

THE SYNTHESIS OF SUBSTITUTED TETRAMATES FOR ANTIBACTERIAL STUDIES



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

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Abstract

The Synthesis of Substituted Tetramates for Antibacterial Studies

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Chapter 1 gives a brief introduction into the history of antibacterial drug discovery, the previous work carried out in the Moloney group in synthesising antibacterial tetramates, and the rationale for this DPhil research project.

Chapter 2 describes the synthesis of tetramic acids from *threo*-phenylserine derivatives. It demonstrates how bicyclic tetramates could be obtained chemoselectively and diastereoselectively. Additionally, it was shown that a library of densely functionalised C7-carboxamidotetramic acids could be synthesised and these compounds have the ability to bind to metal ions and may exhibit tautomeric behaviour in solution.

Chapter 3 describes the synthesis of tetramic acids from *erythro*-phenylserine derivatives with excellent diastereoselectivity and chemoselectivity observed. Additionally, also described is the synthesis of C7-carboxamides and C7-acyltetramates, where it was shown that these compounds also bind to metal ions and may exhibit tautomeric behaviour in solution. Finally discussed is the diastereoselective reduction of bicyclic tetramates and Suzuki couplings with mesylates to form densely functionalised pyrrolidinone derivatives.

Chapter 4 describes the attempted synthetic methodology of obtaining C2, C4 and C7-functionalised tetramates from *threo*-phenylserine and *allo/threo*-phenylcysteine derivatives. Moreover, this chapter describes the synthesis of imidazolidine-derived tetramic acids in a chemoselective and diastereoselective manner, in which the C2 and C4-substituents are readily functionalised. However, a C7-carboxamide library could not be synthesised chemoselectively.

Chapter 5 discusses the antibacterial activity and physicochemical properties of tetramates synthesised. None of the compounds synthesised exhibited any bioactivity against *E. coli*, however, many compounds exhibited potent antibacterial activity against *S. aureus*. However, this activity was compromised when tested in the presence of human serum albumin and/or blood.

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Contents

Contents	i
Abbreviations	vi
Nomenclature	x
Chapter 1: Introduction	1
1.1: The Discovery and History of Antibiotics	1
1.2: Antibiotic Drug Discovery Programmes	3
1.2.1: Natural Product Drug Discovery and the Semi-Synthesis of Natural Products	4
1.2.2: Target-Oriented Synthesis (TOS)	6
1.2.3: Combinatorial Chemistry and High-Throughput Screens (HTS)	7
1.2.4: Diversity-Oriented Synthesis (DOS)	8
1.2.5: Biology-Oriented Synthesis (BIOS) and Pseudo-Natural Products	9
1.3: The Growth of Antimicrobial Resistance (AMR)	13
1.4: Antibiotic Resistance Mechanisms	17
1.5: Tetramic Acids	22
1.5.1: Natural Product Tetramic Acids with Antibacterial Activity	22
1.6: Previous Work in the Moloney Group	26
1.6.1: Synthesis of Tetramate Cores	26
1.6.2: Tetramate Library Generation Inspired by Natural Products	27
1.6.2.1: C6-Pyroglutamate Library Generation Inspired by Oxazolomycin and Lajollamycin	28
1.6.2.2: C7-Acyltetramate Library Generation Inspired by Pramanicin and Harzianic Acid	29
1.6.2.3: C7-Carboxamidotetramate Library Generation Inspired by Streptolydigin, Kibdelomycin and Novartis' UPPS Inhibitor	33
1.6.2.4: C2-Functionalised-C7-Carboxamidotetramate Library Generation Inspired by Streptolydigin, Kibdelomycin and Novartis' UPPS Inhibitor	36
1.7: Aim of Research	38

Chapter 2: <i>threo</i>-Phenylserine-Derived <i>N,O</i>-Bicyclic Tetramic Acids	41
2.1: Previous Work in the Moloney Group	41
2.2: Synthesis of Tetramic Acids from <i>threo</i> -Phenylserine Derivatives	44
2.2.1: Synthesis of <i>threo</i> -Phenylserine Derivatives	44
2.2.2: Synthesis of Oxazolidines	52
2.2.3: Synthesis of <i>N</i> -Acylated Oxazolidines	55
2.2.4: Synthesis of Tetramates	59
2.2.5: Density Functional Theory (DFT) Calculations	64
2.2.6: Synthesis of C7-Carboxamides	67
2.3: Summary	75
 Chapter 3: <i>erythro</i>-Phenylserine-Derived <i>N,O</i>-Bicyclic Tetramic Acids	 76
3.1: Previous Work in the Moloney Group	76
3.2: Synthesis of Tetramic Acids from <i>erythro</i> -Phenylserine Derivatives	77
3.2.1: Synthesis of <i>erythro</i> -Phenylserine Derivatives	77
3.2.2: Synthesis of Oxazolidines	83
3.2.3: Synthesis of <i>N</i> -Acylated Oxazolidines	85
3.2.4: Synthesis of Tetramates	92
3.2.5: Synthesis of C7-Carboxamides	97
3.2.6: Synthesis of C7-Acyltetramates	103
3.2.7: Alternative Synthesis of <i>erythro</i> -Phenylserine Derivatives	111
3.3: Synthetic Methodologies Towards the Synthesis of the Clausenamide Family	118
3.3.1: Brief Literature Review on the Total Synthesis of the Clausenamide Family	119
3.3.2: Rationale and Retrosynthetic Analysis Towards C3-Deoxy-Clausenamide	123
3.3.3: Suzuki-Miyaura Cross-Coupling with Tetramic Acids	125
3.4: Reduction of the Tetramate Bicyclic Core	126
3.4.1: Previous Work in the Moloney Group	127

3.4.2: Reduction of the Tetramate Bicyclic Core	128
3.5: Summary	129
Chapter 4: Imidazolidine-Derived <i>N,N</i>-Bicyclic Tetramic Acids	131
4.1: Previous Work in the Moloney Group	131
4.2: Synthesis of C2 and C4-Functionalised <i>N,O</i> -Bicyclic Tetramic Acids	133
4.2.1: Synthesis of Oxazolidines	133
4.2.2: Synthesis of <i>N</i> -Acylated Oxazolidines	134
4.2.3: Synthesis of Tetramates	137
4.3: Attempted Synthesis of C2-Functionalised <i>N,S</i> -Bicyclic Tetramic Acids	139
4.3.1: Literature Synthesis of <i>allo/threo</i> -Phenylcysteine	140
4.3.2: Synthesis of <i>N,S</i> -Protected Phenylcysteine	141
4.3.3: Alternative Methodology Towards C4-Functionalised Thiazolidines	143
4.4: Synthesis of C2 and C4-Functionalised <i>N,N</i> -Bicyclic Tetramic Acids	146
4.4.1: Previous Work in the Moloney Group	146
4.4.2: Synthesis of Imidazolidines	147
4.4.3: Synthesis of <i>N</i> -Acylated Imidazolidines	152
4.4.4: Synthesis of Tetramates	157
4.4.5: Density Functional Theory (DFT) Calculations	162
4.4.6: Synthesis of C7-Carboxamides and the Attempted Synthesis of C7-Acyltetramates	163
4.5: Summary	167
Chapter 5: Antibacterial Activity of Bicyclic Tetramic Acids	168
5.1: Evaluation of Antibacterial Activity	168
5.2: Evaluation of Antibacterial Activity from Chapter 2	168
5.2.1: Antibacterial Activity of C7-Ethyl Ester Tetramates	168
5.2.2: Antibacterial Activity of C7-Carboxamides	169

5.3: Evaluation of Antibacterial Activity from Chapter 3	173
5.3.1: Antibacterial Activity of C7-Unfunctionalised Tetramates	173
5.3.2: Antibacterial Activity of C7-Carboxamides	174
5.4: Evaluation of Antibacterial Activity from Chapter 4	175
5.4.1: Antibacterial Activity of C7-Ethyl Ester Tetramates	175
5.4.2: Antibacterial Activity of C5 and C7-Carboxamides	176
5.5: Physicochemical Properties of Known Antibiotics, Natural Product Tetramates and Bicyclic Tetramates with Antibacterial Activity	178
5.5.1: Physicochemical Property Space of Known Antibiotics	179
5.5.2: Physicochemical Property Space of Natural Product Tetramates with Antibacterial Activity	183
5.5.3: Physicochemical Property Space of Bicyclic Tetramates	184
5.6: Toxicity of Bicyclic Tetramates	189
5.7: Activity in the Presence of Metal Ions and Human Serum Albumin	190
5.7.1: Activity in the Presence of Metal Ions	191
5.7.2: Activity in the Presence of Human Serum Albumin	191
5.8: Summary	193
Chapter 6: Experimental Section	198
6.1: General Methods	198
6.2: Experimental Section for Chapter 2	199
6.3: Experimental Section for Chapter 3	235
6.4: Experimental Section for Chapter 4	317
Appendices	359
nOe, NOESY and ROESY Interactions	359
HMBC Interactions	367

Abbreviations

Ac	acetyl
AMR	antimicrobial resistance
aq.	aqueous
Ar	aromatic/aryl
BIOS	biology-oriented synthesis
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
C	Celsius
CDI	1,1'-carbonyldiimidazole
cLog P	calculated partition coefficient between octanol and water
COSY	correlation spectroscopy
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
d.e.	diastereomeric excess
DFT	density functional theory
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DOS	diversity-oriented synthesis

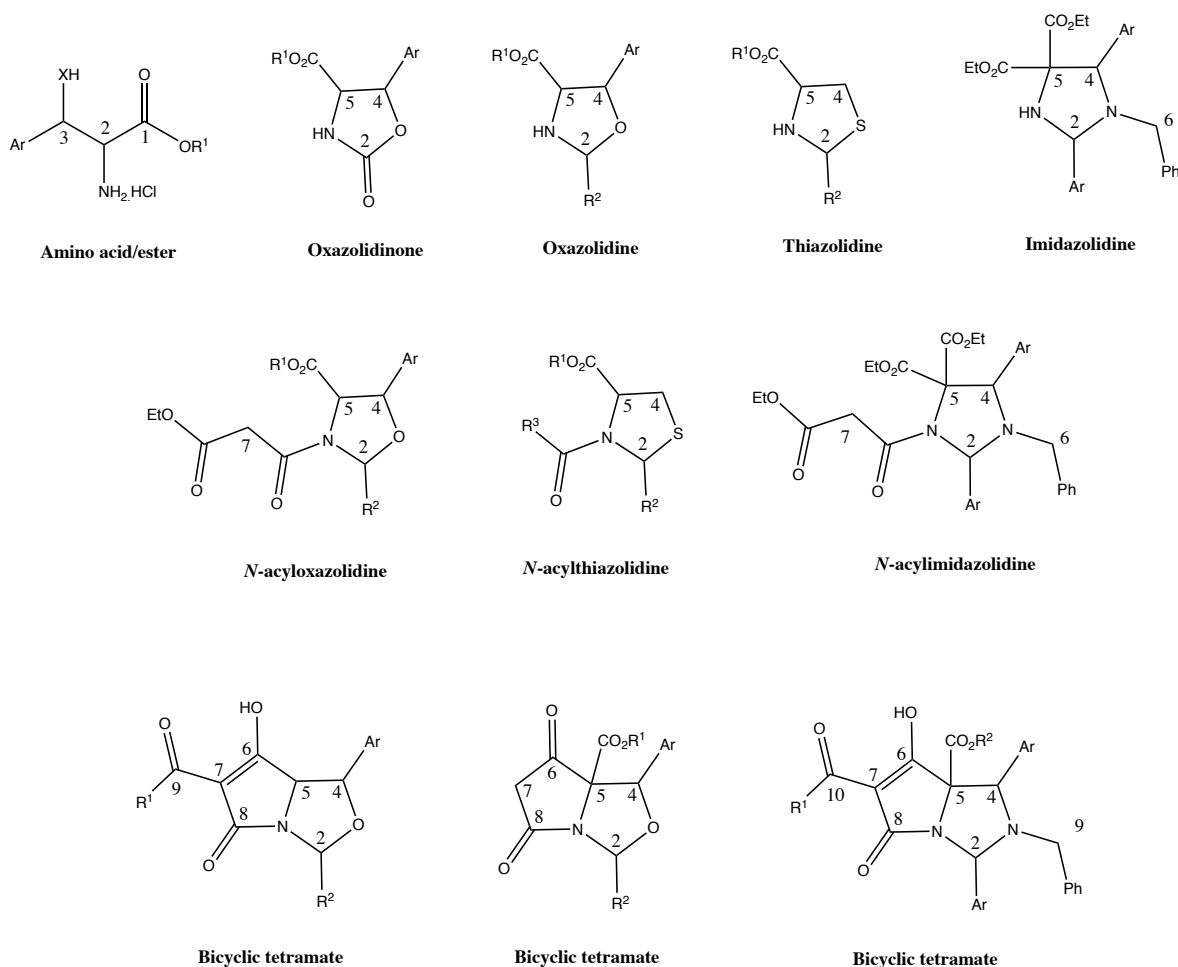
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
<i>E</i>	<i>trans</i>
E _a	activation energy
<i>E. coli</i>	<i>Escherichia coli</i>
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
FT-IR	Fourier-transform infra-red
h	hour
HMBC	heteronuclear multiple-bond correlation
HRMS	high resolution mass spectroscopy
HSA	human serum albumin
HSQC	heteronuclear single-quantum correlation
HTS	high-throughput screen
HWE	Horner-Wadsworth-Emmons
<i>i</i> Pr	isopropyl
IR	infra-red
<i>J</i>	coupling constant
K	Kelvin
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
M ⁺	metal ion
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid

MDR	multidrug-resistant
Me	methyl
MeCN	acetonitrile
MIC	minimum inhibitory concentration
min	minute
m.p.	melting point
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
Ms	mesyl
MSA	molecular surface area
M _w	molecular weight
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	2-D nuclear Overhauser effect spectroscopy
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
Pd-C	palladium on carbon
Pet. ether 40:60	petroleum ether 40:60
Ph	phenyl
PPB	plasma protein binding
ppm	parts per million
Pr	propyl
PSA	polar surface area
quant.	quantitative
R _f	retention factor
RNA	ribonucleic acid
RNAP	RNA polymerase
Ro5	rule of 5

ROESY	rotating frame Overhauser effect spectroscopy
rt	room temperature
SAR	structure-activity relationship
sat.	saturated
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
S _N 2	nucleophilic substitution of the 2 nd order
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
^t Bu	<i>tert</i> -butyl
^t BuLi	<i>tert</i> -butyllithium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOS	target-oriented synthesis
[TS] [‡]	transition state
Ts	tosyl
UPPS	undecaprenyl pyrophosphate synthase
VT-NMR	variable temperature NMR
Z	<i>cis</i>

Nomenclature

The following non-systematic numbering systems have been used throughout this thesis and the assignment of the respective NMR signals is according to the numbering system outlined in this section. However, the naming of these compounds follows the International Union of Pure and Applied Chemistry (IUPAC) nomenclature derived from ChemDraw.



The terms *cis* and *trans* refer to the relative stereochemistry between the H2, H3, H4 and H5 protons within the monocyclic and bicyclic structures. In the case of absolute stereochemistry, the Cahn-Ingold-Prelog convention has been used throughout this thesis to describe the chiral centres as either being *R* or *S*, while *E* and *Z* descriptors have been used to describe the geometry of the double bonds. Additionally, a hashed wedged bond is used to denote a substituent that is behind the plane of the page, and a wedged bond is used to denote a substituent in front of the plane of the page. A wavy bond signifies the presence of a mixture of isomers at the chiral centre.

Chapter 1: Introduction

1.1. The Discovery and History of Antibiotics

The discovery of antibiotics was accelerated during the early 20th century when German scientist, Paul Ehrlich began looking to discover molecules that acted as a ‘magic bullet’ – that is, compounds which selectively target disease-causing microorganisms and are capable of mammalian administration.¹⁻³ At the time, Ehrlich was particularly focused on the research of synthetic dyes and noticed that they selectively stained specific microbes while leaving others unstained.¹⁻³ In 1904, Ehrlich together with Alfred Berthelm and Sahachiro Hata, embarked on a large-scale screening programme to find less toxic derivatives of Béchamp’s atoxyl drug – used at the time to treat African sleeping sickness – to cure syphilis.¹⁻³ In 1909, they discovered the first antibiotics, salvarsan and neosalvarsan (arsphenamine), which were both of synthetic origin.¹⁻³ As a result of his work, Ehrlich’s method of chemical screening became one of the cornerstones for antibacterial drug discovery, which subsequently led to the discovery of sulphadruugs as well (**Figure 1.1**).¹⁻³

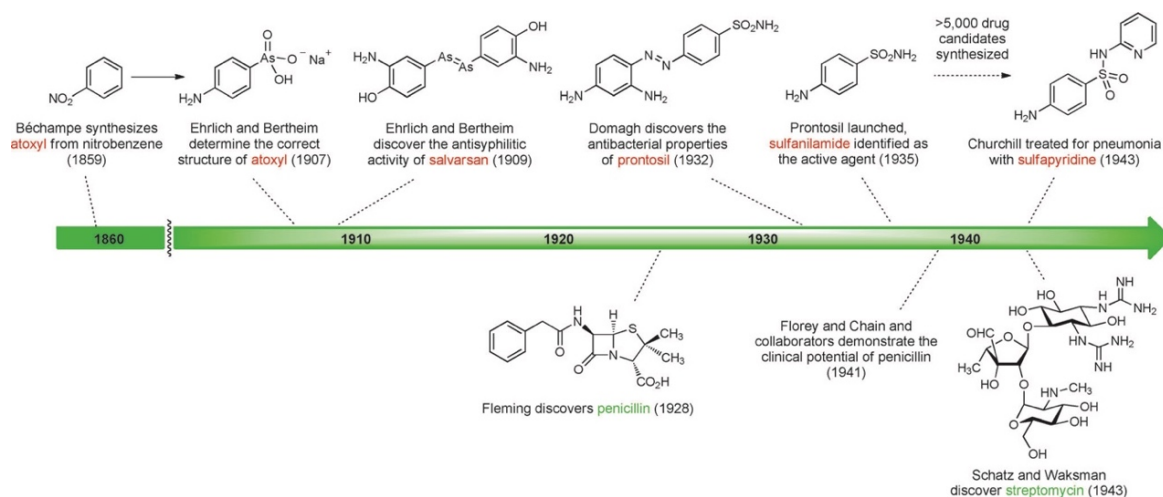


Figure 1.1: Timeline showing the early discovery of antibiotics. Copyright (2014) Wiley. Used with permission from P.M. Wright, I.B. Sieple and A.G. Myers, The Evolving Role of Chemical Synthesis in Antibacterial Drug Discovery, *Angew. Chem. Int. Ed.*, Wiley-VCH.

The later serendipitous discovery of penicillin in 1928 by Sir Alexander Fleming proved to be a great milestone in the history of antibacterial drug discovery.¹⁻³ However, a lack of understanding of the

significance of the discovery, along with issues surrounding the large-scale synthesis of penicillin due to a number of factors such as its isolation, stability and fermentation hindered its widespread use for a period of time.¹⁻³ It was not until the 1940s that a team in Oxford led by Howard Florey and Ernest Chain devised a method that enabled mass production and distribution of penicillin (**Figure 1.1**) – which was particularly important during World War II – and it was not until 1957 that the first chemical synthesis of penicillin (penicillin V) was achieved by John Sheehan, 29 years after the original discovery of penicillin.¹⁻² The importance of Fleming's discoveries were twofold; the discovery of penicillin paved the way towards the wider use of natural product based antibacterial drug discovery and it also led to the methodology for screening chemical compounds against pathogenic bacteria by measuring bacterial inhibition zones on agar plates.^{1,3}

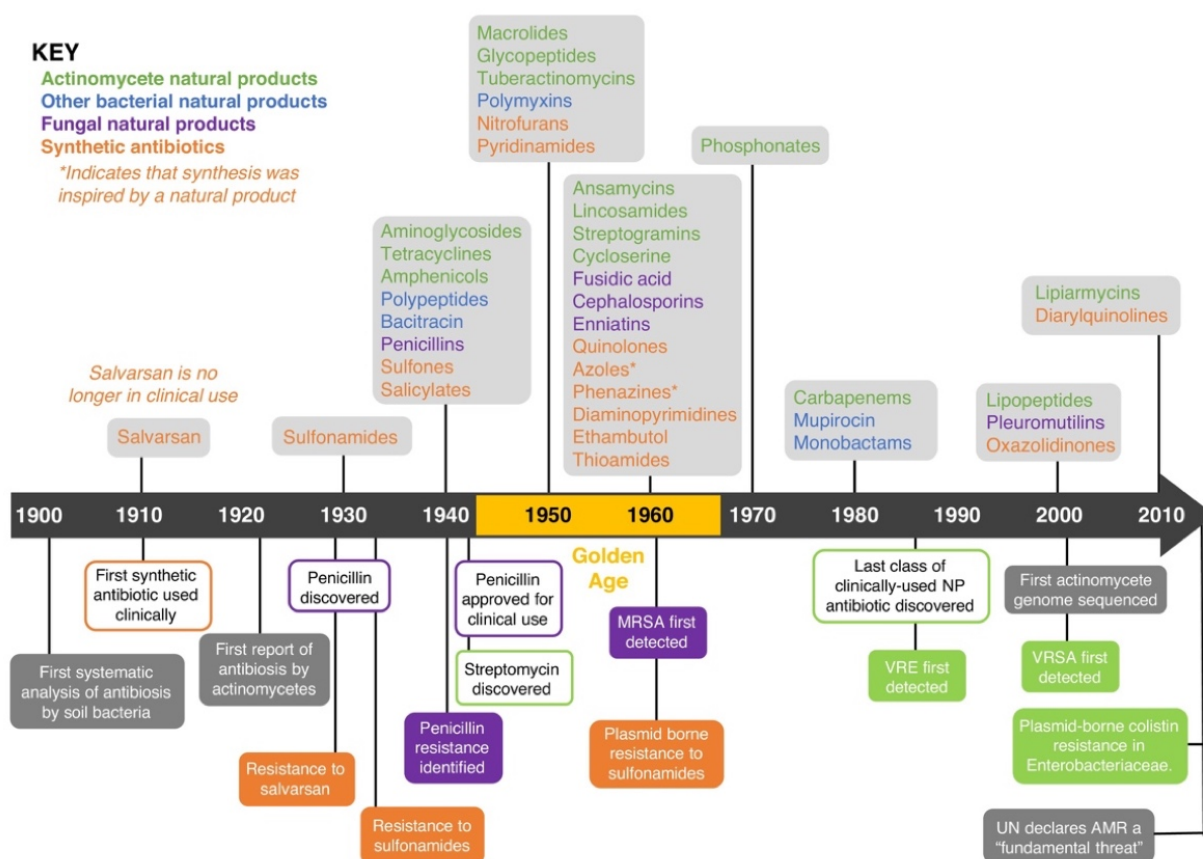


Figure 1.2: Timeline showing the history of antibacterial drug discovery; where MRSA = methicillin-resistant *S. aureus*; NP = natural product; VRE = vancomycin-resistant enterococcus; VRSA = vancomycin-resistant *S. aureus*; AMR = antimicrobial resistance. Reproduced from *Curr. Opin. Microbiol.*, 2019, **51**, 72-80.

After the discovery of penicillin was a period of antibacterial drug discovery dubbed the 'golden era', which was led by microbiologist, Selman Waksman between the periods of 1940-1960.¹⁻⁵ Waksman had noticed that soil bacteria (actinomycetes) produced metabolites that inhibited the growth of other pathogenic bacteria with remarkable potency and efficiency (antibiosis). This subsequently led to the 'Waksman's platform', whereby actinomycetes were mined to discover new antibiotics.¹⁻⁵ This new paradigm shift led to the discovery of many new classes of antibiotics (**Figure 1.2**); however, it was the discovery of streptomycin (aminoglycoside) – used to treat and cure tuberculosis at the time – that earned Waksman a Nobel Prize in 1952.¹⁻⁵ However, 'Waksman's platform' proved to be unsustainable in the long term as the overmining of actinomycetes led to the re-discovery of known antibiotics, and productivity declined.⁴⁻⁵ As a result, this approach was largely abandoned for other drug discovery methods which subsequently led to a discovery void, as depicted in **Figure 1.2**. This is described in more detail below.

1.2. Antibiotic Drug Discovery Programmes

Antibacterial drug discovery has been particularly challenging over the last few decades and many scientists have developed different platforms to try and discover new classes of antibiotics.⁴⁻⁵ Although the first class of antibiotics were of synthetic origin, the predominant drug discovery platforms used to find novel classes of antibiotics have been based on the isolation of natural products tested against whole-cell screens using Waksman's platform.^{1,4-5} An era of medicinal chemistry then followed Waksman's original platform, in which natural products were synthetically modified to optimise their physicochemical properties in order to improve their potency and oral bioavailability.^{1,4-5} These two factors ushered a golden period in antibacterial drug discovery that furnished many different classes of antibiotics.¹ However, after the 1980s, there has been a considerable drug discovery void (**Figures 1.2 and 1.3**).⁶

Since then, more innovative drug discovery platforms have been established. In recent years, target-based screens instead of whole-cell screens have been extremely popular amongst medicinal chemists

(Figure 1.3).^{1,4,6} This led to a concept called ‘rational drug design’, whereby drugs could be rationally designed based on the better understanding of protein-ligand interactions. It was believed that ‘rational drug design’ was more economical than the screening of random soil samples, especially since as noted above, the same natural products tended to be isolated. However, the use of ‘rational drug design’ has rarely yielded fruit in the search for novel antibacterials.⁴⁻⁶ Discussed below are just a few of the antibacterial drug discovery platforms that have been adopted by the scientific community to try and discover novel classes of antibiotics.

Golden Era 1940-1960	Medicinal Chemistry Era 1960-1980	Discovery Void Era 1980-2010
• Natural products • Whole-cell screens • Narrow spectrum • High success	• Semi-synthesis • Whole-cell screens • Broad spectrum • High success	• Modern drug discovery • Target-based screens • Broad spectrum • Low success

Figure 1.3: Different eras of antibiotic drug discovery. Adapted from *Nature*, 2016, **529**, 336-343.

1.2.1. Natural Product Drug Discovery and the Semi-Synthesis of Natural Products

Natural products have been critically important in antibacterial drug discovery, with many of the antibiotics used today either being of natural product origins or derived from natural products. Some examples include β -lactams, aminoglycosides, tetracyclines, macrolides and glycopeptides to name but a few **(Figure 1.2).**¹⁻⁹

However, when Waksman’s platform was eventually superseded, an era of medicinal chemistry (also known as the semi-synthesis of natural products) emerged, which looked at synthetically modifying natural products to make them more potent and give a broader spectrum activity against a range of Gram (+) and Gram (-) pathogens **(Figures 1.3 and 1.4).**^{1,8-9} In fact, this methodology is still very popular today, with many of the new antibiotics introduced into the market being repurposed drugs.^{1,8-9} However, there has been growing antibiotic resistance to these drugs, causing the scientific community to examine other drug discovery methods.

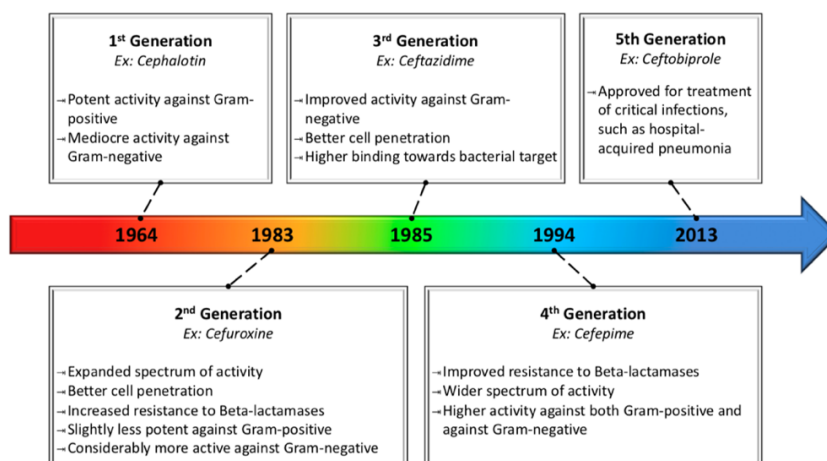


Figure 1.4: Showing how medicinal chemistry is used to create different generations of cephalosporins that have broader spectrum of activity. Reproduced from *Antibiotics*, 2019, **8**, 45.

Although other drug discovery programmes have been developed since the golden era, these new platforms have not yet yielded any significant returns in finding new classes of antibiotics.^{1,4-5} A review from Butler *et al.* illustrated that since the year 2000, 18 out of the 38 new antibiotics introduced into the market have been natural product or natural product-derived antibacterials.⁹ Additionally, Newman *et al.* analysed the heritage of all antibiotics between the periods of 1981-2014 and concluded that 82 out of 112 small molecule antibacterials were natural products or natural product-derived antibacterials (**Figure 1.5**).¹⁰

Small molecule antibiotics introduced between 1981-2014

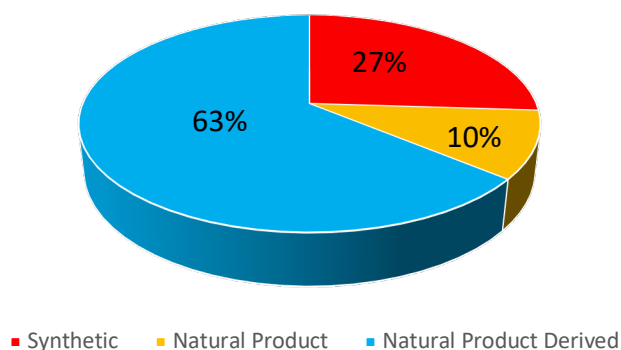


Figure 1.5: Pie chart showing the different classes of small molecule antibiotics introduced between the periods of 1981-2014. Adapted from *J. Nat. Prod.*, 2016, **79**, 629-661.

1.2.2. Target-Oriented Synthesis (TOS)

Target-oriented synthesis (TOS) is a methodology used to synthesise bioactive compounds identified from chemical screens against a pre-selected protein target. Small molecules screened can either be of natural product origins isolated from extracts or be from focused compound libraries.¹¹⁻¹³ Once a hit compound is identified and structurally characterised, retrosynthetic analysis is undertaken to plan its synthesis – or total synthesis in the case of natural products – from simple starting materials (**Figure 1.6**).¹¹⁻¹³

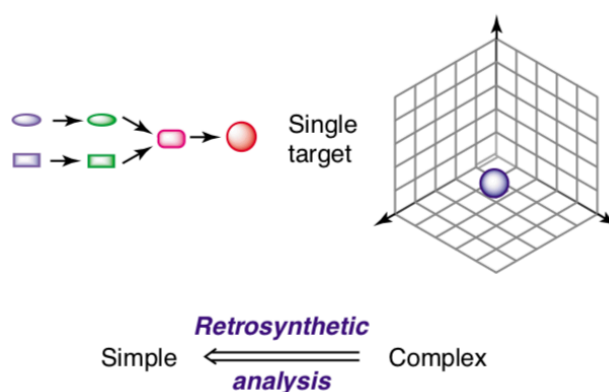


Figure 1.6: Diagram showing the general principle of TOS. Reprinted from *Curr. Opin. Chem. Biol.*, 9, S. Fergus, A. Bender and D.R. Spring, Assessment of Structural Diversity in Combinatorial Synthesis, 304-309, Copyright (2005), with permission from Elsevier.

However, it was soon discovered that a common limitation surrounding TOS was the inability of small molecules to either penetrate bacterial cell walls or be orally bioavailable to humans, and this was particularly true of natural products. Moreover, the total synthesis of these natural products tended to be very laborious and complex. Additionally, in regard to TOS of small molecules arising from compound libraries, although there were compounds that interacted with pre-selected protein targets, these compounds unfortunately could not penetrate the bacterial envelope when tested using whole-cell screens.⁴⁻⁵ As a result, whole-cell screens have significant advantages over target-based screens in that they examine all possible bacterial targets in their physiological context, enabling better lead compounds to be found.¹⁴ As a result, TOS was largely abandoned in favour of other drug discovery processes, at least for the purposes of antibacterial drug discovery.

1.2.3 Combinatorial Chemistry and High-Throughput Screens (HTS)

Combinatorial chemistry was introduced during the resistance era to address the problems which were typically associated with TOS, principally by permitting the examination of a wider region of chemical space by synthesising analogues of the target molecule. Small molecules screened could either be of natural product origins or be from focused compound libraries, where they can be tested against pre-selected protein targets and/or whole-cell screens.^{12-13,15-17} Combinatorial chemistry coupled with high-throughput screens (HTS) has enabled the synthesis and testing of large libraries of compounds in both a rapid and relatively cost-effective manner.^{12-13,15-17} Combinatorial chemistry looks to establish stereochemical diversity, functional group diversity and appendage diversity to explore a wider region of chemical space (**Figures 1.7 and 1.9**).^{12-13,15-17}

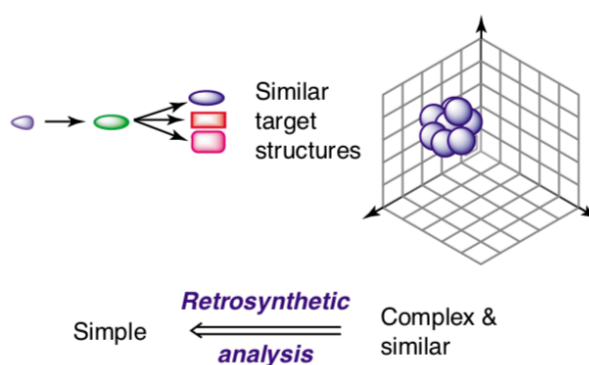


Figure 1.7: Diagram showing the general principle of combinatorial chemistry. Reprinted from *Curr. Opin. Chem. Biol.*, **9**, S. Fergus, A. Bender and D.R. Spring, Assessment of Structural Diversity in Combinatorial Synthesis, 304-309, Copyright (2005), with permission from Elsevier.

However, combinatorial chemistry has also largely failed to deliver new antibiotics.¹⁴ The reason for the lack of success can be attributed to the fact that these compounds lack skeletal diversity. As a result, narrow chemical space is often explored.¹⁴⁻¹⁵ Additionally, it is generally accepted that antibiotics do not tend to follow Lipinski's Rule of Five (Ro5), however, compounds synthesised from combinatorial libraries are heavily skewed towards Lipinski's parameters, which could be a contributory factor as to why combinatorial libraries have failed to deliver new classes of antibiotics thus far.^{5,14-15}

A review by Payne *et al.* detailed a case study whereby GlaxoSmithKline's (GSK) tried to discover new antibiotics through combinatorial-HTS. 70 HTS campaigns were run between 1995-2001, which yielded only 5 lead compounds; amounting to 14 HTS required to discover just 1 lead compound.¹⁴ This approach indicates the difficulties in creating novel antibiotics in an efficient, rapid and cost-effective manner. GSK was not the only big pharma company that struggled to synthesise new antibiotics. Between the period of 1996-2004, 34 pharmaceutical companies ran more than 125 antibacterial screens on more than 60 different bacterial targets, and again, did not find any new antibiotics.¹⁴

1.2.4. Diversity-Oriented Synthesis (DOS)

Diversity-Oriented Synthesis (DOS) was a concept introduced by the Schreiber group during the resistance era to try and address problems which were frequently encountered in combinatorial chemistry, chiefly a lack of chemical diversity.^{11-13,15-17} One of the key features that was considered in DOS was skeletal (scaffold) diversity.^{11-13,15-17} It was believed that a larger chemical space would be explored if skeletal diversity was considered, in addition to other points of diversity which are taken into account with combinatorial libraries (**Figures 1.8 and 1.9**). Thus, it was argued that if a wider region of chemical space was explored, then there was a higher probability of discovering 'drug-like' small molecules.^{11-13,15-17}

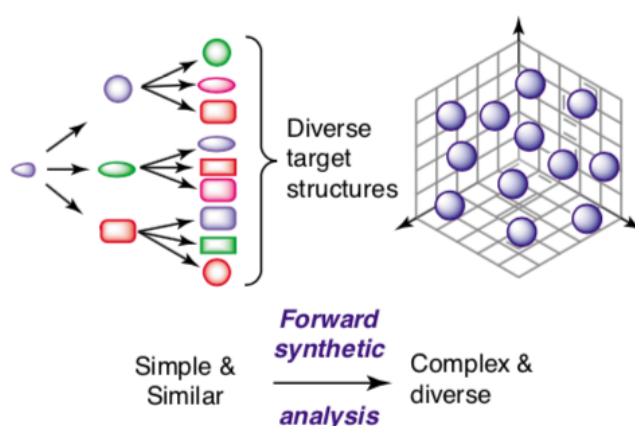


Figure 1.8: Diagram showing the general principle of DOS. Reprinted from *Curr. Opin. Chem. Biol.*, **9**, S. Fergus, A. Bender and D.R. Spring, Assessment of Structural Diversity in Combinatorial Synthesis, 304-309, Copyright (2005), with permission from Elsevier.

DOS adopts a forward synthetic analysis – opposite to that used in TOS and combinatorial libraries – whereby synthetic steps are generally limited to 5 steps to aid both efficiency and cost and often tends to use a build/couple/pair approach.^{11-13,17} As a result, libraries in DOS tend to be much smaller than combinatorial libraries but are structurally more diverse.^{11-13,17} The importance bestowed on skeletal diversity is particularly important as combinatorial libraries tend to be populated by flat small molecules.^{12,17} DOS allows ‘escape from flatland’ with diverse 3-D skeletal structures (**Figure 1.9**) that can allow investigation into potentially untapped or underexplored chemical space in the search for novel antibacterials.¹⁶ However, as of yet, no new classes of antibacterials have been discovered through DOS, although the Spring group has provided a proof-of-concept principle by synthesising compounds that were weakly active against *S. aureus*.¹⁶

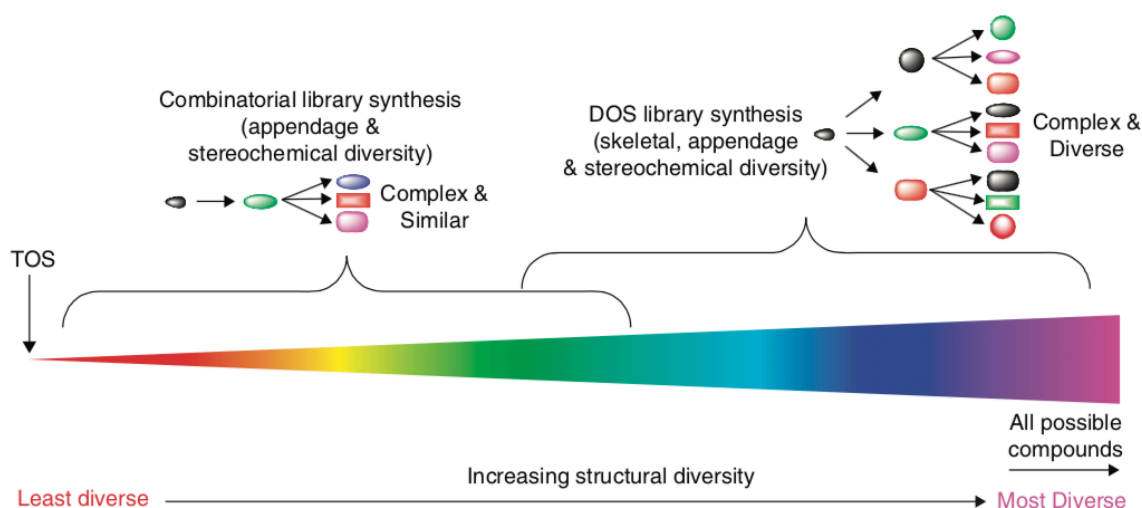


Figure 1.9: Diagram showing the differences in chemical diversity between TOS, combinatorial libraries and DOS. Reproduced from *Expert. Opin. Drug. Discov.*, 2009, **4**, 467-472.

1.2.5. Biology-Oriented Synthesis (BIOS) and Pseudo-Natural Products

Biology-oriented synthesis (BIOS) was a concept devised by the Waldmann group during the resistance era to design compound libraries around natural product scaffolds.¹⁸⁻²¹ It was reasoned that as natural products are bioactive ligands that have evolved over time to bind to specific proteins, they can be considered validated starting points for the design of compound libraries.¹⁸⁻²¹ As natural products tend to have complex structures, compound libraries generated from BIOS tend to be much smaller than

combinatorial libraries but are much more likely to generate lead compounds, as BIOS tends to generate more biologically relevant libraries.¹⁸⁻²¹

Protein Structure Similarity Clustering (PSSC) is an idea originating from BIOS that argues that domains – which are discrete parts of protein that fold independently from the rest of the protein structure – tend to be structurally conserved, either through evolutionary pressures or through thermodynamic stability.¹⁸⁻²¹ As a result, high sequence homology of proteins tend to lead to high structural similarities, although the amino acids encoding these secondary and tertiary structures can be quite different (**Figure 1.10**).¹⁸⁻¹⁹ Hence, if this idea holds true, then natural product ligands can be considered good starting points for ligand identification for other proteins that may have very similar domains.^{18,20-21} Thus, PSSC groups together proteins that have very similar structural binding site subfolds and this allows for the investigation of natural product ligands to be screened against these grouped proteins.^{18,20-21}

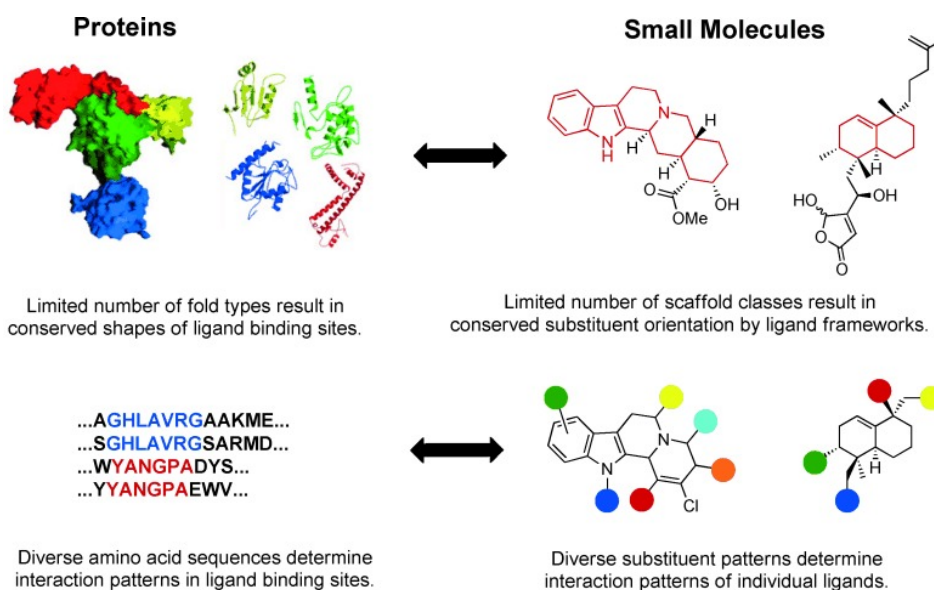


Figure 1.10: Diagram depicting how natural products have conserved scaffolds although the functional groups attached around the periphery of natural product scaffolds can be diverse. Also, protein subfolds tend to be conserved but the amino acid sequence encoding protein's secondary and tertiary structures can be diverse. Copyright (2011) Wiley. Used with permission from S. Wetzel, R.S. Bon, K. Kumar and H. Waldmann, *Biology-Oriented Synthesis, Angew. Chem. Int. Ed.*, Wiley-VCH.

