STUDIES ON THE GENERATION AND USE OF FUNCTIONALISED
ORGANOZINC CARBENOIDs FOR THE SYNTHESIS
OF AMINOCYCLOPROPANES AND RELATED CONGENERS

A Thesis Presented by

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In Partial Fulfilment of the Requirements
for the Award of the Degree of

DOCTOR OF PHILOSOPHY OF THE
UNIVERSITY OF LONDON

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ABSTRACT

The present thesis describes a range of studies on the generation and reactivity of organozinc carbenoid species possessing adjacent nitrogen functionality for the preparation of aminocyclopropanes and related congeners.

This thesis opens with two distinct introductory reviews. The first one focuses on the description of the different general methods already available for the synthesis of aminocyclopropanes. The second one is concerned with the generation and reactivity of organozinc carbenoids encountered in the literature.

The results and discussion chapter firstly describes the successful generation of an organozinc carbenoid from an acetal moiety contiguous to a nitrogen atom of a simple cyclic amide using a mixture of zinc amalgam and chlorotrimethylsilane. This new organometallic species is found to undergo cyclopropanation reactions with a range of alkenes to yield amidocyclopropanes.

Subsequent studies directed towards the design of carbenoid precursors which can lead to the preparation of primary aminocyclopropanes are then discussed. A method for the synthesis of chiral protected aminocyclopropanes in two steps from their corresponding alkenes is described.

An investigation of the preparation of N-substituted cyclopropyl amino alcohols and acids is presented. From this study, an N-substituted cyclopropyl glycine derivative is prepared.

Finally, this thesis discusses the attempted palladium-catalysed cross-coupling reactions between amino cyclopropylsilanes and aryl iodides and the successful Tamao-Fleming oxidation of the carbon-silicon bond of vicinal amino cyclopropylsilanols to give the corresponding amino cyclopropanols.

The thesis terminates with a full description of the experimental procedures used and the compounds prepared.
DECLARATION

The research described in this thesis is, to the best of my knowledge, original except where due reference is made to other authors.
CONTENTS

Abstract 2
Declaration 3
Contents 4
Acknowledgements 7
Abbreviations 8
Stereochemical notation 11

Chapter 1 Introduction 12
1 Introduction 13
1.1 Synthesis of cyclopropylamines 13
1.1.1 By cyclopropyl migration via a Hofmann or Curtius rearrangement 14
1.1.2 By cyclopropanation of enamines and enamides 16
1.1.3 By titanium-mediated cyclopropanation of carboxamides and nitriles 18
1.1.4 Reactions involving 1,3-ring-closure 21
1.1.5 By reaction with a "cyclopropanone equivalent" 22
1.1.6 Via palladium-catalysed C-N bond formation 24
1.1.7 By reduction of nitrocyclopropanes 24
1.1.8 By addition of aminocarbenes or carbenoids to alkenes 25
1.1.9 Summary 26
1.2 Organozinc carbenoids 27
1.2.1 Carbenes and carbenoids 27
1.2.2 Organozinc carbenoid chemistry 28
1.2.2.1 From gem-dihalo compounds 28
1.2.2.1.1 Background 28
1.2.2.1.2 The "cyclopropanating agent" 31
1.2.2.1.3 Theoretical studies on cyclopropanation reactions 32
1.2.2.1.4 Evolution of the "cyclopropanating agent" 34
1.2.2.2 From diazoalkanes and zinc salts 37
1.2.2.3 From carbonyl compounds 38
1.2.2.3.1 The Clemmensen reduction of carbonyl compounds 38
Chapter 2 Results and Discussion

2 Introduction

2.1 Background – The attempted aminocyclopropanation reaction using dimethylformamide dimethyl acetal

2.2 Preliminary study on the amidocyclopropanation reaction using N-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

2.3 Methods used to determine the stereoselectivity of the cyclopropanation reaction

2.4 Further study on the amidocyclopropanation of allylbenzene using N-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

2.5 Scope and limitation of this novel amidocyclopropanation reaction

2.5.1 Cyclopropanation of unfunctionalised alkenes

2.5.2 Cyclopropanation of functionalised alkenes

2.5.2.1 Cyclopropanation of electron rich double bonds

2.5.2.2 Cyclopropanation of electron deficient double bonds

2.6 Extension of this novel amidocyclopropanation reaction

2.6.1 Study of the amidocyclopropanation reaction using N-benzyl-N-diethoxymethylacetamide as the carbenoid precursor

2.6.2 Study of the amidocyclopropanation reaction using N-formyl amides as the carbenoid precursor

2.7 Studies toward the preparation of primary aminocyclopropanes

2.7.1 Study of the cyclopropanation reaction using N-diethoxymethyl phthalimide as the carbenoid precursor

2.7.2 Study of the preparation of primary aminocyclopropanes using N-diethoxymethyl-2,3-dihydroisoindol-1-one as the carbenoid precursor

2.7.3 Preliminary study of the use of N-diethoxymethyl oxazolidinones as carbenoid precursors

2.7.4 A proposed mechanism to account for the stereochemistry observed
<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7.5 Scope of the cyclopropanation reaction using (±)-N-diethoxymethyl-</td>
</tr>
<tr>
<td>-4,5-diphenyloxazolidinone</td>
</tr>
<tr>
<td>74</td>
</tr>
<tr>
<td>2.7.6 Synthesis of chiral cyclopropane derivatives</td>
</tr>
<tr>
<td>76</td>
</tr>
<tr>
<td>2.7.7 Deprotection of 4,5-diphenyloxazolidinone cyclopropanes</td>
</tr>
<tr>
<td>77</td>
</tr>
<tr>
<td>2.7.8 Studies towards the preparation of primary arylcyclopropylamines</td>
</tr>
<tr>
<td>81</td>
</tr>
<tr>
<td>2.7.8.1 Use of a different carbenoid precursor</td>
</tr>
<tr>
<td>81</td>
</tr>
<tr>
<td>2.7.8.2 Studies of alternative methods for the cleavage of the</td>
</tr>
<tr>
<td>diphenyloxazolidinone ring</td>
</tr>
<tr>
<td>82</td>
</tr>
<tr>
<td>2.8 Studies on the synthesis of N-substituted cyclopropyl amino alcohols</td>
</tr>
<tr>
<td>and acids</td>
</tr>
<tr>
<td>85</td>
</tr>
<tr>
<td>2.9 Studies on the synthesis of arylcyclopropanes via a palladium-catalysed</td>
</tr>
<tr>
<td>cross-coupling reaction</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>2.9.1 Palladium-catalysed cross-coupling reactions involving cyclopropyl</td>
</tr>
<tr>
<td>halides</td>
</tr>
<tr>
<td>91</td>
</tr>
<tr>
<td>2.9.2 Palladium-catalysed cross-coupling reactions involving cyclopropyl</td>
</tr>
<tr>
<td>organometallic species</td>
</tr>
<tr>
<td>92</td>
</tr>
<tr>
<td>2.9.3 Palladium-catalysed cross-coupling reactions of organosilicon</td>
</tr>
<tr>
<td>compounds</td>
</tr>
<tr>
<td>93</td>
</tr>
<tr>
<td>2.9.3.1 Background</td>
</tr>
<tr>
<td>93</td>
</tr>
<tr>
<td>2.9.3.2 A preliminary study towards the palladium-catalysed cross-</td>
</tr>
<tr>
<td>coupling reactions of cyclopropylsilanes</td>
</tr>
<tr>
<td>95</td>
</tr>
<tr>
<td>2.10 Preparation of vicinal amino cyclopropanols</td>
</tr>
<tr>
<td>98</td>
</tr>
<tr>
<td>2.10.1 Background</td>
</tr>
<tr>
<td>98</td>
</tr>
<tr>
<td>2.10.2 The use of the Tamao-Fleming oxidation of cyclopropylsilanes</td>
</tr>
<tr>
<td>leading to the preparation of vicinal amino cyclopropanols</td>
</tr>
<tr>
<td>99</td>
</tr>
<tr>
<td>Chapter 3 Conclusions and perspectives</td>
</tr>
<tr>
<td>102</td>
</tr>
<tr>
<td>Chapter 4 Experimental</td>
</tr>
<tr>
<td>108</td>
</tr>
<tr>
<td>4 General experimental</td>
</tr>
<tr>
<td>109</td>
</tr>
<tr>
<td>4.1 Experimental Procedures</td>
</tr>
<tr>
<td>111</td>
</tr>
<tr>
<td>Chapter 5 References</td>
</tr>
<tr>
<td>209</td>
</tr>
<tr>
<td>Chapter 6 Appendix</td>
</tr>
<tr>
<td>219</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

I would firstly like to thank my supervisor, Professor Willie Motherwell, for his guidance, help and encouragements over the past three years. I am also very grateful to my industrial supervisor at AstraZeneca, Doctor David Cladingboel, for his advice, enthusiasm and having arranged my very enjoyable three-month industrial placement in Loughborough.

I would like also to thank various members of the “WBM family”, firstly the ‘Maman’ of the group, Robyn, for her help in the lab and also for her kindness to proofread a part of this manuscript (and for having informed me that the use of “promiscuity” is not proper when one would like to refer to “proximity” of two atoms), Rob and Ela for all the very good time spent inside and outside of the lab, Steve of being always ready to ‘give a hand’, Tom for being the only one always interested in talking about organozinc carbenoids and having proofread the Introduction of this manuscript, Alex for his enthusiasm in the lab and (particularly) in the pub, Lynda, Beatrice, Camilla and Oliver for helping me to settle in my first year.

I am also very grateful to all the ‘technical’ staff at UCL Chemistry Department, especially to Dr. Abil Aliev for NMR and John Hill and his colleagues for mass spectra.

I would like to thank all the people from the AstraZeneca site of Loughborough who have contributed to make my stay a very interesting and pleasant experience. I also wish to express my gratitude to AstraZeneca for its financial support.

A special thank to Dr. Yvain Roué for all his time spent on my initiation to practical organic chemistry.

Most of all I would like to thank my parents, Dominique and Marie-Christine, for their constant support and help, and Mina-chan for her encouragements during my PhD, having left her so loved Japan to join me in Europe and all the happiness that she is bringing to me.
ABBREVIATIONS

Ac acetyl
All allyl
Ar unspecified aryl group
arom aromatic
BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc tert-butoxycarbonyl
Bu butyl
Bn benzyl
br broad
c cyclo
cat. catalytic
CI chemical ionisation
Δ reflux
dba dibenzylideneacetone
DCE dichloroethane
DMF N,N-dimethylformamide
DMS dimethylsulfide
DMSO dimethyl sulfoxide
EI electron impact
ee enantiomeric excess
eq molar equivalent(s)
Et ethyl
FAB fast atom bombardment
g gram(s)
GC gas chromatography
h hour(s)
Hz Hertz
i iso
IPA isopropyl alcohol
J coupling constant
L unspecified ligand
Abbreviations

LA Lewis acid
LiHMDS lithium bis(trimethylsilyl)amide
lit. literature value
M unspecified metal
m medium
m-CPBA 3-chloroperoxybenzoic acid
Me methyl
min minutes
mL millilitre(s)
mp melting point
n neo
NCS N-chlorosuccinimide
NMR nuclear magnetic resonance
Nu nucleophile
p para
ppm parts per million
Ph phenyl
Phth phthalimide
PMP para-methoxyphenyl
Pr propyl
s strong
R unspecified carbon substituent
Rf retention factor
rt room temperature
t tert
TBAF tetrabutylammonium fluoride
TBDMS t-butyldimethylsilyl
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl
Ts para-toluenesulfonic
w weak
wt. weight
X leaving group
Abbreviations

Y functionalised group
STereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr. Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates distance from the viewer.

Chapter 1

Introduction
1 Introduction

The present thesis is concerned with a study of the generation and reactivity of functionalised organozinc carbenoids and in particular their use for the synthesis of aminocyclopropanes and related congeners.

In order to place this work in perspective, the following introduction is divided into two distinct parts. The first focuses on a description of those methods already available for the preparation of aminocyclopropanes. This account is done with a critical eye, trying to present both the advantages and also the drawbacks of these methods, thereby allowing the reader to compare and estimate the value of our own method which is presented in the following chapter of Results and Discussion.

For a better comprehension of the behaviour of the carbenoid species involved in this work, a presentation of the generation, structure and reactivity of organozinc carbenoids reported in the chemical literature is provided in the second part of this introduction. Emphasis has been given to the chemistry developed in this area within our own group.

1.1 Synthesis of cyclopropylamines

The development of new routes towards the synthesis of cyclopropylamines still represents an exciting challenge for chemists since reported approaches for their preparation generally suffer from a lack of generality and/or efficiency. As aminocyclopropanes have recently received increased attention on account of their diverse biological activities,¹ the emergence of more practical methods for their preparation would be highly valuable. From the numerous natural and non-natural biologically active cyclopropylamines the commercially available antidepressant Tranylcypromine 1, the broad-spectrum antibacterial Trovafloxacin 2 and the natural product Belactosin A² 3 are probably the most significant examples at present (Scheme 1).
This introduction will concentrate on describing the different general and reasonably efficient methods which have been employed to prepare cyclopropylamines. Ways to access cyclopropane amino acids, principally 2,3-methanoamino acid derivatives, have been intensively reviewed and will not be included as they usually involve strategies which are not applicable for the synthesis of simple alkyl or aryl aminocyclopropanes.\textsuperscript{3,4} Vilsmaier comprehensively reviewed the chemistry of cyclopropylamines in 1987 but since then, no report covering more recent advances in this field has been published.\textsuperscript{5}

1.1.1 By cyclopropyl migration via a Hofmann or Curtius rearrangement

The most common way to prepare aminocyclopropanes relies on classical Hofmann or Curtius degradation of a carboxylic acid derivative of type 4 or 5 (Scheme 2).\textsuperscript{5} Both processes involve the generation of an acyl nitrene which rearranges to yield an isocyanate 6. This latter intermediate can either be hydrolysed to the corresponding amine 7 or be trapped by an alcohol (usually used as the solvent) to yield a carbamate 8.
From the differing modifications of the Curtius rearrangement, the method introduced by Weinstock\textsuperscript{6} involving the reaction of a mixed anhydride with sodium azide and that developed by Yamada \textit{et al.}\textsuperscript{7} employing the nonexplosive diphenylphosphoryl azide have proven to be the most popular (Scheme 3). It is also important to note that when these conditions are followed, the rearrangement occurs stereospecifically with total retention of both optical and geometrical configuration.

The cyclopropyl carboxylic acid precursors for these transformations are usually derived from saponification of their corresponding esters, and these latter compounds can, in turn, be synthesised in numerous ways (Scheme 4). The most common routes involve metal-catalysed cyclopropanation reaction, either of alkyl diazoacetates with alkenes (usually with Cu and Rh and more recently Ru) or diazomethane with alkyl cinnamates (most commonly with Pd(II)), or the Michael-initiated ring closure reaction of alkyl cinnamates with sulfur ylides.\textsuperscript{8}
**Introduction**

Recent developments of these reactions have allowed the preparation of selected cyclopropyl esters with excellent stereo- and/or enantiospecificities. Interested readers are directed towards the referenced reviews. ⁸

An alternative method, first developed by Wadsworth and Emmons⁹ in 1961 and involving the reaction between an epoxide and a phosphonoacetate enolate, has recently received increased attention.¹⁰ Starting with an enantiomerically pure epoxide, it was demonstrated that this process occurs with almost complete inversion of the epoxide configuration (Scheme 5).

Although the methods outlined above for the preparation of cyclopropylamines involving a Hofmann or Curtius rearrangement are fairly general, the overall process nevertheless requires a minimum of four steps and rarely achieves more than a 50% overall yield.

**1.1.2 By cyclopropanation of enamines and enamides**

The cyclopropanation of enamines and related congeners appears, in principle, to be a very straightforward route towards the synthesis of aminocyclopropanes. This reaction
is commonly performed either with an organozinc carbenoid,\textsuperscript{11,12,13,14} \( \text{IZnCHR} \) (\( R=\text{H}, \text{Me} \) or F), or an alkyl diazo compound, such as diazomethane or diphenyldiazomethane, in the presence of a copper (II)\textsuperscript{12,15} or palladium (II)\textsuperscript{16} salt. The desired products are formed however in very variable yields (Scheme 6).

More recently Aggarwal \textit{et al.} reported a useful practical modification involving \textit{in situ} generation of aryl diazomethanes from hydrazone derivatives, thus avoiding the handling of hazardous diazoalkanes.\textsuperscript{17} When applied to the cyclopropanation reaction of \( N \)-vinylphthalamide this approach appears to be a particularly effective method for preparation of \textit{cis} 2-arylcyclopropylamines (Scheme 7).

Within the scope and uses of copper-catalysed cyclopropanations, reactions using alkyl diazoacetates with enamines have received increasing attention since the product \( \beta \)-aminocyclopropanecarboxylic acids are interesting building blocks for peptide chemistry (Scheme 8).\textsuperscript{3e}
1.1.3 By titanium-mediated cyclopropanation of carboxamides and nitriles

Within the last decade, a new cyclopropanation reaction mediated by titanium species has emerged. Initially developed by Kulinkovich\textsuperscript{18} for the preparation of cyclopropanols from esters, this method was then adapted by de Meijere\textsuperscript{19} for the synthesis of aminocyclopropanes. In this present introduction only a concise overview of this methodology is given, and more details and tables of results can be found in several reviews which have recently appeared.\textsuperscript{20}

In essence, when treated with alkylmagnesium halides, titanium alkoxide derivatives form titanacyclopropane intermediates of type 9\textsuperscript{20} which then act as 1,2-dicarbanionic species and react with $N,N$-dialkylcarboxamides yielding cyclopropylamines (Scheme 9).\textsuperscript{19,21}

This reaction has been applied successfully to a range of carboxamides and Grignard reagents and some selected examples are shown in Scheme 10. The use of methyltitanium triisopropoxide instead of titanium tetraisopropoxide was subsequently found to be preferable as yields of cyclopropylamines are generally higher.\textsuperscript{21} $N,N$-dibenzylcyclopropylamines can yield primary cyclopropylamines by simple hydrogenolysis. However, this method cannot be applied to all substrates, especially those possessing an aryl group attached to the cyclopropane, since cyclopropyl rings are known to be hydrogenated with ring opening under such conditions.
Applying a somewhat modified protocol allows functionalised organozinc derivatives to be employed (Scheme 11).22

The general method was then greatly improved when some titanacyclopropane intermediates were found to undergo rapid ligand exchange with added alkenes.23 Intermediates of type 10, prepared by the reaction of cyclopentyl24- or cyclohexyl25 magnesium halide appeared to be the best for this purpose. This overall process may be considered as a dialkylaminocyclopropanation of alkenes (Scheme 12).
The intramolecular variant of this reaction has also been developed for terminal alkenes as depicted for the example in Scheme 13.24

More recently aliphatic and aryl nitriles were found to undergo similar reactions yielding primary 1-substituted aminocyclopropanes. In most cases a Lewis acid, such as BF₃.OEt₂ or TiCl₄, has to be present to initiate the contraction of the azatitanacycle 8 (Scheme 13).26 A variant using diethyl zinc and methyltitanium triisopropoxide in the presence of lithium salts has also been reported for aryl nitriles and gives comparable results (Scheme 14).27
Introduction

To date, the titanium-mediated cyclopropanation reaction appears to be the most direct route to prepare aminocyclopropanes. However, this new method is usually limited to the preparation of poorly functionalised cyclopropylamines as the use of Grignard reagents is incompatible with a number of functional groups such as carbonyl groups and halogens. In addition, an efficient chiral version of this reaction still remains to be developed.\textsuperscript{20b}

1.1.4 Reactions involving 1,3-ring-closure

A widely applicable method for the preparation of substituted bicyclic cyclopropanes has been developed based on 1,3-ring-closure reaction. The description of this approach has received particular attention in the review written by Vilsmaier\textsuperscript{5} and then in 1997 in a chapter of “Methods of Organic Chemistry” dedicated to the synthesis of cyclopropanes.\textsuperscript{28} The principle of this method is to induce a ring closure reaction by the reaction of a nucleophile with an enamine possessing an adjacent leaving group such as chloride anion or a dimethylsulfonium group (Scheme 15).

Generally, \textit{endo} cyclopropylamines 13, resulting from kinetically preferred attack of nucleophiles at the sterically less hindered face of cyclopropyliminium cation 12 are the
exclusive or predominant products. The reaction has been shown to be very broad in scope as a wide range of nucleophiles can be successfully used.\textsuperscript{5,28}

The synthetically utility of this approach has been recently broadened by the preparation of primary aminocyclopropanes starting with enamines having a removable group for \( R^3 \) and \( R^4 \) (Scheme 15), such as a benzyl or allyl group (Scheme 16).\textsuperscript{29}

\[ \text{Scheme 16} \]

This methodology generally gives good yields and stereoselectivities of cyclopropylamines starting with 6 or 7 member ring enamines, it appeared that for other ring sizes the results obtained are more variable.\textsuperscript{28}

1.1.5 By reaction with a "cyclopropanone equivalent"

An alternative approach for the preparation of cyclopropylamines proceeds via a cyclopropanone derivative.\textsuperscript{30} As cyclopropanone itself is not a stable compound, \([(1-ethoxycyclopropyl)oxy]trimethylsilane \text{14}, which is commercially available, is the starting material commonly used in this chemistry. This reagent is readily desilylated in alcohol to give a cyclopropanone hemiketal which is in equilibrium with the parent ketone (Scheme 17).

\[ \text{Scheme 17} \]

Kang \textit{et al.} have described an \( N \)-cyclopropylation reaction by the direct substitution of the bromine atom of cyclopropane \text{15} by an aromatic amine and subsequent reductive dealkoxylation in the presence of sodium borohydride and a Lewis acid (Scheme 18).\textsuperscript{31}
The presence of an electron-donating group on the same carbon as the bromine atom is imperative for effective displacement by the nucleophile on such a cyclopropyl ring.\textsuperscript{30,32}

![Scheme 18](image_url)

More recently Yoshida \textit{et al.} have simplified this process by performing the condensation of the aniline directly with 14 in an acidic medium to yield the desired product in two straightforward steps (Scheme 19).\textsuperscript{33} The first reaction almost certainly involves the formation of the iminium cation 16 at some stage since most of the ethoxy group of 14 is replaced by the solvent.

![Scheme 19](image_url)

Another method consists of the one-pot reductive amination of aliphatic and aromatic amines with 14. However mono-cyclopropylation of aliphatic primary amines cannot be achieved following this protocol (Scheme 20).\textsuperscript{34}

![Scheme 20](image_url)
These methods are complementary to those already presented, but have so far been restricted to the introduction of the simplest cyclopropyl unit since substituted cyclopropanones are not readily available.

### 1.1.6 Via palladium-catalysed C-N bond formation

A practical method for the synthesis of $N$-arylcyclopropylamines has recently been developed by Loeppky et al.\(^{35}\) Their approach is based on the palladium-catalysed amination reaction of aryl bromides with cyclopropylamine. Using the standard conditions for this type of cross-coupling reaction a range of $N$-cyclopropylaromatic amines were prepared in moderate to excellent yields (Scheme 21).\(^{36}\)

$$\text{ArBr} + \text{H}_2\text{N} \xrightarrow{\text{Pd}_2(\text{dba})_3, \text{BINAP}, \text{NaOtf-Bu}} \text{toluene, 80°C, sealed tube} \xrightarrow{52-99\%} \text{ArHN}$$

**Scheme 21**

### 1.1.7 By reduction of nitrocyclopropanes

Nitrocyclopropanes can of course be considered as obvious precursors of cyclopropylamines by reduction of the nitro group. Their synthesis is commonly performed by Michael-initiated ring closure reactions of nitroalkenes with sulfur ylides followed by reduction of the nitro group either by catalytic hydrogenation or by reaction with iron in the presence of hydrochloric acid (Scheme 22).\(^{37,38}\)

$$\text{R}^1\text{=CH}_2\text{ or Ph} \quad \text{R}^2\text{=H or CH}_3$$

**Scheme 22**

Taking into account the two steps usually required for the preparation of nitroalkenes\(^{39}\) and the relative instability of this class of compounds, the overall process appears to be tedious and low yielding.
Arylcyclopropylamines can also be derived from 1-nitrocyclopropane carboxylates 17 after decarboxylation and subsequent reduction of the nitro function (Scheme 23).\(^{40}\)

### Scheme 23

Compounds of type 17 are conveniently prepared in one step by a rhodium-catalysed cyclopropanation reaction involving either the use of α-nitro-α-diazocarboxylates\(^ {40,41,42}\) or α-nitroesters in the presence of iodobenzene diacetate\(^ {40,42}\).

1.1.8 **By addition of aminocarbenes or carbenoids to alkenes**

In conceptual terms, this strategy can be seen as one of the most convergent since the aminocyclopropane derivative is formed in a single step from readily available alkenes as starting materials (Scheme 24).

### Scheme 24

In practice however, only a few papers, to date, relate the successful use of such aminocarbenes for the cyclopropanation of alkenes and this is usually with limited practical applications.\(^ {43,44}\)

Within the field of carbenoid chemistry, Ogawa *et al.* have shown that, for the specific cases of \(N,N\)-disubstituted aromatic amides, treatment with a mixture of samarium and samarium diiodide yields an organosamarium carbenoid species which is capable of cyclopropanating styrene (Scheme 25).\(^ {45}\) However this reaction has limited efficiency as
it requires the use of a large excess of alkene and the yields obtained are low to moderate.

\[
\text{Scheme 25}
\]

1.1.9 Summary

From the foregoing overview, it is apparent that existing methods for the preparation of various aminocyclopropanes often require multistep sequences and/or are not compatible with a number of functional groups. Moreover, and especially so for those reactions in which formation of the cyclopropane is achieved in two discrete carbon-carbon bond forming steps, stereochemical issues may become complicated. Whilst metal mediated addition of carbenoids to enamine derivatives appears to offer a more direct approach to stereocontrolled aminocyclopropane synthesis, it is however limited in terms of the possible substituents on the carbenoid carbon. As we have seen, the direct addition of a carbenoid bearing useful nitrogen functionality has been reported in only one specific case, involving samarium/samarium diiodide reduction of \(N,N\) disubstituted aromatic amides. The de Meijere variant of the Kulinkovich reaction, which continued to be studied during the course of our own work, is especially noteworthy in terms of conceptual elegance and practicality.
1.2 Organozinc carbenoids

The second section of this present introduction is concerned with the preparation and reactivity of different organozinc carbenoids encountered in the literature. It will start with a definition of carbenoids and then move to the study of common organozinc carbenoids employed for the cyclopropanation of olefins, such as the Simmons-Smith reagent. The final section will then go on to describe in more detail, the discovery, generation and reactivity of organozinc carbenoids from carbonyl compounds and related congeners. This last part is of particular relevance because of its direct link with the evolution of the work carried out in the present thesis.

1.2.1 Carbenes and carbenoids

Carbenes are generally considered as neutral two-coordinate carbon reactive intermediates with two nonbonding electrons which may have either anti parallel spins (singlet state) or parallel spins (triplet state) (Scheme 26).

Free carbenes are generally highly reactive and short-lived species. Singlet carbenes add stereospecifically to alkenes but this reaction is often accompanied by competing insertion reactions into C-H bonds. Triplet carbenes react as diradicals and give nonstereospecific addition to alkenes as well as hydrogen abstraction.

However carbenes can be stabilised by a metal thus becoming more suitable for synthetic purposes. Two types of complexes can formally be considered; viz. transition metal carbene complexes 18 which have formal metal-carbon double bonds (Scheme 27) and organometallic carbenoids 19 which possess a metal atom M (M = Li, Na,
ZnX, ...) and a leaving group X (X = F, Cl, Br, I, OR, ...) attached at the same carbon centre (Scheme 27).

\[
\begin{align*}
\text{Scheme 27} \\
\end{align*}
\]

Transition metal carbene complexes of type 18 undergo a wide range of very useful reactions such as alkene metathesis, alkene and alkyne polymerisation, cyclopropanation, insertion reactions and ylide generation. They are the subject of numerous reviews and books.\textsuperscript{46}

Amongst organometallic compounds of type 19, we will concentrate on organozinc carbenoids and begin with a very common organozinc carbenoid generated from dihalo compounds, the Simmons-Smith reagent.\textsuperscript{47} Since the scope of this carbenoid as well as its use in asymmetric reactions have been intensively reviewed, only a general view of the preparation and reactivity of this reagent will be given.\textsuperscript{48,49,8a}

1.2.2 Organozinc carbenoid chemistry

1.2.2.1 From gem-dihalo compounds

1.2.2.1.1 Background

In 1929, Emschwiller first presented evidence for the formation of iodomethylzinc iodide 20 by the reaction of diiodomethane with zinc-copper couple in ether at reflux.\textsuperscript{50} He observed that the organozinc species formed gave methyl iodide upon hydrolysis, diiodomethane by the addition of iodine and evolution of ethylene when the reaction was heated at prolonged reflux (Scheme 28). These observations led Emschwiller to propose that (iodomethyl)zinc iodide 20 had been formed.
Almost thirty years after this observation, Simmons and Smith discovered that this new organometallic species could be trapped efficiently by alkenes, thus providing a new and very valuable synthetic route to cyclopropane derivatives 21 (Scheme 29). The reaction proved to be stereospecific in terms of strict retention of olefin geometry, usually free from serious side reactions such as C-H insertion reactions and followed second-order kinetics. For these reasons, the Simmons-Smith reaction appeared to transfer a methylene moiety without any free carbene being released. The mechanism proposed for this cyclopropanation reaction proceeds through a "butterfly-type" transition state as depicted in Scheme 30.

It was also observed that the zinc reagent behaved as a weak electrophile since it reacted more readily with electron rich olefins. Another very important characteristic of this reaction is that proximal basic groups (oxygen and nitrogen) could direct the delivery of the methylene group and also enhance the rate of the reaction. The strongly directing effect of oxygen substituents
was recognised early on. Thus, Winstein and Sonnenberg showed that the hydroxyl group of 3-cyclopenten-1-ol 22 controlled the stereochemistry of methylene transfer to give exclusively cis-3-hydroxybicyclo[3.1.0]hexane 23 (Scheme 31).\textsuperscript{52}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{scheme31.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 31}

A few years later, Furukawa found that a similar cyclopropanating agent could be generated by an alkyl exchange reaction between diethyl zinc and a 1,1-dihaloalkane.\textsuperscript{53} Furukawa’s system offers the following advantages over the Simmons-Smith reaction: the reaction is homogenous, reaction times are usually shorter and reactions are not restricted to methylene transfer, but may also be used with alkyl and phenyl carbenoids. For example, the reaction between cyclohexene and benzal iodide in the presence of diethyl zinc affords a mixture of endo-24 and exo-24 in reasonable yield (Scheme 32). The predominant formation of the thermodynamically less favoured isomer is almost always observed for alkylidene and benzylidene transfer.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{scheme32.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 32}

Since these original observations were made, extensive work has been carried out in order to extend the scope of this reaction and to characterise the cyclopropanating agent.
1.2.2.1.2 The “cyclopropanating agent”

The structure of the classical Simmons-Smith reagent, believed to be IZnCH$_2$I 20 or Zn(CH$_3$I)$_2$.ZnI$_2$ 25 (Scheme 33), has been extrapolated from product distribution data (hydrolysis and iodine treatment) and observations of its chemical behaviour.$^{54}$

\[
2 \text{IZnCH}_2\text{I} \xrightarrow{\text{equilibrium}} \text{Zn(CH}_3\text{I)}_2 + \text{ZnI}_2
\]

Scheme 33

On the other hand the active species in Furukawa’s reagent may include species such as ICH$_2$ZnEt 26, ICH$_2$ZnI 20 and/or Zn(ICH$_2$)$_2$ 25 (Scheme 34).$^{55}$

\[
\begin{align*}
\text{CH}_2\text{I}_2 + \text{Et}_2\text{Zn} & \rightarrow \text{ICH}_2\text{ZnEt} + \text{EtI} \\
\text{ICH}_2\text{ZnEt} + \text{R}_1\text{R}_2 & \rightarrow \text{ICH}_2\text{ZnEt} + \text{EtI} \\
\text{ICH}_2\text{ZnI} + \text{CH}_2\text{I}_2 & \rightarrow \text{ICH}_2\text{ZnI} + \text{EtI} \\
\text{ICH}_2\text{ZnI} + \text{Et}_2\text{Zn} & \rightarrow \text{Zn(ICH}_2\text{)}_2
\end{align*}
\]

Scheme 34

X-Ray crystallography and NMR studies have been recently undertaken in order to determine the exact nature of the reactive species involved in both protocols.

Thus, Charette has reported the solid state structure of the IZnCH$_3$I complex 27 formed by the addition of 1 equivalent of CH$_3$I$_2$ to a solution of EtZnI and benzo-18-crown-6 (Scheme 35).$^{56}$ As the solution of this complex was still an effective cyclopropanating reagent, he concluded that IZnCH$_3$I 20 may be the active Simmons-Smith reagent.
A similar conclusion has also been drawn from NMR studies carried out by the same author. Indeed it has been shown that the Schlenk equilibrium, illustrated in Scheme 33, appears to lie heavily on the side of \( \text{IZnCH}_2\text{I} \) as none of the related \( \text{Zn(CH}_2\text{I)}_2 \) could be detected by \( ^{13}\text{C} \) NMR when the experiment was performed in \( \text{CD}_2\text{Cl}_2 \) in the presence of a chiral ether.

Contrastingly, on the basis of NMR studies, Denmark has noted that Simmons-Smith type reagents exist predominantly as \( (\text{ICH}_2)_2\text{Zn.ZnI}_2 \) pairs in acetone solution and thus concluded that this species could be the active reagent in the Simmons-Smith reaction.

These two contradictory conclusions clearly reveal, that at the present time, the exact structural nature of the Simmons-Smith reagent still cannot be unambiguously assigned.

1.2.2.1.3 Theoretical studies on cyclopropanation reactions

Important computational work has also been done to rationalise the experimental findings.

Thus, cyclopropanation reactions using metal carbenoids can, in general, be considered to follow one of two differing pathways involving either carbometallation or methylene transfer. In the carbometallation pathway (path A), \([2+2]\) addition of the ethylene occurs to produce an intermediate 30 through a four-centred transition state 29 (Scheme 36). A subsequent intramolecular substitution reaction of 30 then affords the cyclopropane product 32. Alternatively, in the methylene transfer pathway (path B), direct \([2+1]\) addition takes place to provide the cyclopropane ring in a single step through 31 (Scheme 36).
Through a series of quantum mechanical studies on the cyclopropanation reaction of ethylene and ClZnCH2Cl 28, Nakamura et al. established that the favoured pathway involved methylene transfer (path B).59,60 Indeed, the activation energy of the methylene transfer pathway was much lower (17.3 kcal/mol) than that of carbometallation (30.7 kcal/mol). An intrinsic reaction coordinate analysis from 31 back to the reactants also showed that this pathway takes place in two stages, through an initial $S_N^2$ like displacement reaction by ethylene on halomethylzinc, followed by cleavage of the bond between CH$_2$ and Zn to give the cyclopropane ring. The ease of the $S_N^2$ like reaction depends largely on the polarisation of the C-Cl bond. On this point, the authors, using the same model, showed that the Lewis acid (ZnCl$_2$ for their study) acts on the zinc carbenoid reagent to enhance the rate of the methylene transfer reaction (Scheme 37).60,61
Introduction

It is important to note that this rate-enhancing effect induced by the addition of zinc salts is in accord with the experimental observations reported both by Wittig and Denmark.63

1.2.2.1.4 Evolution of the “cyclopropanating agent”

Many variations of the original Simmons-Smith method, including the use of Zn/CuCl/CH$_2$I$_2$, Zn(Ag) couple/CH$_2$I$_2$, Zn/TiCl$_4$/CH$_2$Br$_2$, Zn/AcCl/CuCl/CH$_2$Br$_2$ and Zn/CH$_2$Br$_2$ under sonication, have been reported in the literature. Shorter reaction times and better yields are reported for some substrates. A more efficient activation of the zinc seems to be one consistent possible explanation to account for almost all of these results.

However, since the yields in cyclopropanation of unfunctionalised olefins still remain unsatisfactory, further efforts have been made to find an even more reactive cyclopropanating reagent.

In 1991, Denmark and Edwards showed that the (chloromethyl)zinc reagent, prepared from ClCH$_2$I/Et$_2$Zn, is generally more reactive that the (iodomethyl)zinc analogue.69 The most striking result of this study was the 94% yield (GC yield) obtained with cis-cyclocodocene 33 with the new reagent in comparison with the 12% using CH$_2$I$_2$/Et$_2$Zn under the same conditions and for the same reaction time (Scheme 38). A noncomplexing solvent such as 1,2-dichloroethane, which is not normally used in organochemistry, was also found to be superior in this reaction.

\[
\text{Et}_2\text{Zn (2 eq.), ClCH}_2\text{I (4 eq)} \quad \text{DCE, 0°C, 15 min} \\
\quad \text{94% (GC yield)}
\]

Scheme 38
The influence of different RX groups in the (iodomethyl)zinc species RXZnCH$_2$I was then investigated.

The two principal methods employed for the generation of RXZnCH$_2$I are shown in Scheme 39. In Method A, Et$_2$Zn is treated with 2 equivalents of CH$_2$I$_2$ to form Zn(CH$_2$I)$_2$, which is subsequently reacted with RX to give RXZnCH$_2$I. In Method B, Et$_2$Zn is firstly combined with RX to form RXZnEt and then reacted with 1 equivalent of CH$_2$I$_2$ to generate RXZnCH$_2$I. It is important to note that the various iodomethylzinc species in Scheme 39 are only proposed on the basis of stoichiometry.

Scheme 39

In this manner, by using Method A, Shi et al. investigated the influence of different RX groups and established that as RXH became more acidic, the reactivity of the novel organozinc species increased.$^{70}$ The best results were obtained when trifluoro- or trichloroacetic acid were used (RX = CF$_3$CO$_2$ or CCl$_3$CO$_2$) since these reagents display a dramatically increased reactivity towards unreactive olefins, such as trans-$\beta$-methylstyrene. A study of the cyclopropanating ability of CF$_3$CO$_2$ZnCH$_2$I toward a wide range of alkenes was then undertaken and showed that this reagent is generally very effective. However, it is interesting to note that other authors have discredited the structure of the active species involved in this reaction (vide infra).

By the same approach, Charette et al. studied the reactivity of new reagents of general structure ArOZnCH$_2$I (RX = ArO) prepared either by Method A or B (Scheme 39).$^{71}$ It was observed that carbenoids possessing electron-withdrawing groups on the aromatic ring (F,Cl or Br in position 2,4 and 6) produced very high yields of cyclopropanes. This higher reactivity could result from an increase in the electrophilicity of the zinc carbenoid and this conclusion is in perfect accord with Shi’s work.
The acyloxymethylzinc carbenoids, recently reported by Charette et al., also appear to be another promising class of cyclopropanating reagents. They were designed having in mind the driving force of the Simmons-Smith reaction catalysed by Lewis acids (vide supra 1.2.2.1.3) and the epoxidation reaction using peracids (Scheme 40).

In this instance, 1:1 mixture of iodomethyl perfluoropentanoate, C₄F₉CO₂CH₂I, and diethyl zinc afforded a reactive carbenoid which cyclopropanated efficiently a variety of unfunctionalised olefins, showing the potential of this new reagent. Once again, the presence of an electron-withdrawing group for R₁ in Scheme 40 is expected to increase the electrophilicity of the carbenoid.

In light of this study, Charette has also proposed that the increased reactivity of Shi’s carbenoid, CF₃CO₂ZnCH₂I, might be attributed to in situ equilibration leading to formation of iodomethylzinc trifluoroacetate 35 under the reaction conditions (Scheme 41). This hypothesis was partially verified as the 35:34 ratio was evaluated as varying between 2:1 (NMR) and 4:1 (GC analysis).

As evidenced above, through studying the mechanism of the Simmons-Smith reaction, chemists have managed to design more reactive cyclopropanating species. As a direct result the Simmons-Smith reagent and their derivatives can now cyclopropane
virtually any alkene with high efficiency. However, to date, this methodology is still restricted to the parent methylene carbenoid species.

### 1.2.3.2 From diazoalkanes and zinc salts

An alternative method for the generation of organozinc carbenoids was reported by Wittig in 1959. This method consisted of treatment of an ethereal suspension of a zinc (II) salt (ZnCl₂, ZnBr₂, ZnI₂, Zn(OBz)₂) with diazomethane⁶² or aryldiazomethanes.⁷³ The active cyclopropanating species are believed to be similar to the Simmons-Smith reagent (*vide supra* 1.2.2.1.2) (Scheme 42).

\[
\begin{align*}
\text{ZnI}_2 + \text{CH}_2\text{N}_2 & \rightarrow \text{CH}_2\text{ZnI} \\
\text{ICH}_2\text{ZnI} + \text{CH}_2\text{N}_2 & \rightarrow \text{Zn}(\text{ICH}_2)_2
\end{align*}
\]

Scheme 42

Thus, a wide range of simple alkenes can be cyclopropanated and the yields are usually good (Scheme 43). In the case of benzylidene transfer the thermodynamically less favoured *endo* isomer is formed predominantly.

\[
\begin{align*}
\text{\text{CH}_2\text{N}_2 / \text{ZnI}_2} & \quad 86\% \\
\text{\text{ZnCl}_2} & \quad 90\% \quad 3:1
\end{align*}
\]

Scheme 43

However this approach has received little attention due to the hazards associated with handling diazo compounds.
1.2.3.3 From carbonyl compounds

The generation of organozinc carbenoids from carbonyl compounds is an attractive alternative to the use of dangerous and/or toxic dihalo and diazo precursors. Before describing the evolution of this chemistry within our own group, it is important to recognise the mechanistic parallel which exists with the venerable Clemmensen reduction.

1.2.3.3.1 The Clemmensen reduction of carbonyl compounds

The Clemmensen reduction of ketones and aldehydes originally using amalgamated zinc and hydrochloric acid with an immiscible co-solvent, \textit{i.e.} toluene, is one of the simplest and most direct methods for conversion of the carbonyl group into a methylene group (Scheme 44).\textsuperscript{74}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{R}_1 \text{R}_2
\end{array}
\xrightarrow{\text{Zn(Hg), 40\% HCl (aq.)}}
\begin{array}{c}
\text{R}_1 \text{R}_2
\end{array}
\end{equation}

\textbf{Scheme 44}

Even though the mechanism of this reaction is not fully understood, the intermediacy of a zinc carbenoid appears to be widely accepted.

One of the first detailed studies into the mechanism of the Clemmensen reduction was performed by Brewster.\textsuperscript{75} He proposed that reduction of the carbonyl group took place following 'chemisorption' of the carbonyl group onto the zinc surface followed by delivery of two electrons and the formation of a covalently bonded organozinc species. As alcohols are not generally reduced under Clemmensen conditions, Brewster also suggested that free alcohols were not intermediates in the Clemmensen reduction.

Later work by Nakabayashi supported this proposal, concluding that reduction was a stepwise process involving the generation of organozinc intermediates.\textsuperscript{76} He also noted, by investigating the kinetics and the electrochemical reduction of substituted
acetophenone, that the electrochemical process could not be directly correlated with the Clemmensen reduction.

In 1986, a study by Burdon provided further indicative results that carbenoid species could be involved in the Clemmensen reduction. Thus when the reaction using acetophenone and substituted acetophenones was performed with amalgamated zinc in 50 % aqueous ethanol self-coupled cyclopropanes were formed. Cross-coupled cyclopropanes can also be obtained by capturing the carbenoid with styrene. Thus 4-bromoacetophenone 36 gave primarily the cis cyclopropane 37 with important reductions in the yields of Clemmensen reduction and carbenoid derived products (Scheme 45).

\[ \text{Scheme 45} \]

Burdon proposed that all of the above products observed originate from a zinc carbenoid intermediate 39 (Scheme 46). In addition deuterium labelling studies demonstrated that the alkene 41 is formed via a vinylic zinc intermediate 40 or directly by C-H insertion reaction.
The explanation for the formation of the carbenoid 39 is speculative. The mechanism proposed would also however account for the pinacol type products obtained in Clemmensen reduction since a radical intermediate 38 is involved.

Strong evidence for initial one electron reduction was also provided by the investigation of the Clemmensen reduction of α,β-unsaturated ketones. Davis and Woodgate demonstrated that such reactions proceeded via a cyclopropanol intermediate, which, depending upon its mode of ring-opening, can give rise to two structurally isomeric saturated ketones. Thus the Clemmensen reduction of 4-methylpent-3-en-2-one 42 or 1,2,2-trimethylcyclopropanol 43 were found to produce a mixture of 44 and 45 in the same proportion (Scheme 47).
Similar evidence for one electron reduction was obtained by Elphimoff-Felkin.\textsuperscript{79} Indeed performing the reduction of the two cyclic enones 46 and 47 in the presence of acetic anhydride allowed the isolation of the bicyclic acetate intermediates 48 and 49 (Scheme 48).

Although a carbenoid species seems to be involved in the Clemmensen reduction, classical carbenoid reactivity is not routinely observed since the vigorous reaction conditions employed favour its further two electron reduction and protonation to deliver the methylene group.

Hence, in order to exploit the synthetic potential of such carbenoids, alternative reaction conditions are required which preclude these latter steps.
1.2.3.3.2 The controlled generation of organozinc carbenoids from carbonyl compounds

Elphimoff-Felkin and Sarda first proposed, in 1969, to replace the protons responsible for the rapid destruction of the carbenoid by a Lewis acid. Thus, by performing a reaction with boron trifluoride diethyletherate in a dry solvent they demonstrated that the carbenoid generated from aromatic aldehydes could be trapped by an alkene to yield a cyclopropane (Scheme 49). It is worth noting that cyclic alkenes gave the more hindered endo isomer preferentially. This particular feature seems to be inherent in benzylidene transfer (vide supra 1.2.2.1.1 and 1.2.2.2).

Scheme 49

The species 50 was proposed to be the carbenoid involved in this reaction (Scheme 50).

Scheme 50

Interestingly, the same authors also reported that the reaction of phenylidiazomethane in the presence of boron trifluoride afforded just traces of the expected cyclopropanes, which can rule out the possibility of 51 as the reactive intermediate (Scheme 51).

Scheme 51
In 1975, Elphimoff-Felkin and Sarda also briefly studied the reactivity of carbenoids, generated from benzaldehyde, using other oxophilic electrophiles. Whilst no cyclopropanation reaction was observed with magnesium bromide diethyletherate, chlorotrimethylsilane and aluminium trichloride both produced 7-phenynorcarane in moderate yield (Scheme 52).

In 1973 Motherwell discovered that cyclohexanones 52, in the presence of zinc and chlorotrimethylsilane, were efficiently converted to the corresponding cyclohexenes 53 (Scheme 53).

Particularly indicative of the intermediacy of a carbenoid species was the case of cyclooctanone 54 which furnished not only cis cyclooctene 55 but also bicyclo[3.3.0]octane 56 as a result of transannular insertion of the carbenoid (Scheme 54).
It is also important to note that the behaviour of this carbenoid is similar to that encountered in the Clemmensen reduction, since a similar C-H insertion reaction had been reported.\textsuperscript{74}

Of equal interest was the observation that the reaction of acetophenone provided the pinacolic product, 2,3-diphenyl-2,3-di(trimethylsilyloxy) butane 57, in 82\% yield (Scheme 55). This emphasises the similarity of the pathway to carbenoid generation with that proposed by Burdon for the Clemmensen reduction (\textit{vide supra} 1.2.2.3.1).

