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JHG 05/2011
New Reactions of Oxetanes

by

Benjamin Oliver Beasley

A thesis submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

September 2013
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Declaration

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick carried out between October 2009 and October 2013.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

At the time of publication, part of this work has appeared in the scientific literature:

Abstract

This thesis describes the synthesis and new reactions of oxetan-3-ones. Chapter 1 gives an introduction to oxetanes and includes discussion of methods for their synthesis, their reactions, specifically those involving the use of oxetan-3-ones, and their relevance in medicinal chemistry and natural products.

Chapter 2 begins with an introduction to multi-component reactions (MCRs) and moves on to describe our efforts in incorporating oxetanes into structurally diverse compounds using Passerini three-component reactions (P-3CRs) and Ugi four-component reactions (U-4CRs). A range of 3,3-disubstituted oxetanes are successfully made in 23-98% yield by reaction of oxetan-3-ones with various carboxylic acids and isocyanides. The synthesis of chiral 2-substituted oxetan-3-ones using the SAMP chiral auxiliary method is also demonstrated, specifically oxetan-3-one is converted into 2-benzyloxetan-3-one in 51% overall yield and 74% ee in three steps.

Chapter 3 details our efforts towards the incorporation of the oxetane unit into tetrahydro-β-carbolines using the Pictet-Spengler reaction. Several oxetan-3-ones are demonstrated to take part in Pictet-Spengler reactions with tryptamine and tryptophan ethyl ester derivatives. The chemistry is successfully extended in azetidinones.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>2D</td>
<td>2-Dimensional</td>
</tr>
<tr>
<td>3-CR</td>
<td>3-Component Reaction</td>
</tr>
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<td>4-CR</td>
<td>4-Component Reaction</td>
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<td>aq.</td>
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<tr>
<td>BOC</td>
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<td>cat.</td>
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<td>Carboxybenzyl</td>
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<td>COSY</td>
<td>Correlation Spectroscopy</td>
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<td>cy</td>
<td>cyclohexyl</td>
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<td>DCE</td>
<td>1,2-Dichloroethane</td>
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<tr>
<td>de</td>
<td>diastereomeric excess</td>
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<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
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<td>DMDO</td>
<td>Dimethyldioxirane</td>
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<td>DMPU</td>
<td>1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
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<td>DMSO</td>
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<td>dr</td>
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<td>er</td>
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<td>equiv.</td>
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<td>FMOC</td>
<td>Fluorenylmethyloxycarbonyl</td>
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<td>Fourier Transform-Infrared</td>
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<td>GC</td>
<td>Gas Chromatography</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>h</td>
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<td>HMBC</td>
<td>Heteronuclear Multiple-Bond Correlation</td>
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<td>HMQC</td>
<td>Heteronuclear Multiple-Quantum Correlation</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>IMCR</td>
<td>Isocyanide-based Multi-Component Reaction</td>
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<tr>
<td>J</td>
<td>Coupling constant</td>
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<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
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<tr>
<td>LogD</td>
<td>Distribution Constant</td>
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<td>Partition Coefficient</td>
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<td>MW</td>
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<td>NMR</td>
<td>Nuclear Magnetic Resonance Imaging</td>
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<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
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<td>Nucleophile</td>
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<td>P-3CR</td>
<td>Passerini 3-component reaction</td>
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<td>PG</td>
<td>Protecting group</td>
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<td>Phthalate</td>
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<td>Piv</td>
<td>Pivoyl</td>
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<td>ppm</td>
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<td>Abbreviation</td>
<td>Full Name (Definition)</td>
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<tr>
<td>quant.</td>
<td>quantitative</td>
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<tr>
<td>r.t.</td>
<td>room temperature</td>
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<td>RAMP</td>
<td>(R)-1-amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-1-amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-N-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>temp.</td>
<td>temperature</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THBC</td>
<td>Tetrahydro-β-carboline</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THQ</td>
<td>Tetrahydroisoquinoline</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-Trichloroethoxycarbonyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
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<tr>
<td>U-4C-3CR</td>
<td>Ugi 4-centre-3-component reaction</td>
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<td>UV</td>
<td>Ultraviolet</td>
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<td>W</td>
<td>Watt</td>
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</table>
Chapter 1:

Synthesis and Medicinal Chemistry of Oxetanes
1.1. Introduction

This thesis will detail efforts to incorporate oxetanes into structurally diverse molecules using multi-component reactions (MCRs) and reactions involving iminooxetanes. With the main subject matter revolving around the chemistry of oxetanes, this chapter provides an introduction to their synthesis, reactions and applications, particularly in the important area of medicinal chemistry.

1.2. Introduction to Oxetanes

Oxetane (1) is a four-membered heterocyclic ring containing a single oxygen atom. The first reported synthesis of this simple molecule was in 1878 by Reboul via the base induced ring closure of chloro-alcohol 2 (Scheme 1.2.1).\(^1\) Interestingly, studies have shown that the oxetane ring is much less puckered than the analogous cyclobutane.\(^2\)\(^-\)\(^4\) Its strong ability as an acceptor for hydrogen bonds compared to other cyclic ethers such as tetrahydrofuran and tetrahydropyran has also been noted.\(^5\)

![Scheme 1.2.1](image)

1.3. Synthesis of Oxetanes

The Williamson ether synthesis has been used to synthesise oxetanes in a number of instances. For example, Soai \textit{et al.} developed a method for their asymmetric synthesis starting from chloro-ketone 3 using a chiral reduction catalyst generated \textit{in situ} from chiral ligand 4 and LiBH\(_4\) (Scheme 1.3.1).\(^6\) Subsequent ring-closure of chiral alcohol 5 afforded 2-phenyl oxetane 6 in good enantiomeric excess.
Wender et al. successfully installed the oxetane substituent of taxol at a late stage in their synthesis.\(^7\) Stereoselective ring closure of the primary alcohol 7 could be achieved using Hünig’s base in excellent yield (Scheme 1.3.2). Subsequent acetylation with acetic anhydride provided 8, which was only 4 steps away from taxol (9).

Another common approach towards the synthesis of oxetanes 10 is the Paternò-Büchi [2+2]-cycloaddition reaction between a carbonyl-containing compound (11) and an alkene (12) under the irradiation of light (Scheme 1.3.3).\(^8\)
Chapter 1: Synthesis and Medicinal Chemistry of Oxetanes

Bach et al. showed that the classical Paternò-Büchi [2+2] cycloaddition reaction may be used for the diastereoselective synthesis of oxetanes.\(^9\)\(^,\)\(^10\) For example, reaction between racemic alkoxy silyl enol ether \(\text{13}\) and benzaldehyde provided diastereomers \(\text{14a}\) and \(\text{14b}\) with good diastereoselectivity (Scheme 1.3.4).\(^10\)

Both the Paternò-Büchi and Williamson ether synthesis have been thoroughly investigated and discussed in reviews.\(^11\)\(^,\)\(^12\) Recent efforts towards the synthesis of structurally diverse oxetanes, including the studies in this thesis, have largely revolved around the chemistry of oxetan-3-ones, the synthesis and chemistry of which are discussed herein.

1.4. Oxetan-3-ones

Oxetan-3-ones provide a useful entry point into the chemistry of oxetanes. Unsubstituted oxetan-3-one (\(\text{15}\)) was first isolated and characterised by Marshall et al. in 1952.\(^{13}\)
1.4.1. Synthesis of Oxetan-3-ones

Oxetan-3-one (15) has been synthesised using a variety of methods, however, traditional methods for its synthesis were generally low yielding.\textsuperscript{13-16} Owing to its known volatility and water solubility,\textsuperscript{14} purification of the final product is often difficult to achieve, requiring preparative gas chromatography (GC).\textsuperscript{14} In response to this, Carreira and co-workers developed a more efficient four-step method, starting from dihydroxyacetone 16. In the final step, refluxing 2,2-dimethoxypropane 17 with Montmorillonite K10 provided oxetan-3-one (15) in an improved yield, although careful distillation of the final mixture was still required (Scheme 1.4.1).\textsuperscript{17} Oxidation of oxetan-3-ol also provides an alternative method for the large scale synthesis of oxetan-3-one (15).\textsuperscript{18}

\begin{center}
\begin{tikzpicture}
\node (16) at (0,0) {16};
\node (17) at (2,0) {17};
\node (15) at (4,0) {15};
\draw[->] (16) -- (17) node[midway,above] {3 steps};
\draw[->] (17) -- (15) node[midway,above] {Montmorillonite K10 reflux};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.4.1}

Chiral 2-substituted oxetan-3-one 18 has been synthesised via a three-step method reported by Zhang and co-workers.\textsuperscript{19} Chiral propargyl alcohol 19 was first synthesised from substituted aldehyde 20 and trimethylsilyl acetylene (21).\textsuperscript{20} The
TMS-protecting group of propargyl alcohol 19 was then removed using TBAF providing 22. Finally, cyclisation to the corresponding 2-substituted oxetan-3-one 18 was possible under acidic, gold-catalysed conditions using a pyridine N-oxide as oxidant (Scheme 1.4.2). A number of racemic, substituted oxetan-3-ones were also synthesised using this methodology. These authors also demonstrated the synthesis of oxetan-3-one (15) itself, although they did not attempt its direct isolation.

![Scheme 1.4.2](image)

As part of their synthesis of (±)-pseudodeflectusin, Maegawa et al. disclosed a new one-pot method for the preparation of substituted oxetan-3-ones via the cyclisation of acyclic phosphonate-esters 23. Treatment of 24 with LDA and TMEDA provided phosphonate 23, which was then subjected to an in situ Horner-Wadsworth-Emmons olefination reaction using a range of aldehydes (Scheme 1.4.3). This method provided a variety of 2,2,4-trisubstituted oxetan-3-ones 25 in good yield.
Substituted allenes have also been shown to be useful precursors in the synthesis of oxetan-3-ones. Sharma et al. demonstrated that after diepoxidation of allenes 26 with dimethyldioxirane (DMDO), two methods could be used to synthesise the corresponding oxetan-3-ones 27 (Scheme 1.4.4). Epoxide opening of 28 with LiBr followed by intramolecular displacement of the halide provided a range of substituted oxetan-3-ones 27 in good yields. Alternatively it was found that simple heating of the bisepoxide intermediates led to 27 in good yield. An enantiomerically enriched 2,2,4-disubstituted oxetan-3-one was also synthesised using this method, although the authors did not report its enantiopurity.
Chapter 1: Synthesis and Medicinal Chemistry of Oxetanes

1.4.2. Reactions of Oxetan-3-ones

Oxetan-3-one (15) is capable of taking part in a variety of useful reactions.²³ The reactivity of oxetan-3-ones can be broadly categorised in two ways; ring opening reactions and transformations of the carbonyl group.²³

1.4.3. Ring-Opening Reactions of Oxetan-3-ones

There have been a number of explorations into the ring opening reactions of oxetan-3-ones.²³ Ring expansion of the oxetane ring is also possible, an early example of which involves the oxidation of tetra-substituted oxetan-3-one 29 with peracetic acid (Scheme 1.4.5).²⁴ The formation of 30 using this method remains the only example of a Baeyer-Villiger type oxidation of an oxetan-3-one.

Scheme 1.4.4

Scheme 1.4.5
1.4.4. Transformations of the Carbonyl Group

Oxetan-3-one (15) is suitable for a variety of carbonyl transformations, a selection of which are depicted Scheme 1.4.6. A variety of methods for the reduction of 15 to the corresponding oxetan-3-ol (31) have been developed\(^{23}\) and work by Carreira and co-workers has shown that the molecule will react with stabilised ylids and nitromethane to form esters 32, nitro alkenes 33 and nitriles 34.\(^{17,25}\) Reaction with aryl lithiums gives compounds such as 35,\(^{17}\) whilst Horner-Wadsworth-Emmons and Wittig type reactions can be used to produce the corresponding phosphonate 36 and aldehyde 37 respectively.\(^{18}\) Oxetan-3-one has also been shown to take part in Wittig-Horner type reactions, providing protected amino ester 38.\(^{26}\) Nassoy et al. have shown that oxetane-substituted sydnones may be generated from 15 and subsequently used in the synthesis of pyrazole building blocks.\(^{27}\)
During their investigations into the synthesis of compounds for the inhibition of phosphoinositide 3-kinase α (P13K-α), Heffron et al. demonstrated that oxetan-3-one (15) could be used to trap lithiated thiophenes 39, producing the corresponding oxetan-3-ol 40. This compound was a key intermediate in the synthesis of oxetane-containing compound 41, which was found to be a good growth inhibitor of the brain tumour glioblastoma.
In research focused on the optimisation of aqueous solubility and metabolic stability of GPR119 agonist 45, Scott et al. sought to replace the tert-butyl constituent with a variety of different functional groups, including oxetane. Nucleophilic addition of a CF$_3$ group onto oxetan-3-one (15), followed by reaction of the intermediate alcohol 43, provided key building block 44. Subsequent transformations led to GPR119 agonist 42, which was shown to have superior solubility, stability and reduced lipophilicity compared with 45.\textsuperscript{29}
1.4.5. Reactions of Iminooxetanes

There are almost no reports of the chemistry of iminooxetanes. Originally reported by Kozikowski et al., the Strecker three-component reaction performed on oxetan-3-one (15), remains as one of the few examples of the reactivity of iminooxetanes.\(^\text{15}\) In this reaction, oxetan-3-one (15) was reacted with sodium cyanide and benzylamine to produce compound 46 via imine 47. Subsequent hydrolysis and reduction of the benzyl group provided amino acid 48 in low yield (Scheme 1.4.9).
Zhang and co-workers similarly presented the Strecker reaction of oxetan-3-one (15), which was formed in situ from propargyl alcohol.\textsuperscript{19}

More recently, Hamzik et al. demonstrated that it is possible to form oxetan-3-N-tert-butylsulfinimine 49 in moderate yield from oxetan-3-one (15) and tert-butylsulfonamide 50 using titanium(IV) ethoxide as a dehydrating reagent (Scheme 1.4.10).\textsuperscript{30} This imine is then a suitable substrate for 1,2-addition reactions with a variety of organo-lithium species, forming 3-aminooxetanes 51 in good yield. Moreover, aziridination of sulfinimine 49 using trimethylloxosulfonium methylide 52 under mild conditions provided sulfinylaziridine 53 in high yield. Ring opening of the aziridine was achieved with a variety of nucleophiles, providing access to substituted 3-aminooxetanes 54 in generally excellent yields.
In related work, Ellman and co-workers reported the Rh-catalysed addition of arylboroxines 55 to N-tert-butylsulfinimines 49 or 56 (Scheme 1.4.11). Under optimised conditions, oxetane and azetidine containing amines 57 or 58 respectively could be synthesised in good to excellent yields.

It is known that oxetan-3-one (15) may form oxime 59 via reaction with hydroxylamine (Scheme 1.4.12). Oxime species 59 can then be hydrogenated to the corresponding 3-aminooxetane 60.

Nu = Grignard, thiol, amine
Chapter 1: Synthesis and Medicinal Chemistry of Oxetanes

Scheme 1.4.12

Finally, it has been reported that preparation of lithium salt 61 is possible. It was subsequently shown that this compound takes part in a fragmentation, providing the ring-opened compound 62, via carbene intermediate 63 (Scheme 1.4.13).

Scheme 1.4.13

1.5. Oxetanes in Natural Products and Drug Discovery

Of the few natural products that contain the oxetane ring, taxol (9) is probably the most well-known (Figure 1.5.1). This complex terpene was first isolated from the bark of the western yew (Taxus brevifolia) and is currently used as a cancer chemotherapeutic drug. The compound is known to act by stabilising microtubules during cell division. Due to the large size and complex nature of taxol, it has been difficult to elucidate the specific role of the oxetane moiety. A computational study deduced that the inclusion of the oxetane unit in taxol leads to greater structural rigidity. Further studies also show that it may act as a hydrogen-bond acceptor. Replacement of the oxygen atom of the oxetane unit with nitrogen, sulfur and selenium provided analogues with lower activity.
Other examples of naturally occurring compounds that contain the oxetane ring include oxetin (64),\textsuperscript{40} thromboxane A\textsubscript{2} (65)\textsuperscript{41} and bradyoxetin (66)\textsuperscript{42} (Figure 1.5.2). Oxetin (64) is an example of a simple 2,3-disubstituted oxetane that was isolated from a broth of \textit{Streptomyces} sp. OM-2317 (Figure 1.5.2).\textsuperscript{40} Studies are on-going into its possible herbicidal and antibacterial properties.\textsuperscript{40} Thromboxane A\textsubscript{2} (65) is a compound that is synthesised by platelets in the blood and promotes vasoconstriction, platelet aggregation and bronchoconstriction. Interestingly, this compound has a short half-life of only thirty seconds, which is controlled by hydrolysis of the oxetane ring.\textsuperscript{35,41} Finally, bradyoxetin (66), which was isolated from symbiotic soybean bacterium \textit{B. Japonicum}, is stated to be a potential antibiotic.\textsuperscript{35,42}
1.6. Oxetanes in Medicinal Chemistry

In the development of potential anticancer compounds, Pei et al. screened a variety of compounds that act by inhibiting the kinase mTOR, which is the mammalian target of the drug rapamycin. They opted to introduce an oxetane unit at the end of the synthesis via a reductive amination between intermediate 67 and oxetan-3-one 15 using sodium triacetoxyborohydride (Scheme 1.6.1). Of all the medicinally relevant compounds that were synthesised, 68 proved to be the most potent and competitive inhibitor of mTOR.

![Scheme 1.6.1](image)

Hirsch et al. utilised the oxetane unit to increase the solubility of a potential drug candidate 69 (Scheme 1.6.2). In order to incorporate the oxetane, a multistep approach was used, starting with the low-yielding Michael addition of 5-iodocytosine 70 to oxetane-ester 32. Iodide 71 was then reacted with alkyne 72 via a Sonogashira cross-coupling, affording 69 in good yield.
Although oxetanes have been known for over a century, until recently there have been very few studies regarding their use in medicinal chemistry. As an early example, in 1959 it was found that 3,3-diethyloxetane (73) displays anticonvulsant activity in rats, whilst 3-ethyloxetane (74) was found to be a toxic but weak anaesthetic (Figure 1.6.1).

**Figure 1.6.1**

1.6.1.  **Isosteric Replacement of Functional Groups with Oxetanes**

In recent years, Carreira and co-workers have carried out a variety of investigations into the medicinally relevant properties of oxetanes and related
Chapter 1: Synthesis and Medicinal Chemistry of Oxetanes

structures. Of particular note is their research into the possible benefits of replacing functionalities commonly used in drug discovery with the oxetane sub-unit.

The incorporation of gem-dimethyl and the related tert-butyl and isopropyl groups into potential drug molecules is often performed in order to improve their metabolic stability. For example, benzylic positions are often prime candidates for gem-dimethyl group incorporation owing to their susceptibility to metabolic attack. There are instances, however, where the gem-dimethyl group itself can become prone to metabolic degradation. Furthermore, its addition can lead to an increase in the lipophilicity of a compound and it can also reduce aqueous solubility. It has been proposed that oxetane can be viewed as an oxygen-bridged gem-dimethyl group (Figure 1.6.2).

![Figure 1.6.2](image)

A comparison of the partial molar volumes of oxetane (61.4 cm$^3$ mol$^{-1}$) and propane (70.7 cm$^3$ mol$^{-1}$) illustrates the compact nature of the oxetane unit. Carreira and co-workers have investigated a variety of properties such as solubility, lipophilicity and metabolic stability of oxetane containing compounds such as 75 (Table 1.6.1). tert-Butyl-containing 76 was used for comparison.
Chapter 1: Synthesis and Medicinal Chemistry of Oxetanes

<table>
<thead>
<tr>
<th>Model compound</th>
<th>75</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility (µg mL(^{-1}))</td>
<td>&lt;1</td>
<td>4400</td>
</tr>
<tr>
<td>Lipophilicity (logP)</td>
<td>4.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Metabolic stability (hCL(_{int}), min(^{-1})mg(^{-1})µL)</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1.6.1

Model compound 76 was considered to be virtually insoluble in water, however, replacement of the tert-butyl component with an oxetane provided 75 with far greater solubility. In order to estimate the lipophilicity of molecules 75 and 76, the authors compared partition coefficient (LogP) values, which are the lipophilicities of the neutral bases, derived from the experimental p\(K_a\) and the distribution coefficient (LogD) values. They found that the incorporation of the oxetane unit lowered the lipophilicity by one unit, 75, compared with 76.

For comparison of the metabolic stabilities of 75 and 76, the researchers incubated the compounds with human and mouse microsomes. The levels of non-metabolised compound were measured by HPLC/MS/MS at regular time intervals. The intrinsic clearance rate measured in human microsomes (hCL\(_{int}\)) was calculated, which, in this case, was the rate constant of the first-order decay of the compounds. The experiments showed that 76 was easily metabolised, however, oxetane-containing 75 was much more stable. Oxetanes have since been successfully used as replacements for gem-dimethyl groups in 1,25-dihydroxyvitamin D\(_3\) analogues, providing compounds of increased polarity, solubility and stability.\(^{52}\)
As a further example of the potential advantages of including oxetanes in drug scaffolds, it has been shown that spirocyclic compound 77 is more soluble and metabolically stable than its morpholine analogue 78 (Table 1.6.2).46,53

<table>
<thead>
<tr>
<th></th>
<th>77</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = piperonyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solubility (µg mL⁻¹)</td>
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<td>24000</td>
</tr>
<tr>
<td>Metabolic stability (hCL₄₄, min⁻¹mg⁻¹µL)</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1.6.2

Carreira and co-workers also went on to explore the synthesis of non-symmetrical azaspiro[3.3]heptanes 79.54 These might prove to be suitable alternatives to potentially metabolically and chemically labile structures such as 80 (Figure 1.6.3).55 The incorporation of an oxetane unit into γ-secretase inhibitors has also been shown to be beneficial to the metabolic stability of the resultant compounds.56

Figure 1.6.3

Finally, carbonyl groups can be problematic when they are included in drug-like scaffolds. This is due to the susceptibility of carbonyl groups towards enzymatic attack, possible epimerisation of adjacent stereogenic centres and their potential
The strong hydrogen-bonding capability of oxetanes has been reported. The lone pair of electrons on both the carbonyl and oxetanes’ oxygen occupies similar spatial arrangements and both species polarise similarly (Figure 1.6.4). In terms of its hydrogen bonding acceptor ability, oxetane compares favourably with other carbonyl compounds such as ketones, aldehydes or esters, however, it is much weaker when compared with amide carbonyl groups. Also, it has been proposed that the greater distance between the ether-oxygen and the 3-position of the oxetane might allow for deeper oxygen placement in a receptor pocket.

