Sustainable Methodology for the Synthesis of Amides, Esters and Polypropionate Fragments

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Abstract

This thesis presents research into the development of sustainable methodology for the synthesis of amides, esters and polypropionate fragments. As well as a literature review of efficient natural product synthesis.

Acylals are a known class of reagent that have been utilized within literature for a wide range of synthetic methodologies. Herein we present acylals as new highly active reagents for the N-/O-acylation of amines and alcohol nucleophiles for the synthesis of a range of formamides, acetamides, formate esters and acetate esters. It has been demonstrated that a range of acyl groups can be transferred including short and long chain alkyls, acryloyl, benzoyl, phenyl acetyl and biologically important trifluoroacetyl group, thus enabling the synthesis of a range of benzylamides and esters. These acylation reagents have also been shown to demonstrate inherent N-/O- selectivity towards the amine and alcohol groups of serine methyl ester.

The scope and limitations of these reagents of the use of acylals has been investigated through the N-formylation of a range of unprotected amino acids, and for the synthesis of the biologically important tripeptide f-MLP. As well as the acylation/formylation of the ω-amino residue of a lysine residue within a decapeptide. Finally, it has also been demonstrated that a simple switch in pH from basic to acidic conditions for diols can change from O-acylation to acetal formation.

The synthesis of enantiomerically enriched dihydropyrans from the hetero-Diels-Alder reaction of 1-alkoxy dienes and ethyl glyoxalate has been presented. A series of stereoselective derivatisation reactions were developed including, hydroboration, hydrogenation, epoxidation, dihydroxylation and epimerization which proceed with stereoselectivity to afford a range of complex enantiomerically enriched polypropionate based building blocks, which are ideally suited for the synthesis of polyketide natural products through a “plug and play” approach. Chemistry has also been presented which makes use of the orthogonally addressable synthetic handles of the pyran building blocks. Utilization of either the masked aldehyde character or the ester functionality present allows for further elaboration of the pyran building blocks by selectively introducing new functionality.
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Contents

Abstract .................................................................................................................................................. II
Acknowledgements ............................................................................................................................ III
Abbreviations ..................................................................................................................................... VII

1.0 Use of Acylals as N- and O- Formylation and Acylation Agents .................................................. 1
  1.1 Introduction .................................................................................................................................. 1
  1.2 Acylation Strategies ...................................................................................................................... 2
  1.3 Phenylmethylene Diacetate as an Acylation Reagent ................................................................. 8
  1.4 Synthetic Utility of Phenylmethylene Diacetate ......................................................................... 9
  1.5 Acylals as Reagents for the N-Acetylation of Amines ................................................................. 27
    1.51 Acylals for the O-Acetylation of Alcohols .............................................................................. 35
  1.52 Use of Acylals for the N-/O-Acylation of Benzylamine and Benzyl Alcohol ...................... 38
  1.6 N-Formylation of Amines ............................................................................................................ 42
    1.61 An N-Formylation Reaction Performed on Scale .................................................................. 46
    1.62 N-Formylation Reactions of Amino Acid and Peptides ......................................................... 48
    1.621 N-Formylation Reactions of α-Amino Acids ...................................................................... 48
    1.622 N-Formylation of Peptides .................................................................................................. 50
  1.63 O-Formylation Reactions of Alcohols ...................................................................................... 52
  1.64 Investigation into the N-/O- Selectivity Profile of Acylals ....................................................... 54
  1.7 Acetalisation of 1,2-Diol and 1,3-Diol Utilizing Acylals .......................................................... 54
  1.8 Preliminary Investigations into the use of Mixed Acylals for N-/O-Acylation Reactions .......... 60
  1.9 Future Work ............................................................................................................................... 61
    1.10 Conclusion ............................................................................................................................... 63

2.0 Efficient Natural Product Synthesis ............................................................................................. 66
  2.1 Introduction .................................................................................................................................. 66

3.0 Early Natural Product Synthesis ................................................................................................. 66
    3.1 Natural products as drug molecules ....................................................................................... 72

4.0 Protecting Group Free Synthesis ................................................................................................. 92
5.0 Polyketides ........................................................................................................ 101

5.1 Introduction to Polyketides .......................................................................... 101

5.2 Synthesis of Ionomycin .............................................................................. 105

5.3 Synthesis of Pironetin ............................................................................... 115

5.4 Synthesis of Spirodienal A ........................................................................... 119

6.0 Conclusion ..................................................................................................... 127

7.0 A Protecting Group Free Strategy towards the Sustainable Synthesis of Polypropionate Fragments ............................................................................................................. 128

7.1 Results and Discussion .................................................................................. 128

7.2 Diene Synthesis ........................................................................................... 134

7.3 Hetero-Diels-Alder Chemistry .................................................................... 139

7.31 Dihydropyran Synthesis .......................................................................... 144

7.4 Dihydropyran Derivatization ....................................................................... 150

7.41 Hydroboration ............................................................................................ 150

7.411 Hydroxyl Inversion ................................................................................ 153

7.42 Hydrogenation .......................................................................................... 156

7.43 Epoxidation ................................................................................................ 160

7.44 Dihydroxylation ........................................................................................ 164

7.45 Epimerization ............................................................................................. 168

7.451 Computational Studies on Epimerization of Dihydropyran 104.2 .......... 173

7.5 Dihydropyran Analogue Synthesis ............................................................... 174

7.51 Synthesis of Diene Analogues .................................................................... 175

7.52 Dihydropyran Analogues Synthesis ......................................................... 176

7.53 Dihydropyran Analogues Derivatisation .................................................. 178

7.6 Further Dihydropyran Derivatisation ......................................................... 184

8.0 Future Work .................................................................................................. 189

9.0 Conclusion ..................................................................................................... 192

Experimental ....................................................................................................... 196
References

263
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</tr>
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<td>Hertz</td>
</tr>
<tr>
<td>HTP</td>
<td>High through put</td>
</tr>
<tr>
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<td>Highest occupied molecular orbital</td>
</tr>
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<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>IAC</td>
<td>Intramolecular acylal cyclisation</td>
</tr>
<tr>
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<td>Infrared</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
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<tr>
<td>LHMDs</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LiAlH$_4$</td>
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</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m/z</td>
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<tr>
<td>MHz</td>
<td>Megahertz</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ts/Tosyl</td>
<td>para-Toluenesulfonyl</td>
</tr>
<tr>
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1.0 Use of Acylals as $N$- and $O$- Formylation and Acylation Agents

1.1 Introduction

Acylation reactions, and in particular acetylation reactions, are some of the most significant and widely used transformations in organic synthesis.$^{1-5}$ The amide bond is ubiquitous throughout nature (e.g. peptides, proteins, etc...) and is found in many pharmaceutically active molecules (Figure 1), resulting in the $N$-acylation of amines and $O$-acylation of alcohols being two of the most widely utilized reactions in drug and agrochemical synthesis.$^{1,6,7}$

*Figure 1. Examples of top selling drugs containing amide or ester acyl groups.*

---

**Atorvastatin**
Cardiovascular Disease

**Lisinopril**
Angiotensin-Converting Enzyme Inhibitor

**Valsartan**
Angiotensin II Receptor Antagonist

**Diltiazem**
Calcium Channel Blocker
1.2 Acylation Strategies

Traditionally, N-acylation reactions are carried out utilizing carboxylic acid derivatives, namely acid anhydrides 1.2 and acyl chlorides 1.3. Variations of these approaches form the basis of the majority of synthetic acylation reactions (Scheme 1).

Modern variations on this theme can be performed in a range of organic solvents and often utilize acyl transfer agents such as dimethylaminopyridine (DMAP) and its derivatives, as well as Lewis acid catalysts. DMAP 2.3 is able to act as a nucleophilic organocatalyst, which attacks an anhydride (or acyl chloride) to generate an activated acyl transfer agent (e.g. acetylpyridinium 2.4) which is then more reactive towards amine and alcohol nucleophiles, thus facilitating the formation of amides and esters. For example the acylation of sterically hindered methylcyclohexanol 2.1 with acetic anhydride to give methylcyclohexyl acetate 2.2 was explored by Goe et al., with three additives tested for this reaction. DMAP performed best giving an 89% yield, of the desired ester 2.2, whereas N-methyl imidazole (NMIM) and pyridine gave only 15% and <5% yields respectively. This increase in yield is attributed to the ability of DMAP to act as a nucleophilic catalyst, which generates a resonance stabilized reactive intermediate in situ (Scheme 2).
However, there are a number of problems associated with the use of acyl chlorides and anhydrides for acylation reactions. For example; reaction of amines with acyl chlorides can be highly exothermic, while anhydrides can form side products (e.g. imides) when reacted with primary amines. Acyl chlorides and anhydrides are also known to be moisture sensitive, with the high reactivity of acid chlorides meaning they are potentially liable to decomposition and competing side reactions. It is worth noting as well, that while anhydrides and acyl chlorides are moisture sensitive, in some cases they have been shown to be stable enough to allow the reaction to be performed in aqueous media.

Some of these disadvantages have been alleviated through the direct use of carboxylic acids as acyl sources, which is of particular interest for peptide synthesis. Whilst an obvious solution is to covert the acid to an acyl chloride in situ, this approach is only really applicable to relatively simple substrates, with problems often encountered when more complex substrates are used. Consequently, a whole suite of coupling reagents have been developed that activate carboxylic acids towards nucleophilic addition of amines and alcohols. Coupling reagents based on carbodiimide (DCC), N-acylimidazoles (CDI), phosphonium salts (BOP) and guanidinium salts (HATU) are regularly used in peptide synthesis, which afford excellent yields for amide bond formation and crucially without evidence of any racemization (Figure 2). However, the use of these coupling reagents can be considered to be expensive and wasteful, since they generate stoichiometric amount of by-products.
In response to this, a range of acylation reagents have been developed in the literature that act directly as acyl transfer agents, rather than relying on the activation of a starting material or intermediate in situ (Scheme 3). One of the first acylation reagents were acyl cyanides 3.3, which were first reported as an alternative reactant to acyl chlorides in 1954.\(^{14}\)

More recently, Murahashi and Naota have reported an efficient acyl cyanide synthesis utilizing a ruthenium catalyzed oxidation of the corresponding cyanohydrins using tert-butylhydroperoxide as an oxidant.\(^{15,16}\) These acyl cyanides were shown to be highly chemoselective with only N-acylation observed for a number of amino alcohol substrates. Kikugawa and co-workers have demonstrated the use of N-methoxydiacetate 3.4 as a highly selective N-acylation reagent, that selectively acylated primary amines over both secondary amines and alcohols.\(^{17}\) This was developed into the bench stable N-diethylcarbonyl-N-methoxyformamide 3.5, which acts as a selective N-formylating reagent. N-acyl-2-phenylimino-oxazolidines 3.6 developed by the Kim group have been shown to be highly active acylation agents, demonstrating high yields with a range of primary and secondary amines, as well as amino alcohols.\(^{18}\) The Murakami group have developed a range of acylation agents based on substituted anilines, including N-acyl-N-(perfluorophenyl)methanesulfonamides 3.7, which have been shown to demonstrate high activity towards primary and secondary amines.\(^{19}\) Yoon et al. have shown that air stable 2-acyl-4,5-dichloropyridazin-3-ones 3.8 are effective N-acylation agents, with the parent 4,5-dichloropyridazin-3-one by-product potentially being isolated and recycled.\(^{20}\) This potentially reduces the impact caused through the use of stoichiometric reagents. More recently, Singh et al. have shown that \(N^1-N^2\)-diacyl-3,4-dihydropyrimidin-2(1H)-ones 3.9 are effective acylation agents for a range of substrates, including ammonia, primary and secondary amines.\(^{21}\)
Katritzky and co-workers have extensively researched the use of N-acylbenzotriazoles 4.4 as stoichiometric acylating reagents. The group have synthesised an impressive number of crystalline and bench stable N-acylbenzotriazoles 4.4 over the past 20 years, and have used them to acylate a wide range of different nucleophiles. Their original synthesis was performed using benzotriazole 4.1 and acyl chlorides, or through the reaction of carboxylic acids with N-sulfonylbenzotriazoles 4.2. These reagents were then developed further to allow the direct reaction of carboxylic acids and benzotriazole, facilitated by thionyl chloride. This modification allowed for the use of potentially unstable acyl chlorides as the acyl donor (Scheme 4).22-25
Summarising their extensive results, \( N \)-acylbenzotriazole 4.4 is active against the range of nucleophiles shown in Scheme 5. As well as the synthesis of amides 5.1,\(^{12}\) \( N \)-acylbenzotriazoles react with a range of \( N \)-substituted hydroxylamines for the synthesis of Weinreb amides 5.2,\(^ {26, 27}\) \( N \)-acysulphonamides 5.3, which represent a common motif in many drug like molecules, can also be accessed through the use of \( N \)-acylbenzotriazoles.\(^ {28}\) \( N \)-acylbenzotriazoles 4.4 can also act as \( O \)-acylation agents. For example, they react with amidoximes in ethanol at rt to form \( O \)-acylated amidoximes 5.4, which upon heating, cyclise to form the corresponding 1,2,4-oxadiazoles 5.5.\(^ {29}\) Their effectiveness as \( S \)-acylation agents has also being demonstrated through the synthesis of a range of thioesters 5.6 (Scheme 5).\(^ {30}\)
Scheme 5. Selective examples of the utility of N-acylbenzotriazole 4.4 as a versatile acylating agent

Bull and co-workers have recently demonstrated N-acyl 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) tetraphenylborate salts 6.1 as acylation reagents. These salts are air stable crystalline solids, which are readily synthesised from DBN and the corresponding acyl chloride, allowing for easy storage and increased shelf life when compared with the corresponding acyl chlorides or acid anhydrides. These DBN salts 6.1 have been shown to be active against a range of amines to give the corresponding amides 5.1. Alcohols and sulphonamides can also be acylated to give the corresponding esters 6.3 and N-acyl sulphonamides 6.2 respectively (Scheme 6).1, 2

To summarize, while there are a number of acylation reagents and strategies, there is still scope to develop new methodologies that afford amide, ester and sulfonamide bonds, since they represent some of the most important functional groups in organic and medicinal chemistry.5 Furthermore, there is still much demand for milder and racemization free reaction conditions, as well as the ability to improve the selectivity of acylation reactions (e.g. N-acylation vs O-acylation, reaction of 1° amine over 2° amine).
This chapter will now describe our investigations into the potential of using acylals as N- and O- acylation agents for amines and alcohols.

1.3 Phenylmethylene Diacetate as an Acylation Reagent

The known compound phenylmethylene diacetate 7.2, can be readily synthesized from benzaldehyde 7.1 and acetic anhydride 1.2 using para-toluenesulfonic acid (p-TSA) as a Brønsted acid catalyst (Scheme 7). These class of compounds have been employed as reagents in a range of synthetic methodologies,31 and are referred to as either gem-diacetates, or acylals.32
It is proposed that the mechanism of formation of acylal 7.2 proceeds via an intermolecular pathway, with the Brønsted acid first protonating benzaldehyde 7.1 to give oxonium 8.1, which then allows for nucleophilic attack of acetic anhydride 1.2 at its carbonyl to afford hemiacetal 8.2. A second anhydride equivalent is then able to acylate the alcohol group of this hemiacetal intermediate to afford acyl oxonium 8.3. Nucleophilic attack of acetic acid then affords the observed phenylmethylene diacetate 7.2 (Scheme 8).33, 34

![Scheme 8. Proposed mechanism for the formation of acylal 7.2.](image)

We envisaged that these type of acylals might be useful as selective acylating agents, and now briefly review the literature to summarize where they have been used prior as versatile reagents for synthesis.

**1.4 Synthetic Utility of Phenylmethylene Diacetate**

Phenylmethylene diacetate 7.2 (or structural analogues) has been used as a reagent for a range of different synthetic methodologies, some of which will now be discussed in detail to highlight the versatility of this class of reagents. One use of acylals is as substrates for transdithioacetalization reactions to afford cyclic dithianes 9.1.35, 36 Exposure of acylal to dithiols under a range of mild acid catalyzed conditions affords cyclic thioacetates 9.1, with the reaction proceeding under relatively mild conditions with improved reactivity when compared to reaction of the parent aldehyde (Scheme 9).35, 36
Acylals have also found application for the synthesis of allylic acetates, with variants of this reaction employing allyl silanes, allyl bromides or allyl samarium bromides as the allylating source. For example, Yadav et al. have developed indium catalyzed allylation reactions of acylals utilizing either allyl bromides or allyl silanes, to afford a wide range of allylic acetates under relatively mild reaction conditions (Scheme 10).

A further extension of this type of allylation methodology has been shown by Song et al. who demonstrated that phenylmethylene diacetate 7.2 could be applied for the synthesis of protected homoallylic amines 11.3. The reaction is proposed to proceed through iron catalysed reaction of CbzNHTMS with diacetate 7.2, to afford imine intermediate 11.2. A Cbz-TMS adduct is formed through reaction of Cbz-Cl and HMDS, in situ, which then reacts with an in situ formed acyl oxonium species 11.1 to generate the desired imine. This imine is then able to undergo nucleophilic attack of the allyl group to give the desired Cbz-protected homoallylic amine 11.3.
Acylals have recently been proposed as key intermediates in the Perkin condensation reaction for the synthesis of cinnamic acids, whereby benzaldehyde, acetic anhydride, potassium acetate, are reacted at 180 °C. The traditionally accepted mechanism for the Perkin reaction is proposed to proceed via formation of an anhydride enolate $12.1$, which is able to undergo nucleophilic attack at benzaldehyde $7.1$ to afford the anhydride alkoxide $12.2$. Intramolecular acyl transfer then occurs to generate carbonate $12.3$, which then undergoes nucleophilic attack at a second equivalent of acetic anhydride $1.2$ to give acetate $12.4$. E1cB elimination of acetate from $12.4$, followed by hydrolysis of anhydride $12.6$ then affords the observed cinnamic acid $12.7$ (Scheme 12).

However, it has been noted that the reaction conditions employed for the Perkin reaction are unlikely to generate enolate $12.1$, because a strong base is not present, with the mechanism proposed in Scheme 12 requiring that a weakly basic acetate ion function to generate the required enolate. Further evidence that the literature mechanism may be incorrect, is that the anhydride, when subjected to the reaction conditions in the absence of aldehyde remains stable. If the enolate $12.1$ is formed under these conditions, then it is likely that is would rapidly fragment to afford a ketene under the high temperatures employed (Scheme 12).
Chandrasekhar et al. proposed that the reaction proceeds via formation of an acylal intermediate, showing that the Perkin reaction proceeds when acylal 7.2 is used as a replacement substrate for benzaldehyde 7.1. They propose that reaction of acylal 7.2 with base affords a cyclic orthoester 13.1, which then undergoes nucleophilic attack at benzaldehyde 7.1 to afford alkoxide 13.2, which then undergoes acyl transfer reaction to generate acetate 13.3 (intermolecular rather than intramolecular?). Elimination of benzaldehyde from 13.3 then occurs to afford carboxylic acid 13.4, which then undergoes E1cB elimination of acetate to give the observed cinnamic acid 12.3 (Scheme 13).\textsuperscript{41}
A recent publication by the Sakai group also identified acylal 7.2 as a key intermediate in their indium catalyzed Knoevenagel condensation of aldehydes with dimethyl malonate for the synthesis of α,β-unsaturated bis-esters 14.1 (Scheme 14). It is proposed that indium catalyzed reaction of benzaldehyde with acetic anhydride affords phenylmethylene diacetate 7.2 in situ, which then undergoes indium catalyzed
deacetylation to give acyl oxonium 15.1. Oxonium 15.1 then reacts with an indium generated enolate 15.2 to afford tris-ester 15.3, that then undergoes E1cB elimination to afford the desired α,β-unsaturated bis-ester 14.1 (Scheme 15).42

Scheme 15. Proposed mechanism for indium catalysed Knoevenagel condensation

As well as these relatively recent examples of the synthetic utility of phenylmethylene diacetate 7.2, Sandberg and Sydnes published an earlier series of work looking at the chemistry of acylals.43-46 The first publication explored the reactivity of acylals towards Grignard and organolithium reagents, with the carbon nucleophile being able to selectively displace one of the acyl ester groups to afford a range of substituted esters 16.1 (Scheme 16).43 It is interesting to note that acylals demonstrated greater reactivity towards Grignard reagents than aldehydes, which was established through a competition experiment between acylal 7.2 (R = p-OMe) and 4-methoxy benzaldehyde, and 0.5 equiv. of Grignard nucleophile, with only the acylal being consumed.43
The mechanism is believed to proceed via formation of acyl oxonium 15.1 which is able to undergo nucleophilic attack of the Grignard reagent at the oxonium carbonyl to give the observed acetate ester 16.1 (Scheme 17).

Their second report focused on reactivity of acylals towards azide species. In efforts originally aimed at performing azide substitution reactions of acylals, they found that reaction with TMS-N₃ (trimethylsilyl azide) in the presence of a Lewis acid catalyst (titanium(IV) chloride) led to the formation of nitriles 18.1 (Scheme 18).
The reaction is believed to proceed via a stepwise route, involving displacement of one of the acyl groups by nucleophilic attack of azide to afford acetate 19.1. Evolution of N₂ from 19.1 then generates an unstable nitrene 19.2, with acyl transfer occurring to afford O-acyl oxime 19.3, that then eliminates acetate to afford the observed nitrile 18.1 (Scheme 19).⁴⁴

Their third contribution explored a similar reaction manifold, investigating the reactivity of acylals towards cyanide reagents.⁴⁵ They found that using TMS-cyanide and titanium(IV) chloride as a Lewis acid catalyst gave the best results, synthesizing a range of O-acyl cyanohydrins 20.1 in good to excellent yields.⁴⁵ The use of TMS-cyanide as a nucleophile in the reaction resulted in mono substitution of one of the acyl groups, allowing the synthesis of cyanohydrin esters 20.1 (Scheme 20).
The final report by Sydnes and Sandberg explored the reactivity of acylal 7.2 with silyl enol ethers 21.1, with boron trifluoride catalyzed reactions leading to the formation of $\alpha,\alpha'$-bis(arylmethylidene)cylocoalkanones 21.2 in moderate to excellent yields (Scheme 21).\textsuperscript{46}

While no detail of the reaction mechanism was proposed, a reasonable mechanism would involve boron trifluoride catalyzed formation of acyl oxonium 15.1. Nucleophilic attack of silyl enol ether 21.1 would then afford acetate 22.1, with an acetate elimination reaction installing the first alkene unit of silyl enol ether 22.4. Reaction of silyl enol ether 22.4 with a second equivalent of acyl oxonium 15.1 would afford acetate 22.5, that could then undergo elimination of a second acetate anion equivalent to give oxonium 22.7, which would lose its silyl ether group to afford the observed bis-$\alpha,\beta$-unsaturated ketone 21.2 (Scheme 22).
Scheme 22. Proposed mechanism for the synthesis of bis(arylmethylidene)cycloalkanones

Acylals have also found application for the synthesis of triarylmethanes (TRAMs) 23.2, which are important targets in a number of fields, including materials chemistry, medicinal applications and for the synthesis of dyes.\textsuperscript{47} Reaction of acylal 7.2 with \textit{para}-xylene in the presence of an iron catalyst and acetic anhydride led to the formation of TRAM 23.2. The reaction was shown to proceed using aldehydes instead of acylals, but the acylal is thought to be formed as a more reactive intermediate \textit{in situ} (Scheme 23).\textsuperscript{47}
No mechanism for the formation of triarylmethane 23.2 was proposed in the paper, however, a potential mechanism is suggested in Scheme 24. An iron catalyzed acetate elimination would afford acyl oxonium 15.1. This intermediate would then undergo electrophilic aromatic substitution of p-xylene 23.1 to give acetate 24.1, with aromaticity being regenerated through deprotonation of 24.1 to give bisarylmethylacetate 24.2. Acetate elimination via an S_n^1 type mechanism would then lead to the generation of stabilized carbocation 24.3, with a second electrophilic aromatic substitution reaction, and subsequent deprotonation event, affording triarylmethane 23.2 (Scheme 24).
Allyl acylals have proven to be one of the most utilized class of reagent, with this area of research being first developed by Trost and coworkers, who published a series of reports on the asymmetric alkylation reactions of allylic acylals, and application of this methodology for natural product synthesis.\textsuperscript{48-53} Their initial report described the reaction of allyl diacetate \textbf{25.1} with sodium malonate \textbf{25.2} to give the monoalkylated product \textbf{25.4} in 92\% yield and 95\% ee, utilizing a palladium catalyst and the chiral bis-phosphine ligand \textbf{25.3} (Scheme 25). This alkylation reaction proceeds through formation of a Pd-π-allyl complex which allows for stereoselective nucleophillic attack of the malonate nucleophile \textbf{25.2}. The reaction was subsequently optimized to accommodate a wide range of allyl acylals and stabilised carbon nucleophiles, affording the corresponding monoalkylation products in good yield and excellent enantiomeric excess.\textsuperscript{51,52}
Trost et al. subsequently applied this methodology to the synthesis of the natural products sphingofungins E and F.\textsuperscript{50,53} Both natural products were synthesised from the common intermediate allyl acetate \textit{26.1}, which was synthesised from \textit{O}-silyl protected allyl diacetate \textit{26.1} and oxazolone \textit{26.2} in 70% yield and 87% ee. Allyl acetate \textit{26.3} was used as an advanced intermediate for the synthesis of the natural products sphingofungins E and F in 5.1% (17 steps) and 17% (15 steps) overall yields respectively (Scheme 26).\textsuperscript{50,53}
Acylals have also been applied as a substrate for a number of other natural product syntheses, including for the synthesis of roelactamine \textbf{27.2} by the Martin group in 2007. The acylal containing tertiary amide \textbf{27.1} was treated with concentrated methanolic hydrochloric acid, resulting in a facile double cyclization reaction to give roelactamine \textbf{27.2} in 71\% yield (Scheme 27).\textsuperscript{54}

The reaction is proposed to proceed \textit{via} acid catalysed formation of acyl oxonium \textbf{28.1}. An intramolecular electrophilic aromatic substitution reaction affords acetate \textbf{28.2} which upon deprotonation by acetate gives bicycle \textbf{28.3}. A second acid catalysed intramolecular $S_{N}^{1}$-like
electrophilic aromatic substitution reaction then affords 28.4, which after further deprotonation event gives the desired roelactamine product in a 71% yield (Scheme 28).

Scheme 28. Proposed mechanism for the synthesis of roelactamine

A second tandem intramolecular acylal cyclisation (IAC) strategy was developed by the Hilton group directed towards the synthesis of erythrina alkaloid derivatives. They first developed the synthesis of a range of key cyclisation precursors 29.1 (one example shown for clarity), which were subjected to a mild BF₃ catalysed cyclisation reaction to give the fused tricycle 29.2 (Scheme 29).
The reaction is believed to proceed via intramolecular nucleophilic addition of an enamine fragment at an acyl oxonium species 30.1 to afford N-acyl-iminium species 30.2. An intramolecular electrophilic aromatic substitution reaction then occurs to afford tricycle 30.3, with an alkyl migration reaction leading to ring expansion to generate carbocation 30.4. Subsequent, deprotonation then generates the observed tetracyclic product 29.2 in a 60:40 trans to cis ratio (Scheme 30).
Allyl acylal substrates have also been utilised by the Krische group for stereoselective iridium catalysed alkoxyallylation reactions\textsuperscript{56} with allyl gem-benzoate \textbf{31.1} affording the highest yields and best diastereoselectivities when compared to other acylal substrates. For example, benzaldehyde \textbf{7.1} reacted with diacyl \textbf{31.1} in the presence of the chiral iridium catalyst \textbf{31.2} to afford the anti-alkoxyallylation product \textbf{31.3} in 63\% yield and an impressive 99\% ee, with a dr ratio of 18:1 (Scheme 31).\textsuperscript{56} The reaction proceeds under iridium catalysed transfer hydrogenation conditions with isopropanol as the terminal reductant, which facilitates the reductive coupling of the gem-dibenzoate \textbf{31.1} and benzaldehyde \textbf{7.1}.
The reaction is believed to proceed through formation of Ir-π-allyl complex \textbf{32.1}. The iridium migrates to form σ-allyl complex \textbf{32.2} (primarily (E)), which then reacts with bezaldehyde \textbf{7.1} via a Zimmerman-Traxler type transition state to afford \textit{anti}-diastereomer \textbf{32.3}. Isopropanol then displaces monobenzoyl diol \textbf{32.4} from the iridium catalyst, which was subsequently reacted with benzoyl chloride to give the desired \textit{anti}-bis-benzoyl diol product \textbf{31.3} (Scheme 32).

As described, phenylmethylene diacetate \textbf{7.2} and acylals are versatile synthetic reagents that have been applied as substrates in a range of synthetic methodologies. However, remarkably and to the best of our knowledge, phenylmethylene diacetate \textbf{7.2} had never been applied as a simple acylating reagent for nitrogen and oxygen nucleophiles. Consequently, we
now report an investigation into the application of acylals as new, bench stable, acylating reagents for the N-/O- acylation of primary and secondary amines and alcohols.

1.5 Acylals as Reagents for the N-Acetylation of Amines

In order to employ acylals as potential new N-/O- acylating agents it was first necessary to devise a route for their synthesis. The most common methods reported in the literature involve reaction of a parent aldehyde with an anhydride in the presence of a suitable catalyst. The catalysts utilized are primarily based on Brønsted acids,\textsuperscript{32, 57-60} Lewis acids,\textsuperscript{61-70} as well as the use of iodine,\textsuperscript{71} NBS,\textsuperscript{72} iron-montmorillonite and zeolites.\textsuperscript{73, 74} All these catalytic systems are believed to afford acylals using the same general mechanism described in Scheme 8. The conditions that were chosen for the synthesis of acylal 7.2 were those of Manjula \textit{et al.}\textsuperscript{32} utilizing p-TSA as a Brønsted acid catalyst. These conditions were reported to afford acylal 7.2 in excellent yield at rt (Scheme 7). Importantly, no arduous purification steps were required, with high purity product obtained after an aqueous sodium carbonate wash, meaning that acylals could potentially be accessed in large quantities.

The choice of parent aldehyde used for the synthesis of the desired acylal was an important consideration. Cost of reagents, ease of synthesis and ease of byproduct removal were some of the factors that were considered. It was decided that either an aromatic aldehyde, or a short chain alkyl aldehyde would best suit our purposes, with benzaldehyde and propionaldehyde identified as potential precursors. Acylal synthesis using benzaldehyde proceeded smoothly to give high purity acylal 7.2 in good yield after 1 h (Table 1 entry 1). However, when propionaldehyde was used as the aldehyde core a number of problems became apparent. Under a range of synthetic conditions the resultant acylal proved to be much less stable and more temperamental than the benzaldehyde derivative, readily decomposing to afford undesired side products, believed to be formed through unwanted elimination or aldol side reactions.

Therefore, while the use of propionaldehyde resulted in 100% conversion, the yield of the desired acylal was significantly reduced to 45% (Table 1 entry 2). In an attempt to alleviate this issue, alternative conditions were explored using Cu(BF\textsubscript{4})\textsubscript{2}·xH\textsubscript{2}O as a Lewis acid catalyst (at 1 mol%).\textsuperscript{70} Although the crude yield of the desired acylal was greatly improved, the presence of multiple minor impurities meant that the acylation reagent required further purification by column chromatography that resulted in a significant loss in yield. This was undesirable, and
essentially rendered the use of propionaldehyde as the aldehyde core unviable. Consequently benzaldehyde was chosen as the core aldehyde for acylal synthesis (Table 1).

Table 1. Synthesis of acylals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Catalyst</th>
<th>Reaction Time</th>
<th>Aldehyde Conversion (%)</th>
<th>Selectivity Towards Acylal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TSA</td>
<td>p-TSA</td>
<td>1 h</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>p-TSA</td>
<td>p-TSA</td>
<td>1 h</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Cu(BF₄)₂·xH₂O</td>
<td>Cu(BF₄)₂·xH₂O</td>
<td>5 min</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Cu(BF₄)₂·xH₂O</td>
<td>Cu(BF₄)₂·xH₂O</td>
<td>1 min</td>
<td>100</td>
<td>68</td>
</tr>
</tbody>
</table>

Reaction conditions: Entries 1 and 2, aldehyde (1 equiv.), acetic anhydride (2 equiv.), cat (0.1 equiv.). Entries 3 and 4, aldehyde (1 equiv.), acetic anhydride (1.5 equiv.), cat (0.01 equiv.).

Acetylation of benzylamine 33.1 using phenylmethylene diacetate 7.2 was the first N-acylation reaction to be investigated. A range of conditions were screened, encompassing solvent, reaction time, reaction temperature and number of equivalents of acylating agent (Table 2). As shown in Table 2 the choice of solvent had little effect on the distribution of products, with the reaction also found to perform well under solvent free conditions (entry 4). However, as shown for entries 1-4, although there was good conversion of benzylamine at rt, selectivity for formation of acetamide 34a was poor at around 50%. Unsurprisingly, the major
Side product formed was due to reaction of benzylamine with benzaldehyde (produced as a byproduct of the acetylation reaction) to form imine 33.2 (Scheme 33).

![Scheme 33. Competing side reaction during acetylation of benzylamine](image)

Imine formation is a reversible process, whereas acetamide formation is irreversible. Therefore, it was proposed that the equilibrium for imine formation could be perturbed towards acetamide formation under more forcing conditions. To achieve this aim, a number of routes were explored. Firstly, the reaction time was extended to 16 h and the amount of acylal 7.2 employed increased from 1.5 to 5 equivalents, however, this had little or no effect on the ratio of amide to imine formed (entries 4-7). Reaction temperature was the next variable to be changed, with increased reaction temperature, leading to greater quantities of acetamide being produced, with the best results achieved at 70 °C. The optimal conditions were found to be 1.5 equivalents of acylating agent 7.2 at 70 °C for 16 h solvent free. The crude amide product could be purified directly via column chromatography, without the need for any aqueous work up.
Table 2. Optimization of N-acetylation reactions of benzylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Equiv. gem-Diacetate</th>
<th>Reaction time (h)</th>
<th>Temperature (°C)</th>
<th>Amine Conversion (%)</th>
<th>Acetamide: Imine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>1.5</td>
<td>2</td>
<td>rt</td>
<td>95</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>Tol</td>
<td>1.5</td>
<td>2</td>
<td>rt</td>
<td>90</td>
<td>48:52</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>1.5</td>
<td>2</td>
<td>rt</td>
<td>92</td>
<td>51:49</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>1.5</td>
<td>2</td>
<td>rt</td>
<td>94</td>
<td>53:47</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>1.5</td>
<td>16</td>
<td>rt</td>
<td>99</td>
<td>54:46</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>2</td>
<td>16</td>
<td>rt</td>
<td>98</td>
<td>55:45</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>5</td>
<td>16</td>
<td>rt</td>
<td>99</td>
<td>52:49</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>1.5</td>
<td>16</td>
<td>50</td>
<td>99</td>
<td>65:35</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>1.5</td>
<td>16</td>
<td>60</td>
<td>99</td>
<td>70:30</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>1.5</td>
<td>16</td>
<td>70</td>
<td>99</td>
<td>95:5</td>
</tr>
</tbody>
</table>

With these optimized conditions in hand a range of amines were screened for reaction with phenylmethylene diacetate 7.2 affording a range of eleven acetamides 34a-k (Reaction conditions; 1 mmol of amine, 1.5 equiv. 7.2, 12 h, 70°C. aToluene required as solvent. b24 h reaction time.

Scheme 34). N-acetylation of both primary, secondary and cyclic amines proceeded with good conversion to afford their corresponding acetamides in 60-95% isolated yield. It is worth noting that typtamine was cleanly N-acetylated to afford 34c in 62% yield, with no acetylation of the indole nitrogen being observed. Pleasingly, even sterically hindered branched amines gave their corresponding acetamides 34d in 70% yield. Less reactive primary and secondary anilines were also efficiently N-acetylated, albeit with slightly reduced isolated yields 60-68%
(34e and 34f), including the electron deficient amide 34g which was formed in a 65% yield. For amines that proved to be insoluble in acylal 7.2, then toluene was used as a co-solvent to ensure a homogeneous reaction mixture.

Reaction conditions; 1 mmol of amine, 1.5 equiv. 7.2, 12 h, 70 °C. a toluene required as solvent. b 24 h reaction time.

Scheme 34. Scope of N-acetylation reactions of amines with acylal 7.2

It was proposed that the mechanism of acetamide formation could potentially proceed via one of two potential pathways. Pathway A would proceed via nucleophilic attack of amine 33.1 into one of the carbonyl bonds of the acetate groups of acylal 7.2 to give tetrahedral carbinolamine intermediate 35.1. Reformation of the carbonyl bond would then lead to formation of acetamide 34a as well as formation of one equivalent of benzaldehyde 7.1 and
acetic acid 35.2. Pathway B would proceed through acetate elimination to give acyl oxonium 15.1, followed by nucleophilic attack of the amine 33.1 at the acyl carbonyl bond to afford the observed acetamide 34a, once again resulting in one equivalent of benzaldehyde 7.1 and acetic acid 35.2 as by-products (Scheme 35).

In order to investigate which pathway was operating a series of experiments were conducted. In both of the proposed reaction pathways, for every equivalent of acetamide produced, then an equivalent of acetic acid would also be produced. It would be expected that every equivalent of acetic acid produced would react with unreacted amine to form an acetate salt, preventing it acting as a nucleophile in the reaction. If this were to happen then the maximum conversion would be expected to be only 50% however, complete conversion was
clearly being observed at elevated temperatures. When the pH of the reaction was monitored overtime the reaction remained neutral (pH 7) throughout the course of the reaction, until the end of the reaction when it became acidic in nature. This would suggest that the reaction is self-buffering. Therefore, it is proposed that the amine acetate salt is indeed being formed \textit{in situ}, but is being formed reversibly allowing for free amine to be continuously generated, in the reaction that can then irreversibly react with excess acylal to afford the observed acetamide (Scheme 36).

\begin{center}
\begin{align*}
\text{Me} & \quad \text{OH} \\
35.2 & + \\
\text{H}_2\text{N} & \quad \text{R} \\
36.1 & \quad \xrightarrow{} \quad \text{Me} & \quad \text{O} & \quad \text{O} \quad \text{H}_3\text{N} & \quad \text{R} \\
36.2
\end{align*}
\end{center}

\textit{Scheme 36. Self-buffering pH control mechanism operating in acetylation reaction}

It is also important to consider the formation of imine by-product. For pathway A it is proposed that the imine would be formed by acid catalysed reaction of unreacted amine and the benzaldehyde produced. However, for pathway B the imine could also be formed through nucleophilic attack of amine at the oxonium carbonyl of intermediate 15.1 to give O-acyl-hemiacetal (Scheme 37). In order to try and investigate which method of imine formation was occurring, the reaction was performed under basic conditions, since conventional imine formation from reaction of an amine and an aldehyde, does not generally occur under basic conditions. 2 equiv. of K$_2$CO$_3$ was added to the reaction to maintain a basic pH throughout the course of the reaction. It was found that imine 33.2 was indeed formed under these basic conditions, suggesting that the reaction proceeds \textit{via} pathway B. It is important to note that under basic conditions the reaction did not reach 100% conversion, with the reaction stalling at 50% acetamide and 50% imine, which is due to the stability of imines under basic conditions.

\begin{center}
\begin{align*}
\text{\textbullet} \quad \text{O} & \quad \text{Me} \\
\text{H}_2\text{N} \quad \text{R} \\
15.1 & \quad 33.1 \\
\text{O} & \quad \text{O} & \quad \text{Me} \\
\text{H}_2\text{N} & \quad \text{R} \\
37.1 & \quad 33.2
\end{align*}
\end{center}

\textit{Scheme 37. Pathway B for imine formation}
The acetylation reaction of benzylamine 34.1 with acylal 7.2 was followed by $^1$H NMR spectroscopic analysis at 70 °C (in toluene-d8), with the data summarised in Figure 3. As can be seen, consumption of the amine occurs within the first 30 minutes (Figure 3). However, imine formation occurs slightly faster than acetamide formation reaching 34% after 30 minutes. Slowly, over time reversible imine formation regenerates the amine, which reacts with oxonium species 15.1 to irreversibly afford acetamide 34a as witnessed by the gradual increase in acetamide and decrease in imine (Figure 3).

![Figure 3](image.png)

*Figure 3. A timeline graph to show acetamide and imine formation during the course of acetylation reaction using acylal 7.2.*

With all this information in hand, a possible overall mechanism for the N-acetylation of amines by acylal 7.2 is presented below (Scheme 38). Acid catalysed formation of acyl oxonium 15.1 from acylal 7.2 is coupled with a loss of acetic acid. Nucleophilic attack of amine 38.1 (which is in equilibrium with its acetate salt 37.2) into the oxonium carbonyl of acyl oxonium 15.1 would lead to the reversible formation of imine 38.2. Alternatively nucleophilic attack of amine 38.1 can occur at the acyl carbonyl of acyl oxonium 15.1 to irreversibly afford acetamide 38.3 and
one equivalent of benzaldehyde 7.1. Benzaldehyde 7.1 is able to further react with one equivalent of amine 38.1 to reversibly generate imine 38.2. Both routes that lead to the formation of imine 38.2 are reversible, so this allows for the irreversible formation of acetamide 38.3 that act as a thermodynamic sink, to perturb all the equilibria allowing for total conversion of amine 38.1 to acetamide 38.3 (Scheme 38).

