The Use of Chiral Auxiliaries in the Synthesis of Chemically and Biologically Important Chiral Compounds

A Thesis Submitted for the Degree of
Masters of Science by:

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Abstract

Chiral synthons of chemical and biological importance have been synthesised using imidazolidinone and Evans' oxazolidinone chiral auxiliaries (CA). The thesis comprises two parts, which were carried out at the Universities of Cape Town, RSA and University of Michigan in the USA.

In part 1, carried out in the Chemistry Department of the University of Cape Town, an imidazolidinone-CA was utilised in developing a malonate-based methodology to synthesise compounds containing a quaternary stereogenic centre (QSC). With this methodology, a small library of malonate-based QSC-containing synthons has been synthesised in both high yields (> 87 %) and high stereoselectivities (dr, ≥ 93 : 7 %). The CA was cleaved using an EtSLi S_NAc reaction followed by a double reduction using the Fukuyama protocol followed by $NaBH_4$ to afford *α,α'*-disubstituted-2-hydroxy synthons in 55-65% yield over two steps respectively.

In part 2, carried out in the Chemistry Department at the University of Michigan, the macrolide core (**10**) of lactimidomycin was synthesised for biological evaluation over 11-linear steps in a 6.1 % overall yield. The synthesis exploited an Evans' oxazolidinone-mediated aldol reaction to construct the Evans *syn*-adduct, a Suzuki cross-coupling for the (*E,Z*)-diene construction, and an intramolecular Horner-Wadsworth-Emmons olefination for construction of the *E*-enone of the macrolide.

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Finally, I would like to thank God “who make all things come together.” Without him this piece of work would not have been what it is today – thank you God, I love you.

I declare that contained in this thesis, "**The Use of Chiral Auxiliaries in the Synthesis of Chemically and Biologically Important Chiral Compounds**" is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

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Thobela Bixa

Date: _____

Foreword:

Staying true to the struggle

We will stay true to the struggle till it comes to the end

We will fight till that last milligram of product is consumed

We will push these arrows till they make sense

We will blow our TLCs till the last breath

We will not be intimidated by NMRs that don't look like our desired products,

and we won't be put off by impurities that dominate our spectra

We won't be satisfied by low yielding reactions.

No time to mourn for failed reactions, instead we press forward towards the higher prize,

which is scientific TRUTH.

By: James Biwi and Thobela Bixa

Abbreviations

$[\alpha]_D$	Optical rotation
Ac	Acetyl
Ar	Aromatic
Bn	Benzyl
Bp	boiling point
n-Bu	*normal*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tertiary*-Butyl
TBDPS	*tert*-butyldiphenylsilyl
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutyl aluminium hydride
DMS-BH_3	Borane dimethyl sulphide
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
d	doublet
dd	doublet of doublets
dt	doublet of triplets
dq	doublet of quartet
Eqn	Equation
eq	equivalents
Et	Ethyl
EtOAc	Ethyl acetate
g	grams

Hz	Hertz
n-Hex	*normal*-Hexane
HPLC	High performance liquid chromatography
HRMS	High resonance mass spectrometry
hr/hrs	Hour(s)
HOBt	1-Hydroxybenzotriazole
IR	Infrared spectroscopy
J	Coupling constant
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
MHz	Megahertz
Mp	Melting point
Me	Methyl
mg	milligrams
ml	millilitres
mmHg	millimetre mercury
mmol	millimole
min	minute
m	multiplet
nm	nanometers
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect spectroscopy

p	para
p	Pentet
Ph	Phenyl
PG	Protecting group
q	quartet
qd	quartet of doublets
rt	Room temperature
s	singlet
sat.	Saturated
NaHMDS	Sodium hexamethyldisilazide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium Iodide
TES	Triethylsilane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	*p*-Toluenesulfonyl
Tf	Triflate
t	triplet

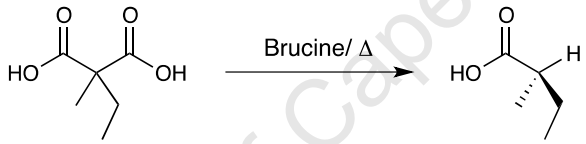
Contents

Part 1

Chapter 1: Introduction

1.1. Asymmetric Synthesis

Asymmetric synthesis (AS), also known as stereoselective synthesis or asymmetric induction is a term that was first used by E. Fischer in his work on carbohydrates.[1] AS is defined as the study of synthesising optically active compounds, and the first enantioselective synthesis example (by the standards of the time) was reported by Willy Marckwald in 1904 in which he decarboxylated an α,α'-disubstituted malonic acid in the presence of the chiral alkaloid brucine to obtain the product in 10 % ee, **Scheme 1.1**.[1] Since then, chemists have sought out a greater understanding and synthesis of chiral compounds.



Scheme 1.1: The first enantioselective synthesis by Willy Marckwald.

Nature consists of a myriad of optically active compounds with attractive architecture as well as useful chemical and medicinal (pharmaceuticals) properties.[2] Both academia and industry have worked tirelessly to access pivotal chiral compounds, and the organic literature attests to the interest in this topic. Many powerful asymmetric methods have emerged over the past century that are used in both academic and industry laboratories. Since the early days of drug-discovery more and more chiral compounds have been used to combat various diseases.[2a] Also, over the years there has been a steady increase in the use of non-racemic active pharmaceutical ingredients (APIs) on the market, **Figure 1.1**.[2a] This shift was brought about by the US Food and Drug Administration (FDA) having to move away from the use of racemates as drugs. The banning of thalidomide in the early 1960's is a classical example of why the use of racemic drugs can be catastrophic, and the shift towards non-racemic drugs has put AS as a lead topic in organic synthesis.

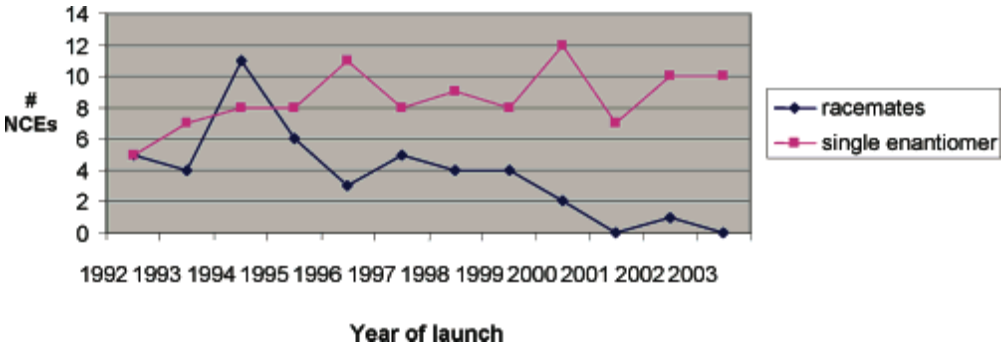
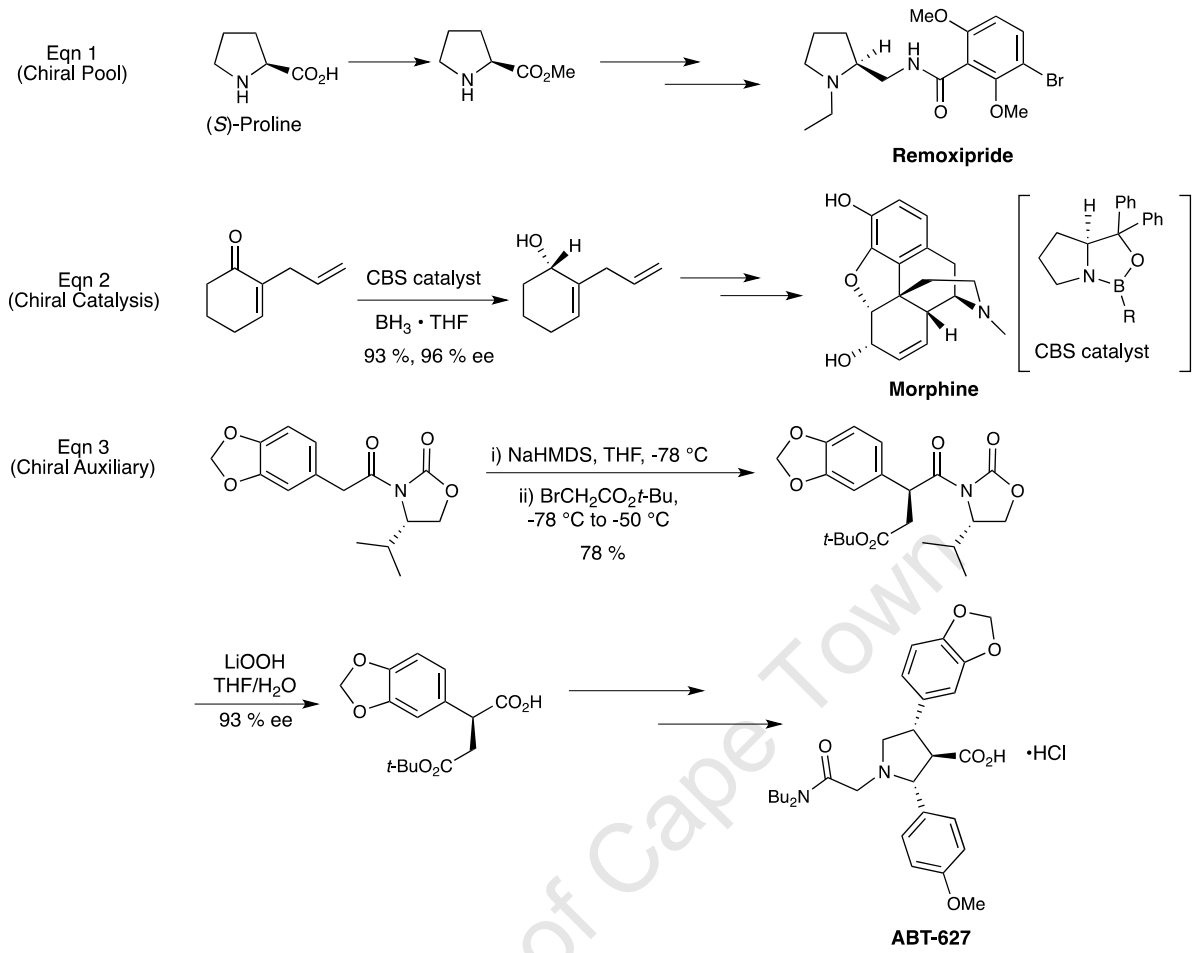


Figure 1.1: New chemical entities (NCEs) on the market as either single enantiomers or racemates.[2a]

The synthesis of chiral compounds is far more challenging than the synthesis of their achiral counterparts, the main issue being the control of facial bias in the bond-forming step leading to high stereoselectivity. To this effect, the following strategies have been employed with great success for accessing chiral compounds in high stereoselectivity include chiral pool (CP), chiral catalysts (CC), and chiral auxiliaries (CA), **Scheme 1.2**.[3] The CP strategy involves the use of a naturally abundant or easily accessible chiral compound that can be transformed into the target compound (Eqn 1). This strategy has been the method of choice especially in industry due to the abundance and accessibility of natural chiral starting materials.[2a, 4] However, a drawback of this strategy is that not all target compounds resemble naturally occurring chiral compounds or can be accessed from naturally occurring starting materials. On the other hand, CC is the use of a chiral ligand (enzymatic, organometallic, and recently organocatalytic) in sub-stoichiometric amounts where the chiral ligand is recycled after the enantioselective asymmetric induction transformation, Eqn 2.[3, 5] By comparison, CAs are used in stoichiometric amounts. The use of a CA is a three-step process, in which the CA is firstly attached to the substrate, which is followed by diastereoselective asymmetric induction, and finally the CA is cleaved and recovered to obtain the product enriched in one of the enantiomers.[1a, 3]

From now on, the CA strategy will be the focus of this review in view of its relevance to both research projects in this dissertation. Where necessary, the other two strategies (CP and CC) will be mentioned for comparison or to clarify concepts.

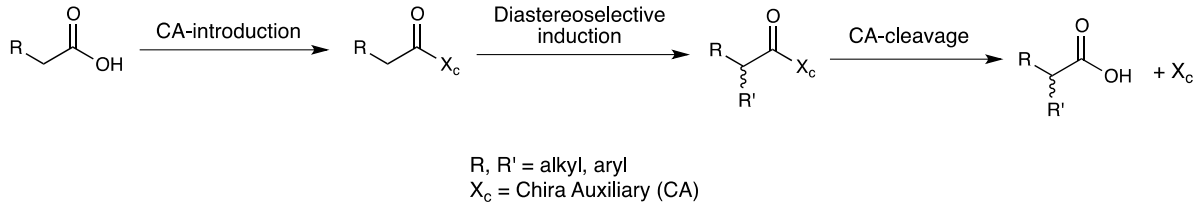


Scheme 1.2: Asymmetric synthesis strategies.[6]

1.2. Chiral Auxiliaries

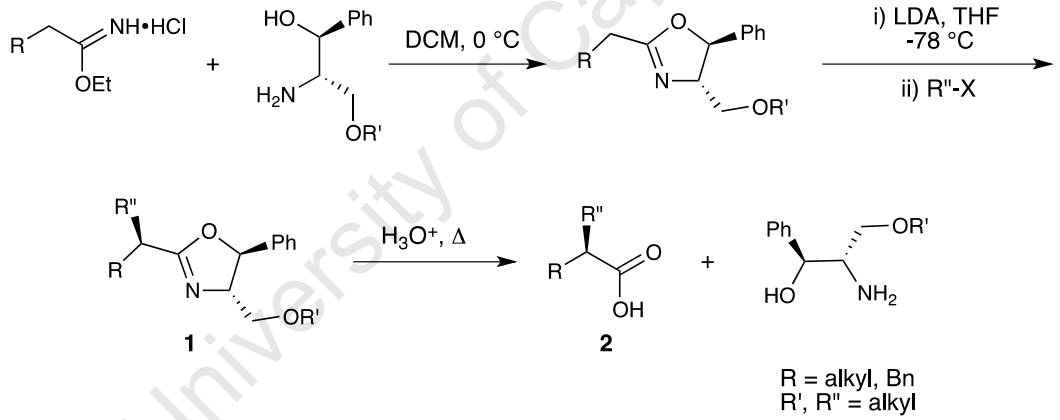
As mentioned earlier, a CA-based method requires that the CA: (i) is attached to the substrate; (ii) induces high diastereofacial selectivity; and (iii) is removed and recovered without racemization of the newly formed stereocentre, **Scheme 1.3**.[7] The effectiveness of a CA depends on the ease with which these three steps are performed and this criterion has been the basis of many successful and widely utilised CAs. For most, if not all CA-based methods, a C-X (X = O, N) covalent bond is used as a point of attachment between the substrate and the CA. This carbon-heteroatom bond is used because C-X bonds are easier to form, strong enough not to break during the asymmetric induction step, but can be cleaved relatively easily afterwards. Another heteroatom on the CA is typically used (especially in acyclic systems) to serve as a site of chelation between the CA and the substrate. This

chelation is pivotal for acyclic CA-mediated reactions as it locks the "substrate-CA" species into one conformer, thus allowing facial bias leading to high diastereoselectivity.



Scheme 1.3: CA-mediated asymmetric induction.[1a]

The use of a CA dates back to the early 1970s from work done by Meyers with oxazolines, **Scheme 1.4**.[8] In his studies he used readily available chiral (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol which he condensed with various nitrile salts forming a 5-membered oxazoline ring in 75 % yield. Subsequently, Meyers mono-alkylated the oxazolines with various electrophiles to afford **1** in high optical purity (de, 82 %) and high yields (62-92 %). Acid hydrolysis afforded α-alkylated carboxylic acid **2** in moderate to high yields (62-84 %).[8]



Scheme 1.4: Oxazoline as CA in asymmetric induction.

In order to explain the stereoselectivity, Meyers invoked a charge-assisted transition-state (TS) model involving a bicyclic chelating ring with the lithium cation, in which the Li^+ ion coordinates to the nitrogen of the aza-enolate, the oxygen of the ether, as well as the leaving group of the electrophile on the *re*-face. This then assists the electrophile to approach and react from the *re*-face, **Figure 1.2**. Formation of the *Z*-aza-enolate in the LDA

step is favoured so as to minimise steric interaction between the chelated ring and the R-substituent on the double bond.

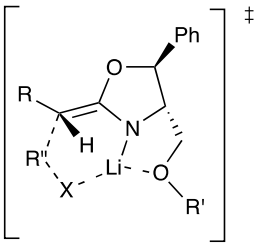


Figure 1.2: Meyers' TS-model for oxazoline alkylation

Following Meyers' report, powerful CAs have emerged to provide a standard procedure for synthesising chiral compounds in both academic and industrial labs, **Figure 1.3**.[2a] The different CAs in **Figure 1.3** complement each other in many ways. For example, while Evans and Evans-type CAs are mostly used in asymmetric aldol reactions,[9] the cyclohexane-based ones (such as Hoffmann)[10] are used in alkylation reactions, while the proline-based (such as Enders)[11] are used in Michael additions. However, it must be said that CAs are meant to be widely used in many types of asymmetric reactions and so there is no CA that is only meant for a particular reaction-type. Instead, different groups have used CAs for various transformations depending on the availability of the CA and the research group's interests. One of the reactions that CAs have been intensely utilised for, is the asymmetric aldol reaction and this subject has been reviewed in many books and journal articles.[9a, 12]

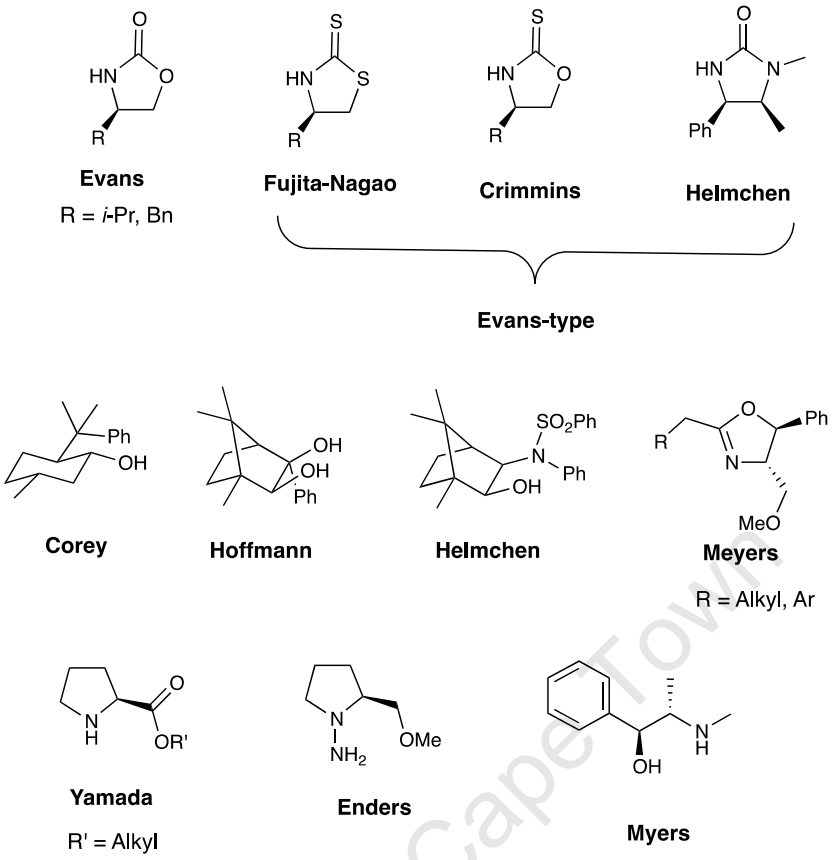
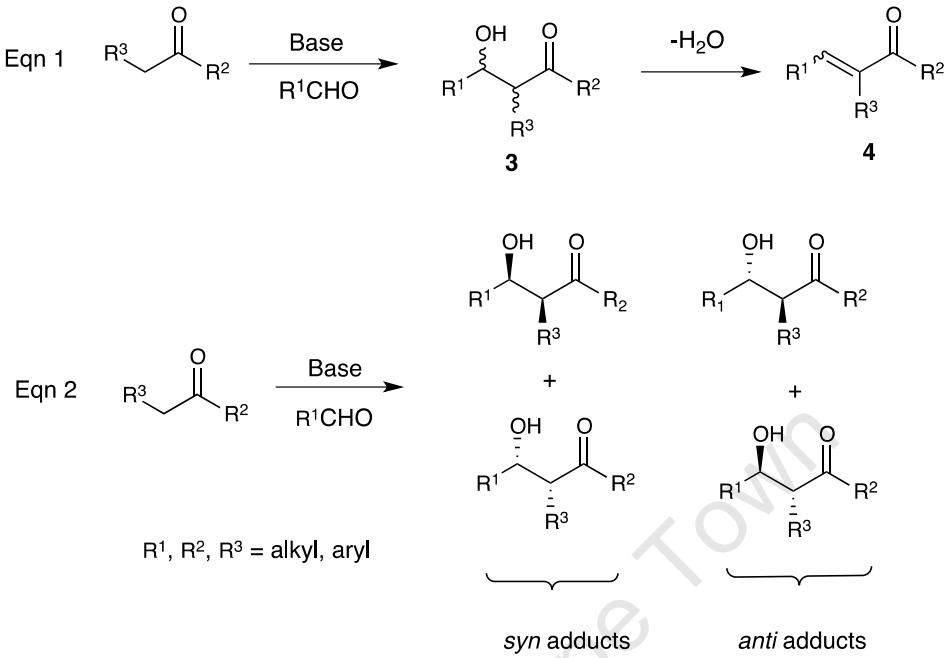


Figure 1.3: Examples of CAs that have been used in asymmetric synthesis.

1.3. The aldol reaction

Enolate chemistry has proven to be one of the most reliable tools for the synthesis of C-X (X = C, N, O, and halogen) bonds in organic synthesis.[13] The aldol reaction, first discovered in the 19th century independently by Charles-Adolphe Wurtz and Alexander Borodin, is a sub-class of enolate transformation in which an enolisable carbonyl compound acts as a nucleophile and adds to an electrophilic carbonyl group to give a β-hydroxycarbonyl product **3** which may eliminate to an α,β-unsaturated carbonyl **4**, **Scheme 1.5**, Eqn 1.[12] The reaction leading to **3** is called the aldol addition while the one leading to **4** is called the aldol condensation. The formation of product **3** or **4** depends on the carbonyl substrate(s) used and the reaction conditions. During an aldol addition reaction where two prochiral carbons in the bond-forming step are involved, two stereogenic centres are concomitantly formed contiguously, leading to four possible stereochemical outcomes, as the two *syn*-enantiomers and the two *anti*-enantiomers, **Scheme 1.5**, Eqn 2. The relative stereocontrol

(*syn* : *anti* ratio) in this reaction can be controlled by the choice of Lewis acid (via chelation), CA (*vide infra*), and the type of base used.



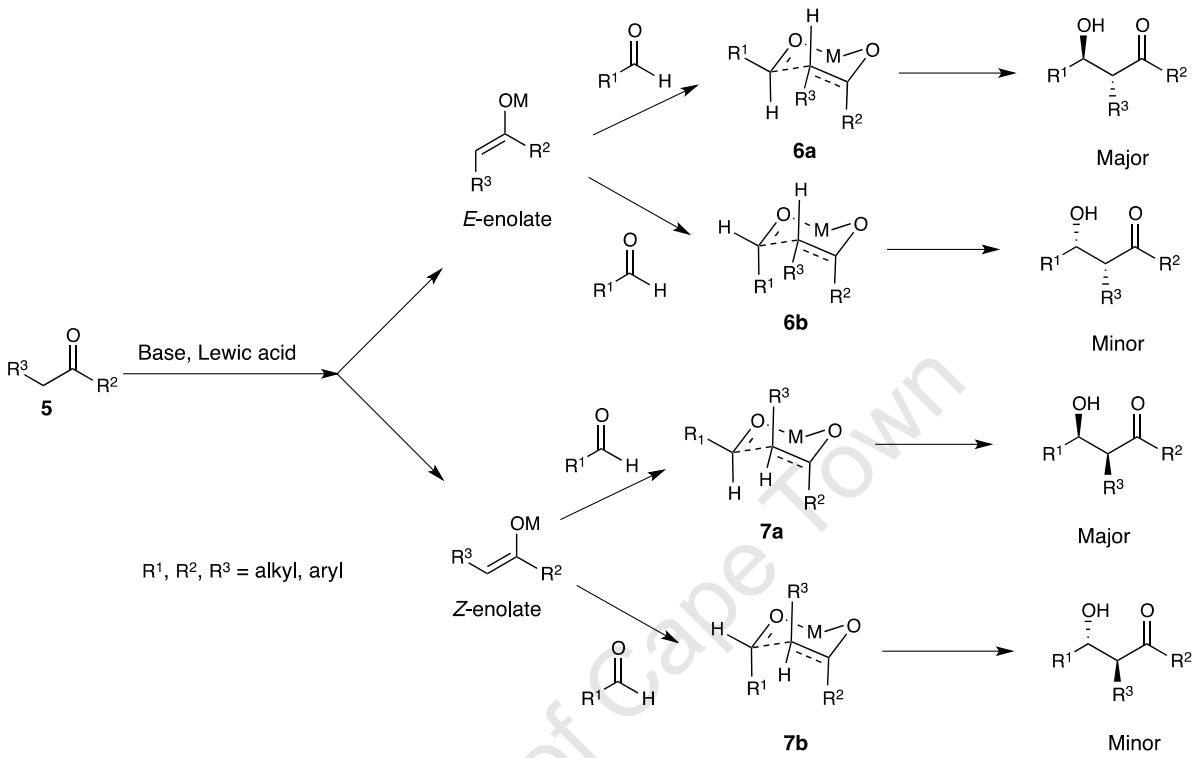
Scheme 1.5: The aldol reaction *syn*- and *anti*-adducts.

1.3.1. Zimmerman-Traxler transition-state model

Since the use of preformed enolates in the 1970's, various plausible TS-models have been proposed to elucidate the stereochemical outcome observed in the aldol addition reaction.[12] Some of the proposed TS-models include the Zimmerman-Traxler,[14] and Hoffmann[15] to mention a few. Owing to relevance and generality, only the Zimmerman-Traxler TS-model will be discussed. Also, the other models were only introduced to explain some results that could not be entirely understood with the Zimmerman-Traxler model.

The Zimmerman-Traxler model invokes a six-membered chelating ring that incorporates both the nucleophilic enolate and the electrophilic carbonyl, as well as the enolate metal cation, **Scheme 1.6**. Enolisation of **5** can form either the *E*- or *Z*-enolate, which individually lead to different stereochemical products. Formation of the *E*-enolate leads to two possible TS-models, **6a** and **6b**, with **6a** as the preferred model because the R^1 substituent is in an equatorial position avoiding 1,3-diaxial interactions. This explains why *E*-enolates give predominantly *anti*-aldol products. By comparison, formation of the *Z*-enolate leads preferentially to **7a**, the low energy model for the same reasons as mentioned above. In

such a case the *syn*-aldol product is favoured. It is worthy to note that a combination of parameters such as Lewis acid, base, CA and so forth can be used to control the selectivity for either *syn*- or *anti*-adduct.

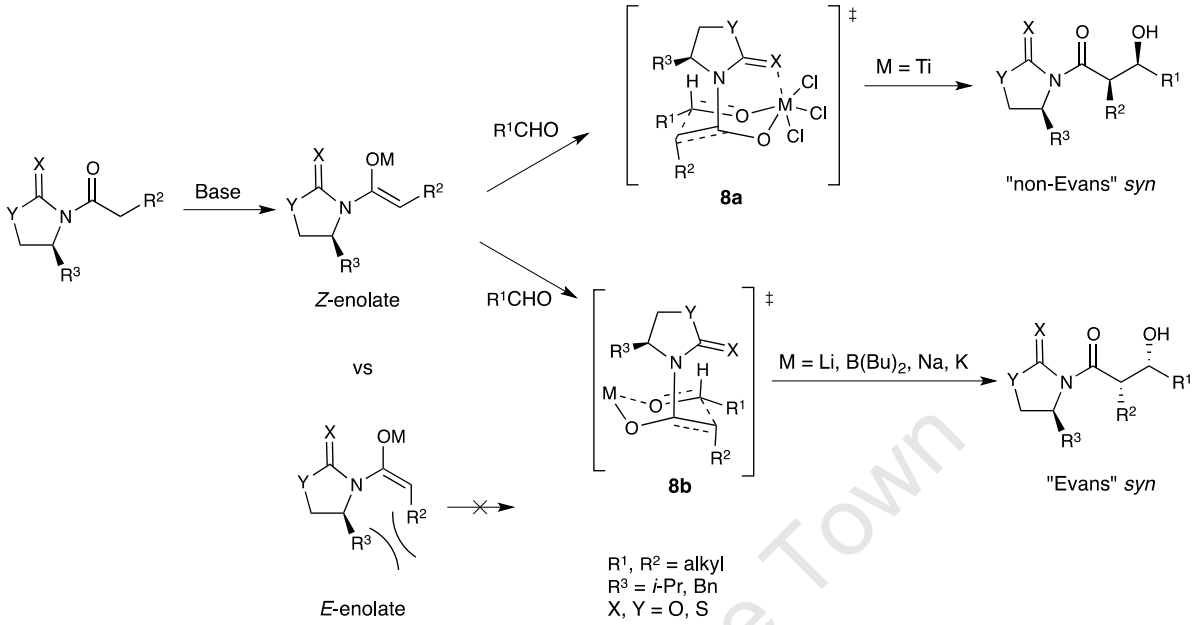


Scheme 1.6: The Zimmerman-Traxler transition-state model for aldol addition.

1.3.2. Chiral auxiliary mediated aldol reaction

The CA-mediated asymmetric aldol reaction is one of the most important and reliable tools in asymmetric synthesis (AS) and has been used in many total synthesis of natural products and APIs (active pharmaceutical ingredients), especially polyketides possessing contiguous stereogenic centres.[16] Evans has made a profound contribution in this field with his pioneering work on *N*-acyl oxazolidinone aldol addition reactions.[9b-d] To account for the stereochemical formation of his products Evans also invoked a Zimmerman-Traxler type-model, **Scheme 1.7**. He proposed that the *Z*-enolate is preferentially formed due to minimised steric interactions between the R^2- and R^3-substituents. Once the enolate geometry is set, the CA carbonyl (C=X, X = O, S) can chelate to the metal (M = Ti) forming **8a**, which leads to the non-Evans *syn*-adducts. Alternatively, it can not chelate to give **8b** (M = Li, B, Na, K), which leads to the Evans *syn*-adduct. The chelation/non-chelation of the

metals changes the π-facial selectivity of addition to the enolate, leading to opposite absolute configurations in the products.

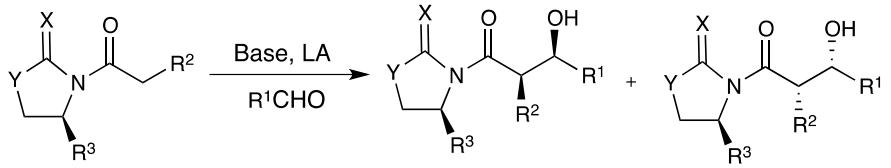


Scheme 1.7: CA-mediated TS-models for the Evans and non-Evans *syn*-adducts.

Owing to relevance to the current research, only the *syn*-aldol products will be discussed. **Table 1.1** is not exhaustive but seeks to highlight ways that have been used to access both Evans and non-Evans *syn*-products in high diastereoselectivity by simply varying reaction conditions. The non-chelation/chelation process (refer to **Scheme 1.7**) acts as a switch between the Evans *syn*- and non-Evans *syn*-products, and has been the main focus for research in this area.[17] The extent of chelation depends on: the type of X atom, the Lewis-acid metal M, and the excess amine base. Entry 1 depicts the pioneering work by Evans with boron enolates to attain the Evans *syn*-adduct (**9b**). Boron can only bond to four groups including coordination to the aldehyde carbonyl as part of the reaction activation. Hence, it cannot coordinate to the CA and the reaction proceeds via a non-CA chelated transition-state (TS) to give the Evans-*syn* product. Since alkali earth-metals (Li, Na, K) have a low coordination number they cannot coordinate to the CA either and therefore they all also afford the Evans *syn*-adduct. On the other hand, titanium has empty *d*-orbitals and can therefore coordinate to X leading to the chelated TS-model which gives the non-Evans *syn*-adduct **9a**, entry 2. A thiazolidinethione CA can also be used to obtain the non-Evans *syn*-

adduct, entry 4. However, one can "switch-off" the titanium-chelation by using excess amine-base, which intercepts the chelation and in so doing reverts the reaction outcome back to the Evans *syn*-adducts, see entry 3.

Table 1.1: The effects of reaction conditions on CA-mediated aldol addition reactions.[12, 17]



9a "non-Evans" *syn* **9b** "Evans" *syn*

Entry	R^3	X	Y	Base (eq)	Lewis Acid (eq)	Ratio **9a : 9b**
1	*i*-Pr	O	O	*i*-Pr_2NEt (1.1)	$(nBu)_2B(OTf)$ (1.2)	> 2: 98
2	Bn	O	O	*i*-Pr_2NEt (1.1)	$TiCl_4$ (1.1)	98 : 2
3	Bn	S	S	(-)-Sparteine (2.5)	$TiCl_4$ (1.0)	1 : 99
4	Bn	S	S	(-)-Sparteine (1.0)	$TiCl_4$ (1.0)	98 : 2

1.4. Quaternary Stereogenic Centres

Quaternary stereogenic centres (QSC) are ubiquitous both in nature and in the pharmaceutical industry. It is therefore imperative to come up with efficient methods that give access to this motif. The term quaternary centre is sometimes a cause of confusion because it is broad. Specifically, a QSC is a fully substituted chiral carbon without any carbon-hydrogen bond, and examples include oxaquaternary (**a**), aza-quaternary (**b**) and so forth, **Figure 1.4**.[18] In this review the term QSC will refer strictly to an all-carbon quaternary chiral centre, such as the one in morphine, **Figure 1.4**. Although this research only concerns itself with QSC-containing compounds, where necessary, other types of quaternary centres will be mentioned for comparison sake.

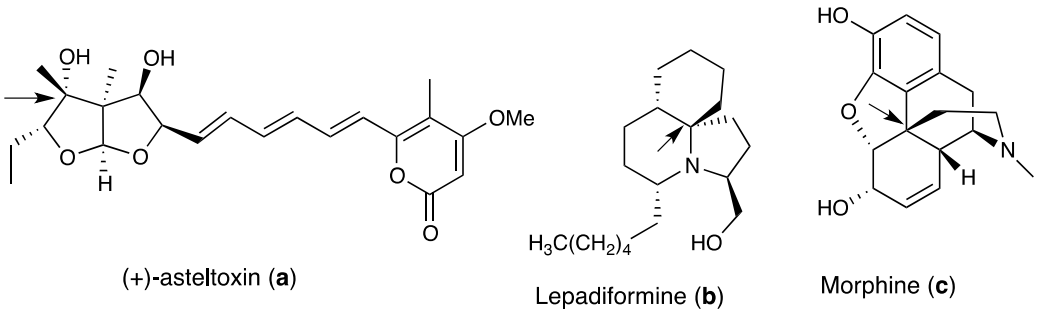


Figure 1.4: QSC-containing compounds with the QSC shown by the arrow.

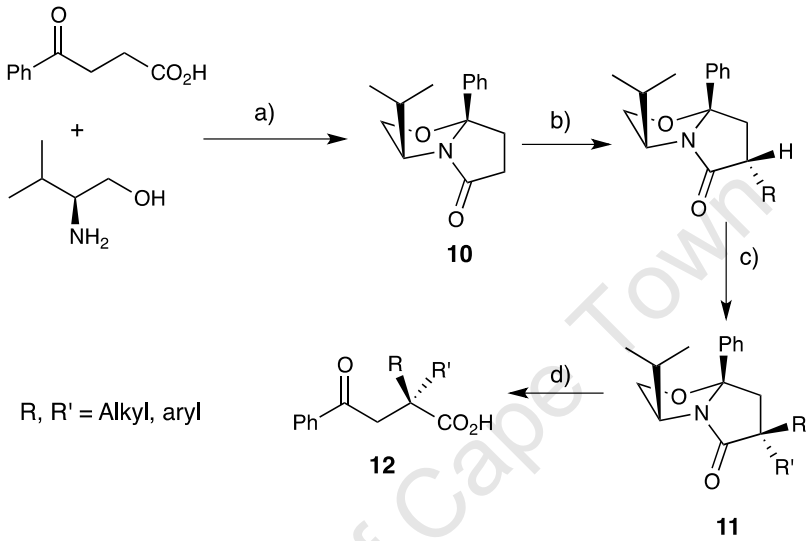
The synthesis of chiral compounds is challenging but an even more demanding task is the synthesis of QSC-containing compounds.[19] Construction of QSCs via a fully substituted sp^2 centre is well-known in organic synthesis, especially via enolate chemistry, and the two main challenges encountered in such a synthesis include: 1) the steric repulsion involved in bringing a fourth substituent to an already congested carbon centre, and 2) generation of a stereo-defined enolate (*E-/Z*-enolate), which is crucial for controlling the stereochemistry in the product.[19] Owing to the demands mentioned above, QSC construction is then arguably a true test of existing asymmetric methods that have been developed for the synthesis of chiral tertiary centres. Constructing this motif is therefore crucial for advancing the repertoire of asymmetric synthesis (AS) methods.

Indeed, powerful diastereoselective and enantioselective methods have emerged over the years to overcome the challenges encountered in QSC construction and examples include the use of reactions such as Michael additions,[20] Diels-Alder,[21] aldol,[22] and enolate alkylations[23] to mention a few. However, more efficient methods are still required to build on the current repertoire to speed-up the synthesis of pharmaceutical drugs and chemically vital advanced synthons. For the purpose of this report only diastereoselective non-catalytic enolate alkylation reactions of relevance to QSC construction will be reviewed and discussed.

