rapidly converted to the corresponding acid chloride using oxalyl chloride and DMF and addition of Weinreb amine furnished amide **2.14**. Reduction of Weinreb amide **2.14** was performed with DIBAL-H at −78 °C to access aldehyde **2.15**, which was directly condensed with (−)-TBSA to secure the synthesis of imine **1.110** in 83% overall yield.



2.13 **2.14** **2.15** **1.110**

Scheme 2.04 *Reagents and conditions:* a) i) $(COCl)_2$, DMF, CH_2Cl_2, rt. ii) Weinreb amine·HCl, Et_3N, CH_2Cl_2, 0 °C to rt. b) i) DIBAL-H, CH_2Cl_2, −78 °C. ii) (−)-TBSA, $CuSO_4$, CH_2Cl_2, rt.

2.2 Synthetic studies into the imino-aldol reaction

2.2.1 Ellman approach to diastereoselective reactions

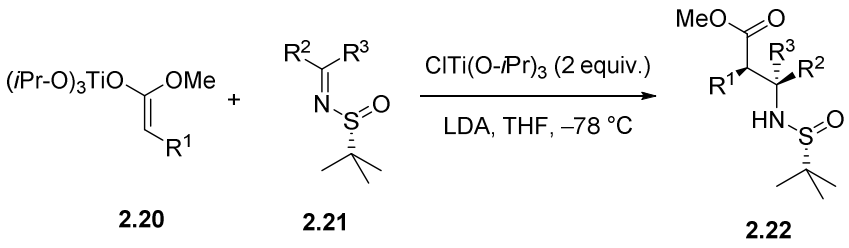
Ellman and co-workers explored the addition of simple ester enolates to chiral sulfinyl imines to access various *β*-amino acids.[71-73] In their preliminary studies, Ellman studied the addition of methyl acetate enolate to *tert*-butylsulfinylimine **2.18**, accessed from the condensation of benzaldehyde with (+)-TBSA (**Table 2.01**).[72] Different bases were employed to generate the metal enolates and solvents were examined to determine diastereoselectivity. Low diastereoselectivity was observed with lithium enolates generated by treatment of methyl acetate with LDA in THF or Et_2O (Entries 1–2, **Table 2.01**).

2.17 **2.18** **2.19**

Entry	Base/Lewis acid	Solvent	Yield (%)	*dr*
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. $ClTi(O\text{-}iPr)_3$	THF	90	87:13
6	LDA/2 equiv. $ClTi(O\text{-}iPr)_3$	THF	90	98:2
7	LDA/3 equiv. $ClTi(O\text{-}iPr)_3$	THF	90	99:1
8	LDA/4 equiv. $ClTi(O\text{-}iPr)_3$	THF	90	99:1

Table 2.01 Diastereomeric outcome of the imino-aldol reaction.

An increase in selectivity was observed when a sodium counterion was used instead on lithium counterion in Et_2O (Entry 4, **Table 2.01**). A significant improvement in diastereoselectivity was achieved when lithium enolates, obtained from the kinetic deprotonation of ester **2.17** using LDA, were transmetallated to titanium enolates prior to the addition of imine **2.18** (Entries 5–8, **Table 2.01**). This transformation increased the covalent character of the metal enolate and provided a better facial selectivity upon the addition of electrophile, possibly due to a more organised cyclic transition state. With such high diastereoselectivity observed in the acetate enolate additions, Ellman and co-workers pursued further investigation of the imino-aldol reaction employing α-substituted esters and imines (**Table 2.02**).[72] High yields and diastereocontrol were achieved when titanium enolates of α-substituted esters were added to aryl- and alkyl-*tert*-butanesulfinyl imines (Entries 1–5, **Table 2.02**).



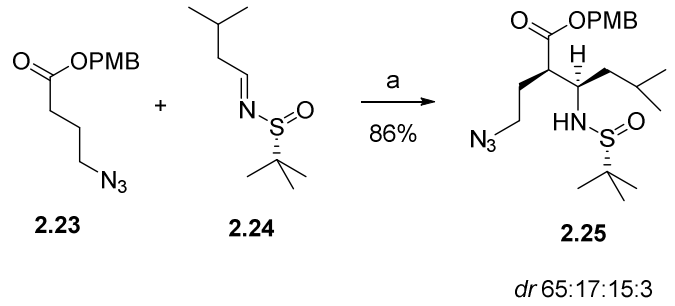
2.20 **2.21** **2.22**

Entry	R^1	R^2	R^2	Yield (%)	*dr*
1	Me	Me	H	96	92:7:1:0
2	Me	*i*Bu	H	81	95:3:2:0
3	Me	Ph	H	85	96:4:0:0
4	Me	Ph	Me	81	91:9:0:0
5	Bn	Et	H	67	90:10:0:0

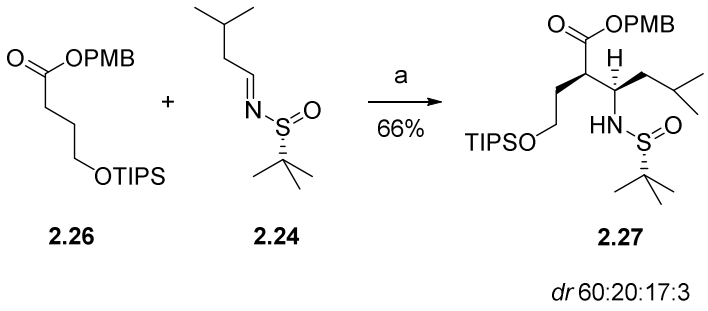
Table 2.02 Diastereomeric outcome of the imino-aldol reaction.

In an attempt to synthesise β-peptides, Ellman and co-workers investigated the imino-aldol reaction using esters bearing functionalised side chains (**Scheme 2.05**).[72] Transmetallation of the lithium enolate of ester **2.23** with $ClTi(O\text{-}iPr)_3$ proved to be

unsuccessful, resulting in the degradation of the starting material due to the azide functionality. The conversion was possible in the presence of NaHMDS but the diastereoselectivity was extremely low, *β*-amino acid derivative **2.25** was isolated in 86% yield as a mixture of four diastereomers *dr* 65:17:15:3.



Scheme 2.05 *Reagents and conditions:* a) i) NaHMDS, Et_2O, −78 °C. ii) imine **2.24**, Et_2O.



Scheme 2.06 *Reagents and conditions:* a) i) LDA, THF, −78 °C. ii) $ClTi(O\text{-}iPr)_3$, −78 °C. iii) imine **2.24**, THF.

An alternative imino-aldol reaction was attempted between ester **2.26** and imine **2.24**. The functionalised side chain was compatible with the conditions of the reaction, however the diastereocontrol remained very low. Imino-aldol adduct **2.27** was isolated in 66% yield as a mixture of 4 diastereoisomers dr 60:20:17:3.[72] These two early examples of imino-aldol reactions of substrates containing azide and silylether groups in their side chains suggested that polar functionality led to diminished diastereoselectivity.

2.2.2 Origin of diastereoselectivity

The diastereoselectivity observed by Ellman *et al.* in the lithium and titanium enolate addition to *tert*-butanesulfinyl imines is consistent with a proposed Zimmerman-Traxler type six-membered transition state model (**Figure 2.02**).[74]

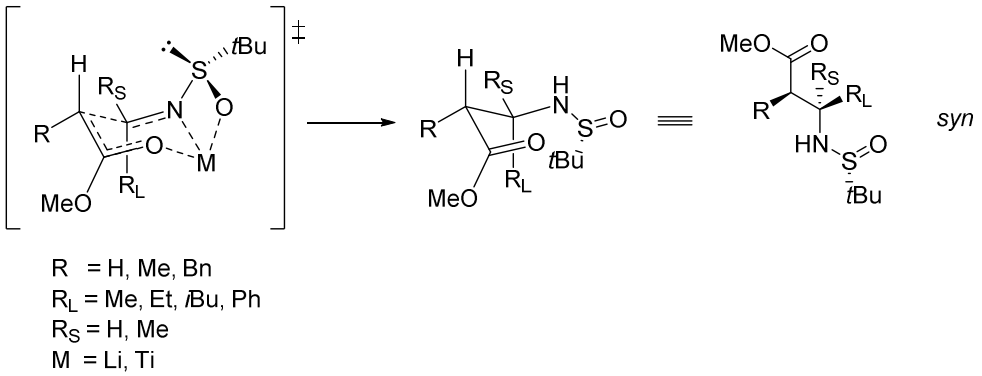


Figure 2.02 Proposed Zimmerman–Traxler transition state model for of the imino-aldol reaction.[72]

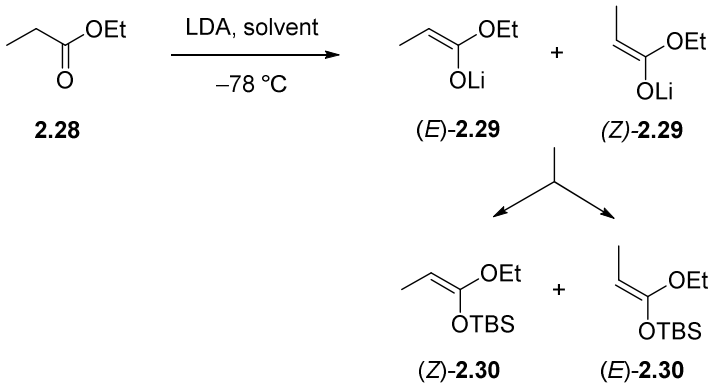
The key features of the transition state model are the placement of the bulky substituent (R_L) in an unexpected axial orientation, which is due to the *trans* geometry of the imine and metal chelation between the oxygen of the sulfinyl group and the nitrogen. The facial selectivity is given by the *tert*-butyl group, which shields the *Re*-face of the imine from reaction of the enolate. The major product obtained from closed chelation control is the so-called *syn* diastereoisomer.

2.2.3 Geometry of the ester enolates

The geometry of the enolate has an important role in the outcome of the reaction, despite this, the enolate geometry has not been closely studied for the imino-aldol reaction.

In the attempts to increase the stereochemical outcome of the ester enolate Claisen rearrangement, Ireland *et al.* showed that the origin of the metal counterion, solvent and

ratio between base:ester have an effect on the enolate geometry and implicitly on the outcome of the reaction while quenching with electrophiles (**Scheme 2.07**).[75-78]



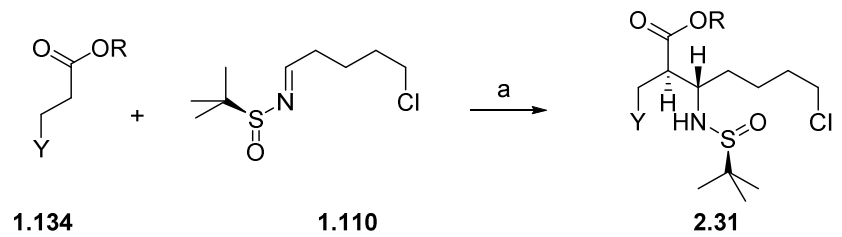
2.28 (*E*)-**2.29** (*Z*)-**2.29** (*Z*)-**2.30** (*E*)-**2.30**

Scheme 2.07 Silyl ketene acetal formation.

Deprotonation of ethyl propionate (**2.28**) with LDA in THF at −78 °C and subsequent treatment with TBSCl lead to the formation of silyl ketene acetal **2.30** as a mixture of diastereomers *dr* 6:94 in favour of product (*E*)-**2.30** (**Scheme 2.07**). A reverse in selectivity was obtained when 45% DMPU in THF was employed as solvent to furnish silyl ketone acetal **2.30** as a mixture of diastereomers *dr* 93:7 in favour of product (*Z*)-**2.30**. Ireland's assignment of the ratio of enolates *E/Z*-**2.29** and *E/Z*-**2.30** was confirmed by X-ray crystallography.[79,80] Heathcock and co-workers reported that deprotonation of methyl propionate with LDA at −78 °C gave a mixture of enolates *dr* 95:5 in favour of the *E*-isomer.[81]

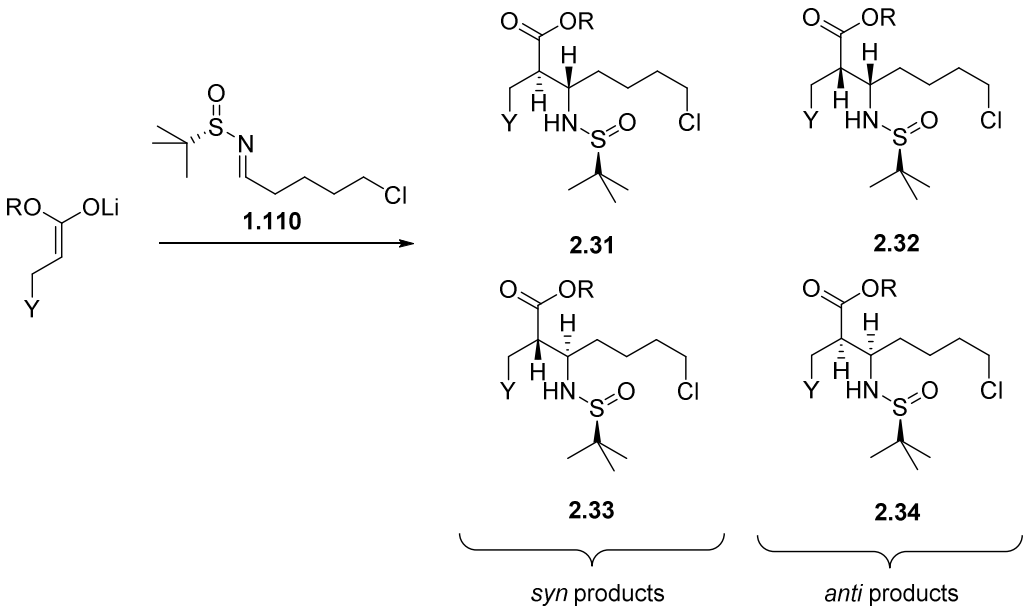
2.2.4 Results of the imino-aldol reaction

As discussed in the retrosynthetic analysis of sparteine described above, the initial objective of the current work was to investigate the imino-aldol reaction between sulfinyl imine **1.110** and various esters determining the diastereoselectivity and yield of the reaction in each case. Functional groups and chain lengths were chosen that would allow access to (−)-sparteine (**1.1**). With only two literature examples previously reported for such functionalised fragments, *β*-amino acids were synthesised derived from the methyl and phenyl esters.



Scheme 2.08 *Reagents and conditions:* a) i) LDA, THF, −78 °C. ii) imine **1.110**, THF.

Using methodology explored previously in the Brown group, deprotonation of esters **1.134** at −78 °C using LDA led to the formation of lithium enolates and subsequent addition to imine **1.110** accessed imino-aldol products with high levels of diastereocontrol (**Scheme 2.08**). The addition of lithium enolates to chiral imine **1.110** can result in four possible diastereomers: **2.31** (S_S,2*R*,3*S*), **2.33** (S_S,2*S*,3*R*) as *syn* adducts and **2.32** (S_S,2*S*,3*S*), **2.34** (S_S,2*R*,3*R*) as *anti* adducts (**Scheme 2.09**).



Scheme 2.09 Diastereomeric products from the imino-aldol reaction.

The stereochemistry of all imino-aldol adducts were tentatively assigned by analogy with the work previously reported for the synthesis of imino-aldol analogues with *syn* adduct **2.31** expected as the major product and *anti* adduct **2.32** as the minor product.[68,]

[69] During this study we focused on two main aspects of the imino-aldol reaction: diastereoselectivity and isolation of the diastereoisomeric products. In the first instance the objective was to determine whether lithium enolates generated from phenyl esters **1.134** would give higher diastereoselectivity compared to the methyl analogues. As anticipated from earlier studies in our laboratory, the selectivity of the imino-aldol reaction was significantly improved when phenyl ester derivatives were employed (Entries 5–8, **Table 2.03**), while the methyl ester derivatives gave moderate diastereoselectivity (Entries 1–4, **Table 2.03**). These results show that functionalised substrates can be coupled together in a highly diastereoselective imino-aldol reaction.

Entry	**R**	**Y**	Yield (%)	*dr*[a] (**2.31**:**2.32**:**2.33**:**2.34**)
1	Me	$(CH_2)_2$-SPh	92[b]	82:10:8:0
2	Me	$(CH_2)_2$-OTIPS	86[b] (18)[c]	80:13:7:0
3	Me	(CH_2)=CH_2	84[b]	85:7:8:0
4	Me	(CH_2)-CH=CH_2	83[b] (24)[c]	80:14:6:0
5	Ph	$(CH_2)_2$-OTIPS	63[c]	90:10:0:0
6	Ph	$(CH_2)_2$-SPh	71[c]	90:10:0:0
7	Ph	(CH_2)=CH_2	75[c,d]	91:9:0:0
8	Ph	(CH_2)-CH=CH_2	82[c,d]	95:5:0:0

[a] *dr* calculated by integration of NH peaks in crude ^{1}H NMR spectrum (400 MHz in $CDCl_3$).

[b] Yield of mixture diastereoisomers isolated by column chromatography.

[c] Yield of major isomer isolated by column chromatography.

[d] The stereochemistry of major diastereoisomer was determined by X-ray crystallography.

Table 2.03 Comparison of the diastereoselectivities observed in the imino-aldol reaction.

A second aspect of the imino-aldol reaction was the separation of the diastereomers. Methyl esters furnished *β*-amino acid derivatives, which were generally inseparable or partially separable giving the pure major diastereomer in very low yields (Entries 2, 4, **Table 2.03**). The major isomer was readily separable by flash chromatography with few mixed fractions when phenyl esters were employed for the synthesis of *β*-amino acid derivatives (Entries 5–8, **Table 2.03**).

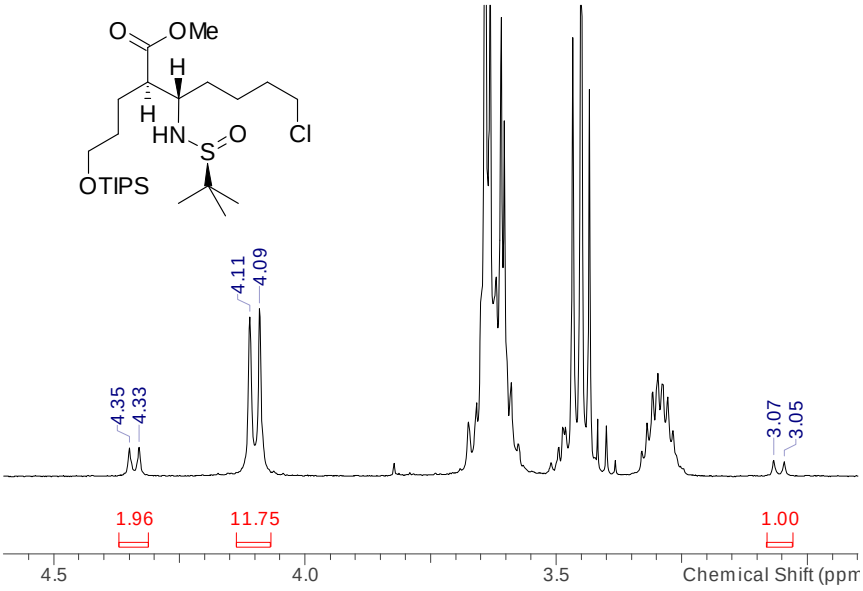


Figure 2.03 Comparison NH doublets in ^{1}H NMR spectra of the imino-aldol crude products.

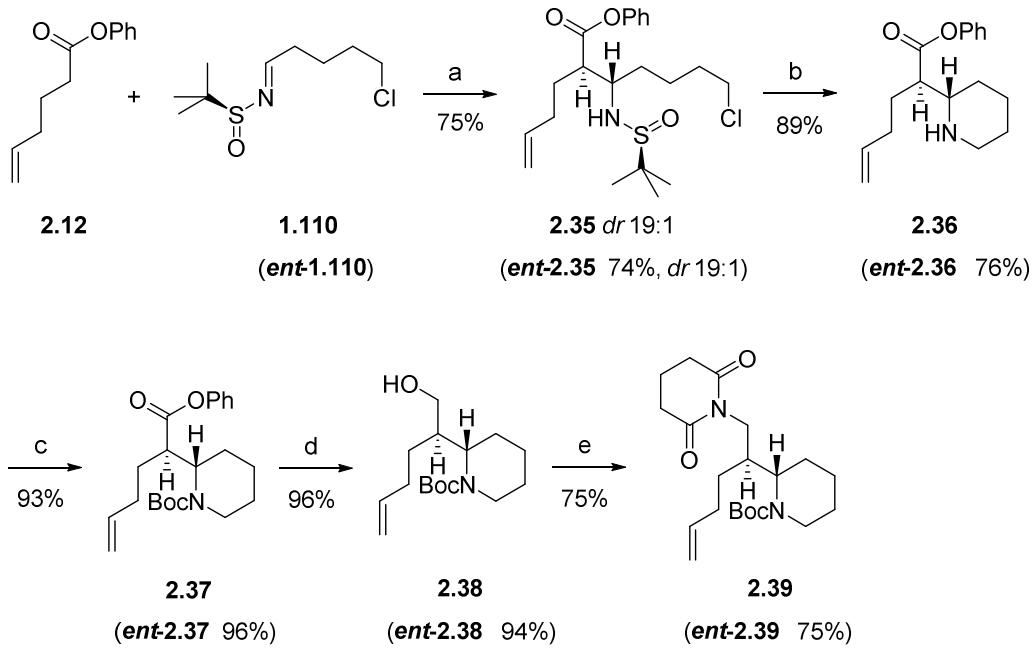
The *dr* of the imino-aldol products were identified by the comparison of the NH doublets from the crude ^{1}H NMR spectra (**Figure 2.03**). The doublet at 3.06 ppm corresponds to minor *syn* diastereoisomer **2.33** (S_S,2*S*,3*R*) which was not observed when lithium enolates generated from phenyl ester **1.134** was used (**Scheme 2.09**). The doublet at 4.10 ppm corresponds to major *syn* diastereoisomer **2.31** (S_S,2*R*,3*S*), whilst the doublet at 4.34 corresponds to *anti* diastereoisomer **2.32** (S_S,2*S*,3*S*).

These studies of the imino-aldol reaction and the previous work reported by Brown and co-workers demonstrated that the choice of ester and the metal counter ion are both important in achieving high stereoselectivity.

2.3 Towards the synthesis of (−)-sparteine

2.3.1 Synthesis of piperidine derivative 2.39

Using chemistry described above,[68,69] two functionalised fragments, ester **2.12** and imine **1.110**, were coupled together in a diastereoselective imino-aldol reaction to give *β*-amino acid derivative **2.35** in good yield and excellent diastereoselectivity *dr* 19:1[a] in the favour of the *syn* adduct (**Scheme 2.10**). The reaction was performed several times on multi-gramme scale to provide enough material to progress the synthesis. The sequence was also performed once using imine (***ent*-1.110**) bearing the enantiomeric chiral auxiliary (*R* configuration).



Scheme 2.10 *Reagents and conditions:* a) LDA, THF, −78 °C. b) i) conc. HCl, dioxane, rt. ii) K_2CO_3, NaI, MeCN, rt. c) Boc_2O, sulfamic acid, rt. d) $LiAlH_4$, THF, 0 °C to rt. e) DIAD, PPh_3, glutarimide, THF, rt.

[a] *dr* calculated by integration of NH peaks in crude ^{1}H NMR spectrum (400 MHz in $CDCl_3$).

The *N*-sulfinyl group was removed by treatment of imino aldol **2.35** with conc. HCl in dioxane, and the resulting crude ammonium salt was treated with excess of K_2CO_3 and NaI to access piperidine **2.36** (**Scheme 2.10**). Crude piperidine **2.36** was Boc protected using a procedure described by Cravotto[82] to access piperidine **2.37** in 81% yield over three steps. When piperidine **2.36** was purified by flash chromatography prior to Boc protection lower yields (10−20%) were obtained than for the one-pot deprotection/cyclication/Boc protection sequence. This decrease in the yield was attributed mainly to the basicity of the piperidine, leading to losses on the silica gel. Imino-aldol adduct **2.35** was recrystallised from hexane and the relative stereochemistry was ascertained by single crystal X-ray crystallography (**Figure 2.04**), thereby confirming the absolute stereochemistry.

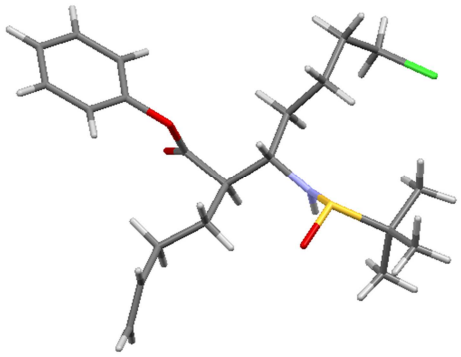


Figure 2.04 X-ray crystal structure of imino-aldol adduct **2.35**.

Compounds containing a *N*-Boc protecting group exhibited broadening of peaks in ^{1}H NMR and some of the peaks were not observed in ^{13}C NMR due to restricted rotation. To aid interpretation of the spectra for selected compounds variable temperature NMR experiments at T = 353 K and 373 K were conducted.

Reduction of the phenyl ester **2.37** in the presence of $LiAlH_4$ proceeded efficiently to access alcohol **2.38** in near-quantitative yield. Mitsunobu reaction of **2.38** and glutarimide led to the formation imide **2.39**. The conversion for this transformation was sensitive to solvent, dilution and number of equivalents of the reagents used. The highest yield was obtained when 2 equiv. of PPh_3, glutarimide and DIAD were employed in a reaction at a concentration 0.1 M of alcohol **2.38** in THF.

Glutarimide **2.39** was recrystallised from a mixture EtOAc/hexane and the relative stereochemistry was ascertained by single crystal X-ray crystallography (**Figure 2.05**).

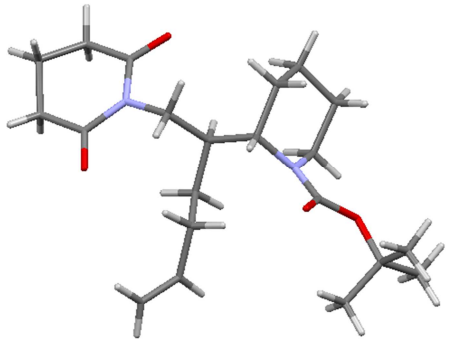
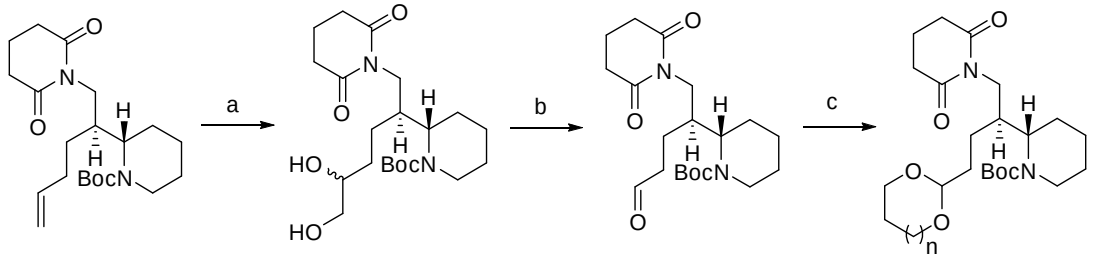


Figure 2.05 X-ray crystal structure of piperidine derivative **2.39**.

2.3.2 Synthesis of an *N*-acyliminium ion precursor

The functionalised imide **2.39** was successfully synthesised employing a Mitsunobu reaction in a concise fashion. The next step required unmasking of the latent aldehyde functionality by oxidative cleavage of the alkene (**Scheme 2.11**). Dihydroxylation of **2.39** to diol **2.40** and $NaIO_4$ cleavage proceeded smoothly in one-pot to access aldehyde **2.41** in 69% yield over two steps.



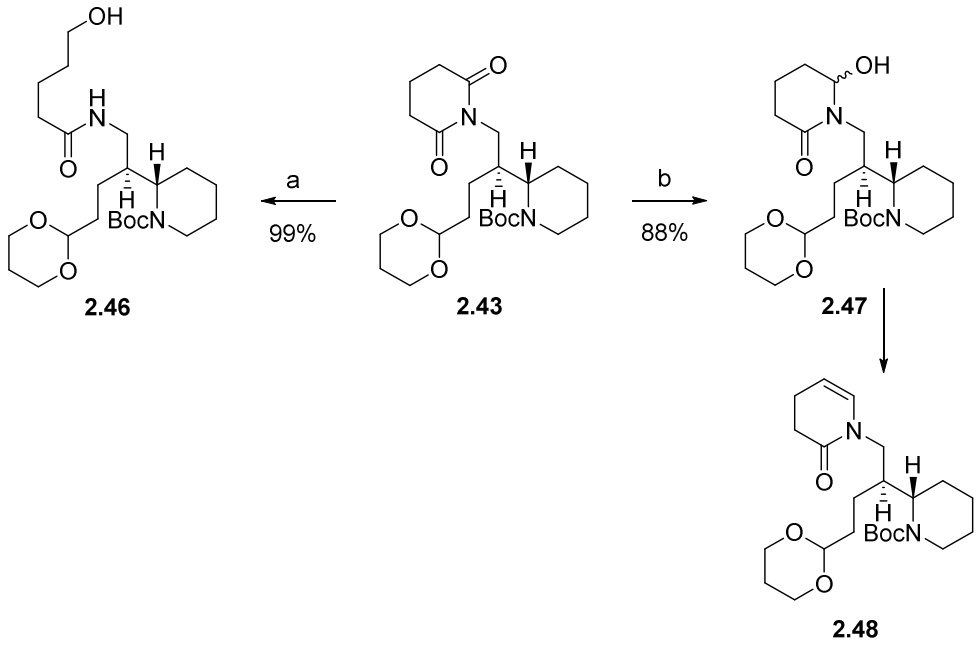
2.39 **2.40** (***ent*-2.40** 92%) **2.41** 69% (***ent*-2.41** 92%) **2.42** n = 0, 92% **2.43** n = 1, 96% (***ent*-2.43** n = 1, 84%)

Scheme 2.11 *Reagents and conditions:* a) $K_2OsO_4{\cdot}2H_2O$, NMO, CH_2Cl_2/H_2O, rt. b) $NaIO_4$, $MeOH/H_2O$, rt. c) TsOH, 1,2-ethanediol (**2.44**) or 1,3-propanediol (**2.45**), THF, rt.

When this transformation was performed stepwise with the isolation of the diol intermediate (***ent*-2.40**) and subsequent oxidative cleavage to access (***ent*-2.41**), the yield increased substantially. Acetalisation of **2.41** proceeded efficiently to access either dioxolane **2.42** or dioxane **2.43** in high yields.

2.3.3 Accessing *N*-acyliminium ion cyclisation precursors

With precedent in the literature for the reduction of the imide, we focused on completing the final steps which would lead us to the synthesis of (–)-sparteine. Initial attempts to reduce the glutarimide **2.43** had been made employing $NaBH_4$ as reducing agent.[83,84] The large excess of the borohydride used in the reaction caused over-reduction of the hydroxy lactam **2.47** to afford the undesired alcohol **2.46** in quantitative yield (**Scheme 2.12**).



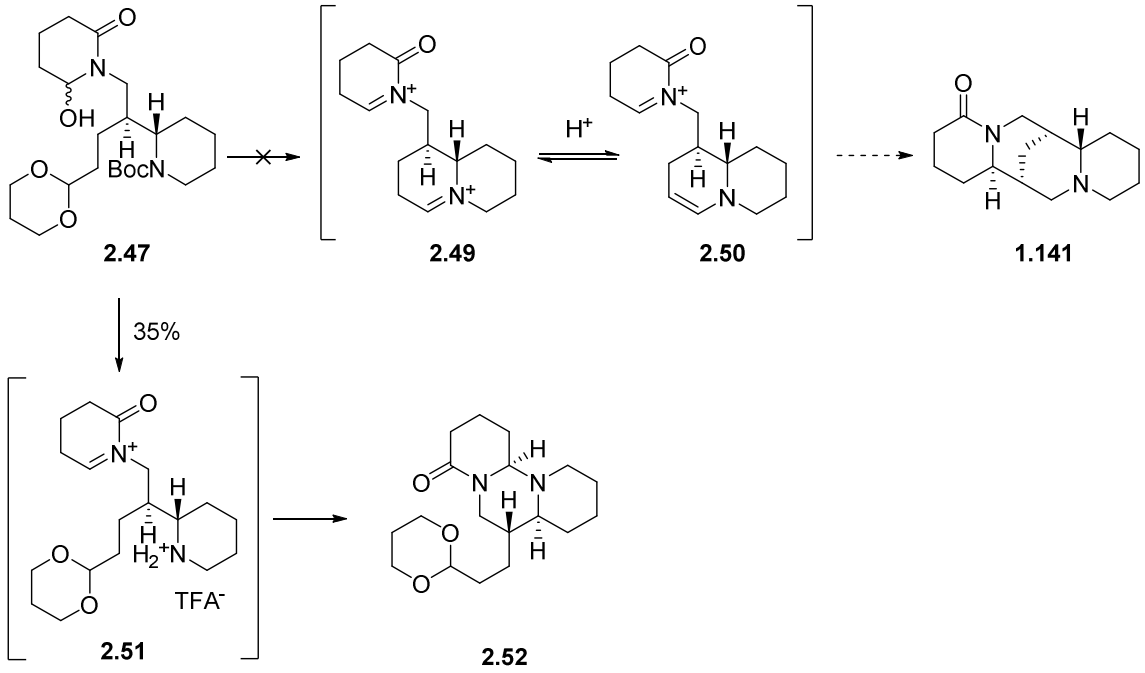
Scheme 2.12 *Reagents and conditions:* a) $NaBH_4$, CH_2Cl_2, rt. b) i) $LiEt_3BH$, CH_2Cl_2, −78 °C. ii) 1 M HCl/EtOH, −20 °C to rt.

Utilising an procedure adapted from Grigg and co-workers,[85] glutarimide **2.43** was successfully reduced to the corresponding hydroxylactam **2.47** with high conversion by

using $LiEt_3BH$ (1.2 equiv.) at −78 °C in CH_2Cl_2. Reaction monitoring by TLC was tedious; aliquots were taken from reaction mixture each half an hour and quenched with 1 M HCl/EtOH. When starting material was consumed, the reaction mixture was allowed to warm to −20 °C and quenched with 1 M HCl/EtOH before allowing the reaction to warm slowly to rt. Employing this methodology, *N*-acyliminium precursor **2.47** was isolated in 88% yield as a 1:1 mixture of epimers, which was used in the next steps without need for further purification. A small quantity of the dehydrated product, the enecarbamate **2.48** was observed when hydroxylactam **2.47** was stored prior to use (**Scheme 2.12**).

2.3.4 Brønsted acid promoted *N*-acyliminium ion cyclisation

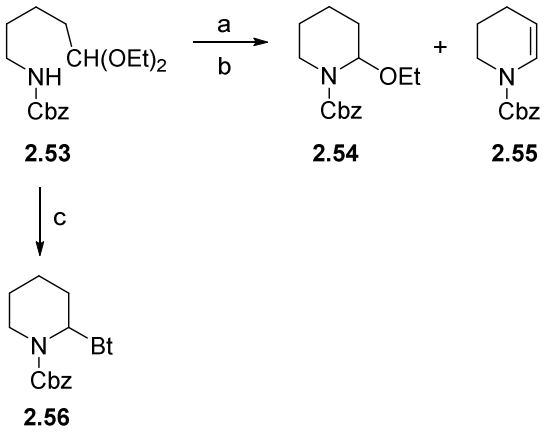
With the desired *N*-acyliminium precursor synthesised in a straightforward manner, we turned our attention to identify conditions to induce one-pot deprotection/cyclisation to the desired compound **1.141** (**Scheme 2.13**). The sequence of these transformations requires in the first instance Boc deprotection to obtain the quaternary ammonium salt and acetal deprotection. Piperidine condensation onto the aldehyde would lead to the formation of iminium **2.49** which we expected to be in equilibrium with its tautomeric enamine **2.50**. Under acidic conditions, an *N*-acyliminium ion will be generated *in situ* and a final intramolecular cyclisation of the enamine will furnish the desired tetracyclic adduct **1.141**.



Scheme 2.13 *Reagents and conditions:* a) TFA, CH_2Cl_2, 0 °C to rt.

Unfortunately, whilst treatment of **2.47** with TFA afforded Boc deprotection and generated the *N*-acyliminium ion *in situ*, the desired intramolecular cyclisation was unsuccessful. The acetal protecting group was still present and intramolecular cyclisation of the nitrogen occurred at the *N*-acyliminium ion leading to the formation of the tricyclic adduct **2.51** as a single isomer.

With no evidence of the desired cyclisation using hydroxylactam **2.47**, we turned our attention to aldehyde **2.41** which could be a useful precursor to the desired quinolizidine. We were attracted to a literature procedure as described by Hiemstra *et al*. in which BtH was used for *in situ* iminium trapping leading to stable piperidine derivatives (**Scheme 2.14**).[86]

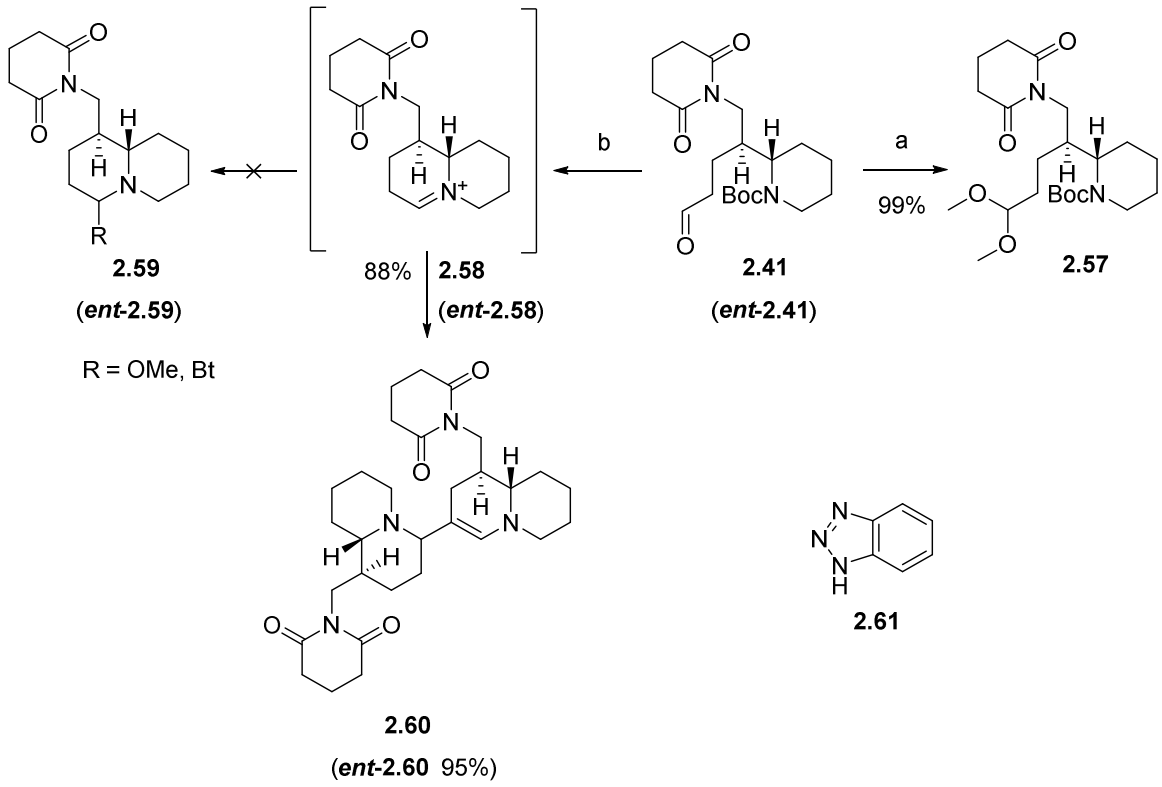


Scheme 2.14 *Reagents and conditions:* a) TsOH, CH_2Cl_2, rt. b) TsOH, CH_2Cl_2/EtOH (2:1), rt. c) i) TsOH, CH_2Cl_2, rt. ii) BtH, CH_2Cl_2, rt.

Addition of TsOH as a catalysts to acetal **2.53** in CH_2Cl_2 afforded *N,O*-acetal **2.54** with partial formation of the undesired dehydration product, enamide **2.55** in a ratio 1:2. Using a CH_2Cl_2/EtOH solvent mixture increased the ratio to 6:1. Nevertheless, the isolation *N,O*-acetal **2.54** proved to be extremely difficult giving mainly enamide **2.55** after column chromatography. Treatment of acetal **2.53** with catalytic TsOH followed by the addition of an excess benzotriazole accessed the benzotriazole derivative **2.56** in 88% yield.

We hypothesised that treatment of the glutarimide derivative **2.41** with various Brønsted acids such TFA, TfOH, or TsOH would provide Boc deprotection and subsequent intramolecular condensation would give quinolizidine derivative **2.58** (**Scheme 2.15**). Quenching intermediate **2.58** with 1*H*-benzotriazole (**2.61**) or various alkoxy species would allow access to quinolizidine derivative **2.59** which could be isolated. Disappointingly, when acids were added to a solution of **2.41** in THF/MeOH, no Boc

deprotection was observed. Instead acetalisation of the aldehyde **2.41** with MeOH was observed to furnish acetal **2.57** in variable yields dependant on whether crude material was purified by flash chromatography or crystallised from hexane (Entries 1−3, **Table 2.04**).



Scheme 2.15 *Reagents and conditions:* a) TFA, THF/MeOH, 0 °C to rt. b) i) TFA, CH_2Cl_2, 0 °C to rt. ii) BtH, CH_2Cl_2, 0 °C to rt.

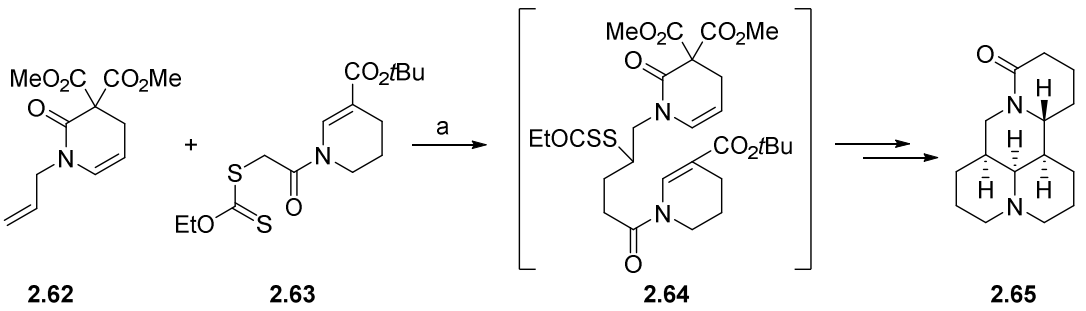
Entry	Acid	Solvent	Product	Yield (%)
1	TFA	THF/MeOH	**2.57**	99
2	TfOH	MeOH	**2.57**	43
3	TsOH	THF/MeOH	**2.57**	48
4	TFA	CH_2Cl_2	***ent*-2.60**	95

Table 2.04 Outcome from the Brønsted acid cyclisation.

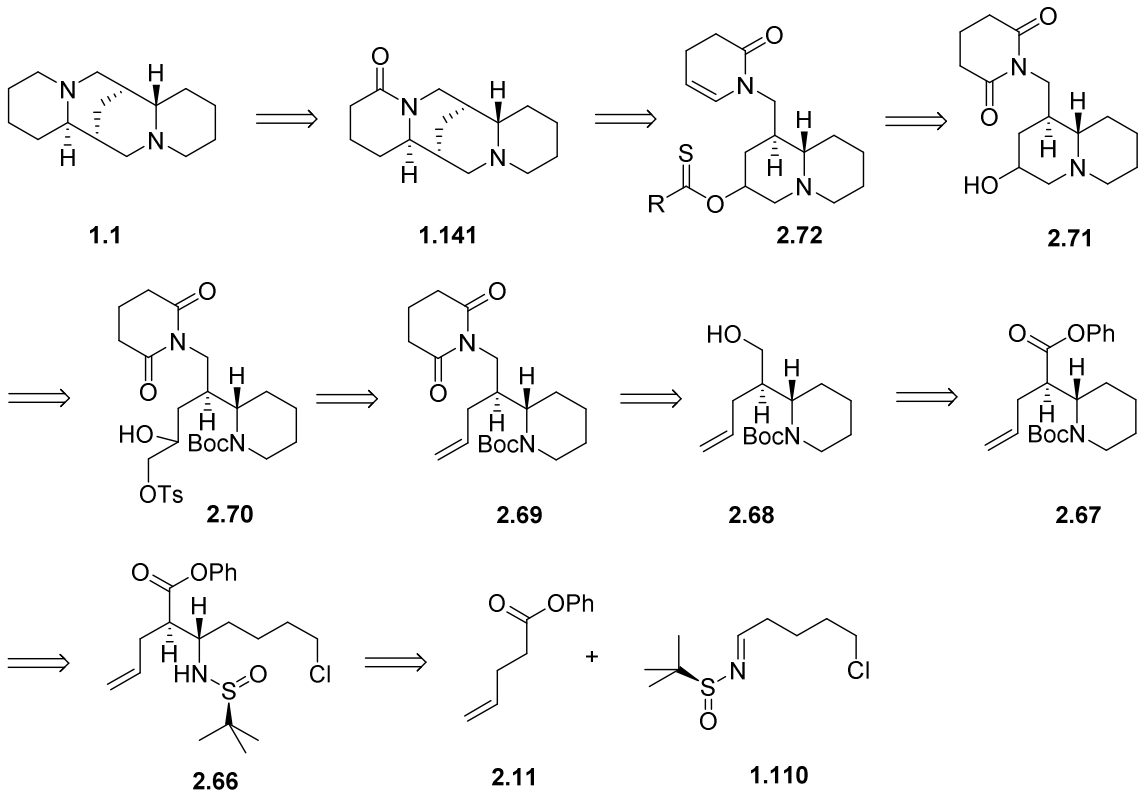
We believe that the presence of the protic solvent interfered with the deprotection step and as a result we decided to investigate the reaction in a non-polar solvent. Boc deprotection using TFA in CH_2Cl_2 gave the quaternary ammonium salt and subsequent treatment with either excess MeOH or benzotriazole did not proceed with the formation of quinolizidine derivatives **2.59** after neutralisation with saturated aqueous $NaHCO_3$ (**Scheme 2.15**). Instead, iminium **2.58** underwent dimerisation to form quinolizidine derivative **2.60**. We suspected that saturated aqueous $NaHCO_3$ may have a role in the dimerisation process and as a consequence the crude mixture was concentrated and purified by column chromatography without basic quench, but the result was the same.

2.4 Alternative approach for the cyclisation

With the quinolizidine derivatives not able to provide the desired cyclisation, we decided to investigate an alternative approach. We felt that we should investigate the radical cyclisation reported by Zard *et al.*[87] for the synthesis of (±)-matrine (**2.65**) (**Scheme 2.16**) to obtain the tetracyclic adduct **1.141** (**Scheme 2.17**).



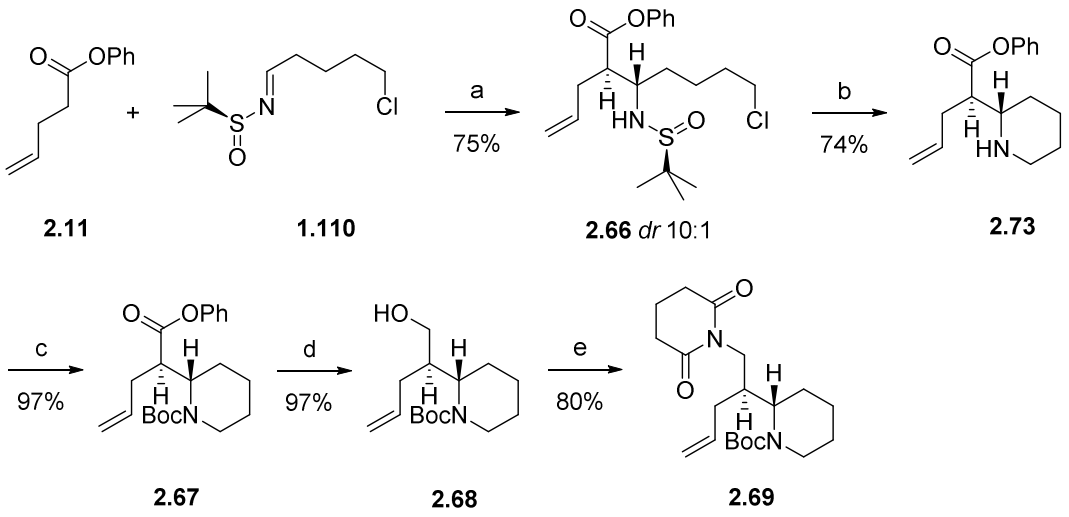
Scheme 2.16 Key cyclisation step towards (±)-matrine. *Reagents and conditions:* a) i) Lauroyl peroxide, C_6H_6. ii) 2-propanol, Δ.



Scheme 2.17 New synthetic approach to (−)-sparteine.

In our new approach to (−)-sparteine, we were looking to keep the general strategy described in the previous retrosynthesis with few modifications. A diastereoselective imino-aldol between ester **2.11** and imine **1.110** would allow access to imino-aldol **2.66**. Deprotection, piperidine formation and suitable protection would allow access to ester **2.67**. Reduction to alcohol **2.68** and subsequent Mitsunobu reaction with glutarimide would allow access to imide **2.69**. Dihydroxylation of alkene **2.69** followed by tosyl protection of the primary alcohol would access piperidine **2.70**. Boc deprotection and nucleophilic substitution would furnish a highly functionalised quinolizidine **2.71**. Employing the same chemistry as before, reduction of glutarimide **2.71** followed by dehydration and xanthate formation would lead to the radical precursor **2.72**. Radical cyclisation involving atom or hydrogen transfer would access (+)-lupanine (**1.141**). Final reduction of the tetracyclic compound **1.141** would furnish (−)-sparteine.

2.4.1 Synthesis of piperidine derivative 2.69



Scheme 2.18 *Reagents and conditions:* a) LDA, THF, −78 °C. b) i) conc. HCl, dioxane, rt. ii) K_2CO_3, NaI, MeCN, rt. c) Boc_2O, sulfamic acid, rt. d) $LiAlH_4$, THF, 0 °C to rt. e) DIAD, PPh_3, glutarimide, THF, rt.

The synthesis commenced with the imino-aldol reaction. The first C—C bond-forming step of the new approach involved the addition of lithium enolate of ester **2.11** to *tert*-butanesulfinyl imine **1.110**, a reaction previously studied in the imino-aldol model studies. Imino-aldol reaction between ester **2.11** and imine **1.110** was performed on multi-gramme scale to furnish *syn* β-amino acid derivative **2.66** in 75% yield and good diastereoselectivity *dr* 10:1[a] (**Scheme 2.18**).

[a] *dr* calculated by integration of NH peaks in the crude ^{1}H NMR spectrum (400 MHz in $CDCl_3$).

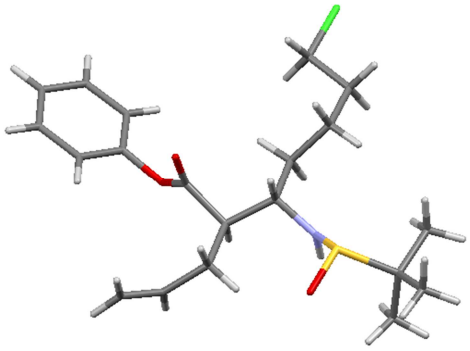


Figure 2.06 X-ray crystal structure of imino-aldol adduct **2.66**.

Imino-aldol product **2.66** could be recrystallised from hexane and the absolute stereochemistry was confirmed by single crystal X-ray structure determination (**Figure 2.06**). The *N*-sulfinyl group was removed by acid treatment and the resulting crude ammonium salt was treated with excess of K_2CO_3 and NaI to access piperidine **2.73**. Piperidine **2.73** was Boc protected using a procedure described by Cravotto[82] to access piperidine **2.67** in 97% yield. Reduction of the ester **2.67** in the presence of $LiAlH_4$ proceeded efficiently to access alcohol **2.68** in quantitative yield. Mitsunobu reaction of **2.68** and glutarimide led to the formation of functionalised piperidine **2.69**. Piperidine **2.69** could be recrystallised from a mixture of EtOAc/hexane and the relative stereochemistry was confirmed by single crystal X-ray crystallography (**Figure 2.07**).

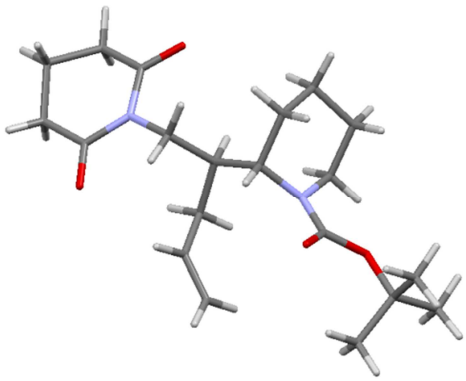
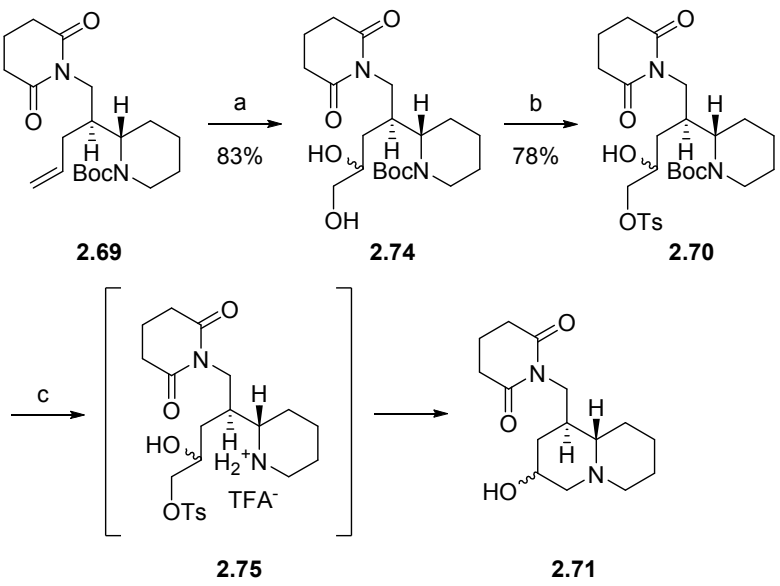


Figure 2.07 X-ray crystal stucture of piperidine derivative **2.69**.

