# University of Southampton

Faculty of Engineering and Physical Sciences

School of Chemistry

**Stereoselective synthesis of lupin alkaloids: total synthesis of (+)-$\beta$-isosparteine and (−)-epilupinine**

by

**Firas Mohammed Younus Al-Saffar**

Thesis for the degree of Doctor of Philosophy

November_2019

# University of Southampton

## <u>Abstract</u>

Faculty of Engineering and Physical Sciences

School of Chemistry

Thesis for the degree of <u>Doctor of Philosophy</u>

Stereoselective synthesis of lupin alkaloids: total synthesis of (+)-$\beta$-isosparteine and (−)-epilupinine

By

Firas Mohammed Younus Al-Saffar

The first stereoselective total synthesis of the tetracyclic lupin alkaloid (+)-$\beta$-isosparteine (+)-**1.4** has been achieved in 15% yield over 4 steps using a two-directional, *syn*-selective, double imino-aldol reaction between diphenyl glutarate **2.1** and *tert*-butanesulfinimine **1.205**. The chiral auxiliary, *tert*-butyl sulfinamide **2.9**, was used to control the stereoselectivity of imino-aldol reaction. This methodology was applied to access diastereomerically pure product, introducing 4 stereogenic centres in a single step. In addition, the minor diastereoisomers from double imino-aldol reaction have been identified and used to synthesise (−)-sparteine (−)-**1.3** and (−)-10,17-dioxo-$\alpha$–isosparteine ((−)-**1.43**). The stereochemistry of intermediates (+)-10,17-dioxo-$\beta$-isosparteine ((+)-**1.33**), and (−)-10,17-dioxo-$\alpha$-isosparteine were confirmed by single crystal X-ray structure determination. A short total synthesis of the bicyclic lupin alkaloid (−)-epilupinine (−)-**1.1** has also been achieved in 31% yield over 2 steps from halo imine **1.205**. Formation of mono cyclised imino-aldol adduct **2.13** was obtained from reaction of the dianion of diphenyl glutarate **2.1** with one equivalent of halo *tert*-butanesulfinimine **1.205**. The stereochemistry of cyclised **2.13** and uncyclised **2.16** mono *syn* imino-aldols were confirmed by single crystal X-ray structure determination. As a part of synthetic studies towards (+)-allomatridine (+)-**1.5**, total synthesis of the bicyclic lupin alkaloid (−)-epilupinine ((−)-**1.1**) was completed in 55% overall yield over 6 steps using single imino-aldol reaction between phenyl ester **1.173** and unsaturated *tert*-butanesulfinimine **1.208**. The stereochemistry of unsaturated quinolizidinone **2.30** and tricyclic imide **2.40** were confirmed by single crystal X-ray structure determination.

# Table of Contents

# List of Tables

# List of Figures

# DECLARATION OF AUTHORSHIP

I Firas Mohammad Al-Saffar declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Stereoselective synthesis of lupin alkaloids: total synthesis of (+)-$\beta$-isosparteine and (−)-epilupinine

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Part of this work have been published as:

    Al-Saffar, F. M.; Brown, R. C. D., *Org. Lett.* **2017,** *19*, 3502-3504.

Signed:   ...........................................................................................................................................

Date:     ...........................................................................................................................................

# Acknowledgements

# Definitions and Abbreviations

| | |
|---|---|
| $[\alpha]_D$ | Alpha D |
| °C | Degrees Celsius |
| 9-BBN | 9-Borabicyclo[3.3.1]-nonane |
| Ac | Acetyl |
| acac | Acetylacetone |
| ADDP | 1,1'-(Azodicarbonyl)dipiperidine |
| AM | Anti-Markovnikov |
| Aq | Aqueous |
| atm | Atmosphere |
| ATMS | Allyltrimethylsilane |
| Bn | Benzyl |
| br | Broad |
| BtH | 1*H*-Benzotriazole |
| Bu | Butyl |
| *ca.* | Circa |
| Cbz | Benzyloxycarbonyl |
| cm | Centimetre |
| CM | Cross metathesis |
| *Conc.* | Concentrated |
| d | Doublet |
| d.r. | Diastereomeric ratio |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N,N'*-dicyclohexylcarbodiimide |
| DEAD | Diethyl azodicarboxylate |
| DIAD | Diisopropyl azodicarboxylate |

| | |
|---|---|
| **DIBAL-H** | Diisobutylaluminium hydride |
| **DMAP** | 4-(Dimethylamino)-pyridine |
| **DMF** | *N,N'*-dimethylformamide |
| **DMSO** | Dimethylsulfoxide |
| **e.e.** | Enantiomeric excess |
| **EI** | Electron ionisation |
| **Equiv.** | Molar equivalents |
| **ESI** | Electrospray Ionisation |
| **Et** | Ethyl |
| **FT** | Fourier Transform |
| **g** | Gram |
| **GC** | Gas Chromatography |
| **h** | Hour(s) |
| **HMDS** | Hexamethyldisilazane |
| **HMPA** | Hexamethylphosphoramide |
| **HPLC** | High-Performance Liquid Chromatography |
| **HRMS** | High-Resolution Mass Spectrometry |
| **HSQC** | Heteronuclear Single Quantum Coherence Spectroscopy |
| *i* | Iso |
| **IR** | Infrared |
| *J* | Coupling constant |
| **K** | Kelvin |
| **L** | Litre |
| **LDA** | Lithium diisopropylamide |
| **LiHMDS** | Lithium bis(trimethylsilyl)amide |
| **LRMS** | Low-Resolution Mass Spectrometry |

| | |
|---|---|
| **m** | Multiplet |
| ***m*-CPBA** | *meta*-Chloroperbenzoic acid |
| **Me** | Methyl |
| **min** | Minute(s) |
| **mmol** | Millimole(s) |
| **Ms** | Mesyl |
| **MS** | Mass Spectrometry |
| **MW** | Molecular weight |
| **n** | Nano |
| **NBS** | *N*-Bromosuccinimide |
| **NMO** | *N*-Methylmorpholine *N*-Oxide |
| **NMR** | Nuclear Magnetic Resonance |
| **NOE** | Nuclear Overhauser Effect |
| **O/N** | Overnight |
| ***p*** | *Para* |
| **Ph** | Phenyl |
| **ppm** | Parts per million |
| **Pr** | Propyl |
| **Py** | Pyridine |
| **q** | Quartet |
| **RBF** | Round Bottom Flask |
| **RCM** | Ring Closing Metathesis |
| **$R_f$** | Retention factor |
| **rt** | Room Temperature |
| **s** | Singlet |
| **sat.** | Saturated |
| ***t*** | Tertiary |

| | |
|---|---|
| **T** | Temperature |
| **T₃P** | Propylphosphonic anhydride |
| **TBS** | *tert*-Dibutyldimethylsilyl |
| **TFA** | Trifluoroacetic Acid |
| **THF** | Tetrahydrofuran |
| **TLC** | Thin Layer Chromatography |
| **TMS** | Trimethylsilyl |
| **Ts** | Tosyl |
| **V$_t$** | Variable Temperature |
| **Δ** | Heating at reflux |

# Chapter 1:    Introduction to the lupin alkaloids sparteine, its stereoisomers, and allomatridine and epilupinine.

## 1.1    Introduction

### 1.1.1    Lupin alkaloids

The Lupin alkaloids are a large family of natural products consisting of more than 200 compounds,[1] the majority of Lupin have a quinolizidine core. They have been isolated from several papilionaceous plant species[1,2] which can be grouped into four structural series named after the parent alkaloids (**Figure 1.1**). These are the bicyclic "epilupinine" alkaloids tricyclic "cytisine" alkaloids tetracyclic "sparteine" alkaloids and another group of tetracyclic alkaloids known as "matrine" alkaloids. The focus of this thesis is the synthesis of compounds belonging to the epilupinine, sparteine and matrine structural classes, and an introduction to these compounds will provided in the following sections.



(−)-epilupinine ((−)-**1.1**)       (+)-cytisine ((+)-**1.2**)    (−)-sparteine ((−)-**1.3**)

(+)-$\beta$-isosparteine ((+)-**1.4**)         (+)-allomatrindine ((+)-**1.5**)
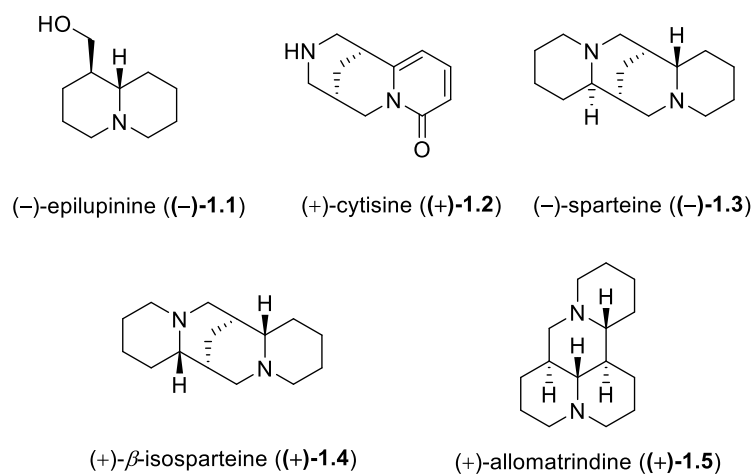
**Figure 1.1**: Exemplar structures of Lupin alkaloids

### 1.1.2    Sparteine alkaloid and its identification

(−)-Sparteine ((−)-**1.3**) is a tetracyclic lupin alkaloid isolated in 1851 by extraction from certain papilionaceous plants (e.g. *Cytius scoparisus*) by Stenhouse who also determined its molecular formula ($C_{15}H_{26}N_2$).[3] In 1903, Moureu and Valeur correctly elucidated the presence of two tertiary nitrogen atoms and four rings,[4] but later incorrectly concluded (−)-sparteine was an asymmetrical compound with bridgehead nitrogen atoms.[5]

In 1928 Clemo and Leitch reported on the reduction of (±)-lupanine ((±)-**1.6**), an alkaloid found as a racemate in *Lupinus albus*, *Lupinus termis*, *Podalyria buxifolia*, *Podalyria sericea*, and *Virgilia capensis*.[6] Reduction of (±)-lupanine using a sealed tube containing red phosphorus and HI, led to a compound identified as "deoxylupanine", which was later shown to be the same as (±)-sparteine ((±)-**1.3**) (found as a racemate in *Cytisus proliferus*). At that time, however, the structure of these alkaloids was not known and the relationship between "deoxylupanine" and sparteine was not recognised. After several years, in 1931, Clemo, Raper, and Tenniswood succeeded in resolving (±)-lupanine ((±)-**1.6**) and reducing (+)- and (−)-lupanine (**Scheme 1.1**).[7] The enantiomeric alkaloids were converted to (−)-sparteine and (+)-sparteine respectively, confirming the equivalence of sparteine and "deoxylupanine".
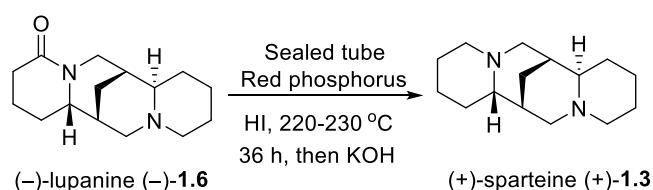


**Scheme 1.1**: Clemo, Raper, and Tenniswood's reduction of lupanine to sparteine.

The structure of sparteine and lupanine were proposed by Clemo and Raper[8] in 1933 adopting the formula suggested by Ing[9] in 1932 for cytisine and also depending on a key factor of Ing's work in 1933.[10,11] The model of sparteine was suggested by Clemo and Raper, they expected the structure of sparteine as shown in photo (**Figure 1.2**).[8]
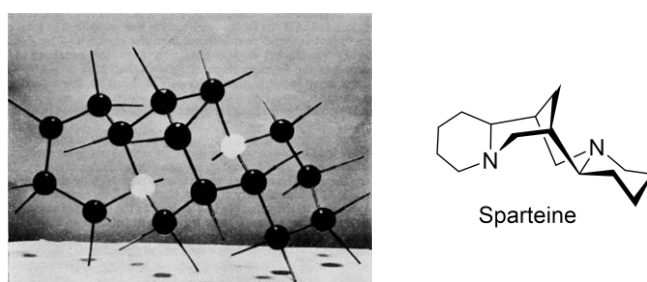


**Figure 1.2**: Model of the structure proposed for sparteine by Clemo and Raper

Furthermore, in 1936 Clemo *et al.* determined the correct structure of (±)-sparteine by its oxidation using potassium ferricyanide to (±)-17-oxosparteine ((±)-**1.7**) which was identical with the known compound (**Scheme 1.2**).[12]

(±)-sparteine (±)-**1.3**                    (±)-17-oxosparteine (±)–**1.7**
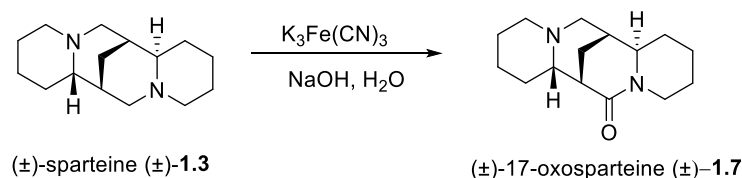
**Scheme 1.2**: Oxidation of (±)-sparteine to (±)-17-oxosparteine by Clemo *et al.*

Three diastereoisomers of sparteine are known; sparteine, $\alpha$-isosparteine and $\beta$-isosparteine (**Figure 1.3**). The absolute stereochemistry and configuration of sparteine were confirmed by Okuda *et al.* in 1965 through chemical interrelations between (−)-cytisine ((−)-**1.2**) and (−)-sparteine ((−)-**1.3**), in which the absolute configuration of the methylene bridge was confirmed to be the same as that of (−)-cytisine.[13]

(−)-$\alpha$-Isosparteine ((−)-**1.8**) was first isolated from *Lupinus caudatus* by Marion *et al.* in 1951,[14] but prior to its isolation, it was obtained *via* a semi-synthesis from (−)-sparteine ((−)-**1.3**) in 1934.[15] (−)-$\beta$-Isosparteine ((−)-**1.4**) also called (spartalupine and pusilline) was isolated from *Lupinus sericeus* by Carmack *et al.* in 1955.[16]



(−)-**1.3**                    (−)-**1.4**                    (−)-**1.8**
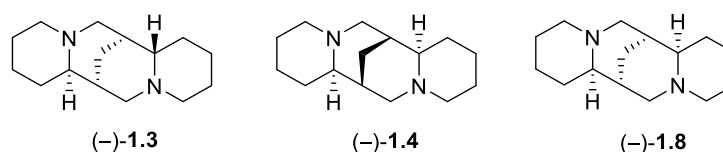
**Figure 1.3**: Structures of (−)-sparteine ((−)-**1.3**), (−)-$\beta$-isosparteine ((−)-**1.4**) and (−)-$\alpha$-isosparteine ((−)-**1.8**)

In terms of pharmacological activity, (−)-sparteine ((−)-**1.3**) is limited in potency as a cardiac agent and has a moderate toxicity,[17] causing unpredictable side effects. However, it has found use in clinical applications.[18-22] At lower doses, increased blood pressure and diuretic effects are common, but dangerous heart rhythms and obstetrical complications are possible at moderately high doses. The use of sparteine as an *anti*-arrhythmic and oxytoxic was banned in 1979, but later it was used in human studies related to metabolism by the CYP2D6 enzyme.[23]

## 1.2    Applications of sparteine as a chiral ligand in enantioselective reactions

(−)-Sparteine (−)-**1.3** is used as a chiral ligand in asymmetric synthesis for a wide range of enantioselective transformations.[24] Since the initial publication of asymmetric deprotonation of alkyl carbamates with *sec*- butyl lithium / (−)-sparteine by Hoppe *et al.* in 1990,[25] there have been

numerous reviews published in the literature.[24, 26-28] The first review was by Caddick and Jenkins in 1996 covering dynamic resolutions in asymmetric synthesis.[28] (−)-Sparteine has found applications as a chiral ligand in organolithium chemistry for enantioselective synthesis with lithium-carbanion pairs, where the metal exists in a tetrahedral coordination geometry with four donor ligands.[29] Studies of the suitability of (−)-sparteine as a chiral additive in carbanion reactions were reported by Nozaki *et al.* between 1968 and 1971.[30-34] Examples included, asymmetric Grignard addition to benzaldehyde,[31] and lithiation of isopropyl ferrocene and ethylbenzene.[32,33] The favoured conformation of sparteine in metal coordination complexes between the two nitrogens was shown by theoretical calculations to adopt in the *chair-chair trans*-quinolizidine A/B system and *boat-chair trans*-quinolizidine C/D system.[35] Free (−)-sparteine exists mostly in *trans*-configuration **1.3b** (*chair/chair/boat/chair*) of the A/B/C/D system because the *cis*-configuration **1.3a** (*chair/chair/chair/chair*) has been computed to be higher in energy by 3.4 kcal/mol than the *trans*-configuration **1.3b** (**Figure 1.4**).[36] On the other hand, the *cis*-configuration was adopted when chelating to a metal centre. In fact, (−)-sparteine could behave as an efficient chiral bidentate ligand, since flipping of **1.3b** into **1.3a** favours formation of two coordinate bonds in the metal complexes (**Figure 1.4**).[37,38]
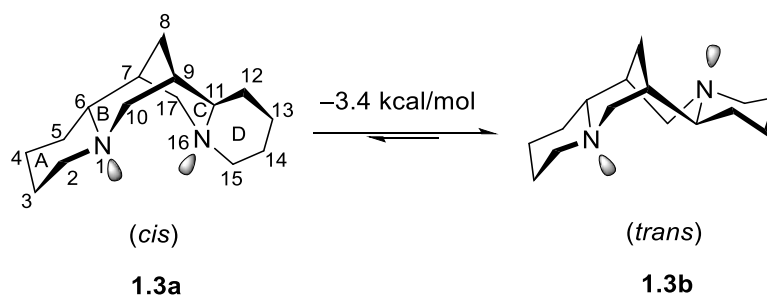


**Figure 1.4**: The conformational-configurational isomerism of (−)-sparteine ((−)-**1.3**)

### 1.2.1    Chiral diamine organolithium complexes

The first highly enantioselective asymmetric deprotonations to prepare organolithium reagents using (−)-sparteine were reported by Beak *et al.* in 1993.[39-41] The ligand tetramethylethylenediamine (**1.9**) (TMEDA) was used with an alkyllithium bases for $\alpha$-deprotonation of *N*-heterocycles by Beak and Lee in 1989 (**Figure 1.5**). An asymmetric synthesis was later developed in 1994 using (−)-sparteine ((−)-**1.3**).[42] Routes to the enantiomeric $\alpha$-substituted *N*-heterocycles were realised by O'Brien and co-workers using a (+)-sparteine surrogate (+)-**1.10**, which provided similar levels of enantioselectivity to sparteine in many reactions.[43]

| TMEDA (**1.9**) | (−)-sparteine (−)-**1.3** | (+)-sparteine surrogate (+)-**1.10** |
|---|---|---|
| (Beak 1989) | (Beak 1994) | (O'Brien 2002) |
| Achiral ligand | Chiral diamine ligands | |
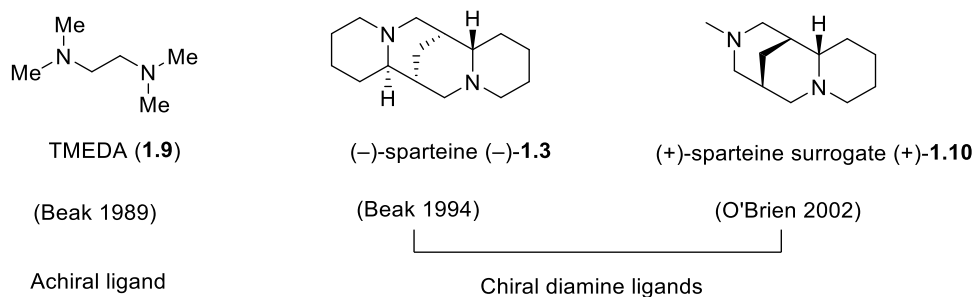
**Figure 1.5**: Achiral and chiral diamine ligands for asymmetric synthesis

The asymmetric lithiation-substitution of the *N*-methyl amide **1.11** using *sec*-BuLi/(−)-sparteine has been reported by Beak *et al.* (**Scheme 1.3**).[40] The amide nitrogen and (−)-sparteine form a chiral complex to the benzylic lithium which was shown to proceed through a process of dynamic thermodynamic resolution. The chiral organolithium **1.12** was obtained from double deprotonation of **1.11** in the presence of (−)-sparteine followed by trimethylsilyl chloride (TMSCl) trapping to afford amide **1.13** with high selectivity and good yield (R = Me). Poor or no selectivity was observed for bulkier amides (R = Et, *i*Pr), and this can be explained by the steric interactions of the substituents which prevented coordination of (−)-sparteine to the organolithium. There are many other reported examples of asymmetric lithiation using (−)-sparteine and these have been reviewed.[44-47]
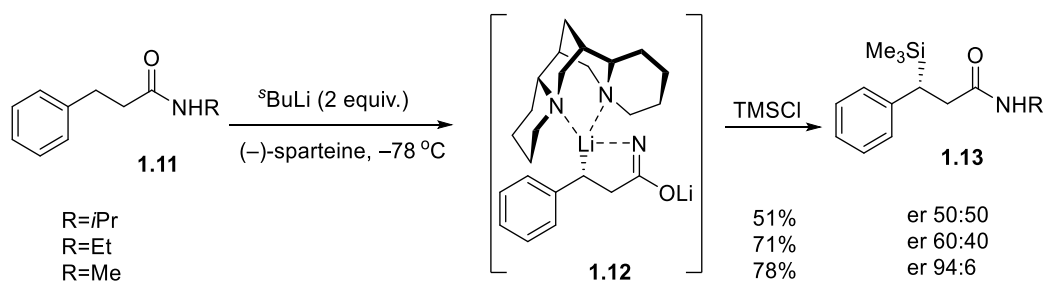


**Scheme 1.3**: Dynamic thermodynamic resolution of benzylic carbanions.

### 1.2.2        (−)-Sparteine and its isomers in metal catalysed enantioselective reactions

(−)-Sparteine and its isomers ((−)-*α*-isosparteine, (−)-*β*-isosparteine) have been used with metal catalysts to form diastereoisomeric PdCl$_2$ complexes (**Figure 1.6**),[48] which provided new reactivity and selectivity in the oxidative kinetic resolution of phenyl ethanol secondary alcohols.
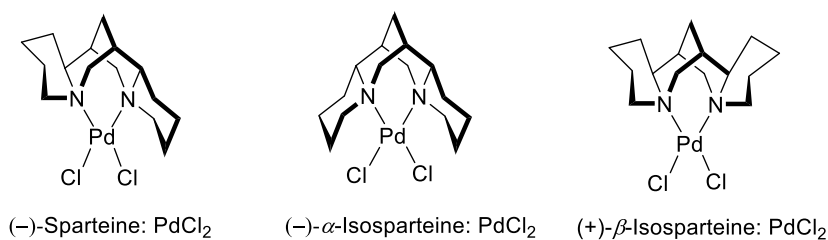
Figure 1.6: PdCl$_2$ complexes of (−)-sparteine and its isomers

The stereoselectivity of the oxidative kinetic resolution of 1-phenylethanol (**1.14**) to the corresponding ketone **1.15** was carried out using (sparteine). PdCl$_2$ and indicated that $C_1$-symmetry of (−)-sparteine is particularly effective (**Scheme 1.4**). (−)-Sparteine was highly selective and more reactive than its $C_2$-symmetric diastereomers (−)-$\alpha$-isosparteine and (−)-$\beta$-isosparteine.
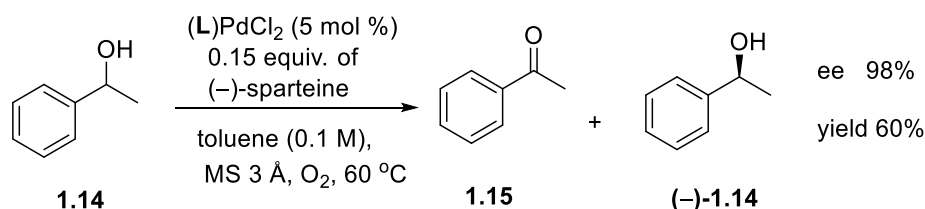


**Scheme 1.4**: Oxidative kinetic resolution with three sparteine PdCl$_2$ diastereoisomers

In 2016, Chopade and co-worker used (−)-sparteine (−)-**1.3** and Cu(acac)$_2$ as a catalyst for the enantioselective Michael addition of nitromethane on chalcone **1.16** to give $\gamma$-nitro ketone **1.17** in 87% yield and 83% ee (**Scheme 1.5**).[49] This methodology was applied to the asymmetric synthesis of anticonvulsant drug (*S*)-pregabalin (88% ee) in four steps with 52% overall yield.
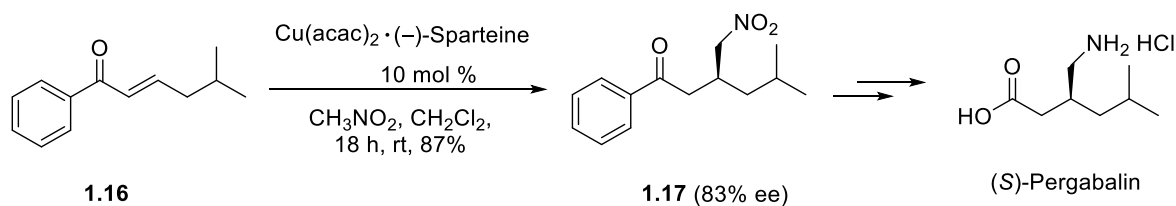


**Scheme 1.5**: The enantioselective Michael addition of nitromethane to chalcone using Cu(acac)$_2$·(−)-sparteine complex

### 1.2.3 Enantioselective electro catalytic oxidative coupling using (−)-sparteine

The enantioselective electrocatalytic oxidative coupling of naphthol (**1.18**) in the presence of (−)-sparteine on a TEMPO-modified electrode was reported by Kashiwagi *et al.* in 1994 (**Scheme 1.6**).[50] Electrolytic coupling of 2-methoxynaphthalene (**1.18**) to (*S*)-(−)-2,2'-dimethoxy-1,1'-binaphthyl

(**1.19**) was shown to proceed with high enantioselectivity (93.3% ee by polarimetry and 93.6% by HPLC). No explanation was given to indicate how enantioselectivity was achieved.
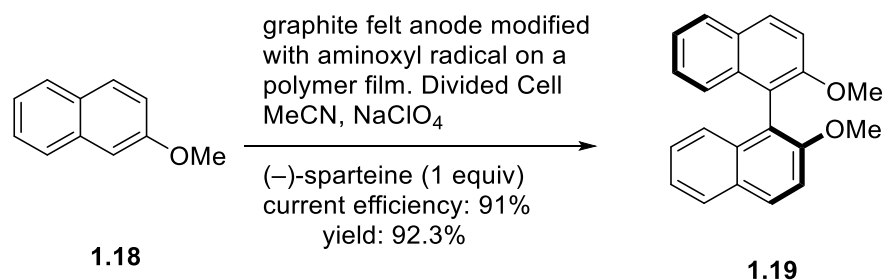


**Scheme 1.6**: The enantioselective oxidative coupling naphthol using sparteine

## 1.3      Previous synthetic studies on the sparteine alkaloids

Syntheses of sparteine have been attempted many times, originally to determine the absolute and relative configuration of the natural product and for the preparation of enantiomerically pure material. More recent synthetic work has focussed on the development of synthetic methodology. There have been over ten total syntheses of sparteine-type alkaloids; an overview of the synthetic work is documented below in chronological order.

### 1.3.1      Ing's semi-synthesis of (+)-sparteine from anagyrine.

In 1933, Ing reduced (−)-anagyrine ((−)-**1.20**) electrochemically to give ''hexa-hydroanagyrine'', which they found to be identical to (+)-sparteine (**Scheme 1.7**). In the same work hydrogenation of (−)-anagyrine afforded ''tetra-hydroanagyrine'', which was determined to be identical to (−)-lupanine ((−)-**1.6**).[9]
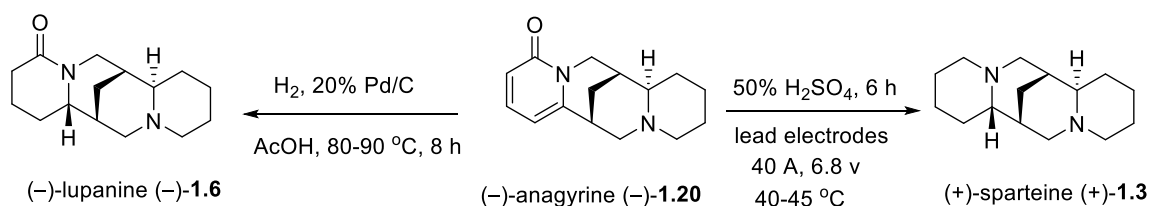


**Scheme 1.7**: Ing's semi-synthesis of (+)-sparteine ((−)-**1.3**) from (−)-anagyrine ((−)-**1.20**)

### 1.3.2      Winterfeld and Rauch's semi-synthesis of (−)-*α*-isosparteine from (−)-sparteine

A semi-synthesis of (−)-*α*-isosparteine ((−)-**1.8**) from (−)-sparteine was published by Winterfeld and Rauch in 1934 (**Scheme 1.8**).[14] A dehydro-spartiene **1.21** was formed using mercuric acetate Hg(OAc)$_2$ under mild conditions. Hydrogenation of **1.21** over Pd/CaCO$_3$ generated (−)-sparteine.

Using more equivalents of Hg(OAc)$_2$, didehydrogenation of (−)-sparteine afforded didehydrosparteine **1.22**. Subsequent hydrogenation of $\alpha$-didehydrosparteine **1.22** furnished (−)-$\alpha$-isosparteine (−)-**1.8**, while $\beta$-isosparteine **1.4** was obtained as an impure product from $\beta$-didehydrosparteine **1.22** under the same conditions.
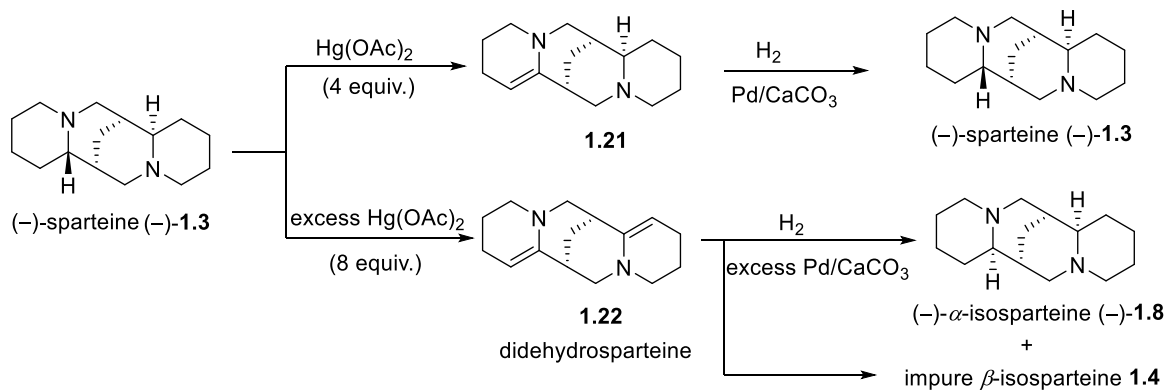


**Scheme 1.8:** Winterfeld and Rauch's semi-synthesis of (−)-$\alpha$-isosparteine from (−)-sparteine

### 1.3.3    Clemo's syntheses of (±)-sparteine

In 1936, Clemo, Morgan, and Raper prepared (±)-17-oxosparteine ((±)-**1.7**) through a multi-step procedure from ethyl 2-pyridylacetate (**1.23**) and ethyl orthoformate (**Scheme 1.9**).[11] Adams' catalyst hydrogenation of pyridocoline **1.24** in AcOH provided piperidyl ethyl carboxylate **1.25**. Reduction of ethyl carboxylate **1.25** using Na in EtOH with heating afforded alcohol **1.26** which was then treated with PBr$_3$ to access bromide **1.27**. Cyclisation of **1.27** under basic conditions gave (±)-(±)-17-oxosparteine ((±)-**1.7**) in 14% overall yield from **1.23**. Reduction of (±)-17-oxosparteine to (±)-sparteine was not completed due to the lack availability of reducing agents at that time. Therefore, this should strictly be considered as formal synthesis of sparteine.
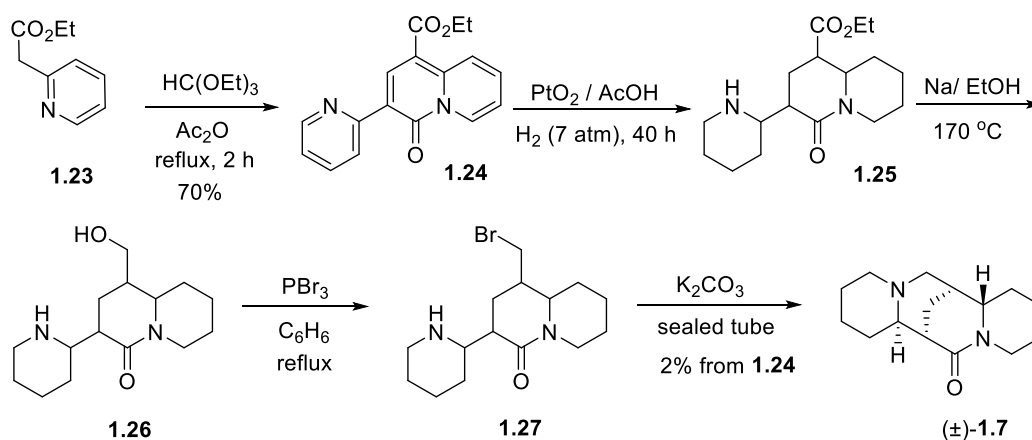


**Scheme 1.9**: Clemo, Morgan and Raper's synthesis of (±)-17-oxosparteine (±)-**1.7**

In 1949, following the discovery of LiAlH$_4$, Clemo, Raper and Short showed that (−)-17-oxosparteine is reduced to (−)-sparteine (**Scheme 1.10**).[51]



(−)-17-Oxosparteine (−)-**1.7**          (−)-Sparteine (−)-**1.3**
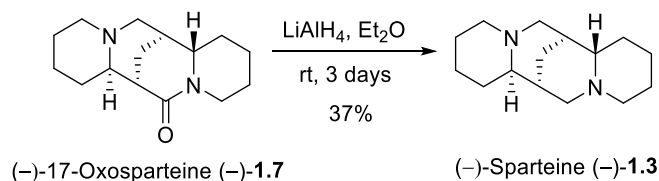
**Scheme 1.10**: Clemo, Raper and Short's semi-synthesis of (−)-sparteine

### 1.3.4      Sorm and Keil's synthesis of (±)-sparteine and (±)-$\beta$-isosparteine

In 1948, Sorm and Keil successfully reported the first total syntheses of (±)-sparteine (±)-**1.3** and (±)-$\beta$-isosparteine (**1.4**) using electrolytic reduction (**Scheme 1.11**).[52,53] The pyridocoline **1.24** was prepared in the previous work by Clemo *et al.* using Knoevenagel condensation of ethyl 2-pyridylacetate (**1.23**) with ethyl orthoformate (**Scheme 1.9**).[11] The same method was applied by Sorm *et al.* using methyl 2-pyridylacetate (**1.28**) as starting material. Condensation with ethyl orthoformate gave 4-oxo-3-(2'-pyridyl)-pyridocoline-1-methylcarboxylate (**1.29**). An alternative condensation of methyl 2-pyridylacetate (**1.28**) with formaldehyde, provided 2,4-di-(2'-pyridyl)-dimethylglutarate (**1.30**). Hydrogenation of pyridyl intermediates **1.29** or **1.30** using Adams's catalyst and subsequent heating of the products under vacuum generated crystalline compounds, after purification by column chromatography. Same conditions
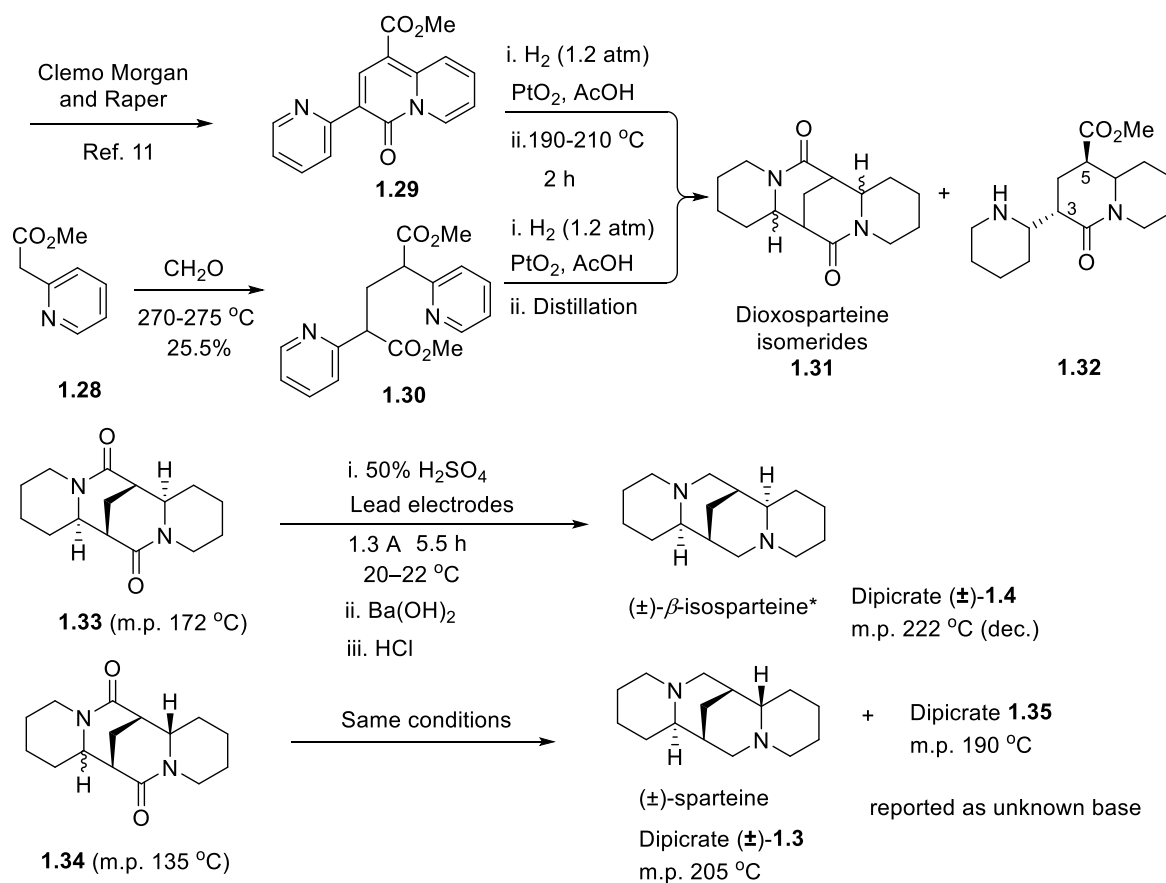
*Note that $\beta$-isosparteine was incorrectly reported as $\alpha$-isosparteine in this work.

**Scheme 1.11**: Sorm & Keil's synthesis of (±)-sparteine & (±)-$\beta$-isosparteine (1948).

The first fraction of dioxosparteine isomers **1.31** were separated into (±)-dioxo-isosparteine (±)-**1.33** (m.p. 172 °C) and (±)-dioxosparteine (±)-**1.34** (m.p. 135 °C). Sorm and Keil reported (±)-$\alpha$-Isosparteine (±)-**1.8** was the product after electrolytic reduction.[52] However, (±)-dioxo-isosparteine (±)-**1.33** was shown later by Carmack *et al.* to be (±)-$\beta$-dioxo-isosparteine (±)-**1.4** (m.p. 172 °C) through repetition of this methodology. In the later work reduction of the dioxosparteine isomers was achieved using LiAlH$_4$ giving three sparteine diastereomers, which were identified by comparasion with the literature.[15,54,55] A second fraction was 4-oxo-3-(2'-piperidyl)-octahydropyridocoline-1-methylcarboxylate (**1.32**) m.p. 161 °C. Formation of uncyclised piperidyl **1.32** after catalytic hydrogenation is likely due to its *trans*-configuration between C3 and C5, therefore it is unable to cyclise. Electrolytic reduction of dioxosparteine isomerides using 50% sulphuric acid with activated lead electrodes gave three C$_{15}$H$_{26}$N$_2$ bases, isolated as their dipicrates (**1.3**, **1.4** and **1.35**). The dipicrates of m.p. 205 °C and 222 °C were identified as racemic (±)-sparteine ((±)-**1.3**) and (±)-$\beta$-isosparteine (±)-**1.4** respectively.

### 1.3.5      Leonard's synthesis of (±)-sparteine and (±)-$\beta$-isosparteine.

A closely related total synthesis of (±)-sparteine was published in 1948 by Leonard *et al.*[56] Leonard and co- workers developed synthesis of (±)-sparteine, from two different precursors.[57] (±)-Sparteine and (±)-$\beta$-isosparteine were synthesised as racemic mixtures in two linear steps (**Scheme 1.12**). The synthesis requires a one-step condensation and reductive cyclisation of either pyridyl intermediates, **1.24** or **1.36**, to furnish (±)-sparteine and (±)-$\beta$-isosparteine respectively. 1-Carbethoxy-4-keto-3-(2'-pyridyl)-pyridocoline (**1.24**) was prepared from condensation of ethyl pyridyl-2-acetate (**1.23**) with ethyl orthoformate in refluxing $Ac_2O$ as reported above.



*Note that $\beta$-isosparteine was reported as $\alpha$-isosparteine based on Sorm and Kiel incorrect assignment
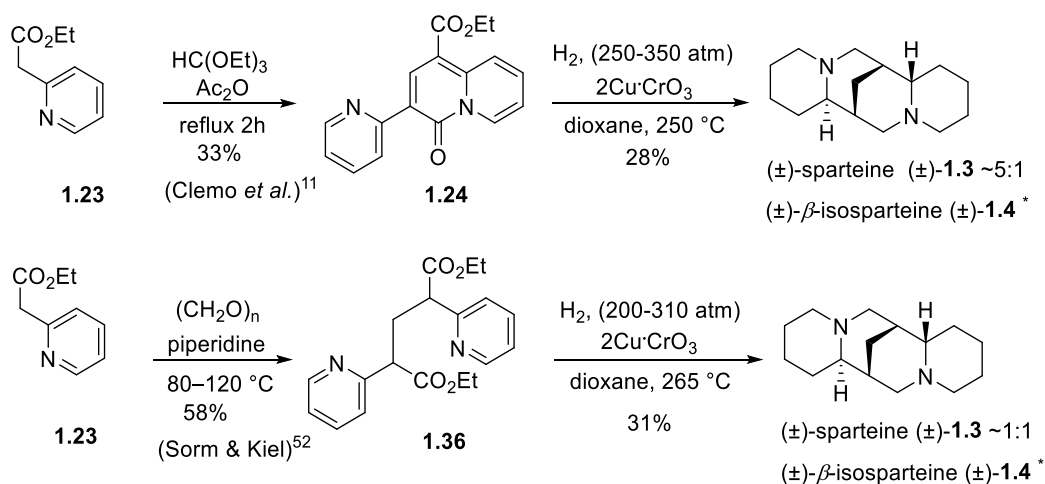
**Scheme 1.12**: Leonard's synthesis of (±)-sparteine and (±)-$\beta$-isosparteine.

Reductive cyclisation of **1.24** in dioxane at 250 °C and 250–350 atm of $H_2$ over copper chromite led to the formation of two bases: (±)-sparteine (±)-**1.3** and a compound identified as (±)-$\alpha$-isosparteine (±)-**1.8**, present in a ratio of (~5:1).[56] The identity of the samples was confirmed by comparison of the monoperchlorate and dipicrate salts which had been previously reported.[52] However, in this work, (±)-$\alpha$-isosparteine  was reported by reference to Sorm and Kiel's isomer which was shown later to be (±)-$\beta$-isosparteine (not (±)-$\alpha$-isosparteine). Using chemistry reported by Sorm *et al.* for the synthesis of dipyridyl dimethyl glutarate **1.30** (Scheme **1.11**),[52] dipyridyl ethyl glutarate **1.36** was synthesised. Reductive cyclisation of **1.36** in dioxane at 265 °C and 200–310 atm of $H_2$ over copper chromite catalyst led to the formation of an equimolar mixture of isomers: (±)-sparteine and (±)-$\beta$-isosparteine in a ratio of (~1:1), which were separated chromatographically.[57] Resolution of racemic sparteine using either (+) or (−)-$\beta$-camphorsulfonic acid in EtOH, followed by recrystallisation from acetone, led to the isolation of either (+)-sparteine or (−)-sparteine.[58]

### 1.3.6        Clemo, Raper, and Short's synthesis of (±)-dioxosparteine isomers

The synthesis of (±)-dioxosparteine isomer (**1.31**) was achieved by Clemo, Raper and Short[51] in 1949 using a method subsequently adopted by Leonard[59] (**Scheme 1.13**).[51] Condensation of ethyl 2-pyridylacetate (**1.23**) with methylene iodide in the presence of potassium metal gave two products: dihydropyridocoline **1.37** as a minor product in 12% and diethyl glutarate **1.36** as the major component in 50-55% yield.[51] Dihydropyridocoline **1.37** was reduced with Adams's catalyst in HCl affording (±)-10,17-dioxosparteine ((±)-**1.34**) as previously described by Sorm and Keil.
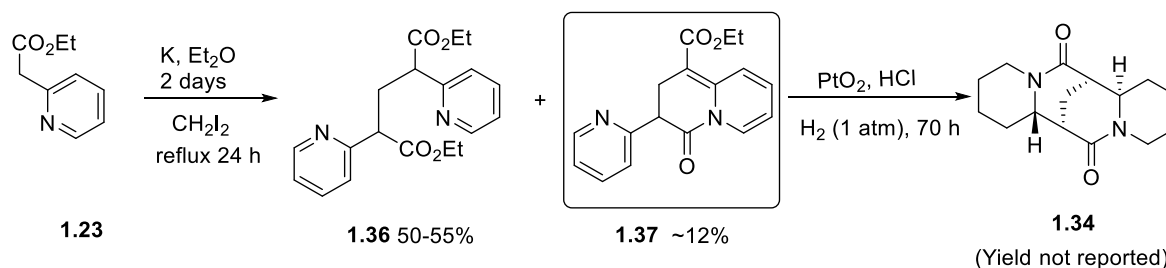


**Scheme 1.13**: Clemo, Raper, and Short's synthesis of (±)-10,17-dioxosparteine isomer

### 1.3.7        Anet, Hughes, & Ritchie's synthesis of (±)-sparteine

A proposed biomimetic route to (±)-sparteine was reported by Anet, Hughes, and Ritchie in 1950 (**Scheme 1.14**).[60,61] A dilute aqueous pH 13 solution of 5-aminopentanal (**1.38**) and acetone dicarboxylic acid (**1.39**) was allowed to stand for 3 days at rt to give dipiperidine glutaric acid derivative **1.40**. The solution of **1.40** was then acidified to pH 3 and was allowed to cyclise by adding formaldehyde to give (±)-8-oxo-sparteine (±)-**1.41**.
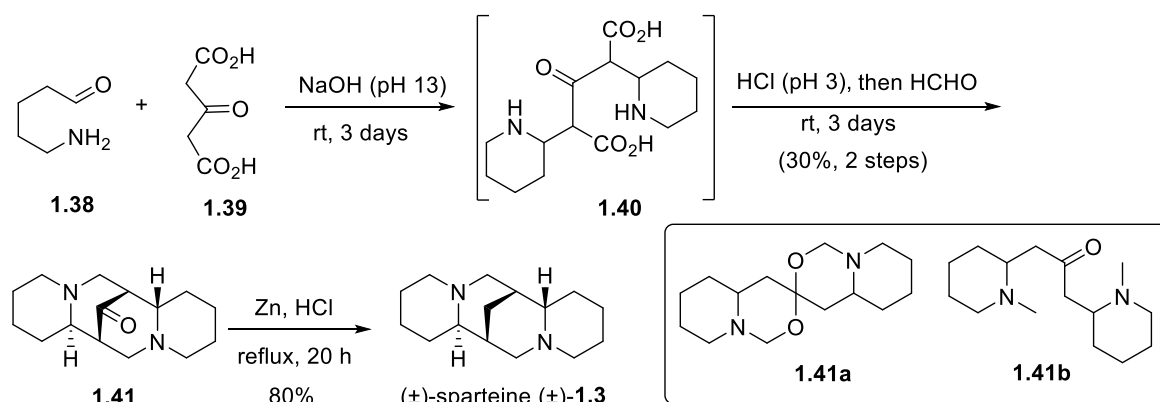


**Scheme 1.14**: Anet, Hughes, and Ritchie's synthesis of (±)-sparteine

Clemmensen reduction of (±)-8-oxo-sparteine ((±)-**1.41**) gave (±)-sparteine in high yield. Minor variations in pH were reported to give substantially lower yield, or none, of the ketone **1.41**. However, the synthetic (±)-sparteine obtained was identified only by a mixed melting point, and several years later the synthesis was questioned by Schöpf and co-workers.[62] The Schöpf group

stated that the intermediate taken to be (±)-8-oxo-sparteine ((±)-**1.41**) was in fact acetal **1.41a**, with melting point 133 °C and a formula $C_{15}H_{26}N_2O_2$ consistent Anet's recorded data.[62] The Clemmensen reduction of **1.41a** would lead to piperidyl propanone **1.41b** instead of (±)-sparteine. However, Schöpf *et al.* reported that (±)-**1.41** could be obtained from **1.41a** with acetic anhydride.[63]

### 1.3.8        Moore and Marion semi-synthesis of (−)-*β*-isosparteine and (+)-sparteine

As a part of their work to investigate the relationship of sparteine alkaloids and proof of structures, Moore and co-workers investigated interconversion of alkaloid. (+)-Lupanoline ((+)-**1.42**) was described by Moore *et al.* in 1953,[64] which was previously isolated from the legume *Lupinus Sericeus*.[65] (+)-Lupanoline was identified as (+)-2-hydroxy-17-oxo-*β*-isosparteine ((+)-**1.42**) by analysis of the IR data and apparent inert character of the carbonyl. Elimination of (+)-2-hydroxy-17-oxo-*β*-isosparteine by treatment with mineral acid gave anhydrolupanoline, identifying the hydroxyl group to be at the $\alpha$ position to one of the nitrogen atoms of the ring. The semi-synthesis of (−)-*β*-isosparteine ((−)-**1.4**) was achieved by reduction of (+)-lupanoline using LiAlH$_4$ (**Scheme 1.15**). Dehydrogenation of (−)-**1.4** using mercuric acetate in acetic acid gave dehydrosparteine **1.21**. Initially, sparteine obtained by hydrogenation of **1.21** using Adam's catalyst and was identified as (−)-sparteine, but Marion later confirmed that the structure was (+)-sparteine ((+)-**1.3**).[54]
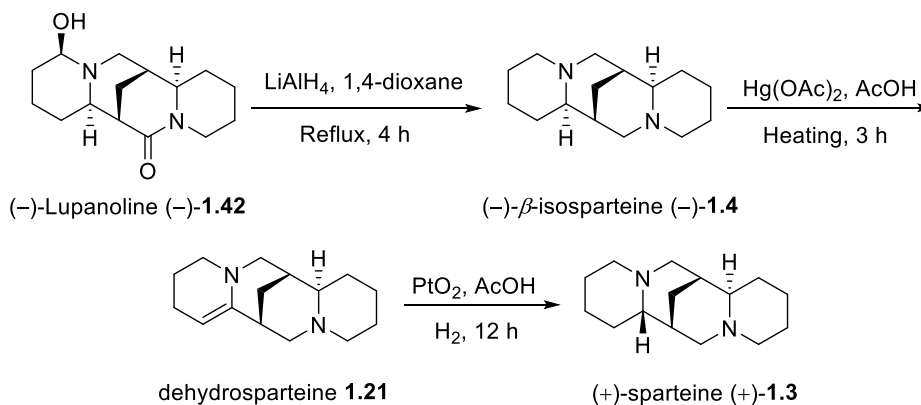


**Scheme 1.15**: Moore and Marion semi-synthesis of (−)-*β*-isosparteine and (+)-sparteine

### 1.3.9        Tsuda and Satoh's synthesis of three isomers of (±)-sparteine

In 1954, Tsuda and Satoh[66] repeated the synthesis of dioxo-sparteine according to the method of Clemo *et al.* and Galinovsky.[11,51,67] Employing pyridocoline **1.24** as an intermediate to produce three isomers of (±)-10,17-dioxo-sparteine *via* catalytic reduction and then cyclisation (**Scheme 1.16**). The three (±)-10,17-dioxo-sparteine isomers were isolated by column chromatoghraphy through alumina and recrystallisation giving: (±)-10,17-dioxo-*α*-isosparteine ((±)-**1.43**), m.p. 159 − 160 °C), (±)-10,17-dioxosparteine ((±)-**1.44**), m.p. 135 − 137 °C) and (±)-10,17-dioxo-*β*-isosparteine ((±)-

**1.33**), m.p. 182 – 184 °C). Reduction of (±)-**1.43** using platinum oxide as a catalyst in 5% HCl at rt

yielded (±)-$\alpha$-isosparteine ((±)-**1.8**) identified as the dipicrate salt, (m.p. 219 °C). Reduction of (±)-

**1.44** using the same conditions provided (±)-17-oxosparteine ((±)-**1.7** m.p.109 – 111 °C). Treatment

of (±)-**1.7** with a solution of D-tartaric acid gave oxosparteine tartrate (m.p. 236 °C (dec.)). (±)-$\beta$-

Isosparteine ((±)-**1.4**) was obtained from (±)-dioxosparteine ((±)-**1.33**) using the same reagents with

heating of the solution at 80 – 90 °C. The diastereoisomer (±)-**1.4** as its dipicrate salt gave a melting

point of 244 – 246 °C was not consistent with the literatures data.[52]
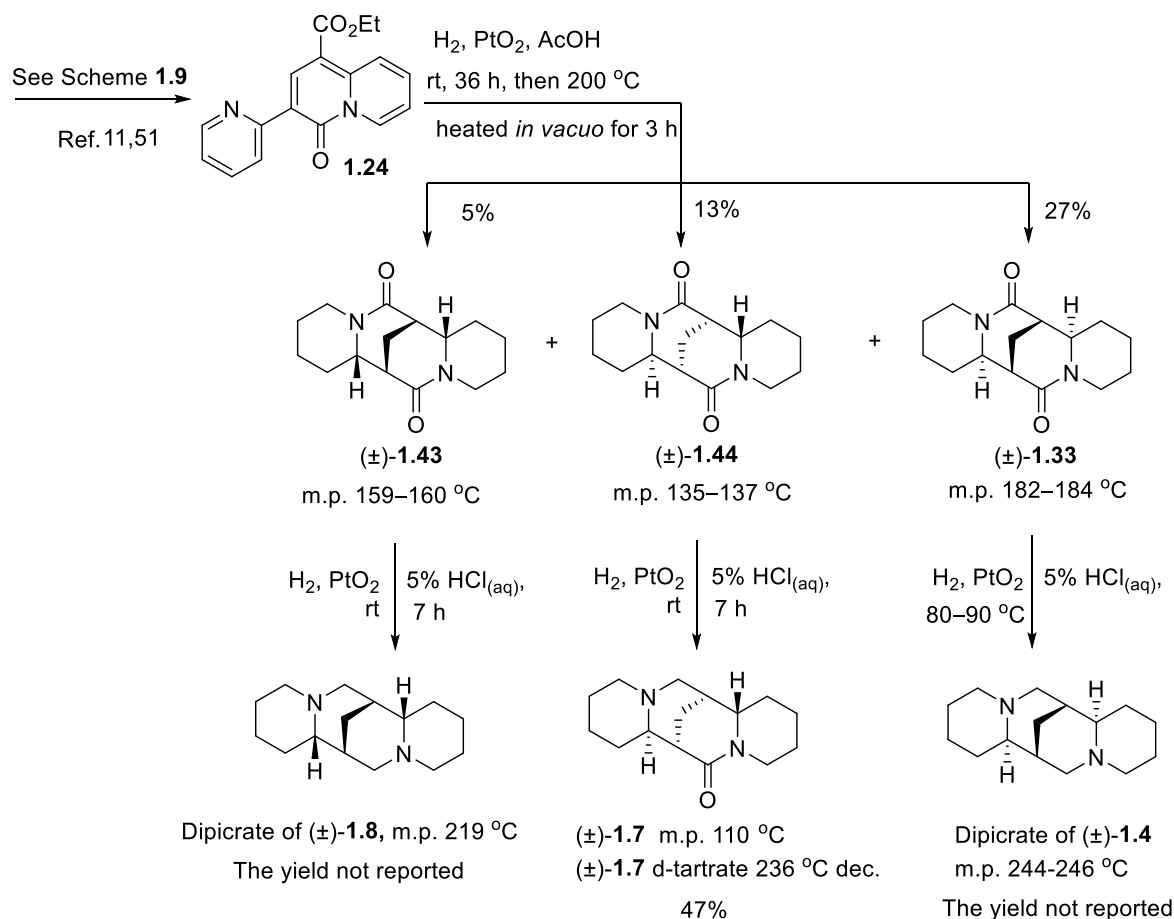


**Scheme 1.16**: Tsuda and Satoh's synthesis of three sparteine diastereoisomers

### 1.3.10    Van Tamelen and Foltz biogenetic synthesis of (±)-sparteine

A biogenic total synthesis of (±)-sparteine (±)-**1.3** was achieved by Van Tamelen *et al.* in 1960,[68] with

full details reported in 1969,[69] using a Mannich type cyclisation as a key step (**Scheme 1.17**).

Condensation of piperidine hydrochloride (**1.45**), formaldehyde and acetone in AcOH gave the

bispiperidine **1.46** *via* a symmetrical bis-Mannich reaction in 13% yield. The activated diiminium

ketone intermediate was established by treatment of the free base **1.46** with an excess of Hg(OAc)$_2$

in 5% AcOH, giving the less stable intermediate **1.47b**. The more stable conformation **1.47a** yielded

(±)-8-oxosparteine (±)-**1.41**. Alternatively, cyclisation from the epimer **1.48** provided racemic

oxosparteine (±)-**1.41**. Reduction of ketone (±)-**1.41** using modified Wolf-Kishner reduction led to (±)-sparteine in 6% yield from **1.46**. The identity of the product was confirmed by comparison of the monoperchlorate and dipicrate salt reported previously by Leonard.[57]
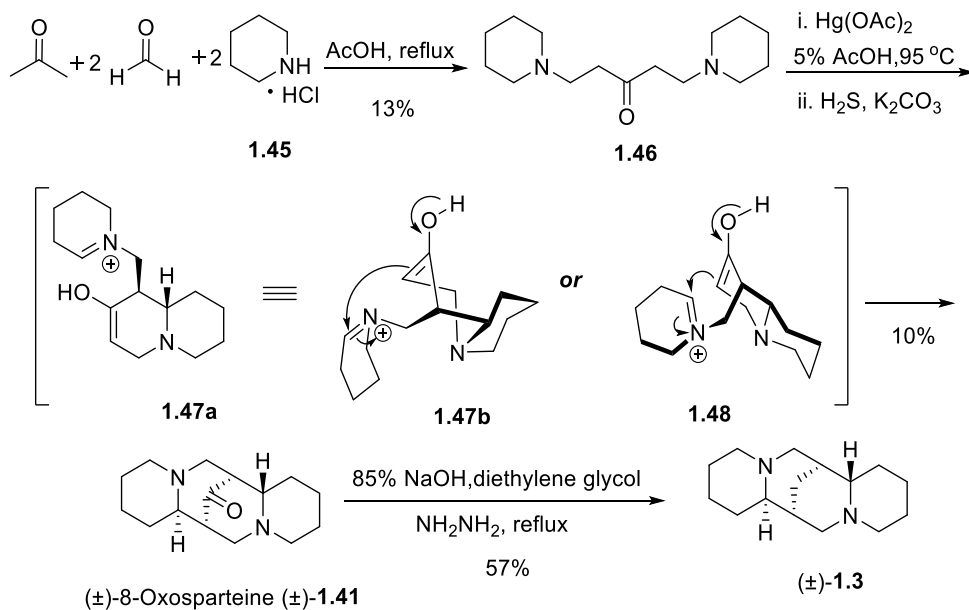


**Scheme 1.17**: Van Tamelen and Foltz's biogenetic synthesis of (±)-sparteine (**3**) synthesis

### 1.3.11    Bohlmann's synthesis of (±)-sparteine

A related approached was reported by Bohlmann *et al*. in 1973 using lactam reduction and Mannich-type cyclisation as the key step (**Scheme 1.18**).[70] Piperidinone was deprotonated using NaH in benzene and alkylated with bromide (±)-**1.49** to afford bisamide (±)-**1.50** in 29 % yield.
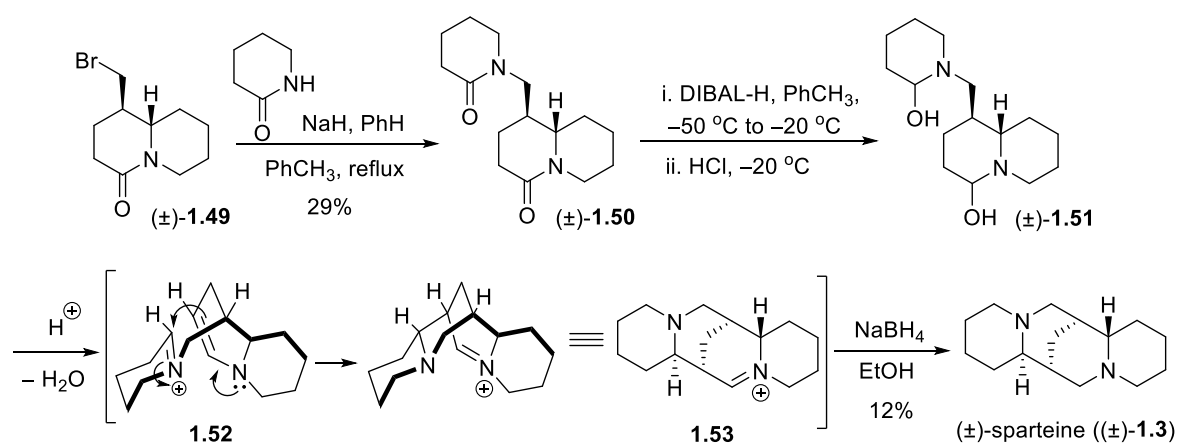


**Scheme 1.18**: Bohlmann's synthesis of (±)-sparteine

Reduction of (±)-**1.50** with DIBAL-H at −78 °C afforded bis-hemiaminal (±)-**1.51**, which was dehydrated under acidic conditions. The intermediate **1.52** underwent intramolecular Mannich-type cyclisation to afford tetracyclic iminium **1.53**. The final reduction was achieved using NaBH₄ in

ethanol to access (±)-sparteine in low yield. No other stereoisomers were reported although the tetracycle was only isolated in very low yield from (±)-**1.50**.

### 1.3.12      Kakisawa's total synthesis of (±)-$\alpha$-isosparteine

In 1983, Kakisawa *et al.* established a diastereoselective synthesis of (±)-$\alpha$-isosparteine ((±)-**1.8**) using 1,3-dipolar cycloadditions as key steps (**Scheme 1.19**).[71,72] Cycloaddition of nitrone **1.54** and 4*H*-pyran (**1.55**) in refluxing benzene proceeded with the formation of adduct **1.56** in 70% yield with high regio- and stereoselectivity. A second cycloaddition reaction between **1.56** and nitrone **1.54** secured **1.57** in 22% yield as 2:1 mixture of isomers. Catalytic hydrogenation of **1.57** over Pd(OH)$_2$ in MeOH provided tetracyclic diiminium cation **158**, which was subsequently reduced to give (±)-$\alpha$-isosparteine (±)-**1.8**. The identity of the sample was confirmed by comparison of physical and $^1$H and $^{13}$C NMR data with an authentic sample of the natural product. The yield of the final step is not reported in the paper.
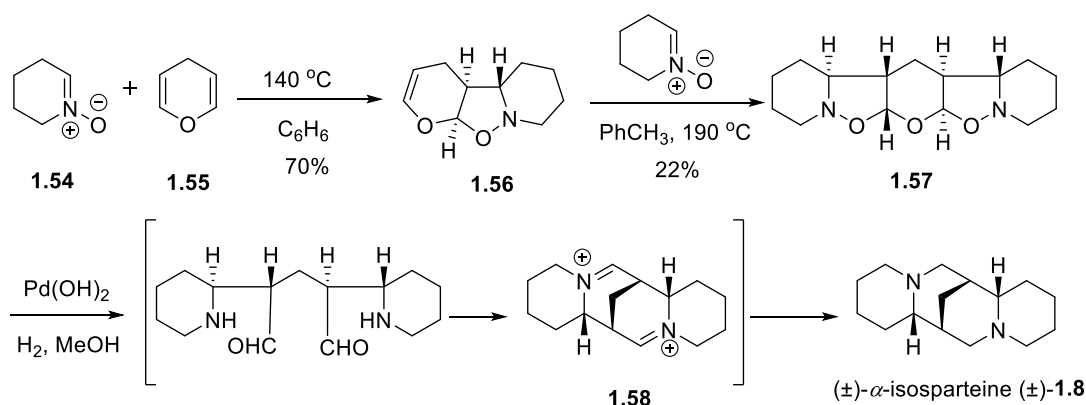


**Scheme 1.19**: Kakisawa's total synthesis of (±)-$\alpha$-isosparteine

### 1.3.13      Otomasu's formal synthesis of (±)-sparteine

Formal synthesis of (±)-sparteine was published by Otomasu *et al.* in 1987, also using a 1,3-dipolar cycloaddition as the key step in the synthesis (**Scheme 1.20**).[73,74] Employing chemistry reported by Tufariello,[75] 1,3-dipolar cycloaddition reaction of 1-pyrrolidine nitrone (**1.54**) and ethyl 3-butenoate (**1.59**) in refluxing toluene provided *exo*-adduct **1.60** as a single racemic diastereoisomer. Hydrogenation of **1.60** in EtOH over Pd/C caused a reductive N–O bond cleavage to produce intermediate **1.61**, which subsequently cyclised to bicyclic hydroxy amide **1.62** as a single isomer in 90% yield. Dehydration of hydroxy amide **1.62** by mesylation and elimination of the mesylate intermediate using DBU generated bicyclic enamide **1.63** in excellent yield. A second 1,3-dipolar cycloaddition reaction of nitrone **1.54** and enamide **1.63** gave tetracycle **1.64**. An inseparable mixture of regioisomers was reported in ratio of approximately 6:1 due to the exo-addition of

nitrone **1.54** from both sides of enone **1.63**. Reduction of the lactam **1.64** was completed with LiAlH$_4$ and the formation of (±)-2-hydroxyleontiformidine (**1.65**) by hydrogenolysis in MeOH over Pd/C. Oxidation of amino alcohol **1.65** using chromic acid generated amino ketone **1.66**. Mannich reaction of (±)-2-oxoleontiformidine (**1.66**) with formaldehyde generated (±)-8-oxosparteine (**1.41**) in 37% yield. Reduction of **1.41** to (±)-sparteine had previously been reported by Van Tamelen and Foltz (**See Scheme 1.17**).[68]
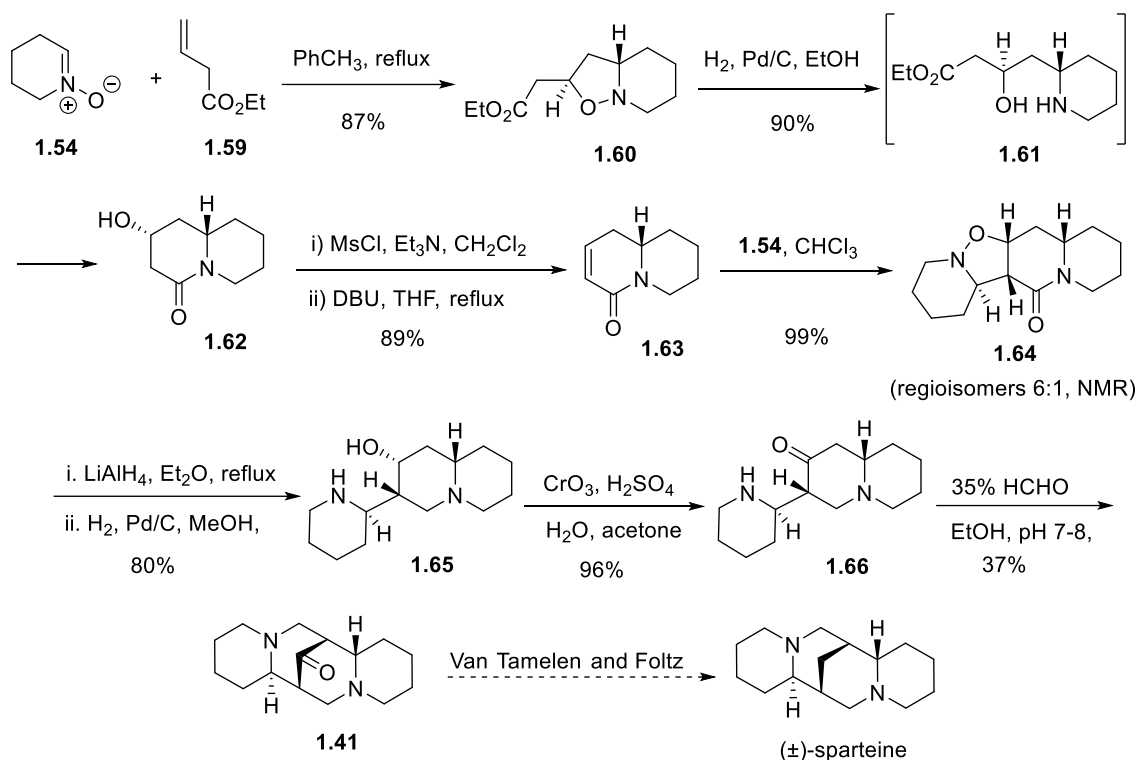


**Scheme 1.20**: Otomasu's synthesis of (±)-sparteine

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

A biomimetic total synthesis of (±)-sparteine was reported in 1996 by Koomen *et al.* (**Scheme 1.21**).[76] Dipiperidine **1.68** was prepared using chemistry reported by Schöpf, starting from a dehydropiperidine **1.67** trimer.[77] (±)-*trans*-Tetrahydroanabasine (**1.68**) was ring-opend in the presence of methoxyamine in aq. MeOH to afford *O*-methoxyoxime **1.69** as a mixture of *cis/trans* isomers. Quinone derivative **1.70** was used to oxidise oxime **1.69** to the dehydroquinolizidine **1.71**. Condensation of enamine **1.71** with *α*-tripiperidine monomer (**1.67**), which was prepared *in situ* from trimer in buffered methanol, provided 3-piperidylquinolizidine **1.72** as a 1:1 mixture of epimers at C12.[78] The synthesis of sparteine followed two approaches (A) and (B). Firstly, oxidative

removal of the oxime **1.72** with ozone under acidic conditions progressed very slowly to obtain

**1.73**, which subsequently gave the ring closed diiminium salt **1.74**. Reduction of the diiminium

salt **1.74** with NaCNBH₃ gave (±)-sparteine in 21% yield. The second approach employed TiCl₃ in

aq. HCl to achieve hydrolysis of oxime **1.72** followed by cyclisation, and finally reduction with

NaCNBH₃ furnished a mixture of (±)-sparteine and (±)-*β*-isosparteine in 9% and 11% yields

respectively. It is not clear why the second approach afforded *β*-isosparteine when none was

isolated from the first route. The overall yield of (±)-sparteine over 7 steps (route A) was 7% from

**1.68**, while route B gave (±)-sparteine and (±)-*β*-isosparteine over 5 steps in 3% and 4% yields

respectively.
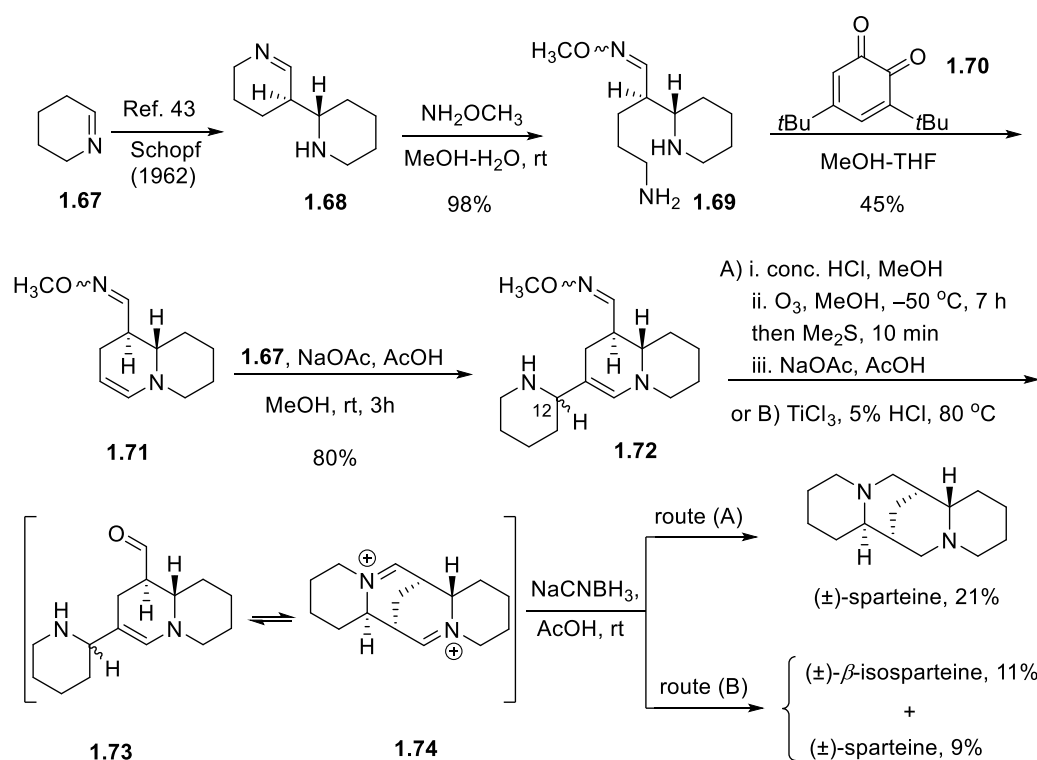


**Scheme 1.21**: Koomen's synthesis of (±)-sparteine and (±)-*β*-isosparteine

### 1.3.15     Aube's synthesis of (+)-sparteine

The first asymmetric total synthesis of optically pure (+)-sparteine ((+)-**1.3**) was reported by Aubé

*et al.* in 2002 (**Scheme 1.22**).[79] (+)-Sparteine was synthesised from 2,5-norbornadiene (**1.75**) which

was converted to a diol with high enantio- and regio-selectivity using chemistry reported by

Hayashi,[80] followed by Swern oxidation to form C2 symmetrical ketone **1.76**.[81] Protection of

diketone **1.76** as the mono acetal **1.77**, and then treatment with LDA at −78 °C followed by slow

addition of aldehyde **1.78** yielded the aldol condensation product **1.79** after mesylation and

elimination. The benzyl protecting group was removed at the same time as hydrogenation of the *exo* face of the olefin, and the formation of the azide **1.80** was completed using a modified Mitsunobu azidation. An intramolecular Schmidt ring expansion of intermediate **1.80** with TiCl$_4$ furnished the functionalised lactam **1.81** as a single isomer.[82] The thioamide of **1.81** was prepared using Lawesson's reagent, then hydrogenation over Raney-Ni accessed the desired quinolizidine **1.82**. Deprotonation of quinolizidine **1.82** using LDA at −78 °C, chloroalkylation and subsequent BocONHBoc displacement afforded hydroxylamine derivative **1.83**. *N*-Boc deprotection using TFA and condensation gave tetracyclic nitrone **1.84**. Photo-Beckmann rearrangement of **1.84** in benzene provided 10-oxosparteine (**1.85**).[83] The synthesis of (+)-sparteine ((+)-**1.3**) was completed by reduction of lactam **1.85** using LiAlH$_4$ in 95% yield. The overall synthetic route involved 15 steps and was achieved in 15.7% yield.
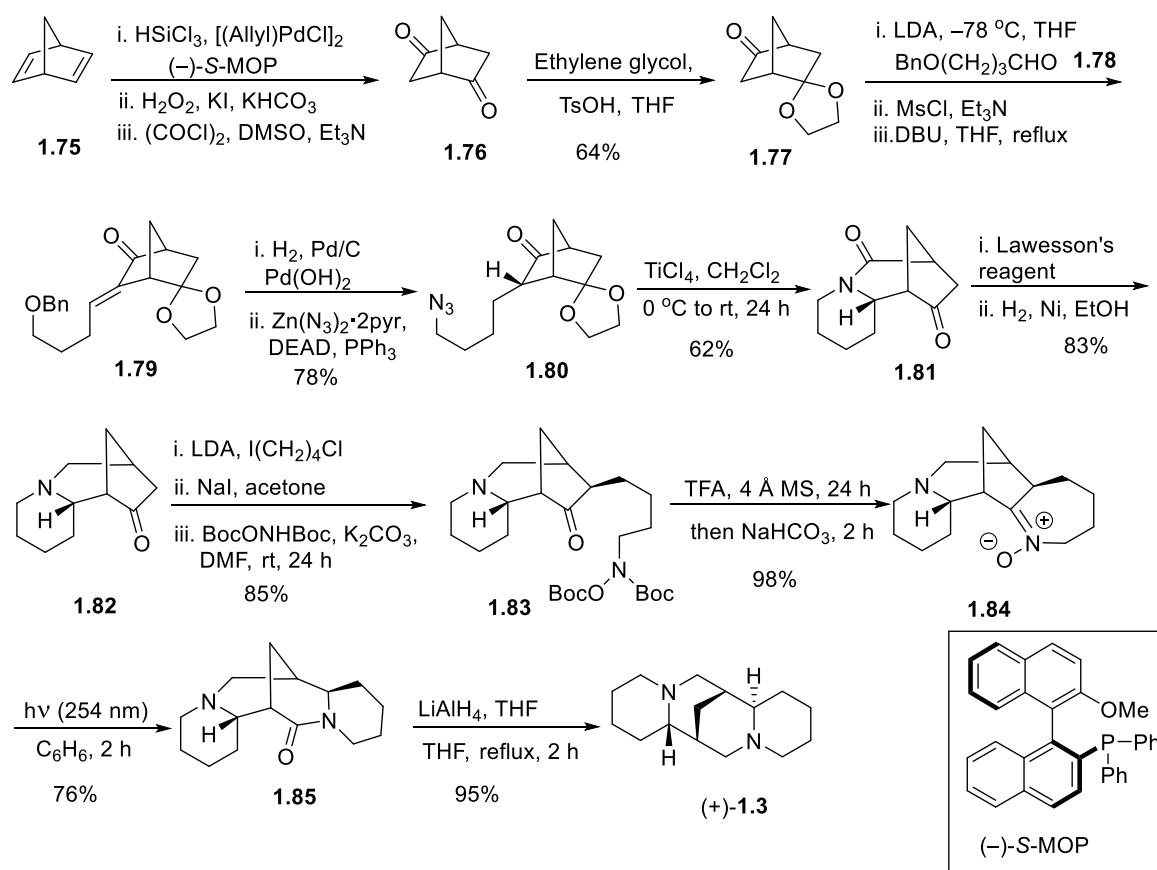


**Scheme 1.22**: Aube's synthesis of (+)-sparteine ((+)-**1.3**)

### 1.3.16    O'Brien's synthesis of (−)-sparteine

The first total synthesis of optically pure (−)-sparteine ((−)-**3**) was reported by O'Brien *et al.* in 2004 (**Scheme 1.23**).[84] Using chemistry reported by Hense,[85] ethyl-7-iodohept-2-enoate (**1.86**) was prepared in 82% yield over three steps from 5-chloropentanol. Alkylation of iodide **1.86** with (*R*)-$\alpha$-methylbenzylamine **1.87** in refluxing EtOH and subsequent intramolecular Michael addition of the

amine furnished piperidine **1.88** and **1.89** as a mixture of diastereoisomer (2:1). Despite the poor

selectivity in the conjugate addition, the mixture was readily separable and the major isomer **1.88**

was accessed in gram quantities. Treatment of **1.88** with LiHMDS at −78 °C followed by enolate

addition to EtOCH$_2$Cl accessed the functionalised piperidine **1.90** as a single isomer. Elimination of

ethoxide from **1.90** was accomplished using a modified procedure reported by Sworin and Lin to

secure the Michael acceptor **1.91**.[86]
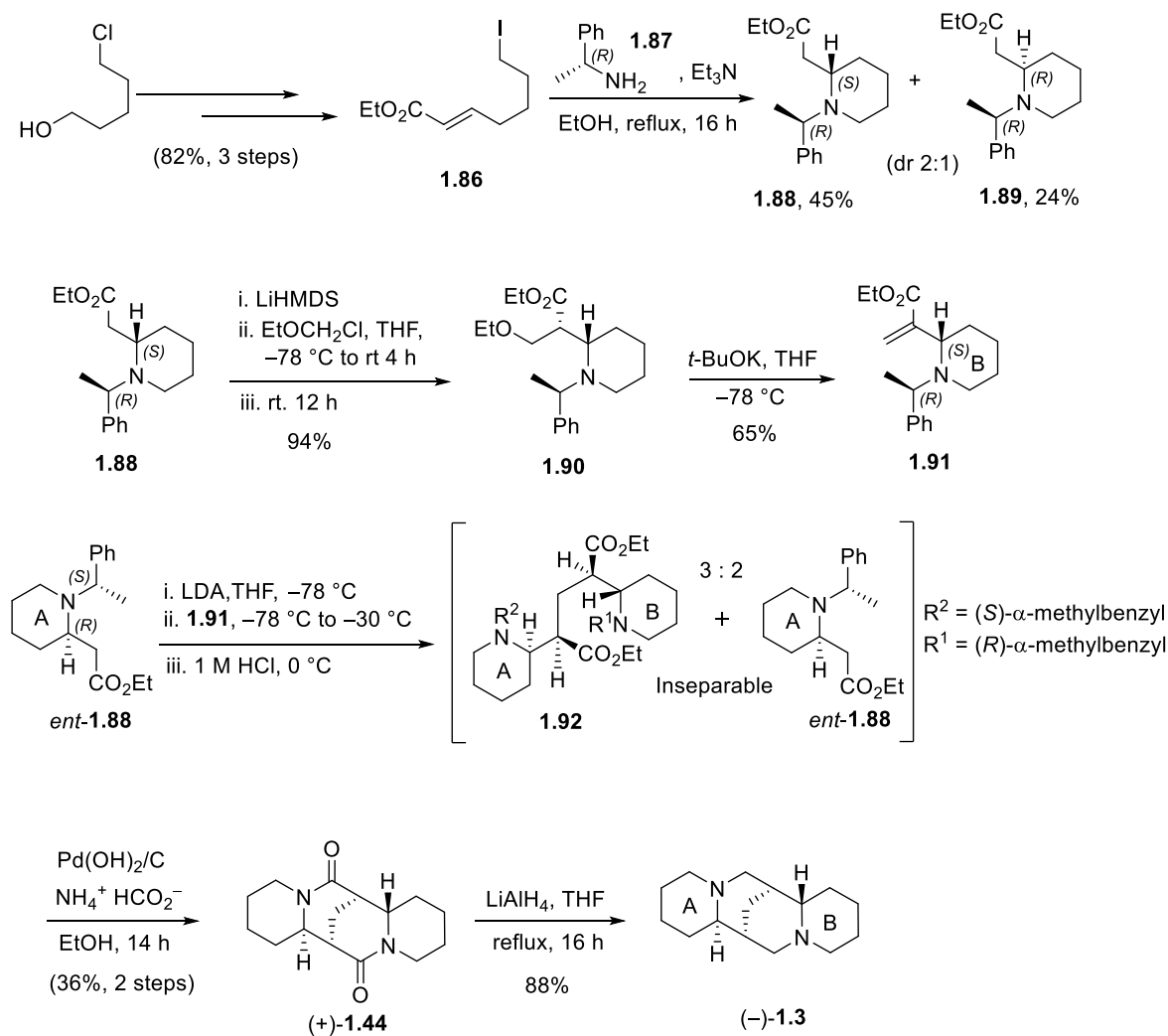


**Scheme 1.23**: O'Brien's synthesis of (−)-sparteine (−)-**1.3**

Deprotonation of *ent*-**1.88** at −78 °C using LDA and subsequent enolate addition to $\alpha,\beta$-

unsaturated amino ester **1.91** led to the formation of the bispiperidine **1.92**. Disappointingly, no

pure sample could be isolated. As a result, an inseparable mixture of **1.92** and *ent*-**1.88** was

submitted to transfer hydrogenation over Pd(OH)$_2$/C (Pearlman's catalyst) to furnish (+)-10,17-

dioxosparteine (+)-**1.44** after removal of the $\alpha$-methylbenzyl ether protecting group and cyclisation

of the free amine. Final reduction of bislactam (+)-**1.44** with LiAlH$_4$ afforded (−)-sparteine (−)-**1.3**.

Overall, the O'Brien group synthesis involved 6 steps from enoate **1.86** and was achieved in 9%

yield.

