N-Heterocyclic Carbene Catalysed
(4+2) Annulations in the Synthesis of
Natural Products

A thesis submitted for the degree of Doctor of Philosophy

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Monash University
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Melbourne, Australia

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To my parents,

who have supported me greatly in all of my endeavours, academic, or otherwise. Thank you for providing me with every opportunity to succeed.
Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the results of original work carried out by me, unless otherwise acknowledged, during the period 2015-2019, and has not been presented for examination for any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publication from which they are derived.

Adam Ametovski

February 2019
Acknowledgements

Shocking though it is, when I first stepped into David Lupton’s office to enquire about honours projects, he had a great deal to say. If I’m honest with myself, in this brief meeting I understood at most 20% of the chemistry related topics. David, thank you for the opportunity to join your group, and in particular for your persistence in the early years of my PhD studies when I was, in my own words, a lousy student. The last 4 years have filled my head, and now, I can claim as much as anyone, to understand all (most) of what you have to say. To the rest of the Lupton family, thank you Mandy for the boxes of fruit and for making David apologise even when he wasn’t being mean, and of course to Elsie for helping with the synthesis of my Δ⁹-THC cake.

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Publications and Presentations

Publications

(3) Enantioselective total synthesis of (-)-Δ⁹-tetrahydrocannabinol via N-heterocyclic carbene catalysis
Adam Ametovski and David W. Lupton

(2) Biomimetic and Biocatalytic Synthesis of Bruceol
Aaron J. Day, Joel H. Z. Lee, Quang D. Phan, Hui C. Lam, Adam Ametovski, Christopher J. Sumby, Stephen G. Bell and Jonathan H. George.

(1) Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis
Alison Levens, Adam Ametovski and David W. Lupton

Presentations

Poster Presentation: Enantioselective total synthesis of (−)-Δ⁹-tetrahydrocannabinol via N-heterocyclic carbene catalysis
RACI 43rd Annual Synthesis Symposium, Melbourne, Victoria, Australia 2018

Poster Presentation: Studies towards the synthesis (+)-bisabolosqual A and (−)-Δ⁹-tetrahydrocannabinol by N-heterocyclic carbene catalysis
BOSS XVI 16th Organic Synthesis Symposium, Brussels, Belgium 2018

Oral Presentation: Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis
RACI 41st Annual Synthesis Symposium, Melbourne, Victoria, Australia 2016 (awarded the prize for best student oral presentation)
Poster Presentation: Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis

MonCat I Inaugural Symposium, Clayton, Melbourne, Victoria 2016
Abstract

Central to the improving the human condition, is the enhancing the efficiency of chemical syntheses that access biologically active natural products and pharmaceuticals. Such an endeavour is underpinned by the development of new catalytic, and robust methodologies that are capable of rapidly constructing complex chemical architectures. In this regard, N-heterocyclic carbenes (NHCs) have been shown to provide stereochemically pure, and polycyclic scaffolds through a range of Umpolung and normal polarity intermediates. Despite this, at the time that doctoral studies commenced, only 4 instances of enantioselective reactions exploiting NHCs had been utilised in target-oriented synthesis and of these, only reactions proceeding through Umpolung intermediates were known.

The first chapter of this thesis provides an overview of the inception of enantioselective organocatalysis and highlights the impact of this catalytic mode with respect to enhancing the efficiency of chemical synthesis. Following this, a brief introduction to the wide variety of intermediates available to NHC catalysis, and the complex structures to which they give access, are presented. Finally, these reactive modes are discussed, where possible, with respect to their application in the synthesis of natural products and biologically relevant compounds.

The second chapter introduces the field of single electron transfer coupled NHC catalysis, with an emphasis on the enantioselective radical coupling reactions that are possible. Following this, efforts to exploit this mode of reactivity to access novel 4-carbon synthons via the radical cleavage of cyclopropanes is discussed. In these studies, both an inter- and intramolecular (4+2) annulation were explored using an appropriate 2-carbon donor, however, these reactions were not viable due unwanted side reactions facile polymerisation, decomposition or benzoin condensation pathways.

The third chapter details the discovery of the first enantioselective (4+2) annulation involving donor-acceptor (DA) cyclobutanes, that was achieved exploiting NHCs. The coupling of DA-cyclobutanes with \( \alpha,\beta \)-unsaturated acyl fluorides generates densely functionalised cyclohexyl \( \beta \)-lactones with excellent stereochemical integrity. To assess the viability of such a reaction in the synthesis of natural products, the utility of the reaction was examined heavily with respect to substrate scope, scale-up, and product derivatisation.
In the fourth chapter, efforts to exploit the (4+2) annulation reaction developed in Chapter 3 in the total synthesis of (+)-bisabolosqual A are detailed. Three model studies were undertaken to assess the viability of this reaction in the prospective synthesis. Although introduction of the alkenyl sidechain, and stereospecific assembly of the tetracyclic core was possible, penta-substituted acyl fluorides mapping to the aromatic backbone of the natural product were poor substrates in the (4+2) annulation.

The fifth chapter describes an enantioselective synthesis of (−)-Δ^9-THC and (−)-Δ^8-THC, enabled by the (4+2) annulation developed in Chapter 3. Several strategies to install the C^9 methyl group via (4+2) annulation reactions are discussed, however, a late stage installation strategy exploiting a new dual Krapcho decarboxylation procedure was developed.

Chapter six details experimental procedures and spectroscopic data of all compounds utilised in the studies of Chapters 2–5.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BBN</td>
<td>Borabicyclo(3.3.1)nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalyst</td>
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<tr>
<td>DABCO</td>
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<tr>
<td>DAST</td>
<td>(Dimethylamino)sulfur trifluoride</td>
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<tr>
<td>DBU</td>
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<td>DCC</td>
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</tr>
<tr>
<td>Dibal-H</td>
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<td>DIPEA</td>
<td>Diisopropylethyl amine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
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<td>Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
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<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-Bis(Diphenylphosphino)ethane</td>
</tr>
<tr>
<td>d.r.</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>E</td>
<td>Electrophile</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron-withdrawing group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
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<td>e.r.</td>
<td>Enantiomeric ratio</td>
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<td>equiv.</td>
<td>Equivalent</td>
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<tr>
<td>ESI</td>
<td>Electrospray ionisation</td>
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<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HFIP</td>
<td>Hexafluoroisopropanol</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
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<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>IMes</td>
<td>1,3-Bis(trimethylphenyl)imidazole-2-ylidene</td>
</tr>
<tr>
<td>Pr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LB</td>
<td>Lewis base</td>
</tr>
<tr>
<td>LRMS</td>
<td>Low-resolution mass spectroscopy</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>Mesityl (2,4,6-trimethylphenyl)</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>M.P.</td>
<td>Melting point</td>
</tr>
<tr>
<td>M.S.</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>N</td>
<td>Nucleophilicity parameter</td>
</tr>
</tbody>
</table>
NHC  N-heterocyclic carbene
NMR  Nuclear magnetic resonance
NR  No reaction
Nu  Nucleophile
PCC  Pyridinium chlorochromate
PG  Protecting group
Ph  Phenyl
PivOH  Pivalic acid
PMP  para-Methoxyphenyl
ppm  Parts per million
PPTS  Pyridinium para-toluensulfonate
pTsOH  para-Toluenesulfonic acid
Rf  Retention factor
rt  Room temperature
SM  Starting material
TBAF  Tetrabutylammonium fluoride
TBS  tert-Butyldimethylsilyl
TBSCI  tert-Butyldimethylsilyl chloride
‘Bu  tert-Butyl
‘BuOH  tert-Butanol
temp.  Temperature
TFA  Trifluoroacetic acid
THF  Tetrahydrofuran
TLC  Thin-layer chromatography
TMEDA  N,N,N’,N’-Tetramethylethylenediamine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMS-Cl</td>
<td>Trimethylsilyl chloride</td>
</tr>
<tr>
<td>TMSF</td>
<td>Trimethylsilyl fluoride</td>
</tr>
<tr>
<td>Tol</td>
<td>Tolyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TTCE</td>
<td>Tetrachloroethylene</td>
</tr>
</tbody>
</table>
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N-Heterocyclic carbene organocatalysis and applications in total syntheses

1.1 Introduction

1.1.1 A brief history of organocatalysis

The potential for small organic molecules to catalyse organic transformations has been known since 1832 when Wöhler and Liebig first discovered the benzoin condensation. In this reaction, cyanide anions were shown to effect the dimerization of aldehydes 1 to give α-hydroxy ketones 2. Despite this early discovery, the action of cyanide was not understood for a further 70 years when Lapworth proposed umpoled intermediate 3 (Scheme 1.1). Building upon this, Ukai and co-workers demonstrated that catalytic quantities of thiazolium salts enabled the same transformation in basic media, while Breslow would later elucidate the mechanism of this reaction, implicating N-eterocyclic carbenes (NHCs) (i.e. thiazolylidene A1) as the active catalyst. Central to this proposal is the formation of Breslow intermediate 4, or, the acyl anion equivalent, an Umpolung event that reverses the natural polarity of the carbonyl centre.

Following these seminal studies, an array of important organocatalytic transformations were discovered in the 20th century, including Morita-Bayliss-Hillman, Stetter, and acyl transfer reactions to name a few. Despite these contributions, there were only sporadic advancements in the field of enantioselective organocatalysis. Most notable in this regard was the discovery of the Hajos–Parish–Eder–Sauer–Wiechert reaction in 1974, an enantioselective modification of the Robinson annulation catalysed by (S)-proline.
Chapter 1

(S) (Scheme 1.2, eq. 1).\(^8\) Importantly, this represented the first example of an organocatalytic, enantioselective Aldol reaction, and has been employed widely in the industrial synthesis of optically pure steroids. In addition, the Benzoin reaction was rendered enantioselective in this time using homochiral NHC A2, however, both the chemical yield and enantioselectivity was poor (Scheme 1.2, eq. 2).\(^9\)

\[\text{Scheme 1.2. Enantioselective Hajos-Parrish and benzoin reactions.}\]

In the late 1990s, these foundational studies were finally built upon, with a series of reports highlighting the potential for organocatalysis to enable highly enantioselective transformations. This commenced with the discovery of chiral ketone (i.e. 6) catalysed enantioselective epoxidations by the groups of Shi (Scheme 1.3, eq. 1), Denmark\(^1\) and Yang\(^12\). Shortly thereafter, Corey (Scheme 1.3, eq. 2)\(^13\) and Jacobsen\(^14\) demonstrated for the first-time enantioselective hydrogen-bonding catalysis of the Strecker reaction using, for example, homochiral guanidine 7. Also of note was Miller and co-workers’ demonstration of a kinetic resolution of secondary alcohols effected by small peptides (i.e. 8, Scheme 1.3, eq. 3).\(^15\).
\begin{equation}
\begin{align*}
\text{Ph-} & \text{Ph} \\
\xrightarrow{25 \text{ mol}\% \text{ 6, Oxone, NaHCO}_3, \\
\text{MeCN-EDTA(aq) (3:2), 0 }^\circ\text{C, 2 h}} & \text{Ph-} \text{Ph} \\
\text{Me} & \text{Me} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{Me} & \text{Me} \\
\text{56\% yield, 97:3 e.r.}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{Ph-} & \text{Ph} \\
\xrightarrow{10 \text{ mol}\% \text{ 7, HCN, toluene, -40 }^\circ\text{C, 20 h}} & \text{Ph-} \text{Ph} \\
\text{Ph} & \text{N} \\
\text{Ph} & \text{CN} \\
\text{96\% yield, 93:7 e.r.}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{HO} & \text{NHC} \\
\xrightarrow{5 \text{ mol}\% \text{ 8, Ac}_2\text{O, toluene, 0 }^\circ\text{C}} & \text{AcO} \text{NHC} \\
\text{BochN} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{58\% yield, 92:8 e.r.}
\end{align*}
\end{equation}

\textbf{Scheme 1.3.} Early enantioselective organocatalytic reactions.

Only in the year 2000 was organocatalysis truly conceptualised, and common modes of activation defined. Underpinning this was the studies of List\textsuperscript{16} and MacMillan,\textsuperscript{17} who demonstrated that the underlying mode of action permitting enamine and iminium catalysis may be adapted, offering wide-spread applicability to a variety of reaction manifolds. In the years following these publications, the field of enantioselective organocatalysis experienced rapid expansion, a phenomenon which continues nearly two decades later.\textsuperscript{18}

A host of organocatalytic activation modes that enable highly enantioselective transformations are now established and have been exploited extensively in the syntheses of pharmaceuticals as well as complex polycyclic natural product targets.\textsuperscript{19} The assembly of these structures has been aided using simple transformations such as desymmetrisation (i.e. (\text{-})-rhizinilim (9)) and Prins cyclisation (i.e. (\text{+})-estrone (10)), or significantly more complex multi-bond forming cascades, for example, in the synthesis of (\text{-})-strychnine (11) and (\text{+})-ibophyllidine (12) (Figure 1.1). Although transient bonding catalysis such as hydrogen-bonding (H-bond),\textsuperscript{20} counterion,\textsuperscript{21} and more recently, chiral Brønsted acid catalysis\textsuperscript{22} have been well examined in this regard, catalysis via Lewis basic interactions has received the most attention. This may be in part due to the remarkable versatility of Lewis bases to enhance or even inverse both the nucleophilic (enamine/phosphine/NHC) and electrophilic (iminium/SOMO/phosphine/NHC) nature of substrates.\textsuperscript{23} From this perspective, the now established field of NHC catalysis is of great interest.
1.2 NHC organocatalysis

Since the development of modern homochiral NHC scaffolds by the groups of Enders, Glorius, and Zeitler, NHC catalysis has emerged as a powerful method for constructing new C-X and C-C bonds with excellent diastereo- and enantioselectivity. Notably, NHCs offer various modes of activation encompassing both Umpolung and normal polarity intermediates and enable cascade reactions capable of...
rapidly constructing molecular complexity. Although not exhaustive, the common reactivity patterns of NHC derived intermediates and the chemical architectures that they access are introduced herein.

Modern NHC catalysis has been dominated by the polarity reversal of aldehydes by formation and reactions of the Breslow intermediate, or, acyl anion 13. In this regard, the benzoin and Stetter reactions are most well-known, which couple 13 with aldehydes and Michael acceptors respectively (Scheme 1.4a). Bode and Glorius independently demonstrated that umpolung reactivity could be shuttled to the β-carbon via proton transfer to the NHC-homoenolate 14, an intermediate typically trapped with aldehydes and ketones (Scheme 1.4b). Polarity reversal at the β-carbon is also possible through conjugate addition of NHCs to α,β-unsaturated compounds. Although the resultant β-azolium ylide 15 was first exploited in 2006 by Fu, only in the last 3 years have enantioselective methods been realised (Scheme 1.4c).

<table>
<thead>
<tr>
<th>Substrates</th>
<th>NHC Intermediate</th>
<th>Reactivity Pattern</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

Scheme 1.4. Umpolung NHC intermediates and reaction patterns.

In the last decade, the utility of NHCs has seen substantial growth, with these versatile catalysts shown to engage transformations showcasing an array of normal polarity intermediates. Initially these reactions exploited intermediates analogous to those accessible through phosphine and pyridine Lewis base catalysis, however, novel reactive modes have now been developed. NHCs undergo conjugate addition to Michael acceptors to give the β-azolium enolate 16, which engages in classic α-functionalisation reactions (i.e. aza-Morita-Bayliss-Hillman, Scheme 1.5, eq. 1). Notably, acyl addition of NHCs with a wide range of unsaturated substrates accesses the α,β-unsaturated acyl azolium 17, an intermediate possessing unique properties that has been implicated in vast array of transformations (Scheme 1.5, eq. 2). From 17, functionalisation of the α, β, acyl, and even γ- carbons has been demonstrated, with several reactivity patterns giving rise to complex and enantioenriched cyclic scaffolds. Most recently Chi and Lupton have...
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have exploited a higher unsaturated homolog, the dienyl acyl azolium \( 18 \), in regio- and enantioselective bond formation at the \( \gamma \)-carbon, with subsequent \( \alpha \)-functionalisation and acylation generating polycyclic frameworks (Scheme 1.5, eq. 3).

<table>
<thead>
<tr>
<th>Substrates</th>
<th>NHC intermediate</th>
<th>Reactivity Pattern</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = C, OR</td>
<td>![Diagram 16]</td>
<td>![Diagram 16]</td>
<td>![Example a]</td>
</tr>
<tr>
<td>R = H or F</td>
<td>![Diagram 17]</td>
<td>![Diagram 17]</td>
<td>![Example b]</td>
</tr>
<tr>
<td>![Diagram 18]</td>
<td>![Diagram 18]</td>
<td>![Diagram 18]</td>
<td>![Example c]</td>
</tr>
</tbody>
</table>

Scheme 1.5. Normal polarity NHC intermediates and reactivity patterns.

It is important to note that the vast series of intermediates are available from similar substrates, and that the high tunability of both the electronic character and the steric environment of NHC scaffolds mediates this divergent reactivity. Such diversity renders NHC catalysis an attractive tool for designing new bond-forming strategies that enhance the efficiency of complex target synthesis. It is not surprising that the number of total syntheses featuring NHC catalysis has increased significantly in recent years, yet in this regard, only several of the abovementioned intermediates have been exploited. In the following sections, these modes of reactivity are discussed with reference to applications in the synthesis of natural products and biologically relevant compounds.
1.3 NHC catalysed benzoin condensations

The benzoin condensation involves the self- and cross-coupling of aldehydes, or, coupling with ketones to produce α-hydroxy ketones (i.e. 19, Scheme 1.6). Since its discovery, the reaction has received significant attention from the synthetic chemistry community, with NHC catalysis at the forefront of methodological development.\textsuperscript{35} Using homochiral NHCs, the groups of Enders, Sheehan, and others, have demonstrated that excellent levels of enantioselectivity can be obtained in this process.\textsuperscript{24b,36} Such synthetic utility has seen the benzoin reaction feature in a number of total syntheses, of which some representative examples are described.

![Scheme 1.6. Representative benzoin condensation.](image)

1.3.1 Synthesis of (±)-glyceollin II

The glyceollins are phytoalexins isolated from parasite-infested soybeans which belong to the hydroxypterocarpan flavonoids.\textsuperscript{37} Products of this family commonly exhibit antidiabetic properties\textsuperscript{38} as well as potent cytotoxicity toward human breast and prostate cancer cells in vivo.\textsuperscript{39} In an initial report by Erhardt and co-workers', the total synthesis of glyceollin II (20)\textsuperscript{40} required highly toxic osmium tetroxide (OsO\textsubscript{4}) to install oxygenation at C\textsuperscript{6a} and C\textsuperscript{11a}. Building upon this, an improved sequence has since been realised,\textsuperscript{41} enabled by an NHC catalysed intramolecular benzoin condensation that eliminates the need for OsO\textsubscript{4} (Scheme 1.7). Typified by the cyclisation of keto-aldehyde 21, the benzoin condensation proceeds via addition of NHC B1 to the aldehyde and subsequent proton transfer to give acyl anion equivalent 22. Intramolecular addition to the pendant ketone then provides alkoxide 23 before a proton transfer and catalyst elimination furnishes α-hydroxy ketone 24 in 86% yield. Interestingly, despite the use of a homochiral NHC, the authors note isolation of the product as a racemate, likely as a consequence of epimerisation. The total synthesis of (±)-glyceollin II (20) was completed from α-hydroxy ketone 24 in an additional four steps, including an elegant epoxidation and cyclisation sequence (i.e. 24→25→20) to forge the cis-cis fused benzofuran.
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1.3.2 Synthesis of (+)-sappanone B
Isolated from the wood of Caesalpinia sappan Leguminosae, (+)-sappanone B (26) is a homoflavonoid\textsuperscript{42} which is known to inhibit xanthine oxidase.\textsuperscript{43} Such inhibitory activity is well suited to the treatment of hyperuricemia and related conditions such as gout.\textsuperscript{44} Suzuki’s 2007 report details the total synthesis of (+)-sappanone B (26) utilising a key intramolecular and enantioselective benzoin condensation step (Scheme 1.8).\textsuperscript{45} The benzoin precursor, ketoaldehyde 27, was derived from commercially available 3-methoxysalicylic acid in two steps. Exposure to NHC B2 effected cyclisation to provide α-hydroxy ketone 28 in 92% yield and 97:3 e.r. It is important to note that through optimisation of the NHCs N-substituent from mesityl to 3,5-trifluoromethylphenyl, undesired aldol side-reactions could be suppressed, highlighting the tunability of these catalysts. The synthesis was completed by a two-step deprotection of α-hydroxy ketone 28, furnishing (+)-sappanone B (26) in 8-steps and 23% overall yield.

1.3.3 Synthesis of (−)-seragakinone A
(−)-Seragakinone A (29) is an anthracycline derived fungal metabolite isolated from an unidentified fungus living symbiotically with marine sponge Ceradictyon spongiosum.\textsuperscript{46} The heavily oxygenated nature and
stereochemistry rich pentacyclic core contains 4 contiguous stereocentres including one quaternary centre and two tertiary alcohols, and as such, poses a significant synthetic challenge. Suzuki and co-workers have cleverly navigated this complex structure, forging two rings using two separate benzoin condensation reactions (Scheme 1.9).\textsuperscript{37} Starting from commercially available aryl bromide 30, ketoaldehyde 31 was prepared in 23\% yield over 6 steps. Upon exposure of ketoaldehyde 31 to homochiral NHC B2, utilised previously by Suzuki (vide supra), the intramolecular benzoin condensation proceeded smoothly generating tetracycle 32 in 86\% yield and 99:1 e.r. A further 11-step sequence was required to generate a second benzoin precursor, aldehyde 33, in 11\% yield. Thus, after treatment with NHC B3, \(\alpha\)-ketol 34 was obtained in 90\% yield as a 15:1 mixture favouring the desired stereoisomer, as determined by X-ray crystallography. Finally, four additional steps were required to complete the synthesis with the natural product prepared in a total of 26 linear steps.

\textbf{Scheme 1.9.} Enantioselective benzoin condensation in the total synthesis of (–)-seragakinone A.

### 1.4 The Stetter reaction

The Michael addition of acyl anion equivalents (i.e. 35) to \(\alpha,\beta\)-unsaturated compounds, or commonly, the Stetter reaction,\textsuperscript{6} represents the most efficient route to 1,4-dicarbonyl containing compounds (e.g. 36, Figure 1.10). These are important synthons en route to biologically relevant pyroles via the Paal-Knorr synthesis, and as such, the Stetter reaction has received significant attention in industrial settings. Although
reports from Enders\textsuperscript{48}, Rovis\textsuperscript{49} and Hamada\textsuperscript{50} have established the viability of enantioselective intramolecular Stetter reactions, intermolecular variants have proved more challenging and are limited by restricted substrate scope.\textsuperscript{24h,24f} With respect to the α,β-unsaturated partner, highly activated substrates are often required to achieve enantioselectivity.\textsuperscript{51} Furthermore, undesired self- and cross-benzoin pathways often plague intermolecular reactions, an issue which can be supressed using exotic Breslow precursors and thiazolium derived NHCs.\textsuperscript{52} Although these strategies are successful, specific substrate requirements and the limited availability of homochiral thiazolium derived NHCs restricts their synthetic utility. Indeed, no enantioselective Stetter reactions feature in total syntheses, therefore, some notable examples of achiral variants are detailed in this section.

**Scheme 1.10.** An example of the Stetter reaction.

### 1.4.1 Synthesis of cis-jasmone and dihydrojasmone

The jasmones are a series of cyclopentenones isolated from the jasmine plant and have considerable applications in the fragrance industry.\textsuperscript{53} Stetter’s noteworthy synthesis of cis-jasmone (37) and dihydrojasmone (38) in 1975 represents the first application of both NHC catalysis and a Stetter reaction in total synthesis (Scheme 1.11).\textsuperscript{54} The Stetter reaction is typified by the formation of the acyl anion equivalent (i.e. the Breslow intermediate) 39 after addition of NHC A3 to aldehyde 40 and proton transfer. Subsequent 1,4-addition of the Breslow intermediate to methyl vinyl ketone (41) then generates enolate 42 before proton transfer and elimination of the catalyst provides the 1,4-diketone 43. Finally, dehydrative aldol cyclisation furnishes cis-jasmone (37) and dihydrojasmone (38) in 76% and 78% yield respectively over two-steps.

**Scheme 1.11.** Intermolecular Stetter reaction in the total synthesis of cis-jasmone and dihydrojasmone.
**1.4.2 Synthesis of (±)-hirsutic acid C**

(±)-Hirsutic acid C (44) is a fungal metabolite isolated from Stereum hirsutum and exhibits both antibiotic and antitumor activity (Scheme 1.12). The tricyclic sesquiterpenoid structure poses a significant challenge as it contains six contiguous stereocentres (7 in total), two of which are quaternary. Trost and co-workers’ synthesis of (±)-hirsutic acid C (44) exemplifies the utility of the Stetter reaction, whereby the transformation forges a polycyclic framework and at the same time, a quaternary carbon. The synthesis begins with the conversion of commercially available nitrile 45 to α,β-unsaturated ester 46 via a 10-step sequence. Upon exposure to thiazolylidene A3, α,β-unsaturated ester 46 underwent cyclisation via the Stetter reaction, delivering tricyclic ketone 47 in 67% yield. In this scenario, super-stoichiometric quantities (2.3 equivalents) of the catalyst were required, which presumably eliminates the opportunity for cross-benzoin pathways through rapid conversion of the aldehyde to the corresponding Breslow intermediate. Nevertheless, subsequent reduction, lactonisation, and ozonolysis accessed the known bicyclic lactone 48, that was converted to (±)-hirsutic acid C (44) in an additional 4-steps (19 total).

![Scheme 1.12. Intramolecular Stetter reaction in the total synthesis of (±)-hirsutic acid C.](image)

**1.4.3 Synthesis of (±)-atorvastatin**

Atorvastatin calcium (49), or Lipitor under its trade name (Pfizer), is a potent anti-hypercholesteremic agent, and is commonly considered the most successful drug in pharmaceutical history. Perhaps the most famous application of the Stetter reaction is within Pfizer’s industrial synthesis of atorvastatin (Scheme 1.13, eq. 1). Specifically, the reaction of 4-fluorobenzaldehyde (50) and carboxamide 51 catalysed by thiazolylidene A3 was employed to great success to generate 1,4-diketone 52 in 80% yield. A Paal-Knorr pyrrole synthesis using amine 53, with subsequent hydrolysis and calcium salt formation, furnished atorvastatin calcium (49).

In 2017, Glorius and Fleige reported a modified procedure whereby the Stetter and Paal-Knorr sequence were conducted as a one-pot, 3-component reaction (Scheme 1.13, eq. 2). In this scenario,
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glycoaldehyde S4 is utilised as a formaldehyde equivalent for the Stetter/hydroformylation reaction with carboxamide S1 under NHC catalysis. Subsequent addition of amine S3 to the reaction mixture enables a rare base mediated Paal-Knorr reaction to generate pyrrole S5 in 33% yield. Importantly, the one-pot procedure is amenable to modest scaling (3 mmol) and the unsubstituted pyrrole product S5 can be derivatised at C5 to deliver atorvastatin as well as various analogues.

Scheme 1.13. Intermolecular Stetter reactions in synthesis of atorvastatin and analogues.

1.5 Lactone formation via the NHC-homoenolate

Addition of NHCs to α,β-unsaturated aldehydes (i.e. S6) gives rise to NHC-homoenolate intermediates (i.e. S7) after tautomerisation of the Breslow intermediate (Scheme 1.14). A typical transformation of S7 is underpinned by electrophilic trapping with aldehydes or ketones, with subsequent acylation providing γ-butyrolactones, however, linear products can also be synthesised using non-tethered reagents. An array of enantioselective annihilations of the NHC-homoenolate have been developed, with several noteworthy examples in total syntheses.246,60

An additional intermediate, the NHC acyl azolium enolate S8, is also available via proton transfer from the homoenolate S7. While this intermediate is of normal polarity, it possesses enhanced nucleophilicity and engages in highly enantioselective transformations to generate cyclic and linear scaffolds, although, in this scenario, with bond formation at the α- and acyl positions. Only a single example
of a reaction proceeding through the NHC-acylazolium enolate has found application in the enantioselective synthesis of complex natural products.

**Scheme 1.14. Generalised reactivity of the NHC homoenolate and acyl azolium enolate.**

### 1.5.1 Formal synthesis of (+)-salinosporamide A

(+)-Salinosporamide A (59) is a secondary metabolite isolated from marine actinomycete bacteria, and has garnered much interest as an anti-cancer agent. The natural product exhibits considerable cytotoxicity towards Human HCT-116 colon carcinoma cells, amongst others, an unsurprising observation considering the cis-fused β-lactone/γ-lactam architecture. Both of these heterocyclic structures are found in a number of compounds that display significant biological activity.

In 2009, Bode and co-workers realised a formal synthesis of salinosporamide A (59), a route that exploits the annulation of an NHC-homoenolate and an internal ketone to access known γ-butyrolactone 60 (Scheme 1.15). This enantiospecific synthesis utilises the chiral pool strategy to access chiral α,β-unsaturated aldehyde 61, the NHC reaction precursor. The key annulation of 61 is initiated by addition of NHC B3 to the aldehyde and subsequent formation of homoenolate 62. Addition of the homoenolate to the methyl ketone then provides alkoxide 63 before tautomerisation and acylation of the pendant alkoxide delivers the known γ-butyrolactone 60. Although initially plagued with undesired side reactions resulting from intramolecular NHC-enolate and aldol pathways, an impressive optimisation led to synthetically practical yields (76%). Unfortunately, a similar improvement in the stereochemical outcome could not be realised, with homochiral NHC B3 providing the greatest, albeit negligible, diastereoselectivity (11:10 d.r.). Lam and co-workers previously demonstrated the elaboration of the intermediate γ-butyrolactone 60 to the natural product 59 over an additional eight steps.
1.5.2 Synthesis of (−)-maremycin B

Diketopiperazine containing alkaloids are a diverse family of natural products with biosynthetic origins in many plants, animals and fungi. These rigid and heteroatom rich diketopiperazine structures allow binding to a wide variety of receptors and are therefore, attractive scaffolds for drug discovery. Isolated from marine bacteria *Streptomyces*, maremycin B represents an example of these privileged structures and exhibits substantial anti-cancer properties.

In 2012, Bode and co-workers developed a general method for the enantioselective synthesis of spirocyclic γ-butyrolactones (i.e. 64) through annulation of NHC-homoenolate equivalents with isatins (i.e. 65, Scheme 1.16). In the same report, application of such a transformation in the synthesis of (−)-maremycin (66) was described. Thus, exposure of crotonaldehyde 67 and isatin 65 to homochiral NHC B4 provided spirocyclic γ-butyrolactone 64 in excellent yield, albeit with modest selectivity (5:1 d.r, 89:11 e.r.). Fortunately, further enantioenrichment was enabled by recrystallisation, before an additional 5-steps sequence was able to provide the natural product 66.

**Scheme 1.15.** Intramolecular NHC-homoenolate annulation in synthesis of (+)-salinosporamide.

**Scheme 1.16.** Enantioselective NHC-homoenolate annulation in the synthesis of (−)-maremycin B.
1.5.3 Synthesis of (−)-bakkenolides I, J and S

The family of bakkane natural products are sesquiterpenes comprised of a cis-fused 5,6-hydroindane core, and a quaternary spirocyclic γ-butyrolactone bearing a rare β-methylene unit. Commonly, these are isolated from the flower stalks of native Japanese Petasites japonicas, however, they are also constituents of plants indigenous to northern European areas. Biologically, the bakkenolides exhibit anti-feedant and anti-cancer activity, and have also been shown to inhibit platelet aggregation.

In 2010, Scheidt and co-workers developed a method for the desymmetrisation of aldehyde tethered 1,3-diketones (i.e. 68) which generates hydroindanone fused β-lactones (i.e. 69) with excellent stereochemical integrity (Scheme 1.17). In this case, trapping of the NHC-homoenolate does not occur, instead, the transformation proceeds via generation and addition of the NHC-azolium enolate (see Scheme 1.14) to a ketone followed by acylation. This procedure was subsequently applied to assemble the cis-fused 5,6-hydroindane core in the synthesis of (−)-bakkenolides S (70), I (71) and J (72). Specifically, aldehyde 73, itself prepared in two steps from methylcyclohexanediol, was treated with NHC B4 to generate β-lactone 74 in 69% yield, >20:1 d.r and 99:1 e.r. Impressively, the reaction can be conducted with modest scaling (up to 5 g); a feature eluding many NHC catalysed reactions. Conversion of β-lactone 74 to propargylic ester 75 was achieved over 13-steps before manganese triacetate (Mn(OAc)₃) mediated cyclisation delivered, with complete diastereoselectivity, the undesired epimer epi-70. Fortunately, a precedent TBAF mediated inversion of the spirocyclic centre, which relies upon a thermodynamic retroaldol/aldol sequence allowed for synthesis (−)-bakkenolide S (74) and subsequently (71) and (72) by virtue of appropriate acylation.

Scheme 1.17. Desymmetrisation via the NHC-acylazolium enolate in the synthesis of (−)-bakkenolides.
1.6 Esterification via the NHC-acylazolium

While more complex reactions of the NHC-homoenolate and -acyl azolium enolate conclude with terminal acylation via an NHC-acylazolium (i.e. 76), its direct formation by oxidation of acyl anion equivalents (i.e. 77) accommodates much simpler, albeit still challenging, acylation reactions (Scheme 1.18). It is important to note that single electron oxidation of NHC-acyl anion equivalents can also be achieved, whereby access to NHC-homoenolic radical 78 and subsequent enantioselective radical combination reactions have been realised. Typically, this mode of reaction also terminates with acylation via the acyl azolium (i.e. 79→80→81), however, as this field is in its infancy, there are no examples of it being exploited in total syntheses.

Scheme 1.18. Formation of the NHC-acylazolium via oxidation of the Breslow intermediate.

1.6.1 Synthesis of (+)-dactylolide

(+)-Dactylolide (82) is an 18-membered macrolide that was isolated from marine sponges Dactylospongia sp. native to Vanuatu and like many macrolactone containing compounds, is of biological interest owing to modest inhibitory activity toward human ovarian cancer and leukaemia cell lines. In 2012, Hong and co-workers reported the total synthesis (+)-dactylolide (82) featuring a key transformation that exemplifies the action of the NHC-acyl azolium (Scheme 1.19). Specifically, when exposed to NHC B5 and quinone oxidant, the late stage hydroxylaldehyde, itself prepared in 11-steps from commercially available materials, engaged in a remarkable oxidative macrolactonisation to assemble the 18-membered lactone 85. From 85, the natural product was synthesised in 4 additional steps in 2% overall yield.
1.7 [3,3]-Sigmatropic rearrangements via the NHC-azolium alkoxide

In the course of studies to access the αβ-unsaturated acyl azolium via acyl substitution from ester oxidation state carbonyl compounds (i.e. 86→87→88), the Lupton group discovered that NHC-azolium alkoxide 87 itself can partake in novel reaction pathways (Scheme 1.20). Lupton’s seminal discovery showed that under NHC catalysis, enol ester substrates (i.e. 89) underwent an unprecedented [3,3]-sigmatropic rearrangement en route to dihydropyranones (i.e. 90) (vide infra). This reactivity is exemplified in the following example whereby the method was exploited in the synthesis of (-)-7-deoxyloganin (91).

Scheme 1.20. Access to the NHC-azolium alkoxide 87 from ester substrates.

1.7.1 Synthesis of (-)-7-deoxyloganin

(-)-7-Deoxyloganin (91) is an iridoid containing natural product, and like many of these monoterpenoids, it contains a cis-fused cyclopentapyran core. These iridoids typically possess significant bioactivity and have been implicated in biosynthesis of a variety of other alkaloid scaffolds. In 2010, Lupton and co-workers exploited the NHC-azolium alkoxide in the synthesis of dihydropyranone 90, an advanced intermediate that was subsequently elaborated to give the natural product 91. An improved sequence to
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The dihydropyranone precursor 89 was later realised, starting from (S)-citronellal (Scheme 1.21). It is proposed that the key NHC catalysed process begins with addition of NHC C1 to enol ester 89 and formation of NHC-azolium alkoxide 92. A typical result of this arrangement is a rate enhanced anionic oxy-Claisen rearrangement, which in this case generates NHC-azolium enolate 93. Finally, a proton transfer yields a subsequent enolate species 94, which upon acyl substitution furnished dihydropyranone 90 in 63% yield and 7:2 d.r. An additional four steps were required to complete the synthesis of (−)-7-deoxyloganin (91) which was obtained 3% overall yield over 10 linear steps.

Scheme 1.21. NHC catalysed Claisen rearrangement of enol esters in the synthesis of (−)-7-deoxyloganin.

1.8 Objectives

At the time that doctoral studies commenced, only four enantioselective NHC-catalysed reactions had been exploited in reports of total synthesis. While enantioselective transformations of almost all NHC derived reactive intermediates are possible, and a number of these enable access to challenging quaternary centres, as well as macrocycles and complex polycyclic architectures, only three of these reactivity modes have found application. Moreover, these examples are dominated by the intramolecular reactions of acyl anion equivalents in single bond forming events; an observation that can be attributed to the often specific substrate requirements and limited scalability that plague many NHC catalysed methods. Ultimately, the studies described herein aimed to address deficiencies in exploitation of enantioselective NHC-catalysed reactions in efforts of total synthesis. It was proposed that this could be achieved by developing new, robust enantioselective NHC catalysed reactions that are scalable, exhibit broad substrate scope, and the products of which, are synthetically useful.
Despite significant advancements in the last 3 years, the field of single electron transfer-coupled NHC catalysis remains in its infancy. Inspired by the application of donor-acceptor cyclopropanes as three-carbon synthons in a wide variety of complex target syntheses, Chapter 2 describes efforts to exploit single electron transfer (SET)-coupled NHC catalysis to access four-carbon synthons from α-cyclopropyl aldehydes 95, and subsequently develop new enantioselective (4+2) annulations (Scheme 1.22).

![Scheme 1.22. SET-NHC catalysed (4+2) annulation of cyclopropanes.]

While the use of donor-acceptor (DA) cyclopropanes as 3 carbon synthons in natural product synthesis has received significant attention, little effort has been directed toward homologous DA-cyclobutanes. Guided by the previously reported NHC-catalysed (3+2) annulation of DA-cyclopropanes, Chapter 3 details the development of an enantioselective (4+2) annulation of DA-cyclobutanes 96 with α,β-unsaturated acyl fluorides 97 in the preparation of densely functionalised cyclohexyl β-lactones 98 (Scheme 1.23)

![Scheme 1.23. NHC catalysed (4+2) annulation of DA-cyclobutanes.]

(+)-Bisabosqual A is fungal metabolite which exhibits broad range anti-fungal properties, as well as having potential use in the treatment of hypercholesterolemia. In addition to this interesting bioactivity, the challenging tetracyclic architecture, as well as the complex stereochemical arrangement, render this natural product an attractive synthetic target. Chapter 4 describes efforts to exploit the (4+2) annulation developed in Chapter 3 to enable the first enantioselective synthesis of (+)-bisabosqual A via an appropriate β-lactone scaffold (i.e 100) (Scheme 1.24).
Although the medicinal properties of \((-\Delta^9\text{-tetrahydrocannabinol}\) have been known for hundreds of years, only recently has significant attention been directed towards exploiting this natural product as a pharmaceutical agent. \textit{Chapter 5} showcases the synthetic utility of the \((4+2)\) annulation developed in \textit{Chapter 3} through access to lactones of type \textit{101}, and ultimately, the enantioselective total synthesis of \((-\Delta^9\text{-tetrahydrocannabinol})(\text{Scheme 1.25}).\)
1.9 References

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64 Margalef, I. V.; Rupnicki, L; Lam, H. W. Tetrahedron 2008, 64, 7896.


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Single electron transfer coupled NHC catalysis for annulations of cyclopropanes

This chapter explores efforts to develop a new (4+2) annulation reaction via single electron transfer (SET) coupled N-heterocyclic carbene (NHC) catalysis. Studies focused on accessing radical cations 103 derived from the Breslow intermediate of cyclopropanes 95, and exploitation of these in a subsequent radical coupling with α,β-unsaturated electrophiles are discussed. Although facile polymerisation, (potentially suggestive of radical recombination via the desired NHC radical intermediate) was observed, no direct evidence for the formation of the radical cation 102 was observed.

2.1 Introduction

The release of ring strain by cyclopropane cleavage provides access to valuable three carbon synthons that have been exploited heavily in the synthesis of natural products. In the course of endeavours to develop new N-heterocyclic carbene (NHC) catalysed methods to assemble complex natural products, the exploitation of cyclopropanes in a novel mode of activation was examined. Specifically, it was recognised that single electron transfer (SET) coupled NHC catalysis, which gives access to
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NHC-derived radical intermediates, could enable radical cleavage of a cyclopropane moiety and therefore provide new opportunities for reaction discovery. In this chapter, SET coupled NHC catalysis is introduced and efforts to exploit this mode of action in the development of a new (4+2) annulation reaction are described.

2.1.1 Inspiration for SET NHC catalysis

As described in Chapter I, NHC catalysis provides access to an array of unique reactive intermediates, and through the interception of these, a multitude of enantioselective methods have been realised. Common to these and indeed all early NHC catalysed transformations is the operation of polar, or two-electron, mechanisms. More recently, the biochemistry of thiamine pyrophosphate (TPP) 103, a thiazolium NHC precursor, has inspired a first generation of NHC mediated reactions that proceed via single electron mechanisms.2

Pyruvate ferredoxin oxidoreductase (PFOR) catalyses the oxidative decarboxylation of pyruvate to form acetyl-CoA, in a reaction critical to glycolysis and the Kreb’s cycle.3 This CoA-dependant enzyme requires TPP (103) as an additional cofactor and operates via single electron transfer (SET) pathways (Scheme 2.1).4 The proposed mechanism begins with addition of the TPP-carbene 104 to pyruvate 105, before protonation assisted by a proximal glutamic acid residue 106, and subsequent decarboxylation of 107 provides Breslow intermediate 108. A single electron oxidation by an iron-sulfur cluster ([Fe₃S₄]) then generates the Breslow centred radical cation 109, an

Scheme 2.1. PFOR catalysed decarboxylation of pyruvate.
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Intermediate that is key to all NHC catalysed reactions proceeding via SET mechanisms. Next, an additional [FeS] mediated oxidation delivers the activated acetyl-TPP adduct 110, which after thioesterification furnishes acetyl-CoA 111 and regenerates the catalyst species. Although extensive EPR and X-ray studies implicate radical cation 109, the nature of this intermediate with respect to charge and radical distribution remains under debate.\(^5\)

Guided by the action of PFOR, Studer and co-workers developed a biomimetic NHC catalysed oxidation of aldehydes using the organic single electron oxidant 2,2,6,6-tetramethylpiperidine N-oxyl radical (TEMPO) 112 (Scheme 2.2).\(^6\) The reaction is initiated by addition of the NHC B5 to aldehyde 113 and subsequent proton transfer to give the Breslow intermediate 114. In this scenario, oxidation of 114 with TEMPO 112 generates Breslow centred radical cation 115 and concomitantly, TEMPO anion 116. Deprotonation of 115 by the TEMPO anion 116 provides new radical species 117 which undergoes a second single electron oxidation to give NHC-acyl azolium 118. Finally, esterification delivers the corresponding TEMPO ester products 119 in excellent yield and regenerates the catalyst. This seminal report was significant in establishing the viability of SET coupled NHC catalysis in non-biological systems and ultimately, opened avenues for exploration of this reactivity mode.

Scheme 2.2. NHC catalysed oxidation of aldehydes with TEMPO.

Despite the pioneering studies by Studer, the field of SET coupled NHC catalysis was inactive for 6 years before a subsequent report was published in 2015. In this study, Chi and co-workers describe the radical β,β-coupling of nitroalkenes 120 whereby the nitroalkene itself serves as a single electron oxidant, itself being reduced over the course of the reaction. In this scenario, benzaldehyde 121 is
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oxidised sacrificially to the corresponding ester 123 through a mechanism analogous to that described above (Scheme 2.3). A range of nitrostyrenes were well tolerated under the reaction conditions, allowing the dimerised products 123 to form in good to excellent yield and with moderate diastereoselectivity. When aliphatic nitroalkenes were employed, the corresponding products were isolated in significantly reduced yield, likely a consequence of no radical stabilisation which was offered by the adjacent phenyl group in the styrene derived substrates. Importantly, the suitability of NHC B6 highlighted the possibility for enantioselective reactions of this class to be developed via known pyrrolidinone derived homochiral NHCs.

Scheme 2.3. NHC catalysed reductive B,B-coupling of nitroalkenes.

2.1.2 Enantioselective SET coupled NHC catalysis

A year later, the groups of Rovis (Scheme 2.4a) and Chi (Scheme 2.4b), almost simultaneously, reported the first in class enantioselective SET coupled NHC catalysed transformations. Specifically, these reactions effect the β-hydroxylation of enals 113 using NHCs B7 or B8 and nitroarene oxidants 125 and 126 to furnish β-hydroxy esters 127 in good yield and with high enantioselectivity. These studies are widely considered a significant advancement as they render the reaction enantioselective and are the first to detail single electron oxidation of the Breslow intermediate to yield a new NHC derived homoenolic radical (i.e. 128).

Detailed mechanistic investigations using electron paramagnetic resonance (EPR) trapping, radical clock reactions, and cyclic voltammetry were carried out, and a plausible mechanism for Rovis’ version is described. According to this proposal, the reaction is initiated by NHC addition to enal 113 and formation of Breslow intermediate 129. Single electron oxidation of 129 by nitropyridine N-oxide 125 generates homoenolic radical cation 128 with concomitant formation of nitro radical anion 130. Radical-radical combination of these species then provides adduct 131 before N-O fragmentation and tautomerisation gives acyl azolium 132 and liberates nitroso pyridine 133. Finally, protonation of the resultant alkoxide and esterification with methanol furnishes β-hydroxy ester 127 and regenerates the catalyst.
In the aforementioned studies, Rovis and co-workers isolated cyclopentanone products (i.e. 134) when the reaction was carried out in non-nucleophilic solvent. They later developed this reaction in earnest to enable the homo- and cross-coupling of enals 113 to give cyclopentanones 134 as a single diastereomer, and with moderate to good enantioselectivity (Scheme 2.5).\(^\text{10}\) Notably, in the absence of non-nucleophilic or protic solvent, \(\beta\)-hydroxylation is suppressed and a rare C-C bond forming NHC turnover is observed.\(^\text{11}\)

Mechanistically, the reaction is thought to proceed by similar initial steps to those described above, however, homoenolic radical 135 undergoes 1,4-addition with a second Breslow intermediate 136 to give bis-enol radical 137. Next, single electron oxidation, deprotonation, and tautomerisation generate acyl azolium 138 which is intercepted by the pendant NHC-azolium enolate to assemble the cyclopentane 139. Finally, acyl substitution with latent water followed by spontaneous decarboxylation provides the enantioenriched cyclopentanone 134.
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Scheme 2.5. NHC catalysed enantioselective synthesis of cyclopentanones from enals.

The most recent example of related enantioselective SET coupled NHC catalysis was reported in 2017 by Ye and co-workers.\textsuperscript{12} They describe the (3+2) annulation of enals 113 and 3-hydroxy-2-oxindoles 140 to generate enantioenriched spirocyclic-γ-lactones 141 (Scheme 2.6). The reaction tolerates aryl and aliphatic substituents on both the aldehyde and as the N-substituent of the oxindole. Consistent with previous reports that exploit homoenolic radicals, was the requirement for a nitroarene derived oxidant (i.e. nitrobenzene 142).

Scheme 2.6. NHC catalysed enantioselective synthesis of spirocyclic-γ-lactones.

Although several additional reports of SET coupled NHC catalysis have been reported since\textsuperscript{13} the four reactions described here represent the only enantioselective examples. Of these, only two generate complex cyclic scaffolds. In the enantioselective examples of Rovis and Ye (see Schemes 2.5 and 2.6), enal 113 is utilised to access homoenolic radical cation 143 which, in both cases, serves as a 3-carbon donor and undergoes trapping with a carbon-centred radical or an alkene tethered nucleophile to deliver cyclic products (i.e. 144, Scheme 2.7).
2.1.3 Reaction design and objectives

Drawing upon inspiration from Rovis’ enantioselective reactions, and the radical cleavage of cyclopropanes, it was proposed that a (4+2) annulation could be achieved by using α-cyclopropyl aldehydes 145 (Scheme 2.8). In the design, addition of an NHC to α-cyclopropyl aldehyde 145 provides Breslow intermediate 146, that can undergo single electron oxidation to generate Breslow radical cation 147. Next radical cleavage of the cyclopropane would provide enolic radical 148 which could be exploited as a 4-carbon donor and engage in a (4+2) annulation with an appropriate 2-carbon coupling partner (i.e. acrylate 149). In this scenario, an enantioselective 1,4-addition of the radical 148 with 149 would generate α-radical 150 which undergoes a second SET to generate acylazolium enolate 151. Finally, a proton transfer and intramolecular aldol/lactonisation sequence (i.e. 151→152→153) would provide enantioenriched β-lactone products 153 and regenerate the catalyst.
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2.2 Research and Discussion

2.2.1 Intermolecular (4+2) annulation of a-cyclopropyl aldehydes

Studies commenced with the preparation of a-cyclopropyl aldehydes 145a and 145b bearing phenyl and diphenyl substituents respectively (Scheme 2.9). It was anticipated that benzylic stabilisation of the resultant radical intermediate would favour radical cleavage of the cyclopropane ring. To this end, benzophenone (154) was converted to the $\alpha,\beta$-unsaturated ester 155a following treatment with triethyolphosphonoacetate\(^{14}\) before reduction with diisobutylaluminium hydride (DIBAL-H) generated the corresponding allylic alcohol 156a. Following the procedures of Lorenz,\(^{15}\) 156a ($R = \text{Ph}$) and commercially available cinnamoyl alcohol 156b ($R = \text{H}$) underwent a modified Simmons-Smith cyclopropanation to provide the corresponding cyclopropyl alcohols 157a and 157b. Finally, oxidation with 2-iodoxybenzoic acid\(^{16}\) (IBX) furnished the required a-cyclopropyl aldehydes 145a and 145b.

![Scheme 2.9. Synthesis of a-cyclopropyl aldehydes 145.](image)

With cyclopropanes 145a and 145b in hand, the proposed (4+2) annulation was examined using chalcone 158 as the 2-carbon electrophilic coupling partner. NHC B6 bearing N-pentafluorophenyl substitution was employed in the course of these experiments as this commonly provided optimal outcomes in previous studies with the coupling of homoenoic radicals. The suitability of this substituent likely relates its electron withdrawing capacity which leads to increased rate of formation of the Breslow intermediate compared to other NHCs.\(^{17}\)

Studies commenced with screening conditions analogous to those developed by Rovis, Chi, and Ye for the enantioselective coupling of homoenoic radicals. As intramolecular $\beta$-lactonisation would facilitate catalyst turnover in our design, methanol was omitted from initial experiments. Thus, a-cyclopropylaldehyde 145a and chalcone 158 were exposed to NHC B6 and single electron oxidant
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125 in carbon tetrachloride at room temperature (conditions of Rovis). Unfortunately, none of the desired β-lactone 159 was formed, instead, only trace amounts hydroxyketone 160 was isolated, a product of benzoin condensation. In addition, an uncharacterisable polymer accounted for the remainder of converted material (Table 2.1, entry 1). When potassium carbonate was employed as the base in toluene (conditions of Chi), benzoin condensation was promoted with 160 isolated in 15% yield, while polymerisation was suppressed (Table 2.1, entry 2). Finally, when DABCO and nitrobenzene 142 were employed (conditions of Ye), the reaction failed (Table 2.1, entry 3).

Given that Chi’s conditions (Table 2.1, entry 2) appeared likely to give the most significant degree of Breslow intermediate formation, we decided to examine alternate single electron oxidants with all other conditions remaining the same. Thus, nitrostyrene (120) was employed, which also served as the electrophile in this case (Scheme 2.1), hydroxyketone 160 was isolated in 5% yield alongside polymeric material (Table 2.1, entry 4). Employing Weitz ammonium salt 161 did not affect the outcome (Table 2.1, entry 5). To ensure alcoholic additives were not crucial for the progress SET pathways, the reaction was repeated with the addition of methanol, however, this caused the reaction to fail (Table 2.1, entry 6). Given preliminary studies through variation of solvents, bases and oxidants were unsuccessful, the reaction was explored with modification of the substrate. In this regard, diphenyl substituted aldehyde 145b (R = Ph), which would generate a more stable radical (i.e. 148, Scheme 2.8), was subjected to the same set of conditions used for the monophenyl substrate 145a. In all cases the desired product was not observed with benzoin condensation completely suppressed and polymerisation occurring to varying degrees (Table 2.1, entries 7-11). In these reactions, it is likely that increased steric bulk introduced by the additional phenyl substituent in 145b suppresses the benzoin condensation observed when monophenyl cyclopropane 145a was employed.
Table 2.1. Selected optimisations for the SET (4+2) annulation of aldehydes 145.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>oxidant</th>
<th>mol% base</th>
<th>solvent</th>
<th>conv$^a$</th>
<th>result$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>125</td>
<td>100% NaOAc</td>
<td>CCl₄</td>
<td>38%</td>
<td>160 (&lt;1%), polymer</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>150% K₂CO₃</td>
<td>toluene</td>
<td>43%</td>
<td>160 (14%), polymer</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>142</td>
<td>20% DABCO</td>
<td>&quot;</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>4$^c$</td>
<td>&quot;</td>
<td>120</td>
<td>150% K₂CO₃</td>
<td>&quot;</td>
<td>20%</td>
<td>160 (5%), polymer</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>161</td>
<td>&quot;</td>
<td>&quot;</td>
<td>40%</td>
<td>160 (5%), polymer</td>
</tr>
<tr>
<td>6$^d$</td>
<td>&quot;</td>
<td>125</td>
<td>&quot;</td>
<td>&quot;</td>
<td>5%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>&quot;</td>
<td>100% NaOAc</td>
<td>CCl₄</td>
<td>21%</td>
<td>polymer</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>&quot;</td>
<td>150% K₂CO₃</td>
<td>toluene</td>
<td>15%</td>
<td>polymer</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>142</td>
<td>20% DABCO</td>
<td>&quot;</td>
<td>7%</td>
<td>-</td>
</tr>
<tr>
<td>10$^c$</td>
<td>&quot;</td>
<td>120</td>
<td>150% K₂CO₃</td>
<td>&quot;</td>
<td>20%</td>
<td>polymer</td>
</tr>
<tr>
<td>11$^d$</td>
<td>&quot;</td>
<td>161</td>
<td>&quot;</td>
<td>&quot;</td>
<td>32%</td>
<td>polymer</td>
</tr>
</tbody>
</table>

$^a$Based on recovered starting material. $^b$Chalcone reisolated. $^c$No chalcone present, nitrostyrene serves as electrophile. $^d$2 equiv. MeOH added.