2.4.2 Synthesis of quinolizidine derivative 2.71



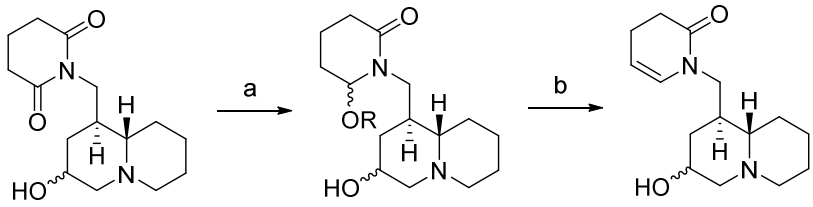
Scheme 2.19 *Reagents and conditions:* a) $K_2OsO_4 \cdot 2H_2O$, NMO, CH_2Cl_2/H_2O, rt. b) TsCl, Bu_2SnO, Et_3N, THF/CH_2Cl_2, rt. c) i) TFA, CH_2Cl_2, 0 °C to rt. ii) DBU, CH_2Cl_2, 0 °C to rt.

Dihydroxylation of olefin **2.69** led to the formation of diol **2.74** as an inseparable mixture of two diastereomers *dr* 1:1[a] and subsequent monoprotection furnished tosylate **2.70** in 65% yield over two steps (**Scheme 2.19**). Deprotection of piperidine **2.70** in the presence of TFA afforded the piperidine TFA salt **2.74**. Initial cyclisation attempts were performed by addition of saturated aqueous $NaHCO_3$ to crude ammonium salt furnishing the cyclised quinolizidine **2.71** in 59% yield as an inseparable mixture of two diastereomers *dr* ~ 1:1.[b] Pleasingly the desired cyclisation was improved by using an excess of DBU to secure quinolizidine **2.71** in 94% yield. When performing flash chromatography on quinolizidine **2.71** highly polar eluent systems were required: 35% NH_4OH/MeOH/EtOAc.

[a,b] *dr* calculated from isolated mixture of epimers using ^1H NMR spectroscopy (400 MHz in $CDCl_3$).

2.4.3 Xanthate formation

Having synthesised the quinolizidine derivative **2.71** in a concise fashion, efforts were focused on the final steps of the synthesis. The next planned sequence was the introduction of a xanthate derivative which could provide a good approach to the tetracyclic framework of (−)-sparteine. The formation of the C—C bond would be achieved using radical chemistry developed by Zard and co-workers, and applied in a radical cascade sequence for the synthesis of (±)-matrine.[87]



Scheme 2.20 *Reagents and conditions:* a) i) $LiEt_3BH$, CH_2Cl_2, −78 °C. ii) 1 M HCl/EtOH, −20 °C to rt. b) NH_4Cl, toluene, Δ.

Using the chemistry employed in the synthesis of **2.47**, imide **2.71** was reduced using $LiEt_3BH$ at −78 °C to afford hydroxy and ethoxy lactam derivatives **2.76** and **2.77** (**Scheme 2.20**).

Entry	Quenching conditions	Product	Yield (%)
1	sat. aq. $NaHCO_3$	**2.76**	30
2	$NaHCO_3$	**2.77**	55

Table 2.05 Outcomes of super hydride reduction of **2.71**.

Each compound was isolated as an inseparable mixture of four diastereoisomers. The conversions to hydroxy lactam **2.76** or ethoxy lactam **2.77** were dependent on the quenching conditions (**Table 2.05**). Initially, the reaction was quenched by addition of

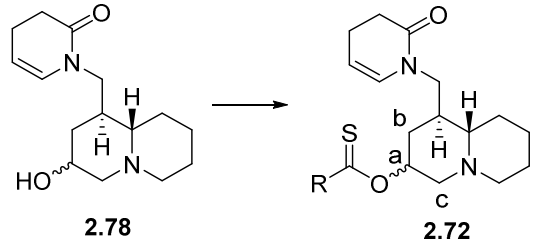
saturated aqueous $NaHCO_3$ to afford lactam **2.76** in 30% yield (Entry 1, **Table 2.05**). When the crude reaction mixture obtained from the imide reduction was quenched with solid $NaHCO_3$ or K_2CO_3 ethoxy lactam **2.77** was isolated in 55% yield (Entry 2, **Table 2.05**). The conversions were very low, and the main issue was purification which required highly polar solvent eluent systems. Furthermore, the hydroxy lactam **2.76** is extremely soluble in water hampering efficient extraction. We decided to adopt an alternative strategy, which required a one-pot imide reduction/dehydration to access **2.78**. Using chemistry reported by Onomura,[88,89] the crude material obtained from the reduction of imide **2.71** was rapidly dehydrated in refluxing toluene using NH_4Cl to access quinolizidine **2.78** in 74% yield as an inseparable mixture of two diastereoisomers *dr* ~ 1:1.[a,b]

[a] *dr* calculated from isolated mixture of epimers using LC-MS.

[b] *dr* calculated from isolated mixture of epimers using ^{1}H NMR spectroscopy (500 MHz in $CDCl_3$).

Since the introduction of the xanthate on a quinolizidine derivative was not well documented we turned our attention to the synthesis of simple xanthates and applied these strategies to our need (**Table 2.06**).[90-92] Deprotonation of alcohol **2.78** using NaH followed by the addition of carbon disulphide led to formation of the dithionocarbonate anion, which was subsequently quenched with MeI to furnish xanthate **2.79**.[93]

This reaction was attempted several times using dry reagents with the isolation of the desired *O*-alkyl-*S*-methyl xanthate in very low yields (Entry 1, **Table 2.06**).



Scheme 2.21 Xanthate formation.

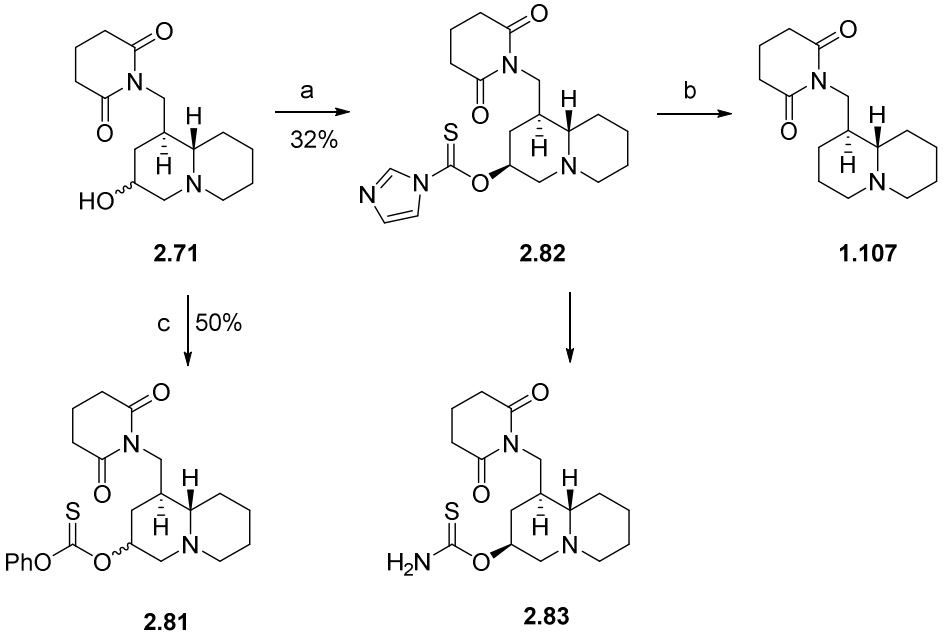
Entry	R	Product	Conditions	Yield (%)
1	SMe	**2.79**	NaH, CS_2, MeI, CH_2Cl_2, 0 °C to rt.	15
2	SMe	**2.79**	Cs_2CO_3, TBAI, CS_2, MeI, DMF, rt.	–
3	Imidazole	**2.80**	Thiocarbonyldiimidazole, DMAP, rt.	48

Table 2.06 Conditions for xanthate formation.

We also explored methodology described by Jung *et al*. for xanthate synthesis.[91,92] Alcohol **2.78** was treated with CS_2 in the presence of Cs_2CO_3, TBAI and MeI but the formation of xanthate **2.79** was unsuccessful. Treatment of alcohol **2.78** with DMAP and excess thiocarbonyldiimidazole led to the formation of *S*-imidazole xanthate **2.80** in 48% (Entry 3, **Table 2.06**). A close inspection to ^{1}H and ^{13}C NMR data shown that the xanthate **2.80** with H_a axial was isolated as the only product. Two vicinal coupling constants to H_a were measured which corresponded to an axial-axial ($^3J_{ab}$ = 10.4 Hz and $^3J_{ac}$ = 11.5 Hz) couplings.

2.4.4 Total synthesis of (−)-lamprolobine

Having successfully synthesised quinolizidine intermediate **2.71**, Barton-McCombie deoxygenation reaction from a xanthate derivative would allow access to (−)-lamprolobine (**1.107**) (**Scheme 2.22**).[94,95]



Scheme 2.22 *Reagents and conditions:* a) DMAP, thiocarbonyldiimidazole, CH_2Cl_2, 0 °C to rt. b) AIBN, TTMSS, toluene, Δ. c) DMAP, *O*-phenyl chlorothionoformate, CH_2Cl_2, 0 °C to rt.

Using a procedure previously employed in our laboratory,[96] alcohol **2.71** was alkylated with *O*-phenyl chlorothionoformate to furnish **2.81** in 50% yield as an inseparable mixture of diastereoisomers *dr* ~ 2:1[a] (**Scheme 2.22**). Alkylation of **2.71** with excess thiocarbonyldiimidazole afforded xanthate derivative **2.82**. The reaction was monitored by TLC and upon completion the crude was concentrated and purified by flash chromatography. Disappointingly, only one diastereoisomer was isolated in 32% yield.

[a] *dr* calculated from isolated mixture of epimers using LC-MS.

Purification of imidazole derivative **2.82** using 35% NH_4OH/MeOH/EtOAc led to the formation of xanthate by-product **2.83** in 31% as a single isomer. Since the purification and work-up conditions affected the outcome of the reaction, we decided to investigate a one-pot process to access (−)-lamprolobine (**1.107**). Xanthate derivative **2.82** was furnished using 1.5 equiv. of the thiocarbonyldiimidazole and subsequent microwave irradiation at 90 °C of the crude material using AIBN and TTMSS as source of hydrogen secured the synthesis of (−)-lamprolobine (**1.107**) in 82% yield over the two steps (**Scheme 2.22**). The total synthesis of the natural product was achieved in 12 linear steps and 21% yield.

Since the natural product was previously synthesised in our research group, we were able to compare the spectroscopic and physical data with that[70] and with literature values recorded for (+)-lamprolobine.[97-99] The optical rotation and the spectral data for our synthetic (−)-lamprolobine were in in excellent agreement with the values previously reported (**Table 2.07** and **Table 2.08**).

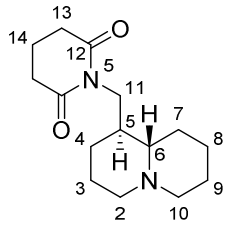


Figure 2.08 (−)-Lamprolobine.

	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14
Lit.[a]	56.7	24.4	27.9	39.3	66.5	29.4	24.6	25.4	56.3	41.5	172.7	33.0	17.2
Lab.[b]	56.7	24.4	27.9	39.4	66.4	29.5	24.7	25.5	56.3	41.4	172.6	32.9	17.1
Obs.	56.8	24.5	28.0	39.5	66.4	29.6	24.8	25.6	56.4	41.6	172.7	32.9	17.2

Table 2.07 ^{13}C NMR spectra of (−)-lamprolobine**.**

[a] Ref[99], ^{13}C NMR spectrum (300 MHz in $CDCl_3$).

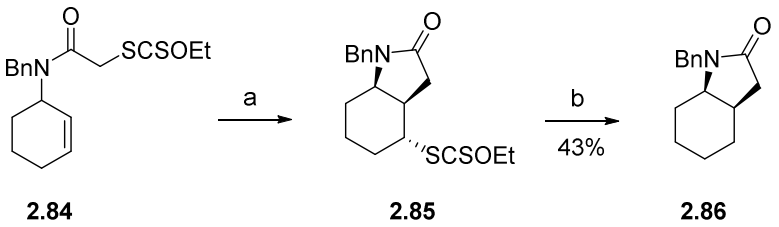
[b] Ref[70], ^{13}C NMR spectrum (400 MHz in $CDCl_3$).

	Optical rotation
Lit.[97]	$[\alpha]_D$: +29.0 (1.50, EtOH)
Lab.[70]	$[\alpha]_D$: −28.9 (1.10, $CHCl_3$, 24 °C)
Obs.	$[\alpha]_D$: −29.0 (1.06, $CHCl_3$, 24 °C)

Table 2.08 Optical rotation (−)-lamprolobine.

2.4.5 Radical approaches to the tetracycles

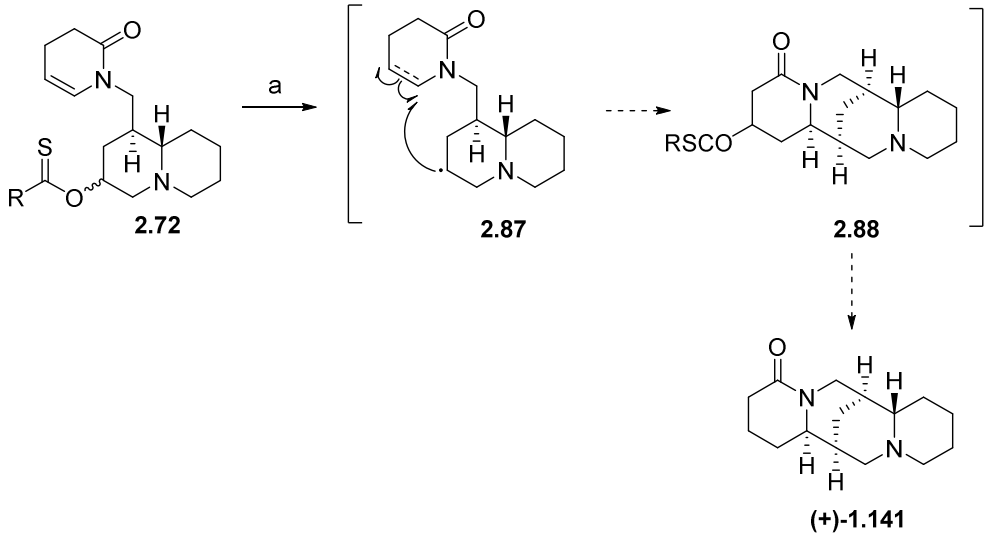
With limited quantities of xanthates **2.79** and **2.80** in hand, we had to be selective on the conditions for the radical cyclisation. Literature precedent for the intramolecular radical cyclisation using xanthates and different peroxides to form bicyclic rings gave encouragement to achieve the tetracyclic skeleton.[100-102]



2.84 **2.85** **2.86**

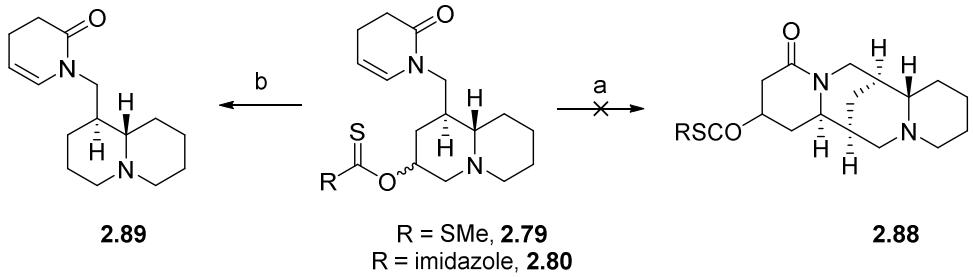
Scheme 2.23 *Reagents and conditions:* a) Di-benzoyl peroxide, C_6H_6, Δ, b) Bu_3SnH, AIBN, C_6H_6, Δ.

In a model study, heating xanthate **2.84** in benzene in the presence of initiators di-benzoyl peroxide or di-lauroyl peroxide in sub-stoichiometric amounts accessed lactam **2.85** as a single isomer (**Scheme 2.23**). The xanthate group was removed in the presence of Bu_3SnH to give lactam derivatives **2.86** in 43% yield over two steps.



Scheme 2.24 *Reagents and conditions:* a) i) Di-benzoyl peroxide, C_6H_6, Δ, ii) Bu_3SnH, AIBN, C_6H_6, Δ.

We hypothesised that treatment of xanthate derivatives **2.72** with catalytic peroxide initiator would generate radical precursor **2.87**, which would undergo intramolecular addition to enecarbamate in a stereoselective manner to access intermediate **2.88**. Final reduction using Bu_3SnH or 2-propanol would secure (+)-lupanine (**1.141**) (**Scheme 2.24**).



Scheme 2.25 Attempted radical cyclisations.

Entry	Starting material	Conditions	Yield (%)
1	**2.79**	di-lauroyl peroxide, C_6H_6, Δ.	−
2	**2.80**	di-lauroyl peroxide, C_6H_6, Δ.	−
3	**2.80**	AIBN, TTMSS, MW (1 h, C_6H_6, 90 °C).	76

Table 2.09 Results from radical cyclisation.

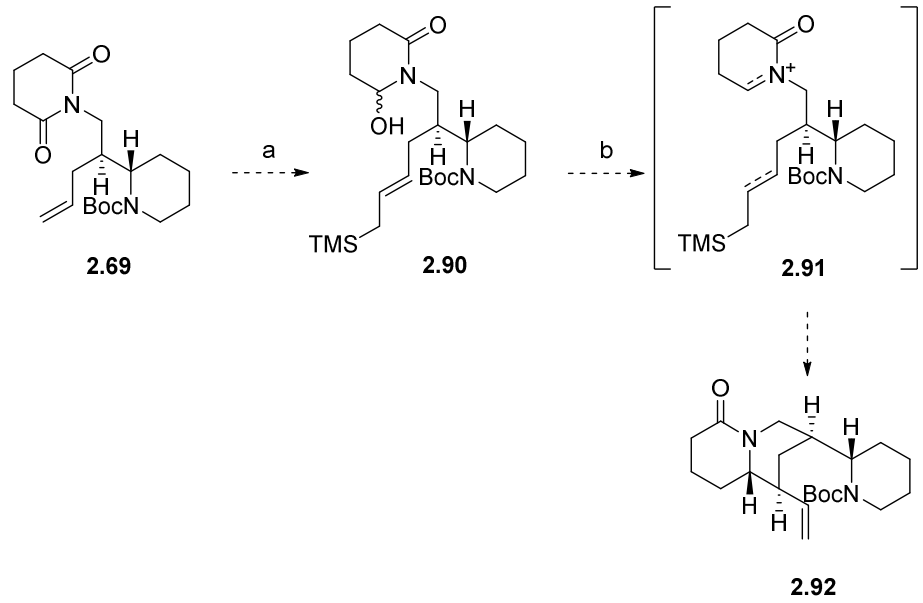
Unfortunately when xanthate derivatives **2.79** and **2.80** were refluxed in benzene employing sub-stoichiometric lauroyl peroxide no intramolecular cyclisation took place (**Scheme 2.25**). Furthermore, degradation of the starting material during the reaction prevented recovery of any identifiable material. Under standard deoxygenation conditions **2.89** was obtained in 76% yield (Entry 3, **Table 2.09**). The unsuccessful cyclisation attempts may be explained by the inability of the quinolizidine radical intermediate to adopt a suitable conformation to allow cyclisation, combined with a lack of robustness of the substrate leading to degradation pathways in the absence of a radical trap.

2.4.6 Synthesis of allylsilane derivatives as alternate cyclisation precursors

From the attempted radical cyclisation we recognised that cyclisations from a fused quinolizidines were not easy to accomplish and we decided to investigate and alternative approach using a less hindered substrate. We decided to introduce an

allylsilane functionality as a nucleophilic species; a strategy exploited within the synthesis of (+)-allomatrine (**1.106**) from this laboratory.[69] Moreover, the literature precedent for the addition of allylsilanes to *N*-acyliminium ions gave us encouragement to complete the synthesis.[103-108]

We felt that incorporating the allylsilane into a previous precursor synthesised for the radical approach could provide a successful cyclisation. A cross-metathesis between alkene **2.69** and allyltrimethylsilane (ATMS) followed by selective reduction of the imide would allow access to the desired cyclisation precursor **2.90** (**Scheme 2.26**). Treatment of **2.90** with TFA would access the *N*-acyliminium ion and activate the allylsilane nucleophile towards a stereoselective cyclisation to access quinolizidine **2.92.**



Scheme 2.26 *Reagents and conditions:* a) i) Grubbs II (**2.94**) (10 mol %), ATMS, Δ. ii) $LiEt_3BH$, CH_2Cl_2, −78 °C. iii) 1 M HCl/EtOH, −20 °C to rt. b) TFA, CH_2Cl_2, 0 °C to rt.

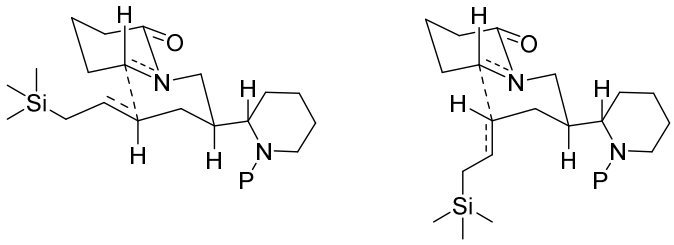


Figure 2.09: Expected cyclisation modes proceeding by chair-like transition states.

The first synthetic challenge of the new approach was to incorporate the allylsilane *via* cross metathesis into one of the intermediates previously synthesised. Two CM catalysts were applied to effect the desired metathesis: Hoveyda-Grubbs II (**2.93**) and Grubbs II (**2.94**) (**Figure 2.10**).

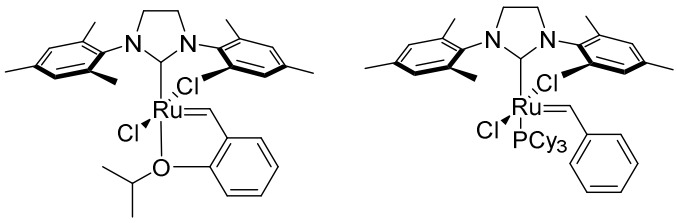
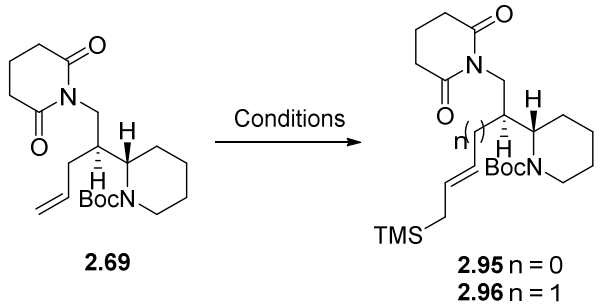


Figure 2.10: Ruthenium metathesis catalysts.



Scheme 2.27 Attempted cross metathesis of alkene **2.69**.

Entry	Conditions	Yield (%)
1	**2.93**, MW (2 h, CH_2Cl_2, 80 °C).	27
2	**2.93**, CH_2Cl_2, 16 h, Δ.	34
3	**2.94**, CH_2Cl_2, 16 h, Δ.	–

Table 2.10 Cross metathesis reactions of **2.69**.

Exposure of **2.69** to Grubbs II (**2.94**) under microwave irradiation for 2 h in CH_2Cl_2 did not afford the cross metathesis product; rapid degradation of the catalyst was observed which made the recovery of any identifiable material impossible.

Treatment of alkene **2.69** with catalyst **2.93** afforded a mixture of cross metathesis products **2.95** and **2.96** in 27% yield in a 2:1 ratio in favour of the undesired allylsilane derivative **2.95** (Entry 1, **Table 2.10**). Exposure of **2.69** to Hoveyda-Grubbs II (**2.93**) for a longer period of time afforded allylsilane **2.95** in 34% yield. It has been reported that amides and carbamates can chelate ruthenium species resulting in inhibition of the CM or generally slowing down the metathesis process.[109,110] Some solutions have been proposed which require addition of a Lewis acid before the catalyst is added, which may supress chelation.[109,111] The isomerisation of the alkene could be the reason for a non-productive catalytic cycle in the presence of the amides as previously observed by Miller and co-workers.[112] However, we believe that steric hindrance of the alkene could be the main reason of failure for the CM giving time for catalyst degradation, and subsequent isomerisation pathways.

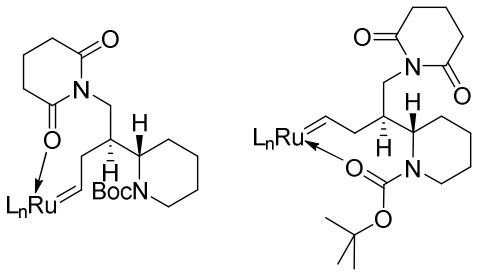
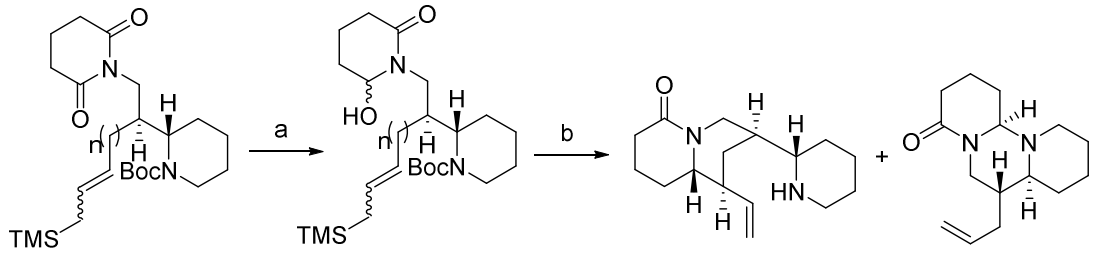


Figure 2.11: Possible chelation of ruthenium carbene.

At this point, we were unable to test the cross metathesis reaction in the presence of Lewis acids since limited amounts of the **2.69** were available. An inseparable mixture of allylsilane derivatives obtained from CM was taken forward in the synthesis. Selective reduction of **2.95** and **2.96** using $LiEt_3BH$ afforded a crude mixture of the hydroxy lactams **2.97** and **2.98** which were subsequently treated with $BF_3{\cdot}OEt_2$ to afford quinolizidine **2.99** and pyrimidinone derivative **2.100** (**Scheme 2.28**). On exposure to the $BF_3{\cdot}OEt_2$, Boc deprotection took place to afford the free amine which attacked the *N*-acyliminium ion to obtain **2.100**. The allylsilane cyclisation to *N*-acyliminium ion was faster from hydroxylactam **2.98** compared with the competitive amine addition resulting in the formation of quinolizidine **2.99**.



Scheme 2.28 *Reagents and conditions:* a) $LiEt_3BH$, CH_2Cl_2, −78 °C. ii) 1 M HCl/EtOH, −20 °C to rt. b) TFA, 0 °C to rt.

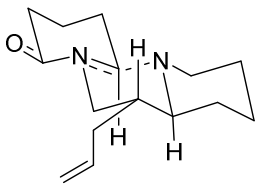
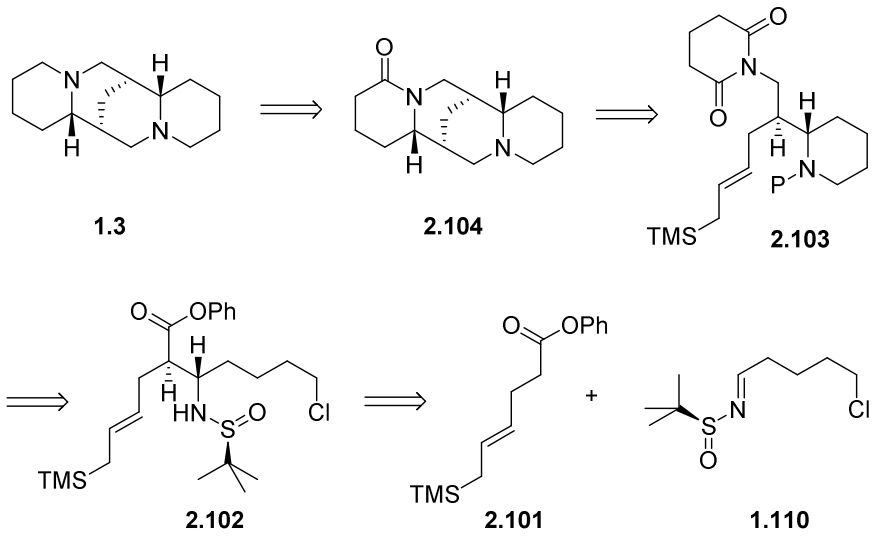


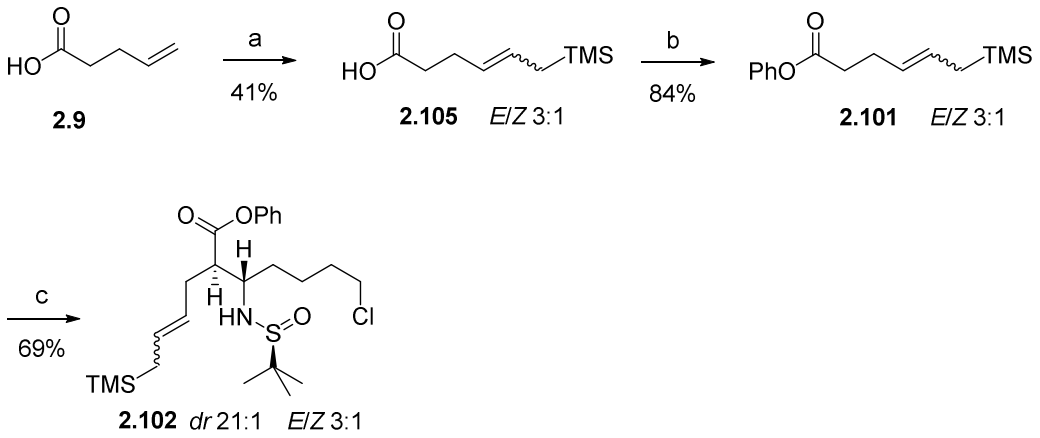
Figure 2.12: Expected cyclisation mode to obtain **2.100**.

Since the allylsilane derivative afforded the desired cyclisation, we needed to re-evaluate our retrosynthetic analysis. The incorporation of the allylsilane was initially performed at a late stage as part of a synthetic study on the cyclisation step and as such we used an intermediate synthesised for the radical approach. We could repeat the synthesis up to the point of CM and evaluate this step in the presence of a Lewis acid, however the probability of performing this step in high yield could not be reliably predicted. A more efficient strategy would be to incorporate the allylsilane within the phenyl ester as side chain.



Scheme 2.29 Alternative approach to sparteine.

In our proposed alternative approach to sparteine (**1.3**), we plan to build upon the strategy described previously with the incorporation of allylsilane in the side chain. A diastereoselective imino-aldol between ester **2.101** and imine **1.110** would allow access to imino-aldol **2.102**. Deprotection/cyclisation and protection of the piperidine with a non labile acid group, followed by ester reduction and Mitsunobu reaction with glutarimide would allow access to imide **2.103**. Imide reduction and Lewis or Brønsted acid promoted cyclisation, followed by amide reduction would furnish sparteine.



Scheme 2.30 *Reagents and conditions:* a) Grubbs II (**2.94**) (2.5 mol %), CH_2Cl_2, Δ. b) PhOH, EDAC, DMAP, Et_3N, CH_2Cl_2, rt. c) i) LDA, THF, −78 °C. ii) imine **1.110**, THF.

Synthesis of functionalised phenylester **2.101** was achieved from acid **2.9** in 34% yield over two steps. Exposure of acid **2.9** to Grubbs II (**2.94**) in refluxing CH_2Cl_2 afforded allylsilane derivative **2.105** as an inseparable mixture of olefin isomers *E*/*Z* 3:1. Esterification of **2.105** with PhOH in presence of EDAC successfully provided the desired fragment for the imino-aldol reaction, ester **2.101**. The first C—C bond was formed using an imino-aldol reaction between ester **2.101** and *tert*-butanesulfinyl imine **1.110** to furnish *β*-amino acid derivative **2.102** in 69% yield and high *dr* 19:1.[a] Unfortunately, due to time constraints we could not pursue the synthesis.

[a] *dr* calculated by integration of NH peaks in the crude ^{1}H NMR spectrum (400 MHz in $CDCl_3$).

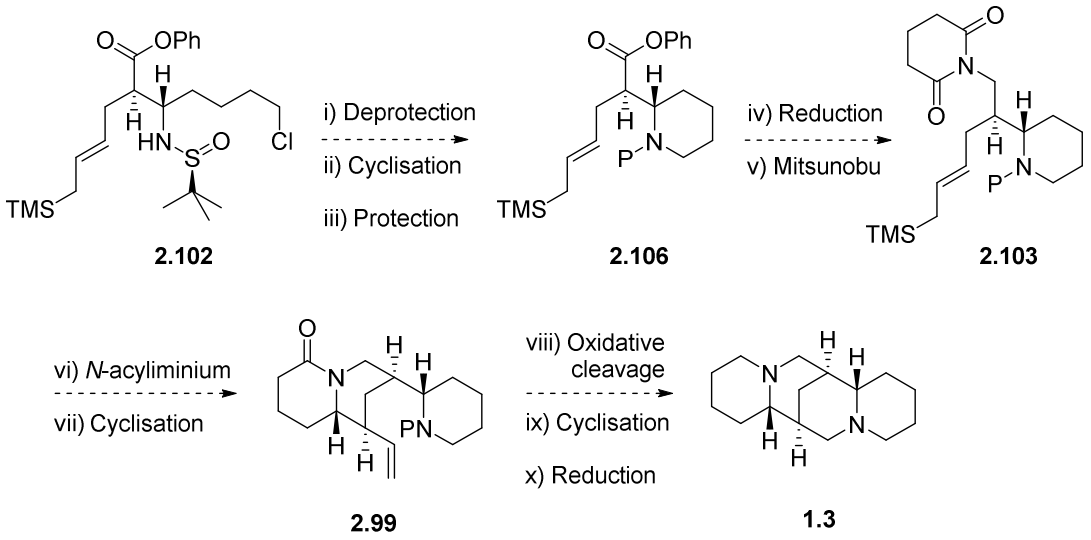
2.5 Conclusion

Significant progress has been made towards the asymmetric total synthesis of (−)-sparteine. As part of the synthetic studies, total synthesis of (−)-lamprolobine was accomplished in 21% yield over 12 steps. The bicyclic quinolizidine precursor was assembled using a diastereoselective imino-aldol reaction to install the stereochemistry at C-5 and C-6. Several imino-aldol reactions have been evaluated with ester enolates bearing functionalised side-chains and *tert*-butylsulfinimines to investigate diastereoselectivity. In all cases studied, it was observed that imino-aldol reactions of phenylesters proceeded with improved diastereocontrol compaired to the corresponding methylesters. We have developed a methodology in which imino-aldol products have been obtained in 69% to 75% yield with high diastereoselectivity (up to 95:5:0:0) in favour of the desired *syn* diastereoisomer. A selection of esters containing thioethers, silyl protected alcohols and olefins as side chain were employed in the imino-aldol reaction to determine the tolerance of different functionalities. Esters containing alkenyl side chains were found to give higher diastereoselectivity and easier separation of the isomeric products on column chromatography. The stereochemistry on the *syn* product was confirmed by single crystal X-ray crystallography. In addition, the absolute stereochemistry of the major product was confirmed by comparison of the physical data of the synthetic (−)-lamprolobine (**1.107**) with literature values.

The initial *N*-acyliminium cyclisation approach to (−)-sparteine failed at the stage of the final attempt to close the **2.47** ring with an enamine nucleophile. The reactivity of the enamine was confirmed through reaction of the substrate **2.41** containing the glutarimide, where dimerisation was observed between the enamine and imnium tautomers. In a modified synthetic route we were able to install a xanthate group into the quinolizidine system as a precursor for a radical cyclisation. Different cyclisation conditions where attempted with none of the desired product isolated. Finally, incorporation of allylsilane functionality as a precursor to the **2.90** ring was achieved. Initial allylsilane-*N*-acyliminium cyclisation attempts indicated that the sparteine framework could be assembled in this way, although further work will be needed to confirm the stereoselectivity of the process.

2.6 Future work

Based upon the results of the studies described above, the outlined synthetic transformations towards sparteine can now be investigated (**Scheme 2.31**). Imino-aldol reaction to give **2.102** followed by a sequence of deprotection/cyclisation/protection will provide piperidine **2.106** and subsequent reduction and Mitsunobu would access imide **2.103**. The intramolecular *N*-acylimnium cyclisation will lead to formation of quinolizidine **2.99**, which can then elaborated to access the tetracyclic alkaloid **1.3**.



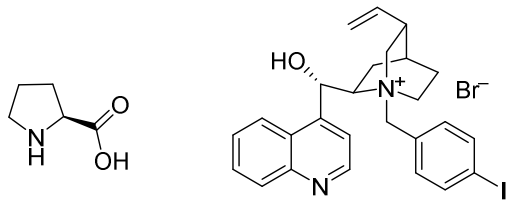
Scheme 2.31 Proposed route to complete the synthesis.

Chapter 3: New chiral catalysts for asymmetric epoxidations

3.1 Introduction

3.1.1 Organocatalysis

Organocatalysis is a powerful tool that re-emerged during the past two decades as a complementary strategy to metal-catalysed reactions in organic synthesis. An organocatalyst is an organic molecule, which does not contain a metal and is used in sub-stoichiometric loadings to provide an acceleration in the rate of a chemical transformations.[113,114] The potential of organocatalysis is immense. Typical catalysts are generally robust, low molecular weight molecules that are easy to prepare, or ideally commercially available. In many cases organocatalysts enable mild reaction conditions to be used. The most common known organocatalysts are amino acids and amine derivatives (L-proline derivatives and cinchona alkaloid derivatives) (**Figure 3.01**).[115,116]



3.1 **3.2**

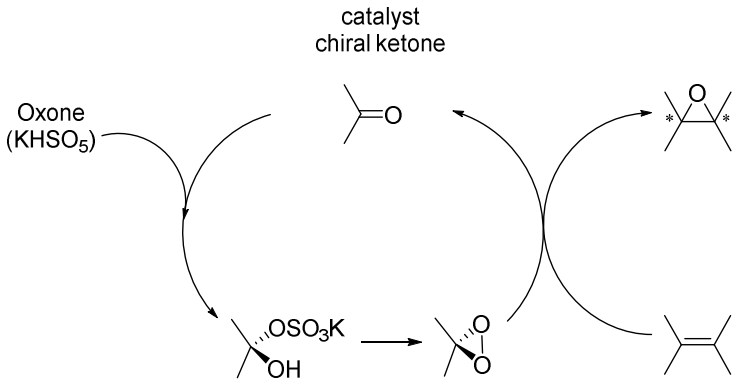
Figure 3.01 L-Proline (**3.1**) and cinchona alkaloid derived **3.2** organocatalysts.

3.1.2 Epoxidation mediated by organocatalysts

Asymmetric epoxidation of alkenes continues to be an important process for synthetic organic chemistry due to the widespread use of epoxides as chiral buildings blocks in the synthesis of complex molecules. Powerful strategies have been developed for the

synthesis of chiral epoxides. Potassium peroxomonosulfate known as Oxone® combined with a chiral ketone (organocatalyst) provides a versatile method for asymmetric epoxidation via *in situ* formation of chiral non-racemic dioxiranes.[117-119] The first attempt to describe the formation of dioxiranes was postulated by Baeyer and Villiger in 1899 when $KHSO_5$ was use for the oxidation of menthone into the corresponding lactone.[120]

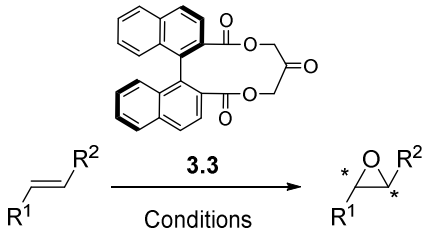
Later, studies undertaken for the epoxidation of alkenes by Edwards and Curci have clarified the decomposition of the Oxone, by acetone *via* dioxiranes using kinetic data and ^{18}O labelling experiments.[121,122] Isolation and preparation of dimethyloxiranes from acetone was reported by Murray in 1985.[123] Despite the good reactivity of certain ketones, the dioxirane-mediated asymmetric epoxidation has been limited in terms of enantioselectivity (5–20 %) until 1996. Subsequently, important processes have been developed for epoxidation of unfunctionalised *cis*-olefins and *trans*-olefins, conjugated olefins and allylic alcohols using chiral ketones as organocatalysts.[124]



Scheme 3.01 Organocatalytic dioxirane-mediated epoxidation of alkenes.

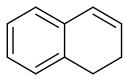
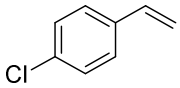
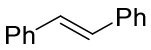
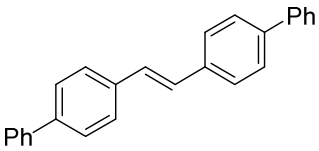
3.1.3 Asymmetric epoxidation using chiral ketones and iminium salts

Enantioselective epoxidation of alkenes by dioxiranes generated *in situ* from chiral ketones through oxidation with Oxone® was achieved in 1996 when Shi *et al*. and Yang *et al*. published their catalysts.[124,125] Yang and co-workers designed a C_2-symmetrical chiral ketone **3.3** derived from 1,1'-binaphthyl-2,2'-dicarboxylic acid for asymmetric epoxidation (**Scheme 3.02**). The catalyst design was based on several considerations that resulted in improved enantioselectivity and activity. A C_2-symmetry was introduced to limit the competing diastereomeric epoxidation pathways of the dioxirane. The chiral information was placed away from the reactive centre in order to avoid racemisation. Two electron-withdrawing ester groups were used to activate the carbonyl to facilitate dioxirane formation.



Scheme 3.02 Asymmetric epoxidation using Yang's binaphthyl-based organocatalyst.

Derivatives bearing different substituents on the binaphthyl ring were designed to improve the reactivity and selectivity.[125-127] Very high conversions were obtained with a loading of 10 mol % of catalyst **3.3**. In terms of selectivity ee values were in most cases lower than 50%; in one case 87% could be obtained for the epoxidation of *E*-stilbene (**Table 3.01**).

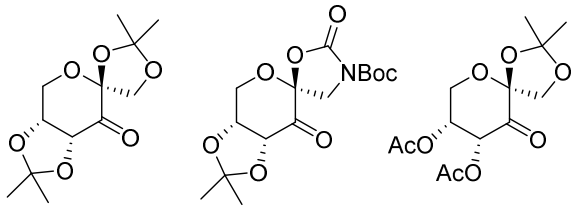
Entry	Substrate	Yield (%)	ee
1[a]		85	<5
2[a]		70	18
3[a]		83	18
4[a]		99	47
5[a]		82	87

[a] Ref[125,128], ketone **3.3** (0.1 equiv.), Oxone (5 equiv.), $NaHCO_3$ (15.5 equiv.), $MeCN/H_2O$ EDTA at rt or 0 °C.

Table 3.01 Selected examples of asymmetric epoxidation using ketone **3.3**.

A major breakthrough in asymmetric epoxidation was realised by Shi and co-workers who reported a fructose-derived chiral ketone **3.4** as an efficient catalyst for asymmetric epoxidation of disubstituted and trisubstituted *E*-alkenes (**Figure 3.02**).[124] The catalyst model was based on a few considerations that enhanced not only the conversion but also the enantioselectivity (up to 99%). The chiral element was placed close to the reacting centre, resulting in a better chiral induction from the catalyst to the substrate. The presence of a fused ring and a quaternary centre α to the ketone carbonyl minimised racemisation. One face of the catalyst is sterically blocked to limit the competing approaches.[129]

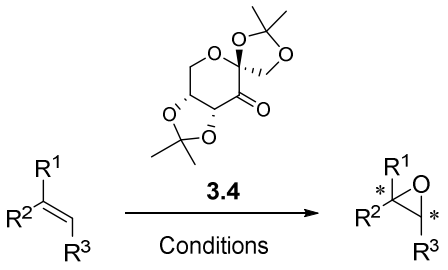
In order to increase reactivity and stability a number of other fructose-derived ketones such as **3.5**[130-132] and **3.6**[133,134] were synthesised and very high selectivities could be obtained for the epoxidation of certain *Z*-alkenes, *E*-cinammates and styrenes (**Figure 3.02**).[135-137]



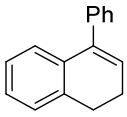
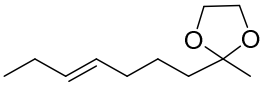
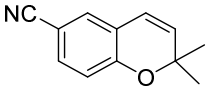
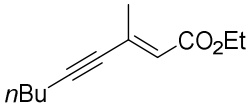
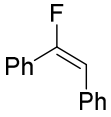
3.4 **3.5** **3.6**

Figure 3.02 Examples of Shi's fructose based organocatalysts.

Important efforts have been made to optimise asymmetric epoxidation. The ketones can be used catalytically (10–30 mol %), Oxone was used as co-oxidant in solvents such as DMM and CH_3CN which provided higher enantioselectivities at pH = 10.5 and reaction temperatures ranging from −10 to 20 ºC can be employed (**Table 3.02**).[138-140] Despite the mild reaction conditions, the ketone catalyst decomposes over time, which provides a limitation in terms of turn-over and does not make it very attractive for large scale epoxidation applications. In comparison to Sharpless epoxidation which provides high enantiocontrol only for primary and secondary allylic alcohol or Jacobsen epoxidation which mainly give high selectivity for *cis* alkenes; Shi epoxidation is very important due to the broad substrate scope (di-tri substituted (*Z*/*E*) and terminal alkenes) which can be epoxidised with high enantioselectivity (up to 98%).



Scheme 3.03 Asymmetric epoxidation using Shi's fructose-based organocatalyst **3.4**.

Entry	Substrate	Yield (%)	ee
1[a]		74	94
2[a]		92	92
3[b]		46	94
4[c]		74	98
5[c]		86	91

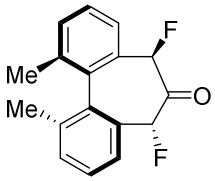
[a] Ref[124,129], ketone **3.4** (3 equiv.), Oxone (5 equiv.), $NaHCO_3$ (15.5 equiv.), MeCN/H_2O EDTA (4×10^{-4} M) (~ 1.5:1) at −10 °C or 0 °C.

[b] Ref[130], ketone **3.5** (0.3 equiv.), Oxone (1.8 equiv.), and K_2CO_3 (4 equiv.), DME/DMM–(0.2 M K_2CO_3–AcOH, pH = 8) (~ 1.5:1) at −10 °C or 0 °C .

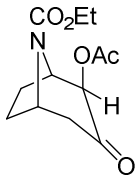
[c] Ref[134,141], ketone **3.6** (0.3 equiv.), Oxone (1.8 equiv.), and K_2CO_3 (5 equiv.), MeCN/H_2O EDTA (4×10^{-4} M) (~ 1.5:1) at 0 °C.

Table 3.02 Selected examples of asymmetric epoxidation using ketones **3.4**, **3.5** and **3.6**.

A variety of ketones were tested as alternative catalysts to the fructose and binaphthyl derivatives for asymmetric epoxidation. Chiral fluoroketone **3.7** was reported by Denmark *et al*. in 2002 for asymmetric epoxidation with Oxone (**Figure 3.03**).[142] Fluoro substituents in close proximity to the ketone carbonyl increased the reactivity of the catalyst, although modest ee values were obtained. In the same year, Armstrong *et al.* published a tropinone derivative **3.8** which provided enantioselectivities up to 83% for a range of *E*-alkenes.[143]



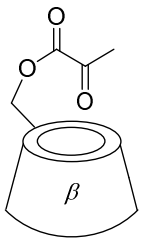
3.7



3.8

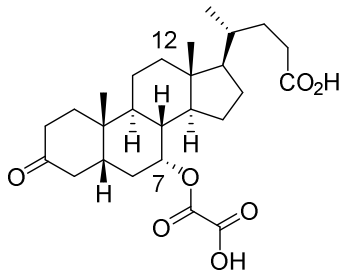
Figure 3.03 Representative ketones for asymmetric epoxidation.

In 2003 Wong and co-workers designed a *β*-cyclodextrin modified ketoester **3.9** as catalyst for asymmetric epoxidation (**Figure 3.04**).[144] Despite the fact that the keto-cyclodextrins were derived from non-regioselective bromine oxidation of the secondary hydroxyl of the cyclodextrins, enantioselective epoxidation of styrenes has been achieved with up to 40% ee.



3.09

Figure 3.04 Wong's *β*-cyclodextrin-based epoxidation catalyst.

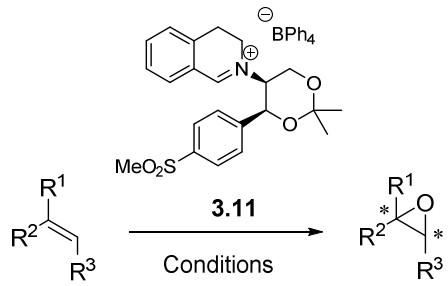


3.10

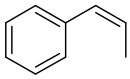
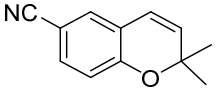
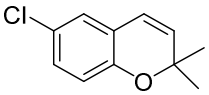
Figure 3.05 Bortolini's bile-acid epoxidation organocatalyst.

Bortolini and co-workers explored the use of dehydrocholic acid derivative **3.10** as active carbonyl inducer for asymmetric epoxidation (**Figure 3.05**).[145] The organocatalyst is based on few considerations that improved the selectivity and reactivity: a carbon skeleton that confers conformational rigidity, a reactive ketone carbonyl and carboxylic acid functionality as side chain to make the molecule soluble in aqueous media. Derivatives bearing hydroxy and keto acids substituents at C-7 and C-12 were introduced giving ee up to 90% for the asymmetric epoxidation of stilbene derivatives.[146-148]

Cyclic iminium salts are another class of important catalysts for alkene epoxidation. Isolated oxaziridinium salts or oxaziridiniums generated *in situ* were found to be effective epoxidation catalysts for several olefins.[149-151] Page and co-workers reported a dihydroisoquinoline related iminium salt **3.11** as a useful catalyst for asymmetric epoxidation (**Scheme 3.04**).[152] The epoxidations were carried out with 0.5–10 mol % of the iminium salt with Oxone® in a mixture of H_2O and CH_3CN. Due to good aqueous solubility of the iminium salt most of the epoxidations could be carried out in H_2O. Various iminium salt derivatives have been synthesised and enantioselectivities up to 97% were obtained (**Table 3.03**).[152-155]



Scheme 3.04 Asymmetric epoxidation using Page's isoquinoline-based organocatalyst.

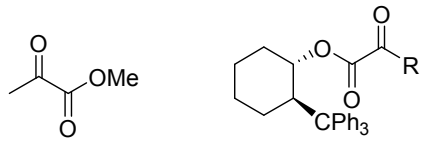
Entry	Substrate	Yield (%)	ee
1[a]		85	70
2[a]		59	97
3[a]		76	93

[a] Ref[154], ketone **3.11** (0.1 equiv.), TPPP, $CHCl_3$ at −40 °C

Table 3.03 Examples of alkenes undergoing asymmetric epoxidation catalysed by iminium salt **3.11**.

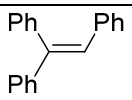
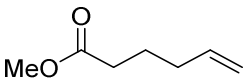
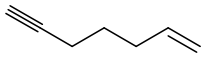
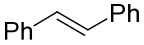
3.1.4 Preliminary epoxidation studies in the Brown group

In preliminary studies with regard to new environmentally friendly procedures for oxidation, Brown and co-workers explored the use of pyruvic acid and pyruvate derivatives as catalysts for epoxidation of various alkenes using Oxone as co-oxidant. Despite the poor enantiomeric excess (< 15%), it was shown that pyruvate derivatives possessing both a ketone and an adjacent carboxylic acid are capable of efficient epoxidation at low catalyst loadings.[156]



3.12 **3.13**

Figure 3.06 Organocatalysts for epoxidation investigated by Brown and co-workers.

Entry	Substrate[a]	Catalyst	Conversion[b] Alkene/Epoxide	ee[c]
1		**3.12**	64/36	–
2		**3.12**	0/100	–
3		**3.12**	10/90	–
4		**3.13** R = Me	64/36	12
5[d]		**3.13** R = Et	71/29	11

[a] All epoxidations reactions were carried out at rt with substrate (1 equiv.), ketone (10–20 mol %), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN/H_2O (~ 3:1) pH = 7.0. The reactions were stopped after 4 h.

[b] Conversions determined from crude ^1H NMR spectra (300 MHz in $CDCl_3$).

[c] Enantiomeric excess determined by chiral HPLC (Chiralcel OD-H or OJ).

[d] See substrate above.