### 1.3.17      Buttler and Fleming's synthesis of (±)-sparteine

In 2005, Fleming and co-workers reported a synthesis of racemic (±)-sparteine ((±)-**1.3**) using a Diels-Alder reaction and a Beckman rearrangement as key steps (**Scheme 1.24**).[87,88] Diels-Alder cycloaddition between diene **1.93** and *Z*-diester **1.94** gave a mixture of bromides **1.95** and **1.96** in a ratio of 3:1. Treatment of these intermediates with NaOMe in refluxing toluene afforded a mixture of cyclopropanes **1.97** and **1.98** in the same ratio. Reductive ring expansion of the mixture of cyclopropanes **1.97** and **1.98** with lithium in ammonia established a 68% yield of the *dis*symmetric *R,R,R,S*-diastereomer **1.99** and 21% of the corresponding *meso-R,S,R,S*-diastereomer. In theory, from protonation of the enolates, three possible diastereomers could be formed, and quenching with methanol was important for selective to formation of the *dis*symmetric diastereomer **1.99**. Biscyclopentanone **1.100** was obtained from the oxidative cleavage of alkene **1.99** with ozone in acetone at −78 °C, which was optimized to prevent epimerization of intermediate ketone oxide by the addition of acetaldehyde. Bisoxime **1.101** obtained by treatment of **1.100** with hydroxylamine followed by Beckmann rearrangement to provide bislactam diester **1.102** in 52% yield over two steps. Reduction of bislactam diester **1.102** using LiAlH$_4$ afforded the corresponding bispiperidine diol which on cyclisation, *via* Appel reaction, furnished racemic sparteine. Overall, the synthesis was achieved in 8% yield and 9 steps from **1.93** & **1.94**.
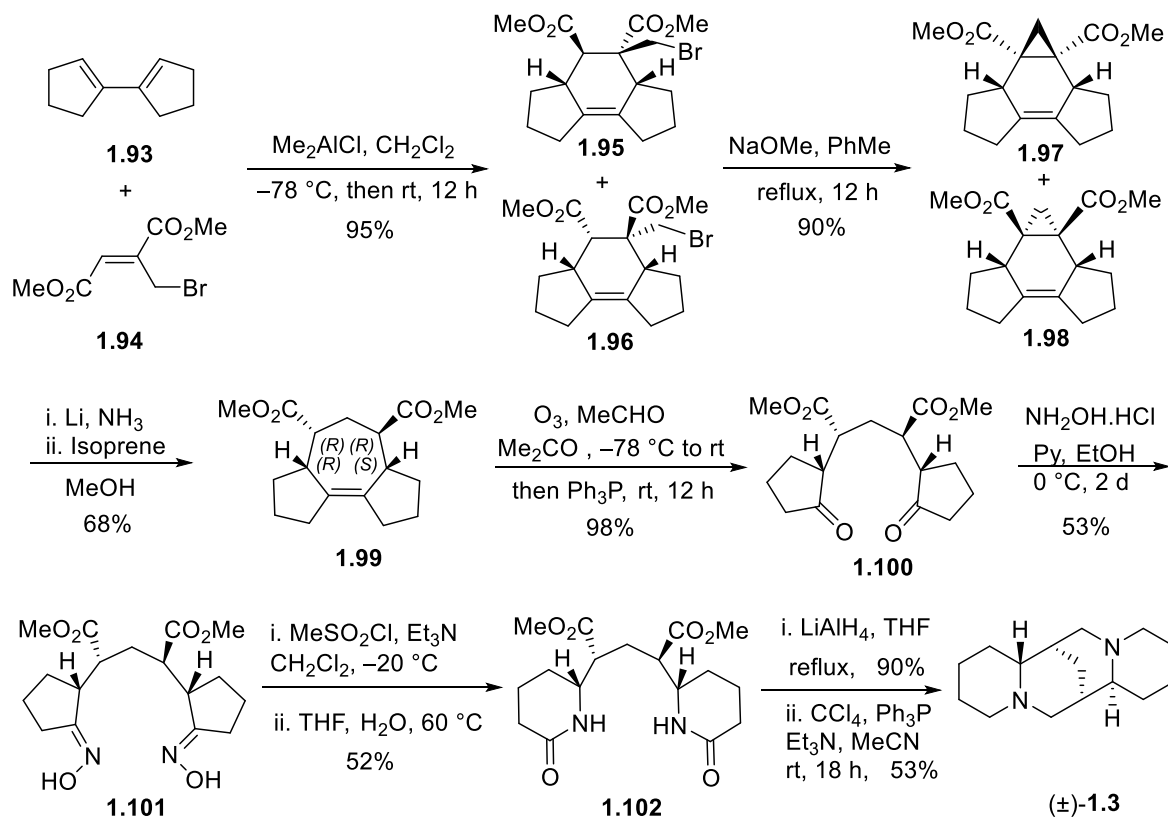


**Scheme 1.24**: Butler & Fleming's synthesis of (±)-sparteine

## 1.3.18       Blakemore's synthesis of (±)-sparteine, (±)-$\alpha$-isosparteine and (±)-$\beta$-isosparteine

In 2008, Blakemore and co-workers developed a general strategy to access any of the three racemic sparteine diastereoisomers from a common tetraoxobispidine intermediate **1.104** (**Scheme 1.25**).[55,89,90] Tetraoxobispidine **1.104** (obtained in 16% over three steps from dimethyl malonate **1.103** and paraformaldehyde),[90] was treated with NaBH$_4$ in THF to give hydroxylactam **1.105**. Using chemistry reported by Sakurai, the crude aminol **1.105** was alkylated with allyltrimethylsilane in the presence of BF$_3$•OEt$_2$, subsequent addition of the nucleophile afforded imidolactam **1.106** in 33% yield over two steps. The treatment of **1.106** with allylmagnesium bromide gave the functionalised pseudo-C2-symmetrical amide **1.107** as a single stereoisomer. Double RCM of **1.107** using Grubbs II afforded the tetracyclic diene **1.108** in 92% yield. Tetracyclic amide **1.109** was formed from hydrogenation of diene **1.108** over Pd/C, and reduction of bisamide **1.109** using LiAlH$_4$ completed the synthesis of (±)-sparteine in 6 steps and 12% yield from tetraoxobispidine **1.104**. The stereochemistry of **1.109** was confirmed by single crystal X-ray crystallography.
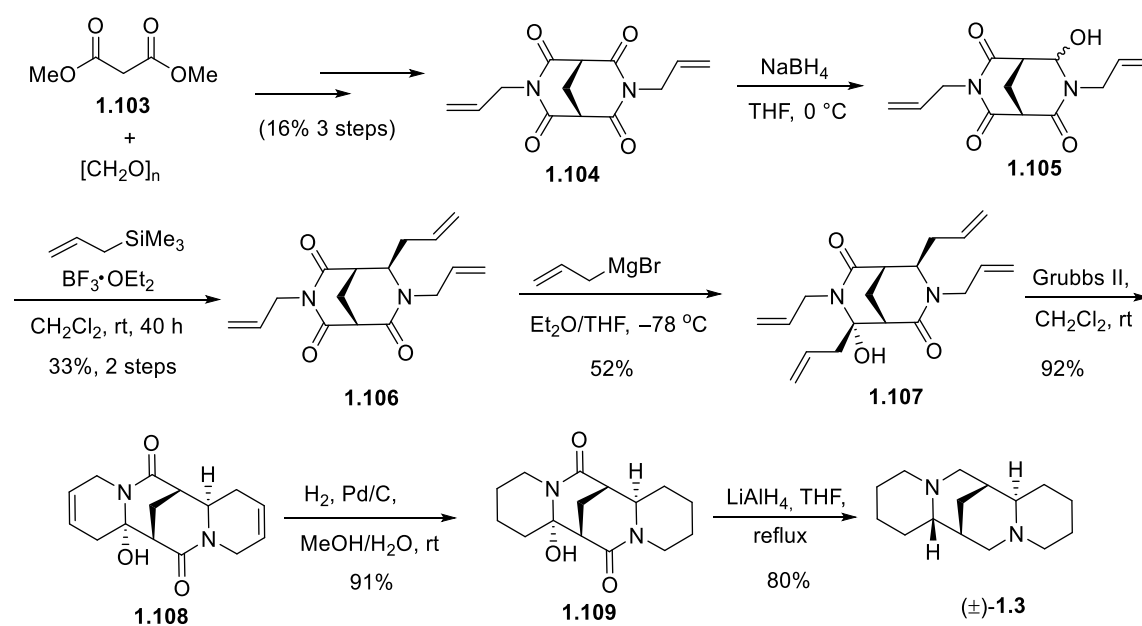


**Scheme 1.25**: Blakemore's synthesis of (±)-sparteine ((±)-**1.3**)

A similar approach was used for the stereocontrolled synthesis of (±)-$\beta$-isosparteine (**Scheme 1.26**),[55] again from tetraoxobispidine **1.104** as a key intermediate. Reduction of bispidine **1.104** using NaBH$_4$ gave the bishydroxylactam **1.110**. It is noteworthy that reduction of **1.104** using NaBH$_4$ showed a marked improvement in 16% overall yield in 2 steps instead of using LiBHEt$_3$. Double Sakurai-type allylation of **1.110** using allyltrimethylsilane with BF$_3$•OEt$_2$ formed tetraene **1.111** in 16% yield over two steps. Double RCM of tetraene **1.111** using Grubbs I provided tetracyclic diene **1.112** in 97% yield, and hydrogenation of diene **1.112** over Pd/C afforded (±)-10,17-dioxo-$\beta$-

isosparteine, which was reduced to complete the synthesis of (±)-$\beta$-isosparteine. The total synthesis was achieved in 13% in 5 steps from **1.104**.
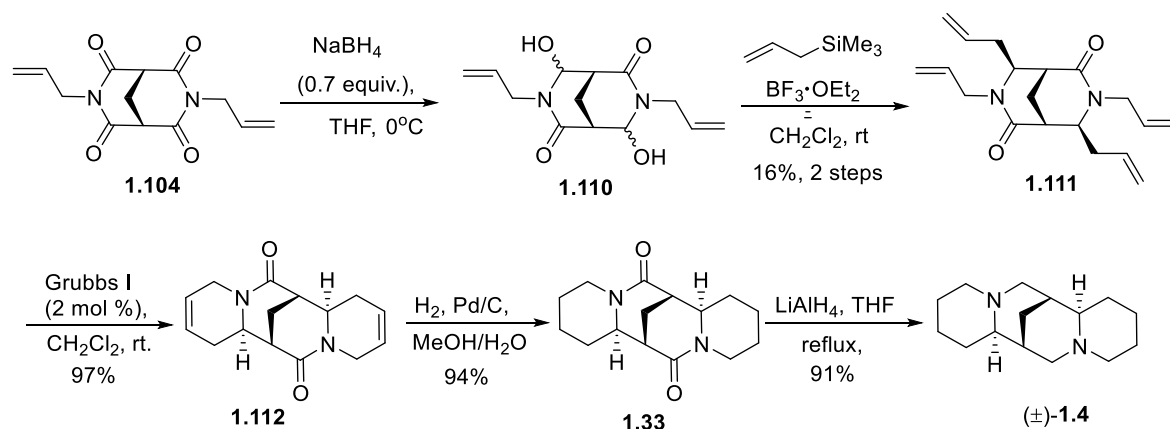


**Scheme 1.26**: Blakemore's synthesis of (±)-$\beta$-isosparteine (±)-**1.4**

The reverse addition order of the allyl and hydride groups were used to obtain (±)-$\alpha$-isosparteine ((±)-**1.8**) (**Scheme 1.27**), where double allylation of tetraoxobispidine **1.104** first formed bishydroxylactam **1.113**. Grubbs I was used to achieve double RCM of **1.113** to yield the tetracyclic diene **1.114** in 81%. Hydrogenation of **1.114** over of Pd/C in (EtOH/EtOAc, 2:1) furnished the symmetric bis-hemiaminal **1.115a** in 21% yield while the hydrogenation in a more polar solvent mixture (MeOH/H$_2$O, 5:1) gave the nonsymmetric bis-hemiaminal **1.115b** as a single isomer in 93-96% yield. Reduction of the symmetric and nonsymmetric bis-hemiaminals was achieved in a stereocontrolled manner using a large excess of BH$_3$ to give (±)-$\alpha$-isosparteine.[90] Overall, the synthesis was achieved in 28% yield and 4 steps from tetraoxobispidine **1.104**.
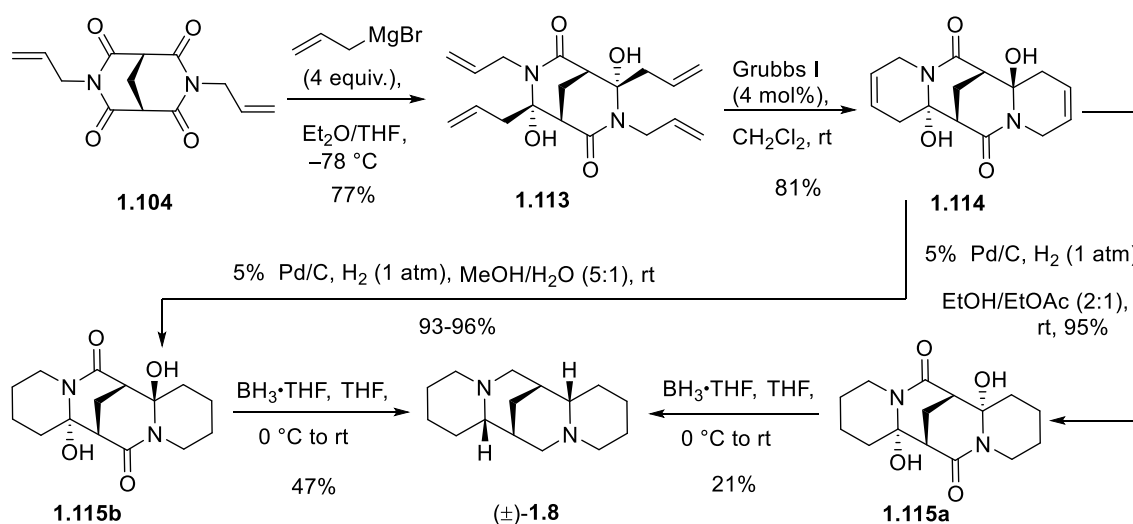


**Scheme 1.27**: Blakemore's synthesis of (±)-$\alpha$-isosparteine ((±)-**1.8**)

**1.3.19    O'Brien's synthesis of (−)-sparteine bis-sulfate**

A synthesis of (−)-sparteine was published early 2018 by O'Brien *et al.* in using *B. cepacia* lipase to obtain enantiopure ester piperidine *R*-**1.116** as starting point (**Scheme 1.28**).[91] Racemic ester (*rac*-**1.116**) was prepared by hydrogenation of pyridine and *N*-Boc protection by following previous method.[92,93] Using chemistry reported by Pousset *et al.* in 2004,[94] enzymatic resolution of *rac*-**1.116** using lipase gave enantiopure ester piperidine *R*-**1.116** in 46% yield and chiral *β*-amino acid **1.117** in 49% yield. *β*-Amino acid **1.117** is the first fragment to access (−)-sparteine, which was esterified to obtain *S*-**1.116**. Enolisation of *S*-**1.116** using LiHMDS and reaction with Eschenmoser's salt gave methyl amine **1.118** as a single diastereoisomer. Methylation and elimination using MeI and DBU formed *α,β*-unsaturated ester **1.119** with no racemisation. Deprotection *N*-Boc of **1.119** and then benzyl protection gave **1.120** in 97% over 2 steps.
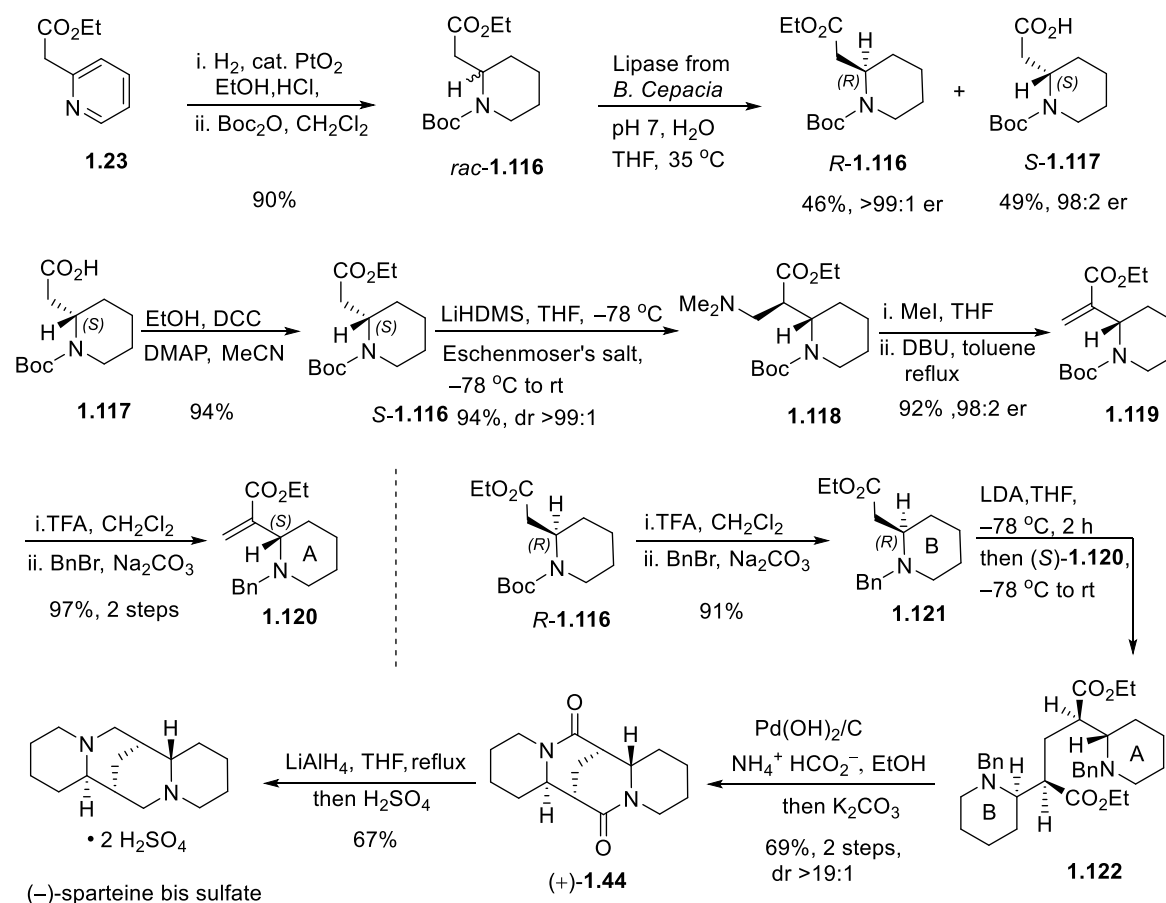


**Scheme 1.28**: O'Brien's synthesis of (−)-sparteine bis-sulfate

The second fragment is *R*-**1.116** which was also deprotected and re-protected using a benzyl group under the previously described conditions giving **1.121**. Deprotonation of ester **1.121** using LDA followed by addition of *α,β*-unsaturated ester **1.120** produced **1.122**. Transfer hydrogenation of **1.122** over Pd(OH)$_2$/C cleaved the *N*-benzyl protecting groups, and subsequently, cyclisation using K$_2$CO$_3$ provided (+)-10,17-dioxo-sparteine as a single diastereoisomer in 69% yield over 2 steps.

Finally, the synthesis of (−)-sparteine bis sulfate was completed by reduction of bis-lactam **1.44** in the presence of LiAlH$_4$ and then salt formation with H$_2$SO$_4$ in 67%. Overall, the synthesis was achieved in 31% yield over 10 steps, on a scale of one gram.

### 1.3.20    Breuning and co-workers synthesis of bisquinolizidine alkaloids

Breuning *et al.* published the asymmetric syntheses of 21 natural products in total in 2018 using bispidine **1.123** which was reported by Blakemore to build the tetracyclic cores of the sparteine isomers (**Scheme 1.25**).[95] Breuning succeded in directly desymmetring achiral 2,4,6,8-tetraoxobisbidine **1.125** (**Scheme 1.29**). The bispidine **1.123** used by Blakemore as an excellent key starting point to an "inside out" route towards the core of the lupin alkaloids. Breuning attempted to desymmetrise this core.[89] With careful manipulation, this would allow the preparation of a key late-stage tricyclic intermediate that could be further functionalised to afford the desired alkaloids. The authors used Blakemore's originally reported synthesis of **1.123**, which presumably suffered the same modest yields, but gave high throughput of matrial.[90]
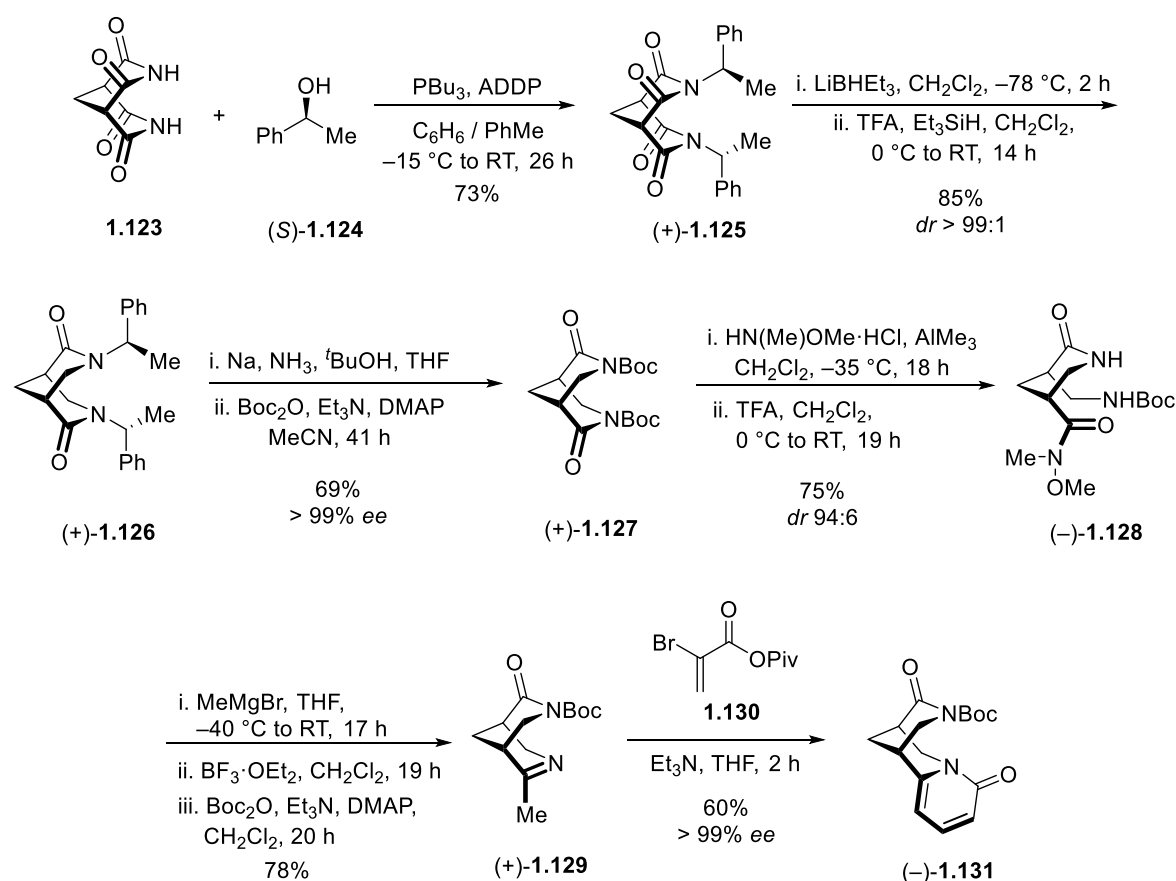


**Scheme 1.29**: Breuning's desymmetrization of achiral bispidine **1.123**, and subsequent preparation of key intermediate (−)-**1.131**.

Deoxygenation one pair of enantiotopic carbonyls from achiral bispidine **1.123** began with a Mitsunobu-type reaction using (*S*)-phenyl ethanol ((*S*)-**1.124**) to give diimide (+)-**1.125**. Diastereoeselective reduction of **1.125** using LiBHEt$_3$ followed by treatment with TFA provided diamide (+)-**1.126** with excellent regio- and stereo-control. Removal of the chiral auxiliary using Birch conditions and subsequent Boc protection afforded the successfully desymmetrised dioxo-bispidine (+)-**1.127**. Selective modification of one of the amide groups was carried out by Lewis acid-catalysed ring opening with *N,O*-Dimethyl hydroxylamine. *N*-Boc removal of the resultant lactam furnished Weinreb amide (−)-**1.128**, with a slight loss in diastereoselectivity by epimerisation at the bridgehead positions. Grignard addition to the Weinreb amide (−)-**1.128** and subsequent reclosure of the amine *via* Boc deprotection and reprotection gave cyclic imine (+)-**1.129**. Michael addition to anhydride **1.130**, and elimination of HBr provided the key tricyclic bispidine (−)-**1.131**, the enantiomer of which was also prepared from **1.123** and (*R*)-**1.124**.

The synthesis of (+)-sparteine ((+)-**1.3**) was achieved using the key intermediate bispidine (−)-**1.31**(**Scheme 1.30**). Reduction of the imide functionality of (−)-**1.131** using NaBH$_4$ afforded *N,O*-acetal (−)-**1.132**, which was subjected to an *exo*-selective Sakurai allylation and simultaneous Boc deprotection to obtain alkene (−)-**1.133**. The free amine was allylated to provide diene (−)-**1.134**, which after RCM and hydrogenation afforded (−)-anagyrine ((−)-**1.20**) which was subsequently hydrogenated to (−)-lupanine ((−)-**1.6**), and finally reduced to ((+)-**1.3**). (−)-Sparteine ((−)-**1.3**) also obtained in this approach from (+)-**1.131**, with the exception that reduction of the pyridone moiety would occur at the start (**Scheme 1.30**).
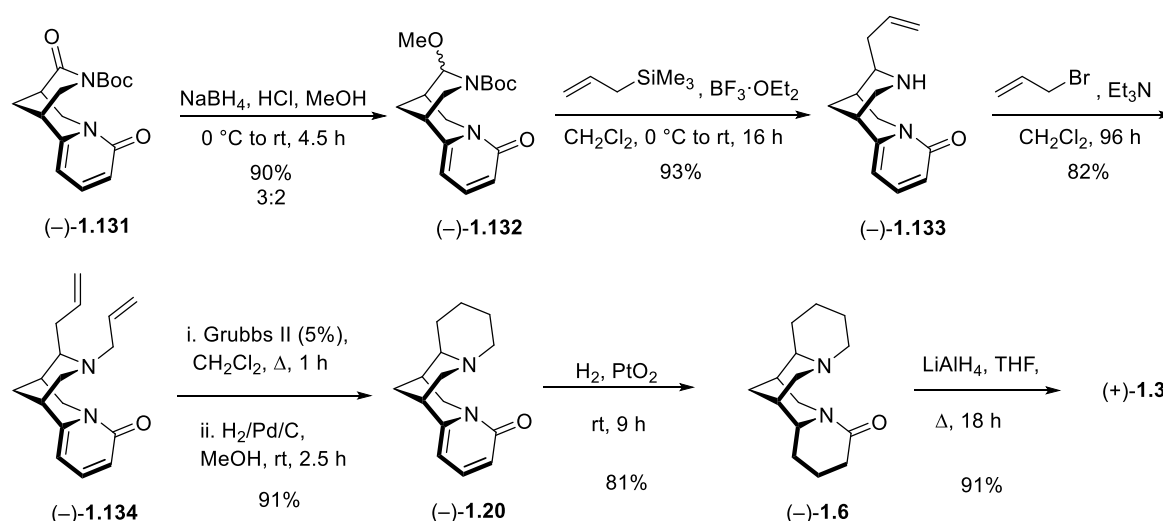


**Scheme 1.30**: Breuning's total synthesis of (+)-**1.3** from tricyclic bispidine (−)-**1.131**

The synthesis of $\alpha$-isosparteine ((−)-**1.8**) was accomplished by hydrogenation of imide (+)-**1.131** using H$_2$/PtO$_2$ to obtain piperidone (+)-**1.135** (**Scheme 1.31**). Treatment of (+)-**1.135** with 4-

chlorobutylmagnesium bromide, followed by *N*-deprotection and reductive amination afforded the *endo*-piperidone product (+)-isolupanine ((+)-**1.136**), which was converted into (–)-*α*-isosparteine ((–)-**1.8**) by LiAlH$_4$ reduction. The synthesis of (–)-**1.3** was obtained through *exo*-functionalisation by reduction of imide (+)-**1.135** to *N,O*-acetal, and then following the steps described earlier (**Scheme 1.29**).
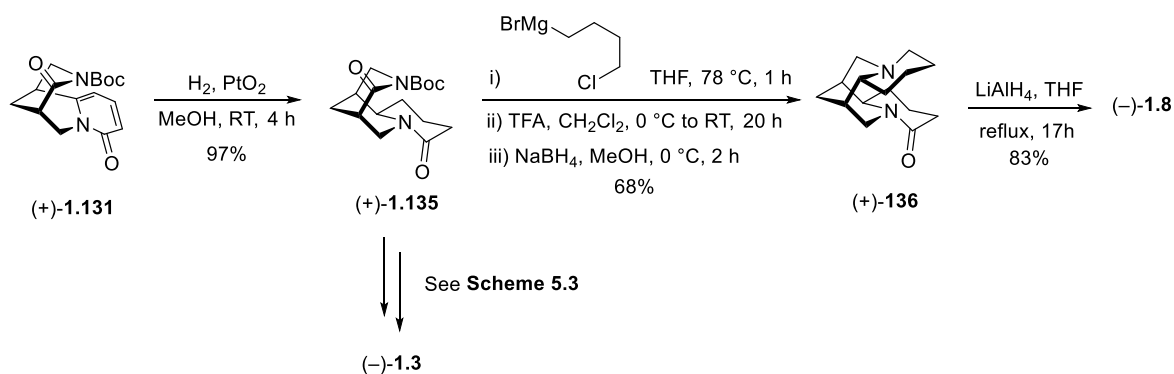


**Scheme 1.31**: The total synthesis of (–)-**1.8** using of (+)-**1.131** by *endo*-annulation, and using *exo*-functionalisation to synthesise (–)-**1.3**

The ability to syntheses of (–)-*β*-isosparteine ((–)-**1.4**) and the (–)-*α*-isosparteine ((–)-**1.8**) from the *exo /endo* annulation strategies were applied using both antipodes of bispidine **1.127** (**Scheme 1.32**). Double reduction of the imides to bis-*N,O*-acetal (+)-**1.137** was effected by the use of Schwartz's reagent, which was found to be higher-yielding than other alternatives. Alkylation by Lewis acid assisted organozinc addition of the required alkyl chain, followed by cyclisation, subsequently delivered (–)-**1.4** by *exo* annulation. Double alkylation of (–)-**1.127** followed by *N*-deprotection and endo reduction as before completed a short route to (–)-**1.8**.
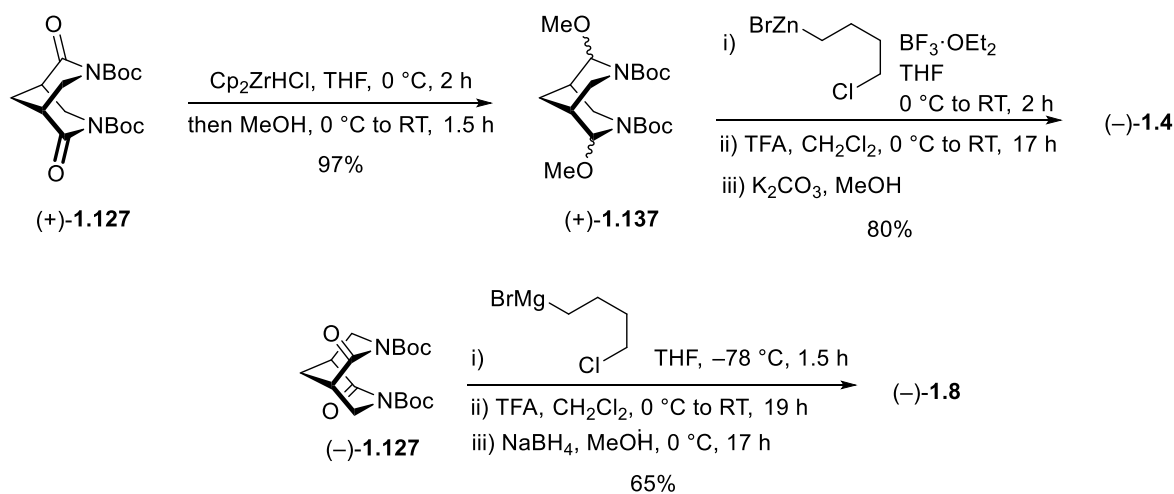


**Scheme 1.32**: Total syntheses of (–)-**1.4** and (–)-**1.8** following the *exo/endo* additions from enantiomeric bispidine precursors (+)- and (–)-**1.127**.

## 1.4      Matrine alkaloids

(+)-Matrine ((+)-**1.138**) was first isolated from the traditional medicinal herb *Sophora flavenscens* by Nagai in 1889, and has been the subject of many studies due to its biological activities.[96] (+)-Allomatridine ((+)-**1.5**) is a tetracyclic lupin alkaloid of the matrine series, which can be obtained by the reduction of (+)-allomatrine ((+)-**1.139**) (**Figure 1.7**). (+)-Allomatrine has been reported as a chemical component from the *Sophora* species.[97-99] It was found to have *anti*-nociceptive activity in mice through action at the opioid receptors,[100,101] and also reported to possess antitumor activity in vitro and in vivo.[102]
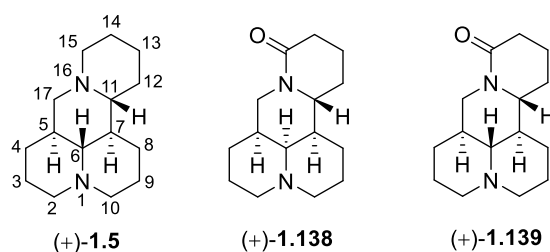


**Figure 1.7**: Structures of (+)-allomatridine ((+)-**1.5**), (+)-matrine ((+)-**1.138**) and (+)-allomatrine ((+)-**1.139**).

### 1.4.1      Previous total syntheses of matrine isomers

There have been several synthetic preparations of tetracyclic lupin alkaloids of the matrine structural series. The total synthesis approaches to this class of natural products and semi synthesis published have been documented below in chronological order of their publication in the literature.[103-109] The target natural products were originally synthesised as mixtures of diastereoisomers and enantiomers with the first asymmetric total syntheses reported by Brown and co-workers.[109] The first preparation of (+)-allomatrine ((+)-**1.139**) was by epimerization of (+)-matrine ((+)-**1.138**) at C6.[110] A semi synthesis detailed by Okuda[106] has been included in this brief overview as this publication details the first preparation of enantiomerically pure matrine and allomatrine *via* synthetic methods.

### 1.4.2      Bohlmann's "biogenetic" synthesis of (±)-allomatridine and other tetracyclic lupin alkaloids

The tetracyclic lupin alkaloids (±)-allomatridine ((±)-**1.5**), (±)-*α*-isosparteine ((±)-**1.8**) and (±)-sparteine ((±)-**1.3**) were prepared in 1963 by Bohlmann *et al.* using *N*-acyliminum ion cyclisation as a key step.[103] There are three routes to access the target compounds starting from bromo lupinine

**1.140** with piperidine in the presence of K$_2$CO$_3$ in Et$_2$O to produce piperidino-lupinine **1.141** (**Scheme 1.33**). The epimeric piperidino-epilupinine **1.142** was obtained analogously from bromo epilupinane. Dehydrogenation of piperidino-lupinine **1.142** in the presence of mercury acetate in acetic acid gave tricyclic diiminium cations **1.143** and **1.144**, which underwent a Mannich type cyclisation. The yield for this transformation was not reported. The iminium cation **1.145** was isolated through column chromatography on Al$_2$O$_3$ (*eluent*, petroleum ether:Et$_2$O, (1:1)). Subsequent reduction of **1.145** using sodium borohydride (NaBH$_4$) generated two tetracycles, (±)-allomatridine ((±)-**1.5**), and 5-hydroxy-allomatridine (**1.146**) as a minor component. While, using (*eluent*, Et$_2$O:MeOH, (10:1)), the iminium cation **1.147** was obtained by column chromatography on Al$_2$O$_3$. Reduction of **1.147** using NaBH$_4$ gave (±)-$\alpha$-isosparteine in 7% yield from **1.141**. (±)-Sparteine was obtained using the diastereoisomeric piperidino-epilupinine **1.142** as starting point followed by dehydrogenation and cyclisation using Hg(OAc)$_2$ and subsequent reduction of **1.148** using NaBH$_4$. The syntheses of (±)-allomatridine and (±)-$\alpha$-isosparteine involved 3 steps each, which were achieved in 7% and 5% overall yields, respectively from **1.140**.
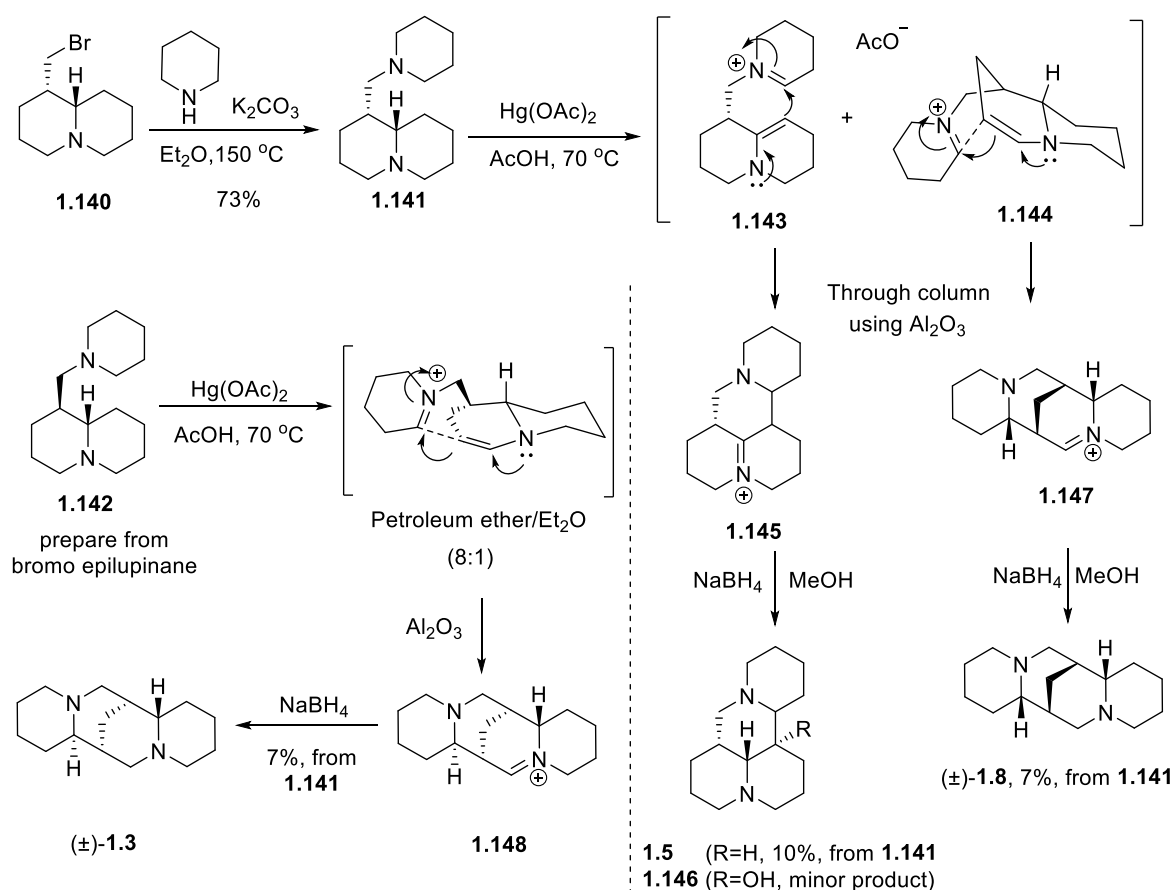


**Scheme 1.33**: Bohlmann's "biogenetic" syntheses of (±)-allomatrine and another tetracyclic lupin alkaloids

### 1.4.3        Mandell's total syntheses of (±)-matrine and (±)-allomatrine

Mandell *et al.* reported the first total synthesis of (±)-matrine ((±)-**1.138**) in 1963.[104] The same synthetic strategy was later reported in 1965 as a full paper including the synthesis of (±)-matrine and (±)-allomatrine ((±)-**1.139**) from a common intermediate **1.149** (**Scheme 1.34**).[105] Racemic mixtures of matrine and allomatrine were synthesised in 2.5% and 1.6% overall yield respectively in 6 linear steps from **1.149**. Condensation of ethyl $\beta$-alaninate with diethyl $\beta$-oxopimelate (**1.134**) in refluxing benzene afforded enamine **1.150**. Hydrogenation of the crude enamine **1.150** over Adam's catalyst led to formation of lactam **1.151** which was completed by heating on a steam bath. Dieckmann cyclisation using NaH led to the formation of quinolizidinedione **1.152**. Decarboxylation of ketoester **1.152** by refluxing in glacial AcOH produced 8-oxo-2-quinolizidone (**1.153**), which underwent double alkylation with acrylonitrile to give a mixture of the bis nitrile product **1.154**, along with the mono-addition product.
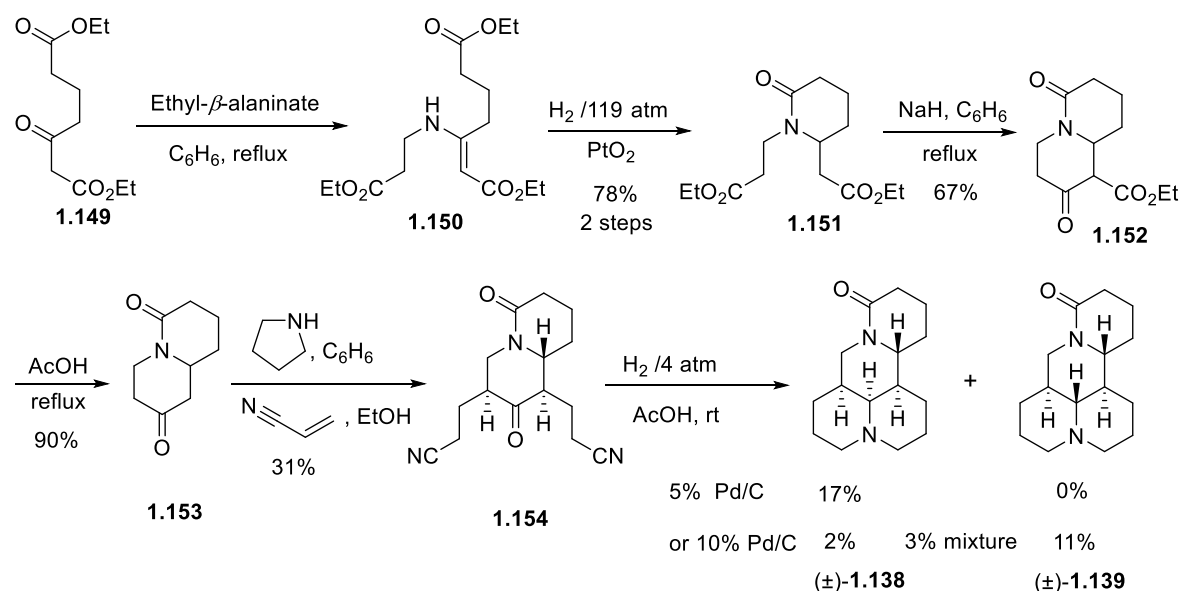


**Scheme 1.34**: Mandell's total synthesis of (±)-matrine and (±)-allomatrine

The major component was reductively cyclised to either (±)-matrine using 5% Pd on charcoal at rt under 4 atm of $H_2$ in 17% yield or the thermodynamically more stable (±)-allomatrine (±)-**1.139** using 10% Pd on charcoal at rt in 11% yield with 2% yield of (±)-matrine and 3% of a mixture. The identities of the products was confirmed by comparison of their infrared spectra and melting points with authentic samples obtained from natural sources.

### 1.4.4        Okuda's semi-synthesis of optically active (+)-allomatrine

The semi-synthesis of optically active (+)-allomatrine ((+)-**1.139**) was accomplished by Okuda *et al.* in 1966 from (+)-matrine.[106] Their approach proceeded by oxidation of (+)-matrine ((+)-**1.138**) to didehydromatrine (**1.156**), using a procedure which was reported by Tsuda and co-workers in 1962.[111] Dehydrogenation of (+)-matrine over Pd/asbestos provided octadehydromatrine (**1.155**) (**Scheme 1.35**). Catalytic hydrogenation over $PtO_2$ in AcOH afforded didehydromatrine (**1.156**). Reduction of **1.156** with Na in refluxing EtOH generated a mixture of two racemic diastereoisomers; (±)-allomatrinol ((±)-**1.157**) and (±)-matrinol ((+)-**1.158**) present in a ratio of (11:1). The resolution of diastereoisomers (±)-allomatrinol and (±)-matrinol was performed by recrystallisation of the dibenzoyl-(+)-tartaric acid salts from acetone-ether. (+)-Allomatrinol ((+)-**1.157**) and (+)-matrinol ((+)-**1.158**) were transformed to corresponding amino acid derivatives by oxidation with $CrO_3$ in 20% $H_2SO_4$. The crude material was cyclised without purification in refluxing acetic anhydride to access (+)-allomatrine in 56% from (+)-allomatrinol, and (+)-matrine in 30% from (+)-matrinol ((+)-**1.158**).
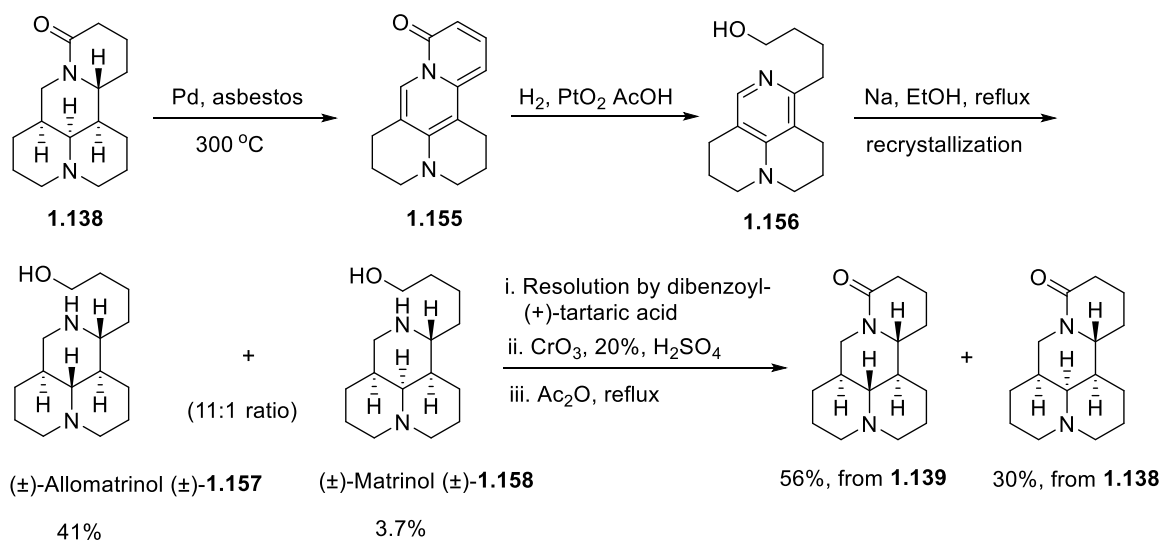


Scheme 1.35: Okuda's semi-synthesis of (+)-allomatrine from (+)-matrine

## 1.4.5      Matsunaga's synthesis of (±)-allomatridine

(±)-Allomatridine (±)-**1.5** was synthesised by Matsunaga *et al.* in 1970.[112] Oxoquinolizine **1.159** was used as starting material, which was prepared as described in previous work in 1969 in 2 steps and 37% yield.[113] Cyclization of oxoquinolizine **1.159** in the presence of polyphosphoric acid (PPA) provided keto-amide **1.160** in HBr (**Scheme 1.36**). Reduction of **1.160** using Adams' catalyst afforded a carboxamide **1.161**. Removal the carboxamide group from **1.161** to gave tricycle **1.162** under heating with conc. HBr. Formal cycloaddition of tricycle **1.162** with ethyl acrylate generated tetracycle **1.163**. Finally, reduction of tetracycle **1.163** using copper chromite catalyst (CuCr$_2$O$_4$) at high temperature gave (±)-allomatridine (±)-**1.5** in 70% yield. The identity of (±)-allomatridine was confirmed by mixed melting point, infrared comparison and elemental analysis. The synthesis was achieved in 5 steps and in 11% yield from oxoquinolizine **1.159**.
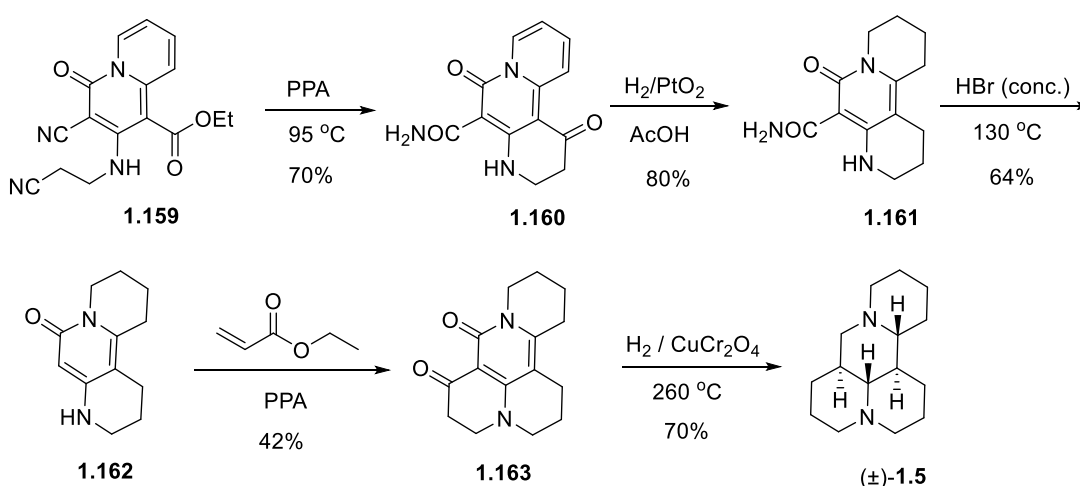


**Scheme 1.36**: Matsunaga's synthesis of (±)-allomatridine (±)-**1.5**

## 1.4.6      Chen's total synthesis of (±)-matrine

A synthesis of (±)-matrine ((±)-**1.138**) was published by Chen *et al*. in 1986 by employing an acetal mediated *N*-acyliminum ion cyclisation to assemble both the C and D rings of the natural product (**Scheme 1.37**).[107] Using the chemistry reported by Wenkert and Jeffcoat,[114] alkylation of nicotinonitrile **1.164** with 4-bromo-2-butanone ethyleneketal followed by hydrogenation led to piperidine **1.165** in 63% yield. Treatment of piperidine **1.165** with TsOH furnished quinolizidine derivative **1.166** through addition of the enol to the iminum ion intermediate in 15% yield (these yields were reported by Wenkert and Jeffcoat).[114] Reduction of the nitrile functionality of **1.166** using LiAlH$_4$ accessed primary amine **1.167**. Primary amine **1.167** was treated with glutaric anhydride to afford glutarimide intermediate **1.168** in 56% over 2 steps. The desired *N*-acyliminium cyclisation precursor **1.169** was obtained *via* the reduction of the imide moiety with L-selectride. The *N*-acyliminum cyclisation **1.170** was achieved using MsOH to generate the tetracyclic core **1.171**

of the natural product which was deprotected with aq. $H_2SO_4$ to give 8-oxomatrine (**1.172**) in 46%

yield over the three steps. The stereochemistry of 8-oxomatrine (**1.157**) was determined by single

crystal X-ray analysis. The synthesis of (±)-matrine was completed by reduction of oxomatrine **1.172**

followed by a Barton radical de-oxygenation in 23% yield. The synthesis was completed in 11 steps

with 1% overall yield.
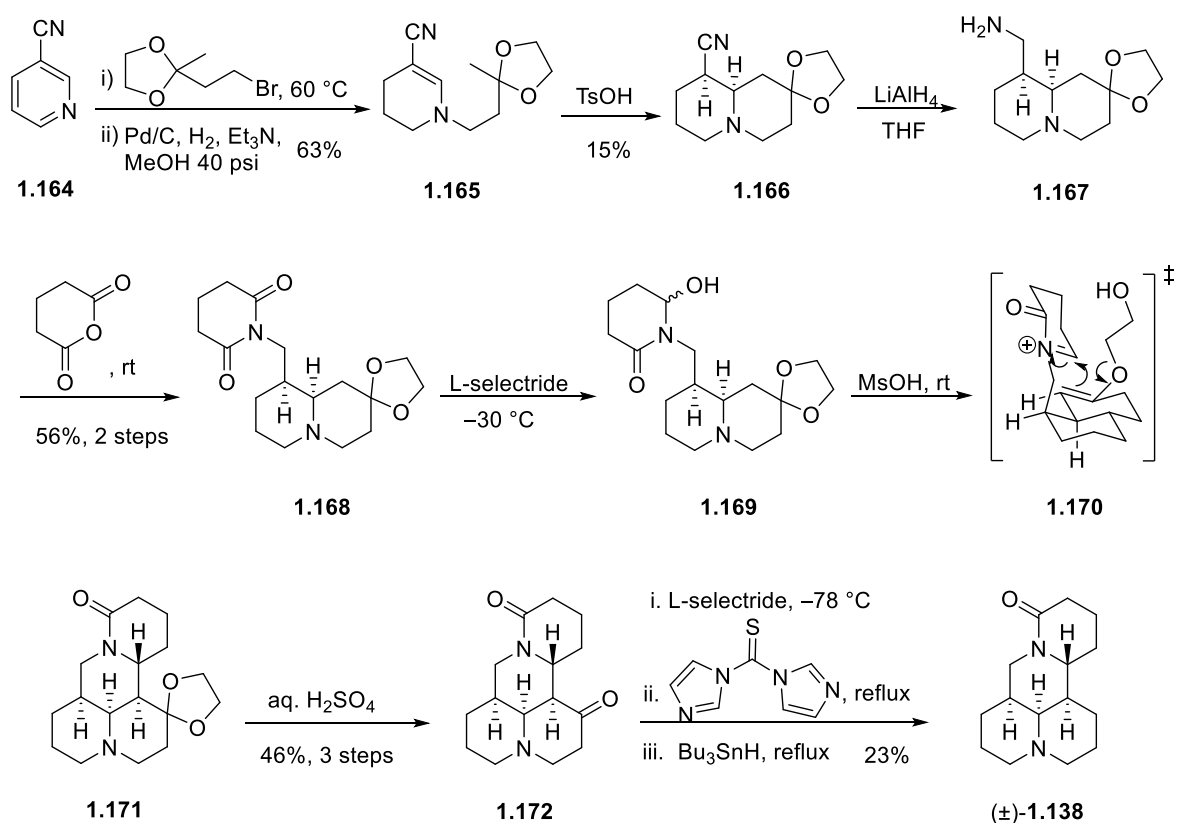


**Scheme 1.37**: Chen's total synthesis of (±)-matrine

### 1.4.7       Brown's total synthesis of (+)-allomatrine

The first stereocontrolled total synthesis of (+)-allomatrine ((+)-**1.139**) was accomplished in 2013 by Brown and co-workers (**Scheme 1.38**).[109] The synthesis was described utilising imino-aldol and *N*-acyliminium cyclisation reactions as key steps. The lithium enolate of phenyl 5-chlorovalerate (**1.173**) underwent addition to $\alpha,\beta$-unsaturated imine **1.174** to provide *syn* $\beta$-amino acid **1.175** in 75% yield as a single diastereoisomer. Removal of the *N*-sulfinyl protecting group using 1 equiv. of HCl produced the primary amine, and subsequent treatment with $K_2CO_3$ and NaI furnished the piperidine intermediate. *N*-Alkylation of this piperidine intermediate *in situ* with allyl bromide to give the piperidine derivative **1.176**. Reduction of ester **1.176** using $LiAlH_4$ afforded alcohol **1.177**, which was subjected to modified Mitsunobu reaction to introduce the azide functionality. Subsequent reduction using $LiAlH_4$ generated the primary amine **1.178**, which was treated with 5,5-dimethoxypentanoic acid in the presence of propylphosphonic anhydride coupling agent ($T_3P$) to secure the acyliminium cyclisation precursor **1.179**.
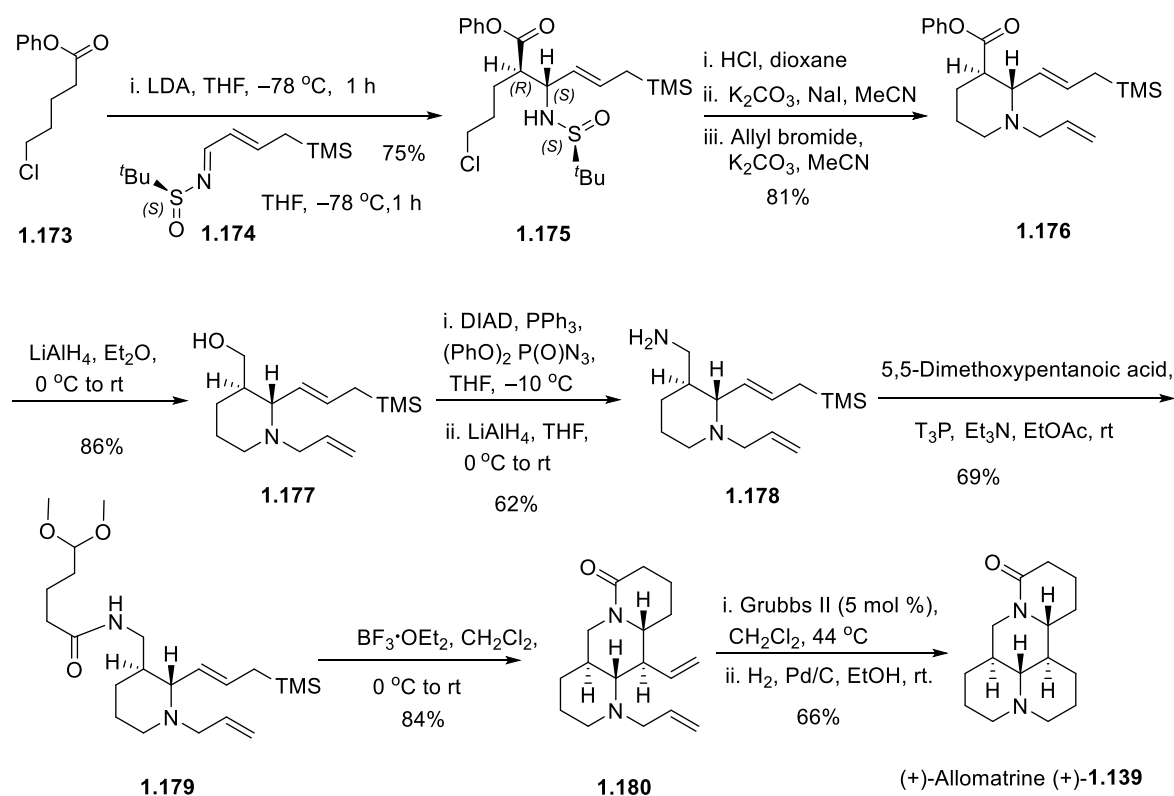


**Scheme 1.38**: Brown's synthesis of (+)-allomatrine

Employing the Lewis acid $BF_3 \cdot OEt_2$ with the intermediate **1.179** initiated a sequence of reactions and with addition of the TMS activated alkene onto the *in situ N*-acyliminium ion to form the tricycle **1.180**. Treatment of diene **1.180** with Grubbs II catalyst followed by hydrogenation over Pd/C accessed (+)-allomatrine (**1.139**). The first total synthesis of (+)-allomatrine was completed in 13 steps and 14% overall yield.

## 1.5    Epilupinine

This section describes synthetic strategies of early and recent synthetic interest in the quinolizidine alkaloids. (+)-Epilupinine ((+)-**1.1**) was reported to show *in vitro* inhibitory activity against P-388 (LD$_{50}$=28 µg/mL) and L1210 (LD$_{50}$ = 20 µg/mL) cell lines.[115] In recent years, quinolizidines have been employed as intermediates or pharmacophores in drug discovery. Many molecules bearing epilupinyl unit are antiviral, antiarrhythmic, antimalarial or platelet antiaggregation agents.[116-121] Due to its biologically important properties, and the fact that it is an excellent structure for validation of new synthetic methodology and strategy, (−)-epilupinine ((−)-**1.1**) and lupinine ((+)-**1.181**) have attracted great interest as targets for total synthesis.
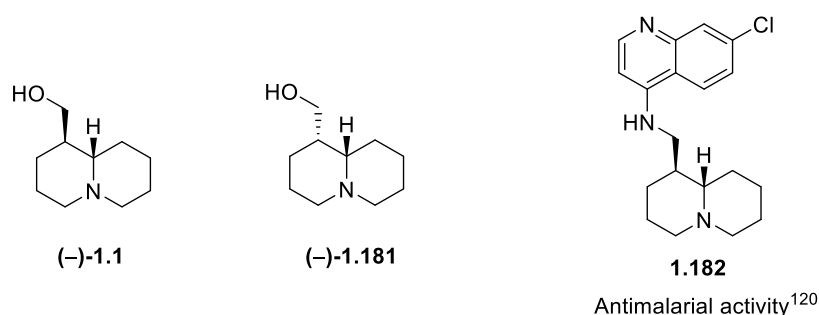


**Figure 1.8**: Structure of (−)-epilupinine ((−)-**1.1**) and (+)-lupinine ((+)-**1.181**) and **1.182**

### 1.5.1    Pohmakotr's synthesis of (±)-epilupinine and (±)-lupinine

A general synthetic route to 1-azabicyles was reported by Pohmakotr *et al*. in 2003 using $\alpha$-sulfinyl carbanions for intramolecular carbon-carbon bond forming reactions.[122] This approach relies on the capability of cyclic amides to undergo nucleophilic addition reactions. In 2008, Pohmakotr *et al.* prepared (±)-epilupinine ((±)-**1.1**) and (±)-lupinine ((±)-**1.181**) by *N*-alkylation of 2-piperidinone (**1.183**) with 4-bromobutylphenylsulfane (**Scheme 1.39**).[123] Subsequent oxidation of **1.167** using sodium periodate provided the sulfoxide **1.184**. Base promoted cyclisation of the sulfoxide produced **1.185**. Reduction of **1.185** using NaBH$_4$ and subsequent acylation using ethyl chloroformate yielded the sulfoxide **1.186** as a mixture of diastereoisomers. Elimination of sulfoxide from **1.186** afforded **1.187**, followed by reduction under appropriate conditions generated either (±)-epilupinine or (±)-lupinine.
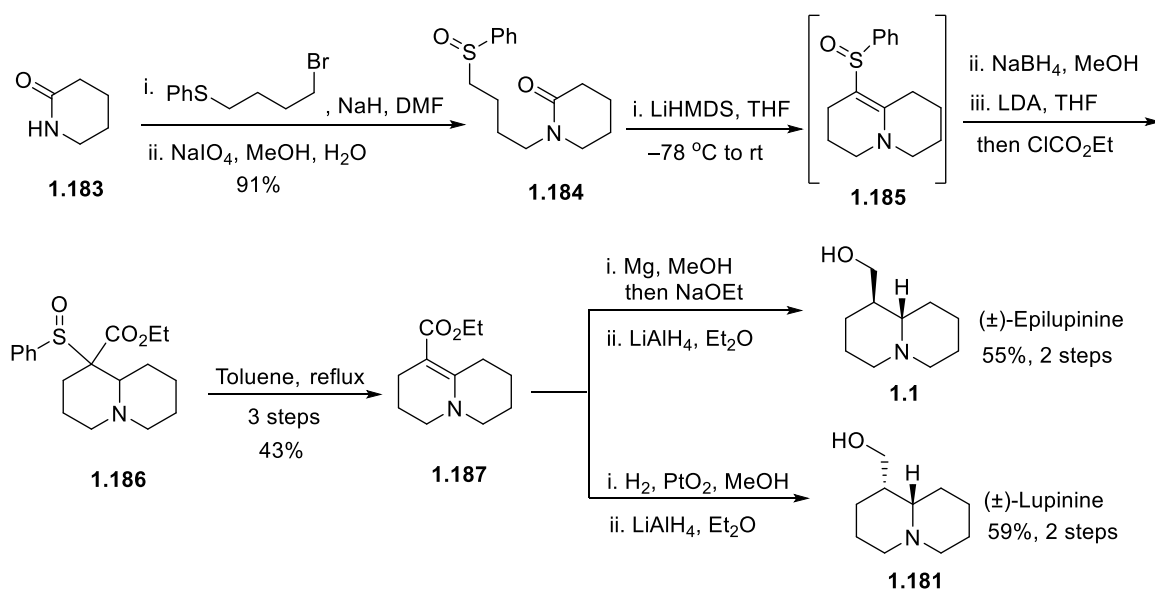
**Scheme 1.39**: Pohmakotr's synthesis of (±)-epilupinine and (±)-lupinine

Reduction of **1.187** with Mg in MeOH, and subsequent epimerization of the ester followed by LiAlH₄ reduction furnished (±)-epilupinine as a single diastereomer in 55% over two steps. Alternatively, access (±)-lupinine was through hydrogenation of **1.187** followed by ester reduction using LiAlH₄ to afford a single diastereomer in 59% over two steps.

## 1.5.2      Martin's synthesis of (±)-epilupinine,

Remuson reviewed *N*-acyliminium ions in the synthesis of alkaloids with a focus on products containing a piperidine ring.[124] Strategies using *N*-acyliminium ions can be very efficient and are generally attractive for their rapid formation of heterocyclic rings from acyclic precursors. A concise synthesis of (±)-epilupinine was developed by Martin and co-workers in 2009, which depends on the intramolecular allylation and *N*-alkylation of an imine (**Scheme 1.40**).[125]
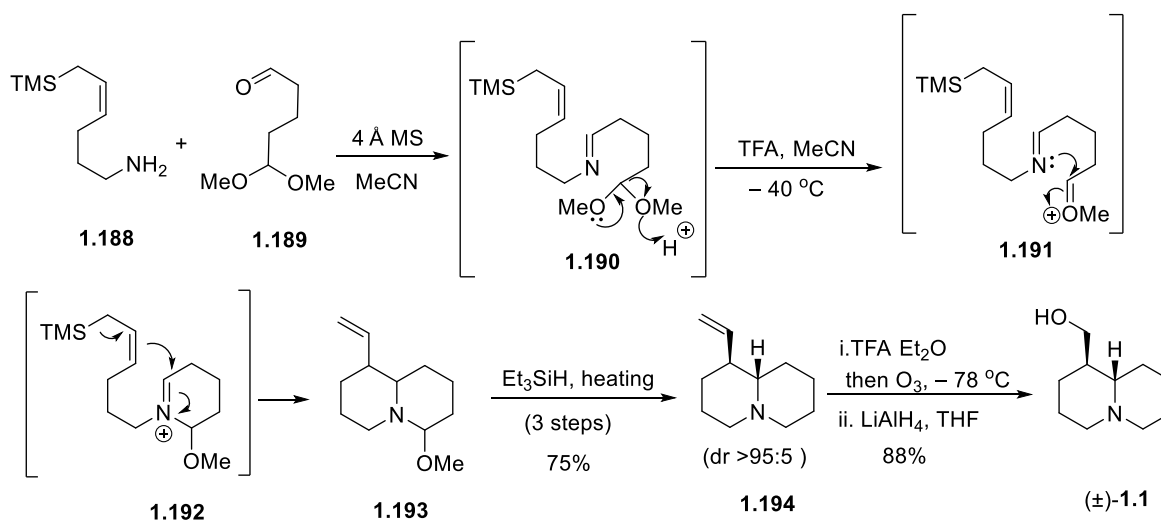


**Scheme 1.40**: Martin's synthesis of (±)-epilupinine

The synthetic approach started from the aminosilane **1.188**, which was prepared in 6 steps and 43%

yield by Speckamp in 1985.[126,127] Condensation of **1.188** with the mono protected dialdehyde **1.189**

(prepared in 2 steps and 48% yield)[128] afforded the corresponding imine **1.190**. Removal the

methanol group under acid conditions to afford oxonium ion **1.191**, which generated iminium ion

**1.192**. Intramolecular nucleophilic addition of the allylsilane to the iminium ion **1.192** produced the

bicyclic *N,O*-acetal **1.193** (not isolated). Triethylsilane (Et₃SiH) was added to the crude reaction

mixture to reduce **1.193** affording **1.194**. Ozonolysis of the TFA salt of **1.194** followed by reduction

of the corresponding aldehyde secured (±)-epilupinine ((±)-**1.1**). Overall, the synthesis of (±)-

epilupinine was achieved in 5 steps with 66% yield from the aminosilane **1.188** (Note that an

additional 6 steps were required to make **1.188**).

### 1.5.3    Hu and Wang's synthesis of (+)-epilupinine

A synthesis of (+)-epilupinine published in 2011 by Hu, Wang and co-workers utilised nitrile oxide

cycloaddition chemistry as the pivotal step (**Scheme 1.41**).[129] The known enantiopure 2-vinyl

piperidine **1.195** was used as starting point for their synthesis, which was prepared in 4 steps with

86% overall yield.[130] *N*-Alkylation of **1.195** with 3-chloropropanol and subsequent conversion of the

alcohol into the *N*-tosyl-O-TBS hydroxyl amine derivative **1.196** was achieved using the Fukuyama

procedure.[131]
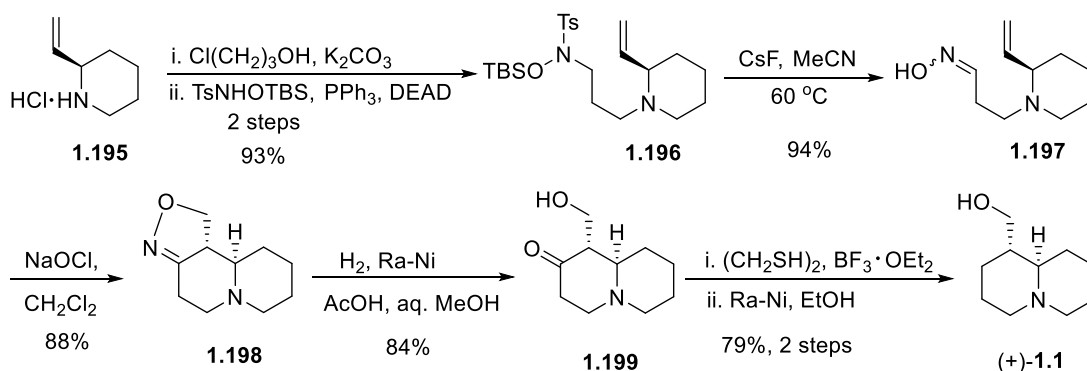


**Scheme 1.41**: Synthesis of (+)-epilupinine *via* an intramolecular nitrile oxide cycloaddition

Treatment of protected hydroxyl amine **1.196** with CsF generated the oxime **1.197**, which was

oxidised to the nitrile oxide **1.198** using NaOCl. The intramolecular [3+2] cycloaddition provided the

isoxazoline **1.198** as a single diastereomer. Reductive N-O bond cleavage followed by *in situ*

hydrolysis of the resulting imine gave the intermediate aldol **1.199**. Conversion of **1.199** to (+)-

epilupinine ((+)-**1.1**) was accomplished by dithiolane formation followed by desulfurisation using

Raney Ni. The synthesis of (+)-epilupinine was achieved in 9 steps and in 48% overall yield from

**1.195** (13 steps from commercial starting materials).

### 1.5.4        Szymoniak synthesis of (+)-epilupinine

In 2008, Szymoniak *et al.* published a synthetic strategy that applied a hydrozirconation / iodination / cyclization protocol for the formation of the piperidine ring in (+)-epilupinine.[132] In 2013, the same group also reported a synthesis of (±)-lupinine by employing a hydrozirconation cyclization of a functionalized pyridine moiety.[133] For the synthesis of epilupinine, enantiomerically pure amine **1.200** was used as the starting material. Conjugate addition of lithiated chiral amine **1.200** to the enoate **1.201** generated **1.202** as a single diastereomer (**Scheme 1.42**).
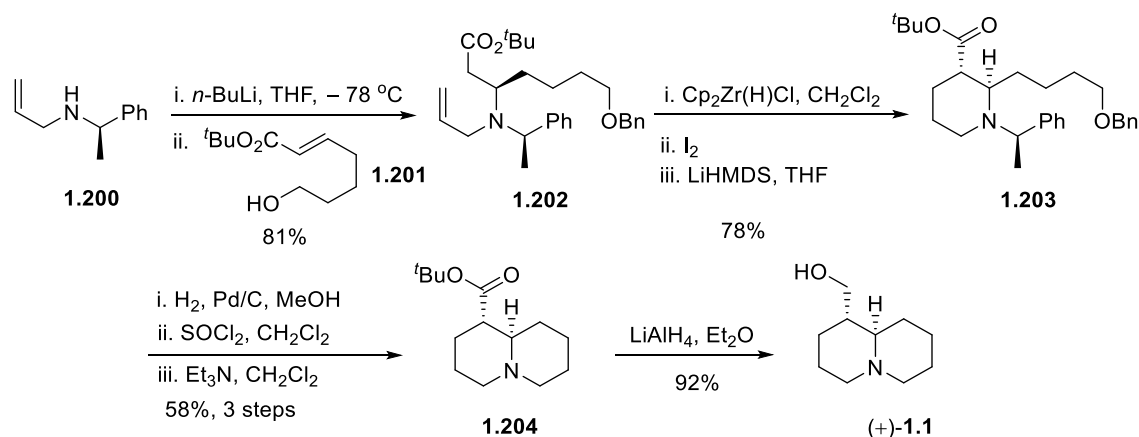


**Scheme 1.42**: Szymoniak synthesis of (+)-epilupinine

Hydrozirconation of the *N*-allyl group in **1.202** followed by treatment with iodine generated the corresponding primary iodide. Treatment of this iodoester intermediate with LiHMDS resulted in intramolecular alkylation of the ester enolate to provide piperidine **1.203**. This strategy was also used in the synthesis of other *trans*-2,3-disubstituted piperidines. Hydrogenolysis of **1.203** over Pd/C gave the corresponding amino alcohol, which was treated with SOCl$_2$ to give the corresponding primary chloride that cyclised to provide quinolizidine **1.204**. Finally, reduction of the ester **1.204** using LiAlH$_4$ gave (+)-epilupinine ((+)-**1.1**) in 92% yield. Overall, the synthesis involved 7 steps and proceeded in 34% yield. Additional steps were required to prepare the starting materials.

### 1.5.5        Brown's synthesis of (−)-epilupinine

In 2013 Brown and co-workers described the use of an imino-aldol reaction approach to the synthesis of (−)-epilupinine.[134] This strategy was efficient for the fused ring systems ([5, 6], [6, 6]) with varying degrees of substitution. Methodology involving cyclization of open chain precursors, where the stereochemistry has already been established, appears more commonly in the literature. The synthesis of (−)-epilupinine was reported twice by the Brown group beginning from two

different imines.[134,135] A stereoselective imino-aldol reaction of the enolate of phenyl 5-chloropentanoate (**1.173**) with halo imine **1.205** (**Scheme 1.43**) furnished *syn* imino-aldol adduct **1.206** in 70% yield and high diastereoselectivity. Deprotection of the *N*-sulfinyl auxilliary of **1.206** using conc. HCl followed by treatment with $K_2CO_3$ and NaI induced double cyclisation of the primary amine onto the chloroalkyl side chains to give bicycle **1.207**. The synthesis of (−)-epilupinine ((−)-**1.1**) was completed by reduction of the phenyl ester **1.207** to a primary alcohol using $LiAlH_4$ in just four steps and 15% overall yield.
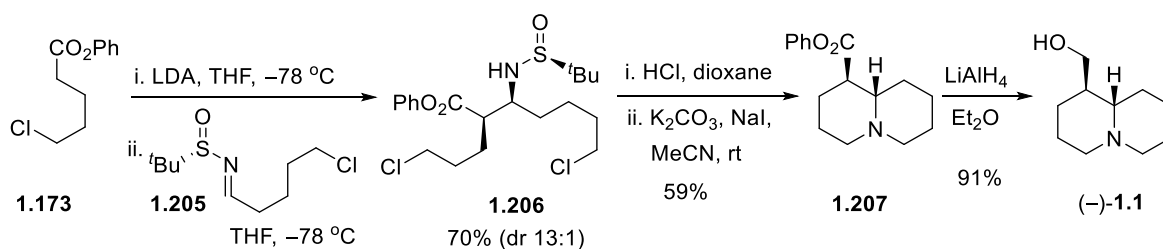


**Scheme 1.43:** Brown's synthesis of (−)-epilupinine from halo imine **1.205**

A second approach reported in a PhD thesis,[135] employed unsaturated sulfinylimine **1.208** with phenyl ester **1.173** in the presence of LDA to give *syn* imino-aldol adduct **1.209** in 80% yield and high diastereoselectivity (**Scheme 1.44**). Removal of *N*-sulfinyl group from *syn*-adduct **1.209** under acidic conditions and subsequent treatment with $K_2CO_3$ and NaI provided piperidine **1.210**. *N*-Alkylation of piperidine **1.210** with 4-bromo-1-butene afforded **1.211**, which was treated with Grubbs I catalyst to produce quinolizidine **1.212**. Reduction of ester **1.212** in the presence of $LiAlH_4$ gave **1.213** and hydrogenation over Pd/C completed the synthesis of (−)-epilupinine in seven steps and 39% overall yield. Although the overall yield for this route is higher, it should be noted that the earlier shorter route was not optimised.
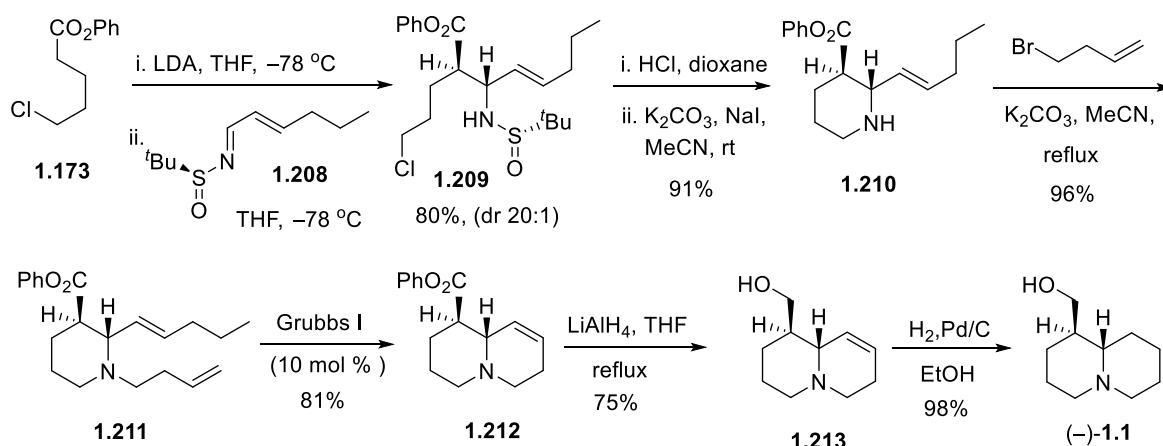


**Scheme 1.44**: Walkin and Brown's synthesis of (−)-epilupinine from unsaturated imine **1.208**

### 1.5.6        Kise's synthesis of (±)-epilupinine *via* electroreductive coupling

In 2013 Kise *et al*. reported the synthesis of (±)-epilupinine (±)-**1.1** using an electroreductive intramolecular cyclisation as a key step (**Scheme 1.45**).[136] Electroreductive coupling of glutarimide **1.214** in the presence of chlorotrimethylsilane (TMSCl) and subsequent de-silylation with TBAF provided bicycle **1.215**. Dehydration of cyclised ester **1.215** using *P*-TsOH in refluxing benzene afforded $\alpha,\beta$-unsaturated ketone **1.216**. Hydrogenation of **1.216** over Pd/C generated *syn* quinolizidine derivative **1.217** with good diastereoselectivity (dr 9:1). Oxidation of **1.217** under Baeyer-Villager conditions using trifluoroperacetic acid followed by reduction in the presence LiAlH$_4$ accessed (±)-epilupinine in six steps and in 34% overall yield from **1.214**.
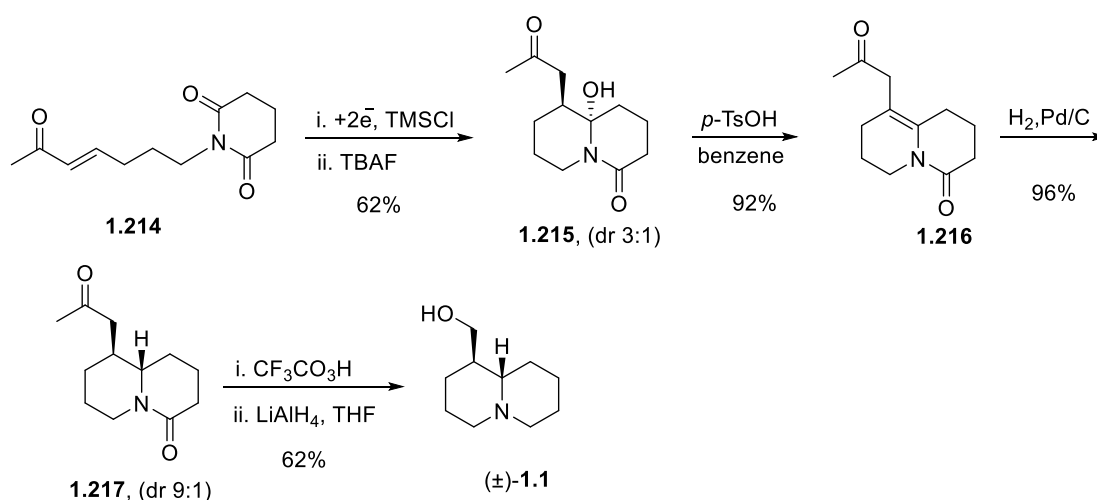


**Scheme 1.45**: Kise's synthesis of (±)-epilupinine *via* electroreductive coupling

### 1.5.7        Davies's synthesis of (+)-epilupinine *via* a double reductive cyclisation protocol

A concise asymmetric synthesis of (+)-epilupinine ((+)-**1.1**) was reported by Davies *et al.* in 2016 making use of double reductive cyclisation.[137,138] Intially (+)-eplupinine was obtained in low overall yield after several attempts through alkylation and double reductive cyclisation. However, a higher yielding synthesis of (+)-epilupinine was achieved *via* diastereoselective conjugate addition of (*R*) - **1.221** to $\alpha$-alkenyl substituted $\alpha,\beta$-unsaturated ester **1.220** (**Scheme 1.46**). Deprotonation of ester **1.218** using NaH and subsequent addition of but-3-enyl bromide provided ester **1.219**. Wadsworth-Emmons olefination of 5-hexenal with phosphonate **1.219** using an organomagnesium reagent as the base afforded $\alpha,\beta$-unsaturated ester **1.220** with moderate selectivity [(*E*):(*Z*)] (dr 3:1). The (*Z*)-configuration of $\alpha,\beta$-unsaturated ester **1.220** was not considered to be a problem because the lithium amide only undergoes conjugate addition to the (*E*)-stereoisomer. Conjugate addition of (*R*)-*N*-benzyl-*N*-($\alpha$-methylbenzyl) amide (*R*)-**1.221** to (*E*)-$\alpha,\beta$-unsaturated ester **1.220** was followed by addition of 2,6-di-*tert*-butylphenol to generate $\beta$-amino ester **1.222** as a single diastereoisomer

(dr >99:1). Oxidative cleavage of unsaturated $\beta$-amino ester **1.222** in the presence of OsO$_4$ and NaIO$_4$ with 2,6-lutidine gave dialdehyde **1.223**. *N*-Debenzylation and double reductive cyclization of dialdehyde **1.223** in the presence of H$_2$ at 5 atm, followed by reduction of the resulting azabicycle using LiAlH$_4$ furnished (+)-epilupinine. Overall, the synthesis was achieved in 6 steps and in 6% yield.



**Scheme 1.46**: Davies's synthesis of (+)-epilupinine *via* a double reductive cyclisation

# Chapter 2:    Results and Discussion

The development of general strategies towards bicyclic and tetracyclic lupin alkaloids using imino-aldol reactions is described in this chapter. In these strategies, imino-aldol adducts provide key backbones to access the desired lupin alkaloids (**Figure 2.1**).
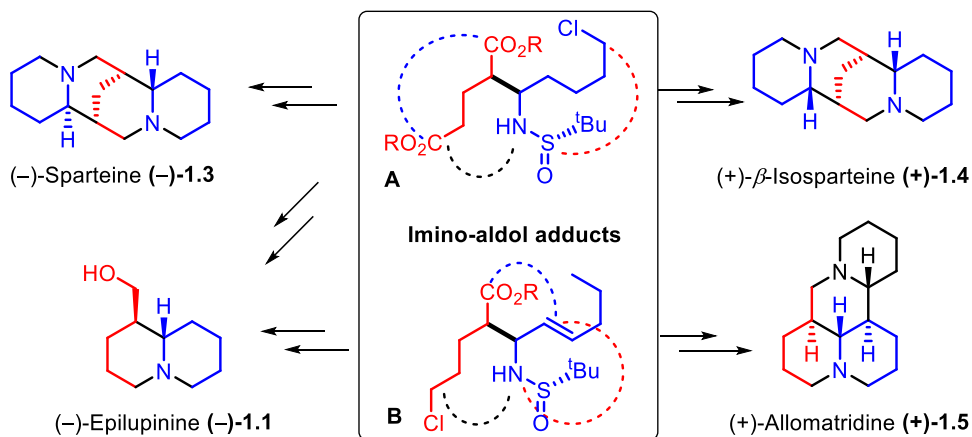


**Figure 2.1**: Overview of strategy towards the synthesis of lupin alkaloids

Synthetic pathways towards (+)-$\beta$-isosparteine ((+)-**1.4**), (−)-sparteine ((−)-**1.3**), (−)-epilupinine ((−)-**1.1**) and (+)-allomatridine ((+)-**1.5**) will be discussed from two different imino-aldol adducts **A** and **B**. The first strategy involves imino-aldol adduct **A** to access (+)-$\beta$-isosparteine, (−)-sparteine, and (−)-epilupinine. The second strategy investigates the use of a mono imino-aldol reaction to access (−)-epilupinine and (+)-allomatridine from imino-aldol adduct **B**.

## 2.1    Synthesis of the tetracyclic alkaloid (+)-$\beta$-isosparteine ((+)-1.4)

Our approach towards (+)-$\beta$-isosparteine ((+)-**1.4**) using a novel double imino-aldol reaction of glutaric acid diesters and imine derivatives is described in this section.

### 2.1.1    Retrosynthetic analysis of (+)-$\beta$-isosparteine

Our retrosynthetic analysis of (+)-$\beta$-isosparteine ((+)-**1.4**) led us to consider two approaches using two different *syn,syn* double imino-aldol adducts (**Figure 2.2** & **2.3**). The first approach involves cleavage of C-C bonds of the A and D rings in ((+)-**1.4**) (**Figure 2.2**). Ring closing metathesis (RCM) followed by hydrogenation and reduction would give (+)-$\beta$-isosparteine from tetraene **2.4**. Disconnection of *N*-homoallyl group from **2.4** and subsequent cleavage of the lactam bonds leads back to the *syn,syn* adduct **2.2**. The key intermediate is therefore double imino-aldol adduct **2.2**,

which may be obtained from two *syn*-selective imino-aldol reactions of diphenyl glutarate (**2.1**) with two equivalents of unsaturated imine **1.208**.
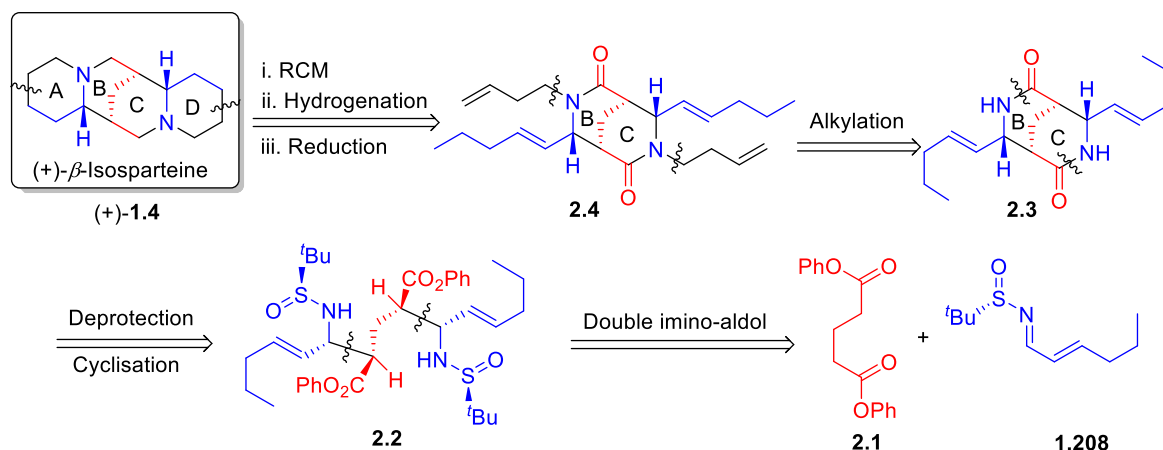
**Figure 2.2**: Retrosynthetic analysis of (+)-$\beta$-isosparteine from unsaturated imine **1.208**.

A shorter approach to $\beta$-isosparteine may be achieved by using halo imine **1.205** instead of unsaturated imine **1.208** (**Figure 2.3**). Cleavage of C-N bonds in (+)-$\beta$-isospartine led back to open chain double imino-aldol adduct **2.5** (**Figure 2.3**). Formation of the B and C rings will require cyclisation of **2.5** by deprotection of the *N*-sulfinyl groups and cyclisation onto the ester groups. Double imino-aldol adduct **2.5** requires two functionalised fragments **2.1** and **1.205**. Although this approach is clearly shorter and more attractive, both routes were initially investigated in parallel.
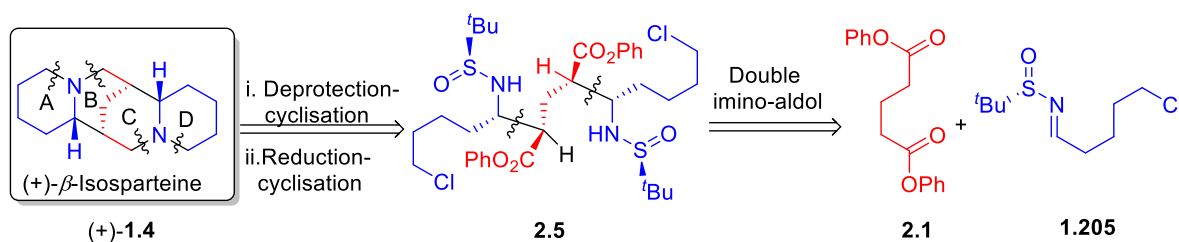
**Figure 2.3:** Retrosynthetic analysis of (+)-$\beta$-isosparteine from halo imine **1.205**.

### 2.1.2       Double imino-aldol reaction of glutarate esters

Double imino-aldol reactions of diesters of glutaric acid were investigated. Previous studies of the imino-aldol reaction by Brown and co-workers demonstrated that the choice of ester and the metal counter ion are both important in achieving high stereoselectivity.[134,135,139] During the current work we have used two different esters to generate lithium dienolates. Diastereoselectivity and isolation

of the major diastereoisomeric double imino-aldol products will be covered in this section. Initially, suitable functional groups and chain lengths in the imine were chosen that would ultimately allow access to (+)-$\beta$-isosparteine ((+)-**1.4**). In the first instance, our goal was to achieve high diastereoselectivity in the imino-aldol reaction between sulfinyl imine and dimethyl and diphenyl esters of glutaric acid *via* the corresponding lithium dienolates. Dimethyl glutarate (**2.7**) was prepared from glutaric acid (**2.6**) using oxalyl chloride and subsequent esterification in the presence of excess methanol in 90% yield. Diphenyl glutarate (**2.1**) was prepared in high yield by reaction of the diacid chloride with two equivalents of phenol under basic conditions in the presence of the phase transfer catalyst tetrabutylammonium chloride (TBAC) (**Scheme 2.1**).
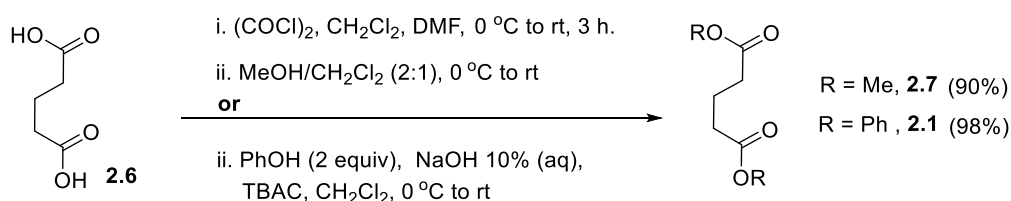


**Scheme 2.1**: Synthesis of diphenyl and dimethyl glutarates (**2.1** & **2.7**)

$\alpha,\beta$-Unsaturated sulfinyl imine **1.208** was conveniently prepared from condensation of commercially available starting materials *trans*-2-hexen-1-al (**2.10**) and *tert*-butyl sulfinamide (**2.9**) using a procedure described by Raghavan *et al*. (**Scheme 2.2**). Reaction of the sulfinamide **2.9** with aldehyde **2.10** in the presence of Ti(OEt)$_4$ in THF gave the required sulfinyl imine as the *trans* stereoisomer in excellent yield. A lower yield of 75% was obtained using CuSO$_4$ in CH$_2$Cl$_2$.[134]
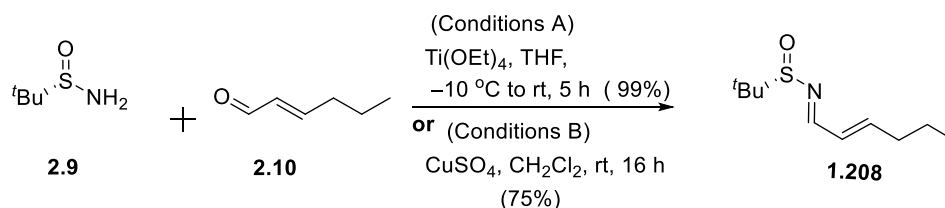


**Scheme 2.2**: Preparation of $\alpha,\beta$-unsaturated sulfinyl imine **1.208**

The double imino-aldol reaction of unsaturated sulfinyl imine **1.208** with dimethyl glutarate **2.7** was investigated using two equivalents of LDA to generate the dienolate in THF at −78 °C (**Scheme 2.3**). After 1 h of stirring at −78 °C, the imine **1.208** was then added dropwise and stirred for 1 h. The reaction mixture was quenched by dropwise addition of aq. NH$_4$Cl at −78 °C, then the crude material was purified by column chromatography to obtain the mixture of products and recovery of unsaturated imine **1.208**. The mixture of products was repeatedly purified by column chromatography to separate double imino-aldol adduct **2.8** in low yield along with a complex mixture of other products. The diastereoselectivity of double imino-aldol adduct **2.8** was found to

be low. Although the composition of the mixture of diastereoisomers of **2.8** was hard to determine by $^1$H NMR spectroscopy. However, the double imino-aldol adduct **2.8** was identified by MS spectrometry and characteristic peaks present in the $^1$H NMR spectrum. Based on this result, it was concluded that the use of dimethyl glutarate (**2.7**) in double imino-aldol reaction is not appropriate due to the poor stereoselectivity and low yields of 2.8.
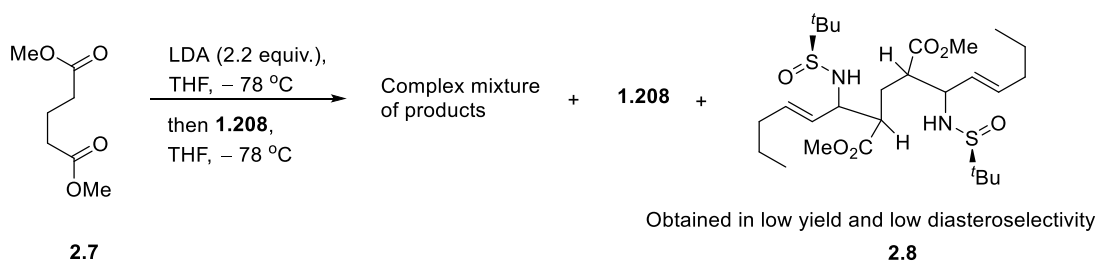


**Scheme 2.3**: Double imino-aldol reaction of dimethyl glutarate **2.7**

Due to the complex nature of the reaction product mixture and the difficulty in isolating any pure products, the double imino-aldol reaction of dimethyl glutarate (**2.7**) was not explored further. As anticipated from earlier studies in our laboratory, the diastereoselectivity of the double imino-aldol reaction may be significantly improved by employing diphenyl glutarate (**2.1**) in place of dimethyl glutarate (**2.7**). Therefore, diphenyl glutarate (**2.1**) was used for further studies described below.

### 2.1.3       Double imino-aldol reaction of diphenyl glutarate with unsaturated imine 1.208

A diastereoselective double imino-aldol reaction was first achieved using one equivalent of diphenyl glutarate (**2.1**), two equivalents of LDA and two equivalents of imine **1.208** at −78 °C (**Scheme 2.4**). It was found that allowing the imino-aldol reaction mixture to warm above −70 °C led to partial decomposition giving phenol and recovery of starting materials following work-up. The reaction was carefully quenched by dropwise addition of aq. NH$_4$Cl at −78 °C in order to avoid decomposition of the products, and then the solution was allowed to warm to rt. The *syn,syn* diastereoisomer **2.2** was obtained as a major product of the double imino-aldol reaction in 25% yield. The mono *syn* imino-aldol adduct **2.11** was also obtained in 12% yield. Fortunately, it was possible to recrystallise the double imino-aldol product **2.2** from hexane and its absolute stereochemistry was confirmed to be *syn,syn* by single crystal X-ray (**Figure 2.4**). Other imino-aldol products were also present in the crude reaction mixture. However, no other pure diastereoisomers were isolated from this reaction.
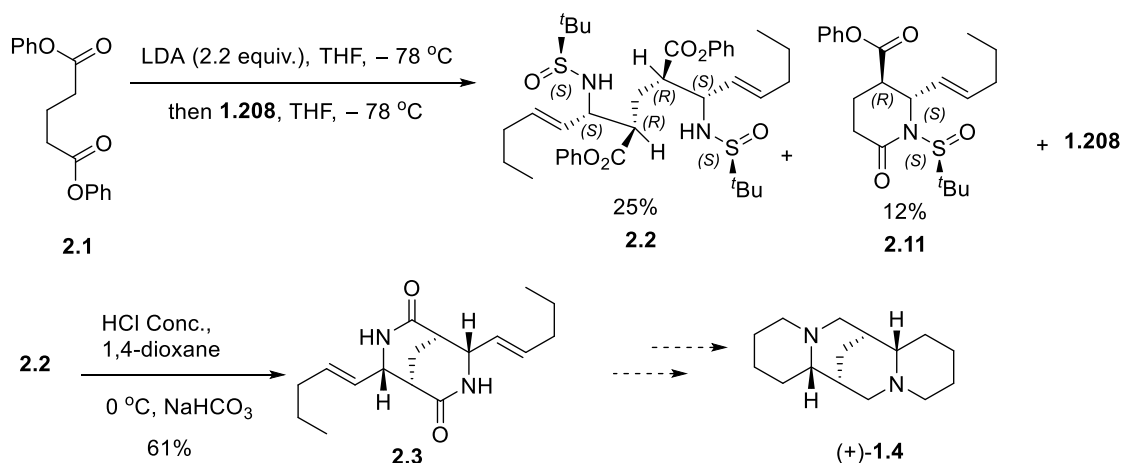
**Scheme 2.4**: Diastereoselective double imino-aldol adduct of unsaturated imine **1.208**
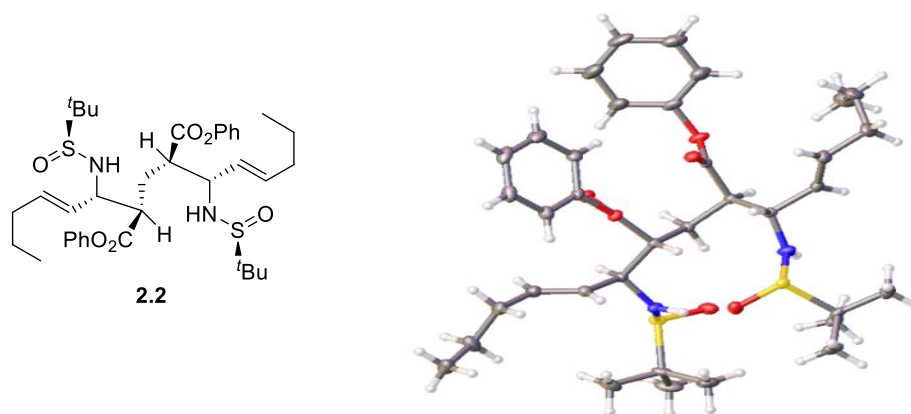


**Figure 2.4**: X-ray crystal structure of *syn,syn* double imino-aldol adduct **2.2**.

Deprotection and cyclisation of **2.2** using conc. HCl and subsequent neutralisation with saturated aq. NaHCO$_3$ gave *syn,syn* dioxo-bispidine **2.3**. Although high diastereoselectivity was achieved for the double imino-aldol adduct **2.2**, and its absolute stereochemistry was confirmed by X-ray, this route was not progressed further towards (+)-$\beta$-isosparteine as our attention turned to the shorter route using the chloroalkyl imine **1.205**, which is discussed in the following section.