2.2.2 Intramolecular (4+2) annulation of α-cyclopropyl aldehyde 162a

Since the proposed intermolecular (4+2) annulation could not be achieved through variation of the base, solvent, oxidant and substrate, more significant modification of the reaction design was undertaken. Given that polymerisation remained the dominant pathway throughout these studies, it was proposed that a new substrate bearing a tethered electrophile (i.e. 162) could enable the desired pathway through an intramolecular reaction (Scheme 2.10). Specifically, the corresponding enolic radical 163 generated from such a substrate would be poised to undergo a rapid S-exo-trig cyclisation, and therefore, may outcompete polymerisation that may be occurring through potential radical intermediates.
Accordingly, aldehyde 162a was targeted, which contained the required α,β-unsaturated electrophile and a phenyl substituted cyclopropane motif (Scheme 2.11). The synthesis commenced with the conversion of commercially available 2-bromobenzaldehyde (164) to the corresponding α-cyclopropyl aldehyde 145c using the sequence developed previously for the synthesis of cyclopropanes 145a and 145b (Scheme 2.9). To attach the desired electrophile, a modified procedure of Hsieh\(^8\) was followed to effect a palladium catalysed borylation which gave boronate ester 165 (61% yield) before finally, Suzuki coupling with bromoethyl crotonate\(^9\) furnished the desired tethered substrate 162a (55% yield.)

Having synthesised the required α-cyclopropyl aldehyde 162a, the intramolecular reaction was examined with a series of single electron oxidants. It was thought that the correct oxidant, in conjunction with conditions that were shown previously to promote formation of the Breslow intermediate (i.e. which formed benzoin product 160, Table 2.1), would allow the transformation to be realised. To this end, 162a was exposed to NHC B6 and nitropyridine N-oxide 125. Unfortunately, only decomposition of the converted material (15% conversion) was observed (Table 2.2, entry 1). Using nitrobenzene 142 as the oxidant allowed for greater conversion of the starting material 162a.
(21% conversion), however, no discernible products were isolated (Table 2.2, entry 2). Conversion of 162a was further increased to 63% when the reaction was conducted with Weitz salt 161, however, once again only decomposition of the starting material was observed (Table 2.2, entry 3). The reaction failed in the presence of nitrostyrene 120 (Table 2.2, entry 4), whilst ceric ammonium nitrate (CAN), a strong single electron oxidant, led to decomposition of the converted material (Table 2.2, entry 5).

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>%conv&lt;sup&gt;a&lt;/sup&gt;</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>125</td>
<td>15</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>21</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>63</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>N/R</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>(NH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ce(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>53</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on recovered starting material.

### 2.2.3 Radical trapping experiments

In an effort to gain insight into the nature of the decomposition and polymerisation pathways, and therefore inform subsequent directions, a radical trapping experiment was performed. Given that TEMPO 112 effects single electron oxidation of the Breslow intermediate (see Scheme 2.2), it was proposed that employing TEMPO in this reaction design may reveal if decomposition occurs through radical cleavage of the cyclopropane or even the targeted enolic radical intermediate. To this end, a reaction of tethered aldehyde 162a was conducted in the presence of TEMPO, however, none of the desired β-lactone or any radical trapped species were observed (Scheme 2.12). Instead, TEMPO ester 166 was isolated in 24% yield, which presumably forms via the mechanism described by Studer (see Scheme 2.2). This suggests that the Breslow radical cation of 162a is indeed formed under these reaction conditions, however, instead of the desired cyclopropane cleavage, subsequent single electron oxidation via another equivalent of TEMPO occurs followed by esterification with the TEMPO anion.
Concurrent to these studies, work from within our group demonstrated that donor-acceptor (DA) cyclobutanes, which are valuable 4-carbon synthons, engage in an enantioselective (4+2) annulation catalysed by NHCs. Keeping in mind our ultimate goals to develop methods for natural product synthesis, we were encouraged by this discovery, and given the challenges facing the exploitation of SET NHC catalysis to access 4-carbon synthons from cyclopropanes, efforts were redirected towards developing this (4+2) annulation.

2.3 Conclusions and outlook

Exploiting SET NHC catalysis to develop a new (4+2) annulation using a-cyclopropyl aldehydes was ultimately unsuccessful. The intermolecular reaction of a-cyclopropyl aldehydes 145a and 145b with chalcone or nitrostyrene resulted only in dimerisation of the aldehyde via benzoin condensation, or in polymerisation. While polymerisation may be suggestive of radical cleavage and recombination of the cyclopropane motif, a definitive conclusion could not be reached due to the absence of any characterisable products. Additionally, attempts to overcome polymerisation through an intramolecular reaction of a tethered substrate, a-cyclopropyl aldehyde 162a, were also unsuccessful. Reactions with this substrate resulted only in decomposition. Finally, a radical trapping experiment using TEMPO revealed that single electron oxidation of the Breslow intermediate occurred under our conditions however, no direct evidence supporting formation of the desired enolic radical intermediate was observed.

Given these outcomes, future studies would focus on exploitation of a known homoenoic radical 167 which can be accessed from α,β-unsaturated aldehyde 113. Akin to Rovis’ coupling of 167 with a Breslow intermediate, a (4+2) annulation may be possible through coupling of this same intermediate with the Breslow intermediate derived from cyclopropyl aldehydes (i.e. 168, Scheme 2.13)
Scheme 2.13. Proposed coupling of a homoenolic radical and Breslow intermediate 168.
2.4 References


2 For a review encompassing this topic, see: Zhao, K.; Enders, D. *Angew. Chem. Int. Ed.* 2017, 56, 3754.


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Chapter 3

Enantioselective N-heterocyclic carbene catalysed (4+2) annulation of donor-acceptor cyclobutanes

Using N-heterocyclic carbene catalysis, the first enantioselective (4+2) annulation of donor-acceptor cyclobutanes has been realised. Their reaction with α,β-unsaturated acyl fluorides generates densely functionalised, cyclohexyl-fused β-lactones in excellent yield and with excellent stereochemical integrity. The reaction is amenable to modest scale up and the β-lactone products have been shown to have extensive synthetic utility. Specifically, decarboxylative and ring-opening derivatisations deliver heavily functionalised cyclohexanes, cyclohexenes, and quinolones. Additionally, antimicrobial screening revealed some products and their derivatives exhibit promising activity against several nosocomial pathogens.

3.1 Introduction

The development of new molecular synthons underpins the synthesis of complex chemical structures. To this end, donor-acceptor (DA) cyclopropanes (i.e. 169) have received significant attention within organic synthesis. The polarised C-C bond between donor (D) and acceptor (A) substituents undergoes facile cleavage, driven by the release of ring strain, to yield 1,3-zwitterionic intermediates (i.e. 170, Scheme 3.1, eq. 1). The formal 1,3-dipole synthon is commonly intercepted with dipolarophiles (X=Y), thereby providing cyclic scaffolds (i.e 171). Despite possessing similar strain energy (cf. cyclopropanes), reactions
exploiting analogous DA-cyclobutanes 172 as 1,4-dipoles (i.e. 17, Scheme 3.1 eq. 2) are limited, particularly when considering enantioselective reactions.\(^3\)

\[
\begin{align*}
\text{Scheme 3.1. Strain energy and generalised reactivity of DA-cyclopropanes and DA-cyclobutanes.}
\end{align*}
\]

3.1.1 Annulation reactions of DA-cyclobutanes

In 1964 Hollis and co-workers reported the first ring-opening transformation of DA-cyclobutanes whereby the treatment of amino-substituted DA-cyclobutane 174 with phenylmagnesium bromide provided aminoketone 175 in 90% yield (Scheme 3.2, eq. 1).\(^4\) Mechanistically, the reaction is thought to proceed by Grignard addition to the ester and loss of methoxide followed by formation of magnesiumbromide-carbonyl complex 176. This results in weakening of the C-C bond and therefore ring-opening of the cyclobutane to deliver imine 177 before a second Grignard addition and disassociation of magnesium bromide delivers amino-ketone 175. To examine the viability of magnesium bromide in the reaction, DA-cyclobutane 174 was exposed to magnesium bromide etherate \((\text{MgBr}_2 \cdot \text{Et}_2\text{O})_2\), which induced ring-opening to give the corresponding aldehyde 178 after hydrolytic workup (Scheme 3.2, eq. 2).
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Scheme 3.2. Ring opening of amino-activated DA-cyclobutanes.

Despite this study and numerous reports of annihilations of DA-cyclopropanes, exploitation of DA-cyclobutanes as a 1,4-dipole in analogous fashion was not realised until 1991. In this report, Saigo and co-workers detail the titanium (IV) chloride mediated (4+2) annulation of amino substituted DA-cyclobutanes 179 with aldehydes 180, which generates δ-lactols 181 in modest yields and diastereoselectivity (Scheme 3.3).

Scheme 3.3. TiCl mediated (4+2) annulation of DA-cyclobutanes with aldehydes.

Surprisingly, 20 years separated this seminal report and subsequent studies of DA-cyclobutane annihilations. In 2009, concurrent communications by Pritchard and Johnson described the scandium(III) triflate (Sc(OTf)₃) catalysed (4+2) annulation of DA-cyclobutanes bearing malonate acceptors and carbon based donors. Pritchard and co-workers demonstrated that cobalt alkyn complexes can be utilised as donor substituents as they offer stabilisation of the resultant 1,4 zwitterion intermediate as the Nicholas cation. Thus, a Sc(OTf)₃ catalysed annulation of DA-cyclobutanes 182 with aldehydes was realised, with tetraydropyrans 183 obtained in modest to good yield and with excellent diastereoselectivity (Scheme 3.4, eq.1). Although a range of aldehydes were tolerated, these were limited to electron rich or neutral aromatic species.

Johnson and co-workers were able to exploit DA-cyclobutanes 184 bearing aryl donor groups in the synthesis of tetraydropyrans 185 (Scheme 3.4, eq. 2). Notably, as Sc(OTf)₃ can catalyse the (2+2) cycloaddition of methylene malonates 186 and styrenes 187, a one-pot synthesis of DA-cyclobutane 184 and its subsequent annulation could be achieved. With respect to generality, electron rich, electron poor and neutral aromatic substituents on both aldehyde and DA-cyclobutane partners were well tolerated.
Scheme 3.4. (4+2) annulations of DA-cyclobutanes with alkyne-cobalt complex and aryl donors.

Pagenkopf and Waser have since thoroughly explored the use of heteroatom donors on the cyclobutane and in these studies, the scope of dipolarophiles was also extended to allow the synthesis of more challenging heterocycles and even cyclohexanes. Specifically, Pagenkopf and co-workers demonstrated the utility of alkoxy-substituted DA-cyclobutane 188 in ytterbium(III) triflate catalysed annulations with a range of dipolarophiles (Scheme 3.5).\(^8\) Aldehydes,\(^{8a}\) imines,\(^{8b}\) nitrones\(^{8c}\) and nitrosoarenes\(^{8d}\) reacted smoothly with 188 to deliver tetrahydropyran 189, piperidines 190, oxazepanes 191 and tetrahydrooxazines 192 in good yield and with complete diastereoselectivity.

Scheme 3.5. Annulations of alkoxy-substituted DA-cyclobutanes with various dipolarophiles.
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Waser was able to employ pthalimide protected amino DA-cyclobutanes 193 in the synthesis of amine substituted tetrahydropyran 194, catalysed by Sc(OTf)₃ (Scheme 3.6, eq. 1). Unlike the early work of Saigo where the nitrogen functionality is lost upon hydrolytic work up, retention of the nitrogen was achieved by the use of pthalimide protection. The (4+2) annulation tolerates a variety of aromatic aldehydes, however, the diastereoselectivity was limited compared to analogous reactions using DA-cyclobutanes with alkoxy or aryl donors. Importantly, a more challenging all carbon variant was also possible using tin(IV) chloride as the catalyst and tert-butyldimethylsilyl enol ethers 195 as coupling partners. In this scenario, cyclohexylamines 196 were generated in excellent yield however, with varying diastereoselectivity (Scheme 3.6, eq. 2).

![Scheme 3.6](image)

Scheme 3.6. (4+2) Annulations of pthalimide substituted DA-cyclobutanes.

The electrophilic centre generated upon ring opening of DA-cyclobutanes can also be trapped with an internal nucleophile. France and co-workers describe the (5+2) annulation of amido-acrylate 197 and styrene 199 to deliver indolylazepines 200 in varying yields and with moderate diastereoselectivity (Scheme 3.7). The reaction is thought to proceed via (2+2) cycloaddition to give DA-cyclobutane 201, an isolable intermediate, which delivers the products following ring-cleavage and trapping with the tethered indole.

![Scheme 3.7](image)

Scheme 3.7. (5+2) Annulation of DA-cyclobutanes with an internal nucleophile.

It is important to note that while most transformations of DA-cyclobutanes proceed with good to excellent diastereocntrol, achieving enantioselectivity in this class of reaction is significantly more challenging. At
the conception of these studies only a single example of enantioselective catalysis using DA-cyclobutanes was known. In 2015, Xie and Tang reported the enantioselective (4+3) annulation of DA-cyclobutanes 202 nitrones 203 catalysed by a homochiral copper complex (Scheme 3.8, eq. 1).\textsuperscript{11} In this reaction, oxazepanes 204 were isolated in good to excellent yields and with excellent stereochemical integrity. In addition to aryl donors, the reaction tolerated both alkoxy and thioether based donor components.

More recently, Xie and Tang have now developed a protocol for the enantioselective synthesis of tetrahydropyranos 205 (Scheme 3.8, eq. 2).\textsuperscript{12} Building upon Johnsons work with the non-enantioselective variant of this reaction, and using the same homochiral catalyst as used in their (4+3) annulation, the (4+2) annulation of DA-cyclobutanes 202 and aldehydes delivers various pyrans 206 in moderate to good yield and with excellent stereochemical integrity.

\textbf{Scheme 3.8}. Xie and Tang’s enantioselective annulations of DA-cyclobutanes.

\subsection*{3.1.2 Reaction design and objectives}

Examining the potential mechanisms through which 1,4-dipoles (i.e. 207) and aldehydes react provides insight into the challenges in achieving enantiocontrol for this class of reaction (Scheme 3.9). Two mechanistic scenarios are possible for the synthesis of tetrahydropyran products 208; initial O-addition of the aldehydic carbonyl or initial C-addition of the malonate nucleophile. In the former pathway, oxocarbenium formation sets a stereocentre remote from the Lewis acid catalyst, and is therefore a potential explanation for difficulties in achieving good stereochemical relay.

In the studies of Pritchard and co-workers,\textsuperscript{6} electron rich aldehydes are required for the reaction to proceed, an observation that can be explained by a predominating O-addition mechanism whereby increased electron density provides a more nucleophilic oxygen, and stabilises the resulting oxocarbenium...
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ion. This is supported by Xie and Tang's\textsuperscript{11} observations in their (4+3) annulation whereby the use of electron poor nitrones leads to decreased enantioinduction. An exception to this proposal is of course the recent enantioselective (4+2) annulation (Scheme 3.8, eq. 2) reported after the conclusion of these studies, in which both electron rich and electron poor aldehydes were well tolerated. Although this example overcomes issues with poor enantioselectivity, no mechanistic information is offered and it still remains likely that in the former examples, an O-addition mechanism predominates leading to difficulties in the transfer of chiral information.

![Scheme 3.9](image)

**Scheme 3.9.** Mechanistic scenarios for the (4+2) annulation of DA-cyclobutanes with aldehydes.

While our ultimate goal was the development of new NHC catalysed methodologies to enable the synthesis of natural products, we wished to concurrently address deficiencies in the enantioselective reactions of DA-cyclobutanes. Accordingly, attention turned to the (3+2) annulation of analogous DA-cyclopropanes discovered previously in the research group.\textsuperscript{13} In this reaction, TMS ether-bearing DA-cyclopropanes 209 and α,β-unsaturated acyl fluorides 210 underwent coupling when treated with NHC B9 to give cyclopentyl β-lactones 211 in excellent yield and stereochemical integrity.\textsuperscript{13b} The reaction is initiated upon substitution of α,β-unsaturated acyl fluoride 210 by the NHC B9 and concomitant desilylation of the cyclopropane 209. Strain-induced retro-aldol cleavage of the cyclopropane then provides bifunctional enolate 212, which undergoes O-addition to acyl azolium 213 to provide hemiacetal alkoide 214. Next, an enantioselective anionic oxy-Claisen (AOC) rearrangement results in formation of acylazolium enolate 215 before an asynchronous aldol/β-lactonisation process furnishes the heavily functionalised cyclopentanones 211.
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**Scheme 3.10.** NHC catalysed enantioselective (3+2) annulation of DA-cyclopropanes.

Guided by these previous studies, it was proposed that a related Lewis base approach exploiting DA-cyclobutanes 216, would allow an enantioselective (4+2) annulation to be realised (Scheme 3.11). Specifically, Lewis base substitution of the acyl fluoride 210 and concurrent defluorination/desilylation would generate α,β-unsaturated acyl azolium 217 and 1,4-dipole 218 after retro-aldol cleavage of the cyclobutane. The close proximity of a covalently bound homochiral Lewis base catalyst provides good opportunity for chirality transfer in the postulated C-O bond formation and Claisen rearrangement sequence. In this scenario, enantioenriched cyclohexyl fused β-lactones 219 would be prepared.

**Scheme 3.11.** Proposed enantioselective (4+2) annulation of DA-cyclobutanes and acyl fluorides.

### 3.2 Discovery and optimisation

The entirety of experiments relating to reaction discovery and optimisation of the proposed (4+2) annulation were carried out by a co-worker, Dr. Alison Levens.\(^\text{14}\) A summary of key findings from these studies is detailed in this section, with particular emphasis on substrate modifications and reaction conditions which enabled a high yielding and enantioselective reaction. In this regard, the success of the reaction relied heavily upon the exploitation of diester-bearing DA-cyclobutanes (i.e 216a), which provided superior outcomes compared to their mono-ester counterparts. Thus, when 216a and
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α,β-unsaturated acyl fluoride 210b were exposed to NHC C2, the desired β-lactone 220a was isolated in quantitative yield and with complete diastereoselectivity (Scheme 3.12). Screening of homochiral NHC catalysts revealed that the least nucleophilic and Lewis basic NHCs\(^\text{15}\) were able to catalyse the reaction most effectively, with morpholinone-derived N-Bu-substituted NHC B9 providing β-lactone 220a with optimal yield (44%) and stereoselectivity (>20:1 d.r, 96:4 e.r).

![Scheme 3.12](image)

**Scheme 3.12.** (4+2) annulation of malonate bearing DA-cyclobutanes and acyl fluoroide.

Having established the optimal substrate and homochiral NHC catalyst, the reaction was optimised through variation of solvent and temperature. The parent result is provided for reference (Table 3.1, entry 1). Heating the reaction to 80 °C after addition of catalyst provided β-lactone 220a with increased yield (59%) and enantiopurity\(^\text{16}\) (97:3 e.r) (Table 3.1, entry 2). Conducting the reaction in dimethyl formamide (DMF) significantly improved the yield of 220a (86%) however, with loss of enantioselectivity (93:7 e.r) (Table 3.1, entry 3). A compromise between yield and enantioselectivity was reached by employing a 9:1 mixture of THF:DMF, with β-lactone 220a isolated in 73% yield and 97:3 e.r (Table 3.1, entry 4). Given the sensitivity to temperature, addition of the catalyst to a pre-heated solution (80 °C) of the substrates was trialled. Using this operation, the yield was increased (81%) while the enantiopurity of the product was unchanged (Table 3.1, entry 5). Finally, when potassium tetrafluoroborate (KBF\(_\text{4}\)), a Lewis acidic salt formed during NHC generation, was removed from the reaction media, 220a was obtained with increased yield (93%) and identical enantioselectivity (Table 3.1, entry 6).
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#### Table 3.1. Selected optimisation of reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>T (°C)</th>
<th>solvent</th>
<th>yield</th>
<th>e.r*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>THF</td>
<td>44</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>rt→80</td>
<td>&quot;</td>
<td>59</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>DMF</td>
<td>86</td>
<td>93:7</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>9:1 THF:DMF</td>
<td>73</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>80d</td>
<td>&quot;</td>
<td>81</td>
<td>97:3</td>
</tr>
<tr>
<td>6c</td>
<td>&quot;</td>
<td>&quot;</td>
<td>93</td>
<td>97:3</td>
</tr>
</tbody>
</table>

* Determined by *1*H NMR analysis of the crude reaction mixture. Isolated yield after flash chromatography. Enantiomeric ratio determined by chiral column HPLC analysis. NHC added to mixture of substrates in 80 °C oil bath. B9 generated with equimolar KHMDS and separated from HMDS and KBF₄ by-products.

#### 3.3 Reaction scope

##### 3.3.1 Synthesis of DA-cyclobutanes and α,β-unsaturated acyl fluorides

With optimal reaction conditions established, my role in this project was to aid in examining the generality of the (4+2) annulation and, in particular, to explore the synthetic utility of the reaction. In this endeavour, a number of new DA-cyclobutanes 216 and α,β-unsaturated acyl fluorides 210 were required. Preparation of the latter was relatively trivial with an array of electronically distinct α,β-unsaturated acyl fluorides 210a-I prepared in good to moderate yield (26-96%) by treatment of the corresponding carboxylic acids 221 with diethylaminosulfur trifluoride (DAST) (Scheme 3.13). Although these substrates were successfully purified via flash column chromatography on silica gel, varying degrees of hydrolysis during purification was observed, leading to variations in the isolated yield.
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Scheme 3.13. Synthesis of \(\alpha,\beta\) unsaturated acyl fluorides.

DA-cyclobutanes 216 were synthesized via a 2-step sequence, the first being treatment of commercially available acetaldehydes 222 with trimethylsilyl (TMS) chloride and triethylamine to provide TMS-enol ethers 223a-g (Scheme 3.14). Using a modified procedure of Roberts, DA-cyclobutanes 216a-k were then obtained in serviceable yields by zinc bromide-mediated (2+2) annulation of TMS-enol ethers 223a-g and methylene malonates 224a-d.


\(^a\) Isolated yield over three-steps from cyclobutane methanol.
3.3.2 Scope of the (4+2) annulation with respect to the acyl fluoride

With acyl fluorides 210a-i in hand, their viability in the (4+2) annulation with DA-cyclobutane 216a was examined. Electron poor, neutral and rich acyl fluorides reacted smoothly, providing the corresponding β-lactones in good to excellent yields (72-100%). While these were all well tolerated with respect to yield, the enantioselectivity was sensitive to the electronic properties of the β-aryl substituent. Thus, 4-methylphenyl and cinnamoyl acyl fluorides provided 220a and 220b with 95:5 and 97:3 e.r respectively (Table 3.2, entries 1 and 2). Increasing the electron density was beneficial for enantioselectivity with 4-methoxyphenyl, 4-dimethylaminophenyl and 2,4-dimethoxyphenyl acyl fluorides delivering β-lactones 220c-e in 98:2-99:1 e.r (Table 3.2, entries 3–5). Despite the suitability of electron-rich acyl fluorides, introduction of methoxy groups to the meta position proved detrimental, with 220f isolated in 96:4 e.r (Table 3.2, entry 6). Compared with electron-rich substrates, electron-poor 4-chlorophenyl and 4-bromophenyl substitution gave β-lactones 220g and 220h with reduced e.r (87:13 and 92:8 respectively) (Table 3.2, entries 7 and 8). Heteroaryl 3-indolyl and 2-furyl acyl fluorides were also well tolerated, with β-lactones 220i and 220j prepared with high enantipurity (99:1 and 92:8 e.r) and yield (Table 3.2, entries 9 and 10).

Table 3.2. Scope of α,β-unsaturated acyl fluorides 210.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>220</th>
<th>yield*</th>
<th>e.r&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄</td>
<td>220a</td>
<td>93%</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅</td>
<td>220b</td>
<td>86%</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>4-OMeC₆H₄</td>
<td>220c</td>
<td>100%</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>2,4-(O)Me₂C₆H₄</td>
<td>220d</td>
<td>90%</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>4-(Me)₂NC₆H₄</td>
<td>220e</td>
<td>97%</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>3,4,5-(O)Me₃C₆H₂</td>
<td>220f</td>
<td>93%</td>
<td>96:4</td>
</tr>
<tr>
<td>7</td>
<td>4-BrC₆H₄</td>
<td>220g</td>
<td>80%</td>
<td>92:8</td>
</tr>
<tr>
<td>8</td>
<td>4-ClC₆H₄</td>
<td>220h</td>
<td>81%</td>
<td>87:13</td>
</tr>
<tr>
<td>9</td>
<td>3-Ts-indolyl</td>
<td>220i</td>
<td>83%</td>
<td>99:1</td>
</tr>
<tr>
<td>10</td>
<td>2-furyl</td>
<td>220j</td>
<td>72%</td>
<td>92:8</td>
</tr>
</tbody>
</table>

*Diastereomeric ratio determined by ¹H NMR analysis of the crude reaction mixture. †Isolated yield after flash chromatography. Enantiomeric ratio determined by chiral column HPLC analysis.
3.3.3 Scope of the (4+2) annulation with respect to the DA-cyclobutane

The scope of the (4+2) annulation with respect to the DA-cyclobutanes 216a-j was examined with a selection of acyl fluorides. Exchanging the ethyl ester component with methyl or allyl esters provided a similar outcome to the parent reaction, with β-lactones 220k and 220l obtained in excellent yield and with excellent stereochemical integrity (Table 3.3, entries 1 and 2). Increasing the steric bulk at this position using iso-propyl esters was detrimental to enantioselectivity, with the corresponding β-lactone 220m isolated in good yield albeit with 94:6 e.r (Table 3.3, entry 3).

Next, the effect of substitution about the cyclobutane motif was explored. Removing the spirocyclic substitution was well tolerated, with dimethyl substituted DA-cyclobutane 216f providing β-lactones 220n-p in excellent yield (93–100%) and with excellent stereochemical integrity (97:3–99:1 e.r) (Table 3.3, entries 4-6). Removing all substitution via DA-cyclobutane 216e decreased the enantioselectivity with 220q isolated in 90:10 e.r (Table 3.3, entry 7) however, this could be improved by exploiting 4-dimethylaminophenyl, 2,4-dimethoxyphenyl and 2-methoxyphenyl acyl fluorides (Table 3.3, entries 8–10). The viability of unsubstituted DA-cyclobutanes 216e and 216d is particularly pleasing as substrates lacking substitution were not suitable in the analogous (3+2) annulation using DA-cyclopropanes (Scheme 3.10).13a Moreover, such generality renders reactions more valuable in the design and the synthesis of complex targets, a topic explored in depth in Chapters 4 and 5.

Increasing the size of the spirocycle was tolerated with cyclooctyl or -heptyl-fused cyclobutanes affording 220u-x in good yields (75–94%) and with enantioselectivities (98:2–99:1 e.r) similar to the parent cyclohexyl analogues (Table 3.3, entries 11–14). Similarly, decreasing ring-size was also tolerated (except for 220y), with cyclopentyl fused DA-cyclobutane 216 providing 220y-aa in good yield and enantioselectivity (Table 3.3, entries 15–17). Finally, bis-cyclobutane 216g was also viable, with the reaction providing β-lactones 220ab and 220ac in excellent yield, albeit with reduced enantioselectivity (93:7 e.r) (Table 3.3, entries 18 and 19).
Table 3.3. Scope of DA-cyclobutanes 216.

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>Ar</th>
<th>R²</th>
<th>220</th>
<th>yieldᵇ</th>
<th>e.rᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-OMeC₆H₄</td>
<td>Me</td>
<td>220k</td>
<td>84%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>Ally</td>
<td>220l</td>
<td>88%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>Pr</td>
<td>220m</td>
<td>86%</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-OMeC₆H₄</td>
<td>Et</td>
<td>220n</td>
<td>93%</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220o</td>
<td>100%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2-Bn(Me)₃C₆H₄</td>
<td>&quot;</td>
<td>220p</td>
<td>98%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-OMeC₆H₄</td>
<td>&quot;</td>
<td>220q</td>
<td>70%</td>
<td>90:10</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-(Me)₂NC₆H₄</td>
<td>&quot;</td>
<td>220r</td>
<td>90%</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220s</td>
<td>83%</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2-OMeC₆H₄</td>
<td>Me</td>
<td>220t</td>
<td>87%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4-OMeC₆H₄</td>
<td>Et</td>
<td>220u</td>
<td>75%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220v</td>
<td>91%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4-OMeC₆H₄</td>
<td>&quot;</td>
<td>220w</td>
<td>94%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220x</td>
<td>80%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4-OMeC₆H₄</td>
<td>&quot;</td>
<td>220y</td>
<td>100%</td>
<td>89:11</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4-(Me)₂NC₆H₄</td>
<td>&quot;</td>
<td>220z</td>
<td>98%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220aa</td>
<td>99%</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4-(Me)₂NC₆H₄</td>
<td>&quot;</td>
<td>220ab</td>
<td>88%</td>
<td>93:7</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2,4-(OMe)₂C₆H₃</td>
<td>&quot;</td>
<td>220ac</td>
<td>81%</td>
<td>90:10</td>
<td></td>
</tr>
</tbody>
</table>

ᵃDiastereomeric ratio determined by ¹H NMR analysis of the crude reaction mixture.ᵇIsolated yield after flash chromatography.ᶜEnantiomeric ratio determined by chiral column HPLC analysis.
Pleasingly, crystals of diallyl malonate 220I suitable for XRD analysis were grown by recrystallisation from n-hexane/isopropanol solution. Analysis using Cu Ka radiation source allowed the absolute stereochemical configuration of the β-lactone products 220 to be assigned as 1S, 2R, 6S (Figure 3.1). This assignment was important for selecting the correct enantiomer of NHC catalyst to obtain β-lactones that translate to the naturally occurring enantiomer of natural products in later studies (see Chapters 4 and 5).

![Figure 3.1. Crystal structure of β-lactone 220I.](image)

In addition to geminal diesters, the β-ketoester containing DA-cyclobutane 216k was assessed. This was synthesised as described previously by zinc bromide-mediated (2+2) annulation of acrylate 225 and TMS enol ether 224a (Scheme 3.15).

![Scheme 3.15. Synthesis of a β-ketoester containing DA-cyclobutane.](image)

Unfortunately, when β-ketoester 216k and acyl fluoride 210c was subjected to the optimised reaction conditions, none of the expected β-lactone 220ad was observed. Instead, lactol ester 226 was isolated in 91% yield and as the sole reaction product (Scheme 3.16). Presumably this is formed by cyclisation of enolate 227 followed by O-acylation with α,β-unsaturated acyl azolium 228. The divergence in reaction outcome may pertain to the removal of C2 oxygenation in the hemiacetal alkoxide 229, which in the former substrates, offers additional Ireland-type activation and therefore acceleration of the Claisen rearrangement.
Scheme 3.16. Annulation of keto-ester derived DA-cyclobutane 216k

Interestingly, across all optimisation experiments with malonate derived DA-cyclobutanes analogous lactol products (i.e. 230) were not observed, despite the frequent isolation of quenched enolate products (i.e. 231, Scheme 3.17) It is possible that under the reaction conditions these oxygenated products 231 are indeed formed, however, as these are α-esterketene acetals, their detection is likely complicated due to rapid hydrolysis upon purification.

Scheme 3.17. Proposed formation and hydrolysis of ketene acetal 230.

Next, the viability of the reaction with vinylogous DA-cyclobutane (i.e. 232) systems was examined While the synthesis of DA-cyclobutane 232 (OTBS = OTMS) was not possible due to difficulties isolating the precursor diene (i.e. 233, OTBS = OTMS), utilising the more stable tert-butylimidemethyl silyl protecting group enabled the isolation of cyclobutane 232, albeit, as a partially separable mixture with the corresponding Diels-alder adduct 234 (Scheme 3.18).

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When \( \text{232} \) was exposed to 10 mol% \( \text{C3} \), the annulation with 4-methoxyphenyl acyl fluoride \( \text{210c} \) proceeded without event to give \( \delta \)-lactone \( \text{235} \) in 91% yield as a single diastereoisomer (Scheme 3.19). Unfortunately, the reaction failed when NHC \( \text{B9} \) or indeed any homochiral catalysts were trialled. This result may be due to the more stable TBS protection (cf TMS) requiring a more nucleophilic catalyst (i.e. \( \text{C3} \)) to initiate the reaction.

![Scheme 3.19. (4+2) Annulation of vinylogous DA-cyclobutane 232.](image)

The structure of \( \delta \)-lactone \( \text{235} \) was confirmed by spectroscopic analysis. Comparison of the \( ^1 \text{H} \) NMR spectrum of the product to the starting acyl fluoride showed loss of \( \alpha,\beta \)-unsaturation, and the presence of a para-substituted aromatic ring (7.33 ppm, 2H and 6.75 ppm, 2H) (Figure 3.2). Comparison to the starting DA-cyclobutane revealed the disappearance of the cyclobutane methylene signals as well as the peak at 0.10 ppm corresponding to the TMS group, whilst indicating the presence of a diethyl malonate moiety. Most tellingly, the \( ^1 \text{H} \) NMR spectrum of the product contained 2 downfield signals and 3 upfield signals each integrating for one proton, indicative of the alkene and methine protons respectively.

The most downfield of these signals at 6.52 ppm, is characteristic of an alkene proton with further deshielding by an adjacent oxygen atom and was assigned as \( \text{H}^\text{e} \). It’s splitting as a doublet of doublets is due to the doublet of doublet of doublets (overlapping) at 5.05 ppm, which is consistent an olefinic proton on the vicinal carbon, and as such, this signal was assigned to \( \text{H}^\text{b} \). The overlapping methine signal at 3.90 ppm was assigned as \( \text{H}^\text{d} \) due to observed coupling (based on COSY NMR) to two methine signals at 3.41 ppm and 3.10 ppm, with the chemical shift suggestive of deshielding by carbonyl anisotropy. In turn, the methine doublet at 3.41 ppm was assigned as \( \text{H}^\text{b} \) based on its isolated coupling to \( \text{H}^\text{d} \) and the chemical shift which is typical of a cyclic and benzylic proton. The final methine signal at 3.10 ppm showed coupling (COSY NMR) to \( \text{H}^\text{b} \), \( \text{H}^\text{a} \), \( \text{H}^\text{d} \), and the methylene signal at 2.21 ppm, which is consistent with assignment as \( \text{H}^\text{f} \).

The downfield region of the \( ^{13} \text{C} \)NMR spectrum contained the required 3 peaks indicative of ester/lactone carbonyl groups, as well as 4 aromatic and two olefinic signals. In the upfield region, the required 11 aliphatic signals were all observed. IR analysis provided evidence for the the \( \delta \)-lactone
functionality with the presence of a signal at 1771 cm\(^{-1}\), separate from the resonance at 1724 cm\(^{-1}\) pertaining to the malonate esters.

\[ \text{H- and } ^{13}\text{C NMR and COSY interactions of } \delta\text{-lactone 235 in CDCl}_3 (400 and 100 MHz).} \]

\[ \text{Figure 3.2 } ^1\text{H- and } ^{13}\text{C NMR and COSY interactions of } \delta\text{-lactone 235 in CDCl}_3 (400 and 100 MHz).} \]

The relative stereochemistry was determined by NOESY NMR. A nuclear Overhauser effect was observed between H\(^d\) and H\(^f\), supporting a cis-fused \(\delta\)-lactone structure, whilst the absence of cross relaxation between H\(^d\) and H\(^e\) is suggestive of a trans-relationship between the lactone and aryl group (Figure 3.3). Furthermore, this stereochemical arrangement is consistent with the related \(\beta\)-lactones 220.
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Figure 3.3. NOESY interactions of δ-lactone 235 in CDCl₃ (400 and 100 MHz).

3.4 Reaction utility

3.4.1 Reaction scale-up

Given the ultimate goal of applying this chemistry in natural product synthesis, the viability of larger scale (4+2) annihilations was examined. Due to the long sequence (6-steps) required for catalyst synthesis, we wished to explore the viability of reducing catalyst loading. The parent reaction using 10 mol% B9 is provided for reference (Table 3.4, entry 1). When conducted with 1 mol% B9 the reaction proceeded sluggishly, with β-lactone 220c isolated in significantly reduced yield (23%) and slightly decreased enantioselectivity (92:8) (Table 3.4, entry 2). Gratifyingly, using 3 mol% B9, β-lactone 220c was obtained in good yield and with similar enantioselectivity to the reaction with 10 mol% B9 (Table 3.4, entry 3).

Table 3.4. Optimisation of reduced catalyst loading.

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>yield</th>
<th>e.r&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>100%</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>23%</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>73%</td>
<td>96:4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Diastereomeric ratio determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup>Isolated yield after flash chromatography. <sup>c</sup>Enantiomeric ratio determined by chiral column HPLC analysis.

Pleasingly, with the newly revised conditions, 1.78 g DA-cyclobutane 216a (5 mmol) and 1.78 g of acyl fluoride 210c (5 mmol) was coupled to produce 1.98 g of β-lactone 220c in 89% yield and 95:5 e.r (cf
100% yield, 97:3 e.r), using only 45 mg of NHC B9 (Scheme 3.20). This result was later surpassed, with related substrates coupled on up to 20 mol scale (see Chapters 4 and 5).

**Scheme 3.20.** (4+2) annulation on 5 mmol scale.

### 3.4.2 Product derivatisation

As part of studies to assess the utility of the (4+2) annulation, derivatisations of the β-lactone products were investigated. Initial studies focused on decarboxylative methods with respect to the β-lactone and malonate functionality. Upon heating cyclohexene 220c in DMF, thermal decarboxylation of the β-lactone proceeded smoothly and cyclohexene 236 was obtained in excellent yield (94%) and with complete stereo-retention (Scheme 3.21).

**Scheme 3.21.** Thermal B-lactone decarboxylation.

Thermal decarboxylation of the β-lactone could also be coupled with decarboxylative allylation diallylmalonate ester moiety. Thus, treatment of diallylmalonate 220l with 10 mol% tetrakis palladium triphenylphosphine (Pd[PPh₃]₄) effected β-lactone decarboxylation, and decarboxylative allylation to give cyclohexene 237, albeit in a modest 19% yield and 3:1 d.r (Scheme 3.22). In this case, the remainder of the converted material consisted of the corresponding protonation product 238. Pleasingly, switching the catalyst to bis[1,2-bis(diphenylphosphino)ethane]palladium(0) (Pd[dpppe]₂) suppressed undesired protonation and cyclohexene 237 was obtained in 57% yield, 3:1 d.r and with complete enantiotretention. The reaction was also conducted at reduced temperature (90 °C) in an effort to engender greater
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diastereoecontrol. Unfortunately, minimal conversion was observed at these temperatures and 237 was isolated with identical diastereoselectivity (3:1 d.r). This is not unexpected as effecting the decarboxylative allylation of α,α-dialkyl malonates is sluggish due to thermodynamic challenges of ester enolate formation.21

Scheme 3.22. Palladium catalysed decarboxylative allylation of diallyl malonate 220I.

Simple Krapcho decarboxylation22 could also be coupled with β-lactone decarboxylation. When dimethyl malonate 220k with was treated with sodium chloride and heated to 170 °C, monoester 239 formed in 37% yield, as a 2:1 mixture of diastereomers and with complete enantioretention (Scheme 3.23). Using lithium chloride gave a significant increase in yield (64%), however the diastereoselectivity was unchanged. The limited diastereoselectivity is consistent with related reactions described in the literature, whereby diastereoselectivity is substrate dependant, and can only be controlled by an internal proton source.23

Scheme 3.23. Krapcho decarboxylation of dimethyl malonate 220k.

Derivatisations which avoid β-lactone decarboxylation were also investigated. Careful moderation of reaction time and temperature allowed a highly chemoselective reduction of the β-lactone motif in the presence of two ester functionalities. Thus, treatment of β-lactone 220c with lithium aluminium hydride (LiAlH₄) at −78 °C for 30 minutes provided diol 240 in 83% yield and with complete stereoretention (Scheme 3.24, eq. 1). Simple β-lactone cleavage using benzylamine was also possible with amide 241 isolated in 86% yield and with complete stereoretention (Scheme 3.24, eq. 2).
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Scheme 3.24. Reduction and aminolysis of β-lactone 220c.

When ring-opening was attempted using alcoholic nucleophiles, an unexpected transannular lactonisation occurred and [2.2.2]-bicyclic lactone 242a was isolated. This process occurred in 8 hours under acidic conditions using p-toluenesulphonic acid (Scheme 3.25a) however, was significantly more facile (1 h) when mediated by base (Scheme 3.25b). In both cases the lactone 242a was isolated in excellent yield (91% and 98%) and with complete stereoretention.

Scheme 3.25. Acid and base mediated ethanolysis of β-lactone 220c.

Finally, deprotection of aniline 220p by treatment with palladium on activated charcoal under a hydrogen atmosphere allowed access to the corresponding quinolone 243 (Scheme 3.26). Lactamisation with the pendant ethyl esters occurred spontaneously upon exposure to silica, or in deuterated chloroform, or even when stored as a neat material. Unfortunately, under any of these conditions, the cyclisation occurred with no diastereoselectivity. Addition of potassium carbonate in situ following debenzylation improved diastereoselectivity, with dihydroquinolinone 243 isolated in 94% yield as a 5:1 mixture of diastereomers, and with complete enantioretention.
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3.4.3 Antimicrobial screening of β-lactones and derivatives

Antibiotic resistance represents one of the greatest challenges facing the modern era of medicinal chemistry. The ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Psuedomonas aeruginosa, and Enterobacter species) account for the majority of hospital-born infections and as such, are developing antibiotic resistance at an alarming rate. To combat resistance, there is an increasing demand for new chemical structures which exhibit antimicrobial activity via novel mechanisms.

The CO-ADD (The Community for Antimicrobial Drug Discovery) is an organisation which conducts widespread screening of novel chemical compounds for antimicrobial activity. Racemates of most β-lactones and their derivatives synthesized here were subjected to screening against 4 ESKAPE bacteria (S. aureus, K. pneumoniae, A. baumannii and P. aeruginosa) in addition to E. coli and the fungi Candida albicans and Cryptococcus neoformans. The pathogens were exposed to these compounds at a concentration of 32 μg/ml in whole cell growth inhibition assays.

Pleasingly, several of our compounds displayed promising activity. Specifically, β-lactones 220a and 220d in addition to cyclohexene 237, effected almost 50% inhibition of bacterial growth against the Gram-negative bacteria K. pneumonia (Figure 3.4). Compounds 220a, 220m, and 239 were considerably more effective against another Gram-negative bacteria, A. baumannii, inhibiting 79%, 69%, and 70% of cell growth respectively. Finally, indole-derived β-lactone 220i showed similar activity (76%) against C. albicans. All other screened compounds displayed almost no antimicrobial activity.
Figure 3.4. Antimicrobial activity of β-lactones and derivatives represented as percentage inhibition at 32 μg/ml.

3.5 Mechanistic insights

3.5.1 Divergent mechanisms for initial C-C bond formation

While we envisage the (4+2) annulation to proceed via O-addition of enolate 244 to acyl azolium 245, followed by anionic-oxy Claisen rearrangement (i.e. 246 → 247), an alternate mechanistic scenario proceeding through C-centred 1,4-addition of enolate 244 to 245, is plausible (Scheme 3.27).
To probe these mechanistic proposals, our attention turned to previous studies by Evans in which the effect of alkoxide counterions on the rate of the anionic oxy-Cope rearrangement was assessed (Scheme 3.28).\(^\text{28}\) Evans demonstrated that a strongly coordinating lithium counterion failed to promote the reaction. When a sodium counterion was used, the rearrangement proceeded with a half-life \(t_{1/2}\) of 1.2 hours and finally, weakly coordinating potassium counterions allowed the rapid rearrangement of \(247\) \(t_{1/2} = 1.4\) minutes.

With this in mind, the (4+2) annulation between \(216a\) and \(210a\) was carried out with variation of the counterion source,\(^\text{29}\) and the reaction displayed a similar sensitivity to that observed in Evans’ sigmatropic rearrangement. Tellingly, the reaction failed when lithium- and sodium-derived bases were used for carbene generation and when potassium and caesium derived bases were employed, the reaction proceeded smoothly (Scheme 3.29). We believe that these findings support a [3,3] sigmatropic rearrangement pathway, which is accelerated by weakly coordinating counterions.

The effect of alkali metal counterions with respect to enolate reactivity\(^\text{30}\) is in keeping with these mechanistic insights. Strongly associating counterions (i.e. lithium and sodium) sterically shield oxygen and therefore favour carbon-centred enolate reactivity. Conversely, weakly coordinating counterions (i.e. potassium and caesium) result in a more naked oxygen leading to increased reactivity at oxygen. Moreover, the reaction shows a preference for polar solvents which are capable of coordinating counterions and, therefore, would favour reaction at oxygen. Given that the reaction fails under conditions which would
support C-centred enolate reactivity and proceeds smoothly under conditions which support O-centered reactivity, we suspect that C-O bond formation and anionic oxy-Claisen rearrangement accounts for the initial C-C bond formation.

![Scheme 3.29. Counterion effect on the yield of the (4+2) annulation.](image)

Based on these observations, a complete mechanism for the (4+2) annulation is proposed (Scheme 3.30). The reaction is likely initiated by an NHC mediated desilylation/defluorination cascade which generates acyl azolium 245 and bifunctional enolate 244 upon retro-aldol opening of cyclobutane 216a. Addition of the enolate 244 to the acyl azolium 245 then gives hemiacetal alkoxide 246 which undergoes anionic-oxy Claisen rearrangement, generating acyl azolium enolate 247. Finally, an asynchronous (2+2) aldol/laconitisation process\(^1\) furnishes the β-lactone products 220 and regenerates the catalyst.

![Scheme 3.30. Proposed mechanism of the (4+2) annulation.](image)
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3.6 Conclusions and outlook

Using a Lewis base approach, the first enantioselective (4+2) annulation of donor-acceptor cyclobutanes 216 has been realised. The NHC catalysed reaction with α,β-unsaturated acyl fluorides 210 generates densely functionalised cyclohexyl fused β-lactones 220 in excellent yield and with excellent stereochemical integrity (>20:1 d.r, most >98:2 d.r). The reaction is amenable to modest scale-up and the β-lactone products have extensive synthetic utility. Decarboxylative and ring-opening based derivatisations deliver highly functionalised cyclohexanes, cyclohexenes, and quinolinones. Additionally, antimicrobial screening revealed some products and their derivatives exhibit promising activity against nosocomial pathogens K. pneumoniae, A. baumannii and C. albicans. Preliminary mechanistic investigations support the first C-C bond forming event proceeding through a O-C addition and anionic oxy-Claisen rearrangement pathway.

Future investigations will focus on translation of this reaction manifold to incorporate analogous nitrogen bearing DA-cyclobutanes (i.e. 248) for the synthesis of β-lactams (i.e. 249) (Scheme 3.31). If successful, we believe this methodology will provide access to a host of novel β-lactam products and thus support our research program surrounding the discovery of novel antimicrobial agents.

![Scheme 3.31. Nitrogen bearing DA-cyclobutanes for the synthesis of β-lactams](image)

Having developed a new NHC catalysed (4+2) annulation which offers remarkable utility, its application in total synthesis was pursued. Studies towards this end are detailed in the following chapters.
3.7 References

14 Reaction discovery and optimisation was carried out by Dr. Alison Levens. I would like to acknowledge her contribution to this project.
16 Increased enantiocontrol at elevated temperatures has been observed previously and have been attributed to entropic control of the enantiodetermining step: (a) Saito, R.; Naruse, S.; Takano, K;
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24 Reactions concerning aniline 220i were conducted by Dr. Alison Levens (Monash University).
27 CO-ADD (The Community for Antimicrobial Drug Discovery) is funded by the Wellcome Trust (UK) and The University of Queensland (Australia).
29 All mechanistic experiments were conducted by Dr. Alison Levens (Monash University).
Chapter 4

Towards the synthesis of (+)-bisabosqual A

Examination of key strategies towards the synthesis of (+)-bisabosqual A are described in Chapter 3. The N-heterocyclic carbene catalysed (4+2) annulation of donor-acceptor cyclobutanones and \(a,\beta\)-unsaturated acyl fluorides is utilised to construct a cyclohexyl \(\beta\)-lactone which can be elaborated into the cis-cis fused tetracyclic core. Additionally, modification of the reaction substrates to facilitate incorporation of the penta-substituted aromatic motif and the alkenyl sidechain was examined.

4.1 Introduction

In 2001 Minagawa and co-workers isolated bisabosquals A-D from the culture broth of Stachybotrys sp. RF-7260, a mould found growing on decaying tree leaves from coastal Japan (Figure 4.1). Biological screening revealed that a suite of natural products that inhibit microsomal squalene synthases in Saccharomyces cerevisiae and Candida albicans (CA) were produced. Consequently, they exhibit broad spectrum anti-fungal activity in vitro, which is particularly true of bisabosqual A. Additionally, bisabosquals A-D inhibit mammalian squalene synthases from rat liver and HepG2 cells, and as such, have garnered interest for their use as antihypercholesteremic agents.
4.1.1 **Snider’s synthesis of the tetracyclic core of the bisabosquals**

In 2007, Snider and co-workers reported a biomimetic approach for the synthesis of the alkenyl substituted tetracyclic core of the bisabosquals (Scheme 4.1).\(^5\) Notably, the synthesis utilises an inverse demand, hetereatomatic intramolecular Diels-Alder (IMDA) reaction of ortho-quinone methide 250, accessed via hydrolysis and elimination of alcohol 251. This powerful transformation forges the cyclohexane and fuses the benzopyran in a single step to give 252 with complete stereocontrol. Unfortunately, subsequent epoxidation occurred on the α-face, leading to the incorrect configuration of tertiary alcohol 253 after cyclisation of the pendant phenol. A series of functional group interconversions (253→254) were required to invert the tertiary alcohol stereocentre. Thus, elimination of alcohol 253 with Martin’s sulfurane delivered exocyclic alkene 255 albeit as a 2:1 mixture of with regioisomer 256. Next, ozonolysis of the required exocyclic alkene 255, and subsequent reductive deoxygenation of the epoxide provided ketone 257. Finally, addition of methylmagnesium bromide occurred with complete facial selectivity to furnish tertiary alcohol 254, and in turn the tetracyclic core of the bisabosquals.
Despite a sequence of undesirable functional group interconversions to invert the tertiary alcohol stereocentre from 253, Snider’s strategy successfully generates the challenging tetracyclic core 254 with the correct stereochemical configuration. It is probable that a total synthesis has not been realised through this strategy due to the potential challenges in achieving chemo- and, in particular, regioselectivity in the key IMDA reaction with the unsymmetrical and electron-poor aromatic fragment required for (+)-bisabosqual A (258).

**4.1.2 Parker’s total synthesis of (±)-bisabosqual A**

Parker’s reported synthesis of (±)-bisabosqual A (258) in 2012 represents the only successful total synthesis. A convergent approach was employed, with fragments 259, 260, and 261 utilised to build the ether linkages and merge both the cyclohexane and aromatic motif (Scheme 4.2). Thus, a DABCO catalysed 1,4-addition of resorcinol 259 to ynone 260 provided phenol 262 before a Mitsunobu protocol with alcohol 261 furnished aryl iodide 263. Next, aryl radical 264 is generated via treatment with tri-butylborane, which undergoes a tandem 5-exo-trig/6-exo-trig cyclisation cascade, thereby generating
the entire hexahydrobenzofurobenzopyran framework (i.e. 265) in 72% yield after reductive trapping. Unfortunately, the desired isomer 265a was formed alongside the C7 epimer epi-265 in a 2:1 ratio, with limited epimerisation possible by treatment with 1,5,7-triazacyclo[4.4.0]dec-5-ene (TBD). Next, a series of functional group interconversions to effect deprotection, oxidation, and deoxygenation were executed in excellent yield to provide ketone 266. A diastereoselective addition of methylithium then establishes the tertiary alcohol 267 with the correct configuration. Finally, global reduction of the phthalate esters followed by oxidation with Dess-Martin periodinane (DMP) provides the phthalaldehyde motif and ultimately, (±)-bisabosqual A (258).

Notably, Parker’s synthesis features a powerful tandem radical cyclisation which constructs two rings and sets 3 stereogenic centres (two stereospecifically) in a single step. The authors suggest with simple adaptation, this sequence offers significant opportunity for an enantioselective synthesis and therefore analogue development. Despite this, no asymmetric variant or indeed any synthesis of the bisabosquals has been reported in the following 6 years.

Scheme 4.2. Parker’s total synthesis of (±)-bisabosqual A
4.2 Synthetic design and objectives

4.2.1 Retrosynthetic analysis of (+)-bisabosqual A

To address the lack of an enantioselective synthesis of (+)-bisabosqual A, and to showcase the previously introduced chemistry of NHCs with DA-cyclobutanes (Chapter 3), a synthetic strategy to the natural product was developed. The approach stems from recognition that the previously developed (4+2) accesses highly enantioenriched and densely functionalised cyclohexyl β-lactones which we believe, could be valuable substrates in the synthesis of the bisabosqual core. Thus, retrosynthetic analysis led us to propose a route to ketone 266, a known precursor of bisabosqual A (258), which would itself, be constructed via epoxidation and cyclisation from alkene 268 (Scheme 4.3). In turn, alkene 268 could be obtained from ketone 269 exploiting Grignard addition/deprotection, and carbocationic cyclisation procedures reported by Trost or Carreira. Krapcho decarboxylation, as explored in Chapter 3, and concomitant thermal decarboxylation of β-lactone 270 was expected to provide ketone 269. Finally, the NHC catalysed (4+2) annulation would give access to β-lactone 270 after coupling of a suitable α,β-unsaturated acyl fluoride (i.e. 271) and donor-acceptor (DA) cyclobutane 2161. To enable the proposed enantioselective synthesis of (+)-bisabosqual A, we wished to first examine the viability of our general strategy through several model studies.

Scheme 4.3. Proposed retrosynthesis of (+)-bisabosqual A (258).
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4.2.2 Model study 1: Construction of the cis-cis fused tetracyclic core

Our first endeavour aimed to establish a route for constructing the cis-cis fused tetracyclic core of the bisabosquals (Scheme 4.4). Given that our earlier methodological studies did not examine 2,6-disubstituted cinnamoyl fluorides (i.e. 210m), their viability in the (4+2) annulation needed to assessed. Presuming the synthesis of proposed the proposed model β-lactone 220ad is viable, its elaboration to the tetracyclic core 272 would be examined. Central to our strategy is a Krapcho decarboxylation which establishes the stereochemical configuration for the construction of cis-fused benzo-furan ring. From 273 we anticipate the remaining rings and stereocentres can be formed by exploiting procedures established previously by Snider and Parker.

![Scheme 4.4. Proposed construction of the tetracyclic core of the bisabosquals.](image)

4.2.3 Model study 2: β-Keto ester derived DA-cyclobutanes

Central to our second investigation is assessing the suitability of β-keto ester derived DA-cyclobutanes in the (4+2) annulation. If found to be valuable substrates, we anticipate that the application of an appropriate DA-cyclobutane (i.e. 216l) would allow convenient early stage incorporation of the alkenyl side chain (Scheme 4.6).

![Scheme 4.5. Examination of β-keto ester derived DA-cyclobutanes](image)

Previously it was shown (see Chapter 3, section 3.3.3) that when β-ketoester derived DA-cyclobutane 216 (R = -(CH₂)₇-) was employed in the reaction, lactol 226 was isolated as the sole product (Scheme 4.6).¹⁰ Although this reaction pathway was non-productive, we reasoned that with DA-cyclobutane 216 (R = H), the absence of Thorpe-Ingold effects, introduced by spirocyclic annulation, should disfavour lactolisation.
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of bifunctional enolate 274. Thus, O-addition of enolate 274 to acyl azonium 275 and subsequent anionic oxy Claisen (AOC) rearrangement would predominate, thereby leading to the desired β-lactone (i.e. 220ae)

Scheme 4.6. Lactolisation of vs O-addition and AOC.