As BIOS looks to create compound libraries which are centred around natural product scaffolds, the Waldmann group has established the Structural Classification of Natural Products (SCONP) to create a tree-like classification system that allows investigation into ‘privileged’ scaffolds.¹⁸⁻²¹ SCONP looks to break down complex natural products into simpler scaffolds, known as ‘parent scaffolds’. This allows the generation of compound libraries to be centred around parent scaffolds, whereby diverse functional groups can be attached around the periphery of the scaffold to better aid protein-ligand interactions (**Figures 1.10 and 1.11**).¹⁸⁻²¹ As a result, it is reasoned that BIOS should produce more compound libraries that bind to protein with better affinity and specificity than compound libraries that are generated randomly from DOS and combinatorial chemistry.¹⁸⁻²¹

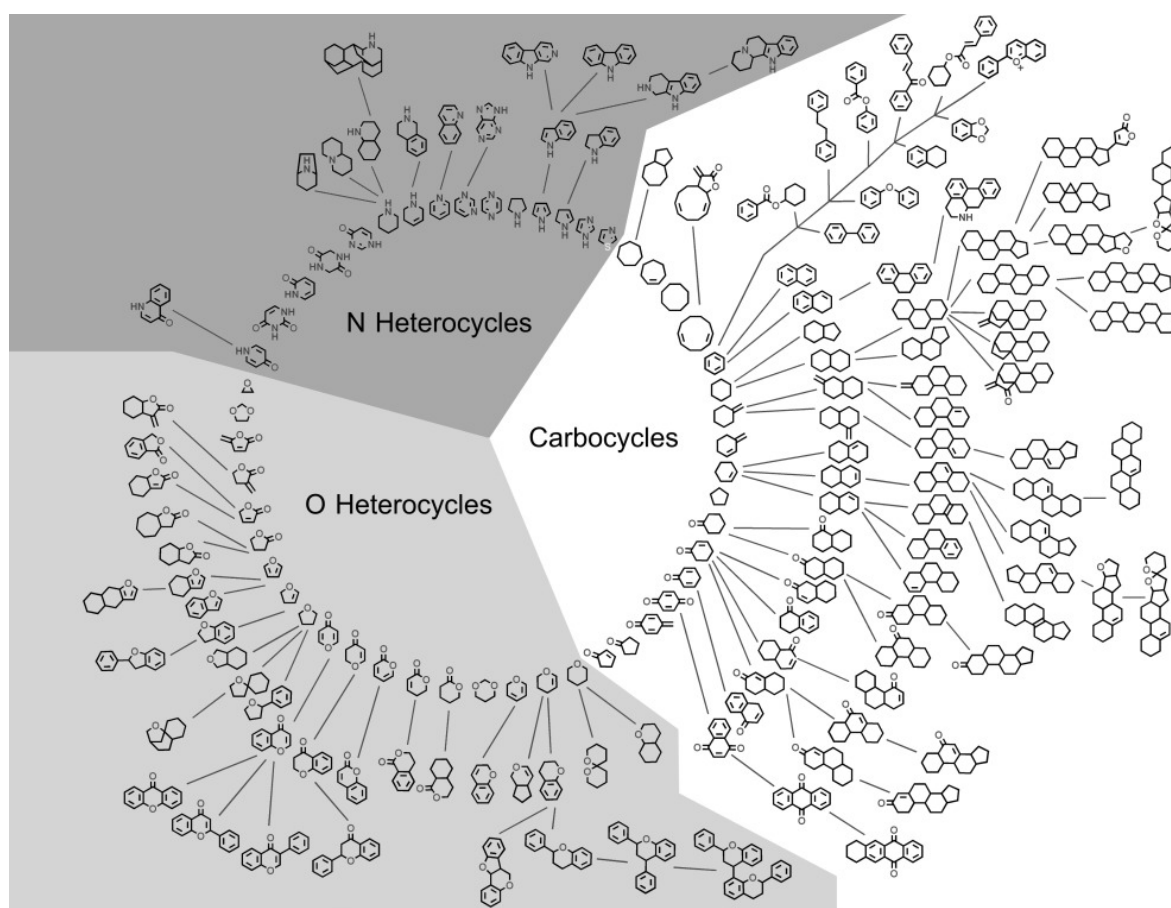


Figure 1.11: Diagram illustrating the SCONP scaffold tree; whereby natural products are reduced to their parent scaffolds. This diagram only shows scaffolds that represent 0.2% of the natural product population in the Dictionary of Natural Products (DNPs). Copyright (2011) Wiley. Used with permission from S. Wetzel, R.S. Bon, K. Kumar and H. Waldmann, Biology-Oriented Synthesis, *Angew. Chem. Int. Ed.*, Wiley-VCH.

However, there is a degree of caution regarding the use of BIOS for antibacterial drug discovery as BIOS tends to conserve the core structural scaffold of natural products. Hence, small molecules synthesised through BIOS are potentially susceptible to the same resistance mechanisms that are also encountered by natural products, similar to that encountered in the semi-synthesis of natural products. However, there has been many antibiotics introduced into the market using BIOS drug discovery, many of which are natural product-derived (**Figure 1.5**). Shown below in **Figure 1.12** are the different methodological approaches of BIOS drug discovery.

However, as compounds synthesised from BIOS tends to occupy the chemical space that is already covered by the guiding natural products, limited chemical space is often explored in comparison to DOS. The Waldmann group have proposed a new theory, dubbed pseudo-natural products. It is theorised that the synthesis of pseudo-natural products could go beyond the chemical and biological space that is often explored by natural products by combining natural product fragments in novel arrangements that is not found in nature, thus making new chemical entities (or scaffolds) in the process.²¹⁻²²

The Dictionary of Natural Products (DNP) is used to identify natural product fragments – of which 2000 natural product fragment clusters were found.²¹⁻²² Unlike the build/couple/pair approach that is often used in DOS, these fragments tend to be combined in many different ways to obtain topologically diverse compounds that may have novel biological activities (**Figure 1.12**).²¹⁻²² The combination of these fragments typically falls into four categories: monopodial connectivity, spirocyclic connectivity, fused ring connectivity and bridged scaffold connectivity.²¹⁻²² However, as of yet, no new antibacterial classes have been uncovered, but this methodology is relatively new and has the potential to unearth new antibacterial classes.

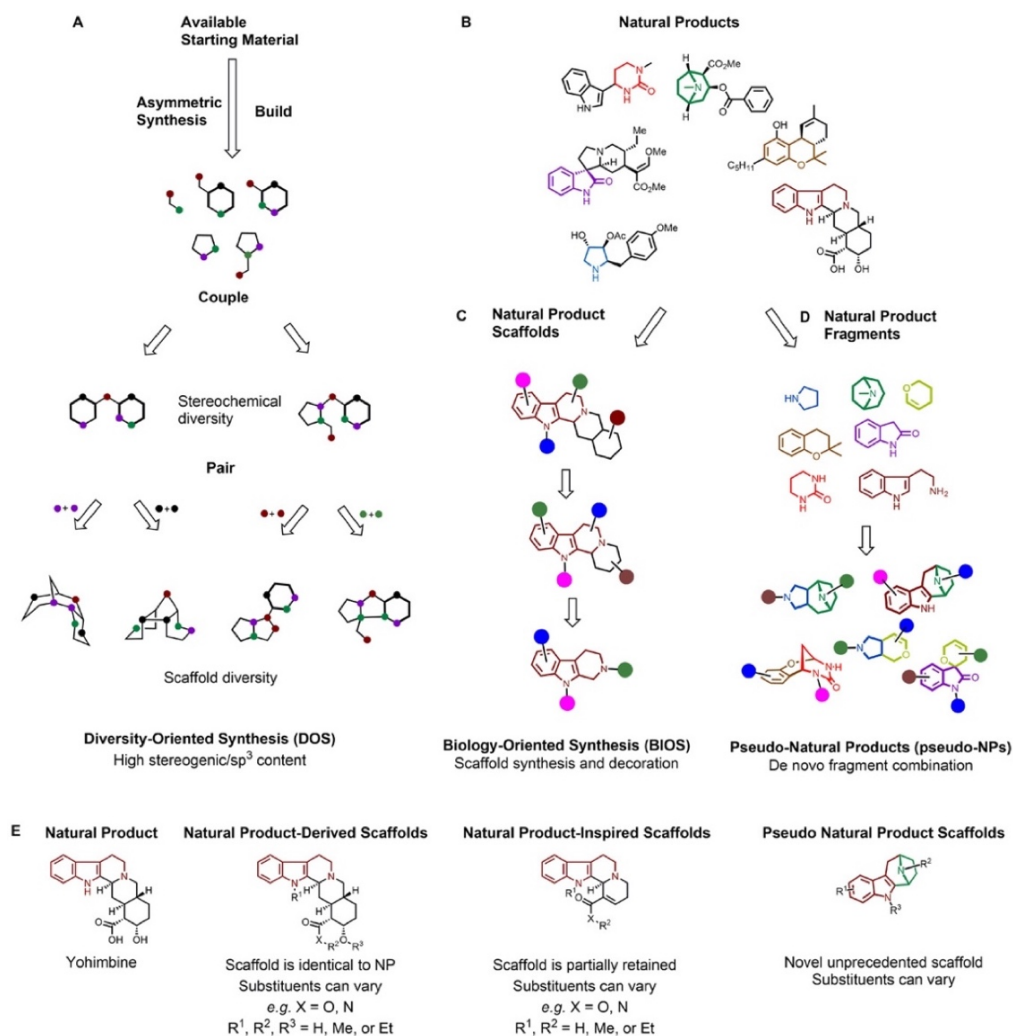


Figure 1.12: Diagram depicting different methodologies towards novel molecular scaffolds with **(A)** highlighting DOS build/couple/pair approach; **(B)** showing a few examples of NPs; **(C)** demonstrating the BIOS methodology of synthesising molecular scaffolds that are inspired by NPs; **(D)** illustrating the unique combination of NP-fragments to yield novel pseudo-natural products and **(E)** highlighting the difference between NP-derived, NP-inspired and pseudo-natural product scaffolds using yohimbine as an example; where NP = natural product. Reproduced from *Angew. Chem. Int. Ed.*, 2021, **60**, 15705-15723.

1.3 The Growth of Antimicrobial Resistance (AMR)

During the early 20th century, infectious diseases was one of the leading causes of death throughout the world, approximately accounting for 25% of England's mortality in the year 1900.¹ However, by 1945, the mortality rate in England for infectious diseases collapsed to under 1% and many argue that

this was due to the widespread use of antibiotics.¹ However, the introduction of antibiotics, was soon followed by antibiotic resistance. It was Sir Alexander Fleming that proposed the idea of antibiotic resistance during his Nobel Prize acceptance speech in 1945, where he argued that either the underuse or overuse of antibiotics can apply selective pressures for bacteria to evolve antibiotic resistance.^{2-3,8} This idea proved to be true, as nearly all antibiotic classes which were introduced into the market have quickly developed antimicrobial resistance; as depicted in **Table 1.1**.⁴⁻⁵

Antibiotic Class	Mode of Action	Year of Discovery	Year of Introduction	Year Resistance Observed
β -Lactams	Inhibition of cell-wall biosynthesis	1928	1938	1945
Sulphonamides	Inhibition of Folate Biosynthesis	1932	1936	1942
Aminoglycosides	Binding of 30S ribosomal subunit	1943	1946	1946
Tetracyclines	Binding of 30S ribosomal subunit	1944	1952	1950
Chloramphenicols	Binding of 50S ribosomal subunit	1946	1948	1950
Macrolides	Binding of 50S ribosomal subunit	1948	1951	1955
Glycopeptides	Inhibition of cell-wall biosynthesis	1953	1958	1960
Oxazolidinones	Binding of 50S ribosomal subunit	1955	2000	2001
Ansamycins	Binding of RNA polymerase β -subunit	1957	1958	1962
Quinolones	Inhibition of DNA Synthesis	1961	1968	1968
Streptogramins	Binding of 50S ribosomal subunit	1963	1998	1964

Table 1.1: Showing the mode of action, year of discovery, year of introduction and year of resistance observed for major antibiotic classes used in public consumption today. Adapted from *Nature*, 2016, **529**, 336-343 and *Nat. Rev. Drug Discov.*, 2013, **12**, 371-387.

Although there were many new antibiotics discovered between the periods of 1930-1980 which minimised antimicrobial resistance (AMR), the dearth of new antibiotics with novel modes of action currently in the antibiotic pipeline has subsequently led to resistance occurring at a much faster rate

than novel antibiotics being produced. If this trajectory continues for the foreseeable future, there are significant worries that medicine might be heading towards the “post-antibiotic era”; where simple infections start to become much more difficult to cure, potentially leading to many deaths. Many argue that this has already come to pass, especially in hospital settings.^{1,4,8}

As of 2013, the US Centre for Disease Control (CDC) have reported 2 million cases of drug-resistant bacterial infections occurring annually, resulting in 23,000 deaths and Europe has reported 700,000 cases associated with antibiotic resistance, resulting in 33,000 deaths annually – and these cases have been steadily rising over the years.¹ It has been predicted by 2050, there will be 10 million deaths per annum if this issue goes unresolved.^{1,23} This has led to many governmental agencies and policymakers together with academics establishing charities and think tanks to strategise methods to overcome AMR with an example being the creation of Antibiotic Research UK (ANTRUK).^{1,7,23}

The lack of new antibiotics in the drug discovery pipeline have compounded the issues of AMR. The problems surrounding antibacterial drug discovery for big pharma companies are multifaceted. Many big pharma companies have spent huge amount of resources to try to find new classes of antibiotics with novel modes of action – usually to no avail – and those that do find a new drug spend on average \$1.7 billion per drug.^{1,7,23-24} As antibiotic therapies tend to only be prescribed for a short period of time – even only a few days – this lowers potential profits.^{1,23} Furthermore, resistance to any new antibiotics introduced into the market is sure to arise overtime, leading to poorer efficacy and thus, a limited lifespan.¹ Thus, novel antibiotics which are introduced into the market today tend to be last resort drugs, again, lowering returns on investments.¹

As a result, antibiotic drug discovery has become unattractive for many big pharmaceutical companies.^{1,23} In fact, as of 2013, there are only 4 big multinational pharma companies left with antibiotic research divisions; with most big pharma companies either curtailing, eliminating or spinning off their antibiotic research divisions.²⁴ This has mainly left small and medium sized (SME) businesses

in addition to academic institutions trying to overcome the problem of AMR.²⁴ As a consequence of this, governmental and intergovernmental agencies have partnered with private companies to try and address the issue of AMR; with an example being the establishment of the Innovative Medicines Initiative – A European Union backed project which looks to find new classes of antibiotics under the New Drugs for Bad Bugs programme.^{1,24}

Additionally, the excessive use of antibiotics for human consumption, agriculture and livestock has proliferated the AMR problem (**Figure 1.13**).^{1,4,23-25} For example, it has been estimated that the US livestock industry consumes 80% of all antibiotics which are produced in the US.⁸ Moreover, there has been a 36% rise in the use of antibiotics for human consumption worldwide between the periods of 2010-2014, with the unregulated misuse of antibiotics being of prime concern.^{1,8}

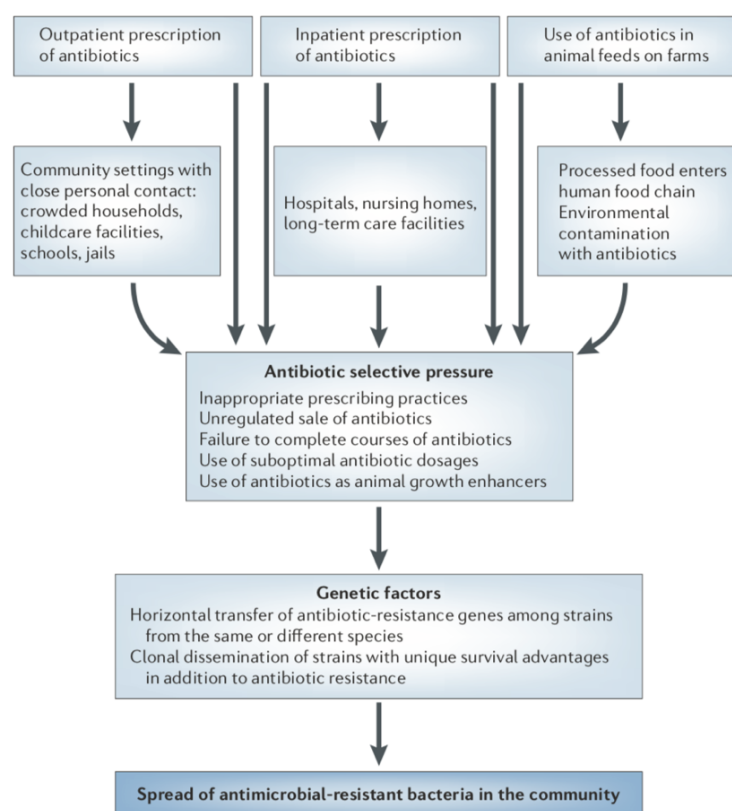


Figure 1.13: Diagram showing how antibiotics are distributed throughout the environment resulting in the subsequent rise in AMR. Reprinted by permission from Springer Nature: *Nat. Rev. Microbiol.*, Antimicrobial-Resistant Bacteria in the Community Setting, E.Y. Furuya and F.D. Lowy, Copyright (2006).

This has led to the development of multidrug-resistant (MDR) bacteria with particularly hard to treat pathogens; *Mycobacterium tuberculosis* and the ESKAPE pathogens – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species – becoming of international concern.^{5,7,26} In addition to this, hospitals are becoming one of the main spreaders of MDR bacteria with 15% of all nosocomial (hospital acquired) infections being due to MDR bacteria; where for some pathogens, there are no effective antibiotics, with an example being the recent emergence of colistin-resistant bacteria in the UK.^{1,7} Furthermore, the sharp rise in the use of last resort antibiotics, in both hospital and community settings has been extremely worrying, with the use of polymyxins and carbapenems seeing rises of 13% and 45% respectively.⁸

1.4. Antibiotic Resistance Mechanisms

Antibiotics work by disrupting key bacterial processes. This can be grouped into 3 categories; the inhibition of cell wall biosynthesis (such as peptidoglycan formation), the inhibition of protein synthesis (such as 30S and 50S ribosomes) and the inhibition of DNA/RNA synthesis (such as DNA topoisomerase and RNA polymerase), outlined in **Table 1.1** and **Figure 1.14**.^{4-5,8}

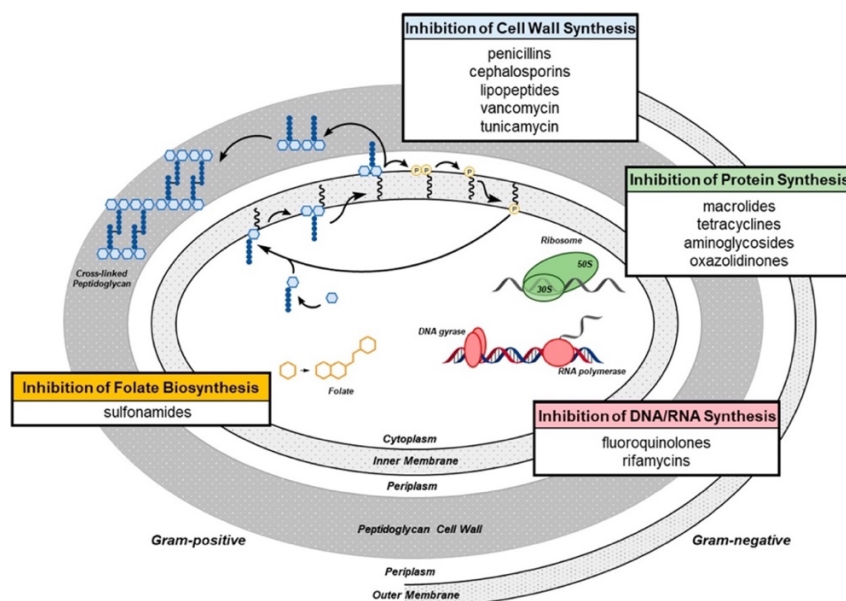


Figure 1.14: Diagram illustrating the different modes of action used by antibiotics to inhibit the growth of bacteria. Reproduced from *Chem. Rev.*, 2017, **117**, 12415-12474.

Although antibiotics target critical pathways which are vital to the survival of bacteria, there has been a growing rise in the number of bacteria developing resistance mechanisms to stop antibiotics hitting bacterial targets. One of the methods adopted by bacteria to evade the effects of antibiotics are efflux pumps. Efflux pumps are transport proteins located in cell membranes that actively transport toxic substances out of bacterial cells (**Figure 1.15**). Efflux pumps are found in both Gram (+) and Gram (-) bacteria and are key contributors to the rise of MDR bacteria; where over the decades, there have been growing reports that more and more efflux pumps are transporting out multiple classes of antibiotics.^{8,26-27}

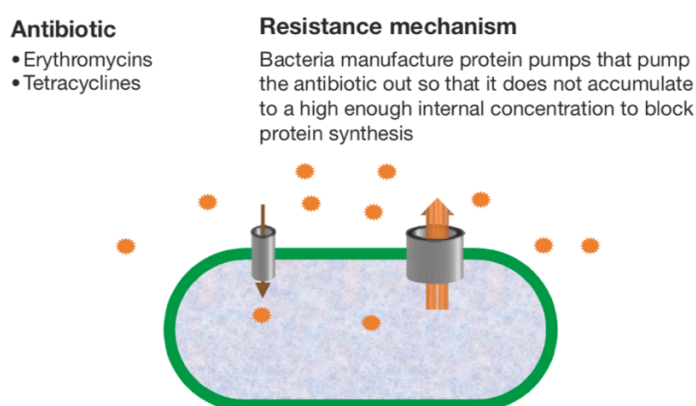


Figure 1.15: Diagram showing how efflux pumps transports antibiotics out of bacterial cells. Reprinted by permission from Springer Nature: *Nature*, Molecular Mechanisms that Confer Antibacterial Drug Resistance, C. Walsh, Copyright (2000).

Another resistance mechanism that some bacteria employ to evade antibiotics is the metabolism of antibiotics via degradation or inactivation, whereby chemical modifications weaken the potency of antibiotics.⁸ A prime example of drug metabolism is the inactivation of β -lactam antibiotics. Many MDR bacteria now produce β -lactamases – that is, enzymes that are produced by bacteria to cleave the highly reactive lactam ring through hydrolysis – to inactivate β -lactams before they enter the bacterial cell (**Figure 1.16**).^{2,8,27}

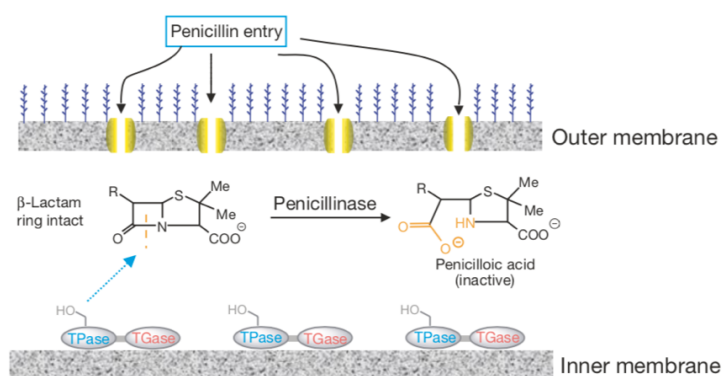


Figure 1.16: Diagram showing how β -lactamases (in this case, penicillinase) inactivates penicillin.

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Modification of protein targets either through chemical modifications and/or single point mutations to binding sites tend to lead to AMR.⁸ Well studied examples of modified protein targets that confer AMR to commonly used antibiotics is the methylation of ribosomes which causes steric congestion, and as a result, leads to the inhibition of macrolide antibiotics.⁸ Additionally, one of the main resistance mechanisms in Enterococci bacteria that confers strong antibiotic resistance to vancomycin (VRE) is the single point mutation in an amino acid sequence, whereby a switch from an amide to an ester linkage causes a 1,000 fold drop in vancomycin's binding affinity (**Figure 1.17**).²⁷

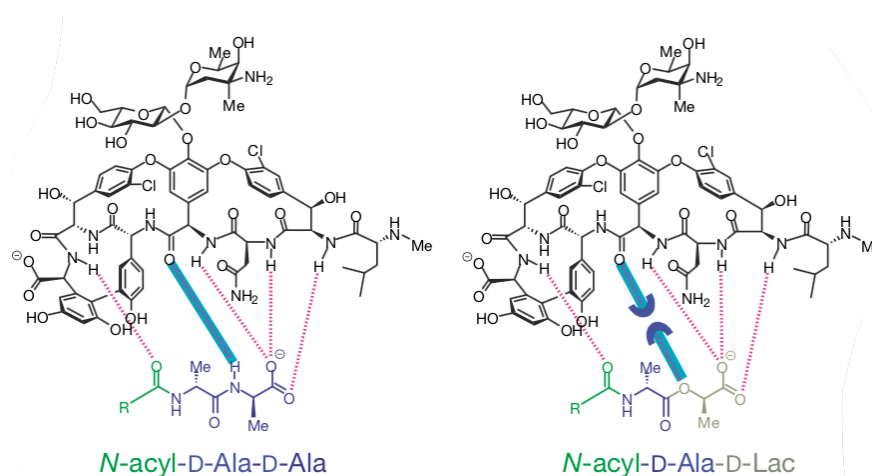


Figure 1.17: Illustrating how modification to a protein target can cause species of Enterococci to develop resistance against vancomycin. Reprinted by permission from Springer Nature: *Nature*, Molecular Mechanisms that Confer Antibacterial Drug Resistance, C. Walsh, Copyright (2000).

It has been hypothesised that the development of antibiotics arose through bacterial competition – whereby bacteria developed metabolites to kill other competing bacteria (antibiosis). If this idea holds true, then resistance mechanisms have been developing for billions of years against various antibiotics mainly found in actinomycetes.⁸ As the ‘fittest’ bacteria survive, resistance mechanisms are passed on to the next generation through various processes outlined below.⁸ However, there is a significant difference between natural evolution occurring over billions of years and the recent phenomena dubbed ‘antibiotic selective pressure’ that has been exacerbated by human activity (**Figure 1.13**).²⁸ Antibiotic selective pressure argues that MDR pathogens gain significant advantage, not only because they are resistant to antibiotics which are used by humans today, but because antibiotic-susceptible bacteria are also eliminated, enabling MDR bacteria to spread rapidly, thus contributing to the AMR problem encountered throughout society today.²⁸

Vertical gene transfer (VGT) is a process whereby bacteria directly transfers genetic material to their offspring through replication. Thus, if a bacterium develops a chance mutation that confers resistance to antibiotics, this chance mutation (also called resistance genes) can be passed onto their offspring. As the replication rate of bacteria is extremely fast, this tends to lead to large colonies of drug resistant bacteria being rapidly formed.

Horizontal gene transfer (HGT) occurs when bacteria transfers genetic material to another bacteria that is not directly their offspring through multiple avenues, such as conjugation, transformation and transduction. It has been argued that HGT has been complicit in the rise of AMR across a range of different species of bacteria, leading to the development of MDR bacteria; as resistance genes are spread throughout bacterial populations through many different avenues (**Figure 1.13**).

Conjugation is the transfer of genetic material through cell-to-cell contact between bacteria via plasmids, enabling resistance genes to be spread from one bacterium to another. Plasmids are circular pieces of DNA that can replicate in bacterial cells, independently from chromosomes (**Figure 1.18**). It

is believed that conjugation is by far one of the most favourable methods to transfer resistance genes, with an example being the spread of the New Delhi Metallo- β -lactamase-1 (NDM-1) genes from *K. pneumoniae* to *E. coli* through plasmids.²⁴ This has allowed some *E. coli* bacteria to develop broad spectrum resistance against most β -lactam antibiotics.²⁴

Transformation is another method of HGT used by bacteria to uptake extracellular genetic material in the form of DNA. This extracellular DNA tends to come from dead bacteria undergoing a process called lysis – whereby the bacterial cell wall starts to break apart – releasing extracellular DNA into their neighbouring environments. Once this extracellular genetic information is taken up by other bacteria, it is then integrated and expressed (**Figure 1.18**). If this extracellular genetic information encodes for resistance against a specific antibiotic, this allows the host bacteria to acquire AMR against this specific antibiotic.

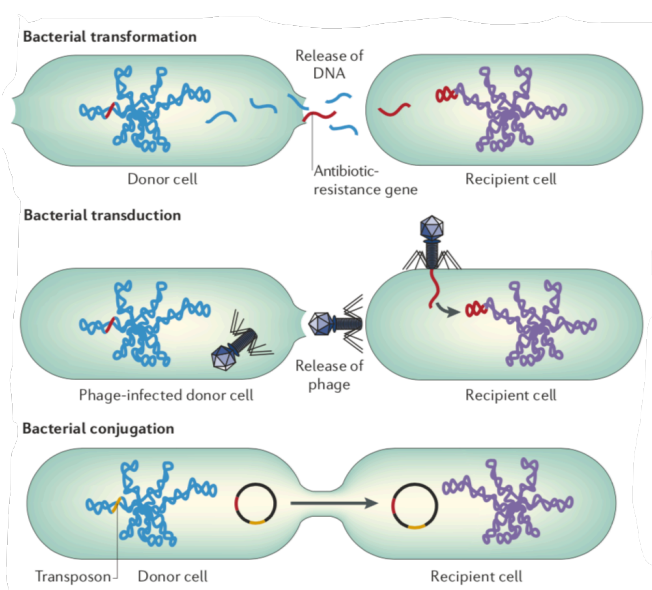


Figure 1.18: Schematic diagram showing different methods used for HGT. Reprinted by permission from Springer Nature: *Nat. Rev. Microbiol.*, Antimicrobial-Resistant Bacteria in the Community Setting, E.Y. Furuya and F.D. Lowy, Copyright (2006).

Lastly, bacteria also use a process called transduction to horizontally transfer genetic material from one bacterium to another through bacteriophages (also known as a phage or bacterial viruses). Bacteriophages attach to bacterial cell walls and release their genetic information into the host's cell and produce enzymes that break down the host's DNA into smaller fragments. This allows phage DNA to be replicated to produce phage proteins. This phage protein replication process continues until the

bacterial cell undergoes lysis, releasing phage material that contains both bacterial DNA and phage DNA into the surrounding area. Phage particles that contain bacterial DNA then infect other bacteria, causing new DNA to be introduced into the recipient's cell, where it integrates into the chromosome. If these phage particles contain bacterial DNA that encode for resistance mechanisms, this allows infected bacteria to develop resistance against many different antibiotics, compounding the AMR problem (**Figure 1.18**).

1.5: Tetramic Acids

Tetramates **1a** are a class of compounds that contain a pyrrolidine-2,4-dione ring but can readily tautomerise to the enolic tetramic acids **1b** (**Figure 1.19**); as a result, this thesis will frequently interchange terminology between the use of tetramic acids and tetramates. Tetramates are widely found in many natural products and are often isolated from fungi, mould, bacteria and sponges.²⁹⁻³¹ Tetramates have been gaining widespread attention in recent years, principally due to their structural complexity and vast biological activities – ranging from antimicrobial, antitumour, antiviral and antifungal activities.²⁹⁻³¹

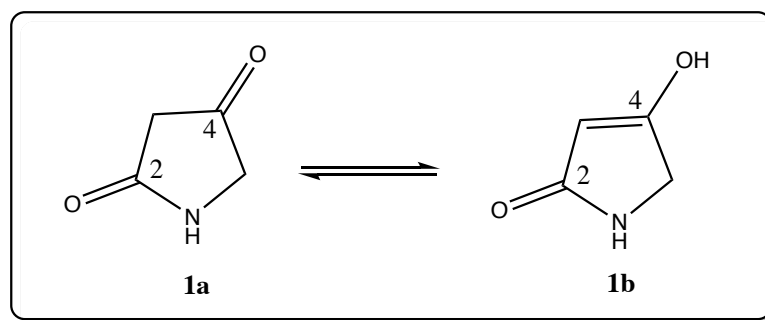


Figure: 1.19: Showing the pyrrolidine-2,4-dione ring system **1a** and its tautomer **1b**.

1.5.1 Natural Product Tetramic Acids with Antibacterial Activity

There is a need to find new classes of antibiotics to tackle the AMR problem. Natural products that contain the tetramate scaffold offer significant promise in this regard.³² There are many tetramic acid natural products that have potent antibacterial activity against Gram (+) and Gram (-) bacteria with

various modes of action detected. As a result, tetramates have captured the attention of the chemical and biological community as a whole.²⁹⁻³³

Tetramic acid natural products tend to be divided into six classes; C3-acyltetramic acids (which are subdivided into simple C3-acyltetramic acids, C3-dienoyltetramic acids, C3-polyenoyltetramic acids and C3-decalinoyltetramic acids), C3-spirotetramic acids, macrocyclic tetramic acids, *N*-acyl tetramic acids, α -cyclopiazonic acid (CPA)-type tetramic acids and other (uncategorised) tetramic acids.³⁰ This research will specifically focus on C3-acyltetramic acids as many of these natural products tend to have antibacterial activity.

N-Acyl tetramic acids are a common motif that are frequently discovered in nature, which display diverse biological activities. An example is reutericyclin **2** – isolated from *Lactobacillus reuteri* – which has potent antibacterial activity against a range of Gram (+) bacteria; with a minimum inhibitory concentration range – that is, the minimum concentration required to inhibit the growth of bacteria – between 0.08-6.25 $\mu\text{g/ml}$ (**Figure 1.20**).³⁰ Reutericyclin **2** works by behaving as a proton ionophore which depolarises bacterial membranes.³⁰ However, reutericyclin **2** does not show any antibacterial activity against Gram (-) bacteria.³⁰

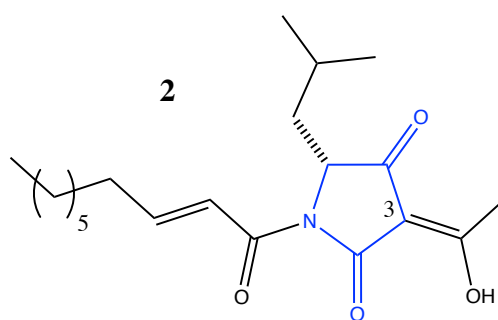


Figure 1.20: Showing the structure of reutericyclin **2**.

Equisetin **3** is a natural product that was isolated from *Fusarium equisetin* and *F. heterosporum* that showed various biological activities; ranging from HIV inhibitory activity to cytotoxic activity (**Figure 1.21**).³⁰ Equisetin **3** also exhibits antibacterial activity against *S. aureus* with a MIC value of 1 $\mu\text{g/ml}$

observed.³¹⁻³² There are many tetramic acid natural products that have the C3-decalin systems incorporated into their respective structures and they are generally known as C3-decalinoyltetramic acids; with another antibacterial example being altersetin.³¹

Streptolydigin **4** is a C3-acyltetramic acid natural product that was isolated from *Streptomyces lydicus* in 1955 (**Figure 1.21**).³⁰ Streptolydigin **4** is an interesting molecule as it is known to inhibit bacterial RNA polymerase (RNAP) by interfering with RNA chain elongation during transcription.³⁰ Bacterial RNAP has recently become an attractive target in antibacterial chemotherapy, as it is highly conserved while being different to eukaryotic RNAP, thus potentially permitting broad spectrum activity while having therapeutic selectivity, thus making streptolydigin **4** an attractive molecule to build focused compound libraries around – this will be further discussed later on in this chapter.³³ Streptolydigin **4** are also classed as C3-dienoyltetramic acids; with another antibacterial example being the tirandamycin family.²⁹⁻³¹

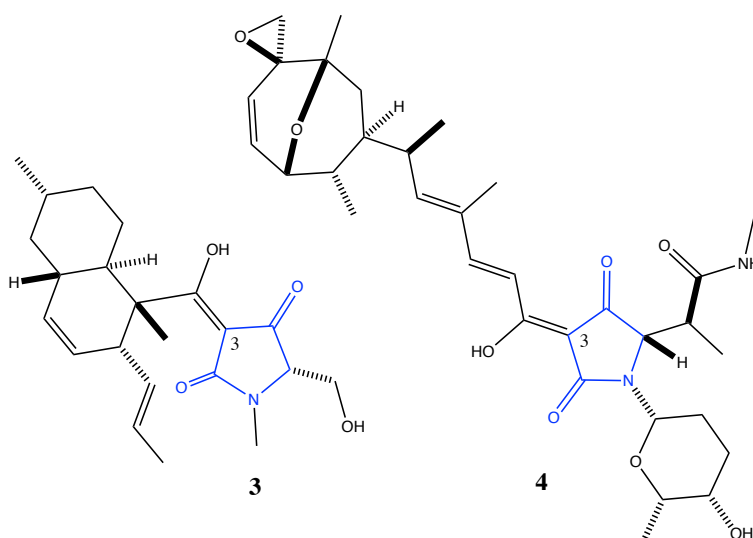


Figure 1.21: Showing the structures of equisetin **3** and streptolydigin **4**.

Kibdelomycin **5** was isolated from *Kibdelosporangium* sp. and displays broad spectrum activity against a range of Gram (+) and some Gram (-) bacteria; with kibdelomycin **5** having a MIC value of 0.5 $\mu\text{g/ml}$ against *S. aureus* (**Figure 1.22**).³⁰ Kibdelomycin's **5** mode of action involves the inhibition of bacterial type II topoisomerase.³⁰ Moreover, kibdelomycin **5** has also shown no cross-resistance to other known

bacterial type II topoisomerase inhibitors such as novobiocin and ciprofloxacin, making this natural product an attractive target for antibacterial drug discovery; particularly as kibelomycin **5** has a unique binding site interaction with DNA gyrase and topoisomerase IV, but also shows low frequency of resistance against *S. aureus*.³⁰

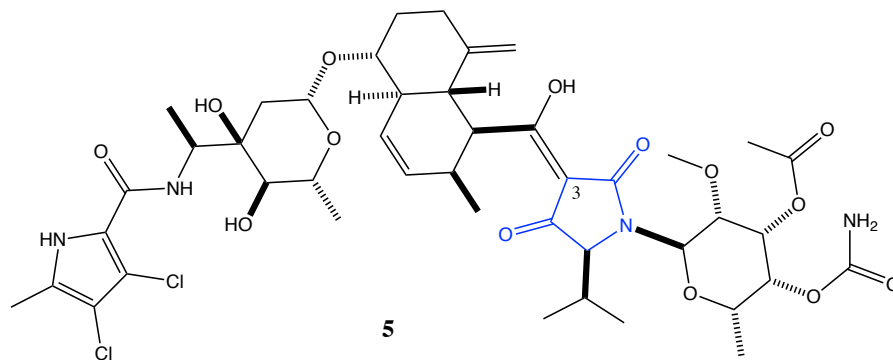


Figure 1.22: Showing the structure of kibelomycin **5**.

Virgineone **6** is a tyrosine-derived C3-acyltetramic acid that was isolated from *Lachnum virgineum*, and subsequently isolated from other species such as *Bionectria* as well.³⁰ Additionally, its aglycone counterpart **7** was also isolated (**Figure 1.23**), and it has been shown that the aglycone **7** is more potent than its sugar counterpart **6**; with virgineone aglycone **7** having a MIC value between 2.8-5.5 $\mu\text{g/ml}$ against MRSA in comparison to virgineone **6**, which has a MIC value of 7.2 $\mu\text{g/ml}$.³⁰

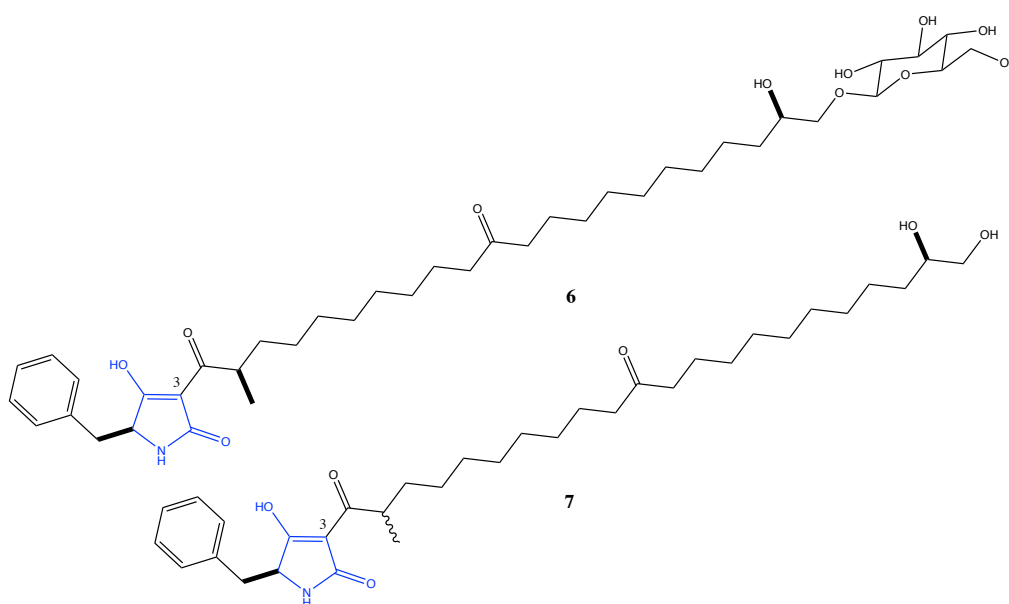
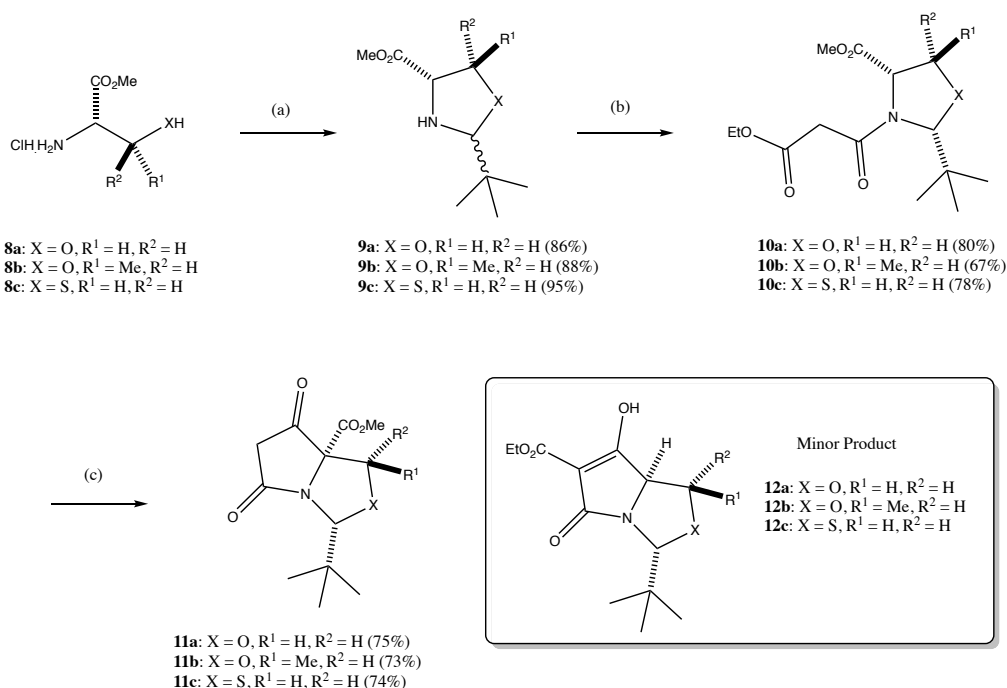


Figure 1.23: Showing the structures of virgineone **6** and its aglycone counterpart **7**.