1.4.1. Bicyclic enolate alkylation for QSC construction

The first diastereoselective CA-mediated via enolate alkylation towards QSC construction was reported by Meyers in 1984 in which a bicyclic ring-system was used to control the stereogenicity of the quaternised product. In his studies, Meyers condensed a γ-keto

carboxylic acid with L-valinol to form bicyclic lactam **10**.[24] Dialkylation of **10** with various R-groups gave QSC-containing compounds in high yield and stereoselectivity, **Scheme 1.8**. After quaternisation, the CA was removed with ease under acidic conditions to liberate an α,α'-disubstituted γ-keto acid **12** in high yield (70-90 %) and good stereoselectivity (> 90 % ee for some products). Changing the order of introduction of R- and R'-group inverts the stereochemistry in **12**.



Scheme 1.8: Reaction conditions- a) Δ, Tol/*p*-TsOH. b) i) LDA, –78 °C, THF; ii) R-X. c) LDA, –78 °C, THF; ii) R'-X. d) 10 % H_2SO_4, Δ.

The stereoselectivity of this strategy relies on the formation of a rigid/inflexible bicyclic structure which imposes particular geometry on the enolate, as well as the shielding of the *exo*-face by the bulky substituents, isopropyl and phenyl. The transition-state model (TS) invoked by Meyers involves the isopropyl and phenyl group shielding the top face of the enolate and thus directing alkylation with various R- and R'-groups to predominantly occur on the underneath, **Figure 1.5**.

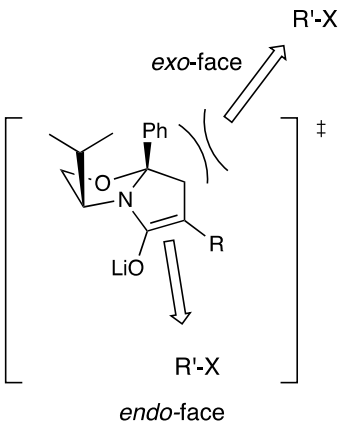


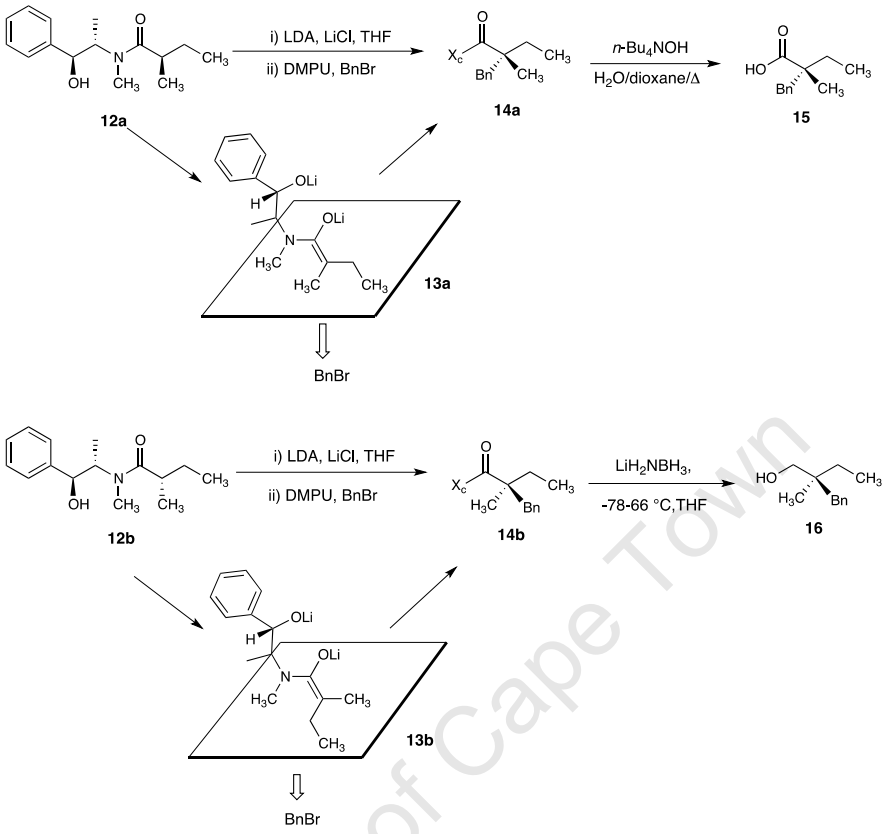
Figure 1.5: Meyers bicyclic enolate TS-model.

1.4.2. Acyclic enolate alkylation for QSC construction

The stereocontrolled alkylation of acyclic chiral enolates is more challenging than that of a bicyclic chiral enolate owing to the freedom of rotation in acyclic systems. Important factors that affect the stereochemical outcome in acyclic systems include the enolate geometry, steric effects and chelation effects. It is crucial to control the geometry of the forming *E*-/*Z*-enolate because alkylation of either isomer leads to different diastereomeric products. Unlike in bicyclic enolates where the enolate geometry is enforced by the bicyclic structure, in acyclic systems the enolate which is lower in energy is favoured. Steric interactions between the forming enolate and the group(s) on the CA favour formation of the enolate geometry lower in energy. Once the enolate geometry is set, steric hindrance from bulky-groups on the CA play a role in controlling the facial selectivity of addition to the enolate. Owing to the freedom of rotation in an acyclic system, strong chelation becomes a necessity so as to lock the already set enolate geometry into one conformer.

A noteworthy example of an acyclic system utilised in QSC construction was reported by Myers with his studies using pseudoephedrine as a CA.[25] α-Methylbutyramides **12a** and **12b**, differing only in α-stereogenicity, undergo stereospecific enolisation with LDA at –40 °C to the *Z*-enolate **13a** and *E*-enolate **13b** respectively. Benzylation of **13a** and **13b** with benzyl bromide at –40 °C is from the same face, away from the benzylic alkoxide, **Scheme 1.9**. With this method various alkyl, allyl, and benzyl quaternised compounds were synthesised in high yields (> 72 %) with average to good selectivity (dr, 6.2 : 1 to 19 : 1). The

pseudoephedrine CA was removed via hydrolysis to carboxylic acid **15**, or under reductive conditions with LiH_2NBH_3 to the primary alcohol **16**.



Scheme 1.9: Pseudoephedrine in QSC construction.

To explain the observed stereospecific enolisation, Myers' proposed a TS-model that is similar to Askin's model with alkylating prolinol based enolates.[26] The enolisation can be elucidated by a pre-transition state model (a steric-model) that requires the base to come from the opposite face of the benzylic alkoxide to avoid steric interaction, **Figure 1.6**.[27] This TS-model suggests that the benzylic alkoxide coordinates to the THF solvent, blocking the top face and resulting the base coming in from the bottom face. During enolisation, **12a'** has the preferred conformation where the α-hydrogen atom is positioned on the opposite face to the benzylic alkoxide, and deprotonation leads to the *Z*-enolate. On the other hand, **12b'** has the α-hydrogen on the same face as the benzylic alkoxide, thus a conformational change in the chain is required to position the α-hydrogen on the opposite face to the benzylic alkoxide. This switch on deprotonation leads to formation of the *E*-enolate.

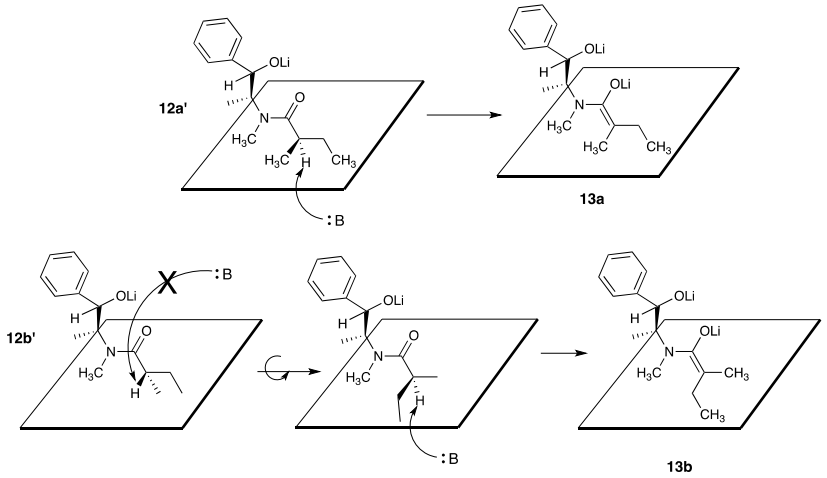
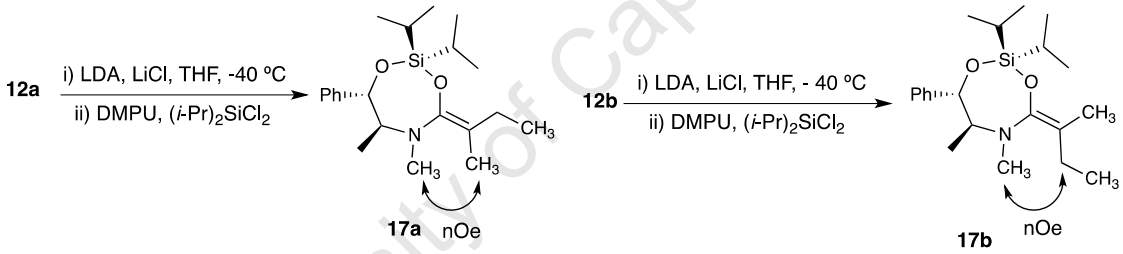


Figure 1.6: Stereospecific deprotonation.

Myers confirmed the stereospecific enolisation by trapping the two enolates at –40 °C with dichloro(diisopropyl)silane to **17a** and **17b** and performing NOESY experiments on the silyl enol ether products, **Scheme 1.10**.

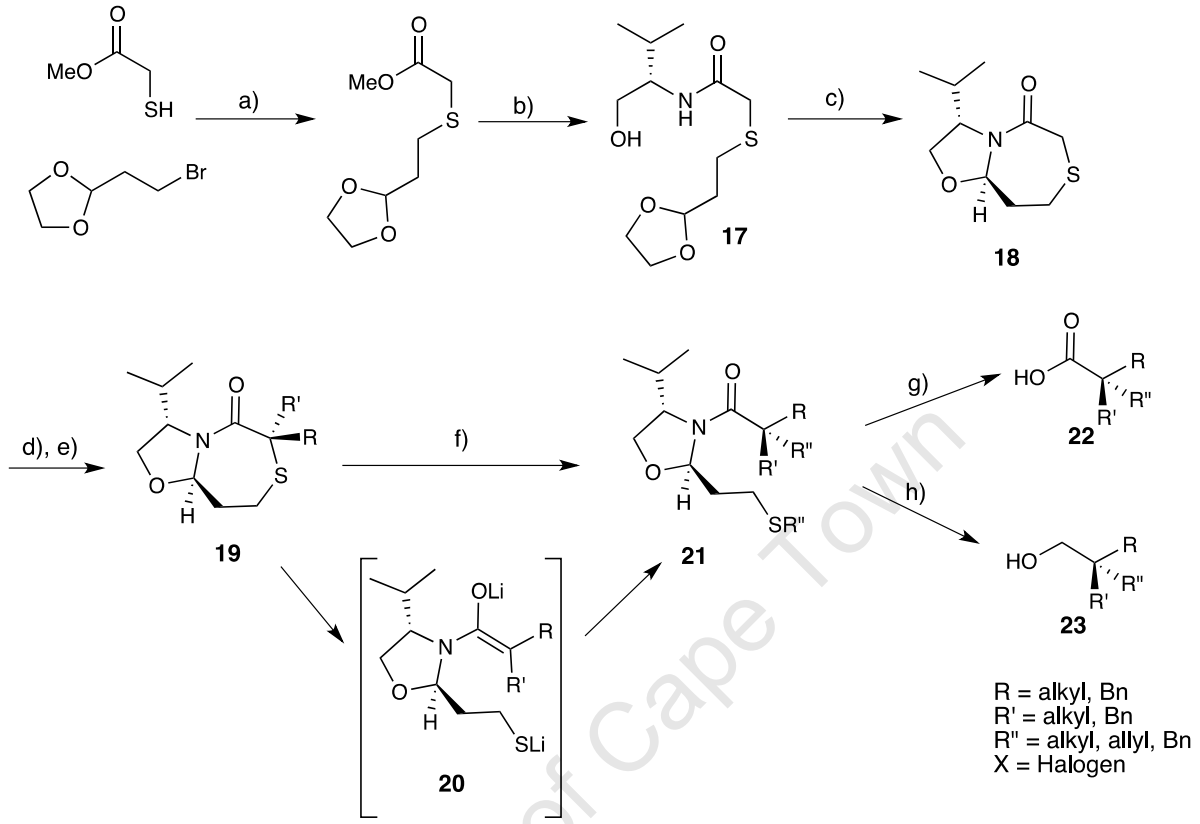


Scheme 1.10: Silyl enolate trapping.

1.4.3. Bicyclic thioglycolate enolate alkylation for QSC construction

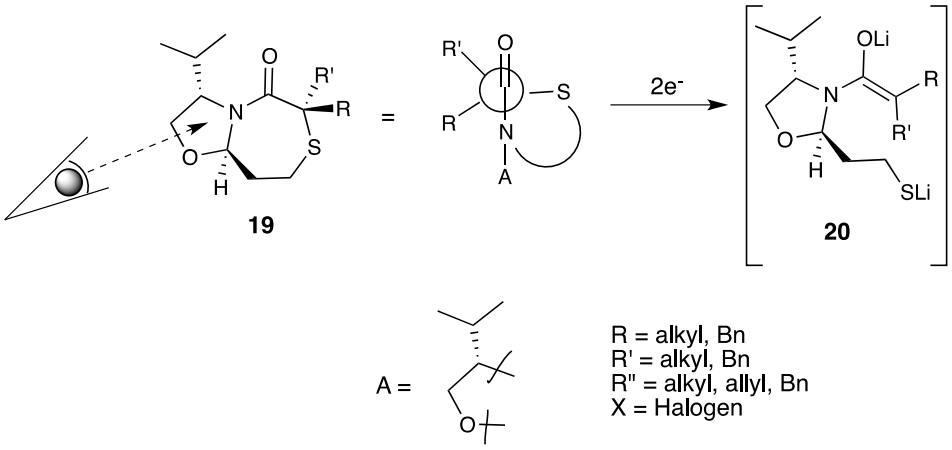
Gleason's work on bicyclic thioglycolate is particularly interesting.[28] Although it uses a bicyclic-lactam intermediate **18**, similar to that of Meyers (*vide supra*), it is more subtle than that. Compound **18** was readily accessible over three steps in an overall yield of 71 % and was double alkylated as in Meyers' bicyclic lactam to afford **19**, the all-carbon QSC precursor. Compound **19** was then reduced under Birch conditions (Li/NH_3) to afford the tetra-substituted chiral enolate **20**, which was subsequently alkylated to the QSC-containing compound (**21**) in a one-pot reaction, **Scheme 1.11**. During quaternisation the free alkyl-SLi tether in **20** blocks one face of the enolate so that alkylation predominantly occurs on the other face. The CA cleavage was carried out under two sets of conditions involving either

acid hydrolysis to the carboxylic acid **22** in which the yields were low (≈ 20 %), or under reductive conditions which gave the primary alcohol **23** in good yield (≈ 74 %).



Scheme 1.11: Reaction conditions- a) NaH, THF, rt. b) *n*-BuLi, L- valinol, THF, 0 °C. c) BF_3•OEt_2, DCM, rt. d) (i) LDA, LiCl, THF, 0 °C; (ii) R-X. e) (i) LDA, LiCl, THF, 0 °C; (ii) R'-X. f) (i) Li, NH_3, THF, –78 °C; (ii) R"-X. g) 6M H_2SO_4, dioxane, Δ. h) LiH_2NBH_3, THF, –78 to 66 °C.

In his articles,[28] Gleason argued that the *E-/Z*-enolate geometry does not depend on the size of R- and R'-groups but solely depends on their order of introduction. He further suggested that the dihedral angle (O-C-C-S) on **19** is held as close as possible to 90° which ensures the stereospecific reductive enolisation, **Scheme 1.12**. Interestingly, Gleason's strategy gives access to QSC synthons in high diastereoselectivity (de, > 87 %) without using the conventional methods such as bicyclic chiral enolates or acyclic chiral enolates. Apart from the drawback experienced in CA cleavage via acid hydrolysis to **22**, Gleason's method is a true contribution towards advancing the repertoire of QSC construction.



Scheme 1.12: Stereospecific enolate generation.

Part 2: University of Cape Town research

Chapter 2: Rationale for the research undertaken

2.1. Overview

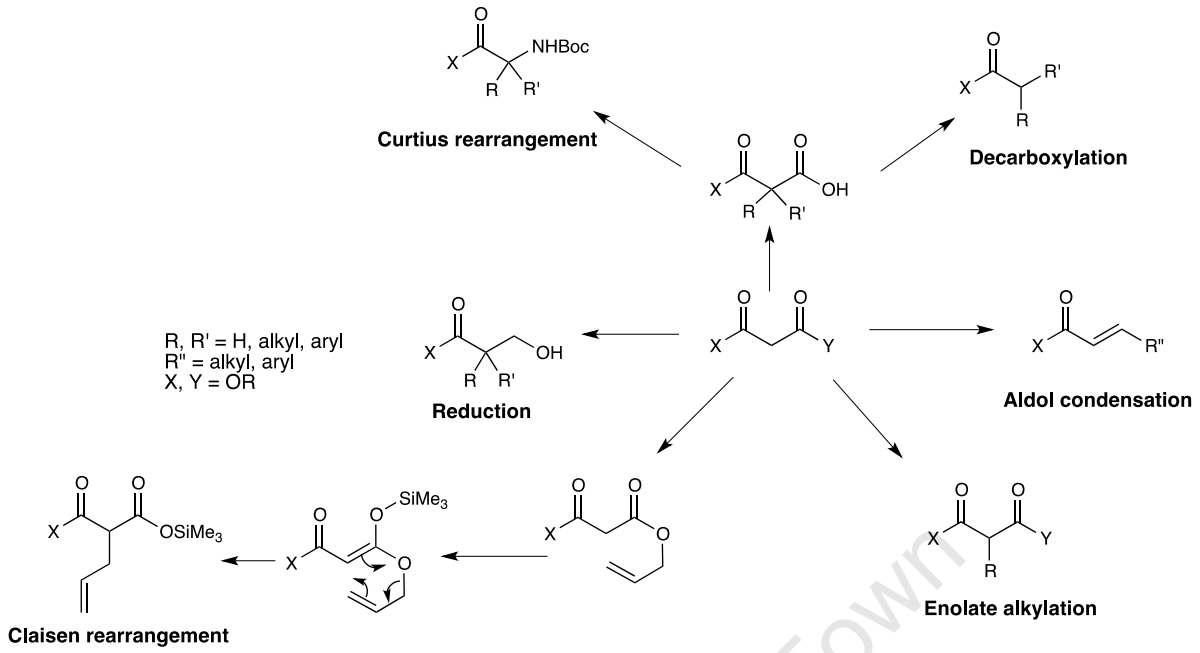
As already discussed, the use of chiral auxiliaries (CA) has become a standard procedure for the synthesis of chiral compounds. CA-based methods are robust, scalable to industrial scale, and the CAs are usually relatively cheap and easy to synthesise from readily available chiral starting materials. Therefore, with this in mind our efforts in advancing the repertoire in asymmetric synthesis (AS) methods focused on the use of a CA.

2.2. Objectives

The main objective of this research project was to develop a method for constructing versatile synthons containing an all-carbon quaternary stereogenic centre (QSC) using a CA-mediated reaction. With this objective in mind the two things that became crucial were the choice of substrate such that versatile synthons could be easily accessible, as well as the choice of the CA for stereoselective step.

2.2.1. Malonates as versatile templates

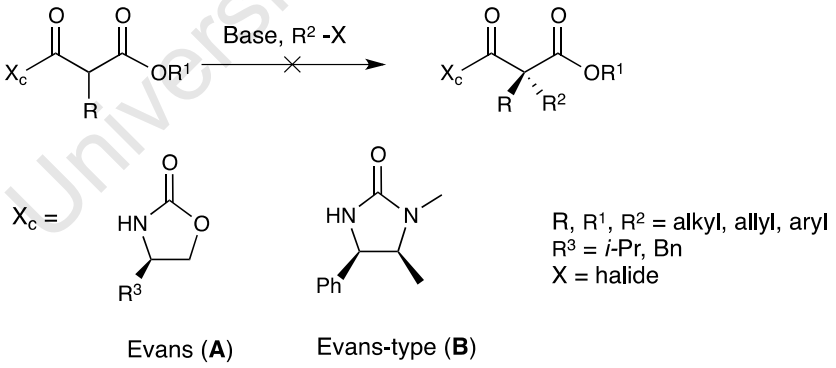
Malonate-based compounds are versatile, cheap and have a well-established chemistry repertoire such as chemoselective hydrolysis and reduction, enolate chemistry at the α-position and sigmatropic rearrangements of allyl esters to mention just a few, **Scheme 2.1**. In light of these various possible reactions as well as examination of the literature failed to reveal any malonate system containing CA for asymmetric quaternisation, we became interested in synthesising malonate-based QSC synthons via a CA-mediated reaction.



Scheme 2.1: Versatility of malonate esters.

2.2.2. Evans and Evans-type CA in QSC construction

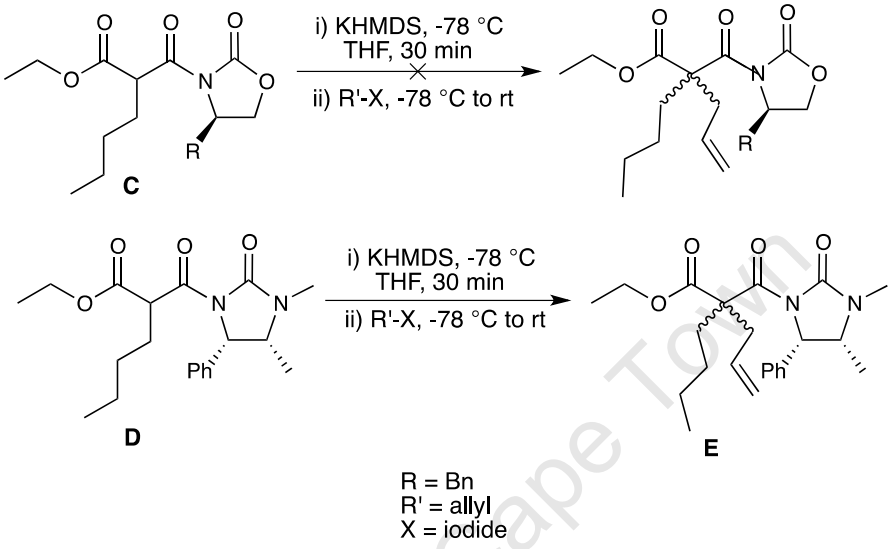
Evans-based CAs (**A** and **B**) are popular for synthesising chiral, non-racemic tertiary centres and have a well-established chemistry. Surprisingly there were no reports found in the literature depicting an **A**- or **B**-mediated alkylation in malonate systems to construct a QSC on the Scifinder structure search tool, **Scheme 2.2**.



Scheme 2.2: Quaternisation of **A**- and **B**-based CA systems.

Thus, we decided to develop a malonate-CA method based on **A** and **B** for synthesising QSC-containing synthons. Preliminary studies by a colleague in our labs established that quaternisation of **C** results in elimination of the CA with little production of the quaternised

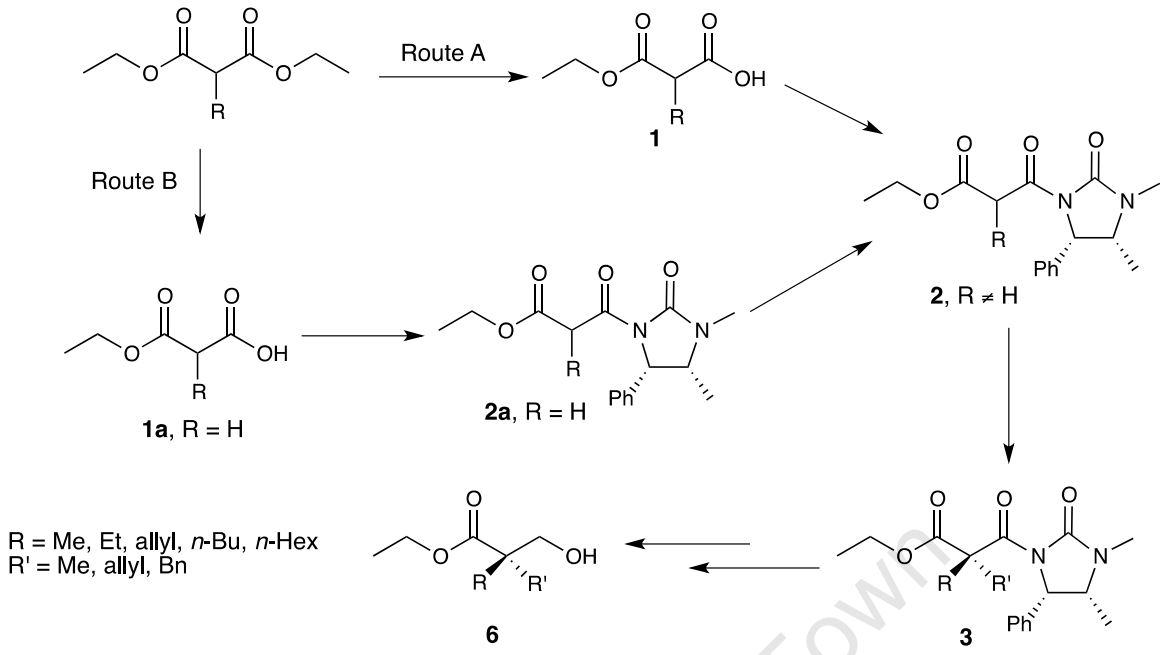
product, **Scheme 2.3**. The CA elimination was observed on warming the alkylation reaction which was necessary for the reaction to proceed. On the other hand, when **D** was subjected to the same alkylation conditions no CA elimination was observed after warming the reaction to room temperature. With this knowledge then, current research focused on studying the quaternisation of α-substituted auxiliary-malonate systems.



Scheme 2.3: Preliminary studies on oxazolidinone and imidazolidinone malonate-based QSC construction.

2.3. The synthesis plan for constructing malonate-based QSC compounds

Synthesis of α-substituted auxiliary malonate (**2**) involved a malonate mono-hydrolysis/ CA-coupling sequence in which the R-group could be introduced early (starting with α-substituted malonate – Route A) or late (alkylation of auxiliary-malonate – Route B), **Scheme 2.4**. From a cost perspective route A was preferred. However, both routes will be discussed depicting their advantages and disadvantages.

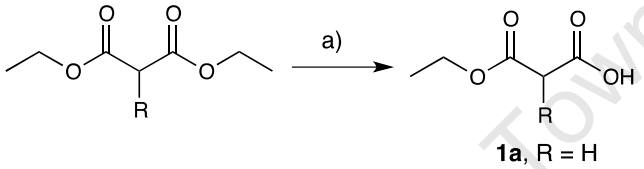


Scheme 2.4: The synthesis plan used to construct QSC-containing synthons.

Chapter 3: Results and Discussion

3.1. Mono-hydrolysis of diethyl malonate

The synthesis toward malonate-based quaternary stereogenic centres (QSC) commenced with the mono-hydrolysis of diethyl malonate (R = H) performed under basic-conditions (KOH) to afford monoacid **1a** in excellent yield (90 %). The reaction was carefully monitored by TLC using an iodine stain so as to avoid formation of the diacid which would have involved a difficult separation of the mono- (Rf = 0.2 in 100 % EtOAc) from the diacid (Rf = 0.1 in 100 % EtOAc) in product isolation.

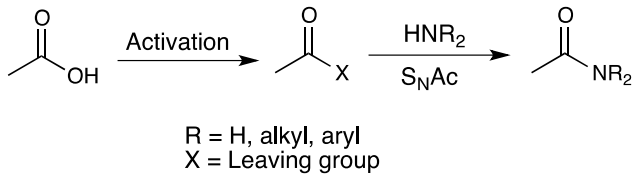


Scheme 3.1: Reaction conditions- a) KOH (2.5 M, in H_2O), EtOH, 0 °C to rt.

The formation of monoacid **1a** was confirmed by its ^{1}H NMR spectrum only, since it was a known compound. A conspicuous resonance at 9.75 ppm integrating for 1-proton confirmed the formation of one carboxylic acid group while a quartet at 4.23 ppm integrating for 2-protons and a triplet at 1.29 ppm integrating for 3-protons confirmed the presence of only one ethyl ester in **1a**. The resonance at 3.40 (s, 2H) was assigned to the α-methylene protons.

3.2. Amide bond synthesis

With the monoacid in hand the next step was to couple it to the CA – (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one – using amide bond-forming chemistry. Over the years a plethora of methods have been developed for amide bond synthesis all of which involve activation of the carboxylic acid in preparation for a nucleophilic acyl substitution (S_NAc), **Scheme 3.2**. The current research exploited 1-chlorobenzotriazole (BtCl) as a coupling agent, acyl chlorides and carbodiimide chemistry to synthesise the amide bond, and their advantages as well as disadvantages will be discussed herein.



Scheme 3.2: A general reaction for amide bond synthesis.

3.2.1 BtCl in amide bond-formation

There are various reaction methods based on using the benzotriazole moiety as a leaving group in which Katritzky *et al* has been the main research group in the field. Katritzky and our group have shown that a combination of triphenylphosphine and BtCl converts a carboxylic acid into its acyl Bt-derivative, which can subsequently be converted via a S_NAc reaction into an amide, as well as other carboxylic derivatives, **Figure 3.1**.[29]

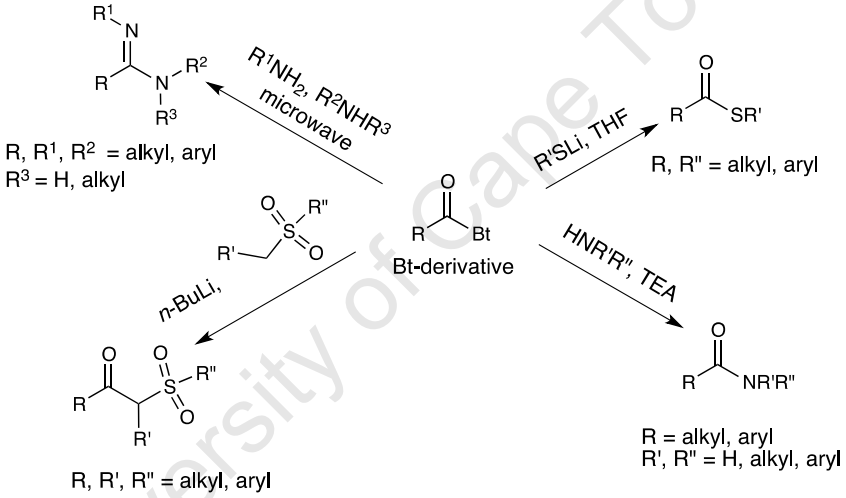
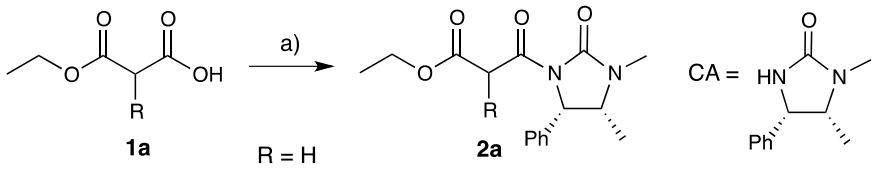


Figure 3.1: Examples of acyl Bt-derivative reaction transformation.

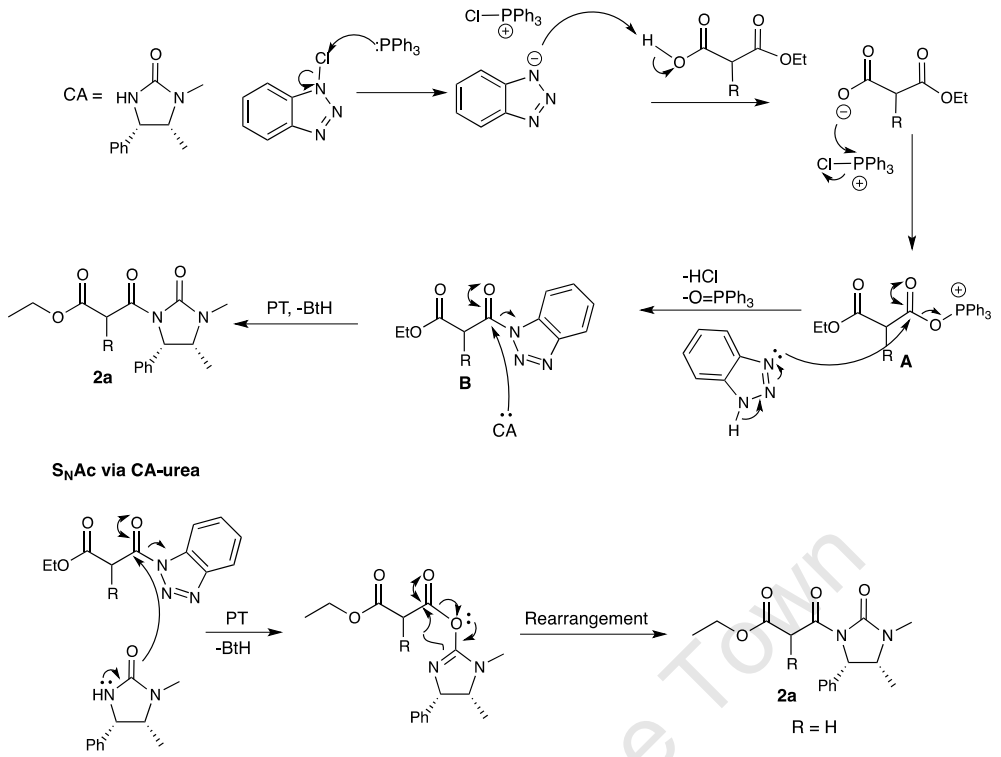
With that in mind, monoacid **1a** was subjected to coupling with the imidazolidinone-CA using BtCl and PPh_3 in a one-pot reaction. Although conversion to the acyl Bt-derivative occurred at room temperature according to TLC, the coupling (S_NAc) step required heating in acetonitrile because the CA is a relatively poor nucleophile. In such a way, following chromatography **2a** was obtained as a colourless solid in a moderate yield (68 %), **Scheme 3.3**.



Scheme 3.3: Reaction conditions- a) i) PPh_3, BtCl, MeCN, **1a**, 0 °C; ii) CA, MeCN, 84 °C.

Of significance here was the coupling of a relatively poorly nucleophilic CA, and one is tempted to speculate that the *N*-acylation occurs through the relatively nucleophilic urea carbonyl oxygen, followed by a rearrangement, **Scheme 3.4**. Unfortunately, co-elution of the product with 1*H*-benzotriazole (BtH, a by-product) occurred as the desired product had a similar Rf to that of BtH – Rf values of 0.30 and 0.35 respectively in 40 % EtOAc in hexane – and this hampered isolation of **2a**. Efforts to remove BtH with a KOH base-wash at 0 °C were unsuccessful in that trace amounts of BtH were still visible on TLC.

The BtCl reaction mechanism (**Scheme 3.4**) begins with a reaction between triphenylphosphine and BtCl to give a chlorotriphenylphosphonium salt, in which the Bt anion is stabilised by resonance. Following proton-transfer between the acid and the Bt anion, nucleophilic substitution with the chlorotriphenylphosphonium salt ensues to afford an acyloxyphosphonium intermediate **A**, which then undergoes a rapid S_NAc reaction with BtH to form the acyl Bt-derivative and triphenylphosphine oxide. The driving force in this step is the formation of the strong O-P bond in $O{=}PPh_3$. Although intermediate **B** was not isolated, the TLC studies in 40 % EtOAc in hexane showed a spot with an Rf = 0.6 that initially formed and disappeared over time after adding the CA, and this supports Katritzky's reports regarding its formation.[29c, d] Assisted by higher temperatures, the CA does a S_NAc reaction with the Bt-derivative to afford **2a**.



Scheme 3.4: The BtCl reaction mechanism.

Synthon **2a** was a new compound and was therefore fully characterised and confirmed by IR and NMR spectroscopy, elemental analysis, and $[\alpha]_D$ obtained. The IR bands at 3008 (Ar), 1736 (2 x C=O, amide and ester) and 1687 (C=O, urea) were observed confirming the various functional groups present in **2a**. The absence of the CA-N<u>H</u> and the COO<u>H</u> resonance peaks in the ^{1}H NMR spectrum confirmed the successful coupling of the imidazolidinone-CA to **1a**. The ^{1}H NMR spectrum revealed resonances at 7.35 (m, 3H, H-3' + H-4'), 7.18 (m, 2H, H-2'), 5.32 (d, *J* = 8.7 Hz, 1H, H-1), 3.93 (dq, *J* = 8.7, 6.6 Hz, 1H, H-2), 2.81 (s, 3H, H-4) and 0.80 (d, *J* = 6.6 Hz, 3H, H-3) confirming the CA in **2a**, **Figure 3.2**. The H-2 methine appears as a dq due to the vicinal H-1 coupling (*J* = 8.7 Hz) with a low dihedral angle (*syn* stereochemistry) while the smaller *J* = 6.6 Hz arose from coupling to the vicinal methyl group. The ethyl ester resonances were observed at 4.18 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O) and 1.26 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O). Two signlets at 4.02 and 3.97 ppm integrating for 2-protons were assigned to the diastereotopic methylene H-a protons. The ^{13}C NMR spectrum revealed three resonances at 167.7 (C=O, ester), 165.1 (C=O, amide) and 155.6 (C=O, urea) confirming the three carbonyl groups present in **2a**. Four resonances observed in the 126-

137 ppm region diagnostic for aromatic carbons confirmed the presence of the CA Ph-group while other CA resonances were observed at 59.5 (C-1), 54.2 (C-2), 28.3 (C-4) and 15.1 (C-3). The ethyl ester resonances were observed at 61.3 (Me<u>C</u>H_2O) and 14.2 (<u>Me</u>CH_2O) while the α-methylene carbon was observed at 43.5 ppm. Elemental analysis further confirmed the synthesis of **2a**, with anal. calc. for $C_{16}H_{20}N_2O_4$ (%): C, 63.14; H, 6.61; N, 9.20 and found (%): C, 63.19; H, 6.57; N, 9.24 on a recrystallised sample.