4.2.4 Model study 3: Pentasubstituted α,β-unsaturated acyl fluorides

Two key enquiries compose the final model investigation; the first relates to the viability of preparing unsymmetrical, pentasubstituted α,β-unsaturated acyl fluorides (i.e. 210), while the second pertains to the suitability of such substrates in the requisite (4+2) annulation (Scheme 4.7). Resorcinol 259 utilised by Parker and co-workers, represents a potential source for the aromatic fragment. We anticipate that an orthogonal protecting group strategy may be required to enable regioselective formation of the benzopyran and benzofuran rings later in the prospective synthesis.

Scheme 4.7. Examination of pentasubstituted α,β-unsaturated acyl fluorides.
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4.3 Model study 1: Assembly of the cis-cis fused tetracyclic core

4.3.1 Synthesis and reactivity of 2,6-disubstituted acyl fluorides

Studies commenced with the synthesis of model DA-cyclobutane 216e and α,β-unsaturated acyl fluoride 210m. To this end, cyclobutane 216e was prepared as described previously (see Chapter 3, section 3.3.1) from a (2+2) cycloaddition of methylene malonate 224b and enol ether 223b mediated by zinc bromide ZnBr₂ (Scheme 4.8). ¹¹ In regards to the acyl fluoride, lithiation of 1,3-dimethoxybenzene (276) and subsequent formylation with N,N-dimethylformamide ¹² gave access to 1,3-dimethoxybenzaldehyde (277) in 78% yield. Next, Doebner-modified Knoevenagel condensation provided α,β-unsaturated acid 278 before fluorination with diethylaminosulfur trifluoride (DAST) ¹⁴ delivered the desired α,β-unsaturated acyl fluoride 210m in 94% yield.

![Scheme 4.8. Synthesis of DA-cyclobutane 216e and α,β-unsaturated acyl fluoride 210m.](image)

With 2,6-dimethoxy substituted acyl fluoride 210m in hand, its viability in the NHC catalysed step was assessed through annulation with DA-cyclobutane 216e. When these substrates were exposed to NHC B⁹, β-lactone 220ad was obtained in 45% yield, as a single diastereomer and with 92:8 e.r (Scheme 4.9a). In contrast, 2,4-dimethoxy-substituted acyl fluorides were shown to give the corresponding β-lactone in comparatively greater yield (83%) and enantioselectivity (98:2 e.r) (see Chapter 3, section 3.3.3), thus highlighting the sensitivity of the reaction to steric factors. In regard to the decreased yield observed here, ³H NMR analysis of the crude reaction mixture indicated the presence of multiple cinnamate derived side-products.
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It is possible that the 2,6-disubstitution of the aryl group introduces steric interactions in the transition state 279, therefore slowing the asynchronous (2+2) aldol/lactonisation process (283→220ad).\(^\text{15}\) Given that the O-addition and Claisen rearrangement sequence ([281+282]→283) is reversible, this scenario may favour side reactions of acyl azolium 282 which leads to unreactive cinnamate derived products and therefore erosion of yield. The reaction was also conducted with achiral catalyst C3, and a similar but less pronounced decrease in yield (73%) was observed (Scheme 4.9b). Due to the higher yield, and ready availability of the non-chiral NHC C3, racemic β-lactone 220ad was used in the subsequent model investigations.

![Scheme 4.9. (4+2) Annulation of α,β-unsaturated acyl fluoride 210m.](image)

The $^1$H NMR spectrum of β-lactone 220ad contained the three required methine signals between 5.2 and 3.8 ppm corresponding to H$^1$, H$^6$ and H$^8$, however, the chemical shifts and coupling constants were, in part, inconsistent with analogous signals in 2-methoxy substituted β-lactone 220t (Figure 4.2). The most downfield signal in 220t corresponds to the β-lactone proton H$^4$. In the case of 2,6-dimethoxy substituted 220ad, the analogous H$^4$ was assigned to the second most downfield methine signal at 4.85 ppm due to observed coupling to both methine signals and a methylene unit (as observed in COSY NMR). Given that the doublet of doublets at 3.85 ppm couples to H$^4$ and additionally, a methylene unit, it was assigned as H$^6$. Consequently, H$^8$ was assigned to the most downfield methine signal, a narrow doublet at 5.20 ppm.

Data from $^{13}$C NMR and IR analysis were also in agreement with this assignment and supported the presence of a β-lactone.
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![Figure 4.2. 1H NMR spectrum of β-lactone 220ad in CDCl₃ (400 MHz) with 220t shown for comparison.](image)

In regard to β-lactone 220ad, the significant downfield shift (δ 5.20 ppm) and decreased coupling constant (J = 1.5 Hz) of benzylic proton H₃ compared to the related mono-methoxy substituted product 220t (H⁺ δ 4.43 ppm, J = 3.6 Hz) prompted us to question the relative stereochemical arrangement between the β-lactone and aromatic substituent. Fortunately, crystals of 220ad sufficient for X-ray diffraction analysis were grown, and the corresponding crystal structure was obtained (Figure 4.3), confirming that the structure and relative stereochemistry was consistent with previously prepared β-lactone products. Inspection of the crystal structure reveals the proximity of H₃ to the neighbouring carbonyl and aromatic p-orbitals. It is probable that the steric bulk introduced by the 2,6-dimethoxy substituted aromatic forces the cyclohexane to adopt a conformation whereby H₃ has greater overlap with these neighbouring p-orbitals. In this scenario, increased anisotropic deshielding of H₃ then explains the unusually large chemical shift, while the dihedral angle between H₃ and H⁺ is close to 90° (90.42°), leading to the lower coupling constant.

![Figure 4.3. 1X-ray crystal structure of β-lactone 220ad.](image)
4.3.2 Decarboxylation of β-lactone 220ad

With β-lactone 220ad in hand, it was treated with LiCl in DMSO at 170 °C following the procedures developed in Chapter 3. Both thermal and Krapcho decarboxylation proceeded as expected to give monoester 284 in 66% yield, albeit with modest diastereoselectivity (2:1) favouring the required cis configuration. In related work, Sugai and co-workers reported that diastereoselectivity of the Krapcho decarboxylation of cyclobutyl geminal diesters can be improved using phenol based proton sources. We reasoned that a bulkier phenol should favour protonation of enolate 285 on the opposite face to the aryl substituent and therefore increase cis selectivity. Unfortunately, when butylated hydroxytoluene (BHT) was employed, the yield of monoester 284 decreased (24%) and the diastereoselectivity was unchanged (2:1).

![Scheme 4.10. Krapcho decarboxylation of β-lactone 220ad with water and BHT.](image)

It has been shown previously that closely related cis-monoesters (i.e. cis-284) are amenable to epimerisation to the trans-arrangement by treatment with NaOMe in refluxing methanol, suggesting that trans-monoester 284 is the thermodynamic product and cis-monoester 284 is the kinetic product. These findings are consistent with the dealkoxy carbonylation of cyclohexyl gem-diesters reported by Krapcho and co-workers.

Given these observations, we proposed that generation of enolate 285 and quenching at low temperature may enable epimerisation to the kinetic product. To probe this scenario, enolate 285 was generated directly from a cis/trans mixture of monoester 284 using lithium bis(trimethylsilyl)amide (LiHMDS) and subsequently quenched at low temperature (Scheme 4.11). In the event, this did not alter the diastereomeric ratio (2:1 cis/trans) of monoester 284 when either water (R = H) or the bulkier tert-butanol (R = ‘Bu) were used as the quenching agent. Despite modest diastereoselectivity, cis-monoester
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284 and trans-monoester 284 were separable by flash column chromatography, which was sufficient for the subsequent studies.

![Scheme 4.11. Krapcho decarboxylation of β-lactone 220ad.](image)

4.3.3 Synthesis of the tetracyclic core

With cis-284 in hand, it was subjected to a two-step procedure developed previously by Carrera which effects methylation, aryl ether deprotection, and carbocationic cyclisation in the synthesis of Δ⁵-tetrahydrocannabinol. Thus, after treatment of cis-284 with methylmagnesium bromide and heating, followed by addition of zinc bromide, the benzopyran ring was formed and, cis-cis-fused hexahydrobenzopyran 286 was obtained in 54% yield (Scheme 4.12). Unfortunately, direct epoxidation and cyclisation of 286 with meta-chloroperbenzoic acid (m-CPBA) and sodium hydroxide (NaOH) resulted in rapid decomposition. In Snider’s synthesis of the tetracyclic core of bisabosqual A, instability and decomposition of similar materials was observed, an issue which could be resolved by acetylation of the phenol prior to epoxidation (see Scheme 4.1). Thus, following Snider’s procedures, acetylation of 286 with acetic anhydride provided acetate 287 in 84% yield, and epoxidation/cyclisation was attempted. Unfortunately, when NaOH was used to mediate the cyclisation step, decomposition was again observed. Concerned that hydroxide was leading to premature cleavage of the epoxide, the reaction was conducted with a milder base. Pleasingly, when potassium carbonate (K₂CO₃) was employed, closure of the benzofuran ring was successful, with the desired tetracyclic alcohol 273 isolated in 40% yield.

![Scheme 4.12. Construction of hexahydrobenzofurobenzopyran 273.](image)
The structure of tetracycle 273 was confirmed by spectroscopic analysis and with comparison to Parker’s related material 265b. Comparison of the $^1$H NMR spectrum of 273 to the starting cyclohexene 287 showed the loss of two alkene protons and the signal at 2.29 ppm corresponding to the acetate methyl group. Most tellingly, the $^1$H NMR spectrum of the product contained 3 resonances between 4.8 and 3.3 ppm, each integrating to one proton which is indicative of the three labelled methine protons (Figure 4.4). The most downfield of these signals (4.72 ppm), has a chemical shift which is suggestive of deshielding by the adjacent ether oxygen in addition to ring strain in the benzofuran and, therefore, was assigned as $H^b$. This doublet of doublets couples (based on coupling constant and COSY NMR) to the triplet at 3.35 ppm in addition to a methine signal at 1.91 ppm, which were assigned as $H^0$ and $H^a$ respectively. This triplet in turn couples (based on COSY NMR) to the overlapping doublet of doublet of doublets at 3.35 ppm, which couples also to the methylene signal at 1.92 ppm, and was therefore assigned to $H^a$. The chemical shift of this signal is indicative of deshielding by the adjacent alcohol oxygen. Comparison of the $^1$H NMR data for 273 to that derived from Parkers material 265b, reveals a close relationship in both chemical shift, and coupling constant, between the related methine protons $H^b$/$H^a$, $H^0$/$H^b$, and $H^a$/$H^c$ therefore supporting this assignment. In addition, the $^{13}$C NMR data are entirely consistent with this assignment while IR analysis (br 3400 cm$^{-1}$), as well as the broad singlet at 2.10 ppm in the $^1$H NMR, are supportive of the presence of a hydroxyl proton.

![Figure 4.4. $^1$H NMR of hexahydrobenzofurobenzopyran 273 and 265b in CDCl$_3$ (400 MHz).](image-url)
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These model studies have demonstrated that 2,6-disubstituted cinnamoyl fluorides (i.e. 210m) are valuable substrates for the NHC catalysed (4+2) annulation with DA-cyclobutane 216e. Pleasingly, the β-lactone product 220ad was utilised in the assembly of the hexahydrobenzofurobenzopyran core 273, which was achieved in 10 steps from commercially available starting materials, therefore supporting the viability of a synthesis of the natural product. Inspired by the success of this sequence, our efforts focused next on establishing β-keto ester derived DA-cyclobutanes and examining their utility for installation the alkenyl side chain.

4.4 Model study 2: B-Keto ester derived DA-cyclobutanes

4.4.1 Synthesis and reactivity of β-ketoester derived DA-cyclobutane 216m

Studies commenced with identification of β-keto ester derived DA-cyclobutane 216m as a suitable model substrate (Scheme 4.13). Although the required alkenyl sidechain is absent, 216m serves as a suitable surrogate to investigate if the (4+2) annulation of β-keto ester-derived DA-cyclobutanes lacking spirocyclic annulation, can deliver β-lactone products. Starting from β-ketoester 288, deprotonation with sodium hydride (NaH) and quenching with phenylselenium chloride (PhSeCl) provided selenide 289 which underwent selenoxide elimination to furnish methylene acetoacetate 290. Next, procedures described previously for the (2+2) cycloaddition with enol ether 223b were transferred successfully, with a diastereomeric mixture of DA-cyclobutane 216m obtained in 34% yield over 3 steps.

As retro-aldol ring-opening of DA-cyclobutanes in the (4+2) annulation ablates any stereochemical information, 216m was employed as a mixture of stereoisomers. Unfortunately, when 216m was treated with NHC B9 in the presence of acyl fluoride 210m, only the previously observed lactolisation pathway occurred, with lactol 291 isolated in 69% yield. Furthermore, no evidence of desired the β-lactone 220af could be observed by 1H NMR analysis of the crude reaction mixture. Therefore, it is likely that for reasons discussed previously (see Chapter 3, section 3.3.3), β-ketoester derived DA-cyclobutanes are not viable in this reaction.
Whilst the desired reaction pathway could not be realised, we recognised that lactol 291 itself offers opportunity for NHC-mediated cyclisation, as activation of ester substrates by NHC addition is well studied.\textsuperscript{21} Specifically, we proposed that NHC addition and fragmentation of lactol 291 could regenerate α,β-unsaturated acyl azolium 292 and hemiacetal alkoxide 292, which may then reform enolate 294 (Scheme 4.14). Thus, it may be possible to effect the synthesis of β-lactone 220af from lactol 291 using more forcing conditions. To investigate this scenario, lactol 291 was resubjected to the original conditions, however, no reaction was observed. To promote conversion of the substrate, the reaction was conducted in refluxing toluene, however, again, the starting material was reisolated unchanged. Given the apparent stability of lactol 291, we proposed that a more nucleophilic catalyst may be required to facilitate fragmentation, however, no reaction occurred upon treatment of this substrate with the more nucleophilic C3 in either refluxing THF or toluene.
4.4.2 Alkylation strategy for incorporation of the alkenyl side-chain

Given the lack of viability of DA-cyclobutanes (and indeed lactols) containing β-ketoesters, a new strategy was required to install the alkenyl side chain. An alternate route was proposed, whereby a series of routine transformations using cis-monoester-284 would provide access to ketone 295, and subsequently allow incorporation of an alkenyl fragment through alkylation (Scheme 4.15). To this end, reduction of cis-284 with DIBAL-H proceeded smoothly to give alcohol 296 before Swern oxidation gave the corresponding aldehyde 297. Next, addition of methyl magnesium bromide (MeMgBr) provided the secondary alcohol 298 before a second Swern oxidation furnished the desired ketone 295. To investigate the suitability of alkylation, ketone 295 was treated with lithium diisopropyl amide before the addition of a suitable alkenyl sidechain surrogate (allyl bromide).22 To our delight, the alkylation proceeded without event, and ketone 299 was obtained in 54% yield.

![Scheme 4.15. Incorporation of the alkenyl sidechain.](image)

Although attempts to implement β-ketoester derived DA-cyclobutane 210m in the (4+2) annulation were unsuccessful, an alternate strategy to install the alkenyl sidechain was realised. While this strategy was quite step intensive, at this point no attempts to revise the sequence were made, although many obvious strategies to decrease the step count exist. After the success of the first two model studies, attention was directed to the synthesis of a suitably substituted α,β-unsaturated acyl fluoride and its reactivity in the NHC catalysed (4+2) annulation.
4.5 Model study 3: Pentasubstituted α,β-unsaturated acyl fluorides

Careful consideration of the aromatic fragment 259 used in Parkers synthesis of bisabosqual A, led to the development of a modified route to pentasubstituted α,β-unsaturated cinnamates (i.e. 300, Scheme 4.16). Specifically, we envisaged Mizoroki-Heck coupling of an orthogonally protected aryl halide (i.e. 301) to give the desired cinnamate.

![Scheme 4.16. Proposed route to access pentasubstituted α,β-unsaturated cinnamates.](image)

4.5.1 Synthesis of pentasubstituted α,β-unsaturated scaffolds

It was anticipated that installing orthogonal protecting groups from resorcinol 259 would be challenging, therefore, the synthesis commenced with the preparation of known phenol 302, an aromatic material which eliminates these difficulties (Scheme 4.17). To this end, commercially available methyl ether 303 was prepared in 31% yield after exposure of cyclohexanedione 304 to iodine (I₂) in methanol. Deprotonation of 303 with LDA and subsequent addition of trimethylsilyl chloride (TMSCl) generated diene 305 which was utilised directly in a Diels-Alder reaction with dimethylacetylene dicarboxylate (DMAD) (306). After expulsion of ethylene via a retro-Diels Alder mechanism followed by hydrolysis, the reaction generates pthalate 302 in 68% yield. Lastly, conversion of pthalate 303, to the corresponding allyl ether 307 was achieved by treatment with potassium carbonate and allyl bromide.

![Scheme 4.17. Synthesis and protection of pentasubstituted aromatic scaffold 307.](image)
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With phthalate 302 in hand, it was subjected to a range of conditions for selective functionalisation at C4. Unfortunately, treatment with I₂ and periodic acid, which effected regioselective iodination of the corresponding resorcinol in Parker’s work, gave a complex mixture of products (Scheme 4.18). ¹H NMR analysis of the crude reaction mixture indicated non-selective iodination of the aromatic positions, and the allyl group, leading to a mixture of regioisomers (i.e. X = H or I). Hoping that milder conditions would preclude reaction of the allyl group, 307 was treated with N-bromosuccinimide. This proceeded with chemo- and regioselectivity, however, bromination occurred at the undesired C6 position to give 308. Finally, attempts to effect ortho-directed lithiation and subsequent formylation with DMF were unsuccessful, presumably due to competing lithiation of the allyl phenyl ether and potential addition of n-butyl lithium (⁶BuLi) to the phthalate esters.

![Scheme 4.18. Attempted C4 functionalisation of benzene 307.](image)

Given the reactivity of the allyl ether in these attempted functionalisation’s, and that phenols engender greater regioselectivity in the iodination reaction, the halogenation was attempted prior to installation of the allyl group (Scheme 4.19). In these cases, both iodination and bromination of phthalate 302 proceeded to give a single regioisomer, however, single crystal X-ray diffraction of aryl bromide 309 determined C6 as the site of bromination and, iodination in the case of 310, based on comparison of their ¹H NMR spectra (Figure 4.5).

![Scheme 4.19. Halogenation of arene 302.](image)
To achieve site-selective C4 functionalisation and ultimately access the required cinnamate scaffold a new route was devised. Closer inspection of the literature surrounding aromatic ether protecting group strategies revealed a host of procedures which enable selective mono-demethylation of electronically distinct bis-methylaryl ethers.\textsuperscript{26} Notably, selective deprotection of methyl ethers with a neighbouring carbonyl group (i.e. 311$\rightarrow$312, Scheme 4.20, eq. 1)\textsuperscript{26c} is possible, which is the case with the proposed aromatic fragment. With this in mind, we reasoned that selective demethylation of a bis-methyl ether would preclude the requirement for orthogonal protection and enable the synthesis of a suitable cinnamate (i.e. 313) after methylation and Heck coupling from resorcinol 259.

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node at (0,0) {311};
\node at (3,0) {312};
\node at (0,-3) {259};
\node at (3,-3) {313};
\draw[arrow] (0,0) -- (3,0) node[midway,above] {LICl, DMF, $\mu$W, 100 $^\circ$C 0.5 h 49\% yield};
\draw[arrow] (0,-3) -- (3,-3) node[midway,above] {Heck};
\end{tikzpicture}
\end{center}
\caption{Selective demethylation of aryl ether 311 and revised strategy for synthesis of 313.}
\end{scheme}
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To this end, exposure of cyclohexanedione 304 to trimethylsilyltrifluoromethane sulfonate (TMSOTf) and triethylamine provided bis-silyl ether 314 which was used directly in a Diels-Alder reaction with DMAD (Scheme 4.21). After expulsion of ethylene and hydrolysis, resorcinol 315 was obtained in 68% yield over 2 steps. Next, procedures reported by Hathaway25 effected regioselective iodination at C4 to give aryl iodide 259 in 85% yield. Finally, treatment with iodomethane and K₂CO₃ delivered the corresponding aryl iodide 316 in 54% yield. Notably, upon exposure of 259 to K₂CO₃ the reaction mixture became increasingly yellow over time, suggesting the presence of free iodine. This observation, coupled with the isolation of the deiodinated arene 317 from the reaction mixture, is indicative of a base-mediated deiodination which provided a rationale for the moderate yield.


With aryl iodide 316 in hand, a Heck coupling with tert-butyl acrylate was explored. The tert-butyl derivative was selected initially to facilitate selective hydrolysis in the presence of methyl esters in the subsequent step. Traditional conditions utilising palladium acetate with or without a phosphine ligand or under aqueous conditions provided unsatisfactory yields of cinnamate 318, with unreacted starting materials isolated (Table 4.1, entries 1-3). These observations are indicative of catalyst decomposition, a consequence of the elevated temperatures required for oxidative addition to hindered aryl halides (i.e. 316).29

Fortunately, Ying and co-workers have developed a new robust palladacycle IMes-Pd(dmba)Cl for catalysis of the Heck reaction, that is stable at high temperatures and tolerates hindered substrates.30 When applied to the Heck coupling of aryl iodide 316 with tert-butyl acrylate, their conditions provided cinnamate 318 with an increased yield (19%), albeit with significant decomposition (Table 4.1, entry 4).
Pleasingly, by reducing the reaction time to 6 hours, decomposition was suppressed and cinnamate 318 was isolated in 71% yield (Table 4.1, entry 5).

### Table 4.1: Heck coupling of aryl iodide 316 with tert-butyl acrylate.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield 318(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol% Pd(OAc)(_2), 20 mol% PPh(_3), Et(_3)N, DMF, 140 °C, 16 h</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>10 mol% Pd(OAc)(_2), Et(_3)N, DMF, 140 °C, 16 h</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>10 mol% Pd(OAc)(_2), TBAB, Na(_2)CO(_3), H(_2)O, 100 °C, 16 h</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>4 mol% IMes-Pd(dmba)Cl, K(_2)CO(_3), NMP, 120 °C, 16 h</td>
<td>19%</td>
</tr>
<tr>
<td>5</td>
<td>4 mol% IMes-Pd(dmba)Cl, K(_2)CO(_3), NMP, 120 °C, 6 h</td>
<td>71%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield following flash column chromatography.

With cinnamate 318 in hand, all that remained was conversion to the corresponding acyl fluoride 210n. Thus, selective hydrolysis of the tert-butyl ester using trifluoroacetic acid\(^{31}\) provided carboxylic acid 319 before fluorination with DAST delivered the desired acyl fluoride 210n in 60% yield over 2-steps (Scheme 4.22).

### Scheme 4.22. Synthesis of α,β unsaturated cinnamoyl fluoride 210n.

Unfortunately, when acyl fluoride 210n was exposed to NHCB\(_9\)n in the presence of DA-cyclobutane 216e, the desired β-lactone 220ag was not observed. Instead, aldehyde 320 was isolated as the major reaction product (Scheme 4.23). Premature enolate quenching leading to aldehyde 320 is commonly observed when acyl fluorides bearing electron withdrawing β-aryl substituents are employed in the (4+2) annulation. However, in these reactions, the corresponding β-lactones were still isolated, albeit with reduced yields and enantioselectivity. Given that 2,6-disubstituted acyl fluorides have been established as viable, although
not ideal, substrates for (4+2) annulation, these results presumably relate to the highly electron withdrawing nature of the phthalate esters. In keeping with previous, and indeed later observations (see Scheme 4.9 and Chapter 5, Scheme 5.10), we suspect that this substitution pattern slows the rate of the asynchronous (2+2) aldol/lactonisation process and allows non-productive pathways to dominate.

![Scheme 4.23](image)

Scheme 4.23. (4+2) annulation of α,β-unsaturated cinnamoyl fluoride 210n.

### 4.5.2 Acyl fluorides without electron withdrawing substituents

If the previously described reaction failed due to the presence of the two ester groups then we reasoned that global reduction of the phthalate esters and etherification would eliminate enable the synthesis of β-lactone suitable for elaboration to the natural product. Due to the presence of reducible functionality on both acid 319 and acyl fluoride 210n, the synthesis of this material commenced with the previously prepared aryl iodide 316. Upon treatment of 316 with lithium aluminium hydride (LiAlH₄), global reduction of the phthalate moiety proceeded, however, as an unforeseen consequence, this also resulted in complete reduction of the iodide to give diol 321 in 93% yield (Scheme 4.24).

In our previous studies, the presence of phthalate esters in addition to an allyl ether, complicated the lithiation and formylation of the C4 position (see Scheme 4.18). Given that the newly formed arene 321 is free of these functional groups, we proposed that with appropriate protection of the benzylic alcohols, lithiation and formylation may be possible. To investigate such a scenario, two derivatives 322a and 322b bearing benzyl and methyl ethers respectively, were prepared by treatment of diol 321 with benzyl bromide or iodomethane in the presence of sodium hydride. Unfortunately, subsequent formylation of 322a and 322b using n-BuLi and DMF was not viable, with only trace amounts of the desired benzaldehydes 323a and 323b observed in addition to uncharacterisable decomposition products. It was suspected that in these cases, formylation is complicated by competing lateral lithiation at benzylic positions.32

To suppress lithiation at the benzylic positions, sterically demanding tert-butyl dimethyl silyl (TBS) ether protection was examined. To this end, bis-silyl ether 322c was synthesised from diol 321 by silylation with TBSCI mediated by imidazole\(^3\) (Scheme 4.25). Gratifyingly, this strategy was successful and enabled the desired C4 formylation, with the corresponding benzaldehyde 323c isolated in 51% yield. As described previously, the procedures for Doebner-modified Knovenagel condensation and fluorination with DAST were applied to deliver the desired \(\alpha,\beta\) unsaturated acyl fluoride 210o in 59% yield over two-steps from 323c.

Scheme 4.25. Synthesis of \(\alpha,\beta\) unsaturated acyl fluoride 210o.

With \(\alpha,\beta\)-unsaturated acyl fluoride 210i in hand, its viability in the (4+2) annulation with DA-cyclobutane 216e was assessed. Exposure of these substrates to NHC B9 resulted in isolation of the desired \(\beta\)-lactone 220ah with moderate enantioselectivity (80:20 e.r.), however in poor chemical yield (7%) (Scheme 4.26). It is not clear what leads to the poor yield observed here, however, given that alkyl \(\beta\)-aryl substituents are well tolerated in the (4+2) annulation (see Chapter 3, section 3.3.2), we suspect that the presence of tert-butylidimethyl silyl groups interferes with the concomitant defluorination/desilylation event which
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initiates the reaction. While pleasing that the synthesis of β-lactone 220ah in part supported to prospective synthesis of (+)-bisabosqual, due to time constraints, alternate protecting group strategies were not explored for this scaffold.

![Scheme 4.26.](image)

Our efforts to synthesise pentasubstituted α,β-unsaturated acyl fluorides (i.e. 210n and 210o) were ultimately successful, however, these were poor substrates for the NHC catalysed (4+2) annulation with DA-cyclobutane 216e. Unfortunately, due to the challenges introduced in Model study 2 and 3, the pursuit of bisabosqual A was deemed unviable within the time constraints of these doctoral studies.

### 4.6 Conclusions and outlook

Model studies were carried out to determine the viability of the NHC catalysed (4+2) annulation of DA-cyclobutanes and α,β-unsaturated acyl fluorides toward the synthesis of bisabosqual A. It was shown that β-lactone 220ad (R = H), following dual decarboxylation to give cis-monoester 284 and subsequent cyclisations to close the benzopyran and benzofuran, gave the tetracyclic core of the bisabosquals (Scheme 4.27). Although β-ketoester derived DA-cyclobutanes did not provide β-lactone products, a route for the installation of the alkenyl sidechain was developed via a series of functional group interconversions from cis-monoester 284. Finally, the synthesis of two pentasubstituted α,β-unsaturated acyl fluorides 210n (R = CO₂Me) and 210o (R = CH₂OTBS) and assessment of their reactivity, established that these were poor substrates for the (4+2) annulation. Unfortunately, asthese acyl fluorides were not viable in the reaction, the synthesis of bisabosqual A was abandoned. Although the synthesis of bisabosqual A could not be realised, we recognised that trans-monoester 284 represented a valuable scaffold well-suited to the preparation of simpler, but related cannabinoid natural products. Studies towards this end are described in Chapter 5.
Scheme 4.27 Overview of model studies towards (+)-bisabolosqual A

R = H, 45% yield, 92:8 e.r

Polysubstituted acyl fluorides

R = CO₂Me, 0% yield
R = CH₂OTBS, 7% yield, 80:20 e.r
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4.7 References


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Enantioselective total synthesis of $\Delta^8$- and $\Delta^9$-tetrahydrocannabinol

An enantioselective total synthesis of ($-$)$\Delta^8$-tetrahydrocannabinol (($-$)$\Delta^8$-THC) and ($-$)$\Delta^9$-tetrahydrocannabinol (($-$)$\Delta^9$-THC) has been enabled by the NHC-catalysed (4+2) annulation of donor-acceptor cyclobutanes and $\alpha$$\beta$-unsaturated acyl fluorides. The reaction provides a heavily functionalised cyclohexyl $\beta$-lactone in good yield and with excellent stereochemical integrity. Elaboration of the cyclohexane core into the natural products is achieved over an additional 8 and 10 steps for ($-$)$\Delta^8$-THC and ($-$)$\Delta^9$-THC respectively.

5.1 Introduction

The use of cannabis in traditional medicine dates back thousands of years.\(^1\) Reports of analgesic and sedative properties, amongst others, saw its introduction to Western medicine in the 1830's,\(^2\) before its eventual prohibition in the US (1970) amid concerns related to psychoactivity.\(^3\) The isolation of cannabinoids from female Cannabis sativa in 1964,\(^4\) and elucidation of their structures, triggered intense synthetic and neurobiological investigations. (Figure 5.1). Discovery of the human endocannabinoid
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system revealed the bioactivity of cannabinoids is elicited through binding to G-coupled protein receptors CB₁ and CB₂. Surprisingly, only in the last 2 years has information regarding the mode of binding been elucidated. These discoveries coupled with the relaxation of laws surrounding therapeutic and even recreational use of cannabinoids has sparked a modern era of synthetic chemistry and medicinal interest.

Of the cannabinoids isolated from Cannabis sativa, (−)-Δ⁹-THC (325) has received the most attention from the synthetic community, with over 30 total syntheses reported as of 2018. The tricyclic structure consists of a tetra-substituted aromatic motif (A-ring) and a challenging tertiary alcohol-bearing benzopyran (B-ring) which is trans-fused to the final cyclohexene (C-ring).

![Cannabinoids of Cannabis sativa.](image)

**5.1.1 Synthetic strategies for the synthesis of (−)-Δ⁹-THC**

In almost all synthetic reports, the A-ring is derived from olivetol (326) with the syntheses diverging only with the source of the C-ring fragment and the strategy used to unify them. Early enantiospecific syntheses utilise a chiral pool strategy, with terpene derived C-ring precursors employed to access a hypothetical dication (Figure 5.2a). Brønsted or Lewis acid catalysed condensation with olivetol then gives rise to (−)-Δ⁹-THC (325). C-ring fragments (i.e. 328, 329 and 330) derived from commercially available cyclohexenes have also found use in the synthesis of (−)-Δ⁹-THC (325) through coupling with suitable olivetol derivatives (i.e. 331, Figure 5.2b). Several syntheses employ acyclic materials to construct the C-ring (Figure 5.2c). For instance, diol 332 is prepared through an enantioselective Diels-Alder reaction while others construct the cyclohexene around the aromatic motif using ring closing metathesis (RCM). Of all enantiospecific syntheses reported for (−)-Δ⁹-THC (325), only 5 employ enantioselective methods starting from achiral materials. These approaches are reviewed in detail herein.
5.1.2 Evans’ enantioselective Diels-Alder approach to Δ⁹-THC

In 1997 Evans and co-workers reported the first enantioselective synthesis of Δ⁹-THC from achiral materials (Scheme 5.1). Their strategy features three key disconnections. The first constructs the C-ring using a stereoselective Diels-Alder reaction between commercially available acrylamide 333 and diene 334, catalysed by the Cu(II) BOX complex 335. The cyclohexene adduct 336 was formed in 57% yield as a 73:26 ratio of diastereomers and with excellent enantiopurity (99:1 e.r.). Following functional group interconversion, diol 332 was united with olivetol via an acid catalysed alkylation, which delivered tertiary alcohol 337. Finally, the B-ring was closed using a zinc bromide (ZnBr₂) mediated carbocationic cyclisation, which delivered the unnatural (+)-Δ⁹-THC enantiomer. Evans’ synthesis prepares enantiomerically pure (+)-Δ⁹-THC (325) in 21% yield over 6 steps from commercially available starting materials. Importantly, no protecting group strategies were required and few functional group manipulations were performed.
5.1.3 Trost’s enantioselective allylic alkylation approach to \((-\Delta^9\text{-THC})\)

Ten years separated Evans’ Diels-Alder approach and the second enantioselective synthesis, in this case reported by Trost and Dogra (Scheme 5.2).\(^{134}\) Their synthesis commences with an enantioselective allylic alkylation of with dimethyl malonate with cinnamoyl alcohol (338) using a complex of molybdenum and chiral ligand L2. The resultant malonate 339 was prepared in 95% yield and with excellent regio- and enantioselectivity (98:2 e.r.). Following conversion to the carboxylic acid 340, alkylation with iodide 341 provided diene 342 in good yield, albeit with modest diastereoselectivity. Next, ring closing metathesis (RCM) introduces the C-ring, giving trans-ester 343 in excellent yield with subsequent functional group interconversion providing alcohol 344. Finally, the carbocationic cyclisation developed by Evans was utilised to forge the benzopyran B-ring before deprotection furnished \((-\Delta^9\text{-THC})\) (325). Despite the use of additional functional group manipulations and phenol protection strategies, enantiomerically pure \((-\Delta^9\text{-THC})\) (325) was prepared with a higher overall yield (30%, cf. Evans 21%), however the step count was increased by 7 operations.
Scheme 5.2. Trost’s synthesis of \((−)-\Delta^9\)-THC.

5.1.4 Zhou’s enantioselective hydrogenation approach to \((−)-\Delta^9\)-THC

Unlike the previous syntheses, a 2013 report by Zhou and co-workers describes an approach whereby the C-ring was obtained from commercially available iodide 330 (Scheme 5.3). Zhou’s synthesis features two key disconnections. Firstly, Suzuki coupling of iodide 330 and boronic acid 331a unified the C-ring and the aromatic motif to give enone 345 in 93% yield. Next, the enantioselective hydrogenation catalysed by ruthenium complex 346 delivered alcohol 347 in 98% yield with excellent selectivity (98:2 e.r.). A series of functional group manipulations then generated diol 348, an intermediate from which both \((−)-\Delta^9\)-THC (325) and \((−)-\Delta^8\)-THC (349) isomers are available. Thus, treatment with sodium hydride (NaH) facilitated intramolecular S_{Ar} cyclisation to form the B-ring before deprotection and elimination using p-TsOH furnished \((−)-\Delta^8\)-THC (349). Alternatively, a one pot S_{Ar}/deprotection protocol followed by
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chlorination and elimination with potassium tert-pentoxide provided the \((-)\-\Delta^9\)-THC (325) isomer. Despite a similar step count and yield (30%, 14 steps, cf. Trost 30%, 13 steps), Zhou’s synthesis suffers from multiple protection/deprotection strategies and features a series of transformations that build little molecular complexity (i.e. 347→348).

\(\text{Scheme 5.3. Zhou’s synthesis of } (\text{-})\-\Delta^9\text{-THC and } (\text{-})\-\Delta^9\text{-THC.} \)

5.1.5 Carreira’s stereodivergent approach to \((-)\-\Delta^9\text{-THC}

Inspired by the complex receptor interactions of cannabinoids, Carreira and co-workers developed methodology to access all possible \(\Delta^9\)-THC stereoisomers. They hoped this would enable pharmacological examination of each isomer in earnest and in doing so, further our understanding of the bioactivity of these compounds. Carreira’s approach features 3 key disconnections which resemble those of Trost (Scheme 5.4). Notably, a dual catalytic allylic alkylation with an iridium phosphoramidate complex and Jørgensen/Hayashi catalyst 350 enabled the \(\alpha\)-allylation of aldehyde 351 with olivetol derived allyl alcohol 352. The resultant aldehyde 353 was isolated in 62% yield and with excellent stereochemical integrity (15:1 d.r, 99:1 e.r). Remarkably, each chiral catalyst exerts independent control of one stereocentre, allowing for control of both stereocentres through the selection of the sense of each catalyst. Next, RCM with Grubbs II catalyst forged the cyclohexene 354 in 92% yield before functional group interconversion delivered the known trans-ester 343. Finally, a two-step procedure was developed
for the methylation, deprotection and carbocationic cyclisation which provided $(-\Delta^9$-THC (325) in 8% overall yield (7 steps). Despite lower overall yield, Carreira’s synthesis improves upon Trost’s studies through the development of a highly stereocontrolled $\alpha$-allylation reaction.

Scheme 5.4. Carreira’s synthesis of $(-\Delta^9$-THC).

### 5.1.6 Leahy’s enzymatic resolution approach to $(-\Delta^9$-THC)

The most recent enantioselective synthesis of $(-\Delta^9$-THC (325) was reported in 2018 by Leahy and co-workers and features key disconnections similar to Carreira. Starting with olivetol derived $\alpha,\beta$-unsaturated ketone 355, after reduction and enzymatic resolution with Savinase 12T alcohol, allylic alcohol 356 was obtained in 38% yield and 99:1 e.r (Scheme 5.5). Next, esterification of carboxylic acid 357 with 356 followed by silylketene acetal fromation allowed for a diastereoselective Ireland-Claisen rearrangement to occur, with carboxylic acid 358 obtained in 72% and with complete diastereoselectivity. After esterification using trimethylsilyl diazomethane, the RCM and cyclisation protocols developed by Carreira were applied to furnish $(-\Delta^9$-THC (325) in 10% yield over 13 steps.
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Scheme 5.5. Leahy’s synthesis of (−)-Δ⁹-THC.

5.2 Synthetic strategy for (−)-Δ⁹-THC

5.2.1 Retrosynthetic analysis of (−)-Δ⁹-THC

Our own approach to (−)-Δ⁹-THC (325) stems from the recognition that NHC catalysis enables potentially valuable (4+2) annulations which generate highly enantioenriched cyclohexanes and, which we believe, are suitable C-ring precursors. Retrosynthetic analysis of (−)-Δ⁹-THC (325) led to the identification of trans-343, a known (−)-Δ⁹-THC (325) precursor that we proposed is accessible through dual decarboxylation from β-lactone 220ai (Scheme 5.6). Thermal decarboxylation of the β-lactone would introduce the alkene whilst concurrent Krapcho decarboxylation would provide the mono-ester and establish the diastereomeric configuration. Finally, the entire synthetic strategy is underpinned by the synthesis of enantiopure β-lactone 220ai which should be available through an enantioselective NHC catalysed (4+2) annulation with appropriate substrates (i.e. 216n and 210p or 359a and 360a).
**5.2.2 NHC catalysed (4+2) annulations**

Specifically, two candidate NHC catalysed (4+2) annulations were targeted which generate cyclohexyl fused β-lactones (i.e. 220ai). The first involves the coupling of donor-acceptor cyclobutane 216n with α,β-unsaturated acyl fluoride 210p using conditions discussed in Chapter 3 (Scheme 5.7, eq. 1). The second is an analogous transformation reported by Studer utilising α,β-unsaturated aldehyde 360a and methyl ketone 359a in the presence of homochiral NHC B10 and an oxidant 83 (Scheme 5.7, eq. 2). In Studer’s reaction, only a single example was reported, with the viability of alternate substrates currently unknown.
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5.2.3 Objectives

The ultimate objectives of this study are to implement the proposed enantioselective NHC catalysed (4+2) annulation reactions in the synthesis β-lactone 220ai, and, if successful, to execute the synthesis of (−)-Δ⁹-THC (325). In doing so, we hope to expand the scope of enantioselective syntheses of (−)-Δ⁹-THC (325), in addition to the scope of complex targets available using NHC catalysed cascade reactions. Key to our investigation is the synthesis of methyl bearing DA-cyclobutane 216n and acyl fluoride 210p, and the application of these substrates in the subsequent coupling. The reaction must provide synthetically practical yields of enantioenriched β-lactone 220ai to allow elaboration to the natural product. In an analogous fashion, the preparation and application of ketone 359a and aldehyde 360a for Studer’s variant will be examined.

5.3 Preliminary investigations of the strategy

5.3.1 Synthesis of (−)-normethyl-Δ⁹-THC (361)

Studies commenced by examining our general strategy with the synthesis of (−)-normethyl-Δ⁹-THC (361). To enable this, the proposed α,β-unsaturated acyl fluoride 210p was synthesised from olivetol (326), which could be sourced commercially ($8 USD per gram, Combi-Blocks). The synthesis commenced with protection of 326 as the known bis methyl ether 362[15] by treatment with iodomethane (MeI) under basic conditions (Scheme 5.8). Formylation with n-butyllithium and N,N-dimethylformamide then afforded aldehyde 363 which was subsequently converted to the corresponding carboxylic acid 364 following Doebner-modified Knoevenagel condensation with malonic acid.[16] Finally, treatment with DAST delivered the desired α,β-unsaturated acyl fluoride 210p in 83% yield.[17]

In contrast to previously synthesised polysubstituted acyl fluorides, which generated the expected products in 7% yield at best (see Chapter 4, section 4.1), annulation of acyl fluoride 210p with DA-cyclobutane 216e proceeded smoothly to give β-lactone 220aj in 45% yield and with 98:2 e.r. The modest yield of β-lactone 220aj is consistent with the use of 2,6-dimethoxy substituted acyl fluorides as discussed in Chapter 4 (section 4.3.1).[18] Nevertheless, Krapcho decarboxylation [19] with concomitant decarboxylation of the β-lactone gave rise to cyclohexene cis/trans-365 as a 2:1 cis/trans mixture. Pleasingly, cis-365 could be converted to the desired trans-365 using a base-mediated epimerisation as reported by Trost.[13d] Finally, conditions developed by Carreira effected exhaustive methylation, deprotection of the aryl methyl ethers, and carbocationic cyclisation to deliver enantiopure
(-)-normethyl-Δ9-THC (361) in 9% overall yield (9-steps). This synthesis represents the only direct and regioselective route to 361, with only two prior syntheses are reported; both generate 361 as a mixture of alkene isomers and, in one case, as an undesired side-product.\textsuperscript{20}


With (-)-normethyl-Δ9-THC (361) in hand, the spectroscopic data were compared with those found in the literature. Despite the compound appearing in several publications, only the report by Wilson and May\textsuperscript{20b} contained spectral data. Pleasently, the $^1$H NMR spectrum derived from (-)-normethyl-Δ9-THC (361) synthesised in these studies, matched closely with the partial $^1$H NMR analysis detailed in this literature (Figure 5.3 and Table 5.1). The downfield area (δ 160-105 ppm) of the JMOD $^{13}$C NMR spectrum contained the 8 required signals indicating the presence of an aromatic ring and an endocyclic olefin. Moreover, the phasing pattern (four positive and four negative signals) is indicative of four methine and four fully substituted carbon centres. The upfield region contains a peak at 77.4 ppm which is characteristic of deshielding by the adjacent benzopyran oxygen and the negative phasing supports a fully substituted carbon. Additionally, the required 11 aliphatic signals with correct phasing are present. Finally, the presence of the phenol is supported by a broad signal at 3300 cm\textsuperscript{-1} in the IR spectrum whilst the HRMS
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is consistent with the proposed structure (m/z Found: (M+H)^+, C_{20}H_{28}O_{2}, 301.2159, requires 301.2162.)

**Figure 5.3.** ^1^H- and ^13^C NMR spectra of normethyl-Δ^9^-THC (361) in CDCl₃ (400 and 100 MHz)

### 5.4 Introduction of C9-methyl group via (4+2) annulation

#### 5.4.1 Synthesis of a methyl substituted DA-cyclobutane

Having demonstrated the viability of the general strategy, efforts were directed towards introduction of the C9-methyl group using methyl substituted DA-cyclobutane 216n was targeted. To prepare this substrate, studies commenced with exposure of methylene malonate 224b and enol ether 223g to zinc bromide (ZnBr₂) at low temperature, conditions analogous to those used for the desmethyl variant (i.e. 216e). Unfortunately, none of the desired DA-cyclobutane was observed and only malonate 359a could be isolated from the reaction mixture (Table S2, entry 1).

The isolation of 359a implicates the formation of the desired cyclobutane 216n which is subsequently cleaved by ZnBr₂. When the reaction temperature or the catalyst loading were decreased to

<table>
<thead>
<tr>
<th>Proton</th>
<th>Reference δ (ppm)</th>
<th>Experimental δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(^{13})</td>
<td>6.61 10.0, 2.0</td>
<td>6.62 10.0, 2.1</td>
</tr>
<tr>
<td>H(^2)</td>
<td>6.25 1.4</td>
<td>6.28 1.5</td>
</tr>
<tr>
<td>H(^3)</td>
<td>6.10 1.5</td>
<td>6.13 1.5</td>
</tr>
<tr>
<td>H(^4)</td>
<td>5.65 10.0</td>
<td>5.66 10.0, 3.2</td>
</tr>
<tr>
<td>OH</td>
<td>4.98 -</td>
<td>4.77 -</td>
</tr>
<tr>
<td>H(^{13})</td>
<td>3.24 10.0</td>
<td>3.26 11.0</td>
</tr>
<tr>
<td>C(^{13})Me</td>
<td>1.41, 1.09 -</td>
<td>1.42, 1.10 -</td>
</tr>
<tr>
<td>H(^{15})</td>
<td>0.82 7.0</td>
<td>0.88 6.6</td>
</tr>
</tbody>
</table>
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suppress this undesired cleavage, a similar outcome was observed (Table 5.2, entries 2 and 3). Given the apparent propensity for ring opening, a more stable silyl ether was trialled. Unfortunately, even the slightly more stable TES enol ether 223h failed to react with 224b (Table 5.2, entry 4). Increasing reaction time to allow conversion of these substrates gave only trace amounts of the cleaved product 359a (Table 5.2, entry 5). Finally, a range of Lewis acids known to promote related (2+2) cycloadditions were also applied however, in these reactions, the desired cyclobutane was never observed under any circumstances (Table 5.2, entries 6-10).

Table 5.2. Attempted synthesis of DA-cyclobutane 216n.

<table>
<thead>
<tr>
<th>entry</th>
<th>mol% LA</th>
<th>R</th>
<th>temp.(°C)</th>
<th>result&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 mol ZnB&lt;sub&gt;2&lt;/sub&gt;</td>
<td>SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>−78</td>
<td>0% 216n, 25% 359a</td>
</tr>
<tr>
<td>2</td>
<td>100 mol ZnB&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&quot;</td>
<td>−100</td>
<td>0% 216n, 21% 359a</td>
</tr>
<tr>
<td>3</td>
<td>50 mol% ZnB&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&quot;</td>
<td>−78</td>
<td>0% 216n, 17% 359a</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>SiEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&quot;</td>
<td>N/R</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>trace 359a</td>
</tr>
<tr>
<td>6</td>
<td>10 mol% FeCl&lt;sub&gt;3&lt;/sub&gt;•Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>−78</td>
<td>&quot;</td>
</tr>
<tr>
<td>7</td>
<td>5 mol% Tf&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>8</td>
<td>10 mol% Yb(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>9</td>
<td>10 mol% AlCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>10</td>
<td>10 mol% AlMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield of 359a following flash column chromatography. <sup>b</sup>Trace quantities and complex mixtures observed in the <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup>Reaction conducted for 6 h.

While product 359 potentially implicates formation of the desired cyclobutane, it could not be isolated or even observed by <sup>1</sup>H NMR analysis of the crude reaction mixture. Given these difficulties, attempts to install the C9-methyl group using this route were abandoned and attention was directed towards examining Studer’s variant of the (4+2) annulation.

5.4.2 Aryl 2,6 disubstitution of in Studer’s (4+2) annulation

To probe the viability of 2,6-disubstituted cinnamaldehydes in Studer’s (4+2) annulation, methyl ketone 359 and α,β-unsaturated aldehyde 360b were identified for model studies. Methyl ketone 359 was
prepared in 64% yield via potassium carbonate (K₂CO₃)-mediated 1,4-addition of dimethyl malonate (366) to methyl vinyl ketone (367) (Scheme 5.9, eq. 1). After formylation of 1,3-dimethoxybenzene (276), a one-pot Wittig/deprotection procedure was developed for the efficient conversion of benzaldehyde 277 to α,β-unsaturated aldehyde 360b in 96% yield.

Scheme 5.9. Synthesis of model acyl fluoride 360b and methyl ketone 359.

With key substrates in hand, their viability in the proposed (4+2) annulation was examined. Exposure of 359a and 360b to conditions reported by Studer failed to produce the desired β-lactone. Instead, cinnamate ester 368 was the sole product (Table 5.3, entry 1). Given that the mechanism of Studer’s annulation is likely to resemble our (4+2) annulation, we next trialled conditions which were found to be favourable in the latter reaction (see Chapter 3, section 3.2).

Unfortunately, when the reaction was conducted at higher temperatures, as used in our work, a similar outcome was observed (Table 5.3, entry 2). The reaction was also repeated using potassium hexamethyl disilazide to generate the NHC, however this did not improve the outcome (Table 5.3, entry 3). Finally, utilising the solvent system which was successful in our reaction was found to be incompatible, even at elevated temperatures, with substrates returned unchanged (Table 5.3, entries 4 and 5). In these cases, it is possible that solvation of lithium chloride (LiCl) by the solvent system prevents activation of the malonate to liberate methoxide, thereby suppressing formation of cinnamate ester 368.18b
Table 5.3: Selected optimisations of Studer’s (4+2) annulation.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>T (°C)</th>
<th>solvent</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>rt</td>
<td>CH₂Cl₂</td>
<td>20% 368</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>40</td>
<td>&quot;</td>
<td>23% 368</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS</td>
<td>&quot;</td>
<td>&quot;</td>
<td>14% 368</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>9:1 THF:DMF</td>
<td>N/R</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>80</td>
<td>&quot;</td>
<td>N/R</td>
</tr>
</tbody>
</table>

*a* Isolated yield of 368 following flash column chromatography.

Isolation of cinnamate ester 368 from a number of reactions suggests that the α,β-unsaturated acyl azolium 369 intermediate is forming, however, it reacts through non-productive pathways (Scheme 5.10). Mechanistically, Studer proposes that 1,4-addition of enolate 370 to α,β-unsaturated acyl azolium 369 followed by an asynchronous (2+2) aldol/lactonisation process delivers the β-lactone products. Given that 1,4-addition is a reversible process, it is possible that unfavourable steric interactions slow the subsequent (2+2) process (371 → 220ad) an allow competing transesterification of the acyl azolium (370 → 368) to predominate. In this case, transesterification occurs via methoxide liberated from addition to the malonate esters. This is consistent with side-reactivity observed where 2,6-substituted α,β-unsaturated acyl azoliums were used in the analogous reaction of acyl fluorides and DA-cyclobutanes (Chapter 4, Scheme 4.9).

Scheme 5.10. Application of Studer’s (4+2) annulation.
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5.4.3 Silicon free acyl fluoride activation

Concurrent to these studies, research within our group revealed that α,β-unsaturated acyl fluorides can undergo NHC catalysed reactions with some 1,3-dicarbonyl substrates without silicon masking. For example, malonitrile 372 and α,β-unsaturated acyl fluoride 210b undergo a (3+2) annulation, providing cyclopentyl fused β-lactone 373 upon exposure to NHC B11 (Scheme 5.11, eq. 1). This result suggested that it should be possible to exploit a ketone (i.e. 359) in a direct annulation with the cinnamoyl fluoride 210m to give access to the desired C9-methyl-bearing β-lactone scaffold (i.e. 220) (Scheme 5.11, eq. 2).

Scheme 5.11. Silicon-free acyl fluoride activation

To investigate such a scenario, keto-ester 359b was prepared by 1,4-addition of methylacetoacetate 374 to methyl vinyl ketone 367 in the presence of cerium chloride (Scheme 5.12, eq. 1). This material, rather than the previously discussed malonate was initially examined due to its potential in approaches to other phytocannabinoids. As described previously in Chapter 4, Doebner-modified Knoevenagel condensation of benzaldehyde 277 followed by fluorination with DAST provided the model α,β-unsaturated acyl fluoride 220m.

Scheme 5.12. Synthesis of ketoester 359b and acyl fluoride 210m.
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With methyl ketones 359a and 359b in hand, their viability in the (4+2) annulation with acyl fluoride 210m was examined. When keto ester-derived 359b (R = Me) was exposed to either B9 or achiral C3 in the presence of unsaturated acyl fluoride 210m, no reaction was observed (Table 5.4, entries 1 and 2). Similarly, when malonate derived 359a (R = OMe) was subjected to the same conditions, the reaction also failed (Table 5.4, entries 3 and 4). To promote reactivity, and therefore conversion of the substrates, the series of reactions were repeated at increased temperatures using toluene, however, this did not change the outcome (Table 5.4, entry 5).

Table 5.4: Optimisation of silicon free (4+2) annulation

<table>
<thead>
<tr>
<th>Entry</th>
<th>NHC</th>
<th>R</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C3</td>
<td>Me</td>
<td>THF</td>
<td>N/R</td>
</tr>
<tr>
<td>2</td>
<td>B9</td>
<td>&quot;</td>
<td>&quot;</td>
<td>N/R</td>
</tr>
<tr>
<td>3</td>
<td>C3</td>
<td>OMe</td>
<td>&quot;</td>
<td>N/R</td>
</tr>
<tr>
<td>4</td>
<td>B9</td>
<td>&quot;</td>
<td>&quot;</td>
<td>N/R</td>
</tr>
<tr>
<td>5</td>
<td>C3 or B9</td>
<td>OMe or Me</td>
<td>toluene</td>
<td>N/R</td>
</tr>
</tbody>
</table>

5.5 Late stage introduction of C9-methyl group

5.5.1 Design of alternate strategies for C9-methyl group installation

As all efforts to synthesise a methyl bearing β-lactone were not fruitful, alternate strategies to install the C9-methyl group were developed. Specifically, we revisited the synthesis of (−)-normethyl-Δ⁹-THC (361) and recognised that with appropriate derivatisation of β-lactone 220aj, the C9-methyl group could be introduced. In this regard, two strategies were proposed (Scheme 5.13).

The first strategy invokes a regioselective elimination of alcohol 375a, a known precursor of (−)-Δ⁹-THC (325), which in turn can be prepared via methylmagnesium bromide (MeMgBr) addition to ketone 376a. The ketone 376a should be accessible though oxidation of the alcohol generated by hydroboration/oxidation of (−)-normethyl-Δ⁹-THC (361). If successful, appropriate modification of the
alkyl chain of the acyl fluoride, would also offer a route to pharmaceutical cannabinoid nabilone (376b, R = C(CH₃)₂C₆H₁₃).²⁷

In the second route, the known Δ⁹-THC precursor trans 343, which features in the initial strategy, could be synthesised via Krapcho decarboxylation of malonate 377a with concomitant decarboxylation of the mono-ester. The C9-methyl group can then be introduced via cross-coupling ofenol phosphate 378a with lithium dimethyl cuprate (Me₂LiCu), itself available from β-keto ester 379a. Finally, we envisaged reductive β-lactone cleavage of 220aj and global oxidation of the resultant diol would provide the required β-keto ester 379a.

Scheme 5.13. Alternate strategies for synthesis of (−)-Δ⁹-THC.