Thus the formation of the organozinc carbenoid from a carbonyl group in the presence of zinc and chlorotrimethylsilane can be expected to occur by a pathway which is similar to carbenoid formation under Clemmensen conditions. Bearing in mind the mechanism proposed by Burdon\textsuperscript{77} for the Clemmensen reduction (\textit{vide supra} 1.2.2.3.1), one can expect that the carbonyl group successively receives two electrons from the zinc to generate the organozinc intermediate 58 and that the oxophilic chlorotrimethylsilane serves as a direct substitute for the proton in the mechanism of Clemmensen reduction (Scheme 56). The final organozinc carbenoid can then be viewed, either as a species bonded to the zinc surface 59 (path A), as postulated by Burdon\textsuperscript{77}, or as a tetrahedral chloro congener 60 by analogy with the Simmons-Smith reagent\textsuperscript{51} (path B).
1.2.3.3 Evolution of organozinc carbenoid chemistry within our group

Following on from the observation that dicarbonyl coupling of certain aryl and \( \alpha, \beta \)-unsaturated carbonyl compounds can be achieved under Clemmensen conditions, Motherwell, in collaboration with Banerjee’s group, investigated the possibility of performing similar reactions using the zinc/chlorotrimethylsilane system. Although good results were obtained with certain enones, pinacolic coupling and dimerisation at the softer \( \beta \)-carbon atom were the major reactions observed for other substrates (Scheme 57).
These side reactions are presumably due to the longevity of the carbon centred radicals produced by a single electron transfer from zinc (vidra supra 1.2.2.3.1). In order to combat this problem, since the overall stoichiometry of carbenoid generation requires two molecules of chlorotrimethylsilane per carbonyl group, a bis-silicon electrophile 61 which would allow intramolecular delivery of the second silicon electrophile and hence facilitate carbenoid generation was selected (Scheme 58).\(^{84}\)

The use of 1,2-bis (chlorodimethylsilyl) ethane 62 as the bis-silicon electrophile in the symmetrical coupling reaction led to an improvement in yield which was especially significant for aromatic carbonyl compounds (Scheme 59).\(^{84}\)
Introduction

From the results obtained in the aromatic aldehyde series, it seems reasonable to think that an electron donating group in the para position to the aldehyde may promote expulsion of the cyclic siloxane, as implied in Scheme 60 and hence accelerate carbenoid generation.

Scheme 60

To understand the mechanism of the dicarbonyl coupling reaction, it is worth noting that neither vicinal diols nor their silylated derivatives can be converted to olefins using the zinc/chlorotrimethylsilane system. However, under the same conditions, it has been observed that stilbene epoxides led to alkene formation, implying that epoxides are viable intermediates.

It is reasonable to envisage in turn that these epoxides can be derived from a carbonyl ylide intermediate. Indeed the attempted intramolecular dicarbonyl coupling of 63 afforded the dihydropyran 67 along with the alkene 66 and the diene 65 (Scheme 61). Formation of the dihydropyran may be rationalised as proceeding via the carbonyl ylide 64, which fails to close to an epoxide by virtue of a combination of electronic effects and ring strain.

Scheme 61
As a logical extension to this work, Motherwell and Roberts investigated the cyclopropanating ability of this type of carbenoid.\(^{85}\) They found that a series of simple alkenes and enol acetates could be readily cyclopropanated by the carbenoids derived from a range of \textit{para} substituted arylaldehydes (Scheme 62). As already noted, the more hindered \textit{cis} or \textit{endo} isomers were predominant and yields were best for electron rich aromatic aldehydes.\(^{86}\)

![Scheme 62](image)

A range of organozinc carbenoids generated in a similar fashion can also be trapped efficiently by Z-1-acetoxybutadienes thus yielding functionalised vinylcyclopropanes, as illustrated by the example shown in Scheme 63.\(^{87}\)

![Scheme 63](image)
The complete regioselectivity and the high cis selectivity observed support the idea that the cyclopropanation reaction is directed by the acetoxy group as depicted in Scheme 64. As mentioned previously, similar observations have also been reported with the Simmons-Smith reagent (vide supra 1.2.2.1.1).

Interestingly and in apparent contrast to the studies of both Woodgate\textsuperscript{78} and Elphimoff-Felkin\textsuperscript{79}, it was shown that \(\alpha,\beta\)-unsaturated organozinc carbenoids, known to undergo reductions of the double bond or rearrangements under Clemmensen reduction (vide supra 1.2.2.3.1), can also be trapped by alkenes to yield cyclopropanes if they are generated using the zinc/bis-silicon electrophile system (Scheme 65).
Curiously however, certain simple unsubstituted α,β-unsaturated carbonyl compounds, such as cyclohexenone or cyclopentenone, failed to give cyclopropanes under the same conditions. This observation suggests that some degree of substitution either at or around the β carbon of the unsaturated carbonyl group is required (vide infra).

During a study of intramolecular cyclisation using this methodology, Motherwell and Roberts found that efficient cyclopropanation could occur even when the initial geometry around the α,β-unsaturated carbonyl group was unfavourably located with respect to the alkene trap. Thus, Δ2-carene 69 can be synthesised starting either from neral 68 or from the monoterpenne geranial 70 in comparable yield (Scheme 66).

![Scheme 66](image)

This result, when taken in conjunction with the necessity for some degree of steric hindrance around the β carbon, suggests that 1,3-allyl migration of the carbon zinc bond can occur to relieve congestion, but with consequent loss of alkene geometry (Scheme 67).

![Scheme 67](image)

More recently, Motherwell and Popkin demonstrated that organozinc carbenoids could also be generated from acetals, ketal and orthoformates. From a mechanistic standpoint, and in contrast to the reactions of the carbonyl group which are postulated to involve initial formation of a zinc-oxygen bond, these transformations may proceed via
an oxonium intermediate 71 before evolving to the organozinc carbenoid 72 or the 
α-alkoxy- or α-aryloxyorganozinc carbenoid 73 (Scheme 68).

\[
\begin{align*}
R & \quad O-R' \\
Y & \quad O-R' \\
\text{ZnCl}_2 & \quad Y = \text{R}_1 \text{ or OR}_2 \\
& \quad R = \text{H or alkyl} \\
& \quad R' = \text{alkyl or aryl} \\
& \quad 72 : Y = \text{R}_1 \\
& \quad 73 : Y = \text{OR}_2 \\
\end{align*}
\]

Scheme 68

Thus ketal 74 was found to give the corresponding alkene via a C-H insertion reaction 
and aryl acetals 75 furnished cyclopropanes (Scheme 69).89

\[
\begin{align*}
\text{t-Bu} & \quad \text{OMe} \\
Y & \quad \text{OMe} \\
\text{Zn(Hg), Me}_3\text{SiCl} & \quad \text{Et}_2\text{O, } \Delta \\
& \quad 56 \% \\
\text{Y} & \quad \text{OMe} \quad 65 \% \\
& \quad \text{Y} = \text{Me} \quad 34 \% \\
& \quad 23.5: 1 \\
& \quad 5.6: 1 \\
\end{align*}
\]

Scheme 69

In terms of generating functionalised organozinc carbenoids, the selection of an 
orthoformate as reagent provided a series of alkoxy- and aryloxycyclopropanes in a 
method which avoided the handling of highly toxic α-halo or α-dihaloethers (Scheme 70). Surprisingly such carbenoids, which should exhibit nucleophilic character, seem to react preferentially with electron-rich alkenes (last example in Scheme 70).90
1.3 Summary and perspectives

The foregoing introductory overviews have hopefully highlighted several important aspects both in current methodology for aminocyclopropanes construction and in recent advances in the generation and reactivity of organozinc carbenoids. In particular, for both of these areas, it should be emphasised that simple and effective methods for the addition of heteroatom functionalised carbenoids to alkenes are not generally used by the synthetic organic chemist, who continues to consider that the use of organozinc carbenoids invariably involves methylene transfer and that the copper or rhodium catalysed addition of diazo esters to alkenes allows for functionalised carbenoid addition. Clearly, considerable scope therefore exists for progress in this area.
Chapter 2

Results and Discussion
2 Introduction

The following programme of research was initiated with the objectives of studying the generation and the behaviour of hitherto unknown organozinc carbenoids possessing nitrogen functionalities attached to the carbenoid carbon (Scheme 71).

As we shall see, the primary discovery that such species, when attached to a cyclic amide, can cyclopropanate alkenes efficiently led us to an exciting quest toward the development of a versatile method for the preparation of chiral primary aminocyclopropanes. Throughout this study, our curiosity drove us to investigate original sequences for the synthesis of structurally interesting compounds such as trans amino cyclopropanols and N-substituted cyclopropyl amino acids.

2.1 Background – The attempted aminocyclopropanation reaction using dimethylformamide dimethyl acetal

The starting point for the work presented in this thesis follows an initial study of the attempted synthesis of aminocyclopropanes carried out by Popkin. Indeed, as an extension of their work on alkoxycyclopropanation reactions using orthoformates, Motherwell and Popkin recognised the potential for a similar generation of aminocarbenoids from dimethylformamide dimethylacetal 76. However, in the presence of chlorotrimethylsilane, using either zinc amalgam or samarium diiodide as the electron source, no cyclopropanation reaction occurred with allylbenzene (Scheme 72).
Thus, when compared to an aryl or an alkoxy group, the selection of the dimethylamino moiety has an evident negative impact on the potential generation, stability and/or the reactivity of the putative carbenoid species. In particular, we considered that a possible problem might lie in the ability of zinc to deliver two electrons to the amino substituted carbenium ion 77 as compared with the successful reduction of the oxonium ion in the alkoxy cyclopropanation (Scheme 73).

![Scheme 73](image)

This situation would arise naturally as a consequence of the fact that the nitrogen atom is less electronegative and hence able to “neutralise” the positive charge on the adjacent carbocation more effectively than an oxygen atom. With this perspective in mind, we therefore decided to attenuate the strong electron-donating ability of the nitrogen lone pair by addition of an adjacent electron-withdrawing group. Interestingly, such an approach has been applied to Fisher aminocarbenes and has shown that the complexes become more similar to alkoxy carbenes in character.92

### 2.2 Preliminary study on the amidocyclopropanation reaction using N-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

In order to examine the above hypothesis, the cyclopropanating ability of the carbenoid generated from N-diethoxymethyl-2-pyrrolidinone 78 was accordingly investigated. The required substrate was very simply prepared in 70 % yield by reaction of 2-pyrrolidinone with triethylorthoformate in the presence of a catalytic amount of aluminium chloride.93
Results and Discussion

To our delight, when the reaction between 78 and allylbenzene was first attempted under the same experimental conditions as used for alkoxy cyclopropanation, the desired product 79 was obtained, albeit in low yield (Scheme 74). Contrary to the usual stereoselectivity observed in a cyclopropanation reaction involving an organozinc carbenoid (vide supra), the trans isomer was formed predominately.

![Scheme 74](image)

Scheme 74

From a mechanistic standpoint, a plausible sequence for the formal generation of the \( \alpha \)-amidoorganozinc carbenoid from 81 is shown in Scheme 75 and involves Lewis acid assisted cleavage of one ethoxy group by chlorotrimethylsilane and subsequent two electron reduction of the resultant acyliminium ion 80 (or its covalent congener). Reaction with a second equivalent of chlorotrimethylsilane then furnishes carbenoid 81.

![Scheme 75](image)

Scheme 75
2.3 Methods used to determine the stereoselectivity of the cyclopropanation reaction

The stereochemistry of the two cyclopropanes obtained from the above reaction was determined by NMR spectroscopy. After assigning the signals of cyclopropyl protons, their coupling constants were examined and the relationship between them determined. From the Karplus equation, the values of the coupling constants of vicinal protons are larger for cis couplings than for trans couplings. As usual for cyclopropane rings, the geminal coupling constant $2J_{\alpha\beta}$ was in the typical range of 4.5-6.5 Hertz (Table 1).

<table>
<thead>
<tr>
<th>Relationship</th>
<th>$J$ (Hz)</th>
<th>Relationship</th>
<th>$J$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>geminal</td>
<td>5.8</td>
<td>geminal</td>
<td>6.0</td>
</tr>
<tr>
<td>trans</td>
<td>4.1</td>
<td>$trans$</td>
<td>4.6</td>
</tr>
<tr>
<td>cis</td>
<td>7.5</td>
<td>cis</td>
<td>8.0</td>
</tr>
<tr>
<td>trans</td>
<td>3.5</td>
<td>$trans$</td>
<td>7.0</td>
</tr>
<tr>
<td>cis</td>
<td>9.4</td>
<td>$trans$</td>
<td>6.3</td>
</tr>
<tr>
<td>trans</td>
<td>6.1</td>
<td>$cis$</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Table 1

The determination of the stereochemistry for other cyclopropanes described in the present thesis has been made in a similar manner. In some cases, NOESY experiments were carried out to confirm their assignments in an unambiguous way. Detailed characterisation of the molecules presented can be found in the Experimental section.
2.4 Further study on the amidocyclopropanation of allylbenzene using N-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

As the yield obtained from the exploratory reaction between allylbenzene and 78 was relatively low, further improvements were required.

The optimisation of the amidocyclopropanation reaction began with the study of the influence of the ratio of the amount of alkene to the carbenoid precursor employed (Table 2).

A typical experimental procedure involved slow addition of a solution of N-diethoxymethyl-2-pyrrolidinone 78 in diethyl ether to a suspension of zinc amalgam (10 eq / carbenoid precursor), chlorotrimethylsilane (5 eq / carbenoid precursor), anhydrous ZnCl$_2$ (1 eq / carbenoid precursor) and allylbenzene in diethyl ether at reflux.

<table>
<thead>
<tr>
<th>Alkene (eq)</th>
<th>Carbenoid precursor (eq)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2

From this study it appears that the carbenoid species which derived from 78 could be efficiently trapped by allylbenzene (entries 1-3), and when a two-fold excess of carbenoid precursor relative to the alkene was used, the desired product was obtained in very high yield (entry 3).

Surprisingly, it was noticed that during the addition of the N-diethoxy amide 78 the zinc amalgam gradually formed soft balls before ending as a gum like substance. As this observation had no precedent in the history of the study of organozinc carbenoids within our group, an interaction between the nitrogen functionality and the zinc was suspected. As the early formation of some form of zinc aggregate is likely to result in a diminution of the surface area and hence the reaction conversion rate, we were therefore interested to investigate the experimental parameters which can have a direct influence on the physical stability of the zinc amalgam.
Initially, it was found that a very slow addition (ca 0.1 mmol/hour) of a solution of N-diethoxymethyl-2-pyrrolidinone 78 greatly delayed the aggregation of the zinc. The use of THF as solvent or co-solvent with diethyl ether also suppressed the formation of zinc balls although ring-opening by-products from THF arose during such reactions, leading to some difficulties in the isolation of pure product.

Surprisingly, the presence of zinc chloride also proved to be very important to ensure an increase in the stability of the zinc amalgam. If the reaction was performed without zinc chloride, hard zinc balls were formed at a very early stage during the addition of the diethoxymethyl amide 78. When a catalytic amount of zinc chloride (0.25 eq/carbenoid precursor) was employed, the zinc quickly formed a gum. As a consequence, the use of stoichiometric quantities of ZnCl₂ and carbenoid precursor appeared to produce the best results.

Thus, having now an efficient procedure for performing amidocyclopropanation reactions, our attention was then directed towards a study of the scope of this reaction.\textsuperscript{95}

### 2.5 Scope and limitation of this novel amidocyclopropanation reaction

#### 2.5.1 Cyclopropanation of unfunctionalised alkenes

A typical experimental procedure involved slow addition of a solution of N-diethoxymethyl-2-pyrrolidinone 78 (2 eq) in diethyl ether to a suspension of vigorously stirred zinc amalgam (20 eq), chlorotrimethylsilane (10 eq), anhydrous ZnCl₂ (2 eq) and an alkene (1 eq) in diethyl ether at reflux. These conditions were examined for a range of alkenes as shown in Table 3.
### Results and Discussion

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Product</th>
<th>Addition / reaction time</th>
<th>Isomer ratio(^a) (\text{trans:} \text{cis})</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image 1" /></td>
<td>14 h / 6 h</td>
<td>11.5:1</td>
<td>88%</td>
</tr>
<tr>
<td>2 a</td>
<td><img src="image2.png" alt="Image 2" /></td>
<td>14 h / 6 h</td>
<td>1.1:1</td>
<td>49%</td>
</tr>
<tr>
<td>2 b</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td>2 h / 12 h(^b)</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>3 a</td>
<td><img src="image4.png" alt="Image 4" /></td>
<td>14 h / 6 h</td>
<td>&gt;95:&lt;5</td>
<td>61%</td>
</tr>
<tr>
<td>3 b</td>
<td><img src="image5.png" alt="Image 5" /></td>
<td>16 h / 6 h</td>
<td>&gt;95:&lt;5</td>
<td>58%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image6.png" alt="Image 6" /></td>
<td>16 h / 6 h</td>
<td>—</td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image7.png" alt="Image 7" /></td>
<td>14 h / 6 h</td>
<td>1:1</td>
<td>52%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image8.png" alt="Image 8" /></td>
<td>16 h / 6 h</td>
<td>10:1</td>
<td>66%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image9.png" alt="Image 9" /></td>
<td>16 h / 6 h</td>
<td>1.3:1</td>
<td>63%</td>
</tr>
</tbody>
</table>

\(^a\) Determined using \(^1\)H NMR spectroscopy. \(^b\) Performed at room temperature. For convenience, only the \(\text{trans}\) isomer is shown.

### Table 3
Further examination of the results in Table 3 confirms that preparatively useful yields of amidocyclopropanes can be obtained from mono- (entries 1-3), di- (entries 4-6) and tri- (entry 7) substituted alkenes and that reaction occurs with retention of the original alkene geometry (entries 4 and 5). Although the stereochemical outcome of these reactions can clearly be influenced by substrate structure (compare entries 1 and 2), it is also significant that there is a distinct preference for the formation of the less hindered trans (or exo) isomer (entries 1-3, 6 and 7), which is even more evident when the alkene bears a bulky group (entries 3a and 3b).

It is also important to note that the standard procedure initially failed to give a satisfactory yield for the amidocyclopropanation reaction of styrene as dimers and cyclopropanated dimers were obtained along with the desired product (entry 2a). The formation of these by-products was suppressed by shortening the addition time of the carbenoid precursor and thus the yield of the cyclopropanated product was improved from 49% to 70% (entry 2b).

2.5.2 Cyclopropanation of functionalised alkenes

2.5.2.1 Cyclopropanation of electron rich double bonds

As in the study of the alkoxy cyclopropanation reaction, simple enol esters, such as isopropenyl acetate, failed to yield the desired product in contrast to the enol ester 89 possessing a bulkier alkyl chain (Scheme 76). Due to the presence of a chiral centre 90 was obtained as a mixture of two trans and cis isomers. The ratios between the two isomers trans and the two isomers cis have appeared to be equal as determined by $^1$H NMR.

![Scheme 76](image)
When the cyclopropanation of 89 was first attempted, the reaction proceeded in 31% yield. On examination of the $^1$H NMR of the crude reaction mixture, the major product obtained appeared to be the reduced starting material (Table 4, entry 1). At this stage, it was the first time that an alkene was reduced under our experimental conditions. This surprising result shows that although every effort was made to perform the reaction under strictly anhydrous conditions, hydrogen chloride was generated during the reaction and this particular alkene was prone to being reduced, presumably through the sequence presented in Scheme 77.

\[
\text{Me}_3\text{SiCl} + \text{H}_2\text{O} \rightarrow \text{Me}_3\text{SiOH} + \text{HCl}
\]

\[
\begin{align*}
\text{Cl}^{-} \rightarrow \\
\text{Zn (2 eq.)}, \text{HCl} & \rightarrow \text{ZnCl}_2 \\
\text{O} & \rightarrow \text{H}
\end{align*}
\]

Scheme 77

Efforts were then made to optimise this reaction. Shortening of the addition time allowed us to improve the yield of this reaction to 57% (Table 4, entry 3). However, if the addition of the solution of 78 was too rapid, the zinc tended to form a gum within the first hour of the addition leading to a dramatic reduction in the zinc contact surface and this effect, in turn, could explain the observed decrease in the amount of starting material cyclopropanated (Table 4, entry 2).

<table>
<thead>
<tr>
<th>Addition time / temperature</th>
<th>Reaction time / temperature</th>
<th>Yield</th>
<th>Ratio of*</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 6 h at reflux</td>
<td>14 h at rt</td>
<td>31%</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>2 2.5 h at reflux</td>
<td>14 h at rt</td>
<td>45%</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>3 4 h at reflux</td>
<td>14 h at rt</td>
<td>57%</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

* Determined from the crude reaction mixture after work-up using $^1$H NMR spectroscopy.

Table 4
Results and Discussion

By following similar experimental conditions, vinyl benzoate 91 was cyclopropanated in comparable yield (Scheme 78).

\[
\begin{align*}
\text{O} & \quad \text{EtO} \quad \text{OEt} \\
\text{78} & \\
\rightarrow & \\
\text{O} & \quad \text{O} \\
\text{92} & \\
\text{trans:cis} & \quad 2:1
\end{align*}
\]

Scheme 78

2.5.2.2 Cyclopropanation of electron deficient double bonds

Although no cyclopropanation reaction was observed using methyl cinnamate, the acrylate derivative 93 was cyclopropanated, albeit in very low yield (Scheme 79).

\[
\begin{align*}
\text{O} & \quad \text{Et} \\
\text{Bu} & \quad \text{93} \\
\rightarrow & \\
\text{O} & \quad \text{Et} \\
\text{Bu} & \quad \text{94} \\
\text{trans:cis} & \quad 1:1
\end{align*}
\]

Scheme 79

Thus, from these results, electron deficient double bonds appear less likely to be cyclopropanated than electron rich ones, indicating that chemoselective cyclopropanation of electron rich double bonds in the presence of electron deficient double bonds is conceivable.
2.6 Extension of this novel amidocyclopropanation reaction

2.6.1 Study of the amidocyclopropanation reaction using $N$-benzyl-$N$-diethoxy-

methylacetamide as the carbenoid precursor

We were then interested in extending the newly developed amidocyclopropanation
reaction to different carbenoid precursors. Initially our attention was focused on the
$N$-diethoxymethyl derivative of acyclic amides and more particularly on $N$-benzyl-
$N$-diethoxymethylacetamide 96.

The preparation of the required reagent appeared to be much less efficient giving a poor
yield of the desired carbenoid precursor (Scheme 80). This can be explained by the
increased C=N double bond character of the amide resulting in a decrease of the
nucleophilicity of the nitrogen atom.

When the reaction was carried out with allylbenzene, under standard experimental
conditions, cyclopropane products were obtained in low yield (Scheme 81).

On examining the $^1$H NMR of the crude reaction mixture, the principal component of
the reaction was the starting amide 95. This observation may indicate, as implied in
Scheme 82, that competitive silylation on oxygen provides a facile pathway for elimination of ethyl formate via 98.

The formation of an analogous intermediate from the cyclic derivative 78 is of course less favourable on the grounds of ring strain (Scheme 83).

2.6.1 Study of the amidocyclopropanation reaction using N-formyl amides as the carbenoid precursor

As organozinc carbenoids can be generated from carbonyl compounds (vide supra), we decided to evaluate the cyclopropanating ability of N-formyl amides. Logically, we initially turned our attention to the study of N-formyl-2-pyrrolidinone 100 whose synthesis was performed in two straightforward steps with, as the key step, the ozonolysis of the enamide 99 (Scheme 84).
Under standard conditions, the reaction between allylbenzene and 100 did yield the expected cyclopropanes but in a much lower yield than when the corresponding acetal derivative 78 was employed (entry 1 in Table 3) (Scheme 85). Attempts to improve the yield of this reaction using more powerful silicon electrophiles, such as trimethylsilyl triflate or 1,2-bis (chlorodimethylsilyl) ethane 62, were fruitless.

Very interestingly, this experiment provides strong presumptive evidence that the generation of the carbenoid species employing the N-diethoxymethyl amide 78 does not involve initial formation of its N-formyl derivative.

### 2.7 Studies toward the preparation of primary aminocyclopropanes

The discovery that organozinc carbenoids can be efficiently generated from an N-diethoxymethyl moiety attached to a simple cyclic amide was for us a significant breakthrough. In order to broaden the synthetic utility of this novel amidocyclopropanation reaction, we decided to focus our attention on the design of carbenoid precursors which could easily lead to free aminocyclopropanes. The preliminary studies undertaken with cyclic and acyclic amides indicated that the nitrogen functionality of such entities should preferably be incorporated into a cyclic structure in the first instance.

#### 2.7.1 Study of the cyclopropanation reaction using N-diethoxymethyl phthalimide as the carbenoid precursor

Amongst the cyclic amino derivatives known for facile liberation of free amines, imides, such as phthalimide, are certainly those which have been the most frequently
used in organic chemistry. Consequently, the synthesis of aminocyclopropanes from N-diethoxymethyl phthalimide 101 was investigated.

N-diethoxymethyl phthalimide 101 was prepared following the same procedure employed for the preparation of N-diethoxymethyl-2-pyrrolidinone 78 and was obtained in 63% yield. Regrettably, the reaction between 101 and allylbenzene gave a complex mixture of products (as observed by NMR) which could be explained either by the instability of the carbenoid precursor 101 or the cyclopropanated product if it was formed, under the experimental conditions employed. Reduction of the phthalimide derivative could also have occurred and, indeed, N-alkylphthalimides of type 102 are known to be reduced to phthalimidines 103 in the presence of zinc in an acidic medium (Scheme 86).

![Scheme 86](image)

As the reduction of the carbonyl group of 102 may also involve the generation of an organozinc carbenoid, we were curious to investigate if an alkene would be able to trap such a species. In consequence, the cyclopropanation reaction of allylbenzene with N-methylphthalimide 104 in the presence of zinc amalgam and the bis-silicon electrophile 62 was attempted. However, this reaction produced no cyclopropanes amongst the complex mixture of different products obtained (Scheme 87).

![Scheme 87](image)
Results and Discussion

Because $N$-alkylsuccinimides are generally not prone to such reduction, it was then envisaged to study the behaviour of the carbenoid species generated from $N$-diethoxymethyl succinimide.\textsuperscript{97} The synthesis of this carbenoid precursor was attempted using different experimental procedures (reaction of succinimide with triethyl orthoformate or diethyl phenyl orthoformate in the presence or not of AlCl$_3$ at 150°C), but furnished only minute quantities of the desired product. These discouraging results prompted us to study alternative carbenoid precursors.

2.7.2 Study of the preparation of primary aminocyclopropanes using $N$-diethoxymethyl-2,3-dihydro-1-isoindolinone as the carbenoid precursor

The 2,3-dihydro-1-isoindolinone moiety is another substrate likely to lead to a primary amine. The cleavage of this auxiliary was expected to be achieved by catalytic hydrogenation and subsequent hydrolysis of the resulting secondary amide (Scheme 88).

![Scheme 88](image)

As depicted in the following Scheme 89, the reduction of phthalimide with tin in an acidic medium, followed by the reaction of the intermediate amide with triethyl orthoformate yielded the required $N$-diethoxymethyl-2,3-dihydro-1-isoindolinone 106 in a straightforward manner (Scheme 89).

![Scheme 89](image)
Results and Discussion

Pleasingly, the amidocyclopropanation reaction with this novel carbenoid precursor proved successful and gave the expected cyclopropanes 107 (Scheme 90).

\[ \text{Ph} \quad \Rightarrow \quad \text{106} \quad \xrightarrow{\text{Zn(Hg), Me}_3\text{SiCl, ZnCl}} \quad \text{Ph} \quad \text{107} \]

\[ \text{trans/cis} \ 6:1 \]

Scheme 90

We subsequently investigated the stepwise deprotection of the amine functionality. Unfortunately all attempts to debenzylate 107 by catalytic hydrogenation failed and led to the complete recovery of the starting material. Although alternative methods or routes to cleave the present auxiliary could have been attempted, a more promising candidate, developed simultaneously with 106, received all our attention and consequently the study involving this carbenoid precursor was not further pursued.

2.7.3 Preliminary study of the use of N-diethoxymethyl oxazolidinones as carbenoid precursors

The focus of our research turned towards an alternative carbenoid precursor, N-diethoxymethyl-4,5-diphenyloxazolidinone 113. This compound appeared to be a very attractive one to develop our methodology. Firstly, deprotection of the amino functionality can be performed in a single step by catalytic hydrogenation. Secondly, both enantiomers of 113 should be easily accessible and their use could lead to the preparation of chiral primary cyclopropylamines. Finally, 4,5-diphenyloxazolidinone derivatives are usually highly crystalline products, making their handling and purification simpler.\(^9\)
As iodotrimethylsilane has been known to initiate the ring opening of an oxazolidinone, we were concerned that, during the cyclopropanation step, chlorotrimethylsilane in combination with ZnCl₂, a powerful Lewis acid, might behave in a similar manner (Scheme 91).

\[
\begin{align*}
\text{As a model reaction, we therefore investigated the cyclopropanation of allylbenzene with the simple } & \text{N-diethoxymethyloxazolidinone 108, which was prepared in 67% yield using the standard conditions, and were pleased to note that the cyclopropanation reaction proceeded in 57% yield without production of any ring-opened by-products (Scheme 92).} \\
\end{align*}
\]

Encouraged by this result, we then decided to evaluate the ability of N-diethoxymethyl-4,5-diphenyloxazolidinone 113 to yield aminocyclopropanes. Initially we planned to conduct this study using (±)-113 in its racemic form.

The synthesis of (±)-113 was achieved in three steps from α-benzoin oxime 110 (Scheme 93). The first step consisted of the hydrogenation of 110 at 4 bar in the presence of a catalytic amount of palladium on charcoal (Pd/C) in an acidic medium where two reactions occurred successively: the C=N oxime bond of 110 was initially
hydrogenated followed by cleavage of the N-O bond of the resulting hydroxylamine. In contrast to the results reported in the literature, the hydrogenation of the oxime bond was not completely stereoselective and gave rise to a 93:7 mixture of *erythro* and *threo* amino alcohols. This mixture was then reacted with triphosgene in the presence of triethylamine to furnish, after recrystallisation, pure *cis*-4,5-diphenyloxazolidinone (±)-112. Finally, this oxazolidinone was treated with triethylorthoformate in the presence of a catalytic quantity of aluminium chloride to yield the desired product (±)-113 in 80% yield. The compound is crystalline and can be stored for long periods of time in a desiccator. It has been noticed that the acetal moiety of (±)-113, and other *N*-diethoxymethyl compounds presented in this thesis, was partially hydrolysed in CDCl₃ depending on its source and manufacturer, therefore the use of DMSO-δ₆ is preferable as the NMR solvent for these compounds.

The procedure followed in the preliminary cyclopropanation using (±)-113 varied from that used previously. The first significant difference was the use of dichloromethane to prepare the solution of carbenoid precursor, due to its insolubility in diethyl ether, and the second factor was the number of equivalents of carbenoid precursor employed relative to the alkene, being reduced from 2 to 1.5. Thus the conditions followed for the cyclopropanation reaction of allylbenzene involved the slow addition of (±)-113 (1.5 eq) in dichloromethane to a suspension of zinc amalgam (15 eq), chlorotrimethylsilane (7.5 eq), ZnCl₂ (1.5 eq) and allylbenzene (1 eq) in diethyl ether at reflux. The expected cyclopropanes (±)-114 were obtained in 83% yield as a 84:12:<2:<2 mixture of isomers A, B, C and D as depicted in the following Scheme 94 (with R=PhCH₂).
As well as the cyclopropane products, degradation by-products of (±)-113 were also observed. Traces of (±)-4,5-diphenyloxazolidinone (vide supra) and small quantities of 4,5-diphenyl-N-methyl-oxazolidinone (±)-115 and 4,5-diphenyl-N-formyl-oxazolidinone (±)-116 were also formed. (±)-115 could be derived from the hydrolysis and reduction of the organozinc carbenoid and (±)-116 from hydrolysis of the acetal moiety (Scheme 95). However their formation would imply that water was present in the reaction mixture, even though extra care was taken to exclude any traces of it.
determined by $^1$H NMR. Fortunately however, for the other cyclopropanes synthesised using 113, no such problem was encountered (vide infra).

2.7.4 A proposed mechanism to account for the observed stereochemistry

It was of course of considerable interest to rationalise the observed stereochemical outcome in terms of a model which might ultimately lead to predictive power. Our initial ideas are developed in Scheme 96. Thus, the oxazolidinone ring and the ring including the carbenoid centre and linked by the chelation between the zinc atom and the oxygen atom of the carbonyl group are firstly considered to be in the same plane. During the cyclopropanation reaction the alkene can then either approach from the bottom or the top face of this plane. As the top face is more hindered by the presence of the two phenyl rings, the alkene would consequently approach from beneath the plane and thus lead to the predominate formation of isomer A over B (Scheme 96 with R = CH$_2$Ph).

X-Ray analysis of the major isomer obtained from a similar cyclopropanation reaction has confirmed the stereochemistry given for isomer A (vide infra). Attempts to determine the isomers structure by NMR, for example by looking for the presence or not of an interaction between the cyclopropylic protons in beta of the nitrogen atom and the aromatic rings of the oxazolidinone, failed.
A similar mechanism can be speculated for the cis isomers and account for the structures given for isomers C and D (Scheme 97).

![Scheme 97](image)

2.7.5 Scope of the cyclopropanation reaction using (±)-N-diethoxymethyl-4,5-diphenyloxazolidinone

The scope of the cyclopropanation reaction using N-diethoxymethyl-4,5-diphenyloxazolidinone (±)-113 was then investigated using a range of alkenes as shown in Table 5.

Two experimental procedures were followed, one using a slight excess of the carbenoid precursor relative to the alkene (method A) and, for selected alkenes, the alternative of employing an excess of alkene (method B). In each case, the major isomer was isolated as a pure product after careful chromatography. Pleasingly, the zinc amalgam did not form either soft balls or gum during these reactions.

The typical experimental procedure involved the addition of a solution of N-diethoxymethyl-4,5-diphenyloxazolidinone (±)-113 (method A: 1.25 eq; method B: 1 eq) in dichloromethane over 6 hours to a suspension of vigorously stirred zinc amalgam (method A: 12.5 eq; method B: 10 eq), chlorotrimethylsilane (method A: 6.25 eq; method B: 5 eq), ZnCl₂ (method A: 1.25 eq; method B: 1 eq) and an alkene (method A: 1 eq; method B: 4 eq) in diethyl ether at reflux with further reaction for 16 hours.
### Results and Discussion

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Product</th>
<th>Isomer ratio&lt;sup&gt;a&lt;/sup&gt; A:B:C:D</th>
<th>Method</th>
<th>Overall yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield of isomer A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Alkene 1" /></td>
<td>88:8:&lt;2:&lt;2</td>
<td>A</td>
<td>74%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>52%</td>
<td>44%</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Alkene 2" /></td>
<td>90:&lt;2:6:&lt;2</td>
<td>A</td>
<td>58%</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>49%</td>
<td>46%</td>
</tr>
<tr>
<td>4</td>
<td><img src="" alt="Alkene 4" /></td>
<td>56:6:28:6</td>
<td>A</td>
<td>55%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>31%</td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="Alkene 5" /></td>
<td>94:&lt;2:&lt;2:&lt;2</td>
<td>A</td>
<td>59%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>6</td>
<td><img src="" alt="Alkene 6" /></td>
<td>94:&lt;2:&lt;2:&lt;2</td>
<td>A</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="" alt="Alkene 7" /></td>
<td>64:10:13:13</td>
<td>A</td>
<td>65%</td>
<td>43%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined using <sup>1</sup>H NMR spectroscopy.  
<sup>b</sup> Overall yield refers to the total isolated yield of all isomers.  
<sup>c</sup> Traces of 4,5-diphenyl-N-formyl-oxazolidinone (±)-116 were isolated with the products.  
<sup>d</sup> Addition of (±)-113 over 2.5 hours. For convenience, only the major isomer is shown.

Table 5

From this study, it appears that both procedures give moderate to good yields of cyclopropanes (entries 1-5 and 7), although method A, involving the use of an excess of carbenoid precursor, was slightly more efficient (entries 1, 2 and 4). A preference for the formation of isomer A (Scheme 96) was observed for all the substrates studied (entries 1-7), and in some cases almost no other isomers could be detected (entries 5 and 6). In entry 6, the instability of tributyl(vinyl)tin under the experimental conditions could account for the low yield obtained. This result was particularly disappointing as this substrate would have made an interesting precursor for further chemistry (*vide infra*).<sup>101</sup>
2.7.6 Synthesis of chiral cyclopropane derivatives

As both enantiomers, (+)-113 and (-)-113, could be easily prepared from commercially available (+)- and (-)-2-amino-1,2-diphenylethanol (Scheme 98), the extension of the methodology developed became straightforward for the synthesis of optically active aminocyclopropanes.\(^{102}\)

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Product using ((+)-113)</th>
<th>Overall yield (yield of A)</th>
<th>Product using ((-)-113)</th>
<th>Overall yield (yield of A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>63 % (56 %)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>57 % (50 %)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>61 % (53 %)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>58 % (51 %)</td>
</tr>
</tbody>
</table>

For convenience, only the major isomer is shown.

Table 6
The determination of the absolute configuration of these compounds was extrapolated from the absolute configuration established by an X-Ray crystallographic analysis of one of the cyclopropane derivatives prepared in a similar way using (+)-113 (vide infra). Concurrently with the study of these cyclopropanation reactions, the conditions for the deprotection of the derived products were also under investigation.

2.7.7 Deprotection of 4,5-diphenyloxazolidinone cyclopropanes

Preliminary studies for the deprotection of (±)-4,5-diphenyloxazolidinone cyclopropanes were carried out using (±)-114A. The hydrogenolysis of (±)-114A appeared to be very dependent on the catalyst and conditions employed. Hydrogenation for 24 hours at 4 bar using 5% Pd/C as the catalyst in an acidic medium achieved only partial deprotection yielding (±)-123 as the only product isolated after work-up (Scheme 99).

Transfer hydrogenation using ammonium formate and the same catalyst was also attempted and led unsatisfactorily to a mixture of products.

Pleasingly, complete cleavage of the oxazolidinone ring was obtained using Pearlman’s catalyst (20 % Pd(OH)₂/C) in a mixture of THF:AcOH at 4 bar. However, isolation of the resultant pure free primary amine was difficult. In order to overcome this problem, we decided that the amino function would be protected, as the Boc derivative, prior to its purification.

The protection of the amine was performed by treating the crude reaction mixture after hydrogenation with Boc₂O in the presence of an excess of triethylamine in CH₂Cl₂. The desired carbamate was then easily purified by chromatography on silica gel.
This procedure was applied to the deprotection of the following racemic cyclopropane derivatives (Table 7).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Time of hydrogenation</th>
<th>Overall yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>12 h</td>
<td>64%</td>
</tr>
<tr>
<td>2</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>17 h</td>
<td>58%</td>
</tr>
<tr>
<td>3</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>13 h</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>11.5 h</td>
<td>~15%</td>
</tr>
</tbody>
</table>

* Trace of an unidentified by-product was isolated with the product.

Table 7

From Table 7, the two step procedure was particularly effective for the first two substrates (entries 1 and 2), whereas, with the trimethylsilyl substituted cyclopropane, the overall yield of carbamate formation was low (entry 3). This may have resulted from the partial loss of the somewhat volatile intermediate amine during work up, as the crude reaction mixture was concentrated at high temperature *in vacuo* in order to remove the acetic acid which was used as solvent. However this problem was avoided by performing the hydrogenation under different conditions and by using a 'heavier' silyl group (*vide infra*). From entry 4, the presence of an ester group was clearly not well tolerated under the acidic conditions employed for the hydrogenation step, since numerous by-products were formed leading to a very low overall yield of the desired product (entry 4).
As expected the deprotection of the Boc protecting group of (±)-124 and 125 was easily achieved using a solution of hydrochloric acid in isopropanol thereby affording the aminocyclopropanes as their hydrochloride salts (Scheme 100).

![Scheme 100](image)

As the overall efficiency of the two-step protocol developed for the preparation of the Boc protected amines was not completely satisfactory, an alternative approach was investigated. This latter consisted in performing the two steps in one, in other words, carrying out the hydrogenolysis of the oxazolidinone ring in the presence of Boc$_2$O in order to obtain the protected amines directly. To our delight, when this approach was applied to the deprotection of the set of chiral oxazolidinones previously studied (vide supra), excellent yields of the carbamates were consistently obtained (Table 8). The deprotection of (+)- and (-)-118A furnishes, of course, the same meso compound 125. The general procedure involved the hydrogenation of the substrate in the presence of Pearlman's catalyst and Boc$_2$O (2 eq) in THF at 5.5-6 bar and at 30-35°C. However, these conditions have not been fully optimised.
Results and Discussion

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Experimental conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>5.5 bar / 7 h / 30°C</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>5.5 bar / 8 h / 30°C</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>6 bar / 8 h / 35°C</td>
<td>95%</td>
</tr>
</tbody>
</table>

Table 8

Some limitations of these deprotection procedures were nevertheless highlighted when substrates possessing a phenyl ring adjacent to the cyclopropyl unit were used. Indeed, the cyclopropane of (±)-119A was found to undergo ring opening during the hydrogenation step and to yield a mixture of carbamates 130 and 131 (Scheme 101). This feature appears to be an inherent problem with α-arylcyclopropyl compounds.40

![Scheme 101](image4.png)

Hence, in order to obtain the corresponding primary phenylcyclopropylamine, alternative methods such as the use of carbenoid precursors which would require different deprotection conditions or the development of other sequences for the deprotection of diphenyloxazolidinone derivatives were then considered.
2.7.8 Studies towards the preparation of primary arylcyclopropylamines

2.7.8.1 Use of a different carbenoid precursor

In order to overcome the problem raised by the hydrogenolysis of the cyclopropane ring observed with (±)-119A, we first considered employing a carbenoid precursor which would require a different procedure for its deprotection. For this purpose, we decided to study the reactivity and deprotection of the 4-(4-methoxyphenyl)-oxazolidin-2-one derivative 136. This auxiliary was expected to be cleaved by alkaline hydrolysis and subsequent mild oxidative cleavage of the 4-methoxy benzyl group using for example cerium ammonium nitrate (Scheme 102).

Scheme 102

4-(4-methoxyphenyl)-oxazolidin-2-one 135 was synthesised, on a multigram scale, in four straightforward steps from D-(4-hydroxyphenyl)-glycine in an overall yield of 64 % (Scheme 103). The key step of this sequence was the formation of the oxazolidinone ring by treating the Boc protected amino alcohol 134 with an excess of thionyl chloride.

Scheme 103
Disappointingly however, the treatment of 135 with triethyl orthoformate in the presence of a catalytic amount of AlCl₃ gave a mixture of products from which the N-diethoxymethyl derivative 136 could be isolated in only 25% yield (Scheme 104).

![Scheme 104](image)

This result prompted us to investigate a more general method for deprotection of oxazolidinone rings.

### 2.7.8.2 Studies of alternative methods for the cleavage of the diphenyloxazolidinone ring

We then reasoned that any vicinal amino alcohols could be cleaved by oxidation and thus lead to the free amine after hydrolysis of the intermediate imine (Scheme 105). This would allow us to employ the diphenyloxazolidinone derivatives whose chemistry has already been developed.

![Scheme 105](image)

The most common reagent used for such oxidations is lead tetraacetate, which is known to be compatible with the presence of a cyclopropane ring. However, when this cleavage reaction was investigated using (±)-137 and (±)-138, it was found that, in both cases, a complex mixture of products was produced (Scheme 106).
Results and Discussion

Scheme 106

From the literature, one similar reaction using lead tetraacetate required optimised conditions to finally give the expected product in a moderate yield (Scheme 107).\textsuperscript{105}

Scheme 107

In complete contrast, when the reference product 139 was treated with lead tetraacetate the expected imine and benzaldehyde were obtained in almost quantitative yield (Scheme 108) showing clearly that the proximity of the cyclopropyl ring to the nitrogen atom is not well tolerated when lead tetraacetate is employed.

Scheme 108
Extensive work was then carried out to find conditions to achieve the efficient oxidative cleavage of amino alcohols using 'non metallic' oxidising reagents such as periodic acid, H$_5$IO$_6$, and sodium metaperiodate, NaIO$_4$. The reference product 139 and the phenylcyclopropyl amino alcohol (+)-140, which was obtained in 70 % by hydrolysis of (+)-119A using KOSiMe$_3$ in THF at 60 °C, were both used in this study. Reactions involving either H$_5$IO$_6$ or NaIO$_4$ are generally performed in a mixture of alcohol and water. However our substrates were found to be rather insoluble in this medium and the oxidation reactions did not proceed satisfactorily. When supported on silica gel, NaIO$_4$ is effective in dichloromethane, a solvent in which our substrates are soluble. Using this reagent, the reactions employing both substrates were complete in one hour as observed by TLC. However, after filtration, extensive washing of the filtered silica gel, and concentration of the reaction mixture, the recovered mass of the crude reaction mixture was curiously much lower than expected. A number of reactions using NaIO$_4$ in a mixture of THF or dichloromethane with various amounts of water were then carried out, however the results obtained were variable and not reproducible. This approach, which appeared at first to be promising, had therefore to be abandoned.

For the preparation of arylcyclopropylamines, a totally different strategy involving a palladium cross-coupling reaction was accordingly envisaged and is presented in section 2.9 (vide infra).
2.8 Studies on the synthesis of N-substituted cyclopropyl amino alcohols and acids

A number of N-cyclopropyl amino acids and their derivatives are present in molecules showing interesting biological activities although in general, no substituents are present on the cyclopropyl ring since simple aminicyclopropane is always selected as a building block (Scheme 109).\textsuperscript{108}

To date, no methods which would lead easily to the preparation of N-substituted cyclopropyl amino acids have been reported, even although these compounds could be very valuable either for medicinal or peptide chemistry. Consequently, we elected to investigate the application of our newly developed methodology towards the synthesis of amino alcohols and acids possessing substituted cyclopropyl unit adjacent to the nitrogen atom.

Initially we considered the cyclopropanation of alkenes with N-diethoxymethyl oxazolidinones derived from different amino acids. Subsequent hydrolysis of the oxazolidinone ring would then furnish amino alcohols and the N-substituted
cyclopropyl amino acids would then be obtained by oxidation of their corresponding alcohols (Scheme 110).

The feasibility of this approach was initially verified by the preparation of the N-substituted cyclopropyl glycine derivative 144. The synthesis, commencing with the cyclopropanation reaction between 108 and 3,3-dimethylbutene, proceeded with very good stereocontrol to yield almost exclusively the trans cyclopropane 141. Hydrolysis of the oxazolidinone ring and subsequent protection of the resulting secondary amine gave the amino alcohol 143, which was then oxidised very cleanly with potassium permanganate in alkaline medium to furnish the desired amino acid 144 (Scheme 111).

Encouraged by this result, we decided to attempt a similar sequence with different amino acids. Curiously however, when the oxazolidinones derived from phenylalanine
and valine were treated with triethyl orthoformate, a mixture of products was obtained and the desired products could only be isolated in poor yields (Scheme 112).

![Scheme 112](image)

As a comparison, under similar conditions, N-diethoxymethylloxazolidinone 108 and 4,5-diphenyloxazolidinone 113 were obtained in 67 % and 68-80 % yield respectively. In an attempt to rationalise this surprising substrate dependence, the same reaction was performed with compounds structurally similar to 4,5-diphenyloxazolidinone 112, such as 4-phenyloxazolidinone 149 and 4-methyl-5-phenyloxazolidinone 151, but once again, the yields for these transformations were low (Scheme 113). At present, we therefore have no logical rationalisation for the substituent dependence on the yields of these products.

![Scheme 113](image)

As the carbenoid precursors in this series could not be obtained in good yields, we were led to consider an alternative sequence. Another strategy was therefore envisaged, starting from serine derivatives and preparing the tosylate 153 which could then react with nucleophiles (Scheme 114). This sequence appeared attractive as it would lead to the preparation of a wide range of products by varying the nucleophile employed.
In this respect, work by Sibi et al. was particularly informative. This group has shown that, with an unsubstituted oxazolidinone, the displacement of the tosylate group is achieved very effectively using cuprates (Scheme 115).\(^{109}\)

The study of this novel route commenced with the preparation of 155 in two steps from L serine ethyl ester hydrochloride (Scheme 116). Using oxazolidinone 154, the synthesis of the N-dieoxymethyl derivative was, in this case, obtained in a moderate but acceptable yield.