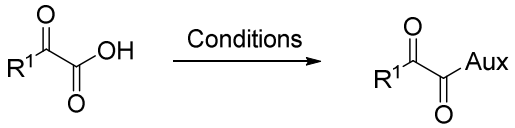
Table 3.04 Selected examples of epoxidation using ketones **3.12** and **3.13**.

Several of the chiral ketones and other derivatives published in the literature shown high enantioselectivity for epoxidation of a wide range of olefins. Despite the good selectivity and reactivity these organocatalysts have some limitations such as: the requirement for high catalyst loading; long synthetic routes for their preparation or high commercial cost; degradation and difficult recovery, which makes them less attractive for industrial processes. These are all features that limit the practical utility of chiral ketone epoxidation catalysts, particularly for industrial processes. Our group became interested at the prospect of new structurally simple, selective organocatalysts based upon α-ketoesters and amides, obtained in short syntheses from readily available and cheap starting materials, and their subsequent use as catalysts in asymmetric epoxidation. Although, epoxidation using α-ketoacid derivatives had been explored using relatively complex catalysts, we felt that structurally simple catalysts could provide similar selectivity and would be more attractive for industrial applications, or heterogenisation on solid supports. The latter could lead to facile recycling of the catalyst.

3.2 Designing new ketone catalysts for asymmetric epoxidation

3.2.1 Synthesis of acyclic *α*-ketoamides

The current work commenced with the synthesis of simple acyclic α-ketoamides to explore their application in olefin epoxidation, with a view to developing chiral variants. An investigation of various coupling agents was carried out to develop a facile amide bond formation methodology. As an initial study, it was important to verify whether simple pyruvamides displayed sufficient reactivity as epoxidation catalysts, thus avoiding lengthy synthetic routes to more complex systems.



3.14 R = Me
3.15 R = Ph

3.16

Scheme 3.05 Preparation of acyclic *α*-ketoamides using chiral amines.

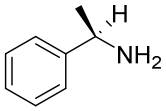
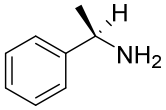
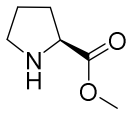
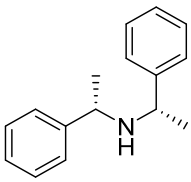
Entry	R^1	Aux	Conditions	Product	Yield (%)[a]
1	Me		DCC, HOBt, CH_2Cl_2, 0 °C to rt.	**3.17**	26
2	Ph		EDAC, CH_2Cl_2, 0 °C to rt.	**3.18**	94
3	Me		$(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt.	**3.19**	60
4	Me		i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt. ii) MeMgBr, CuCl, LiCl, THF, −78 °C to rt.	**3.20**	10

Table 3.05 Synthesis of acyclic *α*-ketoamides.

α-Ketoamides **3.17** and **3.18** were successfully obtained in 26% and 94% yield using DCC/HOBt and EDAC respectively (Entries 1, 2, **Table 3.05**). Pyruvic acid was converted to the corresponding acid chloride using $(COCl)_2$ and was added slowly to a solution of L-proline methyl ester to access pyruvamide **3.19** in 60% yield (Entry 3, **Table 3.05**). The *α*-ketoamide **3.20** was obtained from reaction of a pre-formed copper

[a] Yield isolated by column chromatography.

amide with the acid chloride in a modest 10% yield, with starting material recovered up to 80% (Entry 4, **Table 3.05**).

3.2.2 Synthesis of cyclic *α*-ketoamides

Before starting the synthesis of cyclic pyruvamides we searched current suppliers to verify whether any potential compounds were readily available, leading to identification of cyclic *α*-ketoamide, 1*H*-indole-2,3-dione (**3.21**), commonly known as isatin (**Figure 3.07**).

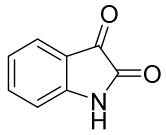
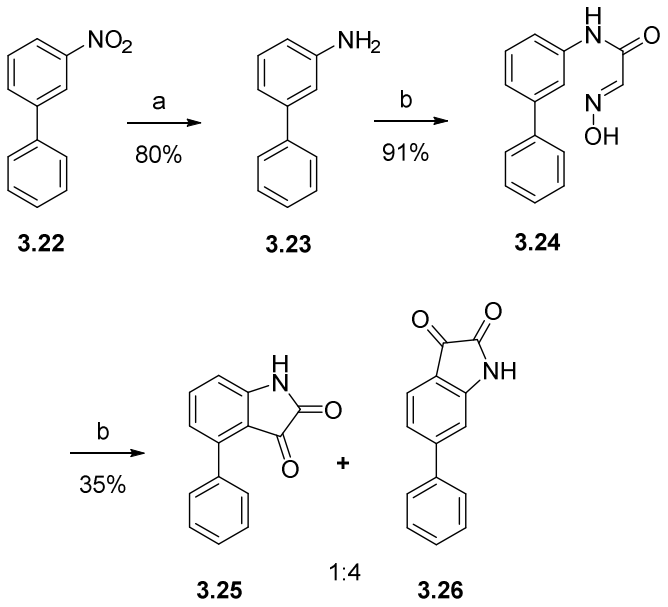


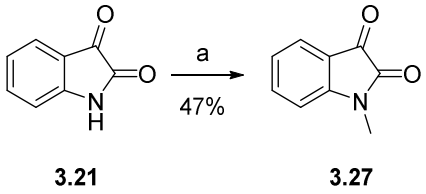
Figure 3.07 1*H*-indole-2,3-dione (**3.21**).

Several isatin derivatives were then synthesised bearing substituents on the aromatic ring and at the ring nitrogen to verify the reactivity and solubility towards the epoxidation reaction.

In the literature a few syntheses are reported for the formation of the isatin scaffold,[157-159] and we investigated the synthetic routes which seemed more appropriate for our substrates. The synthesis of isatin derivatives started from commercially available 3-nitro-1,1'-biphenyl (**3.22**) (**Scheme 3.06**). Hydrogenation of **3.22** over Pd/C accessed amine **3.23** in 80% yield. Heating biphenyl **3.23** in 2 M HCl with chloral hydrate afforded hydroxyaminoacetanilide **3.24** in 91% yield.[160] Slow addition of **3.24** to hot H_2SO_4 afforded a mixture of two isomeric cyclisation products: 4-phenylisatin (**3.25**) and 6-phenylisatin (**3.26**) in 35% combined yields (ratio **3.25:3.26**, ~ 1:4 by ^{1}H NMR).



Scheme 3.06 *Reagents and conditions*: a) H_2, Pd/C, MeOH, rt. b) $Cl_3CCH(OH)_2$, $NH_2OH{\cdot}HCl$, Na_2SO_4, 2 M HCl, H_2O, Δ. c) H_2SO_4, Δ.



Scheme 3.07 *Reagents and conditions*: a) KOH, MeI, TBAB, THF, rt.

N-Methylisatin (**3.27**), to be used for preliminary epoxidation studies was obtained from the alkylation of isatin (**3.21**) with MeI in the presence of TBAB, as a phase-transfer catalyst in 47% yield (**Scheme 3.07**).

3.3 Asymmetric epoxidation of alkenes by ketones

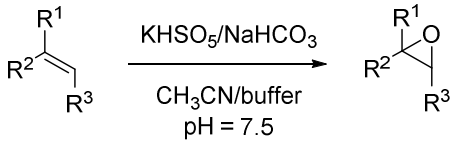
From the studies undertaken previously in the group and by others, it was known that ketone mediated epoxidation requires the control of the several parameters such as pH, rate of addition of the co-oxidant and stoichiometry of the catalyst. An extensive work published by Denmark *et al*. showed that epoxidation *via* dioxiranes requires the control of the pH between 7–8 in order to avoid rapid decomposition of Oxone, although optimal conditions could alter depending on the ketone catalyst used.[119,137] Since the formation of dioxirane involves the generation of acid, a biphasic mixture formed between organic solvent and buffer was employed. We were aware that Oxone, an inorganic peroxide could also oxidise alkenes directly, thus providing a potential racemic epoxidation pathway leading to reduced enantioselectivities. Therefore in parallel to the epoxidation studies with *in situ* generated dioxiranes, a background reaction was conducted in which the ketone was not present.

General procedure for ketone mediated epoxidation:

The following procedure was developed based on the work of Brown:[156] A mixture of alkene (1 mmol) and ketone catalyst (5–30 mol %) in CH_3CN–phosphate buffer pH = 7.5 (2:1, v/v) was vigorously stirred (using a magnetic stirring) at rt for 5 min. A mixture of $NaHCO_3$ (5 mmol) and Oxone® (2 mmol) was ground to a fine powder and then added portion-wise to the reaction in five equal batches over 2 h. The reaction mixture was filtered through cotton wool to remove solids, then the filtrate was diluted with H_2O (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with brine (3 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo* and the conversions determined by integration of the crude ^1H NMR spectra for the crude reaction mixtures (300 MHz in $CDCl_3$).

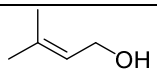
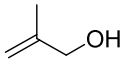
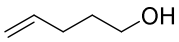
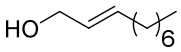
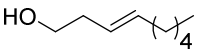
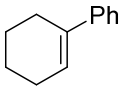
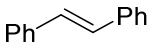
3.3.1 Epoxidation with Oxone®

Our preliminary results showed that a direct oxidation by potassium peroxymonosulfate (Oxone®) under the reaction conditions employed competed with the ketone catalysed asymmetric epoxidation. The outcome was unexpected since in the literature this secondary reaction was indicated to be insignificant.



Scheme 3.08 Oxone epoxidation.

Surprisingly, conversions in the range 75–100% were observed at pH = 7.5 in the absence of ketone catalyst for a range of alkenes (**Table 3.06**). Due to the fact the system we use is biphasic (organic and aqueous), studies concerning the ratio of solvent were carried out for the background epoxidation. Complete conversions were obtained for the alkenes (Entries 1–3, **Table 3.06**) when a ratio organic/aqueous (1:1) was employed. Despite the good conversion low isolated yields were obtained, probably due to the high volatility of the epoxides. As the carbon chain length of the olefin increased, the conversion efficiency decreased substantially 63–85% (Entries 4, 6, **Table 3.06**), which could be explained by reduced aqueous solubility of the substrate. In the absence of the aqueous phase little or no conversion was observed even when the reaction was left up to 20 h (Entries 8, 10, **Table 3.06**). This could be explained by very low solubility of the inorganic peroxide salt in the organic solvent. When the ratio of organic phase was increased the conversion also decreased for the epoxidation of alkenes (Entries 5, 7, **Table 3.06**). Low conversions were obtained for the epoxidation of 1-phenyl-1-cyclohexene and *E*-stilbene (Entries 9, 11, **Table 3.06**), which is poorly soluble in aqueous mixtures.

Entry	Substrate[a]	Conversions[b] Alkene/Epoxide	Ratio Organic/Aqueous
1		0/100[d]	1:1
2		0/100[d]	1:1
3		0/100[d]	1:1
4		47/63	1:1
5[c]		75/25	2:1
6		15/85	1:1
7[c]		66/34	2:1
8[c]		88/12	1:0
9		83/17	1:1
10[c]		100/0	1:0
11		90/10	1:1

[a] All epoxidations reactions were carried out at rt with substrate (1 equiv.), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN–phosphate buffer pH = 7.5. The reactions were stopped after 3 h.

[b] Conversions determined by integration of crude ^1H NMR spectra (300 MHz in $CDCl_3$).

[c] See substrate above.

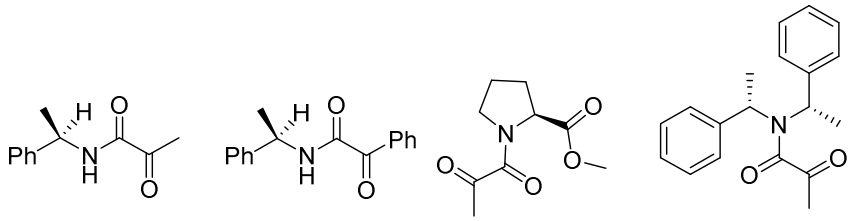
[d] No starting material was present after 1.5 h

Table 3.06 Background epoxidation reactions of alkenes with Oxone.

We can conclude that epoxidation with oxone proceeds with good conversion for hydrophilic substrates in the absence of ketone catalysts. The oxidation takes place in the aqueous environment since Oxone is soluble in H_2O. Polar alcohol or ester functionalised olefins have greater solubility in aqueous media (H_2O or buffer), which facilitates the oxidation by Oxone. In the cases where the alkyl chain length increases, hydrophilicity decreases and low conversion efficiency could be observed.

3.3.2 Ketone-mediated dioxirane asymmetric epoxidation

After the studies on the background reaction (**Table 3.06**), we focused our attention on ketone-catalysed asymmetric epoxidation. Substrates and conditions for the oxidation were chosen in order that the rate of the background epoxidation would be slow compared to the ketone-mediated epoxidation. However, when loadings between 10–20 mol % of the organocatalysts were employed epoxide conversions were improved compared with the background reaction (**Table 3.07**). The dioxiranes generated *in situ* from *α*-ketoamides and Oxone are more efficient epoxidising agents than Oxone itself. Consequently, the solubility of the alkenes in the aqueous was considered to be less important for the asymmetric epoxidation since the dioxiranes formed *in situ* are soluble in both phases.

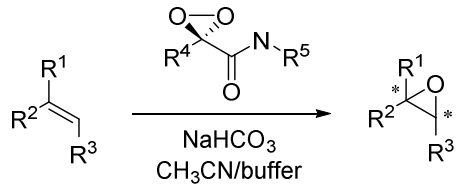


3.17 **3.18** **3.19** **3.20**

Figure 3.08 Chiral acyclic *α*-ketoamides.

Overall acyclic *α*-ketoamides displayed relatively poor reactivity in dioxirane-mediated epoxidation. In most cases conversions were lower than 50% (**Table 3.07**) and the enantioselectivities observed were less than 5% for the epoxidation of most substrates. There were two examples where higher ee values of 14% and 34% were obtained (Entries 9, 14, **Table 3.07**). We have attempted to recover the ketone organocatalysts at the end of the reaction but without success. However, the quantities of ketone used in the reactions were low (5–10 mg), and when combined with the potential ketone degradation during epoxidation and work-up, may account for the lack of catalyst recovery.

All the epoxidations were carried out at low catalysts loadings (< 20 mol %) and a fixed period of time, usually 2–3 h. It is possible that use of stoichiometric amounts of the ketone catalysts could lead to higher enantioselectivity.



Scheme 3.09 Asymmetric epoxidation with acyclic α-ketoamides.

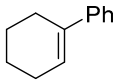
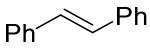
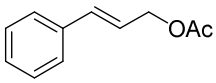
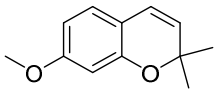
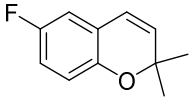
Entry	Substrate[a]	Catalyst	Conversion[b] Alkene/Epoxide	ee[e]
1		**3.17**	58/42	4
2[c]		**3.17**	33/67	
3[d]		**3.18**	75/25	2
4[d]		**3.19**	72/28	
5[f]			90/10	
6		**3.17**	50/50	
7[d]		**3.19**	100/0	
8[f]			100/0	
9		**3.18**	70/30	14
10[d]		**3.19**	67/33	2
11[d]		**3.20**	60/40	3
12[f]			88/12	
13		**3.19**	78/22	
14		**3.19**	80/20	34

Table 3.07 Selected substrates for dioxirane-mediated epoxidation with acyclic α-ketoamides.

[a] All epoxidation reactions were carried out at rt with substrate (1 equiv.), ketone (20 mol %), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), DMM/CH_3CN–phosphate buffer pH = 7.5 (v/v - 2:1). The reactions were stopped after 4 h.

[b] Conversions determined by integration of crude ^1H NMR spectra (300 MHz in $CDCl_3$).

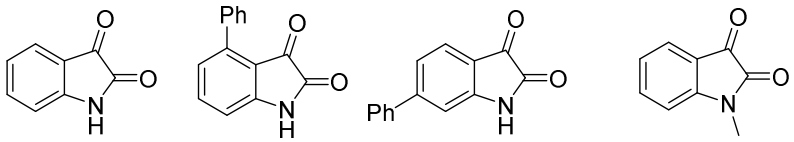
[c] 50 mol % of ketone **3.17** was used.

[d] See substrate above.

[e] Enantiomeric excess determined by chiral HPLC (Chiralcel OD-H or OB-H).

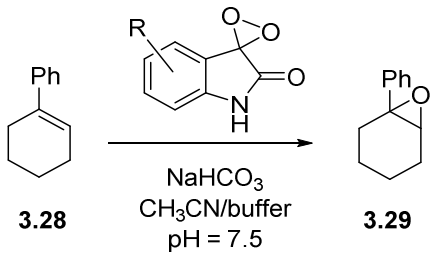
[f] Background reaction without the ketone.

We also evaluated a set of cyclic α-ketoamides as organocatalysts for ketone-mediated epoxidation (**Figure 3.09**). In order to determine the relative reactivity of isatin derivatives we compared the conversions for the epoxidation of 1-phenyl-1-cyclohexene (**3.28**) to the corresponding epoxide **3.29** (**Scheme 3.10**). Initial results were encouraging requiring only 5 mol % of the catalyst **3.21** to achieve complete conversion within two hours. The conversions decreased (48–58%) when the isatin core was modified with substituents (Entries 2–4, **Table 3.08**). These results were encouraging since background epoxidation reactions, conducted in parallel with the ketone-catalysed reactions, showed low levels of conversion (< 10%) (Entry 5, **Table 3.08**).



3.21 **3.25** **3.26** **3.27**

Figure 3.09 Cyclic α-ketoamides.



3.28 **3.29**

Scheme 3.10 Asymmetric epoxidation with cyclic α-ketoamides.

Entry[a]	Ketone	Conversions[b] Alkene/Epoxide
1	**3.21**	0/100
2	**3.25**	42/58
3	**3.26**	45/55
4	**3.27**	52/48
5[c]		90/10

[a] All epoxidations reactions were carried out at rt with substrate (1 equiv.), ketone (5 mol %), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN–phosphate buffer pH = 7.5 (v/v - 2:1)–, EDTA. The reactions were stopped after 3 h.

[b] Conversions determined by integration of crude ^1H NMR spectra (300 MHz in $CDCl_3$).

[c] Background reaction without the ketone.

Table 3.08 Epoxidation of **3.28** with dioxiranes generated *in situ* from cyclic *α*-ketoamides

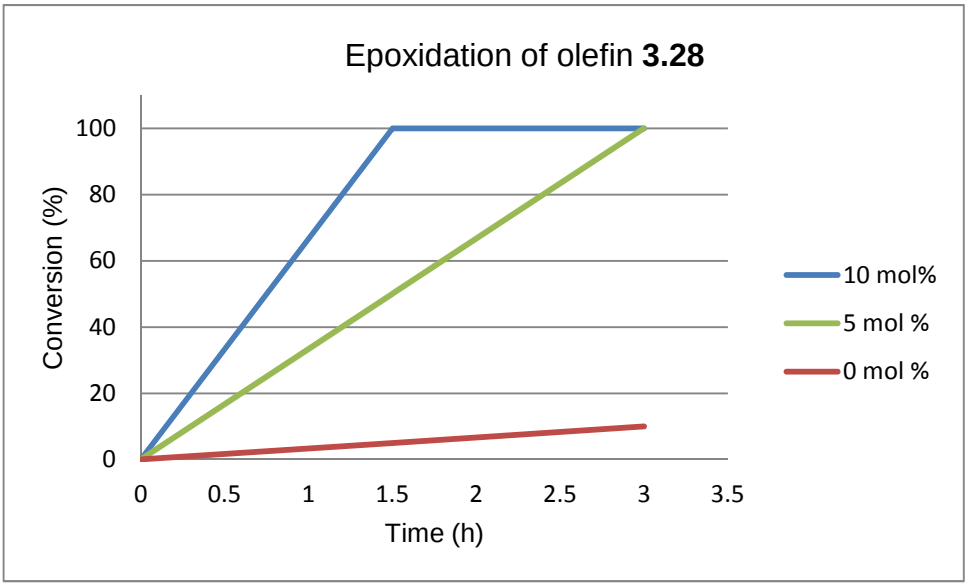
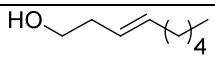
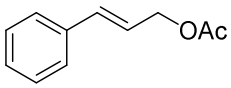


Figure 3.10 Time vs conversion using different loadings of 1*H*-indole-2,3-dione (**3.21**).

Following the high reactivity of isatin (**3.21**) for the epoxidation of alkene **3.28** we investigated the catalyst for epoxidation of other substrates. High conversions were obtained for the epoxidation of alkenes (Entries 1, 3, **Table 3.09**). Reactions without the ketone catalyst were conduct in parallel with the ketone-mediated dioxirane epoxidation and lower conversions were obtained (Entries 2, 4, **Table 3.09**). However, decreasing the temperature to 0 °C or/and employing a higher catalyst loading could be beneficial for the dioxirane epoxidation making the background reaction insignificant.

Entry	**Substrate**[a]	**Conversion**[b] **Alkene/Epoxide**
1		20/80
2[c,d]		73/27
3		30/70
4[c,d]		80/20

[a] All epoxidation reactions were carried out at rt with substrate (1 equiv.), ketone (10 mol %), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN–phosphate buffer pH = 7.5 (v/v - 2:1). The reactions were stopped after 1.5 h.

[b] Conversions determined by integration of crude ^1H NMR spectra (300 MHz in $CDCl_3$).

[c] Background reaction without the ketone.

[d] See substrate above.

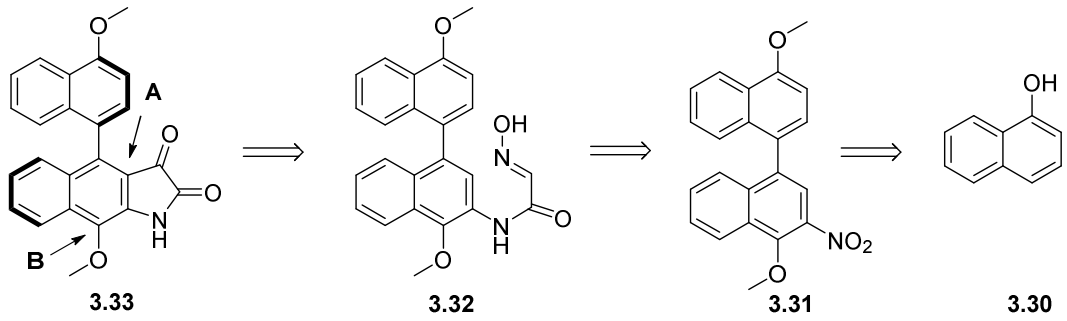
Table 3.09 Selected substrates for dioxirane-mediated epoxidation with isatin **3.21**.

3.4 Designing a chiral cyclic *α*-ketoamide

Following the promising results obtained for the epoxidation of alkenes using isatin (**3.21**) we decided to design a chiral model which could provide enantioselectivity. Although, the original objective of this work was to avoid a rather long and complicated synthetic route to synthesise a chiral ketone catalyst, we felt that incorporation of the isatin moiety in a chiral catalyst could provide advantages such as higher activity and reduced catalyst loading requirement. Ultimately, isatin might provide a novel scaffold for the development of practical asymmetric epoxidation catalysts.

3.4.1 Retrosynthetic analysis

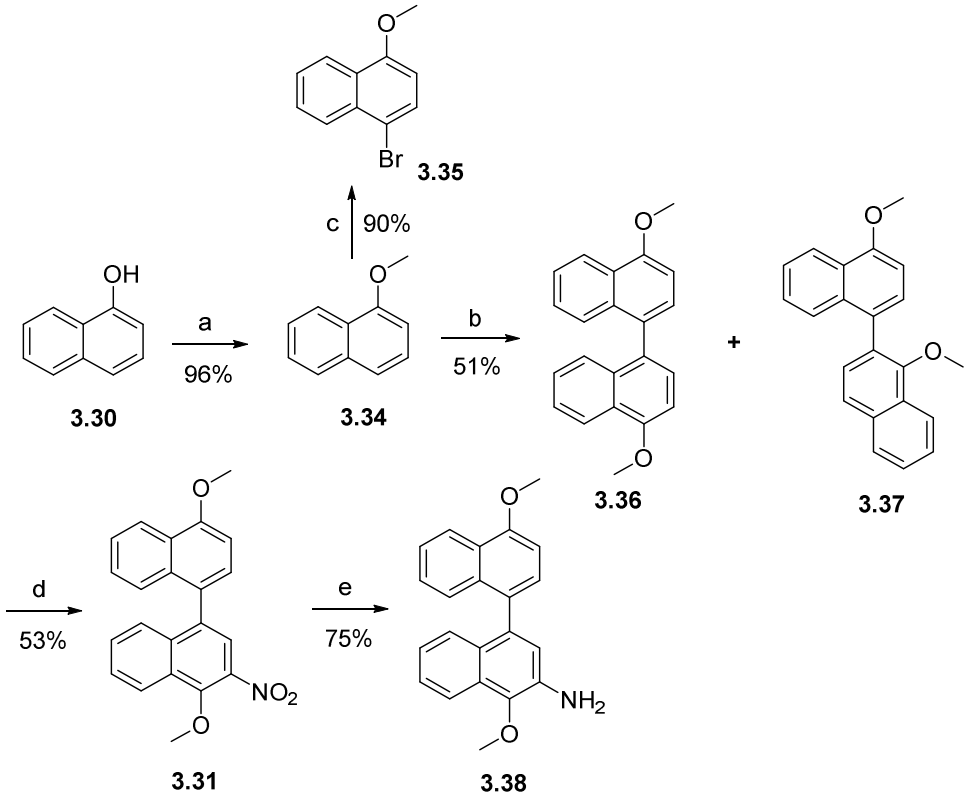
The catalyst design was based upon incorporation of the isatin motif into a biaryl system **3.33**, which exhibited axial chirality (**Scheme 3.11**). Our plan was to apply the Sandmeyer procedure for closure of the heterocyclic ring, a strategy previous studied for the synthesis of isatin derivatives **3.25** and **3.26**. Several modifications are required to obtain a single isomer during the cyclisation. Introduction of a methoxy substituent at position **B** on the binaphthyl system would force the cyclisation to take place only at position **A**, thus avoiding the formation of the undesired regioisomer. As a result the reactive ketone would be located close to chiral information. Methylation of 1-naphthol (**3.30**) followed by biaryl coupling and nitration would allow access to binaphthalene derivative **3.31**. Reduction of nitro coumpound **3.31** and subsequent treatment with chloral hydrate would give hydroxyiminoacetanilide **3.32**, which upon treatement with H_2SO_4 would undergo the desired cyclisation to form **3.33**.



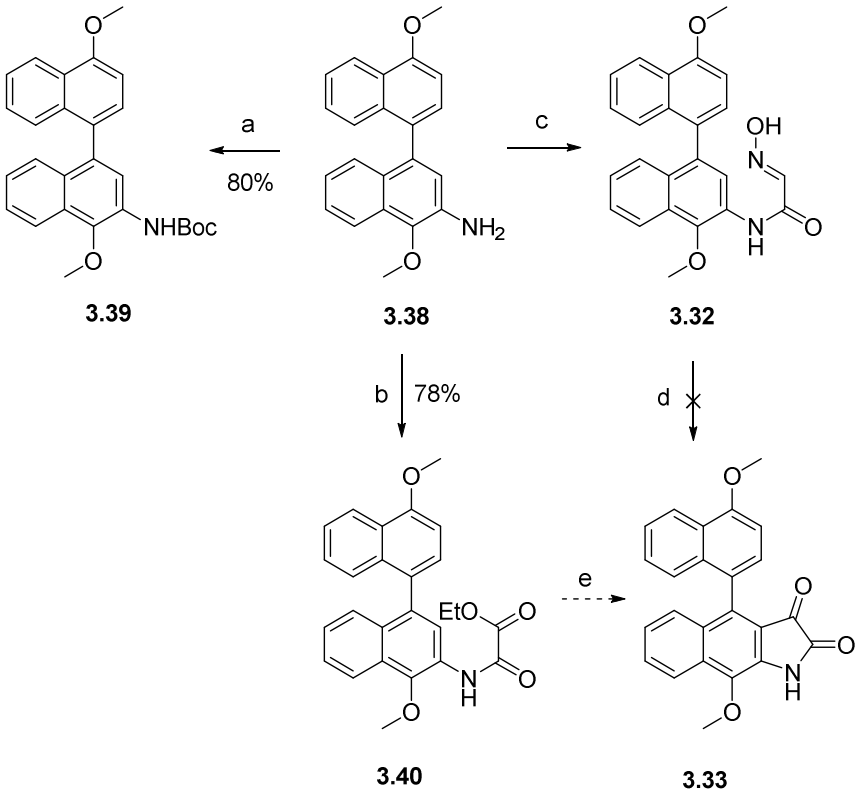
Scheme 3.11 Retrosynthetic analysis of a chiral ketone.

3.4.2 Efforts towards the synthesis of a chiral isatin derivative

Alkylation of commercially available 1-naphthol (**3.30**) proceeded smoothly to access 1-methoxynaphthalene (**3.34**) in 96% yield (**Scheme 3.12**). Synthesis of binaphthyl **3.36** was difficult giving some unexpected results. Applying the procedure reported by Kodomari resulted in the formation of bromo derivative **3.35** instead of the expected binapthyl **3.36**. Binapthyl **3.36** was obtained in 51% yield when naphthalene **3.34** was treated with Meerwein's salt (triethyloxonium hexachloroantimonate), although other manipulations such as heating or increasing the reaction time afforded the binaphthyl **3.37** as a by-product. Nitration of **3.36** with $Cu(NO_3)_2{\cdot}2H_2O$ afforded the nitro compound **3.31** in 52% yield which was subsequently reduced over Pd/C to secure amine **3.38** in 75% yield.



Scheme 3.12 *Reagents and conditions*: a) *t*-BuOK, MeI, THF, rt. b) $EtO_3^+SbCl_6^-$, CH_2Cl_2, rt. c) $CuBr_2$, C_6H_6, Δ. d) $Cu(NO_3)_2{\cdot}2H_2O$, AcOH, Δ. e) H_2 over Pd/C, MeOH, rt.



Scheme 3.13 *Reagents and conditions*: a) Boc_2O, THF, Δ. b) i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C t rt. ii) EtOH, rt. c) $Cl_3CCH(OH)_2$, $NH_2OH{\cdot}HCl$, Na_2SO_4, 2 M HCl, H_2O, Δ d) H_2SO_4, Δ. e) $AlCl_3$, THF, Δ.

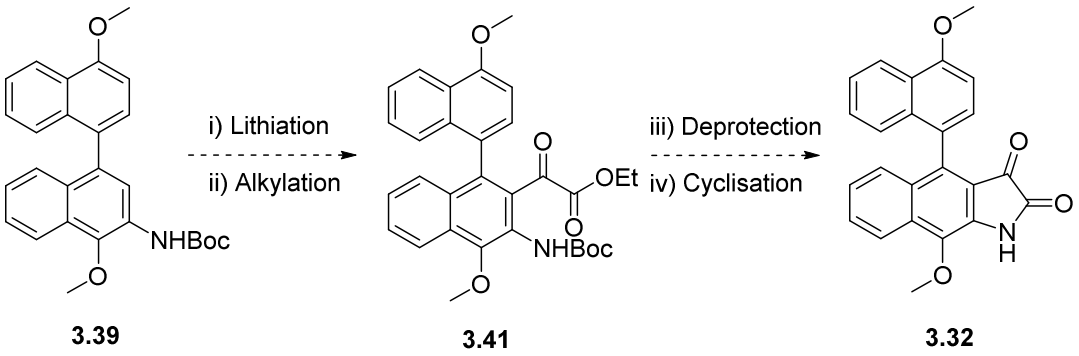
Hydroxyaminoacetanilide **3.32** was obtained from amine **3.38** and chloral hydrate in aqueous HCl, but the yield was extremely low. We believe that **3.38** was not very soluble in the aqueous media and methanol was added with the hope to increase solubility. However the yield was not improved. Unfortunately, when **3.32** was added to hot sulphuric acid, no cyclisation took place. At this point we were limited by the quantities available and we decided to investigate precursors for different cyclisation conditions. Amine **3.38** was treated with $(COCl)_2$ and DMF to obtain the corresponding acid chloride which was conc. *in vacuo* and subsequent treatment with EtOH furnished ester **3.40** in 78% overall yield. Boc protection of amine **3.38** was achieved using Boc_2O to secure binaphthyl **3.39** in 80% yield. The progress towards the synthesis of a chiral isatin derivative was very slow, combined with the low enantioselectivities obtained for epoxidation forced us to stop the work, and start the project on lupin alkaloids.

3.5 Conclusion

Several cyclic and acyclic α-ketoamides have been synthesised from readily available and cheap starting materials in yields that ranged from 10% to 98%. *α*-Ketoamides were employed as organocatalysts for the asymmetric epoxidation of different olefins. Isatin (**3.21**) was found to be an effective catalyst of the epoxidation of alkene **3.28** at a loading of 5 mol %. Acyclic chiral *α*-ketoamides gave modest conversions when used at sub-stoichiometric loadings for the asymmetric epoxidation of alkenes. Enantiomeric excess were disappointing in most cases (< 5%), although two examples where 14% and 34% ee were obtained, but with low conversions. Isatin was found to be an effective organocatalyst in dioxirane-mediated epoxidation of a number of alkenes, giving us the prospect of designing chiral derivatives for asymmetric epoxidation. Significant progress was made towards a chiral isatin derivative, although closure of the heterocyclic ring using the Sandmeyer procedure has so far been unsuccessful. Epoxidation of olefins by Oxone was found to proceed with good conversion in the absence of ketone catalysts where the substrates were more hydrophilic; polar alcohol or ester functionalised olefins were readily oxidised by oxone. More hydrophobic substrates with increased alkyl chain length led to reduced conversion efficiency due to poor solubility of the substrates in the aqueous media.

3.6 Future work

A synthetic route towards chiral isatin derivatives is presented in Scheme 3.10. The final synthetic steps towards the desired racemic chiral heterocycle can now be investigated. The proposed *o*-lithiation of *N*-Boc **3.39** and alkylation with ethyl chlorooxoacetate will give *α*-ketoester **3.41** (**Scheme 3.14**). Subsequent amine deprotection and acid promoted cyclisation will furnish the desired organocatalysts **3.32**. Fortunately, the synthesis of functionalised isatin by Meanwell and co-workers provides precedent for the *o*-lithiated anilines and regioselective cyclisation to isatins.[161] A resolution process would ultimately be required.



Scheme 3.14 Proposed route to complete the synthesis.

Regarding the epoxidation using our organocalysts, several modifications could be made to study the epoxidation process. The ketone catalysts can be used in stoichiometric amounts to investigate enantioinduction, with reduced contribution from the background racemic epoxidation. Slow addition of the co-oxidant and buffer solution using syringe pump and low temperature reaction could then be investigated to determine whether the reactivity and selectivity of the organocatalyst was sufficient.

Chapter 4: Experimental

4.1 General Methods

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Fluorochem or Apollo Scientific. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame dried glassware. The solvents toluene, THF and Et_2O (from Na/benzophenone), MeCN, MeOH and CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified using standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 containing F_{254} indicator; visualised under UV light (254 nm) and/or by staining with anisaldehyde, ceric ammonium molybdate, iodine, phosphomolybdic acid, potassium permanganate or vanillin. Flash column chromatography was performed using; high purity silica gel, Geduran®, pore size 60 Å, 230-400 mesh particle size, purchased from Merck.

Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 fitted with a Smart Orbit Goldengate attachment using OMNIC software package. Optical rotations were collected on an Optical Activity PolAAr 2001 machine. The solvents used for the measurement of the optical activity are detailed in the experimental.

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, Acetone-d_6 solutions (purchased from Cambridge Isotope Laboratories, Inc.) at 298 K using Bruker AC300, AV300 (300 and 75 MHz respectively) or Bruker DPX400, AVII400, AVIIHD400 (400 and 100 MHz respectively) and at 353 K using Bruker AVII400 (400 and 100 MHz respetively) or Bruker AVIIHD500 (500 and 125 MHz respetively) spectrometers. Chemical shifts values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^1H, δ 77.00 ppm for ^{13}C), dimethyl sulfoxide (δ 2.50 ppm for ^1H, δ 39.51 ppm for ^{13}C) and acetone (δ 2.05 ppm for ^1H, δ 29.92 ppm ^{13}C). All spectra were reprocessed using ACD/Labs software version: 12.1. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks

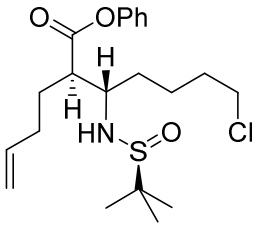
are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), br (broad), and m (multiplet).

Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected. Analytical HPLC was performed on an Agilent 1220 Infinity LC System utilising the Agilent EZChrom software package eluting either from Daicel Chiralcel® OD-H or AD-H columns eluting with IPA/hexane mixtures (details in the experimental). Electrospray low resolution mass spectra were recorded on a Waters ZMD quadrupole spectrometer or Waters (Manchester, UK) TQD triple quadrupole analyser. High resolution mass spectra were obtained using Bruker APEX III FT-ICR mass spectrometer or MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight analyser. HRMS were recorded using positive ion electrospray ionization (ESI^+). Microwave synthesis was performed in a sealed tube using a CEM discover microwave synthesizer.

Compounds containing a *N*-Boc protecting group exhibited broadening of peaks in ^1H NMR and some of the peaks were not observed in ^{13}C NMR due to restricted rotation. To aid interpretation of the spectra for selected compounds variable temperature NMR experiments at T = 353 K and 373 K were conducted.

4.2 Procedures and Characterisation Data

2.35 - (2*R*,3*S*)-Phenyl-2-(but-3-en-1-yl)-3-((*S*)-2-methyl-propane-2-sulfinylamino)-7-chloroheptanoate



$C_{21}H_{32}ClNO_3S$
Mol Wt: 414.0010

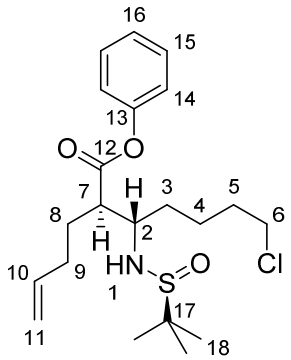
To a solution of LDA (4.40 mL, 7.91 mmol) in THF (40 mL) at −78 °C under N_2 was added ester **2.12** (1.45 g, 7.62 mmol) in THF (3 mL) dropwise over 30 min. The reaction was stirred for 45 min at −78 °C, then a solution of imine **1.110** (1.31 g, 5.86 mmol) in THF (3 mL) was added dropwise over 30 min. The reaction was stirred for 45 min before quenching with sat. aq. NH_4Cl (40 mL). The reaction was allowed to warm to rt and stirred for 1 h. The phases were separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The organic phases were combined, washed with brine (3 x 40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of two diastereoisomers (integration of NH peaks in the ^1H NMR gives *syn/anti dr* 95:5). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereoisomer **2.35** (2.05 g, 4.95 mmol, 84%) as a white solid. Recrystallisation of **2.35** from hexane gave large colourless needles (1.81 g, 4.37 mmol, 75%).

$[\alpha]^{27}_D$ +15.0 (*c* 1.04, $CHCl_3$).

M.p. (hexane) 52–55 °C.

R_f 0.15 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3224, 3074, 2953, 2866, 1750, 1641, 1593, 1491, 1190 cm^{-1}.



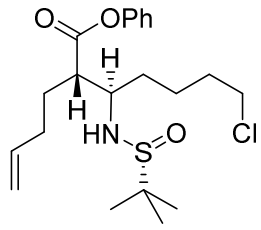
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.36 (2H, m, $\mathbf{H}_{15}$), 7.25 (1H, m, $\mathbf{H}_{16}$), 7.10 - 7.07 (2H, m, $\mathbf{H}_{14}$), 5.84 (1H, ddt, *J* = 17.1, 10.1, 6.7 Hz, $\mathbf{H}_{10}$), 5.10 (1H, ddt, *J* = 17.1, 1.6 Hz, $\mathbf{H}_{11'}$), 5.05 (1H, ddt, *J* = 10.1, 1.6 Hz, $\mathbf{H}_{11''}$), 4.16 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_{1}$), 3.55 (2H, t, *J* = 6.6 Hz, $\mathbf{H}_{6}$), 3.49 (1H, ddt, *J* = 9.1, 8.4, 4.2 Hz, $\mathbf{H}_{2}$), 3.17 (1H, dt, *J* = 9.1, 4.5 Hz, $\mathbf{H}_{7}$), 2.33 - 2.14 (2H, m, $\mathbf{H}_{9}$), 2.04 (1H, m, $\mathbf{H}_{8'}$), 1.88 - 1.46 (7H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4}$, $\mathbf{H}_{5}$ & $\mathbf{H}_{8''}$), 1.24 (9H, m, $\mathbf{H}_{18}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 ($\mathbf{C}_{12}$), 150.3 ($\mathbf{C}_{13}$), 137.2 ($\mathbf{C}_{10}$), 129.5 ($\mathbf{C}_{15}$), 126.1 ($\mathbf{C}_{16}$), 121.5 ($\mathbf{C}_{14}$), 115.9 ($\mathbf{C}_{11}$), 58.2 ($\mathbf{C}_{2}$), 56.2 ($\mathbf{C}_{17}$), 50.0 ($\mathbf{C}_{7}$), 44.7 ($\mathbf{C}_{6}$), 32.1 ($\mathbf{C}_{5}$), 31.8 ($\mathbf{C}_{9}$), 31.5 ($\mathbf{C}_{3}$), 28.0 ($\mathbf{C}_{8}$), 23.6 ($\mathbf{C}_{4}$), 22.7 ($\mathbf{C}_{18}$) ppm.

LRMS (ES^+) *m/z* 436.1 $[M^{35}Cl+Na]^+$, 438.1 $[M^{37}Cl+Na]^+$, 477.1 $[M^{35}Cl+CH_3CN+Na]^+$, 479.1 $[M^{37}Cl+CH_3CN+Na]^+$.

HRMS (ES^+) for $C_{21}H_{32}ClNNaO_3S^+$ $[M+Na]^+$, calculated 436.1684 found 436.1682.

***ent*-2.35 - (2*S*,3*R*)-Phenyl-2-(but-3-en-1-yl)-3-((*S*)-2-methyl-propane-2-sulfinylamino)-7-chloroheptanoate**

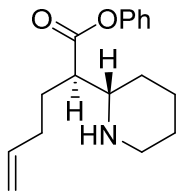


$C_{21}H_{32}ClNO_3S$
Mol Wt: 414.0010

Following the procedure described for the synthesis of **2.35**, imine ***ent*-1.110** (4.00 g, 17.88 mmol) afforded the crude product as a separable mixture of two diastereomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti dr* 95:5). Purification by column chromatography eluting with EtOAc/hexane (20:80) and recrystallisation from hexane afforded the major diastereoisomer ***ent*-2.35** (5.55 g, 13.29 mmol, 74%) as large colourless needles. Physical and spectroscopic data were consistent with those for the enantiomer.

$[\alpha]^{21}_D$ −13.8 (*c* 0.58, $CHCl_3$).

2.36 - (*R*)-Phenyl-2-((*S*)-piperidin-2-yl)hex-5-enoate



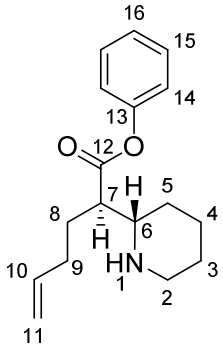
$C_{17}H_{23}NO_2$
Mol Wt: 273.3760

To a solution of imino-aldol **2.35** (3.00 g, 7.25 mmol) in dioxane (120 mL) at 0 °C under N_2 was added conc. HCl (1.81 mL of ~ 36%, 21.74 mmol) dropwise. The resulting colourless mixture was stirred at rt for 3 h over which time it became yellow. The solvent was removed *in vacuo*, the yellow oil dissolved in $CHCl_3$ (15 mL) and evaporated (3 times) giving a pale yellow oil. The residue was redissolved in MeCN (120 mL), then K_2CO_3 (5.00 g, 36.23 mmol) and NaI (0.10 g, 0.73 mmol) were added portionwise. The resulting bright yellow solution was stirred for 24 h over which time a white precipitate formed. The solvent was removed *in vacuo*, the residue partitioned between EtOAc/H_2O (1:1 - 120 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography eluting with 100% EtOAc afforded the title compound **2.36** (1.76 g, 6.44 mmol, 89%) as a pale yellow oil.

$[\alpha]^{27}_D$ +3.2 (*c* 0.98, $CHCl_3$).

R_f 0.21 (*eluent*: MeOH/EtOAc - 10:90).

FT-IR (neat) ν_{max} 3074, 2930, 2853, 1750, 1593, 1491, 1192, 1112, 746 cm^{-1}.



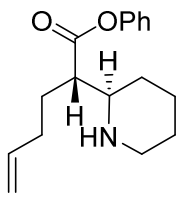
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.35 (2H, m, $\mathbf{H}_{15}$), 7.23 (1H, m, $\mathbf{H}_{16}$), 7.12 -7.07 (2H, m, $\mathbf{H}_{14}$), 5.84 (1H, ddt, *J* = 17.1, 10.1, 6.6 Hz, $\mathbf{H}_{10}$), 5.09 (1H, ddt, *J* = 17.1, 1.5 Hz, $\mathbf{H}_{11'}$), 5.02 (1H, ddt, *J* = 10.1, 1.5 Hz, $\mathbf{H}_{11''}$), 3.12 (1H, dd, *J* = 11.9, 3.3 Hz, $\mathbf{H}_{2eq}$), 2.85 (1H, ddd, *J* = 10.6, 6.3, 2.8 Hz, $\mathbf{H}_{6}$), 2.66 (1H, td, *J* = 11.9, 3.0 Hz, $\mathbf{H}_{2ax}$), 2.62 (1H, ddd, *J* = 10.6, 6.3, 4.0 Hz, $\mathbf{H}_{7}$), 2.29 - 2.09 (2H, m, $\mathbf{H}_{9}$), 1.98 - 1.76 (3H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{8}$), 1.75 - 1.58 (2H, m, $\mathbf{H}_{3eq}$ & $\mathbf{H}_{5eq}$), 1.48 - 1.32 (3H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 ($\mathbf{C}_{12}$), 150.6 ($\mathbf{C}_{13}$), 137.5 ($\mathbf{C}_{10}$), 129.4 ($\mathbf{C}_{15}$), 125.8 ($\mathbf{C}_{16}$), 121.5 ($\mathbf{C}_{14}$), 115.5 ($\mathbf{C}_{11}$), 58.5 ($\mathbf{C}_{6}$), 51.1 ($\mathbf{C}_{7}$), 47.2 ($\mathbf{C}_{2}$), 32.0 ($\mathbf{C}_{9}$), 30.5 (C_5), 27.8 ($\mathbf{C}_{8}$), 26.5 ($\mathbf{C}_{3}$), 24.8 ($\mathbf{C}_{4}$) ppm.

LRMS (ES^+) *m/z* 274.2 $[M+H]^+$.

HRMS (ES^+) for $C_{17}H_{24}NO_2^+$ $[M+H]^+$, calculated 274.1802 found 274.1802.

***ent*-2.36 - (*S*)-Phenyl-2-((*R*)-piperidin-2-yl)hex-5-enoate**

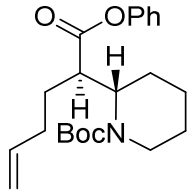


$C_{17}H_{23}NO_2$
Mol Wt: 273.3760

Following the procedure described for the synthesis of **2.36**, imino-aldol ***ent*-2.35** (3.80 g, 9.18 mmol) afforded the title compound ***ent*-2.36** (1.90. g, 6.95 mmol, 76%) as a pale yellow oil. Physical and spectroscopic data were consistent to those for the enantiomer.

$[\alpha]^{21}_{D}$ −4.0 (*c* 0.80, $CHCl_3$).

2.37 - **(*S*)-*tert*-Butyl-2-((*R*)-1-oxo-1-phenoxyhex-5-en-2-yl))piperidine-1-carboxylate**



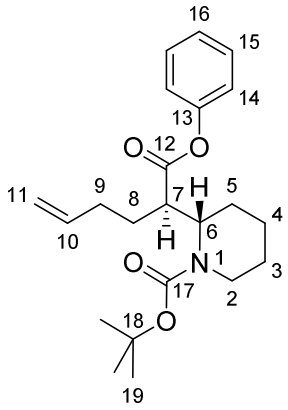
$C_{22}H_{31}NO_4$
Mol Wt: 373.4930

To neat amine **2.36** (1.69 g, 6.18 mmol) were added Boc_2O (1.63 g, 7.47 mmol) and sulfamic acid (0.03 g, 0.31 mmol). The resulting mixture was sonicated at rt for 1 h in an ultrasonic bath having a frequency of 50 kHz and an input of 240 W. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **2.37** (2.15 g, 5.75 mmol, 93%) as a colourless oil.

$[\alpha]^{25.5}_{D}$ +14.3 (*c* 0.83, $CHCl_3$).

R_f 0.43 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 2936, 2864, 1754, 1690, 1641, 1593, 1414, 1191 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.34 (2H, m, $\mathbf{H}_{15}$), 7.23 (1H, m, $\mathbf{H}_{16}$), 7.11 - 7.03 (2H, m, $\mathbf{H}_{15}$), 5.82 (1H, ddt, *J* = 16.8, 10.6, 6.6 Hz, $\mathbf{H}_{10}$), 5.15 - 5.00 (2H, m, $\mathbf{H}_{11}$), 4.61 (1H, m, $\mathbf{H}_6$), 4.08 (1H, m, $\mathbf{H}_{2eq}$), 3.17 (1H, m, $\mathbf{H}_7$), 2.67 (1H, m, $\mathbf{H}_{2ax}$), 2.33 - 2.04 (2H, m, $\mathbf{H}_9$), 1.97 - 1.52 (8H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$ & $\mathbf{H}_8$), 1.48 (9H, s, $\mathbf{H}_{19}$) ppm.

^{1}H NMR (V_T, T = 373 K) (400 MHz, DMSO-d_6) δ 7.47 - 7.41 (2H, m, $\mathbf{H}_{15}$), 7.28 (1H, m, $\mathbf{H}_{16}$), 7.14 - 7.07 (2H, m, $\mathbf{H}_{14}$), 5.85 (1H, ddt, *J* = 17.2, 10.1, 6.5 Hz, $\mathbf{H}_{10}$), 5.07 (1H, ddt, *J* = 17.2, 2.1 Hz, $\mathbf{H}_{11'}$), 5.02 (1H, ddt, *J* = 10.1, 2.1, 1.2 Hz, $\mathbf{H}_{11''}$), 4.44 (1H, dt, *J* = 10.7, 3.5 Hz, $\mathbf{H}_6$), 3.95 (1H, dd, *J* = 13.1, 3.9 Hz, $\mathbf{H}_{2eq}$), 3.21 (1H, ddd, *J* = 10.7, 3.9 Hz, $\mathbf{H}_7$), 2.75 (1H, td, *J* = 13.1, 2.3 Hz, $\mathbf{H}_{2ax}$), 2.24 - 2.07 (2H, m, $\mathbf{H}_9$), 1.81 - 1.53 (7H, m, $\mathbf{H}_{3eq}$, $\mathbf{H}_4$, $\mathbf{H}_5$ & $\mathbf{H}_8$), 1.43 (9H, s, $\mathbf{H}_{19}$), 1.33 (1H, m, $\mathbf{H}_{3ax}$) ppm.

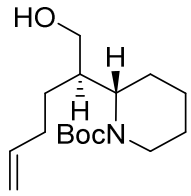
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 ($\mathbf{C}_{12}$), 154.9 ($\mathbf{C}_{17}$), 150.4 ($\mathbf{C}_{13}$), 137.2 ($\mathbf{C}_{10}$), 129.4 ($\mathbf{C}_{15}$), 125.8 ($\mathbf{C}_{16}$), 121.3 ($\mathbf{C}_{14}$), 115.7 ($\mathbf{C}_{11}$), 79.8 ($\mathbf{C}_{18}$), 52.7 ($\mathbf{C}_6$), 44.9 ($\mathbf{C}_7$), 39.7 ($\mathbf{C}_2$), 38.3 ($\mathbf{C}_8$), 31.4 ($\mathbf{C}_9$), 28.3 ($\mathbf{C}_{19}$), 27.4 ($\mathbf{C}_5$), 25.1 ($\mathbf{C}_3$), 19.1 ($\mathbf{C}_4$) ppm.

^{13}C NMR (V_T, T = 353 K) (100 MHz, DMSO-d_6) δ 172.1 (**C**$_{12}$), 153.8 (**C**$_{17}$), 149.9 (**C**$_{13}$), 137.3 (**C**$_{10}$), 129.1 (**C**$_{15}$), 125.5 (**C**$_{16}$), 121.0 (**C**$_{14}$), 114.8 (**C**$_{11}$), 78.5 (**C**$_{18}$), 51.5 (**C**$_{14}$), 44.2 (**C**$_{7}$), 38.4 (**C**$_{2}$), 30.3 (**C**$_{9}$), 28.0 (**C**$_{8}$), 27.7 (**C**$_{19}$), 26.8 (**C**$_{5}$), 24.4 (**C**$_{3}$), 18.3 (**C**$_{4}$) ppm.

LRMS (ES$^+$) *m/z* 396.2 [M+Na]$^+$, 437.2 [M+CH_3CN+Na]$^+$.

HRMS (ES$^+$) for $C_{22}H_{31}NNaO_4^+$ [M+Na]$^+$, calculated 396.2145 found 396.2143.