1.6: Previous Work in the Moloney Group

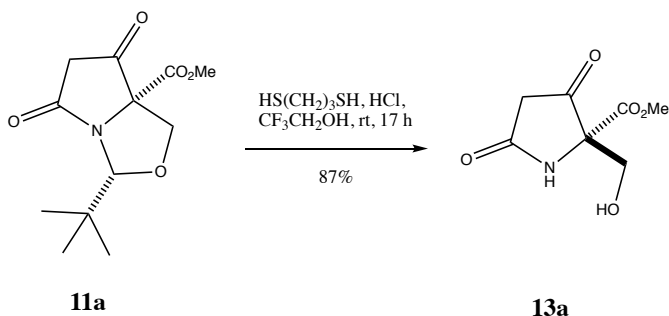
1.6.1. Synthesis of Tetramate Cores

The Moloney group have long been interested in devising synthetic methodologies for obtaining tetramic acids for the purposes of total synthesis and medicinal chemistry. The Moloney group have developed various strategies of obtaining enantiopure bicyclic tetramic acids in a rapid, stereoselective manner, using cheap chiral starting materials (**Scheme 1.1**).³⁴ Moloney's strategy looks to condense methyl ester hydrochlorides **8a-c** with pivaldehyde to form oxa(thia)zolidines **9a-c** as a mixture of diastereomers. Subsequent *N*-acylation with ethyl hydrogen malonate under DCC/DMAP coupling conditions were used to form stereoselective malonamides **10a-c**, where predominantly 1 diastereomer was formed.³⁴ Utilising Seebach's 'Self-Regeneration of Stereocenters' principle, chemoselective Dieckmann cyclisation using KO^tBu yielded enantiopure, stereoselective bicyclic tetramates **11a-c** and **12a-c** – where the minor product **12a-c** could be separated from the major product **11a-c** through a simple extraction process (**Scheme 1.1**).³⁴⁻³⁵



Scheme 1.1: Stereoselective synthesis of bicyclic tetramates **11a-c** and **12a-c** from methyl ester hydrochlorides **8a-c**; (a) pivaldehyde, Et₃N, petroleum ether 40:60, >100°C, Dean-Stark, 18 h; (b) ethyl hydrogen malonate, DCC, DMAP, DCM, rt, 5 h; (c) KO^tBu, THF, reflux, 3 h.

N,O-acetal deprotection of bicyclic tetramates **11a-c** could then be undertaken using Corey-Reichard's protocols to form stereoselective monocyclic tetramic acids **13a-c** (**Scheme 1.2**).³⁴



Scheme 1.2: The synthesis of monocyclic tetramate **13a** using Corey-Reichard's protocol.

Extensive antibacterial studies of monocyclic **13a-c** and bicyclic tetramic acids **11a-c**, **12a-c** derived from amino ester hydrochlorides **8a-c** have shown that the core tetramate scaffolds are inactive against a panel of Gram (+) and Gram (-) bacteria.³² However, it has been demonstrated that appropriate structural appendage around the core tetramate scaffold can restore potent antibacterial activity, analogues to that seen in natural product tetramates.³²

1.6.2: Tetramate Library Generation Inspired by Natural Products

The Moloney group have extensively investigated functionalisation at the C6 and C7-position of bicyclic tetramates **11a-c** to probe for antibacterial activity; with many natural product tetramates tending to have complex structures at these two positions which is thought to bring about the potent bioactivities generally seen across the tetramate system (**Figure 1.24**).³⁰⁻³¹

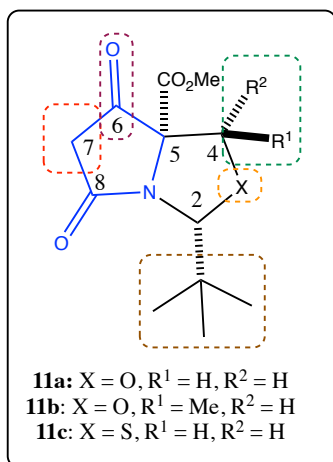


Figure 1.24: Various points of functionalisation possible across the bicyclic tetramate core **11a-c**.

1.6.2.1. C6-Pyroglutamate Library Generation Inspired by Oxazolomycin and Lajollamycin

Both oxazolomycin **14a-d** and lajollamycin **15a-c** have become the focus of attention for many total synthesis research groups; principally due to its unique scaffold – consisting of a spiro- β -lactone- γ -lactam ring – and diverse bioactivities; where for example, lajollamycin A has a MIC value between 1.5-20 $\mu\text{g/ml}$ against a panel of Gram (+) bacteria (**Figure 1.25**).^{31,36}

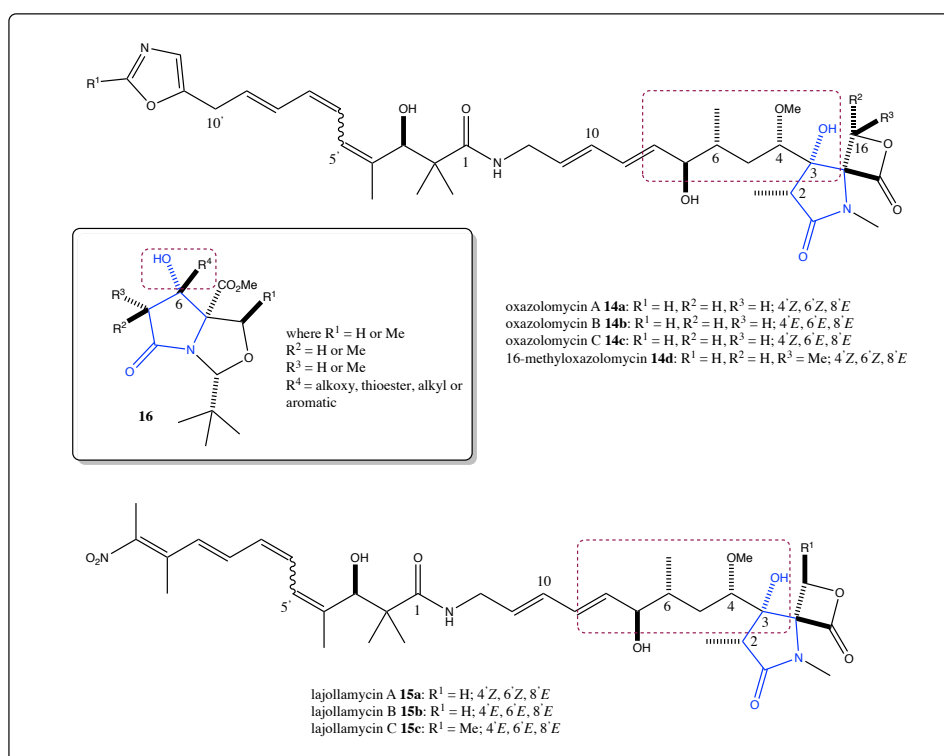
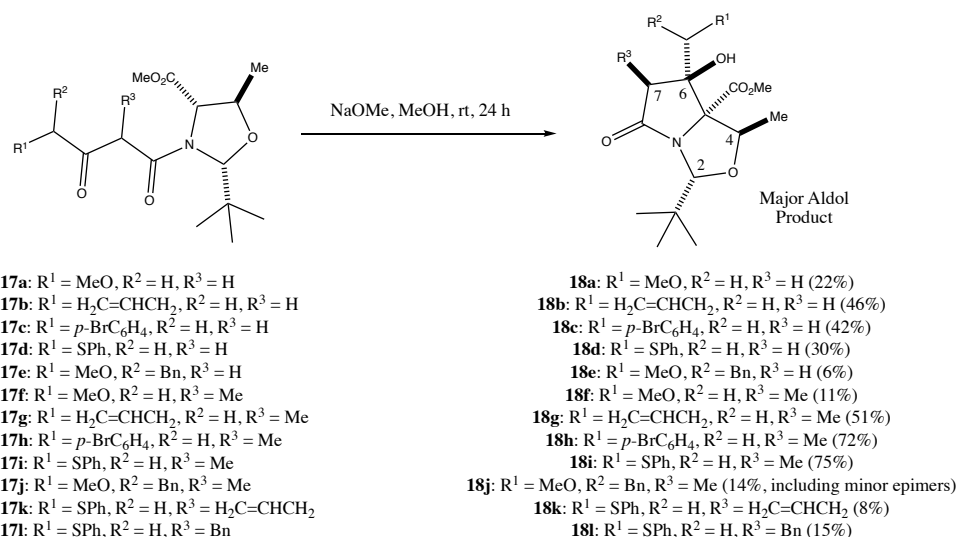


Figure 1.25: Showing the structures of the oxazolomycin **14a-d** and lajollamycin **15a-c** families, and the bicyclic pyroglutamate **16** that was synthesised to mimic these natural products.

Heavyside *et al.* established a methodology for obtaining simple mimics of oxazolomycin **14** and lajollamycin **15** by functionalising the C6-position of the bicyclic core **16**.³⁶ The critical step for these reactions was the intramolecular aldol ring closure of malonamides **17a-l** to form a library of densely functionalised pyroglutamates from commercially available starting materials with high levels of diastereoselectivity.³⁶ *N*-Acylation of oxazolidine **9b** with various β -ketoacids provided the opportunity for ample side-chain manipulation **17a-l**.³⁶ This enabled cyclised products **18a-l** to be obtained with functional group diversity attached at the C6-position, thus, allowing for investigation into the chemical components which are necessary for antibacterial activity (**Scheme 1.3**).³⁶



Scheme 1.3: The synthesis of densely functionalised pyroglutamates **18a-l** from malonamides **17a-l**.

Adapted from *RSC Adv.*, 2014, **4**, 16233-16249.

However, issues surrounding modest to poor yields frequently obtained when coupling β -ketoacids with oxazolidines **9b** in addition to the modest yields obtained for cyclised products **18a-l** severely limited the development of an extensive library.³⁶ Additionally, these oxazolomycin mimics had very little antibacterial activity against *S. aureus* and *E. coli*, similar to that experienced by the oxazolomycin family.³⁶ Angelov *et al.* and Almahli *et al.* also examined the antibacterial activity of intramolecular aldol cyclised pyroglutamates derived from L-serine and L-cysteine-based oxa(thia)zolidines **9a/9c**, and again concluded that there was very weak antibacterial activity in these systems.³⁷⁻³⁸ As a result, it was reasoned that C6-functionalisation did not contribute extensively to the antibacterial activity within these bicyclic structures.

1.6.2.2: C7-Acyltetramate Library Generation Inspired by Pramanicin and Harzianic Acid

Hydroxylated pyrrolidinone, pramanicin **19**, and tetramic acids, harzianic acid **20** and ravenic acid **21** have diverse bioactivities – displaying antibacterial, antifungal and anti-cancer activities (**Figure 1.26**).^{30,32,39-40} The common structural motif shared between these natural products is the C3-acyl substituent. As the tetramate nucleus is devoid of antibacterial activity, it was reasoned that the antibacterial activity seen across a range of natural products (shown in **Figure 1.26**) was due to the

diverse structures that were commonly attached at the C3-position – where chemical diversity mostly lies. This, as a result, warranted extensive examination, whereby bicyclic tetramates of type **22** were functionalised at the C7-position to examine for potential antibacterial activity against a range of Gram (+) and Gram (-) bacteria (**Figure 1.26**).

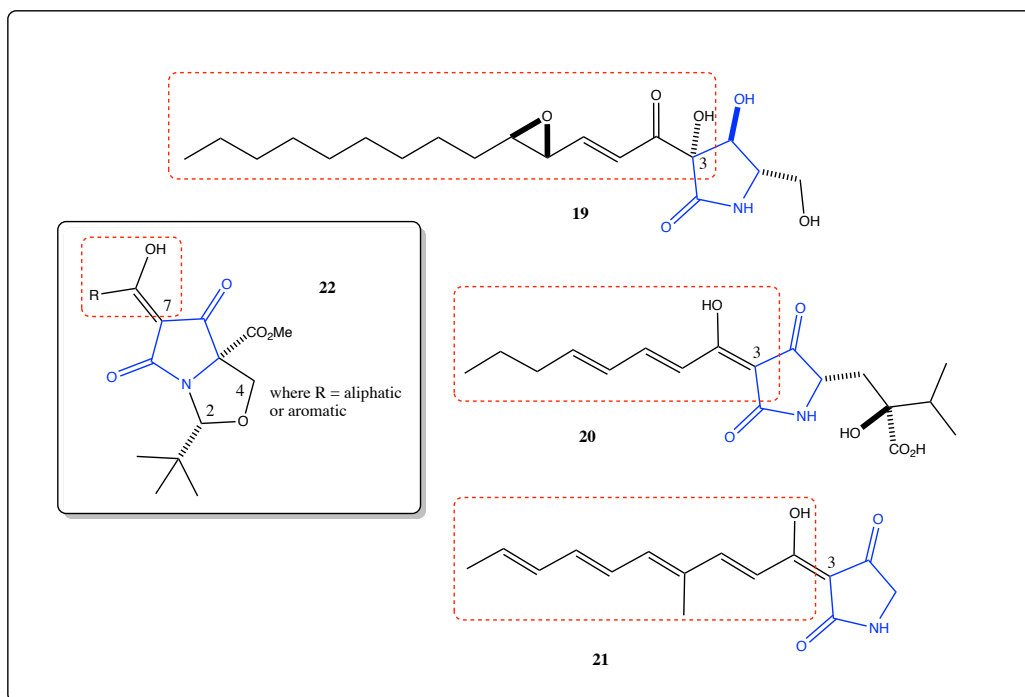
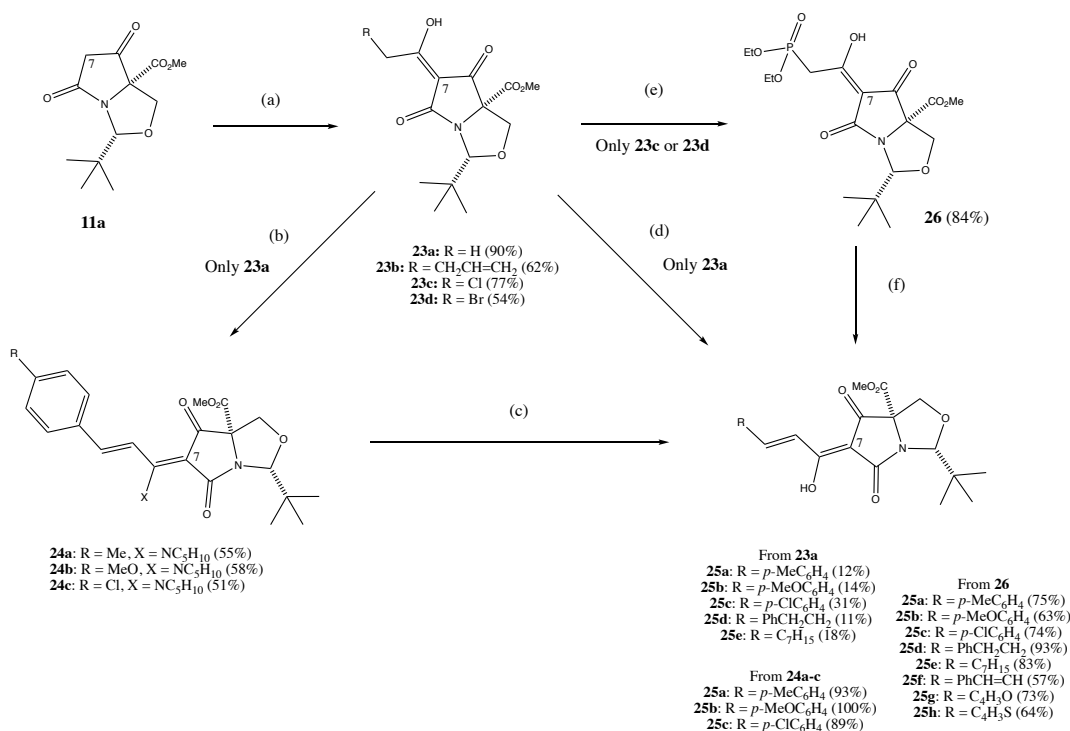


Figure 1.26: Showing the structures of pramanicin **19**, harzianic acid **20** and ravenic acid **21**, and the core bicyclic structure **22** that was synthesised in the Moloney group.

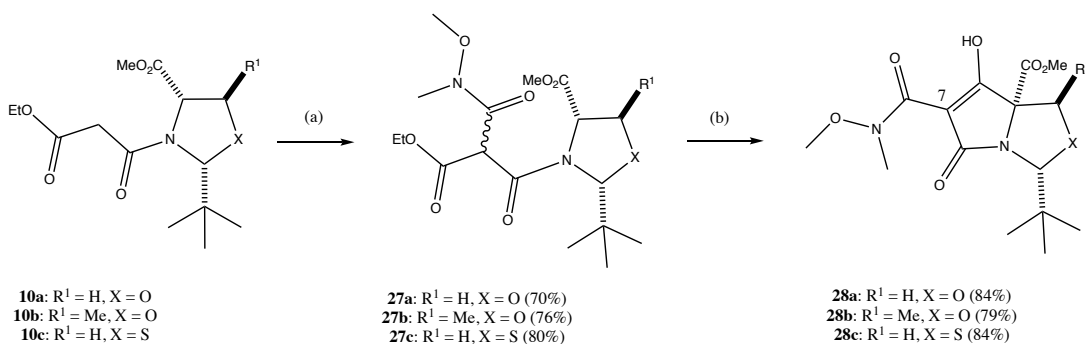
Tan *et al.* introduced C7-acyl sidechains by coupling tetramate **11a** to carboxylic acids to obtain tetramates **23a-d** in good to excellent yields.³⁹ This allowed the opportunity to further functionalise the C7-acyl moiety by reacting tetramates **23a** with aldehydes in the presence of a mild base to form enamines **24a-c**.³⁹ These enamines **24a-c** could then be hydrolysed to form enols **25a-c**.³⁹ Alternatively, tetramates **23c-d** could be reacted with diethyl phosphite to form phosphonate **26**, which would allow for a Horner-Wadsworth-Emmons (HWE) reaction to take place with a series of aldehydes using KO^tBu as a base to form compounds **25a-h** (**Scheme 1.4**).³⁹ Tetramates **25a-h** served as structural mimics of pramanicin **19**, harzianic acid **20** and ravenic acid **21** and were subsequently tested for antibacterial activity.



Scheme 1.4: Reaction scheme showing the incorporation of C7-acyl sidechains from bicyclic tetramate **11a**; (a) $\text{RCH}_2\text{C(O)OH}$, DCC, DMAP, DCM, rt; (b) $\text{RC}_6\text{H}_4\text{CHO}$, piperidine, toluene, reflux; (c) LiOH, THF-H₂O, rt; (d) LDA, RCHO, -10°C - rt; (e) NaH, (EtO)₂P(O)H, THF, rt; (f) KO^tBu, THF, 0°C.

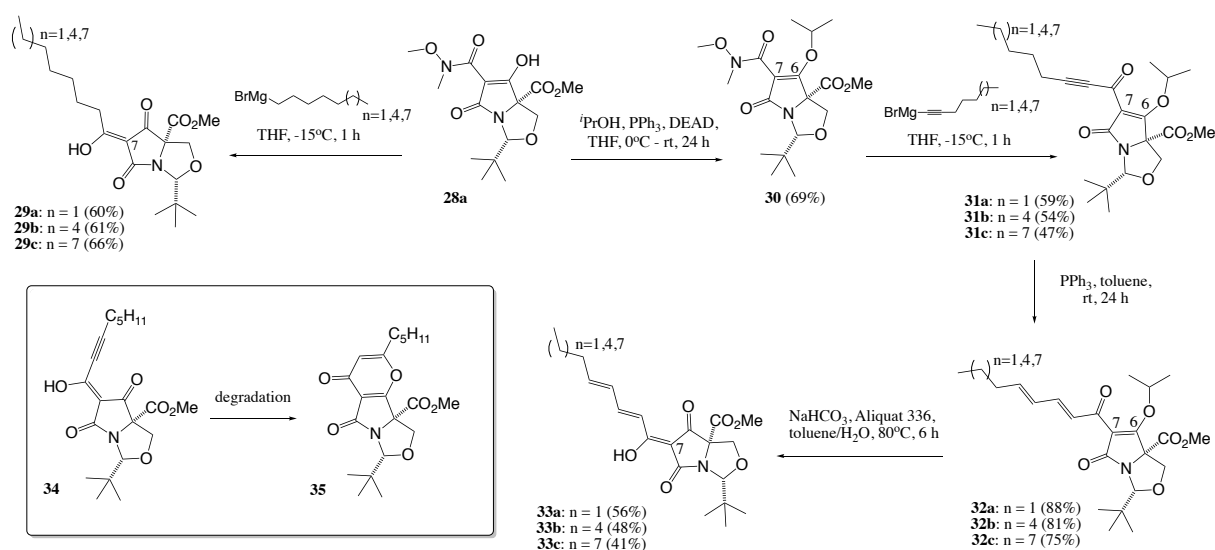
Many of the compounds examined exhibited antibacterial activity against *S. aureus*, where longer hydrophobic side chains led to more potent bioactivity.³⁹ However, no activity was observed against *E. coli*. Tan *et al.* extended this approach by synthesising monocyclic and bicyclic epoxyprolidinones from pyroglutamate starting materials.⁴⁰ These systems demonstrated good antibacterial activity against both *S. aureus* and *E. coli* bacteria – where it was reasoned that the bioactivity observed against *E. coli* was probably due to increased polarity within the molecule, thus, enabling better cell membrane permeability within *E. coli* bacteria.⁴⁰

Josa-Culleré *et al.* further elaborated on C7-functionalisation by introducing C7-Weinreb amides into tetramates **28a-c**.⁴¹⁻⁴² This was achieved by reacting malonamides **10a-c** with methoxy(methyl)carbamic chloride to furnish malonamides **27a-c** in good yields as mixture of diastereomers.⁴¹⁻⁴² Chemoselective Dieckmann cyclisation with DBU led to the formation of C7-Weinreb amides **28a-c** in excellent yields (**Scheme 1.5**).⁴¹⁻⁴²



Scheme 1.5: Showing the synthesis of Weinreb amide **28a-c** from malonamide **27a-c**; (a) methoxy(methyl)carbamic chloride, pyridine, MgBr₂, DCM, rt, 24 h; (b) DBU, THF, rt, 24 h.

With the C7-Weinreb amide **28a-c** in place, a library of alkyl and alkenyl substituents was examined. Reaction of tetramate **28a** with alkyl Grignard reagents led to the formation of tetramates **29a-c** in modest yields.⁴² Additionally, it was shown that C7-ynone **34** decomposes to tricyclic compound **35**,⁴² however, if the C6-hydroxyl group was protected to form enol **30** – using Mitsunobu-like conditions – this prevented decomposition (**Scheme 1.6**).⁴¹⁻⁴² This allowed alkynyl Grignard additions to be undertaken in acceptable yields **31a-c**. Isomerisation followed by C6-deprotection led to the formation of C7-dienoyltetramates **32a-c** that served as close structural mimics to pramanicin **19**, harzianic acid **20** and ravenic acid **21**; with the antibacterial activity of these compounds shown in **Table 1.2** below.⁴²



Scheme 1.6: Reaction scheme demonstrating how mimics of harzianic acid **20** and ravenic acid **21** could be obtained from Weinreb amide **28a**. Adapted from *J. Org. Chem.*, 2018, **83**, 10303-10317.

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>E. faecalis</i>	<i>S. pneumoniae</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>C. krusei</i>	<i>A. fumigatus</i>
29a	n.a.	2	2	6	500	500	500	200
29b	n.a.	2	2	2	n.a.	250	250	8
29c	n.a.	2	2	2	n.a.	250	250	250
33a	n.a.	31	16	31	n.a.	250	250	250
33b	n.a.	1	1	1	250	250	250	62
33c	n.a.	2	2	2	n.a.	500	500	n.a

Table 1.2: *In-vitro* antibacterial and antifungal activity (MIC, $\mu\text{g/ml}$) of C7-acyltetramic acids **29a-c** and **33a-c**; where n.a. = not active. Adapted from *J. Org. Chem.*, 2018, **83**, 10303-10317.

C7-Acyltetramates **29a-c** and **33a-c** exhibited antibacterial activity against *S. aureus*, with MIC values ranging between 1-31 $\mu\text{g/ml}$.⁴² The length of the C7-sidechain influenced bioactivity, whereby an increase in lipophilicity led to more potent bioactivity (**Table 1.2**).⁴² However, no activity was observed against *E. coli*.⁴² Additionally, the C6-isopropyl protected tetramate **32c** was completely inactive against *S. aureus* and *E. coli* – indicating that the C6-hydroxyl group in the tetramate pharmacophore is potentially important for bioactivity, possibly due to favourable protein-ligands interactions.⁴²

1.6.2.3: C7-Carboxamidotetramate Library Generation Inspired by Streptolydigin, Kibdelomycin and Novartis' UPPS Inhibitor

As discussed earlier in **Chapter 1.5.1**, streptolydigin **4** and kibdelomycin **5** are attractive targets in antibacterial drug discovery, principally due to their mode of action – whereby streptolydigin **4** is known to target RNAP and kibdelomycin **5** is known to inhibit bacterial type II topoisomerase.³⁰ Recently, Novartis discovered a potent antibacterial agent **36** that targeted undecaprenyl pyrophosphate synthase (UPPS) – an enzyme that serves as a lipid carrier for peptidoglycan synthesis of bacterial cell walls (**Figure 1.27**).^{33,43} Thus, a question arose as to whether the C3-carboxamido moiety was critical to the novel mode of action seen, and whether this can be extended to bicyclic tetramates of type **37** (**Figure 1.28**).

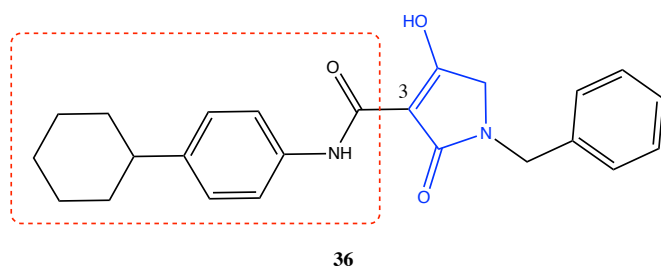


Figure 1.27: Showing the structure of Novartis' UPPS inhibitor **36**.

As a result, the Moloney group synthesised a large library of C7-carboxamido/acyl tetramic acids to study their respective modes of action, taking inspiration from streptolydigin **4**, kibdelomycin **5** and Novartis' UPPS inhibitor **36**. Jeong *et al.* synthesised 162 tetramic acids and discovered that several bicyclic C7-carboxamides of type **37** were potent against a range of Gram (+) bacteria that displayed dual modes of action against UPPS and RNAP, thus illustrating the power of using natural product-inspired/BIOS drug discovery to discover novel antibiotics (**Figure 1.28**).⁴³ Moreover, this dual mode of action could prove to be very important in potentially reducing the chances of resistance occurring against this class of compound, as it targets two independent bacterial processes which are vital to bacterial survival.⁴³

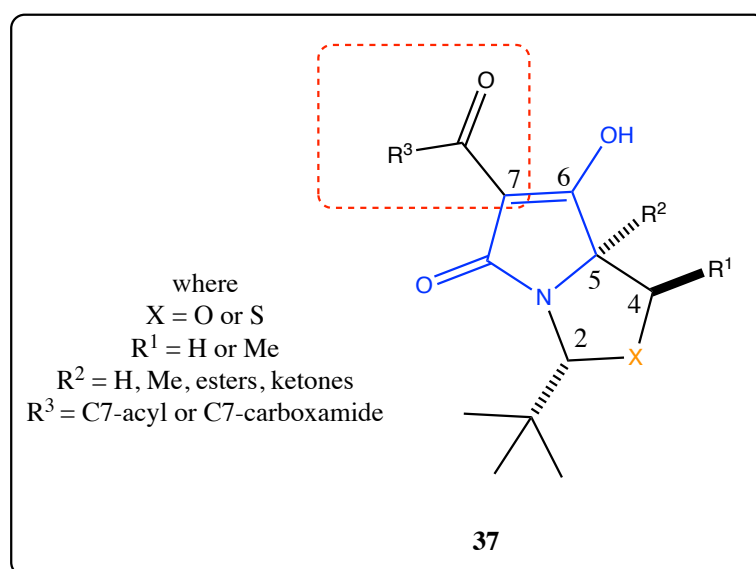


Figure 1.28: General structure of bicyclic tetramic acid **37** that possessed dual modes of action.

Structure-activity relationship (SAR) analysis demonstrated that C7-carboxamides (R^3) (**Figure 1.28**) which displayed the most potent antibacterial activity against a wide range of Gram (+) bacteria and

also had a dual mode of action, tended to either have large aliphatic C7-carboxamide pendants or bulky aromatic C7-carboxamide pendants.⁴³ Additionally, enzyme inhibition of UPPS and RNAP was weakly affected by substitutions patterns at the C4 (where $R^1 = \text{H}$ or Me), C5 (where $R^2 = \text{H}$, Me, ester or ketone) and heteroatom positions (where $X = \text{O}$, S) (**Figure 1.28**).⁴³ It was also shown that some bicyclic C7-acyl pendants had dual modes of action, however, their effectiveness at inhibiting UPPS in comparison to C7-carboxamidotetramates was considerably lower, illustrating that the C7-carboxamido functionality plays a critical role in inhibiting UPPS – probably due to favourable protein-ligand interactions.⁴³ Unfortunately, none of the compounds synthesised were active against *E. coli*. – presumably due to bacterial cell membrane impermeability or elimination via efflux pump transportation. Jeong *et al.* had also shown that tetramates of type **37** were selective at targeting bacteria, as none exhibited activity against *C. albicans* ($\text{MIC} > 32 \mu\text{g/ml}$) and did not disrupt mammalian red blood cells ($\text{IC}_{50} > 100 \mu\text{M}$).⁴³

Against this backdrop, compounds **38-40** were selected as the most promising compounds due to their dual mode of action, potent antibacterial activity (MIC values = $0.25\text{--}2 \mu\text{g/ml}$ against MRSA), low toxicity profile and selectivity for bacteria (**Figure 1.29**).⁴³ Additionally, these compounds have favourable physicochemical properties and generally observed Lipinski's Rule of 5 (Ro5), thus, being good compounds for hit-to-lead development for future studies.⁴³

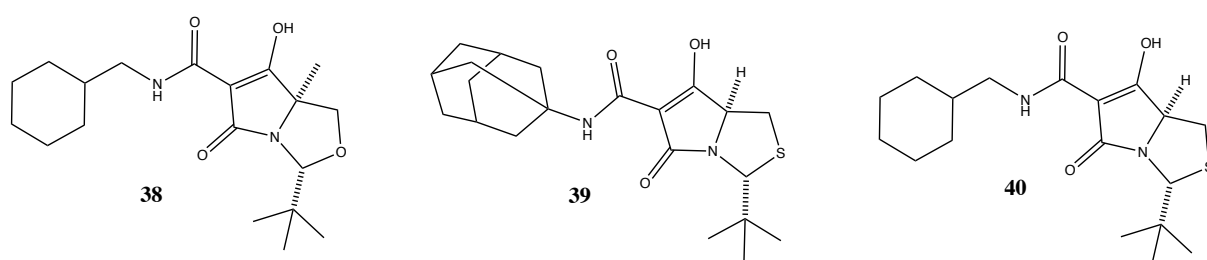


Figure 1.29: The most promising compounds **38-40** identified from Jeong *et al.* compound library.

However, the main drawback to these compounds was competitive binding phenomena to plasma proteins when tested *in-vitro* in the presence of 10% serum – where MIC values plummeted to $> 64 \mu\text{g/ml}$.⁴³ As lipophilicity is generally correlated with plasma protein binding (PPB), of interest was to

increase polarity within these bicyclic systems to reduce PPB, making these compounds more suitable for *in-vivo* studies.^{33,43}

1.6.2.4: C2-Functionalised-C7-Carboxamidotetramate Library Generation Inspired by Streptolydigin, Kibdelomycin and Novartis' UPPS Inhibitor

Past research conducted in the Moloney group have heavily relied on the synthesis of oxa(thia)zolidines that were condensed with pivaldehyde. This is because the bulky ^tBu group seems to be pivotal towards oxazolidine stability by driving ring-chain equilibria towards ring closure.⁴⁴⁻⁴⁵ In addition to this, the ^tBu group tends to drive diastereoselectivity and chemoselectivity towards the synthesis of tetramates **11a-c**.³⁵ As a result, the libraries of compounds discussed thus far have been limited towards the use of pivaldehyde, particularly as other aldehydes and ketones were not found to be suitable when using L-serine methyl ester hydrochloride **8a**. However, the ^tBu group is a hydrophobic substituent and is thought to play a negative role in PPB due to its lipophilicity.⁴³ Thus, the question arose as to whether C2-functionalisation was permissible within these bicyclic systems while retaining favourable antibacterial activity as well.

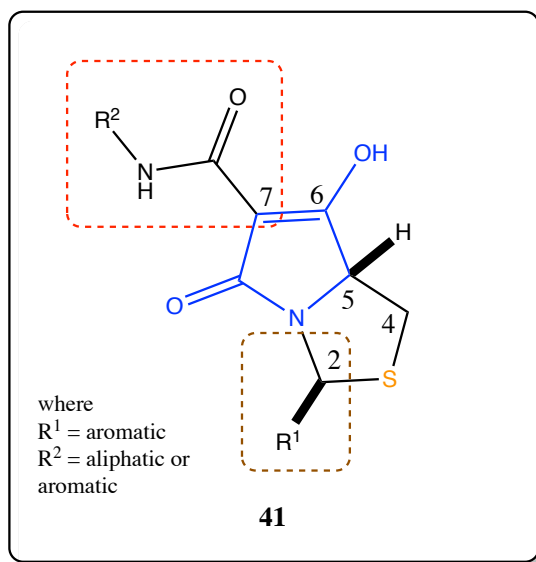
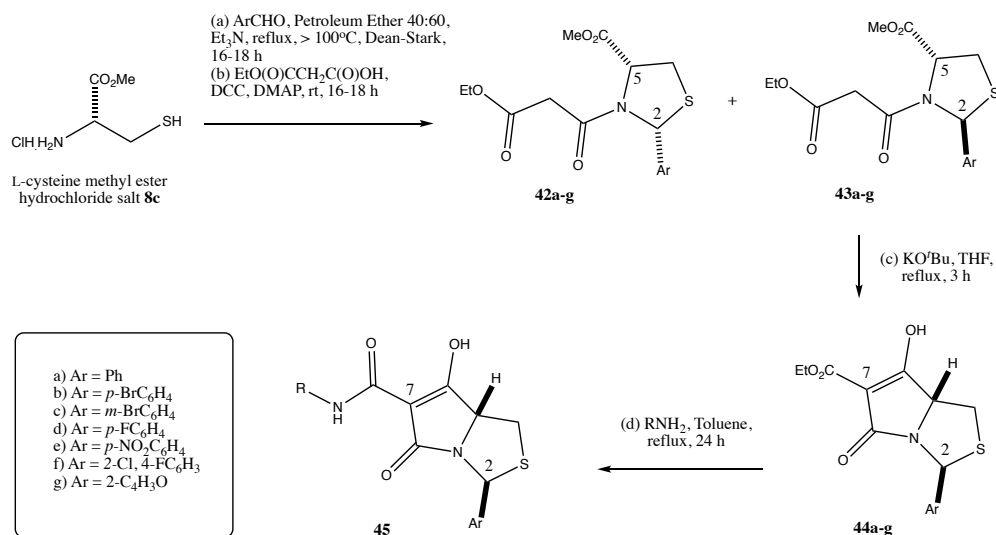


Figure 1.30: General structure of bicyclic tetramate **41** that was studied by Panduwawala *et al.* for antibacterial activity, mode of action and physicochemical parameters.

Thiazolidines are known in literature to be far more stable than oxazolidines.⁴⁴⁻⁴⁵ This potentially permits a wide range of thiazolidines to be synthesised by condensing L-cysteine methyl ester hydrochloride **8c** with various aldehydes (R^1) to form C2-functionalised bicyclic tetramates of type **41** (**Figure 1.30**).^{33,44} The use of thiazolidine scaffolds allows the ^tBu group to be phased out, thus allowing more polarity to be introduced within these bicyclic structures. It was reasoned that the introduction of more polarity at the C2-position would result in reduced PPB.³³ Additionally, as thiazolidine scaffolds of type **37** were generally well tolerated, (**Figure 1.28**) it was reasoned that C2-functionalised thiazolidines of type **41** might also be well tolerated (**Figure 1.30**).^{33,43}

Panduwawala *et al.* condensed commercially available L-cysteine methyl ester hydrochloride **8c** with various aromatic aldehydes to form thiazolidine derivatives in excellent yields as a mixture of diastereomers.^{33,44} These thiazolidines were then coupled with ethyl hydrogen malonate using DCC/DMAP coupling conditions to form *N*-acyl thiazolidines **42a-g** and **43a-g** in excellent yields as a mixture of 2 diastereomers at the C2-position; in roughly a 1:1 ratio.^{33,44} This was an interesting outcome as the *N*-acylation of oxa(thia)zolidines condensed from pivaldehyde were obtained mostly as single diastereomers **10a-c** – demonstrating the importance the ^tBu group has in driving diastereoselectivity (compare **Schemes 1.1** with **1.7**).³⁵ The 2,5-*trans*-diastereomer of *N*-acyl thiazolidines **43a-g** preferentially cyclised towards bicyclic tetramates **44a-g** in excellent yields – with a switch in chemoselectivity observed when compared with tetramates **11a-c**.^{33,44} With the C7-ethyl ester in place, simple aminolysis reactions with various aliphatic and aromatic amines yielded C7-carboxamides of type **45**.³³

This methodology enabled compound libraries to be rapidly generated with the incorporation of 2 points of diversity (as shown in **Figure 1.30**), enabling an extensive SAR analysis to be undertaken at the C2 and C7-positions of the bicyclic core to find the optimum physicochemical parameters required to make these classes of compounds more ‘drug-like’ – particularly in regard to addressing PPB.³³



Scheme 1.7: Reaction scheme demonstrating the rapid synthesis of C7-carboxamidotetramic acids **45** from L-cysteine methyl ester hydrochloride **8c**.

Panduwawala *et al.* had demonstrated that broad and diverse C2-functionalisation with aromatic substituents was possible while retaining potent antibacterial activity, with dual modes of action.³³ However, even with the introduction of more polarity at the C2 and C7-positions, these tetramates still had an affinity to PPB, thereby significantly reducing the therapeutic efficacy of these antibacterials if tested *in-vivo*.³³

1.7 Aim of Research

One area of research that has not received extensive investigation within the core bicyclic structure **37** is the C4-position. Taking inspiration from natural product, virgineone aglycone **7**, the aim of this project will be to devise synthetic strategies of incorporating C4-aromatic substituents within the bicyclic core and to synthesise compound libraries to examine for antibacterial activity using a natural product-inspired/BIOS drug discovery programme. The hypothesis behind this research was driven by two factors; that is reducing PPB associated with compounds **37** and **41** and reduce metal-chelation across the tricarbonyl core.

Natural product tetramates are often isolated as metal-chelates, although the role metal ions play in biological activity is relatively unknown.³⁰ However, it has been theorised that metal-chelation in tetramic acids **37**, **41** and **46** tended to void antibacterial activity when tested in the presence of blood. This is because these tetramates bind to red blood cells with very strong affinity due to their strong siderophore-like behaviour – that is, compounds that chelate to Fe^{2+} and Fe^{3+} with strong affinity. Lockett had hypothesised that C4-substituents were relatively close in proximity to the metal-chelation site by examining the NMR line broadening of metal-chelated tetramic acids in comparison to metal-free tetramic acids.⁴⁶ It was reasoned that if a bulky substituent in the form of an aromatic ring was introduced at the C4-position, it could potentially disrupt metal-chelation across the tricarbonyl core, thus potentially restoring antibacterial activity when tested in the presence of blood (**Figure 1.31**). It was also believed that the introduction of a C4-aromatic substituent could potentially allow more polarity to be introduced into these bicyclic systems **47**, thus, making these compounds more suitable for *in-vivo* studies.

C4-substituent close in proximity to the metal-chelation site

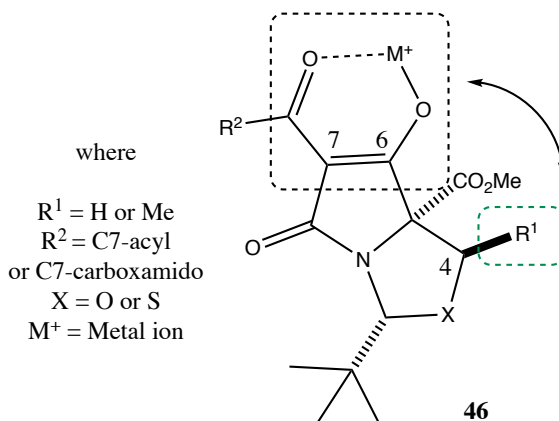


Figure 1.31: Showing the structure of metal-chelated tetramic acid **46**.