![Figure 1.6.4](image.png)

A series of spirooxetane analogues of pyrrolidones, piperidones and azetidinones have been synthesised. For example, piperidone 81 was synthesised along with oxetane analogue 82 (Table 1.6.3). For comparison, piperidone 83 containing a gem-dimethyl group in the 4-position was also synthesised.
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As can be seen, the inclusion of an oxetane in the 4-position of the piperidone lowers the solubility of the compound and leads to a small increase in lipophilicity. This places the oxetane ring between a carbonyl and a *gem*-dimethyl group in terms of solubility and lipophilicity. More strikingly, 82 appears to have the best metabolic stability. A change in the lipophilicity and $pK_a$ of the piperidones, depending on the position of the group on the ring has been noted.46

1.7. Conclusions

The synthetic chemistry and medicinal applications of oxetanes continues to be of considerable interest. Recent research has shown that the parent oxetane may be a useful medicinally relevant isostere for numerous functional groups and efforts into exploring its properties and incorporation into larger scaffolds are on-going.
Chapter 2:

Synthesis of Oxetanones and their Applications in MCRs
2.1. Introduction

As highlighted in Chapter One, oxetanes are useful scaffolds for drug discovery. It became apparent to us that the development of new efficient routes to drug-like molecules containing this heterocycle would be of considerable value. In this regard, we became interested in their synthesis through multi-component reactions (MCRs). This chapter describes our attempts to synthesise oxetanes using isocyanide-based MCRs. Before describing our studies, it is important to highlight the key features of isocyanide-based MCRs which are of relevance to our studies.

2.2. Introduction to Multi-Component Reactions

The traditional method of synthesis involves the often laborious, costly and inefficient process of the repeated combination of two molecules over a series of steps (Scheme 2.2.1).

*Traditional Synthesis:*

![Scheme 2.2.1](image)

Although often effective, this method remains a long way from the “ideal synthesis”. An alternative approach is to combine all of the reagents in a single reaction vessel, whereby the multiple-components react cleanly to form the product in quantitative yield through multiple, controlled bond formation (Scheme 2.2.2).
Multi-Component Reaction:

MCRs may be defined as “…reactions where more than two starting materials react to form a product, incorporating essentially all of the atoms of the educts.” Historically significant MCRs include the Strecker synthesis and the Mannich, Biginelli, Passerini, and Ugi reactions. The power and scope of MCRs has been well documented in numerous reviews over the years and interest in the area continues to grow.

2.2.1. The Passerini 3-Component Reaction (P-3CR)

The three-component reaction (3-CR) between a carboxylic acid, an isocyanide and an aldehyde or ketone, first discovered by Mario Passerini in 1924, allows for the one-step synthesis of α-alkoxy carboxamides. Although Passerini originally proposed that during the reaction, hemiacetals are formed between the aldehyde and carboxylic acid components, a more commonly accepted mechanism is depicted in Scheme 2.2.3. Combination of the acid and aldehyde or ketone leads to hydrogen-bonded intermediate 84. After α-addition of the isocyanide onto the electrophilic carbonyl carbon, followed by nucleophilic attack of the acid oxygen onto the isocyanide carbon, adduct 85 is formed. This then undergoes irreversible acyl migration, forming the stable α-alkoxy carboxamide 86. Recent
computational studies have shown that a further equivalent of the carboxylic acid component may take part in one of the intermediate steps.\textsuperscript{73}

\[ \text{Scheme 2.2.3} \]

2.2.2. The P-3CR in Natural Product Synthesis

The \( \alpha \)-acyloxy-carboxamide unit \textbf{86} is found in numerous medicinally relevant natural products, such as azinomycin B (\textbf{87}) (Figure 2.2.1).

Indeed, an early use of the P-3CR in natural product synthesis was by Armstrong \textit{et al.}, whereby a variety of isocyanides, aldehydes and carboxylic acids such as \textbf{88}, \textbf{89} and \textbf{90} respectively, were reacted in a combinatorial approach to produce
several simple analogues of the azinomycins (Scheme 2.2.4). For example, 91 was readily produced via a solution-based combinatorial method and found to display \textit{in vitro} cytotoxicity in human colon cancer cell lines (IC\textsubscript{50} 4.4 µM).\textsuperscript{74}

![Scheme 2.2.4](image)

2.2.3. The Synthesis of Heterocycles Using the P-3CR

Passerini-type reactions have also found use in key steps towards the synthesis of heterocyclic compounds. It has been demonstrated that oxazoles such as 92 may be assembled using \(\alpha\)-oxoaldehydes 93, carboxylic acids 94 and cyclohexyl isocyanide (95). Cyclisation of the intermediate \(N\)-alkyl-2-acyloxy-3-aryl-3-oxopropanoic amides 96 to the corresponding oxazoles 92 occurs upon refluxing with ammonium formate in acetic acid (Scheme 2.2.5).\textsuperscript{75}
2.2.4. Stereoselectivity in the P-3CR

Although a new stereocenter is formed during the P-3CR, the ability to control the diastereochemical outcome of the reaction is seldom reported. Chiral isocyanides generally exert no influence on the diastereoselectivity.\(^\text{68}\) One exception to this is the use of chiral, camphor isocyanide 97 in the reaction with acetic acid and simple aldehydes such as 98, providing the Passerini product 99 with good diastereoselectivity (Scheme 2.2.6).\(^\text{76}\) The authors did not, however, confirm the stereochemistry of the major diastereomer formed in the reaction.
Chapter 2: Synthesis of Oxetanones and their Applications in MCRs

*N*-Boc and phthaloyl-protected α-amino acids 100a and 100b have been shown to take part in P-3CRs with cyclohexanone 101 and chiral isocyanide 102 (Scheme 2.2.7). The authors noted that the choice of protecting group was crucial in order to prevent racemisation of the isocyanide. The reactions generally proceeded in good yields providing the products (R,S)-103a/b.\(^77\)

![Scheme 2.2.7](image)

Building on their earlier work, Denmark et al. showed that Lewis base catalysed Passerini-type reactions could be performed with high yields and enantiomeric ratio (er), using a catalytic system of silicon tetrachloride and chiral, Lewis base bisphosphoramidate 104 (Scheme 2.2.8).\(^78,79\) It was postulated that the reaction proceeded via imidoyl chloride species 105. By using an aqueous workup they were able to synthesise α-hydroxy tert-butyl amides 106. Quenching the reaction at low temperature with MeOH, followed by basic workup provided the α-hydroxy methyl esters 107. A multitude of aldehydes could be used in the
reaction, however, it was found that using isocyanides other than \textit{tert}-butyl isocyanide led to a drop in enantioselectivity.

Scheme 2.2.8

Wang \textit{et al.} showed that salen-aluminium catalysts of type 108 effectively promoted the P-3CR, providing the Passerini products in good yields and enantiomeric excesses of up to $>99\%$.\textsuperscript{80} Also, the same researchers demonstrated that chiral 5-(1-hydroxyalkyl)tetrazoles 109 can be synthesised in high yield and \textit{ee} via a catalytic, enantioselective, Passerini-type 3-CR of aldehydes, isocyanides and hydrazoic acid 110 (Scheme 2.2.9).\textsuperscript{81}
The enantioselectivity arising from these types of reactions is believed to derive from coordination of the Lewis acidic catalyst 108 to the oxygen of the aldehyde, blocking the Si-face. Addition of the isocyanide onto the aldehyde then occurs from the Re-face (Figure 2.2.2).
2.2.5. The Ugi 4-Component Reaction (U-4CR)

Probably one of the most widely studied MCRs, the U-4CR, was first documented by Ugi et al. in 1959. The reaction is essentially an expansion of the P-3CR as it consists of the union of an isocyanide, a carboxylic acid, an aldehyde or ketone and an additional amine component. In the first step of the reaction, the amine condenses with the aldehyde or ketone providing an imine, which is then protonated by the acid. Attack of the nucleophilic isocyanide followed by nucleophilic addition of the carboxylate onto the electrophilic iminium forms intermediate 111. This then undergoes irreversible acyl migration, forming the final product 112 (Scheme 2.2.10). The formation of one new C–C bond and two heteroatom–C bonds in one single step makes the U-4CR particularly powerful. Unlike the P-3CR, the U-4CR is more commonly carried out in polar, protic solvents such as MeOH or EtOH.

![Scheme 2.2.10](image-url)
2.2.6. The U-4CR in Drug Discovery and Natural Product Synthesis

From its inception, the U-4CR has been used as a key step in the synthesis of potential drug candidates and natural products. Ugi et al. showed that a three-component Ugi-like reaction could be used in the one-pot synthesis of a variety of local anaesthetics, such as those shown in Scheme 2.2.11.

![Chemical structures](image)

**Scheme 2.2.11**

Fukuyama and co-workers demonstrated the power of the U-4CR in the synthesis of natural product analogues. The group wanted to explore the chemistry of the core 3,8-diazabicyclo[3.2.1] skeleton found in (-)-lemonomycin (113) and employed the U-4CR as an early key step. Reaction between simple aldehyde 114, chiral, primary amine 115, chiral carboxylic acid 116 and phenol carbonate isocyanide 117 led directly to key precursor 118. After a further 15 steps, the synthesis of 119 was accomplished (Scheme 2.2.12).
Recently, powerful methodology featuring an Ugi/Michael/aza-Michael cascade sequence has been developed. This reaction brings together a variety of substituents, forming six bonds contiguously as well as four stereocentres and one quaternary centre. The use of 4-hydroxy-1-naphthaldehyde 120 and fumaric acid monoethyl ester 121 as the aldehyde and acid components respectively, along with tert-butyl isocyanide and benzylamine, set up the Ugi product 122 for the cascade process (Scheme 2.2.13). After conjugate addition of the hydroxyl-substituted naphthyl group onto the ester to form intermediate 123, a 5-exo-trig aza-Michael addition then occurs, providing azaspiro tricycle 124 in excellent yield and dr.
Recent work by Dömling and co-workers illustrates how a variation of the U-4CR can be combined with a Pictet-Spengler cyclisation, forming a variety of heterocyclic scaffolds. Through the combination of an aldehyde or ketone, isocyanide, aminoacetaldehyde dimethyl acetal and tryptophan derivative, a number of indoles could be synthesised (Scheme 2.2.13). If the tryptophan derivative was substituted with a phenylalanine, then isoquinoline compounds were obtained. Also, in contrast to much of the literature regarding Ugi reactions (see section 2.2.8), the main substrates chosen were both cyclic and heterocyclic ketones, including strained systems such as cyclobutanones.
2.2.7. Stereoselectivity in the U-4CR

As the product of the U-4CR may be viewed as an amino acid-derived bisamide, there have been numerous attempts to perform the process enantioselectively.\textsuperscript{86} Indeed, Joullié and co-workers were able to demonstrate the synthesis of unnatural, heterocyclic α-amino acids, using U-4CR methodology.\textsuperscript{87} Unfortunately in contrast to the P-3CR, there are no reports of efficient enantioselective U-4CRs. As with the P-3CR, modified U-4CRs are known, however, as List and co-workers demonstrated with a catalytic U-3CR, such reactions do not proceed with appreciable levels of enantioselectivity.\textsuperscript{88}
Although enantioselective U-4CRs are unknown, examples of diastereoselective U-4CRs have been published. Kunz et al. demonstrated that chiral amine 130 could be used with formic acid and a Lewis acid such as zinc chloride, forming Ugi product 131, before hydrolysis to the target α-amino acids 132 (Scheme 2.2.15). The same research group later expanded this methodology in the synthesis of L-amino acids.

Recently it was reported by Sureshbabu and co-workers that β-lactam peptidomimetics such as 133 may be synthesised in good yields and excellent de, using chiral Nβ-Fmoc amino alkyl isocyanides such as 134 (Scheme 2.2.16). Combination of isocyanide 134 with simple acid 135 and chiral amino ester 136 under mild conditions provided the expected β-lactam product in good yield and excellent dr. In order to rationalise the high dr, it was postulated that the reaction proceeds via oxazepinone intermediate 137.
Although the classical U-4CR involves one-pot imine formation, it is possible to start the reaction with the imine preformed. When conducted with chiral, cyclic imines, the products of the reaction can be quite diverse. Commonly referred to as the Ugi-Joullié reaction, this Ugi four-centre three-component reaction (U-4C-3CR) may begin with chiral, 5-membered imines such as 138. As demonstrated by Znabet et al., these preformed imines take part in U-4C-3CRs with simple isocyanides and carboxylic acids to form substituted prolyl peptides 139 in very good yield and as single diastereomers, with almost no racemisation (Scheme 2.2.17).\textsuperscript{93}
2.2.8. Ugi Reactions of Ketones

Although there are a variety of P-3CR reactions of ketones in the literature, there are very few examples of U-4CR reactions. Simple ketones are known to react, albeit in low yields. For example Kalinski et al. have shown that acetone and cyclohexanone perform modestly as Ugi components in a one-pot Ugi-tetrazole reaction, which is a key step in their synthesis of quinoxalines 140 (Scheme 2.2.18).94
Ugi reactions of \( N \)-benzyl substituted piperidones are also known\(^95,96 \) and a variety of \( N \)-alkyl and aryl substituted piperidinones have been employed in Ugi reactions for the synthesis of spiroadiketopiperazines 141, as demonstrated by Habashita et al. (Scheme 2.2.19).\(^97 \) For this chemistry, the isocyanide component 142 was immobilised on a solid support and a variety of ketones, such as \( N \)-benzylpiperidinone 143 were used.

![Scheme 2.2.19](image)

During the course of their investigations into the formation of alkaloids and other natural products, Martin and co-workers reported the Ugi reaction of several heterocyclic, ketones such as 144, forming Ugi products such as 145 (Scheme 2.2.20).\(^71 \)
2.2.9. Other Isocyanide-Based MCRs

Although the P-3CR and U-4CR remain the most widely exploited isocyanide-based MCRs (IMCRs), a variety of other IMCRs have been developed. For example, isocyanides have been shown to take part in transition metal catalysed MCRs to form indoles\(^{98}\) and in cycloaddition-type reactions with acetylenes, to form a variety of heterocycles.\(^{99}\)

2.3. Passerini Reaction of Oxetan-3-ones

Due to its operational simplicity, we decided to begin our own studies by exploring the Passerini reaction of simple oxetan-3-ones. At the outset of our work, we were aware of only a single MCR of an oxetane, originally reported by Kozikowski \textit{et al.}\(^{15}\) This involved Strecker reaction of oxetan-3-one (15) with benzylamine and sodium cyanide to give 46 in 90% yield (Scheme 2.3.1).
We imagined that a Passerini reaction involving an oxetan-3-one 146, an isocyanide 147 and a carboxylic acid 148, could provide a simple and flexible route to 3,3-disubstituted oxetanes 149 (Scheme 2.3.2).

Scheme 2.3.2

Owing to the considerable expense of commercially available oxetan-3-one (15) (supplied by Sigma Aldrich Ltd. at approximately £39.70 g⁻¹), we decided to make it in situ from propargyl alcohol (150) according to a modified procedure of Zhang and co-workers.¹⁹ These researchers had synthesised oxetan-3-one (15) starting from propargyl alcohol (150) and subsequently performed an in situ Strecker reaction, forming 46 in good overall yield (Scheme 2.3.3). This process required the use of pyridine N-oxide 151 and also a gold catalyst, both of which are not commercially available.

Scheme 2.3.3
We decided to modify this procedure for the synthesis of oxetane-3-one (15) by using commercially available pyridine N-oxide 152 and gold catalyst 153 (see Scheme 2.3.5). The gold catalyst 153 was synthesised over two steps. This catalyst was chosen due to the limited expense and high availability of PPh\textsubscript{3} compared to (2-biphenyl)Cy\textsubscript{2}P. Compound 154 (1.0 equiv.) was reacted with PPh\textsubscript{3} (1.0 equiv.) and the resultant compound was subsequently treated with AgNTf\textsubscript{2} (1 equiv.), producing 153 in high overall yield (Scheme 2.3.4). We were confident that both 153 and 152 would be suitable for the reaction as both were reported to be effective under similar conditions, albeit in lower yields.\textsuperscript{19}

![Scheme 2.3.4](image)

With the starting materials in hand we next attempted the synthesis and subsequent P-3CR of oxetan-3-one (15). Propargyl alcohol (150) (1 equiv.) was treated with N-oxide 152 (2 equiv.) and HNTf\textsubscript{2} (1.2 equiv.) under gold-catalysed conditions in DCE (Scheme 2.3.5). After stirring for 2 h, the DCE solution was washed with a saturated aqueous solution of NaHCO\textsubscript{3} in order to neutralise any remaining acid and the organic layer dried over MgSO\textsubscript{4}. The organic layer was then treated with tert-butyl isocyanide (0.5 equiv.) and acetic acid (1 equiv.) and the reaction mixture stirred for 18 h, providing 155 in 48% yield after column chromatography.
Confirmation of the structure of 155 was initially achieved using $^1$H and $^{13}$C NMR. $^1$H NMR analysis of 155 in CDCl$_3$ provided a pair of AB-doublets at 4.91 and 4.73 ppm, which integrated to a total of four hydrogens and were assigned as the two methylenes of the oxetane ring. A broad singlet at 5.91 ppm, corresponding to the NH was also observed. The CH$_3$ and tert-butyl groups gave rise to singlets at 2.17 and 1.37 ppm, integrating to three hydrogens and nine hydrogens respectively. The $^{13}$C NMR provided two carbonyl signals at 169.5 and 167.0 ppm, along with a quaternary signal for the oxetane C–3 at 78.4 ppm. Confirmation of the structure of 155 was later achieved using X-ray crystallography on a single crystal of 155, which was grown from CH$_2$Cl$_2$/pentane (Figure 2.3.1).
Although this process used the widely available and cheap propargyl alcohol, the costs associated with using HNTf₂ and the gold catalyst, alongside the difficulties of handling the volatile oxetan-3-one offered little benefit. Also, it was difficult to optimise the reaction as the intermediate oxetan-3-one (15) was not isolated. Thus, we decided to purchase oxetan-3-one (15) for further studies. We repeated the reaction using 15 purchased from Synthonix, U.S.A. Treatment of 15 (1 equiv.) with acetic acid (1.2 equiv.) and tert-butyl isocyanide (1.2 equiv.) in DCE for 18 h, followed by simple filtration of the crude reaction mixture through a plug of silica gel provided the Passerini product 155 in excellent yield (Scheme 2.3.6). The reaction also worked well in other aprotic solvents such as CH₂Cl₂.

Figure 2.3.1 X-ray structure of 155
(91%), however, switching to a polar, protic solvent such as MeOH led to much lower yields (20%).

![Scheme 2.3.6](image)

**Scheme 2.3.6**

The scope of this reaction was then explored using a variety of different, commercially available isocyanides (Table 2.3.1, entries 1-4) and carboxylic acids (Table 2.3.1, entries 5-8). Good to excellent yields were observed in most cases, however, (S)-α-methylbenzyl isocyanide provided Passerini product 159 in only modest yield (entry 4).
Chapter 2: Synthesis of Oxetanones and their Applications in MCRs

![Chemical Structures]

<table>
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<th>Entry</th>
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<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
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</tr>
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<tr>
<td>1</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cy</td>
<td>![Product Structure 156]</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&quot;Bu</td>
<td>![Product Structure 157]</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Bn</td>
<td>![Product Structure 158]</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CHCH&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>![Product Structure 159]</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>CbzNHCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>'Bu</td>
<td>![Product Structure 160]</td>
<td>47</td>
</tr>
</tbody>
</table>
Chapter 2: Synthesis of Oxetanones and their Applications in MCRs

The chemistry was subsequently applied to oxetan-3-ones bearing 2- and 2,4-substituents. In order to synthesise these substituted oxetan-3-ones, it was first necessary for us to prepare the corresponding propargyl alcohol precursors.

Known propargyl alcohols 164-165 were readily synthesised according to the procedure of Zhang and co-workers.\textsuperscript{19} We chose these examples as we wanted to ensure that the final product oxetan-3-ones had a high molecular weight and hence a lower volatility, which would facilitate their isolation and handling. Treatment of TMS acetylene (1.5 equiv.) with \textsuperscript{iso}butyllithium (1.6 equiv.), quenching with aldehyde 166 or 167 (1.0 equiv.) and subsequent TMS deprotection using TBAF provided the expected propargyl alcohols 164 and 165 in good yield over two steps (Scheme 2.3.7).
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Scheme 2.3.7

For the synthesis of 2,2,4-trisubstituted oxetan-3-one 168, the propargyl alcohol precursor 169 was made using different methodology. Treatment of ethyl propiolate 170 (1.0 equiv.) with LDA (1.05 equiv.), made in situ from n-butyllithium and diisopropylamine (DIPA), and subsequently quenching with acetone (171) (2.0 equiv.) gave propargyl alcohol 169 in excellent yield (Scheme 2.3.8).

Scheme 2.3.8

Conversion of these propargyl alcohols to their corresponding oxetan-3-ones was realised using the same procedure as we had previously used for the in situ synthesis of unsubstituted oxetan-3-one (15). Propargyl alcohols 164, 165 and 169 were treated with pyridine N-oxide 152 (2 equiv.), PPh₃AuNTf₂ (153) (5 mol %), and HNTf₂ (1.2 equiv.) in DCE (Scheme 2.3.9). For the synthesis of 2-substituted oxetan-3-ones 170 and 171, this reaction was performed at room temperature for 4 hours, however, warming to 50 °C for 18 hours was required for trisubstituted oxetan-3-one 168. Gratifyingly, although the yields obtained for
these compounds were lower than those reported in the literature, it was possible to produce them in large enough quantities for subsequent reactions. The lower yields presumably arise because we used cheaper and more readily accessed pyridine N-oxide and Au-catalyst components, 152 and 153 respectively. Although this multi-step route was efficient in providing these substituted oxetan-3-ones in modest yield, our development of an alternative, less laborious and enantioselective route for their synthesis is discussed later in this chapter.

![Scheme 2.3.9](image)

Treatment of these mono- and tri-substituted oxetanones under the same conditions previously described afforded the Passerini products in good yields (Table 2.3.2). Switching from acetic acid to benzoic acid, however, led to a lower yield of the expected product 175 (Table 2.3.2, entry 4). It was found that good levels of stereoselectivity were seen in these reactions when the substituent at C–2 of the oxetane was relatively large. For example, 173 with a cyclohexyl group at C–2 gave better levels of diastereoccontrol than 172 bearing the corresponding phenyl-ethyl substituent (Table 2.3.2, entry 1 cf. entry 2).
## Table 2.3.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxetan-3-one</th>
<th>R²</th>
<th>Product a/b</th>
<th>Yield (%)</th>
<th>dr[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>170</td>
<td>CH₃</td>
<td>172a/b</td>
<td>76</td>
<td>1.7:1</td>
</tr>
<tr>
<td>2</td>
<td>171</td>
<td>CH₃</td>
<td>173a/b</td>
<td>97</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
<td>CH₃</td>
<td>174a/b</td>
<td>79</td>
<td>2.8:1</td>
</tr>
<tr>
<td>4</td>
<td>171</td>
<td>Ph</td>
<td>175a/b</td>
<td>49</td>
<td>3.4:1</td>
</tr>
</tbody>
</table>

[a] Estimated from 1H NMR.
In order to determine the stereochemical course of these reactions, it was possible to separate 173a and 173b by column chromatography. Minor diastereomer 173b was sufficiently crystalline to enable elucidation of the structure using X-ray crystallography, which was performed upon a single crystal of 173b grown from CH₂Cl₂/pentane (Figure 3.3.2).