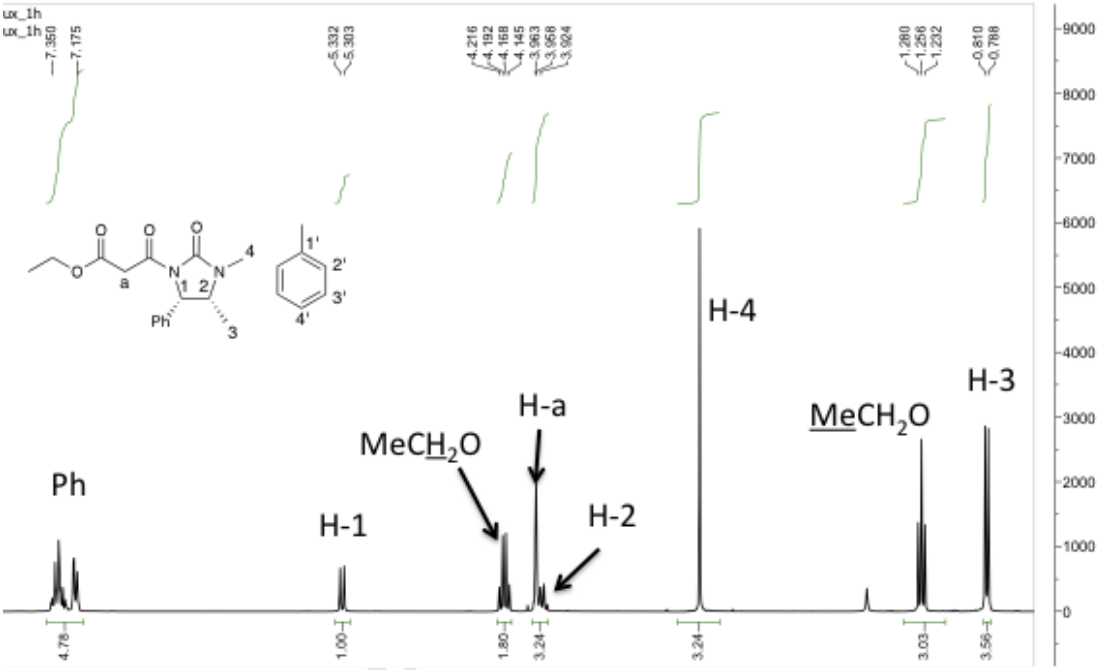
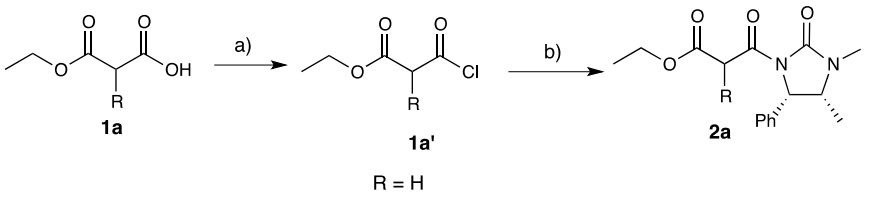


Figure 3.2: The ^{1}H NMR spectrum for **2a**.

3.2.2. Acyl halides in amide bond-formation

The BtCl-based amide coupling reaction did not work as well as anticipated in view of the modest 68 % yield due to the issue in product isolation by chromatography. An obvious alternative was to synthesise the amide bond via acyl activation with thionyl chloride ($SOCl_2$). This method was not chosen initially in order to avoid distillation of the corresponding acyl chloride. To this effect, monoacid **1a** was chlorinated with $SOCl_2$ at room temperature after which DCM and excess $SOCl_2$ were removed under reduced pressure on the rotary-evaporator and the acyl chloride residue directly used to acylate the imidazolidinone-CA under refluxing conditions in acetonitrile, **Scheme 3.5**. A moderate yield

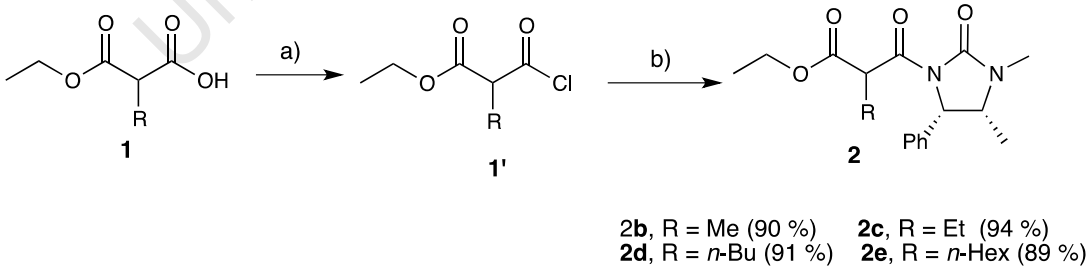
for **2a** (62 %) was obtained and that was reasoned to be because some of the acid chloride product may have escaped on the rotary-evaporator during removal of excess $SOCl_2$.



Scheme 3.5: Reaction conditions- a) $SOCl_2$, DCM, rt. b) CA, MeCN, 84 °C.

The low yield prompted a change to the α-substituted malonate-CA systems in which the acid chloride would have a higher boiling point and thus be separable from excess $SOCl_2$ by distillation. Thus, α-substituted diethyl malonates were hydrolysed with KOH as outlined in **Scheme 3.1** to afford the various monoacids in excellent yields (> 90 %). The α-substituted monoacids were also confirmed by ^{1}H NMR spectroscopy only and resonance peaks assigned as outlined for **1a**.

Monoacid **1b** was chlorinated with $SOCl_2$ and the crude mixture distilled at atmospheric pressure under nitrogen with DCM and excess $SOCl_2$ distilling off at 40 °C and 74-75 °C respectively.[30] Acyl chloride **1b'** distilled off at 70-74 °C under reduced pressure (≈ 0.75 mmHg) and was immediately used to acylate the CA to afford **2b** after chromatography in an excellent yield of 90%, **Scheme 3.6**. The rapid synthesis of other α-substituted malonate-CA derivatives was achieved similarly obtaining a range of α-substituted malonate-CA compound **2b**-**2e** in excellent yields (> 89 %) and as a ≈50/50 mixture of diastereomers.



Scheme 3.6: Acylation of the CA with α-substituted acyl chlorides.

The formation of the acyl chlorides **1'** was confirmed by ^{1}H NMR spectroscopy which showed a slight downfield shift of all the resonances compared to the monoacid **1** as well as the disappearance of the carboxylic acid proton at around 9.75 ppm.

All the α-substituted malonate-CA synthons were new compounds and were therefore fully characterised by IR and NMR spectroscopy, elemental analysis for **2b** and **2c**, HRMS for **2d** and **2e**, and $[\alpha]_D$. Spectroscopic assignments were made similarly to compound **2a**. All the α-substituted malonate-CA compounds were obtained as a 50/50 mixture of diastereomers and this was expected because the α-substituted diethyl malonates used in the first step was a racemic mixture to begin with.

After column chromatography, compounds **2b** and **2c** were obtained as solids while **2d** and **2e** were obtained as colourless oils. The fractional recrystallisation of compounds **2b** and **2c** (in EtOAc/hexane) to a constant melting point enriched the mixture to only one diastereomer. Unlike enantiomers, diastereomers have different physical properties and can thus be separated by recrystallisation. This was the case for **2b** and **2c**, which was confirmed by the ^{1}H NMR spectrum, which revealed a resolution of the doubled diastereomeric resonances at around 5.33, 4.65 and 2.82 ppm – compare **Figures 3.3.1** and **3.3.2**.

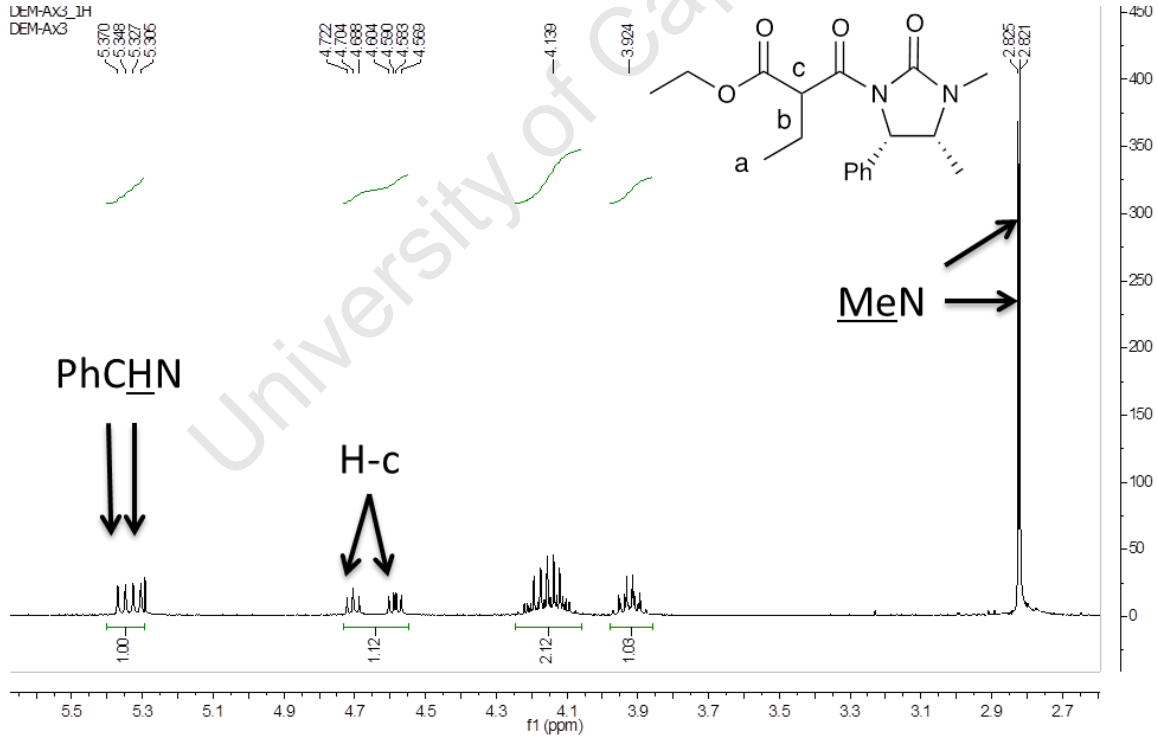


Figure 3.3.1: The ^{1}H NMR spectrum for **2c** before recrystallisation. The two-arrows depict the two diastereomers.

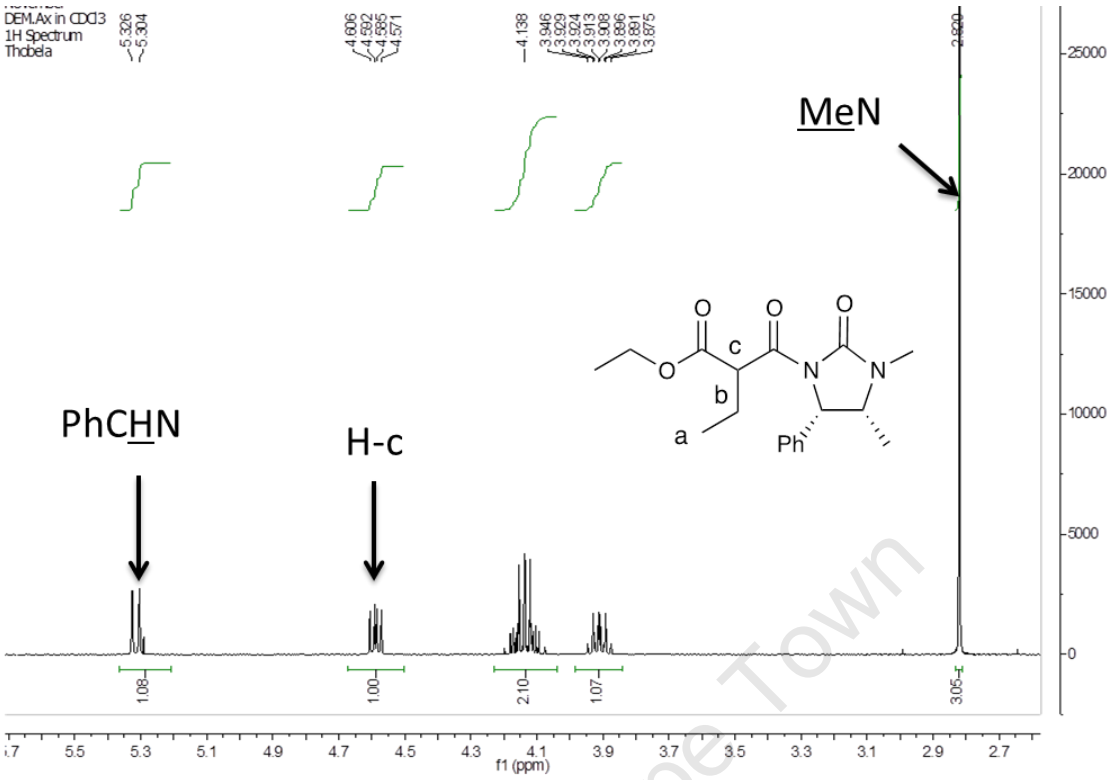
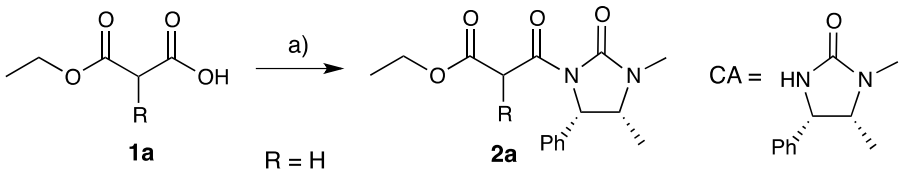


Figure 3.3.2: The ^{1}H NMR spectrum for **2c** after recrystallisation.

In spite of the excellent yields, this procedure was tedious and time-consuming. Also, acyl halides are toxic, easily hydrolysable in air and generally difficult to handle. Another set-back with this method was that one could not synthesise **2a** in high yield, the core intermediate for accessing a broad range of α-substituted malonate-CA compounds. Therefore, another method was sought to access **2a** for which carbodiimide chemistry was chosen.

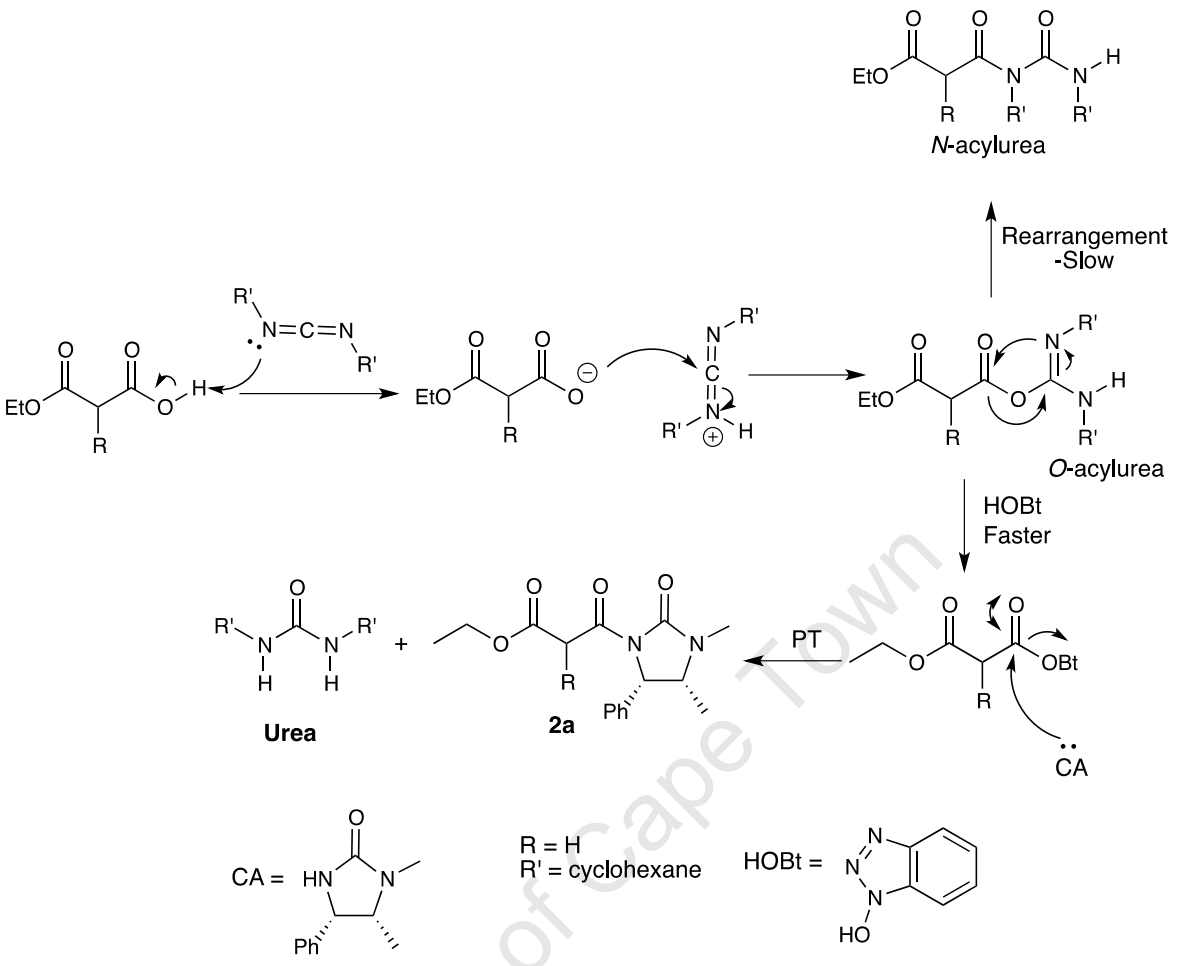
3.2.3. Carbodiimide in amide bond-formation

Like the other amide bond-forming reactions, the carbodiimide reaction relies on forming an activated intermediate (the *O*-acylurea) which activates the carboxylic acid by converting the hydroxy-group into a good leaving group.[31] In this research *N,N'*-dicyclohexylcarbodiimide (DCC) was utilised as the coupling agent to afford **2a** after chromatography as an off-white solid in good yield (80 % yield), whose structure was confirmed as before, **Scheme 3.7**.



Scheme 3.7: Reaction conditions- a) DCC, CA, DCM, BtOH (cat., 50 % mmol), 0 to 40 °C.

The DCC reaction mechanism commences with a proton-exchange between **1a** and DCC followed by the negatively charged acid adding to the carbodiimide species to give an *O*-acylurea intermediate (a mixed anhydride). HOBt was added to avoid rearrangement of the *O*-acylurea intermediate to the *N*-acylurea by substituting the former to an acyloxybenzotriazole intermediate which is attacked by the CA.[31] Once again, it is attractive to speculate that the coupling with the imidazolidinone-CA proceeds via the carbonyl urea oxygen followed by a rearrangement to form **2a**, **Scheme 3.8**. Overall, the results obtained with DCC were far more satisfactory than the previously obtained results from the BtCl and acyl halides methods.



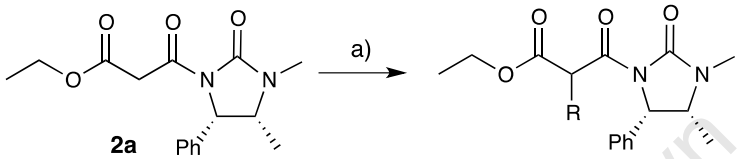
Scheme 3.8: The DCC-coupling reaction mechanism.

3.3. Synthesis of α-substituted malonate-CA compounds via alkylation

For initiation of the alkylation studies, α-substituted malonate-CA compounds **2b**-**2f** were also synthesised via alkylation of **2a** with various electrophiles, **Table 3.1**. Preliminary studies with potassium hexamethyldisilazide (KHMDS) gave satisfactory results and thus other bases were not examined in this reaction. Reaction with iodomethane proceeded well to afford a diastereomeric mixture of **2b** (90 % yield) as a colourless solid. Alkylating with longer alkyl inactivated electrophiles such as iodoethane, 1-bromobutane and 1-bromohexane required heating the mixture at 66 °C, in which for 1-bromobutane and 1-bromohexane an *in situ* iodine-bromine exchange via the TBAI salt was required for complete conversion of the starting material. Nevertheless, compounds **2c**, **2d** and **2e** were obtained in good yields of 89 %, 87 % and 90 % respectively as a mixture of diastereomers.

Allylation with allyl bromide, a more reactive electrophile, proceeded well without refluxing or iodine exchange to give a diastereomeric mixture of **2f** (87 %) as a colourless oil. It was pleasing to be able to install with ease various α-substituents on **2a** as this could allow access to a wide variety of pivotal α-substituted intermediates as useful starting materials for the quaternisation.

Table 3.1: Installation of the first α-group



2b, R = Me **2c**, R = Et
2d, R = *n*-Bu **2e**, R = *n*-Hex **2f**, R = Allyl

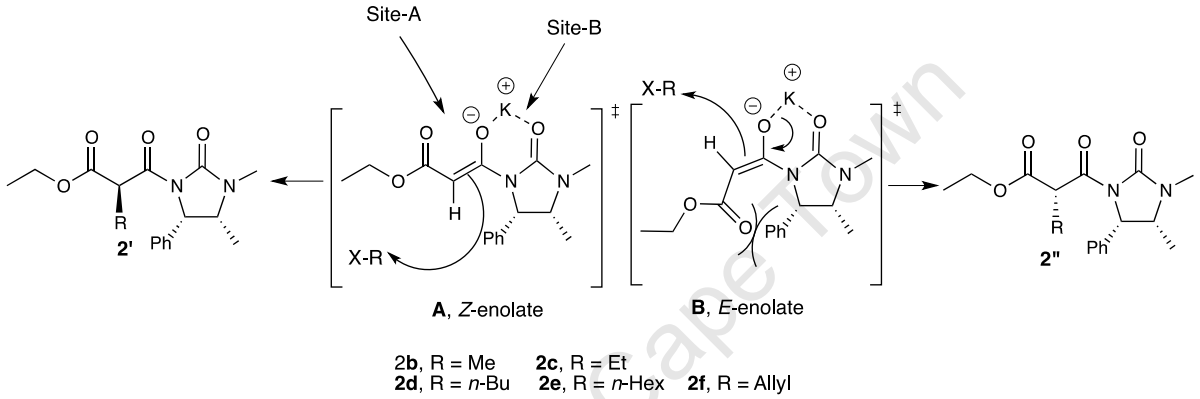
a) i) KHMDS, –78 °C, THF; ii) R-X, –78 to 66 °C.

Compound	Electrophile (R-group)	Yield (%)	dr (%)
2b	Methyl iodide	90	50 : 50[c]
2c	Ethyl iodide[a]	89	50 : 50[c]
2e	Butyl bromide[b]	87	50 : 50[d]
2e	Hexyl bromide[b]	90	51 : 49[d]
2f	Allyl bromide	87	50 : 50[c]

[a] Heat assisted. [b] Heat and TBAI assisted. [c] Observed by NMR. [d] Observed by HPLC after column chromatography.

Installation of the first α-group was observed to be non-stereoselective and this was not considered to be an issue for the quaternisation step. As discussed in more depth in Chapter 1, the stereoselectivity of an acyclic enolate-based reaction depends on the stereoselectivity of formation of the *E*- or *Z*-enolate. The potassium cation has two possible chelation sites, site-A or site-B (depicted by arrows in **Scheme 3.9**) of which site-B is expected to be preferred because of the stronger donating effect from the nitrogen atom in the CA-urea moiety compared to that of the oxygen of the ester. During enolisation, the *Z*-enolate might be expected to form preferentially due to the minimised steric interactions in

which the ester points away from the CA. Once the enolate geometry is set, the incoming electrophile approaches on the opposite face to that of the CA bulky groups. However, since the final products were obtained as a 50/50 mixture of diastereomers one may speculate that the *E*- and *Z*-enolates were formed in almost equal amounts. Also, epimerisation of the α-stereocentre post-alkylation cannot be ruled out. The subtleties of these mechanistic questions were not pursued any further as the purpose of this research was to study the synthesis of the QSC selectivity in the next step. The α-substituted malonate-CA compounds were characterised and confirmed as described above.



Scheme 3.9: The TS-model for the first alkylation.

3.4. Quaternisation of α-substituted malonate-CA compounds

With regards to the objectives of the current research, the quaternisation step was the most crucial aspect. As discussed in Chapter 1, the stereoselectivity of quaternising an acyclic enolate depends on the enolate geometry, strong chelation effects as well as steric effects provided by bulky substituents on the CA. With that in mind a set of reaction conditions was sought that would enable access to QSC compounds in both high yield and stereoselectivity.

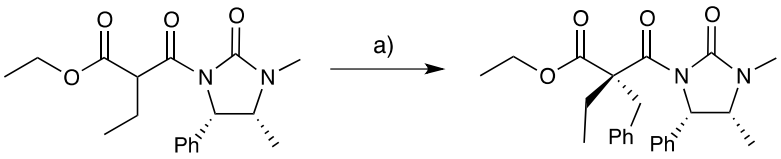
3.4.1. Choosing the base for quaternisation

In pursuing plausible reaction conditions for the QSC construction, a couple of bases were screened including lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS), sodium hydride (NaH), sodium hexamethyldisilazide (NaHMDS) and potassium hexamethyldisilazide (KHMDS), **Table 3.2**. All these bases are strong enough to completely deprotonate the malonyl α-proton in **2c** but have different metal cations and therefore one

can speculate that their ability to quaternise **2c** under identical reaction conditions in the presence of an electrophile (benzyl bromide in this case) should only depend on the metal cation.

Table 3.2 reveals that the reaction conversion increased with the size of the metal cation with only the K^+ giving 100 % conversion (evaluated by TLC). The low reactivity of the lithium-enolate was thought to be due to the formation of a relatively stable lithium-enolate conglomerate. The small lithium cation has several potential chelating partners (four oxygen atoms in **2c**), so one may speculate a higher coordination to the Li^+ which would lead to the congested inactive conglomerate.[32] In this effect, core salts and core solvents have been used in various reactions to hinder the formation of conglomerates. Such studies were not pursued in this research, instead other bases were pursued. The sodium cation is larger and therefore promotes the formation of conglomerates to a lesser degree resulting in a slightly improved reaction conversion, entry 3 and 5. Finally, the potassium cation is much bigger resulting in a complete prevention of formation of the inactive conglomerates, thus the 100 % reaction conversion. Also, one cannot rule out the correlation between the reaction conversion (enolate reactivity) and the ionicity of the alkoxide metal bond (O-M). The O-M bond increases in ionicity from Li^+ to K^+, and the more ionic the O-M bond the more reactive the enolate.

Table 3.2: Screening different bases for QSC construction.



2c 3c

a) i) Base (1.3 eq), –78 °C, THF; ii) BnBr, –78 °C to rt.

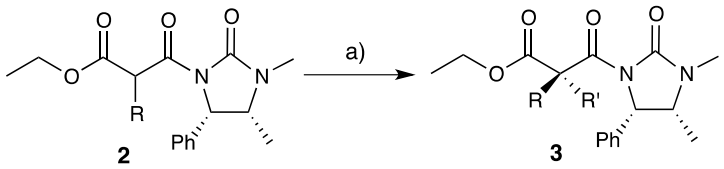
Entry	Base	Reaction Conversion (%)
1	LDA	< 10[a]
2	LiHMDS	< 10[a]
3	NaH	40[a]
4	NaHMDS	50[a]
5	KHMDS	100[b]

[a] Observed by TLC after 72 hrs.[b] Within 20 hrs all the starting material had been consumed, observed by TLC.

3.4.2. Quaternisation studies

Now that suitable conditions had been established, KHMDS base was used throughout the research project for the construction of malonate-based QSC compounds. Low reaction conversion (< 30 % by TLC) were observed with moderately reactive electrophiles such as iodoethane and 1-iodopropane for quaternising R = Me and were therefore not pursued further. These quaternisation studies also revealed that allyl iodide was preferred to allyl bromide for R > Me. Thus, only reactive electrophiles quaternised the different α-substituted malonate-CA compounds obtaining products in excellent yields after chromatography (> 83 %), based on a complete conversion of starting material, **Table 3.3**.

Table 3.3: Constructing malonate-based QSC compounds.



2 3

a) i) KHMDS , –78 °C, THF; ii) R'-X, –78 °C to rt.

Compound	R-group	R'-group	Yield (%)	dr (%)
3a	Me	Allyl bromide	—	51:49[a]
3b	Allyl	Iodomethane	83	> 99:1[b]
3c	Et	Iodomethane	95	> 99:1[b]
3d	Et	Allyl iodide	92	95:5[a]
3e	Et	Benzyl bromide	89	> 99:1[b]
3f	*n*-Bu	Iodomethane	88	93:7[a]
3g	*n*-Bu	Allyl iodide	85	> 99:1[b]
3h	*n*-Bu	Benzyl bromide	84	> 99:1[a]
3i	*n*-Hex	Iodomethane	90	> 99:1[b]
3j	*n*-Hex	Allyl iodide	87	> 99:1[a]
3k	*n*-Hex	Benzyl bromide	82	> 99:1[a]

[a] Obtained by HPLC after column chromatography. [b] Obtained by ^{1}H NMR spectroscopy.

Compounds **3e** and **3g** were obtained as solids after column chromatography and were recrystallised in EtOAc/hexane to give crystals, of which **3g** was suitable for analysis by an X-ray evaluation. The X-ray data allowed identification of the absolute stereochemistry of **3g** and this allowed a transition-state model to be proposed, **Figure 3.4**. Also, other crystal structures have been obtained by colleagues on similar systems and support this TS-model.

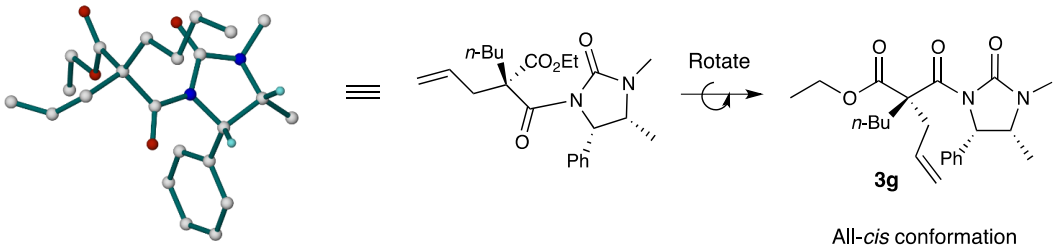
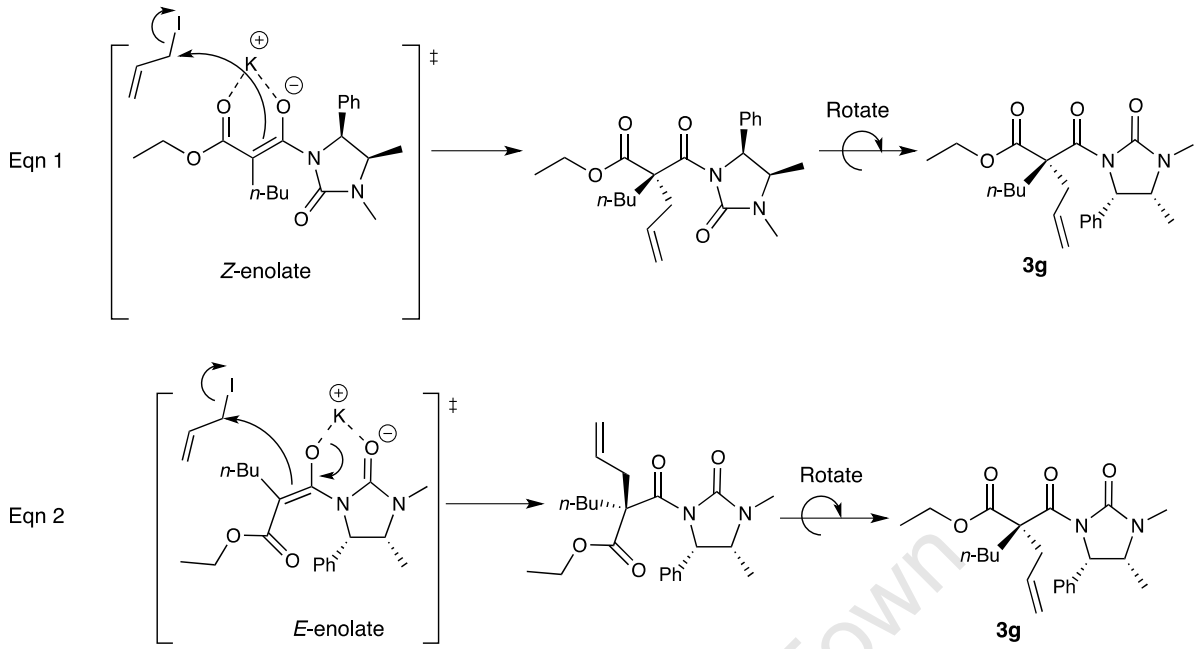


Figure 3.4: The crystal structure for **3g** obtained by X-ray diffractometer.

Adjusting the X-ray picture into the all *cis*-carbonyl conformation, one sees that the allyl-group in the final product ends up on the same face as the bulky substituents in the CA. At first glance, this seems counterintuitive because one would expect the incoming R'-group to have an *anti*-relationship with the bulky substituents in the CA according to the Evans' model developed for tertiary centres.[33] There are two possible TS-models that explain the observed stereochemistry in the major product (**3g**), **Scheme 3.10** (Eqn 1 and Eqn 2). If the *Z*-enolate forms then the CA swings around to minimise steric interaction between R (*n*-Bu) and the Ph-group on the CA forming the s-*trans* conformer (Eqn 1). Allylation of this enolates predominantly occurs from the underneath face, away from the CA bulky substituents and thus leads to **3g**. On the other hand, if one assumes an auxiliary chelated TS-model then the *E*-enolate forms to minimise the steric interactions between R (*n*-Bu) the Ph-group on the CA. Chelation of the potassium cation to the CA-carbonyl locks the CA in one conformation and thus allowing allylation of the enolate to predominantly occur on the top face and gives **3g** with the allyl on the same face as the bulky substituents on the CA.



Scheme 3.10: The proposed TS-model for quaternisation.

Such a model allows one to explain the low stereoselectivity obtained for **3a** (R = Me; dr, 50 : 49) where one may speculate that there was no preference in the formation of either *E*-/*Z*-enolate because the R-group was not big enough to force *E*-enolate formation only. On the other hand, when the R-group is significantly larger than the ethoxycarbonyl grouping it positions itself away from the CA thus minimising steric interactions, resulting in high stereoselectivity for R > Me. The best selectivity (> 99 : 1) was observed with R = *n*-Bu, *n*-Hex (**3h**, **3j**, **3k**). Since there was no stereoselectivity for **3a**, compound **3b** was synthesised by reversing the order of introduction of R- and R'-group so as to get the spectroscopic data.

The QSC-containing synthons were all new compounds and were fully characterised by IR and NMR spectroscopy, elemental analysis (for **3e** and **3g**) and HRMS (for oils), and $[\alpha]_D$. Only the spectroscopic data for **3e** will be discussed in detail as a representative case, **Figure 3.5**. Diagnostic IR stretches were observed at 3008 (Ar), 2998 (Bn), 1732 (2x C=O, amide and ester) and 1689 (C=O, urea) for the functional groups in **3e**. The CA and ethyl ester resonances were observed as before in the ^{1}H NMR spectrum, while the α-ethyl protons were observed at 1.91 (m, 2H, H-b) and 0.87 (t, *J* = 7.5 Hz, 3H, H-a). The disappearance of the malonyl α-proton resonance at 4.59 ppm accompanied by a new

resonance observed as a broad singlet at 3.37 ppm integrating for 2-benzylic methylene protons confirmed the quaternisation with the benzyl group to **3e**. Also, an extra set of peaks integrating for 5-protons was observed in the aromatic region further confirming introduction of the benzyl group. Carbonyl resonances were observed in the ^{13}C NMR spectrum similarly as before at 171.5 (C=O, ester), 169.8 (C=O, amide) and 155.3 (C=O, urea). New resonances observed in the aromatic region 136.7 (C-1”), 130.7 (C-2”), 127.8 (C-3”) and 126.41 (C-4”) as well as the methylene benzylic carbon at 39.5 (C-d’) confirmed the introduction of the benzyl group. The α-ethyl resonances were observed at 26.6 (C-b) and 9.1 (C-a) in the ^{13}C NMR spectrum. The formation of **3e** was further confirmed by elemental analysis: anal. calc. for $C_{18}H_{24}N_2O_4$ (%): C, 71.07; H, 7.16; N, 6.63 and found (%), C, 70.81; H, 7.05; N, 6.54.