Scheme 38. Overall mechanism for the N-acetylation of amines by acylal 7.2

1.51 Acylals for the O-Acetylation of Alcohols

O-acylation reactions of alcohols are also an important synthetic tool, either through their use as a reversible protecting group strategy for alcohols, or for the synthesis of ester products. Consequently, it was decided to explore whether acylal 7.2 could also be used for the O-acetylation of alcohols. The neutral solvent free conditions that were applied for the N-acetylation of amines were unsuccessful for the O-acetylation of less nucleophilic alcohols. In the absence of the self-buffering nature of the amine (Scheme 36) the acetic acid formed as a by-product appeared to retard the O-acetylation reaction and degrade acylal 7.2. However, it was found that the inclusion of an inorganic base resulted in clean O-acetylation of the alcohol, which functions to neutralize the acetic acid as it is produced, as well as deprotonating the alcohol to increase its nucleophilicity.
After a brief optimization study, optimal conditions were found to be an elevated reaction temperature to 80 °C, and inclusion of two equivalents of potassium carbonate (K₂CO₃), using 1.5 equivalents of acylal 7.2. These optimized conditions were applied to a range of eleven primary and secondary alcohols which gave the corresponding acetate esters in 68-92% yield (Scheme 39). Alcohol substrates that were successfully O-acetylated include; cyclic, acyclic, alkyl, vinyl, heterocyclic alcohols and diols 39a-l. Although phenols were not acylated under these conditions. Important observations to note include the fact that O-acetylation of 2-pyridinemethanol proceeded to give acetate 39b, with no evidence of products arising from N-acetylation of the pyridine nitrogen. The diol fragment of benzylidene-protected glucose derivative underwent bis-acetylation to give diacetate 39g in 65% yield. Carveol acetate 39l was formed with no evidence of any competing base catalyzed elimination reaction having occurred to afford diene products. Good yields were obtained for the formation allylic alcohol acetates 39i-l, which are useful products that are often used as substrates for palladium allyl nucleophilic addition chemistry.
Reaction conditions; 1 mmol of alcohol, 1.5 equiv. 7.2, 2.0 equiv. K$_2$CO$_3$, 16 h, 80 °C.

a 24 h reaction time.

b 3 equiv. 7.2

Scheme 39. Scope of O-acetylation reactions of alcohols using acylal 7.2

The mechanism of the O-acetylation of alcohols using acylal 7.2 is believed to proceed in a much more simplistic manor than that for the N-acetylation of amines. Nucleophilic attack of alcohol 40.1 into the acyl carbonyl of acyl oxonium 15.1 will lead to the formation of of protonated ester 40.2. Deprotonation with K$_2$CO$_3$ will lead to formation of ester 40.3, as well as formation of one equivalent of benzaldehyde 7.1 and potassium acetate 40.4 (Scheme 40).
1.52 Use of Acylals for the \(N/-O\)-Acylation of Benzylamine and Benzyl Alcohol

After carrying out successful \(N/-O\)-acylation reactions of a range of amines and alcohols, it was decided to broaden the scope of the acylating reagent to determine whether other acyl groups could be transferred in this manner. A range of five acylals 41a-e containing different acyl donor groups were synthesized using the same methodology developed previously for the synthesis of phenylmethylene diacetate 7.2. Synthesis of the trifluoroacetyl derivative 41f required more forcing conditions that employed trifluoroacetic acid as a catalyst, which afforded an acylal product that was used without further purification. Exposure of acylal 41f to water or atmospheric moisture, led to its rapid decomposition (Scheme 41).
Reaction conditions; 1 equiv. 7.1, 1.5 equiv. anhydride, 0.1 equiv. p-TSA. 2 equiv. 7.1, 1.5 equiv. anhydride, 0.1 equiv. TFA.

Scheme 41. Synthesis of a range of acylals 40a-f

These diacyl reagents 41a-f were then used for a series of representative N-/O-acylation reactions of benzylamine and benzyl alcohol respectively. N- and O-acylation reactions using this range of acylals 41a-f (including short and long chain alkyl, acryloyl, benzoyl, phenyl acetyl and trifluoroacetyl groups) proved successful without the need for any further optimization affording a range of six benzylamides 42a-f and six benzyl esters 43a-f in 79-96% and 62-94% yields respectively (Scheme 42 and Scheme 43).
Reaction conditions; 1 mmol of amine, 1.5 equiv. diacylate, 16 h, 70 °C. \(^a\)1 mmol of amine, 1.5 equiv. diacylate, rt 1 h.

Scheme 42. N-acylation reactions of benzylamine using acylals 41a-f

Reaction conditions; 1 mmol of alcohol, 1.5 equiv. diacylate, 2.0 equiv. \(\text{K}_2\text{CO}_3\), 16 h, 90 °C. \(^a\)1 mmol of alcohol, 1.5 equiv. diacylate, 2.0 equiv. \(\text{K}_2\text{CO}_3\), rt 1 h.

Scheme 43. O-acylation reactions of benzyl alcohol using acylals 41a-f
These type of amide and ester compounds have numerous potential applications. For example, acrylamides are routinely used as monomers for polymerization chemistry, whilst trifluoroacetyl amides are privileged medicinal chemistry motifs, which are often used for the synthesis of highly active drug molecules. Such as Valrubicin which is used for bladder cancer treatment (Figure 4).

![Valrubicin](image)

*Figure 4. Structure of Valrubicin*

Having demonstrated that acylals could be used for the acylation of amines and alcohols, our attention turned to developing an analogous formylating reagent. *N*-formylation of amines is a highly important reaction in organic synthesis and medicinal chemistry, with formamides used as versatile synthetic intermediates, and often present as fragments in a number of medicinally active compounds. For example, formylation chemistry has been heavily utilized in peptide synthesis due to the ease of carrying out late-stage formyl deprotection, while formamides have also found widespread application as precursors for the synthesis of isocyanides and formamidines. With this utility in mind, our efforts next turned towards the synthesis of a formyl version of acylal. As well as the methods covered earlier in this report, there a number of techniques for the synthesis of formamides. Including the use of chloral, formic acid, formaldehyde and formates as the formyl source. These are either reacted directly or in conjunction with a range of catalyst including, mild base (ammonium carbonate), mild acid (pTSA, MTSA), polymer supported acid/base catalyst and metal catalyzed formation.
1.6 N-Formylation of Amines

It was decided that a gem-diformyl variant was likely to be unviable due to the inherent instability of formic anhydride, and so it was decided to attempt to synthesize a mixed 1,1-formyl acetate 44.2, reasoning that its more reactive formyl group would be selectively transferred. In order to obtain the desired compound our standard synthesis needed to be altered. An adaptation of the Chakraborti 1,1-diacetate synthesis was utilized (Scheme 44), involving treatment of benzaldehyde 7.2 and O-formylacetate 44.1 with a catalytic amount of Cu(BF$_4$)$_2$$\cdot$H$_2$O at -20 °C. This reaction gave a mixture of products containing (formyloxy)(phenyl)methyl acetate 44.2, phenylmethylene diacetate 7.2 and gem-diformal 44.3 in a 16:9:2 ratio (Scheme 44). These products could be easily separated by chromatography to afford pure (formyloxy)(phenyl)methyl acetate 44.2 in 59% yield and phenylmethylene diacetate 7.2 in 25% yield respectively. Although resonances for gem-diformal 44.3 could be seen in $^1$H NMR spectra of the crude reaction product, is proved to be unstable, as predicted decomposing on exposure to silica. The observed formation of a mixture of products is a consequence of this reaction proceeding via an intermolecular pathway. To the best of our knowledge, (formyloxy)(phenyl)methyl acetate 44.2 has only been prepared once previously, where it was isolated as a side product of an oxidation reaction in a meagre 8% yield by Syper et al. (Scheme 45).
Therefore we decided to investigate the use of (formyloxy)(phenyl)methyl acetate 44.2 for the N-formylation of amines. The mechanism for the formation of 44.2 is likely to proceed as described earlier, with attack of mixed anhydride 44.1 into the carbonyl bond of oxonium 8.1 affording acyloxonium 46.1. The hydroxy group present in acyloxonium 46.1 is able to attack into the formyl fragment of anhydride 44.1 to afford acyl oxonium 46.2. Anhydride regeneration then affords the observed (formyloxy)(phenyl)methyl acetate 44.2 (Scheme 46a, shown in black). Formation of acylal 7.2 (shown in red) proceeds via a similar mechanism, however, attack of the hydroxyl group of 46.1 at anhydride 44.1 occurs at the acyl carbonyl (Scheme 46b). Finally, formation of gem-diformal 44.3 (shown in blue) proceeds via attack of the formate half of mixed anhydride 44.1 into the carbonyl bond of oxonium 8.1 affording acyloxonium 46.5. The hydroxy group present in acyloxonium 46.5 then attacks the formate carbonyl of anhydride 44.1 to afford acyl oxonium 46.6. Anhydride regeneration then affords the observed 44.3 (Scheme 46c).
Scheme 46a. Mechanism for formation of 44.2

Scheme 46b. Mechanism for formation of 7.2

Scheme 46c. Mechanism for formation of 44.3

Scheme 46. Mechanism for formation of mixture of products 44.2, 7.2 and 44.3
Pure (formyloxy)(phenyl)methyl acetate 44.2 was then applied as an N-formylating reagent for amines. Pleasingly, (formyloxy)(phenyl)methyl acetate 44.2 proved to be highly selective for N-formylation reactions, providing good to excellent yields for N-formylation of a range of 16 primary and secondary amines, with no evidence of any competing acyl transfer occurring. These formylating reactions afforded a range of 16 formamides 47a-p in 53-95% isolated yields. Again, the reactions were able to be purified directly via column chromatography, without the need for an aqueous work up. For non-volatile products, removal of by-products could be achieved by distillation under high vacuum. It is also worth noting that due to the increased reactivity of this formylating agent, these reactions could be carried out at rt, with the reaction time reduced to just 1 h (Scheme 47).

When tryptamine was used as a substrate there was no evidence of competing formamide formation at the indole nitrogen (47d). It is also important to note that when (S)-valine methyl ester was formylated, there was no evidence of any racemization of its stereocentre (determined by alpha D for 47g, [α]₀²⁰ = -22; Lit = -23.45°), which is often a problem with other acylating reagents. The low yield of tert-butylformamide 47h can be ascribed to the steric hindrance of the amine and the volatile nature of both the starting amine and product formamide. A range of electron deficient anilines were also successfully formylated 47l-p, including the sterically hindered N-methyl aniline that gave formamide 47p in 91% yield. In some instances where the amine was not soluble in the formylating reagent, EtOAc was added as a co-solvent leading to significantly longer reaction times.
Reaction conditions; 2 mmol of amine, 1.5 equiv. 24 h reaction time.

Scheme 47. N-formylation reactions of amines using acylal 44.2

1.61 An N-Formylation Reaction Performed on Scale

The N-acylation and N-formylation reactions described in previous sections were all purified via column chromatography, however, this kind of purification approach is clearly not compatible to process scale-up. With potential large scale application of these reagents in mind, it was decided to develop an alternative purification route that would not rely on chromatography. It was found that when the desired amide or formamide products were
crystalline, or oils with a suitably high boiling point, then both the acetic acid and benzaldehyde by-products could be easily removed by distillation *in vacuo*. However, when this approach was not a viable option (e.g. for volatile 47j), an aqueous work up with saturated NaHCO₃ could be used to remove the acetic acid, followed by extraction with a solution of saturated NaHSO₃ that removes the benzaldehyde by-product as its water soluble bisulfite adduct. For example, this purification approach was performed on a crude formylation product produced from reaction of 5g of benzylamine 33.1 with 9.06 g of formylation agent 44.2 under standard conditions. ¹H NMR spectroscopic analysis revealed that the reaction afforded a mixture of the desired *N*-benzylformamide 47a, benzaldehyde and acetic acid. An aqueous work up with NaHCO₃ resulted in removal of sodium acetate 48.1. Secondly, a bisulfite extraction then allowed for removal of benzaldehyde as its bisulfite adduct 48.2, affording 5.36 g of *N*-benzylformamide 47a in a slightly reduced 85% yield (Scheme 48).
Scheme 48. Chromatography free purification of a large scale $N$-formylation reaction of benzylamine

1.62 $N$-Formylation Reactions of Amino Acid and Peptides

1.621 $N$-Formylation Reactions of $\alpha$-Amino Acids

The direct $N$-formylation of unprotected $\alpha$-amino acids remains an attractive goal in organic synthesis with only a limited range of synthetic protocols currently available.\textsuperscript{76, 80, 86, 87} One of the main issues arises from the poor solubility of amino acids in organic solvents and the incompatibility of many formylating reagents with water, which may act as a competing
nucleophile. Of the synthetic protocols that are available for N-formylation of unprotected α-amino acids, the formyl source is either formic acid or formamide, both of which have a high tolerance to water. We observed that reagent 44.2 was relatively resistant to hydrolysis by water, and therefore it was decided to attempt the direct N-formylation of unprotected α-amino acids using water as a solvent. Pleasingly, it was found that (formyloxy)(phenyl)methyl acetate 44.2 could be used for N-formylation of α-amino acids under aqueous conditions. Formylation conditions were optimized for these α-amino acid substrates resulting in the use of 5 equivalents of NaHCO₃ as a base, extended reactions times of 16 h, and addition of a second 1.5 equivalents of (formyloxy)(phenyl)methyl acetate 44.2 after 8 h. This resulted in N-formylation of unprotected amino acids proceeding to afford a range of six N-formyl α-amino acids 49a-f with good to excellent yields 71-89% (Scheme 49). The purification of N-formyl α-amino acids was performed using an aqueous NaHCO₃ wash to remove the acetic acid and any unreacted amino acid. This was followed by recrystallization of the crude N-formyl-α-amino acid from a mixed solvent system of EtOAc and pentane. Comparison of the [α]₀ D of 49a-f with those of literature revealed no evidence of any racemization having occurred. These type of N-formyl amino acids have found numerous applications; for example through conversion to isocyanides as substrates for multicomponent reactions, and their use in peptide synthesis.88
Reaction conditions; 1 mmol of amino acid, 1.5 equiv 44.2, 5 equiv NaHCO₃ 16 h, rt (after 8 h 2nd 1.5 equiv. of 44.2).

Scheme 49. N-formylation of unprotected amino acids.

1.622 N-Formylation of Peptides

Formylation is not only used extensively in peptide synthesis as a protecting group, there are a number of naturally occurring and synthetic peptides which contain a formamide group that are essential for their biological activity.⁸⁹ One of the best known examples is N-formylmethionyl-leucyl-phenylalanine (f-MLP), which is a potent polymorphonuclear leucocyte chemotactic factor and macrophage activator.⁸⁹⁻⁹¹ F-MLP has been used extensively in biological and medicinal research,⁹⁰,⁹¹ therefore its synthesis was identified as a challenging substrate to test the scope and limitation of formylating agent 44.2. The tripeptide 50.5 was first synthesized according to literature,⁹² dipeptide 50.3 was formed using DCC coupling of phenylalanine methyl ester 50.1 and N-Boc leucine 50.2, followed by N-Boc-deprotection using methanolic HCl. A HATU facilitated amide bond formation reaction was then carried out between dipeptide 50.3 and N-Boc methionine 50.4 to afford the desired N-boc protected tripeptide, which upon treatment with methanolic HCl resulted in tripeptide 50.5. This tripeptide was then treated with formylating reagent 44.2 in the presence of EtOAc as a co-solvent to afford N-formyl tripeptide 50.6 in 87% yield. Subsequent ester deprotection through base hydrolysis then afforded f-MLP in 93% yield (Scheme 50).
It was then decided to further test the limitations of these reagents as formylating and acylating agents, for the ω-amino residue of a lysine residue of a more complex peptide. A small amount of decapetide **51.1** with the sequence Ac-ADGIVNGVKA-NH₂, whose N-terminus protected as an acetamide and whose C-terminus was protected as a primary amide, was acquired from Dr Jody Mason (Department of Biology and Biochemistry, University of Bath). This peptide was reacted with both the acetylating and formylating reagents **7.2** and **44.2** with the aim of selectively acylating the free ω-amino group of its lysine residue. Previous control experiments had demonstrated that neither of these reagents could acylate or formylate primary amides. The acylation conditions used were altered slightly to accommodate the other amino acid residues present in this peptide. To ensure that the ω-amino group of the lysine residue was present as its free amine, the reaction was buffered at pH 8. The co-solvent system

Scheme 50. Synthesis of f-MLP.
used was a mixture of MeCN, H$_2$O and a few drops of DMSO. Satisfyingly, both acetylating and formylating reactions proceeded to successfully produce formamide peptide 51.2 and acetamide peptide 51.3. Formation of both peptide products was confirmed by the presence of the correct molecular ions for 51.2 (HRMS (ESI): m/z calculated for C$_{44}$H$_{74}$N$_{13}$O$_{15}$: requires: 1025.5433 for [M-H]; found: 1025.5483) and 51.3 (HRMS (ESI): m/z calculated for C$_{43}$H$_{73}$N$_{13}$O$_{15}$: requires: 1010.5276 for [M-H]; found: 1010.5292) in their HRMS respectively (Scheme 51).

![Chemical structure](image)

Reaction conditions;

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**Scheme 51. N-Acylation and N-formylation reactions of peptide 51.1**

### 1.63 O-Formylation Reactions of Alcohols

The corresponding O-formylation reactions of a range of alcohols using reagent 44.2 were then carried out, for the synthesis of a range of ten formate esters using NaHCO$_3$ as a base, at a slightly lower temperature of 60 °C. Pleasingly, these O-formylation reactions were compatible with a wide range of alcohols including phenols, primary, secondary and allylic alcohols, producing a range of ten formate esters 52a-j in 71-88% yield (Scheme 52). It is known
that 4-methoxyphenyl formate 52j is susceptible to hydrolysis due to the low pKa of its resultant phenol hydrolysis product, so an isolated 75% yield for 52j highlights the generally mild nature of the reaction conditions.

![Scheme 52. O-formylation reaction of alcohols.](image)
1.64 Investigation into the $N$-$O$- Selectivity Profile of Acylals

The $N$-$O$- selectivity profile of these acylating/formylating agents was then investigated utilizing serine methyl ester $53.1$ as a bifunctional test substrate. $N$-acetylation was performed under neutral conditions using acylal $7.2$ to selectively give $N$-acetyl-serine methyl ester $53.2$ as the sole product in 83% yield. O-formylation was then conducted using reagent $44.2$ under the standard basic conditions to give $N$-acetyl-$O$-formylserine methyl ester $53.3$ in a 78% yield, with no evidence of any $N$-$O$-acyl scrambling having occurred, a phenomenon which has been documented previously using acylated serine substrates (Scheme 53).$^{93}$ There was also no evidence of racemization which can be a concern when using protected amino acid esters (determined by alpha D, $[\alpha]_{D}^{20} = -9.5$; Lit = -10.1$^{94}$ $53.2$, $[\alpha]_{D}^{20} = +56$ $53.3$). When these reactions were attempted in alternative order (formylation followed by acetylation), $N$-formylation of serine methyl ester $53.1$ proceeded well, however, the relatively high temperature required for $O$-acylation led to decomposition of the formamide starting material.

![Scheme 53. N-O-selectivity demonstration with serine methyl ester](image)

1.7 Acetalisation of 1,2-Diol and 1,3-Diol Utilizing Acylals

In order to further explore the reactivity and utility of acylals it was decided to assess their reactivity towards diols under acidic conditions for the potential synthesis of cyclic acetals. Reactions to afford acetal and ketal groups are highly important reactions in organic synthesis, where they are often used to reversibly protect the functionality of carbonyl groups. This is particularly prevalent in natural product syntheses, which often utilize multiple acetal and ketal forming reactions to protect diols present in synthetic intermediates. In these more complex systems it is important to have mild reaction conditions to introduce the acetal protecting group as many natural product intermediates contain functionality that are not stable to strong acids,
or high temperatures. It was proposed that phenylmethylene diacetate 7.2 might serve as a useful reagent for the protection of diols as their cyclic benzaldehyde acetals.

An initial reaction was performed involving reaction of phenylmethylene diacetate 7.2 with 1-phenyl-1,3-propandiol 54.1 in CH₂Cl₂ using a catalytic amount of acetic acid (Scheme 54). The reaction proceeded at rt, to afford a modest conversion of 30% for formation of acetal 54.2, along with a significant amount of monoacetate 54.3 (10%). This was a promising result that warranted further optimization, and so a solvent screen was conducted with the results presented in Table 3. Five solvents were screened with acetonitrile and dichloromethane, entries 2 and 3, giving the best results, showing 85% and 80% conversion to acetal 54.2 respectively. Unfortunately formation of monoacetate 54.3 could not be completely suppressed (Table 3), however, it is worth noting that the cyclic acetal was formed with total syn-diastereoselectivity under these conditions, with no evidence of any anti-diastereomer being present.

![Scheme 54. Acetal protection of diol 54.1](image-url)
Table 3. Solvent screen for the optimisation of acetal protection of diol 54.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Monoacetate 54.3 (%)</th>
<th>Acetal 54.2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>Dichloromethane</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>9</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>13</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Dichloromethane</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl Acetate</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Hexane</td>
<td>31</td>
<td>66</td>
</tr>
</tbody>
</table>

Reaction conditions; 0.5 mmol of diol, 5 equiv. 7.2, 1 mol% AcOH, 3 mL solvent, 12 h, 40 °C a = rt.

In order to investigate the mechanism of this acetalisation reaction a number of control experiments were conducted, with some of the key reactions carried out shown below (Scheme 55). Firstly, it was important to show that benzaldehyde was not acting as the acetalising agent under these conditions, since acid catalysed breakdown of phenylmethylene diacetate 7.2 could afford benzaldehyde 7.1, which could potentially undergo a normal acid catalyzed acetal protection reaction. Pleasingly, as shown in reaction a), no acetal product was produced when benzaldehyde 7.1 was substituted in place of acylal 7.2. We next determined whether monoacetate 54.3 might be an intermediate in the reaction pathway. Therefore, monoacetate 54.3 was synthesised separately (from reaction of diol 54.1 with acetic anhydride, isolated from a mixture of products) and subjected to the standard reaction conditions. As shown in reaction b), these conditions afforded no evidence of any acetal formation. Finally, reaction of monoacetate 54.3 with benzaldehyde 7.1 in the presence of acetic acid in MeCN at 40 °C (reaction c), once again gave no evidence of any acetal formation (Scheme 55).
Given these results, the reaction is proposed to proceed via initial protonation of acylal 7.2 to afford oxonium 56.1, with elimination of one of its acetate groups to produce $O$-acyl oxonium species 15.1, which is then primed for nucleophilic attack of the primary alcohol functionality of diol 54.1 to give acetate 56.2. A second protonation step then occurs to give oxonium 56.3, which eliminates a second acetate group to produce alkyl oxonium 56.4. Intramolecular attack of the free secondary hydroxyl group of 56.4 then leads to formation of the desired cyclic acetal 54.2 (Scheme 56).
It was then decided to investigate the substrate scope of this new acetal protection protocol. A small selection of seven 1,2-diols and 1,3-diols were protected as their benzylidene acetals, using acylal 7.2 as the acetalising agent in acetonitrile at 40 °C, in the presence of a catalytic amount of acetic acid. These acetalisation conditions were applied to a range of diols to afford a range of cyclic acetals 54.2, 57a-f in 66-88% yield, including substrates containing methyl, phenyl and the sterically demanding tert-butyl group. Again, where enantiopure diols 57c/57f were used, the acetalisation reaction proceeded without racemization ([α]_D^{20} = -100 57f; [α]_D^{20} = -33; Lit = +32° (opposite enantiomer) 57f) (Scheme 57). The 1,3-diols formed 6 membered ring acetals, with syn-diastereoselectivity, whereas 1,2-diols formed 5 membered ring acetals predominantly with anti-diastereoselectivity.
The majority of the reactions proceeded to afford a single diastereomer, however, acetals 57d and 57e were isolated as a mixture of syn/anti diastereomers. Importantly, acylal 7.2 could also be used for the synthesis of acyclic acetals such as acetal 57g, albeit with a slight reduction in yield when using the alcohol substrate as the limiting reagent.

Reaction conditions; 1 mmol of diol, 3 equiv. 7.2, 1 mol% AcOH, 3 mL solvent, 12 h, 40 °C. aProduct isolated as a mixture of diastereomers.

Scheme 57. Acetal protection of diols
One area where this project could be advanced is through the use of a mixed acylal reagent that contains a sterically hindered pivaloyl whose steric bulk would ensure that it was not transferred as an acyl group. This would allow for the selective transfer of the acyl group of choice, allowing for a much more efficient process, especially if a valuable and complex acyl group needs to be transferred. Synthesis of a mixed acylal was performed in the same way as for the preparation of (formyloxy)(phenyl)methyl acetate 44.2, substituting O-formaylacetate 44.1 for acetic pivalic anhydride 58.2. Reaction of this mixed anhydride with benzaldehyde 7.1 gave the desired mixed acylal acetoxy(phenyl)methyl pivalate 58.3 in 60% yield (Scheme 58).

Two preliminary experiments were carried out to determine whether this approach was viable using acetoxy(phenyl)methyl pivalate 58.2 as the acylating agent, in the hope that the acetate group would be transferred, due to the steric bulk of the tert-butyl group preventing nucleophilic attack at its proximal carbonyl. Pleasingly, these reactions proceeded well, affording the desired acetamide 34a in 85% yield, and the corresponding acetate ester 39a in a 83% yield, with no evidence of any N-benzylpivalamide or pivalic ester being formed (Scheme 59). It is anticipated that this type of mixed acylal reagent will have the most impact, where a more complex or expensive acyl group needs to be transferred. However, due to time constraints this area could not be fully explored, and further experiments to explore the scope and limitation of this approach will be carried out in the near future.
1.9 Future Work

There are a number of potential routes where this project could be taken forward. A key area would be to fully explore the use of mixed acylals for acylation reactions. One potential powerful application could be the use of a mixed acylal for peptide synthesis. For example, acylal 60.1 containing a protected amino acid fragment could be used as an acylating agent for a range of amines, with acylation of an amino acid methyl ester 60.2 potentially enabling facile dipeptide synthesis (Scheme 60).

These mixed acylals could also be potentially used for labelling the amine/alcohol groups of serine/lysine residues of proteins with fluorophores, allowing the targeted protein to be visualised within the cell. Labelling using a mixed acylal should be selective for tagging only
those residues that are solvent exposed on the surface of the protein. Which should mean that
the labelling event should not affect the protein activity. Furthermore, transfer of acyl units
containing alkyne functionality would allow for “click” chemistry to be carried out to modify
protein surfaces, or for immobilising proteins to surfaces.

Another exciting area where acylals could be applied is as potential suicide inhibitors
(pro-drugs). There are a number of drug molecules which contain aldehyde functionalities.
However, while this aldehyde functionality accounts for the impressive biological activity they
possess, it also results in some highly undesirable side effects, usually caused by the toxicity
related to the high reactivity of an aldehyde group towards nucleophile in a cellular
environment. One such drug is MG-132 which is a specific, potent, reversible, and cell-
permeable proteasome inhibitor (Figure 5). MG-132 activates c-Jun N-terminal kinase (JNK1),
which initiates apoptosis, allowing for its use in anti-cancer therapies.

![Figure 5. MG-132](image)

One way in which the toxicity of this compound could be reduced is to mask the
aldehyde as an acylal. This acylal could be designed in such a way that the aldehyde functionality
is only revealed in cells that contain high levels of cell activity (cancer cells which also have an
acidic pH which would also accelerate acylal cleavage). Proteasome cleavage of the phenyl
alanine motif present in acylal 61.1 could potentially lead to the generation of free amine 61.2.
This amine would then be able to undergo an intramolecular acylation causing the elimination
of acetate and generation of the aldehyde functionality of the parent compound MG-132
(Scheme 61).
1.10 Conclusion

In conclusion a new branch of reactivity has been discovered for acylals which had previously been shown to exhibit a wide range of reactivity towards a range of nucleophiles. We have shown them to be highly active reagents for the N-/O-acylation of amines and alcohol nucleophiles for the synthesis of a range of formamides, acetamides, formate esters and acetate esters. It has been demonstrated that a range of acyl groups can be transferred including short and long chain alkyls, acryloyl, benzoyl, phenyl acetyl and biologically important trifluoroacetyl group, thus enabling the synthesis of a range of benzylamides and esters. These acylation reagents have also been shown to demonstrate inherent N-/O- selectivity towards the amine and alcohol groups of serine methyl ester.
To explore further the scope and limitations of these reagents (formyloxy)(phenyl)methyl acetate 44.2 has been applied for the $N$-formylation of a range of unprotected amino acids, and for the synthesis of the biologically important tripeptide f-MLP. As well as this, both phenylmethylene diacetate 7.2 and (formyloxy)(phenyl)methyl acetate 44.2, have been applied for the acylation/formylation of the $\omega$-amino residue of a lysine residue within a decapeptide. Finally, it has also been demonstrated that a simple switch in pH from basic to acidic conditions for diols can change from $O$-acylation to acetal formation.
In conjunction with the research described above, work was also been carried out towards A protecting group free strategy for the sustainable synthesis of polyketide natural products and their analogues. An introduction into this area will now be presented.
2.0 Efficient Natural Product Synthesis

2.1 Introduction

Throughout documented human history chemical substances derived from natural sources; plants, animals and microbes have been utilised as medicines in the treatment of diseases and ailments. However, the first chemical synthesis of a natural product did not occur until 1828 with the synthesis of urea from inorganic ammonium cyanate by Wöhler. Wöhler demonstrated that natural products, despite being derived from living organisms, could also be synthesised in the laboratory. This breakthrough led to the first targeted synthesis of an “organic” natural product; acetic acid in 1884. Up until the 1960’s, natural product synthesis was predominantly a tool to either confirm, or decipher the structure of the natural product under investigation. Common spectroscopic techniques taken for granted today were either in their infancy, or yet to be discovered; i.e. UV/vis spectroscopy (1930’s), Infra-Red spectroscopy (1940’s) and perhaps the most important, nuclear magnetic resonance (NMR) (1950’s). Before this, the total synthesis of a complex molecule from known building blocks to give the proposed structure was one of the best methods of structural determination and confirmation. A comparison of physical properties with an isolated genuine sample of the natural product was then used to confirm that the correct compound had been assigned/synthesised.

3.0 Early Natural Product Synthesis

An example of early natural product synthesis is the relay synthesis of oestrone; which relied on a combination of synthetic techniques from Robinson, Bachmann, Anner and Miescher. The synthesis shown in Scheme 62 is known as a “relay”, because it targets a known intermediate that could also be generated from degradation of the natural product. For example, ketone 62.6 had been previously isolated through the degradation of oestrone, and a synthesis of oestrone from ketone 62.6 had been established. The synthesis shown is typical of the time: the molecular skeleton is formed using reactions that only introduce small changes to the overall structure, maintaining a level of control over the desired product, and increasing the likelihood that the predicted transformation would occur. This concept relied heavily on the use of established skeletal building reactions, resulting in natural product synthesis at the time not employing many new “risky” reaction steps. In the synthesis of oestrone, the main skeletal building step was introduction of malonic ester fragment, followed by C-acylation of the malonate intermediate to give ketone 62.2. This intermediate then underwent a series of
hydrolysis, cyclisation and elimination reactions to give the diacid 62.3. Decarboxylation of diacid 62.3 then occurred, with alkene bond migration affording the more thermodynamically stable tetra-substituted alkene 62.4. Alkene hydrogenation, followed by esterification generated bis-ester 62.5, which underwent Dieckmann cyclisation to afford bis-ester 62.5, whose enolate was methylated to give β-keto-ester 62.6. However, 62.6 was formed as one of three racemic diastereomers, which needed to be separated by fractional crystallisation. A Reformatsky reaction on the desired diastereomer, followed by dehydration of the resultant β-hydroxyester, afforded α,β-unsaturated ester 62.7. Alkene hydrogenation, followed by further fractional crystallisation purification of the resultant mixture gave the pure diester of diastereomers 62.8. Formation of acyl chloride 62.9 was followed by Arndt-Eistert homologation to afford C1-homologated ester 62.10, which was then cyclised/decarboxylated to afford oestrone 62.11. At the time the Arndt-Eistert homologation was a relatively new reaction, so its inclusion as a key step at a late stage of a natural product synthesis was considered quite revolutionary. Only the yields for the first four steps are available, therefore comments about overall yield cannot be made.

While it may seem unfair to compare this synthesis to modern day efforts, by so doing it can help demonstrate how far synthesis has evolved over the years, and highlight areas where progress is still lacking. Key features of this oestrone synthesis are:

- Atom economy = 15%
- 9 Functional Group Interconversion (FGI) steps, including a number of ester hydrolysis/esterification steps
- 2 reductive steps
- Lack of stereocontrol during the cyclisation and hydrogenation steps
- Use of toxic Pb(CO$_3$)$_2$ as a base
- Use of toxic/explosive diazomethane in the C1-homologation reaction

An atom economy of 15% for the synthesis of a complex molecule is relatively good, however a more strategic synthetic plan might have resulted in a number of the inherently inefficient functional group interconversion (FGI) steps being avoided. A number of reagents used would no longer be acceptable by modern industrial standards, Pb(CO$_3$)$_2$ is highly toxic and lead regents are avoided where possible, whilst carrying out the cyclisation reaction at 300 °C seems excessive. Diazomethane is toxic but also presents an explosion risk, while the use of these reagents was common place, a greater awareness of health and safety might result in an alternative flow protocol being considered for this step.
Scheme 62. An early pioneering synthesis of oestrone\(^{98}\)
It is important to remember that during these early years of synthesis, how limited the synthetic “tool box” was, with many fewer reactions being available for consideration for natural product synthesis. This is particularly highlighted in the creation of stereogenic centres where the ability to control stereoselectivity in a reaction was much less well developed, often resulting in low yielding formation of complex mixtures of racemic diastereomers that were difficult to purify.

The success or failure of natural product syntheses at this time relied heavily on the choice of the original starting material, which meant that each synthesis was ‘bespoke’ relying on a level of intuition from the chemist. This level of “intuition” is well illustrated in the total synthesis of homoeroquinene reported by Woodward and Doering in 1945 (Scheme 63). This achievement generated a lot of interest, both within the scientific community and the wider population. This was due to the therapeutic properties of quinine for the treatment of malaria, which had become an acute problem, due to the British, Dutch and French Empires having expanded their influence into malaria infected territories.

This synthesis was again a relay synthesis based on the work of Kindler and Prelog, who had isolated quinotoxine and homoeroquinene from the degradation of quinine, and subsequently demonstrated that quinine could be reconstructed from these compounds (Figure 6).

![Figure 6. Structural relationship between quinine, quinotoxine and homoeroquinene](image)

The choice of the hydroxyquinoline 63.1 as the starting material highlights the shrewd thinking of Woodward, as all of the skeletal atoms required for the desired intermediate homoeroquinene were already in place from the offset.

Initially, the nitrogen containing ring of the hydroxyquinoline 63.1 was selectively hydrogenated to give hydroquinoline 63.2. N-Acetylation followed by de-aromatisation gave the
fully saturated hydroquinoline 63.3. Complete control over the facial selectivity of the hydrogenation of 63.2 to give the desired cis arrangement was unsuccessful and therefore after oxidation to ketone 63.4 a separation of diastereomers was required. The cyclohexanone ring was then oxidatively cleaved with ethoxy nitrite to give oxime 63.5, which was subsequently reduced and N-methylated to give the quaternary ammonium salt 63.6. Hofmann elimination resulted in selective alkene formation followed treatment with potassium isocyanate to give urea 63.7 (required for purification), which after acid catalysed hydrolysis of both its urea and ester functionalities gave the desired homoeroquinene (Scheme 63).

Key features of this homoerquinene synthesis are:

- Atom economy = 17%
- 10 steps, 10% overall yield from 63.1
- 2 oxidation steps (including use of stoichiometric chromium oxidants)
- 3 reductive steps
- Poor stereocontrol during the hydrogenation step
- Creation and then destruction of 2 stereocentres
Scheme 63. Woodward and Doering synthesis of homoeroquinene.98,104

With the development of modern day analytical spectroscopic techniques (UV/vis, IR and NMR) and with X-ray crystal structure analysis becoming the established techniques for structure elucidation, Synthetic organic chemists were suddenly free to explore more ambitious syntheses. This new freedom for natural product synthesis was perhaps best captured by Eschenmoser.98,107

"Elimination of the classical function of providing structural proof for natural products implied liberation from the restriction that only very well established reactions may be applied in a synthesis. Natural product synthesis henceforth provides a challenge to invent and to develop novel reactions and to discover novel reactivity patterns."

However, developments in the art of the synthesis were not purely about developing new reactions, since access to new reactivity profiles also enabled increasingly complex natural product targets to be prepared. These synthetic breakthroughs allowed many new drug molecules to be prepared, as well as enabling chemical probes to be synthesised that enabled biochemical pathways to be interrogated.108 As soon as a new complex natural product was
isolated, then the race was on to achieve its total synthesis, with the research groups of internationally renowned scientist such as Danishefsky, Evans and Nicolaou, (and numerous others), having achieved impressive syntheses of many different of highly complex natural products.

This change in direction led to large surge in natural product synthesis research culminating in a peak in output during the 1970-90s. This increase in interest had a dramatic impact on the pharmaceutical industry during this time, with 49% of the 877 new molecular entities introduced as drugs between 1981-2001 being derived from natural product leads. Indeed this percentage increases further when two of the most crucial therapeutic areas are considered; with natural product inspired leads responsible for 60% of the drug molecules approved in the areas of anti-cancer and anti-infection during the period 1984-1995.

3.1 Natural products as drug molecules

The inherent biological activity, high structural diversity and specificity profiles of the large number of natural products that have been isolated, means that they may be considered to be privileged lead molecules for drug discovery purposes. However, the complexity of many natural products often makes them difficult to modify chemically, which is often required when the pharmacokinetic properties of the parent natural product need to be modified. Natural products are also often not available in sufficiently large enough quantities from renewable natural sources. Instead, advances in increasing the efficiency of synthetic organic chemistry protocols are still needed, to help remove perceived barriers associated with using natural product derived lead compounds in drug discovery programs. Indeed, one of the main driving forces in modern natural product synthesis is to develop new reaction protocols that address efficiency/sustainability issues, and demonstrate that they can be applied to the synthesis of structurally complex structures.

A prominent example of the type of problems that are often faced, is for the multigram total synthesis of the potent anticancer marine polyketide natural product (+)-discodermolide carried out by Merck process chemists in collaboration with Paterson and co-workers. The demand for this compound could not be met through isolation from its natural source; a marine sponge Discodermia sp., with repeated attempts to culture Discodermia sp. expressing the correct symbiotic microorganisms that produce discodermolide having proven unsuccessful to date. Therefore, a viable synthetic route to large multigram quantities of discodermolide was required, with the first total synthesis by the Schreiber group requiring a 32 step synthesis in
only 3.2% overall yield.\textsuperscript{120} While an impressive example of natural product synthesis, the low yield rendered this route unviable for the production of (+)-discodermolide on a large scale, and as a consequence a new more scalable route was required. Many attempted improvements were made to increase the yield of its synthesis,\textsuperscript{121-127} with the semi-industrial route that was eventually devised for the synthesis of multigram quantities of (+)-discodermolide ultimately being a hybrid of previous syntheses.

Initial efforts focused on the production of the common Weinreb amide intermediate 64.6 which had been identified as a key synthon by Smith in an earlier synthesis.\textsuperscript{121-123} This route begins with the readily available Roche ester 64.1 which was first O-protected as its p-methoxybenzyl ether 64.2. Upon reduction, alcohol 3.3 was obtained which was readily oxidised via a TEMPO oxidation to give aldehyde 64.4. This aldehyde 64.4 was then reacted with the boron enolate of a chiral N-acyl-oxazolidin-2-one to afford an Evans syn-aldol product 64.5. The aldol product 64.5 was purified by recrystallization, hydrolysed, and then subjected to Weinreb amide formation using the coupling reagent CDMT. This sequence of reactions gave Weinreb amide 64.6 in six steps, in large quantities (1.6 kg) and required no chromatographic purification steps (Scheme 64).\textsuperscript{115}

While this route was clearly compatible for synthesis on a medium scale, there are still, a number of areas in which the synthesis of this fragment could be improved. Roche ester 64.1 is a commercially available starting material, however, at a cost of \textasciitilde£20/g for the (S) isomer and \textasciitilde£30/g for the (R) isomer, it is perhaps not the best choice as starting material for a large scale multi-step synthesis of a drug compound. The synthesis of intermediate 64.6 also utilises protecting group chemistry in the form of the PMB (p-methoxybenzyl) protecting group which accommodates for 37 wt.% of intermediate 64.6.

Protecting group chemistry continues to be an invaluable tool for organic chemists in the synthesis of highly complex compounds, through their ability to mask the reactivity profiles of competing functional groups, which offers an increased level of security and predictability.\textsuperscript{128} However, the use of a protecting group introduces at least two additional synthetic steps,\textsuperscript{129} which greatly reduces the atom efficiency of the synthesis, as well as impacting overall yield, since quantitative yields are rarely possible.\textsuperscript{128} The atom efficiency for this five step sequence from Roche’s ester 64.1 to the common intermediate 64.6 is very low at only 1.33%, and it still has a PMB protecting group in place. The use of a chiral auxiliary also has a large impact on atom efficiency as it involves incorporation and removal of a stoichiometric chiral unit, although efficient recycling of the auxiliary can potentially mitigate these concerns. Furthermore, global
ester reduction of an ester group to alcohol 64.3, followed by an oxidation step to afford an aldehyde is inherently inefficient.

Once intermediate 64.6 was obtained in synthetically useful quantities it was used as a core intermediate for the divergent synthesis of the three key compounds; alkene 65.2, acetal 65.5 and ketone 65.7 in four, seven and five steps respectively.\textsuperscript{121-123, 126, 127} Alkene 65.1 was prepared via O-TBS protection, and Weinreb amide reduction reactions to afford aldehyde 65.1 in 61% yield over two steps. Wittig olefination of aldehyde 65.1 using iodoethyl triphenylphosphonium ylide then gave iodo-(Z)-alkene 65.2 in a low 30% yield.

Acetal 65.4 synthesis began with a DDQ catalysed oxidative cyclisation reaction to form acetal 65.3, which represents a clever way to manipulate a protecting group, whilst changing its overall oxidation state (e.g. alcohol to aldehyde). Weinreb amide reduction to aldehyde, was followed by an Evans-aldol reaction to generate syn-aldol 65.4. O-silyl protection of 65.4, was followed by reductive auxiliary cleavage with LiBH\textsubscript{4}, with the resultant alcohol then subjected to an iodide mediated Appel reaction to afford acetal 65.5.
Ketone **65.2** synthesis also started with a TBS protection, followed by PMB deprotection to afford alcohol **65.6**. Subsequent alcohol oxidation of **65.6** to its corresponding aldehyde, followed by Grignard addition of MeMgBr and secondary alcohol oxidation generated ketone **65.2** in 66% yield from Weinreb amide **64.6** (Scheme 65).
Scheme 65. Key intermediate synthesis
Alkene 65.2 and acetal 65.5 were then combined and functionalised in an 11 step process to give diene 66.5. The initial reaction proceeds through metalation of iodide and reaction with 9-MeOBBN to afford borane 66.1 that underwent a Suzuki-type cross-coupling reaction with vinyl iodide 65.2 to generate trisubstituted alkene 66.2. Selective reductive cleavage of the PMB group of 66.3 with DIBAL-H and subsequent oxidation of the resultant alcohol gave an aldehyde which was subjected to a Nozaki-Hiyama allylation reaction with 2-TMS-allyl bromide to afford diene 66.3. Deprotection of both PMB groups of 5.3 with DDQ, was followed by TEMPO oxidation to afford an aldehyde that was reacted with the potassium anion of bis-2,2,2-trifluoroethyl-phosphonoacetic acid methyl ester utilising a Still-Gennari variation of the Horner-Wadsworth-Emmons reaction gave vinyl ester 66.4. The free secondary alcohol of 66.4 was derivatised with isocyanate CICCON=C=O to afford a carbamate whose ester group was reduced with DIBAL-H followed by alcohol oxidation to afford α,β-unsaturated aldehyde 66.5 in 27% yield over 11 steps.