### 2.1.4    A concise double imino-aldol approach to the synthesis of (+)-$\beta$-isosparteine

An alternative, short synthesis of (+)-$\beta$-isosparteine was investigated from diphenyl glutarate (**2.1**) and halo imine **1.205**. The requisite *tert*-butylsulfinyl halo imine **1.205** was obtained over two steps (**Scheme 2.5**). Reduction of commercially available methyl 5-chlorovalerate (**2.12**) with DIBAL-H afforded the corresponding aldehyde, which due to its volatility, was used without purification in

the next step. Condensation of the crude aldehyde with the chiral auxiliary **2.9** in the presence of Ti(OEt)$_4$ afforded halo imine **1.205** over two steps in 70% yield. Alternatively, halo imine **1.205** was formed in the presence of CuSO$_4$ in CH$_2$Cl$_2$ in 66% yield over two steps.



i. DIBAL-H, CH$_2$Cl$_2$, −78 °C, 45 min.

ii. Ti(OEt)$_4$, THF, then **2.9**, −10 °C to rt, 5 h   70%

**or**

ii. CuSO$_4$, CH$_2$Cl$_2$, then **2.9**, rt, 16 h     66%
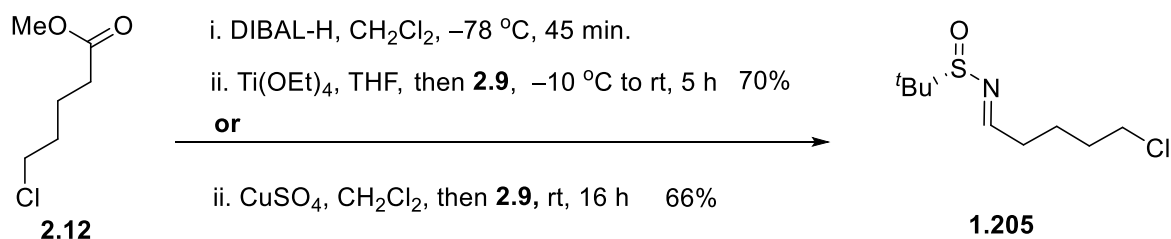
**Scheme 2.5**: Preparation of *tert*-butylsulfinyl halo imine **1.205**

The key double imino-aldol reaction was successfully achieved by adding two-equivalents of LDA to diphenyl glutarate (**2.1**) to form the corresponding dienolate, which was treated with halo imine **1.205** (**Scheme 2.6**). These conditions were adapted from the previous work conducted in Brown's group for related imino-aldol reactions. The *syn,syn* double imino-aldol adduct **2.5a** was obtained in 30% yield as a main product together with cyclised mono imino-aldol adduct **2.13** in 16% yield. In addition, a mixture of components including minor diastereomers of mono and double imino-aldol products was obtained. Although we obtained 30% yield of **2.5a**, and were able to continue the synthesis of (+)-$\beta$-isosparteine ((+)-**1.4**), we were keenly interested in optimizing the double imino-aldol reaction. This is discussed in the next section. The stereochemical determination of all the products from the imino-aldol reaction will also be discussed below.
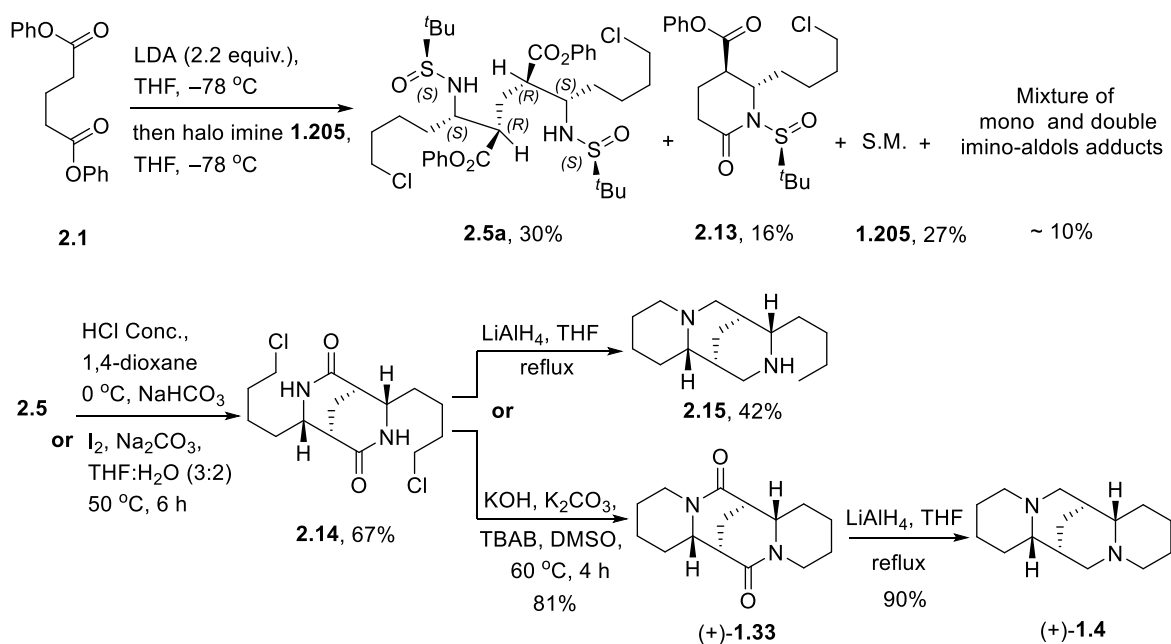


**Scheme 2.6**: The total synthesis of (+)-$\beta$-isosparteine ((+)-**1.4**) from halo imine **1.205**.

The chloroalkyl side chains present in **2.5** contained the functionality required to access *syn,syn* dioxo-bispidine **2.14** after double deprotection and cyclisation. Deprotection was achieved using either conc. HCl followed by neutralising with aq. $Na_2CO_3$, or under basic conditions using $I_2$ with $Na_2CO_3$ in THF:$H_2O$ (3:2) to give *syn,syn* dioxo-bispidine **2.14** in 67% yield. Reduction of dioxo-bispidine **2.14** using $LiAlH_4$ and final double cyclisation was expected to give access to (+)-$\beta$-isosparteine. Unfortunately, double concomitant reduction-cyclisation of bispidine **2.14** was unsuccessful due to dehalogenation of the alkyl halide side chain by $LiAlH_4$ giving the tricyclic derivative **2.15** as major product in 42% yield together with unidentified by-products.[140] At this stage, to gain selective access to (+)-$\beta$-isosparteine, either selective reduction of the lactams in **2.14** and double cyclisation is required, or cyclisation needs to be performed before reduction. Cyclisation of **2.14** was successfully carried out under basic conditions using phase transfer catalysis to provide (+)-10,17-dioxo-$\beta$-isosparteine ((+)-**1.33**) in good yield. The relative stereochemistry of dioxo-$\beta$-isosparteine was confirmed by single crystal X-ray crystallography after recrystallisation from hexane (**Figure 2.5**). (+)-10,17-Dioxo-$\beta$-isosparteine is also natural product, isolated in small quantity from *lupines sericeus* by Kinghorn *et al.* in 1982.[141] Initially, this natural product **1.33** was identified by GC/MS, and later confirmed by semi-synthesis.
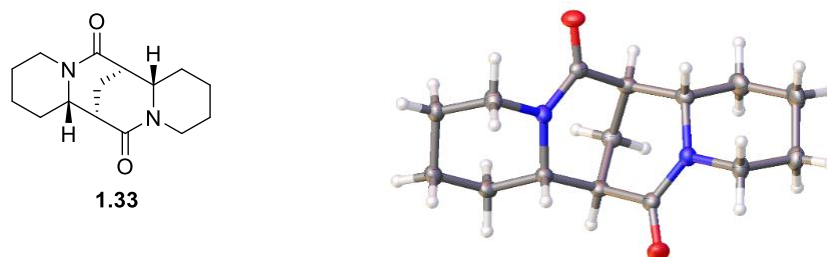


**Figure 2.5**: X-ray crystal structure of (+)-10,17-dioxo-$\beta$-isosparteine ((+)-**1.33**)

Finally, (+)-$\beta$-isosparteine ((+)-**1.4**) was obtained by reduction of bislactam **1.33** using $LiAlH_4$ under reflux in THF. The spectral and physical data for our synthetic (+)-10,17-dioxo-$\beta$-isosparteine and (+)-$\beta$-isosparteine are in excellent agreement with the values previously reported (**Table 2.1** and **Table 2.2**).[48,76,55] The optical rotation of (+)-10,17-dioxo-$\beta$-isosparteine ((+)-**1.33**) was not recorded previously in the literature due to the lack of material, or its preparation as a racemic product.

**Table 2.1**. $^{13}C$ NMR data for (+)-10,17-dioxo-$\beta$-isosparteine ((+)-**1.33**)



(+)-**1.33**

| Carbon | $\delta_C{}^a$ | Lit.[55] $\delta_C{}^b$ |
|--------|--------|--------|
| 10,17 | 169.0 | 169.2 |
| 6,11 | 60.4 | 60.6 |
| 2,15 | 43.5 | 43.6 |
| 9,7 | 42.5 | 42.7 |
| 5,12 | 32.2 | 32.3 |
| 3,14 | 25.3 | 25.4 |
| 4,13 | 24.9 | 25.0 |
| 8 | 18.7 | 18.9 |
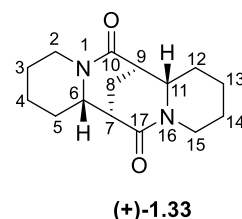
**Physical data:** m.p.= $170 - 172\,°C$

Lit.[15] m.p.= $173 - 173.5\,°C$

Lit.[55] m.p.= $172 - 174\,°C$

**Optical Rotation:**

*Recorded data current work:*

$[\alpha]_D$ : +47.3  (*c* 1.5, MeOH, 23 °C)

*Literature data:* not reported

$^a$ The current work: recorded in $CDCl_3$ at 101 MHz. $^b$ Recorded in $CDCl_3$ at 75 MHz.

**Table 2.2**. $^{13}C$ NMR data for (+)-$\beta$-isosparteine ((+)-**1.4**)



(+)-**1.4**

| Carbon | $\delta_C{}^a$ | Lit.[55] $\delta_C{}^b$ | Lit.[48] $\delta_C{}^c$ | Lit.[76] $\delta_C{}^d$ |
|--------|--------|--------|--------|--------|
| 6,11 | 62.8 | 63.0 | 63.3 | 62.8 |
| 2,15 | 55.2 | 55.3 | 55.9 | 55.1 |
| 10,17 | 55.0 | 55.1 | 55.7 | 54.9 |
| 9,7 | 34.5 | 35.6 | 35.6 | 34.4 |
| 5,12 | 28.8 | 28.8 | 29.4 | 28.6 |
| 3,14 | 25.5 | 25.6 | 26.4 | 25.4 |
| 4,13 | 22.7 | 22.8 | 23.6 | 22.6 |
| 8 | 19.8 | 20.0 | 20.6 | 19.8 |
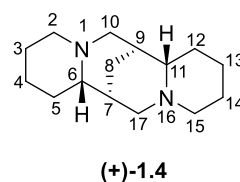
**Optical Rotation:**

*Recorded data current work:*

$[\alpha]_D$ : +15.1 (*c* 0.75 absolute EtOH, 23 °C)

*Literature data:*

$[\alpha]_D$ : + 15.38 (*c* 0.142,  absolute EtOH, 21.1 °C) Lit.[48]

$^a$ The current work: recorded in $CDCl_3$ at 101 MHz. $^b$ Recorded in $CDCl_3$ at 75 MHz. $^c$ Recorded in $CDCl_3$ at 125 MHz. $^d$ Not recoded.

**2.1.5      Optimisation of the double imino-aldol reaction**

For optimisation of the double imino-aldol reaction to improve the yield of the double imino-aldol adduct **2.5a**, we investigated different conditions (**Table 2.3**). Unfortunately, extensive investigation of different reaction conditions only gave a small increase in yield of the *syn,syn* double imino-aldol product **2.5a**. The best conditions included using 1 equiv. of diphenyl glutarate **2.1** and 2 equiv. of halo imine **1.205** in the presence 2.2 equiv. of LDA at – 80 to –78 °C, generating pure cyclised imino-aldol **2.13** in 16% yield, double imino-aldol **2.5a** in 30% yield, and recovery of stating halo imine **1.205** in 27% yield (entry 4). In addition, a complex mixture of products was obtained, which contained uncyclised-*syn* imino-aldol **2.16** and *anti* **2.17**, and a mixture of *anti,anti* **2.5b** and *syn,anti* **2.5c** double imino-aldol products. The analysis of this mixture will be discussed below.

**Table 2.3.** Optimisation of the double imino-aldol reaction.
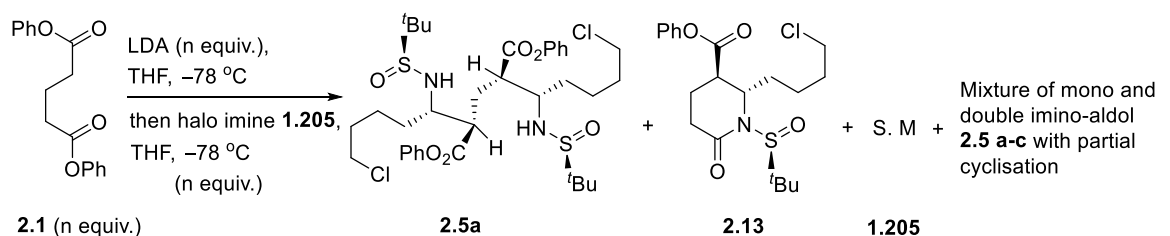


| | Diester 2.1 (equiv) | Imine 1.205 (equiv) | Base and (equiv) | Temp (°C) | Double 2.5a | mono 2.13 | S.M 1.205 | Mixture of by products[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.3 | 2 | LDA (2.6) | −78 | 26% | 22% | 34% | 22% |
| 2 | 1 | 2.2 | LDA (2.0) | −78 | 18% | 34% | 32% | 23% |
| 3 | 1 | 2 | LDA (2.0) | −78 | 20% | 22% | 30% | 26% |
| 4 | 1 | 2 | LDA (2.2) | −78 | 30% | 16% | 27% | 24% |
| 5 | 1 | 2 | LDA (3.0) | −78 | 25% | 20% | 35% | 27% |
| 6 | 1 | 2 | LHMDS (2.0) | −78 | 22% | 15% | 33% | 22% |
| 7 | 1 | 2 | LHMDS (2.0) | −78 - −70 | 9% | 23% | 32% | 23% |
| 8 | 1 | 2 | LDA (2.0) | −98 - −90 | 23% | 18% | 31% | 26% |
| 9 | 1 | 2 | LDA (2.0) | −78 - −70 | 13% | 25% | 34% | 26% |
| 10 | 1 | 2 | LDA (2.0) + DMPU | −78 | 24% | 19% | 30% | 25% |

[a] The mixture contained uncyclised-*syn* imino-aldol **2.16**, cyclised-*anti* **2.17**, *anti,anti* **2.5b** and *syn,anti* **2.5c** double imino-aldol products, the yield is estimated based upon the mw. of the major components.

### 2.1.6    Determination of the structures and stereochemistry of the major and minor products from the double imino-aldol reaction

In this section, we will describe the stages of separation and structural determination of the mixture of products from the double imino-aldol reaction. The first major components **2.5a** and **2.13** were directly isolated from the double imino-aldol reaction as pure compounds together with a mixture of minor imino-aldol products (**Scheme 2.7**). The recovered imine **1.205** was also isolated as a pure compound from the reaction mixture in 27% yield.
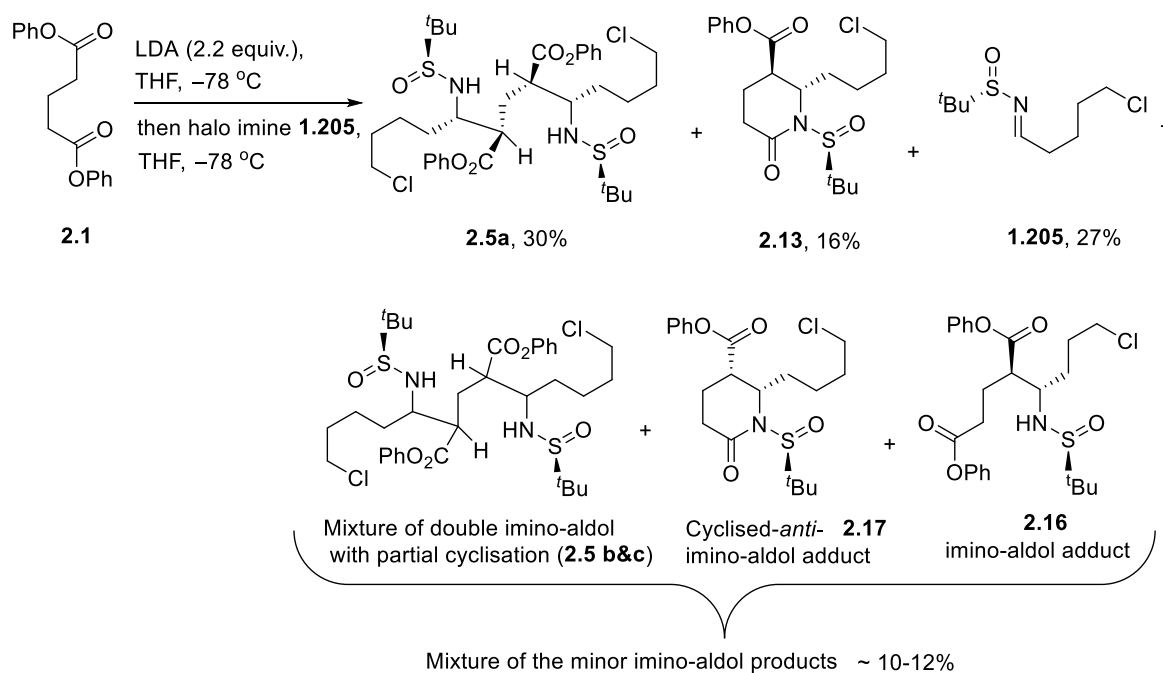


**Scheme 2.7**: The major and minor products from double imino-aldol reaction

Initially, we were not able to identify all the products from the double imino-aldol reaction due to their difficult separation by column chromatography. Careful separation of the reaction mixture by column chromatography gave two groups of imino-aldol products. The first group consists of mono imino-aldol products **2.13**, **2.16** and **2.17** while the other components are double imino-aldols (**2.5a**) *syn,syn* and the mixture of (**2.5b**) *anti,anti* and (**2.5c**) *syn,anti* diastereoisomers which had also undergone partial cyclisation (**Figure 2.6**). Due to the complexity of this mixture, repeated chromatographic separation and further reactions were required to fully elucidate their structures. The imino-aldol products **2.5a** and **2.13** were separated as major components by the first column chromatography, while the remaining mixture of imino-aldol adducts was separated by repeated column chromatography (**Figure 2.6**). After purification by column chromatography eluting with Et$_2$O / hexane (2:8 to 9:1), almost all imino-aldol products and mixture of products were separated as follows:

The first fraction is phenol, the second is halo imine **1.205**, the third is cyclised *syn*-mono **2.13**, the fourth is *syn* imino-aldol (uncyclised) **2.16** and the fifth is cyclised *anti*-mono **2.17**. The fractions of the mono imino-aldol adducts **2.16** and **2.17** were separable by repeated column chromatography. The next fractions isolated by careful column chromatography were shown to be (**2.5a**) *syn,syn* double uncyclised imino aldol as the major fraction and the last fraction is mixture of uncyclised (**2.5b**) *anti,anti* and (**2.5c**) *syn,*a*nti* double imino aldols, complicated due to some partial cyclisation. Since, the mixture of (**2.5b**) *anti,anti* and (**2.5c**) *syn,*a*nti* the double imino-aldol adducts were inseparable by column chromatography, this mixture was taken forwards in the next step of the synthesis by deprotection and cyclisation (**see Scheme 2.8**). Further analysis of the mixture of double imino-aldols is described in the next section.
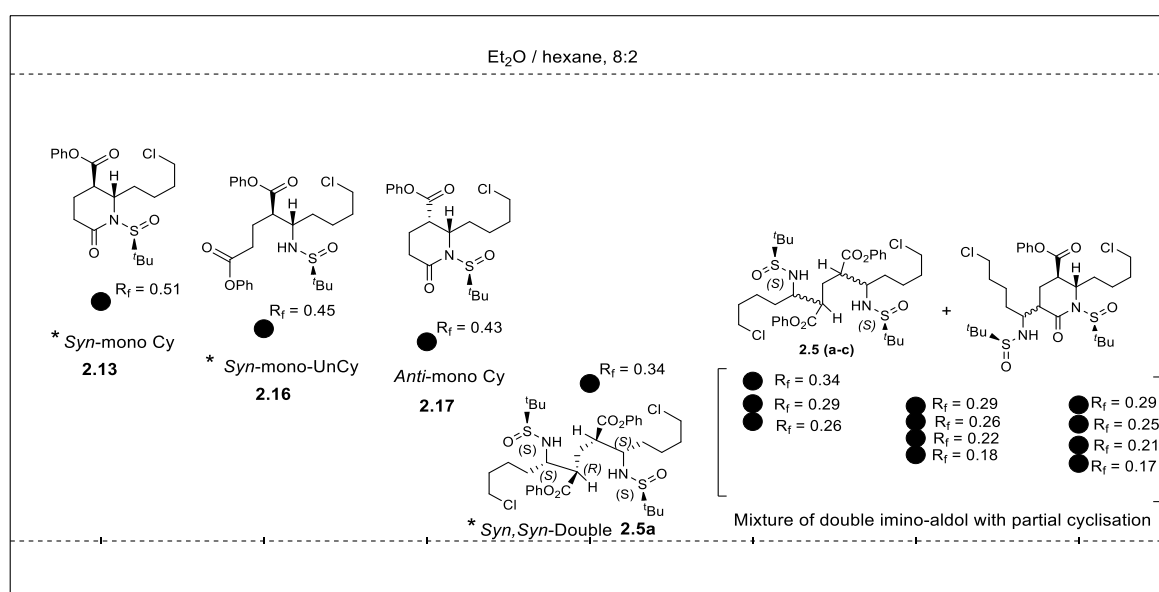


* The products of imino-aldol reaction **2.13**, **2.16** and **2.5a** were separated by careful column chromatography.

**Figure 2.6**: Representation of the TLC plate showing Rf values for different imino-aldol products

The structures of major imino-aldol adducts **2.5a** and **2.13** can be identified in the crude material by ^{1}H NMR spectroscopy (**Figure 2.7 B**). The inset figure A shows an expansion of characteristic peaks for the mono and double imino-aldol adducts **2.13** and **2.5a** respectively (**Figure 2.7 A**). From the crude ^{1}H NMR, it was difficult to determine the ratios of imino-aldol products due to significant overlapping signals. However, the presence of the minor products are indicated by the signals from the free N-H bonds (4-5 ppm) of double adducts **2.5a** and $\beta$-H of mono adducts **2.13** at (>4 ppm).
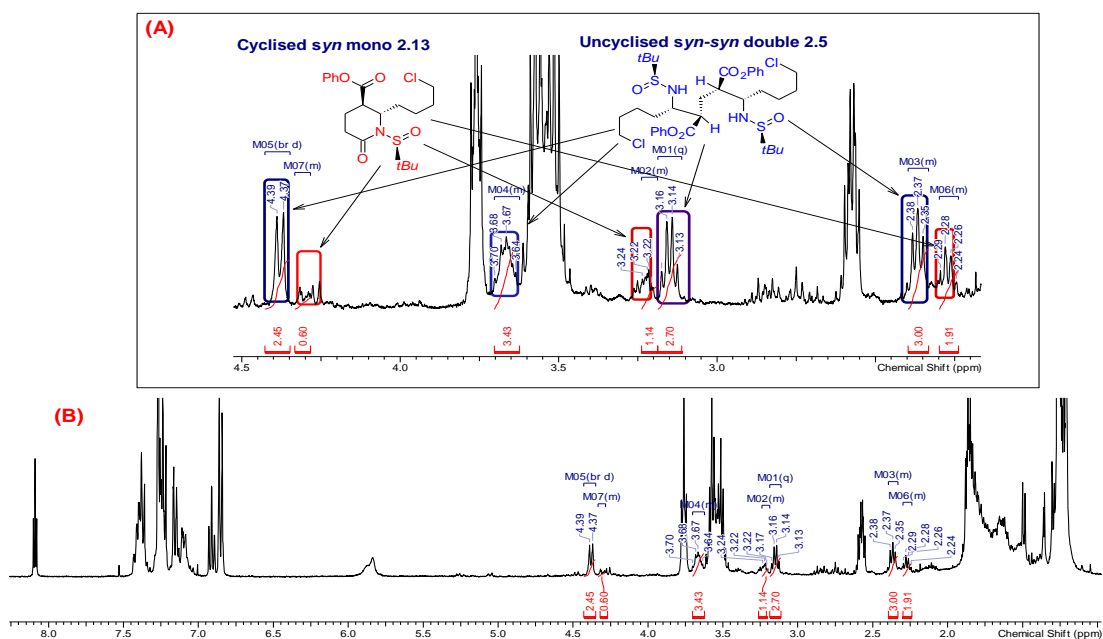
**Figure 2.7:** The ${}^{1}$H NMR spectrum of the crude double imino-aldol reaction mixture

The mixture of mono imino-aldol products was separated to give three components; the major product was the cyclised *syn* mono imino-aldol **2.13**, initially isolated as an oil. Fortunately, on storage in the freezer **2.13** gave crystals suitable for determining the stereochemistry by single crystal X-ray (**Figure 2.8**). The mono *syn* imino-aldol (uncyclised) **2.16** was also present as a minor product with some small amount of cyclised *anti*-mono **2.17**. The diastereoisomer of *syn*-imino-aldol adduct **2.16** was recrystallised from hexane and its structure confirmed by single crystal X-ray (**Figure 2.8**).
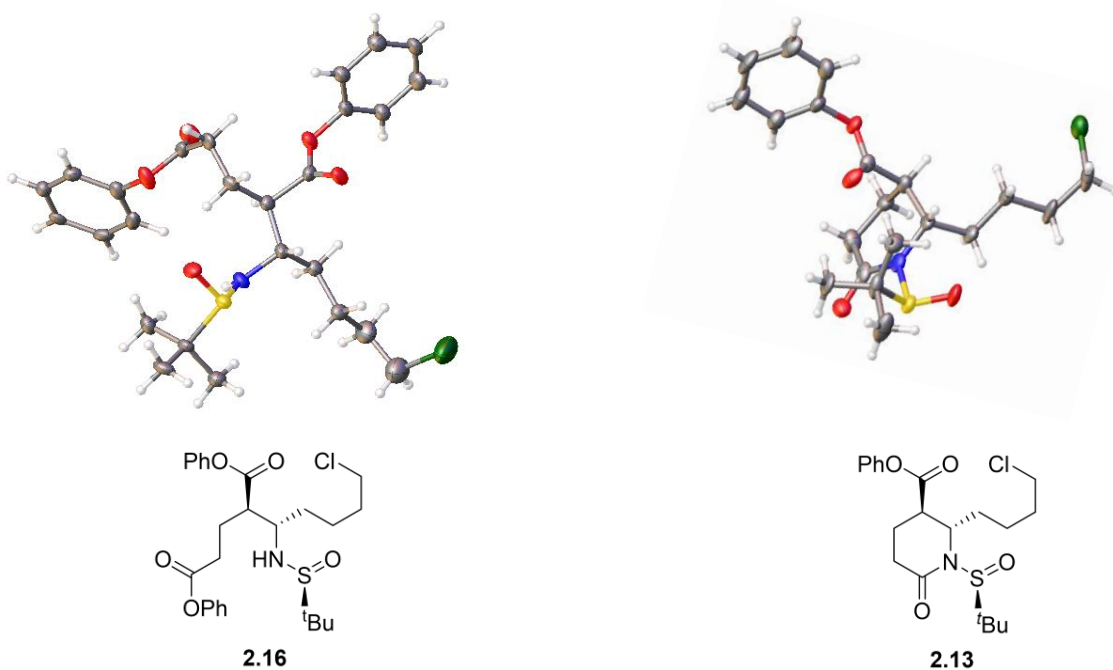


**Figure 2.8**: X-ray crystal structures of mono *syn* imino-aldol **2.16** and its cyclised product **2.13**

In different experiments the ratios of *syn*-mono imino-aldol **2.16** and its cyclised product **2.13** were found to vary, this can be seen by ^{1}H NMR spectroscopy (**Figure 2.9**). Several diagnostic chemical shifts were identified in the ^{1}H NMR spectra allowing identification of **2.16** and **2.13** in the crude mixtures. The N-H proton in mono imino-aldol **2.16** (labelled B) is observed as a 1 H doublet with a chemical shift of 4.20 ppm. During the course of the reaction a (dt) with chemical shift of 4.30 ppm was observed, which indicated formation of the cyclised adduct **2.13**. This ^{1}H NMR shift is consistent with the cyclisation of **2.16** to **2.13**, which proceeds slowly under the reaction conditions. Also, the $\beta$-methine proton of **2.16** labelled D is observed as a 1 H multiplet with a chemical shift of 3.28–3.21 ppm, and under the reaction conditions converted to (td, *J* = 5.7, 2.0 Hz, 1H) with a chemical shift of 3.21 ppm in **2.13**.
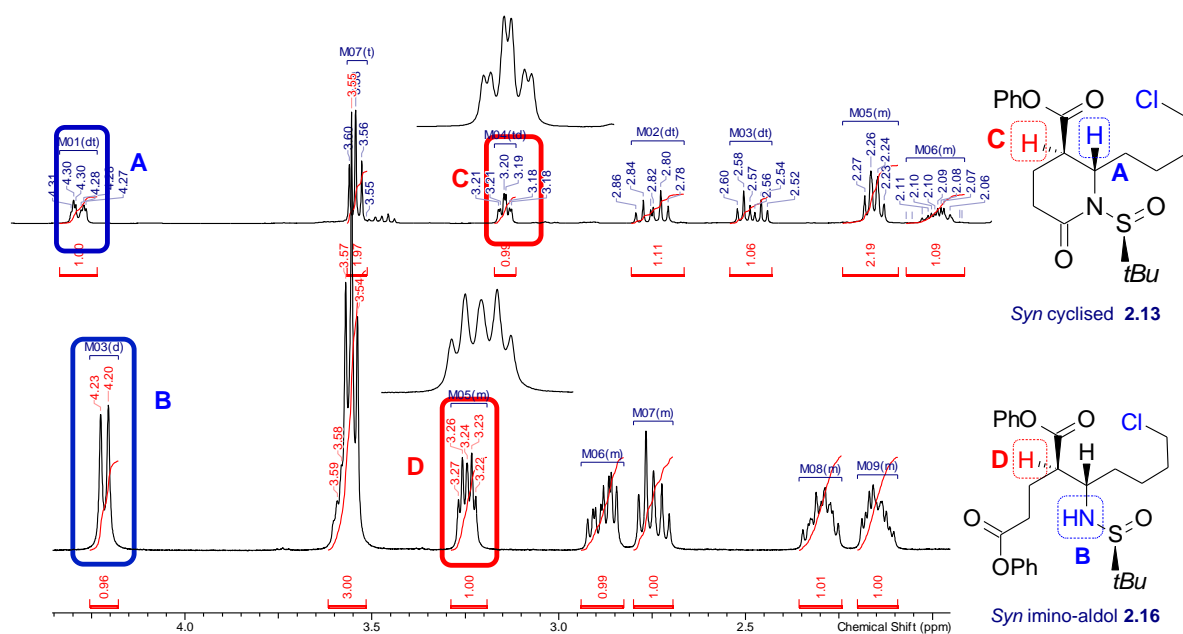


**Figure 2.9**: ^{1}H NMR spectra for mono *syn* imino-aldol **2.16** and its cyclised *syn* product **2.13**

Now that the structural and stereochemical determination of the products **2.5**, **2.13, 2.16** and **2.17** had been achieved. Attention moved on to the complex mixture of double imino-aldol products, which will be described in the next section.

### 2.1.7        Determination of the remaining structures from imino-aldol reaction

Having completed the first total syntheses of (+)-10,17-dioxo-$\beta$-isosparteine (+)-**1.33** and (+)-$\beta$-isosparteine (+)-**1.4**, work began to determine the structures of the remaining products from the double imino-aldol reaction. Despite the presence of multiple products, we succeeded in determining the stereochemistry of double imino-aldol adducts by a sequence of reactions and separations described below (**Scheme 2.8**).
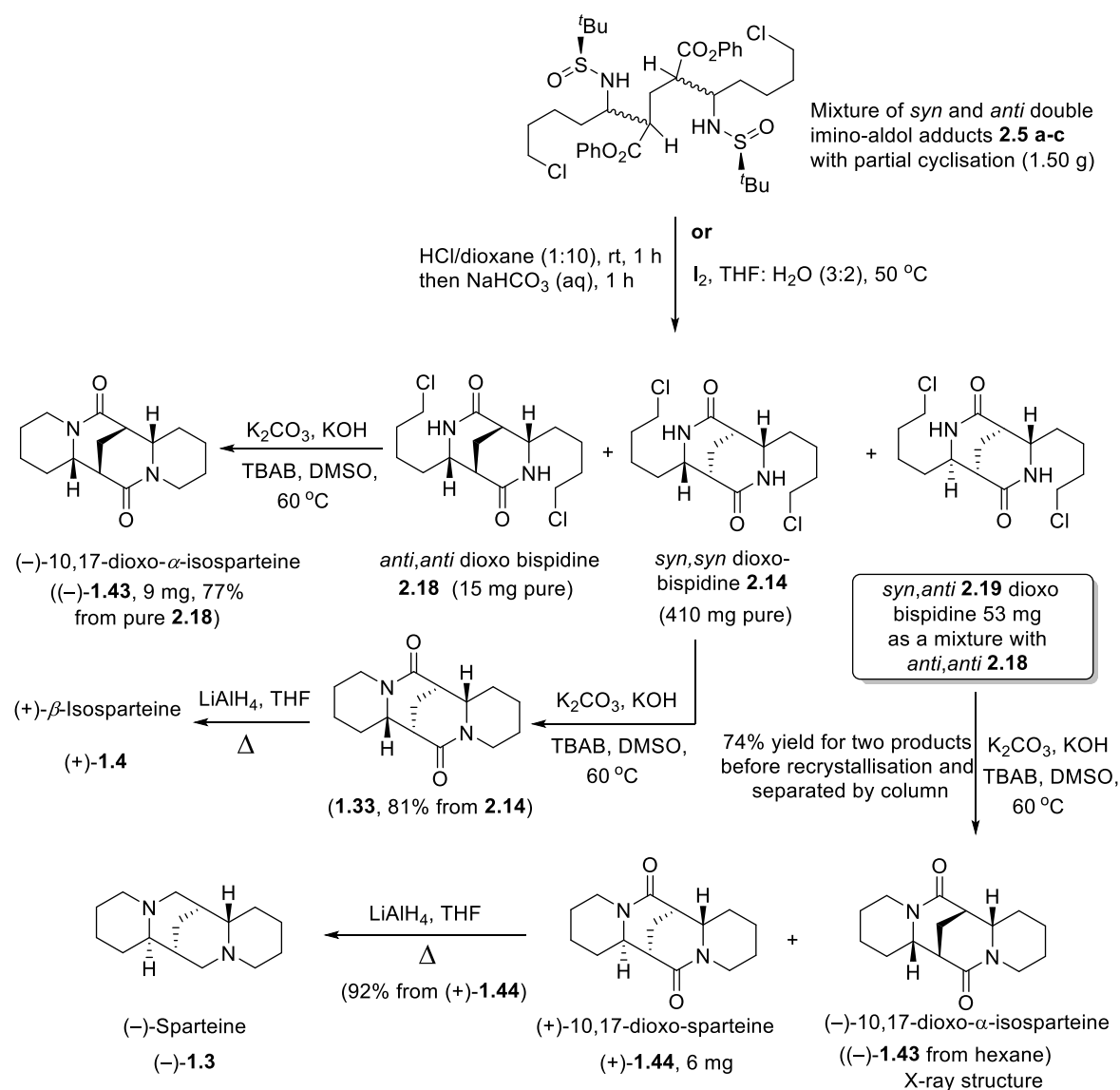


**Scheme 2.8**: Characterisation of the double imino-aldols by conversion to (−)-10,17-dioxo-$\alpha$-isosparteine and (−)-sparteine.

The mixture of double imino-aldol products was collected after separation from the mono imino-aldol adducts **2.13, 2.16** and **2.17** by careful column chromatography. The mixture of double imino-aldol products included uncyclised and partially cyclised components (*syn,syn* (**2.5a**), *anti,anti* (**2.5b**) and *syn,anti* (**2.5c**)).

Two methods for deprotection and cyclisation of the crude materials were used. The first involved deprotection of *N*-sulfinyl group of the mixture using conc. HCl followed by neutralisation with saturated aq. NaHCO$_3$. The second method used I$_2$ and THF:H$_2$O (3:2) (**Scheme 2.8**). Both methods gave similar results, which can be seen as three components by TLC (*eluent*: EtOAc/MeOH, 19:1) (**Figure 2.10**). Following column chromatography three fractions were separated; the first fraction is *syn,syn* dioxobispidine **2.14**, the second fraction *anti,anti* dioxobispidine **2.18** and the last fraction is *syn,anti* dioxobispidine **2.19**.
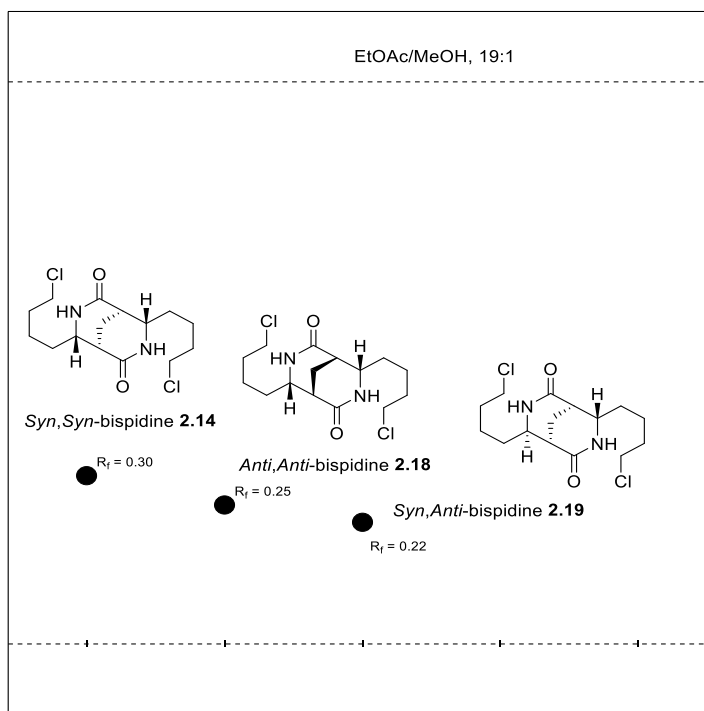


**Figure 2.10**: Representation of the TLC plate showing R$_f$ values for bicyclised products

*Syn,syn* dioxo-bispidine **2.14** and *anti,anti* dioxo-bispidine **2.18** were separated as pure diastereoisomers by careful column chromatography (silica gel, *eluent*: EtOAc/hexane 9:1 then EtOAc/MeOH, 19:1). While, *syn,anti* dioxo-bispidine **2.19** was isolated as a mixture contaminated with *anti,anti* **2.18**. Although it was not possible to separate the *anti,anti* and *syn,anti* bispidines **2.18** and **2.19** completely, cyclisation under basic conditions provided (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-**1.43**) as a crystalline solid from hexane. The X-ray structure confirmed the relative stereochemistry of (−)-**1.43**. Double cyclisation of the mixture of dioxo-bisbidines (**2.18**, **2.19**) under the same basic conditions afforded dioxo-sparteine diastereoisomers (**1.43**, **1.44**) in ratio of (10:1), which were separated by careful column chromatography (silica gel, *eluent*: EtOAc 100% then EtOAc/MeOH, 98:2 to 95:5) giving (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-**1.43**) as the less polar minor fraction and (+)-10,17-dioxosparteine ((+)-**1.44**) as the more polar fraction. The dioxosparteine isomers (**1.33**, **1.43** and **1.44**) were identified by analysis of their $^1$H-NMR spectra and the absolute stereochemistry of (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-**143**) was confirmed by optical rotation

(**Figure 2.11**). Finally, (−)-sparteine was obtained by reduction of (+)-10,17-dioxosparteine using LiAlH$_4$.
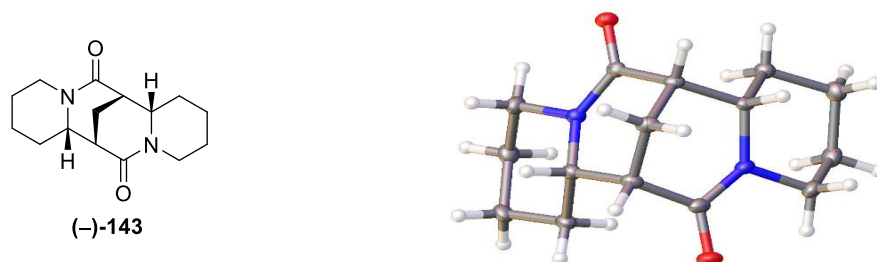


**Figure 2.11**: X-ray crystal structure of (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-**143**)

### 2.1.8 Determination of the absolute stereochemical assignment of sparteine isomers

The spectroscopic ($^1$H, $^{13}$C NMR and FT-IR), and physical data for our synthetic (+)-10,17-dioxo-sparteine and (−)-sparteine were consistent with literature values (**Table 2.4** and **Table 2.5**).[84,92] While optically pure 10,17-dioxo-$\alpha$-isosparteine has not been previously reported in the literature, melting point values were consistent with literature (**Table 2.6**).[15,66]

**Table 2.4**. $^{13}$C NMR data for (+)-10,17-dioxo-sparteine ((+)-**1.44**) and recorded physical data.

| Carbon | δC[a] | Lit.[84] δC[b] |
|--------|-------|-----------------|
| 17 | 170.2 | 170.2 |
| 10 | 166.4 | 166.3 |
| 11 | 60.0 | 59.9 |
| 6 | 59.2 | 59.1 |
| 15 | 43.4 | 43.3 |
| 9 | 42.8 | 42.7 |
| 2 | 42.3 | 42.2 |
| 7 | 42.0 | 41.9 |
| 12 | 32.6 | 32.5 |
| 5 | 31.2 | 31.2 |
| 14 | 25.1 | 25.1 |
| 3 | 25.0 | 24.9 |
| 13 | 24.9 | 24.8 |
| 4 | 24.2 | 24.1 |
| 8 | 21.9 | 21.8 |

[a] The current work: recorded in CDCl$_3$ at 101 MHz. [b] Recorded in CDCl$_3$ at 75 MHz.



(+)-**1.44**
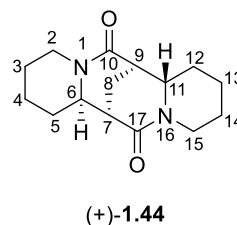
**Physical data:**
*Recorded data:* m.p. = 62 – 66 °C
*Literature data:* Lit.[84] m.p. = 60 – 65 °C

**Optical Rotation:**
*Recorded data current work:*
$[\alpha]_D$ : +70.3 (*c* 0.6, CH$_3$Cl, 20 °C)
*Literature data:*
$[\alpha]_D$ : +72.3 (*c* 1.0 in CH$_3$Cl, 20 °C) Lit.[84]

**Table 2.5**. $^{13}$C NMR data for (−)-sparteine ((−)-**1.3**) and recorded physical data

| Carbon | $\delta_C{}^a$ | Lit.[84] $\delta_C{}^b$ | Lit.[92] $\delta_C{}^c$ |
|--------|-------|----------|----------|
| 6 | 66.4 | 66.5 | 66.5 |
| 11 | 64.5 | 64.4 | 64.4 |
| 10 | 61.8 | 61.9 | 61.9 |
| 2 | 56.2 | 56.2 | 56.2 |
| 15 | 55.3 | 55.4 | 55.4 |
| 17 | 53.4 | 53.6 | 53.6 |
| 7 | 35.9 | 36.1 | 36.0 |
| 12 | 34.3 | 33.0 | 34.7 |
| 9 | 33.0 | 32.5 | 33.0 |
| 5 | 29.3 | 29.3 | 29.3 |
| 8 | 27.5 | 27.6 | 27.6 |
| 3 | 25.8 | 25.9 | 25.9 |
| 14 | 25.6 | 25.8 | 25.8 |
| 4 | 24.6 | 24.8 | 24.8 |
| 13 | 24.4 | 24.7 | 24.7 |
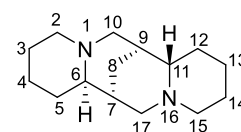


(−)-**1.3**

**Optical Rotation:**

*Recorded data current work:*

$[\alpha]_D$ : −16.9 (*c* 0.5 absolute EtOH, 20 °C)

*Literature data:*

($[\alpha]_D$ −18.1 (*c* 1.3 in EtOH)) Lit.[84] ; ($[\alpha]_D$ −20.4 (*c* 1.3 in EtOH) Lit.[92]

$^a$ The current work: recorded in CDCl$_3$ at 101 MHz. $^b$ Recorded in CDCl$_3$ at 75 MHz. $^c$ Recorded in CDCl$_3$ at 100.6 MHz.

**Table 2.6**. $^{13}$C NMR data for (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-**1.43**) and recorded physical data

| Carbon | $\delta_C{}^a$ |
|--------|-------|
| 10,17 | 167.9 |
| 6,11 | 58.8 |
| 2,15 | 42.4 |
| 7,9 | 41.8 |
| 5,12 | 31.3 |
| 3,14 | 25.2 |
| 8 | 24.4 |
| 4,13 | 24.3 |

**Physical data:**

*Recorded data:* m.p. = 160 − 164 °C

*Literature data:*

  Lit.[15,66] m.p.= 159 − 160 °C

**Optical Rotation:**

*Recorded data current work:*

$[\alpha]_D$ : −58.8 (*c* 1.0, MeOH, 20 °C)

*Literature data:*   Not recorded
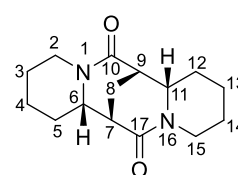


(−)-**1.43**

$^a$ The current work: recorded in CDCl$_3$ at 101 MHz.

### 2.1.9      Elaboration of *syn* mono imino-aldol product towards a synthesis of (–)-sparteine

In this section, attempts to synthesise sparteine from *syn* mono imino-aldol adduct **2.16** will be described. Exploitation of the *syn* mono imino-aldol adduct **2.16** as a starting point to access (–)-sparteine requires a second imino-aldol reaction with *anti*-selectivity (**Figure 2.12**). The imino-aldol reaction requires deprotonation of adduct **2.16** in the presence of a suitable base followed by selective alkylation using halo imine to give *syn*,*anti* (**2.5c**) double imino-aldol. Deprotection of the sulfinyl groups and then cyclisation could give access to dioxo-sparteine **1.44**. Finally, reduction of dioxo-sparteine would complete a synthesis of sparteine.
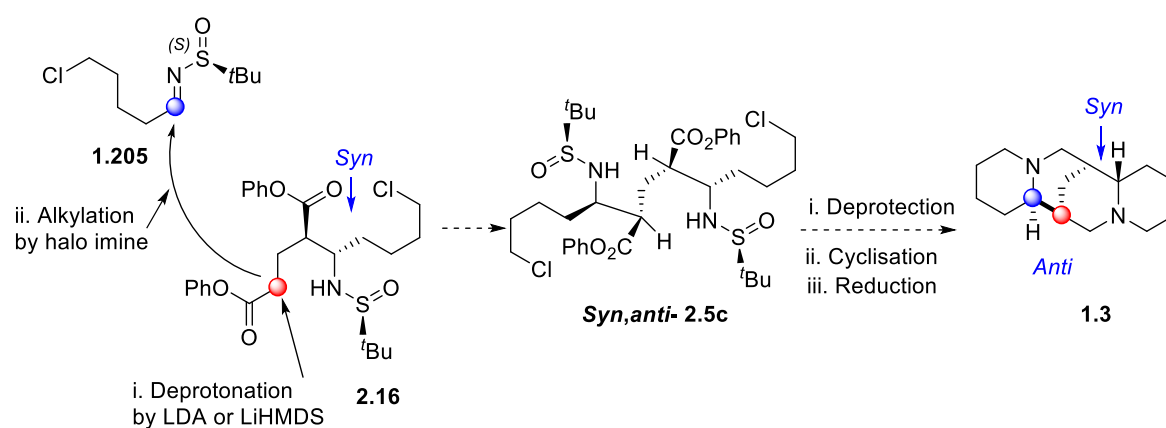


**Figure 2.12**: Proposed synthesis of (–)-sparteine from *syn* imino-aldol adduct **2.16**

Although *syn* imino-aldol **2.16** was only obtained as a minor product from different imino-aldol reactions in yields from 5 to 15%, we wished to use it as a starting point to access sparteine. We would need to go back and optimise the formation of **2.16** later if this route to sparteine proved to be successful. Formation of **2.23** required deprotonation of **2.16** using two equivalents of base to form the dianion followed by dropwise addition of one equivalent of halo imine **1.205** at −78 °C (**Scheme 2.9**). The crude mixture of products was separated by column chromatography giving different components which were difficult to identify. Several imino-aldol reactions were performed using LDA or LiHMDS giving different products including; cyclised-*syn* **2.13**, partially cyclised double imino-aldol **2.20**, double imino-aldol **2.5a** and recovered halo imine **1.205**. The major product **2.20** was identified firstly by mass spectrometry (MS) as a partially cyclised.
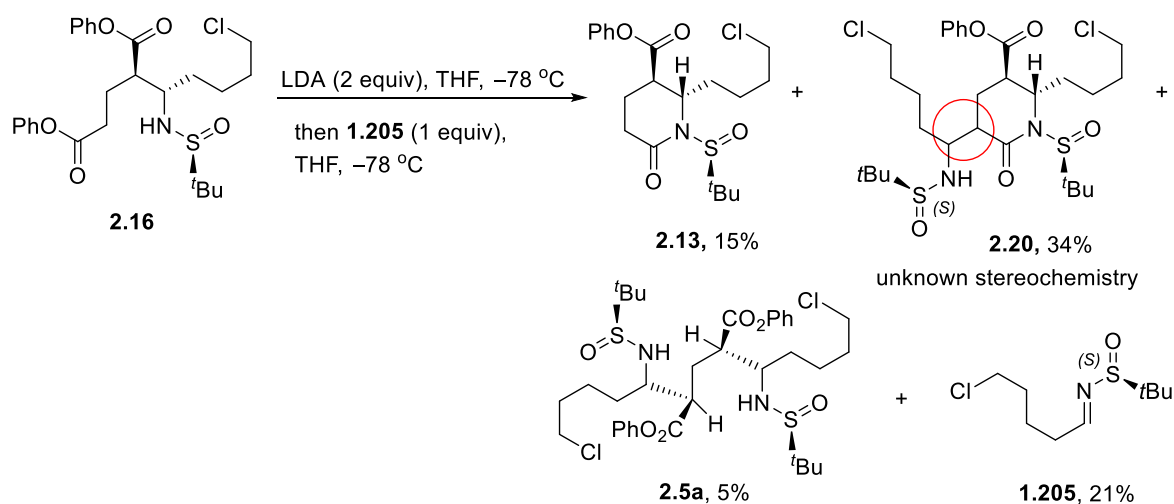
**Scheme 2.9**: Imino-aldol reaction of *syn* mono imino-aldol adduct **2.16**

The imino-aldol products were obtained in better yield by using LDA compared to LiHMDS. Unfortunately, we were not able to identify the stereochemistry of the double imino-aldol product **2.20** from analysis of their $^1$H NMR spectra. The main double imino-aldol product **2.20** was forwarded to the next step to form bispidine by deprotection and cyclisation under acidic conditions (**Scheme 2.10**), as described below.
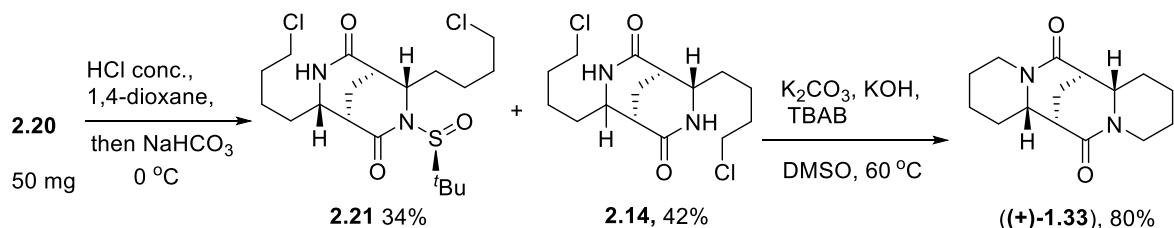


**Scheme 2.10**: The synthesis of (+)-10,17-dioxo-$\beta$-isosparteine from imino-aldol adduct **2.20**

Deprotection and cyclisation of the partial cyclised adduct **2.20** under acidic conditions and then NaHCO$_3$ afforded bispidine **2.14** and mono protected bispidine **2.21** (**Scheme 2.10**). The stereochemistry of both bispidines **2.14** and **2.21** were shown clearly by $^1$H NMR. Cyclisation of both bispidines **2.14** and **2.21** under basic conditions using phase transfer catalyst TBAB gave impure dioxo-$\beta$-isosparteine. The stereochemistry of dioxo-$\beta$-isosparteine confirms the stereochemistry of the cyclised double imino-aldol adduct **2.20** and bispidine **2.14**, and it also validates the stereoselectivity assumptions regarding imino-aldol reaction of adduct **2.16**, ultimately leading to the synthesis of (+)-10,17-dioxo-$\beta$-isosparteine, rather than (+)-10,17-dioxo-sparteine (**Figure 2.12**).

## 2.1.10       Conclusions:

The total synthesis of (+)-$\beta$-isosparteine was achieved in 15% yield over 4 steps from halo imine **1.205** by using a diastereoselective double imino-aldol reaction (**Scheme 2.11**). The double imino-aldol reaction was carried out using diphenyl glutarate (**2.1**) and halo imine **1.205** to generate four stereocentres within double imino-aldol adduct **2.5a** with *syn,syn* relative stereochemistry in 30% yield. In addition, *syn* and *anti*-cyclised mono imino-aldol adducts (**2.13** & **2.17**), and mixture of double imino-aldol adducts (**2.5a-c**) were obtained as minor products. The stereochemistry of the minor double imino-aldol adducts (**2.5b** & **c**) have been investigated in order to determine their stereochemistry, and shown to be (*anti,anti* **2.5b** and *syn,anti* **2.5c**). The stereochemistry of *anti,anti*-product **2.5b** provides the skeleton of (+)-$\alpha$-isosparteine whose stereochemistry was confirmed by single crystal X-ray after conversion to (+)-10,17-dioxo-$\alpha$-isosparteine. The synthesis of (−)-sparteine from the minor product *syn,anti* diastereoisomer **2.5c** confirmed its relative and absolute stereochemistry.
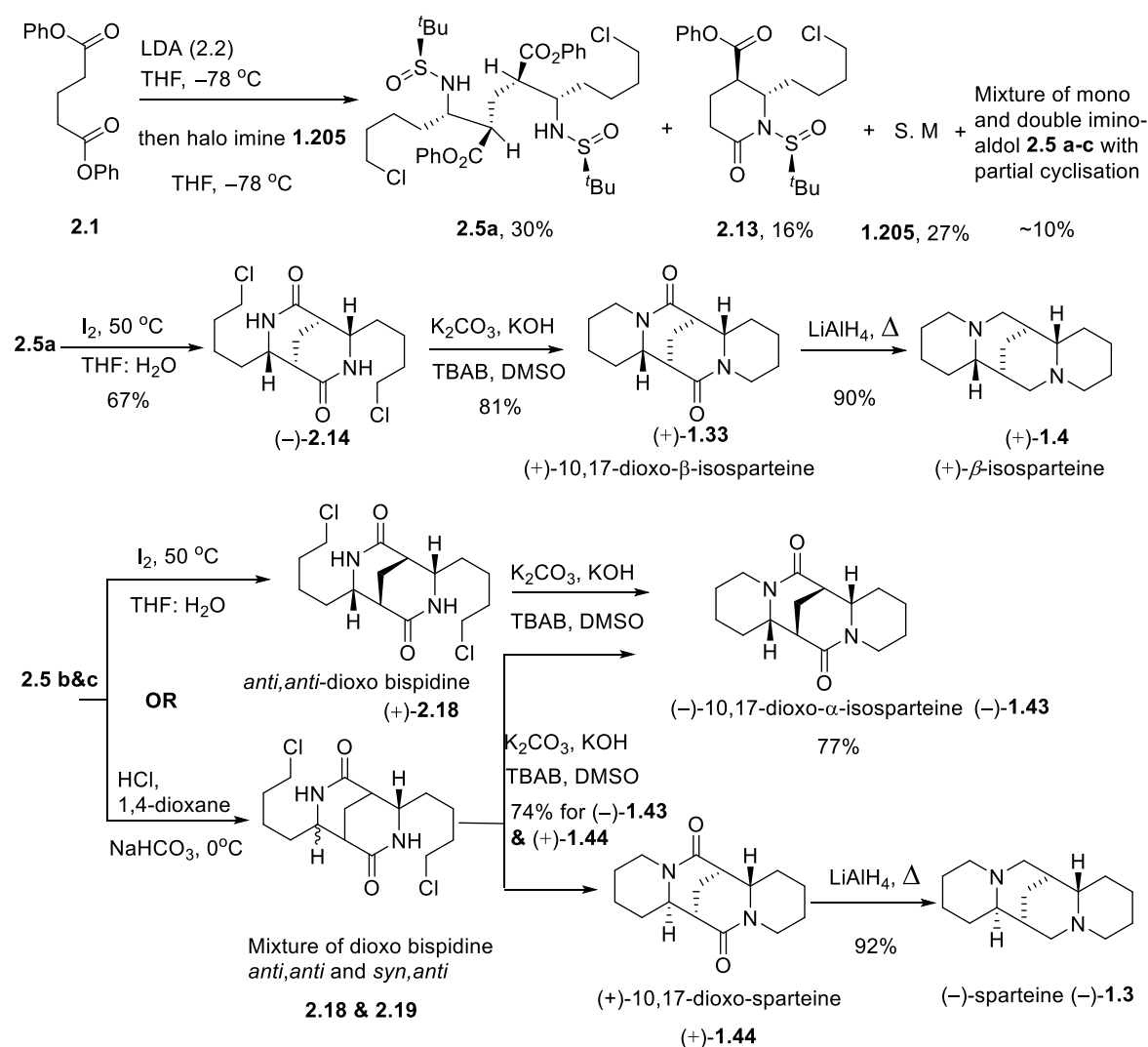


**Scheme 2.11:** The total synthesis of (+)-$\beta$-isosparteine and (−)-sparteine

## 2.2 Synthesis of (−)-epilupinine from mono imino-aldol adducts of diphenyl glutarate.

The following section will discuss an approach to the synthesis of (−)-epilupinine ((−)-**1.1**) using mono imino-aldol adduct **2.13** obtained from diphenyl glutarate (**2.1**) reacting with halo imine **1.205**. The cyclised imino-aldol **2.13** was described as a minor by-product in the previous section from the double imino-aldol reaction. Here we will also discuss attempts to optimise the mono imino-aldol adducts of different side chain functionalised imines.

### 2.2.1 Retrosynthetic analysis of (−)-epilupinine

Our approach exploits the selective formation of the cyclised imino-aldol adduct **2.13** from diphenyl glutarate to access (−)-epilupinine by reductive cyclisation (**Figure 2.13**). A short synthesis of (−)-epilupinine requires *N*-sulfinyl deprotection of cyclised adduct **2.13** followed by reduction of lactam and ester groups and then cyclisation of the amine onto the side chain halide. The cyclised adduct **2.13** was previously obtained from double imino-aldol reaction as a minor product in low yield. This strategy first requires optimisation to favour the mono adduct **2.13** from diphenyl glutarate (**2.1**) with one equivalent of halo imine **1.205**.
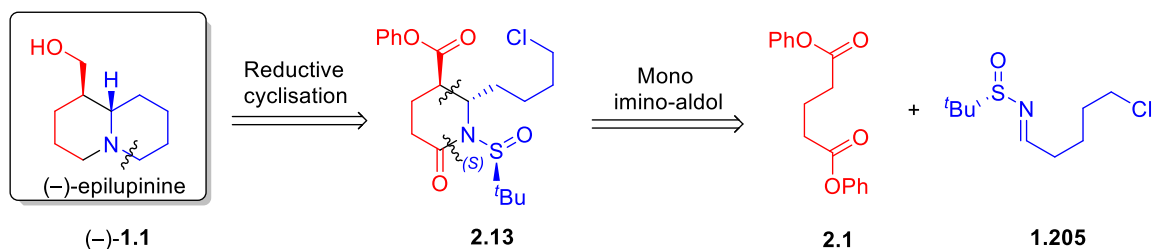


**Figure 2.13**: Retrosynthetic analysis of (−)-epilupinine from halo imine **1.205**

### 2.2.2 Optimisation of mono imino-aldol adduct formation

Our attention first focused on the synthesis of (−)-epilupinine (−)-**1.1** from mono imino-aldol product **2.13**.[134,135] The amount of the mono imino-aldol adduct **2.13** obtained from double imino-aldol reaction was clearly not sufficient as a starting point to the synthesis of (−)-epilupinine. Different conditions and imine derivatives were investigated to obtain mono imino-aldol adducts such as **2.13** using equal amounts of diphenyl glutarate (**2.1**) and imines. The optimisation of mono imino-aldol reaction was investigated using 3 different imines with diphenyl glutarate (**2.1**) using different amounts of LDA (**Table 2.7**). Employing an equal amount of diphenyl glutarate and imine derivatives with one equivalent of LDA gave mono imino-aldol adducts in low isolated yield together with recovered imine (**entries 1**, **4** & **7**, **Table 2.7**). We believe that the low isolated yield may be

due to side reactions as such intermolecular Claisen condensation of the mono enolate of diphenyl glutarate (**2.1**), although the keto-ester product was not observed. Therefore, the quantity of LDA was increased 2 equivalents (**entries 2**, **5** & **8**, **Table 2.7**) leading to significantly improved yields. The dianion of diphenyl glutarate is likely to possess increased nucleophilicity, leading to more efficient reaction with imine, and also avoiding intermolecular Claisen condensation.

**Table 2.7**: Optimisation of mono imino-aldol reaction using different imines
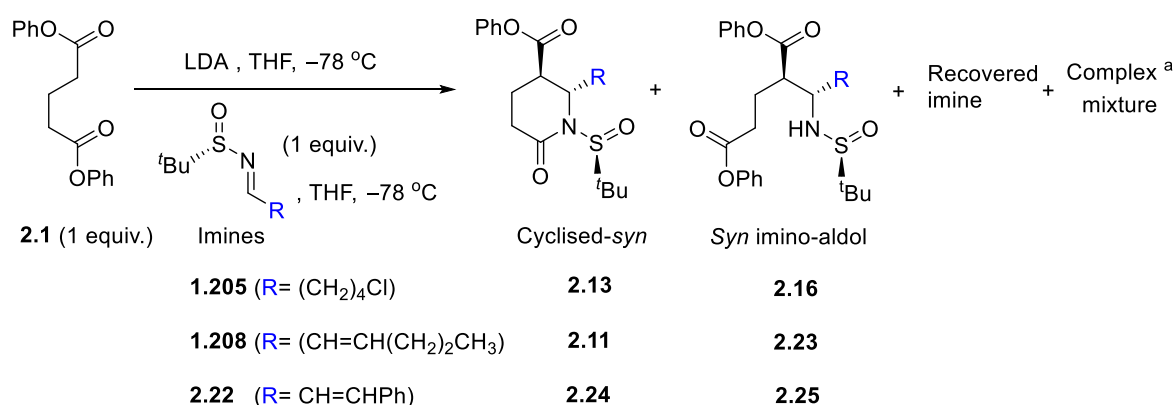


| | | Cyclised-*syn* | *Syn* imino-aldol |
|---|---|---|---|
| **1.205** (R= (CH$_2$)$_4$Cl) | | **2.13** | **2.16** |
| **1.208** (R= (CH=CH(CH$_2$)$_2$CH$_3$) | | **2.11** | **2.23** |
| **2.22** (R= CH=CHPh) | | **2.24** | **2.25** |

| R | Entry | Amount of LDA (equiv.) | Yield of *syn* cyclised | Yield of *syn* imino-aldol | Recovered imine |
|---|---|---|---|---|---|
| | 1 | 1.0 | **2.13** (21%) | **2.16** (6%) | 34% |
| Cl | 2 | 2.0 | **2.13** (40%) | **2.16** (11%) | 1% |
| | 3 | 3.0 | **2.13** (38%) | **2.16** (10%) | 5% |
| | 4 | 1.0 | **2.11** (20%) | **2.23** (N.D) | 30% |
| | 5 | 2.0 | **2.11** (38%) | **2.23** (12%) | 19% |
| | 6 | 3.0 | **2.11** (35%) | **2.23** (N.D.) | 3% |
| | 7 | 1.0 | **2.24** (19%) | **2.25** (N.D) | 35% |
| Ph | 8 | 2.0 | **2.24** (35%) | **2.25** (3%)[b] | 12% |
| | 9 | 3.0 | **2.24** (33%) | **2.25** (N.D) | 5% |

[a] The complex mixture containing small amounts of mono *anti* imino-aldols adducts derivatives were separated by column chromatography, see details in experimental part. [b] Isolated as an impure and no assignment was reported. N.D= not determined

Small amounts of imine derivatives were recovered despite increasing the amount of LDA to 3 equivalents (**entries 3, 6** & **9**, **Table 2.7**). A mixture of minor products including cyclised-*anti* **2.17** and double imino-aldol products **2.5** (**a-c**) were also obtained from the reactions after careful separation by column chromatography. Although the best yield of desired product **2.13** was obtained (**entry 2**, **Table 2.7**), isolation of the *syn*-imino-aldol **2.16** as a minor product suggested

that the yield could be improved further. It was found that the amount of **2.16** could be minimised through slow addition of halo imine **1.205** by syringe pump. The best result was obtained from the mono imino-aldol reaction of halo imine **1.205** giving the highest yield of 51% of cyclised *syn* **2.13** using 2.6 equivalent of LDA at −78 °C, and slow addition of imine **1.205** to the dienolate solution using a syringe pump at −78 °C (**Scheme 2.12**). Subsequently, careful quench of the reaction by keeping the temperature under −70 °C, and then leaving the quenched reaction solution warm to rt. These conditions also gave cyclised-*anti* **2.17** as impure product and complex mixture of double imino-aldol products but avoided isolation of *syn* imino-aldol **2.16** and recovery of halo imine **1.205**. The yields were consistent over several experiments giving cyclised-*syn* **2.13** in 48-51% and cyclised-*anti* **2.17** in 10-15% and complex mixture of double imino-aldol products as minor components. Separation of remaining mono imino-aldol mixture was completed by careful column chromatography.
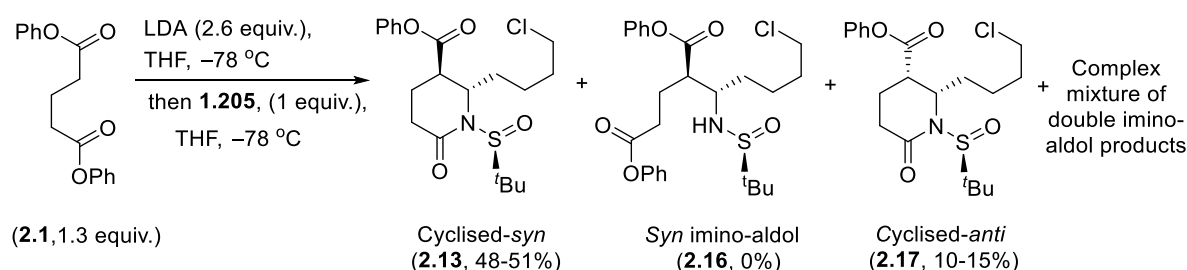


**Scheme 2.12**: Optimised mono imino-aldol reaction

### 2.2.3      Determination the diastereoselectivity of imino-aldol products

The ratio of *syn* and *anti* imino-aldols **2.13** and **2.17**, determined from the crude ^{1}H NMR spectra, varied under the reaction conditions between ~3:1 and 5:1 (**Scheme 2.13**). The diastereoselectivity was improved by slow addition of imine **1.205** around the bottom of the flask wall and keeping the reaction temperature around at −78 °C. However, when the reaction temperature was allowed to warm above −70 °C during the addition, the yield and the selectivity decreased.
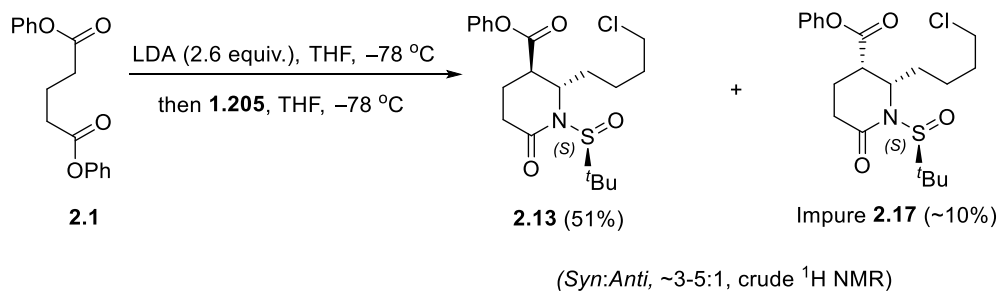


**Scheme 2.13**: The diastereoselectivity of the mono imino-aldol reaction

The cyclised mono imino-aldol products were identified by comparison of their $\beta$ methine protons in $^1$H NMR spectra. The multiplet at 4.30 ppm corresponds to cyclised *syn*-adduct **2.13** ($S_S$, *2S*, *3R*) (**Figure 2.14**). The multiplet at 4.46 ppm corresponds to the minor cyclised *anti*-adduct **2.17** ($S_S$, *2S*, *3S*). The NH doublet for *syn* imino-aldol adduct **2.16** ($S_S$, 2*S*, 3*R*) at 4.22 ppm was not observed in $^1$H NMR spectra from crude reaction mixtures obtained under the optimised conditions (**see experimental part**).
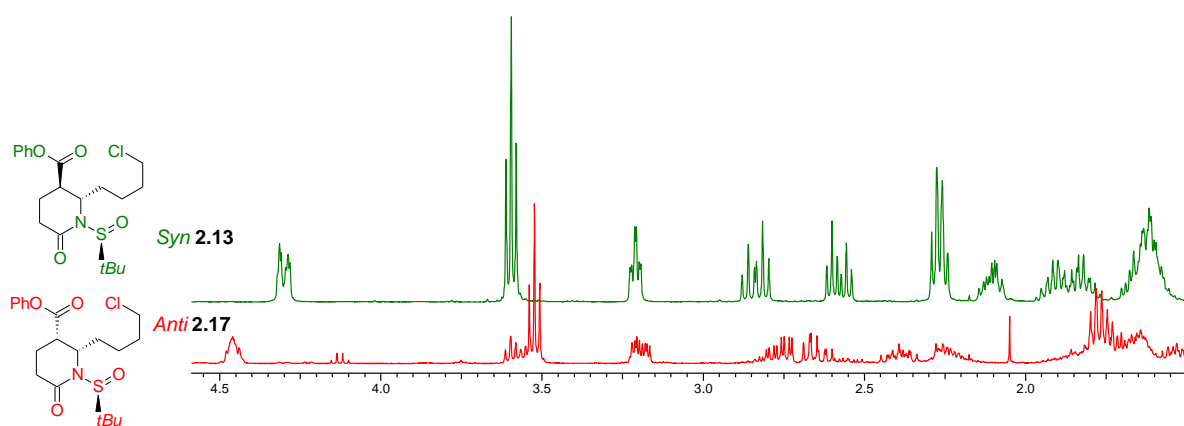


**Figure 2.14**: $^1$H NMR (400 MHz) for cyclised *syn* and *anti*-adducts **2.13** and **2.17**

## 2.2.4      The mechanism of mono imino-aldol reaction

A proposed mechanistic pathway to account for the formation of the cyclised mono imino-aldol product is outlined in Scheme **2.14**. The dianion of diphenyl glutarate **2.1a** undergoes an initial *syn*-selective imino-aldol reaction with the imine to give enolate intermediate **A**. The enolate **A** can convert to ketene intermediate **B** after loss of phenoxide ion. The highly reactive ketene intermediate **B** can then undergo cyclisation to form enolate lactam **C**, which gives cyclised imino-aldol adduct **2.13** upon acidic work-up. Alternatively, protonation of the enolate intermediate **A** on work-up will give the uncyclised (normal) imino-aldol **2.16**. Both **2.13** and **2.16** have been isolated and their relative amounts were dependent on the reaction conditions. Slow cyclisation of the mono imino-aldol **2.16** can also occur under reaction and work-up conditions.
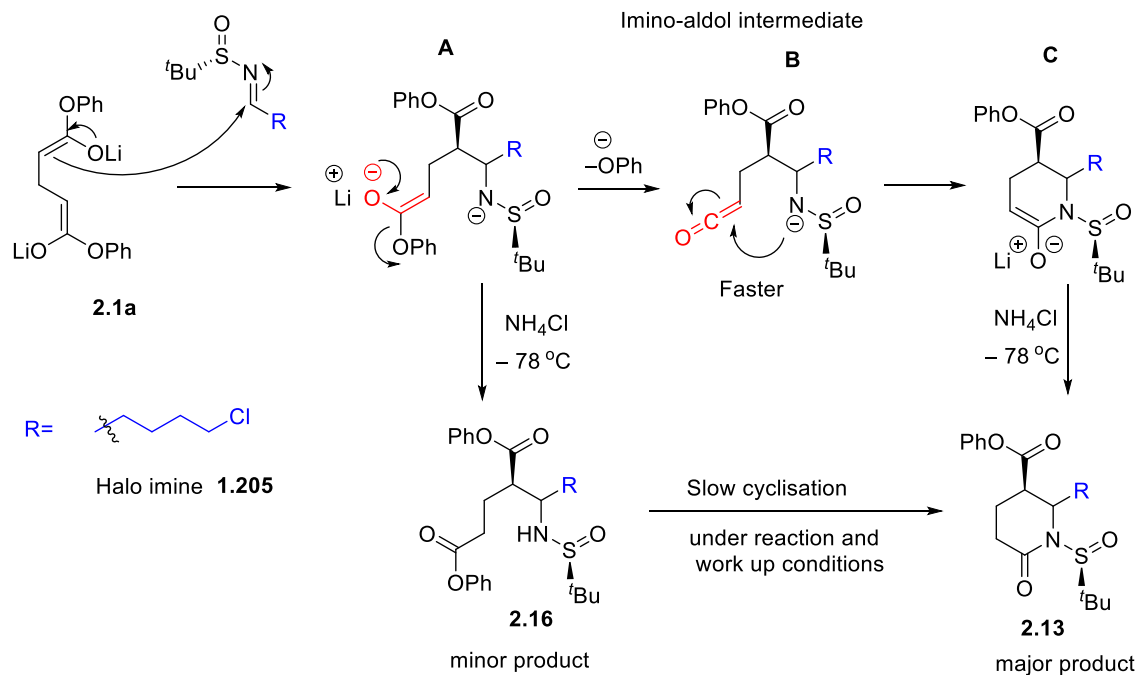
**Scheme 2.14**: Proposed mechanism for cyclisation of imino-aldol intermediates

### 2.2.5        Completion of the synthesis of (–)-epilupinine from cyclised-*syn* imino-aldol 2.13

The synthetic route to (–)-epilupinine (**1.1**) was completed by reductive cyclisation of *syn*-adduct **2.13** in refluxing LiAlH$_4$ giving (–)-epilupinine along with over reduced by-product **2.26** (**Scheme 2.15**). The total synthesis of (–)-epilupinine (**1.1**) was achieved over two steps in 31% overall yield from halo imine **1.205**.
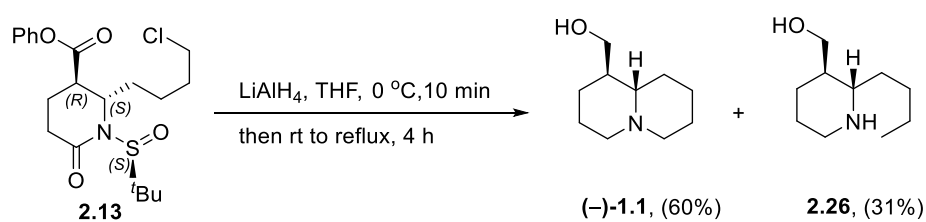


**Scheme 2.15**: Synthesis of (–)-epilupinine from **2.13**

## 2.2.6        Confirmation of the absolute stereochemistry of (−)-epilupinine

The analytical data obtained for synthetic (−)-epilupinine was in good agreement with that previously reported by us and with literature values.[134,140,142,143] Specific rotation of epilupinine showed a negative value supporting the assigned major enantiomeric product of our imino-aldol reaction.[140,142] Comparison of physical and ^{1}H and ^{13}C NMR data with the reported literature values is provided in (**Table 2.8**).[134,135,143]

**Table 2.8**: Comparison of recorded and literature spectroscopic data for (−)-epilupinine

| assignment | Recorded δ ppm[a] | Lit. [134] δ ppm[b] | Lit.[135] δ ppm[c] | Lit.[143] δ ppm[d] |
|---|---|---|---|---|
| C2 | 56.9 | 56.9 | 56.8 | 56.9 |
| C3 | 25.1 | 25.0 | 24.9 | 25.0 |
| C4 | 24.6 | 24.5 | 24.4 | 24.5 |
| C5 | 44.0 | 43.9 | 43.8 | 43.9 |
| C6 | 64.2 | 64.3 | 64.4 | 64.3 |
| C7 | 28.2 | 28.2 | 28.1 | 28.2 |
| C8 | 29.8 | 29.7 | 29.6 | 29.7 |
| C9 | 25.6 | 25.5 | 25.4 | 25.6 |
| C10 | 56.6 | 56.6 | 56.5 | 56.6 |
| C11 | 64.8 | 64.5 | 64.4 | 64.6 |

(−)-**1.1**
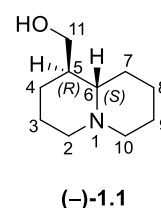
**Optical Rotation:**

*Recorded data current work* :
$[\alpha]_D$ : −31.2 (*c* 0.5 absolute EtOH, 20 °C)

*Literature data:*
lit.[134] $[\alpha]_D$ : −29.2 (*c* 1.00, EtOH, 26 °C),

lit.[135] $[\alpha]_D$ : −30.0 (*c* 0.90, EtOH, 22 °C)
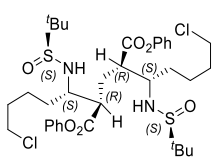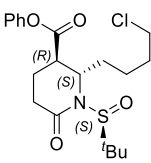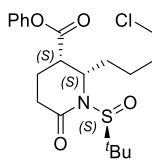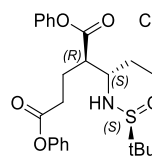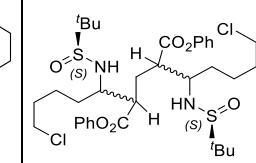
lit.[143] $[\alpha]_D$ : −28.5 (*c* 0.72, EtOH, 27 °C)

[a] The current work: recorded in CDCl$_3$ at 101 MHz. [b] Recorded in CDCl$_3$ at 100 MHz. [c] Recorded in CDCl$_3$ at 100 MHz. [d] Recorded in CDCl$_3$ at 100 MHz.

## 2.2.7        Comparison of the product distribution observed for the mono and double imino-aldol reactions.

Both ''single'' and ''double'' imino-aldol reaction conditions gave the same products but with different yields (**Table 2.9**). The double imino-aldol was performed by using 1 equiv. of diphenyl glutarate **1.173** with 2 equiv. of halo imine **1.205** and 2.2 equiv. of LDA at −78 °C as explained in the previous section. However, the mono imino-aldol reaction could be favoured by using 1.3 equiv. of diphenyl glutarate **1.173** with 1 equiv. of halo imine **1.205** and 2.6 equiv. of LDA at −78 °C. The yields of the different products were obtained from isolation of pure compounds, and estimation using ^{1}H NMR for mixed fractions (**Table 2.9**).

**Table 2.9**: Summary of the main identified components[a] from reaction under optimised double (conditions A)[b] and mono (conditions B)[c] imino-aldol reactions:

| Products | *Syn,syn* double imino-aldol **2.5a** | Cyclised-*syn* **2.13** | Cyclised-*anti* **2.17** | *Syn* imino-aldol **2.16** | Mixture of diastereoisomers[d] |
|---|---|---|---|---|---|
| Yield from conditions A | 30%[f] | 16%[f] | ~5%[f] | ~7%[f] | ~10%[e] |
| Yield from conditions B | (2% - 15%)[e,f] | (38% - 51%)[e,f] | (3% - 13%)[e,f] | (0% - 15%)[e,f] | ~5% (26 : 3 : 1)[e] |

[a.] Isolated purified products obtained from reactions. Other very minor components not identified.
[b.] Conditions A: optimised double imino-aldol reaction conditions: 1 equiv. of **1.173** with 2 equiv. of **1.205** in 2.2 equiv. of LDA at −78 °C. [c.] Conditions B: optimised mono imino-aldol reaction conditions: 1.3 equiv. of **1.173** with 1 equiv. of **1.205** in 2.6 equiv. of LDA −78 °C. [d.] Unseparated mixture of diastereoisomers (*syn,anti* (**2.5c**) and *anti,anti* (**2.5b**)). [e.] Determined by $^1$H NMR spectra from the crude product. [f.] Determined by column chromatography.

### 2.2.8    Structure determination of the minor imino-aldol products

To confirm the absolute stereochemistry of cyclised-*anti* mono adduct **2.17**, we employed acidic conditions to remove the *N*-sulfinyl protection (**Scheme 2.16**). Following neutralisation with aq. NaHCO$_3$, the *anti*-lactam **2.27** was obtained as a white crystalline solid. Recrystallisation from hexane gave crystals suitable for X-ray structure determination, confirming the *anti*-relationship.
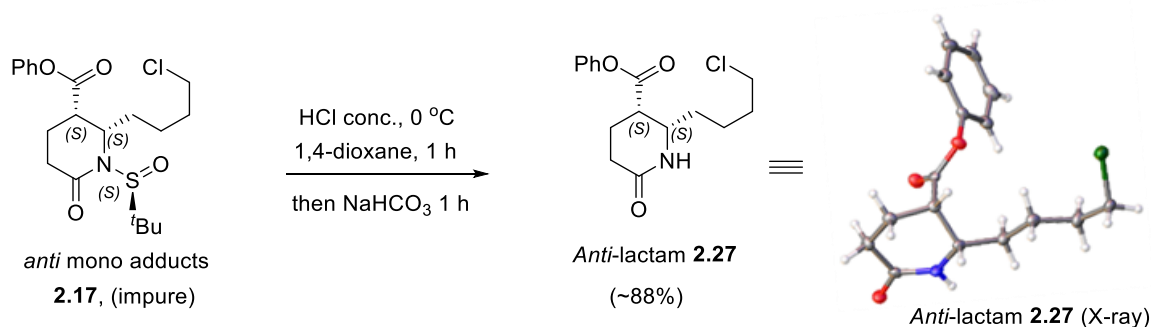


**Scheme 2.16**: Confirmation of the structure for *anti*-lactam **2.27** by X-ray

The stereochemistry of the cyclised *syn*-imino-aldol **2.13** and the *syn*-imino-aldol **2.16** were confirmed by converting them to a common product (**Scheme 2.17**). Treatment of either compound

**2.13** or **2.16** with acid led to removal of the sulfinyl-protecting group, and subsequent base treatment gave *syn*-lactam **2.28**.