The cyclopropanation reaction of vinyl cyclohexane with 155 was then carried out under standard conditions and gave predominantly a 3:1 inseparable mixture of the two \textit{trans} diastereoisomers 156 and 157, the major isomer was not identified (Scheme 117).
Results and Discussion

We consequently reasoned that better stereocontrol of the cyclopropanation reaction might be achieved using a carbenoid precursor possessing a more hindered side chain. As the use of an excess of triethylorthoformate, in the presence of aluminium chloride, will transform any ester to the ethyl ester 155, we had to turn our attention to carbenoid precursors possessing functional groups other than esters. The derivatives which would offer the most flexibility appeared to us to be the derived protected alcohols. We thus prepared the two alcohols 160 and 163 bearing a TBDMS and a benzyl group. 160 was synthesised in two steps from the alcohol 158 obtained by reduction of the ester moiety of 154 (Scheme 118). Treatment of 158 using sodium hydride and benzyl bromide was found to give mainly the N-benzylated product rather than the expected O-benzylated derivative due to the increased acidity of the N-H proton of the carbamate when incorporated into a cyclic structure. The route finally followed involved the use of the commercially available O-benzyl-DL-serine 161 and yielded the desired product 163 in three steps (Scheme 118).
Cyclopropanation reactions were then performed with vinyl cyclohexane and gave for both carbenoid precursors 160 or 163 approximately a 4:1 mixture of the two trans diastereoisomers as determined by a study of the $^1$H NMR of the crude reaction mixture; the major isomers for these reactions were not identified (Scheme 119). For the reaction involving 160, no yield was calculated as the addition of the carbenoid precursor was interrupted at an early stage due to the formation of hard zinc balls.

These results demonstrated that the use of carbenoid precursors possessing a hindered side chain induced a certain degree of stereocontrol. In order to increase this stereocontrol, a wider range of protecting groups for the alcohol functionality should of course be screened. However, this study was not further developed because of time constraints.

2.9 Studies on the synthesis of arylcyclopropanes via a palladium-catalysed cross-coupling reaction

Although a range of free aminocyclopropanes was accessible by our newly developed method, the synthesis of primary arylcyclopropylamines still represented a challenge (vide supra). As a cyclopropyl ring adjacent to a phenyl group was found to be hydrogenolysed during the deprotection step, we considered introducing the aryl functionality at a later stage via a palladium-catalysed cross-coupling reaction. Two
approaches were postulated for creation of a new cyclopropyl-aryl bond; either by reaction between a cyclopropyl halide and an aryl organometallic species (route A) or between an aryl halide or triflate and a cyclopropyl organometallic species (route B) (Scheme 120).

\[
\begin{align*}
&\text{M} = \text{metal} \\
&\text{X} = \text{halide or triflate}
\end{align*}
\]

Scheme 120

2.9.1 Palladium-catalysed cross-coupling reactions involving cyclopropyl halides

The successful insertion of palladium (0) into a cyclopropyl iodide bond was first reported by Charette et al. and allowed the effective preparation of arylcyclopropanes via the Suzuki type cross-coupling reaction (Scheme 121).\(^{110}\)

\[
\begin{align*}
\text{PhB(OH)}_2, \text{Pd(OAc)}_2 & , \text{PPPh}_3, \text{K}_2\text{CO}_3, \text{Bu}_4\text{NCl} \\
\text{DMF/H}_2\text{O}, 90^\circ\text{C} & , 80\% \\
\text{same conditions} & , 88\%
\end{align*}
\]

Scheme 121

However such an approach is not feasible using our methodology, as cyclopropyl iodides cannot be prepared under the reductive conditions employed for the cyclopropanation reaction.
2.9.2 Palladium-catalysed cross-coupling reactions involving cyclopropyl organometallic species

Cyclopropylzincs,\textsuperscript{110c,111} -boronic acids,\textsuperscript{110b,112} -boranes,\textsuperscript{113} -borates\textsuperscript{114} and -stannanes\textsuperscript{101} have all been shown to undergo palladium-catalysed cross-coupling reactions with aryl halides and triflates to generally yield arylcyclopropane products in good yields. We have previously reported the preparation of the cyclopropylstannane derivative (±)-121 using our methodology. However, this compound was obtained in low yield due to the instability of tributyl(vinyl)tin under the cyclopropanation reaction conditions (\textit{vide supra} 2.7.4). Furthermore, in order to achieve the synthesis of primary arylcyclopropanes, the carbon-tin bond would have to withstand hydrogenation at high pressure and this is unprecedented in the literature (Scheme 122).

\[ \text{Scheme 122} \]

The preparation of free aminocyclopropanes using boron derivatives would also suffer from the same limitations. In addition, cyclopropylboron compounds have not been previously prepared employing an organozinc carbenoid generated by the zinc/chlorotrimethylsilane system and thus the reactivity of their alkenyl precursors would therefore have to be demonstrated.

At this stage, it was realised that none of the previously reported cyclopropyl organometallic species would be entirely appropriate for the cyclopropanation and/or hydrogenation steps of the sequence studied. As a consequence, the use of more robust substrates was investigated. Recently, organosilicon compounds have been shown to be competent coupling partners for palladium-catalysed cross-coupling reactions.\textsuperscript{115} Under our standard cyclopropanation conditions, vinyl trimethylsilane was found to be cyclopropanated effectively to provide almost exclusively one isomer (\textit{vide supra}).
Additionally, a carbon-silicon bond is not expected to be cleaved upon hydrogenation, making this class of compounds ideal to study using our methodology. We therefore decided to investigate the ability of cyclopropylsilanes to undergo cross-coupling reactions. Although such transformations have been routinely performed with alkenyl, aryl and alkynyl organosilicon compounds, cyclopropylsilanes have, to date, not been utilised.

2.9.3 Palladium-catalysed cross-coupling reactions of organosilicon compounds

2.9.3.1 Background

Recently, the use of organosilicon compounds to create carbon-carbon bonds has received increased attention, especially due to the low toxicity, ready accessibility and high chemical stability of these reagents. Activated by a nucleophilic promoter, fluoro-, chloro-, alkoxy-, hydroxy- and alkylsilanes undergo palladium-catalysed cross-coupling reactions and usually provide the coupled products in very high yields under mild conditions. To avoid any complications during the cyclopropanation reaction, the use of an all-carbon silicon species was considered. The effective and general application of alkylsilanes in cross-coupling reactions was initially reported by Denmark. His pioneering work demonstrated that alkenylsilacyclobutanes, in the presence of TBAF and a catalytic amount of a palladium (0) source, underwent facile cross-coupling with aryl and vinyl iodides with excellent stereocontrol (Scheme 123).

![Scheme 123](image)

The active species in the reaction described above were finally found to be the silanol 169 and the disiloxane 170 both of which were produced when the silacyclobutane 168
was treated with TBAF and water; water which is present in the commercial THF solution of TBAF employed (Scheme 124).\(^\text{117}\)

\[
\begin{align*}
\text{n-CsH}_{11} & \quad \text{Si}^\text{Me} \\
\text{Me} & \quad \text{THF/H}_2\text{O} \\
\text{TBAF (1 eq)} & \\
\text{n-CsH}_{11} & \quad \text{Me}^\text{n-Pr} \\
\text{Si} & \quad \text{OH} \\
\text{169} & \quad 42\% \\
\text{n-CsH}_{11} & \quad \text{n-Pr} \\
\text{Si} & \quad \text{Me} \\
\text{170} & \quad 45\%
\end{align*}
\]

**Scheme 124**

On the basis of these findings, the reactivity of silanols, siloxanes and silyl ethers were investigated and they were found to be very efficient coupling partners.\(^\text{115,118}\) With silanols, effective couplings could be promoted with the use of a base, such as potassium trimethylsilanolate or cesium carbonate, instead of a fluoride source (Scheme 125).\(^\text{119}\)

\[
\begin{align*}
\text{n-CsH}_{11} & \quad \text{Si}^\text{Me} \\
\text{Me} & \quad \text{THF} \\
\text{KOSiMe}_3 & \quad (2 \text{ eq}) \\
\text{Pd(dba)}_2 & \quad (5 \text{ mol}\%) \\
\text{rt, 15 min} & \quad 95\%
\end{align*}
\]

**Scheme 125**

Recently, Denmark *et al.* undertook both NMR and kinetic studies to gain a better understanding of the mechanism of the fluoride promoted cross-coupling reaction and postulated that 171 could be an intermediate involved in the transmetallation step (Scheme 126).\(^\text{120}\)

\[
\begin{align*}
\text{n-CsH}_{11} & \quad \text{Si}^\text{Me} \\
\text{Me} & \quad \text{OH} \\
\text{O}_2\text{N}- & \quad \text{I} \\
\text{Pd(dba)}_2 & \quad (5 \text{ mol}\%) \\
\text{KOSiMe}_3 & \quad (2 \text{ eq}) \\
\text{THF} & \quad 95.5:1.5
\end{align*}
\]

**Scheme 126**
In parallel with Denmark's work, Mori et al. demonstrated that, as an alternative, alkenyl- and arylsilanols could be activated with silver(I) oxide.\textsuperscript{121} The silver atom was believed to promote halide atom abstraction from the arylpalladium iodide intermediate to form a more reactive cationic palladium species, while the oxygen atom reacted as a nucleophilic activator thus generating the silicate intermediate involved in the transmetallation (Scheme 127).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme127.png}
\end{center}

\textbf{Scheme 127}

\subsection*{2.9.3.2 A preliminary study towards the palladium-catalysed cross-coupling reactions of cyclopropylsilanes}

As cyclopropanes are known to have some sp\textsuperscript{2} character\textsuperscript{122} and, when appropriately functionalised, to be successfully cross-coupled under Negishi, Suzuki and Stille conditions (\textit{vide supra}), we were confident that cyclopropylsilanes would also act as coupling partners. Amongst the different silyl groups involved in cross-coupling reactions, the benzyldimethylsilyl moiety appeared to be the most appropriate to study as it is a stable all-carbon silicon species which undergoes rapid debenzylation upon treatment with TBAF to yield its corresponding silanol, the active species involved in this type of cross-coupling reaction. Alkenyl benzyldimethylsilanes are also easily prepared.\textsuperscript{123}

In a very encouraging initial experiment, we demonstrated that the benzyldimethylvinylsilane 172, readily synthesised in 62\% yield from the reaction of benzylmagnesium chloride and chlorodimethylvinylsilane, was stable under the experimental conditions used for the cyclopropanation/hydrogenation sequence and led to the formation of the desired vicinal amino cyclopropylsilane (+)-174 (Scheme 128).
Results and Discussion

The absolute configuration of (+)-173A was determined by its X-Ray diffraction (Scheme 129) and its structure also supports the proposed mechanism for this cyclopropanation reaction (vide supra).

Scheme 128

Cyclopropylsilane 175 was also prepared and chosen for the investigation of the cross-coupling reaction, as it was more conveniently prepared from inexpensive N-diethoxymethylpyrrolidinone 78.

The general procedure consisted of the initial in situ formation of the corresponding silanol of 176 by treatment with TBAF (2.2 eq) in THF followed by the addition of aryl iodide (1.5 eq), palladium catalyst and, in some cases, phosphines. The reaction mixture was then heated for 20 hours (Scheme 130 and Table 9).

Scheme 129

Scheme 130
Results and Discussion

<table>
<thead>
<tr>
<th>Aryl iodide</th>
<th>Pd catalyst</th>
<th>Phosphine</th>
<th>Solvent</th>
<th>Temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 iodo benzene</td>
<td>Pd(dba)_2 (5%)</td>
<td>—</td>
<td>THF</td>
<td>60°C</td>
</tr>
<tr>
<td>2 iodo benzene</td>
<td>Pd(OAc)_2 (5%)</td>
<td>PPh_3 (10%)</td>
<td>THF</td>
<td>60°C</td>
</tr>
<tr>
<td>3* iodo benzene</td>
<td>Pd(OAc)_2 (5%)</td>
<td>PPh_3 (10%)</td>
<td>THF→toluene</td>
<td>110°C</td>
</tr>
<tr>
<td>4* iodo-4-nitrobenzene</td>
<td>Pd(dba)_2 (10%)</td>
<td>—</td>
<td>THF</td>
<td>100°C</td>
</tr>
</tbody>
</table>

* THF was removed after the first step and replaced by toluene. b The reaction was performed in a sealed tube.

Table 9

Unfortunately, although silane 175 was completely converted to its corresponding silanol 176, as evidenced by the \(^1\)H NMR of the crude reaction mixture, none of these reactions actually yielded the desired cross-coupled products. As the oxidative addition of aryl iodides is normally a facile process, the inability of the TBAF-activated silanol 176 to undergo transmetallation could therefore provide a possible explanation for the failure of these reactions.

As silanols are also known to be activated by silver(I) oxide or bases (vide supra), we decided to prepare and isolate the silanol 176 and then conduct the cross-coupling reaction with these promoters. Unfortunately, once again, under these conditions no reaction occurred (Scheme 131).

![Scheme 131](https://example.com/scheme131.png)

However, cross-coupling reactions may proceed if the starting cyclopropylsilanes bore more reactive silyl groups, such as trifluorosilane group, but these compounds may not be stable enough under the experimental conditions employed for our methodology. A fine balance between the reactivity and the stability of the silane derivative would...
thus have to be found in order to achieve an appropriate cyclopropylsilane coupling partner.

2.10 Preparation of vicinal amino cyclopropanols

Concurrently with the study of palladium-catalysed cross-coupling reactions discussed above, we were also interested in synthesising amino cyclopropanols by the transformation of the silyl moiety of cyclopropylsilanes via the Tamao-Fleming oxidation reaction.

2.10.1 Background

The conversion of a silicon group into a hydroxyl group by the oxidative cleavage of a carbon-silicon bond is a valuable transformation which is widely applied in organic synthesis at the present time. Two different methods have been developed. The first by Tamao and Kumada, relied on the facile oxidative cleavage of a silicon-carbon bond of a silyl group activated by the presence of a heteroatom. This reaction was performed either with hydrogen peroxide or m-CPBA in the presence of a source of fluoride, most commonly potassium fluoride (Scheme 132).

\[
R-SiX_3 \xrightarrow{30 \% H_2O_2 or m-CPBA} R-OH \\
SiX_3 = SiMe_3(OR), SiMeOR_2, Si(OR)_3, SiCl_3, SiMe_2F, SiMeF, SiF_3, ...
\]

Scheme 132

Independently, Fleming et al. described a two step protocol for the conversion of the SiMe_2Ph moiety to a hydroxy group. Their approach consisted of the initial substitution of the phenyl ring through protodesilylation and subsequent oxidation of the carbon-silicon bond of the resulting intermediate (Scheme 133).

\[
R-SiMe_2Ph \xrightarrow{HBF_4.OEt_2 or BF_3.2AcOH} R-SiMe_2X \xrightarrow{m-CPBA or AcOOH} R-OH \\
X = F, OAc
\]

Scheme 133
The formation of a silyl peroxide of the type 177 which then underwent a migration analogous to that encountered in a Baeyer-Villiger rearrangement was postulated for this reaction (Scheme 134).\(^{125}\)

\[\text{Scheme 134}\]

### 2.10.2 The use of the Tamao-Fleming oxidation of cyclopropylsilanes leading to the preparation of vicinal amino cyclopropanols

As in the case of the cross-coupling reaction that we attempted to develop using cyclopropylsilanes, the selection of the silyl group for the Tamao-Fleming oxidation was crucial.

It was expected that reactive silanes, such as trichloro- or fluorosilanes, would not be stable under our cyclopropanation conditions and as a consequence these were not used. Additionally, the electrophilic conditions employed for the protodesilylation of the more robust SiMe\(_2\)Ph moiety are known to be incompatible with the presence of a cyclopropane which would undergo ring opening in this situation (Scheme 135).\(^{128}\)

\[\text{Scheme 135}\]

Recently, alternative silyl groups which offer the advantages of having comparable stability to SiMe\(_2\)Ph but also being converted to the hydroxyl group under milder conditions have emerged.\(^{129}\) Amongst these, the benzylidemethylsilyl group, previously
used for our study on cross-coupling reactions, has appeared as a very effective hydroxy surrogate (Scheme 136).

![Scheme 136](image)

Also, it has been shown that the cyclopropylsilanol 178 can be converted to its corresponding cyclopropanol 179 using hydrogen peroxide in the presence of an inorganic base thus demonstrating the stability of a cyclopropyl ring under these experimental conditions (Scheme 137).

![Scheme 137](image)

In order to synthesise vicinal amino cyclopropanols, we accordingly chose to investigate the oxidation of the carbon-silicon bond of the two cyclopropylsilanes 175 and (+)-174 prepared previously. The optimum conditions for this sequence were found to involve treatment of the silane with TBAF in the first instance, to form its corresponding silanol \textit{in situ} prior to oxidation (Scheme 138). Both reactions occurred with complete retention of configuration at the carbon centre as reported by Tamao and Fleming. This ‘one pot’ procedure was found particularly effective for the synthesis of the chiral \textit{trans} amino alcohol (+)-181. Because of its well-defined and rigid structure, this latter compound could be a very interesting and valuable intermediate in medicinal chemistry.
This study consequently confirmed the versatility of the benzyldimethylsilane group as a robust and very effective latent hydroxyl group and provided the first successful examples of the Tamao-Fleming oxidation of an all-carbon silicon species in the presence of a cyclopropyl ring.
Chapter 3

Conclusions and Perspectives
Conclusions and Perspectives

The present work has involved a study of the generation and the reactivity of novel organozinc carbenoids possessing adjacent nitrogen functionalities. Firstly, it was discovered that the presence of an electron-withdrawing group on the nitrogen atom was necessary to ensure the generation and the cyclopropanating ability of the carbenoid species. When derived from an “acetal” moiety, the organozinc carbenoid attached to pyrrolidinone underwent cyclopropanation reactions with a wide range of alkenes. The preferred formation of the less hindered trans or exo isomer was observed, especially when the alkene employed bore a bulky group (Scheme 139).

If organozinc carbenoids were generated from an acyclic N-diethoxymethyl amide or from an N-formyl derivative, the yields of cyclopropanes obtained were lower, showing the advantages of the constrained cyclic amide as the source of the amino functionality and the superior reactivity of the acetal moiety.

The value of this methodology was greatly increased when primary aminocyclopropanes were found to be accessible from diphenyloxazolidinone derivatives of type 182 (Scheme 140). Chiral protected aminocyclopropanes were thus prepared in only two steps from alkenes (Scheme 140).

Scheme 139

Scheme 140
In terms of future work in this area, it would certainly be of interest to assess the efficiency of this newly developed methodology by applying it towards the synthesis of both natural and non-natural molecules of biological importance. Thus, a concise synthesis of 3-(trans-2-aminocyclopropyl)alanine, a component of the antitumor agent Belactosin A 3 could be envisaged from the allylglycine derivative 183 (Scheme 141).

Scheme 141

However aryl substituted cyclopropylamines were found not to be accessible using the methodology involving the use of N-diethoxymethyl diphenyloxazolidinone 113 since the cyclopropyl ring underwent hydrogenolysis during the hydrogenation step. In a complementary strategy to those different alternative approaches already investigated, the use of 184 as a carbenoid precursor could also be considered, since the amine functionality could be revealed after hydrolysis of the oxazolidinone ring and oxidation, two steps both of which should be compatible with the presence of the cyclopropane ring (Scheme 142).

Scheme 142
The preparation of \( N \)-substituted amino acids by cyclopropanation of alkenes with diverse \( N \)-diethoxymethyl oxazolidinones was also studied. Even although the reference compound 144 was obtained following this approach, the curious variation in yield as a function of substitution pattern around the oxazolidinone ring when synthesising a range of \( N \)-diethoxymethyl oxazolidinones prompted us to abandon this route (Scheme 143).

![Scheme 143](image)

Alternatively, the tosylate 153 derived from serine derivatives could be employed as a modifiable scaffold and thus lead to the formation of a wide range of natural and unnatural \( N \)-substituted amino acids (Scheme 144). However, in order to become a more general method, this would require finding a serine derivative which would exhibit a high degree of stereocontrol in the cyclopropanation reaction.

![Scheme 144](image)
Conclusions and Perspectives

Cyclopropylsilanes were tested as substrates in palladium-catalysed cross-coupling reactions with aryl iodides. However these reactions did not yield any of the desired products, probably due the failure of the silyl component to undergo transmetallation (Scheme 145). Employing more reactive silicon groups and different catalysts and/or additives might encourage the reaction to proceed.

By way of contrast however, the Tamao-Fleming oxidation was successfully applied to cyclopropylsilanes prepared using our methodology. This work allowed us to synthesise the structurally rigid chiral amino cyclopropanol (+)-181 (Scheme 146). As (Z) and (E) alkenylsilanes are easily accessible, it will be of interest to extend this methodology to substituted cyclopropanols of type 185 and 186 (Scheme 146).\textsuperscript{115,123}

Equally interesting would be the preparation of chiral \textit{trans} diamines. These compounds could be conveniently synthesised from the cyclopropanation of enamide of type 187 (Scheme 147). However, preliminary studies on the cyclopropanation of the enamides 188 and (+)-189 have indicated that our standard experimental conditions must be modified to increase the stability of the zinc amalgam in the presence of such functionalised alkenes.
Although this newly developed methodology allows for the rapid and easy preparation of aminocyclopropanes derivatives, the cyclopropanation reactions currently proceed only in moderate to good yields, undoubtedly due to the ability of zinc amalgam to form aggregates. The inability to predict for any given substrate and carbenoid precursor whether or not such destructive physical characteristics will occur has been an ongoing frustration. It would thus be very interesting to investigate the reactivity of other metallocarbenoids which could be generated from different electron donor metals such as indium or ytterbium.
Chapter 4

Experimental
4.1 General information

Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 (using the sodium D-line, 529 nm) polarimeter and [α]_D values are given in 10° deg cm g⁻¹, concentration (c) in g per 100 mL. Infrared (IR) were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer, and were recorded as thin films (NaCl) either of pure sample or of solution of sample in the stated solvent. Absorption maxima are reported in wavenumbers (cm⁻¹). Only selected absorbances are reported.

¹H NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker Avance 500 spectrometer in the stated solvent using residual protic solvent CHCl₃ (δ = 7.24 ppm, s), DMSO (δ = 2.49 ppm, qn) or CH₂Cl₂ (δ = 7.15 ppm, s) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (J) are reported as measured and recorded in Hertz.

2D-noesy NMR experiments were carried out on a Bruker Avance 500 spectrometer. ¹³C NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on a Bruker AMX400 spectrometer or at 125 MHz on a Bruker Avance 500 spectrometer in the stated solvent using the central reference of CHCl₃ (δ = 77.0 ppm, t), DMSO (δ = 39.5 ppm, septuplet) or CH₂Cl₂ (δ = 128.0 ppm, s) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. If more than one peak is observed within 0.1 ppm accuracy, the number of peaks will be indicated.

Mass spectra and accurate mass measurements were recorded on a Micromass 70-SE Magnetic Sector spectrometer at the University College London Chemistry department. Elementary analyses were performed at University College London Chemistry department. The X-ray crystal structure of (+)-173 was determined using a Bruker Smart Apex diffractometer at the University College London Chemistry department.
All reactions using dry solvents were carried out in oven-dried glassware under a nitrogen atmosphere. Diethyl ether and THF were distilled from sodium-benzophenone ketyl. Toluene was distilled from sodium. DMF was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Methanol was distilled from magnesium turnings and iodine. Triethylamine was pre-dried with potassium hydroxide pellets, filtered, distilled and stored over potassium hydroxide pellets. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use.

Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F<sub>254</sub>, and visualised with ultraviolet light (254nm), plus either basic potassium permanganate or acidic ammonium molybdate solution. Flash chromatography was performed using BDH silica gel (40-60μm).

All compounds were used as supplied by the manufacturers unless otherwise stated.

**Zinc amalgam**

Zinc dust (10.0 g, 153 mol) was added to a vigorously stirred solution of mercury (II) chloride (2.0 g, 7.20 mmol) and concentrated aqueous solution of hydrochloric acid (12M, 0.5 mL) in water (30 mL). The mixture was stirred for 10 minutes, the zinc filtered off and then washed with water (3 x 20 mL), acetone (3 x 20 mL), ethanol (3 x 20 mL) and ether (3 x 20 mL) before being dried under high vacuum. The zinc amalgam was thereafter stored under vacuum, and was always flame dried under a stream of nitrogen immediately prior to use.
4.2 Experimental Procedures

**N-Diethoxymethyl-2-pyrrolidinone 78**

![Structural formula]

The *title compound* was prepared by a literature method. A mixture of 2-pyrrolidinone (2.0 g, 23.5 mmol, 1 eq), aluminium chloride (0.31 g, 2.35 mmol, 0.1 eq) and triethyl orthoformate (77.3 mL, 0.47 mol, 20 eq) was heated at 150°C for 48 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (35 mL). The aqueous phase was extracted with diethyl ether (70 mL then 35 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2 to 1:1) to give the *title compound* 78 (3.08 g, 16.45 mmol, 70%) as a yellow oil.

**R**<sub>f</sub> (P.E. 30-40°C/EtOAc 1:1) 0.33; **IR** (film): ν<sub>max</sub> 2977 (s), 2897 (m), 1693 (s, C=O), 1418 (s), 1104 (s), 1062 (s) cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 1.20 (t, ³J₇,₆=7.0 Hz, 6H, H₇), 2.00 (qn, ³J₃,₂=³J₅,₄=7.9 Hz, 2H, H₃), 2.41 (t, ³J₂,₃=8.2 Hz, 2H, H₂), 3.42 (t, ³J₄,₃=7.3 Hz, 2H, H₄), 3.48 (dq, ³J₆,₇=7.0 Hz, ²J=9.4 Hz, 2H, H₆), 3.62 (dq, ³J₆,₇=7.0 Hz, ²J=9.4 Hz, 2H, H₆), 5.87 (s, 1H, H₅); **¹³C NMR** (75 MHz, CDCl₃): δ 14.5 (C₇), 17.8 (C₃), 31.4 (C₂), 40.5 (C₄), 61.9 (C₆), 98.8 (C₅), 175.2 (C₁); **EI-MS** m/z (%): 188 (MH⁺, 4), 142 ([M-OC₂H₅]+, 100); **HMRS**: MH⁺, found 188.13052. C₉H₁₈NO₃ requires 188.12867.
Experimental

1-(2-Benzylcyclopropyl)-2-pyrrolidinone 79

\[
\text{C}_{14}\text{H}_{17}\text{NO} \quad 215.29 \text{ g.mol}^{-1}
\]

A solution of \(N\)-diethoxymethy-2-pyrrolidinone 78 (0.393 g, 2.11 mmol, 2 eq) in dry diethyl ether (3 mL) was added via a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (1.38 g, 21.1 mmol, 20 eq), anhydrous zinc chloride (0.29 g, 2.11 mmol, 2 eq), chlorotrimethylsilane (1.34 mL, 10.56 mmol, 10 eq) and freshly distilled allylbenzene (0.125 g, 1.06 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO\(_3\) solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 99:1 to 98:2) to give an inseparable mixture of \(cis\) and \(trans\) cyclopropanes 79 (0.199 g, 0.93 mmol, 88\%, \(trans/cis\): 11.5:1 as determined by NMR) as a colourless oil.

\(R_f\) (EtOAc/MeOH 98:2) 0.35; IR (mixture of \(trans\) and \(cis\), film): \(\nu_{\max}\) 2992 (m), 2958 (m), 1688 (s, C=O), 1495 (m), 1454 (m), 1421 (s), 1292 (s), 1030 (w), 742 (m), cm\(^{-1}\); \(^1\)H NMR (trans, 500 MHz, CDCl\(_3\)): \(\delta\) 0.75 (ddd, \(^3J_{6\beta-6\alpha}=5.8\) Hz, \(^1J_{6\beta-7}=6.1\) Hz, \(^3J_{6\beta-5}=7.5\) Hz, 1H, H\(_{6\beta}\)), 0.95 (ddd, \(^3J_{6\alpha-5}=4.1\) Hz, \(^2J_{6\alpha-6\beta}=5.8\) Hz, \(^1J_{6\alpha-7}=9.4\) Hz, 1H, H\(_{6\alpha}\)), 1.28 (dddt, \(^3J_{7.5}=3.5\) Hz, \(^3J_{7.6\beta}=6.1\) Hz, \(^1J_{7.8}=6.9\) Hz, \(^1J_{7.6\alpha}=9.4\) Hz, 1H, H\(_7\)), 1.86-1.93 (m, 2H, H\(_3\)), 2.32 (t, \(^3J_{2.3}=8.0\) Hz, 2H, H\(_2\)), 2.50-2.55 (m, 2H, H\(_5\) and H\(_8\)), 2.70 (dd, \(^3J_{8.7}=6.7\) Hz, \(^2J=14.7\) Hz, 1H, H\(_8\)), 3.16 (t, \(^3J_{4.3}=7.0\) Hz, 2H, H\(_4\)), 7.18-7.30 (m, 5H, \(\text{H}_{\text{arom}}\)), \(^{13}\)C NMR (trans, 125 MHz, CDCl\(_3\)): \(\delta\) 12.1 (C\(_6\)), 17.8 (C\(_3\)), 19.0 (C\(_7\)), 31.6
Experimental

(C2 and C3), 38.0 (C8), 47.2 (C4), 125.9 (CH), 128.2 (CH), 140.5 (Cq), 175.8 (Ci); \(^1\)H NMR (cis, 500 MHz, CDCl3): \(\delta 0.71\) (ddd, \(^3\)J6\(_{\alpha}\)\(_{6\beta}\)=4.6 Hz, \(^2\)J6\(_{\alpha}\)\(_{6\gamma}\)=6.0 Hz, \(^3\)J5\(_{\alpha}\)\(_{6\gamma}\)=6.3 Hz, 1H, H6\(_{\alpha}\)), 1.00 (ddd, \(^2\)J6\(_{\alpha}\)\(_{6\beta}\)=6.0 Hz, \(^3\)J6\(_{\beta}\)\(_{6\gamma}\)=8.0 Hz, \(^3\)J6\(_{\gamma}\)\(_{6\alpha}\)=8.8 Hz, 1H, H6\(_{\beta}\)), 1.34 (dddt, \(^3\)J7\(_{\alpha}\)\(_{6\beta}\)=4.9 Hz, \(^3\)J7\(_{\alpha}\)\(_{6\gamma}\)=6.5 Hz, \(^3\)J7\(_{\beta}\)\(_{6\gamma}\)=7.1 Hz, \(^3\)J7\(_{\gamma}\)\(_{6\alpha}\)=8.9 Hz, 1H, H7), 1.94-2.01 (m, 2H, H3), 2.19 (ddd, \(^3\)J8\(_{\alpha}\)\(_{6\beta}\)=9.0 Hz, \(^2\)J=14.4 Hz, 1H, H8), 2.38-2.42 (m, 2H, H2), 2.66 (ddd, \(^3\)J5\(_{\alpha}\)\(_{6\beta}\)=4.6 Hz, \(^3\)J5\(_{\alpha}\)\(_{6\gamma}\)=7.0 Hz, \(^3\)J5\(_{\beta}\)\(_{6\gamma}\)=8.0 Hz, 1H, H5), 3.02 (dd, \(^3\)J8\(_{\alpha}\)\(_{6\gamma}\)=4.8 Hz, \(^2\)J=14.4 Hz, 1H, H8), 3.29-3.39 (m, 2H, H4), 7.18-7.30 (m, 5H, H\(_{\text{arom}}\)); \(^{13}\)C NMR (cis, 125 MHz, CDCl3): \(\delta 10.3\) (C6), 18.2 (C3), 18.5 (C7), 30.4 (C5), 31.6 (C2), 33.8 (C8), 49.1 (C4), 125.8 (CH), 128.2 (CH), 141.1 (Cq), 176.9 (C1); FAB-MS m/z (%): 216 (MH\(^+\), 100), 124 ([M-Bn]\(^+\), 63), 91 (Bn\(^+\), 29); HMRS: M\(^+\), found 215.13149. C\(_{14}\)H\(_{17}\)NO requires 215.1310.

1-(2-Phenylcyclopropyl)-2-pyrrolidinone 82

\[\text{C}_{13}\text{H}_{15}\text{NO} \quad 201.27 \text{g.mol}^{-1}\]

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.50 g, 2.70 mmol, 2 eq) in dry diethyl ether (2 mL) was added via a motorised syringe pump over 2 h to a vigorously stirred mixture of zinc amalgam (1.77 g, 27.0 mmol, 20 eq), anhydrous zinc chloride (0.37 g, 2.70 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol, 10 eq) and freshly distilled styrene (0.141 g, 1.35 mmol, 1 eq) in dry diethyl ether (9 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous NaHCO\(_3\) solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by flash
column chromatography (silica, EtOAc) to give a mixture mixture of cis and trans cyclopropanes 82 (0.189 g, 0.94 mmol, 70%, trans/cis: 1.1:1 as determined by $^1$H NMR) as a colourless oil.

$R_f$ (EtOAc) 0.42; IR (mixture of trans and cis, film): $\nu_{\text{max}}$ 2980 (s), 2886 (s), 1680 (s, C=O), 1499 (m), 1459 (m), 1030 (w), 773 (w), 737 (w), 701 (s) cm$^{-1}$; $^1$H NMR (trans, 500 MHz, CDCl$_3$): $\delta$ 1.28 (td, $^2J_{6\beta,6\alpha}=^3J_{6\beta,7}=6.3$ Hz, $^3J_{6\alpha,7}=7.6$ Hz, 1H, H$_{6\alpha}$), 1.39 (ddd, $^3J_{6\alpha,5}=4.6$ Hz, $^2J_{6\alpha,6\beta}=6.0$ Hz, $^3J_{6\alpha,7}=9.7$ Hz, 1H, H$_{6\alpha}$), 1.96-2.03 (m, 2H, H$_3$), 2.17 (ddd, $^3J_{7,5}=3.5$ Hz, $^2J_{7,6\beta}=6.5$ Hz, $^3J_{7,6\alpha}=9.9$ Hz, 1H, H$_7$), 2.39 (t, $^3J_{2,3}=8.1$ Hz, 2H, H$_2$), 2.78 (ddd, $^3J_{6\alpha,7}=3.7$ Hz, $^3J_{5,6\alpha}=4.5$ Hz, $^3J_{5,6\beta}=7.8$ Hz, 1H, H$_3$), 3.35-3.40 (m, 2H, H$_4$), 7.10-7.19 (m, 3H, H$_{arom}$), 7.22-7.28 (m, 2H, H$_{arom}$); $^{13}$C NMR (trans, 125 MHz, CDCl$_3$): $\delta$ 14.7 (C$_6$), 18.1 (C$_3$), 22.7 (C$_7$), 31.8 (C$_2$), 34.9 (C$_5$), 47.5 (C$_4$), 126.1 (CH), 126.4 (CH), 128.4 (CH), 140.4 (C$_{arom}$), 175.9 (C$_1$); $^1$H NMR (cis, 500 MHz, CDCl$_3$): $\delta$ 1.10 (ddd, $^3J_{6\beta,6\alpha}=6.8$ Hz, $^2J_{6\beta,5}=8.0$ Hz, $^3J_{6\beta,7}=9.1$ Hz, 1H, H$_{6\beta}$), 1.45-1.53 (m, 1H, H$_3$), 1.56-1.65 (m, 2H, H$_3$ and H$_{6\alpha}$), 2.10-2.22 (m, 3H, H$_2$ and H$_3$), 2.64 (ddd, $^3J_{4,3}=4.8$ Hz, $^3J_{4,3}=8.5$ Hz, $^2J=9.5$ Hz, 1H, H$_4$), 2.79 (dt, $^3J_{5,6\alpha}=4.9$ Hz, $^3J_{5,6\beta}=7.6$ Hz, 1H, H$_3$), 2.85 (ddd, $^3J=6.8$ Hz, $^3J=8.0$ Hz, $^2J=9.5$ Hz, 1H, H$_4$), 7.07-7.14 (m, 3H, H$_{arom}$), 7.17-7.21 (m, 2H, H$_{arom}$); $^{13}$C NMR (cis, 125 MHz, CDCl$_3$): $\delta$ 10.7 (C$_6$), 18.0 (C$_3$), 21.7 (C$_7$), 31.5 (C$_2$), 32.4 (C$_5$), 48.0 (C$_4$), 126.1 (CH), 127.8 (CH), 127.9 (CH), 136.8 (C$_q$), 176.7 (C$_1$); EI-MS m/z (%): 201 (M$^+$, 7), 172 (21), 144 (24), 130 (69), 115 (100), 103 (72), 11 (Bn$^+$, 52), 77 (Ph$^+$, 74); HMRS: M$^+$, found 201.11549. C$_{13}$H$_{15}$NO requires 201.11482.
A solution of N-diethoxymethy-2-pyrrolidinone 78 (0.66 g, 3.56 mmol, 2 eq) in dry diethyl ether (3.5 mL) was added via a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (2.33 g, 35.64 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3.56 mL, 3.56 mmol, 2 eq), chlorotrimethylsilane (2.26 mL, 17.8 mmol, 10 eq) and 3,3-dimethylbut-1-ene (0.15 g, 1.78 mmol, 1 eq) in dry diethyl ether (4 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product (trans/cis: >95:<5 as determined by ¹H NMR) was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 88:12) to give almost exclusively the trans cyclopropane 83 (0.197 g, 1.08 mmol, 61%) as a colourless oil.

**Rf** (EtOAc/P.E. 40-60°C 9:1) 0.30; **IR** (film): \(\nu_{max} 2955 \text{ (s)}, 2868 \text{ (m)}, 1694 \text{ (s, C=O)}, 1462 \text{ (m)}, 1421 \text{ (s)}, 1296 \text{ (s)}, 1192 \text{ (w)}, 1022 \text{ (w)}, 905 \text{ (w)}, 845 \text{ (w) cm}^{-1} \); **¹H NMR** (trans, 500 MHz, CDCl₃): \(\delta 0.67-0.74 \text{ (m, 2H, H₆α and H₆β)}, 0.81 \text{ (s, 9H, H₉)}, 0.86 \text{ (ddd, } J₇.₅=4.1 \text{ Hz, } J₇.₆α=6.8 \text{ Hz, } J₇.₆β=9.9 \text{ Hz, 1H, H₇)}, 1.84-1.94 \text{ (m, 2H, H₃)}, 2.29 \text{ (t, } J₄.₃=8.2 \text{ Hz, 2H, H₂)}, 2.47 \text{ (td, } J₅.₆α=J₅.₇=4.1 \text{ Hz, } J₅.₆β=7.5 \text{ Hz, 1H, H₅)}, 3.26 \text{ (t, } J₆.₃=7.1 \text{ Hz, 2H, H₄}); **¹³C NMR** (trans, 125 MHz, CDCl₃): \(\delta 8.7 \text{ (C₆)}, 17.9 \text{ (C₁)}, 28.1 \text{ (C₃ and C₉)}, 29.0 \text{ (C₉)}, 29.5 \text{ (C₇)}, 31.8 \text{ (C₂)}, 47.5 \text{ (C₄), 175.8 (C₁)}; **EI-MS m/z (%):**
181 (M+, 20), 166 ([M-CH₃]+, 10), 124 ([M-C₄H₉]⁺, 100), 96 (29), 81 (23), 69 (14), 57 (C₄H₉⁺, 12); **HMRS**: M⁺, found 181.146380. C₁₁H₁₉NO requires 181.146655.

1-(2-Trimethylsilanylcyclopropyl)-2-pyrrolidinone 84

A solution of N-diethoxymethy-2-pyrrolidinone 78 (0.56 g, 3.0 mmol, 2 eq) in dry diethyl ether (4 mL) was added via a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (1.95 g, 30 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3 mL, 3 mmol, 2 eq), chlorotrimethylsilane (1.9 mL, 15 mmol, 10 eq) and vinyltrimethylsilane (0.15 g, 1.5 mmol, 1 eq) in dry diethyl ether (5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product (trans/cis: >95:<5 as determined by ¹H NMR) was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 7:3) to give almost exclusively the trans cyclopropane 84 (0.172 g, 0.87 mmol, 58%) as a colourless oil.

**Rᵣ** (EtOAc/P.E. 40-60°C 7:3) 0.35; **IR** (film): νₑₛₐₓ 2954 (s), 2894 (m), 1694 (s, C=O), 1419 (s), 1375 (m), 1296 (m), 1249 (s, Si-C), 886 (s), 837 (s, Si-C), 753 (m) cm⁻¹; **¹H NMR** (trans, 500 MHz, CDCl₃): δ -0.12 (ddd, 3J₇,δ=5.3 Hz, 3J₇,6δ=8.2 Hz, 3J₇,6α=11.3 Hz, 1H, H₇), -0.06 (s, 9H, Si(CH₃)₃), 0.63 (ddd, 2J₆δ-6α=4.8 Hz, 3J₆δ-5=6.7 Hz, 3J₆δ-7=8.2 Hz, 1H, H₆δ), 0.89 (ddd, 3J₆α-5=3.6 Hz, 2J₆α-6δ=4.8 Hz, 3J₆α-7=11.3 Hz, 1H, H₆α),
Experimental

1.84-1.94 (m, 2H, H₃), 2.31 (t, ³J₂₃=8.0 Hz, 2H, H₂), 2.50 (dd, ³J₅₆₉=3.6 Hz, ³J₅₇=5.3 Hz, ³J₅₆=6.2 Hz, 1H, H₅), 3.18-3.22 (m, 2H, H₄); ¹³C NMR (trans, 125 MHz, CDCl₃): δ -2.6 (CH₃), 4.2 (C₇), 8.6 (C₆), 18.0 (C₃), 29.1 (C₂), 31.2 (C₂), 47.2 (C₄), 175.8 (C); EI-MS m/z (%): 197 (M⁺, 40), 182 ([M-CH₃]⁺, 66), 168 ([M-C₂H₅]⁺, 36), 154 (27), 142 (66), 124 ([M-SiC₃H₉]⁺, 11), 73 (SiC₃H₉⁺, 100), 59 (22); HMRS: M⁺, found 197.12332. C₁₀H₁₉NOSi requires 197.12355.

1-(2,3-Dibutylcyclopropyl)-2-pyrrolidinone 85

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.53 g, 2.85 mmol, 2 eq) in dry diethyl ether (4 mL) was added via a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (1.86 g, 28.5 mmol, 20 eq), anhydrous zinc chloride (0.39 g, 2.85 mmol, 2 eq), chlorotrimethylsilane (1.80 mL, 14.25 mmol, 10 eq) and trans-dec-5-ene (0.2 g, 1.42 mmol, 1 eq) in dry diethyl ether (7 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 3:2) to give the cyclopropane 85 (0.28 g, 1.25 mmol, 88%) as a colourless oil.

Rₜ (EtOAc/P.E. 40-60°C 3:2) 0.43; IR (film): νmax 2954 (s), 2924 (s), 2856 (m), 1694 (s, C=O), 1416 (m), 1293 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.68-0.79 (m, 3H), 0.82 (t, ³J=7.0 Hz, 3H, CH₃), 0.83 (t, ³J=7.0 Hz, 3H, CH₃), 1.14-1.36 (m, 10H),
Experimental

1.45-1.53 (m, 1H), 1.87-1.96 (m, 2H, H3), 2.25 (dd, J=4.2 Hz, J=6.4 Hz, 1H, H5), 2.32 (t, J2-3=8.0 Hz, 2H, H2), 3.20-3.31 (m, 2H, H4); 13C NMR (125 MHz, CDCl3): δ 13.9 (CH3), 14.0 (CH3), 18.8 (C3), 22.4 (CH2), 22.5 (CH2), 24.1 (CH), 25.5 (CH), 27.5 (CH2), 31.0 (CH2), 31.6 (CH2 and C2), 32.5 (CH2), 36.6 (C5), 49.0 (C4), 176.6 (C1);

EI-MS m/z (%): 237 (M+, 43), 194 ([M-C3H7]+, 21), 180 ([M-C4H9]+, 100), 138 ([M-C7H15]+, 15), 124 ([M-C8H17]+, 35), 98 (53), 86 (35), 67 (C5H7+, 13), 55 (15);

HMRS: M+, found 237.2084. C15H27NO requires 237.20925.

1-(2,3-Dibutylcyclopropyl)-2-pyrrolidinone 86

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.48 g, 2.57 mmol, 2 eq) in dry diethyl ether (3.5 mL) was added via a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (1.68 g, 25.7 mmol, 20 eq), anhydrous zinc chloride (0.31 g, 2.57 mmol, 2 eq), chlorotrimethylsilane (1.63 mL, 12.85 mmol, 10 eq) and cis-dec-5-ene (0.18 g, 1.28 mmol, 1 eq) in dry diethyl ether (6.7 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO3 solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 3:2) to give an inseparable mixture of cis and trans cyclopropanes 86 (0.142 g, 0.60 mmol, 47%, trans/cis 1:1 as determined by 1H NMR) as a colourless oil.
**Experimental**

*R* (EtOAc/P.E. 40-60°C 3:2) 0.4; **IR** (mixture of *trans* and *cis*, film): *ν*<sub>max</sub> 2956 (s), 2929 (s), 2857 (m), 1699 (s, C=O), 1464 (m), 1293 (m), 1251 (w) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (*trans*, 400 MHz, CDCl<sub>3</sub>): δ 0.88 (t, *J*=7.1 Hz, 6H, 2 x CH<sub>3</sub>), 0.98-1.02 (m, 2H, H<sub>6</sub> and H<sub>7</sub>), 1.22-1.50 (m, 12H, 6 x CH<sub>2</sub>), 1.98 (qn, *J*<sub>2.2</sub>=*J*<sub>3.4</sub>=7.5 Hz, 2H, H<sub>3</sub>), 2.01 (t, *J*<sub>2.5</sub>=*J*<sub>3.7</sub>=3.8 Hz, 1H, H<sub>5</sub>), 2.32 (t, *J*<sub>2.3</sub>=8.1 Hz, 2H, H<sub>2</sub>), 3.25 (t, *J*<sub>4.3</sub>=7.0 Hz, 2H, H<sub>4</sub>); **<sup>13</sup>C NMR** (*trans*, 100 MHz, CDCl<sub>3</sub>): δ 14.1 (CH<sub>3</sub>), 18.0 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>), 23.5 (C<sub>6</sub> and C<sub>7</sub>), 26.8 (CH<sub>2</sub>), 31.8 (C<sub>2</sub>), 37.8 (C<sub>3</sub>), 47.4 (C<sub>4</sub>), 175.6 (C<sub>1</sub>); **<sup>1</sup>H NMR** (*cis*, 400 MHz, CDCl<sub>3</sub>): δ 0.88 (t, *J*=7.2 Hz, 6H, 2 x CH<sub>3</sub>), 0.91-0.98 (m, 2H, H<sub>6</sub> and H<sub>7</sub>), 1.16-1.51 (m, 12H, 6 x CH<sub>2</sub>), 1.98 (qn, *J*<sub>2.2</sub>=*J*<sub>3.4</sub>=7.5 Hz, 2H, H<sub>3</sub>), 2.31 (t, *J*<sub>2.3</sub>=8.2 Hz, 2H, H<sub>2</sub>), 2.38 (t, *J*<sub>2.5</sub>=*J*<sub>3.7</sub>=7.7 Hz, 1H, H<sub>5</sub>), 3.25 (t, *J*<sub>4.3</sub>=7.0 Hz, 2H, H<sub>4</sub>); **<sup>13</sup>C NMR** (*cis*, 100 MHz, CDCl<sub>3</sub>): δ 14.1 (CH<sub>3</sub>), 18.9 (CH<sub>2</sub>), 19.8 (C<sub>6</sub> and C<sub>7</sub>), 22.9 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>), 31.0 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 33.4 (C<sub>2</sub>), 48.8 (C<sub>4</sub>), 178.5 (C<sub>1</sub>); **EI-MS** *m/z* (%): 238 (MH<sup>+</sup>, 100), 194 ([M-C<sub>9</sub>H<sub>11</sub>]+, 25), 180 ([M-C<sub>6</sub>H<sub>9</sub>]+, 95), 138 ([M-C<sub>7</sub>H<sub>13</sub>]+, 13), 124 ([M-C<sub>6</sub>H<sub>13</sub>]+, 43), 98 (73), 86 (43), 67 (C<sub>5</sub>H<sub>7</sub>+, 10), 55 (13), 41 (34); **HMRS**: M<sup>+</sup>, found 237.20916. C<sub>11</sub>H<sub>17</sub>NO requires 237.20925.