2.38 - (*S*)-*tert*-Butyl-2-((*R*)-1-hydroxyhex-5-en-2-yl)piperidine-1-carboxylate



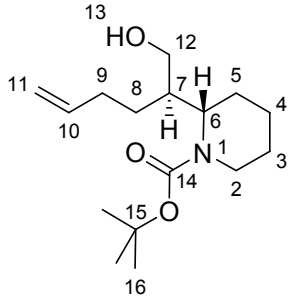
$C_{16}H_{29}NO_3$
Mol Wt: 283.4120

To a solution of phenyl ester **2.37** (2.00 g, 5.35 mmol) in THF (15 mL) at 0 °C under N_2 was added $LiAlH_4$ (0.20 g, 5.35 mmol) portionwise. The reaction was allowed to warm to rt and stirred for 30 min. The reaction mixture was cooled to 0 °C and quenched by slow addition of H_2O (1.60 mL), aq. 20% NaOH (4.30 mL) and H_2O (1.60 mL) sequentially. The white suspension was filtered through celite and the residue washed with EtOAc (2 x 25 mL), then CH_2Cl_2 (2 x 25 mL). The phases were separated and the organic layer washed with brine (3 x 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the title compound **2.38** (1.46 g, 5.15 mmol, 96%) as a colourless oil.

$[\alpha]^{25.5}_D$ −25.1 (*c* 0.67, $CHCl_3$).

R_f 0.38 (*eluent* EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 3442, 3075, 2974, 2932, 2865, 1660, 1419, 1272, 1164 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.1, 10.1, 6.7 Hz, $\mathbf{H}_{10}$), 5.03 (1H, ddt, *J* = 17.1, 1.9 Hz, $\mathbf{H}_{11'}$), 4.96 (1H, ddt, *J* = 10.1, 1.9, 1.2 Hz, $\mathbf{H}_{11''}$), 4.21 (1H, dd, *J* = 10.1, 4.5 Hz, $\mathbf{H}_6$), 4.02 (1H, dd, *J* = 12.8, 4.5 Hz, $\mathbf{H}_{2eq}$), 3.71 - 3.61 (2H, m, $\mathbf{H}_{12}$), 2.69 (1H, td, *J* = 12.8, 2.7 Hz, $\mathbf{H}_{2ax}$), 2.21 (1H, m, $\mathbf{H}_9$), 2.01 (1H, m, $\mathbf{H}_9$), 1.93 (1H, m, $\mathbf{H}_7$), 1.81 (1H, m, $\mathbf{H}_{5eq}$), 1.67 - 1.49 (4H, m, $\mathbf{H}_{3eq}$, $\mathbf{H}_4$ & $\mathbf{H}_{5ax}$), 1.46 (9H, s, $\mathbf{H}_{16}$), 1.45 - 1.39 (3H, m, $\mathbf{H}_{3ax}$ & $\mathbf{H}_8$) ppm.

^{1}H NMR (V_T, T = 353 K) (400 MHz, DMSO-d_6) δ 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.6 Hz, $\mathbf{H}_{10}$), 4.98 (1H, ddt, *J* = 17.0, 1.9 Hz, $\mathbf{H}_{11'}$), 4.92 (1H, ddt, *J* = 10.2, 1.9, 1.2 Hz, $\mathbf{H}_{11''}$), 4.16 (1H, t, *J* = 4.5 Hz, $\mathbf{H}_{13}$), 4.08 (1H, ddd, *J* = 11.0, 5.2, 2.2 Hz, $\mathbf{H}_6$), 3.89 (1H, dd, *J* = 13.4, 5.0 Hz, $\mathbf{H}_{2eq}$), 3.51 (2H, dt, *J* = 11.3, 4.5 Hz, $\mathbf{H}_{12'}$), 3.44 (2H, dt, *J* = 11.3, 4.5 Hz, $\mathbf{H}_{12''}$), 2.67 (1H, td, *J* = 13.4, 2.8 Hz, $\mathbf{H}_{2ax}$), 2.15 (1H, ddddt, *J* = 14.6, 9.7, 6.4, 5.1, 1.5 Hz, $\mathbf{H}_{9'}$), 1.98 (1H, ddddt, *J* = 14.6, 9.7, 6.4, 5.1, 1.5 Hz, $\mathbf{H}_{9''}$), 1.88 (1H, m, $\mathbf{H}_7$), 1.84 (1H, m, $\mathbf{H}_{5eq}$), 1.61 - 1.46 (3H, m, $\mathbf{H}_{3eq}$ & $\mathbf{H}_4$), 1.46 - 1.23 (4H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_8$), 1.40 (9H, s, $\mathbf{H}_{16}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 ($\mathbf{C}_{14}$), 138.8 ($\mathbf{C}_{10}$), 114.7 ($\mathbf{C}_{11}$), 79.4 ($\mathbf{C}_{15}$), 61.8 ($\mathbf{C}_{12}$), 51.3 ($\mathbf{C}_6$), 39.5 ($\mathbf{C}_2$), 38.7 ($\mathbf{C}_7$), 31.1 ($\mathbf{C}_9$), 28.5

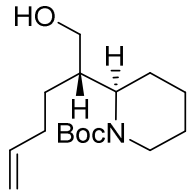
($\mathbf{C}_{16}$), 26.5 ($\mathbf{C}_5$), 26.0 ($\mathbf{C}_8$), 25.2 ($\mathbf{C}_3$), 19.4 ($\mathbf{C}_4$) ppm.

^{13}C NMR ($\mathbf{V_T}$, T = 353 K) (100 MHz, DMSO-d_6) δ 153.9 ($\mathbf{C}_{14}$), 138.9 ($\mathbf{C}_{10}$), 113.6 ($\mathbf{C}_{11}$), 77.7 ($\mathbf{C}_{15}$), 59.7 ($\mathbf{C}_{12}$), 51.2 ($\mathbf{C}_6$), 38.5 ($\mathbf{C}_2$), 37.1 ($\mathbf{C}_7$), 30.1 ($\mathbf{C}_9$), 27.8 ($\mathbf{C}_{16}$), 26.1 ($\mathbf{C}_5$), 25.8 ($\mathbf{C}_8$), 24.8 ($\mathbf{C}_3$), 18.5 ($\mathbf{C}_4$) ppm.

LRMS (ES^+) *m/z* 306.2 $[M+Na]^+$, 347.2 $[M+CH_3CN+Na]^+$.

HRMS (ES^+) for $C_{16}H_{29}NNaO_3^+$ $[M+Na]^+$, calculated 306.2040 found 306.2039.

***ent*-2.38 - (*R*)-*tert*-Butyl-2-((*S*)-1-hydroxyhex-5-en-2-yl)piperidine-1-carboxylate**

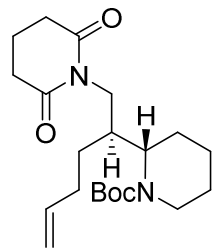


$C_{16}H_{29}NO_3$
Mol Wt: 283.4120

Following the procedure described for the synthesis of **2.38**, ester ***ent*-2.37** (2.15 g, 5.76 mmol) afforded the title compound ***ent*-2.38** (1.54 g, 5.43 mmol, 94%) as a colourless oil. Physical and spectroscopic data were consistent to those for the enantiomer.

$[\alpha]^{21}_D$ +13.7 (*c* 0.90, $CHCl_3$).

2.39 - (*S*)-*tert*-Butyl-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)hex-5-en-2-yl)piperidine-1-carboxylate



$C_{21}H_{34}N_2O_4$
Mol Wt: 378.5130

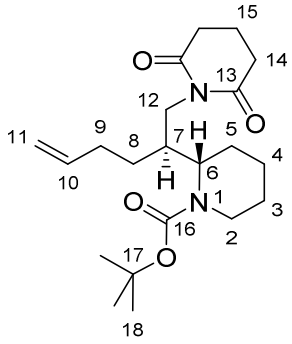
To a solution of alcohol **2.38** (1.15 g, 4.06 mmol), PPh_3 (2.13 g, 8.12 mmol) and glutarimide (0.92 g, 8.12 mmol) in THF (40 mL) at 0 °C under N_2 was added DIAD (1.60 mL, 8.12 mmol) dropwise. The resulting yellow solution was stirred at rt for 48 h before quenching with H_2O (40 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with EtOAc/hexane (40:60) afforded the title compound **2.39** (1.27 g, 3.36 mmol, 83%) as a white solid. Recrystallisation of **2.39** from hexane gave fine colourless needles (1.15 g, 3.04 mmol, 75%).

$[\alpha]^{26}_D$ −40.7 (*c* 1.67, $CHCl_3$).

M.p. (hexane) 84–87 °C.

R_f 0.14 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3075, 2974, 2933, 1725, 1671, 1416, 1360, 1270, 1166, 1039 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, $\mathbf{H}_{10}$), 4.95 (1H, ddt, *J* = 17.0, 1.9 Hz, $\mathbf{H}_{11'}$), 4.89 (1H, ddt, *J* = 10.1, 1.9, 1.1 Hz, $\mathbf{H}_{11''}$), 4.12 - 3.89 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_6$), 3.96 (1H, dd, *J* = 13.1, 10.1 Hz, $\mathbf{H}_{12'}$), 3.58 (1H, dd, *J* = 13.1, 4.0 Hz, $\mathbf{H}_{12''}$), 2.67 (4H, t, *J* = 6.6 Hz, 2 x $\mathbf{H}_{14}$), 2.66 (1H, m, $\mathbf{H}_{2ax}$), 2.44 (1H, m, $\mathbf{H}_7$), 2.11 - 2.01 (2H, m, $\mathbf{H}_9$) 1.94 (2H, quin, *J* = 6.6 Hz, $\mathbf{H}_{15}$), 1.86 - 1.67 (2H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{5eq}$), 1.65 - 1.36 (4H, m, $\mathbf{H}_3$, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$), 1.46 (9H, s, $\mathbf{H}_{18}$), 1.33 - 1.17 (2H, m, $\mathbf{H}_8$) ppm.

^{1}H NMR (V_T, T = 353 K) (400 MHz, DMSO-d_6) δ 5.70 (1H, ddt, *J* = 17.0, 10.0, 6.6 Hz, $\mathbf{H}_{10}$), 4.95 - 4.86 (2H, m, $\mathbf{H}_{11}$), 3.94 (1H, ddd, *J* = 11.0, 5.1, 2.1 Hz, $\mathbf{H}_6$), 3.88 (1H, dd, *J* = 13.2, 4.9 Hz, $\mathbf{H}_{2eq}$), 3.79 (1H, dd, *J* = 13.1, 9.2 Hz, $\mathbf{H}_{12'}$), 3.53 (1H, dd, *J* = 13.1, 4.4 Hz, $\mathbf{H}_{12''}$), 2.63 (1H, td, *J* = 13.2, 2.3 Hz, $\mathbf{H}_{2ax}$), 2.63 (4H, t, *J* = 6.6 Hz, 2 x $\mathbf{H}_{14}$), 2.31 (1H, m, $\mathbf{H}_7$), 2.09 - 1.98 (2H, m, $\mathbf{H}_9$), 1.84 (2H, quin, *J* = 6.6 Hz, $\mathbf{H}_{15}$), 1.79 (1H, m, $\mathbf{H}_{5eq}$), 1.65 (1H, m, $\mathbf{H}_{4eq}$), 1.57 - 1.49 (2H, m, $\mathbf{H}_{3eq}$ & $\mathbf{H}_{4ax}$), 1.48 - 1.27 (2H, m, $\mathbf{H}_{3ax}$ & $\mathbf{H}_{5ax}$), 1.41 (9H, s, $\mathbf{H}_{18}$), 1.26 - 1.12 (2H, m, $\mathbf{H}_8$) ppm.

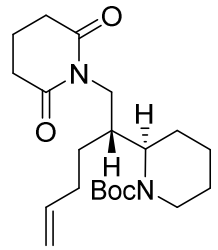
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 ($\mathbf{C}_{13}$), 154.9 ($\mathbf{C}_{16}$), 139.1 ($\mathbf{C}_{10}$), 114.2 ($\mathbf{C}_{11}$), 79.3 ($\mathbf{C}_{17}$), 40.6 ($\mathbf{C}_{12}$), 33.4 ($\mathbf{C}_7$), 33.0 ($\mathbf{C}_{14}$), 29.6 ($\mathbf{C}_9$), 28.5 ($\mathbf{C}_{18}$), 27.5 ($\mathbf{C}_8$), 26.7 ($\mathbf{C}_5$), 25.4 (C_3), 19.2 ($\mathbf{C}_4$), 17.1 ($\mathbf{C}_{15}$) (2 carbons missing: C_2 & C_6, observed in the V_T NMR) ppm.

^{13}C NMR (V_T, T = 353 K) (100 MHz, DMSO-d_6) δ 172.5 (**C**$_{13}$), 153.7 (**C**$_{16}$), 138.8 (**C**$_{10}$), 113.7 (**C**$_{11}$), 78.0 (**C**$_{17}$), 51.9 (**C**$_6$), 39.7 (**C**$_{12}$), 38.9 (**C**$_2$), 33.4 (**C**$_7$), 32.0 (**C**$_{14}$), 29.0 (**C**$_9$), 27.8 (**C**$_{18}$), 27.0 (**C**$_8$), 25.9 (**C**$_5$), 24.5 (**C**$_3$), 18.4 (**C**$_4$), 16.2 (**C**$_{15}$) ppm.

LRMS (ES$^+$) *m/z* 401.2 [M+Na]$^+$, 442.2 [M+CH_3CN+Na]$^+$.

HRMS (ES$^+$) for $C_{21}H_{34}N_2NaO_4^+$ [M+Na]$^+$, calculated 401.2411 found 401.2409.

***ent*-2.39 - (*R*)-*tert*-Butyl-2-((*R*)-1-(2,6-dioxopiperidin-1-yl)hex-5-en-2-yl)piperidine-1-carboxylate**

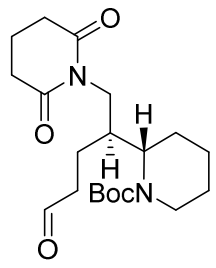


$C_{21}H_{34}N_2O_4$
Mol Wt: 378.5130

Following the procedure described for the synthesis of **2.39**, alcohol ***ent*-2.38** (1.50 g, 5.29 mmol) afforded the title compound ***ent*-2.39** (1.55 g, 3.96 mmol, 75%) as fine colourless needles. Physical and spectroscopic data were consistent to those for the enantiomer.

$[\alpha]^{21}_D$ +61.7 (*c* 0.67, $CHCl_3$).

2.41 - (*S*)-*tert*-Butyl-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)-5-oxopentan-2-yl)piperidine-1-carboxylate



$C_{20}H_{32}N_2O_5$
Mol Wt: 380.4850

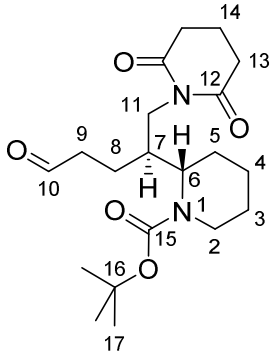
To a solution of olefin **2.39** (1.00 g, 2.64 mmol), $K_2OsO_4 \cdot 2H_2O$ (0.05 g, 0.13 mol) and $NaIO_4$ (2.82 g, 13.2 mmol) in dioxane/H_2O (3:1 - 120 mL) was added 2,6-lutidine (0.62 mL, 5.28 mmol) dropwise. The resulting white suspension was stirred at rt for 24 h. The suspension was filtered under vacuum through a sintered funnel and the residue washed with EtOAc (2 x 80 mL). The combined organic phases were washed with H_2O (3 x 80 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a grey oil. Purification by column chromatography eluting with EtOAc/hexane (50:50) afforded the title compound **2.41** (0.80 g, 2.10 mmol, 80%) as a white solid. Recrystallisation of **2.41** from hexane/EtOAc gave fine white needles (0.69 g, 1.81 mmol, 69%).

$[\alpha]^{24.5}_D$ −59.5 (*c* 0.51, $CHCl_3$).

M.p. (hexane/EtOAc) 124–129 °C.

R_f: 0.20 (*eluent*: EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 3294, 2978, 2872, 2936, 1725, 1677, 1419, 1365, 1270, 1170 cm^{-1}.



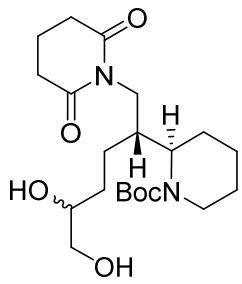
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s, $\mathbf{H}_{10}$), 4.05 (1H, m, $\mathbf{H}_{6}$), 4.03 (1H, m, $\mathbf{H}_{2eq}$), 3.88 (1H, dd, *J* = 13.1, 9.9 Hz, $\mathbf{H}_{11'}$), 3.55 (1H, dd, *J* = 13.1, 3.5 Hz, $\mathbf{H}_{11''}$), 2.72 - 2.57 (4H, t, *J* = 6.6 Hz, $\mathbf{H}_{13}$), 2.60 (3H, m, $\mathbf{H}_{2ax}$ & $\mathbf{H}_{9}$),2.46 (1H, m, $\mathbf{H}_{7}$), 1.95 (2H, quin, *J* = 6.6 Hz, $\mathbf{H}_{14}$), 1.82 (1H, m, $\mathbf{H}_{5eq}$), 1.72 (1H, m, $\mathbf{H}_{4eq}$), 1.42 (9H, s, $\mathbf{H}_{17}$), 1.66 - 1.35 (6H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5x}$ & $\mathbf{H}_{8}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 ($\mathbf{C}_{10}$), 172.9 ($\mathbf{C}_{12}$), 154.8 ($\mathbf{C}_{15}$), 79.5 ($\mathbf{C}_{16}$), 50.4 ($\mathbf{C}_{6}$), 39.5 ($\mathbf{C}_{11}$), 39.2 ($\mathbf{C}_{9}$), 39.2 ($\mathbf{C}_{2}$), 32.9 ($\mathbf{C}_{13}$), 32.8 ($\mathbf{C}_{7}$), 28.4 (C_{17}), 26.4 ($\mathbf{C}_{5}$), 25.4 ($\mathbf{C}_{3}$), 19.1 ($\mathbf{C}_{8}$), 18.4 ($\mathbf{C}_{4}$), 17.0 ($\mathbf{C}_{14}$) ppm.

LRMS (ES^+) *m/z* 419.1 $[M+K]^+$.

HRMS (ES^+) for $C_{20}H_{32}N_2NaO_5^+$ $[M+Na]^+$, calculated 403.2203 found 403.2206.

***ent*-2.40 - (2*R*)-*tert*-Butyl-2-((2*R*)-1-(2,6-dioxopiperidin-1-yl)-5,6-dihydroxyhexan-2-yl)piperidine-1-carboxylate**



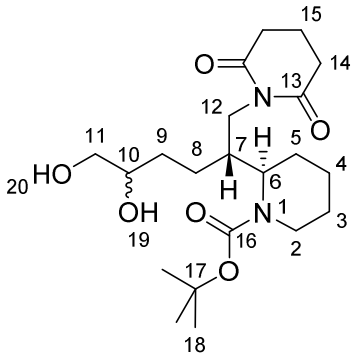
$C_{21}H_{36}N_2O_6$
Mol Wt: 412.5270

To a solution of olefin ***ent*-2.39** (0.85 g, 2.25 mmol) in CH_2Cl_2/H_2O (8:1 - 27 mL) were added $K_2OsO_4 \cdot 2H_2O$ (0.04 g, 0.11 mmol) and NMO (0.32 g, 2.70 mol) portionwise. The resulting white suspension was stirred at rt for 64 h before quenching with sat. aq. Na_2SO_3 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), EtOAc (3 x 10 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with MeOH/EtOAc (5:95) afforded the title compound ***ent*-2.40** (0.86 g, 2.08 mmol, 92%) as an inseparable mixture of two diastereoisomers *dr* ~ 1:1.

$[\alpha]^{20}_D$ +34.5 (*c* 0.64, $CHCl_3$).

R_f 0.20 (*eluent*: MeOH/EtOAc - 10:90).

FT-IR (neat) ν_{max} 3432, 2933, 2867, 1722, 1663, 1422, 1361, 1272, 1166 cm^{-1}.



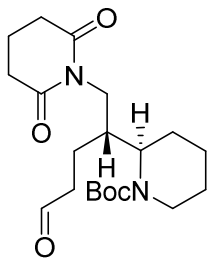
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 - 3.99 (4H, m, 2 x $\mathbf{H}_{2eq}$ & 2 x $\mathbf{H}_{6}$), 3.95 (2H, dd, *J* = 13.2, 10.5 Hz, 2 x $\mathbf{H}_{12'}$), 3.54 (6H, m, 2 x $\mathbf{H}_{10}$, & 2 x $\mathbf{H}_{11}$), 3.58 (2H, dd, *J* = 13.2, 3.5 Hz, $\mathbf{H}_{12''}$), 2.69 (4H, t, *J* = 6.5 Hz, 2 x $\mathbf{H}_{14'}$), 2.68 (4H, t, *J* = 6.5 Hz, 2 x $\mathbf{H}_{14''}$), 2.75 - 2.61 (2H, m, 2 x $\mathbf{H}_{2ax}$), 2.63 - 2.38 (2H, m, 2 x $\mathbf{H}_{7}$), 2.24 (2H, br. s., 2 x $\mathbf{H}_{19}$), 2.17 (2H, br.s, 2 x $\mathbf{H}_{20}$), 1.96 (4H, quin, *J* = 6.5 Hz, 2 x $\mathbf{H}_{15}$), 1.88 - 1.49 (14H, m, 2 x $\mathbf{H}_{3eq}$, 2 x $\mathbf{H}_{4eq}$, 2 x $\mathbf{H}_{4ax}$, 2 x $\mathbf{H}_{5eq}$, 2 x $\mathbf{H}_{5ax}$, 2 x $\mathbf{H}_{9'}$, & 2 x $\mathbf{H}_{9''}$), 1.46 (9H, s, $\mathbf{H}_{18}$), 1.45 (9H, s, $\mathbf{H}_{18}$), 1.43 - 1.22 (6H, m, 2 x $\mathbf{H}_{3ax}$, 2 x $\mathbf{H}_{8'}$, & 2 x $\mathbf{H}_{8''}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 ($\mathbf{C}_{13'}$), 173.1 ($\mathbf{C}_{13''}$), 155.0 (2 x $\mathbf{C}_{16}$), 79.7 ($\mathbf{C}_{17'}$), 79.5 ($\mathbf{C}_{17''}$), 72.3 (2 x $\mathbf{C}_{10}$), 39.6 (2 x $\mathbf{C}_{12}$), 33.7 (2 x $\mathbf{C}_{7}$), 33.6 (2 x $\mathbf{C}_{9}$), 33.1 (2 x $\mathbf{C}_{14}$), 28.5 (2 x $\mathbf{C}_{18}$), 26.6 (2 x $\mathbf{C}_{5}$), 25.5 (2 x $\mathbf{C}_{3}$), 22.7 (2 x $\mathbf{C}_{8}$), 19.1 (2 x $\mathbf{C}_{4}$), 17.1 ($\mathbf{C}_{15'}$), 17.1 ($\mathbf{C}_{15''}$) ppm.

LC-MS (ES^+) *m/z* 313.0 $[M–Boc+H]^+$, 413.1 $[M+H]^+$, 847.1 $[2M+Na]^+$.

HRMS (ES^+) for $C_{21}H_{36}N_2NaO_6^+$ $[M+Na]^+$, calculated 435.2466 found 435.2469.

***ent*-2.41 - (*R*)-*tert*-Butyl-2-((*R*)-1-(2,6-dioxopiperidin-1-yl)-5-oxopentan-2-yl)piperidine-1-carboxylate**

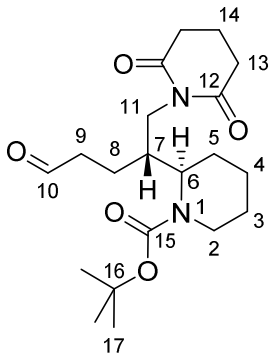


$C_{20}H_{32}N_2O_5$
Mol Wt: 380.4850

To a solution of diol ***ent*-2.40** (0.83 g, 2.01 mmol) in MeOH/H_2O (5:1 - 18 mL) was added $NaIO_4$ (0.65 g, 3.02 mol) portionwise. The resulting white suspension was stirred at rt for 3 h, diluted with MeOH (10 mL) and filtered under vacuum through a sintered funnel. The filtrate was concentrated *in vacuo* and the residue partitioned between EtOAc/H_2O (1:1 - 20 mL). The phases were separated, the organic phase washed with brine (3 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid. Purification by column chromatography eluting with EtOAc/hexane (50:50) afforded the title compound ***ent*-2.41** (0.70 g, 1.84 mmol, 92%) as a white solid.

$[\alpha]^{19}_D$ +68.2 (*c* 1.05, $CHCl_3$).

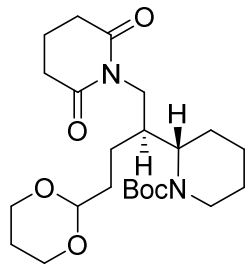
M.p. 124–130 °C.
(hexane/EtOAc)



^{1}H NMR (V_T, T = 353 K) (500 MHz, DMSO-d_6) δ 9.62 (1H, s, $\mathbf{H}_{10}$), 3.93 (1H, ddd, J = 10.8, 4.8, 2.1 Hz, $\mathbf{H}_6$), 3.87 (1H, dd, J = 13.6, 3.6 Hz, $\mathbf{H}_{2eq}$), 3.75 (1H, dd, J = 13.3, 9.2 Hz, $\mathbf{H}_{11'}$), 3.55 (1H, dd, J = 13.3, 4.2 Hz, $\mathbf{H}_{11''}$), 2.66 (1H, td, J = 13.6, 3.6 Hz, $\mathbf{H}_{2ax}$), 2.63 (4H, t, J = 6.5 Hz, $\mathbf{H}_{13}$), 2.53 - 2.40 (2H, m, $\mathbf{H}_9$), 2.34 (1H, m, $\mathbf{H}_7$), 1.86 (2H, quin, J = 6.5 Hz, $\mathbf{H}_{14}$), 1.82 (1H, m, $\mathbf{H}_{5eq}$), 1.66 (1H, m, $\mathbf{H}_{4eq}$), 1.57 - 1.50 (2H, m, $\mathbf{H}_{3eq}$ & $\mathbf{H}_{4ax}$), 1.49 - 1.26 (4H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{5ax}$, $\mathbf{H}_8$), 1.41 (9H, s, $\mathbf{H}_{17}$) ppm.

^{13}C NMR (V_T, T = 353 K) (125 MHz, DMSO-d_6) δ 202.1 ($\mathbf{C}_{10}$), 172.5 ($\mathbf{C}_{12}$), 153.7 ($\mathbf{C}_{15}$), 78.2 ($\mathbf{C}_{16}$), 51.5 ($\mathbf{C}_6$), 39.2 ($\mathbf{C}_{11}$), 39.0 ($\mathbf{C}_9$), 38.8 ($\mathbf{C}_2$), 33.3 ($\mathbf{C}_7$), 31.9 ($\mathbf{C}_{13}$), 27.7 ($\mathbf{C}_{17}$), 25.7 ($\mathbf{C}_5$), 24.4 ($\mathbf{C}_3$), 19.3 ($\mathbf{C}_8$), 18.3 ($\mathbf{C}_4$), 16.0 ($\mathbf{C}_{14}$) ppm.

2.43 - (*S*)-*tert*-Butyl-2-((*S*)-4-(1,3-dioxan-2-yl)-1-(2,6-dioxopiperidin-1-yl)butan-2-yl)piperidine-1-carboxylate



$C_{23}H_{38}N_2O_6$
Mol Wt: 438.5650

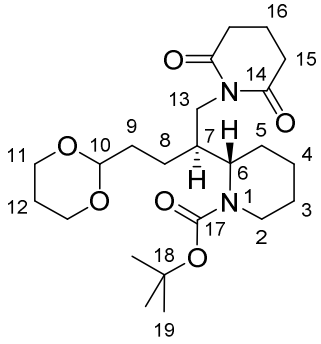
To a solution of aldehyde **2.41** (0.17 g, 0.45 mmol) and TsOH (10 mg, 0.05 mmol) in THF (3 mL) at rt under N_2 was added 1,3-propandiol (**2.45**) (0.04 mL, 0.47 mmol) dropwise. The reaction mixture was stirred at rt for 3 h before quenching with sat. aq. $NaHCO_3$ (3 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), the organic phases combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by column chromatography eluting with EtOAc/hexane

(50:50) afforded the title compound **2.43** (0.19 g, 0.43 mmol, 96%) as a colourless oil.

$[\alpha]^{19}_{D}$ −32.0 (*c* 0.50, $CHCl_3$).

R_f 0.17 (*eluent*: EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 2933, 2855, 1725, 1678, 1417, 1362, 1170 cm^{-1}.



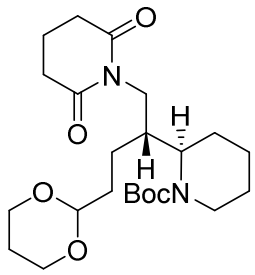
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (1H, t, *J* = 5.1 Hz, $\mathbf{H}_{10}$), 4.08 - 3.97 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_6$), 4.03 (2H, ddd, *J* = 11.6, 5.1, 1.5 Hz, $\mathbf{H}_{11eq}$), 3.93 (1H, dd, *J* = 12.9, 10.1 Hz, $\mathbf{H}_{13'}$), 3.68 (2H, tdd, *J* = 11.6, 2.5, 1.5 Hz, $\mathbf{H}_{11ax}$), 3.56 (1H, dd, *J* = 12.9, 4.3 Hz, $\mathbf{H}_{13'}$), 2.67 (1H, m, $\mathbf{H}_{2ax}$), 2.66 (4H, t, *J* = 6.6 Hz, $\mathbf{H}_{15}$), 2.44 (1H, m, $\mathbf{H}_7$), 2.03 (1H, m, $\mathbf{H}_{12}$), 1.95 (2H, quin, *J* = 6.6 Hz, $\mathbf{H}_{16}$), 1.83 - 1.64 (2H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{5eq}$), 1.63 - 1.37 (6H, m, $\mathbf{H}_3$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_9$), 1.46 (9H, s, $\mathbf{H}_{19}$), 1.35 - 1.20 (2H, m, $\mathbf{H}_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 ($\mathbf{C}_{14}$), 155.0 ($\mathbf{C}_{17}$), 102.6 ($\mathbf{C}_{10}$), 79.3 ($\mathbf{C}_{18}$), 66.7 ($\mathbf{C}_{11}$), 41.0 ($\mathbf{C}_{13}$), 33.4 ($\mathbf{C}_7$), 33.1 ($\mathbf{C}_{15}$), 31.6 ($\mathbf{C}_9$), 28.4 ($\mathbf{C}_{19}$), 26.7 ($\mathbf{C}_5$), 25.9 ($\mathbf{C}_3$), 25.4 ($\mathbf{C}_{12}$), 22.3 ($\mathbf{C}_8$), 19.2 ($\mathbf{C}_4$), 17.0 ($\mathbf{C}_{16}$) ppm.

LRMS (ES^+) *m/z* 461.1 $[M+Na]^+$, 502.0 $[M+CH_3CN+Na]^+$.

HRMS (ES^+) for $C_{23}H_{38}N_2NaO_6^+$ $[M+Na]^+$, calculated 461.2622 found 461.2624.

***ent*-2.43 - (*R*)-*tert*-Butyl-2-((*R*)-4-(1,3-dioxan-2-yl)-1-(2,6-dioxopiperidin-1-yl)butan-2-yl)piperidine-1-carboxylate**

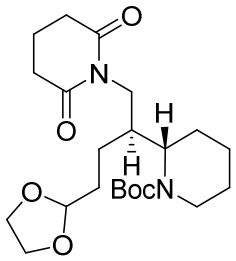


$C_{23}H_{38}N_2O_6$
Mol Wt: 438.5650

Following the procedure described for the synthesis of **2.43**, aldehyde ***ent*-2.41** (0.30 g, 0.79 mmol) afforded the title compound ***ent*-2.43** (0.29 g, 0.66 mmol, 84%) as a colourless oil.

$[\alpha]^{19}_D$ +37.8 (*c* 0.48, $CHCl_3$).

2.42 - (*S*)-*tert*-Butyl-2-((S)-4-(1,3-dioxolan-2-yl)-1-(2,6-dioxopiperidin-1-yl)butan-2-yl)piperidine-1-carboxylate



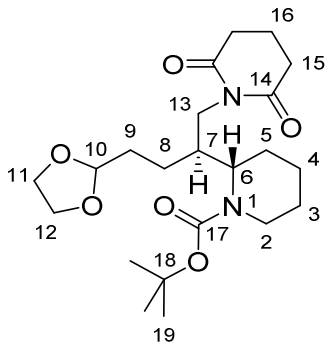
$C_{22}H_{36}N_2O_6$
Mol Wt: 424.5380

Following the procedure described for the synthesis of **2.43**, aldehyde **2.41** (0.20 g, 0.53 mmol) afforded the title compound **2.42** (0.21 g, 0.49 mmol, 92%) as a colourless oil.

$[\alpha]^{19}_D$ −31.6 (*c* 1.61, $CHCl_3$).

R_f 0.33 (*eluent*: hexane/EtOAc - 20:80).

FT-IR (neat) ν_{max} 2933, 2855, 1725, 1678, 1417, 1362, 1170 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (2H, t, *J* = 4.8 Hz, $\mathbf{H}_{10}$), 4.07 - 3.92 (2H, m, $\mathbf{H}_6$ & $\mathbf{H}_{2eq}$), 3.96 (1H, dd, *J* = 13.0, 10.3 Hz, $\mathbf{H}_{13'}$), 3.92 - 3.85 (2H, m, $\mathbf{H}_{11eq}$ & $\mathbf{H}_{12eq}$), 3.83 - 3.76 (2H, m, $\mathbf{H}_{11ax}$ & $\mathbf{H}_{12ax}$), 3.56 (2H, dd, *J* = 13.0, 4.3 Hz, $\mathbf{H}_{13''}$), 2.71 (1H, m, $\mathbf{H}_{2ax}$), 2.67

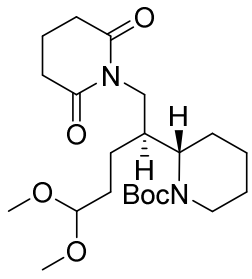
(4H, t, J = 6.5 Hz, $\mathbf{H}_{15}$), 2.58 - 2.45 (1H, m, $\mathbf{H}_{7}$), 1.95 (2H, quin, J = 6.5 Hz, $\mathbf{H}_{16}$), 1.84 - 1.71 (2H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{5eq}$), 1.70 - 1.50 (6H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_{9}$), 1.46 (9H, s, $\mathbf{H}_{19}$), 1.36 - 1.21 (2H, m, $\mathbf{H}_{8}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 ($\mathbf{C}_{14}$), 154.9 ($\mathbf{C}_{17}$), 104.9 ($\mathbf{C}_{10}$), 79.3 ($\mathbf{C}_{18}$), 64.7 ($\mathbf{C}_{11}$), 64.7 ($\mathbf{C}_{12}$), 52.0 ($\mathbf{C}_{6}$), 40.4 ($\mathbf{C}_{13}$), 33.2 ($\mathbf{C}_{7}$), 33.1 ($\mathbf{C}_{15}$), 29.4 ($\mathbf{C}_{9}$), 28.5 ($\mathbf{C}_{19}$), 26.7 ($\mathbf{C}_{5}$), 25.4 ($\mathbf{C}_{3}$), 21.7 ($\mathbf{C}_{8}$), 19.2 ($\mathbf{C}_{4}$), 17.0 ($\mathbf{C}_{16}$) ppm.

LRMS (ES^+) *m/z* 447.3 $[M+Na]^+$, 488.3 $[M+CH_3CN+Na]^+$, 871.5 $[2M+Na]^+$.

HRMS (ES^+) for $C_{22}H_{36}N_2NaO_6^+$ $[M+Na]^+$, calculated 447.2466 found 447.2466.

2.57 - (*S*)-*tert*-Butyl-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)-5,5-dimethoxypentan-2-yl)piperidine-1-carboxylate



$C_{22}H_{38}N_2O_6$
Mol Wt: 426.5540

To a solution of aldehyde **2.41** (50 mg, 0.13 mmol) in THF/MeOH (2:1 - 1.5 mL) at rt under N_2 was added TFA (10 μL, 0.13 mmol) dropwise. The reaction mixture was stirred at rt for 12 h before quenching with sat. aq. $NaHCO_3$ (1.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL), EtOAc (3 x 3 mL), the organic phases

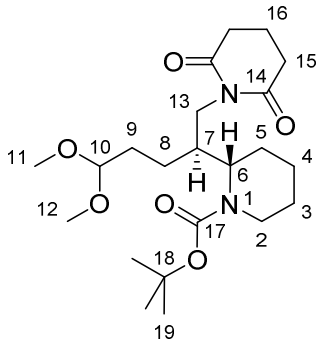
combined, washed with brine (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **2.57** (55 mg, 0.13 mmol, 99%) as white solid. Recrystallisation of **2.57** from hexane gave fine white needles (50 mg, 0.12 mmol, 92%).

$[\alpha]^{19}_D$ −42.5 (*c* 0.51, $CHCl_3$).

M.p. (hexane) 112–114 °C.

R_f 0.29 (*eluent*: hexane/EtOAc - 20:80).

FT-IR (neat) ν_{max} 2934, 2877, 2831, 1724, 1678, 1417, 1361, 1168 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1H, t, *J* = 5.7 Hz, $\mathbf{H}_{10}$), 3.95 (1H, dd, *J* = 13.0, 10.3 Hz, $\mathbf{H}_{13'}$), 4.10 - 3.88 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_6$), 3.56 (1H, dd, *J* = 13.0, 4.2 Hz, $\mathbf{H}_{13''}$), 3.26 (3H, s, $\mathbf{H}_{11}$), 3.25 (3H, s, $\mathbf{H}_{12}$), 2.66 (1H, m, $\mathbf{H}_{2ax}$), 2.66 (4H, t, *J* = 6.5 Hz, $\mathbf{H}_{15}$), 2.45 (1H, m, $\mathbf{H}_7$), 1.95 (2H, quin, *J* = 6.5 Hz, $\mathbf{H}_{16}$), 1.84 - 1.68 (2H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{5eq}$), 1.67 - 1.49 (6H, m, $\mathbf{H}_3$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_9$), 1.46 (9H, m, $\mathbf{H}_{19}$), 1.35 - 1.12 (2H, m, $\mathbf{H}_8$) ppm.

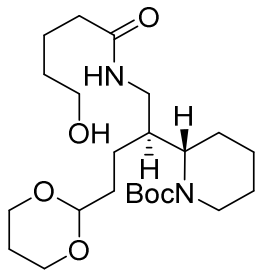
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 ($\mathbf{C}_{14}$), 154.9 ($\mathbf{C}_{17}$), 104.9 ($\mathbf{C}_{10}$), 79.3 ($\mathbf{C}_{18}$), 52.5 ($\mathbf{C}_{11}$), 52.4 ($\mathbf{C}_6$), 40.5 ($\mathbf{C}_{13}$), 33.3 ($\mathbf{C}_7$), 33.0 ($\mathbf{C}_{15}$), 28.4 ($\mathbf{C}_{19}$), 28.0 ($\mathbf{C}_9$), 26.7 ($\mathbf{C}_5$), 25.4 ($\mathbf{C}_3$), 22.5 ($\mathbf{C}_8$), 19.2 ($\mathbf{C}_4$), 17.0

(**C**$_{16}$) ppm.

LRMS (ES$^+$) *m/z* 449.3 [M+Na]$^+$, 875.8 [2M+Na]$^+$.

HRMS (ES$^+$) for $C_{22}H_{38}N_2NaO_6^+$ [M+Na]$^+$, calculated 449.2622 found 449.2621.

2.46 - (*S*)-*tert*-Butyl-2-((*S*)-4-(1,3-dioxan-2-yl)-1-(5-hydroxypentanamido)butan-2-yl)piperidine-1-carboxylate



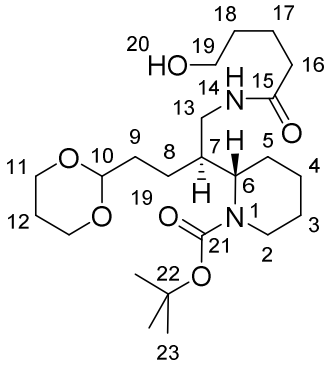
$C_{23}H_{42}N_2O_6$
Mol Wt: 442.5970

To a stirred solution of imide **2.43** (50 mg, 0.11 mmol) in MeOH (5 mL) at 0 °C under N_2 was added $NaBH_4$ (9 mg, 2.28 mmol) portionwise. The resulting mixture was stirred at 0 °C for 4 h before quenching with sat. aq. $NaHCO_3$ (10 mL). The phases were separated, the organic layer washed with sat. aq. $NaHCO_3$ (3 x10 mL), brine (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **2.46** (50 mg, 0.11 mmol, 99%) as a viscous oil.

$[\alpha]^{19}_D$ −28.9 (*c* 0.57, $CHCl_3$).

R_f 0.28 (*eluent*: MeOH/EtOAc - 10:90).

FT-IR (neat) ν_{max} 3335, 2932, 2861, 1655, 1553, 1421, 1273, 1145, 998 cm^{-1}.



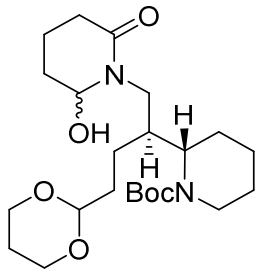
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (1H, t, *J* = 5.1 Hz, $\mathbf{H}_{14}$), 4.50 (1H, t, *J* = 4.8 Hz, $\mathbf{H}_{10}$), 4.08 (2H, ddd, *J* = 11.9, 4.8, 1.0 Hz, $\mathbf{H}_{11eq}$), 4.02 - 3.91 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_{6}$), 3.74 (2H, tdd, *J* = 11.6, 2.6, 1.0 Hz, $\mathbf{H}_{11ax}$), 3.69 - 3.60 (2H, qd, *J* = 5.8, 1.8 Hz, $\mathbf{H}_{19}$), 3.39 - 3.23 (2H, m, $\mathbf{H}_{13}$), 2.79 (1H, br. s., $\mathbf{H}_{20}$), 2.65 (1H, td, *J* = 12.3, 2.3 Hz, $\mathbf{H}_{2ax}$), 2.25 (2H, t, *J* = 7.1 Hz, $\mathbf{H}_{16}$), 2.14 - 1.94 (3H, m, $\mathbf{H}_{7}$ & $\mathbf{H}_{12}$), 1.87 (1H, m, $\mathbf{H}_{5eq}$), 1.80 - 1.66 (3H, m, $\mathbf{H}_{9'}$ & $\mathbf{H}_{17}$), 1.66 - 1.38 (6H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_{9''}$), 1.45 (9H, s, $\mathbf{H}_{23}$), 1.37 - 1.21 (2H, m, $\mathbf{H}_{8}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 ($\mathbf{C}_{15}$), 155.3 ($\mathbf{C}_{21}$), 102.3 ($\mathbf{C}_{10}$), 79.4 ($\mathbf{C}_{22}$), 66.8 ($\mathbf{C}_{11}$), 62.2 ($\mathbf{C}_{19}$), 51.4 ($\mathbf{C}_{6}$), 39.6 ($\mathbf{C}_{2}$), 38.2 ($\mathbf{C}_{13}$), 36.1 ($\mathbf{C}_{16}$), 35.5 ($\mathbf{C}_{7}$), 31.9 ($\mathbf{C}_{9}$), 31.5 ($\mathbf{C}_{18}$), 28.4 ($\mathbf{C}_{23}$), 26.2 ($\mathbf{C}_{5}$), 25.8 ($\mathbf{C}_{12}$), 25.3 ($\mathbf{C}_{3}$), 22.0 ($\mathbf{C}_{17}$), 21.0 ($\mathbf{C}_{8}$), 19.1 ($\mathbf{C}_{4}$) ppm.

LRMS (ES^+) *m/z* 465.2 $[M+Na]^+$, 907.5 $[2M+Na]^+$.

HRMS (ES^+) for $C_{23}H_{42}N_2NaO_6^+$ $[M+Na]^+$, calculated 465.2935 found 465.2947.

2.47 - (*S*)-*tert*-Butyl-2-((*S*-4-(1,3-dioxan-2-yl)-1-(2-hydroxy-6-oxopiperidin-1-yl)butan-2-yl)piperidine-1-carboxylate



$C_{23}H_{40}N_2O_6$
Mol Wt: 440.5810

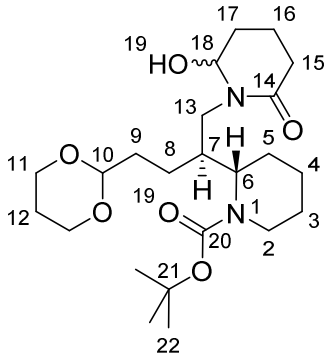
2.47 was prepared using an adapted procedure as detailed by Grigg *et al*.[85]

To a stirred solution of imide **2.43** (0.10 g, 0.23 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C under N_2 was added $LiEt_3BH$ (0.32 mL of 1 M sol. in THF, 0.32 mmol) dropwise. The resulting mixture was stirred at −78 °C for 3 h, then was allowed to warm to −20 °C and a solution of HCl (0.11 mL of 2 M sol. in EtOH, 0.23 mmol) was added dropwise. The mixture was allowed to warm to rt and stirred for 1 h before quenching with sat. aq. $NaHCO_3$ (1.5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL), the organic phases combined, washed with sat. aq. $NaHCO_3$ (3 x 3 mL), brine (3 x 3 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **2.47** (0.09 g, 0.20 mmol, 87%) as a white foam.

$[\alpha]^{19}_D$ −33.3 (*c* 0.38, $CHCl_3$).

R_f 0.09 (*eluent*: hexane/EtOAc - 20:80).

FT-IR (neat) ν_{max} 3339, 2933, 2859, 1683, 1659, 1420, 1366, 1272, 1146 cm^{-1}.



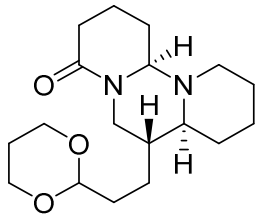
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (1H, dt, *J* = 6.3, 3.4 Hz,), 4.88 (1H, dt, *J* = 7.3, 3.4 Hz,), 4.53 - 4.40 (2H, m), 4.35 (1H, t, *J* = 5.1 Hz,), 4.10 - 3.85 (7H, m), 3.83 - 3.63 (4H, m), 3.54 (1H, m), 3.18 (1H, dd, *J* = 13.4, 9.9 Hz,), 2.94 (1H, dd, *J* = 13.9, 8.8 Hz,), 2.75 - 2.55 (3H, m), 2.48 (2H, m), 2.30 (2H, m), 2.04 (3H, m), 1.90 (3H, m), 1.84 - 1.66 (6H, m), 1.57 - 1.36 (7H, m), 1.44 (18H, s), 1.33 - 1.22 (3H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (**C**), 171.4 (**C**), 171.0 (**C**), 155.2 (**C**), 155.0 (**C**), 155.0 (**C**), 102.7 (**C**H), 102.6 (**C**H), 102.5 (**C**H), 81.2 (**C**H), 80.7 (**C**H), 79.3 (**C**H), 79.3 (**C**H), 66.8 (**C**H_2), 66.8 (**C**H_2), 66.7 (**C**H_2), 52.2 (**C**H), 47.3 (**C**H_2), 40.9 (**C**H_2), 39.6 (**C**H_2), 33.5 (**C**H), 33.3 (**C**H), 33.0 (**C**H_2), 32.6 (**C**H), 32.6 (**C**H_2), 32.3 (**C**H_2), 31.4 (**C**H_2), 31.0 (**C**H_2), 30.4 (**C**H_2), 28.4 (**C**H_3), 26.6 (**C**H_2), 25.6 (**C**H_2), 22.3 (**C**H_2), 21.3 (**C**H_2), 19.2 (**C**H_2), 19.2 (**C**H_2), 16.9 (**C**H_2), 15.8 (**C**H_2), 15.8 (**C**H_2) ppm.

LRMS (ES$^+$) *m/z* 463.1 $[M+Na]^+$, 903.2 $[2M+Na]^+$.

HRMS (ES$^+$) for $C_{23}H_{40}N_2NaO_6^+$ $[M+Na]^+$, calculated 463.2784 found 463.2779.

2.52 - (7*R*,7a*S*,12a*S*)-7-(2-(1,3-dioxan-2-yl)ethyl)decahydro-4H,6H-dipyrido [1,2-a:1',2'-c]pyrimidin-4-one



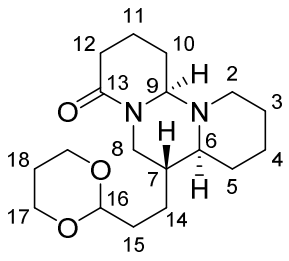
$C_{18}H_{30}N_2O_3$
Mol Wt: 322.4490

To a stirred solution of hydroxy lactam **2.47** (70 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 was added TFA (0.05 ml, 0.64 mmol) dropwise. The resulting mixture was stirred at 0 °C for 1 h, then was allowed to warm to rt and stirred for 1 h before quenching with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 x 2.5 mL), CH_2Cl_2 (2 x 2.5 mL), the organic phases combined, washed with H_2O (3 x 7.5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (1:4:95) afforded the title compound **2.52** (18 mg, 0.056 mmol, 35%) as a yellow oil.

$[\alpha]^{19}_D$ +22.2 (*c* 0.25, $CHCl_3$).

R_f 0.16 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 1:9:90).

FT-IR (neat) ν_{max} 2931, 2857, 1643, 1467, 1350, 1265, 1143 cm^{-1}.

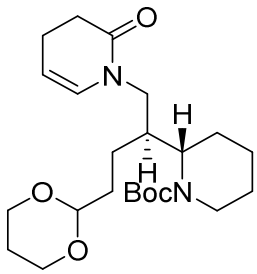


^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (1H, dd, *J* = 5.3 Hz, $\mathbf{H}_{8eq}$), 4.55 (1H, d,

J = 4.5 Hz, $\mathbf{H}_{10}$), 4.52 (1H, t, *J* = 5.1 Hz, $\mathbf{H}_{16}$), 4.09 (2H, ddd, *J* = 12.1, 4.9, 1.0 Hz, $\mathbf{H}_{17eq}$), 3.75 (2H, td, *J* = 12.1, 2.5 Hz, $\mathbf{H}_{17ax}$), 3.34 (1H, dd, *J* = 14.4, 2.8 Hz, $\mathbf{H}_{2eq}$), 3.08 (1H, ddd, *J* = 12.4, 4.6, 2.3 Hz, $\mathbf{H}_{6}$), 2.76 (1H, ddd, *J* = 14.4, 13.1, 2.3 Hz, $\mathbf{H}_{2ax}$), 2.46 - 2.25 (3H, m, $\mathbf{H}_{8ax}$ & $\mathbf{H}_{12}$), 2.14 - 2.00 (2H, m, $\mathbf{H}_{5eq}$ & $\mathbf{H}_{18eq}$), 1.98 - 1.82 (3H, m, $\mathbf{H}_{3eq}$, $\mathbf{H}_{7}$ & $\mathbf{H}_{11eq}$), 1.80 - 1.67 (2H, m, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{5ax}$), 1.65 - 1.46 (5H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{11ax}$ & $\mathbf{H}_{15}$), 1.38 - 1.18 (5H, m, $\mathbf{H}_{18ax}$, $\mathbf{H}_{10}$ & $\mathbf{H}_{14}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 ($\mathbf{C}_{13}$), 101.9 ($\mathbf{C}_{16}$), 66.9 ($\mathbf{C}_{17}$), 66.3 ($\mathbf{C}_{9}$), 59.5 ($\mathbf{C}_{6}$), 49.8 ($\mathbf{C}_{2}$), 42.0 ($\mathbf{C}_{8}$), 37.8 ($\mathbf{C}_{7}$), 32.6 ($\mathbf{C}_{12}$), 32.0 ($\mathbf{C}_{15}$), 27.4 ($\mathbf{C}_{5}$), 25.8 ($\mathbf{C}_{18}$), 25.1 ($\mathbf{C}_{3}$), 23.6 ($\mathbf{C}_{10}$), 19.1 ($\mathbf{C}_{4}$), 17.8 ($\mathbf{C}_{11}$), 16.3 ($\mathbf{C}_{14}$) ppm.

2.48 - (*S*)-*tert*-Butyl-2-((*S*)-4-(1,3-dioxan-2-yl)-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)butan-2-yl)piperidine-1-carboxylate



$C_{23}H_{38}N_2O_5$
Mol Wt: 422.5660

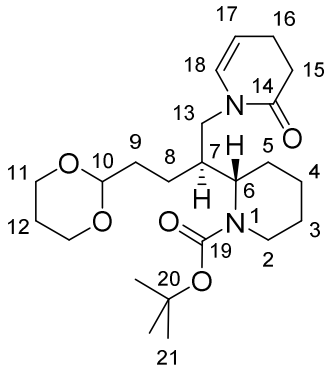
To a stirred solution of imide **2.43** (75 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2 was added $LiEt_3BH$ (0.24 mL of 1 M sol. in THF, 0.24 mmol) dropwise. The resulting mixture was stirred at −78 °C for 3 h, then was allowed to warm to −20 °C and a solution of HCl (0.34 mL of 1 M sol. in EtOH, 0.34 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 1 h before quenching with $NaHCO_3$ (72 mg, 0.86 mmol). The white suspension was stirred at rt for 12 h and filtered under

vacuum through a sintered funnel. The residue was washed with EtOAc (10 mL) and CH_2Cl_2 (10 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil. The crude oil was redissolved in degassed $PhCH_3$ (2 mL) and NH_4Cl (1 mg, 0.02 mmol) was added. The colourless suspension was irradiated for 1 h at 120 °C in the MW and the solvent removed *in vacuo* to yield a colouless oil. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **2.48** (32 mg, 0.075 mmol, 44%) as a colourless oil.