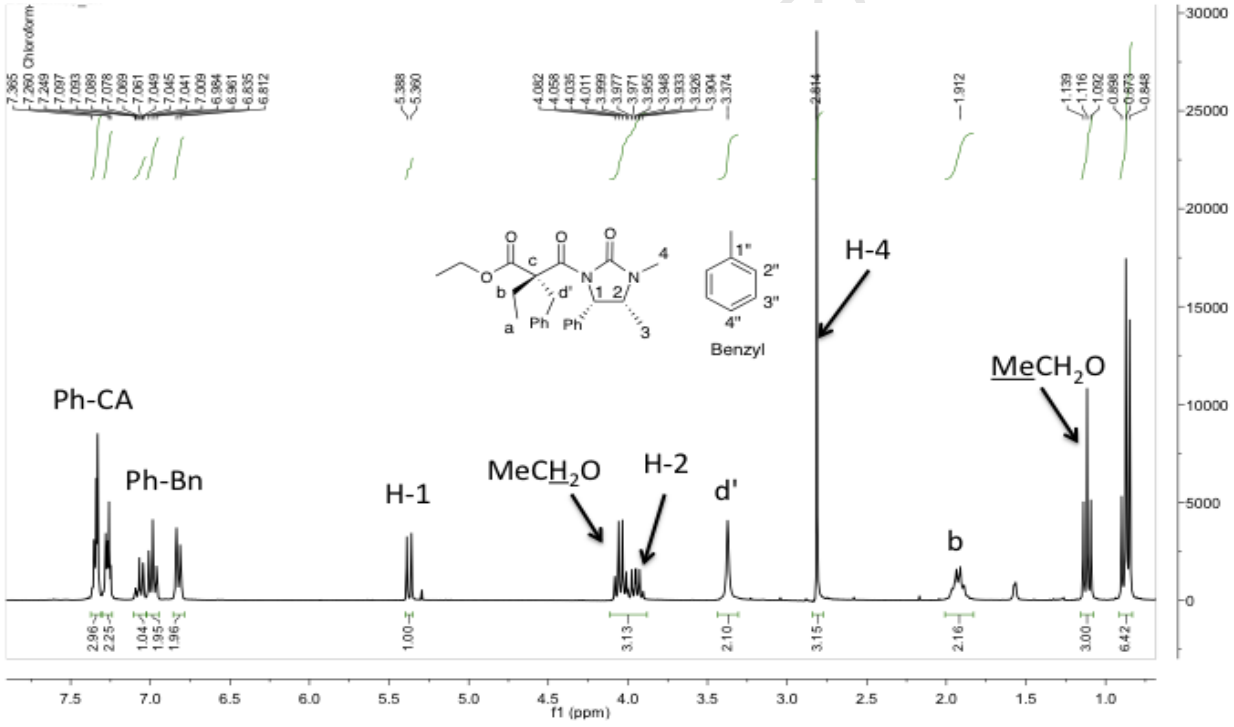


Figure 3.5: The ^{1}H NMR for compound **3e**.

Owing to the sterically congested environment around the QSC in **3e**, the initial ^{13}C NMR spectrum (in $CDCl_3$) on recrystallised material was complicated, portraying broad signals, and this was speculated to arise because of different conformational isomers. To eliminate the different conformational isomers the ^{13}C NMR experiment was conducted at a higher

temperature (35 °C) to overcome the rotational barrier. Indeed, at this temperature (though only a 5 °C increase) the broad signals resolved into single resonance peaks, compare **Figures 3.6.1** and **3.6.2**. The different conformational isomers observed for **3e** in the ^{13}C NMR spectrum attests to the steric challenge encountered in constructing the QSCs and also illustrates the elegance of the current method.

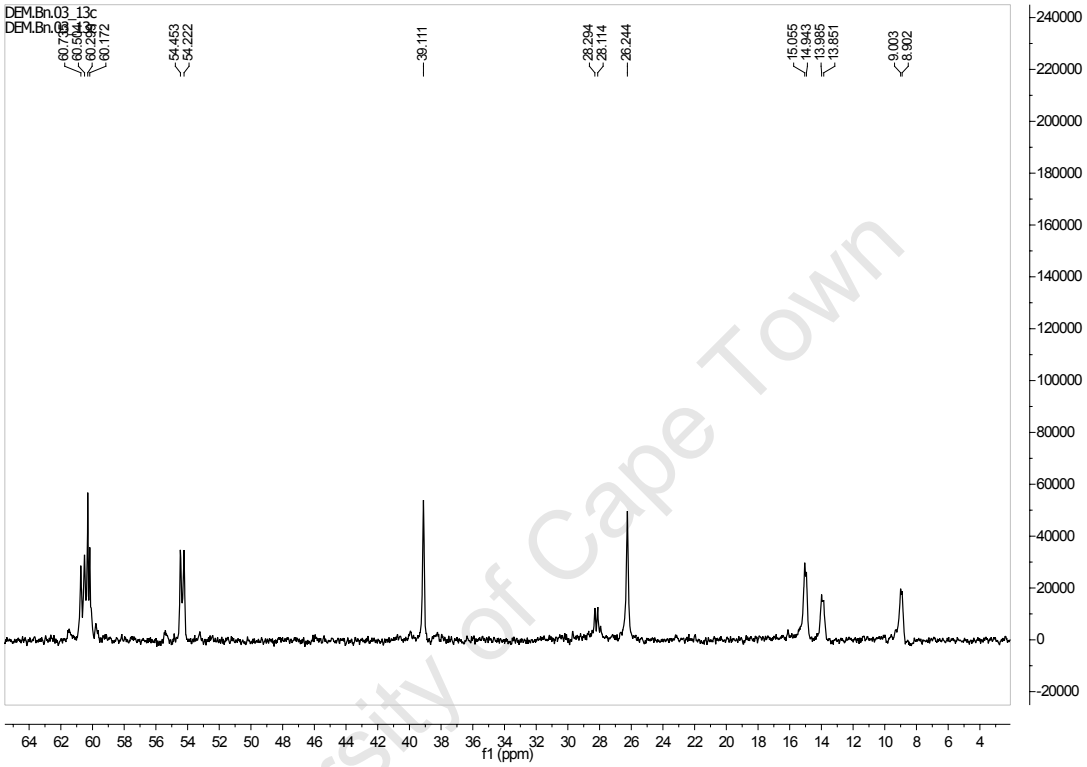


Figure 3.6.1: The ^{13}C NMR spectrum of **3e** at 30 °C.

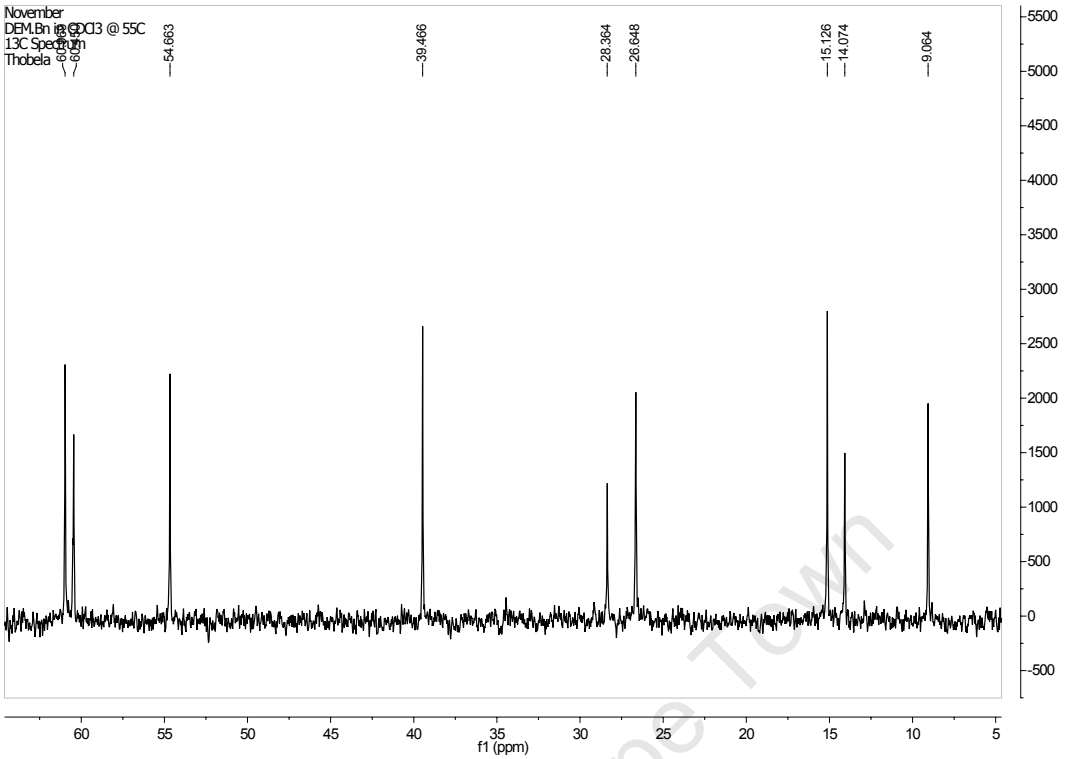
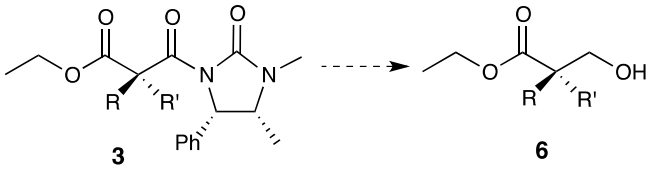


Figure 3.6.2: The ^{13}C NMR spectrum of **3e** at 35 °C.

3.5. Cleaving the imidazolidinone-CA

As described in Chapter 1, the effectiveness of a CA-based method depends on the ease with which the following steps are performed: 1) coupling the CA to a substrate, 2) stereoinduction such that high diastereomeric ratios are obtained, and 3) the cleavage of the CA to obtain the enantioenriched product with recovery of the CA. The first two steps had been performed well thus far and the products were obtained in good yields - malonate-CA compounds (**2**) were obtained in > 87 % yield while QSC-containing synthons (**3**) were obtained in > 82 % yield with dr ≥ 93 : 7. Various reaction conditions were sought for a facile cleavage of the imidazolidinone-CA such that the QSC-containing compounds could be obtained in good yield while recovering the CA. An acceptable QSC-containing target compound was **6**, **Scheme 3.11**. The main challenge in this transformation, however, was the relatively non-trivial chemo-differentiation of the amide from the ester functional groups, which have similar reactivity.

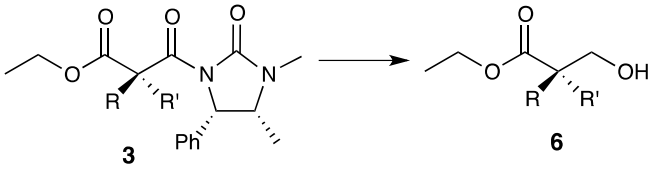


Scheme 3.11: The desired QSC-containing synthon.

3.5.1. Reductive cleavage of the CA

Reductive cleavage was investigated first because of the possibility of obtaining the desired alcohol in just one step. The reductive cleavage reactions investigated included the use of $NaBH_4$, $LiBH_4$, DMS-BH_3, DIBAL and $LiAlH_4$ in which **3j** (R = *n*-Hex, R' = allyl) was the model substrate chosen, **Table 3.4**. No reaction was observed with $NaBH_4$ in MeOH at 66 °C after 48 hrs and the starting material was recovered. This was attributed to the low reactivity of $NaBH_4$ and thus more reactive reducing agents were pursued. A $LiBH_4$ (2.5 eq) reduction at 0 °C revealed complete conversion of starting material after 3hrs, but the TLC reaction profile was complicated with streaks and several spots which made the isolation of the product difficult. The complicated TLC profile suggested that $LiBH_4$ had reduced all of the carbonyl groups including the ester, amide and urea. The cleaved CA was visible on TLC (Rf = 0.2 in 40 % EtOAc in hexane) giving a bright yellow stain when sprayed with *p*-anisaldehyde. Lower temperatures (–20 and –40 °C) were utilised to improve the chemoselectivity, and although the TLC profiles were slightly better than before in that the streak had disappeared, several close spots were still visible that made the isolation of the product difficult. Also, not all of the starting material was consumed even after 24 hrs (< 50 % reaction conversion). Efforts to separate and recover the starting material, imidazolidinone-CA, and what was thought to be the product were unsuccessful and thus the $LiBH_4$ reactions were abandoned and attention turned to a DMS-borane reduction.

Table 3.4: Reductive cleavage



R = *n*-Hex, R' = Allyl

Entry	Reduction agent	Reaction Conditions	Conclusion
1	$NaBH_4$	**3j**, 0 to 66 °C, MeOH, 48 hrs	No reaction
2	$LiBH_4$	**3j**, –20 °C, Et_2O, 24 hrs	Complex TLC
3	DMS-BH_3	**3j**, –20 °C, THF, 8 hrs	Complex TLC
4	DIBAL	**3j**, –78 to 66 °C, THF, 24 hrs	Complex TLC
5	$LiAlH_4$	**3j**, –78 °C, THF, 15 min	Complex TLC

A DMS-borane reductive cleavage was thus performed at 0 °C and within 2 hrs all the starting material had been consumed to reveal a complicated TLC profile. Unlike in the $LiBH_4$ reduction, this time there was no sign of the CA on the TLC plate at Rf = 0.2 (in 40 % EtOAc in hexane), but a major product spot with Rf = 0.3 was observed. Another reaction was conducted at –40 °C to improve the TLC plate profile and the reaction was complete within 8 hrs. Indeed the TLC plate was not as complicated as before but still there was no sign of the CA at Rf = 0.2. The major product spot obtained after chromatography through its ^{1}H NMR spectrum, revealed that the ethyl ester was not reduced and that the CA was indeed still attached to the substrate. Two extra set of resonance peaks in the ^{1}H NMR spectrum at 3.49 and 2.28 ppm each integrating for 2-protons suggested that the amide and the urea carbonyl groups had been reduced. This was not surprising, since borane-based reducing agents are known to chemoselectively reduce amides and ureas to form amines via carbonyl complexation.[3] This was unsatisfactory and therefore the DMS-borane reduction was also abandoned.

Since no concrete results were obtained with boron-based reducing agents, aluminium-based reducing agents were therefore utilised and the first one tried out was a DIBAL reduction, which was conducted with 2.5 equivalents of DIBAL at –78 °C in THF. There was no sign of reaction observed after 2 hrs at this temperature and therefore the contents

were slowly warmed to rt (over 3 hrs) to no avail. After 2 hrs at rt, the reaction contents were refluxed overnight, which resulted in < 5 % reaction conversion. On the TLC plate there was a faint UV-active spot forming just below the starting material with Rf = 0.4 (in 40 % EtOAc in hexane) but no sign of the CA at the diagnostic Rf. The faint UV-active spot was speculated to be the corresponding aldehyde forming from ester reduction. The reaction was not pursued further so finally a lithium aluminium hydride reaction was carried out. A $LiAlH_4$ reduction was not chosen initially because $LiAlH_4$ is a strong and highly reactive reducing agent with the possibility of reducing all the carbonyl functional groups in **3j**, resulting in the destruction of the chiral centre. A $LiAlH_4$ (0.6 eq) reduction in THF was conducted at –78 °C and within 15 minutes all of the starting material had been consumed, with the TLC profile showing a complicated streak with no sign of the CA at the diagnostic Rf region in 40 % EtOAc in hexane. It was reasoned that the $LiAlH_4$ had reduced all carbonyl groups including the urea on the CA.

3.5.2. Base hydrolysis

Another route pursued to cleave the CA involved base hydrolysis utilising LiOH, NaOH or KOH. This method was not chosen initially because such bases were speculated to be non-chemoselective. Also, even if the chemoselective hydrolysis of the CA was achieved one would have to further reduce the monoacid formed to the alcohol and this would add an extra step to the synthesis. Another concern was that under basic conditions sterically congested half-acids such as **3** may decarboxylation to relieve steric strain. As suspected, base hydrolysis also proved to be unsatisfactory in that low conversions (< 50 %) were observed in which the diacid was always formed, and efforts to separate the mono- from the diacid by chromatography were unsuccessful. Nevertheless, it is noteworthy that the CA could easily be recovered (85 % yield, corrected) without the use of column chromatography by simply removing the EtOH under reduced pressure and using an acid-base extraction.

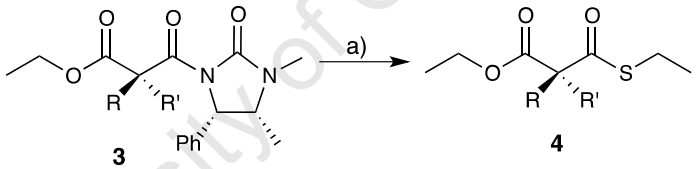
3.5.3. The CA cleavage via S_NAc reaction via EtSLi

RSLi has recently gained prominence in oxazolidinone cleavage via S_NAc as it provides a versatile synthon, the thioester, which can undergo a myriad of reaction transformations

including reduction to the aldehyde and hydrolysis to mention just a few.[34] This EtSLi route was not chosen initially because it requires a three-step process to transform **3** to the desired alcohol **6**.

Reaction of **3** with EtSLi (2.5 eq) in THF at 60 °C revealed chemoselectivity once again to be a challenge as judged by the formation of the dithioester observed by running a ^{1}H NMR spectrum on the crude material after a work-up. Optimisation studies revealed that it was necessary to have a high number of equivalents (10 eq) of EtSLi, which resulted in shorter reaction times with no formation of the dithioester. The temperature also played a pivotal role in these reactions, and an optimum temperature of 40 °C was found to minimise dithioester formation. Results using these optimised conditions are shown in **Table 3.5** in which reaction times were found to be substrate-dependent in which there was a correlation with the degree of steric congestion at the QSC. In all cases the CA was recovered with > 80 % yield.

Table 3.5: The S_NAc reaction via EtSLi



3 **4**

a) i) EtSH (10.5 eq), *n*-BuLi (10 eq), THF, –78 °C, 30 min; ii) **3** in THF, –78 to 40 °C, 2-5 hrs

Compound	Product	R-group	R'-group	Reaction Time (hrs)	Yields (%)
3e	**4a**	Et	Bn	5	82
3f	**4b**	*n*-Bu	Me	2	77
3j	**4c**	*n*-Hex	Allyl	4	89

The respective thioester compounds were all oils and thus fully characterised by IR and NMR spectroscopy, HRMS, and $[\alpha]_D$. Only compound **4a** will be discussed as a representative case. The IR bands of **4a** were observed at 2999 (Bn), 1742 (C=O, ester) and 1691 (C=O, thioester) confirming the presence of these functional groups. The disappearance of the CA resonances at the diagnostic regions was accompanied by the

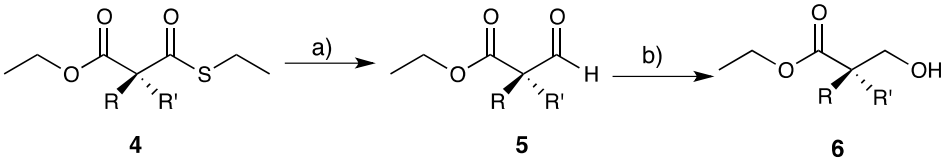
appearance of the new thioethyl resonances at 2.92 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$S) and 1.26 ppm (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$S) in the ^{1}H NMR spectrum confirming **4a**. The ethyl ester, α-ethyl and benzyl resonances were observed and assigned similarly as before. The ^{13}C NMR spectrum also showed the disappearance of the CA carbons while all the other resonances were assigned similarly as in **3e**. Three new resonances were observed at 199.2 (C=O, thioester), 23.7 (Me<u>C</u>H$_2$S) and 14.1 (<u>Me</u>CH$_2$S) in the ^{13}C NMR spectrum for the ethyl thioester and further confirmed the facile cleavage of the CA. The structure was further confirmed by mass spectrometry for which HRMS (ES): *m/z* calc. 295.1363 for $C_{16}H_{22}O_3S$, $[M + H]^+$ requires 295.1370.

3.6. Chemoselective reduction of the thioester

Now that thioester **4** was in hand, a chemoselective reduction of the thioester was envisioned to be possible via DIBAL reduction of thioesters to aldehydes.[35] The DIBAL (1.5 eq) reaction was conducted at –78 °C in DCM and kept at this temperature for 3 hrs, but no reaction was observed so the temperature was slowly increased to rt over 3 hrs. After three more hours at rt reaction was observed after which the contents were then left overnight at rt. After 24 hrs a 40 % reaction conversion was observed by TLC, for which the crude ^{1}H NMR spectrum revealed the reduction of both the ester and the thioester. The non-chemoselective reduction is thought to be due to the increased temperature, but that was necessary as there was no reaction observed at lower temperatures.

Since the DIBAL reduction was unsuccessful, another method was sought to chemoselectively reduce the thioester in the presence of the ester. In the event, **4a** was subjected to the Fukuyama reduction protocol involving reduction with triethylsilane and Pd/C, which resulted in complete conversion of starting material within 2 hrs at rt.[36] Aldehyde formation was confirmed by the crude ^{1}H NMR spectrum which showed a conspicuous aldehyde resonance at around 9.80 ppm, **Scheme 3.12**. Efforts to purify aldehyde **5a** by column chromatography were unsuccessful and therefore was subjected to a further reduction with $NaBH_4$ to afford alcohol **6a** (66 % yield) over two steps. Thioester **4b** was also subjected to the same double sequential reductive conditions to obtain the alcohol in moderate yield (**6b**, 55 %) over two steps. The moderate yields obtained in this

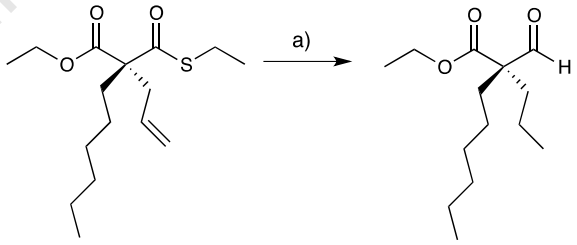
two-step process were consistent with the TLC reaction profile which showed several spots, and one is also tempted to speculate aldehyde instability to be a cause for the moderate overall yield.



6a; R = Et, R' = Bn
6b; R = *n*-Bu, R' = Me

Scheme 3.12: Reaction conditions- a) Pd/C, Et_3SiH, THF, rt. b) $NaBH_4$, **5**, THF, 0 °C to rt.

Subjecting thioester **4c** containing an allyl group to the Fukuyama reduction conditions resulted in the reduction of both the thioester and the allyl group, **Scheme 3.13**. This was revealed by the crude ^1H NMR spectrum which showed the appearance of the aldehyde resonance at 9.84 ppm as well as the disappearance of the allyl resonances at 5.61, 5.09 and 2.71 ppm, **Figure 3.7**. This was not surprising because Pd (0) is used in various hydrogenation reactions of alkenes, but it was hoped that the thioester would be reduced faster than the allyl group. In fact the crude ^1H NMR spectrum suggested that the allyl reduction was faster than the thioester as some of the thioester resonances were still observed at 2.90 ppm when the olefin resonances had completely disappeared. Reduction of compound **4c** was not pursued any further.



4c

Scheme 3.13: Reaction conditions- a) Pd/C, Et_3SiH, THF, rt.

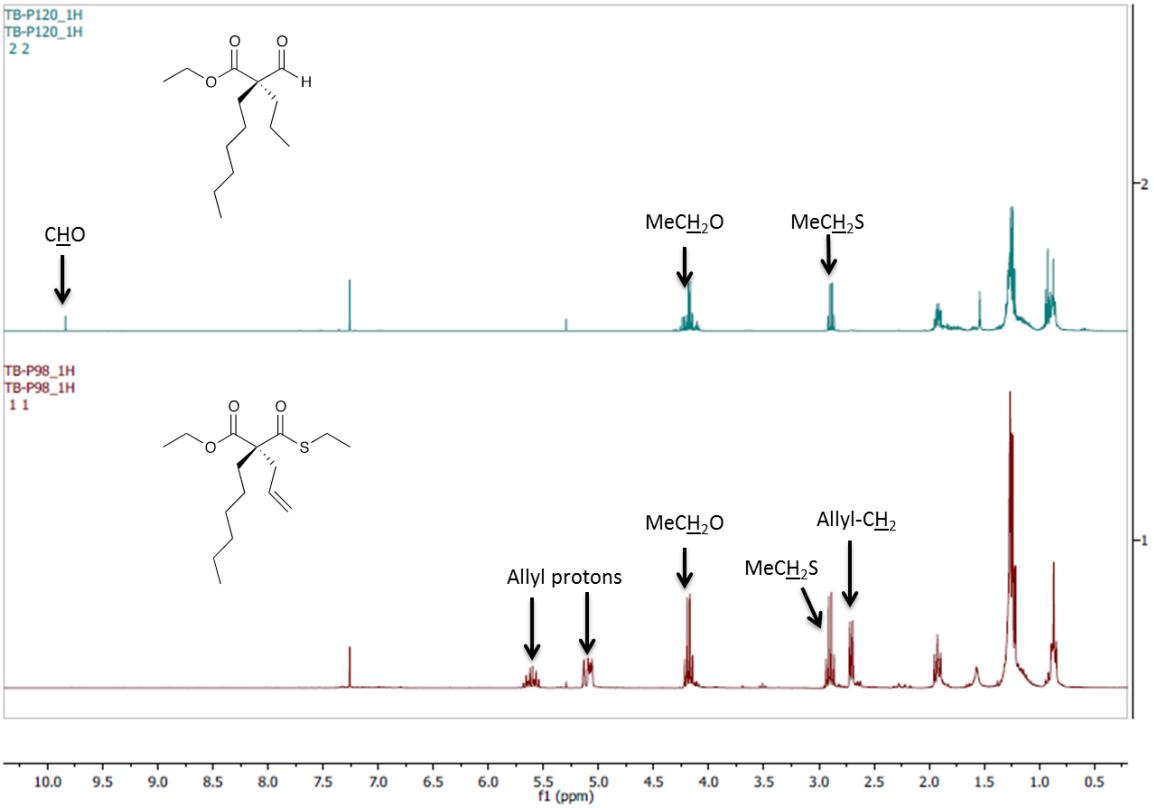
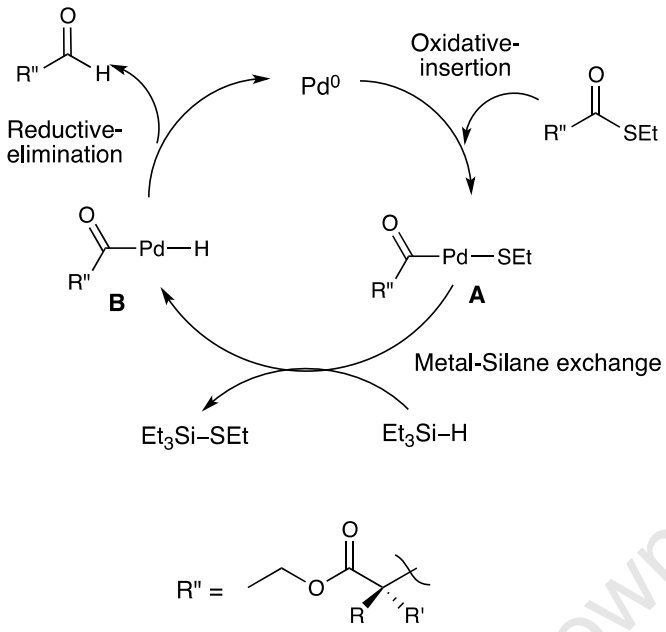


Figure 3.7: Crude ^{1}H NMR spectra of **4c** under Fukuyama reduction.

The Fukuyama reduction is thought to proceed in a similar fashion to olefin cross-coupling reactions such as the Suzuki cross-coupling, in which the first step is the oxidative insertion of the thioester to Pd (0) forming Pd (II), **Scheme 3.14**. This is followed by reduction of the Pd-S bond forming species **B**, the organopalladium complex, which then undergoes reductive elimination to give aldehyde **5** with regeneration of the Pd (0) catalyst.



Scheme 3.14: The Fukuyama thioester reduction.

IR bands observed at 3339 (OH), 3002 (Bn), and 1713 (C=O, ester) confirmed the functional groups in **6a**. The new resonances in the ^{1}H NMR spectrum observed at 3.71 (d, *J* = 11.2 Hz, 1H) and 3.51 (d, *J* = 11.2 Hz, 1H) were assigned to the diastereotopic (AB) methylene protons (C$\underline{H}_2$OH) due to the reduced thioester group, **Figure 3.8**. Similarly, the diastereotopic (AB) benzylic resonances were observed at 3.08 (d, *J* = 12.8 Hz, 1H) and 2.86 (d, *J* = 12.8 Hz, 1H). The high J_{AB} values (11.2 and 12.8 Hz) observed are indicative of the geminal coupling of diastereotopic protons. The –O$\underline{H}$ resonance at 2.15 ppm further confirmed the product. The replacement of the thioester carbonyl at 199.2 ppm by a methylene carbon at 63.6 ($\underline{C}H_2$OH) resonance in the ^{13}C NMR spectrum confirmed the formation of **6a**. All the other ^{1}H NMR and ^{13}C NMR spectrum resonances were observed and assigned similarly as before.

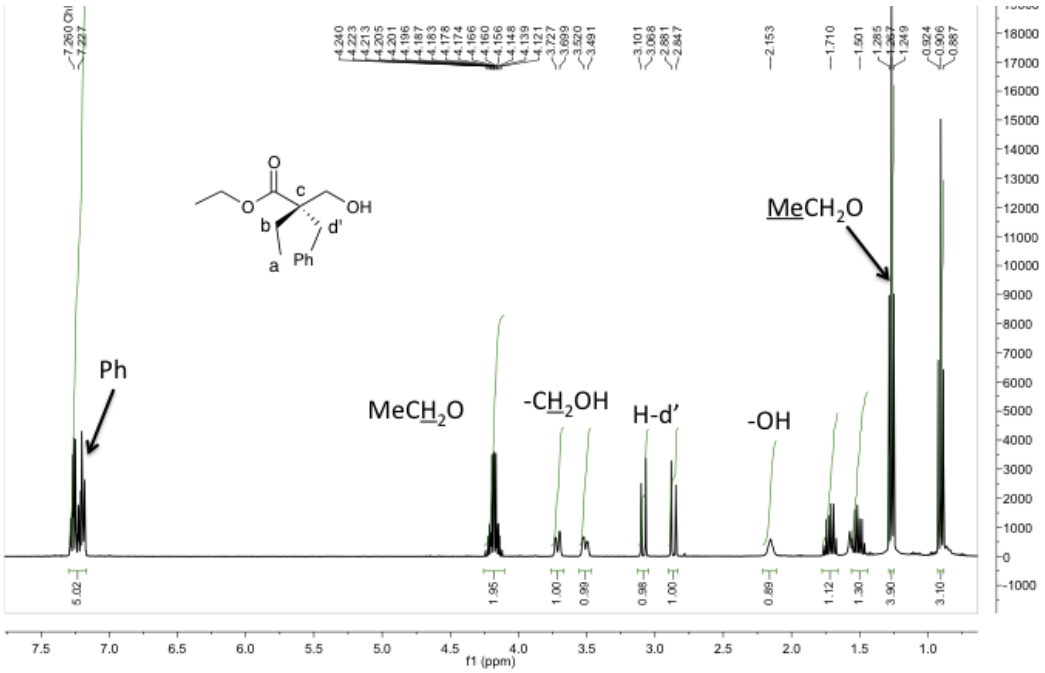


Figure 3.8: The ^{1}H NMR spectrum for **6a**.

Chapter 4: Conclusions and Future work

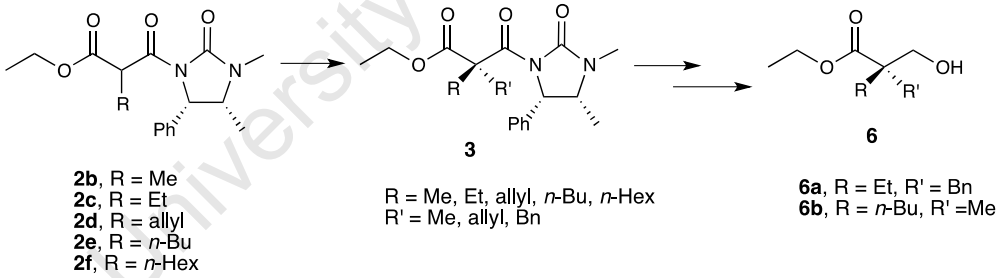
4.1. Conclusions

An imidazolidinone chiral auxiliary (CA) method has been developed for the synthesis of quaternary stereogenic centres (QSC) based on malonate substrates. A range of α-monosubstituted malonate-CA compounds (**2b**-**2f**, > 89 % yield) was synthesised in preparation for the QSC construction. The non-trivial quaternisation of the α-monosubstituted malonate-CA was achieved accessing a small library of malonate QSC-containing synthons (**3**) in good yield (> 82 %) and good stereoselectivity (dr, ≥ 93 : 7 %).

From quaternisation studies it is evident that:

1) The second substituent R' must be introduced as a highly activated electrophile such as iodomethane, allyl iodide or benzyl bromide.
2) For high stereoselectivity R should be greater than Me, where exceptional selectivity was observed for R = *n*-Hex (dr, > 99 : 1).

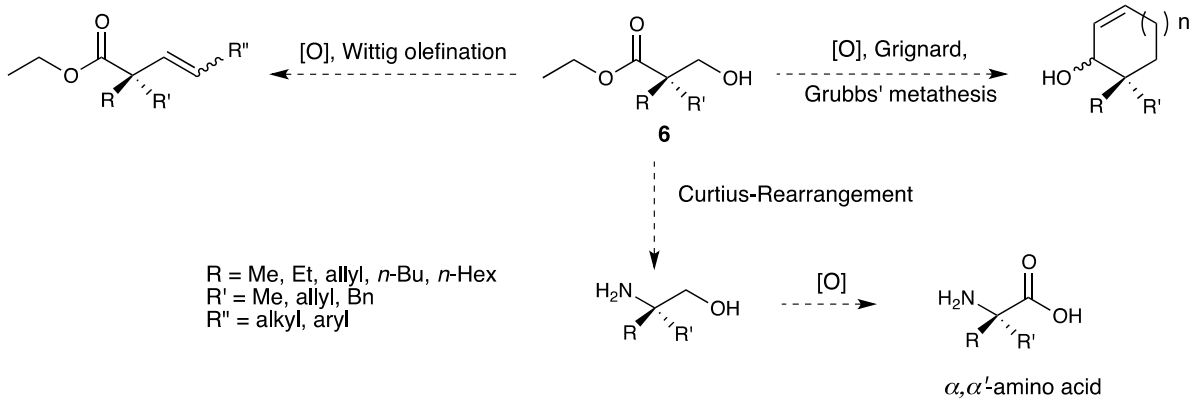
The CA could be cleaved from the products using the EtSLi S_NAc reaction followed by a double sequential reduction via a Fukuyama protocol followed by $NaBH_4$ to afford the *α,α'*-disubstituted-2-hydroxy synthons (**6a** and **6b**).



Scheme 4.1: The synthesis of advanced QSC-containing synthons.

4.2. Future work

Moving forward with the research project would include derivatising the other malonate-QSC compounds into **6**, including finding compatible reaction conditions for allyl-containing synthons which are hydrogenated in the Fukuyama protocol. The QSC-containing advanced synthons such as **6** can be used in the synthesis of natural compounds and pharmaceuticals such as those containing the moiety shown in **Scheme 4.2**.



Scheme 4.2: The versatility of compound **6** explored.

Also, one could vary the R- and R'-substituents using electrophiles such as Michael-acceptors, acyl halides, aldehydes, crotyl-derivatives and so forth to access an even broader library. Preliminary studies based on TLC have shown positive results in quaternisation with acetyl chloride, although the product could not be isolated by column chromatography.

Chapter 5: Experimental

5.1. General

All reaction solvents were freshly distilled under nitrogen, in which THF was distilled from sodium wire with benzophenone, MeCN distilled from calcium hydride, and DCM distilled from phosphorus pentoxide. Reagents were obtained from commercial sources (Sigma–Aldrich, Fluka, Merck, Kimix) and used as obtained unless stated.

All reactions were carried out in oven-dried glassware with a magnetic stirrer, and performed under a nitrogen atmosphere unless otherwise stated. Reaction temperatures were achieved with heat/silicone oil (for > 25 °C), ice/NH_4Cl salt (for 0 °C), and acetone/liquid nitrogen (< -20 °C). Aqueous solutions were prepared using deionized water.

All reactions were monitored by TLC using aluminium-backed Merck silica-gel 60 F254 plates, and column chromatography was carried out using Kieselgel 60 silica-gel (Merck). Active compounds were observed under UV-lamp (ultraviolet), while non-UV active compounds were sprayed with a 2.5% solution of *p*-anisaldehyde in a mixture of sulphuric acid and ethanol (1:10 v/v), iodine vapour, or ceric ammonium sulphate solution and then heated.

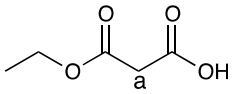
Nuclear Magnetic Resonance (NMR) spectra were recorded on either a Bruker XR400 MHz spectrometer (^{1}H at 399.95 MHz and ^{13}C at 100.6 MHz), Varian Mercury XR400 MHz spectrometer (^{1}H at 399.95 MHz and ^{13}C at 75.46 MHz), or a Varian Mercury XR300 MHz spectrometer (^{1}H at 300.08 MHz and ^{13}C at 75.46 MHz). Chemical shifts (δ) and *J*-coupling values were reported in units of ppm and Hz respectively. Chemical shifts for ^{1}H and ^{13}C were recorded relative to residual chloroform, 7.26 and 77.16 ppm respectively. High resolution mass spectra (HRMS) were recorded on a VG70 SEQ micromass spectrometer in electrospray positive mode. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyzer. Infra-Red (IR) spectroscopy was performed on a Bruker FT-IR Spectrometer with vibrations measured in units of cm^{-1}. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20 °C and are reported as: $[\alpha]_D^{20}$ (*c* g/ml, solvent).