**1-Bicyclo[4.1.0]hept-7-yl-2-pyrrolidinone 87**

\[
\begin{align*}
\text{exo} & \quad \text{C}_{11} \text{H}_{17} \text{NO} \quad 179.26 \text{ g.mol}^{-1} \\
\text{endo} &
\end{align*}
\]

A solution of *N*-diethoxymethyl-2-pyrrolidinone 78 (0.68 g, 3.65 mmol, 2 eq) in dry diethyl ether (4 mL) was added *via* a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (2.39 g, 36.5 mmol, 20 eq), anhydrous zinc chloride (0.50 g, 3.65 mmol, 2 eq), chlorotrimethylsilane (2.32 mL, 18.25 mmol, 10 eq) and freshly distilled cyclohexene (0.15 g, 1.82 mmol, 1 eq) in dry diethyl ether (10.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the
Experimental

separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 98:2 to 95:5) to give an inseparable mixture of endo and exo cyclopropanes 87 (0.215 g, 1.2 mmol, 66%, exo/endo: 10:1 as determined by ¹H NMR) as a colourless oil.

Rᵣ (EtOAc/MeOH 95:5) 0.38; IR (mixture of exo and endo, film): νmax 2927 (s), 2853 (s), 1682 (s, C=O), 1418 (s), 1291 (s), 1248 (m) cm⁻¹; ¹H NMR (exo, 500 MHz, C₆D₆): δ 0.93-1.00 (m, 2H), 1.03-1.11 (m, 4H), 1.21 (qn, 3J₃₂=3J₃₄=7.5 Hz, 2H, H₃), 1.65-1.79 (m, 4H), 1.97 (t, 3J₄₃=8.0 Hz, 2H, H₂), 2.22 (t, 3J₅₆=3J₅₇=3.7 Hz, 1H, H₃), 2.57 (t, 3J₆₇=7.0 Hz, 2H, H₄); ¹³C NMR (exo, 125 MHz, C₆D₆): δ 17.2 (C₆ and C₇), 18.1 (C₃), 21.6 (2 x CH₂), 22.7 (2 x CH₂), 31.6 (C₂), 36.9 (C₃), 46.4 (C₄), 174.4 (C₁); ¹H NMR (endo, 500 MHz, C₆D₆): δ 0.87-0.92 (m, 2H, H₆ and H₇), 0.93-1.13 (m, 4H), 1.29 (qn, 3J₃₂=3J₃₄=7.5 Hz, 2H, H₁), 1.65-1.79 (m, 4H); 1.93 (t, 3J₂₃=7.9 Hz, 2H, H₂), 2.04 (t, 3J₃₄=7.7 Hz, 1H, H₃), 2.79 (t, 3J₄₅=6.9 Hz, 2H, H₄); ¹³C NMR (endo, 125 MHz, C₆D₆): δ 13.0 (C₆ and C₇), 18.9 (C₃), 20.2 (2 x CH₂), 22.5 (2 x CH₂), 30.9 (C₂), 34.0 (C₃), 48.0 (C₄), 176.7 (C₁); EI-MS m/z (%): 179 (M⁺, 100), 150 (32), 136 (15), 124 (20), 108 (10), 98 (32), 94 (30), 79 (19), 72 (30), 59 (57), 55 (48); HMRS: M⁺, found 179.13102. C₁₂H₁₉NO requires 179.1310.

1-(1-Methylbicyclo[4.1.0]hept-7-yl)-2-pyrrolidinone 88

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.58 g, 3.12 mmol, 2 eq) in dry diethyl ether (4 mL) was added via a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (2.04 g, 31.2 mmol, 20 eq), anhydrous zinc chloride

120
Experimental

(0.425 g, 3.12 mmol, 2 eq), chlorotrimethylsilane (1.98 mL, 15.6 mmol, 10 eq) and 1-methylcyclohex-1-ene (0.15 g, 1.56 mmol, 1 eq) in dry diethyl ether (8.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 98:2) to give an inseparable mixture of \textit{endo} and \textit{exo} cyclopropanes 88 (0.189 g, 0.98 mmol, 63\%, \textit{exo/endo} 1.3:1 as determined by $^1$H NMR) as a colourless oil.

$R_T$ (EtOAc) 0.33; IR (mixture of \textit{exo} and \textit{endo}, film): $\nu_{\text{max}}$ 2929 (s), 2861 (m), 1693 (s, C=O), 1492 (w), 1412 (m), 1286 (m), 1090 (w) cm⁻¹; $^1$H NMR (mixture of \textit{exo} and \textit{endo}, 500 MHz, C₆D₆): $\delta$ 0.73 (dt, $^3J$=2.6 Hz, $^3J$=3$^3J_{6.5}$=7.9 Hz, 1H, $H_6$), 0.90 (ddt, $^3J$=1.7 Hz, $^3J_{6.5}$=4.1 Hz, $^3J$=7.5 Hz, 1H, $H_6$), 0.96-1.22 (m, 14H), 1.27-1.35 (m, 4H, $H_3$ and $H_7$), 1.47-1.66 (m, 4H), 1.75-1.90 (m, 5H), 1.91-1.96 (m, 2H, $H_2$), 1.98-2.03 (m, 2H, $H_2$), 2.09 (d, $^3J_{5.6}$=4.2 Hz, 1H, $H_5$), 2.66 (td, $^3J_{4.3}$=7.0 Hz, $^3J$=9.3 Hz, 1H, $H_4$), 2.68 (td, $^3J_{4.3}$=7.0 Hz, $^3J$=9.3 Hz, 1H, $H_4$), 2.78 (td, $^3J_{4.3}$=7.0 Hz, $^3J$=9.3 Hz, 1H, $H_4$), 2.80 (td, $^3J_{4.3}$=6.3 Hz, $^3J$=9.3 Hz, 1H, $H_4$); $^{13}$C NMR (mixture of \textit{exo} and \textit{endo}, 125 MHz, C₆D₆): $\delta$ 18.2 (C₆), 18.6 (C₃), 19.0 (C₇), 20.4 (CH₂), 21.6 (CH₂), 21.7 (C₇ and C₆, 21.9 (CH₂), 22.1 (C₆), 22.3 (CH₂), 22.4 (CH₂), 23.2 (CH₂), 23.5 (C₇), 27.8 (CH₂), 28.0 (C₈), 30.5 (C₂), 31.0 (CH₂), 31.4 (C₂), 41.2 (C₅), 41.4 (C₃), 47.9 (C₄), 48.1 (C₄'), 175.2 (C₇), 176.6 (C₇); EI-MS $m/z$ (%): 193 (M⁺, 67), 178 ([M-CH₃]⁺, 45), 164 ([M-C₅H₃]⁺, 20), 150 ([M-C₅H₃]⁺, 15), 124 (10), 108 (83), 98 (53), 93 (55), 86 (100), 79 (18), 55 (14). HMRS: M⁺, found 193.14610. C₁₂H₁₉NO requires 193.14655.
2-Ethylhexyl-[2-(2-oxopyrrolidin-1-yl)-cyclopropyl] carboxylate 90

A solution of N-diethoxymethy-2-pyrrolidinone 78 (0.44 g, 2.35 mmol, 2 eq) in dry diethyl ether (3 mL) was added via a motorised syringe pump over 4 h to a vigorously stirred mixture of zinc amalgam (1.54 g, 23.5 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.35 mL, 2.35 mmol, 2 eq), chlorotrimethylsilane (1.49 mL, 11.7 mmol, 10 eq) and vinyl 2-ethylhexanoate (0.2 g, 1.17 mmol, 1 eq) in dry diethyl ether (4 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 4:1 to 8:3:1.5) to give a diastereomeric mixture of cis and trans cyclopropanes 90 (0.179 g, 0.67 mmol, 57%, trans/cis: 2:1 as determined by ¹H NMR) as a colourless oil.

Rₜ (EtOAc/P.E. 40-60°C 4:1) 0.34; IR (diastereomeric mixture of trans and cis, film): νmax 2961 (s), 2934 (s), 2875 (m), 2862 (m), 1741 (s, C=O), 1698 (s, C=O), 1460 (s), 1420 (s), 1296 (s), 1208 (m), 1170 (s), 1150 (s) cm⁻¹; ¹H NMR (diastereomeric mixture of trans, 500 MHz, CDCl₃): δ 0.74 (t, J₃=7.2 Hz, 12H, 4 × CH₃), 1.05-1.21 (m, 10H, H₆ and 4 × CH₂), 1.22 (dt, J₃.₅=5.5 Hz, J₃=J₆.₇=7.6 Hz, 2H, H₆), 1.26-1.51 (m, 8H, 4 × CH₂), 1.50-1.93 (m, 4H, H₃), 2.10 (tt, J₃=5.5 Hz, J₃=J₆.₇=8.8 Hz, 2H, H₆), 2.22 (t, J₂.₃=8.3 Hz, 4H, H₂), 2.57 (ddd, J₃.₇=1.8 Hz, J₃.₆=5.3 Hz, J₅.₆=7.4 Hz, 2H, H₃), 3.26-3.38 (m, 4H), 3.97 (ddd, J₇.₅=1.8 Hz, J₇.₆=4.4 Hz, J₆.₇=7.4 Hz, 2H, H₇); ¹³C NMR
(diastereomeric mixture of trans, 125 MHz, CDCl₃): δ 11.5 (CH₃), 13.6 (C₆ and CH₃), 17.8 (C₃), 22.3 (2 x CH₂), 25.0 (CH₂), 29.2 (2 x CH₂), 31.1 (2 x C₃), 31.3 (C₂ and CH₂), 46.6 (2 x C₉), 47.0 (C₄), 51.7 (C₇), 175.8 (C=O), 176.2 (C=O), 176.7 (C=O); ¹H NMR (diastereomeric mixture of cis, 300 MHz, CDCl₃): δ 0.83 (t, 3J=7.3 Hz, 12H, 4 x CH₃), 1.13-1.57 (m, 20H), 1.89-2.01 (m, 4H, H₃), 2.19 (tt, 3J=5.6 Hz, 3J=8.2 Hz, 2H, H₆), 2.34 (t, 3J₂,₃=8.1 Hz, 4H, H₂), 2.65-2.70 (m, 2H, H₃), 3.26-3.43 (m, 4H, H₄), 4.14 (dt, 3J=4.1 Hz, 3J=7.1 Hz, 1H, H₇).

¹³C NMR (diastereomeric mixture of cis, 125 MHz, CDCl₃): δ 11.2 (2 x C₆), 11.6 (CH₃), 13.8 (CH₃), 18.3 (C₃), 22.5 (2 x CH₂), 25.0 (CH₂), 25.3 (CH₂), 28.7 (C₃), 29.4 (2 x CH₂), 31.3 (CH₂), 31.5 (CH₂), 31.6 (CH₂), 47.0 (2 x C₉), 48.1 (C₄), 49.7 (C₇), 176.3 (2 x C=O), 176.5 (C=O); EI-MS m/z (%): 268 (MH⁺, 49), 140 (99), 124 (32), 112 (87), 99 (C₇H₁₅⁺, 28), 84 (11), 69 (42), 57 (C₄H₉⁺, 100), 41 (73); HMRS: MH⁺, found 268.19116. C₁₅H₂₆NO₃ requires 268.19124.

[2-(2-oxopyrrolidin-1-yl)-cyclopropyl] benzoate 92

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.50 g, 2.70 mmol, 2 eq) in dry diethyl ether (2 mL) was added via a motorised syringe pump over 4.5 h to a vigorously stirred mixture of zinc amalgam (1.76 g, 27.0 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.70 mL, 2.70 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol,
Experimental

10 eq) and vinyl benzoate (0.20 g, 1.35 mmol, 1 eq) in dry diethyl ether (5 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 96:4) to give a diastereomeric mixture of cis and trans cyclopropanes 92 (0.185 g, 0.75 mmol, 56%, trans/cis: 2:1 as determined by ¹H NMR) as a colourless oil.

**Rf** (EtOAc) 0.23; **IR** (mixture of trans and cis, film): ν_max 2961 (m), 1726 (s, C=O), 1689 (s, C=O), 1615 (w, C=C), 1452 (m), 1420 (s), 1271 (s), 1138 (m), 1111 (m), 1070 (m), 1026 (m), 713 (s) cm⁻¹; **¹H NMR** (trans, 500 MHz, CDCl₃): δ 1.40-1.43 (m, 2H, H₆), 1.89-1.98 (m, 2H, H₃), 2.36 (t, J₂₃=8.4 Hz, 2H, H₂), 2.80 (ddd, J₅₆=5.4 Hz, J₅₇=7.0 Hz, J₇₈=7.8 Hz, 1H, H₇), 3.33-3.43 (m, 2H, H₄), 4.44 (q, J₇₈=J₆₇=9.0 Hz, 1H, H₇), 7.38-7.42 (m, 2H, H₉₅), 7.51-7.56 (m, 1H, H₉₆), 7.90-7.94 (m, 2H, H₉₇₈); **¹³C NMR** (trans, 125 MHz, CDCl₃): δ 11.2 (C₆), 18.5 (C₃), 29.0 (C₅), 31.5 (C₂), 48.2 (C₄), 50.6 (C₇), 128.4 (CH), 129.3 (CH and C₉), 133.2 (CH), 166.8 (C₈), 176.7 (C₁); **¹H NMR** (cis, 500 MHz, CDCl₃): δ 1.44-1.48 (m, 2H, H₆), 1.95-2.07 (m, 2H, H₃), 2.37 (t, J₂₃=8.4 Hz, 2H, H₂), 2.85 (ddd, J₅₆=1.8 Hz, J₅₇=6.7 Hz, J₇₈=9.0 Hz, 1H, H₇), 3.45-3.53 (m, 2H, H₄), 4.33 (ddd, J₇₈=J₆₇=1.8 Hz, J₇₉=5.4 Hz, J₉₈₉=6.5 Hz, 1H, H₉₇₈), 7.38-7.42 (m, 2H, H₉₅), 7.51-7.56 (m, 1H, H₉₆), 7.90-7.94 (m, 2H, H₉₇₈); **¹³C NMR** (cis, 125 MHz, CDCl₃): δ 14.0 (C₆), 18.5 (C₃), 31.4 (C₅), 31.6 (C₂), 47.4 (C₄), 52.6 (C₇), 128.4 (CH), 129.3 (C₉), 129.6 (CH), 133.3 (CH), 167.1 (C₈), 176.2 (C₁); **EI-MS m/z (%)**: 245 (M⁺, 74), 216 (24), 162 ([M+H-C₄H₈NO]⁺, 61), 154 (22), 141 (86), 124 ([M-Ph-CO₂]⁺, 100), 114 (100), 106 (89), 94 (87), 84 (90), 77 (Ph⁺, 86); **HMRS**: MH⁺, found 245.10578. C₁₄H₁₅NO₃ requires 245.10519.
2-Ethylhexyl-[1-methyl-2-(2-oxopyrrolidin-1-yl)-cyclopropyl] carboxylate 94

A solution of N-diethoxymethyl-2-pyrrolidinone 78 (0.375 g, 2.02 mmol, 2 eq) in dry diethyl ether (3 mL) was added via a motorised syringe pump over 12 h to a vigorously stirred mixture of zinc amalgam (1.32 g, 20.2 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2 mL, 2.0 mmol, 2 eq), chlorotrimethylsilane (1.28 mL, 10.1 mmol, 10 eq) and 2-ethylhexyl methacrylate (0.2 g, 1.01 mmol, 1 eq) in dry diethyl ether (3 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 7:3 to 4:1) to give an inseparable diastereomeric mixture of cis and trans cyclopropanes 94 (26 mg, 0.09 mmol, 9%, *trans/cis* 1:1 as determined by ¹H NMR) as a colourless oil.

**R<sub>f</sub>** (EtOAc/P.E. 30-40°C 4:1) 0.43; **IR** (diastereomeric mixture of *trans* and *cis*, film): \( \nu_{\text{max}} \) 2975 (s), 2931 (s), 2865 (m), 1700 (s, C=O), 1459 (w), 1419 (w), 1297 (w), 1170 (w), 913 (w), 732 (m) cm⁻¹; **¹H NMR** (diastereomeric mixture of *trans* and *cis*, 500 MHz, CDCl₃): \( \delta \) 0.85 (t, \( 3J=7.0 \) Hz, 24H, 8 x CH₃), 1.04 (t, \( 3J_{6-5}=2J=6.8 \) Hz, 2H, H₆), 1.18-1.35 (m, 46H, H₈, H₉, 16 x CH₂), 1.49-1.56 (m, 4H, H₁₁ and H₁₁'), 1.63 (dd, \( J=5.8 \) Hz, \( J=8.7 \) Hz, 2H, H₆'), 1.67-1.71 (m, 2H, H₆), 1.89-2.03 (m, 8H, H₃ and H₃'), 2.25-2.31 (m, 4H, CH₂), 2.37 (t, \( 3J=8.4 \) Hz, 4H, CH₂), 2.69 (t, \( 3J_{5-6}=6.8 \) Hz, 2H, H₅), 2.99 (dd, \( 3J=5.7 \) Hz, \( 3J=8.5 \) Hz, 2H, H₅'), 3.20-3.36 (m, 6H), 3.49 (td, \( 3J=7.5 \) Hz,
Experimental

$^2$J=8.9 Hz, 2H), 3.85-3.98 (m, 8H, H$_{10}$ and H$_{10}'$); $^{13}$C NMR (diastereomeric mixture of trans and cis, 125 MHz, CDCl$_3$): δ 10.9 (2 x CH$_3$), 11.0 (CH$_3$), 13.3 (CH$_3$), 18.3 (CH$_2$), 18.4 (CH$_2$), 19.2 (2 x CH$_3$), 20.5 (C$_6$), 20.8 (C$_5$), 22.9 (CH$_2$), 23.7 (2 x CH$_2$), 23.8 (CH$_2$), 24.3 (CH$_2$), 26.2 (C$_7$ and C$_7'$), 29.3 (CH$_2$), 30.3 (CH$_2$), 30.4 (CH$_2$), 38.6 (C$_{11}$ and C$_{11}$'), 38.7 (C$_7$), 40.4 (C$_5$), 48.0 (CH$_2$), 48.9 (CH$_2$), 67.1 (CH$_2$), 67.2 (2 x CH$_2$), 67.3 (CH$_2$), 172.2 (C=O), 174.0 (C=O), 176.4 (C=O), 176.5 (C=O); EI-MS m/z (%): 296 (MH$, 100$), 183 (60), 165 (65), 138 (85), 98 (64), 71 (C$_5$H$_{11}^+$, 14), 57 (C$_4$H$_9^+$, 27), 41 (49); HMRS: MH$, found 296.22254. C_{17}H$_{30}$NO$_3$ requires 296.22234.

$N$-Benzyl-$N$-diethoxymethylacetamide 96

\[
\text{Ph} \quad \text{N} \\
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{C}_{14}H_{21}NO_3 \\
251.33 \text{ g.mol}^{-1}
\end{array}
\]

A mixture of $N$-benzylacetamide (1.0 g, 6.7 mmol, 1 eq), aluminium chloride (0.13 g, 1.0 mmol, 0.15 eq) and triethyl orthoformate (22 mL, 0.13 mol, 20 eq) was heated at 155°C for 72 h. The reaction mixture was allowed to cool to room temperature and then quenched with saturated aqueous NaHCO$_3$ solution (25 mL). The aqueous phase was extracted with diethyl ether (50 mL then 2 x 25 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the title compound 96 (0.3 g, 1.19 mmol, 18%, 7:3 mixture of rotamers at 353 K) as a yellow oil.

$R_I$ (P.E. 30-40°C/EtOAc 7:3) 0.35; IR (film): $\nu_{max}$ 2978 (m), 2933 (w), 1670 (s, C=O), 1497 (w), 1103 (s), 1063 (s), 974 (m), 733 (w), 700 (s) cm$^{-1}$; $^1$H NMR (400 MHz, 353 K, DMSO): δ 1.10 (t, $^3$J=7.1 Hz, 6H, CH$_2$CH$_3$), 2.05 (s, 0.7 x 3H, COCH$_3$), 2.98 (s, 0.3 x 3H, COCH$_3$), 3.37-3.63 (m, 4H, CH$_2$CH$_3$), 4.41 (s, 0.3 x 2H, PhCH$_2$N), 4.50 (s, 0.7 x 2H, PhCH$_2$N), 5.58 (br s, 0.3 x 1H, OCHO), 6.00 (br s, 0.7 x 1H, OCHO), 7.16-7.35 (m, 5H, H$_{arom}$); $^{13}$C NMR (major rotamer, 100 MHz, 353 K, DMSO): δ 14.0 (CH$_3$), 21.4 (COCH$_3$), 43.7 (PhCH$_2$N), 61.2 (CH$_2$CH$_3$), 102.2 (OCHO), 125.8 (CH), 126.7 (CH), 126.9 (CH), 130.5 (CH), 139.7 (CH), 144.7 (CH), 172.2 (C=O), 176.2 (C=O), 176.4 (C=O), 176.5 (C=O).
Experimental

127.3 (CH), 138.9 (Cq), 169.0 (C=O); CI(methane)-MS m/z (%): 252 (MH+, 3), 206 ([M-OC₂H₅]+, 62), 150 (100), 103 (61), 91 (Bn+, 68); HMRS: MH+, found 252.16019. C₁₄H₂₂NO₃ requires 252.15997.

**N-Benzyl-N-(2-benzycyclopropyl)-acetamide 97**

A solution of N-benzyl-N-diethoxymethylacetamide 96 (0.80 g, 3.18 mmol, 2 eq) in dry diethyl ether (3 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (2.08 g, 31.8 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3.18 mL, 3.18 mmol, 2 eq), chlorotrimethylsilane (2.02 mL, 15.9 mmol, 10 eq) and allylbenzene (0.188 g, 1.59 mmol, 1 eq) in dry diethyl ether (6.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (30 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 3:2 to 5.5:4.5) to give an inseparable mixture of cis and trans cyclopropanes 97 (61 mg, 0.22 mmol, 14%, *trans/cis*: 13.5:1 as determined by ¹H NMR) as a colourless oil.

*R* (P.E. 40-60°C/EtOAc 3:2) 0.3; **IR** (mixture of *trans* and *cis*, film): ν max 3026 (w), 2924 (w), 1655 (s, C=O), 1603 (w, C=C), 1495 (w), 1452 (w), 1398 (m), 1358 (w), 1294 (w), 725 (w), 698 (m) cm⁻¹; **¹H NMR** (*trans*, 500 MHz, CDCl₃): δ 0.78 (ddd, 2*J*₅₆.₅₅=5.4 Hz, 3*J*₅₆.₆=6.2 Hz, 3*J*₅₆.₄=7.1 Hz, 1H, H₅₆), 0.95 (ddd, 3*J*₅₆.₄=4.0 Hz,
Experimental

2\(J_{6a-6b}=5.5\) Hz, 3\(J_{6a-6b}=9.5\) Hz, 1H, H5a), 1.37 (dtdd, 3\(J_{6a-6b}=3.5\) Hz, 3\(J_{6a-6b}=J_{6a-6b}=6.1\) Hz, 3\(J_{6a-6b}=7.5\) Hz, 3\(J_{6a-6b}=9.4\) Hz, 1H, H6), 2.16 (s, 3H, H1), 2.33-2.44 (m, 1H, H4), 2.42 (dd, 3\(J_{6a-6b}=7.5\) Hz, 2\(J=14.5\) Hz, 1H, H7), 2.66 (dd, 3\(J_{6a-6b}=6.1\) Hz, 2\(J=14.5\) Hz, 1H, H7), 4.45 (d, 2\(J=14.8\) Hz, 1H, H3), 4.53 (d, 2\(J=14.8\) Hz, 1H, H3), 7.08-7.12 (m, 4H, H3, 7.19-7.31 (m, 6H, H arom); 13C NMR (trans, 125 MHz, CDCl3): \(\delta 15.9\) (C5), 22.7 (C1), 23.3 (C6), 36.8 (C4), 37.7 (C7), 49.6 (C3), 126.3 (CH), 126.9 (CH), 128.4 (CH), 128.5 (CH), 138.1 (Cq), 139.7 (Cq), 173.3 (C2); ESI-MS m/z (%): 279 (M+, 65), 264 ([M-CH3]+, 37), 236 ([M-COCH3]+, 100), 188 ([M-Bn]+, 100), 148 (74), 131 (C19H11+, 66), 106 (52), 91 (Bn+, 82), 77 (Ph+, 24); HMRS: M+, found 279.16205. C19H21NO requires 279.16231.

1-(2-Methylpropenyl)-2-pyrrolidinone 99

\[ \begin{align*}
\text{C}_8\text{H}_{13}\text{NO} & \quad 139.20 \text{ g.mol}\text{ }^{-1} \\
\end{align*} \]

The title compound was prepared by a literature method.\(^{131}\) A mixture of 2-pyrrolidinone (8.51 g, 10 mmol, 1 eq), isobutylaldehyde (13.5 mL, 0.15 mmol, 1.5 eq) and catalytic amount of p-toluenesulfonic acid (~20 mg) in toluene (150 mL) was heated at reflux for 7 h in conjunction with a Dean-Stark apparatus for water removal. The reaction mixture was cooled to room temperature and then washed with saturated aqueous NaHCO\(_3\) solution (100 mL) and water (100 mL). The combined aqueous layers were extracted with diethyl ether (100 mL) and the combined organic extracts were then dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo to give the enamide 99 (9.0 g, 6.46 mmol, 65%) as a yellow oil which was used without further purification.

IR (film): \(\nu_{\text{max}}\) 2991 (w), 2960 (w), 2885 (w), 1697 (s, C=O), 1672 (s, C=C), 1406 (m), 1379 (w), 1292 (s) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3): \(\delta 1.63\) (s, 3H, CH3), 1.70 (s, 3H, CH3), 1.97-2.03 (m, 2H, CH\(_2\)CH\(_2\)CH\(_2\)H), 2.36 (t, 3\(J=8.1\) Hz, 2H, CH\(_2\)CO), 3.53 (t, 3\(J=7.1\) Hz, 2H, CH\(_2\)N), 5.86 (s, 1H, NCH=); \(^13\)C NMR (75 MHz, CDCl3): \(\delta 18.3\)
Experimental

(CH₂CH₂CH₂), 18.7 (CH₃), 23.0 (CH₃), 30.6 (CH₂CO), 49.2 (CH₂N), 119.4 (NCH=), 128.4 (=C(CH₃)₂), 174.5 (C=O).

*N-Formyl-2-pyrrolidinone 100*

![Chemical Structure](image)

C₅H₇NO₂  113.12 g·mol⁻¹

Ozone was bubbled through a solution of crude enamide 99 (9 g, 64.65 mmol, 1 eq) in dichloromethane (500 mL) at -78°C. When the reaction mixture turned blue (approximately after 2.5 h of reaction), ozone addition was stopped and nitrogen was passed through the solution until the blue colour was discharged. Dimethylsulfide (9.5 mL, 0.13 mol, 2 eq) was added and the mixture was allowed to warm to room temperature. After 18 h of stirring, the reaction mixture was washed with water (2 x 150 mL) and then dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2 to 2:3) to give the *title compound 100* (4.01 g, 35.45 mmol, 55%) as a yellow oil.

Rᵣ (P.E. 40-60°C/EtOAc 1:1) 0.28; **IR** (film): νmax 2985 (w), 2968 (w), 2904 (w), 1751 (s, C=O), 1695 (s, C=O), 1396 (m), 1352 (s), 1325 (w), 1301 (m), 1244 (m), 1220 (m), 1018 (w), 790 (w) cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 2.04-2.16 (m, 2H, CH₂CH₂CH₂), 2.57 (7J=8.0 Hz, 2H, CH₂CO), 3.71 (7J=7.1 Hz, 2H, CH₂N), 9.08 (s, 1H, CHO); **¹³C NMR** (100 MHz, CDCl₃): δ 17.8 (CH₂CH₂CH₂), 32.1 (CH₂CO), 42.0 (CH₂N), 160.2 (CHO), 176.6 (C=O); **Cl(ammonia)-MS** m/z (%): 112 ([M-H]+, 100), 83 (24), 55 (25); **HMRS**: (M-H)+, found 112.03977. C₅H₆NO₂ requires 112.03985.
N-Diethoxymethylphthalimide 101

\[
\text{\includegraphics[width=0.3\textwidth]{diagram}}
\]

\[\text{C}_{13}\text{H}_{15}\text{NO}_{4} \quad 249.26 \text{ g.mol}^{-1}\]

A mixture of phthalimide (3.0 g, 20.4 mmol, 1 eq), aluminium chloride (0.3 g, 2.24 mmol, 0.11 eq) and triethyl orthoformate (67 mL, 0.41 mol, 20 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO\textsubscript{3} solution (40 mL). The aqueous phase was extracted with diethyl ether (60 mL then 40 mL) and the combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The resulting solid was triturated in isopropanol, filtered, washed with isopropanol (10 mL), dried at 50°C \textit{in vacuo} for 4 h to give the title compound 101 (3.19 g, 12.8 mmol, 63%) as a white solid.

\textbf{Mp} 73-74°C (lit.,\textsuperscript{132} 73°C); \textbf{Rf} (P.E. 40-60°C/EtOAc 1:1) 0.59; \textbf{IR} (film): \(\nu_{\text{max}}\) 2977 (w), 1774 (m), 1720 (s), 1694 (w), 1469 (w), 1370 (m), 1348 (m), 1328 (m), 1140 (m), 1110 (m), 1070 (m), 911 (m), 718 (m) cm\textsuperscript{-1}; \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}): \(\delta\) 1.25 (t, \(\text{J}=7.1\) Hz, 6H, CH\textsubscript{3}), 3.62 (qd, \(\text{J}=7.1\) Hz, \(\text{J}=9.4\) Hz, 2H, CH\textsubscript{2}), 3.77 (qd, \(\text{J}=7.1\) Hz, \(\text{J}=9.4\) Hz, 2H, CH\textsubscript{2}), 6.09 (s, 1H, OCHO), 7.68-7.77 (m, 2H, H\textsubscript{arom}), 7.82-7.90 (m, 2H, H\textsubscript{arom}); \textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}): \(\delta\) 14.8 (CH\textsubscript{3}), 63.4 (CH\textsubscript{2}), 99.8 (OCHO), 123.6 (CH), 131.7 (C\textsubscript{arom}), 134.3 (CH), 166.6 (C=O); \textbf{Cl(ammonia)-MS} \(m/z\) (%): 249 (M\textsuperscript{+}, 100), 175 ([M-OC\textsubscript{3}H\textsubscript{5}-C\textsubscript{2}H\textsubscript{5}]\textsuperscript{+}, 56), 147 (78); \textbf{HMRS}: M\textsuperscript{+}, found 249.09952. \text{C}_{13}\text{H}_{15}\text{NO}_{4} \text{ requires 249.1001.}
2,3-Dihydro-1-isooindolinone 105

![Chemical Structure](image)

C₈H₇NO  133.15 g.mol⁻¹

The *title compound* was prepared by a literature method.¹³³ Tin powder (41.7 g, 0.35 mol, 2.6 eq) was added to a vigorously stirred suspension of phthalimide (20 g, 0.136 mol, 1 eq) in a mixture of glacial acetic acid (100 mL) and concentrated hydrochloric acid (50 mL). The reaction mixture was heated at reflux for 2 h and then filtered hot. The filtrate was concentrated *in vacuo* and the residue partitioned between dichloromethane (300 mL) and water (150 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (silica, EtOAc) and then triturated in toluene to give the *title compound* 105 (4.2 g, 31.5 mmol, 23%) as a white solid.

Mp 149-150°C (lit.,¹³³ 150-151°C); \( R_f \) (EtOAc) 0.20; IR (CH₂Cl₂): \( \nu_{\text{max}} \) 3214 (br s, NH), 1658 (s, C=O), 1471 (m), 1450 (m), 1361 (w), 764 (s), 749 (s), 726 (s) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 4.48 (s, 2H, CH₂), 7.18 (br s, 1H, NH), 7.47-7.60 (m, 4H, H arom); \(^13\)C NMR (100 MHz, CDCl₃): \( \delta \) 45.8 (CH₂), 123.2 (CH), 123.6 (CH), 128.0 (CH), 131.7 (CH), 132.6 (C₆), 143.7 (C₆), 172.6 (C=O).

2-Diethoxymethyl-2,3-dihydro-1-isooindolinone 106

![Chemical Structure](image)

C₁₃H₁₇NO₃  235.28 g.mol⁻¹

A mixture of 1-isooindolinone 105 (4.0 g, 30.04 mmol, 1 eq), aluminium chloride (0.44 g, 3.3 mmol, 0.11 eq) and triethyl orthoformate (100 mL, 0.61 mol, 20 eq) was heated at
155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (100 mL). The aqueous phase was extracted with diethyl ether (2 x 150 mL then 100 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 1:1) to give the title compound 106 (6.58 g, 27.97 mmol, 93%) as a brown oil.

Rf (isohexane/EtOAc 1:1) 0.51; IR (film): νmax 2977 (m), 2932 (w), 1694 (s, C=O), 1620 (w, C=C), 1470 (m), 1452 (w), 1388 (s), 1325 (m), 1302 (m), 1242 (m), 1166 (s), 1099 (s), 1055 (s), 918 (w), 890 (w), 839 (w), 798 (w), 734 (s), 703 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.25 (t, 3J=7.0 Hz, 6H, CH₃), 3.57 (qd, 3J=7.0 Hz, 2J=9.5 Hz, 2H, CH₂CH₃), 3.74 (qd, 3J=7.0 Hz, 2J=9.5 Hz, 2H, CH₂CH₃), 4.49 (s, 2H, CH₂N), 6.23 (s, 1H, OCHO), 7.45-7.51 (m, 2H, H arom), 7.58 (t, 3J=7.5 Hz, 1H, H arom), 7.87 (d, 2J=7.5 Hz, 1H, H arom); ¹³C NMR (100 MHz, CDCl₃): δ 14.8 (CH₃), 44.2 (CH₂N), 62.5 (CH₂), 99.2 (OCHO), 123.2 (CH), 124.1 (CH), 128.0 (CH), 132.0 (Cq), 132.1 (CH), 142.0 (Cq), 168.9 (C=O); CI(methane)-MS m/z (%): 236 (MH⁺, 6), 190 ([M-OC₂H₅] -, 44), 134 (59), 103 (46); HMRS: MH⁺, found 236.12847. C₁₃H₁₈NO₃ requires 236.12866.

2-(2-Benzylcyclopropyl)-2,3-dihydro-1-isoindolinone 107

A solution of 2-diethoxymethyl-1-isoindolinone 106 (2.35 g, 10 mmol, 2 eq) in dry diethyl ether (5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (6.6 g, 0.1 mol, 20 eq), zinc chloride (1M solution in diethyl ether, 10 mL, 10 mmol, 2 eq), chlorotrimethylsilane (6.36 mL, 50 mmol, 10 eq) and allylbenezene (0.59 g, 5 mmol, 1 eq) in dry diethyl ether (25 mL) under nitrogen at
reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Saturated aqueous NaHCO₃ solution (75 mL) and dichloromethane (25 mL) were added to the reaction mixture and after stirring for 20 min, the mixture was filtered through celite and the separated zinc was washed with dichloromethane (75 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with brine (75 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified twice by flash column chromatography (silica, EtOAc/MeOH 99:1 to 95:5 and then silica, diethyl ether/P. 40-60°C 1:1 to 3:1) to give a mixture of cis and trans cyclopropanes 107 (0.733 g, 2.78 mmol, 56%, trans/cis: 6:1 as determined by ¹H NMR) as a yellow oil. Trituration of the resulting oil in a mixture of isohexane (5 mL) and ether (1 mL) yields a mixture of cis and trans cyclopropanes 107 (0.655 g, 2.49 mmol, 50%, trans/cis: 15:1 as determined by ¹H NMR) as a yellowish solid.

Mp (trans) 62-63°C (i-Pr₂O); Rf (P.E. 40-60°C/EtOAc 3:7) 0.30; IR (mixture of trans and cis, CDCl₃): νmax 3027 (w), 2914 (w), 1685 (s, C=O), 1620 (w, C=C), 1496 (w), 1469 (m), 1453 (m), 1408 (m), 1304 (m), 1214 (w), 1005 (w), 797 (w), 735 (s), 701 (m), 684 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.93 (dt, 3J4δ-4α=3J4δ-5=6.1 Hz, 3J4δ-3=7.4 Hz, 1H, H₄αβ), 1.15 (ddd, 3J₄α-₃=4.0 Hz, 2J₄α-₄δ=5.9 Hz, 3J₄α-₅=9.6 Hz, 1H, H₄αδ), 1.50 (dddt, 3J₅-₃=3.4 Hz, 3J₅-₄δ=6.4 Hz, 3J₅-₅=6.9 Hz, 3J₅-₄α=9.6 Hz, 1H, H₅), 2.67 (dd, 3J₆-₅=7.1 Hz, 2J=14.7 Hz, 1H, H₆), 2.80-2.89 (m, 2H, H₃ and H₆), 4.20 (s, 2H, H₂), 7.20-7.53 (m, 8H, Haryl), 7.82 (dd, 3J=1.0 Hz, 3J=7.5 Hz, 1H, Haryl); ¹³C NMR (trans, 125 MHz, CDCl₃): δ 12.8 (C₄), 20.0 (C₃), 31.6 (C₃), 38.2 (C₆), 50.1 (C₁), 122.5 (CH), 123.4 (CH), 126.2 (CH), 127.9 (CH), 128.4 (2 x CH), 131.2 (CH), 133.2 (C₆), 140.6 (C₆), 140.9 (C₆), 169.3 (C₁); ¹H NMR (cis, 500 MHz, CDCl₃): δ 0.90-0.97 (m, 1H), 1.11-1.19 (m, 2H), 2.24 (dd, 3J₆-₅=4.9 Hz, 2J=15.0 Hz, 1H, H₆), 3.03 (dt, 3J₃₄₄=4.5 Hz, 3J₃₄₅=3J₃₅=7.5 Hz, 1H, H₃), 3.15 (dd, 3J₆-₅=4.9 Hz, 2J=15.0 Hz, 1H, H₇), 4.30 (d, 2J=17.0 Hz, 1H, H₂), 4.32 (d, 2J=17.0 Hz, 1H, H₂), 7.17-7.57 (m, 8H, Haryl), 7.88 (dt, 3J=1.0 Hz, 3J=7.4 Hz, 1H, Haryl); ¹³C NMR (cis, 125 MHz, CDCl₃): δ 10.6 (C₄), 19.2 (C₃), 30.5 (C₃), 34.0 (C₆), 51.8 (C₁), 122.6 (CH), 123.6 (CH), 125.9 (CH), 128.0 (CH), 128.3 (CH), 131.3 (CH), 133.1 (C₆), 141.1 (C₁), 141.3 (C₆), 170.3 (C₁); EI-MS m/z (%): 263 (M⁺, 13), 222 (8), 172 ([M-Bn]⁺, 100), 146 (9), 132 (7), 115
Experimental

(9), 91 (Bn<sup>+</sup>, 29), 77 (Ph<sup>+</sup>, 8), 65 (8), 51 (7); HMRS: M<sup>+</sup>, found 263.13096. C<sub>18</sub>H<sub>17</sub>NO requires 263.13101.

**N-Diethoxymethyl-2-oxazolidinone 108**

![Image of chemical structure](image)

C<sub>8</sub>H<sub>15</sub>NO<sub>4</sub> 189.21 g.mol<sup>-1</sup>

A mixture of 2-oxazolidinone (2.0 g, 22.97 mmol, 1 eq), aluminium chloride (0.31 g, 2.30 mmol, 0.1 eq) and triethyl orthoformate (57 mL, 0.34 mol, 15 eq) was heated at 150°C for 22 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO<sub>3</sub> solution (75 mL). The aqueous phase was extracted with diethyl ether (150 mL then 75 mL) and the combined organic extracts were washed with brine (75 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 1:1) to give the **title compound 108** (2.92 g, 15.4 mmol, 67%) as a yellow oil.

**R<sub>f</sub>** (isohexane/EtOAc 1:1) 0.47; IR (film): <i>ν</i><sub>max</sub> 2979 (w), 2904 (w), 1747 (s, C=O), 1483 (w), 1416 (m), 1246 (m), 1060 (s), 1037 (m), 975 (m), 897 (w), 763 (s), 704 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.25 (t, <i>J</i><sub>6,5</sub>=7.1 Hz, 6H, H<sub>6</sub>), 3.53-3.73 (m, 6H, H<sub>3</sub> and H<sub>5</sub>), 4.39 (t, <i>J</i><sub>2,3</sub>=8.2 Hz, 2H, H<sub>2</sub>), 5.74 (s, 1H, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.8 (C<sub>6</sub>), 38.6 (C<sub>3</sub>), 62.6 (C<sub>5</sub>), 62.8 (C<sub>2</sub>), 101.3 (C<sub>4</sub>), 157.4 (C<sub>1</sub>); CI(methane)-MS <i>m/z</i> (%): 190 (MH<sup>+</sup>, 2), 144 ([M-OC<sub>2</sub>H<sub>5</sub>]<sup>+</sup>, 100), 116 (12), 103 (100), 75 (14), 44 (16); HMRS: MH<sup>+</sup>, found 190.10785. C<sub>8</sub>H<sub>16</sub>NO<sub>4</sub> requires 190.10793.
Experimental

3-(2-Benzylcyclopropyl)-2-oxazolidinone 109

A solution of N-diethoxymethyl-2-oxazolidinone 108 (0.51 g, 2.71 mmol, 2 eq) in dry diethyl ether (2 mL) was added via a motorised syringe pump over 5 h to a vigorously stirred mixture of zinc amalgam (1.77 g, 27.1 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.71 mL, 2.71 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol, 10 eq) and allylbenzene (0.16 g, 1.35 mmol, 1 eq) in dry diethyl ether (6 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2) to give an inseparable mixture of cis and trans cyclopropanes 109 (0.167 g, 0.77 mmol, 57%, trans/cis: 15:1 as determined by ¹H NMR) as a colourless oil.

Rᵣ (EtOAc/P.E. 40-60°C 3:2) 0.33; IR (mixture of trans and cis, film): νₘₐₓ 3003 (w), 2915 (w), 1742 (s, C=O), 1604 (w, C=C), 1482 (w), 1419 (w), 1281 (m), 1219 (m), 1129 (w), 1067 (m), 1033 (s), 979 (w), 763 (m), 742 (m), 690 (s) cm⁻¹; ¹H NMR (trans, 500 MHz, CDCl₃): δ 8.02 (dt, ³J₆₇=3J₅₆=8.1 Hz, ³J₅₄=7.1 Hz, 1H, H₅₄), 1.03 (ddd, ³J₅₆=3.7 Hz, ³J₅₆=5.9 Hz, ³J₅₆=9.5 Hz, 1H, H₅₆), 1.36 (dddt, ³J₆₇=3.2 Hz, ³J₆₇=6.2 Hz, ³J₆₇=6.9 Hz, ³J₆₇=9.5 Hz, 1H, H₆), 2.40 (td, ³J₅₆=3.5 Hz, ³J₅₆=7.1 Hz, 1H, H₄), 2.59 (dd, ³J₇₈=6.9 Hz, ²J=14.7 Hz, 1H, H₇), 2.72 (dd, ³J₇₈=6.9 Hz, ²J=14.7 Hz, 1H, H₇), 3.38-3.42 (m, 2H, H₃), 4.19-4.25 (m, 2H, H₂), 5.32-5.35 (m, 2H, H₂), 6.92-7.00 (m, 2H, H₆), 7.01-7.05 (m, 2H, H₅).
Experimental

7.20-7.32 (m, 5H, Harom); $^{13}$C NMR (trans, 125 MHz, CDCl$_3$): $\delta$ 13.0 (C$_5$), 20.3 (C$_8$), 32.1 (C$_4$), 37.8 (C$_7$), 45.7 (C$_3$), 61.8 (C$_2$), 126.2 (CH), 128.2 (CH), 128.3 (CH), 140.5 (C$_q$), 158.4 (C$_i$); $^1$H NMR (cis, 500 MHz, CDCl$_3$): $\delta$ 0.78 (dt, $^3$J$_{5a-4}$=4.2 Hz, $^3$J$_{5a-5b}$=6.3 Hz, 1H, H$_{5a}$), 1.05-1.15 (m, 2H, H$_{5b}$ and H$_6$), 2.44 (dd, $^3$J$_{7.6}$=9.2 Hz, $^2$J=15.7 Hz, 1H, H$_7$), 2.65 (ddd, $^3$J$_{4,5a}$=4.2 Hz, $^3$J=6.9 Hz, $^3$J$_{7.6}$=7.7 Hz, 1H, H$_4$), 3.11 (dd, $^3$J$_{7.6}$=5.1 Hz, $^2$J=15.0 Hz, 1H, H$_7$), 3.51-3.57 (m, 2H, H$_3$), 4.28-4.33 (m, 2H, H$_2$), 7.20-7.32 (m, 5H, Harom); $^{13}$C NMR (cis, 100 MHz, CDCl$_3$): $\delta$ 11.1 (C$_5$), 18.7 (C$_6$), 31.0 (C$_4$), 33.7 (C$_7$), 46.9 (C$_3$), 62.0 (C$_2$), 126.0 (CH), 128.2 (CH), 141.0 (C$_q$), 159.7 (C$_i$); CI(methane)-MS m/z (%): 218 (MH$^+$, 17), 126 ([M-Bn]$^+$, 100), 115 (11), 104 (15), 91 (Bn$^+$, 22), 82 (12), 77 (Ph$^+$, 7), 65 (8), 54 (9); HMR: MH$^+$, found 218.11777. C$_{13}$H$_{16}$NO$_2$ requires 218.11809.

($\pm$)-1,2-diphenyl-2-aminoethanol 111

![Chemical Structure](image)

C$_{14}$H$_{15}$NO 213.28 g.mol$^{-1}$

A mixture of $\alpha$-benzoin oxime (25.0 g, 0.11 mol, 1 eq), Pd/C (5%, 2 g, 0.71 mmol, 0.0065 eq), absolute ethanol (325 mL) and hydrochloric acid (5-6M solution in isopropanol, 30 mL) was hydrogenated at 4 bar for 1 h. Water (200 mL) was added in order to dissolve the amine hydrochloride and the reaction mixture was then filtered. The filtrate was diluted to 800 mL with water and concentrated ammonia solution (100 mL) was added. The resulting precipitate was filtered, washed with water (3 x 50 mL), dried at 50°C in vacuo for 18 h to give the title compound 111 (22.1 g, 0.104 mol, 94%, erythro/threo: 93:7 as determined by $^1$H NMR) as a white solid which was used without further purification.

IR (CH$_2$Cl$_2$): $\nu_{\text{max}}$ 3465 (w), 3380 (w), 3063 (m), 2963 (m), 2891 (w), 1593 (w), 1453 (m), 1277 (w), 1019 (m), 978 (w), 752 (s), 697 (s) cm$^{-1}$; $^1$H NMR (erythro, 300 MHz, CDCl$_3$): $\delta$ 4.16 (d, $^3$J=6.3 Hz, 1H, CHNH$_2$), 4.75 (d, $^3$J=6.3 Hz, 1H, CHOH), 7.15-7.7.35 (m, 10H, Harom); $^{13}$C NMR (erythro, 75 MHz, CDCl$_3$): $\delta$ 61.9 (CHNH$_2$),
Experimental

78.4 (CHOH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 140.6 (Cq), 141.5 (Cq); $^1$H NMR (threo, 300 MHz, CDCl₃): $\delta$ 3.98 (d, $^3J$=6.5 Hz, 1H, CHNH₂), 4.65 (d, $^3J$=6.5 Hz, 1H, CHOH), 7.15-7.35 (m, 10H, Hₐromatic).

($\pm$)-cis-4,5-Diphenyl-2-oxazolidinone ($\pm$)-112

A solution of triphosgene (2.58 g, 8.68 mmol, 0.35 eq) in dry dichloromethane (10 mL) was added dropwise over 45 min to a suspension of amino alcohol 111 (5.3 g, 24.8 mmol, 1 eq) and triethylamine (7.6 mL, 54.56 mmol, 2.2 eq) in dry dichloromethane (70 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 15 min at 4°C and then allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH₄Cl solution (25 mL) and dichloromethane (50 mL) were added to the reaction mixture and after stirring for 20 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with water (25 mL). The combined aqueous layers were extracted with dichloromethane (50 mL) and the combined organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo. The crude product was recrystallised twice from EtOAc-isohexane to give the title compound 112 (4.07 g, 17.0 mmol, 69%) as a white solid.