Following on from the success of C2 and C7-functionalisation to introduce antibacterial activity with favourable physicochemical parameters, this research will look to establish compound libraries that have 2/3 points of diversity – particularly at the C2, C4 and C7-positions – to examine for antibacterial activity (**Figure 1.32**).

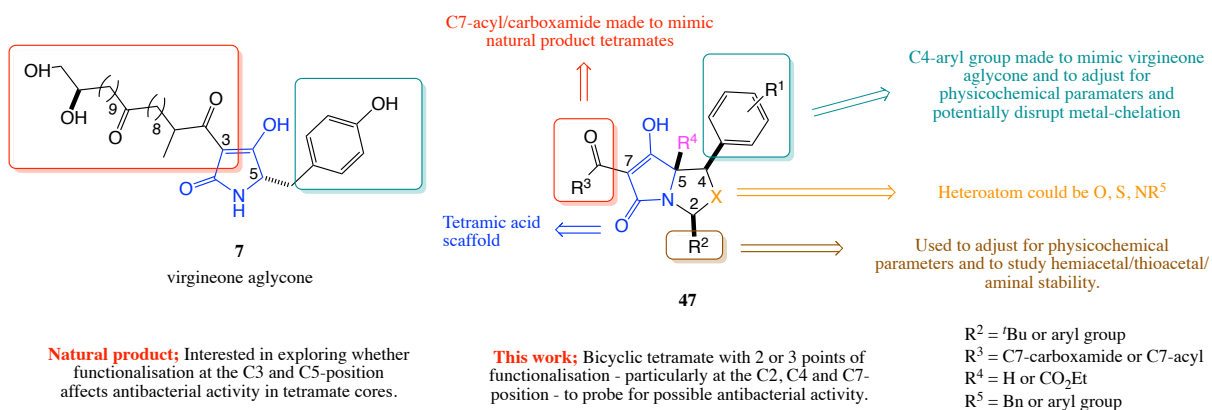


Figure 1.32: Illustrating the 2/3 points of diversity that will be studied in detail; where C4-aromatic functionalisation is of particular interest within the bicyclic core **47**.

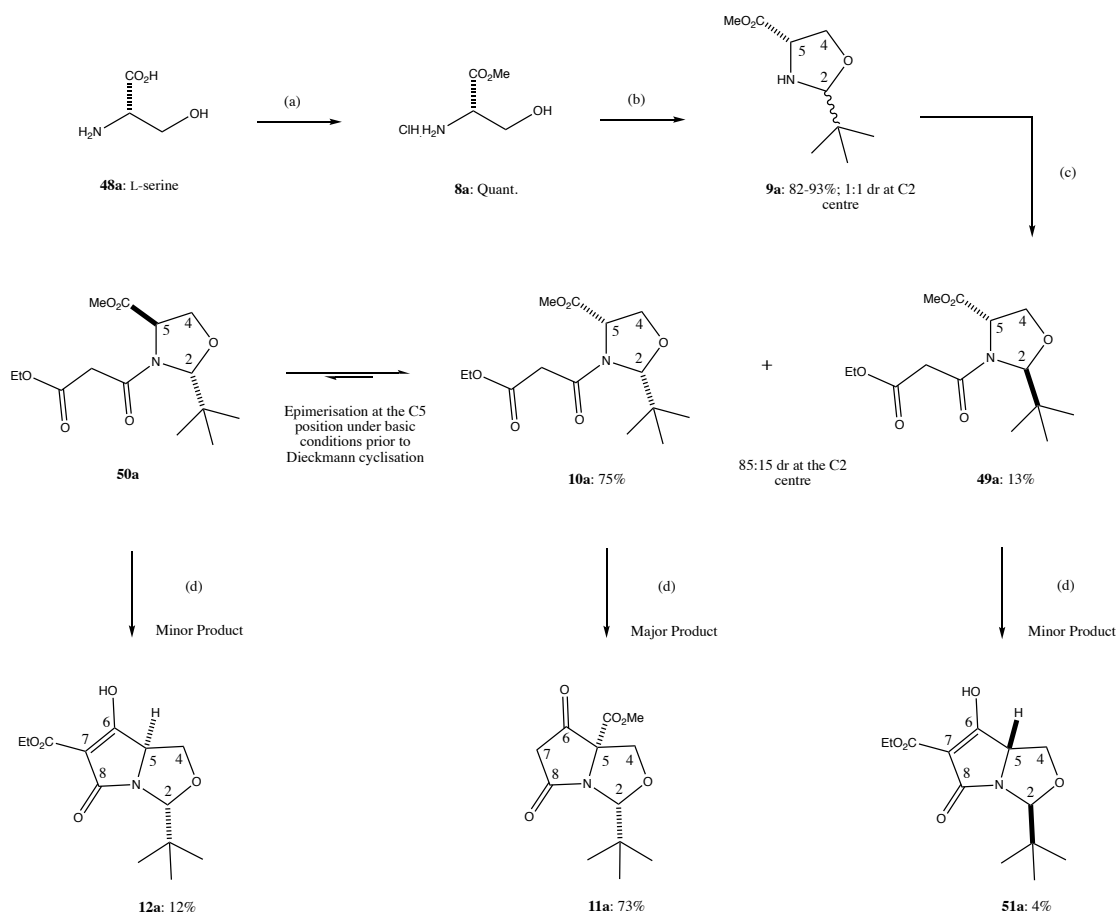
Chapter 2: *threo*-Phenylserine-Derived *N,O*-Bicyclic Tetramic Acids

This chapter describes the synthetic methodology used to make oxazolidine-derived tetramic acids from *threo*-phenylserine derivatives. DFT calculations (conducted by Dr. Xiang Li) were performed to rationalise the stereochemical outcomes that were observed experimentally. Additionally, the tautomeric behaviour and metal-binding properties of C7-carboxamides will also be discussed.

2.1: Previous Work in the Moloney Group

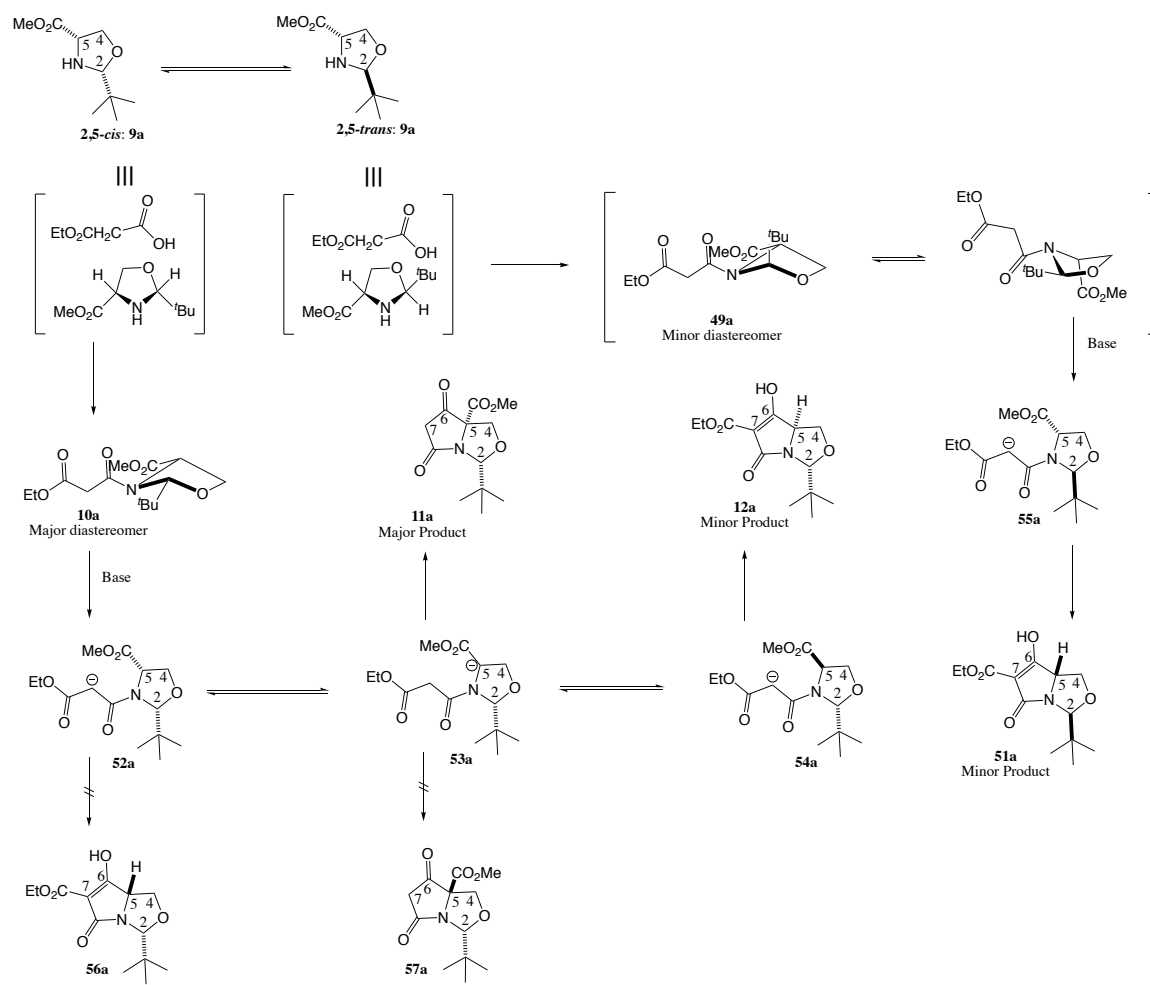
As discussed in **Chapter 1.6.1**, the Moloney group have developed a reliable methodology for synthesising tetramic acids **11a** from L-serine **48a** (**Scheme 2.1**).³⁴⁻³⁵ L-Serine **48a**, dissolved in MeOH, was typically reacted with thionyl chloride to form methyl ester hydrochloride salt **8a** in quantitative yield.³⁵ Methyl ester hydrochloride salt **8a** was then subsequently reacted with pivaldehyde and heated in a Dean-Stark apparatus for 16-18 h in the presence of petroleum ether 40:60 and Et₃N to obtain oxazolidines **9a** in high yields – typically between 82-93% – as a 1:1 mixture of diastereomers at the C2-position.^{34,47} *N*-Acylation of oxazolidines **9a** using ethyl hydrogen malonate under DCC/DMAP coupling conditions in DCM furnished diastereoselective malonamide **10a** (2,5-*cis/trans* 85:15 dr at the C2-centre) in good yields in addition to the minor malonamide diastereomer, **49a**, which was obtained in 13% yield.^{34,47} The major malonamide diastereomer **10a** was subsequently reacted with KO^tBu to give bicyclic tetramate **11a** in good yield as the major product, where the enantiopurity of **11a** was deemed to be >90%; this illustrates the diastereoselective, chemoselective and enantioselective nature of this approach.^{34,47} Tetramate **12a** was also formed as a minor product arising from C5 epimerisation of malonamide **10a**.^{34,47} Additionally, tetramate **51a** was also formed via the ring closure of malonamide **49a**, albeit in very low yields.⁴⁷ The relative stereochemistry of malonamides **10a** and **49a** in addition to tetramates **11a**, **12a** and **51a** was determined using nOe experiments.⁴⁷ The major product **11a** could easily be separated from the minor products **12a** and **49a** by simply washing the reaction mixture with 1 M NaH₂PO₄ solution.³⁴ This would allow the major product **11a** to be extracted

from the organic layer with high levels of purity, whereas the minor products **12a** and **51a** would remain in the aqueous layer as their respective enolates.³⁴



Scheme 2.1: Reaction scheme showing the synthetic routes towards bicyclic tetramates **11a**, **12a** and **51a** from malonamides **10a**, **49a** and **50a**; (a) MeOH, SOCl₂, 40°C, 3 h; (b) pivaldehyde, Et₃N, petroleum ether 40:60, >100°C, Dean-Stark, 16-18 h; (c) ethyl hydrogen malonate, DCC, DMAP, DCM, rt, 6 h; (d) KO^tBu, THF, reflux, 3 h.

Of interest was the diastereoselectivity of the *N*-acylation of oxazolidines **9a**. Although oxazolidines **9a** freely equilibrate at the C2-centre via ring chain tautomerisation, *N*-acylation of oxazolidines **9a** form diastereoselective malonamide **10a** (2,5-*cis/trans* 85:15 dr at the C2-position) (**Scheme 2.1**).^{34,47} It was rationalised that the high levels of diastereoselectivity seen for the *N*-acylation of oxazolidines **9a** was likely due to the fact that all bulky substituents were *pseudo*-equatorial to each other, thus, minimising steric interactions – assuming that the malonamide ring system **10a** adopts an envelope conformation, in which the nitrogen is slightly pyramidalised (**Scheme 2.2**).^{34,47}



Scheme 2.2: Reaction scheme showing the diastereoselective and chemoselective routes towards the synthesis of bicyclic tetramates **11a**, **12a** and **51a** from oxazolidines **9a**.

Additionally, the chemoselectivity of the Dieckmann cyclisation was particularly interesting in these bicyclic systems. When malonamide **10a** was reacted with KO^tBu , an equilibrium between enolates **52a**, **53a** and **54a** was expected to be established. The ring closure of enolate **53a** led to the formation of major product **11a** and the ring closure of enolates **54a** and **55a** led to the minor products **12a** and **51a** being formed respectively.⁴⁷ It was reasoned that the chemoselectivity of the Dieckmann cyclisation was driven by the fact that the bulky ^tBu group preferred to reside on the less hindered *exo*-face of the bicyclic lactam, causing products **11a**, **12a** and **51a** to be preferentially formed over **56a** and **57a**.⁴⁷ It was also reasoned that the equilibrium between enolates **53a** and **54a** lied towards enolate **53a** and this could possibly explain why **11a** was formed as the major product over tetramate **12a** (Schemes 2.1 and 2.2).⁴⁷

2.2: Synthesis of Tetramic Acids from *threo*-Phenylserine Derivatives

Although the Dieckmann cyclisation was effective, it was limited to readily available amino acids L-serine **48a**, L-threonine **48b** and L-cysteine **48c**.^{34-35,47} In order to expand this scope, the research described in this section is focused on the synthesis of C4-functionalised tetramic acids **58** derived from *threo*-phenylserine derivatives **61** – analogous to that of L-threonine **48b** – with **Figure 2.1** illustrating the retrosynthetic analysis used as the rationale towards synthesising bicyclic tetramate **58**.

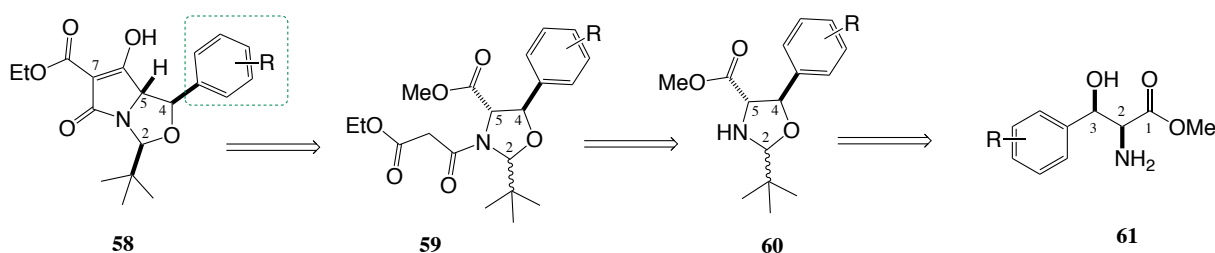


Figure 2.1: Retrosynthetic analysis for the synthesis of tetramic acid **58** from amino ester **61**.

2.2.1 Synthesis of *threo*-Phenylserine Derivatives

β -Hydroxy- α -amino acids are considered an important class of compounds as they are found in many natural product structures.⁴⁸ Although there are two proteinogenic amino acids that have the β -hydroxy- α -amino acid unit – serine and threonine – there are many natural product structures that contain non-proteinogenic β -hydroxy- α -amino acids that also display antimicrobial activity such as cyclomarin C **62**, lysobactin **63**, vancomycin **64** and cyclothialidine **65** (**Figure 2.2**).⁴⁸

Over the past 30 years, there has been growing literature reports of the asymmetric synthesis of β -hydroxy- α -amino acids.⁴⁸ Many routes have been discovered such as the aldol reaction between glycine equivalents and aldehydes to form β -hydroxy- α -amino acids.⁴⁸ Another well-known example is the asymmetric hydrogenation of β -ketoesters, which uses dynamic kinetic resolution to obtain enantioselective amino acids (**Figure 2.3**).

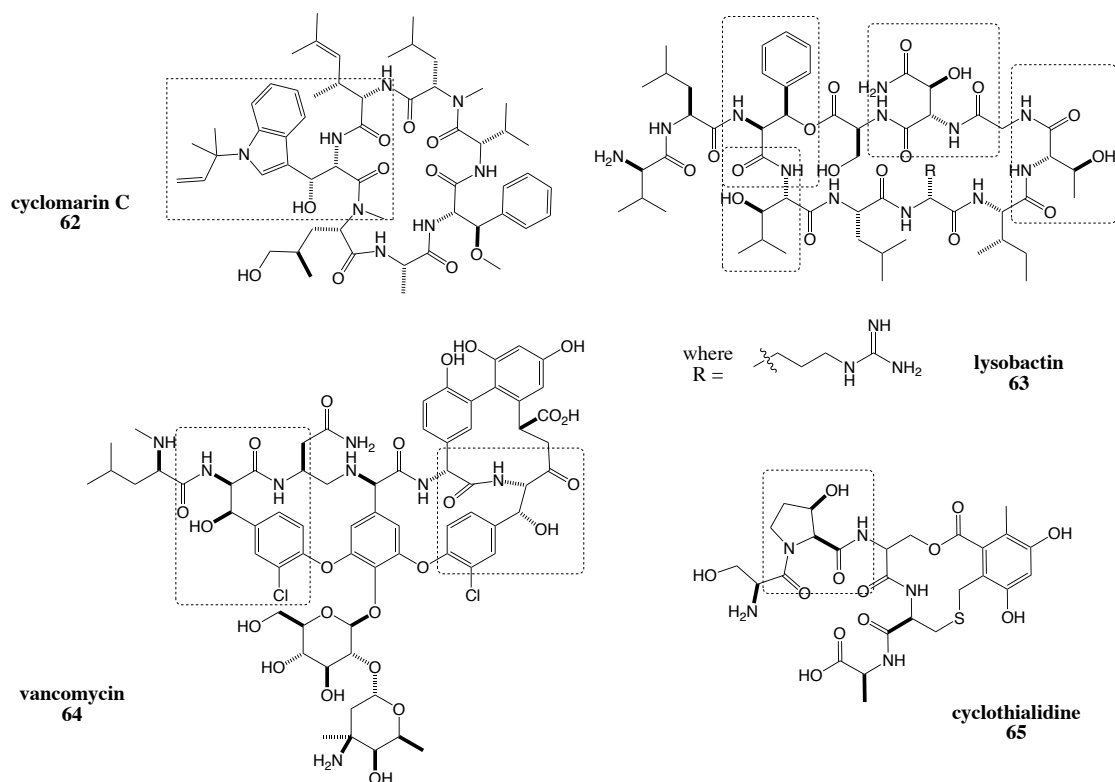


Figure 2.2: Structures of cyclomarin C 62, lysobactin 63, vancomycin 64 and cyclothialidine 65

(rectangles highlight the β -hydroxy- α -amino amide unit within the natural product structure).

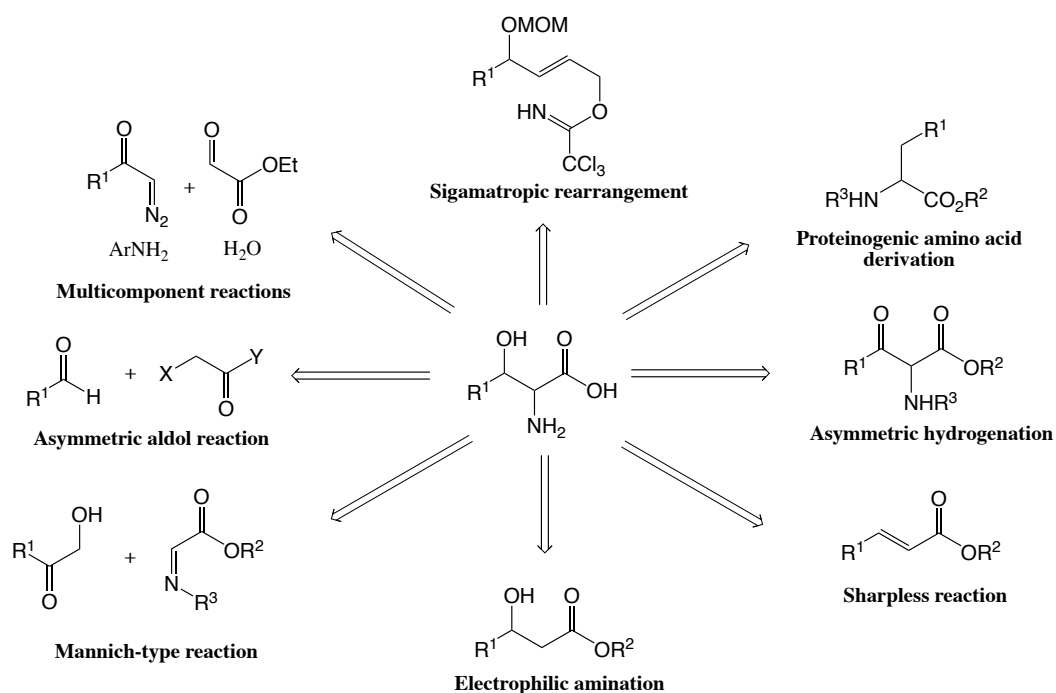
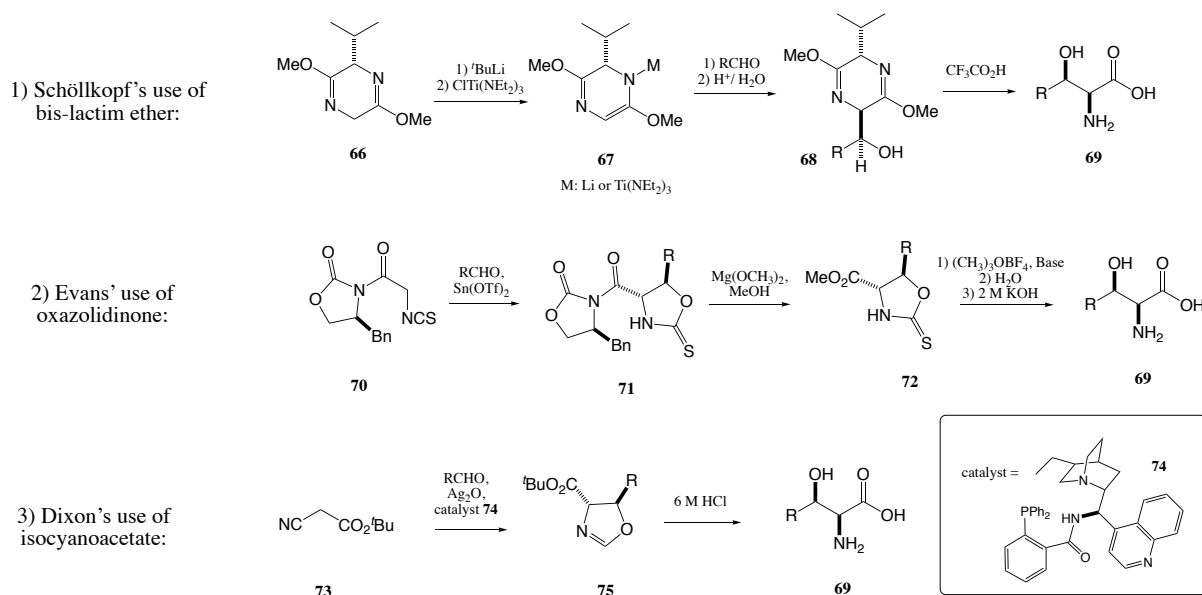


Figure 2.3: Some of the different methods that can be used to obtain β -hydroxy- α -amino acids.

Adapted from *Chem. Asian J.*, 2014, **9**, 1752-1764.

The research described in this chapter is focused on the facile synthesis of *threo*-phenylserine derivatives from commercially available, cheap starting materials that could allow rapid access to densely functionalised tetramic acids in a short synthetic sequence and exploiting the current methodology outlined in **Chapter 1**. This project was mainly focused on the aldol reaction towards the synthesis of β -hydroxy- α -amino acid due to its versatility, simplicity and the ability to use commercially available, cheap starting materials. Additionally, this reaction had the advantage of forming two contiguous stereocentres in one synthetic step in high yields and good diastereoselectivities, making this approach highly attractive. Many asymmetric aldol reactions have been reported in literature where ‘masked’ glycine compounds have been used, such as Schöllkopf’s use of bis-lactim ethers **66**, Evans’ use of oxazolidinone auxiliaries **70** and Dixon’s use of isocyanoacetate derivatives **73** (**Scheme 2.3**).⁴⁸ However, there were some drawbacks to these reactions, at least for our research purposes, which are discussed below.⁴⁸

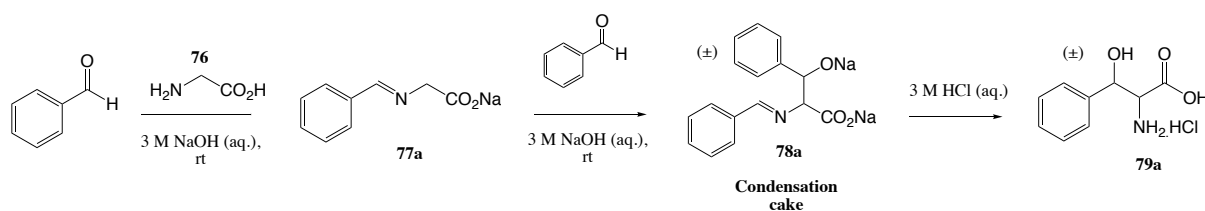


Scheme 2.3: Different aldol approaches to making enantioselective β -hydroxy- α -amino acids; **(1)** Schöllkopf use of chiral bis-lactim ethers **66**; **(2)** Evans’ use of chiral oxazolidinones **70**; **(3)** Dixon’s use of isocyanoacetate derivatives **73**.

In the case of Schöllkopf’s bislactim ethers, a multi-step synthesis was required to form bislactim ether **66** – typically by reacting valine with glycine to form a dipeptide which was subsequently reacted with

Meerwein's salt.⁴⁸ Additionally, the hydrolysis of the aldol product **68** tended to release valine and β -hydroxy- α -amino acids **69** which were difficult to separate via chromatographic purification.⁴⁸ This made Schöllkopf's synthesis undesirable for this particular research project (**Scheme 2.3**). Additionally, Evans' synthesis also suffered from the same issues as Schöllkopf synthesis – in that a multi-step synthesis was required to form the chiral oxazolidinone **70** unit.⁴⁸ Moreover, multiple synthetic manipulations were required to make β -hydroxy- α -amino acids **69**, making this synthesis unattractive.⁴⁸ And finally, although Dixon's synthesis towards making β -hydroxy- α -amino acids **69** was relatively mild and elegant, the use of both expensive catalysts and malodorous isocyanoacetate derivatives **73** made this synthesis less appealing, especially if this reaction was conducted on large scale. Moreover, we did not have the equipment to carry out reactions at -20°C for 24-36 h.⁴⁸⁻⁵⁰

Instead, we took inspiration from Erlenmeyer's research, where glycine **76** was reacted with two equivalents of benzaldehyde to form β -aryl serines **79a** under basic conditions via an aldol reaction.⁵¹⁻⁵² We were not particularly interested in the asymmetric synthesis of *threo*-phenylserine derivatives for our research purposes, as the main objective was to test the overall synthetic methodology, examine for antibacterial activity and examine for possible PPB. However, of interest was the rapid formation of these β -aryl serines in high yields and good diastereoselectivities to enable testing of the overall concept.



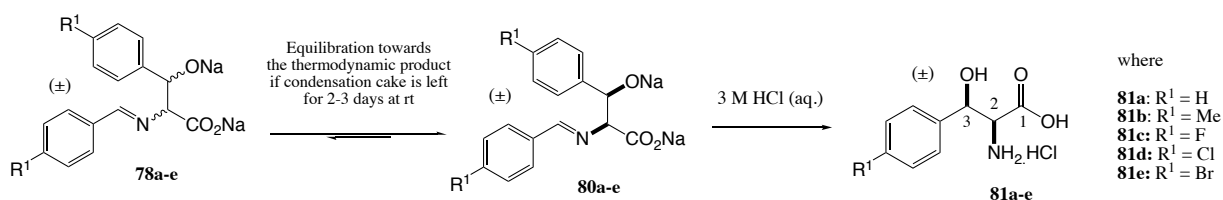
Scheme 2.4: The possible intermediates formed in the synthesis of β -aryl serine **79a**.

It was rationalised that glycine **76** would react with the first equivalent of benzaldehyde to form imine **77a**.⁵¹ Imine **77a** would then react with a second equivalent of benzaldehyde via an aldol reaction under basic conditions to form the aldol product **78a** – which precipitates out of solution as a

condensation cake – and mass spectrometry confirmed the presence of this compound **78a**. The condensation cake **78a** can then be subsequently hydrolysed to form β -arylserine **79a**, with benzaldehyde being regenerated again (**Scheme 2.4**).

Base concentration was found not to adversely affect the diastereoselectivity of **79a** (compare entries 1 with 2; **Table 2.1**), however, it should be noted that when 3 M NaOH (aq.) solution was used, it took much longer for the condensation cake **78a** to form – typically more than 3 hours – in comparison to approximately 20-30 mins it took for the condensation cake **78a** to form when using a 6 M NaOH (aq.) solution. Immediate acid hydrolysis of the condensation cake **78a** led to quantitative mass recovery being obtained for **79a** in both instances, in which the product was contaminated with NaCl salt and some unreacted glycine. Unfortunately, the diastereoselectivity of these reactions was poor.

However, interestingly the condensation cake seemed to play a pivotal role towards achieving high diastereoselectivities, and it was found that leaving the condensation cake **78a** for a period of 3 days at room temperature prior to acid hydrolysis led to much higher diastereoselectivities (93:7 dr), than when the condensation cake **78a** was immediately hydrolysed, which gave much lower diastereoselectivity (58:42 dr) (compare entries 1 with 3; **Table 2.1**). It was believed that the higher levels of diastereoselectivity observed when the condensation cake **78a** was left for a longer period of time was most likely due to equilibration towards the thermodynamic aldol product **80a** (**Scheme 2.5**).



Scheme 2.5: Equilibration towards the thermodynamic aldol product **80a-e** to form diastereoselective β -aryl serines **81a-e**.

To test this theory, the condensation cake **78a** was heated to 50°C overnight to speed up the equilibrium process towards the thermodynamic product, and an excellent 98:2 dr was obtained for the *threo* isomer **81a**, indicating that these systems undergo aldol/retro-aldol equilibration in the solid state to form the thermodynamic aldol product **81a** (compare entries 2 with 4; **Table 2.1**). When leaving the condensation cake in the fridge overnight prior to acid hydrolysis, the diastereoselectivity was once again much poorer (compare entries 4 with 5; **Table 2.1**). Additionally, the sole recovery of benzaldehyde from the organic layer after acid hydrolysis acted as evidence for the proposed mechanism outlined in **Schemes 2.4** and **2.5**.

Entry	Solvent	Temperature used after the formation of the condensation cake prior to acid hydrolysis	Base concentration	Reaction time before the condensation cake was hydrolysed	dr between <i>threo-erythro</i> isomers ^a
1 ^b	Water	25°C	3 M NaOH	Immediate acid hydrolysis	58:42
2 ^b	Water	25°C	6 M NaOH	Immediate acid hydrolysis	7:3
3 ^b	Water	25°C	3 M NaOH	72 h before acid hydrolysis	93:7
4 ^b	Water	50°C	6 M NaOH	24 h before acid hydrolysis	98:2
5 ^b	Water	5-8°C	6 M NaOH	24 h before acid hydrolysis	7:3
6 ^c	Water	25°C	3 M NaOH	72 h before acid hydrolysis	66:34
7 ^d	EtOH	25°C	3 M KOH	72 h before acid hydrolysis	94:6

Table 2.1: Optimisation studies for the formation of amino acids **81a** and **81e**; ^a Determined from ¹H-NMR studies of the crude material; ^b 0.084 mol of benzaldehyde (2.1 eq.) was reacted with 0.04 mol of glycine (1 eq.) in a NaOH solution (1.5 eq.) to form **81a**; ^c 0.084 mol of 4-bromobenzaldehyde (2.1 eq.) was reacted with 0.04 mol of glycine (1 eq.) in a NaOH solution (1.5 eq.) to form **81e**; ^d 0.084 mol of 4-bromobenzaldehyde (2.1 eq.) was reacted with 0.04 mol of glycine (1 eq.) in a KOH solution (1.5 eq.) to form **81e**.

It was found that entries 3 and 4 were the optimum conditions for the synthesis of **81a**, however, in most cases entry 3 was our preferred optimum condition, as the reaction conditions were milder with less chance of side-products being formed. However, when attempting to extend these optimum

conditions to *para*-substituted aromatic aldehydes – with the exception of *p*-tolualdehyde – β -aryl serines were formed in very poor yields and diastereoselectivities, where in most cases unreacted glycine was mostly recovered from the aqueous layer (consider entry 6, **Table 2.1** for the synthesis of **81e**). This was thought to be due to solubility differences between various aldehydes that were used in an aqueous media. Thus, an ethanolic 3 M KOH solution was used, which led to the formation of β -aryl serines **81c-e** in much better yields and diastereoselectivities (compare entries 6 with 7; **Table 2.1**) – with the exception of 4-fluorobenzaldehyde, which was obtained in slightly poorer diastereoselectivity, as shown in **Table 2.2**.

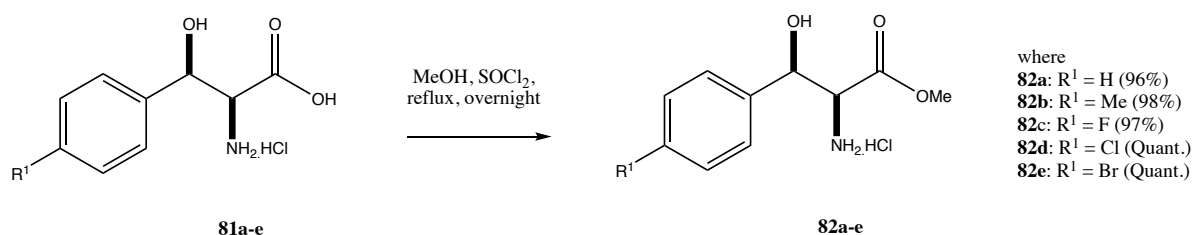
Compound	R	δ H2 (ppm)	δ H3 (ppm)	J_{H2-H3} (Hz)	dr between <i>threo-erythro</i> isomers ^a	Crude yield (%) ^b
81a	H	4.07	5.37	4.1	93:7	Quant.
81b	Me	4.26	5.40	4.2	19:1	Quant.
81c	F	4.10	5.35	4.3	84:16	76
81d	Cl	4.22	5.39	4.0	9:1	68
81e	Br	4.28	5.38	3.9	94:6	Quant.
81f	OMe	4.23	5.32	4.2	3:2	Quant.

Table 2.2: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and crude yields of β -aryl serines **81a-f**; D₂O solvent, 400 MHz; ^a Determined from ¹H-NMR studies of crude material; ^b Contaminated with KCl/NaCl salt.

In the case of *p*-anisaldehyde, no solid condensation cake was formed, even after 3 days of stirring, and only a liquid sludge had predominantly formed. Acid hydrolysis of the resultant liquid mixture on average led to a 3:2 mixture of diastereomers for **81f**, however, the diastereomeric ratio differed wildly from reaction to reaction. The highest diastereoselectivity achieved was a 19:1 dr, however, this could never be replicated. This outcome highlighted the importance the condensation cake has in driving diastereoselectivity towards the synthesis of *threo*- β -aryl serine – as a result, **81f** was discontinued. However, access to the small library of β -aryl serines **81a-e** was sufficient for our purposes, with the

main focus of this project being the synthesis of *threo*-phenylserine **81a**, which was obtained in excellent crude yields and diastereoselectivity, albeit contaminated with NaCl or KCl salt.

With β -aryl serines **81a-e** in hand, we sought to esterify amino acids **81a-e** using thionyl chloride in MeOH. It was found that stirring at 40°C for 3 h led to an incomplete reaction – as determined from NMR studies – however, refluxing overnight led to the complete conversion to the methyl ester hydrochloride salt, **82a-e** in excellent yields (**Scheme 2.6**).⁵³

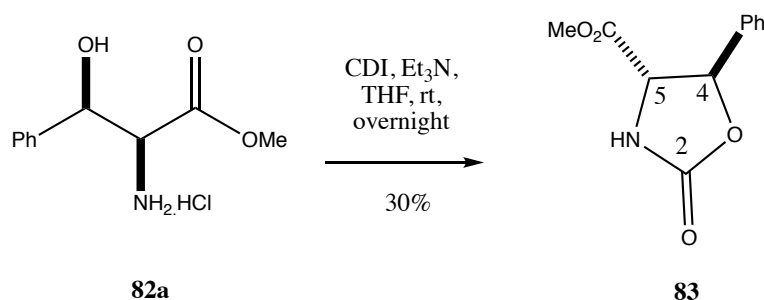


Scheme 2.6: The synthesis and yields of amino esters **82a-e**.

As amino esters **82a-e** were formed in high yields and good diastereoselectivity in just 2 synthetic steps, Erlenmeyer's synthesis had ticked off the key objective which was sought. However, questions quickly arose as to whether the amino acids **81a-e** formed were indeed the *threo* diastereomer as stated in literature; specifically, as the *threo* isomers had very similar coupling constants – and in some cases, the same coupling constants – and very similar chemical shifts to the *erythro* isomer. Additionally, nOe could not be used to establish relative stereochemistry as there was too much conformational flexibility within this molecule.

Thus, we sought to form oxazolidinone **83** by reacting amino ester **82a** with 1,1'-carbonyldiimidazole (CDI) and Et₃N at rt overnight (**Scheme 2.7**). It was hoped that the formation of the ring system would lock the conformation of the stereogenic centres, thus enabling nOe spectroscopy to be used to determine relative stereochemistry between the adjacent C4 and C5 hydrogens of oxazolidinone **83**. This would allow us to backtrack as to whether the amino acid **81a** formed was indeed the *threo* or

erythro isomer. Fortunately, oxazolidinone **83** was a known literature compound.⁵⁴ The ¹H-NMR data for oxazolidinone **83** synthesised from amino ester **82a** was consistent with literature NMR data,⁵⁴ confirming that the amino acid **81a** formed was indeed the *threo* isomer; **Table 2.3** illustrates the ¹H-NMR data of oxazolidinone **83** that had been synthesised in this research in comparison to literature ¹H-NMR data for oxazolidinones that had been derived from *threo* and *erythro* amino esters.



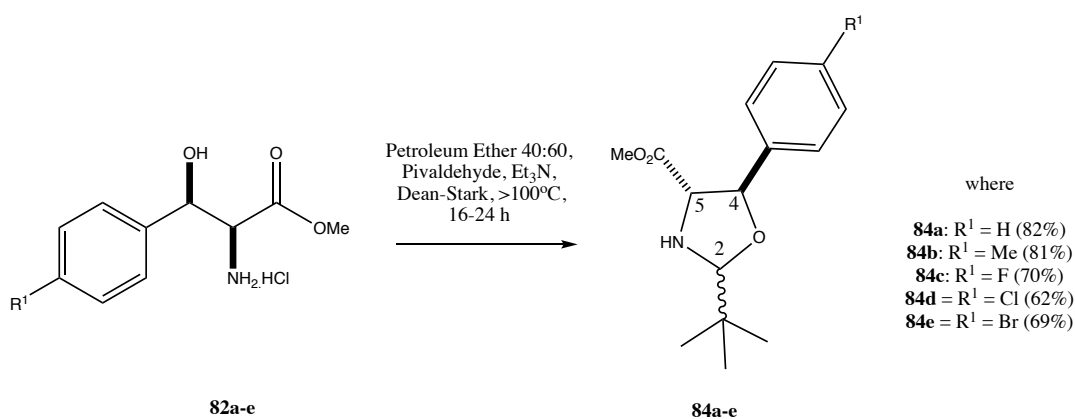
Scheme 2.7: Synthesis of oxazolidinone **83** from amino ester **82a**.

Compound	δ H4 (ppm)	δ H5 (ppm)	$J_{\text{H4-H5}}$ (Hz)
83	5.63	4.31	5.0
Literature data on <i>threo</i> -derived oxazolidinone ⁵⁴	5.65	4.33	5.0
Literature data on <i>erythro</i> -derived oxazolidinone ⁵⁵	5.84	4.67	9.0

Table 2.3: Comparing literature ¹H-NMR data with oxazolidinone **83**; CDCl₃ solvent, 400 MHz.

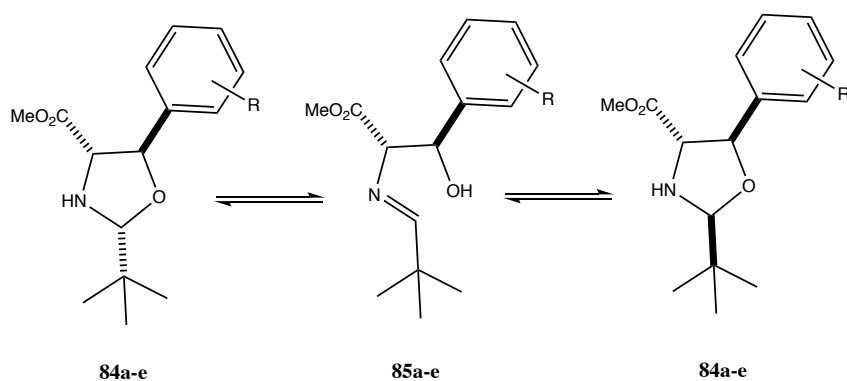
2.2.2. Synthesis of Oxazolidines

Amino esters **82a-e** were subsequently reacted with pivaldehyde in the presence of Et₃N and petroleum ether 40:60, and heated to over 100°C in a Dean-Stark trap for 16-24 h to form oxazolidines **84a-e** in good yields – typically between 62-82% – as roughly a 1:1 mixture of diastereomers at the C2-position, as determined from ¹H-NMR studies of the crude material (**Scheme 2.8**).^{34-35,56}



Scheme 2.8: Synthesis of oxazolidines **84a-e** from amino esters **82a-e**.