Cyclised-*syn* mono adduct
**2.13**

S*yn* mono adduct
**2.16**

HCl conc., 0 °C
1,4-dioxane, 1 h
then NaHCO$_3$ 1 h
(95% from **2.13**)
(91% from **2.16**)
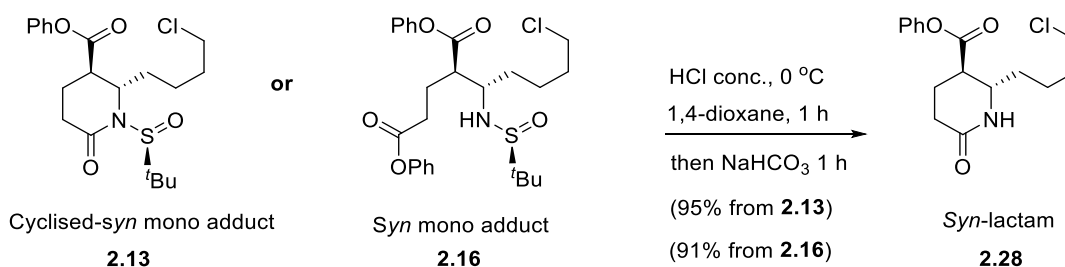
*Syn*-lactam
**2.28**

**Scheme 2.17:** Formation of *syn*-lactam **2.28** from cyclised and imino-aldol adducts **2.13** & **2.16**

The stereochemistry of *syn*-lactam **2.28** and *anti*-lactam **2.27** were supported by analysis of their ^{1}H NMR spectra (**Figure 2.15**). As a result, the mixture of diastereoisomers present in the mono imino-aldol reaction can be identified from the crude ^{1}H NMR spectra (**Figure 2.15**). Inspection of the $\alpha$ H and $\beta$ H multiplet for the diastereomers of lactam *syn* (*R,S*) and *anti* (*S,S*) at 2.69 and 3.22 ppm respectively show a clear difference. In addition, the NH lactam signal for *syn* (*R,S*) and *anti* (*S,S*) show a broad peaks at 6.8 and 6.0 ppm, respectively. The identification of the double imino-aldol adducts **2.5** (**a-c**) was described in the previous section (**Scheme 2.8**).
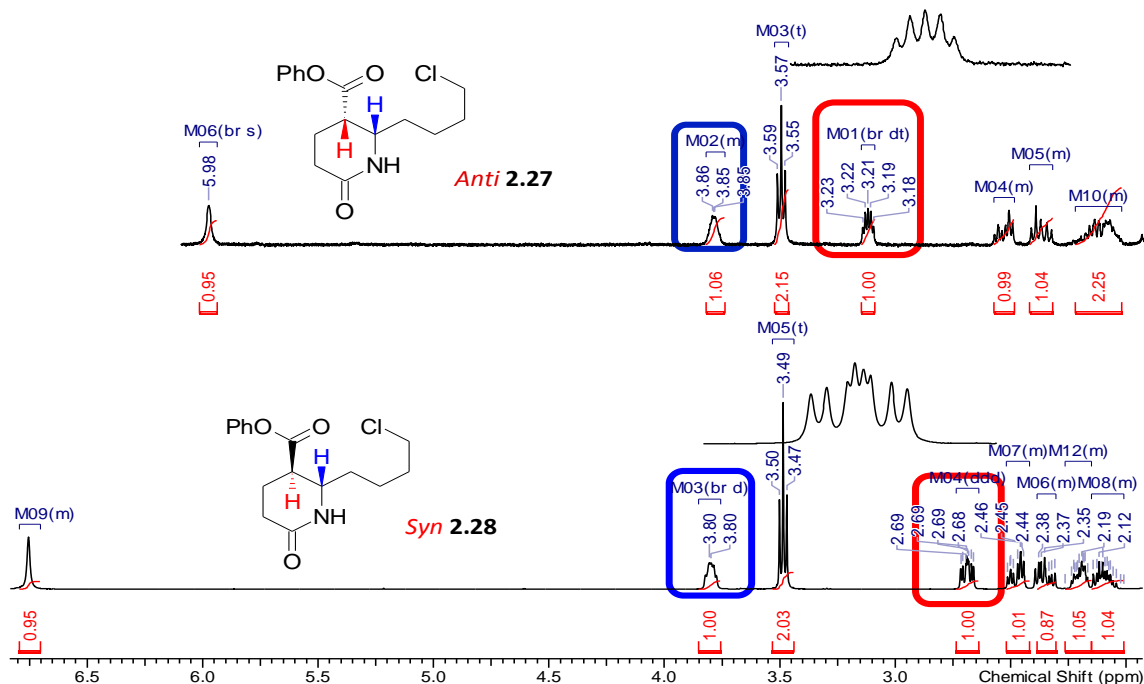


**Figure 2.15:** ^{1}H NMR (400 MHz) for comparison of *syn*- and *anti*-mono imino-aldol adducts

### 2.2.9    Conclusion:

The mono imino-aldol reaction was carried out by using diphenyl glutarate (**2.1**) with halo imine **1.205** to produce cyclised *syn* imino-aldol **2.13** in 51% yield. The impure *anti*-imino-aldol **2.17** was obtained as the main by-product in 10% yield (**Scheme 2.18**). Minor products from the mono imino-aldol reaction were identified to be *syn,syn*, *anti,anti* and *syn,anti* double imino-aldol adducts. The stereochemistry of *anti* imino-aldol **2.17** was determined by deprotection of the sulfinyl group and cyclisation to give *anti*-lactam **2.27**. The structure of the *anti*-lactam was confirmed by X-ray structure determination. A total synthesis of (−)-epilupinine ((−)-**1.1**) was accomplished over two steps from halo imine **1.205** in 31% overall yield by reducing the **2.13** and cyclisation of alkyl halide in the presence of LiAlH$_4$. The mono imino-aldol adduct **2.13** may provide a useful intermediate for the synthesis of (−)-sparteine and other nitrogen-containing bicyclic natural products, and our progress in this direction will be discussed later.
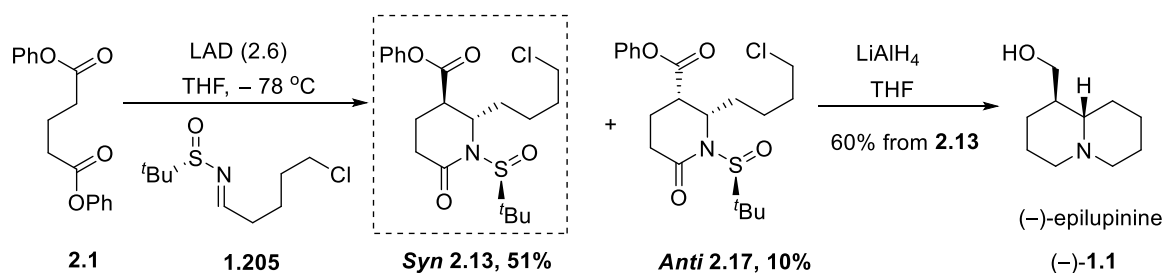


**Scheme 2.18:** The total synthesis of (−)-epilupinine ((−)-**1.1**) from halo imine **1.205**

## 2.3    RCM approach to the total synthesis of (−)-epilupinine from 5-chlorovalerate and an unsaturated imine

### 2.3.1    Retrosynthetic analysis of (−)-epilupinine

This approach will use ring closing metathesis (RCM) to access the quinolizidinone **2.30**, and *syn*-selective imino-aldol reaction between phenyl ester **1.173** and an unsaturated imine **1.208** (**Figure 2.16**). The retrosynthesis of (−)-epilupinine ((−)-**1.1**) requires hydrogenation and reduction of quinolizidinone **2.30**. Disconnection carbonyl-amine bond of **2.29**, and the piperidine **1.210** C-N bond leads back to imino-aldol adduct **1.209**. The imino-aldol product **1.209** can be formed from two functionalised fragments **1.173** and **1.208** to be brought together in a diastereoselective imino-aldol reaction.
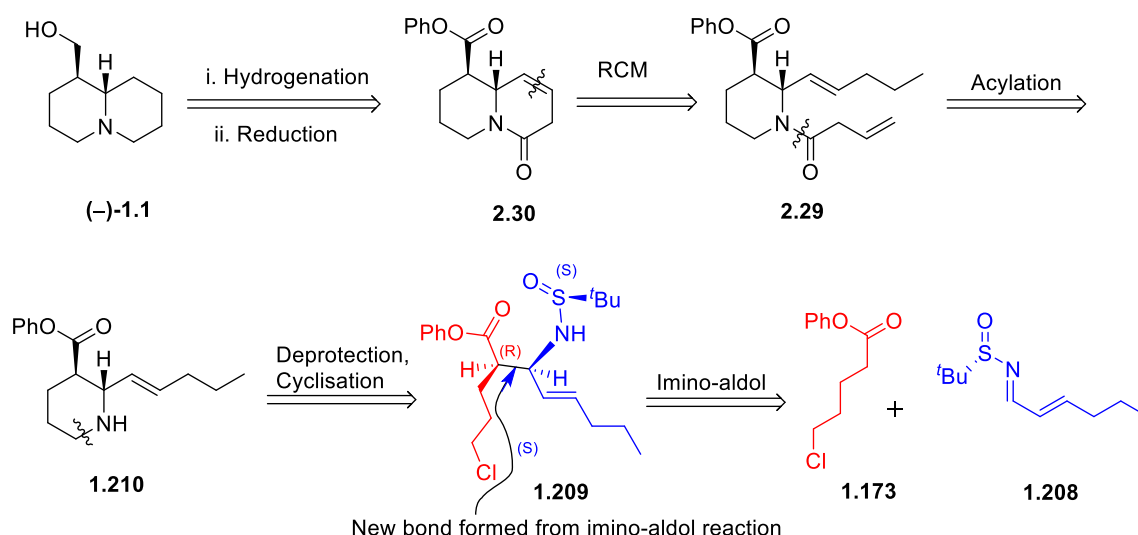


**Figure 2.16:** Retrosynthetic analysis of (−)-epilupinine

### 2.3.2    Towards the synthesis of (−)-epilupinine

5-Chlorovaleric acid (**2.31**) was used as a commercially available starting material which was converted to the acid chloride **2.32** using oxalyl chloride and (**Scheme 2.19**). The crude acid chloride **2.32** was esterified with phenol to afford phenyl 5-Chlorovalerate (**1.173**) in 75% yield. A more efficient synthesis of phenyl ester **1.173** used equimolecular amounts of phenol and acyl chloride **2.32** under phase-transfer catalysis (PTC) conditions, giving the product in near quantitative yield and shorter reaction time.[25]
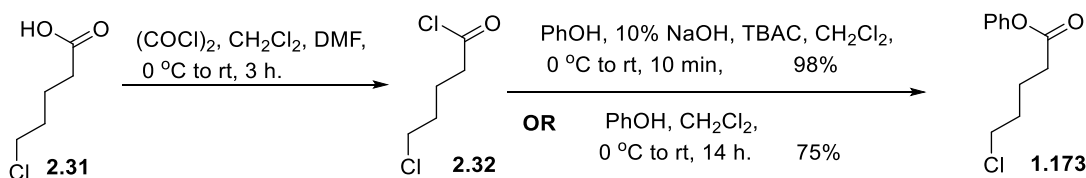
**Scheme 2.19**: Synthesis of phenyl 5-chlorovalerate (**1.173**)

### 2.3.3    Imino-aldol reaction of unsaturated imine 1.208

The imino-aldol reaction conditions optimised within the Brown group were applied using the lithium enolate of ester **1.173** (**Scheme 2.20**). Addition of the lithium enolate to unsaturated sulfinyl imine **1.208** provided imino-aldol **1.209** with high diastereocontrol (dr 22:1, ^{1}H NMR of the crude reaction mixture). It was essential that the reaction was quenched at −78 °C. If allowed to warm to rt prior to quench, none of the desired product was isolated. In addition, a 1:1 stoichiometry of LDA to phenyl ester **1.173** provided the best result. The desired *syn*-product **1.209** was isolated by column chromatography on silica gel in 88% yield. In addition, the minor diastereomer (*S*,*S*) **2.33** was obtained in ~4% and 8% of mixed fractions were also isolated. The stereochemical outcome can be rationalised using a Zimmerman-Traxler type six-membered transition state model (**Figure 2.17**), where reaction of the *E*-enolate from the *Re* face of the sulfinyl imine gives the major product. The *E*-enolate is known to favour the *syn* product for phenyl esters.[144]
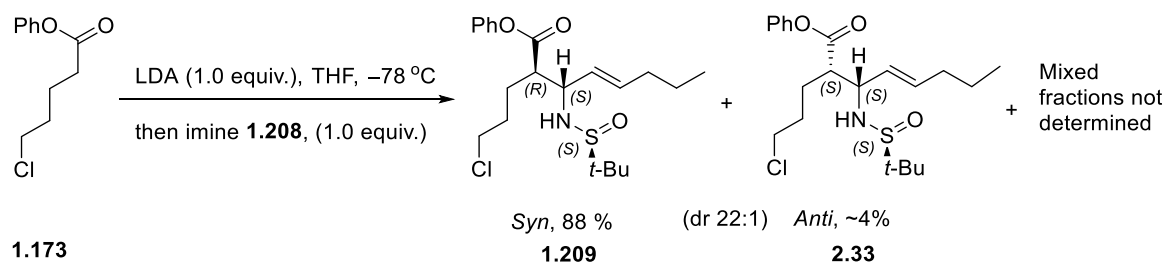


**Scheme 2.20**: Synthesis of imino-aldol adducts.



*trans*-unsaturated imine
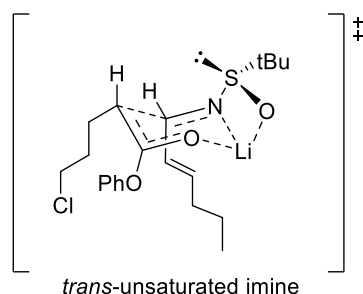
**Figure 2.17**: Proposed Zimmerman-Traxler transition state model for the imino-aldol reaction leading to the major *syn* product.[145]

### 2.3.4    Total synthesis of (−)-epilupinine from imino-aldol 1.208

The synthesis of (−)-epilupinine was proposed through two pathways, starting from *syn* imino-aldol **1.209** (**Figure 2.18**). The first pathway **A** *via* lactam derivative **2.35**, requires initial acylation of **1.209** to form **2.34**, while the second pathway **B** requires, firstly preparation of piperidine intermediate **1.210** and then acylation of **2.29** to access (−)-epilupinine *via* RCM.
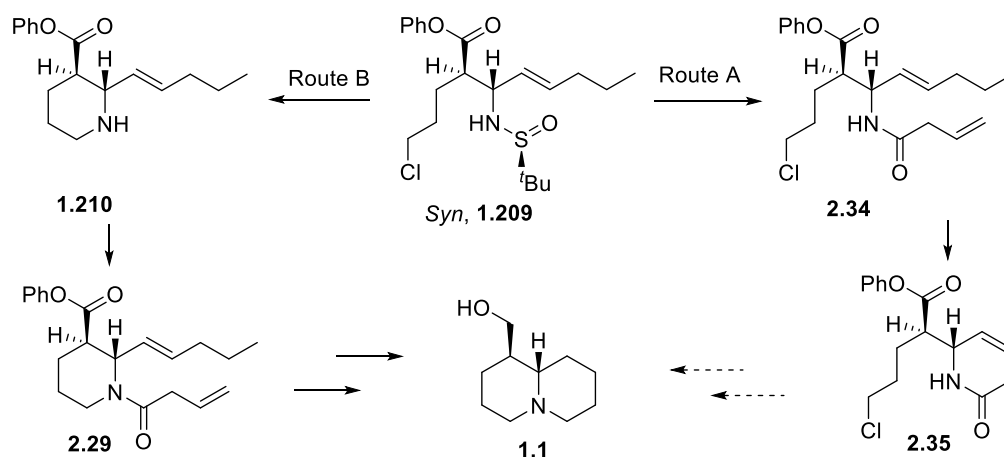


**Figure 2.18**: Proposed routes towards the synthesis of (−)-epilupinine

The first pathway to the synthesis of (−)-epilupinine started by removal of the *N*-sulfinyl group from *syn*-adduct **1.209** under acidic conditions, providing amine salt **2.36**, which was followed by acylation to obtain amide **2.34** in 78% yield over two steps (**Scheme 2.21**). RCM using Grubbs II catalyst (**2.37**) gave two products; the desired unsaturated δ-lactam **2.35** as the major product in 37% yield and dimer **2.34** as a minor product in 12% yield. This approach was not continued due to the relatively low yield of the desired product **2.38**.
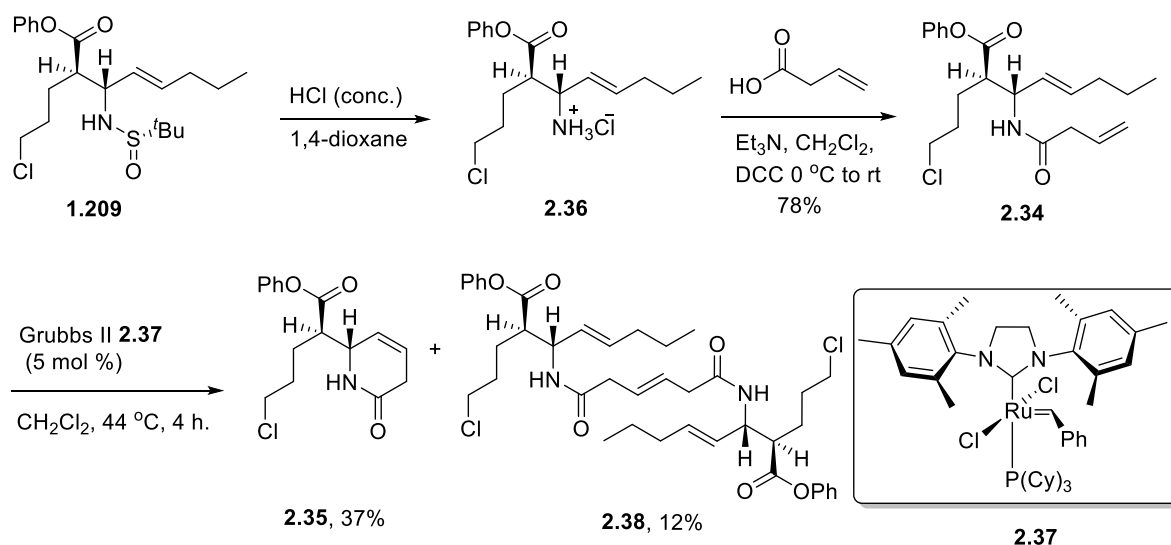


**Scheme 2.21**: Approach to synthesis of (−)-epilupinine *via* lactam intermediate **2.35**.

An alternative synthetic pathway to access (−)-epilupinine, proceeding *via* piperidine intermediate **1.210** was investigated. Piperidine **1.210** was prepared by two methods, firstly removal *N*-sulfinyl group from **1.209** using 3 equiv. of conc. HCl (~36 %) at 0 °C in dioxane, and subsequent cyclisation in the presence of $K_2CO_3$ and catalytic NaI gave 83% over two steps. An alternative method was investigated by deprotection-cyclisation using molecular iodine under basic conditions. Initially, the reaction was carried out using $I_2$ and $Na_2CO_3$ for 24 h giving the amine salt **2.36** in 90% (**entry 1**, **Table 2.10**), while increasing the amount of $Na_2CO_3$ and heating in the presence of $I_2$ in a mixture of THF and $H_2O$ gave the piperidine intermediate **1.210** directly (**entries 4&5, Table 2.10**). The best conditions used excess of base with $I_2$ at 50 °C giving piperidine **1.210** in high yield and short reaction time in one-step compared to the two-step procedure described below. Piperidine **1.210** was recrystallised from *n*-hexane to provide the pure product in 95% yield as a white solid.

**Table 2.10**: Optimisation and the deprotection-cyclisation reaction of the *syn*-adduct.**1.209**.
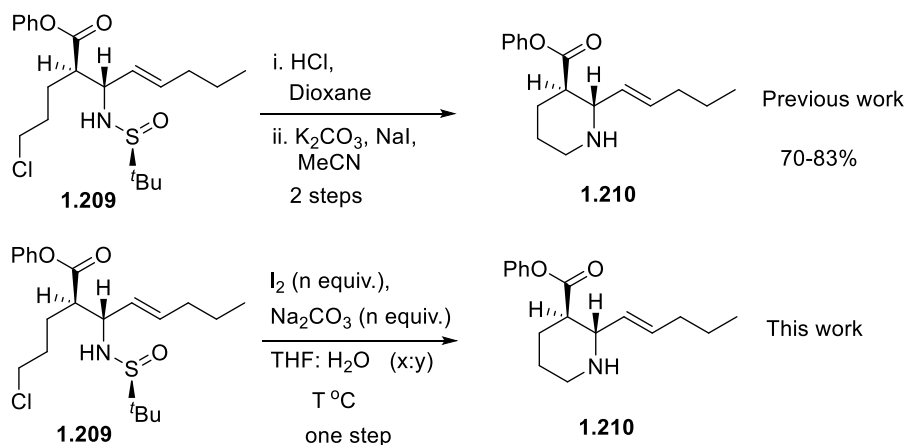


| Entry | THF:H₂O | Na₂CO₃ equiv. | I₂ equiv. | NaI | T °C | Reaction time | Yield of 1.210 |
|-------|---------|---------------|-----------|-----|------|---------------|----------------|
| 1 | 1:1 | 3 | 2.5 | - | rt | I₂, Na₂CO₃, 24 h | - * |
| 2 | 1:1 | 5 | 2.0 | 0.1 | rt | I₂, Na₂CO₃ 1 h, then NaI, 18 h | 90% |
| 3 | 2:1 | 12 | 1.5 | - | rt | I₂ 1 h, then Na₂CO₃, 18 h | 88% |
| 4 | 4:1 | 12 | 1.0 | - | 50 | I₂ 1 h, then Na₂CO₃, 18 h | 90% |
| 5 | 3:2 | 12 | 2.0 | - | 50 | I₂ 2 h, then Na₂CO₃, 6 h | 95% |

*The amine salt **2.36** was obtained in 90% yield.

Piperidine **1.210** was acylated with 3-butenoic acid using *N,N'*-dicyclohexylcarbodiimide (DCC) to give $\beta,\gamma$-unsaturated amide **2.29** in 85% yield (**Scheme 2.22**). RCM of **2.29** using Grubbs I was

unsuccessful even at high loading of the Grubbs catalyst I and long reaction time (30 h). However, RCM of **2.29** using Grubbs catalyst II (**2.37**) afforded the unsaturated quinolizidinone **2.30** in excellent yield. Quinolizidinone **2.30** was recrystallised from hexane and its stereochemistry was confirmed by single crystal X-ray crystallography (**Figure 2.19**). The unsaturated quinolizidinone **2.30** was hydrogenated over Pd/C to give quinolizidinone **2.39**, and finally reduction of **2.39** using LiAlH$_4$ furnished (−)-epilupinine ((−)-**1.1**) in 87% yield.
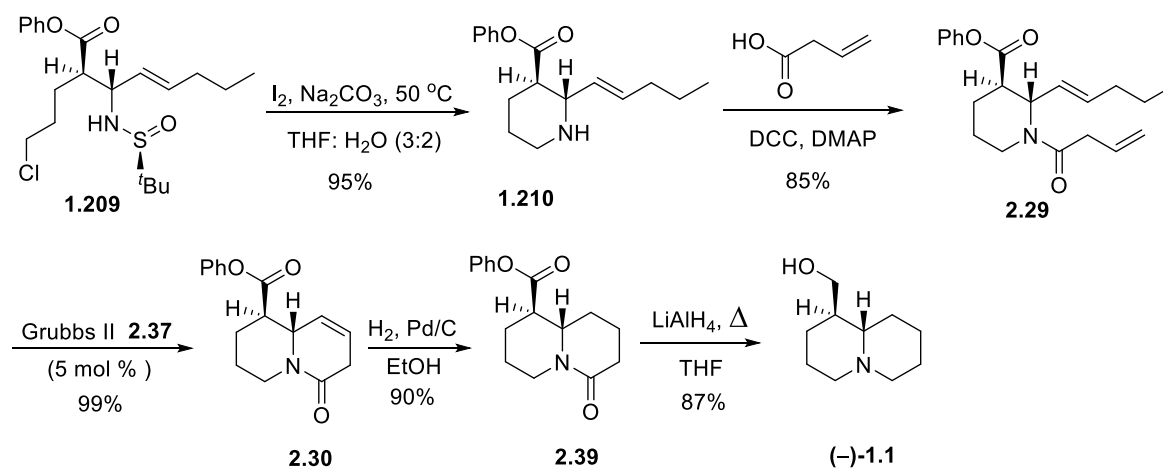


**Scheme 2.22**: The total synthesis of (−)-epilupinine
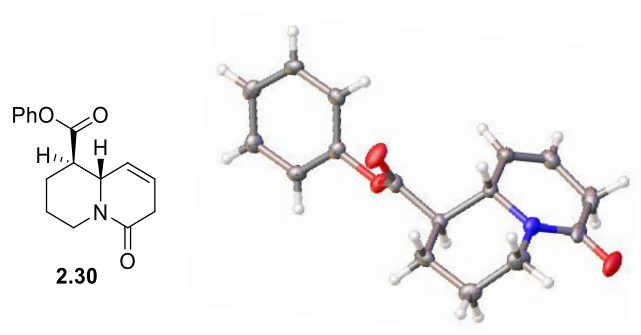


**Figure 2.19**: X-ray crystal structure of the unsaturated quinolizidinone **2.30**

Although we were delighted to have completed a short total synthesis of (−)-epilupinine, our interest in this relatively long route was derived from the ability to introduce a functionalised quinolizidine system **2.30** that could be used in the synthesis of other lupin alkaloids. These efforts will be described in the following section. Although the synthesis of (−)-epilupinine is similar to our previous synthesis (**Scheme 1.44**),[135] the overall yield of (−)-epilupinine was increased from 39% in seven steps compared to previous work,[134,135] now achieving 55% in six steps from the unsaturated imine **1.208**.

### 2.3.5         Conclusions:

The total synthesis of (−)-epilupinine was achieved in 55% overall yield over six steps from unsaturated imine **1.208** by using a RCM approach (**Scheme 2.23**). *Syn*-selective of imino-aldol reaction was provided **1.209** with high diastereocontrol (*dr* 22:1). Initially, deprotection and acylation of *syn* imino-aldol adduct **1.209** gave an intermediate **2.34** followed by ring-closing metathesis. Although this gave the desired unsaturated lactam **2.35**, cross-metathesis also occurred leading to a by-product **2.38**. Several reaction conditions have been explored for deprotection and cyclisation of imino-aldol adduct **1.209** giving the piperidine **1.210** in 95%. The stereochemistry of quinolizidinone **2.30** was confirmed by single crystal X-ray crystallography. The functionalised quinolizidine system was converted to (−)-epilupinine in two further steps.
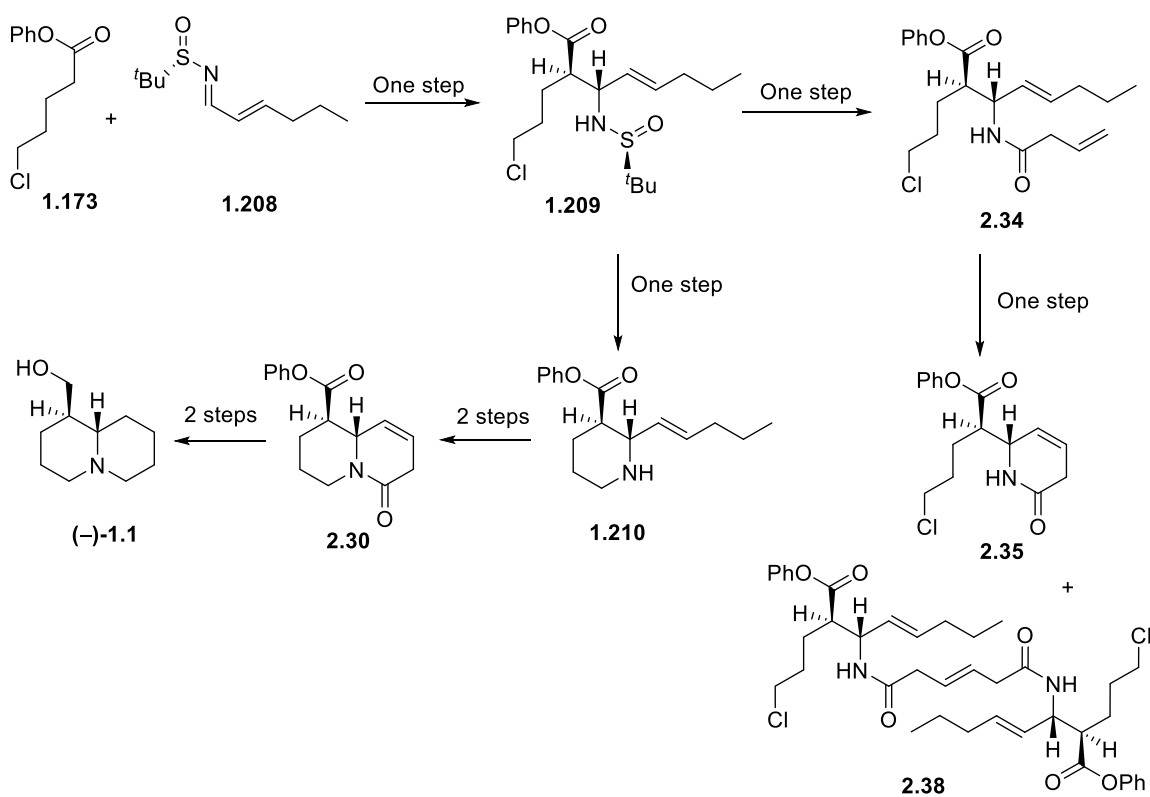


**Scheme 2.23**: Overview of the total synthesis of (−)-epilupinine from unsaturated imine **1.208**

## 2.4      Towards the synthesis of (+)-allomatridine and (−)-sparteine

A synthesis of (+)-allomatrine ((+)-**1.139**) was reported by Brown and co-workers, from an imino-aldol intermediate and using *N*-acyliminium ion cyclisation as a key step (**Scheme 1.38**).[109] Our plan in this section is to progress a new cyclisation strategy for the synthesis of (+)-allomatridine, starting from *syn* imino-aldol adduct **1.209** (**Figure 2.20**, route **A**). Tricyclic imide **2.45** will be a key intermediate to access (+)-allomatridine. A synthetic route to (−)-sparteine (route **B**) will also be investigated starting from cyclised *syn* imino-aldol **2.13**, which was described in the previous section (**Scheme 2.13**). Sulfinyl piperidine **2.13** can be used to generate an imide intermediate **2.46** to access (−)-sparteine ((−)-**1.3**) by using *N*-acyliminium ion cyclisation approach.
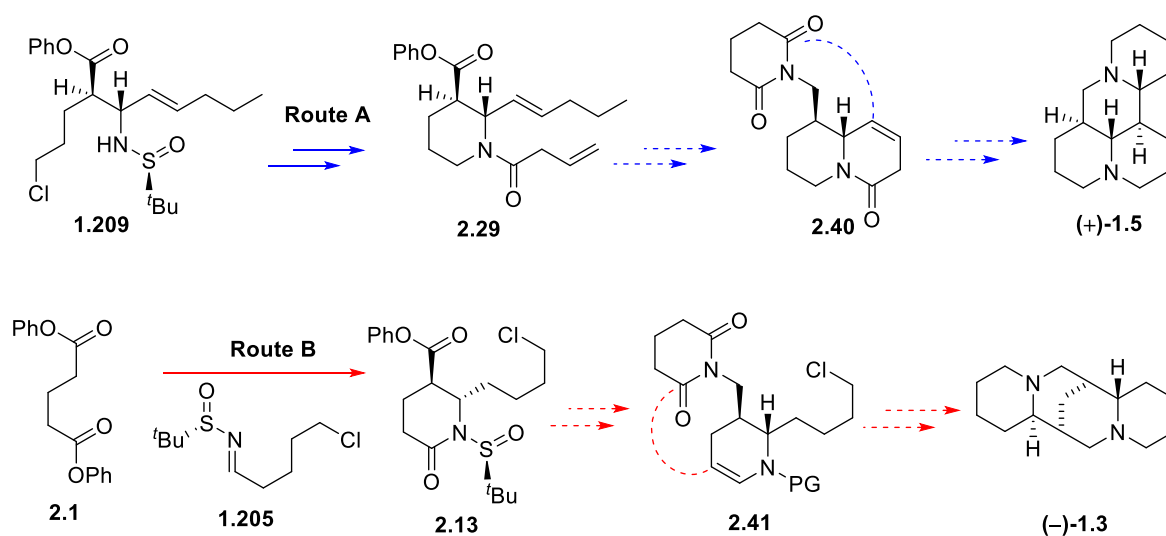


**Figure 2.20**: Routes towards (+)-allomatridine ((+)-**1.5**) and (−)-sparteine ((−)-**1.3**) from piperidine and quinolizidine intermediates

### 2.4.1      Retrosynthetic analysis of (+)-allomatridine

Our approach to the synthesis of (+)-allomatridine ((+)-**1.5**) was designed to exploit $\beta,\gamma$-unsaturated amide **2.29** which was previously prepared during our synthesis of (−)-epilupinine (**Scheme 2.22**). RCM of intermediate **2.29** followed by selective reduction of ester will provide the corresponding alcohol **2.42** (**Figure 2.21**). Mitsunobu reaction of alcohol **2.42** with glutarimide will give tricyclic imide **2.40**. Selective reduction of imide **2.40** will give intermediate **2.43**, which can be cyclised using Brønsted acid, basic conditions, or reduction under acidic conditions using Mannich-type or *N*-acyliminium ion cyclisation. (+)-Allomatridine will be generated by hydrogenation and reduction at a late stage.
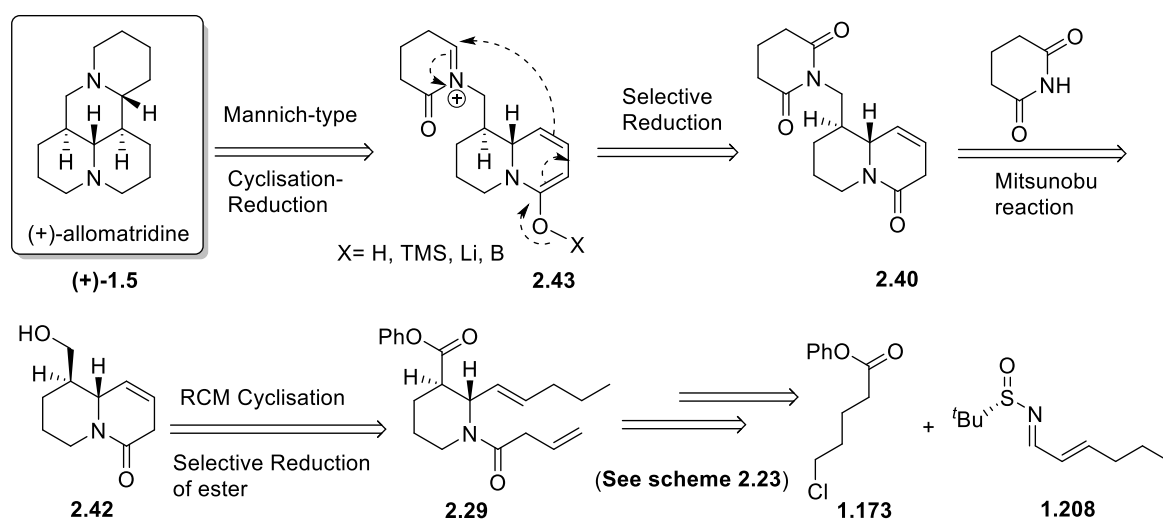
**Figure 2.21**: Retrosynthetic analysis of (+)-allomatridine ((+)-**1.5**)

### 2.4.1.1      The synthesis of a tricyclic imide intermediate towards (+)-allomatridine

The attempted synthesis of (+)-allomatridine started from the intermediate **2.29** which was used previously during the synthesis of (−)-epilupinine (**Scheme 2.22**). There are two pathways leading to tricyclic imide **2.40**; the first route involved cyclisation of **2.29** using Grubbs II catalyst to provide quinolizidinone **2.30** (**Scheme 2.24**). Selective reduction of ester **2.30** using LiAlH$_4$ at −20 °C for 30 min gave the corresponding alcohol **2.42**. Mitsunobu reaction with glutarimide was unsuccessful in the presence of DEAD and triphenylphosphine. Several attempts to couple glutarimide with primary alcohol **2.47**, under different Mitsunobu conditions failed.
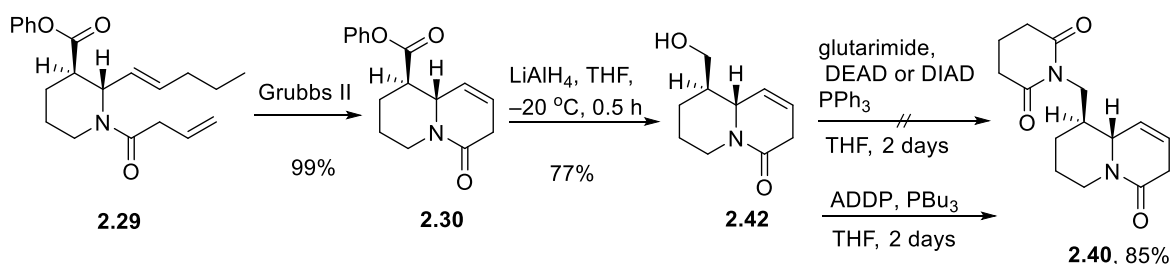


**Scheme 2.24**: A first pathway toward the synthesis of tricyclic imide **2.40**

Both DIAD and DEAD were applied to this transformation, but none of the desired product was obtained in the reaction and quantitative recovery of alcohol **2.42** was observed. In this case, both DIAD and DEAD were not efficient in deprotonating the acidic hydrogen,[146] due to attack of the hydrazo anion **2.45** on the alkoxyphosphonium **2.46** directly to afford alkylated hydrazine derivative **2.47** as the by-product (**Scheme 2.25**). However, using strong electron donating groups such as are present in 1,1'-(azodicarbonyl) dipiperidine (ADDP)[147] and Bu$_3$P in the modified Mitsunobu reaction under more concentrated conditions successfully generated imide **2.40** in high yield (**Scheme 2.24**). Using ADDP increases reactivity of phosphonium intermediate **2.44** in order to facilitate the

nucleophilic attack of alcohol, and increase its basicity in the intermediate **2.45**, and to be more efficient in deprotonating the acidic hydrogen of glutarimide to form **2.48** (**Scheme 2.25**).
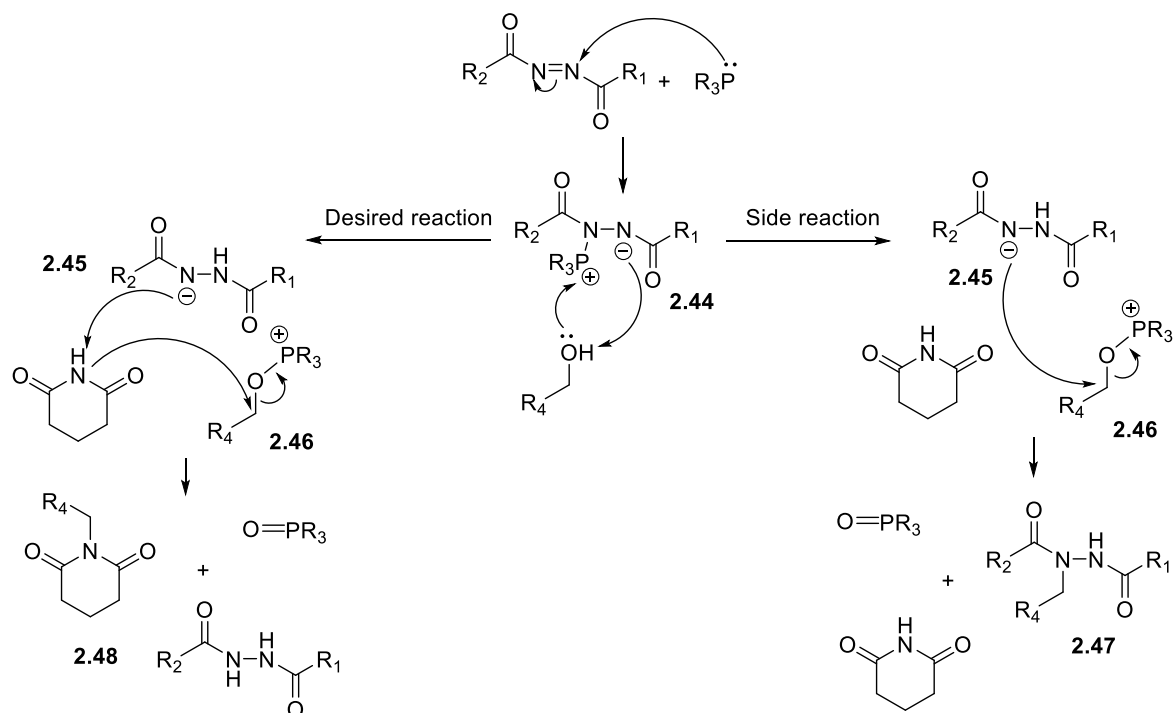


**Scheme 2.25**: Proposed mechanism of the Mitsunobu reaction.

The second pathway begins from selective reduction of ester **2.29** using LiAlH$_4$ to give the corresponding alcohol **2.49** (**Scheme 2.26**). Partial isomerisation of the $\beta,\gamma$-unsaturated alcohol **2.49** was obtained under the reaction conditions to give $\alpha,\beta$-unsaturated alcohol **2.50** as by-product in 10% yield. Mitsunobu reaction of alcohol **2.49** with glutarimide in the presence of ADDP provided the corresponding imide **2.51**.
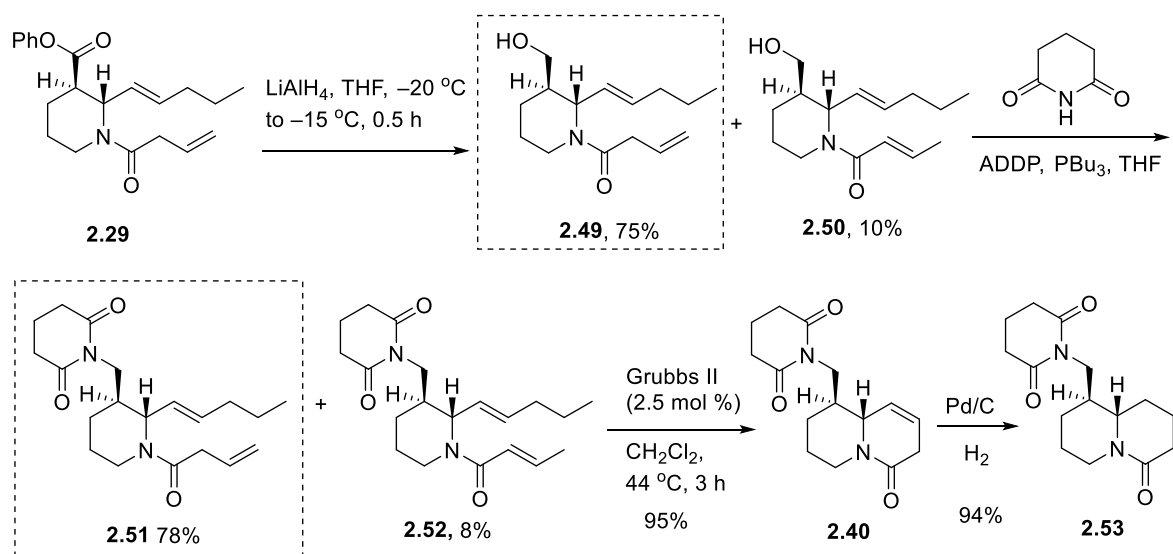


**Scheme 2.26**: Alternative pathway toward the synthesis of tricyclic imide **2.40**

The undesired $\alpha,\beta$-unsaturated amide **2.52** was also formed from partial isomerisation of $\beta,\gamma$-unsaturated amide **2.51**. Although partial transformation into the corresponding $\alpha,\beta$-unsaturated amide **2.52** was observed, RCM of $\beta,\gamma$-unsaturated amide **2.51** afforded the tricyclic imide **2.40** in 95% yield. The stereochemistry of tricyclic imide **2.40** was confirmed by single crystal X-ray structure determination (**Figure 2.22**). Hydrogenation of tricyclic imide **2.40** led to form (−)-10-oxo-lamprolobine **2.53** in 94% yield (**Scheme 2.26**).



**2.40**
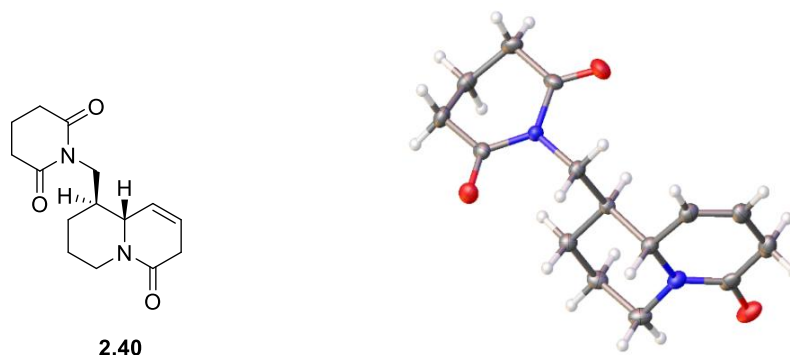
**Figure 2.22**: X-ray crystal structure of tricyclic imide **2.40**

The first route is clearly preferred, as it avoids the undesired isomerisation that complicated the second approach and gives the desired tricyclic intermediate **2.40** in good overall yield. With the tricyclic imide **2.40** in hand, we explored its use as a key intermediate for the *N*-acyliminium ion cyclisation. Cyclisation of tricyclic imide **2.40** was attempted using several different approaches, followed by hydrogenation and reduction to access (+)-allomatridine ((+)-**1.5**), and these efforts are described in the next section.

### 2.4.1.2      Efforts towards the synthesis of (+)-allomatridine

The final cyclisation towards the synthesis of (+)-allomatridine ((+)-**1.5**) focused on establishing a suitable *N*-acyliminium ion precursor (**Scheme 2.28**). Utilising a procedure adapted from Grigg and co-workers (**Scheme 2.27**),[148] selective reduction of the tricyclic imide **2.40** was achieved to provide hydroxylactam **2.56** and enamide **2.57** using LiEt$_3$BH at −78 °C in CH$_2$Cl$_2$ (**Scheme 2.28**).



**2.54**                                                   **2.55**
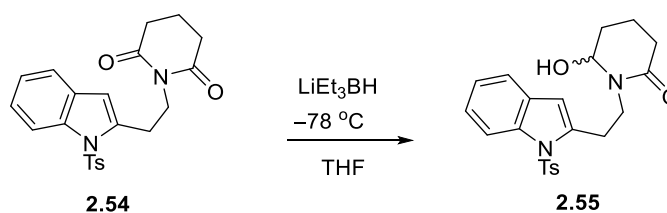
**Scheme 2.27**: Grigg's selective reduction of imide

Subsequent, attempted *N*-acyliminium ion cyclisation of **2.56** and **2.57** in the presence of TFA in CH₂Cl₂ resulted only the tricyclic enamide **2.57**, even after extended reaction periods.
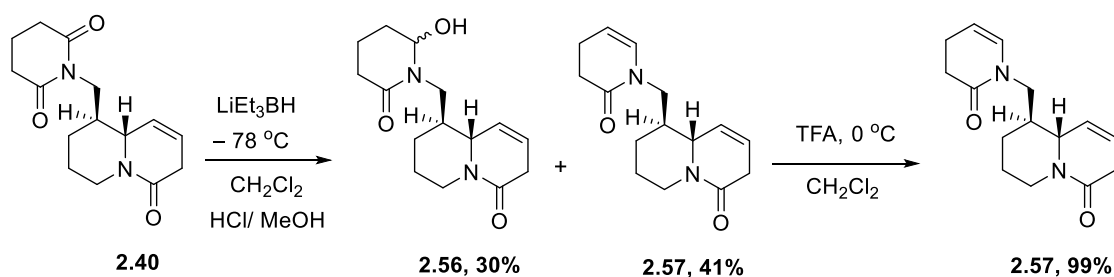


**Scheme 2.28**: Selective reduction of tricyclic imide

In an attempt to induce cyclisation *via* enolisation-Mannich-type cyclisation, we used Et₃N in the presence of a Lewis acid at 0 °C. Even after extended reaction time at rt cyclisation products were not observed, and only tricyclic enamide **2.57** was obtained (**Scheme 2.29**). We could infer that the desired reactive *N*-acyliminium ion **2.58** was being formed under the reaction conditions, but the cyclisation was not taking place. Instead of undergoing cyclisation, the intermediate *N*-acyliminium eliminated to give the enamide **2.57** (during the reaction or upon work-up). A proposed mechanism is shown below. Due to the failure of these attempted Mannich cyclisation, we considered different approaches towards cyclisation.
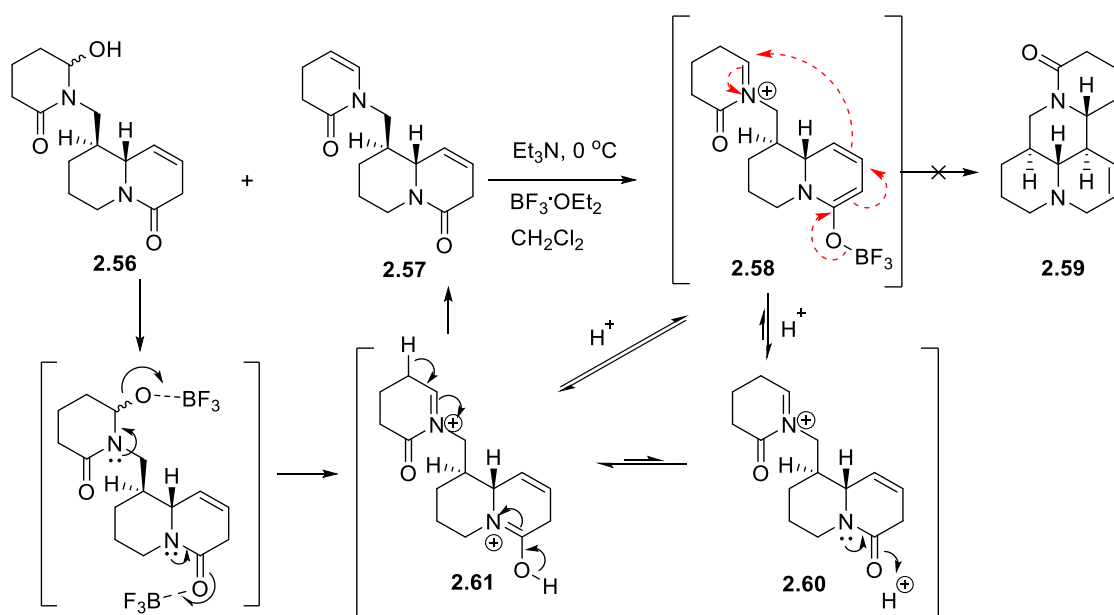


**Scheme 2.29**: Mannich cyclisation of iminium ion from tricyclic imide

### 2.4.1.3      Further attempts to cyclise tricyclic intermediates

It is worthwhile to mention here the numerous experiments that went into establishing the above sequence of reactions. In the beginning, we attempted to use LDA to deprotonate the amide followed by aldol type condensation by activation of the imide carbonyl using Lewis acid (**Scheme**

**2.30**, **A**). This procedure was not effective and gave tricyclic imide **2.40** as the major product. A small amount (~1 mg) of a compound tentatively assigned to be the tetracycle **2.62** was obtained.

However, evidence for this structure only came from mass spectrometry. We attempted alternative methods for cyclisation by aldol condensation using LDA again to deprotonate the amide, trapping the enolate with trimethylsilyl chloride (TMSCl) to form silyl enol ether **2.63** (**Scheme 2.30, B**). Only partial conversion was obtained due to instability of silyl enol ether **2.63**, with recovery of tricyclic imide **2.40**. No further reaction was attempted of silyl enol ether **2.63** due to its instability and conversion to the tricyclic imide **2.40**.
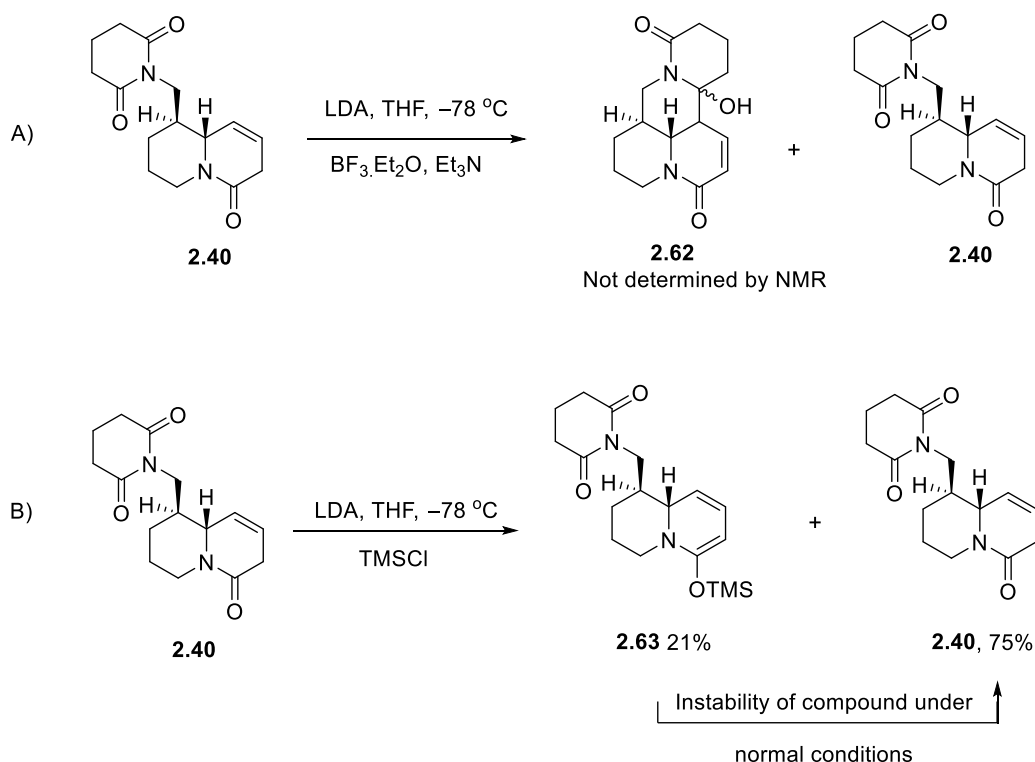


**Scheme 2.30**: Attempts to cyclisation of tricyclic imide **2.40** using LDA

Efforts turned toward reduction of both the imide and amide groups present in tricycle **2.40** followed by Mannich-type cyclisation (**Scheme 2.31**). First DIBAL-H (conditions **A**) were investigated to generate bishydroxyl lactam **2.64**, followed by addition of Lewis acid BF$_3$•OEt$_2$ for activation to form diiminium cation **2.65**. Under these conditions, the allomatridine precursor **2.40** was not obtained, but tricyclic enamide **2.57** was observed. Under basic conditions **B**, using an excess of DIBAL-H to form bishydroxyl lactam **2.65** followed by addition of Lewis acid and Et$_3$N also failed to access **2.57**.
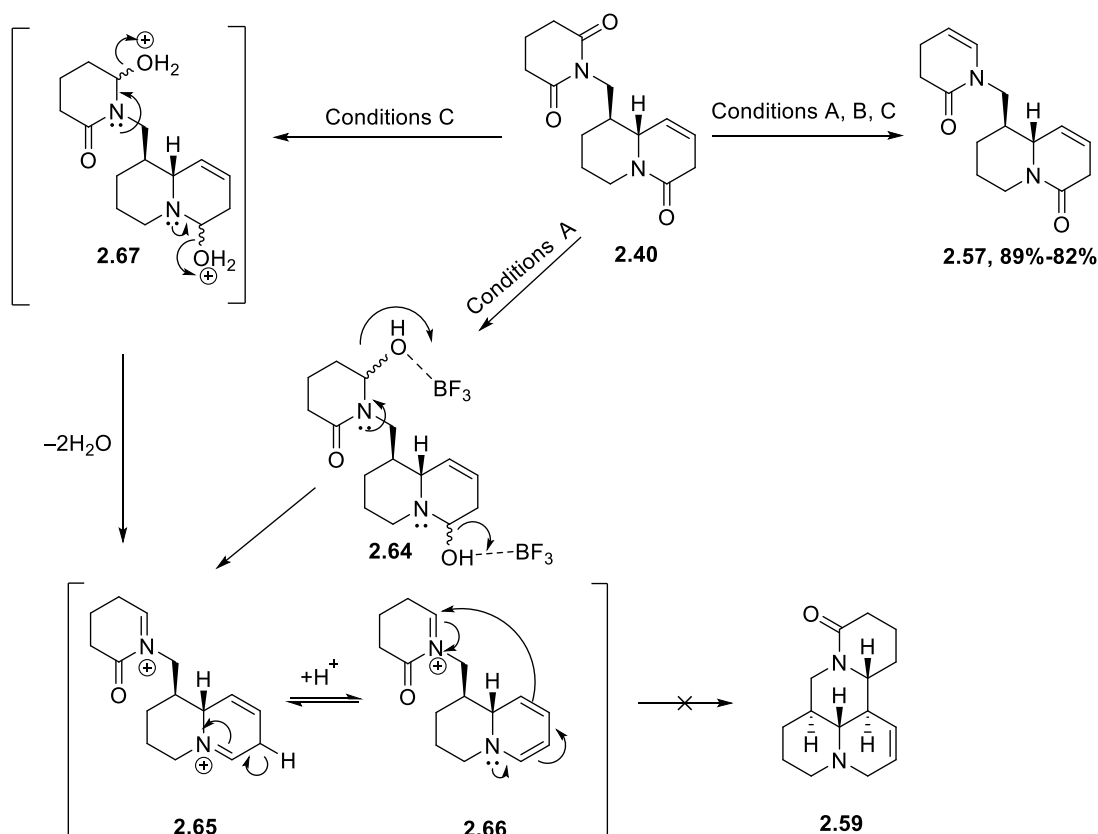
**Conditions A**    DIBAL-H (3 equiv.)      BF$_3$•OEt$_2$, CH$_2$Cl$_2$        −78 °C, rt 24 h

**Conditions B**    DIBAL-H (6 equiv.)      Et$_3$N, BF$_3$•OEt$_2$, CH$_2$Cl$_2$   −78 °C, then 0 °C, rt 24 h

**Conditions C**    DIBAL-H (3-6 equiv.)   aq. HCl 1N, CH$_2$Cl$_2$        −78 °C, to −60 °C, rt 24 h

**Scheme 2.31**: Attempts to access tetracycle **2.59** *via N*-acyliminum ion from tricyclic imide **2.40**

Finally, reduction of **2.40** followed by acidic conditions (conditions **C**) for dehydration of **2.67** only gave tricyclic enamide **2.57** in 89% − 82% yield for conditions **A**, **B** or **C**. It is possible that this general strategy could succeed under the right conditions, and with a suitable precursor. However, no further investigation of this route was carried out due to lack of time.

## 2.4.2      Retrosynthetic analysis of (−)-sparteine

We proposed an asymmetric synthesis of (−)-sparteine using the previously described imino aldol products. (−)-Sparteine possesses two stereochemical relationships: *syn* (*S,S*) and *anti* (*R,S*). The *syn* relationship is present in mono cyclised imino-aldol **2.13**. To build *anti* relationship might be achieved by *N*-acyliminium ion cyclisation of an intermediate **2.70** (**Figure 2.23**). Deprotection of mono imino-aldol adduct **2.13** followed by re-protection using Cbz group will provide **2.68**. Reduction of ester imide **2.68** will give the corresponding alcohol enamide, and subsequent Mitsunobu reaction in the presence of glutramide will afford **2.69**. Selective reduction of imide **2.69**

followed by cyclisation of intermediate **2.70** *via N*-acyliminium ion will establish tricyclic cation **2.71**. Reduction of iminum ion of **2.71** and then deprotective cyclisation, will generate oxo-sparteine **1.6** followed by reduction of amide **1.6** to access (−)-sparteine (−)-**1.3**.
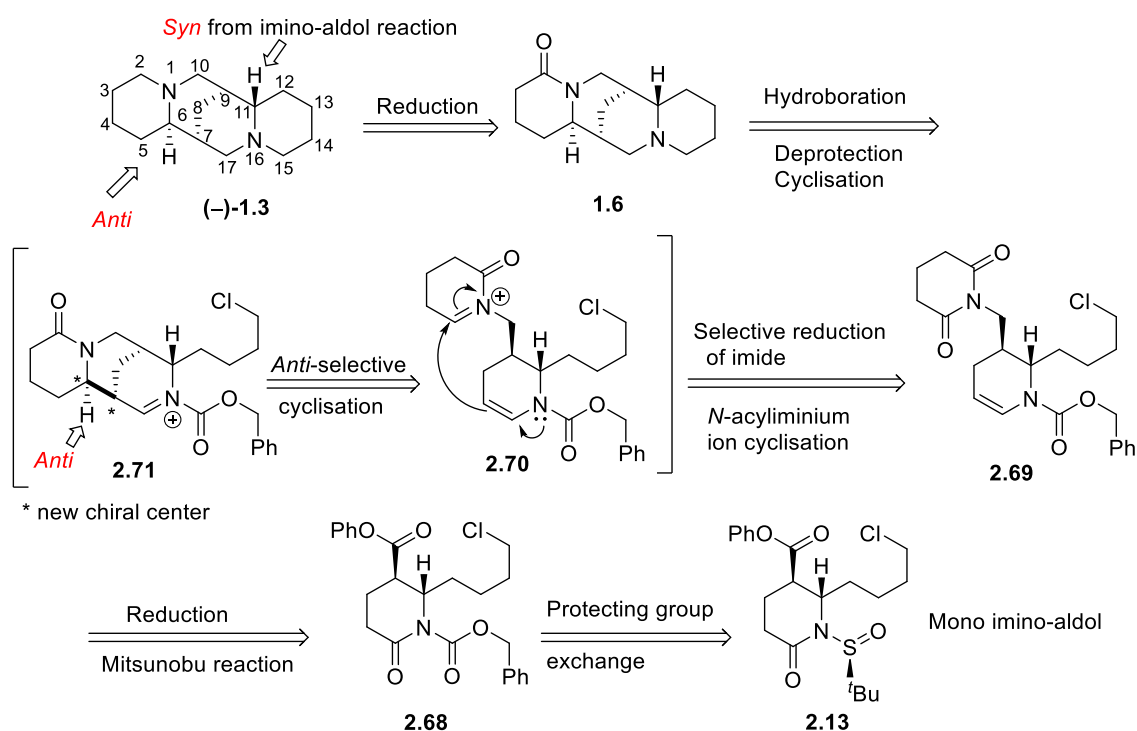


**Figure 2.23**: Retrosynthetic analysis of (−)-sparteine over *N*-acyliminium ion cyclisation

### 2.4.2.1        Towards a stereocontrolled synthesis of (−)-sparteine

The mono imino-aldol reaction to give cyclised-*syn* mono **2.13** was described in section 2.2. Our plan to synthesise (−)-sparteine requires a stereocontrolled *N*-acyliminium ion cyclisation to generate the *syn,anti*-product **1.53** (**Figure 2.24**). The *syn*-stereochemistry is present in the intermediate **2.13**, while the *anti*-stereochemistry **2.71** may be achieved by *N*-acyliminum ion cyclisation (**Figure 2.23**). Previous work by Bohlmann *et al.* reported a similar cyclisation to give (±)-sparteine, which suggested a chair transition state cyclisation *via an* iminium ion intermediate (**Figure 2.24**).[70] The cyclised *syn* imino-aldol adduct **2.13** was used as starting point to access (−)-sparteine.
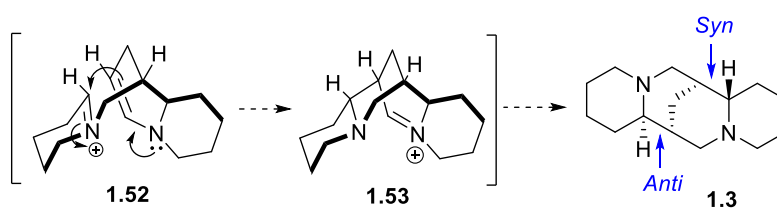


**Figure 2.24**: Bohlmann's reported synthesis of (±)-sparteine

However, sulfinyl auxiliary group in **2.13** proved to be unstable under a variety of conditions attempted cyclisation. Therefore, we replaced the *N*-sulfinyl auxiliary group with a more stable protecting group. Deprotection of *N*-sulfinyl auxiliary of **2.13** under acidic conditions followed by re-protection of *syn*-lactam **2.28** using LDA or *n*-BuLi with benzyl chloroformate (CbzCl) gave imide **2.68** (**Scheme 2.32**).
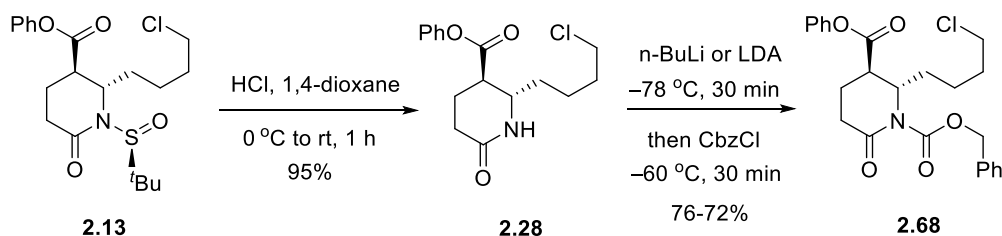


**Scheme 2.32**: The early stages towards the synthesis of (−)-sparteine

In our proposed approach to the synthesis of (−)-sparteine, we planned to introduce a new ring *via* reduction of the ester imide **2.68** followed by treatment of alcohol enamide **2.72** with glutarimide under Mitsunobu conditions to give imide **2.69** (**Scheme 2.33**). The reduction of ester imide **2.68** gave the product **2.72** and equilibrium with hemiaminal **2.73**, and a mixture of alcohol imide **2.74** and enamide **2.75** were identified only by mass spectrometry (MS). In addition, the selective reduction of the ester group in **2.68** using different reducing agents was not possible due to the reactivity of the imide towards the reducing agent. Although this procedure was not satisfactory to produce the desired product **2.72** in good yield, we thought that the corresponding alcohol **2.74** could undergo Mitsunobu coupling with glutarimide later to access (−)-sparteine by *N*-acyliminium cyclisation approach. Unfortunately, insufficient time was available to optimise the reduction.
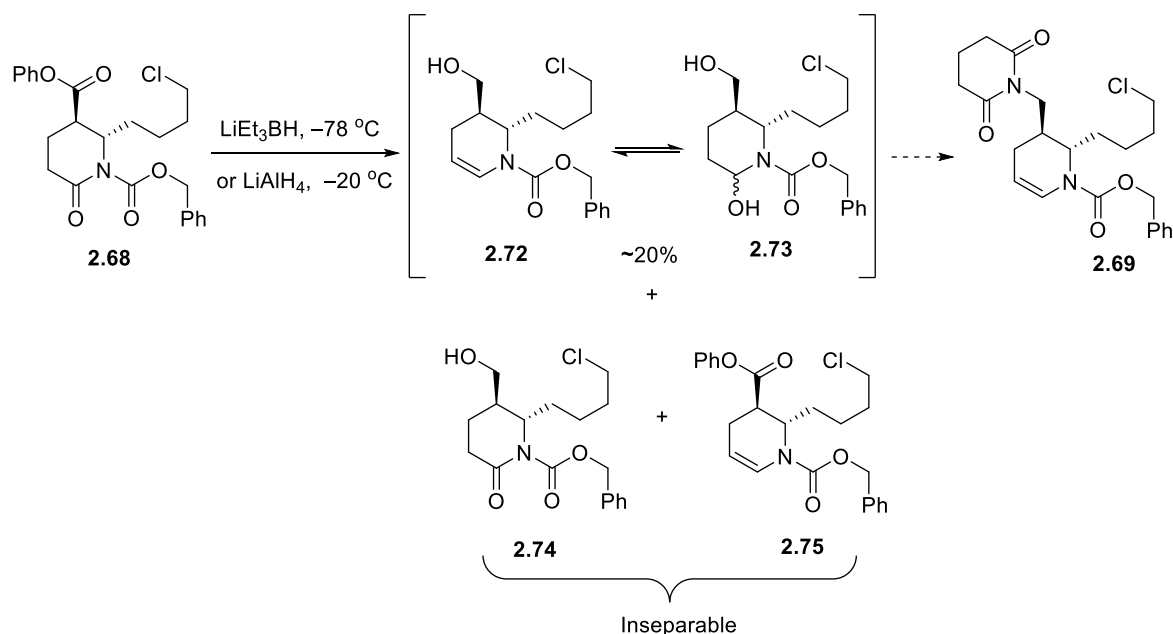


**Scheme 2.33**: Failed attempt to synthesise the key intermediate imide **2.69**

At this point, we proposed an alternative way to prepare *anti*-adduct **2.76** using soft enolisation of **2.68** in the presence of Lewis acid to perform an imino-aldol reaction with halo imine **1.205** to access (−)-sparteine (**Scheme 2.34**).
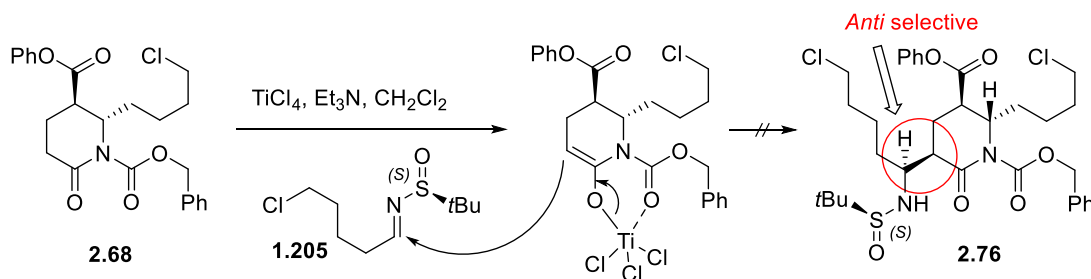


**Scheme 2.34**: Proposed an alternative way using soft enolisation of **2.68**

Unfortunately, the soft enolisation of **2.68** was not successful under Lewis acid conditions to achieve *anti*-selective addition. By this stage in the project, we not able to further investigate introduction of the new ring due to time constraints, and could not pursue the synthesis further. It also became clear that the substrate **2.68** used in this route also had the same underlying problems in terms of selective reduction of the imide and ester groups needed for the synthesis of (−)-sparteine.

### 2.4.3       Conclusions and future work:

Two approaches towards the syntheses of (+)-allomatridine and (−)-sparteine are described in this section. The attempted synthesis of (+)-allomatridine started from imino-aldol reaction between unsaturated imine **1.208** and phenyl ester **1.173** to give the intermediate **2.29** (**Scheme 2.35**). In a modified synthetic route, we were able to form a tricyclic imide **2.40** from the hydroxy quinolizidinone **2.42** as a precursor for *N*-acyliminium cyclisation. The structure of enamide intermediate **2.40** was confirmed by single crystal X-ray crystallography. Different cyclisation conditions where attempted for *N*-acyliminium cyclisation towards to allomatridine, but all of them failed at the stage of the final cyclisation. However, the *N*-acyliminium cyclisation approach to allomatridine could still be viable under appropriate conditions, and using a suitable precursor.
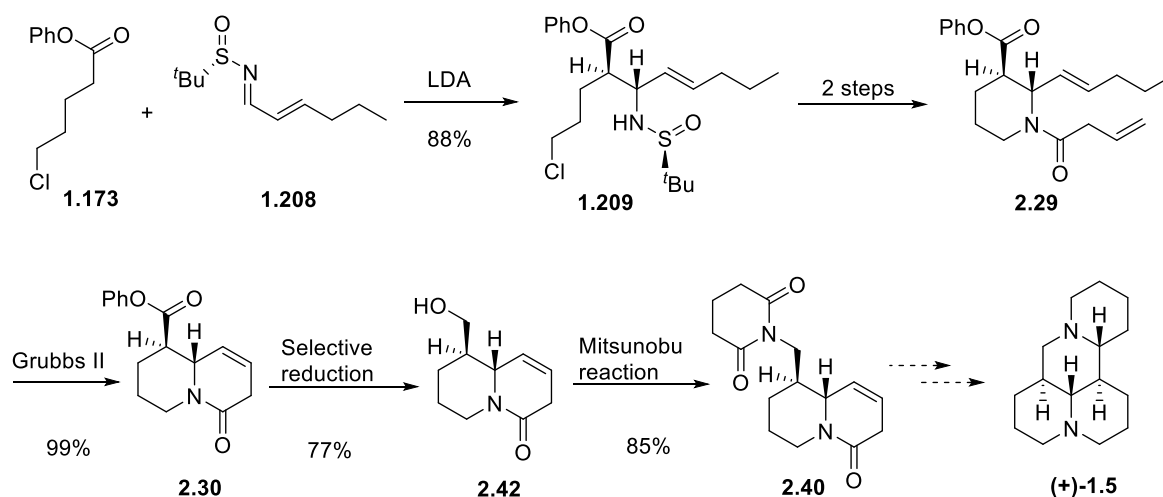
**Scheme 2.35:** Towards the synthesis of (+)-allomatridine ((+)-**1.5**)

Toward the synthesis of (+)-allomatridine ((+)-**1.5**) using mono imino-aldol **2.11** as starting point (**Scheme 2.36**) to access a key intermediate of tricyclic imide **2.80**. Deprotection of **2.11** gave unsaturated lactam **2.77** following by acylation with 3-butinoic acid could give **2.78**. RCM of **2.78**, and subsequence reduction could form bicyclic **2.79**. Mitsunobu reaction of hydroxy quinolizidinone **2.79** with glutarimide could afford **2.80**. Selective reduction of imide **2.80** followed by *N*-acyliminium cyclisation of **2.81** could generate tetracycle **2.82**. Finally, hydrogenation and reduction of **2.82** could furnish to (+)-allomatridine ((+)-**1.5**).
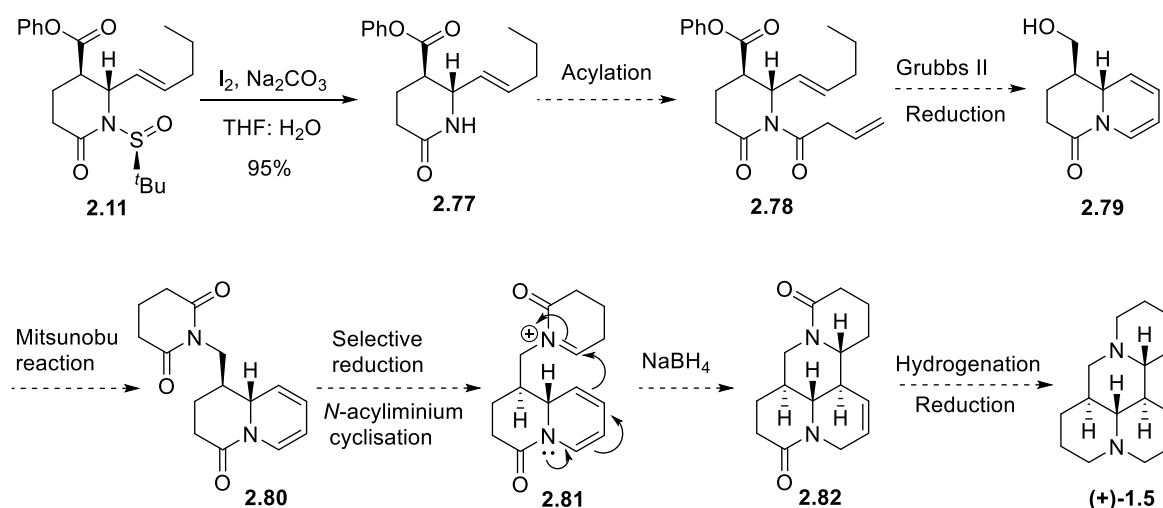


**Scheme 2.36:** Alternative approach towards the synthesis of (+)-allomatridine ((+)-**1.5**)

The *N*-acyliminium cyclisation approach to sparteine was investigated from an advanced intermediate at the stage of the cyclisation of imide enamide **2.69** (**Scheme 2.37**). *Syn*-lactam **2.28** was used as starting point for synthetic route to sparteine, where **2.28** was obtained from mono imino-aldol reaction of halo imine **1.205** and diphenyl glutarate (**2.1**). Several reductive conditions were attempted to reduce the ester imide **2.68** to hydroxy enamide **2.72**. However, reduction of **2.68** gave a mixture of the desired hydroxy enamide **2.72** and equilibrium with hemiaminal **2.73**, also the minor products **2.74** and **2.75** were identified only by mass spectrometry (MS). Attempted intermolecular imino-aldol reaction of **2.68** with a sulfinyl imine **1.205** was also unsuccessful.
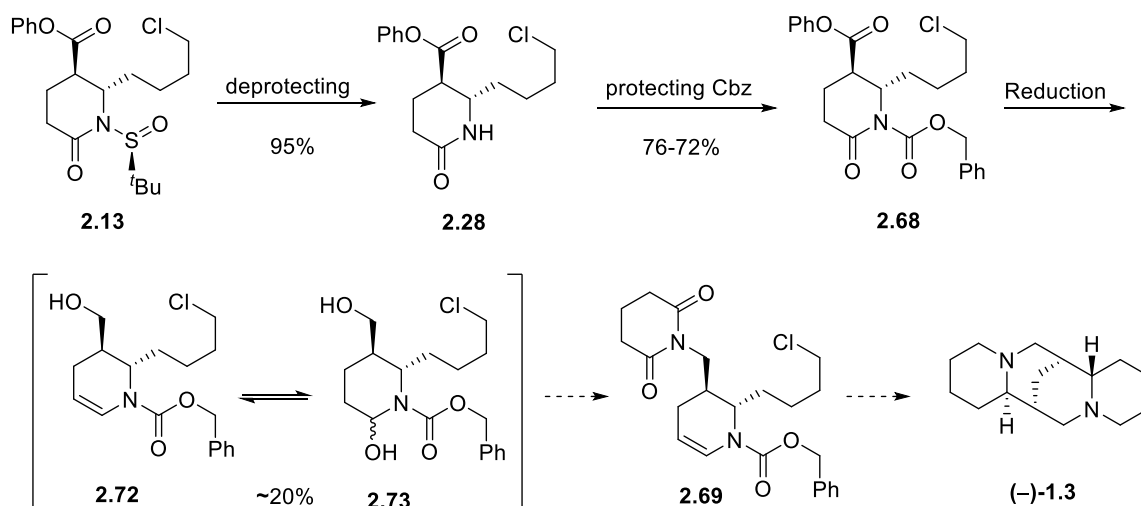


**Scheme 2.37**: Attempted route towards the synthesis of (−)-sparteine (−)-**1.3**

# Chapter 3:    Experimental Details

## 3.1    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 solvent THF (from Na/benzophenone), MeCN, $CH_2Cl_2$ (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, ninhydrin, potassium permanganate or vanillin. Flash column chromatography was proceeded 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 ($cm^{-1}$).

$^{1}$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$, DMSO-*d6*, solutions (purchased from Cambridge Isotope Laboratories, Inc.) at 298 K using Bruker DPX400, AVII400, AVIIHD400 (400 and 100 MHz respectively) and at 353 K using Bruker AVII400 (400 and 101 MHz respectively) or Bruker AVIIHD500 (500 and 125 MHz respectively) spectrometers. Chemical shifts values ($\delta$) are reported in ppm relative to residual chloroform ($\delta$7.27 ppm for $^{1}$H, $\delta$77.00 ppm for $^{13}$C), dimethyl sulfoxide ($\delta$2.50 ppm for $^{1}$H, $\delta$39.51 ppm for $^{13}$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 100 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. Electrospray (ESI) low resolution mass spectra were recorded on a Waters TQD quadrupole spectrometer.

Compounds containing a $\alpha,\beta$- and $\beta,\gamma$-unsaturated amide and dioxo-bispidine 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.

## 3.2      Procedures and Characterisation Data

### 3.2.1       Diphenyl glutarate (2.1)
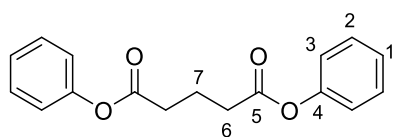


$C_{17}H_{16}O_4$
Mol Wt: 284.31

**Method A:** Following the procedure described by Watkin.[135]

To a solution of glutaric acid (**2.6**, 0.216 g, 15.5 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C under Ar was added anhydrous DMF (0.10 mL, 1.3 mmol) followed by oxalyl chloride (1.64 mL, 19.4 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then was allowed to warm to rt. The reaction was stirred at rt for 3 h. Upon completion the reaction mixture was concentrated *in vacuo* giving colourless oil. To the neat acid chloride at rt under Ar was added phenol (1.60 g, 17.1 mmol) in one portion with $CH_2Cl_2$ (20 mL) and the solution was stirred for 14 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 10 mL). The organics were combined, washed with 10% $K_2CO_3$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The desired product was isolated by column chromatography (silica gel, *eluent* gradient: EtOAc/Hexane 1:9 → 3:7) yielding the title diphenyl glutarate (**2.1**) as a colourless oil (2.43 g, 11.4 mmol, 73% yield). Physical and spectroscopic data are consistent with reported values.[148]

**Method B:** Following the procedure described by Simion *et al*.;[149]

To a solution of glutaric acid (**2.6**, 1.92 g, 14.5 mmol) in $CH_2Cl_2$ (18.7 mL) at 0 °C under Ar was added DMF (500 µL, 6.45 mmol) followed by oxalyl chloride (3.00 mL, 36.2 mmol) dropwise over 15 min. The reaction mixture was stirred at 0 °C for 1 h, and allowed to warm to rt. After 3 h the solution was re-cooled to 0 °C.

In a separate flask, a solution of phenol (2.73 g, 29.0 mmol) was dissolved in 10% aqueous NaOH (38.6 mL) and a solution of tetrabutylammonium chloride (TBAC) (800 mg, 2.90 mmol) in $CH_2Cl_2$ (9.6 mL) was added. The resulting mixture was cooled to 0 °C and the solution of diacyl chloride (prepared above) was added in one portion. The reaction mixture was stirred vigorously at 0 °C for 10 min and was then poured onto ice water (50 mL). The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and the solvent was removed *in vacuo*. The resulting golden syrup was

purified by column chromatography (silica gel, hexane/EtOAc, 9:1) to afford the title diester **2** as a white solid, which was recrystallised from benzene (4.05 g, 14.2 mmol, 98%). Physical and spectroscopic data are consistent with reported values.[148,149]

| **M.P.** | 46 – 47 °C. (Lit.[149] 45 – 46 °C ) |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3068, 3041, 2945, 1749, 1591, 1491, 1195, 1124 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.40 (4H, t, $J$ = 7.8 Hz, 2 x **H$_2$**), 7. 28 – 7.23 (2H, m, 2 x **H$_1$**), 7.12 (4H, d, $J$ = 7.8 Hz, 2 x **H$_3$**), 2.75 (4H, t, $J$ = 7.3 Hz, 2 x **H$_6$**), 2.22 (2H, quin, $J$ = 7.3 Hz, **H$_7$**) ppm. |
| **$^{13}$C NMR** | (100 MHz, CDCl$_3$) δ 171.4 (2 x **C$_5$**), 150.6 (2 x **C$_4$**), 129.4 (4 x **C$_2$**), 125.8 (2 x **C$_1$**), 121.5 (4 x **C$_3$**), 33.2 (2 x **C$_6$**), 20.0 (**C$_7$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 307.2 [M+Na]$^+$. |

### 3.2.2    (−)-(*S*)-*N*-((1*E*,2*E*)-Hex-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (1.208)



C$_{10}$H$_{19}$NOS
Mol wt. 201.33
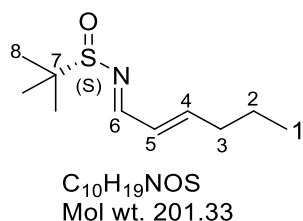
**Method A:** Following the procedure described by Cutter.[134]

To a solution of (*S*)-tertbutylsulfinamide (**2.9**, 1.21 g, 10.0 mmol) in CH$_2$Cl$_2$ (20 mL) at 40 °C under Ar were added CuSO$_4$ (6.38 g, 40.0 mmol) and *trans*-2-hexen1-al (**2.10**) (0.98 g, 10 mmol). After 20 h the reaction was filtered through a pad of celite and the residue washed with EtOAc (3 × 10 mL). The organic phases were combined and the solvent removed *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/*n*-hexane 1:19 → 3:17) to afford the title compound as a yellow oil (1.51 g, 7.50 mmol, 75%). Physical and spectroscopic data are consistent with reported values.[135]

**Method B:** Following the procedure described by Raghaven *et al*.[150]

To a solution of (*S*)-tertbutylsulfinamide (**2.9**, 3.27 g, 27.0 mmol) and *trans*-2-hexen-1-al (**2.10**, 4.80 mL, 40.5 mmol) in THF (30 mL) at 0 °C under $N_2$ was added Ti(OEt)$_4$ (9.00 mL, 42.9 mmol) dropwise turning the solution yellow. The reaction was stirred for 1 h and additional Ti(OEt)$_4$ (6 mL, 28.58 mmmol) was added dropwise at 0 °C. The reaction was monitored by TLC (*eluent*: EtOAc/ Hexane 1:4) and upon completion was poured onto brine (100 mL). The reaction was stirred rapidly for 5 min and filtered through a sintered funnel. The filter cake was washed with hot EtOAc (4 × 50 mL) and the phases separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), the organics combined, washed with brine (2 × 30 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The title compound was isolated by column chromatography (silica gel, *eluent*: EtOAc/*n*-hexane 1:4) as a pale yellow oil (5.40 g, 26.8 mmol, 99%). Physical and spectroscopic data are consistent with reported values.[135]

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 2959 ( m), 2929 , 2871 , 1639 , 1579 , 1171 , 1079  cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 8.07 (1H, d, *J* = 9.0 Hz, **H$_6$**), 6.38 (1H, m, **H$_4$**), 6.32 (1H, m, **H$_5$**), 2.24 (2H, q, *J* = 6.8 Hz, **H$_3$**), 1.42 (2H, sxt, *J* = 7.3 Hz, **H$_2$**), 1.09 (9H, s, **H$_8$**), 0.84 (3H, t, *J* = 7.4 Hz, **H$_1$**) ppm |
| **$^{13}$C NMR** | (100 MHz, CDCl$_3$) δ 164.8 (**C$_6$**), 151.1 (**C$_4$**), 128.6 (**C$_5$**), 56.8 (**C$_7$**), 34.7 (**C$_5$**), 22.1 (**C$_3$**), 21.2 (**C$_8$**), 13.4 (**C$_1$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 202.2 [M+H]$^+$. |

### 3.2.3    Phenyl 5-chloropentanoate (1.173)
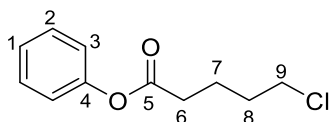


$C_{11}H_{13}ClO_2$
Mol wt. 212.67

**Method A:** Following the procedure described by Watkin.[135]

To a solution of 5-chlorovaleric acid (**2.31**, 0.216 g, 15.5 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C under Ar was added anhydrous DMF (0.100 mL, 1.30 mmol) followed by oxalyl chloride (1.64 mL, 19.4 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then was allowed to warm to rt. The reaction was stirred at rt for 3 h. Upon completion the reaction mixture was concentrated *in vacuo* giving colourless oil. To the neat crude acid chloride **2.32** at rt under Ar was added phenol (1.60 g, 17.0 mmol) in one portion with $CH_2Cl_2$ (20 mL) and stirred for 14 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 10 mL). The organics were combined, washed with 10% $K_2CO_3$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The desired product was isolated by column chromatography (silica gel, *eluent:* EtOAc/Hexane 1:9 → 3:7) yielding the title compound **1.173** as a colourless oil (2.43 g, 11.4 mmol, 73% yield). Physical and spectroscopic data are consistent with reported values.[135]

**Method B:**

Following the procedure B described for the synthesis of **2.1**, 5-chlorovaleric acid (**2.31**, 5.40 g, 39.5 mmol) afforded the title compound (8.25 g, 38.8 mmol, 98%) as a colourless oil. Physical and spectroscopic data are consistent with reported values.[135]

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 2957, 1754, 1593, 1492, 1192, 1121 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.39 (2H t, *J* = 7.3 Hz, **H$_2$**), 7.25 (1H, m, **H$_1$**), 7.09 (2H, d, *J* = 7.9 Hz, **H$_3$**), 3.66 – 3.56 (2H, m, **H$_9$**), 2.67 – 2.58 (2H, m, **H$_6$**), 1.99 – 1.88 (4H, m, **H$_7$** & **H$_8$**) ppm. |
| **$^{13}$C NMR** | (100 MHz, CDCl$_3$): δ 171.2 (**C$_5$**), 150.4 (**C$_4$**), 129.1 (2 x **C$_2$**), 125.5 (**C$_1$**), 121.2 (2 x **C$_3$**), 44.1 (**C$_9$**), 33.1 (**C$_6$**), 31.4 (**C$_8$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 213.1 [M$^{35}$Cl+H]$^+$, 215.1 [M$^{37}$Cl+H]$^+$. |

### 3.2.4    Phenyl (2*R*,3*S*,*E*)-3-(((*S*)-tert-butylsulfinyl)amino)-2-(3-chloropropyl)oct-4-enoate (1.209)



$C_{21}H_{32}ClNO_3S$
Mol wt.414.00
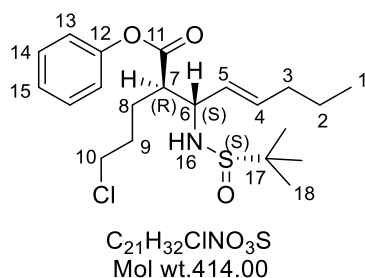
Following the general procedure described by Cutter.[134]

To a solution of LDA (7.20 mL, 0.9 M in THF, 4.48 mmol) at −78 °C under Ar was added to solution of phenyl 5-chloropentanoate (**1.173**, 1.35 g, 6.47 mmol) in THF (50 mL) dropwise over 45 min. The reaction was stirred for 30 min at −78 °C then a solution of sulfinylimine **1.208** (1.00 g, 4.98 mmol) in THF (5 mL) was added dropwise over 10 min. The reaction was stirred at −78 °C for 1 h and quenched with sat. NH₄Cl (25 mL) dropwise. The reaction was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer extracted with EtOAc (3 × 20 mL) and Et₂O (3 × 20 mL). The organic phases were combined and washed with brine (12.5 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude was purified by column chromatography (silica gel, *eluent* gradient EtOAc/hexane 1:9 → 1:1) yielding the major diastereomer **1.209** (*R*,*S*) as a yellow oil (1.81 g, 4.38 mmol, 88 %), the minor diastereomer (*S*,*S*) **2.33** was isolated as a yellow oil (120 mg, 0.290 mmol, 1%), and the mixed fractions as a yellow oil (116 mg, 5%). Physical and spectroscopic data are consistent with reported values.[135]

**Data for major product (2*R*,3*S*,*E*)- 1.209:**

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3190, 2959, 2929, 2870, 1752, 1191, 1161, 1129, 1054 cm⁻¹. |
| **¹H NMR** | (400 MHz, CDCl₃) δ 7.39 (2H, t, *J* = 7.6 Hz, **H₁₄**), 7.25 (1H, m, **H₁₅**), 7.06 (2H, d, *J* = 7.8 Hz, **H₁₃**), 5.81 (1H, m, **H₄**), 5.48 (1H, dd, *J* = 15.3, 8.3 Hz, **H₅**), 4.11 (1H, m, **H₆**), 3.94 (1H, d, *J* = 4.2 Hz, **H₁₆**), 3.59 (2H, m, **H₁₀**) 2.94 (1H, dt, *J* = 9.4, 4.7 Hz, **H₇**), 2.12 − 2.04 (2H, m, **H₃**), 2.04 − 1.8 (4 H, m, **H₈** & **H₉**), 1.44 (2H, sxt, *J* = 7.3, **H₂**), 1.23 (9H, s, **H₁₈**), 0.91 (3H t, *J* = 7.4 Hz, **H₁**) ppm. |
| **¹³C NMR** | (101 MHz, CDCl₃) δ 171.8 (**C₁₁**), 150.3 (**C₁₂**), 136.4 (**C₄**), 129.5 (2 x **C₁₄**), 126.5 (**C₅**), 126.1 (**C₁₅**), 121.4 (2 x **C₁₃**), 58.7 (**C₆**), 55.6 (**C₁₇**), 50.4 (**C₇**), 44.3 (**C₁₀**), 34.3 **C₃**), 30.3 (**C₉**), 25.9 (**C₈**), 22.6 (**C₁₈**), 22.1 (**C₂**), 13.6 (**C₁**) ppm. |

| **LRMS** | (ESI$^+$) *m/z* 414.25 [M$^{35}$Cl+H]$^+$, 416.2 [M$^{37}$Cl+H]$^+$, 436.13 [M$^{35}$Cl+Na]$^+$, 438.3 [M$^{37}$Cl+Na]$^+$. |

**Selected data for minor product (2*S*,3*S*,*E*)- 2.33:**

| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.40 (2H, t, *J* = 7.7 Hz, **H$_{14}$**), 7.25 (1H, m, **H$_{15}$**), 7.08 (2H, d, *J* = 7.8 Hz, **H$_{13}$**), 5.79 (1H, m, **H$_4$**), 5.41 (1H, dd, *J* = 15.3, 7.6 Hz, **H$_5$**), 4.20 − 4.01 (2H, m, **H$_6$** & **H$_{16}$**), 3.61 (2H, t, *J* = 5.0 Hz, **H$_{10}$**), 2.83 (1H, m, **H$_7$**), 2.09 (2H, q, *J* = 6.9 Hz, **H$_3$**), 2.02 − 1.91 (4H, m, **H$_8$** & **H$_9$**), 1.50 − 1.37 (2H, m, **H$_2$**), 1.22 (9H, s, **H$_{18}$**), 0.92 (3H, t, *J* = 7.3 Hz, **H$_1$**) ppm. |

| **$^{13}$C NMR** | (100 MHz, CDCl$_3$) δ 172.5 (**C$_{11}$**), 150.3 (**C$_{12}$**), 135.4 (**C$_4$**), 129.6 (2 x **C$_{14}$**), 128.2 (**C$_5$**), 126.2 (**C$_{15}$**), 121.4 (2 x **C$_{13}$**), 58.9 (**C$_6$**), 55.8 (**C$_{17}$**), 50.1 (**C$_7$**), 44.3 (**C$_{10}$**), 34.3 **C$_3$**), 30.2 (**C$_9$**), 26.5 (**C$_8$**), 22.7 (**C$_{18}$**), 22.2 (**C$_2$**), 13.6 (**C$_1$**) ppm. |

### 3.2.5      Phenyl (2*S*,3*R*)-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate ( 1.210)
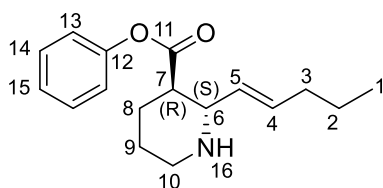


C$_{17}$H$_{23}$NO$_2$
Mol wt. 273.37

**Method A:**

Following the procedure described by Watkin.[135]

To a solution of imino-aldol adduct (**1.209**, 1.30 g, 3.14 mmol) in 1,4-dioxane (52 mL) at 0 °C was added conc. HCl (2.30 mL of ~36%, 9.42 mmol) dropwise. The mixture was stirred under Ar for 2 h. The reaction mixture was concentrated *in vacuo*. The crude material was dissolved in MeCN (52 mL) then K$_2$CO$_3$ (2.35 g, 15.7 mmol) and NaI (0.010 g, 0.10 mmol) were added portionwise. The resulting bright yellow solution was stirred at rt for 16 h, and then the solvent was removed *in vacuo*. The crude was re-dissolved in EtOAc/H$_2$O (1:1, 100 mL). The organic phases were separated. The aqueous phase was extracted with Et$_2$O (3 x 10 mL) and EtOAc (3 x 10 mL). The combined organic phases were washed with H$_2$O (20 mL) and brine (20 mL), dried (MgSO$_4$) and concentrated *in vacuo* to yield a white solid. The crude was passed through a plug of alumina (*eluent:* EtOAc) to

give the title piperidine **1.210** as a white solid (0.800 g, 2.92 mmol, 93%). The material was recrystallised from *n*-hexane to give pale yellow needles. Physical and spectroscopic data are consistent with reported values.[135]

**Method B:**

Following the procedure described by Chen *et al.*[151]

To a solution of imino-aldol adduct (**1.209**, 130 mg, 0.310 mmol) in THF/$H_2O$ (3:2, 6 mL) at rt was added $I_2$ (160 mg, 0.63 mmol). The reaction mixture was heated at 50 °C under Ar for 2 h before $Na_2CO_3$ (800 mg, 7.54 mmol) was added portionwise. The resulting dark brown solution was stirred at 50 °C for 4 h over which time it become light brown. The reaction mixture was diluted with $H_2O$ (5 mL). After removal of THF *in vacuo*, aqueous saturated $Na_2S_2O_3$ (0.100 mL) was added. The resulting mixture was extracted with $Et_2O$ (3 x 5 mL) and the combined organic phases were washed with brine (20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a white solid. The crude was passed through a plug of alumina (*eluent:* EtOAc) to give the title piperidine **1.210** as a white solid (82 mg, 0.30 mmol, 95%). Physical and spectroscopic data are consistent with reported values.[1]

| | |
|---|---|
| **M.P.** | 89 – 94 °C. |
| **FT-IR (neat)** | $v_{max}$ 3238, 2934, 2861, 2809, 1747, 1190, 1161, 1123 $cm^{-1}$. |
| **^{1}H NMR** | (400 MHz, $CDCl_3$) δ 7.36 (2H, t, *J* = 7.6 Hz, **H$_{14}$**), 7.21 (1H, m, **H$_{15}$**), 7.01 (2H, d, *J* = 7.6 Hz, **H$_{13}$**), 5.76 (1H, dt, *J* = 15.4, 7.1 Hz, **H$_4$**), 5.51 (1H, dd, *J* = 15.4, 7.8 Hz, **H$_5$**), 3.34 (1H, dd, *J* = 9.5, 8.3 Hz, **H$_6$**), 3.12 (1H, dt, *J* = 11.8, 1.9 Hz, **H$_7$**), 2.76 (1H, td, *J* = 12.1, 2.5 Hz, **H$_{10ax}$**), 2.50 (1H, ddd, *J* = 11.8, 10.0, 3. 7 Hz, **H$_{10eq}$**), 2.17 (1H, m, **H$_{8eq}$**), 2.03 (2H, q, *J* = 7.0 Hz, **H$_3$**), 1.85 – 1.67 (2H, m, **H$_{8ax}$ & H$_{9ax}$**), 1.65 – 1.45 (2H, m, **H$_{16}$ & H$_{9eq}$**), 1.40 (2H, sxt, *J* = 7.4 Hz, **H$_2$**), 0.89 (3H, t, *J* = 7.4 Hz, **H$_1$**) ppm. |
| **^{13}C NMR** | (100 MHz, $CDCl_3$) δ 172.8 (**C$_{11}$**), 150.6 (**C$_{12}$**), 133.5 (**C$_4$**), 130.7 (**C$_5$**), 129.3 (**C$_{14}$**), 125.7 (**C$_{15}$**), 121.5 (**C$_{13}$**), 61.1 (**C$_6$**), 49.3 (**C$_7$**), 46.2 (**C$_{10}$**), 34.4 (**C$_3$**), 28.1 (**C$_8$**), 24.9 (**C$_9$**), 22.2 (**C$_2$**), 13.6 (**C$_1$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 274.23 [M+H]$^+$. |

### 3.2.6 Phenyl (2*S*,3*R*)-1-(but-3-enoyl)-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate (2.29)
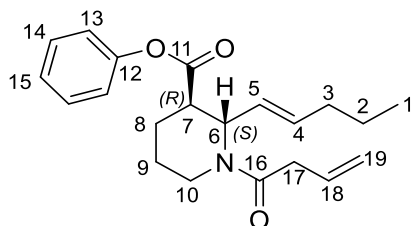


$C_{21}H_{27}NO_3$
Mol Wt: 341.45

To a solution of 3-butenoic acid (0.40 mL, 4.60 mmol) in $CH_2Cl_2$ (30 mL) was added DCC (61 mg, 1.72 mmol), then the reaction mixture was stirred at 0 °C for 15 min under Ar. To the reaction mixture was added a solution of piperidine (**1.210**, 600 mg, 2.20 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C over 15 min. The resulting mixture was stirred at rt for 4 h. The mixture was washed with water, sat. aq. $NaHCO_3$, brine (25 mL), dried over ($MgSO_4$) and concentrated *in vacuo* to give **2.21** as an oil. Purification by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane 1:19 → 3:7) yielded the title amide **2.29** as light yellow oil (640 mg, 1.88 mmol, 85%).