![Figure 2.3.2 X-ray structure of 173b](image)

For major diastereomer 173a, the acetate group was first removed via simple ester hydrolysis with K₂CO₃ in MeOH (Scheme 2.3.10).
It was then possible to solve the structure of the resultant α-hydroxyamide 176 using X-ray crystallography (Figure 2.3.3). Knowing the relative stereochemistry of 176, that of 173a could be deduced with confidence.
The formation of $\text{173a}$ as the major diastereomer from $\text{171}$, with the bulky tert-butyl and cyclohexyl groups on the same face of the oxetane ring was not anticipated. It was expected that the isocyanide would attack the ketone from the opposite face to that of the C–2 substituent (Scheme 2.3.12). The literature contains very few examples of investigations into the stereochemical outcome of such reactions. However, the examples we have found support our initial incorrect expectation. For example, it has been reported that chiral 2-substituted cyclopentanone $\text{177}$ takes part in Passerini-type, pyridinium trifluoroacetate-mediated reactions producing $\text{178}$ in low yield as a single diastereomer (Scheme 2.3.11).$^{60,100}$

\[ \text{Scheme 2.3.11} \]

In order to account for the formation of the seemingly more hindered diastereomer $\text{173a}$ as the major product, it is necessary to refer to the commonly accepted mechanism of the reaction (Scheme 2.3.12). Both $\text{179a}$ and $\text{179b}$ are produced under equilibrating conditions through the addition of $\text{tBuNC}$ and $\text{AcOH}$ to both faces of $\text{171}$. The diastereoselectivity likely then arises from differences in the rates of acyl migration from $\text{179a}$ to $\text{173a}$ and from $\text{179b}$ to $\text{173b}$. The preference for the formation of $\text{173a}$ is explained by suggesting that increased steric crowding between the cyclohexyl group and imidate substituent in $\text{179a}$
encourages faster acyl transfer. Adjustment of the equilibrium therefore funnels both 179a and 179b through to the observed major product 173a.

![Scheme 2.3.12](image)

By analogy, we postulate that the major diastereomers in the other examples reported in Table 2.3.2 have the same sense of stereochemical induction.

### 2.3.1. Attempted Ugi Reaction of Oxetan-3-ones

Encouraged by the success with the P-3CR of oxetan-3-ones reported in the previous section, we were interested in exploring the more challenging, but potentially more useful U-4CR of oxetan-3-ones. As discussed previously, examples of Ugi reactions involving cyclic ketones (see section 2.2.8) are rather scarce. To begin with, treatment of oxetan-3-one (15) (1 equiv.) with
benzylamine (1.2 equiv.), acetic acid (1.2 equiv.) and tert-butyl isocyanide (1.2 equiv.), under the same conditions used in the Passerini reactions did not provide the expected Ugi product \textbf{180} (Scheme 2.3.13).

Scheme 2.3.13

Although this reaction was attempted at room temperature, we were concerned that the volatile oxetan-3-one (15) might still have the potential to evaporate from the reaction mixture and lead to a failed reaction. With this in mind, the reaction was repeated with 2-substituted oxetanone 170 in either DCE or MeOH, however, this reaction also failed to provide the expected Ugi product \textbf{181}. Significant amounts of the Passerini product \textbf{172} were isolated when the reaction was performed in DCE (Scheme 2.3.14).

Scheme 2.3.14

The preference for the formation of the Passerini product was unexpected, although there is some precedent in the literature. For example, Pirrung \textit{et al.}
noted that when they attempted an U-4CR with diketone 182, they observed only the Passerini product 183 in a low yield and none of the expected Ugi product 184.\textsuperscript{101}

![Scheme 2.3.15](image)

The mechanisms of the U-4CR and P-3CR share similarities, however, the Ugi reaction begins with an additional condensation step between a carbonyl compound such as an oxetan-3-one (185) and an amine to form imine 186 (Scheme 2.3.16). Presumably, the formation of 186 is slow compared to the direct addition of the isocyanide to the protonated carbonyl species 187. Owing to the slow formation of 186 compared to 187, under equilibrating conditions, the Passerini route effectively out-competes the Ugi route leading to the favourable formation of Passerini product 188 over 189. The strain associated with the four-membered ring may discourage formation of an sp\textsuperscript{3} centre at C–3 of the intermediate hemiaminal species that leads to imine 186.
The rationale that imine formation of oxetan-3-ones may be difficult is in contrast to the known Strecker MCR of oxetan-3-one, which also proceeds via an iminooxetane species (see Scheme 2.3.1). Therefore, dissatisfied with our explanation, we sought to further study the synthesis and chemistry of iminooxetane species. In order to probe the imine formation, a study was carried out by an MChem student, Abimbola Alli-Balogun, under my supervision. In this study, oxetan-3-one 170 (1 equiv.) was stirred with benzylamine (1.2 equiv.) and 4 Å molecular sieves in CDCl₃ (Scheme 2.3.17). Molecular sieves were added to the reaction mixture in order to remove the water produced during the condensation and therefore encourage imine formation.
The reaction was monitored using $^1$H NMR spectroscopy, with samples taken from the reaction mixture at 20 h and 45 h. At 20 h, $^1$H NMR still indicated the presence of benzylamine, characterised by a singlet at 3.8 ppm. However, after 45 h a decrease in the intensity of this signal and the appearance of several new signals, tentatively assigned as the hydrogens of the iminooxetane species 190 were observed. At this point, an attempt was made to isolate the imine, however, efforts to purify the reaction mixture using column chromatography met with failure, with complex mixtures being obtained. With this result in mind, an alternative approach was subsequently developed to explore the formation of iminooxetane species, by using Pictet-Spengler reactions (see Chapter 3), and further efforts to develop U-4CRs of oxetanes were abandoned.

2.4. Conclusions
In summary, oxetan-3-ones have been shown to be excellent substrates for Passerini reactions providing a direct, simple and efficient route to the pharmaceutically important 3,3-disubstituted oxetane scaffold. High yields are observed when the reaction is performed using a variety isocyanides and carboxylic acids and useful levels of diastereocontrol are observed with oxetanes bearing bulky substituents at C-2. Interestingly, the stereochemical outcome was contrary to our initial expectations. Extension of this P-3CR into an U-4CR,

Scheme 2.3.17

\[ \text{BnNH}_2, 4 \text{ Å molecular sieves, CDCl}_3, \text{ r.t.} \]

170 \[ \rightarrow \]
190

The reaction was monitored using $^1$H NMR spectroscopy, with samples taken from the reaction mixture at 20 h and 45 h. At 20 h, $^1$H NMR still indicated the presence of benzylamine, characterised by a singlet at 3.8 ppm. However, after 45 h a decrease in the intensity of this signal and the appearance of several new signals, tentatively assigned as the hydrogens of the iminooxetane species 190 were observed. At this point, an attempt was made to isolate the imine, however, efforts to purify the reaction mixture using column chromatography met with failure, with complex mixtures being obtained. With this result in mind, an alternative approach was subsequently developed to explore the formation of iminooxetane species, by using Pictet-Spengler reactions (see Chapter 3), and further efforts to develop U-4CRs of oxetanes were abandoned.

2.4. Conclusions
In summary, oxetan-3-ones have been shown to be excellent substrates for Passerini reactions providing a direct, simple and efficient route to the pharmaceutically important 3,3-disubstituted oxetane scaffold. High yields are observed when the reaction is performed using a variety isocyanides and carboxylic acids and useful levels of diastereocontrol are observed with oxetanes bearing bulky substituents at C-2. Interestingly, the stereochemical outcome was contrary to our initial expectations. Extension of this P-3CR into an U-4CR,
however, was unsuccessful. The Passerini reaction appears to be competitive and initial attempts to pre-form the iminooxetane were unsuccessful.

2.5. **Synthesis of Chiral 2-Substituted Oxetan-3-ones**

The chemistry used earlier in this chapter to produce the 2-substituted oxetan-3-ones is far from ideal (see Scheme 2.3.9). It is lengthy, employs expensive reagents and catalysts, and generates racemic products. Although Zhang and co-workers have shown it can be used for the formation of chiral derivatives, this further increases the length of the reaction sequence. To address these issues, we wished to examine an alternative approach to 2-substituted oxetan-3-ones that might be applicable to asymmetric synthesis.

We imagined that the asymmetric synthesis of chiral 2-substituted oxetan-3-ones might be achieved via the diastereoselective alkylation of either the SAMP or RAMP hydrazone, followed by cleavage of 2-substituted oxetane-hydrazone intermediate to give the enantiomerically enriched oxetan-3-one (Scheme 2.5.1). We reasoned that this method would be operationally simple and direct, and provide a potentially general route to chiral 2-substituted oxetan-3-ones.

![Scheme 2.5.1](image.png)

Prior to detailing our work in this area, it is pertinent to discuss the relevant literature.
2.5.1. Asymmetric Synthesis using SAMP/RAMP Methodology

In 1976, Enders et al. pioneered alkylation reactions of (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (R)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazones. A number of reviews on the subject have been published and a brief overview of the chemistry is discussed herein.

Alkylations based on SAMP hydrazones usually follow a common sequence of steps, allowing for the stereochemistry of the alkylated products to be reliably predicted. Firstly, the pre-formed SAMP hydrazone is treated with a base such as LDA to form azaenolate species (Scheme 2.5.2). Although there is the possibility of four geometrical isomers at this stage, only the isomer depicted in Scheme 2.5.2 results upon deprotonation with LDA. Chelation of the lithium to the methoxy group allows only for electrophilic addition from the least-hindered face of az烯olate, allowing for the stereochemical outcome of alkylated hydrazone products to be accurately predicted. Final cleavage of hydrazone to the free, chiral ketone may be achieved using a number of methods.
Alkylations of strained ring systems are infrequently found within the literature. During their investigations, Hazelard et al. disclosed that chiral hydrazone derivatives of cyclobutane could be alkylated with a limited selection of electrophiles in moderate yields and enantiomeric excess. For example, RAMP cyclobutane hydrazone 198 was treated with LDA at low temperatures and then quenched with octyl bromide. The resulting product was treated in situ with oxalic acid, providing alkylated cyclobutanone 199 (Scheme 2.5.3).

Scheme 2.5.2

Scheme 2.5.3
2.5.2. Metallation/Alkylation of SAMP-Hydrazones

Lithium and potassium azaenolates are the most commonly used metallated hydrazones.\textsuperscript{105,110,111} Other metallated hydrazones such as zinc and copper azaenolates have also been used effectively.\textsuperscript{112,113} For example, Nakamura \textit{et al.} showed that both cyclic and acyclic SAMP hydrazones such as 200 may be alkylated with cyclopropene acetal 201 using zinc chloride and \textsuperscript{6}butyllithium. It was postulated that intermediate azaenolate 202 was formed in the reaction mixture. Compound 203 was then formed in high yield and diastereoselectivity (Scheme 2.5.4).\textsuperscript{112}

\begin{center}
\textbf{Scheme 2.5.4}
\end{center}

Other lithium bases commonly used for the formation of azaenolates include \textsuperscript{6}butyllithium as well as \textit{tert}-butyllithium. For example, it was shown that heteroatom-containing ketones take part in azaenolate formation using \textsuperscript{6}butyllithium as base.\textsuperscript{114} Similarly, Enders \textit{et al.} showed that dioxanone-SAMP-hydrazone 204 may be metallated using \textit{tert}-butyllithium.\textsuperscript{115,116} Moreover, these researchers showed that hydrazone 204 could be metallated up to four-times,
allowing for the synthesis of multi-substituted SAMP-hydrazones such as 205 (Scheme 2.5.5). Good overall yields and excellent de’s were obtained, although it was found that the final alkylation would only proceed in high yields in the presence of DMPU.

Scheme 2.5.5

The alkylations of SAMP/RAMP metallated hydrazones have found many uses in organic synthesis. The methodology tolerates a large number of electrophilic partners, and has been especially well used in natural product synthesis.\textsuperscript{104,105} For example Smith \textit{et al.} reported the low temperature alkylation of SAMP hydrazone 206 using benzylic bromide 207 as the electrophile.\textsuperscript{117} Only one diastereomer of 208 was formed, which was a key intermediate in their synthesis of heptacyclic core 209, found in (-)-nodulisporic acid D (Scheme 2.5.6).
2.5.3. Formation of SAMP-Oxetane Hydrazones

The synthesis of SAMP hydrazones is usually achieved by the gentle heating of a mixture of SAMP and the ketone, whilst the condensation with aldehydes may take place at lower temperatures. Less reactive species such as aromatic ketones often require the addition of an acid catalyst, refluxing in benzene with removal of the water generated during the condensation.\textsuperscript{118,119}

We began with the synthesis of oxetane-SAMP hydrazone 210 (Scheme 2.5.7). Heating oxetan-3-one (15) with commercially available SAMP overnight afforded the expected oxetane-SAMP hydrazone 210 in excellent yield after column chromatography.\textsuperscript{109} The $^{13}$C NMR of 210 displayed a downfield, quaternary
signal indicative of the C=N bond at 140.0 ppm, whilst high resolution mass spectrometry (HRMS) showed the expected [M+H]+ at 185.1288. The IR spectrum also contained the characteristic C=N absorption at 1662 cm⁻¹. Further assignment of the structure was possible using 2D NMR spectroscopy. Compound 210 was also found to have an optical rotation of [α]D²⁵⁻₈.₈ (c 0.12, CHCl₃), confirming it was enantiomerically enriched.

Scheme 2.5.7

2.5.4. Metallation of Oxetane-SAMP-Hydrazone

In order to investigate the metallation of oxetane-SAMP-hydrazone derivatives, we decided to carry out a screen of suitable bases. By treating hydrazone 210 with different bases and then quenching the reaction with deuterated methanol, it was possible to estimate the extent of deuterium incorporation in product 211 by mass spectrometry (Table 2.5.1). LDA was found to be less effective, failing to lead to complete azaenolate formation even with excess base (entries 1-3) or extended reaction times (entry 4). In contrast, the same reaction with tert-butyllithium for 1 h or 2 h (entries 5 and 6 respectively) allowed for much higher incorporation of up to 90%. tert-Butyllithium also allowed for near complete lithiation within 1 h with 1.1 equiv. of base (entry 7).
2.5.5. Alkylation of Oxetane-SAMP-Hydrazones

Having identified alkyl锂iums as good bases for the reaction, the next task was to investigate the ability of the hydrazone to be alkylated. tert-Butyllithium was selected for the initial studies as it is less basic and less hazardous than tert-butyllithium. After deprotonation of 210 with tert-butyllithium (1.1 equiv.) at −78 °C and subsequent quenching with benzyl bromide (1.1 equiv.), the reaction was allowed to warm slowly to room temperature. The expected alkylated hydrazone 212 was obtained in an encouraging 45% yield after column chromatography (Scheme 2.5.8).
Although 212 was separable as, what appeared to be a single compound by TLC, the NMR spectra was complicated by the possible presence of diastereomers. By NMR spectroscopy, it was difficult to determine whether these diastereomers arose from low selectivity in the alkylation step, racemisation at C–2 of the oxetane, or from E/Z isomerism about the C=N bond. To answer this question, cleavage to the corresponding ketone was pursued (see section 2.5.6).

Characterisation of 212 was made possible using \(^1\)H NMR, which indicated the presence of signals in the aromatic region which integrated to five hydrogens, corresponding to the benzylic group. The loss of one hydrogen from the oxetane ring was also evident from examination of the \(^1\)H NMR. Inspection of the COSY also revealed the coupling between the C–2 hydrogen of the oxetane ring and the newly installed benzylic CH\(_2\). Further to this, as well as displaying the benzylic CH\(_2\) signal at 39.0 ppm, the \(^{13}\)C NMR revealed the presence of a new CH signal at 93.3 ppm which corresponded to the new CH at C–2 of the oxetane ring. HMQC and HMBC spectra were also used to identify these key correlations. HRMS of 212 provided a [M+H]\(^+\) peak at 275.1759 and IR was also useful, displaying a strong absorption at 1686 cm\(^{-1}\) which indicated the continued presence of the C=N bond.
In order to improve the efficiency of the alkylation step, we reasoned that the addition of an additive such as TMEDA (1.1 equiv.) might help (Scheme 2.5.9). In fact, no change in yield was observed by introduction of TMEDA. Use of a less polar solvent, namely diethyl ether, proved detrimental, with no alkylated product observed.

We thought that the alkylation might benefit from higher temperatures. However, performing the lithiation at –40 °C and, after addition of the electrophile and subsequent warming to r.t., provided a trace amount of product 212, as indicated by crude $^1$H NMR. Performing the reaction at 0 °C failed to give any of the expected product 212. Consideration was also given to the sterics of the reaction, specifically the bulkiness of benzyl bromide, therefore a less bulky electrophile, namely iodomethane was tried (Scheme 2.5.10). Unfortunately, the crude $^1$H NMR of this reaction indicated a complex mixture of unidentifiable signals and none of the expected product 213 could be isolated.
Although \(^{n}\)butyllithium had provided some of the desired hydrazone 212, we wanted to find a way of improving the modest 45% yield. With this in mind, we next decided to examine the use of tert-butyllithium, which we knew was also effective from the deuteration studies (see Table 2.5.1). Hydrazone 210 (1 equiv.) was deprotonated with tert-butyllithium (1.1 equiv.) and then quenched with benzyl bromide (1.2 equiv.) (Scheme 2.5.11). In this case, 1.2 equiv. benzyl bromide was used to ensure complete quenching of any nucleophilic species left in solution. Initially, the reaction mixture was stirred at –78 °C for 1 h before quenching with benzyl bromide, providing the expected product 212 in a much improved 67% yield when compared with \(^{n}\)butyllithium. Gratifyingly, the yield improved to 73% when stirred at –78 °C for 2 h, before quenching with benzyl bromide. The sense of induction at the newly generated stereocenter was initially assigned on the basis of the established mnemonic (Scheme 2.5.2). This was later confirmed through experiment (\textit{vide infra}).

**Scheme 2.5.10**

![Scheme 2.5.10](image)

**Scheme 2.5.11**

![Scheme 2.5.11](image)
2.5.6. Cleavage of Hydrazones

Methods for the cleavage of hydrazones generally fall into three categories: oxidative, hydrolytic and reductive cleavage.\textsuperscript{108} In many cases it is possible to recycle the chiral hydrazine starting material.\textsuperscript{118} In all these procedures, it is essential to provide the aldehyde or ketone in high yield and without racemisation of the newly formed chiral centre.

A particularly well studied method is ozonolysis. Among the advantages of using O\textsubscript{3} are its mild reaction conditions, low temperatures, short reaction times and its tolerance to a wide range of potentially sensitive functional groups such as thioethers,\textsuperscript{121} \(\alpha\)-hydrazino- and \(\alpha\)-aminoketones,\textsuperscript{122} and borane-protected phosphines.\textsuperscript{108,123} The procedure generally involves the bubbling of O\textsubscript{3} through a cooled solution of the hydrazone. The mechanism is believed to proceed as depicted in Scheme 2.5.12. After [3+2] cycloaddition of the hydrazone \textsuperscript{214} with O\textsubscript{3} to give \textsuperscript{215}, rearrangement of either \textsuperscript{215} or \textsuperscript{216} occurs, providing one equivalent of oxygen and the expected aldehyde or ketone \textsuperscript{217} (Scheme 2.5.12). A further equivalent of O\textsubscript{3} is then used to convert the diazene \textsuperscript{218} side product into nitrosamine \textsuperscript{219}.\textsuperscript{108,110}
Hydrolytic cleavage of hydrazones using oxalic acid is an attractive alternative. Enders *et al.* reported that a variety of hydrazones such as 220 could be cleaved using saturated oxalic acid under mild conditions, providing the expected ketone 221 in excellent yield and enantiomeric excess\(^\text{124}\). Oxidation-sensitive vinyl groups and acid-sensitive acetals withstand these reaction conditions. From a practical perspective the reaction is also notable in that, unlike ozonolysis, no toxic nitrosamine by-products are formed. A simple method for the recovery of the chiral hydrazine was also reported.
The use of a methyl iodide/HCl mixture is also used for the cleavage of hydrazones, as are low valent TiCl$_3$ and SnCl$_2$.\(^{125}\)

### 2.5.7. Formation of Substituted Oxetanones via Hydrazone Cleavage

Of the variety of methods for SAMP-hydrazone cleavage in the literature, we began by trialling ozonolysis. After bubbling the gas through a solution of 212 in dichloromethane for 1 h, the expected oxetan-3-one 212 was obtained in an encouraging 51% yield (Scheme 2.5.14).

The structure of 222 was identified using a number of techniques. $^1$H NMR displayed a benzylic doublet at 3.11 ppm which integrated to two hydrogens and coupled with the C–2 methine of the oxetane ring. Also, the $^{13}$C NMR contained a carbonyl signal at 201.2 ppm, which corresponds with the ketone in 222. Both $^1$H and $^{13}$C NMR spectra showed the absence of signals that correspond to the SAMP hydrazone protons and carbons respectively. The IR also no longer
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contained the characteristic C=N absorption band that was previously present. Finally, the HRMS displayed the [M+H]^+ peak at 163.0759 expected for 222. Further evidence for its structure was later obtained via an X-ray crystal structure of its corresponding Pictet-Spengler adduct (see section 2.5.8).

Although oxetan-3-one 222 was successfully obtained, we sought methods to improve the yield. Due to procedural simplicity, the use of saturated aqueous oxalic acid was next explored for hydrazone cleavage. Rapid stirring of hydrazone 212 with saturated oxalic acid produced the expected oxetan-3-one 222 in a much improved yield (Scheme 2.5.15). Encouragingly, the optical rotation of \([\alpha]_D^{26} -60 (c \ 0.07, \text{CHCl}_3)\) derived from the oxalic acid hydrolysis suggested it was enantiomerically enriched to a significant extent.

![Scheme 2.5.15](image)

Next, we wanted to determine the % ee of ketone 222. Prior to commencing this, however, it was necessary to synthesise a racemic sample of 222 for comparison. To this end, in collaboration with co-worker Dr Joanna Geden, we developed a route to a racemic sample of 222. The reaction between oxetan-3-one (15) (1.2 equiv.) and dimethylhydrazine (223) (1.0 equiv.) produced achiral dimethyl hydrazone 224 in excellent yield, which was used without further purification (Scheme 2.5.16).
Hydrazone 224 (1.0 equiv.) was treated with tert-butyllithium (1.1 equiv.) and stirred at −78 °C for 2 h. Benzyl bromide (1.2 equiv.) was then added and the mixture allowed to warm slowly to room temperature (Scheme 2.5.17). Initial attempts to purify the intermediate alkylated oxetane-hydrazone led to large material losses, therefore, after removal of the solvent, the crude mixture was dissolved in diethyl ether and treated with excess saturated oxalic acid. Purification using column chromatography yielded (±)-222 in a low 11% yield. Although this yield was disappointing, only a small amount of (±)-222 was required for analysis, therefore, no attempts to improve this yield were made.