(+)-DIP-Cl boron was then used to generate the boron enolate of ketone 65.7 which underwent an aldol reaction with α,β-unsaturated aldehyde 66.5, followed by ketone reduction, lactonization and global silyl deprotection to give the final compound (+)-discodermolide in a total of 39 steps, achieving a final mass of >60 g of (+)-discodermolide (Scheme 66).115-119

The synthetic steps presented in Scheme 65 and Scheme 66 follow the same general trend as those in the synthesis of common intermediate 64.6:

- Use of numerous protection/deprotection steps;
- A series of ester reduction reactions to afford alcohol intermediates that were then oxidised to afford reactive aldehyde group;
- Use of stoichiometric amounts of chiral auxiliaries/reagents to induce stereocontrol

Finally, the question could be posed whether this synthesis could ever really be used to commercialise (+)-discodermolide for clinical use, since the cost of treatment would likely be too expensive to prevent its widespread use for treatment of cancer in the wider population.
Scheme 66. Convergent synthesis of (+)-discodermolide.\textsuperscript{115}
Contemporary drug discovery is often based on the high throughput (HTP) screening of small molecules for biological activities associated with their ability to selectively bind to specific target proteins. Given the limitless number of small molecule structures that are accessible for screening, it is important that chemical libraries are designed to address as broad a range of chemical space as possible, and that they contain functional groups that are biased towards biological compatibility and drug likeness. Consideration of these requirements can lead to the identification of “privileged” structures from which a whole host of compounds can then be developed for optimisation.

As mentioned earlier, natural products, can be viewed as an entire population of “privileged” structures, since they have been selected by evolutionary pressure to be able to interact with proteins, and other biological targets. The application of Nature’s library of structures to identify lead compounds, has already led to a large number of natural products and their derivatives being used as drug compounds, a few of which are shown below. Vancomycin is a clinically relevant antibiotic; staurosporine was used as a lead compound for development of the indolecarbazole structure of anticancer drugs; rapamycin is a protein kinase inhibitor used for immunosuppression; and Taxol® is a highly potent anti-cancer drug (Figure 7).
Compared to purely synthetic drug molecules, natural products derived leads often have a far greater level of complexity in terms of the number of stereogenic centres, number of rotatable bonds, number of sp³ hybridised stereogenic carbons that are present, and they often contain significantly fewer nitrogen, sulfur and halogen containing groups. They also normally contain a higher number of oxygen atoms and have a lower ratio of aromatic rings to heavy atoms when compared to their purely synthetic counterparts.  Natural products are also typically larger than synthetic drugs, with molecular weights >500 increasingly common. Indeed most natural product derived drugs do not comply at all with Lipinski’s “rule of five”: a general rule based on analysis of the structure of current drug molecules that is often used to predict the likelihood of a drug being orally bioavailable. However, despite these considerations, the current prevalence of natural product derived drugs with two or more “rule of five”
violations is still relatively low at around 10%, approximately equal to the incidence of current synthetic drugs.\textsuperscript{96, 131, 133}

There are many challenges facing natural product synthesis in the 21\textsuperscript{st} century. One of these is to push the boundaries of what many would consider to be beyond the scope of traditional natural product synthesis, with chemists becoming increasingly more daring in tackling the size and complexity of target molecules. An example of this, is the quite remarkable glycoprotein synthesis described by the Danishefsky group.\textsuperscript{96, 134} Through targeted synthesis, Danishefsky and co-workers were able to synthesise the β-subunit of the human follicle-stimulating hormone, which is a glycoprotein with a molecular mass of 17868, setting a new benchmark for peptide synthesis.

The β-subunit of the human follicle-stimulating hormone contains 111 amino acids with two \textit{N}-linked dodecasaccharides at Asn\textsuperscript{7} and Asn\textsuperscript{24}, with the high number of cysteine residues present in the peptide backbone allowing for the use of native chemical ligation (NCL) to assemble the protein.\textsuperscript{135} The β-subunit was split into smaller fragments which were synthesised through Fmoc-based solid phase peptide synthesis (SPPS), with each C-terminus functionalised as a thioester ready for NCL. The cysteine residues not required for NCL were protected as acetamidomethyl (Acm) groups to prevent unwanted cross linkages being formed. The anomeric hydroxyl group of the dodecasaccharide was converted to a primary amine group using Kochetkov amination conditions, allowing for a Lansbury aspartylation reaction to be used to link the dodecasaccharide to the desired fragments. The dodecasaccharide was prepared through a highly convergent series of glycosylation reactions linking known monosaccharide building blocks. In each case, protecting groups were carefully selected to maximize stereoselectivity during glycosidic bond formation and to minimize the number of deprotection steps necessary to complete the synthesis. Subsequent deprotection and sequential NCL steps resulted in the synthesis of the β-subunit of the human follicle-stimulating hormone, which represents the largest glycoprotein to have been synthesized in a homogeneous state, using strictly chemical methods (Figure 8).\textsuperscript{134}
Another area of development is the emergence of divergent total syntheses for the rapid synthesis of structurally complex lead compounds for screening purposes, which has the potential to have a large impact on the drug-discovery process. Specific intermediates generated during a natural product synthesis contain partial structural elements of the parent compound that can be used to help define which fragments of the natural product are necessary for biological activity. This presents an opportunity to improve on the original compound through synthetic divergence from key intermediates, whilst also interrogating which functionality is required to elicit the observed biological activity.

One example of this type of synthesis has been recently reviewed by the Taylor group. They illustrated how the use of conformational-activity relationships (CAR), could be used to understand how natural products induce their biological activity, by exploring how the most active conformer of a complex natural product is bound to its biological target. This structural information could then be used to design simpler structural analogues that are easier to prepare and still demonstrate high levels of biological activity.

An impressive example of this approach has been reported for development of conformational mimics of bryostatin (Figure 9). Bryostatin is a polyketide natural product that elicits a wide array of biological responses, such as restoring apoptotic function in cancer cells, improving memory in animal models, and inducing latent HIV activation. This impressive range of biological activities is believed to be due to the ability of bryostatin to activate protein...
kinase C (PKC) by binding to its C1 domain. However, limited access to sufficient quantities of bryostatin has hindered its advancement into clinical trials. Synthetic techniques, while elegant, have only been successful in producing limited amounts, and isolation from its natural source is environmentally unviable (18 g of bryostatin from 40,000 L of wet bryozoan!).\textsuperscript{127} Wender and co-workers have instead approached this problem in a different manner, using conformational analysis of bryostatin to gain an understanding of how it binds to PKC. They then employed this information to propose structural changes to bryostatin that would simplify its synthesis, whilst maintaining biological activity.\textsuperscript{138-140} Their work culminated in the synthesis of a salicylate analogue of bryostatin (Figure 9), which still bound to PKC in low nanomolar concentrations, approaching the affinity of bryostatin itself. As is evident from considering the two structures, the salicylate analogue of bryostatin is synthetically a lot easier to access, resulting in this compound being used as a promising lead for further functionalisation and development.\textsuperscript{137, 139}

Halaven\textsuperscript{®} (eribulin mesylate) is a potent antitumor agent that is a derivative of the structurally complex marine natural product halichondrin B (Figure 10).\textsuperscript{141-146} It can be seen, that while Halaven\textsuperscript{®} has a simplified polyether structure when compared to halichondrin B, it is still a highly complex molecule that is difficult to access in large quantities. However, due to the impressive biological activity observed when Halaven\textsuperscript{®} was screened in clinical trials, a viable synthetic route to significant amounts of this compound was necessary. The Kishi group and Eisai Inc. embarked on this daunting undertaking, leading to a truly impressive synthetic route which allows for the synthesis of 200-300 g batches of the complex natural product derived Halaven\textsuperscript{®}.\textsuperscript{142-145, 147}
The synthesis of Halaven® proceeds through the generation of three key intermediates, aldehyde 67.8, vinyl triflate 68.9 and vinyl iodide 69.5. Synthesis of aldehyde 67.8 begins with the readily available D-glucurono-3,6-lactone 67.1, involving ketal formation followed by α-chlorination and subsequent reductive dehalogenation to afford lactone 67.2 as a crystalline solid. DIBAL-H reduction of lactone 67.2 followed by addition of TMSCH$_2$MgCl provides a β-hydroxysilane adduct which eliminates on treatment with KHMDS to afford alkene 67.3. Protection of the alcohol group of alkene 67.3 with benzyl bromide and base afforded a benzylic ether, which underwent a Sharpless asymmetric dihydroxylation reaction, with the resultant diol group then protected as their benzoyl esters to afford pyran 67.4. A titanium catalysed C-glycosidation reaction of pyran 67.4 using allyltrimethylsilane, was followed by modified Moffat oxidation (DMSO-trichloroacetic anhydride) of its secondary alcohol functionality to afford ketone 67.5. Horner-Wadsworth-Emmons reaction of ketone 67.5 was then used to introduce a vinyl sulfone functionality followed by benzyl ether cleavage using iodomethylsilane to afford
alcohol 67.6. Hydroxyl-directed conjugate reduction reaction of the vinyl sulfone fragment of 67.6, was followed by base mediated cleavage of both its benzoyl groups to afford a crystalline triol intermediate that could be purified to homogeneity. This triol intermediate was then re-protected to afford acetonide 67.7. The alcohol functionality of 67.7 was then methylated, followed by a further protecting group swap to afford vicinal TBS ethers was then required to create protecting group uniformity later in the synthesis (vide supra). Ozonolysis of the terminal alkene using a reductive workup (Lindlars catalyst) then afforded crystalline aldehyde 67.8 (Scheme 67). While the use of a biorenewable sugar based starting material represents an admirable feature of this synthesis it should be noted that chiral sugars are highly functionalised substrates that often require multiple synthetic steps to remove redundant functionality.
The synthesis of triflate \(68.9\) began with acid catalysed hydration of dihydrofuran \(68.1\), followed by a tin-mediated 2-bromoallylation reaction to afford a crystalline racemic diol, whose primary alcohol was selectively O-silyl protected to afford vinyl bromide \(68.2\). The enantiomers of \(68.2\) were resolved through chiral-simulated moving bed (SMB) chromatography using...
Chiralpak OD as a chiral stationary phase, affording the desired (R)-alcohol \textit{68.2} in >98% ee. The unwanted (S)-enantiomer could then be inverted to the desired (R)-enantiomer through the use of Mitsunobu chemistry. Tosylation of alcohol \textit{68.2} using tosyl chloride and DMAP afforded vinyl bromide \textit{68.3}, that underwent a Nozaki–Hiyama–Kishi (NHK) Ni(II) catalysed cross-coupling reaction with Weinreb amide \textit{68.6} (obtained in 7 steps from epoxide \textit{68.4}), to afford a coupled allylic alcohol that was treated with SiO\textsubscript{2} in iso-propanol, resulting in cyclisation with loss of its tosyl group to generate the tetrahydrofuran ring of \textit{68.7}. Grignard addition of MeMgBr to Weinreb amide \textit{68.7} generated a ketone, which when treated with KHMDS and phenyl triflimide gave its kinetic enol triflate that was O-silyl deprotected to give alcohol \textit{68.8}. Subsequent O-pivaloyl and O-mesyl protections led to the synthesis of vinyl triflate \textit{68.9} in 2.1% yield over a total of 15 steps (Scheme 68).\textsuperscript{145}
Synthesis of aldehyde 69.6 began with acid catalysed bis-diol protection of D-glucuronolactone 69.1 with cyclohexanone to afford a bis-cyclohexylidene lactone, with subsequent DIBAL-H reduction of its lactone functionality generating lactol 69.2. A series of transformations including Wittig reaction of MeOCH₂PPh₃⁺Cl⁻, dihydroxylation reaction of the resultant alkene, and bis-acetylation led to the formation of bis-acetate 69.3. A key Lewis acid catalysed C-glycosidation reaction of bis-acetate 69.3 was carried out with 3-trimethylsilyl-4-pentenoate to give the important fused pyran functionality of ester 69.4. Periodate mediated cleavage of the diol fragment of 69.4 was followed by subsequent NHK reaction of the resultant aldehyde with 1-bromo-2-trimethylsilylethene afforded allylic alcohol 69.5. A protecting group swap from cyclohexylidene to tert-butyldimethylsilyl ether groups, was then followed by
conversion of the vinyl-silane fragment into a vinyl-iodide group to generate >3 kg of vinyl iodide 69.6 (Scheme 69).

Scheme 69. Synthesis of aldehyde 69.5

Aldehyde 67.8 and vinyl triflate 68.9 (prepared in 15 steps) were then combined utilising a third NHK Ni(II) catalysed cross-coupling reaction, with subsequent cyclic etherification to afford the pyran ring being achieved through titration with KHMDS, which resulted in intramolecular mesylate displacement by its δ-alkoxide substituent. Reductive cleavage of the pivolate with DIBAL-H then afforded alcohol 70.1, which was prepared on a 1.85 kg scale. Coupling of the sulfonyl anion of alcohol 70.1 with the aldehyde functionality of vinyl iodide 69.6 (prepared on a 3.04 kg scale in 12 steps), was followed by alcohol oxidation and samarium
iodide mediated reduction of the sulphonyl group to afford ketone 70.2. An intramolecular NHK reaction and subsequent alcohol oxidation was then followed by global O-Silyl deprotection and intramolecular ketalization reactions to afford diol 70.3. Introduction of the amine functionality was then achieved by tosylation of the primary alcohol, allowing for in situ epoxide formation. Epoxide opening with ammonium hydroxide, and generation of a stable mesylate salt afforded Halaven® in 200-300 g batches (Scheme 70).142, 145, 147

A highly convergent approach combined with a strategy for targeting crystalline intermediates, were key factors in bringing this incredible syntheses to fruition, and ultimately generating usable quantities of Halaven® to allow for biological testing in the clinic. These trials proved successful and Halaven® is currently used as a cancer therapy drug for patients suffering with advanced breast cancers and inoperable liposarcoma. However, the National Institute for Clinical Excellence (NICE) originally rejected its availability on the NHS, with its cost of >£10,000 for a 6 month treatment programme for only an average 3 month life expectancy extension deemed too costly. However, public pressure eventually forced NICE to reverse their decision and this drug is now available in the UK.

This synthesis is of course an incredible achievement of organic chemistry, however, as mentioned above there are a number of protection/deprotection steps and inherently inefficient protecting group swaps. This results in an additional 17 synthetic steps, and as the art of organic synthesis evolves, it is hoped that these kind of wasteful, but currently necessary, protecting group processes may ultimately be removed completely.
Scheme 70. Synthesis of Halaven®

1. NiCl₂, CrCl₂, NEt₃, MeCN, THF
2. Dess-Martin, CH₂Cl₂, 60-80% (2 steps)
3. TBAF, imidazole HCl
4. PPTS, CH₂Cl₂, MeCN, H₂O, 55-75% (2 steps)

1. nBuLi, 69.6, THF
-50 °C, 75-95%
2. Dess-Martin
CH₂Cl₂, 75-95%
3. Sml₂, THF
H₂O, <-65 °C
75-95%

1. NiCl₂, CrCl₂, NEt₃, THF, rt
2. KHMDs, THF-toluene
-20 °C 65% (2 steps)
3. DIBAL-H, toluene
-70 °C, 79%

Halaven®
200-300 g batches
The emergence of divergent total synthesis and the recent decrease in new pharmaceutical leads based on natural products, potentially highlights some of the perceived shortcomings of natural product synthesis. It has long been argued that semi-synthesis is the only way to produce sufficiently large enough amounts of naturally occurring materials for drug-discovery applications. However, it must be accepted that this promise is rarely met. Therefore, it can be argued that natural product synthesis in the 21st century should always seek to provide the target compound in multigram quantities, with synthesis on this scale presenting many challenges associated with logistics, the sustainable use of reagent and disposal of side products and waste. In this respect the defined principles and metrics of green and sustainable chemistry are likely to be increasingly used as a tool to devise efficient syntheses that meet these demands.

4.0 Protecting Group Free Synthesis

As mentioned earlier the use of protecting groups are common place in many complex synthetic routes towards natural products. However, their use is acknowledged as a necessary evil, “synthetic chemists would dearly like to be able to work without protecting groups, but they are very glad that they exist” (P. Kocienski). The disadvantages associated with the use of protecting groups are obvious, an increase in the number of synthetic steps, a reduction in overall yield, and an increase in the amount of waste produced. However, the reason that their use is so prolific is because of the inherent security and predictability that they confer, allowing for increased functional group compatibility that allows for a vast increase in the completion rate of structurally complex targets. Therefore, organic synthesis faces an enormous challenge in trying to change this reliance and move towards more efficient protecting group free synthetic protocols. However, this can also be seen as a “opportunity for invention”. New reactions, regents and catalysts will need to be developed with a focus on chemoselectivity and functional group compatibility if this challenge is to be met. While this is clearly a daunting task there are a number of research groups that are embracing this challenge, resulting in the number of reported protecting group free syntheses of natural products increasing significantly over the past decade or more.

An impressive early landmark example of a protecting group free synthesis, where protecting groups were deliberately avoided through synthetic design, rather than being found to be unnecessary, was the synthesis of (+)-hapalindole Q by Baran and Richter in 2004 (Scheme 71).
Their synthesis began by inventing a new reaction to couple together the naturally available starting materials indole 71.1 and carvone 71.2. Deprotonation of both reagents, gave the aza-anion of indole and the enolate of carvone, which were subjected to copper mediated oxidation to afford their corresponding radicals that underwent radical coupling to give the 3-substituted indole 71.3. Deprotonation of indole followed by conjugate reduction of the resultant aza-anion with L-selectride, afforded an enolate intermediate 71.4, treatment with acetaldehyde gave aldol 71.5. The secondary alcohol functionality of 71.5 was then dehydrated using Martin’s Sulfurane to give bis-alkene 71.6. Reductive amination of the ketone functionality of 71.6 resulted in primary amine 71.7 which was converted into its corresponding isothiocyanate via treatment with thiocarbonyldiimidazole to give the final compound (+)-hapalindole Q.155 This synthesis is not only a great example of protecting group free natural product synthesis, but also an example where natural product synthesis served as a driving force for the development of a new indole coupling reaction.128, 155
Since this outstanding demonstration of protecting group free synthesis, interest in this area has increased steadily, resulting in the publication of some exciting and inspiring natural product syntheses. This report will now focus on a few recent examples of protecting group free natural product synthesis, starting with a discussion of a formal synthesis of (-)-platencin (Figure 11).
(-)-Platencin is a potent, broad spectrum Gram-positive antibiotic. The first total synthesis by Nicolaou et al. in 2008 followed a traditional protecting group strategy in 23 steps, however, this publication was quickly followed by an efficient “protecting group free” formal synthesis by Tiefenbacher and Mulzer affording platencin in 13 steps from perillaldehyde (Scheme 72). Their formal synthesis began with a Diels-Alder cyclisation of Rawal diene 72.1 and (-)-perillaldehyde 72.2 to give α,β-unsaturated ketone 72.3. A selective Wittig reaction of the aldehyde group was then performed to give a bis-terminal alkene which upon treatment with Grubbs 2nd generation catalyst, resulted in a ring closing metathesis reaction to afford fused tricycle 72.4. Alkene bond migration was performed via bromoalkene formation with NBS, which upon treatment with CrCl₃ and LiAlH₄ gave the desired tricycle 72.5, containing an exocyclic alkene bond which was a common intermediate in both syntheses (Scheme 72). The remaining synthetic steps (shown in red) show the completion of the synthesis according Nicolaou’s methodology. Sequential enolate alkylation with methyl iodide and allyl iodide afforded triene 72.6, which underwent regioselective cross-metathesis with vinyl boronate using a 2nd generation Hoveyda–Grubbs catalyst and benzoquinone to afford boronate 72.7. Boronate oxidation (using Me₃NO), followed by Pinnick oxidation of the resultant alcohol afforded carboxylic acid 72.8. This acid then underwent an amide bond coupling reaction with aniline 72.9, using a HATU facilitated coupling agent, followed by acid deprotection to afford (-)-Platencin (Scheme 72).
Hippolachnin A is a recently isolated marine polyketide, possessing an intriguing fused molecular framework that displays promising antifungal activity. The first total synthesis of (±)-hippolachnin A was completed in 2015 by the Carreira group, who described a protecting group free synthesis of (±)-hippolachnin A in nine linear steps and an overall yield of 9%. The synthesis began with commercially available cyclopentenone 73.1 which was irradiated with
hex-3-yne at $\lambda>$270 nm, undergoing a [2+2] photocycloaddition reaction to afford bicyclo[4.2.0]heptanone 73.2. This photoadduct was found to be susceptible to elimination during purification, therefore it was reacted directly with K$_2$CO$_3$ to generate enone 73.3. 1,4-cuprate addition of an ethyl fragment, followed by 1,2-Grignard addition of a second ethyl fragment afforded alcohol 73.5 with complete exo diastereoselectivity. Treatment of alcohol 73.5 with methyl acrylate in the presence of pyridinium para-toluenesulfonate (PPTS) then gave ester 73.6 as a cyclisation precursor. Reaction of ester 73.6 with BF$_3$·2AcOH resulted in an ene cyclization reaction occurring to give the desired tricyclic annulated product 73.7 in a 6:1 diastereomeric ratio. Heterogeneous platinum catalysed hydrogenation of 73.7 then gave the exo product 73.8. The synthesis of (±)-hippolachnin A was completed by $\alpha$-phenylselenylation of the enolate of the ester functionality of 73.8, followed by oxidation of the crude reaction mixture with concomitant selenoxide elimination to afford the desired alkene (Scheme 73).
The pallambins are terpene natural products, that whilst exhibiting no known bioactivity, possess a fascinating structural architecture, containing 4-6 rings and 7-10 contiguous stereocentres. A recent report by the Baran group has demonstrated a highly strategic and protecting group free synthesis of pallambins C and D, with their syntheses having been intentionally designed to eliminate extraneous redox operations and functional group interconversions.
The synthesis began with the abundant feed stock chemical furfuryl alcohol $74.1$ which is sourced from furfural that is a major biorenewable feedstock obtained from sugar cane bagasse. Tandem Eschenmoser-Claisen rearrangement and reduction of the resultant amide was carried out in a one-pot reaction to afford aldehyde $74.2$ (a significant improvement on the previous synthesis of aldehyde $74.2$). A Robinson annulation of aldehyde $74.2$ with ethyl vinyl ketone was then used to generate cyclohexenone $74.3$. 1,4-Vinyl cuprate addition of $74.3$, was followed by work-up with TMSCl to afford the activated TMS-enol ether $74.4$. Photosensitised chemoselective oxidative cleavage of the furan heterocycle resulted in keto-aldehye $74.5$ which was used in its crude form in the next step, as decomposition occurred during attempted purification. A titanium catalysed Mukaiyama aldol cyclisation of the TMS-enol ether fragment of $74.5$ onto its ketone fragment generated the pivotal bicyclo[3.2.1]octane skeleton of $74.6$. It is believed that the reaction proceeds via reaction at the less electrophilic methyl ketone group due to geometric constraints preventing the enol ether engaging with the aldehyde group. Intramolecular BF$_3$ catalysed acetal formation led to the spontaneous generation of the pyran ring to afford a mixed acetal, which on treatment with AcBr furnished bromide $74.7$. Halogen removal via treatment with AIBN/Bu$_3$SnH then afforded alkene $74.8$. Treatment of $74.8$ with LiHMDS and PhSeCl, followed by oxidation, afforded a selenoxide that underwent spontaneous elimination to afford $\alpha,\beta$-unsaturated ketone $74.9$. Subsequent acid catalysed methanol elimination then afforded the sensitive, but thermally stable dihydrofuran $74.10$. A new enol-ether difunctionalisation reaction, involving reaction of the tin-enolate of dimethyl malonate with dihydrofuran $74.10$, followed by addition of I$_2$ afforded the desired iodo-diester $74.11$. The final cyclisation sequence to generate the desired fused tetracycle was performed utilising a one pot sequence: (i) alkaline hydrolysis of the esters (2 M NaOH); (ii) Et$_3$N-induced lactonisation and decarboxylation; (iii) aldol addition to acetaldehyde, and (iv) elimination of the $\beta$-hydroxyl group using MsCl/NET$_3$ to give the desired pallambin C (Z alkene) and pallambin D (E alkene) in a 1:2 ratio (Scheme $74$). This impressive synthesis was completed in just 16 steps (11 one pot reactions), with only two steps not being involved in forming bonds present in the final natural products. While this is an elegant and efficient synthesis, it does however, utilise some undesirable reaction conditions. In particular the tin based reagents (Bu$_3$SnH, SnCl$_4$) are highly toxic and should be avoided wherever possible, while the use of phenylselenyl chloride is also highly toxic, leads to generation of stoichiometric amounts of toxic waste.
Scheme 74. Synthesis of Pallambins C and D
In conclusion, although protecting group free syntheses often require reaction ingenuity, invention and significant reaction optimisation, the end results more than justify the effort required, due to the significant reduction in the number of steps required, the improvement in atom economy and the reduction in the number of redox steps required. However, while there are many elegant protecting group free publications emerging, it should be noted that the vast majority of these natural product syntheses do not contain multiple free hydroxyl groups, or other functional groups that have highly acidic protons. This clearly highlights an area of natural product synthesis where there is still room for further development.

5.0 Polyketides

5.1 Introduction to Polyketides

Polyketides are an enormous class of natural products synthesised by a wide range of organisms; bacteria, fungi and plants. They are biosynthesised through a series of polycondensation reactions using simple carboxylic acid donors in the form of their corresponding thioesters; acetyl-SCoA, propionyl-SCoA and malonyl-SCoA. These polycondensation reactions are performed by a range of polyketide synthases (PKS) to form a series of acyclic or cyclic molecules, containing contiguous stereocentres, with a simplified representation of their biosynthesis shown below (Scheme 75).

![Scheme 75. Biosynthetic pathway to polyketides](image)
In order to further exemplify this complex process, a ‘cartoon’ version of the erythromycin PKS assembly line is shown in Figure 12, in which circles depict enzymatic domains whose linker regions have been omitted for clarity. From this figure it can be seen that each of the DEBS (6-deoxyerythronolide B synthase) proteins contains two functional units or modules. Each module contains the three domains required to catalyse one cycle of chain extension (ketosynthase (KS), acyltransferase (AT) and acyl carrier protein (ACP)) as well as a variable set of domains (ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER)) associated with functional group modification. Throughout the entire biosynthetic sequence, the polyketide chains remain bound to the PKS. The three essential domains KS, AT and ACP, co-operate to catalyse carbon–carbon bond formation by Claisen condensation, which results in a β-keto ester intermediate. The variable set of domains positioned between the AT and ACP (depicted as a loop above the line of essential domains) carry out reductive modification of the keto group before the next round of chain extension.

Once the acyclic polyketides are synthesised, further enzymatic transformations can be performed to produce a bewildering array of natural products, including those containing cyclic, acyclic, small, large, simple, aromatic, and highly complex structures (Figure 12 and Figure 13).
Figure 12. Domain organisation of the erythromycin polyketide synthase \cite{72}
Due to the large variety in their structure, polyketides exhibit a wide range of biological activities including; antibiotic, cancer chemotherapeutic, antifungal and cholesterol lowering agents. There are around 10000 known polyketide structures, however, this number is ever increasing with new natural product sources being discovered almost daily. Of these compounds about 1% have been shown to possess useful drug activity, which is about five times higher than the average normally found for natural products. This highlights that polyketides are a potentially excellent source of lead compounds for the discovery of future drug molecules.

Polyketides can be grouped into three smaller subclasses; fatty acids, polypropionates and aromatic polyketides. Although these groups are structurally diverse, there are several structural features which are common among many polyketides, including the stereotetrad motif shown in Figure 14.
The presence of four contiguous stereogenic centres gives rise to the possibility of eight stereoisomeric combinations occurring as fragments within the structure of a polyketide natural products (Figure 15). Indeed, all of these tetrad combinations are known to be present in polyketide natural products.\(^\text{169}\)

![Figure 14. General structure of a stereotetrad](image)

Figure 14. General structure of a stereotetrad

![Figure 15. Possible diastereomeric combinations of the stereotetrad](image)

Figure 15. Possible diastereomeric combinations of the stereotetrad

Although, polyketides containing these stereotetrad fragments are abundant in nature, their stereoselective synthesis still represents a formidable challenge to chemists, who have developed an armamentarium of synthetic strategies that they currently employ for their preparation. Consequently, the following section briefly reviews methodology that has been employed for the synthesis of representative polyketide natural products.

### 5.2 Synthesis of Ionomycin

Ionomycin (Figure 16) is a polyether antibiotic containing an *anti, anti, anti* stereotetrad which was first isolated in 1978 from the fermentation broths of *Streptomyces congoblatus*.\(^\text{173}\)

Ionomycin is able to chelate to inorganic cations, with a particular affinity for calcium. This allows ionomycin to act as an ionophore to transfer cations across cell membranes,\(^\text{169, 175, 176}\) which has made it an important molecule in neurochemical research.\(^\text{169}\)
There have been a number of total syntheses of ionomycin starting in 1990 by the Evans group\textsuperscript{177} which based their synthesis on the use of chiral auxiliaries to achieve stereocontrol. The Evans auxiliary methodology utilises an iterative approach to build up vicinal stereocentres, whereby small fragments are gradually lengthened and functionalised through addition and removal of chiral auxiliaries to confer stereocontrol to aldol/alkylation reactions. This methodology allows for high levels of stereocontrol of these aldol reactions, and as such has become one of the most widely used methods for the synthesis of highly complex acyclic polyketides. However, it must be recognised that it is inherently wasteful due to the use of multiple stoichiometric auxiliary steps. Which cause extra steps introducing and removing the chiral auxiliary fragment (Scheme 76).

The synthesis of key fragment 76.11 that was employed for the synthesis of ionomycin can be used to illustrate this. The boron enolate of norephedrine-based auxiliary 76.1 was reacted with acetaldehyde to afford aldol adduct 76.2 in 93\% yield and >98\% de. The secondary alcohol was then O-silyl protected prior to auxiliary removal,\textit{via} treatment with LiO\textsubscript{Bn} to afford benzyl ester 76.3. The ester functionality was then reduced to the primary alcohol and subsequently re-oxidised to the aldehyde 76.4. Wittig olefination of 76.4 with ylide 76.5, followed by ester reduction and subsequent iodination gave alkyl iodide 76.6. Alkylation of the sodium enolate of \textit{N}-propionyl-oxazolidin-2-one 76.1 afforded carboximide 76.7, the auxiliary fragment of which was then reduced to give primary alcohol 76.8. A Swern oxidation and Wittig olefination with ylide 76.9 then afforded diene 76.10. Silyl ether cleavage with HF\textsubscript{aq}, was then followed by a stereoselective rhodium catalysed hydrogenation reaction to reduce the alkene
functionality, with a final alcohol oxidation step then affording the key $\text{C}_1$-$\text{C}_{10}$ fragment 76.11 (Scheme 76). This part of the synthesis is a good example of how Evans auxiliaries are deployed in natural product synthesis. While they offer excellent diastereoselective control, their inclusion and removal considerably lengthens the synthesis. Furthermore, there are normally a number of redox manipulations (5 in a 15 step synthesis), including the global reduction of an ester followed by re-oxidation back to the aldehyde. While this approach can keep the yield high it is an incredibly wasteful method.

Scheme 76. Evans auxiliary methodology used for the synthesis of a key fragment 76.11 used for the synthesis of ionomycin
A more recent synthesis by Lautens et al. in 2002\textsuperscript{175} based their stereotetrad methodology on ring opening strategies which are shown below in Scheme 77-Scheme 80. Their synthesis began with the symmetric oxabicyclic-[3.2.1]-alkenes \textbf{77.1} and \textbf{78.1} whose synthesis had previously been developed within their group, with each bicycle being used to synthesise separate fragments of the final compound. Oxabicyclic-[3.2.1]-alkene \textbf{77.1} was treated with a chiral nickel BINAP system to reductively desymmetrise the oxabicyclic ring to give alkene \textbf{77.2} in excellent yield (95%) and 93-95% ee. The alcohol stereocentre was then inverted via a 2-step oxidation/reduction protocol, followed by O-PMB protection to afford the protected diol \textbf{77.3}. Cleavage of the alkene via ozonolysis, followed by aldehyde reduction afforded acyclic diol \textbf{77.4}. Oxidative cyclisation of \textbf{77.4} using DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) gave cyclic PMP acetal \textbf{77.5}. The remaining unprotected primary alcohol was then \textit{O}-trityl protected, and the acetal reductively cleaved to give alcohol \textbf{77.6}, which was then oxidised using a Swern oxidation reaction to give the desired aldehyde \textbf{77.7} (Scheme 77).

\begin{center}
\textbf{Scheme 77. Synthesis of aldehyde fragment 77.7\textsuperscript{175}}
\end{center}
Synthesis of the ketone fragment 78.11 began with the symmetrical unprotected alcohol 78.1 that was also used as a substrate for reductive desymmetrisation. A palladium catalysed asymmetric ring opening reaction afforded diol 78.2 in high yield (80%) and excellent 94% ee. The alcohol groups of diol 78.2 were then selectively protected with silyl and PMB protecting groups to give protected diol 78.3, with ozonolysis followed by reduction affording acyclic $\alpha$-diol 78.4. Oxidative cyclisation to afford a cyclic PMP acetal, followed by $O$-silyl deprotection gave acetal 78.5. Treatment of acetal 78.5 with TCDI (thiocarbonyl diimidazole) protected the 1,3-diol fragment to afford cyclic thiocarbonate 78.6. A radical mediated reduction reaction selectively gave primary alcohol 78.7; which was then oxidised to its corresponding aldehyde followed by a Wittig reaction to give $\alpha,\beta$-unsaturated ester 78.8. Hydrogenation of 78.8 resulted in both the alkene bond being reduced and cleavage of the PMP acetal to give diol 78.9. A second thiocarbonate formation and radical catalysed deoxygenation then reaction gave primary alcohol 78.10. Subsequent oxidation of 78.10, Grignard addition of MeMgBr and a further oxidation step then gave the desired ketone fragment 78.11 (Scheme 78).
The Lautens synthesis also required synthesis of the key furan fragment 79.7. Its synthesis began with allylic oxidation of the terminal methyl group of geranyl acetate 79.1 using SeO₂, followed by Appel bromination of the resultant alcohol to give allyl bromide 79.2. Alkylation of the enolate of a sulfone with allyl bromide 79.2 with concomitant removal of its acetate group, gave alcohol 79.3. Sharpless asymmetric epoxidation reaction and tosyl protection of the primary alcohol afforded tosylate 79.4. Acid catalysed epoxide ring opening and secondary alcohol O-silyl protection then afforded the protected triol 79.5. A vanadium catalysed oxidative furan ring forming reaction was then carried out to afford tetrahydrofuran 79.6. Iodination and subsequent radical catalysed dehalogenation was then followed by alcohol silyl protection to give the key sulfone fragment 79.7 (Scheme 79).
Once these fragments had been prepared, then they were combined to give ionomycin. The enolate of sulfone 79.7 underwent coupling with aldehyde 77.7 to give the alcohol 80.1 which was then oxidised to afford ketone 80.2. The sulfone moiety of 80.2 was then reductively cleaved using samarium iodide, followed by DDQ mediated PMB deprotection to obtain alcohol 80.4. Treatment with samarium iodide and benzaldehyde gave β-hydroxy benzoate 80.5, with no other regioisomer being formed. The alcohol group of 80.5 was then activated for cyclisation by tosylation, followed by O-TMS deprotection, to afford a crude hydroxy tosylate that was treated with sodium hydride to construct the second ring of bis-tetrahydrofuran compound 80.6. Trityl deprotection, followed by oxidation then afforded aldehyde 80.7, which underwent a modified Julia coupling with sulfonamide 80.8 to give alkene 80.9. PMB deprotection of 80.9
gave alcohol 80.10, followed by Swern oxidation to a ketone, and aldol coupling with the boron enolate of ketone 78.11, with a further alcohol oxidation step then affording hydroxy alkene 80.11. Subsequent removal of the remaining three protecting groups, followed by ester hydrolysis afforded ionomycin (Scheme 80) in a 5.6% overall yield.

While the Lauten synthesis of the complex natural product ionomycin is highly impressive, utilising a wide range of elegant chemistry, the synthetic route is clearly not perfect. It has a heavy reliance on protecting group chemistry, with the use of 25 protection/deprotection steps dramatically increasing the number of synthetic steps and amount of waste and by-products produced. It is also a very redox reliant synthesis, with a large number of oxidation and reduction steps being employed, with a number of redox processes occurring at the same carbon position! During the synthesis of ketone fragment 78.11 there are also two deoxygenation steps to give alcohols 78.7 and 78.10 respectively, with this process involving removal of previously installed stereocentres.
Scheme 80. Synthesis of ionomycin\textsuperscript{175}
The recent ionomycin synthesis by the Kocienski group in 2009\textsuperscript{176} is similar to the Lautens synthesis with respect to the strategy of assembling ionomycin from four very similar fragments, however, these fragments were obtained in a much more efficient manner (Figure 17).

\begin{center}
\textbf{Figure 17. Kocienski retrosynthetic fragmentation of ionomycin}\textsuperscript{176}
\end{center}
The most impressive fragment synthesis was that employed for the preparation of bis-hydrofuran 81.4, which was constructed in the following manner. Allene 81.2 was obtained from alkyne 81.1 via a stereoselective copper(I)-mediated *anti*-selective *S*₂ reaction, which after deprotection of the tetrahydropyranyl group using PPTS (pyridinium *p*-toluenesulfonate) gave diol 81.3. Diol 81.3 then underwent highly stereoselective gold(III) catalysed cycloisomerisation of its *α*-hydroxyallene fragment to afford 2,5-dihydrofuran 81.4 (Scheme 81). This catalytic construction of the second hydrofuran ring was far more efficient than approaches employed in previous syntheses (Scheme 79).

While this synthesis clearly is an improvement upon previous attempts, it still cannot be considered to really provide a viable route for the large scale production of ionomycin, with an overall yield of only 0.68% being achieved over the 33 step synthesis.

### 5.3 Synthesis of Pironetin

Pironetin (Figure 18) was first isolated independently, by two Japanese groups in 1993 from the fermentation broths of both *Streptomyces* sp. NK10958 and *Streptomyces prunicolor* PA-48153, Pironetin is an unsaturated δ-lactone attached to a *syn, anti, syn.* stereotetrad. It was originally of interest due to its plant growth regulatory and immunosuppressive activities, however, more recently it has also been identified as a strong antitumor agent. It has been
synthesised a number of times, the first of which was by Yasui et al.\textsuperscript{178} in 1995 (shown in red). This first synthesis was then quickly followed by those of Gurjar et al. (shown in green)\textsuperscript{182} and Chida et al. (shown in blue)\textsuperscript{183}

![Figure 18. Selected syntheses of Pironetin](image)

A more recent impressive synthesis of pironetin is that by the Cossy group.\textsuperscript{181} Compared to previous syntheses it is much more concise, achieving the final product in only 14 steps from the commercially available starting material (S)-Roche ester 82.1 (Scheme 82).

(S)-Roche ester 82.1 was tosyl protected followed by reduction of its ester functionality with DIBALH which afforded aldehyde 82.2. This aldehyde was then subjected to a diastereo- and enantioselective crotonylation reaction using chiral titanium complex [Ti]\textsuperscript{1*} to generate the homoallylic alcohol, which was subsequently O-methylated to give alkene 82.3. Ozonolysis of
the alkene bond of 82.5 followed by a further diastereoselective allylation reaction using chiral titanium complex [Ti]²⁺ gave alcohol 82.4. O-Silyl alcohol protection was followed by treatment with a lithium acetylide ethylenediamine complex to introduce the terminal alkyne functionality of alkyne 82.5. Once the terminal lithium anion of alkyne 82.5 was methylated, its alkene functionality was dihydroxylated with osmium tetroxide to afford a diol which was then oxidatively cleaved with sodium periodate to give aldehyde 82.6. A stereoselective boron-mediated pentenylation reaction using cis-2-pentene was then carried out to afford alkene 82.7, acylation of its alcohol gave bis-alkene 82.8. The diene functionality of 82.8 then underwent a ruthenium catalysed hydrosilylation reaction, followed by a RCM (ring closing metathesis) reaction and acid mediated protodesilylation to give pironetin in an impressive overall yield of 8.2%
While this is clearly an impressive synthesis there are still a number of steps that are still less than ideal. For example, the two diastereo- and enantioselective crotonylation steps to...
obtain 82.3 and 82.4 proceed through the use of a stoichiometric amounts of chiral titanium and boron reagents, which considering their level of complexity and cost would prevent this synthesis from being conducted on a large scale. Furthermore, allylation of 82.2 is immediately followed by ozonolysis, resulting in the cleavage of a C1 carbon fragment, which had previously been installed as part of a C3-allyl unit. There is also a loss of ethylene associated with the RCM reaction, which also affects the overall atom economy of the synthesis. The synthesis also contains an alkyne hydrosilylation reaction and subsequent protodesilylation step for this RCM strategy to be effective. All of these requirements have a considerable impact on the efficiency and cost of this synthesis, resulting is an overall atom economy for this synthesis of only 6.6%.

5.4 Synthesis of Spirodienal A

Spirodienal A (Figure 19) is a spiroketal that was isolated from fermentation broths of the myxobacteria Sorangium cellulosum in 2009,184 which was shown to exhibit potent antibiotic and cytotoxic activity.184

![Spirodienal A](image)

*Figure 19. Spirodienal A*

The first total synthesis of spirodienal A was completed by the Ley group in 2014.185 Synthesis was conducted predominantly in flow systems which were proposed to allow for high levels of control and the use of otherwise ‘challenging’ conditions; including high pressure; the use of gaseous reagents; and the use of highly toxic reagents – all of which led to a highly convergent and efficient approach.185

Synthesis began with 2,3-butane diacetal protected aldehyde 83.1 which underwent a solid supported Wittig reaction, where the ylid reagent 83.2 was supported on a monolith. This
approach meant that upon reaction completion, the triphenylphosphine oxide by-product was left attached to the monolith and could be simply filtered off, vastly improving the ease of purification. The resultant α,β-unsaturated ester 83.3, was then hydrogenated at 20 bar utilising Pfaltz’s iridium catalyst to afford methyl ester 83.4. A protecting group switch led to the formation of acetal 83.5. The methyl ester of 83.5 was then reduced to aldehyde 83.6 using DIBALH which was immediately reacted with the stoichiometric amounts of chiral tartrate derived crotylation reagent (R, R)-83.7, to give the key homoallylic alcohol intermediate 83.8. All of the reactions from aldehyde 83.1 to alkene 83.8 were conducted entirely in flow in an overall 73% yield (Scheme 83).