It was reasoned that the 1:1 mixture of diastereomers observed for oxazolidines **84a-e** presumably arose due to epimerisation at the C2-position between oxazolidines **84a-e** (Scheme 2.9), however, none of the imine **85a-e** was detected in the NMR spectrum. Fulop *et al.* had observed this phenomenon from oxa(thia)zolidines which were derived from serine, threonine and cysteine, which was termed ring-chain tautomerisation.⁴⁵



Scheme 2.9: Epimerisation of oxazolidines **84a-e**.

Oxazolidine **84a** was subjected to chromatographic purification, however this proved to be a tedious process, where little product was recovered. It was reasoned that potential retro-aldol reactions might have occurred during chromatographic purification – a phenomenon which was observed by Lou *et al.* for oxazolidines that had C2-aromatic substituents.⁵⁷ As the crude oxazolidines **84a-e** were relatively pure by NMR analysis (Figure 2.4), they were used into the next reaction sequence.

Compound	2,5- <i>trans</i> oxazolidine δ (ppm)				2,5- <i>cis</i> oxazolidine δ (ppm)				dr between 2,5- <i>trans</i> / <i>cis</i> ^a	Yield (%) ^b
	H2	H4	H5	J_{H4-H5} (Hz)	H2	H4	H5	J_{H4-H5} (Hz)		
84a	4.42	4.74	3.63	6.6	4.42	4.67	3.77	7.0	1:1.1	82%
84b	4.41	4.69	3.61	6.7	4.41	4.63	3.77	7.0	1:1.1	81%
84c	4.41	4.70	3.58	6.7	4.40	4.62	3.70	7.0	1:1.1	70%
84d	4.41	4.70	3.58	6.6	4.39	4.62	3.71	7.0	1:1.2	62%
84e	4.41	4.69	3.58	6.6	4.38	4.60	3.71	6.9	1:1.2	69%

Table 2.4: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of oxazolidines **84a-e**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material;

^b Yields include both diastereomers.

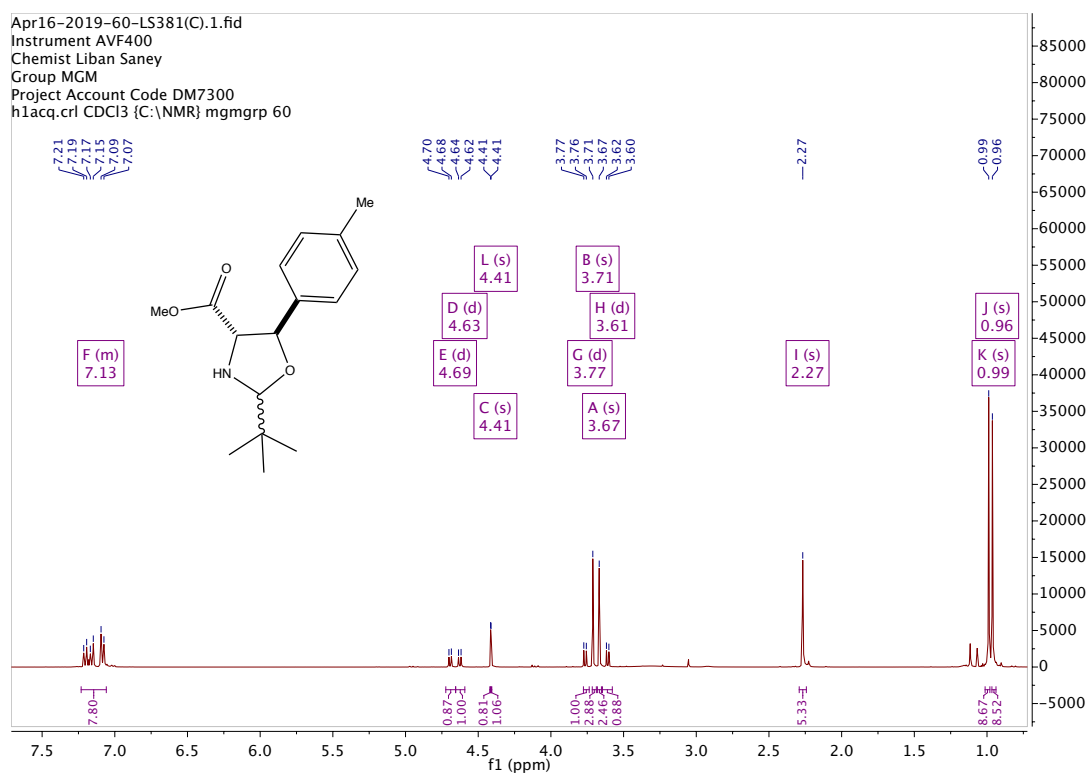


Figure 2.4: ¹H-NMR spectrum of oxazolidine **84b**, showing the relative purity of the crude material; CDCl₃ solution, 400 MHz.

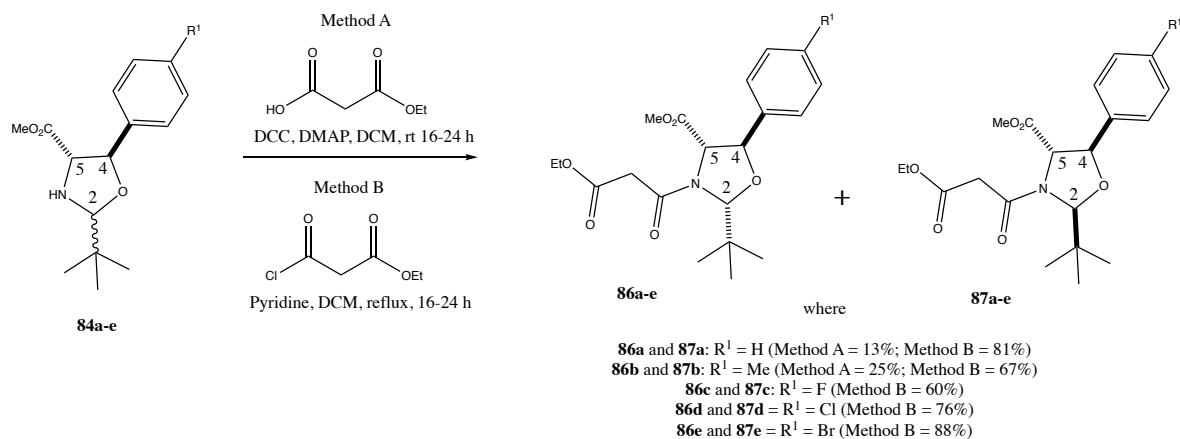
nOe studies were used to distinguish between 2,5-*cis*/*trans* oxazolidine diastereomers; **Table 2.4** illustrates the key chemical shifts, coupling constants and yields of the oxazolidine diastereomers **84a-e**.

e. Thankfully, the relative stereochemistry of oxazolidines **84a-e** at the C4 and C5-positions were conserved from the starting amino esters **82a-e**, indicating no epimerisation had occurred under basic conditions.

2.2.3. Synthesis of *N*-Acylated Oxazolidines

Oxazolidines **84a-e** were *N*-acylated using two methods. In the case of **Method A**, ethyl hydrogen malonate was used under DCC/DMAP coupling conditions to furnish malonamides **86a-b** which were obtained in poor yields (13% and 25% respectively), where the minor diastereomer **87a-b** was not isolated (**Scheme 2.10**).³⁴ It was reasoned that more forcing conditions were required to improve the yields. As a result, oxazolidines **84a-e** were reacted with ethyl malonyl chloride (**Method B**)³⁴ under basic conditions to form malonamides **86a-e** and **87a-e** in good yields – typically between 60-88% – as roughly a 3:2 mixture of diastereomers at the C2-centre, in which there was a slight diastereomeric preference for the 2,5-*cis* malonamides **86a-e** (**Scheme 2.10** and **Table 2.5**).

Unfortunately, the mixture of diastereomers were extremely difficult to separate via chromatographic purification. However, these malonamides were stable to chromatographic purification, and were also stable in their native thick, sticky oils or in CDCl₃ solution for many months. Interestingly, the NMR peaks for the H2, H4 and H5-protons for malonamides **86a-e** were typically more downfield compared with malonamides **87a-e** (**Table 2.5**).



Scheme 2.10: *N*-acylation of oxazolidines **84a-e** including yields.

Compound	2,5- <i>cis</i> diastereomer δ (ppm) ^a				Compound	2,5- <i>trans</i> diastereomer δ (ppm) ^{b,c}				dr between 86:87 ^d	Yield (%) ^e
	H2	H4	H5	J_{H4-H5} (Hz)		H2	H4	H5	J_{H4-H5} (Hz)		
86a	5.77	5.69	4.59	4.2	87a	5.36	5.14	4.00	9.2	65:35	81
86b	5.76	5.65	4.58	4.3	87b	5.28	5.03	3.93	9.2	59:41	67
86c	5.77	5.66	4.57	4.4	87c	5.27	5.05	3.91	9.2	59:41	60
86d	5.75	5.68	4.62	4.0	87d	5.29	5.07	3.91	9.2	60:40	76
86e	5.76	5.66	4.58	4.2	87e	5.27	5.04	3.89	9.2	60:40	88

Table 2.5: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of malonamides **86a-e** and **87a-e**; ^a CDCl₃ solvent, 400 MHz at room temperature; ^b CD₂Cl₂ solvent, 500 MHz, low temperature VT ¹H-NMR; ^c ¹H-NMR peaks are for the major conformer; ^d Determined from ¹H-NMR studies of the crude material at room temperature; ^e Yields include both diastereomers from **Method B**.

The relative stereochemistry of malonamides **86b-d** was assigned using nOe and NOESY spectroscopy (**Figure 2.5**) and was confirmed by a single crystal X-ray structure of **86f** – derived from the ethyl ester derivative **82f** of phenylserine **81a** (**Figure 2.6**).

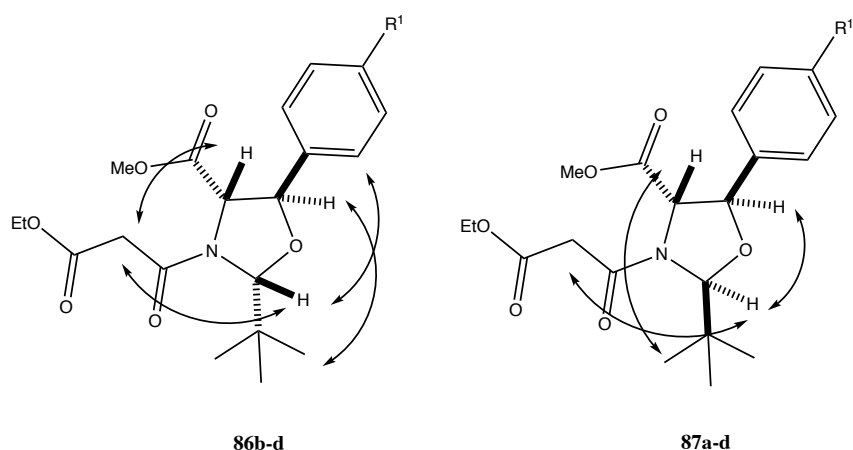


Figure 2.5: Relative stereochemistry of malonamides **86b-d** determined from nOe and NOESY studies.

In the case of malonamides **87a-d**, low temperature VT-ROESY studies was used to determine relative stereochemistry.

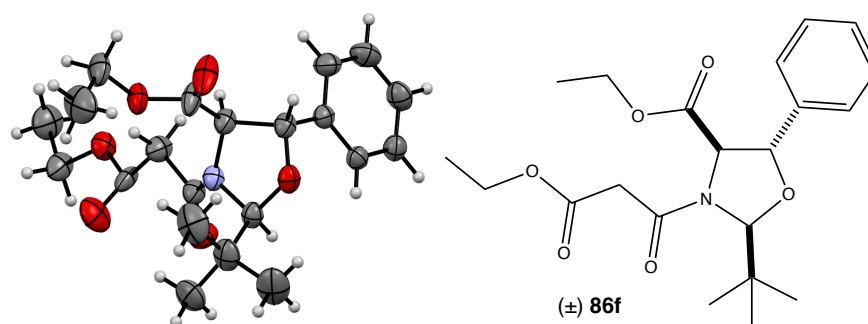


Figure 2.6: Single-crystal X-ray structure of **86f**.

In the case of malonamides **87a-d**, low temperature VT-ROESY experiments had to be used to determine relative stereochemistry, as nOe and NOESY studies – conducted at room temperature – gave inconclusive results due to broad peaks that was observed at room temperature; this is further discussed below (**Figures 2.5 and 2.8**). Fortunately, there was no evidence of epimerisation seen under basic conditions at the C4 and C5-positions of malonamides **86a-e** and **87a-e** after *N*-acylation.

Surprisingly, the *N*-acylation of oxazolidines **84a-e** was not diastereoselective, especially when compared with the *N*-acylation of oxa(thia)zolidines derived from L-serine **48a**, L-threonine **48b** and L-cysteine **48c** (see **Schemes 1.1 and 2.1**). It can be assumed therefore that there were no substantial energy differences between malonamides **86a-e** and **87a-e** when considering thermodynamics or kinetics – consider **Figure 2.7**. However, the formation of a 3:2 mixture of malonamide diastereomers from a 1:1 mixture of oxazolidine diastereomers indicates dynamic kinetic separation maybe occurring through epimerisation at the C2-position, whereby one diastereomer reacts faster than the other.

Additionally, what was interesting to observe was the contrasting NMR peaks of malonamides **86a-e** with **87a-e**. Malonamides **86a-e** had sharp NMR peaks at room temperature (**Figure 2.8a**) whereas in the case of malonamides **87a-e**, the ring protons had very broad NMR peaks at room temperature (**Figure 2.8b**). It was reasoned that the broad NMR peaks for malonamides **87a-e** was probably due to conformational dynamics, where ring fluxionality was possibly the main culprit behind the peak broadening, particularly as the ring protons were extremely broad, whereas the rest of the peaks

around the periphery of the ring system were relatively sharp at room temperature (**Figure 2.8b**). However, rotameric exchange could not be ruled out as the reason for peak broadening, although, no chemical exchange processes were detected in the low temperature VT-ROESY spectra. Low temperature VT-NMR experiments sharpen the NMR peaks and showed the presence of different conformers, which again, acted as evidence that conformational dynamics were probably contributing towards the broad NMR peaks that were observed at room temperature (**Figure 2.8c**).

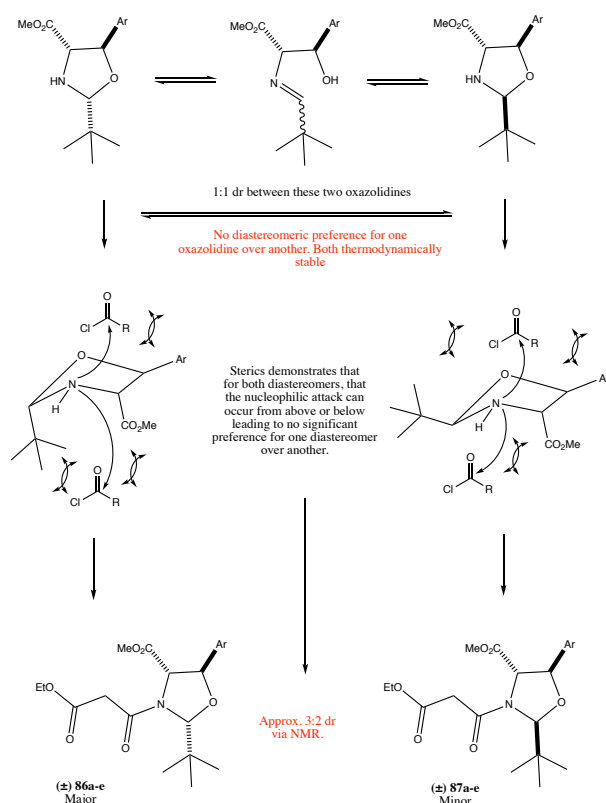
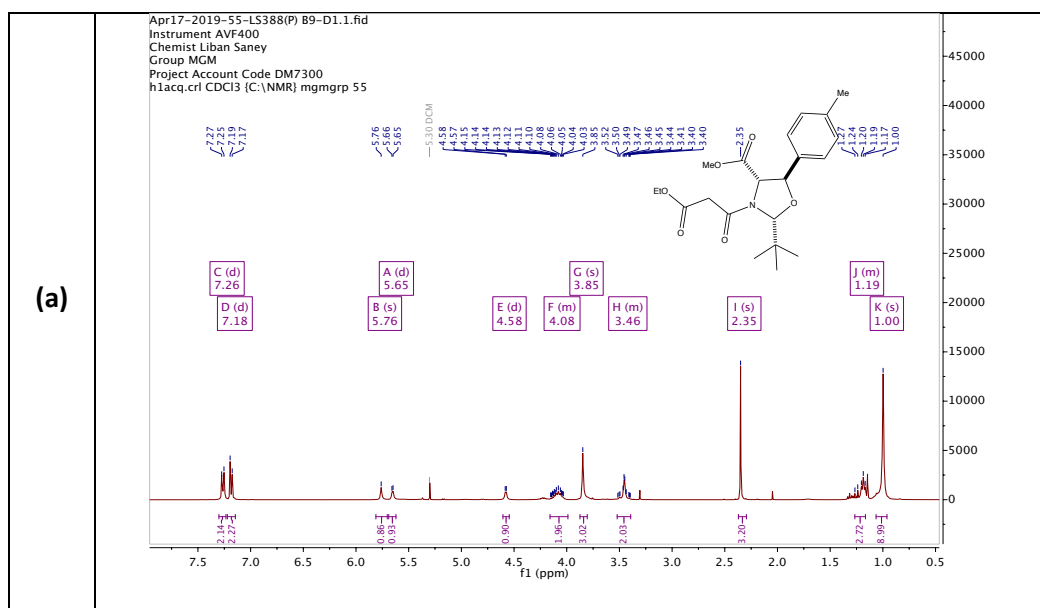


Figure 2.7: Diagram rationalising the lack of diastereoselectivity observed for the *N*-acylation of oxazolidines **84a-e** by considering both kinetics and thermodynamics.



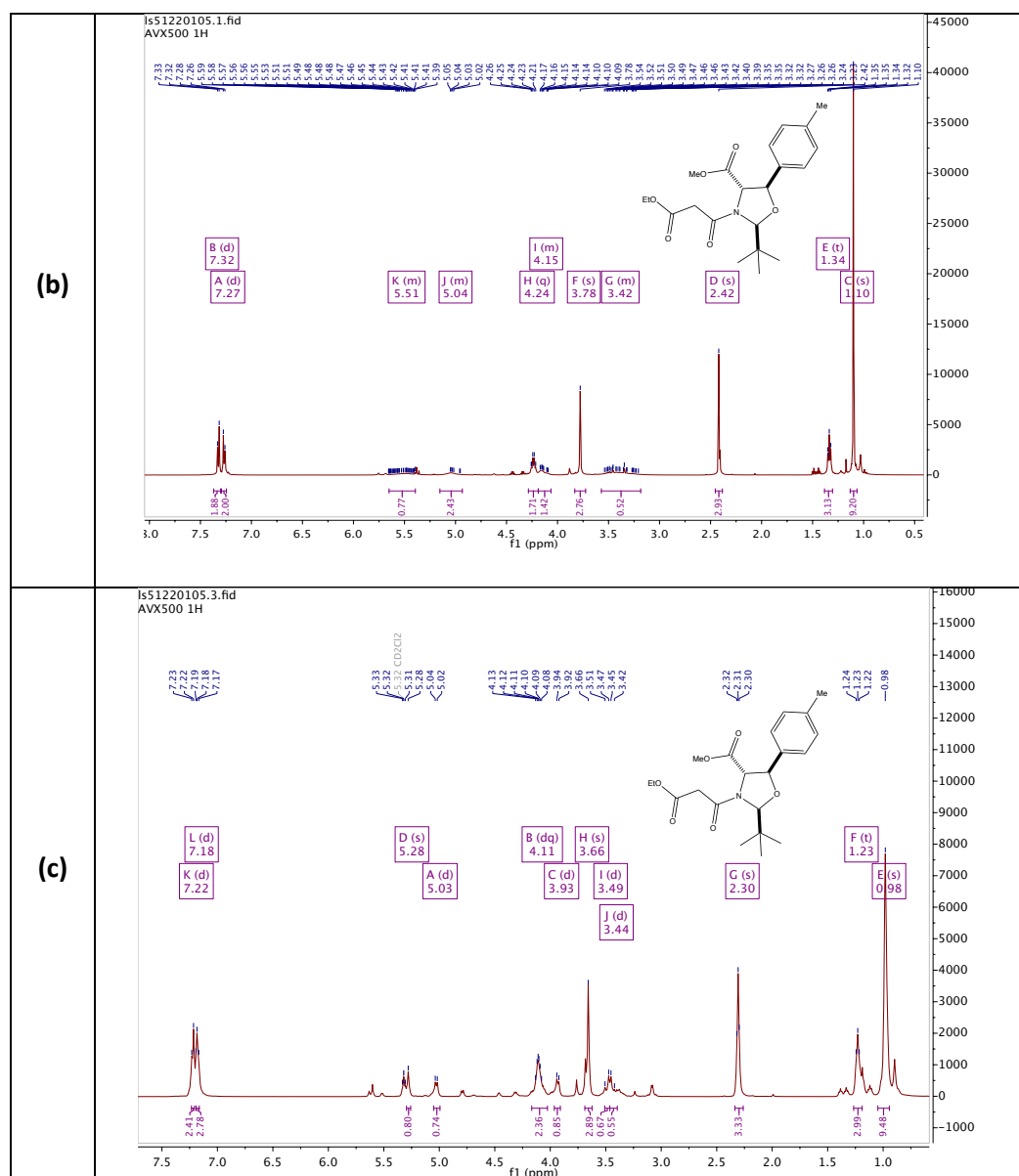


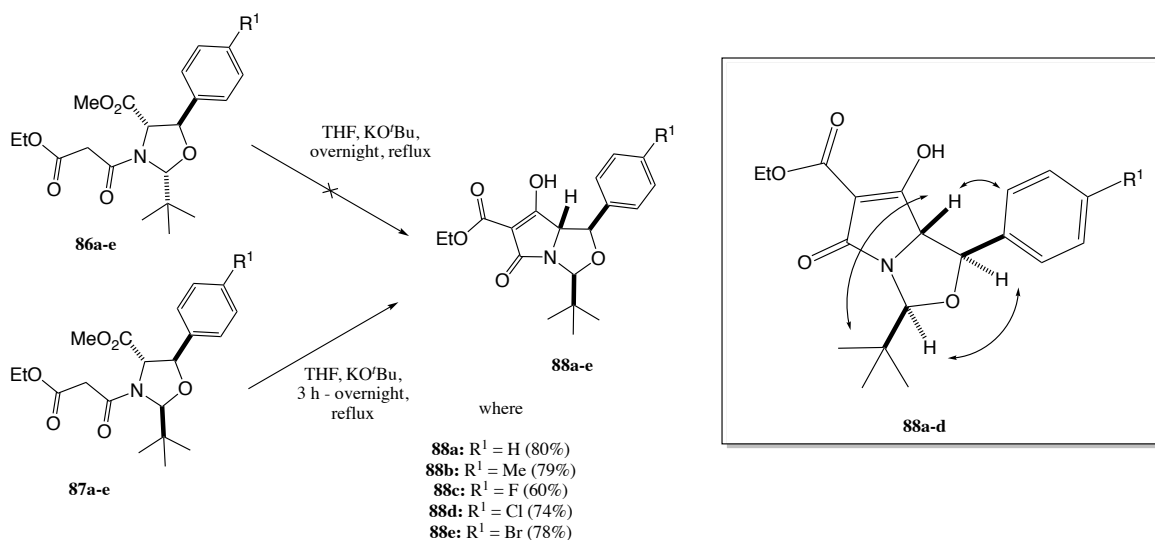
Figure 2.8: (a) ^1H -NMR spectrum of malonamide **86b** at room temperature in CDCl_3 solution, 400 MHz; (b) ^1H -NMR spectrum of malonamide **87b** at room temperature in CD_2Cl_2 solution, 500 MHz; (c) ^1H -NMR spectrum of malonamide **87b** at 193K in CD_2Cl_2 solution, 500 MHz.

2.2.4. Synthesis of Tetramates

Due to the difficulties of separating malonamide diastereomers **86a-e** and **87a-e** through chromatographic purification, a diastereomeric mixture of malonamides **86a-e** and **87a-e** was reacted with KO^tBu in THF, overnight at reflux.³⁴⁻³⁵ However, poor yields were obtained for tetramates **88a-e** – typically between 30-40% – in addition to other unidentified side products that were also formed. It became apparent that a more in-depth analysis was required to understand why poor yields of

tetramates were being obtained in this case. Thus, a small amount of each malonamide diastereomer was separated and reacted on individually. Malonamides **86a-c** were reacted with KO^tBu in THF overnight at reflux, however, starting material was mostly recovered – as determined from TLC and ¹H-NMR studies – in addition to other unidentified side-products that were also formed. This indicated that malonamides **86a-e** were resistant to the Dieckmann cyclisation (**Scheme 2.11**), and this could give some explanation as to why poor yields of tetramates were often obtained when a gross diastereomeric mixture was used.

Malonamides **87a-e** were also reacted separately with KO^tBu. In this case, tetramates **88a-e** were obtained in good yields – typically between 60-80% (**Table 2.6**). This demonstrated that malonamides **87a-e** preferentially cyclised towards tetramates **88a-e** (**Scheme 2.11**). The relative stereochemistry of tetramates **88a-e** were determined from nOe studies (**Scheme 2.11**). Interestingly, the Dieckmann cyclisation was chemoselective with respect to the synthesis of tetramates **88a-e**; which will be discussed in more detail below.



Scheme 2.11: The synthesis of tetramates **88a-e** from malonamides **87a-e**, and the relative stereochemistry of tetramates **88a-d** determined from nOe studies.

Tetramates **88a-e** were found to be unstable during chromatographic purification and this is similar to that observed by Andrews *et al.* for analogous C7-ethyl ester tetramates **12a** that were derived from

L-serine **48a**.³⁴ It was also found that tetramates **88a-e** were unstable in CDCl₃ solution as well, where they rapidly degraded to C7-decarboxylated tetramates **89a-e** – as determined from NMR and mass spectroscopic analysis (**Scheme 2.12**). Fortunately, the crude tetramates **88a-e** synthesised were relatively pure by NMR analysis and could be used into the next reaction sequence (**Figure 2.9**).

Compound	R ¹	δ (ppm)				Yield (%)
		H2	H4	H5	J_{H4-H5} (Hz)	
88a	H	4.99	4.53	4.17	8.4	80
88b	Me	5.00	4.51	4.18	8.5	79
88c	F	5.00	4.54	4.16	8.4	60
88d	Cl	5.01	4.54	4.14	8.4	74
88e	Br	5.00	4.52	4.13	8.4	78

Table 2.6: Key chemical shifts (δ), coupling constants (J) and yields of tetramates **88a-e**; CDCl₃ solvent, 400 MHz.

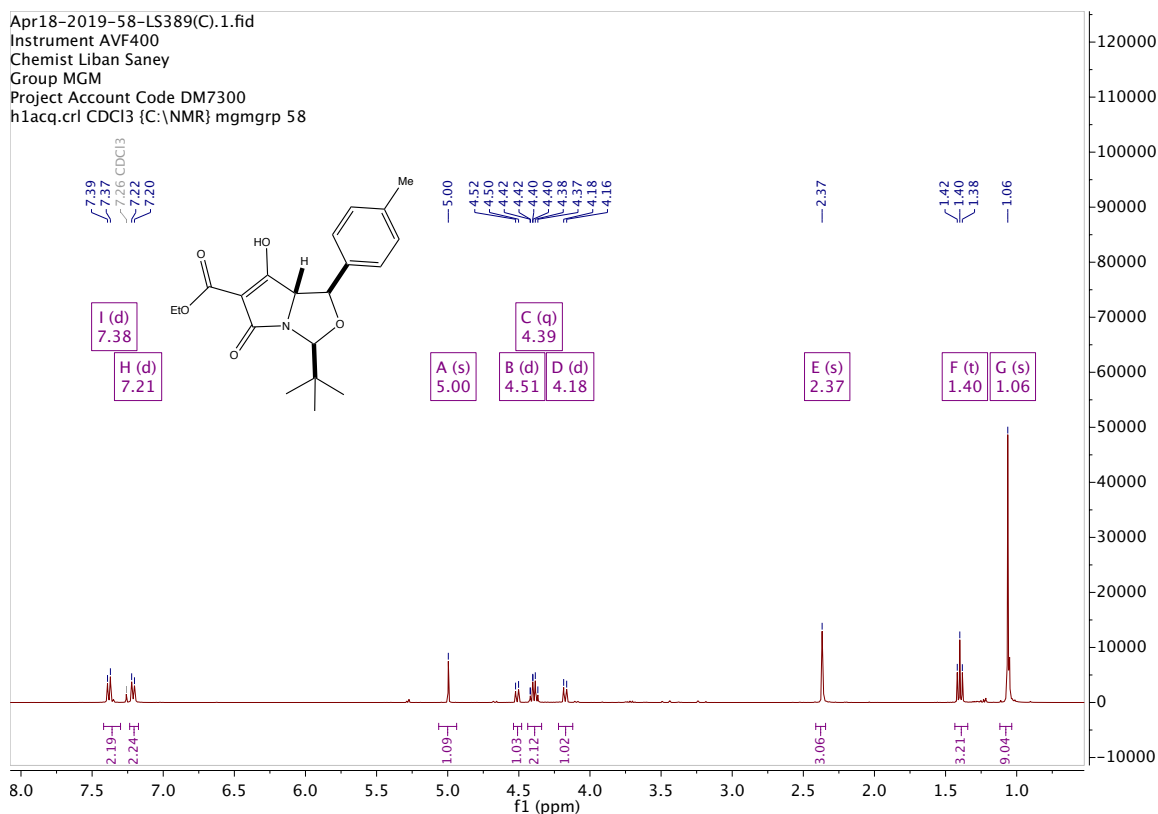
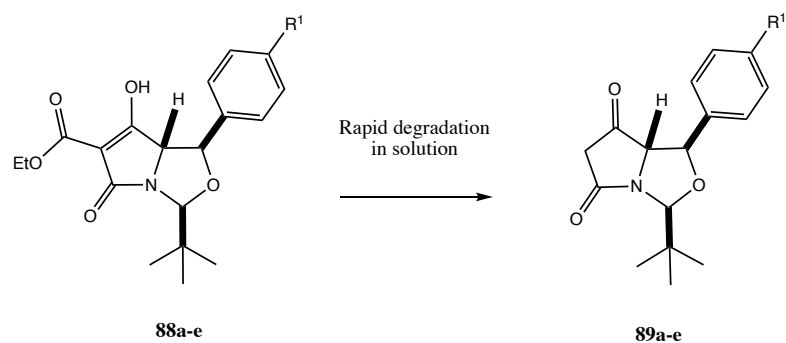
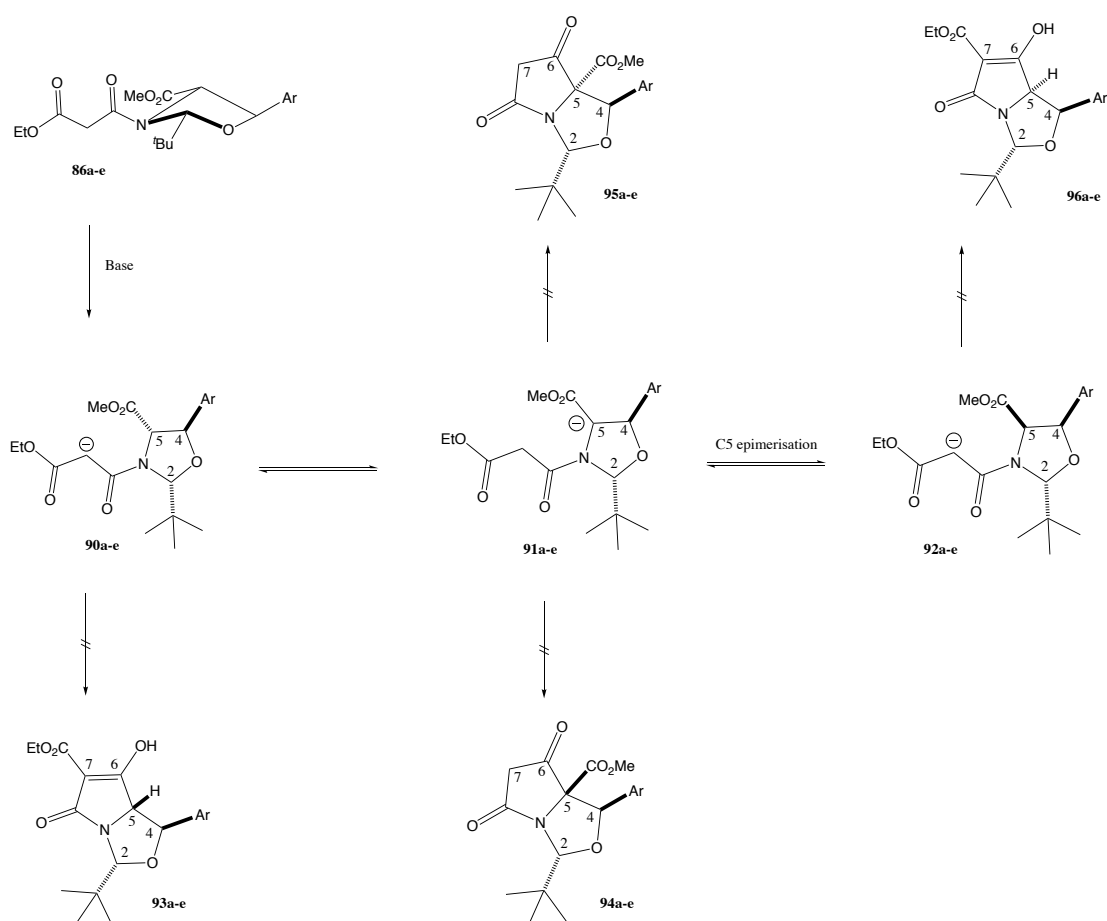


Figure 2.9: ¹H-NMR spectrum of tetramate **88b**, showing the relative purity of the crude material; CDCl₃ solution, 400 MHz.



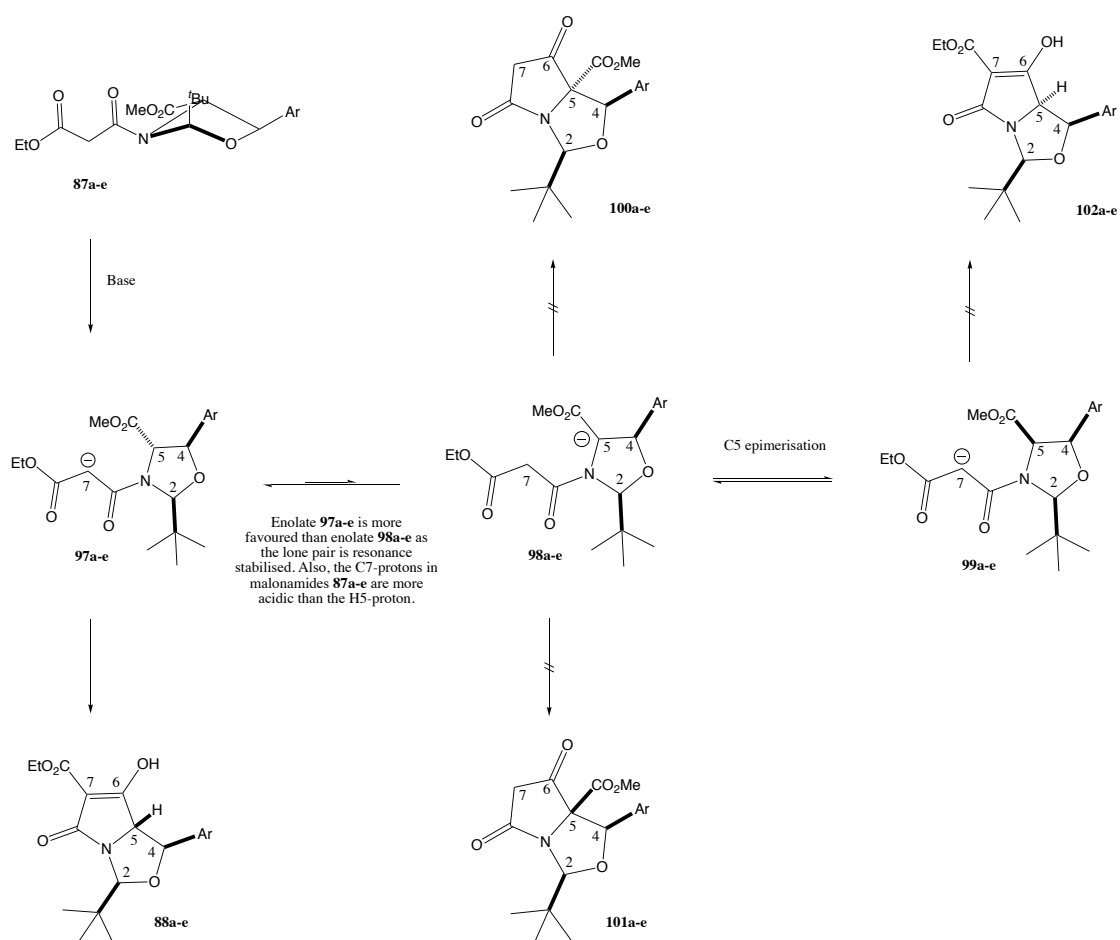
Scheme 2.12: Reaction scheme showing the degradation to tetramate **89a-e** in CDCl_3 solution.

Of interest was the high levels of chemoselectivity observed towards the synthesis of tetramates **88a-e** from malonamides **87a-e**. Malonamides **86a-e** were clearly resistant towards the Dieckmann cyclisation as none of the tetramate products **88a-e**, **93a-e**, **94a-e**, **95a-e** and **96a-e** were formed (**Scheme 2.13**).



Scheme 2.13: The possible chemoselective routes towards the failed synthesis of tetramates from malonamides **86a-e**.

It was reasoned that tetramates **93a-e** and **94a-e** did not form from enolates **90a-e** and **91a-e** as the bulky *t*Bu substituent would reside on the *endo*-face of the bicyclic lactam, causing unfavourable steric congestion. However, more surprising was the fact that tetramates **95a-e** or **96a-e** did not form from enolates **91a-e** or **92a-e**, particularly as they were analogous to that of L-threonine-derived tetramic acids **11b** (see **Schemes 1.1** and **2.2**). It was concluded that the increase in steric bulk at the C4-position in the form of an aromatic ring placed on the *endo*-face of the bicyclic lactam caused too much steric hinderance, and this could possibly explain why tetramates **95a-e** or **96a-e** did not form in any measurable amount.



Scheme 2.14: The chemoselective routes towards the synthesis of tetramates from malonamides **87a-e**.

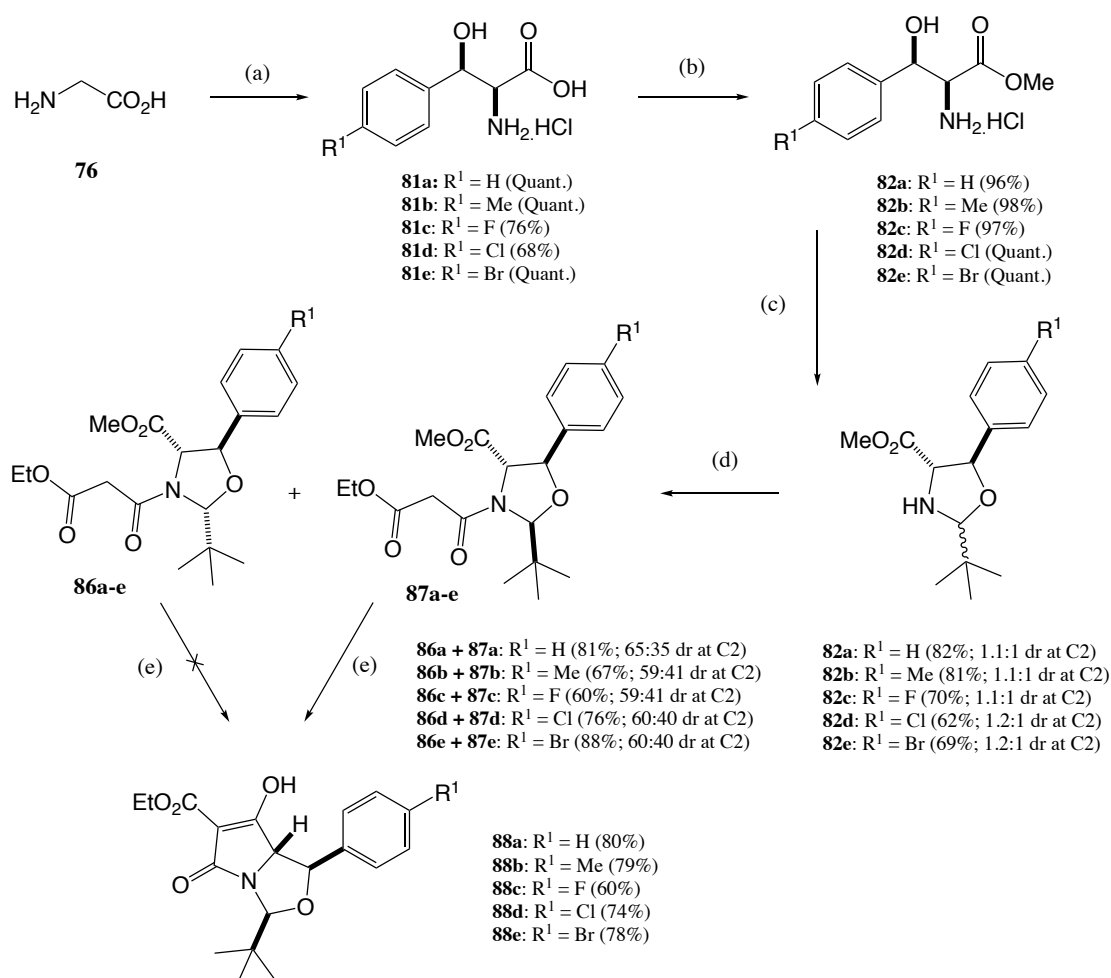
In the case of malonamides **87a-e**, enolate **97a-e** led to the ring closure to tetramate product, **88a-e** (**Scheme 2.14**). It was interesting to note that in this case, the bulky *t*Bu and aromatic groups were on

the less hindered *exo*-face of the bicyclic lactam and this could have been the reason as to why tetramate **88a-e** preferentially formed via the Dieckmann cyclisation. Interestingly, tetramate **101a-e** in theory could have formed via the ring closure of enolate **98a-e**, as both the ^tBu and aromatic groups were on the less hindered *exo*-face of the bicyclic lactam, but this was not observed experimentally. It was reasoned that the formation of enolate **97a-e** was more favoured than enolate **98a-e** as the C7-hydrogens in malonamide **87a-e** were more acidic than the C5-hydrogen. As a result, enolate **97a-e** would potentially form quicker than enolate **98a-e** under basic conditions and has the added bonus of being resonance stabilised as well, thus resulting in the formation of the kinetic and thermodynamic product, **88a-e**, through an irreversible Dieckmann cyclisation. Additionally, tetramates **100a-e** and **102a-e** were not observed, due to steric congestion at the C2 and C4-positions (**Scheme 2.14**).