With both racemic and enantiomerically enriched 222 in hand, we next set about trying to determine the % ee of (S)-222 using chiral shift NMR reagents such as Pirkle’s alcohol126 and lanthanide shift reagents, however, these methods were unsuccessful.127 No separation of the enantiomers was seen using HPLC on CHIRALPAK® IA, IB, IC, OD, OB and AD columns. Limited separation of the
enantiomers was observed using GC, using both CP-ChiraSil-DEX CB and Chrompac cyclodextrin-B columns.

As determining the enantiomeric excess of (S)-222 was proving difficult, it was decided that ketone (S)-222 (1.0 equiv.) should be reduced to alcohols 225a/b using NaBH₄ (1.5 equiv.), with the hope that it may provide improved separation on GC (Scheme 2.5.18). As one might expect, the reduction proceeded with very little diastereoselectivity, as determined by integration of the ¹H NMR signals.

Gratifyingly, it was then possible to analyse the diastereomeric mixture containing oxetan-3-ol 225a/b, after routine conversion to its corresponding acetate, using GC analysis on a CP-ChiraSil-DEX CB column (Figure 2.5.1). This separated the sample into two major and two minor peaks. For comparison, (±)-222 was also reduced and converted to its corresponding acetate and subjected to the same analysis (Figure 2.5.2). As the reduction was virtually non-selective, it was possible to assign the peaks and derive an estimate of 74% ee for 225 and hence (S)-222, from which it was derived. The method that was used to establish the absolute stereochemistry of (S)-222 is discussed in section 2.5.8.
Figure 2.5.1 GC chromatograms of enantioenriched 225 CP-ChiraSil-DEX CB 25m x 0.25 m x 0.25 µm, T = 160°C, P = 18 psi, carrier gas = He

Figure 2.5.2 GC chromatograms of (±)-225 CP-ChiraSil-DEX CB 25m x 0.25 m x 0.25 µm, T = 160°C, P = 18 psi, carrier gas = He
2.5.8. Pictet-Spengler Reaction of Chiral Oxetan-3-ones

Later in this thesis, we demonstrate that Pictet-Spengler reactions on 2-substituted oxetan-3-ones proceed in good yields (see section 3.3). Moreover, the products are highly crystalline and the structures and stereochemistry can be obtained using X-ray crystallography. In contemplating a method for the determination of the absolute configuration of 222, we imagined that Pictet-Spengler reaction of it with enantiopure L-tryptophan ethyl ester 226 could be used to produce a diastereomERICALLY pure adduct, whose relative configuration could be established by X-ray crystallography. Knowing the (S)-configuration of the L-tryptophan, the absolute configuration of the oxetane centre could then be derived.

L-tryptophan ethyl ester (226) was obtained in good yield via reaction between L-tryptophan (227) (1.0 equiv.) and SOCl₂ (1.5 equiv.) in ethanol (Scheme 2.5.19).

Chiral 2-benzyl oxetan-3-one (222) (1 equiv., 75% ee) was then reacted with (S)-226 (1.2 equiv.), with a catalytic amount of I₂, in acetonitrile producing tetrahydro-β-carbolines 228a/b in good yield and in high diastereoselectivity. Separation of the diastereomers was possible using column chromatography and, as expected from the work in Chapter 3, only two diastereomers were isolated.
It was possible to crystallise both of the isolated diastereomers from this reaction and subject them separately to X-ray crystallography, in order to determine their relative configurations (Figure 2.5.3 and Figure 2.5.4). The (S)-enantiomer of 222 produced major diastereomer 228a, whilst the small amount of (R)-enantiomer was responsible for minor diastereomer 228b. It should be noted that the dr in this reaction broadly parallels the ee of oxetan-3-one 222, indicating no racemisation of 222 under the cyclisation conditions. From the Pictet-Spengler reaction and product stereochemistries, it was then possible to confidently assign the stereochemistry of the major enantiomer of oxetane 222 as (S)-configured.
Chapter 2: Synthesis of Oxetanones and their Applications in MCRs

2.5.9. Conclusions and Future Work

For the first time we have shown that oxetan-3-one (15) is a suitable candidate for enantioselective alkylations using SAMP-hydrazone methodology. Specifically, we have shown that this paves the way for the fast and efficient synthesis of 2-substituted oxetan-3-ones. The synthesis begins with reaction of oxetan-3-one (15) with SAMP hydrazine under mild heating to produce SAMP-oxetane hydrazone 210 in excellent yield. This may then be lithiated using tert-butyllithium at –78 °C before being diastereoselectively alkylated with benzyl bromide, producing alkylated hydrazone 212 in very good yield. Conversion of this product to enantioenriched oxetan-3-one 222 is made possible by hydrolysis.
using saturated aqueous oxalic acid under mild conditions in good yield and ee (Scheme 2.5.21).

\[
\begin{align*}
\text{O} & \quad \text{Me} \\
\text{NH}_2 & \quad \text{SAMP} \\
\text{O} & \quad \text{Ph} \\
\text{Ph} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OMe} \\
\text{N} & \quad \text{Ph}
\end{align*}
\]

**Scheme 2.5.21**

The stereoselectivity that arises in this reaction has been unambiguously established and can be explained by referring to studies carried out by Enders (see section 2.5.1). Preferential attack of the electrophile to the less hindered Si-face of the conformationally rigid and chelated structure 229 occurs (Figure 2.5.5).

\[
\begin{align*}
\text{O} & \quad \text{OMe} \\
\text{N} & \quad \text{Ph}
\end{align*}
\]
Time constraints did not allow the full development of this chemistry, however, in future work, the scope of the alkylation will be explored by using different electrophiles. Indeed, ongoing work by co-worker Dr Joanna Geden has demonstrated that alkyl and allylic electrophiles work well. To improve the enantioselectivity, alkylations could be attempted at lower temperatures. In keeping with the idea of using oxetan-3-ones as building blocks, multiple alkyations could be attempted on the 2- and 4-positions of the oxetane ring in \( \text{210} \), which would allow for a variety of interesting oxetane-containing structures \( \text{230} \) to be synthesised (Scheme 2.5.22). These preliminary results should pave the way for the development of a simple, direct new method of chiral 2-substituted oxetane synthesis.

\[ \text{Scheme 2.5.22} \]
Chapter 3:
Reactions of Iminooxetanes
3.1. Introduction

In the previous chapter we had little success in performing U-4CRs with oxetan-3-ones (section 2.3.1) and as such, we were interested in further exploring whether the reason for this failure might be the inability of oxetan-3-ones to efficiently form reactive imines.

Condensation between tryptamine (231) and oxetan-3-ones 146 would give imine intermediate 232 which, if successful, would rearrange to give access to the pharmaceutically important tetrahydro-β-carboline (THBC) 233, containing the oxetane nucleus (Scheme 3.1.1). As well as verifying the broader feasibility of using iminooxetanes in synthesis, the introduction of the oxetane nucleus might modulate the properties of the resulting THBC. For example, the inclusion of the oxetane unit might enrich the metabolic stability of such compounds, or perhaps alter other biological properties such as bioactivity and bioavailability.

![Scheme 3.1.1](image-url)
This chapter describes our efforts to do this through the development of Pictet-Spengler reactions of oxetanones and related heterocycles. Before discussing our work, it is pertinent to highlight key literature relating to Pictet-Spengler reactions.

3.2. The Pictet-Spengler Reaction

The Pictet-Spengler reaction, first discovered by Pictet and Spengler in 1911, remains one of the simplest and most successful methods for synthesising the isoquinoline and indole alkaloid scaffolds.\(^{128}\) Through the combination of $\beta$-phenylethylamine \(234\) and formaldehyde \(235\), under acidic conditions, 1,2,3,4-tetrahydroisoquinoline (THQ) \(236\) was formed in one step (Scheme 3.2.1).

\[
\text{\textbf{Scheme 3.2.1}}
\]

Later, Tatsui discovered that a modified procedure, using tryptamine \(231\) as the amine component, allowed for the synthesis of the tetrahydro-\(\beta\)-carboline THBC skeleton \(237\) (Scheme 3.2.2).

\[
\text{\textbf{Scheme 3.2.2}}
\]
Chapter 3: Reactions of Iminooxetanes

The mechanism for the formation of THBCs via the Pictet-Spengler reaction has been the subject of debate. Condensation between tryptamine (231) and a suitable carbonyl compound first occurs to form imine species 238. The indole then attacks the iminium ion from either the 2-position to form 239, or as is more commonly accepted, via the 3-position to form spiroindolenine 240 (Scheme 3.2.3). Further proton loss from 239 provides the observed THBC 241.\textsuperscript{129}

![Scheme 3.2.3](image)

Although some studies have suggested that 238 directly rearranges to 241,\textsuperscript{130} strong evidence for the involvement of 240 exists from isotopic labelling studies performed by Bailey (Scheme 3.2.4).\textsuperscript{131} Hydrazine 242 was condensed with isotopically enriched formaldehyde. Analysis of the mixture using \textsuperscript{1}H NMR and mass spectrometry revealed the formation of a roughly equal mixture of 244, 245, 246, and 247. It was reasoned that the reaction mechanism must go via the spiro-intermediate 248 in order to obtain 246 and 247. The statistical mixture obtained was consistent with an equilibrium formed between a spiro-intermediate and
reversible imine formation-hydrolysis. From this it was possible to conclude that formation of the tetrahydro-3-aza-β-carboline 244 was slow in comparison with these processes.

Scheme 3.2.4

3.2.1. Tetrahydro-β-Carbolines (THBCs)

A large number of biologically active compounds contain the THBC functionality.\textsuperscript{132,133} For nearly 60 years, naturally occurring, THBC-containing reserpine has been used extensively in the treatment of hypertension and mental disorders (Figure 3.2.1).\textsuperscript{134} The use of THBCs in other therapeutic areas has also been explored, most notably in the synthesis of tadalafil, which is primarily used in the treatment of erectile dysfunction.\textsuperscript{135,136}
THBCs have also been found in every day commodities such as chocolate\(^9\) and fruit juices,\(^{137,138}\) where they are thought to be associated with the prevention of oxidative decay.\(^{138}\) Compounds containing the THBC have also been located in the human brain and other tissues.\(^{139}\)

![Figure 3.2.1](image)

### 3.2.2. Stereocontrol in the Pictet-Spengler Reaction

The use of enzymes to control the stereochemical outcome of Pictet-Spengler reactions has been widely developed.\(^{140}\) Beyond these biosynthetic examples of stereocontrol, there are a number of notable, non-enzymatic, stereochemically-controlled Pictet-Spengler reactions.\(^{140}\) Investigations initially led by Cook and co-workers showed that tryptophan derived THBCs could be formed under aprotic conditions.\(^{141}\) Later on, it was shown that \(N\)-benzyltryptophan ethyl ester \(^{249}\) takes part in a stereospecific Pictet-Spengler reaction with various aldehydes, exclusively providing the \textit{trans}-isomer of \(N\)-benzyl derivatives \(^{250}\) (Scheme 3.2.5).\(^{142}\) The benzyl group could then be removed \textit{via} hydrogenation affording \(\beta\)-carbolines \(^{251}\) in very good yields.
Following on from the diastereoselective Pictet-Spengler reaction of tryptophan derivatives, a number of attempts have been made to emulate its success when using tryptamines. The use of chiral auxiliary groups to influence the diastereoselectivity in Pictet-Spengler reactions of tryptamines with aldehydes has also been studied. For example, Gremmen et al. showed that chiral sulfoxide-tethered tryptamines 252 react with a variety of alkyl aldehydes, providing 253 as single diastereomers (Scheme 3.2.6). Removal of the chiral auxiliary under mild, racemisation-free conditions gave the enantiopure THBCs 254 in good yield.
Scheme 3.2.6

Lewis and Brønsted acids have also been used to influence the enantioselectivity of Pictet-Spengler reactions. The asymmetric formation of 1,1-disubstituted THBCs via Lewis acid mediated processes has recently been achieved by Leighton and co-workers.\(^\text{144}\) By using chiral, silyl-compund 255, a variety of tryptamines 256 could be reacted in a one-pot reaction with both alkyl and aryl \(\alpha\)-(alkyl)ketoamides 257. The product \(\alpha\)-amino amides 258 were isolated in good yield and high enantioselectivity, however, the Lewis acid had to be used in stoichiometric quantities.

Scheme 3.2.7
In 2004 Jacobsen and co-workers presented the first catalytic enantioselective Pictet-Spengler reaction. They employed the use of chiral thiourea catalysts as weak Brønsted acids. Later work by Jacobsen and co-workers showed that a combination of thiourea catalyst 259 and benzoic acid as a co-catalyst could be used to induce higher yields and enantioselectivities in the reaction between tryptamine 260 and several aldehydes, producing THBCs 261 (Scheme 3.2.8).

![Scheme 3.2.8](image)

Chiral carbonyl compounds have also found use in the enantioselective synthesis of THBCs. Of particular note is the enantioselective one-pot Michael addition-Pictet-Spengler sequence developed by Wu et al., which allows for the synthesis of indoloquinolizidines 262 (Scheme 3.2.9). This sequence begins with the organocatalysed Michael addition of β-keto ester 263 onto allyl aldehyde 264, using catalytic 265. The resulting chiral hemiacetal 266 is then condensed with tryptamine (231), selectively providing indoloquinolizidines 262 in good yield and enantioselectivity.
Chapter 3: Reactions of Iminooxetanes

3.3. Pictet-Spengler Reaction of Oxetan-3-ones

In response to the scant literature coverage of reactions involving iminooxetanes, we began by exploring their chemistry using the Pictet-Spengler reaction. In order to test the feasibility of performing Pictet-Spengler reactions on oxetanones, oxetan-3-one (15) (1 equiv.) was reacted with tryptamine (231) (1.2 equiv.) under various conditions, altering the catalyst and solvent (Table 3.3.1).

1 Preliminary investigations into the Pictet-Spengler reactions of oxetan-3-ones were carried out by an MChem student, Abimbola Alli-Balogun, under my supervision.
### Table 3.3.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conversion(^{[a]}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>CH(_3)CN</td>
<td>82</td>
<td>75(^{b})</td>
</tr>
<tr>
<td>2</td>
<td>CF(_3)COOH (2%)</td>
<td>CH(_2)Cl</td>
<td>r.t.</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>CF(_3)COOH (2%)</td>
<td>CH(_3)CN</td>
<td>82</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)(_3) (10%)</td>
<td>CH(_2)Cl</td>
<td>r.t.</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>BF(_3)·OEt (3 equiv.)</td>
<td>CH(_2)Cl</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>I(_2) (5%)</td>
<td>CH(_3)CN</td>
<td>82</td>
<td>48(^{b})</td>
</tr>
</tbody>
</table>

\(^{[a]}\)Calculated from \(^{1}H\) NMR using 1,3,5-trimethoxybenzene as an internal standard.

\(^{[b]}\)Yield after column chromatography.

Gratifyingly, THBC 267 was produced under a variety of conditions. The structure of 267 was confirmed using NMR spectroscopy. \(^{1}H\) NMR of 267 displayed a set of aromatic signals integrating to a total of four hydrogens, which correspond to the indole hydrogens of 267. The oxetane signals became split into a pair of AB doublets at 5.02 and 4.74 ppm respectively and integrating to a total of four hydrogens. As well as providing the necessary aromatics (specifically four CH carbons and four quaternary carbons) the \(^{13}C\) NMR also revealed signals for the oxetane methylenes at 84.2 ppm, along with the quaternary carbon at 57.3 ppm. HRMS of 267 also gave the expected \([M+H]^+\) peak at 215.1178.

It was noteworthy that the best yield was obtained when no activator was employed in the reaction (Table 3.3.1, entry 1). This result was unexpected as uncatalysed Pictet-Spengler reactions are not commonly reported.\(^{141,148}\) Catalytic
I$_2$ in acetonitrile also provided the expected product in a reasonable yield (entry 6). We were inspired to use iodine as a catalyst because it had previously been reported as a useful catalyst in the Pictet-Spengler reactions of tryptamines and a variety of unactivated ketones.$^{149,150}$ Catalytic TFA in both dichloromethane and acetonitrile did not provide appreciable amounts of 267 (entries 2 and 3 respectively). Lewis acid catalysts proved ineffective for this transformation (entries 4 and 5).

With the knowledge that several conditions could be employed, the scope of the reaction was next investigated. Oxetan-3-one (15) (1 equiv.) was reacted with three different amines 226, 268 and 269 (1.2 equiv.), providing products 270-272 (Table 3.3.2). As with the synthesis of 267, amine 268 bearing a 5-methoxy group on the indole worked well without any catalyst in acetonitrile, giving product 270 (entry 1). Repetition of this reaction in acetonitrile with catalytic I$_2$ led to a lower yield. Reaction with enantiopure L-tryptophan ethyl ester (226), which was synthesised from L-tryptophan (227) (see Chapter 2, Scheme 2.5.19), in the presence of I$_2$ in acetonitrile gave 271 in excellent yield (entry 2), whilst lower yields were observed when the reaction was attempted using no catalyst. For the N-substituted indole-containing product 272, a low yield was obtained using catalytic I$_2$ (entry 3). Unfortunately, due to the lack of the necessary amine starting material, the synthesis of compound 272 was not attempted under any other conditions.
### Table 3.3.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Amine" /></td>
<td><img src="image2" alt="Product" /></td>
<td>85[^{[a]}]/69[^{[b]}]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Amine" /></td>
<td><img src="image4" alt="Product" /></td>
<td>50[^{[a]}]/89[^{[b]}] ee \geq 96[^{[c]}]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Amine" /></td>
<td><img src="image6" alt="Product" /></td>
<td>52[^{[b]}]</td>
</tr>
</tbody>
</table>

\[^{[a]}\] No catalyst  
\[^{[b]}\] I\(_2\) (5 mol %)  
\[^{[c]}\] ee determined using chiral shift \(^1\)H NMR with \((S)-1\)-Anthracen-9-yl-2,2,2-trifluoroethanol (Pirkle’s alcohol).\(^{126}\)

In the case of \((S)-271\), we verified that little or no racemisation occurred during the reaction. This was done by chiral shift NMR analysis using \((S)-1\)-anthracen-9-yl-2,2,2-trifluoroethanol (Pirkle’s alcohol) [(S)-273] (1 equiv.) in CDCl\(_3\) as an NMR solvent (see Figure 3.3.1). For comparison, the corresponding racemic derivative of \((S)-271\), \((\pm)-271\), was made starting from \((\pm)-226\) via a route identical to that used in the synthesis of \((S)-271\). A region in the \(^1\)H NMR where the two sets of peaks are well separated was selected for analysis. In this case, it was convenient to select a doublet at 5.0 ppm which corresponds to one of the
hydrogens on the oxetane ring. When the NMR sample contained only (S)-271 and (S)-273, only one set of peaks are present (Figure 3.3.1, A). Conversely, when the NMR sample containing (±)-271 and (S)-273 was analysed, two sets of peaks became apparent, which corresponded to the presence of both (S)-271 and (R)-271 (Figure 3.2.1, B). From this, it was possible to obtain the chemical shift values for the (R)-enantiomer. Subsequent integration of these areas for the sample containing predominantly (S)-271 allowed for an estimation of the quantity of (R)-271 in the sample and, hence, its enantiomeric excess (≥ 96% ee).
Chapter 3: Reactions of Iminooxetanes

Figure 3.3.1 - A: (S)-271 (1.0 equiv.), (S)-273 (1.0 equiv.) B: (±)-271 (1.0 equiv.), (S)-273 (1.0 equiv.).
The scope of the reaction was further extended by performing it with substituted oxetan-3-one 170 (1.0 equiv.) and amines 231 or 268 (1.2 equiv.), producing THBCs 274 and 275 in good yields (Scheme 3.3.1). For compound 274, the use of catalytic I₂ gave a yield of 62%, however, the use of no catalyst led to a lower yield. The stereochemistry of 274 was solved by X-ray crystallography (vide infra). With these results in mind, the synthesis of structurally similar product 275 was only attempted using I₂ as a catalyst, providing 275 in 72% yield.

As catalytic I₂ appeared to be working well for this transformation, we decided to continue with its use in further reactions of 2-substituted oxetan-3-ones. Thus, reaction of 170 with L-tryptophan ethyl ester (226) with catalytic I₂ provided 276a/b in very good yield (Scheme 3.3.2).
When the reaction was attempted using the bulky 2-cyclohexyl oxetan-3-one (171) and 226, the product 277 was obtained in low yield (Scheme 3.3.3).

Scheme 3.3.3
Chapter 3: Reactions of Iminooxetanes

In all of these Pictet-Spengler reactions, all of the oxetane starting materials were used as racemic mixtures. Generally, the reactions proceeded in a relatively clean fashion by TLC analysis and products 274, 275 and 276 and 277 were isolated as single diastereomers after column chromatography.

Further analysis of the crude $^1$H NMRs of 274, 275, 276 and 277 revealed a separate set of unidentifiable signals, estimated by integration at 20%, 15%, 13% and 63% respectively of the samples. These signals could result from the presence of other diastereomers or perhaps the imine intermediate. In this regard, it is notable that the lowest yielding example (277) appeared to contain a large amount (63%) of this impurity. This might be due to the bulky cyclohexyl group preventing efficient cyclisation to 277 and therefore stalling at the imine intermediate, which is subsequently present in the NMR solution. However, despite numerous attempts using column chromatography, the compounds giving rise to these signals could not be isolated.

Crucially, it was possible to grow crystals of 274 from CH$_2$Cl$_2$/pentane that were suitable for X-ray crystallography. This revealed the relative configuration of the isolated diastereomer. The X-ray crystal structure revealed the bulky ethyl phenyl chain of the oxetane ring and the large indole system to be on opposite faces of the oxetane ring (Figure 3.3.2).
Figure 3.3.2 X-ray structure of 274

An explanation for the high level of diastereoselectivity is proposed in Scheme 3.3.4. After condensation of tryptamine (226) and oxetan-3-one 170 to form imine 278, the indole preferentially attacks C-3 of the oxetane-iminium species from the face opposite to that of the oxetane C-2 substituent, before finally rearranging to give 274 as the major diastereomer (Scheme 3.3.4).
The relative stereochemistry of 274 could be deduced using NOE experiments (Table 3.3.3). Irradiation of the indole NH (H$^1$) gave enhancements of oxetane hydrogens H$^2$ and H$^3$ but, crucially, not H$^4$. Irradiation of H$^2$ gave a strong enhancement of the signal corresponding to H$^4$ and H$^3$, however, irradiation of H$^3$ did not lead to an enhancement of the signal corresponding to H$^4$. H$^2$ and H$^3$ were therefore determined to reside on the same face of the oxetane ring. No enhancement of the H$^5$ signal was observed when any of the other hydrogens were irradiated.