With homoallylic alcohol 83.8 in hand, the synthesis then diverged into a parallel synthesis, to form the two coupling partners aldehyde 84.10 and dialkyne 85.8 (Scheme 84 and Scheme 85).

To acquire aldehyde 84.10, the homoallylic alcohol 83.8 was O-silyl protected and then subjected to ozonolysis to give aldehyde 84.1. This was then reacted with the crotylation reagent (S, S)-83.7 to give the homoallylic alcohol 84.2. Silyl deprotection and acetal protection of the resultant diol fragment were performed simultaneously through the use of polymer supported sulfonic acid to give the diacetal 84.3. Ozonolysis, followed by borohydride reduction afforded alcohol 84.4, which was then O-silyl protected to give the fully protected polyol 84.5. A two-step batch sequence was then required to achieve aldehyde 84.6 involving selective hydrolysis of the
external acetal to afford the corresponding vicinal diol, which then underwent periodate oxidative cleavage to afford aldehyde 84.6. This aldehyde 84.6 was then subjected to a Seyferth-Gilbert homologation reaction through use of the Bestmann-Ohira reagent (dimethyl (diazomethyl)phosphonate) to afford alkyne 84.7. A copper catalysed hydrosilylation reaction on 84.7 gave the corresponding alkene 84.8, which underwent silyl-iodide exchange to give the corresponding allyl iodide, that was then subjected to a Pd(0) mediated Negishi cross-coupling with Me2Zn to give alkene 84.9. Silyl deprotection of 84.9 was followed by TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) catalysed oxidation to afford the desired aldehyde 84.10 (Scheme 84).
O-Silyl protection of intermediate homoallylic alcohol 83.8 with TESOTf/DIPEA resulted in cleavage of the acetonide ring to afford a primary silyl protected alcohol and secondary enol ether in situ (of the acetonide). The resulting alkene was then subjected to ozonolysis to oxidatively cleave the enol ether and terminal alkene to afford aldehyde 85.1. Propargylic
mesylate 85.2 was then used as a substrate to generate a chiral allenylzinc reagent in situ which was reacted with aldehyde 85.1 through an SE2’ mechanism to afford alkyne 85.3. Silyl deprotection using polymer supported sulfonic acid and selective protection of the two secondary alcohols via acetal formation, was followed by a TEMPO oxidation of the terminal alcohol to afford aldehyde 85.4. A monolith supported Wittig olefination was then carried out to afford dibromo alkene 85.6. Reductive acetate cleavage followed by further silyl deprotection afforded acetal 85.7, which upon treatment with n-BuLi gave the desired bis-alkyne functionality of 85.8 via a Corey-Fuchs reaction (Scheme 85).
Of all the previous steps used to the coupling intermediates, all except 5 transformations were conducted in flow (marked in schemes), however, some synthetic steps were unable to be conducted in flow and were instead completed using traditional “batch” conditions. However, it can also be argued that this synthesis represents one of the worst cases of the ‘abuse’ of protecting group usage, with 14 of the 26 synthetic steps used to generate coupling
intermediates 84.10 and 85.8 involving either formation or removal of a protecting group! There are also 10 oxidation/reduction reactions, and this along with the high use of protecting groups, obviously has a huge detrimental effect on the efficiency and sustainability of the synthesis.

The synthesis of spirodienal A was completed through the use of the following batch techniques. Treatment of the bis-alkyne 85.8 with n-BuLi followed by addition of aldehyde 23.10 gave alcohol 86.1, which was subsequently oxidised to the ynone and stereoselectively reduced using the chiral Corey-Bakshi-Shibata reagent 86.2. The chiral ynal was then methylated followed by global deprotection via sequential treatment with TBAF and a polymer supported acid to afford pentol 86.3. Spiroketalization was then induced using gold catalysis to give spiroketal 86.4 in only moderate yield (30%). This kind of low yield towards the end of a natural product synthesis can be disastrous, as it results in the loss of 70% of painstakingly made material. Spiroketal 86.4 then underwent a Sonogashira reaction with vinyl iodide 86.5 to give alcohol 86.6. Which was subjected to a mixed metal (Zn/Cu) catalysed cis-selective alkyne reduction reaction to afford a diene fragment, followed by alcohol oxidation to afford the aldehyde functionality of spirodienal A (Scheme 86).
This synthesis of spirodienal A was conducted in a divergent manner to try and maximise efficiency by which analogues of the parent natural product could be synthesised. This synthesis by the Ley group is an exciting example of modern natural product synthesis that illustrates the
potential of using flow synthesis for the preparation of complex molecules. However, the use of these expensive flow-systems is currently limited to academia and research labs. With few syntheses having been reported ‘on-scale’. Furthermore, their use can be restrictively expensive, with liquid-liquid extraction equipment being expensive and having a high running cost, whilst optimisation of flow transformations can be lengthy and consume a lot of substrate. A necessity of flow chemistry is the use of scavenger or polymer supported reagents to ensure that material of sufficient purity is available to be taken on to the next step. This potentially creates a stoichiometric amount of waste, and whilst these scavenger and polymer supported reagents can be regenerated, these processes often comes with a large energy and commercial cost.

6.0 Conclusion

Huge advances have been made since the dawn of natural product synthesis, with organic chemists given enough time, resource and manpower now being able to synthesise even the most complex molecules. However there is still room for improvement, particularly in the efficiency of reactions, and design of syntheses to embrace the ethos of sustainable chemistry, with the aim of minimising the number of protection/deprotection steps and maximising the number of catalytic rather than stoichiometric reactions used. There are also a number of other aspects that should be considered when trying to move towards a “perfect” synthesis. These include minimising the number of redox steps, maximising yield, use of biorenewable substrates, development of convergent synthetic strategies, invention of new reactions, and the target of crystalline intermediates to facilitate purification. A focus should also be placed on performing reactions at room temperature, under atmospheric conditions using “green” solvents.¹⁰⁹
7.0 A Protecting Group Free Strategy towards the Sustainable Synthesis of Polypropionate Fragments

7.1 Results and Discussion

Organic synthesis has evolved immensely over the last 100 years to afford an impressive arsenal of reactions and techniques for the synthesis of a wide range of complex molecules. As described in the preceding chapter, this has led to many ‘state-of-the-art’ syntheses of important medicinally active compounds that can be considered to be at the forefront of 21st century scientific development. However, despite the elegance of many of these synthetic protocols, methods for the synthesis of polyketide derivatives are far from optimal, with multistep synthetic routes often requiring protecting groups, stoichiometric and/or undesirable reagents, and harsh reaction conditions that afford low yields. 98, 109, 172

This offers the opportunity to develop alternative more efficient ‘protecting group free’ strategies for the synthesis of chiral building blocks for polyketide natural products. As mentioned earlier a key structural feature of polyketides are the presence of polypropionate (stereotetrad) fragments, with these structural motifs having been the target of a number of synthetic methodologies (Figure 20). One of the most important of these is the aldol reaction, with extensive work by Evans186-190 and Paterson191-194 allowing for regio-, stereo-, and enantioselective carbon-carbon bond forming reactions to be performed under either chiral auxiliary or substrate control (e.g. through the use of boron enolates for Evans aldol reactions and for Paterson anti-aldol reactions). A further use of the aldol reaction is the Mukaiyama aldol addition,195 utilising silyl enolates of ketones that add to aldehydes with excellent levels of stereocontrol.

As well as the aldol reaction there are a number of other well established methodologies for the construction of polypropionate fragments, including, the reductive aldol reaction,196-200 crotylation,201-208 allenylation,209-212 epoxide ring opening,213-216 thiopyran chemistry,217, 218 [2+2] cycloaddition reactions,219-223 and sequential substitution reactions (Figure 20).224-227
The aim of this project was to develop a sustainable synthetic route to polyketide natural product fragments using a protecting group free strategy. Based on the use of a Lewis acid (LA) catalysed enantioselective hetero-Diels-Alder (HDA) reaction to construct a six-membered dihydropyran ring. This ring could then be derivatized in a number of ways, one of which would be hydroboration to afford a chiral pyran as a masked stereotetrad containing four contiguous stereocentres that was ideally suited for natural product synthesis (Scheme 87). It was envisaged that derivatisation of dihydropyran 87.3 using a range of different chemistries would result in a range of useful chiral building blocks. These could then be used for the synthesis of a range of polyketide natural products (and their analogues), in a “plug and play” manner.
This strategy was inspired by some of the ground breaking work carried out by the Danishefsky group. Their work also focused on development of new synthetic methodology for the synthesis of polypropionate, based on cyclo-addition reactions of Danishefsky type dienes 88.1 with an appropriate aldehyde, which gave rise to silyl enol ether 88.3, or α,β-unsaturated ketone 88.4. They showed that application of a series of selective derivatisation reactions to 88.3 and 88.4, enabled a series of highly functional pyran rings 88.5, containing four chiral centres to be prepared (Scheme 88).
This elegant methodology has since been applied to a range of syntheses, including complex polyketide natural products and saccharides, where stereochemical control is achieved through derivatisation of cyclic structures using simple reagents, which would not be possible using an acyclic substrate.229-241 Once the derivatized pyran has been constructed cleavage of the ring can be easily achieved by exploiting the masked aldehyde character of the hemi-acetal linkage. “Hence both the construction and the disassembly of the cyclic edifice need not add steps to the total program and, therefore, need not be regarded as contrivances” (S. Danishefsky).229 Two examples of where this methodology has been applied for the synthesis of polypropionate fragments towards natural product synthesis are shown below.

The first example is the synthesis of lactone 89.6, which is a subunit of monensin (a polyether antibiotic). A ytterbium catalysed cycloaddition reaction of aldehyde 89.1 and Danishefsky diene 89.2, affords silyl enol ether 89.3. Treatment of 89.3 with HF resulted in silyl deprotection to afford ketone 89.4, which was then reduced to its corresponding alcohol. Methylation of this alcohol followed by acetal cleavage gave lactol 89.5. Treatment of lactol 89.5 with catalytic ruthenium dioxide in the presence of NaIO₄ afforded a crude lactone acid which was then esterified with diazomethane to afford racemic lactone 89.6 (Scheme 89).
A second selected example is the synthesis of aldehyde 90.6, as a masked polypropionate fragment present in migrastatin, which is a natural product that has anti-cancer properties. A titanium catalysed diene aldehyde cyclocondensation reaction of aldehyde 90.1 (4 steps from dimethyl tartrate) and Danishefsky diene 90.2 gave α,β-unsaturated ketone 90.3. Luche reduction of ketone 90.3 afforded an allylic alcohol which underwent an aqueous Ferrier arrangement to give lactol 90.4. Reduction of lactol 90.4 with LiBH₄ afforded the acyclic diol 90.5, with selective acetate protection of the primary alcohol functionality being followed by O-silyl protection of the secondary alcohol. Acetate removal and subsequent alcohol oxidation then afforded the core polypropionate fragment 90.6 (Scheme 90).²²⁹
It was proposed to modify this powerful methodology for the synthesis of a range of complex enantiomerically enriched pyran based building blocks, that could be accessed in a highly efficient manner, that would be ideally suited for the synthesis of polyketide natural products through a “plug and play” approach. If the structure of the advanced alcohol intermediate 90.5 is considered, then a retrosynthetic analysis can be performed to highlight how our proposed methodology was envisaged to proceed. Lactol 90.4 could potentially be accessed from dihydropyran 91.1, with the presence of the terminal alkene allowing for late stage derivatisation. This alkene unit could be introduced via addition of a vinyl Grignard reagent to the corresponding aldehyde 91.2. Aldehyde 91.2 could then be accessible directly from an enantioselective HDA reaction of 1-alkoxy diene 91.3 with methyl glyoxalate, the ester group of which would function as a synthetic handle for subsequent derivatization (Scheme 91).
7.2 Diene Synthesis

The diene 91.3 shown below (Figure 21) was identified as the target starting material for this methodology, however, a review of the literature revealed that routes for the preparation of 1-alkoxy dienes were somewhat limited. This resulted in the synthesis of this target diene becoming problematic, and significant effort was expended to identify an efficient route for their synthesis.

Initial attempts were based on the use of a strong electrophilic methylating agent, such as Meerwein’s salt (Me₃OBF₄), which we hoped would react with the α,β-unsaturated aldehyde
in the presence of base, to form the desired enol ether. However, this proved to be unsuccessful with no product formation being observed via $^1$H NMR analysis (Scheme 92).

Scheme 92. Unsuccessful synthesis of diene 91.3

Multiple attempts were made along these lines with no success, with attempts at other elimination strategies also proving fruitless. Examination of the literature revealed that one successful approach for the synthesis of small diene molecules was the use of Wittig olefination.\textsuperscript{242} From this precedent, two carbonyl species were identified as potential targets, 93.1 and 93.2, with the aim of using them as substrates for a Wittig olefination reaction to obtain the desired diene 91.3 (Scheme 93).

Scheme 93. Proposed Wittig synthesis of diene 91.3

It was decided proceed with diene synthesis using an anologue of aldehyde 93.1, since protocols for the synthesis of 3-ethoxy-2-methyl-2-propanal 94.2 were known in the literature. 3-Ethoxy-2-methyl-2-propanal 94.2 was formed by the reaction of propionaldehyde diethyl acetal 94.1 with POCl$_3$ via a Vilsmeier-type reaction (Scheme 94).\textsuperscript{243, 244}
This reaction is proposed to proceed via a similar mechanism to the classical Vilsmeier reaction. Protonation of acetal 94.1 is followed by elimination of ethanol to give vinyl ether 95.3, which then reacts with chloroiminium 95.2, to afford oxonium 95.4. This oxonium species 95.4 then eliminates chloride to give iminium species 95.5, which is then hydrolysed to afford aldehyde 94.2 (Scheme 95).

In our hands, formation of aldehyde 94.2 proceeded with 100% E-selectivity, with this aldehyde then being carried forward to complete the desired diene synthesis via Wittig
olefination with ethyltriphenylphosphonium bromide in the presence of LDA as a strong base. Purification by distillation gave the desired diene 96.1 in good yield and in a ratio of 15:1 (1E,3E):(1E,3Z), as assigned by $^1$H NMR spectroscopic analysis (E, E)-isomer (δ 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CH=CHCH$_3$)) (E, Z)-isomer (δ 5.31 (qd, J = 7.2, 11.7 Hz, 1 H, CH=CHCH$_3$)). However, to our delight, when this mixture of geometric isomers was left at room temperature for two days, it was found to equilibrate in favour of its thermodynamically favourable (1E,3E)-isomer in a ratio of 50:1.

Concurrent to the syntheses described above, an alternative synthetic strategy to diene 96.1 was investigated. An interesting report from the literature caught our attention involving the synthesis of acetal and carbonyl substituted allyl chlorides from α,β-unsaturated acetals, which was proposed to proceed through alkoxy diene 97.2 (Scheme 97). It was reported that treatment of α,β-unsaturated acetal 97.1 with an excess of n-butyl lithium and potassium tert-butoxide (known as LICKOR), afforded diene 97.2, which in the presence of excess base and methyl iodide gave the substituted diene 97.4. Addition of N-chlorosuccinimide, base and methanol then gave the acetal substituted allyl chloride 97.5.

Scheme 96. Synthesis of (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene
It was hoped that the first step of this methodology (97.1 to 97.2) could be applied for the synthesis of our target diene 96.1. Therefore, synthesis of α,β-unsaturated acetal 98.2 from α,β-unsaturated aldehyde 98.1 was achieved through treatment of α,β-unsaturated ketone 98.1 with triethyl orthoformate and ammonium nitrate, in 95% yield. The conditions of the LICKOR mediated elimination reaction were adjusted for use with α,β-unsaturated acetal 98.2; with increased amounts of base, extended reaction time and elevated temperatures required, when compared to the literature procedure (Scheme 98). Diene 96.1 was isolated in 60% yield, affording a second viable route to the necessary diene. This route proved to be a significant improvement, with many of the reagents employed for synthesis accessible from biorenewable starting materials.

For example, propionaldehyde 99.1 is readily obtained from biorenewable propanol. Consequently, an aldol self-condensation reaction was carried out to afford α,β-unsaturated aldehyde 98.1 in 85% yield, with the reaction proceeding as a biphasic mixture, allowing for easy work up and purification. Acetal formation was achieved in the same manner as above, through
the use of ammonium nitrate which is commonly used as a high nitrogen fertiliser, and as such is available at large quantities and in low cost. More benign conditions were then developed to carry out elimination of 98.1 to 96.1. It has been reported that use of solutions of potassium tert-butoxide in dimethyl sulfoxide results in a highly basic system.\textsuperscript{246, 247} This is believed to occur due to the solvent strongly complexing with the potassium cations, producing an activated ligand-separated and dissociated tert-butoxide anion in a medium of high dielectric constant.\textsuperscript{246} This base system is known to be a powerful reagent for carrying out β-elimination reactions,\textsuperscript{246, 247} and its application to the elimination of 98.2 proved successful affording diene 96.1 in 80% yield (Scheme 99).

With diene 96.1 obtained in synthetically useful quantities, our attention then turned to development of asymmetric hetero-Diels-Alder methodology to synthesise dihydropyran 87.3.

### 7.3 Hetero-Diels-Alder Chemistry

Since its discovery in 1928, by Otto Diels and his then student Kurt Alder,\textsuperscript{248-250} the Diels-Alder reaction has become one of the cornerstone reactions of organic chemistry for the construction of six membered rings.\textsuperscript{249} The conventional Diels-Alder reaction is a [4+2] cycloaddition reaction of a conjugated diene 100.1 and a dieneophile 100.2 (usually an electron deficient alkene) to form a cyclohexene ring 100.3 (Scheme 100).
Since its discovery, an understanding of the molecular orbital theory developed by Woodward and Hoffmann,\textsuperscript{251} has enabled the Diels-Alder reaction to be used for the asymmetric synthesis of compounds, with reactions often proceeding with excellent levels of region- and stereocontrol.\textsuperscript{252-254} A prominent example of this is the use of copper bisoxazoline catalyst \textsuperscript{101.3}, for the enantioselective Diels-Alder reaction of acrylimide \textsuperscript{101.1} and furan \textsuperscript{101.2} to afford cycloadduct \textsuperscript{101.4} in 67\% yield, which was achieved in 80:20 endo selectivity and 97\% ee.\textsuperscript{253} It is proposed that the chiral ligand of complex \textsuperscript{101.3} is able to create a stereoselective environment around the metal centre, that forces the furan dienophile to approach the diene from “below” the ligand, as shown for transition state \textsuperscript{101.5}.
A further development in Diels-Alder methodology was replacing the alkene as the dieneophile with a heteroatom containing dieneophile, in what has become known as the hetero-Diels-Alder (HDA) reaction. The HDA reaction is less well investigated than the original Diels-Alder reaction, but its synthetic utility is becoming increasingly recognised. One of the most notable areas where the HDA reaction has been well utilised is for the synthesis of monosaccharides, which was pioneered by the Danishefsky group, who developed HDA methodology for their synthesis using Danishefsky type dienes, summarised in Figure 22.

![Chemical structures and reactions](image)

*Figure 22. Danishefsky’s route to totally synthetic hexoses*

An excellent example where this methodology has been applied to natural product synthesis is for the total synthesis of avermectin A₃A.
reaction of diene 102.1 (using L-phenylmenthol as a chiral auxiliary to introduce stereocontrol) and acetaldehyde 102.2 afforded the cycloadduct 102.3, which was oxidised with Mn(OAc)₃ to give dihydropyranone 102.4. Pyranone reduction with sodium borohydride in the presence of CeCl₃ afforded a vinyl alcohol that was O-methylated followed by acetate hydrolysis to afford alcohol 102.5. Methoxybromination of 102.5 followed by debromination (using Bu₃SnH) afforded methyl glycoside 102.6. Reaction of methyl glycoside 102.6 with dihydropyran 102.7 (obtained from 102.4) with N-iodosuccinimide afforded the protected disaccharide 102.8, that proved to be a crucial fragment for the synthesis of the disaccharide fragment of avermectin A₅₆.

**Scheme 102. Total synthesis of avermectin A₅₆ using HDA chemistry**

1. NaBH₄, CeCl₃ 7H₂O, MeOH, 0 °C, 87%
2. Ag₂O, MeI, 91%
3. K₂CO₃, MeOH, 96%
HDA reactions involving a diene and a carbonyl dienophile proceed with normal electron demand, (HOMO of the diene overlap with LUMO of the dienophile Figure 23), however, hetero atom containing dieneophiles are generally not as reactive as alkenes for Diels-Alder chemistry. To overcome this, Lewis acids (LA) are often required to catalyse the reaction by improving overlap of the HOMO and LUMO orbitals of the respective diene and heterodienophile (Figure 24). The LA coordinates to a lone pair of the hetero atom of the dienophile acting as an electron withdrawing group to lower the energy of the LUMO orbital. This the energy of the LUMO of the dieneophile closer to the HOMO of the diene allowing for more efficient overlap and cyclisation to occur.

![Figure 23. Hetero-Diels-Alder reaction](image)

![Figure 24. Frontier molecular orbitals of Lewis acid catalysed HDA reaction](image)

The LA may not only act as a catalyst to facilitate the HDA reaction, but also presents an opportunity to confer further control over the reaction, with extensive work having been conducted into using chiral auxiliaries and chiral catalysts for achieving enantio- and diastereoselective control.\(^{249}\)
7.31 Dihydropyran Synthesis

Initial HDA studies were performed with the commercially available Jacobsen bidentate catalyst 103.1. This catalyst was chosen not only for the convenience of being commercially available, but it has also been shown in literature to be active for a range of asymmetric HDA reactions. It had been reported that HDA reaction between Danishefsky’s diene 90.2 and benzaldehyde 7.1 using this catalyst, followed by O-silyl cleavage with TBAF (tetra-n-butylammonium fluoride), gave chiral ketone 103.3 in 85% yield and 87% ee (Scheme 103). This reaction was successfully repeated to ensure the integrity of the commercial catalyst, successfully affording α,β-unsaturated ketone 103.2 in 80% yield and 85% ee.

\[ \text{Scheme 103. Literature example of using Jacobsen catalyst for an enantioselective HDA reaction}^{262} \]

1-Alkoxy dienes are known to be generally deactivated towards cycloaddition reactions, whilst diene 96.1 lacks the activating silyl enol ether fragment of diene 90.1, so therefore the choice of a reactive carbonyl reaction partner was important. Consequently, the carbonyl substrate chosen for HDA reaction with diene 96.1 was the activated aldehyde ethyl glyoxalate 104.1; which we proposed would afford a HDA adduct 104.2 that would be ideally suited for further synthetic elaboration.

The reaction proceeded with good diastereoselectivity producing two diastereomers 104.2 and 104.3 in a ratio of 11:1, the two diastereomers, which were separable by column chromatography allowing the single major diastereomer 104.2 to be obtained in 86% yield (Scheme 104).
The relative stereochemistry of the major diastereomer 104.2 was predicted to be syn, due to the endo selectivity normally observed for Diels-Alder reactions. However, confirmation was needed, the first piece of evidence was the difference in the coupling constants of Hd and He in the two isolated diastereomers 104.2 (J = 3.5 Hz) and 104.3 (J = 10.4 Hz). A large coupling constant of $J_{d,e} = 10.4$ Hz for dihydropyran 104.3 is characteristic of an axial-axial relationship, which would require both groups to be anti to each other. A small coupling constant on the other hand, such as $J_{d,e} = 3.5$ Hz for dihydropyran 104.2 is characteristic of a axial-equatorial relationship that would be expected if the protons had a syn-relationship. Another way of obtaining evidence of relative stereochemistry is through nOe (nuclear Overhauser effect) NMR experiments. If, as expected, the three protons Ha, Hd and He of the major diastereomer had a syn geometry, then nOe interactions would be expected between them, as represented for the major ring conformer shown in Scheme 105. Since nOe interactions occur by through space interactions between protons, these interactions would only be possible if the protons of the dihydropyran ring were on the same face (Figure 26). The use of coupling constants can also help assign relative stereochemistry.
In order to determine the relative stereochemistry by nOe NMR it is necessary that $^1$H NMR of the compound in question is fully assigned. The full assignment of dihydropyran 104.2 is presented below (Figure 25). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.71 - 5.68 (m, 1H, $H_c$), 5.09 (s, 1H, $H_a$), 4.34 (d, $J = 3.5$ Hz, 1H, $H_e$), 4.28 - 4.22 (m, 2H, CH$_2$), 3.87 (dq, $J = 9.6$, 7.0 Hz, 1H, $H_d$), 3.66 (dq, $J = 9.5$, 7.1 Hz, 1H, $H_d$), 2.48 - 2.42 (m, 1H, $H_d$), 1.66 (s, 3H, Me$^3$), 1.30 (t, $J = 7.1$ Hz, 3H, Me$^3$), 1.25 (t, $J = 7.1$ Hz, 3H, Me$^4$), 1.01 (d, $J = 6.9$ Hz, 3H, Me$^5$). Due to restricted rotation, the acetal ethoxy protons $H_f$ and $H_g$ of dihydropyran 104.2 are diastereotopic. This is confirmed by analysis of the NOESY spectrum which reveals an interaction between $H_a$ and $H_g$. Once full assignment has been made then inspection of the nOe spectrum allows the relative stereochemistry to be assigned.

*Figure 25. Assignment of $^1$H NMR of dihydropyran 104.1*
With the relative stereochemistry of dihydropyran 104.2 confirmed the enantiopurity was then determined. A genuine racemic sample of 104.2 was prepared using a racemic sample of catalyst 103.1. Enantiomeric excess was then determined using chiral GC, using a β-Dex column as the stationary phase. Unfortunately, the enantiomeric excess measured was found to be low at only 15% ee. In an attempt to improve this ee a number of changes were made to the reaction conditions, with an ultimately important modification being prior purification of ethyl glyoxalate 104.1. Ethyl glyoxalate 104.1 is commercially available as 50% solution in toluene. However, the glyoxalate is commercially available predominantly as its polymeric hydrate, rather than its aldehyde form. Consequently the glyoxalate was distilled/cracked under nitrogen and stored as a 50% solution in anhydrous CH₂Cl₂ at -20 °C to ensure it was present as its reactive aldehyde form. However, this change in this instance (and numerous other modifications), gave no improvement in ee.
These results were highly disappointing, and with the critical need to improve ee of the HDA reaction it was decided to investigate a different chiral catalyst. A catalytic system that had been used on a paramount, similar system was titanium-BINOL $^{106.3}$, which had been reported to catalyse the reaction of diene $106.1$ and methyl glyoxalate $106.2$, to afford the cycloadduct $106.4$ in 77% yield and 94% ee.

![Scheme 106. Mikami et al. HDA reaction using Ti-BINOL 106.3](image)

Catalyst $106.3$ was synthesised by addition of diisoproxytitanium dichloride $107.1$ to a stirred mixture of BINOL $107.2$ and 4 Å molecular sieves in anhydrous CH$_2$Cl$_2$. The reaction was stirred for 1 h and the molecular sieves allowed to settle overnight. The solution was then decanted from the molecular sieves utilizing Schlenk techniques, concentrated and the resultant residue was suspended in anhydrous pentane. The pentane was then removed via syringe and the residue dried under vacuum to give the titanium-BINOL complex $106.3$, which was stored under an inert atmosphere and used without further purification (Scheme 107).$^{242}$ Complete removal of the molecular sieves was shown in the original paper to be essential to achieve good enantioselective control over the reaction.

![Scheme 107. Synthesis of titanium-BINOL catalyst 106.3](image)
This new catalyst was then applied to the HDA reaction of diene 96.1 and purified ethyl glyoxalate 104.1, pleasingly this change had the desired effect, with very high enantioselectivity achieved of 99% ee. A small optimization study was carried out, which identified that use of diene 96.1 as the limiting reagent, resulted in the reaction proceeding to 104.2 as a single diastereomer in 65% yield and most importantly, in 99% ee (Scheme 108).

Scheme 108. Enantioselective synthesis of dihydropyran 104.2

Enantioselective induction from the BINOL ligand is believed to result from binding of the when the Ti-BINOL complex to glyoxalate to create a highly chiral environment around the aldehyde. This only allows the diene to approach from one face of the aldehyde, resulting in formation of both a single diastereomer and a single enantiomer (Figure 27).

Figure 27. Ti-Binol-glyoxalate transition state for the enantioselective synthesis of dihydropyran 104.2.
However, while this was an important step forward in validating this HDA project, it was found that different batches of Ti-BINOL 106.3 resulted in widely different ee’s of dihydropyran 104.2, ranging from 99% to 0% ee! In order to address this issue of reproducibility it was decided to subsequently synthesise Ti-BINOL catalyst 106.3 in a glove box to ensure the quality of the catalyst produced. This change was made under the assumption that the reaction and performance of the catalyst were highly sensitive to the presence of adventitious water. Pleasingly, this change in synthetic procedure rectified the reproducibility issue associated with using catalyst 106.3 in our HDA reaction, enabling access to gram quantities of enantiomerically enriched dihydropyran 104.2. Consequently our attention then switched to employing 104.2 as a chiral template for carrying out a series of diastereoselective derivatisation reactions to afford a library of chiral building blocks.

7.4 Dihydropyran Derivatization

It was proposed that subsequent reactions performed on the dihydropyran ring should proceed with a high level of diastereoselectivity due to its cyclic conformation, which ideally would mean that chiral reagents would not be necessary, with all the stereocontrol ultimately being controlled by the original enantioselective HDA reaction.

7.41 Hydroboration

The first reaction considered was hydroboration of the alkene functionality of 104.2; which would lead to the introduction of the desired hydroxyl group and the generation of two new stereocentres. There are a number of similar literature examples that suggested that this hydroboration reaction would occur with good facial selectivity. In particular, the seminal work of Danishefsky has demonstrated that good selectivity could be achieved for hydroboration reactions of dihydropyran 109.2, using simple hydroborating reagents such as borane (Scheme 109).237

![Scheme 109. Stereoselective hydroboration reaction of dihydropyran 109.2](image-url)
The hydroboration reaction of dihydropyran 104.2 proved to be successful and proceeded with good selectivity, affording a single diastereomer in 85% yield (Scheme 110).

\[ \text{Scheme 110. Stereoselective hydroboration of dihydropyran 104.2} \]

The borane approaches the alkene via its least hindered face and undergoes anti-Markovnikov addition, which upon oxidative workup affords pyran 110.1, whose hydroxyl group has an anti relationship relative to the other substituents, with the relative stereochemistry again being confirmed by NOESY NMR spectroscopic studies. Key nOe interactions between H₅, H₆, H₇ and H₈ confirm that all four protons are on the same face of the pyran ring, with H₈ not interacting with any of the other pyran protons other than H₇ due to their vicinal equatorial relationship (Figure 28).
The incorporation of a hydroxyl group not only creates two new stereocentres, but also gives the potential for further derivatization reactions towards the synthesis of a wide range of natural products, potentially making it a highly valuable building block. Hydroboration also results in the generation of a stereotetrad, which as mentioned previously is a highly common structural motif in polyketide natural products. For example, the diastereomer of pyran produced is stereochemically equivalent to the stereotetrad containing a syn, syn, syn relative stereochemistry, which is present in polyketide natural products such as Erythromycin A (Figure 29).
However, in order to gain complementary access to another diastereomeric tetrad it was decided to oxidise the hydroxyl group of 110.1 and then subsequently reduce the resulting ketone to afford an inverted hydroxyl functionality. The success of this method would rely on the inverted hydroxyl group product being produced via attack of the hydride from the least hindered face of the ketone functionality of pyranone 111.1. Therefore, alcohol 110.1 was oxidised to ketone 111.1 under Swern conditions, with the reaction proceeding well to afford pyranone 111.1 in 80% isolated yield. The ketone reduction was performed with sodium borohydride in ethanol at 0 °C to give the inverted alcohol 111.2 in a 95% yield (Scheme 111). Pleasingly, this reduction reaction proceeded to give a single diastereomer, confirming that pyran 111.2 could be successfully accessed as a sole diastereomer under kinetic control. Access to ketone 111.1 potentially presents an opportunity for carrying out other derivatisation reactions, via treatment with different nucleophiles to afford a range of natural and non-natural synthons.

7.411 Hydroxyl Inversion

Figure 29. Erythromycin A.
The relative stereochemistry of pyran 110.2 was again confirmed by nOe NMR spectroscopic studies, with key nOe interactions between H_a, H_b, H_c, H_d and H_e confirming that they are all present the same face of the pyran ring, and therefore have all syn-relationship (Figure 30).
The tetrad stereochemistry of pyran 111.2 produced is equivalent to the anti, anti, syn relative stereochemistry, which is found as a pair of enantiomeric fragments present in the natural product Aplyronine A (one of each enantiomer) (Figure 31).
7.42 Hydrogenation

We next targeted another derivatization reaction of dihydropyran 104.2 involving hydrogenation of the alkene functionality. This transformation was expected to proceed with good stereoselectivity, due to the mechanism of hydrogenation reaction; whereby the alkene substrate is adsorbed onto the heterogeneous metal catalyst surface, followed by syn addition of hydrogen across the double bond. However, initial hydrogenation attempts proved to be unsuccessful, instead unexpectedly affording acyclic bis-ester 112.1 as the sole product from the reaction (Scheme 112).

Scheme 112. Hydrogenation of 104.2 affording bis-ester 112.1
A proposed mechanism for this unexpected transformation is shown below in Scheme 113. Pd-H addition across the alkene bond of dihydropyran 104.2 affords a syn adduct 113.1. However, at low pressures of hydrogen, this process is reversible, enabling competing elimination of the Ha proton to afford alkene 113.2. Stereoselective protonation of the enol ether fragment of 113.1 affords an oxacarbenium species 113.3, which is then hydrolysed to give bis-ester 112.1 (Scheme 113).

Scheme 113. Proposed mechanism for the formation of bis-ester 112.1

As a consequence of this unexpected reaction, it was decided to perform the hydrogenation reaction in an aprotic solvent under a high pressure of Hydrogen, since a related literature example by the Danishefsky group suggested this might be successful. It was reported that when alkene 114.1 was subjected to a H₂ atmosphere of 50 PSI in the presence of
a palladium on alumina catalysts, it afforded the fully saturated pyran 114.2 in 80% yield (Scheme 114).

Scheme 114. Literature hydrogenation example

Under these conditions, the hydrogenation of dihydropyran 104.2 with palladium on alumina under an atmosphere of 50 PSI hydrogen for 24 h afforded tetrahydropyran 112.2 as a single diastereomer in 85% yield (Scheme 115).

Scheme 115. Synthesis of pyran 112.2

The relative stereochemistry of pyran 112.2 was once again confirmed by nOe interactions. The key nOe interactions that confirm the assignment of the configuration of the methyl group, are that of H_b which is shown to interact with both H_a and H_e confirming the relative stereochemistry of pyran 112.2 (Figure 32). Pyran 112.2 has been previously synthesised by the Evans group as its enantiomer,264 with a comparison of the analytical data confirming the
structure of pyran 112.2, as well as a comparison of the optical purity ([α]_D^{20} = +82, literature [α]_D^{20} -88 for opposite enantiomer).

Figure 32. NOESY NMR of pyran 112.1

Pyran 112.2 contains a polydeoxypropionate fragment which is also present in many natural products, with a tetrad fragment with the same relative configuration being present in the natural product bourgeanic acid (Figure 33).
7.43 Epoxidation

Epoxidation of alkenes is an important reaction in synthetic chemistry not only for generation of epoxides, but also for their synthetic capacity to introduce further functionality into a molecule. One of the most utilized methods of epoxidation is through the use of \(m\)-chloroperbenzoic acid (mCPBA). Initial attempts to epoxidise dihydropyran 104.2 were made using mCPBA, with the reaction proceeding well at 0 °C in four hours, using potassium carbonate as a buffer to prevent the chlorobenzoic acid by-product from ring opening the epoxide 116.1 product (Scheme 116). The relative stereochemistry of the resultant epoxide 116.1 can be explained due to the mCPBA approaching the double bond from the least hindered face. However, this methodology proved unreliable, with yields varying considerably when the reaction was repeated on scale, and with isolation of epoxide 116.1 proving problematic.
Due to these issues it was decided to try and identify an alternative epoxidation method for trisubstituted alkenes. An example that came to our attention was the methodology described by Venturello and Noyori, who have both published excellent methods employing H$_2$O$_2$ and in situ-generated, or preformed metal complexes. The most commonly employed catalyst is a tungstate complex, composed of quaternary ammonium tetrakis(diperoxotungsto)phosphates (-3), which not only acts as the epoxidation catalyst, but also acts as a phase transfer catalyst. The reaction utilises H$_2$O$_2$ as the oxidant, which is one of the greenest oxidants available, producing water as a by-product. The method chosen to follow was using a preformed tungstate complex as described by Venturello, which was prepared by heating tungstic acid in 30% H$_2$O$_2$ at 60 °C until the reaction becomes homogeneous. The reaction was then cooled to rt and 40% phosphoric acid solution added, and the reaction diluted with H$_2$O followed by the addition of Aliquat 336. Aqueous work-up followed by concentration en vacuo then provided the desired tungstate complex. The epoxidation reaction of dihydropyran 104.2 proceeded in excellent yield at rt in 4 h, under solvent free conditions, to give epoxide 116.1 in a 95% yield as a single diastereomer (Scheme 117). The reaction was demonstrated to have excellent reproducibility, and was a significant improvement on the original mCPBA epoxidation conditions.

Reduction of epoxide 116.1 with LiAlH$_4$ proceeded well to give the expected Markovnikov tertiary alcohol 118.1 in 90% yield after 1 h, with the ester functionality also being reduced to a primary alcohol to afford diol 118.1 (Scheme 118), containing orthogonally addressable groups for further derivatization. This reduction reaction proceeds via an S$_{N}$2 type mechanism, because the reaction in performed in a polar aprotic solvent, which results in the hydride nucleophile approaching the epoxide with an axial trajectory at the least hindered carbon.
Attempts were also made to access the opposite diastereomer of epoxide 116.1 through base mediated ring-closure of bromohydrin 119.1. Dihydropyran 104.2 was subjected to standard bromohydrin synthesis conditions utilising N-bromosuccinimide (NBS) and water. However, rather than producing the expected bromohydrin 119.1 via approach of NBS from the least hindered face, it was found that bromohydrin 119.2 was generated as the only product in 86% yield (Scheme 119). Fortunately, the bromohydrin produced could be isolated as a crystalline solid which allowed for confirmation of its structure by single crystal X-ray crystallography (Figure 34).

Scheme 118. Reduction of epoxide 30.1 with LiAlH₄

Scheme 119. Synthesis of bromohydrin 119.1

Figure 34. X-ray crystal structure of bromohydrin 119.1 (hydrogens omitted for clarity)
As confirmation that the epoxide generated using the Venturello conditions had been assigned correctly, bromohydrin 119.1 was cyclised using potassium carbonate as base to afford epoxide 116.1 in 90% yield (Scheme 120). Comparison of the $^1$H NMR and $^{13}$C NMR spectra of both synthesised epoxides and a mixed NMR sample provided confirmation that both routes had led to generation of the same epoxide diastereomer 116.1.

![Scheme 120. Ring closing to form epoxide 116.1](image)

This unexpected bromohydrin result is proposed to be due to two contributing factors. Firstly, electrophilic bromination of an alkene double bond is known to proceed via reversible formation of a bromonium ion.268-271 Secondly, the trans-diaxial effect (Fürst-Plattner rule),272 states that nucleophilic attack of cyclohexyl derivatives such as epoxides, imines and halonium ions occurs to preferentially afford trans-diaxial product.272, 273

If formation of bromohydrin 119.2 is considered, the bromonium ion would be expected to arise from approach of Br$^+$ from the least hindered face, resulting in formation of bromonium ion 121.1. If this is considered as a “bow-tie” conformation, then hydroxyl attack of the bromonium ion to produce a trans-diaxial product would proceed via a highly disfavoured “twist boat” conformation. However, since bromonium ion formation is potentially reversible, small quantities of the more sterically hindered bromonium ion 121.2 may also be formed. Hydroxyl attack of bromonium ion 121.2 could then proceed smoothly to give the “chair” conformation of the bromohydrin, which acts as a “thermodynamic sink” to afford the unexpected bromohydrin 119.1 (Scheme 121).
7.44 Dihydroxylation

Reactions of osmium tetroxide with alkenes to give syn-vicinal diols was discovered in the early 1900’s and was first published by Makowka in 1908. Since then, this methodology has undergone incredible development with the introduction of a number of catalytic methods aimed at minimising the amount expensive and toxic osmium employed. One of the most well-known and successful examples of employing catalytic amount of OsO₄ is the Upjohn process, which regenerates the active osmium species through the use of stoichiometric amounts of N-methylmorpholine N-oxide (NMO) as a sacrificial oxidant. In the 1980’s Sharpless developed an asymmetric dihydroxylation protocol on the basis of this earlier work, based on observations by Criegee that tertiary amines (e.g. pyridine) accelerated the reaction of osmium tetroxide with alkenes. Continued development of their asymmetric methodology eventually led to a commercially available mixture of chiral ligand, oxidant and an osmium source being made available. These reagents are collectively known as AD-mix α and Ad-mix β, with opposite enantiomers of the (DHQ)²PHAL ligand potentially allowing for synthesis of the diol enantiomer of choice (Figure 35).
It was proposed that the use of AD-mix α or Ad-mix β for dihydroxylation of dihydropyran 104.2 could potentially afford both diastereomers of syn-diol 122.1 under catalyst control. However, it was found that irrespective of which Ad-mix was used, the same diol diastereomer 122.1 was obtained, indicating that substrate control overrides the ligand directiving effect of the AD-mix reagents (Scheme 122). As seems to be common for use of AD-mix, the dihydroxylation reaction was slow, taking 4 days to afford diol 122.1 in only 45% isolated yield.

The relative stereochemistry of diol 122.1 was assigned by NOESY NMR, with Hc demonstrating interactions with Hd due to the fact that they are both equatorial, whilst displaying no nOe interactions with Ha or He (Figure 36).
In order to provide further confirmation of the configuration of the diol produced, it was decided to synthesise the more structurally rigid acetonide 123.1, which was formed via treatment with dimethylacetal and pTSA in acetone in 95% yield (Scheme 123).

Figure 36. NOESY of diol 122.1
nOe analysis confirmed the relative stereochemistry as previously assigned with H_c having nOe interactions with H_d due to their equatorial relationship, and no other interactions with any other protons of the pyran ring (Figure 37). The low coupling constant of 1.8 Hz for H_c and H_d also denotes an anti-relationship, with this low coupling constant value characteristic of an equatorial-equatorial relationship.

Figure 37. NOESY NMR of acetonide 123.1
Dihydroxylation of dihydropyran 104.2 to give diol 123.1 gives rise to a stereotetrad containing a quaternary carbon centre, which is present as a stereotetrad fragment in the natural product yokonolide B, which is a novel inhibitor of auxin signalling (Figure 38).  