M.p 191-192°C (EtOAc/isohexane) (lit., 134 193.5-194.5°C (EtOAc/hexane)); $R_f$ (isohexane/EtOAc 5.5/4.5) 0.3; IR (CDCl₃): $\nu_{max}$ 3278 (br, NH), 1752 (s, C=O), 1499 (w), 1446 (m), 1393 (w), 1350 (w), 1221 (w), 1071 (w), 1022 (w), 914 (w), 749 (m), 670 (s) cm⁻¹; $^1$H NMR (400 MHz, CDCl₃): $\delta$ 5.17 (d, $^3J$=8.0 Hz, 1H, CHNH), 5.94 (d, $^3J$=8.0 Hz, 1H, CHO), 6.90-6.98 (m, 4H, Hₐromatic), 7.06-7.11 (m, 6H, Hₐromatic); $^{13}$C NMR (75 MHz, CDCl₃): $\delta$ 61.4 (CHNH), 82.3 (CHO), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 134.4 (Cq), 136.0 (Cq), 159.6 (C=O).
Experimental

(4R,5S)-(+)-4,5-Diphenyl-2-oxazolidinone (+)-112

\[
\begin{align*}
\text{C}_{15}\text{H}_{13}\text{NO}_2 & \quad 239.27 \text{ g.mol}^{-1} \\
\end{align*}
\]

A solution of triphosgene (1.70 g, 5.74 mmol, 0.35 eq) in dry dichloromethane (8 mL) was added dropwise over 1.5 h to a suspension of (1S,2R)-2-amino-1,2-diphenylethanol (3.5 g, 16.41 mmol, 1 eq) and triethylamine (5.03 mL, 36.1 mmol, 2.2 eq) in dry dichloromethane (80 mL) under nitrogen at 4°C. The reaction mixture was stirred for 1.5 h at 4°C, followed by a further addition of triphosgene (0.25 g, 0.84 mmol, 0.05 eq) and stirring for 30 min. Saturated aqueous NH₄Cl solution (25 mL) was added to the reaction mixture and after stirring for 5 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with water (25 mL). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic extracts were then dried (MgSO₄), filtered and concentrated \textit{in vacuo} to give the \textit{title compound} (+)-112 contaminated by traces of triethylamine hydrochloride (3.21 g, 13.42 mmol, 82%) as a white solid.

R₆, IR, \(^1\)H and \(^{13}\)C NMR data were identical to the one given for the corresponding racemate (±)-112.

\textbf{Mp} 232-233°C (lit.,\textsuperscript{13} 232.5-233.5°C (toluene)); \([\alpha]_\text{D}^{25} +66.3 \ (c \ 0.85, \text{MeOH}) \ (\text{lit.,}\textsuperscript{13} \ [\alpha]_\text{D}^{25} +60.6 \ (c \ 0.858, \text{MeOH})).\)
Experimental

(4S,5R)-(−)-4,5-Diphenyl-2-oxazolidinone (-)-112

\[
\begin{align*}
\text{C}_{15}\text{H}_{13}\text{NO}_2 & \quad 239.27 \text{ g.mol}^{-1} \\
\end{align*}
\]

A solution of triphosgene (1.05 g, 3.53 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 1 h to a suspension of (1R,2S)-2-amino-1,2-diphenylethanol (2.15 g, 10.08 mmol, 1 eq) and triethylamine (3.09 mL, 22.18 mmol, 2.2 eq) in dry dichloromethane (45 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 1 h at 4°C and saturated aqueous NH₄Cl solution (25 mL) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (2 x 25 mL) and the combined organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo. The residue was partitioned between EtOAc (150 mL) and aqueous NaHCO₃ solution (5%, 50 mL). The organic layer was separated and then washed with brine (25 mL), dried (MgSO₄), filtered and concentrated in vacuo to give the title compound (-)-112 (2.05 g, 8.57 mmol, 85%) as a white solid.

\[R_f, \text{IR, } ^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR data were identical to the one given for the corresponding racemate (±)-112.}\]

\[\text{Mp 231-232°C; } [\alpha]_D^{30} -59.6 \text{ (c 0.86, MeOH)} \text{ (lit., } ^{135} [\alpha]_D^{30} -58.4 \text{ (c 0.91, MeOH))}.\]

139
(±)-3-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113

A mixture of 4,5-diphenyl-2-oxazolidinone (±)-112 (5.0 g, 20.9 mmol, 1 eq), aluminium chloride (0.41 g, 3.1 mmol, 0.15 eq) and triethyl orthoformate (103 mL, 0.63 mol, 30 eq) was heated at 155°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (50 mL). The aqueous phase was extracted with diethyl ether (200 mL then 100 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 6.5:3.5) to give the title compound (±)-113 (5.72 g, 16.75 mmol, 80%) as a white solid which can readily be recrystallised in hexane.

Mp 93.5-94.5°C (hexane); Rₖ (isohexane/EtOAc 5.5/4.5) 0.6; IR (film): ν_max 2979 (m, C=O), 1735 (s, O=O), 1455 (m), 1385 (m), 1161 (m), 1066 (s), 1037 (m), 1025 (m), 763 (m), 713 (m), 697 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.72 (t, 3J=7.1 Hz, 3H, CH₂CH₃), 1.30 (t, 3J=7.1 Hz, 3H, CH₂CH₃), 3.24 (qd, 3J=7.1 Hz, 2J=9.2 Hz, 1H, CH₂CH₃), 3.47 (qd, 3J=7.1 Hz, 2J=9.2 Hz, 1H, CH₂CH₃), 3.66 (qd, 2J=7.1 Hz, 2J=9.2 Hz, 1H, CH₂CH₃), 5.25 (d, 3J=8.2 Hz, 1H, CHN), 5.87 (s, 1H, OCHO), 5.91 (d, 3J=8.2 Hz, 1H, CHO), 6.93-7.12 (m, 10H, H_arom); ¹³C NMR (100 MHz, CDCl₃): δ 14.0 (CH₃), 14.9 (CH₃), 60.5 (CH₂), 62.7 (CH₂), 81.5 (CHO), 102.0 (OCHO), 126.0 (CH), 127.6 (CH), 127.7 (2 x CH), 134.2 (C_q), 136.4 (C_q), 157.4 (C=O); ¹H NMR (400 MHz, DMSO): δ 0.65 (t, 3J=7.1 Hz, 3H, CH₂CH₃), 1.19 (t, 3J=7.1 Hz, 3H, CH₂CH₃), 3.20 (qd, 3J=7.1 Hz, 2J=9.3 Hz, 1H, CH₂CH₃), 3.41 (qd, 3J=7.1 Hz, 2J=9.3 Hz, 1H, CH₂CH₃), 3.58-3.66 (m, 2H, CH₂CH₃), 5.35 (d, 3J=8.1 Hz, 1H, CHN), 5.77 (s, 1H, OCHO), 6.03 (d, 3J=8.1 Hz, 1H, CHO), 6.90-7.12 (m, 10H, H_arom); ¹³C
**Experimental**

NMR (100 MHz, DMSO): $\delta$ 14.0 (CH$_3$), 14.8 (CH$_3$), 59.4 (CHN), 61.6 (CH$_2$), 61.9 (CH$_2$), 80.3 (CHO), 101.6 (OCHO), 126.0 (CH), 127.2 (CH), 127.3 (CH), 127.5 (2 x CH), 127.6 (CH), 134.7 (C$_q$), 136.9 (C$_q$), 156.5 (C=O); FAB-MS $m/z$ (%): 364 (MNa$^+$, 100), 296 ([M-EtO]$^+$, 14), 262 (46), 180 (5); HMRS: MNa$^+$, found 364.15313; C$_{20}$H$_{23}$NNaO$_4$ requires 364.15313; Anal. found: C, 70.32; H, 6.80; N, 4.10. Calcd for C$_{20}$H$_{23}$NO$_4$: C, 70.36; H, 6.79; N, 4.10.

(4R,5S)-(+)-3-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113

![Chemical Structure](image)

C$_{20}$H$_{23}$NO$_4$ 341.41 g mol$^{-1}$

A mixture of (4R,5S)-(+)-4,5-diphenyl-2-oxazolidinone (+)-112 (2.19 g, 9.15 mmol, 1 eq), aluminium chloride (0.18 g, 1.37 mmol, 0.15 eq) and triethyl orthoformate (45 mL, 0.27 mol, 30 eq) was heated at 155°C for 44 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO$_3$ solution (25 mL). The aqueous phase was extracted with diethyl ether (90 mL then 45 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 3:1) to give the title compound (+)-113 (2.29 g, 6.71 mmol, 74%) as a white solid which can readily be recrystallised in hexane.

$R_f$, IR, $^1$H and $^{13}$C NMR, and mass spectra data were identical to the one given for the corresponding racemate (±)-113.

Mp 93-95°C (hexane); [α]$_D$ +6.0 (c 0.55, CH$_2$Cl$_2$); Anal. found: C, 70.19; H, 6.79; N, 4.15. Calcd for C$_{20}$H$_{23}$NO$_4$: C, 70.36; H, 6.79; N, 4.10.
Experimental

\((4S,5R)-(\text{-})-3\text{-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (}\text{-})\text{-}113\)

A mixture of \((4S,5R)-(\text{-})-4,5\text{-diphenyl-2-oxazolidinone (}\text{-})\text{-}112\) (0.8 g, 3.34 mmol, 1 eq), aluminium chloride (67 mg, 0.5 mmol, 0.15 eq) and triethyl orthoformate (16.5 mL, 0.1 mol, 30 eq) was heated at 160°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (10 mL). The aqueous phase was extracted with EtOAc (30 mL then 2 x 15 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 3:1) to give the title compound \((\text{-})\text{-}113\) (0.78 g, 2.28 mmol, 68%) as a white solid which can readily be recrystallised in hexane.

Please note: Rf, IR, \(^1\)H and \(^{13}\)C NMR, and mass spectra data were identical to the one given for the corresponding racemate (±)-113.

\textbf{Mp} 92.5-94.5°C (hexane); [\(\alpha\)]\(_{D}\) \text{-}4.5 (c 1.12, CH₂Cl₂); \textbf{Anal.} found: C, 70.32; H, 6.75; N, 4.12. Calcd for C\(_{20}\)H\(_{23}\)NO\(_{4}\): C, 70.36; H, 6.79; N, 4.10.
Experimental

(±)-3-(2-Benzylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (±)-114

\[
\text{C}_{25}\text{H}_{23}\text{NO} \quad 369.47 \text{ g mol}^{-1}
\]

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.80 g, 2.34 mmol, 1.5 eq) in dry dichloromethane (2.5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (1.53 g, 23.4 mmol, 15 eq), zinc chloride (1 M solution in diethyl ether, 2.34 mL, 2.34 mmol, 1.5 eq), chlorotrimethylsilane (1.48 mL, 11.7 mmol, 7.5 eq) and allylbenzene (0.184 g, 1.56 mmol, 1 eq) in dry diethyl ether (7.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (10 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 3:1 to 7:3) to give a mixture of cyclopropanes (±)-114 contaminated by 10 wt. % of 4,5-diphenyl-N-formyl-2-oxazolidinone (531 mg, 1.29 mmol of (±)-114 after correction, 83% of (±)-114 after correction; (±)-114A: (±)-114B:(±)-114C:(±)-114D: 84:12:<2:<2 as determined by ¹H NMR) as a white solid.

**Isomer A:** $R_f$ (P.E. 40-60°C/EtOAc 3:1) 0.33; **IR** (CDCl₃): \( \nu_{\max } \) 3064 (w), 3031 (w), 2920 (w), 1756 (s, C=O), 1606 (w, C=C), 1497 (w), 1451 (w), 1405 (m), 1217 (w), 1194 (w), 1137 (w), 1079 (w), 1026 (w), 762 (w), 722 (w), 697 (s) cm⁻¹; **¹H NMR** (500 MHz, CDCl₃): δ 0.93 (dt, \(^3J_{5\alpha,5\beta} = 3J_{5\alpha,6} = 5.9 \text{ Hz}, \ ^2J_{5\alpha,4} = 7.0 \text{ Hz}, 1H, H_{5\alpha}), 1.24 \text{ (m, 1H, H}_6), 1.31 \text{ (ddd,} \ ^3J_{8\alpha,4} = 3J_{8\alpha,6} = 3.7 \text{ Hz,} \ ^2J_{8\alpha,5\alpha} = 5.7 \text{ Hz,} \ ^3J_{8\alpha,6} = 9.4 \text{ Hz,} \ ^1H, H_{8\alpha}), 2.18 \text{ (dd,} \ ^3J_{7,6} = 7.7 \text{ Hz,} \ ^2J = 14.5 \text{ Hz,} \ ^1H, H_7), 2.31 \text{ (dt,} \ ^3J_{4,5\beta} = 3J_{4,6} = 3.5 \text{ Hz,} \ ^3J_{4,5\alpha} = 7.0 \text{ Hz,} \ ^1H, H_8), 2.57 \text{ (dd,} \ ^3J_{7,6} = 5.6 \text{ Hz,} \ ^2J = 14.5 \text{ Hz,} \ ^1H, H_7), 4.68 \text{ (d,} \ ^3J_{3,2} = 7.9 \text{ Hz,} \ ^1H, H_3), 5.69 \text{ (d,} \ ^3J_{2,3} = 7.9
Hz, 1H, H₂), 6.72-6.78 (m, 2H, H₂arom), 6.86-6.97 (m, 4H, H₂arom), 7.03-7.14 (m, 9H, H₂arom); ¹³C NMR (125 MHz, CDCl₃): δ 14.2 (C₅), 20.9 (C₆), 31.2 (C₄), 37.7 (C₁), 66.8 (C₃), 79.7 (C₂), 126.0 (CH), 126.1 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 134.3 (2 × C₂), 140.3 (C₃), 158.0 (C₄); Cl(methane)-MS m/z (%): 370 (MH⁺, 100), 354 (8), 326 ([M+H-CO₂]+, 52), 292 ([M-Ph]+, 13), 278 ([M-Bn]+, 17), 248 (12), 234 (19), 208 (7), 197 (12), 180 (37), 131 (17), 117 (11), 91 (Bn⁺, 19), 77 (Ph⁺, 4); HMRS: MH⁺, found 370.18044. C₂₅H₂₄N₂0₂ requires 370.18069.

Isomer B: Rₜ (P.E. 40-60°C/EtOAc 3:1) 0.27; ¹H NMR (500 MHz, CDCl₃): δ 0.53 (dt, 2J₅ₖ=6.2 Hz, 3J₅₆=7.1 Hz, 1H, H₅₆), 0.85 (ddd, 3J₅₆=3.7 Hz, 2J₅₆=5.6 Hz, 3J₆₅=9.4 Hz, 1H, H₅₆), 1.61 (dddd, 3J₇₆=3.1 Hz, 3J₆₇=5.6 Hz, 2J₆₅=6.2 Hz, 3J₆₇=8.6 Hz, 3J₆₅=9.3 Hz, 1H, H₆), 2.29 (dd, 3J₇₆=8.6 Hz, 2J=14.8 Hz, 1H, H₇), 2.35 (dt, 3J₄₅=3J₄₆=3.4 Hz, 3J₄₅=7.0 Hz, 1H, H₄), 3.05 (dd, 3J₇₆=5.4 Hz, 2J=14.8 Hz, 1H, H₇), 4.80 (d, 3J₃₂=7.9 Hz, 1H, H₃), 5.74 (d, 3J₂₃=7.9 Hz, 1H, H₂), 6.70-7.15 (m, 15H, H₂arom); ¹³C NMR (125 MHz, CDCl₃): δ 12.3 (C₃), 21.5 (C₆), 31.5 (C₄), 37.9 (C₁), 66.5 (C₃), 79.7 (C₂), 126.0 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 134.7 (2 × C₂), 140.3 (C₃), 158.3 (C₁).

(±)-3-(2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (±)-117

C₂₄H₂₇NO₂ 361.48 g·mol⁻¹

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.47 g, 1.375 mmol, 1.25 eq) in dry dichloromethane (1.5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.90 g, 13.75 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.38 mL, 1.38 mmol, 1.25 eq), chlorotrimethylsilane (0.87 mL, 6.875 mmol, 6.25 eq) and vinlycyclohexane (0.121 g, 1.1 mmol, 1 eq) in dry diethyl ether (6 mL) under nitrogen at reflux. The mixture was
stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product ((±)-117A:(±)-117B:(±)-117C:(±)-117D: 88:8:<2:<2 as determined by ¹H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 9:1 to 4:1) to give the cyclopropanes (±)-117 (mixture of (±)-117A, (±)-117B, (±)-117C, (±)-117D 33 mg, 0.09 mmol, 8%, white solid; (±)-117A 263 mg, 0.73 mmol, 66%, white solid; 0.82 mmol, 74%).

**Isomer A:** Mp 146-148°C; **Rf** (P.E. 40-60°C/EtOAc 8.5:1.5) 0.26; **IR** (CDCl₃): νmax 2924 (s), 2851 (m), 1751 (s, C=O), 1456 (m), 1406 (s), 1265 (s), 1196 (m), 1078 (m), 1026 (m), 741 (s), 698 (s) cm⁻¹; **¹H NMR** (500 MHz, CDCl₃): δ 0.28-0.37 (m, 1H, H₇), 0.67-0.73 (m, 1H), 0.73-0.81 (m, 2H, H₆ and H₅), 0.88-0.97 (m, 2H), 0.99-1.15 (m, 4H), 1.39-1.52 (m, 2H), 1.55-1.66 (m, 2H), 2.17 (td, 3J₄,₅=3J₄,₆=3.5 Hz, 3J₅,₆=6.7 Hz, 1H, H₄), 4.82 (d, 3J₃,₂=8.0 Hz, 1H, H₃), 5.73 (d, 3J₂,₃=8.0 Hz, 1H, H₂), 6.86-6.90 (m, 2H, H arom); 13C NMR (125 MHz, CDCl₃): δ 13.6 (C₅), 25.7 (CH₂), 25.8 (C₆ and CH₂), 26.2 (CH₂), 30.2 (C₄), 32.1 (2 x CH₂), 40.4 (C₇), 66.8 (C₈), 79.6 (C₉), 125.9 (CH), 127.6 (CH), 127.7 (2 x CH), 128.1 (CH), 128.2 (CH), 134.3 (C₃), 134.5 (C₉), 158.2 (C₁); **EI-MS** m/z (%): 361 (M⁺, 3), 278 (11), 234 (43), 180 (100), 165 (7), 132 (5), 104 (9), 77 (Ph⁺, 5); **HMRS:** M⁺, found 361.20933. C₂₄H₂₇N₂O₂ requires 361.20417. Anal. found: C, 79.56; H, 7.82; N, 3.74. Caled for C₂₄H₂₇N₂O₂: C, 79.74; H, 7.53; N, 3.87.

**Isomer B:** **Rf** (P.E. 40-60°C/EtOAc 8.5:1.5) 0.35; **¹H NMR** (500 MHz, CDCl₃): δ 0.36 (ddd, 3J₅₆=5.5 Hz, 3J₅₆=6.4 Hz, 3J₄₅=7.3 Hz, 1H, H₅), 0.53-0.62 (m, 1H, H₆), 0.67 (ddd, 3J₅₆=3.7 Hz, 3J₅₆=5.4 Hz, 3J₅₆=9.2 Hz, 1H, H₅), 0.94-1.33 (m, 6H), 1.54-1.76 (m, 4H), 1.94-2.02 (m, 1H), 2.18 (dt, 3J₄₅=3J₄₆=3.5 Hz, 3J₄₅=7.1 Hz, 1H, H₄), 4.80 (d, 3J₃₂=7.9 Hz, 1H, H₃), 5.70 (d, 3J₂₃=7.9 Hz, 1H, H₂), 6.85-7.14 (m, 10H, H arom); 13C NMR (125 MHz, CDCl₃): δ 10.9 (C₅), 26.1 (2 x CH₂), 26.4 (CH₂), 27.3 (C₆), 30.5 (C₇), 32.0 (CH₂), 32.4 (CH₂), 41.0 (C₈), 66.6 (C₉), 79.5 (C₉), 126.0 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 134.5 (C₃), 134.8 (C₉), 158.2 (C₁).
General procedure for the cyclopropanation of vinyl cyclohexane using chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113

A solution of chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113 (1.25 mmol, 1.25 eq) in dry dichloromethane (1.5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and vinyl cyclohexane (0.11 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution (10 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (10 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo.

R₆, IR, ¹H and ¹³C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate (±)-117.

(4R,5S)-3-((1S,2R)-2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (+)-117

Following the general procedure, the crude product ((+)-117A:(+)-117B:(+)-117C:(+)-117D: 88:8:<2:<2 as determined by ¹H NMR), obtained by the reaction between vinyl cyclohexane and (+)-113, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 9:1 to 4:1) to give the cyclopropanes (+)-117 (mixture of (+)-117A, (+)-117B, (+)-117C, (+)-117D 26 mg, 0.072 mmol, 7%, white solid; (+)-117A 179 mg, 0.50 mmol, 50%, white solid; 0.57 mmol, 57%).
**Experimental**

**Isomer A:** Mp 136.5-138.5°C (EtOAc/hexane); [α]° +98.7 (c 1.07, CHCl₃); Anal. found: C, 79.64; H, 7.56; N, 3.87. Calcd for C₂₄H₂₇NO₂: C, 79.74; H, 7.53; N, 3.87.

(4S,5R)-3-((1R,2S)-2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (-)-117

![Chemical Structure](image1)

C₂₄H₂₇NO₂ 361.48 g·mol⁻¹

Following the general procedure, the crude product ((-)-117A:(-)-117B:(-)-117C:(-)-117D: 88:8:<2:<2 as determined by ¹H NMR), obtained by the reaction between vinyl cyclohexane (110 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of (-)-113 in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 9:1 to 4:1) to give the cyclopropanes (-)-117 (mixture of (-)-117A, (-)-117B, (-)-117C, (-)-117D 33 mg, 0.09 mmol, 8%, white solid; (-)-117A 263 mg, 0.73 mmol, 66%, white solid; 0.82 mmol, 74%).

**Isomer A:** Mp 136-139°C (EtOAc/hexane); [α]° -106.9 (c 1.07, CHCl₃).

(±)-3-Bicyclo[4.1.0]hept-7-yl-4,5-diphenyl-2-oxazolidinone (±)-118

![Chemical Structure](image2)

C₂₂H₂₃NO₂ 333.43 g·mol⁻¹

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.64 g, 1.88 mmol, 1.25 eq) in dry dichloromethane (2.5 mL) was added via a motorised syringe pump over 6.5 h to a vigorously stirred mixture of zinc amalgam (1.23 g, 18.8 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.88 mL, 1.88 mmol, 1.25 eq),
Experimental

chlorotrimethylsilane (1.19 mL, 9.38 mmol, 6.25 eq) and cyclohexene (0.123 g, 1.50 mmol, 1 eq) in dry diethyl ether (7.6 mL) under nitrogen at reflux. The mixture was stirred for 14 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product ((±)-118A:(±)-118B:(±)-118C:(±)-118D: 90:<2:<6:<2 as determined by ¹H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 4:1 to 3:1) to give the cyclopropanes (±)-118 (mixture of (±)-118A, (±)-118B, (±)-118C, (±)-118D 19 mg, 0.06 mmol, 4%, white solid; (±)-118A 0.271 mg, 0.81 mmol, 54%, white solid; 0.87 mmol, 58%).

Isomer A: Mp 154-156°C; Rf (isohexane/EtOAc 3:1) 0.34; IR (CDCl₃): νmax 3035 (w), 2929 (m), 2855 (w), 1755 (s, C=O), 1499 (m), 1404 (m), 1218 (w), 1197 (w), 1121 (w), 1080 (w), 1026 (w), 763 (m), 702 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.86-1.06 (m, 2H), 1.07-1.24 (m, 4H), 1.48 (ddddd, 3 J=2.2 Hz, 3 J=3.4 Hz, 3 J=7.1 Hz, 3 J=10.0 Hz, 1H), 1.68-1.95 (m, 3H), 2.10 (t, 3 J=3.4 Hz, 1H, H₄), 4.86 (d, 3 J₃₂=8.0 Hz, 1H, H₃), 5.75 (d, 3 J₂₃=8.0 Hz, 1H, H₂), 6.89-6.93 (m, 2H, Harom), 6.97-7.01 (m, 2H, Harom); ¹³C NMR (125 MHz, CDCl₃): δ 17.5 (CH), 20.0 (CH), 21.0 (CH₂), 21.1 (CH₂), 22.0 (CH₂), 22.2 (CH₂), 36.1 (C₄), 66.3 (C₃), 79.5 (C₂), 125.9 (CH), 127.7 (2 x CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 134.6 (2 x C₃), 158.1 (C₁); Cl(methane)-MS m/z (%): 334 (MH⁺, 100), 290 ([M+H-CO₂]⁺, 100), 256 ([M-Ph]⁺, 16), 208 (12), 130 (11), 91 (6); HMRS: MH⁺, found 334.18079. C₂₂H₂₄N₂O₂ requires 334.18069. Anal. found: C, 79.13; H, 6.98; N, 4.24. Calcd for C₂₂H₂₃N₂O₂: C, 79.25; H, 6.95; N, 4.20.

Isomer C: Rf (isohexane/EtOAc 3:1) 0.43, ¹H NMR (500 MHz, CDCl₃): δ 0.85 (ddddd, 3 J=2.1 Hz, 3 J=7.3 Hz, 3 J=9.5 Hz, 3 J=11.6 Hz, 1H), 1.15-2.11 (m, 9H), 2.30 (t, 3 J=7.4 Hz, 1H, H₄), 4.98 (d, 3 J₃₂=7.4 Hz, 1H, H₃), 5.84 (d, 3 J₂₃=7.4 Hz, 1H, H₂), 6.89-7.16 (m, 10H, Harom); ¹³C NMR (125 MHz, CDCl₃): δ 12.3 (CH), 13.7 (CH), 18.7 (CH₂), 20.3 (CH₂), 22.3 (2 x CH₂), 32.3 (C₄), 67.0 (C₃), 79.9 (C₂), 126.0 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 134.1 (2 x C₃), 159.6 (C₁).
**General procedure for the cyclopropanation of cyclohexene using chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113**

A solution of chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113 (1.25 mmol, 1.25 eq) in dry dichloromethane (1.5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and cyclohexene (82 mg, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution (10 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (10 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo.

R₆, IR, ¹H and ¹³C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate (±)-118.

(4R,5S)-3-((1R,6S)-Bicyclo[4.1.0]hept-7-yl)-4,5-diphenyl-2-oxazolidinone (+)-118

Following the general procedure, the crude product ((+)-118A:(+)-118B:(+)-118C:(+)-118D: 90:<2:6:<2 as determined by ¹H NMR), obtained by the reaction between cyclohexene (82 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of (+)-113 in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:1) to give the cyclopropanes (+)-118 (mixture of (+)-118A, (+)-118B, (+)-118C, (+)-118D 27 mg, 0.08 mmol, 4%, white solid; (+)-118A 0.175 mg, 0.53 mmol, 53%, white solid; 0.61 mmol, 61%).
**Experimental**

Isomer A: Mp 176-179°C (EtOAc); [\(\alpha\)]\(_D\) \(+90.2\) (c 1.05, CHCl\(_3\)); Anal. found: C, 79.32; H, 7.00; N, 4.20. Calcd for C\(_{22}\)H\(_{23}\)NO\(_2\): C, 79.25; H, 6.95; N, 4.20.

\((4S,5R)-3-((1S,6R)-\text{Bicyclo}[4.1.0]\text{hept}-7-\text{yl})-4,5\text{-diphenyl}-2\text{-oxazolidinone} (-)-118\)

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{O}
\end{array}
\]

\[
\text{C}_{22}\text{H}_{23}\text{NO}_2 \quad 333.43 \text{ g.mol}^{-1}
\]

Following the general procedure, the crude product \((-)-118\):\((-)-118\):\((-)-118\):\((-)-118\): 90:<2:6:<2 as determined by \(^1\)H NMR, obtained by the reaction between cyclohexene (82 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of \((-)-113\) in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1) to give the cyclopropanes \((-)-118\) (mixture of \((-)-118\), \((-)-118\), \((-)-118\), \((-)-118\) 22 mg, 0.066 mmol, 7%, white solid; \((-)-118\) 0.171 mg, 0.51 mmol, 51%, white solid; 0.58 mmol, 58%).

**Isomer A: M_p 174-177°C (EtOAc); [\(\alpha\)]\(_D\) \(-86.0\) (c 0.86, CHCl\(_3\)).**
Experimental

(±)-3-(2-Phenylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (±)-119

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.615 g, 1.8 mmol, 1.25 eq) in dry dichloromethane (2.5 mL) was added via a motorised syringe pump over 2 h to a vigorously stirred mixture of zinc amalgam (1.18 g, 18.0 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.8mL, 1.8 mmol, 1.25 eq), chlorotrimethylsilane (1.14 mL, 9.0 mmol, 6.25 eq) and styrene (0.15 g, 1.44 mmol, 1 eq) in dry diethyl ether (6.2 mL) under nitrogen at reflux. The mixture was stirred for 17 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product ((±)-119A:(+)-119B:(+)-119C:(±)-119D: 56:6:28:6 as determined by ¹H NMR) was purified by flash column chromatography (silica, isohexane/diethyl ether 3:2 to 1:1) to give a mixture of cyclopropanes (±)-119 contaminated by traces of 4,5-diphenyl-N-formyl-2-oxazolidinone (mixture of (±)-119A, (±)-119B, (±)-119C, (±)-119D 0.121 g, 0.34 mmol, 24%, white solid; (±)-119A 0.161 g, 0.45 mmol, 31%, white solid; 0.79 mmol, 55%).

Isomer A: Mp 153-154°C (EtOAc/P.E. 40-60°C); Rf (isohexane/diethyl ether 1:1) 0.22; IR (CDCl₃): νmax 3035 (w), 3000 (w), 2920 (w), 1738 (s, C=O), 1604 (w, C=C), 1499 (w), 1455 (m), 1403 (s), 1227 (m), 1194 (m), 1137 (w), 1134 (m); 1025 (s), 762 (s), 721 (s), 696 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.37 (td, 2J₅₆₋₅₇=3J₆₋₅₆=6.6 Hz, 151
Experimental

$^{3}J_{5\alpha,4}=7.4$ Hz, 1H, H$_{3\alpha}$), 1.37 (ddd, $^{3}J_{5\beta,4}=4.2$ Hz, $^{3}J_{5\beta,5\alpha}=6.1$ Hz, $^{3}J_{5\beta,\delta}=10.1$ Hz, 1H, H$_{5\beta}$), 2.22 (ddd, $^{3}J_{6,4}=3.3$ Hz, $^{3}J_{6,5\alpha}=6.5$ Hz, $^{3}J_{6,5\beta}=9.8$ Hz, 1H, H$_{6}$), 2.63 (td, $^{3}J_{4,5\beta}=3.9$ Hz, $^{3}J_{4,5\alpha}=7.4$ Hz, 1H, H$_{4}$), 5.04 (d, $^{3}J_{5,2}=8.0$ Hz, 1H, H$_{3}$), 5.83 (d, $^{3}J_{2,3}=8.0$ Hz, 1H, H$_{2}$), 6.80-7.15 (m, 15H, H$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_{3}$): $\delta$ 15.9 (C$_{5}$), 23.4 (C$_{6}$), 33.9 (C$_{4}$), 66.7 (C$_{3}$), 79.7 (C$_{2}$), 126.0 (CH), 126.3 (CH), 126.8 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 134.3 (C$_{q}$), 134.4 (C$_{q}$), 139.4 (C$_{q}$), 157.9 (C$_{1}$); EI-MS m/z (%): 356 (MH$^{+}$, 2), 240 (79), 220 (24), 180 (100), 117 (90), 91 (68), 77 (Ph$^{+}$, 52); HMRS: MH$^{+}$, found 356.16306. C$_{24}$H$_{22}$NO$_{2}$ requires 356.16505.

Isomer B: $R_{f}$ (isohexane/diethyl ether 1:1) 0.37; $^{1}$H NMR (300 MHz, CDCl$_{3}$): $\delta$ 1.05-1.29 (m, 2H, H$_{3}$), 2.40-2.57 (m, 2H, H$_{4}$ and H$_{5}$), 4.94 (d, $^{3}J_{3,2}=7.9$ Hz, 1H, H$_{3}$), 5.81 (d, $^{3}J_{2,3}=7.9$ Hz, 1H, H$_{2}$), 6.72-7.44 (m, 15H, H$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_{3}$): $\delta$ 13.5 (C$_{5}$), 24.9 (C$_{6}$), 34.4 (C$_{4}$), 66.4 (C$_{3}$), 79.7 (C$_{2}$), 126.3 (CH), 127.0 (CH), 127.4 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH), 134.4 (C$_{q}$), 134.6 (C$_{q}$), 139.4 (C$_{q}$), 158.6 (C$_{1}$).

Isomer C: $R_{f}$ (isohexane/diethyl ether 1:1) 0.37; $^{1}$H NMR (300 MHz, CDCl$_{3}$): $\delta$ 1.05-1.15 (m, 2H, H$_{5}$), 2.44 (td, $^{3}J_{5,4}=3.9$ Hz, $^{3}J_{5,\delta}=9.0$ Hz, 1H, H$_{5\delta}$), 1.96 (dt, $^{3}J_{5\beta,4}=4.3$ Hz, $^{3}J_{5\beta,5}=7.1$ Hz, 1H, H$_{5\beta}$), 2.15 (td, $^{3}J_{6,4}=3.9$ Hz, $^{3}J_{6,5}=7.1$ Hz, $^{3}J_{6,5\alpha}=9.0$ Hz, 1H, H$_{6}$), 2.60 (dt, $^{3}J_{4,5\beta}=4.3$ Hz, $^{3}J_{4,5\alpha}=3.9$ Hz, $^{3}J_{4,6}=7.3$ Hz, 1H, H$_{4}$), 3.80 (d, $^{3}J_{3,2}=7.8$ Hz, 1H, H$_{3}$), 5.15 (d, $^{3}J_{2,3}=7.8$ Hz, 1H, H$_{2}$), 6.71-7.45 (m, 15H, H$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_{3}$): $\delta$ 11.7 (C$_{5}$), 22.5 (C$_{6}$), 31.5 (C$_{4}$), 65.4 (C$_{3}$), 79.6 (C$_{2}$), 125.8 (CH), 126.7 (CH), 127.6 (2 x CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 133.8 (C$_{q}$), 134.0 (C$_{q}$), 134.6 (C$_{q}$), 158.7 (C$_{1}$).

Isomer D: $R_{f}$ (isohexane/diethyl ether 1:1) 0.37; $^{1}$H NMR (300 MHz, CDCl$_{3}$): $\delta$ 1.05-1.15 (m, 2H, H$_{3}$), 2.44 (td, $^{3}J_{6,4}=3.9$ Hz, $^{3}J_{6,5}=7.1$ Hz, $^{3}J_{6,5\beta}=8.8$ Hz, 1H, H$_{6}$), 3.09 (dd, $^{3}J_{4,5\alpha}=4.8$ Hz, $^{3}J_{4,6}=7.1$ Hz, $^{3}J_{4,5\beta}=7.7$ Hz, 1H, H$_{4}$), 4.51 (d, $^{3}J_{3,2}=7.7$ Hz, 1H, H$_{3}$), 5.32 (d, $^{3}J_{2,3}=7.7$ Hz, 1H, H$_{2}$), 6.71-7.45 (m, 15H, H$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_{3}$): $\delta$ 9.9 (C$_{5}$), 23.7 (C$_{6}$), 31.7 (C$_{4}$), 66.7 (C$_{3}$), 79.7 (C$_{2}$), 125.8 (CH), 126.0 (CH), 126.7 (CH), 127.0 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 134.0 (C$_{q}$), 134.8 (C$_{q}$), 136.5 (C$_{q}$), 158.6 (C$_{1}$).
Experimental

\((4R,5S)-3-((1S,2R)-2-\text{Phenylcyclopropyl})-4,5-\text{diphenyl-2-oxazolidinone} \) (+)-119

\[
\begin{align*}
\text{C}_2\text{dH}_2\text{1NO}_2 & \quad 355.43 \text{ g.mol}^{-1} \\
\end{align*}
\]

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 (0.683 g, 2.0 mmol, 1.25 eq) in dry dichloromethane (2.4 mL) was added via a motorised syringe pump over 1.5 h to a vigorously stirred mixture of zinc amalgam (1.31 g, 20.0 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 2.0 mL, 2.0 mmol, 1.25 eq), chlorotrimethylsilane (1.27 mL, 10 mmol, 6.25 eq) and styrene (0.167 g, 1.6 mmol, 1 eq) in dry diethyl ether (8.4 mL) under nitrogen at reflux. The mixture was stirred for 2 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO\textsubscript{3} solution (15 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (15 mL). The organic solvents were removed \textit{in vacuo} and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The crude product \((+)-119A:(+)-119B:(+)-119C:(+)-119D: 56:6:28:6\) as determined by \textit{H} NMR was purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 3:2 to 1:1) to give a mixture of cyclopropanes \(+)-119 \) contaminated by traces of 4,5-diphenyl-N-formyl-2-oxazolidinone (mixture of \(+)-119A, (+)-119B, (+)-119C, (+)-119D 178 mg, 0.5 mmol, 31%, white solid; \(+)-119A 130 mg, 0.37 mmol, 23%, white solid; 0.87 mmol, 54%).

\(R_f, \text{IR, } ^1\text{H and } ^{13}\text{C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate } (\pm)-119\).

\textit{Isomer A: Mp} 181-183°C (EtOAc/hexane); \([\alpha]_D^{25} +135.0 \ (c \ 0.9, \ \text{CHCl}_3)\); \textit{Anal. found:}

\begin{align*}
\text{C, } 80.91; \ \text{H, } 5.92; \ \text{N, } 3.95. \ \text{Calcd for } \text{C}_{24}\text{H}_{27}\text{NO}_2: \ \text{C, } 81.10; \ \text{H, } 5.96; \ \text{N, } 3.94.
\end{align*}
Experimental

(±)-4,5-Diphenyl-3-[2-(trimethylsilanyl)-cyclopropyl]-2-oxazolidinone (±)-120

\[
\begin{align*}
\text{C}_{21}\text{H}_{25}\text{NO}_2\text{Si} & & 351.52 \text{ g.mol}^{-1} \\
\end{align*}
\]

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.64 g, 1.88 mmol, 1.25 eq) in dry dichloromethane (2.5 mL) was added via a motorised syringe pump over 6.5 h to a vigorously stirred mixture of zinc amalgam (1.23 g, 18.8 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.88 mL, 1.88 mmol, 1.25 eq), chlorotrimethylsilane (1.19 mL, 9.38 mmol, 6.25 eq) and vinyltrimethylsilane (0.15 g, 1.50 mmol, 1 eq) in dry diethyl ether (7.6 mL) under nitrogen at reflux. The mixture was stirred for 14 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product (±)-120A:(±)-120B:(±)-120C:(±)-120D: 94:<2:<2 as determined by ¹H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 4:1) to give the cyclopropanes (±)-120 (mixture of (±)-120A, (±)-120B, (±)-120C, (±)-120D 0.042 g, 0.12 mmol, 8%, white solid; (±)-120A 0.268 g, 0.76 mmol, 51%, white solid; 0.88 mmol, 59%).

Isomer A: Mp 145-146°C; \text{Rf} (isohexane/EtOAc 4:1) 0.36; \text{IR} (CDCl₃): \nu_{max} 3035 (w), 2955 (w), 1734 (s, C=O), 1499 (w), 1455 (w), 1409 (m), 1380 (m), 1247 (w), 1200 (m), 1135 (w), 1025 (w), 991 (w), 898 (w), 834 (s, Si-C), 762 (m), 718 (m), 695 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ-0.30 (s, 9H, Si(CH₃)₃), δ-0.08 (ddd, 3J₆₅₆=5.0 Hz, 3J₆₅₅₆=8.2 Hz, 3J₆₅₆₇=11.4 Hz, 1H, H₆), 0.87 (ddd, 2J₅₆₅₆=4.8 Hz, 3J₅₆₅₆=6.2 Hz, 3J₅₆₅₆=8.2 Hz, 1H, H₅a), 1.23 (ddd, 3J₅₆₅₆=3.2 Hz, 2J₅₆₅₆=4.8 Hz, 3J₅₆₅₆=11.4 Hz, 1H, H₅b), 2.39 (ddd, 3J₅₆₅₆=3.2 Hz, 2J₅₆₅₆=5.0 Hz, 3J₅₆₅₆=6.2 Hz, 1H, H₄), 4.86 (d, 3J₅₆₅₆=8.0 Hz, 1H, H₃), 5.78 (d, 3J₅₆₅₆=8.0 Hz, 1H, H₄), 6.86-7.15 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃):
\[ \delta 5.3 (C_5), 11.5 (C_3), 28.9 (C_4), 66.9 (C_2), 79.6 (C_2), 125.9 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 134.3 (C_2), 134.4 (C_2), 158.5 (C_2) \]; 

**Cl(methane)-MS**

\[ m/z \text{%}: \ 352 (\text{MH}^+, 100), \ 308 ([\text{M}+\text{H}-\text{CO}_2]^+, 86), \ 292 ([\text{M}-\text{Ph}]^+, 15), \ 230 (10), \ 180 (62), \ 130 (7), \ 100 (3), \ 73 (\text{SiC}_3\text{H}_9^+, 17); \ **HMRS:** \ \text{MH}^+, \text{found} 352.17348. \ C_{21}H_{26}NO_2Si \text{ requires} 352.17327; \ **Anal:** \text{found:} \ C, 71.92; \ H, 7.18; \ N, 3.98. \text{Calcd for} \ C_{21}H_{25}NO_2Si: \ C, 71.75; \ H, 7.17; \ N, 3.98.

\((\pm)-4,5\text{-Diphenyl-3-[2-(tributylstannanyI)-cyclopropyl]-2-oxazolidinone (\pm)-121}\)

\[
\begin{align*}
\text{trans} & \quad \text{isomer A} \\
\text{SnBu}_3 & \\
\text{O} & \\
H & \\
H & \\
N & \\
O & \\
H & \\
H & \\
H & \\
\end{align*}
\]

\[ C_{30}H_{39}NO_2Sn \quad 568.37 \text{g.mol}^{-1} \]

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone \((\pm)-113\) (0.43 g, 1.25 mmol, 1.25 eq) in dry dichloromethane (1.5 mL) was added \textit{via} a motorised syringe pump over 3 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and tributyl(vinyl)tin (0.317 g, 1 mmol, 1 eq) in dry diethyl ether (5.25 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO\textsubscript{3} solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed \textit{in vacuo} and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The crude product \((\pm)-121A:(\pm)-121B:(\pm)-121C:(\pm)-121D: 94:<2:<2:<2\) as determined by \textsuperscript{1}H NMR was purified by flash column chromatography (silica, isohexane/EtOAc 4:1) to give the cyclopropanes \((\pm)-121\) (mixture of \((\pm)-121A, (\pm)-121B, (\pm)-121C, (\pm)-121D\) 11 mg, 0.02 mmol, 2%, yellow oil; \((\pm)-121A\) 0.126 g, 0.22 mmol, 22%, amorphous solid; 0.24 mmol, 24%).
**Isomer A:** $R_f$ (P.E. 40-60°C/ether 7:3) 0.23; IR (CDCl$_3$): $\nu_{max}$ 2959 (s), 2923 (s), 2872 (m), 2849 (s), 1745 (m), 1374 (m), 1218 (m), 1025 (w), 761 (w), 698 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.02 (ddd, $^3$J$_{6,4}$=5.0 Hz, $^3$J$_{6,5a}$=8.3 Hz, $^3$J$_{6,5\beta}$=11.5 Hz, 1H, H$_6$), 0.48-0.64 (m, 6H, 3 x CH$_2$), 0.82 (t, $J$=7.2 Hz, 9H, 3 x CH$_3$), 0.90 (ddd, $^3$J$_{5a,5\beta}$=5.0 Hz, $^3$J$_{5a,4}$=5.9 Hz, $^3$J$_{5a,6}$=8.3 Hz, 1H, H$_{5a}$), 1.10-1.33 (m, 13H, 6 x CH$_2$ and H$_{5a}$), 2.44 (ddd, $^3$J$_{5a,5\beta}$=3.0 Hz, $^3$J$_{4,6}$=5.1 Hz, $^3$J$_{4,5a}$=5.9 Hz, 1H, H$_4$), 4.80 (d, $^3$J$_{3,2}$=7.9 Hz, 1H, H$_3$), 5.73 (d, $^3$J$_{2,3}$=7.9 Hz, 1H, H$_2$), 6.86-6.90 (m, 2H, H$_{arom}$), 6.94-6.99 (m, 2H, H$_{arom}$), 7.01-7.11 (m, 6H, H$_{arom}$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.8 ($^1$J=172.5 Hz, $^1$J=180.7 Hz, C$_6$), 8.3 ($^1$J=163.1 Hz, $^1$J=170.3 Hz, CH$_2$), 11.9 ($^2$J=9.4 Hz, C$_5$), 13.5 (CH$_2$), 27.1 ($^2$J=26.9 Hz, $^2$J=28.1 Hz, CH$_2$), 28.7 ($^3$J=10.3 Hz, $^3$J=17.0 Hz, CH$_2$), 29.1 ($^2$J=5.0 Hz, C$_6$), 65.8 (C$_1$), 79.7 (C$_2$), 125.9 (CH), 127.5 (CH), 127.7 (2 x CH), 127.8 (2 x CH), 128.1 (CH), 128.2 (CH), 134.4 (C$_2$), 134.5 (C$_3$), 158.4 (C$_4$); EI-MS $m/z$ (%): 569 (M$^+$, 2), 512 ([M-C$_4$H$_9$]$^+$, 64), 398 ([M-C$_{12}$H$_{27}$]$^+$, 3), 332 (6), 288 (9), 234 (32), 180 (100), 143 (6), 91 (11); HMRS: MH$^+$, found 570.23942. C$_{30}$H$_{44}$NO$_2$Sn requires 570.23885.

(±)-2-Ethylhexyl-[2-(2-oxo-4,5-diphenyloxazolidin-3yl)cyclopropyl]carboxylate (±)-122

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113 (0.555 g, 1.625 mmol, 1.25 eq) in dry dichloromethane (2 mL) was added via a motorised syringe pump over 2.5 h to a vigorously stirred mixture of zinc amalgam (1.09 g, 16.25 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.63 mL, 1.63 mmol, 1.25 eq), chlorotrimethylsilane (1.03 mL, 8.125 mmol, 6.25 eq) and vinyl 2-ethylhexanoate.
Experimental

(0.221 g, 1.3 mmol, 1 eq) in dry diethyl ether (6.75 mL) under nitrogen at reflux. The
mixture was stirred for 20 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product ((±)-122A:(±)-122B:(±)-122C:(±)-122D: 64:10:13:13 as determined by ¹H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 9:1 to 4:1) to give the cyclopropanes (±)-122 ((±)-122A 0.237 g, 0.56 mmol, 43%, white solid; mixture of (±)-122A, (±)-122B, (±)-122C, (±)-122D 0.118 g, 0.28 mmol, 22%, yellow oil; 0.84 mmol, 65%).