![Diagram of 274]

<table>
<thead>
<tr>
<th>Irradiated</th>
<th>H$^1$ (%)</th>
<th>H$^2$ (%)</th>
<th>H$^3$ (%)</th>
<th>H$^4$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$^1$</td>
<td>-</td>
<td>1.61</td>
<td>2.64</td>
<td>0</td>
</tr>
<tr>
<td>H$^2$</td>
<td>1.73</td>
<td>-</td>
<td>0.58</td>
<td>13.3</td>
</tr>
<tr>
<td>H$^3$</td>
<td>2.34</td>
<td>0.35</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>H$^4$</td>
<td>0</td>
<td>13.3</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.3.3

As we had determined the relative configuration of 274 using NOE experiments, and conclusively confirmed these findings by using X-ray crystallography, we were able to use NOE to assist in the stereochemical assignment of 276 and 277. The relative (1$S^*$, 2$S^*$) stereochemistry of 277 was readily determined using NOESY $^1$H NMR experiments. Specifically, NOE enhancements (cross-peaks) between H$^1$, H$^2$ and the indole NH were observed (Figure 3.3.3), as were
Chapter 3: Reactions of Iminooxetanes

interactions between H\(^3\) of the oxetane and H\(^4\) of the cyclohexyl ring. These findings were identical to those seen for 274.

![Figure 3.3.3](image)

**Figure 3.3.3**

Reaction between (±)-170 and 226 provided two diastereomers; 276a and 276b as an inseparable mixture after column chromatography in near equal quantities (Scheme 3.3.5). Both of these diastereomers derive from nucleophilic attack of the indole nucleophile onto the face of the iminooxetanes species opposite the phenethyl substituent (see Scheme 3.3.4). The fact there was no diastereoselectivity (dr 1.1:1) is consistent with the fact that the oxetan-3-one starting material is a racemic mixture, hence both (R)-170 and (S)-170 could equally take part in the reaction.

![Scheme 3.3.5](image)

**Scheme 3.3.5**
The stereochemical assignments of 276a and 276b were determined using NOESY $^1$H NMR experiments. In each case, interactions between the indole NH and H$^1$ and H$^2$ were observed, with no interaction between the indole NH and either H$^3$ or the oxetane 2-substituent, confirming that the C–2 substituent and indole NH are on opposite faces of the oxetane ring, as depicted in Figure 3.3.4. These NOESY experiments did not enable us to unambiguously differentiate between these two diastereomers. The close structural similarity between 276a/b and 228a/b, whose structures were deduced by X-ray crystallography (Figure 2.3.3) lends further weight to these assignments.

![Figure 3.3.4](image-url)
3.3.1. Pictet-Spengler Reactions of Azetidin-3-ones

Having shown that oxetanes can be successfully incorporated into THBC skeletons, we were interested to see if other four-membered heterocyclic ketones, such as N-tosylazetidin-3-one 279 would also take part in the reaction (Scheme 3.3.6). Reaction of 279 (1.0 equiv.), which was provided by laboratory co-worker Nicola Powell, with amine 231 (1.2 equiv.) and catalytic I₂ afforded the expected product 280 in low yield. However, use of catalytic TFA led to a significant improvement in yield. Satisfied with these results and also due to the small amount of 279 available, the same reaction was not performed in the absence of a catalyst. The structure of 280 was assigned using NMR spectroscopy, as well as HRMS. The ¹H NMR in d₆-DMSO displayed a downfield singlet at 10.94 ppm characteristic of the indole NH, as well as eight aromatic hydrogens. The oxetane signals appear as a set of AB-doublets at 4.07 and 3.67 ppm. The ¹³C NMR provided eight aromatic CH carbons, as well as a quaternary carbon at 50.8 ppm for the oxetane C–3. By use of the HMQC and HMBC experiments, it was possible to further assign all of the hydrogen and carbon atoms of 280. The HRMS provided the expected [M+H]⁺ peak at 368.1424.

![Scheme 3.3.6](image-url)
As with the oxetanones, it was possible to expand the scope of the reaction further via the use of L-tryptophan ethyl ester \(226\) (1.2 equiv.) (Scheme 3.3.7). In this case catalytic \(\text{I}_2\) was used, producing \(281\) in good yield with essentially no racemisation.

![Scheme 3.3.7](image)

The enantiomeric excess of \((S)-281\) was determined using chiral shift \(^1\text{H}\) NMR, using \((S)-1\text{-anthracen-9-yl}-2,2,2\text{-trifluoroethanol}\) (Pirkle’s alcohol) \([\text{(S)-273}]\) as chiral shift reagent.\(^{126}\) For comparison, \((\pm)-281\) was synthesised via a route analogous to that used in the synthesis of \((S)-281\), using \((\pm)-\text{tryptophan}\) \([\text{(±)-226}]\) (1.2 equiv.) as the starting material.

The \(^1\text{H}\) NMR of a 1:1 mixture of \((S)-281\) and \((S)-273\) in \(\text{CDCl}_3\) displays a doublet at 3.81 ppm that corresponds to one of the hydrogens attached to the oxetane ring (Figure 3.3.5, A). This NMR sample was then doped with \((\pm)-281\) and the resultant mixture analysed by \(^1\text{H}\) NMR (Figure 3.3.5). This experiment provided the chemical shift of one of the oxetane hydrogens of the \((R)\)-enantiomer. By integration of these regions in the \(^1\text{H}\) NMR of the \((S)-281\) and \((S)-273\) mixture (Figure 3.3.5, A), it was possible to estimate an enantiomeric excess of \(\text{ca} \geq 98\%\).
Chapter 3: Reactions of Iminooxetanes

3.3.2. Attempted Synthesis of Tetrahydroisoquinolines

The Pictet-Spengler reaction was originally used for the synthesis of tetrahydroisoquinolines (THQs).\textsuperscript{128} In an effort to further extend the scope of the Pictet-Spengler reaction of oxetan-3-ones, it was of interest to examine if THQ products 282 could also be synthesised using this newly developed methodology (Scheme 3.3.8).

**Figure 3.3.5** – A: (S)-281 (1 equiv.), (S)-273 (1 equiv.); B: (S)-281 (1 equiv.), (S)-273 (1 equiv.), (±)-281.

**Scheme 3.3.8**
To begin with, the reaction was attempted with substituted oxetanone 170 (1 equiv.) and 3,4-dimethoxyphenylamine (283) (1.2 equiv.), using I$_2$ as a catalyst (Scheme 3.3.9). Although there was no starting material left at the end of the reaction and the $^1$H NMR splitting pattern of oxetane hydrogens had become more complex, it was not possible to isolate any of the expected product, 284, cleanly from the crude mixture.

Undeterred, we repeated the reaction using the parent oxetanone 15 under the same conditions (Scheme 3.3.10). Initially, the crude $^1$H NMR looked promising; the oxetane signals were clearly split into two separate signals at 4.82 and 5.19 ppm. However, careful inspection of the aromatic region indicated the presence of an additional aromatic hydrogen, which was inconsistent with ring closure. Analysis of the $^{13}$C NMR also revealed three aromatic CH signals, rather than the two required. These observations are consistent with the reaction stalling at iminooxetane 285. Although LRMS revealed the expected [M+H]$^+$ peak at 236, this was unhelpful as both the expected product 286 and intermediate 285 have the same molecular mass.
Although this result was disappointing, similar situations are reported in the literature\textsuperscript{151,152}. In the case of ketones, the reaction often has to be performed stepwise by preforming the imine using a Lewis acid catalyst and subsequently heating in acid\textsuperscript{153}. The difficulty associated with the cyclisation may also be attributed to the lower nucleophilicity of the phenyl ring in 283 compared to the indole ring in tryptamine derivatives\textsuperscript{154}. Our attempts to promote the cyclisation by repeating the reaction using ethanol as a solvent, using TFA (10 mol %) as a catalyst or subjecting the reaction to microwave irradiation (300W, 20 min, 100 °C) all provided the imine, rather than the desired THQ. With no signs of the desired THQ by NMR, attempts to explore the synthesis of these compounds were abandoned.

### 3.3.3. Conclusions and Future Work

We have shown that both oxetan-3-ones and azetidin-3-ones take part in Pictet-Spengler reactions with both tryptamines and tryptophan ethyl ester (Figure 3.3.6). Generally, the reactions proceed in very good yields and, in some cases, good yields can be obtained without the addition of any catalyst. Iodine and TFA
were also shown to be effective catalysts for other examples. A total of nine compounds were synthesised, with the reaction tolerating substitution of the indole ring nitrogen and substituents at C–2 of the oxetane ring. Where applicable, only one diastereomer of the products was isolated from the reaction mixture. The stereochemical course of the reaction can be rationalised through addition of the indole nucleophile to the least hindered face of the imine intermediate.

![Figure 3.3.6](image)

This work confirms that oxetan-3-ones and azetidine-3-ones may be converted to their ketimine analogues, allowing for exploitation of the imine functionality in subsequent reactions. Interestingly these reactions appear to proceed with excellent diastereoselectivity and we were able to assign the stereochemistry of the products using a combination of X-ray crystal structures and NOE/NOESY measurements. In our hands the chemistry could not be extended to the synthesis of THQs, however, by conducting a more thorough screen of suitable conditions success might be achieved in the future.

The THBC skeleton is of particular pharmacological interest. It would therefore be interesting to test the compounds in relevant biological assays in order to
ascertain whether they have useful pharmacological properties and to explore how the properties of the THBC nucleus are modulated by the introduction of the oxetane ring.
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General Information

Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma-Aldrich Co. All other solvents and reagents were used as received or purified by standard protocols. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60°C. All experiments were performed under an inert atmosphere in oven-dried or flame-dried glassware as required. Column chromatography was carried out using Fluorochem LC60A 40-63 micron silica. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck TLC silica gel 60 F$_{254}$) and visualised using UV light and staining with potassium permanganate or ceric ammonium molybdate followed by heating. Melting points were recorded on a Gallenkamp MPD350 apparatus. Single crystal X-ray diffraction data were obtained using an Oxford Diffraction Gemini XRD system. Optical rotations were measured using an AA1000 polarimeter. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Bruker Alpha Platinum ATR spectrometer with internal calibration and are given in cm$^{-1}$. $^1$H and $^{13}$C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker Spectrospin DPX300; at 400 MHz and 100 MHz respectively on a Bruker Spectrospin DPX400; at 500 MHz and 125 MHz respectively on a Bruker Spectrospin DPX500. Chemical shifts are reported in ppm. Signals are reported as singlets (s), doublets (d), triplets (t) etc., which refer to the spin-spin coupling patterns. Coupling constants are reported in Hertz. High resolution mass spectra were obtained using a Bruker ESI-Micro TOF instrument. Warwick Analytical Service carried out all elemental analysis.
Silver carbonate (720 mg, 2.60 mmol) and bis(trifluoromethane)sulfonimide (1.50 g, 5.20 mmol) were dissolved in H$_2$O (26 mL) and the reaction mixture was heated at reflux for 3 h. After cooling, the reaction mixture was concentrated in vacuo to give silver bis(trifluoromethanesulfonyl)imide as a cream solid. Meanwhile, chloro(dimethylsulfide)gold(I) (553 mg, 1.88 mmol) and triphenylphosphine (493 mg, 1.88 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (50 mL) and the solution was stirred at r.t. for 30 minutes. The reaction mixture was concentrated in vacuo and the resultant solid was washed with hexane, filtered and the remaining solvent removed in vacuo to give chloro(triphenylphosphine)gold(I) (678 mg, 93%) as a white solid. Chloro(triphenylphosphine)gold(I) (572 mg, 1.16 mmol) was added to a solution of silver bis(trifluoromethanesulfonyl)imide (448 mg, 1.16 mmol) in anhydrous CH$_2$Cl$_2$ (29 mL) and the reaction mixture was stirred at r.t. for 30 min. The solution was filtered through celite®, washing through with CH$_2$Cl$_2$ and the solvent removed in vacuo to give the title compound as a white solid (825 mg, 96%). $\delta_H$ (300 MHz, CDCl$_3$) 7.40-7.10 (m, ArH); $\delta_C$ (75 MHz, CDCl$_3$) 133.6 (CH, Ar), 133.5 (CH, Ar), 133.4 (CH, Ar), 132.4 (CH, Ar), 131.9 (CH, Ar), 129.5 (CH, Ar), 129.45 (CH, Ar), 129.4 (CH, Ar), 129.0 (CH, Ar), 128.8 (CH, Ar), aromatic quaternary carbons not observed; $\delta_P$ (121.5 MHz, CDCl$_3$) 30.31. Procedure taken from literature.$^{155}$
3-(tert-Butylcarbamoyl)oxetan-3-yl acetate (by one pot method from propargyl alcohol (150)) (155)

To a stirred solution of 150 (29 µL, 0.5 mmol), 152 (164 mg, 1 mmol) and HNTf₂ (169 mg, 0.6 mmol) in DCE (2.5 mL) was added 153 (19 mg, 0.025 mmol). The mixture was stirred at r.t. for 2 h and then washed with a saturated NaHCO₃ solution (5 mL) and the organic layer was dried over MgSO₄ and filtered. Acetic acid (29 µL, 0.5 mmol) was then added to the stirred solution followed by tert-butyl isocyanide (28 µL, 0.25 mmol) and the reaction mixture was then stirred at r.t. for 18 h. The crude mixture was diluted with CH₂Cl₂ and then washed with saturated aqueous NaHCO₃ solution (2 x 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed in vacuo. Purification was achieved using column chromatography (40% EtOAc in petroleum ether) affording the title compound (10 mg, 48%) as a white solid.

M.p. 105-107 °C; IR (solid) 3381, 2972, 2150, 1745, 1668, 1533, 1448, 1367, 1228, 1198 cm⁻¹; δH (400 MHz, CDCl₃) 5.91 (1H, br s, NH), 4.91 (2H, d, J = 7.9, CH₂), 4.73 (2H, d, J = 7.9, CH₂), 2.17 (3H, s, CH₃), 1.37 (9H, s, CH₃); δC (100 MHz, CDCl₃) 169.5 (C=O), 167.0 (C=O), 78.4 (CH₂), 78.4 (C), 51.7 (C), 28.6 (CH₃), 20.7 (CH₃); MS (ES⁺) 238 [M+Na]⁺; HRMS (ES⁺) calcd. for C₁₀H₁₇NNaO₄ [M+Na]⁺: 238.1050; found: 238.1047.
Synthesis of 3-substituted oxetanes 155-163:

\[
\text{\begin{array}{c}
\text{O} \\
\text{O} \\
R^1 \text{CO}_2\text{H}, R^2\text{NC}, \\
\text{DCE, r.t.} \\
\text{O} \\
\text{O} \\
\text{NH}
\end{array}} 
\]

**General Method 1.**

To a stirred solution of oxetan-3-one (15) (0.5 mmol) in DCE (1 mL) was added the carboxylic acid (0.6 mmol) and isocyanide (0.6 mmol). The reaction was stirred for 18 h at r.t. then diluted with CH$_2$Cl$_2$ (10 mL), washed with a saturated aqueous NaHCO$_3$ solution (2 x 10 mL) followed by brine (10 mL). The organic layer was dried over MgSO$_4$, filtered through a plug of silica gel, washing with CH$_2$Cl$_2$, and the solvents removed *in vacuo*.

**3-(tert-Butylcarbamoyl)oxetan-3-yl acetate (from oxetan-3-one (15)) (155).**

Reaction of 15 (32 µL) with acetic acid (34 µL) and tert-butyl isocyanide (68 µL) according to General Method 1 afforded the title compound (97 mg, 90%) as a white solid.

Data as previously reported.

**3-(Cyclohexylcarbamoyl)oxetan-3-yl acetate (156).**

Reaction of 15 (32 µL) with acetic acid (34 µL) and cyclohexyl isocyanide (74 µL) according to General Method 1 afforded the title compound (95 mg, 79%) as a white solid. M.p. 125-127 °C; IR (film) 3307, 2934, 2852, 1736, 1656, 1541, 1451, 1371, 1348, 1240, 1188, 1166 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 5.95 (1H, br d, $J = 7.2$, NH), 4.93 (2H, d, $J = 7.9$, CH$_2$), 4.75 (2H, d, $J = 7.9$, CH$_2$), 3.86-3.76 (1H,
Chapter 4: Experimental

3-(Butylcarbamoyl)oxetan-3-yl acetate (157).

Reaction of 15 (32 µL) with acetic acid (34 µL) and n-butyl isocyanide (63 µL) according to General Method 1 afforded the title compound (55 mg, 51%) as a white solid. M.p. 60-65 ºC; IR (film) 3388, 2959, 2346, 1744, 1665, 1541, 1350, 1193 cm⁻¹; ΔH (400 MHz, CDCl₃) 6.11 (1H, br s, NH), 4.94 (2H, d, J = 8.4, CH₂), 4.76 (2H, d, J = 8.4, CH₂), 3.35-3.30 (2H, m, CH₂), 2.18 (3H, s, CH₃), 1.55-1.47 (2H, m, CH₂), 1.38-1.29 (2H, m, CH₂), 0.93 (3H, t, J = 7.4, CH₃); ΔC (100 MHz, CDCl₃) 169.6 (C=O), 167.8 (C=O), 78.4 (C), 78.3 (CH₂), 39.5 (CH₂), 31.5 (CH₂), 20.7 (CH₂), 20.0 (CH₃), 13.7 (CH₃); MS (ES⁺) 238 [M+Na]⁺; HRMS (ES⁺) calcd. for C₁₀H₁₇NNaO₄ [M+Na]⁺: 283.1050; found: 283.1048.

3-(Benzy1carbamoyl)oxetan-3-yl acetate (158)

Reaction of 15 (32 µL) with acetic acid (34 µL) and benzyl isocyanide (73 µL) according to General Method 1 afforded the title compound (77 mg, 62%) as a white solid. M.p. 100-103 ºC; IR (film) 3316, 2936, 2358, 1744, 1665, 1534, 1352, 1189 cm⁻¹; ΔH (400 MHz, CDCl₃) 7.32-7.21 (5H, m, ArH), 6.36 (1H, br s,
NH), 4.95 (2H, d,  J = 8.1, CH₂), 4.76 (2H, d,  J = 8.1, CH₂), 4.49 (2H, d,  J = 5.9, CH₂), 2.14 (3H, s, CH₃); δC (100 MHz, CDCl₃) 169.7 (C=O), 167.9 (C=O), 137.6 (C, Ar), 128.9 (CH, Ar), 127.8 (CH, Ar), 127.6 (CH, Ar), 78.3 (CH₂), 78.3 (C) 43.7 (CH₂), 20.7 (CH₃); MS (ES⁺) 272 [M+Na]⁺; HRMS (ES⁺) calcd. for C₁₃H₁₅NNaO₄ [M+Na]⁺: 282.0893; found: 272.0893.

(S)-3-(1-phenylethylcarbamoyl)oxetan-3-yl acetate (159).

Reation of 15 (32 µL) with acetic acid (34 µL) and (S)-α-methylbenzyl isocyanide (81 µL) according to General Method 1 afforded the title compound (30 mg, 23%) as a white solid. IR (film) 1743, 1666, 1530, 1450, 1350, 1237, 1190, 1136, 1061; δH (400 MHz, CDCl₃) 7.33-7.22 (5H, m, ArH), 6.28 (1H, br d, J = 7.3, NH), 5.13 (1H, p, J = 7.3, CH), 4.90 (2H, dd, J = 10.8, 7.5, CH₂), 4.73 (2H, d, J = 7.5, CH₂), 2.12 (3H, s, COCH₃), 1.49 (3H, d, J = 6.8, CHCH₃); δC (700 MHz, CDCl₃) 169.6 (C=O), 167.0 (C=O), 142.4 (C, Ar), 128.8 (CH, Ar), 127.6 (CH, Ar), 126.0 (CH, Ar), 78.3 (OCH₂), 78.2 (OCH₂), 78.1 (C), 49.0 (CH), 21.4 (CH₃), 20.6 (CH₃); MS (ES⁺) 286 [M+Na]⁺; HRMS (ES⁺) calcd. for C₁₄H₁₇NNaO₄ [M+Na]⁺: 286.1049; found: 286.1050.

3-(tert-Butylcarbamoyl)oxetan-3-yl 2-(benzyloxycarbonylamino)acetate (160)

Reaction of 15 (32 µL) with Cbz-glycine (125 mg) and tert-butyl isocyanide (68 µL) according to General Method 1 afforded the title compound (87 mg, 47%) as a white solid. M.p. 126-128 °C; IR (film) 3361, 2970,
1704, 1678, 1530, 1456, 1349, 1188, 1135, 1056 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.35-7.32 (5H, m, ArH), 6.26 (1H, br s, NH), 5.39-5.28 (1H, br m, NH), 5.14 (2H, s, CH\(_2\)), 4.97 (2H, d, \(J = 7.8\), CH\(_2\)), 4.64 (2H, d, \(J = 7.8\), CH\(_2\)), 4.00 (2H, d, \(J = 5.8\), CH\(_2\)), 1.36 (9H, s, CH\(_3\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 168.4 (C=O), 166.5 (C=O), 157.0 (C=O), 136.1 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.0 (CH, Ar), 79.6 (C), 78.1 (CH\(_2\)), 67.4 (CH\(_2\)), 51.9 (C), 43.2 (CH\(_2\)), 28.5 (CH\(_3\)); MS (ES\(^+\)) 387 [M+Na]\(^+\); HRMS (ES\(^+\)) calcd. for C\(_{18}\)H\(_{24}\)N\(_2\)NaO\(_6\) [M+Na]\(^+\): 387.1527; found: 387.1529.

3-(tert-Butylcarbamoyl)oxetan-3-yl benzoate (161).

Reaction of 15 (32 \(\mu\)L) with benzoic acid (73 mg) and tert-butyl isocyanide (68 \(\mu\)L) according to General Method 1 afforded the title compound (127 mg, 92%) as a white solid. M.p. 108-111 °C; IR (film) 3409, 2917, 1989, 1710, 1688, 1520, 1281, 716 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 8.05-8.00 (2H, m, ArH), 7.64 (1H, dd, \(J = 7.7\), 1.3, ArH), 7.49 (2H, dd, \(J = 7.7\), 1.3, ArH), 5.92 (1H, br s, NH), 5.08 (2H, d, \(J = 8.2\), CH\(_2\)), 4.88 (2H, d, \(J = 8.2\), CH\(_2\)), 1.35 (9H, s, CH\(_3\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 167.0 (C=O), 165.1 (C=O), 134.0 (CH, Ar), 130.0 (CH, Ar), 128.7 (CH, Ar), 128.6 (C, Ar), 79.0 (C), 78.3 (CH\(_2\)), 51.7 (C), 28.6 (CH\(_3\)); MS (ES\(^+\)) 300 [M+Na]\(^+\); HRMS (ES\(^+\)) calcd. for C\(_{15}\)H\(_{19}\)NNaO\(_4\) [M+Na]\(^+\): 300.1206; found: 300.1202.
3-(tert-Butylcarbamoyl)oxetan-3-yl thiophene-2-carboxylate (162).