Determination of melting points was done using a Reichert-Jung Thermovar hot stage microscope (HSM) and are uncorrected

5.2. Monohydrolysis of diethyl malonates

A representative typical procedure described below was followed for monohydrolysis diethyl malonates:[37]

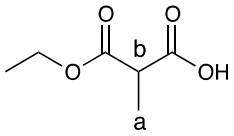
3-Ethoxy-3-oxopropanoic acid (1a)



To a solution of diethyl malonate (8.0 g, 49.9 mmol) in EtOH at 0 °C, was added dropwise a solution of aq. KOH (24.0 ml, 59.9 mmol, 1.2 eq, 2.5 M) and the contents allowed to slowly warm up to rt. After 1 hour EtOH was removed under reduced pressure, the concentrate diluted with water (25 ml) and washed with DCM (2 × 25 ml). The aqueous layer was acidified with conc. HCl to pH = 2 and the re-extracted with DCM (3 × 30 ml), the organic extracts combined, dried over $MgSO_4$, filtered under vacuum, and concentrated *in vacuo* to obtain **1a** (5.9 g, 90 % yield) as a colourless oils.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (bs, 1H, COO<u>H</u>), 4.23 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.42 (s, 2H, H-a), 1.29 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH_2O).

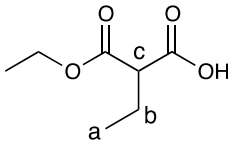
2-(Ethoxycarbonyl)propanoic acid (1b)



Following the procedure outlined above: diethyl 2-methylmalonate (8.0 g, 45.9 mmol) and KOH (22.0 ml, 55.0 mmol, 1.2 eq, 2.5 M) were reacted in EtOH (20 ml) to obtained **1b** as a colourless oil (6.3 g, 94 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (bs, 1H, COO<u>H</u>), 4.20 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.46 (q, *J* = 7.2 Hz, 1H, H-b), 1.43 (d, *J* = 7.2 Hz, 3H, H-a), 1.27 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH_2O).

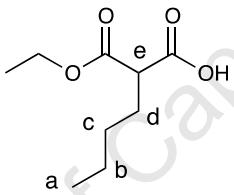
2-(Ethoxycarbonyl)butanoic acid (1c)



Following the procedure outlined above: diethyl 2-ethylmalonate (8.0 g, 42.5 mmol) and KOH (20.4 ml, 51.0 mmol, 1.2 eq, 2.5 M) were reacted in EtOH (20 ml) to obtained **1c** as a colourless oil (6.5 g, 95 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (bs, 1H, COO<u>H</u>), 4.22 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.31 (t, *J* = 7.2 Hz, 1H, H-c), 1.96 (m, 2H, H-b), 1.28 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH_2O), 1.00 (t, *J* = 7.2 Hz, 3H, H-a).

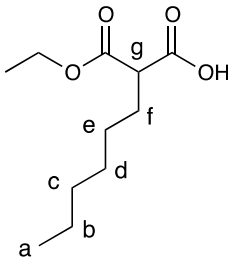
2-(Ethoxycarbonyl)hexanoic acid (1d)



Following the procedure outlined above: diethyl 2-butylmalonate (8.0 g, 37.0 mmol) and KOH (17.8 ml, 44.4 mmol, 1.2 eq, 2.5 M) were reacted in EtOH (20 ml) to obtained **1d** as a colourless oil (6.6 g, 97 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (bs, 1H, CO<u>OH</u>), 4.21 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.36 (t, *J* = 7.2 Hz, 1H, H-e), 1.96-1.86 (m, 2H, H-d), 1.40-125 (m, 4H, H-b + H-c), 1.27 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH_2O), 0.90 (t, *J* = 7.2 Hz, 3H, H-a).

2-(Ethoxycarbonyl)octanoic acid (1e)



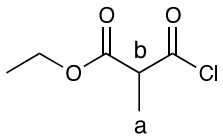
Following the procedure outlined above: diethyl 2-hexylmalonate (8.0 g, 32.7 mmol) and KOH (39.3 ml, 15.7 mmol 1.2 eq, 2.5 M) were reacted in EtOH (20 ml) to obtained **1e** as a colourless oil (6.6 g, 93 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 2H, MeC$\underline{H_2}$O), 3.31 (t, *J* = 7.6 Hz, 1H, H-g), 1.88 (q, *J* = 7.6 Hz, 2H, H-f), 1.35-1.25 (m, 8H, H-b to H-e), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.88 (t, *J* = 7.2 Hz, 3H, H-a).

5.3. Synthesis of α-substituted acyl chlorides

A representative typical procedure described below was followed to chlorinate the monoacids:[30]

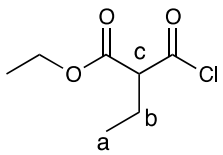
Ethyl 3-chloro-2-methyl-3-oxopropanoate (1b')



To a solution of monoacid **1b** (5.0 g, 34.2 mmol) in DCM (30 ml), was added $SOCl_2$ (4.9 ml, 68.4 mmol, 2.0 eq) dropwise at 0 °C and the reaction contents allowed to warm up to rt. After 4 hrs, DCM and excess $SOCl_2$ were removed via distillation under nitrogen in atmospheric pressure and the crude residue further purified by distillation *in vacuo* (≈ 1 mmHg) to obtain acid chloride **1b'** (4.3 g, 77 % yield). Compound **1b'** was confirmed by ^{1}H NMR only and immediately used to acylate the (*4S*,*5R*)-1,5-dimethyl-4-phenylimidazolidin-2-one CA.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31-4.22 (m, 2H, MeC$\underline{H_2}$O), 3.84 (q, *J* = 7.2 Hz, 1H, H-b), 1.53 (d, *J* = 7.2 Hz, 3H, H-a), 1.31 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$).

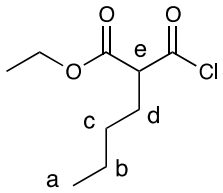
Ethyl 2-(chlorocarbonyl)butanoate (1c')



Following the procedure outlined above: **1c** (5.0 g, 31.2 mmol) and $SOCl_2$ (4.5 ml, 62.4 mmol, 2.0 eq) were reacted in DCM (20 ml) to obtain **1c'** (3.9 g, 70 % yield) which distilled at 77- 80 °C *in vacuo* as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27-4.15 (m, 2H, MeC<u>H</u>$_2$O), 3.65 (t, *J* = 7.2 Hz, 1H, H-c), 2.10-1.85 (m, 2H, H-b), 1.26 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.98 (t, *J* = 7.2 Hz, 3H, H-a).

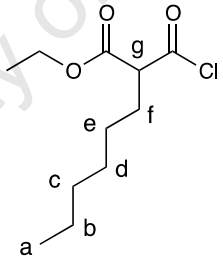
Ethyl 2-(chlorocarbonyl)hexanoate (1d')



Following the procedure outlined above: **1d** (5.0 g, 26.6 mmol) and $SOCl_2$ (3.8 ml, 53.1 mmol, 2.0 eq) were reacted in DCM (20 ml) to obtain **1d'** (4.5 g, 82 % yield) distilled at 100-102 °C *in vacuo* as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (m, 2H, MeC<u>H</u>$_2$O), 3.72 (t, *J* = 7.2 Hz, 1H, H-g), 1.97 (m, 2H, H-f), 1.46-1.30 (m, 4H, H-b + H-c), 1.28 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.90 (t, *J* = 7.2 Hz, 3H, H-a).

Ethyl 2-(chlorocarbonyl)octanoate (1e').



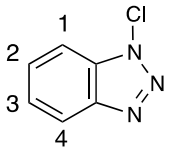
Following the procedure outlined above: **1e** (5.0 g, 23.1 mmol) and $SOCl_2$ (3.3 ml, 46.2 mmol, 2.0 eq) were reacted in DCM (20 ml) to obtain **1e'** (4.1 g, 75 %) distilled at 138-140 °C *in vacuo* as a clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.37 (t, *J* = 7.2 Hz, 1H, H-g), 1.95-1.86 (m, 2H, H-f), 1.45-1.25 (m, 8H, H-b to H-e), 1.29 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.88 (t, *J* = 7.2 Hz, 3H, H-a).

5.4. Synthesis of malonate-auxiliary adducts

5.4.1. Amide-coupling via BtCl

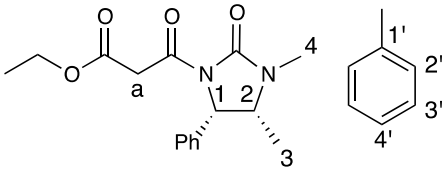
1-Chlorobenzotriazole[29a] **(i)**



1*H*-Benzotriazole (3.00 g, 25.2 mmol) was dissolved in acetic acid (≈ 20 ml) with heating. Once dissolved, the contents were cooled down to rt and further cooled to 0 °C making sure no crystals form. Aqueous NaOCl (22.5 ml, m/v 12.5 %, 37.8 mmol, 1.5 eq) was added dropwise with a pressure funnel and thereafter the reaction contents allowed to stir at rt for 20 hrs. The yellowish precipitate that had formed, was filtered under vacuum and washed with cold water (500 ml), dissolved in DCM (30 ml), dried over $MgSO_4$, filtered under vacuum, and concentrated under reduced pressure to obtain BtCl as off-white crystals (2.64 g, 68 %).

Mp 100-102 °C (lit. 103-106); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H, H-1), 7.62-7.58 (m, 2H, H-2 + H-3), 7.48-7.43 (m, 1H, H-4).

Ethyl 3-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidinone-1'-yl)-3-oxopropanoate (2a)



To a solution of PPh_3 (1.55 g, 5.90 mmol, 1.3 eq) and **i** (0.907 g, 5.90 mmol, 1.3 eq) in MeCN (5.0 ml) at 0 °C was added a solution of monoacid **1a** (0.600 g, 5.45 mmol, 1.2 eq) in MeCN (5.0 ml) slowly and the reaction contents allowed to stir at 0 °C for 30 min. The contents were then warmed to ambient temperature and a solution of (*4S*,*5R*)-1,5-dimethyl-4-phenylimidazolidin-2-one (0.865 g, 4.54 mmol, 1.0 eq) in MeCN (8.0 ml) slowly added and the reaction contents refluxed at 85 °C overnight. After 16 hrs, the reaction mixture was cooled to rt, the organic solvent removed under reduced pressure, and the crude residue

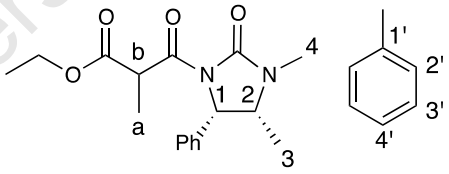
chilled to 0 °C, diluted with KOH (15 ml, 1.0 M) and stirred for 30 min at this temperature. The crude residue was extracted with DCM (3 x 25 ml), the organic extracts dried over $MgSO_4$, filtered under vacuum and concentrated *in vacuo*. The crude residue was purified by column chromatography (40 % EtOAc in hexanes) to afford **2a** as a colourless solid (0.762 g, 69 % yield).

Mp 84 °C; $[\alpha]_D^{20}$ = –6.2, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3008 (Ar), 1736 (2 x C=O, amide and ester), 1687 (C=O, urea); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 3H, H-3' + H-4'), 7.18 (m, 2H, H-2'), 5.32 (d, *J* = 8.7 Hz, 1H, H-1), 4.18 (q, *J* = 7.2 Hz, 2H, MeC$\underline{H}_2$O), 4.02 (s, 1H, H-a), 3.97 (s, 1H, H-a), 3.93 (dq, *J* = 8.7, 6.6 Hz, 1H, H-2), 2.81 (s, 3H, H-4), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.80 (d, *J* = 6.6 Hz, 3H, H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.7 (C=O, ester), 165.1 (C=O, amide), 155.6 (C=O, urea), 136.1 (C-1'), 128.6 (C-3'), 128.3 (C-4'), 127.2 (C-2'), 61.3 (Me$\underline{C}H_2O$), 59.5 (C-1), 54.2 (C-2), 43.5 (C-a), 28.3 (C-4), 15.1 (C-3), 14.2 ($\underline{Me}CH_2O$); anal. calc. for $C_{16}H_{20}N_2O_4$ (%): C, 63.14; H, 6.61; N, 9.20. Found (%): C, 63.19; H, 6.57; N, 9.24.

5.4.2. Amide-coupling via acyl chlorides

A representative typical procedure described below was followed to acylate (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one with malonate acyl chlorides:

Ethyl 3-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidin-1'-yl)-2-methyl-3-oxopropanoate (2b)

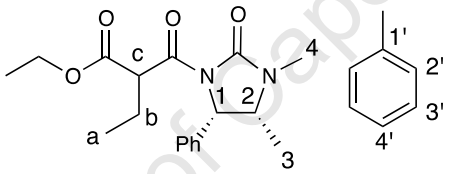


To a solution of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (1.0 g, 5.4 mmol, 1.0 eq) in MeCN (7.0 ml), was added slowly a solution of **1b'** (10.50 ml, 10.5 mmol, 2.0 eq, 1.0 M) in MeCN and the contents refluxed at 85 °C. After 4 hrs, the contents were cooled to rt, slowly quenched with $NaHCO_3$ (25 ml), extracted with DCM (3 × 25 ml), the organic extracts dried over $MgSO_4$, filtered under reduced pressure, and organic solvents removed under reduced pressure. The concentrate was purified by column chromatography (30 % EtOAc in hexane) to afford **2b** (0.961 g, 90 % yield) as a mixture of diastereomers. Recrystallising the

diastereomeric mixture in EtOAc/ Hex to a constant Mp afforded one single diastereomer of **2b** which was fully charaterised.

Mp 152-153 °C; $[\alpha]_D^{20}$ = –31.9, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3010 (Ar), 1732 (2 × C=O, ester and amide), 1689 (C=O, urea); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H, H-3' + H-4'), 7.22 (m, 2H, H-2'), 5.30 (d, *J* = 8.7 Hz, 1H, H-1), 4.65 (q, *J* = 7.5 Hz, 1H, H-b), 4.25-4.05 (m, 2H, MeC$\underline{H}_2$O), 3.90 (dq, *J* = 8.7, 6.6 Hz, 1H, H-2), 2.81 (s, 3H, H-4), 1.39 (d, *J* = 7.5 Hz, 3H, H-a), 1.21 (t, *J* = 7.6 Hz, 3H, $\underline{Me}CH_2O$), 0.8 (d, *J* = 6.6 Hz, 3H, H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1 (C=O, ester), 169.0 (C=O, amide), 155.7 (C=O, urea), 136.2 (C-1'), 128.5 (C-3'), 128.2 (C-4'), 127.3 (C-2'), 61.2 (Me$\underline{C}H_2O$), 59.8 (C-1), 54.3 (C-2), 45.9 (C-b), 28.4 (C-4), 15.2 (C-3), 14.2 ($\underline{Me}CH_2O$), 13.5 (C-a); anal. cal. for $C_{17}H_{22}N_2O_4$ (%): C, 64.13; H, 6.97; N, 8.80. Found (%): C, 64.02; H, 7.04; N, 8.89.

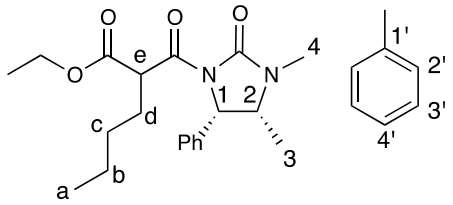
Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)butanoate (2c)



Following the procedure outlined above: CA (1.0 g, 5.4 mmol, 1.0 eq) in MeCN (10 ml) was reacted with **1c'** (10.50 ml, 2.0 eq, 1.0 M). Chromatography (25 % EtOAc in hexane) afforded a mixture of diastereomers (**2c**, 0.757 g, 94 % yield) as off-white solid. Recrystallising the diastereomeric mixture of **2c** in EtOAc/ Hex to a constant Mp afforded a single diastereomer which was fully characterised.

Mp 126-129 °C; $[\alpha]_D^{20}$ = –4.5, (*c* = 1.0, DCM); ν_{max} (cm^{-1}) 3010 (Ar), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H, H-3' + H-4'), 7.21 (m, 2H, H-2'), 5.31 (d, *J* = 8.8 Hz, 1H, H-1), 4.59 (dd, *J* = 5.6, 2.8 Hz 1H, H-c), 4.25-4.08 (m, 2H, MeC$\underline{H}_2$O), 3.91 (dq, *J* = 8.8, 6.8 Hz, 1H, H-2), 2.82 (s, 3H, H-4), 2.04-1.86 (m, 2H, H-b), 1.20 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.97 (t, *J* = 8.0 Hz, 3H, H-a), 0.80 (d, *J* = 6.8 Hz, 3H, H-3); ^{13}C (100.6 MHz, $CDCl_3$) δ 170.3 (C=O, ester), 168.1 (C=O, amide), 155.7 (C=O, urea), 136.2 (C-1'), 128.5 (C-'3), 128.2 (C-4'), 127.3 (C-2'), 61.0 (Me$\underline{C}H_2O$), 59.8 (C-1), 54.2 (C-2), 52.7 (C-c), 28.3 (C-4), 22.1 (C-b), 15.2 (C-3), 14.2 ($\underline{Me}CH_2O$), 12.2 (C-a); anal. cal. for $C_{18}H_{24}N_2O_4$ (%): C, 65.04; H, 7.28; N, 8.43. Found (%): C, 64.85; H, 7.06; N, 8.36.

Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)hexanoate (2d)



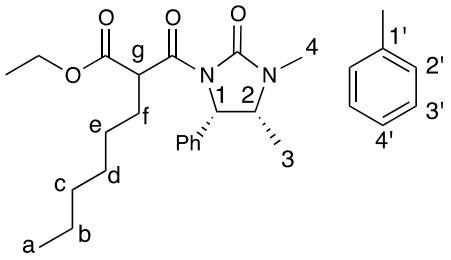
Following the procedure outlined above: CA (1.0 g, 5.4 mmol, 1.0 eq) in MeCN (10 ml) was reacted with **1d'** (10.50 ml, 2.0 eq, 1.0 M). Chromatography (25 % EtOAc in hexane) afforded a mixture of diastereomers (**2d**, 0.757 g, 94 % yield) as colourless oil.

The diastereomeric ratio of the purified product was determined to be 50 : 50 by chiral HPLC analysis (Chiracel OD, 95:5 hexanes: *i*-PrOH, 1 mL/min, λ = 254 nm, (retention time)$_{major}$ = 8.02 min, (retention time)$_{minor}$ = 8.12 min; ν_{max} (cm^{-1}) 3010 (Ar), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 361. 2127 for $C_{20}H_{29}N_2O_4$, $[M + H]^+$ requires 361.2125.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H, H-3' + H-4'), 7.23 (m, 1H, H-2'), 7.12 (m, 1H, H-2'), 5.31 (d, *J* = 8.6 Hz, 1H, H-1), 4.63 (dd, *J* = 5.3, 3.4 Hz, 1H, H-e), 4.24-4.19-4.09 (m, 2H, MeC$\underline{H}_2$O), 3.96-3.88 (m, 1H, H-2), 2.82 (s, 3H, H-4), 2.00-1.75 (m, 2H, H-d), 1.35-1.28 (m, 2H, H-b), 1.25-1.18 (m, 2H, H-c), 1.20 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.82 (t, *J* = 7.2 Hz, 3H, H-a), 0.80 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O, ester), 168.4 (C=O, amide), 155.7 (C=O, urea), 136.2 (C-1'), 128.4 (C-3'), 128.2 (C-4'), 127.2 (C-2'), 61.1 (Me$\underline{C}H_2$O), 59.7 (C-1), 54.0 (C-2), 51.1 (C-e), 29.2 (C-d), 28.3 (C-4), 27.6 (C-c), 22.6 (C-b), 15.1 (C-3), 14.3 ($\underline{Me}CH_2O$) 14.2 (C-a).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H, H-3' + H-4'), 7.23 (m, 1H, H-2'), 7.12 (m, 1H, H-2'), 5.36 (d, *J* = 8.6 Hz, 1H, H-1), 4.61 (dd, *J* = 6.4, 1.2 Hz, 1H, H-e), 4.24-4.19-4.09 (m, 2H, MeC$\underline{H}_2$O), 3.96-3.88 (m, 1H, H-2), 2.81 (s, 3H, H-4), 2.00-1.75 (m, 2H, H-d), 1.35-1.28 (m, 2H, H-b), 1.25-1.18 (m, 2H, H-c), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.87 (t, *J* = 7.2 Hz, 3H, H-a), 0.79 (d, *J* = 6.4 Hz, 3H, $\underline{Me}$CHN); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (C=O, ester), 168.8 (C=O, amide), 155.7 (C=O, urea), 136.7 (C-1'), 128.6 (C-3'), 128.3 (C-4'), 127.3 (C-2'), 61.1 (Me$\underline{C}H_2$O), 59.8 (C-1), 54.2 (C-2), 51.3 (C-e), 29.3 (C-d), 28.7 (C-4), 27.9 (C-c), 22.7 (C-b), 15.1 (C-3), 14.3 ($\underline{Me}CH_2O$) 14.2 (C-a).

Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)octanoate (2e)



Following the procedure outlined above: CA (1.0 g, 5.4 mmol, 1.0 eq) in MeCN (10 ml) was reacted with **1e'** (10.50 ml, 2.0 eq, 1.0 M). Chromatography (25 % EtOAc in hexane) afforded a mixture of diastereomers (**2e**, 0.757 g, 94 % yield) as colourless oil.

The diastereomeric ratio of the purified product was determined to be 51 : 49 by chiral HPLC analysis (Chiracel OD, 95:5 hexanes: *i*-PrOH, 1 mL/min, λ = 254 nm, (retention time)$_{major}$ = 7.42 min, (retention time)$_{minor}$ = 9.01 min; ν_{max} (cm^{-1}) 3010 (Ar), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 389.2440 for $C_{22}H_{33}N_2O_4$, $[M + H]^+$ requires 389.2443.

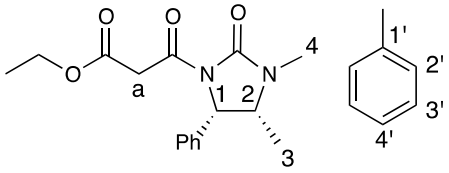
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.20 (m, 1H, H-2), 7.17 (m, 1H, H-2), 5.31 (d, *J* = 8.8 Hz, 1H, H-1), 4.63 (dd, *J* = 4.6, 3.6 Hz, 1H, H-g), 4.24-4.24-4.08 (m, 2H, MeC<u>H</u>$_2$O), 3.97-3.88 (m, 1H, H-2), 2.82 (s, 3H, H-4), 1.95-1.86 (m, 2H, H-f), 1.35-1.17 (m, 8H, H-b to H-e), 1.20 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.84 (t, *J* = 7.2 Hz, 3H, H-a), 0.80 (d, *J* = 6.8 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O, ester), 168.4 (C=O, amide), 155.7 (C=O, urea), 136.2 (C-1'), 128.4 (C-3'), 128.2 (C-4'), 127.2 (C-2'), 61.1 (Me<u>C</u>H$_2$O), 59.7 (C-1), 54.2 (C-2), 51.3 (C-g), 29.3 (C-e), 29.2 (C-d), 28.9 (C-f), 28.3 (C-4), 27.6 (C-c), 22.6 (C-b), 15.1 (C-3), 14.2 (<u>Me</u>CH$_2$O), 14.2 (C-a).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.17 (m, 2H, H-2'), 5.36 (d, *J* = 8.4 Hz, 1H, H-1), 4.79 (dd, *J* = 6.0, 2.4 Hz, 1H, H-g), 4.24-4.08 (m, 2H, MeC<u>H</u>$_2$O), 3.97-3.88 (m 1H, H-2), 2.82 (s, 3H, H-4), 1.95-1.86 (m, 2H, H-f), 1.35-1.17 (m, 8H, H-b to H-e), 1.25 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.85 (t, *J* = 7.2 Hz, 3H, H-a), 0.79 (d, *J* = 6.8 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (C=O, ester), 168.8 (C=O, amide), 155.7 (C=O, urea), 136.7 (C-1'), 128.6 (C-3'), 128.3 (C-4'), 127.3 (C-2'), 61.1 (Me<u>C</u>H$_2$O), 59.8 (C-2), 54.2

(C-2), 51.3 (C-g), 29.3 (C-e), 29.2 (C-d), 28.9 (C-f), 28.7 (C-4), 27.9 (C-c), 22.7 (C-b), 15.2 (C-3), 14.2 (MeCH$_2$O), 14.2 (C-a).

5.4.3 Amide-coupling using carbodiimide chemistry [31c, 38]

Ethyl 3-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidinone-1'-yl)-3-oxopropanoate (2a)

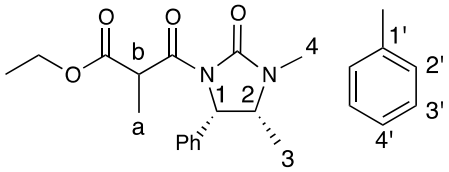


To a solution of **1a** (1.24 g, 9.46 mmol, 1.2 eq) and *N,N'*-dicyclohexylcarbodiimide (1.95 g, 9.46 mmol, 1.2 eq) in DCM (8.0 ml) at 0 °C was added a solution of HOBt (0.603 g, 3.94 mmol, 0.5 eq) in DCM (3.0 ml) followed by (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (1.50 g, 7.88 mmol) also in DCM (3.5 ml). The contents stirred at 0 °C, slowly warmed to rt and left overnight. After 15 hr, the organic solvent was removed *in vacuo*, crude residue diluted with EtOAc (20 ml) and filtered through Celite under reduced pressure washing with EtOAc (3 x 20 ml). The organic extracts were combined, dried over $MgSO_4$, concentrated *in vacuo* and the crude residue purified by column chromatography (40 % EtOAc in hexane) to afford a colourless solid (**2a**, 1.918 g, 80 % yield). The solid was recrystallised in EtOAc/ hexane and characterised as before.

5.5. Synthesis of α-monosubstituted malonate-CA compounds

A representative typical procedure described below was followed to alkylate **2a** to various α-monosubstituted malonate-CA:

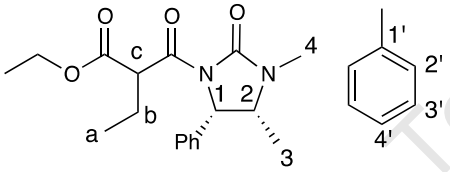
Ethyl 3-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidin-1'-yl)-2-methyl-3-oxopropanoate (2b)



To a solution of **2a** (0.40 g, 1.31 mmol) in THF (3.5 ml) at –78 °C was added KHMDS (3.15 ml, 1.58 mmol, 1.2 eq) and the contents allowed to stir at this temperature for 30 min.

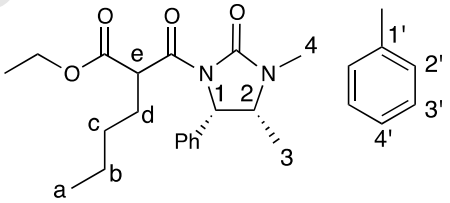
Thereafter, iodomethane (0.49 ml, 3.93 mmol, 3.0 eq) was added at –78 °C and the contents allowed to slowly warm up to rt and left to stir overnight. After 14 hrs, the reaction was quenched with sat. $NH_4Cl/Na_2S_2O_3$ (25 ml), extracted with DCM (2 x 25 ml), the organic solvents combined and dried over $MgSO_4$, filtered under pressure, and the organic solvent removed under reduced pressure. The concentrate purified by column chromatography (30 % EtOAc in hexane) to afford a mixture of diastereomers (**2b**, 0.375 g, 90 % yield) as off-white solid. The product was crystallised and characterised as before.

Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)butanoate (2c)



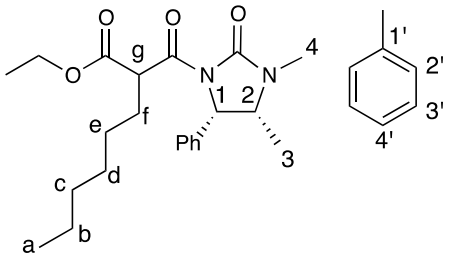
Following the procedure outlined above: **2a** (0.40 g, 1.31 mmol), KHMDS (3.15 ml, 1.58 mmol, 1.2 eq) and iodoethane (0.31 ml, 3.93 mmol, 3.0 eq) were reacted in THF (3.5 ml). The contents were refluxed for 12 hrs. Chromatography (25 % EtOAc in hexane) afforded a mixture of diastereomers (**2c**, 0.388 g, 94 % yield) as a colourless solid. Compound **2b** was recrystallised and characterised as before.

Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)hexanoate (2d)



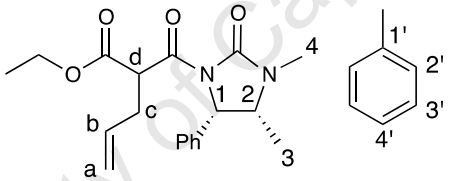
Following the procedure outlined above: **2a** (0.40 g, 1.31 mmol), KHMDS (3.15 ml, 1.58 mmol, 1.2 eq), TBAI (0.241 g, 0.655 mmol, 0.5 eq) and 1-bromobutane (0.42 ml, 3.93 mmol, 3.0 eq) were reacted in THF (4.5 ml). The contents were refluxed for 12 hrs. Chromatography (15 % EtOAc in hexane) afforded a mixture of diastereomers (**2d**, 0.411 g, 87 % yield) as a colourless oil and was characterised as before.

Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)octanoate (2e)



Following the procedure outlined above: **2a** (0.40 g, 1.31 mmol), KHMDS (3.15 ml, 1.58 mmol, 1.2 eq), TBAI (0.241 g, 0.655 mmol, 0.5 eq) and 1-bromohexane (0.72 ml, 3.93 mmol, 3.0 eq) were reacted in THF (4.5 ml). The contents were refluxed for 12 hrs. Chromatography (15 % EtOAc in hexane) afforded a mixture of diastereomers (**2e**, 0.458 g, 90 % yield) as a colourless oil and was characterised as before.

Ethyl 2-((4'*R*,5'*S*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)pent-4-enoate (2c)



Following the above procedure: **2a** (0.40 g, 1.31 mmol), KHMDS (3.15 ml, 1.58 mmol, 1.2 eq) and 1-allyl bromide (0.44 ml, 3.93 mmol, 3.0 eq) were reacted in THF (3.0 ml). Chromatography (20 % EtOAc in hexane) afforded a mixture of diastereomers (**3f**, 0.393 g, 87 % yield) as a colourless oil.

ν_{max} (cm^{-1}) 3010 (Ar), 2959 (alkene), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): *m/z* calc. 345.1814 for $C_{19}H_{25}N_2O_4$, $[M + H]^+$ requires 345.1813.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.20 (m, 1H, H2'), 7.17 (m, 1H, H2'), 5.81-5.45 (m, 1H, H-b), 5.35 (d, *J* = 8.8 Hz, 1H, H-1), 5.12-5.02 (m, 1H, H-a), 5.01-4.92 (m, 1H, H-a), 4.91 (dd, *J* = 4.2, 2.6 Hz, 1H, H-d), 4.25-4.11 (m, 2H, Me$\underline{CH_2}$O), 3.98-3.85 (m, 1H, H-2), 2.83 (s, 3H, H-4), 2.50-2.21 (m, 2H, H-c), 1.25 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.80 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 169.7 (C=O, amide), 155.1 (C=O, urea), 136.1 (C-1'), 135.0 (C-b), 128.5 (C-3'), 128.2 (C-4'),

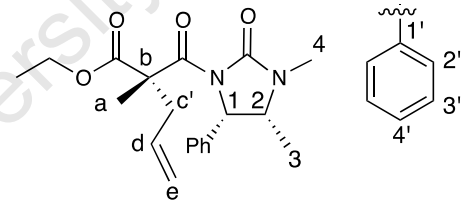
127.2 (C-2'), 117.1 (C-a), 61.3 (MeC$\underline{H}_2$O), 58.8 (C-1), 54.1 (C-2), 50.9 (C-d), 32.8 (C-c), 28.3 (C-4), 15.2 (C-3), 14.3 ($\underline{Me}CH_2O$).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.20 (m, 1H, H2'), 7.17 (m, 1H, H2'), 5.81-5.45 (m, 1H, H-b), 5.30 (d, *J* = 8.8 Hz, 1H, H-1), 5.12-5.02 (m, 1H, H-a), 5.01-4.92 (m, 1H, H-a), 4.80 (dd, *J* = 5.4, 3.6 Hz, 1H, H-d), 4.25-4.11 (m, 2H, MeC$\underline{H}_2$O), 3.98-3.85 (m, 1H, H-2), 2.82 (s, 3H, H-4), 2.50-2.21 (m, 2H, H-c), 1.21 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.80 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.7 (C=O, amide), 155.1 (C=O, urea), 136.7 (C-1'), 135.4 (C-b), 128.6 (C-3'), 128.3 (C-4'), 127.3 (C-2'), 117.1 (C-a), 61.3 (MeC$\underline{H}_2$O), 58.8 (C-1), 54.2 (C-2), 51.1 (C-d), 32.8 (C-c), 28.3 (C-4), 15.2 (C-3), 14.3 ($\underline{Me}CH_2O$).

5.6. Synthesis of malonate-based QSCs compounds

A representative typical procedure described below for **2a** was followed for the alkylation of α-monosubstituted malonate-CA compounds:

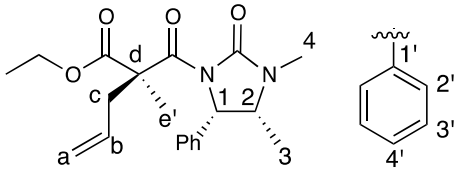
(*2S*)-Ethyl 2-((4'*S*,5'*R*)-1'-carbonyl-3',4'-dimethyl-5'-phenylimidazolidin-2'-one)-2-methylpent-4-enoate (3a)



To a solution of **2b** (100 mg, 0.314 mmol) in THF (1.5 ml) at –78 °C was added a solution of KHMDS (0.82 ml, 0.408 mmol, 1.3 eq, 0.5 M) was slowly added to the reaction contents allowed to stir at this temperature for 30 min. Thereafter, allyl bromide (0.10 ml, 942 mmol, 3.0 eq) was slowly added, the reaction contents allowed to slowly warm up to rt and left to stir overnight for 20 hrs. The reaction was quenched with sat. NH_4Cl (15 ml), extracted with DCM (3 x 15 ml), the organic extracts dried over $MgSO_4$, filtered under vacuum and the organic solvent removed *in vacuo*. The crude ^{1}H NMR of **3a** revealed a diastereomeric

mixture of 51 : 49 and was not purified. Instead, **3b** was synthesised as a single diastereomer via reversing R/R' group introduction.

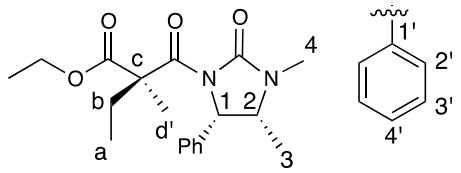
(2*R*)-Ethyl 2-((4'*S*,5'*R*)-1'-carbonyl-3',4'-dimethyl-5'-phenylimidazolidin-2'-one)-2-methylpent-4-enoate (3b)



Following the procedure outlined above: **2f** (200 mg, 0.581 mmol), KHMDS (1.51 ml, 0.756 mmol, 1.3 eq, 0.5 M) and iodomethane (0.12 ml, 1.743 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (25 % EtOAc in hexane) afforded **3b** as a colourless oil (172.8 mg, 83 % yield).

$[\alpha]_D^{20}$ = –33.3, (DCM, *c* = 1.0); ν_{max} 3010 (Ar), 2991 (alkene), 1735 (2 x C=O, ester and amide), 1675 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H, H-3' + H-4'), 7.17 (m, 2H, H-2'), 5.71-5.80 (m, 1H, H-b), 5.29 (d, *J* = 8.4 Hz, 1H, H-1), 5.04-4.98 (m, 1H, H-a), 4.97-4.89 (m, 1H, H-a), 4.25-4.13 (m, 2H, MeC<u>H</u>$_2$O), 3.90 (dq, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.79 (s, 3H, H-4), 2.78-2.63 (m, 2H, H-c), 1.45 (s, 3H, H-e'), 1.27 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.79 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O, ester), 170.2 (C=O, amide), 155.9 (C=O, urea), 136.7 (C-1'), 133.8 (C-b), 128.6 (C-3'), 128.2 (C-4'), 127.0 (C-2'), 118.2 (C-a), 60.8 (Me<u>C</u>H$_2$O), 60.5 (C-1), 54.5 (C-d), 54.5 (C-2), 40.5 (C-c), 28.3 (C-4), 21.4 (C-e'), 15.1 (C-3), 14.3 (<u>Me</u>CH$_2$O); HRMS (ES): *m/z* calc. 359.1971 $C_{20}H_{27}N_2O_4$, $[M + H]^+$ requires 358.1971.