![Figure 38. Yokonolide B](image)

### 7.45 Epimerization

The aim of this project was to not only gain access to a library of chiral building blocks for polyketide synthesis, but also enable access to other possible diastereomeric tetrad combinations. An obvious simple change, which would double the current number of diastereomers accessible, would be to synthesise the anti-hetero Diels-Alder product, as opposed to the syn-hetero Diels-Alder product 104.2. A publication by Terada in 2009 reported that use of chiral phosphoric acid 124.2, as a chiral catalyst had afforded an anti-diastereoselective and enantioselective hetero-Diels-Alder reaction to be carried out.  

In this instance, silyloxy diene 124.1 was coupled with ethyl glyoxalate 104.1 to give dihydropyran 124.3 in 95% yield with >99:1 anti:syn selectivity and 99% ee (Scheme 124).
It was decided to synthesise chiral phosphoric acid **124.2** and apply this methodology to our system, with the synthesis of chiral phosphoric acid **124.2** being performed utilising the protocols of Kobayashi and Gestwicki as shown in Scheme 125.\(^{285, 286}\)
However, while Terada was able to demonstrate that this catalytic system was active for 1-alkoxy dienes for the formation of anti-HDA products, in our hands its HDA reactions proceeded to give the same syn-diastereomer 104.2 obtained previously observed using the Ti-BINOL catalyst 106.3.

Therefore, it was decided instead to tackle this problem using a different approach. A literature search revealed that an epimerization protocol could potentially be a solution to this problem, since the Evans group had previously reported selective epimerization of pyran 126.1 (enantiomer of pyran 112.2) through the use of potassium tert-butoxide as base at -50 °C in THF to give its epimer 126.2 in quantitative yield (Scheme 126).
This epimerisation protocol was applied to dihydropyran 104.2, which on treatment with potassium tert-butoxide at 0 °C in THF for 2 h gave epimer 104.3 in 96% yield (Scheme 127).

\[
\text{Scheme 127. Epimerization of dihydropyran 104.2}
\]

nOe analysis of dihydropyran 104.3 confirmed that epimerization had occurred (when compared to the nOe of dihydropyran 104.2), with the key proton-proton interactions that would indicate a syn-geometric relationship having disappeared (Figure 39). The analytical data for 104.3 also matches that for the minor diastereomer originally synthesised previously (see Scheme 104).
To demonstrate that the epimerization of this stereocentre does not affect the stereoselectivity of subsequent reactions, dihydropyran 104.3 was epoxidised to give epoxide 128.1 in 96% yield as the sole diastereomer. This result shows that the previous diastereoselective hydroboration/hydrodenation/dihydroxylation methods developed for dihydropyran 104.2 should also be applicable to dihydropyran 104.3 (Scheme 128).

Scheme 128. Epoxidation of dihydropyran 104.1
To further understand this epimerization reaction a deuterium experiment was performed. The reaction was conducted in deuterated THF with KO\textsuperscript{t}Bu at room temperature, after 5 min a small amount of D\textsubscript{2}O was then added to the NMR tube, with \textsuperscript{1}H NMR spectroscopic analysis showing a 20% deuterium incorporation (Scheme 129). This results suggests that the epimerization proceeds through deprotonation at the ester proton, it also suggests that the deprotonation event of the epimerized dihydropyran 104.3 occurs at a much slower rate than for dihydropyran 104.2, as shown by the low deuterium incorporation.

![Scheme 129. Deuterium incorporation experiment for dihydropyran 104.2](image)

**7.451 Computational Studies on Epimerization of Dihydropyran 104.2**

In an attempt to fully understand how this epimerization process is able to achieve complete stereocentre inversion, density functional theory (DFT) computational studies on the two diastereomers 104.2 and 104.3 were undertaken.

All calculations were performed using the Gaussian09 suite of codes (revision D.01). Geometries were fully optimised without any symmetry or geometry constraints. The calculations were all carried out using a temperature of 298 K and solvent effects in tetrahydrofuran considered using conductor-like polarisable continuum model (CPCM). The nature of all the stationary points as minima were verified by calculations of the vibrational frequency spectrum. Free energies were calculated within the harmonic approximation for vibrational frequencies.

Figure 40 shows a summary of the data gained from these computational analysis, with the Gibbs free energy of pyran 104.3 set to zero so that a comparison to the other three conformers can be made. As can be seen both the low energy syn-conformers of dihydropyran 104.2 possess Gibbs free energies significantly higher than the epimerized product 104.3 (Figure 41).
Figure 40. Computed Gibbs free energies at the 6-311++G(d, p)/B3LYP/cpcm=THF/298 K level of theory for the epimerization of dihydropyran 104.2

Figure 41. Lowest energy conformers of dihydropyran 104.2 and 104.3

7.5 Dihydropyran Analogue Synthesis

While the stereotetrad is present in a wide range of polyketide natural products, access to other motifs such as deoxy-1,3-methyl-methyl substitution would also be useful to access other types of polyketide natural product targets (Figure 42). Furthermore, access to this type of methodology would potentially allow for structure activity relationships (SAR) study to be performed to help decipher which structural elements in a natural product were responsible for their biological activity, by allowing facile access to non-natural analogues.
7.51 Synthesis of Diene Analogues

In order to access these dihydropyran analogues the diene utilized in the hetero-Diels-Alder methodology had to be altered. Diene 130.1 was first targeted as it could be accessed from aldehyde 94.2 which was an intermediate that had been generated previously on route to diene 96.1. Employing methyltriphenylphosphonium bromide in the Wittig reaction of 94.2 enabled the desired diene 130.1 to be prepared in 70% yield (Scheme 130).

\[ \text{MeCOEt} \xrightarrow{\text{Ph}_3\text{P-Br}} \text{MeOEt} \]

Scheme 130. Synthesis of diene 130.1

Wittig chemistry was also utilized for the synthesis of diene 131.2, with crotonaldehyde 131.1 being reacted with (ethoxymethyl)triphenylphosphonium chloride under standard Wittig conditions to afford (E, E)-diene 131.2 in 75% yield (Scheme 131).

\[ \text{HOC} \xrightarrow{\text{Ph}_3\text{P-Cl}} \text{OEt} \]

Scheme 131. Synthesis of (E, E)-diene 131.2
7.52 Dihydropyran Analogues Synthesis

Dienes 130.1 and 131.2 were then subjected to the catalytic enantioselective hetero-Diels-Alder conditions previously utilized for the synthesis of dihydropyran 104.2 in 99% ee. The HDA reaction of diene 130.1 proceeded in 68% yield with poor diastereoselectivity to afford an epimeric mixture of 132.1 and 132.2 in a ratio of 1:1. However, it was found that over time, this mixture readily epimerized to give a single diastereomer assigned as dihydropyran 132.2 in 68% yield and 76% ee (Scheme 132).

The configuration of dihydropyran formed after epimerization was assigned as the anti-diastereomer 132.2, from consideration of its nOe NMR spectrum. As shown in Figure 43, the key nOe interactions between Ha and He which would denote a syn relationship as if present in the nOe of dihydropyran 104.2 were not present, suggesting that the anti-diastereomer is the final product of this HDA/epimerisation protocol.

Scheme 132. Synthesis of dihydropyran 132.2
The HDA reaction of diene 131.2 proceeded with good diastereoselectivity to give a single diastereomer of dihydropyran 133.1 in 55% yield and 74% ee (Scheme 133).
Once again the relative stereochemistry of this diastereomer was confirmed by nOe NMR with the key interactions between Ha, Hc and He confirming the syn geometry, and with the J\textsubscript{d,e} coupling constant of 3.5 Hz being indicative of a syn-relationship.

![Figure 44. NOESY NMR of dihydropyran 133.1](image)

The ee’s of both dihydropyran 132.2 and 133.1 of 76% and 74% ee were relatively low when compared to the parent dihydropyran 104.2, which was formed in 99% ee. It is believed that with further optimization the ee of both these reactions should be able to be increased to a level much closer to that of dihydropyran 104.2, however, due to time constraints this optimisation study will be conducted in the near future.

7.53 Dihydropyran Analogues Derivatisation

As with the original chiral dihydropyran template 104.2, it was hoped that all subsequent derivatization reactions performed on analogues 132.2 and 133.1 would proceed
stereoselectively to afford a single diastereomer. Hydroboration of dihydropyran 132.2 proceeded well to afford a single diastereomer in 65% yield (Scheme 134). Surprisingly upon further characterisation is appeared that the syn-diastereomer had been formed. This would suggest that hydroboration had occurred in conjunction with an epimerisation event. This could potentially occur in solution either before borane addition, or after the hydroboration step had occurred. It is believed to be the first option, where epimerisation of dihydropyran 132.2 occurs before borane addition. This is due to evidence of unreacted dihydropyran 132.1 being present in the crude ¹H NMR (Scheme 134).

![Scheme 134. Hydroboration of dihydropyran 132.2](image)

Examination of the nOe NMR confirms the syn relative stereochemistry, with key interactions between Ha and Hf showing that these two protons are present on the same face of pyran ring, confirming their syn-relationship. Importantly, as well Hc shows no interactions with Ha, Hb and crucially Hf, confirming its anti-relationship to other protons (Figure 45).
Pyran 134.1 contains a sterotriad with syn-syn relative stereochemistry, which contains the same relative stereochemistry as that present in the recently discovered marine polyhydroxy polyketides nahuoic acid D and nahuoic acid E (Figure 46).\textsuperscript{288}
Epoxidation of dihydropyran 132.2, using the Venturello conditions used previously, resulted in a mixture of syn-epoxide 135.1 and anti-epoxide 135.2. The two epoxides were produced in 80% yield and a diastereomeric ratio of 85:15 in favour of the syn-epoxide 135.1 (Scheme 135).

Scheme 135. Epoxidation of dihydropyran 132.2

Examination of the nOe NMR confirmed the all syn relative stereochemistry of the major diastereomer, with key interactions between Ha and He showing that these two protons are present on the same face of the pyran ring, thus confirming their syn-relationship (Figure 47).
Hydroboration of dihydropyran 133.1 led to the formation of two regioisomers pyran 136.1 and pyran 136.2 in a 3:2 ratio in an overall yield of 75% (Scheme 136). This loss of regiocontrol is due to the absence of the alkene methyl groups that were present in dihydropyrans 104.2 and 132.2. Pyran 136.1 was formed as a single diastereomer, showing that the directive nature of the cyclic system is still effective. However, the minor pyran 136.2 was formed as a 1:1 mixture of diastereomers (unassigned), as evidenced by doubling of the peaks present in both the $^1$H and $^{13}$C NMR spectra.
Scheme 136. Hydroboration of pyran 133.1

COSY NMR was used to help identify the structure of pyran 136.1, which revealed that Hb$_1$ and Hb$_2$ showed coupling to each other and with Hc (the hydroxyl proton) (Figure 48).
7.6 Further Dihydropyran Derivatization

By gaining access to enantiomerically enriched dihydropyrans 104.2, 132.2 and 133.1 as well as their subsequent derivatives, methodology has been developed to allow for rapid derivatization of chiral templates with potential for the synthesis of polyketides. These dihydropyran compounds possess bi-functional aldehyde and ester groups at their termini, which can potentially be functionalised in a selective manner. This would potentially allow access to the “plug and play” approach originally devised at the outset of this project, with a representative range of transformations that could be utilised to achieve this aim presented in Scheme 137.

Hydrolytic cleavage of the masked acetal of dihydropyran 104.2 would give access to a “sugar” analogue 137.1, that would exist in both its cyclic hemi-acetal form 137.1 and also as its acyclic aldehyde 137.2. This aldehyde represents a highly reactive functional handle that can be derivatized in a number of ways, such as through the use of Wittig olefination chemistry to give diene 137.3. Another method of utilising this aldehyde functionality would be through titanium salen catalysed asymmetric synthesis of cyanohydrin ethyl carbonates, which would potentially give access to β-aminoalcohols and γ-azido-α,β-unsaturated nitriles. This aldehyde functionality could also be utilised to carry out boron or silicon allylation chemistry to allow access homoallylic alcohol 137.5, which are a highly prized class of synthetic intermediates for the construction of a wide variety of complex polyketides. Sugar compound 137.1 can also be utilised as a synthetic reagent in its own right, utilising carbohydrate chemistry to form glycosidic bonds to natural sugars, to give rise to potentially exciting polyketide-sugar hybrids 137.6.

The ester functional handle present in dihydropyran 104.2 can also be utilised in a number of ways. Global reduction would give rise to primary alcohol 137.7, with activation as its mesylate/tosylate (or as a halogen via Appel reaction), enabling a wide range of nucleophiles to be introduced into the compound. However, use of a mild selective reducing agent such as lithium diisobutyl-tert-butoxaluminium hydride (LDBBA) which is formed through a combination of 'BuOH, nBuLi and DIBAL-H, might allow access to aldehyde 137.8, which could then be subjected to the wide range of derivatization chemistries available for aldehyde 137.2. A further more complex elaboration of dihydropyran 104.2 would be to utilise the chemistry developed for epimerization of pyran 104.2. Therefore, deprotonation of pyran 104.2 at its Cτ-position would afford an enolate, which could be alkylated with a range of electrophiles. Hydrolysis of the ester functionality to afford carboxylic acid 137.9, would then allow for implementation of photoredox decarboxylation chemistry. Decarboxylation of carboxylic acid
137.9 through irradiation of an Ir/Ni catalytic system, would potentially afford advanced pyran intermediates 137.10 containing different side-chains with high levels of diastereoocontrol. The stereoselectivity of this process would be controlled by the formation of an antiperiplanar radical intermediate preferentially adopting a trans-diaxial orientation due to the anomeric effect. While the example shown replaces the carboxylic acid with a proton, this could also be used as an opportunity to introduce a wide range of new functionality. For example, recent reports by MacMillan and Waser have demonstrated how photoredox chemistry can be used to replace carboxylic acids groups with alkene and alkynyl groups,291,292 which would represent a highly efficient way of joining together fragments enroute to a complex natural product (Scheme 137).
Scheme 137. Potential synthetic elaborations of dihydropyran 104.2
As proof of concept that these dihydropyran 104.2 could be further elaborated, it was decided to pick two of these examples shown for the further derivatization of dihydropyran 104.2. It was decided to first investigate utilization of the masked aldehyde functionality, of 104.2 through a Wittig-olefination reaction. Treatment of dihydropyran 104.2 with mild acid at 50 °C led to formation of sugar-like intermediate, which exists in both its cyclic lactol 137.1 form and an acyclic aldehyde 137.2. The aldehyde group was then intercepted by treatment with phosphonium ylide 138.1 to give diene 138.2 in a 70% yield over the two steps. Diene 138.2 was formed as an inseparable 2:1 ratio of E:Z geometric isomers, which contained orthogonally addressable ester groups that would allow for selective derivatisation (Scheme 138).

![Scheme 138](image)

Scheme 138. Exploiting the masked aldehyde functionality of 104.2 for the synthesis of diene 138.2

It was hoped that diene 138.2 would be set up, to allow for the utilization of Evans methodology for the diastereoselective synthesis of a protected syn 1,3-Diols.293 The Evans methodology proceeds through formation of an acetal alkoxide which is then able to act as tethered oxygen nucleophile. This nucleophile is then able to undergo diastereoselective
intramolecular conjugate addition to a Michael acceptor in a stereoselective manner to afford a benzylidene acetal 139.2 (Scheme 139). This methodology represents a potentially exciting way of installing a hydroxyl group (through subsequent hydrolysis of the benzylidene acetal) in a stereoselective manner.

![Chemical Structure](image)

**Scheme 139.** Evans methodology for diastereoselective synthesis of protected syn 1,3-diols.

It was hoped that this Evans’ methodology could be applied to vinylogous diene 138.2, where it was proposed that this conjugated system would also be able to undergo a similar intramolecular conjugate addition. However, this reaction proved to be unsuccessful (Scheme 140), which is believed to be due to the fact that the distal alkene is not sufficiently conjugated, and may possess more “normal” electron rich alkene character. Evidence of this can be seen when similar diene systems are subjected to dihydroxylation conditions, with only the remote alkene group undergoing dihydroxylation. It is hoped that with more investigation this methodology could be applied to diene 138.2, however, due to time constraints this was beyond the current scope of this thesis.

![Chemical Structure](image)

**Scheme 140.** Unsuccessful attempt at employing Evans methodology for the diastereoselective synthesis of protected syn 1,3-diols

Finally, as a method of showing the utility of the ester functionality it was decided to perform a global reduction, and then demonstrated that the resultant alcohol could be activated for further derivatisation. Reduction of ester 104.2 through treatment with LiAlH₄ afforded
alcohol 137.7 in 95% yield, leaving the hemi-acetal and alkene functionality untouched. This alcohol presents an excellent intermediate for further elaboration, via its corresponding tosylate 141.1, which was prepared in 82% yield using standard (Scheme 141). Tosylate 141.1 is a key compound to demonstrate how these chiral building blocks could be implemented into a synthetic route, since it can be reacted with a range of nucleophiles to provide advanced intermediates for polyketide synthesis.

Scheme 141. Route to exploiting the ester functionality

8.0 Future Work

There are a number of ways in which this research project could be taken forward. An obvious choice would be to identify a late stage synthetic intermediate of a polyketide natural product and conduct a formal synthesis where the methodology developed leads to a significant reduction in step count and a more efficient synthesis. However, an equally important application where this methodology could have a large impact is in the field of precursor directed biosynthesis.²⁹⁵-²⁹⁸ For example, the Khosla and Cane groups have conducted extensive research into precursor-directed biosynthesis of 16-membered macrolides by the erythromycin polyketide synthase. They were able to utilize a range of SNAC thioester precursors (such as alkene 142.1) as substrates for deoxyerythronolide B synthase (DEBS) a polyketide synthase. The synthase was shown to be able to use these substrates to construct a series of macrolides. By varying the diastereomer and functionality of the substrate used, a range of natural and non-natural polyketides could be synthesised (Scheme 142).²⁹⁵-²⁹⁸
By utilizing the methodology developed throughout this project, quick and efficient access to this type of substrate could be achieved, that would allow variation of the functionality and diastereoselectivity incorporated into the corresponding macrolide. Shown below is a proposed route for the synthesis of SNAC thioester precursor 142.1. Substitution of the tosyl group of pyran 142.1 with a carbon nucleophile (e.g. Me₂CuLi) could then afford alkene 143.1. Hemi-acetal formation, followed by oxidation would generate lactone 143.3, which if treated with N-Acetylcysteamine 143.4 would generate thioester 142.1 as a precursor for feeding studies (Scheme 143).
Further development of diene synthesis might also be considered, with a potential route to attempt to utilise flow technology shown in Scheme 144. For example, treatment of propionaldehyde 99.1 with a solid-supported base ‘in-flow’ should generate an enolate species 144.1 that will be flowed into the stream of another aldehyde (shown propionaldehyde 99.1) to afford a homo-aldol product 144.2 that could then be dehydrated via contact with base to afford an enone 98.1, that could be reacted with EtOH/H+ to afford diene 96.1 (Scheme 144).
9.0 Conclusion

A potential route towards the synthesis of a library of building blocks for the synthesis of polyketide natural products has been presented. Two reliable synthetic routes to multigram quantities of substituted 1-alkoxy dienes have been established. The first of these approaches utilises a non-aromatic Vilsmeier reaction, followed by Wittig chemistry to construct the conjugated diene. The second more efficient route involves acetal formation, followed by base facilitated elimination resulting in diene formation.

These dienes have been shown to be active in HDA chemistry with the reaction proceeding with good enantiomeric and diastereoselective control around the dihydropyran ring, using a titanium-BINOL catalyst developed by Mikami et al.
A series of stereoselective derivatisation reactions were then conducted on pyran 104.2 including, hydroboration, hydrogenation, epoxidation, dihydroxylation and epimerization to afford a range of complex enantiomerically pure pyran based building blocks, which are ideally suited for the synthesis of polyketide natural products through a “plug and play” approach. All the performed derivatization reactions proceed with good selectively producing a single diastereomer in good yield. This represents a highly efficient route to the generation of up to five contiguous stereocentres that are a common feature of polyketide natural products (Scheme 147).
Methodology has also been developed to allow further elaboration of the pyran structure through exploiting the masked aldehyde character of the hemi-acetal, and through utilization of the ester functionality.

This HDA chemistry was also applied to two other diene analogues which gave rise to a new series of mono-methyl dihydropyrans 132.2 and 133.1, which differ in position of their methyl groups around the ring. By gaining access to analogues of this motif, through substitution of the methyl groups for protons, a greater number of potential natural product targets can potentially be reached. Furthermore, this approach could potentially allow for structure activity relationship (SAR) studies to be performed, to help decipher which structural elements within a natural product are responsible for its biological activity, by allowing access to non-natural isomers.

Scheme 147. Range of diastereoselective derivatisation reactions of dihydropyran 104.2
Figure 49. Dihydropyran analogues

132.2 $R^1 = \text{Me}, R^2 = \text{H}$
133.1 $R^1 = \text{H}, R^2 = \text{Me}$
Experimental

General conditions

Infrared spectra (4000 cm\(^{-1}\) to 650 cm\(^{-1}\)) were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a Universal ATR accessory for sampling. The machine has internal calibration and only selected peaks are quoted in \(\nu\) (wavenumbers, cm\(^{-1}\)).

Proton magnetic resonance spectra were recorded at 300.22 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (\(\delta H\)) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), quartet of doublets (qd), triplet of triplets (tt), multiplet (m), aromatic (Ar), and apparent (app.). Coupling constants (\(J\)) are quoted to the nearest 0.1 Hz. Carbon magnetic resonance spectra were recorded at 75.5 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (\(\delta C\)) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (\(J\)) are quoted to the nearest 0.1 Hz.

Mass spectra were recorded on a Bruker Daltonics micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer. Samples were introduced either by syringe pump or flow injection using an auto-sampler. Samples were diluted in either methanol or acetonitrile.

All capillary melting point determinations were carried out using Büchi 535 melting point apparatus and reported to the nearest degree Celsius (°C).

Analytical thin layer chromatography was carried out using commercially available polyethylene backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, \(p\)-anisaldehyde or phosphomolybdic acid followed by heating. Flash chromatography was performed under medium pressure using Merck 60 H silica gel (35-75 μm). Samples were loaded as saturated solutions in an appropriate solvent.

Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus, which was allowed to cool under nitrogen prior to use. Anhydrous solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at
40-60 °C. Ether refers to diethyl ether. Hexanes refer to the hexane fraction of petroleum. Solvents were evaporated on a Büchi Rotorvapor.

All commercially available compounds were used as obtained from the chemical suppliers, unless otherwise stated. All temperatures quoted are external.

**General Procedures**

**General Procedure A: N-Acetylation of amines**

Amine (1.0 mmol) was added to phenylmethylene diacetate 7.2 (0.291 g, 1.5 mmol) the reaction was stirred at 70 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated acetamide. Where the reaction mixture was not homogeneous 2 mL of EtOAc was added at the start of the reaction.

**General Procedure B: O-Acetylation of alcohols**

Alcohol (1.0 mmol) was added to phenylmethylene diacetate 7.2 (0.291 g, 1.5 mmol) and K$_2$CO$_3$ (0.270 g, 2.0 mmol) the reaction was stirred at 80 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated ester. Where the alcohol was a solid at 60 °C 2 mL of toluene was added at the start of the reaction.

**General Procedure C: Synthesis of acylation reagents**

*para-*Toluenesulphonic acid (mono hydrate) (0.18 g, 0.94 mmol) was added to a mixture of benzddehyde (1.0 g, 9.4 mmol) and anhydride (18.8 mmol) at rt. The reaction was stirred for 12 h and then diluted with Et$_2$O (50 mL) and washed with saturated Na$_2$CO$_3$ (3 x 20 mL). The organics were dried (MgSO$_4$) and concentrated *in vacuo* to give the title compound which was used in subsequent steps without further purification unless otherwise stated.

**General Procedure D: N-acylation of amines**

Amine (1.0 mmol) was added to the acylation reagent (1.5 mmol) the reaction was stirred at 70 °C for 16 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated amide.

**General Procedure E: O-acylation of alcohols**

Alcohol (1.0 mmol) was added to the acylation reagent (1.5 mmol) and K$_2$CO$_3$ (0.270 g, 2.0 mmol). The reaction was stirred at 90 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated ester.
General Procedure F: \(N\)-formylation of amines

Amine (2.0 mmol) was added to (Formyloxy)(phenyl)methyl acetate 44.2 (0.582 g, 3.0 mmol), the reaction was stirred at rt for 1 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated formamide. Where the reaction mixture was not homogeneous 2 mL of EtOAc was added at the start of the reaction.

General Procedure G: \(N\)-formylation of \(\alpha\)-amino acids

(Formyloxy)(phenyl)methyl acetate 44.2 (0.291 g, 1.5 mmol) was added to a mixture of amino acid (1.0 mmol) and NaHCO\(_3\) in H\(_2\)O (4 mL). The reaction was stirred at rt for 16 h. The reaction mixture when then made acidic with 1 M HCl and extracted with CH\(_2\)Cl\(_2\) (3x 10 mL), the organics were combined, dried (MgSO\(_4\)) and concentrated in vacuo. The residue was then purified via recrystallization with EtOAc and petroleum ether to give the isolated formyl carboxylic acid.

General Procedure H: \(O\)-formylation of alcohols

Alcohol (1.0 mmol) was added to (Formyloxy)(phenyl)methyl acetate 44.2 (0.291 g, 1.5 mmol) and NaHCO\(_3\) (0.168 g, 2.0 mmol), the reaction was stirred at 60 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated formate ester. Where the alcohol was a solid at 60 °C, 2 mL of EtOAc was added at the start of the reaction.

General Procedure I: Acetal synthesis from 1,2- and 1,3-diols

Diol (1.0 mmol) and acetic acid (0.65 μL, 0.01 mmol) were added to phenylmethylene diacetate 7.2 (0.582 g, 3.0 mmol) in MeCN (3 mL) and heated to 40 °C for 12 h. The crude reaction mixture was concentrated under vacuum and the resulting residue was purified by column chromatography to give the isolated acetal.
Phenylmethylene diacetate 7.2

General procedure C was followed to afford the title compound as a clear oil in 98% yield (1.92 g, 9.21 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.7 (s, 1H, CH(OAc)\(_2\)), 7.6 – 7.5 (m, 2H, ArH), 7.5 – 7.4 (m, 3H, ArH), 2.1 (s, 6H, 2 x CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.0, 135.6, 129.9, 128.8, 126.8, 89.8, 21.0. I.R (thinfilm) \(\nu\) max (cm\(^{-1}\)) : 2981 (ArC-H), 1746 (C=O); HRMS (ESI): m/z calculated for C\(_{11}\)H\(_{12}\)O\(_4\) requires: 231.0633 for [M+Na]\(^+\); found: 231.0683.

\(N\)-Benzylacetamide 34a

General procedure A was followed. Eluent 30% EtOAc in CH\(_2\)Cl\(_2\) the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 86% yield (0.128 g, 0.86 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.4 – 7.2 (m, 5H, ArH), 5.9 (s, 1H, NH), 4.4 (d, \(J = 5.7\) Hz, 2H, CH\(_2\)), 2.0 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.0, 138.3, 128.8, 128.0, 127.7, 43.9, 23.4.

Analytical data in accordance with literature.\(^{299}\)

\(N\)-(pyridin-4-ylmethyl)acetamide 34b

General procedure A was followed. Eluent 30% EtOAc and 1% NEt\(_3\) in CH\(_2\)Cl\(_2\) the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a orange oil in 84% yield (0.126 g, 0.84 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.6 – 8.5 (m, 2H, ArH), 7.2 – 7.1 (m, 2H, ArH), 6.1 (s, 1H, NH), 4.4 (d, \(J = 6.1\) Hz, 2H, CH\(_2\)), 2.1 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.4, 150.1, 147.5, 122.4, 42.6, 23.3.

Analytical data in accordance with literature.\(^{1}\)
**N-(2-(1H-indol-3-yl)ethyl)acetamide 34c**

![Structure of N-(2-(1H-indol-3-yl)ethyl)acetamide](image)

General procedure A was followed. Eluent 100% EtOAc, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale brown solid in 62% yield (0.125 g, 0.62 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.2 (s, 1H, NH), 7.6 (ddt, $J = 7.8, 1.5, 0.8$ Hz, 1H, ArH), 7.4 (dt, $J = 8.1, 1.0$ Hz, 1H, ArH), 7.2 (ddd, $J = 8.2, 7.0, 1.3$ Hz, 1H, ArH), 7.1 (dd, $J = 8.1, 1.2$ Hz, 1H, ArH), 7.1 – 7.0 (m, 1H, ArH), 5.5 (s, 1H, NH), 3.6 (q, $J = 6.5$ Hz, 2H, CH$_2$CH$_2$NH), 3.0 (td, $J = 6.7, 0.9$ Hz, 2H, CH$_2$CH$_2$NH). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.2, 136.5, 127.5, 122.4, 122.2, 119.7, 118.8, 113.1, 111.4, 77.4, 39.9, 25.4, 23.6.

Analytical data in accordance with literature.$^{300}$

**N-Benzhydrylacetamide 34d**

![Structure of N-Benzhydrylacetamide](image)

General procedure A was followed. Eluent 20% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as crystalline white solid in 70% yield (0.158 g, 0.70 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.3 (qt, $J = 6.2, 1.8$ Hz, 5H, ArH), 7.3 (s, 5H, ArH), 6.3 (d, $J = 8.0$ Hz, 1H, CH), 6.0 (s, 1H, NH), 2.1 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.2, 141.6, 128.8, 127.6, 127.5, 57.1, 23.6.

Analytical data in accordance with literature.$^{301}$
**N-Phenylacetamide 34e**

![N-Phenylacetamide](image)

General procedure A was followed. Eluent 20% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid in 68% yield (0.92 g, 0.68 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.5 – 7.5 (m, 2H, ArH), 7.3 (t, J = 7.9 Hz, 2H, ArH), 7.2 – 7.1 (m, 1H, ArH), 2.2 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 168.4, 138.0, 129.2, 124.5, 119.9, 24.8.

Analytical data in accordance with literature.

**N-methyl-N-phenylacetamide 34f**

![N-methyl-N-phenylacetamide](image)

General procedure A was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale green solid in 60% yield (0.089 g, 0.60 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.4 (dd, J = 8.3, 6.5 Hz, 2H, ArH), 7.4 – 7.3 (m, 1H, ArH), 7.2 – 7.1 (m, 2H, ArH), 3.3 (s, 3H, NCH₃), 1.9 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 170.7, 144.7, 129.9, 127.8, 127.2, 37.3, 22.6.

Analytical data in accordance with literature.

**Methyl 4-acetamidobenzoate 34g**

![Methyl 4-acetamidobenzoate](image)

General procedure A was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid in 65% yield (0.126 g, 0.65 mmol). ¹H NMR (300 MHz, CDCl₃) δ 8.1 – 7.9 (m, 2H, ArH), 7.6 (d, J = 8.4 Hz, 2H, ArH), 7.4 (s, 1H, NH), 3.9 (s, 3H, CO₂CH₃), 2.2 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 166.7, 142.2, 131.0, 125.7, 118.8, 52.2, 25.0.
Analytical data in accordance with literature.\textsuperscript{303}

$N,N$-dibutylacetamide 34h

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{Bu}^- \\
\text{Bu}^+
\end{array}
\]

General procedure A was followed. Eluent 30\% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90\% yield (0.154 g, 0.90 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.3 – 3.2 (m, 2H, NCH$_2$), 3.2 – 3.2 (m, 2H, NCH$_2$), 2.1 (s, 3H, CH$_3$), 1.5 (dd, $J = 15.2, 9.2, 7.8, 5.4$ Hz, 4H, CH$_2$CH$_2$CH$_3$), 1.3 (hept, $J = 7.4$ Hz, 4H, CH$_2$CH$_2$CH$_3$), 0.9 (dt, $J = 10.0, 7.3$ Hz, 6H, 2x CH$_2$CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.2, 48.7, 45.6, 31.1, 30.0, 21.7, 20.4, 20.2, 14.0, 14.0.

Analytical data in accordance with literature.\textsuperscript{304}

1-(piperidin-1-yl)ethanone 34i

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

General procedure A was followed. Eluent 20\% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 95\% yield (0.121 g, 0.95 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.6 – 3.5 (m, 2H, NCH$_2$), 3.4 (dd, $J = 6.2$, 4.6 Hz, 2H, NCH$_2$), 2.1 (s, 3H, CH$_3$), 1.7 – 1.4 (m, 6H, CH$_2$CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.9, 47.6, 42.6, 26.6, 25.6, 24.6, 21.7.

Analytical data in accordance with literature.\textsuperscript{299}

1-(4-methylpiperazin-1-yl)ethanone 34j

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]

General procedure A was followed. Eluent 30\% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow in 92\% yield (0.131 g, 0.92 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.7 –
3.6 (m, 2H, AcNCH\textsubscript{ax}), 3.5 – 3.4 (m, 2H, AcNCH\textsubscript{eq}), 2.4 (dt, \(J = 10.0, 5.2\) Hz, 4H, \(\text{CH}_2\text{NCH}_3\)), 2.3 (s, 3H, \(\text{CH}_2\text{NCH}_3\)), 2.1 (s, 3H, (C=O)\text{CH}_3). \(^{13}\text{C}\) NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 169.1, 55.2, 54.7, 46.3, 46.1, 41.4, 21.5.

Analytical data in accordance with literature.\(^{305}\)

**\(\textit{N,N}\)-diallylacetamide 34k**

![Structure of N,N-diallylacetamide 34k]

General procedure A was followed. Eluent 30% EtOAc in CH\textsubscript{2}Cl\textsubscript{2} the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 88% yield (0.122 g, 0.88 mmol). \(^1\text{H}\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 5.9 – 5.6 (m, 2H, \(\text{CH}=\text{CH}_2\)), 5.3 – 5.0 (m, 4H, \(\text{CH}=\text{CH}_2\)), 4.0 (dt, \(J = 6.1, 1.4\) Hz, 2H, NCH\textsubscript{a}H\textsubscript{b}), 3.9 (dt, \(J = 4.9, 1.8\) Hz, 2H, NCH\textsubscript{a}H\textsubscript{b}), 2.1 (s, 3H, CH\textsubscript{3}). \(^{13}\text{C}\) NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 170.8, 133.4, 132.7, 117.4, 116.7, 50.1, 47.9, 21.5.

Analytical data in accordance with literature.\(^{304}\)

**Benzyl acetate 39a**

![Structure of Benzyl acetate 39a]

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90% yield (0.135 g, 0.90 mmol). \(^1\text{H}\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.5 – 7.3 (m, 5H, ArH), 5.1 (s, 2H, \(\text{CH}_2\text{Ph}\)), 2.1 (s, 3H, CH\textsubscript{3}). \(^{13}\text{C}\) NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 171.1, 136.0, 128.7, 128.4, 66.5, 21.2.

Analytical data in accordance with literature.\(^{306}\)

**Pyridin-2-ylmethyl acetate 39b**

![Structure of Pyridin-2-ylmethyl acetate 39b]
General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 70% yield (0.105 g, 0.70 mmol). ¹H NMR (300 MHz, CDCl₃) δ 8.6 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H, ArH), 7.7 (td, J = 7.7, 1.8 Hz, 1H, ArH), 7.3 (d, J = 7.8 Hz, 1H, ArH), 7.3 (s, 1H, ArH), 5.2 (s, 2H, CH₂), 2.2 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 155.8, 149.7, 136.9, 123.0, 122.0, 67.0, 21.1.

Analytical data in accordance with literature.

2-Bromophenethyl acetate 39c

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 76% yield (0.184 g, 0.76 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.6 (dt, J = 7.9, 0.9 Hz, 1H, ArH), 7.3 – 7.2 (m, 2H, ArH), 7.1 (ddd, J = 7.9, 5.1, 4.1 Hz, 1H, ArH), 4.3 (t, J = 7.0 Hz, 2H, CH₂OC(O)CH₃), 3.1 (t, J = 7.0 Hz, 2H, ArCH₂), 2.0 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 137.3, 133.1, 131.2, 128.5, 127.6, 124.8, 63.5, 35.4, 21.1.

Analytical data in accordance with literature.

[1,1’-biphenyl]-4-ylmethyl acetate 39d

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 68% yield (0.153 g, 0.68 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.6 – 7.6 (m, 4H, ArH), 7.5 – 7.4 (m, 4H, ArH), 7.4 – 7.3 (m, 1H, ArH), 5.2 (s, 2H, CH₂), 2.1 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 141.4, 140.8, 135.0, 128.9, 127.6, 127.5, 127.3, 66.2, 21.2.

Analytical data in accordance with literature.
3,7-Dimethyloct-6-en-1-yl acetate 39e

![Structure of 3,7-Dimethyloct-6-en-1-yl acetate](image)

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90% yield (0.178 g, 0.90 mmol). $^1$H NMR (300 MHz, CDCl₃) δ 5.1 (tdt, $J = 5.8, 3.0, 1.5$ Hz, 1H, C=CH), 4.2 – 4.0 (m, 2H, CH₂OAc), 2.0 (s, 3H, (C=O)CH₃), 2.0 (dt, $J = 15.0, 7.7$ Hz, 2H, CH₂), 1.7 – 1.6 (m, 4H, CH₂), 1.6 (d, $J = 1.4$ Hz, 3H, CH₃(CH)CH₃), 1.6 – 1.3 (m, 3H, CH₃(CH)CH₃), 1.2 (ddddd, $J = 13.5, 9.1, 7.5, 6.2$ Hz, 1H, (CHCH₃)), 0.9 (d, $J = 6.4$ Hz, 3H, CHCH₃). $^{13}$C NMR (75 MHz, CDCl₃) δ 171.4, 131.5, 124.7, 63.2, 37.1, 35.5, 29.6, 25.9, 25.5, 21.2, 19.5, 17.8.

Analytical data in accordance with literature.³⁰⁷

(rac)-1-phenylethyl acetate 39f

![Structure of (rac)-1-phenylethyl acetate](image)

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 77% yield (0.126 g, 0.77 mmol). $^1$H NMR (300 MHz, CDCl₃) δ 7.4 – 7.3 (m, 5H, ArH), 5.9 (q, $J = 6.6$ Hz, 1H, CH), 2.1 (s, 3H, C(O)CH₃), 1.5 (d, $J = 6.6$ Hz, 3H, CHCH₃). $^{13}$C NMR (75 MHz, CDCl₃) δ 170.5, 141.8, 128.6, 128.0, 126.2, 72.5, 22.4, 21.5.

Analytical data in accordance with literature.³¹⁰
(4aR,6S,7S,8R,8aS)-6-Methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl diacetate 39g

(4aR,6S,7S,8S,8aR)-6-Methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (0.282 g, 1.0 mmol) was added to phenylmethylene diacetate (0.582 g, 3.0 mmol) and K₂CO₃ (0.270 g, 2.0 mmol) the reaction was stirred at 90 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the title compound. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 65% yield (0.238 g, 0.65 mmol).

¹H NMR (300 MHz, CDCl₃) δ 7.4 (qd, J = 5.4, 4.5, 1.9 Hz, 2H, ArH), 7.4 (dt, J = 4.6, 2.8 Hz, 3H, ArH), 5.6 (t, J = 9.6 Hz, 1H, CH₂CH₃), 5.5 (s, 1H, PhCH), 5.0 – 4.8 (m, 2H, 2 x CH₂C(O)CH₃), 4.3 (dd, J = 10.1, 4.7 Hz, 1H, CH₂CH(O)CH(O)), 4.1 (tdd, J = 10.7, 7.0, 3.3 Hz, 2H, OCH₂CHO), 2.1 (s, 3H, C(O)C(CH₃)₂), 1.5 (s, 3H, OCH₂). ¹³C NMR (75 MHz, CDCl₃) δ 170.6, 169.9, 137.0, 129.2, 128.4, 126.3, 101.7, 97.7, 79.3, 71.7, 69.1, 69.0, 62.4, 55.5, 21.0, 20.9.

Analytical data in accordance with literature.³¹¹

(3aR,5R,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate 39h

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 70% yield (0.21 g, 0.69 mmol). [α]D²⁰ = -32 in CHCl₃.

¹H NMR (300 MHz, Chloroform-d) δ 5.9 (d, J = 3.7 Hz, 1H, OCHO), 5.2 (d, J = 2.4 Hz, 1H, OCH(OH)CH₂), 4.5 (d, J = 3.7 Hz, 1H, OCHOCH₂), 4.3 – 4.2 (m, 2H, OCHOCH₂OCH(O)CH₃ and CH(O)CH₃), 4.1 (tdd, J = 10.7, 7.0, 3.3 Hz, 2H, OCH₂CHO), 2.1 (s, 3H, CH(OH)CH₂), 1.5 (s, 3H,
OCO(CH₃CH₃), 1.4 (s, 3H, OCO(CH₃CH₃)), 1.3 (s, 3H, OCO(CH₃CH₃)), 1.3 (s, 3H, OCO(CH₃CH₃)). ¹³C NMR (75 MHz, CDCl₃) δ 169.8, 112.4, 109.5, 105.1, 83.4, 79.8, 76.3, 72.5, 67.3, 27.0, 26.8, 26.3, 25.4, 21.1.

Analytical data in accordance with literature. ³¹²

**Cinnamyl acetate 39i**

![Cinnamyl acetate](attachment:image)

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 83% yield (0.146 g, 0.83 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.3 (s, 5H, ArH), 6.7 (dt, J = 15.9, 1.4 Hz, 1H, CH=CHCH₂), 6.3 (dt, J = 15.9, 6.5 Hz, 1H, CH=CHCH₂), 4.7 (dd, J = 6.5, 1.4 Hz, 2H, CH=CHCH₂), 2.1 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 171.0, 136.3, 134.4, 128.7, 128.2, 126.7, 123.3, 65.2, 21.2.

Analytical data in accordance with literature. ³¹³

**(E)-3,7-dimethylocta-2,6-dien-1-yl acetate 39j**

![3,7-dimethylocta-2,6-dien-1-yl acetate](attachment:image)

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a waxy white solid in 89% yield (0.174 g, 0.89 mmol). ¹H NMR (300 MHz, CDCl₃) δ 5.3 (tq, J = 7.2, 1.3 Hz, 1H, C=CHCH₂O), 5.1 (tq, J = 5.5, 1.5 Hz, 1H, C=CHCH₂), 4.6 (d, J = 7.1 Hz, 2H, CH₂OAc), 2.2 – 2.0 (m, 7H, 2 x CH₂ and (C=O)CH₃), 1.7 (dd, J = 5.9, 1.3 Hz, 6H, CH₃(C)CH₃), 1.6 (d, J = 1.4 Hz, 3H, CH₃C(CH₃)=CH). ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 142.5, 132.0, 123.9, 118.3, 61.6, 39.7, 26.4, 25.8, 21.2, 17.8, 16.6.