Reaction of 15 (32 µL) with thiophene-2-carboxylic acid (77 mg) and tert-butyl isocyanide (68 µL) according to General Method 1 afforded the title compound (120 mg, 85%) as a white solid. M.p. 99-102 °C; IR (film) 3408, 3110, 2968, 1706, 1682, 1516, 1451, 1412, 1358, 1262, 751 cm⁻¹; δH (400 MHz, CDCl₃) 7.80 (1H, dd, J = 3.7, 1.2, ArH), 7.66 (1H, dd, J = 4.9, 1.2, ArH), 7.17-7.15 (1H, m, ArH), 5.93 (1H, br s, NH), 5.04 (2H, d, J = 8.2, CH₂), 4.86 (2H, d, J = 8.2, CH₂), 1.36 (9H, s, CH₃); δC (100 MHz, CDCl₃) 166.8 (C=O), 160.5 (C=O), 135.0 (CH, Ar), 134.0 (CH, Ar), 131.7 (C, Ar), 128.2 (CH, Ar), 79.2 (C), 78.2 (CH₂), 51.7 (C), 28.6 (CH₃); MS (ES⁺) 306 [M+Na]⁺; HRMS (ES⁺) calcd. for C₁₁H₁₇NNaO₄S [M+Na]⁺: 306.0770; found: 306.0771.

3-(tert-Butylcarbamoyl)oxetan-3-yl 3-bromothiophene-2-carboxylate (163).

Reaction of 15 (32 µL) with 3-bromothiophene-2-carboxylic acid (64 mg) and tert-butyl isocyanide (68 µL) according to General Method 1 afforded the title compound (95 mg, 52%) as a white solid. M.p. 98-102 °C; IR (film) 3405, 3108, 2964, 2364, 2344, 1723, 1684, 1522, 1407, 1363, 768 cm⁻¹; δH (400 MHz, CDCl₃) 7.57 (1H, d, J = 5.2, ArH), 7.16 (1H, d, J = 5.2, ArH), 5.99 (1H, br s, NH), 5.04 (2H, d, J = 7.4, CH₂), 4.90 (2H, d, J = 7.4, CH₂), 1.37 (9H, s, CH₃); δC (100 MHz, CDCl₃) 166.5 (C=O), 159.2 (C=O), 133.4 (CH, Ar), 132.7 (CH, Ar), 126.0 (C, Ar), 118.6 (C, Ar), 79.4 (C), 78.2 (CH₂), 51.8 (C), 28.6 (CH₃); MS
(ES\(^+\)) 365 \([\text{M}^{81}\text{Br}+\text{H}]^+\), 363 \([\text{M}^{79}\text{Br}+\text{H}]^+\); HRMS (ES\(^+\)) calcd. for C\(_{13}\)H\(_{16}\)\(^{79}\)BrNaO\(_4\)S [M+Na\(^+\)]\(^+\): 383.9876; found: 383.9874.

5-Phenylpent-1-yn-3-ol (164)

A solution of n-butyllithium in hexanes (2.5 M, 7.24 mL, 18.1 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (2.42 mL, 17 mmol) in THF (40 mL) at \(-78^\circ\)C. After 15 min, a solution of 3-phenylpropanal (166) (1.0 mL, 8.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture and the mixture was then stirred for a further 4 h. The reaction was quenched via the slow addition of a saturated aqueous NH\(_4\)Cl solution (30 mL) and allowed to warm to r.t. before extraction into Et\(_2\)O (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO\(_4\), filtered and the solvent removed in vacuo affording the TMS-protected alcohol after column chromatography. To a stirred solution of this alcohol (1.43 g, 6.15 mmol) in THF (50 mL) at 0 \(^\circ\)C was added a solution of tetrabutylammonium fluoride in THF (1 M, 7.40 mL, 7.40 mmol). The mixture was stirred at 0 \(^\circ\)C for 1 h before the addition of a saturated aqueous NH\(_4\)Cl solution (20 mL). After warming to r.t. the organics were extracted into Et\(_2\)O (3 x 10 mL), washed with brine (10 mL), dried over MgSO\(_4\), filtered and the solvents removed in vacuo. The mixture was then subjected to column chromatography (25% petroleum ether in CH\(_2\)Cl\(_2\)) affording the title compound as a colourless oil (860 mg, 65% over 2 steps). \(\delta\)\(^H\) (300 MHz, CDCl\(_3\)) 7.32-7.29 (2H, m, ArH), 7.23-7.19 (3H, m, ArH), 4.40-4.36 (1H, m, CH), 2.82 (2H, t, \(J = 8.0\), CH\(_2\)), 2.52 (1H, d, \(J = 2.4\), CH), 2.10-1.98 (2H, m, CH\(_2\)), OH not observed; \(\delta\)\(^C\) (75 MHz, CDCl\(_3\))
141.2 (C, Ar), 128.5 (CH, Ar), 126.0 (CH, Ar), 84.7 (CH), 73.4 (C), 61.6 (CH), 39.0 (CH₂), 31.2 (CH₂); MS (ES⁺) 183 [M+Na]⁺. Data is in accordance with literature values.¹⁹

1-Cyclohexylprop-2-yn-1-ol (165)

![1-Cyclohexylprop-2-yn-1-ol (165)](image)

A solution of n-butyllithium in hexanes (2.5 M, 6.8 mL, 17 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (2.28 mL, 16 mmol) in THF (40 mL) at −78 °C. After 15 min, a solution of cyclohexanecarboxaldehyde (167) (1.44 mL, 10.6 mmol) in THF (40 mL) was added dropwise to the reaction mixture and the mixture was then stirred for a further 4 h. The reaction was quenched by the slow addition of a saturated aqueous of NH₄Cl solution (30 mL) and allowed to warm to r.t. before extraction into Et₂O (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and the solvent removed in vacuo affording the TMS-protected alcohol after column chromatography. To a stirred solution of this alcohol (2.30 g, 11 mmol) in THF (94 mL) at 0 °C was added a solution of tetrabutylammonium fluoride in THF (1 M, 13.2 mL, 13.2 mmol). The mixture was stirred at 0 °C for 1 h before the addition of a saturated aqueous NH₄Cl solution (20 mL). After warming to r.t. the organics were extracted into Et₂O (3 x 10 mL), washed with brine (10 mL), dried over MgSO₄, filtered and the solvents removed in vacuo. The mixture was then subjected to column chromatography (15% EtOAc in petroleum ether) affording the title compound as a colourless oil (1.41 g, 84% over 2 steps). δH (300 MHz, CDCl₃) 4.18-4.14 (1H, m, CH), 2.47 (1H, d, J = 2.1, CH), 1.88-1.76 (5H, m), 1.70-1.66 (1H, m), 1.62-1.51 (1H, m),
1.32-1.00 (5H, m); δ_C (75 MHz, CDCl_3) 83.3 (CH), 73.0 (C), 66.5 (CH), 43.3 (CH), 27.8 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 25.2 (CH_2). Data is in accordance with literature values.  

**Ethyl 4-hydroxy-4-methylpent-2-ynoate (169)**

To a solution of diisopropylamine (4.6 mL, 33.0 mmol) in THF (30 mL) at 0 °C, was added, a solution of n-butyllithium in hexanes (1.6 M, 20.7 mL, 33.0 mmol). The reaction mixture was stirred at 0 °C for 1 h and then cooled to –78 °C before the dropwise addition of ethyl propiolate (170) (3.2 mL, 31.6 mmol) in THF (10 mL). After stirring for 1 h at –78 °C, anhydrous acetone (171) (4.6 mL, 62.6 mmol) was added to the mixture and stirring was continued for a further 3 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (30 mL) and then allowed to warm to r.t. The organics were extracted into Et_2O (4 x 20 mL) and washed with brine (20 mL). The organic layer was dried over MgSO_4, filtered, and the solvents removed in vacuo affording the title compound after column chromatography (20% EtOAc in petroleum ether) as an orange oil (4.6 g, 95%). δ_H (400 MHz, CDCl_3) 4.23 (2H, q, J = 7.0, CH_2), 2.17 (1H, s, OH), 1.56 (6H, s, CH_3), 1.31 (3H, t, J = 7.3, CH_3); δ_C (100 MHz, CDCl_3) 153.6 (C), 90.9 (C), 74.2 (C), 65.0 (C), 62.1 (CH_2), 30.6 (CH_3), 14.0 (CH_3); MS (ES^+) 179 [M+Na]^+. Data is in accordance with literature values.
2-Phenethyloxetan-3-one (170).

To a solution of propargyl alcohol 164 (700 mg, 4.4 mmol) in 1,2-dichloroethane (129 mL) was added at r.t. 3,5-dichloropyridine N-oxide (152) (1.44 g, 8.8 mmol), bis(trifluoromethane)sulfonimide (1.48 g, 5.28 mmol) and PPh₃AuNTf₂ (153) (162.7 mg, 0.22 mmol). The mixture was stirred at r.t. for 4 h and then washed with a saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was washed with CH₂Cl₂ (25 mL) and the combined organic layers were dried over MgSO₄, filtered and the solvents removed in vacuo. Purification was achieved using column chromatography (12.5% EtOAc in petroleum ether) affording the title compound as a pale yellow oil (494 mg, 64%). δH (400 MHz, CDCl₃) 7.32-7.28 (2H, m, ArH), 7.23-7.19 (3H, m, ArH), 5.48-5.44 (1H, m, CH), 5.33-5.23 (2H, m, CH₂), 2.86-2.74 (2H, m, CH₂), 2.24-2.08 (2H, m, CH₂); δC (100 MHz, CDCl₃) 203.2 (C=O), 140.4 (C, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 126.3 (CH, Ar), 102.8 (CH), 88.9 (CH₂), 32.8 (CH₂), 30.2 (CH₂). Data is in accordance with literature values.¹⁹

2-Cyclohexyloxetan-3-one (171)

To a solution of propargyl alcohol 165 (1 g, 7.2 mmol) in 1,2-dichloroethane (212 mL) was added at r.t. 3,5-dichloropyridine N-oxide (152) (2.36 g, 14.4 mmol), bis(trifluoromethane)sulfonimide (153) (2.43 g, 8.64 mmol) and PPh₃AuNTf₂ (266 mg, 0.36 mmol). The mixture was stirred at r.t. for 4 h and then washed with a saturated aqueous NaHCO₃ solution (75 mL). The aqueous layer was washed with CH₂Cl₂ (35 mL) and the combined organic
layers were dried over MgSO₄, filtered and the solvents removed in vacuo. Purification was achieved using column chromatography (5% EtOAc in petroleum ether) providing the title compound as a pale yellow oil (693 mg, 62%).

δ_H (300 MHz, CDCl₃) 5.26-5.21 (2H, m, CH₂), 5.14 (1H, dd, J = 15.1, 4.1, CH), 1.88-1.66 (6H, m), 1.29-1.02 (5H, m); δ_C (75 MHz, CDCl₃) 203.0 (C=O), 107.2 (CH), 88.1 (CH₂), 39.5 (CH), 26.8 (CH₂), 26.8 (CH₂), 25.5 (CH₂), 24.9 (CH₂).

Data is in accordance with literature values.

**Ethyl 4,4-dimethyl-3-oxetane-2-carboxylate (168)**

To a solution of propargyl alcohol 169 (400 mg, 2.6 mmol) in DCE (51 mL) was added at r.t. 3, 5-dichloropyridine-N-oxide (152) (840 mg, 5.1 mmol), bis(trifluoromethane)sulfonimide (863 mg, 3.1 mmol) and PPh₃AuNTf₂ (153) (95 mg, 0.13 mmol, 5 mol %). The mixture was stirred at 50 °C for 18 h, cooled to r.t. and then washed with a saturated aqueous NaHCO₃ solution (2 x 10 mL). The aqueous layer was washed with CH₂Cl₂ (2 x 30 mL) and the combined organic layers were dried over MgSO₄, filtered and the solvents removed in vacuo. Purification was achieved using column chromatography (10% EtOAc in petroleum ether) affording the title compound as a light yellow oil (229 mg, 51%). δ_H (400 MHz, CDCl₃) 5.71 (1H, s, CH), 4.37-4.22 (2H, m, CH₂), 1.58 (3H, s, CH₃), 1.55 (3H, s, CH₃), 1.31 (3H, t, J = 7.3, CH₃); δ_C (100 MHz, CDCl₃) 198.0 (C=O), 165.1 (C=O), 108.6 (C), 93.7 (CH), 62.2 (CH₂), 22.9 (CH₃), 22.5 (CH₃), 14.2 (CH₃); GC-MS (EI) 173 [M+H]^+. Data is in accordance with literature values.
3-(tert-Butylcarbamoyl)-2-phenethoxetan-3-yl acetate (172a/b)

To a solution of 170 (88 mg, 0.5 mmol) in DCE (1 mL) was added acetic acid (34 µL, 0.6 mmol) and tert-butyl isocyanide (68 µL, 0.6 mmol). The mixture was stirred at r.t. overnight before being diluted with CH₂Cl₂ (10 mL), washed with a saturated aqueous NaHCO₃ solution (2 x 10 mL), brine (10 mL), then the combined organic layers dried over MgSO₄, filtered and the solvents removed in vacuo. Purification by column chromatography (10% EtOAc in petroleum ether) provided 172a/b (122 mg, 76%) as an inseparable ca 1.7:1 mixture of diastereomers as determined by ¹H NMR spectroscopy. Repeated chromatography provided less polar, minor diastereomer 172b: White solid, M.p. 90-93°C; IR (film) 3344, 2932, 1738, 1659, 1525, 1455, 1367, 1329, 754 cm⁻¹; ³H (300 MHz, CDCl₃) 7.24-7.10 (5H, m, ArH), 5.77 (1H, br s, NH), 4.95 (1H, d, J = 7.9, OCHH), 4.72 (1H, dd, J = 8.8, 4.8, OCH), 4.53 (1H, d, J = 7.9, OCHH), 2.75-2.65 (1H, m, CHH) 2.59-2.49 (1H, m, CHH), 2.12 (3H, s, CH₃), 2.21-1.95 (2H, m, CH₂), 1.28 (9H, s, CH₃); ³C (75 MHz, CDCl₃) 169.0 (C=O), 166.9 (C=O), 140.5 (C, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 125.5 (CH, Ar), 85.9 (CH), 79.0 (C), 75.5 (CH₂), 51.1 (C), 32.1 (CH₂), 30.0 (CH₂), 28.0 (CH₃), 20.1 (CH₃); MS (ES⁺) 342 [M+Na]⁺; HRMS (ES⁺) calcd for C₁₈H₂₅N₉NaO₄ [M+Na]⁺: 342.1676; found: 342.1672; and more polar, major diastereomer 172a: white solid, M.p. 109-112°C; IR (film) 3346, 2928, 2932, 1751, 1739, 1665, 1526, 1454, 1366, 750 cm⁻¹; ³H (300 MHz, CDCl₃) 7.23-7.08 (5H, m, ArH), 5.59 (1H, br s, NH), 5.04 (1H, d, J = 7.7, OCHH), 4.71 (1H, dd, J = 9.4, 5.0, OCH), 4.39 (1H, d, J = 7.7, OCHH), 2.70-2.60 (1H, m, CHH) 2.56-2.46 (1H, m, CHH), 2.12 (3H, s,
CH₃), 2.13-2.00 (1H, m, CHH), 1.87-1.75 (1H, m, CHH), 1.27 (9H, s, CH₃); δC (75 MHz, CDCl₃) 169.0 (C=O), 166.9 (C=O), 140.5 (C, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 125.5 (CH, Ar), 85.9 (CH), 79.0 (C), 75.5 (CH₂), 51.1 (C), 32.1 (CH₂), 30.0 (CH₂), 28.0 (CH₃), 20.1 (CH₃); MS (ES⁺) 342 [M+Na]+; HRMS (ES⁺) calcd. for C₁₈H₂₅NNaO₄ [M+Na]+: 342.1676; found: 342.1674.

3-(tert-Butylcarbamoyl)-2-cyclohexyloxetan-3-yl acetate (173a/b)

To a solution of the 171 (77 mg, 0.5 mmol) in DCE (1 mL) was added acetic acid (34 µL, 0.6 mmol) and tert-butyl isocyanide (68 µL, 0.6 mmol). The mixture was stirred at r.t. for 48h before being diluted with CH₂Cl₂ (10 mL), washed with a saturated aqueous NaHCO₃ solution (2 x 10 mL), brine (10 mL) and the combined organic layers dried over MgSO₄, filtered and the solvents removed in vacuo. Purification by column chromatography (20% EtOAc in petroleum ether) provided 173a/b (145 mg, 97%) as an inseparable ca 4:1 mixture of diastereomers as determined by 1H NMR spectroscopy. Repeated chromatography provided less polar, minor diastereomer (2R*, 3R*)-173: white solid, M.p. 114-119 °C; IR (film) 3355, 2918, 1743, 1657, 1516, 1447, 1369 cm⁻¹; δH (600 MHz, CDCl₃) 5.70 (1H, br s, NH), 5.16 (1H, d, J = 8.4, OCHH), 4.44 (1H, d, J = 8.4 OCHH), 4.36 (1H, d, J = 9.7, CH), 2.19 (3H, s, CH₃), 2.08-2.01 (1H, m, cy), 1.91 (1H, br d, J = 12.9, cy), 1.78-1.65 (4H, m, cy), 1.29 (9H, s, CH₃) 1.27-1.16 (3H, m, cy), 0.94-0.84 (2H, m, cy); δC (150 MHz, CDCl₃) 169.4 (C=O), 167.6 (C=O), 90.4 (CH), 80.9 (C), 75.1 (CH₂), 51.5 (C), 38.7 (CH), 28.8 (CH₃), 28.6 (CH₂), 28.1 (CH₂), 27.2 (CH₂), 26.4 (CH₂), 25.3 (CH₂), 20.9 (CH₃); MS (ES⁺) m/z = 320 [M+Na]⁺;
HRMS (ES\(^+\)) calcd for C\(_{16}\)H\(_{27}\)NNaO\(_4\) [M+Na]\(^+\): 320.1832; found: 320.1829; and more polar, major diastereomer (2R\(^*\), 3S\(^*\))-173: white solid, M.p. 154-156 °C; IR (film) 3355, 2918, 1743, 1657, 1516, 1447, 1369 cm\(^{-1}\); \(\delta\)\(_{H}\) (400 MHz, CDCl\(_3\)) 5.73 (1H, br s, NH), 4.88 (1H, d, \(J = 7.5\), CHH), 4.40 (1H, d, \(J = 7.5\), CHH), 4.36 (1H, d, \(J = 10.5\), CH), 2.09 (3H, s, CH\(_3\)), 1.84-1.48 (6H, m, cy), 1.32 (9H, s, CH\(_3\)), 1.20-1.07 (3H, m, cy), 0.85-0.72 (2H, m, cy); \(\delta\)\(_{C}\) (100 MHz, CDCl\(_3\)) 169.4 (C=O), 165.5 (C=O), 91.4 (CH), 81.0 (C), 74.9 (CH\(_2\)), 51.8 (C), 39.3 (CH), 28.7 (CH\(_3\)), 27.8 (CH\(_2\)), 27.5 (CH\(_2\)), 26.2 (CH\(_2\)), 25.1 (CH\(_2\)), 24.9 (CH\(_2\)), 20.7 (CH\(_3\)); MS (ES\(^+\)) 320 [M+Na]\(^+\); HRMS (ES\(^+\)) calcd. for C\(_{16}\)H\(_{27}\)NNaO\(_4\) [M+Na]\(^+\): 320.1832; found: 320.1830.

Ethyl-3-acetoxy-3-(tert-butylcarbamoyl)-4,4-dimethyloxetane-2-carboxylate (174a/b)

To a solution of 168 (86 mg, 0.5 mmol) in DCE (1 mL) was added acetic acid (34 µL, 0.6 mmol) and tert-butyl isocyanide (68 µL, 0.6 mmol). The mixture was stirred at r.t. overnight before being diluted with CH\(_2\)Cl\(_2\) (10 mL), washed with a saturated aqueous NaHCO\(_3\) solution (2 x 10 mL), brine (10 mL) and then the organic layers dried over MgSO\(_4\), filtered and the solvents removed in vacuo. Purification by column chromatography (40% EtOAc in petroleum ether) provided the separable diastereomers. Less polar, minor diastereomer 174b (35 mg, 22%): White solid, M.p. 109-111°C; IR (film) 3360, 2979, 1750, 1668, 1524, 1459, 1370, 1221, 1033 cm\(^{-1}\); \(\delta\)\(_{H}\) (400 MHz, CDCl\(_3\)) 5.75 (1H, s, CH), 5.47 (1H, br s, NH), 4.24-4.10 (2H, m, CH\(_2\)), 2.06 (3H, s, CH\(_3\)), 1.60 (3H, s, CH\(_3\)), 1.42 (3H, s, CH\(_3\)), 1.35 (9H, s,
CH$_3$), 1.26 (3H, t, $J = 7.2$, CH$_3$); $\delta$C (100 MHz, CDCl$_3$) 169.3 (C=O), 169.2 (C=O), 165.1 (C=O), 88.1 (C), 82.7 (C), 76.4 (CH), 61.4 (CH$_2$), 51.8 (C), 28.6 (CH$_3$), 24.7 (CH$_3$), 23.9 (CH$_3$), 20.7 (CH$_3$), 14.0 (CH$_3$); MS (ES$^+$) 338 [M+Na]$^+$; HRMS (ES$^+$) calcd for C$_{15}$H$_{25}$NNaO$_6$ [M+Na]$^+$: 338.1574; found: 338.1573.; and more polar, major diastereomer 174a (90 mg, 57%): White solid, M.p. 125-127°C; IR (film) 3347, 2978, 2917, 1738, 1729, 1685, 1534, 1467, 1368, 1232, 1036 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 6.07 (1H, br s, NH), 4.93 (1H, s, CH), 4.37-4.23 (2H, m, CH$_2$), 2.20 (3H, s, CH$_3$), 1.54 (3H, s, CH$_3$), 1.53 (3H, s, CH$_3$), 1.27 (9H, s, CH$_3$), 1.33-1.29 (3H, m, CH$_3$); $\delta$C (100 MHz, CDCl$_3$) 169.1 (C=O), 163.5 (C=O), 87.5 (C), 85.0 (C), 79.8 (CH), 61.5 (CH$_2$), 51.9 (C), 28.5 (CH$_3$), 24.2 (CH$_3$), 23.9 (CH$_3$), 20.9 (CH$_3$), 14.1 (CH$_3$), C=O not observed; MS (ES$^+$) 272 [M+Na]$^+$; HRMS (ES$^+$) calcd. for C$_{15}$H$_{25}$NNaO$_6$ [M+Na]$^+$: 338.1574; found: 338.1572.