(2*R*)-Ethyl 2-((4'*S*,5'*R*) -1'-carbonyl-3',4'-dimethyl-5'-phenylimidazolidin-2'-one)-2-methylbutanoate (3c)

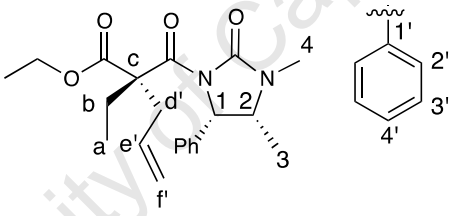


Following the procedure outlined above: **2c** (200 mg, 0.602 mmol), KHMDS (1.57 ml, 0.783 mmol, 1.3 eq, 0.5 M) and iodomethane (0.12 ml, 1.806 mmol, 3.0 eq) were reacted in THF

(1.5 ml). Chromatography (25 % EtOAc in hexane) afforded **3c** as a colourless oil (198 mg, 95 % yield).

$[\alpha]_D^{20}$ = –32.6, (DCM, *c* = 0.65); ν_{max} 3012 (Ar), 1737 (2 x C=O, ester and amide), 1676 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H, H-3' + H-4'), 7.16 (m, 2H, H-2'), 5.28 (d, *J* = 8.4 Hz, 1H, H-1), 4.25-4.11 (m, 2H, MeC<u>H</u>$_2$O), 3.89 (dq, *J* = 8.4, 6.4 Hz, 1H, H-1), 2.76 (s, 3H, H-4), 2.02-1.90 (m, 2H, H-b), 1.42 (s, 3H, H-d'), 1.25 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.82 (t, *J* = 7.2 Hz, 3H, H-a), 0.76 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O, ester), 170.8 (C=O, amide), 155.4 (C=O, urea), 136.9 (C-1'), 128.6 (C-3'), 128.2 (C-4'), 127.1 (C-2'), 60.6 (Me<u>C</u>H$_2$O), 60.5 (C-1), 55.5 (C-c), 54.4 (C-2), 29.0 (C-b), 28.3 (C-4), 21.0 (C-d'), 15.1 (C-3), 14.3 (<u>Me</u>CH$_2$O), 9.1 (C-a); HRMS (ES): *m/z* calc. 347.1971 $C_{19}H_{27}N_2O_4$, $[M + H]^+$ requires 347.1967.

(*2S*)-Ethyl 2-((4'*S*,5'*R*)-1'-carbonyl-3',4'-dimethyl-5'-phenylimidazolidin-2'-one)-2-ethylpent-4-enoate (3d)

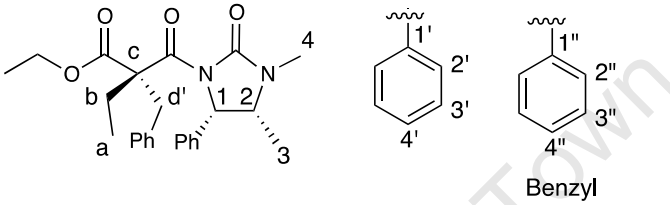


Following the procedure outlined above: **2c** (200 mg, 0.602 mmol), KHMDS (1.57 ml, 0.783 mmol, 1.3 eq, 0.5 M) and allyl iodide (0.17 ml, 1.806 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (25 % EtOAc in hexane) afforded **3d** as a colourless oil (203 mg, 92 % yield).

The diastereomeric ratio of the purified product was determined to be 95 : 5 by chiral HPLC analysis (Chiracel OD, 95 : 5 hexanes : *i*-PrOH, 1 mL/min, λ = 254 nm, $(\text{retention time})_{major}$ = 8.23 min, $(\text{retention time})_{minor}$ = 9.56 min; $[\alpha]_D^{20}$ = –23.6, (DCM, *c* = 1.0); ν_{max} 3010 (Ar), 2987 (alkene), 1737 (2 x C=O, ester and amide), 1675 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.19 (m, 2H, H-2'), 5.49-5.37 (m, 1H, H-e'), 5.32 (d, *J* = 8.4 Hz, 1H, H-1), 5.00-4.94 (m, 1H, H-f'), 4.91-4.85 (m, 1H, H-f'), 4.25-4.11 (m, 2H, MeC<u>H</u>$_2$O), 3.91 (dq, *J* = 8.4, 6.4 Hz, H-2), 2.93-2.85 (m, 1H, H-d'), 2.78 (s, 3H, H-4), 2.74-2.68 (m, 1H, H-d'), 2.00 (q, *J* = 7.6 Hz, 2H, H-b), 1.26 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 0.81 (t, *J* = 7.6 Hz, 3H, H-a), 0.79 (d, *J* =

7.6 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O, ester), 169.8 (C=O, amide), 155.3 (C=O, urea), 136.7 (C-1'), 133.3 (C-e'), 128.5 (C-3'), 128.2 (C-4'), 127.3 (C-2'), 118.0 (C-f'), 60.6 (Me<u>C</u>H_2O), 60.5 (C-1), 58.8 (C-c), 54.4 (C-2), 37.5 (C-d'), 28.3 (C-4), 26.0 (C-b), 15.1 (C-3), 14.4 (<u>Me</u>CH_2O), 8.7 (C-a); HRMS (ES): *m/z* calc. 373.2127 $C_{21}H_{29}N_2O_4$, $[M + H]^+$ requires 373.2126.

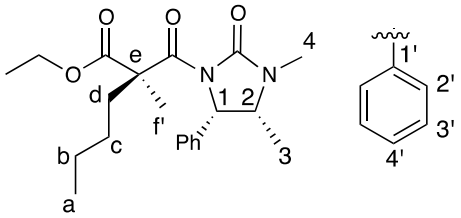
(2*S*)-Ethyl 2-benzyl-2-((4'*S*,5'*R*)-1'-carbonyl-3',4'-dimethyl-5'-phenylimidazolidin-2'-one)butanoate (3e)



Following the procedure outlined above: **2c** (200 mg, 0.602 mmol), KHMDS (1.57 ml, 0.783 mmol, 1.3 eq, 0.5 M) and benzyl bromide (0.21 ml, 1.806 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (25 % EtOAc in hexane) afforded **3e** as a colourless solid (219 mg, 89 % yield). Compound **3e** was recrystallised to a constant Mp and characterised.

Mp 107-110 °C; $[\alpha]_D^{20}$ = –42.0, (DCM, *c* = 0.8); ν_{max} (cm^{-1}) 3008 (Ar), 2998 (Bn), 1739 (2 x C=O, ester and amide), 1635 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H, H-3' + H-4'), 7.25 (m, 2H, H-2'), 7.07 (m, 1H, H-4"), 6.98 (m, 2H, H-3"), 6.84 (m, 2H, H-2"), 5.37 (d, *J* = 8.5 Hz, 1H, H-1), 4.04 (q, *J* = 9.6 Hz, 2H, MeC<u>H_2</u>O), 3.95 (dq, *J* = 8.5, 6.6 Hz, 1H, H-2), 3.37 (bs, 2H, H-d'), 2.81 (s, 3H, H-4), 1.98-1.89 (m, 2H, H-b), 1.12 (t, *J* = 9.6 Hz, 3H, <u>Me</u>CH_2O), 0.87 (t, *J* = 7.5 Hz, 3H, H-a), 0.86 (d, *J* = 6.6 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O, ester), 169.9 (C=O, amide), 155.6 (C=O, urea), 137.12 (C-1), 136.7 (C-1"), 130.7 (C-2"), 128.6 (C-3'), 128.2 (C-4'), 128.0 (C-2'), 127.8 (C-3"), 126.41 (C-4"), 61.0 (Me<u>C</u>H_2O), 60.5 (C-1), 55.4 (C-c), 54.7 (C-2), 39.5 (C-d'), 28.36 (C-4), 26.65 (C-b), 15.1 (C-3), 14.1 (<u>Me</u>CH_2O), 9.1 (C-a); anal. calc. $C_{25}H_{30}N_2O_4$ (%): C, 71.07; H, 7.16; N, 6.63. Found (%): C, 70.81; H, 6.99; N, 6.67.

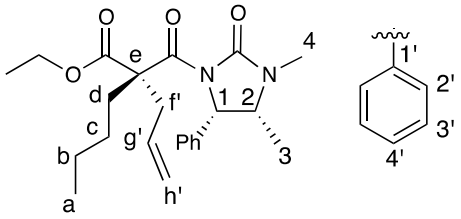
(2*R*)-Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)-2-methylhexanoate (3f)



Following the procedure outlined above: **2d** (200 mg, 0.555 mmol), KHMDS (1.44 ml, 0.721 mmol, 1.3 eq, 0.5 M) and iodomethane (0.10 ml, 1.665 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (20 % EtOAc in hexane) afforded **3f** as a colourless oil (283 mg, 88 % yield).

The diastereomeric ratio of the purified product was determined to be 97 : 3 by chiral HPLC analysis (Chiracel OD, 95 : 5 hexanes : *i*-PrOH, 1 mL/min, λ = 254 nm, (retention time)$_{major}$ = 7.12 min, (retention time)$_{minor}$ = 8.01 min; $[\alpha]_D^{20}$ = –40.5, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3010 (Ar), 1739 (2 x C=O, ester and amide), 1677 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.17 (m, 2H, H-2'), 5.30 (d, *J* = 8.4 Hz, 1H, H-1), 4.20 (m, 2H, MeC$\underline{H_2}$O), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.78 (s, 3H, H-4), 1.92 (m, 2H, H-d), 1.45 (s, 3H, H-f'), 1.37-1.80 (m, 3H, 1H-c + H-b), 1.27 (t, *J* = 6.8 Hz, 3H, $\underline{Me}CH_2O$), 1.10-1.00 (m, 1H, 1H-c), 0.86 (t, *J* = 7.2 Hz, 3H, H-a), 0.78 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O, ester), 170.9 (C=O, amide), 155.3 (C=O, urea), 136.8 (C-1'), 128.6 (C-3'), 128.2 (C-4'), 127.0 (C-2'), 60.7 (Me$\underline{C}H_2O$), 60.5 (C-1), 55.0 (C-e), 54.4 (C-2), 35.8 (C-d), 28.3 (C-4), 26.7 (C-c), 23.2 (C-b), 21.6 (C-f'), 15.1 (C-3), 14.3 ($\underline{Me}CH_2O$), 14.1 (C-a). HRMS (ES): *m/z* calc. 375.2284 $C_{21}H_{31}N_2O_4$, $[M + H]^+$ requires 374. 2286.

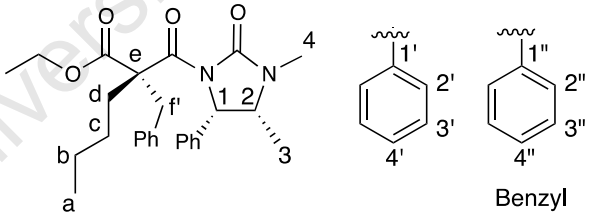
(2*S*)-Ethyl 2-allyl-2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)hexanoate (3g)



Following the procedure outlined above: **2d** (200 mg, 0.555 mmol), KHMDS (1.44 ml, 0.721 mmol, 1.3 eq, 0.5 M) and allyl iodide (0.15 ml, 1.665 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (20 % EtOAc in hexane) afforded **3g** as a colourless solid (189 mg, 85 % yield). Compound **3g** was recrystallised to a constant Mp and characterised.

Mp 88-90 °C; $[\alpha]_D^{20}$ = 30.2, (DCM, *c* = 0.8); ν_{max} (cm^{-1}) 3009 (Ar), 2989 (alkene), 1738 (2 x C=O, ester and amide), 1674 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.20 (m, 2H, H-2'), 5.49-5.40 (m, 1H, H-g'), 5.31 (d, *J* = 8.4 Hz, 1H, H-1), 5.00-4.95 (m, 1H, H-h'), 4.90-4.87 (m, 1H, H-h'), 4.25-4.09 (m, 2H, Me$\underline{C}H_2$O), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.90-2.89 (m, 1H, H-f'), 2.79 (s, 3H, H-4), 2.75-2.69 (m, 1H, H-f'), 2.00-1.92 (m, 2H, H-d), 1.35-1.19 (m, 3H, H-b + 1H-c), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2$O), 1.08-0.98 (m, 1H, 1H-c), 0.86 (t, *J* = 7.2 Hz, 3H, H-a), 0.79 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.0 (C=O, amide), 155.3 (C=O, urea), 136.7 (C-1'), 133.4 (C-g'), 128.5 (C-3'), 128.2 (C-4'), 127.3 (C-2'), 118.0 (C-h'), 60.6 (Me$\underline{C}H_2$O), 60.5 (C-1), 58.4 (C-e), 54.4 (C-1), 38.1 (C-f'), 32.8 (C-d), 28.3 (C-4), 26.3 (C-c), 23.1 (C-b), 15.1 (C-3), 14.4 ($\underline{Me}CH_2$O), 14.1 (C-a); anal. calc. $C_{23}H_{32}N_2O_4$ (%):C, 68.53; H, 8.05; N, 6.99. Found (%): C, 68.53; H, 7.89; N, 7.00.

(2*S*)-Ethyl 2-benzyl-2-((4'*S*,5'*R*)-3',4'-dimethyl-2-oxo-5'-phenylimidazolidine-1-carbonyl)hexanoate (3h)

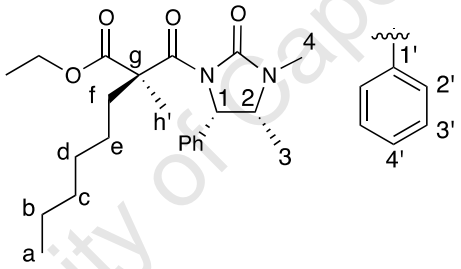


Following the procedure outlined above: **2d** (200 mg, 0.555 mmol), KHMDS (1.44 ml, 0.721 mmol, 1.3 eq, 0.5 M) and benzyl bromide (0.20 ml, 1.665 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (20 % EtOAc in hexane) afforded **3h** as a colourless oil (163 mg, 84 % yield).

The diastereomeric ratio of the purified product was determined to be 99 : 1 by chiral HPLC analysis (Chiracel OD, 95 : 5 hexanes : *i*-PrOH, 1 mL/min, λ = 254 nm, $(\text{retention time})_{major}$ = 7.58 min, $(\text{retention time})_{minor}$ = 8.31 min; $[\alpha]_D^{20}$ = –10.7, (DCM, *c* = 2.3); ν_{max} (cm^{-1}) 3111 (Ar), 3002 (Bn), 1737 (2 x C=O, ester and amide), 1674 (C=O, urea); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.34 (m, 3H, H-3' + H-4'), 7.26 (m, 2H, H-2'), 7.07 (m, 1H, H-4"), 6.99 (m, 2H, H-3"), 6.82 (m, 2H, H-2"), 5.36 (d, *J* = 8.4 Hz, 1H, H-1), 4.04 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 3.95 (dq, *J* = 8.4, 6.8 Hz, 1H, H-2), 3.38 (bs, 2H, H-f'), 2.81 (s, 3H, H-4), 1.87-1.77 (m, 2H, H-d), 1.42-1.30 (m, 1H, 1H-c), 1.29-1.20 (m, 2H, H-b), 1.12 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 1.10-1.05 (m, 1H, 1H-c), 0.87 (t, *J* = 6.8 Hz, 3H, H-a), 0.85 (d, *J* = 7.2 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.1 (C=O, amide), 155.5 (C=O, urea), 137.0 (C-1), 136.6 (C-1"), 130.6 (C-2"), 128.5 (C-3'), 128.2 (C-4'), 127.8 (C-2' + C-3"), 126.4 (C-4"), 60.8 (Me<u>C</u>H$_2$O), 60.5 (C-1), 59.9 (C-e), 54.5 (C-2), 39.7 (C-f'), 33.1 (C-d), 28.4 (C-4), 26.7 (C-c), 23.1 (C-b), 15.1 (C-3), 14.1 (<u>Me</u>CH$_2$O), 14.1 (C-a); HRMS (ES): *m/z* calc. 451.2590 $C_{27}H_{35}N_2O_4$, $[M + H]^+$ requires 450. 2593.

(2*R*)-Ethyl 2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)-2-methyloctanoate (3i)

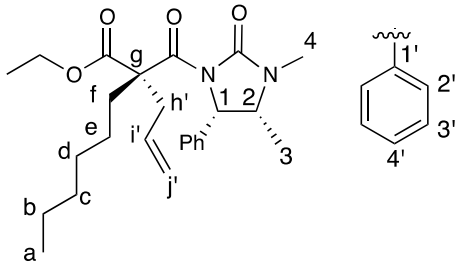


Following the procedure outlined above: **2e** (200 mg, 0.515 mmol), KHMDS (1.34 ml, 0.669 mmol, 1.3 eq, 0.5 M) and iodomethane (0.10 ml, 1.544 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (15 % EtOAc in hexane) afforded **3i** as a colourless oil (187 mg, 90 % yield).

$[\alpha]_D^{20}$ = –47.0, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3011 (Ar), 1735 (2 x C=O, ester and amide), 1675 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.17 (m, 2H, H-2'), 5.29 (d, *J* = 8.4 Hz, 1H, H-1), 4.26-4.12 (m, 2H, MeC<u>H</u>$_2$O), 3.90 (dq, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.78 (s, 3H, H-4), 1.98-1.85 (m, 2H, H-f), 1.45 (s, 3H, H-h'), 1.38-1.31 (m, 1H, 1H-e), 1.27 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 1.26-1.22 (m, 6H, H-b to H-d), 1.13-0.98 (m, 1H, 1H-e), 0.85 (t, *J* = 6.8 Hz, 3H, H-a), 0.78 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O, ester), 170.9 (C=O, amide), 155.3 (C=O, urea), 136.8 (C-1'), 128.6 (C-3'), 128.2 (C-4'), 127.0 (C-2'), 60.7 (Me<u>C</u>H$_2$O), 60.5 (C-1), 55.1 (C-g), 54.4 (C-2), 36.0 (C-f), 31.7 (C-d), 29.7 (C-c), 28.3 (C-4),

24,4 (C-e), 22.7 (C-b), 21.6 (C-h'), 15.1 (C-3), 14.3 (MeCH$_2$O), 14.2 (C-a); HRMS (ES): *m/z* calc. 403.2587 $C_{23}H_{35}N_2O_4$, $[M + H]^+$ requires 403.2590.

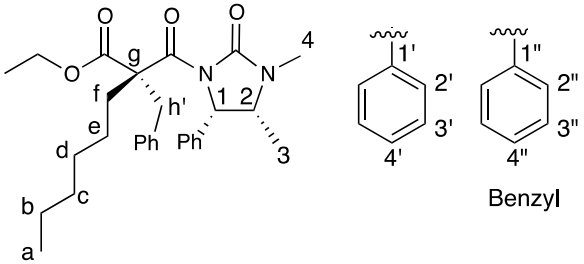
(2*S*)-Ethyl 2-allyl-2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)octanoate (3j)



Following the procedure outlined above: **2e** (200 mg, 0.515 mmol), KHMDS (1.34 ml, 0.669 mmol, 1.3 eq, 0.5 M) and allyl iodide (0.14 ml, 1.544 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (15 % EtOAc in hexane) afforded **3j** as a colourless oil (192 mg, 87 % yield).

The diastereomeric ratio of the purified product was determined to be > 99 : 1 by chiral HPLC analysis (Chiracel OD, 95 : 5 hexanes : *i*-PrOH, 1 mL/min, λ = 254 nm, (retention time)$_{major}$ = 11.21 min, (retention time)$_{minor}$ = 11.56 min; $[\alpha]_D^{20}$ = –27.2, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3010 (Ar), 2988 (alkene), 1735 (2 x C=O, ester and amide), 1674 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H-3' + H-4'), 7.18 (m, 2H, H-2'), 5.50-5.41 (m, 1H, H-i'), 5.31 (d, *J* = 8.4 Hz, 1H, H-1), 5.00-4.96 (m, 1H, H-j'), 4.91-4.87 (m, 1H, H-j'), 4.24-4.11 (m, 2H, MeC<u>H</u>$_2$O), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.96-2.88 (m, 1H, H-h'), 2.79 (s, 3H, H-4), 2.76-2.69 (m, 1H, H-h'), 1.97-1.88 (m, 2H, H-f), 1.28-1.22 (m, 7H, H-b to H-d + 1H-e), 1.26 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 1.19-1.00 (m, 1H, 1H-e), 0.85 (t, *J* = 6.8 Hz, 3H, H-a), 0.80 (d, *J* = 6.4 Hz, 3H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.0 (C=O, amide), 155.3 (C=O, urea), 136.7 (C-1'), 133.4 (C-i'), 128.5 (C-3'), 128.2 (C-4'), 127.3 (C-2'), 118.0 (C-j'), 60.6 (Me<u>C</u>H$_2$O), 60.5 (C-1), 58.4 (C-g), 54.4 (C-2), 38.1 (C-h'), 33.0 (C-f), 31.7 (C-d), 29.6 (C-c), 28.3 (C-4), 24.0 (C-e), 22.7 (C-b), 15.1 (C-3), 14.4 (<u>Me</u>CH$_2$O), 14.2 (C-a). HRMS (ES): *m/z* calc. 429.2753 $C_{25}H_{37}N_2O_4$, $[M + H]^+$ requires 429.2762.

(2*S*)-Ethyl 2-benzyl-2-((4'*S*,5'*R*)-3',4'-dimethyl-2'-oxo-5'-phenylimidazolidine-1'-carbonyl)octanoate (3k)



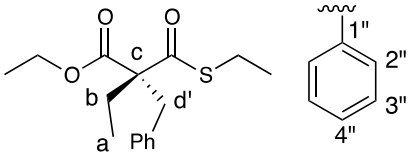
Following the procedure outlined above: **2e** (200 mg, 0.515 mmol), KHMDS (1.34 ml, 0.669 mmol, 1.3 eq, 0.5 M) and benzyl bromide (0.18 ml, 1.544 mmol, 3.0 eq) were reacted in THF (1.5 ml). Chromatography (15 % EtOAc in hexane) afforded **3k** as a colourless oil (202 mg, 82 % yield).

The diastereomeric ratio of the purified product was determined to be > 99 : 1 by chiral HPLC analysis (Chiracel OD, 95 : 5 hexanes : *i*-PrOH, 1 mL/min, λ = 254 nm, (retention time)$_{major}$ = 11.45 min, (retention time)$_{minor}$ = 12.36 min; $[\alpha]_D^{20}$ = 3.2, (DCM, *c* = 2.1); ν_{max} (cm^{-1}) 3013 (Ar), 1739 (2 x C=O, ester and amide), 1677 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H, H-3' + H-4'), 7.26 (m, 2H, H-2'), 7.07 (m, 1H, H-4"), 6.99 (m, 2H, H-3"), 6.82 (m, 2H, H-2"), 5.36 (d, *J* = 8.4 Hz, 1H, H-1), 4.04 (q, *J* = 7.2 Hz, 2H, MeC$\underline{H}_2$O), 3.94 (dq, *J* = 8.4, 6.6 Hz, 1H, H-1), 3.38 (bs, 2H, H-h'), 2.81 (s, 3H, H-4), 1.90-1.80 (m, 2H, H-f), 1.42-1.35 (m, 1H, H-e), 1.30-1.20 (m, 6H, H-b to H-d), 1.11 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 1.16-1.08 (m, 1H, 1H-e), 0.86 (d, *J* = 6.6 Hz, 3H, H-3), 0.85 (t, *J* = 6.8 Hz, 3H, H-a); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.0 (C=O, amide), 155.5 (C=O, urea), 137.0 (C-1'), 136.6 (C-1"), 130.6 (C-2"), 128.5 (C-3'), 128.2 (C-4'), 127.8 (C-2' + C-3"), 126.4 (C-4"), 60.8 (Me$\underline{C}H_2$O), 60.5 (C-1), 60.0 (C-g), 54.5 (C-2), 39.7 (C-h'), 33.2 (C-f), 31.8 (C-d), 29.6 (C-c), 28.4 (C-4), 24.4 (C-e), 22.7 (C-b), 15.1 (C-3), 14.2 ($\underline{Me}CH_2O$), 14.1 (C-a). HRMS (ES): *m/z* calc. 479.2910 $C_{29}H_{39}N_2O_4$, $[M + H]^+$ requires 479.2916.

5.7. The CA cleavage via thioester synthesis

A representative typical procedure described below was followed for CA cleavage via the thioester synthesis:

(2*S*)-Ethyl 2-benzyl-2-((ethylthio)carbonyl)butanoate (4a)

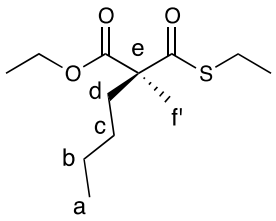


Benzyl

To a suspension of ethanethiol (0.18 ml, 2.49 mmol, 10.5 eq) in THF (2.0 ml) at –78 °C was slowly added *n*-BuLi (0.94 ml, 2.37 mmol, 10 eq, 2.5 M). After 30 min, a solution of **3e** (100 mg, 0.237 mmol) in THF (1.5 ml) was slowly added to the reaction mixture at –78 °C and the contents allowed to gradually warm up to rt over 1 hr. Thereafter, the reaction mixture was warmed to 40 °C and stirred at this temperature for 5 hrs. The contents were cooled to rt and quenched with sat. $NaHCO_3$ (15 ml), extracted with DCM (3 x 20 ml), the organic extracts combined and dried over $MgSO_4$. Following the removal of organic solvent under reduced pressure, the crude residue was purified by column chromatography using (5 % EtOAc in hexane) to afford **4a** as a yellowish liquid (60 mg, 82 %).

$[\alpha]_D^{20}$ = –17.5, (DCM, *c* = 1.2); ν_{max} (cm^{-1}) = 3109 (Ar), 2999 (Bn), 1742 (C=O, ester), 1691 (C=O, thioester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 3H, H-3" + H-4"), 7.10 (m, 2H, H-2"), 4.27-4.13 (m, 2H, MeC$\underline{H}_2$O), 3.33 (d, *J* = 14.4 Hz, 1H, H-d'), 3.27 (d, *J* = 14.4 Hz, 1H, H-d'), 2.92 (q, *J* = 7.2 Hz, 2H, MeC$\underline{H}_2$S), 1.95-1.87 (m, 2H, H-b), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 1.26 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2S$), 0.94 (t, *J* = 7.2 Hz, 3H, H-a); ^{13}C NMR δ (101 MHz, $CDCl_3$) 199.2 (C=O, thioester), 171.1 (C=O, ester), 136.2 (C-1"), 130.1 (C-2"), 128.3 (C-3"), 127.0 (C-4"), 66.4 (C-c), 61.6 (Me$\underline{C}H_2$O), 37.5 (C-d'), 24.9 (C-b), 23.7 (Me$\underline{C}H_2$S), 14.6 ($\underline{Me}CH_2O$), 14.1 ($\underline{Me}CH_2S$), 8.51 (C-a); HRMS (ES): *m/z* calc. 295.1363 $C_{16}H_{23}O_3S$, $[M + H]^+$ requires 295.1370.

(2*R*)-Ethyl 2-((ethylthio)carbonyl)-2-methylhexanoate (4b)

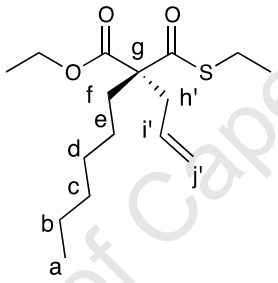


Following the procedure outlined above, ethane thiol (0.20 ml, 2.804 mmol, 10.5 eq), *n*-BuLi (1.07 ml, 2.67 mmol, 2.5 M, 10.0 eq), **3f** (100 mg, 0.267 mmol) were reacted in THF (3.5 ml).

After 2 hrs at 40 °C the reaction was complete. The crude was purified by column chromatography using (5 % EtOAc in hexane) to obtain **4b** as a clear liquid (53 mg, 77 %).

$[\alpha]_D^{20}$ = –1.5, (DCM, *c* = 1.2); ν_{max} (cm^{-1}) 1740 (C=O, ester), 1689 (C=O, thioester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 2.88 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$S), 2.00-1.79 (m, 2H, H-d), 1.44 (s, 3H, H-f), 1.36-1.28 (m, 2H, H-b), 1.25 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 1.24 (t, *J* = 7.2 Hz, 3H, MeC<u>H</u>$_2$S), 1.27-1.12 (m, 2H, H-c), 0.90 (t, *J* = 6.8 Hz, H-a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C=O, thioester), 172.1 (C=O, ester), 61.5 (Me<u>C</u>H$_2$O), 61.2 (C-e), 35.8 (C-d), 26.5 (C-c), 23.6 (Me<u>C</u>H$_2$S), 23.2 (C-b), 20.0 (C-f'), 14.6 (<u>Me</u>CH$_2$O), 14.1 (<u>Me</u>CH$_2$S), 14.0 (C-a).

(2*S*)-Ethyl 2-allyl-2-((ethylthio)carbonyl)octanoate (4c)

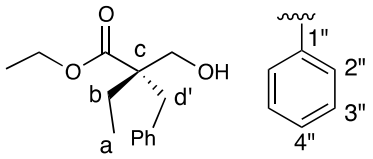


Following the procedure outlined above: ethanethiol (0.18 ml, 2.450 mmol, 10.5 eq) *n*-BuLi (0.93 ml, 2.33 mmol, 2.5 M, 10.0 eq) **3i** (100 mg, 0.233 mmol) were used. After 4 hrs at 40 °C the reaction was found to be complete. The crude mixture was purified by column chromatography using (5 % EtOAc in hexane) to obtain **4c** as a brownish liquid (66 mg, 89 %).

$[\alpha]_D^{20}$ = –5.9, (DCM, *c* = 1.2); ν_{max} (cm^{-1}) 2985 (alkene), 1741 (C=O, ester), 1689 (C=O, thioester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65-5.57 (m, 1H, H-i'), 5.12-5.04 (m, 2H, H-j'), 4.18 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$O), 2.90 (q, *J* = 7.2 Hz, 2H, MeC<u>H</u>$_2$S), 2.72-2.70 (m, 2H, H-h'), 1.93 (m, 2H, H-f), 1.30-1.21 (m, 7H, H-b + 1H-c to H-e), 1.25 (t, *J* = 7.2 Hz, 3H, <u>Me</u>CH$_2$O), 1.24 (t, *J* = 7.2 Hz, 3H, MeC<u>H</u>$_2$S), 1.18-1.09 (m, 1H, 1H-c), 0.87 (t, *J* = 6.8 Hz, 3H, H-a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (C=O, thioester), 171.1 (C=O, ester), 132.4 (C-i'), 119.1 (C-j'), 64.7 (C-g'), 61.5 (Me<u>C</u>H$_2$O), 36.9 (C-h'), 32.3 (C-f), 31.6 (C-e), 29.6 (C-d), 23.6 (C-c), 23.6 (Me<u>C</u>H$_2$S), 22.7 (C-b), 14.7 (<u>Me</u>CH$_2$O), 14.1 (<u>Me</u>CH$_2$S), 14.1 (C-a).

5.8. Reduction via a Fukuyama protocol

(2*S*)-Ethyl 2-benzyl-2-(hydroxymethyl)butanoate (6a)



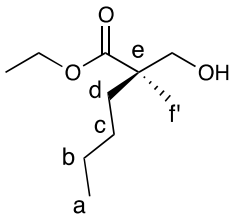
Benzyl

A reaction flask with Pd/C (5.4 mg, 0.051 mmol, 0.30 eq) was purged with argon for 10 min and dry THF (1.0 ml) added. To this suspension was slowly added a solution of **4a** (50 mg, 0.170 mmol) in THF (1.5 ml) followed by triethylsilane (0.09 ml, 0.509 mmol, 3.0 eq) and the contents allowed to stir at rt. After 2 hrs, the contents were diluted with EtOAc (10 ml), filtered through Celite under reduced pressure, washed with EtOAc (2 x 20 ml) and the organic extracts concentrated *in vacuo*. Aldehyde **5a** was pure enough by ^{1}H NMR spectroscopy to be used without further purification in the next step.

$NaBH_4$ (32 mg, 0.85 mmol, 5.0 eq) was suspended in dry THF (1.0 ml) at 0 °C under nitrogen. To this solution was slowly added the crude mixture of **5a** (40 mg, 0.170 mmol) in THF (1.5 ml) at the same temperature. After 2 hrs the reaction mixture was slowly quenched with HCl (1.0 M, 10 ml), extracted with DCM (3 x 15 ml), the organic extracts dried over $MgSO_4$, which were filtered under reduced pressure and concentrated *in vacuo*. The crude residue was purified by column chromatography (20 % EtOAc in hexane) to afford the alcohol (**6a**, 26 mg, 66 % over two steps) as a clear oil.

$[\alpha]_D^{20}$ = –21.9, (DCM, *c* = 0.9); ν_{max} (cm^{-1}) 3339 (OH), 3112 (Ar), 3002 (Bn), 1730 (C=O, ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H, Ph), 4.24-4.12 (m, 2H, MeC$\underline{H}_2$O), 3.71 (d, *J* = 11.2 Hz, 1H, C$\underline{H}_2$OH), 3.51 (d, *J* = 11.2 Hz, 1H, C$\underline{H}_2$OH), 3.08 (d, *J* = 13.4 Hz, 1H, H-d'), 2.86 (d, *J* = 13.4 Hz, 1H, H-d'), 2.15 (bs, 1H, OH), 1.75-1.65 (m, 1H, H-b), 1.51-1.42 (m, 1H, H-b), 1.27 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 0.91 (t, *J* = 7.2 Hz, 3H, H-a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3 (C=O, ester), 137.2 (C-1), 130.5 (C-2), 128.3 (C-3), 126.7 (C-4), 63.6 ($\underline{C}H_2OH$), 60.7 (Me$\underline{C}H_2O$), 52.6 (C-c), 39.0 (C-d'), 26.5 (C-b), 14.3 ($\underline{Me}CH_2O$), 8.9 (C-a).

(2*R*)-Ethyl 2-(hydroxymethyl)-2-methylhexanoate (6b)



Thioester **4b** (50 mg, 0.202 mmol) was subjected to the same conditions as **4a**, where Pd/C (5.4 mg, 0.051 mmol, 0.30 eq); **4b** (50 mg, 0.170 mmol); triethylsilane (0.09 ml, 0.509 mmol, 3.0 eq) were used to afford aldehyde **5b** which was subsequently used in the next reaction withouth further purification. The aldehyde **5b** (38 mg, 0.202 mmol) was reduced as before with $NaBH_4$ (39 mg, 1.015 mmol, 5.0 eq) to afford alcohol **6b** (21 mg, 55 % over two steps) as a clear oil.

$[\alpha]_D^{20}$ = –2.6, (DCM, *c* = 1.3); ν_{max} (cm^{-1}) 3337 (OH), 1732 (C=O, ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.2 Hz, 2H, MeC$\underline{H}_2$O), 3.71 (d, *J* = 11.2 Hz, 1H, C$\underline{H}_2$OH), 3.47 (d, *J* = 11.2 Hz, 1H, C$\underline{H}_2$OH), 2.16 (bs, 1H, OH), 1.65-1.51 (m, 2H, H-d), 1.27 (t, *J* = 7.2 Hz, 3H, $\underline{Me}CH_2O$), 1.29-1.18 (m, 4H, H-b + H-c), 1.17 (s, 3H, H-f'), 0.89 (t, *J* = 7.2 Hz, 3H, H-a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4 (C=O, ester), 68.5 ($\underline{C}H_2OH$), 60.7 (Me$\underline{C}H_2O$), 47.8 (C-e), 35.8 (C-d), 26.5 (C-c), 23.3 (C-b), 19.8 (C-f'), 14.4 ($\underline{Me}CH_2O$), 14.0 (C-a); HRMS (ES): *m/z* calc 189.1491 $C_{10}H_{21}O_3$, $[M + H]^+$ requires 189.1496.

Subjecting thioester **4c** to the Fukuyama reduction conditions resulted in the reduction allyl-and the thioester. This was proven by ^{1}H NMR and is discussed in Chapter 3.

Part 3: University of Michigan Research

Chapter 6: Introduction to Lactimidomycin

6.1. Cancer

Cancer is a class of diseases characterised by the uncontrolled growth of abnormal cells that are capable of migrating from one part of the body to another.[39] Such a migration is known as metastasis. Under normal circumstances, a defective or abnormal cell that is 'beyond-repair,' is killed so as to avoid replicating its defective material (during cell division) by a process known as "programmed cell-death" or simply "apoptosis". However, cancerous cells are able to survive and reproduce other cancerous cells because of their ability to elude apoptosis. Cancer is a worldwide challenge that claims millions of lives annually and accounted for 7.6 million deaths in 2008.[40]

Over the past century various chemotherapeutic drugs have been developed and used with success to combat different types of cancer.[41] In particular, natural compounds have been used with great success in the fight against cancer. Examples of natural compounds or derivatives thereof on the market include paclitaxel from the bark of the *pacific yew tree*, camptothecin derivatives from *camptotheca acuminata plant*, daunorubicin from *Streptomyces peucetius* to mention a few.[41]

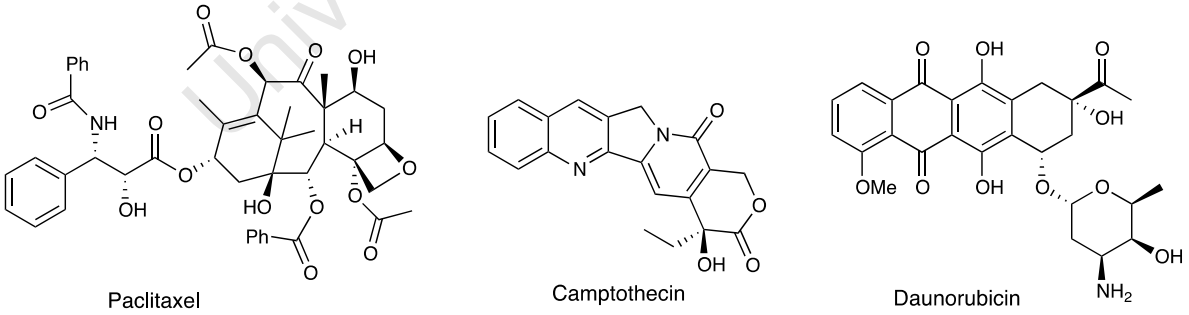


Figure 6.1: Anti-cancer drugs derived from Nature.