5.5.2 Hydroboration/oxidation strategy using (−)-normethyl-Δ⁹-THC

With (−)-normethylΔ⁹-THC (361) available through the previously developed route (Scheme 5.8), its viability in a hydroboration/oxidation protocol was examined. Initial experiments were conducted with 9-BBN (381) to enable the regioselective introduction of the alcohol. When 361 was exposed to one equivalent of 9-BBN in THF, no reaction was observed and the starting material was reisolated unchanged (Table 5.5, entry 1). It is possible that the phenolic functionality was either coordinating or quenching the
borane reagent, hence two and four equivalents of 9-BBN were used, however this failed to promote the reaction (Table 5.5, entries 2 and 3). Repeating the reaction higher temperature to enable conversion of the substrate did not allow the synthesis of 380, though some decomposition was observed (Table 5.5, entry 4). Conducting the reaction in toluene provided a similar outcome, with reflux inducing further decomposition (Table 5.5, entries 5 and 6). Finally, the sterically demanding 9-BBN was substituted with borane dimethylsulfide complex (BH$_3$·SMe$_2$), however no hydroboration products were observed (Table 5.5, entry 7).

**Table 5.5: Attempted hydroboration of (−)-normethyl-Δ$^9$-THC (361)**

<table>
<thead>
<tr>
<th>entry</th>
<th>X equiv.</th>
<th>solvent</th>
<th>T (°C)</th>
<th>result$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF</td>
<td>rt</td>
<td>361 reisolated</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>66</td>
<td>90% 361 reisolated</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>toluene</td>
<td>&quot;</td>
<td>85% 361 reisolated</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>&quot;</td>
<td>110</td>
<td>70% 361 reisolated</td>
</tr>
<tr>
<td>7</td>
<td>4 equiv. BH$_3$·SMe$_2$</td>
<td>THF</td>
<td>rt</td>
<td>87% 361 reisolated</td>
</tr>
</tbody>
</table>

$^a$Reisolation of 361 following flash column chromatography.

Upon closer review of the literature, the inert nature of the alkene in 361 toward hydroboration is unsurprising, with only few examples of the hydroboration of internal 3-phenylcyclohexene motifs reported. These reactions were sluggish, often requiring super-stoichiometric (>10 equivalents) of BH$_3$·SMe$_2$ and extended reaction times (>4 days). In addition, the yields for these reactions are modest, hence, it was decided to examine the enol phosphate cross-coupling strategy.

### 5.5.3 Enol phosphate/cuprate cross-coupling strategy

Investigations into our proposed cross-coupling strategy required the synthesis of a suitable enol phosphate 378b (Scheme 5.14). Having prepared surplus β-lactone 220ad during our studies towards (+)-bisabosqual A (see Chapter 4, Scheme 4.9), studies here were conducted without 4-pentyl substitution on the aromatic ring. Thus, reductive β-lactone cleavage developed previously (see Chapter
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3, Scheme 3.24) allowed conversion of β-lactone 220ad to the corresponding diol 240b. Unfortunately, global oxidation was not viable using either Jones reagent or potassium permanganate, with both procedures leading to complex mixtures. Although formation of acid 382 was suspected based upon 1H NMR analysis of the crude residue, purification from the complex reaction mixture proved difficult. Given the difficulties in executing this oxidation, we envisaged an alternate synthesis of enol phosphate 378b via methanolysis, oxidation and enolisation from β-lactone 220ad.


In regard to subjecting 220ad to methanolysis, derivatisation studies described in Chapter 3 demonstrated that facile transactonisation occurs upon ethanolsysis of β-lactone 220c which results in bicyclic lactone 242a (Scheme 5.15). Presumably this occurs by ethoxide opening of the β-lactone followed by transannular lactonisation however, it was proposed that if the second step in this process could be supressed then it should be possible to isolate alcohol 383a.

Scheme 5.15. Ethanolysis/transactonisation of β-lactone 220c.

Studies commenced with exposure of β-lactone 220ad to sodium methoxide (NaOMe) for one hour, after which TLC analysis revealed the presence of 2 compounds. Pleasingly, analysis of the crude reaction mixture revealed desired the alcohol 383b had indeed formed, albeit, as a minor product alongside the
bicyclic lactone 242b (Table 5.6, entry 1). Upon purification, silica-mediated lactonisation converted the alcohol 383b through the bicyclic lactone 242b, highlighting the propensity for this reaction pathway. Further reduction of the reaction time increased the proportion of alcohol 383b significantly although now incomplete consumption of the β-lactone was observed (Table 5.6, entry 2).

It was hoped that less basic sodium carbonate (Na2CO3) would suppress lactonisation, however, its poor solubility in MeOH prevented any reaction (Table 5.6, entry 3). Pleasingly, more soluble potassium carbonate (K2CO3) allowed the reaction to proceed and with improved selectivity (Table 5.6, entry 4). Given that alcohol/alkoxide reactivity can be affected by ion pairing, we examined the effect of counterions on selectivity. Pleasingly, when the reaction was repeated with a larger caesium counterion, selectivity for alcohol 383b was improved (Table 5.6, entry 5). Conversely, smaller counter-ions (i.e. lithium) resulted in rapid conversion to the lactone 242b (Table 5.6, entry 6). Reducing the reaction temperature also improved the selectivity for 383b (Table 5.6, entry 7), however, all further attempts to optimise using CsCO3 were unsuccessful. Fortuitously, the reaction exhibited a particular sensitivity to the nature of the base, with potassium cyanide (KCN) providing optimal selectivity (Table 5.6, entry 7).

Table 5.6: Selected optimisations for methanolysis of β-lactone 220ad.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>T (°C)</th>
<th>time</th>
<th>ratio* 220a : 383b : 242b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe</td>
<td>rt</td>
<td>1 h</td>
<td>10 : 90 : 0</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.5 h</td>
<td>32 : 50 : 18</td>
</tr>
<tr>
<td>3b</td>
<td>Na2CO3</td>
<td>&quot;</td>
<td>16 h</td>
<td>N/R</td>
</tr>
<tr>
<td>4b</td>
<td>K2CO3</td>
<td>&quot;</td>
<td>1 h</td>
<td>55 : 43 : 2</td>
</tr>
<tr>
<td>5b</td>
<td>CsCO3</td>
<td>&quot;</td>
<td>1 h</td>
<td>60 : 38 : 2</td>
</tr>
<tr>
<td>6b</td>
<td>LiOMe</td>
<td>&quot;</td>
<td>0.5 h</td>
<td>23 : 77 : 0</td>
</tr>
<tr>
<td>7b</td>
<td>CsCO3</td>
<td>0</td>
<td>1.5 h</td>
<td>66 : 33 : 1</td>
</tr>
<tr>
<td>8b</td>
<td>KCN</td>
<td>0</td>
<td>0.75 h</td>
<td>74 : 23 : 3</td>
</tr>
</tbody>
</table>

*a Determined by 1H NMR analysis of the crude reaction mixture. b Monitored closely by TLC for consumption of 220ad and quenched with H2O immediately.

Due to the transannular lactonisation that occurs upon exposure to silica (vide supra), purification was avoided, and the crude mixture of alcohol 383b and lactone 242b was immediately subjected to with 2-iodooxybenzoic acid (IBX). Unfortunately, purification was also hindered at this step due to the presence
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of lactone 242b and a mixture of the keto and enol tautomers (379b and 384, Scheme 5.16). In contrast enol phosphate 378b was easily isolated in 44% yield by telescoping the methanolysis, oxidation, and enolisation and by finally introducing chlorodiethylphosphate to the reaction mixture.

Unfortunately, all attempts to cross-couple enol phosphate 378b with Me₂LiCu were unsuccessful, with no reaction observed at low temperature whilst decomposition and competing side reactions leading to the formation of 385 predominated at elevated temperatures. Although the desired cross-coupled product 377b was suspected based on LCMS analysis of the crude reaction mixture (M+H⁺ = 407.2), it could not be isolated in synthetically viable yields.

![Scheme 5.16. Synthesis and cross-coupling of enol phosphate 378b.](image)

We propose that the formation of diene 385 proceeds through initial 1,4-addition of Me₂LiCu with enol phosphate 378b to give enolate 386 (Scheme 5.17). Subsequent elimination of phosphate would provide the desired product 377b, however, retro 1,4-addition predominates before base-mediated elimination gives the observed diene 385. Stabilisation of carbanion 387 by the malonate and development of extended conjugation in diene 386 are likely key factors driving this pathway.

![Scheme 5.17. Proposed formation of diene 385.](image)
Whilst it is disappointing that both of the revised strategies were not viable, we were encouraged by the formation of keto-ester 379b. An alternate strategy using an intermediate of this type to access the natural product would exploit a dual Krapcho decarboxylation procedure of 379a to generate ketone 389a, with exhaustive methylation providing diol 389 and, after carbocationic cyclisation and elimination, (−)-Δ⁹-THC (325) (Scheme 5.18).

![Scheme 5.18. Proposed strategy for synthesis of (−)-Δ⁹-THC (325) from 379a.]

### 5.5.4 Dual Krapcho decarboxylation strategy

Using the model system, it seemed probable that model β-keto ester 379b, bearing two 1,3-dicarbonyl motifs, could undergo dual Krapcho decarboxylation, thereby generating ketone 388b. Unfortunately, when the β-keto ester 379b was subjected to standard decarboxylation conditions, complete decomposition was observed after 16 h (Scheme 5.19). Fortuitously, simply reducing the reaction time to 2 hours allowed the isolation of ketone cis/trans-388b in 33% yield over 3-steps as a 2:1 (cis : trans) mixture. Intriguingly, the dual Krapcho procedure occurred at an enhanced rate compared to the monocarboxylation described previously, which required upwards of 12 hours reaction time. Potential reasons for this divergence are are discussed later (see Scheme 5.21).

Pleasingly, the undesired cis-388b isomer was amenable to NaOME-mediated epimerisation using conditions exploited previously for the synthesis of ester 365. It was hoped that from trans-388b, application of the Grignard/carbocationic cyclisation procedure would then provide alcohol 375b and subsequently both despentyl-Δ⁹-THC (390) and despentyl-Δ⁸-THC (391) following Zhou's methods. Under the standard conditions, facile elimination gave rise to a mixture of despentyl-Δ⁹-THC (390) and despentyl-Δ⁸-THC (391) isomers in addition to the desired alcohol 375b. It was not possible to suppress elimination, however, the reaction was rendered selective for despentyl-Δ⁸-THC (391) by increasing the reaction temperatures and reaction time (30 h). Finally, conversion of despentyl-Δ⁸-THC (391) to despentyl-Δ⁸-THC (390) was achieved in 68% yield using a two-step procedure involving chlorination with gaseous HCl, and a regioselective elimination with potassium tert-amylate that is directed by the pendant phenolate.
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Scheme 5.19. Dual Krapcho decarboxylation of 379a and synthesis of 390 and 391.

5.5.5 Synthesis of (−)-Δ⁸-THC and (−)-Δ⁹-THC

With the overall strategy established, all that remained was to employ enantioenriched β-lactone 220aj bearing the 4-pentyl chain on the aromatic A ring in the developed sequence. Pleasingly, methanolation, oxidation, dual Krapcho decarboxylation with this substrate proceeded without event to deliver ketone trans-388a in 27% yield after epimerisation, albeit with some erosion of enantiopurity (87:13 e.r) (Scheme 5.20). Nevertheless, Grignard addition, and ZnBr₂ mediated carbocationic cyclisation and elimination was viable with (−)-Δ⁸-THC (3) isolated in 40% yield. Finally, the isomerisation procedure described previously furnished (−)-Δ⁹-THC (325) in 89% yield over two subsequent steps.
With (−)-Δ⁸-THC (325) in hand, it was possible to compare the ¹H NMR (Figure 5.4) and ¹³C NMR (Figure 5.5) data to those reported in the literature. Pleasingly, the spectroscopic data derived from the purified material matched in every respect, that described by Trost¹³d (see Table 5.7 for relevant comparison of ¹³C NMR data). The specific rotation of (−)-Δ⁸-THC (325) prepared here ([α]^{25}_D = -112.0°) was accordingly lower compared to the enantiopure sample ([α]^{25}_D = -152.3°) reported in the same literature and is consistent with the enantiomeric ratio (87:13) determined by chiral HPCL (87:13 e.r) analysis.
Figure 5.5. $^{13}$C NMR spectra of $\Delta^9$-THC (325) in CDCl$_3$ (100 MHz).

Table 5.7. Comparison of $^{13}$C NMR signals from $\Delta^9$-THC (325) derived from Trost's work and the present study.

<table>
<thead>
<tr>
<th></th>
<th>δ &gt;100 ppm</th>
<th></th>
<th>δ &lt;100 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trost's sample</td>
<td>Experimental</td>
<td>Trost's sample</td>
<td>Experimental</td>
</tr>
<tr>
<td>154.8</td>
<td>154.9</td>
<td>77.2</td>
<td>77.3</td>
</tr>
<tr>
<td>154.1</td>
<td>154.3</td>
<td>45.8</td>
<td>46.0</td>
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<tr>
<td>142.8</td>
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<td>34.5</td>
<td>35.6</td>
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<td>134.6</td>
<td>33.5</td>
<td>33.7</td>
</tr>
<tr>
<td>123.7</td>
<td>123.9</td>
<td>31.5</td>
<td>31.7</td>
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<td>31.3</td>
</tr>
<tr>
<td>109.0</td>
<td>109.2</td>
<td>30.7</td>
<td>30.8</td>
</tr>
<tr>
<td>107.6</td>
<td>107.7</td>
<td>27.6</td>
<td>27.7</td>
</tr>
</tbody>
</table>

The decrease in enantiopurity in the conversion of 379a to 388a is potentially due to retro 1,4-addition chemistry akin to that proposed previously (Scheme 5.17) for the formation of diene 385. Specifically, presuming dealkoxycarbonylation of $\beta$-keto ester 379a generates enolate 392, two pathways may prevail; firstly, protonation and a second dealkoxycarbonylation results in the desired ketone 388a, while a second pathway invokes retro 1,4-addition to give enolate 393, before 1,4-addition regenerates the enolate 392 and provides ketone 388a after an additional decarboxylation event (Scheme 5.21). Through this mechanism, the benzylic stereocentre is becomes sp$^2$ hybridised (i.e. 393), leading to some loss of enantiopurity. Additionally, this resonance between 392 and 393 may explain the rate enhancement observed for the dual Krapcho decarboxylation compared to that of the mono decarboxylation event.
5.5.6 Model studies toward the synthesis of Nabilone

During studies to effect the hydroboration of (−)-normethyl-Δ⁹-THC (361), a pharmaceutical cannabinoid analogue nabilone (376b) was also targeted. Although access to this scaffold through hydroboration was not possible, the route developed here which accesses β-ketoesters 388a and 388b offered new opportunity to explore the synthesis of nabilone. Specifically, a ketal protection/deprotection strategy was envisaged (Scheme 5.22). Thus, protection of model β-ketoester 388b with ethylene glycol in the presence of p-TsOH provided ketal 394 in 78% yield. Unfortunately, when subjected to the forcing conditions for two step methylation, deprotection and carbocationic cyclisation, a complex mixture of products was obtained.

To overcome this, a stepwise sequence utilising milder conditions was assessed. Addition of MeMgl proceeded smoothly to provide tertiary alcohol 395 before methyl ether deprotection mediated by sodium ethyl thiolate (NaSMe), liberated phenol 396 in 89% yield over two steps (Scheme 5.23). Although the desired phenol 396 was initially isolated, rapid transketalisation in deuterated chloroform resulted in quantitative conversion to diol 397. It was hoped that an equilibrium could be established between ketals 396 and 397 and thereby allow in situ resolution to give pyran 398 however, when 387 was subjected to ZnBr₂, none of the desired product was observed. Instead, partial transketalisation and/or elimination resulted in the formation of hemiacetal 399 and suspected products 400 and 401. It is probable a similar
transketalisation operates in the harsh two-step procedure described above, resulting in the complex mixture of products observed.

Scheme 5.23. Stepwise addition, deprotection and cyclisation of 394.

### 5.6 Conclusions and outlook

Several NHC catalysed (4+2) annulations were examined for the construction of the cyclohexyl core en route to (−)-Δ⁸-THC (349) and (−)-Δ⁹-THC (325). Of these, the enantioselective (4+2) annulation of donor-acceptor cyclobutane 216e and α,β-unsaturated acyl fluoride 210p was shown to be most valuable in realising the synthesis. After examination of several strategies to install the C9-methyl group, including use of methyl bearing DA-cyclobutane 216n, hydroboration and enol phosphate coupling, a dual Krapcho decarboxylation procedure was established to access ketone 388a. Subsequent methylation, and carbocationic cyclisation and elimination, generated (−)-Δ⁸-THC (349) in 10-steps from commercially available olivetol, with isomerisation of the alkene providing (−)-Δ⁹-THC (325) in two additional operations. In addition, studies toward the pharmaceutical cannabinoidnablone were presented, however the proposed ketal protection strategy was found to be unviable due to problematic transketalisation.

The outlook of this study centres on analogue development for biological evaluation. Surprisingly, while significant attention has been given to substitution of the aromatic motif and C3, the biology of THC analogues possessing modification at C8 and C6a (Scheme 5.24) is far less studied.⁷ We believe the sequence developed here offers opportunity for substitution of C8 and C6a for normethyl-Δ⁸-THC analogues and C8, C6a, and C9 for Δ⁹-THC analogues.
Scheme 5.24. Proposed nor-methyl-Δ⁹-THC and Δ⁹-THC analogue development

To enable the development of Δ⁹-THC analogues, further optimisation of the sequence may be prudent. To address issues with enantioerosion, examination of its mechanism may inform future directions. By utilising lithium iodide (LiI), iodomethane (MeI) would be liberated upon dealkoxycarbonylation of β-keto ester 379a (Scheme 5.25). If retro 1,4-addition operates, it may be possible to trap the cleaved enolate 393 with MeI under anhydrous conditions to give 402. In addition, if enantioerosion of the product is occurring, this could be determined by resubjecting the ketone 388a itself to the reaction conditions.

Scheme 5.25. Proposed studies for determining mechanism of enantioerosion.
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5.7 References


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Chapter 6. Experimental Section

6.1 General experimental

Proton (^1H) and carbon (^13C) NMR spectra were recorded on a Bruker DRX600 spectrometer operating at 150 MHz for carbon nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei or a Bruker DRX300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Infrared spectra (v_{max}) were recorded on an Agilent Cary 630 FTIR Spectrometer. High resolution mass spectra (HRMS) (ESI) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration.

Analytical chiral HPLC was performed with an Agilent Technologies 1260 HPLC or a Perkin Elmer Series 200 HPLC using either a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. or using a RegisCell™ 5μm column (4.6 mm x 25 cm) obtained from Regis Technologies, Inc. with visualization at, 230, 220 or 210 nm.

Flash column chromatography was performed on silica gel (Davasil LC60A, 40-63 μm silica media) using compressed air. Thin layer chromatography (TLC) was performed using aluminum-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F254 plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with potassium permanganate or vanillin stain followed by heating.

Starting materials and reagents were purchased from Sigma-Aldrich, Merck, Oakwood, Combi-Blocks or Alfa-Aesar and were used as supplied. Diethyl ether (Et₂O) and tetrahydrofuran (THF) and 1,4-dioxane were dried over sodium benzphenone ketyl. Dichloromethane (CH₂Cl₂) was dried by passing over activated alumina. Toluene, acetonitrile and benzene were dried by passing over activated 3 Å molecular sieves. DMF was dried by stirring with calcium hydride overnight before being filtered and distilled under reduced pressure, and stored over 3 Å molecular sieves. DMSO was dried by stirring over activated 3 Å molecular sieves overnight and then distilled under reduced pressure and stored over 3Å molecular sieves. Methanol was dried over and distilled from magnesium methoxide. Anhydrous diglyme was purchased from Sigma-Aldrich and used as supplied. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an atmosphere of nitrogen.

Compounds 210a, 210f-l, 216a, 216f, 216h, 220a, 220b, 220d-j, 220n-p, 220y-aa, 223g, 223h and 243 were prepared by Dr. Alison Levens.


Chapter 6

6.1.1 Preparation of catalysts

Tetrafluoro-l4-borane, 2-(6,6,6,6-pentafluoro-6l8-hexa-1,3,5-triyn-1-yl)-6,7-dihydro-SHpyrrolo[2,1-c][1,2,4]triazol-2-ium salt (B6-HBF₄)¹

Following the procedure by Rovis,¹ a flame-dried RBF under N₂ was charged with 2-pyrrolidinone (10 mmol) and CH₂Cl₂ (50 mL) before trimethylloxonium tetrafluoroborate (10 mmol) was added in one portion. The suspension was stirred for 16 h at room temperature beforepentafluorophenylhydrazine (10 mmol) was added and the mixture stirred for an additional 16 h at this temperature. The CH₂Cl₂ was removed under reduced pressure and the flask heated to 100 °C under vacuum for 2 h before chlorobenzene (50 mL) and triethylorthoformate (20 mmol) were added. The flask was heated to 130 °C for 16 h and then allowed to cool to room temperature before a second portion of triethylorthoformate (20 mmol) was added and the flask heated to 130 °C for an additional 16 h. After cooling to room temperature the mixture was poured into 50 mL of toluene, stirred for 30 minutes and filtered. The resulting solid was washed with toluene and hexanes and triturated (EtOAc and MeOH) to afford the title compound B6-HBF₄ as an ivory solid in 26 % yield.

¹H NMR (300 MHz, acetone-D₆) δ 10.24 (s, 1H), 4.78 (dd, J = 7.5, 7.4 Hz, 2H), 3.42 (dd, J = 7.5, 7.4 Hz, 2H), 3.02 (ddd, J = 15.5, 8.1, 8.1 Hz, 2H) ppm

(1Z,2E)-N₁,N₂-Dimesitylethane-1,2-diimine (SI-1)²

Following the procedure of Delaude,² A round bottom flask was charged with 2,4,6-trimethylaniline (10.1 g, 75 mmol) and isopropanol (50 mL). With vigorous stirring, a solution of glyoxal (4.3 mL, 40% aqueous solution, 38 mmol) was added dropwise. After 16 h, the yellow slurry was filtered and the precipitate washed with water (2 x 50 mL). The solid was dried at 60 °C for 3 h under reduced pressure (0.1 mbar) to afford the title compound SI-1 (12.0 g, 87% yield) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 2H), 6.91 (s, 4H), 2.29 (s, 6H), 2.18 (s, 12 H) ppm

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1,3-Dimesityl-1H-imidazol-3-ium chloride (C3•HCl)$^2$

Following the procedure of Delaude,$^2$ a round bottom flask was charged with diimine SI-1 (9.8 g, 33 mmol), paraformaldehyde (1.0 g, 33 mmol) and EtOAc (120 mL) and heated to 70 °C. A solution of chlorotrimethylsilane (4.2 mL, 33 mmol) in EtOAc (10 mL) was then added dropwise over 30 minutes and the suspension stirred at this temperature for 2 h. The mixture was then cooled to 0 °C before being filtered, and the white precipitate washed with EtOAc (2 x 50 mL) and Et₂O (50 mL). The solid was dried at 60 °C for 3 h under reduced pressure (0.1 mbar) to afford the title compound C3•HCl (9.5 g, 84% yield) as a white crystalline solid.

$^1$H NMR (400 MHz, CDCl₃) δ 10.49 (s, 1 H), 7.75 (s, 2H), 6.99 (s, 4H), 2.33 (s, 6H), 2.13 (s, 12 H) ppm

**Synthesis of B9•HBF₄**

Catalyst B9•HBF₄ was prepared according to the overall sequence shown in the scheme and procedures described below.

$(S)$-3-Amino-2-methyl-4-phenylbutan-2-ol (SI-2)$^3$

Following the procedure of Glorius,$^4$ a 2-necked round bottom flask was charged with methylmagnesium bromide (3.0 M in Et₂O, 131 mL, 391 mmol) and anhydrous diethyl ether (150 mL). L-phenylalanine methyl ester hydrochloride (12.1, 60 mmol) was added portionwise over 20 minutes and the mixture heated to reflux for 3 h. NaOH (1 M, 200 mL) was then added slowly, the slurry filtered through pad of celite and the filtrate was extracted with EtOAc (3 x 200 mL). The combined organics were washed with
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brine, dried (Na$_2$SO$_4$), concentrated under reduced pressure to afford amino alcohol SI-2 (9.5 g, 99% yield) which was used immediately without further purification.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.28 (m, 2H), 7.26-7.15 (m, 3H), 3.03 (dd, $J = 13.6$, 2.6 Hz, 1H, 6H), 2.81 (dd, $J = 11.2$, 2.6 Hz), 2.27 (dd, $J = 13.6$, 11.2 Hz, 1H), 1.31 (s, 3H), 1.21 (s, 3H) ppm

(5)-5-Benzyl-6,6-dimethylmorpholin-3-one (SI-3)$^4$

Following the procedure of Glorius,$^4$ a round bottom flask was charged with amino alcohol SI-2 (9.0 g, 53 mmol), Et$_3$N (9.5 mL, 71 mmol), CH$_2$Cl$_2$ and the mixture cooled to 0 °C. Chloroacetyl chloride (4.7 mL, 56 mmol) was added dropwise and the mixture stirred for 2 h before being quenched by the addition of NH$_4$Cl (40 mL of a saturated aqueous solution). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 100 mL), the combined organics dried (Na$_2$SO$_4$) and then concentrated under reduced pressure. The resultant purple residue was then dissolved in THF (250 mL), cooled to 0 °C and NaH (3.2 g, 60% in mineral oil, 79 mmol) added portionwise over 1 h. The mixture was heated to reflux for 1 h before being cooled and quenched by the addition of NH$_4$Cl (30 mL of a saturated aqueous solution). The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organics dried (Na$_2$SO$_4$), concentrated under reduced pressure and the crude residue purified by flash column chromatography. The title compound SI-3 was obtained in 45% yield as a yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40-7.27 (m, 3H), 7.22-7.16 (m, 2H), 5.62 (bs, 1H), 4.16 (s, 2H), 3.59 (dd, $J = 11.8$, 2.9 Hz, 1H), 2.96 (dd, $J = 13.5$, 2.9 Hz, 1H), 2.40 (dd, $J = 13.5$, 11.8 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H) ppm
(S)-3-Benzyl-5-methoxy-2,2-dimethyl-3,6-dihydro-2H-1,4-oxazine (SI-4)$^4$

Following the procedure of Glorius,$^4$ a round bottom flask was charged with morpholinone SI-3 (800 mg, 3.7 mmol) and CH$_2$Cl$_2$ (20 mL). Trimethylxonium tetrafluoroborate (650 mg, 4.5 mmol) was added in one portion, and the mixture stirred for 16 h at room temperature. The reaction was quenched by the slow addition of NaHCO$_3$ (25 mL of a saturated aqueous solution) before being extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organics were washed with water (20 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure, to afford the title compound SI-4 as a brown solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.25 (m, 4H), 7.24-7.16 (m, 1H), 4.02 (d, $J$ = 1.5 Hz, 2H), 3.65 (s, 3H), 3.47 (ddt, $J$ = 10.1, 3.3, 1.5 Hz, 1H), 2.79 (dd, $J$ = 13.2, 3.3 Hz, 1H), 2.51 (dd, $J$ = 13.2, 10.1 Hz, 1H), 1.28 (s, 3H), 1.17 (s, 3H) ppm

(S)-5-Benzyl-2-(tert-butyl)-6,6-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (B9•HBF$_4$)$^5$

Following the procedure of Lupton,$^4$ an RBF was charged with imidate SI-4 (450 mg, 2 mmol), tert-butylhydrazine hydrochloride (250 mg, 2 mmol) and anhydrous methanol (10 mL). Anhydrous hydrogen chloride (50 µL, 4.0 M solution in 1,4-dioxane, 0.2 mmol) was then added and the mixture stirred for 12 h at room temperature before being concentrated to afford the crude amidrazone. The crude material was suspended in chlorobenzene and triethylorthoformate (2.6 mL, 16 mmol) and anhydrous hydrogen chloride (0.5 mL, 4.0 M solution in 1,4-dioxane, 2 mmol) were added. The vessel was sealed and heated to 120 °C for 1 h, before the solvent was removed under reduced pressure and the crude residue purified by flash column chromatography. The resulting residue of B9•HCl was then taken up in CH$_2$Cl$_2$ (5 mL) and sodium tetrafluoroborate (1.1 g, 10 mmol) was added. The suspension was stirred for 2 h at room temperature before being filtered, and the filtrate concentrated under reduced pressure. The resulting
white solid was recrystallised via trituration with CH₂Cl₂ and EtOAc to afford the title compound B9-HBF₄ (412 mg, 46% yield) as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.38-7.35 (m, 3H), 7.04-7.01 (m, 2H), 5.09 and 4.93 (ABq, J = 17.1 Hz, 2H), 4.89 (dd, J = 11.6, 4.7 Hz, 1H), 3.39 (dd, J = 13.5, 4.7 Hz, 1H), 2.83 (t, J = 13.5 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.41 (s, 9H) ppm

Synthesis of IMes-Pd(dmba)Cl⁶

Following the procedure of Ying⁶ a two-necked RBF was charged with PdCl₂ (1.0 g, 5.6 mmol), N,N-dimethylbenzylamine (0.9 mL, 4 mmol) and acetonitrile (15 mL). The suspension was heated to reflux until the PdCl₂ had dissolved before finely powdered K₂CO₃ was added in one portion. The mixture was stirred for 20 min at reflux before C₃-HCl (2.0 g, 4 mmol) was added in one portion and reflux continued for 1 h. The mixture was then cooled to room temperature, diluted with CH₂Cl₂ (20 mL), filtered, and the filtrate concentrated under reduced pressure. The crude residue was purified by recrystallization from acetonitrile to afford the title compound IMes-Pd(dmba)Cl (2.5 g, 75% yield) as an off white crystalline solid.

¹H NMR (400 MHz, CDCl₃) δ 7.11 (s, 2H), 6.98 (s, 2H), 6.84-6.77 (m, 4H), 6.70 (td, J = 7.5, 1.2 Hz, 1H), 6.58 (dd, J = 7.5, 1.2 Hz, 1H), 3.53 (s, 2H), 2.45 (s, 6H), 2.43 (s, 6H), 2.29 (s, 6H), 2.22 (s, 6H) ppm
6.2 Experimental section for Chapter 2

6.2.1 Synthesis of α-cyclopropyl aldehydes 145

Ethyl 3,3-diphenylacrylate (155a)\textsuperscript{7}

Following a modified procedure by Teichert,\textsuperscript{7} a flame-dried RBF under N\textsubscript{2} was charged with NaH (0.60 g, 60% w/w in mineral oil, 15 mmol) and THF (20 mL). The suspension was cooled to 0 °C before triethylphosphonoacetate (2.98 mL, 15 mmol) was added dropwise and the mixture allowed to stir for 30 minutes at this temperature. Benzophenone (1.8 g, 10 mmol) in THF (10 mL) was added before the mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with the addition of NH\textsubscript{4}Cl (20 mL, saturated aqueous solution), the phases separated and the aqueous extracted with EtOAc (3 x 15 mL). The combined organics were dried (MgSO\textsubscript{4}), the solvent removed under reduced pressure and the crude material purified by flash chromatography to afford the title compound 155a (1.9 g, 7.4 mmol) as a clear oil.

R\textsubscript{f} 0.4 (3:7, v/v EtOAc : hexanes).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta 7.40-7.29 \) (m, 8H), 7.24-7.20 (m, 2H), 6.37 (s, 1H), 4.05 (q, \( J = 7.2 \) Hz, 2H), 1.11 (t, \( J = 7.2 \) Hz, 3H) ppm

Ethyl (E)-3-(2-bromophenyl)acrylate (155b)\textsuperscript{8}

The title compound was prepared according to the representative procedure for 155a. Following purification by flash column chromatography, the title compound 155b (2.3 g, 70% yield) was isolated as a colourless oil.

R\textsubscript{f} 0.5 (1:4, v/v EtOAc : hexanes).
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\(^1\)H NMR (400 MHz, CDCl₃) δ 8.04 (d, \(J = 16.0\) Hz, 1H), 7.60–7.57 (m, 2H), 7.34–7.29 (m, 1H), 7.24–7.17 (m, 1H), 6.38 (d, \(J = 16.0\) Hz, 1H), 4.27 (q, \(J = 7.2\) Hz, 2H), 1.34 (t, \(J = 7.2\) Hz, 3H) ppm

\(^{13}\)C NMR (100 MHz, CDCl₃) δ 167.0, 143.0 134.7, 133.5, 131.2, 127.8, 125.4, 121.2, 60.8, 14.4 ppm

3,3-Diphenylprop-2-en-1-ol (156a)

\[ \text{O} \quad \begin{array}{c|c}
\text{Ph} & \text{OEt} \\
\hline
\text{Ph} & \text{OH} \\
\end{array} \]

Following a modified procedure by Teichert, the flame-dried RBF under N₂ was charged with acrylate 155a (9.3 mmol) and THF (40 mL). The suspension was cooled to −78 °C before DIBAL-H (21.4 mL, 1 M solution in cyclohexane, 21.4 mmol) was added dropwise and the mixture allowed to stir for 3 h at this temperature. The reaction was quenched with the addition of MeOH (10 mL) and water (10 mL) and the mixture was allowed to warm to room temperature. NaOH (10 mL, 15% w/w) was added dropwise and the mixture filtered before the filtrate was concentrated under reduced pressure. The aqueous layer was extracted with Et₂O (3 x 30 mL) and the combined organics dried (MgSO₄), the solvent removed under reduced pressure and the crude material purified by flash by flash chromatography to afford the title compound 156a (1.3 g, 99% yield) as a yellow oil.

\( R_f 0.2 \) (3:7, v/v EtOAc : hexanes).

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.42–7.38 (m, 2H), 7.37–7.24 (m, 4H), 7.21–7.17 (m, 2H), 7.15–7.12 (m, 2H), 6.19–6.16 (m, 1H), 4.80–4.76 (m, 1H), 4.00–3.96 (m, 2H) ppm

\((E)\)-3-(2-Bromophenyl)prop-2-en-1-ol (156c)

\[ \text{O} \quad \begin{array}{c|c}
\text{Br} & \text{OEt} \\
\hline
\text{Br} & \text{OH} \\
\end{array} \]

The title compound was prepared according to the representative procedure for 156a. Following purification by flash column chromatography, the title compound 156c (1.8 g, 76% yield) was isolated as a colourless oil.

\( R_f 0.3 \) (1:1, v/v EtOAc : hexanes)

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\[ ^1\text{H NMR} \] (300 MHz, CDCl\(_3\)) \& 7.49–7.57 (m, 2H), 7.28–7.22 (m, 1H), 7.12–7.09 (m, 1H), 6.96 (dt, \(J = 15.8, 1.7 \text{ Hz} \, 1\text{H}\)), 6.31 (dt, \(J = 15.8, 5.5 \text{ Hz} \, 1\text{H}\)), (dd, \(J = 5.5, 1.7 \text{ Hz} \, 2\text{H}\)), 4.36 (dd, \(J = 5.5, 1.7 \text{ Hz} \, 2\text{H}\)), 1.68 (br s, 1 H) ppm

\[((1S,2S)-2-Phenylcyclopropyl)methanol (157a)\]^9

 Following a modified procedure by Lorenz,\(^1\) a flame-dried RBF under N\(_2\) was charged with CH\(_2\)Cl\(_2\) (20 mL). The flask was cooled to 0 °C and Et\(_2\)Zn (10 mmol, 1 M in hexanes) was added dropwise followed by the dropwise addition of TFA (5 mmol) in CH\(_2\)Cl\(_2\) (10 mL). The mixture was allowed to stir for 20 minutes at this temperature before CH\(_3\)I (20 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added slowly. Upon stirring for 20 minutes, cinnamoyl alcohol (156b) (10 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added slowly before the mixture was warmed to room temperature and allowed to stir for an additional 30 minutes. The reaction was quenched by the addition of HCl (50 mL of a 0.1 N solution), the layers were separated and the aqueous extracted with Et\(_2\)O (3 x 50 mL). The combined organics were washed with NaHCO\(_3\) (50 mL of a saturated aqueous solution), water (50 mL) and brine (50 mL) before being dried (MgSO\(_4\)), concentrated under reduced pressure and the crude material purified by flash chromatography to afford the title compound 157a (1.3 g, 87% yield) as a yellow oil.

R\(_f\) 0.3 (1:1 EtOAc : hexanes)

\[ ^1\text{H NMR} \] (400 MHz, CDCl\(_3\)) \& 7.30–7.24 (m, 2H), 7.22–7.17 (m, 1H), 7.09–7.01 (m, 2H), 3.63 (ABq, \(J = 11.2, 6.4 \text{ Hz} \, 1\text{H}\)), 3.59 (ABq, \(J = 11.2, 6.4 \text{ Hz} \, 1\text{H}\)), 1.82 (dt, \(J = 8.4, 4.6 \text{ Hz} \, 1\text{H}\)), 1.59–1.54 (s, 1H), 1.48–1.42 (m, 1H), 1.00–0.96 (m, 2H) ppm

\[(2,2-Diphenylcyclopropyl)methanol (157b)\]^11

The title compound was prepared according to the representative procedure for 157a. Following purification by flash column chromatography, the title compound 157b (1.1 g, 59% yield) was isolated as a colourless oil

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Rf 0.3 (1:1 EtOAc : hexanes).

\[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.44–7.17 (m, 10H), 3.48 (dd, \(J = 11.8, 6.6\) Hz, 1H), 3.38 (dd, \(J = 11.8, 7.8\) Hz, 1H), 1.96–2.03 (m, 1H), 1.71 (bs, 1H), 1.40 (dd, \(J = 5.4, 4.8\) Hz, 1H), 1.30 (dd, \(J = 8.6, 4.8\) Hz, 1H) ppm

\((2-(2\text{-Bromophenyl})\text{cyclopropyl})\text{methanol (157c)}\)

![Diagram of the reaction](image)

The title compound was prepared according to the representative procedure for 157a. Following purification by flash column chromatography, the title compound 157c (1.6 g, 68% yield) was isolated as a yellow oil.

Rf 0.3 (1:1 EtOAc : hexanes).

IR \(v_\text{max}\) 3400, 2854, 1456, 1253 cm\(^{-1}\)

\[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.54 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.22 (td, \(J = 7.8, 1.2\) Hz, 1H), 7.05 (td, \(J = 7.6, 1.6\) Hz, 1H), 6.99 (dd, \(J = 7.6, 1.6\) Hz, 1H), 3.75–3.62 (m, 2H), 2.09–2.00 (m, 1H), 1.39–1.29 (m, 1H), 1.05 (dt, \(J = 8.5, 5.3\) Hz, 1H), 0.95 (dt, \(J = 8.7, 5.3\) Hz, 1H) ppm

\[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\) 140.9, 132.6, 127.6(3), 127.6(0), 127.3, 126.2, 66.7, 24.9, 22.5, 11.7 ppm

HRMS (ESI) \(m/z\) Found: (M+H\(^+\)), \(C_{10}H_{13}BrO\), 227.0063, requires 227.0066.

\(\text{trans-2-Phenylcyclopropane-1-carbaldehyde (145a)}\)\(^{12}\)

![Diagram of the reaction](image)

Following the procedure of Finney,\(^{13}\) An RBF was charged with alcohol 157a (2 mmol), IBX (0.84 g, 3 mmol) and EtOAc (15 mL). The suspension was heated to 70 °C and stirred 16 h before it was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the crude material purified by flash chromatography to afford the title compound 145a (111 mg, 38% yield) as a white solid.

Rf 0.3 (1:1 EtOAc : hexanes)
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.13–7.10 (m, 2H), 2.63 (ddd, $J$ =10.6, 5.2, 4.0 Hz, 1H), 2.21–2.15 (dt, $J$ =9.2, 5.2 Hz, 1H), 1.56–1.51 (m, 2H) ppm

2,2-Diphenylcyclopropane-1-carbaldehyde (145b)$^{11}$

The title compound was prepared according to the representative procedure for 145a. Following purification by flash column chromatography, the title compound 145b (142 mg, 59% yield) was isolated as a white solid. 

$R_f$ 0.3 (1:1 EtOAc : hexanes).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.67 (d, $J$ = 6.8 Hz, 1H), 7.43–7.18 (m, 10H), 2.58–2.51 (m, 1H), 2.26 (t, $J$ = 5.2 Hz, 1H), 1.88 (dd, $J$ = 8.2, 5.2 Hz, 1H) ppm

trans-2-(2-Bromophenyl)cyclopropane-1-carbaldehyde (145c)

The title compound was prepared according to the representative procedure for 145a. Following purification by flash column chromatography, the title compound 145c (323 mg, 85% yield) was isolated as a white solid.

$R_f$ 0.5 (1:9 EtOAc : hexanes)

IR $\nu_{max}$ 2854, 1684, 1456, 1253 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.39 (d, $J$ = 4.6 Hz, 1H), 7.57 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.25 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.15–7.08 (m, 1H), 7.04 (dd, $J$ = 7.6, 1.6 Hz, 1H), 2.78 (ddd, $J$ = 11.2, 7.0, 4.2 Hz, 1H), 2.06–2.00 (m, 1H), 1.75 (dt, $J$ = 9.0, 5.0 Hz, 1H), 1.54 (ddd, $J$ = 12.0, 7.0, 5.0 Hz, 1H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 199.7, 138.1, 132.8, 128.7, 127.8, 127.6, 126.3, 32.5, 27.4, 15.2 ppm

HRMS (ESI) $m/z$ Found: (M+H)$^+$, C$_{10}$H$_8$BrO, 224.9913, requires 224.9910.

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trans-2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carbaldehyde (165)

Following a modified procedure of Miyaura, an oven dried pressure tube was charged with Pd(dppf)Cl₂ (65 mg, 0.09 mmol), B₃Pin₂ (0.83 g, 3.3 mmol) and KOAc (0.88 g, 9 mmol) before a septum was attached and the vessel flushed with argon. A solution of aldehyde 145c (0.68 g, 3 mmol) in dioxane (10 mL) was then added and the vessel sealed and heated to 100 °C for 7 h. The mixture was cooled to room temperature, diluted with water (20 mL) and the mixture extracted with EtOAc (3 x 15 mL). The combined organics were dried (MgSO₄), the solvent removed under reduced pressure and the crude material purified by flash chromatography to afford the title compound 165 (0.5 g, 61% yield) as a yellow oil.

R₄0.2 (1:9, v/v EtOAc : hexanes)

¹H NMR (400 MHz, CDCl₃) δ 9.16 (d, J = 5.4 Hz, 1H), 7.82 (dd, J = 7.4, 1.2 Hz, 1H), 7.37 (td, J = 7.6, 1.4 Hz, 1H), 7.23 (td, J = 7.4, 1.0 Hz, 2H), 7.02 (d, J = 7.6 Hz, 1H), 3.25 (ddd, J = 11.8, 7.6 Hz, 4.2 Hz 1H), 1.95–1.87 (m, 1H), 1.70–1.61 (m, 2H), 1.32 (d, J = 1.6 Hz, 12H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 200.4, 1450, 136.4, 131.4, 126.3, 125.0 83.9, 34.3, 26.6, 25.1, 24.9, 14.1 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₆H₁₂BO₃ 273.1654, requires 273.1657

Ethyl (E)-4-(2-(2-formylcyclopropyl)phenyl)but-2-enoate (162a)

Following a modified procedure of Wang, an oven dried pressure tube under N₂ was charged with boronate 165 (0.5 g, 1.8 mmol), KF (0.47 g, 8.1 mmol) and dioxane (5 mL). The suspension was allowed to stir for 20 minutes followed by the addition of ethyl 4-bromocrotonate (0.70 g, 2.7 mmol) and
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6.2.2 SET coupled NHC (4+2) annulation of α-cyclopropyl aldehydes

General procedure for the intermolecular NHC catalysed annulation of cyclopropyl aldehydes

A flame-dried Schlenk flask was charged with B6-BF₄ (0.2 mmol) and solvent (3 mL) followed by the addition of the appropriate base (0.2 mmol). The solution was allowed to stir for 30 min before being subjected to 3 x freeze-pump-thaw cycles. The cyclopropyl aldehydes 145a (0.01 mmol), electrophile (0.1 mmol) and oxidant (0.2 mmol) were then added and the flask sealed and heated at the appropriate temperature and time. The solvent was removed under reduced pressure and the crude reaction mixture subjected to column chromatography.

General procedure for the intramolecular NHC catalysed annulation of cyclopropyl aldehyde

A flame-dried Schlenk flask was charged with B6-BF₄ (0.2 mmol) and solvent (3 mL) followed by the addition of the appropriate base (0.2 mmol). The solution was allowed to stir for 30 min before being subjected to 3 x freeze-pump-thaw cycles. The cyclopropyl aldehyde 162a (0.01 mmol) and oxidant (0.2 mmol) were then added and the flask sealed and heated at the appropriate temperature and time. The
solvent was removed under reduced pressure and the crude reaction mixture subject to column chromatography

6.3 Experimental section for Chapter 3

6.3.1 Synthesis of α,β-unsaturated acyl fluorides 210

(E)-3-(p-Tolyl)acyloyl fluoride (210a)

Following the procedure of Fu,16 to a suspension of trans-4-methyl cinnamic acid 221a (1.62 g, 10 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added diethylaminosulfur trifluoride (1.45 mL, 11 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of NaHCO$_3$ (10 mL of a saturated aqueous solution). The mixture was extracted with CH$_2$Cl$_2$ (3 x 5 mL), the organic phase dried (Na$_2$SO$_4$), concentrated under reduced pressure to give a yellow oil. The crude material purified via flash column chromatography to afford the title compound 210a (0.83 g, 50% yield) as a white solid.

R$_f$ 0.5 (19:1, v/v hexanes : EtOAc)

MP 68-69 °C

IR $\nu_{max}$ 2928, 1782, 1626, 1601, 1568, 1513, 1307, 1270, 1225 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 16.0$ Hz, 1H), 7.46 (AA'BB', $J = 8.4$ Hz, 2H), 7.24 (AA'BB', $J = 8.4$ Hz, 2H), 6.32 (dd, $J = 16.0, 7.2$ Hz, 1H), 2.41 (s, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4 (d, $J = 335.6$ Hz), 151.5 (d, $J = 6.1$ Hz), 142.8, 130.5, 130.0, 128.9, 110.9 (d, $J = 66.7$ Hz), 21.7 ppm

HRMS (ESI) m/z Found: (M−HF+H)$^+$, C$_{10}$H$_9$FO, 145.0644, requires 145.0648

Cinnamoyl fluoride (210b)
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The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210b (0.81 g, 54% yield) was isolated as a white solid.

\[ ^1H \text{NMR} \ 500 \text{ MHz, CDCl}_3 \ \delta \ 7.85 \ (d, J = 16.0 \text{ Hz}, 1 \text{H}), 7.58-7.56 \ (m, 2 \text{H}), 7.48-7.43 \ (m, 2 \text{H}), (dd, J = 16.0, 7.5 \text{ Hz}, 1 \text{H}). \]

\((E)-3-(4\text{-Methoxyphenyl})\text{acyloyl fluoride (210c)}^{17}\)

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210c (2.3 g, 62% yield) was isolated as a white solid.

\[ ^1H \text{NMR} \ 400 \text{ MHz, CDCl}_3 \ \delta \ 7.76 \ (d, J = 16.0 \text{ Hz}, 1 \text{H}), 7.50 \ (AA'BB', J = 8.8 \text{ Hz}, 2 \text{H}), 6.93 \ (AA'BB', J = 8.8 \text{ Hz}, 2 \text{H}), 6.19 \ (dd, J = 16.0, 7.2 \text{ Hz}, 1 \text{H}), 3.85 \ (s, 3 \text{H}) \text{ ppm} \]

\((E)-3-(2\text{-Methoxyphenyl})\text{acyloyl fluoride (210d)}^{17}\)

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210d (1.67 g, 96% yield) was isolated as a colourless oil.

\[ ^1H \text{NMR} \ 400 \text{ MHz, CDCl}_3 \ \delta \ 8.12 \ (d, J = 16.0 \text{ Hz}, 1 \text{H}), 7.51-41 \ (m, 2 \text{H}), 7.02-6.94 \ (m, 2 \text{H}), 6.48 \ (dd, J = 16.0, 7.2 \text{ Hz}, 1 \text{H}), 3.90 \ (s, 3 \text{H}) \text{ ppm} \]

\((E)-3-(2,4\text{-Dimethoxyphenyl})\text{acyloyl fluoride (210e)}^{18}\)
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The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210e (1.12 g, 81% yield) was isolated as a white solid.

Rf 0.5 (7:3, v/v hexanes : EtOAc)

MP 68-69 °C

IR νmax 2950, 1767, 1607, 1561, 1298, 1281, 1212 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 16.0 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 6.52 (dd, J = 8.8, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.34 (dd, J = 16.0, 7.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 164.2, 160.8, 158.5 (d, J = 333.9 Hz), 147.0 (d, J = 6.8 Hz), 131.8, 115.5, 109.2 (d, J = 65.7 Hz), 105.9, 98.4, 55.6 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₁H₁₄FO₃, 211.0759, requires 211.0765.

(E)-3-(3,4,5-Trimethoxyphenyl)acryloyl fluoride (210f)

![Chemical structure of (E)-3-(3,4,5-Trimethoxyphenyl)acryloyl fluoride (210f)]

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210f (0.42 g, 63% yield) was isolated as a white solid.

IR νmax 2940, 2839, 1778, 1578, 1454, 1327, 1199, 1117 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 15.8 Hz, 1H), 6.77 (s, 2H), 6.25 (dd, J = 15.8, 7.2 Hz, 1H), 3.90 (brs, 9 H) ppm

13C NMR (100 MHz, CDCl₃) δ 157.3 (d, J = 337.2 Hz), 153.7, 151.5 (d, J = 5.7 Hz), 141.6, 128.6, 111.2 (d, J = 67.2 Hz), 106.1, 61.1, 56.3 ppm

(E)-3-(4-(Dimethylamino)phenyl)acryloyl fluoride (210g)

![Chemical structure of (E)-3-(4-(Dimethylamino)phenyl)acryloyl fluoride (210g)]

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The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210g (0.12 g, 26% yield) was isolated as a yellow solid.

R<sub>r</sub> 0.5 (4:1, v/v hexanes : EtOAc)

MP 164-165 °C

IR ν<sub>max</sub> 2914, 1769, 1590, 1525, 1227 cm<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 (d, J = 15.6 Hz, 1H), 7.43 (AA'BB', J = 8.8 Hz, 2H), 6.67 (AA'BB', J = 8.8 Hz, 2H), 6.06 (dd, J = 15.6, 7.6 Hz, 1H), 3.06 (s, 6H) ppm

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.5 (d, J = 331.5 Hz), 152.8, 152.1 (d, J = 6.7 Hz), 130.9, 120.9, 111.8, 105.0 (d, J = 66.3 Hz), 40.1 ppm

HRMS (ESI) m/z Found: (M+H)<sup>+</sup>, C<sub>11</sub>H<sub>12</sub>FNO, 194.0973, requires 194.0976

(E)-3-(2-(Benzyl(methyl)amino)phenyl)acryloyl fluoride (210h)

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210h (0.23 g, 30% yield) was isolated as a yellow solid.

R<sub>r</sub> 0.4 (19:1, v/v hexanes : EtOAc)

IR ν<sub>max</sub> 3029, 2949, 1788, 1618, 1595, 1484, 1452, 1214 cm<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.40 (d, J = 16.4 Hz, 1H), 7.57 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.36-7.31 (m, 2H), 7.30-7.25 (m, 3H), 7.12-7.07 (m, 2H), 6.34 (dd, J = 16.4, 8.0 Hz, 1H), 4.12 (s, 2H), 2.69 (s, 3H) ppm

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 157.8 (d, J = 336.0 Hz), 153.8, 149.4 (d, J = 5.7 Hz), 137.6, 132.4, 128.6(2), 128.5(8), 127.7, 127.6, 123.1, 120.7, 111.4 (d, J = 65.6 Hz), 62.2, 41.8 ppm

HRMS (ESI) m/z Found: (M+H)<sup>+</sup>, C<sub>17</sub>H<sub>16</sub>FNO, 270.1286, requires 270.1289

(E)-3-(4-Chlorophenyl)acryloyl fluoride (210i)
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The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210ai (0.92 g, 29% yield) was isolated as a white solid.

R<sub>f</sub> 0.7 (4:1 v/v hexanes:EtOAc)

IR ν<sub>max</sub> 2922, 1784, 1628, 1590, 1491, 1408, 1306, 1217 cm<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, J = 16.0 Hz, 1H), 7.46 (AA'BB', J = 8.4 Hz, 2H), 7.37 (AA'BB', J = 8.4 Hz, 2H), 6.32 (dd, J = 16.0, 6.8 Hz, 1H) ppm

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.8 (d, J = 336.6 Hz), 149.8 (d, J = 6.1 Hz), 137.9, 131.7, 129.9, 129.5, 112.7 (d, J = 67.5 Hz) ppm

HRMS (ESI) m/z Found: (M-HF+H) C₃H₆<sup>35</sup>ClF₂, 166.0107, requires 165.0102

(E)-3-(4-Bromophenyl)acryloyl fluoride (210j)<sup>16</sup>

![Chemical Structure](image)

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210j (2.12 g, 55% yield) was isolated as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d, J = 16.0 Hz, 1H), 7.58 (AA'BB', J = 9.0 Hz, 2H), 7.43 (AA'BB', J = 9.0 Hz, 2H), 6.32 (dd, J = 16.0, 7.0 Hz, 1H) ppm

(E)-3-(1-Tosyl-1H-indol-2-yl)acryloyl fluoride (210k)<sup>19</sup>

![Chemical Structure](image)

The title compound was prepared according to the representative procedure for 210a. Following purification by flash column chromatography, the title compound 210k (0.25 g, 61% yield) was isolated as a white solid.

IR ν<sub>max</sub> 3137, 2921, 1784, 1628, 1372, 1169, 1099, 972, 740, 658 cm<sup>-1</sup>
**6.3.2 Synthesis of DA-cyclobutanes 216**

**(Cyclohexylidenedimethoxy)trimethylsilane** (223a)

Following the procedure of Reiissig, a round bottom flask was charged with sodium iodide (oven-dried, 0.45 g, 3 mmol), triethylamine (9.9 mL, 71 mmol) and dimethylformamide (15 mL). Chlorotrimethylsilane (4.5 mL, 35 mmol) was then added dropwise to the suspension, followed by the dropwise addition of cyclohexanecarboxaldehyde (3.6 mL, 30 mmol). The resulting mixture was then heated to 120 °C for 16 hours to give a brown slurry, which was cooled to room temperature and poured into NaHCO₃ (30 mL of a saturated aqueous solution). The mixture was extracted with hexanes (3 x 30 mL) and the combined organics washed with ice-cold HCl (4 x 30 mL, 1 M aqueous solution) and NaHCO₃ (30 mL of a saturated aqueous solution). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude material was purified by short path distillation (70 °C, 1 mbar) to afford the title compound 223a (5.1 g, 93% yield) as a colourless liquid.
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^1H NMR (500 MHz, CDCl₃) δ 5.99 (m, 1 H), 2.18-2.15 (m, 2H), 1.95-1.92 (m, 2H), 1.55-1.45 (m, 6H), 0.16 (s, 9H) ppm

Trimethyl(vinyloxy)silane (223b)^22

Following the procedure of Denmark,^22 a flame-dried Schlenk flask was charged with anhydrous THF (80 mL) and cooled to 0°C. BuLi (80 mL, 1.6 M solution in hexanes, 128 mmol) was added slowly and the mixture was stirred for 24 hours at room temperature before the solvent was removed under reduced pressure (inert under high vacuum). Anhydrous diglyme (24 mL) was then added slowly and the mixture was again concentrated under reduced pressure (high vacuum). Anhydrous diglyme (50 mL) was then added slowly, before the slow addition of chlorotrimethylsilane (12.2 mL, 96 mmol) to give a white suspension. The mixture was stirred for 12 h at room temperature before being subjected to bulb to bulb distillation, (10→0.1 mbar, with liquid N₂ cooling on the receiving flask). The distillate was purified by redistillation (short path, 100→120 °C oil bath, atmospheric pressure) to afford the title compound 223b (9.41 g, 84% yield) as a colourless liquid.