$[\alpha]^{24}_D$ -42.1 (*c* 1.6, $CHCl_3$).

R_f 0.52 (*eluent*: MeOH/EtOAc - 10:90).

FT-IR (neat) ν_{max} 2932, 2851, 1669, 1453, 1425, 1269, 1143 cm^{-1}.



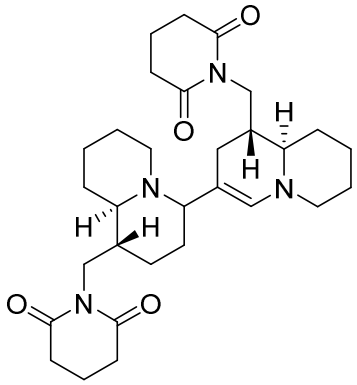
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1H, d, *J* = 7.7 Hz, $\mathbf{H}_{18}$), 5.15 (1H, dt, *J* = 7.7, 4.4 Hz, $\mathbf{H}_{17}$), 4.41 (1H, t, *J* = 5.0 Hz, $\mathbf{H}_{10}$), 4.04 (2H, ddd, *J* = 11.7, 5.0, 1.2 Hz, $\mathbf{H}_{11eq}$), 4.01 - 3.94 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_6$), 3.69 (2H, tdd, *J* = 11.7, 2.7, 1.2 Hz, $\mathbf{H}_{11ax}$), 3.60 (1H, dd, *J* = 13.8, 4.6 Hz, $\mathbf{H}_{13'}$), 3.22 (1H, dd, *J* = 13.8, 8.1 Hz, $\mathbf{H}_{13''}$), 2.66 (1H, td, *J* = 13.2, 2.3 Hz, $\mathbf{H}_{2ax}$), 2.52 - 2.44 (2H, *J* = 7.9 Hz, $\mathbf{H}_{15}$), 2.36 - 2.24 (3H, m, $\mathbf{H}_7$ & $\mathbf{H}_{16}$), 2.02 (1H, qt, *J* = 12.7, 5.1 Hz, $\mathbf{H}_{12eq}$), 1.45 (9H, s, $\mathbf{H}_{21}$), 1.70 (1H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$, $\mathbf{H}_{8'}$ & $\mathbf{H}_9$), 1.36 - 1.19 (2H, m, $\mathbf{H}_{8''}$ & $\mathbf{H}_{12ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (**C_{14}**), 155.0 (**C_{19}**), 130.6 (**C_{18}**), 106.1 (**C_{17}**), 102.6 (**C_{10}**), 79.3 (**C_{20}**), 66.7 (**C_{11}**), 52.5 (**C_6**), 47.5 (**C_{13}**), 39.3 (**C_2**), 34.8 (**C_7**), 31.6 (**C_{15}**), 31.4 (**C_9**), 28.4 (**C_{11}**), 26.5 (**C_5**), 25.8 (**C_{12}**), 25.3 (**C_3**), 22.4 (**C_8**), 20.1 (**C_{16}**), 19.1 (**C_4**) ppm.

LRMS (ES^+) *m/z* 423.0 $[M+H]^+$, 445.1 $[M+Na]^+$, 867.3 $[2M+Na]^+$.

HRMS (ES^+) for $C_{23}H_{38}N_2NaO_5^+$ $[M+Na]^+$, calculated 445.2673 found 445.2681.

***ent*-2.60 - 1-(((1*R*,9a*R*)-4-((4*S*,4a*S*)-4-((2,6-dioxopiperidin-1-yl)methyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)octahydro-2*H*-quinolizin-1-yl)methyl)piperidine-2,6-dione**



$C_{30}H_{44}N_4O_4$
Mol Wt: 524.7060

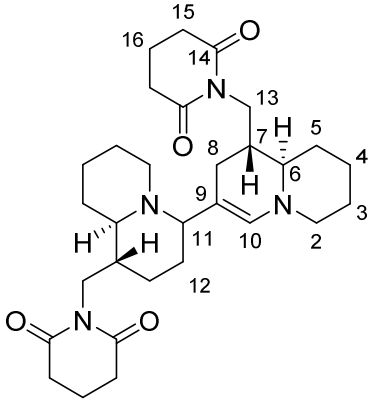
To a stirred solution of aldehyde ***ent*-2.41** (75 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 was added TFA (0.12 ml, 1.60 mmol) dropwise. The resulting mixture was stirred at 0 °C for 1 h, then was allowed to warm to rt and stirred for 4 h before the solvent removed *in vacuo*. The residue was redissolved in CH_2Cl_2 (2 mL) and BtH (0.12 g, 1.00 mmol) was added portionwise. The resulting mixture was stirred at rt for 12 h before the solvent was removed *in vacuo*. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (1:4:95) afforded the title compound ***ent*-2.60**

(50 mg, 0.19 mmol, 95%) as a yellow oil.

$[\alpha]^{24}_{D}$ +44.6 (*c* 0.55, $CHCl_3$).

R_f 0.58 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 2930, 2854, 2782, 2729, 1722, 1666, 1437, 1350, 1225 cm^{-1}.



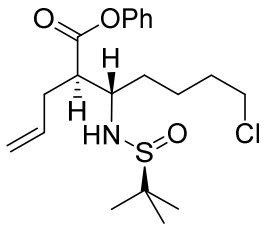
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (1H, br. s, **H_{10}**), 3.84 - 3.66 (4H, m, 2 x **H_{13}**), 3.14 (1H, d, *J* = 9.3 Hz, **H_{2eq}**), 3.05 (1H, d, *J* = 12.2 Hz, **H_{2eq}**), 2.65 (1H, m, **H_{2ax}**), 2.66 (4H, t, *J* = 6.5 Hz, 2 x **$H_{15'}$**), 2.64 (4H, t, *J* = 6.5 Hz, 2 x **$H_{15''}$**), 2.50 (1H, m, **$H_{6'}$**), 2.17 (1H, m, **$H_{6''}$**), 1.97 - 1.90 (4H, m, 2 x **H_{16}**), 2.08 - 1.15 (19H, m, **H_{2ax}**, 2 x **H_3**, 2 x **H_4**, 2 x **H_5**, 2 x **H_{8eq}**, **H_{8ax}**, **H_{11}** & **H_{12}**), 1.00 (1H, m, **H_{8ax}**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (2 x **$C_{14'}$** & 2 x **$C_{14''}$**), 132.7 (**C_{10}**), 110.7 (**C_9**), 68.8 (**$C_{6'}$**), 66.8 (**C_{11}**), 59.0 (**$C_{6''}$**), 53.7 (2 x **$C_{2'eq}$**), 53.1 (2 x **$C_{2''eq}$**), 42.4 (2 x **$C_{13'}$**), 41.9 (2 x **$C_{13''}$**), 39.1 (**$C_{7'}$**), 36.6 (**$C_{7''}$**), 33.0 (2 x **$C_{15'}$**), 32.9 (2 x **$C_{15''}$**), 31.5 (2 x **$C_{5'}$**), 30.1 (2 x **$C_{5''}$**), 28.2 (**C_{12}**), 27.7 (2 x **$C_{3'}$**), 26.2 (2 x **$C_{3''}$**), 25.3 (2 x **$C_{8'}$** & 2 x **$C_{8''}$**), 24.9 (2 x **$C_{4'}$** & 2 x **$C_{4''}$**), 17.2 (2 x **C_{16}**) ppm.

LC-MS (ES^+) *m/z* 263.0 $[M/2+H]^+$, 525.3 $[M+H]^+$.

HRMS (ES$^+$) for $C_{30}H_{45}N_4O_4^+$ $[M+H]^+$, calculated 525.3435 found 525.3428.

2.66 - (2*R*,3*S*)-Phenyl-2-allyl-3-((*S*)-2-methyl-propane-2-sulfinylamino)-7-chloroheptanoate



$C_{20}H_{30}ClNO_3S$
Mol Wt: 399.9740

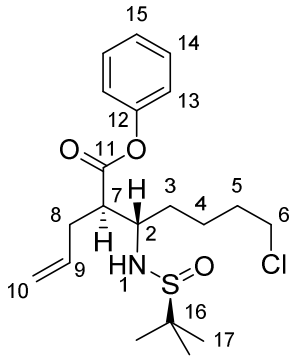
Following the procedure described for the synthesis of **2.35**, imine **1.110** (5.00 g, 22.35 mmol) afforded the crude product as a separable mixture of two diastereoisomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti dr* 91:9). Purification by column chromatography eluting with EtOAc/hexane (20:80) and recrystallisation from hexane afforded the major diastereomer **2.66** (6.70 g, 16.75 mmol, 75%) as large colouless needles.

$[\alpha]^{19}_D$ +14.7 (*c* 1.02, $CHCl_3$).

M.p. (hexane) 51–54 °C.

R_f 0.47 (*eluent*: MeOH/EtOAc - 2:98).

FT-IR (neat) ν_{max} 3218, 3076, 2953, 2867, 1752, 1642, 1593, 1491, 1363, 1188 cm^{-1}.



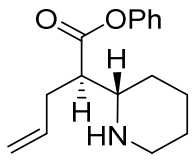
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, t, *J* = 7.6 Hz, $\mathbf{H}_{14}$), 7.25 (2H, t, *J* = 7.6 Hz, $\mathbf{H}_{15}$), 7.08 (2H, d, *J* = 7.6 Hz, $\mathbf{H}_{13}$), 5.90 (1H, ddt, *J* = 17.3, 10.3, 6.7 Hz, $\mathbf{H}_{9}$), 5.21 (1H, ddt, *J* = 17.3, 1.5 Hz, $\mathbf{H}_{10'}$), 5.16 (1H, ddt, *J* = 10.3, 1.5 Hz, $\mathbf{H}_{10''}$), 4.22 (1H, d, *J* = 8.8 Hz, $\mathbf{H}_{1}$), 3.55 (2H, t, *J* = 6.4 Hz, $\mathbf{H}_{6}$), 3.51 (1H, m, $\mathbf{H}_{2}$), 3.31 (1H, ddd, *J* = 7.5, 4.3 Hz, $\mathbf{H}_{7}$), 2.71 (1H, dddt, *J* = 14.5, 7.5, 6.3, 1.5 Hz, $\mathbf{H}_{8'}$), 2.42 (1H, dddt, *J* = 14.5, 7.5, 1.2 Hz, $\mathbf{H}_{8''}$), 1.87 - 1.46 (6H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4}$ & $\mathbf{H}_{5}$), 1.25 (9H, s, $\mathbf{H}_{17}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 ($\mathbf{C}_{11}$), 150.3 ($\mathbf{C}_{12}$), 134.8 ($\mathbf{C}_{9}$), 129.5 ($\mathbf{C}_{14}$), 126.1 ($\mathbf{C}_{15}$), 121.5 ($\mathbf{C}_{13}$), 117.8 ($\mathbf{C}_{10}$), 57.5 ($\mathbf{C}_{2}$), 56.2 ($\mathbf{C}_{16}$), 50.0 ($\mathbf{C}_{7}$), 44.7 ($\mathbf{C}_{6}$), 33.0 ($\mathbf{C}_{8}$), 32.0 ($\mathbf{C}_{5}$), 31.0 ($\mathbf{C}_{3}$), 23.5 ($\mathbf{C}_{4}$), 22.7 ($\mathbf{C}_{17}$) ppm.

LC-MS (ES^+) *m/z* 400.0 $[M^{35}Cl+H]^+$, 402.1 $[M^{37}Cl+H]^+$, 422.1 $[M^{35}Cl+Na]^+$, 424.1 $[M^{37}Cl+Na]^+$.

HRMS (ES^+) for $C_{20}H_{30}ClNNaO_3S^+$ $[M+Na]^+$, calculated 422.1527 found 422.1530.

2.73 - (*R*)-Phenyl-2-((*S*)-piperidin-2-yl)pent-4-enoate



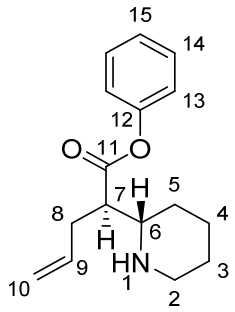
$C_{16}H_{21}NO_2$
Mol Wt: 259.3490

Following the procedure described for the synthesis of **2.36**, imino-aldol **2.66** (6.00 g, 15.00 mmol) afforded the title compound **2.73** (2.89 g, 11.14 mmol, 74%) as pale yellow oil.

$[\alpha]^{27}_D$ −15.6 (*c* 0.97, $CHCl_3$).

R_f 0.17 (*eluent*: MeOH/EtOAc - 2:98).

FT-IR (neat) ν_{max} 3337, 3075, 2931, 2854, 2807, 1753, 1641, 1593, 1492, 1142 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.34 (2H, m, $\mathbf{H}_{14}$), 7.23 (1H, m, $\mathbf{H}_{15}$), 7.10 - 7.03 (2H, m, $\mathbf{H}_{13}$), 5.89 (1H, ddt, *J* = 17.1, 10.1, 6.9 Hz, $\mathbf{H}_9$), 5.19 (1H, ddt, *J* = 17.1, 1.5 Hz, $\mathbf{H}_{10'}$), 5.16 (1H, ddt, *J* = 10.1, 1.5, 1.1 Hz, $\mathbf{H}_{10''}$), 3.12 (1H, m, $\mathbf{H}_{2eq}$), 2.89 (1H, ddd, *J* = 10.1, 7.5, 2.7 Hz, $\mathbf{H}_6$), 2.71 (1H, dt, *J* = 7.5 Hz, $\mathbf{H}_7$), 2.67 (1H, td, *J* = 11.9, 2.9 Hz, $\mathbf{H}_{2ax}$), 2.60 - 2.48 (2H, m, $\mathbf{H}_8$), 1.91 - 1.69 (2H, m, $\mathbf{H}_{4eq}$ &

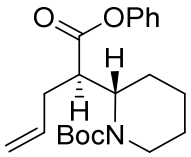
$\mathbf{H}_{5eq}$), 1.62 (1H, m, $\mathbf{H}_{3eq}$), 1.50 - 1.31 (3H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 ($\mathbf{C}_{11}$), 150.6 ($\mathbf{C}_{12}$), 135.4 ($\mathbf{C}_9$), 129.4 ($\mathbf{C}_{14}$), 125.8 ($\mathbf{C}_{15}$), 121.6 ($\mathbf{C}_{13}$), 117.1 ($\mathbf{C}_{10}$), 58.0 ($\mathbf{C}_6$), 51.3 ($\mathbf{C}_7$), 47.1 ($\mathbf{C}_2$), 32.9 ($\mathbf{C}_8$), 30.5 ($\mathbf{C}_5$), 26.5 ($\mathbf{C}_3$), 24.7 ($\mathbf{C}_4$) ppm.

LC-MS (ES^+) *m/z* 260.1 $[M+H]^+$.

HRMS (ES^+) for $C_{16}H_{22}NO_2^+$ $[M+H]^+$, calculated 260.1645 found 260.1639.

2.67 - (*S*)-*tert*-Butyl-2-((*R*)-1-oxo-1-phenoxypent-4-en-2-yl)piperidine-1-carboxylate



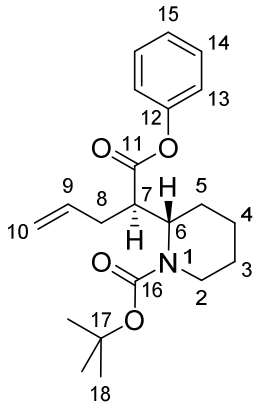
$C_{21}H_{29}NO_4$
Mol Wt: 359.4660

Following the procedure described for the synthesis of **2.37**, piperidine **2.73** (2.10 g, 8.10 mmol) afforded the title compound **2.67** (2.83 g, 7.87 mmol, 97%) as a colourless oil.

$[\alpha]^{20}_D$ +0.11 (*c* 0.9, $CHCl_3$).

R_f 0.30 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3077, 2975, 2936, 1755, 1686, 1642, 1593, 1413, 1250, 1158 cm^{-1}.



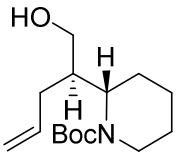
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 -7.34 (2H, m, $\mathbf{H}_{14}$), 7.23 (1H, m, $\mathbf{H}_{15}$), 7.08 - 7.01 (2H, m, $\mathbf{H}_{13}$), 5.88 (1H, ddt, *J* = 17.2, 10.0, 6.7 Hz, $\mathbf{H}_{9}$), 5.24 - 5.07 (2H, m, $\mathbf{H}_{10}$), 4.64 (1H, m, $\mathbf{H}_{6}$), 4.09 (1H, m, $\mathbf{H}_{2eq}$), 3.24 (1H, td, *J* = 11.0, 3.7 Hz, $\mathbf{H}_{7}$), 2.86 - 2.26 (3H, m, $\mathbf{H}_{2ax}$ & $\mathbf{H}_{8}$), 1.79 - 1.63 (5H, m, $\mathbf{H}_{3eq}$, $\mathbf{H}_{4}$ & $\mathbf{H}_{5}$), 1.50 (9H, s, $\mathbf{H}_{18}$), 1.31 (1H, m, $\mathbf{H}_{3ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 ($\mathbf{C}_{11}$), 154.9 ($\mathbf{C}_{16}$), 150.5 ($\mathbf{C}_{12}$), 134.6 ($\mathbf{C}_{9}$), 129.4 ($\mathbf{C}_{14}$), 125.9 ($\mathbf{C}_{15}$), 121.7 ($\mathbf{C}_{13}$), 117.4 ($\mathbf{C}_{10}$), 79.9 ($\mathbf{C}_{17}$), 52.4 ($\mathbf{C}_{6}$), 45.5 ($\mathbf{C}_{7}$), 38.4 ($\mathbf{C}_{2}$), 34.2 ($\mathbf{C}_{8}$), 28.4 ($\mathbf{C}_{18}$), 27.8 ($\mathbf{C}_{5}$), 25.3 ($\mathbf{C}_{3}$), 19.1 ($\mathbf{C}_{4}$) ppm.

LC-MS (ES^+) *m/z* 160.1 $[M–Boc+H]^+$, 360.1 $[M+H]^+$.

HRMS (ES^+) for $C_{21}H_{29}NNaO_4^+$ $[M+Na]^+$, calculated 382.1989 found 382.1982.

2.68 - (*S*)-*tert*-Butyl-2-((*R*)-1-hydroxypent-4-en-2-yl)piperidine-1-carboxylate



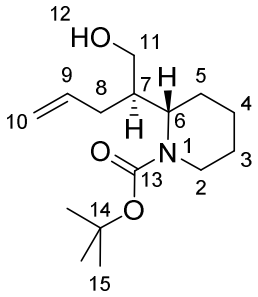
$C_{15}H_{27}NO_3$
Mol Wt: 269.3850

Following the procedure described for the synthesis of **2.38**, ester **2.67** (2.80 g, 7.79 mmol) afforded the title compound **2.68** (2.04 g, 7.57 mmol, 97%) as a colourless oil.

$[\alpha]^{20}_D$ −14.8 (*c* 1.00, $CHCl_3$).

R_f 0.13 (*eluent* EtOAc/hexane - 20:80).

FT-IR (neat) ν_{max} 3443, 3075, 2974, 2932, 1659, 1418, 1273, 1163 cm^{-1}.



^{1}H NMR (400 MHz, DMSO-d_6) δ 5.78 (1H, ddt, *J* = 17.1, 10.1, 7.0 Hz, $\mathbf{H}_9$), 5.03 - 4.93 (2H, m, $\mathbf{H}_{10}$), 4.40 (1H, t, *J* = 5.0 Hz, $\mathbf{H}_{12}$), 4.08 (1H, dd, *J* = 9.7, 3.5 Hz, $\mathbf{H}_6$), 3.87 (1H, d, *J* = 11.5 Hz, $\mathbf{H}_{2eq}$), 3.45 - 3.35 (2H, m, $\mathbf{H}_{11}$), 2.67 (1H, t, *J* = 11.5 Hz, $\mathbf{H}_{2ax}$), 2.05 - 1.80 (4H, m, $\mathbf{H}_{5eq}$, $\mathbf{H}_7$ & $\mathbf{H}_8$), 1.59 - 1.43 (3H, m, $\mathbf{H}_{3eq}$ & $\mathbf{H}_4$), 1.40 - 1.19 (2H, m, $\mathbf{H}_{3ax}$ & $\mathbf{H}_{5ax}$), 1.38 (9H, s, $\mathbf{H}_{15}$) ppm.

^{1}H NMR (V_T, T = 373 K) (500 MHz, DMSO-d_6) δ 5.85 (1H, ddt, J = 17.1, 10.2, 7.0 Hz, **H**$_9$), 5.01 (1H, ddt, J = 17.1, 2.3, 1.5 Hz, **H**$_{10'}$), 4.96 (1H, ddt, J = 10.2, 2.3, 1.1 Hz, **H**$_{10''}$), 4.09 (1H, ddd, J = 10.5, 5.2, 2.4 Hz, **H**$_6$), 3.96 (1H, t, J = 4.9 Hz, **H**$_{12}$), 3.90 (1H, dddt, J = 13.6, 4.8, 2.1, 3.0 Hz, **H**$_{2eq}$), 3.51 - 3.43 (2H, m, **H**$_{11}$), 2.73 (1H, ddd, J = 13.6, 12.6 3.0 Hz, **H**$_{2ax}$), 2.10 - 1.93 (3H, m, **H**$_7$ & **H**$_8$), 1.86 (1H, m, **H**$_{5eq}$), 1.63 - 1.47 (3H, m, **H**$_{3eq}$ & **H**$_4$), 1.42 (9H, s, **H**$_{15}$), 1.47 - 1.29 (2H, m, **H**$_{3ax}$ & **H**$_{5ax}$) ppm.

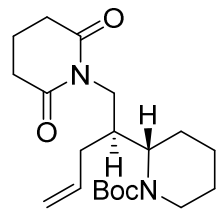
^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1 (**C**$_{13}$), 137.6 (**C**$_9$), 115.9 (**C**$_{10}$), 78.1 (**C**$_{14}$), 59.3 (**C**$_{11}$), 50.9 (**C**$_6$), 37.6 (**C**$_7$), 31.5 (**C**$_8$), 28.1 (**C**$_{15}$), 26.1 (**C**$_5$), 25.3 (**C**$_3$), 18.8 (**C**$_4$) (1 carbon missing: C_2, observed in the V_T NMR) ppm.

^{13}C NMR (V_T, T = 353 K) (125 MHz, DMSO-d_6) δ 153.9 (**C**$_{13}$), 137.2 (**C**$_9$), 114.9 (**C**$_{10}$), 77.7 (**C**$_{14}$), 59.8 (**C**$_{11}$), 51.2 (**C**$_6$), 38.5 (**C**$_2$), 38.1 (**C**$_7$), 31.4 (**C**$_8$), 27.7 (**C**$_{15}$), 25.7 (**C**$_5$), 24.7 (**C**$_3$), 18.5 (**C**$_4$) ppm.

LC-MS (ES$^+$) *m/z* 170.1 $[M-Boc+H]^+$, 292.1 $[M+Na]^+$.

HRMS (ES$^+$) for $C_{15}H_{27}NNaO_3^+$ $[M+Na]^+$, calculated 292.1883 found 292.1884.

2.69 - (*S*)-*tert*-Butyl-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)pent-4-en-2-yl)piperidine-1-carboxylate



$C_{20}H_{32}N_2O_4$
Mol Wt: 364.4860

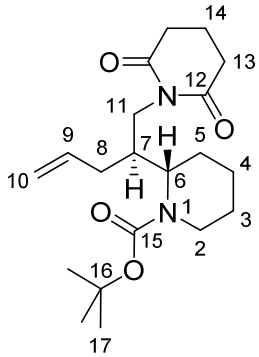
Following the procedure described for the synthesis of **2.39**, alcohol **2.68** (1.70 g, 6.31 mmol) afforded the title compound **2.69** (1.84 g, 5.05 mmol, 80%) as fine colourless needles.

$[\alpha]^{20}_D$ −46.0 (*c* 0.63, $CHCl_3$).

M.p. (hexane) 72–74 °C.

R_f 0.25 (*eluent*: EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 3078, 3008, 2969, 2932, 2849, 2879, 1723 1669, 1412, 1354, 1267, 1167 cm^{-1}.



^{1}H NMR (400 MHz, DMSO-d_6) δ 5.69 (1H, m, **H**$_9$), 4.93 - 4.84 (2H, m, **H**$_{10}$), 3.86 (1H, m, **H**$_6$), 3.87 (1H, m, **H**$_{2eq}$), 3.77 (1H, dd, *J* = 13.1, 9.8 Hz, **H**$_{11'}$), 3.45 (1H, dd, *J* = 13.1, 4.1 Hz, **H**$_{11''}$), 2.59 (1H, m, **H**$_{2ax}$), 2.58 (4H, t, *J* = 6.5 Hz, **H**$_{13}$), 2.40 (1H, m, **H**$_7$), 1.93 - 1.74 (5H, m, **H**$_{5eq}$, **H**$_8$ & **H**$_{14}$), 1.69 - 1.48 (3H, m, **H**$_{3eq}$ & **H**$_4$), 1.43 - 1.20 (2H, m, **H**$_{3ax}$ & **H**$_{5ax}$), 1.38 (9H, s, **H**$_{17}$) ppm.

^{1}H NMR (V_T, T = 353 K) (500 MHz, DMSO-d_6) δ 5.73 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, **H**$_9$), 4.94 - 4.88 (2H, m, **H**$_{10}$), 3.92 (1H, ddd, *J* = 10.7, 5.0, 2.4 Hz, **H**$_6$), 3.87 (1H, m, **H**$_{2eq}$), 3.80 (1H, dd, *J* = 13.1, 9.3 Hz, **H**$_{11'}$), 3.54 (1H, dd, *J* = 13.1, 4.6 Hz, **H**$_{11''}$), 2.66 (1H, ddd, *J* = 13.6, 12.7, 3.1 Hz, **H**$_{2ax}$), 2.59 (4H, t, *J* = 6.5 Hz, **H**$_{13}$), 2.42 (1H, dddt, *J* = 11.0, 9.0, 6.7, 4.5 Hz, **H**$_7$), 1.97 (1H, m, **H**$_{8'}$), 1.92 - 1.75 (5H, m, **H**$_{5eq}$, **H**$_{8''}$ & **H**$_{14}$), 1.65 (1H, m, **H**$_{4eq}$), 1.59 - 1.50 (2H, m, **H**$_{3eq}$ & **H**$_{4ax}$), 1.45 (1H, m, **H**$_{5ax}$), 1.41 (9H, s, **H**$_{17}$), 1.33 (1H, m, **H**$_{3ax}$) ppm.

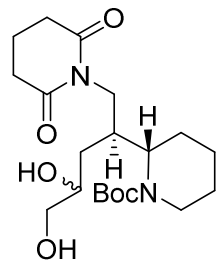
^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (**C**$_{12}$), 154.0 (**C**$_{15}$), 137.0 (**C**$_9$), 115.4 (**C**$_{10}$), 78.4 (**C**$_{16}$), 40.6 (**C**$_{11}$), 34.0 (**C**$_7$), 32.8 (**C**$_8$), 32.3 (**C**$_{13}$), 28.1 (**C**$_{17}$), 26.1 (**C**$_5$), 25.0 (**C**$_3$), 18.7 (**C**$_4$), 16.4 (**C**$_{14}$) (2 carbons missing: C_2 & C_6, observed in the V_T NMR) ppm.

^{13}C NMR (V_T, T = 353 K) (125 MHz, DMSO-d_6) δ 172.3 (**C**$_{12}$), 153.8 (**C**$_{15}$), 136.6 (**C**$_9$), 114.6 (**C**$_{10}$), 78.0 (**C**$_{12}$), 52.4 (**C**$_6$), 40.4 (**C**$_{11}$), 38.8 (**C**$_2$), 34.4 (**C**$_7$), 32.5 (**C**$_8$), 31.9 (**C**$_{13}$), 27.7 (**C**$_{17}$), 25.6 (**C**$_5$), 24.3 (**C**$_3$), 18.3 (**C**$_4$), 15.9 (**C**$_{14}$) ppm.

LC-MS (ES$^+$) *m/z* 265.1 [M−Boc+H]$^+$, 387.1 [M+Na]$^+$.

HRMS (ES$^+$) for $C_{20}H_{32}N_2NaO_4^+$ [M+Na]$^+$, calculated 387.2254 found 387.2252.

2.74 - (*2S*)-*tert*-Butyl-2-((*2S*)-1-(2,6-dioxopiperidin-1-yl)-4,5-dihydroxypentan-2-yl)piperidine-1-carboxylate



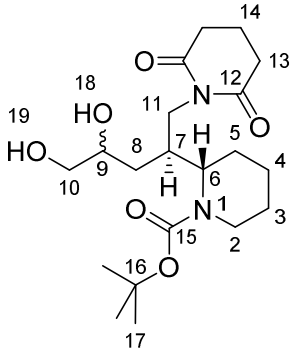
$C_{20}H_{34}N_2O_6$
Mol Wt: 398.5000

Following the procedure described for the synthesis of ***ent*-2.40**, alkene **2.69** (1.45 g, 3.98 mmol) afforded the title compound **2.74** (1.32 g, 3.31 mmol, 83%) as an inseparable mixture of two diastereoisomers *dr* ~ 1:1.

$[\alpha]^{20}_D$ −31.9 (*c* 0.80, $CHCl_3$).

R_f: 0.26 (*eluent*: MeOH/EtOAc - 4:96).

FT-IR (neat) ν_{max} 3432, 3055, 2935, 2871, 1722, 1663, 1420, 1272, 1166 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 - 4.02 (2H, m, 2 x $\mathbf{H}_6$), 4.02 - 3.93 (2H, m, 2 x $\mathbf{H}_{2eq}$), 3.92 - 3.79 (4H, m, 2 x $\mathbf{H}_9$ & 2 x $\mathbf{H}_{11'}$), 3.72 (2H, dd, *J* = 13.0, 4.1 Hz, 2 x $\mathbf{H}_{11''}$), 3.55 - 3.44 (2H, m, 2 x $\mathbf{H}_{10'}$), 3.30 -

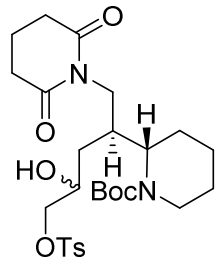
3.22 (2H, m, 2 x $\mathbf{H}_{10''}$), 2.89 - 2.62 (2H, m, 2 x $\mathbf{H}_{2ax}$), 2.69 (4H, t, *J* = 6.5 Hz, 2 x $\mathbf{H}_{13'}$), 2.66 (4H, t, *J* = 6.5 Hz, 2 x $\mathbf{H}_{13''}$), 2.59 - 2.43 (2H, m, 2 x $\mathbf{H}_{7}$), 2.25 (2H, br.s, 2 x $\mathbf{H}_{18}$), 2.18 (2H, br.s, 2 x $\mathbf{H}_{19}$), 2.00 - 1.89 (4H, m, 2 x $\mathbf{H}_{14}$), 1.87 - 1.49 (10H, m, 2 x $\mathbf{H}_{3eq}$, 2 x $\mathbf{H}_{4eq}$, 2 x $\mathbf{H}_{4ax}$, 2 x $\mathbf{H}_{5eq}$ & 2 x $\mathbf{H}_{5ax}$), 1.47 (18H, s, 2 x $\mathbf{H}_{17}$), 1.42 - 1.19 (6H, m, 2 x $\mathbf{H}_{3ax}$, 2 x $\mathbf{H}_{8'}$ & 2 x $\mathbf{H}_{8''}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 ($\mathbf{C}_{12'}$), 173.3 ($\mathbf{C}_{12''}$), 155.2 (2 x $\mathbf{C}_{15}$), 79.9 ($\mathbf{C}_{16'}$), 79.6 ($\mathbf{C}_{16''}$), 69.5 ($\mathbf{C}_{9'}$), 67.4 ($\mathbf{C}_{9''}$), 67.2 (2 x $\mathbf{C}_{10}$), 53.3 (2 x $\mathbf{C}_{6}$), 41.4 (2 x $\mathbf{C}_{14}$), 39.9 (2 x $\mathbf{C}_{2}$), 33.1 (2 x $\mathbf{C}_{13}$), 31.8 (2 x $\mathbf{C}_{8}$), 31.6 (2 x $\mathbf{C}_{7}$), 28.5 (2 x $\mathbf{C}_{17}$), 26.6 (2 x $\mathbf{C}_{5}$), 25.3 ($\mathbf{C}_{3'}$), 25.3 ($\mathbf{C}_{3''}$), 19.3 ($\mathbf{C}_{4'}$), 19.1 ($\mathbf{C}_{4''}$), 16.9 (2 x $\mathbf{C}_{14}$) ppm.

LC-MS (ES^+) *m/z* 299.1 $[M-Boc+H]^+$, 421.1 $[M+Na]^+$.

HRMS (ES^+) for $C_{20}H_{34}N_2NaO_6^+$ $[M+Na]^+$, caculated 421.2309 found 421.2303.

2.70 - (*2S*)-*tert*-Butyl-2-((*2S*)-1-(2,6-dioxopiperidin-1-yl)-4-hydroxy-5-(tosyloxy) pentan-2-yl)piperidine-1-carboxylate



$C_{27}H_{40}N_2O_8S$
Mol Wt: 552.6830

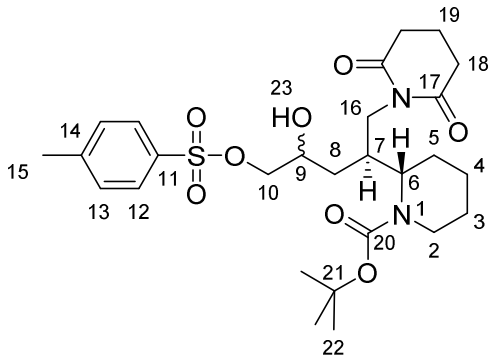
To a suspension of diol **2.74** (1.00 g, 2.51 mmol) and Bu_2SnO (0.03 g, 0.13 mmol) in THF/CH_2Cl_2 (1:1 - 35 mL) at 0 ° C under N_2 were added Et_3N (0.53 mL, 3.77 mol) and

a solution of TsCl (0.49 g, 2.56 mmol) in THF/CH_2Cl_2 (1:1 - 5 mL) dropwise. The resulting white suspension was stirred at rt for 12 h before quenching with sat. aq. $NaHCO_3$ (40 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the organic phases combined, washed with brine (3 x 40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white foam. Purification by column chromatography eluting with hexane/EtOAc (20:80) afforded the title compound **2.70** (1.09 g, 1.97 mmol, 78%) as an inseparable mixture of two diastereomers *dr* ~ 1:1.

$[\alpha]^{24}_D$ −26.8 (*c* 0.60, $CHCl_3$).

R_f 0.20 (*eluent*: EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 3429, 2970, 2936, 2871, 1722, 1668, 1598, 1359, 1174 cm^{-1}.



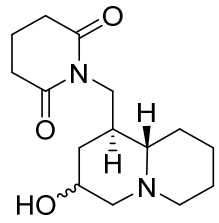
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (4H, t, *J* = 8.0 Hz, 2 x $\mathbf{H}_{12}$), 7.35 (4H, dd, *J* = 8.0, 1.2 Hz, 2 x $\mathbf{H}_{13}$), 4.20 - 4.02 (2H, m, 2 x $\mathbf{H}_6$), 4.00 - 3.71 (10H, m, 2 x $\mathbf{H}_{2eq}$, 2 x $\mathbf{H}_9$, 2 x $\mathbf{H}_{10}$ & 2 x $\mathbf{H}_{16'}$), 3.63 (2H, dd, *J* = 13.0, 4.1 Hz, 2 x $\mathbf{H}_{16''}$), 3.10 (2H, d, *J* = 6.4 Hz, $\mathbf{H}_{23}$), 2.79 - 2.48 (4H, m, 2 x $\mathbf{H}_{2ax}$ & 2 x $\mathbf{H}_7$), 2.70 (4H, t, *J* = 7.0 Hz, 2 x $\mathbf{H}_{18'}$), 2.66 (4H, t, *J* = 7.0 Hz, 2 x $\mathbf{H}_{18''}$), 2.45 (6H, s, 2 x $\mathbf{H}_{15}$), 1.95 (4H, quin, *J* = 6.6 Hz, 2 x $\mathbf{H}_{19}$), 1.86 - 1.77 (2H, m, 2 x $\mathbf{H}_{5eq}$), 1.76 - 1.51 (8H, m, 2 x $\mathbf{H}_{3eq}$, 2 x $\mathbf{H}_{4eq}$, 2 x $\mathbf{H}_{4ax}$ & 2 x $\mathbf{H}_{5ax}$), 1.42 (9H, s, $\mathbf{H}_{22'}$), 1.41 (9H, s, $\mathbf{H}_{22''}$), 1.48 - 1.19 (6H, m, 2 x $\mathbf{H}_{3ax}$, 2 x $\mathbf{H}_{8'}$ & 2 x $\mathbf{H}_{8''}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (**C**$_{17'}$), 173.3 (**C**$_{17''}$), 155.1 (2 x **C**$_{20}$), 144.9 (2 x **C**$_{11}$), 132.7 (**C**$_{14'}$), 132.6 (**C**$_{14''}$), 129.9 (2 x **C**$_{13}$), 128.0 (2 x **C**$_{12}$), 79.9 (**C**$_{21'}$), 79.5 (**C**$_{21''}$), 74.4 (2 x **C**$_{10}$), 67.2 (2 x **C**$_{9}$), 53.4 (2 x **C**$_{6}$), 41.4 (2 x **C**$_{16}$), 33.0 (**C**$_{18'}$), 32.9 (**C**$_{18''}$), 31.1 (2 x **C**$_{8}$), 28.4 (**C**$_{22'}$), 28.4 (**C**$_{22''}$), 26.5 (2 x **C**$_{5}$), 25.4 (2 x **C**$_{3}$), 21.6 (2 x **C**$_{15}$), 19.2 (**C**$_{4'}$), 19.0 (**C**$_{4''}$), 16.9 (2 x **C**$_{19}$) ppm.

LC-MS (ES^+) *m/z* 453.1 $[M-Boc+H]^+$, 575.1 $[M+Na]^+$.

HRMS (ES^+) for $C_{27}H_{40}N_2NaO_8S^+$ $[M+Na]^+$, calculated 575.2398 found 575.2405.

2.71 - (−)-(((1*S*,9a*S*)-1-(3-hydroxyoctahydro-2*H*-quinolizin-1-yl)methyl))piperidine-2,6-dione



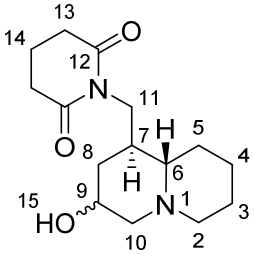
$C_{15}H_{24}N_2O_3$
Mol Wt: 280.3680

To a solution of alcohol **2.70** (1.00 g, 1.81 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added TFA (1.11 mL, 14.48 mmol) dropwise. The resulting colourless mixture was stirred at rt for 4 h. The solvent was removed *in vacuo*, the viscous oil dissolved in $PhCH_3$ (10 mL) and evaporated (3 times). The crude oil was redissolved in CH_2Cl_2 (10 mL) and DBU (0.81 mL, 5.43 mmol) was added dropwise. The mixture was stirred at rt for 4 h and concentrated *in vacuo* to yield a pale brown foam. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (1:4:95) afforded the title compound **2.71** (0.48 g, 1.71 mmol, 94%) as an inseparable mixture of two diastereoisomers *dr* ~ 1:1.

$[\alpha]^{20}_{D}$ −15.00 (*c* 0.31, $CHCl_3$).

R_f 0.18 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3380, 2933, 2855, 2763, 1722, 1666, 1437, 1392, 1169 cm^{-1}.



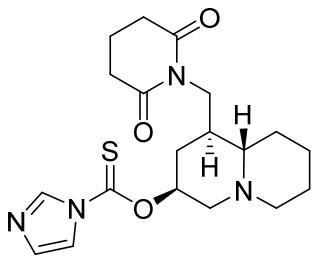
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 - 3.64 (6H, m, 2 x $\mathbf{H}_9$ & 2 x $\mathbf{H}_{11}$), 3.12 (1H, br.s, $\mathbf{H}_{15}$), 2.96 (1H, ddd, *J* = 10.5, 4.3, 1.9 Hz, $\mathbf{H}_{10eq'}$), 2.86 (1H, m, $\mathbf{H}_{2eq'}$), 2.81 - 2.70 (2H, m, $\mathbf{H}_{2eq''}$ & $\mathbf{H}_{10eq''}$), 2.65 (4H, t, *J* = 6.7 Hz, 2 x $\mathbf{H}_{13'}$), 2.63 (4H, t, *J* = 6.7 Hz, 2 x $\mathbf{H}_{13''}$), 2.23 (1H, dd, *J* = 11.7, 1.3 Hz, $\mathbf{H}_{10ax'}$), 2.15 - 1.87 (10H, m, 2 x $\mathbf{H}_{2ax}$, 2 x $\mathbf{H}_{5eq}$, $\mathbf{H}_{7'}$, $\mathbf{H}_{10ax''}$ & 2 x $\mathbf{H}_{14}$), 1.85 - 1.68 (5H, m, 2 x $\mathbf{H}_{4eq}$, $\mathbf{H}_{6'}$, $\mathbf{H}_{7''}$ & $\mathbf{H}_{8eq'}$), 1.65 - 1.52 (6H, m, 2 x $\mathbf{H}_{3eq}$, 2 x $\mathbf{H}_{3ax}$, $\mathbf{H}_{6''}$ & $\mathbf{H}_{8eq''}$), 1.40 - 1.16 (5H, m, 2 x $\mathbf{H}_{4ax}$, 2 x $\mathbf{H}_{5ax}$ & $\mathbf{H}_{8ax'}$), 0.96 (1H, q, *J* = 12.0 Hz, $\mathbf{H}_{8ax''}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 ($\mathbf{C}_{12'}$), 172.7 ($\mathbf{C}_{12''}$), 66.4 ($\mathbf{C}_{9'}$), 65.6 ($\mathbf{C}_{6'}$), 65.3 ($\mathbf{C}_{6''}$), 64.2 ($\mathbf{C}_{9''}$), 63.3 ($\mathbf{C}_{10'}$), 61.5 ($\mathbf{C}_{10''}$), 56.5 ($\mathbf{C}_{2'}$), 56.4 ($\mathbf{C}_{2''}$), 41.1 ($\mathbf{C}_{11'}$), 40.8 ($C_{11''}$), 38.2 ($\mathbf{C}_{7'}$), 37.1 ($\mathbf{C}_{8'}$), 34.6 ($\mathbf{C}_{7''}$), 34.6 ($\mathbf{C}_{8''}$), 32.9 (2 x $\mathbf{C}_{13}$), 29.5 ($\mathbf{C}_{5'}$), 29.2 ($\mathbf{C}_{5''}$), 25.4 ($\mathbf{C}_{3'}$), 25.2 ($\mathbf{C}_{3''}$), 24.2 ($\mathbf{C}_{4'}$), 24.2 ($\mathbf{C}_{4''}$), 17.1 ($\mathbf{C}_{14'}$), 17.1 ($\mathbf{C}_{14''}$) ppm.

LC-MS (ES^+) *m/z* 281.1 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{25}N_2O_3^+$ $[M+H]^+$, calculated 281.1860 found 281.1863.

2.82 - (−)-O-((1*S*,3*S*,9a*S*)-1-((2,6-dioxopiperidin-1-yl)methyl)octahydro-2*H*-quinolizin-3-yl)-1*H*-imidazole-1-carbothioate



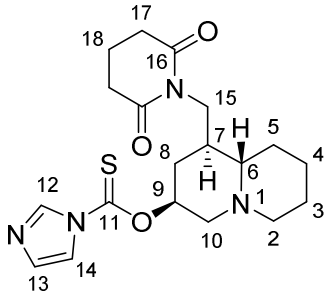
$C_{19}H_{26}N_4O_3S$
Mol Wt: 390.5020

To a solution of quinolizidine **2.71** (75 mg, 0.27 mmol) and DMAP (3 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) at 0 ° C under N_2 was added 1,1'-thiocarbonyldiimidazole (0.19 g, 1.07 mmol) in CH_2Cl_2 (2 mL) dropwise. The resulting yellow mixture was stirred at rt for 16 h and the solvent removed *in vacuo*. Purification by column chromatography eluting with MeOH/EtOAc (1:99) afforded the title compound **2.82** (33 mg, 0.085 mmol, 32%) as a pale brown oil.

$[\alpha]^{19}_D$ −28.5 (*c* 1.00, $CHCl_3$).

R_f 0.25 (*eluent*: MeOH/EtOAc - 4:96).

FT-IR (neat) ν_{max} 3125, 2933, 2854, 2767, 1722, 1673, 1530, 1466, 1353, 1284 cm^{-1}.



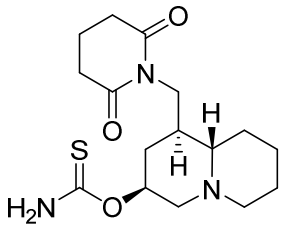
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, dd, *J* = 1.1, 0.8 Hz, $\mathbf{H}_{12}$), 7.57 (1H, dd, *J* = 1.7, 1.1 Hz, $\mathbf{H}_{14}$), 7.00 (1H, dd, *J* = 1.7, 0.8 Hz, $\mathbf{H}_{13}$), 5.47 (1H, ddt, *J* = 11.4, 10.4, 4.5 Hz, $\mathbf{H}_{9}$), 3.85 (1H, dd, *J* = 12.7, 5.6 Hz, $\mathbf{H}_{15'}$), 3.80 (1H, dd, *J* = 12.7, 9.7 Hz, $\mathbf{H}_{15''}$),3.15 (1H, ddd, *J* = 10.2, 4.5, 2.0 Hz, $\mathbf{H}_{10eq}$), 2.84 (1H, m, $\mathbf{H}_{2eq}$), 2.66 (4H, t, *J* = 6.5 Hz, $\mathbf{H}_{17}$), 2.17 (1H, dd, *J* = 10.2 Hz, $\mathbf{H}_{10ax}$), 2.12 (1H, td, *J* = 11.4, 4.0 Hz, $\mathbf{H}_{2ax}$), 2.03 - 1.78 (6H, m, $\mathbf{H}_{4eq}$, $\mathbf{H}_{5eq}$, $\mathbf{H}_{8eq}$, $\mathbf{H}_{7}$ & $\mathbf{H}_{18}$), 1.73 - 1.52 (3H, m, $\mathbf{H}_{3}$ & $\mathbf{H}_{6}$), 1.37 - 1.19 (3H, m, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5ax}$ & $\mathbf{H}_{8ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0 ($\mathbf{C}_{11}$), 172.7 ($\mathbf{C}_{16}$), 136.8 ($\mathbf{C}_{12}$), 130.7 ($\mathbf{C}_{13}$), 117.8 ($\mathbf{C}_{14}$), 78.2 ($\mathbf{C}_{9}$), 64.9 ($\mathbf{C}_{6}$), 58.3 ($\mathbf{C}_{10}$), 56.5 ($\mathbf{C}_{2}$), 40.8 ($\mathbf{C}_{15}$), 38.4 ($\mathbf{C}_{7}$), 32.9 ($\mathbf{C}_{17}$), 32.8 ($\mathbf{C}_{5}$), 29.3 ($\mathbf{C}_{8}$), 25.4 ($\mathbf{C}_{3}$), 24.2 ($\mathbf{C}_{4}$), 17.1 ($\mathbf{C}_{18}$) ppm.

LC-MS (ES^+) *m/z* 391.1 $[M+H]^+$.

HRMS (ES^+) for $C_{19}H_{27}N_4O_3S^+$ $[M+H]^+$, calculated 391.1798 found 391.1797.

2.83 - (−)-O-((1*S*,3*S*,9a*S*)-1-((2,6-dioxopiperidin-1-yl)methyl)octahydro-2*H*-quinolizin-3-yl)carbamothioate



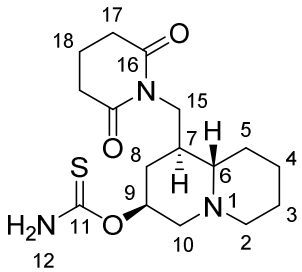
$C_{16}H_{25}N_3O_3S$
Mol Wt: 339.4540

Compound **2.83** was isolated as a by-product after purification. Material isolated from alkylation of **2.71** with 1,1'-thiocarbonyldiimidazole as a white solid (19 mg, 0.056 mmol, 31%).

$[\alpha]^{19}_D$ −19.5 (*c* 0.52, $CHCl_3$).

R_f 0.52 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 3:7:90).

FT-IR (neat) ν_{max} 3270, 3117, 2933, 2772, 1720, 1668, 1422, 1352, 1273, 1171 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (1H, br. s., $\mathbf{H}_{12'}$), 6.11 (1H, br. s., $\mathbf{H}_{12''}$), 5.21 (1H, ddt, *J* = 11.4, 10.4, 4.5 Hz, $\mathbf{H}_9$), 3.83 (1H, dd, *J* = 12.7, 4.9 Hz, $\mathbf{H}_{15'}$), 3.77 (1H, dd, *J* = 12.7, 9.9 Hz, $\mathbf{H}_{15''}$), 3.09 (1H, ddd, *J* = 10.2, 4.3, 1.7 Hz, $\mathbf{H}_{10eq}$), 2.82 (1H, m, $\mathbf{H}_{2eq}$), 2.67 (4H, t, *J* =

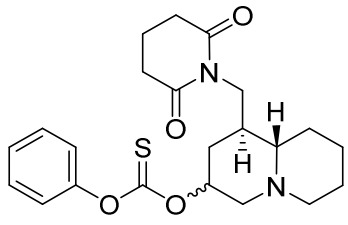
6.5 Hz, $\mathbf{H}_{17}$), 2.08 (1H, m, $\mathbf{H}_{2ax}$), 2.01 - 1.76 (7H, m, $\mathbf{H}_{4eq}$, $\mathbf{H}_{5eq}$, $\mathbf{H}_{7}$, $\mathbf{H}_{8eq}$, $\mathbf{H}_{10ax}$ & $\mathbf{H}_{18}$), 1.68 - 1.52 (3H, m, $\mathbf{H}_{3}$ & $\mathbf{H}_{6}$), 1.34 - 1.19 (2H, m, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$), 1.13 (1H, q, J = 11.4 Hz, $\mathbf{H}_{8ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5 ($\mathbf{C}_{11}$), 172.8 ($\mathbf{C}_{16}$), 76.0 ($\mathbf{C}_{9}$), 64.9 ($\mathbf{C}_{6}$), 59.1 ($\mathbf{C}_{10}$), 56.5 ($\mathbf{C}_{2}$), 40.9 ($\mathbf{C}_{15}$), 38.3 ($\mathbf{C}_{7}$), 33.4 ($\mathbf{C}_{8}$), 32.9 ($\mathbf{C}_{17}$), 29.3 ($\mathbf{C}_{5}$), 25.4 ($\mathbf{C}_{3}$), 24.3 ($\mathbf{C}_{4}$), 17.1 ($\mathbf{C}_{18}$) ppm.

LC-MS (ES^+) *m/z* 339.9 $[M+H]^+$.

HRMS (ES^+) for $C_{16}H_{26}N_3O_3S^+$ $[M+H]^+$, calculated 340.1689 found 340.1695.

2.81 - O-((1*S*,9a*S*)-1-((2,6-dioxopiperidin-1-yl)methyl)octahydro-2*H*-quinolizin-3-yl)-O-phenylcarbonothioate



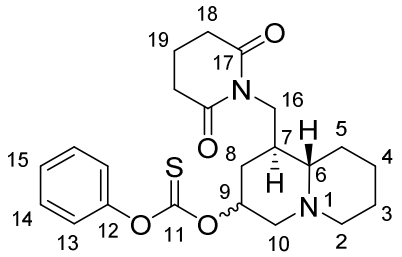
$C_{22}H_{28}N_2O_4S$
Mol Wt: 416.5360

Following the procedure described for the synthesis of **2.82**, quinolizidine **2.71**(50 mg, 0.18 mmol) afforded the title compound **2.81** (36 mg, 0.09 mmol, 50%) as an inseparable mixture of two diastereoisomers *dr* ~ 2:1.

$[\alpha]^{25}_{D}$ −15.9 (*c* 0.61, $CHCl_3$).

R_f 0.20 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 2934, 2855, 2807, 2767, 1723, 1670, 1591, 1438, 1350, 1188 cm^{-1}.