6.2. Biosynthesis of the GcP family

A family of glutarimide-containing polyketide (GcP) compounds isolated from *Streptomyces plantesis* have shown to possess potent anti-cancer, anti-tumour, anti-metastasis and anti-

fungal activity.[42] Some of the compounds known to date from this family include lactimidomycin (**a**), iso-migrastatin (**b**), migrastatin (**c**), dorrigocin A (**d**), and dorrigocin B (**e**), **Figure 6.2**. Lactimidomycin was isolated in 1992,[42a] followed by dorrigocin A and B in 1994.[42c] Six years later Imoto *et al* reported the isolation and characterisation of migrastatin,[42d] and thereafter Licari *et al* reported iso-migrastatin in 2002.[42e]

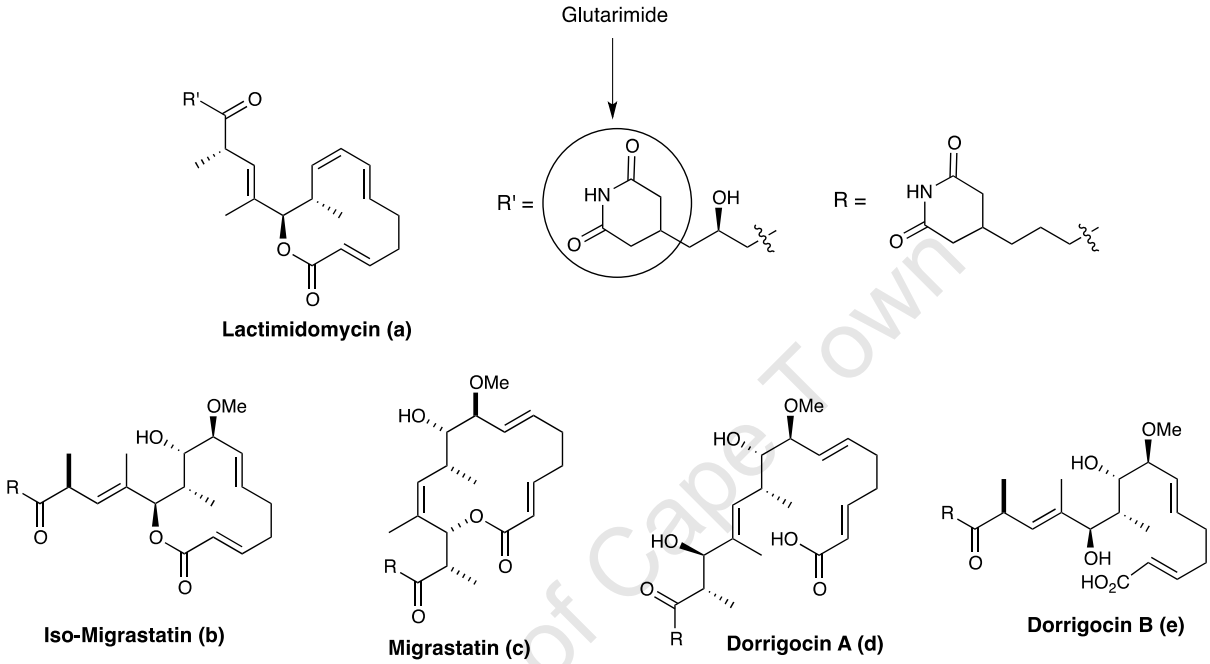


Figure 6.2: Compounds from the GcP family known to date.

Compounds from this family are characterised by the presence of a glutarimide moiety in the side chain, together with an unsaturated cyclic macrolide core (12- or 14-membered ring) or its acyclic version.[42b] In his biosynthesis studies, Shen suggested that (**b)** is the parent natural compound from this family, while the other compounds are shunt metabolites (derivatives).[43] The biological properties as well as the structural relatedness of these compounds has captured great interest in studying this family of compounds as one can potentially synthesise the natural compounds including their analogues by a few transformations from a core intermediate.

6.3. The GcP family as potential anti-metastasis agents

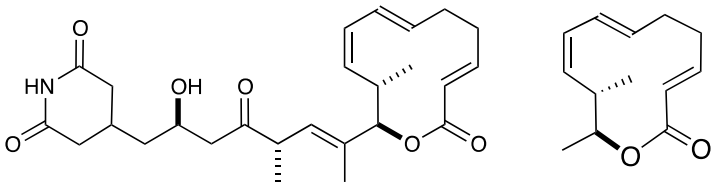
Conventional cancer chemotherapy relies on the cytotoxicity of the therapeutic agent even though studies reveal that the high mortality rate of cancer patients is due to metastatic

lesion of cancerous cells.[44] However, in recent years there has been a shift to address the issue of metastasis, and the GcP compounds have immerged as potential drug leads as anti-metastasis agents. Sugawara *et al* has demonstrated that lactimidomycin exhibits the inhibition of fungal growth and prolongs the survival time of mice with P388 leukaemia.[42a] Also, *in vitro* studies by Shen *et al* indicate that lactimidomycin is a strong migration inhibitor of human MDA-MB-231 (IC_{50} = 0.6 nM) and mouse 4T1 (IC_{50} = 5.03 nM) mammary adenocarcinoma cell lines.[45] In addition, lactimidomycin is a strong inhibitor of eukaryotic translation elongation (IC_{50} = 38 nM), and has a potent antiproliferative effect on tumour cell-lines *in vivo*.[45]

The current research was inspired by Shen's[45] report (2009) that claimed lactimidomycin as one of the most potential anti-metastasis agents, although a recent report by Fürstner[46] (2013) questions the integrity of lactimidomycin as a potential anti-metastasis agent. Thus far, the total synthesis of lactimidomycin has been achieved by Fürstner,[47] Nagorny[48] and Kuwahara,[49] and it is hoped that such research may shed some light on the verification of lactimidomycin's biological activity. Also, Danishefsky has reported the total synthesis of migrastatin and its analogues. [50]

6.4. Aims and Objectives

In view of the biological evidence before Fürstner's 2013 report and before any total synthesis of lactimidomycin had been reported, the Nagorny group sought to design a versatile total synthesis to lactimidomycin such that a rapid synthesis of its analogues could be achieved for biological evaluation. When I joined the Nagorny group in late 2011, the objective was to design a versatile route for analogue synthesis, with the first target analogue being the truncated macrolide **10**, **Figure 6.3**. The interest in the macrolide ring moiety as opposed to the polyketide glutarimide moiety was inspired by Danishefsky's studies on migrastatin (**c**) which revealed that its truncated 14-membered macrolide was more potent than (**c**).[50a]



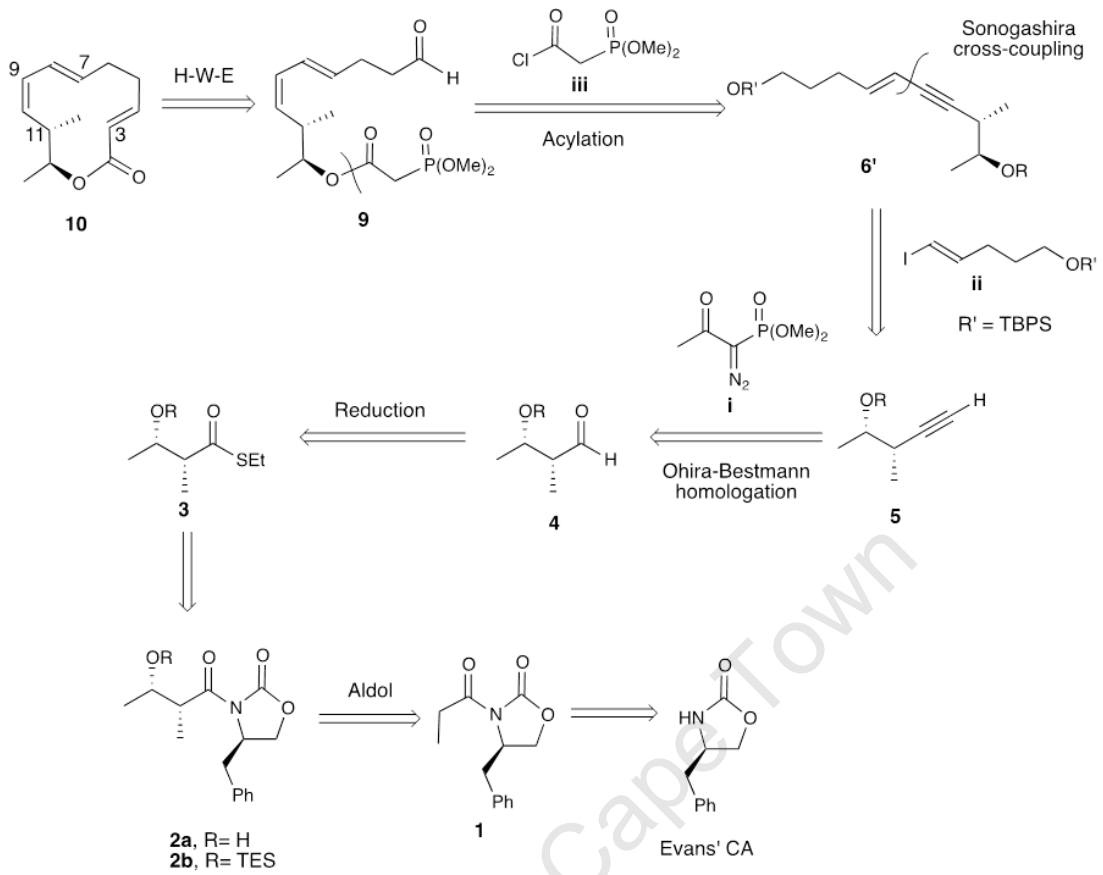
Lactimidomycin (a) **10**

Figure 6.3: Lactimidomycin and its macrolide analogue (**10**).

6.5. Retrosynthetic Analysis of 10

There are three important structural sites in macrolide **10**, which are the *anti*-relationship between C-11 and C-12, the (*E,Z*)-diene, and the *trans*-enone. It was thought that the *anti*-stereochemistry could be synthesised via the Evans' chiral auxiliary (CA) mediated aldol reaction. The (*E,Z*)-diene moiety was envisaged as constructible via a cross-coupling method, while the lactenone should be accessed via an intramolecular Horner-Wadsworth-Emmons (HWE) olefination reaction that would simultaneously cyclise to the macrolide.

Based on these ideas a retrosynthetic analysis identified **10** being disconnected to aldehyde **9**, the HWE precursor, which in turn disconnects to **6'** via a stereoselective reduction using Lindlar's catalyst to obtain the (*E,Z*)-diene, **Scheme 6.2**. Of note was that a chemoselective deprotection of the TES-PG followed by acylation with **iii** needed to be done once **6'** had been reduced to the (*E,Z*)-diene. Compound **6'** disconnects via Sonogashira cross-coupling to alkyne **5'** involving a TBPS-protected *trans*-vinyl iodide (**ii**). Alkyne **5'** was to be accessed via the Ohira-Bestmann homologation of **i** and aldehyde **4** which in turn is a product of Evans' CA cleavage via thioester **3**. Compound **3** can be accessed from an Evans' mediated aldol reaction which establishes the *anti*-relationship between C-11 and C-12.

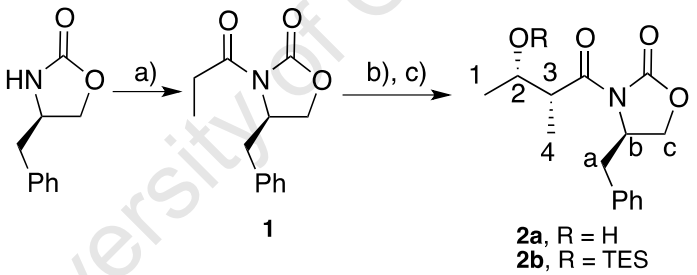


Scheme 6.2: Route 1 retrosynthetic analysis via the Ohira-Bestmann homologation.

Chapter 7: Results and Discussion

7.1. Route 1: synthesis of macrolide 10 via the Ohira-Bestmann homologation

Synthesis towards macrolide **10** commenced with a facile acylation of (*R*)-4-benzyloxazolidin-2-one with propionyl chloride to afford **1** (91 % yield) a known compound, whose spectroscopic characteristics corresponded with literature data.[9b, 51] To install the *anti*-stereochemistry in **10**, an Evans' aldol reaction between **1** and freshly distilled acetaldehyde was utilised to obtain **2a** (75 % yield) as a colourless solid.[9b, 51] Evans' CA-mediated boron-enolate aldol addition reactions are known to go via the well-known chelated Zimmerman-Traxler TS-model (discussed in Chapter 1) to give the Evans *syn*-aldol adduct **2a**, **Scheme 7.1**.[14] The *anti*-aldol adduct was undetectable by both ^{1}H NMR and ^{13}C NMR spectroscopy. Compound **2a** was subsequently protected with a TES-protecting group (PG) to obtain **2b** (94 % yield) as a colourless oil, whose data corresponded with the literature. A TES-PG was chosen because it could be chemosectively removed in the presence of a TBDPS-PG.

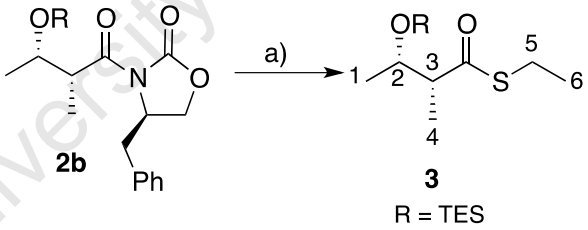


Scheme 7.1: Reaction Conditions- a) *n*-BuLi, propionyl chloride, THF, –78 °C. b) **1**, $Bu_2B(OTf)$, $EtN(i\text{-}Pr)_2$, MeCHO, DCM, –78 °C. c) **2a**, Imidazole, TES-Cl, DCM, 0 °C to rt.

Compounds **1**-**2b** are known compounds and therefore only the spectroscopic data of **2b** will be discussed in detail. The IR bands at 2995 (Ar), 1784 (C=O, carbamate) and 1696 (C=O, amide) were observed for **2b**. The upfield resonances at 0.96 (t, *J* = 7.4 Hz, 9H, TES-Me) and 0.61 (q, *J* = 7.4 Hz, 6H, TES-CH_2) in the ^{1}H NMR spectrum confirmed the TES-PG in **2b**. Two doublets at 1.20 and 1.12 ppm, each integrating for 3-protons were assigned to the methyl groups H-1 and H-4 respectively, while two quintet resonances at 4.25 and 3.91 ppm, each integrating for 1-proton, were assigned to the methine *cis*-protons H-2 and H-3

respectively. The resonances at 7.32 (m, 3H, Ar), 7.24 (m, 2H, Ar), 4.69 (m, 1H, H-b), 4.14 (m, 2H, H-c) and 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H, H-a) and 2.70 (dd, *J* = 13.3, 9.8 Hz, 1H, H-a) confirmed the CA protons. The diastereotopic benzylic protons appeared as a dd due to geminal coupling (*J* = 13.3 Hz) and vicinal coupling (*J* = 9.8, 3.3 Hz). The presence of two carbonyl peaks at 175.5 (C=O, carbamate) and 153.3 (C=O, amide) ppm in the ^{13}C NMR spectrum confirmed the carbonyl groups in **2b**. The resonance peaks in the aromatic region (136.0-128.0 ppm) were assigned to the Ph-carbons while 66.1 (C-2), 55.8 (C-b) and 45.0 (C-3) were assigned to the methine carbons. The resonances at 69.8 (C-c), 40.0 (C-a) and 5.0 (TES-$\underline{C}H_2$) were observed accordingly for the methylene carbons while 21.8 (C-1), 13.0 (C-4), and 7.0 (TES-Me) were observed for the methyl carbons. With the help of HSQC, the TES-$\underline{C}H_2$ was assigned quite upfield, and was reasoned to arise due to shielding effect by the silyl group. The synthesis of **2b** was further confirmed by an HRMS determination in which, HRMS (ES): *m/z* calc. 392.2252 for $C_{21}H_{34}NO_4Si$, $[M+H]^+$ requires 392.2261.

Now that the desired stereochemistry had been installed in **2b**, the cleavage of the CA was pursued of which a plethora of reactions were available.[52] In this research the CA was cleaved via the EtSLi S_NAc reaction to give the thioester **3** in good yield (93 %) with a 90 % recovery of the CA.[35, 53]

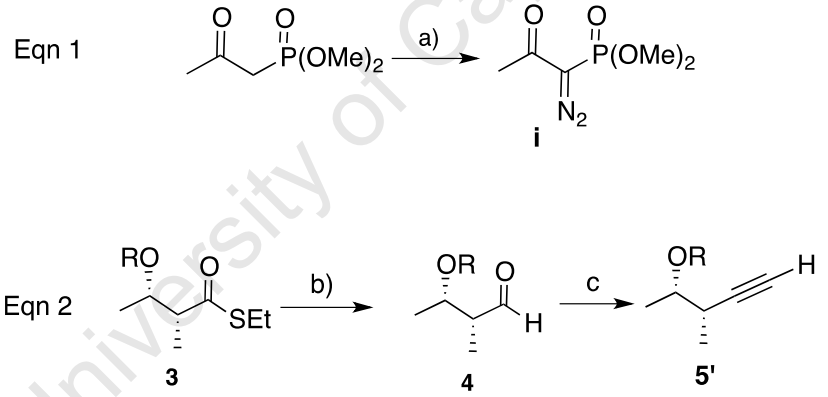


Scheme 7.2: Reaction conditions- a) i) *n*-BuLi, EtSH, THF, –78 °C; ii) **2b**, THF, –78 to –50 °C.

The disappearance of the 1784 (C=O, carbamate) and 1696 (C=O, amide) IR bands accompanied by the appearance of a 1688 (C=O thioester) band confirmed the facile cleavage of the CA. The thioethyl resonances observed at 2.85 (q, *J* = 7.4 Hz, 2H, H-5) and 1.24 (t, *J* = 7.4 Hz, 3H, H-6) in the ^{1}H NMR spectrum as well as the disappearance of the CA resonances at the respective chemical shifts confirmed **3**. Also, in the ^{13}C NMR spectrum the thioester carbonyl observed at 202.6 ppm accompanied by the disappearance of the 175.5 (C=O, carbamate) and 153.3 (C=O, amide). The thioethyl resonances were observed

at 23.4 (C-5) and 22.4 (C-6) with the disappearance of the CA carbons resonances, while all the other resonances were assigned similarly as before in both the ^{1}H NMR and ^{13}C NMR spectrum. A HRMS determination further confirmed product **3**, HRMS (ES): *m/z* calc. 276.1652 for $C_{13}H_{29}O_2SSi$, $[M + H]^+$ requires 276.1657.

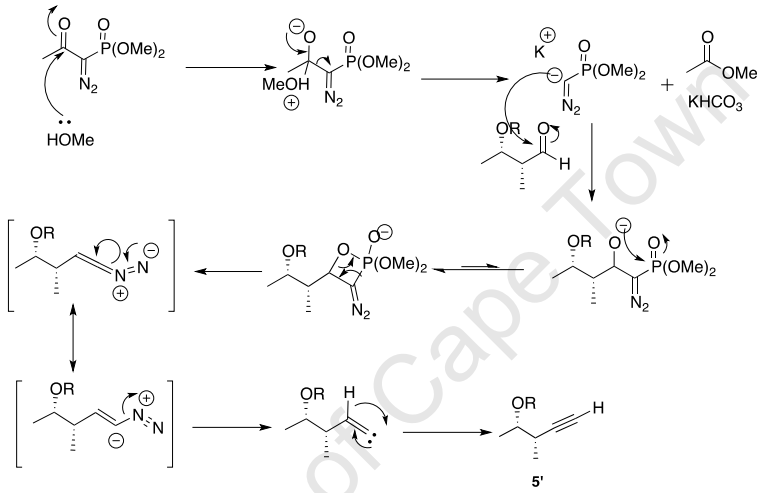
The Ohira-Bestmann reagent **i** was readily accessed via an azide transfer reaction between *p*-tosyl azide and dimethyl (2-oxopropyl)phosphonate and was obtained in 60 % yield, **Scheme 7.3** (Eqn 1).[54] With the Ohira-Bestmann reagent in hand, **3** was subjected to DIBAL reduction to afford aldehyde **4**, which was subsequently used without further purification with the Ohira-Bestmann homologation conditions (Eqn 2), **Scheme 7.3**. The alkyne TLC profile showed several spots which made the isolation of the product difficult to achieve. To try and improve the TLC profile various reaction conditions were sought including increasing the equivalents of **i**, lowering the reaction temperature, purifying the aldehyde (**4**, 60 % yield) and so on but unfortunately this did not improve the outcome.



Scheme 7.3: Reaction condition- a) *p*-$TosN_3$, NaH, THF, 0 °C. b) DIBAL-H, DCM, –78 °C. c) K_2CO_3, **i**, MeOH, rt.

The Ohira-Bestmann homologation is an improvement on the Seyferth-Gilbert homologation and uses dimethyl (1-diazo-2-oxopropyl)phosphonate (DOPP) as opposed to the dimethyl (diazomethyl)phosphonate (DAMP) used in the Seyferth-Gilbert protocol.[55] The Seyferth-Gilbert homologation provides synthesis to alkynes via deprotonation of DAMP with a strong base (such as *t*-BuOK) to form a DAMP anion which adds to the aldehyde. By comparison, the Ohira-Bestmann modification uses DOPP and a mild base (K_2CO_3) to generate the DAMP anion. In such a way the Ohira-Bestmann modification

allows the conversion of base-labile substrates such as enolisable aldehydes, which tend to undergo aldol-condensation under the Seyferth-Gilbert conditions.[56] During the Ohira-Bestmann homologation, methanol (a relatively weak nucleophile) is thought to do a S_NAc reaction with **i** in the presence of K_2CO_3 to give the resonance-stabilised DAMP anion which then adds to the aldehyde, **Scheme 7.4**. This is followed by an intramolecular addition to the electrophilic phosphonate ester by the alkoxide to form a Wittig-type oxaphosphetane intermediate that eliminates to form the diazo alkene. This intermediate then loses N_2 to afford a carbene, which rapidly rearranges to the alkyne.

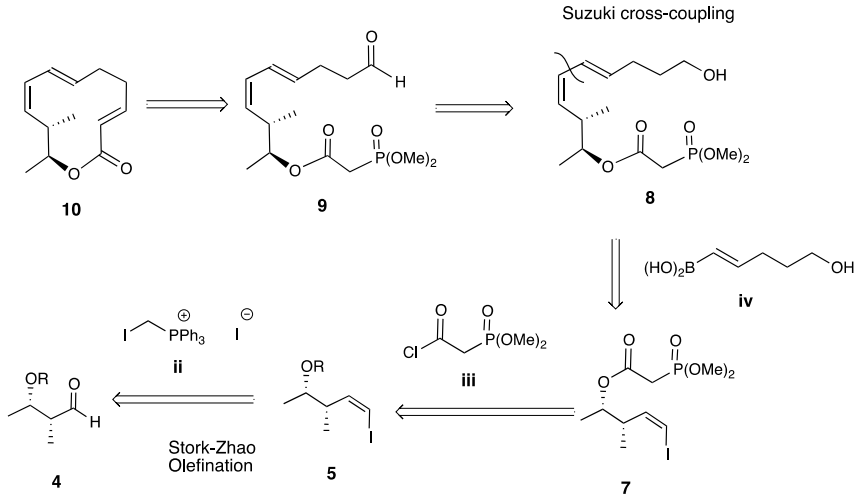


Scheme 7.4: Ohira-Bestmann homologation mechanism.

7.2. Route 2: synthesis of macrolide 10 via the Stork-Zhao olefination

Since the Ohira-Bestmann homologation reaction did not work as well as anticipated, another route that could potentially use the intermediates already in hand was sought to establish the (*Z*-*E*)-diene moiety in **10**.

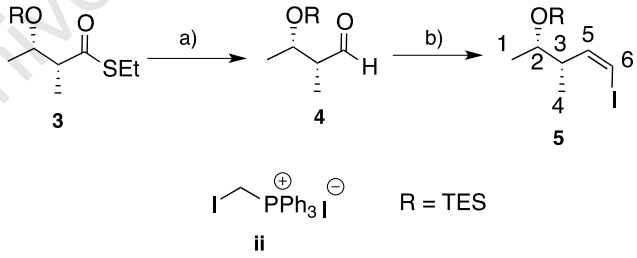
As with Route 1, the final step to **10** in Route 2 was envisaged to be achieved via an intramolecular HWE olefination of aldehyde **9**, **Scheme 7.5**. The (*Z*-*E*)-diene moiety in **8** was thought to be accessed via a Suzuki cross-coupling reaction in which the coupling partners would be the *cis*-vinyl iodide **7** and (*E*)-(5-hydroxypent-1-en-1-yl)boronic acid **iv**. Compound **7** was thought to be accessed similarly to the alkyne **5'**, but instead of subjecting aldehyde **4** to Ohira-Bestmann conditions it would be subjected to the Stork-Zhao olefination conditions to afford the *cis*-vinyl iodide **5**. Indeed the Stork-Zhao olefination gave better results and therefore this route was pursued further.



Scheme 7.5: Route 2- retrosynthesis via the Stork-Zhao olefination.

7.3. Macrolide 10 synthesis via Stork-Zhao olefination

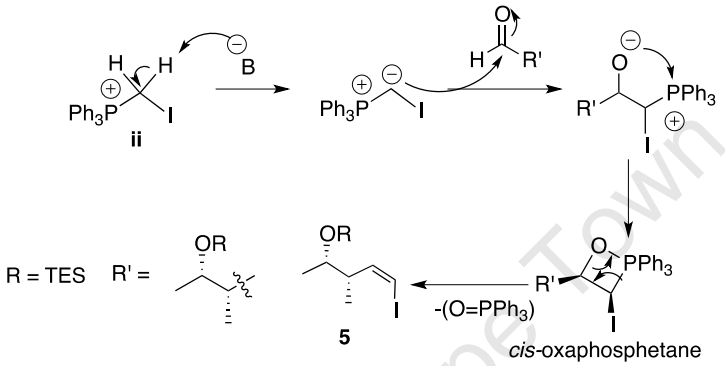
Aldehyde **4** was accessed as described above and was subjected without further purification to Stork-Zhao olefination conditions with **ii** (a commercially available synthon) to afford **5** in a moderate yield (57 %) over two steps, **Scheme 7.6**.[57] In an attempt to improve the yield, the aldehyde was purified by column chromatography, which gave a 57 % yield but this resulted in an even lower overall yield (**5**, 40 %). Although it was not clear how the moderate yields came about, one cannot rule out aldehyde decomposition. Also, it was noted that most examples found in the literature for similar reaction transformations obtained the respective *cis*-vinyl iodide also only in moderate to good (48-76 %) yields.



Scheme 7.6: Reaction conditions- a) DIBAL, DCM, –78 °C. b) i) NaHMDS, **ii**, THF, 0 °C to rt, ii) **4**, THF, –50 to 0 °C.

The Stork-Zhao olefination is a subclass of the Wittig olefination reaction and uses an unstabilised ylide to synthesise *cis*-vinyl halides.[57] The reaction mechanism of the Stork-Zhao olefination begins with deprotonation of the Wittig salt by a strong base such as

NaHMDS to afford the ylide which in turn adds to **4**, and thereafter the normal Wittig mechanism applies, **Scheme 7.7**. Unstabilised ylides are known to be *Z*-olefin selective due to the irreversible formation of the *cis*-oxaphosphetane (kinetically favoured over formation of the *anti*-isomer), which collapses to the kinetic product, the *Z*-isomer. The presence of an electron-withdrawing group in stabilised ylides allows equilibration to the more stable *anti*-oxaphosphetane which collapses to the thermodynamic product, the *E*-isomer (*vide infra*).

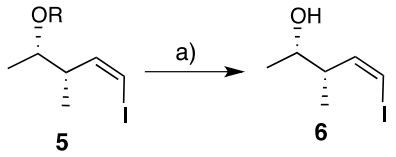


Scheme 7.7: Stork-Zhao olefination reaction mechanism.

The IR spectrum of **5** showed the disappearance of the carbonyl band with the appearance of the alkene band at 2957 cm^{-1}. New resonances at 6.26 (d, *J* = 9.2 Hz, 1H, H-6) and 6.07 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5) were observed for the *cis*-alkene illustrating the lower coupling constant compared to that of the (*E*)-isomer. The ^{13}C NMR spectrum also confirmed the disappearance of the carbonyl resonance with the appearance of two alkene peaks at 144.4 (C-5) and 81.5 (C-6). The resonance for C-6 was observed quite upfield (81.5 ppm) due to the shielding effect by the iodine group attached to it. All the other ^{1}H NMR and ^{13}C NMR resonances were observed similarly as before and were assigned accordingly.

Although the *cis*-vinyl iodide was obtained in modest overall yields it was thought best to continue with the macrolide synthesis. Moving forward, the silyl-PG was deprotected with TBAF to afford alcohol **6** in good yield (75 %).[64] Owing to the low carbon percentage by-mass and the presence of the vinyl halide moiety, compound **6** was found to be relatively volatile and as such had to be treated with care when removing organic solvents in order to

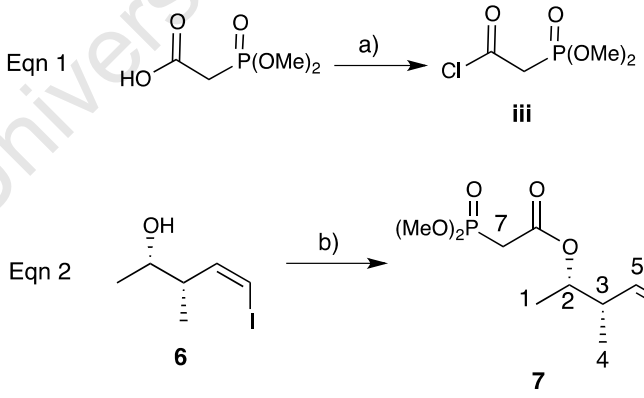
avoid loss of the product. Also, vinyl iodides are known to be light sensitive, so the product was exposed to minimum light as possible and used immediately in the next step.[58]



Scheme 7.8: Reaction conditions- a) TBAF, THF, 0 °C to rt.

The presence of the O-H band at 3351 cm^{-1} as well as the disappearance of the triethylsilane resonances in both the ^{1}H NMR and ^{13}C NMR spectrum at the diagnostic regions was indicative of a successful deprotection. All the other resonances shifted slightly downfield because of the withdrawing effects from the hydroxyl group in **6** and were assigned accordingly as in **5**.

Commercially available 2-(dimethoxyphosphoryl) acetic acid was treated with oxalyl chloride to afford **iii** (Eqn 1), which was sufficiently pure to be used without further purification, **Scheme 7.9**.[59] Alcohol **6** was acylated with **iii** to afford **7** (80 % yield) (Eqn 2) in preparation for an intramolecular HWE reaction to be carried out in the last step. In such a way, the first cross-coupling partner (the *cis*-vinyl halide) of the Suzuki reaction had been obtained over eight linear steps.



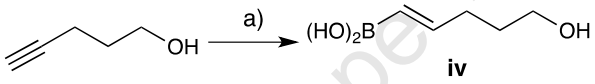
Scheme 7.9: a) DMF, $(COCl)_2$, DCM. b) DMAP, Pyridine, **iii**, 0 °C to rt.

The disappearance of the O-H stretch at 3351 cm^{-1} in **6** accompanied by a new C=O stretch at 1730 cm^{-1} in the IR spectrum of **7** confirmed the acylation of **6** to **7**. The new resonances at 3.83 (d, $J_{H\text{-}P}$ = 1.5 Hz, 3H, O<u>Me</u>), 3.80 (d, $J_{H\text{-}P}$ = 1.5 Hz, 3H, O<u>Me</u>), 3.01 (dd, J = 12.6, $J_{H\text{-}P}$ =

1.7 Hz, 1H, H-7) and 2.98 (dd, J = 12.6, $J_{H\text{-}P}$ = 1.7 Hz, 1H, H-7) in the ^{1}H NMR spectrum were assigned to the phosphonate ester. In the ^{1}H NMR spectrum, apart from normal H-H couplings, the phosphonate ester resonances experienced additional coupling to phosphorus resulting in the additional doubling of peaks (^{13}P, I = 0.5). The phosphonate ester ^{13}C NMR resonances observed C-P coupling too to give doublets: 165.3 (d, $J_{C\text{-}P}$ = 6.4 Hz, C=O), 53.3 (d, $J_{C\text{-}P}$ = 7.5 Hz, OMe), 53.3 (d, $J_{C\text{-}P}$ = 6.4 Hz, OMe), 33.8 (d, $J_{C\text{-}P}$ = 10.5 Hz, C-7). Other resonances were observed as before and assigned accordingly. A HRMS determination further confirmed **7**, with HRMS: *m/z* calc. 377.0009 for $C_{10}H_{19}IO_5P$, $[M + H]^+$ requires 377.0012.

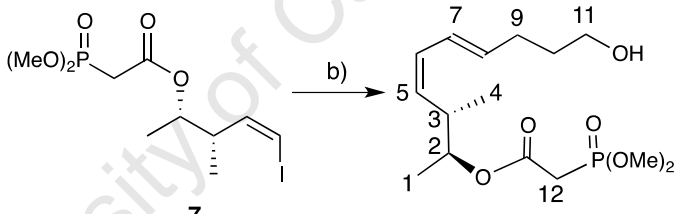
To access the second coupling partner (the boronic acid), pent-4-yn-1-ol was treated with catecholborane to afford **iv** after work-up in 40 % yield (Eqn 1).[60] Subjecting **7** and **iv** to Suzuki cross-coupling conditions afforded the (*E,Z*)-diene **8** in good yield 70 % (Eqn 2).[61]

Eqn 1



iv

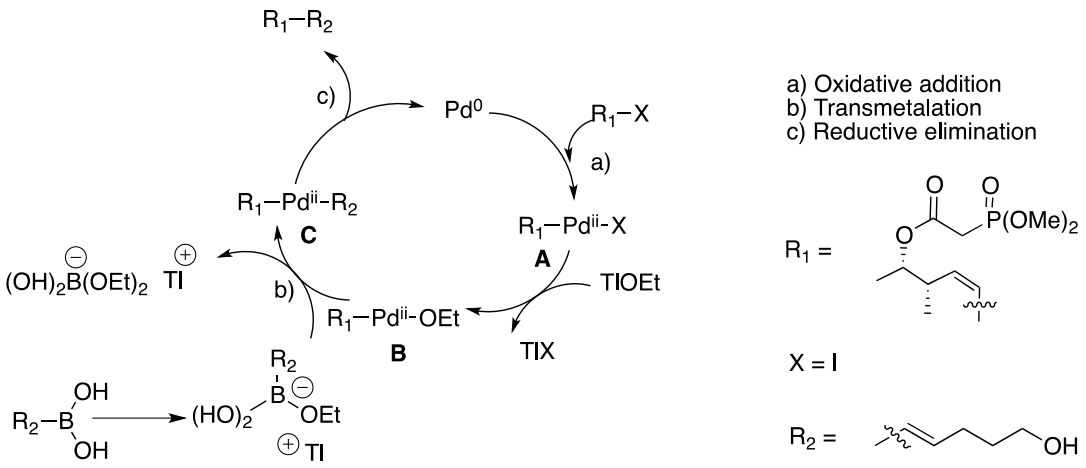
Eqn 2



7 **8**

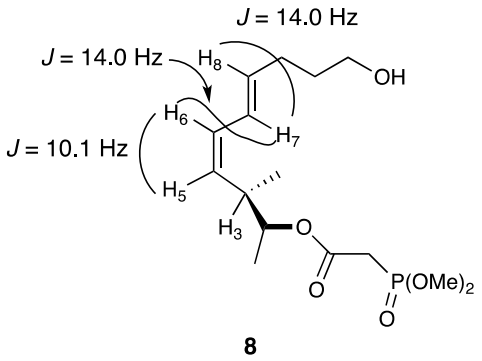
Scheme 7.10: Reaction conditions- a) Catecholborane, pent-4-yn-1-ol, 66 °C, THF : H_2O (3 : 1); b) **iv**, **7**, THF : H_2O (3 : 1), $Pd(PPh_3)_4$, TlOEt.

The Suzuki cross-coupling reaction mechanism commences with the oxidative addition of Pd (0) to the *cis*-vinyl iodide (R_1X) forming Pd (II) species **A**, **Scheme 7.11**. A transmetallation between **A** and thallium ethoxide affords intermediate **B** which in turn undergoes a second transmetallation to give the cross-coupled organopalladium **C**. The organopalladium species **C** collapses via reductive elimination to give the (*E,Z*)-diene R_1-R_2 **8**, restoring the catalyst as Pd (0).



Scheme 7.11: Suzuki cross-coupling reaction mechanism.