^1H NMR (400 MHz, CDCl₃) δ 6.40 (dd, J = 13.6, 5.6 Hz, 1 H), 4.44 (dd, J = 13.6, 0.8 Hz, 1H), 0.21 (s, 9H) ppm

trimethyl((2-methylprop-1-en-1-yl)oxy)silane (223c)^23

The title compound was prepared according to the representative procedure for 223a. Following purification distillation (1 mbar, short path, room temperature), the title compound 223c (5.74 g, 80% yield) was isolated as colourless oil.

^1H NMR (400 MHz, CDCl₃) δ 6.00 (sept, J = 1.6 Hz, 1H), 1.59 (dd, J = 1.6 Hz, 3H), 1.54 (dd, J = 1.6 Hz, 3H), 0.16 (s, 9H) ppm
(Cyclopentylidenemethoxy)trimethylsilane (223d)\textsuperscript{24}

![](image1)

The title compound was prepared according to the representative procedure for 223a. Following purification distillation (2 mbar, short path, 50 °C oil bath), the title compound 223d (2.68 g, 79% yield) was isolated as colourless oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 6.16 (p, \(J = 2.0\) Hz, 1H), 2.25-2.22 (m, 2H), 1.66-1.56 (m, 4 H) 0.16 (s, 9H) ppm

(Cycloheptylidenemethoxy)trimethylsilane (223e)

![](image2)

The title compound was prepared according to the representative procedure for 223a. Following purification distillation (0.1 mbar, short path, 40 °C oil bath), the title compound 223e (0.52 g, 55% yield) was isolated as colourless oil.

\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\)) \(\delta\) 6.09-5.97 (m, 1H), 2.34-2.19 (m, 2H), 2.12-1.97 (m, 2H), 1.64-1.39 (m, 9H), 0.16 (s, 9H) ppm

(Cyclooctylidenemethoxy)trimethylsilane (223f)

![](image3)

The title compound was prepared according to the representative procedure for 223a. Following purification distillation (0.1 mbar, short path, 50 °C oil bath), the title compound 223f (0.45 g, 62% yield) was isolated as colourless oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 6.07-5.94 (m, 1H), 2.25-2.12 (m, 2H), 2.05-1.97 (m, 2H), 1.65-1.41 (m, 10H) ppm

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(E)-(Buta-1,3-dien-1-yloxy)(tert-butyl)dimethylsilane (233)²⁵

\[
\begin{align*}
\text{MeCN, } 20^\circ C, 16 \text{ h} & \quad \rightarrow \\
\text{OTBS}
\end{align*}
\]

Following the procedure of Pietruszka,²⁴ a round bottom flask was charged with crotonaldehyde (2.0 mL, 24 mmol), NaI (5.8 g, 39 mmol), Et₃N (5.4 mL, 39 mmol) and anhydrous acetonitrile (25 mL). The reaction vessel was sealed and stirred vigorously for 16 h at room temperature to give a brown slurry. The mixture was extracted with pentane (3 x 40 mL), the organics washed with NaHCO₃ (20 mL of a saturated aqueous solution) before being dried (Na₂SO₄). The organics were concentrated at atmospheric pressure on a rotary evaporator (60 °C water bath, and the resultant oil purified by distillation (short path, 60 °C, 2 mbar) to afford the title compound 233 (2.3 g 52% yield) as a colourless oil.

³¹H NMR (600 MHz, CDCl₃) δ 6.22 (ddd, J = 17.0, 10.8, 10.4 Hz, 1H), 5.73 (dd, J = 11.8, 10.8 Hz, 1H), 5.56 (d, J = 11.8 Hz, 1H), 4.98 (dd, J = 17.0, 2.0 Hz, 1H), 4.81 (dd, J = 10.4, 2.0 Hz, 1H), 0.92 (s, 9H) 0.16 (s, 6H) ppm

Diethyl 2-methylene malonate (224a)²⁶

\[
\begin{align*}
\text{THF, } \Delta, 16 \text{ h} & \quad \rightarrow \\
\text{OEt} & \quad \text{OEt}
\end{align*}
\]

Following the procedure of Waser,²⁷ a flamed dried RBF was charged with diethylmalonate (3.8 mL, 25 mmol), Pr₂NH•TFA (5.4 g, 25 mmol), TFA (0.19 mL, 2.5 mmol), paraformaldehyde (1.5 g, 50 mmol) and THF (40 mL). The suspension was heated to reflux for 2 h, cooled to room temperature and an additional portion of paraformaldehyde (1.5 g, 50 mmol) was added. The suspension was again heated to reflux and stirred for additional 16 h, cooled to room temperature and the solvent removed under reduced pressure. The mixture was diluted with Et₂O (50 mL), filtered through cotton wool into a separating funnel and washed with HCl (2 x 20 mL, 1 M, aq). The organic layer was dried (MgSO₄), concentrated under reduced pressure to afford crude 224a (3.5 g) as a colourless oil, which was used without further purification.

³¹H NMR (400 MHz, CDCl₃) δ 6.51 (s, 2H), 4.28 (q, J = 7.2 Hz, 4H), 1.33 (t, J = 7.2 Hz, 6H) ppm
Dimethyl 2-methylenemalonate (224b)

\[
\text{MeO} \quad \text{O} \quad \text{O} \quad \text{Me} \quad \overset{\Pr_2NH \cdot TFA, 10 \text{ mol\% TFA, paraformaldehyde, THF, } \Delta, 16 \text{ h}}{\longrightarrow} \quad \text{MeO} \quad \text{O} \quad \text{O} \quad \text{Me}
\]

The title compound 224n was prepared according to the representative procedure for 224a and was obtained crude as a colourless oil.

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta 6.65\) (s, 2H), 3.85 (s, 6H) ppm

Diallyl 2-methylenemalonate (224c)

\[
\text{AllylO} \quad \text{O} \quad \text{OAllyl} \quad \overset{\Pr_2NH \cdot TFA, 10 \text{ mol\% TFA, paraformaldehyde, THF, } \Delta, 16 \text{ h}}{\longrightarrow} \quad \text{AllylO} \quad \text{O} \quad \text{OAllyl}
\]

The title compound 224c was prepared according to the representative procedure for 224a and was obtained crude as a colourless oil.

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta 6.59\) (s, 2H), 6.00-5.90 (m, 2H), 5.40-5.35 (m, 2H), 5.29-5.25 (m, 2H), 4.73 (dt, \(J = 5.7, 1.4\) Hz, 4H) ppm

Diisopropl 2-methylenemalonate (224d)

\[
\text{PrO} \quad \text{O} \quad \text{OPr} \quad \overset{\Pr_2NH \cdot TFA, 10 \text{ mol\% TFA, paraformaldehyde, THF, } \Delta, 16 \text{ h}}{\longrightarrow} \quad \text{PrO} \quad \text{O} \quad \text{OPr}
\]

The title compound 225 was prepared according to the representative procedure for 224a and was obtained crude as a colourless oil.

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta 6.47\) (s, 2H), 5.15, (hept, \(J = 6.3\) Hz, 2H), 1.30, (d, \(J = 6.3\) Hz, 12H) ppm

Methyl 2-benzoylacrylate (225)\(^{28}\)

\[
\text{PhOC} \quad \text{CO}_2\text{Me} \quad \overset{\Pr_2NH \cdot TFA, 10 \text{ mol\% TFA, paraformaldehyde, THF, } \Delta, 16 \text{ h}}{\longrightarrow} \quad \text{PhOC} \quad \text{CO}_2\text{Me}
\]
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The title compound 225 was prepared according to the representative procedure for 224a and was obtained crude as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.93–7.82 (m, 1H), 7.65–7.55 (m, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 6.72 (d, $J = 0.6$ Hz, 1H), 6.06 (d, $J = 0.5$ Hz, 1H), 3.77 (s, 2H).

Diethyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216a)

Following a modification of the procedure of Roberts,$^{29}$ to a suspension of ZnBr$_2$ (2.73 g, 16 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) at −78 °C was added a solution of the methylenemalonate 224a (3.57 g, 16 mmol) in CH$_2$Cl$_2$ (30 mL) followed by a solution of trimethylsilyl enol ether 223a (3.51 g, 19 mmol) in CH$_2$Cl$_2$ (30 mL). After stirring at −78 °C for 2 hours, the reaction was quenched by the addition of a cold (−78 °C) solution of pyridine (15.1 mL, 63 mmol) in CH$_2$Cl$_2$ (10 mL). The mixture was allowed to warm to room temperature, then washed with Na$_2$EDTA (2 x 40 mL of a saturated aqueous solution), water (40 mL) and brine (40 mL) before the organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude oil was purified by flash column chromatography on neutralized silica gel to afford the title compound 216a (3.71 g, 66% yield) as a colourless oil.

R$_f$0.3 (19:1, v/v hexanes : EtOAc)

IR $\nu$max 2927, 2854, 1730, 1252 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.45 (brs, 1H), 4.28-4.07 (m, 4H), 2.61 (d, $J = 12.4$ Hz, 1H), 1.69-1.62 (m, 1H), 1.59-1.15 (m, 9H), 1.53 (d, $J = 12.4$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 0.10 (s, 9H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.7, 169.3, 76.6, 61.3, 61.2, 56.7, 41.6, 38.6, 33.9, 30.2, 26.2, 23.0, 22.2, 14.3, 14.2, 0.0 ppm

HRMS (ESI) m/z Found: (M+Na)$^+$, C$_{18}$H$_{32}$O$_6$Si, 379.1908, requires 379.1911
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Dimethyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216b)

\[
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{ZnBr}_2, \text{CH}_2\text{C}l_2, \text{–78 °C}, 2 \text{ h} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{OTMS} \quad \text{OTMS}
\]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216b (0.43 g, 31% yield) was obtained as a viscous oil.

\[R_f 0.4 \text{ (9:1, v/v hexanes : EtOAc)}\]

\[\text{IR } \tilde{\nu}_{\text{max}} 2921, 2851, 1731, 1242 \text{ cm}^{-1}\]

\[\text{\textsuperscript{1}H NMR} (300 \text{ MHz, CDCl}_3) \delta 4.46 \text{ (bres, 1H), 3.71 (s, 6H), 2.63 (d, } J = 12.4 \text{ Hz, 1H), 1.7-1.60 (m, 1H), 1.56 (d, } J = 12.4 \text{ Hz, 1H), 1.51-1.15 (m, 9H), 0.10 (s, 9H) ppm}\]

\[\text{\textsuperscript{13}C NMR} (100 \text{ MHz, CDCl}_3) \delta 172.1, 169.7, 76.8, 56.6, 52.5, 52.3, 41.7, 38.6, 34.0, 30.3, 26.1, 23.0, 22.2, -0.1 \text{ ppm}\]

HRMS (ESI) m/z Found: (M+H)^+, \(C_{16}H_{33}O_2Si\), 329.1772 requires 329.1779

Diallyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216c)

\[
\text{OTMS} \\
\text{ZnBr}_2, \text{CH}_2\text{C}l_2, \text{–78 °C}, 2 \text{ h} \\
\text{OTMS}
\]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216c (0.36 g, 57% yield) was obtained as a viscous oil.

\[R_f 0.8 \text{ (7:3, v/v hexanes : EtOAc)}\]

\[\text{IR } \tilde{\nu}_{\text{max}} 3084, 2926, 2854, 1730, 1649, 1249 \text{ cm}^{-1}\]

\[\text{\textsuperscript{1}H NMR} (400 \text{ MHz, CDCl}_3) \delta 5.93-5.82 \text{ (m, 2H), 5.33-5.31 (m, 1H), 5.29-5.26 (m, 1H), 5.23-5.18 (m, 2H), 4.70 (ABMX\textsubscript{2}J = 14.8, 7.0, 1.4 Hz, 1H), 4.66-4.57 (m, 2H), 4.72-4.54 (ABMX\textsubscript{2}J = 14.8, 7.0, 1.4 Hz, 1H), 4.48 (bres, 1H), 2.65 (d, } J = 12.4 \text{ Hz, 1H), 1.74-1.62 (m, 1H), 1.57 (d, } J = 12.4 \text{ Hz, 1H), 1.55-1.19 (m, 9H), 0.10 (s, 9H) ppm}\]

\[\text{\textsuperscript{13}C NMR} (100 \text{ MHz, CDCl}_3) \delta 171.2, 169.0, 132.2, 132.0, 118.5, 118.3, 76.7, 66.1, 65.9, 56.7, 41.8, 38.6, 34.0, 30.2, 26.2, 22.9, 22.2, 0.0 \text{ ppm}\]

HRMS (ESI) m/z Found: (M+Na)^+, \(C_{26}H_{53}O_2Si\), 403.1909, requires 403.1911
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Diisopropyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216d)

![Chemical Structure]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216d (0.24 g, 22% yield) was obtained as a viscous oil.

Rf 0.2 (19:1, v/v hexanes : EtOAc)

IR νmax 2981, 2922, 2855, 1728, 1250 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 5.05 (sept, J = 6.2 Hz, 1H), 5.03 (sept, J = 6.2 Hz 1H), 4.47 (bs, 1H), 2.60 (d, J = 12.4 Hz, 1H), 1.79-1.67 (m, 1H), 1.60-1.26 (m, 9H), 1.49 (d, J = 12.4 Hz, 1H), 1.26-1.20 (m, 12H), 0.11 (s, 9H) ppm

13C-NMR (100 MHz, CDCl₃) δ 171.2, 168.9, 76.4, 68.8, 68.4, 56.7, 41.6, 38.6, 33.7, 299, 26.2, 23.0, 22.2, 22.0, 21.8, 21.7, 0.0 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₀H₂₆O₂Si, 385.2404, requires 385.2405

Diethyl 2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216d)

![Chemical Structure]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216d (1.41 g, 25% yield) was obtained as a colourless oil.

Rf 0.2 (19:1, v/v hexanes : EtOAc)

IR νmax 2958, 2905, 1730, 1264, 1252, 1193 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 4.75 (td, J = 8.0, 0.8 Hz, 1H), 4.29-4.13 (m, 4H), 2.50 (dddd, J = 11.6, 8.8, 4.4, 0.8 Hz, 1H), 2.20-2.0 (m, 2H), 1.68 (dt, J = 11.6, 9.6 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H) ppm

13C NMR (100 MHz, CDCl₃) δ 170.8, 168.7, 68.8, 61.7, 61.1, 60.9, 28.8, 21.0, 14.3, 14.1, -0.1 ppm

HRMS (ESI) m/z Found: (M+Na)+, C₁₃H₂₄O₆Si, 311.1296, requires 311.1285
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Dimethyl 2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216e)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{OTMS} & \quad \text{ZnBr}_2, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}, 2 \text{ h} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{OTMS} & 
\end{align*}
\]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216d (1.41 g, 38% yield) was obtained as a colourless oil.

Rf 0.4 (7:3, v/v hexanes : EtOAc)

IR \(\nu_{max}\) 2958, 2905, 1730, 1264, 1252, 1193 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.75 (t, \(J = 8.1\) Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.54-2.48 (m, 1H), 2.21-2.10 (m, 2H), 1.74-1.67 (m, 1H), 0.10 (s, 9H) ppm

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.4, 169.3, 69.2, 61.9, 52.4, 28.9, 21.2, 0.0 ppm

HRMS (ESI) m/z Found: (M+H)+, C\(_{11}\)H\(_{27}\)O\(_3\)Si, 261.1149, requires 261.1153

Diethyl 3,3-dimethyl-2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216f)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Et} \\
\text{OTMS} & \quad \text{ZnBr}_2, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}, 2 \text{ h} \\
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{OTMS} & 
\end{align*}
\]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216f (0.83 g, 36% yield) was obtained as a viscous oil.

Rf 0.3 (19:1, v/v hexanes : EtOAc)

IR \(\nu_{max}\) 2956, 2907, 1729, 1250, 1129 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.48 (brs, 1H), 4.26-4.09 (m, 4H), 2.55 (dd, \(J = 12.4, 0.8\) Hz, 1H), 1.58 (d, \(J = 12.4\) Hz, 1H), 1.24 (t, \(J = 7.2\) Hz, 3H), 1.22 (t, \(J = 7.2\) Hz, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.09 (s, 9H) ppm

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.5, 169.1, 76.2, 61.1(4), 61.1(1), 56.6, 37.5, 35.8, 29.0, 21.4, 14.3, 14.1, -0.2 ppm

HRMS (ESI) m/z Found: (M+Na)+, C\(_{13}\)H\(_{28}\)O\(_3\)Si, 339.1596, requires 339.1598

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Diethyl 1-((trimethylsilyl)oxy)spiro[3.7]undecane-2,2-dicarboxylate (216g)

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216g (0.34 g, 32% yield) was obtained as a colourless oil. 

Rf 0.7 (9:1, v/v hexanes : EtOAc) 

IR νmax 2917, 2853, 1728, 1250 cm⁻¹ 

¹H NMR (400 MHz, CDCl₃) δ 4.46 (bres, 1H), 4.30-4.06 (m, 4H), 2.55 (d, J = 12.4 Hz, 1H), 1.77-1.62 (m, 3H), 1.59-1.41 (m, 12H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.11 (s, 9H) ppm 

¹³C NMR (100 MHz, CDCl₃) δ 171.8, 169.3, 77.3, 61.3, 61.2, 56.5, 44.2, 37.3, 34.6, 28.9, 28.3, 27.8, 24.8, 22.7, 22.5, 14.3, 14.2, 0.0 ppm 

LRMS (ESI) m/z Found: (M+Na)⁺, C₂₀H₃₆O₆Si, 407.1, requires 407.2

Diethyl 1-((trimethylsilyl)oxy)spiro[3.6]decan-2,2-dicarboxylate (216h)

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216h (0.15 g, 59% yield) was obtained as a colourless oil. 

Rf 0.6 (9:1, v/v hexanes : EtOAc) 

IR νmax 2981, 2926, 2854, 1723, 1250 cm⁻¹ 

¹H NMR (400 MHz, CDCl₃) δ 4.47 (bres, 1H), 4.28-4.17 (m, 2H), 4.16-3.08 (m, 2H), 2.61 (d, J = 12.4 Hz, 1H), 1.76-1.68 (m, 1H), 1.66-1.29 (m, 11H), 1.57 (d, J = 12.4 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H) ppm 

¹³C NMR (100 MHz, CDCl₃) δ 171.7, 169.3, 77.3, 61.3, 61.2, 59.7, 44.4, 42.2, 34.7, 32.4, 28.9, 28.4, 23.4, 22.8, 14.3, 14.2, 0.0 ppm 

HRMS (ESI) m/z Found: (M+Na)⁺, C₁₉H₃₄O₆Si, 393.2061, requires 393.2068
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Diethyl 2-((trimethylsilyl)oxy)spro[3.3]heptane-1,1-dicarboxylate (216i)

\[
\begin{align*}
\text{OTMS} & \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\text{ZnBr}_2, \text{CH}_2\text{Cl}_2, -78 \degree \text{C}, 2 \text{ h} & \quad \text{EtO}_2\text{C} \quad \text{OTMS}
\end{align*}
\]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216i (0.77 g, 32% yield) was obtained as a colourless oil. 

R, 0.3 (19:1, v/v hexanes : EtOAc)

IR \( \nu_{\text{max}} \) 2954, 2908, 1728, 1250 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.60 (brs, 1H), 4.28-4.09 (m, 4H), 2.60 (d, \( J = 12.4 \) Hz, 1H), 2.04-1.96 (m, 1H), 1.72 (d, \( J = 12.4 \) Hz, 1H), 1.64-1.54 (m, 3H), 1.53-1.44 (m, 4H), 1.25 (t, \( J = 7.2 \) Hz, 3H), 1.24 (t, \( J = 7.2 \) Hz, 3H), 0.10 (s, 9H) ppm

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.3, 168.9, 76.1, 61.1, 61.0, 57.6, 48.7, 40.7, 35.1, 31.8, 25.1, 24.5, 14.2, 14.1, -0.1 ppm

HRMS (ESI) m/z Found: (M+Na)\(^+\), C\(_{17}\)H\(_{36}\)O\(_3\)Si, 365.1758, requires 365.1755

Diethyl 2-((trimethylsilyl)oxy)spro[3.3]heptane-1,1-dicarboxylate (216j)

A round bottom flask was charged with cyclobutane methanol (1.7 g, 20 mmol), pyridinium chlorochromate (8.6 g, 40 mmol), silica (8.6 g) and CH\(_2\)Cl\(_2\) (30 mL). The brown suspension was stirred for 4 h at room temperature before it was filtered through a plug of silica (4 cm x 3 cm), and washed through with CH\(_2\)Cl\(_2\) (20 mL). The organics were concentrated at atmospheric pressure on a rotary evaporator (50 \degree C water bath) to afford crude aldehyde SI-5 which was used without further purification. A round bottom flask was charged with sodium iodide (oven-dried, 0.3 g, 2 mmol), triethylamine (6.6 mL, 47 mmol) and dimethylformamide (15 mL). Chlorotrimethylsilane (3.0 mL, 23 mmol) was then added dropwise to the suspension, followed by the dropwise addition of cyclobutanecarboxaldehyde SI-5 prepared in the last step. The resulting mixture was then heated to 120 \degree C for 16 hours to give a brown slurry, which was cooled to room temperature and poured into NaHCO\(_3\) (20 mL of a saturated aqueous
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solution). The mixture was extracted with pentane (3 x 20 mL) and the combined organics washed with ice-cold HCl (2 x 20 mL, 1 M aqueous solution) and NaHCO₃ (20 mL of a saturated aqueous solution). The organic phase was dried (Na₂SO₄) and concentrated at atmospheric pressure on a rotary evaporator (50 °C water bath) to afford crude enol ether SI-6 which was used without further purification. The title compound was then prepared according to the representative procedure for 216a (at 20 mmol scale). Following flash column chromatography the title compound 216j (0.59 g, 9% yield over three steps) was obtained as a colourless oil.

R₇0.3 (9:1, v/v hexanes : EtOAc)

IR ν_max 2981, 2959, 2936, 1730, 1251, 1109 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 4.49 (brs, 1H), 4.24-4.09 (m, 4H), 2.64 (dd, J = 12.0, 0.8 Hz, 1H), 2.44-2.35 (m, 1H), 2.00-1.86 (m, 3H), 1.84-1.65 (m, 2H), 1.71 (d, J = 12.0 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.16 (s, 9H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 169.0, 75.2, 61.2, 61.1, 58.5, 45.7, 34.7, 32.9, 27.8, 16.7, 14.3, 14.2, 0.0 ppm

LRMS (ESI) m/z Found: (M+Na)⁺, C₁₉H₂₅O₃Si, 351.1, requires 351.2

Ethyl 2-benzoyl-1-((trimethylsilyl)oxy)spiro[3.5]nonane-2-carboxylate (216k)

![Chemical Structure of 216k]

The title compound was prepared according to the representative procedure for 216a. Following flash column chromatography the title compound 216k (0.39 g, 31% yield) was obtained as a white solid.

diethyl (E)-2-(( tert-butyldimethylsilyl)oxy)vinyl)cyclobutane-1,1-dicarboxylate (232)

![Chemical Structure of 232]
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6.3.4 Synthesis of β-lactones 220

Diethyl (1S,5R,6S)-7-oxo-5-(p-tolyl)-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220a)

A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane 216a (36 mg, 0.1 mmol), α,β-unsaturated acyl fluoride 210a (16 mg, 0.1 mmol), THF (0.65 mL) and DMF (0.15 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC B9 (0.01 mmol) in THF (0.7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound 220a (37 mg, 86% yield, >20:1 d.r) as a viscous oil.

Rf 0.2 (9:1, v/v hexanes : EtOAc)

IR νmax 2930, 2858, 1829, 1723, 1267, 1235 cm⁻¹
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HPLC RegisCell™ S5μm, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tₐ = 6.32 (major enantiomer) and 10.11 (minor enantiomer); er = 96:4

\[ [\text{1}]^b_{\text{D}} = +43.8^\circ \ (c = 1.83, \text{CHCl}_3) \]

\( ^1\text{H} \) NMR (400 MHz, CDCl₃) δ 7.12 (AA’BB’, J = 8.4 Hz, 2H), 7.07 (AA’BB’, J = 8.4 Hz, 2H), 4.61 (d, J = 6.4 Hz, 1H), 4.18 (dd, J = 7.6, 6.4 Hz, 1H), 4.08 (ABX₃, J = 10.8, 7.2 Hz, 1H), 4.05 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.96 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.91 (d, J = 7.6 Hz, 1H), 3.85 (ABX₃, J = 10.8, 7.2 Hz, 1H), 2.30 (ABq, J = 15.2 Hz, 1H), 2.29 (s, 3H), 2.13 (ABq, J = 15.2 Hz, 1H), 1.84-1.75 (m, 1H), 1.66-1.30 (m, 9H), 1.10 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H) ppm

\( ^{13}\text{C} \) NMR (100 MHz, CDCl₃) δ 171.4, 170.6, 170.3, 137.6, 135.9, 129.2(0), 129.1(6), 76.5, 61.8, 61.4, 57.7, 53.5, 43.5, 39.7, 34.0, 33.7, 25.6, 22.2, 22.1, 21.2, 13.8(4), 13.7(7) ppm (1 peak missing or overlapping) HRMS (ESI) m/z Found: (M+H)+, C₉₅H₉₅O₆ 429.2264, requires 429.2272.

Diethyl \( (1S,5R,6S)-7\)-oxo-5-phenyl-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220b)

![Diagram of the compound]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography, the title compound 220b (40 mg, 93% yield, >20:1 d.r) was obtained as a white solid.

Rₙ 0.2 (9:1, v/v hexanes : EtOAc)

IR \( \nu_{\text{max}} \) 2936, 2863, 1830, 1723, 1269, 1236 cm⁻¹

HPLC RegisCell™ S5μm, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tₐ = 6.66 (major enantiomer) and 9.47 (minor enantiomer); er = 95:5 \[ [\text{1}]^b_{\text{D}} = +36.1^\circ \ (c = 1.73, \text{CHCl}_3) \]

\( ^1\text{H} \) NMR (400 MHz, CDCl₃) δ 7.28-7.23 (m, 5H), 4.61 (d, J = 6.4 Hz, 1H), 4.22 (dd, J = 8.0, 6.4 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.95 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.92 (d, J = 8.0 Hz, 1H), 3.84 (ABX₃, J = 10.8, 7.2 Hz, 1H), 2.31 (ABq, J = 15.2 Hz, 1H), 2.15 (ABq, J = 15.2 Hz, 1H), 1.84-1.75 (m, 1H), 1.64-1.32 (m, 9H), 1.07 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm
\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta \ 171.3, 170.5, 170.2, 138.9, 129.3, 128.5, 127.9, 76.5, 61.8, 61.4, 57.7, 53.3, 43.9, 39.6, 33.9, 33.7, 25.6, 22.2, 22.0, 13.8, 13.7 \text{ ppm} \]

\[ \text{HRMS (ESI) } m/z \text{ Found: (M+H)}^+, C_{25}H_{36}O_5 \text{ 445.2225, requires 445.2221} \]

**Diethyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220c)**

![Chemical structure](image)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220c (45 mg, 100% yield, >20:1 d.r.) was obtained as a white solid.

**Rf 0.3 (4:1, v/v hexanes : EtOAc)**

**IR** \( \nu_{\text{max}} \) 2931, 2857, 1825, 1720, 1512, 1247, 1178 cm\(^{-1}\)

**HPLC** RegisCell\(^{\text{TM}}\) 5\(^{\mu}\)m, hexane : iPrOH 85:15, 1 mL/min, \( \lambda = 230 \text{ nm} \), fraction \( t = 8.03 \) (major enantiomer) and 11.10 (minor enantiomer); \( \text{er} = 97:3 \)

\[ \left[ \begin{array}{c} \text{B} \\ 25 \end{array} \right] = +33.2^\circ \ (c = 2.00, \text{CHCl}_3) \]

**\(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.19 \text{ (AA'BB', } J = 8.8 \text{ Hz, 2H), 6.80 (AA'BB', } J = 8.8 \text{ Hz, 2H), 4.59 (d, } J = 6.4 \text{ Hz, 1H), 4.18 (dd, } J = 8.4, 6.4 \text{ Hz, 1H), 4.06 (ABX}_y, J = 10.8, 7.2 \text{ Hz, 1H), 4.03 (ABX}_y, J = 10.8, 7.2 \text{ Hz, 1H), 3.97 (ABX}_y, J = 10.8, 7.2 \text{ Hz, 1H), 3.87 (ABX}_y, J = 10.8, 7.2 \text{ Hz, 1H), 3.85 (d, } J = 8.4 \text{ Hz, 1H), 3.77 (s, 3H), 2.30 (ABq, } J = 15.2 \text{ Hz, 1H), 2.15 (ABq, } J = 15.2 \text{ Hz, 1H), 1.84-1.75 (m, 1H), 1.66-1.32 (m, 9H), 1.09 (t, } J = 7.2 \text{ Hz, 6H) ppm} \]

**\(^{13}\text{C NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta \ 171.4, 170.6, 170.4, 159.2, 130.8, 130.5, 113.9, 76.6, 61.8, 61.4, 57.9, 55.4, 53.5, 43.5, 39.4, 34.0, 33.7, 25.6, 22.2, 22.1, 13.9, 13.8 \text{ ppm} \]

**HRMS (ESI) m/z Found: (M+H)^+, C_{25}H_{36}O_5 \text{ 445.2225, requires 445.2221}**
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Diethyl (1S,5R,6S)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220d)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220d (43 mg, 90% yield, >20:1 d.r) was obtained as a white solid.

$^1$H-NMR (>20:1 dr). Rf 0.2 (4:1, v/v hexanes : EtOAc)

IR $\nu_{max}$ 2932, 2853, 1827, 1730, 1235, 1210 cm$^{-1}$

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, $\lambda$ = 238 nm, fraction t$\text{r}$ = 18.48 (minor enantiomer) and 20.76 (major enantiomer); er = 99:1

[ $\text{D}^{25}$ = +30.8$^o$ (c = 2.02, CHCl$_3$)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (d, $J$ = 8.4 Hz, 1H), 6.43 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.37 (d, $J$ = 2.4 Hz, 1H), 4.59 (d, $J$ = 6.4 Hz, 1H), 4.26 (dd, $J$ = 6.8, 6.4 Hz, 1H), 4.17 (d, $J$ = 6.8 Hz, 1H), 4.08-3.85 (m, 4H), 3.77 (s, 3H), 3.73 (s, 3H), 2.25 (s, 2H), 1.82-1.74 (m, 1H), 1.66-1.28 (m, 9H), 1.12 (t, $J$ = 7.2 Hz, 3H), 1.07 (t, $J$ = 7.2 Hz, 3H) ppm

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 171.3, 170.6, 160.3, 158.7, 131.9, 119.8, 104.5, 98.6, 76.8, 61.5, 61.1, 57.0, 55.6, 55.4, 53.3, 39.3, 37.7, 34.3, 33.7, 31.1, 25.7, 22.3, 22.0, 13.9, 13.8 ppm

HRMS (ESI) m/z Found: (M+H)$^+$, C$_{26}$H$_{34}$O$_8$, 475.2321, requires 475.2326.
Diethyl \((1S,5R,6S)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[5.2.1.0^{1,4}]octane-2,1'-cyclohexane\)-4,4-dicarboxylate (220e)

![Chemical Structure](image)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220e (44 mg, 97% yield, >20:1 d.r.) was obtained as a viscous oil.

\[\text{H-NMR} \ (\text{DMSO}) \ (400 \text{ MHz}, \text{CDCl}_3) \delta \ 7.13 \ (\text{AA'BB'}, J=8.8 \text{ Hz}, 2 \text{H}), \ 6.63 \ (\text{AA'BB'}, J=8.8 \text{ Hz}, 2 \text{H}), \ 4.55 \ (d, J=6.4 \text{ Hz}, 1 \text{H}), \ 4.18 \ (dd, J=8.4, 6.4 \text{ Hz}, 1 \text{H}), \ 4.10 \ (\text{ABX}_3, J=10.8, 7.2 \text{ Hz}, 1 \text{H}), \ 4.05 \ (\text{ABX}_3, J=10.8, 7.2 \text{ Hz}, 1 \text{H}), \ 3.98 \ (\text{ABX}_3, J=10.8, 7.2 \text{ Hz}, 1 \text{H}), \ 3.90 \ (\text{ABX}_3, J=10.8, 7.2 \text{ Hz}, 1 \text{H}), \ 3.85 \ (d, J=8.4 \text{ Hz}, 1 \text{H}), \ 2.91 \ (s, 6 \text{H}), \ 2.33 \ (\text{ABq}, J=15.2 \text{ Hz}, 1 \text{H}), \ 2.17 \ (\text{ABq}, J=15.2 \text{ Hz}, 1 \text{H}), \ 1.87-1.78 \ (m, 1 \text{H}), \ 1.66-1.36 \ (m, 9 \text{H}), \ 1.12 \ (t, J=7.2 \text{ Hz}, 3 \text{H}), \ 1.09 \ (t, J=7.2 \text{ Hz}, 3 \text{H}) \ ppm\]

\[\text{C-NMR} \ (100 \text{ MHz}, \text{CDCl}_3) \delta \ 171.5, \ 170.6, \ 170.4, \ 150.5, \ 130.2, \ 126.8, \ 112.7, \ 76.8, \ 61.6, \ 61.2, \ 58.4, \ 54.0, \ 43.6, \ 40.6, \ 39.8, \ 34.3, \ 33.9, \ 25.8, \ 22.4, \ 22.3, \ 13.8(4), \ 13.7(5) \ ppm\]

\[\text{HRMS (ESI) m/z} \text{ Found: (M+H)^+}, \text{C}_{26}H_{35}NO_{6s}, \text{458.2535}, \text{requires 458.2537}\]
Diethyl (1S,5R,6S)-7-oxo-5-(3,4,5-trimethoxyphenyl)-8-oxaspiro[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220f)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220f (47 mg, 93% yield, >20:1 d.r) was obtained as viscous oil.

Rf 0.2 (7:3, v/v hexanes : EtOAc)

IR νmax 2937, 2857, 1828, 1724, 1590, 1243, 1127 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 238 nm, fraction tᵣ = 14.39 (minor enantiomer) and 19.18 (major enantiomer); er = 96:4

[α]D²⁵ = +22.8° (c = 1.80, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 6.58 (s, 2H), 4.59 (d, J = 6.4 Hz, 1H), 4.27 (dd, J = 9.6, 6.4 Hz, 1H), 4.04 (ABX, J = 10.8, 7.2 Hz, 1H), 4.00 (ABX, J = 10.8, 7.2 Hz, 1H), 3.97 (ABX, J = 10.8, 7.2 Hz, 1H), 3.90 (ABX, J = 10.8, 7.2 Hz, 1H), 3.83 (s, 6H), 3.81 (s, 3H), 3.74 (d, J = 9.6 Hz, 1H), 2.31 (ABq, J = 15.2 Hz, 1H), 2.21 (ABq, J = 15.2 Hz, 1H), 1.83-1.76 (m, 1H), 1.63-1.32 (m, 9H), 1.08 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 170.7, 170.6, 152.9, 137.7, 134.0, 106.8, 76.6, 61.8, 61.4, 60.9, 58.1, 56.2, 53.2, 45.0, 38.8, 34.0, 33.8, 25.6, 22.2, 22.1, 13.9, 13.8 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₇H₅₀O₉, 505.2439, requires 505.2432
Diethyl \((1S,SR,6S)-5-(4\text{-bromophenyl})-7\text{-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate}\) (220g)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound \(220\text{g} \) (40 mg, 80% yield, >20:1 d.r) was obtained as viscous oil.

\(R_f 0.3\) (9:1, v/v hexanes : EtOAc)

IR \(v_{\text{max}}\) 2933, 2859, 1827, 1722, 1267, 1235 cm\(^{-1}\)

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, \(\lambda = 230\) nm, fraction \(t_r = 15.25\) (major enantiomer) and 18.14 (minor enantiomer); \(\text{er} = 92:8\)

\(\left[\text{D}\right]^{25}_D = +21.3^\circ\) (c = 1.54, CHCl\(_3\))

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 (AA’BB’, \(J = 8.8\) Hz, 2H), 7.20 (AA’BB’, \(J = 8.8\) Hz, 2H), 4.59 (d, \(J = 6.4\) Hz, 1H), 4.19 (dd, \(J = 9.2, 6.4\) Hz, 1H), 4.05 (ABX\(_y\), \(J = 10.8, 7.2\) Hz, 1H), 4.01 (ABX\(_y\), \(J = 10.8, 7.2\) Hz, 1H), 3.97 (ABX\(_x\), \(J = 10.8, 7.2\) Hz, 1H), 3.89 (ABX\(_x\), \(J = 10.8, 7.2\) Hz, 1H), 3.79 (d, \(J = 9.2\) Hz, 1H), 2.30 (ABq, \(J = 15.2\) Hz, 1H), 2.17 (ABq, \(J = 15.2\) Hz, 1H), 1.83-1.74 (m, 1H), 1.66-1.32 (m, 9H), 1.08 (t, \(J = 7.2\) Hz, 3H), 1.06 (t, \(J = 7.2\) Hz, 3H) ppm

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 171.1, 170.3(3), 170.3(2), 137.6, 131.6, 131.3, 122.2, 76.5, 619, 61.6, 57.8, 53.0, 44.2, 39.0, 34.1, 33.7, 25.6, 22.2, 22.1, 13.8(4), 13.7(7) ppm

HRMS (ESI) \(m/z\) Found: (M+H\(^+\)), \(C_{24}H_{28}O_6\) requires 493.1220
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Diethyl (1S,5R,6S)-5-(4-chlorophenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1’-cyclohexane]-4,4-dicarboxylate (220h)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220h (36 mg, 81% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.3 (9:1, v/v hexanes: EtOAc)

IR νmax 2933, 2857, 1828, 1723, 1266, 1235 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tᵣ = 12.56 (major enantiomer) and 14.35 (minor enantiomer); er = 87:13

[α]D²⁵ = +23.3° (c = 1.41, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.26 (m, 4H), 4.59 (d, J = 6.4 Hz, 1H), 4.19 (dd, J = 9.2, 6.4 Hz, 1H), 4.05 (ABX₉, J = 10.8, 7.2 Hz, 1H), 4.00 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.97 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.89 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.81 (d, J = 9.2 Hz, 1H), 2.31 (ABq, J = 15.2 Hz, 1H), 2.17 (ABq, J = 15.2 Hz, 1H), 1.82-1.76 (m, 1H), 1.65-1.33 (m, 9H), 1.08 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.1, 170.3(4), 170.3(3), 137.1, 134.0 130.9, 128.6, 76.5, 61.9, 61.5, 57.8, 53.0, 44.1, 39.0, 34.1, 33.7, 25.6, 22.2, 22.0, 13.8(4), 13.7(7) ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₂₄H₂₉³ClO₆ requires 449.1725
Diethyl (1S,5S,6S)-7-oxo-5-(1-tosyl-1H-indol-2-yl)-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220i)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220i (50 mg, 83% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR νmax 2935, 2861, 1824, 1719, 1448, 1370, 1175 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 70:30, 1 mL/min, λ = 238 nm, fraction tᵢ = 8.60 (minor enantiomer) and 17.31 (major enantiomer); en = 98:2

[α]D²⁵ = +6.7° (c = 0.46, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.71 (AA’BB’, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.28-7.23 (m, 1H), 7.19 (AA’BB’, J = 8.4 Hz, 2H), 7.20-7.17 (m, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.29 (dd, J = 9.2, 6.0 Hz, 1H), 3.94 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.90 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.70 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.40 (ABX₃, J = 10.8, 7.2 Hz, 1H), 2.32 (s, 3H), 2.23 (ABq, J = 15.2 Hz, 1H), 2.28 (ABq, J = 15.2 Hz, 1H), 1.86-1.77 (m, 1H), 1.67-1.31 (m, 9H), 1.05 (t, J = 7.2 Hz, 3H), 0.52 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 170.9, 170.5, 170.4, 145.0, 135.3, 134.4, 130.8, 129.9, 127.0, 126.6, 124.9, 123.3, 120.3, 119.3, 113.6, 75.9, 61.8, 61.3, 56.6, 54.0, 37.6, 36.3, 34.7, 33.8, 25.6, 22.1, 21.9, 21.6, 13.7, 13.1 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₃₅H₅₇NO₈S, 608.2310, requires 608.2313
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Diethyl (1S,5S,6S)-5-(furan-2-yl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220j)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220j (29 mg, 72% yield, >20:1 d.r) was obtained as a viscous oil.

RT 0.2 (9:1, v/v hexanes : EtOAc)

IR \( \nu_{\text{max}} \) 2933, 2859, 1827, 1725, 1448, 1239 cm\(^{-1}\)

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, \( \lambda = 230 \) nm, fraction t = 12.32 (major enantiomer) and 17.91 (minor enantiomer); er = 92:8

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.30 (dd, \( J = 2.0, 0.8 \) Hz, 1H), 6.29 (dd, \( J = 3.2, 2.0, 1H \)), 6.20 (brd, \( J = 3.2, 1H \)), 4.57 (d, \( J = 6.4 \) Hz, 1H), 4.24-4.12 (m, 4H), 4.04 (ABX\(_y\), \( J = 10.8, 7.2, 1H \)), 3.93 (ABX\(_y\), \( J = 10.8, 7.2, 1H \)), 2.33 (AB, \( J = 15.2, 1H \)), 2.12 (AB, \( J = 15.2, 1H \)), 2.33 (s, 3H), 1.78-1.72 (m, 1H), 1.62-1.30 (m, 9H), 1.22 (t, \( J = 7.2, 3H \)), 1.13 (t, \( J = 7.2, 3H \)) ppm

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.0, 170.0, 169.9, 152.2, 142.3, 110.7, 108.8, 76.3, 62.1, 61.9, 56.7, 51.2, 39.7, 36.9, 34.0, 33.2, 25.6, 22.1, 22.0, 14.0, 13.9 ppm

HRMS (ESI) m/z Found: (M+H)+, C\(_{22}\)H\(_{30}\)O\(_7\), 405.1911, requires 405.1908
Dimethyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220k)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220k (32 mg, 84% yield, >20:1 d.r) was obtained as white solid.

Rf 0.2 (9:1, v/v hexanes : EtOAc)

IR νmax 2941, 2915, 2856, 1824, 1734, 1256, 1239 cm⁻¹

HPLC RegisCell™ Sμm, hexane : iP rOH 85:15, 1 mL/min, λ = 230 nm, fraction t_r = 10.84 (major enantiomer) and 14.17 (minor enantiomer); er = 98:2

[α]D²⁵ = +34.2° (c = 0.46, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.17 (AA'BB', J = 8.8 Hz, 2H), 6.81 (AA'BB', J = 8.8 Hz, 2H), 4.60 (d, J = 6.4 Hz, 1H), 4.19 (dd, J = 8.4, 6.4 Hz, 1H), 3.88 (d, J = 8.4 Hz, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 3.48 (s, 3H), 2.32 (ABq, J = 15.0 Hz, 1H), 2.16 (ABq, J = 15.0 Hz, 1H), 1.80-1.75 (m, 1H), 1.60-1.25 (m, 9H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.8, 170.8, 170.5, 159.3, 130.5, 130.3, 114.0, 76.4, 57.9, 55.3, 53.3, 52.7, 52.3, 43.4, 39.3, 33.9, 33.6, 25.6, 22.2, 22.0 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₂₃H₂₃O₇, 417.1902, requires 417.1908
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Diallyl \((1S,5R,6S)-5-(4\text{-}methoxyphenyl)\text{-}7\text{-}oxo\text{-}8\text{-}oxaspiro[4.2.0]\text{-}octane\text{-}2,1\text{-}cyclohexane\)\text{-}4,4\text{-}dicarboxylate (220l)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220l (41 mg, 88% yield, >20:1 d.r.) was obtained as a white solid.

\(R_f 0.5\) (7:3, v/v hexanes: EtOAc)

\(\text{IR } \nu_{\text{max}}\) 2932, 2848, 1826, 1735, 1513, 1252, 1223 cm\(^{-1}\)

\(\text{HPLC RegisCell}^{\text{TM}} \quad \Sigma_{\text{mm}}\text{, hexane : iPrOH } 90:10, 1 \text{ mL/min, } \lambda = 230 \text{ nm, fraction } t_r = 10.15\) (major enantiomer) and 14.12 (minor enantiomer); ee = 99:1

\[ ^{1}D_{25} = +12.7^\circ \text{ (c = 0.13, CHCl}_3) \]

\(^{1}H \text{ NMR (400 MHz, CDCl}_3\) \(\delta 7.18\) (AA'BB', \(J = 8.8 \text{ Hz, } 2H\)), 6.80 (AA'BB', \(J = 8.8 \text{ Hz, } 2H\)), 5.78-5.62 (m, 2H), 5.25-5.19 (m, 1H), 5.20-5.16 (m, 2H), 5.16-5.14 (m, 1H) 4.60 (d, \(J = 6.4 \text{ Hz, } 1H\)), 4.50 (ABMX\(_3\), \(J = 13.0, 6.0, 1.2 \text{ Hz, } 1H\)), 4.27 (ABMX\(_3\), \(J = 13.0, 6.0, 1.2 \text{ Hz, } 1H\)), 4.40 (ABMX\(_3\), \(J = 14.4, 5.8, 1.2 \text{ Hz, } 1H\)), 4.27 (ABMX\(_3\), \(J = 14.4, 5.8, 1.2 \text{ Hz, } 1H\)), 4.19 (dd, \(J = 8.0, 6.4 \text{ Hz, } 1H\)), 3.88 (d, \(J = 8.0 \text{ Hz, } 1H\)), 3.77 (s, 3H), 2.32 (ABq, \(J = 15.2 \text{ Hz, } 1H\)), 2.16 (ABq, \(J = 15.2 \text{ Hz, } 1H\)), 1.84-1.74 (m, 1H), 1.65-1.32 (m, 9H) ppm

\(^{13}C \text{ NMR (100 MHz, CDCl}_3\) \(\delta 171.0, 170.5, 169.9, 159.3, 131.2, 131.1, 130.6, 130.4, 119.2, 119.1, 113.9, 76.5, 66.5, 66.2, 58.0, 55.3, 53.4, 43.4, 39.5, 34.0, 33.7, 25.6, 22.2, 22.1 \text{ ppm (1 peak missing or overlapping)}

\(\text{HRMS (ESI) } m/z\text{ Found: (M+H)}^+, C_{27}H_{38}O_7, 469.2220, \text{ requires 469.2221}\)
Diisopropyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220m)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220m (41 mg, 86% yield, >20:1 d.r) was obtained as a white solid.

Rf 0.3 (4:1, v/v hexanes : EtOAc)

IR νmax 2975, 2934, 2872, 1828, 1732, 1514, 1236, 1217, 1105 cm⁻¹

HPLC RegisCell™ Sum, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tr = 7.48 (major enantiomer) and 9.09 (minor enantiomer); er = 94:6

[α]D²⁵ = +26.0° (c = 0.20, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.23 (AA'BB', J = 8.8 Hz, 2H), 6.80 (AA'BB', J = 8.8 Hz, 2H), 4.89 (sept, J = 6.2 Hz, 1H), 4.74 (sept, J = 6.2 Hz, 1H), 4.59 (d, J = 6.2 Hz, 1H), 4.17 (dd, J = 8.8, 6.2 Hz, 1H), 3.79 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 2.32 (ABq, J = 15.2 Hz, 1H), 2.16 (ABq, J = 15.2 Hz, 1H), 1.82-1.74 (m, 1H), 1.62-1.32 (m, 9H), 1.18 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.0, 170.8, 170.1, 159.3, 130.9, 130.7, 113.9, 76.7, 69.7, 69.5, 57.8, 55.4, 53.7, 43.8, 39.5, 34.0, 33.9, 25.6, 22.3, 22.1, 21.7, 21.6, 21.5, 21.3 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₇H₃₆O₇, 473.2517, requires 473.2534
Diethyl (1S,2R,6S)-2-[(4-methoxyphenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220n)

\[
\begin{align*}
&\text{EtO}_2C \quad \text{OTMS} \quad \text{Me} \\
&\text{EtO}_2C \quad \text{Me} \quad \text{Ome} \\
\end{align*}
\]

10 mol\% B9 (9:1) THF:DMF, 80 °C, 2 h

\[
\begin{align*}
&\text{EtO}_2C \quad \text{OTMS} \quad \text{Me} \\
&\text{EtO}_2C \quad \text{Me} \quad \text{Ome} \\
\end{align*}
\]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220n (38 mg, 93% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.2 (4:1, v/v hexanes : EtOAc)

IR νmax 2962, 2939, 1826, 1720, 1514, 1251 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction t = 10.45 (major enantiomer) and 13.71 (minor enantiomer); er = 97:3

\[
\left[ \begin{array}{c} \text{D} \\ \text{D} \end{array} \right] ^{25} = +23.6° (c = 1.82, \text{CHCl}_3)
\]

H NMR (400 MHz, CDCl₃) δ 7.22 (AA'BB', J = 8.8 Hz, 2H), 6.81 (AA'BB', J = 8.8 Hz, 2H), 4.49 (d, J = 6.4 Hz, 1H), 4.18 (dd, J = 9.2, 6.4 Hz, 1H), 4.08 (ABX₃, J = 10.8, 7.2 Hz, 1H), 4.03 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.97 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.86 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.86 (d, J = 9.2 Hz, 1H), 3.77 (s, 3H), 2.24 (ABq, J = 15.2 Hz, 1H), 2.20 (ABq, J = 15.2 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm

C NMR (100 MHz, CDCl₃) δ 171.4, 170.5, 170.4, 159.2, 130.5, 130.4, 113.8, 77.0, 61.8, 61.4, 58.5, 55.3, 53.3, 43.1, 41.9, 31.3, 31.1, 24.8, 13.9, 13.7 ppm

HRMS (ESI) m/z Found: (M+Na)⁺, C₂₂H₂₉O₇, 427.1724, requires 427.1727.
Diethyl (1S,2R,6S)-2-(2,4-dimethoxyphenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220a)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220o (43 mg, 100% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.3 (7:3, v/v hexanes : EtOAc)

IR νmax 2975, 2941, 1827, 1729, 1612, 1507, 1210 cm

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 230 nm, fraction t = 6.77 (minor enantiomer) and 7.59 (major enantiomer); er = 99:1

[α]D
25^18 = +30.7° (c = 1.91, CHCl3)

^1H NMR (400 MHz, CDCl3) δ 7.35 (d, J = 8.4 Hz, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 4.48 (d, J = 6.4 Hz, 1H), 4.25 (dd, J = 7.2, 6.4 Hz, 1H), 4.18 (d, J = 7.2 Hz, 1H), 4.10-3.84 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.29 (ABq, J = 14.8 Hz, 1H), 2.19 (ABq, J = 14.8 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm

^13C NMR (100 MHz, CDCl3) δ 171.2(4), 171.2(0), 170.5, 160.3, 158.7, 132.0, 119.7, 104.4, 98.5, 77.3, 61.6, 61.1, 57.5, 55.5, 55.4, 53.2, 41.7, 37.4, 31.4, 31.2, 25.6, 13.8(0), 13.7(7) ppm

HRMS (ESI) m/z Found: (M+H)^+, C_{23}H_{36}O_6 435.2007, requires 435.2013
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Diethyl (1S,2R,6S)-2-(2-(benzyl(methyl)amino)phenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220p)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220p (48 mg, 98% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.3 (9:1, v/v hexanes : EtOAc)

IR νmax 2962, 1824, 1723, 1257 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction t = 8.51 (major enantiomer) and 10.09 (minor enantiomer); er = 99:1

[α]D²⁵ = -5.6° (c = 0.16, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 7.6, 1.6 Hz, 1H), 7.44-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.21 (m, 3H), 7.13 (ddd, J = 7.6, 6.4, 2.4 Hz, 1H), 4.85 (d, J = 10.0 Hz, 1H), 4.43 (d, J = 6.0 Hz, 1H), 4.39 (dd, J = 10.0, 6.0 Hz, 1H), 4.08 (ABX, J = 10.8, 7.2 Hz, 1H), 4.04 (d, J = 14.4 Hz, 1H), 4.00 (ABX, J = 10.8, 7.2 Hz, 1H), 3.94 (ABX, J = 10.8, 7.2 Hz, 1H), 3.78 (d, J = 14.4 Hz, 1H), 3.74 (ABX, J = 10.8, 7.2 Hz, 1H), 2.47 (s, 3H), 2.37 (ABq, J = 14.8 Hz, 1H), 2.26 (ABq, J = 14.8 Hz, 1H), 1.18 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H), 1.12 (s, 3H), 0.87 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 170.6, 170.2, 154.1, 139.0, 135.7, 129.8, 128.6, 128.4, 128.3, 127.0, 125.0, 122.4, 77.1, 63.0, 61.3, 61.1, 58.1, 54.7, 44.9, 42.3, 36.9, 31.4, 30.8, 27.0, 13.8, 13.5 ppm HRMS (ESI) m/z Found: (M+H)+, C₂₉H₂₆NO₆, 494.2535, requires 494.2537
Diethyl (1S,2R,6R)-2-(4-methoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220q)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography, the title compound 220q (26 mg, 70% yield, >20:1 d.r.) was obtained as a viscous oil.

$R_f 0.4$ (7:3, v/v hexanes : EtOAc)

IR $\nu_{\text{max}} 2980, 2940, 1824, 1731, 1611, 1514, 1250, 1179$ cm$^{-1}$

HPLC Daicel AD-H, hexane : tPrOH 80:20, 1 mL/min, $\lambda = 238$ nm, fraction $t = 8.10$ (minor enantiomer) and 9.48 (major enantiomer); er $= 90:10$

$^1H$ NMR (400 MHz, CDCl$_3$) $\delta 7.15$ (AA'BB, $J = 8.8$ Hz 2H), $6.80$ (AA'BB, $J = 8.8$ Hz 2H), $4.91-4.87$ (m, 1H), $4.17-4.07$ (m, 3H), $4.02$ (ABX$_3$, $J = 10.8$, 7.2 Hz, 1H), $3.91$ (d, $J = 4.8$ Hz, 1H), $3.91$ (ABX$_3$, $J = 10.8$, 7.2 Hz, 1H), $3.78$ (d, $J = 14.4$ Hz, 1H), $3.37$ (s, 3H), $2.28-2.17$ (m, 3H), $2.07-1.97$ (m, 1H), $1.12$ (t, $J = 7.2$ Hz, 3H), $1.11$ (t, $J = 7.2$ Hz, 3H) ppm

$^{13}C$ NMR (100 MHz, CDCl$_3$) $\delta 170.8, 170.6, 169.8, 159.2, 131.8, 130.3, 113.9, 69.0, 61.9, 61.4, 58.1, 55.3, 53.5, 43.2, 26.2, 24.2, 13.9(4), 13.9(2)$ ppm

HRMS (ESI) $m/z$ Found: (M+H)$^+$, C$_{20}$H$_{35}$NO$_6$ 494.2535, requires 494.2537
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Diethyl (1S,2R,6R)-2-(4-(dimethylamino)phenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220r)

![Chemical structure]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220r (35 mg, 90% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.2 (7:3, v/v hexanes : EtOAc)

IR v max 2981, 2903, 1824, 1733, 1614, 1523, 1248, 1224 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 238 nm, fraction t = 8.51 (minor enantiomer) and 10.09 (major enantiomer); er = 96:4

[α]D²⁵ = +42.9° (c = 1.73, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.05 (AA'BB', J = 8.8 Hz, 2H), 6.61 (AA'BB', J = 8.8 Hz, 2H), 4.92-4.87 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.08 (dd, J = 6.8, 4.8 Hz, 1H), 4.01 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.93 (d, J = 4.8 Hz, 1H), 3.88 (ABX₉, J = 10.8, 7.2 Hz, 1H), 2.91 (s, 6H), 2.33-2.15 (m, 3H), 2.01-1.93 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.0, 170.7, 169.9, 150.0, 129.7, 127.4, 112.3, 69.0, 61.9, 61.3, 58.2, 53.6, 42.7, 40.6, 25.7, 24.4, 14.0, 13.9 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₁H₂₆NO₆, 390.1899, requires 390.1911
Diethyl (1S,2R,6R)-2-(2,4-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220s)

![Chemical structure]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220s (34 mg, 83% yield, >20:1 d.r) was obtained as a white solid.