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 2957, 2928, 2870, 1751, 1632, 1492, 1192 cm$^{-1}$. |
| **$^1$H NMR** | (500 MHz, DMSO-*d6*, T= 373 K) δ 7.41 (2H, t, *J* = 7.5 Hz, **H$_{14}$**), 7.25 (1H, m, **H$_{15}$**), 7.10 (2H, d, *J* = 8.1 Hz, **H$_{13}$**), 5.91 (1H, ddt, *J* = 17.1, 10.4, 6.5 Hz, **H$_{18}$**), 5.66 −5.56 (2H, m, **H$_5$ & H$_4$**), 5.04 − 5.11 (2H, m, **H$_{19}$**), 4.00 (1H, br s, **H$_6$**), 3.18 (2H, d, *J* = 6.5 Hz, **H$_{17}$**), 3.1– 3.03 (1H, m, **H$_7$**), 2.97 (2H, m, **H$_{10}$**), 2.03 − 2.13 (3H, m, **H$_{8eq}$ & H$_3$**), 1.85 − 1.95 (1H, m, **H$_{8ax}$**), 1.56 − 1.73 (2H, m, **H$_9$**), 1.43 (2H, sxt, *J* = 7.3 Hz, **H$_2$**), 0.91 (3H, t, *J* = 7.3 Hz, **H$_1$**) ppm. |
| **$^{13}$C NMR** | (125 MHz, CDCl$_3$, T= 373 K) δ 171.1 (**C$_{11}$**), 168.9 (**C$_{16}$**), 150.4 (**C$_{12}$**), 132.2 (**C$_{11}$**), 132.1 (**C$_4$**), 129.0 (**C$_{14}$**), 127.1 (**C$_{18}$**), 125.3 (**C$_{15}$**), 121.1 (**C$_{13}$**), 116.4 (**C$_{19}$**), 51.9 (**C$_6$**), 42.9 (**C$_7$**), 39.5 (**C$_{10}$**), 37.4 (**C$_{17}$**), 33.3 (**C$_3$**), 21.4 (**C$_9$**), 21.2 (**C$_8$**), 20.8 (**C$_2$**), 12.8 (**C$_1$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 342.13 [M+H]$^+$. |
| **HRMS** | (ESI$^+$) for $C_{21}H_{27}NNaO_3^+$ [M+Na]$^+$, calculated 364.18883; found 364.18888. |

### 3.2.7        Phenyl (2*R*,3*S*,*E*)-3-(but-3-enamido)-2-(3-chloropropyl)oct-4-enoate (2.34)
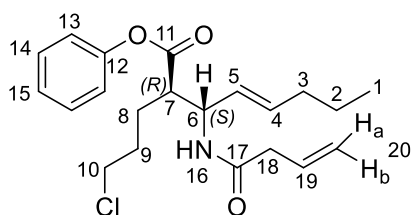


$C_{21}H_{28}ClNO_3$
Mol Wt: 377.91

**Method A:** Following the procedure described by Cropper *et al.*[152]

To a solution of 3-butenoic acid (0.200 g, 2.32 mmol) in $CH_2Cl_2$ (2.5 mL) was added 3 drops of DMF. The mixture was cooled to 0 °C, and oxalyl chloride (0.220 mL, 2.55 mmol) was added dropwise. The reaction mixture was stirred for 15 min, before being allowed to warm to rt, then stirred at rt for 3 h.

In a separate flask, to a solution of the imino-aldol adduct (**1.209**, 0.480 g, 1.16 mmol) in 1,4-dioxane (4.5 mL) was added conc. HCl (0.85 mL of ~36%, 3.48 mmol) under Ar. The reaction mixture was stirred for 1 h at rt. The solvent was removed *in vacuo* to give the crude amine **2.36** as its HCl salt.

The amine salt **2.36** was dissolved in $CH_2Cl_2$ (4 mL), and cooled to 0 °C under Ar. To this solution was added $Et_3N$ (0.650 mL, 4.65 mmol), followed by the dropwise addition of the freshly prepared acid chloride at 0 °C. The mixture reaction was allowed to warm to rt and stirred for 16 h, before it was quenched by dropwise addition of $H_2O$ (5 mL) and $CH_2Cl_2$ (5 mL) at 0 °C. The organic layer was separated, and the aqueous layer extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic solution was washed with aq. $NaHCO_3$, water (10 mL) and brine (10 mL), and then dried ($MgSO_4$). The solvent was evaporated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent:* $Et_2O/CH_2Cl_2$, 1:9) to give the title compound **2.34** as a light yellow oil (243 mg, 0.640 mmol, 55%).

**Method B:**

To a solution imino-aldol adduct (**1.209**, 0.660 g, 1.59 mmol) in 1,4-dioxane (17 mL) under Ar was added conc. HCl (1.17 mL of ~36%, 4.77 mmol) dropwise. The reaction mixture was stirred for 1 h then concentrated *in vacuo*. The amine salt **2.36** was dissolved in $CH_2Cl_2$ (50 mL) and $Et_3N$ (0.300 mL, 1.90 mmol) was added dropwise at 0 °C.

In a separate flask, to a solution of vinylacetic acid (0.160 ml, 1.90 mmol) in $CH_2Cl_2$ (20 mL) was added DCC (0.700 g, 3.19 mmol). After 15 min, to this solution was added the solution of the amine **2.36** dropwise at 0 °C over 30 min. The resulting mixture was stirred at rt for 4 h. The organic layers were washed with water, saturated aq. $NaHCO_3$, brine (50 mL), and dried ($MgSO_4$), then concentrated *in vacuo* to give crude amide **2.34**. Purification by column chromatography (silica gel, *eluent* EtOAc/Hexane, 1:19 → 2:8) gave the title compound as a white solid (470 mg, 1.24 mmol, 78%).

| | |
|---|---|
| **M.P.** | 47 – 49 °C |
| **FT-IR (neat)** | $v_{max}$ 3336, 2963, 2924, 2860, 1747, 1638, 1520, 1158 $cm^{-1}$. |
| **$^1$H NMR** | (500 MHz, $CDCl_3$) δ 7.39 (2H, t, $J$ = 7.4 Hz, $H_{14}$), 7.25 (1H, m, $H_{15}$), 7.05 (2H, d, $J$ = 7.4 Hz, $H_{13}$), 6.11 (1H, d, $J$ = 8.3 Hz, $H_{16}$), 5.98 – 5.88 (1H, m, $H_{19}$), 5.80 – 5.67 (1H, m, $H_5$), 5.51 (1H, m, $H_4$), 5.24 (1H, d, $J$ = 1.0 Hz, $H_{20a}$), 5.22 (1H, dd, $J$ = 6.9, 1.0 Hz, $H_{20b}$), 4.81 (1H, m, $H_6$), 3.64 – 3.54 (2H, m, $H_{10}$), 3.03 (2H, d, $J$ = 7.0 Hz, $H_{18}$), 2.88 (1H, dt, $J$ = 8.7, 5.3 Hz, $H_7$), 2.04 (2H, q, $J$ = 7.1 Hz, $H_3$), 2.0 – 1.73 (4H, m, $H_8$ & $H_9$), 1.41 (2H, sxt, $J$ = 7.4 Hz, $H_2$), 0.89 (3H, t, $J$ = 7.4 Hz, $H_1$) ppm. |
| **$^{13}$C NMR** | (125 MHz, $CDCl_3$) δ 171.5 ($C_{11}$), 169.3 ($C_{17}$), 150.0 ($C_{12}$), 134.7 ($C_4$), 130.8 ($C_{19}$), 129.2 ($C_{14}$), 125.8 ($C_5$), 125.4 ($C_{15}$), 121.1 ($C_{13}$), 119.8 ($C_{20}$), 52.0 ($C_6$), 48.8 ($C_7$), 44.2 ($C_{10}$), 41.4 ($C_{18}$), 34.1 ($C_3$), 30.0 ($C_9$), 25.5 ($C_8$), 21.8 ($C_2$), 13.3 ($C_1$) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 378.1 [M$^{35}$Cl+H]$^+$, 380.1 [M$^{37}$Cl+H]$^+$. |
| **HRMS** | (ESI$^+$) for $C_{21}H_{28}ClNNaO_3^+$ [M+Na]$^+$, calculated 400.1650; found 400.1649. |

### 3.2.8      Phenyl (*R*)-5-chloro-2-((*S*)-6-oxo-1,2,5,6-tetrahydropyridin-2-yl)pentanoate (2.35)
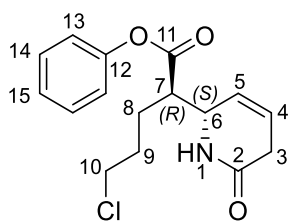


$C_{16}H_{18}ClNO_3$
Mol.Wt: 307.77

Following the procedure described by Miller.[153]

To a solution of amide (**2.34**, 100 mg, 0.264 mmol) in degassed $CH_2Cl_2$ (900 mL) was added Grubbs's II catalyst (20 mg, 0.024 mmol, 10 mol %) under Ar. The reaction mixture was heated at 44 °C for 3 h over which time the dark red solution turned dark brown in colour. The solvent was removed *in vacuo* to afford dark brown oil. The crude was purified by column chromatography (silica gel, *eluent gradient*: EtOAc/Hexane 1:9 → 7:3) yielding the title lactam **2.35** as a tan solid (30 mg, 0.097 mmol, 37%), and **2.30** as a tan solid (22 mg, 0.03 mmol, 12%).

**Data for major product 2.35:**

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3212, 3044, 2920, 2850, 1748, 1661, 1591, 1189 cm$^{-1}$. |
| **$^1$H NMR** | (500 MHz, CDCl$_3$) δ 7.40 (2H, t, *J* = 7.3 Hz, **H$_{14}$**), 7.27 (1H, m, **H$_{15}$**), 7.10 – 7.06 (2H, m, **H$_{13}$**), 6.64 (1H, br, **H$_1$**), 5.97 (1H, dtd, *J*=10.1, 3.5, 1.9 Hz, **H$_4$**), 5.69 (1H, ddq, *J* = 10.1, 3.4, 1.9 Hz, **H$_5$**), 4.57 (1H, m, **H$_6$**), 3.63 – 3.55 (2H, m, **H$_{10}$**), 3.03 – 2.95 (2H, m, **H$_3$**), 2.83 – 2.76 (1H, m, **H$_7$**), 2.09 – 1.80 (4H, m, **H$_8$** & **H$_9$**) ppm. |
| **$^{13}$C NMR** | (125 MHz, CDCl$_3$) δ 172.2 (**C$_{11}$**), 169.3 (**C$_2$**), 150.1 (**C$_{12}$**), 129.6 (**C$_{14}$**), 126.3 (**C$_4$**), 124.9 (**C$_5$**), 122.6 (**C$_{15}$**), 121.2 (**C$_{13}$**), 54.9 (**C$_6$**), 49.4 (**C$_7$**), 44.3 (**C$_{10}$**), 31.2 (**C$_3$**), 30.5 (**C$_9$**), 23.9 (**C$_8$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 308 [M$^{35}$Cl +H]$^+$, 310.1 [M$^{37}$Cl+H]$^+$. |
| **HRMS** | (ESI$^+$) for $C_{16}H_{18}ClNNaO_3^+$ [M+Na]$^+$, calculated 330.0867; found 330.0861. |

### 3.2.9 Diphenyl 3,3'-(((*E*)-hex-3-enedioyl)bis(azanediyl))(2*R*,2'*R*,3*S*,3'*S*,4*E*,4'*E*)-bis(2-(3-chloropropyl) oct-4-enoate) (2.38)
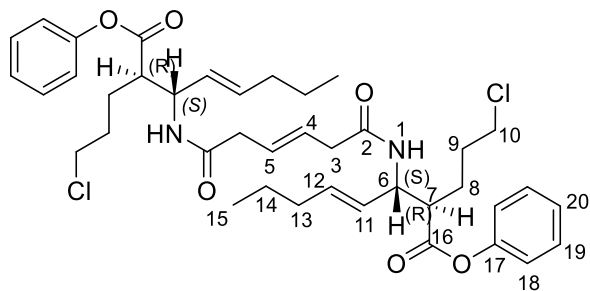


C$_{40}$H$_{52}$Cl$_2$N$_2$O$_6$
Mol.Wt: 727.76

**Data for minor product 2.38:**

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3283, 2956, 2921, 2851, 1743, 1647, 1636, 1521, 1195 cm$^{-1}$. |

**$^1$H NMR**    (400 MHz, CDCl$_3$) δ 7.39 (4H, t, *J* = 7.6 Hz, 2 x **H$_{19}$**), 7.27 − 7.21 (2H, m, 2 x **H$_{20}$**), 7.05 (4H, d, *J* = 7.7 Hz, 2 x **H$_{18}$**), 6.25 (2H, d, *J* = 8.8 Hz, 2 x **H$_1$**), 5.80 − 5.68 (4H, m, **H$_4$** & **H$_5$** & 2 x **H$_{12}$**), 5.50 (2H, dd, *J* = 7.5, 15.3 Hz, 2 x **H$_{11}$**), 4.78 (2H, q, *J* = 7.7 Hz, 2 x **H$_6$**), 3.65 − 3.53 (4H, m, 2 x **H$_{10}$**), 2.99 (4H, d, *J* = 5.3 Hz, 2 x **H$_3$**), 2.88 (2H, dt, *J* = 8.7, 5.4 Hz, 2 x **H$_7$**), 2.08 − 2.01 (4H, m, 2 x **H$_{13}$**), 2.00 − 1.74 (8H, m, 2 x **H$_8$** & **H$_9$**), 1.41 (4H, sxt, *J*=7.3 Hz, 2 x **H$_{14}$**), 0.90 (6H, t, *J* = 7.3 Hz, 2 x **H$_{15}$**) ppm.

**$^{13}$C NMR**    (101 MHz, CDCl$_3$) δ 171.8 (2 x **C$_{16}$**), 169.8 (2 x **C$_2$**), 150.4 (2 x **C$_{17}$**), 135.0 (2 x **C$_{12}$**), 129.5 (4 x **C$_{19}$**), 128.3 (2 x **C$_{11}$**), 126.1 (2 x **C$_{20}$**), 125.9 (**C$_4$** & **C$_{5)}$**, 121.4 (4 x **C$_{18}$**), 52.6 (2 x **C$_6$**), 49.2 (2 x **C$_7$**), 44.5 (2 x **C$_{10}$**), 40.0 (2 x **C$_3$**), 34.4 (2 x **C$_{13}$**), 30.2 (2 x **C$_9$**), 29.7 (**C$_{8a}$**), 25.9 (**C$_{8b}$**), 22.1 (2 x **C$_{14}$**), 13.7 (2 x **C$_{15}$**) ppm.

**LRMS**    (ESI$^+$) *m/z* 727.4  [M$^{35}$Cl +H]$^+$, 729.2 [M$^{37}$Cl+H]$^+$.

**HRMS**    (ESI$^+$) for C$_{40}$H$_{52}$Cl$_2$N$_2$NaO$_6$$^+$ [M+Na]$^+$, calculated 749.3095; found 749.3092.

### 3.2.10      Phenyl (1*R*,9a*S*)-6-oxo-1,3,4,6,7,9a-hexahydro-2H-quinolizine-1-carboxylate (2.30)



$C_{16}H_{17}NO_3$
Mol.Wt: 271.32

Following the procedure described for the synthesis of **2.35**, amide (**2.29**, 330 mg, 0.966 mmol) and Grubbs's II catalyst (41 mg, 0.048 mmol, 5 mol %) afforded the title compound **2.30** (260 mg, 0.958 mmol, 99%) as a white solid.

| | |
|---|---|
| **M.P.** | 108 – 109 °C |
| **FT-IR (neat)** | $\nu_{max}$ 3521, 2944, 2858, 2354, 1742, 1628, 1470 cm$^{-1}$. |
| **$^1$H NMR** | (500 MHz, CDCl$_3$) δ 7.41 (2H, t, *J* = 7.5 Hz, **H$_{14}$**), 7.27 (1H, tt, *J* = 7.4, 1.1 Hz, **H$_{13}$**), 7.27 (1H, m, **H$_{15}$**), 5.89 – 5.81 (2H, m, **H$_7$** & **H$_8$**), 4.97 (1H, ddt, *J* = 13.2, 4.2, 2.0 Hz, **H$_6$**), 4.21 (1H, dt, *J* = 10.5, 2.7 Hz, **H$_{2eq}$**), 3.02 (2H, dd, *J* = 4.1, 1.2 Hz, **H$_9$**), 2.61 – 2.53 (2H, m, **H$_{2ax}$** & **H$_5$**), 2.38 – 2.32 (1H, m, **H$_{4eq}$**), 1.98 – 1.82 (2H, m, **H$_{3eq}$** & **H$_{4ax}$**), 1.60 (1H, m, **H$_{3ax}$**) ppm. |
| **$^{13}$C NMR** | (126 MHz, CDCl$_3$) δ 171.8 (**C$_{11}$**), 166.0 (**C$_{10}$**), 150.2 (**C$_{12}$**), 129.5 (**C$_{14}$**), 126.1 (**C$_7$**), 123.6 (**C$_8$**), 122.6 (**C$_{15}$**), 121.3 (**C$_{13}$**), 58.9 (**C$_6$**), 50.1 (**C$_7$**), 41.9 (**C$_2$**), 31.6 (**C$_9$**), 29.1 (**C$_4$**), 24.0 (**C$_3$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 372 [M+H]$^+$. |
| **HRMS** | (ESI$^+$) for C$_{16}$H$_{17}$NNaO$_3$$^+$ [M+Na]$^+$, calculated 294.1101; found 294.1105. |
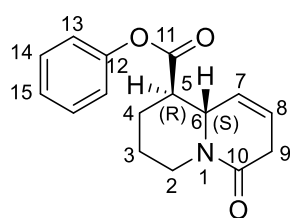
### 3.2.11    Phenyl (1*R*,9a*S*)-6-oxooctahydro-2H-quinolizine-1-carboxylate (2.39)



$C_{16}H_{19}NO_3$
Mol.Wt:  273.33
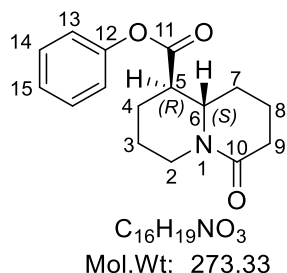
Following the procedure described by Watkin.[135]

To a solution of **2.30** (83 mg, 0.306 mmol) in EtOH (10 mL) was added 5 wt % Pd/C (22 mg, 0.09 mmol) and the reaction mixture was placed under an $H_2$ atmosphere. The reaction was stirred at rt for 16 h, filtered through celite, washing with EtOH (5 × 5 mL) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent*: EtOAc/hexane 9:1) to give the title compound **2.39** as a white solid (76 mg, 0.278 mmol, 90%).

| | |
|---|---|
| **M.P.** | 51 – 53 °C. |
| **FT-IR (neat)** | $v_{max}$ 2921, 2854, 1744, 1621, 1184, 1127 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.44 – 7.35 (2H, m, **H$_{14}$**), 7.26 (1H, m, **H$_{15}$**), 7.07 (2H, d, *J* = 8.4 Hz, **H$_{13}$**), 4.88 (1H, m, **H$_6$**), 3.66 – 3.56 (1H, m, **H$_5$**), 2.61 – 2.33 (4H, m, **H$_2$** & **H$_9$**), 2.32 – 2.14 (2H, m, **H$_{4eq}$** & **H$_{8eq}$**), 1.95 – 1.63 (5H, m, **H$_{3eq}$**, **H$_{4ax}$**, **H$_{8ax}$** & **H$_7$**), 1.52 (1H, m, **H$_{3ax}$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 172.0 (**C$_{11}$**), 169.4 (**C$_{10}$**), 150.2 (**C$_{12}$**), 129.5 (**C$_{14}$**), 126.1 (**C$_{15}$**), 121.2 (**C$_{13}$**), 57.5 (**C$_6$**), 49.6 (**C$_5$**), 42.1 (**C$_2$**), 32.8 (**C$_9$**), 28.8 (**C$_7$**), 27.9 (**C$_4$**), 23.9 (**C$_3$**), 18.6 (**C$_8$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 374.1 [M+H]$^+$. |
| **HRMS** | (ESI$^+$) for C$_{16}$H$_{20}$NO$_3$$^+$ [M+H]$^+$, calculated 274.1438; found 274.1436. |

### 3.2.12    ((1*R*,9a*S*)- Octahydro-2*H*-quinolizin-1-yl)methanol/ (−)-epilupinine ((−)1.1)

HO$_{11}$

H·,$_5$ H $_7$
$_4$ (R) $_6$ (S) $_8$
$_3$ N $_{10}$ $_9$
$_2$ $_1$

$C_{10}H_{19}NO$
Mol Wt: 169.27

Following the procedure described by Koly *et al.*[143]

To a solution of (**2.39**, 35 mg, 0.128 mmol) in THF (4 mL) at 0 °C a solution of LiAlH$_4$ (0. 770 mL of 1M in THF, 0.770 mmol) was added dropwise. The reaction mixture was stirred for 15 min, and then heated at reflux for 2 h. the reaction mixture was cooled to 0 °C and saturated aq. Na$_2$SO$_4$ (0.2 mL) was added carefully and was stirred for further 30 min at rt. The mixture was diluted with THF (5 mL), and the suspension was filtered through celite and washed with THF (3 x 5 mL). The solvent was removed *in vacuo*. Purification by column chromatography on basic alumina (*eluent* gradient: CHCl$_3$/MeOH, 19:1 → 9:1) gave (−)-epilupinine (**1.1**, 19 mg, 0.112 mmol, 87%). Physical and spectroscopic data were consistent with reported values.[135,143]

The spectrographic data for the synthetic material closely matched those reported for the natural products epilupinine.

**M. P.**    79 – 81 °C.

**[α]$_D$**    −31.2 (*c* 0.5, EtOH, 20 °C), lit.[143] −28.0 (*c* 0.72, EtOH, 26 °C)

**FT-IR (neat)**    v$_{max}$ 3209, 2925, 2856, 2805, 2758, 2676, 1465, 1442, 1070 cm$^{-1}$.

**$^1$H NMR**    (400 MHz, CDCl$_3$) δ 3.67 (1H, dd, *J* = 10.8, 3.6 Hz, **H$_{11a}$**), 3.59 (1H, dd, *J* = 10.8, 5.8 Hz, **H$_{11b}$**), 2.87 − 2.76 (2H, m, **H$_{2eq}$** & **H$_{10ax}$**), 2.11 − 1.95 (2H, m, **H$_{2ax}$** & **H$_{10eq}$**), 1.93 − 1.75 (3H, m, **H$_5$**, **H$_6$** & **OH**), 1.70 (2H, tdd, *J* = 9.8, 6.4, 3.3 Hz, **H$_7$**), 1.64 − 1.56 (2H m, **H$_3$**), 1.49 − 1.36 (2H, m, **H$_9$**), 1.34 − 1.13 (4H, m, **H$_4$** & **H$_8$**) ppm.

**$^{13}$C NMR**    (101 MHz, CDCl$_3$) δ 64.8 (**C$_{11}$**), 64.2 (**C$_6$**), 56.9 (**C$_2$**), 56.6 (**C$_{10}$**), 44.0 (**C$_5$**), 29.8 (**C$_8$**), 28.2 (**C$_7$**), 25.6 (**C$_9$**), 25.1 (**C$_3$**), 24.6 (C$_4$) ppm

**LRMS**    (ESI$^+$) *m/z* 170.2 [M+H]$^+$.

### 3.2.13    (9R,9aS)-9-(Hydroxymethyl)-3,6,7,8,9,9a-hexahydro-4H-quinolizin-4-one (2.42)



$C_{10}H_{15}NO_2$
Mol Wt: 181.24

Following the procedure described by Gallagher *et al.*[154]

To a solution of **2.30** (50 mg, 0.200 mmol) in THF (0.85 mL) was added a solution LiAlH$_4$ (0.100 mL of 1.0 M in THF, 0.1 mmol) dropwise. The reaction mixture was stirred at −15 °C for 15 min then quenched by careful addition of 1 M NaOH (0.100 mL). The suspension was filtered through celite and washed with THF (3 × 5 mL), dried (Na$_2$SO$_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *eluent*: EtOAc/MeOH, 95:5) gave the desired alcohol **2.42** (28 mg, 0.155 mmol, 77 %) as a white solid.

| | |
|---|---|
| **M. P.** | 89 – 91°C. |
| **FT-IR (neat)** | $v_{max}$ 3242, 2998, 2918, 2857, 1608, 1488, 1446, 1071 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 5.96 (1H, tdd, *J* = 10.3, 3.7, 1.8 Hz, **H$_8$**), 5.76 (1H, dtd, *J* = 10.4, 3.4, 1.3 Hz, **H$_7$**), 4.86 (1H, m, **H$_5$**), 3.83 (1H, m, **H$_6$**), 3.77 − 3.60 (2H, m, **H$_{11}$**), 2.98 − 2.90 (2H m, **H$_9$**), 2.45 (1H, dt, *J* = 12.6, 2.9 Hz, **H$_{2ax}$**), 2.06 (1H, br s, **OH**), 1.94 − 1.70 (2H m, **H$_{3ax}$ & H$_{4eq}$**), 1.64 − 1.44 (3H, m, **H$_{2eq}$, H$_{3eq}$ & H$_{4ax}$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 166.2 (**C$_{10}$**), 123.5 (**C$_7$**), 122.0 (**C$_8$**), 64.0 (**C$_{11}$**), 60.2 (**C$_7$**), 46.4 (**C$_5$**), 42.5 (**C$_2$**), 31.6 (**C$_9$**), 28.4 (**C$_4$**), 25.0 (**C$_3$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 182.2 [M+H]$^+$. |
| **HRMS** | (ESI$^+$) for $C_{10}H_{15}NNaO_2^+$ [M+Na]$^+$, calculated 204.0995; found 204.0994. |

### 3.2.14    Phenyl (2S,3R)-1-((S)-tert-butylsulfinyl)-6-oxo-2-((E)-pent-1-en-1-yl)piperidine-3-carboxylate (2.11)



C$_{21}$H$_{29}$NO$_4$S
Mol Wt: 391.53

To a solution of LDA (0.61 mL of 0.8 M, 0.49 mmol) at −78 °C under N$_2$ was added to solution of diphenyl glutarate (**2.1**, 140 mg, 0.49 mmol) in THF (7.6 mL) dropwise over 15 min. The reaction was stirred at −78 °C for 1 h, then a solution of sulfinylimine (**1.208**, 100 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise over 5 min. The reaction was stirred at −78 °C for 1.5 h before it was quenched by dropwise addition of saturated aq. NH$_4$Cl (10 mL). The reaction was allowed to warm to rt with rapid stirring. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL) and Et$_2$O (3 × 5 mL). The organic phases were combined and washed with brine (2.5 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane 1:9 → 8:2) to give the title compound **2.11** as the major product as a colourless oil (38 mg, 0.097 mmol, 20%) and mixture imino-aldol product ~28%, which were not characterised, and recovered sulfinylimine (**1.208**, 30 mg, 0.149 mmol, 30%).

Following the procedure described above for 2 equivalents of LDA (1.24 mL of 0.8 M, 0.980 mmol), diphenyl glutarate (**2.1**, 140 mg, 0.490 mmol) and sulfinylimine (**1.208**, 100 mg, 0.500 mmol) afforded the title cyclised *syn* imino-aldol (**2.11**, 73 mg, 0.186 mmol, 38%), and uncyclised imino-aldol (**2.23**, 30 mg, 0.060 mmol, 12%). and recovered sulfinylimine (**1.208**, 19 mg, 0.094 mmol, 19%). In addition, impure cyclised *anti* imino-aldol (9 mg) was obtained; see selected its data below.

**FT-IR (neat)**      ν$_{max}$ 2959, 2927, 2871, 1754, 1658, 1492, 1136 cm$^{−1}$.

**$^1$H NMR**        (400 MHz, CDCl$_3$) δ 7.44 − 7.37 (2H, m, **H$_{17}$**), 7.26 (1H, m, **H$_{18}$**), 7.12 − 7.07 (2H, m, **H$_{16}$**), 5.69 − 5.59 (1H, m, **H$_8$**), 5.55 (1H, dd, *J* = 15.4, 4.2 Hz, **H$_7$**), 4.93 (1H, br s, **H$_6$**), 3.18 (1H, td, *J* = 4.7, 2.1 Hz, **H$_5$**), 2.83 (1H, m, **H$_{3a}$**), 2.57 (1H, dt, *J* = 18.0, 5.5 Hz, **H$_{3b}$**), 2.27 − 2.17 (2H, m, **H$_{4a}$** & **H$_{9a}$**), 2.14 − 2.04 (2H, m, **H$_{4b}$** & **H$_{9b}$**), 1.48 − 1.38 (2H, m, **H$_{10}$**), 1.23 (9H, s, **H$_{13}$**), 0.92 (3H, t, *J* = 7.3 Hz, **H$_{11}$**) ppm.

<sup>13</sup>**C NMR**        (101 MHz, CDCl$_3$) δ 173.5 (**C$_{14}$**), 170.9 (**C$_2$**), 150.3 (**C$_{15}$**), 132.7 (**C$_8$**), 130.7 (**C$_7$**), 129.6 (**C$_{17}$**), 126.2 (**C$_{18}$**), 121.1 (**C$_{16}$**), 62.4 (**C$_{12}$**), 53.6 (**C$_6$**), 43.4 (**C$_5$**), 34.1 (**C$_9$**), 30.6 (**C$_3$**), 22.5 (**C$_{13}$**), 22.4 (**C$_{10}$**), 22.2 (**C$_4$**), 13.6 (**C$_{11}$**) ppm.

**LRMS**        (ESI$^+$) *m/z* 392.1 [M+H]$^+$, 413.9 [M+Na]$^+$, 805.3 [2M+Na]$^+$

**HRMS**        (ESI$^+$) for C$_{21}$H$_{29}$NNaO$_4$S$^+$ [M+Na]$^+$, calculated 414.1710; found 414.1708.

### 3.2.15    Phenyl (2*S*,3*S*)-1-((*S*)-tert-butylsulfinyl)-6-oxo-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate



C$_{21}$H$_{29}$NO$_4$S
Mol. Wt: 391.53

**Selected data for impure cyclised *anti* imino-aldol:**

**FT-IR (neat)**        ν$_{max}$ 2966, 2945, 2876, 1745, 1663, 1491, 1162 cm$^{-1}$.

<sup>1</sup>**H NMR**        (400 MHz, CDCl$_3$) δ 7.44 – 7.35 (2H, m, **H$_{15}$**), 7.29 – 7.25 (1H, m, **H$_{16}$**), 7.06 (2H, d, *J* = 7.7 Hz, **H$_{14}$**), 5.77 – 5.67 (1H, m, **H$_8$**), 5.48 (1H, dd, *J* = 15.3, 5.1 Hz, **H$_7$**), 4.97 (1H, t, *J* = 3.9 Hz, **H$_6$**), 3.20 (1H, dt, *J* = 12.5, 4.5 Hz, **H$_5$**), 2.75 – 2.65 (1H, m, **H$_{3eq}$**), 2.62 – 2.50 (1H, m, **H$_{9ax}$**), 2.28 (1H, tt, *J* =13.4, 8.8 Hz, **H$_{4ax}$**), 2.18 – 2.10 (1H, m, **H$_{4eq}$**), 2.06 (2H, q, *J*=7.0 Hz, **H$_9$**), 1.41 (3H, qd, *J* = 14.5, 7.3, Hz, **H$_{10}$**), 1.30 (9H, s, **H$_{18}$**), 0.89 (3H, t, *J* = 7.4 Hz, **H$_{11}$**) ppm.

<sup>13</sup>**C NMR**        (101 MHz, CDCl$_3$) δ 172.4 (**C$_{12}$**), 169.3 (**C$_2$**), 150.3 (**C$_{13}$**), 135.7 (**C$_8$**), 129.5 (2 x **C$_{15}$**), 126.2 (**C$_7$**), 125.7 (**C$_{16}$**), 121.2 (**C$_{14}$**), 62.4 (**C$_{17}$**), 52.8 (**C$_6$**), 44.3 (**C$_5$**), 34.3 (**C$_9$**), 30.9 (**C$_3$**), 22.7 (**C$_{18}$**), 22.1 (**C$_{10}$**), 17.9 (**C$_4$**), 13.5 (**C$_{11}$**) ppm.

**LRMS**        (ESI$^+$) *m/z* 392.2 [M+H]$^+$.

**3.2.16     Diphenyl (2R,4R)-2,4-bis((S,E)-1-(((S)-tert-butylsulfinyl)amino)hex-2-en-1-yl) pentanedioate (2.2)**

**Double imino-aldol conditions from unsaturated imine 1.208.**



$C_{37}H_{54}N_2O_6S_2$
Mol.Wt: 686.97

To a solution of LDA (1.50 mL of 0.85 M in THF, 1.30 mmol) at −78 °C under $N_2$ was added a solution of diphenyl glutarate (**2.1**, 370 mg, 1.30 mmol) in THF (10 mL) dropwise over 15 min. The reaction was stirred at −78 °C for 1 h. A second portion of LDA (1.5 mL of 0.85 M in THF, 1.30 mmol) at −78 °C was added dropwise. The reaction was stirred at −78 °C for 1 h, and a solution of sulfinylimine **1.208** (400 mg, 2.00 mmol) in THF (2 mL) was added dropwise over 15 min. The reaction was stirred for 1 h and quenched at −78 °C by dropwise addition of saturated aq. $NH_4Cl$ (10 mL). The reaction was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer extracted with EtOAc (3 × 5 mL) and $Et_2O$ (3 × 5 mL). The organic phases were combined and washed with brine (2.5 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane 1:9 → 8:2) to give the title compound **2.32** as the major product (228 mg, 0.330 mmol, 25%) and mixture of other imino-aldol products ~30%, which were not characterised. The double imino-aldol adduct **2.2** was recrystallised from *n*-hexane to give white needles.

| | |
|---|---|
| **M.P.** | 123 − 127 °C |

**FT-IR (neat)**     $v_{max}$ 3174, 2958, 2927, 2871, 1751, 1667, 1592, 1190, 1049 cm$^{-1}$.

**¹H NMR**     (400 MHz, CDCl₃) δ 7.38 (4H, t, *J* = 7.6 Hz, 2 x **H₇**), 7.27 − 7.22 (2H, m, 2 x **H₈**), 7.09 (4H, d, *J* = 7.6 Hz, 2 x **H₆**), 5.81 (2H, dt, *J* = 15.3, 6.7 Hz, 2 x **H₁₁**), 5.47 (2H, dd, *J* = 15.3, 8.4 Hz, 2 x **H₁₀**), 4.19 − 4.12 (2H, m, 2 x **H₂**), 3.98 (2H, d, *J* = 3.8 Hz, 2 x **H₁**), 3.04 (2H, br dt, *J* = 7.9, 6.1 Hz, 2 x **H₃**), 2.20 (2H, dd, *J* = 7.7, 6.6, Hz, **H₉**), 2.07 (4H, q, *J* = 7.0 Hz, 2 x **H₁₂**), 1.42 (4H, sxt, *J* = 7.3 Hz, 2 x **H₁₃**), 1.23 (18H, s, 2 x **H₁₆**), 0.91 (6H, t, *J* = 7.3 Hz, 2 x **H₁₄**) ppm.

**¹³C NMR**          (100 MHz, CDCl₃) δ 171.6 (2 x **C₄**), 150.3 (2 x **C₅**), 136.5 (2 x **C₁₁**), 129.5 (2 x **C₇**), 126.8 (2 x **C₁₀**), 126.1 (2 x **C₈**), 121.5 (2 x **C₆**), 59.1 (2 x **C₂**), 55.7 (2 x **C₁₅**), 48.6 (2 x **C₃**), 34.3 (2 x **C₁₂**), 27.5 (**C₉**), 22.7 (2 x **C₁₆**), 22.1 (2 x **C₁₃**), 13.6 (2 x **C₁₄**) ppm.

**LRMS**            (ESI⁺) *m/z* 687.2 [M+H]⁺.

**HRMS**            (ESI⁺) for $C_{37}H_{54}N_2NaO_6S_2^+$ [M+Na]⁺, calculated 709.3315; found 709.3309.

### 3.2.17      Diphenyl (*R*)-2-((*S*,*E*)-1-(((*S*)-tert-butylsulfinyl)amino)hex-2-en-1-yl)pentanedioate (2.23)



$C_{27}H_{35}NO_5S$
Mol. Wt: 485.64

**Data for uncyclised *syn* imino-aldol 2.23:**

**FT-IR (neat)**     $v_{max}$ 2964, 2877, 2835, 1745, 1665, 1493, 1163 cm⁻¹.

**¹H NMR**          (400 MHz, CDCl₃) δ 7.40 (4H, q, *J* = 7.3 Hz, **H₁₅**), 7.32 – 7.21 (2H, m, **H₁₆**), 7.17 – 7.03 (4H, m, **H₁₄**), 5.86 (1H, dt, *J* = 15.2, 6.8 Hz, **H₈**), 5.53 (1H, br dd, *J* = 15.3, 8.2 Hz, **H₇**), 4.19 (1H, dt, *J* = 8.5, 4.5 Hz, **H₆**), 4.05 (1H, d, *J* = 3.9 Hz, **H₁**), 3.08 (1H, dt, *J* = 9.9, 4.8 Hz, **H₅**), 2.90 – 2.66 (2H, m, **H₃**), 2.32 – 2.15 (2H, m, **H₄**), 2.11 (2H, q, *J* = 6.9 Hz, **H₉**), 1.46 (2H, dq, *J* = 14.7, 7.4 Hz, **H₁₀**), 1.25 (9H, s, **H₁₈**), 0.94 (3H, t, *J* = 7.4 Hz, **H₁₁**) ppm.

**¹³C NMR**          (101 MHz, CDCl₃) δ 171.7 (**C₁₂**), 171.1 (**C₂**), 150.5 (**C₁₃**), 150.2 (**C₁₉**), 136.5 (**C₇**), 129.5 (2 x **C₁₅**), 129.4 (2 x **C₂₁**), 126.5 (**C₈**), 126.1 (**C₁₆**), 125.8 (**C₂₂**), 121.5 (2 x **C₂₀**), 121.4 (2 x **C₁₄**), 58.7 (**C₆**), 55.6 (**C₁₇**), 50.1 (**C₅**), 34.30 (**C₉**), 32.0 (**C₃**), 23.6 (**C₄**), 22.6 (**C₁₈**), 22.07 (**C₁₀**), 13.6 (**C₁₁**) ppm.

**LRMS**            (ESI⁺) *m/z* 486.2 [M+H]⁺.

### 3.2.18    (*1R,4S,5R,8S*)-4,8-di ((*E*)-Pent-1-en-1-yl)-3,7-diazabicyclo[3.3.1]nonane-2,6-dione

### (2.3)



$C_{17}H_{26}N_2O_2$
Mole Wt: 290.41

To a solution of double imino-aldol adduct (**2.2**, 100 mg, 0.150 mmol) in 1,4-dioxane (2.2 mL) at 0 °C was added conc. HCl (0.210 mL of ~36%, 0.87 mmol) dropwise, then the mixture was stirred for 2 h under Ar. The reaction mixture was concentrated *in vacuo*. The crude was dissolved in EtOAc (2 mL) and saturated aq. NaHCO$_3$ (1 mL) at 0 °C was added dropwise. The phases were separated and the aqueous phase was extracted with Et$_2$O (3 × 3 mL), H$_2$O (3 × 3 mL) and the organic combined solution was washed with brine (2 × 3 mL), dried (MgSO$_4$) and the solvent was removed *in vacuo.* The crude material was purified by column chromatography (silica gel, *eluent*: EtOAc/hexane 9:1 then EtOAc/MeOH 19:1) to give the title compound **2.3** as a pale yellow oil (26 mg, 0.089 mmol 61%).

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3444, 2924, 1655, 1464, 1023, 1004 cm$^{-1}$. |
| **$^1$H NMR** | (500 MHz, DMSO-*d$_6$*, T= 373 K) δ 7.48 (2H, m, 2 x **H$_1$**), 5.64 (1H, td, *J* = 6.6, 1.3 Hz, **H$_{3a}$**), 5.61 (1H, td, *J* = 6.5, 1.3 Hz, **H$_{3b}$**), 5.54 (1H, dt, *J* = 5.1, 1.2 Hz, **H$_{4a}$**), 5.51 (1H, dt, *J* = 5.1, 1.2 Hz, **H$_{4b}$**), 3.97 (2H, dd, *J* = 4.7, 3.6 Hz, 2 x **H$_2$**), 3.01 (4H, br, 2 x **H$_9$**), 2.38 – 2.34 (2H, m, **H$_{10}$**), 2.08 – 2.00 (4H, m, 2 x **H$_5$**), 1.41 (4H, sxt, *J* = 7.3 Hz, 2 x **H$_6$**), 0.90 (6H, t, *J* = 7.3 Hz, 2 x **H$_7$**) ppm. |
| **$^{13}$C NMR** | (125 MHz, DMSO-*d$_6$*, T= 373 K) δ 170.3 (2 x **C$_8$**), 131.1 (2 x **C$_4$**), 130.3 (2 x **C$_3$**), 55.6 (2 x **C$_2$**), 40.0 (2 x **C$_9$**), 32.9 (2 x **C$_5$**), 21.2 (2 x **C$_6$**), 15.3 (**C$_{10}$**), 12.7 (2 x **C$_7$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 290.9 [M+H]$^+$, 581.2 [2M+H]$^+$. |
| **HRMS** | (ESI$^+$) for $C_{17}H_{26}N_2NaO_2{}^+$ [M+Na]$^+$, calculated 313.1886; found 313.1895. |

### 3.2.19    (–)-(*S*)-*N*-[(1*E*)-5-Chloropentylidene]-2-methylpropane-2-sulfinamide (1.205)



C$_9$H$_{18}$ClNOS
Mol. Wt. : 223.76

Following a modified procedure from Cutter *et al.*;[134] to a solution of methyl-5-chloropentanoate (**2.12**, 1.90 mL, 13.3 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (40 mL) at −78 °C was added a solution of DIBAL-H (14.6 mL of 1 M in CH$_2$Cl$_2$, 14.6 mmol, 1.1 equiv) dropwise over 10 min. The reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched with saturated aqueous Rochelle's salt solution (50 mL). The suspension was filtered and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO$_4$) and the solvent was removed *in vacuo* to give 5-chloropentanal as a yellow oil (1.45 g, 12.0 mmol, 90%). The crude material was used in the subsequent reaction without further purification. $^1$H NMR spectroscopic data were consistent with reported values.[4] **$^1$H NMR** (400 MHz, CDCl$_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H), 3.55 (t, *J* = 6.2, 2H), 2.52 − 2.45 (m, 2H), 1.85 − 1.74 (m, 4H) ppm. **$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 201.8, 44.4, 42.9, 31.7, 19.3 ppm. Following a procedure described by Ellman *et al.*;[155] (*S*)-2-methylpropane-2-sulfinamide (**2.9**, 1.48 g, 12.2 mmol, 1.2 equiv) was dissolved in dry CH$_2$Cl$_2$ (20 mL) before anhydrous CuSO$_4$ (7.66 g, 48.0 mmol, 4.0 equiv) was added in one portion followed by 5-chloropentanal (1.45 g, 12.0 mmol, 1.0 equiv). The reaction mixture was heated at 40 °C for 24 h then filtered through celite and washed with CH$_2$Cl$_2$. The solvent was removed *in vacuo* and the crude reaction mixture was purified by column chromatography (SiO$_2$, hexane/EtOAc, 3:1) to afford the title sulfinylimine **1.205** as a mobile pale yellow oil (2.08 g, 9.30 mmol, 77%). Physical and spectroscopic data are consistent with the reported values.[134,135]

| | |
|---|---|
| **FT-IR (neat)** | ν$_{max}$ 2957, 2868, 1622, 1456, 1078 cm$^{−1}$. |
| **$^1$H NMR** | (500 MHz, CDCl$_3$) δ 8.09 (1H, t, *J* = 4.5 Hz, **H$_3$**), 3.57 (2H, t, *J* = 6.1 Hz, **H$_7$**), 2.57 (2H, td, *J* = 6.9, 4.5 Hz, **H$_4$**), 1.90 − 1.77 (4H, m, **H$_5$** & **H$_6$**), 1.20 (9H, s, **H$_1$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 168.7 (**C$_3$**), 56.6 (**C$_2$**), 44.4 (**C$_7$**), 35.2 (**C$_4$**), 31.9 (**C$_6$**), 22.7 (**C$_5$**), 22.3 (**C$_1$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 224.3 [M$^{35}$Cl+H]$^+$, 226.3 [M$^{37}$Cl+H]$^+$. |

### 3.2.20      Diphenyl (*2R,4R*)-2,4-bis((*S*)-1-(((*S*)-*tert*-butylsulfinyl)amino)-5-chloropentyl) pentanedioate (2.5a).

**Double imino-aldol conditions from halo imine 1.205.**



$C_{35}H_{52}Cl_2N_2O_6S_2$
Mol Wt: 731.83

To a solution of LDA (4.90 mL of 1.0 M in THF/hexane, 4.90 mmol) in THF (20 mL) at −78 °C under Ar was added a solution of diphenyl glutarate (**2.1**, 635 mg, 2.23 mmol) in THF (5 mL) dropwise. The reaction was stirred at −78 °C for 1 h, and then a solution of sulfinylimine (**1.205**, 1.00 g, 4.47 mmol) in THF (5 mL) was added dropwise over 10 min at −78 °C. After 1 h, the reaction was quenched at −78 °C by dropwise addition of saturated aq $NH_4Cl$ (12 mL) over 30 min. The reaction was allowed to warm to rt with rapid stirring for 30 min. The phases were separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The organic phase was combined, washed with brine (2 x 10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane, 2:8 → 8:2) affording several fractions: *Fraction 1* ($R_f$ = 0.51, $Et_2O$/hexane, 8:2) contained the pure cyclsed mono *syn* imino-aldol **2.13** as off-white solid (149 mg, 0.36 mmol, 16%); *Fraction 2* ($R_f$ =0.45, $Et_2O$/hexane, 8:2) contained *syn*-uncyclised mono imino-aldol **2.16** as a white solid (71 mg, 0.14 mmol, 6 %); *Fraction 3*  ($R_f$ = 0.43, $Et_2O$/hexane, 8:2) contained cyclised-*anti*- **2.17** as a an impure yellow oil (50 mg, 0.12 mmol, 5%); *Fraction 4* ($R_f$ = 0.34, $Et_2O$/hexane, 8:2) contained the pure *syn,syn* double imino-aldol product **2.5a** as a colourless viscous syrup (488 mg, 0.66 mmol, 30%); *Fraction 5* ($R_f$ = 0.34–0.18, $Et_2O$/hexane, 8:2) contained unseparated mixture of double imino-aldol products (see below) as a yellow oil (168 mg).[a] Sulfinylimine **1.205** ($R_f$ = 0.64, 270 mg, 1.2 mmol, 27%) was also recovered.

**Data for *syn,syn* double imino-aldol adduct 2.5a:**

| | |
|---|---|
| $[\alpha]_D$ | +29 (*c* 1.8, MeOH, 24 °C) |

**FT-IR (neat)**     $v_{max}$ 3356, 2971, 2925, 1751, 1592, 1456, 1190, 1163, 1045 cm$^{-1}$.

**$^1$H NMR**     (400 MHz, CDCl$_3$) δ 7.39 (4H, t, *J* = 7.6 Hz, 2 x **H$_7$**), 7.26 – 7.22 (2H, m, 2 x **H$_8$**), 7.18 (4H, d, *J* = 7.6 Hz, 2 x **H$_6$**), 4.25 (2H, d, *J* = 8.1 Hz, 2 x **H$_1$**), 3.72 – 3.63 (2H, m, 2 x **H$_2$**), 3.52 (4H, *J* = 6.3 Hz, 2 x **H$_{13}$**), 3.17 (2H, q, *J* = 6.3 Hz, 2 x **H$_3$**), 2.40 – 2.31 (2H, m, 2 x **H$_9$**), 1.88 – 1.59 (12H, m, 2 x **H$_{10}$**, **H$_{11}$** & **H$_{12}$**), 1.26 (18H, s, 2 x **H$_{15}$**) ppm.

**$^{13}$C NMR**     (100 MHz, CDCl$_3$) δ 172.4 (2 x **C$_4$**), 150.3 (2 x **C$_5$**), 129.5 (2 x **C$_7$**), 126.2 (2 x **C$_8$**), 121.6 (2 x **C$_6$**), 58.4 (2 x **C$_2$**), 56.4 (2 x **C$_{14}$**), 48.2 (2 x **C$_3$**), 44.7 (2 x **C$_{13}$**), 33.4 (2 x **C$_{10}$**), 32.1 (2 x **C$_{12}$**), 27.3 (**C$_9$**), 23.2 (2 x **C$_{11}$**), 22.9 (2 x **C$_{15}$**) ppm.

**LRMS**     (ESI$^+$) *m/z* 753.4 [M$^{35}$Cl+Na]$^+$, 755.4 [M$^{37}$Cl+Na]$^+$.

**HRMS**     (ESI$^+$) for C$_{35}$H$_{52}$$^{35}$Cl$_2$N$_2$NaO$_6$S$_2$$^+$ [M+Na]$^+$, calculated 753.2536; found 753.2520.


**3.2.21     Phenyl (2*S*,3*R*)-1-((*S*)-tert-butylsulfinyl)-2-(4-chlorobutyl)-6-oxopiperidine-3-carboxylate (2.13)**



C$_{20}$H$_{28}$ClNO$_4$S
Mol Wt: 413.96

**Data for cyclised mono *syn* imino-aldol 2.13**: Slow evaporation of a solution of **2.13** in CHCl$_3$ gave crystals suitable for X-ray structure determination.

| | |
|---|---|
| $[\alpha]_D$ | −74 (*c* 2.1, MeOH, 24 °C) |

**M.P.**     56 – 58 °C

**FT-IR (neat)**     $v_{max}$ 2960, 2929, 2866, 1753, 1660, 1492, 1163 cm$^{-1}$.

**¹H NMR**          (400 MHz, CDCl$_3$) δ 7.43 – 7.37 (2H, m, **H$_{16}$**), 7.30 – 7.23 (1H, m, **H$_{17}$**), 7.09 (2H, d, $J$ = 7.5 Hz, **H$_{15}$**), 4.30 (1H, dt, $J$ = 10.5, 2.4 Hz, **H$_6$**), 3.60 (2H, t, $J$ = 6.4 Hz, **H$_{10}$**), 3.21 (1H, td, $J$ = 5.7, 2.0 Hz, **H$_5$**), 2.84 (1H, dt, $J$ = 17.8, 7.7 Hz, **H$_{3eq}$**), 2.58 (1H, dt, $J$ = 17.9, 6.5 Hz, **H$_{3ax}$**), 2.30 – 2.23 (2H, m, **H$_4$**), 2.16 – 2.06 (1H, m, **H$_{7a}$**), 1.96 – 1.76 (2H, m, **H$_9$**), 1.71 - 1.55 (3H, m, **H$_{7b}$** & **H$_8$**), 1.22 (9H, s, **H$_{12}$**) ppm.

**¹³C NMR**        (100 MHz, CDCl$_3$) δ 173.1 (**C$_{13}$**), 171.6 (**C$_2$**), 150.3 (**C$_{14}$**), 129.6 (**C$_{16}$**), 126.2 (**C$_{17}$**), 121.0 (**C$_{15}$**), 62.3 (**C$_{11}$**), 53.0 (**C$_6$**), 44.7 (**C$_5$**), 40.9 (**C$_{10}$**), 36.9 (**C$_7$**), 31.5 (**C$_3$**), 30.8 (**C$_9$**), 23.2 (**C$_8$**), 22.4 (**C$_{12}$**), 19.3 (**C$_4$**) ppm.

**LRMS**           (ESI$^+$) $m/z$ 436.2 [M$^{35}$Cl+Na]$^+$, 438.2 [M$^{37}$Cl+Na]$^+$.

**HRMS**           (ESI$^+$) for C$_{20}$H$_{28}$$^{35}$ClNNaO$_4$S$^+$ [M+Na]$^+$, calculated 436.1320; found 436.1324.
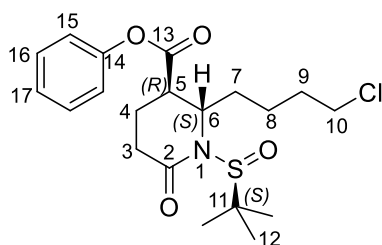
### 3.2.22      Diphenyl (*R*)-2-((*S*)-1-(((*S*)-tert-butylsulfinyl)amino)-5-chloropentyl)pentanedioate (2.16)
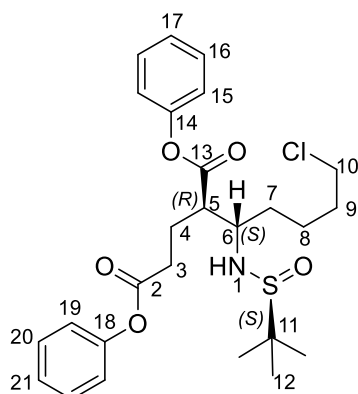


C$_{26}$H$_{34}$ClNO$_5$S
Mol Wt: 508.07

**Data for uncyclised mono *syn* imino-aldol 2.16:** recrystallisation from hexane and EtOAc gave crystals suitable for X-ray structure determination.

**M.P.**           93 – 96 °C

**[α]$_D$**         +31 (*c* 1.5, MeOH, 20 °C)

**FT-IR (neat)**    ν$_{max}$ 3322, 2991, 2928, 2869, 1739, 1591, 1483, 1454, 1236, 1184, 1049 cm$^{-1}$.

| $^1$H NMR | (400 MHz, CDCl$_3$) δ 7.40 (4H, m, 2 x **H$_{16}$** & **H$_{20}$**), 7.30 − 7.20 (2H, m, **H$_{17}$** & **H$_{21}$**), 7.12 (4H, t, $J$ = 8.5 Hz, 2 x **H$_{15}$** & **H$_{19}$**), 4.22 (1H, d, $J$ = 8.5 Hz, **H$_1$**), 3.62 − 3.51 (3H, m, **H$_6$** & **H$_{10}$**), 3.28 − 3.21 (1H, m, **H$_5$**), 2.93 − 2.83 (1H, m, **H$_{3a}$**), 2.77 (1H, s, **H$_{3b}$**), 2.36 − 2.23 (1H, m, **H$_{4a}$**), 2.2 − 2.09 (1H, m, **H$_{4b}$**), 1.90 − 1.50 (6H, m, **H$_7$**, **H$_8$** & **H$_9$**), 1.26 (9H, s, **H$_{12}$**) ppm. |

| $^{13}$C NMR | (100 MHz, CDCl$_3$) δ 172.1 (**C$_{13}$**), 171.40 (**C$_2$**), 150.6 (**C$_{14}$**), 150.2 (**C$_{18}$**), 129.6 (**C$_{16}$**), 129.4 (**C$_{20}$**), 126.3 (**C$_{17}$**), 125.9 (**C$_{21}$**), 121.5 (**C$_{15}$**), 121.5 (**C$_{19}$**), 58.4 (**C$_6$**), 56.3 (**C$_{14}$** & **C$_{18}$**), 49.8 (**C$_5$**), 44.70 (**C$_{10}$**), 32.4 (**C$_3$**), 32.0 (**C$_7$**), 31.9 (**C$_9$**), 23.7 (**C$_4$**), 23.5 (**C$_8$**), 22.8 (**C$_{12}$**) ppm. |

| LRMS | (ESI$^+$) $m/z$ 508.2 [M$^{35}$Cl+H]$^+$, 510.2 [M$^{37}$Cl+H]$^+$. |

| HRMS | (ESI$^+$) for C$_{26}$H$_{35}$$^{35}$ClNO$_5$S$^+$ [M+H]$^+$, calculated 508.1919; found 508.1923; for C$_{26}$H$_{34}$$^{35}$ClNNaO$_5$S$^+$ [M+Na]$^+$, calculated 530.1738; found 530.1740. |

### 3.2.23    Phenyl (*2S,3R*)-1-((*S*)-*tert*-butylsulfinyl)-2-(4-chlorobutyl)-6-oxopiperidine-3-carboxylate (2.13).

**Prepared under conditions optimised to favour mono imino-aldol products.**



C$_{20}$H$_{28}$ClNO$_4$S
Mol Wt: 413.96
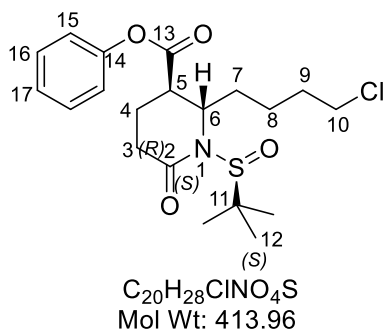
To a solution of LDA (7.0 mL of 1.0 M in THF/hexane, 7.00 mmol) in THF (15 mL) at −78 °C under Ar was added a solution of diphenyl glutarate (**2.1**, 991 mg, 3.48 mmol) in THF (14 mL) dropwise. The reaction was stirred at −78 °C for 1 h, and then a solution of sulfinylimine (**1.205**, 650 mg, 2.90 mmol) in THF (3 mL) was added dropwise using a syringe pump at −78 °C. After addition was complete, the reaction mixture was maintained at this temperature for 1 h, then quenched by dropwise addition of saturated aq NH$_4$Cl (14 mL) over 30 min at −78 °C. The reaction was allowed to warm to rt with rapid stirring. After 30 min, the phases were separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The major components of the crude material were

*syn-* and *anti*-cyclised mono imino-aldol products **2.13** and **2.17** (3:1), respectively see crude spectrta in appendex part. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane, 2:8 → 1:1) affording several fraction: *Fraction 1* ($R_f$ = 0.51, Et$_2$O/hexane, 8:2) contained the pure cyclised mono *syn* imino-aldol **2.13** as off-white solid (615 mg, 1.49 mmol, 51%); *Fraction 2* ($R_f$ = 0.43, Et$_2$O/hexane, 8:2) contained *anti*-cyclised **2.17** as an impure yellow oil (163 mg, 0.390 mmol, 13%); *Fraction 3* ($R_f$ = 0.34 − 0.18, Et$_2$O/hexane, 8:2) contained unseparated mixture of double imino-aldol products as yellow oil (44 mg).

Data for cyclised mono *syn* imino-aldol **2.13** are consistent with those reported above.
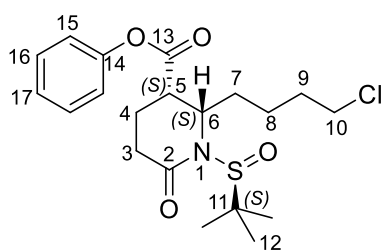


$C_{20}H_{28}ClNO_4S$
Mol Wt: 413.96

**Selected data for impure cyclised mono *anti* imino-aldol 2.17:**

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 2962,2873, 2930, 2866, 1751, 1661, 1492, 1164 cm$^{-1}$. |

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.44 − 7.38 (2H, m, **H$_{16}$**), 7.26 − 7.19 (1H, m, **H$_{17}$**), 7.13 − 7.07 (2H, m, **H$_{15}$**), 4.49 − 4.42 (1H, m, **H$_6$**), 3.52 (2H, t, *J* = 6.5 Hz, **H$_{10}$**), 3.19 (1H, ddd, *J* = 12.6, 5.7, 3.6 Hz, **H$_5$**), 2.81 − 2.72 (1H, m, **H$_{3eq}$**), 2.70 − 2.59 (1H, m, **H$_{3ax}$**), 2.47 − 2.32 (1H, m, **H$_{4eq}$**), 2.29 − 2.17 (1H, m, **H$_{3ax}$**), 1.83 − 1.61 (6H, m, **H$_7$, H$_8$ & H$_9$**), 1.32 − 1.28 (9H, m,) ppm.

**$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 171.9 (**C$_{13}$**), 169.7 (**C$_2$**), 150.2 (**C$_{14}$**), 129.6 (2 x **C$_{16}$**), 126.3 (**C$_{17}$**), 121.1 (2 x **C$_{15}$**), 62.4 (**C$_{11}$**), 51.3 (**C$_6$**), 44.5 (**C$_5$**), 44.0 (**C$_{10}$**), 33.3 (**C$_3$**), 32.4 (**C$_9$**), 30.6 (**C$_7$**), 24.0 (**C$_8$**), 23.2 (**C$_{12}$**), 22.8 (**C$_4$**) ppm.

**LRMS** (ESI$^+$) *m/z* 436.2 [M$^{35}$Cl+Na]$^+$, 438.2 [M$^{37}$Cl+Na]$^+$.

### 3.2.24     (*1R,4S,5R,8S*)-4,8-bis (4-Chlorobutyl)-3,7-diazabicyclo [3.3.1] nonane-2,6-dione (2.14)
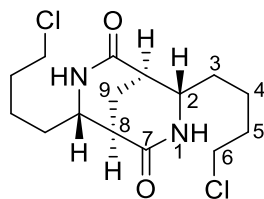


C$_{15}$H$_{24}$Cl$_2$N$_2$O$_2$
Mol Wt: 335.27

**Method A:** under basic conditions

To a solution of double imino-aldol adduct (**2.5a**, 400 mg, 0.550 mmol) in THF/ H$_2$O (3:2, 11 mL) at rt was added I$_2$ (555 mg, 2.18 mmol). The reaction mixture was heated at 50 °C under Ar. After 1 h, then Na$_2$CO$_3$ (463 mg, 4.36 mmol) was added portionwise. The resulting dark brown mixture lightened in colour. After 1 h, the mixture was allowed to cool to rt, then diluted with H$_2$O (5 mL). After removal of THF under reduced pressure, EtOAc (10 mL) was added, followed by dropwise addition of an aqueous saturated solution of Na$_2$S$_2$O$_3$ until the solution became colourless. The resulting mixture was extracted with EtOAc (3 x 10 mL) and the combined organic phase was washed with brine (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo* to yield a white solid. Purification by column chromatography (silica gel, *eluent:* EtOAc/hexane 9:1 then EtOAc/MeOH, 9:1) afforded the title bispidine **2.14** as a white solid (124 mg, 0.370 mmol, 67%).

**Method B:** under acidic conditions

To a solution of double imino-aldol adduct (**2.5a,** 50 mg, 0.068 mmol) in 1,4-dioxane (1.1 mL) at 0 °C was added conc. HCl (0.100 mL of ~36%, 0.410 mmol) dropwise and then stirred for 2 h under Ar. The reaction mixture was concentrated *in vacuo*. The crude was dissolved in EtOAc (2 mL) and saturated aq. NaHCO$_3$ was added dropwise at 0 °C. The phases were separated and aqueous phase was extracted with Et$_2$O (3 × 3 mL), H$_2$O (3 × 3 mL). The combined organics solution were washed with brine (2 × 3 mL), dried (MgSO$_4$) the solvent was removed *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent:* EtOAc/hexane 9:1 then EtOAc/MeOH, 19:1) to give the title compound **2.14** as a white solid (15 mg, 0.048 mmol, 66%). The material was recrystallised from EtOH to give white fluffy solid.
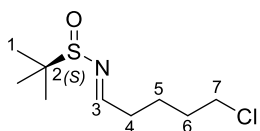
| | |
|---|---|
| **M.P.** | 270 – 273 °C |
| [*α*]$_D$ | −50.3 (*c* 1.5, MeOH, 24 °C) |
| **FT-IR (neat)** | ν$_{max}$ 3356, 2972, 2927, 1653, 1541, 1456, 1045 cm$^{-1}$. |

**¹H NMR**        (400 MHz, CDCl₃) δ 8.29 (2H, br s, 2 x **H₁**), 3.56 (6H, t, *J* = 5.4 Hz, 2 x **H₂** & **H₆**), 2.54 (2H, br, 2 x **H₉**), 2.03 (2H, br, 2 x **H₈**), 1.87 − 1.77 (4H, m, 2 x **H₅**), 1.76 − 1.47 (8H, m, 2 x **H₃** & **H₄**) ppm.

**¹³C NMR**       (101 MHz, CDCl₃) δ 173.5 (2 x **C₇**), 55.3 (2 x **C₂**), 44.6 (2 x **C₆**), 39.2 (2 x **C₈**), 34.8 (2 x **C₃**), 32.0 (2 x **C₅**), 23.3 (**C₉**), 16.6 (2 x **C₄**) ppm.

**LRMS**          (ESI⁺) *m/z* 335.2 [M³⁵Cl+H]⁺, 337.2 [M³⁷Cl+H]⁺.

**HRMS**          (ESI⁺) for $C_{15}H_{24}Cl_2N_2NaO_2^+$ [M+Na]⁺, calculated 357.1107; found 357.1100.

### 3.2.25      (1*S*,4*S*,5*S*,11a*S*)-4-Butyldecahydro-2H-1,5-methanopyrido[1,2-a][1,5]diazocine (2.15)
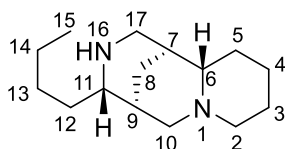


$C_{15}H_{28}N_2$
Mol Wt: 236.40

Following the procedure described by Nagao *et al.*;[140] to a solution of **2.14**, 16 mg, 0.050 mmol) in THF (0.3 mL) at 0 °C was added a solution of LiAlH₄ (0.150 ml of 1 M in THF, 0.150 mmoL,) dropwise. The reaction mixture was stirred at rt for 3 h, then heated under reflux for 3 h. Reaction progress was monitored by TLC (*eluent*: EtOAc/MeOH/NH₄OH 8:1.5:0.5). The mixture was allowed to cool to 0 °C, then it was diluted with Et₂O (1 mL), and quenched by careful addition of 30% NaOH (0.5 mL) and water (0.5 mL). The suspension was stirred at rt for 30 min then filtered through celite and washed with 10% Et₃N in THF (3 × 5 mL), dried (Na₂SO₄) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, *eluent*: EtOAc/hexane 9:1 then EtOAc/MeOH, 8:2) gave sparteine derivative **2.15** as a pale yellow (5 mg, 0.021 mmol, 42%).

**FT-IR (neat)**    ν_max 2923, 2853, 1733, 1457, 1377, 1260, cm⁻¹.

**¹H NMR**        (400 MHz CDCl₃) δ 3.27 (1H, dd, *J* = 11.1, 6.5 Hz, **H₁₇ₑq**), 2.99 (1H, dd, *J* = 13.1, 2.9 Hz, **H₁₀ₑq**), 2.85 − 2.76 (1H, m, **H₂ₑq**), 2.68 − 2.56 (2H, m, **H₁₁** & **H₁₆**), 2.55 − 2.41 (2H, m, **H₆** & **H₁₇ₐₓ**), 2.34 − 2.13 (2H, m, **H₂ₐₓ** & **H₁₀ₐₓ**), 1.84 − 1.50 (7H, m, **H₈, H₉, H₁₂** & **H₁₃**), 1.47 − 1.18 (9H, m, **H₃, H₄, H₅, H₇** & **H₁₄**), 0.91 (3H, br t, *J* = 7.0 Hz, **H₁₅**)

**¹³C NMR**     (101 MHz, CDCl₃) δ 63.0 ($C_{11}$), 58.4 ($C_6$), 56.0 ($C_{10}$), 55.2 ($C_2$), 54.7 ($C_{17}$), 47.4 ($C_9$), 34.9 ($C_{12}$), 34.5 ($C_7$), 32.1 ($C_5$), 30.8 ($C_8$), 25.5 ($C_3$), 25.5 ($C_4$), 22.9 ($C_{14}$), 21.1 ($C_{13}$), 14.1 ($C_{15}$) ppm.

**LRMS**        (ESI⁺) *m/z* 237.1 [M+H]⁺.

**HRMS**        (ESI⁺) for $C_{15}H_{29}N_2^+$ [M+H]⁺, calculated 237.2325; found 237.2326.

### 3.2.26      (+)-10,17-Dioxo-*β*-isosparteine ((+)-1.33)



$C_{15}H_{22}N_2O_2$
Mol.Wt: 262.353
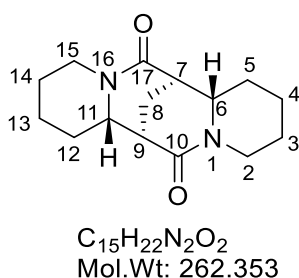
Following a modified procedure from Bogdal;[156] to a solution of halo dioxobispidine (**2.14**, 100 mg, 0.300 mmol) in DMSO (3 mL) was added K₂CO₃ (205 mg, 1.490 mmol), and KOH (84 mg, 1.490 mmol) portionwise, followed by TBAB (20 mg, 0.060 mmol). The reaction mixture was heated at 60 °C for 4 h. The mixture was cooled to rt and extracted with EtOAc (5 x 10 mL), washing with iced water (5 x 5 mL). The organic phase was dried (MgSO₄), and the solvent was removed using a high vacuum pump. The title bislactam (+)-**1.33** was obtained as a white solid (64 mg, 0.240 mmol, 81%). Physical and spectroscopic data are consistent with the reported values.[55]

**M.P.**          170 – 172 °C (Lit.[55] 172 – 174 °C for racemate).

**[α]_D**         +47.3 (*c* 1.5, MeOH, 23 °C)

**FT-IR (neat)**  ν_max 2928, 2850, 1628, 1458, 1436, 1356, 1269, 1211 cm⁻¹.

**¹H NMR**        (400 MHz, CDCl₃) δ 4.71 (2H, ddt, *J* = 13.1, 4.0, 1.8 Hz, **H₂eq** & **H₁₅eq**), 3.58 – 3.46 (2H, m, **H₆** & **H₁₁**), 2.58 (2H, t, *J* = 3.0 Hz, **H₂ₐₓ** & **H₁₅ₐₓ**), 2.45 (2H, td, *J* = 13.0, 2.7 Hz, **H₇** & **H₉**), 2.10 (2H, t, *J* = 3.0 Hz, **H₈**), 2.01 – 1.89 (2H m, **H₅ₐ** & **H₁₂ₐ**), 1.77 – 1.53 (8H, m,), 1.46 – 1.32 (2H, m,) ppm.

**¹³C NMR**       (101 MHz, CDCl₃) δ 169.0 ($C_{10}$ & $C_{17}$), 60.4 ($C_6$ & $C_{11}$), 43.5 ($C_2$ & $C_{15}$), 42.5 ($C_7$ & $C_9$), 32.2 ($C_5$ & $C_{12}$), 25.3 ($C_3$ & $C_{14}$), 24.9 ($C_4$ & $C_{13}$), 18.7 ($C_8$) ppm.

**LRMS**          (ESI⁺) *m/z* 363.3 [M+H]⁺

**HRMS**          (ESI⁺) for $C_{15}H_{23}N_2O_2^+$ [M+H]⁺, calculated 263.1754; found 263.1757.

### 3.2.27      (+)-*β*-Isosparteine ((+)-1.4)
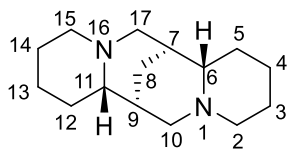


$C_{15}H_{26}N_2$
Mol. Wt: 234.39

Following the procedure of Hermet *et al.*;[84] to a solution of bislactam (**1.33**, 30 mg, 0.11 mmol) in THF (1 mL) at 0 °C under $N_2$ was added LiAlH₄ (1.00 mL, 1 M in THF, 1.00 mmol) dropwise. The resulting suspension was heated at reflux for 4 h. After cooling to rt, the suspension was diluted with Et₂O (10 mL) and excess solid hydrated sodium sulfate was added portionwise until effervescence ceased. The suspension was stirred for 30 min at rt during which it became pale grey. The solids were removed by filtration through celite and the filter cake was washed with CH₂Cl₂-MeOH (9:1, 40 mL). The filtrate and combined washing were dried (NaSO₄) and concentrated *in vacuo* to access (+)-*β*-isosparteine ((+)-**1.4**, 24 mg, 0.100 mmol, 90%) as a colourless oil. Physical and spectroscopic data are consistent with the reported values.[48,55]

**[α]ᴅ**          +15.1 (*c* 0.75 absolute EtOH, 23 °C), Lit.[48] +15.38 (*c* 0.142 absolute EtOH, 21.1 °C)

**FT-IR (neat)**   v_max 2924, 2850, 1443, 1354, 1130 cm⁻¹.

**¹H NMR**        (400 MHz, CDCl₃) δ 3.02 (2H, dd, *J* = 10.9, 6.7 Hz, **H₁₀eq**), 2.80 (dt, *J* = 12.7, 2.0 Hz, 2H, **H₂eq**), 2.45 (2H, td, *J* = 12.6, 2.6 Hz, **H₂ax**), 2.26 (2H, dt, *J* = 11. 7, 2.5 Hz, **H₆ax**), 2.17 (2H, dd, *J* = 10.8, 2.9 Hz, **H₁₀ax**), 1.82 − 1.74 (2H, m, **H₄eq**), 1.71 − 1.50 (8H, m, **H₃eq, H₅eq, H₇ax & H₈**), 1.44 − 1.32 (4H, m, **H₃ax & H₅ax**), 1.25 − 1.20 (m, 2H, **H₄ax**) ppm.

**¹³C NMR**       (101 MHz, CDCl₃) δ 62.8 (2 x **C₆**), 55.2 (2 x **C₂**), 55.0 (2 x **C₉**), 34.5 (2 x **C₇**), 28.8 (2 x **C₅**), 25.5 (2 x **C₄**), 22.7 (2 x **C₃**), 19.8 (**C₈**) ppm.

**LRMS**          (ESI⁺) *m/z* 235.2 [M+H]⁺.

**HRMS**          (ESI⁺) for $C_{15}H_{27}N_2^+$ [M+H]⁺, calculated 235.2169; found 235.2168.

### 3.2.28    (1*S*,4*S*,5*S*,8*S*)-4,8-bis(4-Chlorobutyl)-3,7-diazabicyclo[3.3.1]nonane-2,6-dione (2.18)

**Complex mixture of double imino-aldol products isolated from double and mono imino-aldol reactions.**
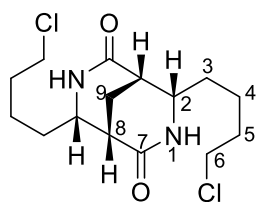
$C_{15}H_{24}Cl_2N_2O_2$
Mol Wt: 335.27

To a solution of a mixture of double imino-aldol adduct (**2.5a-c**, 1.50 g, 2.050 mmol) in 1,4-dioxane (41 mL) at 0 °C was added conc. HCl (4 mL of ~36%, 16.4 mmol) dropwise and then the mixture was stirred at rt for 1 h under Ar. The reaction mixture was basified by the dropwise addition of saturated aq. NaHCO$_3$ at 0 °C, then stirred at rt for 1 h. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 25 mL), washing with saturated aq. NaHCO$_3$ (3 × 20 mL). The combined organic solutions were washed with brine (2 × 25 mL), dried (NaSO$_4$) the solvent was removed *in vacuo*. The crude material contained three diastereomers (*anti,anti*:*syn,anti*:*syn,syn*). The mixture of diastereomers was purified by repeated column chromatography (silica gel, *eluent:* EtOAc/MeOH 98:2 then EtOAc/MeOH, 19:1) to provide the first diastereomer *anti,anti* dioxo-bispidine (**2.18**), followed quickly by *syn,anti* dioxo-bispidine (**2.19**) as a second diastereomer, and later, the third diastereomer *syn,syn* dioxo-bispidine (**2.14**). The *syn,syn* dioxo-bispidine (**2.14** ) was obtained as a white solid (410 mg, 1.220 mmol). The *anti,anti* dioxo-bispidine (**2.18**) was also obtained as a white solid (15 mg, 0.040 mmol). The mixture of *anti,anti* and *syn,anti* dioxo-bispidines was obtained as a white solid (53 mg, 0.160 mmol).

**Data for *anti,anti* dioxo-bispidine (2.18):**

| | |
|---|---|
| **M.P.** | 133 – 135 °C. |
| **[$\alpha$]$_D$** | +21.4 (*c* 1.5, MeOH, 20 °C) |
| **FT-IR (neat)** | v$_{max}$ 3199, 2944, 1661, 1418, 1317, 1066 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 5.97 (2H, s, 2 x **H$_1$**), 3.54 – 3.43 (6H, m, 2 x **H$_2$** & **H$_6$**), 2.69 (2H, br d, *J* = 3.3 Hz, 2 x **H$_9$**), 2.12 (2H, t, *J* = 3.1 Hz, 2 x **H$_8$**), 1.82 – 1.56 (8H, m, 2 x **H$_{4a}$**, **H$_{3a}$** & **H$_5$**), 1.52 – 1.44 (2H, m, **H$_{4b}$**), 1.40 – 1.27 (2H, m, **H$_{3b}$**) ppm. |

| | |
|---|---|
| **¹³C NMR** | (101 MHz, CDCl₃) δ 169.5 (2 x **C₇**), 56.3 (2 x **C₂**), 44.6 (2 x **C₆**), 38.7 (2 x **C₈**), 33.3 (2 x **C₃**), 32.2 (2 x **C₅**), 27.2 (**C₉**), 23.1 (2 x **C₄**) ppm. |
| **LRMS** | (ESI⁺) *m/z* 335.2 [M³⁵Cl+H]⁺, 337.2 [M³⁷Cl+H]⁺. |

### 3.2.29    (7*S*,7a*S*,14*S*,14a*S*)-Dodecahydro-6H,13H-7,14-methanodipyrido[1,2-a:1',2'-e][1,5]diazocine-6,13-dione, (−)-10,17-dioxo-*α*-isosparteine ((−)-1.43)
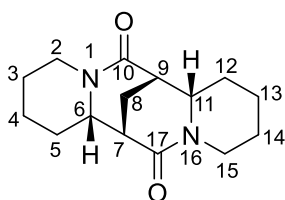


C₁₅H₂₂N₂O₂
Mol.Wt: 262.353

Following a modified procedure from Bogdal;[156] to a solution containing a mixture of *anti,anti* and *syn,anti* dioxo-bispidines (**2.18** & **2.19**, 50 mg, 0.150 mmol) in DMSO (2 mL) was added K₂CO₃ (100 mg, 0.720 mmol), and KOH (40 mg, 0.710 mmol) portionwise, followed by TBAB (10 mg, 0.030 mmol). The reaction mixture was heated at 60 °C for 6 h. The mixture was cooled to rt and extracted with EtOAc (5 x 10 mL), and iced water (5 x 5 mL). The organic phase was dried (NaSO₄), and the solvent was removed under high vacuum. The mixture of *anti,anti* and *syn,anti* bislactams were obtained as a white solid (29 mg, 0.110 mmol, 74%). The mixture was recrystallised from hexane. Careful separation of the needles provided (−)-10,17-dioxo-α-isosparteine ((−)-**1.43**), 9 mg, 0.030 mmol).

Alternatively, purification of the mixture of diastereomers by column chromatography (silica gel, *eluent*: EtOAc/MeOH 98:2 then EtOAc/MeOH, 19:1) provided the first diastereomer (+)-10,17-dioxo-sparteine (**1.44**, 7 mg, 0.026 mmol), followed by (−)-10,17-dioxo-α-isosparteine ((−)-**1.43**) as a white solid (11 mg, 0.042 mmol). Physical and spectroscopic data for (+)-**1.44** are consistent with the reported values.[84]

**Data for (–)-10,17-dioxo-$\alpha$-isosparteine ((–)-1.43):**

**M.P.**            160 – 164 °C.

**[$\alpha$]$_D$**            −58.8 (*c* 1.0, MeOH, 20 °C)

**FT-IR (neat)**    $v_{max}$ 2922, 2850, 1632, 1427, 1361, 1263, 1112 cm$^{-1}$.

**$^1$H NMR**    (400 MHz, CDCl$_3$) δ 4.74 (2H, ddt, *J* = 13.3, 4.1, 2.0 Hz, **H$_{2eq}$ & H$_{15eq}$**), 3.33 (2H, ddd, *J* = 12.0, 5.1, 2.4 Hz, **H$_6$ & H$_{11}$**), 2.85 – 2.81 (2H, m, **H$_{2ax}$ & H$_{15ax}$**), 2.46 (2H, td, *J* = 13.1, 3.0 Hz, **H$_7$ & H$_9$**), 2.06 (2H, t, *J* = 3.1 Hz, **H$_8$**), 2.04 – 1.97 (2H, m, **H$_{5a}$ & H$_{12a}$**), 1.92 – 1.84 (2H, m, **H$_{4a}$ & H$_{13a}$**), 1.77 – 1.69 (2H, m, **H$_{3a}$ & H$_{14a}$**), 1.46 – 1.13 (6H, m, **H$_{3b}$, H$_{4b}$, H$_{5b}$, H$_{12b}$, H$_{13b}$ & H$_{14b}$**) ppm

**$^{13}$C NMR**    (101 MHz, CDCl$_3$) δ 167.9 (**C$_{10}$ & C$_{17}$**), 58.8 (**C$_6$ & C$_{11}$**), 42.4 (**C$_2$ & C$_{15}$**), 41.8 (**C$_7$ & C$_9$**), 31.3 (**C$_5$ & C$_{12}$**), 25.2 (**C$_3$ & C$_{14}$**), 24.4 (**C$_8$**), 24.3 (**C$_4$ & C$_{13}$**) ppm.

**LRMS**    *m/z* 263.2 [M+H]$^+$.

**HRMS**    (ESI$^+$) for C$_{15}$H$_{23}$N$_2$O$_2$$^+$ [M+H]$^+$, calculated 263.1754; found 263.1755.


### 3.2.30    (7*R*,7a*R*,14*R*,14a*S*)-Dodecahydro-6H,13H-7,14-methanodipyrido[1,2-a:1',2'-e][1,5]diazocine-6,13-dione, (+)-10,17-dioxo-sparteine ((+)-1.44)



C$_{15}$H$_{22}$N$_2$O$_2$
Mol.Wt: 262.353

**Data for (+)-10,17-dioxo-sparteine ((+)-1.44):**

**M.P.**            62 – 66 °C.

**[$\alpha$]$_D$**            +70.3 (*c* 0.6, CH$_3$Cl, 20 °C), Lit[84] +72.3 (*c* 1.0 in CH$_3$Cl, 20 °C)

**FT-IR (neat)**    $v_{max}$ 2922, 2850, 1632, 1427, 1361, 1263, 1112 cm$^{-1}$.

**$^1$H NMR**    (400 MHz, CDCl$_3$) δ 4.79 – 4.70 (2H, m, **H$_{2eq}$ & H$_{15eq}$**), 3.56 (1H, dd, *J* = 11.7, 2.0 Hz, **H$_{11}$**), 3.37 (1H, ddd, *J* = 11.8, 5.2, 2.6 Hz, **H$_6$**), 2.80 – 2.75 (1H, m, **H$_7$**), 2.62 (br

s, 1H **H₉**), 2.53 – 2.41 (2H, m, **H₂ₐₓ** & **H₁₅ₐₓ**), 2.22 (1H, ddd, *J* = 13.0, 4.0, 2.0 Hz, **H₈ₑq**), 1.99 – 1.91 (3H, m, **H₅**, **H₈ₐₓ**), 1.90 – 1.83 (1H, m, **H₃ₐ**), 1.76 – 1.57 (5H, m, **H₃ᵦ, H₄ₐ, H₁₂ & H₁₄ₐ**), 1.45 – 1.33 (3H, m, **H₄ᵦ, H₁₃ₐ & H₁₄ᵦ**), 1.24 – 1.19 (1H, m, **H₁₃ᵦ**) ppm.

| | |
|---|---|
| **¹³C NMR** | (101 MHz, CDCl₃) δ 170.2 (**C₁₇**), 166.4 (**C₁₀**), 60.0 (**C₁₁**), 59.2 (**C₆**), 43.4 (**C₁₅**), 42.8 (**C₉**), 42.3 (**C₂**), 42.0 (**C₇**), 32.6 (**C₁₂**), 31.2 (**C₅**), 25.1 (**C₁₄**), 25.0 (**C₃**), 24.9 (**C₁₃**), 24.2 (**C₄**), 21.9 (**C₈**) ppm. |
| **LRMS** | *m/z* 263.2 [M+H]⁺. |

### 3.2.31        (–)-sparteine ((–)-1.3)



C₁₅H₂₆N₂
Mol.Wt: 234.39

Following the procedure of Hermet *et al*.;[84] to a solution of (+)-10,17-dioxo-sparteine ((+)-**1.44**, 6 mg, 0.023 mmol) in THF (1 mL) at 0 °C under N₂ was added a solution of LiAlH₄ (0.14 mL of 1.0 M, , 0.14 mmol) dropwise. The resulting suspension was heated at reflux for 6 h. After cooling to rt, the suspension was diluted with Et₂O (10 mL) and excess solid hydrated sodium sulfate was added portionwise until effervescence ceased. The suspension was stirred for 30 min at rt during which it became pale grey. The solids were removed by filtration through celite and the filter cake was washed with CH₂Cl₂-MeOH (9:1) (20 mL). The filtrate and combined washing were dried (Na₂SO₄) and concentrated *in vacuo* to access (–)-sparteine ((–)-**1.3**, 5 mg, 0.021 mmol, 92%) as a yellow oil. Physical and spectroscopic data are consistent with the reported values.[84]

| | |
|---|---|
| $[\alpha]_D$ | –16.9 (*c* 0.5 absolute EtOH, 20 °C), Lit.[84] (–18.1 (*c* 1.3 in EtOH)), Lit[92] –20.4 (*c* 1.3 in EtOH). |
| **FT-IR (neat)** | ν_max 2922, 2850, 1632, 1427, 1361, 1263, 1112 cm⁻¹. |
| **¹H NMR** | ¹H NMR (400 MHz, CDCl₃) δ 2.81 (1H, br d, *J* = 11.4 Hz, **H₁₅ₑq**), 2.77 – 2.65 (2H, m, **H₂ₑq** & **H₁₇ₑq**), 2.54 (1H, br d, *J* = 10.0 Hz, **H₁₀ₑq**), 2.36 (1H, br dd, *J* = 10.2, 2.1 Hz, **H₁₇ₐₓ**), 2.11 – 1.91 (5H, m, **H₂ₐₓ, H₈ₑq, H₁₀ₐₓ, H₁₁ & H₁₅ₐₓ**), 1.89 – 1.81 (1H, m, **H₇**), |

1.77 – 1.66 (3H, m, **H$_{4eq}$, H$_6$ & H$_{13eq}$**), 1.66 – 1.43 (6H, m, **H$_3$, H$_9$, H$_{12ax}$ & H$_{14}$**), 1.42 – 1.19 (5H, m, **H$_{4ax}$, H$_5$, H$_{12eq}$ & H$_{13ax}$**), 1.07 (1H, d, *J* = 12.0 Hz, **H$_{8ax}$**) ppm.

**$^{13}$C NMR**     (101 MHz, CDCl$_3$) δ 66.4 (**C$_6$**), 64.4 (**C$_{11}$**), 61.8 (**C$_{10}$**), 56.2 (**C$_2$**), 55.3 (**C$_{15}$**), 53.4 (**C$_{17}$**), 35.9 (**C$_7$**), 34.3 (**C$_{12}$**), 33.0 (**C$_9$**), 29.3 (**C$_5$**), 27.5 (**C$_8$**), 25.8 (**C$_3$ & C$_{14}$**), 24.6 (**C$_4$**), 24.4 (**C$_{13}$**) ppm.

**LRMS**     *m/z* 235.2 [M+H]$^+$.

### 3.2.32     2-Methyl-N-((1*E*,2*E*)-3-phenylallylidene)propane-2-sulfinamide (2.22)



C$_{13}$H$_{17}$NOS
Mol Wt: 235.35

To a solution of (*S*)-tertbutylsulfinamide (**2.9**, 2.5 g, 20.7 mmol) and cinnamaldehyde (3.12 mL, 24.75 mmol) in THF (30 mL) at 0 °C under N$_2$ was added Ti(OEt)$_4$ (4.50 mL, 18.8 mmol) dropwise turning the solution yellow. The reaction was stirred for 1 h and additional Ti(OEt)$_4$ (2.50 mL, 9.51 mmmol) was added dropwise at 0 °C. The reaction was monitored by TLC (eluent: EtOAc/ hexane 1:4) and upon completion for 4 h. The reaction mixture was poured onto brine (100 mL). The reaction was stirred rapidly for 5 min and filtered through a sintered funnel. The filter cake was washed with hot EtOAc (4 × 25 mL) and the phases separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), the organics combined, washed with brine (2 × 20 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The title compound **2.22** was isolated by column chromatography (silica gel, eluent: EtOAc/*n*-hexane 1:4) as a pale yellow oil (4.02 g, 17.0 mmol, 82%). Physical and spectroscopic data are consistent with reported values.[157]

**FT-IR (neat)**     ν$_{max}$ 1622, 1578, 1565, 1151, 1075, 749, 686 cm$^{-1}$.

**$^1$H NMR**     (400 MHz, CDCl$_3$) δ 8.39 (1H, d, *J* = 9.2 Hz, **H$_3$**), 7.58 – 7.52 (2H, m, **H$_7$**), 7.45 – 7.36 (3H, m, **H$_8$ & H$_9$**), 7.23 (1H, d, *J* = 16.0 Hz, **H$_5$**), 7.14 – 7.06 (1H, m, **H$_4$**), 1.25 (9H, s, **H$_1$**) ppm.

| | |
|---|---|
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 163.8 (**C$_3$**), 146.3 (C5), 135.0 (**C$_6$**), 130.2 (**C$_9$**), 128.9 (2 x **C$_7$**), 127.9 (2 x **C$_8$**), 125.6 (**C$_4$**), 57.5 (**C$_2$**), 22.5 (**C$_1$**) ppm. |
| **LRMS** | (ESI+) *m/z* 236.2 [M+H]$^+$. |

### 3.2.33    Phenyl (2*R*,3*R*)-1-((*S*)-tert-butylsulfinyl)-6-oxo-2-((*E*)-styryl) piperidine-3-carboxylate (2.24)



C$_{24}$H$_{27}$NO$_4$S
Mol. Wt: 425.54

To a solution of LDA (2.93 mL of 2.0 M in THF, 5.860 mmol) at −78 °C under Ar was added a solution of diphenyl glutarate (**2.1**, 832 mg, 2.930 mmol) in THF (22.5 mL) dropwise over 15 min. The reaction was stirred at −78 °C for 1 h, and then a solution of phenyl imine (**2.22**, 530 mg, 2.250 mmol) in THF (2.5 mL) at −78 °C was added dropwise over 5 min. The reaction was stirred at between −78 and −70 °C for 1 h, and quenched by dropwise addition of saturated aq. NH$_4$Cl (9 mL). The reaction was allowed to warm to rt with rapid stirring for 30 min. The phases were separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The organic phases were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The crude mixture of diastereomers were purified by column chromatography (silica gel, *eluent* gradient: Et$_2$O/hexane, 2:8 → 7:2) to provide the first diastereomer (cyclised mono *syn* imino-aldol **2.24**), as a colourless oil (400 mg, 0.940 mmol, 41%). The second diastereomer was the cyclised mono *anti* imino-aldol, which was isolated impure in low quantity. The uncyclised *syn* imino-aldol **2.25** was instable with no assignment recoreded.

| | |
|---|---|
| **FT-IR (neat)** | v$_{max}$ 2958, 2925, 2876, 1757, 1660, 1496, 1471, 1136 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.45 − 7.38 (4H, m, **H$_{11}$**, **H$_{13}$**, **H$_{18}$** & **H$_{20}$**), 7.35 − 7.29 (2H, m, **H$_{10}$** & **H$_{14}$**), 7.29 − 7.25 (2H, m, **H$_{12}$** & **H$_{19}$**), 7.16 − 7.11 (2H, m, **H$_{17}$** & **H$_{21}$**), 6.55 (1H, dd, *J* = 16.0, 1.3 Hz, **H$_8$**), 6.29 (1H, dd, *J* = 16.0, 4.8 Hz, **H$_7$**), 5.17 − 5.13 (1H, m, **H$_6$**), 3.31 (1H, td, *J* = 4.7, 2.1 Hz, **H$_5$**), 2.94 − 2.83 (1H, m, **H$_{3eq}$**), 2.69 − 2.59 (1H, m, **H$_{3ax}$**), 2.31 − 2.24 (2H, m, **H$_4$**), 1.27 (9H, s, **H$_{23}$**) ppm. |

**¹³C NMR**          (100 MHz, CDCl₃) δ 173.2 ($C_2$), 170.6 ($C_{15}$), 150.2 ($C_{16}$), 135.7 ($C_9$), 131.2 ($C_8$), 130.1 ($C_7$), 129.5 ($C_{18}$ & $C_{20}$), 128.5 ($C_{11}$ & $C_{13}$), 128.0 ($C_{12}$), 126.6 ($C_{10}$ & $C_{14}$), 126.2 ($C_{19}$), 121.0 ($C_{17}$ & $C_{21}$), 62.5 ($C_{22}$), 53.9 ($C_6$), 43.5 ($C_5$), 30.6 ($C_3$), 22.5 (3 x $C_{23}$), 18.8 ($C_4$) ppm.