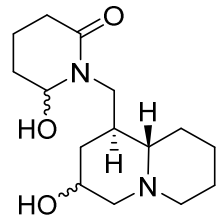
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.36 (4H, m, 2 x $\mathbf{H}_{14}$), 7.31 - 7.24 (2H, m, 2 x $\mathbf{H}_{15}$), 7.15 - 7.05 (4H, m, 2 x $\mathbf{H}_{13}$), 5.38 (1H, dt, *J* = 5.3, 2.8 Hz, $\mathbf{H}_{9'}$), 5.23 (1H, ddt, *J* = 11.4, 10.4, 4.5 Hz, $\mathbf{H}_{9''}$), 3.87 (1H, dd, *J* = 12.8, 5.0 Hz, $\mathbf{H}_{16'}$), 3.91 - 3.77 (2H, m, 2 x $\mathbf{H}_{16''}$), 3.73 (1H, dd, *J* = 12.8, 10.3 Hz, $\mathbf{H}_{16'}$), 3.31 - 3.06 (2H, m, 2 x $\mathbf{H}_{10eq}$), 2.92 - 2.74 (2H, m, 2 x $\mathbf{H}_{2eq}$), 2.67 (4H, t, *J* = 7.0 Hz, 2 x $\mathbf{H}_{18'}$), 2.65 (4H, t, *J* = 7.0 Hz, 2 x $\mathbf{H}_{18''}$), 2.28 (2H, dd, *J* = 13.2, 1.8 Hz, 2 x $\mathbf{H}_{10ax}$), 2.19 - 1.77 (14H, m, 2 x $\mathbf{H}_{2ax}$, 2 x $\mathbf{H}_{5eq}$, 2 x $\mathbf{H}_{7}$, 2 x $\mathbf{H}_{8eq}$, 2 x $\mathbf{H}_{10ax}$ & 2 x $\mathbf{H}_{19}$), 1.75 - 1.52 (6H, m, 2 x $\mathbf{H}_{3eq}$, 2 x $\mathbf{H}_{3ax}$ & 2 x $\mathbf{H}_{6}$), 1.42 - 1.19 (6H, m, 2 x $\mathbf{H}_{4ax}$, 2 x $\mathbf{H}_{5ax}$ & 2 x $\mathbf{H}_{8ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6 ($\mathbf{C}_{11'}$), 194.1 ($\mathbf{C}_{11''}$), 172.7 ($\mathbf{C}_{17'}$), 172.7 ($\mathbf{C}_{17''}$), 153.3 (2 x $\mathbf{C}_{12}$), 129.4 ($\mathbf{C}_{14'}$), 129.3 ($\mathbf{C}_{14''}$), 126.5 (2 x $\mathbf{C}_{15}$), 126.3 (2 x $\mathbf{C}_{11}$), 122.0 ($\mathbf{C}_{13'}$), 122.0 (C $\mathbf{C}_{13''}$), 78.9 ($\mathbf{C}_{9'}$), 78.4 ($\mathbf{C}_{9''}$), 65.4 ($\mathbf{C}_{6'}$), 64.9 ($\mathbf{C}_{6''}$), 58.5 ($\mathbf{C}_{10'}$), 57.6 ($\mathbf{C}_{10''}$), 56.5 ($\mathbf{C}_{2'}$), 56.4 ($\mathbf{C}_{2''}$), 41.0 ($\mathbf{C}_{16'}$), 40.8 ($\mathbf{C}_{16''}$), 38.4 ($\mathbf{C}_{7'}$), 35.0 ($\mathbf{C}_{7''}$), 32.9 (2 x $\mathbf{C}_{18}$), 32.9 ($\mathbf{C}_{8'}$), 31.0 ($\mathbf{C}_{5'}$), 29.4 ($\mathbf{C}_{8''}$), 29.1 ($\mathbf{C}_{5''}$), 25.5 ($\mathbf{C}_{3'}$), 25.2 ($\mathbf{C}_{3''}$), 24.4 ($\mathbf{C}_{4'}$), 24.3 ($\mathbf{C}_{4''}$), 17.2 ($\mathbf{C}_{19'}$), 17.1 ($\mathbf{C}_{19''}$) ppm.

LC-MS (ES^+) *m/z* 416.9 $[M+H]^+$.

HRMS (ES^+) for $C_{22}H_{29}N_2O_4S^+$ $[M+H]^+$, calculated 417.1843 found 417.1837.

2.76 - 6-Hydroxy-1-(((1*S*,9a*S*)-3-hydroxyoctahydro-2*H*-quinolizin-1-yl)methyl)piperidin-2-one

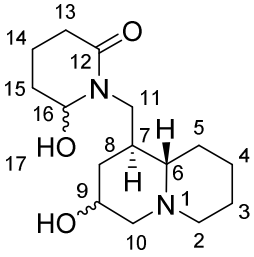


$C_{15}H_{26}N_2O_3$
Mol Wt: 282.3840

To a stirred solution of imide **2.71** (115 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C under N_2 was added $LiEt_3BH$ (0.90 mL of 1 M sol. in THF, 0.90 mmol) dropwise. The resulting mixture was stirred at −78 °C for 3 h, then was allowed to warm to −20 °C and a solution of HCl (0.75 mL of 2 M sol. in EtOH, 1.57 mmol) was added dropwise. The mixture was allowed to warm to rt and stirred for 1 h before quenching with sat. aq. $NaHCO_3$ (1.5 mL) and concentrated *in vacuo*. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (2:8:90) afforded the title compound **2.76** (35 mg, 0.12 mmol, 30%) as an inseparable mixture of four diastereoisomers.

R_f: 0.08 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3319, 2937, 2810, 2766, 1620, 1481, 1332, 1185 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 - 4.82 (4H, m), 3.92 - 3.77 (5H, m), 3.76 - 3.56 (3H, m), 3.41 (3H, m), 3.22 (2H, dd, *J* = 13.4, 4.6 Hz), 3.17 (1H, dd, *J* = 13.2, 10.8 Hz), 3.03 - 2.87 (2H, m), 2.87 - 2.79

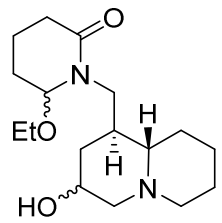
(2H, m), 2.79 - 2.68 (5H, m), 2.47 - 2.38 (4H, m), 2.38 - 2.18 (7H, m), 2.14 - 2.02 (7H, m), 1.96 - 1.47 (40H, m), 1.39 - 1.14 (10H, m), 1.11 - 0.81 (6H, m), 0.81 - 0.54 (3H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (**C**), 171.0 (**C**), 170.9 (**C**), 81.8 (**C**H), 81.5 (**C**H), 77.8 (**C**H), 77.4 (**C**H), 66.4 (**C**H), 66.2 (**C**H), 65.7 (**C**H), 65.6 (**C**H), 65.1 (**C**H), 64.6 (**C**H), 64.5 (**C**H), 63.4 (**C**H_2), 61.5 (**C**H_2), 56.6 (**C**H_2), 56.3 (**C**H_2), 48.0 (**C**H_2), 43.6 (**C**H_2), 42.9 (**C**H_2), 39.2 (**C**H), 38.1 (**C**H), 38.0 (**C**H), 37.3 (**C**H), 35.8 (**C**H), 35.0 (**C**H_2), 34.4 (**C**H_2), 33.7 (**C**H), 32.4 (**C**H_2), 32.3 (**C**H_2), 31.5 (**C**H_2), 31.2 (**C**H_2), 29.5 (**C**H_2), 29.3 (**C**H_2), 29.2 (**C**H_2), 25.4 (**C**H_2), 25.2 (**C**H_2), 24.3 (**C**H_2), 24.2 (**C**H_2), 22.6 (**C**H), 15.9 (**C**H_2), 15.8 (**C**H_2), 15.7 (**C**H_2) ppm.

LC-MS (ES^+) *m/z* 283.1 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{27}N_2O_3^+$ $[M+H]^+$, calculated 283.2016 found 283.2012.

2.77 - 6-Ethoxy-1-(((1*S*,9a*S*)-3-hydroxyoctahydro-2*H*-quinolizin-1-yl)methyl)piperidin-2-one



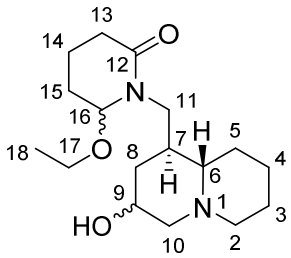
$C_{17}H_{30}N_2O_3$
Mol Wt: 310.4380

Following the procedure described for the synthesis of **2.76**, imide **2.71** (0.18 g, 0.64 mmol) afforded the title compound **2.77** (0.11 g, 0.35 mmol, 55%) as an inseparable mixture of four diastereoisomers.

$[\alpha]^{20}_D$ −22.55 (*c* 0.49, $CHCl_3$).

R_f 0.18 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3373, 2935, 2852, 2805, 2762, 1632, 1469, 1335, 1185 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (2H, br s), 4.51 (1H, t, *J* = 2.9 Hz), 3.97 (2H, ddd, *J* = 13.6, 10.8, 3.1 Hz,), 3.86 (2H, dd, *J* = 14.1, 5.0 Hz,), 3.82 - 3.72 (3H, m), 3.60 - 3.37 (8H, m), 3.09 (2H, dt, *J* = 13.5, 4.8 Hz,), 3.00 (2H, dd, *J* = 4.4, 2.2 Hz,), 2.96 (2H, dd, *J* = 13.6, 10.0 Hz,), 2.90 - 2.72 (6H, m), 2.54 - 2.42 (4H, m), 2.38 - 2.21 (6H, m), 2.18 - 1.85 (24H, m), 1.84 - 1.47 (28H, m), 1.34 - 1.12 (19H, m),

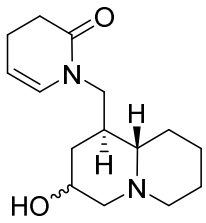
1.08 (2H, q, *J* = 11.8 Hz,), 0.96 (2H, q, *J* = 11.8 Hz,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (**C**), 170.6 (**C**), 88.6 (**C**H), 88.3 (**C**H), 84.6 (**C**H), 84.4 (**C**H), 66.9 (**C**H), 66.0 (**C**H), 65.6 (**C**H), 65.3 (**C**H), 64.8 (**C**H), 64.6 (**C**H), 64.5 (**C**H), 63.7 (**C**H_2), 63.4 (**C**H_2), 63.4 (**C**H_2), 61.7 (**C**H_2), 56.7 (**C**H_2), 56.6 (**C**H_2), 56.6 (**C**H_2), 56.4 (**C**H_2), 49.0 (**C**H_2), 43.5 (**C**H_2), 43.4 (**C**H_2), 39.2 (**C**H), 38.6 (**C**H), 38.2 (**C**H_2), 37.6 (**C**H_2), 35.9 (**C**H_2), 35.5 (**C**H), 34.6 (**C**H_2), 34.4 (**C**H), 32.4 (**C**H_2), 29.9 (**C**H_2), 29.7 (**C**H_2), 29.6 (**C**H_2), 29.5 (**C**H_2), 27.2 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2) , 25.6 (**C**H_2), 25.5 (**C**H_2), 25.4 (**C**H_2), 24.5 (**C**H_2), 24.4 (**C**H_2), 24.3 (**C**H_2), 24.3 (**C**H_2), 15.9 (**C**H) , 15.8 (**C**H_3), 15.4 (**C**H_3), 15.4 (**C**H_3), 15.4 (**C**H_3) ppm.

LC-MS (ES^+) *m/z* 311.0 $[M+H]^+$.

HRMS (ES^+) for $C_{17}H_{31}N_2O_3^+$ $[M+H]^+$, calculated 311.2329 found 311.2334.

2.78 - (−)-1-(((1*S*,9a*S*)-3-Hydroxyoctahydro-2*H*-quinolizin-1-yl)methyl)-3,4-dihydropyridin-2(1*H*)-one



$C_{15}H_{24}N_2O_2$
264.3690

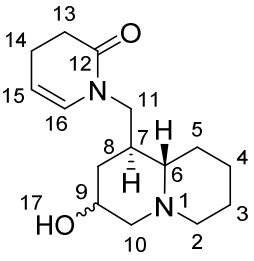
To a stirred solution of imide **2.71** (0.30 g, 1.07 mmol) in CH_2Cl_2 (6 mL) at −78 °C under N_2 was added $LiEt_3BH$ (2.68 mL of 1 M sol. in THF, 2.68 mmol) dropwise. The

resulting mixture was stirred at −78 °C for 3 h, then was allowed to warm to −20 °C and a solution of HCl (3.21 mL of 1 M sol. in EtOH, 3.21 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 1 h before quenching with $NaHCO_3$ (0.45 mg, 5.36 mmol). The white suspension was stirred at rt for 12 h and filtered under vacuum through a sintered funnel. The residue was washed with EtOAc (10 mL) and CH_2Cl_2 (10 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil. The crude oil was redissolved in degassed $PhCH_3$ (2 mL) and NH_4Cl (3 mg, 0.05 mmol) was added. The colourless suspension was irradiated for 1 h at 120 °C in the MW and the solvent removed *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (2:8:90) afforded the title compound **2.78** (0.23 g, 0.87 mmol, 81%) as an inseparable mixture of two diastereoisomers *dr* ~ 1:1.

$[\alpha]^{25}_D$ −9.09 (*c* 0.28, $CHCl_3$).

R_f 0.34 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 3:10:87).

FT-IR (neat) ν_{max} 3396, 2934, 2854, 2804, 2761, 1656, 1415, 1272, 1227 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (1H, ddd, *J* = 1.6, 0.8 Hz, $\mathbf{H}_{16'}$), 5.94 (1H, ddd, *J* = 1.6, 0.8 Hz, $\mathbf{H}_{16''}$), 5.15 (2H, m, 2 x $\mathbf{H}_{15}$), 3.87 (1H, br.s, $\mathbf{H}_{9'}$), 3.75 (1H, ddt, *J* = 11.3, 10.3, 4.4 Hz, $\mathbf{H}_{9''}$), 3.52 (1H, dd, *J* = 13.5, 10.1 Hz, $\mathbf{H}_{11'}$), 3.48 (2H, m, 2 x $\mathbf{H}_{11''}$), 3.38 (1H, dd, *J* = 13.5, 4.7 Hz, $\mathbf{H}_{11'}$), 2.97 (1H, ddd, *J* = 10.6, 4.5, 2.2 Hz, $\mathbf{H}_{10eq'}$), 2.90 (1H, br.s, $\mathbf{H}_{17}$), 2.85 (1H, m, $\mathbf{H}_{2eq'}$), 2.79 - 2.70 (2H, m, $\mathbf{H}_{10eq''}$ & $\mathbf{H}_{2eq''}$), 2.54 - 2.47 (4H, m, 2 x $\mathbf{H}_{13}$), 2.34 - 2.27 (4H, m, 2 x

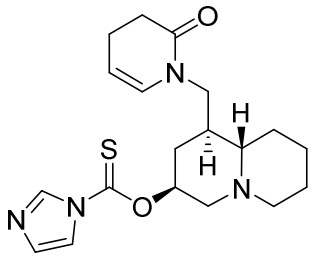
$\mathbf{H}_{14}$), 2.22 (1H, dd, *J* = 11.7, 1.5 Hz, $\mathbf{H}_{10ax'}$), 2.11 (1H, td, *J* = 10.6, 3.6 Hz, $\mathbf{H}_{2ax'}$), 2.08 (1H, td, *J* = 11.0, 3.4 Hz, $\mathbf{H}_{2ax''}$), 2.00 - 1.85 (4H, m, 2 x $\mathbf{H}_{5eq}$, $\mathbf{H}_{8eq'}$ & $\mathbf{H}_{10ax''}$), 1.83 - 1.51 (11H, m, 2 x $\mathbf{H}_{3}$, 2 x $\mathbf{H}_{4eq}$, 2 x $\mathbf{H}_{6}$, 2 x $\mathbf{H}_{7}$ & $\mathbf{H}_{8eq''}$), 1.29 - 1.11 (5H, m, 2 x $\mathbf{H}_{4ax}$, 2 x $\mathbf{H}_{5ax}$ & $\mathbf{H}_{8ax'}$), 0.98 (1H, m, $\mathbf{H}_{8ax''}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 ($\mathbf{C}_{12'}$), 169.6 ($\mathbf{C}_{12''}$), 129.9 ($\mathbf{C}_{16'}$), 129.8 ($\mathbf{C}_{16''}$), 106.3 (2 x $\mathbf{C}_{15}$), 66.8 ($\mathbf{C}_{9'}$), 65.2 ($\mathbf{C}_{6''}$), 64.7 ($\mathbf{C}_{6'}$), 64.4 ($\mathbf{C}_{9''}$), 63.6 ($\mathbf{C}_{10'}$), 61.7 ($\mathbf{C}_{10''}$), 56.6 ($\mathbf{C}_{2'}$), 56.4 ($\mathbf{C}_{2''}$), 47.4 ($\mathbf{C}_{11'}$), 47.4 ($\mathbf{C}_{11''}$), 39.7 ($\mathbf{C}_{7'}$), 37.6 ($\mathbf{C}_{8'}$), 35.9 ($\mathbf{C}_{7''}$), 34.9 ($\mathbf{C}_{8''}$), 31.4 (2 x $\mathbf{C}_{13}$), 30.0 ($\mathbf{C}_{5'}$), 29.6 ($\mathbf{C}_{5''}$), 25.6 ($\mathbf{C}_{3'}$), 25.5 ($\mathbf{C}_{3''}$), 24.4 ($\mathbf{C}_{4'}$), 24.3 ($\mathbf{C}_{4''}$), 20.2 (2 x $\mathbf{C}_{14}$) ppm.

LC-MS (ES^+) *m/z* 265.0 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{25}N_2O_2^+$ $[M+H]^+$, calculated 265.1911 found 265.1910.

2.80 - (−)-O-((1*S*,3*S*,9a*S*)-1-((2-oxo-3,4-dihydropyridin-1(2*H*)-yl)methyl)octahydro-2H-quinolizin-3-yl)-1*H*-imidazole-1-carbothioate



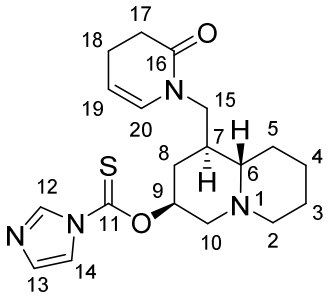
$C_{19}H_{26}N_4O_2S$
Mol Wt: 374.5030

Following the procedure described for the synthesis of **2.82**, alcohol **2.78** (105 mg, 0.40 mmol) afforded the title compound **2.82** (72 mg, 0.19 mmol, 48%) as a pale brown oil.

$[\alpha]^{27}_{D}$ −2.87 (*c* 0.47, $CHCl_3$).

R_f 0.50 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 1:9:90).

FT-IR (neat) ν_{max} 3121, 2934, 2853, 2767, 1660, 1531, 1465, 1386, 1311, 1229 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, s, $\mathbf{H}_{12}$), 7.59 (1H, s, $\mathbf{H}_{14}$), 7.02 (1H, s, $\mathbf{H}_{13}$), 5.96 (1H, d, *J* = 7.7 Hz, $\mathbf{H}_{20}$), 5.53 (1H, ddt, *J* = 11.5, 10.4, 4.5 Hz, $\mathbf{H}_{9}$), 5.20 (1H, dt, *J* = 7.7, 4.4 Hz, $\mathbf{H}_{19}$), 3.65 (1H, dd, *J* = 13.6, 10.1 Hz, $\mathbf{H}_{15'}$), 3.40 (1H, dd, *J* = 13.6, 4.5 Hz, $\mathbf{H}_{15''}$), 3.20 (1H, ddd, *J* = 10.4, 4.5, 1.8 Hz, $\mathbf{H}_{10eq}$), 2.86 (1H, m, $\mathbf{H}_{2eq}$), 2.52 (2H, t, *J* = 8.1 Hz, $\mathbf{H}_{17}$), 2.36 - 2.28 (2H, m, $\mathbf{H}_{18}$), 2.27 - 2.12 (3H, m, $\mathbf{H}_{2ax}$, $\mathbf{H}_{8eq}$ & $\mathbf{H}_{10ax}$), 1.94 (1H, m, $\mathbf{H}_{5eq}$), 1.86 - 1.49 (5H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4eq}$, $\mathbf{H}_{6}$ & $\mathbf{H}_{7}$), 1.31 (1H, q, *J* = 11.9 Hz, $\mathbf{H}_{8ax}$), 1.27 - 1.14 (2H, m, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$) ppm.

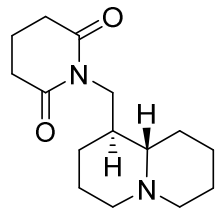
^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0 ($\mathbf{C}_{11}$), 169.7 ($\mathbf{C}_{16}$), 136.8 ($\mathbf{C}_{12}$), 130.7 ($\mathbf{C}_{13}$), 129.5 ($\mathbf{C}_{20}$), 117.8 ($\mathbf{C}_{14}$), 106.9 ($\mathbf{C}_{19}$), 78.1 ($\mathbf{C}_{9}$), 64.5 ($\mathbf{C}_{6}$), 58.4 ($\mathbf{C}_{10}$), 56.5 ($\mathbf{C}_{2}$), 46.9 ($\mathbf{C}_{15}$), 39.7 ($\mathbf{C}_{7}$), 32.9 ($\mathbf{C}_{8}$), 31.4 ($\mathbf{C}_{17}$), 29.6 ($\mathbf{C}_{5}$), 25.4 ($\mathbf{C}_{3}$), 24.2 ($\mathbf{C}_{4}$), 20.2 ($\mathbf{C}_{18}$) ppm.

LC-MS (ES^+) *m/z* 374.9 $[M+H]^+$.

HRMS (ES^+) for $C_{19}H_{27}N_4O_2S^+$ $[M+H]^+$, calculated 375.1849 found

375.1845.

1.107 - 1-(((1*S*,9a*S*)-2,3,4,6,7,9a-Hexahydro-1*H*-quinolizin-1-yl)methyl)piperidine-2,6-dione - (−)-Lamprolobine



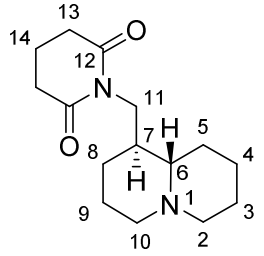
$C_{15}H_{24}N_2O_2$
Mol Wt: 264.3690

To a solution of xanthate **2.82** (65 mg, 0.17 mmol) in toluene (2 mL) were added TTMSS (0.26 mL, 0.83 mmol) dropwise and AIBN (1 mg, 0.01 mmol) in one portion. The resulting suspension was irradiated for 1 h at 90 °C in the MW and the solvent removed *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (2:8:90) afforded the title compound **1.107** (36 mg, 0.14 mmol, 80%) as a green oil. Physical and spectroscopic data were consistent with reported values.[70,97,99]

$[\alpha]^{24}_D$ −29.0 (*c* 1.06, $CHCl_3$).

R_f 0.42 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 2929, 2855, 2804, 2759, 2668, 1722, 1666, 1462, 1351 cm^{-1}.



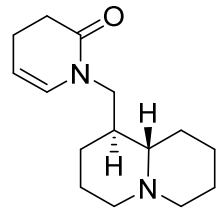
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (1H, dd, *J* = 12.6, 4.9 Hz, $\mathbf{H}_{11'}$), 3.71 (1H, dd, *J* = 12.6, 10.4 Hz, $\mathbf{H}_{11''}$), 2.80 (1H, dddd, *J* = 11.4, 3.4, 1.7 Hz, $\mathbf{H}_{2eq}$), 2.73 (1H, dddd, *J* = 11.4, 4.0, 2.6, 1.7 Hz, $\mathbf{H}_{10eq}$), 2.65 (4H, t, *J* = 6.6 Hz, $\mathbf{H}_{13}$), 2.05 - 1.87 (6H, m, $\mathbf{H}_{2ax}$, $\mathbf{H}_{4eq}$, $\mathbf{H}_{5eq}$, $\mathbf{H}_{10ax}$ & $\mathbf{H}_{14}$), 1.79 - 1.65 (2H, m, $\mathbf{H}_6$ & $\mathbf{H}_7$), 1.63 - 1.49 (4H, m, $\mathbf{H}_3$ & $\mathbf{H}_9$), 1.43 (1H, m, $\mathbf{H}_{8eq}$), 1.34 - 1.16 (2H, m, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$), 0.97 (1H, qd, *J* = 12.6, 4.6 Hz, $\mathbf{H}_{8ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 ($\mathbf{C}_{12}$), 66.4 ($\mathbf{C}_6$), 56.8 ($\mathbf{C}_{10}$), 56.4 (C $\mathbf{C}_2$), 41.6 ($\mathbf{C}_{11}$), 39.5 ($\mathbf{C}_7$), 32.9 ($\mathbf{C}_{13}$), 29.6 ($\mathbf{C}_5$), 28.0 ($\mathbf{C}_8$), 25.6 ($\mathbf{C}_3$), 24.8 ($\mathbf{C}_4$), 24.5 ($\mathbf{C}_9$), 17.2 ($\mathbf{C}_{14}$) ppm.

LC-MS (ES^+) *m/z* 265.0 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{25}N_2O_2^+$ $[M+H]^+$, calculated 265.1911 found 265.1907.

2.89 - 1-(((1S,9aS)-octahydro-2*H*-quinolizin-1-yl)methyl)-3,4-dihydropyridin-2(1*H*)-one



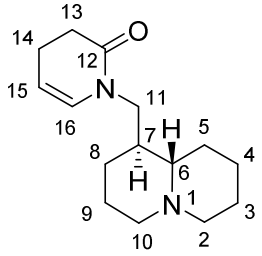
$C_{15}H_{24}N_2O$
Mol Wt: 248.3700

Following the procedure described for the synthesis of **1.107**, xanthate **2.80** (20 mg, 0.05 mmol) afforded the title compound **2.89** (10 mg, 0.04 mmol, 80%) as a pale brown oil.

$[\alpha]^{22}_D$ −9.6 (*c* 0.36, $CHCl_3$).

R_f 0.28 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3431, 2934, 2856, 2803, 2758, 2668, 1658, 1444, 1266 cm^{-1}.



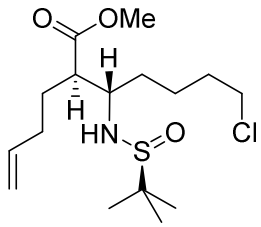
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (1H, dt, *J* = 7.7, 1.3 Hz, $\mathbf{H}_{16}$), 5.14 (1H, dt, *J* = 7.7, 4.4 Hz, $\mathbf{H}_{15}$), 3.51 (1H, dd, *J* = 13.5, 9.7 Hz, $\mathbf{H}_{11'}$), 3.36 (1H, dd, *J* = 13.5, 4.0 Hz, $\mathbf{H}_{11''}$), 2.86 - 2.73 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_{10eq}$), 2.59 - 2.42 (2H, t, *J* = 7.8 Hz, $\mathbf{H}_{13}$), 2.36 - 2.25 (2H, m, $\mathbf{H}_{14}$), 2.09 - 1.72 (4H, m, $\mathbf{H}_{2ax}$, $\mathbf{H}_{5eq}$, $\mathbf{H}_{9eq}$ & $\mathbf{H}_{10ax}$), 1.70 - 1.53 (7H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_6$, $\mathbf{H}_7$ & $\mathbf{H}_{8eq}$), 1.38 - 1.13 (2H, m, $\mathbf{H}_{5ax}$ & $\mathbf{H}_{9ax}$), 1.00 (1H, qd, *J* = 12.6, 4.6 Hz, $\mathbf{H}_{8ax}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 ($\mathbf{C}_{12}$), 129.9 ($\mathbf{C}_{16}$), 106.1 ($\mathbf{C}_{15}$), 65.9 ($\mathbf{C}_6$), 56.8 ($\mathbf{C}_{10}$), 56.5 ($\mathbf{C}_2$), 47.6 ($\mathbf{C}_{11}$), 40.8 ($\mathbf{C}_{17}$), 31.5 ($\mathbf{C}_{13}$), 29.8 ($\mathbf{C}_5$), 28.2 ($\mathbf{C}_8$), 25.6 ($\mathbf{C}_3$), 24.9 ($\mathbf{C}_4$), 24.5 ($\mathbf{C}_9$), 20.3 ($\mathbf{C}_{14}$) ppm.

LC-MS (ES^+) *m/z* 249.0 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{25}N_2O^+$ $[M+H]^+$, calculated 249.1961 found 249.1955.

2.107 - (2*R*,3*S*)-Methyl-2-(but-3-en-1-yl)-3-((*S*)-2-methyl-propane-2-sulfinylamino)-7-chloroheptanoate



$C_{16}H_{30}ClNO_3S$
Mol Wt: 351.9300

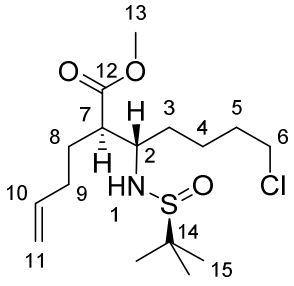
Following the procedure described for the synthesis of **2.35**, imine **1.110** (100 mg, 0.45 mmol) afforded the crude product as a partially separable mixture of three diastereoisomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti/syn/anti dr* 80:14:6:0). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereoisomer ***syn*-2.107** (40 mg, 0.11 mmol, 24%) as a colourless oil, minor diastereoisomer ***anti*-2.107** (20 mg, 0.06 mmol, 13%) as a colourless oil and inseparable mixture of diastereoisomers (76 mg, 0.21 mmol, 46%).

Data for major diastereoisomer ***syn*-2.107**:

$[\alpha]^{24}_D$ +25.4 (*c* 0.45, $CHCl_3$).

R_f 0.10 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3237, 3077, 2952, 2867, 1732, 1641, 1453, 1169, 1054 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, $\mathbf{H}_{10}$), 5.08 - 4.99 (2H, m, $\mathbf{H}_{11}$), 4.15 (1H, d, *J* = 8.3 Hz, $\mathbf{H}_1$), 3.73 (3H, s, $\mathbf{H}_{13}$), 3.53 (2H, t, *J* = 6.5 Hz, $\mathbf{H}_6$), 3.35 (1H, ddt, *J* = 9.2, 8.3, 4.0 Hz, $\mathbf{H}_2$), 2.92 (1H, ddd, *J* = 9.2, 4.6 Hz, $\mathbf{H}_7$), 2.20 - 2.01 (2H, m, $\mathbf{H}_9$), 1.95 - 1.37 (8H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$ & $\mathbf{H}_8$), 1.23 (9H, s, $\mathbf{H}_{15}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 ($\mathbf{C}_{12}$), 137.3 ($\mathbf{C}_{10}$), 115.6 ($\mathbf{C}_{11}$), 58.1 ($\mathbf{C}_{15}$), 56.1 ($\mathbf{C}_2$), 51.8 ($\mathbf{C}_7$), 49.6 ($\mathbf{C}_{13}$), 44.8 ($\mathbf{C}_6$), 32.1 ($\mathbf{C}_5$), 31.8 ($\mathbf{C}_9$), 31.2 ($\mathbf{C}_3$), 27.7 ($\mathbf{C}_8$), 23.6 ($\mathbf{C}_4$), 22.7 ($\mathbf{C}_{15}$) ppm.

LRMS (ES^+) *m/z* 374.2 $[M^{35}Cl+Na]^+$, 376.2 $[M^{37}Cl+Na]^+$, 415.2 $[M^{35}Cl+CH_3CN+Na]^+$, 417.2 $[M^{37}Cl+CH_3CN+Na]^+$.

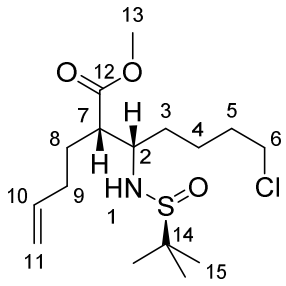
HRMS (ES^+) for $C_{16}H_{31}ClNO_3S^+$ $[M+H]^+$, calculated 352.1708 found 352.1709.

Data for minor diastereoisomer ***anti*-2.102**:

$[\alpha]^{24}_D$ +24.43 (*c* 0.31, $CHCl_3$).

R_f 0.13 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3308, 3076, 2952, 2866, 1721, 1641, 11439, 1365, 1170 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, $\mathbf{H}_{10}$),

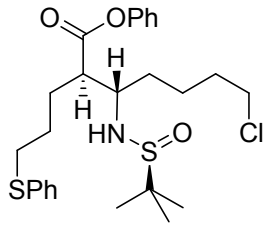
5.08 - 4.99 (2H, m, $\mathbf{H}_{11}$), 4.5 (1H, d, *J* = 7.7 Hz, $\mathbf{H}_1$), 3.73 (3H, s, $\mathbf{H}_{13}$), 3.53 (2H, t, *J* = 6.5 Hz, $\mathbf{H}_6$), 3.35 (1H, ddt, *J* = 7.7, 5.3, 3.7 Hz, $\mathbf{H}_2$), 2.92 (1H, ddd, *J* = 9.2, 5.3, 3.8 Hz, $\mathbf{H}_7$), 2.20 - 2.01 (2H, m, $\mathbf{H}_9$), 1.95 - 1.37 (8H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$ & $\mathbf{H}_8$), 1.23 (9H, s, $\mathbf{H}_{15}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 ($\mathbf{C}_{12}$), 137.3 ($\mathbf{C}_{10}$), 115.6 ($\mathbf{C}_{11}$), 58.1 ($\mathbf{C}_{14}$), 56.1 ($\mathbf{C}_2$), 51.8 ($\mathbf{C}_7$), 49.6 ($\mathbf{C}_{13}$), 44.8 ($\mathbf{C}_6$), 32.1 ($\mathbf{C}_5$), 31.8 ($\mathbf{C}_9$), 31.2 ($\mathbf{C}_3$), 27.7 ($\mathbf{C}_8$), 23.6 ($\mathbf{C}_4$), 22.7 ($\mathbf{C}_{15}$) ppm.

LC-MS (ES$^+$) *m/z* 352.0 $[M^{35}Cl+H]^+$, 354.0 $[M^{37}Cl+H]^+$, 374.0 $[M^{35}Cl+Na]^+$, 375.8 $[M^{37}Cl+Na]^+$.

HRMS (ES$^+$) for $C_{16}H_{31}ClNO_3S^+$ $[M+H]^+$, calculated 352.1708 found 352.1712.

2.108 - (2*R*,3*S*)-Phenyl-7-chloro-2-(3-(phenylthio)propyl))-3-((*S*)-2-methyl-propane-2-sulfinylamino)heptanoate



$C_{26}H_{36}ClNO_3S_2$
Mol Wt: 510.1480

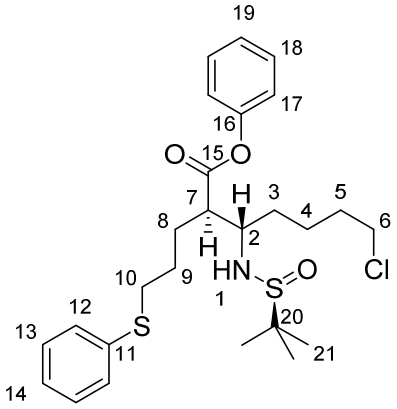
Following the procedure described for the synthesis of **2.35**, imine **1.110** (78 mg, 0.35 mmol) afforded the crude product as a separable mixture of two diastereoisomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti dr* 90:10). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereoisomer **2.108** (130 mg, 0.25 mmol, 71%) as a white solid.

$[\alpha]^{24}_{D}$ −17.8 (*c* 0.52, $CHCl_3$).

M.p. (hexane) 54–57 °C.

R_f 0.13 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3335, 3056, 2957, 1746, 1588, 1481, 1385, 1191, 1017 cm^{-1}.



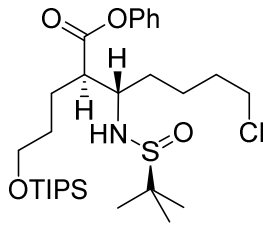
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.24 (4H, m, $\mathbf{H}_{12}$ & $\mathbf{H}_{18}$), 7.22 - 7.07 (4H, m, $\mathbf{H}_{13}$ & $\mathbf{H}_{14}$ & $\mathbf{H}_{19}$), 6.97 - 6.93 (2H, m, $\mathbf{H}_{17}$), 4.06 (1H, d, *J* = 8.6 Hz, $\mathbf{H}_1$), 3.46 (2H, t, *J* = 6.6 Hz, $\mathbf{H}_6$), 3.37 (1H, ddt, *J* = 9.2, 8.6, 4.2 Hz, $\mathbf{H}_2$), 3.05 (1H, ddd, *J* = 9.2, 4.6 Hz, $\mathbf{H}_7$), 2.99 - 2.84 (2H, m, $\mathbf{H}_{10}$), 1.96 (1H, m, $\mathbf{H}_8$), 1.85 - 1.29 (9H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$, $\mathbf{H}_8$ & $\mathbf{H}_9$), 1.58 (9H, s, $\mathbf{H}_{21}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 ($\mathbf{C}_{15}$), 150.2 ($\mathbf{C}_{16}$), 136.1 ($\mathbf{C}_{11}$), 129.5 ($\mathbf{C}_{18}$), 129.4 ($\mathbf{C}_{12}$), 128.9 ($\mathbf{C}_{13}$), 126.1 ($\mathbf{C}_{19}$), 126.0 ($\mathbf{C}_{14}$), 121.4 ($\mathbf{C}_{17}$), 58.3 ($\mathbf{C}_2$), 56.2 ($\mathbf{C}_{20}$), 50.2 ($\mathbf{C}_7$), 44.7 ($\mathbf{C}_6$), 33.5 ($\mathbf{C}_{10}$), 32.0 ($\mathbf{C}_5$), 31.5 ($\mathbf{C}_3$), 27.8 ($\mathbf{C}_8$), 27.2 ($\mathbf{C}_9$), 23.6 ($\mathbf{C}_4$), 22.7 ($\mathbf{C}_{21}$) ppm.

LRMS (ES^+) *m/z* 532.1 $[M^{35}Cl+Na]^+$, 534.1 $[M^{37}Cl+Na]^+$.

HRMS (ES^+) for $C_{26}H_{36}ClNNaO_3S_2^+$ $[M+Na]^+$, calculated 532.1717 found 532.1722.

2.109 - (2*R*,3*S*)-Phenyl-7-chloro-2-(3-(triisopropylsilyloxy)propyl)-3-((*S*)-2-methyl-propane-2-sulfinylamino)heptanoate



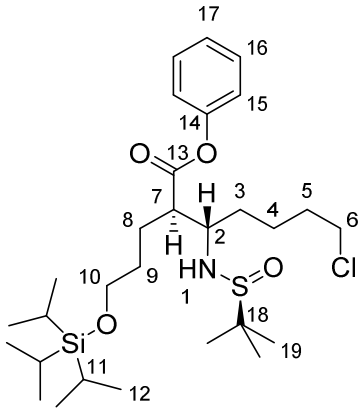
$C_{29}H_{52}ClNO_4SSi$
Mol Wt: 574.3330

Following the procedure described for the synthesis of **2.35**, imine **1.110** (0.15 g, 0.67 mmol) afforded the crude product as a separable mixture of two diastereomers (integration of NH peaks in the ^1H NMR gives *syn/anti dr* 90:10). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereomer **2.109** (0.24 g, 0.42 mmol, 63%) as a colourless oil.

$[\alpha]^{24}_D$ −12.2 (*c* 0.54, $CHCl_3$).

R_f 0.30 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 2942, 2865, 1753, 1593, 1460, 1386, 1191, 1069 cm^{-1}.



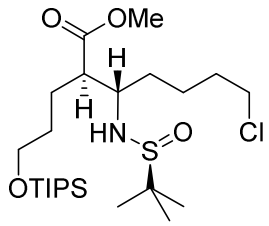
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.37 (2H, m, $\mathbf{H}_{16}$), 7.24 (1H, m, $\mathbf{H}_{17}$), 7.12 - 7.08 (2H, m, $\mathbf{H}_{15}$), 4.19 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{1}$), 3.82 - 3.71 (2H, m, $\mathbf{H}_{10}$), 3.55 (2H, t, *J* = 6.6 Hz, $\mathbf{H}_{6}$), 3.52 (1H, ddt, *J* = 8.6, 8.1, 4.2 Hz, $\mathbf{H}_{2}$), 3.17 (1H, ddd, *J* = 8.6, 4.6 Hz, $\mathbf{H}_{7}$), 1.98 (1H, m, $\mathbf{H}_{8}$), 1.86 - 1.47 (9H, m, $\mathbf{H}_{3}$, $\mathbf{H}_{4}$, $\mathbf{H}_{5}$, $\mathbf{H}_{8}$ & $\mathbf{H}_{9}$), 1.24 (9H, s, $\mathbf{H}_{19}$), 1.08 (18H, m, $\mathbf{H}_{12}$), 1.15 - 1.00 (3H, m, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 ($\mathbf{C}_{13}$), 150.4 ($\mathbf{C}_{14}$), 129.5 ($\mathbf{C}_{16}$), 126.0 ($\mathbf{C}_{17}$), 121.5 ($\mathbf{C}_{15}$), 62.9 ($\mathbf{C}_{10}$), 57.9 ($\mathbf{C}_{2}$), 56.1 ($\mathbf{C}_{18}$), 50.3 ($\mathbf{C}_{7}$), 44.7 ($\mathbf{C}_{6}$), 32.1 ($\mathbf{C}_{5}$), 31.3 ($\mathbf{C}_{9}$), 31.2 ($\mathbf{C}_{3}$), 25.1 ($\mathbf{C}_{8}$), 23.7 ($\mathbf{C}_{4}$), 22.7 ($\mathbf{C}_{19}$), 18.0 ($\mathbf{C}_{12}$), 12.0 ($\mathbf{C}_{11}$) ppm.

LRMS (ES^+) *m/z* 596.1 $[M^{35}Cl+Na]^+$, 598.1 $[M^{37}Cl+Na]^+$.

HRMS (ES^+) for $C_{29}H_{52}ClNNaO_4SSi^+$ $[M+Na]^+$, calculated 596.2967 found 596.2976.

2.110 - (2*R*,3*S*)-Methyl-7-chloro-2-(3-(triisopropylsilyloxy)propyl)-3-((*S*)-2-methyl-propane-2-sulfinylamino)heptanoate



$C_{24}H_{50}ClNO_4SSi$
Mol Wt: 512.2620

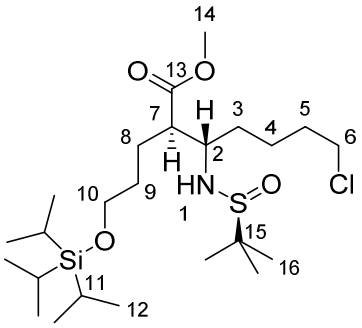
Following the procedure described for the synthesis of **2.35**, imine **1.110** (100 mg, 0.45 mmol) afforded the crude product as a partially separable mixture of two diastereoisomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti/syn/anti dr* 80:13:7:0). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereoisomer ***syn*-2.110** (40 mg, 0.08 mmol, 18%) as a colourless oil, minor diastereoisomer ***anti*-2.110** (20 mg, 0.04 mmol, 9%) as a colourless oil and mixture of diastereoisomers (130 mg, 0.26 mmol, 59%)

Data for major diastereoisomer ***syn*-2.110**:

$[\alpha]^{24}_D$ +20.1 (*c* 1.30, $CHCl_3$).

R_f 0.17 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3335, 2945, 2865, 1734, 1460, 1386, 1167, 1064 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_1$), 3.71 (3H, s, $\mathbf{H}_{14}$), 3.74 - 3.64 (2H, m, $\mathbf{H}_{10}$), 3.52 (2H, t, *J* = 6.5 Hz, $\mathbf{H}_6$), 3.37 (1H, ddt, *J* = 8.9, 7.8, 4.2 Hz, $\mathbf{H}_2$), 2.90 (1H, ddd, *J* = 8.9, 4.2 Hz, $\mathbf{H}_7$), 1.88 - 1.69 (3H, m, $\mathbf{H}_5$ & $\mathbf{H}_{8'}$), 1.68 - 1.39 (7H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_{8''}$ & $\mathbf{H}_9$), 1.23 (9H, s, $\mathbf{H}_{16}$), 1.06 (18H, m, $\mathbf{H}_{12}$), 1.13 - 0.98 (3H, m, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 ($\mathbf{C}_{13}$), 62.9 ($\mathbf{C}_{10}$), 57.8 ($\mathbf{C}_2$), 56.0 ($\mathbf{C}_{15}$), 51.8 ($\mathbf{C}_7$), 50.0 ($\mathbf{C}_{14}$), 44.7 ($\mathbf{C}_6$), 32.1 ($\mathbf{C}_5$), 31.2 ($\mathbf{C}_9$), 31.1 ($\mathbf{C}_3$), 24.7 ($\mathbf{C}_8$), 23.6 ($\mathbf{C}_4$), 22.7 ($\mathbf{C}_{16}$), 18.0 ($\mathbf{C}_{12}$), 11.9 ($\mathbf{C}_{11}$) ppm.

LC-MS (ES^+) *m/z* 512.2 $[M^{35}Cl+H]^+$, 514.3 $[M^{37}Cl+H]^+$, 534.1 $[M^{35}Cl+Na]^+$, 536.0 $[M^{37}Cl+Na]^+$.

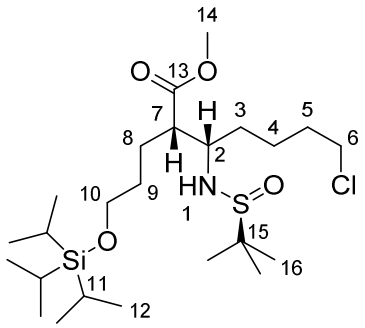
HRMS (ES^+) for $C_{24}H_{50}ClNaO_4SSi^+$ $[M+Na]^+$, calculated 534.2811 found 534.2803.

Data for minor diastereoisomer ***anti*-2.110**:

$[\alpha]^{24}_D$ +25.9 (*c* 0.28, $CHCl_3$).

R_f 0.22 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3310, 2945, 2865, 1722, 1460, 1364, 1169, 1072 cm^{-1}.



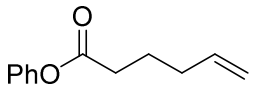
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (1H, d, *J* = 7.5 Hz, $\mathbf{H}_1$), 3.71 (3H, s, $\mathbf{H}_{14}$), 3.76 - 3.66 (2H, m, $\mathbf{H}_{10}$), 3.53 (2H, t, *J* = 6.5 Hz, $\mathbf{H}_6$), 3.35 (1H, ddt, *J* = 9.7, 7.2, 4.6 Hz, $\mathbf{H}_2$), 2.66 (1H, ddd, *J* = 9.7, 5.6, 4.6 Hz, $\mathbf{H}_7$), 1.90 - 1.69 (4H, m, $\mathbf{H}_5$ & $\mathbf{H}_8$), 1.59 - 1.39 (6H, m, $\mathbf{H}_3$, $\mathbf{H}_4$ & $\mathbf{H}_9$), 1.24 (9H, s, $\mathbf{H}_{16}$), 1.06 (18H, m, $\mathbf{H}_{12}$), 1.15 - 0.97 (3H, m, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 ($\mathbf{C}_{13}$), 62.9 ($\mathbf{C}_{10}$), 57.7 ($\mathbf{C}_2$), 56.2 ($\mathbf{C}_{15}$), 51.7 ($\mathbf{C}_7$), 48.9 ($\mathbf{C}_{14}$), 44.7 ($\mathbf{C}_6$), 35.1 ($\mathbf{C}_5$), 32.2 ($\mathbf{C}_3$), 30.7 ($\mathbf{C}_9$), 26.2 ($\mathbf{C}_8$), 23.3 ($\mathbf{C}_4$), 22.9 ($\mathbf{C}_{16}$), 18.0 ($\mathbf{C}_{12}$), 12.0 ($\mathbf{C}_{11}$) ppm.

LC-MS (ES^+) *m/z* 512.2 $[M^{35}Cl+H]^+$, 514.3 $[M^{37}Cl+H]^+$, 534.2 $[M^{35}Cl+Na]^+$, 536.3 $[M^{37}Cl+Na]^+$.

HRMS (ES^+) for $C_{24}H_{50}ClNaO_4SSi^+$ $[M+Na]^+$, calculated 534.2811 found 534.2805.

2.12 - Phenyl-hex-5-enoate



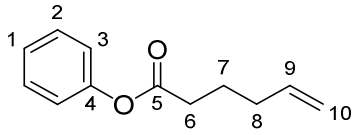
$C_{12}H_{14}O_2$
Mol Wt: 190.2420

To a solution of acid **2.10** (5.00 g, 43.81 mmol) in CH_2Cl_2 (50 mL) at 0 °C under N_2 were added oxalyl chloride (4.08 mL, 48.19 mmol) and DMF (3 drops) dropwise. The reaction mixture was stirred for 30 min at 0 °C, then allowed to warm to rt and stirred until gas evolution ceased (*ca*. 2 h).

To a solution of phenol (5.15 g, 54.76 mmol) in CH_2Cl_2 (150 mL) at 0 °C under N_2 was added Et_3N (15.27 mL, 109.53 mmol) dropwise over 15 min. The reaction mixture was stirred for 30 min at 0 °C before the dropwise addition of freshly prepared acid chloride over 30 min. The reaction mixture was stirred for 30 min at 0 °C, then allowed to warm to rt and stirred for 3 h. The mixture was poured onto sat. aq. NH_4Cl (150 mL) and stirred for 15 min. The phases were separated, the organic phase was washed with brine (2 x 150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **2.12** (8.11 g, 42.58 mmol, 97%) as colourless oil. Physical and spectroscopic data were consistent with reported values.[162]

R_f 0.53 (*eluent*: EtOAc/hexane - 40:60).

FT-IR (neat) ν_{max} 3075, 2936, 1756, 1593, 1492, 1193, 1133, 913 cm^{-1}.

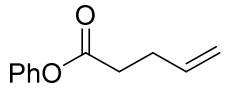


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.36 (2H, m, $\mathbf{H}_2$), 7.24 (1H, m, $\mathbf{H}_1$), 7.13 - 7.07 (2H, m, $\mathbf{H}_3$), 5.85 (1H, ddt, *J* = 17.0, 10.1, 6.8 Hz, $\mathbf{H}_9$),

5.14 - 5.03 (2H, m, $\mathbf{H}_{10}$), 2.59 (2H, t, *J* = 7.5 Hz, $\mathbf{H}_6$), 2.21 (2H, q, *J* = 7.4 Hz, $\mathbf{H}_8$), 1.89 (2H, quin, *J* = 7.4 Hz, $\mathbf{H}_7$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 ($\mathbf{C}_5$), 150.7 ($\mathbf{C}_4$), 137.5 ($\mathbf{C}_9$), 129.4 ($\mathbf{C}_2$), 125.7 ($\mathbf{C}_1$), 121.5 ($\mathbf{C}_3$), 115.6 ($\mathbf{C}_{10}$), 33.6 ($\mathbf{C}_6$), 33.0 ($\mathbf{C}_8$), 24.0 ($\mathbf{C}_7$) ppm.

2.11 - Phenyl-pent-4-enoate

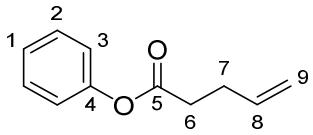


$C_{11}H_{12}O_2$
Mol Wt: 176.2150

Following the procedure described for the synthesis of **2.12**, acid **2.9** (7.5 g, 74.91 mmol) afforded the title compound **2.11** (11.8 g, 66.96 mmol, 89%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[163]

R_f 0.58 (*eluent*: EtOAc/hexane - 40:60).

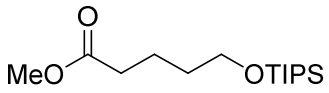
FT-IR (neat) ν_{max} 3077, 2980, 2921, 1756, 1641, 1593, 1492, 1193 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 -7.36 (2H, m, $\mathbf{H}_2$), 7.24 (1H, m, $\mathbf{H}_1$), 7.13 - 7.04 (2H, d, *J* = 7.7 Hz, $\mathbf{H}_3$), 5.93 (1H, ddt, *J* = 16.9, 10.5, 6.4 Hz, $\mathbf{H}_8$), 5.21-5.07 (2H, m, $\mathbf{H}_9$), 2.69 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_6$), 2.53 (2H, quin, *J* = 7.3 Hz, $\mathbf{H}_7$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.46 (**C**$_5$), 150.69 (**C**$_4$), 136.29 (**C**$_8$), 129.35 (**C**$_2$), 125.72 (**C**$_1$), 121.52 (**C**$_3$), 115.88 (**C**$_9$), 33.61 (**C**$_6$), 28.87 (**C**$_7$) ppm.

2.2 - Methyl-5-(triisopropylsilyloxy)pentanoate

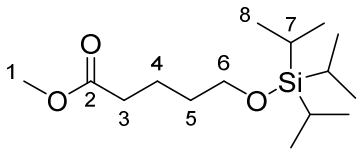


$C_{15}H_{32}O_3Si$
Mol Wt: 288.5030

To a solution of alcohol **2.1** (1.80 g, 13.62 mmol) and DMAP (0.18 g, 1. 47 mmol) in CH_2Cl_2 (50 mL) at 0 °C under N_2 were added Et_3N (4.22 mL, 30.26 mmol) and TIPSCl (4.05 mL, 18.91 mmol) dropwise. The resulting mixture was stirred at rt for 64 h before quenching with ice cold H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), EtOAc (3 x 50 mL), the organic phases combined, washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **2.2** (3.17 g, 10.98 mmol, 81%) as colourless oil. Physical and spectroscopic data were consistent with reported values.[164]

R$_f$ 0.32 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 2942, 2865, 1741, 1164, 1105, 882 cm^{-1}.

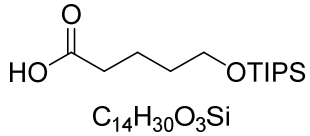


^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, t, *J* = 6.3 Hz, **H**$_6$), 3.67 (3H, s, **H**$_1$), 2.35 (2H, t, *J* = 7.6 Hz, **H**$_3$), 1.72 (2H, m, **H**$_4$), 1.57 (2H, m, **H**$_5$),

1.12 - 1.00 (3H, m, $\mathbf{H}_7$), 1.07 (18H, m, $\mathbf{H}_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 ($\mathbf{C}_2$), 62.9 ($\mathbf{C}_6$), 51.4 ($\mathbf{C}_1$), 33.9 ($\mathbf{C}_3$), 32.3 ($\mathbf{C}_5$), 21.5 ($\mathbf{C}_4$), 18.0 ($\mathbf{C}_8$), 12.0 ($\mathbf{C}_7$) ppm.