Isomer A (diastereomeric mixture): Mp 116-120°C (diethyl ether); Rf (P.E. 30-40°C/EtOAc 4:1) 0.62; IR (CDCl₃): νmax 2950 (m), 2931 (m), 1742 (s, C=O), 1454 (m), 1215 (m), 1175 (s), 1022 (w), 762 (m), 696 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.50 (t, 3 J=7.5 Hz, 3H, CH₃), 0.66 (t, 3 J=7.5 Hz, 3H, CH₃), 0.68 (t, 3 J=7.5 Hz, 3H, CH₃), 0.75 (t, 3 J=7.5 Hz, 3H, CH₃), 0.77-0.88 (m, 2H, CH₂), 0.91-1.40 (m, 14H, 7 x CH₂), 1.46 (ddd, 3 J=1.8 Hz, 3 J=4.6 Hz, 3 Jsp,4=8.8 Hz, 1H, H5p), 1.47 (ddd, 3 J=1.8 Hz, 3 J=4.6 Hz, 3 Jsp,4=8.8 Hz, 1H, H5p), 1.66 (ddd, 3 J=1.7 Hz, 3 J=5.0 Hz, 3 J5a-6=7.9 Hz, 1H, H5a), 1.67 (ddd, 3 J=1.7 Hz, 3 J=5.0 Hz, 3 J5a-6=7.9 Hz, 1H, H5a), 2.04 (tt, 3 J=5.2 Hz, 3 J=8.9 Hz, 2H, H8), 2.27 (ddd, 3 J=1.7 Hz, 3 J=5.0 Hz, 3 J4,5a=8.9 Hz, 1H, H4), 2.28 (ddd, 3 J=1.7 Hz, 3 J=5.0 Hz, 3 J4,5a=8.9 Hz, 1H, H4), 4.17 (ddd, 3 J=1.6 Hz, 3 J=4.7 Hz, 3 J6,5a=7.9 Hz, 2H, H6), 5.17 (d, 3 J=7.8 Hz, 1H, H3), 5.18 (d, 3 J=7.8 Hz, 1H, H3), 5.78 (d, 3 J=7.8 Hz, 2H, H2), 6.92-7.08 (m, 20H, H arom); ¹³C NMR (125 MHz, CDCl₃): δ 11.2 (CH₃), 11.5 (CH₃), 13.6 (CH₃), 13.7 (CH₃), 13.9 (2 x C₃), 14.1 (CH₂), 22.3 (CH₂), 22.4 (CH₂), 25.2 (CH₂), 25.3 (CH₂), 29.0 (CH₂), 29.2 (CH₂), 31.1 (C₄), 31.2 (C₄), 31.5 (CH₂), 31.6 (CH₂), 46.7 (2 x C₈), 52.4 (C₆), 52.5 (C₆), 66.3 (2 x C₃), 79.7 (2 x C₂), 125.8 (CH), 127.7 (CH), 127.8 (CH), 128.1 (4 x CH), 133.7 (2 x C₆), 134.1 (C₈), 134.2 (C₈), 157.4 (2 x C₁), 179.6 (2 x C₁); Cl(methane)-MS m/z (%): 422 (MH⁺, 100), 406 ([M-CH₃]⁺, 9), 378 ([M-C₃H₇]⁺, 54), 338 (12), 294 (27), 278 (15), 250 (25), 234 (55),
Experimental

180 (21), 145 (7), 127 (10), 99 (9); HMRS: MH+, found 422.23309. C_{26}H_{32}NO_4 requires 422.23312.

**Isomer B and one cis isomer** (diastereomeric mixture): R_f (P.E. 30-40°C/EtOAc 4:1) 0.46; ^1H NMR (500 MHz, CDCl_3): δ 0.79 (t, ^3J=7.5 Hz, 3H, CH_3B), 0.80-0.86 (m, 12H, 2 x CH_3B and 2 x CH_3c), 0.89-0.95 (m, 9H, 2 x H_5B and CH_3B and 2 x CH_2c), 0.97 (t, ^3J=7.5 Hz, 3H, CH_3B), 1.01 (t, ^3J=7.5 Hz, 3H, CH_3c), 1.10-1.16 (m, 34H, 9 x CH_2B and 9 x CH_2c), 2.17 (tt, ^3J=5.5 Hz, ^3J=8.6 Hz, 1H, H_8B), 2.18 (tt, ^3J=5.5 Hz, ^3J=8.6 Hz, 1H, H_8B), 2.35 (td, ^3J=3.5 Hz, ^3J=8.7 Hz, 2H, H_4c), 2.37-2.43 (m, 2H, H_8c), 2.79 (ddd, ^3J=1.7 Hz, ^3J=5.2 Hz, ^3J=7.9 Hz, 1H, H_4B), 4.23 (td, ^3J=3.5 Hz, ^3J=4.2 Hz, 1H, H_6B), 4.24 (td, ^3J=3.5 Hz, ^3J=4.2 Hz, 1H, H_6B), 4.93 (d, ^3J=7.9 Hz, 2H, H_3B), 4.97 (d, ^3J=7.8 Hz, 2H, H_3B), 5.73 (d, ^3J=7.8 Hz, 2H, H_2c), 5.78 (d, ^3J=7.9 Hz, 1H, H_2c), 5.79 (d, ^3J=7.9 Hz, 1H, H_2c), 6.87-7.13 (m, 40H, 20 x CH_B and 20 x CH_c).

Cis isomer (diastereomeric mixture): R_f (P.E. 30-40°C/EtOAc 4:1) 0.35; ^1H NMR (500 MHz, CDCl_3): δ 11.6, 11.7, 11.8, 12.0, 12.4 (x2), 14.0 (x3), 22.5 (x2), 22.6, 22.7, 25.1, 25.2, 25.3, 25.5, 27.9 (x2), 29.4, 29.5, 29.6, 29.8, 31.0, 31.4, 31.5, 31.6, 31.8, 46.7, 46.8, 47.2 (x2), 50.5, 52.4 (x2), 60.3, 65.5, 66.6, 79.7, 80.0, 125.8, 125.9, 127.5, 127.8, 127.9 (x2), 128.3, 128.4, 133.8, 134.0, 134.6, 157.9, 158.3, 176.5 (x2), 176.7 (x2).

**13C NMR** (125 MHz, CDCl_3): δ 11.6, 11.7, 11.8, 12.0, 12.4 (x2), 14.0 (x3), 22.5 (x2), 22.6, 22.7, 25.1, 25.2, 25.3, 25.5, 27.9 (x2), 29.4, 29.5, 29.6, 29.8, 31.0, 31.4, 31.5, 31.6, 31.8, 46.7, 46.8, 47.2 (x2), 50.5, 52.4 (x2), 60.3, 65.5, 66.6, 79.7, 80.0, 125.8, 125.9, 127.5, 127.8, 127.9 (x2), 128.3, 128.4, 133.8, 134.0, 134.6, 157.9, 158.3, 176.5 (x2), 176.7 (x2).

Cis isomer (diastereomeric mixture): R_f (P.E. 30-40°C/EtOAc 4:1) 0.35; ^1H NMR (500 MHz, CDCl_3): δ 0.76 (ddd, ^3J=4.3 Hz, ^3J=5.3 Hz, ^3J=7.9 Hz, 2H, H_3), 0.88-0.96 (m, 12H, 4 x CH_3), 1.05 (dt, ^3J=7.0 Hz, ^3J=8.0 Hz, 1H, H_2), 1.06 (dt, ^3J=7.0 Hz, ^3J=8.0 Hz, 1H, H_2), 1.24-1.39 (m, 8H, 4 x CH_2), 1.45-1.74 (m, 8H, 4 x CH_2), 2.33 (tt, ^3J=5.6 Hz, ^3J=8.4 Hz, 2H, H_6), 2.78 (td, ^3J=5.4 Hz, ^3J=8.7 Hz, 2H, H_4), 4.37 (ddd, ^3J=4.3 Hz, ^3J=5.4 Hz, ^3J=7.0 Hz, 2H, H_6), 4.83 (d, ^3J=7.8 Hz, 1H, H_5), 4.84 (d, ^3J=7.8 Hz, 1H, H_5), 5.78 (d, ^3J=7.8 Hz, 1H, H_2), 5.79 (d, ^3J=7.8 Hz, 1H, H_2), 6.87-7.11 (m, 20H, H_aom); ^13C NMR (125 MHz, CDCl_3):
Experimental

\[ \delta 11.7 \ (2 \times C_5), \ 11.8 \ (2 \times CH_3), \ 13.9 \ (CH_3), \ 14.0 \ (CH_3), \ 22.6 \ (CH_2), \ 22.7 \ (CH_2), \ 25.1 \ (CH_2), \ 25.3 \ (CH_2), \ 28.4 \ (2 \times C_4), \ 29.5 \ (CH_2), \ 29.6 \ (CH_2), \ 31.3 \ (CH_2), \ 31.6 \ (CH_2), \ 47.0 \ (2 \times C_8), \ 50.6 \ (2 \times C_6), \ 66.4 \ (2 \times C_3), \ 80.0 \ (2 \times C_2), \ 125.9 \ (2 \times CH), \ 127.4 \ (CH), \ 127.9 \ (CH), \ 128.0 \ (CH), \ 128.3 \ (CH), \ 128.4 \ (CH), \ 134.1 \ (2 \times C_4), \ 134.4 \ (2 \times C_4), \ 158.3 \ (2 \times C_1), \ 176.1 \ (C_7), \ 176.2 \ (C_7). \]

(±)-1-(2-Benzylecyclopropyl)-2-pyrrolidinone (±)-123

\[ \begin{align*}
\text{C}_{24}\text{H}_{22}\text{N.HCl} & \quad 363.92 \text{g.mol}^{-1}
\end{align*} \]

A mixture of cyclopropane (±)-114A (100 mg, 0.27 mmol, 1 eq), Pd/C (5%, 35 mg, 12.4 \( \mu \)mol, 0.046 eq), absolute ethanol (2.5 mL), THF (2.5 mL) and a solution of hydrochloric acid (5-6M solution in isopropanol, 5 drops) was hydrogenated at 4 bar for 24 h. The reaction mixture was filtered, concentrated in vacuo and the residue was taken up in a solution of hydrochloric acid (5-6M solution in isopropanol, 3 mL). The solvent was then evaporated in vacuo and the residue triturated in dry diethyl ether (2 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 mL) to give the title compound (±)-123 (63 mg, 0.18 mmol, 67%) as a white solid.

**Mp** 214-217°C; **IR** (CH\(_2\)Cl\(_2\)): \( \nu_{\text{max}} \) 3215 (br, NH), 2960 (m), 1581 (w, C=C), 1456 (m), 1157 (w), 1069 (w), 1039 (w), 771 (w), 746 (m), 737 (m), 698 (s) cm\(^{-1}\); **\(^1\)H NMR** (300 MHz, CDCl\(_3\)): \( \delta \) 0.56-0.64 (m, 1H, H\(_4\)), 1.58-1.71 (m, 2H, H\(_3\) and H\(_4\)), 1.96-2.03 (m, 1H, H\(_3\)), 2.39 (dd, \( ^3J_{6.5}=6.0 \text{ Hz, } ^2J=14.4 \text{ Hz, } 1H, H_6 \)), 2.54 (dd, \( ^3J_{6.5}=6.0 \text{ Hz, } ^2J=14.4 \text{ Hz, } 1H, H_6 \)), 3.38 (t, \( ^3J_{1.2}=12.5 \text{ Hz, } 1H, H_1 \)), 3.90 (dd, \( ^3J_{1.2}=2.5 \text{ Hz, } ^2J=12.5 \text{ Hz, } 1H, H_1 \)), 4.01-4.14 (m, 1H, H\(_2\)) 6.81-6.96 (m, 4H, H\(_{\text{arom}}\)), 7.02-7.37 (m, 11H, H\(_{\text{arom}}\)), 10.23 (br s, 1H, NH\(_3\)), 10.44 (br s, 1H, NH\(_3\)); **\(^13\)C NMR** (75 MHz, CDCl\(_3\)): \( \delta \) 11.0 (C\(_4\)), 17.3 (C\(_5\)), 33.6 (C\(_3\)), 36.4 (CH\(_2\)), 40.4 (CH\(_2\)), 66.5 (C\(_2\)), 126.5 (CH), 126.6 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.4 (CH), 133.9
(±)-tert-Butyl N-(2-cyclohexylcyclopropyl)carbamate (±)-124

\[
\text{C}_{24}\text{H}_{25}\text{N} \text{ requires 327.199253.}
\]

A mixture of cyclopropane (±)-117A (200 mg, 0.55 mmol, 1 eq), Pd(OH)\textsubscript{2}/C (20%, 52 wt. % water, 200 mg, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 6 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 6 h. The reaction mixture was filtered, concentrated \textit{in vacuo} and used in the next step without further purification.

Di-tert-butyl dicarbonate (145 mg, 0.66 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.55 mmol, 1 eq) and triethylamine (0.19 mL, 1.38 mmol, 2.5 eq) in dry dichloromethane (3 mL) under nitrogen. After stirring for 18 h, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5/1.5) to give the protected amine 124 (84 mg, 0.36 mmol, 65% for the 2 steps) as a yellow oil.

\[R_f\ (\text{P.E. 30-40°C/ether 85:15}) \ 0.42; \text{IR (film): } \nu_{\text{max}} \ 3335 \text{ (br, NH), } 2978 \text{ (m), } 2924 \text{ (s), 2851 (w), 1705 (s, C=O), 1514 (m), 1365 (m), 1171 (m) cm}^{-1}; \text{H NMR (500 MHz, 330 K, CDC}13\text{)}: \delta 0.47-0.53 \text{ (m, 2H, H}_2\text{), 0.59-0.68 \text{ (m, 2H, H}_3\text{ and H}_4\text{), 0.95-1.19 \text{ (m, 5H), 1.40 \text{ (s, 9H, C(CH}_3)_3\text{), 1.54-1.71 \text{ (m, 4H), 1.84-1.89 \text{ (m, 1H), 2.23-2.28 \text{ (m, 1H, H}_1\text{), 4.54 \text{ (br s, 1H, NH); C NMR (125 MHz, 330 K, CDC}13\text{): } \delta 12.3 \text{ (C}_2\text{), 26.1 \text{ (CH}_2\text{), 26.2 \text{ (CH}_3\text{), 26.5 \text{ (CH}_2\text{), 27.2 \text{ (C}_3\text{), 28.4 \text{ (C}_1\text{ and C(CH}_3)_3\text{), 32.1 \text{ (CH}_2\text{), 32.7 \text{ (CH}_2\text{), 40.7 \text{ (C}_4\text{, 79.1 (C(CH}_3)_3\text{), 156.4 (C=O); Cl(methane)-MS } m/z (%): 240 (MH}^+\text{, 36), 184 (100),}
\]
Experimental

140 (41), 57 (C₄H₉⁺, 36); **HMRS**: MH⁺, found 240.19634. C₁₄H₂₆NO₂ requires 240.19634.

**(+)-tert-Butyl N-((1S,2R)-2-cyclohexylcyclopropyl)carbamate (+)-124**

\[
\begin{array}{c}
\text{C}_{14}\text{H}_{25}\text{NO}_2 
\end{array}
\]

A mixture of cyclopropane (+)-117A (121 mg, 0.336 mmol, 1 eq), di-tert-butyl dicarbonate (146 mg, 0.672 mmol, 2 eq), Pd(OH)₂/C (20%, 52 wt. % water, 71 mg, 0.051 mmol, 0.15 eq) and THF (8.5 mL) was hydrogenated at 5.5 bar at 30°C for 7 h. The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5:1.5) to give the title compound (+)-124 (76 mg, 0.317 mmol, 95%) as a white solid.

Rᵣ, IR, ¹H and ¹³C NMR, and mass spectra data were identical to the one given for the corresponding racemate (±)-124.

**Mp** 64-67°C; [α]ᵥ +47.0 (c 1.32, CHCl₃); **Anal.** found: C, 70.08; H, 10.61; N, 5.82. Calcd for C₁₄H₂₅NO₂: C, 70.25; H, 10.53; N, 5.83.

**(-)-tert-Butyl N-((1S,2R)-2-cyclohexylcyclopropyl)carbamate (-)-124**

\[
\begin{array}{c}
\text{C}_{14}\text{H}_{25}\text{NO}_2 
\end{array}
\]

A mixture of cyclopropane (-)-117A (122 mg, 0.337 mmol, 1 eq), di-tert-butyl dicarbonate (147 mg, 0.675 mmol, 2 eq), Pd(OH)₂/C (20%, 52 wt. % water, 71 mg,
0.051 mmol, 0.15 eq) and THF (8.5 mL) was hydrogenated at 5.5 bar at 30°C for 8 h. The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 8.5:1.5) to give the title compound (−)-124 (75 mg, 0.313 mmol, 93%) as a white solid.

Rf, IR, \( ^1 \text{H} \) and \(^{13} \text{C} \) NMR, and mass spectra data were identical to the one given for the corresponding racemate (±)-124.

\textbf{Mp} 65-67°C; \([\alpha]_D^-47.7 \ (c \ 1.32, \text{CHCl}_3)\); \textbf{Anal.} found: C, 70.39; H, 10.74; N, 5.82. Calcd for C\(_{14}\)H\(_{25}\)NO\(_2\): C, 70.25; H, 10.53; N, 5.83.

\textit{tert-Butyl N-(bicyclo[4.1.0]hept-7-yl)carbamate 125}

A mixture of cyclopropane (±)-118A (0.2 g, 0.60 mmol, 1 eq), Pd(OH)\(_2\)/C (20%, 52 wt. % water, 0.2 g, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 9 hours, left for 18 hours under nitrogen and then hydrogenated at 4 bar hydrogen for a further 9 hours. The reaction mixture was filtered, concentrated in vacuo and used in the next step without further purification.

Di-\textit{tert}-butyl dicarbonate (157 mg, 0.72 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.6 mmol, 1 eq) and distilled triethylamine (0.17 mL, 1.2 mmol, 2 eq) in dry dichloromethane (2.4 mL) under nitrogen. After stirring for 18 hours, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 8.5:1.5 to 4:1) to give the protected amine 125 (74 mg, 0.35 mmol, 58% for the 2 steps) as a white solid.
Alternatively, a mixture of cyclopropane (+)-118A (100 mg, 0.3 mmol, 1 eq), di-tert-butyl dicarbonate (131 mg, 0.6 mmol, 2 eq), Pd(OH)$_2$/C (20%, 52 wt. % water, 86 mg, 0.06 mmol, 0.2 eq) and THF (10 mL) was hydrogenated at 5.5 bar at 35°C for 8 h. The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 4:1) to give the title compound 125 (60 mg, 0.284 mmol, 95%) as a white solid.

Mp 103-104°C (hexane); $R_f$ (P.E. 30-40°C/ether 85:15) 0.38; IR (CDCl$_3$): $\nu_{\text{max}}$ 3340 (br, NH), 2925 (m), 2852 (w), 1682 (s, C=O), 1518 (m), 1366 (m), 1251 (m), 1170 (m), 1143 (m); 1058 (w) cm$^{-1}$; $^1$H NMR (500 MHz, 330 K, CDCl$_3$): $\delta$ 0.93-0.96 (m, 2 x CH), 1.04-1.13 (m, 2H), 1.17-1.25 (m, 2H), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.64-1.71 (m, 2H), 1.80-1.88 (m, 2H), 2.16-2.19 (m, 1H, CHNH), 4.53 (br s, 1H, NH); $^{13}$C NMR (125 MHz, 330K, CDCl$_3$): $\delta$ 19.4 (2 x CH), 21.5 (2 x CH$_2$), 22.5 (2 x CH$_2$), 28.5 (C(CH$_3$)$_3$), 34.8 (CHNH), 79.1 (C(CH$_3$)$_3$), 156.6 (C=O); CI(methane)-MS m/z (%): 212 (MH$^+$, 92), 184 (18), 156 (94), 138 (15), 112 (92, 110 ([M-Boc]$^+$, 90), 74 (47), 57 (C$_4$H$_9^+$, 100); HMRS: MH$^+$, found 212.16589. C$_{12}$H$_{22}$NO$_2$ requires 212.16505; Anal. found: C, 68.28; H, 10.21; N, 6.66. Calcd for C$_{12}$H$_{21}$NO$_2$: C, 68.21; H, 10.02; N, 6.63.

(±)-tert-Butyl N-[2-(trimethylsilanyl)-cyclopropyl]carbamate (±)-126

A mixture of cyclopropane (±)-120A (200 mg, 0.57 mmol, 1 eq), Pd(OH)$_2$/C (20%, 52 wt. % water, 200 mg, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 9 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 7 h. The reaction mixture was filtered, concentrated in vacuo and used in the next step without further purification.

Di-tert-butyl dicarbonate (145 mg, 0.66 mmol, 1.2 eq) was added portionwise to a solution of crude amine (maximum 0.57 mmol, 1 eq) and triethylamine (0.19 mL, 1.38 mmol, 2.5 eq) in dry dichloromethane (4 mL) under nitrogen. After stirring for 18 h,
dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5/1.5) to give the protected amine (±)-126 (28 mg, 0.12 mmol, 21% for the 2 steps) as an amorphous solid.

\[ R_f \text{(P.E. 30-40°C/ether 9:1)} \ 0.35; \ \text{IR (film): } \nu_{\text{max}} 3348 \text{ (br, NH), 3295 (m), 1701 (s, C=O), 1406 (w), 1366 (m), 1249 (s), 1172 (s), 1096 (m), 1077 (m), 836 (s, Si-C) cm}^{-1}; \ 
\text{^1H NMR (400 MHz, 328 K, CDCl}_3): \ \delta \ -0.27 \ \text{(ddd, } J_{3,1} = 5.0 \text{ Hz, } J_{3,2a} = 8.0 \text{ Hz, } J_{2a,3} = 11.2 \text{ Hz, 1H, H}_6), -0.05 \ \text{(s, 9H, Si(CH}_3)_3), \ 0.56 \ \text{(ddd, } J_{2p,2a} = 4.6 \text{ Hz, } J_{2a,1} = 6.5 \text{ Hz, } J_{2a,3} = 8.0 \text{ Hz, 1H, H}_{-2p}), \ 0.67 \ \text{(ddd, } J_{2a,1} = 3.4 \text{ Hz, } J_{2a,2p} = 4.6 \text{ Hz, } J_{2a,3} = 11.2 \text{ Hz, 1H, H}_{2a}), \ 1.42 \ \text{(s, 9H, C(CH}_3)_3), \ 2.42-2.48 \ \text{(m, 1H, H}_1), \ 4.62 \ \text{(br s, 1H, NH); } \text{^13C NMR (100 MHz, 328 K, CDCl}_3): \ \delta \ -2.4 \ \text{(Si(CH}_3)_3), \ 7.0 \ \text{(C}_3), \ 10.6 \ \text{(C}_2), \ 27.3 \ \text{(C}_1), \ 28.5 \ \text{(C(CH}_3)_3), \ 79.2 \ \text{(C(CH}_3)_3), \ 156.5 \ \text{(C=O); Positive electrospray-MS m/z (%): } 252 \ \text{(MNa}^+, \ 100), \ 217 \ (6); \ \text{HMRS: MNa}^+, \ \text{found 252.13933. } C_{11}H_{23}NNaO_2Si \ \text{requires 252.13903.}

(±)-2-Ethylhexyl-[2-(tert-butoxycarbonylamino)-cyclopropyl] carboxylate (±)-127

![Diagram of the molecule](image)

\[ C_{18}H_{29}NO_4 \ \text{299.41 g.mol}^{-1} \]

A mixture of cyclopropane (±)-122A (19 mg, 0.45 mmol, 1 eq), Pd(OH)_2/C (20%, 52 wt. % water, 190 mg, 0.135 mmol, 0.3 eq), glacial acetic acid (5 mL) and (5 mL) was hydrogenated at 4 bar for 6.5 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 5 h. The reaction mixture was filtered, concentrated \textit{in vacuo} and used in the next step without further purification.

Di-tert-butyl dicarbonate (118 mg, 0.54 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.45 mmol, 1 eq) and triethylamine (0.13 mL, 0.9 mmol, 2 eq)
in dry dichloromethane (3 mL) under nitrogen. After stirring for 16 h, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified twice by flash column chromatography (silica, P.E. 30-40°C/EtOAc 9:1 then DCM/EtOAc 9.5:0.5 to 9:1) to give a diastereomeric mixture of the protected amine (±)-127 contaminated by a small amount of an unidentified by-product (20 mg, 0.067 mmol, 15%) as an amorphous solid.

**Rf** (P.E. 30-40°C/ether 4:1) 0.22; **IR** (film): ν max 3371 (br, NH), 2962 (s), 2933 (s), 2862 (m), 1741 (s, C=O), 1711 (s, C=O), 1518 (w), 1460 (m), 1367 (m), 1125 (m), 1167 (s) cm⁻¹; **¹H NMR** (diastereomeric mixture, 500 MHz, 330 K, CDCl₃): δ 0.83-0.90 (m, 12H, 4 x CH₃), 1.03 (dt, 2 J₅₋₆=5.0 Hz, 2 J₅₋₅=7.4 Hz, 3 J₆₋₅=7.4 Hz, 2H, H₅₉), 1.11 (ddd, 3 J₅₋₆=4.1 Hz, 2 J₅₋₅=7.3 Hz, 3 J₅₋₄=8.5 Hz, 2H, H₅₄), 1.18-1.35 (m, 8H), 1.40-1.69 (m, 8H), 1.43 (s, 18H, H₁), 2.20 (tt, 3 J=5.5 Hz, 3 J=8.5 Hz, 2H, H₅₃), 2.69 (ddd, 3 J₄₋₅=1.8 Hz, 3 J₄₋₅=5.0 Hz, 3 J₄₋₅=8.5 Hz, 2H, H₄), 4.03 (ddd, 3 J₆₋₅=1.8 Hz, 3 J₆₋₅=5.0 Hz, 3 J₆₋₅=8.5 Hz, 2H, H₆), 4.04 (ddd, 3 J₆₋₅=1.8 Hz, 3 J₆₋₅=4.1 Hz, 3 J₆₋₅=7.5 Hz, 1H, H₆), 4.75 (br s, 2H, NH); **¹³C NMR** (diastereomeric mixture, 125 MHz, 330 K, CDCl₃): δ 11.6 (2 x CH₃), 11.7 (CH₃), 13.8 (CH₃), 15.1 (C₅), 15.2 (C₅), 22.5 (CH₂), 22.6 (2 x CH₂), 25.2 (CH₂), 25.3 (2 x CH₂), 28.4 (C₁), 29.3 (C₄), 29.5 (CH₂), 29.6 (CH₂), 31.5 (2 x CH₂), 47.0 (2 x C₈), 53.8 (2 x C₆), 80.0 (C₂), 156.1 (2 x C₃), 176.6 (C₇), 176.7 (C₇); **Cl(methane)-MS** m/z (%): 300 (MH⁺, 15), 272 ([M-C₂H₅]⁺, 4), 244 ([M+H-C₆H₅]⁺, 4), 200 ([M-Boc]⁺, 7), 145 (16), 127 (39), 99 (16), 72 (23); **HMRS**: MH⁺, found 300.21748. C₁₆H₂₇NO₄ requires 300.21747.
Experimental

(±)-2-Cyclohexylcyclopropylamine hydrochloride (±)-128

Protected amine (±)-124 (38 mg, 0.18 mol) in a solution of hydrochloric acid (5-6M solution in isopropanol, 2 mL) was stirred for 10 min. The solvent was removed in vacuo and the residue triturated in dry diethyl ether (5 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 x 4 mL) and dried in vacuo to give the title compound (±)-128 (19.5 mg, 0.13 mmol, 74%) as a white solid.

Mp 182-184°C; IR (CH₂Cl₂): \( \nu_{\text{max}} \) 2922 (s), 1620 (w), 1520 (w), 1446 (w), 1020 (w) cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO): \( \delta \) 0.53 (td, \( ^3J_{2\beta-3} = ^2J_{2\beta-2a} = 5.9 \) Hz, \( ^3J_{2\beta-1} = 7.6 \) Hz, 1H, H₂β), 0.58-0.68 (m, 1H, H₄), 0.81 (ddd, \( ^3J_{2\alpha-1} = 3.8 \) Hz, \( ^2J_{2\alpha-2\beta} = 5.7 \) Hz, \( ^3J_{2\alpha-3} = 9.4 \), 1H, H₂α), 0.95 (ddddd, \( ^3J_{3-1} = 3.4 \) Hz, \( ^3J_{3-2\beta} = 6.1 \) Hz, \( ^3J_{3-2a} = 9.4 \) Hz, \( ^3J_{3,4} = 12.8 \) Hz, 1H, H₃), 0.95-1.20 (m, 5H), 1.50-1.72 (m, 4H), 1.75-1.79 (m, 1H), 2.27 (td, \( ^3J_{1-3} = ^3J_{1-2a} = 3.7 \) Hz, \( ^3J_{1-2\beta} = 7.5 \) Hz, 1H, H₁), 8.37 (br s, 3H, NH₃⁺); \(^13\)C NMR (125 MHz, DMSO): \( \delta \) 8.7 (C₂), 23.0 (C₃), 25.5 (2 x CH₂), 25.8 (CH₂), 26.6 (C₁), 31.5 (CH₂), 32.1 (CH₂), 39.4 (C₄); EI-MS m/z (%): 139 ([M+H-HCl]⁺, 2), 110 (4), 96 (5), 82 (7), 67 (5), 56 ([M-HCl-C₆H₁₁]⁺, 100); HMRS: (M+H-HCl)⁺, found 140.14343. C₉H₁₇N requires 140.14338.
Experimental

(±)-Bicyclo[4.1.0]hept-7-ylamine hydrochloride 129

\[
\begin{align*}
\text{C}_7\text{H}_{13}\text{N.HCl} & \quad 147.65 \text{ g.mol}^{-1} \\
\end{align*}
\]

Protected amine 125 (38 mg, 0.18 mol) in a solution of hydrochloric acid (5-6M solution in isopropanol, 2 mL) was heated with a heat gun for a few seconds in order to dissolve all organic material and then stirred for 10 min. The solvent was removed \textit{in vacuo} and the residue triturated in dry diethyl ether (2 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 x 4 mL) and dried \textit{in vacuo} to give the \textit{title compound} 129 (19.5 mg, 0.13 mmol, 74%) as a colourless solid.

\textbf{Mp} (decomposition) 225-227°C (lit., 136 224-225°C (decomposition)); \textbf{IR} (CH\textsubscript{2}Cl\textsubscript{2}): \nu\textsubscript{max} 3430 (br, NH), 2922 (w), 2855 (w), 1590 (w), 1496 (w), 1160 (w), 1124 (w) cm\textsuperscript{-1}; \textbf{\textsuperscript{1}H} NMR (500 MHz, DMSO): \delta 1.03-1.20 (m, 4H), 1.21-1.28 (m, 2H), 1.52-1.60 (m, 2H), 1.75-1.84 (m, 2H), 2.23 (br s, 1H, CH\textsubscript{2}NH\textsubscript{3}\textsuperscript{+}), 8.23 (br s, 3H, NH\textsubscript{3}\textsuperscript{+}); \textbf{\textsuperscript{13}C} NMR (75 MHz, DMSO): \delta 15.7 (CH), 21.4 (2 x CH\textsubscript{2}), 22.0 (2 x CH\textsubscript{2}), 32.9 (CH\textsubscript{2}NH\textsubscript{3}\textsuperscript{+}); \textbf{EI-MS m/z} (%): 111 ([M-HCl]\textsuperscript{+}, 28), 94 (17), 82 (100) 69 (16); \textbf{HMRS}: (M-HCl)\textsuperscript{+}, found 111.10458. 
\textbf{C}_7\textbf{H}_{13}\textbf{N} requires 111.104795.

tert-Butyl \textit{N}-(3-phenylpropyl)carbamate 130 and (±)-\textit{tert}-butyl \textit{N}-(1-methyl-2-phenylethyl)carbamate 131

\[
\text{C}_{14}\text{H}_{21}\text{NO}_2 \quad 235.32 \text{ g.mol}^{-1}
\]

A mixture of cyclopropane (±)-119A (136 mg, 0.38 mmol, 1 eq), Pd(OH)\textsubscript{2}/C (20%, 52 wt. % water, 136 mg, 0.097 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL)
was hydrogenated at 3.5 bar for 7 h, left for 18 h under nitrogen and then hydrogenated at 3.5 bar for a further 8 h. The reaction mixture was filtered, concentrated in vacuo and used in the next step without further purification.

Di-tert-butyl dicarbonate (100 mg, 0.46 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.38 mmol, 1 eq) and triethylamine (0.11 mL, 0.76 mmol, 2.5 eq) in dry dichloromethane (2 mL) under nitrogen. After stirring for 18 h, dichloromethane (6 mL) and brine (4 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (6 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 8.5/1.5) to give a mixture of the title compounds 130 and 131 (59 mg, 0.26 mmol, 66% for the 2 steps, 130X:131Y: 3:2 as determined by ¹H NMR) as a white solid.

¹H NMR (mixture of isomer X and Y, 500 MHz, CDCl₃): δ 1.08 (d, ³J=6.7 Hz, 3H, CH₃Y), 1.42 (s, 9H, C(CH₃)₃Y), 1.44 (s, 9H, C(CH₃)₃X), 1.81 (qn, ³J=7.4 Hz, 2H, CH₂CH₂CH₂), 2.62-2.68 (m, 3H, CHH₂Y and CH₂X), 2.84 (dd, ³J=5.2 Hz, ²J=13.3 Hz, 1H, CHH₂Y), 3.15 (q, ³J=6.5 Hz, 2H, CH₂X), 3.91 (br s, 1H, CH₂N), 4.39 (br s, 1H, NHY), 4.54 (br s, 1H, NHX), 7.15-7.31 (m, 10H, Hₐrom); ¹³C NMR (mixture of isomer X and Y, 125 MHz, CDCl₃): δ 20.3 (CH₃Y), 28.5 (C(CH₃)₃X and C(CH₃)₃Y), 31.7 (CH₂X), 33.1 (CH₂X), 40.2 (CH₂X), 43.0 (CH₂Y), 47.4 (CH₂), 79.1 (C(CH₃)₃X and C(CH₃)₃Y), 125.9 (CH), 126.3 (CH), 128.3 (CH), 128.4 (CH), 129.5 (CH), 138.2 (C₉X), 141.5 (C₉Y), 155.2 (C=O), 155.9 (C=O).
Methyl (R)-2-(tert-butoxycarbonyl)amino-2-(4-methoxyphenyl)acetate 133

\[
\begin{align*}
\text{MeO} & \\
\text{O} & \\
\text{NHBOc} & \\
\text{C}_{15}H_{21}NO_5 & 295.34 \text{ g mol}^{-1}
\end{align*}
\]

(R)-2-tert-butoxycarbonylamino-2-(4-hydroxyphenyl)acetic acid 132

D-4-hydroxyphenylglycine (10.03 g, 60 mmol, 1 eq) and di-tert-butyl dicarbonate (18.33 g, 84 mmol, 1.4 eq) was added to a mixture of sodium hydroxide (1M solution in water, 60 mL, 60.0 mmol, 1 eq) and dioxane (60 mL). The reaction mixture was stirred for 4 h and then dioxane was removed in vacuo. Diethyl ether (50 mL) was added and the mixture was transferred into a separating funnel. The aqueous layer was separated and acidified to pH 2-3 with solid KHSO\textsubscript{4}. The mixture was then extracted with EtOAc (3 x 60 mL) and the combined organic extracts were washed with brine (60 mL), dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo to give 132 (15.13 g, 56.6 mmol, 94%) as a yellow oil which was used without further purification.

\(^1\text{H NMR}\) (300 MHz, DMSO): \(\delta \) 1.36 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 3.33 (br s, 1H, OH), 4.93 (d, \(J=8.2\) Hz, 1H, CH), 6.69 (d, \(J=8.6\) Hz, 2H, H\text{arom}), 7.15 (d, \(J=8.6\) Hz, 2H, H\text{arom}), 7.38 (d, \(J=8.2\) Hz, 1H, NH), 9.42 (br s, 1H, OH); \(^{13}\text{C NMR}\) (75 MHz, DMSO): \(\delta \) 28.1 (C(CH\textsubscript{3})\textsubscript{3}), 57.0 (CH), 78.1 (C(CH\textsubscript{3})\textsubscript{3}), 115.0 (CH), 127.5 (CH), 128.8 (CH), 155.0 (C=O), 159.9 (C=O).

Methyl (R)-2-(tert-butoxycarbonyl)amino-2-(4-methoxyphenyl)acetate

Anhydrous potassium carbonate (3.1 g, 22.45 mmol, 3 eq) and dimethyl sulfate (1.77 mL, 18.7 mmol, 2.5 eq) was added successively to a solution of crude glycine derivative 132 (2.0 g, 7.48 mmol, 1 eq) in acetone (50 mL) under nitrogen. The reaction mixture was heated at reflux for 4 h and then allowed to cool to room temperature, filtered and concentrated in vacuo. The residue was taken up in EtOAc (150 mL) and the organic extract was then washed with an aqueous NaHCO\textsubscript{3} solution (5%, 50 mL) and brine (50
mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1) to give the title compound 133 (1.95 g, 6.6 mmol, 88%) as a white solid.

Mp 82-83°C (lit.,¹³⁷ 66-67°C); Rf (P.E. 40-60°C/EtOAc 3:1) 0.35; [α]ᵦ²⁰ -145.6 (c 1.14, CHCl₃) (lit.,¹³⁷ [α]ᵦ²⁰ -95.3 (c 1.2, CHCl₃)); IR (CH₂Cl₂): νmax 3365 (br, NH), 2955 (m), 1746 (s, C=O), 1714 (s, C=O), 1611 (w, C=C), 1514 (s), 1367 (w), 1249 (m), 1166 (s), 1055 (m), 1031 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.42 (s, 9H, C(CH₃)₃), 3.71 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 5.22-5.27 (m, 1H, CH), 5.48 (br s, 1H, NH), 6.87 (d, 3J=8.6 Hz, 2H, Harm), 7.27 (d, 3J=8.6 Hz, 2H, Harm); ¹³C NMR (75 MHz, CDCl₃): δ 28.3 (C(CH₃)₃), 52.6, 55.3, 57.0, 80.1 (C(CH₃)₃), 114.3 (CH), 128.4 (CH), 129.0 (CH), 154.8 (Cq), 159.7 (Cq), 171.9 (C=O); CI(methane)-MS m/z (%): 296 (MH⁺, 21), 240 (52), 207 (53), 180 (100), 136 (94), 121 (22); HMRS: MH⁺, found 296.14985. C₁₅H₂₂NO₅ requires 296.14979.

(R)-2-(tert-butoxycarbonyl)amino-2-(4(methoxyphenyl)ethanol 134

Anhydrous lithium chloride (1.15 g, 27.09 mmol, 4 eq) and sodium borohydride (1.02 g, 27.09 mmol, 4 eq) was added successively to a solution of ester 133 (2.0 g, 6.77 mmol, 1 eq) in dry THF (30 mL) under nitrogen. The reaction mixture was stirred for 4 h and then cooled to 4°C prior the addition of saturated NH₄Cl solution (10 mL). The mixture was stirred for 30 min and the precipate filtered and washed with EtOAc (20 mL). The organic layer was separated and washed with brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo to give the title compound 134 (1.55 g, 5.8 mmol, 86%) as a white solid.
Mp 141-142°C (EtOAc) (lit., 138 130-132°C (EtOH/EtOAc); R$_f$ (P.E. 40-60°C/EtOAc 1:1) 0.31; $[\alpha]_D^{20}$ -38.3 (c 0.6, CHCl$_3$) (lit., 138 $[\alpha]_D^{20}$ -38.1 (c 1.31, CHCl$_3$); IR (CH$_2$Cl$_2$):

$\nu_{\text{max}}$ 3372 (br, NH), 2998 (m), 1682 (s, C=O), 1514 (s), 1446 (w), 1245 (m), 1171 (m), 1053 (m), 1031 (m), 739 (m) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.38 (s, 9H, C(CH$_3$)$_3$), 1.91 (br s, 1H, OH), 3.78 (s, 3H, OCH$_3$), 3.79-3.81 (m, 2H, CH$_2$OH), 4.67-4.72 (m, 1H, CHN), 5.04 (br s, 1H, NH), 6.86-6.89 (m, 2H, H$_{\text{arom}}$), 7.18-7.22 (m, 2H, H$_{\text{arom}}$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 28.4 (C(CH$_3$)$_3$), 55.3, 56.6, 66.9 (CH$_2$), 79.9 (C(CH$_3$)$_3$), 114.4 (CH), 127.8 (CH), 131.8 (CH), 156.1 (C$_q$), 159.4 (C$_q$); Cl(methane)-MS m/z (%): 268 (MH$^+$, 41), 194 (99), 151 (100), 104 (62); HMRS: MH$^+$, found 268.15511 Ci$_{14}$H$_{22}$NO$_4$ requires 268.15488; Anal. found: C, 62.75; H, 7.95; N, 5.27. Calcd for Ci$_{14}$H$_{22}$NO$_4$: C, 62.90; H, 7.92; N, 5.24.

(R)-4-(4-methoxyphenyl)-2-oxazolidinone 135

Thionyl chloride (0.92 mL, 12.57 mmol, 8 eq) was added dropwise to a solution of alcohol 134 (0.42 g, 1.57 mmol, 1 eq) in dry THF (10.5 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 10 min at 4 °C and then allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then concentrated in vacuum and the crude product purified by flash column chromatography (silica, EtOAc/ P.E. 30-40°C 7:3 to 4:1) to give the title compound 135 (0.27 g, 1.4 mmol, 90%) as a white solid.

Mp 149-151°C; R$_f$ (EtOAc/P.E. 40-60°C 4:1) 0.44; $[\alpha]_D^{20}$ -34.0 (c 0.5, CHCl$_3$); IR (CH$_2$Cl$_2$): $\nu_{\text{max}}$ 3372 (br, NH), 1684 (s, C=O), 1517 (m), 1367 (w), 1245 (m), 1172 (m), 1053 (m), 1032 (m), 668 (s) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.81 (s, 3H, OCH$_3$), 4.16 (dd, $^3$$J$=7.0 Hz, $^2$$J$=8.5 Hz, 1H, CHHO), 4.70 (t, $^3$$J$=$^2$$J$=8.5 Hz, 1H, CHHO), 4.91
Experimental

(dd, $^3J=7.2$ Hz, $^2J=8.5$ Hz, 1H, CHN), 5.46 (br s, 1H, NH), 6.89-6.95 (m, 2H, $H_{arom}$), 7.24-7.30 (m, 2H, $H_{arom}$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 55.4 (CH$_3$), 56.0 (CH), 72.7 (CH$_2$), 114.5 (CH), 127.4 (CH), 131.2 (CH), 159.3 (C$_O$), 160.0 (C$_O$); EI-MS m/z (%): 193 (M$^+$, 49), 163 (22), 135 (100), 121 (18), 77 (15); HMRS: M$^+$, found 193.07398. C$_{10}$H$_{11}$NO$_3$ requires 193.07389; Anal. found: C, 62.06; H, 5.84; N, 7.16. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 62.17; H, 5.74; N, 7.25.

(R)-3-Diethoxymethyl-4-(4-methoxyphenyl)-2-oxazolidinone 136

\[\text{C}_{13}\text{H}_{21}\text{NO}_3\] 295.33 g.mol$^{-1}$

A mixture of oxazolidinone 135 (180 mg, 0.93 mmol, 1 eq), aluminium chloride (18.6 mg, 0.14 mmol, 0.15 eq) and triethyl orthoformate (4.6 mL, 27.9 mmol, 30 eq) was heated at 150°C for 36 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO$_3$ solution (10 mL). The aqueous phase was extracted with diethyl ether (20 mL then 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 7:3 to 6.5:3.5) to give the title compound 136 (73 mg, 0.25 mmol, 26%) as a colourless oil.

$R_f$ (P.E. 40-60°C/EtOAc 6.5:3.5) 0.41; $[\alpha]_{D}^{20}$ -57.6 (c 0.92, CH$_2$Cl$_2$); IR (film): $\nu_{max}$ 2978 (m), 2935 (w), 2910 (w), 1757 (s, C=O), 1662 (m, C=C), 1516 (m), 1436 (m), 1381 (m), 1248 (m), 1067 (m), 1036 (m), 833 (w), 704 (w) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO): $\delta$ 0.68 (t, $^3J=7.1$ Hz, 3H, CH$_3$CH$_2$), 1.14 (t, $^3J=7.0$ Hz, 3H, CH$_3$CH$_2$), 3.19 (qd, $^3J=6.5$ Hz, $^2J=8.8$ Hz, 1H, $H_{CH3}$), 3.27-3.34 (m, 1H, CHH$_2$), 3.48-3.59 (m, 2H, CH$_2$CH$_3$), 3.72 (s, 3H, OCH$_3$), 4.63 (dd, $^3J=6.5$ Hz, $^2J=8.8$ Hz, 1H, CH$_2$O), 4.63 (t, $^3J=2J=8.8$ Hz, 1H, CH$_2$O), 4.95 (dd, $^3J=6.5$ Hz, $^3J=8.8$ Hz, CH$_2$CH$_3$), 5.61 (s, 1H, OCHO), 6.89 (d, $^3J=8.4$ Hz, 2H, $H_{arom}$), 7.27 (d, $^3J=8.4$ Hz, 2H, $H_{arom}$); $^{13}$C NMR (125 MHz, DMSO):
Experimental

δ 14.0 (CH₂CH₃), 14.7 (CH₂CH₃), 54.6 (CH₂CH₂N), 55.1 (OCH₃), 61.1 (CH₂CH₃), 61.9 (CH₂CH₃), 70.5 (CHCH₂O), 102.1 (OCHO), 113.6 (CH), 128.4 (CH), 132.0 (C₂), 157.2 (C₄), 158.9 (C₆); EI-MS m/z (%): 295 (M⁺, 59), 250 ([M-C₂H₅O]⁺, 100), 194 (22), 162 (37), 134 (78), 103 (89), 75 (94); HMRS: M⁺, found 295.14199. C₁₅H₂₁NO₅ requires 295.14197.

(±)-2-(2-Cyclohexylcyclopropylamino)-1,2-diphenylethanol (±)-137

\[
\begin{align*}
\text{C}_{23}\text{H}_{29}\text{NO} & \quad 335.49 \text{g.mol}^{-1}
\end{align*}
\]

Lithium hydroxide monohydrate (0.745 g, 17.7 mmol, 30 eq) was added in one portion to a suspension of cyclopropane (±)-117 (0.214 g, 0.59 mmol, 1 eq) in a mixture of absolute ethanol (8 mL) and water (3.5 mL). The reaction mixture was heated at reflux for 48 h and then allowed to cool to room temperature. Most of the ethanol was removed in vacuo and saturated aqueous NH₄Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were then dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 7:3) to give the amino alcohol (±)-137 (0.155 g, 0.44 mmol, 74%) as a white solid.

Mp 90-92°C; Rf (P.E. 30-40°C/EtOAc 7:3) 0.3; IR (CDCl₃): ν max 3380 (br), 3028 (w), 2922 (s), 2850 (m), 1495 (m), 1450 (m), 1100 (w), 1053 (w), 1028 (w), 910 (w), 734 (m), 702 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.23-0.30 (m, 1H, H₄), 0.34-0.42 (m, 1H, H₅), 0.50-0.58 (m, 2H, H₄ and H₅), 0.96-1.18 (m, 5H), 1.57-1.72 (m, 5H), 1.79 (td, 3J₃₄=3J₃₅=3.2 Hz, 3J₃₄=6.9 Hz, 1H, H₅), 2.07 (br s, 1H), 3.62 (br s, 1H), 4.04 (d, 3J₂₁=4.7 Hz, 1H, H₄), 4.91 (d, 3J₁₂=4.7 Hz, 1H, H₁), 6.91-6.95 (m, 2H, H₉₂), 6.98-7.01 (m, 2H, H₉₉), 7.14-7.24 (m, 6H, H₉₉); ¹³C NMR (125 MHz, CDCl₃): δ 12.5 (C₄), 26.1 (CH₃), 26.4 (CH₂), 27.7 (C₃), 32.4 (CH₂), 32.8 (CH₂), 34.3 (C₃), 40.8 (C₆), 68.6 (C₂), 75.2 (C₁), 126.5 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.8
Experimental

(CH), 127.9 (CH), 139.3 (C₆), 140.3 (C₆); EI-MS m/z (%): 336 (MH⁺, 100); HMRS: MH⁺, found 336.23246. C₂₃H₃₀NO requires 336.23219.