R<sub>r</sub> 0.3 (7:3, v/v hexanes : EtOAc)

IR ν<sub>max</sub> 2981, 2939, 1821, 1728, 1611, 1507, 1263, 1210 cm<sup>-1</sup>

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 238 nm, fraction t = 7.49 (minor enantiomer) and 9.31 (major enantiomer); er = 97:3

[ ]<sup>25</sup><sub>D</sub> = +46.5° (c = 1.84, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.17 (d, J = 8.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 4.87 (td, J = 6.4, 4.0 Hz, 1H), 4.34 (dd, J = 3.6 Hz, 1H), 4.17 (ABX<sub>7</sub>, J = 10.8, 7.2 Hz, 1H), 4.14 (ABX<sub>7</sub>, J = 10.8, 7.2 Hz, 1H), 4.04 (dd, J = 6.4, 3.6 Hz, 1H), 3.93 (ABX<sub>7</sub>, J = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.77 (ABX<sub>7</sub>, J = 10.8, 7.2 Hz, 1H), 3.75 (s, 3H), 2.41-2.32 (m, 2H), 2.17-2.09 (m, 1H), 2.00-1.92 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.6, 171.0, 170.1, 160.4, 158.3, 132.1, 121.1, 104.3, 98.7, 70.0, 61.9, 61.2, 57.7, 55.5, 55.3, 53.1, 37.4, 25.6, 24.5, 14.0, 13.8 ppm

HRMS (ESI) m/z Found: (M+H)<sup>+</sup>, C<sub>21</sub>H<sub>26</sub>O<sub>8</sub> 407.1692, requires 407.1700
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Diethyl (1S,2R,6R)-2-(2-methoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octene-3,3-dicarboxylate (220t)

![Chemical Structure]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220t (30 mg, 87% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.2 (7:3, v/v hexanes : EtOAc)

IR νmax 2953, 2926, 1819, 1730, 1494, 1434, 1268, 1243 cm⁻¹

HPLC RegisCell™ 5μm, hexane : iPrOH 92:8, 1 mL/min, λ = 230 nm, fraction tr = 16.93 (minor enantiomer) and 18.02 (major enantiomer); er = 97:3

[α]D²⁵ = +42.4° (c = 1.06, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.27-7.20 (m, 2H), 6.89 (td, J = 7.6, 1.2 Hz, 1H), 6.83 (brd, J = 7.6 Hz, 1H), 4.90 (td, J = 6.8, 4.0 Hz, 1H), 4.43 (d, J = 3.6 Hz, 1H), 4.08 (dd, J = 6.8, 3.6 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.35 (s, 3H), 2.44-2.36 (m, 2H), 2.17-2.10 (m, 1H), 2.01-1.92 (m, 1H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.4(1), 171.4(0), 170.3(8), 157.2, 131.5, 129.2, 128.4, 120.7, 110.9, 69.9, 57.7, 55.3, 52.9, 52.7, 52.1, 25.5, 24.6 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₉H₂₀O₇, 349.1279, requires 349.1282
Diethyl \((1S,5R,6R)-5-(4\text{-methoxyphenyl})-7\text{-oxo-8-oxaspiro[4.2]octane-2,1'-cyclooctane}]4,4\text{-dicarboxylate}(220u)\)

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{OTMS} \quad \text{OMe} \\
\text{EtO}_2\text{C} \quad \text{F} \\
\end{array}
\] 

\[\text{10 mol\% } \text{B9, (9:1) THF-DMF, 80°C, 2 h}\]

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220u (37 mg, 75% yield, >20:1 d.r) was obtained as a viscous oil.

\(R_f 0.3\) (4:1 v/v hexanes : EtOAc)

IR \(v\text{max} 2919, 2854, 1823, 1719, 1610, 1513, 1248, 1180\) cm\(^{-1}\)

HPLC RegisCell™ S5m, hexane : iPrOH 90:10, 1 mL/min, \(\lambda = 238\) nm, fraction

\(t_r = 10.21\) (major enantiomer) and 16.59 (minor enantiomer); \(\text{er} = 98:2\)

\[\beta^\text{25} = +26.3^\circ\ (c = 1.10, \text{CHCl}_3)\]

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 7.20\) (AA′BB′, \(J = 8.8\) Hz, 2H), 6.80 (AA′BB′, \(J = 8.8\) Hz, 2H), 4.51 (d, \(J = 6.4\) Hz, 1H), 4.16 (dd, \(J = 8.8, 6.4\) Hz, 1H), 4.06 (q, \(J = 7.2\) Hz, 2H), 3.98-3.79 (m, 2H), 3.89 (d, \(J = 8.8\) Hz, 1H), 3.76 (s, 3H), 2.27 (AB\(_q\), \(J = 15.2\) Hz, 1H), 2.15 (AB\(_q\), \(J = 15.2\) Hz, 1H), 1.93-1.83 (m, 1H), 1.73-1.41 (m, 13H), 1.10 (t, \(J = 7.2\) Hz, 3H), 1.05 (t, \(J = 7.2\) Hz, 3H) ppm

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta 171.5, 170.6, 170.5, 159.2, 130.7, 130.5, 113.8, 77.4, 61.8, 61.4, 58.1, 55.4, 53.4, 43.0, 38.2, 37.4, 36.8, 29.0, 28.0, 25.5, 22.8, 22.2, 13.9, 13.8 ppm

LRMS (ESI) \text{m/z} \text{Found:} \ (\text{M+Na})^+; \text{C}_{27}\text{H}_{36}\text{O}_{14}, 495.1, \text{requires 495.2} \)
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Diethyl (1S,5R,6S)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[4.2.0]octane-2,1'-cyclooctane]-4,4-dicarboxylate (220v)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220v (48 mg, 91% yield, >20:1 d.r) was obtained as a viscous oil.

\[ R_f 0.4 \ (7:3, \text{v/v hexanes : EtOAc}) \]

IR: \( \nu_{\text{max}} 2921, 2854, 1822, 1724, 1610, 1585, 1507, 1207, 1126 \ \text{cm}^{-1} \)

HPLC: Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, \( \lambda = 238 \ \text{nm} \), fraction \( t_r = 16.83 \) (minor enantiomer) and 22.63 (major enantiomer); \( \text{er} = 99:1 \)

\[ [\Delta]_D^{25} = +19.7^o \ (c = 0.85, \text{CHCl}_3) \]

\( ^1H \ \text{NMR} \ (400 \text{MHz, CDCl}_3) \delta 7.37 \ (d, J = 8.8 \text{ Hz, 1H}), 6.43 \ (dd, J = 8.8, 2.4 \text{ Hz, 1H}), 6.37 \ (d, J = 2.4 \text{ Hz, 1H}), 4.47 \ (d, J = 6.0 \text{ Hz, 1H}), 4.26 \ (dd, J = 7.6, 6.0 \text{ Hz, 1H}), 4.17 \ (d, J = 7.6 \text{ Hz, 1H}), 4.07-3.85 \ (m, 4H), 3.77 \ (s, 3H), 3.72 \ (s, 3H), 2.28 \ (ABq, J = 15.2 \text{ Hz, 1H}), 2.15 \ (ABq, J = 15.2 \text{ Hz, 1H}), 1.91-1.85 \ (m, 1H), 1.68-1.46 \ (m, 13H), 1.10 \ (t, J = 7.2 \text{ Hz, 3H}), 1.06 \ (t, J = 7.2 \text{ Hz, 3H}) \ \text{ppm} \]

\( ^13C \ \text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta 171.2(8), 171.2(6), 170.7, 160.3, 158.7, 131.9, 119.7, 104.4, 98.5, 77.5, 61.5, 61.1, 57.1, 55.5, 55.4, 53.2, 38.6, 37.5, 37.1, 30.4, 28.9, 28.3, 25.6, 22.7, 22.4, 13.8(4), 13.8(0) \ \text{ppm} \)

LRMS (ESI) m/z Found: (M+Na)+, C_{29}H_{33}O_{9} 525.3, requires 525.2

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Diethyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cycloheptane]-4,4-dicarboxylate (220w)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220w (43 mg, 94% yield, >20:1 d.r) was obtained as a viscous oil.

R<sub>f</sub> 0.2 (9:1, v/v hexanes : EtOAc)

IR <i>v</i><sub>max</sub> 2925, 2856, 1824, 1720, 1513, 1248, 1180, 1033 cm<sup>-1</sup>

HPLC RegisCell<sup>TM</sup> S<sub>Um</sub>, hexane : iPrOH 90:10, 1 mL/min, <i>λ</i> = 230 nm, fraction <i>t</i> = 9.57 (major enantiomer) and 13.35 (minor enantiomer); er = 98:2

[<i>α</i>]<sub>D</sub><sup>25</sup> = +17.8° (c = 0.87, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) <i>δ</i> 7.21 (AA’BB’, <i>J</i> = 8.8 Hz, 2H), 6.80 (AA’BB’, <i>J</i> = 8.8 Hz, 2H), 4.50 (d, <i>J</i> = 6.4 Hz, 1H), 4.16-4.03 (m, 3H), 3.98-3.90 (m, 2H), 3.81-3.73 (m, 1H), 3.77 (s, 3H), 2.35 (ABq, <i>J</i> = 14.8 Hz, 1H), 2.15 (ABq, <i>J</i> = 14.8 Hz, 1H), 1.91-1.85 (m, 1H), 1.79-1.73 (m, 1H), 1.63-1.43 (m, 10H), 1.13 (t, <i>J</i> = 6.8 Hz, 3H), 1.02 (t, <i>J</i> = 6.8 Hz, 3H) ppm

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) <i>δ</i> 171.7, 170.6, 170.5, 159.2, 130.5, 113.8, 78.0, 61.8, 61.5, 58.3, 55.4, 53.2, 42.4, 42.3, 40.8, 37.6, 34.5, 30.7, 30.6, 29.8, 23.0, 22.8, 14.0, 13.7 ppm

HRMS (ESI) <i>m/z</i> Found: (M+H)<sup>+</sup>, C<sub>26</sub>H<sub>34</sub>O<sub>7</sub> 459.2366, requires 459.2377
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Diethyl (1S,5R,6S)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1’-cycloheptane]-4,4-dicarboxylate (220x)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220x (41 mg, 80% yield, >20:1 d.r) was obtained as a white solid.

RF 0.1 (4:1, v/v hexanes : EtOAc)

IR νmax 2920, 2855, 1816, 1725, 1508, 1260, 1183, 1031 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tᵣ = 18.43 (minor enantiomer) and 24.09 (major enantiomer); er = 98:2

[Δ]D²⁵ = +16.3° (c = 0.53, CHCl₃)

¹H NMR (300 MHz, CDCl₃) δ 7.37 (d, J = 8.4 Hz, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 1H), 4.25 (dd, J = 8.2, 6.0 Hz, 1H), 4.19 (d, J = 8.2 Hz, 1H), 4.10-4.03 (m, 1H), 4.02-3.93 (m, 2H), 3.90-3.82 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.31 (ABq, J = 15.0 Hz, 1H), 2.26 (ABq, J = 15.0 Hz, 1H), 1.86-1.82 (m, 1H), 1.75-1.70 (m, 1H) 1.65-1.42 (m, 10H), 1.09 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 171.4, 171.3, 170.7, 160.3, 158.7, 131.9, 119.7, 104.4, 98.4, 78.1, 61.6, 61.1, 57.2, 55.5, 55.4, 52.9, 41.9, 31.3, 37.3, 37.3(4), 37.2(7), 35.5, 30.8, 30.6, 22.8, 22.7 ppm

HRMS (ESI) m/z Found: (M+Na)+, C₂₂H₃₆O₉Na 511.2301, requires 511.2302.
Diethyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220y)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220y (43 mg, 100% yield, >20:1 d.r) was obtained as a white solid.

Rf 0.3 (4:1, v/v hexanes : EtOAc)

IR ν<sub>max</sub> 2957, 2878, 1828, 1722, 1612, 1514, 1253, 1182 cm<sup>-1</sup>

HPLC Daicel A-DH hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction t<sub>r</sub> = 16.95 (major enantiomer) and 18.52 (minor enantiomer); er = 89:11 e.r

<sup>1</sup>H NMR (400 MHz, CDCl₃) δ 7.23 (AA'BB', J = 8.8 Hz, 2H), 6.81 (AA'BB', J = 8.8 Hz, 2H), 4.52 (d, J = 6.4 Hz, 1H), 4.17 (dd, J = 9.6, 6.4 Hz, 1H), 4.08 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.99 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.89 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.77 (s, 3H), 2.34 (ABq, J = 15.2 Hz, 1H), 2.29 (ABq, J = 15.2 Hz, 1H), 2.12-2.03 (m, 1H), 1.79-1.63 (m, 5H), 1.09 (t, J = 7.2 Hz, 6H), 1.06 (t, J = 7.2 Hz, 6H) ppm

<sup>13</sup>C NMR (100 MHz, CDCl₃) δ 171.5, 170.6, 1592, 130.5, 130.3, 113.8, 76.6, 61.7, 61.4, 58.8, 55.3, 53.2, 43.3, 43.0, 34.1, 24.5, 23.7, 13.9, 13.8 ppm

HRMS (ESI) m/z Found: (M+Na)<sup>+</sup>, C₂₃H₂₆O₇, 431.2067, requires 431.2064
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Diethyl (1S,SR,6S)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220z)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220z (44 mg, 98% yield, >20:1 d.r) was obtained as a viscous oil.

\[ \text{Rf} 0.3 \text{ (4:1, v/v hexanes : EtOAc) } \]

IR \[ \nu_{\text{max}} \text{2957, 2877, 1828, 1722, 1615, 1523, 1244, 1225 cm}^{-1} \]

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, \[ \bar{\lambda} = 238 \text{ nm} \], fraction \( t_r = 11.19 \) (major enantiomer) and 15.05 (minor enantiomer); \( \text{er} = 97:3 \)

\[ \left[ \begin{array}{c}
\text{H} \\
\text{C}
\end{array} \right]_{\text{D}}^{25} = +27.5^\circ \text{ (c} = 2.09, \text{ CHCl}_3 \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3 \] \[ \delta 7.12 \text{ (AA'BB', } J = 8.8 \text{ Hz, 2H), 6.62 \text{ (AA'BB', } J = 8.8 \text{ Hz, 2H), 4.52 \text{ (d, } J = 6.0 \text{ Hz, 1H), 4.}16 \text{ (dd, } J = 8.8, 6.0 \text{ Hz, 1H), 4.09 \text{ (ABX}_3, J = 10.8, 7.2 \text{ Hz, 1H), 4.08 \text{ (ABX}_3, J = 10.8, 7.2 \text{ Hz, 1H), 4.00 \text{ (ABX}_3, J = 10.8, 7.2 \text{ Hz, 1H), 3.89 \text{ (ABX}_3, J = 10.8, 7.2 \text{ Hz, 1H), 3.81 \text{ (d, } J = 8.8 \text{ Hz, 1H), 2.90 \text{ (s, 6H), 2.30 (s, 2H), 2.11-2.02 (m, 1H), 1.78-1.63 (m, 5H), 1.56-1.48 (m, 1H), 1.40-1.30 (m, 1H), 1.11 \text{ (t, } J = 7.2 \text{ Hz, 3H), 1.07 (t, } J = 7.2 \text{ Hz, 3H) ppm}} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \] \[ \delta 171.7, 170.8, 170.6, 150.2, 129.9, 126.0, 112.4, 76.6, 61.6, 61.3, 58.8, 53.4, 43.0(1), 42.9(6), 41.5, 40.6, 39.9, 34.2, 24.5, 23.5, 13.9, 13.8 \text{ ppm HRMS (ESI) } m/z \text{ Found: (M+H)}^+ \text{,} \]

C\text{23H}\text{33N}\text{O}_\text{6} \text{ requires 444.2381.} \]
Diethyl (1S,5R,6S)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220aa)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220aa (46 mg, 99% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.2 (4:1, v/v hexanes : EtOAc)

IR $\nu_{max}$ 2958, 2875, 1825, 1726, 1507, 1239, 1209 cm$^{-1}$

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, $\lambda = 238$ nm, fraction $t_c = 15.60$ (minor enantiomer) and 18.31 (major enantiomer); er = 98:2

$[\alpha]_D^{25} = +27.4^\circ$ (c = 1.87, CHCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 (d, $J = 8.4$ Hz, 1H), 6.43 (dd, $J = 8.4, 2.8$ Hz, 1H), 6.38 (d, $J = 2.8$ Hz, 1H), 4.48 (d, $J = 6.0$ Hz, 1H), 4.27 (dd, $J = 7.2, 6.0$ Hz, 1H), 4.15 (d, $J = 7.2$ Hz, 1H), 4.10-3.88 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.36 (ABq, $J = 14.8$ Hz, 1H), 2.31 (ABq, $J = 14.8$ Hz, 1H), 2.12-2.04 (m, 1H), 1.79-1.63 (m, 5H), 1.54-1.44 (m, 1H), 1.41-1.32 (m, 1H), 1.13 (t, $J = 7.2$ Hz, 3H), 1.07 (t, $J = 7.2$ Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.3(2), 171.3(0), 170.7, 160.3, 158.7, 131.8, 119.6, 104.4, 98.5, 76.8, 61.5, 61.1, 57.9, 55.5, 55.4, 53.1, 43.0, 41.5, 40.1, 37.4, 35.0, 24.1, 23.4, 13.9, 13.8 ppm

HRMS (ESI) m/z Found: (M+Na)$^+$, C$_{25}$H$_{32}$O$_8$ 483.1984, requires 483.1989.
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Diethyl (1S,5R,6S)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclobutane]-4,4-dicarboxylate (220ab)

![Chemical structure](image)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220ab (38 mg, 88% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.3 (7:3, v/v hexanes : EtOAc)

IR $\nu_{\text{max}}$ 2981, 2941, 2874, 1826, 1720, 1614, 1523, 1268, 1240 cm$^{-1}$

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, $\lambda = 238$ nm, fraction $t_r = 13.32$ (major enantiomer) and 17.40 (minor enantiomer); $\text{er} = 93:7$

$[\alpha]_D^{25} = +18.5^\circ$ (c = 0.6, CHCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.10 (AA'BB', $J = 8.8$ Hz, 2H), 6.61 (AA'BB', $J = 8.8$ Hz, 2H), 4.69 (d, $J = 6.4$ Hz, 1H), 4.16 (dd, $J = 9.6, 6.4$ Hz, 1H), 4.13-3.90 (m, 4H), 3.56 (d, $J = 9.6$ Hz, 1H), 2.90 (s, 6H), 2.47 (ABq, $J = 14.8$ Hz, 1H), 2.44-2.39 (m, 1H), 2.43 (ABq, $J = 14.8$ Hz, 1H), 2.10-1.83 (m, 5H), 1.09 (t, $J = 7.2$ Hz, 6H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.3(2), 171.3(0), 170.7, 160.3, 158.7, 131.8, 119.6, 104.4, 98.5, 76.8, 61.5, 57.9, 55.5, 53.1, 43.0, 41.5, 40.1, 37.4, 35.0, 24.1, 23.4, 13.9, 13.8 ppm

LRMS (ESI) m/z Found: (M+H)$^+$, C$_2$H$_{11}$NO$_6$ 430.1, requires 430.2
Diethyl (1S,5R,6S)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclobutane]-4,4-dicarboxylate (220ac)

The title compound was prepared according to the representative procedure for 220a. Following flash column chromatography the title compound 220ac (38 mg, 81% yield, >20:1 d.r) was obtained as a viscous oil.

Rf 0.3 (7:3, v/v hexanes : EtOAc)

IR νmax 2980, 2941, 1825, 1725, 1612, 1507, 1264, 1237, 1208 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction

tr = 12.36 (minor enantiomer) and 15.82 (major enantiomer); er = 90:10

[α]D²⁵ = +13.3° (c = 0.52, CHCl₃)

1H-NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 8.8 Hz, 1H), 6.42 (dd, J = 8.8, 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.72 (d, J = 6.4 Hz, 1H), 4.28 (dd, J = 8.4, 6.4 Hz, 1H), 4.10- 3.88 (m, 5H), 3.77 (s, 3H), 3.70 (s, 3H), 2.52 (ABq, J = 14.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.33 (ABq, J = 14.8 Hz, 1H), 2.07-1.86 (m, 5H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 171.2, 170.9, 170.5, 160.2, 158.9, 131.5, 119.4, 104.4, 98.3, 77.0, 61.4, 61.1, 57.3, 55.5, 55.4, 52.8, 40.4, 38.5, 36.8, 34.4, 28.8, 16.1, 13.9, 13.8 ppm

LRMS (ESI) m/z Found: (M+Na)⁺, C₂₄H₂₆O₈ 469.1, requires 469.2
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6.3.5 Synthesis of δ-lactone 235

Diethyl 8-(4-methoxyphenyl)-1-oxo-5,6,8,8a-tetrahydro-1H-isochromene-7,7(4aH)-dicarboxylate (235)

Potassium hexamethyldisilazide (0.02 mL of a 0.5 M solution in toluene, 0.01 mmol) was added to an stirred solution of C3•HCl (3.4 mg, 0.01 mmol) in THF (2 mL) at room temperature. After 15 minutes, this solution was added in one portion to a stirred solution of donor-acceptor cyclobutane 232 (36 mg, 0.1 mmol) and α,β-unsaturated acyl fluoride 210c (18 mg, 0.1 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 2 hours then concentrated under reduced pressure and purified via flash column chromatography to afford the title compound 235 (37 mg, 93% yield) as a single diastereoisomer as observed by 1H NMR (>20:1 dr).

Rf 0.3 (7:3, v/v hexanes : EtOAc)

IR νmax 2981, 2939, 1771, 1724, 1513, 1254, 1225, 1178 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 7.33 (brs, 2H), 6.75 (brd, J = 9.2 Hz, 2H), 6.54 (dd, J = 6.0, 3.2 Hz, 1H), 5.05 (dm, J = 6.0 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.95-3.87 (m, 2H), 3.77-3.69 (m, 1H), 3.74 (s, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.14-3.10 (m, 1H), 2.30-2.20 (m, 2H), 1.84-1.68 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 171.0, 169.9, 168.1, 159.1, 141.8, 131.7, 128.7, 113.1, 108.5, 61.3, 61.0, 59.6, 55.2, 45.0, 42.4, 31.3, 29.9, 25.0, 14.1, 13.7 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₂H₂₆O₇, 403.1753, requires 403.1751.
6.3.5 Derivatisation studies

Diethyl (R)-3-(2,4-dimethoxyphenyl)spiro[5.5]undec-4-ene-2,2-dicarboxylate (236)

![Chemical Structure](image)

A solution of β-lactone 220d (61.7 mg, 0.13 mmol) in DMF (2.5 mL) was heated at 110 °C for 14 hours. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with Et₂O (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 236 (43 mg, 94%) yield as a white solid

Rфр 0.4 (4:1, v/v hexanes : EtOAc)

IR νmax 2931, 2853, 1732, 1504, 1208 cm⁻¹

HPLC Daicel AD-H, hexane : tPrOH 90:10, 1 mL/min, λ = 238 nm, fraction tᵣ = 8.28 (minor enantiomer) and 9.24 (major enantiomer); er = 99:1

[ ]D²⁵ = +211° (c = 2.59, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, J = 8.4 Hz, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 5.66 (brd, J = 10.0 Hz, 1H), 5.58 (dd, J = 10.0, 4.8 Hz, 1H), 4.84 (brd, J = 4.8 Hz, 1H), 4.22 (ABX₉, J = 10.8, 7.2 Hz, 1H), 4.07 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.96 (ABX₉, J = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.66 (ABX₉, J = 10.8, 7.2 Hz, 1H), 2.47 (ABq, J = 14.8 Hz, 1H), 2.06 (ABq, J = 14.8 Hz, 1H), 1.65-1.18 (m, 10H), 1.24 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 172.5, 170.9, 159.9, 158.2, 134.6, 131.8, 126.5, 119.9, 103.8, 98.3, 61.1, 60.8, 56.4, 55.4, 55.3, 41.4, 35.4, 33.9, 26.1, 21.8, 21.5, 14.0, 13.9 ppm

HRMS (ESI) m/z Found: (M+Na)⁺, C₂₂H₂₀O₉ 453.2246, requires 453.2248.
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Allyl (2S,3R)-2-allyl-3-(4-methoxyphenyl)spiro[5.5]undec-4-ene-2-carboxylate (237)

In an oven-dried pressure tube, a solution of β-lactone 220l (23.4 mg, 50 µmol) in DMF (0.5 mL) was heated at 120 °C under an atmosphere of argon for 6 hours. Upon cooling to room temperature, a solution of Pd(dppe)$_2$ (4.5 mg, 5 µmol) in DMF (0.5 mL) was added via cannula and the reaction mixture heated to 120 °C for 16 h. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried (MgSO$_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 235 (43 mg, 57%) as mixture of diastereoisomers as observed by $^1$H NMR (3:1 dr).

Major diastereoisomer:

R$_f$ 0.5 (19:1, v/v hexanes : EtOAc)

IR $\nu_{max}$ 3076, 3011, 2923, 2852, 1730, 1608, 1509, 1254, 1164, 1133 cm$^{-1}$

HPLC RegisCell$^\text{TM}$ $\mu$m, hexane : PrOH 99:1, 1 mL/min, $\lambda$ = 230 nm, fraction $t_c$ = 3.89 (minor enantiomer) and 4.15 (major enantiomer); er = 99:1

$[\alpha]_D^{25} = +178.2^\circ$ (c = 0.20, CHCl$_3$)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.14 (AA′BB′, $J = 8.7$ Hz, 2H), 6.83 (AA′BB′, $J = 8.7$ Hz, 2H), 5.92 (ddt, $J = 17.0, 10.4, 6.0$ Hz, 1H), 5.76-5.66 (m, 2H), 5.63-5.60 (m, 1H), 5.34 (ddt, $J = 17.0$ Hz, 1.5 Hz, 1.3 Hz, 1H), 5.23 (ddt, $J = 10.4$ Hz, 1.5 Hz, 1.3 Hz, 1H), 5.01-4.98 (m, 1H), 4.91-4.85 (m, 1H), 4.56 (ABMX$_2$, $J = 13.0$, 6.0, 1.3 Hz, 1H), 4.44 (ABMX$_2$, $J = 13.0$, 6.0, 1.3 Hz, 1H), 4.02 (d, $J = 5.2$ Hz, 1H), 3.79 (s, 3H), 2.26 (ABq, $J = 14.3$ Hz, 1H), 2.07 (ABX, $J = 14.1$, 8.3, Hz, 1H), 1.75 (ABX, $J = 14.1$, 6.0 Hz, 1H), 1.60-1.37 (m, 10H), 1.50 (ABq, $J = 14.3$ Hz, 1H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.0, 158.6, 133.6, 132.4, 132.3, 131.6, 127.6, 118.7, 118.1, 113.5, 65.5, 55.4, 49.1, 44.4, 42.8, 41.3, 36.4, 35.0, 29.9, 26.1, 21.9, 21.6 ppm

HRMS (ESI) m/z Found: (M+H)$^+$. $C_{25}H_{33}O_3$. 381.2420, requires 381.2424
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Methyl (3S)-3-(4-methoxyphenyl)spiro[5.5]undec-4-ene-2-carboxylate (239)

In a pressure tube, a solution of β-lactone 220k (20.8 mg, 50 µmol) in DMSO (0.5 mL) was heated at 120 °C for 6 hours. Upon cooling to room temperature, lithium chloride (4 mg, 0.1 mmol) and water (1.8 µL, 50 µmol) were added and the reaction mixture heated to 170 °C for 16 hours. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried (MgSO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 239 (10 mg, 64% yield) as a mixture of diastereoisomers as observed by ¹H NMR (2:1 cis/trans).

Trans-isomer:

Rₜ 0.2 (19:1, v/v hexanes : EtOAc)

IR ʋₘₐₓ 2996, 2923, 2852, 1735, 1610, 1510, 1242, 1160, 1035 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 99:1, 0.5 mL/min, ʋ = 230 nm, fraction ʋ = 13.23 (minor enantiomer) and 19.30 (major enantiomer); ε = 98:2

[ ]²⁵ D = +106.2° (c = 0.20, CHCl₃)

¹H NMR (300 MHz, CDCl₃) δ 7.08 (AA'BB', J = 8.4 Hz, 2H), 6.81 (AA'BB', J = 8.4 Hz, 2H), 5.74 (d, J = 10.4 Hz, 1H), 5.49 (dd, J = 10.4, 2.2 Hz, 1H), 3.78 (s, 3H), 3.61 (dt, J = 10.4, 2.2 Hz, 1H) 3.55 (s, 3H), 2.63 (ddd, J = 13.0, 10.4, 2.8 Hz, 1H), 2.01 (brd, J = 14.0 Hz, 1H), 1.60-1.37 (m, 11H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 176.3, 158.4, 136.3, 129.0, 128.3, 114.0, 55.4, 51.7, 46.2, 44.7, 39.6, 37.9, 36.8, 34.9, 26.3, 22.0, 21.6 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₂₀H₂₆O₆⁺ 315.1957 requires 315.1955.
Chapter 6

Diethyl (3R,4R,5S)-5-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)spiro[5.5]undecane-2,2-dicarboxylate (240a)

Lithium aluminium hydride (0.2 mL of a 1 M aqueous solution, 0.2 mmol) was added dropwise to a solution of β-lactone 220c (89 mg, 0.2 mmol) in THF (3 mL) at −78 °C. After 30 minutes, the reaction was quenched with water (0.2 mL) then sodium hydroxide (0.2 mL of a 1 M aqueous solution) and Et₂O (5 mL) were added sequentially. The reaction was allowed to warm to 0 °C in an ice-water bath, then magnesium sulfate was added and the mixture filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 240a (78 mg, 83% yield) as a single diastereoisomer as observed by ¹H NMR (>20:1 dr).

R₄0.3 (1:1, v/v hexanes : EtOAc)

IR νmax 3443, 2929, 2857, 1721, 1610, 1511, 1241, 1176 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 230 nm, fraction tr = 11.52 (minor enantiomer) and 12.43 (major enantiomer); er = 96:4

[ρ]D²⁵ = -10.1° (c = 1.35, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.81 (brs, 1H), 6.97 (brs, 1H), 6.78 (brs, 2H), 4.13 (ABX, J = 10.8, 7.2 Hz, 1H), 4.01-3.91 (m, 3H), 3.77 (s, 3H), 3.78-3.68 (m, 3H), 3.51 (d, J = 12.4 Hz, 1H), 3.10 (brs, 1H), 2.76 (dm, J = 12.4 Hz, 1H), 2.39 (d, J = 14.4 Hz, 1H), 2.24 (d, J = 14.4 Hz, 1H), 1.86 (brs, 1H), 1.57-1.24 (m, 10H), 1.18 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 172.2, 172.0, 158.6, 130.9, 130.2, 114.0, 65.4, 61.2, 60.6, 59.1, 55.3, 44.1, 38.0, 37.5, 36.0, 32.8, 26.4, 21.7, 21.5, 13.9, 13.7 ppm

LRMS (ESI) m/z Found: (M+Na)+, C₂₃H₂₈O₇, 471.3, requires 471.2
Diethyl \((3R,4S,5S)-4\)-(benzyl carbamoyl)-5-hydroxy-3-(4-methoxyphenyl) spiro[5.5]undecane-2,2-dicarboxylate (241)

\[
\begin{align*}
\text{OMe} & \quad \text{EtO}_{2}C \\ \\
\text{EtO}_{2}C & \quad \text{O} \\
\quad & \quad \text{BrNH}_{2}, \quad \text{THF, rt, 16 h} \\
\quad & \quad \text{OMe} \\
& \quad \text{EtO}_{2}C \\
\end{align*}
\]

Benzylamine (44 µL, 0.4 mmol) was added to a solution of β-lactone 220c (89 mg, 0.2 mmol) in THF (3 mL) at room temperature. After 24 hours, the mixture was concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 241 (99 mg, 86% yield) as a single diastereoisomer as observed by \(^1\)H NMR (>20:1 dr).

\(R_f 0.3\) (4:1, v/v hexanes : EtOAc)

\(\text{IR } v_{\text{max}} 3432, 3383, 2996, 2916, 1750, 1706, 1657, 1512, 1242 \text{ cm}^{-1}\)

\(\text{HPLC Daicel AD-H, hexane : } \pi \text{PrOH 90:10, 1 mL/min, } \lambda = 230 \text{ nm, fraction } t = 7.08 \text{ (major enantiomer)} \text{ and } 7.97 \text{ (minor enantiomer); } \text{er } 95:5\)

[\(\alpha\)]\(_D^{25}\) = +49.9\(^o\) (c = 1.35, CHCl\(_3\))

\(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) 7.39-7.73 (m, 2H), 7.22-7.17 (m, 3H), 6.83-6.81 (m, 2H), 6.71-6.69 (m, 2H), 5.86 (brt, \(J = 5.4 \text{ Hz, 1H}\)), 4.64 (brs, 1H), 4.29 (dd, \(J = 14.8, 6.4 \text{ Hz, 1H}\)), 4.18 (ABX\(_g\), \(J = 10.8, 7.2 \text{ Hz, 1H}\)), 4.03 (dd, \(J = 14.8, 5.4 \text{ Hz, 1H}\)) 4.03-3.91 (m, 2H), 3.89 (brs, 1H), 3.78 (d, \(J = 12.4 \text{ Hz, 1H}\)), 3.76 (s, 3H), 3.72 (ABX\(_g\), \(J = 10.8, 7.2 \text{ Hz, 1H}\)), 3.51 (dd, \(J = 12.4, 1.6 \text{ Hz, 1H}\)), 2.51 (ABq, \(J = 14.4 \text{ Hz, 1H}\)), 2.22 (ABq, \(J = 14.4 \text{ Hz, 1H}\)), 1.64-1.31 (m, 10H), 1.20 (t, \(J = 7.2 \text{ Hz, 3H}\)), 0.86 (t, \(J = 7.2 \text{ Hz, 3H}\)) ppm

\(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) 174.6, 172.4, 171.3, 1587, 137.4, 132.1, 130.0, 128.6, 127.9, 127.5, 113.1, 61.2, 60.8, 58.7, 55.2, 45.9, 44.8, 43.6, 37.4, 36.3, 32.2, 26.4, 21.7, 21.5, 14.0, 13.7 ppm

HRMS (ESI) m/z Found: (M+Na\(^+\)), \(C_{32}H_{31}NO_5\) 574.2777, requires 574.2775
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Diethyl (1S,4S,7S,8R)-8-(4-methoxyphenyl)-5-oxo-6-oxaspiro[bicyclo[2.2.2]octane-2,1'-cyclohexane]-4,7-dicarboxylate (242a)

A solution of β-lactone 220c (89 mg, 0.2 mmol) and p-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) in EtOH (2 mL) was heated at reflux for 20 hours. The mixture was then concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 242a (87mg, 98% yield) as a single diastereoisomer as observed by 1H NMR (>20:1 dr).

Rf 0.4 (4:1, v/v hexanes : EtOAc)

IR ν_max 2935, 2836, 1746, 1723, 1612, 1513, 1237, 1213, 1161, 1096 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tr = 15.65 (major enantiomer) and 23.49 (minor enantiomer); er = 95:5

[α]_D^25 = -10.4° (c = 0.99, CHCl₃)

1H NMR (400 MHz, CDCl₃) δ 7.22 (AA'BB', J = 8.8 Hz, 2H), 6.83 (AA'BB', J = 8.8 Hz, 2H) 4.71 (s, 1H),
4.24-4.09 (m, 4H), 4.03 (ABX₂, J = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.17 (d, J = 7.6 Hz, 1H), 2.18 (ABq, J = 14.8 Hz, 1H), 2.02 (ABq, J = 14.8, 2.0 Hz, 1H), 1.80-1.57 (m, 5H), 1.53-1.28 (m, 5H), 1.24 (t, J = 7.2
Hz, 3H), 1.17 (s, J = 7.2 Hz, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 171.6(4), 171.5(8), 168.5, 159.2, 130.5, 129.3, 114.1, 85.1, 61.9, 61.7,
55.3, 54.0, 45.8, 42.8, 38.0, 35.4, 34.8, 25.5, 22.5, 21.2, 14.2, 14.0 ppm

HRMS (ESI) m/z Found: (M+H)^+, C₂₅H₂₀O₇, 445.2224, requires 445.2221
Ethyl (2aS,4aS,10bR,10cS)-3,3,6-trimethyl-1,5-dioxo-3,4,5,6,10b,10c-hexahydro-1H-oxeto[2,3-k]phenanthridine-4a(2aH)-carboxylate (243)

A suspension of β-lactone 220p (30 mg, 60 μmol) and palladium on carbon (4.6 mg, 10 wt%) in THF (1.5 mL) was stirred at room temperature under an atmosphere of hydrogen for 4 hours. The mixture was then filtered through a pad of Celite, concentrated under reduced pressure and used immediately in the next step. The residue was dissolved in THF (1 mL), potassium carbonate (12.3 mg, 89 μmol) was added and the mixture was heated under reflux for 14 hours. The mixture was allowed to cool to room temperature then concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 243 (20 mg, 94% yield as a mixture of diastereoisomers as observed by 1H NMR (5:1 cis/trans).

cis-isomer:

Rf 0.3 (7:3 v/v hexanes : EtOAc)

IR νmax 2977, 2962, 2934, 1825, 1732, 1676, 1472, 1367, 1278, 1243 cm⁻¹

HPLC Daicel AD-H, hexane : iPrOH 80:20, 1 mL/min, λ = 238 nm, fraction t₁ = 6.75 (minor enantiomer) and 9.71 (major enantiomer); er = 99:1

[α]D²⁵ = +30.6° (c = 0.34, CHCl₃)

1H NMR (400 MHz, CDCl₃) δ 7.36-7.30 (m, 2H), 7.09 (td, J = 7.2, 1.2 Hz, 1H), 7.00 (brd, J = 8.4 Hz, 1H), 4.32 (d, J = 6.8 Hz, 1H), 4.02 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.94 (ABX₃, J = 10.8, 7.2 Hz, 1H), 3.46 (dd, J = 11.2, 6.8 Hz, 1H), 3.42 (s, 3H), 2.78 (ABq, J = 15.2 Hz, 1H), 2.01 (ABq, J = 15.2 Hz, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 171.6, 170.1, 167.4, 138.2, 129.2, 129.1, 124.3, 124.0, 115.0, 76.6, 62.2, 52.6, 51.0, 38.6, 36.9, 32.0, 31.0, 30.9, 25.5, 13.8 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₀H₂₃NO₅ 358.1648, requires 358.1649.

trans-isomer:

Rf 0.4 (7:3 v/v hexanes : EtOAc)

IR νmax 2967, 2932, 1820, 1725, 1675, 1460, 1353, 1272, 1218 cm⁻¹
6.4 Experimental section for Chapter 4

6.4.1 Synthesis of hexahydrobenzopyrobenzofuran 277

2,6-Dimethoxybenzaldehyde (277)\textsuperscript{30}

\[
\begin{align*}
\text{(MeO)}_2C\text{H}_4\text{CHO} & \xrightarrow{\text{tBuLi, TMEDA, THF, 0 °C, then DMF, 0 °C \rightarrow rt, 1 h}} \text{(MeO)}_2C\text{H}_4\text{C(O)}\text{Me}_2
\end{align*}
\]

Following a modified procedure of Krupadanam\textsuperscript{30}, a round bottom flask was charged with 1,3-dimethoxybenzene (9.48 mL, 60 mmol), TMEDA (12.4 mL, 82 mmol) and anhydrous THF (110 mL). The mixture was cooled to 0 °C before tBuLi (1.6 M in hexanes, 54 mL, 87 mmol) was added via syringe over 15 minutes. The reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (5.1 mL, 90 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH\textsubscript{4}Cl (60 mL of a saturated aqueous solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 60 mL) and washed with water (1 x 60 mL) and brine (1 x 60 mL). The combined organics were dried (Na\textsubscript{2}SO\textsubscript{4}), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound 277 (6.5 g, 72% yield) as a yellow solid.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ 10.46 (s, 1H), 7.43 (t, J = 9.1 Hz, 1H), 6.55 (d, J = 9.1 Hz, 2H), 3.89 (s, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 170.8(6), 170.7(7), 168.1, 139.3, 128.5, 126.4, 125.1, 124.0, 115.0, 77.3, 61.8, 51.9, 49.7, 40.0, 36.1, 32.6, 31.2, 30.8, 25.9, 13.8 ppm.
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(E)-3-(2,6-dimethoxyphenyl)acrylic acid (278)\textsuperscript{31}

Following a modified procedure of Diederich,\textsuperscript{32} a round bottom flask was charged with aldehyde 277 (1.1 g, 6.4 mmol), malonic acid (1.33 g, 12.8 mmol), piperidine (0.5 mL) and pyridine (30 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification with concentrated HCl, the precipitate was washed with H\textsubscript{2}O (500 mL) and hexanes (500 mL) before being dried at 60 °C \textit{in vacuo}. The title compound 278 (1.2 g, 87%) was isolated as an off white solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.25 (d, \(J = 16.3\) Hz, 1H), 7.29 (t, \(J = 8.4\) Hz, 1H), 6.91 (d, \(J = 16.3\) Hz, 1H), 6.57 (d, \(J = 8.4\) Hz, 2H), 3.90 (s, 6H) ppm

(E)-3-(2,6-dimethoxyphenyl)acryloyl fluoride (210m)

Following the procedure of Fu\textsuperscript{16} to a suspension of \(\alpha,\beta\)-unsaturated carboxylic acid 278 (0.84 g, 4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) at 0 °C was added diethylaminosulfur trifluoride (0.58 mL, 4.4 mmol mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by the slow addition of NaHCO\textsubscript{3} (20 mL of a saturated aqueous solution). The mixture was then extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 20 mL), and washed with NaHCO\textsubscript{3} (2 x 20 mL of a saturated aqueous solution). The combined organics were dried (Na\textsubscript{2}SO\textsubscript{4}), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 210m (0.79 g, 94% yield) as an off white solid.

R\textsubscript{f} 0.8 (1:1, v/v hexanes : EtOAc)

MP 90-92 °C

IR \(\nu_{\max}\) 2948, 2843, 1776, 1575, 1474, 1101 cm\textsuperscript{-1}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.31 (d, \(J = 16.2\) Hz, 2H), 7.34 (t, \(J = 8.4\) Hz, 1H) 6.82 (dd, \(J = 16.2, 7.5\) Hz, 1H), 6.57 (d, \(J = 8.4\) Hz, 2H), 3.89 (s, 3H) ppm
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$^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.9, 160.7, 157.4, 142.5, 133.3, 114.2, 113.6, 111.5, 56.0 ppm

HRMS (ESI) m/z Found: (M–F)$^+$, C$_{17}$H$_{11}$FO$_3$, 191.0708, requires 191.0699

Dimethyl [(1S,2R,6R)-2-(2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ad)

A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane 216e (3.6 g, 10 mmol), α,β-unsaturated acyl fluoride 210m (2.1 g, 10 mmol), THF (65 mL) and DMF (1.5 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC B9 (0.1 mmol) in THF (7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound 220ad (1.6 g, 45% yield, >20:1 d.r) as a yellow solid.

R$_f$ 0.4 (1:1, v/v hexanes : EtOAc)

MP 117-119 °C

IR $\nu_{max}$ 2951, 2841, 1815, 1728, 1592, 1474, 1231, 1105 cm$^{-1}$

HPLC RegisCell$^\text{TM}$ S$\mu$m, hexane : iPrOH 80:20, 1 mL/min, $\lambda$ = 230 nm, fraction $t_r$ = 10.09 (major enantiomer) and 11.09 (minor enantiomer); $\text{er} = 92:8$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.15 (t, $J$ = 8.3 Hz, 1H), 6.49 (d, $J$ = 8.3 Hz, 2H), 5.21 (d, $J$ = 1.3 Hz, 1H), 4.89-4.84 (m, 1H), 3.85 (dd, $J$ = 6.9, 1.3 Hz, 1H), 3.79 (brs, 3H), 3.78 (s, 3H), 3.77 (brs, 3H), 3.16 (s, 3H), 2.60-2.48 (m, 2H), 2.03-1.98 (m, 1H), 1.89-1.81 (m, 1H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.0, 171.9, 158.2, 129.0, 118.0, 110.4, 104.0, 103.9, 70.4, 57.4, 56.0 55.2, 52.9, 52.8, 51.7, 29.3, 25.0, 24.6 ppm

HRMS (ESI) m/z Found: (M+H)$^+$, C$_{19}$H$_{13}$O$_8$, 379.1381, requires 379.1387
cis-Methyl 2',6'-dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (cis-284) and trans-methyl 2',6'-dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (trans-284)

Following a modified procedure of Ban, a round bottom flask was charged with β-lactone 220ad (0.79 g, 2.1 mmol), LiCl (0.36 g, 8.6 mmol), water (77 µL, 4.3 mmol) and DMSO (8 mL). The flask was sealed and heated to 170 °C for 16 hours. The mixture was cooled to room temperature before water (10 mL) was added and the aqueous extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (1 x 20 mL), dried (MgSO₄), concentrated under reduced pressure and the crude material purified by flash chromatography to afford the title compounds cis- and trans-284 (0.38 g, 66% yield, 2:1 d.r cis:trans).

cis-isomer:

Rf 0.6 (2:1, v/v hexanes : EtOAc)

IR ν₂₉₃₃, 2836, 1731, 1590, 1472, 1432, 1243, 1103 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.13 (t, J = 8.3 Hz, 1H), 6.51 (d, J = 8.3 Hz, 2H), 5.78-5.73 (m, 1H), 5.69-5.59 (m, 1H), 4.53-4.38 (m, 1H), 3.75 (s, 6H), 3.32 (s, 3H), 2.97 (ddd, J = 9.3, 7.5, 3.8 Hz, 1H), 2.48-2.36 (m, 1H), 2.29-2.18 (m, 1H), 2.12-1.99 (m, 1H), 1.88-1.77 (m, 1H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 175.0, 159.2, 128.9, 127.9, 124.6, 118.4, 104.3, 55.8, 50.8, 43.1, 32.7, 23.4, 22.9 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₆H₂₀O₆ 277.1437, requires 277.1434

trans-isomer:

Rf 0.6 (2:1, v/v hexanes : EtOAc)

IR ν₂₉₃₆, 2836, 1734, 1590, 1465, 1431, 1243, 1110 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.13 (t, J = 8.3 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.72-5.65 (m, 1H), 5.49-5.45 (m, 1H), 4.35-4.31 (m, 1H), 2.52-2.36 (m, 1H), 2.21-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.95-1.86 (m, 1H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 176.5, 159.1, 130.6, 127.8, 124.1, 119.7, 104.7, 56.1, 51.3, 43.5, 34.9, 26.8, 24.6 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₆H₂₀O₆ 277.1437, requires 277.1434
6,6-Dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (286)

Following the procedure of Carreira, to a solution of cis-284 (69 mg, 0.25 mmol) in Et₂O (2 mL) was added MeMgI (0.84 mL, 3.75 M in Et₂O, 2.5 mmol) dropwise. The mixture was stirred for 16 h at room temperature before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et₂O (3 mL) and quenched with NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et₂O (3 x 3 mL), the organic phase dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was then taken up in CH₂Cl₂ (2 mL), and ZnBr₂ (86 mg, 0.4 mmol) and MgSO₄ (120 mg, 1 mmol) were added. The mixture was stirred for 4 h at room temperature before the reaction was quenched with the addition of NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH₂Cl₂ (3 x 2 mL), the organic phase dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 286 (31 mg, 54% yield) as a yellow oil.

IR ν max: 3382, 2975, 2930, 2872, 1612, 1585, 1457, 1263, 1133, 1018 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 6.98-6.89 (m, 1H), 6.60-6.54 (m, 1H), 6.47-6.39 (m, 1H), 6.27 (dd, J = 7.9, 1.0 Hz, 1H), 5.79 (ddd, J = 9.4, 5.1, 3.4 Hz, 1H), 5.81-5.77 (m, 1H), 4.97 (s, 1H), 3.63 (brs, 1H), 2.12-2.05 (m, 1H), 1.99-1.89 (m, 1H), 1.84-1.74 (m, 1H), 1.42 (s, 3H), 1.42-1.39 (m, 1H), 1.29 (s, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 155.2, 154.5, 129.7, 128.0, 127.3, 112.1, 110.5, 107.7, 70.7, 40.3, 31.6, 26.0, 25.3, 25.1, 20.4 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₈H₁₀O₂, 231.1380, requires 231.1383

6,6-Dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-yl acetate (287)

Following the procedure of Snider, a round bottom flask was charged with benzopyran 284 (31 mg, 0.13 mmol) and pyridine (0.5 mL). Acetic anhydride (0.25 mL) was then added dropwise and the mixture was
stirred for 16 h at room temperature. Et₂O (3 mL) was then added, and the mixture washed with water (2 x 3 mL), NaHCO₃ (2 x 3 mL of a saturated aqueous solution) and brine (3 mL). The combined organics were dried (MgSO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 287 (31 mg, 85% yield) as a colourless oil.

IR νmax 2978, 2933, 2839, 1763, 1459, 1369, 1203, 1027 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.09 (td, J = 8.1, 0.7 Hz, 1H), 6.71 (td, J = 8.1, 1.2 Hz, 1H), 6.58 (dd, J = 8.1, 1.2 Hz, 1H), 6.21-6.15 (m, 1H), 5.84-5.76 (m, 1H), 3.51 (brs, 1H), 2.33 (s, 3H), 2.09-2.04 (m, 1H), 1.98-1.88 (m, 1H), 1.80-1.75 (m, 1H), 1.42 (s, 3H), 1.41-1.38 (m, 1H), 1.27 (s, 3H) ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₇H₂₆O₅ 273.1490, requires 273.1485

9,9-Dimethyl-2,3,3a,3a1,9,9a-hexahydro-1H-benzofuro[4,3,2-cde]chromen-3-ol (273)

Following a modified procedure of Snider, m-chloroperbenzoic acid (12 mg, 71 µmol) was added to a solution of acetate 287 (19 mg, 70 µmol) in CH₂Cl₂ (1 mL). The solution was stirred for 2 h at room temperature before the solvent was removed under reduced pressure. The residue was then taken up in EtOAc (3 mL) and washed with Na₂SO₃ (2 x 3 mL of a saturated aqueous solution), NaHCO₃ (2 x 3 mL of a saturated aqueous solution) and brine (3 mL). The combined organics were dried (MgSO₄), concentrated under reduced pressure to afford the crude epoxide which was used without further purification. The crude epoxide was taken up in MeOH (1 mL), and K₂CO₃ (10 mg, 71 µmol) was added. The mixture was stirred for 2 h at room temperature before being diluted with the addition of NH₄Cl (3 mL of a saturated aqueous solution). The aqueous layer was extracted with EtOAc (3 x 2 mL), and the combined organics dried (MgSO₄), concentrated under reduced pressure and purified via flash column chromatography to afford the title compound 273 (7 mg, 40% yield) as a yellow oil.

IR νmax 2978, 2933, 2839, 1763, 1459, 1369, 1203, 1027

¹H NMR (400 MHz, CDCl₃) δ 7.01 (td, J = 8.1, 1.0 Hz, 1H), 6.41 (d, J = 8.1 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 4.72 (dd, J = 7.7, 7.0 Hz, 1H), 3.71-3.66 (m, 1H), 2.10 (brs, 1H) 3.37-3.31 (m, 1H), 1.96-1.86 (m, 1H), 1.84-1.73 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H) ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₅H₁₅O₃ 247.1331, requires 247.1329
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6.4.2 Synthesis of DA-cyclobutane 216m

Ethyl 2-methylene-3-oxobutanoate (290)

Following the procedure of Tardella,\textsuperscript{36} a round bottom flask was charged with NaH (0.37 g, 60% in mineral oil 3 mmol) and THF (20 mL). The suspension was cooled to 0 °C and ethyl 2-methyl-3-oxobutanoate (0.28 mL, 2 mmol) was added dropwise over 15 minutes. After one hour of stirring at 0 °C, a solution of phenylselenium chloride (0.38 g, 2 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 30 minutes. Et\textsubscript{2}O (30 mL) was added and the mixture was washed with NaHCO\textsubscript{3} (2 x 15 mL of a saturated aqueous solution). The combined organics were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to afford the crude selenoxide which was used without further purification. The crude residue was taken up in CH\textsubscript{2}Cl\textsubscript{2} (20 mL) and cooled to 0 °C before H\textsubscript{2}O\textsubscript{2} (0.8 mL, 30% in H\textsubscript{2}O) was added slowly. The biphasic mixture was stirred vigorously for 2 h at this temperature before being washed with NaHCO\textsubscript{3} (2 x 20 mL of a saturated aqueous solution) and brine (20 mL). The combined organics were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to afford the title compound 290 which was used without further purification.

Ethyl 1-acetyl-2-((trimethylsilyl)oxy)cyclobutane-1-carboxylate (cis/trans-216m)

Following a modification of the procedure of Roberts,\textsuperscript{39} to a suspension of ZnBr\textsubscript{2} (0.45 g, 2 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL) at -78 °C was added a solution of the methylene acetoacetate 290 (2 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) followed by a solution of trimethylsilyl enol ether 223b (0.36 mL, 2.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL). After stirring at -78 °C for 30 minutes, the reaction was quenched by the addition of a cold (-78 °C) solution of pyridine (0.65 mL, 8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL). The mixture was allowed to warm to room temperature, then washed with Na\textsubscript{2}EDTA (2 x 10 mL of a saturated aqueous solution), water (10 mL) and brine (10 mL) before the organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure.
pressure. The crude oil was purified by flash column chromatography on neutralized silica gel to afford the title compound 216m (0.14 g, 26% yield) as a mixture of diastereomers (3:2 d.r) as observed by $^1$H NMR analysis.