2.3 - 5-(Triisopropylsilyloxy)pentanoic acid

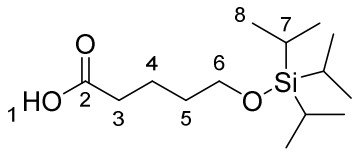


$C_{14}H_{30}O_3Si$
Mol Wt: 274.4760

To a stirred solution of ester **2.2** (2.00 g, 6.93 mmol) in MeOH/THF (30 mL - 3:1) at 0 °C was added NaOH (0.55 g, 13.75 mmol). The reaction mixture was heated at reflux for 24 h, then was allowed to cool to rt and concentrated *in vacuo* to yield a white solid. The residue was diluted with H_2O (50 mL) and acidified to pH ~ 2 using 2 M solution of HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), EtOAC (3 x 50 mL), the organic phases combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound **2.3** (1.88 g, 6.85 mmol, 99%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[164]

R_f 0.34 (*eluent*: EtOAc/hexane - 40:60).

FT-IR (neat) ν_{max} 2942, 2865, 1710, 1462, 1246, 1109, 882 cm^{-1}.



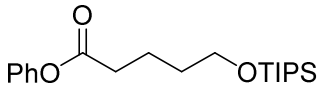
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (1H, br.s, $\mathbf{H}_1$), 3.72 (2H, t, J = 6.1 Hz, $\mathbf{H}_6$), 2.41 (2H, t, J = 7.3 Hz, $\mathbf{H}_3$), 1.74 (2H, m, $\mathbf{H}_5$), 1.60 (2H, m,

H$_5$), 1.15 - 1.01 (3H, m, **H**$_7$), 1.06 (18H, m, **H**$_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9 (**C**$_2$), 62.8 (**C**$_6$), 33.8 (**C**$_3$), 32.2 (**C**$_5$), 21.2 (**C**$_4$), 18.0 (**C**$_8$), 12.0 (**C**$_7$) ppm.

LRMS (ES$^-$) *m/z* 273.2 $[M-H]^+$.

2.4 - Phenyl-5-(triisopropylsilyloxy)pentanoate

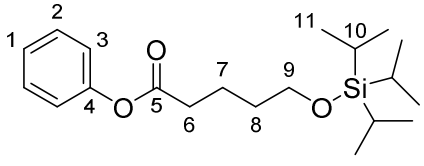


$C_{20}H_{34}O_3Si$
Mol Wt: 350.5740

To a stirred solution of acid **2.3** (0.95 g, 3.46 mmol), PhOH (0.36 g, 3.81 mmol) and DMAP (0.04 g, 0.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added DCC (1.07 g, 5.19 mmol) in CH_2Cl_2 (5 mL) dropwise. The resulting mixture was stirred at 0 °C for 30 min, then was allowed to warm to rt and stirred for 24 h. The white suspension was filtered under vacuum through a sintered funnel and the spent residue washed with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a pale yellow oil. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **2.4** (0.85 g, 2.42 mmol, 70%) as a colourless oil.

R$_f$ 0.63 (*eluent*: EtOAc/hexane - 20:80).

FT-IR (neat) ν_{max} 2940, 2865, 1761, 1594, 1461, 1195, 1105 cm^{-1}.



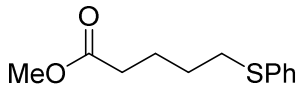
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.36 (2H, m, $\mathbf{H}_2$), 7.20 (1H, m, $\mathbf{H}_1$), 7.16 - 7.04 (2H, m, $\mathbf{H}_3$), 3.76 (2H, t, *J* = 6.3 Hz, $\mathbf{H}_9$), 2.62 (2H, t, *J* = 7.6 Hz, $\mathbf{H}_6$), 1.87 (2H, m, $\mathbf{H}_7$), 1.68 (2H, m, $\mathbf{H}_8$), 1.15 - 1.05 (3H, m, $\mathbf{H}_{10}$),1.09 (18H, m, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 ($\mathbf{C}_5$), 150.8 ($\mathbf{C}_4$), 129.4 ($\mathbf{C}_2$), 125.7 ($\mathbf{C}_1$), 121.6 ($\mathbf{C}_3$), 62.9 ($\mathbf{C}_9$), 34.2 ($\mathbf{C}_6$), 32.3 ($\mathbf{C}_8$), 21.6 ($\mathbf{C}_7$), 18.0 ($\mathbf{C}_{11}$), 12.0 ($\mathbf{C}_{10}$) ppm.

LRMS (ES$^+$) *m/z* 351.4 $[M+H]^+$, 373.3 $[M+Na]^+$.

HRMS (ES$^+$) for $C_{20}H_{34}NaO_3Si^+$ $[M+Na]^+$, calculated 373.2169 found 373.2176.

2.6 - Methyl-5-(phenylthio)pentanoate

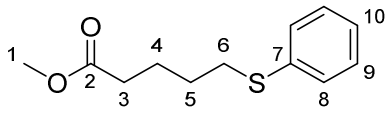


$C_{12}H_{16}O_2S$
Mol Wt: 224.3180

To a suspension of *t*-BuOK (0.75 g, 6.66 mmol) and TBAB (0.14 g, 0.44 mmol) in THF (15 mL) at 0 °C under N_2 was added PhSH (0.46 mL, 4.44 mmol) dropwise. The resulting mixture was stirred for 15 min at 0 °C before the dropwise addition of ester **2.5** (1.27 g, 4.44 mmol) in THF (15 mL). The white suspension was stirred at rt for 3 h before quenching with H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **2.6** (0.91 g, 4.06 mmol, 91%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[165]

R_f 0.40 (*eluent*: EtOAc/hexane - 10:90).

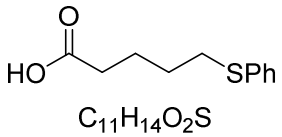
FT-IR (neat) ν_{max} 2948, 1733, 1583, 1436, 1202, 1024, 738 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.26 (4H, m, $\mathbf{H}_8$ & $\mathbf{H}_9$), 7.18 (1H, m, $\mathbf{H}_{10}$), 3.67 (3H, s, $\mathbf{H}_1$), 2.94 (2H, t, *J* = 7.2 Hz, $\mathbf{H}_6$), 2.34 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_3$), 1.79 (2H, m, $\mathbf{H}_4$), 1.69 (2H, m, $\mathbf{H}_5$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7 ($\mathbf{C}_2$), 136.5 ($\mathbf{C}_7$), 129.1 ($\mathbf{C}_8$), 128.8 ($\mathbf{C}_9$), 125.8 ($\mathbf{C}_{10}$), 51.5 ($\mathbf{C}_1$), 33.5 ($\mathbf{C}_3$), 33.2 ($\mathbf{C}_6$), 28.5 ($\mathbf{C}_5$), 24.0 ($\mathbf{C}_4$) ppm.

2.7 - 5-(Phenylthio)pentanoic acid



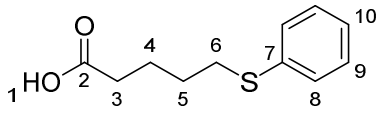
$C_{11}H_{14}O_2S$
Mol Wt: 210.2910

Following the procedure described for the synthesis of **2.3**, ester **2.6** (0.50 g, 2.23 mmol) afforded the title compound **2.7** (0.42 g, 2.00 mmol, 90%) as a white solid. Physical and spectroscopic data were consistent with reported values.[166]

M.p. (hexane) 61–63 °C; [Lit.[167] (hexane/Et_2O), 61–62°C].

R_f 0.26 (*eluent*: EtOAc/hexane - 50:50).

FT-IR (neat) ν_{max} 3053, 2920, 2870, 1700, 1584, 1434, 1294, 1238, 903 cm^{-1}.

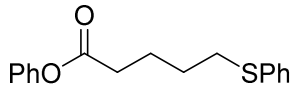


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (1H, br.s, $\mathbf{H}_1$), 7.28 - 7.19 (4H, m, $\mathbf{H}_8$ & $\mathbf{H}_9$), 7.11 (1H, m, $\mathbf{H}_{10}$), 2.87 (2H, t, J = 7.1 Hz, $\mathbf{H}_6$), 2.31 (2H, t, J = 7.2 Hz, $\mathbf{H}_3$), 1.72 (2H, m, $\mathbf{H}_4$), 1.63 (2H, m, $\mathbf{H}_5$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5 ($\mathbf{C}_2$), 136.4 ($\mathbf{C}_7$), 129.2 ($\mathbf{C}_8$), 128.9 ($\mathbf{C}_9$), 125.9 ($\mathbf{C}_{10}$), 33.5 ($\mathbf{C}_3$), 33.3 ($\mathbf{C}_6$), 28.4 ($\mathbf{C}_5$), 23.7 ($\mathbf{C}_4$) ppm.

LRMS (ES$^-$) *m/z* 209.1 $[M-H]^+$.

2.8 - Phenyl-5-(phenylthio)pentanoate

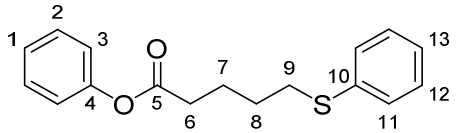


$C_{17}H_{18}O_2S$
Mol Wt: 286.3890

Following the procedure described for the synthesis of **2.4**, acid **2.7** (0.30 g, 1.43 mmol) afforded the title compound **2.8** (0.19 g, 0.66 mmol, 46%) as a colourless oil.

R_f 0.29 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3059, 2934, 1754, 1590, 1481, 1192, 1119, 738 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.34 (4H, m, $\mathbf{H}_2$ & $\mathbf{H}_{11}$), 7.33 - 7.17

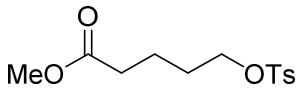
(4H, m, $\mathbf{H}_1$ & $\mathbf{H}_{12}$ & $\mathbf{H}_{13}$), 7.09 - 7.03 (2H, m, $\mathbf{H}_3$), 2.99 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_9$), 2.59 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_6$), 1.92 (2H, m, $\mathbf{H}_7$), 1.79 (2H, m, $\mathbf{H}_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 ($\mathbf{C}_5$), 150.6 ($\mathbf{C}_4$), 136.4 ($\mathbf{C}_{10}$), 129.4 ($\mathbf{C}_2$), 129.3 ($\mathbf{C}_{11}$), 128.9 ($\mathbf{C}_{12}$), 126.0 ($\mathbf{C}_1$), 125.8 ($\mathbf{C}_{13}$), 121.5 ($\mathbf{C}_3$), 33.9 ($\mathbf{C}_6$), 33.3 ($\mathbf{C}_9$), 28.5 ($\mathbf{C}_8$), 24.0 ($\mathbf{C}_7$) ppm.

LRMS (ES^+) *m/z* 325.2 $[M+K]^+$, 366.1 $[M+CH_3CN+K]^+$.

HRMS (ES^+) for $C_{17}H_{18}NaO_2S^+$ $[M+Na]^+$, calculated 309.0920 found 309.0919.

2.5 - Methyl-5-(tosyloxy)pentanoate

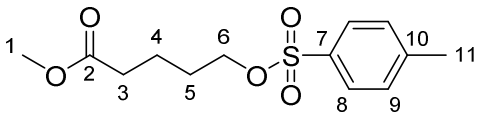


$C_{13}H_{18}O_5S$
Mol Wt: 286.3420

To a stirred solution of alcohol **2.1** (1.50 g, 11.35 mmol) and DMAP (0.04 g, 0.35 mmol) in CH_2Cl_2 (60 mL) at 0 °C under N_2 were added Et_3N (2.37 ml, 17.03 mmol) and TsCl (2.38 g, 12.49 mmol) in CH_2Cl_2 (25 mL) dropwise. The resulting suspension was stirred at 0 °C for 30 min, then was allowed to warm to rt and stirred for 24 h before quenching with sat. aq. $NaHCO_3$ (75 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 75 ml), the organic phases combined, washed with brine (3 x 75mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the title compound **2.5** (1.28 g, 4.47 mmol, 39%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[168]

R_f 0.13 (*eluent*: EtOAc/hexane - 10:90).

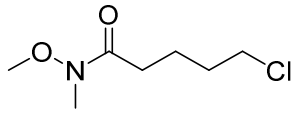
FT-IR (neat) ν_{max} 2953, 1734, 1598, 1356, 1173, 1097, 935 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.1 Hz, $\mathbf{H}_8$), 7.35 (2H, d, *J* = 8.1 Hz, $\mathbf{H}_9$), 4.04 (2H, t, *J* = 6.1 Hz, $\mathbf{H}_6$), 3.65 (3H, s, $\mathbf{H}_1$), 2.45 (3H, s, $\mathbf{H}_{11}$), 2.28 (2H, t, *J* = 6.9 Hz, $\mathbf{H}_3$), 1.75 - 1.61 (4H, m, $\mathbf{H}_4$ & $\mathbf{H}_5$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 ($\mathbf{C}_2$), 144.7 ($\mathbf{C}_{10}$), 133.0 ($\mathbf{C}_7$), 129.8 ($\mathbf{C}_9$), 127.8 ($\mathbf{C}_8$), 69.9 ($\mathbf{C}_6$), 51.5 ($\mathbf{C}_1$), 33.1 ($\mathbf{C}_3$), 28.2 ($\mathbf{C}_5$), 21.6 ($\mathbf{C}_{11}$), 20.8 ($\mathbf{C}_4$) ppm.

2.14 - 5-Chloro-*N*,*N*-methoxymethylpentanamide



$C_7H_{14}ClNO_2$
Mol Wt: 179.6440

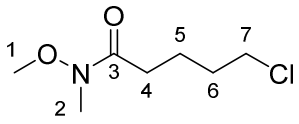
To a solution of acid **2.13** (5.00 g, 36.61 mmol) in CH_2Cl_2 (45 mL) at 0 °C under N_2 were added oxalyl chloride (3.41 mL, 40.27 mmol) and DMF (3 drops). The reaction mixture was stirred for 30 min at 0 °C, then was allowed to warm to rt and stirred until gas evolution ceased (*ca*. 2 h).

To a solution of Weinreb amine hydrochloride (4.63 g, 45.76 mmol) in CH_2Cl_2 (150 mL) at 0 °C under N_2 was added Et_3N (12.76 mL, 91.53 mmol) dropwise over 15 min. The reaction mixture was stirred for 30 min at 0 °C before the dropwise addition of

freshly prepared acid chloride over 30 min. The reaction mixture was stirred for 30 min at 0 °C, then was allowed to warm to rt and stirred for 24 h before quenching with sat. aq. NH_4Cl (130 mL). The phases were separated, the organic phase was washed with brine (2 x 130 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **2.14** (6.33 g, 35.24 mmol, 96%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[169]

R_f 0.35 (*eluent*: EtOAc/hexane - 50:50).

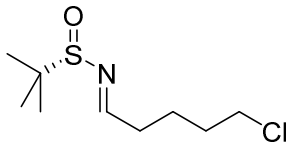
FT-IR (neat) ν_{max} 2940, 1658, 1444, 1385, 1177, 1106, 993 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (3H, s, $\mathbf{H}_1$), 3.56 (2H, t, J = 6.1 Hz, $\mathbf{H}_7$), 3.18 (3H, s, $\mathbf{H}_2$), 2.46 (2H, t, J = 6.8 Hz, $\mathbf{H}_4$), 1.89 - 1.75 (4H, m, $\mathbf{H}_5$ & $\mathbf{H}_6$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 ($\mathbf{C}_3$), 61.2 ($\mathbf{C}_1$), 44.6 ($\mathbf{C}_7$), 32.1 ($\mathbf{C}_2$ & $\mathbf{C}_5$), 30.9 ($\mathbf{C}_4$), 21.8 ($\mathbf{C}_6$) ppm.

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



$C_9H_{18}ClNOS$
Mol Wt: 223.7590

1.110 was performed using an adapted procedure as detailed by Brown.[68]

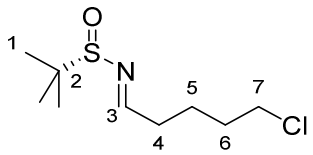
To a solution of amide **2.14** (11.90 g, 66.24 mmol) in CH_2Cl_2 (200 mL) at −78 °C under N_2 was added DIBAL-H (79.49 mL of 1M sol. in CH_2Cl_2, 79.49 mmol) dropwise *via* dropping funnel over 1 h. The reaction mixture was stirred for 2 h at −78 °C before quenching with 2 M HCl (200 mL).The mixture was stirred vigorously for 2 h, then the phases were separated and the organic phase was washed with brine (3 x 75 mL) and dried ($MgSO_4$).

To a suspension of (−)-TBSA (8.80 g, 72.86 mmol) and $CuSO_4$ (42.29 g, 264.96 mmol) in CH_2Cl_2 (200 mL) at 0 °C under N_2 was added a freshly prepared aldehyde **2.15** dropwise over 30 min. The reaction mixture was stirred for 30 min at 0 °C, then was allowed to warm to rt and stirred for 16 h. The mixture was filtered and the spent residue washed with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid. Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the title compound **1.110** (11.80 g, 52.74 mmol, 80%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[68]

$[\alpha]^{27}_D$ +225.1 (*c* 3.02, $CHCl_3$).

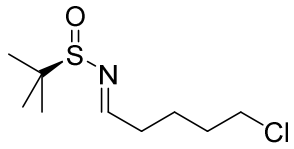
R_f 0.27 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 2957, 1662, 1455, 1362, 1184, 1178 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, t, *J* = 4.5 Hz, $\mathbf{H}_3$), 3.59 - 3.52 (2H, t, *J* = 6.4 Hz, $\mathbf{H}_7$), 2.56 (2H, td, *J* = 7.1, 4.5 Hz, $\mathbf{H}_4$), 1.88 - 1.76 (4H, m, $\mathbf{H}_5$ & $\mathbf{H}_6$), 1.19 (9H, s, $\mathbf{H}_1$) ppm.

***ent*-1.110- (−)-(*R*)-*N*-[(1*E*)-5-Chloropentylidene]-2-methylpropane-2-sulfinamide**

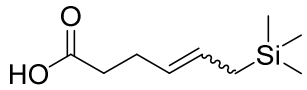


$C_9H_{18}ClNOS$
Mol Wt: 223.7590

Following the procedure described for the synthesis of **1.110**, amide **2.14** (3.70 g, 20.60 mmol) afforded the title compound ***ent*-1.110** (2.87 g, 12.82 mmol, 78%) as a colourless oil. Physical and spectroscopic data were consistent with those of the enantiomer.

$[\alpha]^{21}_D$ −236.9 (*c* 0.72, $CHCl_3$).

2.105 - 6-(Trimethylsilyl)hex-4-enoic acid

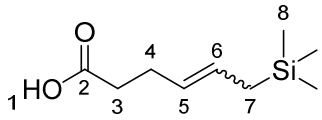


$C_9H_{18}O_2Si$
Mol Wt: 186.3260

To a stirred solution of alkene **2.9** (0.20 g, 2.0 mmol) and ATMS (0.95 mL, 6 mmol) in CH_2Cl_2 (4 mL) at rt under N_2 was added the Grubbs II (**2.94**) (0.04 g, 0.05 mmol) in one portion. The resulting brown solution was heated at reflux for 16 h before the solvent was removed *in vacuo*. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **2.105** (0.15 g, 0.81 mmol, 41%) (*E*/*Z* 3:1) as a colourless oil.

R_f 0.18 (*eluent*: EtOAc/hexane - 20:80).

FT-IR (neat) ν_{max} 3330, 2953, 2861, 1715, 1612, 1592, 1492, 1412, 1247 cm^{-1}.



Data for major isomer ***E*-2.105**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (1H, m, $\mathbf{H}_1$), 5.48 (1H, m, $\mathbf{H}_6$), 5.26 (1H, m, $\mathbf{H}_5$), 2.45 - 2.37 (2H, m, $\mathbf{H}_3$), 2.45 - 2.37 (2H, m, $\mathbf{H}_4$), 1.42 (2H, dd, J = 8.1, 1.1 Hz, $\mathbf{H}_7$), -0.01 (9H, s, $\mathbf{H}_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 ($\mathbf{C}_2$), 128.1 ($\mathbf{C}_5$), 126.0 ($\mathbf{C}_6$), 34.4 ($\mathbf{C}_3$), 27.9 ($\mathbf{C}_4$), 22.7 ($\mathbf{C}_7$), -2.1 ($\mathbf{C}_8$) ppm.

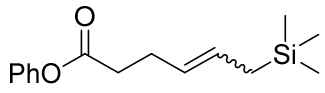
Data for minor isomer ***Z*-2.105**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (1H, m, $\mathbf{H}_1$), 5.48 (1H, m, $\mathbf{H}_6$), 5.26 (1H, m, $\mathbf{H}_5$), 2.45 - 2.37 (2H, m, $\mathbf{H}_3$), 2.45 - 2.37 (2H, m, $\mathbf{H}_4$), 1.50 (1H, dd, J = 8.7, 1.5 Hz, $\mathbf{H}_7$), 0.02 (9H, s, $\mathbf{H}_8$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 ($\mathbf{C}_2$), 127.4 ($\mathbf{C}_5$), 124.7 ($\mathbf{C}_6$), 34.0 ($\mathbf{C}_3$), 22.3 ($\mathbf{C}_4$), 18.6 ($\mathbf{C}_7$), -1.8 ($\mathbf{C}_8$) ppm.

HRMS (ES^+) for $C_9H_{17}O_2Si^+$ $[M-H]^+$, calculated 185.1003 found 185.0999.

2.101 - Phenyl-6-(trimethylsilyl)hex-4-enoate

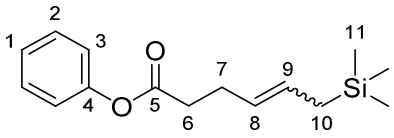


$C_{15}H_{22}O_2Si$
Mol Wt: 262.4240

To a stirred solution of acid **2.100** (0.56 g, 3 mmol), PhOH (0.34 g, 3.6 mmol), DMAP (0.07 g, 0.6 mmol) and Et_3N (0.84 mL, 6 mmol) in CH_2Cl_2/THF (3:1 - 80 mL) at rt under N_2 was added the EDAC (0.86 g, 4.4 mmol) in CH_2Cl_2 (10 mL) dropwise over 20 min. The reaction mixture was stirred for 30 min at 0 °C, then allowed to warm to rt and stirred for 6 h before the solvent was removed *in vacuo*. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **2.97** (0.66 g, 0.25 mmol, 83%) as an inseparable mixture of isomers (*E*/*Z* 3:1).

R_f 0.59 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3017, 2954, 2899, 1760, 1593, 1483, 1417, 1361, 1247 cm^{-1}.



Data for major isomer ***E*-2.101**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.35 (2H, m, $\mathbf{H}_2$), 7.23 (1H, m, $\mathbf{H}_1$), 7.12 - 7.06 (2H, m, $\mathbf{H}_3$), 5.53 (1H, m, $\mathbf{H}_9$), 5.34 (1H, m, $\mathbf{H}_8$), 2.62 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_6$), 2.50 - 2.41 (2H, m, $\mathbf{H}_7$), 1.46 (2H, dd, *J* = 8.1, 1.1 Hz, $\mathbf{H}_{10}$), 0.01 (9H, s, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 ($\mathbf{C}_5$), 150.8 ($\mathbf{C}_4$), 129.4 ($\mathbf{C}_2$), 128.2 (C $\mathbf{C}_8$), 126.1 ($\mathbf{C}_9$), 125.7 ($\mathbf{C}_1$), 121.6 ($\mathbf{C}_3$), 34.9 ($\mathbf{C}_6$), 28.2 ($\mathbf{C}_7$), 22.7

($\mathbf{C}_{10}$), -2.0 ($\mathbf{C}_{11}$) ppm.

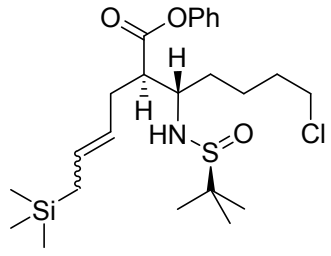
Data for minor isomer ***Z*-2.101**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.35 (2H, m, $\mathbf{H}_2$), 7.23 (1H, m, $\mathbf{H}_1$), 7.12 - 7.06 (2H, m, $\mathbf{H}_3$), 5.53 (1H, m, $\mathbf{H}_9$), 5.34 (1H, m, $\mathbf{H}_8$), 2.62 (2H, t, *J* = 7.3 Hz, $\mathbf{H}_6$), 2.50 - 2.41 (2H, m, $\mathbf{H}_7$), 1.55 (2H, dd, *J* = 8.7, 1.2 Hz, $\mathbf{H}_{10}$), 0.04 (9H, s, $\mathbf{H}_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 ($\mathbf{C}_5$), 150.8 ($\mathbf{C}_4$), 129.4 ($\mathbf{C}_2$), 127.6 ($\mathbf{C}_8$), 125.7 ($\mathbf{C}_1$), 124.6 ($\mathbf{C}_9$), 121.6 ($\mathbf{C}_3$), 34.5 ($\mathbf{C}_6$), 22.6 ($\mathbf{C}_7$), 18.6 ($\mathbf{C}_{10}$), -1.8 ($\mathbf{C}_{11}$) ppm.

HRMS (ES^+) for $C_{15}H_{22}NaO_2Si^+$ $[M+H]^+$, calculated 285.1281 found 285.1283.

2.102 - (2*R*,3*S*)-Phenyl-3-((*S*)- 2-methyl-propane-2-sulfinylamino)-7-chloro-2-(4-(trimethylsilyl)but-2-en-1-yl)heptanoate



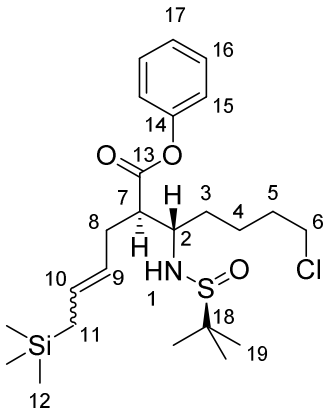
$C_{24}H_{40}ClNO_3SSi$
Mol Wt: 486.1830

Following the procedure described for the synthesis of **2.35**, imine **1.110** (0.85 g, 3.74 mmol) afforded the crude product as a separable mixture of two diastereoisomers (integration of NH peaks in the ^{1}H NMR gives *syn/anti dr* 95:5). Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the major diastereoisomer

2.102 (1.25 g, 2.57 mmol, 69%) (*E*/*Z* 3:1) as a colourless oil.

R_f 0.36 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 2953, 2865, 1754, 1593, 1492, 1363, 1247, 1192 cm^{-1}.

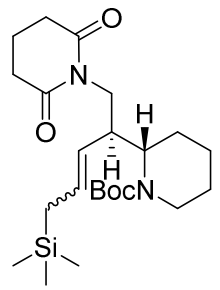


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.35 (2H, m, $\mathbf{H}_{16}$), 7.24 (1H, m, $\mathbf{H}_{17}$), 7.12 - 7.04 (2H, m, $\mathbf{H}_{15}$), 5.58 (1H, dt, *J* = 15.0, 7.9 Hz, $\mathbf{H}_{10}$), 5.31 (1H, dtd, *J* = 15.0 ,7.7, 6.4 Hz, $\mathbf{H}_9$), 4.20 (1H, d, *J* = 8.7 Hz, $\mathbf{H}_1$), 3.55 (1H, t, *J* = 6.4 Hz, $\mathbf{H}_6$), 3.51 (1H, m, $\mathbf{H}_2$), 3.23 (1H, ddd, *J* = 7.6, 4.3 Hz, $\mathbf{H}_7$), 2.64 (1H, dddd, *J* = 14.4, 7.7, 6.4, 1.1 Hz, $\mathbf{H}_{8'}$), 2.35 (1H, dd, *J* = 15.4, 7.7 Hz, $\mathbf{H}_{8''}$), 1.86 - 1.46 (8H, m, $\mathbf{H}_3$, $\mathbf{H}_4$, $\mathbf{H}_5$ & $\mathbf{H}_{11}$), 1.24 (9H, s, $\mathbf{H}_{19}$), 0.01 (9H, s, $\mathbf{H}_{12}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 ($\mathbf{C}_{13}$), 150.4 ($\mathbf{C}_{14}$), 130.1 ($\mathbf{C}_{11}$), 129.5 ($\mathbf{C}_{16}$), 126.0 ($\mathbf{C}_{17}$), 124.4 ($\mathbf{C}_{11}$), 121.5 ($\mathbf{C}_{15}$), 57.4 ($\mathbf{C}_{18}$), 56.2 ($\mathbf{C}_2$), 50.8 ($\mathbf{C}_7$), 44.8 ($\mathbf{C}_6$), 32.1 ($\mathbf{C}_8$), 32.1 ($\mathbf{C}_3$), 31.0 ($\mathbf{C}_5$), 23.6 ($\mathbf{C}_{11}$), 22.9 ($\mathbf{C}_4$), 22.8 ($\mathbf{C}_{19}$), -1.9 ($\mathbf{C}_{12}$) ppm.

LC-MS (ES^+) *m/z* 486.1 $[M^{35}Cl+H]^+$, 488.1 $[M^{37}Cl+H]^+$, 508.1 $[M^{35}Cl+Na]^+$, 510.1 $[M^{37}Cl+Na]^+$.

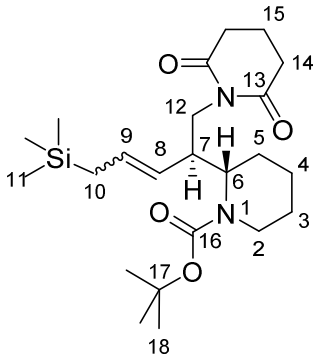
2.95 - (*S*)-tert-Butyl-2-((*S*,*E*)-1-(2,6-dioxopiperidin-1-yl)-5-(trimethylsilyl)pent-3-en-2-yl)piperidine-1-carboxylate



$C_{23}H_{40}N_2O_4Si$
Mol Wt: 436.6680

Following the procedure described for the synthesis of **2.105**, alkene **2.65** (75 mg, 0.21 mmol) afforded the crude as a mixture of cross-metathesis products. Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded an inseparable mixture of allylsilane **2.95** and **2.96** (25 mg, 0.06 mmol, 29%) as a colourless oil.

R_f 0.42 (*eluent*: EtOAc/hexane - 50:50).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, $\mathbf{H}_{15}$), 5.90 (1H, dt, *J* = 18.5, 6.3 Hz, $\mathbf{H}_9$), 5.54 (1H, d, *J* = 18.5 Hz, $\mathbf{H}_8$), 4.09 - 3.86 (2H, m, $\mathbf{H}_{2eq}$ & $\mathbf{H}_6$), 3.95 (1H, dd, *J* = 12.8, 7.4 Hz, $\mathbf{H}_{12'}$), 3.58 (1H, dd, *J* = 12.8, 4.5 Hz, $\mathbf{H}_{12''}$), 2.61 (4H, t, *J* = 6.5 Hz,), 2.64 - 2.50 (2H, m, $\mathbf{H}_{2ax}$ & $\mathbf{H}_7$), 2.17 - 1.95 (3H, m, $\mathbf{H}_{5eq}$ & $\mathbf{H}_{10}$), 1.91 (2H, quin, *J* = 6.5 Hz, $\mathbf{H}_{15}$), 1.83 - 1.51 (5H, m, $\mathbf{H}_3$, $\mathbf{H}_4$

& **H**$_{10}$), 1.46 (9H, s, **H**$_{18}$), 0.04 (9H, s, **H**$_{11}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 (**C**), 173.7 (**C**), 156.1 (**C**H), 156.1 (**C**H), 147.5 (**C**H), 131.2 (**C**H), 128.2 (**C**H), 127.9 (**C**H), 126.7 (**C**H), 80.4 (**C**H), 43.1 (**C**H$_2$), 42.8 (**C**H$_2$), 36.5(**C**H$_2$), 35.5 (**C**H), 34.4 (**C**H), 33.0 (**C**H$_2$), 32.9 (**C**H$_2$), 32.9 (**C**H$_2$), 32.4 (**C**H$_2$), 28.5 , (**C**H$_3$), 23.2 (**C**H$_2$), 19.2 (**C**H$_2$), 17.0 (**C**H$_2$), 16.9 (**C**H$_2$), -1.1 (**C**H$_3$), -1.7 (**C**H$_3$), -1.9 (**C**H$_3$) ppm.

LC-MS (ES$^+$) *m/z* 337.0 $[M-Boc+H]^+$, 436.9 $[M+H]^+$.

HRMS (ES$^+$) for $C_{23}H_{41}N_2O_4Si^+$ $[M+H]^+$, calculated 437.2830 found 437.2840.

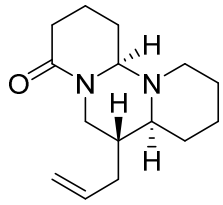
Selected data for **2.96:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (1H, dt, *J* = 15.3, 7.8 Hz, **H**$_9$), 5.14 (1H, dd, *J* = 13.9, 7.8 Hz, **H**$_8$), 1.45 (9H, s, **H**$_{18}$), -0.03 (9H, s, **H**$_{11}$) ppm.

LC-MS (ES$^+$) *m/z* 351.0 $[M-Boc+H]^+$, 451.1 $[M+H]^+$.

HRMS (ES$^+$) for $C_{24}H_{43}N_2O_4Si^+$ $[M+H]^+$, calculated 451.2987 found 451.2978.

2.100 - (7*R*,7a*S*,12a*S*)-7-allyldecahydro-4*H*,6*H*-dipyrido[1,2-a:1',2'-c]pyrimidin-4-one

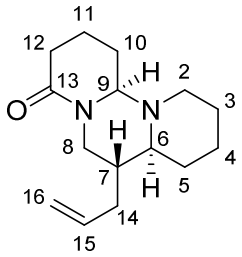


$C_{15}H_{24}N_2O$
Mol Wt: 248.3700

Following the procedure described for the synthesis of **2.47**, an inseparable mixture of allylsilanes **2.95** and **2.96** (3:1) (50 mg, 0.11 mmol) afforded the crude product as an inseparable mixture of hydroxy lactams **2.97** and **2.98** (45 mg, 0.10 mmol, 91%). The crude material was redissolved in CH_2Cl_2 (1.5 mL) and at 0 C under N_2 was added BF_3·OEt (0.02 mL 1 M sol. in THF, 0.02 mmol) dropwise. The reaction mixture was allowed to warm to rt and stirred for 24 h before the solvent was concentrated *in vacuo*. Purification by column chromatography eluting with 35% NH_4OH/MeOH/EtOAc (1:9:90) afforded the title compound **2.100** (7 mg, 0.03 mmol, 38%) as a green oil.

R_f 0.28 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3394, 3077, 2936, 2865, 1720, 1639, 1447, 1354 cm^{-1}.



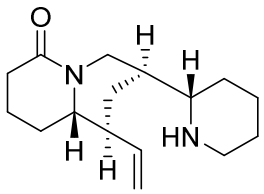
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, $\mathbf{H}_{15}$), 5.10 - 4.98 (2H, m, $\mathbf{H}_{16}$), 4.60 (1H, d, *J* = 3.6 Hz, $\mathbf{H}_{8eq}$), 4.57 (1H, dd, *J* = 7.7, 5.0 Hz, $\mathbf{H}_9$), 3.35 (1H, dd, *J* = 14.7, 2.6 Hz, $\mathbf{H}_{2eq}$), 3.07

(1H, dt, J = 12.5, 3.1 Hz, $\mathbf{H}_6$), 2.76 (1H, td, J = 13.1, 2.6 Hz, $\mathbf{H}_{2ax}$), 2.47 - 2.27 (3H, m, $\mathbf{H}_{8ax}$ & $\mathbf{H}_{14}$), 2.17 - 1.44 (9H, m, $\mathbf{H}_4$, $\mathbf{H}_7$, $\mathbf{H}_{10}$, $\mathbf{H}_{11}$ & $\mathbf{H}_{12}$), 1.39 - 1.15 (2H, m, $\mathbf{H}_3$ & $\mathbf{H}_5$) ppm.

^{135}DEPT NMR (100 MHz, $CDCl_3$) δ 135.6 ($\mathbf{C}_{15}$), 116.7 ($\mathbf{C}_{16}$), 66.4 ($\mathbf{C}_9$), 59.5 ($\mathbf{C}_6$), 49.8 ($\mathbf{C}_2$), 41.8 ($\mathbf{C}_8$), 38.1 ($\mathbf{C}_7$), 34.1 ($\mathbf{C}_{10}$), 32.7 ($\mathbf{C}_{14}$), 27.4 ($\mathbf{C}_{12}$), 25.0 ($\mathbf{C}_{11}$), 19.1 ($\mathbf{C}_3$), 17.8 ($\mathbf{C}_4$), 16.4 ($\mathbf{C}_5$) ppm.

LC-MS (ES^+) *m/z* 248.9 $[M+H]^+$.

2.99 - (7*S*,9*S*,9a*S*)-7-((S)-piperidin-2-yl)-9-vinyloctahydro-4*H*-quinolizin-4-one

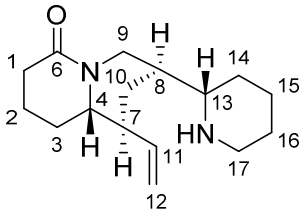


$C_{16}H_{26}N_2O$
Mol Wt: 262.3970

Material isolated from the cyclisation of **2.98** as colourless oil (5 mg, 0.02 mmol, 67%).

R_f 0.15 (*eluent*: 35% NH_4OH/MeOH/EtOAc - 2:8:90).

FT-IR (neat) ν_{max} 3423, 3078, 2929, 2855, 1620, 1443, 1334, 1270 cm^{-1}.

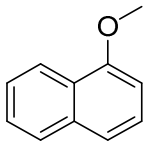


^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, ddd, *J* = 17.1, 10.1, 8.8 Hz, $\mathbf{H}_{11}$), 5.16 - 5.01 (2H, m, $\mathbf{H}_{12}$), 4.88 (1H, ddd, *J* = 12.7, 3.8, 2.2 Hz, $\mathbf{H}_{9eq}$), 3.10 (1H, m, $\mathbf{H}_{17eq}$), 2.97 (1H, m, $\mathbf{H}_{4}$), 2.60 (1H, td, *J* = 11.8, 3.0 Hz, $\mathbf{H}_{8ax}$), 2.48 - 2.22 (3H, m, $\mathbf{H}_{1}$ & $\mathbf{H}_{13}$), 2.18 (1H, t, *J* = 12.7 Hz, $\mathbf{H}_{9ax}$), 2.11 - 1.88 (3H, m, $\mathbf{H}_{7}$, $\mathbf{H}_{10eq}$ & $\mathbf{H}_{14eq}$), 1.85 - 1.67 (3H, m, $\mathbf{H}_{2eq}$, $\mathbf{H}_{15eq}$ & $\mathbf{H}_{16eq}$), 1.65 - 1.53 (3H, m, $\mathbf{H}_{2ax}$, $\mathbf{H}_{3eq}$ & $\mathbf{H}_{10ax}$), 1.49 - 1.31 (3H, m, $\mathbf{H}_{3ax}$, $\mathbf{H}_{8}$ & $\mathbf{H}_{15ax}$), 1.29 - 1.17 (2H, m, $\mathbf{H}_{14ax}$ & $\mathbf{H}_{16ax}$) ppm.

^{135}DEPT NMR (100 MHz, $CDCl_3$) δ 139.4 ($\mathbf{C}_{11}$), 116.4 ($\mathbf{C}_{12}$), 59.9 ($\mathbf{C}_{4}$), 59.6 ($\mathbf{C}_{13}$), 48.4 ($\mathbf{C}_{7}$), 47.4 ($\mathbf{C}_{17}$), 45.0 ($\mathbf{C}_{9}$), 40.8 ($\mathbf{C}_{8}$), 34.5 ($\mathbf{C}_{14}$), 33.0 ($\mathbf{C}_{1}$), 30.3 ($\mathbf{C}_{16}$), 27.8 ($\mathbf{C}_{10}$), 26.7 ($\mathbf{C}_{3}$), 24.8 ($\mathbf{C}_{15}$), 18.7 ($\mathbf{C}_{2}$) ppm.

LC-MS (ES^+) *m/z* 263.1 $[M+H]^+$.

3.34 - 1-Methoxynaphthalene

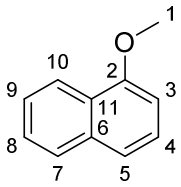


$C_{11}H_{10}O$
Mol Wt: 158.2000

To a solution of alcohol **3.30** (3.00 g, 20.81 mmol), *t*-BuOK (1.75 g, 31.22 mmol) and TBAB (0.67 g, 2.08 mmol) in THF (80 mL) at 0 °C under N_2 was added MeI (1.46 mL, 22.89 mmol) dropwise. The resulting cloudy grey suspension was stirred at 0 °C for 30 min, then was allowed to warm to rt and stirred for 5 h before quenching with H_2O (10 mL). The mixture was filtered under vaccum through a sintered funnel and concentrated *in vacuo* to yield a pale purple oil. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **3.34** (3.16 g, 19.98 mmol, 96%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[170]

R_f 0.51 (*eluent*: EtOAc/hexane - 10:90).

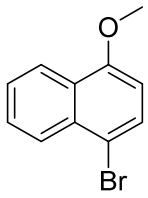
FT-IR (neat) ν_{max} 3052, 3003, 2936, 2847, 1579, 1462, 1265, 1100, 790 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_{10}$), 7.83 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_7$), 7.56 - 7.43 (3H, m, $\mathbf{H}_5$, $\mathbf{H}_8$ & $\mathbf{H}_9$), 7.41 (1H, dd, *J* = 8.2, 7.6 Hz, $\mathbf{H}_4$), 6.84 (1H, d, *J* = 7.6 Hz, $\mathbf{H}_3$), 4.03 (3H, s, $\mathbf{H}_1$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 ($\mathbf{C}_2$), 134.5 ($\mathbf{C}_6$), 127.4 ($\mathbf{C}_7$), 126.4 ($\mathbf{C}_8$), 125.8 ($\mathbf{C}_4$), 125.6 ($\mathbf{C}_{11}$), 125.1 ($\mathbf{C}_9$), 121.9 ($\mathbf{C}_{10}$), 120.2 ($\mathbf{C}_5$), 103.8 ($\mathbf{C}_3$), 55.5 ($\mathbf{C}_1$) ppm.

3.35 - 1-Bromo-4-methoxynaphthlene



$C_{11}H_9BrO$
Mol Wt: 237.0960

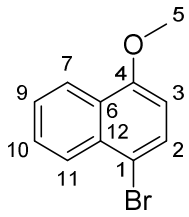
3.35 was performed using a procedure as detailed by Kodomari.[171]

To a solution of **3.34** (0.50 g, 3.16 mmol) in C_6H_6 (10 mL) was added $CuBr_2$ (1.41 g, 6.32 mmol) portionwise. The resulting cloudy suspension was stirred at reflux for 6 h.

The reaction mixture was filtered, the spent residue washed with hot C_6H_6 (10 mL) and the combined organic phases concentrated *in vacuo* to yield a pale yellow oil. Purification by crystallisation in MeOH from the crude reaction mixture removed the impurities and afforded the title compound **3.35** (0.67 g, 2.83 mmol, 90%) as a colourless oil. Physical and spectroscopic data were consistent with reported values.[171]

R_f 0.47 (*eluent*: EtOAc/hexane - 10:90).

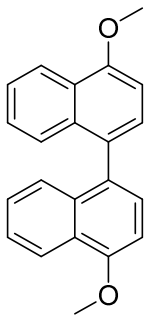
FT-IR (neat) ν_{max} 2934, 2838, 1589, 1454, 1260, 1084, 757 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_{11}$), 8.20 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_7$), 7.68 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_2$), 7.63 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, $\mathbf{H}_{10}$), 7.55 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, $\mathbf{H}_9$), 6.68 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_3$), 4.00 (3H, s, $\mathbf{H}_5$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 ($\mathbf{C}_4$), 132.4 ($\mathbf{C}_{12}$), 129.4 ($\mathbf{C}_2$), 127.7 ($\mathbf{C}_{10}$), 126.8 ($\mathbf{C}_{11}$), 126.8 ($\mathbf{C}_6$), 125.9 ($\mathbf{C}_9$), 122.4 ($\mathbf{C}_7$), 113.2 ($\mathbf{C}_1$), 104.5 ($\mathbf{C}_3$), 55.6 ($\mathbf{C}_5$) ppm.

3.36 - 4.4'-Dimethoxy-1,1'-binaphthalene



$C_{22}H_{18}O_2$
Mol Wt: 314.3840

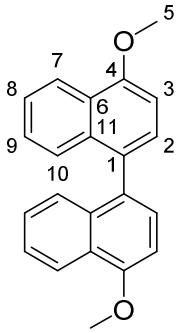
3.36 was performed using a procedure as detailed by Kochi.[172]

To a solution of **3.34** (0.50 g, 3.16 mmol) in CH_2Cl_2 (60 mL) was added $Et_3O^+SbCl_6^-$ (1.52 g, 3.48 mmol) portionwise. The resulting brown solution was stirred at rt for 1 h before quenching with sat. aq. $NaHCO_3$ (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), the organic phases combined, washed with brine (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown solid. Purification by crystallisation in MeOH from the crude reaction mixture removed the impurities and afforded the title compound **3.32** as a white powder (0.25 g, 0.80 mmol, 51%). Physical and spectroscopic data were consistent with reported values.[173]

M.p. (MeOH) 250–252°C; [Lit.[174] (C_6H_6, 252–254 °C)].

R_f 0.48 (*eluent*: CH_2Cl_2/hexane - 50:50).

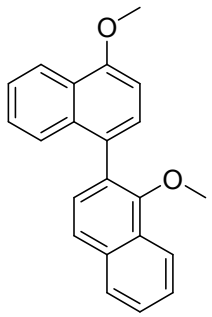
FT-IR (neat) ν_{max} 3016, 2955, 2836, 1585, 1458, 1263, 1084 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (2H, d, *J* = 8.4 Hz, $\mathbf{H}_7$), 7.47 (2H, ddd, *J* = 8.4, 6.8, 1.3 Hz, $\mathbf{H}_8$), 7.37 (2H, d, *J* = 6.8 Hz, $\mathbf{H}_{10}$), 7.39 (2H, d, *J* = 7.6 Hz, $\mathbf{H}_2$), 7.30 (2H, ddd, *J* = 8.4, 6.8, 1.3 Hz, $\mathbf{H}_9$), 6.94 (2H, d, *J* = 7.6 Hz, $\mathbf{H}_3$), 4.10 (6H, s, $\mathbf{H}_5$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 ($\mathbf{C}_4$), 134.1 ($\mathbf{C}_{11}$), 130.8 ($\mathbf{C}_1$), 128.0 ($\mathbf{C}_2$), 126.4 ($\mathbf{C}_9$), 126.3 ($\mathbf{C}_{10}$), 125.5 ($\mathbf{C}_6$), 125.0 ($\mathbf{C}_8$), 122.0 ($\mathbf{C}_7$), 103.4 ($\mathbf{C}_3$), 55.6 ($\mathbf{C}_5$) ppm.

3.37 - 4,1'-Dimethoxy-1,2'-binaphthalene



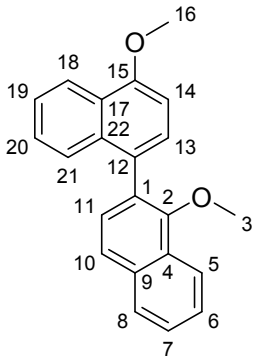
$C_{22}H_{18}O_2$
Mol Wt: 314.3840

Material isolated as a by-product from the attempted biaryl cyclisation of **3.34** as grey powder (0.44 g, 1.40 mmol, 37%). Physical and spectroscopic data were consistent with reported values.[175]

M.p. (MeOH) 132–136 °C; [Lit.[175] 126–128 °C, Lit.[176] (Pet. ether, 125.6–126.5 °C)].

R_f 0.42 (*eluent*: CH_2Cl_2/hexane - 50:50).

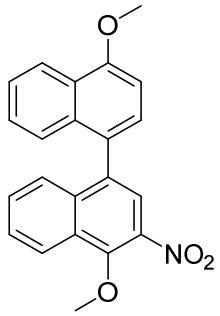
FT-IR (neat) ν_{max} 3068, 3001, 2935, 2839, 1581, 1455, 1259, 1089 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* = 8.8 Hz, $\mathbf{H}_{18}$), 8.03 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_5$), 7.35 - 7.24 (3H, m, $\mathbf{H}_6$, $\mathbf{H}_7$ & $\mathbf{H}_{19}$), 7.20 - 7.04 (6H, m $\mathbf{H}_8$, $\mathbf{H}_{10}$, $\mathbf{H}_{11}$, $\mathbf{H}_{13}$, $\mathbf{H}_{20}$ & $\mathbf{H}_{21}$), 6.72 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_{14}$), 3.93 (3H, s, $\mathbf{H}_{16}$), 3.88 (3H, s, $\mathbf{H}_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 ($\mathbf{C}_{15}$), 151.2 ($\mathbf{C}_2$), 136.0 ($\mathbf{C}_{22}$), 133.6 ($\mathbf{C}_9$), 133.2 ($\mathbf{C}_{12}$), 129.5 ($\mathbf{C}_{13}$), 129.0 ($\mathbf{C}_4$), 129.0 ($\mathbf{C}_1$), 127.9 ($\mathbf{C}_{11}$), 127.1 ($\mathbf{C}_{20}$), 126.7 ($\mathbf{C}_8$), 126.6 ($\mathbf{C}_7$), 126.3 ($\mathbf{C}_6$), 126.1 ($\mathbf{C}_{21}$), 125.5 ($\mathbf{C}_{17}$), 125.2 ($\mathbf{C}_{19}$), 122.5 ($\mathbf{C}_5$), 122.2 ($\mathbf{C}_{18}$), 122.0 ($\mathbf{C}_{10}$), 103.3 ($\mathbf{C}_{14}$), 61.5 ($\mathbf{C}_3$), 55.6 ($\mathbf{C}_{16}$) ppm.

3.31 - 4.4'-Dimethoxy-3-nitro-1,1'-binaphthalene



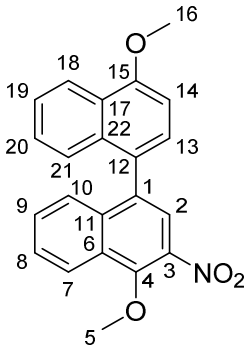
$C_{22}H_{17}NO_4$
Mol Wt: 359.3810

To a solution of **3.36** (0.50 g, 1.59 mmol) in AcOH (15 mL) was added $Cu(NO_3)_2 \cdot 2.5 H_2O$ (0.20 g, 0.87 mmol) portionwise. The resulting blue suspension was stirred at 50 °C for 24 h over which time it changed colour to dark-brown. The reaction mixture was poured onto ice cold H_2O (150 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL), the organic phases combined, washed with H_2O (3 x 50 mL), sat. aq. $NaHCO_3$ (3 x 50 mL), brine (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield an orange solid. Purification by column chromatography eluting with Et_2O/hexane (5:95) afforded the title compound **3.31** (0.30 g, 0.83 mmol, 52%) as a yellow solid. Physical and spectroscopic data were consistent with reported values.[174]

M.p. (hexane) 164–165 °C; [Lit.[174] (C_6H_6/light petroleum, 161–162 °C)].

R_f 0.22 (*eluent*: EtOAc/hexane - 10:90).

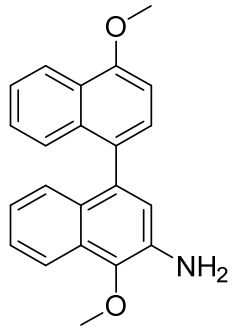
FT-IR (neat) ν_{max} 3071, 2939, 2841, 1586, 1526 1459, 1369 1262, 1091 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (1H, d, *J* = 9.3 Hz, $\mathbf{H}_{18}$), 8.31 (1H, d, *J* = 9.3 Hz, $\mathbf{H}_{7}$), 7.84 (1H, s, $\mathbf{H}_{2}$), 7.54 (1H, m, $\mathbf{H}_{8}$), 7.43 - 7.35 (3H, m, $\mathbf{H}_{9}$, $\mathbf{H}_{11}$ & $\mathbf{H}_{21}$), 7.31 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_{13}$), 7.26 (1H, m, $\mathbf{H}_{20}$), 7.19 (1H, m, $\mathbf{H}_{10}$), 6.86 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_{14}$), 4.16 (3H, s, $\mathbf{H}_{5}$), 4.02 (3H, s, $\mathbf{H}_{16}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 ($\mathbf{C}_{15}$), 150.9 ($\mathbf{C}_{4}$), 138.5 ($\mathbf{C}_{11}$), 136.4 ($\mathbf{C}_{3}$), 135.7 ($\mathbf{C}_{12}$), 133.4 ($\mathbf{C}_{22}$), 129.3 ($\mathbf{C}_{9}$), 128.6 ($\mathbf{C}_{1}$), 128.2 ($\mathbf{C}_{13}$), 128.1 ($\mathbf{C}_{6}$), 127.4 ($\mathbf{C}_{21}$), 127.4 ($\mathbf{C}_{8}$), 126.9 ($\mathbf{C}_{20}$), 125.7 ($\mathbf{C}_{10}$), 125.5 ($\mathbf{C}_{17}$), 125.4 ($\mathbf{C}_{19}$), 124.3 ($\mathbf{C}_{7}$), 122.7 ($\mathbf{C}_{2}$), 122.3 ($\mathbf{C}_{18}$), 103.3 ($\mathbf{C}_{14}$), 63.8 ($\mathbf{C}_{5}$), 55.7 ($\mathbf{C}_{16}$) ppm.