2-(Bicyclo[4.1.0]hept-7-ylamino)-1,2-diphenylethanol 138

\[
\text{C}_2\text{H}_{25}\text{NO} \quad 307.44 \text{ g.mol}^{-1}
\]

Lithium hydroxide monohydrate (0.566 g, 13.5 mmol, 30 eq) was added in one portion to a suspension of cyclopropane 118 (0.15 g, 0.45 mmol, 1 eq) in a mixture of absolute ethanol (7 mL) and water (3 mL). The reaction mixture was heated at reflux for 24 h and then allowed to cool to room temperature. Most of the ethanol was removed in vacuo and saturated aqueous NH₄Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were then dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, DCM/MeOH 96:4) to give the amino alcohol 138 (0.116 g, 0.38 mmol, 84%) as a white solid.

\[\text{M} \quad 154-156^\circ\text{C}; \quad \text{R}_f (\text{P.E.} 30-40^\circ\text{C/EtOAc 1:1}) 0.4; \quad \text{IR} (\text{CDCl₃}): \nu_{\text{max}} 3427 (\text{br}), 2987 (m), 2926 (w), 1660 (m), 1541 (w), 735 (m), 702 (s) \text{ cm}^{-1}; \quad \text{H NMR (500 MHz, CDCl₃)}: \delta 0.81-0.87 (m, 2H, H₄), 0.88-0.99 (m, 2H), 1.03-1.07 (m, 2H), 1.36-1.49 (m, 2H), 1.64-1.72 (m, 1H), 1.67 (t, 3J₃,₄=3.4 Hz, 1H, H₃), 1.76-1.83 (m, 1H), 3.97 (d, 3J₂,₁=5.4 Hz, 1H, H₂), 4.89 (d, 3J₁,₂=5.4 Hz, 1H, H₁), 6.99-7.02 (m, 2H, H₆), 7.03-7.06 (m, 2H, H₆), 7.16-7.23 (m, 6H, H₆); \quad \text{C NMR (125 MHz, CDCl₃)}: \delta 18.9 (C₄), 19.0 (C₄), 21.5 (CH₂), 21.6 (CH₂), 22.6 (CH₂), 22.8 (CH₂), 41.1 (C₃), 69.1 (C₂), 75.3 (C₁), 125.9 (CH), 126.6 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 139.4 (C₆), 140.4 (C₆); \quad \text{EI-MS m/z (%):} 307 (M⁺, 3), 200 (100), 149 (15), 117 (12), 106 (52), 91 (100), 77 (37), 67 (21), 55 (16); \quad \text{HMRS:} \quad \text{M}⁺, \quad \text{found} \quad 307.19268. \quad \text{C}_{23}\text{H}_{30}\text{NO requires 307.19307.} \]
Experimental

2-Cyclohexylamino-1,2-diphenylethanol 139

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NH} & \quad \text{OH} \\
\text{C}_{20}\text{H}_{26}\text{NO} & \quad 295.42 \text{ g.mol}^{-1}
\end{align*}
\]

A mixture of trans-stilbene oxide (1.42 g, 7.23 mmol, 1 eq) and cyclohexylamine (4.15 mL, 36.15 mmol, 5 eq) in methanol (15 mL) was heated at reflux for 60 h. The reaction mixture was cooled to room temperature and then concentrated in vacuo. The residue was triturated in hexane and the resulting precipitate was filtered and then with hexane (2 x 10 mL) to give the title compound 139 (1.96 g, 6.66 mmol, 92%) as a white solid.

Mp 164-166°C (lit. 139 163-164°C (EtOH)); \textbf{R}_f (\text{EtOAc}) 0.5; \textbf{IR} (\text{CH}_2\text{Cl}_2): \nu_{\text{max}} 3390 (br), 3290 (br), 2920 (w), 2852 (w), 1653 (m), 1055 (s), 730 (m) cm\(^{-1}\); \textbf{^1H NMR} (300 MHz, CDCl\(_3\)): \(\delta 0.92-1.22\) (m, 5H), 1.42-1.79 (m, 4H), 1.82-1.99 (m, 1H), 2.27-2.41 (m, 1H), 3.40 (br s, 1H), 4.13 (d, J=5.2 Hz, 1H, PhCH\(_2\)NH), 4.80 (d, J=5.2 Hz, 1H, PhCHOH), 6.95-7.12 (m, 4H, H\(_{\text{arom}}\)), 7.13-7.41 (m, 6H, H\(_{\text{arom}}\)); \textbf{^13C NMR} (75 MHz, CDCl\(_3\)): \(\delta 24.6\) (CH\(_2\)), 25.0 (CH\(_2\)), 26.0 (CH\(_2\)), 33.0 (CH\(_2\)), 34.5 (CH\(_2\)), 53.2 (CH), 65.0 (PhCH\(_2\)NH), 76.1 (PhCHOH), 126.7 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 139.6 (C\(_{\text{arom}}\)), 140.4 (C\(_{\text{arom}}\)); \textbf{EI-MS} \textit{m/z}: 296 (MH\(^+\), 15), 188 (100), 106 (63), 91 (8), 77 (Ph\(^+\), 17); \textbf{HMRS}: MH\(^+\), found 296.20200. C\(_{20}\)H\(_{26}\)NO requires 296.20143.
Potassium trimethylsilanolate (90% pure, 323 mg, 2.52 mmol, 8 eq) was added to a solution of cyclopropane (+)-119A (112 mg, 0.315 mmol, 1 eq) in dry THF (1.6 mL) under nitrogen. The reaction mixture was heated at 60°C for 3.5 h and, as the reaction was not complete (as determined by TLC), additional potassium trimethylsilanolate (90% pure, 81 mg, 0.63 mmol, 2 eq) was added. The mixture was heated for a further 30 min and then allowed to cool to room temperature. EtOAc (10 mL) and water (5 mL) were added and the mixture was transferred into a separating funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the amino alcohol (+)-140 (73 mg, 0.22 mmol, 70%) as a white solid.

Mp 138-141°C; Rₐ (P.E. 30-40°C/EtOAc 7:3) 0.26; [α]ᵦ +22.0 (c 1.0, CHCl₃); IR (CHCl₃): νmax 3405 (br), 3066 (w), 3018 (m), 1558 (m), 1499 (m), 1051 (w), 1028 (w), 734 (m), 762 (s), 700 (m), 669 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.92 (ddd, 3J₄b,₅=5.3 Hz, ²J₄b,₄a=5.8 Hz, ³J₄b,₃=7.1 Hz, 1H, H₄b), 1.05 (ddd, ³J₄a,₃=4.2 Hz, ²J₄a,₄b=5.2 Hz, ³J₄a,₅=9.3 Hz, 1H, H₄a), 1.90 (ddd, ³J₅,₃=3.1 Hz, ³J₅,₄b=5.8 Hz, ³J₅,₄a=9.2 Hz, 1H, H₅), 2.24 (ddd, ³J₃,₅=3.1 Hz, ³J₃,₄a=4.2 Hz, ³J₃,₄b=7.2 Hz, 1H, H₃), 3.00 (br s, 2H, OH and NH), 4.08 (d, ³J₂,₁=5.3 Hz, 1H, H₂), 4.93 (d, ³J₁,₂=5.3 Hz, 1H, H₁), 6.83-7.31 (m, 15H, H arom); ¹³C NMR (125 MHz, CDCl₃): δ 16.8 (C₄), 25.4 (C₃), 39.3 (C₅), 69.1 (C₆), 75.6 (C₁), 125.5 (CH), 125.9 (CH), 126.6 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 139.1 (C₉), 140.2 (C₇), 141.7 (C₈); EI-MS
Experimental

$m/z$ (%): 329 (M+, 6) 222 (100), 132 (52), 117 (98), 91 (Bn+, 86), 77 (Ph+, 32); HMRS: MH+, found 329.17795. C_{23}H_{23}NO requires 329.17742.

3-(2-tert-Butylcyclopropyl)-2-oxazolidinone 141

\[
\text{C}_{10}\text{H}_{17}\text{NO} \quad 183.25 \text{ g.mol}^{-1}
\]

A solution of N-diethoxymethyl-2-oxazolidinone 108 (0.946 g, 5.0 mmol, 1 eq) in dry diethyl ether (8 mL) was added via a motorised syringe pump over 3.45 h to a vigorously stirred mixture of zinc amalgam (3.27 g, 50 mmol, 10 eq), zinc chloride (1M solution in diethyl ether, 5 mL, 5 mmol, 1 eq), chlorotrimethylsilane (3.17 mL, 25 mmol, 5 eq) and 3,3-dimethylbut-1-ene (3.24 mL, 25 mmol, 5 eq) in dry diethyl ether (27 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated saturated NaHCO₃ solution (40 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (3 x 10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product (trans/cis: >95:<5 as determined by $^1$H NMR) was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 1:1) to give almost exclusively the trans cyclopropane 141 (0.425 g, 2.32 mmol, 46%) as a yellow oil.

$R_f$ (P.E. 40-60°C/EtOAc 1:1) 0.36; IR (film): $\nu_{max}$ 2958 (m), 2869 (s), 1755 (s, C=O), 1482 (w), 1423 (m), 1223 (w), 1094 (w), 1039 (m), 765 (m) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 0.75 (dt, $^2J_{\beta-\gamma}$=5.9 Hz, $^3J_{\beta-\gamma}$=7.2 Hz, 1H, H$_{\beta}$), 0.80 (ddd, $^3J_{\gamma-\delta}$=3.7 Hz, $^2J_{\gamma-\delta}$=5.9 Hz, $^3J_{\gamma-\delta}$=9.7 Hz, 1H, H$_{\gamma}$), 0.85 (s, 9H, H$_8$), 0.95 (ddd, $^3J_{\delta-\epsilon}$=3.7 Hz, $^3J_{\delta-\epsilon}$=7.2 Hz, $^3J_{\delta-\epsilon}$=9.8 Hz, 1H, H$_6$), 2.35 (td, $^3J_{\epsilon-\delta}$=3.7 Hz, $^3J_{\epsilon-\delta}$=7.3 Hz, 1H, H$_7$).
Experimental

H₄), 3.45-3.50 (m, 2H, H₃), 4.22 (dt, 3J₂,₃=3.1 Hz, 3J₂,₃=2J₃=8.0 Hz, 2H, H₂); ¹³C NMR (125 MHz, CDCl₃): δ 9.4 (C₅), 28.2 (C₈), 28.7 (C₇), 29.0 (C₄), 30.6 (C₆), 45.8 (C₃), 61.6 (C₂), 158.4 (C₁); EI-MS m/z (%): 183 (M⁺, 7), 168 ([M-CH₃]⁺, 6), 127 ([M+H-C₄H₉]⁺, 100), 114 (31), 82 (18), 70 (31), 55 (43), 49 (12), 42 (CH₂=C=O, 60); HMRS: MH⁺, found 184.13305. C₁₀H₁₈NO₂ requires 184.13321.

2-(2-tert-Butylcyclopropylamino)ethanol 142

Lithium hydroxide monohydrate (1.24 g, 29.5 mmol, 30 eq) was added in one portion to a suspension of cyclopropane 141 (0.18 g, 0.98 mmol, 1 eq) in a mixture of absolute ethanol (14 mL) and water (6 mL). The reaction mixture was heated at reflux for 20 h and then allowed to cool to room temperature. Most of the ethanol was removed in vacuo and saturated aqueous NH₄Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (2 x 10 mL then 2 x 5 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to give the amino alcohol 142 (75 mg, 0.48 mmol, 49%) as a yellow oil.

IR (film): νmax 3300 (br), 2953 (s), 2866 (m), 1468 (m), 1387 (m), 1364 (m), 1068 (m), 1043 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.34-0.41 (m, 2H, H₄), 0.59 (ddd, 3J₃,₄=3.5 Hz, 3J₃,₄=6.2 Hz, 3J₃,₄=9.9 Hz, 1H, H₃), 0.77 (s, 9H, H₇), 1.95 (td, 3J₃,₄=3J₃,₄=3.5 Hz, 3J₃,₄=7.2 Hz, 1H, H₃), 2.71-2.77 (m, 2H, H₂), 2.90 (br s, 3H, OH and NH₂), 3.57 (t, 3J₁₋₂=5.5 Hz, 2H, H₁), ¹³C NMR (100 MHz, CDCl₃): δ 9.4 (C₅), 28.5 (C₇), 28.9 (C₈), 31.8 (C₉), 33.3 (C₃), 51.1 (C₂), 60.5 (C₁); Cl(methane)-MS m/z (%): 158 (MH⁺, 100), 100 ([M-C₄H₉]⁺, 86); HMRS: MH⁺, found 158.154382. C₉H₁₉NO requires 158.15448.
Di-tert-butyl dicarbonate (106 mg, 0.49 mmol, 1.2 eq) was added portionwise to a solution of amino alcohol 142 (64 mg, 0.407 mmol, 1 eq) and triethylamine (0.07 mL, 0.51 mmol, 1.25 eq) in dry dichloromethane (2 mL) under nitrogen. After stirring for 24 h, the reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 3:1) to give the title compound 143 (76 mg, 0.295 mmol, 72%) as a colourless oil.

**R** (P.E. 30-40°C/EtOAc 4:1) 0.29; **IR** (film): \( \nu_{\text{max}} \) 3450 (br, OH), 2955 (s), 2870 (m), 1685 (s, C=O), 1387 (m), 1365 (m), 1180 (m), 1149 (m), 1059 (m) cm\(^{-1}\); **\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \( \delta \) 0.65 (ddd, \( ^3J_{4a,3}=3.9 \) Hz, \( ^2J_{4a,4\beta}=5.8 \) Hz, \( ^3J_{4a,5}=9.7 \) Hz, 1H, H\(_{4a}\)), 0.71 (ddd, \( ^3J_{4\beta,4a}=5.8 \) Hz, \( ^3J_{4\beta,5}=6.9 \) Hz, \( ^3J_{4\beta,3}=7.4 \) Hz, 1H, H\(_{4\beta}\)), 0.82 (s, 9H, H\(_7\)), 0.85 (ddd, \( ^3J_{5,3}=3.9 \) Hz, \( ^3J_{5,4\beta}=6.7 \) Hz, \( ^3J_{5,4\alpha}=10.1 \) Hz, 1H, H\(_5\)), 1.42 (s, 9H, OC(CH\(_3\))\(_3\)), 2.45 (td, \( ^3J_{3,4\alpha}=3.8 \) Hz, \( ^3J_{3,4\beta}=7.5 \) Hz, 1H, H\(_3\)), 3.29 (ddd, \( ^3J_{2,1}=4.6 \) Hz, \( ^3J_{2,1}=6.2 \) Hz, \( ^2J=14.6 \) Hz, 1H, H\(_2\)), 3.41 (ddd, \( ^3J_{2,1}=4.5 \) Hz, \( ^3J_{2,1}=6.5 \) Hz, \( ^2J=14.5 \) Hz, 1H, H\(_2\)), 3.57 (t, \( ^3J_{1,2}=5.5 \) Hz, 2H, H\(_1\)); **\(^13\)C NMR** (125 MHz, CDCl\(_3\)): \( \delta \) 12.2 (C\(_4\)), 28.4 (C\(_7\) and OC(CH\(_3\))\(_3\)), 29.1 (C\(_6\)), 32.1 (C\(_5\)), 32.2 (C\(_3\)), 50.7 (C\(_2\)), 62.4 (C\(_1\)), 80.1 (OC(CH\(_3\))\(_3\)), 158.2 (C=O); **CI(ammonia)-MS** \( m/z \) (%): 256 ([M-H])\(^+\), 100, 200 ([M-C\(_4\)H\(_9\)])\(^+\), 30, 182 (32), 156 ([M-Boc])\(^+\), 45, 147 (65), 138 (29); **HMRS**: (M-H)\(^+\), found 256.191464. C\(_{14}\)H\(_{26}\)N\(_4\)O\(_4\) requires 256.19126.
Experimental

[tert-Butoxycarbonyl-(2-tert-butyldicyclopropyl)-amino]acetic acid 144

Aqueous solution of sodium hydroxide (0.5M in water, 2.2 mL, 1.1 mmol, 4 eq) and potassium permanganate (0.65M in water, 1.7 mL, 1.1 mmol, 4 eq) were added successively to a solution of alcohol 143 (70 mg, 0.27 mmol, 1 eq) in tert-butanol (2.7 mL). The reaction mixture was stirred for 24 h and then quenched with sodium thiosulfate (5% in water, 7.75 mL). Diethyl ether (10 mL) was added and the mixture was transferred into a separating funnel. The aqueous layer was separated and then acidified to pH 2 with an aqueous hydrochloric acid solution (1M) at 4°C. The mixture was then extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to give the title compound 144 (62 mg, 0.23 mmol, 84%) as a white amorphous solid.

**IR (film):** $\nu_{\text{max}}$ 3450 (br, OH), 2954 (m), 1699 (s, C=O), 1385 (m), 1367 (m), 1153 (m), cm$^{-1}$; $^1$H NMR (500 MHz, 328K, CDCl$_3$): $\delta$ 0.71 (ddd, $^3J_{4a-3}$=3.9 Hz, $^2J_{4a-4b}$=5.7 Hz, $^3J_{4a-5}$=9.7 Hz, 1H, H$_{4a}$), 0.75 (ddd, $^2J_{4b-4a}$=5.7 Hz, $^3J_{4b-5}$=6.6 Hz, $^3J_{4b-3}$=7.3 Hz, 1H, H$_{4b}$), 0.84 (s, 9H, H$_7$), 0.87 (ddd, $^3J_{5-3}$=3.9 Hz, $^3J_{5-4b}$=6.7 Hz, $^3J_{5-4a}$=10.1 Hz, 1H, H$_5$), 1.44 (s, 9H, OC(CH$_3$)$_3$), 2.59 (td, $^3J_{3-4a}$=$^2J_{5-3}$=3.9 Hz, $^3J_{3-4b}$=7.5 Hz, 1H, H$_3$), 3.83 (d, $^2J$=17.7 Hz, 1H, H$_2$), 4.04 (d, $^2J$=17.7 Hz, 1H, H$_2$), 8.73 (br s, 1H, OH); $^{13}$C NMR (125 MHz, 328K, CDCl$_3$): $\delta$ 12.2 (C$_4$), 28.4 (C$_7$ and OC(CH$_3$)$_3$), 29.0 (C$_6$), 32.3 (C$_5$), 32.5 (C$_3$), 50.0 (C$_2$), 80.7 (OC(CH$_3$)$_3$), 156.7 (C=O), 175.3 (C$_1$); CI(methane)-MS m/z (%): 272 (MH$^+$, 33), 216 ([M-C$_4$H$_9$]+, 92), 172 ([M+H-Boc]$^+$, 52), 154 (100); HMRS: MH$^+$, found 272.18676. C$_{14}$H$_{26}$NO$_4$ requires 272.18617.
Experimental

(S)-4-Benzyl-2-oxazolidinone 145

A solution of triphosgene (2.05 g, 6.9 mmol, 0.35 eq) in dry dichloromethane (10 mL) was added dropwise over 1 h to a suspension of L-phenylalaninol (3.0 g, 19.71 mmol, 1 eq) and triethylamine (6.04 mL, 43.36 mmol, 2.2 eq) in dry dichloromethane (40 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further hour at 4°C and then allowed to warm to room temperature and stirred for 2 h. Saturated aqueous NH₄Cl solution (25 mL) and dichloromethane (50 mL) mixture were added to the reaction and after stirring for 20 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous NaHCO₃ solution (25 mL) and brine (25 mL). The combined organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo. The crude product was recrystallised from EtOAc/hexane to give the title compound 145 (2.60 g, 19.2 mmol, 75%) as a white solid.

Mp 85-86°C (EtOAc/hexane) (lit., 140 85-87°C (EtOAc/hexane)); Rf (EtOAc) 0.6; [α]° = -56.0 (c 1.0, CHCl₃) (lit., 140 [α]° = -62.0 (c 1.0, CHCl₃)); IR (CHCl₃): νmax 3285 (br, NH), 3018 (m), 1755 (s, C=O), 1404 (m), 1216 (s), 1032 (w), 756 (s), 702 (w), 667 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.86 (d, 3J=8, 6.6 Hz, 2H, CH₂Ph), 4.01-4.11 (m, 1H, CHN), 4.12 (dd, 3J=5.5 Hz, 2J=8.3 Hz, 1H, CH-HO), 4.42 (t, 3J=2, 8.3 Hz, 1H, CH/70), 5.67 (br s, 1H, NH), 7.13-7.18 (m, 2H, Ha-rim), 7.21-7.35 (m, 3H, Hα-rim); ¹³C NMR (75 MHz, CDCl₃): δ 41.4 (CH₂Ph), 53.8 (CHN), 69.6 (CH₂O), 127.2 (CH), 129.0 (CH), 135.9 (Cq), 159.3 (C=O); EI-MS m/z (%): 177 (MH⁺, 100), 91 (Bn⁺, 66).
(S)-4-Benzyl-3-diethoxymethyl-2-oxazolidinone 146

A mixture of oxazolidinone 145 (500 mg, 2.82 mmol, 1 eq), aluminium chloride (56 mg, 0.42 mmol, 0.15 eq) and triethyl orthoformate (14 mL, 84.6 mmol, 30 eq) was heated at 155°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (10 mL). The aqueous phase was extracted with diethyl ether (20 mL then 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 4:1) to give the title compound 146 (195 mg, 0.70 mmol, 25%) as a colourless oil.

\[ R_f \text{(P.E. 40-60°C/EtOAc 4:1)} = 0.35; [\alpha]_D^2 = +50.4 \text{ (c 2.58, CH}_2\text{Cl}_2) ; \text{IR (film)}: \nu_{\text{max}} 2978 \text{ (m), 2935 (w), 2903 (w), 1759 (s, C=O), 1410 (m), 1236 (m), 1065 (s), 748 (m), 702 (m) cm}^{-1} ; \text{H NMR (300 MHz, CDCl}_3\text{)}: \delta 1.22 \text{ (t, } J_{7,6} = 7.0 \text{ Hz, 3H, H}_7\text{), 1.24 (t, } J_{7,6} = 7.0 \text{ Hz, 3H, H}_7\text{), 2.58-2.67 (m, 1H, H}_4\text{), 3.44-3.75 (m, 5H, H}_6\text{ and H}_4\text{), 3.97 (t, } J_{2,3} = 2J = 8.0 \text{ Hz, 1H, H}_2\text{), 4.02 (t, } J_{2,3} = 2J = 8.0 \text{ Hz, 1H, H}_2\text{), 4.14-4.25 (m, 1H, H}_3\text{), 5.79 (s, 1H, H}_5\text{), 7.10-7.29 (m, 5H, H}_\text{arom}\text{)} ; \text{C NMR (75 MHz, CDCl}_3\text{)}: \delta 14.6 \text{ (C}_7\text{), 14.7 \text{ (C}_7\text{), 39.5 \text{(C}_4\text{), 52.8 \text{(C}_3\text{), 62.3 \text{(C}_6\text{), 67.1 \text{(C}_2\text{), 102.3 \text{(C}_5\text{), 126.6 \text{(CH), 128.4 \text{(CH), 128.8 \text{(CH), 136.0 \text{(C}_6\text{), 157.2 \text{(C}_1\text{)}})} ; \text{Positive electrospray-MS m/z} (%) \text{: 302 (MNa}^+\text{, 100), 234 ([M-C}_2\text{H}_3\text{O}^+\text{, 37), 220 (13); HMRS: MNa}^+, \text{found 302.13563. C}_{15}\text{H}_{21}\text{NaNO}_4 \text{ requires 302.13628).} \]
Experimental

(S)-4-Isopropyl-2-oxazolidinone 147

\[
\begin{align*}
\text{C}_6\text{H}_{11}\text{NO}_2 & \quad 129.16 \text{ g.mol}^{-1} \\
\end{align*}
\]

\[\text{L-valinol}\]

\[
\begin{align*}
\text{L-valinol was prepared by a literature method.}^{141} \text{ L-valine (5 g, 42.68 mmol, 1 eq) was added to a suspension of sodium borohydride (4.03 g, 106.7 mmol, 2.5 eq) in dry THF (115 mL) under nitrogen. The reaction mixture was cooled to 4°C and a solution of iodine (10.83 g, 42.68 mmol, 1 eq) in dry THF (30 mL) was then added dropwise over 1 h. After the gas evolution had ceased, the reaction mixture was heated to reflux for 18 h and then allowed to cool to room temperature. Methanol was added slowly until the mixture became clear and the solution was stirred for 15 min. The organic solvents were removed \textit{in vacuo} and the residue was dissolved in aqueous KOH solution (3M, 100 mL). The mixture was stirred for 3 h and then extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated \textit{in vacuo} to give L-valinol (3.67 g, 35.57 mmol, 83%) as a colourless oil which was used without further purification. \\
\text{^1H NMR (300 MHz, CDCl}_3\text{: }\delta 0.88 \text{ (d, }^3J=6.8 \text{ Hz, 3H, CH}_3\text{), 0.89 \text{ (d, }^3J=6.8 \text{ Hz, 3H, CH}_3\text{), 1.46-1.60 \text{ (m, 1H, CH(CH}_3)_2\text{), 2.05 \text{ (br s, 2H), 2.47-2.58 \text{ (m, 1H, CHNH}_2\text{), 3.26 \text{ (t, }^3J=9.9 \text{ Hz, 1H, CHHOH), 3.61 \text{ (dd, }^3J=3.9 \text{ Hz, }^2J=10.4 \text{ Hz, 1H, CHHOH); }^{13}\text{C NMR (75 MHz, CDCl}_3\text{): }\delta 18.3 \text{ (CH}_3\text{), 19.2 \text{ (CH}_3\text{), 31.5 \text{ (CH(CH}_3)_2\text{), 58.4 \text{ (CHN), 64.7 \text{ (CH}_2\text{OH).}}}
\end{align*}
\]

(S)-4-Isopropyl-2-oxazolidinone 147

A solution of triphosgene (3.69 g, 12.45 mmol, 0.35 eq) in dry dichloromethane (15 mL) was added dropwise over 1.25 h to a solution of the crude amino alcohol (3.67 g, 35.57 mmol, 1 eq) and triethylamine (10.9 mL, 78.26 mmol, 2.2 eq) in dry dichloromethane (65 mL) under nitrogen at 4°C. The reaction mixture was stirred for a
Experimental

Further 2.5 h at 4 °C and then allowed to warm to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NH₄Cl solution (30 mL) and after stirring for 20 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL). The combined organic extracts were then dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was twice recrystallised from diethyl ether to give the title compound 147 (2.48 g, 19.2 mmol, 45% for the 2 steps) as fine white needles.

Mp 70-71°C (diethyl ether) (lit., 140 70-71.5°C (EtOAc/hexane)); R(f (EtOAc) 0.56; [a]_D +8.6 (c 1.0, CHCl₃) (lit., 140 [a]_D +4.38 (c 1.0, CHCl₃)); IR (CHCl₃): νmax 3300 (br, NH), 3018 (m), 2968 (w), 1751 (s, C=O), 1407 (w) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.88 (d, 3J=6.9 Hz, 3H, CH₃), 0.94 (d, 3J=6.8 Hz, 3H, CH₃), 1.64-1.77 (m, 1H, CH(CH₃)₂), 3.58 (q, 3J=3J=6.7 Hz, CHN), 4.08 (dd, 3J=6.3 Hz, 2J=8.7 Hz, 1H, CHHO), 4.42 (t, 3J=2J=8.7 Hz, 1H, CHHO), 6.53 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 17.6 (CH₃), 18.0 (CH₃), 32.7 (CH(CH₃)₂), 58.3 (CHN), 68.6 (CH₂O), 160.2 (C=O); CI(methane)-MS m/z (%): 130 (MH⁺, 100); HMRS: MH⁺, found 130.08645.

(S)-3-Diethoxymethyl-4-isopropyl-2-oxazolidinone 148

\[ \text{C}_{11}\text{H}_{21}\text{NO}_4 \quad 231.29 \text{g.mol}^{-1} \]

A mixture of oxazolidinone 147 (120 mg, 0.93 mmol, 1 eq), aluminium chloride (18.6 mg, 0.14 mmol, 0.15 eq) and triethyl orthoformate (4.6 mL, 27.9 mmol, 30 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (5 mL). The aqueous phase was extracted with diethyl ether (10 mL then 5 mL) and the combined organic extracts
were washed with brine (5 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 3:1) to give the title compound 148 (63 mg, 0.27 mmol, 29%) as a colourless oil.

**R f** (P.E. 40-60°C/EtOAc 3:1) 0.38; [α]²⁰° +26.2 (c 1.26, CH₂Cl₂); **IR** (film): υmax 2976 (s), 2945 (m), 2878 (m), 1763 (s, C=O), 1414 (m), 1232 (m), 1063 (s) cm⁻¹; **¹H NMR** (400 MHz, DMSO): δ 0.79 (d, J₅.₄=8.6 Hz, 3H, H₅), 0.81 (d, J₅.₄=8.6 Hz, 3H, H₅), 1.12 (t, J₆.₇=7.1 Hz, 3H, H₆), 1.15 (t, J₆.₇=7.1 Hz, 3H, H₆), 2.09-2.18 (m, 1H, H₄), 3.45-3.67 (m, 4H, H₇), 3.90 (ddd, J₃.₂=3.3 Hz, J₃.₂=4.8 Hz, J₃.₂=9.0 Hz, 1H, H₃), 4.12 (dd, J₂.₃=4.8 Hz, J₂.₃=9.0 Hz, 1H, H₂), 4.24 (t, J₂.₃=4.8 Hz, J₂.₃=9.0 Hz, 1H, H₂), 5.64 (s, 1H, H₆); **¹³C NMR** (100 MHz, DMSO): δ 14.1 (C₃), 14.7 (C₈), 17.6 (C₅), 29.0 (C₄), 55.8 (C₃), 61.9 (CH₂), 62.2 (CH₂), 63.1 (CH₂), 102.1 (C₆), 157.0 (C₁); **EI-MS** m/z (%): 232 (MH⁺, 8), 187 ([M-C₆H₅O]⁺, 100), 158 (36), 130 (48), 103 (77); **HMRS**: MH⁺, found 232.15519. C₉H₉N₈O₂ requires 232.15488.

(R)-(--)-4-Phenyl-2-oxazolidinone 149

![Chemical structure of R-(--)4-Phenyl-2-oxazolidinone 149](image)

C₉H₉NO₂ 163.18 g.mol⁻¹

A solution of triphosgene (0.826 g, 2.78 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 2 h to a solution of (R)-(--)-2-phenylglycinol (1.09 g, 7.95 mmol, 1 eq) and triethylamine (2.44 mL, 17.49 mmol, 2.2 eq) in dry dichloromethane (30 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4 °C and the triethylamine hydrochloride precipitate was then filtered and washed with dry dichloromethane (5 mL). The filtrate was washed with saturated aqueous NH₄Cl solution (15 mL), brine (15 mL), dried (MgSO₄), filtered and concentrated in vacuo. As the product was contaminated by triethylamine hydrochloride, the crude product was taken up in EtOAC (60 mL) and the organic layer was washed with saturated aqueous NaHCO₃ solution (2 x 20 mL) and brine (20 mL), dried (MgSO₄), filtered and
concentrated in vacuo to give the title compound 149 (0.94 g, 5.76 mmol, 72%) as a white solid.

\[ \text{M} \text{p} \ 129-130^\circ \text{C (lit.,} 13 \ 132-134^\circ \text{C (EtOAc/hexane)); } R_1 \text{(EtOAc) 0.67; } [\alpha]_D^{19} -60.4 \text{ (c 1.0, CHCl}_3 \text{)(lit.,} 13 [\alpha]_D^{19} -57.7 \text{ (c 1.083, CHCl}_3 \text{)); } \text{IR (CHCl}_3 \text{: } \nu_{\text{max}} \text{ 3268 (br, NH), 2915 (w), 1757 (s, C=O), 1399 (w), 1216 (m), 1042 (w), 925 (w), 757 (s) cm}^{-1}; \text{H NMR (300 MHz, CDCl}_3 \text{: } \delta 4.15 \text{ (dd, } J=6.9 \text{ Hz, } J=8.6 \text{ Hz, 1H, CH}_{\text{H}}\text{O), 4.69 (t, } J=2 J=8.6 \text{ Hz, 1H, CHN), 6.32 (br s, 1H, NH), 7.227-7.41 \text{ (m, } 5\text{H arom); } \text{C NMR (75 MHz, CDCl}_3 \text{: } \delta 56.3 \text{ (CHN), 72.5 \text{(CH}_2\text{O), 126.0 \text{(CH), 128.7 \text{(CH), 129.1 \text{(CH), 139.5 (C}_4\text{), 159.9 (C=O); EI-MS } m/z \text{ (%): 163 (M}^+\text{, 24), 133 (73), 104 (100), 91 (30), 77 (Ph},^+\text{, 32).}}}

\text{(R)-(--)3-Diethoxymethyl-4-phenyl-2-oxazolidinone 150}

A mixture of oxazolidinone 149 (0.87 g, 5.33 mmol, 1 eq), aluminium chloride (0.107 g, 0.80 mmol, 0.15 eq) and triethyl orthoformate (26.3 mL, 0.16 mol, 30 eq) was heated at 140°C for 16 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO\textsubscript{3} solution (25 mL). The aqueous phase was extracted with diethyl ether (2 x 50 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 7:3) to give the title compound 150 (0.464 g, 1.75 mmol, 33%) as a colourless oil.

\[ R_1 \text{(P.E. 40-60°C/EtOAc 7:3) 0.47; } [\alpha]_D^{19} -49.9 \text{ (c 1.8, CH}_2\text{Cl}_2\text{); } \text{IR (film): } \nu_{\text{max}} \text{ 2978 (m), 2903 (w), 1761 (s, C=O), 1458 (m), 1402 (m), 1216 (m), 1066 (s), 765 (w), 707} \]
Experimental

(500 MHz, CDCl₃):  δ 0.65 (t,  3J=6.5=7.1 Hz, 3H, H₆), 1.21 (t,  3J=6.5=7.1 Hz, 3H, H₇), 3.10 (qd,  3J=6.5=7.1 Hz, 2J=9.1 Hz, 1H, H₃), 3.32 (qd,  3J=6.5=7.1 Hz, 2J=9.3 Hz, 1H, H₃), 3.66 (qd,  3J=6.5=7.1 Hz, 2J=9.4 Hz, 1H, H₃), 4.19 (qd,  3J=6.5=7.1 Hz, 2J=9.4 Hz, 1H, H₃), 4.19 (dd,  3J=6.5=5.9 Hz, 2J=8.7 Hz, 1H, H₂), 4.60 (t,  3J=6.5=5.9 Hz, 2J=8.8 Hz, 1H, H₂), 5.00 (dd,  3J=6.5=5.9 Hz, 2J=9.0 Hz, 1H, H₃), 5.71 (s, 1H, H₄), 7.24-7.36 (m, 5H, H₆).  

13C NMR (125 MHz, CDCl₃):  δ 13.8 (C₆), 14.7 (C₆), 55.4 (C₃), 61.8 (C₃), 62.8 (C₃), 70.9 (C₂), 102.5 (C₄), 126.9 (CH), 128.2 (CH), 128.5 (CH), 140.1 (C₉), 157.9 (C₆); EI-MS m/z: 265 (M⁺, 14), 220 ([M-C₄H₉O]⁺, 86), 192 (77), 148 (62), 121 (71), 103 (100), 91 (38), 77 (Ph⁺, 53), 75 (92); HMRS: M⁺, found 265.12982.  

C₁₄H₁₉NO₄ requires 265.13086.

4-Methyl-5-phenyl-2-oxazolidinone 151

C₁₀H₁₁NO₂  177.20 g.mol⁻¹

A solution of triphosgene (1.22 g, 4.1 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 1 h to a suspension of norephedrine hydrochloride (2.2 g, 11.72 mmol, 1 eq) and triethylamine (5.23 mL, 37.51 mmol, 3.2 eq) in dry dichloromethane (40 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4°C and the triethylamine hydrochloride precipitate filtered and washed with dichloromethane (2 x 20 mL). The filtrate was washed with saturated aqueous NH₄Cl solution (20 mL), saturated aqueous NaHCO₃ solution (20 mL) and brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo to give the title compound 151 (1.52 g, 8.56 mmol, 73%) as a white solid.

Mp 146-148°C (lit., 142 146-146.5°C); Rf (EtOAc) 0.54; IR (CDCl₃): νmax 3261 (br, NH), 2998 (w), 1747 (s, C=O), 1724 (s), 1379 (m), 1230 (m), 908 (s), 732 (s) cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 0.79 (d,  3J=6.5 Hz, 3H, CH₃), 4.19 (qd,  3J=6.5 Hz, 3J=8.0 Hz, 1H, CHN), 5.70 (d,  3J=8.0 Hz, 1H, CHO), 5.68 (br s, 1H, NH), 7.25-7.39 (m, 5H, H₆).
13C NMR (75 MHz, CDCl3): δ 17.5 (CH₃), 52.4 (CHN), 81.0 (CH₂O), 125.9 (CH), 128.5 (CH), 134.8 (Cₗ), 159.4 (C=O).

3-Diethoxymethyl-4-methyl-5-phenyl-2-oxazolidinone 152

A mixture of oxazolidinone 151 (1.3 g, 7.34 mmol, 1 eq), aluminium chloride (0.147 g, 1.1 mmol, 0.15 eq) and triethyl orthoformate (36.2 mL, 0.22 mol, 30 eq) was heated at 150°C for 16 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (35 mL). The aqueous phase was extracted with diethyl ether (70 mL then 35 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 4:1) to give the title compound 152 (0.77 g, 2.76 mmol, 38%) as a yellow oil.

Rᵣ (P.E. 30-40°C/EtOAc 4:1) 0.3; IR (film): νmax 2978 (m), 2935 (w), 1759 (s, C=O), 1410 (m), 1236 (m), 1064 (s), 747 (m), 702 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.86 (d, 3Jₜₗ=6.5 Hz, 3H, H₄), 1.19 (t, 3Jₜₗ=7.0 Hz, 3H, H₇), 1.23 (t, 3Jₜₗ=7.0 Hz, 3H, H₇), 3.53-3.75 (m, 4H, He), 4.32 (qd, 3Jₜₗ=6.5 Hz, 3Jₜₗ=8.1 Hz, 1H, H₃), 5.56 (d, 3Jₜₗ=8.1 Hz, 1H, H₂), 5.82 (s, 1H, H₃), 7.22-7.39 (m, 5H, H₆); ¹³C NMR (125 MHz, CDCl₃): δ 14.7 (C₇), 14.8 (C₆), 16.4 (C₆), 52.1 (C₅), 62.4 (C₆), 63.0 (C₆), 79.7 (C₇), 102.3 (C₈), 126.0 (CH), 128.4 (CH), 134.8 (C₅), 157.1 (C₁); CI(ammonia)-MS m/z (%): 279 (M⁺, 15), 249 (76), 175 (100), 160 (80); HMRS: M⁺, found 279.14751. C₁₅H₂₁NO₄ requires 279.14705.
Experimental

(S)-Ethyl-2-oxazolidinone-4-carboxylate 154

A solution of triphosgene (3.67 g, 12.38 mmol, 0.35 eq) in dry dichloromethane (20 mL) was added dropwise over 1.25 h to a suspension of L-serine ethyl ester hydrochloride (6.0 g, 35.37 mmol, 1 eq) and triethylamine (15.78 mL, 113.2 mmol, 3.2 eq) in dry dichloromethane (120 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 2.25 h at 4 °C and then allowed to warm to room temperature and stirred for 30 min. Saturated aqueous NH₄Cl solution (30 mL) and dichloromethane (40 mL) were added to the reaction mixture and after stirring for 10 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL). The combined organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo to give the title compound 154 contaminated by traces of triethylamine hydrochloride (4.47 g, 28.1 mmol, 79%) as a white solid.

Mp 69-71°C (EtOAc/hexane); Rf (P.E. 40-60°C/EtOAc 1:1) 0.15; [α]D²⁺²⁻24.0 (c 1.0, CH₂Cl₂); IR (CHCl₃): νmax 3270 (br, NH), 1745 (s, C=O), 1402 (m), 1379 (m), 1214 (s), 1131 (m), 1019 (m), 932 (w), 769 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.30 (t, ³J₆,₅=7.2 Hz, 3H, H₆), 4.26 (q, ³J₅,₆=7.2 Hz, 2H, H₅), 4.37 (dd, ³J₂,₃=4.6 Hz, ²J=9.6 Hz, 1H, H₂), 4.52 (dd, ³J₃,₂=4.6 Hz, ³J₃,₂=9.0 Hz, H₃), 4.60 (dd, ³J₂,₃=9.0 Hz, ²J=9.6 Hz, 1H, H₂), 5.58 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ 13.9 (C₆), 53.7 (C₃), 62.2 (CH₂), 66.6 (CH₂), 159.1 (C₁), 170.1 (C₄); FAB-MS m/z (%): 160 (MH⁺, 100); HMRS: MH⁺, found 160.06086. C₆H₁₀NO₄ requires 160.06098.
Experimental

(S)-Ethyl-3-diethoxymethyl-2-oxazolidinone-4-carboxylate 155

\[
\begin{align*}
C_{11}H_{19}NO_6 & \quad 261.27 \text{ g.mol}^{-1} \\
\end{align*}
\]

A mixture of oxazolidinone 154 (1.5 g, 9.42 mmol, 1 eq), aluminium chloride (0.19 g, 1.41 mmol, 0.15 eq) and triethyl orthoformate (46 mL, 0.28 mol, 30 eq) was heated at 160°C for 18 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO$_3$ solution (40 mL). The aqueous phase was extracted with diethyl ether (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1 to 7:3) to give the title compound 155 (1.35 g, 5.17 mmol, 55%) as a yellow oil.

\[ R_f \text{ (P.E. } 40-60^\circ\text{C/EtOAc } 7:3\text{) 0.29; } [\alpha]^{n}_{D} -22.4 \text{ (c } 1.02, \text{ CHCl}_3) \text{; IR (film): } \nu_{\max} 2981 \text{ (m), 2955 (w), 2905 (w), 1770 (s, C=O), 1751 (s, C=O), 1405 (m), 1375 (m), 1066 (s), 1025 (m) cm}^{-1}; \text{ }^1\text{H NMR (500 MHz, DMSO): } \delta 1.05 \text{ (t, } J_{9,8}=7.0 \text{ Hz, } 3\text{H, H}_8), 1.13 \text{ (t, } J_{9,8}=7.0 \text{ Hz, } 3\text{H, H}_9), 1.21 \text{ (t, } J_{6,5}=7.0 \text{ Hz, } 3\text{H, H}_6), 3.45-3.59 \text{ (m, } 4\text{H, H}_8), 4.07-4.17 \text{ (m, } 2\text{H, H}_3), 4.20 \text{ (dd, } J_{5,2}=3.7 \text{ Hz, } J_{2,3}=9.0 \text{ Hz, } 1\text{H, H}_2), 4.42 \text{ (dd, } J_{3,2}=3.7 \text{ Hz, } J_{1,2}=9.1 \text{ Hz, } 1\text{H, H}_3), 4.53 \text{ (t, } J_{3,2}=2J_{1,2}=9.0 \text{ Hz, } 1\text{H, H}_2), 5.65 \text{ (s, } 1\text{H, H}_7); \text{ }^{13}\text{C NMR (125 MHz, DMSO): } \delta 13.8 \text{ (C}_6), 14.4 \text{ (C}_9), 14.7 \text{ (C}_9), 52.7 \text{ (C}_8), 61.1 \text{ (C}_8), 61.1 \text{ (C}_3), 62.2 \text{ (C}_8), 65.8 \text{ (C}_2), 100.8 \text{ (C}_7), 156.1 \text{ (C}_1), 170.6 \text{ (C}_4); \text{ ESI-MS m/z (%): } 261 \text{ (M}^+, 49), 216 \text{ ([M-C}_2\text{H}_5\text{O}]^+, 90), 188 \text{ (100), 160 (95)); HMRS: M}^+, \text{ found } 261.12092. \text{ C}_{11}\text{H}_{19}\text{NO}_6 \text{ requires } 261.12069. \]
**Experimental**

**Ethyl-3-(2-cyclohexylcyclopropyl)-2-oxazolidinone-4-carboxylate 156 and 157**

![Chemical Structure](image)

C\(_{13}\)H\(_{23}\)NO\(_4\) 281.35 g.mol\(^{-1}\)

A solution of \(N\)-diethoxymethyl-2-oxazolidinone 155 (0.74 g, 2.83 mmol, 1.25 eq) in dry diethyl ether (3.5 mL) was added via a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (1.85 g, 28.3 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 2.83 mL, 2.83 mmol, 1.25 eq), chlorotrimethylsilane (1.79 mL, 14.12 mmol, 6.25 eq) and vinylcyclohexane (0.25 g, 2.26 mmol, 1 eq) in dry diethyl ether (11.75 mL) under nitrogen at reflux. The mixture was stirred for 10 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHC\(_\text{O}_3\) solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1 to 6.5:3.5) to give an inseparable mixture of cyclopropanes 156 and 157 contaminated by 10 wt. % of ethyl-\(N\)-formyl-2-oxazolidinone-4-carboxylate (0.34 g, 1.09 mmol of 156 and 157 after correction, 48% of 156 and 157 after correction) as a yellow oil.

Mixture of trans A and B isomers: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 0.47-0.79 (m, 6H), 0.79-0.92 (m, 12H), 1.27 (t, \(J_{6.5}=7.2\) Hz, 3H, H\(_{6\beta}\)), 1.28 (t, \(J_{6.5}=7.1\) Hz, 3H, H\(_{6\alpha}\)), 1.55-1.72 (m, 10H), 2.37 (td, \(J_{7.8\alpha}=J_{7.9}=3.4\) Hz, \(J_{7.8\beta}=7.2\) Hz, 1H, H\(_7\alpha\)), 2.42 (td, \(J_{7.8\alpha}=J_{7.9}=3.4\) Hz, \(J_{7.8\beta}=7.0\) Hz, 1H, H\(_7\alpha\)), 4.14-4.36 (m, 10H).
(R)-4-Hydroxymethyl-2-oxazolidinone 158

Sodium borohydride (0.45 g, 11.74 mmol, 1.05 eq) was added portionwise to a solution of (S)-ethyl-2-oxazolidinone-4-carboxylate 154 (1.78 g, 11.18 mmol, 1 eq) in absolute ethanol (22 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 10 min at 4 °C and then allowed to warm to room temperature and stirred for 2 h. The reaction was quenched carefully with saturated aqueous NH₄Cl solution (1.8 mL) and after stirring for 30 min the mixture was filtered through celite. The solvents were removed in vacuo and the crude product was purified by flash column chromatography (silica, EtOAc/MeOH 9:1 to 8.5:1.5) to give the alcohol 158 (0.99 g, 8.45 mmol, 76%) as a yellowish solid.

Mp 96-99°C (lit.109 96-99°C (MeOH)); Rf (EtOAc/MeOH 9:1) 0.27; [α]_D^20 +25.7 (c 1.24, MeOH) (lit.,109 [α]_D^20 +32.25 (c 1.044, MeOH)); IR (CHCl₃): v_max 3330 (br, NH), 2927 (w), 2880 (w), 1735 (s, C=O), 1418 (m), 1258 (m), 1094 (w), 1038 (m), 939 (w), 771 (w), 711 (w) cm⁻¹; ¹H NMR (300 MHz, DMSO): δ 3.36 (t, 3 J_2,3=3 J_4,OH=4.9 Hz, 2H, H₄), 3.75 (qd, 3 J_3,2=3 J_3,4=4.9 Hz, 3 J_5,2=8.5 Hz, 1H, H₃), 4.05 (dd, 3 J_2,3=4.9 Hz, 2 J=8.5 Hz, 1H, H₂), 4.30 (t, 3 J_2,3=2 J=8.5 Hz, H₂), 4.92 (t, 3 J_5,2=4.9 Hz, 1H, OH), 7.54 (br s, 1H, NH); ¹³C NMR (125 MHz, DMSO): δ 53.1 (C₃), 62.7 (C₄), 66.3 (C₂), 159.0 (C₁); EI-MS m/z (%): 118 (MH⁺, 7), 86 ([M-CH₂OH]^+, 100); HMRS: MH⁺, found 118.04966. C₄H₇NO₃ requires 118.04987.
(S)-4-[[tert-Butyldimethylsilyl]oxy]methyl]-2-oxazolidinone 159

\[
\text{TBDMSO} \quad \begin{array}{c}
\text{O} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4}
\end{array}
\]

\[\text{C}_{10}\text{H}_{21}\text{NO}_3\text{Si} \quad 231.37 \text{ g.mol}^{-1}\]

Tert-butyldimethylsilyl chloride (1.23 g, 8.17 mmol, 1.1 eq) and imidazole (1.11 g, 16.35 mmol, 2.2 eq) were added successively to a solution of alcohol 158 (0.87 g, 7.43 mmol, 1 eq) in dry DMF (10 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4 °C and then allowed to warm to room temperature and stirred for 44 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (40 mL) and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 1:1) to give the \textit{title compound} 159 (1.39 g, 6.01 mmol, 81%), as a white solid.