**major diastereomer:**

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.72 (t, $J = 7.6$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 2.52-2.42 (m, 1H), 2.16-2.11 (m, 1H), 2.10 (s, 3H), 1.62-1.53 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.09 (s, 9H) ppm

**minor diastereomer:**

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.79 (t, $J = 7.6$ Hz, 1H), 4.22-4.13 (m, $J = 7.1$ Hz, 2H), 2.62-2.56 (m, 1H), 2.17 (s, 3H), 1.94-1.82 (m, 1H), 1.62-1.53 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.11 (s, 9H) ppm

Ethyl (E)-2-((3-(2,6-dimethoxyphenyl)acryloyl)oxy)-6-methyl-3,4-dihydro-2H-pyran-5-carboxylate (291)

A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane 216m (26 mg, 0.1 mmol), α,β-unsaturated acyl fluoride 210m (21 mg, 0.1 mmol), THF (0.65 mL) and DMF (0.15 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC B9 (0.01 mmol) in THF (0.7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound 291 (26 mg, 69% yield) as a viscous oil.

**IR** $\nu_{max}$ 2938, 2841, 1705, 1618, 1594, 1476, 1255, 1107, 1017 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.21 (d, $J = 16.3$ Hz, 1H), 7.28 (t, $J = 8.4$ Hz, 1H), 6.85 (d, $J = 16.3$ Hz, 1H), 6.55 (d, $J = 8.4$ Hz, 2H), 6.45 (dd, $J = 3.5$, 2.7 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.88 (s, 6H), 2.52-2.41 (m, 2H), 2.25 (s, 3H), 2.10-1.99 (m, 1H), 1.95-1.80 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.2, 167.1, 161.5, 160.3, 137.4, 131.8, 119.5, 112.2, 103.8, 102.7, 89.9, 60.0, 55.9, 24.9, 20.0, 17.2, 14.5 ppm

**HRMS (ESI) m/z Found:** (M+H)$^+$, C$_{30}$H$_{27}$O$_5$, 377.1592, requires 377.1595
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6.4.3 Synthesis of alkenyl side-chain bearing ketone 299

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)methanol (296)

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{H} & \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

DIBAL-H THF, -78 °C, 2 h

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{H} & \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

A round bottom flask was charged with cis-ester 284 (0.23 g, 0.83 mmol) and THF (5 mL) and cooled to -78 °C. A solution of DIBAL-H (1.83 mL, 1.0 M, 1.83 mmol) was then added dropwise and the mixture stirred for 1.5 hours at this temperature. The reaction was then warmed to 0 °C and diluted with Et₂O (10 mL) before the sequential dropwise addition of water (80 µL), NaOH (80 µL of a 15 wt% solution in water) and again, water (0.18 mL). The suspension was allowed to warm to room temperature and stirred for 15 minutes before MgSO₄ was added and the mixture stirred for an additional 15 minutes. The cloudy suspension was filtered through a pad of celite, the filtrate was concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 296 (0.19 g, 94% yield) as a clear oil.

R_f 0.3 (6:4, v/v hexanes : EtOAc)

IR \( \nu_{max} \) 3370, 3018, 2932, 2835, 1589, 1471, 1241, 1103 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.09 (t, \( J = 8.3 \) Hz, 1H), 6.49 (d, \( J = 8.3 \) Hz, 1H), 5.63-5.60 (m, 1H), 5.59-5.55 (m, 1H), 4.20-4.16 (m, 1H), 3.42 (dd, \( J = 11.3 \), 5.8 Hz, 1H), 3.32-3.26 (m, 1H), 2.12-1.96 (m, 4H), 1.88-1.81 (m, 1H), 1.72-1.65 (m, 1H) ppm

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 129.9, 127.9, 124.6, 118.7, 104.9, 65.5, 55.9, 40.3, 33.5, 24.0, 23.5 ppm

HRMS (ESI) \( m/z \) Found: (M+H\(^+\)), \( C_{15}H_{20}O_9 \) 249.1485, requires

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (297)

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{H} & \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{H} & \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

A round bottom flask was charged with dimethylsulfoxide (1.4 mL, 20 mmol) and CH₂Cl₂ (10 mL) and cooled to -78 °C. Oxalyl chloride (0.86 mL, 10 mmol) was then added slowly and the mixture stirred for 10 minutes before a solution of alcohol 296 (0.62 g, 2.5 mmol) in CH₂Cl₂ (10 mL) was added dropwise.
The mixture was allowed to stir for 30 minutes at this temperature before triethylamine (7 mL, 50 mmol) was added slowly. The cloudy suspension was then placed in an ice bath for 10 minutes and then warmed to room temperature. Water (50 mL) was then added and the mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 297 (0.54 g, 87% yield) as a yellow oil.

Rf 0.3 (4:1, v/v hexanes : EtOAc)

IR v max 3024, 2934, 2838, 2727, 1717, 1591, 1472, 1244, 1106 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 9.59 (d, J = 1.7 Hz, 1H), 7.18 (t, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 2H), 5.78-5.65 (m, 2H), 4.45 (brs, 1H), 3.76 (s, 6H), 2.65 (brs 1H), 2.35-2.39 (m 1H), 1.95-1.88 (m, 1H), 1.76-1.64 (m, 1H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 206.3, 158.7, 130.3, 128.3, 123.6, 117.7, 104.3, 55.6, 49.2, 33.1, 23.2, 22.0 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₅H₁₉O₄ 247.1331, requires 247.1329

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (295)

A round bottom flask was charged with aldehyde 297 (0.1 g, 0.73 mmol) and THF (5 mL) and cooled to 0 °C. A solution of MeMgBr (0.32 mL, 3.0 M in Et₂O, 0.94 mmol) was added slowly and the solution stirred for 1 hour at this temperature. The reaction was then quenched with the addition of NH₄Cl (10 mL of a saturated aqueous solution) and extracted with Et₂O (3 x 10 mL). The combined organics were dried (Na₂SO₄) and concentrated under reduced pressure to afford the secondary alcohol 298 which was used immediately in the next step. A round bottom flask was charged with dimethylsulfoxide (0.41 mL, 5.8 mmol) and CH₂Cl₂ (5 mL) and cooled to −78 °C. Oxalyl chloride (0.25 mL, 2.9 mmol) was then added slowly and the mixture stirred for 10 minutes before a solution of alcohol 298 (0.73 mmol) in CH₂Cl₂ (5 mL) was added dropwise. The mixture was allowed to stir for 30 minutes at this temperature before triethylamine (20 mL, 14.6 mmol) was added slowly. The cloudy suspension was then placed in an ice bath for 10 minutes and then warmed to room temperature. Water (20 mL) was then added and the mixture was extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried (Na₂SO₄),
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conzented under reduced pressure and the crude material purified via flash column chromatography to
afford the title compound 295 (0.13 g, 67% yield over two steps) as a yellow oil.
RF 0.4 (1:1, v/v hexanes : EtOAc)
IR νmax 3021, 2933, 2837, 1708, 1592, 1473, 1244, 1196 cm⁻¹
1H NMR (400 MHz, CDCl₃) δ 7.13 (t, J = 8.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 5.82-5.74 (m, 1H), 5.60
(brd, J = 9.9 Hz, 1H), 4.57 (brs, 1H), 3.74 (s, 6H), 3.03 (m, 1H), 2.34-2.23 (m, 2H) 2.09-2.04 (m, 1H),
1.85 (s, 3H), 1.76-1.67 (m, 1H) ppm
13C NMR (100 MHz, CDCl₃) δ 211.0, 158.9, 128.9, 128.2, 125.4, 117.9, 104.5, 55.6, 51.7, 31.9, 29.4, 24.1,
21.8 ppm
HRMS (ESI) m/z Found: (M+H)⁺, C₁₆H₂₀O₈ 261.1482, requires 261.1485

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-ylpent-4-en-1-one (299)

Following a modified procedure of Shi,⁰⁷ to a freshly prepared solution of lithium diisopropylamide (0.4
mL, 0.4 M in THF, 0.4 mmol) at -78 °C was added methylketone 295 (25 mg, 0.1 mmol) in THF (1 mL).
The mixture was stirred for 45 minutes at this temperature before hexamethylphosphoramide (35 μL, 0.2
mmol) was added followed by the addition of allyl bromide (17 μL, 0.2 mmol). The solution was then
warmed to room temperature and stirred for 20 hours before the solvent was removed under reduced
pressure. The residue was taken up in Et₂O (3 mL), and washed with water (2 mL) and brine (2 mL). The
combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the residue purified
via flash column chromatography to afford the title compound 299 (16 mg, 54% yield) as a colourless oil.
RF 0.4 (9:1, v/v hexanes : EtOAc)
IR νmax 3020, 2932, 1836, 1709, 1591, 1472, 1243, 1106 cm⁻¹
1H NMR (400 MHz, CDCl₃) δ 7.12 (t, J = 8.3 Hz, 1H), 6.49 (d, J = 8.3 Hz, 2H), 5.81-5.76 (m, 1H), 5.64-
5.53 (m, 2H), 4.91-4.81 (m, 2H), 4.58-4.55 (m, 1H), 3.74 (s, 6H), 3.05 (ddd, J = 11.5, 8.0, 3.6 Hz, 1H),
2.41 (ddd, J = 17.1, 9.5, 5.7 Hz, 1H), 2.35-2.28 (m, 1H), 2.20 (ddd, J = 17.1, 9.5, 5.7 Hz, 2H), 2.12-1.99
(m, 2H), 1.83-1.73 (m, 1H), 1.67 (m, 1H) ppm
6.4.4 Synthesis of α,β-unsaturated acyl fluoride 210n

3-Methoxycyclohex-2-en-1-one (303)₃₈

Following the procedure of Jadhav,₉⁰ a round bottom flasked was charged with cyclohexadione (5.6 g, 50 mmol), iodine (0.63 g, 2.5 mmol) and MeOH (100 mL). The solution was stirred at room temperature for 20 minutes before the solvent was removed under reduced pressure. The residue was taken up in EtOAc (60 mL) and washed with Na₂SO₃ (3 x 50 mL, 10 wt% aqueous solution). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the residue purified via flash column chromatography to afford the title compound 303 (2.0 g, 31% yield) as colourless low melting solid.

³H NMR (400 MHz, CDCl₃) δ 5.36 (s, 1H), 3.68 (s, 3H), 2.39 (t, J = 6.1 Hz, 2 H), 2.32 (t, J = 6.1 Hz, 2 H), 1.95 (m, 2 H)

Dimethyl 5-hydroxy-3-methoxystyphthalate (302)₄₀

To a freshly prepared solution of lithiumdiisopropylamide (11 mmol) in THF (10 mL) at –78 °C was added a solution of enone 303 (1.26 g, 10 mmol) in THF (5 mL) over 20 minutes. The mixture was stirred for 1 hour at this temperature before chlorotrimethylsilane (1.46 mL, 11.5 mmol) was added slowly. After an additional 1 hour stirring at this temperature, the reaction mixture was poured into an ice cold solution of NaHCO₃ (50 mL of a saturated aqueous solution). The mixture was extracted with Et₂O (2 x 30 mL) and washed with brine, before the combined organics were dried (Na₂SO₄) and concentrated under reduced pressure to afford the diene 305 as a colourless oil which was used immediately in the next reaction. Diene 305 was taken up in toluene (5 mL) and cooled to 0 °C before dimethylethylene
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dicarboxylate (1.0 mL, 8 mmol) was added and the reaction vessel sealed and heated to 150 °C for 16 hours. After this time, the mixture was cooled to room temperature and THF (15 mL) and HCl (4 mL of a 2.0 M aqueous solution) were added. The orange solution was stirred for 1 h at room temperature and then extracted with Et₂O (3 x 20 mL). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the crude residue purified via flash column chromatography to afford the title compound 302 (1.3 g, 68% yield) as a yellow solid.

R₇0.3 (1:1, v/v hexanes : EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, J = 2.0 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 5.98 (brs, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 168.0, 165.9, 160.2, 157.9, 132.5, 130.0, 118.6, 118.4, 106.4, 103.8, 69.3, 56.4, 52.7, 52.7 ppm

Dimethyl 5-(allyloxy)-3-methoxyphthalate (307)

A round bottom flask was charged with phthalate 302 (1.31 g, 5.4 mmol), potassium carbonate (1.50 g, 10.8 mmol), allyl bromide (0.93 mL, 10.8 mmol) and acetone (40 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified via flash column chromatography to afford the title compound 307 (1.46 g, 96% yield) as an off white solid.

IR νₐₐ₉max2998, 2952, 2845, 1726, 1603, 1329, 1269, 1152, 1062 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, J = 2.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 5.97 (m, 1H), 5.36 (brd, J = 17.3 Hz, 1H), 5.25 (brd, J = 10.4 Hz, 1H), 4.52 (d, J = 5.2 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H) ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₄H₂₆O₆, 281.1015, requires 281.1020

Dimethyl 4-(allyloxy)-3-bromo-6-methoxyphthalate (308)
A round bottom flask was charged with allyl ether 307 (1.40 g, 5 mmol), p-toluenesulfonic acid (95 mg, 0.5 mmol) and methanol (20 mL). A solution of N-bromosuccinimide (0.89 g, 5 mmol) in MeOH (10 mL) was then added over 20 minutes and the mixture stirred for an additional 10 minutes at room temperature. The reaction mixture was then concentrated under reduced pressure, and the residue purified via flash column chromatography (dry loaded) to afford the title compound 308 (1.49 g, 82% yield) as a white solid.

**IR** ν<sub>max</sub> 2977, 2951, 2852, 1732, 1582, 1434, 1334, 1252, 1040 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.52 (s, 1H), 6.08-5.98 (m, 1H), 5.48 (d, J = 17.2 Hz, 1H), 5.34 (d, J = 10.6 Hz, 1H), 4.66 (d, J = 4.1 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 167.09, 165.20, 159.07, 158.20, 138.33, 131.83, 118.58, 113.91, 101.26, 99.01, 70.32, 56.74, 52.92, 52.58 ppm

**HRMS (ESI) m/z Found:** (M+)<sup>+</sup>, C<sub>14</sub>H<sub>12</sub>BrO<sub>6</sub> 359.0128, requires 359.0125

**Dimethyl 3-bromo-4-hydroxy-6-methoxyphthalate (309)**

The title compound was prepared according the representative procedure for compound 307. The title compound 309 (1.24 g, 84% yield) was purified via flash column chromatography and isolated as a white solid.

**IR** ν<sub>max</sub> 3197, 2955, 2853, 1734, 1685, 1582, 1438, 1353, 1219, 1021 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.70 (s, 1H), 6.15 (s, 1H), 3.91 (s, 3H), 3.84 (s, 6H) ppm

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 166.7, 165.3, 159.2, 155.9, 136.8, 114.8, 101.1, 99.2, 56.7, 53.1, 52.7 ppm

**HRMS (ESI) m/z Found:** (M+)<sup>+</sup>, C<sub>13</sub>H<sub>12</sub>BrO<sub>6</sub> 318.9649 requires 318.9812

**Dimethyl 4-hydroxy-3-iodo-6-methoxyphthalate (310)**

Following the procedure of Parker, a round bottom flask was charged with phthalate 302 (0.28 g, 1 mmol), iodine (0.15 g, 0.6 mmol) and EtOH (7 mL). A solution of H<sub>2</sub>IO<sub>6</sub> (46 mg, 0.2 mmol) in water (0.5 mL)
was then added in one portion and the solution stirred for 8 hours at room temperature. After this time, the solvent was removed under reduced pressure, and the residue was taken up in EtOAc (20 mL) and washed with Na₂S₂O₃ (3 x 10 mL of a saturated aqueous solution) and brine (20 mL). The organics layer was dried (Na₂SO₄), concentrated under reduced pressure and the crude residue purified via flash column chromatography to afford the title compound 310 (0.31 g, 72% yield) as a white solid.

Rf 0.2 (1:1, v/v hexanes : EtOAc)

IR v max 3264, 2953, 1734, 1696, 1577, 1354, 1219, 1017 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 6.70 (s, 1H), 6.03 (brs, 1H), 3.92 (s, 3H), 3.84 (s, 6H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 168.0, 165.4, 160.3, 158.5, 140.9, 115.2, 103.4, 100.0, 56.6, 53.1, 52.8 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₁H₁₂O₉, 366.9677 requires 366.9673

### Dimethyl 3,5-dihydroxyphthalate (315)

A flame-dried Schlenk flask was charged with cyclohexanedione (2.24 g, 20 mmol), triethylamine (5.70 mL, 40.8 mmol) and anhydrous Et₂O (40 mL). The flask was cooled to 0°C and TMSOTf (7.16 mL, 39.6 mmol) was added dropwise before the solution was allowed to stir for 2 hours at this temperature. After this time, two distinct layers had formed and the top layer was transferred via syringe into a freshly dried Schlenk flask. The solvent was then removed under reduced pressure to afford bis-TMS enol ether 314. Dimethylacetylene dicarboxylate (2.40 mL, 15 mmol) was then added to the neat material and the vessel was sealed and heated to 120°C for 2 hours to give an orange oil. The crude residue was purified via flash column chromatography to afford the title compound 315 (2.6 g, 64% yield) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 10.97 (s, 1H), 7.25 (s, 1H), 6.45 (d, J = 2.3 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 3.89 (s, 3H), 3.87 ppm (s, 3H) ppm

### Dimethyl 3,5-dihydroxy-4-iodophthalate (259)
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The title compound was prepared according the representative procedure for compound 310. The title compound 259 (0.55 g, 65% yield) was purified via flash column chromatography and isolated as a white solid.

\[ ^{1}H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 12.01 \ (s, \ 1\text{H}), \ 6.63 \ (s, \ 1\text{H}), \ 6.19 \ (s, \ 1\text{H}), \ 3.90 \ (s, \ 3\text{H}), \ 3.88 \text{ ppm} \ (s, \ 3\text{H}) \ \text{ppm} \]

**Dimethyl 4-iodo-3,5-dimethoxyphthalate (316)**

A round bottom flask was charged with phthalate 259 (0.55 g, 1.6 mmol), potassium carbonate (0.86 g, 6.2 mmol), iodomethane (0.39 mL, 6.2 mmol) and acetone (20 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified via flash column chromatography to afford the title compound 316 (0.32 g, 54% yield) as an off white solid.

\[ R_f 0.5 \ (3:2, \ \text{v/v hexanes}: \text{EtOAc}) \]

**IR** \( \nu_{\text{max}} \) 2949, 2855, 1736, 1724, 1578, 1325, 1253, 1164, 1071 cm\(^{-1}\)

\[ ^{1}H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 7.19 \ (s, \ 1\text{H}), \ 3.96 \ (s, \ 2\text{H}), \ 3.93 \ (s, \ 2\text{H}), \ 3.90 \ (s, \ 2\text{H}), \ 3.89 \ (s, \ 2\text{H}) \ \text{ppm} \]

\[ ^{13}C\text{NMR} \ (100 \text{ MHz}, \text{CDCl}_3) \delta 167.2, \ 165.4, \ 160.3, \ 158.8, \ 130.0, \ 123.8, \ 107.5, \ 90.6, \ 62.9, \ 57.1, \ 52.9(8), \ 52.9(5) \ \text{ppm} \]

**HRMS** (ESI) \( m/z \text{Found: (M+Na)+} \)

\[ C_{12}H_{13}IO_{6} \ 402.1154 \text{ requires 402.9649} \]

**Dimethyl (E)-4-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-3,5-dimethoxyphthalate (318)**

Following a modified procedure of Ying,\(^6\) an oven dried pressure tube was charged with iodide 316 (380 mg, 1 mmol), \( \text{tBu} \) acrylate, (175 \( \mu \text{L}, \ 1.2 \text{ mmol}), \) potassium carbonate (275 mg, 2 mmol),
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IMes-Pd(dmab)Cl (12 mg, 0.4 mmol) and N-methylpyrrolidine (1 mL). The flask was sealed and heated to 120 °C for 5 h to give a dark solution before being cooled to room temperature and diluted with Et₂O (20 mL). The mixture was then filtered through a pad of celite, concentrated under reduced pressure and the crude residue purified via flash column chromatography to afford the title compound 318 (270 mg, 71% yield) as a white solid.

Rf 0.2 (1:1, v/v hexanes : EtOAc)

IR νmax 2946, 2844, 1722, 1706, 1627, 1237, 1145, 1099, 1043

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 16.3 Hz, 1H), 7.26 (s, 1H), 6.83 (d, J = 16.3 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 1.48 (s, 9H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 167.8, 166.94, 165.3, 159.9, 157.8, 132.7, 129.4, 127.0, 123.93, 121.9, 108.22, 80.7, 63.4, 56.34, 52.9, 52.9, 28.3 ppm

LRMS (ESI) m/z Found: (M+Na)⁺, C₁₀H₂₉O₉, 403.1 requires 403.1

Dimethyl (E)-4-(3-fluoro-3-oxoprop-1-en-1-yl)-3,5-dimethoxyphtalate (220n)

![Diagram of chemical reaction](image)

A round bottom flask was charged with cinnamate 318 (182 mg, 0.5 mmol) trifluoroacetic acid (1 mL) and CH₂Cl₂. The solution was stirred vigorously for 6 hours at room temperature before the solvent was removed under reduced pressure. Toluene (5 mL) was then added to the residue, and the solution subjected to rotary evaporation under reduced pressure. This was repeated an additional two times to remove the excess trifluoroacetic acid as an azeotrope which afforded the crude a,b-unsaturated carboxylic acid 319 as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, J = 16.3 Hz, 1H), 7.33 (s, 1H), 7.01 (d, J = 16.3 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H).

The crude acid 319 was taken up in anhydrous CH₂Cl₂ (2 mL) and diethylaminosulfurtrifluoride (79 μL, 0.6 mmol) was added dropwise at 0 °C. After 30 minutes of stirring at this temperature the reaction was quenched by slow addition of NaHCO₃ (1 mL of a saturated aqueous solution). The mixture was extracted with CH₂Cl₂ (3 x 2 mL), the organic phase dried (Na₂SO₄) and concentrated under reduced pressure to

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6.4.5 Synthesis of β-lactone 220ah

\[ ((((3,5-Dimethoxy-1,2-phenylene)bis(methylene))bis(oxy))bis(methylene))dibenzene (322a) \]

To a solution of phthalate 316 (0.86 g, 3.4 mmol) in THF at −78 °C was added LiAlH₄ (8.4 mL, 1.0 M in THF, 8.4 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 hour before it was diluted with Et₂O (20 mL). The reaction was then quenched by the sequential dropwise addition of water (0.33 mL), NaOH (0.33 mL of a 15 wt% solution in water) and again, water (3.4 mL). The suspension was stirred for 15 minutes before MgSO₄ was added and the mixture stirred for an additional 15 minutes. The cloudy suspension was then filtered through a pad of celite, the filtrate was concentrated under reduced pressure and to afford diol 321 which was used immediately in the next reaction.

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 6.54 (d, J = 2.4 \text{ Hz, 1H}), 6.45 (d, J = 2.4 \text{ Hz, 1H}), 4.78 (s, 2H), 4.71 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.55 (brs, 1H), 1.57 (brs, 1H) \text{ ppm} \]

The diol 321 was taken up in THF (17 mL) and DMF (4 mL) and cooled to 0 °C before NaH (0.4 g, 60% in mineral oil, 10 mmol) was added in portions. The reaction mixture was warmed top room temperature and stirred for 16. After this time the reaction was quenched by the addition of water (10 mL) and the aqueous was extracted with EtOAc (3 × 10 mL). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the crude residue purified via flash column chromatography to afford the title compound 322a (0.61 g, 47% yield) as a viscous, colourless oil.

Rₜ 0.6 (4:1, v/v hexanes : EtOAc)
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IR ν\textsubscript{max} 3029, 2937, 2839, 1604, 1453, 1316, 1199, 1147, 1057 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.39-7.26 (m, 10H), 6.68 (d, \(J = 2.4\) Hz, 1H), 6.42 (d, \(J = 2.4\) Hz, 1H), 4.61 (s, 2H), 4.58 (s, 2H), 4.52 (s, 2H), 4.48 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H) ppm

\(^{13}\)CNMR (100 MHz, CDCl\(_3\)) δ 160.7, 159.5, 140.9, 138.90, 138.5, 128.5, 128.4, 128.1, 127.97, 127.8, 127.6, 117.0, 105.0, 97.9, 72.6, 72.2, 69.7, 62.20, 55.9, 55.5 ppm

HRMS (ESI) \(m/z\) Found: (M+H)+, \(C_{25}H_{26}O_9\) 379.1900 requires 379.1904

1,5-Dimethoxy-2,3-bis(methoxymethyl)benzene (322b)

![Chemical structure of 1,5-Dimethoxy-2,3-bis(methoxymethyl)benzene](image)

The title compound was prepared according the representative procedure for compound 322a, however using iodomethane in place of benzyl bromide. The title compound 322b (0.15 g, 66% yield) was purified via flash column chromatography and isolated as a white solid.

\(R_f\) 0.3 (7:3, v/v hexanes : EtOAc)

IR ν\textsubscript{max} 2925, 2889, 2820, 1603, 1459, 1303, 1199, 1145, 1076 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.62 (d, \(J = 2.4\) Hz, 1H), 6.41 (d, \(J = 2.4\) Hz, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.42 (s, 3H), 3.34 (s, 3H) ppm

\(^{13}\)CNMR (100 MHz, CDCl\(_3\)) δ 160.7, 159.5, 140.7, 116.8, 104.6, 97.9, 72.0, 64.4, 58.5, 58.0, 55.9, 55.5 ppm

HRMS (ESI) \(m/z\) Found: (M+H)+, \(C_{25}H_{26}O_9\) 227.1270 requires 227.1278

\(((3,5\text{-Dimethoxy-1,2-phenylene})\text{bis(methylene)})\text{bis(oxy)}\text{bis(tert-butyldimethylsilane)}\) (322c)

![Chemical structure of \(((3,5\text{-Dimethoxy-1,2-phenylene})\text{bis(methylene)})\text{bis(oxy)}\text{bis(tert-butyldimethylsilane)}\)](image)

To a solution of phthalate 316 (0.25 g, 3.4 mmol) in THF at -78 °C was added LiAlH\(_4\) (2.5 mL, 1.0 M in THF, 2.5 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 hour before it was diluted with Et\(_2\)O (20 mL). The reaction was then quenched by the sequential dropwise addition of water (0.08 mL), NaOH (0.08 mL of a 15 wt% solution in water) and again, water (0.8 mL). The suspension was stirred for 15 minutes before MgSO\(_4\) was added and the mixture stirred for an additional
15 minutes. The cloudy suspension was then filtered through a pad of celite, the filtrate was concentrated under reduced pressure and to afford diol 321 which was used immediately in the next reaction. The residue was taken up in DMF (3 mL) and TBSCl (0.45 g, 3 mmol) and imidazole (0.19 g, 3 mmol) were added. The solution was stirred for 16 h at room temperature before water (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified via flash column chromatography to afford the title compound 322c (0.26 g, 62% yield) as a colourless oil.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

IR \nu_max 2953, 2929, 2856, 1605, 1462, 1253, 1146, 1064 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 6.81 (d, J = 1.7 Hz, 1H), 6.35 (d, J = 1.7 Hz, 1H), 4.90 (s, 2H), 4.70 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 0.97 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H), 0.03 (s, 6H) ppm

\(^13\)CNMR (100 MHz, CDCl\(_3\)) \delta 160.3, 158.0, 144.1, 117.9, 102.8, 97.0, 62.4, 55.8, 55.5, 55.3, 26.1, 26.1, -5.1, -52 ppm

HRMS (ESI) m/z Found: (M+H)^+, C\(_{13}\)H\(_{18}\)O\(_6\) 227.1270 requires 227.1278

3,4-Bis(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (323c)

Following a modified procedure of Krupadanam,\(^3\) a round bottom flask was charged with arene 322c (0.91 g, 2.1 mmol), TMEDA (0.40 mL, 2.6 mmol) and anhydrous THF (10 mL). The mixture was cooled to 0 °C before \(^t^\)BuLi (1.6 mL, 1.6 M in hexanes, 2.6 mmol) was added via syringe over 15 minutes. The reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (0.20 mL, 2.7 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH\(_4\)Cl (60 mL of a saturated aqueous solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 10 mL) and washed with water (1 x 10 mL) and brine (1 x 10mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound 323c (0.54 g, 57% yield) as a colourless oil.

R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR \nu_max 2953, 2930, 2857, 1689, 1599, 1462, 1253, 1111, 1051 cm\(^{-1}\)
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1H NMR (400 MHz, CDCl₃) δ 10.43 (s, 1H), 7.15 (s, 1H), 4.92 (s, 2H), 4.65 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 0.97 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.10 (s, 6H) ppm

13CNMR (100 MHz, CDCl₃) δ 189.3, 162.0, 160.54, 151.4, 122.6, 116.6, 105.0, 64.3, 62.2, 56.0, 55.4, 26.0, 26.0, -5.2, -5.3 ppm

HRMS (ESI) m/z Found: (M+H)+, C23H20O3Si2, 469.2761 requires 469.2644

(E)-3-(3,4-Bis(((tert-butylidimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)acrylic acid (324)

Following a modified procedure of Diederich, a round bottom flask was charged with aldehyde 323c (0.46 g, 1 mmol), malonic acid (0.21 g, 2 mmol), piperidine (0.1 mL) and pyridine (3 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification (pH = 4) with concentrated HCl, the precipitate was washed with H₂O (50 mL) and hexanes (50 mL) before being dried at 60 °C in vacuo. The α,β-unsaturated acid 324 (0.30 g, 60%) was isolated as an off white solid.

IR νₘₐₓ 2953, 2930, 2857, 1684, 1601, 1463, 1255, 1130, 1050, 842 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 8.26 (d, J = 16.2 Hz, 1H), 7.42 (s, 1H), 7.09 (d, J = 16.2 Hz, 1H), 5.07 (s, 2H), 4.83 (s, 2H), 4.08 (s, 3H), 3.91 (s, 3H), 1.14 (s, 9H), 1.06 (s, 9H), 0.29 (s, 6H), 0.27 (s, 6H) ppm

13CNMR (100 MHz, CDCl₃) δ 173.3, 159.9, 159.1, 146.8, 122.3, 120.3, 119.7, 114.5, 104.7, 63.8, 62.8, 56.1, 26.2, 25.8, -5.5, -5.6 ppm

HRMS (ESI) m/z Found: (M+H)+, C25H24O3Si2, 469.2617 requires 496.2676

(E)-3-(3,4-Bis(((tert-butylidimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)acryloyl fluoride (210o)
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Following the procedure of Fu\textsuperscript{16} to a suspension of $\alpha,\beta$-unsaturated acid 324 (1.0 g, 2 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) at 0 °C was added diethylaminosulfur trifluoride (0.29 mL, 2.2 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of NaHCO\textsubscript{3} (30 mL of a saturated aqueous solution). The mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL), the organic phase dried (Na\textsubscript{2}SO\textsubscript{4}), concentrated under reduced pressure to give a yellow oil. The crude material purified via flash column chromatography to afford the title compound 210o (0.59 g, 59% yield) as a white solid.

R\textsubscript{f}0.6 (4:1, v/v hexanes : EtOAc)

\textbf{IR} \nu\textsubscript{max} 2955, 2932, 2858, 1796, 1618, 1464, 1258, 1133, 835 cm\textsuperscript{-1}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ 8.15 (d, $J = 16.2$ Hz, 1H), 7.13 (s, 1H), 6.86 (dd, $J = 16.2$, 7.3 Hz, 1H), 4.91 (s, 2H), 4.66 (s, 2H), 3.93 (s, 3H), 3.76 (s, 3H), 0.98 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.11 (s, 6H) ppm

\textbf{\textsuperscript{13}CNMR} (100 MHz, CDCl\textsubscript{3}) $\delta$ 160.3, 159.5, 159.0 (d, $J = 337.9$ Hz), 148.4, 143.0, 142.9 (d, $J = 7.3$ Hz), 122.5, 114.5 (d, $J = 64.6$ Hz), 113.9, 105.0, 63.2, 62.1, 5615, 55.8, 26.0, 26.0, 18.5, 18.4, -5.2, -5.3 ppm

\textbf{HRMS (ESI)} m/z Found: (M-HF+H\textsuperscript{+}), C\textsubscript{23}H\textsubscript{18}O\textsubscript{6}Si\textsubscript{3}, 479.2627 requires 496.2649

Diethyl (1S,2R,6R)-2-(3,4-bis((tert-butyl(dimethyl)silyl)oxy)methyl)-2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ah)

![Chemical structure of diethyl (1S,2R,6R)-2-(3,4-bis((tert-butyl(dimethyl)silyl)oxy)methyl)-2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ah)](image)

A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane 216e (52 mg, 0.2 mmol), $\alpha,\beta$-unsaturated acyl fluoride 210o (100 mg, 0.2 mmol), THF (1.3 mL) and DMF (0.3 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC B9 (0.02 mmol) in THF (1.4 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound 220ah (9 mg, 7% yield, >20:1 d.r) as a viscous oil.

R\textsubscript{f}0.4 (4:1, v/v hexanes : EtOAc)

\textbf{IR} \nu\textsubscript{max} 2953, 2857, 1824, 1735, 1258, 1126, 1050, 836 cm\textsuperscript{-1}
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6.5.1 Synthesis of (−)-normethyl-Δ⁹-THC (36)

1,3-Dimethoxy-5-pentylbenzene (362)

Following the procedure of Vanek, a round bottom flask was charged with olivetol (326) (3.6 g, 20 mmol), potassium carbonate (13.8 g, 100 mmol), iodomethane (6.2 mL, 100 mmol) and acetone (60 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified via flash column chromatography to afford the title compound 362 (3.83 g, 90% yield) as a viscous yellow oil.

1H NMR (400 MHz, CDCl₃) δ 6.34 (d, J = 2.2 Hz, 2 H), 6.30 (t, J = 2.2 Hz, 1 H), 3.78 (s, 6 H), 2.54 (t, J = 7.4 Hz, 2 H), 1.66-1.57 (m, 2 H), 1.37-1.28 (m, 4 H), 0.90 (t, J = 6.6 Hz, 3 H) ppm

2,6-Dimethoxy-4-pentylbenzaldehyde (363)

Following a modified procedure of Krupadanam, a round bottom flask was charged with arene 362 (3.1 g mL, 15 mmol), TMEDA (2.5 mL 16.5 mmol) and anhydrous THF (30). The mixture was cooled to 0 °C before BuLi (10.3 mL, 1.6 M in hexanes, 16.5 mmol) was added via syringe over 15 minutes. The
reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (1.3 mL, 16.5 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH₄Cl (30 mL of a saturated aqueous solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 30 mL) and washed with water (30 mL) and brine (60 mL). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound 363 (2.72 g, 77% yield) as a yellow oil.

1H NMR (400 MHz, CDCl₃) δ 10.45 (s, 1H), 6.38 (s, 2H), 3.89 (s, 6H), 2.63 (t, J = 7.6 Hz, 2H), 1.56-1.47 (m, 2H), 1.41-1.28 (m, 4H), 0.91 (t, J = 6.592 Hz, 3H) ppm

(E)-3-(2,6-Dimethoxy-4-pentylphenyl)acrylic acid (364)

Following a modified procedure of Ling,⁴⁴ a 250 mL RBF was charged with aldehyde 363 (19.2 g, 81 mmol), malonic acid (16.9 g, 162 mmol), piperidine (6.5 mL), and pyridine (100 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification with concentrated HCl, the precipitate was washed with H₂O (500 mL) and hexanes (500 mL) before being dried at 60 °C in vacuo. The title compound 364 (18.7 g, 83%) was isolated as an off-white solid.

R₉ 0.1 (1:1, v/v hexanes : EtOAc)

MP 180-182 °C

IR νmax 2930, 2862, 2688, 1675, 1599, 1563, 1409 1201, 1121 cm⁻¹

1H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 16.2 Hz, 1H), 7.86 (d, J = 16.2 Hz, 1H), 6.38 (s, 2H), 3.87 (s, 3H), 2.60-2.57 (m, 2H), 1.67-1.59 (m, 2H), 1.36-1.33 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H) ppm

13C NMR (100 MHz, CDCl₃) δ 174.3, 160.3, 148.0, 138.0, 115.9, 111.6, 110.9, 106.0, 55.8, 37.1, 31.0, 22.7, 14.2 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₆H₂₃O₄, 279.1591, requires 279.1591
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(E)-3-(2,6-Dimethoxy-4-pentylphenyl)acryloyl fluoride (210p)

Following the procedure of Georg, to a suspension of α,β-unsaturated carboxylic acid 364 (8.4 g, 30 mmol) in CH₂Cl₂ (60 mL) at 0 °C was added diethylaminosulfur trifluoride (6.0 mL, 45 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of NaHCO₃ (200 mL of a saturated aqueous solution). The mixture was extracted with CH₂Cl₂ (3 x 50 mL), the organic phase dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound 210p (7.3 g, 83%) was isolated as an off-white solid.

Rᵢ 0.8 (10:3, v/v hexanes : EtOAc)

MP 30-32 °C

IR νmax 2932, 2858, 1781, 1602, 1565, 1459, 1118, 1089 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, J = 16.2 Hz, 1H), 6.77 (dd, J = 16.2, 7.6 Hz, 1H), 6.39 (s, 2H), 3.89 (s, 6H), 2.62-2.58 (m, 2H), 1.67-1.60 (m, 2H), 1.38-1.30 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 160.6, 159.8 (d, J = 334.4 Hz), 149.8, 142.6 (d, J = 7.4 Hz), 112.4 (d, J = 63.9 Hz), 112.0, 109.2, 104.0, 55.8, 37.1, 31.6, 30.8, 22.6, 14.1 ppm

HRMS (ESI) m/z Found: (M–H), C₁₆H₁₃FO₄, 279.1398, requires 279.1396

Dimethyl (1R,2S,6S)-2-(2,6-dimethoxy-4-pentylphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220aj)

A two-neck flask equipped with a reflux condenser and septum was charged with DA-cyclobutane 216e (2.1 g, 10.7 mmol), α,β-unsaturated acyl fluoride 210p (3.0 g, 10.7 mmol), THF (85 mL) and DMF (10 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC B9 (0.58 g, 1.6 mmol) in THF (5 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at 80 °C...
for 2 hours. The mixture was then allowed to cool to room temperature, before being concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound X (7.3 g, 45%) was isolated as a yellow oil and as a single diastereoisomer as observed by $^1$H-NMR (>20:1 dr).

$\text{R}_t 0.3$ (10:3, v/v hexanes : EtOAc)

**HPLC** RegisCell$^\text{TM}$ 5 $\mu$m, hexane : iPrOH 95:5, 1 mL/min, $\lambda = 230$ nm, fraction $t_r = 16.82$ min (major enantiomer) and 20.30 min (minor enantiomer); $\text{er} = 98:2$

$\left[ \beta \right]_D^{25} = -129.8^\circ$ (c = 0.03 CHCl$_3$)

**MP** 95-97 °C;

**IR** $\nu_{\text{max}}$ 2932, 1857, 1819, 1731, 1608, 1230, 1118 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.30 (s, 1H); 6.29 (s, 1H) 5.14 (d, $J = 1.1$ Hz, 1H), 4.88-4.83 (m, 1H), 3.85 (dd, $J = 6.9, 1.1$ Hz, 1H), 3.77 (s, 6H), 3.75 (brs, 3H), 3.16 (s, 3H) 2.61-2.48 (m, 4H), 2.02-1.96 (m, 1H), 1.86-1.77 (m, 1H), 1.61-1.53 (m, 2H), 1.37-1.25 (m, 4H) 0.88 (t, $J = 6.8$ Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.1 (1), 172.0 (7), 170.9 158.0, 157.7, 144.3, 115.3, 104.1 (3), 104.0 (5), 70.5, 57.5, 56.0, 55.1, 53.0, 52.9, 51.7, 36.6, 31.6, 31.1 29.3, 25.0, 24.7, 22.6, 14.2 ppm

**HRMS** (ESI) $m/z$ Found: (M+H)$^+$, C$_2$H$_{32}$O$_6$ 449.2170, requires 449.2167

**Methyl (1R,2R)-2',6'-dimethoxy-4'-pentyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (trans-365)**

![Methyl (1R,2R)-2',6'-dimethoxy-4'-pentyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (trans-365)]

A solution of β-lactone 220aj (0.96 g, 2.1 mmol), LiCl (0.36 g, 8.6 mmol) and H$_2$O (77 μL, 4.3 mmol) in DMSO (8 mL) was heated to 170 °C for 16 hours. The mixture was cooled to rt, H$_2$O (10 mL) added and the mixture extracted with EtOAc (3 x 15 mL). The organic phase was washed with brine (1 x 20 mL), dried (MgSO$_4$), concentrated under reduced pressure and the crude material passed through a silica plug (2:10, v/v hexanes : EtOAc). The crude residue was dissolved in a freshly prepared solution of NaOMe (10 mL, 1 M, 10 mmol) and heated to 65 °C for 3 d. The mixture was cooled to rt, neutralized with HCl (0.1 M) and extracted with Et$_2$O (3 x 3 mL). The organic phase was washed with H$_2$O (2 x 10 mL), dried
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(Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound trans-365 in 54% yield.

Rᵣ0.3 (20:1, v/v hexanes : EtOAc)

IR νmax 2933, 2836, 1731, 1590, 1472, 1243, 1103 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 6.35 (s, 2H), 5.71-5.65 (m, 1H), 5.47 (d, J = 9.9 Hz, 1H), 4.28 (brd, J = 9.9 Hz, 1H), 3.76 (s, 6H), 3.47 (s, 3H), 3.25-3.19 (m, 1H), 2.56-2.53 (m, 2H), 2.23-2.11 (m, 2H), 2.10-1.98 (m, 1H), 1.94-1.83 (m, 1H), 1.65-1.58 (m, 2H), 1.38-1.27 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 176.7, 158.8, 142.9, 130.9, 123.9, 116.8, 104.9, 56.0, 51.2, 43.7, 36.6, 34.8, 31.8, 31.1, 26.9, 24.6, 22.7, 14.2 ppm

HRMS (ESI) m/z Found: (M+H)+, C₂₁H₃₀O₄, 347.2216, requires 347.2217

(6aR,10aR)-6,6-Dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (normethyl(−)-Δ²-THC (361))

Following the procedure of Carreira, to a solution of trans-365 (88 mg, 0.25 mmol) in Et₂O (2 mL) was added MeMgl (0.84 mL, 3.75 M in Et₂O, 2.5 mmol) dropwise. The mixture was stirred for 16 h at rt before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et₂O (3 mL) and quenched with NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et₂O (3 x 3 mL), the organic phase dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was taken up in CH₂Cl₂ (2 mL), and ZnBr₂ (86 mg, 0.4 mmol) and MgSO₄ (120 mg, 1 mmol) were added. The mixture was stirred for 4 h at rt before the reaction was quenched by the addition of NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH₂Cl₂ (3 x 2 mL), the organic phase dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound 361 in 62% yield.

Rᵣ0.2 (10:1, v/v hexanes : EtOAc)

IR νmax 3405, 2928, 2859, 1703, 1621, 1578, 1425, 1046 cm⁻¹

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6.5.2 Alternate (4+2) annulations for introduction of the C9 methyl group

Dimethyl 2-(3-oxobutyl)malonate (359a)

Following the procedure of Campeau, a round bottom flask was charged with methylacetoacetate (1.27 mL, 10 mmol), 3-buten-2-one (0.82 mL, 11 mmol) and FeCl₃ (16 mg, 0.1 mmol). The neat mixture was stirred for 16 h at room temperature and the resulting residue purified via flash column chromatography to afford the title compound 359a (0.93 g, 53% yield) as a yellow oil.

$^1$H NMR (400 MHz, CDCl₃) δ 3.66 (s, 6H), 3.38 (t, $J = 7.3$ Hz, 1H), 2.48 (t, $J = 7.3$ Hz, 1H), 2.09 (d, $J = 7.4$ Hz, 2H), 2.07 (s, 3H)
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(E)-3-(2,6-Dimethoxyphenyl)acrylaldehyde (360b)

\[
\begin{align*}
\text{MeO-} & \quad \text{O-} \\
\text{MeO-} & \quad \text{O-} \\
\end{align*}
\]

A round bottom flask was charged with ((1,3-dioxolan-2-yl)methyl)triphenylphosphonium bromide (2.58 g, 6 mmol) and THF (40 mL) before NaHMDS (6 mL, 1.0 M solution in toluene, 6 mmol) was added over 1 minute. The resulting yellow suspension was allowed to stir for 30 minutes before aldehyde 277 (0.71 g, 3 mmol) in THF (10 mL) was added. The suspension was heated to reflux for 16 hours before being cooled to room temperature, and HCl (50 mL of a 10% aqueous solution) was added. The suspension was stirred for an additional 2 h at this temperature before being extracted with EtOAc (3 x 60 mL). The combined organics were dried (Na₂SO₄), concentrated under reduced pressure and the crude residue purified via flash column chromatography (dry loaded) to afford the title compound 360b (0.76 g, 96% yield) as a yellow solid.

\(^1\)H NMR (400 MHz, CDCl₃) δ 9.63 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 16.2 Hz, 1H), 7.33 (t, J = 8.3 Hz, 2H), 7.18 (dd, J = 16.2, 8.0 Hz, 1H), 6.57 (d, J = 8.3 Hz, 1H), 3.89 (s, 6H).

Methyl 2-acetyl-5-oxohexanoate (374)

\[
\begin{align*}
\text{MeO-} & \quad \text{C-} \\
\text{Me-} & \quad \text{O-} \\
\end{align*}
\]

The title compound was prepared according to the representative procedure for compound 359a. The title compound 374 (0.53 g, 51% yield) was purified via flash column chromatography and was isolated as a colourless oil.

\(^1\)H NMR (400 MHz, CDCl₃) δ 3.68 (s, 3H), 3.45 (t, J = 7.3 Hz, 1H), 2.46-2.42 (m, 2H), 2.18 (s, 3H), 2.07 (s, 3H), 2.04-2.00 (m, 2H) ppm.
6.5.3 Revised strategies to install the C9 methyl group

Dimethyl 5-(2,6-dimethoxyphenyl)-3-oxo-2-oxabicyclo[2.2.2]octane-4,6-dicarboxylate (2242b)

To a solution of β-lactone 220ad (1.81 g, 5 mmol) in MeOH (20 mL) was added K₂CO₃ (1.4 g, 10 mmol) in one portion. The mixture was stirred at room temperature for 2 h before the solvent removed under reduced pressure. H₂O (20 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic phase was dried, concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound 242b (1.64 g, 87%) was isolated as a yellow oil and as a single diastereomer as observed by ¹H-NMR.

Rᵢ 0.5 (5:2, v/v hexanes : EtOAc)

IR ʋmax 2951, 2843, 1755, 1732, 15793, 1474, 1242, 1116 cm⁻¹

¹H NMR (400MHz, CDCl₃) δ 7.18 (t, J = 8.4 Hz, 1H), 6.53 (d, J = 8.4 Hz, 2H), 5.15 (d, J = 3.9 Hz, 1H), 5.06 (d, J = 7.5 Hz, 1H), 3.81 (s, 6H), 3.65 (s, 3H), 3.61 (d, J = 7.5 Hz, 1H), 3.53 (s, 3H), 2.80 (ddd, J = 13.9, 11.2, 5.3 Hz, 1H), 2.19-2.13 (m, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 172.4, 172.1, 169.3, 159.2, 129.5, 112.7, 104.6, 78.0, 54.1, 52.4, 52.0, 45.2, 33.7, 25.9, 22.1 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₁₉H₂₂O₇, 379.1384, requires 379.1387

Trimethyl (R)-5-((diethoxyphosphoryl)oxy)-2',6'-dimethoxy-3,4-dihydro-[1,1'-biphenyl]-2,6(1H)-tricarboxylate (378b)

To a suspension of the β-lactone 220ad (0.76 g, 2 mmol) in MeOH (10 mL) at 0 °C was added KCN (0.13 g, 2 mmol) in one portion. The mixture was stirred at this temperature until consumption of the starting material (monitored carefully by TLC) after which ice cold H₂O (15 mL) was added immediately. The mixture was extracted with EtOAc (3 x 15 mL), the organic phase dried (Na₂SO₄) and concentrated under
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reduced pressure to afford the crude alcohol 383b which was used immediately without further purification.

$^1$H NMR of 383b (400MHz, CDCl$_3$) δ 7.12 (t, $J = 8.3$ Hz, 1H), 6.54 (dd, $J = 8.3$, 0.7 Hz, 1H), 6.41 (d, $J = 8.3$ Hz, 1H), 4.80 (d, $J = 12.4$ Hz, 1H), 4.23 (dd, $J = 5.0$, 3.0 Hz, 1H), 3.86 (s, 3H), 3.82 (dd, $J = 12.4$, 1.9 Hz, 1H), 3.72 (s, 3H), 3.58 (s, 3H), 3.52 (s, 3H), 3.24 (s, 3H), 2.54-2.38 (m, 1H), 2.29-2.16 (m, 2H), 1.86 (ddd, $J = 14.1$, 7.4, 4.0 Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 1H) ppm

The crude alcohol 383b was dissolved in EtOAc (20 mL), IBX (1.12 g, 4 mmol) added and the suspension heated under reflux for 16 h. The suspension was cooled to room temperature, filtered through a pad of Celite and the solvent removed under reduced pressure to afford the crude β-ketoester 379b which was used immediately in the next step.

$^1$H NMR of 383b (400MHz, CDCl$_3$) δ 7.15 (t, $J = 8.3$ Hz, 1H), 6.56-6.44 (m, 2H), 5.42 (d, $J = 6.4$ Hz, 1H), 4.04 (d, $J = 6.5$ Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.25 (s, 3H), 2.98 (m, 1H), 2.66-2.55 (m, 1H), 2.42-2.24 (m, 2H) ppm

The crude ester 379b was taken up in CH$_2$Cl$_2$ (20 mL) and sodium hydride (75 mg, 3 mmol) was added portion wise at 0 °C. The mixture was allowed to stir for 45 minutes at this temperature before chlorodiethyphosphate (0.35 mL, 2.4 mmol) was added dropwise. After this, the reaction was warmed to room temperature and stirred for an additional 2 hours before being quenched by the addition of NaHCO$_3$ (10 mL of a saturated aqueous solution). The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and washed with water (10 mL) and brine (10 mL). The combined organics were dried (Na$_2$SO$_4$), concentrated under reduced pressure, and the crude residue purified via flash column chromatography to afford the title compound 378b (0.48 g, 44% yield over 3 steps) as a viscous, colourless oil.

R$_f$ 0.2 (3:2, v/v hexanes : EtOAc)

IR $\nu_{max}$ 2955, 2841, 2366, 1736, 1435, 1258, 1031 cm$^{-1}$

$^1$H NMR (400MHz, CDCl$_3$) δ 7.12 (t, $J = 8.3$ Hz, 1H), 6.46 (d, $J = 8.3$ Hz, 2H), 5.62 (brs, 1H), 4.27-4.10 (m, 4H), 3.76 (s, 9H), 3.51 (s, 3H), 3.32 (s, 3H), 2.87 (m, 1H), 2.70 (dd, $J = 19.1$, 6.8 Hz, 1H), 2.43-2.29 (m, 1H), 2.28-2.19 (m, 1H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.34 (t, $J = 7.1$ Hz, 3H) ppm

$^{13}$C NMR (100MHz, CDCl$_3$) δ 170.7, 170.0, 165.3, 165.2, 151.03 (d, $J = 7.6$ Hz), 128.7, 116.6, 116.5, 114.0(3), 114.0(1), 67.5, 64.2 (d, $J = 6.0$ Hz), 64.1 (d, $J = 6.0$ Hz), 57.6, 55.7, 52.4, 51.5 (d, $J = 1.6$ Hz), 50.9 (d, $J = 1.6$ Hz), 34.6, 25.8, 25.2, 25.0, 15.72 (d, $J = 6.0$ Hz) ppm
cis-Methyl \((1R,2R)-2-(2,6\text{-dimethoxyphenyl})-4\text{-oxocyclohexane-1-carboxylate}\) (cis-388b) and trans-methyl \((1R,2R)-2-(2,6\text{-dimethoxyphenyl})-4\text{-oxocyclohexane-1-carboxylate}\) and (trans-388b)

To a suspension of the \(\beta\)-lactone \textbf{220ad} (1.9 g, 5 mmol) in MeOH (20 mL) at 0 °C was added KCN (0.32 g, 5 mmol) in one portion. The mixture was stirred at this temperature until consumption of the starting material (monitored carefully by TLC) after which ice cold H\(_2\)O (30 mL) was added immediately. The mixture was extracted with EtOAc (3 x 30 mL), the organic phase dried \((\text{Na}_2\text{SO}_4)\) and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (20 mL), IBX (2.8 g, 10 mmol) added and the suspension heated under reflux for 16 h. The suspension was cooled to rt, filtered through a pad of Celite and the solvent removed under reduced pressure. The crude residue was dissolved in DMSO (10 mL), LiCl (10 mmol) and H\(_2\)O (7.5 mmol) were added, and the vessel sealed and heated to 170 °C for 2 h. The mixture was cooled to rt, H\(_2\)O (20 mL) added and the mixture extracted with EtOAc (3 x 20 mL). The organic phase was washed with brine (1 x 20 mL), dried \((\text{MgSO}_4)\), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound \textbf{338} (0.48 g, 33%) was isolated as a yellow oil as a separable mixture of a diastereomers as observed by \(^1\text{H} \text{NMR}\) (3:2 cis/trans).

\textit{cis-isomer:}

\(R_f 0.5\) (1:1, v/v hexanes : EtOAc)

\(\text{IR } \nu_{\text{max}} 2931, 2857, 1732, 1709, 1579, 1454, 1119 \text{ cm}^{-1}\)

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\) 7.17 \((t, J = 8.3\text{ Hz}, 1\text{H})\), 6.52 \((d, J = 8.3\text{ Hz}, 2\text{H})\), 4.24-4.20 \((m, 1\text{H})\), 3.70 \((s, 6\text{H})\), 3.55 \((s, 3\text{H})\), 3.04 \((\text{ddd}, J = 16.2, 6.1, 1.5\text{ Hz}, 1\text{H})\), 2.97-2.95 \((m, 1\text{H})\), 2.82-2.78 \((m, 1\text{H})\), 2.50 \((\text{ddd}, J = 16.2, 6.1, 0.8\text{ Hz}, 1\text{H})\), 2.33-2.15 \((m, 2\text{H})\), 1.92-1.85 \((m, 1\text{H})\) ppm

\(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\(_3\)) \(\delta\) 209.0, 174.5, 158.7, 128.6, 116.7, 106.1, 104.1, 55.0, 51.3, 44.9, 43.8, 39.1, 34.3, 25.4 ppm

\(\text{HRMS (ESI) } m/z \text{ Found: } \text{(M+H)}^+, C_{16}H_{16}O_{10} 293.1380, \text{ requires 293.13843}\)

\textit{trans-isomer:}

\(R_f 0.6\) (1:1, v/v hexanes : EtOAc)

\(\text{IR } \nu_{\text{max}} 2950, 2840, 1734, 1716, 1593, 1474, 1245, 1108 \text{ cm}^{-1}\)
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$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.14 (t, $J = 8.3$ Hz, 1H), 6.52 (d, $J = 8.3$ Hz, 2H), 4.07-4.03 (m, 1H) 3.80 (s, 6H), 3.54 (td, $J = 11.0, 3.6$ Hz 1H), 3.43 (s, 3H), 3.02 (dd, $J = 15.1, 12.0$, 1H), 2.50-2.39 (m, 3H), 2.24-2.20 (m, 1H), 2.04-1.97 (m, 1H) ppm

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 210.3, 175.0, 128.3, 117.6, 104.5, 55.8, 51.5, 44.7, 44.0, 39.9, 35.8, 28.3 ppm

HRMS (ESI) m/z Found: (M+H)$^+$, C$_{16}$H$_{20}$O$_5$, 293.1384, requires 293.1384

Methyl (1R,2R)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (trans-388b)

Following a modification of the procedure of Trost,$^{42}$ a solution of cis-388b (181 mg, 0.5 mmol) in freshly prepared NaOMe (2.5 mL, 1 M, 2.5 mmol) was heated to 50 °C for 16 h. The mixture was cooled to rt, neutralized with HCl (0.1 M) and the mixture extracted with Et$_2$O (3 x 3 mL). The organic phase was washed with H$_2$O (2 x 10 mL), dried (Na$_2$SO$_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography afford trans-388b in 83% yield.