Analytical data in accordance with literature. ³⁰⁷
(S)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl acetate 39k

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 85% yield (0.165 g, 0.85 mmol). [α]D20 = -65.5 in CHCl3.

1H NMR (300 MHz, CDCl3) δ 5.8 (dd, J = 4.6, 2.4 Hz, 1H, CH2C=CH), 4.8 – 4.7 (m, 2H, C=CH2), 4.5 (d, J = 1.7 Hz, 2H, CH2OAc), 2.2 – 2.0 (m, 7H, 2 x CH2 and (C=O)CH3), 2.0 – 1.8 (m, 2H, CH2), 1.7 (t, J = 1.1 Hz, 3H, CH3C=CH2), 1.5 – 1.4 (m, 1H, CH). 13C NMR (75 MHz, CDCl3) δ 171.2, 149.8, 132.7, 126.0, 108.9, 68.7, 40.9, 30.6, 27.4, 26.5, 21.2, 20.9.

Analytical data in accordance with literature.314

2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate (mix of isomers) 39l

General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 68% yield (0.132 g, 0.68 mmol). 1H NMR (300 MHz, CDCl3) δ 5.7 (dt, J = 5.3, 1.8 Hz, 1H), 5.6 (dq, J = 5.5, 1.8 Hz, 1H), 5.4 (d, J = 1.5 Hz, 1H), 5.3 – 5.2 (m, 1H), 4.8 – 4.7 (m, 4H), 2.4 – 2.1 (m, 4H), 2.1 (d, J = 1.0 Hz, 6H), 2.0 – 1.8 (m, 3H), 1.7 (dt, J = 4.4, 1.1 Hz, 5H), 1.7 (dd, J = 2.7, 1.4 Hz, 3H), 1.6 (dp, J = 2.5, 1.3 Hz, 3H), 1.6 – 1.5 (m, 1H), 1.5 – 1.4 (m, 1H). 13C NMR (75 MHz, CDCl3) δ 171.1, 171.1, 148.9, 148.4, 133.0, 131.1, 128.1, 126.1, 109.5, 109.3, 73.4, 70.8, 40.4, 35.9, 34.1, 33.7, 31.0, 30.9, 21.6, 21.4, 21.0, 20.8, 20.6, 19.0.

Analytical data in accordance with literature.315
Phenylmethylene dipropionate 41a

![Structural formula](attachment:structure.png)

General procedure C was followed to afford the title compound as a clear oil in 97% yield (2.15 g, 9.12 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.7 (s, 1H, CH(OCOEt)$_2$), 7.5 (qd, $J = 3.8, 1.5$ Hz, 2H, ArH), 7.4 (ddt, $J = 4.3, 3.1, 1.6$ Hz, 3H, ArH), 2.5 – 2.3 (m, 4H, 2 x CH$_2$CH$_3$), 1.2 (dt, $J = 8.5, 7.5$ Hz, 6H, 2 x CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.4, 170.4, 135.8, 129.8, 128.7, 126.8, 89.7, 28.9, 27.5, 8.9, 8.5. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 2983 (ArC-H), 1756 (C=O); HRMS (ESI): m/z calculated for C$_{13}$H$_{12}$O$_4$: requires: 259.0946 for [M+Na]$^+$; found: 259.0995.

Phenylmethylene dibenzoate 41b

![Structural formula](attachment:structure.png)

General procedure C was followed to afford the title compound as a clear oil in 99% yield (3.09 g, 9.30 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.3 – 8.1 (m, 5H, CH and ArH), 7.8 – 7.6 (m, 3H, ArH), 7.6 – 7.5 (m, 4H, ArH), 7.5 – 7.4 (m, 4H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.6, 162.5, 134.7, 133.7, 130.7, 130.2, 129.9, 129.2, 129.0, 128.6, 126.9, 90.8. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 3064 (ArC-H), 1722 (C=O); HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$O$_4$: requires: 355.0946 for [M+Na]$^+$; found: 355.0929.

Phenylmethylene diacrylate 41c

![Structural formula](attachment:structure.png)

General procedure C was followed to afford the title compound as a clear oil in 97% yield (2.12 g, 9.12 mmol). $^1$H NMR (300 MHz, Chloroform-d) δ 7.9 (s, 1H, CHPh), 7.7 – 7.5 (m, 2H, ArH), 7.5 – 7.4 (m, 3H, ArH), 6.5 (dd, $J = 17.3, 1.4$ Hz, 2H, CH$_3$H$_5$=CH), 6.3 – 6.0 (m, 2H, CH$_3$H$_5$=CH),
5.9 (dd, J = 10.5, 1.3 Hz, 2H, CH$_3$H$_6$=CH). $^{13}$C NMR (75 MHz, Chloroform-d) δ 164.0, 134.8, 132.8, 129.9, 128.8, 127.6, 126.8, 90.1. I.R (thinfilm) ν max (cm$^{-1}$): 3040 (ArC-H), 1732 (C=O); HRMS (ESI): m/z calculated for C$_{13}$H$_{12}$O$_4$: requires: 255.0633 for [M+Na]$^+$; found: 255.0667.

**Phenylmethylene dihexanoate 41d**

![Diagram of Phenylmethylene dihexanoate 41d]

General procedure C was followed to afford the title compound as a clear oil in 96% yield (2.89 g, 9.02 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.7 (s, 1H, CHPh), 7.5 – 7.5 (m, 2H, ArH), 7.5 – 7.3 (m, 3H, ArH), 2.4 (td, J = 7.4, 2.3 Hz, 4H, 2 x (C=O)CH$_2$CH$_2$), 1.7 – 1.6 (m, 4H, 2 x (C=O)CH$_2$CH$_2$), 1.3 (dtq, J = 10.4, 7.0, 3.1 Hz, 8H, 2 x CH$_2$CH$_2$CH$_3$), 0.9 – 0.9 (m, 6H, 2 x CH$_2$CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.8, 135.9, 129.8, 128.7, 126.8, 89.6, 35.4, 34.2, 31.3, 24.5, 22.4, 14.0. I.R (thinfilm) ν max (cm$^{-1}$): 2956 (ArC-H), 1752 (C=O); HRMS (ESI): m/z calculated for C$_{19}$H$_{28}$O$_4$: requires: 343.1885 for [M+Na]$^+$; found: 343.1898.

**Phenylmethylene bis(2-phenylacetate) 41e**

![Diagram of Phenylmethylene bis(2-phenylacetate) 41e]

General procedure C was followed to afford the title compound as a clear oil in a 94% yield (3.18 g, 8.84 mmol). $^1$H NMR (250 MHz, CDCl$_3$) δ 7.7 (s, 1H, CHPh), 7.4 – 7.2 (m, 15H, ArH), 3.6 (s, 4H, 2 x CH$_2$Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.5, 135.3, 133.2, 129.9, 129.5, 129.4, 128.7, 127.4, 126.7, 90.3, 41.1. I.R (thinfilm) ν max (cm$^{-1}$): 2956, 2981 (ArC-H), 1752 (C=O); HRMS (ESI): m/z calculated for C$_{23}$H$_{20}$O$_4$: requires: 383.1259 for [M+Na]$^+$; found: 383.1259.

**Phenylmethylene bis(2,2,2-trifluoroacetate) 41f**

![Diagram of Phenylmethylene bis(2,2,2-trifluoroacetate) 41f]

To a solution of benzaldehyde (0.50 g, 4.7 mmol) and trifluoroacetic anhydride (0.98 mL, 7.08 mmol) was added trifluoroacetic acid (0.035 mL, 0.47 mmol) dropwise at rt. After 2 h the
reaction was concentrated *en vacuo* to give the title compound as a yellow oil in 95% yield (1.4 g, 4.5 mmol). Taken forward to be used in subsequent steps without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.8 (s, 1H, ArH), 7.6 (dd, $J = 7.8$, 1.9 Hz, 2H, ArH), 7.6 – 7.5 (m, 3H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.3 (q, $^2$J$_{C-F}$ = 44.7 Hz), 134.4, 131.8, 129.4, 127.0, 114.1 (q, $^2$J$_{C-F}$ = 285.5 Hz), 93.8. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 1809 (C=O)

*N*-benzylpropionamide 42a

![N-benzylpropionamide 42a](image)

General procedure D was followed. Eluent 30% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a fluffy white solid in 95% yield (0.155 g, 0.95 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.4 – 7.2 (m, 5H, ArH), 5.8 (s, 1H, NH), 4.4 (d, $J = 5.7$ Hz, 2H, CH$_2$Ph), 2.2 (q, $J = 7.6$ Hz, 2H, CH$_2$CH$_3$), 1.2 (t, $J = 7.6$ Hz, 3H, CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.7, 138.5, 128.8, 128.0, 127.6, 43.7, 29.8, 10.0.

Analytical data in accordance with literature.$^{316}$

*N*-benzylbenzamide 42b

![N-benzylbenzamide 42b](image)

General procedure D was followed. Eluent 30% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 87% yield (0.184 g, 0.87 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.8 – 7.7 (m, 2H, ArH), 7.6 – 7.3 (m, 8H, ArH), 6.4 (s, 1H, NH), 4.7 (d, $J = 5.6$ Hz, 2H, CH$_2$Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.5, 138.3, 134.5, 131.7, 129.0, 128.8, 128.1, 127.8, 127.1, 44.3.

Analytical data in accordance with literature.$^{316}$
**N-benzylacrylamide 42c**

General procedure D was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 96% yield (0.154 g, 0.96 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.4 – 7.3 (m, 5H, ArH), 6.3 (dd, J = 16.9, 1.5 Hz, 1H, CH=CH₂H₆), 6.1 (dd, J = 17.0, 10.2 Hz, 1H, CH=CH₂H₆), 5.9 (s, 1H, NH), 5.7 (dd, J = 10.2, 1.5 Hz, 1H, CH=CH₂H₆), 4.5 (d, J = 5.8 Hz, 2H, CH₂Ph). ¹³C NMR (75 MHz, CDCl₃) δ 165.5, 138.1, 130.7, 128.9, 128.7, 128.0, 127.8, 127.0, 126.8, 43.8.

Analytical data in accordance with literature.³¹⁷

**N-benzylhexanamide 42d**

General procedure D was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 91% yield (0.186 g, 0.91 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.4 – 7.3 (m, 5H, ArH), 5.7 (s, 1H, NH), 4.4 (d, J = 5.7 Hz, 2H, CH₂Ph), 2.2 (dd, J = 8.6, 6.7 Hz, 2H, (C=O)CH₂CH₂CH₂), 1.7 – 1.6 (m, 2H, (C=O)CH₂CH₂CH₂), 1.3 (dq, J = 7.2, 3.8, 3.2 Hz, 4H, (C=O)CH₂CH₂CH₂), 0.9 – 0.8 (m, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 173.1, 138.5, 128.9, 128.0, 127.7, 43.7, 37.0, 31.6, 25.6, 22.6, 14.1.

Analytical data in accordance with literature.³¹⁸

**N-benzyl-2-phenylacetamide 42e**

General procedure D was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the
title compound as a pale brown solid in a 79% yield (0.178 g, 0.79 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.3 (s, 8H, ArH), 7.2 – 7.1 (m, 2H, ArH), 5.7 (s, 1H, NH), 4.4 (d, J = 5.8 Hz, 2H, PhCH$_2$NH), 3.6 (s, 2H, PhCH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.0, 138.2, 134.9, 129.6, 129.2, 128.8, 127.6, 127.6, 44.0, 43.7.

Analytical data in accordance with literature.$^{318}$

**N-benzyl-2,2,2-trifluoroacetamide 42f**

![N-benzyl-2,2,2-trifluoroacetamide 42f](image)

Benzylamine (0.107 g, 1.0 mmol) was added to phenylmethylene bis(2,2,2-trifluoroacetate) (0.474 g, 1.5 mmol) the reaction was stirred at rt for 1 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated title product. Eluent 30% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 91% yield (0.184 g, 0.91 mmol); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.4 – 7.3 (m, 3H, ArH), 7.32 – 7.27 (m, 2H, ArH), 6.6 (s, 1H, NH), 4.5 (d, J = 5.8 Hz, 2H, CH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.3 (q, $^2$JC-F = 37.2 Hz), 135.9, 129.1, 128.4, 128.1, 116.0 (q, $^1$JC-F = 287.8 Hz), 44.0.

Analytical data in accordance with literature.$^{319}$

**Benzyl propionate 43a**

![Benzyl propionate 43a](image)

General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 94% yield (0.154 g, 0.94 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.4 – 7.3 (m, 5H, ArH), 5.1 (s, 2H, CH$_2$Ph), 2.4 (q, J = 7.6 Hz, 2H, CH$_2$CH$_3$), 1.2 (t, J = 7.6 Hz, 3H, CH$_3$CH$_2$). C NMR (75 MHz, CDCl$_3$) δ 174.5, 136.3, 128.7, 128.3, 126.8, 66.3, 27.8, 9.3.

Analytical data in accordance with literature.$^{320}$
Benzyl benzoate 43b

General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 78% yield (0.166 g, 0.78 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.2 – 7.9 (m, 2H, ArH), 7.6 – 7.5 (m, 1H, ArH), 7.5 – 7.3 (m, 7H, ArH), 5.4 (s, 2H, CH$_2$Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.6, 136.2, 133.2, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8.

Analytical data in accordance with literature.$^{320}$

Benzyl acrylate 43c

General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 81% yield (0.131 g, 0.81 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.4 – 7.3 (m, 5H, ArH), 6.5 (dd, $J$ = 17.3, 1.4 Hz, 1H, CH=CH$_2$H$_3$), 6.2 (dd, $J$ = 17.3, 10.4 Hz, 1H, CH=CH$_2$H$_3$), 5.9 (dd, $J$ = 10.4, 1.4 Hz, 1H, CH=CH$_2$H$_3$), 5.2 (s, 2H, CH$_2$Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.2, 136.0, 131.2, 128.7, 128.5, 128.4, 128.4, 66.5.

Analytical data in accordance with literature.$^{320}$

Benzyl hexanoate 43d

General procedure E was followed. Eluent 3% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 70% yield (0.144 g, 0.70 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.4 – 7.3 (m, 5H, ArH), 5.1 (s, 2H, CH$_2$Ph), 2.4 (t, $J$ = 7.5 Hz, 2H, (C=O)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.7 – 1.6 (m, 2H, (C=O)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.3 (dq, $J$ = 7.5, 3.8, 3.2 Hz, 4H, (C=O)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 0.9 –
0.8 (m, 3H, (C=O)CH₂CH₂CH₂CH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 173.8, 136.3, 128.7, 128.3, 126.8, 66.2, 34.4, 31.4, 24.8, 22.4, 14.0.

Analytical data in accordance with literature.³²¹

**Benzyl 2-phenylacetate 43e**

![Benzyl 2-phenylacetate](image)

General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 62% yield (0.140 g, 0.62 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.4 – 7.3 (m, 10H, ArH), 5.2 (s, 2H, PhCH₂O), 3.7 (s, 2H, (C=O)CH₂Ph). ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 136.0, 134.0, 129.4, 128.7, 128.3, 128.2, 127.2, 66.7, 41.5.

Analytical data in accordance with literature.³²¹

**Benzyl 2,2,2-trifluoroacetate 43f**

![Benzyl 2,2,2-trifluoroacetate](image)

Benzyl alcohol (0.108 g, 1.0 mmol) was added to phenylmethylene bis(2,2,2-trifluoroacetate) (0.474 g, 1.5 mmol) and K₂CO₃ (2.0 mmol, 0.270 g) the reaction was stirred at rt for 1 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated title compound. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 89% yield (0.181 g, 0.89 mmol); ¹H NMR (300 MHz, CDCl₃) δ 7.4 (s, 5H), 5.4 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 157.5 (q, ²JC-F = 42.5 Hz), 133.4, 129.4, 129.0, 128.8, 114.6 (q, ¹JC-F = 285.8 Hz), 69.7.

Analytical data in accordance with literature.³²²
**(formyloxy)(phenyl)methyl acetate 44.2**

![Structure](image)

Copper(II) tetrafluoroborate hydrate (0.044 g, 1.80 mmol) was added to a mixture of benzaldehyde (2.0 g, 18.0 mmol) and acetic formic anhydride (2.40 g, 27.0 mmol) at -20 °C and stirred for 5 min. The reaction was then quenched with saturated Na$_2$CO$_3$ (10 mL) and diluted with Et$_2$O (50 mL). The reaction was then washed with saturated Na$_2$CO$_3$ (3 x 20 mL). The organics were dried (MgSO$_4$) and concentrated in vacuo. The resulting residue was purified by column chromatography (5% EtOAc in pet ether Rf = 0.56) to give the title compound as a clear oil in 59% yield.

$^1$H NMR (300MHz, CDCl$_3$) δ = 8.12 (d, J = 0.9 Hz, 1H, (C=O)H), 7.77 (s, 1H, CHAr), 7.59 - 7.50 (m, 2H, ArH), 7.47 - 7.41 (m, 3H, ArH), 2.16 (s, 3H, CH$_3$).

$^{13}$C NMR (75MHz, CDCl$_3$) δ = 168.8, 158.7, 134.7, 130.0, 128.7, 126.7, 89.2, 20.8. I.R (thinfilm) ν max (cm$^{-1}$): 3040 (ArC-H), 1750, 1732 (C=O);


**N-benzylformamide 47a**

![Structure](image)

General procedure F was followed. Eluent 30% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white solid in 89% yield (0.24 g, 1.78 mmol). m.p. 60-61 °C

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (s, 1 H, (C=O)H) (major), 8.00 (d, J = 11.9 Hz, 1H, (C=O)H) (minor), 7.34 - 7.06 (m, 5H, ArH), 6.38 (br. s., 1H, NH), 4.34 (d, J = 6.0 Hz, 2H, CH$_2$NH) (major), 4.27 (d, J = 6.6 Hz, 2H, CH$_2$NH) (minor). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.7 (minor), 161.1 (major), 137.5, 128.8 (minor), 128.6 (major), 127.8 (minor), 127.6 (major), 127.5 (major), 126.8 (minor), 45.5 (minor), 42.0 (major).

Analytical data in accordance with literature.
**N-(furan-2-ylmethyl)formamide 47b**

![furan-2-ylmethyl formamide](image)

General procedure F was followed. Eluent 25% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 80% yield (0.20 g, 1.60 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.19 (s, 1H, (C=O)H) (major), 8.16 (d, $J$ = 11.9 Hz, 1H, (C=O)H) (minor), 7.38 (dd, $J$ = 0.8, 1.8 Hz, 1H, CHC(H)O) (minor), 7.35 (dd, $J$ = 0.8, 1.9 Hz, 1H, CHC(H)O) (major), 6.32 (dd, $J$ = 1.8, 3.3 Hz, 1H, CHC(H)O), 6.24 (dd, $J$ = 0.8, 3.2 Hz, 1H, CCH), 4.46 (d, $J$ = 5.7 Hz, 2H, CH$_2$NH) (major), 4.36 (d, $J$ = 6.4 Hz, 2H, CH$_2$NH) (minor). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.6 (minor), 160.9 (major), 150.5, 142.8 (minor), 142.3 (major), 110.4, 107.6 (major), 107.4 (minor), 38.8 (minor), 34.9 (major).

Analytical data in accordance with literature.$^{323}$

**N-(benzo[d][1,3]dioxol-5-ylmethyl)formamide 47c**

![benzo[d][1,3]dioxol-5-ylmethyl formamide](image)

General procedure F was followed. Eluent 30% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white crystalline solid in 82% yield (0.293 g, 1.64 mmol). m.p. 96-98 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (s, 1H, (C=O)H) (major), 8.12 (d, $J$ = 12.1 Hz, 1H, (C=O)H) (minor), 6.79 - 6.66 (m, 3H, ArH), 6.18 (br. s., 1H, NH), 5.96 (s, 2H, OCH$_2$O) (minor), 5.93 (s, 2H, OCH$_2$O) (major), 4.35 (d, $J$ = 5.8 Hz, 2H, CH$_2$NH) (major), 4.29 (d, $J$ = 6.4 Hz, 2H, CH$_2$NH) (minor). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.5 (minor), 161.0 (major), 147.9, 147.0, 131.4, 121.0 (major), 120.3 (minor), 108.4 (minor), 108.3 (major), 108.2 (major), 107.4 (minor), 101.2 (minor), 101.0 (major), 45.5 (minor), 41.9 (major).

Analytical data in accordance with literature.$^{299}$
**N-(2-{1H-indol-3-yl}ethyl)formamide 47d**

General procedure F was followed. Eluent 100% EtOAc the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as pale brown viscous oil in 90% yield (0.339 g, 1.80 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.46 (br. s., 1 H, ArN$_2$H) (major), 8.05 (s, 1 H, (C=O)H) (major), 7.84 (d, $J = 12.1$ Hz, 1 H, (C=O)H) (minor), 7.60 (d, $J = 7.9$ Hz, 1 H, ArH) (major), 7.56 (d, $J = 7.9$ Hz, 1 H, ArH) (minor), 7.37 (d, $J = 8.1$ Hz, 1 H, ArH), 7.28 - 7.09 (m, 3 H, ArH), 7.01 (d, $J = 2.1$ Hz, 1 H, ArH) (major), 6.96 (d, $J = 2.3$ Hz, 1 H, ArH) (minor), 5.80 (br. s., 1 H, CH$_2$N$_2$H) (major), 3.63 (q, $J = 6.5$ Hz, 2 H, CH$_2$NH) (major), 3.48 (q, $J = 6.5$ Hz, 2 H, CH$_2$NH) (minor), 3.02 - 2.90 (app m, 2 H, CH$_2$CH$_2$NH) (major and minor). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.7 (minor), 161.3 (major), 136.4 (minor), 136.3 (major), 127.1 (major), 126.7 (minor), 122.8 (minor), 122.2 (major), 122.2 (minor), 119.4 (minor), 119.4 (major), 118.5 (major), 118.3 (minor), 112.2 (major), 111.5 (minor), 111.3 (major), 111.2 (minor), 41.9 (minor), 38.3 (major), 27.2 (minor), 25.0 (major).

Analytical data in accordance with literature.$^{299}$

**N-(2,2-dimethoxyethyl)formamide 47e**

General procedure F was followed. Eluent 20% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 95% yield (0.253 g, 1.9 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.17 (s, 1 H, (C=O)H) (major), 8.02 (d, $J = 12.1$ Hz, 1H, (C=O)H) (minor), 6.03 (br. s., 1H, NH), 4.39 (t, $J = 5.2$ Hz, 1H, CH(OMe)$_2$) (major), 4.31 (t, $J = 5.2$ Hz, 1H, CH(OMe)$_2$) (minor), 3.46 - 3.41 (m, 2H CH$_2$NH) (major), 3.40 (s, 6H, OCH$_3$) (minor), 3.39 (s, 6H, OCH$_3$) (major), 3.29 (dd, $J = 5.1$, 6.6 Hz, 2H, CH$_2$NH) (minor). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.9 (minor), 161.3 (major), 103.4 (minor), 102.3 (major), 54.7 (minor), 54.4 (major), 43.6 (minor), 39.4 (major). I.R (thinfilm) $\nu$ max (cm$^{-1}$):
3295 (N-H), 1658 (C=O); HRMS (ESI): m/z calculated for C₅H₁₁NO₃: requires: 134.0817 for [M+H]+; found: 134.0824.

*N-benzhydrylformamide 47f*

![N-benzhydrylformamide](image)

General procedure F was followed. Eluent 20% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white crystalline solid in 83% yield (0.35 g, 1.66 mmol). m.p. 133-134 °C ¹H NMR (300 MHz, CDCl₃) δ 8.30 (s, 1H, (C=O)H) (major), 8.21 (d, J = 11.9 Hz, 1H, (C=O)H) (minor), 7.39 - 7.27 (m, 5H, ArH), 7.27 - 7.19 (m, 5H, ArH), 6.33 (d, J = 8.3 Hz, 1H, ArCH) (major), 6.25 (br. s., 1H, NH), 5.77 (d, J = 8.3 Hz, 1H, ArCH) (minor). ¹³C NMR (75 MHz, CDCl₃) δ 160.1, 140.8, 128.9 (minor), 128.7 (major), 128.0 (minor), 127.6 (major), 127.3 (major), 127.2 (minor), 55.6.

Analytical data in accordance with literature.²⁹⁹

*(S)-methyl 2-formamido-3-methylbutanoate 47g*

![Methyl 2-formamido-3-methylbutanoate](image)

General procedure F was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale pink crystalline solid in 93% yield (0.296 g, 1.86 mmol). m.p. 68-69 °C; [α]D²⁰ = -22 in EtOH; ¹H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H, (C=O)H) (major), 7.98 (d, J = 11.7 Hz, 1H, (C=O)H) (minor), 6.53 (br. s., 1H, NH), 4.62 (ddd, J = 0.8, 4.9, 9.1 Hz, 1H, CHNH) (major), 3.91 (dd, J = 5.1, 10.2 Hz, 1H, CHNH) (minor), 3.74 (s, 3H, OCH₃) (minor), 3.72 (s, 3H, OCH₃) (major), 2.23 - 2.08 (m, 1H, CH(CH₃)₂), 0.93 (d, J = 6.8 Hz, 3H, CH(CH₃)₂), 0.88 (d, J = 6.8 Hz, 3H, CH(CH₃)₂). ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (major), 171.3 (minor), 163.9 (minor), 161.0 (major), 60.3 (minor), 55.5 (major), 52.4 (minor), 52.2 (major), 31.3 (minor), 31.1 (major), 19.0 (minor), 18.8 (major), 17.5 (major), 17.0 (minor)
Analytical data in accordance with literature.\textsuperscript{87}

\textit{N-tert-butylformamide 47h}

\begin{center}
\includegraphics[width=0.2\textwidth]{n tert butylformamide.png}
\end{center}

General procedure F was followed. Eluent 20\% EtOAc in CH\(_2\)Cl\(_2\) the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 53\% yield (0.107 g, 1.06 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.26 (d, \(J = 12.4\) Hz, 1H, (C=O)H) (minor), 8.03 (s, 1H, (C=O)H) (major), 6.15 (br. s., 1H, NH) (minor), 5.40 (br. s., 1H, NH) (major), 1.38 (s, 9H, CH\(_3\)) (minor), 1.33 (s, 9H, CH\(_3\)) (major). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.0 (major), 160.6 (minor), 51.3 (major), 50.3 (minor), 30.8 (major), 28.9 (minor).

Analytical data in accordance with literature.\textsuperscript{323}

\textit{N,N-dipropylformamide 47i}

\begin{center}
\includegraphics[width=0.2\textwidth]{n n dipropylformamide.png}
\end{center}

General procedure F was followed. Eluent 20\% EtOAc in CH\(_2\)Cl\(_2\) the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 74\% yield (0.191 g, 1.48 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.04 (s, 1H, (C=O)H), 3.27 - 3.19 (m, 2H, CH\(_2\)CH\(_2\)CH\(_3\)), 3.15 (t, \(J = 7.1\) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_3\)), 1.63 - 1.46 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)), 0.88 (dt, \(J = 2.2, 7.4\) Hz, 6H, CH\(_2\)CH\(_2\)CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 162.8, 49.1, 43.6, 21.7, 20.4, 11.2, 10.8.

Analytical data in accordance with literature.\textsuperscript{87}

\textit{N,N-diallylformamide 47j}

\begin{center}
\includegraphics[width=0.2\textwidth]{n n diallylformamide.png}
\end{center}

General procedure F was followed. Eluent 20\% EtOAc in CH\(_2\)Cl\(_2\) the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 58\% yield (0.145 g, 1.16 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\))
δ 8.10 (s, 1H, (C=O)H), 5.79 - 5.58 (m, 2H, CH₂CH=CH₂), 5.25 - 5.21 (m, 1H, CH₂CH=CH₂H₃), 5.19 (qd, J = 1.3, 4.1 Hz, 1H, CH₂CH=CH₂H₃), 5.17 - 5.14 (m, 2H, CH₂CH=CH₂H₃), 3.91 (td, J = 1.3, 5.9 Hz, 2H, CH₂CH=CH₂H₃), 3.79 (td, J = 1.2, 5.8 Hz, 2H, CH₂CH=CH₂H₃). ¹³C NMR (75 MHz, CDCl₃) δ 162.5, 132.9, 131.9, 118.5, 118.0, 49.1, 44.1. I.R (thinfilm) ν max (cm⁻¹): 1665 (C=O); HRMS (ESI): m/z calculated for C₇H₁₁NO: requires: 126.0918 for [M+H]⁺; found: 126.0932.

4-phenylpiperazine-1-carbaldehyde 47k

General procedure F was followed. Eluent 30% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale pink crystalline solid in 96% yield (0.365 g, 1.92 mmol). m.p. 83-85 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1H, (C=O)H), 7.33 - 7.21 (m, 2H, ArH), 6.97 - 6.87 (m, 3H, ArH), 3.74 - 3.63 (m, 2H CH₂CH₂NC(O)H), 3.56 - 3.44 (m, 2H, CH₂CH₂NC(O)H), 3.14 (td, J = 5.3, 11.1 Hz, 4H, CH₂CH₂NC(O)H). ¹³C NMR (75 MHz, CDCl₃) δ 160.6, 150.8, 129.1, 120.7, 116.9, 50.3, 49.2, 45.3, 39.8

Analytical data in accordance with literature.³²₄

N-phenylformamide 47l

General procedure F was followed. Eluent 20% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 90% yield (0.218 g, 1.80 mmol). ¹H NMR (300 MHz, CDCl₃) δ 8.98 (br. s., 1H, NH) (minor), 8.62 (d, J = 11.3 Hz, 1H, (C=O)H) (minor), 8.25 (d, J = 1.7 Hz, 1H, (C=O)H) (major), 8.13 (br. s., 1H, NH) (major), 7.51 - 7.42 (m, 1H, ArH), 7.30 - 7.17 (m, 2H, ArH), 7.13 - 6.97 (m, 2H, ArH). ¹³C NMR (75MHz, CDCl₃) δ 163.0 (major), 159.5 (minor), 136.9 (minor), 136.7 (major), 129.6 (major), 129.0 (minor), 125.2 (major), 124.7 (minor), 120.0 (minor), 118.6 (major)

Analytical data in accordance with literature.⁸₀
**N-(4-bromophenyl)formamide 47m**

![Structure of N-(4-bromophenyl)formamide](image)

General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended reaction time of 24 h. The solvent was re-moved before purification. Eluent 15% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white crystalline solid in 95% yield (0.380 g, 1.90 mmol). m.p. 115-117 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.67 (d, J = 11.3 Hz, 1H, (C=O)H) (minor), 8.40 (d, J = 1.5 Hz, 1H, (C=O)H) (major), 8.09 (br. s., 1H, NH) (minor), 7.52 - 7.47 (m, 2H, ArH), 7.46 (s, 4H, ArH) (major and minor), 7.32 (br. s., 1H, NH) (major), 7.02 - 6.95 (m, 2H, ArH). ¹³C NMR (75 MHz, CDCl₃) δ 162.5 (minor), 159.0 (major), 135.8 (major), 135.7 (minor), 132.7 (minor), 126.1 (major), 121.5 (major), 120.2 (minor), 118.2 (minor), 117.4 (major)

Analytical data in accordance with literature.

**N-(4-chlorophenyl)formamide 47n**

![Structure of N-(4-chlorophenyl)formamide](image)

General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended reaction time of 24 h. The solvent was re-moved before purification. Eluent 15% EtOAc in CH₂Cl₂ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a beige crystalline solid in 94% yield (0.292 g, 1.88 mmol). m.p. 101-102 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (br. s., 1H, NH) (minor), 8.52 - 8.44 (m, 1H, (C=O)H) (minor), 8.19 (d, J = 1.9 Hz, 1H, (C=O)H) (major), 7.38 - 7.29 (m, 2H, ArH), 7.63 (br. s., 1H, NH) (major), 7.19 - 7.07 (m, 4H, ArH), 6.93 - 6.82 (m, 2H, ArH). ¹³C NMR (75 MHz, CDCl₃) δ 162.7 (minor), 159.2 (major), 135.4 (major), 135.2 (minor), 130.7, 129.8, 129.1, 121.2, 120.0

Analytical data in accordance with literature.
Methyl 4-formamidobenzoate 47o

![Methyl 4-formamidobenzoate](image)

General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended reaction time of 24 h. The solvent was removed before purification. Eluent 15% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white crystalline solid in 87% yield (0.311 g, 1.74 mmol). m.p. 123-125 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.87 (d, J = 11.1 Hz, 1 H, (C=O)H) (minor), 8.66 (d, J = 11.1 Hz, 1H, NH) (minor), 8.44 (d, J = 1.7 Hz, 1H, (C=O)H) (major), 8.09 - 7.97 (m, 4H, ArH), 7.80 (br. s., 1H, NH) (major), 7.69 - 7.59 (m, 2H, ArH), 7.19 - 7.12 (m, 2H, ArH), 3.92 (s, 3H, OCH$_3$) (minor), 3.91 (s, 3H, OCH$_3$) (major).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.5, 166.3, 162.0, 159.1, 140.9, 131.5, 130.9, 126.5, 126.1, 119.1, 117.1, 52.2, 52.1.

Analytical data in accordance with literature.$^{325}$

$N$-methyl-$N$-phenylformamide 47p

![N-methyl-N-phenylformamide](image)

General procedure F was followed. Eluent 10% EtOAc in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale brown oil in 91% yield (0.243 g, 1.82 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.28 (s, 1H, (C=O)H) (major), 8.17 (s, 1H, (C=O)H) (minor), 7.26 - 7.18 (m, 2H, ArH), 7.13 - 7.04 (m, 1H, ArH), 7.02 - 6.95 (m, 2H, ArH), 3.16 (s, 3H, NCH$_3$) (minor), 3.13 (s, 3H, NCH$_3$) (major). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.1 (major), 162.0 (minor), 141.9, 129.4 (major), 128.8 (minor), 126.1 (major), 126.0 (minor), 123.3 (minor), 122.0 (major), 36.6 (minor), 31.8 (major)

Analytical data in accordance with literature.$^{323}$
N-Formyl valine 49a

![N-Formyl valine structure]

General procedure G was followed. Recrystallized to give the title compound as a white solid in 78% yield (0.113 g, 0.78 mmol). $[\alpha]_D^{20} = -11$ in MeOH. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.8 (s, 1H, OH), 8.3 (d, $J = 8.7$ Hz, 1H, NH), 8.1 (s, 1H, (C=O)H), 4.2 (dd, $J = 8.8, 5.3$ Hz, 1H, CHNH), 2.1 (tq, $J = 13.6, 6.8$ Hz, 1H, CH(CH$_3$)$_2$), 0.9 (dd, $J = 6.8, 4.7$ Hz, 6H, CH(CH$_3$)$_2$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 172.7, 161.2, 55.6, 29.9, 19.2, 17.7.

Analytical data in accordance with literature.$^{80}$

N-Formyl phenylalanine 49b

![N-Formyl phenylalanine structure]

General procedure G was followed. Recrystallized to give the title compound as a cream solid in 86% yield (0.166 g, 0.86 mmol). $[\alpha]_D^{20} = +63$ in MeOH. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.8 (s, 1H, OH), 8.4 (d, $J = 8.0$ Hz, 1H, NH), 8.0 (dd, $J = 1.7, 0.8$ Hz, 1H, (C=O)H), 7.3 – 7.2 (m, 2H, ArH), 7.3 – 7.2 (m, 4H, ArH), 4.5 (dddd, $J = 9.1, 8.2, 5.0, 0.9$ Hz, 1H, CHNH), 3.1 – 2.8 (m, 2H, CH$_2$Ph). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 172.5, 160.9, 137.3, 129.1, 128.2, 126.5, 51.9, 36.7.

Analytical data in accordance with literature.$^{80}$

N-Formyl leucine 49c

![N-Formyl leucine structure]

General procedure G was followed. Recrystallized to give the title compound as a white solid in a 74% yield (0.118 g, 0.74 mmol). $[\alpha]_D^{20} = -19$ in MeOH. $^1$H NMR (300 MHz, MeOD-$d_4$) $\delta$ 8.1 (s, 1H, (C=O)H), 4.5 (dd, $J = 9.2, 5.1$ Hz, 1H, CHNH), 1.8 – 1.5 (m, 3H, CH(CH$_3$)$_2$ and CH$_2$CHNH),
1.0 (dd, J = 8.0, 6.1 Hz, 6H, CH(CH$_3$)$_2$). $^{13}$C NMR (75 MHz, MeOD-$_d_4$) δ 175.4, 163.6, 50.6, 41.9, 26.0, 23.3, 21.8.

Analytical data in accordance with literature.$^{80}$

**N-Formyl methionine 49d**

![N-Formyl methionine 49d](image)

General procedure G was followed. Recrystallized to give the title compound as a pale yellow solid in 81% yield (0.143 g, 0.81 mmol). [α]$_D^{20}$ = +7.5 in MeOH. $^1$H NMR (300 MHz, MeOD-$_d_4$) δ 8.1 (s, 1H, (C=O)H), 4.6 (dd, J = 8.7, 4.7 Hz, 1H, CHNH), 2.7 – 2.4 (m, 2H, CH$_3$SCH$_2$), 2.2 – 2.1 (m, 1H, CH$_3$SCH$_2$CH$_2$H$_3$), 2.1 (s, 3H, CH$_3$), 2.0 (dt, J = 14.1, 8.4, 5.8 Hz, 1H, CH$_3$SCH$_2$CH$_2$H$_3$). $^{13}$C NMR (75 MHz, MeOD-$_d_4$) δ 174.4, 163.6, 51.3, 32.4, 31.0, 15.2.

Analytical data in accordance with literature.$^{80}$

**N-Formyl alanine 49e**

![N-Formyl alanine 49e](image)

General procedure G was followed. Recrystallized to give the title compound as a white solid in 89% yield (0.104 g, 0.89 mmol). [α]$_D^{20}$ = -35.5 in MeOH. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.1 (s, 1H, (C=O)H), 4.5 (q, J = 7.3 Hz, 1H, CHCH$_3$), 1.4 (d, J = 7.3 Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.4, 163.3, 48.0, 18.0.

Analytical data in accordance with literature.$^{80}$
General procedure G was followed. Recrystallized to give the title compound as a pale brown solid in a 71% yield (0.165 g, 0.71 mmol). $[^{[α]}]_{{D}}^{20}$ = -36 in MeOH. $^1$H NMR (300 MHz, MeOD-d$_4$) δ 8.0 (s, 1H, (C=O)H), 7.6 (d, $J = 7.6$ Hz, 1H, ArH), 7.3 (dd, $J = 7.8$, 1.2 Hz, 1H, ArH), 7.1 – 7.0 (m, 2H, ArH), 7.1 – 6.9 (m, 2H, ArH), 4.8 (dd, $J = 7.3$, 5.1 Hz, 1H, CHNH), 3.4 – 3.3 (m, 1H, CH$_a$H$_b$Ar), 3.2 (dd, $J = 14.7$, 7.4 Hz, 1H, CH$_a$H$_b$Ar). $^{13}$C NMR (75 MHz, MeOD-d$_4$) δ 174.6, 163.6, 138.0, 128.8, 124.4, 122.4, 119.8, 119.3, 112.2, 110.5, 53.2, 28.6.

Analytical data in accordance with literature.$^80$

(S)-Methyl 2-((S)-2-((S)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (Formyl-methionine-leucine-phenylalanine-OMe) 56.6

(65,95,125)-methyl 12-benzyl-9-isobutyl-2,2-dimethyl-6-((2-(methylthio)ethyl)-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate$^{92}$ (0.80 g, 1.5 mmol) was dissolved in saturated methanolic HCl and stirred at rt for 1 h. The reaction was then concentrated in vacuo, the residue was suspended in EtOAc and neutralised with saturated NaHCO$_3$. The aqueous layers was further extracted with EtOAc (3x 30 mL), the organics were combined dried (MgSO$_4$) and concentrated in vacuo to give (S)-methyl 2-((S)-2-((S)-2-amino-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate which was taken forward to the next step without further purification.

(formyloxy)(phenyl)methyl acetate (0.145 g, 0.75 mmol) was added to (S)-methyl 2-((S)-2-((S)-2-amino-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (0.213 g, 0.50 mmol) in EtOAc (4 mL) the reaction was stirred at rt for 5 h. The crude reaction mixture was diluted with EtOAc and washed with saturated NaHCO$_3$, the organics were then dried
(MgSO₄) and concentrated in vacuo. The residue was purified via recrystallization (MeOH/H₂O) to give the title compound in 87% yield (0.20 g, 0.44 mmol); m.p. 133-135 °C, [α]₀° = -38 in MeOH. ¹H NMR (300 MHz, MeOD-d₄) δ 8.09 (s, 1H, (C=O)H), 7.34 - 7.15 (m, 5H, ArH), 4.64 (dd, J = 5.8, 8.5 Hz, 1H, PhCH₂CH), 4.51 (dd, J = 5.5, 8.1 Hz, 1H, MeSCH₂CH₂CH), 4.41 (dd, J = 7.0, 8.1 Hz, 1H, CH(CH₃)₂CH₂CH), 3.68 (s, 3H, OCH₃), 3.15 (dd, J = 5.8, 13.8 Hz, 1H, PhCH₃H₆CH), 3.00 (dd, J = 8.7, 13.9 Hz, 1H, PhCH₃H₆CH), 2.56 - 2.38 (m, 2H, MeSCH₂CH₂CH), 2.07 (s, 3H, SCH₃), 2.03 - 1.80 (m, 2H, MeSCH₂CH₂CH), 1.72 - 1.59 (m, 1H, CH(CH₃)₂CH₂CH), 1.52 (t, J = 7.0 Hz, 2H, CH(CH₃)₂CH₂CH), 0.92 (dd, J = 12.8, 6.4 Hz, 6H, CH(CH₃)₂CH₂CH). ¹³C NMR (75 MHz, MeOD-d₄) δ 174.4, 173.2, 173.0, 163.8, 138.4, 130.5, 129.6, 128.0, 55.1, 53.1, 52.5, 33.0, 30.8, 25.8, 23.4, 22.0, 15.2. I.R (thinfilm) ν max (cm⁻¹): 3279 ((C=O)NH), 1738, 1664, 1632 (C=O); HRMS (ESI): m/z calculated for C₂₂H₄₅N₂O₅S: requires: 452.2219 for [M+H]⁺; found: 452.2245.