2.2.5. Density Functional Theory (DFT) Calculations

DFT calculations, conducted by Dr. Xiang Li, were used to rationalise what had been observed experimentally, as this methodology clearly deviated from Moloney's original methodology of synthesising bicyclic tetramates **11a-c** from L-serine **48a**, L-threonine **48b** and L-cysteine **48c** (compare **Schemes 1.1** or **2.1** with **2.15**). More surprisingly, these systems tended to behave more like thiazolidine-derived tetramic acids **44** that were condensed with aromatic aldehydes (compare **Schemes 1.7** with **2.15**).

Malonamides **86a** and **87a** were considered for DFT calculations towards the synthesis of tetramate **88a**. Depicted in **Figure 2.10** are all the intermediates and transition states that were taken into account. Additionally, the solvent (THF) and base (KO^tBu) used experimentally was also taken into consideration for the DFT calculations. It was interesting to observe that malonamide **86a** was slightly more stable than malonamide **87a** – by approximately 4.1 kcal/mol (17.2 kJ/mol) – and this could give some explanation as to why there was a slight diastereomeric preference for malonamide **86a-e** in comparison to malonamide **87a-e** (**Table 2.5** and **Figure 2.11**).



Scheme 2.15: Overview of the synthesis towards tetramates **88a-e** from *threo*-phenylserine derivatives

81a-e; (a) (i) 3 M NaOH (aq.) or 3 M KOH (eth.), ArCHO, 2-3 d, rt; (ii) 3 M HCl (aq.); (b) MeOH, SOCl₂, reflux, overnight; (c) ^tBuCHO, Et₃N, petroleum ether 40:60, Dean-Stark, >100°C, overnight; (d) ethyl malonyl chloride, pyridine, DCM, reflux, overnight; (e) KO^tBu, THF, reflux, 3 h-overnight.

When considering the reaction energy profile for the deprotonation of malonamides **86a** and **87a** using KO^tBu as a base, there was significant energy differences between enolate **98a** and the next enolate highest in energy, **97a** – typically about 20.3 kcal/mol (84.9 kJ/mol) (**Figure 2.11**). Thus, it was assumed that enolate **98a** did not form under basic conditions to produce tetramates **100a** or **101a** – and this was in agreement to the chemoselective analysis that was discussed in **Scheme 2.14**, particularly in regard to enolate **97a** being more favoured than enolate **98a**. In relation to enolates **90a**, **91a** and **97a**, there were minimal energy differences between these enolate intermediates, and which therefore became of particular interest when studying the different reaction pathways that were possible.

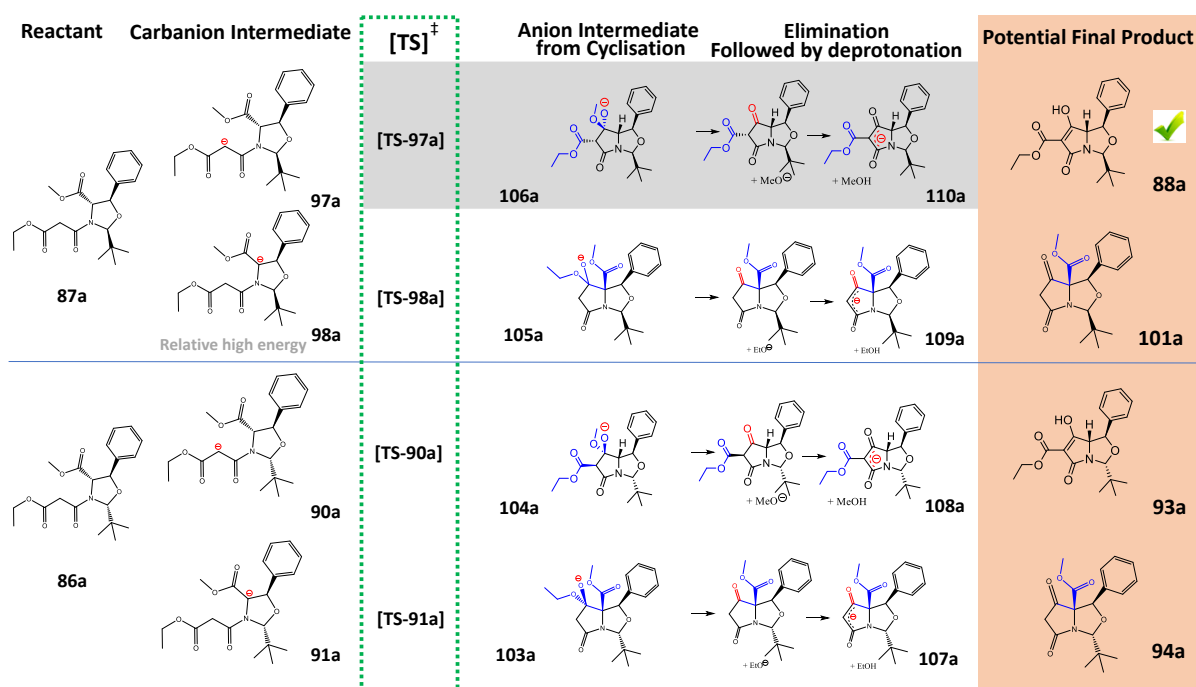


Figure 2.10: Malonamides, intermediates and transition states [TS][‡] considered for the synthesis of tetramates.

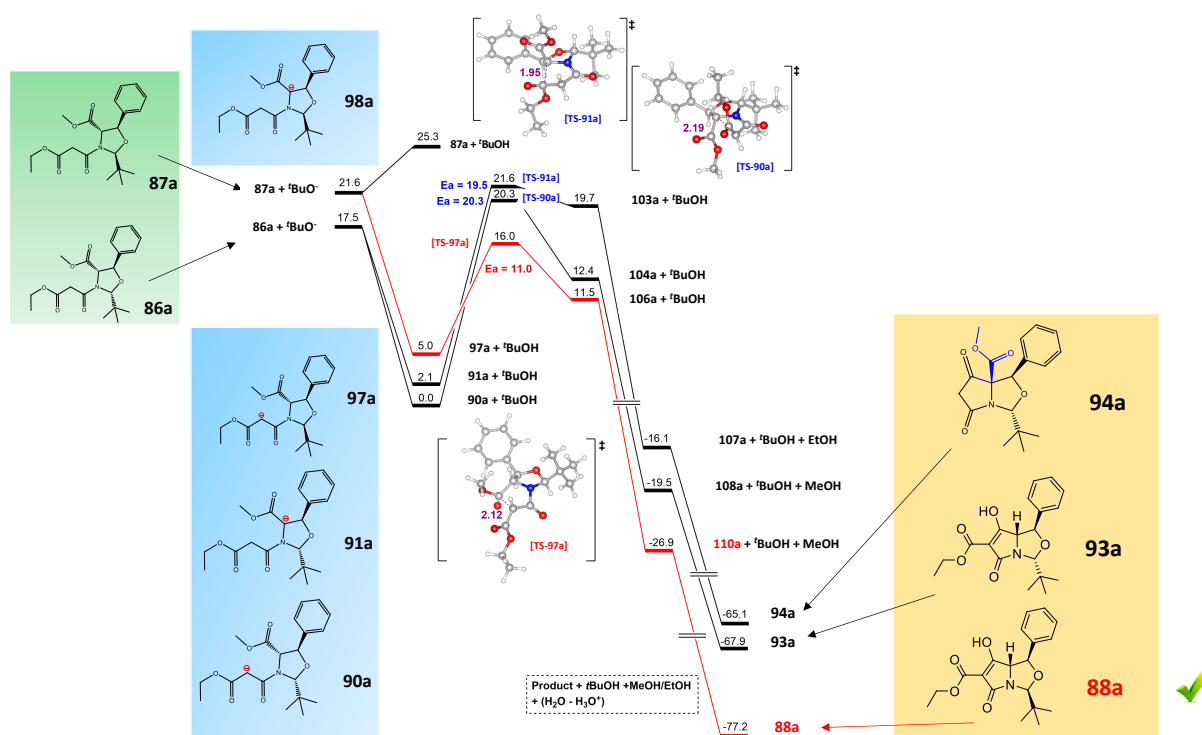


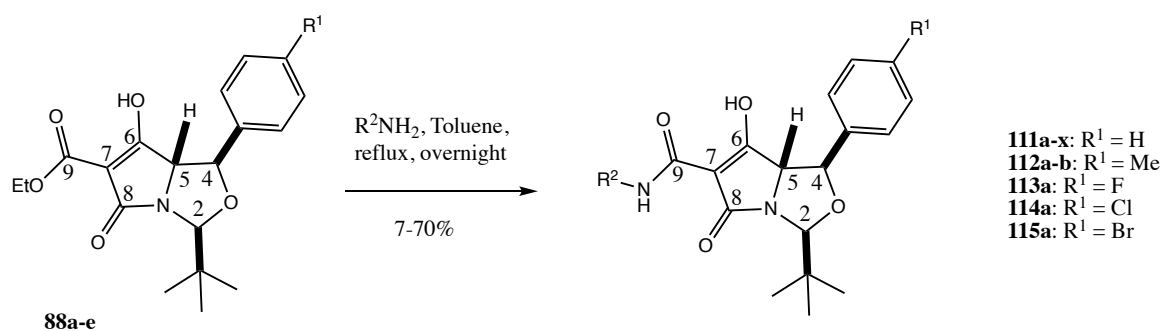
Figure 2.11: DFT calculated reaction energy profile for the Dieckmann cyclisation of malonamides **86a** and **87a** using the B3LYP/6-311++g(d,p) level of theory with SMD solvation (THF). All energies are reported in kcal/mol and are referenced to the lowest energy carbanion generated after initial deprotonation.

The activation energy, E_a , for the lowest energy transition state was calculated to be **[TS-97a][‡]**, which had an E_a = 11 kcal/mol (46 kJ/mol). The next highest energy transition states were **[TS-91a][‡]**, which had an E_a = 19.5 kcal/mol (81.59 kJ/mol) and **[TS-90a][‡]**, which had an E_a = 20.3 kcal/mol (84.9 kJ/mol). As both **[TS-90a][‡]** and **[TS-91a][‡]** had considerably larger E_a than **[TS-97a][‡]**, it was reasoned that **[TS-97a][‡]** was the more favoured reaction pathway towards the synthesis of tetramate **88a** (energy pathway highlighted in red in **Figure 2.11**) which was again, consistent with what was observed experimentally. Moreover, tetramate **88a**, was considerably more stable than tetramates **93a** and **94a** – typically by 9.3 kcal/mol (38.9 kJ/mol) and 12.1 kcal/mol (50.6 kJ/mol) respectively – indicating that tetramate **88a-e** was both the kinetic and thermodynamic product.

2.2.6. Synthesis of C7-Carboxamides

As it has been noted that simple tetramic acids are devoid of antibacterial activity, of interest was functionalising the C7-position of tetramic acids **88a-e** to mimic natural product antibacterial tetramates that tended to have long aliphatic chains or fused polycyclic skeletons at that position, such as that of equisetin **3** and virgineone aglycone **7**.^{33,43} Due to the recent success of synthesising C7-carboxamides which had potent antibacterial activity – as discussed in **Chapter 1.6.2.3** – C7-carboxamides were synthesised in this research to test for possible antibacterial activity against Gram (+) and Gram (-) bacteria – where the antibacterial activity is discussed in **Chapter 5**.

The chemoselective Dieckmann cyclisation of malonamides **87a-e** fortuitously established the C7-ethyl ester moiety in tetramic acids **88a-e**, which could allow a simple aminolysis reaction to take place using aliphatic or aromatic amines to form C7-carboxamides. Thus, 29 C7-carboxamides **111a-x**, **112a-b**, **113a**, **114a**, **115a** were synthesised in this research in variable yields, ranging between 7-70% (**Scheme 2.16**). Interestingly, these tetramic acids were far more stable than their ethyl ester precursors **88a-e**, as the C7-carboxamides were both stable to chromatographic purification and in CDCl₃ solution for many months.



Scheme 2.16: The synthesis of C7-carboxamides **111a-x**, **112a-b**, **113a**, **114a** and **115a**.

However, when these C7-carboxamides were chromatographically purified on silica gel, they picked up trace metal ions to form metal-chelates across the tricarbonyl core as shown in **Figure 1.31**. This was mainly detected in the NMR spectrum, where broad peaks were observed post-chromatographic purification.^{33,39,43} **Figure 2.12a** showed that in the case of compound **111a**, the NMR peaks for the H4 and H5-protons were extremely broad after chromatographic purification – indicating that these protons were relatively close to the metal-chelation site – whereas the ^tBu, aromatic and adamantyl groups were relatively sharp in comparison, indicating that these groups were further away from the metal-chelation site.

However, when metal-chelated tetramic acids were washed with 10% citric acid solution (aq.), the NMR peaks of C7-carboxamides significantly sharpened, with slight changes in chemical shifts also observed (**Figure 2.12b**). The resolution of the NMR peaks with a simple acid wash acted as qualitative evidence that these tetramic acids formed metal-chelates, however, the fact that they only required a mild acid wash – 10% citric acid (aq.) – in comparison to the reported 2 M HCl (aq.) washes which are usually required to remove metal ions in C7-carboxamides, indicated that C4-functionalisation with aromatic substituents might potentially disrupt metal-chelation across the tricarbonyl core.^{33,43}

Additionally, C7-carboxamides can also exist as a mixture of tautomers – **AB:CD** – as shown in **Figure 2.13**. The tautomeric behaviour of C7-carboxamides can typically be detected in NMR studies;^{33,43} with **Figure 2.12b** showing an 80:20 **AB:CD** tautomeric mixture of C7-carboxamide, **111a**. The internal

tautomeric pairs (A and B, C and D) cannot be readily distinguished by NMR spectroscopy and are generally observed as a hybridised average, however, the external tautomeric pairs (**AB:CD**) have distinct ^{13}C -NMR chemical shift differences at the C6, C8 and C9-positions, enabling the different tautomeric forms to be distinguished readily by NMR studies.^{33,43}

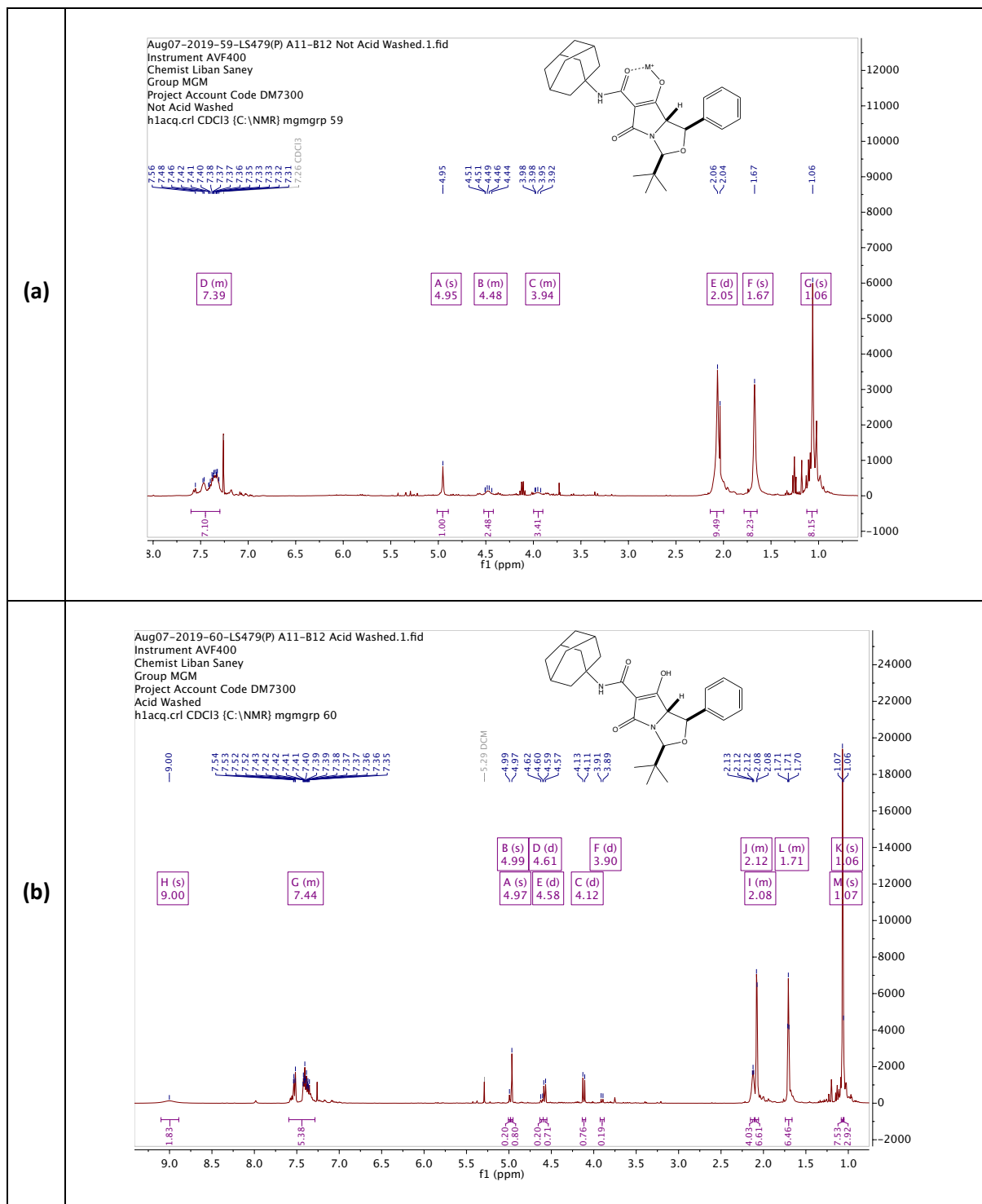


Figure 2.12: ^1H -NMR spectrum of C7-carboxamide **111a** post-chromatographic purification, before (a) acid wash and (b) after 10% citric acid wash; CDCl₃ solution, 400 MHz.

Panduwawala *et al.* also deduced that the major tautomeric form for C7-carboxamides were **Type A** (**Figure 2.13**) based on NOESY studies and computational analysis.³³ As a result, it was also assumed that the major tautomeric form of C7-carboxamidotetramic acids, **111a-x**, **112a-b**, **113a**, **114a** and **115a** were also of **Type A**, based upon similar ¹³C-NMR chemical shift values at the C6, C8 and C9-positions in comparison to Panduwawala *et al.* ¹³C-NMR values – in which the carbonyl assignments could be made using HMBC analysis.³³

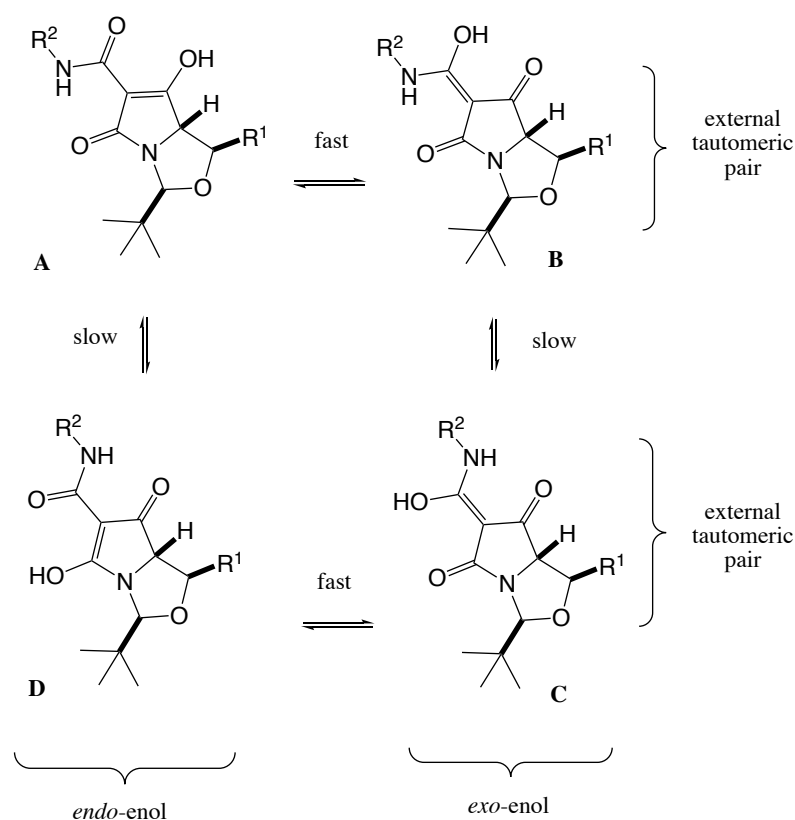
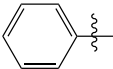
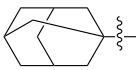
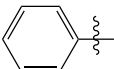
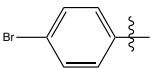
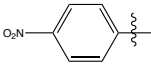
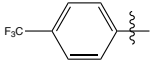
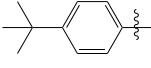
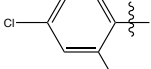
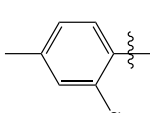


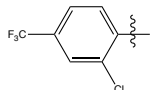
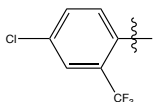
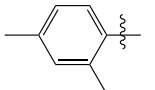
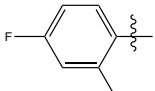
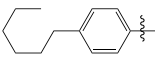
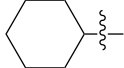
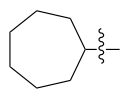
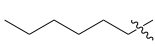
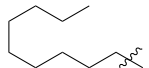
Figure 2.13: Tautomeric behaviour of C7-carboxamides.

The ¹³C-NMR chemical shift values for C6, C8 and C9 tended to be more downfield for the minor tautomeric pair, **CD**, in comparison to the major tautomeric pair **AB** (**Table 2.7**).^{33,43} Additionally, the use of deuterated solvents and the size and nature of the R² group (**Figure 2.13**) tended to affect tautomeric behaviour, which Panduwawala *et al.* had also observed.³³

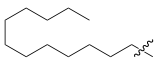
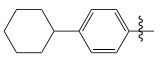
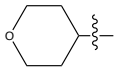
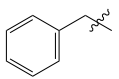
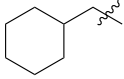
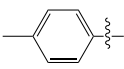
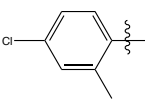
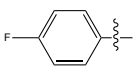
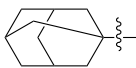
Chapter 2: *threo*-Phenylserine-Derived *N,O*-Bicyclic Tetramic Acids

Compound	R ¹	R ²	δ (ppm)							Tautomeric ratio ^a	Yield (%)
			H2	H4	H5	J_{H4-H5} (Hz)	C6	C8	C9		
111a			4.97	4.58	4.12	8.6	186.9	175.1	166.3	Major (AB) 80%	55
			4.99	4.61	3.90	8.9	190.5	181.3	167.1	Minor (CD) 20%	
111b			5.02	4.63	4.27	8.5	184.0	174.4	164.1	AB only	42
111c			5.01	4.61	4.27	8.5	183.7	174.2	164.0	AB only	42
111d			5.02	4.64	4.31	8.5	184.0	174.0	164.3	AB only	15
111e			5.02	4.63	4.30	8.5	183.9	174.2	164.3	AB only	38
111f			4.90	4.44	4.00	8.5	185.1	175.4	164.1	AB only	27
111g			5.03	4.63	4.27	8.5	183.6	174.4	163.9	AB only	40
111h			5.06	4.63	4.27	8.4	183.9	174.0	164.2	AB only	44

Chapter 2: *threo*-Phenylserine-Derived *N,O*-Bicyclic Tetramic Acids

111i		5.07	4.64	4.31	8.5	184.0	173.8	164.5	AB only	21
111j		5.06	4.64	4.28	8.5	183.8	173.7	164.5	AB only	43
111k		5.05	4.65	4.27	8.5	184.2	174.5	164.2	AB only	41
111l		5.04	4.64	4.27	8.5	183.8	174.4	164.0	AB only	51
111m		5.02	4.62	4.26	8.5	184.1	174.4	164.0	AB only	18
111n		4.97 4.99	4.58 4.61	4.15 3.90	8.6 8.9	186.1 190.6	174.9 181.0	165.5 166.0	Major (AB) 82% Minor (CD) 18%	45
111o		4.97 4.99	4.58 4.61	4.15 3.90	8.5 8.8	186.1 190.6	174.9 181.0	165.2 165.7	Major (AB) 83% Minor (CD) 17%	24
111p		4.97 5.00	4.58 4.61	4.16 3.90	8.5 8.9	185.6 188.4	174.8 181.0	166.3 167.0	Major (AB) 82% Minor (CD) 18%	19
111q		4.97	4.58	4.17	8.6	185.6	174.8	166.3	AB only	40

Chapter 2: *threo*-Phenylserine-Derived *N,O*-Bicyclic Tetramic Acids

111r			4.97 5.00	4.58 4.60	4.16 3.90	8.6 8.9	185.6 190.7	174.8 180.4	166.3 167.0	Major (AB) 84% Minor (CD) 16%	57
111s			5.02	4.63	4.26	8.5	184.1	174.4	164.0	AB only	25
111t			4.97 4.99	4.58 4.62	4.19 3.92	8.6 8.9	184.9 190.6	174.6 181.1	165.6 166.4	Major (AB) 88% Minor (CD) 12%	31
111u			4.96	4.59	4.20	8.5	184.6	174.5	166.0	AB only	33
111v			4.96 4.99	4.58 4.61	4.13 3.91	8.6 8.8	186.5 190.5	175.1 181.2	166.3 167.2	Major (AB) 82% Minor (CD) 18%	41
111w			4.98	4.58	4.16	8.5	185.6	174.8	166.3	AB only	37
112a			4.94 4.97	4.53 4.57	4.10 3.88	8.6 8.8	186.6 190.5	175.1 181.2	166.2 167.0	Major (AB) 80% Minor (CD) 20%	52
112b			5.01	4.59	4.27	8.5	183.8	174.4	164.1	AB only	7
113a			4.94 4.97	4.53 4.57	4.04 3.83	8.9 9.3	187.1 190.4	175.1 181.1	166.2 167.0	Major (AB) 78% Minor (CD) 22%	70

114a			4.96	4.55	4.04	8.6	187.3	175.1	166.3	Major (AB) 76% Minor (CD) 24%	44
			4.99	4.58	3.84	8.9	190.3	181.1	167.0		
115a			4.95	4.53	4.03	8.6	187.3	175.1	166.3	Major (AB) 77% Minor (CD) 23%	49
			4.98	4.56	3.83	8.9	190.3	181.1	166.9		

Table 2.7: Key ^1H and ^{13}C -NMR chemical shifts (δ) and coupling constants (J) of the major and minor tautomeric pairs **AB:CD** of C7-carboxamidotetramic acids; CDCl_3 solvent, 400 MHz; ^a Determined from the H2 signal from the ^1H -NMR spectrum.

Many nOe and NOESY studies were conducted to determine the relative stereochemistry of these C7-carboxamidotetramic acids (**Figure 2.14**). There appeared to be no epimerisation after aminolysis at any of the stereogenic centres within the bicyclic molecule (also see the **Appendices Section** to see all the relative stereochemistry of C7-carboxamidotetramic acids collected).

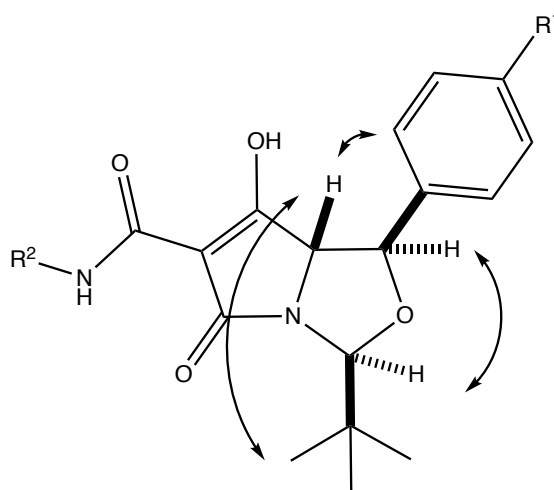


Figure 2.14: The relative stereochemistry of C7-carboxamidotetramic acids determined from nOe and NOESY studies.

Furthermore, a single crystal X-ray structure of compound **111a** was obtained (**Figure 2.15**) that confirmed the relative stereochemistry that was assigned by nOe and NOESY studies. As the NMR-

chemical shifts of **111a** was consistent with the rest of the C7-carboxamide series (**Table 2.7**), it was assumed that all C7-carboxamidotetramic acids had the same relative stereochemistry.

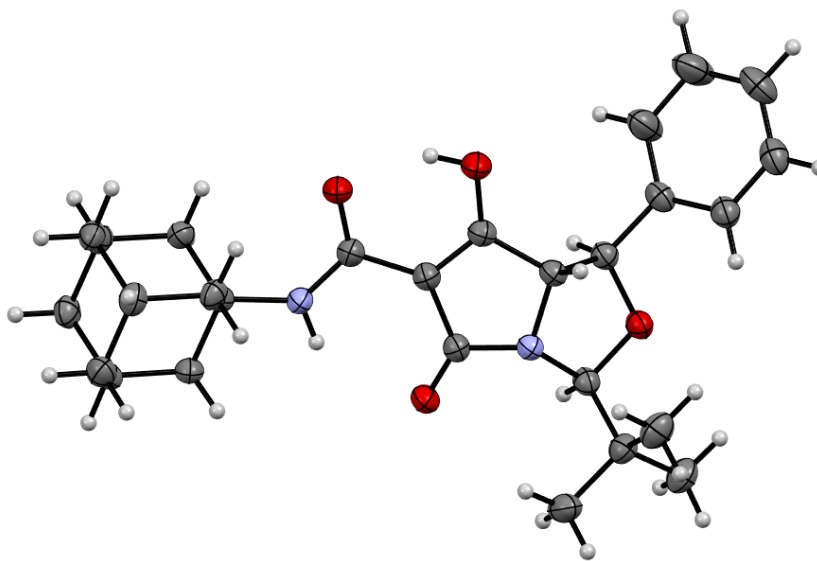


Figure 2.15: Single-crystal X-ray structure of C7-carboxamidotetramic acid, **111a**, confirming relative stereochemistry assigned by nOe and NOESY studies.

2.3: Summary

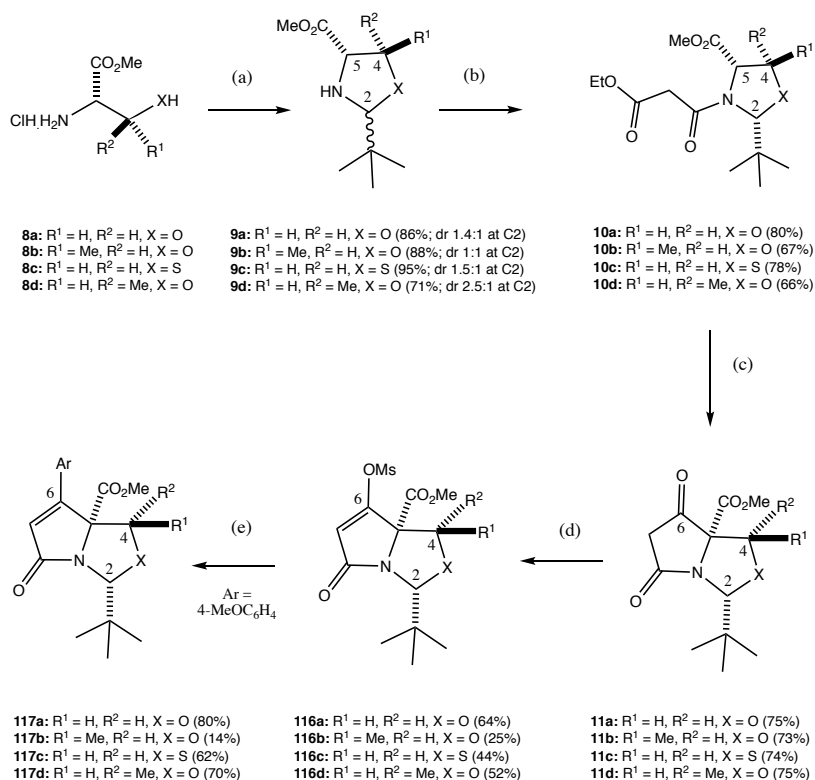
This research has demonstrated that *threo*-phenylserine derivatives **81** could be obtained with excellent diastereoselectivity. That bicyclic tetramates **88** could be synthesised from the *threo* isomers of substituted phenylserine derivatives **81**. That the synthesis towards highly substituted tetramates **88** could be accomplished diastereoselectively and chemoselectively – in which only one malonamide diastereomer **87** cyclises to form tetramates **88** with high levels of chemoselectivity – and was supported with computational data. That a library of C7-carboxamides **111-115** were synthesised and in many cases were observed as a tautomeric mixture. Moreover, it was established that these compounds bind to metal ions after chromatographic purification, however, a simple acid wash in the form of citric acid solution (aq.) can remove metal ions from the tetramate core.

Chapter 3: *erythro*-Phenylserine-Derived *N,O*-Bicyclic Tetramic Acids

This chapter describes the synthetic methodology used to make oxazolidine-derived tetramic acids from *erythro*-phenylserine derivatives. Additionally, the tautomeric behaviour and metal-binding properties of C7-carboxamides and C7-acyltetramates will also be discussed and finally, synthetic methodologies towards the clausenamide family and the formation of pyrrolidinone derivatives from tetramate scaffolds will also be discussed.

3.1: Previous Work in the Moloney Group

Bagum *et al.* developed a methodology for synthesising pyroglutamate derivatives from tetramates scaffolds using L-serine **8a**, L-threonine **8b**, L-cysteine **8c** and L-*allo*-threonine **8d** as starting materials.³⁵ This was the first example of bicyclic tetramates **11d** that were derived from L-*allo*-threonine **8d** and the reactivity of these tetramates **11d** were vastly superior to tetramates **11b** which were derived from L-threonine **8b**, particularly when utilising the Suzuki-Miyaura cross-coupling reaction (**Scheme 3.1**).³⁵



Scheme 3.1: Suzuki-Miyaura cross-coupling of mesylates **116a-d** with 4-methoxyphenylboronic acid;

(a) pivaldehyde, petroleum ether 40:60, Et₃N, Dean-Stark, >100°C, 18 h; (b) ethyl hydrogen malonate,

DCC, DMAP, DCM, rt, 5 h; (c) KO^tBu, THF, reflux, 3 h; (d) MsCl, DIPEA, DCM, rt, 2-6 h; (e) 4-methoxyphenylboronic acid, PdCl₂(dppb), Na₂CO₃, toluene, ethanol, reflux, 3-4 h.

3.2: Synthesis of Tetramic Acids from *erythro*-Phenylserine Derivatives

Taking inspiration from Bagum's use of tetramic acids **11d** which were derived from L-*allo*-threonine **8d**, this chapter describes the synthesis of oxazolidine-derived tetramic acids **118** from *erythro* (or *allo*)-phenylserine derivatives **121**, with **Figure 3.1** illustrating the retrosynthetic analysis used as the rationale towards the synthesis of tetramate **118** – assuming *allo*-phenylserine derivatives **121** followed the same reaction pathway as L-*allo*-threonine **8d** (shown in **Scheme 3.1**).

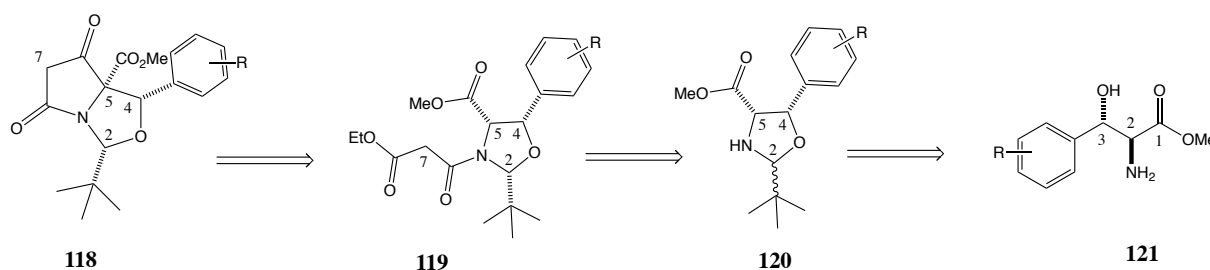
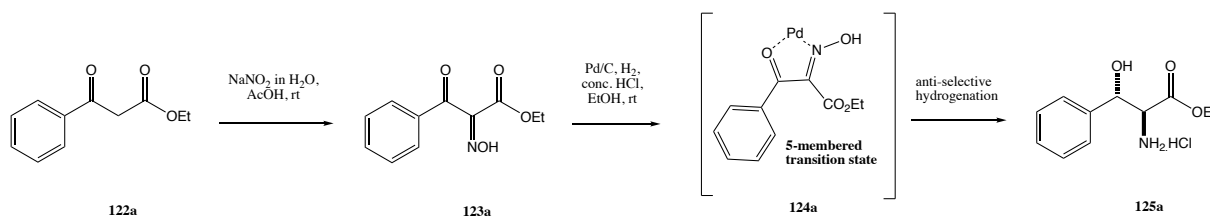


Figure 3.1: Retrosynthetic analysis for the synthesis of tetramates **118** from amino esters **121**.

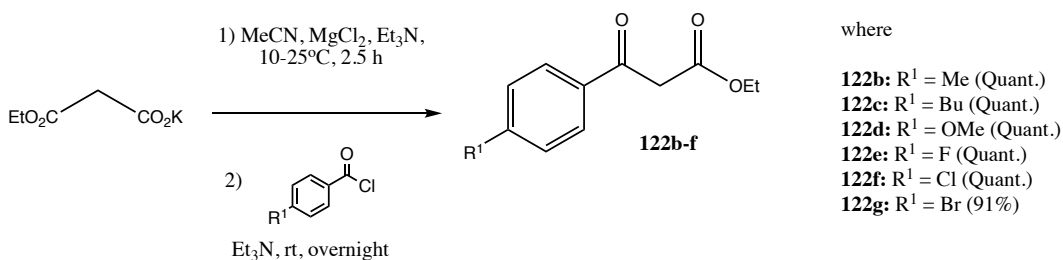
3.2.1: Synthesis of *erythro*-Phenylserine Derivatives

Chang *et al.* had synthesised *allo*-phenylserine **125a** from the hydrogenation of oxime **123a** using palladium on carbon as a catalyst.⁵⁸ The synthesis of *allo*-phenylserine **125a** was completely diastereoselective – where only 1 diastereomer was isolated after hydrogenation.⁵⁸ It was theorised that the diastereoselectivity arose through a ‘substrate-catalyst complex’, whereby the palladium coordinates with both the oxygen and nitrogen atoms to induce high levels of diastereoselectivity upon hydrogenation, through a 5-membered ring transition state **124a** (**Scheme 3.2**).⁵⁸ Inoue *et al.* extended this methodology towards the synthesis of 4-methoxyphenylserine derivatives **125d**.⁵⁹ As *allo*-phenylserine **125a** could be synthesised from β -oxoesters **122a** in 2 synthetic steps using relatively mild reaction conditions, we took inspiration from the work of Chang *et al.* and Inoue *et al.* and synthesised a small library of *allo*-phenylserine derivatives **125a-f**.



Scheme 3.2: Proposed 5-membered transition state towards the synthesis of *allo*- β -arylserine **125a**.

Ethyl benzoylacetate **122a** was commercially available, however, its derivatives **122b-g** were expensive to purchase, thus had to be made synthetically. Clay *et al.* synthesis of β -oxoesters ticked many boxes, as their reaction conditions were mild, easily up-scalable, had a large substrate scope and could be obtained in a single synthetic step in high yields (**Scheme 3.3**).⁶⁰ As a result, the work of Clay *et al.* was replicated, and ethyl potassium malonate was dissolved in acetonitrile and was reacted with acid chlorides using a $\text{MgCl}_2\text{-Et}_3\text{N}$ base system to obtain β -oxoesters **122b-g**, typically in quantitative yields. It must be noted that more than 3 eq. of Et_3N was required to suppress the formation of side products.⁶⁰ NMR analysis indicated that these compounds existed as a mixture of keto-enol tautomers (**Table 3.1**). Fortunately, the crude β -oxoesters **122b-g** synthesised were pure by NMR analysis and thus did not require chromatographic purification, although they could easily be chromatographically purified if required.



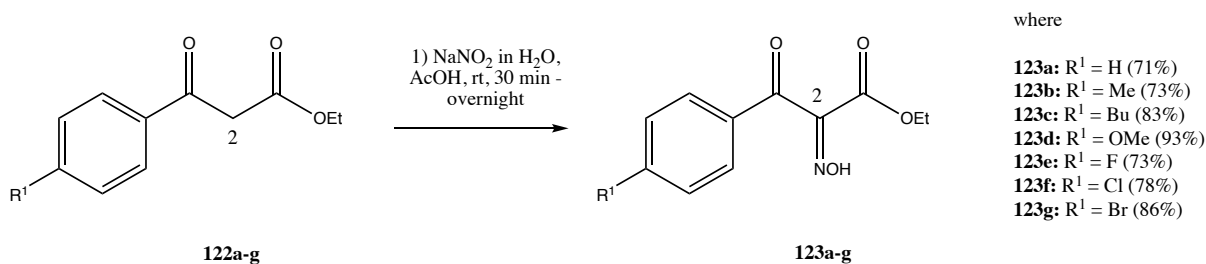
Scheme 3.3: Synthesis of β -oxoesters **122b-g** from ethyl potassium malonate.