3-(tert-Butylcarbamoyl)-2-cyclohexyloxetan-3-yl benzoate (175a/b)

To a solution of 171 (64 mg, 0.4 mmol) in DCE (1 mL) was added benzoic acid (61 mg, 0.5 mmol) and tert-butyl isocyanide (56 µL, 0.5 mmol). The mixture was stirred overnight at r.t. before being diluted with CH$_2$Cl$_2$ (10 mL), washed with a saturated aqueous NaHCO$_3$ solution (2 x 10 mL), brine (10 mL), then the organic layers dried over MgSO$_4$, filtered and the solvents removed in vacuo. Purification by column chromatography (10% EtOAc in petroleum ether) provided 175a/b (74 mg, 49%) as an inseparable ca 3.4:1 mixture of diastereomers as determined by $^1$H NMR spectroscopy. IR (film) 3326, 2921, 1724, 1677, 1534, 1452, 1362,
1273 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 8.05-8.04 (2H, m, ArH), 7.66-7.59 (1H, m, ArH), 7.52-7.45 (2H, m, ArH), 5.81 (0.77H, br s, NH), 5.73 (0.23H, br s, NH), 5.32 (0.23H, d, $J = 8.2$, OCHH), 5.10 (0.77H, d, $J = 7.8$, OCHH), 4.60 (0.77H, d, $J = 9.6$, OCH), 4.57 (0.77H, d, $J = 7.8$, OCHH), 4.52 (0.23H, d, $J = 8.2$, OCHH), 4.50 (0.23H, d, $J = 10.1$, OCH), 1.97-1.67 (6H, m), 1.34 (6.95H, s), 1.32 (2.05H, s), 1.24-0.84 (5H, m); $\delta$C (100 MHz, CDCl$_3$) 167.5 (C=O), 165.5 (C=O), 164.9 (C=O), 164.8 (C=O), 134.0 (CH, Ar), 133.9 (CH, Ar), 129.9 (CH, Ar), 129.8 (CH, Ar), 129.7 (C, Ar), 128.8 (CH, Ar), 128.7 (CH, Ar), 128.4 (C, Ar), 91.4 (CH), 90.3 (CH), 81.5 (C), 81.3 (C), 75.0 (CH$_2$), 74.8 (CH$_2$), 51.7 (C), 51.5 (C), 39.2 (CH), 39.2 (CH), 28.6 (CH$_3$), 28.6 (CH$_3$), 28.3 (CH$_2$), 27.9 (CH$_2$), 27.5 (CH$_2$), 27.3 (CH$_2$), 26.4 (CH$_2$), 26.3 (CH$_2$), 25.5 (CH$_2$), 25.3 (CH$_2$), 25.1 (CH$_2$), 24.9 (CH$_2$); MS (mixture) (ES$^+$) 360 [M+H]$^+$; HRMS (ES$^+$) calcd. for C$_{21}$H$_{30}$NO$_4$ [M+H]$^+$: 360.2169; found: 360.2163.

**N-tert-Butyl-2-cyclohexyl-3-hydroxyoxetane-3-carboxamide (176)**

To a solution of 173a (70 mg, 0.24 mmol) in MeOH (7.5 mL) was added K$_2$CO$_3$ (80 mg, 0.58 mmol) and the mixture stirred overnight at r.t. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (10 mL), washed with water (10 mL) and the organic layer filtered through a plug of silica gel and the solvent removed *in vacuo* affording the title compound (61 mg, 100%) as a white solid. M.p. 107-110 °C; IR (film) 3566, 2039, 1610, 1509, 1442, 1244, 1179, 1066, 1026 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 6.45 (1H, br s), 4.58 (1H, d, $J = 6.6$, OCHH), 4.44 (1H, d, $J = 10.4$, OCH), 4.44 (1H, s), 3.38 (1H, d, $J = 6.6$, OCHH), 1.88-1.65 (5H, m, cy), 1.44
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(9H, s, CH₃), 1.28-1.11 (3H, m, cy), 0.91-0.77 (3H, m, cy); δC (75 MHz, CDCl₃) 170.6 (C), 96.6 (CH), 77.5 (CH₂), 75.9 (C), 52.0 (C), 40.0 (CH), 28.9 (CH₃), 28.6 (CH₂), 26.2 (CH₂), 25.2 (CH₂); MS (ES⁺) 256 [M+H]⁺; HRMS (ES⁺) calcd. for C₁₄H₂₆NO₃ [M+H]⁺: 256.1907; found: 256.1902.

(S)-2-(methoxymethyl)-N-(oxetan-3-ylidene)pyrrolidin-1-amine (210)

15 (986 µL, 15.4 mmol) was combined with (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) (1.0 mL, 7.7 mmol) and heated to 65 °C without solvent for 18 h. After cooling to r.t. excess 15 was removed in vacuo. Purification by column chromatography (20% EtOAc in hexanes, 1% Et₃N) afforded the title compound (1.25 g, 88%) as a colourless oil. [α]D₂⁵ –8.8 (c 0.12, CHCl₃); IR (film) 2923, 2857, 1712, 1662, 1459, 1344, 1196, 1113, 1092, 1040, 956 cm⁻¹; δH (300 MHz, CDCl₃) 5.44-5.36 (1H, m, OCHH), 5.34-5.21 (3H, m, OCHH, OCH₂), 3.47 (1H, dd, J = 9.2, 4.0, CH₃OCHH), 3.42-3.37 (1H, m, CH₃OCHH), 3.37-3.28 (1H, m, NCH), 3.35 (3H, s, CH₃), 3.17-3.10 (1H, m, NCHH), 2.79-2.71 (1H, m, NCHH), 1.96-1.80 (3H, m, CHH, CH₂), 1.75-1.67 (1H, m, CHH); δC (100 MHz, CDCl₃) 140.0 (C=N), 82.3 (CH₂), 81.9 (CH₂), 74.2 (CH₂), 64.3 (CH), 58.7 (CH₃), 51.9 (CH₂), 25.2 (CH₂), 22.0 (CH₂); MS (ES⁺) 185 [M+H]⁺; HRMS (ES⁺) calcd. for C₉H₁₇N₂O₂ [M+H]⁺: 185.1285; found: 185.1288.
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*N-*(S)-2-benzylloxetan-3-ylidene)-2-(methoxymethyl)pyrrolidin-1-amine (212)*

To a solution of 210 (64 mg, 0.35 mmol) in THF (2.5 mL) at –78°C was added dropwise a solution of tert-butyllithium in pentanes (1.7 M, 0.23 mL, 0.39 mmol). The reaction was stirred at –78°C for a further 2 h before the addition of benzyl bromide (50 µL, 0.42 mmol). The reaction mixture was stirred at –78 °C for 2 h and then allowed to warm to r.t. over 18 h before being diluted with Et₂O (5 mL), washed with pH 7 buffer (5 mL), brine (5 mL), dried over MgSO₄, filtered and the solvents removed *in vacuo*. Purification by column chromatography (20% EtOAc in hexanes, 1% Et₃N) afforded the title compound (70 mg, 73%) as a colourless oil. IR (film) 3345, 2973, 2884, 1686, 1453, 1380, 1087, 1087, 1045, 879 cm⁻¹; δH (400 MHz, CDCl₃) 7.25-7.13 (5H, m, ArH), 5.58-5.54 (1H, m, OCH), 4.91-4.88 (1H, m, OCHH), 4.60 (1H, dd, J = 11.4, 3.5, OCHH), 3.49-3.64 (1H, m, CH₃OCHH), 3.37-3.28 (2H, m, CH₃OCHH, NCH), 3.39 (3H, s, CH₃), 3.25-3.20 (1H, m, NCHH), 3.07-2.96 (2H, m, OCH₂CH₂), 2.66 (1H, q, J = 8.4, NCHH), 1.97-1.89 (1H, m, CHH), 1.87-1.80 (2H, m, CH₂), 1.68-1.60 (1H, m, CHH); δC (100 MHz, CDCl₃) 145.4 (C=N), 136.4 (C, Ar), 129.9 (CH, Ar), 128.1 (CH, Ar), 126.4 (CH, Ar), 93.3 (OCH), 79.3 (OCH₂), 75.7 (CH₃OCH₂), 65.9 (NCH), 59.2 (CH₂), 53.6 (NCH₂), 39.0 (OCH₂CH₂), 26.6 (CH₂), 23.1 (CH₂); MS (ES⁺) 275 [M+H]⁺; HRMS (ES⁺) calcd. For C₁₆H₂₃N₂O₂ [M+H]⁺: 275.1754; found: 275.1759.

*¹H and ¹³C NMR data provided for the signals corresponding to the major product obtained from the reaction (see 2.5.5).*
(S)-2-Benzoxetan-3-one (by ozonolysis) (222)

O₃ (1-2 L h⁻¹) was bubbled through a solution of 212 (67 mg, 0.25 mmol) in CH₂Cl₂ (10 mL) at −78 °C for 1 h. The flow of O₃ was then ceased and the solution was allowed to warm to r.t. The solution was then diluted with CH₂Cl₂ (10 mL), washed with aqueous NaHSO₄ solution (3.5 M, 20 mL), dried over MgSO₄, filtered and the solvent removed in vacuo. Purification by column chromatography (5% EtOAc in hexanes, 1% Et₃N) provided the title compound (21 mg, 51%) as a colourless oil. IR (film) 3031, 2917, 1818, 1726, 1496, 1454, 1422, 1219, 1147, 1079, 728, 697 cm⁻¹; δH (300 MHz, CDCl₃) 7.32-7.19 (5H, m, ArH), 5.66-5.61 (1H, m, CH), 5.17 (1H, d, J = 15.1, CHH), 4.92 (1H, dd, J = 15.1, 4.5, CHH), 3.11 (2H, d, J = 6.0, CH₂); δC (100 MHz, CDCl₃) 201.2 (C=O), 134.2 (C, Ar), 128.5 (CH, Ar), 127.6 (CH, Ar), 126.0 (CH, Ar), 102.5 (OCH), 88.0 (OCH₂), 36.5 (CHOCH₂); HRMS (ES⁺) calcd. for C₁₀H₁₁O₂ [M+H⁺]: 163.0754; found: 163.0759.

(S)-2-Benzoxetan-3-one (by cleavage with oxalic acid) (222)

To a solution of 212 (260 mg, 0.95 mmol) in Et₂O (4 mL) was added with vigorous stirring saturated aqueous oxalic acid (1.5 mL). After stirring at r.t. for 2.5 h, the mixture was extracted into Et₂O (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent removed in vacuo. The residue was then dissolved in hexanes (50 mL) and the solid precipitate removed via suction filtration through a fine porosity sinter and discarded, before removing the solvent in vacuo. Purification by column chromatography (5% EtOAc in hexanes, 1% Et₃N)
provided the title compound (30 mg, 79%) as a colourless oil. $[\alpha]_{D}^{25} - 60 (c \ 0.07, CHCl_3)$; Data as previously reported.

**N,N-Dimethyl-N’-oxetan-3-ylidene-hydrazine (224)**

$N,N$-Dimethylhydrazine (888 µl, 11.7 mmol) was added dropwise to 15 (898 µl, 14.0 mmol). The mixture was heated to 65 °C for 18 h, and the excess 3-oxetanone and water was removed under reduced pressure to give the title compound as a pale yellow oil (1.26 g, 94%) which was used without further purification. IR (film) 3363, 2952, 2861, 1820, 1685, 1467, 1446, 1240, 1144, 1024, 960, 857 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 5.42 (2H, t, $J = 2.9$, OCH$_2$), 5.29 (2H, t, $J = 2.9$, OCH$_2$), 2.68 (6H, s, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 142.4 (OCH$_2$C), 82.2 (OCH$_2$), 81.3 (OCH$_2$), 45.7 (NCH$_3$); MS (ES$^+$) 115 [M+H]$^+$; HRMS (ES$^+$) calcd. For C$_5$H$_{11}$N$_2$O 115.0866 [M+H]$^+$; Found: 115.0870.

**(+)-2-Benzyl oxetan-3-one (by cleavage with oxalic acid) ((+)-222)**

$tert$-Butyllithium in pentanes (1.7 M, 0.23 mL, 0.39 mmol) was added dropwise to a stirred solution of $N,N$-dimethyl-$N'$-oxetan-3-ylidene-hydrazine (224) (40 mg, 0.35 mmol) in anhydrous THF (2.5 mL) at $-78^\circ$C. After 2 h, benzyl bromide (50 µL, 0.42 mmol) was added, and the solution allowed to warm slowly to r.t. over 18 h. The reaction mixture was diluted with ether (20 mL), and washed with pH 7 buffer solution (1 mL) and brine (2 x 5 mL). The organic layer was dried over MgSO$_4$, filtered, and the solvent removed in vacuo. The residue was dissolved in a mixture of saturated aqueous oxalic acid solution (1 ml) and diethyl ether (1 mL) and stirred
vigorously at r.t. for 2 h. The reaction mixture was diluted with diethyl ether (10 mL) and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were then dried over MgSO₄, filtered and the solvent removed in vacuo. The residue was taken up in hexane (10 mL), filtered and then the solvent removed in vacuo. Purification was achieved using column chromatography (5% EtOAc in hexanes, 1% Et₃N) affording the title compound (6 mg, 11%) as a colourless oil. Data as previously reported.

(2S’,3R*)- and (2S’,3S*)-2-benzylloxetan-3-ol (225a/b)

\[
\begin{align*}
\text{To a solution of 222 (13 mg, 0.08 mmol) in} \\
\text{MeOH (1 mL) was added at r.t. NaBH}_4 \text{ (5 mg,} \\
\text{0.12 mmol). The reaction mixture was stirred} \\
\text{for 30 min and then partitioned between CH}_2\text{Cl}_2 \text{ (10 mL) and brine (10 mL). The} \\
aqueous phase was extracted with CH}_2\text{Cl}_2 \text{ (3 x 20 mL), dried over MgSO}_4, \\
\text{filtered and the solvents removed in vacuo, providing 225a/b (12mg, 92%, 74\% ee\(^3\)) as a ca 1:1:1 mixture of diastereomers as determined by }^1\text{H NMR} \\
\text{spectroscopy. IR (film) 3387, 2920, 1731, 1495, 1454, 1373, 1326, 1124, 957,} \\
907, 727, 698 \text{ cm}^{-1}; \delta_\text{H} \text{ (400 MHz, CDCl}_3\text{) 7.26-7.13 (5H, m, ArH), 4.96 (0.52H,} \\
\text{q, } J = 6.9, \text{ OCHBn), 4.48-0.47 (0.52H, m, CHO)} \text{H), 4.74 (0.52H, m, OCHH), 4.73} \\
(0.48H, m, OCHBn), 4.52 (0.48H, t, } J = 6.5, \text{ OCHH), 4.43-4.36 (0.48H, m,} \\
\text{CHOH), 4.37 (0.52H, m, OCHH), 4.31 (0.48H, t, } J = 6.5, \text{ OCHH), 3.14 (0.52H,} \\
dd, } J = 14.2, 6.9, \text{ OCHCCHHPh}, 3.03 (0.52H, dd, } J = 14.2, 6.9, \text{ OCHCCHHPh),} \\
\end{align*}
\]

\(^3\) ee calculated after conversion of alcohol to corresponding acetate by Dr Joanna Geden.
2.98 (0.48H, dd, J = 14.1, 6.8, OCHCHPh), 2.90 (0.48H, dd, J = 14.1, 6.8, OCHCHPh), 2.10 (1H, br s, OH); (100 MHz, CDCl₃) 137.3 (C, Ar), 136.4 (C, Ar), 129.2 (CH, Ar), 128.6 (CH, Ar), 126.7 (CH, Ar), 126.4 (CH, Ar), 91.5 (OCHBₙₙₙₙ), 87.9 (OCHBₙₙₙₙ), 77.8 (OCH₂ₙₙₙₙ), 76.4 (OCH₂ₙₙₙₙ), 70.1 (CHOHₙₙₙₙ), 67.5 (CHOHₙₙₙₙ), 41.0 (CH₂Phₙₙₙₙ), 36.4 (CH₂Phₙₙₙₙ); MS (ES+) 187 [M+Na]⁺; HRMS (ES+) calcd. For C₁₀H₁₂NaO₂ [M+Na]⁺: 187.0730; found: 187.0736.

(S)-Ethyl 2-amino-3-(1H-indol-3-yl)propanoate (226)

To a solution of L-tryptophan (227) (1.00 g, 4.9 mmol) in EtOH (20 mL) at r.t. was added thionyl chloride (0.54 mL, 7.35 mmol). The mixture was refluxed for 18 h before cooling to r.t. and the volatiles removed in vacuo. The solid residue was suspended in EtOAc (20 mL) and vigorously washed with a saturated aqueous NaHCO₃ solution (4 x 20 mL). The combined aqueous layers were extracted into EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent removed in vacuo affording the title compound (1.00 g, 88%) as a white solid, which was used without further purification. δH (400 MHz, CDCl₃) 8.32 (1H, br s, NHₙₙₙₙ), 7.63, (1H, d, J = 8.1, ArH), 7.34 (1H, d, J = 8.1, ArH), 7.19 – 7.09(2H, m, ArH), 7.02 (1H, d, J = 2.3, ArH), 4.20-4.15 (2H, m, OCH₂), 3.82 (1H, dd, J= 7.8, 4.9, CH), 3.29 (1H, dd, J = 14.3, 4.9, CHH), 3.05 (1H, dd, J = 14.3, 7.8, CHH), 1.57 (2H, br s, NH₂), 1.25 (3H, t, J = 7.2, CH₃); δC (100 MHz, CDCl₃) 175.0 (C=O), 136.3 (C, Ar), 127.5 (C, Ar), 123.0 (CH, Ar), 122.2 (CH, Ar), 119.5 (CH, Ar), 118.8 (CH, Ar), 111.2 (CH, Ar), 110.0 (C, Ar),
61.0 (CH₂), 55.0 (CH), 30.8 (CH₂), 14.2 (CH₃); MS (ES⁺) 233 [M+H]⁺. Data is in accordance with literature values.¹⁵⁶

**General Method 2a**

To a stirred solution of the relevant oxetan-3-one (1 equiv.) in CH₃CN was added, the amine (1.2 equiv.) and I₂ (5 mol %) and the mixture stirred at reflux for 18 h. After cooling to r.t. the solvent was removed *in vacuo* and the residue dissolved in EtOAc (10 mL). The solution was washed sequentially with saturated aqueous Na₂S₂O₃ solution (10 mL), saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL). The organic layers were dried over Na₂SO₄, filtered and the solvents removed *in vacuo*. Purification of the product was achieved by column chromatography.

**General Method 2b**

To a stirred solution of the oxetan-3-one (1 equiv.) in CH₃CN was added, the amine (1.2 equiv.) and the mixture stirred at reflux for 18 h. After cooling to r.t. the solvent was removed *in vacuo*. Purification was achieved by column chromatography.
(1'S,2S,3'S)- and (1'S,2R,3'R)-Ethyl-2-benzyl-2',3',4',9'-tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole]-3'-carboxylate (228a/b)

Prepared according to General Method 2a from (S)-222 (57 mg, 0.35 mmol) and 5-methoxytryptamine (98 mg, 0.42 mmol) in CH₂CN (2.5 mL) providing the title compounds as ca 7.4:1 mixture of diastereomers as determined by $^1$H NMR spectroscopy. Purification by column chromatography (20% EtOAc in petroleum ether, 1% Et₃N) gave the separable diastereomers. Less polar, major diastereomer (1'S, 2'S, 3'S)-228 (89 mg, 67%), off-white solid. M.p. 60-65 °C; IR (film): 3263, 2937, 1731, 1494, 1453, 1369, 1182, 742, 701; δ (CDCl₃, 400 MHz): 8.97 (1H, br s, NH indole, Ar), 7.53 (1H, d, J = 7.9, ArH), 7.40 (1H, d, J = 7.9, ArH), 7.28-7.22 (5H, m, ArH), 7.20-7.14 (2H, m, ArH), 5.16 (1H, dd, J = 9.5, 3.7, OCH), 4.83 (1H, d, J = 6.2, OCH₂), 4.80 (1H, d, J = 6.2, OCH₂), 4.33 (2H, q, J = 7.1, OCH₂CH₃), 3.77 (1H, dd, J = 10.5, 4.1, NHCH), 3.39 (1H, dd, J = 14.1, 9.5, OCH₂CH₃), 2.86 (1H, dd, J = 15.3, 10.5, NHCH₂CH₃), 2.78 (1H, br s, NHpip), 1.39 (3H, t, J = 7.1, CH₃); δ (CDCl₃, 75 MHz): 173.0 (C=O), 137.1 (C, Ar), 136.4 (C, Ar), 133.9 (C, Ar), 129.3 (CH, Ar), 128.6 (CH, Ar), 126.6 (CH, Ar), 126.6 (C, Ar) 122.3 (CH, Ar), 119.7 (CH, Ar), 118.3 (CH, Ar), 111.3 (CH, Ar), 108.5 (C, Ar), 91.7 (OCHC), 83.1 (OCH₂), 61.4 (OCH₂CH₃), 58.3 (NHC), 53.8 (NHCH), 36.8 (CH₃Bn), 25.5 (NHCH₂CH₃), 14.2 (CH₃); HRMS (ESI) calcd. for C₂₃H₂₅N₂O₃ [M+H]+: 377.1860. Found 377.1863. And more polar, minor diastereomer (1'S, 2'R, 3'R)-228 (12 mg, 9%): Off-white solid, IR (film): 3307,
2926, 1730, 1495, 1453, 1370, 1182, 977, 744, 701; \( \delta_H \) (CDCl\(_3\), 400 MHz): 8.75 (1H, br s, NH\(_{\text{indole, Ar}}\)), 7.53 (1H, d, \( J = 8.1 \), ArH), 7.42 (1H, d, \( J = 8.1 \), ArH), 7.30-7.15 (7H, m, ArH), 5.06 (1H, dd, \( J = 8.2 \), 5.8, OCH), 4.94 (1H, d, \( J = 6.8 \), OCH/HC), 4.86 (1H, d, \( J = 6.8 \), OCH/HC), 4.29 (2H, q, \( J = 7.1 \), OCH\(_2\)), 3.41 (1H, dd, \( J = 9.5 \), 4.4, NHC\(_2\)), 3.38 (1H, dd, \( J = 10.8 \), 5.8, OCH\(_2\)HC), 3.19 (1H, dd, \( J = 14.1 \), 8.2, OCHCH\(_2\)), 3.08 (1H, dd, \( J = 15.1 \), 4.4, NHCH\(_2\)), 2.85 (1H, br s, NH\(_{\text{pip}}\)), 1.37 (3H, t, \( J = 7.1 \), CH\(_3\)); \( \delta_C \) (CDCl\(_3\), 75 MHz): 173.1 (C=O), 137.7 (C, Ar), 136.3 (C, Ar), 134.7 (C, Ar), 129.2 (CH, Ar), 128.6 (CH, Ar), 126.6 (CH, Ar), 126.5 (C, Ar) 122.4 (CH, Ar), 119.8 (CH, Ar), 118.3 (CH, Ar), 111.2 (CH, Ar), 108.3 (CH, Ar), 93.5 (OCHC), 81.2 (OCH\(_2\)C), 61.3 (OCH\(_2\)CH\(_3\)), 57.9 (NHC), 54.1 (NHCH), 37.0 (CH\(_2\)Bn), 25.3 (NHCH\(_2\)CH\(_2\)), 14.3 (CH\(_3\)); HRMS (ESI) calcd. for C\(_{23}\)H\(_{25}\)N\(_2\)O\(_3\) [M+H]\(^+\): 377.1860. Found 377.1865.