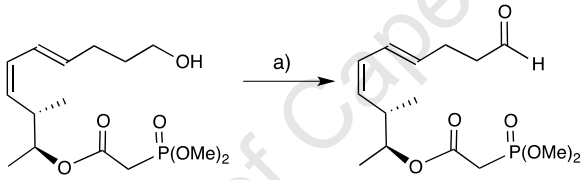
A new IR band at 3429 cm^{-1} for the O-H group was observed in **8** while the C=O band at 1739 was observed as in **7**. The resonances at 6.31 (dd, *J* = 14.0, 10.1 Hz, 1H, H-6), 6.01 (t, *J* = 10.1 Hz, 1H, H-5), 5.72 (dt, *J* = 14.0, 7.0 Hz, 1H, H-8) and 5.11 (t, *J* = 14.0 Hz, 1H, H-7) in the ^{1}H NMR spectrum were assigned to the (*E,Z*)-diene. In order to explain the observed *J*-values, compound **8** has to be drawn as shown in **Figure 7.1**, the speculated lower energy conformer. The observed *J*-values for H-6 arise due to the *cis*-coupling to H-5 (11.1 Hz) and the *trans*-coupling to H-7 (14.0 Hz). H-5 is a triplet with (*cis,cis*)-coupling to H-6 and H-3 having *J* = 10.1 Hz. H-7 is another triplet with a (*trans,trans*)-coupling to H-6 and H-8 having *J* = 14.0 Hz, while H-8 couples to H-7 (*J* = 14.0 Hz) and the methylene protons, H-9 (*J* = 7.0 Hz). Three new resonance peaks at 3.66 (q, *J* = 6.2 Hz, 2H, H-11), 2.21 (m, 2H, H-10) and 1.68 (m, 2H, H-9) were observed and assigned to the three-methylene protons. The resonances at 135.3 (C-8), 130.5 (C-7), 129.8 (C-5) and 126.2 (C-6) in the ^{13}C NMR spectrum were assigned to the (*E,Z*)-diene while 62.4 (C-11), 32.3 (C-10) and 29.2 (C-9) were assigned to the methylene carbons, all together confirming **8**. Resonance C-6 shifted downfield from 83.3 to 126.2 ppm as a result of the (*E,Z*)-diene conjugation present in **8**. All the other resonances were observed similarly as in **7** for both the ^{1}H NMR and ^{13}C NMR spectrum. The phosphorus-couplings were again observed as before in the ^{1}H NMR and ^{13}C NMR spectra. Further evidence for **8** was given by mass spectrometry, HRMS (ES): *m/z* calc. 335.1618 for $C_{15}H_{28}O_6P$, $[M + H]^+$ requires 335.1624.



8

Figure 7.1: The *J*-coupling constants for compound **8**.

Now that the (*E,Z*)-diene moiety had been installed we sought to construct the lactenone moiety by an intramolecular cyclization to macrolide **10**. To do so, alcohol **8** was oxidised via the well-known Dess-Martin periodinane (DMP) oxidation protocol to afford **9** in a moderate yield of 59 %, the aldehyde once again proving difficult to purify.[62]

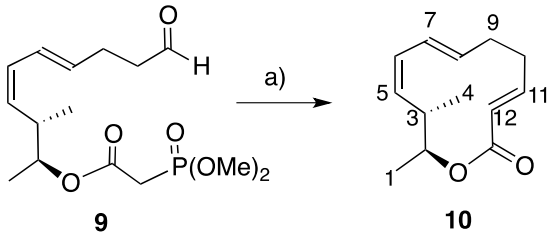


8 **9**

Scheme 7.12: Reaction conditions- a) **8**, DMP, $NaHCO_3$, DCM, rt.

The replacement of the O-H band at 3429 cm^{-1} by a C=O band at 1725 cm^{-1} in the IR spectrum confirmed the synthesis of **9**. A conspicuous aldehyde resonance was observed at 9.98 ppm with the disappearance of the H-11 methylene protons at 3.66 ppm in the ^{1}H NMR spectrum, also supporting the oxidation. A new carbonyl resonance peak in the ^{13}C NMR spectrum observed at 201.7 ppm for the –CHO group and the disappearance of the C-11 methylene resonance, also confirmed the oxidation. All the other resonances were observed as before with a slight downfield shift, which was significant for the methylene (H-/C-10) next to the aldehyde due to the electron withdrawing effects of the –CHO group. Aldehyde **9** was further confirmed by mass spectrometry, HRMS (ES): *m/z* calc. 333.1462 for $C_{15}H_{26}O_6P$, $[M + H]^+$ requires 333.1470.

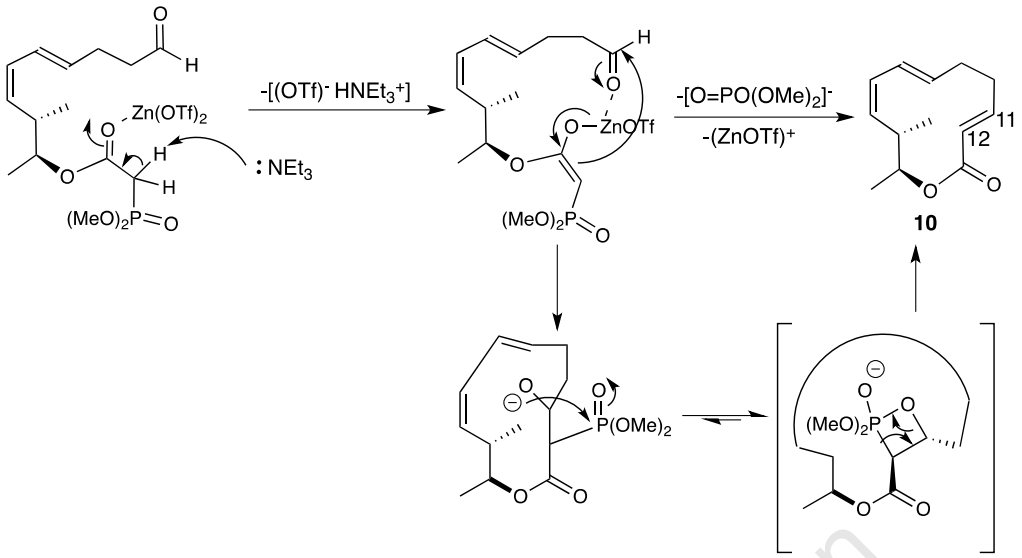
Finally, **9** was subjected to a HWE olefination to afford macrolide **10** in a good yield of 72 %.[63] Using the crude aldehyde residue from the previous step only slightly increased the yield to 76 %. The HWE olefination is another subclass of the Wittig olefination except involves a stabilised carbanion for the synthesis of *E*-olefins and goes via a similar mechanism as the one described above for the synthesis of the *cis*-vinyl iodide.



9 **10**

Scheme 7.13: Reaction conditions- a) $Zn(OTf)_2$, TMEDA, TEA, **9** (1.5 mM), THF, rt.

The mild conditions used in this synthesis were inspired by Pirrung *et al* in his total synthesis of Syringolin A and B.[63] Stronger bases were avoided as they could have enolised the aldehyde moiety to promote an aldol addition instead of the desired olefination reaction. Zinc-triflate (a Lewis acid) coordinates to the ester and in so doing increases the acidity of the α-protons for deprotonation by a mild base such as triethylamine (TEA), **Scheme 7.14**. Also, the zinc-triflate is thought to coordinate to the aldehyde moiety as well, and in so doing it brings the two reacting groups into close proximity, thus favouring the intramolecular olefination. TMEDA is used to mop-up triflic acid that may form and consequently hinder the reaction progression. High dilutions (1.5 mM) were used in this reaction to favour an intramolecular cyclisation as opposed to an intermolecular variant leading to the dimer.



Scheme 7.14: The intramolecular HWE reaction mechanism.

The disappearance of the aldehyde C=O stretch at 1729 cm^{-1} in **9** accompanied by the appearance of a lactone carbonyl at 1723 cm^{-1} in **10** supported the formation of **10**. The disappearance of the phosphonate methoxy resonances in the ^{1}H NMR spectrum also supported this. The resonances at 6.43 (m, 1H, H-11) and 5.49 (d, *J* = 15.1 Hz, 1H, H-12) were assigned to the newly formed *E*-olefin. H-6 no longer appeared as a dd with (*cis,trans*)-coupling but was observed as a triplet with (*cis,cis*)-coupling due to conformational change in the C_6-C_7 bond upon cyclisation and this further confirms macrolide **10**. Also, the multiplicity of H-7 changed from a triplet to a dd for the same reasons as H-6. The ^{13}C NMR spectrum also showed the disappearance of the phosphonate methoxy carbon resonances as well as the downfield shifting of C-12 from 34.2 to 128.7 ppm, confirming the newly installed enone. Finally, mass spectrometry confirmed macrolide **10**, with HRMS (ES): calc. 207.1380 for $C_{13}H_{18}O_2$, $[M + Na]^+$ requires 207.1387.

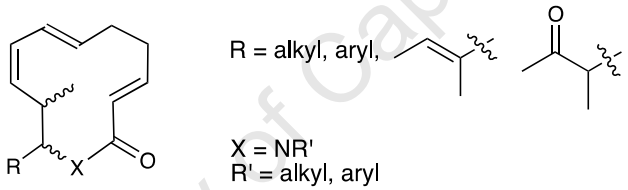
Chapter 8: Conclusion and Future work

8.1. Conclusion

A versatile synthesis of macrolide core (**10**) of lactimidomycin has been achieved in 11-linear steps in 6.1 % overall yield. The synthesis exploited three core reactions to construct the pivotal sites in **10** and those include Evans oxazolidinone-mediated aldol reaction (for the contiguous *syn-stereocentres*), the Suzuki cross-coupling to access the (*E,Z*-diene), and finally the Horner-Wadsworth-Emmons olefination to construct the enone and cyclise simultaneously.

8.2. Future work

Exploiting this synthesis, a versatile library of lactimidomycin can be rapidly accessed by small variations, **Figure 8.1**. Once the analogues have been obtained they can all be evaluated for biological activity including **10**.



10'

Figure 8.1: Macrolide **10** derivatives.

Chapter 9: Experimental

9.1. General

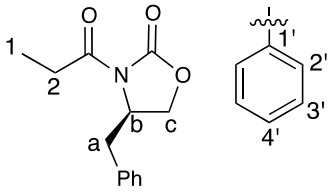
All reagents and solvents were purchased from Sigma-Aldrich or Fischer Scientific and were used without further purification unless stated.

All reactions were carried out in oven dry glassware with a magnetic stirrer. All reactions were done under nitrogen atmosphere unless stated. Reaction solvents including THF, DCM, toluene and Et_2O were filtered through a column (Innovative Technologies) of activated alumina under nitrogen atmosphere. Reaction temperatures were achieved via: heat/silicone oil bath (for Temp > 25 °C), ice bath (for Temp ≈ 0 °C), Neslab CB 80 immersion cooler (–20 to –60 °C), or acetone/dry ice bath (for –78 °C). Aqueous solutions were prepared using deionized water. All solvents used for extractions and column chromatography were either ACS- or HPLC-grade. Crude mixtures were purified by flash chromatography using SiliCycle SiliaFlash P60 (230-400 mesh) silica gel.

Nuclear Magnetic Resonance (NMR) spectra were recorded on either Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), Varian INOVA 500 (500 MHz), or Varian MR400 (401 MHz) spectrometers and chemical shifts (δ) are reported in ppm while the *J*-coupling constants are recorded in Hz. Chemical shifts for ^{1}H and ^{13}C were recorded relative to residual chloroform, 7.26 and 77.16 ppm respectively. High resolution mass spectra (HRMS) were recorded on Micromass AutoSpec Ultima or VG (Micromass) 70-250-S magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were performed on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO P-2000 or Autopol III digital polarimeter at 589 nm (D-line) and are reported as: $[\alpha]_D^{20}$ (*c* g/ml, solvent).

9.2. Synthesis of macrolide 10

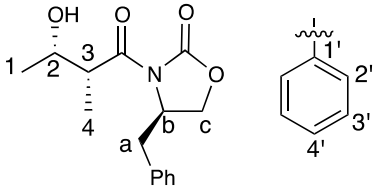
(4*R*)-4-benzyl-3-propionyloxazolidin-2-one[9b, 51] (1)



To a solution of (*R*)-4-benzyloxazolidin-2-one (2.00 g, 11.29 mmol) in dry THF (23.00 ml) at –78 °C was added slowly *n*-BuLi (5.42 ml, 13.54 mmol, 2.5 M, 1.2 eq) and the contents allowed to stir at this temperature. After 30 min, propionyl chloride (1.47 ml, 16.93 mmol, 1.5 eq) was added slowly at –78 °C and the contents allowed to slowly warm up to 0 °C over 2 hrs. The reaction was quenched with sat. NH_4Cl (45 ml) and warmed to ambient temperature and extracted with DCM (3 x 40 ml). The organic extracts were dried over $MgSO_4$, concentrated *in vacuo*, and the crude residue purified by column chromatography (10 % EtOAc in hexane) to obtain **1** (2.40 g, 91 % yield) as a colourless oil. The ^{1}H NMR spectrum agreed with literature data.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.29 (m, 3H, H-3' + H-4'), 7.20 (m, 2H, H-2'), 4.66 (m, 1H, H-b), 4.17 (m, 2H, H-c), 3.29 (dd, *J* = 13.4, 3.2 Hz, 1H, H-a), 2.95 (m, 2H, H-2), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, H-a), 1.19 (t, *J* = 7.3 Hz, 3H, H-1).

(4*R*)-4-benzyl-3-((2'*R*,3'*S*)-3'-hydroxy-2'-methylbutanoyl)oxazolidin-2-one[9b, 51] (2a)

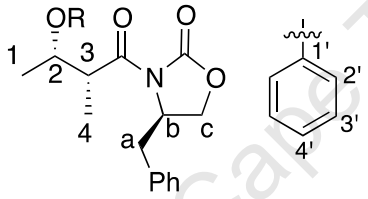


To a solution of **1** (2.296 g, 9.840 mmol) in DCM (9.0 ml) under argon atmosphere at –78 °C was added slowly dibutylboron triflate (14.76 ml, 14.76 mmol, 1.5 eq, 1.0 M) followed by *i*-Pr_2NEt *(*3.09 ml, 17.71 mmol, 1.8 eq) and allowing the contents to slightly warming up to –45 °C. After 1 hr, the contents were re-cooled to –78 °C and freshly distilled acetaldehyde (2.20 ml, 39.36 mmol, 4.0 eq) was added and the reaction mixture allowed to warm up to –10 °C over 2 hrs. Upon completion, the reaction was quenched with MeOH : H_2O_2 (30 %) : buffer (pH = 7), (2 : 1 : 1, 40 ml), stirred at 0 °C for 1 hr. Thereafter, the reaction mixture

was concentrated *in vacuo*, sat. $NaHCO_3$ (30 ml) added and extracted with EtOAc (2 x 30 ml). The organic extracts were further washed with sat. NaCl (30 ml), re-extracted with EtOAc (3 x 40 ml), combined and dried over $MgSO_4$, concentrated *in vacuo* and the crude residue purified by column chromatography (40 % EtOAc in Hexane) to obtain **2a** (2.05 g, 75 % yield) as a colourless oil. The ^{1}H NMR spectrum agreed with literature data.[9b, c]

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.32 (m, 3H, H-3' + H-4'), 7.21 (m, 2H, H-2'), 4.71 (m, 1H, H-b), 4.22 (m, 2H, H-c), 4.18 (m, 1H, H-2) 3.74 (qd, *J* = 7.1, 2.9 Hz, 1H, H-3), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H, H-a), 2.90 (s, 1H, OH), 2.79 (dd, *J* = 13.4, 9.5 Hz, 1H, H-a), 1.27 (d, *J* = 7.1 Hz, 3H, H-1), 1.21 (d, *J* = 6.4 Hz, 3H, H-4).

(4*R*)-4-benzyl-3-((2'*R*,3'*S*)-2'-methyl-3'-((triethylsilyl)oxy)butanoyl)oxazolidin-2-one[35] **(2b)**

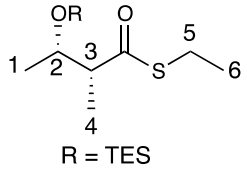


To a solution of **2a** (2.00 g, 7.21 mmol) in DCM (10 ml) at 0 °C was added a solution of imidazole (1.44 g, 21.19 mmol, 2.8 eq) in DCM (7.0 ml). After 30 min, TES-Cl (1.69 ml, 10.10 mmol, 1.4 eq) was added at 0 °C and the contents allowed to slowly warm up to rt. After 5 hrs, sat. $NaHCO_3$ (30 ml) was added, the reaction contents extracted with DCM (3 x 40 ml), the organic extracts combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (10 % EtOAc in hexane) to obtain **2b** (2.661 g, 94 % yield) as a colourless oil.

$[\alpha]_D^{20} = -64.9$, (DCM, *c* = 2.0); ν_{max} (cm^{-1}) 2995 (Ar), 1784 (C=O, carbamate), 1696 (C=O, amide); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.32 (m, 3H, H-3' + H-4'), 7.24 (m, 2H, H-2'), 4.73-4.65 (m, 1H, H-b), 4.25 (p, *J* = 6.2 Hz, 1H, H-2), 4.20-4.10 (m, 2H, H-c), 3.91 (p, *J* = 6.2 Hz, 1H, H-3), 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H, H-a), 2.70 (dd, *J* = 13.3, 9.8 Hz, 1H, H-a), 1.20 (d, *J* = 6.2 Hz, 3H, H-1), 1.12 (d, *J* = 6.2 Hz, 3H, H-4), 0.96 (t, *J* = 7.4 Hz, 9H, TES-Me), 0.61 (q, *J* = 7.4 Hz, 6H, TES-CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5 (C=O, carbamate), 153.3 (C=O, amide), 135.6 (C-1'), 129.6 (C-2'), 129.1 (C-3'), 127.5 (C-4'), 69.8 (C-c), 66.1 (C-2), 55.8 (C-b), 45.0 (C-3), 40.0 (C-a),

21.8 (C-1), 13.0 (C-4), 7.0 (TES-Me), 5.0 (TES-CH$_2$); HRMS (ES): *m/z* calc. for $C_{21}H_{34}NO_4Si$, $[M+H]^+$ requires 392.2252 requires 392.2261.

(2*R*,3*S*)-S-ethyl 2-methyl-3-((triethylsilyl)oxy)butanethioate[35] (3)

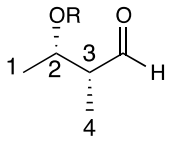


R = TES

To a solution of ethanethiol (0.24 ml, 3.22 mmol, 1.4 eq) in THF (2.0 ml) at –78 °C was added *n*-BuLi (1.11 ml, 2.76 mmol, 1.2 eq, 2.5 M). After 30 min, a solution of **2b** (0.904 g, 2.303 mmol) in THF (5.0 ml) was slowly added at –78 °C and the contents allowed to warm to –50 °C. After 1 hr, the reaction was quenched with sat. NH_4Cl (40 ml) and extracted with DCM (3 x 50 ml). The organic fractions were combined, dried over $MgSO_4$, concentrated *in vacuo* and the crude residue purified by column chromatography (1 % EtOAc in hexane) to give **3** (0.595 g, 93 %) as a colourless liquid and the auxiliary recovered as colourless solid (93 %, 0.380 g).

$[\alpha]_D^{20} = -10.8$, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 1688 (C=O, thioester); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (p, *J* = 6.2 Hz, 1H, H-2), 2.85 (q, *J* = 7.4 Hz, 2H, H-5), 2.59 (p, *J* = 6.4 Hz, 1H, H-3), 1.24 (t, *J* = 7.4 Hz, 3H, H-6), 1.19 (d, *J* = 6.2 Hz, 3H, H-1), 1.16 (d, *J* = 6.4 Hz, 3H, H-4), 0.95 (t, *J* = 7.6 Hz, 9H, TES-Me), 0.59 (q, *J* = 7.6 Hz, 6H, TES-CH$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (C=O, thioester), 70.1 (C-2), 56.8 (C-3), 23.4 (C-5), 22.4 (C-6), 14.8 (C-1), 14.1 (C-4), 7.0 (TES-Me), 5.1 (TES-CH$_2$); HRMS (ES): *m/z* calc. 276.1652 $C_{13}H_{29}O_2SSi$, $[M+H]^+$ requires 276.1657.

(2*R*,3*S*)-2-Methyl-3-((triethylsilyl)oxy)butanal (4)

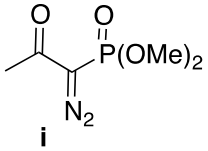


R = TES

To a solution of **3** (1.00 g, 3.61 mmol) in DCM (8.0 ml) at –78 °C was slowly added (over 15 min) DIBAL (4.34 ml, 4.34 mmol, 1.15 eq, 1.0 M). After 30 min at –78 °C, the reaction was quenched by slow addition of (pre-cooled to –78 °C) MeOH (3.0 ml) and stirred for 30 min.

Thereafter, sat. Rochelle's salt (15 ml) was added, the reaction contents diluted with EtOAc (20 ml) and allowed to stir for further 30 min. The reaction was extracted with EtOAc (2 x 20 ml), the organic extracts washed with sat. NaCl (30 ml) and re-extracted with EtOAc (3 x 30 ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude mixture of aldehyde **4**, which was used without further in the next step.

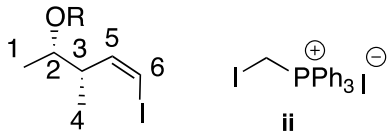
Dimethy (1-diazo-2-oxopropyl)phosphonate[54] (i)



i

To a solution of dimethyl (2-oxopropyl)phosphonate (1.00 g, 6.02 mmol) and *p*-Ts-azide (2.37 mg, 12.04 mmol, 2.0 eq) in THF (12 ml) was added triethylamine (1.26 ml, 9.03 mmol, 1.5 eq) and the contents allowed to stir at ambient temperature. After 8 hrs, the contents were filtered *in vacuo* and washed with EtOAc (20 ml). Thereafter, the organic extracts were washed with sat. NaCl (30 ml), extracted with EtOAc (3 x 20 ml), organic extracts combined and dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was flashed on a small column (60 % EtOAc in hexane) to afford **i** (0.693 g, 60 % yield) as a colourless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.78 (d, *J* = 3.2 Hz, 3H, OMe), 3.72 (d, *J* = 3.2 Hz, 3H, OMe), 2.17 (s, 3H, Me).

Triethyl(((2*S*,3*S*,*Z*)-5-iodo-3-methylpent-4-en-2-yl)oxy)silane (5)



ii

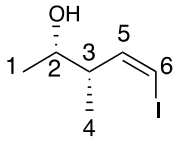
R = TES

To a solution of **ii** (6.04 g, 11.39 mmol, 3.2 eq) in THF (12 ml) was added NaHMDS (10.84 ml, 1.0 M, 10.84 mmol, 3.0 eq) at ambient temperature and the solution stirred for 30 min. Thereafter, the reaction was cooled to –78 °C followed by slow addition of crude aldehyde **4** (0.782 g, 3.61 mmol) allowing the contents to warm up to –20 °C. After 2 hrs, sat. NH_4Cl (35 ml) was added and the reaction allowed to warm up to rt. The reaction was extracted

with DCM (3 x 40 ml), the organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The concentrate was purified by column chromatography (5 % EtOAc in hexane) to afford the *cis*-vinyl iodide **5** (0.700 g, 57 % yield) as a colourless oil.

$[\alpha]_D^{20}$= 36.2, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 2957 (alkene); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.18 (d, *J* = 9.2 Hz, 1H, H-6), 6.06 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5), 3.76 (p, *J* = 6.4 Hz, 1H, H-2), 2.52-2.49 (m, 1H, H-3), 1.15 (d, *J* = 6.4 Hz, 3H, H-1), 0.99 (d, *J* = 6.4 Hz, 3H, H-4), 0.96 (t, *J* = 7.4 Hz, 9H, TES-Me), 0.60 (q, *J* = 7.4 Hz, 6H, TES-CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ 144.4 (C-5), 81.5 (C-6), 70.9 (C-2), 47.2 (C-3), 21.8 (C-1), 14.6 (C-4), 7.1 (TES-Me), 5.2 (TES-CH_2).

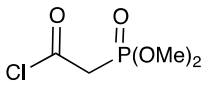
(2*S*,3*S*,*Z*)-5-iodo-3-methylpent-4-en-2-ol (6)



To a solution of **5** (0.700 g, 2.06 mmol) in THF (5.0 ml) at 0 °C was added TBAF (2.67 ml, 2.67 mmol, 1.0 M, 1.3 eq) and contents allowed to slowly warm up to rt. After 2 hrs, sat. $NaHCO_3$ (20 ml) was added, the reaction extracted with DCM (3 x 30 ml), the organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The concentrate was purified by column chromatography (10 % EtOAc in hexane) to afford **7** (0.372 g, 80 % yield) as a colourless oil.

$[\alpha]_D^{20}$= –26.8, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3351 (O-H), 2971 (alkene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 9.2 Hz, 1H, H-6), 6.07 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5), 3.77 (p, *J* = 6.3 Hz, 1H, H-2), 2.61-2.55 (m, 1H, H-3), 1.20 (d, *J* = 6.3 Hz, 3H, H-1), 1.04 (d, *J* = 6.6 Hz, 3H, H-4); ^{13}C NMR (176 MHz, $CDCl_3$) δ 143.3 (C-5), 82.6 (C-6), 70.9 (C-2), 46.7 (C-3), 21.0 (C-1), 14.7 (C-4).

Dimethyl (2-chloro-2-oxoethyl)phosphonate (iii)

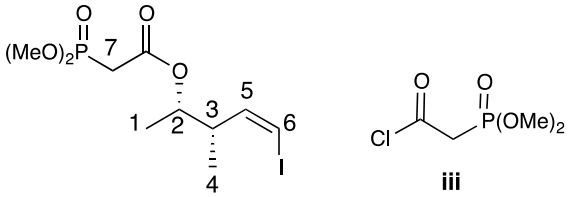


iii

To a solution of 2-(dimethoxyphosphoryl) acetic acid (0.840 g, 5.00 mmol) and DMF (0.1 ml**,** 1.3 mmol, 0.25 eq) in DCM (10 ml) was added oxalyl chloride (1.27 g, 10.0 mmol) slowly at 0

°C. The mixture was stirred at room temperature for 1 hr before the solvent was removed *in vacuo*. The acyl chloride **iii** was dried under high vacuum for 2 hrs before it was used.

(2*S*,3*S*,*Z*)-5-iodo-3-methylpent-4-en-2-yl 2-(dimethoxyphosphoryl)acetate (7)

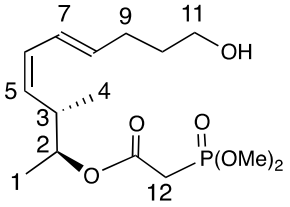


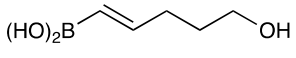
iii

To a solution of **6** (0.653 g, 2.89 mmol) and DMAP (0.177 g, 1.446 mmol, 0.5 eq) in DCM (8.0 ml) at ambient temperature was added pyridine (1.21 ml, 15.035 mmol, 5.2 eq). Thereafter, the reaction contents were cooled to 0 °C followed by slow addition of **iii** (11.56 ml, 11.56 mmol, 1.0 M, 4.0 eq) in DCM and the contents allowed to warm up to rt. After 2 hrs, HCl (15.0 ml, 1.0 N) and $CuSO_4$ (15.0 ml, 1.0 M) were added and contents allowed to stir for 1 hr. Thereafter, sat. $NaHCO_3$ (20.0 ml) was added and the reaction mixture extracted with DCM (3 x 40 ml). The organic extracts were dried over $MgSO_4$, concentrated *in vacuo*, and the concentrate purified by column chromatography (30 % EtOAc in hexane) to afford **7** (0.761 g, 70 % yield) as a light yellow oil.

$[\alpha]_D^{20}$= 20.2, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 2971 (alkene), 1730 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, *J* = 9.2 Hz, 1H, H-6), 6.04 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5), 4.93 (p, *J* = 6.4 Hz, 1H, H-2), 3.83 (d, $J_{H\text{-}P}$ = 1.5 Hz, 3H, OMe), 3.80 (d, $J_{H\text{-}P}$ = 1.5 Hz, 3H, OMe), 3.01 (dd, *J* = 12.6, $J_{H\text{-}P}$ = 1.7 Hz, 1H, H-7), 2.98 (dd, *J* = 12.6, $J_{H\text{-}P}$ = 1.7 Hz, 1H, H-7), 2.81-2.73 (m, 1H, H-3), 1.25 (d, *J* = 6.4 Hz, 3H, H-1), 1.04 (d, *J* = 6.4 Hz, 3H, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 (d, $J_{C\text{-}P}$ = 6.4 Hz, C=O ester), 142.1 (C-5), 83.3 (C-6), 74.5 (C-2), 53.4 (d, $J_{C\text{-}P}$ = 7.5 Hz, OMe), 53.3 (d, $J_{C\text{-}P}$ = 7.5 Hz, OMe), 44.3 (C-3), 34.3 (d, $J_{C\text{-}P}$ = 10.5 Hz, C-7), 17.6 (C-1), 15.0 (C-4); HRMS (ES): *m/z* calc. 377.0009 for $C_{10}H_{19}IO_5P$, $[M + H]^+$ requires 377.0012.

(2*S*,3*S*,4*Z*,6*E*)-10-hydroxy-3-methyldeca-4,6-dien-2-yl 2-(dimethoxyphosphoryl)acetate (8)



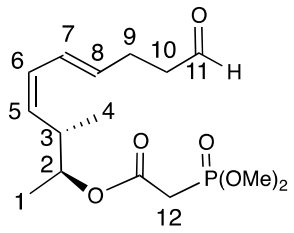


iv

Compound **7** (0.200 g, 0.532 mmol) and the boronic acid **iv**[60] (0.105 g, 0.744 mmol, 1.4 eq) were dissolved in (THF : H_2O, 3 : 1, 5.0 ml). To this mixture was added a sonicated solution of $Pd(PPh_3)_4$ (0.061 g, 0.053 mmol, 0.1 eq) in (THF : H_2O, 3 : 1, 1.5 ml) followed by TlOEt (124 µl, 0.175 mmol, 0.35 eq). After 30 min, pH 7 buffer (15 ml) was added and the contents allowed to stir for 30 min. Thereafter, the reaction mixture was extracted with EtOAc (3 x 25 ml), the organic extracts washed with sat. NaCl (35 ml), re-extracted with EtOAc (3 x 35 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (20 % EtOAc in hexane) to afford **8** (0.124 g, 70 %) as a yellowish oil.

$[\alpha]_D^{20}$= –2.0, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 3429 (O-H), 2931 (alkene), 1739 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 14.0, 10.1 Hz, 1H, H-6), 6.01 (t, *J* = 10.1 Hz, 1H, H-5), 5.72 (dt, *J* = 14.0, 7.0 Hz, 1H, H-8), 5.11 (t, *J* = 14.0 Hz, 1H, H-7), 4.80 (p, *J* = 6.4 Hz, 1H, H-2), 3.83 (d, J_{H-P} = 3.1 Hz, 3H, OMe), 3.80 (d, J_{H-P} = 3.1 Hz, 3H, OMe), 3.66 (q, *J* = 6.2 Hz, 2H, H-11), 3.00 (dd, *J* = 12.6, J_{H-P} = 1.7 Hz, 1H, H-12), 2.94 (dd, *J* = 12.6, J_{H-P} = 1.7 Hz, 1H, H-12), 2.92-2.80 (m, 1H, H-3), 2.24-2.19 (m, 2H, H-10), 1.72-1.64 (m, 2H, H-9), 1.20 (d, *J* = 6.4 Hz, 3H, H-1), 1.01 (d, *J* = 6.4 Hz, 3H, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) 165.3 (d, J_{C-P} = 6.4 Hz, C=O ester), 135.3 (C-8), 130.5 (C-7), 129.8 (C-5), 126.2 (C-6), 76.2 (C-2), 62.4 (C-11), 53.3 (d, J_{C-P} = 7.5 Hz, OMe), 53.3 (d, J_{C-P} = 6.4 Hz, OMe), 37.2 (C-3), 34.5 (d, J_{C-P} = 10.5 Hz, C-12), 32.3 (C-10), 29.2 (C-9), 17.4 (C-1), 17.2 (C-4); HRMS (ES): *m/z* calc. 335.1618 for $C_{15}H_{28}O_6P$, $[M + H]^+$ requires 335.1624.

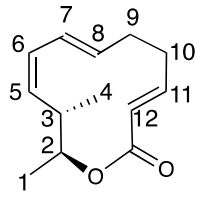
(2*S*,3*S*,4*Z*,6*E*)-3-methyl-10-oxodeca-4,6-dien-2-yl 2-(dimethoxyphosphoryl)acetate (9)



To a suspension of **8** (0.200 g, 0.592 mmol) and $NaHCO_3$ (0.058 g, 0.688 mmol, 1.15 eq) in DCM (6.0 ml) was added a sonnicated solution of DMP (0.507 g, 1.196 mmol, 2.0 eq) in DCM (2.5 ml). After 2.5 hrs, the mixture was diluted with sat. $NaHCO_3$ (20 ml), extracted with DCM (3 x 25 ml), the organic extracts dried over $MgSO_4$ and organic solvents removed *in vacuo*. The crude residue was purified by column chromatography (20 % EtOAc in hexane) to afford aldehyde **9** (0.113 g, 59 %) as a colourless oil.

$[\alpha]_D^{20}$= 5.2, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 2958 (alkene), 1739 (C=O, ester), 1725 (C=O, aldehyde); ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.4 Hz,1H, H-11), 6.30 (dd, *J* = 14.0, 10.0 Hz, 1H, H-6), 5.97 (t, *J* = 10.0 Hz, 1H, H-5), 5.69 (dt, *J* = 14.0, 6.8 Hz, 1H, H-8), 5.14 (t, *J* = 14.0 Hz, 1H, H-7), 4.78 (p, *J* = 6.4 Hz, 1H, H-2), 3.82 (d, $J_{H\text{-}P}$ = 3.1 Hz, 3H, OMe), 3.79 (d, $J_{H\text{-}P}$ = 3.1 Hz, 3H, OMe), 3.00 (dd, *J* = 12.6, $J_{H\text{-}P}$ = 1.7 Hz, 1H, H-12), 2.94 (dd, *J* = 12.6, $J_{H\text{-}P}$ = 1.7 Hz, 1H, H-12), 2.84-2.75 (m, 1H, H-3), 2.58-2.54 (m, 2H, H-10), 2.47-2.42 (m, 2H, H-9), 1.19 (d, *J* = 6.3 Hz, 3H, H-1), 1.01 (d, *J* = 6.4 Hz, 3H, H-4); ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.7 (C-11), 165.4 (d, $J_{C\text{-}P}$ = 6.4 Hz, C=O ester), 133.2 (C-8), 131.5 (C-7), 129.3 (C-5), 126.8 (C-6), 76.0 (C-2), 53.4 (d, $J_{C\text{-}P}$ = 6.4 Hz, OMe), 53.3 (d, $J_{C\text{-}P}$ = 6.4 Hz, OMe), 43.4 (C-10), 37.4 (C-3), 33.5 (d, $J_{C\text{-}P}$ = 10.5 Hz, C-12), 25.5 (C-9), 17.8 (C-1), 17.1 (C-4); HRMS (ES): *m/z* calc. for 333.1462 $C_{15}H_{26}O_6P$, $[M + H]^+$ requires 333.1470.

(3*E*,7*E*,9*Z*,11*S*,12*S*)-11,12-dimethyloxacyclododeca-3,7,9-trien-2-one (10)



To a suspension of $Zn(OTf)_2$ (0.199 g, 0.546 mmol, 2.2 eq) in THF (35 ml) under argon atmosphere was added TMEDA (44 µl, 0.298 mmol, 1.2 eq) followed by TEA (138 µl, 0.993 mmol, 4.0 eq) and the contents further diluted with THF (100 ml). After 30 min, a solution of aldehyde **9** (83 mg, 0.248 mmol) in THF (25 ml) was slowly added over 45 min. After 24 hrs, excess THF was removed *in vacuo* and sat. NaCl (20 ml) added. The contents were extracted with EtOAc (2 x 20 ml), organic extracts combined and washed with HCl (25 ml, 1 % M), back extracted with EtOAc (2 x 30 ml). Furthermore, the organic extracts were washed with $NaHCO_3$ (25 ml), re-extracted with EtOAc (2 x 40 ml), the organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The concentrate was purified by column chromatography to afford macrolide **10** (37 mg, 72 %) as a colourless oil.

$[\alpha]_D^{20}$= –42.9, (DCM, *c* = 1.0); ν_{max} (cm^{-1}) 2936 (alkene), 1723 (C=O, ester); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.48-6.38 (m, 1H, H-11), 6.11 (t, *J* = 10.8 Hz, 1H, H-6), 5.71 (dd, *J* = 14.7, 10.8 Hz, 1H, H-7), 5.49 (d, *J* = 15.1 Hz, 1H, 12), 5.50-5.35 (m, 1H, H-8), 5.24-5.19 (m, 1H, H-5), 5.11-5.05 (m, 1H, H-2), 3.10-3.02 (m, 1H, H-3), 2.60-2.48 (m, 2H, H-10), 2.00-1.80 (m, 2H, H-9), 1.18 (d, *J* = 6.7 Hz, 3H, H-1), 0.97 (d, *J* = 6.7 Hz, 3H, H-4); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.4 (C=O, ester), 146.3 (C-11), 134.7 (C-7), 130.7 (C-5), 130.0 (C-6), 128.7 (C-12), 128.1 (C-8), 75.2 (C-2), 35.0 (C-3), 32.5 (C-10), 31.3 (C-9), 17.1 (C-1), 12.8 (C-4); HRMS (ES): *m/z* calc. 207.1380 for $C_{13}H_{18}O_2$, $[M + H]^+$ requires 207.1387.

Part 4

Chapter 10: Summary

The two research projects undertaken utilised chiral auxiliaries (CAs) to synthesise chiral synthons of chemical and biological importance. In both cases high diastereoselectivities were achieved and the products obtained in high yields. Overall, both research studies demonstrate the utility of CA-based methods in advancing asymmetric synthesis.

Part 5

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