Compound	δ_{keto} (ppm)	δ_{enol} (ppm)	Ratio between keto:enol ^a	Yield (%)
122b	1.26 (3H, t, $J=7.1$ Hz), 2.42 (3H, s), 3.97 (2H, s), 4.22 (2H, q, $J=7.2$ Hz), 7.28 (2H, d, $J=8.1$ Hz), 7.85 (2H, d, $J=8.3$ Hz)	1.34 (3H, t, $J=7.1$ Hz), 2.39 (3H, s), 4.27 (2H, m), 5.64 (1H, s), 7.28-8.00 (4H, m), 12.59 (1H, s)	5.5:1	Quant.

122c	0.94 (3H, m), 1.26 (3H, t, <i>J</i> =7.1 Hz), 1.36 (2H, m), 1.62 (2H, m), 2.67 (2H, m), 3.97 (2H, s), 4.22 (2H, q, <i>J</i> =7.1 Hz), 7.28 (2H, d, <i>J</i> =8.3 Hz), 7.86 (2H, d, <i>J</i> =8.3 Hz)	0.94 (3H, m), 1.26-1.42 (5H, m), 1.62 (2H, m), 2.67 (2H, m), 4.28 (2H, m), 5.64 (1H, s), 7.23-8.04 (4H, m), 12.58 (1H, s)	2.8:1	Quant.
122d	1.24 (3H, t, <i>J</i> =7.1 Hz), 3.86 (3H, s), 3.93 (2H, s), 4.19 (2H, q, <i>J</i> =7.1 Hz), 6.93 (2H, d, <i>J</i> =8.9 Hz), 7.91 (2H, d, <i>J</i> =8.9 Hz)	1.31 (3H, t, <i>J</i> =7.1 Hz), 3.86 (3H, s), 4.25 (2H, m), 5.56 (1H, s), 6.93-8.05 (4H, m), 12.62 (1H, s)	13:1	Quant.
122e	1.24 (3H, t, <i>J</i> =7.1 Hz), 3.95 (2H, s), 4.20 (2H, q, <i>J</i> =7.1 Hz), 7.14 (2H, app t, <i>J</i> =8.9 Hz), 7.97 (2H, dd, <i>J</i> =5.3 Hz, 8.9 Hz)	1.32 (3H, t, <i>J</i> =7.1 Hz), 4.26 (2H, m), 5.59 (1H, s), 7.06-8.10 (4H, m), 12.60 (1H, s)	4.9:1	Quant.
122f	1.18 (3H, t, <i>J</i> =7.1 Hz), 3.88 (2H, s), 4.13 (2H, q, <i>J</i> =7.1 Hz), 7.38 (2H, d, <i>J</i> =8.6 Hz), 7.81 (2H, d, <i>J</i> =8.7 Hz)	1.26 (3H, t, <i>J</i> =7.1 Hz), 4.19 (2H, m), 5.56 (1H, s), 7.31-7.81 (4H, m), 12.50 (1H, s)	3.2:1	Quant.
122g	1.25 (3H, t, <i>J</i> =7.1 Hz), 3.95 (2H, s), 4.20 (2H, q, <i>J</i> =7.1 Hz), 7.62 (2H, d, <i>J</i> =8.6 Hz), 7.80 (2H, d, <i>J</i> =8.6 Hz)	1.33 (3H, t, <i>J</i> =7.1 Hz), 4.26 (2H, m), 5.63 (1H, s), 7.53-7.81 (4H, m), 12.55 (1H, s)	2.7:1	91

Table 3.1: ¹H-NMR data and yields of keto-enol tautomeric mixtures of β -oxoesters **122b-g**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material.

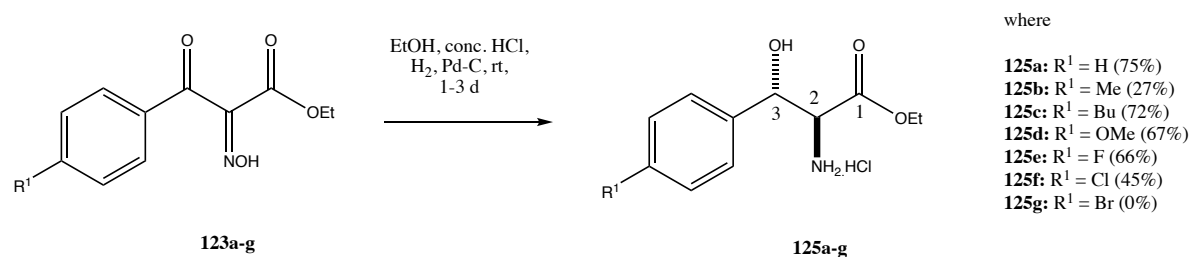
With β -oxoesters **122a-g** in place, we sought to form the oxime derivatives **123a-g** by reacting β -oxoesters **122a-g** with sodium nitrite using glacial acetic acid as a solvent – following the reaction conditions of Fell *et al.* (**Scheme 3.4**).⁶¹ Upon addition of sodium nitrite, it was important to keep the reaction temperature below 10°C.⁶¹ The crude yields of oximes **123a-g** ranged between 71-93%. Moreover, since the NMR analysis showed the crude material being relatively pure, these products were not chromatographically purified. The formation of oxime products **123a-g** was determined from NMR, IR and mass spectroscopic analysis. The large change in the ¹³C-NMR chemical shift values at the C2-position of β -oxoesters **122a-g** and oximes **123a-g**, in addition to the absence of the hydrogen signals at the C2-position for oximes **123a-g** acted as evidence for the formation of oximes **123a-g** – as shown in **Table 3.2**. Additionally, the major isomer for **123a** was assumed to be *E*, based upon the work of Fell *et al.*,⁶¹ however, it was not possible to assign which was the major or minor isomers for the rest of the oxime series.

**Scheme 3.4:** The synthesis of oximes **123a-g** from β -oxoesters **122a-g**.

Compound	R ¹	$\delta_{\text{keto C2}}$ (ppm) ^a	Compound	Major isomer δ C2 (ppm) ^a	<i>E/Z</i> ratio of isomers ^a	Yield (%)
122a	H	46.1	123a	149.6	21:1	71
122b	Me	46.1	123b	149.8	17:1	73
122c	Bu	46.1	123c	149.4	3.8:1	83
122d	OMe	45.9	123d	150.0	5.7:1	93
122e	F	46.1	123e	149.5	3.6:1	73
122f	Cl	46.1	123f	149.4	3:1	78
122g	Br	46.1	123g	149.4	3.5:1	86

Table 3.2: ¹³C-NMR data of **122a-g** and **123a-g** at the C2-position, *E/Z* isomeric ratio and yields of oximes **123a-g**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material.

Following the reaction conditions of Inoune *et al.*, oximes **123a-g** were dissolved in ethanol and conc. HCl and hydrogenated at ambient temperature and pressure for a period of 1-3 days to form *allo*- β -arylserines **125a-f** diastereoselectively in variable yields, using palladium on carbon as a catalyst (**Scheme 3.5, Table 3.3**).⁵⁸⁻⁵⁹ It should be noted however that a sizable amount of catalyst was required to produce the desired product in acceptable yields. Unfortunately, oxime **123g** produced compound **125a** instead of the desired bromo substituent **125g** – as determined by NMR and mass spectroscopic analysis – and with the exception of compound **125f**, the crude *allo*-phenylserine derivatives **125a-e** synthesised were pure by NMR analysis – as shown in **Figure 3.2** – and thus were not chromatographically purified.



Scheme 3.5: The synthesis of *allo*-phenylserines **125a-f** from oximes **123a-f**.

Compound	R ¹	δ H2 (ppm)	δ H3 (ppm)	J_{H2-H3} (Hz)	Yield (%)
125a ^a	H	4.51	5.43	4.2	75
125b ^a	Me	4.46	5.38	4.2	27
125c ^b	Bu	4.31	5.27	3.8	72
125d ^a	OMe	4.46	5.37	4.3	67
125e ^a	F	4.50	5.43	4.1	66
125f ^a	Cl	4.51	5.42	4.0	45

Table 3.3: Key chemical shifts (δ), coupling constants (J) and yields of *allo*- β -arylserines **125a-f**; ^a D₂O solvent, 400 MHz; ^b CD₃OD solvent, 400 MHz.

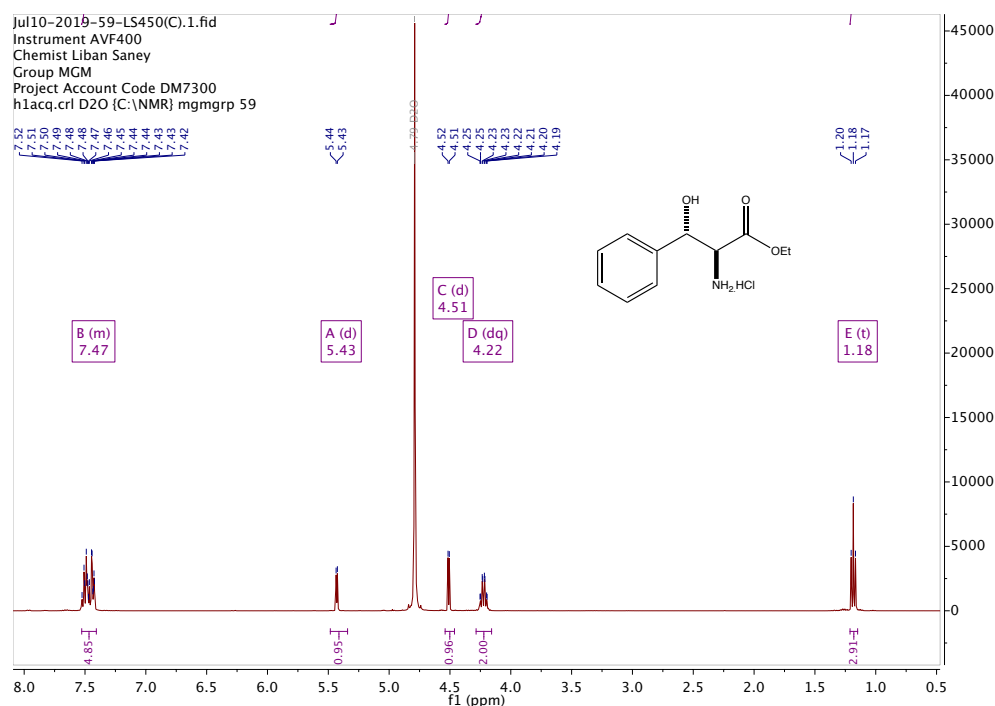
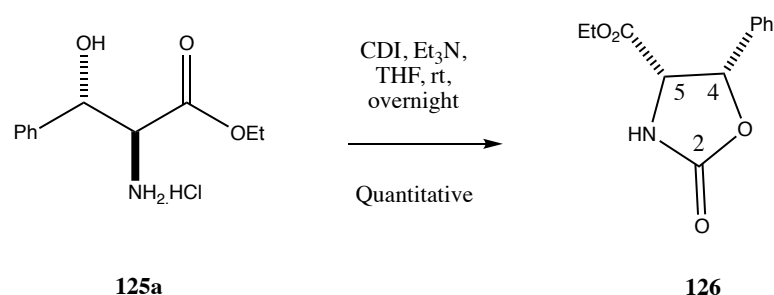


Figure 3.2: ¹H-NMR spectrum of *allo*-phenylserine **125a**, showing the relative purity of the crude material; D₂O solvent, 400 MHz.

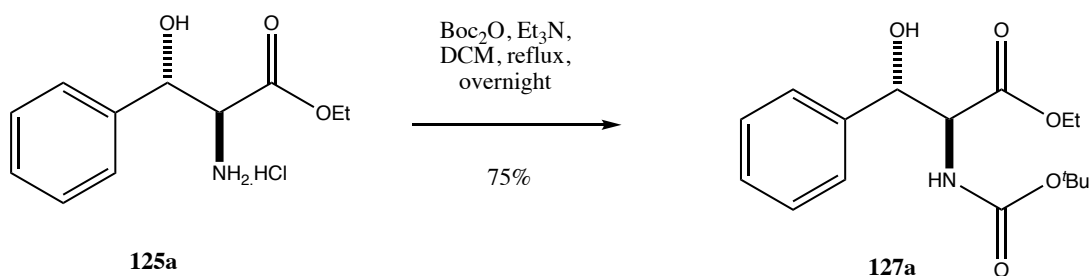
To confirm the phenylserine derivatives **125a-f** synthesised in this research were indeed the *erythro* isomers, phenylserine **125a** was suspended in THF and was reacted with CDI to produce oxazolidinone **126** in high crude yields (**Scheme 3.6**). The ^1H -NMR data of oxazolidinone **126** was compared to literature data, and this confirmed that the phenylserine derivatives **125a-f** synthesised were indeed the *erythro* isomers (**Table 3.4**).⁶²



Scheme 3.6: The synthesis of oxazolidinone **126** from amino ester **125a**.

Compound	δ H4 (ppm)	δ H5 (ppm)	$J_{\text{H4-H5}}$ (Hz)
126 ^a	5.83	4.66	9.1
Literature data for <i>threo</i> - derived oxazolidinone ^b	5.62	4.25	5.0
Literature data for <i>erythro</i> - derived oxazolidinone ^b	5.80	4.64	9.1

Table 3.4: Comparing literature ^1H -NMR data⁶² with oxazolidinone **126**; ^a CDCl_3 solvent, 400 MHz; ^b CDCl_3 solvent, 300 MHz.



Scheme 3.7: The synthesis of Boc-protected *allo*-phenylserine **127a** from amino ester **125a**.

allo-Phenylserine **125a** was reacted with Boc_2O to form Boc-protected *allo*-phenylserine **127a** (Scheme 3.7). Fortunately, a single-crystal X-ray structure of **127a** was obtained which confirmed the *allo*-phenylserine derivatives **125a-f** synthesised were indeed the *erythro* form (Figure 3.3).

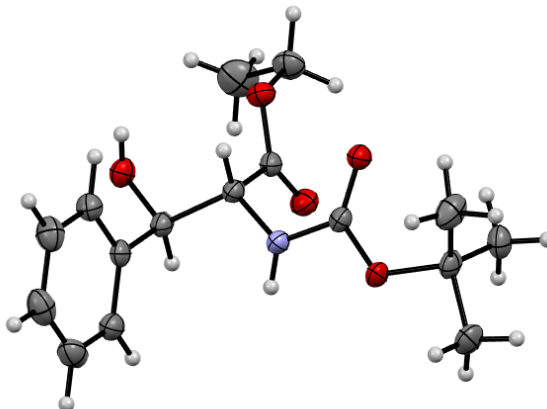
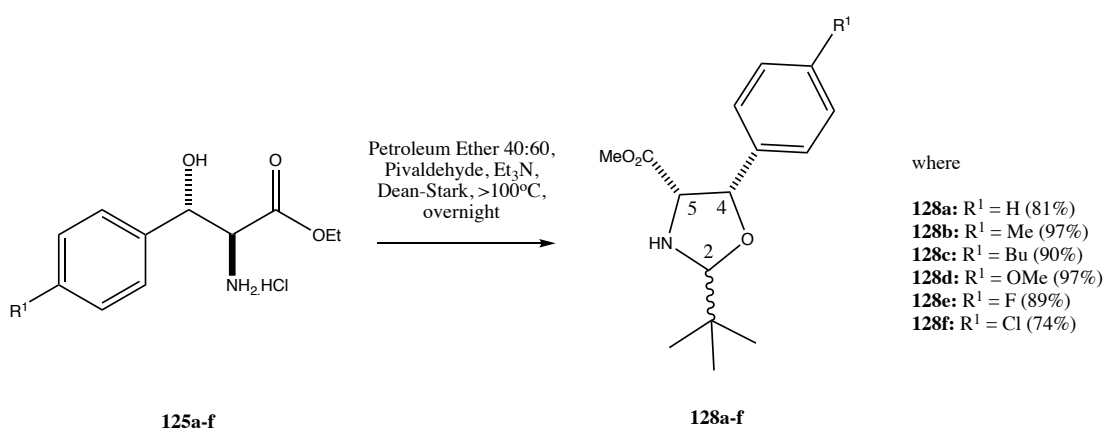


Figure 3.3: Single-crystal X-ray structure of Boc-protected *allo*-phenylserine **127a**.

3.2.2: Synthesis of Oxazolidines

Amino esters **125a-f** were reacted with pivaldehyde in the presence of Et_3N and petroleum ether 40:60 and heated to over 100°C in a Dean-Stark trap for 16-24 h to form oxazolidines **128a-f** in good yields – typically between 74-97% – as roughly a 5:1 mixture of diastereomers at the C2-centre – as determined from NMR analysis (Scheme 3.8 and Table 3.5).³⁴⁻³⁵



Scheme 3.8: The synthesis of oxazolidines **128a-f** from amino esters **125a-f**.

Due to the issues encountered for the chromatographic purification of oxazolidine **84a** derived from *threo*-phenylserine **81a**, these oxazolidines **128a-f** were not purified. Moreover, the crude material of

the oxazolidines **128a-f** were relatively pure by NMR analysis and was used crude into the next reaction sequence (**Figure 3.4**).

Compound	2,5- <i>cis</i> oxazolidine				2,5- <i>trans</i> oxazolidine				dr at the C2-position ^a	Yield (%) ^b
	δ H2 (ppm)	δ H4 (ppm)	δ H5 (ppm)	J_{H4-H5} (Hz)	δ H2 (ppm)	δ H4 (ppm)	δ H5 (ppm)	J_{H4-H5} (Hz)		
128a	4.15	4.98	4.09	9.0	4.94	5.23	4.22	7.4	5.6:1	81
128b	4.20	5.02	4.13	9.0	4.99	5.26	4.26	7.3	3.7:1	97
128c	4.21	5.04	4.17	9.0	4.99	5.26	4.27	7.4	5.3:1	90
128d	4.19	5.02	4.13	9.0	4.99	5.26	4.25	7.3	3.9:1	97
128e	4.13	4.97	4.07	9.0	4.92	5.20	4.21	7.3	4.8:1	89
128f	4.21	5.03	4.16	9.1	4.99	5.26	4.29	7.3	5.6:1	74

Table 3.5: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of oxazolidines **128a-f**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material;

^b Yields include both diastereomers.

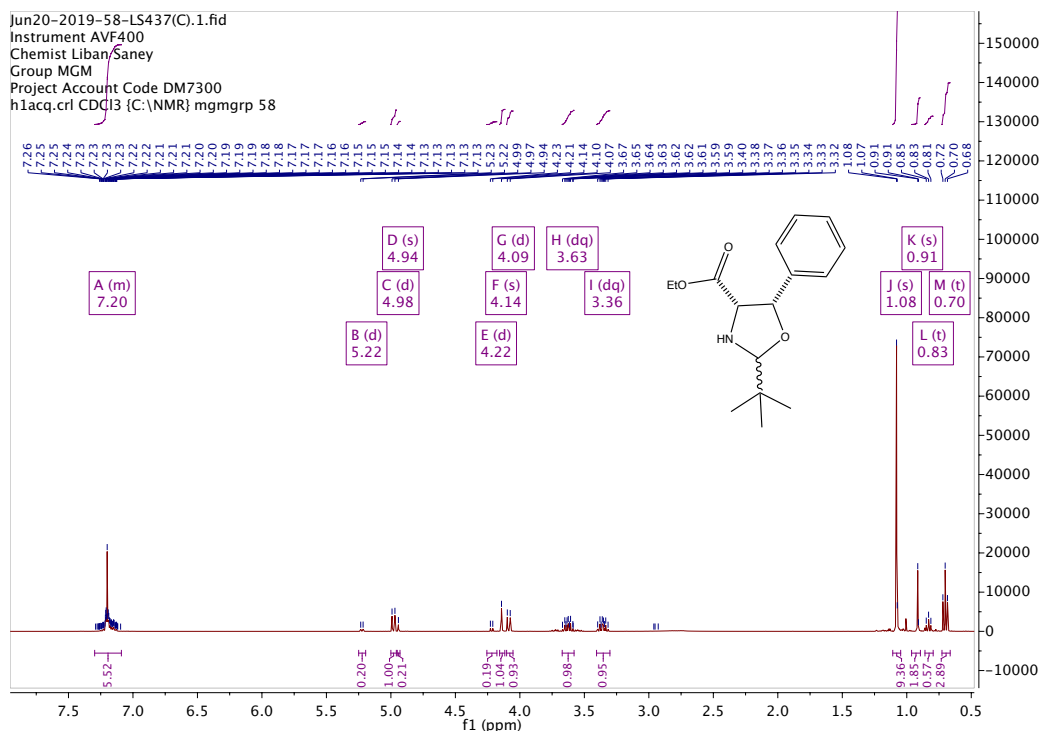


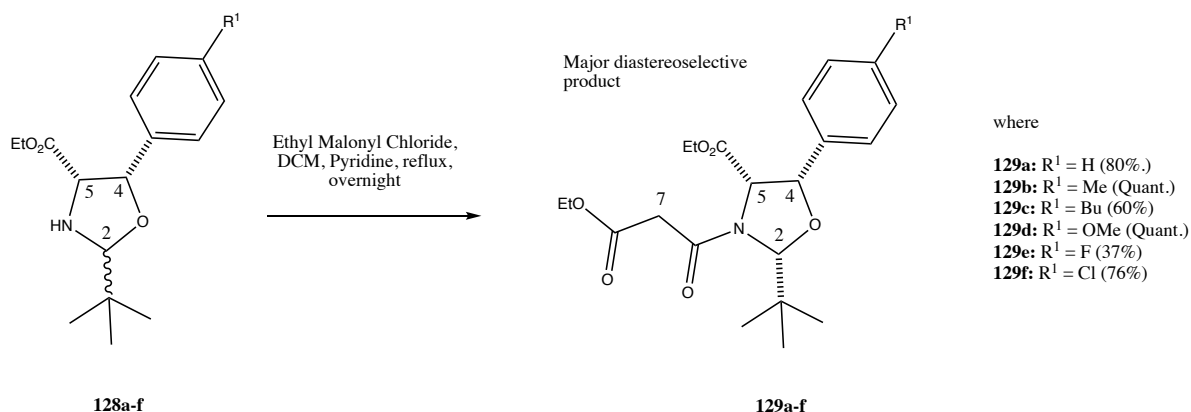
Figure 3.4: ¹H-NMR spectrum of oxazolidine **128a**, showing the relative purity of the crude material; CDCl₃ solvent, 400 MHz.

Additionally, nOe analysis was used to distinguish between 2,5-*cis/trans* diastereomers, where the major diastereomer was the 2,5-*cis* oxazolidine and thankfully, the relative stereochemistry at the H4 and H5-positions were conserved from the starting amino esters **125a-f** used, indicating no epimerisation had occurred under basic conditions – which was good news as oxazolidinone **126** was known to epimerise under basic conditions.⁶²

3.2.3: Synthesis of *N*-Acylated Oxazolidines

Oxazolidines **128a-f** were *N*-acylated by reacting it with ethyl malonyl chloride under basic conditions to form malonamides **129a-f** in good to acceptable yields (**Scheme 3.9**) – typically between 37%-quantitative yields. The crude products were relatively pure by NMR analysis but could easily be chromatographically purified if required to obtained malonamides **129a-f** with high levels of purity (**Table 3.6** and **Figure 3.6**).

NMR studies showed roughly a 9:1 mixture of diastereomers at the C2-position (**Table 3.6**). Interestingly, the *N*-acylation of oxazolidines **128a-f** was extremely diastereoselective, particularly when compared with malonamides **86a-e** and **87a-e** which were derived from *threo*-phenylserine derivatives **81a-e** (**Table 2.5** and **Scheme 2.15**). It was interesting to note the effect the *cis*-C4-C5 stereochemistry had on the diastereoselectivity of the *N*-acylation reaction.



Scheme 3.9: Synthesis of diastereoselective malonamides **129a-f** from oxazolidines **128a-f**.

Compound	R ¹	δ (ppm)			J_{H4-H5} (Hz)	dr at the C2- position ^a	Yield (%)
		H2	H4	H5			
129a	H	5.37	5.21	4.80	6.9	11.5:1	80
129b	Me	5.36	5.18	4.77	6.9	9:1	Quant. ^b
129c	Bu	5.37	5.19	4.77	6.9	9:1	60
129d	OMe	5.36	5.17	4.75	6.9	9:1	Quant. ^b
129e	F	5.36	5.18	4.79	6.8	9:1	37
129f	Cl	5.37	5.17	4.81	6.8	9:1	76

Table 3.6: Key chemical shifts (δ) and coupling constants (J) of the major malonamide diastereomer including the diastereomeric ratio (dr) and yields of malonamides **129a-f**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material; ^b Crude yield.

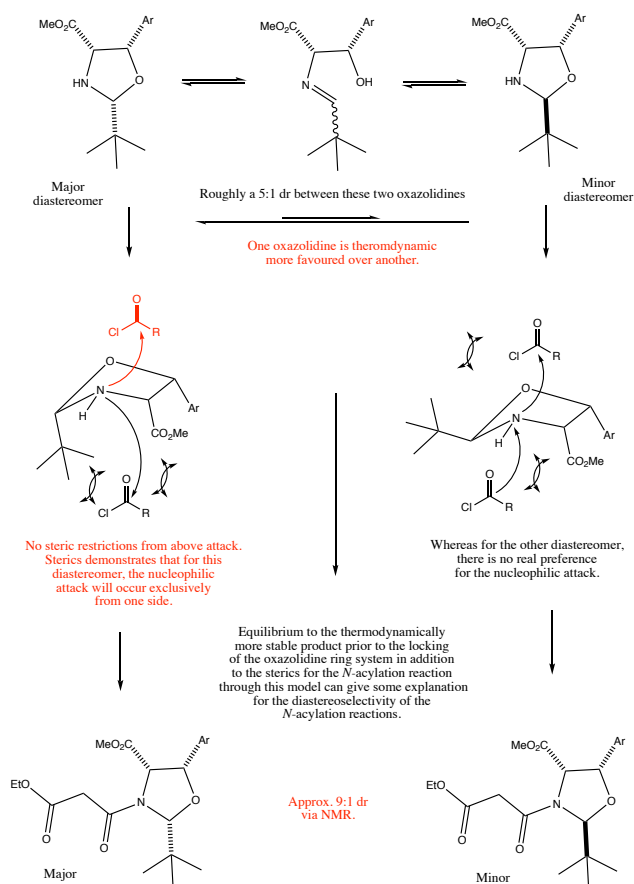


Figure 3.5: Diagram rationalising the high diastereoselectivity observed for the *N*-acylation of oxazolidines **128a-f** considering both kinetics and thermodynamics.

Thus, it was assumed that during the *N*-acylation of oxazolidines, that presumably epimerisation of oxazolidines at the C2-position permits equilibration towards the thermodynamically stable product, giving rise to its diastereoselectivity. Additionally, kinetics can also explain the high diastereoselectivity observed by considering the sterics of the *N*-acylation of oxazolidines **128a-f** (**Figure 3.5**). The 9:1

mixture of malonamide diastereomers **129a-f** from roughly a 5:1 mixture of oxazolidine diastereomers **128a-f** indicates dynamic kinetic separation may also be occurring, whereby the oxazolidine diastereomers can interconvert to form the major malonamide diastereomer **129a-f** through epimerisation, indicating that one oxazolidine diastereomer possibly having a lower energy transition state than the other diastereomer during the *N*-acylation reaction, resulting in one diastereomer reacting much faster than the other.

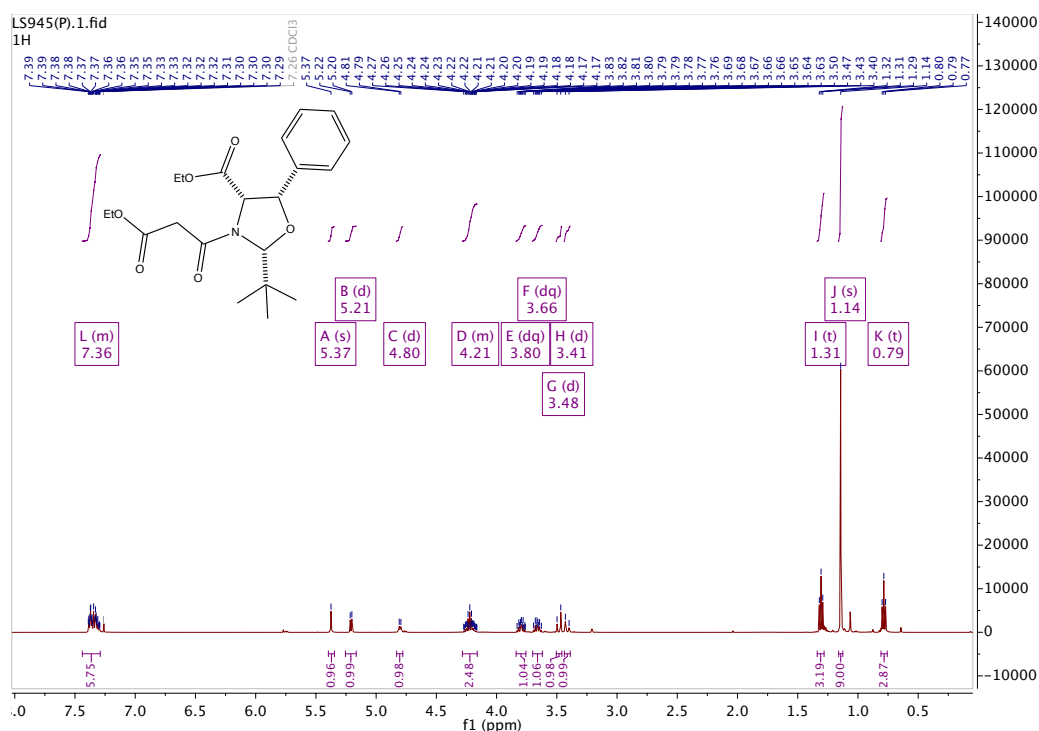


Figure 3.6: ^1H -NMR spectrum of malonamide **129a**; CDCl_3 solvent, 500 MHz.

nOe studies were conducted to establish relative stereochemistry – shown below in **Figure 3.7** – which showed that the H2, H4 and H5-protons were all *cis* to each other. This had also demonstrated that no epimerisation had occurred under basic conditions at the H4 or H5-positions.

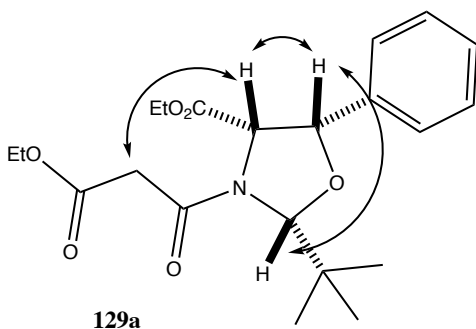


Figure 3.7: The relative stereochemistry of malonamide **129a** determined from nOe and NOESY studies.

Fortunately, a single-crystal X-ray structure of malonamide **129a** was obtained which confirmed the relative stereochemistry that was assigned by nOe and NOESY studies (**Figure 3.8**). As the NMR chemical shifts of **129a** were consistent with the rest of the malonamide series **129b-f** (**Table 3.6**), it was assumed that all malonamides **129b-f** had the same relative stereochemistry.

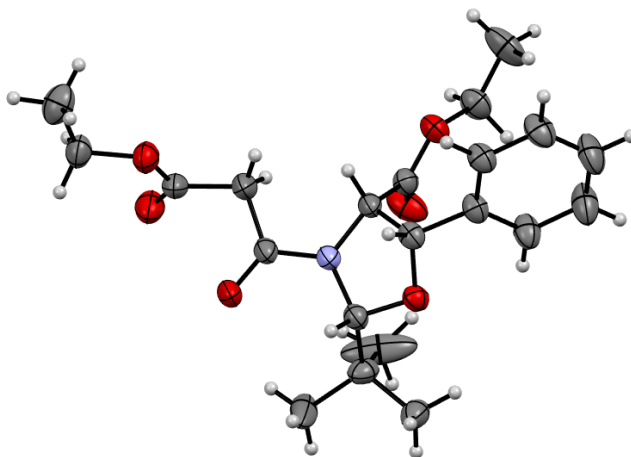
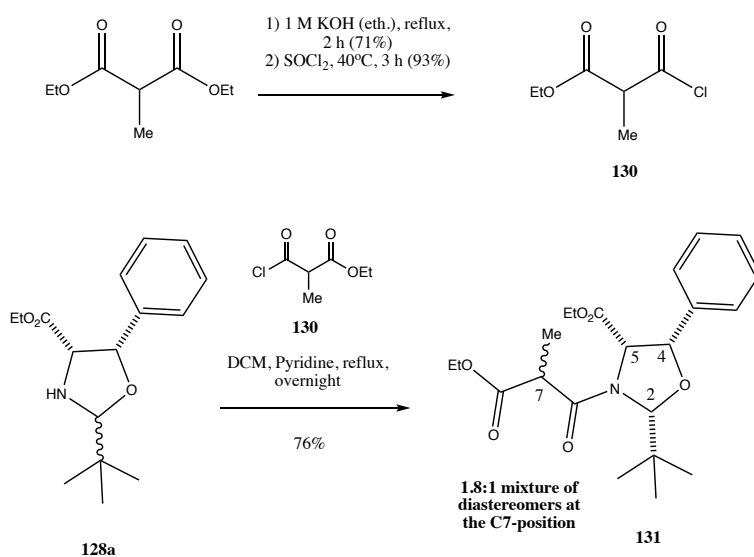


Figure 3.8: Single-crystal X-ray structure of malonamide **129a**, confirming the relative stereochemistry that was assigned by nOe and NOESY studies.

Furthermore, oxazolidine **128a** was reacted with ethyl methylmalonyl chloride **130** (**Scheme 3.10**).⁶³ Malonamide **131** was obtained as a 1.8:1 mixture of diastereomers at the C7-position and could be partially separated by careful chromatographic purification.



Scheme 3.10: The synthesis of malonamide **131** from ethyl methylmalonyl chloride **130**.

There was a significant difference in the H5 chemical shift values between malonamide diastereomers **131** – as shown in **Table 3.7**. It was not immediately obvious why there was a substantial difference in the H5 chemical shift values between both diastereomers, particularly as the C7-methyl substituent was 6 bonds away from the H5-proton.

Compound	δ (ppm)					J_{H4-H5} (Hz)	dr at the C7-position ^a	Yield (%) ^b
	H2	H4	H5	H7	C7-Methyl			
Major diastereomer 131	5.41	5.19	4.99	3.50	1.43	6.8	1.8:1	76
Minor diastereomer 131	5.39	5.17	4.63	3.49	1.42	7.0		

Table 3.7: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of malonamide diastereomers **131**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material; ^b Yield include both diastereomers.

The relative stereochemistry of malonamides **131** was assigned by nOe and NOESY analysis, where the H2, H4 and H5-protons for both diastereomers were all *cis* to each other – consistent with malonamides **129a-f**. However, it was not possible to determine the relative stereochemistry at the malonamide sidechain by nOe or NOESY analysis (**Figure 3.9**). Fortunately, a single-crystal X-ray structure for one of the malonamide diastereomers **131** was obtained which confirmed the relative stereochemistry that was assigned for the oxazolidine ring protons (**Figure 3.10**).

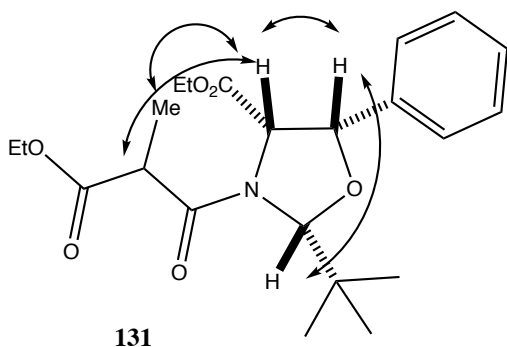


Figure 3.9: The relative stereochemistry of malonamides **131** assigned by nOe and NOESY analysis.

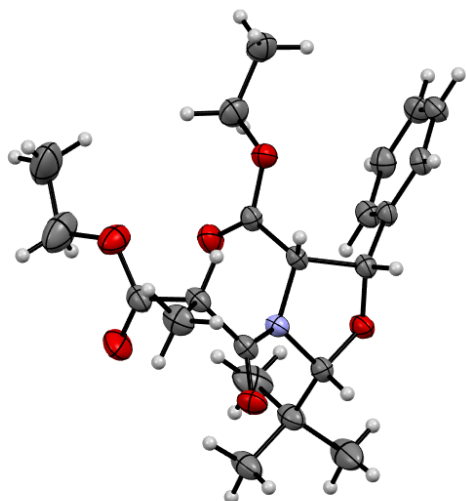
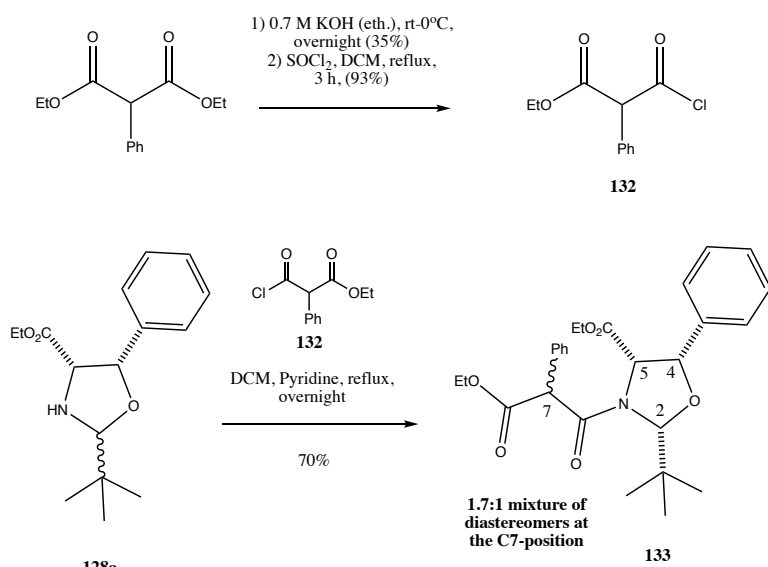


Figure 3.10: Single-crystal X-ray structure of one of the malonamide diastereomers **131**, confirming relative stereochemistry assigned by nOe and NOESY analysis for the oxazolidine ring protons.

Additionally, oxazolidine **128a** was reacted with ethyl phenylmalonyl chloride **132** (**Scheme 3.11**). Malonamide **133** was obtained as a 1.7:1 mixture of diastereomers at the C7-position – as determined from ^1H -NMR studies – and was obtained in good yields. However, the malonamide diastereomers **133** were inseparable via chromatographic purification.⁶³



Scheme 3.11: The synthesis of malonamides **133** from ethyl phenylmalonyl chloride **132**.

Again, there were surprising differences in the H5 chemical shift values between the major and minor malonamide diastereomers of **133** – as shown in **Table 3.8** – which was consistent with what was observed for malonamide diastereomers **131**. Moreover, there were significant changes in the chemical shift values for the H4-protons of malonamide diastereomers **133**. This was an unexpected observation, particularly when compared with malonamide **131** which had similar H4 chemical shift

values between its two diastereomers (compare **Tables 3.7** with **3.8**). Again, it was not immediately obvious why there were substantial differences in the chemical shift values, particularly as the H4-protons were very distant from the C7-phenyl protons.

Compound	δ (ppm)				$J_{\text{H4-H5}}$ (Hz)	dr at the C7-position ^a	Yield (%) ^b
	H2	H4	H5	H7			
Major diastereomer 133	5.44	5.22	4.84	4.77	6.9	1.7:1	70
Minor diastereomer 133	5.36	4.89	4.59	4.66	6.9		

Table 3.8: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of malonamide diastereomers **133**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material; ^b Yield includes both diastereomers.

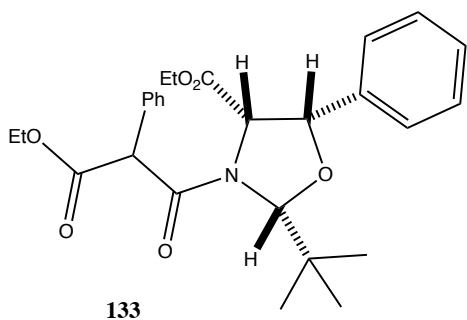


Figure 3.11: The relative stereochemistry of malonamides **133** assigned by analogy to malonamides **129a-f** and **131**.

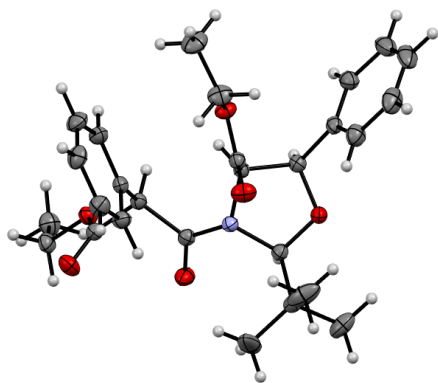


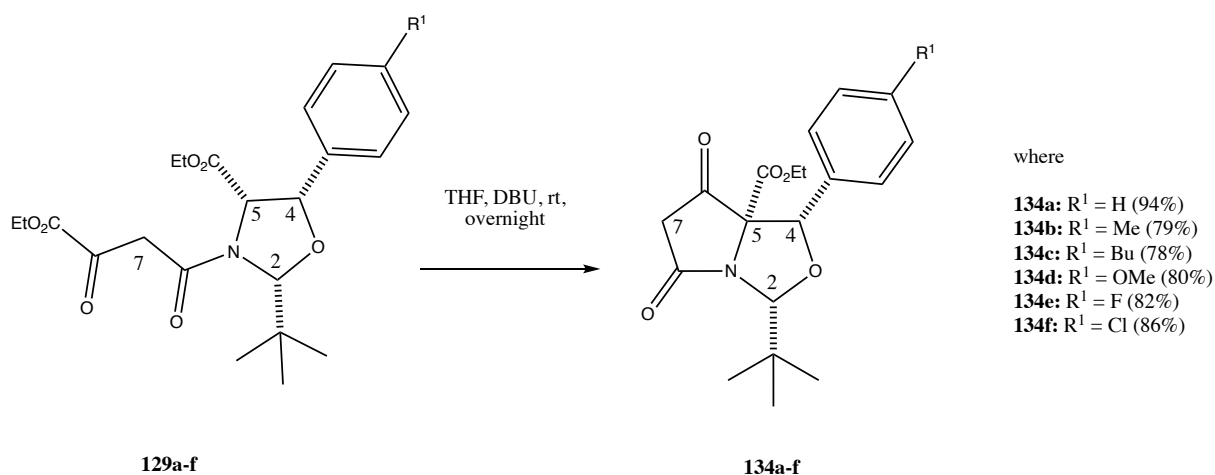
Figure 3.12: Single-crystal X-ray structure of one of the malonamide diastereomers **133**, confirming the relative stereochemistry assigned for the oxazolidine ring protons.