(S)-2-((S)-2-((S)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoic acid (Formyl-methionine-leucine-phenylalanine-OH) 56.7

2 M NaOH(aq) (1 mL) was added to a stirred solution of (S)-Methyl 2-((S)-2-((S)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (0.20 g, 0.44 mmol) dissolved in MeOH (5mL). The reaction was stirred at rt for 2 h. The MeOH was removed under reduced pressure and the reaction was diluted with H₂O, the aqueous solution was then extracted with Et₂O (3x 15 mL). The aqueous layers was then acidified with 1 M HCl(aq) and extracted with EtOAc (3x 20 mL). The second organics were then dried (MgSO₄) and concentrated in vacuo, the residue was then purified via recrystallization (MeOH/H₂O) to give the title compound in 93% yield (0.179 g, 0.40 mmol); m.p. 208-210 °C, [α]₀° = -18 in MeOH/9 in AcOH. ¹H NMR (300 MHz, MeOD-d₄) δ 8.08 (s, 1H, (C=O)H), 7.33 - 7.14 (m, 5H, ArH), 4.69 - 4.59 (m, 1H, PhCH₂CH), 4.51 (dd, J = 5.7, 7.9 Hz, 1H, MeSCH₂CH₂CH), 4.42 (t, J = 7.7 Hz, 1H, CH(CH₃)₂CH₂CH), 3.27 - 3.13 (m, 1H, PhCH₂H₆CH), 3.08 - 2.91 (m, 1H, PhCH₂H₆CH), 2.55 - 2.39 (m, 2H, MeSCH₂CH₂CH), 2.06 (s, 3H, SCH₃), 2.02 - 1.78 (m, 2H, MeSCH₂CH₂CH), 1.65 (dt, J = 6.6, 13.5 Hz, 1H, CH(CH₃)₂CH₂CH), 1.58 - 1.47 (m, 2H, CH(CH₃)₂CH₂CH), 0.96 - 0.85 (m, 6H, CH(CH₃)₂CH₂CH). ¹³C NMR (75MHz, MeOD-d₄) δ 174.5, 173.2, 163.8, 138.4, 130.5, 129.6, 128.0, 55.1, 53.1, 52.5,
42.1, 38.4, 33.1, 31.0, 25.9, 23.5, 22.1, 15.4. I.R (thinfilm) ν max (cm⁻¹): 3284 ((C=O)NH), 1729, 1634, 1621 (C=O); HRMS (ESI): m/z calculated for C_{21}H_{31}N_{3}O_{5}S: requires: 438.2062 for [M+H]^+; found: 438.2080.

2-Bromobenzyl alcohol formate 52a

![2-Bromobenzyl alcohol formate](image)

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 80% yield (0.172 g, 0.80 mmol). ^1H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H, (C=O)H), 7.61 (dd, J = 1.2, 8.1 Hz, 1H, ArH), 7.45 (dd, J = 2.0, 7.8 Hz, 1H, ArH), 7.34 (dt, J = 1.2, 7.5 Hz, 1H, ArH), 7.25 - 7.20 (m, 1H, ArH), 5.31 (s, 2H, CH₂). ^13C NMR (126 MHz, CDCl₃) δ 160.5, 134.5, 132.9, 130.1, 130.0, 127.6, 123.5, 65.2. I.R (thinfilm) ν max (cm⁻¹): 1719 (C=O); HRMS (ESI): m/z calculated for C₈H₇BrO₂: requires: 214.9629 for [M+H]^+; found: 214.9974.

Citronellyl formate 52b

![Citronellyl formate](image)

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 83% yield (0.153 g, 0.83 mmol). ^1H NMR (300 MHz, CDCl₃) δ 8.06 (s, 1H, (C=O)H), 5.19 - 4.98 (m, 1H, C=CH), 4.29 - 4.11 (m, 2H, CH₂O(C=O)H), 2.12 - 1.83 (m, 2H), 1.81 - 1.64 (m, 4H), 1.61 (s, 3H, C=CCH₃), 1.58 - 1.29 (m, 3H), 1.27 - 1.14 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H, CHCH₃). ^13C NMR (75 MHz, CDCl₃) δ 161.2, 131.4, 124.5, 62.5, 36.9, 35.3, 29.4, 25.7, 25.4, 19.3, 17.6.

Analytical data in accordance with literature. 326
Biphenyl-4-methanol formate 52c

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\text{O} \\
\text{H}
\end{array}}
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General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as crystalline white solid in 80% yield (0.170 g, 0.80 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.18 (t, J = 0.9 \text{ Hz}, 1 \text{H}, (\text{C}=\text{O})\text{H}), 7.65 - 7.57 (m, 4 \text{H}, \text{ArH}), 7.50 - 7.42 (m, 4 \text{H}, \text{ArH}), 7.41 - 7.34 (m, 1 \text{H}, \text{ArH}), 5.27 (s, 2 \text{H}, \text{CH}_2\text{O(C}=\text{O)}). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 160.8, 141.5, 140.5, 134.1, 128.9, 128.8, 127.5, 127.4, 127.1, 65.5.\) I.R (thinfilm) \(\nu_{\text{max}} (\text{cm}^{-1})\): 1702 (C=O); HRMS (ESI): m/z calculated for \(\text{C}_{14}\text{H}_{12}\text{O}_2\): requires: 213.0915 for [M+H]\(^+\); found: 213.1055.

4-Methoxy phenethyl alcohol formate 52d

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\text{MeO}
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General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 71% yield (0.127 g, 0.71 mmol). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.05 (s, 1 \text{H}, (\text{C}=\text{O})\text{H}), 7.19 - 7.10 (m, 2 \text{H}, \text{ArH}), 6.91 - 6.81 (m, 2 \text{H}, \text{ArH}), 4.36 (t, J = 7.0 \text{ Hz}, 2 \text{H}, \text{CH}_2\text{OC(O)=O}), 3.81 (s, 3 \text{H}, \text{CH}_3), 2.93 (t, J = 7.2 \text{ Hz}, 2 \text{H}, \text{CH}_2\text{CH}_2\text{OC(O)=O}). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 161.0, 158.4, 129.8, 129.3, 113.9, 64.6, 55.2, 34.0.\)

Analytical data in accordance with literature.\(^{326}\)

1-Phenylethanol formate 52e

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\text{Me}
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General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 75% yield (0.112 g, 0.75 mmol). \(^1\)H NMR (300 MHz,
CDCl$_3$ $\delta$ 8.11 (s, 1 H, (C=O)H), 7.42 - 7.28 (m, 5H, ArH), 6.18 - 5.85 (m, 1H, CH(OC=O)), 1.60 (d, $J$ = 7.2 Hz, 3H, CH$_3$). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 160.4, 140.8, 128.6, 128.1, 126.1, 72.2, 22.1.

Analytical data in accordance with literature.$^{326}$

**Menthol formate 52f**

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 78% yield (0.143 g, 0.78 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J$ = 0.8 Hz, 1H, (C=O)H), 4.81 (dt, $J$ = 4.3, 10.8 Hz, 1H, CH(OC=O)), 2.07 - 1.97 (m, 1H, CH), 1.91 (dtd, $J$ = 2.6, 7.0, 13.9 Hz, 1H, CH), 1.76 - 1.64 (m, 2H, CH$_2$), 1.59 - 1.33 (m, 2H, CH$_2$), 1.14 - 0.98 (m, 2H, CH), 0.95 - 0.84 (m, 7H, CH & CH(CH$_3$)$_2$), 0.77 (d, $J$ = 6.8 Hz, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.9, 74.1, 46.8, 40.8, 34.1, 31.4, 26.0, 23.2, 22.0, 20.7, 16.0.

Analytical data in accordance with literature.$^{327}$

**Perillyl alcohol formate 52g**

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 88% yield (0.159 g, 0.88 mmol). $[\alpha]_{D}^{20}$ = -62.5 in MeOH. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.11 (s, 1H, (C=O)H), 5.86 - 5.76 (m, 1H, CH$_2$C=CH), 4.77 - 4.70 (m, 2H, C=CH$_2$), 4.57 (s, 2H, CH$_2$O(C=O)), 2.26 - 2.06 (m, 4H, CH$_2$), 2.05 - 1.94 (m, 1H, CH), 1.93 - 1.80 (m, 1H, CH), 1.75 (s, 3H, CH$_3$), 1.60 - 1.41 (m, 1H, CH). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 161.0, 149.4, 132.0, 126.8, 108.8, 68.0, 40.7, 30.4, 27.2, 26.3, 20.7. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 1722 (C=O); HRMS (ESI): m/z calculated for C$_{11}$H$_{16}$O$_2$: requires: 181.1228 for [M+H]$^+$; found: 181.1210.
Carveol formate 52h

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in a 84% yield (0.150 g, 0.84 mmol)

Product obtained as a mixture of diastereomers (1:1) in the same ratio as the starting material.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.17 (d, $J = 1.1$ Hz, 1H, (C=O)H), 8.14 (s, 1H, (C=O)H), 5.82 - 5.75 (m, 1H), 5.68 - 5.53 (m, 2H), 5.44 - 5.37 (m, 1H), 4.78 - 4.74 (m, 2H), 4.74 - 4.70 (m, 2H), 2.40 - 2.06 (m, 5H), 2.04 - 1.82 (m, 4H), 1.76 - 1.68 (m, 10H), 1.68 - 1.63 (m, 3H), 1.61 - 1.56 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 161.1 (\(\alpha\)), 161.0 (\(\beta\)), 148.5 (\(\alpha\)), 148.1(\(\beta\)), 132.1 (\(\alpha\)), 130.2(\(\beta\)), 128.6 (\(\alpha\), 126.5(\(\beta\)), 109.5 (\(\alpha\), 109.4(\(\beta\)), 73.1 (\(\alpha\)), 70.5(\(\beta\)), 40.2 (\(\alpha\)), 35.7(\(\beta\)), 33.9 (\(\alpha\)), 33.7(\(\beta\)), 30.8 (\(\alpha\), 30.7(\(\beta\)), 20.8 (\(\alpha\)), 20.5(\(\beta\)), 20.5 (\(\alpha\)), 18.8 (\(\beta\)). I.R (thin film) $\nu$ max (cm$^{-1}$): 1717 (C=O); HRMS (ESI): m/z calculated for C$_{11}$H$_{16}$O$_2$: requires: 181.1228; found: 181.1190.

Geranyl formate 52i

General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 85% yield (0.155 g, 0.85 mmol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.08 (s, 1H, (C=O)H), 5.45 - 5.31 (m, 1H C=CHCH$_2$O), 5.20 - 5.00 (m, 1H, C=CHCH$_3$), 4.70 (d, $J = 7.2$ Hz, 2H, CH$_2$O(C=O)), 2.17-2.06 (m, 4H, CH$_2$CH$_2$), 1.76 - 1.71 (m, 3H CH$_3$C(CH$_3$)=CH), 1.71 - 1.67 (m, 3H, CH$_3$C(CH$_3$)=CH), 1.61 (s, 3H, CH$_3$C(CH$_3$)=CH). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 161.1, 143.2, 131.9, 123.6, 117.6, 60.8, 39.5, 26.2, 25.7, 17.7, 16.5.

Analytical data in accordance with literature.$^{328}$

4-Methoxyphenol formate 52j
General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an orange oil in a 75% yield (0.114 g, 0.75 mmol). $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 8.30 (s, 1H, (C=O)H), 7.12 - 7.01 (m, 2H, ArH), 6.96 - 6.87 (m, 2H, ArH), 3.82 (s, 3H, CH$_3$). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 159.7, 157.6, 143.3, 122.0, 114.6, 55.

Analytical data in accordance with literature.$^{329}$

(S)-methyl 2-acetamido-3-hydroxypropanoate 53.2

Serine methyl ester hydrochloride salt (0.5 g, 3.21 mmol) was suspended in acetone (3 mL), to this was added NEt$_3$ (0.42 mL, 3.21 mmol) dropwise. The mixture was stirred for 10 min and then filtered through a Celite® pad. The filtrate was concentrated in vacuo to give serine methyl ester which was used without further purification.

General procedure A was followed. Eluent 5% MeOH in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a brown oil in 83% yield (0.428 g, 2.56 mmol), $[\alpha]_D^{20} = -9.5$ MeOH; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.5 (s, 1H, NH), 4.7 (dt, $J = 7.3, 3.6$ Hz, 1H, CHNH), 4.0 – 3.9 (m, 2H, CH$_2$OH), 3.8 (s, 3H, OCH$_3$), 2.8 (s, 1H, OH), 2.1 (s, 3H, (C=O)CH$_3$), $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.1, 170.8, 63.6, 54.9, 52.9, 23.3. $[\alpha]_D^{20} = -9.5$ in MeOH. I.R (thinfilm) $\nu_{\text{max}}$ (cm$^{-1}$): 3291 ((C=O)NH and OH), 1738, 1648 (C=O); HRMS (ESI): m/z calculated for C$_6$H$_{11}$NO$_4$: requires: 162.0766 for [M+H]$^+$; found: 162.0788.
(S)-methyl 2-acetamido-3-(formyloxy)propanoate 53.3

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\text{O} \quad \text{O} \\
\text{H} \quad \text{N} \\
\text{Me} \quad \text{Me}
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General procedure H was followed. Eluent 5% MeOH in CH$_2$Cl$_2$ the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 78% yield (0.377 g, 2.0 mmol); m.p. 95-97 °C, [α]$_{D}^{20}$ = -56 CHCl$_3$.

$^1$H NMR (300 MHz, Chloroform-d) δ 8.0 (q, $J = 0.9$ Hz, 1H, (C=O)H), 6.3 (s, 1H, NH), 4.9 (dt, $J = 7.1, 3.3$ Hz, 1H, CH(NH)), 4.6 – 4.4 (m, 2H, CH$_2$O(C=O)H), 3.8 (s, 3H, OCH$_3$), 2.1 (s, 3H, (C=O)CH$_3$). $^{13}$C NMR (75 MHz, Chloroform-d) δ 170.0, 169.9, 160.3, 63.6, 53.2, 51.6, 23.2. I.R (thinfilm) ν max (cm$^{-1}$): 3292 ((C=O)NH), 1727, 1713, 1703 (C=O); HRMS (ESI): m/z calculated for C$_7$H$_{11}$NO$_5$: requires: 190.0715 for [M+H]$^+$; found: 190.0739.

2,4-diphenyl-1,3-dioxane 54.2

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\text{O} \\
\text{Ph} \quad \text{Ph}
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General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 85% yield. (0.204 g, 0.85 mmol); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.6 – 7.5 (m, 2H, ArH), 7.5 – 7.3 (m, 8H, ArH), 5.7 (s, 1H, OCHO), 4.9 (dd, $J = 11.4, 2.6$ Hz, 1H, OCH$_2$H$_b$), 4.4 (ddd, $J = 11.5, 5.0, 1.4$ Hz, 1H, OCH$_2$H$_a$), 4.2 (td, $J = 11.9, 2.5$ Hz, 1H, OCH$_2$H$_b$), 2.3 – 2.0 (m, 1H, OCH$_2$H$_b$), 1.8 (dt, $J = 13.5, 2.5, 1.4$ Hz, 1H, OCH$_2$H$_b$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 141.8, 138.8, 129.0, 128.6, 128.3, 127.9, 126.3, 126.0, 101.7, 79.2, 67.5, 33.6. I.R (thinfilm) ν max (cm$^{-1}$): 2962, 2853 (Ar C-H); HRMS (ESI): m/z calculated for C$_{16}$H$_{16}$O$_2$: requires: 263.1048 for [M+H]$^+$; found: 263.1030.
4-methyl-2-phenyl-1,3-dioxane 57a

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 80% yield. (0.142 g, 0.80 mmol); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.5 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.5 (s, 1H, OCHO), 4.3 (ddd, $J = 11.4, 5.0, 1.4$ Hz, 1H, CHCH$_3$), 4.1 – 3.8 (m, 2H, OCH$_2$CH$_3$H$_2$), 1.8 (dddd, $J = 13.4, 12.4, 11.0, 5.0$ Hz, 1H, OCH$_2$CH$_3$H$_2$), 1.5 (dtt, $J = 13.3, 2.5, 1.4$ Hz, 1H, OCH$_2$CH$_3$H$_2$), 1.3 (d, $J = 6.2$ Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.9, 128.9, 128.4, 126.2, 101.5, 73.6, 67.2, 33.1, 22.0.

Analytical data in accordance with literature.$^{330}$

2-phenyl-1,3-dioxane 57b

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 80% yield. (0.131 g, 0.80 mmol); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.6 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.5 (s, 1H, OCHO), 4.3 (ddt, $J = 10.5, 5.0, 1.4$ Hz, 2H, 2 x OCH$_2$H$_2$), 4.1 – 3.9 (m, 2H, 2 x OCH$_2$H$_2$), 2.2 (dtt, $J = 13.5, 12.4, 5.0$ Hz, 1H, CH$_2$H$_2$CH$_2$H$_2$), 1.5 (dtt, $J = 13.5, 2.7, 1.4$ Hz, 1H, CH$_2$H$_2$CH$_2$H$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.8, 128.9, 128.4, 126.1, 101.8, 67.5, 25.9.

Analytical data in accordance with literature.$^{331}$
(2R,4R)-2,4-diphenyl-1,3-dioxolane 57c

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 88% yield. (0.199 g, 0.88 mmol), \([\alpha]_D^{20} = -100\) in CHCl$_3$. \(^1\)H NMR (300 MHz, CDCl$_3$) $\delta$ 7.6 – 7.5 (m, 2H, Ar$H$), 7.5 – 7.3 (m, 8H, Ar$H$), 6.2 (s, 1H, OCHO), 5.2 (dd, $J$ = 7.7, 6.4 Hz, 1H, OCH$_2$CH$_3$), 4.5 (dd, $J$ = 8.3, 6.3 Hz, 1H, OCH$_2$CH$_3$), 4.0 – 3.8 (m, 1H, OCH$_2$H$_3$). \(^{13}\)C NMR (75 MHz, CDCl$_3$) $\delta$ 139.5, 138.3, 129.4, 128.8, 128.6, 128.3, 126.3, 126.2, 104.7, 78.0, 72.9. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 2965, 2848 (Ar C-H); HRMS (ESI): m/z calculated for C$_{15}$H$_{14}$O$_2$: requires: 227.1072 for [M+H]$^+$; found: 227.1068.

4-methyl-2-phenyl-1,3-dioxolane 57d

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 82% yield as a mix of diastereomers (2:3 syn:anti). (0.134 g, 0.82 mmol); \(^1\)H NMR (300 MHz, CDCl$_3$) $\delta$ 7.5 – 7.4 (m, 4H, Ar$H$, syn and anti), 7.4 – 7.3 (m, 6H, Ar$H$, syn and anti), 6.0 (s, 1H, OCHO, syn), 5.8 (s, 1H, OCHO, anti), 4.4 – 4.3 (m, 2H, CH$_3$CH$_3$, syn and anti), 4.3 (dd, $J$ = 7.8, 6.0 Hz, 1H, CH$_2$CH$_3$H$_3$, syn), 4.1 (dd, $J$ = 7.5, 6.5 Hz, 1H, CH$_2$CH$_3$H$_3$, anti), 3.7 – 3.5 (m, 2H, CH$_2$CH$_3$H$_3$, syn and anti), 1.4 (d, $J$ = 6.1 Hz, 3H, CH$_3$CH$_3$, anti), 1.4 (d, $J$ = 6.1 Hz, 3H, CH$_3$CH$_3$, syn). \(^{13}\)C NMR (75 MHz, CDCl$_3$) $\delta$ 129.4, 129.2, 128.5, 126.7, 126.5, 104.2, 103.2, 73.6, 72.5, 72.2, 71.6, 18.7, 18.5, mix of syn and anti. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 2961, 2868 (Ar C-H); HRMS (ESI): m/z calculated for C$_{10}$H$_{12}$O$_2$: requires: 187.0735 for [M+Na]$^+$; found: 187.0376.
4-( tert-butyl)-2-phenyl-1,3-dioxolane 57e

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 78% yield, as a mixture of separable diastereomers (0.161 g, 0.78 mmol); **Syn**: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.5 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.9 (s, 1H, OCHO), 4.1 (dd, $J$ = 8.0, 6.3 Hz, 1H, CH(CH)$_3$), 3.9 (dd, $J$ = 8.1, 6.3 Hz, 1H, CH$_2$H$_3$), 3.8 (t, $J$ = 8.1 Hz, 1H, CH$_2$H$_3$), 1.0 (s, 9H, CHC(CH)$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.9, 129.1, 128.5, 126.5, 104.4, 84.2, 66.8, 33.5, 25.7. **Anti**: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.6 – 7.5 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.8 (s, 1H, OCHO), 4.0 – 3.9 (m, 3H, CHCH$_2$), 1.0 (s, 9H, CHC(CH)$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 137.6, 129.5, 128.5, 127.0, 104.1, 84.8, 66.4, 33.1, 25.7. I.R (thinfilm) $\nu$ max (cm$^{-1}$): 2956, 2871 (Ar C-H); HRMS (ESI): m/z calculated for C$_{13}$H$_{18}$O$_2$: requires: 205.1228 for [M-H]$^-$; found: 205.1229.

(4R,5R)-4,5-dimethyl-2-phenyl-1,3-dioxolane 57f

General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 84% yield. (0.150 g, 0.84 mmol), $[\alpha]_{D}^{20} = -33$ in CHCl$_3$. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.5 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.9 (s, 1H, OCHO), 3.8 (dt, $J$ = 7.4, 5.3, 2.7 Hz, 2H, 2 x CHCH$_3$), 1.4 – 1.3 (m, 3H, CHCH$_3$), 1.4 – 1.3 (m, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.7, 129.3, 128.5, 126.6, 102.8, 80.5, 78.8, 17.4, 17.1.

Analytical data in accordance with literature.$^{332,333}$
Benzyl alcohol (0.216 g, 2.0 mmol) and acetic acid (0.65 μL, 0.01 mmol) were added to phenylmethylene diacetate (0.208 g, 1.0 mmol) in MeCN (3 mL) and heated to 40 °C for 12 h. The crude reaction mixture was concentrated under vacuum and the resulting residue was purified by column chromatography to give the isolated acetal. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 66% yield (0.200 g, 0.66 mmol); 1H NMR (300 MHz, DMSO-d6) δ 7.6 – 7.2 (m, 15H, ArH), 5.8 (d, J = 3.6 Hz, 1H, OCHO), 4.6 (s, 4H, CH2Ph). 13C NMR (75 MHz, DMSO-d6) δ 138.5, 138.1, 128.6, 128.3, 127.6, 127.5, 126.6, 100.6, 67.1.

Analytical data in accordance with literature.334

Acetoxy(phenyl)methyl pivalate 58.3

General procedure C was followed. Further purified by column chromatography, eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil a 60% yield (1.41 g, 5.64 mmol). 1H NMR (300 MHz, CDCl3) δ 7.7 (s, 1H, OCHO), 7.6 – 7.4 (m, 2H, ArH), 7.5 – 7.3 (m, 3H, ArH), 2.1 (s, 3H, C(O)CH3), 1.2 (s, 9H, C(O)C(CH3)3). 13C NMR (75 MHz, CDCl3) δ 176.4, 169.1, 135.8, 129.7, 128.7, 126.7, 89.9, 39.0, 27.0, 21.1.

Protecting Group Free Synthesis towards Polyketide Natural Products

Enantiomeric excess analysis

Enantiomeric excess was determined by gas chromatography (GC), model Agilent 7890A fitted with three detectors. A flame ionisation detector (FID), a thermal conductivity detector (TCD) and an Agilent 5975C Mass Spec. The column used for analysis was a β-Dex 30 m long
0.530 mm in diameter. Method initial temperature: 80 °C held for 2 min, heated to 230 °C at a ramp of 10 °C min⁻¹ and held at that final temperature for 2 min.

**Synthesis of (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1 Route one**

\[ \text{EtO} \quad \text{Me} \quad \text{Me} \quad \text{OEt} \quad \text{Me} \quad \text{Me} \]

**Step 1: (E)-3-ethoxy-2-methylacrylaldehyde 94.2**

*N,N*-Dimethylformamide (14 mL, 182.4 mmol) was added dropwise to phosphorus(V) oxychloride (15.6 mL, 167.2 mmol) at 0 °C with vigorous stirring. Propionaldehyde diethyl acetal 94.1 (10 g, 12.3 mL, 76 mmol) was then slowly added to the reaction mixture ensuring that reaction temperature does not exceed 40 °C. Upon completion of addition the reaction was heated to 70 °C for 2 h, the reaction was then poured over ice (30 g) and left overnight. The solution was then basified with K₂CO₃ and extracted with Et₂O (3x 100 mL), the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give the title compound as a pale yellow oil (2.6 g, 30%, 54.7 mmol).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \quad \delta \quad 9.24 (s, 1 H, C(O)H), 6.97 (d, J = 1.1 Hz, 1 H, CHOEt), 4.18 (q, J = 7.2 Hz, 2 H, CH₃CH₃), 1.69 (d, J = 1.1 Hz, 3 H, CH₃), 1.40 (t, J = 7.2 Hz, 3 H, CH₂CH₃). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)} \quad \delta \quad 192.0, 167.9, 120.0, 71.0, 15.3. \]

I.R (thin film) \( \nu \text{max (cm}^{-1} \text{):} \) 2983 (C=C-H), 1631 (C=O). HRMS (ESI): m/z calculated. C₆H₁₀O₂ requires 115.075905 for [M+H⁺]; found: 115.0776; requires: 137.057849 for [M+Na⁺]; found: 137.0590.

**Step 2: (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1**

nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of ethyltriphenylphosphonium bromide (9.18 g, 25 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. (E)-3-ethoxy-2-methylacrylaldehyde 20.2 (2.35 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H₂O (100 mL) and extracted with Et₂O (3x 50 mL), the combined organic layers were dried (MgSO₄) and carefully concentrated in vacuo to give a crude mixture of product and triphenylphosphate oxide. The product was purified by kugelrohr distillation under reduced pressure to give the title compound as a yellow oil (2.08 g, 80%, 16.5 mmol, B.P 75 °C at 40 milibar). (1E, 3E): \[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \quad \delta \quad 6.15 - 6.07 (m, 1 H, CHOEt), 5.96 (dd, J = 1.4, 15.4 Hz, 1 H, CHCHCH₃), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHCHCH₃), 3.83 (q, J =
7.2 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCHCH₃), 1.71 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.27 (t, J = 7.1 Hz, 3 H, OCH₂CH₃). (1E, 3E): ¹H NMR (300 MHz, CDCl₃) δ 6.15 - 6.07 (m, 1 H, CHOEt), 5.70 (app d, J = 11.3 Hz, 1 H, CHCH₂CH₃), 5.31 (qd, J = 7.2, 11.7 Hz, 1 H, CHCH₂CH₃), 3.83 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCH₂CH₃), 1.71 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.28 (t, J = 7.1 Hz, 3 H, OCH₂CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thin film) ν max (cm⁻¹): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C).

**Synthesis of (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1 Route two**

![Reaction Scheme](image)

**Step 1: (E)-1,1-diethoxy-2-methylpent-2-ene 98.2**

(E)-2-methylpentenal 98.1 (2 g, 2.4 mL, 20.36 mmol) was added to a stirred solution of triethylorthoformate (4.1 mL, 24.4 mmol) and ammonium nitrate (0.16 g, 2.04 mmol) in EtOH (15 mL) and stirred at rt for 18 h. The reaction was concentrated in vacuo the residues was then dissolved in Et₂O (50 mL) and washed with H₂O (3 x 20 mL). The organic layer was then dried (MgSO₄) and concentrated in vacuo to give the title compound as a yellow oil (3.33 g, 95%, 19.34 mmol). ¹H NMR (300 MHz, CDCl₃) δ 5.52 (app t, J = 7.0 Hz, 1 H, CHCH₂CH₃), 4.58 (s, 1 H, (EtO)₂CH), 3.63 - 3.53 (m, 2 H, OCH₂CH₃), 3.50 - 3.39 (m, 2 H, OCH₂CH₃), 2.07 (ap quin, J = 7.4 Hz, 2 H, CHCH₂CH₃), 1.62 (s, 3 H, CH₃), 1.29 - 1.17 (m, 6 H, 2 X OCH₂CH₃), 0.98 (t, J = 7.5 Hz, 3 H, CHCH₂CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 130.8, 106.1, 61.7, 20.6, 15.1, 13.9, 10.9. I.R (thin film) ν max (cm⁻¹): 2974 (C=C-H), 1693 (C=C). HRMS (ESI): m/z calculated. C₁₀H₂₀O₂: requires 195.135551 for [M+Na]⁺; found: 195.1206.

**Step 2: (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1**

nBuLi (11.7 mL, 1.5M in hexanes) was added dropwise to a mixture of KOtBu (2 g, 17.6 mmol) in THF (20 mL) at -78 °C under a N₂ environment. (E)-1,1-diethoxy-2-methylpent-2-ene 98.2 (1.5 g, 1.7 mL, 8.8 mmol) was added dropwise to the reaction mixture to give a red mixture. The reaction was allowed to warm to rt and stirred for 24 h. The reaction was quenched with H₂O (15 mL) and extracted with Et₂O (3 x 20 mL), the combined organic layers were dried (MgSO₄) and carefully concentrated in vacuo to give crude product. The residue was purified by short path distillation under reduced pressure to give the title compound as a yellow oil (0.66 g, 60%, 5.28 mmol, B.P 75 °C at 40 milibar). (1E, 3E): ¹H NMR (300 MHz, CDCl₃) δ 6.15 - 6.07 (m, 1 H,
CHOEt), 5.96 (dd, J = 1.4, 15.4 Hz, 1 H, CHCHCH₃), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHCHCH₃), 3.83 (q, J = 7.2 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCHCH₃), 1.71 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.27 (t, J = 7.1 Hz, 3 H, OCH₂CH₃). (1E, 3Z): ¹H NMR (300 MHz, CDCl₃) δ 6.15 - 6.07 (m, 1 H, CHOEt), 5.70 (app d, J = 11.3 Hz, 1 H, CHCHCH₃), 5.31 (qd, J = 7.2, 11.7 Hz, 1 H, CHCHCH₃), 3.83 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCHCH₃), 1.69 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.28 (t, J = 7.1 Hz, 3 H, OCH₂CH₃). ¹C NMR (75 MHz, CDCl₃) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thinfilm) ν max (cm⁻¹): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C)

Step 2: (1E,3E)-1-ethoxy-2-methylpent-1,3-diene 96.1

KO'Bu (4.94 g, 44 mmol) was added to a solution of (E)-1,1-diethoxy-2-methylpent-2-ene 98.2 (3 g, 3.4 mL, 17.6 mmol) in DMSO (15 mL). The stirred solution was heated at 80 °C under a N₂ environment for 4 h. The reaction was quenched with H₂O (15 mL) and extracted with Et₂O (3x 20 mL), the combined organic layers were dried (MgSO₄) and carefully concentrated in vacuo to give a crude product. The residue was purified by short path distillation under reduced pressure to give the title compound as a clear oil (1.77 g, 80%, 14.08 mmol, B.P 75 °C at 40 milibar). (1E, 3E): ¹H NMR (300 MHz, CDCl₃) δ 6.15 - 6.07 (m, 1 H, CHOEt), 5.96 (dd, J = 1.4, 15.4 Hz, 1 H, CHCHCH₃), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHCHCH₃), 3.83 (q, J = 7.2 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCHCH₃), 1.71 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.27 (t, J = 7.1 Hz, 3 H, OCH₂CH₃). (1E, 3Z): ¹H NMR (300 MHz, CDCl₃) δ 6.15 - 6.07 (m, 1 H, CHOEt), 5.70 (app d, J = 11.3 Hz, 1 H, CHCHCH₃), 5.31 (qd, J = 7.2, 11.7 Hz, 1 H, CHCHCH₃), 3.83 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 1.76 (dd, J = 1.3, 6.6 Hz, 3 H, CHCHCH₃), 1.69 (d, J = 1.1 Hz, 3 H, EtOCHCH₃), 1.28 (t, J = 7.1 Hz, 3 H, OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thinfilm) ν max (cm⁻¹): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C)

Synthesis of BINOL-Ti complex 106.3²

A 250 mL Schlenk tube was charged with powdered molecular sieves 4Å (15.0 g) and (R)-(+)-binaphthol (0.859 g, 3.0 mmol). The Schlenk was then transferred into a glovebox where anhydrous CH₂Cl₂ (90 mL) was added and the reaction was stirred for 20 min. Diisopropoxytitanium(IV) chloride (0.711 g, 3.0 mmol) was added in one portion resulting in a
red brown reaction mixture. The reaction was removed from the glove box and allowed to stir at rt for 1 h. The reaction mixture was then allowed to settle overnight. The reaction solution was transferred via cannula into a new Schlenk flask leaving the molecular sieves behind. The stirred reaction was evaporated at 0 °C under reduced pressure to afford a deep red/brown residue. The resulting residue is suspended in anhydrous pentane (50 mL) and stirred for 20 min. The pentane was decanted via syringe and the resulting precipitate was vacuum-dried to give the binaphthol-titanium complex in 90-95% yield and used as catalyst in subsequent reactions.

**Synthesis of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 104.2**

\[
\text{CH}_2\text{Cl}_2 \ (3.0 \text{ mL}) \text{ was added to binaphthol-titanium complex 106.3 (0.016 g, 0.04 mmol) under a N}_2 \text{ environment. Ethyl glyoxalate 50% in toluene (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1 (0.1 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated in vacuo to give a crude mixture which was purified by column chromatography (15% EtOAc in pentane Rf = 0.7) the fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.118 g, 65%, 0.52 mmol).} \]

\( ^1\text{H NMR (500 MHz, CDCl}_3 \) \( \delta = 5.71 - 5.68 \) (m, 1 H, C=CH), 5.09 (s, 1 H, EtOCH), 4.34 (d, J = 3.5 Hz, 1 H, CHCO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.28 - 4.22 (m, 2 H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 3.87 (dq, J = 9.6, 7.0 Hz, 1 H, OCH\textsubscript{a}H\textsubscript{b}CH\textsubscript{3}), 3.66 (dq, J = 9.5, 7.1 Hz, 1 H, OCH\textsubscript{a}H\textsubscript{b}CH\textsubscript{3}), 2.48 - 2.42 (m, 1 H, CHCH\textsubscript{3}), 1.66 (s, 3 H, CH\textsubscript{3}C=C), 1.30 (t, J = 7.1 Hz, 3 H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.25 (t, J = 7.1 Hz, 3 H, OCH\textsubscript{a}H\textsubscript{b}CH\textsubscript{3}), 1.01 (d, J = 6.9 Hz, 3 H, CHCH\textsubscript{3}). \(^{13}\text{C NMR (75 MHz, CDCl}_3 \) \( \delta = 170.0, 132.9, 129.3, 100.3, 74.1, 62.8, 60.8, 31.7, 17.5, 15.2, 14.7, 14.3. ) I.R (thin film) \( \nu \text{max (cm}^{-1}): 2975 \) (C=C-H), 1759 (C=O), 1730 (C=C). HRMS (ESI): m/z calculated. C\textsubscript{12}H\textsubscript{20}O\textsubscript{4}: requires 251.1259 for [M+Na]\textsuperscript{+}; found: 251.1264.
Purification of ethyl glyoxalate

![Ethyl glyoxalate structure](image)

Commercially available ethyl glyoxalate 50% in toluene was concentrated to remove the toluene. The remaining glyoxalate is then distilled under reduced pressure to afford pure ethyl glyoxalate. The collection vessel is kept at -78 °C for the duration of the distillation. The pure ethyl glyoxalate was then diluted to a 50% solution with fresh anhydrous CH₂Cl₂ and transferred to a Schlenk flask. Allowing for freezer storage of the pure ethyl glyoxalate.

Synthesis of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 104.2

![Chemical structure](image)

CH₂Cl₂ (3.0 mL) was added to binaphthol-titanium complex 106.3 (0.016 g, 0.04 mmol) under a N₂ environment, ethyl glyoxalate 50% in CH₂Cl₂ (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (1E,3E)-1-ethoxy-2-methylpenta-1,3-diene 96.1 (0.1 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated in vacuo to give a crude mixture which was purified by column chromatography (15% EtOAc in pentane Rf = 0.7). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.118 g, 65%), [α]D₂₀ = +114 (MeOH). ¹H NMR (500 MHz, CDCl₃) δ = 5.71 - 5.68 (m, 1 H, C=CH), 5.09 (s, 1 H, EtOCH), 4.34 (d, J = 3.5 Hz, 1 H, CHCO₂CH₃CH₃), 4.28 -
4.22 (m, 2 H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 3.87 (dq, J = 9.6, 7.0 Hz, 1 H, OCHaH\textsubscript{6}CH\textsubscript{3}), 3.66 (dq, J = 9.5, 7.1 Hz, 1 H, OCHAH\textsubscript{6}CH\textsubscript{3}), 2.48 - 2.42 (m, 1 H, CHCH\textsubscript{3}), 1.66 (s, 3 H, CH\textsubscript{3}C=C), 1.30 (t, J = 7.1 Hz, 3 H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.25 (t, J = 7.1 Hz, 3 H, OCHAH\textsubscript{6}CH\textsubscript{3}), 1.01 (d, J = 6.9 Hz, 3 H, CHC\textsubscript{3}H\textsubscript{3}). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \textdelta 170.0, 132.9, 129.3, 100.3, 74.1, 62.8, 60.8, 31.7, 17.5, 15.2, 14.7, 14.3. I.R (thin film) \textnu max (cm\textsuperscript{-1}): 2975 (C=C-H), 1759 (C=O), 1730 (C=C).

HRMS (ESI): m/z calculated. C\textsubscript{12}H\textsubscript{20}O\textsubscript{4} requires 251.1259 for [M+Na]\textsuperscript{+}; found: 251.1264.

**Synthesis of ethyl 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 110.1**

Borane dimethyl sulfide complex (0.2 mL, 1.75 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 27.3 (0.2 g, 0.87 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H\textsubscript{2}O\textsubscript{2} (30 % w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H\textsubscript{2}O (10 mL) and Et\textsubscript{2}O (20 mL) the layers were separated and the organics were washed with H\textsubscript{2}O (10 mL X 3), dried (MgSO\textsubscript{4}) and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in pentane Rf = 0.3). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.18 g, 85%, 0.74 mmol). [\alpha]\textsubscript{D}\textsuperscript{20} = +21 (MeOH). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textdelta 4.76 (d, J = 3.5 Hz, 1H, EtOC\textsubscript{2}H\textsubscript{2}CH\textsubscript{3}), 4.31 (d, J = 4.4 Hz, 1H, CHCO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.24 (dq, J = 10.8, 7.1 Hz, 1H, CO\textsubscript{2}CHaH\textsubscript{6}CH\textsubscript{3}), 4.14 (dq, J = 10.8, 7.1 Hz, 1H, CO\textsubscript{2}CHaH\textsubscript{6}CH\textsubscript{3}), 3.93 (t, J = 7.4 Hz, 1H, CHO\textsubscript{2}, 3.83 (dq, J =9.8, 7.0 Hz, 1H, OCHAH\textsubscript{6}CH\textsubscript{3}), 3.45 (dq, J = 9.8, 7.0 Hz, 1H, OCHAH\textsubscript{6}CH\textsubscript{3}), 1.99 (app quin d, J = 7.3, 4.6 Hz, 1H, CH(CO\textsubscript{2}Et)CHCH\textsubscript{3}).
1.79 (app quin d, J = 7.2, 3.5 Hz, 1H, CH(OEt)CH$_3$), 1.70 (br. s, 1H, OH), 1.30 (t, J = 7.3 Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.18 - 1.11 (m, 6H, OCH$_2$CH$_3$ and EtOCHCH$_3$), 1.04 (d, J = 6.9 Hz, 3H, CH(CO$_2$Et)CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 170.7, 102.3, 74.2, 72.5, 64.7, 60.6, 42.1, 39.6, 14.7, 14.2, 12.7, 12.1. I.R (thin film) $\nu_{max}$ (cm$^{-1}$): 3505 (OH), 1736 (C=O).

HRMS (ESI): m/z calculated. C$_{12}$H$_{22}$O$_5$: requires: 269.1365 for [M+Na]$^+$; found: 269.1355.

**Synthesis of ethyl 6-ethoxy-3,5-dimethyl-4-oxotetrahydro-2H-pyran-2-carboxylate 111.1**

Oxalyl chloride (0.056 g, 0.44 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (5 mL) at -55 °C under N$_2$. DMSO (0.062 g, 0.80 mmol) was added and the resulting solution was stirred for 2 min. 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate (0.10 g, 0.40 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for a further 15 mins at -55 °C. NEt$_3$ (0.26 mL, 2.0 mmol) was then added and the resulting solution was stirred for 15 mins at -55 °C. The white slurry was then allowed to warm to rt and was quenched with H$_2$O (10 mL). The layers were separated and the aqueous layer was extracted three times with CH$_2$Cl$_2$ (20 mL). The organics were combined and washed with 1 M HCl and saturated NaHCO$_3$, before being dried (MgSO$_4$) and concentrated under vacuum. The resulting residue was purified by column chromatography (5% EtOAc in pet ether). The fractions containing product were combined and concentrated under vacuum to give the title compound as a waxy oil (0.079 g, 80%, 0.32 mmol).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.1 (d, J = 4.0 Hz, 1H, OCHOCH$_3$CH$_3$), 4.7 (d, J = 4.9 Hz, 1H, CHC(O)OCH$_2$CH$_3$), 4.2 (q, J = 7.1 Hz, 2H, CHC(O)OCH$_2$CH$_3$), 3.9 (dq, J = 9.7, 7.1 Hz, 1H, OCH$_3$H$_2$CH$_3$), 3.5 (dq, J = 9.7, 7.1 Hz, 1H, OCH$_3$H$_2$CH$_3$), 2.9 - 2.8 (m, 2H, 2 x CH$_2$CH$_3$), 1.3 (t, J = 7.2 Hz, 3H, CHC(O)OCH$_2$CH$_3$), 1.2 - 1.1 (m, 6H, OCH$_2$CH$_3$ and CHCH$_3$), 1.1 (d, J = 6.8 Hz, 3H, CHCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.5, 169.7, 102.8, 75.3, 64.5, 61.3, 47.9, 45.5, 14.8, 14.2, 11.6, 9.6. I.R (thin film) $\nu_{max}$ (cm$^{-1}$): 2979, 2936 (C-H), 1727 (C=O). HRMS (ESI): m/z calculated. C$_{12}$H$_{20}$O$_5$: requires: 267.1208 for [M+Na]$^+$; found: 267.1259.
Synthesis of (2R,3S,4R,5R,6S)-ethyl 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 111.2

Sodium borohydride (0.011 g, 0.30 mmol) was added to a stirred solution of ethyl 6-ethoxy-3,5-dimethyl-4-oxotetrahydro-2H-pyran-2-carboxylate (0.065 g, 0.266 mmol) in EtOH (5 mL) at 0 °C under a N₂ environment. The reaction was allowed to reach rt and stirred for 1 h, the reaction was concentrated under vacuum. The resulting residue was partitioned between CH₂Cl₂ and H₂O, the layers were separated and the aqueous layer was further extracted with CH₂Cl₂ (20 mL x 2), the organics were combined dried (MgSO₄) and concentrated under vacuum to give the title compound as a clear oil (0.062 g, 95%, 0.25 mmol).