**LRMS**          (ESI⁺) *m/z* 448.2 [M+Na]⁺.

### 3.2.34     Phenyl (2*S*,3*S*)-1-((*S*)-tert-butylsulfinyl)-6-oxo-2-((*E*)-styryl)piperidine-3-carboxylate.



$C_{24}H_{27}NO_4S$
Mol. Wt: 425.54

**Selected data for impure cyclised *anti* mono imino-aldol:**

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.31 (8H, m, $H_{10}$, $H_{11}$, $H_{12}$, $H_{13}$, $H_{14}$, $H_{15}$, $H_{18}$, $H_{19}$ & $H_{20}$), 7.07 (2H, br d, *J* = 7.7 Hz, $H_{17}$ & $H_{21}$), 6.67 – 6.60 (1H, m, $H_8$), 6.28 – 6.20 (1H, m, $H_7$), 5.18 (1H, dd, *J* = 5.1, 4.2 Hz, $H_6$), 3.32 (1H, dt, *J* = 12.4, 4.5 Hz, $H_5$), 2.83 – 2.73 (1H, m, $H_{3eq}$), 2.70 – 2.58 (1H, m, $H_{3ax}$), 2.39 – 2.28 (1H, m, $H_{4eq}$), 2.26 – 2.17 (1H, m, $H_{4ax}$), 1.39 – 1.30 (9H, m, $H_{23}$) ppm.

### 3.2.35     ((1*R*,9a*S*)- Octahydro-2*H*-quinolizin-1-yl)methanol

**Preparation of (−)-epilupinine ((−) 1.1) from *syn*-mono imino-aldol adduct 2.13**



$C_{10}H_{19}NO$
Mol Wt: 169.27

Following a modified procedure from Nagao *et al.*;[140] to a solution of **2.13**, 55 mg, 0.133 mmol) in THF (1.0 mL) at 0 °C was added a solution of LiAlH₄ (0.150 ml of 1 M in THF, 0.150 mmoL,) dropwise. The reaction mixture was stirred at rt for 1 h, then heated under reflux for 3 h. Reaction progress

was monitored by TLC (*eluent*: EtOAc/MeOH/NH$_4$OH 8:1.5:0.5). The mixture was allowed to cool to 0 °C, then it was diluted with Et$_2$O (1 mL), and quenched by careful addition saturated aq. Na$_2$SO$_4$ (0.5 mL). The suspension was stirred at rt for 30 min then filtered through celite and washed with EtOAc (3 × 5 mL), dried (Na$_2$SO$_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, *eluent*: EtOAc/hexane 9:1 then EtOAc/MeOH, 8:2) gave (−)-epilupinine ((−)-**1.1**) as a white solid (13.5 mg, 0.080 mmol, 60%). Data for (−)-epilupinine are consistent with those reported above.

### 3.2.36　　Phenyl (2*S*,3*R*)-1-((*S*)-tert-butylsulfinyl)-5-((*R*)-1-(((*S*)-tert-butylsulfinyl)amino)-5-chloropentyl)-2-(4-chlorobutyl)-6-oxopiperidine-3-carboxylate (2.20)



C$_{29}$H$_{46}$Cl$_2$N$_2$O$_5$S$_2$
Mol. Wt: 637.72

To a solution of LDA (0.80 mL of 1.0 M in THF/hexane, 0.800 mmol) in THF (10 mL) at −78 °C under Ar was added a solution of mono *syn*-imino-aldol (unsyclised) (**2.16**, 200 mg, 0.390 mmol) in THF (2.5 mL) dropwise. The reaction was stirred at −78 °C for 1 h, and then a solution of sulfinylimine **1.205** (85 mg, 0.380 mmol) in THF (2.5 mL) was added dropwise over 10 min at −78 °C. After 1 h, the reaction was quenched at −78 °C by dropwise addition of saturated aq NH$_4$Cl (10 mL) over 10 min. The reaction was allowed to warm to rt with rapid stirring for 30 min. The phases were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The organic phase was combined, washed with brine (2 x 5 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent* gradient: EtOAc/hexane, 2:8 → 8:2) affording several fractions: *Fraction 1* (Rf = 0.64, Et$_2$O/hexane, 8:2) contained sulfinylimine **1.205** (18 mg, 0.080 mmol, 21%) was recovered; *Fraction 2* (R$_f$ = 0.51, Et$_2$O/hexane, 8:2) contained cyclised mono *syn* imino-aldol **2.13** as off-white solid (24 mg, 0.057 mmol, 15%); *Fraction 3* (R$_f$ =0.34, Et$_2$O/hexane, 8:2) contained impure *syn-syn* double imino-aldol **2.5a** as an yellow oil (15 mg, 0.020 mmol, 5 %); *Fraction 4* (R$_f$ = 0.26, Et$_2$O/hexane, 8:2) contained partial cyclised of double imino-aldol **2.20** as a pale  yellow oil (82 mg, 0.130 mmol, 34%) recorded as unknown stereochemistry.

**Selected data for partial cyclised double imino-aldol 2.20:**

**FT-IR (neat)**      $v_{max}$ 3322, 2991, 2928, 2869, 1739, 1591, 1483, 1454, 1236, 1184, 1049 cm$^{-1}$.

**$^1$H NMR**      (400 MHz, CDCl) δ 7.37 – 7.44 (2H, m, 2 x **H$_{19}$**), 7.27 (1H, m, **H$_{20}$**), 7.02 – 7.09 (2H, m, 2 x **H$_{18}$**), 4.20 – 4.28 (1H, m, **H$_6$**), 4.06 (1H, d, $J$ = 8.3 Hz, **H$_{23}$**), 3.55 – 3.62 (4H, m, **H$_{10}$** & **H$_{15}$**), 3.35 – 3.43 (1H, m, **H$_{11}$**), 3.16 - 3.24 (1H, m, **H$_5$**), 2.88 (1H, ddd, $J$ = 11.9, 5.9, 3.1 Hz, **H$_3$**), 2.23 – 2.35 (2H, m, **H$_4$**), 1.66 – 2.01 (12H, m, **H$_7$, H$_8$, H$_9$, H$_{12}$, H$_{13}$** & **H$_{14}$**), 1.21 (18H, d, $J$ = 5.4 Hz, **H$_{22}$** & **H$_{25}$**) ppm.

**$^{13}$C NMR**      (100 MHz, CDCl$_3$) δ 175.1 (**C$_{16}$**), 172.1 (**C$_2$**), 150.3 (**C$_{17}$**), 129.7 (**2 x C$_{19}$**), 126.3 (**C$_{20}$**), 121.0 (**2 x C$_{18}$**), 61.6 (**C$_{24}$**), 59.4 (**C$_{11}$**), 56.3 (**C$_{21}$**), 51.3 (**C$_6$**), 45.3 (**C$_3$**), 44.8 (**C$_{15}$**), 44.7 (**C$_{10}$**), 42.5 (**C$_5$**), 39.0 (**C$_{12}$**), 34.1 (**C$_7$**), 32.1 (**C$_{14}$**), 31.4 (**C$_9$**), 27.3 (**C$_4$**), 24.0 (**C$_{13}$**), 22.9 (**C$_8$**), 22.8 (**C$_{25}$**), 22.3 (**C$_{22}$**) ppm.

**LRMS**      (ESI$^+$) $m/z$ 637.4 [M$^{35}$Cl+H]$^+$, 639.3 [M$^{37}$Cl+H]$^+$.

**HRMS**      (ESI$^+$) for C$_{29}$H$_{47}$$^{35}$Cl$_2$N$_2$O$_5$S$_2$$^+$ [M+H]$^+$, calculated 637.2299; found 639.2298; for C$_{29}$H$_{46}$$^{35}$Cl$_2$N$_2$NaO$_5$S$_2$$^+$ [M+Na]$^+$, calculated 659.2118; found 659.2117.

### 3.2.37    (1*R*,4*S*,5*R*,8*S*)-3-((*R*)-*tert*-Butylsulfinyl)-4,8-bis(4-chlorobutyl)-3,7-diazabicyclo [3.3.1] nonane-2,6-dione (2.21)
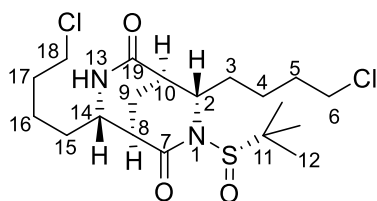


C$_{19}$H$_{32}$Cl$_2$N$_2$O$_3$S
Mol Wt: 339.44

Following the procedure described for the synthesis of **2.14**, method B; partial double imino-aldol adduct (**2.20**, 50 mg, 0.0784 mmol) afforded the title *syn,syn*-dioxo-bispidine **2.14** (11 mg, 0.0328 mmol, 42%) and mono protection bispidine **2.21** (9 mg, 0.0265 mmol, 34%).

Data for *syn,syn*-dioxo-bispidine **2.14** are consistent with those reported above.

**Data for mono protection bispidine 2.21:**

**FT-IR (neat)**      $v_{max}$ 3356 2972, 2927, 1653, 1541, 1456, 1045 cm$^{-1}$.

**¹H NMR**          (400 MHz, CDCl₃) δ 8.03 (2H, br s, **H₁₃**), 4.02 (1H, m, **H₂**), 3.62 – 3.48 (5H, m, **H₁₂** &

                    2 x **H₆**), 2.80 (1H, br s, **H₉ₐ**), 2.70 (1H, brs, **H₉ᵦ**), 2.35 – 2.16 (2H, m, **H₈** & **H₁₀**), 2.08

                    (1H, m, **H₅ₐ**), 1.91 – 1.71 (5H, m, 2 x (**H₃, H₁₇**) & **H₅ᵦ**), 1.70 – 1.46 (6H, m, 2 x (**H₄** &

                    **H₁₅**) & **H₁₆**) 1.23 – 1.19 (9H, m, **H₁₂**) ppm.

**¹³C NMR**         (100 MHz, CDCl₃) δ 173.3 (**C₁₉**), 171.7 (**C₇**), 63.9 (**C₁₁**), 56.9 (**C₂**), 46.4 (**C₁₄**), 44.6

                    (**C₁₈**), 44.5 (**C₆**), 41.8 (**C₈**), 38.8 (**C₁₀**), 35.0 (**C₁₅**), 34.0 (**C₃**), 31.9 (**C₁₇**), 31.6 (**C₅**), 23.4

                    (**C₉**), 23.3 (**C₄**), 22.7 (**C₁₂**), 16.2 (**C₁₆**) ppm.

**LRMS**            (ESI⁺) *m/z* 461.3 [M³⁵Cl+Na]⁺, 463.4 [M³⁷Cl+Na]⁺, 879.5 [2M³⁵Cl+H]⁺, 381.3

                    [2M³⁷Cl+H]⁺, 901.5 [2M³⁵Cl+Na]⁺, 903.5 [2M³⁷Cl+Na]⁺.

### 3.2.38    1-((2*S*,3*R*)-3-(Hydroxymethyl)-2-((*E*)-pent-1-en-1-yl)piperidin-1-yl)but-3-en-1-one (2.49)
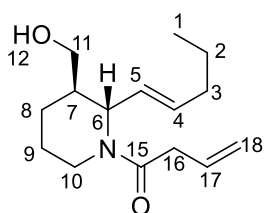


$C_{15}H_{25}NO_2$
Mol Wt: 251.37

To a solution of ester amide **2.21** (600 mg, 1.76 mmol) in THF (20 mL) at −10 °C LiAlH₄ (1M solution in THF 0.88 mL, 0.88 mmol) was added dropwise. The reaction mixture was stirred at −10 °C to −5 °C for 30 min. The reaction mixture was cooled to 0 °C and saturated aq. Na₂SO₄ (3 mL) was added carefully and was stirred for further 30 min at rt. The mixture was diluted with CH₂Cl₂ (20 mL), and the suspension was filtered through celite and washed with CH₂Cl₂ (3 x 10 mL). The solvent was removed *in vacuo*. Purification by column chromatography on basic alumina (EtOAc /MeOH, 19:1 → 9:1) gave the title compound **249** (332 mg, 1.32 mmol, 75%). Also it was isolated small quantity of *α,β*-unsaturated hydroxyl amide **2.50** (43 mg, 0.17 mmol, 10%)

Selected data for mixture of rotamers **2.49**:

**FT-IR (neat)**      ν_max 3042, 2962, 2883, 2910, 2856, 1741, 1661, 1492, 1164 cm⁻¹.

**¹H NMR**   (400 MHz, CDCl₃) δ 6.05 – 5.83 (2H, m, 2 x **H₁₇**), 5.59 – 5.38 (4H, m, 2 x **H₄** & **H₅**), 5.34 – 5.22 (1H, m, **H₆′**), 5.19 – 5.05 (4H, m, 2 x **H₁₈**), 4.62 – 4.52 (1H, m, **H₆″**), 4.48 – 4.36 (1H, m, **H₁₆′ₐ**), 3.72 – 3.38 (5H, m, 2 x **H₁₁** & **H₁₀′ₑq**), 3.37 – 3.08 (6H, m, **H₁₀′ₐx, H₁₀″, OH₁₂′** & **H₁₆″**), 3.01 (1H, br s, **H₁₂″**) 2.77 – 2.59 (1H, m, **H₁₆′b**), 2.00 (4H, q, *J* = 6.9 Hz, 2 x **H₃**), 1.97 – 1.67 (4H, m, 2 x **H₅, H₈′** & **H₉′**), 1.55 – 1.31 (10H, m, **H₂, H₈″,** & **H₉″**), 0.86 (6H, t, *J* = 7.3 Hz, **H₁**) ppm.

**¹³C NMR**   (101 MHz, CDCl₃) δ 171.3, 170.9 (**C₁₅**), 133.2, 132.5 (**C₄**), 132.2, 131.3 (**C₁₇**), 127.9, 127.5 (**C₅**), 117.8, 117.4 (**C₁₈**), 62.4, 62.1 (**C₁₁**), 54.2, 49.8 (**C₆**), 41.7 (**C₁₀**), 40.6, 39.4 (2 x **C₇**), 38.9, (**C₁₀**), 38.2, 36.9 (**C₁₆**), 34.4, 34.3 (**C₃**), 22.2 (2 x **C₂**), 21.6, 21.5 (**C₉**), 20.8, 20.4 (**C₈**), 13.5 (2 x **C₁**) ppm.

**LRMS**   (ESI⁺) *m/z* 274.2 [M³⁵Cl+Na]⁺, 276.2 [M³⁷Cl+Na]⁺.


### 3.2.39   (*E*)-1-((2*S*,3*R*)-3-(Hydroxymethyl)-2-((*E*)-pent-1-en-1-yl)piperidin-1-yl)but-2-en-1-one (2.50)
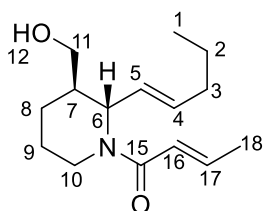


C₁₅H₂₅NO₂
Mol Wt: 251.37

**Data for α,β-unsaturated hydroxyl amide 2.50:**

**FT-IR (neat)**   ν_max 3043, 2964, 2883, 2913, 2849, 1745, 1663, 1492, 1164 cm⁻¹.

**¹H NMR**   (400 MHz, CDCl₃) δ 6.94 – 6.80 (1H, br dd, *J* = 14.3, 6.7 Hz, **H₁₇**), 6.27 (1H, dd, *J* = 15.0, 1.6 Hz, **H₁₆**), 5.64 – 5.41 (2H, m, **H₄** & **H₅**), 5.25 – 5.06 (1H, m, **H₆**), 3.76 – 3.12 (4H, m, **H₁₀** & **H₁₁**), 2.09 – 1.98 (2H, m, **H₃**), 1.87 (3H, br d, *J* = 6.4 Hz, **H₁₈**), 1.94 – 1.81 (1H, m, **H₇**), 1.58 – 1.41 (4H, m, **H₈** & **H₉**), 1.39 (2H, sxt, *J* = 7.3 Hz, **H₂**), 0.89 (3H, t, *J* = 7.4 Hz, **H₁**) ppm.

**¹³C NMR**          (101 MHz, CDCl₃) δ 167.4 (**C₁₅**), 142.1 (**C₁₇**), 133.2 (**C₄**), 127.9 (**C₅**), 121.5 (**C₁₆**), 62.1

(**C₁₁**), 49.8 (**C₆**), 41.8 (**C₇**), 34.5 (**C₁₀**), 33.0 (**C₃**), 25.4 (**C₉**), 24.7 (**C₈**), 22.3 (**C₂**), 18.2

(**C₁₈**), 13.6 (**C₁**) ppm.

**LRMS**          (ESI⁺) *m/z* 274.3 [M³⁵Cl+Na]⁺, 276.3 [M³⁷Cl+Na]⁺.

### 3.2.40      1-(((2*S*,3*S*)-1-(But-3-enoyl)-2-((*E*)-pent-1-en-1-yl)piperidin-3-yl)methyl)piperidine-2,6-dione (2.51)
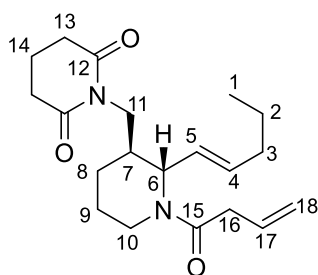


C₂₀H₃₀N₂O₃
Mol Wt: 346.47

To a solution of alcohol (**2.49**, 385 mg, 1.53 mmol) in anhydrous THF (10 mL) was added glutarimide (190 mg, 1.68 mmol), ADDP (424 mg, 1.68 mmol) and PBu₃ (415 µL, 1.68 mmol). The solution turned bright orange on addition of ADDP, and off-yellow after 5 min upon addition of PBu₃. The solution was stirred for 2 days, then quenched by the addition of H₂O (8 mL). The phases were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The mixture was acidified with 2M HCl (1 mL) in order to aid separation. The combined organic extract was washed with 2M HCl (40 mL), brine (40 mL), dried (MgSO₄) then concentrated *in vacuo* to afford the crude product as a colourless oil. Purification by chromatography (silica gel, 40:60 EtOAc / hexane) afforded the title compound **2.51** as a colourless oil (415 mg, 1.20 mmol, 78%) and the product of partial isomerisation of *α,β*-unsaturated amide (**2.52**, 41 mg, 0.12 mmol, 8%).

**Data for *β,γ*-unsaturated amide 2.51:**

**FT-IR (neat)**      ν_max 2974, 2893, 2922, 2859, 1755, 1668, 1495, 1174 cm⁻¹.

**¹H NMR**          (400 MHz, CDCl₃) δ 5.94 (1H, br s, **H₅**), 5.47 − 5.38 (1H, m, **H₄**), 5.38 − 5.28 (1H,

m, **H₁₇**), 5.10 (2H, d, *J* = 14.2 Hz, **H₁₈**), 4.53 − 4.22 (1H, m, **H₆**), 4.03 − 3.45 (3H, m,

**H₁₀eq** & **H₁₁**), 3.31 − 2.95 (3H, m, **H₁₀ax** & **H₁₆**), 2.62 (4H, br t, *J* = 6.1 Hz, 2 x **H₁₃**),

2.34 − 2.12 (1H, m, **H₇**), 2.01 − 1.88 (4H, m, **H₃** & **H₁₄**), 1.78 − 1.47 (2H, **H₈ₑq** & **H₉ₑq**), 1.43 − 1.21 (4H, m, **H₈ₐₓ, H₉ₐₓ** & **H₂**), 0.83 (3H, q, *J* = 7.5 Hz, **H₁**) ppm.

**¹³C NMR**    (101 MHz, CDCl₃) δ 172.6 (**C₁₂**), 169.9 (**C₁₅**), 132.6 (**C₄**), 131.6 (**C₅**), 127.4 (**C₁₇**), 117.4 (**C₁₈**), 57.0 (**C₆**), 41.3 (**C₁₀**), 40.0 (**C₁₁**), 39.0 (**C₁₆**), 34.90 (**C₇**), 34.3 (**C₃**), 32.80 (2 x **C₁₃**), 22.1 (**C₂**), 21.6 (**C₉**), 20.6 (**C₈**),17.01 (**C₁₄**), 13.49 (**C₁**) ppm. The ¹³C NMR spectrum was complicated by the presence of rotamers only selected peaks are reported.

**LRMS**      (ESI⁺) *m/z* 347.3 [M + H]⁺.

### 3.2.41    1-(((2*S*,3*S*)-1-((*E*)-But-2-enoyl)-2-((*E*)-pent-1-en-1-yl)piperidin-3-yl)methyl)piperidine-2,6-dione (2.52)
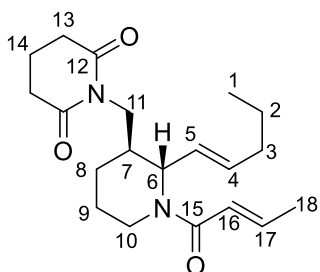


$C_{20}H_{30}N_2O_3$
Mol Wt: 346.47

**Data of unclear *α,β*-unsaturated amide 2.52:**

**FT-IR (neat)**    ν_max 2974,2894, 2924, 2856, 1752, 1668, 1485, 1171 cm⁻¹.

**¹H NMR**    (400 MHz, CDCl₃) δ 6.89 − 6.76 (1H, m, **H₁₇**), 6.27 (1H, br d, *J* = 14.9 Hz, **H₁₆**), 5.52 − 5.43 (1H, m, **H₄**), 5.41 − 5.33 (1H, m, **H₅**), ~5.20 − 5.08 (missing **H₆**), 4.03 − 3.68 (2H, m, **H₁₁**), 2.66 (4H, t, *J* = 6.5 Hz, **H₁₃**), ~3.60 (missing **H₁₀**), 2.00 (2H, q, *J* = 7.5 Hz, **H₃**) 1.97 − 1.91 (2H, m, **H₁₄**), 1.86 (3H, dd, *J* = 6.8, 1.4 Hz, **H₁₈**), 1.84 − 1.54 (3H, m, **H₇, H₈ₐ** & **H₉ₐ**), 1.48 − 1.28 (4H, m, **H₂, H₈ᵦ** & **H₉ᵦ**), 0.87 (3H, t, *J* = 7.3 Hz, **H₁**) ppm. The ¹H NMR spectrum was complicated by the presence of rotamers only selected peaks are reported, additional broad signals.

**¹³C NMR**    (101 MHz, CDCl₃) δ 172.7 (2 x **C₁₂, C₁₅**), 140.8 (**C₁₇**), 132.8 (**C₄**), 127.7 (**C₅**), 122.2 (**C₁₆**), 58.0 (**C₆**), 44.6 (**C₁₀**), 40.7 (**C₇** & **C₁₁**), 34.4 (**C₃**), 32.9 (2 x **C₁₃**), 31.6 (**C₇**) 22.2 (**C₂**), 21.3 (**C₉**), 20.4 (**C₈**), 18.2 (**C₁₈**), 17.1 (**C₁₄**), 13.6 (**C₁**) ppm.

**LRMS**      (ESI⁺) *m/z* 347.2 [M + H]⁺.

### 3.2.42    1-(((1S,9aS)-6-Oxo-1,3,4,6,7,9a-hexahydro-2H-quinolizin-1-yl)methyl)piperidine-2,6-dione (2.40)
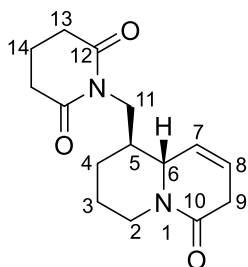


C$_{15}$H$_{20}$N$_2$O$_3$
Mol Wt: 276.34

To a solution of **2.51** (400 mg, 1.15 mmol) in degassed CH$_2$Cl$_2$ was added Grubbs II pre-catalyst (25 mg, 0.029 mmol, 2.5 mol%) in one portion and the reaction heated under reflux for 4 h. The reaction mixture was concentrated *in vacuo* to give a viscous darck brown oil. The residue was partitioned between sat. aq. K$_2$CO$_3$ (30 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The crude material was extracted with EtOAc (2 × 30 mL), the organic phases combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent*: 35% NH$_4$OH/MeOH/CH$_2$Cl$_2$ 1:10:190) to give the title compound **2.40** as a white solid (303 mg, 1.10 mmol, 95%). Recrystallisation with hexane gave fine needles.

Alternatively, **2.40** was prepared from hydroxy quinolisidine **2.42** following the procedure described for the synthesis of **2.51**; alcohol (**2.42**, 230 mg, 1.27 mmol), glutarimide (157 mg, 1.39 mmol), ADDP (350 mg, 1.39 mmol) and PBu$_3$ (345 μL, 1.39 mmol); to afforded the title tricyclic imide (**2.40**, 298 mg, 1.08 mmol, 85%) as a white solid.

**FT-IR (neat)**    $v_{max}$ 3041, 2925, 2853, 2832, 2791, 2723, 1734, 1722, 1668 cm$^{-1}$.

**$^1$H NMR**    (400 MHz, CDCl$_3$) δ 5.89 (1H, ddt, *J* = 10.3, 3.6, 1.8, Hz, **H$_7$**), 5.84 – 5.76 (1H, m, **H$_8$**), 4.83 (1H, dt, *J* = 2.1, 13.0 Hz, **H$_{2eq}$**), 3.87 – 3.79 (2H, m, **H$_{11}$**), 3.69 – 3.62 (1H, m, **H$_6$**), 2.97 – 2.91 (2H, m, **H$_9$**), 2.66 (4H, t, *J* = 6.5 Hz, **H$_{13}$**), 2.40 (1H, td, *J* = 12.8, 2.6 Hz, **H$_{2ax}$**), 1.94 (2H, quin, *J* = 6.6 Hz, **H$_{14}$**), 1.89 – 1.77 (1H, m, **H$_5$**), 1.71 – 1.57 (2H, m, **H$_{3eq}$** & **H$_{4eq}$**), 1.46 – 1.33 (1H, m, **H$_{3ax}$**), 1.32 – 1.19 (1H, m, **H$_{4ax}$**)

**¹³C NMR**         (101 MHz, CDCl₃) δ 172.68 (2 × **C₁₂**), 165.94 (**C₁₀**), 123.07 (**C₇**), 122.61 (**C₈**), 61.68 (**C₆**), 42.40 (**C₂** & **C₁₁**), 40.84 (**C₅**), 32.84 (**C₁₃**), 31.64 (**C₉**), 28.43 (**C₄**), 24.69 (**C₃**), 17.04 (**C₁₄**) ppm.

**LRMS**           (ES⁺) *m/z* 347.2 [M + H]⁺.

### 3.2.43      1-(((1*S*,9a*S*)-6-Oxooctahydro-2H-quinolizin-1-yl)methyl)piperidine-2,6-dione (2.53), (−)-10-oxo-Lamprolobine
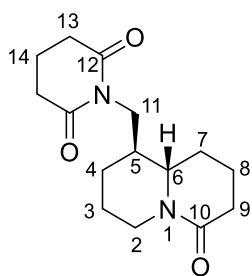


$C_{15}H_{22}N_2O_3$
Mol Wt: 278.35

To a solution of **2.40** (50 mg, 1.160 mmol) in EtOH (5 mL) was added 5 wt% Pd/C (10 mg, 0.130 mmol) and placed under an H₂ atmosphere. The reaction was stirred at rt for 16 h, filtered through celite, washing with EtOH (5 × 5 mL) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (silica gel, *eluent*: 35% NH₄OH/MeOH/CH₂Cl₂ 1:20:180) to give the title compound **2.53** (48 mg, 1.140 mmol, 94%).

**M.P.**           133 − 135 °C.

**[α]_D**          −15.9 (*c* 0.5, CHCl₃, 21°C).

**FT-IR (neat)**   v_max 2925, 2844, 2805, 2739, 1734, 1721, 1670 cm⁻¹.

**¹H NMR**         (400 MHz, CDCl₃) δ 4.79 (1H, br d, *J* = 13.1 Hz, **H₂ₑq**), 3.77 (1H, br d, *J* = 7.0 Hz, **H₁₁ₑq**), 3.74 − 3.67 (1H, m, **H₁₁ₐₓ**), 3.16 − 3.02 (1H, m, **H₆**), 2.67 (4H, t, *J* = 6.4 Hz, **H₁₃**), 2.47 − 2.22 (3H, m, **H₂ₐₓ** & **H₉**), 2.20 − 2.09 (1H, m, **H₅**), 2.01 − 1.80 (4H, m, **H₄ₑq**, **H₈ₑq** & **H₁₄**), 1.77 − 1.67 (2H, m, **H₃ₐₓ** & **H₇ₐₓ**), 1.58 − 1.50 (1H, m, **H₈ₐₓ**), 1.35 − 1.15 (3H, m, **H₃ₑq**, **H₄ₐₓ** & **H₇ₑq**) ppm.

**¹³C NMR**        (101 MHz, CDCl₃) δ 172.71 (2 × **C₁₂**), 169.30 (**C₁₀**), 60.13 (**C₆**), 42.44 (**C₂**), 41.14 (**C₁₁**), 40.94 (**C₅**), 32.87 (2 × **C₁₃**), 32.75 (**C₉**), 28.21 (**C₇**), 27.24 (**C₄**), 24.60 (**C₃**), 18.80 (**C₈**), 17.12 (**C₁₄**) ppm.

**LRMS**           (ESI+) 279.3 [M+H⁺]⁺.

**HRMS:**            (ESI$^+$) for $C_{15}H_{23}N_2O_3$ [M+H]$^+$, calculated 279.1704; found 279.1703, for

$C_{15}H_{22}N_2NaO_3$ [M+Na]$^+$, calculated 301.1520; found 301.1523.

### 3.2.44    (9*S*,9a*S*)-9-((2-Oxo-3,4-dihydropyridin-1(2H)-yl)methyl)-3,6,7,8,9,9a-hexahydro-4H-quinolizin-4-one (2.57)
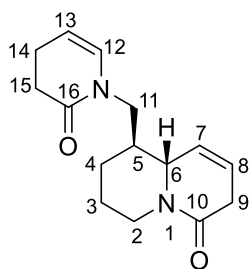


$C_{15}H_{20}N_2O_2$
Mol Wt: 260.34

To a stirred solution of imide (**2.40**, 25 mg, 0.410 mmol) in $CH_2Cl_2$ (1.5 mL) at −78 °C under $N_2$ was added a solution of LiEt$_3$BH (0.90 mL of 1.0 M in THF, 0.900 mmol) dropwise. The resulting mixture was stirred at −78 °C for 3 h, then it was allowed to warm to −20 °C and a solution of HCl (0.75 mL of 2.0 M in EtOH, 1.570 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 (silica gel, *eluent*: 35% NH$_4$OH/MeOH/EtOAc 2:8:90) afforded the title tricyclic enamide (**2.57**, 12 mg, 0.12 mmol, 41%) as a yellow oil, and tricyclic hydroxy lactam (**2.56**, 8 mg, 0.120 mmol, 30%) as an inseparable mixture of two diastereoisomers *dr* ∼ 1:1.

**Data for tricyclic enamid 2.57:**

**FT-IR (neat)**    ν$_{max}$ 2935, 2858, 2842, 2771, 2743, 1738, 1721, 1668, 1578 cm$^{−1}$.

**$^1$H NMR**       (400 MHz, CDCl$_3$) δ 5.96 (1H, dt, *J* = 7.7, 1.5 Hz, **H$_{12}$**), 5.94 − 5.88 (1H, m, **H$_7$**), 5.84 − 5.78 (1H, m, **H$_8$**), 5.22 − 5.15 (1H, m, **H$_{13}$**), 4.88 (1H, ddt, *J* = 12.9, 4.1, 1.9 Hz, **H$_{2eq}$**), 3.71 − 3.64 (1H, m, **H$_6$**), 3.64 − 3.56 (1H, m, **H$_{11a}$**), 3.52 − 3.43 (1H, m, **H$_{11b}$**), 2.99 − 2.94 (2H, m, **H$_9$**), 2.56 − 2.50 (2H, m, **H$_{15}$**), 2.43 (1H, td, *J* = 12.9, 2.7 Hz,

**H₂ₐₓ**), 2.36 – 2.28 (2H, m, **H₁₄**), 1.87 – 1.79 (m, 1H, **H₄ₑq**), 1.78 – 1.67 (2H, m, **H₃ₑq & H₅**), 1.51 – 1.43 (1H, m, **H₃ₑq**), 1.38 – 1.30 (1H, m, **H₄ₐₓ**) ppm.

**¹³C NMR**     (101 MHz, CDCl₃) δ 169.7 (**C₁₆**), 166.0 (**C₁₀**), 129.9 (**C₁₂**), 123.2 (**C₇**), 122.8 (**C₈**), 106.6 (**C₁₃**), 61.5 (**C₆**), 47.4 (**C₁₁**), 43.7 (**C₅**), 42.6 (**C₂**), 31.7 (**C₉**), 31.4 (**C₁₅**), 28.8 (**C₄**), 24.8 (**C₃**), 20.2 (**C₁₄**) ppm.

**LRMS**        (ESI⁺) *m/z* 261.2 [M + H]⁺.

### 3.2.45     (9*S*,9a*S*)-9-((2-Hydroxy-6-oxopiperidin-1-yl)methyl)-3,6,7,8,9,9a-hexahydro-4H-quinolizin-4-one (2.56)
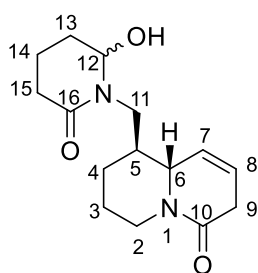


$C_{15}H_{22}N_2O_3$
Mol Wt: 278.35

**Data for tricyclic hydroxy lactam 2.56:**

**FT-IR (neat)**     ν$_{max}$ 3047, 2946, 2854, 2840, 2761, 2742, 1735, 1720, 1670, 1568 cm⁻¹.

**¹H NMR**     (400 MHz, CDCl₃) δ 5.94 – 5.75 (4H, m, 2 x **H₇** & **H₈**), 4.98 (1H, br t, *J* = 3.1 Hz, **H₁₂′**), 4.91 (1H, br t, *J* = 3.0 Hz, **H₁₂″**), 4.89 – 4.86 (1H, m, **H₂′ₑq**), 4.86 – 4.82 (1H, m, **H₂″ₑq**), 3.98 (1H, dd, *J* = 13.6, 10.2 Hz, **H₁₁′ₐ**), 3.81 (1H, dd, *J* = 13.7, 5.5 Hz, **H₁₁″b**), 3.76 – 3.69 (1H, m, **H₆′**), 3.67 – 3.59 (1H, m, **H₆″**), 3.27 (1H, dd, *J* = 13.6, 4.6 Hz, **H₁₁′b**), 3.18 (1H dd, *J* = 13.6, 9.4 Hz, **H₁₁″ₐ**), 2.98 – 2.92 (4H, m, 2 x **H₉**), 2.57 – 2.30 (6H, m, 2 x **H₂ₐₓ** & **H₁₅**), 2.11 – 1.89 (7H, m, **H₅′**, **H₁₄′** & **2 x H₁₃**), 1.79 – 1.64 (7H, m, **H₅″**, **H₁₄″**, **H₃′** & **H₄′**), 1.50 – 1.30 (4H, m, **H₃″** & **H₄″**) ppm.

**¹³C NMR**     (101MHz, CDCl₃) δ 170.6 (2 x **C₁₀**), 166.1 (2 x **C₁₆**), 123.0 (2 x **C₇**), 122.8 (2 x **C₈**), 81.5 (**C₁₂ₐ**), 78.5 (**C₁₂b**), 62.1 (**C₆′**), 61.7 (**C₆″**), 47.5 (2 x **C₁₁′**), 43.7 (**C₁₁″**), 43.4 (**C₅′**), 42.9 (**C₅″**), 42.7 (**C₂′**), 42.6 (**C₂′**), 32.4 (**C₁₅′**), 32.3 (**C₁₅″**), 31.7 (2 x **C₉**), 31.0 (2 x **C₁₃**), 29.4 (**C₄″**), 28.6 (**C₄″**), 24.9 (2 x **C₃**), 15.7 (2 x **C₁₄**) ppm.

**LRMS**        (ESI⁺) *m/z* 279.2 [M + H]⁺.

### 3.2.46      Phenyl (2S,3R)-2-(4-chlorobutyl)-6-oxopiperidine-3-carboxylate (2.28)
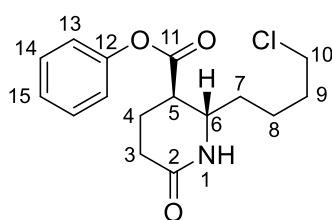


$C_{16}H_{20}ClNO_3$
Mol Wt: 309.79

To a solution of cyclised *syn* imino-aldol adduct (**2.13**, 350 mg, 0.850 mmol) in THF/H$_2$O (3:2, 20 mL) at rt was added I$_2$ (430 mg, 1.70 mmol) and Na$_2$CO$_3$ (1.08 g, 10.20 mmol) portionwise. The reaction mixture was heating at 50 °C under Ar and stirred for 2 h. The resulting dark brown solution became light brown. The reaction mixture was diluted with H$_2$O (10 mL). After removal of THF *in vacuo*, an aqueous saturated Na$_2$S$_2$O$_3$ (0.100 mL) was added. The resulting aqueous mixture was extracted with Et$_2$O (3 x 10 mL) and the combined organic phase was washed with brine (20 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo* to yield a white solid. The crude was passed through a plug of alumina (*eluent:* EtOAc) to give the title compound *syn* lactam **2.28** as a white solid (251 mg, 0.810 mmol, 95%).

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3134, 2951, 2857, 2844, 2772, 2742, 1725, 1670, 1567, 1546 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.41 (2H, t, *J* = 7.3 Hz, **H$_{14}$**), 7.31 – 7.23 (1H, m, **H$_{15}$**), 7.08 (2H, d, *J* = 7.9 Hz, **H$_{13}$**), 6.45 (1H br s, **H$_1$**), 3.93 – 3.84 (1H, m, **H$_6$**), 3.57 (2H, t, *J* = 6.4 Hz, **H$_{10}$**), 2.77 (1H, ddd, *J* =10.2, 8.5, 3.7 Hz, **H$_5$**), 2.62 – 2.51 (1H, m, **H$_{3ax}$**), 2.50 – 2.39 (1H, m, **H$_{4eq}$**), 2.35 – 2.11 (2H m, **H$_{3eq}$** & **H$_{4ax}$**), 1.91 – 1.76 (2H, m, **H$_9$**), 1.76 – 1.51 (4H, m, **H$_7$** & **H$_8$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 171.4 (**C$_2$**), 171.2 (**C$_{11}$**), 150.2 (**C$_{12}$**), 129.6 (2 x **C$_{14}$**), 126.2 (**C$_{15}$**), 121.2 (2 x **C$_{13}$**), 53.7 (**C$_6$**), 44.5 (**C$_5$**), 44.1 (**C$_{10}$**), 34.7 (**C$_7$**), 32.0 (**C$_3$**), 29.8 (**C$_9$**), 23.5 (**C$_4$**), 22.1 (**C$_8$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 310.2 [M + H]$^+$. |

### 3.2.47    Phenyl (2*S*,3*S*)-2-(4-Chlorobutyl)-6-oxopiperidine-3-carboxylate (2.27)
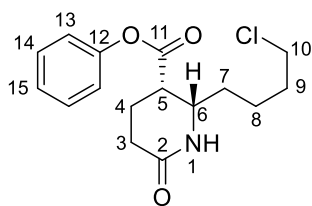


$C_{16}H_{20}ClNO_3$
Mol Wt: 309.79

To a solution of cyclised *anti* imino-aldol adduct (**2.16**, 40 mg, 0.100 mmol) in 1,4-dioxane (10 mL) at 0 °C was added conc. HCl (1.00 mL of ~36%, 0.40 mmol) dropwise and the mixture was stirred at rt for 1 h under Ar. The reaction mixture was basified by the dropwise addition of sat. aq. NaHCO$_3$ at 0 °C, and stirring was continued at rt for 1 h. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL), washing with saturated aq. NaHCO$_3$ (3 × 10 mL). The combined organic solution was washed with brine (2 × 25 mL), dried (NaSO$_4$) the solvent was removed *in vacuo*. The crude was passed through a plug of alumina (*eluent:* EtOAc) to give the title *anti* lactam **2.27** as a white solid (27 mg, 0.87 mmol, 87%). Recrystallisation with CHCl$_3$/ Et$_2$O 1:4 gave fine needles.

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3136, 2953, 2860, 2847, 2770, 2741, 1724, 1670, 1567, 1545 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.46 – 7.36 (2H, m, **H$_{14}$**), 7.33 – 7.28 (1H, m, **H$_{15}$**), 7.07 (2H, d, *J* = 7.8 Hz, **H$_{13}$**), 5.98 (1H, br s, **H$_1$**), 3.89 – 3.82 (1H, m, **H$_6$**), 3.57 (2H, t, *J* = 6.4 Hz, **H$_{10}$**), 3.23 – 3.18 (1H, m, **H$_5$**), 2.68 – 2.59 (1H, m, **H$_{3eq}$**), 2.53 – 2.43 (1H, m, **H$_{4eq}$**), 2.34 – 2.14 (2H, m, **H$_{3ax}$ & H$_{4ax}$**), 1.89 – 1.79 (2H, m, **H$_9$**), 1.72 – 1.61 (4H, m, **H$_7$ & H$_8$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 171.05 (**C$_2$**), 169.96 (**C$_{11}$**), 150.18 (**C$_{12}$**), 129.61 (**C2 x C$_{14}$**), 126.24 (**C$_{15}$**), 121.24 (2 x **C$_{13}$**), 53.25 (**C$_6$**), 44.46 (**C$_5$**), 42.35 (**C$_{10}$**), 32.34 (**C$_7$**), 32.06 (**C$_3$**), 29.27 (**C$_9$**), 23.34 (**C$_4$**), 20.29 (**C$_8$**) ppm. |
| **LRMS** | (ESI$^+$) *m/z* 310.3 [M + H]$^+$. |

### 3.2.48　　　Phenyl (2*S*,3*R*)-6-oxo-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate (2.77)
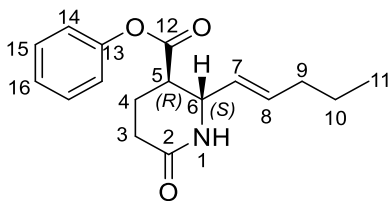


$C_{17}H_{21}NO_3$
Mol Wt: 287.36

Following the procedure described for the synthesis of **2.28**, imino-aldol adduct (**2.11**, 130 mg, 0.33 mmol) afforded the title compound unsaturated lactam (**2.77**, 86 mg, 0.30 mmol, 91%).

**M.P.**　　　　　88 – 90 °C.

**FT-IR (neat)**　　$\nu_{max}$ 3238, 2934, 2861, 2809, 1747, 1190, 1161, 1123 cm$^{-1}$.

**$^1$H NMR**　　　(400 MHz, CDCl$_3$) δ 7.39 (2H, t, *J* = 7.3 Hz, **H$_{15}$**), 7.27 – 7.23 (1H, m, **H$_{16}$**), 7.06 – 7.00 (2H, m, **H$_{14}$**), 5.81 (1H, dtd, *J* = 15.2, 6.8, 0.7 Hz, **H$_7$**), 5.74 (1H, s br, **H$_1$**), 5.46 (1H, ddt, *J* = 15.3, 7.9, 1.5 Hz, **H$_8$**), 4.29 (1H, t, *J* = 8.4 Hz, **H$_6$**), 2.76 (1H, ddd, *J* = 10.7, 8.9, 3.5 Hz, **H$_5$**), 2.62 – 2.53 (1H, m, **H$_{3eq}$**), 2.50 – 2.40 (1H, m, **H$_{4eq}$**), 2.32 – 2.13 (2H, m, **H$_{3ax}$** & **H$_{4ax}$**), 206 (2H, td, *J* = 7.2, 5.9 Hz, H$_9$), 1.42 (2H, sxt, *J* = 7.4 Hz, **H$_{10}$**), 0.91 (3H, t, *J* = 7.3 Hz, **H$_{11}$**) ppm.

**$^{13}$C NMR**　　(101 MHz, CDCl$_3$) δ 170.9 (**C$_2$**), 170.5 (**C$_{12}$**), 150.3 (**C$_{13}$**), 135.9 (**C$_7$**), 129.5 (2 x **C$_{15}$**), 128.4 (**C$_8$**), 126.1 (2 x **C$_{16}$**), 121.2 (2 x **C$_{14}$**), 57.2 (**C$_6$**), 45.7 (**C$_5$**), 34.1 (**C$_9$**), 29.9 (**C$_3$**), 23.5 (**C$_{10}$**), 22.0 (**C$_4$**), 13.6 (**C$_{11}$**) ppm.

**LRMS**　　　　(ESI$^+$) *m/z* 288.23 [M+H]$^+$.

### 3.2.49      1-Benzyl 3-phenyl (2*S*,3*R*)-2-(4-chlorobutyl)-6-oxopiperidine-1,3-dicarboxylate (2.68)
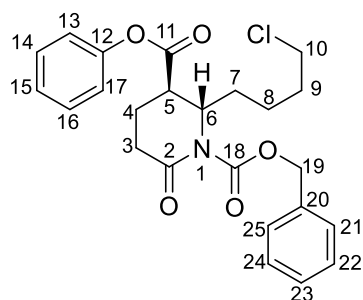


$C_{24}H_{26}ClNO_5$
Mol Wt: 443.92

Following a modified procedure from Han *et al.*,[158] to a solution of *n*-BuLi (0.700 mL of 1.0 M in THF, 0.700 mmol) in THF (15 mL) at −78 °C under $N_2$ was added a solution of *syn* lactam (**2.28**, 200 mg, 0.650 mmol) in THF (14 mL) dropwise. The mixture was stirred at −78 °C for 30 min, and then benzyl chloroformate (1.49 mL, 9.930 mmol) was added dropwise over 5 min. The yellow suspension was stirred at −60 °C for 30 min. The reaction was quenched by the addition of aq $NH_4Cl$ (10 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by chromatography (silica gel, EtOAc/hexane 5:95) afforded the title compound **2.68** as a pale yellow oil (208 mg, 0.470 mmol, 72%).

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 2938, 2871, 2819, 1735, 1720, 1678, 1542, 1164, 1133 cm$^{-1}$. |
| **$^1$H NMR** | (400 MHz, CDCl$_3$) δ 7.36 − 7.14 (8H, m, **H$_{14}$, H$_{15}$, H$_{16}$, H$_{21}$, H$_{22}$, H$_{23}$, H$_{24}$ & H$_{25}$**), 6.92 − 6.86 (2H, m, **H$_{13}$ & H$_{17}$**), 5.26 − 5.19 (2H, m, **H$_{19}$**), 4.93 (1H, ddd, *J* = 8.3, 6.2, 1.9 Hz, **H$_6$**), 3.45 (2H, t, *J* = 6.4 Hz, **H$_{10}$**), 3.04 − 2.99 (1H, m, **H$_5$**), 2.76 (1H, dq, *J* = 9.0, 7.7 Hz, **H$_{3eq}$**), 2.56 − 2.45 (1H, m, **H$_{3ax}$**), 2.35 − 2.25 (1H, m, **H$_{4eq}$**), 2.21 − 2.10 (1H, m, **H$_{4ax}$**), 1.83 − 1.68 (3H m, **H$_7$ & H$_{9a}$**), 1.64 − 1.42 (3H, m, **H$_8$ & H$_{9b}$**) ppm. |
| **$^{13}$C NMR** | (101 MHz, CDCl$_3$) δ 171.0 (**C$_{11}$**), 170.6 (**C$_2$**), 154.0 (**C$_{18}$**), 150.3 (**C$_2$**), 135.2 (**C$_{12}$**), 129.5 (**C$_{20}$**), 128.5 (**C$_{14}$ & C$_{16}$**), 128.3 (**C$_{22}$ & C$_{24}$**), 128.0 (**C$_{24}$**), 126.1 (**C$_{21}$ & C$_{25}$**), 121.2 (**C$_{13}$ & C$_{17}$**), 68.7 (**C$_{19}$**), 56.5 (**C$_6$**), 44.5 (**C$_{10}$**), 41.1 (**C$_5$**), 34.3 (**C$_9$**), 31.8 (**C$_7$**), 31.4 (**C$_3$**), 23.2 (**C$_8$**), 19.1 (**C$_4$**) ppm. |
| **LRMS** | (ESI+) m/z 444.3 (100%) [M+H$^+$]$^+$, 466.3 (100%) [M+Na]$^+$. |
| **HRMS:** | (ESI$^+$) for $C_{24}H_{26}ClN_2NaO_5$ [M+Na]$^+$, calculated 466.1393; found 466.1392. |
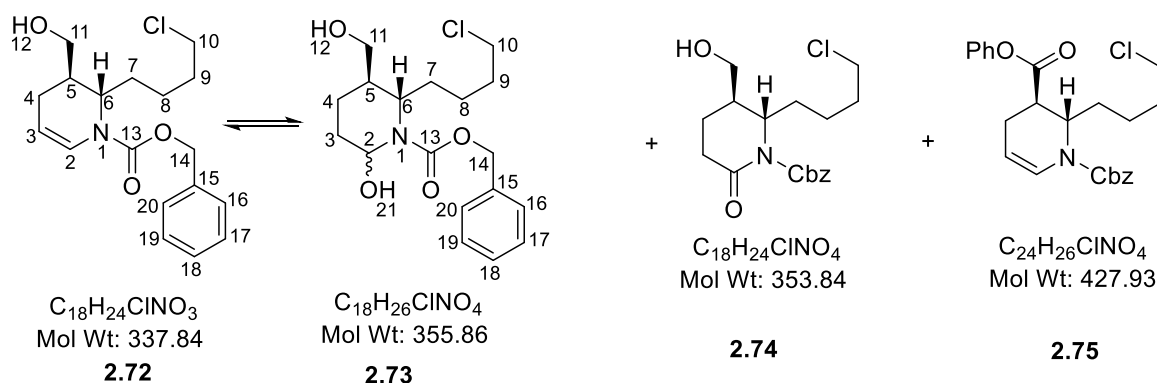
Following a modified procedure from Han *et al.*,[158] to a stirred solution of **2.68** (100 mg, 0.225 mmol) in $CH_2Cl_2$ (1.0 mL) at −78 °C under $N_2$ was added $LiEt_3BH$ (0.250 mL of 1.0 M in THF, 0.250 mmol) dropwise. The resulting mixture was stirred for 1 h, then was allowed to warm to 0 °C and the solution was quenched by careful addition of aq. $Na_2SO_4$ (1.00 mL). The suspension was filtered through celite, washing with THF (3 × 5 mL), dried ($Na_2SO_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *eluent:* EtOAc/MeOH, 95:5) gave the products: (**2.72**, 14 mg, 0.044 mmol, 20%) and equilibrium with hemiaminal (**2.73**, 17 mg, 0.048 mmol, 21%), and inseparable alcohol imide (**2.74**, **LRMS** (ESI+) m/z 354.3 $[M^{35}Cl+H^+]^+$, 356.3 $[M^{37}Cl+H]^+$, and enamide (**2.75**, **LRMS** (ESI+) m/z 338.3 $[M^{35}Cl+H^+]^+$, 340.3 $[M^{37}Cl+H]^+$).

Alternative reduction of **2.68**, using $LiAlH_4$ (0.23 mL of 1.0 M in THF, 0.225 mmol) was added dropwise to a solution of **2.68** (100 mg, 0.225 mmol) in $CH_2Cl_2$ (1.00 mL) at −20 °C under $N_2$. The resulting mixture was stirred for 30 min, then was allowed to warm to 0 °C and the solution was quenched by careful addition of aq. $Na_2SO_4$ (1.00 mL). The suspension was filtered through celite, washing with THF (3 × 5 mL), dried ($Na_2SO_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *eluent:* EtOAc/MeOH, 95:5) gave the products: (**2.72**, 13 mg, 0.038 mmol, 17%) and equilibrium with hemiaminal (**2.73**, 16 mg, 0.045 mmol, 20%), and inseparable alcohol imide (**2.74**, **LRMS** (ESI+) m/z 354.3 $[M^{35}Cl+H^+]^+$, 356.3 $[M^{37}Cl+H]^+$, and enamide (**2.75**, **LRMS** (ESI+) m/z 338.3 $[M^{35}Cl+H^+]^+$, 340.3 $[M^{37}Cl+H]^+$).

^{13}C NMR data for hydroxyl enamide **2.72** was not reported due to instability of compound, only data for hemiaminal **2.73** are reported.

**Selected data for hydroxyl enamide 2.72:**

| | |
|---|---|
| **FT-IR (neat)** | $v_{max}$ 3089, 2938, 2871, 2819, 1720, 1542, 1164, 1133 cm$^{-1}$. |
| **^{1}H NMR** | (400 MHz, CDCl$_3$) δ 7.40 − 7.33 (5H, m, **H$_{16}$, H$_{17}$, H$_{18}$, H$_{19}$ & H$_{20}$**), 6.80 − 6.64 (1H, m, **H$_2$**), 5.28 − 5.13 (2H, m, **H$_{14}$**), 4.89 − 4.74 (1H, m, **H$_3$**), 4.42 − 4.27 (1H, m, **H$_6$**), 3.56 − 3.39 (4H, m, **H$_{10}$ & H$_{11}$**), 2.26 − 2.14 (1H, m, **H$_{4eq}$**), 2.09 − 1.96 (1H, m, **H$_5$**), |

1.93 – 1.76 (m, 3H, **H$_7$** & **H$_{12}$**), 1.75 – 1.59 (3H, m, **H$_{4ax}$** & **H$_9$**), 1.50 – 1.39 (2H, m, **H$_8$**) ppm.

**LRMS**     (ESI+) m/z 338.3 [M$^{35}$Cl+H$^+$]$^+$, 340.3 [M$^{37}$Cl+H]$^+$, 360.3 [M$^{35}$Cl+Na]$^+$ 362.3 [M$^{37}$Cl+Na]$^+$.

**HRMS:**    (ESI$^+$) for C$_{18}$H$_{24}$ClNNaO$_3$ [M+Na]$^+$, calculated 360.1330; found 360.1337.

### 3.2.50     Benzyl (2*S*,3*R*)-2-(4-chlorobutyl)-6-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate 2.73
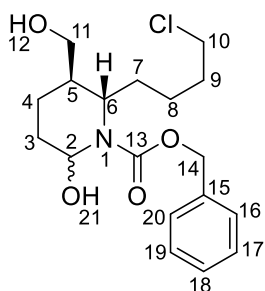


C$_{18}$H$_{26}$ClNO$_4$
Mol Wt: 355.86

**2.73**

**Selected data for two diastereoisomers of hemiaminal 2.73:**

**FT-IR (neat)**     v$_{max}$ 3168, 3088, 2938, 2871, 2819, 1723, 1542, 1164, 1132 cm$^{-1}$.

**$^1$H NMR**     (400 MHz, CDCl$_3$) δ 7.39 – 7.32 (10H, m, 2 x **H$_{16}$, H$_{17}$, H$_{18}$, H$_{19}$** & **H$_{20}$**), 5.18 (1H, d, *J* = 2.3 Hz, **H$_{2'}$**), 5.15 – 5.05 (4H, m, 2 x **H$_{14}$**), 4.72 – 4.66 (m, 1H, **H$_{6'}$**), 4.59 – 4.43 (m, 2H, **H$_{2''}$**), 4.05 – 3.96 (m, 1H, **H$_{6''}$**), 3.86 – 3.77 (m, 1H, **H$_{11'a}$**), 3.58 (br d, *J* = 11.1 Hz, 3H, **H$_{11'b}$** & **H$_{11''}$**), 3.51 (m, 4H, 2 x **H$_{10}$**), 3.34 (dd, *J* = 10.4, 11.4 Hz, 1H, **H$_{5'}$**), 3.11 – 3.06 (d, *J* = 5.7 Hz, 1H, **H$_{21}$**), 2.60 (d, *J* = 3.2 Hz, 1H, **H$_{12}$**), 2.02 – 1.27 (m, 27H, **H$_{5''}$**, 2 x **H$_3$, H$_4$, H$_7$, H$_8$** & **H$_9$**) ppm.

**$^{13}$C NMR**     (101 MHz, CDCl$_3$) δ 156.3 (**C$_{13}$**), 136.5, 136.4 (**C$_{15}$**), 128.6 (**C$_{17'}$** & **C$_{19'}$**), 128.5 (**C$_{16'}$** & **C$_{20'}$**), 128.2, 128.1 (**C$_{18}$**), 128.1 (**C$_{17''}$** & **C$_{19''}$**), 128.0 (**C$_{16''}$** & **C$_{20''}$**), 95.8, 91.4 (**C$_2$**), 67.8, 66.8 (**C$_{14}$**), 66.8, 62.4 (**C$_{11}$**), 52.0, 51.5 (**C$_6$**), 44.7, 44.7 (**C$_{10}$**), 39.7, 39.5 (**C$_5$**), 32.3, 32.2 (**C$_9$**), 32.1, 31.9 (**C$_7$**), 31.7, 29.7 (**C$_3$**), 23.5, 23.2 (**C$_8$**), 23.1, 19.2 (**C$_4$**) ppm.

**HRMS:**     (ESI$^+$) for C$_{18}$H$_{26}$ClNNaO$_4$ [M+Na]$^+$, calculated 378.1445; found 378.1443.

# Appendix A    Selected NMR Spectra

**A.1.1**    $^1$H (400 MHz) spectrum of (+)-10,17-Dioxo-$\beta$-isosparteine ((+)-1.33) (CDCl$_3$)
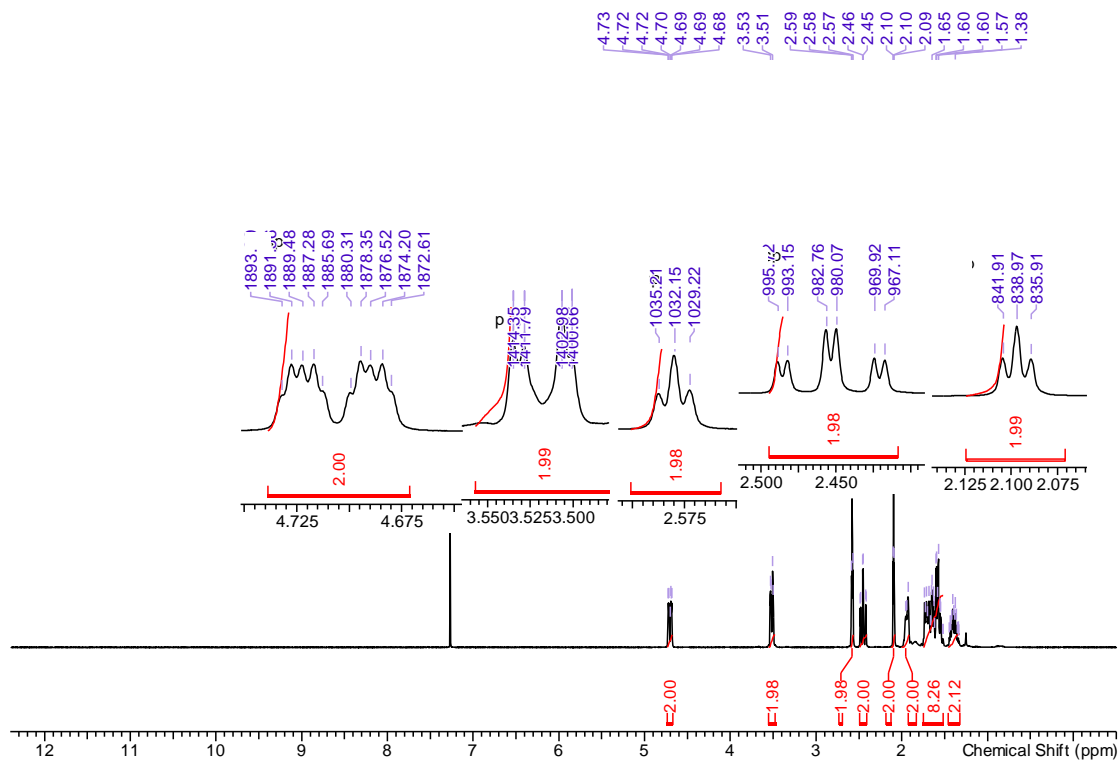


**A.1.2**    $^{13}$C NMR (101 MHz) spectrum of (+)-10,17-Dioxo-$\beta$-isosparteine ((+)-1.33) (CDCl$_3$)
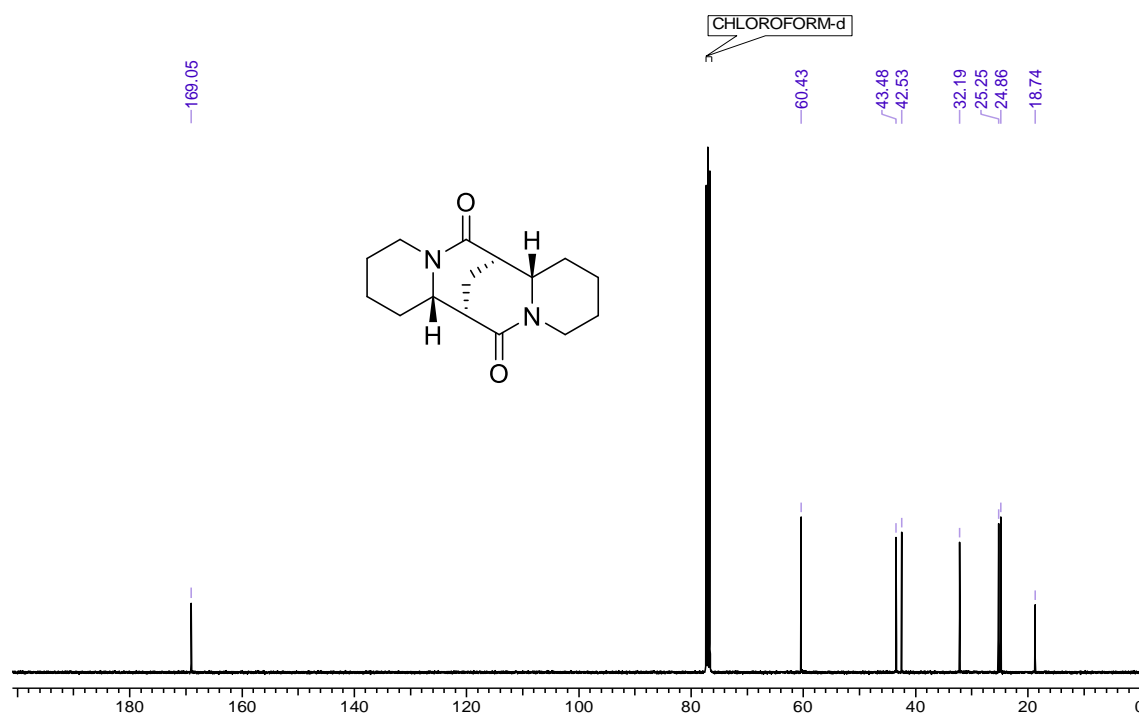
## A.1.3 $^1$H (400 MHz) spectrum of (+)-$\beta$-Isosparteine ((+)-1.4) (CDCl$_3$)
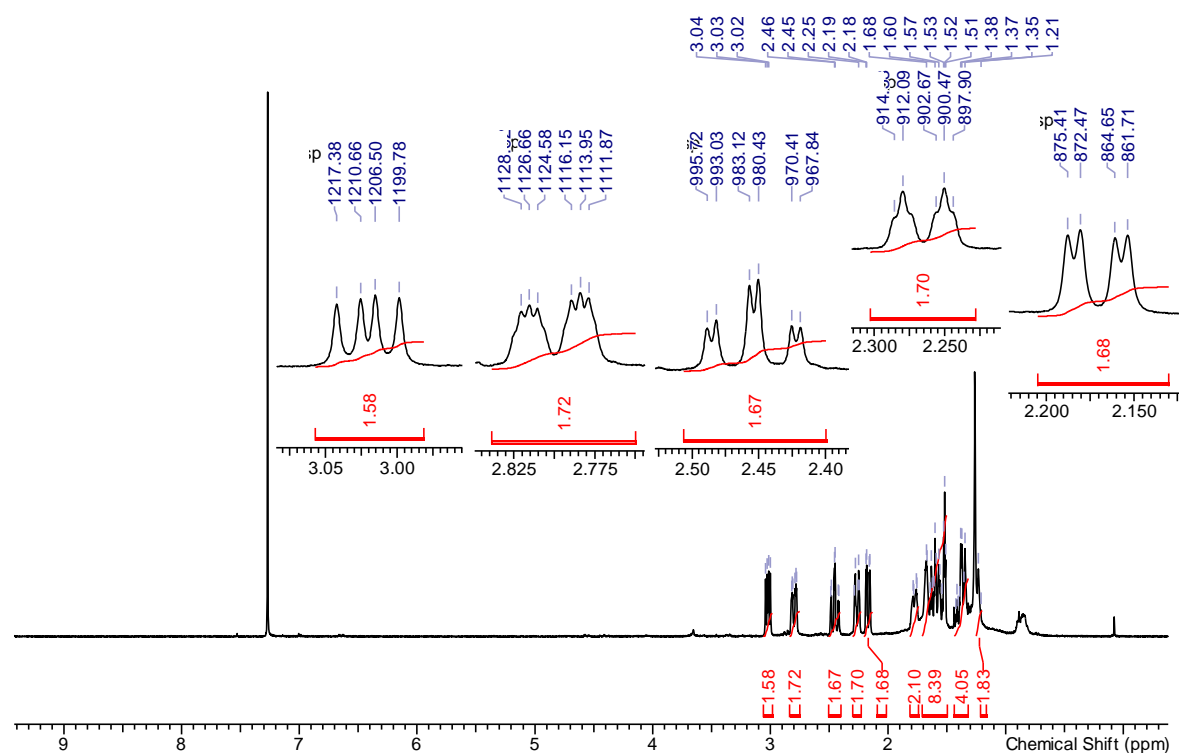


## A.1.4 $^{13}$C NMR (101 MHz) spectrum of (+)-$\beta$-isosparteine ((+)-1.4) (CDCl$_3$)
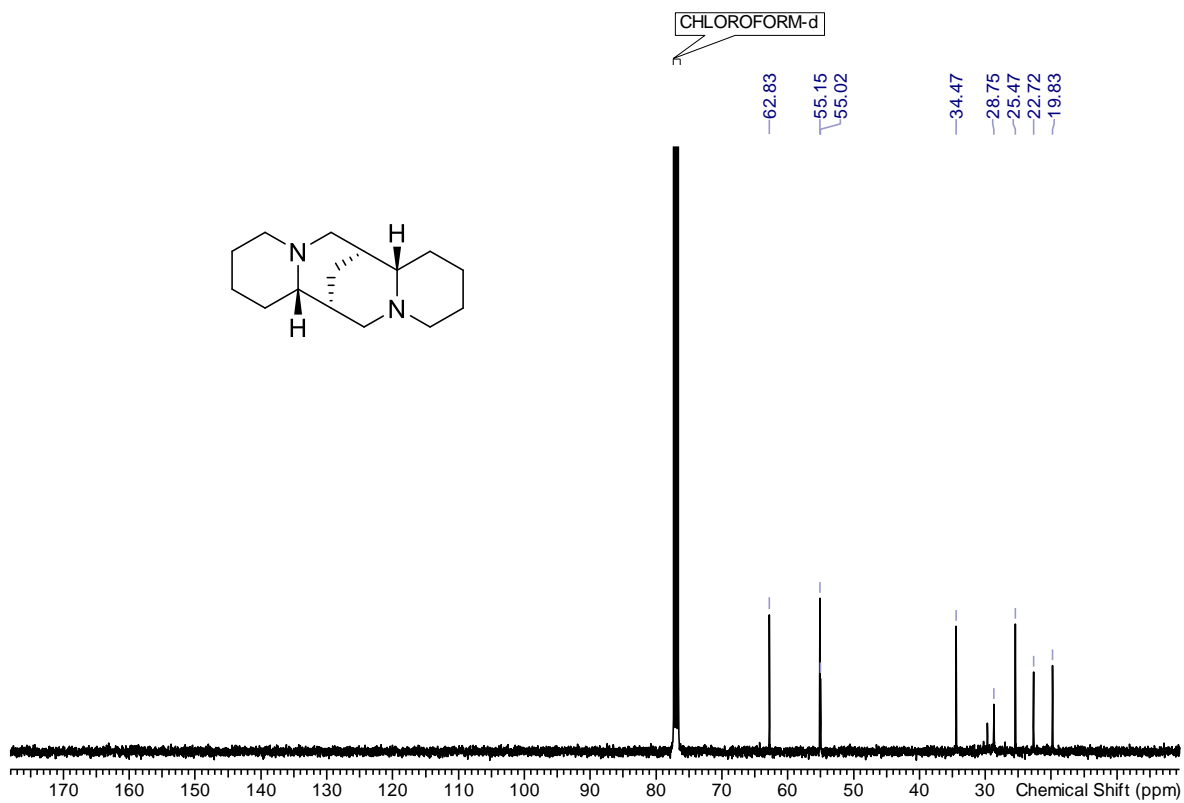
**A.1.5** **$^1$H (400 MHz) spectrum of (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-1.43) (CDCl₃)**
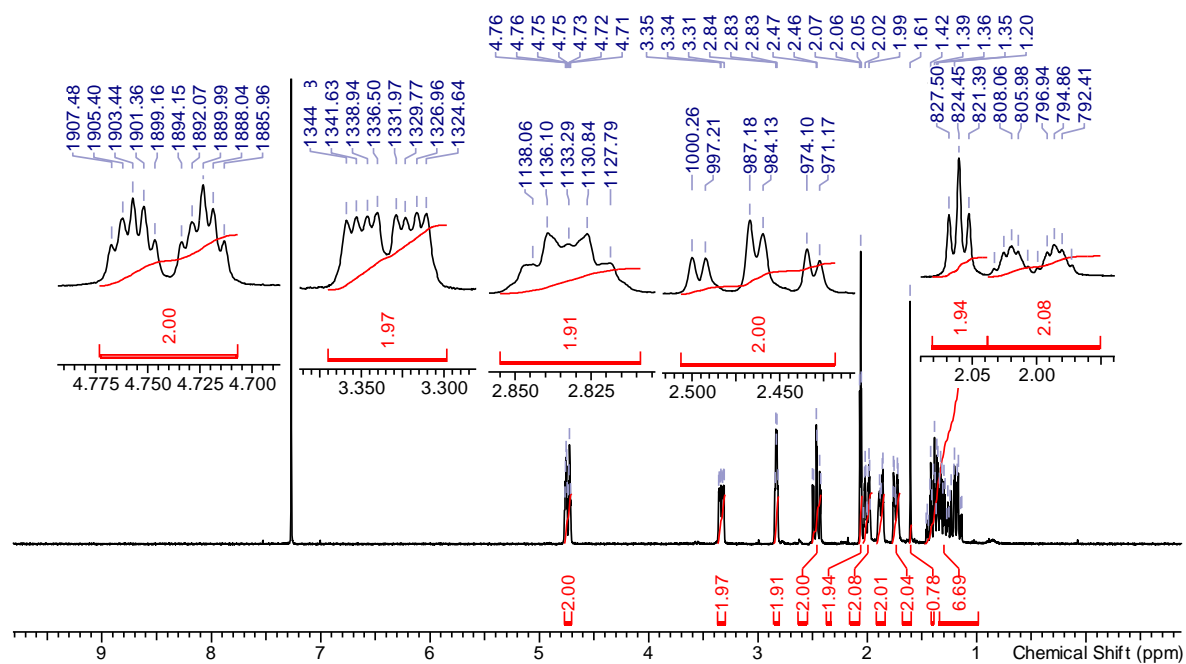


**A.1.6** **$^{13}$C NMR (101 MHz) spectrum of (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-1.43) (CDCl₃)**
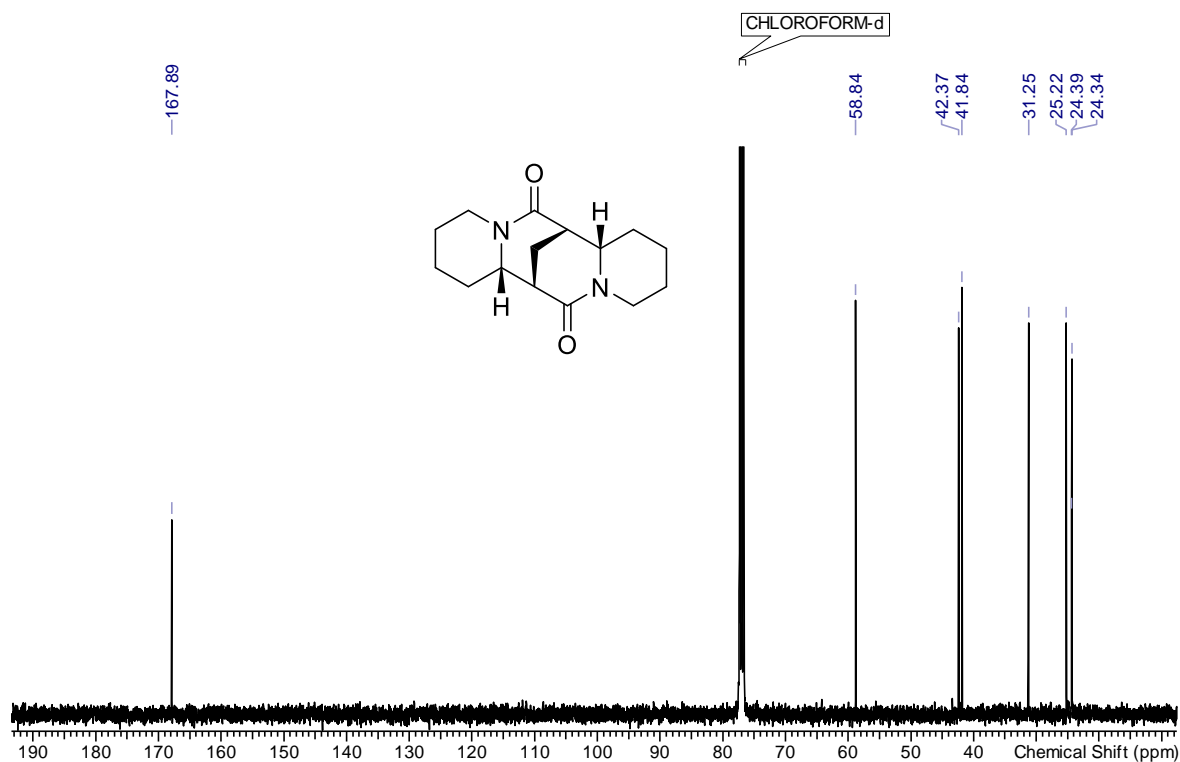
Appendices

## A.1.7 ¹H (400 MHz) spectrum of (+)-10,17-dioxo-sparteine ((+)-1.44) (CDCl₃)
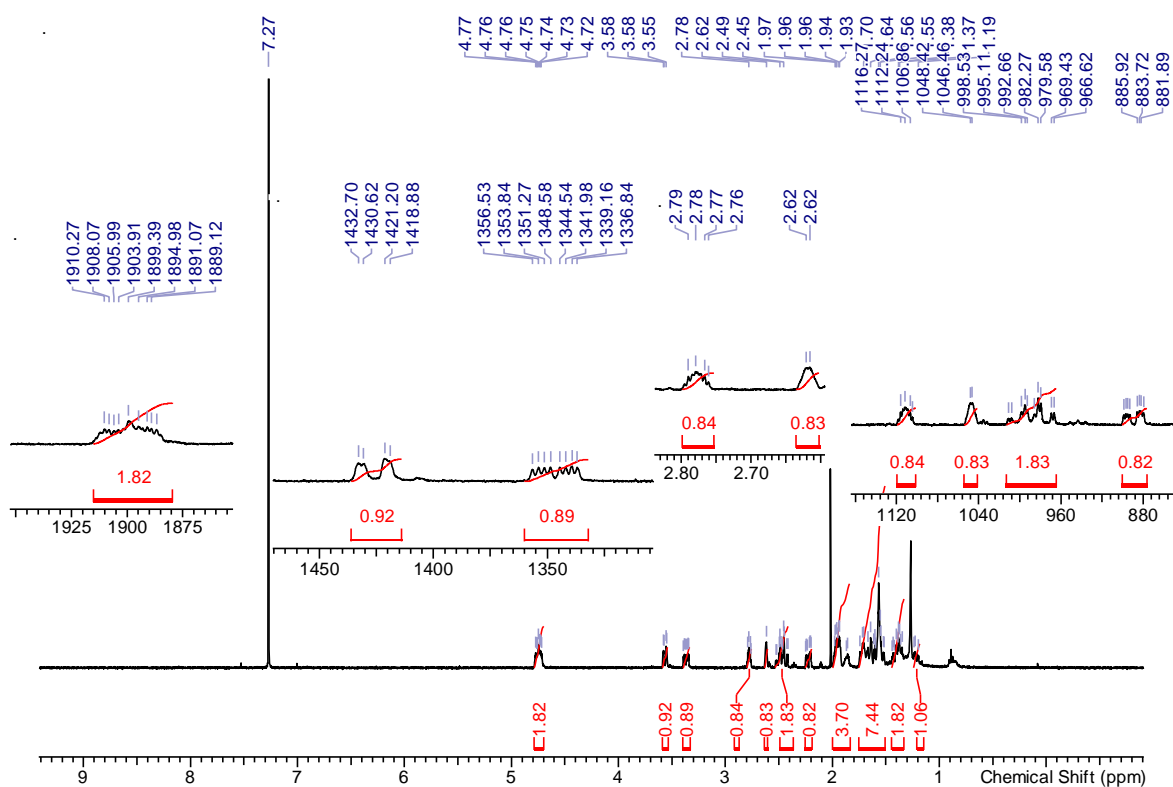


## A.1.8 ¹³C NMR (101 MHz) spectrum of (+)-10,17-dioxo-sparteine ((+)-1.44) (CDCl₃)
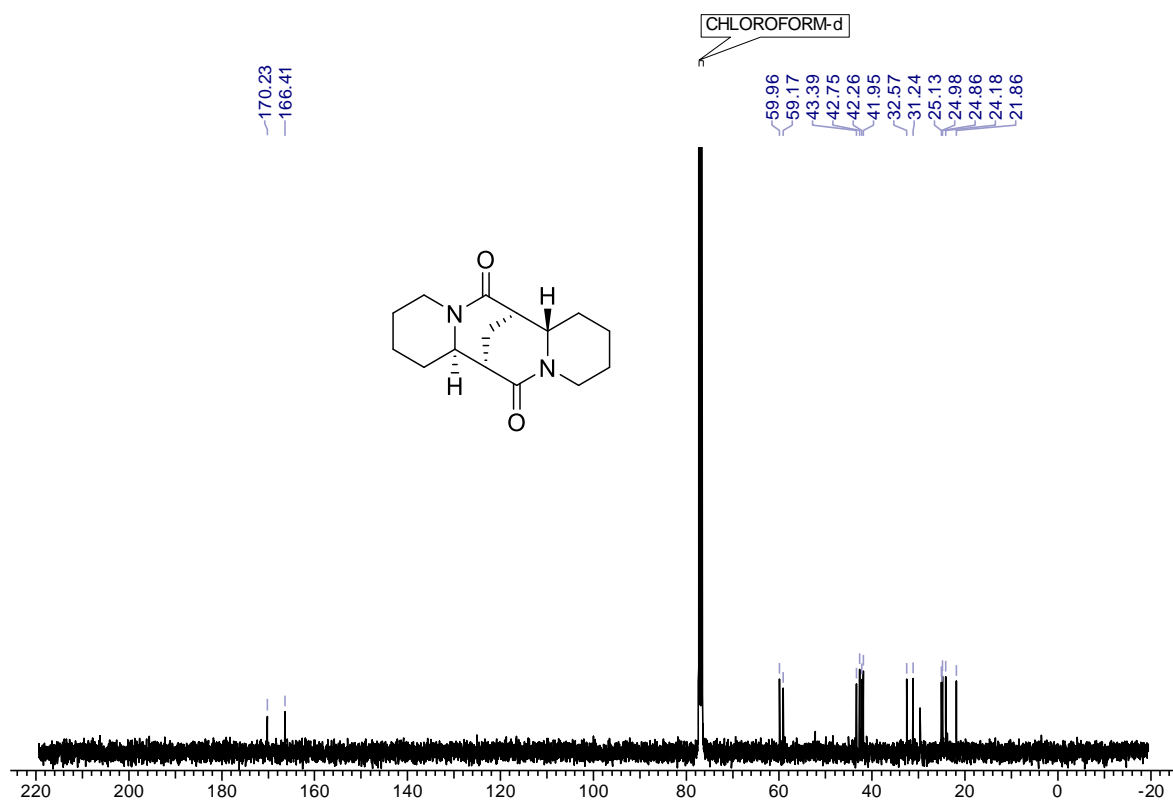
## A.1.9      $^1$H (400 MHz) spectrum of (–)-sparteine ((–)-1.3) (CDCl$_3$)
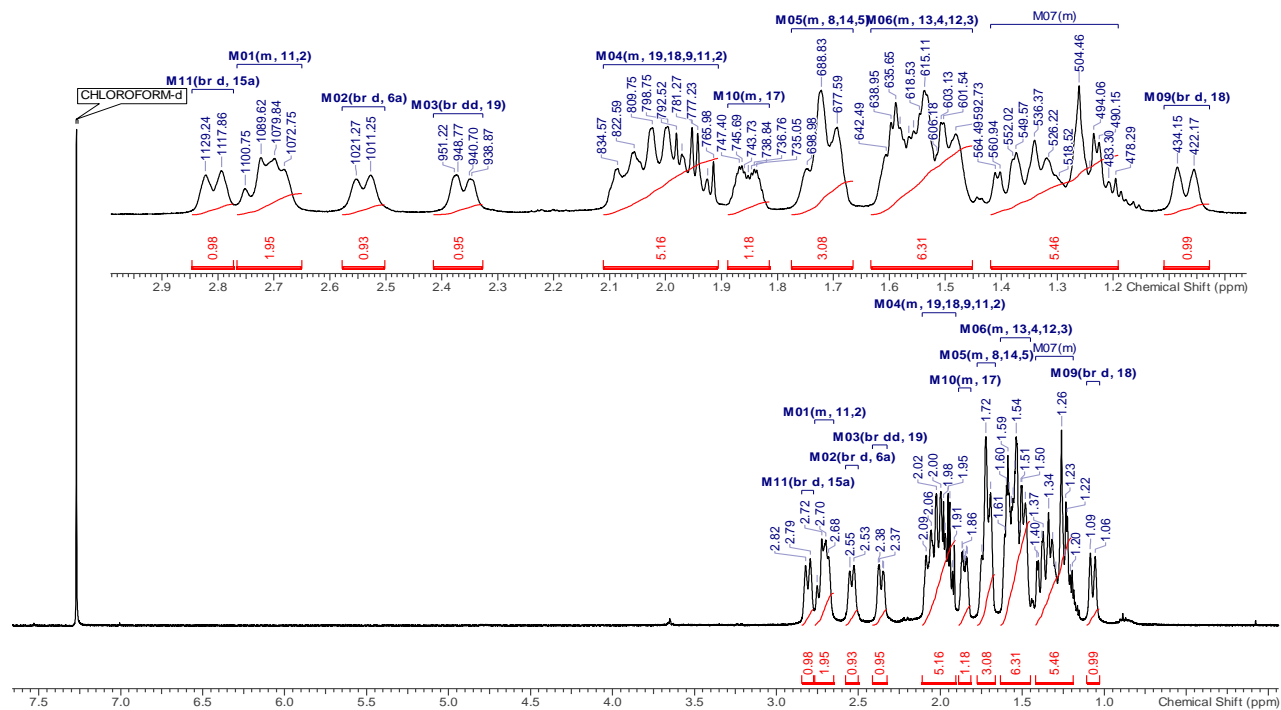


## A.1.10      $^{13}$C NMR (101 MHz) spectrum of (–)-sparteine ((–)-1.3) (CDCl$_3$)



151
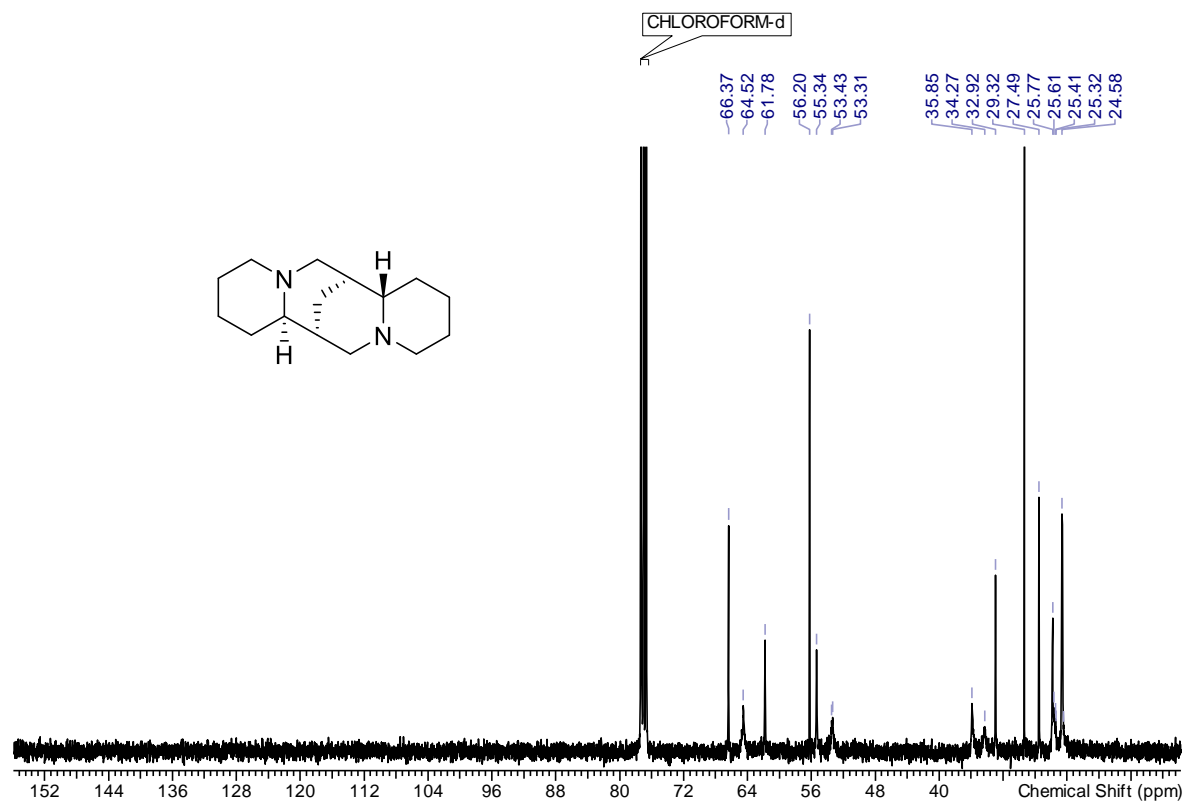
Appendices

**A.1.11**     **^{1}H NMR spectrum of the crude mono imino-aldol reaction shows the mono *anti* and *syn* imino-aldol adducts 2.17 and 2.13 with impure *anti* imino-aldol adduct separated.**
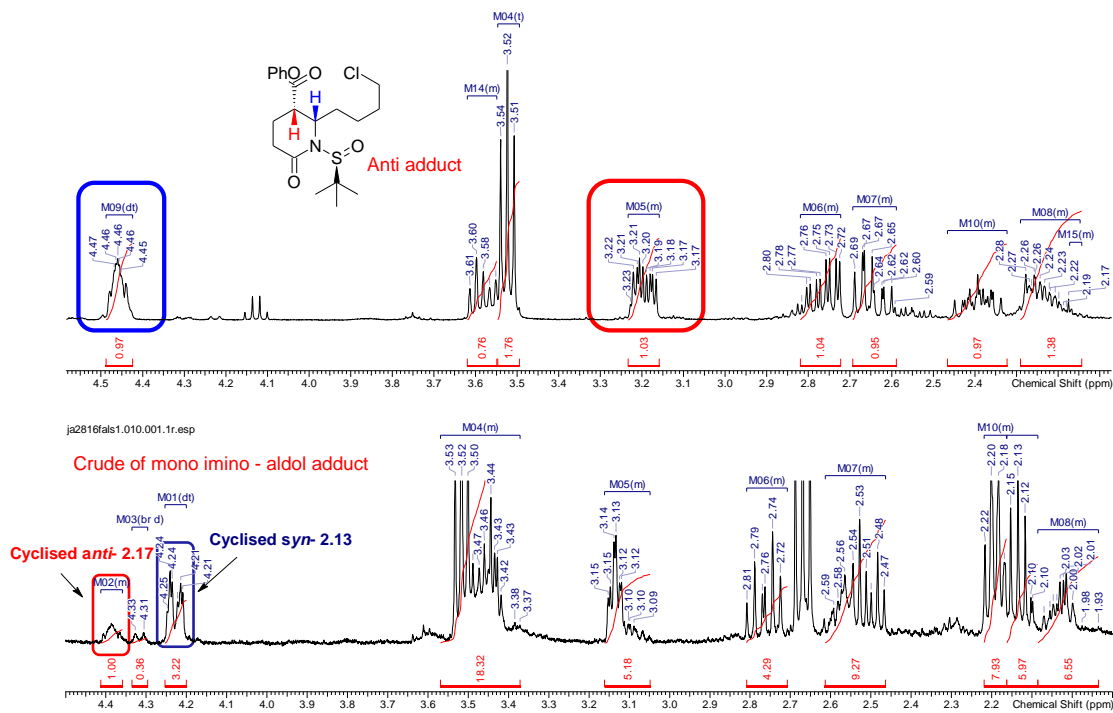
# Appendix B      X-Ray crystallography Data

### B.1.1      Tricyclic imide product 2.40

**Crystal Data and Experimental**
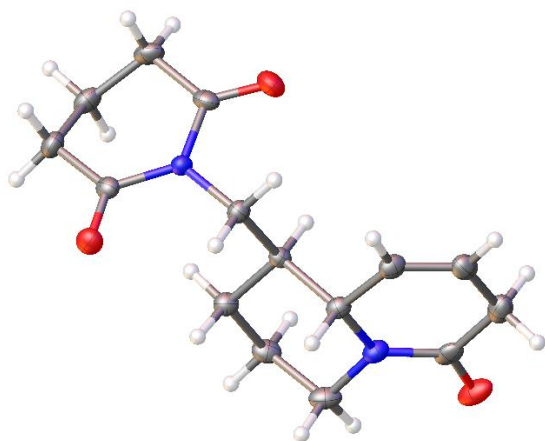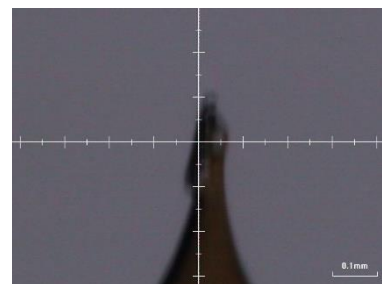




**Figure 1**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless fragment-shaped crystals of (**2016sot0040_R1_100K**) were recrystallised from DCM by slow evaporation. A suitable crystal $(0.21 \times 0.05 \times 0.02)$ mm$^3$ was selected and mounted on a MITIGEN holder with silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** $C_{15}H_{20}N_2O_3$, $M_r$ = 276.33, monoclinic, P2$_1$ (No. 4), a = 10.5786(7) Å, b = 5.3217(3) Å, c = 12.9067(9) Å, $\beta$ = 107.716(7)°, $\alpha = \gamma$ = 90°, $V$ = 692.14(8) Å$^3$, $T$ = 100(2) K, $Z$ = 2, $Z'$ = 1, $\mu$(MoK$_\alpha$) = 0.093, 7081 reflections measured, 3515 unique ($R_{int}$ = 0.0296) which were used in all calculations. The final $wR_2$ was 0.0919 (all data) and $R_1$ was 0.0447 (I > 2(I)).

| Compound | 2016sot0040_R_100K |
|---|---|
| Formula | $C_{15}H_{20}N_2O_3$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.326 |
| $\mu$/mm$^{-1}$ | 0.093 |
| Formula Weight | 276.33 |
| Colour | clear colourless |
| Shape | fragment |
| Size/mm$^3$ | 0.21×0.05×0.02 |
| $T$/K | 100(2) |
| Crystal System | monoclinic |
| Flack Parameter | 0.0(8) |
| Hooft Parameter | -0.2(8) |
| Space Group | P2$_1$ |
| a/Å | 10.5786(7) |
| b/Å | 5.3217(3) |
| c/Å | 12.9067(9) |
| $\alpha$/° | 90 |
| $\beta$/° | 107.716(7) |
| $\gamma$/° | 90 |
| V/Å$^3$ | 692.14(8) |
| Z | 2 |
| Z' | 1 |
| Wavelength/Å | 0.71073 |
| Radiation type | MoK$_\alpha$ |
| $\Theta_{min}$/° | 2.978 |
| $\Theta_{max}$/° | 28.699 |
| Measured Refl. | 7081 |
| Independent Refl. | 3515 |
| Reflections Used | 2735 |
| $R_{int}$ | 0.0296 |
| Parameters | 181 |
| Restraints | 1 |
| Largest Peak | 0.232 |
| Deepest Hole | -0.215 |
| GooF | 1.022 |
| $wR_2$ (all data) | 0.0919 |
| $wR_2$ | 0.0853 |
| $R_1$ (all data) | 0.0665 |
| $R_1$ | 0.0447 |

Appendices

## Structure Quality Indicators

**Reflections:**

| d min | 0.74 | I/σ | 15.5 | Rint | 2.96% | complete at 2θ=61° | 98% |
|---|---|---|---|---|---|---|---|

**Refinement:**

| Shift | 0.000 | Max Peak | 0.2 | Min Peak | -0.2 | GooF | 1.022 | -0.0(8) |
|---|---|---|---|---|---|---|---|---|

A clear colourless fragment-shaped crystal with dimensions 0.21×0.05×0.02 was mounted on a MITIGEN holder with silicon oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 10.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 28.699.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) on 4012 reflections, 57 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software, which corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.699 in $\Theta$. The absorption coefficient $\mu$ of this material is 0.093 at this wavelength ($\lambda$ = 0.71073) and the minimum and maximum transmissions are 0.88651 and 1.00000.