3.38 - 3-Amino-4.4'-Dimethoxy-1,1'-binaphthalene



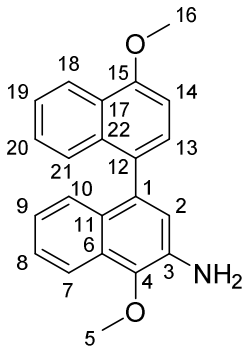
$C_{22}H_{19}NO_2$
Mol Wt: 329.3990

A suspension of **3.31** (0.15 g, 0.42 mmol) and 5 wt % Pd/C (0.80 g) in MeOH (8 mL) was placed under a H_2 atmosphere and stirred for 12 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to yield a pale brown solid. Purification by column chromatography eluting EtOAc/hexane (10:90) afforded the title compound **3.38** (0.10 g, 0.30 mmol, 71%) as pale yellow solid. Physical and spectroscopic data were consistent with reported values.[174]

M.p. (hexane) 140–142 °C; [Lit.[174] (CH_3OH, 140–142 °C)].

R_f 0.14 (*eluent*: EtOAc/hexane - 10:90).

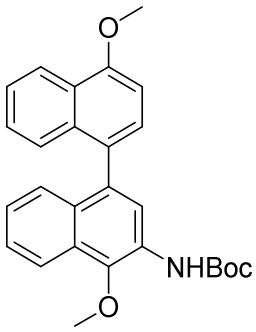
FT-IR (neat) ν_{max} 3369, 3064, 3000, 2936, 2834, 1620, 1586, 1461, 1372, cm^{-1}.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_{18}$), 8.03 (1H, d, *J* = 8.4 Hz, $\mathbf{H}_{7}$), 7.47 (1H, ddd, *J* = 8.4, 6.8, 1.3 Hz, $\mathbf{H}_{19}$), 7.44 (1H, ddd, *J* = 8.4, 6.8, 1.5 Hz, $\mathbf{H}_{8}$), 7.41 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_{21}$), 7.38 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{13}$), 7.32 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz, $\mathbf{H}_{20}$), 7.29 (1H, d, *J* = 8.2 Hz, $\mathbf{H}_{10}$), 7.07 (1H, ddd, *J* = 8.2, 6.8, 1.1 Hz, $\mathbf{H}_{9}$), 7.06 (1H, s, $\mathbf{H}_{2}$), 6.92 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{14}$), 4.10 (3H, s, $\mathbf{H}_{16}$), 4.01 (3H, s, $\mathbf{H}_{5}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 ($\mathbf{C}_{15}$), 138.9 ($\mathbf{C}_{4}$), 135.6 ($\mathbf{C}_{22}$), 135.0 ($\mathbf{C}_{3}$), 133.8 ($\mathbf{C}_{12}$), 130.3 ($\mathbf{C}_{11}$), 128.6 ($\mathbf{C}_{1}$), 127.7 ($\mathbf{C}_{13}$), 127.1 ($\mathbf{C}_{6}$), 126.4 ($\mathbf{C}_{19}$), 126.4 ($\mathbf{C}_{21}$), 126.1 ($\mathbf{C}_{20}$), 125.4 ($\mathbf{C}_{17}$), 125.1 ($\mathbf{C}_{9}$), 122.5 ($\mathbf{C}_{8}$), 122.0 ($\mathbf{C}_{10}$), 120.9 ($\mathbf{C}_{7}$), 120.1 ($\mathbf{C}_{18}$), 111.1 ($\mathbf{C}_{2}$), 103.3 ($\mathbf{C}_{14}$), 60.0 ($\mathbf{C}_{5}$), 55.6 ($\mathbf{C}_{16}$) ppm.

3.39 - *tert*-Butyl-(4,4'-dimethoxy-[1,1'-binaphthalen]-3-yl)carbamate



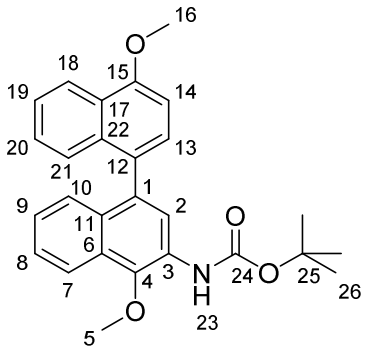
$C_{27}H_{27}NO_4$
Mol Wt: 429.5160

To a solution of **3.38** (0.15 g, 0.46 mmol) in THF (9 mL) was added Boc_2O (0.25 g, 1.14 mmol) portionwise. The resulting solution was stirred at 40 °C for 4 days. The reaction mixture was concentrated *in vacuo* to yield a yellow solid. Purification by column chromatography eluting with EtOAc/hexane (5:95) afforded the title compound **3.39** (0.16 g, 0.37 mmol, 80%) as a white solid.

M.p. (hexane) 102–105 °C.

R_f 0.36 (eluent: EtOAc/hexane - 20:80).

FT-IR (neat) ν_{max} 3431, 3067, 2974, 2933, 2855, 1728, 1601, 1492, 1369, 1261 cm^{-1}.



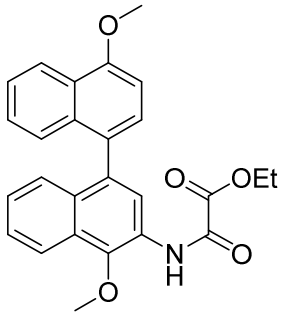
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, s, $\mathbf{H}_2$), 8.39 (1H, d, *J* = 8.6 Hz, $\mathbf{H}_{18}$), 8.11 (1H, d, *J* = 8.5 Hz, $\mathbf{H}_7$), 7.52 - 7.28 (6H, m, $\mathbf{H}_8$, $\mathbf{H}_{10}$, $\mathbf{H}_{13}$, $\mathbf{H}_{19}$, $\mathbf{H}_{20}$ & $\mathbf{H}_{21}$), 7.26 (1H, br.s, $\mathbf{H}_{23}$), 7.21 (4H, ddd, *J* = 8.5, 6.9, 1.3 Hz, $\mathbf{H}_9$), 6.94 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{14}$), 4.10 (3H, s, $\mathbf{H}_5$), 4.06 (3H, s, $\mathbf{H}_{16}$), 1.55 (9H, s, $\mathbf{H}_{26}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 ($\mathbf{C}_{15}$), 152.8 ($\mathbf{C}_{24}$), 141.7 ($\mathbf{C}_4$), 135.5 ($\mathbf{C}_{22}$), 133.7 ($\mathbf{C}_{12}$), 130.4 ($\mathbf{C}_1$), 130.3 ($\mathbf{C}_{11}$), 127.9 ($\mathbf{C}_{13}$), 127.8 ($\mathbf{C}_3$), 127.3 ($\mathbf{C}_6$), 127.2 ($\mathbf{C}_{20}$), 126.4 ($\mathbf{C}_{10}$), 126.4 ($\mathbf{C}_9$) 126.0 ($\mathbf{C}_8$), 125.4 ($\mathbf{C}_{17}$), 125.0 ($\mathbf{C}_{19}$), 124.3 ($\mathbf{C}_{21}$), 122.0 ($\mathbf{C}_{18}$), 121.3 ($\mathbf{C}_2$), 121.1 ($\mathbf{C}_7$), 103.3 ($\mathbf{C}_{14}$), 80.7 ($\mathbf{C}_{25}$), 61.5 (C $\mathbf{C}_5$), 55.6 ($\mathbf{C}_{16}$), 28.3 ($\mathbf{C}_{26}$) ppm.

LRMS (ES^+) *m/z* 493.2 $[M+CH_3CN+Na]^+$, 882.0 $[2M+Na]^+$.

HRMS (ES^+) for $C_{27}H_{27}NNaO_4^+$ $[M+Na]^+$, calculated 452.1832 found 452.1837.

3.40 - *tert*-Butyl-(4,4'-dimethoxy-[1,1'-binaphthalen]-3-yl)carbamate



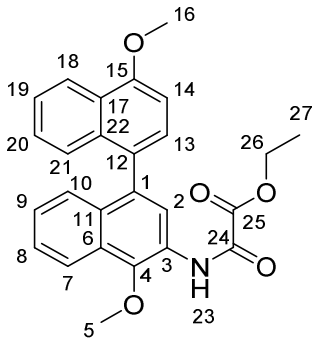
$C_{26}H_{23}NO_5$
Mol Wt: 429.4720

To a solution of **3.38** (30 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2 were added oxalyl chloride (0.01 mL, 0.11 mmol) and DMF (3 drops) dropwise. The resulting yellow suspension was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo* to yield a yellow solid. The crude residue was redissolved in EtOH (2 mL) and stirred at rt for 1 h over which time it changed to pale red suspension. The reaction mixture was concentrated *in vacuo* to yield a red-black solid. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **3.40** (32 mg, 0.07 mmol, 80%) as a white solid.

M.p. (hexane) 197–120 °C.

R_f 0.19 (eluent: EtOAc/hexane - 20:80).

FT-IR (neat) ν_{max} 3376, 3067, 3009, 2939, 2903, 2838, 1763, 1709, 1597, 1499 cm^{-1}.



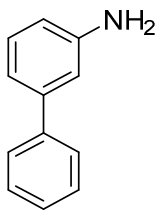
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (1H, br.s, $\mathbf{H}_{23}$), 8.58 (1H, br.s, $\mathbf{H}_{2}$), 8.38 (1H, d, *J* = 8.6 Hz, $\mathbf{H}_{18}$), 8.16 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{7}$), 7.55 - 7.38 (4H, m, $\mathbf{H}_{8}$, $\mathbf{H}_{13}$, $\mathbf{H}_{19}$ & $\mathbf{H}_{21}$), 7.36 - 7.24 (3H, m, $\mathbf{H}_{9}$, $\mathbf{H}_{10}$ & $\mathbf{H}_{20}$), 6.94 (1H, d, *J* = 8.1 Hz, $\mathbf{H}_{14}$), 4.46 (2H, q, *J* = 7.2 Hz, $\mathbf{H}_{26}$), 4.12 (3H, s, $\mathbf{H}_{5}$), 4.10 (3H, s, $\mathbf{H}_{16}$), 1.45 (3H, t, *J* = 7.2 Hz, $\mathbf{H}_{27}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 ($\mathbf{C}_{25}$), 155.4 ($\mathbf{C}_{24}$), 153.8 ($\mathbf{C}_{15}$), 143.7 ($\mathbf{C}_{4}$), 135.9 ($\mathbf{C}_{22}$), 133.6 ($\mathbf{C}_{12}$), 131.9 ($\mathbf{C}_{1}$), 129.7 ($\mathbf{C}_{11}$), 128.0 ($\mathbf{C}_{20}$), 127.4 ($\mathbf{C}_{9}$), 127.2 ($\mathbf{C}_{6}$), 126.5 ($\mathbf{C}_{8}$), 126.4 ($\mathbf{C}_{19}$), 126.2 ($\mathbf{C}_{13}$), 126.0 ($\mathbf{C}_{3}$), 125.5 ($\mathbf{C}_{21}$), 125.4 ($\mathbf{C}_{17}$), 125.1 ($\mathbf{C}_{10}$), 122.1 ($\mathbf{C}_{7}$), 121.6 ($\mathbf{C}_{18}$), 121.1 ($\mathbf{C}_{2}$), 103.4 ($\mathbf{C}_{14}$), 63.6 ($\mathbf{C}_{5}$), 62.1 ($\mathbf{C}_{26}$), 55.6 ($\mathbf{C}_{16}$), 14.0 ($\mathbf{C}_{27}$) ppm.

LRMS (ES^+) *m/z* 493.2 $[M+CH_3CN+Na]^+$, 881.4 $[2M+Na]^+$.

HRMS (ES^+) for $C_{26}H_{23}NNaO_5^+$ $[M+Na]^+$, calculated 452.1468 found 452.1472.

3.23 - 3-Amino-biphenyl



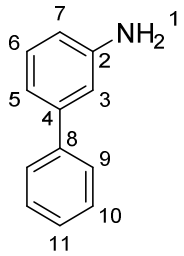
$C_{12}H_{11}N$
Mol Wt: 169.2270

Following the procedure described for the synthesis of **3.38**, biphenyl **3.22** (2.00 g, 10.0 mmol) afforded the title compound **3.23** (1.36 g, 8.0 mmol, 80%) as a brown solid. Physical and spectroscopic data were consistent with reported values.[177]

M.p. (hexane) 28–30 °C; [Lit.[178] 29–30°C].

R_f: 0.27 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3412, 3339, 3057, 3034, 1595, 1476, 1428, 753 cm^{-1}.

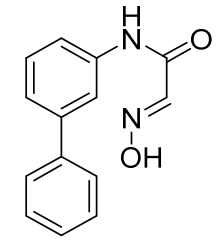


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 7.5 Hz, $\mathbf{H}_9$), 7.49 (2H, t, *J* = 7.5 Hz, $\mathbf{H}_{10}$), 7.40 (1H, m, $\mathbf{H}_{11}$), 7.30 (1H, t, *J* = 7.8 Hz, $\mathbf{H}_6$), 7.07 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_5$), 6.96 (1H, s, $\mathbf{H}_3$), 6.73 (1H, d, *J* = 7.8 Hz, $\mathbf{H}_7$), 3.74 (2H, br. s., $\mathbf{H}_1$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 ($\mathbf{C}_2$), 142.3 ($\mathbf{C}_4$), 141.3 ($\mathbf{C}_8$), 129.6 ($\mathbf{C}_6$), 128.6 ($\mathbf{C}_{10}$), 127.1 ($\mathbf{C}_{11}$), 127.0 ($\mathbf{C}_9$), 117.6 ($\mathbf{C}_5$), 114.0 ($\mathbf{C}_7$),

113.8 (C_3) ppm.

3.24 - (*E*)-*N*-([1,1'-Biphenyl]-3-yl-2-(hydroxyimino))acetamide



$C_{14}H_{12}N_2O_2$
Mol Wt: 240.2620

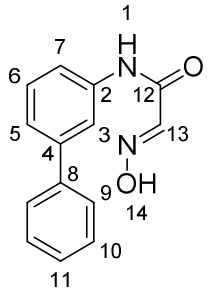
3.24 was performed using a procedure as detailed by Kaila.[160]

To a suspension of **3.23** (0.40 g, 2.36 mmol), $NH_2OH{\cdot}HCl$ (0.65 g, 9.44 mmol), Na_2SO_4 (2.68 g, 18.88 mmol) and 2 M HCl (0.8 mL, 1.6 mmol) in H_2O (19 mL) was added chloral hydrate (0.47 g, 2.83 mmol) portionwise. The resulting yellow suspension was stirred at 50 ºC for 10 h. The reaction mixture was filtered and the residue dried in a vacuum oven at 50 ºC for 6 h to afford the title compound **3.24** as a pale yellow powder (0.52 g, 2.16 mmol, 91%). Physical and spectroscopic data were consistent with reported values.[160]

M.p. (hexane) 162–166 °C.

R_f: 0.16 (*eluent*: EtOAc/hexane - 30:70).

FT-IR (neat) ν_{max} 3412, 3339, 3057, 3034, 1595, 1475, 1427, 753 cm^{-1}.

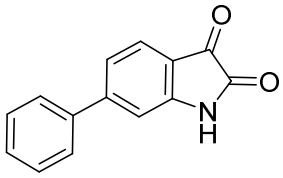


^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (1H, s, $\mathbf{H}_{14}$), 10.28 (1H, s, $\mathbf{H}_1$), 8.03 (1H, s, $\mathbf{H}_{13}$), 7.70 (1H, s, $\mathbf{H}_3$), 7.71 (1H, d, *J* = 7.6 Hz, $\mathbf{H}_7$), 7.62 (2H, d, *J* = 7.6 Hz, $\mathbf{H}_9$), 7.47 (2H, t, *J* = 7.6 Hz, $\mathbf{H}_{10}$), 7.42 (1H, t, *J* = 7.6 Hz, $\mathbf{H}_6$), 7.42 - 7.35 (2H, m, $\mathbf{H}_5$ & $\mathbf{H}_{10}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ ($\mathbf{C}_{12}$), 144.0 ($\mathbf{C}_{13}$), 140.7 ($\mathbf{C}_4$), 140.0 ($\mathbf{C}_8$), 139.0 ($\mathbf{C}_2$), 129.3 ($\mathbf{C}_6$), 129.0 ($\mathbf{C}_{10}$), 127.6 ($\mathbf{C}_{11}$), 126.6 ($\mathbf{C}_8$), 122.2 ($\mathbf{C}_7$), 118.9 ($\mathbf{C}_5$), 118.2 ($\mathbf{C}_3$) ppm.

LCMS (ES^+) *m/z* 279.5 $[M+K]^+$.

3.26 - 6-Phenyl-indole-2,3-dione



$C_{14}H_9NO_2$
Mol Wt: 223.2310

3.26 was performed using a procedure as detailed by Kaila.[160]

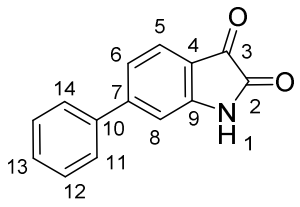
To neat H_2SO_4 (0.8 mL) at 50 °C was added hydroxyiminoacetamide **3.24** (0.33 g, 1.37 mmol) portionwise. The resulting dark solution was stirred at 80 °C for 1 h. The reaction mixture was cooled to rt, poured onto crushed ice and the crude residue was

collected by filtration. Purification by column chromatography eluting with EtOAc/hexane (10:90) afforded the title compound **3.26** (0.08 g, 0.36 mmol, 26%) as an orange solid. Physical and spectroscopic data were consistent with reported values.[179]

M.p. (hexane) 230–232 °C; [Lit.[180] (EtOAc, 231–233°C].

R_f 0.36 (*eluent*: EtOAc/hexane - 50:50).

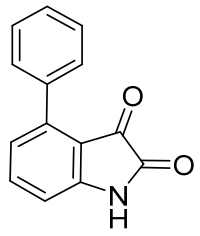
FT-IR (neat) ν_{max} 3447, 3267, 3053, 2961, 2918, 1760, 1731, 1615, 1430, 1346 cm^{-1}.



^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 (1H, br. s., $\mathbf{H}_1$), 7.72 (1H, d, J = 7.7 Hz, $\mathbf{H}_{11}$), 7.71 (1H, d, J = 8.4 Hz, $\mathbf{H}_5$), 7.59 (1H, d, J = 7.7 Hz, $\mathbf{H}_{14}$), 7.57 - 7.44 (3H, m, $\mathbf{H}_{12}$ & $\mathbf{H}_6$), 7.36 (1H, dd, J = 8.0, 1.5 Hz, $\mathbf{H}_{13}$), 7.11 (1H, d, J = 1.5 Hz, $\mathbf{H}_8$) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ 183.7 ($\mathbf{C}_3$), 159.8 ($\mathbf{C}_2$), 151.4 ($\mathbf{C}_9$), 149.9 ($\mathbf{C}_7$), 138.9 ($\mathbf{C}_{10}$), 129.2 ($\mathbf{C}_{12}$), 129.1 ($\mathbf{C}_{13}$), 127.0 ($\mathbf{C}_{11}$), 125.3 ($\mathbf{C}_5$), 121.3 ($\mathbf{C}_6$), 116.8 ($\mathbf{C}_4$), 110.1 ($\mathbf{C}_8$) ppm.

3.25 - 4-Phenyl-indole-2,3-dione

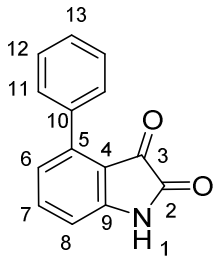


$C_{14}H_9NO_2$
Mol Wt: 223.2310

Material isolated as minor isomer from the above cyclisation (27 mg, 0.12 mmol, 9%) as an orange solid. Physical and spectroscopic data were consistent with reported values.[181]

R_f: 0.27 (*eluent*: EtOAc/hexane - 50:50).

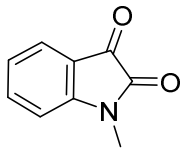
FT-IR (neat) ν_{max} 3447, 3267, 3053, 2961, 2918, 1760, 1731, 1615, 1430, 1346 cm^{-1}.



^{1}H NMR (300 MHz, Acetone-d_6) δ 10.08 (1H, br.s., $\mathbf{H}_1$), 7.63 (1H, t, J = 8.1 Hz, $\mathbf{H}_7$), 7.60 - 7.36 (5H, m, $\mathbf{H}_{11}$, $\mathbf{H}_{12}$ & $\mathbf{H}_{13}$), 7.07 (1H, d, J = 8.1 Hz, $\mathbf{H}_6$), 7.01 (1H, d, J = 8.1 Hz, $\mathbf{H}_8$) ppm.

^{13}C NMR (75 MHz, Acetone-d_6) δ 183.5 ($\mathbf{C}_3$), 159.6 ($\mathbf{C}_2$), 152.5 ($\mathbf{C}_9$), 143.4 ($\mathbf{C}_{10}$), 138.8 ($\mathbf{C}_7$), 137.7 ($\mathbf{C}_5$), 129.9 ($\mathbf{C}_{12}$), 129.6 ($\mathbf{C}_6$), 129.0 ($\mathbf{C}_{11}$), 125.7 ($\mathbf{C}_{13}$), 112.0 ($\mathbf{C}_8$), 112.0 ($\mathbf{C}_4$) ppm.

3.27 *N*-Methylindoline-2,3-dione



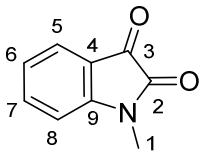
$C_9H_7NO_2$
Mol Wt: 161.1600

To a suspension of isatin **3.21** (0.50 g, 3.40 mmol), KOH (0.30 g, 5.44 mmol) and TBAB (0.11 g, 0.34 mmol) in THF (15 mL) at rt under N_2 was added MeI (0.28 mL, 4.42 mmol) dropwise. The reaction mixture was stirred at rt for 48 h. The mixture was filtered under vaccum through a sintered funnel and concentrated *in vacuo* to yield a dark-brown oil. Purification by column chromatography eluting with EtOAc/hexane (20:80) afforded the title compound **3.27** (0.26 g, 1.61 mmol, 47%) as an orange solid. Physical and spectroscopic data were consistent with reported values.[182]

M.p. (EtOAc) 120–124 °C; [Lit.[182] (EtOAc, 122–125°C].

R_f 0.17 (*eluent*: EtOAc/hexane - 30:70).

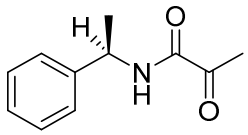
FT-IR (neat) ν_{max} 3097, 3059, 2930, 2848, 1740, 1607, 1468, 1326, 1115 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (10H, d, *J* = 7.6 Hz, $\mathbf{H}_5$), 7.61 (17H, ddd, *J* = 7.6, 1.5 Hz, $\mathbf{H}_7$), 7.14 (1H, td, *J* = 7.6, 0.7 Hz, $\mathbf{H}_6$), 6.90 (1H, d, *J* = 7.6 Hz, $\mathbf{H}_8$), 3.26 (3H, s, $\mathbf{H}_1$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) 183.3 ($\mathbf{C}_3$), 158.2 ($\mathbf{C}_2$), 151.4 ($\mathbf{C}_9$), 138.4 ($\mathbf{C}_7$), 125.3 ($\mathbf{C}_5$), 123.8 ($\mathbf{C}_6$), 117.4 ($\mathbf{C}_4$), 109.9 ($\mathbf{C}_8$), 26.2 ($\mathbf{C}_1$) ppm.

3.17 - (*R*)-2-oxo-*N*-(1-phenylethyl)propanamide



$C_{11}H_{13}NO_2$
Mol Wt: 191.2300

3.17 was performed using an adapted procedure as detailed by Jones.[183]

To a solution of **3.14** (0.64 mL, 9.08 mmol) and HOBt (1.25 g, 9.08 mmol) in CH_2Cl_2 (7 mL) at rt under N_2 was added DCC (1.9 g, 9.08 mmol) in CH_2Cl_2 (3 mL) dropwise. The reaction mixture was cooled to 0 ºC and (*R*)-1-phenylethylamine (1.05 mL, 8.25 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 10 h before quenching with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), the organic phases combined, washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated in *vacuo* to yield a brown oil. Purification by column chromatography eluting with EtOAc/hexane (30:70) afforded the title compound **3.17** (0.45 g, 2.36 mmol, 26%) as a white solid. Physical and spectroscopic data were consistent with reported values.[183]

Literature Data:

$[\alpha]^{25}_D$ +106.8 (*c* 0.33, $CHCl_3$).[183]

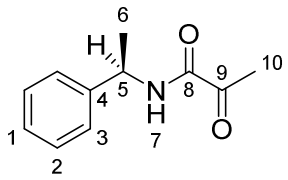
Recorded Data:

$[\alpha]^{20}_D$ +63.2 (*c* 1.10, $CHCl_3$).

M.p. (hexane) 67–69 °C; [Lit.[182] (hexane, 70–71 °C)].

R_f 0.13 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3329, 3029, 2977, 2938, 1721, 1660, 1520, 1452, 1357 cm^{-1}.

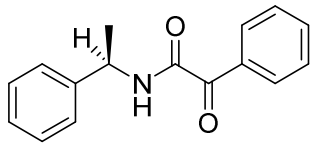


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.19 (5H, m, $\mathbf{H}_1$, $\mathbf{H}_2$ & $\mathbf{H}_3$), 7.11 (1H, br. s., $\mathbf{H}_7$), 4.99 (1H, quin, *J* = 7.2 Hz, $\mathbf{H}_5$), 2.40 (3H, s, $\mathbf{H}_{10}$), 1.47 (3H, d, *J* = 7.2 Hz, $\mathbf{H}_6$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2 ($\mathbf{C}_9$), 159.1 ($\mathbf{C}_8$), 142.0 ($\mathbf{C}_4$), 128.8 ($\mathbf{C}_2$), 127.7 ($\mathbf{C}_1$), 126.1 ($\mathbf{C}_3$), 49.1 ($\mathbf{C}_5$), 24.4 ($\mathbf{C}_{10}$), 21.6 ($\mathbf{C}_6$) ppm.

LRMS (ES^+) *m/z* 192.1 $[M+H]^+$.

3.18 - (*R*)-2-oxo-2-phenyl-*N*-(1-phenylethyl)acetamide



$C_{16}H_{15}NO_2$
Mol Wt: 253.3010

To a solution of **3.15** (0.19 g, 1.29 mmol) in CH_2Cl_2 (7 mL) at 0 ºC under N_2 were added EDAC (0.25 g, 1.29 mmol) and HOBt (0.35 g, 2.60 mmol) portionwise. The reaction mixture was cooled to 0 ºC before the dropwise addition of (*R*)-1-phenylethylamine (0.11 mL, 0.86 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 30 min at 0 ºC, then was allowed to rt and stirred for 12 h before quenching with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), the organic phases combined, washed with sat. aq. $NaHCO_3$ (3 x 15 mL), sat. aq. NH_4Cl (3

x 15 mL), brine (3 x 15 mL), dried ($MgSO_4$) and concentrated in *vacuo* to yield a white solid. Purification by column chromatography eluting with EtOAc/hexane (40:60) afforded the title compound **3.18** (0.20 g, 0.81 mmol, 94%) as a white solid. Recrystallisation from hexane gave fine white needles (0.18 g, 0.71 mmol, 82%). Physical and spectroscopic data were consistent with reported values.[184]

Literature Data:

$[\alpha]^{25}_{D}$ +108.9 (*c* 1.00, $CHCl_3$).[184]

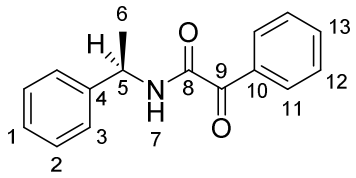
Recorded Data:

$[\alpha]^{20}_{D}$ +109.0 (*c* 0.53, $CHCl_3$).

M.p. (hexane) 100–102 °C; [Lit.[184] (EtOAc/hexane, 113–114 °C].

R_f 0.20 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3257, 3085, 2982, 2929, 1680, 1654, 1553, 1448, 1218 cm^{-1}.

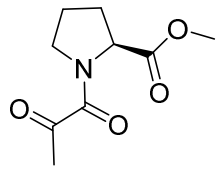


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 - 8.33 (2H, m, $\mathbf{H}_{11}$), 7.63 (1H, m, $\mathbf{H}_{13}$), 7.51 - 7.45 (2H, m, $\mathbf{H}_{12}$), 7.38 - 7.27 (5H, m, $\mathbf{H}_1$, $\mathbf{H}_2$ & $\mathbf{H}_3$), 5.20 (1H, dq, *J* = 8.2, 7.1 Hz, $\mathbf{H}_5$), 1.62 (3H, d, *J* = 7.1Hz, $\mathbf{H}_6$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6 ($\mathbf{C}_9$), 160.7 ($\mathbf{C}_8$), 142.3 ($\mathbf{C}_4$), 134.4 ($\mathbf{C}_{10}$), 133.3 ($\mathbf{C}_{10}$), 131.3 ($\mathbf{C}_{11}$), 128.8 ($\mathbf{C}_{12}$), 128.4 ($\mathbf{C}_2$), 127.7 ($\mathbf{C}_1$), 126.2 ($\mathbf{C}_3$), 49.1 ($\mathbf{C}_5$), 21.7 ($\mathbf{C}_6$) ppm.

LRMS (ES^+) *m/z* 254.1 $[M+H]^+$.

3.19 - *N*-pyruvoyl-(*S*)-proline methyl ester



$C_9H_{13}NO_4$
Mol Wt: 199.2060

To a solution of L-proline methyl ester (0.19 g, 1.14 mmol) in CH_2Cl_2 (4 mL) at 0 ºC under N_2 were added Et_3N (0.32 mL, 2.28 mmol) and a solution of 2-oxopropanoyl chloride (0.24 g, 2.28 mmol) in CH_2CH_2 (2 mL) dropwise. The reaction mixture was stirred for 30 min at 0 ºC, then was allowed to warm to rt and stirred for 12 h before quenching with sat. aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), the organic phases combined, washed with sat. aq. NH_4Cl (3 x 10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification by column chromatography eluting with hexane (100%) afforded the title compound **3.19** (0.14 g, 0.68 mmol, 60%) as a mixture of two rotamers. Physical and spectroscopic data were consistent with reported values.[185]

Literature Data:

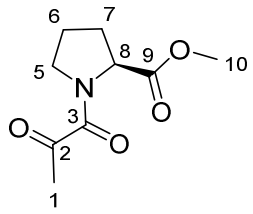
$[\alpha]^{20}_D$ −93.1 (*c* 1.13, $CHCl_3$).[186]

Recorded Data:

$[\alpha]^{30}_D$ −80.4 (*c* 0.60, $CHCl_3$).

R_f 0.28 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 3326, 2963, 2928, 2850, 1742, 1716, 1640, 1573, 1437, 1351 cm^{-1}.



Data for major rotamer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, dd, *J* = 8.6, 4.1 Hz, $\mathbf{H}_8$), 3.69 (3H, s, $\mathbf{H}_{10}$), 3.84 - 3.63 (2H, m, $\mathbf{H}_5$), 2.39 (2H, s, $\mathbf{H}_1$), 2.36 - 1.69 (4H, m, $\mathbf{H}_6$ & $\mathbf{H}_7$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4 ($\mathbf{C}_2$), 171.7 ($\mathbf{C}_9$), 162.0 ($\mathbf{C}_3$), 59.5 ($\mathbf{C}_8$), 52.3 ($\mathbf{C}_{10}$), 47.4 ($\mathbf{C}_5$), 28.4 ($\mathbf{C}_7$), 26.4 ($\mathbf{C}_1$), 22.0 ($\mathbf{C}_6$) ppm.

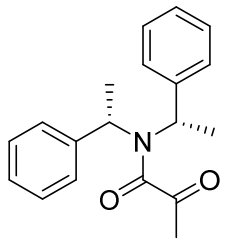
Data for minor rotamer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, dd, *J* = 8.3, 3.8 Hz, $\mathbf{H}_8$), 3.72 (3H, s, $\mathbf{H}_{10}$), 3.56 (1H, dd, *J* = 7.6 Hz, $\mathbf{H}_5$), 3.53 (1H, m, $\mathbf{H}_{5''}$), 2.41 (1H, s, $\mathbf{H}_1$), 2.36 - 1.69 (4H, m, $\mathbf{H}_6$ & $\mathbf{H}_7$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 ($\mathbf{C}_2$), 172.6 ($\mathbf{C}_9$), 162.6 ($\mathbf{C}_3$), 59.5 ($\mathbf{C}_8$), 52.4 ($\mathbf{C}_{10}$), 48.0 ($\mathbf{C}_5$), 31.3 ($\mathbf{C}_7$), 26.9 ($\mathbf{C}_1$), 25.1 ($\mathbf{C}_6$) ppm.

LRMS (ES^+) *m/z* 241.1 $[M+CH_3CN+H]^+$.

3.20 - *N*,*N*-2-Oxo-bis((*S*))-1-phenylethyl)propanamide



$C_{19}H_{21}NO_2$
Mol Wt: 295.3820

To a solution of oxalyl chloride (0.47 mL, 5.55 mmol) in CH_2Cl_2 (13 mL) at 0 ºC under N_2 was added bis[(*S*)-1-phenylethyl]amine (0.51 mL, 2.22 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 30 min at 0 ºC then was allowed to warm to rt and stirred for 3 h before was concentrated *in vacuo*.

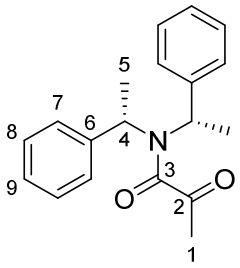
To a suspension of CuCl (0.33 g, 3.33 mmol) in THF (10 mL) at rt was added LiCl (0.28 g, 6.66 mmol) in one portion turning the mixture yellow. The reaction mixture was stirred at rt for 1 h, then was cooled to −78 ºC and MeMgBr (1 mL, 2.66 mmol) was added dropwise. After 30 min the above acid chloride (0.70 g, 2.2 mmol, 1.0) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0 ºC, then was allowed to warm to rt and stirred for 12 h before quenching with sat. aq. NH_4Cl (10 mL) The aqueous layer was extracted with EtOAc (3 x 10 mL), the organic phases combined, washed with sat. aq. NH_4Cl (3 x 10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography eluting with hexane/EtOAc (90:10) afforded the title compound **3.20** (65 mg, 0.22 mmol, 10%) as white solid.

$[\alpha]^{30}_D$ −77.6 (*c* 0.82, $CHCl_3$).

M.p. (hexane) 65–67 °C.

R_f 0.22 (*eluent*: EtOAc/hexane - 10:90).

FT-IR (neat) ν_{max} 2979 , 1706, 1620, 1495, 1445, 1380, 1146 cm^{-1}.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.28 (4H, m, $\mathbf{H}_7$), 7.24 - 7.17 (4H, m, $\mathbf{H}_8$), 6.92 - 6.83 (2H, m, $\mathbf{H}_9$), 5.61 (1H, q, *J* = 7.2 Hz, $\mathbf{H}_{4'}$), 4.79 (1H, q, *J* = 7.0 Hz, $\mathbf{H}_{4''}$), 1.81 (3H, d, *J* = 7.9 Hz, $\mathbf{H}_{5'}$), 1.79 (3H, d, *J* = 7.9 Hz, $\mathbf{H}_{5''}$), 1.63 (3H, s, $\mathbf{H}_1$) ppm.

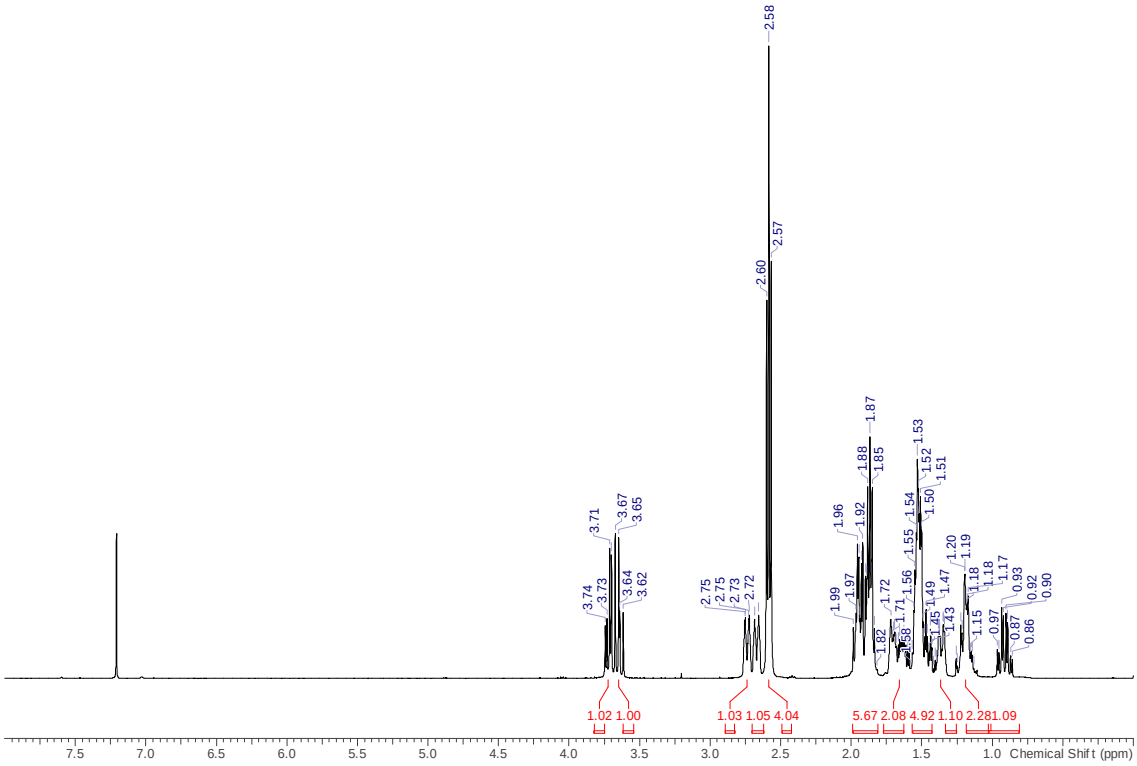
^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 ($\mathbf{C}_2$), 169.0 ($\mathbf{C}_3$), 140.1 ($\mathbf{C}_{6'}$), 139.2 ($\mathbf{C}_{6''}$), 128.5 ($\mathbf{C}_{8'}$), 128.5 ($\mathbf{C}_{8''}$), 128.4 ($\mathbf{C}_{7'}$), 128.1 ($\mathbf{C}_{7''}$), 127.9 ($\mathbf{C}_{9'}$), 127.8 ($\mathbf{C}_{9''}$), 52.7 ($\mathbf{C}_{4'}$), 52.6 ($\mathbf{C}_{4''}$), 26.0 ($\mathbf{C}_1$), 18.8 ($\mathbf{C}_{5'}$), 17.6 ($\mathbf{C}_{5''}$)ppm.

LRMS (ES^+) m/z 359.3 $[M+CH_3CN+Na]^+$.

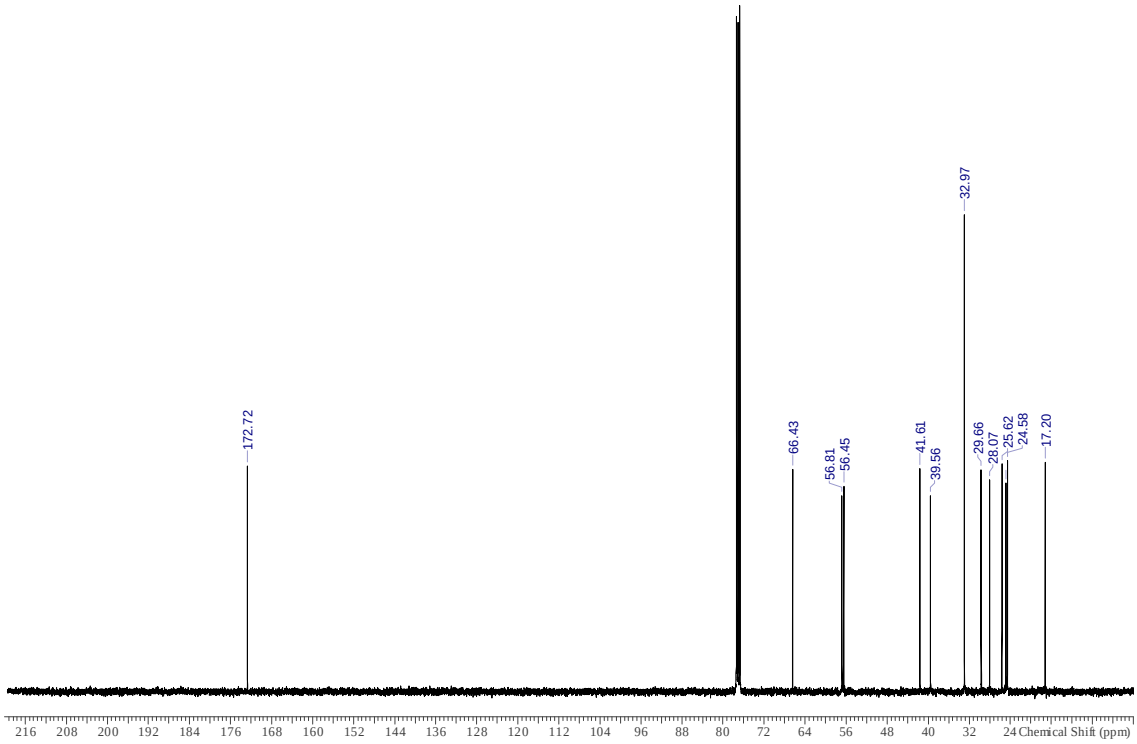
HRMS (ES^+) for $C_{19}H_{21}NNaO_2^+$ $[M+Na]^+$, calculated 318.1465 found 318.1470.

Appendix

5.1 ^{1}H NMR: (−)-lamprolobine



5.2 ^{13}C NMR: (−)-lamprolobine



5.3 X-ray crystal structure of imino-aldol 2.35

UNIVERSITY OF Southampton **Single Crystal X-Ray Diffraction Service**

Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.

Identification code	**2013sot0041** (IAP/6811/12)
Empirical formula	$C_{21}H_{32}ClNO_3S$
Formula weight	413.98
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.524(3) Å
	b = 8.250(4) Å β = 92.306(11)°
	c = 23.817(13) Å
Volume	1084.6(10) Å^3
Z	2
Density (calculated)	1.268 Mg / m^3
Absorption coefficient	0.293 mm^{-1}
$F(000)$	444
Crystal	Plate; Colourless
Crystal size	0.280 × 0.120 × 0.020 mm^3
θ range for data collection	3.004 – 27.483°
Index ranges	$-7 \le h \le 5$, $-10 \le k \le 10$, $-29 \le l \le 30$
Reflections collected	11925
Independent reflections	4764 [R_{int} = 0.0531]
Completeness to θ = 25.242°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.826
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4764 / 1 / 251
Goodness-of-fit on F^2	0.998
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0509, $wR2$ = 0.0980
R indices (all data)	$R1$ = 0.0631, $wR2$ = 0.1040
Absolute structure parameter	0.05(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.330 and –0.368 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst*. **A64**, 112-122). S**tructure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

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

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] 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	16150(2)	692(1)	5878(1)	32(1)	1
S1	9371(1)	5144(1)	6494(1)	16(1)	1
O1	12355(4)	4348(3)	8585(1)	21(1)	1
O2	16007(4)	5579(4)	8589(1)	27(1)	1
O3	7827(4)	6561(3)	6640(1)	23(1)	1
N1	12074(5)	5174(4)	6811(1)	18(1)	1
C1	14446(7)	2969(6)	9370(2)	29(1)	1
C2	14504(7)	2570(6)	9932(2)	32(1)	1
C3	12739(7)	3134(6)	10276(2)	27(1)	1
C4	10880(7)	4097(6)	10055(2)	29(1)	1
C5	10792(6)	4482(5)	9492(2)	24(1)	1
C6	12587(6)	3932(5)	9158(2)	20(1)	1
C7	14120(6)	5253(5)	8354(2)	19(1)	1
C8	13286(6)	5849(5)	7783(2)	18(1)	1
C9	12508(6)	4483(5)	7374(2)	17(1)	1
C10	14346(6)	3097(5)	7351(2)	19(1)	1
C11	13332(6)	1621(5)	7030(2)	20(1)	1
C12	15080(6)	224(5)	6980(2)	24(1)	1
C13	17178(6)	505(5)	6601(2)	26(1)	1
C14	11190(6)	7059(5)	7853(2)	21(1)	1
C15	11642(7)	8339(5)	8306(2)	27(1)	1
C16	9479(8)	9440(6)	8348(2)	30(1)	1
C17	9569(9)	11015(6)	8335(2)	39(1)	1
C18	10366(5)	5520(5)	5775(2)	17(1)	1
C19	11860(6)	4053(5)	5606(2)	21(1)	1
C20	11730(6)	7108(5)	5743(2)	22(1)	1
C21	8020(5)	5581(6)	5409(2)	23(1)	1

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

Cl1–C13	1.799(4)
S1–O3	1.495(3)
S1–N1	1.646(3)
S1–C18	1.846(4)
O1–C7	1.361(4)
O1–C6	1.409(5)
O2–C7	1.194(4)
N1–C9	1.466(5)
C1–C2	1.376(6)
C1–C6	1.378(5)
C2–C3	1.380(6)
C3–C4	1.386(6)
C4–C5	1.376(6)
C5–C6	1.373(5)
C7–C8	1.502(5)
C8–C9	1.540(5)
C8–C14	1.543(5)
C9–C10	1.532(5)
C10–C11	1.531(5)
C11–C12	1.512(5)
C12–C13	1.515(5)
C14–C15	1.524(6)
C15–C16	1.507(6)
C16–C17	1.302(6)
C18–C20	1.515(5)
C18–C19	1.528(5)
C18–C21	1.534(4)
O3–S1–N1	113.43(17)
O3–S1–C18	106.13(17)
N1–S1–C18	97.14(15)
C7–O1–C6	119.1(3)
C9–N1–S1	121.7(2)
C2–C1–C6	118.8(4)
C1–C2–C3	120.5(4)
C2–C3–C4	119.9(4)
C5–C4–C3	119.9(4)
C6–C5–C4	119.3(4)
C5–C6–C1	121.5(4)
C5–C6–O1	116.2(3)
C1–C6–O1	122.2(3)
O2–C7–O1	124.0(3)
O2–C7–C8	125.6(3)
O1–C7–C8	110.3(3)

C7–C8–C9	113.6(3)
C7–C8–C14	108.5(3)
C9–C8–C14	110.5(3)
N1–C9–C10	110.0(3)
N1–C9–C8	108.9(3)
C10–C9–C8	113.6(3)
C11–C10–C9	112.4(3)
C12–C11–C10	115.1(3)
C11–C12–C13	115.9(3)
C12–C13–Cl1	111.3(3)
C15–C14–C8	115.0(3)
C16–C15–C14	110.9(3)
C17–C16–C15	124.7(5)
C20–C18–C19	113.4(3)
C20–C18–C21	110.7(3)
C19–C18–C21	109.2(3)
C20–C18–S1	111.1(3)
C19–C18–S1	107.2(3)
C21–C18–S1	104.9(2)

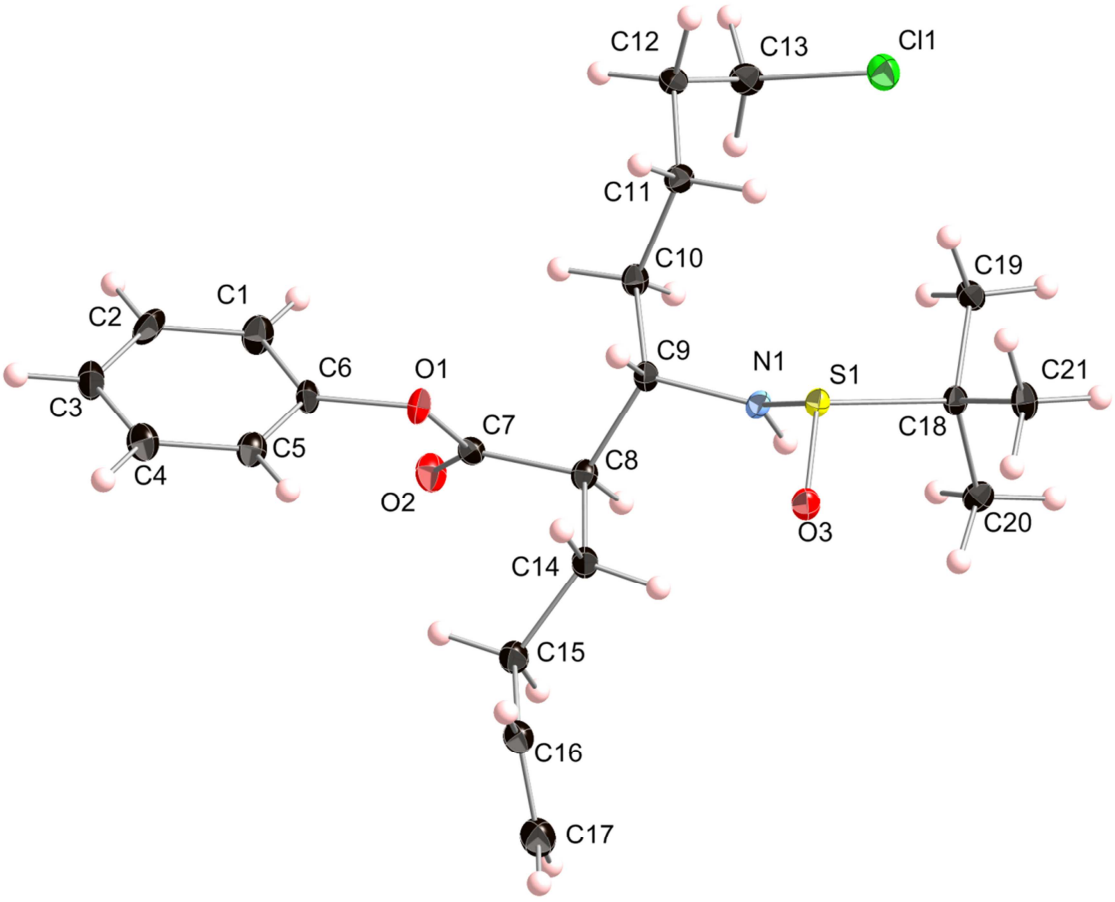
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	37(1)	33(1)	25(1)	0(1)	6(1)	6(1)
S1	16(1)	20(1)	14(1)	2(1)	2(1)	2(1)
O1	20(1)	29(2)	14(2)	6(1)	−1(1)	−1(1)
O2	23(1)	35(2)	22(2)	1(1)	−5(1)	−6(1)
O3	25(1)	26(2)	19(2)	1(1)	2(1)	9(1)
N1	20(1)	19(2)	16(2)	4(2)	2(1)	−2(2)
C1	26(2)	36(3)	25(3)	5(2)	1(2)	8(2)
C2	34(2)	31(3)	29(3)	13(2)	−6(2)	8(2)
C3	30(2)	33(3)	17(2)	3(2)	−1(2)	−7(2)
C4	30(2)	33(3)	24(3)	0(2)	8(2)	−1(2)
C5	22(2)	27(2)	22(2)	3(2)	−1(2)	0(2)
C6	23(2)	25(2)	12(2)	2(2)	−3(1)	−5(2)
C7	21(2)	18(2)	17(2)	−1(2)	3(1)	1(2)
C8	18(2)	19(2)	17(2)	2(2)	0(1)	−2(2)
C9	17(2)	21(2)	14(2)	1(2)	0(1)	2(2)
C10	17(2)	24(2)	17(2)	1(2)	−2(1)	2(2)
C11	21(2)	18(2)	21(2)	2(2)	1(2)	0(2)
C12	34(2)	17(2)	19(2)	−1(2)	−5(2)	−3(2)
C13	25(2)	25(3)	27(2)	−2(2)	−3(2)	5(2)

C14	25(2)	23(2)	16(2)	1(2)	1(2)	4(2)
C15	34(2)	27(2)	20(2)	1(2)	–1(2)	8(2)
C16	41(2)	27(3)	21(3)	–1(2)	6(2)	5(2)
C17	49(3)	39(3)	29(3)	–1(2)	5(2)	12(2)
C18	15(1)	21(2)	14(2)	1(2)	1(1)	2(2)
C19	22(2)	23(2)	18(2)	–3(2)	2(2)	–2(2)
C20	21(2)	21(2)	24(2)	3(2)	1(2)	2(2)
C21	18(2)	35(3)	16(2)	1(2)	–2(1)	1(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	15666	2588	9133	35	1
H2	15768	1901	10083	38	1
H3	12798	2863	10664	32	1
H4	9667	4492	10291	35	1
H5	9502	5121	9336	29	1
H8	14660	6448	7617	22	1
H9	10945	4024	7500	21	1
H10A	15811	3488	7166	23	1
H10B	14835	2767	7738	23	1
H11A	11885	1229	7221	24	1
H11B	12796	1971	6647	24	1
H12A	14160	–732	6838	28	1
H12B	15746	–46	7360	28	1
H13A	18330	–411	6640	31	1
H13B	18045	1507	6719	31	1
H14A	10859	7615	7490	26	1
H14B	9716	6442	7942	26	1
H15A	11979	7800	8673	32	1
H15B	13081	8990	8216	32	1
H16	7940	8948	8388	35	1
H17A	11077	11549	8295	46	1
H17B	8127	11632	8364	46	1
H19A	12229	4139	5208	32	1
H19B	10936	3060	5667	32	1
H19C	13375	4021	5835	32	1
H20A	13273	7021	5959	33	1
H20B	10757	7979	5899	33	1
H20C	12044	7351	5350	33	1
H21A	7017	6487	5530	34	1
H21B	7129	4563	5449	34	1
H21C	8414	5733	5015	34	1
H901	12920(60)	5860(50)	6705(16)	10(10)	1



Thermal ellipsoids drawn at the 35% probability level.

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