¹H NMR (500 MHz, Chloroform-d) δ 4.6 (d, J = 3.4 Hz, 1H, OC₉H₅OCH₂CH₃), 4.3 – 4.2 (m, 1H, (O)OC₉H₅H₂CH₃), 4.2 (d, J = 5.8 Hz, 1H, CHC(O)OCH₂CH₃), 4.2 – 4.1 (m, 1H, (O)OC₉H₅H₂CH₃), 3.8 (dq, J = 9.7, 7.1 Hz, 1H, OCH₃), 3.7 – 3.6 (m, 1H, CH(CH₃)CHOH), 1.9 (qt, J = 7.2, 3.6 Hz, 1H, CH(CH₃)CH(OH)CO₂C₉H₂CH₃), 1.3 (td, J = 7.1, 0.6 Hz, 3H, CHC(O)OCH₂CH₃), 1.2 – 1.1 (m, 6H, OCH₂CH₃ and CHCH₃), 1.1 – 1.0 (m, 3H, CHCH₃). ¹³C NMR (126 MHz, Chloroform-d) δ 172.0, 101.3, 73.6, 70.6, 64.7, 61.2, 39.2, 37.0, 14.8, 14.3, 12.7, 12.3. I.R (thin film) ν max (cm⁻¹): 3480 (OH), 1739 (C=O). HRMS (ESI): m/z calculated. C₁₂H₂₂O₅: requires: 269.1365 for [M+Na]+; found: 269.1362.

Synthesis of diethyl 2-hydroxy-3,5-dimethylhexanedioate 112.1

5% Pd/AlO₃ (0.18 g, 0.088 mmol) was added to a solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.2 g, 0.87 mmol) in EtOH (3 mL) the reaction when then placed under a H₂ environment and stirred at rt for 24 h. The reaction was filtered through Celite® and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in pentane Rf = 0.15). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.16 g, 75%, 0.066 mmol). ¹H NMR (300 MHz, CDCl₃) δ 4.34 - 4.20 (m, 2H, CH(CH₂)CO₂CH₂CH₃), 4.19 - 4.05 (m, 3H, CH(OH)CO₂CH₂CH₃ and
CH(OH)CO₂CH₂CH₃, 2.79 (d, J = 5.3 Hz, 1H, CO₂EtCHCH₃), 2.63 - 2.46 (m, 1H, CH(OH)CHCH₃), 2.08 - 1.93 (m, 1H, CH(CH₃)CH₂CH₃CH(CH₃)), 1.92 - 1.80 (m, 1H, CH(CH₃)CH₂CH₆CH(CH₃)), 1.29 (t, J = 7.2 Hz, 3H, CH(OH)CO₂CH₂CH₃), 1.26 (t, J = 7.2 Hz, 3H, CH(CH₃)CO₂CH₂CH₃), 1.19 (d, J = 7.0 Hz, 3H, CH(OH)CHCH₃), 0.83 (d, J = 6.6 Hz, 3H, CO₂EtCHCH₃).

### Synthesis of ethyl 6-ethoxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 112.2

![Structure of ethyl 6-ethoxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate](structure.png)

5% Pd/Al₂O₃ (0.18 g, 0.088 mmol) was added to a solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 27.3 (0.2 g, 0.87 mmol) in EtOAc (3 mL), the reaction was then placed under a pressurised H₂ environment (50 PSI) and stirred at rt for 24 h. The reaction was filtered through Celite® and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in pentane Rf = 0.4). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.17 g, 85%, 0.075 mmol). [α]D²⁰ = +48 (MeOH), +82 (CHCl₃). [1]H NMR (500 MHz, CDCl₃) δ 4.56 (d, J = 3.2 Hz, 1H, EtOCH), 4.24 (qd, J = 7.1, 10.8 Hz, 1H, OCH₃H₂CH₃), 4.18 - 4.08 (m, 1H, OCH₃H₂CH₃), 4.04 (d, J = 4.7 Hz, 1H, CHCO₂CH₂CH₃), 3.82 (dq, J = 9.8, 7.1 Hz, 1H, CO₂CH₂H₂CH₃), 3.45 (dq, J = 9.8, 7.0 Hz, 1H, CO₂CH₂H₂CH₃), 2.10 - 2.01 (m, 1H, CH(CO₂Et)CHCH₃), 1.90 - 1.84 (m, 1H, CH(OEt)CHCH₃), 1.84 - 1.75 (m, 1H, CH(CH₃)CH₂CH₂CH(CH₃)), 1.56 - 1.49 (m, 1H, CH(CH₃)CH₂CH₆CH(CH₃)), 1.31 (t, J = 7.1 Hz, 3H, CO₂CH₂CH₃), 1.15 (t, J = 6.9 Hz, 3H, OCH₂CH₃), 1.09 (d, J = 7.3 Hz, 3H, CH(OEt)CHCH₃), 0.94 (d, J = 6.6 Hz, 3H, CH(CO₂Et)CHCH₃). [13]C NMR (75 MHz, CDCl₃) δ 170.9, 101.6, 73.9, 64.3, 60.3, 34.5, 32.2, 31.6, 16.9, 16.1, 14.7, 14.2. I.R (thin film) ν max (cm⁻¹): 1739 (C=O). HRMS (ESI): m/z calculated. C₁₂H₂₀O₅: requires: 269.1365 for [M+Na]+; found: 269.1431.

### Preparation of quaternary ammonium tetrakis(diperoxotungsto)phosphates (-3)

[Ca₅H₁₂₅NCH₃]₃PO₄[W(O)O₂]₄⁻²⁶⁶

Tungstic acid (2.5 g, 10.0 mmol) was suspended in 30% H₂O₂ (7 mL) and heated at 60 °C until the reaction becomes a clear solution. The reaction was then cooled to rt, 40% phosphoric acid (0.62 mL, 2.5 mmol) was added and the reaction was diluted to 30 mL with H₂O. Aliquat 336 (2.29 mL,
5 mmol) in CH₂Cl₂ (40 mL) was then added to the reaction and stirred at rt for 15 min. The organic layer was then separated, dried (Na₂SO₄) and concentrated to give the title compound as a clear viscous oil. Used without further purification.

Synthesis of ethyl 2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 116.1

Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.2 g, 0.87 mmol) was added to a mixture of [(C₈H₁₇)₃NCH₃]₃PO₄[WO(O)(O₂)]₄ (0.028 g, 0.0087 mmol) in 30% H₂O₂ (0.155 mL, 0.96 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with NaHCO₃ (aq) (20 mL) and a Et₂O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et₂O/Pentane 1:1 mix (3 X 10 mL). The organic layers were then combined, dried (MgSO₄) and concentrated under vacuum to give pure title compound as a colourless oil in 95% yield (0.201 g, 0.83 mmol). [α]D²⁰ = +62.5 (MeOH).

1H NMR (500 MHz, CDCl₃) δ 4.8 (dd, J = 1.3, 0.5 Hz, 1H, EtOC₂H₂O), 4.2 (d, J = 3.3 Hz, 2H, OCH(O)OEt), 4.2 (qd, J = 7.1, 2.4 Hz, 3H, C(O)OCH₂CH₃), 4.0 (dq, J = 9.6, 7.1 Hz, 1H, OCH₂CH₂CH₃), 3.6 (dq, J = 9.6, 7.0 Hz, 1H, OCH₂CH₂CH₃), 3.0 (dd, J = 2.7, 1.2 Hz, 1H, C(CH₃)OCH), 2.6 – 2.5 (m, 1H, CHCH₃), 1.3 (s, 3H, C(CH₃)OCH), 1.3 (t, J = 7.2 Hz, 3H, C(O)OCH₂CH₃), 1.2 (t, J = 7.0 Hz, 3H, OCH₂CH₂CH₃), 1.0 (d, J = 7.1 Hz, 3H, CHCH₃). 13C NMR (126 MHz, CDCl₃) δ 170.6, 100.2, 69.7, 65.5, 63.0, 61.0, 58.2, 32.0, 18.6, 15.2, 14.4, 10.9. I.R (thin film) ν max (cm⁻¹): 2977, 2935 (C-H), 1758 (C=O). HRMS (ESI): m/z calculated. C₁₂H₂₀O₅ requires: 245.1388 for [M+H]+; found: 245.1370.

Synthesis of 2-ethoxy-6-(hydroxymethyl)-3,5-dimethyltetrahydro-2H-pyran-3-ol 118.1

2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate (0.1 g, 0.41 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred suspension of LiAlH₄ (0.063 g, 0.82 mmol) in anhydrous THF (5 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then poured into a saturated solution of NH₄Cl (20 mL). The reaction was extracted with Et₂O (3 x 20 mL), the organic layers were combined, dried (MgSO₄) and concentrated under vacuum to give pure title
compound as a pale yellow oil in 90\% yield (0.075 g, 0.37 mmol). \([\alpha]_D^{20} = +44\) (MeOH). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.8 (d, \(J = 1.0\) Hz, 1H, OCHOCH\(_2\)CH\(_3\)), 4.0 (dq, \(J = 9.7, 7.1\) Hz, 1H, OCHOCH\(_2\)H\(_3\)CH\(_3\)), 3.7 – 3.5 (m, 4H, OCHOCH\(_2\)H\(_3\)CH\(_3\), OCHCH\(_2\)OH and OCHCH\(_2\)OH), 2.9 (dd, \(J = 2.0, 1.1\) Hz, 1H, CH\(_3\)CH\(_2\)CH\(_3\)), 2.3 (s, 1H, CH\(_3\)CH\(_2\)CH\(_3\)), 2.2 – 2.1 (m, 1H, CH\(_3\)CH\(_2\)CH\(_3\)), 1.3 (s, 3H, C(OH)CH\(_3\)), 1.3 (t, \(J = 7.1\) Hz, 3H, CH\(_2\)CH\(_3\)), 1.0 (d, \(J = 7.2\) Hz, 3H, CHCH\(_3\)). \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 99.6, 71.3, 65.4, 63.5, 63.4, 57.7, 30.8, 18.7, 15.3, 11.4. I.R (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3446 (OH), 2974, 2931 (C-H).

\[\text{HRMS (ESI): m/z calculated. C}_{10}\text{H}_{20}\text{O}_4\text{ requires: 205.1440 for [M+H]}^+; \text{found: 205.1431.}\]

**Synthesis of ethyl 5-bromo-6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 119.1**

\[\text{NBS (0.052 g, 0.43 mmol) was added to a mixture of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.1 g, 0.43 mmol) in acetone/H}_2\text{O 1:1 (6 mL). The reaction was stirred at 10 °C for 2 h and then concentrated under vacuum. The residue was dissolved in EtO}_2\text{ (30 mL) and washed with NaHCO}_3\text{(aq) (3 x 20 mL). The organics were dried (MgSO}_4\text{) and concentrated under vacuum to give the crude product. The residue was purified via column chromatography (20\% EtOAc in pentane Rf = 0.2) the fractions containing product were combined and concentrated in vacuo to give the title compound as a white solid (0.11 g, 86\%, 0.37 mmol). [\alpha]_D^{20} = +38 (MeOH).}\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.6 (s, 1H, OCHOCH\(_2\)CH\(_3\)), 4.4 (d, \(J = 8.3\) Hz, 1H, OCHC(O) OCH\(_2\)CH\(_3\)), 4.3 – 4.3 (m, 1H, CHOH), 4.3 – 4.1 (m, 2H, C(O)CH\(_2\)CH\(_3\)), 3.9 – 3.8 (m, 1H, OCH\(_2\)H\(_3\)CH\(_3\)), 3.6 (dq, \(J = 9.8, 7.0\) Hz, 1H, OCH\(_2\)H\(_3\)CH\(_3\)), 2.3 – 2.2 (m, 1H, CHCH\(_3\)), 2.2 (d, \(J = 3.4\) Hz, 1H, OH), 1.8 (s, 3H, C(Br)CH\(_3\)), 1.3 (t, \(J = 7.2\) Hz, 3H C(O)OCH\(_2\)CH\(_3\)), 1.3 (d, \(J = 7.2\) Hz, 3H, CHCH\(_3\)), 1.2 (t, \(J = 7.1\) Hz, 3H, OCHCH\(_3\)). \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.0, 103.9, 74.2, 65.9, 60.7, 51.4, 37.2, 23.8, 14.5, 14.3 14.2, 13.7. I.R (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3467 (OH), 2971, 2942 (C-H), 1726 (C=O). HRMS (ESI): m/z calculated. C\(_{12}\)H\(_{21}\)BrO\(_5\): requires: 347.0470 for [M+Na]\(^+\); found: 347.0473.

NMR experiment to show that the epoxide formed from bromohydrin ring closure is the same as the epoxide formed directly from dihydropyran 104.2
Comparison of epoxide $^1$H NMR

Synthesis of ethyl 6-ethoxy-4,5-dihydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate

AD-mix-α (or AD-mix-β) (1.4 g) was dissolved in 1:1 tert-butanol:water (10 mL) and stirred at rt to produce two clear phases. Methanesulphonamide (0.095 g, 1.0 mmol) was added and the reaction was cooled to 0 °C. Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.22 g, 1.0 mmol) was then added and the reaction was vigorously stirred at 0 °C for 4 d. Sodium sulphite was added and the reaction was allowed to warm to rt and stirred for a further 1 h. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organics were combined, washed with 2 M KOH (aq), dried (MgSO$_4$) and concentrated under vacuum. The resulting residue was purified via column chromatography (20% EtOAc in pentane Rf = 0.3) to give the title compound as a clear oil (0.118 g, 45%, 0.45 mmol) $[\alpha]_{D}^{20} = +32$ MeOH. $^1$H NMR (300 MHz, CDCl$_3$) δ 4.6 (s, 1H, CHCH$_2$CH$_3$), 4.6 (d, $J = 3.6$ Hz, 1H, OCHC(O) OCH$_2$CH$_3$), 4.2 (qt, $J = 6.9$, 3.5 Hz, 2H, C(O)CH$_2$CH$_3$), 4.0 (dq, $J = 9.7$, 7.1 Hz, 1H, OCH$_2$H$_2$CH$_3$), 3.7 (d, $J = 3.5$ Hz, 1H, CHOH),
3.5 (dq, $J = 9.6, 7.0$ Hz, 1H, OCH$_2$H$_6$CH$_3$), 2.4 (qt, $J = 7.5, 3.6$ Hz, 1H, CHCH$_3$), 1.3 – 1.3 (m, 6H, C(OH)CH$_3$ and C(O)CH$_2$CH$_3$), 1.2 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.0 (d, $J = 7.6$ Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.3, 103.1, 77.3, 73.8, 71.4, 65.6, 61.0, 37.4, 20.5, 15.1, 14.4, 13.0. I.R (thin film) ν max (cm$^{-1}$): 3473 (OH), 2979, 2933 (C-H), 1737 (C=O).

$^{1}H$ NMR (300 MHz, CDCl$_3$) δ 4.5 – 4.4 (m, 2H, OCHOCH$_2$CH$_3$ and CHC(O)OCH$_2$CH$_3$), 4.2 (q, $J = 7.2$ Hz, 2H, CHC(O)OCH$_2$CH$_3$), 4.0 (dq, $J = 9.4, 7.1$ Hz, 1H, OCH$_2$H$_6$CH$_3$), 3.8 (d, $J = 1.8$ Hz, 1H, CHOC(CH$_3$)$_2$), 3.6 (dq, $J = 9.4, 7.0$ Hz, 1H, OCH$_{3 substitute}CH$_3$), 2.5 (qdd, $J = 7.5, 3.1, 1.8$ Hz, 1H, CHCH$_3$), 1.5 (s, 3H, CH$_3$C(O)(O)), 1.4 (s, 3H, OC(CH$_3$)$_2$(CH$_3$)$_2$O), 1.3 (s, 3H, OC(CH$_3$)$_2$(CH$_3$)$_2$O), 1.3 – 1.2 (m, 3H, C(O)OCH$_2$CH$_3$), 1.3 – 1.2 (m, 3H, OCH$_2$CH$_3$), 1.0 (d, $J = 7.5$ Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.0, 108.1, 104.6, 84.5, 78.4, 73.6, 65.7, 61.2, 33.8, 28.5, 26.9, 17.7, 15.0, 14.4, 12.3. I.R (thin film) ν max (cm$^{-1}$): 2979, 2933, 2879 (C-H), 1753 (C=O). HRMS (ESI): m/z calculated. C$_{15}$H$_{26}$O$_6$: requires: 325.1627 for [M+Na]$^+$; found: 325.1657.
Potassium tert-butoxide (0.02 g, 0.16 mmol) in THF (0.5 mL) was added dropwise to a stirred solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.8 mmol) in THF (4 mL) at 0 °C. The reaction as stirred at 0 °C for 2 h, 1 M NaHSO₄(aq) (0.4 mL) was added and the reaction was warmed to rt. The reaction was diluted with Et₂O (20 mL) and extracted with H₂O and brine. The aqueous layers were extracted with Et₂O, the organics were combined, dried (MgSO₄) and concentrated under vacuum to give the title compound as a clear oil (0.192 g, 96%, 0.77 mmol). [α]₀° = +20.5 MeOH. ¹H NMR (300 MHz, Chloroform-d) δ 5.4 (d, J = 2.3 Hz, 1H, C=C), 4.8 (s, 1H, OCHOCH₂CH₃), 4.3 (q, J = 7.1 Hz, 2H, C(O)OCH₂CH₃), 4.0 (d, J = 10.4 Hz, 1H, CHC(O)OCH₂CH₃) 3.8 (dq, J = 9.9, 7.1 Hz, 1H, CH₃CH₂CH₃), 3.6 (dq, J = 9.8, 7.1 Hz, 1H, CH₃CH₂CH₃), 2.5 (ddt, J = 9.2, 5.6, 2.1, 1.1 Hz, 1H, CHCH₂), 1.7 (q, J = 1.9 Hz, 3H, CH₂C=C), 1.3 (t, J = 7.1 Hz, 3H, C(O)OCH₂CH₃), 1.2 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.0 (d, J = 7.1 Hz, 3H, CHCH₂). ¹³C NMR (75 MHz, Chloroform-d) δ 171.2, 131.5, 128.6, 97.3, 72.9, 64.3, 61.2, 32.4, 18.8, 16.7, 15.4, 14.4. I.R (thin film), max (cm⁻¹): 2974, 2876 (C-H), 1740 (C=O). HRMS (ESI): m/z calculated. C₁₂H₂₀O₄: requires 251.1259 for [M+Na]⁺; found: 251.1263.

### Computational results

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Synthesis of ethyl 2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 128.1

Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.1 g, 0.44 mmol) was added to a mixture of [(C₈H₁₇)₃NCH₃]₃PO₄[W(O)(O₂)₂]₄ (0.014 g, 0.0044 mmol) in 30% H₂O₂ (0.078 mL, 0.48 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with NaHCO₃(aq) (20 mL) and a Et₂O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et₂O/Pentane 1:1 mix (3x 10 mL). The organic layers were then combined, dried (MgSO₄) and concentrated under vacuum to give pure title compound as a colourless oil in a 96% yield (0.101 g, 0.42 mmol).

1H NMR (300 MHz, CDCl₃) δ 4.9 (s, 1H, C(H)OCH₂CH₃), 4.2 (q, J = 7.2 Hz, 2H, C(O)OCH₂CH₃), 3.9 (d, J = 10.4 Hz, 1H, OCH₂H₂CH₃), 3.8 (dt, J = 9.8, 7.1 Hz, 1H, CHC(O)OCH₂CH₃), 3.6 (dq, J = 9.8, 7.0 Hz, 1H, OCH₂H₆CH₃), 2.9 (s, 1H, CHO (epoxide)), 2.4 – 2.2 (m, 1H, CHCH₃), 1.3 (s, 3H, CO(CH₃)), 1.3 (dt, J = 13.2, 7.2 Hz, 6H, CHOCOCH₂CH₃ and C(O)OCH₂CH₃), 1.1 (d, J = 7.3 Hz, 3H, CHCH₃). 13C NMR (75 MHz, CDCl₃) δ 170.6, 97.7, 70.3, 64.5, 62.0, 61.4, 55.1, 30.8, 18.0, 15.8, 15.2, 14.3. I.R (thin film) ν max (cm⁻¹): 2985, 2940 (C-H), 1731 (C=O). HRMS (ESI): m/z calculated: C₁₂H₂₀O₅ requires: 245.1388 for [M+H]⁺; found: 245.1370.

Synthesis of (E)-1-ethoxy-2-methylbuta-1,3-diene 130.1

nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of methyltriphenylphosphonium bromide 8.93 g, 25.0 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. (E)-3-ethoxy-2-methylacrylaldehyde 20.2 (2.35 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H₂O (100 mL) and extracted with Et₂O (3x 50 mL), the combined organic layers were dried (MgSO₄) and carefully concentrated in vacuo to give a crude mixture of product and triphenylphosphoxide. The product was purified by distillation under reduced pressure to give the title compound as a clear oil (1.61 g, 70%, 14.42 mmol). 1H NMR (300 MHz, CDCl₃) δ 6.3 (dd, J = 17.2, 10.7 Hz, 1H, CH=CH₂), 6.2 (s, 1H, CHOC₂CH₃), 5.0 (ddd, J =
17.2, 1.4, 0.7 Hz, 1H, CH=CH₂H₆), 4.8 (dd, J = 10.7, 1.4 Hz, 1H, CH=CH₂H₆), 3.9 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 1.7 (d, J = 1.3 Hz, 3H, CH₂C=C), 1.3 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 148.0, 137.0, 114.7, 107.9, 68.3, 15.5, 9.0. I.R (thinfilm) v max (cm⁻¹): 2980, 2939, 2880 (C=C-H), 1651 (C=C).

Synthesis of (ethoxymethyl)triphenylphosphonium chloride

\[
\text{PPH}_3\overset{\oplus}{O}\text{Et} \overset{\ominus}{\text{Cl}}
\]

Triphenylphosphine (20.0 g, 0.076 mol) and chloromethyl ethyl ether (7.9 g, 0.084 mol) were dissolved in CH₂Cl₂ and heated at 42 °C for 12 h. The reaction was concentrated under vacuum, the solid residue was washed with pet ether to give the title compound as a white solid (27.0 g, 99%, 0.0752 mol). ¹H NMR (300 MHz, CDCl₃) δ 7.7 (s, 9H, ArH), 7.6 (dddd, J = 7.7, 6.2, 3.7, 1.2 Hz, 6H, ArH), 5.8 (s, J = 4.0 Hz, 2H, CH₂OCH₂CH₃), 3.9 (q, J = 7.0 Hz, 2H, CH₂OCH₂CH₃), 1.1 (t, J = 7.0 Hz, 3H, CH₂OCH₂CH₃). ³¹P NMR (122 MHz, CDCl₃) δ 18.6.

Analytical data in accordance with literature.

Synthesis of (1E,3E)-1-ethoxypenta-1,3-diene 131.2

nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of (ethoxymethyl)triphenylphosphonium chloride (8.92 g, 25.0 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. Freshly distilled crotonaldehyde (1.44 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H₂O (100 mL) and extracted with Et₂O (3x 50 mL), the combined organic layers were dried (MgSO₄) and carefully concentrated in vacuo to give a crude mixture of product and triphenylphosphine oxide. The product was purified by distillation under reduced pressure to give the title compound as a clear oil (1.73 g, 75%, 15.45 mmol). As a mixture of (E, E) and (E, Z). ¹H NMR (300 MHz, CDCl₃) δ 6.5 – 6.4 (m, 1H), 6.4 (dddd, J = 12.6, 2.7, 1.8, 1.0 Hz, 1H), 6.0 – 5.9 (m, 1H), 5.9 – 5.8 (m, 1H), 5.6 – 5.4 (m, 3H), 5.0 (dd, J = 10.8, 6.2 Hz, 1H), 3.8 (dq, J = 21.3, 7.1 Hz, 4H), 1.8 – 1.7 (m, 6H), 1.3 (t, J =
Synthesis of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate 132.2

CH₂Cl₂ (3.0 mL) was added to binaphthol-titanium complex 106.3 (0.016 g, 0.04 mmol) under a N₂ environment, ethyl glyoxalate 50% in CH₂Cl₂ (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (1E,3E)-1-ethoxypenta-1,3-diene (0.09 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated in vacuo to give a crude mixture which was purified by column chromatography (10% EtOAc in pentane Rf = 0.45). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.116 g, 68%), [α]_D^20 = +88 (MeOH). ¹H NMR (500 MHz, CDCl₃) δ 5.6 (ddddd, J = 3.7, 2.8, 2.2, 1.5, 0.7 Hz, 1H, C=CH), 4.9 (s, 1H, OCHOCH₂CH₃), 4.5 – 4.4 (m, 1H, CHC(O)OCH₂CH₃), 4.2 (qd, J = 7.1, 3.2 Hz, 2H, CHC(O)OCH₂CH₃), 3.9 (dq, J = 9.9, 7.1 Hz, 1H, OCH₂H₆CH₃), 3.6 (dq, J = 9.8, 7.0 Hz, 1H, OCH₂H₆CH₃), 2.3 – 2.2 (m, 2H, C=CHCH₂), 1.7 (q, J = 2.0 Hz, 3H, CH₃C=C), 1.3 (t, J = 7.1 Hz, 3H, CHC(O)OCH₂CH₃), 1.2 (t, J = 7.1 Hz, 3H, OCH₂H₆CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 171.7, 132.7, 121.5, 97.9, 65.9, 64.2, 61.2, 27.9, 19.1, 15.4, 14.4. I.R (thin film) ν max (cm⁻¹): 2977, 2897 (C-H), 1736 (C=O). HRMS (ESI): m/z calculated. C₁₁H₁₆O₄: requires 237.1103 for [M+Na]⁺; found: 237.1168.

‡IC Scan mlk 3.172 D

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Counts vs. Acquisition Time (min)
Synthesis of ethyl 6-ethoxy-3-methyl-3,6-dihydro-2H-pyran-2-carboxylate 133.1

CH₂Cl₂ (3.0 mL) was added to binaphthol-titanium complex 106.3 (0.016 g, 0.04 mmol) under a N₂ environment, ethyl glyoxalate 50% in CH₂Cl₂ (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (E)-1-ethoxy-2-methylbuta-1,3-diene (0.09 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated in vacuo to give a crude mixture which was purified by column chromatography (10% EtOAc in pentane Rf = 0.45). The fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.094 g, 55%), [α]D 20 = +73 (MeOH). ¹H NMR (300 MHz, CDCl₃) δ 6.0 (ddd, J = 10.1, 5.3, 1.5 Hz, 1H, CH=CHCH₃), 5.6 (dt, J = 10.1, 1.2 Hz, 1H, CH=CHCH₃), 5.2 (dt, J = 2.6, 1.4 Hz, 1H, OCHOCH₂CH₃), 4.4 (d, J = 3.5 Hz, 1H, CH(O)OCH₂CH₃), 4.3 (qd, J = 7.1, 1.0 Hz, 2H, CH(O)OCH₂CH₃), 4.0 (dq, J = 9.4, 7.1 Hz, 1H, OCH₃CH₂CH₃), 3.6 (dq, J = 9.4, 7.1 Hz, 1H, OCH₃CH₂CH₃), 3.6 (dq, J = 9.4, 7.1 Hz, 1H, OCH₃CH₂CH₃), 2.6 – 2.4 (m, 1H, CHCH₃), 1.3 (t, J = 7.2 Hz, 3H, CH₃CH(OC)OCH₂CH₃), 1.2 (t, J = 7.1 Hz, 3H, OCH₃CH₂CH₃), 1.0 (d, J = 7.0 Hz, 3H, CHCH₃). ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 134.6, 126.7, 98.5, 74.0, 63.8, 61.1, 31.7, 15.4, 14.8, 14.4. I.R (thin film) ν max (cm⁻¹): 2977, 2897 (C-H), 1759 (C=O), 1731 (C=C). HRMS (ESI): m/z calculated. C₁₁H₁₈O₄ requires 237.1103 for [M+Na]⁺; found: 237.1138.
Synthesis of ethyl 6-ethoxy-4-hydroxy-5-methyltetrahydro-2H-pyran-2-carboxylate 134.1

Borane dimethyl sulfide complex (0.2 mL, 1.75 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.18 g, 0.87 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H₂O₂ (30 % w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H₂O (10 mL) and Et₂O (20 mL) the layers were separated and the organics were washed with H₂O (3x 10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in pentane, Rf = 0.35) the fractions containing product were combined and concentrated in vacuo to give the title compound as a clear oil (0.131 g, 65%). [α]_D^{20} = +63.5 (MeOH).

**1H NMR** (300 MHz, CDCl₃) δ 4.8 (d, J = 2.8 Hz, 1H), 4.4 (dd, J = 7.0, 4.5 Hz, 1H), 4.3 – 4.0 (m, 2H), 4.0 (td, J = 6.7, 3.7 Hz, 1H), 3.9 (dq, J = 9.7, 7.1 Hz, 1H), 3.5 (dq, J = 9.7, 7.1 Hz, 1H), 2.2 (ddd, J = 13.5, 7.2, 3.7 Hz, 1H), 1.9 – 1.7 (m, 2H), 1.3 (t, J = 7.1 Hz, 3H), 1.2 (t, J = 7.1 Hz, 3H), 1.0 (d, J = 6.9 Hz, 3H).

**13C NMR** (75 MHz, CDCl₃) δ 171.8, 101.2, 70.4, 68.3, 65.0, 61.2, 41.3, 32.8, 15.0, 14.3, 11.4. I.R (thin film) ν max (cm⁻¹): 3466 (OH), 2979, 2933 (C–H), 1736 (C=O).


Synthesis of ethyl 2-ethoxy-1-methyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 135.1/135.2

Ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.18 g, 0.87 mmol) was added to a mixture of [(C₈H₁₇)₃NCH₃]₃PO₄[W(O)(O₂)]₂ (0.028 g, 0.0087 mmol) in 30% H₂O₂ (0.155 mL, 0.96 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with NaHCO₃(aq) (20 mL) and a Et₂O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et₂O/Pentane 1:1 mix (3x 10 mL). The organic layers were then combined, dried (MgSO₄) and concentrated under vacuum to give pure title compound as a colourless oil in a 80% yield (0.160 g, 0.69 mmol). [α]_D^{20} = +61
(MeOH). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.8 (s, 1H), 4.3 – 4.1 (m, 3H), 4.0 (dq, $J$ = 9.6, 7.1 Hz, 1H), 3.6 (dq, $J$ = 9.6, 7.0, 4.4 Hz, 1H), 3.3 – 3.1 (m, 1H), 2.3 (ddd, $J$ = 14.7, 5.2, 2.5 Hz, 1H), 2.3 – 2.1 (m, 2H), 1.3 (d, $J$ = 2.0 Hz, 3H), 1.3 – 1.2 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.5, 99.8, 98.0, 66.9, 65.3, 61.3, 56.9, 27.0, 18.2, 15.1, 14.2. I.R (thin film) v max (cm$^{-1}$): 2979, 2932 (C-H), 1756 (C=O). HRMS (ESI): m/z calculated. C$_{12}$H$_{20}$O$_5$: requires: 245.1388 for [M+H]$^+$; found: 245.1378.


Borane dimethyl sulfide complex (0.22 mL, 1.86 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.93 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H$_2$O$_2$ (30% w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H$_2$O (10 mL) and Et$_2$O (20 mL) the layers were separated and the organics were washed with H$_2$O (3x 10 mL), dried (MgSO$_4$) and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in pentane, Rf = 0.37 and 0.35). The fractions containing product were combined and concentrated in vacuo to give ethyl 6-ethoxy-4-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate as a clear oil (0.097 g, 45%) and ethyl 6-ethoxy-5-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate as a mix of diastereomers (0.064 g, 30%).

**Ethyl 6-ethoxy-4-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate 136.1**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.3 – 4.2 (m, 2H, C(O)OCH$_2$CH$_3$), 4.2 (d, $J$ = 2.7 Hz, 1H, CHOCH$_2$CH$_3$), 4.2 (d, $J$ = 7.7 Hz, 1H, CHC(O)OCH$_2$CH$_3$), 4.1 (dq, $J$ = 10.2, 7.3 Hz, 1H, OCH$_3$CH$_3$), 3.7 (ddd, $J$ = 12.3, 7.7, 5.1 Hz, 1H, CHOCH$_2$CH$_3$), 3.6 – 3.5 (m, 1H, OCH$_3$CH$_3$), 2.4 (qdt, $J$ = 7.4, 5.1, 2.6 Hz, 1H, CCH$_2$), 2.0 (ddd, $J$ = 13.1, 5.1, 2.3 Hz, 1H, CH$_3$H$_2$CHOH), 1.8 – 1.7 (m, 1H, CH$_3$H$_2$CHOH), 1.3 – 1.3 (m, 3H, C(O)OCH$_2$CH$_3$), 1.3 – 1.2 (m, 3H, CHOCH$_2$CH$_3$), 1.0 (d, $J$ = 7.2 Hz, 3H, CHCH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.7, 106.0, 77.1, 65.9, 65.4, 61.1, 36.4, 31.9, 15.2, 14.4, 13.9. I.R (thin film) v max (cm$^{-1}$): 3484 (OH), 2976, 2934 (C-H), 1735 (C=O). HRMS (ESI): m/z calculated. C$_{11}$H$_{20}$O$_5$: requires: 255.12084 for [M+Na]; found: 255.1219.
Ethyl 6-ethoxy-5-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate 136.2

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.3 – 4.2 (m, 2H, CH$_2$CH$_2$CH$_3$ and CH(O)OCH$_2$CH$_3$), 4.0 – 3.8 (m, 1H, CHO), 3.6 – 3.5 (m, 2H, CH$_3$CH$_2$CH$_3$), 3.4 (dt, $J = 9.4, 3.0$ Hz, 1H, CH$_2$CH$_2$CH$_3$), 3.3 (ddd, $J = 9.4, 7.9, 3.4$ Hz, 1H, CH$_2$H$_2$CH$_3$), 2.3 (dttt, $J = 12.1, 7.5, 5.2, 2.6$ Hz, 1H, CHCH$_3$), 1.7 – 1.5 (m, 1H, CH$_2$H$_2$CHOH), 1.5 – 1.4 (m, 1H, CH$_2$H$_2$CHOH), 1.3 (ddd, $J = 9.4$, 7.9, 3.4 Hz, 1H, CH$_2$H$_2$CHOH), 2.3 (dt, $J = 7.1, 2.2$ Hz, 3H, C(O)OCH$_2$CH$_3$), 1.2 (td, $J = 7.0, 0.8$ Hz, 3H, CHOCH$_2$CH$_3$), 0.9 (dd, $J = 6.9, 2.3$ Hz, 3H, CHCH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.2, 110.2, 75.4, 75.1, 74.3, 72.4, 68.6, 67.7, 66.9, 66.8, 61.9, 61.8, 36.7, 36.5, 33.8, 33.2, 15.3, 14.4, 14.1, 13.2. I.R (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3466 (OH), 2971, 2932 (C-H), 1737 (C=O).

HRMS (ESI): m/z calculated. C$_{11}$H$_{20}$O$_5$: requires: 255.12084 for [M+Na$^+$]; found: 255.1260.

Synthesis of 1-tert-butyl 8-ethyl 7-hydroxy-2,4,6-trimethylocta-2,4-dienedioate 138.2

5 M HCl (1.2 mL in 0.4 mL of H$_2$O) was added to a stirred solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.8 mmol) in THF (10 mL) at rt. The reaction was heated to 50 °C and heated for 1.5 h. the reaction was cooled and quenched with NaHCO$_3$(aq) (10 mL). The reaction was extracted with Et$_2$O (3x 30 mL) and the organics were combined, dried (MgSO$_4$) and concentrated en vacuo to give the synthetic sugar. The material was carried forward as the crude product for the next step. The residue was dissolved in toluene (5 mL) and stirred at rt. To this was added benzoic acid (0.005 g, 0.04 mmol) and tert-butyl 2-(triphenylphosphoranylidene)propanoate (0.344 g, 0.88 mmol). The reaction was heated to reflux and stirred for 8 h. The reaction was then cooled and concentrated, the resulting residue was purified by column chromatography (20% EtOAc in pet ether Rf = 0.2) to give the title compound as a pale yellow wax in a 70% yield (0.175 g, 0.56 mmol) as a mixture of E/Z isomers.

E isomer

$^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.1 (d, $J = 1.9$ Hz, 1H, (CO$_2$Bu)C=CH=C=CH), 5.4 (dq, $J = 10.2, 1.5$ Hz, 1H, (CO$_2$Bu)C=CH=C=CH), 4.3 – 4.2 (m, 2H, CH$_2$CH$_3$), 4.0 (dd, $J = 6.3, 3.7$ Hz, 1H, CHO), 2.8 – 2.6 (m, 1H, CHCH$_3$), 1.8 (s, 3H, (CO$_2$Bu)CH$_2$C-C-(CH$_3$)C=C), 1.8 (d, $J = 1.4$ Hz, 3H, (CO$_2$Bu)CH$_2$C-C-(CH$_3$)C=C), 1.5 (s, 9H, C(CH$_3$)$_3$), 1.3 – 1.3 (m, 3H, CH$_2$CH$_3$), 0.9 (d, $J = 6.8$ Hz, 3H, CHCH$_3$).
Z isomer

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.1 – 7.0 (m, 1H, (CO$_2$Bu)C=CH=C), 5.5 (d, $J = 9.8$ Hz, 1H, (CO$_2$Bu)C=CH=H), 4.4 – 4.2 (m, 2H, CH$_2$CH$_3$), 4.1 (dd, $J = 6.4$, 4.1 Hz, 1H, CHO), 3.0 – 2.9 (m, 1H, CHCH$_3$), 2.0 (d, $J = 1.5$ Hz, 3H, (CO$_2$Bu)CH$_2$C=C-(CH$_3$)C=C), 1.9 (d, $J = 1.4$ Hz, 3H, (CO$_2$Bu)CH$_3$C=C-(CH$_3$)C=C), 1.5 (s, 3H, C(CH$_3$)$_3$), 1.3 (dd, $J = 7.1$, 5.4 Hz, 3H, CH$_2$CH$_3$), 1.0 (d, $J = 6.9$ Hz, 3H, CHCH$_3$).

$^{13}$C NMR (75 MHz, Chloroform-$d$) $\delta$ 174.4, 168.4, 167.7, 141.5, 137.7, 135.5, 133.1, 132.8, 131.4, 130.3, 130.1, 128.0, 80.5, 80.3, 74.1, 74.0, 61.8, 37.5, 37.2, 28.3, 23.3, 16.8, 14.9, 14.5, 14.4, 14.3, 14.3, 14.2. I.R (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3497 (OH), 2977, 2933 (C-H), 1730, 1702 (C=O).

HRMS (ESI): m/z calculated. C$_{17}$H$_{28}$O$_5$: requires 313.20149 for [M]+; found: 313.2001.

6-Ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)methanol 137.1

LiAlH$_4$ (2.4 M in THF, 4.0 mL) was added dropwise to a solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (1.0 g, 4.8 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then poured into a solution of saturated NH$_4$Cl (20 mL). The reaction mixture was then extracted with Et$_2$O (3x 30 mL) and the organics were combined, dried (MgSO$_4$) and concentrated en vacuo to give pure title compound as a clear oil in 95% yield (0.85 g, 4.56 mmol). $[\alpha]_{D}^{20} = +71$ (MeOH). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.6 (dp, $J = 4.4$, 1.5 Hz, 1H, C=CH), 4.9 (dt, $J = 2.0$, 1.0 Hz, 1H, CHCH$_2$CH$_3$), 3.9 – 3.8 (m, 2H, CHCH$_2$CH$_3$), 3.8 – 3.5 (m, 2H, CHCH$_2$OH), 2.5 (br s, 1H, CHCH$_2$OH), 2.4 (tdd, $J = 7.1$, 3.9, 2.0 Hz, 1H, CHCH$_3$), 1.7 (td, $J = 1.8$, 0.9 Hz, 3H, C=CCCH$_3$), 1.3 (t, $J = 7.1$ Hz, 3H, CHCH$_2$CH$_3$), 1.0 (d, $J = 7.2$ Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 131.7, 129.7, 98.4, 75.3, 63.8, 63.1, 30.8, 18.3, 15.4, 14.8. I.R (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3423 (OH), 2970, 2930, 2875 (C-H). HRMS (ESI): m/z calculated. C$_{10}$H$_{18}$O$_2$: requires 209.1153 for [M+Na]$^+$; found: 209.1162.
NEt$_3$ (0.19 mL, 1.48 mmol) was added to a solution of 6-Ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)methanol (0.25 g, 1.34 mmol) and tosyl chloride (0.28 g, 1.48 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 16 h. The reaction was diluted with 1 M NaOH and extracted with Et$_2$O (3x 30 mL) and the organics were combined, dried (MgSO$_4$) and concentrated *en vacuo*, the resulting residue was purified by column chromatography (10% EtOAc in pet ether Rf = 0.4) to give the title compound as a clear oil in a 82% yield (0.374 g, 1.10 mmol). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.9 – 7.7 (m, 2H, ArH), 7.4 – 7.3 (m, 2H, ArH), 5.5 (dp, J = 4.5, 1.5 Hz, 1H, C=CH), 4.9 (s, 1H, CHOCH$_2$CH$_3$), 4.2 – 3.9 (m, 3H, CHCH$_3$OSO$_2$Ts and CHCH$_2$OSO$_2$Ts), 3.7 (dq, J = 9.5, 7.1 Hz, 1H, CHOCH$_3$H$_2$CH$_3$), 3.5 (dq, J = 9.6, 7.1 Hz, 1H, CHOCH$_3$H$_2$CH$_3$), 2.4 (s, 3H, CH$_3$Ar), 2.2 (dddt, J = 9.3, 5.8, 4.0, 2.1 Hz, 1H, CHCH$_3$), 1.6 (q, J = 1.3 Hz, 3H, C=CHAr), 1.2 (td, J = 7.1, 2.3 Hz, 3H, CHOCH$_3$H$_2$CH$_3$), 0.9 (d, J = 7.1 Hz, 3H, CHCH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.0, 144.0, 132.8, 130.0, 129.0, 128.1, 99.4, 71.9, 69.8, 63.4, 30.7, 21.8, 17.9, 15.3, 14.1. I.R (thin film) ν$_{max}$ (cm$^{-1}$): 2971, 2879 (C-H). HRMS (ESI): m/z calculated. C$_{17}$H$_{24}$O$_3$S$_1$: requires 363.1242 for [M+Na]$^+$; found: 363.1246.
### X-Ray Crystallography Data

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