The structure was solved in the space group P2$_1$ (# 4) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 2 and Z' is 1.

The Flack parameter was refined to 0.0(8). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.2(8). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

## Generated precession images



0kl



h0l



hk0

# Data Plots: Diffraction Data

### Wilson Plot — 2016sot0040_R1_100K

$y = -0.253x + 0.145$

Non-Centrosymmetric    Centrosymmetric

0.736    0.968

$B = 1.676$    $<|E^2-1|> = 0.852$
$K = 0.649$    $\%|E| > 2 = 3.492\%$

### Cumulative Intensity Distribution — 2016sot0040_R1_100K

- Centric
- Acentric
- Twinned Acentric

### Systematic Absences Intensity Distribution — 2016sot0040_R1_100K

### Completeness Plot — 2016sot0040_R1_100K

### I/sigma vs. Resolution — 2016sot0040_R1_100K

# Data Plots: Refinement and Data

### Fobs vs Fcalc — 2016sot0040_R1_100K

$y = 0.996x + 0.102$

- Filtered Data
- Omitted Data

### Normal probability plot — 2016sot0040_R1_100K

$y = 0.993x + 0.078$
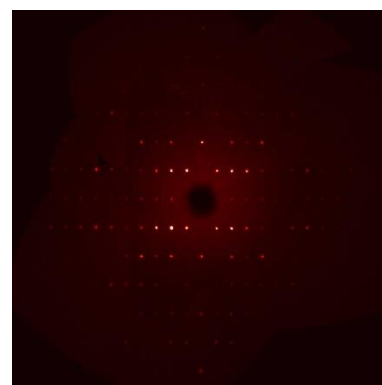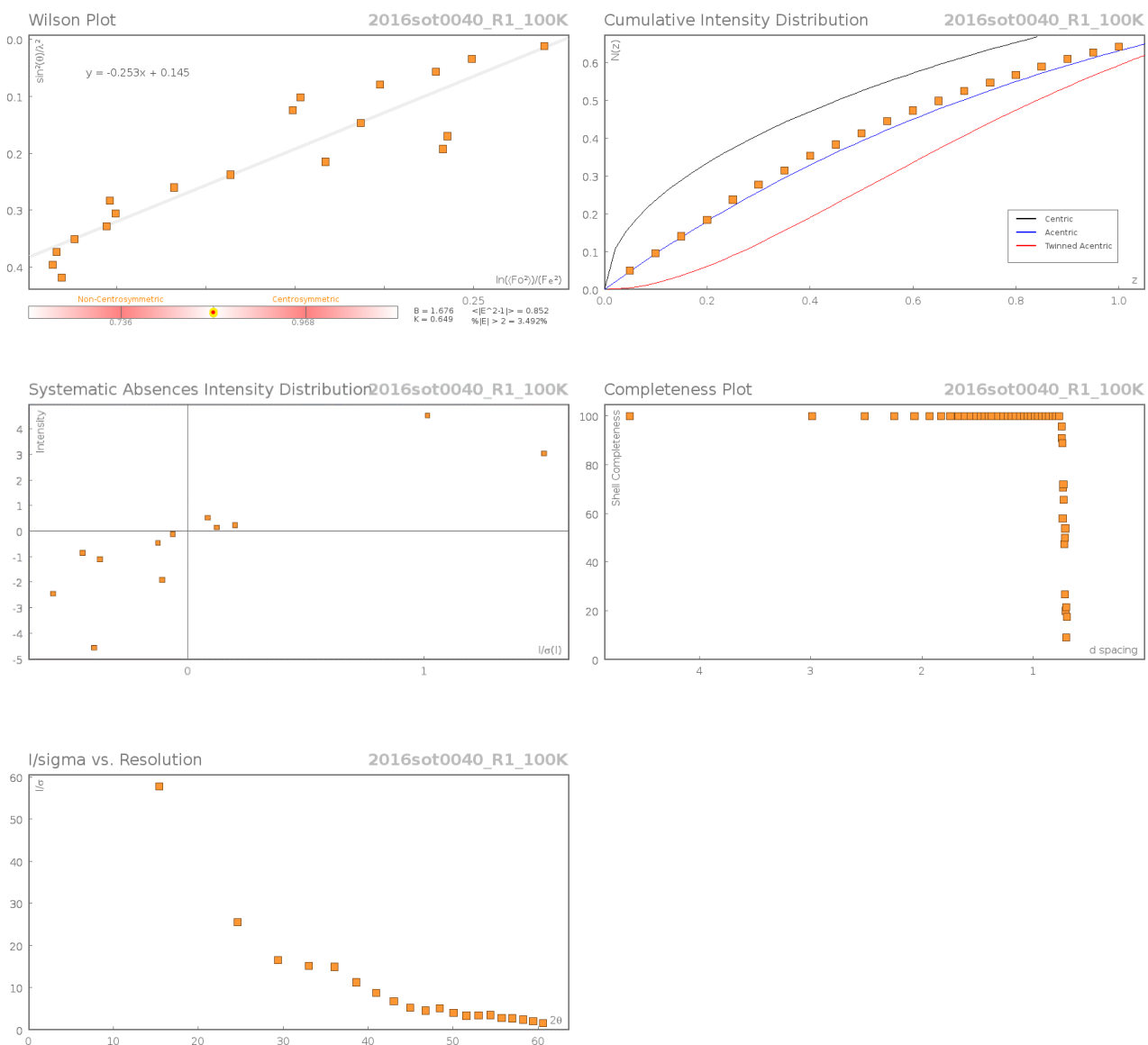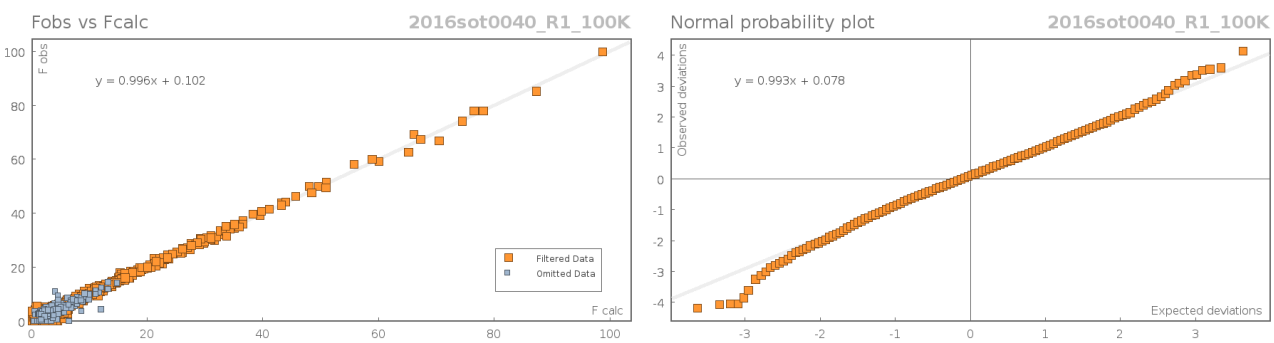
Appendices

## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 7093 | Unique reflections | 3515 |
| Completeness | 0.983 | Mean I/$\sigma$ | 15.52 |
| hkl$_{max}$ collected | (14, 7, 18) | hkl$_{min}$ collected | (-14, -7, -17) |
| hkl$_{max}$ used | (13, 7, 17) | hkl$_{min}$ used | (-14, -7, 0) |
| Lim d$_{max}$ collected | 7.0 | Lim d$_{min}$ collected | 0.74 |
| d$_{max}$ used | 6.84 | d$_{min}$ used | 0.74 |
| Friedel pairs | 2209 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 1 | R$_{int}$ | 0.0296 |
| R$_{sigma}$ | 0.0568 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (4402, 1117, 218, 21, 2) | Maximum multiplicity | 8 |
| Removed systematic absences | 12 | Filtered off (Shel/OMIT) | 291 |

**Table 1**: Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2016sot0040_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 5371.7(15) | 10048(3) | 8544.4(14) | 27.4(4) |
| O2 | 3883.7(15) | 3549(3) | 6200.3(14) | 32.9(5) |
| O3 | 10403.9(15) | -92(3) | 7465.4(16) | 33.5(5) |
| N1 | 4683.3(17) | 6702(4) | 7409.6(15) | 17.4(4) |
| N2 | 9066.7(17) | 3223(4) | 7515.6(16) | 21.7(4) |
| C1 | 4595(2) | 8305(4) | 8248.3(18) | 19.5(5) |
| C2 | 3535(2) | 7752(4) | 8779(2) | 26.1(6) |
| C3 | 3030(2) | 5068(5) | 8615(2) | 26.1(5) |
| C4 | 2619(2) | 4481(4) | 7403(2) | 26.5(6) |
| C5 | 3749(2) | 4808(4) | 6942.5(19) | 22.0(5) |
| C6 | 5816(2) | 6948(4) | 6973.5(19) | 19.3(5) |
| C7 | 6866(2) | 4903(4) | 7449.3(17) | 16.1(4) |
| C8 | 7331(2) | 4988(4) | 8699.4(18) | 20.8(5) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C9 | 8401(2) | 3022(5) | 9179.0(19) | 23.8(5) |
| C10 | 9547(2) | 3317(5) | 8711(2) | 26.7(6) |
| C11 | 8077(2) | 5186(4) | 7022.8(18) | 18.8(5) |
| C12 | 7704(2) | 5203(5) | 5804.9(19) | 23.1(5) |
| C13 | 8172(2) | 3586(5) | 5232(2) | 25.3(5) |
| C14 | 9124(2) | 1542(5) | 5750(2) | 28.9(6) |
| C15 | 9574(2) | 1497(4) | 6976(2) | 23.9(5) |

**Table 2**: Anisotropic Displacement Parameters (×10⁴) **2016sot0040_R1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11}+ ... +2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| O1 | 26.0(8) | 22.4(8) | 34.4(10) | -6.0(8) | 9.9(7) | -4.3(8) |
| O2 | 30.4(9) | 36.2(10) | 28.1(10) | -13.3(9) | 2.7(8) | -3.1(8) |
| O3 | 20.1(8) | 21.4(9) | 57.2(12) | 4.1(10) | 9.1(8) | 2.8(7) |
| N1 | 14.6(9) | 18.4(9) | 19.2(10) | -2.0(8) | 5.4(7) | -1.6(8) |
| N2 | 17.3(9) | 23.4(10) | 23.7(11) | 3.6(9) | 5.4(8) | 2.5(8) |
| C1 | 17.9(10) | 17.5(11) | 21.7(12) | -0.4(10) | 3.8(9) | 2.1(9) |
| C2 | 21.9(12) | 28.7(13) | 31.0(15) | -3.5(11) | 13.0(11) | 2(1) |
| C3 | 18.9(10) | 29.4(12) | 32.5(14) | 5.0(12) | 11.9(10) | 1.0(11) |
| C4 | 17.7(11) | 24.4(13) | 35.5(15) | -1.5(11) | 5.3(11) | -5.7(9) |
| C5 | 18.4(10) | 21.9(11) | 21.0(12) | -1.9(11) | -1.0(9) | -1.4(10) |
| C6 | 18.8(11) | 19.9(11) | 20.5(12) | 1.6(10) | 7.8(10) | 0.3(9) |
| C7 | 17.9(10) | 15.8(10) | 14.4(10) | 1.3(9) | 4.4(8) | -1.9(9) |
| C8 | 20.8(10) | 20.6(11) | 20.5(12) | 1.9(11) | 5.6(9) | -0.7(10) |
| C9 | 24.6(11) | 24.8(12) | 19.1(12) | 4.7(11) | 2.2(10) | -2.5(10) |
| C10 | 19.4(11) | 28.1(13) | 28.1(13) | 6.4(12) | 0.7(10) | -2.5(11) |
| C11 | 16.9(10) | 17.3(10) | 22.0(12) | 2.7(10) | 5.7(9) | -0.5(10) |
| C12 | 20.3(11) | 25.7(12) | 24.4(13) | 4.3(11) | 8.6(10) | -1.1(10) |
| C13 | 24.5(11) | 28.7(13) | 24.4(13) | -1.5(11) | 10.2(10) | -5.4(11) |
| C14 | 27.9(13) | 23.5(12) | 39.6(16) | -6.4(13) | 16.5(12) | -3.7(11) |
| C15 | 15.3(11) | 17.4(11) | 40.0(15) | -0.2(12) | 9.9(10) | -5.2(9) |

Appendices

**Table 3**: Bond Lengths in Å for **2016sot0040_R1_100K**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|----------|------|------|----------|
| O1 | C1 | 1.221(3) | C3 | C4 | 1.523(3) |
| O2 | C5 | 1.212(3) | C4 | C5 | 1.498(3) |
| O3 | C15 | 1.244(3) | C6 | C7 | 1.543(3) |
| N1 | C1 | 1.403(3) | C7 | C8 | 1.538(3) |
| N1 | C5 | 1.412(3) | C7 | C11 | 1.547(3) |
| N1 | C6 | 1.477(3) | C8 | C9 | 1.527(3) |
| N2 | C10 | 1.471(3) | C9 | C10 | 1.518(3) |
| N2 | C11 | 1.479(3) | C11 | C12 | 1.500(3) |
| N2 | C15 | 1.358(3) | C12 | C13 | 1.325(4) |
| C1 | C2 | 1.510(3) | C13 | C14 | 1.495(3) |
| C2 | C3 | 1.517(4) | C14 | C15 | 1.508(3) |

**Table 4**: Bond Angles in ° for **2016sot0040_R1_100K**.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|------|------|------|---------|
| C1 | N1 | C5 | 124.14(19) | O2 | C5 | C4 | 123.3(2) |
| C1 | N1 | C6 | 119.47(17) | N1 | C5 | C4 | 116.9(2) |
| C5 | N1 | C6 | 116.39(18) | N1 | C6 | C7 | 110.80(18) |
| C10 | N2 | C11 | 113.61(19) | C6 | C7 | C11 | 111.30(18) |
| C15 | N2 | C10 | 119.8(2) | C8 | C7 | C6 | 111.00(19) |
| C15 | N2 | C11 | 126.57(19) | C8 | C7 | C11 | 109.60(15) |
| O1 | C1 | N1 | 120.5(2) | C9 | C8 | C7 | 111.47(19) |
| O1 | C1 | C2 | 121.9(2) | C10 | C9 | C8 | 110.56(19) |
| N1 | C1 | C2 | 117.64(18) | N2 | C10 | C9 | 110.54(17) |
| C1 | C2 | C3 | 113.5(2) | N2 | C11 | C7 | 109.43(17) |
| C2 | C3 | C4 | 108.3(2) | N2 | C11 | C12 | 112.40(19) |
| C5 | C4 | C3 | 111.78(18) | C12 | C11 | C7 | 113.04(16) |
| O2 | C5 | N1 | 119.8(2) | C13 | C12 | C11 | 123.9(2) |

| Atom | Atom | Atom | Angle/° | | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|--|------|------|------|---------|
| C12  | C13  | C14  | 122.6(2) | | O3 | C15 | C14 | 119.5(2) |
| C13  | C14  | C15  | 115.8(2) | | N2 | C15 | C14 | 118.7(2) |
| O3   | C15  | N2   | 121.8(2) | |    |     |     |          |

**Table 5**: Torsion Angles in ° for **2016sot0040_R1_100K**.

| Atom | Atom | Atom | Atom | Angle/° |
|------|------|------|------|---------|
| O1 | C1 | C2 | C3 | -158.3(2) |
| N1 | C1 | C2 | C3 | 20.3(3) |
| N1 | C6 | C7 | C8 | -56.1(2) |
| N1 | C6 | C7 | C11 | -178.44(17) |
| N2 | C11 | C12 | C13 | 2.3(3) |
| C1 | N1 | C5 | O2 | 178.1(2) |
| C1 | N1 | C5 | C4 | -1.6(3) |
| C1 | N1 | C6 | C7 | 101.0(2) |
| C1 | C2 | C3 | C4 | -52.3(2) |
| C2 | C3 | C4 | C5 | 58.5(2) |
| C3 | C4 | C5 | O2 | 147.7(2) |
| C3 | C4 | C5 | N1 | -32.7(3) |
| C5 | N1 | C1 | O1 | -173.2(2) |
| C5 | N1 | C1 | C2 | 8.1(3) |
| C5 | N1 | C6 | C7 | -78.6(2) |
| C6 | N1 | C1 | O1 | 7.2(3) |
| C6 | N1 | C1 | C2 | -171.45(19) |
| C6 | N1 | C5 | O2 | -2.3(3) |
| C6 | N1 | C5 | C4 | 178.02(19) |
| C6 | C7 | C8 | C9 | -178.31(18) |
| C6 | C7 | C11 | N2 | 178.88(17) |
| C6 | C7 | C11 | C12 | -55.0(3) |

| Atom | Atom | Atom | Atom | Angle/° |
|------|------|------|------|---------|
| C7 | C8 | C9 | C10 | 54.7(2) |
| C7 | C11 | C12 | C13 | -122.2(2) |
| C8 | C7 | C11 | N2 | 55.7(2) |
| C8 | C7 | C11 | C12 | -178.19(19) |
| C8 | C9 | C10 | N2 | -55.1(3) |
| C10 | N2 | C11 | C7 | -59.1(2) |
| C10 | N2 | C11 | C12 | 174.45(19) |
| C10 | N2 | C15 | O3 | 2.9(3) |
| C10 | N2 | C15 | C14 | -176.4(2) |
| C11 | N2 | C10 | C9 | 58.9(3) |
| C11 | N2 | C15 | O3 | -179.78(19) |
| C11 | N2 | C15 | C14 | 1.0(3) |
| C11 | C7 | C8 | C9 | -55.0(2) |
| C11 | C12 | C13 | C14 | 0.5(4) |
| C12 | C13 | C14 | C15 | -2.6(3) |
| C13 | C14 | C15 | O3 | -177.3(2) |
| C13 | C14 | C15 | N2 | 1.9(3) |
| C15 | N2 | C10 | C9 | -123.4(2) |
| C15 | N2 | C11 | C7 | 123.4(2) |
| C15 | N2 | C11 | C12 | -3.0(3) |

**Table 6**: Hydrogen Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2016sot0040_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H2A | 2779 | 8910 | 8478 | 31 |
| H2B | 3897 | 8089 | 9568 | 31 |
| H3A | 2261 | 4871 | 8894 | 31 |
| H3B | 3736 | 3896 | 9017 | 31 |
| H4A | 2293 | 2729 | 7284 | 32 |
| H4B | 1882 | 5607 | 7015 | 32 |
| H6A | 6224 | 8629 | 7158 | 23 |
| H6B | 5497 | 6796 | 6171 | 23 |
| H7 | 6452 | 3224 | 7216 | 19 |
| H8A | 7687 | 6680 | 8944 | 25 |
| H8B | 6564 | 4684 | 8970 | 25 |
| H9A | 8730 | 3214 | 9979 | 29 |
| H9B | 8016 | 1319 | 9013 | 29 |
| H10A | 9998 | 4942 | 8949 | 32 |
| H10B | 10200 | 1955 | 8988 | 32 |
| H11 | 8496 | 6846 | 7284 | 23 |
| H12 | 7096 | 6447 | 5422 | 28 |
| H13 | 7891 | 3731 | 4462 | 30 |
| H14A | 9918 | 1704 | 5501 | 35 |
| H14B | 8704 | -93 | 5484 | 35 |

**Citations**

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, J. Appl. Cryst., (2009), **42**, 339-341. Sheldrick, G.M., Crystal structure refinement with ShelXL, Acta Cryst., (2015), **C27**, 3-8. Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, Acta Cryst., (2015), **A71**, 3- 8.

## B.1.2    *Anti*-mono imino-aldol product 2.27

**Crystal Data and Experimental**



**Figure 2**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless needle-shaped crystals of (**2016sot0090_R1_100K**) were recrystallised from a mixture of hexane and ethyl acetate by slow evaporation. A suitable crystal (0.28×0.02×0.02) mm³ was selected and mounted on a MITIGEN holder with silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** $C_{16}H_{20}ClNO_3$, $M_r$ = 309.78, monoclinic, P2$_1$/c (No. 14), a = 18.7179(15) Å, b = 5.3770(3) Å, c = 16.4030(12) Å, $\beta$ = 109.501(8)°, $\alpha = \gamma$ = 90°, $V$ = 1556.2(2) Å³, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(Mo K$_\alpha$) = 0.255, 14451 reflections measured, 4003 unique ($R_{int}$ = 0.0794) which were used in all calculations. The final $wR_2$ was 0.1678 (all data) and $R_1$ was 0.0724 (I > 2(I)). **Crystal Data.** $C_{16}H_{20}ClNO_3$, $M_r$ = 309.78, monoclinic, P2$_1$/c (No. 14), a = 18.7179(15) Å, b = 5.3770(3) Å, c = 16.4030(12) Å, $\beta$ = 109.501(8)°, $\alpha = \gamma$ = 90°, $V$ = 1556.2(2) Å³, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(Mo K$_\alpha$) = 0.255,



| Compound | 2016sot0090_R_100 K |
|---|---|
| Formula | $C_{16}H_{20}ClNO_3$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.322 |
| $\mu$/mm$^{-1}$ | 0.255 |
| Formula Weight | 309.78 |
| Colour | clear colourless |
| Shape | needle |
| Size/mm³ | 0.28×0.02×0.02 |
| $T$/K | 100(2) |
| Crystal System | monoclinic |
| Space Group | P2$_1$/c |
| a/Å | 18.7179(15) |
| b/Å | 5.3770(3) |
| c/Å | 16.4030(12) |
| $\alpha$/° | 90 |
| $\beta$/° | 109.501(8) |
| $\gamma$/° | 90 |
| V/Å³ | 1556.2(2) |
| Z | 4 |
| Z' | 1 |
| Wavelength/Å | 0.71075 |
| Radiation type | Mo K$_\alpha$ |
| $\Theta_{min}$/° | 3.211 |
| $\Theta_{max}$/° | 28.696 |
| Measured Refl. | 14451 |
| Independent Refl. | 4003 |
| Reflections Used | 2599 |
| $R_{int}$ | 0.0794 |
| Parameters | 190 |
| Restraints | 0 |
| Largest Peak | 0.451 |
| Deepest Hole | -0.300 |
| GooF | 1.026 |
| $wR_2$ (all data) | 0.1678 |
| $wR_2$ | 0.1487 |
| $R_1$ (all data) | 0.1204 |
| $R_1$ | 0.0724 |

**Structure Quality Indicators**

**Reflections:**

| d min (Mo) | I/σ | Rint | complete at 2θ=61° |
|---|---|---|---|
| 0.74 | 9.2 | 7.94% | 100% |

**Refinement:**

| Shift | Max Peak | Min Peak | GooF |
|---|---|---|---|
| 0.000 | 0.5 | -0.3 | 1.026 |

A clear colourless needle-shaped crystal with dimensions 0.28×0.02×0.02 was mounted on a MITIGEN holder with silicon oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 15.0 s using Mo K$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 28.696.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) on 4225 reflections, 29 of the observed reflections.
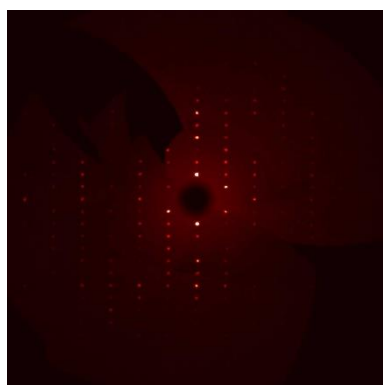
Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software, which corrects for Lorentz polarisation. The final completeness is 92.61 out to 28.696 in $\Theta$. The absorption coefficient $\mu$ of this material is 0.255 at this wavelength ($\lambda$ = 0.71075) and the minimum and maximum transmissions are 0.51747 and 1.00000.

The structure was solved in the space group P2$_1$/c (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

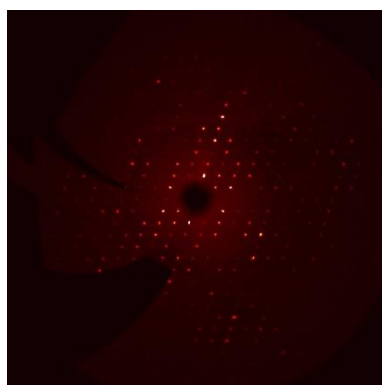There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

**Generated precession images**
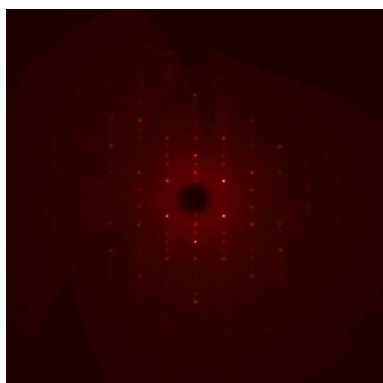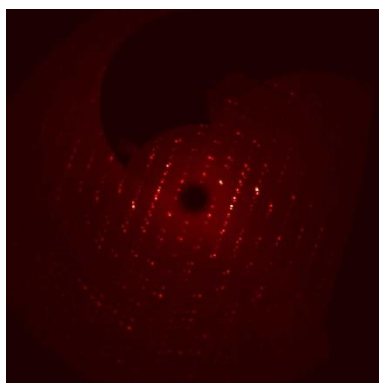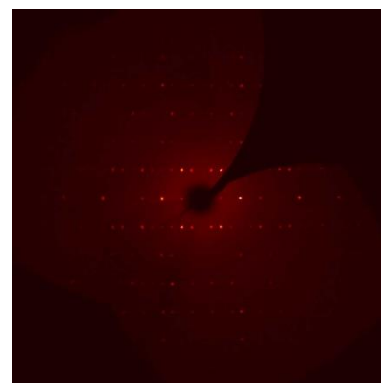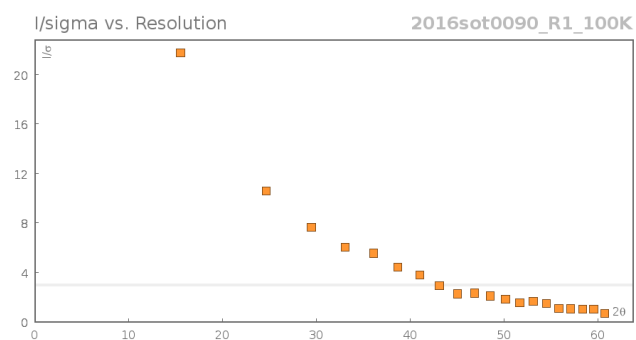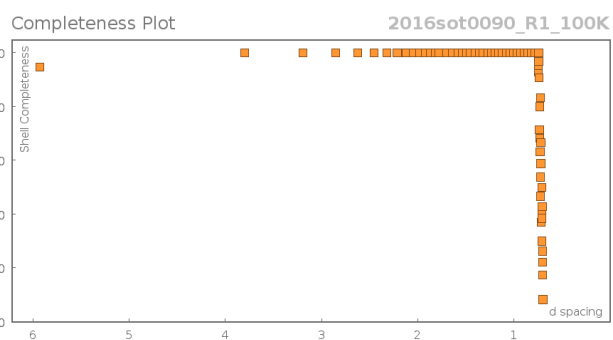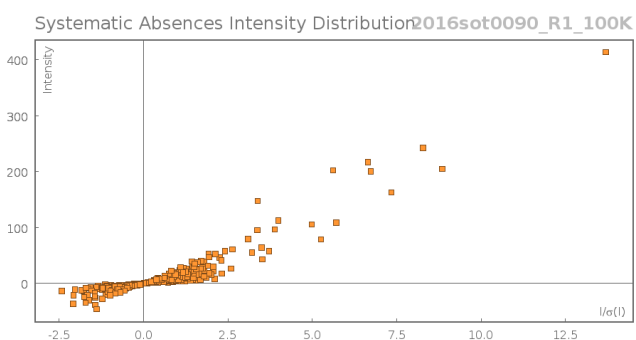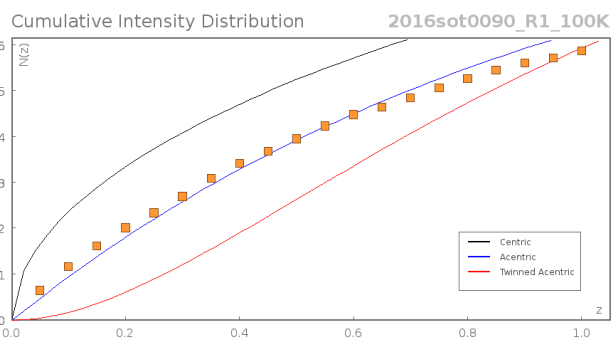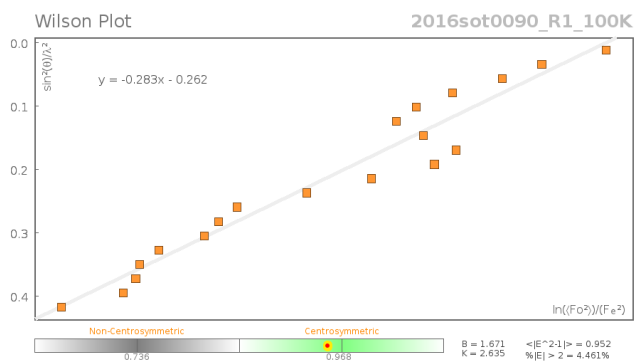


0kl



h0l



hk0

Appendices

## Data Plots: Diffraction Data







## Data Plots: Refinement and Data
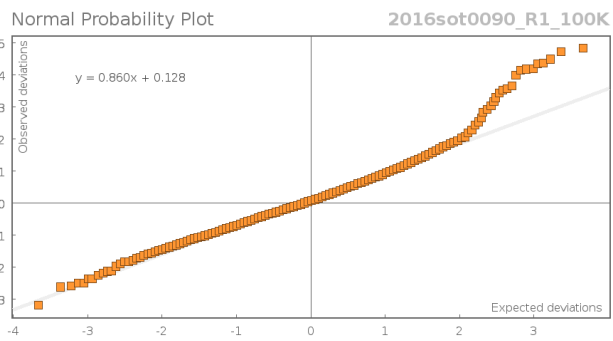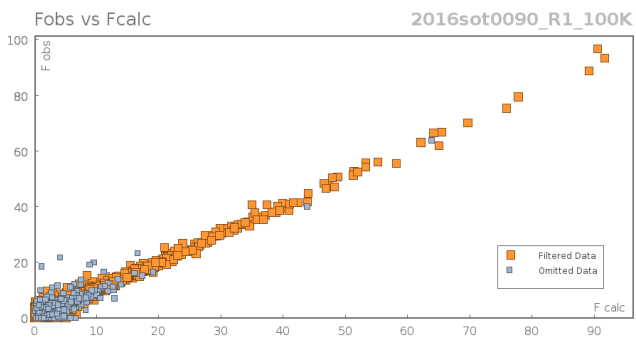
## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 15302 | Unique reflections | 4003 |
| Completeness | 0.996 | Mean I/$\sigma$ | 9.16 |
| hkl$_{max}$ collected | (26, 7, 20) | hkl$_{min}$ collected | (-26, -7, -23) |
| hkl$_{max}$ used | (23, 7, 22) | hkl$_{min}$ used | (-25, 0, 0) |
| Lim d$_{max}$ collected | 7.0 | Lim d$_{min}$ collected | 0.74 |
| d$_{max}$ used | 6.75 | d$_{min}$ used | 0.74 |
| Friedel pairs | 4719 | Friedel pairs merged | 1 |
| Inconsistent equivalents | 1 | R$_{int}$ | 0.0794 |
| R$_{sigma}$ | 0.0896 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 31 |
| Multiplicity | (9198, 2607, 450, 41) | Maximum multiplicity | 13 |
| Removed systematic absences | 820 | Filtered off (Shel/OMIT) | 624 |

**Table 7**: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for **2016sot0090_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Cl01 | 8701.2(5) | 1534.5(16) | 4957.3(5) | 30.5(2) |
| O002 | 7883.5(11) | 6276(4) | 7136.5(13) | 19.8(5) |
| O003 | 6992.1(11) | 9043(4) | 7168.5(14) | 22.3(5) |
| O004 | 4780.6(11) | 9682(4) | 6003.5(13) | 23.3(5) |
| N005 | 5605.7(13) | 7426(4) | 5580.7(15) | 18.3(5) |
| C006 | 7155.0(15) | 6986(5) | 6995.3(17) | 15.5(6) |
| C007 | 6156.9(16) | 5430(5) | 5651.8(18) | 17.2(6) |
| C008 | 8457.8(16) | 8076(5) | 7478.2(19) | 17.6(6) |
| C009 | 5268.7(16) | 8010(5) | 6155.0(19) | 17.9(6) |
| C00A | 6608.6(16) | 4911(5) | 6603.8(18) | 16.3(6) |
| C00B | 6622.2(17) | 6085(5) | 5076.9(19) | 20.0(6) |
| C00C | 8946.6(17) | 7754(6) | 8305(2) | 22.8(7) |
| C00D | 5513.0(17) | 6704(6) | 7012.9(19) | 21.3(6) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C00E | 6045.8(17) | 4498(5) | 7092(2) | 19.9(6) |
| C00F | 8529.9(17) | 10022(6) | 6969(2) | 23.2(7) |
| C00G | 7901.1(17) | 2447(6) | 4042.9(19) | 23.2(7) |
| C00H | 7475.1(19) | 4579(6) | 4276(2) | 24.2(7) |
| C00I | 7104.4(17) | 3950(5) | 4945(2) | 21.9(7) |
| C00J | 9111.2(18) | 11718(6) | 7300(2) | 27.6(7) |
| C00K | 9602.3(17) | 11454(6) | 8132(2) | 29.5(8) |
| C00L | 9526.6(18) | 9463(6) | 8638(2) | 29.4(8) |

**Table 8**: Anisotropic Displacement Parameters ($\times 10^4$) **2016sot0090_R1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11}+ ... +2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| Cl01 | 26.4(4) | 42.4(5) | 21.4(4) | -2.1(4) | 6.3(3) | 7.9(4) |
| O002 | 17.3(10) | 14(1) | 27.2(11) | -0.6(9) | 6.0(9) | 0.0(8) |
| O003 | 22.3(11) | 14.1(10) | 30.3(12) | -3.7(9) | 8.4(9) | 1.5(8) |
| O004 | 22.7(11) | 23.8(11) | 22.1(11) | 2.4(9) | 5.7(9) | 9.2(9) |
| N005 | 21.0(13) | 16.2(12) | 15.5(12) | 4.1(10) | 3.2(10) | 7.1(10) |
| C006 | 16.8(14) | 16.2(14) | 13.3(13) | 4.4(11) | 4.7(11) | 1.4(11) |
| C007 | 17.7(14) | 14.2(13) | 17.5(14) | -3.1(12) | 2.9(11) | 3.7(11) |
| C008 | 16.1(14) | 13.8(13) | 24.4(15) | -1.7(12) | 8.7(12) | -0.3(10) |
| C009 | 15.3(14) | 16.0(14) | 20.2(14) | -0.2(12) | 3.0(11) | -0.9(11) |
| C00A | 19.8(15) | 8.5(12) | 19.3(14) | 0.9(11) | 4.8(12) | 2.3(11) |
| C00B | 24.9(16) | 17.9(14) | 17.1(14) | 1.7(12) | 6.8(12) | 4.5(12) |
| C00C | 22.4(16) | 21.7(15) | 24.1(16) | 1.7(13) | 7.7(13) | 2.8(12) |
| C00D | 21.8(15) | 20.2(15) | 24.0(15) | 3.7(13) | 10.5(12) | -0.1(12) |
| C00E | 21.5(15) | 13.7(13) | 24.4(15) | 1.4(12) | 7.5(12) | -0.5(11) |
| C00F | 19.9(16) | 21.4(16) | 28.9(17) | 3.1(14) | 9.2(13) | 5.2(12) |
| C00G | 24.6(17) | 29.1(16) | 15.9(14) | -1.9(13) | 6.8(13) | 1.6(13) |
| C00H | 32.4(18) | 21.0(15) | 21.0(15) | -0.1(13) | 11.5(13) | 5.1(13) |
| C00I | 24.8(16) | 17.6(14) | 22.6(15) | -1.8(12) | 6.9(13) | 2.9(12) |
| C00J | 27.0(17) | 16.0(15) | 45(2) | 4.7(15) | 18.7(15) | 1.4(13) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C00K | 19.2(16) | 19.4(15) | 54(2) | -11.9(16) | 17.5(15) | -5.4(12) |
| C00L | 20.9(17) | 33.5(18) | 30.0(17) | -8.1(15) | 3.6(14) | 3.2(13) |

**Table 9**: Bond Lengths in Å for **2016sot0090_R1_100K**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| Cl01 | C00G | 1.798(3) | C008 | C00F | 1.373(4) |
| O002 | C006 | 1.359(3) | C009 | C00D | 1.501(4) |
| O002 | C008 | 1.416(3) | C00A | C00E | 1.537(4) |
| O003 | C006 | 1.206(3) | C00B | C00I | 1.519(4) |
| O004 | C009 | 1.246(3) | C00C | C00L | 1.388(4) |
| N005 | C007 | 1.466(3) | C00D | C00E | 1.527(4) |
| N005 | C009 | 1.334(4) | C00F | C00J | 1.384(4) |
| C006 | C00A | 1.505(4) | C00G | C00H | 1.516(4) |
| C007 | C00A | 1.533(4) | C00H | C00I | 1.520(4) |
| C007 | C00B | 1.523(4) | C00J | C00K | 1.374(5) |
| C008 | C00C | 1.371(4) | C00K | C00L | 1.391(5) |

**Table 10**: Bond Angles in ° for **2016sot0090_R1_100K**.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|---|---|---|
| C006 | O002 | C008 | 117.5(2) | C00C | C008 | C00F | 122.0(3) |
| C009 | N005 | C007 | 127.0(2) | C00F | C008 | O002 | 119.7(3) |
| O002 | C006 | C00A | 111.4(2) | O004 | C009 | N005 | 121.1(3) |
| O003 | C006 | O002 | 122.4(3) | O004 | C009 | C00D | 119.9(3) |
| O003 | C006 | C00A | 126.2(3) | N005 | C009 | C00D | 118.9(2) |
| N005 | C007 | C00A | 110.4(2) | C006 | C00A | C007 | 111.4(2) |
| N005 | C007 | C00B | 108.3(2) | C006 | C00A | C00E | 111.8(2) |
| C00B | C007 | C00A | 116.0(2) | C007 | C00A | C00E | 108.4(2) |
| C00C | C008 | O002 | 118.2(3) | C00I | C00B | C007 | 113.7(2) |

| Atom | Atom | Atom | Angle/° |
|------|------|------|---------|
| C008 | C00C | C00L | 118.8(3) |
| C009 | C00D | C00E | 115.4(3) |
| C00D | C00E | C00A | 112.7(2) |
| C008 | C00F | C00J | 119.2(3) |
| C00H | C00G | Cl01 | 111.0(2) |
| C00G | C00H | C00I | 114.8(3) |
| C00B | C00I | C00H | 111.8(2) |
| C00K | C00J | C00F | 120.0(3) |
| C00J | C00K | C00L | 120.3(3) |
| C00C | C00L | C00K | 119.8(3) |

**Table 11**: Hydrogen Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **2016sot0090_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H005 | 5483.87 | 8336.55 | 5108.3 | 22 |
| H007 | 5863.8 | 3888.6 | 5409.59 | 21 |
| H00A | 6905.2 | 3345.67 | 6636.41 | 20 |
| H00B | 6274.05 | 6627.07 | 4505.54 | 24 |
| H00C | 6957.6 | 7504.38 | 5337.32 | 24 |
| H00D | 8889.33 | 6385.04 | 8644.32 | 27 |
| H00E | 5054.74 | 6110.58 | 7127.06 | 26 |
| H00F | 5767.46 | 7927.25 | 7468.47 | 26 |
| H00G | 5741.2 | 2991.88 | 6861 | 24 |
| H00H | 6332.24 | 4201.79 | 7710.65 | 24 |
| H00I | 8185.23 | 10201.42 | 6396.54 | 28 |
| H00J | 8078.13 | 2961.23 | 3562.99 | 28 |
| H00K | 7555.9 | 1010.52 | 3843.31 | 28 |
| H00L | 7077.79 | 5157.45 | 3742.78 | 29 |
| H00M | 7832.02 | 5975.01 | 4497.18 | 29 |
| H00N | 6782.62 | 2455.65 | 4755.75 | 26 |
| H00O | 7502.35 | 3556.88 | 5502.39 | 26 |
| H00P | 9170.46 | 13064.02 | 6953 | 33 |
| H00Q | 9995.32 | 12636.85 | 8361.77 | 35 |
| H00R | 9871.01 | 9273.34 | 9210.03 | 35 |

**Citations**

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

## B.1.3    *Syn,syn*-double imino-aldol product 2.2
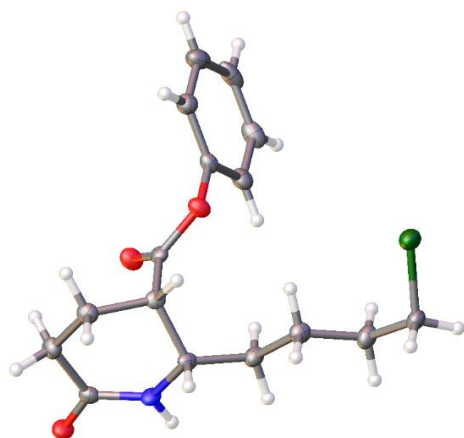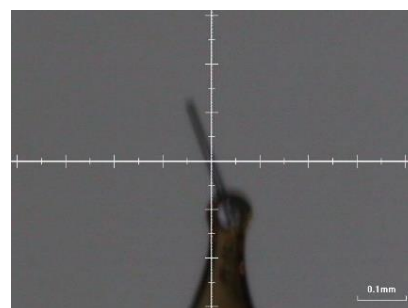
**Crystal Data and Experimental**
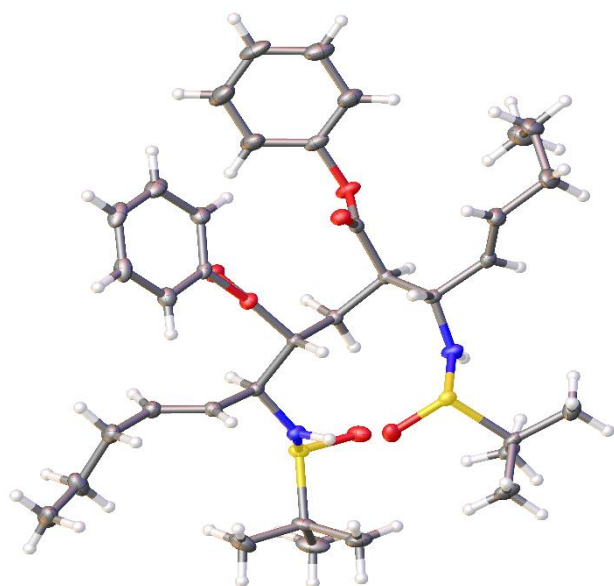


**Figure 3**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless Fragment-shaped crystals of (**2015sot0012**) were recrystallised from hexane by slow evaporation. A suitable crystal (0.20×0.14×0.02) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

**Crystal Data.** $C_{37}H_{54}N_2O_6S_2$, $M_r$ = 686.94, tetragonal, $P4_32_12$ (No. 96), a = 12.99897 Å, b = 12.99897 Å, c = 45.5533 Å, $\alpha$ = $\beta$ = $\gamma$ = 90°, $V$ = 7697.3(2) Å$^3$, $T$ = 100(2) K, $Z$ = 8, $Z'$ = 1, $\mu$(MoK$_\alpha$) = 0.183, 79518 reflections measured, 12692 unique ($R_{int}$ = 0.0611) which were used in all calculations. The final $wR_2$ was 0.0964 (all data) and $R_1$ was 0.0504 (I > 2(I)).
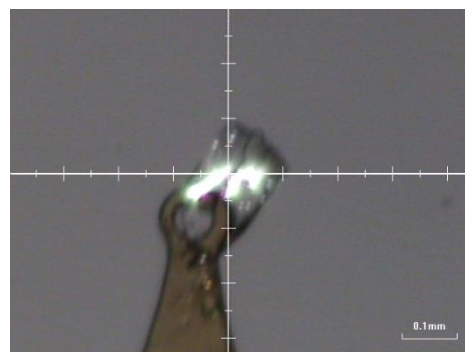


| Compound | 2015sot0012 |
|---|---|
| Formula | $C_{37}H_{54}N_2O_6S_2$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.186 |
| $\mu$/mm$^{-1}$ | 0.183 |
| Formula Weight | 686.94 |
| Colour | clear colourless |
| Shape | Fragment |
| Max Size/mm | 0.20 |
| Mid Size/mm | 0.14 |
| Min Size/mm | 0.02 |
| $T$/K | 100(2) |
| Crystal System | tetragonal |
| Flack Parameter | 0.00(2) |
| Hooft Parameter | 0.004(17) |
| Space Group | $P4_32_12$ |
| a/Å | 12.99897(14) |
| b/Å | 12.99897(14) |
| c/Å | 45.5533(8) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| V/Å$^3$ | 7697.3(2) |
| Z | 8 |
| Z' | 1 |
| $\Theta_{min}$/° | 1.629 |
| $\Theta_{max}$/° | 32.085 |
| Measured Refl. | 79518 |
| Independent Refl. | 12692 |
| Reflections Used | 11093 |
| $R_{int}$ | 0.0611 |
| Parameters | 440 |
| Restraints | 0 |
| Largest Peak | 0.337 |
| Deepest Hole | -0.331 |
| GooF | 1.076 |
| $wR_2$ (all data) | 0.0964 |
| $wR_2$ | 0.0928 |
| $R_1$ (all data) | 0.0622 |
| $R_1$ | 0.0504 |

**Structure Quality Indicators**

**Reflections:**

| d min | 0.67 | I/σ | 20.3 | Rint | 6.11% | complete at 2θ=64° | 94% |

**Refinement:**

| Shift/esd | 0.002 | Max Peak | 0.3 | Min Peak | -0.3 | GooF | 1.076 |

A clear colourless Fragment-shaped crystal with dimensions 0.20×0.14×0.02 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 15.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 32.085.

Cell parameters were retrieved using the **CrysAlisPro** (Agilent, V1.171.37.31, 2014) software and refined using **CrysAlisPro** (Agilent, V1.171.37.31, 2014) on 23670 reflections, 30 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Agilent, V1.171.37.31, 2014) software which corrects for Lorentz polarisation. The final completeness is 100.00 out to 32.085 in $\Theta$. The absorption coefficient ($\mu$) of this material is 0.183 and the minimum and maximum transmissions are 0.89375 and 1.00000.

The structure was solved in the space group P4$_3$2$_1$2 (# 96) by Direct Methods using the ShelXT (Sheldrick, 2015) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model, with the exception of the N-H which were freely refined.

The Flack parameter was refined to 0.00(2), confirming the absolute stereochemistry. Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.004(17). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

**Data Plots: Diffraction Data**

Appendices



Systematic Absences Intensity Distribution — 2015sot0012



Completeness Plot — 2015sot0012

## Data Plots: Refinement and Data



Fobs vs Fcalc — 2015sot0012

y = 0.974x + 0.292



Normal probability plot — 2015sot0012

y = 0.511x + 0.111
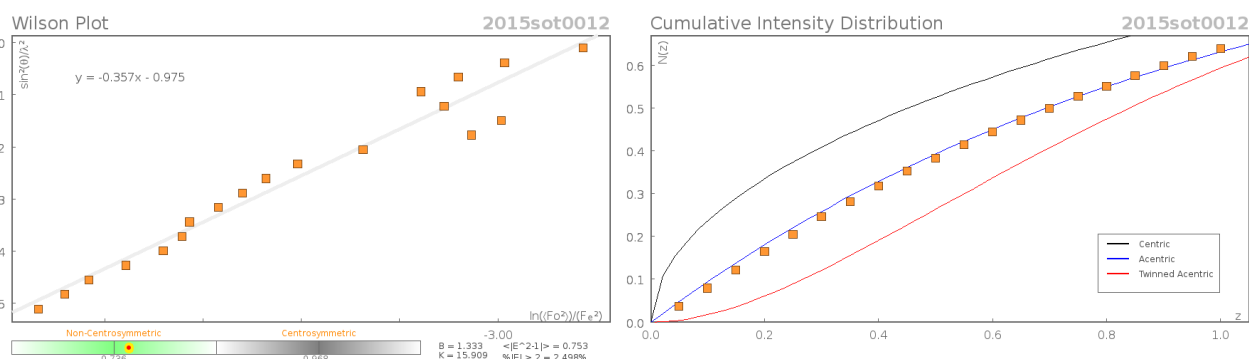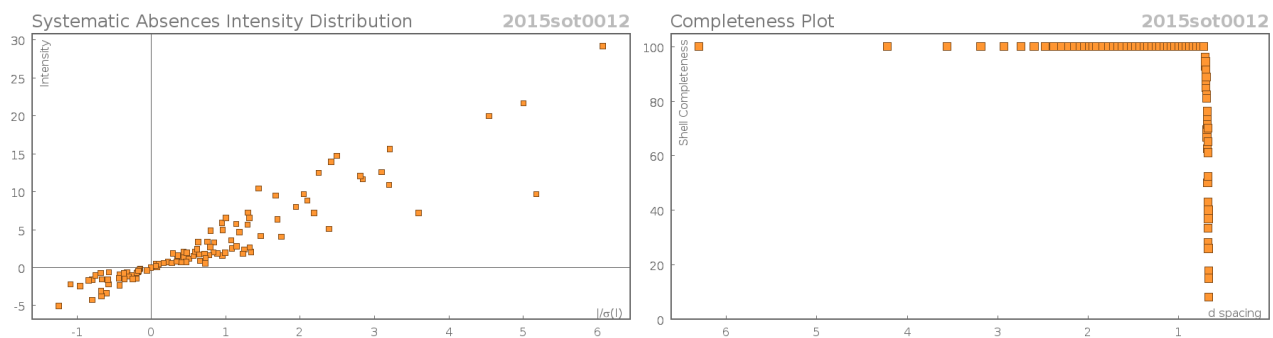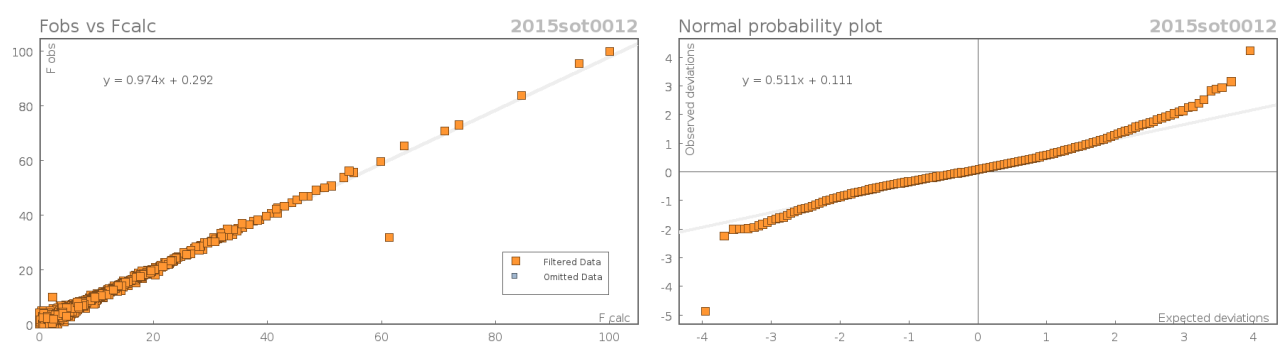
### Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections | 79647 | Unique reflections | 12692 |
| Completeness | 0.941 | Mean I/sigma | 20.33 |
| Max hkl collected | (19, 19, 67) | Min hkl collected | (-19, -19, -68) |
| Max hkl used | (13, 19, 68) | Min hkl used | (-12, 0, 0) |
| Lim d max | 100.0 | Lim d min | 0.36 |
| d max used | 12.5 | d min used | 0.67 |
| Friedel pairs | 24835 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 45 | $R_{int}$ | 0.0611 |
| $R_{\sigma}$ | 0.0471 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user | 0 |
| Multiplicity | (49546, 13012, 1343, 12) | ReflectionAPotMax | 21 |
| Removed Systematic Absences | 129 | Filtered Off | 0 |

**Table 12**: Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2015sot0012**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| S1 | 1867.3(4) | 671.9(4) | 4126.5(2) | 15.16(10) |
| S2 | 3449.7(4) | 30.1(4) | 5122.5(2) | 16.31(10) |
| O2 | 3884.9(12) | 4027.4(12) | 4161.1(3) | 18.1(3) |
| O1 | 3416.5(13) | 4836.6(12) | 4577.6(4) | 21.4(4) |
| O6 | 2402.0(13) | 489.9(12) | 5164.5(4) | 22.1(4) |
| O3 | 5377.9(12) | 2209.1(12) | 4133.1(3) | 16.0(3) |
| O4 | 5593.5(13) | 2976.6(13) | 4576.0(3) | 19.2(3) |
| O5 | 2656.0(12) | -14.2(13) | 4264.8(3) | 20.8(3) |
| N1 | 1669.2(15) | 1717.1(15) | 4318.4(4) | 17.3(4) |
| N2 | 3822.7(15) | 146.7(15) | 4780.6(4) | 15.9(4) |
| C1 | 5100(2) | 5601(2) | 4586.7(6) | 30.3(6) |
| C2 | 5745(2) | 6415(2) | 4517.0(7) | 38.6(7) |
| C3 | 5371(2) | 7251(2) | 4364.6(6) | 34.0(6) |
| C4 | 4349(2) | 7291(2) | 4281.0(6) | 35.0(6) |
| C5 | 3697(2) | 6477(2) | 4349.5(6) | 30.6(6) |
| C6 | 4084.8(19) | 5650.9(19) | 4500.8(5) | 22.3(5) |
| C7 | 3403.3(17) | 4034.6(16) | 4385.8(4) | 14.6(4) |
| C8 | 2739.9(16) | 3161.5(16) | 4498.4(4) | 13.2(4) |
| C9 | 3404.4(17) | 2397.8(17) | 4676.8(4) | 14.6(4) |
| C10 | 4202.8(16) | 1771.0(16) | 4509.0(4) | 13.0(4) |
| C11 | 5123.9(17) | 2409.1(16) | 4417.9(4) | 14.5(4) |
| C12 | 6278.9(16) | 2652.6(18) | 4019.8(4) | 16.3(4) |
| C13 | 6988.6(18) | 1981(2) | 3903.4(5) | 21.4(5) |
| C14 | 7883.6(19) | 2366(2) | 3778.1(5) | 26.5(6) |
| C15 | 8048.5(19) | 3416(2) | 3774.2(5) | 29.2(6) |
| C16 | 7323(2) | 4081(2) | 3890.1(5) | 28.3(6) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C17 | 6419.5(19) | 3703.4(19) | 4013.2(5) | 21.8(5) |
| C18 | 2144.5(17) | 2694.2(17) | 4235.4(4) | 14.6(4) |
| C19 | 1331.3(17) | 3451.3(17) | 4137.7(5) | 17.6(4) |
| C20 | 1430.0(19) | 4153.4(19) | 3928.7(5) | 22.7(5) |
| C21 | 637(2) | 4954(2) | 3855.7(6) | 29.3(6) |
| C22 | 876(2) | 6013(2) | 3986.7(6) | 32.7(6) |
| C23 | 750(2) | 6040(2) | 4319.3(6) | 35.7(6) |
| C24 | 630.1(18) | 23.2(18) | 4195.4(5) | 18.5(4) |
| C25 | -177.3(18) | 602(2) | 4017.7(5) | 26.1(5) |
| C26 | 781(2) | -1069.5(18) | 4077.5(5) | 25.5(5) |
| C27 | 393.3(19) | 11.4(19) | 4524.3(5) | 21.4(5) |
| C28 | 4632.7(16) | 883.0(16) | 4703.3(5) | 14.7(4) |
| C29 | 5485.3(17) | 311.8(17) | 4548.6(5) | 16.3(4) |
| C30 | 6448.5(18) | 249.4(18) | 4637.8(5) | 20.1(4) |
| C31 | 7253.5(19) | -390.1(19) | 4488.7(6) | 24.1(5) |
| C32 | 7581(2) | -1313(2) | 4675.1(6) | 29.8(6) |
| C33 | 8211(2) | -2107(2) | 4508.1(7) | 31.9(6) |
| C34 | 3252(2) | -1378.1(17) | 5142.0(5) | 21.4(5) |
| C35 | 2507(2) | -1741.7(19) | 4908.2(6) | 28.9(6) |
| C36 | 2807(3) | -1561(2) | 5448.1(6) | 35.0(7) |
| C37 | 4309(2) | -1871(2) | 5111.9(6) | 32.9(6) |

**Table 13**: Anisotropic Displacement Parameters (×10$^4$) **2015sot0012**. The anisotropic displacement factor exponent takes the form: *-2$\pi^2$[h$^2$a*$^2$ × U$_{11}$+ ... +2hka* × b* × U$_{12}$]*

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| S1 | 16.8(2) | 15.6(2) | 13.1(2) | -2.51(19) | 0.92(19) | -2.6(2) |
| S2 | 22.0(3) | 14.9(2) | 12.09(19) | 0.86(19) | 2.8(2) | 0.0(2) |
| O2 | 18.8(8) | 19.0(8) | 16.6(7) | 0.3(6) | 3.6(6) | -2.8(6) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O1 | 25.6(9) | 17.8(8) | 20.9(8) | -6.3(6) | 8.5(7) | -8.6(7) |
| O6 | 26.8(9) | 17.9(8) | 21.6(8) | 0.6(6) | 8.4(7) | 1.6(7) |
| O3 | 15.0(7) | 19.9(8) | 13.1(6) | 0.0(6) | 3.7(6) | -2.7(6) |
| O4 | 19.1(8) | 21.4(8) | 17.2(7) | -1.7(6) | -0.5(6) | -4.5(7) |
| O5 | 19.5(8) | 21.3(8) | 21.8(7) | -5.5(7) | -3.5(6) | 1.6(7) |
| N1 | 21.7(10) | 14.6(9) | 15.7(8) | -1.9(7) | 7.3(7) | -4.4(7) |
| N2 | 18.3(9) | 17.6(9) | 11.8(7) | 0.6(7) | 0.4(7) | -2.8(7) |
| C1 | 27.0(13) | 19.7(12) | 44.2(15) | -3.9(11) | 5.4(12) | -4.3(11) |
| C2 | 27.0(14) | 29.7(15) | 59.0(19) | -9.1(14) | 8.4(14) | -9.2(12) |
| C3 | 37.7(15) | 26.8(13) | 37.6(14) | -7.9(12) | 17.0(12) | -17.6(12) |
| C4 | 47.6(17) | 25.7(13) | 31.6(13) | 2.4(11) | 0.6(13) | -12.6(13) |
| C5 | 34.0(14) | 27.4(13) | 30.5(13) | -0.4(11) | -3.4(11) | -10.8(11) |
| C6 | 26.3(12) | 18.3(11) | 22.3(11) | -6.9(9) | 8.0(9) | -8.3(10) |
| C7 | 13.3(9) | 15.3(9) | 15.1(9) | 0.2(8) | -1.3(8) | 1.4(8) |
| C8 | 12.8(9) | 14.1(9) | 12.8(8) | -0.6(8) | 1.8(7) | -0.2(8) |
| C9 | 14.5(9) | 15.9(10) | 13.3(9) | 0.7(8) | 2.4(8) | 0.2(8) |
| C10 | 13.5(9) | 13.8(9) | 11.5(8) | -0.1(7) | 0.8(7) | -1.5(8) |
| C11 | 14.7(10) | 15.1(10) | 13.7(8) | 1.0(8) | 0.8(8) | 1.6(8) |
| C12 | 12.4(10) | 24.4(11) | 12.0(8) | 3.5(8) | 0.7(7) | -2.9(8) |
| C13 | 19.1(11) | 28.6(13) | 16.6(10) | 1.6(9) | 2.5(9) | 1.8(9) |
| C14 | 16.8(11) | 44.9(16) | 17.7(10) | 2.2(11) | 2.8(9) | 2.5(11) |
| C15 | 18.5(11) | 51.0(17) | 17.9(10) | 9.5(11) | 1.7(9) | -10.0(12) |
| C16 | 27.8(13) | 31.4(14) | 25.7(12) | 10.1(11) | -0.5(10) | -9.6(11) |
| C17 | 20.4(11) | 23.4(12) | 21.5(10) | 5.6(9) | 2.0(9) | -0.5(9) |
| C18 | 15.9(10) | 15.1(10) | 12.7(9) | -0.6(8) | 2.1(8) | -2.6(8) |
| C19 | 14.9(10) | 20.4(10) | 17.4(9) | -1.5(9) | -0.9(8) | -2.8(9) |
| C20 | 21.4(12) | 25.9(12) | 20.7(10) | 3.0(9) | -1.9(9) | -1.1(10) |
| C21 | 27.5(13) | 30.8(13) | 29.7(12) | 9.3(11) | -9.4(11) | -0.9(12) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C22 | 33.9(15) | 24.5(13) | 39.7(15) | 12.4(12) | -8.8(12) | 1.0(11) |
| C23 | 39.4(16) | 27.9(14) | 39.9(15) | 2.0(12) | 2.3(13) | 5.4(13) |
| C24 | 18.4(10) | 18.5(10) | 18.6(9) | -2.2(9) | 1.3(8) | -7.7(9) |
| C25 | 19.7(12) | 33.2(14) | 25.4(11) | -0.3(11) | -4.5(9) | -3.5(10) |
| C26 | 33.5(14) | 19.8(11) | 23.2(11) | -5.3(9) | 2.5(10) | -10.4(10) |
| C27 | 22.4(11) | 22.0(11) | 19.7(10) | -1.2(9) | 3.4(9) | -7.6(10) |
| C28 | 14.6(9) | 15.2(10) | 14.4(9) | 0.8(8) | 0.1(8) | -2.0(8) |
| C29 | 17.4(10) | 16.4(10) | 14.9(9) | 0.8(8) | 1.7(8) | 0.6(8) |
| C30 | 18.6(11) | 19.3(11) | 22.4(10) | -0.8(9) | 0.5(9) | -0.3(9) |
| C31 | 16.4(11) | 25.3(12) | 30.7(12) | -0.5(10) | 2.4(9) | -0.4(10) |
| C32 | 28.8(14) | 32.8(14) | 27.9(12) | -4.3(11) | -7.6(11) | 9.8(11) |
| C33 | 22.5(13) | 27.5(14) | 45.7(16) | -8.7(12) | -3.0(12) | 3.1(11) |
| C34 | 31.3(13) | 13(1) | 19.7(10) | 5.2(8) | 5.4(10) | 3.1(9) |
| C35 | 37.2(15) | 16.1(11) | 33.4(13) | 3(1) | 1.1(11) | -6.2(11) |
| C36 | 55.1(19) | 23.3(13) | 26.7(12) | 9.4(11) | 14.4(13) | 2.3(13) |
| C37 | 38.7(15) | 22.9(12) | 37.0(14) | 2.9(11) | 0.4(13) | 11.4(12) |

**Table 14**: Bond Lengths in Å for **2015sot0012**.

| Atom | Atom | Length/Å | | Atom | Atom | Length/Å |
|---|---|---|---|---|---|---|
| S1 | O5 | 1.4978(17) | | O3 | C11 | 1.363(2) |
| S1 | N1 | 1.6358(19) | | O3 | C12 | 1.404(3) |
| S1 | C24 | 1.843(2) | | O4 | C11 | 1.198(3) |
| S2 | O6 | 1.4994(18) | | N1 | C18 | 1.462(3) |
| S2 | N2 | 1.6384(18) | | N2 | C28 | 1.466(3) |
| S2 | C34 | 1.851(2) | | C1 | C2 | 1.388(4) |
| O2 | C7 | 1.200(3) | | C1 | C6 | 1.377(4) |
| O1 | C6 | 1.413(3) | | C2 | C3 | 1.378(4) |
| O1 | C7 | 1.360(3) | | C3 | C4 | 1.382(4) |

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|----------|------|------|----------|
| C4 | C5 | 1.392(4) | C19 | C20 | 1.325(3) |
| C5 | C6 | 1.371(4) | C20 | C21 | 1.502(4) |
| C7 | C8 | 1.515(3) | C21 | C22 | 1.532(4) |
| C8 | C9 | 1.547(3) | C22 | C23 | 1.525(4) |
| C8 | C18 | 1.550(3) | C24 | C25 | 1.524(3) |
| C9 | C10 | 1.525(3) | C24 | C26 | 1.531(3) |
| C10 | C11 | 1.515(3) | C24 | C27 | 1.530(3) |
| C10 | C28 | 1.558(3) | C28 | C29 | 1.509(3) |
| C12 | C13 | 1.376(3) | C29 | C30 | 1.319(3) |
| C12 | C17 | 1.378(3) | C30 | C31 | 1.499(3) |
| C13 | C14 | 1.389(3) | C31 | C32 | 1.530(4) |
| C14 | C15 | 1.382(4) | C32 | C33 | 1.522(4) |
| C15 | C16 | 1.384(4) | C34 | C35 | 1.515(4) |
| C16 | C17 | 1.392(3) | C34 | C36 | 1.529(3) |
| C18 | C19 | 1.511(3) | C34 | C37 | 1.523(4) |

**Table 15**: Bond Angles in ° for **2015sot0012**.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|------|------|------|---------|
| O5 | S1 | N1 | 112.19(10) | C18 | N1 | S1 | 121.13(14) |
| O5 | S1 | C24 | 104.68(10) | C28 | N2 | S2 | 120.09(15) |
| N1 | S1 | C24 | 98.73(10) | C6 | C1 | C2 | 118.5(3) |
| O6 | S2 | N2 | 110.68(10) | C3 | C2 | C1 | 120.2(3) |
| O6 | S2 | C34 | 105.20(11) | C2 | C3 | C4 | 120.5(3) |
| N2 | S2 | C34 | 100.26(10) | C3 | C4 | C5 | 119.6(3) |
| C7 | O1 | C6 | 114.99(17) | C6 | C5 | C4 | 119.0(3) |
| C11 | O3 | C12 | 118.27(17) | C1 | C6 | O1 | 118.9(2) |

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|------|------|------|---------|
| C5 | C6 | O1 | 119.0(2) | C19 | C18 | C8 | 108.77(17) |
| C5 | C6 | C1 | 122.1(2) | C20 | C19 | C18 | 126.3(2) |
| O2 | C7 | O1 | 123.2(2) | C19 | C20 | C21 | 124.7(2) |
| O2 | C7 | C8 | 125.4(2) | C20 | C21 | C22 | 113.4(2) |
| O1 | C7 | C8 | 111.34(17) | C23 | C22 | C21 | 112.7(2) |
| C7 | C8 | C9 | 109.92(17) | C25 | C24 | S1 | 106.54(16) |
| C7 | C8 | C18 | 108.44(16) | C25 | C24 | C26 | 111.1(2) |
| C9 | C8 | C18 | 115.69(18) | C25 | C24 | C27 | 112.7(2) |
| C10 | C9 | C8 | 117.36(17) | C26 | C24 | S1 | 104.65(16) |
| C9 | C10 | C28 | 110.80(16) | C27 | C24 | S1 | 110.29(15) |
| C11 | C10 | C9 | 112.51(17) | C27 | C24 | C26 | 111.1(2) |
| C11 | C10 | C28 | 106.13(17) | N2 | C28 | C10 | 111.26(17) |
| O3 | C11 | C10 | 110.35(17) | N2 | C28 | C29 | 108.57(18) |
| O4 | C11 | O3 | 124.5(2) | C29 | C28 | C10 | 111.26(17) |
| O4 | C11 | C10 | 125.12(19) | C30 | C29 | C28 | 125.7(2) |
| C13 | C12 | O3 | 116.1(2) | C29 | C30 | C31 | 123.9(2) |
| C13 | C12 | C17 | 122.1(2) | C30 | C31 | C32 | 112.2(2) |
| C17 | C12 | O3 | 121.7(2) | C33 | C32 | C31 | 113.8(2) |
| C12 | C13 | C14 | 119.5(2) | C35 | C34 | S2 | 111.32(16) |
| C15 | C14 | C13 | 119.4(2) | C35 | C34 | C36 | 110.5(2) |
| C14 | C15 | C16 | 120.4(2) | C35 | C34 | C37 | 112.5(2) |
| C15 | C16 | C17 | 120.5(3) | C36 | C34 | S2 | 104.47(17) |
| C12 | C17 | C16 | 118.1(2) | C37 | C34 | S2 | 106.67(18) |
| N1 | C18 | C8 | 110.59(17) | C37 | C34 | C36 | 111.0(2) |
| N1 | C18 | C19 | 110.26(18) | | | | |

**Table 16**: Hydrogen Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2015sot0012**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|-----|------|------|-----|
| H1A | 5347 | 5033 | 4689 | 36 |
| H2A | 6432 | 6397 | 4573 | 46 |
| H3 | 5809 | 7792 | 4318 | 41 |
| H4 | 4099 | 7859 | 4179 | 42 |
| H5 | 3009 | 6492 | 4294 | 37 |
| H8 | 2232 | 3458 | 4633 | 16 |
| H9A | 3760 | 2783 | 4828 | 17 |
| H9B | 2945 | 1921 | 4775 | 17 |
| H10 | 3881 | 1477 | 4333 | 16 |
| H13 | 6870 | 1276 | 3909 | 26 |
| H14 | 8367 | 1921 | 3697 | 32 |
| H15 | 8651 | 3678 | 3693 | 35 |
| H16 | 7441 | 4787 | 3886 | 34 |
| H17 | 5925 | 4147 | 4089 | 26 |
| H18 | 2625 | 2575 | 4073 | 17 |
| H19 | 700 | 3421 | 4234 | 21 |
| H20 | 2034 | 4150 | 3819 | 27 |
| H21A | -27 | 4725 | 3928 | 35 |
| H21B | 588 | 5017 | 3644 | 35 |
| H22A | 1577 | 6200 | 3937 | 39 |
| H22B | 422 | 6519 | 3899 | 39 |
| H23A | 53 | 5869 | 4369 | 54 |
| H23B | 907 | 6717 | 4390 | 54 |
| H23C | 1208 | 5550 | 4407 | 54 |
| H25A | -223 | 1298 | 4087 | 39 |
| H25B | -833 | 271 | 4040 | 39 |

Appendices

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H25C | 15 | 602 | 3814 | 39 |
| H26A | 991 | -1038 | 3876 | 38 |
| H26B | 146 | -1443 | 4092 | 38 |
| H26C | 1302 | -1413 | 4190 | 38 |
| H27A | 999 | -187 | 4631 | 32 |
| H27B | -149 | -472 | 4563 | 32 |
| H27C | 182 | 686 | 4586 | 32 |
| H28 | 4909 | 1180 | 4885 | 18 |
| H29 | 5317 | -26 | 4375 | 20 |
| H30 | 6640 | 624 | 4803 | 24 |
| H31A | 7851 | 35 | 4449 | 29 |
| H31B | 6987 | -634 | 4302 | 29 |
| H32A | 7982 | -1067 | 4840 | 36 |
| H32B | 6969 | -1644 | 4753 | 36 |
| H33B | 7822 | -2354 | 4343 | 48 |
| H33C | 8372 | -2672 | 4636 | 48 |
| H33A | 8837 | -1797 | 4440 | 48 |
| H35A | 1863 | -1389 | 4931 | 43 |
| H35B | 2400 | -2469 | 4928 | 43 |
| H35C | 2787 | -1597 | 4717 | 43 |
| H36A | 3262 | -1276 | 5593 | 53 |
| H36B | 2732 | -2286 | 5481 | 53 |
| H36C | 2146 | -1234 | 5463 | 53 |
| H37A | 4579 | -1735 | 4920 | 49 |
| H37B | 4252 | -2601 | 5140 | 49 |
| H37C | 4765 | -1589 | 5257 | 49 |
| H1 | 1340(20) | 1700(20) | 4469(6) | 24(7) |
| H2 | 3370(30) | 0(30) | 4651(7) | 41(9) |

**Table 17**: Hydrogen Bond information for **2015sot0012**.

| D | H | A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/deg |
|---|---|---|---|---|---|---|
| N2 | H2 | O5 | 0.85(3) | 1.99(3) | 2.804(2) | 159(3) |

**Citations**

CrysAlisPro Software System, Agilent Technologies UK Ltd, Yarnton, Oxford, UK (2014).

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

Appendices

## B.1.4 (+)-10,17-dioxo-$\beta$-isosparteine ((+)-1.4)

**Crystal Data and Experimental**
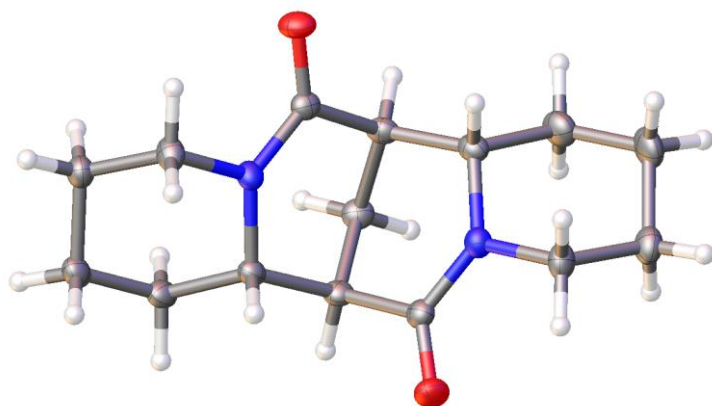


**Figure 4**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless prism-shaped crystals of (**2015sot0075-K-100K**) were recrystallised from DMSO by slow evaporation. A suitable crystal (0.23×0.07×0.04) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

**Crystal Data.** $C_{15}H_{22}N_2O_2$, $M_r$ = 262.34, orthorhombic, P2$_1$2$_1$2$_1$ (No. 19), a = 6.08925(15) Å, b = 10.1967(2) Å, c = 21.7891(7) Å, $\alpha = \beta = \gamma = 90°$, $V$ = 1352.89(6) Å$^3$, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(MoK$_\alpha$) = 0.086, 13342 reflections measured, 3496 unique ($R_{int}$ = 0.0305) which were used in all calculations. The final $wR_2$ was 0.0855 (all data) and $R_1$ was 0.0377 (I > 2(I)).
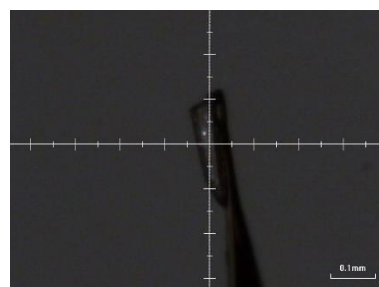
| Compound | 2015sot0075-K-100 K |
|---|---|
| Formula | $C_{15}H_{22}N_2O_2$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.288 |
| $\mu$/mm$^{-1}$ | 0.086 |
| Formula Weight | 262.34 |
| Colour | clear colourless |
| Shape | prism |
| Max Size/mm | 0.23 |
| Mid Size/mm | 0.07 |
| Min Size/mm | 0.04 |
| $T$/K | 100(2) |
| Crystal System | orthorhombic |
| Friediff Mo, Cu | 5, 28 |
| Flack Parameter | 0.2(6) |
| Hooft Parameter | 0.8(4) |
| Space Group | P2$_1$2$_1$2$_1$ |
| $a$/Å | 6.08925(15) |
| $b$/Å | 10.1967(2) |
| $c$/Å | 21.7891(7) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| V/Å$^3$ | 1352.89(6) |
| Z | 4 |
| Z' | 1 |
| $\Theta_{min}$/° | 3.444 |
| $\Theta_{max}$/° | 28.697 |
| Measured Refl. | 13342 |
| Independent Refl. | 3496 |
| Reflections Used | 3173 |
| $R_{int}$ | 0.0305 |
| Parameters | 172 |
| Restraints | 0 |
| Largest Peak | 0.212 |
| Deepest Hole | -0.168 |
| GooF | 1.023 |
| $wR_2$ (all data) | 0.0855 |
| $wR_2$ | 0.0825 |
| $R_1$ (all data) | 0.0436 |
| $R_1$ | 0.0377 |

**Structure Quality Indicators**

**Reflections:**

| d min | | I/σ | | Rint | | complete at 2θ=61° | |
|---|---|---|---|---|---|---|---|
| | 0.74 | | 25.5 | | 3.05% | | 100% |

**Refinement:**

| Shift | | Max Peak | | Min Peak | | GooF | |
|---|---|---|---|---|---|---|---|
| | 0.000 | | 0.2 | | -0.2 | | 1.023 |

A clear colourless prism-shaped crystal with dimensions 0.23×0.07×0.04 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from scans of 10.0° per frame for 1.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 28.697.

Cell parameters were retrieved using the CrysAlisPro (Agilent) software and refined using CrysAlisPro (Agilent) on 8106 reflections, 61 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent) software that corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.697 in $\Theta$. The absorption coefficient ($\mu$) of this material is 0.086 and the minimum and maximum transmissions are 0.80173 and 1.00000.

The structure was solved in the space group P2$_1$2$_1$2$_1$ (# 19) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using **ShelXL** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

The Flack parameter was refined to 0.2(6). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.8(4). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

**Generated precession images**



0kl

h0l

hk0
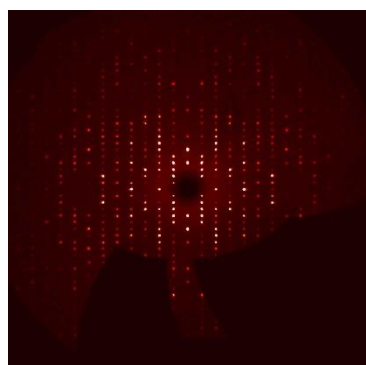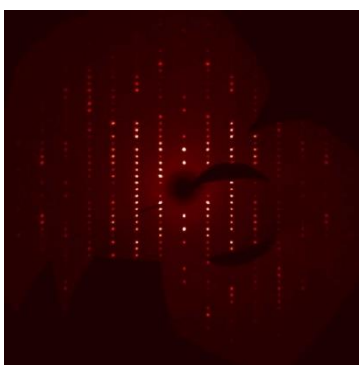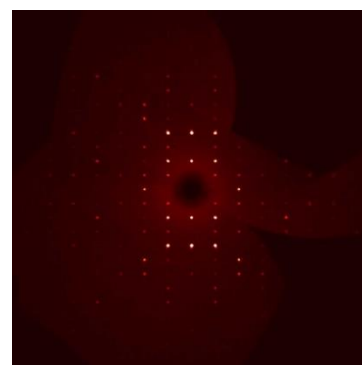
# Appendices

## Data Plots: Diffraction Data
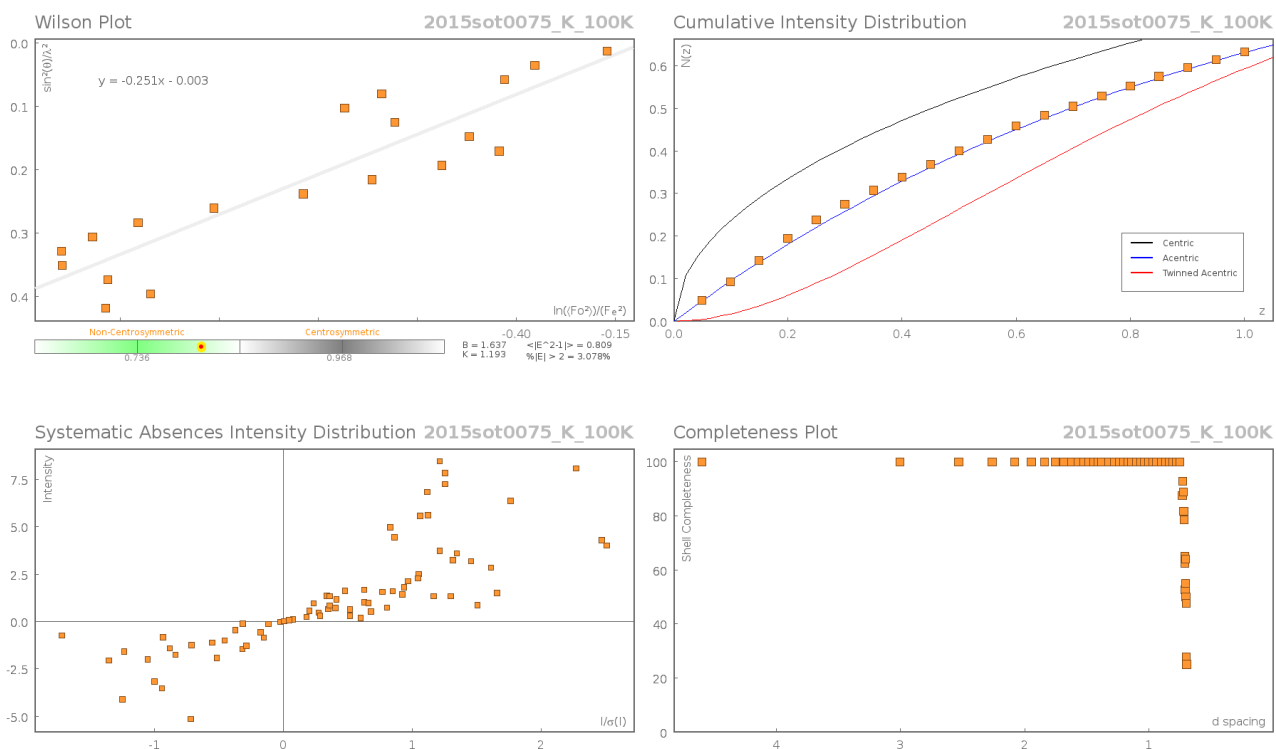


## Data Plots: Refinement and Data
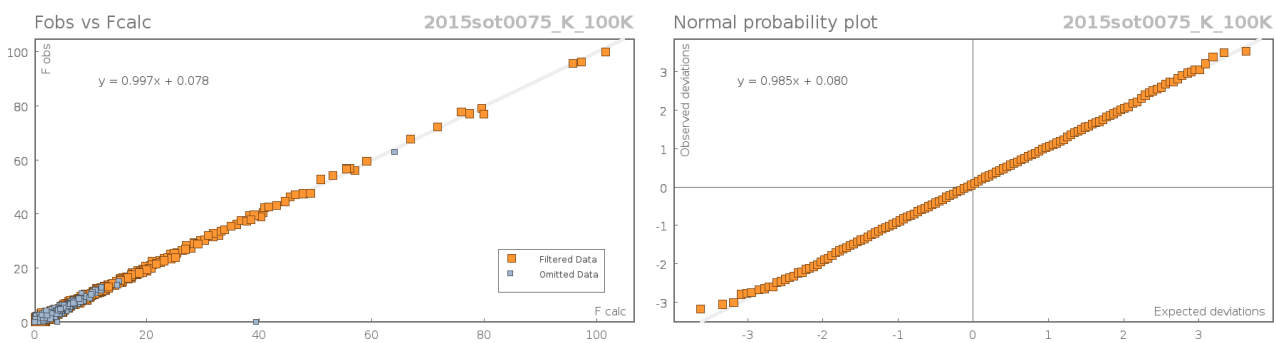


## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 13413 | Unique reflections | 3496 |
| Completeness | 0.999 | Mean I/$\sigma$ | 25.5 |
| hkl$_{max}$ collected | (8, 13, 31) | hkl$_{min}$ collected | (-8, -14, -27) |
| hkl$_{max}$ used | (8, 13, 29) | hkl$_{min}$ used | (-8, 0, 0) |
| Lim d$_{max}$ collected | 7.0 | Lim d$_{min}$ collected | 0.74 |

| | | | |
|---|---|---|---|
| $d_{max}$ used | 6.09 | $d_{min}$ used | 0.74 |
| Friedel pairs | 2486 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 1 | $R_{int}$ | 0.0305 |
| $R_{sigma}$ | 0.0299 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (5041, 3799, 437, 24) | Maximum multiplicity | 13 |
| Removed systematic absences | 71 | Filtered off (Shel/OMIT) | 633 |

**Table 18**: Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2015sot0075_K_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 9480(2) | 5742.5(13) | 4771.9(6) | 26.0(3) |
| O2 | 5798(2) | 6708.8(14) | 2442.2(6) | 30.2(3) |
| N1 | 7169(2) | 4881.4(14) | 4061.1(7) | 18.5(3) |
| N2 | 7998(3) | 7603.1(14) | 3170.1(7) | 19.4(3) |
| C1 | 7887(3) | 3537.6(17) | 4193.9(9) | 23.0(4) |
| C2 | 5997(3) | 2754.3(18) | 4464.8(9) | 23.2(4) |
| C3 | 4038(3) | 2759.4(18) | 4031.2(9) | 22.9(4) |
| C4 | 3373(3) | 4168.6(19) | 3880.0(9) | 22.1(4) |
| C5 | 5317(3) | 4953.3(17) | 3627.2(8) | 17.9(3) |
| C6 | 4690(3) | 6378.1(17) | 3479.8(8) | 18.8(3) |
| C7 | 6205(3) | 6918.9(17) | 2985.7(8) | 19.4(4) |
| C8 | 9423(3) | 8211.5(17) | 2706.0(9) | 23.5(4) |
| C9 | 9290(3) | 9701.7(18) | 2752.9(9) | 27.4(4) |
| C10 | 9863(4) | 10149.6(19) | 3400.5(10) | 32.6(5) |
| C11 | 8410(4) | 9465.1(18) | 3874.6(10) | 29.4(4) |
| C12 | 8520(3) | 7972.8(17) | 3807.4(8) | 20.4(4) |
| C13 | 7071(3) | 7251.1(17) | 4273.1(8) | 19.5(4) |
| C14 | 7994(3) | 5889.0(17) | 4393.8(8) | 18.4(3) |
| C15 | 4706(3) | 7208.6(18) | 4056.2(8) | 20.9(4) |

Appendices

**Table 19**: Anisotropic Displacement Parameters (×10⁴) **2015sot0075_K_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \dots + 2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O1 | 24.7(7) | 29.2(7) | 24.1(7) | -1.1(5) | -8.6(6) | 2.6(6) |
| O2 | 36.8(8) | 35.6(8) | 18.2(7) | 1.5(6) | -3.6(6) | -9.1(7) |
| N1 | 15.1(7) | 16.9(7) | 23.5(7) | 1.3(6) | -1.3(6) | -0.2(6) |
| N2 | 20.1(7) | 17.0(7) | 21.0(7) | 0.3(6) | 1.1(6) | -0.2(6) |
| C1 | 19.6(8) | 17.4(8) | 32.1(10) | 2.7(8) | -0.7(8) | 1.5(7) |
| C2 | 26.6(9) | 18.7(8) | 24.2(9) | 1.9(7) | -0.9(8) | -3.2(8) |
| C3 | 22.9(9) | 23.9(8) | 22.1(9) | -0.2(7) | 0.7(7) | -6.9(7) |
| C4 | 18.3(8) | 26.9(9) | 21.0(9) | 1.5(7) | -1.8(7) | -4.7(7) |
| C5 | 17.1(8) | 19.5(8) | 17.0(8) | -1.2(7) | -0.8(7) | -2.1(7) |
| C6 | 15.2(8) | 20.9(8) | 20.3(8) | -0.4(7) | -3.5(7) | 1.5(7) |
| C7 | 21.4(9) | 16.4(8) | 20.5(8) | 1.3(7) | -2.1(7) | 2.0(7) |
| C8 | 23.4(9) | 19.2(8) | 28.1(10) | 3.4(7) | 4.8(8) | -1.0(8) |
| C9 | 28.1(10) | 19.4(9) | 34.9(11) | 6.4(8) | -0.3(9) | -0.1(8) |
| C10 | 38.7(12) | 16.2(9) | 42.7(12) | -0.8(8) | -2.8(10) | -4.2(8) |
| C11 | 36.0(11) | 18.9(9) | 33.3(11) | -5.0(8) | -3.9(9) | -0.5(8) |
| C12 | 19.5(9) | 18.1(8) | 23.4(9) | -1.8(7) | -3.9(7) | 1.6(7) |
| C13 | 19.4(8) | 20.5(8) | 18.5(8) | -4.8(7) | -2.2(7) | 2.2(7) |
| C14 | 15.8(7) | 21.9(8) | 17.6(8) | 0.1(7) | 1.7(6) | 0.5(7) |
| C15 | 18.1(8) | 22.5(8) | 22.0(9) | -1.5(7) | 1.0(7) | 3.6(7) |

**Table 20**: Bond Lengths in Å for **2015sot0075_K_100K**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| O1 | C14 | 1.233(2) | N2 | C8 | 1.470(2) |
| O2 | C7 | 1.229(2) | N2 | C12 | 1.474(2) |
| N1 | C1 | 1.467(2) | C1 | C2 | 1.520(3) |
| N1 | C5 | 1.474(2) | C2 | C3 | 1.522(3) |
| N1 | C14 | 1.354(2) | C3 | C4 | 1.529(3) |
| N2 | C7 | 1.356(2) | C4 | C5 | 1.531(2) |

| Atom | Atom | Length/Å |
|------|------|----------|
| C5 | C6 | 1.536(2) |
| C6 | C7 | 1.521(2) |
| C6 | C15 | 1.515(2) |
| C8 | C9 | 1.525(2) |
| C9 | C10 | 1.524(3) |

| Atom | Atom | Length/Å |
|------|------|----------|
| C10 | C11 | 1.529(3) |
| C11 | C12 | 1.530(3) |
| C12 | C13 | 1.532(3) |
| C13 | C14 | 1.521(2) |
| C13 | C15 | 1.517(2) |

**Table 21**: Bond Angles in ° for **2015sot0075_K_100K**.

| Atom | Atom | Atom | Angle/° |
|------|------|------|---------|
| C1 | N1 | C5 | 113.64(14) |
| C14 | N1 | C1 | 119.52(15) |
| C14 | N1 | C5 | 126.14(14) |
| C7 | N2 | C8 | 119.24(15) |
| C7 | N2 | C12 | 125.75(15) |
| C8 | N2 | C12 | 114.40(15) |
| N1 | C1 | C2 | 109.99(15) |
| C1 | C2 | C3 | 110.52(15) |
| C2 | C3 | C4 | 110.16(15) |
| C3 | C4 | C5 | 111.34(14) |
| N1 | C5 | C4 | 109.55(14) |
| N1 | C5 | C6 | 111.79(14) |
| C4 | C5 | C6 | 112.18(14) |
| C7 | C6 | C5 | 109.90(14) |
| C15 | C6 | C5 | 110.73(14) |
| C15 | C6 | C7 | 112.36(14) |
| O2 | C7 | N2 | 122.52(17) |

| Atom | Atom | Atom | Angle/° |
|------|------|------|---------|
| O2 | C7 | C6 | 119.77(16) |
| N2 | C7 | C6 | 117.70(15) |
| N2 | C8 | C9 | 110.06(16) |
| C10 | C9 | C8 | 110.41(16) |
| C9 | C10 | C11 | 110.89(17) |
| C10 | C11 | C12 | 111.36(17) |
| N2 | C12 | C11 | 109.58(15) |
| N2 | C12 | C13 | 112.15(14) |
| C11 | C12 | C13 | 112.90(16) |
| C14 | C13 | C12 | 109.91(14) |
| C15 | C13 | C12 | 110.73(15) |
| C15 | C13 | C14 | 112.24(15) |
| O1 | C14 | N1 | 122.55(16) |
| O1 | C14 | C13 | 119.82(16) |
| N1 | C14 | C13 | 117.60(15) |
| C6 | C15 | C13 | 106.27(14) |

**Table 22**: Hydrogen Fractional Atomic Coordinates ($\times 10^4$)
and Equivalent Isotropic Displacement Parameters
($\text{Å}^2 \times 10^3$) for **2015sot0075_K_100K**. $U_{eq}$ is defined as 1/3
of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|------|-------|------|----------|
| H1A | 9127 | 3557 | 4488 | 28 |
| H1B | 8400 | 3113 | 3811 | 28 |
| H2A | 5563 | 3140 | 4864 | 28 |
| H2B | 6476 | 1840 | 4538 | 28 |
| H3A | 2789 | 2297 | 4225 | 28 |
| H3B | 4423 | 2290 | 3648 | 28 |
| H4A | 2812 | 4601 | 4255 | 26 |
| H4B | 2175 | 4159 | 3573 | 26 |
| H5 | 5793 | 4528 | 3236 | 21 |
| H6 | 3161 | 6378 | 3313 | 23 |
| H8A | 8958 | 7929 | 2291 | 28 |
| H8B | 10959 | 7924 | 2770 | 28 |
| H9A | 10322 | 10104 | 2456 | 33 |
| H9B | 7787 | 9995 | 2648 | 33 |
| H10A | 9662 | 11111 | 3432 | 39 |
| H10B | 11423 | 9949 | 3487 | 39 |
| H11A | 6872 | 9759 | 3822 | 35 |
| H11B | 8893 | 9716 | 4292 | 35 |
| H12 | 10073 | 7704 | 3887 | 24 |
| H13 | 7116 | 7752 | 4667 | 23 |
| H15A | 3753 | 6813 | 4375 | 25 |
| H15B | 4167 | 8104 | 3966 | 25 |

**Citations**

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K.
Howard and H. Puschmann, Olex2: A complete structure
solution, refinement and analysis program, *J. Appl. Cryst.*,
(2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*,
(2008), **A64**, 339-341.