\( 2',3',4',9' \)-Tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole] (267)

Prepared according to General Method 2b from 15 (20 mg, 0.28 mmol) and tryptamine (54 mg, 0.34 mmol) in CH\(_3\)CN (5 mL) affording the title compound (44 mg, 75%) after column chromatography (3% MeOH in CH\(_2\)Cl\(_2\), 1% Et\(_3\)N) as a beige solid. M.p. 167-170°C; IR (film): 3260, 1449, 1301, 1186, 976, 730 cm\(^{-1}\); \( \delta_H \) (CD\(_3\)OD, 400 MHz): 7.41 (1H, d, \( J = 7.8 \), ArH), 7.37 (1H, d, \( J = 7.8 \), ArH), 7.12-7.08 (1H, m, ArH), 7.02-6.98 (1H, m, ArH), 5.02 (2H, d, \( J = 6.7 \), OCH\(_2\)), 4.74 (2H, d, \( J = 6.7 \), OCH\(_2\)), 3.14 (2H, t, \( J = 5.8 \), CH\(_2\)), 2.80 (2H, t, \( J = 5.8 \), CH\(_2\)), indole NH and piperidin NH not observed; \( \delta_C \) (CDCl\(_3\), 100 MHz): 136.0 (C, Ar), 133.8 (C, Ar),
126.9 (C, Ar), 122.3 (CH, Ar), 119.7 (CH, Ar), 118.4 (CH, Ar), 111.1 (CH, Ar), 110.1 (C, Ar), 84.2 (OCH₂), 57.3 (C), 41.3 (CH₂), 22.3 (CH₂); HRMS (ESI) calcd. for C₁₃H₁₅N₂O [M+H]⁺: 215.1179. Found 215.1178.

6'-Methoxy-2’,3’,4’,9’-tetrahydrospiro[oxetane-3,1’-pyrido[3,4-b]indole] (270)

Prepared according to General Method 2b from 15 (20 mg, 0.28 mmol) and 5-methoxytryptamine (65 mg, 0.34 mmol) in CH₃CN (5 mL) affording the title compound (58 mg, 85%) after column chromatography (5% MeOH in CH₂Cl₂, 1% Et₃N) as a beige solid. M.p. 179-183 °C; IR (film): 3281, 2947, 1455, 1212, 1168, 970, 800; δ_H (CD₃OD, 300 MHz): 7.25 (1H, d, J = 8.9, ArH), 6.90 (1H, d, J = 2.5, ArH), 6.76 (1H, dd, J = 8.9, 2.5, ArH), 4.98 (2H, d J = 6.6, OCHH), 4.70 (2H, d, J = 6.6, OCHH), 3.80 (3H, s, OCH₃), 3.08 (2H, t, J = 5.8, CH₂), 2.69 (2H, t, J = 5.8, CH₂); δ_C (CD₃OD, 75 MHz): 155.2 (C, Ar), 135.0 (C, Ar), 133.3 (C, Ar), 128.4 (C, Ar), 112.9 (CH, Ar), 112.7 (CH, Ar), 110.0 (C, Ar), 101.1 (CH, Ar), 83.8 (OCH₂), 58.6 (C), 56.2 (CH₃), 41.7 (CH₂), 22.6 (CH₂); HRMS (ESI) calcd. for C₁₄H₁₇N₂O₂ [M+H]⁺: 245.1285. Found 245.1284.

(S)-Ethyl 2’,3’,4’,9’-tetrahydrospiro[oxetane-3,1’-pyrido[3,4-b]indole]-3’-carboxylate (271)

Prepared according to General Method 2a from 15 (50 mg, 0.69 mmol) and tryptophan ethyl ester (226) (193 mg, 0.83 mmol) in CH₃CN (5 mL) affording the title compound (177 mg, 89%) after column chromatography (60% EtOAc in
petroleum ether, 1% Et$_3$N) as a beige solid. M.p. 157-160 °C; [α]$^{22}_{D}$=25 (c 0.1, CHCl$_3$); IR (film): 3428, 2928, 1735, 1592, 1339, 1160, 720; δ$_H$ (CDCl$_3$, 400 MHz): 8.66 (1H, br s, NH$_{indole}$, Ar), 7.51 (1H, d, J = 8.0, ArH), 7.40 (1H, d, J = 8.0, ArH), 7.24-7.20 (1H, m, ArH), 7.15-1.12 (1H, m, ArH), 5.00 (1H, d, J = 6.7, OCHH), 4.90 (1H, d, J = 6.7, OCHH), 4.87 (1H, d, J = 6.1, OCHH), 4.79 (1H, d, J = 6.1, OCHH), 4.20 (2H, m, OCH$_2$CH$_3$), 3.84 (1H, dd, J = 7.8, 5.0, NHCH), 3.14 (1H, dd, J = 15.3, 5.0, NHCHCHH), 2.97 (1H, dd, J = 15.3, 7.8, NHCHCHH), 2.75 (1H, br s, NH$_{pip}$), 1.29 (3H, J = 7.1, CH$_3$); δ$_C$ (CDCl$_3$, 75 MHz): 172.8 (C=O), 135.6 (C, Ar), 133.2 (C, Ar), 125.9 (C, Ar), 121.8 (CH, Ar), 119.2 (CH, Ar), 117.7 (CH, Ar), 110.5 (CH, Ar), 107.4 (C, Ar), 84.9 (OCH$_2$), 83.9 (OCH$_2$), 60.7 (OCH$_2$CH$_3$), 56.4 (NHC), 53.3 (CH), 24.3 (CHCH$_2$), 13.6 (CH$_3$); HRMS (ESI) calcd. for C$_{16}$H$_{19}$N$_2$O$_3$ [M+H]$^+$: 287.1390. Found 287.1389. Anal. calcd. for C$_{16}$H$_{19}$N$_2$O$_3$: C, 67.12; H, 6.34; N, 9.78%. Found: C, 67.05; H, 6.43; N, 9.50%.

9'-Methyl-2',3',4',9'-tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole] (272)

Prepared according to General Method 2a from 15 (24 mg, 0.34 mmol) and 2-(1-methyl-1H-indol-3-yl)ethanamine (72 mg, 0.41 mmol) in CH$_3$CN (5 mL) affording the title compound (40 mg, 52%) after column chromatography (10% petroleum ether in EtOAc, 1% Et$_3$N) as an off-white solid. M.p. 140-142 °C; IR (film): 2951, 2878, 1471, 1442, 1369, 975, 749; δ$_H$ (CDCl$_3$, 400 MHz): 7.50 (1H, d, J = 7.8, ArH), 7.36 (1H, d, J = 7.8, ArH), 7.28-7.24 (1H, m, ArH), 7.14-7.10 (1H, m, ArH), 5.08 (2H, d, J = 7.0, OCH$_2$), 4.82 (2H, d, J = 7.0, OCH$_2$), 4.13 (3H, s, NCH$_3$), 3.10
(2H, t, $J = 5.5$, CH$_2$), 2.76 (2H, t, $J = 5.5$, CH$_2$), 2.26 (1H, br s, NH$_{pip}$); $\delta_C$ (CDCl$_3$, 100 MHz): 137.8 (C, Ar), 133.6 (C, Ar), 126.2 (C, Ar), 122.2 (CH, Ar), 119.4 (CH, Ar), 118.4 (CH, Ar), 110.4 (C, Ar), 109.1 (CH, Ar), 83.5 (OCH$_2$), 57.3 (C), 41.1 (CH$_2$), 30.5 (CH$_3$), 22.9 (CH$_2$); HRMS (ESI) calcd. for C$_{14}$H$_{17}$N$_2$O [M+H]$^+$: 229.1335. Found 229.1336.

$(1R^*,2R^*)$-2-Phenethyl-2',3',4',9'-tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole] (274)

Prepared according to General Method 2a from 170 (18 $\mu$L, 0.28 mmol) and tryptamine (54 mg, 0.34 mmol) in CH$_3$CN (5 mL) affording the title compound (58 mg, 65%) after column chromatography (50% EtOAc in petroleum ether, 1% Et$_3$N) as a beige solid. M.p. 165-168 °C; IR (film): 3236, 1452, 970, 904, 872, 727, 692 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz): 8.72 (1H, br s, NH$_{indole}$), 7.48 (1H, d, $J = 7.8$, Ar), 7.39 (1H, d, $J = 7.8$, ArH), 7.26-7.09 (7H, m, ArH), 4.90 (1H, dd, $J = 9.6$, 3.8, OCH), 4.82 (1H, d, $J = 6.6$, OCHH), 4.64 (1H, d, $J = 6.6$, OCHH), 3.17-3.11 (1H, m, CH$_3$CHH), 3.05-2.99 (1H, m, CH$_2$CHH), 2.88-2.80 (1H, m, PhCHH), 2.72-2.69 (2H, m, CH$_2$), 2.64-2.57 (1H, m, PhCHH), 2.42-2.30 (1H, m, OCHCHH), 2.09-2.01 (1H, m, OCHCHH), 1.91 (1H, br s, NH$_{pip}$); $\delta_C$ (CDCl$_3$, 100 MHz): 141.2 (C, Ar), 136.0 (C, Ar), 134.4 (C, Ar), 128.5 (CH, Ar), 126.9 (C, Ar), 126.1 (CH, Ar), 122.2 (CH, Ar), 119.7 (CH, Ar), 118.4 (CH, Ar), 111.1 (CH, Ar), 110.0 (C, Ar), 91.2 (OCH), 81.3 (OCH$_2$), 58.1 (NHC), 41.6 (CH$_2$), 32.2 (OCHCH$_2$), 30.8 (PhCH$_2$), 22.3 (CH$_2$); HRMS (ESI) calcd. for C$_{21}$H$_{23}$N$_2$O [M+H]$^+$: 319.1805. Found 319.1798.
(1S*, 2S*)-6'-Methoxy-2-phenethyl-2',3',4',9'-tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole] (275)

Prepared according to General Method 2a from 170 (121 mg, 0.69 mmol) and 5-methoxytryptamine (158 mg, 0.83 mmol) in CH$_3$CN (5 mL) affording the title compound (174 mg, 72%) after column chromatography (50% EtOAc in petroleum ether, 1% Et$_3$N) as a beige solid. M.p. 162-165 °C; IR (film): 3268, 2936, 1458, 1434, 1212, 1163, 966, 749, 698; $\delta$$_H$(CDCl$_3$, 400 MHz): 8.70 (1H, s, NH$_{\text{indole}}$), 7.28 (1H, d, $J$ = 8.8, ArH), 7.24-7.22 (2H, m, ArH), 7.19-7.12 (3H, m, ArH), 6.94 (1H, d, $J$ = 2.4, ArH), 6.86 (1H, dd, $J$ = 8.8, 2.4, ArH), 4.89 (1H, dd, $J$ = 9.6, 3.9, OCH), 4.82 (1H, d, $J$ = 6.6, OCHH), 4.63 (1H, d, $J$ = 6.6, OCHH), 3.86 (3H, s, CH$_3$), 3.17-3.11 (1H, m, CH$_2$), 3.05-3.00 (1H, m, CH$_2$), 2.87-2.80 (1H, m, PhCHH), 2.70-2.66 (2H, m, CH$_2$), 2.64-2.56 (1H, m, PhCHH), 2.41-2.32 (1H, m, OCHCHH), 2.09-2.00 (1H, m, OCHCHH), 1.90 (1H, br s, NH$_{\text{pip}}$); $\delta$$_C$(CDCl$_3$, 100 MHz): 154.2 (C, Ar), 141.3 (C, Ar), 135.3 (C, Ar), 131.1 (C, Ar), 128.5 (CH, Ar), 127.3 (C, Ar), 126.1 (C, Ar), 112.0 (CH, Ar), 111.8 (CH, Ar), 111.7 (CH, Ar), 109.9 (CH, Ar), 91.1 (OCH), 81.3 (OCH$_2$), 58.2 (C), 56.0 (CH$_3$), 41.5 (CH$_2$), 32.2 (OCHCH$_2$), 30.8 (PhCH$_2$), 22.3 (CH$_2$); HRMS (ESI) calcd. for C$_{22}$H$_{25}$N$_2$O$_2$ [M+H]$^+$: 349.1911. Found 349.1995.
(1'S,2R,3'R)- and (1'S,2S,3'S) Ethyl 2-phenethyl-2',3',4',9'-
tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole]-3'-carboxylate (276a/b)

Prepared according to General Method 2a from 170 (121 mg, 0.69 mmol) and L-tryptophan ethyl ester 226 (193 mg, 0.83 mmol) affording the title compounds (195 mg, 72%) after column chromatography (25% EtOAc in petroleum ether, 1% Et₃N) as an inseparable ca 1:1:1 mixture of diastereomers as determined by ¹H NMR spectroscopy as a beige solid. M.p. 79-83 °C; IR (film): 3258, 2930, 1728, 1495, 1452, 1179, 694, 739, 697; δₜ (CDCl₃, 400 MHz): 10.45 (1H, br s, NH indole), 7.48-7.43 (2H, m, ArH), 7.26-7.20 (3H, m, ArH), 7.06-7.01 (1H, m, ArH), 5.17 (0.5H, dd, J = 8.0, 5.8, OCH), 4.89 (0.5H, d, J = 6.7, OCH/HC), 4.81 (0.5H, dd, J = 9.5, 4.0, OCH), 4.75 (0.5H, d, J = 6.3, OCHHC), 4.68 (0.5, d, J = 6.7, OCHHC), 4.63 (0.5H, d, J = 6.3, OCHHC), 4.29-4.11 (2H, m, OCH₂CH₃), 3.83-3.77 (1H, m, NHCH), 3.06-2.98 (1H, m, NHCHCHHH), 2.86 (1H, br s, NHpip), 2.84-2.57 (3H, m), 2.40-2.03 (2H, m), 1.30 (1.5H, t, J = 7.2, CH₃), 1.25 (1.5H, t, J = 7.1, CH₃); δₜ (CDCl₃, 100 MHz): 173.1 (C=O), 172.9 (C=O), 141.1 (C, Ar), 141.0 (C, Ar), 136.4 (C, Ar), 134.4 (C, Ar), 134.0 (C, Ar), 128.5 (CH, Ar), 128.5 (CH, Ar), 126.7 (C, Ar), 126.7 (C, Ar), 126 (CH, Ar), 122.4 (CH, Ar), 122.3 (CH, Ar), 119.8 (CH, Ar), 119.7 (CH, Ar), 118.3 (CH, Ar), 111.2 (CH, Ar), 108.7 (C, Ar), 108.2 (C, Ar), 92.4 (OCH), 90.5 (OCH), 83.3 (OCH₂C), 81.5 (OCH₂C), 61.4 (CH₂), 58.2 (C), 57.8 (C), 54.3 (NHCH), 53.7 (NHCH), 32.1 (CH₂), 32.0 (CH₂), 31.0 (CH₂), 30.7 (CH₂), 25.5 (CH₂), 25.2

(1R*,2R*)-2-Cyclohexyl-2',3',4',9'-tetrahydrospiro[oxetane-3,1'-pyrido[3,4-b]indole] 277)

Prepared according to General Method 2a from 171 (106 mg, 0.69 mmol) and tryptamine (133 mg, 0.83 mmol) in CH₃CN (5 mL) affording the title compound (46 mg, 23%) after column chromatography (40% EtOAc in petroleum ether, 1% Et₃N) as an off-white solid. M.p. 242-246 °C; IR (film): 3275, 2918, 1443, 1261, 1080, 1019, 960, 800, 746, 717; δH (CDCl₃, 400 MHz): 8.67 (1H, br s, NHₐndo), 7.49 (1H, d, J = 7.9, ArH), 7.39 (1H, d, J = 7.9, ArH), 7.20 (1H, t, J = 7.4, ArH), 7.11 (1H, t, J = 7.4, ArH), 4.75 (1H, d, J = 6.3, OCHH), 4.65 (1H, d, J = 9.9, OCH), 4.53 (1H, d, J = 6.3, OCHH), 3.27-3.21 (1H, m, CH₂CHH), 3.11-3.05 (1H, m, CH₂CHH), 2.81-2.68 (2H, m, CH₂CH₂), 2.17-2.09 (1H, m, OCHCHₐ), 2.09-1.99 (1H, m, CHₐ), 1.80 (1H, br s, NHₚip), 1.70-1.56 (3H, m, CHₐ), 1.38-1.25 (3H, m, CHₐ), 1.20-1.10 (1H, m, CHₐ), 1.00-0.91 (1H, m, CHCHₐ), 0.81-0.71 (1H, m, CHCHₐ); δC (CDCl₃, 100 MHz): 135.0 (C, Ar), 133.3 (C, Ar), 126.0 (C, Ar), 121.1 (CH, Ar), 118.5 (CH, Ar), 117.3 (CH, Ar), 110.1 (CH, Ar), 108.8 (C, Ar), 93.4 (OCH), 80.3 (OCH₂), 57.7 (C), 40.3 (CH₂), 36.9 (OCHCH), 27.7 (CH₂), 26.8 (CH₂), 25.4 (CH₂), 24.4 (CH₂), 24.2 (CH₂), 21.3 (CH₂). HRMS (ESI) calcd. for C₁₉H₂₅N₂O [M+H]⁺: 297.1961. Found 297.1962.
1-Tosyl-2',3',4',9'-tetrahydrospiro[azetidine-3,1'-pyrido[3,4-b]indole] (280)

To a stirred solution of 279 (52 mg, 0.23 mmol) in toluene (5 mL) was added under an atmosphere of anhydrous nitrogen, tryptamines (231) (44 mg, 0.28 mmol) and TFA (1 mol %) and the mixture stirred at 85 °C for 18 h. After cooling to r.t. the solvent was removed \textit{in vacuo} and the residue dissolved in CH$_2$Cl$_2$ (10 mL). The solution was washed with saturated aqueous NaHCO$_3$ solution (10 mL) and brine (10 mL) and the aqueous layers were extracted into CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and the solvents removed \textit{in vacuo}. The title compound (55 mg, 65%) was provided after column chromatography (40% EtOAc in petroleum ether, 1% Et$_3$N) as a beige solid. M.p. 258-261 °C; IR (film): 3166, 1596, 1339, 1163, 818, 747, 670; $\delta$$_H$ ((CD$_3$)$_2$SO, 400 MHz): 10.94 (1H, s, NH$_{indole}$), 7.79 (2H, d, $J = 8.2$, ArH, Ts), 7.53 (2H, d, $J = 8.2$, ArH, Ts), 7.39-7.34 (2H, m, ArH), 7.09-7.04 (1H, m, ArH), 6.98-6.94 (1H, m, ArH), 4.07 (2H, d, $J = 8.3$, CH$_2$NTs), 3.67 (2H, d, $J = 8.3$, CH$_2$NTs), 2.80 (2H, t, $J = 5.6$, CH$_2$), 2.52-2.49 (2H, m, CH$_2$), 2.47 (3H, s, CH$_3$), piperidine NH not observed; $\delta$$_C$ ((CD$_3$)$_2$SO, 100 MHz): 143.9 (C, Ts), 136.2 (C, Ar), 134.9 (C, Ar), 131.8 (C, Ar), 129.9 (CH, Ar), 128.1 (CH, Ar), 126.4 (C, Ar), 121.2 (CH, Ar), 118.6 (CH, Ar), 117.7 (CH, Ar), 111.6 (CH, Ar), 109.0 (CH, Ar), 62.9 (NTsCH$_2$), 50.8 (C), 40.5 (CH$_2$), 21.7 (CH$_2$), 21.1 (CH$_3$) HRMS (ESI) calcd. for C$_{20}$H$_{22}$N$_3$O$_2$S [M+H]$^+$: 368.1427. Found 368.1424.
(S)-Ethyl 1-tosyl-2',3',4',9'-tetrahydrospiro[azetidine-3,1'-pyrido[3,4-b]indole]-3'-carboxylate (281)

Prepared according to General Method 2a from 279 (40 mg, 0.18 mmol) and tryptophan ethyl ester (226) (49 mg, 0.21 mmol) affording the title compound (50 mg, 64%) after column chromatography (30% EtOAc in petroleum ether, 1% Et$_3$N) as a beige solid. M.p. 180-183 °C; [α]$^2_0$ – 15 (c 0.02, CHCl$_3$); IR (film): 3428, 2928, 1735, 1592, 1339, 1160, 720; δ$_H$ (CDCl$_3$, 400 MHz): 8.39 (1H, s, NH$_{indole}$), 7.82 (2H, d, $J$ = 7.9, ArH, Ts), 7.47 (1H, d, $J$ = 7.7, ArH), 7.46 (2H, d, $J$ = 7.9, ArH, Ts), 7.35 (1H, d, $J$ = 7.7, ArH), 7.24-7.20 (1H, m, ArH), 7.14-7.10 (1H, m, ArH), 4.20 (1H, d, $J$ = 8.4, CHHNTs), 4.16 (2H, q, $J$ = 7.3, OCH$_2$CH$_3$), 4.08 (1H, d, $J$ = 7.8, CHNTs), 3.91 (1H, d, $J$ = 8.4, CHNTs), 3.76 (1H, d, $J$ = 7.8, CHNTs), 3.76-3.73 (1H, m, NHCH), 3.08 (1H, dd, $J$ = 15.2, 5.3, NHCHHH), 2.91 (1H, dd, $J$ = 15.2, 8.1, NHCHHH), 2.53 (3H, s, CH$_3$, Ts), 1.26 (3H, t, $J$ = 7.3, OCH$_2$CH$_3$) piperidine NH not observed; δ$_C$ (CDCl$_3$, 100 MHz): 173.1 (C=O), 144.9 (C, Ar, Ts), 136.3 (C, Ar), 133.3 (C, Ar), 130.4 (C, Ar), 130.1 (CH, Ar), 128.8 (CH, Ar), 126.2 (C, Ar), 122.7 (CH, Ar), 119.9 (CH, Ar), 118.4 (CH, Ar), 111.3 (CH, Ar), 108.3 (C, Ar), 65.1 (CH$_2$NTs), 64.3 (CH$_2$NTs), 61.4 (OCH$_2$), 53.9 (NHCH), 51.1 (C), 24.8 (NHCHCH$_2$), 21.8 (CH$_3$, Ts), 14.2 (CH$_2$CH$_3$); HRMS (ESI) calcd. for C$_{23}$H$_{25}$N$_3$NaO$_4$S [M+Na]$^+$: 362.1458. Found 362.1458.
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