\textbf{Mp} 76-79°C (lit.,¹⁴³ 59-60°C); \textbf{Rₜ} (P.E. 40-60°C/EtOAc 1:1) 0.28; [α]⁺⁺ₚ +34.6 (c 1.44, CHCl₃) (lit.,¹⁴³ [α]⁺⁺ₚ +13.4 (c 1.45, CHCl₃)); \textbf{IR} (CDCl₃): νₚₑₘₐₓ 3300 (br, NH), 2926 (w), 2864 (w), 1751 (s, C=O), 1414 (w), 1252 (w), 1136 (w), 1043 (m), 941 (w), 839 (m), 779 (m) cm⁻¹; \textbf{¹H NMR} (500 MHz, CDCl₃): δ 0.04 (s, 6H, 2 x CH₃Si), 0.86 (s, 9H, C(CH₃)₃), 3.59 (d, 3J=5.5 Hz, 2H, H₄), 3.87-3.93 (m, 1H, H₃), 4.14 (dd, 3J₂⁻=4.9 Hz, 2J=8.8 Hz, 1H, H₂), 4.42 (t, 3J₂⁻=2J=8.7 Hz, 1H, H₂), 5.69 (br s, 1H, NH); \textbf{¹³C NMR} (125 MHz, CDCl₃): δ -5.5 (CH₃Si), 18.1 (C(CH₃)₃), 25.7 (C(CH₃)₃), 53.6 (C₃), 64.8 (CH₂), 67.0 (CH₂), 73.4 (CH₂), 159.6 (C₁); \textbf{EI-MS m/z} (%): 232 (MH⁺, 15), 216 ([M-CH₃]⁺, 62), 174 ([M-C₄H₉]⁺, 82), 131 (100), 101 ([M+H-OTBDMS]⁺, 93), 75 (92); \textbf{HMRS}: MH⁺, found 232.13671. C₁₀H₂₁NO₃Si requires 232.13635; \textbf{Anal. found}: C, 51.94; H, 9.47; N, 6.03. Calcd for C₁₀H₂₃NO₃Si: C, 51.91; H, 9.15; N, 6.05.
Experimental

(S)-3-Diethoxymethyl-4-[[((tert-butyldimethylsilyl)oxy)methyl]-2-oxazolidinone 160

A mixture of oxazolidinone 159 (1.2 g, 5.19 mmol, 1 eq), aluminium chloride (0.104 g, 0.78 mmol, 0.15 eq) and triethyl orthoformate (25.6 mL, 0.16 mol, 30 eq) was heated at 155°C for 18 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was partitioned between EtOAc (60 mL) and saturated aqueous NaHCO₃ solution (20 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:1) to give the title compound 160 (1.04 g, 3.11 mmol, 60%) as a colourless oil. However, the instability of 160 precluded complete characterisation.

Rᵦ (P.E. 40-60°C/EtOAc 75:35) 0.31; IR (film): νmax 2977 (m), 2954 (m), 2858 (m), 1758 (s, C=O), 1408 (m), 1250 (m), 1099 (s), 1065 (s), 854 (m, Si-C), 773 (s) cm⁻¹; ¹H NMR (400 MHz, DMSO): δ 0.02 (s, 3H, CH₃Si), 0.04 (s, 3H, CH₃Si), 0.84 (s, 9H, C(CH₃)₃), 1.12 (t, 3J₂₆=7.3 Hz, 3H, H₂), 1.13 (t, 3J₂₆=7.3 Hz, 3H, H₂), 3.46-3.60 (m, 4H, H₆), 3.71 (dd, 3J₄₃=4.5 Hz, 2J=10.4 Hz, 1H, H₃), 3.98 (dd, 3J₄₃=2.9 Hz, 3J₃₄=3J₂₃=4.5 Hz, 2J=8.5 Hz, 1H, H₂), 4.11 (dd, 3J₂₃=4.5 Hz, 3J₃₄=8.5 Hz, 1H, H₃), 5.64 (s, 1H, H₅); ¹³C NMR (100 MHz, DMSO): δ -5.6(CH₃Si), -5.5 (CH₃Si), 14.7 (2 x C₇), 17.8 (C(CH₃)₃), 25.6 (C(CH₃)₃), 52.3 (C₃), 61.6 (CH₂), 61.8 (CH₂), 62.8 (CH₂), 65.5 (CH₂), 101.6 (C₃), 156.9 (C₁).
Experimental

4-Benzylloxymethyl-2-oxazolidinone 162

![Structure of 4-Benzylloxymethyl-2-oxazolidinone 162]

C_{11}H_{12}NO_3  207.23 g.mol⁻¹

**O-benzyl-DL-serinol**

O-benzyl-DL-serinol was prepared by a modification of the literature method.¹⁴¹ O-benzyl-DL-serine (2.5 g, 12.81 mmol, 1 eq) was added to a suspension of sodium borohydride (1.21 g, 32.01 mmol, 2.5 eq) in dry THF (35 mL) under nitrogen. The reaction mixture was cooled to 4°C and a solution of iodine (3.25 g, 12.81 mmol, 1 eq) in dry THF (7.5 mL) was then added dropwise over 45 min. After the gas evolution had ceased, the reaction mixture was heated to reflux for 16 h and then allowed to cool to room temperature. Methanol was added slowly until the mixture became clear and the solution was stirred for 20 min. The organic solvents were removed *in vacuo* and the residue was dissolved in aqueous KOH solution (20 %, 25 mL). The mixture was stirred for 4 h and water (25 mL) and dichloromethane (50 mL) were added. The mixture was transferred into a separating funnel and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give O-benzyl-DL-serinol (2.13 g, 11.75 mmol, 92 %) as a greyish solid which was used without further purification.

¹H NMR (300 MHz, CDCl₃): δ 2.09 (br s, 3H, OH and NH₂), 3.12 (br s, 1H, CHNH₂), 3.40-3.68 (m, 4H, 2 x CH₂), 4.52 (s, 2H, OCH₂Ph), 7.25-7.42 (m, 5H, Hₓarom); ¹³C NMR (75 MHz, CDCl₃): δ 52.3 (CHN), 64.4 (CH₂OH), 72.9 (CHCH₂O), 73.4 (OCH₂Ph), 127.7 (CH), 127.8 (CH), 128.5 (CH), 138.0 (C₀).

4-Benzylloxymethyl-2-oxazolidinone 162

A solution of triphosgene (1.22 g, 4.11 mmol, 0.35 eq) in dry dichloromethane (4 mL) was added dropwise over 1 h to a suspension of crude O-benzyl-DL-serinol (2.13 g,
Experimental

11.75 mmol, 1 eq) and triethylamine (3.6 mL, 25.85 mmol, 2.2 eq) in dry dichloromethane (50 mL) under nitrogen at 4°C. The mixture was stirred for a further h at 4 °C and then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH₄Cl solution (20 mL) and after stirring for 20 min, the mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer washed with water (20 mL). The combined aqueous layers were extracted with EtOAc (2 x 40 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 3:2 to 7:3) to give the title compound 162 (1.48 g, 7.14 mmol, 56%) as a yellow oil.

Rf (EtOAc/P.E. 40-60°C 7:3) 0.3; IR (CDC1₃): νmax 3320 (br, NH), 2906 (w), 2864 (w), 1752 (s, C=O), 1410 (m), 1232 (m), 1096 (s), 1056 (s), 1036 (s), 742 (w), 700 (w) cm⁻¹; ¹H NMR (400 MHz, CDC1₃): δ 3.43 (d, 3J₄₃=5.7 Hz, 2H, H₄), 3.93-4.02 (m, 1H, H₃), 4.11 (dd, 3J₂₃=5.1 Hz, 2J₂₅=8.7 Hz, 1H, H₂), 4.39 (t, 3J₂₃=2J₂₅=8.7 Hz, 1H, H₂), 4.50 (s, 2H, H₅), 6.46 (br s, 1H, NH), 7.24-7.35 (m, 5H, arom); ¹³C NMR (100 MHz, CDC1₃): δ 51.8 (C₃), 62.2 (CH₂), 71.4 (CH₂), 73.4 (CH₂), 127.6 (CH), 127.8 (CH), 137.3 (C₄), 159.9 (C₁); EI-MS m/z (%): 208 (MH⁺, 4), 146 (100); HMRS: MH⁺, found 208.09751. C₁₁H₁₄N₀₃ requires 208.09682.

4-Benzylxoxymethyl-3-diethoxymethyl-2-oxazolidinone 163

A mixture of oxazolidinone 162 (1.31 g, 6.32 mmol, 1 eq), aluminium chloride (0.126 g, 0.95 mmol, 0.15 eq) and triethyl orthoformate (31 mL, 0.19 mol, 30 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was partitioned between EtOAc (60 mL) and saturated aqueous NaHCO₃ solution (20 mL). The organic layer was separated and the aqueous
Experimental phase was then extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the *title compound* 163 (1.42 g, 4.59 mmol, 73%) as a colourless oil.

\[ R_f \text{ (P.E. 30-40°C/EtOAc 7:3) 0.31; IR (film): } \nu_{\text{max}} \text{ 2978 (m), 1759 (s, C=O), 1414 (m), 1242 (m), 1220 (m), 1063 (s), 739 (m), 700 (m) cm}^{-1}; \]

\[ ^1\text{H NMR (400 MHz, DMSO): } \delta 1.07 \text{ (t, } J_{\text{8},3} = 7.0 \text{ Hz, 3H, H8), 1.13 \text{ (t, } J_{\text{8},7} = 7.0 \text{ Hz, 3H, H8), 3.43-3.57 \text{ (m, 4H, H7), 3.58 (d, } J_{\text{4},3} = 4.2 \text{ Hz, 2H, H4), 4.08 (qd, } J_{\text{3},2} = J_{\text{3},4} = 4.6 \text{ Hz, } J_{\text{3},2} = 8.7 \text{ Hz, 1H, H3), 4.19 (dd, } J_{\text{2},3} = 4.8 \text{ Hz, } J_{\text{2},2} = 8.5 \text{ Hz, 1H, H2), 4.38 (t, } J_{\text{2},2} = J_{\text{2},3} = 8.7 \text{ Hz, 1H, H2), 4.47 (d, } J_{\text{1},1} = 12.1 \text{ Hz, 1H, H5), 4.51 (d, } J_{\text{1},} = 12.1 \text{ Hz, 1H, H3), 5.64 (s, 1H, H6), 7.25-7.37 \text{ (m, 5H, arom)}; \]

\[ ^{13}\text{C NMR (100 MHz, DMSO): } \delta 14.6 \text{ (C8), 14.7 \text{ (C8), 50.8 \text{ (C3), 61.7 \text{ (CH2), 62.0 \text{ (CH2), 65.8 \text{ (CH2), 69.6 \text{ (CH2), 72.5 \text{ (CH2), 101.6 \text{ (C6), 127.6 \text{ (CH), 128.3 \text{ (CH), 138.1 \text{ (C4, 156.9 \text{ (C1); EI-MS } m/z \text{ (%): 309 (M}^+, 6), 280 ([M-C}_2\text{H}_5]^+, 42), 264 ([M-C}_2\text{H}_5\text{O}]^+, 59), 190 (32), 157 (51), 128 (52), 103 (100), 91 (Bn}^+, 98), 77 (Ph}^+, 30); HMRS: M}^+, \text{ found 309.15778. C}_{16}\text{H}_{23}\text{NO}_{3} \text{ requires 309.15707.} \]

4-Benzoxymethyl-3-(2-cyclohexylcyclopropyl)-2-oxazolidinone 166 and 167

![Chemical structure](image)

\[ \text{C}_{20}\text{H}_{27}\text{NO}_{3} \text{ 329.44 g.mol}^{-1} \]

A solution of *N*-diethoxymethyl-2-oxazolidinone 163 (0.387 g, 1.25 mmol, 1.25 eq) in dry diethyl ether (1.25 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and vinylcyclohexane (0.11 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 18 h and then...
allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 7:3) to give a mixture of cyclopropanes 166 and 167 contaminated by 10 wt. % of 4-benzyloxymethyl-N-formyl-2-oxazolidinone (0.168 g, 0.46 mmol of 166 and 167 after correction, 46% of 166 and 167 after correction) as a yellow oil.

**Isomer A:** $^1$H NMR (500 MHz, CDCl₃): $\delta$ 0.45-0.56 (m, 1H, H₅), 0.64-0.74 (m, 2H), 0.90-1.17 (m, 5H), 1.54-1.70 (m, 6H), 2.09 (td, $^3$J₆₋₇ₐ=3$^3$J₆₋₈=3.7 Hz, $^3$J₆₋₇ₐ=6.9 Hz, 1H, H₆), 3.54 (dd, $^3$J₄₋₃=3.4 Hz, $^2$J=9.5 Hz, 1H, H₄), 3.59 (dd, $^3$J₄₋₃=5.7 Hz, $^2$J=9.5 Hz, 1H, H₄), 3.65-3.70 (m, 1H, H₃), 4.16 (dd, $^3$J₂₋₃=4.3 Hz, $^2$J=8.7 Hz, 1H, H₂), 4.19 (t, $^3$J₂₋₃=8.7 Hz, 1H, H₂), 4.52 (d, $^2$J=12.1 Hz, 1H, H₃), 4.56 (d, $^2$J=12.1 Hz, 1H, H₃), 7.23-7.35 (m, 5H, H₉), $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 13.6 (C₇), 25.5 (C₈), 26.0 (2x CH₂), 26.4 (CH₂), 28.9 (C₆), 32.1 (CH₂), 32.7 (CH₂), 40.5 (C₉), 65.1 (C₄), 67.0 (C₄), 73.4 (C₅), 128.5 (CH), 128.8 (CH), 137.3 (C₆), 158.0 (C₇).

**Isomer B:** $^1$H NMR (500 MHz, CDCl₃): $\delta$ 0.45-0.60 (m, 1H, H₅), 0.56-0.63 (m, 1H, H₅), 0.65 (ddd, $^3$J₆₋₇ₐ=3$^3$J₆₋₈=3.5 Hz, $^2$J₆₋₇ₐ=5.4 Hz, $^3$J₆₋₇ₐ=9.2 Hz, 1H, H₆), 0.91-1.20 (m, 6H), 1.55-1.75 (m, 4H), 1.90-1.98 (m, 1H), 2.07 (td, $^3$J₆₋₇ₐ=3$^3$J₆₋₈=3.5 Hz, $^3$J₆₋₇ₐ=7.2 Hz, 1H, H₆), 3.55 (dd, $^3$J₄₋₃=4.1 Hz, $^2$J=9.7 Hz, 1H, H₄), 3.57 (dd, $^3$J₄₋₃=5.3 Hz, $^2$J=9.7 Hz, 1H, H₄), 3.67-3.73 (m, 1H, H₃), 4.13 (dd, $^3$J₂₋₃=4.5 Hz, $^2$J=8.7 Hz, 1H, H₂), 4.20 (t, $^3$J₂₋₃=8.7 Hz, 1H, H₂), 4.54 (s, 2H, H₃), 7.26-7.37 (m, 5H, H₉), $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 10.4 (C₇), 26.1 (CH₂), 26.2 (CH₂), 26.4 (CH₂), 27.5 (CH), 29.2 (CH), 32.0 (CH₂), 32.4 (CH₂), 41.0 (C₉), 56.1 (C₅), 64.8 (CH₂), 68.5 (CH₂), 73.5 (C₅), 127.8 (CH), 128.0 (CH), 128.5 (CH), 137.4 (C₆), 158.1 (C₇).
**Experimental**

**Benzylidimethylvinylsilane 172**

A solution of benzyl chloride (1.15 mL, 10 mmol, 1 eq) in dry diethyl ether (10 mL) was added dropwise to a mixture of magnesium turnings (0.24 g, 10 mmol, 1 eq) and iodine (2 crystals) in dry diethyl ether (10 mL) under nitrogen. The reaction mixture was stirred for 1 h and dimethylvinylchlorosilane (1.64 mL, 12 mmol, 1.2 eq) was added dropwise. The reaction mixture was heated at reflux for 16 h and then quenched carefully with saturated aqueous NH₄Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C) to give the **title compound 172** (1.09 g, 6.18 mmol, 62%) as a colourless oil.

**Chemical Analysis**

- **IR (CDCl₃):** ν max 3024 (m), 2957 (m), 2893 (w), 1601 (m), 1493 (s), 1452 (w), 1404 (m), 1248 (s), 1207 (m), 1155 (w), 1057 (w), 1009 (m), 951 (m), 831 (s, Si-C), 793 (m), 762 (m), 698 (s) cm⁻¹.
- **¹H NMR** (500 MHz, CDCl₃): δ 0.57 (s, 6H, 2x CH₃), 2.15 (s, 2H, CH₂), 5.67 (dd, J c,b = 3.8 Hz, J c-a = 20.3 Hz, 1H, Hc), 5.97 (dd, J b,c = 3.8 Hz, J b-a = 14.7 Hz, 1H, Hb), 6.13 (dd, J a,c = 14.7 Hz, J a-b = 20.3 Hz, 1H, Ha), 6.99-7.02 (m, 2H, Ha r o m), 7.05-7.09 (m, 1H, Ha r o m), 7.18-7.23 (m, 2H, Ha r o m).
- **¹³C NMR** (125 MHz, CDCl₃): δ -3.7 (CH₃), 25.8 (CH₂), 124.0 (CH), 128.1 (CH), 128.2 (CH), 132.2 (=CH₂), 138.2 (SiCH=), 139.9 (C₆), **EI-MS m/z (%):** 176 (M⁺, 13), 91 (Bn⁺, 17), 85 ([M-Bn]⁺, 100); **HMRS:** M⁺, found 176.10155. C₁₁H₁₆Si requires 176.10158.
Experimental

(4R,5S)-3-[(1S,2S)-2-(Benzyldimethylsilyl)-cyclopropyl]-4,5-diphenyl-2-oxazolidinone (+)-173

A solution of (+)-3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-109 (0.427 g, 1.25 mmol, 1.25 eq) in dry dichloromethane (1.25 mL) was added via a motorised syringe pump over 5.5 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and alkene 172 (0.176 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 4 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product ((+)-173A:(+)-173B:(+)-173C:(+)-173D: 94:<2:<2:<2 as determined by ¹H NMR) was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 8.5:1.5 to 3:1) to give the cyclopropanes (+)-173 (mixture of (+)-173A, (+)-173B, (+)-173C, (+)-173D) 14 mg, 0.03 mmol, 3%, white solid; (+)-173A 0.179 g, 0.42 mmol, 42%, white solid; 0.45 mmol, 45%).

Isomer A: Mp 149-151°C (EtOAc); Rf (P.E. 40-60°C/EtOAc 3:1) 0.34; [α]° +84.5 (c 1.06, CHCl₃); IR (CDCl₃): νmax 3025 (w), 2921 (w), 1735 (s, C=O), 1452 (m), 1405 (m), 1247 (w), 1247 (m), 1028 (w), 846 (w), 814 (m, Si-C), 769 (w), 697 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ -0.46 (s, 3H, H7), -0.37 (s, 3H, H7), -0.11 (ddd, 3J₆,₄=5.0 Hz, 3J₆,₅a=8.3 Hz, 3J₆,₅p=11.4 Hz, 1H, H₆), 0.83 (ddd, 3J₅a,₅p=8.2 Hz, 1H, H₅a), 1.23 (ddd, 3J₅p,₄=3.4 Hz, 1H, H₅p), 1.03 (ddd, 3J₅,₆=5.0 Hz, 3J₅,₈=6.3 Hz, 3J₅,₉=11.4 Hz, 1H,
Experimental

H$_3$), 1.81 (d, $^2_J$=13.6 Hz, 1H, H$_8$), 1.85 (d, $^2_J$=13.6 Hz, 1H, H$_8$), 2.37 (ddd, $^3_J$=3.4 Hz, $^3_J$=5.0 Hz, $^3_J$=6.3 Hz, 1H, H$_4$), 4.76 (d, $^3_J$=8.0 Hz, 1H, H$_3$), 5.72 (d, $^3_J$=8.0 Hz, 1H, H$_3$), 6.82-7.18 (m, 15H, Ha rom); $^{13}$C NMR (125 MHz, CDC$_3$): $\delta$ -5.3 (C$_7$), -4.8 (C$_7$), 4.1 (C$_6$), 11.6 (C$_5$), 24.8 (C$_8$), 29.0 (C$_4$), 66.9 (C$_3$), 79.6 (C$_2$), 124.0 (CH), 125.9 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 134.3 (C$_6$), 134.4 (C$_5$), 139.4 (C$_5$), 158.4 (C$_1$); CI(ammonia)-MS m/z (%): 426 ([M-H]$^+$, 29), 382 ([M-H-CO$_2$]$^+$, 100), 308 (26), 238 (16), 195 (57); HMRS: (M-H)$^+$, found 426.18798. C$_{27}$H$_{28}$N$_2$Si requires 426.18892; Anal. found: C, 76.09; H, 6.93; N, 3.30. Calcd for C$_{27}$H$_{29}$N$_2$Si: C, 75.84; H, 6.84; N, 3.38. For the crystallographic details of (+)-173, see Appendix.

**tert-Butyl N-[(1S,2S)-2-(Benzyl(dimethyl)silyl)-cyclopropyl] carbamate (++)-174**

![Structural diagram]

C$_{17}$H$_{27}$NO$_2$Si 305.48 g.mol$^{-1}$

A mixture of cyclopropane (+)-173A (100 mg, 0.234 mmol, 1 eq), di-tert-butyl dicarbonate (102 mg, 0.468 mmol, 2 eq), Pd(OH)$_2$/C (20%, 52 wt. % water, 51 mg, 0.036 mmol, 0.15 eq) and THF (8 mL) was hydrogenated at 5.5 bar at 30°C for 8 h. The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 4:1) to give the title compound (+)-174 (57 mg, 0.187 mmol, 80%) as a colourless oil.

$R_f$ (P.E. 40-60°C/ether 4:1) 0.31; $[\alpha]_D^{20} +16.3$ (c 1.0, CHCl$_3$); IR (film): $\nu_{max}$ 3327 (br, NH), 2976 (m), 2895 (w), 1705 (s, C=O), 1493 (s), 1452 (m), 1365 (s), 1247 (s), 1171 (s), 1078 (m), 833 (s, Si-C), 791 (w), 700 (s) cm$^{-1}$; $^1$H NMR (400 MHz, 328 K, CDC$_3$): $\delta$ -0.28 (ddd, $^3_J$=4.9 Hz, $^3_J$=8.1 Hz, $^3_J$=11.2 Hz, 1H, H$_6$), -0.09 (s, 3H, H$_4$), -0.06 (s, 3H, H$_4$), 0.57 (ddd, $^2_J$=4.7 Hz, $^2_J$=6.4 Hz, $^2_J$=8.1 Hz, 1H, H$_2$), 0.69 (dd), $^3_J$=3.3 Hz, $^2_J$=4.7 Hz, $^3_J$=11.2 Hz, 1H, H$_2$), 1.44 (s, 9H, C(CH$_3$)$_3$), 2.11 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 2.15 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 2.46 (ddd, $^3_J$=3.3 Hz, $^2_J$=4.7 Hz, 1H, H$_3$), 2.82 (dd, $^2_J$=13.6 Hz, 1H, H$_3$), 3.13 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 3.17 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 4.76 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 5.72 (d, $^2_J$=13.6 Hz, 1H, H$_3$), 6.82-7.18 (m, 15H, Ha rom); $^{13}$C NMR (125 MHz, CDC$_3$): $\delta$ -5.3 (C$_7$), -4.8 (C$_7$), 4.1 (C$_6$), 11.6 (C$_5$), 24.8 (C$_8$), 29.0 (C$_4$), 66.9 (C$_3$), 79.6 (C$_2$), 124.0 (CH), 125.9 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 134.3 (C$_6$), 134.4 (C$_5$), 139.4 (C$_5$), 158.4 (C$_1$); CI(ammonia)-MS m/z (%): 426 ([M-H]$^+$, 29), 382 ([M-H-CO$_2$]$^+$, 100), 308 (26), 238 (16), 195 (57); HMRS: (M-H)$^+$, found 426.18798. C$_{27}$H$_{28}$N$_2$Si requires 426.18892; Anal. found: C, 76.09; H, 6.93; N, 3.30. Calcd for C$_{27}$H$_{29}$N$_2$Si: C, 75.84; H, 6.84; N, 3.38. For the crystallographic details of (+)-173, see Appendix.
Experimental

$^{3}J_{1,3}=8.1$ Hz, $^{3}J_{1,2\beta}=6.2$ Hz, 1H, H$_{1}$), 4.53 (br s, 1H, NH), 7.00-7.07 (m, 3H, H$_{arom}$),
7.15-7.21 (m, 2H, H$_{arom}$); $^{13}$C NMR (100 MHz, 328 K, CDCl$_{3}$): $\delta$ -4.5 (2 x C$_{4}$), 5.8
(C$_{3}$), 10.6 (C$_{2}$), 25.5 (C$_{3}$), 27.2 (C$_{1}$), 28.5 (C(CH$_{3}$)$_{3}$), 79.3 (C(CH$_{3}$)$_{3}$), 124.1 (CH), 128.1
(CH), 128.2 (CH), 140.0 (C$_{q}$), 156.4 (C=O); EI-MS m/z (%): 305 (M$^{+}$, 5), 249 ([M+H-
C$_{4}$H$_{9}$]+, 22), 204 ([M-Boc]$^{+}$, 43), 149 (100), 114 (100), 98 (42), 75 (22); HMRS: M$^{+}$,
found 305.18162. C$_{17}$H$_{27}$N$_{2}$Si requires 305.18110.

1-[2-(Benzylidemethylsilanyl)-cyclopropyl]-2-pyrrolidinone 175

A solution of N-diethoxymethy-2-pyrrolidinone 78 (1.5 g, 8.0 mmol, 2 eq) in dry
diethyl ether (8 mL) was added via a motorised syringe pump over 6 h to a vigorously
stirred mixture of zinc amalgam (5.23 g, 80 mmol, 20 eq), zinc chloride (1M solution in
diethyl ether, 8 mL, 8 mmol, 2 eq), chlorotrimethylsilane (5.08 mL, 40 mmol, 10 eq)
and alkene 172 (0.705 g, 4 mmol, 1 eq) in dry diethyl ether (16 mL) under nitrogen at
reflux. The mixture was stirred for 18 h and then allowed to cool to room temperature.
The reaction was quenched with saturated aqueous NaHCO$_{3}$ solution (30 mL) and after
stirring for 20 min, the mixture was filtered and the separated zinc washed with diethyl
ether (20 mL). The organic layer was separated and the aqueous layer was extracted
with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine
(30 mL), dried (MgSO$_{4}$), filtered and concentrated in vacuo. The crude product
(trans/cis: >95:<5 as determined by $^{1}$H NMR) was purified by flash column
chromatography (silica, EtOAc/P.E. 40-60°C 4:1) to give almost exclusively the trans
cyclopropane 175 (0.422 g, 1.54 mmol, 39%) as a colourless oil.

$R_{f}$ (EtOAc) 0.41; IR (film): $\nu_{max}$ 2953 (m), 2891 (w), 1689 (s, C=O), 1493 (m), 1419
(m), 1294 (m), 1248 (m), 1155 (w), 883 (m, Si-C), 833 (s, Si-C), 791 (m), 700 (m) cm$^{-1}$;
**Experimental**

**1H NMR** (500 MHz, CDCl₃): δ -0.10 (s, 3H, H₈), -0.08 (ddd, J₇,₆a = 5.3 Hz, J₇,₆a = 8.2 Hz, J₆,₇ = 11.3 Hz, 1H, H₇), -0.05 (s, 3H, H₈), 0.64 (ddd, J₆b,₆a = 5.0 Hz, J₆b,₅ = 6.7 Hz, J₆b,₇ = 8.2 Hz, 1H, H₆b), 0.92 (ddd, J₅b,₅ = 3.7 Hz, J₅b,₆b = 5.0 Hz, J₅b,₇ = 11.3 Hz, 1H, H₅b), 1.87-1.95 (m, 2H, H₃), 2.13 (s, 2H, H₂b), 2.34 (t, J₆₂-₃ = 8.0 Hz, 2H, H₂), 2.61 (ddd, J₅b,₅ = 3.7 Hz, J₅b,₇ = 5.3 Hz, J₅b,₆b = 6.7 Hz, 1H, H₅b), 3.16 (t, J₄,₃ = 7.0 Hz, 2H, H₄), 6.99-7.06 (m, 3H, H₉ arom), 7.15-7.20 (m, 2H, H₉ arom); **13C NMR** (125 MHz, CDCl₃): δ -4.8 (C₈), -4.6 (C₈), 2.7 (C₇), 8.4 (C₆), 18.0 (C₅), 25.2 (C₂), 29.1 (C₃), 31.9 (C₄), 47.0 (C₄), 124.0 (CH), 128.1 (CH), 128.2 (CH), 139.8 (C₇), 175.9 (C¹); **EI-MS m/z (%):** 273 (M⁺, 62), 258 ([M-CH₃]+, 24), 218 (24), 182 ([M-Bn]+, 92), 149 (100), 121 (86), 97 (31), 91 (Bn⁺, 23); **HMRS:** M⁺, found 273.15083. C₁₆H₂₃NO₂Si requires 273.15488.

1-[2-(Hydroxymethylsilanyl)-cyclopropyl]-2-pyrrolidinone 176

![Chemical Structure](image)

C₉H₁₂NO₂Si 199.33 g.mol⁻¹

Tetrabutylammonium fluoride (1M solution in THF, 4.79 mL, 4.79 mmol, 2.2 eq) was added to a solution of cyclopropane 175 (0.6 g, 2.18 mmol, 1 eq) in THF (3.9 mL) at 4°C. After 10 min of stirring, the reaction mixture was quenched with brine (10 mL). The aqueous layer was extracted with diethyl ether (10 mL) and EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 9.5:0.5 to 9:1) to give the silanol 176 pure at 95% (0.2 g, 1.0 mmol, 46%) as a colourless oil.

Rₜ (EtOAc/MeOH 9:1) 0.4; **IR (film):** ν max 3365 (br, OH), 2955 (s), 2895 (m), 1682 (s, C=O), 1464 (m), 1423 (s), 1375 (m), 1296 (m), 1254 (s), 1059 (s), 886 (s, Si-C), 829 (s, Si-C), 787 (s) cm⁻¹; **1H NMR** (500 MHz, CDCl₃): δ -0.07 (m, 1H, H₇), -0.03 (s, 3H, H₈), 0.64 (ddd, J₆b,₆a = 5.0 Hz, J₆b,₅ = 6.7 Hz, J₆b,₇ = 8.2 Hz, 1H, H₆b), 0.92 (ddd, J₅b,₅ = 3.7 Hz, J₅b,₆b = 5.0 Hz, J₅b,₇ = 11.3 Hz, 1H, H₅b), 1.87-1.95 (m, 2H, H₃), 2.13 (s, 2H, H₂b), 2.34 (t, J₆₂-₃ = 8.0 Hz, 2H, H₂), 2.61 (ddd, J₅b,₅ = 3.7 Hz, J₅b,₇ = 5.3 Hz, J₅b,₆b = 6.7 Hz, 1H, H₅b), 3.16 (t, J₄,₃ = 7.0 Hz, 2H, H₄), 6.99-7.06 (m, 3H, H₉ arom), 7.15-7.20 (m, 2H, H₉ arom); **13C NMR** (125 MHz, CDCl₃): δ -4.8 (C₈), -4.6 (C₈), 2.7 (C₇), 8.4 (C₆), 18.0 (C₅), 25.2 (C₂), 29.1 (C₃), 31.9 (C₄), 47.0 (C₄), 124.0 (CH), 128.1 (CH), 128.2 (CH), 139.8 (C₇), 175.9 (C¹); **EI-MS m/z (%):** 273 (M⁺, 62), 258 ([M-CH₃]+, 24), 218 (24), 182 ([M-Bn]+, 92), 149 (100), 121 (86), 97 (31), 91 (Bn⁺, 23); **HMRS:** M⁺, found 273.15083. C₁₆H₂₃NO₂Si requires 273.15488.

1-[2-(Hydroxymethylsilanyl)-cyclopropyl]-2-pyrrolidinone 176
Experimental

Hg), 0.08 (s, 3H, H8), 0.63-0.72 (m, 1H, H6), 0.81-0.92 (m, 1H, H6), 1.83-1.96 (m, 2H, H3), 2.30 (t, \(^3J_{2,3}=8.0\) Hz, 2H, H2), 2.56-2.65 (m, 1H, H5), 3.23 (t, \(^3J_{4,3}=7.0\) Hz, 2H, H4), 4.79 (br s, 1H, OH); \(^{13}C\) NMR (75 MHz, CDCl3): δ -1.9 (C8), -0.8 (C8), 6.0 (C7), 8.1 (C6), 18.0 (C3), 28.8 (C5), 31.9 (C2), 47.3 (C4), 176.6 (C1); EI-MS \(m/z\) (%): 199 (M\(^+\), 100), 184 ([M-CH\(_3\)]\(^+\), 53), 144 (54), 124 (54), 124 (26), 96 (16), 75 (63); HMRS: M\(^+\), found 199.10127. C\(_9\)H\(_{10}\)NO\(_2\)Si requires 199.10285.

1-[2-(Hydroxycyclopropyl)]-2-pyrrolidinone 180

\[ \text{C}_7\text{H}_{11}\text{NO} \quad 141.17 \text{g.mol}^{-1} \]

Tetrabutylammonium fluoride (1M solution in THF, 1.09 mL, 1.09 mmol, 2 eq) was added to a solution of cyclopropane 175 (0.15 g, 0.544 mmol, 1 eq) in THF (0.3 mL) under nitrogen. After 30 min of stirring, methanol (1.4 mL), potassium hydrogen carbonate (0.11 g, 1.09 mmol, 2 eq) and hydrogen peroxide (30% solution in water, 1.12 mL, 10.9 mmol, 20 eq) were added to the solution. The reaction mixture was stirred for 18 h and then sodium thiosulfate pentahydrate (2.97 g, 11.97 mmol, 22 eq) was added. After stirring for 30 min the mixture was filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 1:0 to 9:1) to give the title compound 180 (27 mg, 0.191 mmol, 35%) as a colourless oil.

\( R_f \) (EtOAc/MeOH 9:1) 0.35; IR (film): \( \nu_{max} \) 3369 (br, OH), 2989 (w), 2957 (w), 2859 (w), 1662 (s, C=O), 1463 (m), 1425 (m), 1300 (s), 1202 (m), 1155 (w), 1020 (w), 927 (w) cm\(^{-1}\); \(^1H\) NMR (500 MHz, CDCl3): δ 0.83 (dt, \(^3J_{6\alpha-5}=5.0\) Hz, \(^2J_{6\alpha-6\beta}=3J_{6\alpha-7}=7.1\) Hz, 1H, H6\(\alpha\)), 1.02 (ddd, \(^3J_{6\beta-7}=4.1\) Hz, \(^2J_{6\beta-6\alpha}=7.1\) Hz, \(^3J_{6\beta-5}=8.8\) Hz, 1H, H6\(\beta\)), 1.85-1.99 (m, 2H, H3), 2.33 (t, \(^3J_{2,3}=8.1\) Hz, 2H, H2), 2.53 (ddd, \(^3J_{5\gamma}=1.6\) Hz, \(^3J_{5-6\alpha}=5.0\) Hz, \(^3J_{5-6\beta}=8.6\) Hz, 1H, H5), 3.20-3.30 (m, 2H, H4), 3.50 (ddd, \(^3J_{7-5}=1.6\) Hz, \(^3J_{7-6\beta}=4.1\) Hz,
Experimental

$^3J_{7-6a}$ = 7.5 Hz, 1H, H$_7$), 4.31 (br s, 1H, OH); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.6 (C$_6$), 17.9 (C$_3$), 31.6 (C$_2$), 32.4 (C$_5$), 47.4 (C$_4$), 51.1 (C$_7$), 176.6 (C$_1$); EI-MS m/z (%): 141 (M$^+$, 7), 112 (100), 98 (24), 84 (23), 69 (47); HMRS: M$^+$, found 141.07832. C$_7$H$_{11}$NO$_2$ requires 141.07843.

tert-Butyl N-[(1S,2S)-2-(Hydroxycyclopropyl)] carbamate (+)-181

![Chemical Structure](image)

C$_8$H$_{15}$NO$_3$ 173.21 g mol$^{-1}$

Tetrabutylammonium fluoride (1M solution in THF, 0.33 mL, 0.33 mmol, 2 eq) was added to a solution of cyclopropane (+)-174 (50 mg, 0.164 mmol, 1 eq) in THF (0.08 mL) under nitrogen. After 30 min of stirring, methanol (0.41 mL), potassium hydrogen carbonate (32.8 mg, 0.33 mmol, 2 eq) and hydrogen peroxide (30% solution in water, 0.34 mL, 3.28 mmol, 20 eq) were added to the solution. The reaction mixture was stirred for 16 h and then sodium thiosulfate pentahydrate (0.9 g, 3.62 mmol, 22 eq) was added. After stirring for 30 min the mixture was filtered and concentrated in vacuo.

The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 1:1) to give the title compound (+)-181 (25 mg, 0.144 mmol, 88%) as a colourless oil.

R$_f$ (P.E. 40-60°C/EtOAc 1:1) 0.3; $[\alpha]_D^{20}$ -14.6 (c 0.99, CHCl$_3$); IR (film): $\nu_{\text{max}}$ 3327 (br, NH), 2978 (m), 2931 (w), 1690 (s, C=O), 1522 (m), 1367 (m), 1278 (m), 1256 (m), 1171 (s), 1020 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.71 (dt, $^3J_{2a,1}$=4.6 Hz, $^2J_{2a-2b}$=$^3J_{2a-3}$=7.0 Hz, 1H, H$_{2a}$), 0.99 (ddd, $^3J_{2b-3}$=3.9 Hz, $^2J_{2b-2a}$=6.8 Hz, $^3J_{2b-1}$=8.5 Hz, 1H, H$_{2b}$), 1.40 (s, 9H, C(CH$_3$)$_3$), 2.48-2.54 (m, 1H, H$_1$), 3.36 (ddd, $^3J_{3-1}$=1.4 Hz, $^3J_{3-2b}$=3.9 Hz, $^3J_{3-2a}$=7.2 Hz, 1H, H$_3$), 4.09 (br s, 1H, OH), 4.68 (br s, 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 15.7 (C$_2$), 28.3 (C(CH$_3$)$_3$), 30.5 (C$_1$), 52.6 (C$_3$), 79.9 (C(CH$_3$)), 156.7 (C=O); EI-MS m/z (%): 173 (M$^+$, 100); HMRS: M$^+$, found 173.10521. C$_8$H$_{15}$NO$_3$ requires 173.10519.
**Experimental**

**N-Benzyl-N-vinylacetamide 188**

![Chemical structure of N-Benzyl-N-vinylacetamide 188](image)

N-vinyl acetamide (1.36 g, 16.0 mmol, 1 eq) was added portionwise to a suspension of NaH (60% in oil, 1.28 g, 32.0 mmol, 2 eq) in dry DMF (32 mL) under nitrogen. The reaction mixture was stirred for 30 min and benzyl bromide (5.71 mL, 48 mmol, 3 eq) was added dropwise. After stirring for 4 h, the reaction was carefully quenched with saturated aqueous NH₄Cl solution (30 mL). Diethyl ether (60 mL) was added and the mixture transferred into a separating funnel. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:2) to give the **title compound 188** (1.79 g, 10.2 mmol, 64%) as a yellow oil.

**Rf** (P.E. 40-60°C/EtOAc 1:1) 0.60; **IR** (film): \( \nu_{\text{max}} \) 3032 (m), 2931 (w), 1674 (s, C=O), 1622 (s), 1420 (m), 1383 (s), 1342 (m), 1213 (m), 1028 (w), 847 (w), 727 (m), 696 (w) cm\(^{-1}\); **\(^1\)H NMR** (400 MHz, 373 K, DMSO): \( \delta \) 2.22 (s, 3H, CH₃), 4.34 (d, \( ^3J = 9.2 \) Hz, 1H, =CH₂), 4.47 (d, \( ^3J = 15.6 \) Hz, 1H, =CH₂), 4.85 (s, 2H, PhCH₂N), 7.15 (dd, \( ^3J = 9.2 \) Hz, \( ^3J = 15.6 \) Hz, 1H, NCH=), 7.20-7.36 (m, 5H, H\(_{\text{arom}}\)); **\(^13\)C NMR** (100 MHz, 373 K, DMSO): \( \delta \) 20.9 (CH₃), 45.4 (CH₂), 93.8 (=CH₂), 125.7 (CH), 126.0 (CH), 127.5 (CH), 132.9 (NCH=), 136.7 (C₆), 168.4 (C=O); **EI-MS** \( m/z \) (%): 175 (M\(^+\), 86), 148 ([M-C₂H₅]\(^+\), 27), 132 ([M-COCH₃]\(^+\), 100), 117 (19), 106 (56).
(4R,5S)-4,5-Diphenyl-3-vinyl-2-oxazolidinone (+)-189

![Image of oxazolidinone structure]

C₁₇H₁₅NO₂ 265.31 g·mol⁻¹

(4R,5S)-3-(1-Ethoxyethyl)-4,5-diphenyl-2-oxazolidinone

The N,O-acetal was prepared by a modification of the literature method. A mixture of oxazolidinone (+)-112 (1.24 g, 5.18 mmol, 1 eq), 10-camphorsulfonic acid (0.09 g, 0.39 mmol, 0.075 eq) and acetaldehyde diethylacetal (11 mL, 77.7 mmol, 15 eq) was heated at 60°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous NaHCO₃ solution (10 mL). The aqueous phase was extracted with diethyl ether (40 mL then 20 mL) and the combined organic extracts were washed with brine (15 mL), filtered and concentrated in vacuo to give the expected N,O-acetal (1.48 g, 5.18 mmol, 100%, 2/3:1/3 mixture of diastereoisomers) as a yellow oil which was used without further purification.

Major isomer: H NMR (500 MHz, CDCl₃): δ 0.89 (d, 3J=6.4 Hz, 3H, CH₃CH), 1.23 (t, 3J=7.1 Hz, 3H, CH₂CH₂), 3.51 (qd, 3J=7.1 Hz, 2J=9.4 Hz, 1H, CHHCH₃), 3.68 (qd, 3J=7.1 Hz, 2J=9.4 Hz, 1H, CHHCH₃), 5.04 (d, 3J=7.9 Hz, 1H, NCHPh), 5.41 (q, 3J=6.4 Hz, 1H, CH₂CH₃), 5.82 (d, 3J=7.9 Hz, 1H, OCHPh), 6.82-7.02 (m, 10H, H₉ arom); 13C NMR (125 MHz, CDCl₃): δ 14.9 (CH₃), 20.6 (CH₃), 59.8 (NCHPh), 63.4 (CH₂CH₃), 80.8 (CH), 80.9 (CH), 125.8 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 133.8 (C₆), 136.4 (C₆), 158.1 (C=O).

Trimethylsilyl trifluoromethanesulfonate (0.68 mL, 3.55 mmol, 1.3 eq) was added dropwise to a solution of the crude N,O-acetal (0.78 g, 2.5 mmol, 1 eq) and
Experimental

triethylamine (0.57 mL, 4.1 mmol, 1.5 eq) in dry dichloromethane (5 mL) under nitrogen at 4°C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was cooled to 4°C and saturated aqueous NaHCO₃ solution (5 mL) was added. After stirring for 5 min, the mixture was transferred into a separating funnel. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1) to give the title compound (+)-189 (0.44 g, 1.66 mmol, 67%) as a white solid.

Mp 166-167°C (lit., 13 170-171°C (EtOAc/hexane); Rf (P.E. 40-60°C/EtOAc 4:1) 0.36; [α]_D +22.0 (c 1.0, CHCl₃) (lit., 13 [α]_D +21.7 (c 0.775, CHCl₃); IR (film): νmax 3070 (w), 3034 (w), 1763 (s, C=O), 1640 (s), 1558 (s), 1456 (m), 1425 (m), 1382 (m), 1364 (m), 1217 (m), 1103 (w), 1043 (w), 908 (s), 733 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 4.07 (dd, J₆₋₇ =1.0 Hz, J₆₋₅ =16.0 Hz, 1H, H₆), 4.34 (dd, J₅₋₆ =1.0 Hz, J₅₋₄ =9.1 Hz, 1H, H₅), 5.24 (d, J₃₋₄ =8.1 Hz, 1H, H₃), 5.82 (d, J₂₋₃ =8.1 Hz, 1H, H₂), 6.79-6.87 (m, 2H, H arom), 6.90-6.93 (m, 2H, H arom), 6.94 (dd, J₆₋₇ =9.1 Hz, J₆₋₅ =16.0 Hz, 1H, H₆), 7.05-7.08 (m, 6H, H arom); ¹³C NMR (125 MHz, CDCl₃): δ 63.1 (C₃), 80.5 (C₂), 96.2 (C₃), 126.3 (CH), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 133.2 (Cq), 133.6 (Cq), 155.3 (C); EI-MS m/z (%): 265 (M⁺, 44), 220 (12), 180 (37), 168 (22), 131 (77), 104 (100); HMRS: M⁺, found 265.11056. C₁₇H₁₅NO₂ requires 265.11027.
Chapter 5

References
References

References

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102 (+)- and (-)-2-amino-1,2-diphenylethanol were purchased from Aldrich.


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Chapter 6

Appendix
Table A. Crystal data and structure refinement for (+)-173A.

<table>
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<tr>
<th>Property</th>
<th>Value</th>
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<td>Unit cell parameters</td>
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</tr>
<tr>
<td>b</td>
<td>13.7564(16) Å</td>
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<tr>
<td>c</td>
<td>26.057(3) Å</td>
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<td>Crystal colour and size</td>
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<td>ω range for data collection</td>
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<td>Index ranges</td>
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<td>Independent reflections</td>
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<td>Reflections with F^2 &gt; 2σ</td>
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<td>Absorption correction</td>
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<td>Min. and max. transmission</td>
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<td>Final R indices [F^2 &gt; 2σ]</td>
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<td>R indices (all data)</td>
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<td>Goodness-of-fit on F^2</td>
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<td>Extinction coefficient</td>
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<td>Largest and mean shift/su</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>1.161 and -0.470 e Å⁻³</td>
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Table B. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for (+)-173A. \( U_{eq} \) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

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<th>Atom</th>
<th>x</th>
<th>y</th>
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<th>( U_{eq} )</th>
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<td>Si(1)</td>
<td>0.0501(3)</td>
<td>0.26869(11)</td>
<td>0.18200(6)</td>
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<td>N(1)</td>
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<td>0.1695(3)</td>
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<td>O(1)</td>
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### Table C. Bond lengths [Å] and angles [°] for (+)-173A.

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222
Table D. Anisotropic displacement parameters (Å²) for (+)-173A. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U^{11} + ... + 2hka^{*b}b^{*U^{12}}]$

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<td>-0.031(6)</td>
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<td>0.005(3)</td>
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<tr>
<td>C(27)</td>
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<td>0.046(4)</td>
<td>0.164(10)</td>
<td>0.040(6)</td>
<td>-0.010(5)</td>
<td>0.000(3)</td>
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### Appendix

**Table E. Hydrogen coordinates and isotropic displacement parameters (Å²) for (+)-173A.**

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<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
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<td>H(2A)</td>
<td>0.2848</td>
<td>0.1122</td>
<td>-0.0316</td>
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<td>H(3A)</td>
<td>0.1177</td>
<td>0.1132</td>
<td>0.0449</td>
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<td>H(5A)</td>
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<td>H(6A)</td>
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<td>-0.1768</td>
<td>-0.0757</td>
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<td>H(8A)</td>
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<td>H(9A)</td>
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<td>-0.0835</td>
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<td>H(11A)</td>
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<td>0.1058</td>
<td>0.062</td>
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<tr>
<td>H(12A)</td>
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<td>0.3629</td>
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<tr>
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<tr>
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<tr>
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<td>0.3797</td>
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<td>0.052</td>
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<tr>
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<tr>
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<td>0.1890</td>
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<td>H(23A)</td>
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Table F. Torsion angles [°] for (+)-173A.

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(+)-173A

Scheme A