## B.1.5     (−)-10,17-dioxo-$\alpha$-isosparteine ((−)-1.43)

**Crystal Data and Experimental**
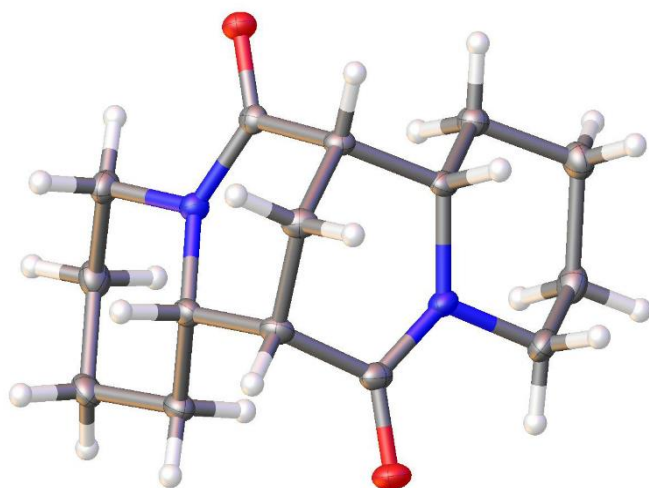




**Figure 5**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless rod-shaped crystals of (**2017sot0020_R1_100K**) were recrystallised from hexane by slow evaporation. A suitable crystal (0.54×0.08×0.05) mm$^3$ was selected and mounted on a MITIGEN holder silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** $C_{15}H_{22}N_2O_2$, $M_r$ = 262.34, orthorhombic, P2$_1$2$_1$2$_1$ (No. 19), a = 6.2737(3) Å, b = 11.5350(5) Å, c = 18.4575(9) Å, $\alpha$ = $\beta$ = $\gamma$ = 90°, $V$ = 1335.72(11) Å$^3$, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(MoK$_\alpha$) = 0.087, 12682 reflections measured, 3454 unique ($R_{int}$ = 0.0206) which were used in all calculations. The final $wR_2$ was 0.0824 (all data) and $R_1$ was 0.0318 (I > 2(I)).
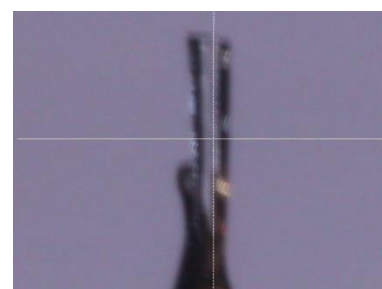
| Compound | 2017sot0020_R_100 K |
|---|---|
| Formula | $C_{15}H_{22}N_2O_2$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.305 |
| $\mu$/mm$^{-1}$ | 0.087 |
| Formula Weight | 262.34 |
| Colour | clear colourless |
| Shape | rod |
| Size/mm$^3$ | 0.54×0.08×0.05 |
| $T$/K | 100(2) |
| Crystal System | orthorhombic |
| Flack Parameter | 0.0(3) |
| Hooft Parameter | -0.0(2) |
| Space Group | P2$_1$2$_1$2$_1$ |
| $a$/Å | 6.2737(3) |
| $b$/Å | 11.5350(5) |
| $c$/Å | 18.4575(9) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| V/Å$^3$ | 1335.72(11) |
| Z | 4 |
| Z' | 1 |
| Wavelength/Å | 0.71073 |
| Radiation type | MoK$_\alpha$ |
| $\Theta_{min}$/° | 3.430 |
| $\Theta_{max}$/° | 28.696 |
| Measured Refl. | 12682 |
| Independent Refl. | 3454 |
| Reflections Used | 3320 |
| $R_{int}$ | 0.0206 |
| Parameters | 172 |
| Restraints | 0 |
| Largest Peak | 0.281 |
| Deepest Hole | -0.180 |
| GooF | 1.064 |
| $wR_2$ (all data) | 0.0824 |
| $wR_2$ | 0.0811 |
| $R_1$ (all data) | 0.0336 |
| $R_1$ | 0.0318 |

Appendices

**Structure Quality Indicators**

| Reflections: | d min (Mo) 0.74 | I/σ 44.1 | Rint 2.06% | complete at 2θ=61° 100% |
|---|---|---|---|---|

| Refinement: | Shift 0.000 | Max Peak 0.3 | Min Peak -0.2 | GooF 1.064 | -0.0(3) |
|---|---|---|---|---|---|

A clear colourless rod-shaped crystal with dimensions 0.54×0.08×0.05 was mounted on a MITIGEN holder silicon oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 8.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 28.696.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) on 7528 reflections, 59 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software which corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.696 in $\Theta$. The absorption coefficient $\mu$ of this material is 0.087 at this wavelength ($\lambda$ = 0.71073) and the minimum and maximum transmissions are 0.90833 and 1.00000.

The structure was solved in the space group P2$_1$2$_1$2$_1$ (# 19) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

The Flack parameter was refined to 0.0(3). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.0(2). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Generated Precession Images



0kl



h0l



hk0
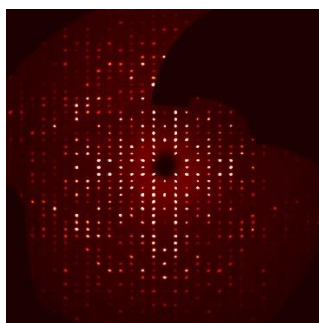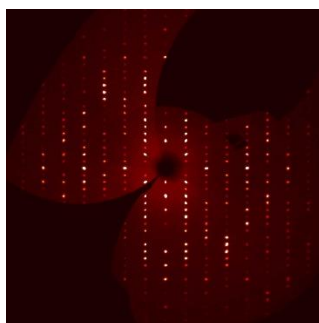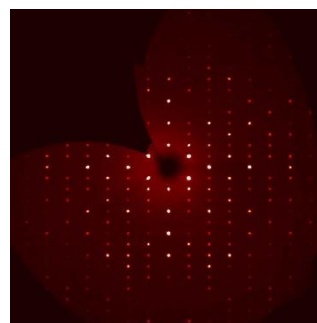
## Data Plots: Diffraction Data
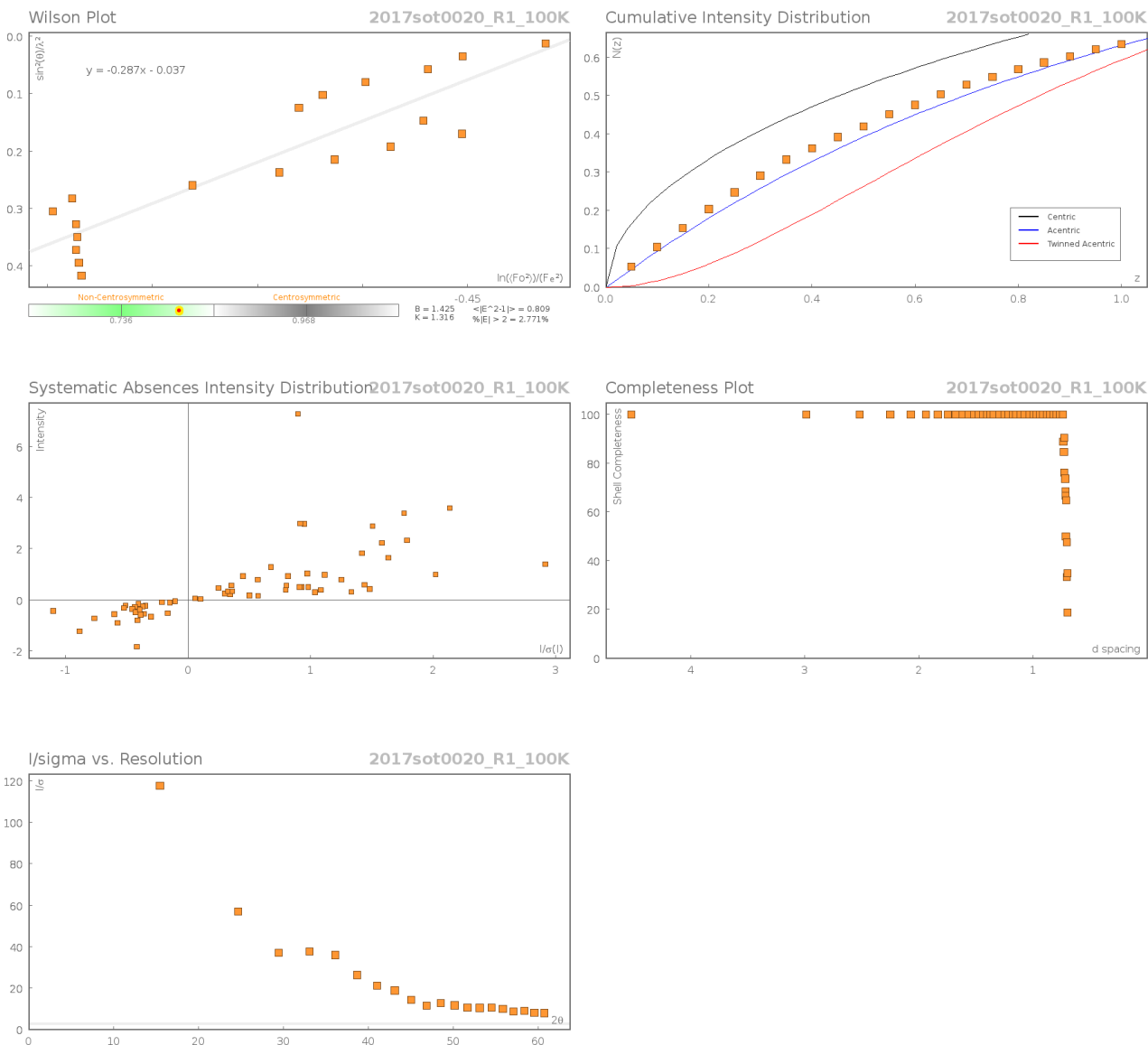


## Data Plots: Refinement and Data
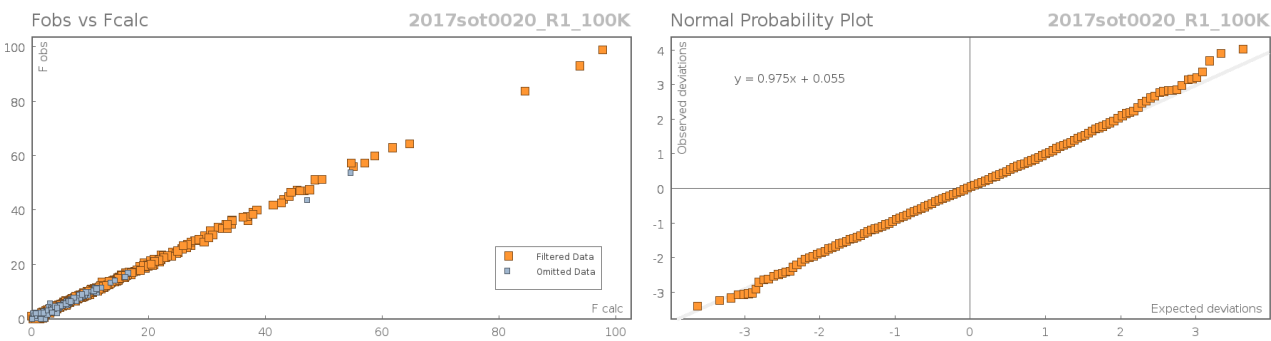
Appendices

## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 12747 | Unique reflections | 3454 |
| Completeness | 0.999 | Mean I/$\sigma$ | 44.06 |
| $hkl_{max}$ collected | (8, 15, 26) | $hkl_{min}$ collected | (-8, -16, -25) |
| $hkl_{max}$ used | (8, 15, 24) | $hkl_{min}$ used | (-8, 0, 0) |
| Lim $d_{max}$ collected | 7.0 | Lim $d_{min}$ collected | 0.74 |
| $d_{max}$ used | 6.27 | $d_{min}$ used | 0.74 |
| Friedel pairs | 3098 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 12 | $R_{int}$ | 0.0206 |
| $R_{sigma}$ | 0.0169 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (6621, 2570, 382, 83, 7) | Maximum multiplicity | 13 |
| Removed systematic absences | 65 | Filtered off (Shel/OMIT) | 527 |

**Table 23**: Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2017sot0020_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 5257.4(16) | 7595.3(9) | 5697.8(6) | 18.8(2) |
| O2 | -575(2) | 4407.2(10) | 7232.0(6) | 25.2(3) |
| N1 | 3371.1(19) | 5916.8(10) | 5610.7(6) | 14.8(2) |
| N2 | 1938(2) | 5801.7(10) | 7387.7(6) | 16.4(2) |
| C1 | 4707(2) | 5517.6(13) | 5008.8(8) | 18.5(3) |
| C2 | 5197(3) | 4227.1(13) | 5079.2(8) | 21.1(3) |
| C3 | 3147(3) | 3525.4(13) | 5140.2(8) | 20.6(3) |
| C4 | 1766(2) | 3991.7(12) | 5755.8(8) | 18.1(3) |
| C5 | 1320(2) | 5291.3(12) | 5668.6(8) | 15.7(3) |
| C6 | -149(2) | 5765.0(12) | 6265.0(8) | 16.6(3) |
| C7 | -74(2) | 7087.6(12) | 6270.0(8) | 17.0(3) |
| C8 | 2202(2) | 7415.4(12) | 6469.5(7) | 14.5(3) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C9 | 3743(2) | 6993.5(12) | 5890.3(7) | 14.2(3) |
| C10 | 367(2) | 5272.0(12) | 7006.5(8) | 17.2(3) |
| C11 | 2393(3) | 5379.3(14) | 8122.4(8) | 21.2(3) |
| C12 | 4768(3) | 5415.4(14) | 8283.9(8) | 22.4(3) |
| C13 | 5643(3) | 6634.3(13) | 8169.3(8) | 21.7(3) |
| C14 | 5135(2) | 7029.5(12) | 7397.8(8) | 17.3(3) |
| C15 | 2747(2) | 6985.5(12) | 7237.5(7) | 14.2(3) |

**Table 24**: Anisotropic Displacement Parameters (×10⁴) **2017sot0020_R1_100K**. The anisotropic displacement factor exponent takes the form: *-2π²[h²a\*² × U₁₁+ ... +2hka\* × b\* × U₁₂]*

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| O1 | 18.1(5) | 18.1(5) | 20.1(5) | 1.2(4) | 2.2(4) | -4.9(4) |
| O2 | 30.2(6) | 19.2(5) | 26.1(6) | 2.5(4) | 3.9(5) | -10.7(5) |
| N1 | 15.0(5) | 14.1(5) | 15.4(5) | 0.1(5) | 1.2(4) | -0.7(4) |
| N2 | 20.8(6) | 13.3(5) | 15.2(5) | 2.2(4) | 2.5(5) | -2.5(5) |
| C1 | 22.9(7) | 17.4(6) | 15.3(6) | -0.7(5) | 3.6(6) | 0.6(6) |
| C2 | 25.2(7) | 18.9(7) | 19.1(6) | -3.2(5) | 1.1(6) | 2.6(6) |
| C3 | 28.4(7) | 14.7(6) | 18.7(7) | -3.1(5) | -2.3(6) | -0.9(6) |
| C4 | 22.8(7) | 13.4(6) | 18.2(6) | -0.1(5) | -1.7(6) | -2.9(6) |
| C5 | 16.6(6) | 14.8(6) | 15.7(6) | 0.4(5) | -2.8(5) | -2.7(5) |
| C6 | 13.2(6) | 14.6(6) | 21.8(6) | 0.4(5) | -0.7(5) | -2.3(5) |
| C7 | 12.7(6) | 14.5(6) | 23.7(7) | 2.3(5) | 0.0(5) | 0.9(5) |
| C8 | 15.1(6) | 10.3(6) | 18.0(6) | 1.0(5) | 1.0(5) | -0.2(5) |
| C9 | 14.6(6) | 14.1(6) | 13.9(6) | 2.3(5) | -2.4(5) | 0.6(5) |
| C10 | 18.7(6) | 13.4(6) | 19.5(6) | -0.5(5) | 4.9(5) | -1.4(5) |
| C11 | 29.9(8) | 19.2(7) | 14.6(6) | 2.6(6) | 2.3(6) | -3.1(6) |
| C12 | 30.4(8) | 20.3(7) | 16.3(6) | 1.8(5) | -1.3(6) | 3.6(6) |
| C13 | 23.8(7) | 22.2(7) | 19.1(6) | -0.8(6) | -4.0(6) | -0.4(6) |
| C14 | 17.8(6) | 15.8(6) | 18.4(6) | 0.5(5) | -0.9(5) | -1.8(5) |
| C15 | 16.6(6) | 10.5(6) | 15.6(6) | -1.2(5) | 2.1(5) | -1.1(5) |

**Table 25**: Bond Lengths in Å for **2017sot0020_R1_100K**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|------|------|------|------|
| O1 | C9 | 1.2293(17) | C4 | C5 | 1.5335(19) |
| O2 | C10 | 1.2319(18) | C5 | C6 | 1.536(2) |
| N1 | C1 | 1.4661(18) | C6 | C7 | 1.5263(18) |
| N1 | C5 | 1.4794(18) | C6 | C10 | 1.517(2) |
| N1 | C9 | 1.3649(18) | C7 | C8 | 1.5222(19) |
| N2 | C10 | 1.356(2) | C8 | C9 | 1.5214(19) |
| N2 | C11 | 1.4690(18) | C8 | C15 | 1.5401(19) |
| N2 | C15 | 1.4829(17) | C11 | C12 | 1.520(2) |
| C1 | C2 | 1.525(2) | C12 | C13 | 1.524(2) |
| C2 | C3 | 1.524(2) | C13 | C14 | 1.529(2) |
| C3 | C4 | 1.527(2) | C14 | C15 | 1.528(2) |

**Table 26**: Bond Angles in ° for **2017sot0020_R1_100K**.

| Atom | Atom | Atom | Angle/° |
|------|------|------|---------|
| C1 | N1 | C5 | 113.52(11) |
| C9 | N1 | C1 | 118.34(12) |
| C9 | N1 | C5 | 124.41(12) |
| C10 | N2 | C11 | 118.07(12) |
| C10 | N2 | C15 | 124.51(12) |
| C11 | N2 | C15 | 114.30(12) |
| N1 | C1 | C2 | 110.92(12) |
| C3 | C2 | C1 | 110.77(13) |
| C2 | C3 | C4 | 110.29(12) |
| C3 | C4 | C5 | 111.71(12) |
| N1 | C5 | C4 | 108.99(12) |
| N1 | C5 | C6 | 113.58(11) |
| C4 | C5 | C6 | 112.46(12) |
| C7 | C6 | C5 | 109.95(12) |
| C10 | C6 | C5 | 112.64(12) |
| C10 | C6 | C7 | 111.27(12) |
| C8 | C7 | C6 | 106.18(11) |
| C7 | C8 | C15 | 110.55(11) |
| C9 | C8 | C7 | 110.27(11) |
| C9 | C8 | C15 | 113.75(11) |
| O1 | C9 | N1 | 122.45(13) |
| O1 | C9 | C8 | 120.91(12) |
| N1 | C9 | C8 | 116.63(12) |
| O2 | C10 | N2 | 122.56(14) |
| O2 | C10 | C6 | 120.38(13) |
| N2 | C10 | C6 | 117.02(12) |
| N2 | C11 | C12 | 111.25(13) |
| C11 | C12 | C13 | 110.55(13) |
| C12 | C13 | C14 | 109.22(12) |
| C15 | C14 | C13 | 112.02(12) |
| N2 | C15 | C8 | 113.11(11) |
| N2 | C15 | C14 | 109.26(11) |
| C14 | C15 | C8 | 112.66(11) |

**Table 27**: Hydrogen Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2017sot0020_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H1A | 6031 | 5953 | 5004 | 22 |
| H1B | 3978 | 5659 | 4554 | 22 |
| H2A | 5997 | 3971 | 4659 | 25 |
| H2B | 6068 | 4097 | 5506 | 25 |
| H3A | 3489 | 2718 | 5231 | 25 |
| H3B | 2365 | 3570 | 4688 | 25 |
| H4A | 2484 | 3859 | 6214 | 22 |
| H4B | 425 | 3573 | 5765 | 22 |
| H5 | 573 | 5392 | 5206 | 19 |
| H6 | -1610 | 5534 | 6145 | 20 |
| H7A | -440 | 7393 | 5796 | 20 |
| H7B | -1069 | 7396 | 6623 | 20 |
| H8 | 2279 | 8264 | 6477 | 17 |
| H11A | 1882 | 4589 | 8170 | 25 |
| H11B | 1639 | 5855 | 8472 | 25 |
| H12A | 5509 | 4877 | 7968 | 27 |
| H12B | 5015 | 5178 | 8781 | 27 |
| H13A | 7173 | 6637 | 8245 | 26 |
| H13B | 5002 | 7163 | 8515 | 26 |
| H14A | 5643 | 7816 | 7331 | 21 |
| H14B | 5882 | 6536 | 7057 | 21 |
| H15 | 2045 | 7511 | 7580 | 17 |

**Citations**

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

Appendices

## B.1.6    *Syn* uncyclised imino-aldol product ((−)-2.17)

**Crystal Data and Experimental**
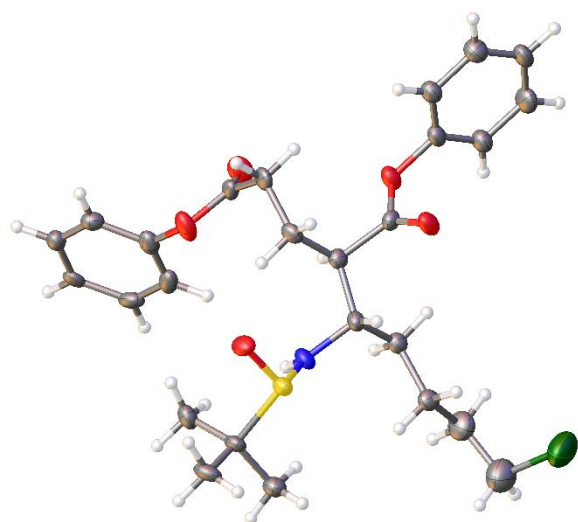


**Figure 6**: Thermal ellipsoids drawn at the 50% probability level. Disorder omitted for clarity.

**Experimental.** Single clear colourless needle-shaped crystals of (**2016sot0091_R1_100K**) were recrystallised from THF by slow evaporation. A suitable crystal (0.14×0.02×0.02) mm$^3$ was selected and mounted on a glass fibre silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at *T* = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** C$_{26}$H$_{34}$ClNO$_5$S, $M_r$ = 508.05, hexagonal, P6$_5$ (No. 170), a = 29.3480(19) Å, b = 29.3480(19) Å, c = 5.4131(4) Å, $\alpha$ = 90°, $\beta$ = 90°, $\gamma$ = 120°, $V$ = 4037.7(6) Å$^3$, $T$ = 100(2) K, $Z$ = 6, $Z'$ = 1, $\mu$(Mo K$_\alpha$) = 0.254, 27278 reflections measured, 6945 unique ($R_{int}$ = 0.1557) which were used in all calculations. The final $wR_2$ was 0.2642 (all data) and $R_1$ was 0.1018 (I > 2(I)).

| Compound | 2016sot0091_R_100K |
|---|---|
| Formula | C$_{26}$H$_{34}$ClNO$_5$S |
| $D_{calc.}$/ g cm$^{-3}$ | 1.254 |
| $\mu$/mm$^{-1}$ | 0.254 |
| Formula Weight | 508.05 |
| Colour | clear colourless |
| Shape | needle |
| Size/mm$^3$ | 0.14×0.02×0.02 |
| $T$/K | 100(2) |
| Crystal System | hexagonal |
| Flack Parameter | 0.02(9) |
| Hooft Parameter | 0.06(8) |
| Space Group | P6$_5$ |
| a/Å | 29.3480(19) |
| b/Å | 29.3480(19) |
| c/Å | 5.4131(4) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 120 |
| V/Å$^3$ | 4037.7(6) |
| Z | 6 |
| Z' | 1 |
| Wavelength/Å | 0.71075 |
| Radiation type | Mo K$_\alpha$ |
| $\Theta_{min}$/° | 3.674 |
| $\Theta_{max}$/° | 28.697 |
| Measured Refl. | 27278 |
| Independent Refl. | 6945 |
| Reflections Used | 3222 |
| $R_{int}$ | 0.1557 |
| Parameters | 325 |
| Restraints | 367 |
| Largest Peak | 0.694 |
| Deepest Hole | -0.910 |
| GooF | 1.005 |
| $wR_2$ (all data) | 0.2642 |
| $wR_2$ | 0.2070 |
| $R_1$ (all data) | 0.2199 |
| $R_1$ | 0.1018 |

## Structure Quality Indicators

**Reflections:**

| d min (Mo) | 0.74 | I/σ | 5.5 | Rint | 15.57% | complete at 2θ=62° | 100% |

**Refinement:**

| Shift | -0.001 | Max Peak | 0.7 | Min Peak | -0.9 | GooF | 1.005 | | 0.02(9) |

A clear colourless needle-shaped crystal with dimensions 0.14×0.02×0.02 was mounted on a glass fibre silicon oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 25.0 s using Mo K$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015). The actually achieved resolution was $\Theta$ = 28.697.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) on 4937 reflections, 18 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software, which corrects for Lorentz polarisation. The final completeness is 93.29 out to 28.697 in $\Theta$. The absorption coefficient $\mu$ of this material is 0.254 at this wavelength ($\lambda$ = 0.71075) and the minimum and maximum transmissions are 0.31574 and 1.00000.

The structure was solved in the space group P6$_5$ (# 170) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 6 and Z' is 1.

The Flack parameter was refined to 0.02(9). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.06(8). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

## Generated precession images



0kl



h0l



hk0
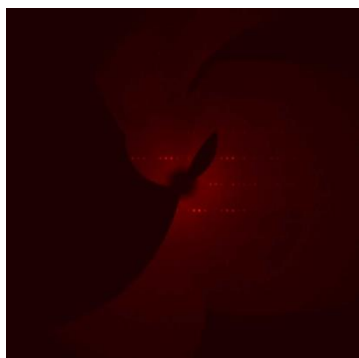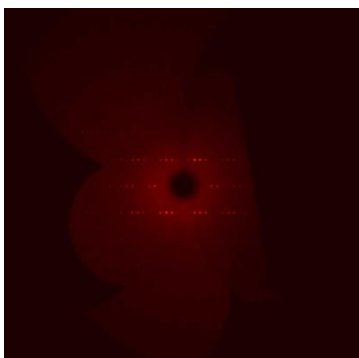
Appendices

# Data Plots: Diffraction Data
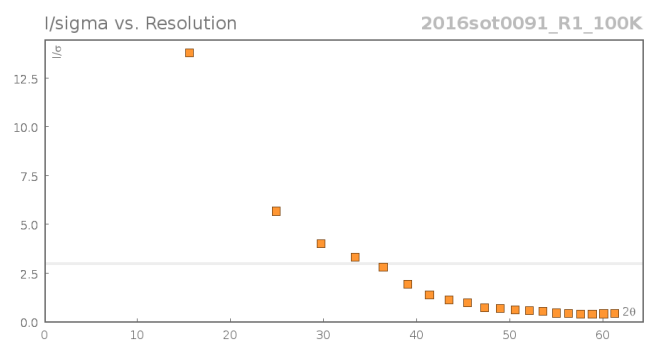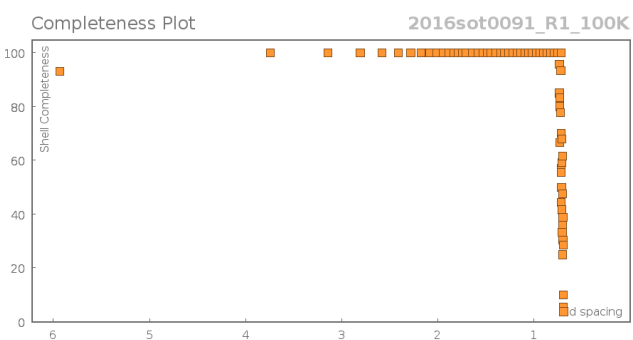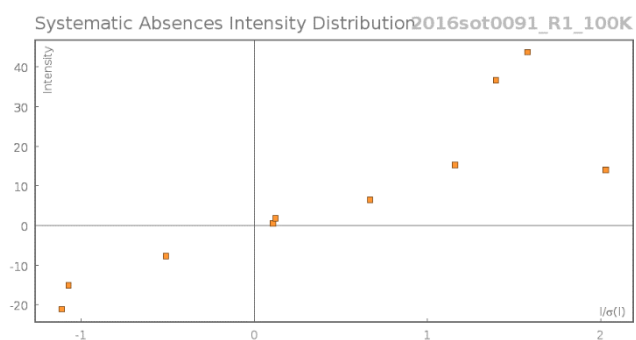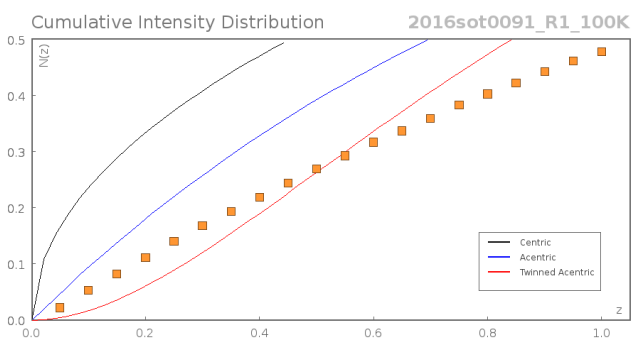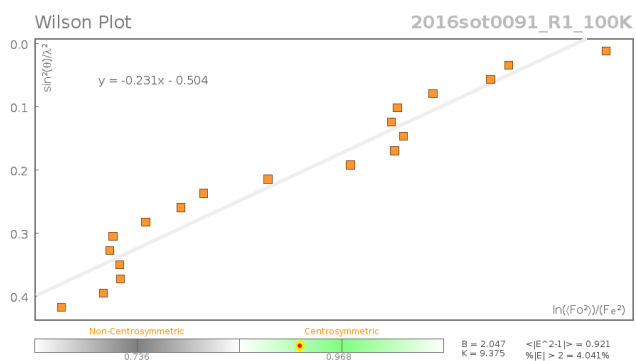


# Data Plots: Refinement and Data
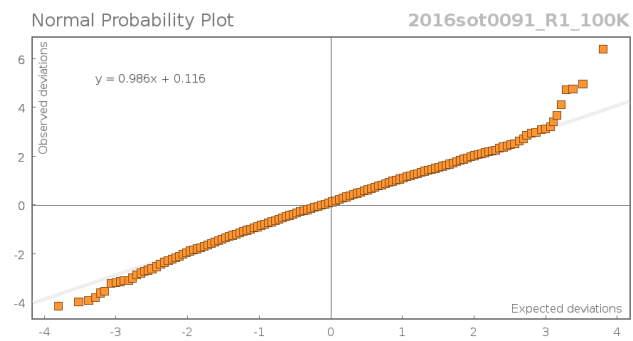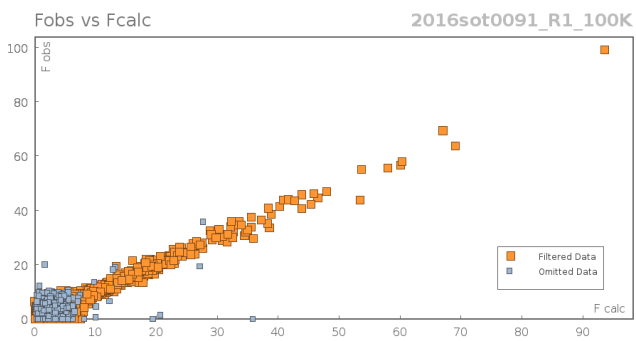
**Reflection Statistics**

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 27321 | Unique reflections | 6945 |
| Completeness | 0.999 | Mean $I/\sigma$ | 5.5 |
| $hkl_{max}$ collected | (36, 39, 7) | $hkl_{min}$ collected | (-40, -40, -7) |
| $hkl_{max}$ used | (0, 39, 7) | $hkl_{min}$ used | (-33, 0, -7) |
| Lim $d_{max}$ collected | 7.0 | Lim $d_{min}$ collected | 0.74 |
| $d_{max}$ used | 6.35 | $d_{min}$ used | 0.74 |
| Friedel pairs | 5200 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 1 | $R_{int}$ | 0.1557 |
| $R_{sigma}$ | 0.2089 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 33 |
| Multiplicity | (17211, 4965, 503, 2) | Maximum multiplicity | 12 |
| Removed systematic absences | 10 | Filtered off (Shel/OMIT) | 1337 |

**Table 28**: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for **2016sot0091_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Cl1A | 1442.7(18) | 1863(2) | 7184(14) | 101.4(18) |
| S1 | 3454.6(9) | 1663.8(8) | 1605(4) | 30.6(5) |
| O1 | 5243(3) | 2936(2) | 4650(12) | 43.3(16) |
| O2 | 5344(3) | 3609(2) | 6965(13) | 45.6(17) |
| O3 | 4261(2) | 3845(2) | 5750(11) | 34.3(14) |
| O4 | 3608(2) | 3455(2) | 2956(12) | 38.5(16) |
| O5 | 3900(2) | 1891(2) | -198(11) | 35.7(15) |
| N1 | 3587(3) | 2018(3) | 4141(14) | 31.7(17) |
| C1 | 5944(3) | 2809(3) | 6123(17) | 32.1(19) |
| C2 | 6124(3) | 2599(3) | 7849(17) | 32(2) |
| C3 | 5837(3) | 2347(3) | 9909(17) | 31.1(19) |
| C4 | 5342(4) | 2298(3) | 10242(18) | 37(2) |
| C5 | 5152(3) | 2501(3) | 8524(19) | 37(2) |
| C6 | 5450(3) | 2754(3) | 6491(17) | 35(2) |
| C7 | 5208(3) | 3368(3) | 5119(18) | 32.7(19) |
| C8 | 4972(3) | 3482(3) | 2885(17) | 34(2) |
| C9 | 4413(3) | 3054(3) | 2377(16) | 29.1(19) |
| C10 | 4030(3) | 2980(3) | 4418(16) | 29.0(18) |
| C11 | 3929(3) | 3434(3) | 4268(16) | 29.2(19) |
| C12 | 4228(3) | 4313(3) | 5568(16) | 30.3(19) |
| C13 | 4470(3) | 4640(3) | 3638(17) | 33(2) |
| C14 | 4443(4) | 5100(4) | 3509(19) | 40(2) |
| C15 | 4168(3) | 5202(3) | 5258(17) | 37(2) |
| C16 | 3937(4) | 4864(4) | 7201(19) | 43(2) |
| C17 | 3969(3) | 4410(3) | 7356(18) | 35(2) |
| C18 | 3503(3) | 2467(3) | 4260(16) | 32(2) |
| C19 | 3445(3) | 1085(3) | 2969(17) | 31.5(19) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C20 | 3355(4) | 718(3) | 816(17) | 38(2) |
| C21 | 3977(3) | 1246(4) | 4172(18) | 38(2) |
| C22 | 2980(3) | 834(3) | 4708(18) | 37(2) |
| C23A | 3184(4) | 2421(7) | 6620(20) | 30(3) |
| C24A | 2603(4) | 1982(5) | 6390(20) | 32(3) |
| C25A | 2320(5) | 1888(6) | 8870(30) | 51(4) |
| C26A | 1735(6) | 1535(8) | 8770(40) | 73(4) |
| Cl1B | 1245(4) | 1477(5) | 10030(30) | 101.4(18) |
| C26B | 1572(12) | 1439(17) | 7410(70) | 73(4) |
| C25B | 2166(12) | 1791(15) | 7610(60) | 51(4) |
| C24B | 2501(11) | 1927(13) | 5260(50) | 32(3) |
| C23B | 3055(9) | 2353(17) | 6050(60) | 30(3) |

**Table 29**: Anisotropic Displacement Parameters (×10$^4$) **2016sot0091_R1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11}+ ... +2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| Cl1A | 49(3) | 89(3) | 173(5) | 43(4) | 19(3) | 40(3) |
| S1 | 26.7(12) | 19.3(11) | 46.5(12) | 2(1) | 4.6(10) | 12(1) |
| O1 | 49(4) | 38(4) | 58(4) | -17(3) | -14(4) | 33(3) |
| O2 | 45(4) | 36(4) | 59(4) | -14(3) | -10(3) | 22(3) |
| O3 | 34(3) | 26(3) | 50(4) | -4(3) | -7(3) | 20(3) |
| O4 | 31(3) | 26(3) | 64(4) | -4(3) | -13(3) | 18(3) |
| O5 | 33(3) | 26(3) | 45(4) | 6(3) | 17(3) | 13(3) |
| N1 | 35(4) | 22(4) | 44(4) | 5(3) | 5(3) | 19(3) |
| C1 | 27(4) | 21(4) | 44(5) | 3(4) | 1(4) | 9(4) |
| C2 | 25(4) | 22(4) | 52(5) | -2(4) | 2(4) | 13(4) |
| C3 | 29(4) | 10(4) | 51(5) | -6(4) | -6(4) | 7(4) |
| C4 | 32(5) | 16(4) | 54(5) | 1(4) | 8(4) | 5(4) |
| C5 | 24(4) | 27(5) | 61(5) | -17(4) | -6(4) | 14(4) |
| C6 | 31(5) | 26(5) | 52(5) | -14(4) | -10(4) | 17(4) |
| C7 | 21(4) | 21(4) | 58(5) | -11(4) | 1(4) | 12(4) |
| C8 | 33(4) | 25(4) | 51(5) | -8(4) | 6(4) | 20(4) |
| C9 | 35(5) | 19(4) | 35(4) | -4(4) | 1(4) | 15(4) |
| C10 | 24(4) | 24(4) | 41(5) | 3(4) | 0(4) | 14(3) |
| C11 | 19(4) | 26(4) | 45(5) | 5(4) | 2(4) | 13(4) |
| C12 | 25(5) | 23(4) | 47(5) | -2(4) | -5(4) | 15(4) |
| C13 | 31(5) | 25(4) | 46(5) | -3(4) | -2(4) | 15(4) |
| C14 | 38(5) | 32(5) | 52(5) | 5(4) | 2(5) | 19(4) |
| C15 | 34(5) | 23(5) | 60(6) | -8(4) | -4(4) | 18(4) |
| C16 | 40(6) | 33(5) | 62(6) | -11(4) | 6(5) | 22(5) |
| C17 | 33(5) | 26(5) | 51(5) | -3(4) | 1(4) | 17(4) |
| C18 | 27(4) | 24(4) | 52(5) | 8(4) | 8(4) | 17(4) |
| C19 | 29(4) | 14(4) | 50(5) | 1(4) | 6(4) | 10(4) |
| C20 | 47(6) | 16(4) | 48(5) | 5(4) | 6(4) | 13(4) |
| C21 | 37(5) | 30(5) | 57(6) | -1(4) | 0(4) | 23(4) |
| C22 | 32(5) | 24(5) | 56(5) | 5(4) | 5(4) | 13(4) |
| C23A | 27(5) | 24(5) | 41(6) | 1(5) | 0(5) | 14(5) |
| C24A | 27(5) | 27(5) | 42(6) | 6(6) | -1(5) | 14(4) |
| C25A | 51(6) | 51(7) | 55(7) | 3(6) | 14(5) | 29(5) |
| C26A | 56(6) | 70(8) | 100(9) | 14(7) | 3(6) | 35(6) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Cl1B | 49(3) | 89(3) | 173(5) | 43(4) | 19(3) | 40(3) |
| C26B | 56(6) | 70(8) | 100(9) | 14(7) | 3(6) | 35(6) |
| C25B | 51(6) | 51(7) | 55(7) | 3(6) | 14(5) | 29(5) |
| C24B | 27(5) | 27(5) | 42(6) | 6(6) | -1(5) | 14(4) |
| C23B | 27(5) | 24(5) | 41(6) | 1(5) | 0(5) | 14(5) |

**Table 30**: Bond Lengths in Å for **2016sot0091_R1_100K**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| Cl1A | C26A | 1.797(18) | C10 | C11 | 1.505(11) |
| S1 | O5 | 1.495(6) | C10 | C18 | 1.529(11) |
| S1 | N1 | 1.647(8) | C12 | C13 | 1.355(12) |
| S1 | C19 | 1.838(8) | C12 | C17 | 1.344(12) |
| O1 | C6 | 1.403(10) | C13 | C14 | 1.393(12) |
| O1 | C7 | 1.347(10) | C14 | C15 | 1.371(12) |
| O2 | C7 | 1.174(10) | C15 | C16 | 1.370(13) |
| O3 | C11 | 1.368(10) | C16 | C17 | 1.386(12) |
| O3 | C12 | 1.429(9) | C18 | C23A | 1.547(13) |
| O4 | C11 | 1.206(9) | C18 | C23B | 1.531(16) |
| N1 | C18 | 1.458(10) | C19 | C20 | 1.518(12) |
| C1 | C2 | 1.364(12) | C19 | C21 | 1.532(12) |
| C1 | C6 | 1.390(12) | C19 | C22 | 1.513(12) |
| C2 | C3 | 1.370(12) | C23A | C24A | 1.545(14) |
| C3 | C4 | 1.400(12) | C24A | C25A | 1.532(15) |
| C4 | C5 | 1.365(13) | C25A | C26A | 1.498(16) |
| C5 | C6 | 1.370(13) | Cl1B | C26B | 1.75(2) |
| C7 | C8 | 1.511(13) | C26B | C25B | 1.52(2) |
| C8 | C9 | 1.511(12) | C25B | C24B | 1.53(2) |
| C9 | C10 | 1.514(12) | C24B | C23B | 1.53(2) |

**Table 31**: Bond Angles in ° for **2016sot0091_R1_100K**.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|---|---|---|
| O5 | S1 | N1 | 112.6(3) | C9 | C8 | C7 | 112.8(7) |
| O5 | S1 | C19 | 106.3(4) | C8 | C9 | C10 | 113.9(7) |
| N1 | S1 | C19 | 97.9(4) | C9 | C10 | C18 | 114.4(7) |
| C7 | O1 | C6 | 118.4(7) | C11 | C10 | C9 | 107.2(7) |
| C11 | O3 | C12 | 116.5(6) | C11 | C10 | C18 | 108.7(7) |
| C18 | N1 | S1 | 120.9(6) | O3 | C11 | C10 | 112.3(7) |
| C2 | C1 | C6 | 117.8(8) | O4 | C11 | O3 | 122.0(8) |
| C1 | C2 | C3 | 121.9(8) | O4 | C11 | C10 | 125.6(8) |
| C2 | C3 | C4 | 119.2(9) | C13 | C12 | O3 | 118.0(7) |
| C5 | C4 | C3 | 119.8(9) | C17 | C12 | O3 | 118.0(8) |
| C4 | C5 | C6 | 119.6(8) | C17 | C12 | C13 | 123.9(8) |
| C1 | C6 | O1 | 118.5(8) | C12 | C13 | C14 | 117.4(9) |
| C5 | C6 | O1 | 119.7(8) | C15 | C14 | C13 | 120.2(9) |
| C5 | C6 | C1 | 121.7(8) | C16 | C15 | C14 | 120.2(8) |
| O1 | C7 | C8 | 108.5(7) | C15 | C16 | C17 | 119.9(9) |
| O2 | C7 | O1 | 124.5(9) | C12 | C17 | C16 | 118.4(9) |
| O2 | C7 | C8 | 127.0(8) | N1 | C18 | C10 | 110.4(7) |

| Atom | Atom | Atom | Angle/° | | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|---|------|------|------|---------|
| N1 | C18 | C23A | 109.0(9) | | C22 | C19 | C21 | 114.7(8) |
| N1 | C18 | C23B | 110(2) | | C24A | C23A | C18 | 112.0(10) |
| C10 | C18 | C23A | 108.0(8) | | C25A | C24A | C23A | 110.8(11) |
| C10 | C18 | C23B | 120.9(15) | | C26A | C25A | C24A | 115.1(14) |
| C20 | C19 | S1 | 105.3(6) | | C25A | C26A | Cl1A | 109.6(13) |
| C20 | C19 | C21 | 109.5(7) | | C25B | C26B | Cl1B | 112(2) |
| C21 | C19 | S1 | 110.1(6) | | C26B | C25B | C24B | 119(3) |
| C22 | C19 | S1 | 107.1(6) | | C25B | C24B | C23B | 105(2) |
| C22 | C19 | C20 | 109.7(7) | | C18 | C23B | C24B | 116(2) |

**Table 32**: Hydrogen Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2016sot0091_R1_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|------|---|---|---|----------|
| H1 | 3710.71 | 1934.95 | 5442.11 | 38 |
| H1A | 6149.24 | 2987.36 | 4715.07 | 39 |
| H2 | 6458.73 | 2627.85 | 7615.94 | 39 |
| H3 | 5972.59 | 2207.09 | 11095.9 | 37 |
| H4 | 5137.88 | 2123.48 | 11660.12 | 45 |
| H5 | 4815.27 | 2468.32 | 8737.81 | 44 |
| H8A | 4977.67 | 3818.75 | 3147.5 | 41 |
| H8B | 5191.98 | 3524.23 | 1421.06 | 41 |
| H9A | 4409.54 | 2717.5 | 2125.19 | 35 |
| H9B | 4292.8 | 3137.47 | 824.31 | 35 |
| H10 | 4196.88 | 2993.75 | 6046.52 | 35 |
| H13 | 4651.42 | 4558.83 | 2419.78 | 40 |
| H14 | 4615.24 | 5343.53 | 2205.52 | 48 |
| H15 | 4136.96 | 5508.63 | 5121.89 | 44 |
| H16 | 3756.52 | 4941.29 | 8438.72 | 52 |
| H17 | 3811.75 | 4171.61 | 8693.41 | 42 |
| H18 | 3305.72 | 2471.6 | 2764.39 | 39 |
| H18A | 3361.05 | 2477.61 | 2595.77 | 39 |
| H20A | 3003.52 | 594.76 | 125.9 | 58 |
| H20B | 3382.17 | 416.32 | 1392.34 | 58 |
| H20C | 3620.64 | 906.9 | -460.56 | 58 |
| H21A | 4261.45 | 1481.32 | 3059.13 | 57 |
| H21B | 4002.96 | 931.33 | 4495.7 | 57 |
| H21C | 4006.66 | 1428.48 | 5732.31 | 57 |
| H22A | 3019.44 | 1086.86 | 5989.01 | 56 |
| H22B | 2962.75 | 523.56 | 5481.54 | 56 |
| H22C | 2654.84 | 726.93 | 3779.43 | 56 |
| H23A | 3346.13 | 2345.94 | 8049.3 | 36 |
| H23B | 3199.95 | 2760.94 | 6921.33 | 36 |
| H24A | 2424.65 | 2083.36 | 5135.73 | 38 |
| H24B | 2586.46 | 1652.49 | 5834.49 | 38 |
| H25A | 2466.75 | 1734.42 | 10033.79 | 61 |
| H25B | 2396.4 | 2232.62 | 9553.04 | 61 |
| H26A | 1591.84 | 1443.15 | 10468.03 | 88 |
| H26B | 1649.18 | 1205.51 | 7894.31 | 88 |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H26C | 1487.3 | 1069.87 | 7169.57 | 88 |
| H26D | 1445.07 | 1543.27 | 5937.71 | 88 |
| H25C | 2295.89 | 1621.44 | 8776.46 | 61 |
| H25D | 2235.74 | 2126.17 | 8374.89 | 61 |
| H24C | 2361.81 | 2061.2 | 3964.2 | 38 |
| H24D | 2506.05 | 1613.23 | 4624.71 | 38 |
| H23C | 3050.45 | 2684.28 | 6321.94 | 36 |
| H23D | 3136.05 | 2248.54 | 7659.8 | 36 |

**Table 33**: Atomic Occupancies for all atoms that are not fully occupied in **2016sot0091_R1_100K**.

| Atom | Occupancy | Atom | Occupancy | Atom | Occupancy | Atom | Occupancy |
|------|-----------|------|-----------|------|-----------|------|-----------|
| Cl1A | 0.7 | H24A | 0.7 | H26B | 0.7 | H25D | 0.3 |
| H18 | 0.7 | H24B | 0.7 | Cl1B | 0.3 | C24B | 0.3 |
| H18A | 0.3 | C25A | 0.7 | C26B | 0.3 | H24C | 0.3 |
| C23A | 0.7 | H25A | 0.7 | H26C | 0.3 | H24D | 0.3 |
| H23A | 0.7 | H25B | 0.7 | H26D | 0.3 | C23B | 0.3 |
| H23B | 0.7 | C26A | 0.7 | C25B | 0.3 | H23C | 0.3 |
| C24A | 0.7 | H26A | 0.7 | H25C | 0.3 | H23D | 0.3 |

## Citations

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

## B.1.7 *Syn* cyclised imino-aldol product ((−)-2.13)

**Crystal Data and Experimental**
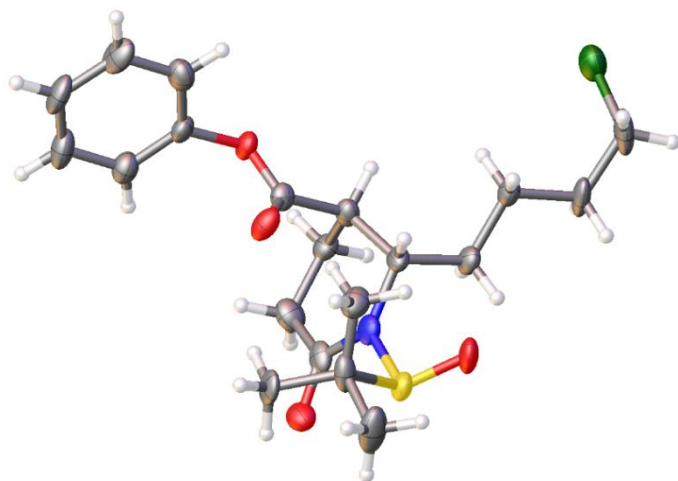


**Figure 7**: Thermal ellipsoids drawn at the 50% probability level.

**Experimental.** Single clear colourless plate-shaped crystals of (**2015sot0035-R-100K**) were recrystallised from chloroform by slow evaporation. A suitable crystal (0.13×0.09×0.02) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at $T$ = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

**Crystal Data.** $C_{20}H_{28}ClNO_4S$, $M_r$ = 413.94, orthorhombic, $P2_12_12_1$ (No. 19), a = 6.4385(7) Å, b = 17.461(2) Å, c = 19.3045(16) Å, $\alpha = \beta = \gamma$ = 90°, $V$ = 2170.3(4) Å³, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(MoK$_\alpha$) = 0.296, 11375 reflections measured, 5336 unique ($R_{int}$ = 0.1294) which were used in all calculations. The final $wR_2$ was 0.3642 (all data) and $R_1$ was 0.1323 (I > 2(I)).
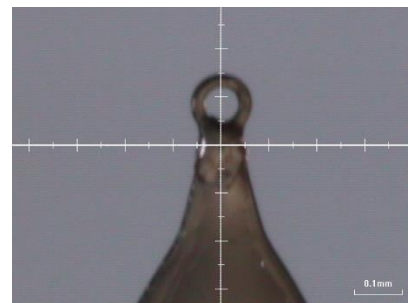
| Compound | 2015sot0035-R-100K |
|---|---|
| Formula | $C_{20}H_{28}ClNO_4S$ |
| $D_{calc.}$/ g cm⁻³ | 1.267 |
| $\mu$/mm⁻¹ | 0.296 |
| Formula Weight | 413.94 |
| Colour | clear colourless |
| Shape | plate |
| Max Size/mm | 0.13 |
| Mid Size/mm | 0.09 |
| Min Size/mm | 0.02 |
| $T$/K | 100(2) |
| Crystal System | orthorhombic |
| Flack Parameter | 0.2(2) |
| Hooft Parameter | 0.14(11) |
| Space Group | $P2_12_12_1$ |
| $a$/Å | 6.4385(7) |
| $b$/Å | 17.461(2) |
| $c$/Å | 19.3045(16) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| V/Å³ | 2170.3(4) |
| Z | 4 |
| Z' | 1 |
| $\Theta_{min}$/° | 3.146 |
| $\Theta_{max}$/° | 28.699 |
| Measured Refl. | 11375 |
| Independent Refl. | 5336 |
| Reflections Used | 2937 |
| $R_{int}$ | 0.1294 |
| Parameters | 247 |
| Restraints | 0 |
| Largest Peak | 1.366 |
| Deepest Hole | -0.620 |
| GooF | 1.066 |
| $wR_2$ (all data) | 0.3642 |
| $wR_2$ | 0.3192 |
| $R_1$ (all data) | 0.1958 |
| $R_1$ | 0.1323 |

205

Appendices

**Structure Quality Indicators**

**Reflections:**

| d min | | I/σ | | Rint | | complete at 2θ=61° | |
|---|---|---|---|---|---|---|---|
| | 0.74 | | 4.7 | | 12.94% | | 95% |

**Refinement:**

| Shift | | Max Peak | | Min Peak | | GooF | |
|---|---|---|---|---|---|---|---|
| | 0.000 | | 1.4 | | -0.6 | | 1.066 |

A clear colourless plate-shaped crystal with dimensions 0.13×0.09×0.02 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T$ = 100(2) K.

Data were measured using profile data from $\omega$-scans of 1.0° per frame for 20.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta$ = 28.699.

Cell parameters were retrieved using the **CrysAlisPro** (Agilent, V1.171.37.35, 2014) software and refined using **CrysAlisPro** (Agilent, V1.171.37.35, 2014) on 3143 reflections, 28 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Agilent, V1.171.37.35, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.50 out to 28.699 in $\Theta$. The absorption coefficient ($\mu$) of this material is 0.296 and the minimum and maximum transmissions are 0.43954 and 1.00000.

The structure was solved in the space group P2$_1$2$_1$2$_1$ (# 19) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.The crystals were poorly formed plates that gave ill-defined reflections when viewed in the h0l plane.

The Flack parameter was refined to 0.2(2). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.14(11). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is

**Generated precession images**
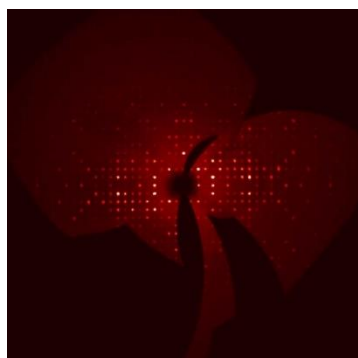


hk0
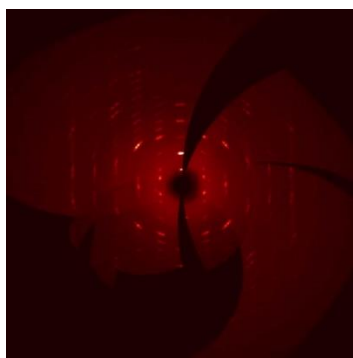


h0l
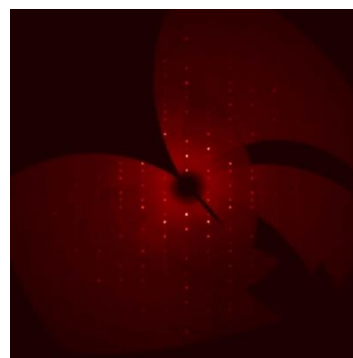


hk0

wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

## Data Plots: Diffraction Data
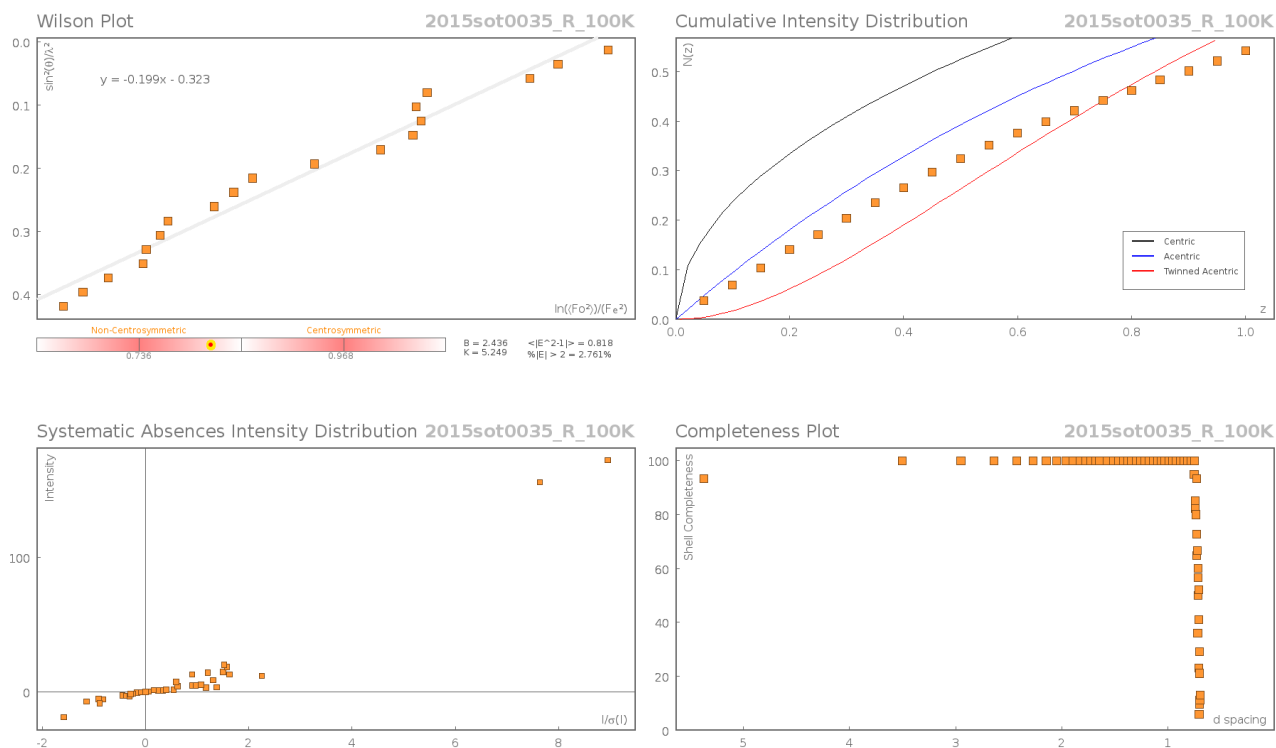


## Data Plots: Refinement and Data
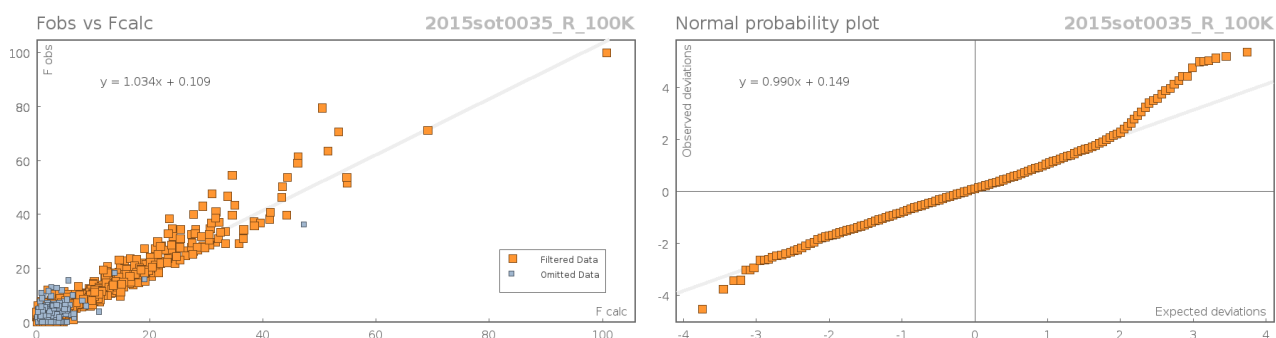
## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 11453 | Unique reflections | 5336 |
| Completeness | 0.954 | Mean I/$\sigma$ | 4.69 |
| hkl$_{max}$ collected | (8, 24, 27) | hkl$_{min}$ collected | (-9, -24, -25) |
| hkl$_{max}$ used | (8, 23, 25) | hkl$_{min}$ used | (-8, 0, 0) |
| Lim d$_{max}$ collected | 7.0 | Lim d$_{min}$ collected | 0.74 |
| d$_{max}$ used | 6.47 | d$_{min}$ used | 0.74 |
| Friedel pairs | 3140 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 91 | R$_{int}$ | 0.1294 |
| R$_{sigma}$ | 0.1639 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 28 |
| Multiplicity | (10809, 544, 4) | Maximum mulitplicity | 8 |
| Removed systematic absences | 50 | Filtered off (Shel/OMIT) | 456 |

**Table 34**: Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2015sot0035_R_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Cl1 | -771(5) | 3355(2) | 508.7(15) | 52.2(9) |
| S1 | 8243(4) | 5732.2(16) | 2436.6(12) | 33.8(7) |
| O1 | 3445(12) | 3364(4) | 3897(3) | 31.4(16) |
| O2 | 4822(12) | 4548(4) | 3894(4) | 36.4(18) |
| O3 | 10622(11) | 4596(5) | 3011(4) | 38.5(18) |
| O4 | 6709(14) | 6038(5) | 1933(3) | 45(2) |
| N1 | 7411(14) | 4800(5) | 2613(4) | 31.7(19) |
| C1 | 1311(19) | 3655(6) | 4876(6) | 39(3) |
| C2 | 980(20) | 3692(7) | 5592(5) | 47(3) |
| C3 | 2630(20) | 3500(7) | 6039(5) | 46(3) |
| C4 | 4510(20) | 3266(7) | 5775(6) | 46(3) |
| C5 | 4825(18) | 3238(6) | 5057(6) | 37(3) |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| C6 | 3192(17) | 3428(6) | 4631(5) | 30(2) |
| C7 | 4355(16) | 3986(6) | 3596(5) | 27(2) |
| C8 | 4677(17) | 3818(6) | 2818(5) | 29(2) |
| C9 | 6367(16) | 3207(6) | 2738(5) | 31(2) |
| C10 | 8409(18) | 3505(7) | 3026(6) | 39(3) |
| C11 | 8893(17) | 4332(6) | 2879(5) | 32(2) |
| C12 | 5270(14) | 4552(6) | 2418(5) | 30(2) |
| C13 | 5084(17) | 4417(6) | 1626(5) | 33(2) |
| C14 | 2834(16) | 4350(6) | 1374(5) | 33(2) |
| C15 | 2690(20) | 4281(7) | 582(5) | 48(3) |
| C16 | 480(20) | 4249(8) | 304(6) | 57(4) |
| C17 | 7640(20) | 6272(6) | 3257(5) | 39(3) |
| C18 | 5341(18) | 6341(7) | 3366(6) | 41(3) |
| C19 | 8779(19) | 5889(7) | 3870(5) | 39(3) |
| C20 | 8630(30) | 7055(7) | 3084(6) | 61(4) |

**Table 35**: Anisotropic Displacement Parameters (×10$^4$) **2015sot0035_R_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11}+ ... +2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|------|------|------|------|------|------|
| Cl1 | 58(2) | 63(2) | 35.5(14) | 3.7(14) | -12.8(14) | -8.6(16) |
| S1 | 39.8(14) | 43.7(15) | 18(1) | 4.9(11) | -0.6(11) | -6.1(11) |
| O1 | 39(4) | 38(4) | 17(3) | 1(3) | 2(3) | -7(3) |
| O2 | 54(5) | 30(4) | 25(3) | -4(3) | 11(3) | -6(3) |
| O3 | 31(4) | 53(5) | 32(4) | -4(3) | 4(3) | 3(4) |
| O4 | 62(6) | 54(5) | 20(3) | 11(3) | -9(4) | -12(4) |
| N1 | 41(5) | 39(5) | 15(3) | -6(3) | 0(4) | -3(4) |
| C1 | 46(7) | 40(6) | 31(5) | -3(5) | -9(5) | -6(5) |
| C2 | 66(8) | 51(7) | 25(5) | -12(5) | 12(6) | -14(6) |
| C3 | 78(9) | 40(7) | 19(4) | 3(5) | 9(6) | -8(6) |
| C4 | 74(9) | 41(7) | 23(5) | 5(5) | -1(6) | -2(6) |
| C5 | 46(7) | 38(6) | 28(5) | 2(5) | 2(5) | -2(5) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C6 | 35(5) | 34(5) | 22(4) | 7(4) | 3(4) | -5(5) |
| C7 | 32(5) | 23(5) | 26(4) | 1(4) | -1(4) | 3(4) |
| C8 | 36(6) | 28(5) | 24(4) | 0(4) | -5(4) | -6(4) |
| C9 | 33(5) | 37(6) | 23(4) | 0(4) | 7(4) | 0(4) |
| C10 | 37(6) | 41(7) | 40(6) | -4(5) | -7(5) | 9(5) |
| C11 | 39(6) | 41(6) | 16(4) | -7(4) | 1(4) | 11(5) |
| C12 | 25(5) | 47(6) | 18(4) | 1(4) | 3(4) | 3(4) |
| C13 | 39(6) | 42(6) | 17(4) | -2(4) | 1(4) | -7(5) |
| C14 | 37(6) | 41(6) | 21(4) | 4(4) | 1(4) | -6(5) |
| C15 | 80(9) | 45(7) | 17(4) | 9(5) | -13(5) | -22(6) |
| C16 | 94(11) | 51(7) | 26(5) | 6(6) | -27(6) | -7(8) |
| C17 | 64(8) | 28(6) | 24(4) | 3(4) | -13(5) | 1(5) |
| C18 | 38(7) | 47(7) | 37(6) | 5(5) | 7(5) | 9(5) |
| C19 | 57(8) | 50(7) | 11(4) | -3(4) | -3(4) | -6(5) |
| C20 | 108(13) | 39(7) | 36(6) | 9(5) | -13(8) | -20(8) |

**Table 36**: Bond Lengths in Å for **2015sot0035_R_100K**.

| Atom | Atom | Length/Å | | Atom | Atom | Length/Å |
|---|---|---|---|---|---|---|
| Cl1 | C16 | 1.800(14) | | C2 | C3 | 1.408(18) |
| S1 | O4 | 1.485(8) | | C3 | C4 | 1.374(18) |
| S1 | N1 | 1.746(9) | | C4 | C5 | 1.401(15) |
| S1 | C17 | 1.883(11) | | C5 | C6 | 1.375(15) |
| O1 | C6 | 1.432(10) | | C7 | C8 | 1.545(13) |
| O1 | C7 | 1.364(12) | | C8 | C9 | 1.531(14) |
| O2 | C7 | 1.176(11) | | C8 | C12 | 1.544(14) |
| O3 | C11 | 1.232(13) | | C9 | C10 | 1.519(15) |
| N1 | C11 | 1.358(13) | | C10 | C11 | 1.504(16) |
| N1 | C12 | 1.493(13) | | C12 | C13 | 1.552(12) |
| C1 | C2 | 1.399(14) | | C13 | C14 | 1.533(14) |
| C1 | C6 | 1.360(16) | | C14 | C15 | 1.538(12) |

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|----------|------|------|----------|
| C15 | C16 | 1.521(18) | C17 | C19 | 1.546(14) |
| C17 | C18 | 1.500(17) | C17 | C20 | 1.544(16) |

**Table 37**: Bond Angles in ° for **2015sot0035_R_100K**.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|------|------|------|---------|
| O4 | S1 | N1 | 105.0(5) | O3 | C11 | C10 | 120.5(9) |
| O4 | S1 | C17 | 103.5(5) | N1 | C11 | C10 | 120.2(9) |
| N1 | S1 | C17 | 103.9(4) | N1 | C12 | C8 | 110.1(8) |
| C7 | O1 | C6 | 114.1(7) | N1 | C12 | C13 | 111.3(8) |
| C11 | N1 | S1 | 114.8(8) | C8 | C12 | C13 | 110.3(8) |
| C11 | N1 | C12 | 124.7(9) | C14 | C13 | C12 | 113.4(8) |
| C12 | N1 | S1 | 120.3(7) | C13 | C14 | C15 | 112.3(9) |
| C6 | C1 | C2 | 119.3(11) | C16 | C15 | C14 | 114.3(11) |
| C1 | C2 | C3 | 118.8(12) | C15 | C16 | Cl1 | 111.8(9) |
| C4 | C3 | C2 | 120.4(10) | C18 | C17 | S1 | 111.2(8) |
| C3 | C4 | C5 | 120.3(12) | C18 | C17 | C19 | 113.3(10) |
| C6 | C5 | C4 | 118.1(11) | C18 | C17 | C20 | 111.5(11) |
| C1 | C6 | O1 | 117.9(9) | C19 | C17 | S1 | 109.2(8) |
| C1 | C6 | C5 | 123.0(10) | C20 | C17 | S1 | 100.2(8) |
| C5 | C6 | O1 | 119.1(9) | C20 | C17 | C19 | 110.7(10) |
| O1 | C7 | C8 | 108.7(8) | | | | |
| O2 | C7 | O1 | 124.5(9) | | | | |
| O2 | C7 | C8 | 126.8(9) | | | | |
| C9 | C8 | C7 | 109.0(8) | | | | |
| C9 | C8 | C12 | 110.6(8) | | | | |
| C12 | C8 | C7 | 111.2(8) | | | | |
| C10 | C9 | C8 | 109.8(8) | | | | |
| C11 | C10 | C9 | 116.1(9) | | | | |
| O3 | C11 | N1 | 119.2(10) | | | | |

Appendices

**Table 38**: Hydrogen Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for **2015sot0035_R_100K**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

Crystals are poorly formed plates with many defects.Diffraction is a little messy and tails off at ca. 1angs.Collected as orthorhombic

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H20A | 10118 | 6988 | 3001 | 92 |
| H20B | 8420 | 7407 | 3473 | 92 |
| H20C | 7972 | 7267 | 2668 | 92 |

| Atom | x | y | z | $U_{eq}$ |
|------|------|------|------|------|
| H1 | 228 | 3788 | 4564 | 47 |
| H2 | -324 | 3843 | 5773 | 57 |
| H3 | 2444 | 3532 | 6526 | 55 |
| H4 | 5600 | 3123 | 6080 | 55 |
| H5 | 6131 | 3092 | 4870 | 45 |
| H8 | 3350 | 3613 | 2623 | 35 |
| H9A | 5954 | 2737 | 2990 | 37 |
| H9B | 6536 | 3076 | 2243 | 37 |
| H10A | 8403 | 3431 | 3534 | 47 |
| H10B | 9548 | 3188 | 2835 | 47 |
| H12 | 4278 | 4967 | 2552 | 36 |
| H13A | 5764 | 4847 | 1380 | 39 |
| H13B | 5838 | 3942 | 1504 | 39 |
| H14A | 2046 | 4807 | 1527 | 39 |
| H14B | 2184 | 3894 | 1589 | 39 |
| H15A | 3407 | 4724 | 370 | 57 |
| H15B | 3430 | 3812 | 435 | 57 |
| H16A | 506 | 4317 | -206 | 68 |
| H16B | -335 | 4676 | 504 | 68 |
| H18A | 4670 | 6477 | 2927 | 61 |
| H18B | 5062 | 6741 | 3710 | 61 |
| H18C | 4789 | 5851 | 3531 | 61 |
| H19A | 8211 | 5375 | 3946 | 59 |
| H19B | 8584 | 6197 | 4289 | 59 |
| H19C | 10264 | 5851 | 3765 | 59 |

**Citations**

CrysAlisPro Software System, Agilent Technologies UK Ltd, Yarnton, Oxford, UK (2014).

CrystalClear, Rigaku, (2009).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

Sheldrick, G.M., ShelXT, *Acta Cryst.*, (2014), **A71**, 3-8.

# List of References

1. Ohmiya, S.; Saito, K.; Murakoshi, I., Chapter 1 Lupine Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*, Academic Press: **1995**; Vol. 47, pp 1-114.

2. Leonard, N. J., Chapter 19 Lupin Alkaloids. In *Alkaloids: Chemistry and Physiology*, Academic Press: **1953**; Vol. 3, pp 119-199.

3. Stenhouse, J. *J. Annalen*, **1851**, *78*, 1–30.

4. Moureu, C.; Valeur, A. *Bull. Soc. Chim.* **1903**, *29*, 1135.

5. Moureu, C.; Valeur, A. *Ann. Chem. Phys*. **1912**, *27*, 245.

6. Clemo, G. R.; Leitch, G. C. *J. Chem. Soc*. **1928**, 1811.

7. Clemo, G. R.; Raper, R.; Tenniswood, C. R. S. *J. Chem. Soc*. **1931**, 429.

8. Clemo, G. R.; Raper, R. *J. Chem. Soc*. **1933**, 644.

9. Ing, H.R. *J. Chem. Soc.* **1932**, 2778.

10. Ing, H.R. *J. Chem. Soc.* **1933**, 504.

11. Clemo, G.R.; Leitch, G.C. *J. Chem. Soc.* **1928**, 1811.

12. Clemo, G.R.; Morgan, W. McG.; Raper, R. *J. Chem. Soc.* **1936**, 1025.

13. Okuda, S.; Kataoka, H.; Kyosuke, T. *Chem. Pharm. Bull.* **1965**, *13*. 491.

14. Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.* **1951**, *29*, 22.

15. Winterfeld, K.; Rauch, C. *Arch. Pharm.* **1934**, 272, 273.

16. Carmack, M.; Douglas, B.; Martin, E. W.; Suss, H. *J. Am. Chem. Soc.* **1955**, *77*, 4435.

17. Seeger, R.; Neumann, H.G. *Inst. Pharmakol. Toxikol.* **1992**, *132*, 1577.

18. Yovo, K.; Huguet, F.; Pothier, J.; Durand, M.; Breteau, M.; Narcisse, G. *Planta Med.* **1984,** *50*, 420.

19. Bobkiewicz-Kozłowska, T.; Dworacka, M.; Kuczyński, S.; Abramczyk, M.; Kolanoś, R.; Wysocka, W.; Garcia Lopez, P. M.; Winiarska, H. *Eur. J. Pharmacol.* **2007,** *565*, 240.

20. Paolisso, G.; Sgambato, S.; Passariello, N.; Pizza, G.; Torella, R.; Tesauro, P.; Varricchio, M.; D'Onofrio, F. *Eur. J. Clin. Pharmacol.* **1988,** *34*, 227.

21. Sgambato, S.; Paolisso, G.; Passariello, N.; Varricchio, M.; D'Onofrio, F. *Eur. J. Clin. Pharmacol.* **1987,** *32*, 477.

22. Paolisso, G.; Sgambato, S.; Passariello, N.; Pizza, G.; Varricchio, M.; Torella, R.; D'Onofrio, F. *Horm. Metab. Res.* **1987,** *19*, 389.

23. Schmeller, T.; Wink, M. In *Alkaloids: Biochemistry, Ecology, and Medicinal Applications*; Robers, M.F.; Wink, M., Eds.; Plenum Press: New York, **1998**, p 435.

24. Chuzel, O.; Riant, O. *Top. Organomet. Chem.* **2005**, *15*, 59.

25. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem*. **1990**, *102*, 1457.

26. Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282.

27. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

28. Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447.

29. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1997**, *29*, 1320

30. Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron Lett.* **1968**, *9*, 2087.

31. Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *9*, 4097.

32. Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, *10*, 2265.

33. Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron* **1970**, *26*, 5453.

34. Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.

35. Haasnoot, C. A. G. *J. Am. Chem. Soc.* **1993**, *115*, 1460

36. De Crisci, A. G.; Annibale, V. T.; Hamer, G. K.; Lough, A. J.; Fekl, U. *Dalton Trans.*, **2010**, *39* , 2888.

37. Galasso, V.; Asaro, F.; Berti, F.; Kovac, B.; Habus, I.; Sacchetti, A. *Chem. Phys.* **2003**, 294, 155.

38. Jasiewicz, B.; Boczonˊ, W.; Warz˙ajtis, B.; Rychlewska, U.; Rafałowicz, T. *J. Mol. Struct.* **2005**, *753*, 45.

39. Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, 115, 2516.

40. Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 11391.

41. Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542.

42. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

43. O'Brien, P. *Chem. Commun.* **2008**, 655.

44. O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480.

45. Würthwein, E.-U.; Hoppe, D. *J. Org. Chem.* **2008**, *73*, 9055.

46. Carbone, G.; O' Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.

47. Fassler, J.; McCubbin, J. A.; Roglans, A.; Kimachi, T.; Hollett, J. W.; Kunz, R. W.; Tinkl, M.; Zhang, Y.; Wang, R.; Campbell, M.; Snieckus, V. *J. Org. Chem.* **2015**, *80*, 3368.

48. Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 15957.

49. Chopade (s), M. U.; Chopade A. U.; Nikalje, M. D. *Adv. Org. Chem. Lett.* **2016**, *3*, 4.

50. Osa, T.; Kashigawa, Y.; Yanagisawa, Y.; Bobbit, J. M. *J. Chem. Soc*. *Chem. Commun*. **1994**, 2535.

51. Clemo, G.R.; Raper, R.; Short, W.S. *J. Chem. Soc.* **1949**, 663.

52. Sorm, F.; Keil, B. *Coll. Czech. Chem. Commun.* **1948**, *13*, 544.

53. Sorm, F.; Keil, B. *Coll. Czech. Chem. Commun.* **1947**, *12*, 655.

54. Greenhalgh, R.; Marion, L. *Can. J. Chem.* **1956**, *34*, 456.

55. Blakemore, P. R.; Norcross, N. R.; Warriner, S. L.; Astles, P. C. *Heterocycles.* **2006**, 70, 609.

56. Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1948**, *70*, 2298.

57. Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316.

58. Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1949**, 71, 757.

59. Leonard, N.J.; Hruda, L.R.; Long, F.W. *J. Am. Chem. Soc.* **1947**, 69, 690.

60. Anet, E.; Hughes, G.K.; Ritchie, E. *Nature* **1950**, 165, 35.

61. Anet, E. F. L. J.; Hughes, G. K.; Ritchie, E. *Aust. J. Sci. Res. A* **1950,** *3*, 635.

62. Schöpf, C.; Benz, G.; Braun, F.; Hinkel, H.; Rokohl, R. *Angew. Chem.* **1953,** *65*, 161.

63. Schöpf, C. *Angew. Chem.* **1957,** *69*, 69.

64. Moore, B.; Marion, L. *Can. J. Chem.* **1953**, 31, 187.

65. Marion, L.; Leonard, N. J.; Moore, B. P. *Can. J. Chem.* **1953**, 31, 181.

66. Tsuda, K.; Satoh, Y. *Pharma. Bull.* (Tokyo) **1954**, *2*, 190.

67. Galinovsky, F.; Kainz, G. *Monatsh. Chem.* **1947,** *77*, 137.

68. Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1960**, 82, 2400.

69. Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1969,** *91*, 7372.

70. Bohlmann, F.; Müller, H.-J.; Schumann, D. *Chem. Ber.* **1973**, 106, 3026.

71. Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Chem. Commun.* **1983**, 12, 654.

72. Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2593.

73. Takatsu, N.; Noguchi, M.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, 35, 4990.

74. Takatsu, N.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, 35, 891.

75. Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, 101, 2435.

76. Wanner, M. J.; Koomen, G.-Jan *J. Org. Chem.* **1996**, *61*, 5581.

77. Schöpf, C.; Braun, F.; Koop, H.; Werner, G.; Bressler, H.; Neisius, K.; Schmadel,E. *Liebigs Ann. Chem.* **1962**, *658*, 156.

78. Schöpf, C.; Braun, F.; Komzak, A. *Chem. Ber.* **1956**, *89*, 1821.

79. Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002,** 4, 2577.

80. Hayashi, T. *Acta Chem. Scand*. **1996**, *50*, 259.

81. Weissfloch, A.; Azerad, R. *Bioorg. Med. Chem.* **1994**, *2*, 493.

82. Milligan, G. L.; Mossman, C. J.; Aube, J. *J. Am. Chem. Soc.* **1995**, 117, 10449.

83. Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declercq, J.-P. *Org. Lett.* **2001**, 3, 3067.

84. Hermet, J.P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004,** *16*, 1830.

85. Hoffmann, R. W.; Sander, T.; Hense, A. *Liebigs Ann. Chem.* **1993**, 771.

86. Sworin, M.; Lin, K. C. *J. Am. Chem. Soc.* **1989**, 111, 1815.

87. Buttler, T.; Fleming, I.; Gonsior, S.; Kim, B.-H.; Sung, A. Y.; Woo, H.-G. *Org. Biomol. Chem.* **2005**, 3, 1557.

88. Buttler, T.; Fleming, I. *Chem. Commun.* **2004**, 2404.

89. Norcross, N. R.; Melbardis, J. P.; Solera, M. F.; Sephton, M. A.; Kilner, C.; Zakharov, L. N.; Astles, P. C.; Warriner, S. L.; Blakemore, P. R. *J. Org. Chem.* **2008**, *73*, 7939.

90. Blakemore, P. R.; Kilner, C.; Norcross, N. R.; Astles, P. C. *Org. Lett.* **2005**, 7, 4721.

91. Firth, J. D.; Canipa, S. J.; Ferris, L. O'Brien. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 223.

92. Firth, J. D.; O'Brien, P.; Ferris, L. *Org. Biomol. Chem.* **2014**, *12*, 9357.

93. Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977.

94. Pousset, C.; Callens, R.; Haddad, M.; Larchevêque, M. *Tetrahedron: Asmmetry*, **2004**, 15, 3407.

95. Scharnagel, D.; Goller, J.; Deibl, N.; Milius, W.; Breuning, M., *Angew. Chem., Int. Ed.* **2018,** *57*, 2432.

96. Nagai, N. Yakugaku Zasshi. **1889**, *9*, 54.

97. Xiao, P.; Li, J.; Kubo, H.; Saito, K.; Murakoshi, I.; Ohmiya, S. *Chem. Pharm. Bull.* **1996**, *44*, 1951.

98. Ding, P.-L.; Liao, Z.-X.; Huang, H.; Zhou, P.; Chen, D.-F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1231.

99. Liu, X.-J.; Cao, M.-A.; Li, W.-H.; Shen, C.-S.; Yan, S.-Q.; Yuan, C.-S. *Fitoterapia* **2010**, *81*, 524.

100. Xiao, P.; Kubo, H.; Ohsawa, M.; Higashiyama, K.; Nagase, H.; Yan, Y.-N.; Li, J.-S.; Kamei, J.; Ohmiya, S. *Planta Med.* **1999**, *65*, 230.

101. Higashiyama, K.; Takeuchi, Y.; Yamauchi, T.; Imai, S.; Kamei, J.; Yajima, Y.; Narita, M.; Suzuki, T. *Biol. Pharm. Bull.* **2005**, *28*, 845.

102. Huang, J.; Xu, H., Matrine: Bioactivities and structural modifications*. Curr. Top. Med. Chem.* **2016**, *16*, (28), 3365.

103. Bohlmann, F., Winterfeldt, E., Friese, U. *Chem. Ber.* **1963**, *96*, 2251.

104. Mandell, L.; Singh, K. P.; Gresham, J. T.; Freeman, W. *J. Am. Chem. Soc.* **1963**, *85*, 2682.

105. Mandell, L.; Singh, K. P.; Gresham, J. T.; Freeman, W. J. *J. Am. Chem. Soc.* **1965**, *87*, 5234.

106. Okuda, S.; Yoshimoto, M.; Tsuda, K. *Chem. Pharm. Bull.* **1966**, *14*, 275.

107. Chen, J.; Browne, L. J.; Gonnela, N. C. *J. Chem. Soc., Chem. Commun.* **1986**, 905.

108. Kobayashi, G.; Furukawa, S.; Matsuda, Y. ; Natsuki, R.; Matsunaga, S. *Chem. Pharm. Bull.* **1970**, *18*, 124.

109. Watkin, S. V.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2013**, *15*, 4596

110. Ochiai, E.; Okuda, S.; Minato, H. *Yakugaku Zasshi.* **1952**, *72*, 781.

111. Okuda, S.; Kamata, H.; Tsuda, K.; Murakoshi, I. *Chem. & Ind.* (London), **1962**, 1326.

112. Kobayashi, G.; Furukawa, S.; Matsuda, Y. ; Natsuki, R.; Matsunaga, S. *Chem. Pharm. Bull.* **1970**, *18*, 124

113. Kobayashi, G.; Furukawa, S.; Matsuda, Y. ; Matsunaga, S. Yakugaku Zasshi, **1969**, *89*, 203 ; Chem. Abstr. **1969**, *70*, 106328.

114. Wenkert, E.; Jeffcoat, A. R. *J. Org. Chem.* **1970**, *35*, 515.

115. Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970.

116. Tonelli, M.; Vazzana, I.; Tasso, B.; Boido, V.; Sparatore, F.; Fermeglia, M.; Paneni, M. S.; Posocco, P.; Pricl, S.; La Colla, P.; Ibba, C.; Secci, B.; Collu, G.; Loddo, R. *Bioorg. Med. Chem.* **2009**, *17*, 4425.

117.  Tonellia, M.; Pagliettib, G.; Boidoa, V.; Sparatore, F.; Marongiuc, F.; Marongiuc, E.; La Collac, P.; Loddoc, R. *Chem. Biodiv.* **2008**, *5*, 2386.

118. Casagrande, M.; Basilico, N.; Parapini, S.; Romeo, S.; Taramelli, D.; Sparatore, *A. Bioorg. Med. Chem.* **2008**, *16*, 6813.

119. Vazzana, I.; Budriesi, R.; Terranova, E.; Ioan, P.; Ugenti, M. P.; Tasso, B.; Chiarini, A.; Sparatore, F. *J.Med. Chem*. **2007**, *50*, 334.

120. Sparatore, A.; Basilico, N.; Parapini, S.; Romeo, S.; Novelli, F.; Sparatorec, F.; Taramelli, D.*Bioorg.Med. Chem.* **2005**, *13*, 5338.

121. Ercoli, M.; Mina, L.; Boido, C. C.; Boido, V.; Sparatore, F.; Armani, U.; Piana, A. *IL Farmaco* **2004**, *59*, 101.

122. Pohmakotr, M.; Numechai, P.; Prateeptongkum, S.; Tuchinda, P.; Reutrakul, V. *Org. Biomol. Chem.* **2003**, *1*, 3495.

123. Pohmakotr, M.; Seubsai, A.; Numeechai, P.; Tuchinda, P. *Synthesis* **2008**, 1733.

124. Remuson, R. Gelas.-Mialhe., Y *Mini-Rev. Org. Chem.* **2008**, *5*, 193.

125. Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222.

126. Wasserman, H. H.; Vu, C. B.; Cook, J. D. *Tetrahedron* **1992**, *48*, 2101.

127. Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014

128. Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

129. Su, D.; Wang, X.; Shao, C.; Xu, J.; Zhu, R.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 188.

130. Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911.

131. Kitahara, K.; Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 2259.

132. Ahari, M. h.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473.

133. Hajri, M.; Blondelle, C.; Martinez, A.; Vasse, J.-L.; Szymoniak, J. *Tetrahedron Lett.* **2013**, *54*, 1029.

134. Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988.

135. Watkin, S. V. *PhD Thesis*. University of Southampton, **2013**.

136. Kise, N.; Inoue, Y.; Sakurai, T. *Tetrahedron Lett*. **2013** *54*, 3281.

137. Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron*, **2016**, *72*, 7417.

138. Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Synlett*, **2017**, *28*, 2697.

139. Ionut, A. P. *PhD Thesis*. University of Southampton, **2015**.

140. Nagao, Y.; Dai, W.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem*, **1990**, 55, 1148.

141. Kinghorn, A. D. *J. Agric. Food Chem*. **1982**, *30*, 796.

142. Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289.

143. Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 13196.

144. Evans, D. A.; Nelson, J. V.; Taber, T. R. Stereoselective Aldol Condensations. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, **1982**; Vol. *13*.

145. Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **2002**, *67*, 7819.

146. Humphries, P. S.; Do, Q-Q. T.; Wilhite, D. M. *Beilstein J Org Chem.* **2006**, *2*, 1.

147. Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639.

148. Gaetjens, E.; Morawetz, H. *J. Am. Chem. Soc.* **1960**, *82*, 5328.

149. Simion, A. M.; Hashimoto, I.; Mitoma, Y.; Egashira, N.; Simion, C. *Synth commun*. **2012**. 42, 921.

150. Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem*. **2010**, 75, 498.

151. Chen W.; Ren J.; Wang M.; Dang L.; Shen X.; Yang X.; Zhang H. *Chem. Commun.* **2014**, 50, 6259.

152. Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem*. **2006**, 71 (4), 1732.

153. Miller, I. R. *PhD Thesis*. University of Southampton, **2008**.

154. Gray, D.; Gallagher, T., *Angew. Chem. Int*. *Ed*, **2006**, 45, 2419.

155. Lui, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278

156. Bogdal, D. *Molecules* **1999**, *4*, 333.

157. Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, *2005*, 1334.

158. Han, P.; Si, C. M.; Mao, Z. Y.; Li, H. T.; Wei, B. G. *Tetrahedron* **2016**, *72*, 862.

List of References