Methyl (1S,2R)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate and methyl (1R,2R)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (cis-388a and trans-388a)

The title compound was prepared according to the representative procedure for 388b. Following flash column chromatography the title compound 388b (0.48 g, 33%) was obtained as a separable mixture of a diastereomers as observed by $^1$H NMR (3:2 cis/trans).

cis-isomer:

R$_f$ 0.4 (5:2, v/v hexanes : EtOAc);

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IR $v_{\text{max}}$ 2931, 2857, 1732, 1709, 1579, 1226, 1119 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.33 (s, 2H), 4.19-4.15, (m, 1H), 3.69 (s, 6H), 3.54 (s, 3H), 3.01 (ddd, $J$ = 16.3, 5.9, 1.4 Hz, 1H), 2.96-2.92 (m, 1H), 2.82-2.75 (m, 1H), 2.56-2.52 (m, 2H), 2.48 (dd, $J$ = 16.3, 6.8 Hz, 1H), 2.32-2.14 (m, 2H), 1.90-1.83 (m, 1H), 1.64-1.57 (m, 2H), 1.37-1.30 (m, 4H) 0.90 (t, $J$ = 7.0 Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 209.1, 174.6, 158.5, 143.8, 113.7, 104.2, 54.9, 51.3, 45.0, 43.9, 39.2, 36.6, 34.2, 31.8, 31.1, 25.3, 22.7, 14.2 ppm; HRMS (ESI) $m/z$ Found: (M+H)$^+$, C$_{21}$H$_{30}$O$_5$ 363.2163, requires 363.2166.

trans-isomer:

R$_f$ 0.3 (10:3, v/v hexanes : EtOAc);

IR $v_{\text{max}}$ 2931, 2857, 1735, 1713, 1580, 1454, 1120 cm$^{-1}$;

$[\alpha]_D^{25} = -190.5^\circ$ (c = 0.05 CHCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.34 (s, 2H), 4.00 (ddd, $J$ = 11.8, 11.0, 5.0 Hz, 1H), 3.79 (s, 6H), 3.51 (td, $J$ = 11.0, 3.7 Hz, 1H) 3.44 (s, 3H), 3.00 (dd, $J$ = 14.5, 11.8 Hz, 1H), 2.55-2.51 (m, 2H), 2.48-2.37 (m, 3H), 2.25-2.18 (m, 1H), 2.05-1.95 (m, 1H), 1.63-1.56 (m, 2H), 1.37-1.29 (m, 4H) 0.90 (t, $J$ = 6.9 Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.4, 175.1, 158.4, 143.6, 114.9, 104.7, 55.8, 51.5, 44.9, 44.2, 39.9, 36.6, 35.8, 31.8, 31.1, 28.3, 22.7, 14.2 ppm

HRMS (ESI) $m/z$ Found: (M+H)$^+$, C$_{21}$H$_{30}$O$_5$ 363.2141, requires 363.2166

Methyl (1R,2R)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (trans-388a)

![Reaction Scheme]

Following a modification of the procedure of Trost, a solution of cis-388a (181 mg, 0.5 mmol) in freshly prepared NaOMe (2.5 mL, 1 M, 2.5 mmol) was heated to 50 °C for 16 h. The mixture was cooled to rt, neutralized with HCl (0.1 M) and the mixture extracted with Et$_2$O (3 x 3 mL). The organic phase was washed with H$_2$O (2 x 10 mL), dried (Na$_2$SO$_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography afford trans-388a in 83% yield.
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6,6,9-Trimethyl-6a,7,10,10a-tetrahydro-6H-benzo[c]chromen-1-ol ((despentyl-Δ8-THC (390))

Following a modified procedure of Carreira,34 to a solution of trans-388b (29 mg, 0.1 mmol) in Et₂O (1 mL) was added MeMgI (0.33 mL, 3.0 M in Et₂O, 1 mmol) dropwise. The yellow suspension was stirred for 16 h at rt before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et₂O (3 mL) and quenched with NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et₂O (3 x 3 mL), the organic phase dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was dissolved in CH₂Cl₂ (2 mL), and ZnBr₂ (113 mg, 0.5 mmol) and MgSO₄ (120 mg, 1 mmol) were added. The flask was sealed and heated to reflux for 30 h before the reaction was quenched by the addition of NH₄Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH₂Cl₂ (3 x 2 mL), the organic phase dried (Na₂SO₄), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound 390 (10 mg, 40%) was isolated as a yellow oil.

Rf 0.3 (9:1, v/v hexanes : EtOAc)

IR νmax 3435, 2972, 2919, 2850, 1612, 1584, 1459, 1184, 1025 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 6.94 (td, J = 8.1, 0.8 Hz, 1H), 6.43 (td, J = 8.1, 1.1 Hz, 1H), 6.26 (td, J = 8.1, 1.1 Hz, 1H), 5.44 (d, J = 4.3 Hz, 1H, 3.23-3.19 (m, 1H), 2.74 (td, J = 10.7, 4.7 Hz, 1H), 2.18-2.13 (m, 1H), 1.89-1.80 (m, 3H), 1.71 (s, 3H), 1.39 (s, 3H), 1.10 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 155.4, 155.2, 134.9, 127.5, 119.5, 113.5, 110.6, 107.4, 45.1, 36.1, 31.9, 28.1, 27.7, 23.6, 18.6 ppm

HRMS (ESI) m/z Found: (M+H)+, C₁₆H₃₆O₂ 245.1531, requires 245.1536.
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(-)-trans-$\Delta^8$-Tetrahydrocannabinol ((-)-$\Delta^8$-THC (349))

The title compound was prepared according to the representative procedure for 390. Following flash column chromatography the title compound 349 (0.48 g, 33%) was obtained as a yellow oil.

$R_f$ 0.5 (10:1, v/v hexanes : EtOAc)

IR $\nu_{max}$: 3443, 2957, 2929, 2857, 1624, 1579, 1426, 1183, 1033 cm$^{-1}$

HPLC Daisel AD-H, hexane : iPrOH 95:5; 1 mL/min, $\lambda$ = 220 nm, fraction $t_r$ = 9.25 (minor enantiomer) and 11.05 (major enantiomer); $er$ = 83:17

[ $\alpha$ ]$^D_{25}$ = −220.3° (c = 0.05, CHCl$_3$); lit.$^{48}$ [ $\alpha$ ]$^D_{25}$ = −232.3° (c = 0.96, CHCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.28 (s, 1H), 6.11 (s, 1H), 5.43, (d, $J$ = 4.1 Hz, 1H), 4.70, (s, 1H), 3.21-3.17, (m, 1H), 2.73-2.67 (m, 1H), 2.46-2.42 (m, 2H), 2.16-2.10 (m, 1H), 1.89-1.75, (m, 3H), 1.70 (s, 3H), 1.61-1.53 (m, 2H), 1.38 (s, 3H), 1.35-1.26 (m, 4H), 1.11 (s, 3H), 0.89 (t, $J$ = 6.8 Hz, 3H) ppm

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.0, 154.9, 142.9, 134.9, 119.5, 110.7, 110.3, 107.8, 76.8, 45.1, 36.2, 35.6, 31.7(4), 31.7(3), 30.7, 28.1, 27.7, 23.6, 22.7, 18.7, 14.2 ppm

HRMS (ESI) m/z Found: (M+H)$^+$, C$_{37}$H$_{49}$O$_{25}$ 314.4715, requires 314.2319

6.5.4 Synthesis of (−)-$\Delta^9$-THC 325

(6aR,10aR)-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol

Following a modified procedure of Petzilka,$^{49}$ dry hydrogen chloride was bubbled through a solution of chromene 390 (14 mg, 0.044 mmol) and ZnCl$_2$ (7.6 mg, 0.031 mmol) in CH$_2$Cl$_2$ (2 mL) for 2 h. Ice water (3 mL) was added, and the mixture extracted with CH$_2$Cl$_2$ (3 x 3 mL) before the organic phase was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude residue was taken up in toluene (2 mL)
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and a solution of potassium tert-amylate (0.7 mL, 0.5 M) added. The mixture was heated to 65 °C for 1 h before ice cold water (3 mL) was added. The mixture was extracted with EtOAc (3 x 3 mL), the organic phase dried (Na₂SO₄), concentrated under reduced pressure, and the crude material purified via flash column chromatography. The title compound 391 (5.2 mg, 68% yield) as a yellow oil.

(-)-Δ⁸-tetrahydrocannabinol ((−)-Δ⁸-THC (325))

The title compound was prepared according to the representative procedure for 391. Following flash column chromatography the title compound 325 (12.3 mg, 89% yield) was obtained as a yellow oil. 

Rf 0.5 (10:1, v/v hexanes : EtOAc)

IR ν max: 3391, 2957, 2928, 2858, 1624, 1578, 1426, 1184, 1035 cm⁻¹

HPLCDaicel AD-H, hexane : iPrOH 95:5, 1 mL/min, λ = 214 nm, fraction t = 11.9 (major enantiomer) and 22.6 (minor enantiomer); er = 84:16 [ ]D²⁸ = -112.0° (c = 0.01, CHCl₃)

[ ]D²⁸ = -112.0° (c = 0.01, CHCl₃); lit.⁴² [ ]D²⁸ = -152.3° (c = 0.79, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 6.31-6.29 (m, 1H), 6.27 (d, J = 1.5 Hz, 1H), 6.14 (d, J = 1.5 Hz, 1H), 4.68 (s, 1H) 3.20 (d, J = 10.9, Hz, 1H), 2.45-2.42 (m, 2H), 2.18-2.15 (m, 2H), 1.93-1.89 (m, 1H), 1.71-1.67 (m, 4H), 1.58-1.53 (m, 2H), 1.45-1.37 (m, 1H), 1.41 (s, 3H) 1.33-1.27 (m, 4H), 1.09 (s, 3H), 0.88 (t, J = 6.8 Hz, 3H) ppm

¹³C NMR (100 MHz, CDCl₃) δ 154.9, 154.3, 143.0, 134.6, 123.9, 110.3, 109.2, 107.7, 77.3, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2 ppm

HRMS (ESI) m/z Found: (M+H)⁺, C₂₁H₂₂O₂₂, 314.2314, requires 314.2319
6.5.5 Studies into the synthesis of Nabilone 376b

Methyl (7R,8R)-7-(2,6-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (394)

A round bottom flask was charged with ketoester trans-388b (53 mg, 0.18 mmol), ethylene glycol (12 µL, 0.22 mmol), p-toluenesulfonic acid (2 mg) and toluene (3 mL). A Dean-Stark apparatus was attached and the solution was heated to 130°C for 2 hours. After this time, the reaction was cooled to room temperature, the solvent removed under reduced pressure, and the crude residue purified via flash column chromatography. The title compound 394 (20 mg, 78% yield) was isolated as a clear oil.

\( R_f 0.3 \) (7:3, v/v hexanes : EtOAc)

\(^1H\) NMR (400 MHz, CDCl₃) \( \delta 7.09 \) (t, \( J = 8.3 \) Hz, 1H), 6.50 (d, \( J = 8.3 \) Hz, 2H), 4.09-3.85 (m, 5H), 3.80 (s, 6H), 3.36 (s, 3H), 3.29 (td, \( J = 11.6, 4.7 \) Hz, 1H), 2.32 (t, \( J = 13.1 \) Hz, 1H), 1.98-1.90 (m, 2H), 1.90-1.81 (m, 1H), 1.72 - 1.63 (m, 2H) ppm

\(^13C\) NMR (100 MHz, CDCl₃) \( \delta 175.80, 159.8, 158.2, 127.7, 118.8, 108.8, 104.7, 64.5, 64.3, 56.5, 55.5, 51.1, 45.3, 37.7, 34.3, 34.1, 27.5 \) ppm
Chapter 6

6.6 References

Chapter 6
Appendix 1

X-Ray Crystal Structures

Diallyl (1S,5R,6S)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220l)

Figure A1. Molecular diagram of 220l
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<tr>
<th>Crystal data and structure refinement for 220l</th>
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<tbody>
<tr>
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<td><strong>Wavelength</strong></td>
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<td><strong>Unit cell dimensions</strong></td>
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<td><strong>Volume</strong></td>
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<td><strong>Crystal size</strong></td>
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<td><strong>Limiting indices</strong></td>
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<td><strong>Refinement method</strong></td>
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<td><strong>Data / restraints / parameters</strong></td>
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<td><strong>Goodness-of-fit on F²</strong></td>
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<td><strong>Final R indices [I&gt;2σ(I)]</strong></td>
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<td><strong>R indices (all data)</strong></td>
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<td><strong>Absolute structure parameter</strong></td>
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<td><strong>Extinction coefficient</strong></td>
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<td><strong>Largest diff. peak and hole</strong></td>
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### Table A2. Bond lengths (Å) and bond angles (°) for 2201

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C(3) - C(4) - C(5)          111.08(17)  
C(8) - C(4) - C(5)          108.16(16)  
C(12) - C(4) - C(5)         112.73(16)  
C(6) - C(5) - C(4)          115.98(16)  
C(5) - C(6) - C(17)         112.34(17)  
C(5) - C(6) - C(13)         108.62(16)  
C(17) - C(6) - C(13)        103.35(15)  
C(5) - C(6) - C(7)          110.96(16)  
C(17) - C(6) - C(7)         111.00(16)  
C(13) - C(6) - C(7)         110.28(16)  
C(21) - C(7) - C(2)         110.98(16)  
C(21) - C(7) - C(6)         112.19(16)  
C(2) - C(7) - C(6)          110.67(16)  
C(9) - C(8) - C(4)          113.80(18)  
C(10) - C(9) - C(8)         110.5(2)    
C(9) - C(10) - C(11)        110.8(2)    
C(10) - C(11) - C(12)       111.7(2)    
C(11) - C(12) - C(11)       112.66(18)  
O(3) - C(13) - O(4)         124.64(18)  
O(3) - C(13) - C(6)         126.00(18)  
O(4) - C(13) - C(6)         109.34(16)  
O(4) - C(14) - C(15)        112.18(19)  
C(16) - C(15) - C(14)       122.7(2)    
O(5) - C(17) - O(6)         124.64(19)  
O(5) - C(17) - C(6)         126.00(19)  
O(6) - C(17) - C(6)         109.34(16)  
C(19) - C(18) - O(6)        108.7(2)    
C(19') - C(18') - O(6)      115.8(6)    
C(20) - C(19) - C(18)       126.4(4)    
C(20') - C(19') - C(18')    142.2(2)    
C(26) - C(21) - C(7)        117.35(19)  
C(22) - C(21) - C(7)        122.09(18)  
C(23) - C(22) - C(21)       121.3(2)    
C(22) - C(23) - C(24)       120.6(2)    
O(7) - C(24) - C(23)        115.9(2)    
O(7) - C(24) - C(25)        124.7(2)    
C(23) - C(24) - C(25)       119.4(2)    
C(24) - C(25) - C(26)       119.25(19)  
C(21) - C(26) - C(25)       122.04(19)  

C (3) - C (4) - C (5)  111.08 (17)  
C (8) - C (4) - C (5)  108.16 (16)  
C (12) - C (4) - C (5) 112.73 (16)  
C (6) - C (5) - C (4)  115.98 (16)  
C (5) - C (6) - C (17) 112.34 (17)  
C (5) - C (6) - C (13) 108.62 (16)  
C (17) - C (6) - C (13) 103.35 (15)  
C (5) - C (6) - C (7)  110.96 (16)  
C (17) - C (6) - C (7) 111.00 (16)  
C (13) - C (6) - C (7)  110.28 (16)  
C (21) - C (7) - C (2)  110.98 (16)  
C (21) - C (7) - C (6)  112.19 (16)  
C (2) - C (7) - C (6)  110.67 (16)  
C (9) - C (8) - C (4)  113.80 (18)  
C (10) - C (9) - C (8)  110.5 (2)    
C (9) - C (10) - C (11) 110.8 (2)    
C (10) - C (11) - C (12) 111.7 (2)   
C (11) - C (12) - C (11) 112.66 (18) 
O (3) - C (13) - O (4)  124.64 (18)  
O (3) - C (13) - C (6)  125.28 (18)  
O (4) - C (13) - C (6)  110.06 (16)  
O (4) - C (14) - C (15)  112.18 (19) 
C (16) - C (15) - C (14) 122.7 (2)   
O (5) - C (17) - O (6)  124.64 (19)  
O (5) - C (17) - C (6)  126.00 (19)  
O (6) - C (17) - C (6)  109.34 (16)  
C (19) - C (18) - O (6)  108.7 (2)   
C (19') - C (18') - O (6) 115.8 (6)   
C (20) - C (19) - C (18) 126.4 (4)   
C (20') - C (19') - C (18') 142.2 (2) 
C (26) - C (21) - C (7)  117.35 (19) 
C (22) - C (21) - C (7)  122.09 (18) 
C (23) - C (22) - C (21) 121.3 (2)   
C (22) - C (23) - C (24) 120.6 (2)   
O (7) - C (24) - C (23) 115.9 (2)   
O (7) - C (24) - C (25) 124.7 (2)   
C (23) - C (24) - C (25) 119.4 (2)   
C (24) - C (25) - C (26) 119.25 (19) 
C (21) - C (26) - C (25) 122.04 (19)
Dimethyl (1S,2R,6R)-2-(2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ad)

Figure A2. Molecular diagram of 220ad
Table A3. Crystal data and structure refinement for 220ad

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Table A4. Bond lengths (Å) and bond angles (°) for 220ad

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O(7)-C(13)-C(14)            122.46(8)
O(7)-C(13)-C(12)            115.52(7)
C(14)-C(13)-C(12)           122.02(8)
C(15)-C(14)-C(13)           119.05(9)
C(15)-C(14)-H(14)           120.5
C(13)-C(14)-H(14)           120.5
C(16)-C(15)-C(14)           121.32(8)
C(16)-C(15)-H(15)           119.3
C(14)-C(15)-H(15)           119.3
C(15)-C(16)-C(17)           118.88(9)
C(15)-C(16)-H(16)           120.6
C(17)-C(16)-H(16)           120.6
O(8)-C(17)-C(16)            121.57(8)
O(8)-C(17)-C(12)            116.45(8)
C(16)-C(17)-C(12)           121.98(8)
O(7)-C(18)-H(18A)           109.5
O(7)-C(18)-H(18B)           109.5
H(18A)-C(18)-H(18B)         109.5
O(7)-C(18)-H(18C)           109.5
H(18A)-C(18)-H(18C)         109.5
H(18B)-C(18)-H(18C)         109.5
O(8)-C(19)-H(19A)           109.5
O(8)-C(19)-H(19B)           109.5
H(19A)-C(19)-H(19B)         109.5
O(8)-C(19)-H(19C)           109.5
H(19A)-C(19)-H(19C)         109.5
H(19B)-C(19)-H(19C)         109.5
Figure A3. Molecular diagram of 309

Dimethyl 3-bromo-4-hydroxy-6-methoxyphthalate (309)
Table A5. Crystal data and structure refinement for 309

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<td>Wavelength</td>
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<td>Crystal system, space group</td>
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<td>Z, Calculated density</td>
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<tr>
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<tr>
<td>Absorption correction</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
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<td>R indices (all data)</td>
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<td>Extinction coefficient</td>
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Table A6. Bond lengths (Å) and bond angles (°) for 309

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<th>Angle 1</th>
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Appendix 2

Publications from Doctoral Studies
Enantioselective (4+2) Annulation of Donor–Acceptor Cyclobutanes by N-Heterocyclic Carbene Catalysis

Alison Levens, Adam Ametovski, and David W. Lupton*

Abstract: Herein we report the enantioselective (4+2) annulation of donor–acceptor cyclobutanes and unsaturated acyl fluorides using N-heterocyclic carbene catalysis. The reaction allows a 3-step synthesis of cyclohexyl β-lactones (25 examples) in excellent chemical yield (most ≥ 90%) and stereochemical integrity (all > 20:1 d.r., most ≥ 97:3 e.r.). Mechanistic studies support ester enolate Claisen rearrangement, while derivatizations provide functionalized cyclohexanes and dihydroquinolinones.

Release of ring-strain provides a powerful driving force for reaction discovery. Perhaps nowhere is this more evident than in the ring-opening annulation of vicinal donor-acceptor (DA) cyclopropanes. Interestingly, while analogous DA-cyclobutanes (i.e. 1) possess similar strain energy, their application in organic synthesis is significantly more limited (Scheme 1). For example, only within the last decade have studies building on the pioneering work of Saigo[3] delivered general Lewis acid catalyzed approaches to the (4+2) annulation of DA-cyclobutanes [Eq. (1)].[4] These reactions define a concise route to tetrahydroprymans, piperidines and cyclohexanes (2) with excellent diastereoselectivity. Despite important advances in catalysis with DA-cyclobutanes, to the best of our knowledge, enantioselective variants of the (4+2) annulation are yet to be discovered. Indeed the only example of enantioselective catalysis using DA-cyclobutanes was reported last year by Xie and Tang with the Lewis acid catalyzed (4+3) annulation of nitroline 3 to afford oxazepane 4 [Eq. (2)].[5] Previously, we have had success with the annulation of DA cyclopropanes to give enantioenriched cyclopentanes [Eq. (3)].[6] Based on these experiences, we envisioned a Lewis base approach to enable the first enantioselective (4+2) annulation of DA-cyclobutanes.

The challenge with enantioselective Lewis acid catalysis using DA-cyclobutanes likely relates to oxocarbenium ion formation from the 1,4-ylde intermediate.[7] Such a scenario allows bond formation remote to the catalyst, thereby limiting chirality transfer [Eq. (1)]. In contrast, a dual activation Lewis base approach would concurrently activate both coupling partners (i.e. I and II), covalently linking the catalyst to the π-system. Their subsequent union in a stepwise (4+2) annulation[8] (I + II → 6) should proceed with enantioselective bond construction [Eq. (4)]. Mechanically related (4+2) annulations exploiting non-cyclobutane substrates have been realized by Romo and Studer, although in both cases only a single example was reported.[9] More generally, dual activation strategies to enable enantioselective catalysis have been reported by ourselves and others using electron rich pyridyl,[10] isothiourea[11] and N-heterocyclic carbene (NHC)[12] catalysts. Herein we communicate the enantioselective (4+2) annulation of DA cyclobutanes using a Lewis base approach, which provides a range of enantioenriched cyclohexyl β-lactones[13] (25 examples, most ≥ 97:3 e.r.).

Preliminary studies focused on DA-cyclobutanes bearing a single ester. While some opening and annulation occurred, these substrates are less reactive than their cyclopropyl analogs. To address this, the more reactive malonate derived DA-cyclobutane 1a was targeted.[14] Gratifyingly, in the presence of acyl fluoride 5a a trace of β-lactone 6a was observed with Fu’s pyridyl catalyst, although isothiourea B gave no product (Table 1, entries 1 and 2). In contrast, NHC[15] CI gave cyclohexyl β-lactone 6a in 18% yield as a 67:33 ratio of enantiomers (Table 1, entry 3). Alternate...
morphpoline catalysts C2–C5 bearing various N-substituents30,31 were not viable (Table 1, entry 4), however tert-butyl NHC C6 gave a 44% yield of enantioenriched β-lactone 6a (96:4 e.r.) as a single diastereoisomer (> 20:1 d.r.) (Table 1, entry 5). Indanol and pyrrolidine tert-butyl catalysts D and E were viable, albeit less enantioselective (Table 1, entries 6 and 7). Enantioselectivity was poorer at lower temperature, while it increased when heated to reflux (97:3 e.r.) (Table 1, entries 8 and 9). The reaction tolerated toluene and DMF, with the later increasing yield but decreasing enantioselectivity (Table 1, entries 8 and 10). A compromise between yield and enantioselectivity was realized, with a 1:9 DMF/THF mixture providing β-lactone 6a in 73% yield and 96:4 e.r. (Table 1, entry 12). Finally a “salt”[17] and HMDS-free version of the reaction increased the yield to 93% without affecting enantioselectivity (Table 1, entry 13). Reinroduction of HMDS had no impact on the reaction (Table 1, entry 14), thus removal of KBF₃ is key to this improvement (see below).

Reaction generality was examined with the coupling of unsaturated acyl fluorides S and DA-cyclobutanes 1. While electron poor, neutral, and rich acyl fluorides reacted with good yields (≥ 80%), enantioselectivity was sensitive to β-aryl electronics. Thus, substrates containing the 4-BrC₆H₄ group gave β-lactone 6b in 92:8 e.r. (Table 2, entry 2), while electron rich 2,4-(CH₃O)₂C₆H₄ and 4-(CH₂)₅NCH₃ gave 6c and 6f in 99:1 e.r. (Table 2, entries 6 and 7). The reaction tolerated N-heterocycles with indole-containing β-lactone 6h prepared in 83% yield and 98:2 e.r. (Table 2, entry 9). Unfortunately, β-alkyl acyl fluorides were not compatible with the reaction, potentially due to acyl azolium dienolate formation as developed by Chi and others with related substrates.[15] Variation of the ester was examined with methyl, isopropyl, and allyl esters (6i, 6j, and 6k) prepared with excellent enantiopurity (98:2, 94:6 and 99:1 e.r.).

### Table 1: Selected optimizations.

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<th>e.r.[f]</th>
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<td>rt</td>
<td>THF/12 h</td>
<td>trace</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>rt</td>
<td>THF/12 h</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
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<td>1:9 DMF/THF/12 h</td>
<td>73</td>
<td>&gt; 20:1</td>
<td>96:4</td>
</tr>
<tr>
<td>12</td>
<td>C6</td>
<td></td>
<td>1:9 DMF/THF/2 h</td>
<td>93</td>
<td>&gt; 20:1</td>
<td>96:4</td>
</tr>
</tbody>
</table>

[a] NHCs generated with KHMDS. [b] Isolated yield. [c] Diastereomeric ratio by 1H-NMR analysis. [d] Enantiomeric ratio by HPLC over chiral stationary phases. [e] 20 mol% catalyst. [f] KBF₃, and HMDS free, see experimental section. [g] 10 mol% HMDS, KBF₃ free.

### Table 2: Scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R²</th>
<th>Yield [%][h]</th>
<th>e.r.[i]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-BrC₆H₄</td>
<td>Et</td>
<td>b</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅</td>
<td>Et</td>
<td>c</td>
<td>96:5</td>
</tr>
<tr>
<td>3</td>
<td>4-CH₃C₂H₅</td>
<td>Et</td>
<td>a</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>4-CH₃OC₂H₅</td>
<td>Et</td>
<td>d</td>
<td>100</td>
</tr>
<tr>
<td>5[h]</td>
<td>4-CH₃OC₂H₅</td>
<td>Et</td>
<td>d</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>2,4-(CH₃O)₂C₂H₅</td>
<td>Et</td>
<td>e</td>
<td>90</td>
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<tr>
<td>7</td>
<td>4-(CH₂)₅NC₂H₅</td>
<td>Et</td>
<td>f</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>3,4,5-(CH₃O)₂C₂H₅</td>
<td>Et</td>
<td>g</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>3-Ts-indolyl</td>
<td>Et</td>
<td>h</td>
<td>83</td>
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<tr>
<td>10</td>
<td>4-CH₃OC₂H₅</td>
<td>CH₃</td>
<td>i</td>
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<tr>
<td>11</td>
<td>4-CH₃OC₂H₅</td>
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<td>86</td>
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<td>12</td>
<td>4-CH₃OC₂H₅</td>
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<td>k</td>
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<td>4-(CH₂)₅NC₂H₅</td>
<td>Et</td>
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<td>90</td>
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<tr>
<td>14</td>
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<td>Et</td>
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<tr>
<td>15</td>
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<td>87</td>
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<td>Et</td>
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<td>Et</td>
<td>q</td>
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<td>4-(CH₂)₅NC₂H₅</td>
<td>Et</td>
<td>r</td>
<td>88</td>
</tr>
<tr>
<td>20</td>
<td>2,4-(CH₃O)₂C₂H₅</td>
<td>Et</td>
<td>s</td>
<td>81</td>
</tr>
<tr>
<td>21</td>
<td>4-(CH₂)₅NC₂H₅</td>
<td>Et</td>
<td>t</td>
<td>98</td>
</tr>
<tr>
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<td>Et</td>
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<td>23</td>
<td>4-CH₃OC₂H₅</td>
<td>Et</td>
<td>v</td>
<td>94</td>
</tr>
<tr>
<td>24</td>
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<td>Et</td>
<td>w</td>
<td>80</td>
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<td>Et</td>
<td>x</td>
<td>75</td>
</tr>
<tr>
<td>26</td>
<td>2,4-(CH₃O)₂C₂H₅</td>
<td>Et</td>
<td>y</td>
<td>91</td>
</tr>
</tbody>
</table>

Absence of substitution about the cyclobutane was tolerated with cyclohexyl \( \beta \)-lactones 6l, 6m and 6n prepared in \( \geq 96:4 \) e.r. (Table 1, entries 13–15). Similarly dimethyl DA-cyclobutane gave \( \beta \)-lactones 6o, 6p and 6q in excellent yield and enantiopurity (97:3, 99:1 and 99:1 e.r.) (Table 1, entries 16–18). The synthesis of spirocyclic cyclobutanes 6r and 6s occurred with decreased enantioselectivity, 93:7 and 90:10 respectively, (Table 2, entries 19 and 20) while cyclopentyl, heptyl, and octyl \( \beta \)-lactones 6t–6y all formed in \( \geq 97:3 \) e.r. (Table 2, entries 21–26). Finally, a vinylogous variant of the reaction was possible using TBS ether 11 and acyl fluoride 5d to give \( \delta \)-lactone 6z [Eq. (7)]. NHC-catalyzed approaches to related products have recently been report by Studer, Ye and Chi, all with high enantioselectivity. While the synthesis of 6z was viable with IMes, suitable chiral catalysts are yet to be identified, presumably due to the enhanced stability of the TBS (cf. TMS) requiring more nucleophilic catalysts.

To allow larger scale (4+2) annihilations lower catalyst loadings were examined. Pleasingly, 3 mol% C6 provided the expected product in good yield and similar enantioselectivity (Table 2, entry 5), allowing a 5 mmol reaction, producing 1.98 grams of \( \beta \)-lactone 6d in 89% yield and 95:5 e.r. (cf. 100% yield; 97:3 e.r.), to be realized [Eq. (8)] (Scheme 2). Derivatization studies commenced with the decarboxylation of \( \beta \)-lactone 6e to afford cyclohexene 7 in 94% yield and 99:1 e.r. [Eq. (9)]. Coupling \( \beta \)-lactone decarboxylation with decarboxylative allylation of diallyl malonate 6k allowed diene 8 to be prepared as a 3:1 mixture of diastereoisomers [Eq. (10)]. Opening of the \( \beta \)-lactone with ethanol triggered desymmetrization of the malonate to afford [2.2.2]-bicyclic \( \delta \)-lactone 9 [Eq. (11)]. Benzylamine, under milder conditions, opened the \( \beta \)-lactone to afford amide 10 in 86% isolated yield [Eq. (12)], while chemoselective reductive opening of the \( \beta \)-lactone led to formation of diol 11 in 83% yield [Eq. (13)]. Finally, hydrolysis of \( \beta \)-lactone 6q followed by cyclization provided quinolinone 12 in 94% yield as a 5:1 mixture of separable diastereomers [Eq. (14)]. Relative stereochemistry, and structural confirmation, were performed by single-crystal X-ray analysis.

Mechanistically, the early stages of this reaction likely involve NHC mediated defluorination–desilylation to afford acyl azolium 9b in a reaction likely to proceed by either Michael addition or \( \text{C}–\text{O} \) bond formation followed by Claisen rearrangement. To investigate these scenarios the reaction was performed using various bases for NHC generation bearing different counterions [Eq. (15)]. Tellingly, the reaction fails with strongly coordinating lithium and sodium bases, which favor Michael addition of the enolate. Similarly adding LiCl (0.5 equiv) to a reaction with Cs2CO3 causes the reaction to fail. In contrast, potassium and cesium salts favor ionic structures, and subsequent \( \text{C}–\text{O} \) bond formation, giving good yields of 6a. Further support for a [3,3]-rearrangement is derived from the known acceleration of such reactions by poorly coordinating counterions.

Thus, we propose that \( \text{C}–\text{O} \) bond formation gives hemiacetal 1 VII that undergoes [3,3]-sigmatropic rearrangement to afford \( \text{VI} \), which after asynchronous (2+2) and loss of the NHC, then delivers \( \beta \)-lactone 6. A striking observation in the optimization was the enhanced enantioselectivity at higher temperatures. Although less common than enhancement at low temperature it has been observed in reactions with large entropic contributions to the diastereomeric transition state energies in the enantiodetermining step (i.e. \( \Delta S^\text{S} \) significant cf. \( \Delta H^\text{S} \)). Although further studies are needed to fully appreciate this interesting observation it seems probable that...
reaction volume is gained in the conversion of V to VI that allows the $\Delta \Delta S^*$ term to make a significant contribution to the overall activation energy. Donor-acceptor cyclobutanes are exceptional substrates for reaction design. Beyond documented ring-strain, they are readily accessible, with all substrates prepared in 2 steps. Thus, the enantioselective (4+2) annulation allows a 3-step synthesis of densely functionalized cyclohexyl $\beta$-lactones. This sequence compares favorably to the state-of-the-art in enantioselective $\beta$-lactone synthesis.[10] The ability of this reaction to rapidly deliver molecular complexity is currently being examined as a vehicle to drive studies in total synthesis and medicinal chemistry.

**Acknowledgements**

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**Keywords:** cyclohexanes · donor–acceptor cyclobutanes · enantioselective catalysis · N-heterocyclic carbene · organocatalysis

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Angew. Chem. 2016, 128, 16370–16374

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[7] In references [4a,b,5a], the oxocarbenium ion is discussed to account for the role of aldehyde electrons on reaction outcome.


[13] For selected examples of enantioselective β-lactone synthesis:


[19] Single crystal X-ray analysis of β-lactone 6k using CuK radiation for absolute stereochemistry (CCDC 1494651), relative stereochemistry and structure of 12 (CCDC 1500815). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


Biomimetic and Biocatalytic Synthesis of Bruceol

Aaron J. Day, Joel H. Z. Lee, Quang D. Phan, Hiu C. Lam, Adam Ametovski, Christopher J. Sumby, Stephen G. Bell,* and Jonathan H. George*

Abstract: The first total synthesis of bruceol has been achieved using a biomimetic cascade cyclization initiated by a stereoselective Jacobsen–Katsuki epoxidation (and kinetic resolution) of racemic protobruceol-I. A bacterial cytochrome P450 monooxygenase was also found to catalyze the conversion of protobruceol-I into bruceol. The first full analysis of the NMR data of natural bruceol suggested that “isobruceol” was a previously unrecognized natural product also isolated from Philotheca brucei. This was confirmed by the re-isolation, synthesis, and X-ray analysis of isobruceol. In total, eight stereoisomers and structural isomers of bruceol have been synthesized in a highly divergent approach.

The meroterpenoid bruceol (1) was first isolated from the Western Australian shrub Philotheca brucei (formerly known as Eriostemon brucei) by Jefferies and co-workers at the University of Western Australia in 1963 (Figure 1).[1] The compact, pentacyclic structure of 1 consists of a 5,7-dioxycoumarin fused to a so-called “citran” ring system that is biosynthetically derived from cyclization of a geranyl group. The relative configuration of 1 was determined by X-ray crystallography of 8-bromobruceol, but given the era of the study, no detailed NMR analysis was conducted.[1] The absolute configuration of natural (−)-1 was later determined by X-ray studies of chloroacetate and iodoacetate derivatives.[2] In 1992 Waterman and co-workers re-investigated natural products from Philotheca brucei, and they published full NMR data of what they believed was re-isolated 1.[3] However, based on the synthetic and isolation work described herein, we report that Waterman actually isolated isobruceol (1), which has an opposite orientation of the dioxycoumarin to the “citran” ring system compared to bruceol. There is also some confusion in the literature between structures 3 and 4, with both compounds being previously referred to as deoxybruceol. Henceforth, we propose that 3 is deoxybruceol and 4 is deoxyisobruceol. (±)-4 was first synthesized by Crombie and Ponsford in 1968 in a remarkable work of both biomimetic synthesis and natural product anticipation.[4] The isolation of 4 from Philotheca brucei was reported in 1981 by Jefferies and co-workers[5] (as a racemate) and again in 1992 by Waterman and co-workers[3] (as a single enantiomer). To date, 3 has not been isolated as a natural product.

Given that bruceol (1) and deoxyisobruceol (4) have different carbon skeletons, with opposite orientations of the upper dioxycoumarin with respect to the lower tricyclic “citran” ring system, they are clearly not biosynthetically related by a direct enzymatic C–H oxidation. However, both 1 and 4 may be derived from the geranlylated dihydroxycoumarin 5 (Scheme 1). In the biosynthesis of 4, Crombie proposed that oxidation and oxa-6π-electrocyclization of 5 gives chromene 6,[5] Tautomerization (and dearomatization) of 6 to give ortho-quinone methide[6] 7 followed by an intramolecular hetero-Diels–Alder reaction would then give deoxyisobruceol (4). Alternatively, and as previously proposed by Trauner,[7] oxidative cyclization of 5 could give protobruceol-I (8), a naturally occurring chromene and structural isomer of 6.[5] Stereoselective epoxidation of 8 (on the opposite face to the bulky homoprenyl substituent) would give the labile epoxide 9, which could ring open (and dearomatize) to give ortho-quinone methide 10, and then form 1 via an intramolecular hetero-Diels–Alder reaction. We speculate that a monooxygenase enzyme might catalyze this epoxidation–cyclization cascade reaction in vivo, either enantioselectively (i.e., kinetic resolution of a racemic chromene 8) or diastereoselectively (if chromene 8 is enantiopure in nature).[9]

Crombie and Ponsford’s landmark two-step total synthesis of (±)-4 was reported over 50 years ago,[4] 5,7-Dihydroxycoumarin (11) was first synthesized in one step from phloroglucinol,[10] and then condensed with citral (12) in

Figure 1. Bruceol-type natural products isolated from Philotheca brucei. Note the variation in the orientation of the dioxycoumarin rings (red) to the “citran” ring systems (blue) of bruceol and isobruceol.
pyridine at 110°C to give (±)-4 in 10% yield (Scheme 2). The product of this reaction was initially incorrectly assigned as (±)-3 by analogy to bruceol (1), until later X-ray studies by Crombie led to a structure revision to (±)-4.[5] The mechanism of the cascade reaction involves initial condensation of 11 with 12 to give chromene (±)-6, followed by tautomerization and intramolecular cycloaddition to give (±)-4, thus closely mirroring the proposed biosynthetic pathway. Later studies by Crombie showed that condensation of 11 with 12 in pyridine at the lower temperature of 90°C gave the isomeric chromenes (±)-8 and (±)-13 in modest yields.[5] Then, heating (±)-8 in pyridine at 110°C formed a mixture of (±)-3 and (±)-4 in 22% combined yield, indicating that some interconversion of chromenes (±)-8 and (±)-6 must occur under these conditions via reversible retro-oxa-6π-electrocyclization and oxa-6π-electrocyclization reactions, prior to the irreversible intramolecular hetero-Diels–Alder reactions. More recently, an improved synthesis of (±)-4 in 45% yield has been achieved by Lee and Kim, who condensed 11 with 12 in the presence of catalytic ethylenediamine diacetate in DMF at 100°C.[11]

Our biomimetic synthesis of both enantiomers of bruceol is outlined in Scheme 3. (±)-8 was first synthesized according to a modified version of Crombie’s procedure (Scheme 2, and see the Supporting Information for full details). We then mimicked the proposed biosynthetic epoxidation of proto-bruceol-I with a stereoselective Jacobsen–Katsuki epoxidation.[12] Jacobsen-type chiral (salen)manganese(III)-complexes are known to efficiently catalyze the epoxidation of (Z)-1,2-disubstituted alkenes in preference to tri-substituted alkenes (as required in our synthesis), and chromenes have been reported to be good substrates for the reaction.[13] Furthermore, Jacobsen has used his epoxidation as a method for the kinetic resolution of chiral, racemic chromenes, which was applied in an asymmetric synthesis of a chromene natural product, (+)-teretifolione B.[14] High catalyst-induced selectivity, but moderate substrate-induced selectivity, was observed in Jacobsen’s kinetic resolution of chromenes, and similar selectivity was observed in our biomimetic synthesis of (−)-1 (Scheme 3). Thus, treatment of (±)-8 with 10 mol% of Jacobsen’s catalyst (R,R)-14 with m-CPBA and NMO as stoichiometric oxidants gave (−)-1 (11% yield, 98:2 e.r.), alongside 2′-epi-bruceol (+)-17 (3% yield, 90:10 e.r.). Both enantiomers of (±)-8 therefore undergo epoxidation to some extent (i.e. low substrate selectivity), but the facial selectivity is good, with addition to the top face (as drawn) of the alkene strongly preferred in each case (i.e. high catalyst-selectivity). A similar result was obtained using (S,S)-14 to give (+)-1 (13% yield, 96:4 e.r.) and (−)-17 (3% yield, 91:9 e.r.). We believe that the low yield for the epoxidation–cyclization cascades of (±)-8 to give (−)-
1 and (±)-I is due to over-oxidation of the electron-rich dioxycoumarin ring system to form some polar, uncharacterized by-products. However, these low yields are partially offset by the significant increase in molecular complexity (three stereocentres, three bonds, and two rings are formed in the cascade) and by the fact that the reactions are kinetic resolutions.

Our synthetic bruceol (1) correlated with the low resolution NMR data that was published in Jefferies’ original 1963 isolation paper alongside their X-ray crystallographic data.[1] However, close comparison of our $^1$H and $^13$C NMR spectra of synthetic 1 with those of the natural “bruceol” reported by Waterman in 1992 revealed slight discrepancies.[3] We postulated that Waterman had in fact isolated isobruceol (2), partly due to its co-isolation with deoxyisobruceol (4), and related Philotheca brucei natural products such as eriobrucinol and hydroxyeriobrucinol,[15] that share the same orientation of the dioxycoumarin with respect to the chromene-derived ring system. To prove our conjecture, we intended to re-isolate both 1 and the suspected 2 from Philotheca brucei, so we contacted natural product chemists at the University of Western Australia for advice on obtaining this plant. To our surprise, we were given several grams of Jefferies’ original, crystalline sample of 1 from the University of Western Australia’s library of natural products. The first detailed NMR analysis of this 55-year-old sample conclusively showed that it matched our synthetic 1, but not Waterman’s re-isolated “bruceol” NMR data. We also obtained an X-ray crystal structure of synthetic 1.[16] Next, we obtained 5 kg of dried Philotheca brucei from the Koolyanobbing Range (500 km east of Perth, WA). Extraction of the dried plant material with Et$_2$O followed by flash column chromatography on silica gel gave multi-gram quantities of a 1:1 mixture of 1 (major component) and a similar compound with $^1$H NMR spectra that matched Waterman’s “bruceol”. Purification of the unknown compound via selective crystallization to remove 1, followed by preparative HPLC, gave a few milligrams of crystalline material that was identified by X-ray analysis as isobruceol (2) (Scheme 4). NMR data for this compound fully agreed with Waterman’s data, thus proving that he isolated isobruceol, not bruceol.

We then conducted a stereoselective synthesis of isobruceol to determine its absolute configuration. This first required the synthesis of chromene (±)-6 (Scheme 4), which is presumably an undiscovered natural product (“protoisobruceol”). Treatment of chromene (±)-13 (a previously undesired by-product in the synthesis of (±)-8 with NaOH in MeOH gave a separable equilibrium mixture of (±)-13 and (±)-6 via methoxide-induced opening of the lactone ring followed by cyclization of the methyl ester intermediate at the C-9 phenol.[17] Jacobsen–Katsuki epoxidation of (±)-6 with...
10 mol% (S,S)-14 gave (−)-2 (5% yield, 93:7 e.r.), which matched the sign of the optical rotation of natural isobruceol, thereby confirming that the absolute configuration of (−)-2 is as shown in Scheme 4. A 2% yield of 2′-epi-isobruceol (±)-18 (96:4 e.r.) was also obtained, and a similar result was obtained using the (R,R)-14 catalyst to give (±)-2 (9% yield, 92:8 e.r.) and (−)-18 (4% yield, 91:9 e.r.).

The low yields obtained in our biomimetic syntheses of 1 and 2 are, to some extent, due to over-oxidation of the electron-rich dioxycoumarin ring systems under the Jacobsen–Katsuki reaction conditions. Jacobsen has also observed that tricyclic chromenes similar to 6 and 8 are poor substrates for stereoselective epoxidation.[14] We therefore demonstrated a more efficient epoxidation–cyclization cascade of the simpler bicyclic chromene (±)-19.[18] Thus, Jacobsen–Katsuki epoxidation of (±)-19 with 10 mol% (R,R)-14 gave the bruceol analogue (−)-20 (23% yield, 92:8 e.r.), alongside the epimer (−)-21 (11% yield, 94:6 e.r.) (Scheme 5). The use of (S,S)-14 gave (+)-20 (29% yield, 91:9 e.r.) and (+)-21 (12% yield, 92:8 e.r.). Chromene (±)-19 is therefore a much better substrate for the epoxidation–cyclization cascade than (±)-8 or (±)-6.


To gain further insight into the biosynthesis of bruceol and isobruceol, chromenes (±)-8, (±)-6 and (±)-19 were screened against a small library of bacterial cytochrome P450 monoxygenase enzymes.[19] A variant of P450BM3, A74G/F87V/L188Q (GVQ) converted ≥80% of (±)-19 into two products (see Figure S1 in the Supporting Information).[19] Co-elution of synthetic standards using chiral phase HPLC and GC-MS, and analysis of the MS spectra enabled their characterization as the bruceol analogue (±)-20 and an epoxide[20] formed by oxidation of the prenyl side chain (Supporting Information, Scheme S1 and Figure S2). Given the larger size of (±)-8 and (±)-6, a series of P450 variants, which had been designed to increase the size of the substrate binding pocket, were screened for oxidation activity (Supporting Information, Table S1). While oxidation of these substrates was less efficient and selective, chiral phase HPLC co-elution experiments of the enzyme turnovers, using the variant KSK19/I263A/A328I,[19e–f] with synthetic standards revealed the formation of (±)-1 and (±)-2 as single enantiomers (Figure 2). Therefore, the P450 monoxygenases could catalyze the enantioselective chromene epoxidation–cyclization cascade proposed in Scheme 1 to form the “citran” ring system of bruceol natural products. The identity of the natural monoxygenase enzyme that catalyzes this cascade reaction in Philotheca brucei remains to be determined.

In summary, we have mimicked the epoxidation–cyclization cascade proposed to occur in the biosynthesis of bruceol by using a Jacobsen–Katsuki epoxidation of an electron-rich chromene. The first full NMR analysis of bruceol, including the original sample isolated by Jefferies in 1963, revealed that isobruceol had been isolated and mistaken for bruceol by Waterman in 1992. This hypothesis was confirmed by the re-isolation and synthesis of isobruceol, thus highlighting the roles that biosynthetic speculation and biomimetic synthesis continue to play in the revision of natural product assignments.[21] Finally, we have shown that bacterial cytochrome P450 monoxygenases are capable of catalyzing the bruceol cascade in a complex example of a P450-mediated oxidative cyclization.[9]

Acknowledgements

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Conflicts of interest

The authors declare no conflict of interest.

Keywords: biomimetic synthesis · biosynthesis · cascade reactions · natural products · total synthesis

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[16] CCDC 1865687 (1), 1865688 (2) and 1865689 (17) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[20] For the synthesis and characterization of this epoxide, see ref. [18]. See Scheme S1 in the Supporting Information for its structure.

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Enantioselective Total Synthesis of (−)-Δ⁹-Tetrahydrocannabinol via N-Heterocyclic Carbene Catalysis

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Supporting Information

ABSTRACT: Enantioselective syntheses of (−)-Δ⁸-tetrahydrocannabinol ((−)-Δ⁸-THC) and (−)-Δ⁹-THC have been achieved in eight and 10 steps, respectively, from a known cinnamic acid. The syntheses take advantage of an enantioselective N-heterocyclic carbene (NHC)-catalyzed (4 + 2) annulation between donor–acceptor cyclobutanes and cinnamoyl fluorides to construct the highly enantioenriched cycloxyll β-lactone shown. Having constructed this A-ring precursor, elaboration to (−)-Δ⁸-THC is achieved through β-lactone alcoholysis followed by oxidation, dual decarboxylation, trimethylation, and cationic cyclization. Finally, the conversion to (−)-Δ⁹-THC is achieved with established chemistry.

While over 200 phytocannabinoids are known, within popular culture their zeitgeist remains strongly linked to (−)-Δ⁹-tetrahydrocannabinol ((−)-Δ⁹-THC, 1) and cannabidiol (2). The bioactivity of the former is elicited through binding to the G protein-coupled receptors CB₁ and CB₂, with structural information regarding the mode of binding emerging in 2017. While these compounds have captured significant attention, other phytocannabinoids (i.e., 3−5) can have distinct bioactivities and unusual molecular structures. The chemical synthesis of Δ⁸-THC has been extensively examined over the last 50 years, and a number of enantiospecific approaches and syntheses of racemic Δ⁸-THC have been developed. Many have been achieved through terpenylation of olivetol (6), as typified by the enantioselective synthesis from (−)-verbenol (7) reported by Mechoulam and Gaoni (Scheme 1a). In contrast, enantioselective routes are far more limited. In 1997 Evans reported the enantioselective total synthesis of (−)-Δ⁸-THC via a bis(oxazoline)-copper-catalyzed Diels−Alder reaction (8 + 9 → 10). Subsequent coupling to 6 and cyclization gave the unnatural enantiomer of THC in an efficient manner. In 2007 Trost and Dogra reported the enantioselective synthesis of 1 through ring-closing metathesis (RCM) to introduce the A ring. Enabled by stereodivergent access to 1,7-diene 11, a related RCM approach was used by Carreira in his elegant synthesis of (−)-Δ⁹-THC. Finally, Leahy recently developed a synthesis enabled by sigmatropic rearrangement followed by RCM, while Zhou exploited high-pressure enantioselective ketone reduction in his approach to 1 and (−)-Δ⁸-THC (12). In 2016 we reported the enantioselective N-heterocyclic carbene (NHC)-catalyzed synthesis of cyclohexyl β-lactones (i.e., 13) from donor−acceptor cyclobutanes (i.e., 14) and cinnamoyl fluorides (i.e., 15a, 15b). The reaction displays broad generality, and we envisioned that it could provide materials (such as 13a or 13b) suited to the preparation of 1 (Scheme 1b). To realize this, decarboxylation and/or decarboxylation would yield cyclohexene 16 or cyclohexanone 17, after which exhaustive methylation and cationic cyclization would give 1. This sequence should define a concise entry to 1 while being amenable to the preparation of materials with a modified A ring by the use of alternate cyclobutanes. Strikingly, modification of the A ring has received limited attention in studies of the bioactivity of (−)-Δ⁹-THC analogues. Here we report the enantioselective total synthesis of normethyl-(−)-Δ⁹-THC (18), (−)-Δ⁸-THC (12), and (−)-Δ⁹-THC (1) in six, eight, and 10 steps, respectively, from commercial cinnamate 15b (X = OH), which itself can be derived from 6 in three steps.
Studies commenced by establishing the viability of the general strategy through the preparation of 18 (Scheme 2). In our methodological studies, 8a, 2,6-disubstituted cinnamoyl fluorides (i.e., 15a) were not examined, and hence, their viability in NHC catalysis needed to be determined. Following conversion of commercially available and readily accessible cinnamate 15b (X = OH) to acyl fluoride 15a (X = F),11 the annulation of 15a was examined. Gratifyingly, reaction with the known donor—acceptor cyclobutane 14a (R = H)12 proceeded without event to provide cyclohexyl β-lactone 13a in 45% yield as a single diastereoisomer with excellent enantioselectivity (98:2 er). While the yield was modest, this result is in keeping with reactions of heavily substituted α,β-unsaturated acyl azoliums.9j Krapcho decarboxylation13 of malonate 13a with concomitant decarboxylation of the β-lactone provided a 2:1 mixture of cis- and trans-cyclohexenes 19 in 66% yield. Conversion of the diastereomeric mixture to the desired trans-19 was achieved in 85% yield using the conditions reported by Trost and Dogra.6a Finally, two-step conversion of trans-19 to normethyl-(-)-Δ⁹-THC (18) using conditions described by Carreira6b closed the B ring and provided the desired product in 62% isolated yield.

Having demonstrated the key reactions necessary for the overall strategy, attention was directed toward the 9-methyl group. Our preferred approach would exploit donor−acceptor cyclobutane 14b (R = Me). However, all attempts to prepare this material proved unsuccessful. An alternate approach exploiting methyl ketone 20, a substrate used by Studer in a related (4 + 2) annulation, was envisaged.8b Unfortunately, union of ketone 20 with enal 15c under oxidative NHC catalysis failed to give the desired cyclohexanone 13b (eq 1), as only cinnamic acid derivatives were isolated.

An alternate strategy to install the 9-methyl group involved the preparation of ketone 17 by methanolysis of β-lactone 13a, oxidation, and dual Krapcho decarboxylation (Scheme 3). Global methylation followed by cationic cyclization and elimination would then provide the cannabinoid targets. This approach was initially met with difficulties due to the facile formation of bicyclic lactone 21 upon cleavage of the β-lactone (Scheme 3). Fortuitously, the reaction was sensitive to the base, with KCN favoring the formation of the desired...
alcohol 22. Using these conditions and immediately subjecting alcohol 22 to oxidation with IBX gave β-keto ester 23 (Scheme 4). This material underwent dual Krapcho decarboxylation to give cyclohexanone 17 in 32% isolated yield over the three steps as a 2:1 mixture of diastereoisomers. Epimerization as previously described then gave trans-17 in 83% isolated yield. Finally, using modified conditions of Carreira, global methylation followed by elimination and cyclization gave (−)-Δ^2-THC (12) in 40% isolated yield over the two steps. Conversion of 12 to (−)-Δ^2-THC (1) was achieved in two steps using reported conditions.13

Methodological discoveries have the potential to enable new approaches in multistep target-oriented synthesis. The studies herein exploited an NHC-catalyzed (4 + 2) annulation to provide cyclohexyl β-lactone 13a, which could be elaborated to (−)-Δ^2-THC (12) in six steps and (−)-Δ^2-THC (1) in eight steps. Overall, a concise approach to these cannabinoids has been developed. In addition, by exploiting alternate cyclobutane starting materials, access to A-ring analogues of the cannabinoids should be possible. The impact of modifications in this region of 1 on CB₁ and CB₂ selectivity will be examined in subsequent studies.

ASSOCIATED CONTENT

# Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00198.

Experimental procedures, ¹H and ¹³C NMR spectra of new materials, and HPLC traces of chiral materials (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES


(11) For the use of DAST to prepare acyl fluorides, see: Bappert, E.; Müller, P.; Fu, G. F. Chem. Commun. 2006, 2604.