The relative stereochemistry of malonamides **133** was assigned by analogy to malonamides **129a-f** and **131**, where the H2, H4 and H5-protons for both diastereomers were all *cis* to each other (**Figure 3.11**). Fortunately, a single-crystal X-ray structure for one of the malonamide diastereomers **133** was obtained, which confirmed the relative stereochemistry that was assigned for the oxazolidine ring

protons for both malonamide diastereomers (**Figure 3.12**). It should be noted however that the diastereomeric ratio at the C7-position for both malonamide diastereomers **131** and **133** changes in CDCl₃ solution over a couple of weeks.

3.2.4: Synthesis of Tetramates

Malonamides **129a-f** were subjected to the Dieckmann cyclisation to form the desired bicyclic tetramates **134a-f**. Firstly, malonamide **129a** was reacted with KO^tBu in THF at reflux overnight, however, surprisingly, this led to a complex mixture of un-identifiable side products. As a result, the base was changed to DBU – following the reaction conditions of Josa-Culleré *et al.* for the synthesis of C7-Weinreb amides, as shown in **Scheme 1.5**.⁴¹ As a result, malonamides **129a-f** were reacted with DBU overnight at rt to form tetramates **134a-f** in excellent yields – as shown in **Scheme 3.12** and **Table 3.9** – as single diastereomers with excellent chemoselectivity observed. Interestingly, there was a switch in chemoselectivity observed for the Dieckmann cyclisation when compared with tetramates **88a-e** – and this is discussed in more depth below.



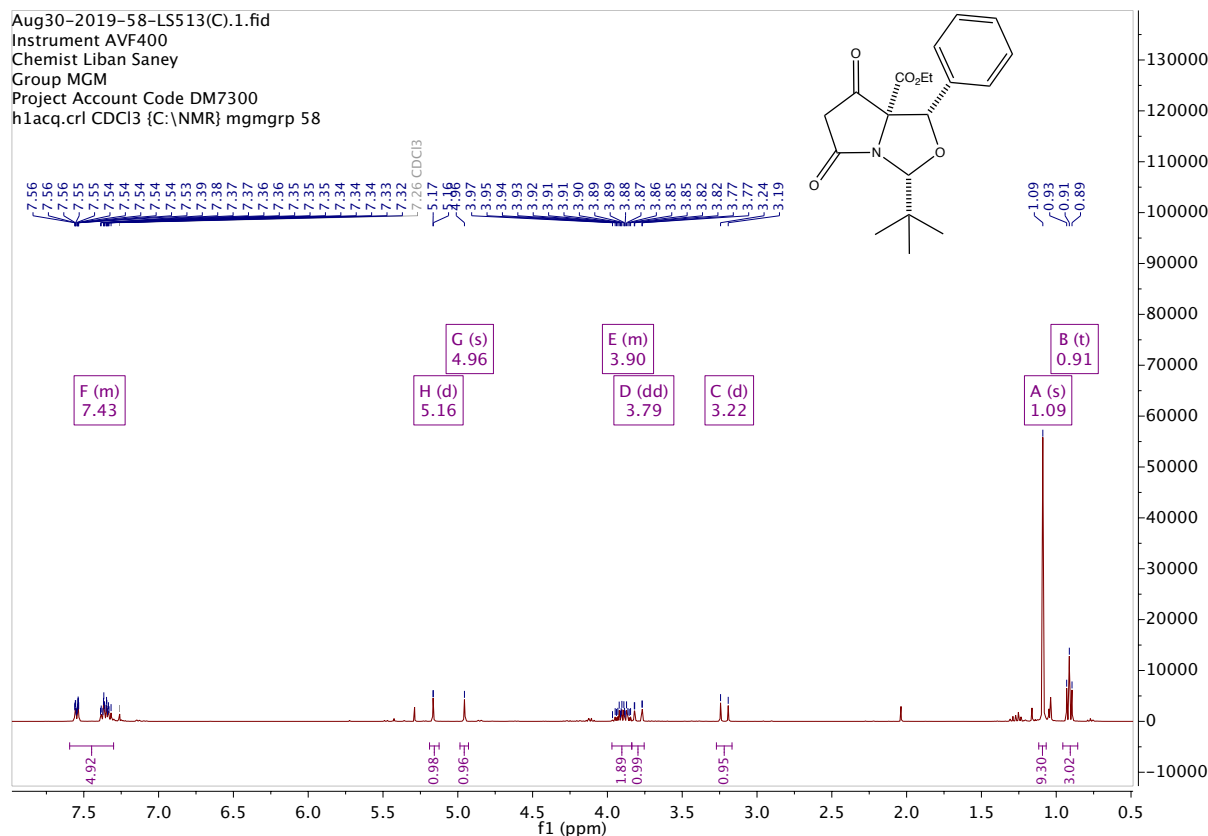
Scheme 3.12: The synthesis of tetramates **134a-f** from malonamides **129a-f**.

These tetramates were not subjected to chromatographic purification as the crude products were pure by NMR analysis – as shown in **Figure 3.13** – and this was mainly due to the extraction process, whereby the tetramate enolate product resided in the aqueous layer prior to acid workup. This allowed

the organic side-products and/or starting materials – that resided in the organic layer – to be removed efficiently. Thus, it has been demonstrated that reasonably pure tetramates **134a-f** could be synthesised from β -oxoesters **122a-g** in 6 synthetic steps without the need to purify at any stage of the reaction sequence if required. Additionally, tetramates **134a-f** were stable in CDCl_3 solution for many months and were also stable in their native oil forms for many months also.

Compound	R ¹	δ (ppm)				$J_{\text{H7-H7}}$ (Hz)	Yield (%)
		H2	H4	H7	H7		
134a	H	5.16	4.96	3.79	3.22	20.5	94
134b	Me	5.15	4.92	3.78	3.22	20.6	79
134c	Bu	5.16	4.94	3.79	3.23	20.5	78
134d	OMe	5.15	4.91	3.80	3.22	20.5	80
134e	F	5.16	4.92	3.80	3.22	20.6	82
134f	Cl	5.16	4.90	3.80	3.23	20.7	86

Table 3.9: Key chemical shifts (δ), coupling constants (J) and yields of tetramates **134a-f**; CDCl_3 solvent, 400 MHz.



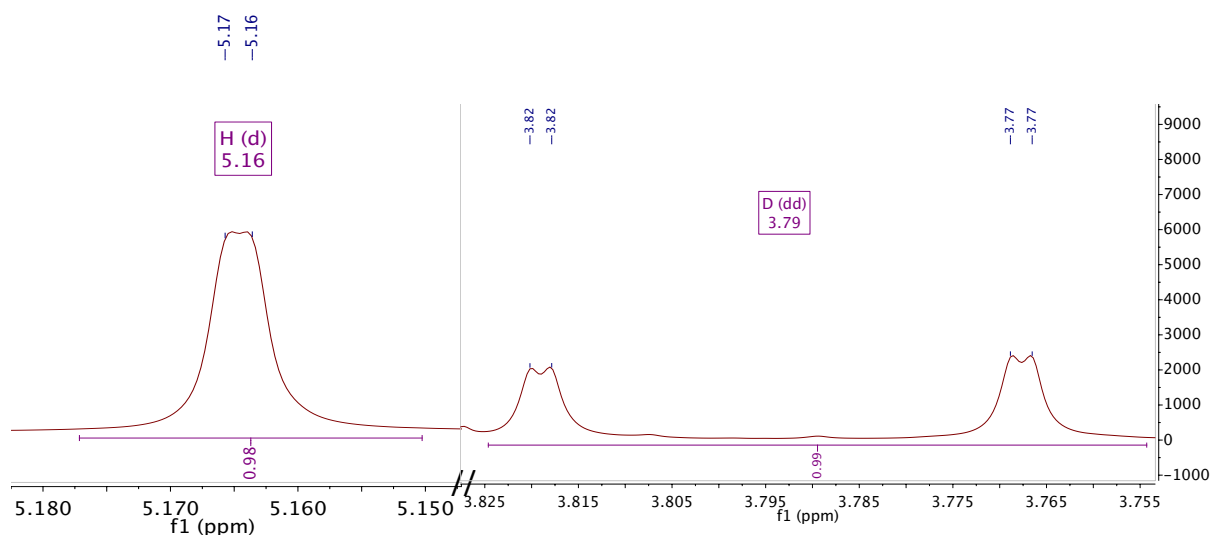
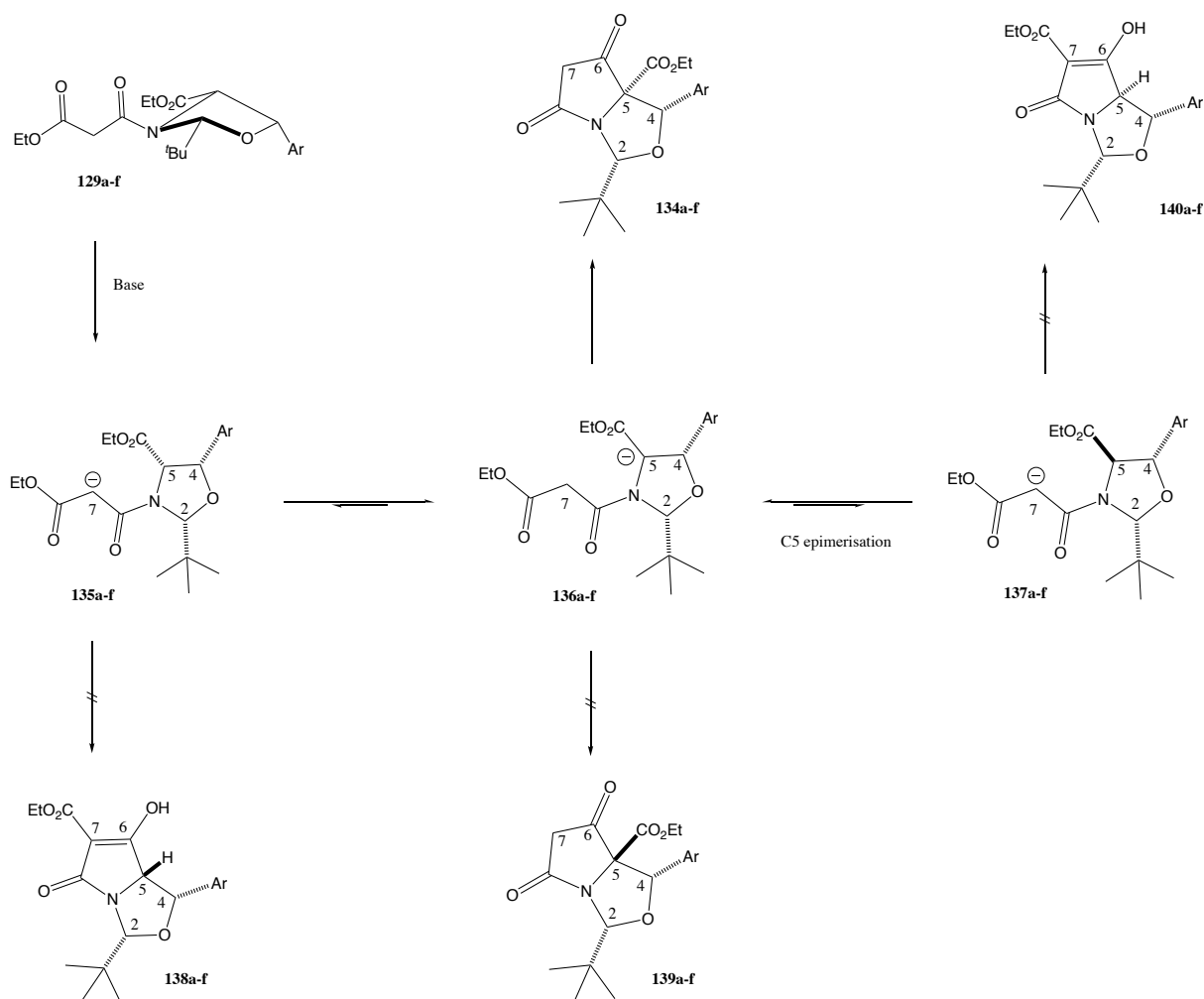


Figure 3.13: ^1H -NMR spectrum of tetramate **134a**, showing the relative purity of the crude material and also the long-range coupling observed between the H2 and H7-protons, with a weak coupling constant of 0.8 Hz observed between these two peaks; CDCl_3 solvent, 400 MHz.

^1H -NMR analysis of tetramates **134a-f** showed long range coupling between the H2 and H7-protons, with a weak coupling constant observed, typically between 0.8-1 Hz – as shown in **Figure 3.13**. It was rationalised that the long-range coupling seen was probably attributable to favourable orbital alignment within the rigid bicyclic structure, however, nOe analysis indicated that the H2 and H7-protons that were coupling together were *trans* to one another (**Figure 3.14**). The C5-ethyl ester stereochemistry was later confirmed from a single-crystal X-ray structure of C7-carboxamide **157a** and **157d** – shown in **Figure 3.15**, *vide infra*.

Of interest was both the high levels of chemoselectivity observed and the switch in chemoselectivity seen in the Dieckmann cyclisation of malonamides **129a-f** when compared with the Dieckmann cyclisation of malonamides **87a-e** derived from *threo*-phenylserine derivatives **81a-e** (compare **Schemes 2.14**, **2.15** with **3.12**, **3.13**). It was rationalised that the formation of enolates **136a-f** from malonamides **129a-f** led to the formation of bicyclic tetramates **134a-f** (**Scheme 3.13**). Again, it was interesting to note that both the $t\text{Bu}$ and aryl groups were on the *exo*-face of the bicyclic lactam **134a-f**, thus minimising steric interactions.



Scheme 3.13: The chemoselective routes towards the synthesis of tetramates from malonamides

129a-f.

Tetramates **140a-f** in theory could have formed via the ring closure of enolates **137a-f**, as both the *t*Bu and aryl groups were on the *exo*-face of the bicyclic lactam, however none of this material was observed experimentally. It was reasoned that tetramates **140a-f** did not form because enolates **136a-f** were either thermodynamically and/or kinetically more favoured than enolates **137a-f** (**Scheme 3.13**), in which the subsequent Dieckmann cyclisation was a fast and irreversible process. Additionally, tetramates **138a-f** and **139a-f** were not observed experimentally and the reason for this could be due to the fact that the *t*Bu and aryl groups were on the *endo*-face of the bicyclic lactam, causing unfavourable steric congestion – consistent with what was observed for the *threo*-phenylserine-derived tetramic acids (**Schemes 2.13** and **2.14**).

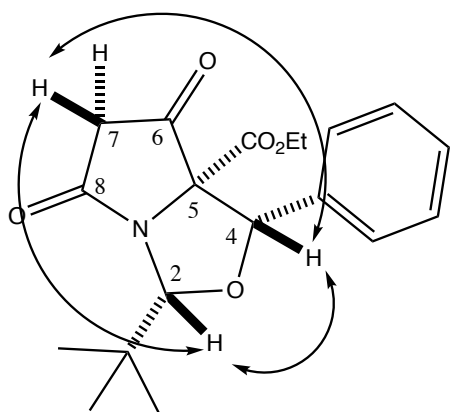
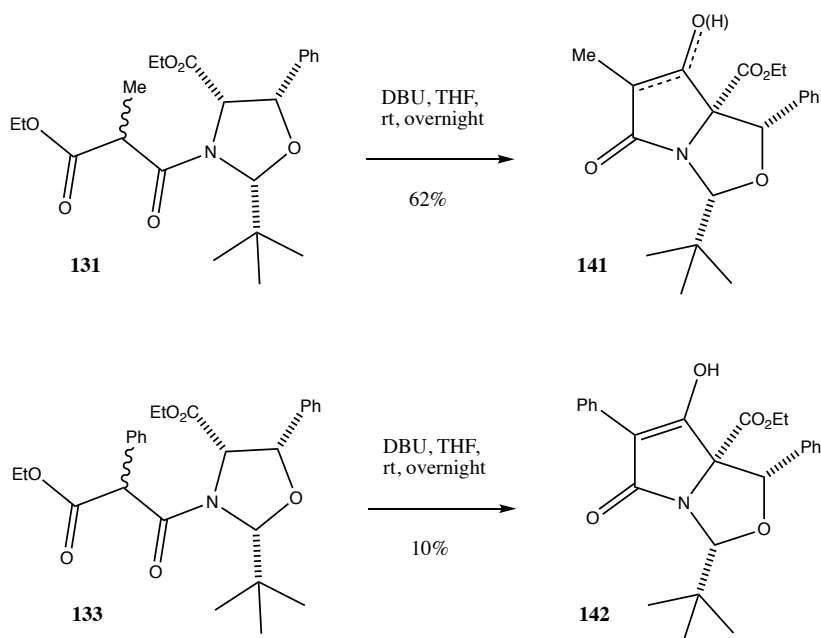


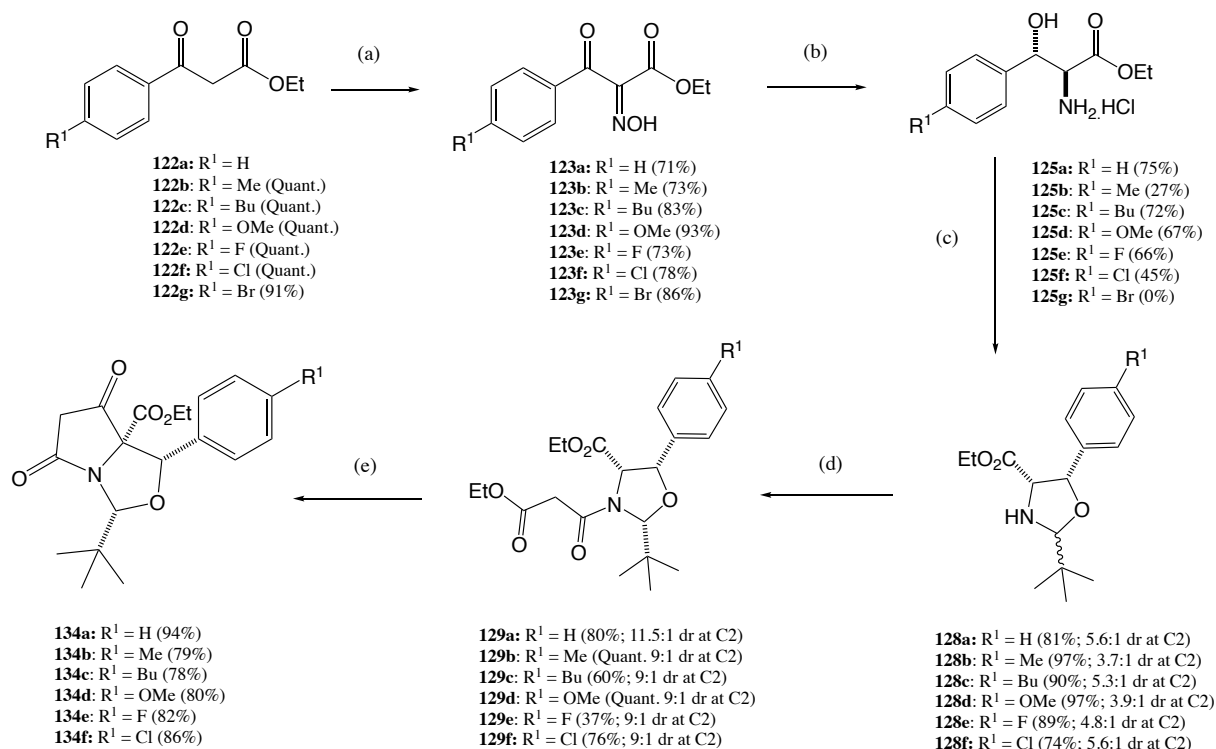
Figure 3.14: Relative stereochemistry of tetramate **134a** assigned by nOe analysis.

Tetramates **141** and **142** were formed via the Dieckmann cyclisation of malonamides **131** and **133** respectively. Tetramate **141** was obtained in 62% yield as a mixture of keto/enol tautomers – as determined from NMR analysis. In the case of tetramate **142**, a yield of 10% was obtained, where the product **142** was observed exclusively in the enolic form in CDCl_3 solvent. However, it was not immediately obvious why poor yields were obtained for tetramate **142** – particularly as C7-phenyltetramates derived from L-serine **8a**, L-cysteine **8c** and L-*allo*-threonine **8d** were obtained in high yields, typically between 70-82%.⁶³



Scheme 3.14: The synthesis of tetramates **141** and **142** from malonamides **131** and **133** respectively.

Thus, it was clear to see that this methodology clearly deviated away from tetramic acids **88a-e** that were derived from *threo*-phenylserine derivatives **81a-e** (compare **Schemes 2.15** with **3.15**). These systems tended to behave more like tetramates that were derived from L-serine **48a**, L-threonine **48b**, L-*allo*-threonine **48d** and L-cysteine **48c**.³⁴⁻³⁵



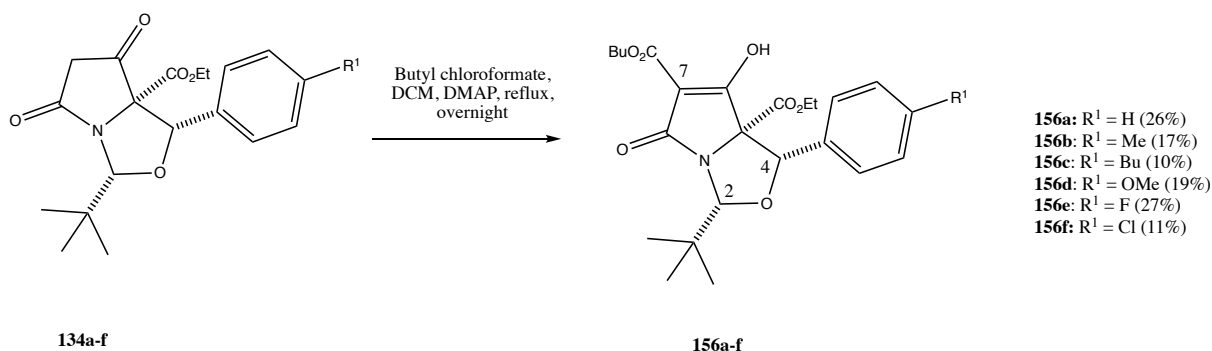
Scheme 3.15: Overview of the synthesis towards tetramates **134a-f** from *allo*-phenylserine derivatives

125a-f; (a) NaNO₂ in H₂O, AcOH, rt, 30 min-overnight; (b) EtOH, conc. HCl, H₂, Pd-C, rt, 1-3 d; (c) pivaldehyde, petroleum ether 40:60, Et₃N, Dean-Stark, >100°C, overnight; (d) ethyl malonyl chloride, pyridine, DCM, reflux, overnight; (e) DBU, THF, rt, overnight.

3.2.5: Synthesis of C7-Carboxamides

Although tetramates **134a-f** were formed chemoselectively from malonamides **129a-f**, the switch in chemoselectivity led to unfunctionalised C7-tetramates. Thus, C7-esters had to be introduced into the bicyclic structure to enable aminolysis reactions to take place to form C7-carboxamides. As a result, tetramates **134a-f** were reacted with butyl chloroformate under basic conditions – following the reaction conditions of Jeong *et al.*⁴³ – to form C7-butyl ester tetramates **156a-f** (**Scheme 3.16**). C7-

Butyl esters were desired over the C7-ethyl esters as it would allow easy differentiation from the C5-ethyl esters in regard to studying the subsequent aminolysis reactions. The yields of these reactions were very poor – typically between 10-27% – with a considerable amount of starting material being present in the reaction mixture after 24 h – as determined from NMR analysis (**Table 3.10**). Additionally, none of the C6-carbonate side-products were formed.



Scheme 3.16: The synthesis of C7-butyl ester tetramates **156a-f** from tetramates **134a-f**.

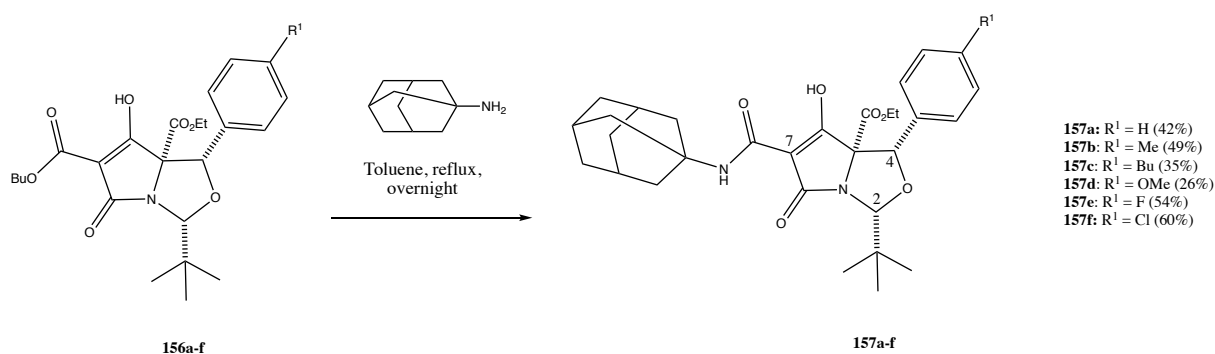
Moreover, C7-butyl ester tetramates **156a-f** were extremely unstable in CDCl₃ solution – analogous to C7-ethyl ester tetramates **88a-e** – thus, these products had to be both chromatographically purified and reacted on very quickly. Additionally, the instability in solution could offer some explanation as to why poor yields were often obtained when conducting these reactions in DCM, and as it is known that the C7-esters decompose to C7-unfunctionalised tetramates, this could also explain why mostly starting material was present in the reaction mixture. Moreover, while these compounds picked up trace metal ions after chromatographic purification, they could be removed with 10% citric acid (aq.) workup.

Due to the poor yields obtained for C7-butyl ester tetramates **156a-f**, a large compound library could not be formed, thus, only the C7-adamantylcarboxamide was examined, specifically due to their potent antibacterial activity – discussed in **Chapter 5** – and their ability to potentially crystallise, possibly allowing X-ray crystal structures to be obtained.

Compound	R ¹	δ H2 (ppm)	δ H4 (ppm)	Yield (%)
156a	H	4.91	4.81	26
156b	Me	4.90	4.77	17
156c	Bu	4.89	4.78	10
156d	OMe	4.89	4.75	19
156e	F	4.91	4.76	27
156f	Cl	4.91	4.75	11

Table 3.10: Key chemical shifts (δ) and yields of tetramates **156a-f**; CDCl₃ solvent, 400 MHz.

The yields of these C7-carboxamidotetramic acids **157a-f** ranged between 26-60% (**Scheme 3.17**, **Table 3.11**) and were stable to chromatographic purification in addition to being stable in both CDCl₃ solution for many months and being stable in their native foamy solids for many months also. The aminolysis reaction was chemoselective, in which the C7-butyl ester was selectively attacked by the adamantylamine. It was reasoned that the C5-ethyl ester was not readily accessible for the aminolysis reaction due to the steric hinderance of the ^tBu and aryl substituents – which resided on the same face as the C5-ethyl ester group – potentially giving rise to its high chemoselectivity.



Scheme 3.17: The synthesis of C7-carboxamidotetramic acids **157a-f** from tetramates **156a-f**.

Moreover, the single-crystal X-ray structures of compounds **157a** and **157d** confirmed the relative stereochemistry that was assigned for tetramates **134a-f** and **157a-f** via nOe analysis, and also confirmed no epimerisation had occurred at any of the stereogenic centres during the aminolysis

reactions (**Figure 3.15**). Additionally, as the NMR chemical shift values for tetramates **157a** and **157d** were very similar to the rest of the C7-carboxamidotetramic acid series (**Table 3.11**, *vide infra*), it was assumed that all C7-carboxamides had the same relative stereochemistry.

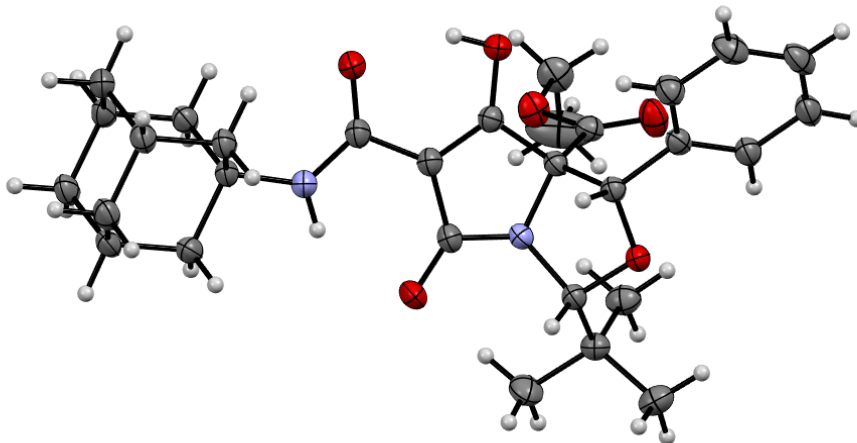


Figure 3.15: Single-crystal X-ray structure of C7-carboxamidotetramic acid **157a**.

When these compounds **157a-f** were chromatographically purified on silica gel, they picked up trace metal ions to form metal-chelates across the tri-carbonyl core as shown in **Figure 1.31**. This was chiefly detected in the NMR spectrum, where broad peaks were observed after chromatographic purification.^{33,43} **Figure 3.16a** showed that in the case of compound **157a**, that the H2 and H4-signals were relatively sharp – indicating these protons were relatively far away from the metal-chelation site – whereas the adamantyl and aromatic peaks were relatively broad – indicating these groups were relatively close to the metal-chelation site.

When comparing the NMR spectrum of metal-chelated tetramic acids **157a** with **111a**, an inference could be made that tetramate **157a** bound to metal ions with less affinity than **111a** when qualitatively looking at the line broadening of the NMR spectrum (compare **Figures 2.12a** with **3.16a**), particularly as the NMR peaks were far sharper for tetramate **157a** in comparison to tetramate **111a**. The only difference between these two compounds was a missing C5-ethyl ester in the case of tetramate **111a**. Thus, it could be theorised that C5-ethyl esters might play a role in potentially reducing metal-chelation across the tricarbonyl core.

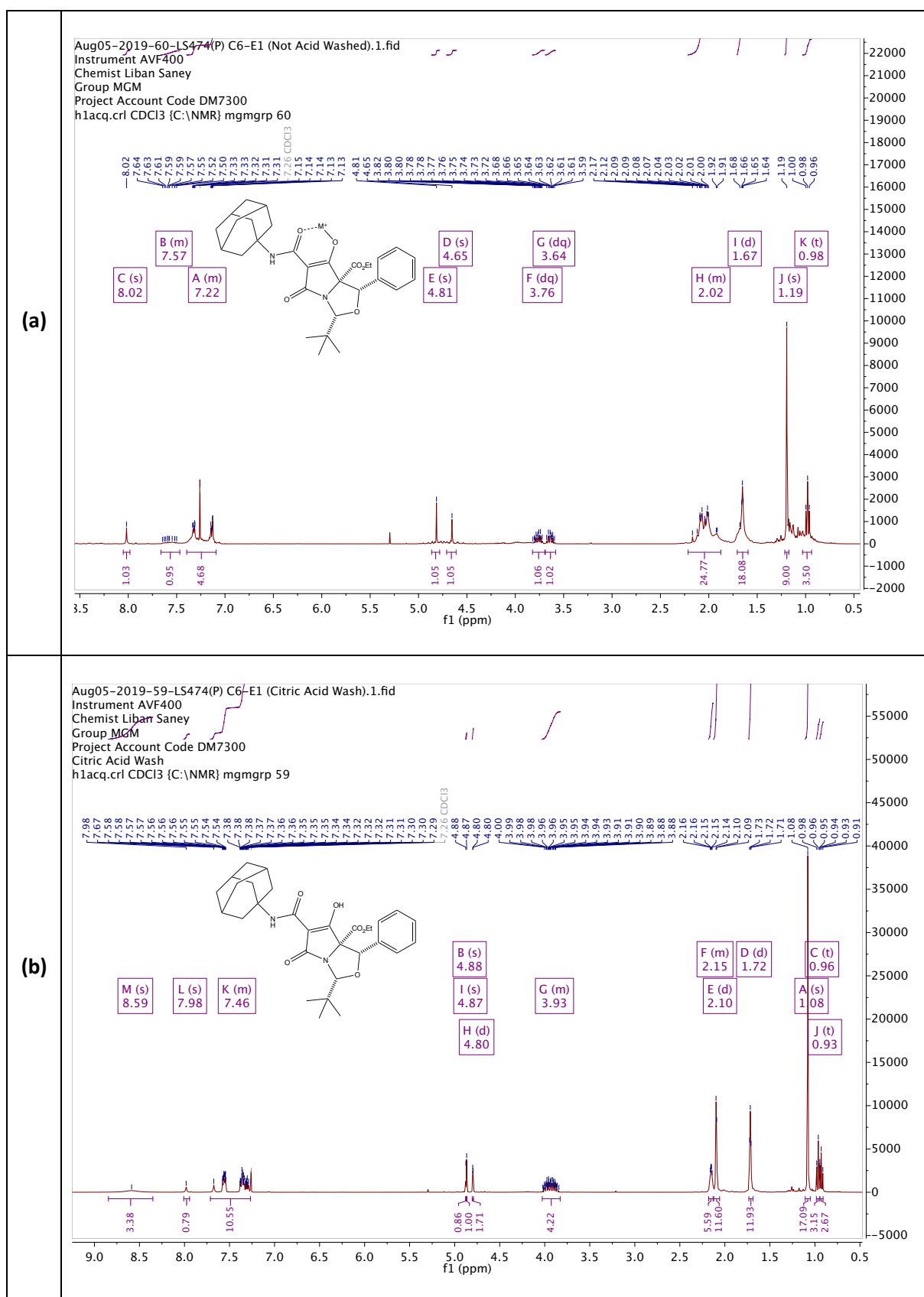


Figure 3.16: ¹H-NMR spectrum of C7-carboxamide **157a** post-chromatographic purification, before **(a)** acid wash and **(b)** after 10% citric acid (aq.) wash; CDCl₃ solution, 400 MHz.

The NMR peaks of tetramates **157a-f** could be sharpened by washing metal-chelated tetramic acids with 10% citric acid solution (aq.) – as seen in **Figure 3.16b** – again, acting as qualitative evidence that these tetramic acids bind to metal ions. Interestingly, the peaks for both the adamantyl and aromatic groups were sharpened by a simple acid wash. Additionally, there were changes in the chemical shift values for the ^tBu, adamantyl and H4-groups before and after acid wash (**Figure 3.16b**).

Compound	R ¹	δ (ppm)				Tautomeric ratio	Yield (%)
		C6	C8	C9	C10		
157a	H	188.0	176.9	166.9	165.5	54:46 ^a	42
		189.4	182.6	167.3	166.2		
157b	Me	187.9	176.8	166.8	165.3	58:42 ^a	49
		189.1	182.6	167.2	166.0		
157c	Bu	187.9	176.9	166.8	165.4	58:42 ^a	35
		189.2	182.6	167.2	166.1		
157d	OMe	188.0	176.9	166.8	165.4	55:45 ^a	26
		189.3	182.7	167.2	166.1		
157e	F	187.9	176.9	166.9	165.5	53:47 ^b	54
		189.7	182.5	167.2	166.1		
157f	Cl	187.9	176.9	166.9	165.5	55:45 ^a	60
		189.8	182.5	167.2	166.1		

Table 3.11: Key ¹³C-NMR chemical shift values (δ) of the tautomeric forms of C7-carboxamides **157a-f**; CDCl₃ solvent, 400 MHz; ^a Determined from the H2 signal from the ¹H-NMR spectrum; ^b Determined from ¹⁹F-NMR spectrum.

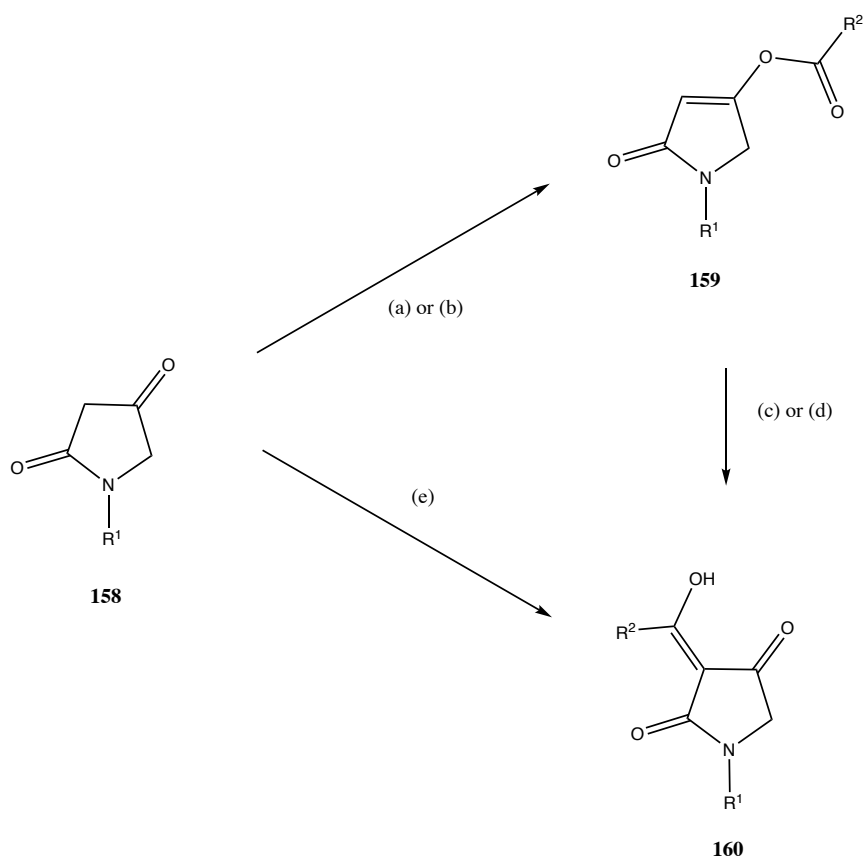
Additionally, when looking at the NMR spectrum of acid-washed tetramic acids (**Figure 3.16b**), they appeared to exist as approximately a 50:50 mixture of **AB:CD** tautomers in CDCl₃ solution (refer to **Figure 2.13** to see the **AB:CD** tautomeric forms). As a result, it was extremely difficult to identify which tautomer was which by NMR spectroscopy. Additionally, it was interesting to observe that C5-ethyl esters affected the tautomeric behaviour, specifically when compared with C7-carboxamides **111a**, **112a**, **113a**, **114a** and **115a** that lacked a C5-ethyl ester – whose tautomeric ratio was roughly an 80:20

AB:CD tautomeric mixture in CDCl₃ solution (compare **Tables 2.7** with **3.11**). However, the tautomeric mixture for carboxamides **157a-f** was consistent with the work of Jeong *et al.*, in which their C7-adamantylcarboxamide that also had a C5-ethyl ester group attached – derived from L-serine **48a** – roughly had a 50:50 **AB:CD** tautomeric mixture also.⁴³

Although the tautomeric forms could not be readily distinguished by ¹H-NMR spectroscopy due to roughly the equal tautomeric mixtures seen in CDCl₃ solution, the carbonyl peaks – which were assigned via the HMBC analysis of **157a** – had distinct ¹³C-NMR chemical shift differences, similar to C7-carboxamides which were derived from *threo*-phenylserine derivatives **81a-e** (compare **Tables 2.7** with **3.11** to see the similarities in the ¹³C-NMR carbonyl chemical shift values). Due to the similarities in the carbonyl ¹³C-NMR chemical shift values between *threo/erythro*-phenylserine derived carboxamides, it was assumed that the carbonyl peaks for tautomeric pair, **CD**, were more downfield than for tautomeric pair **AB** (**Table 3.11**).

3.2.6: Synthesis of C7-Acyltetramates

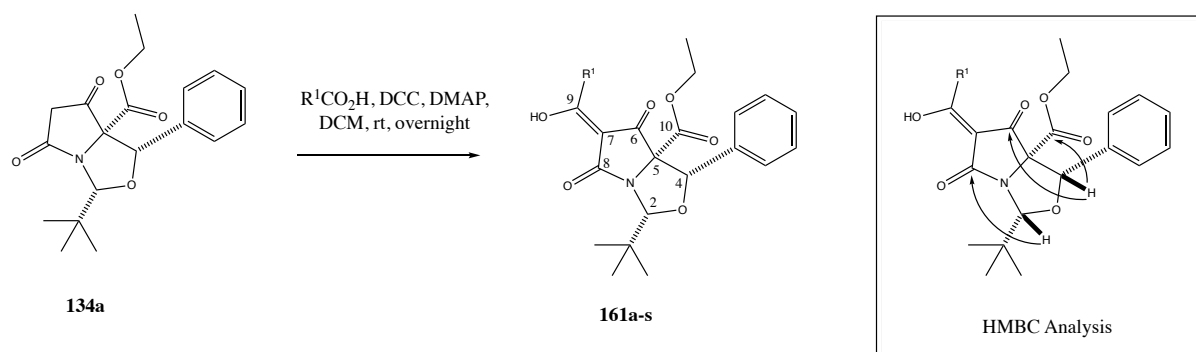
Due to the synthetic limitations in forming C7-carboxamides, of significant interest was to form C7-acyltetramates that were similar to natural product tetramates such as reutericyclin **2**, equisetin **3** and streptolydigin **4**. Jeong *et al.* had demonstrated that monocyclic tetramic acids **158** could be coupled with carboxylic acids using DCC/DMAP coupling conditions or reacted with acyl chlorides under basic conditions to form *O*-acyltetramates **159** (**Scheme 3.18**),⁶⁴⁻⁶⁵ in which the use of DMAP (1.3 eq.) or acetone cyanohydrin (0.5 eq.) under basic conditions could lead to the rearrangement to *C*-acyltetramates **160**.⁶⁴⁻⁶⁵ Intrigued by the use of DMAP to promote *O*-C acyl rearrangements, Jeong *et al.* had promoted an *in-situ* one step *O*-C acyl rearrangement by reacting tetramates **158** with DCC and stoichiometric amounts of DMAP (1.3 eq.) to form tetramates **160**.⁶⁴⁻⁶⁵ Jeong *et al.* and Tan *et al.* later extended this methodology to bicyclic tetramates which were derived from L-serine **8a**, L-threonine **8b** and L-cysteine **8c**.^{39,43}



Scheme 3.18: The synthesis of *O*-acetyltetramates **159** and *C*-acetyltetramates **160**; (a) R^2CO_2H (1.1 eq.), DCC (1.1 eq.), DMAP (0.1 eq.), DCM, rt; (b) R^2COCl (1.1 eq.), Et_3N (1.2 eq.), DCM, rt; (c) acetone cyanohydrin (0.5 eq.), Et_3N (2 eq.), CH_3CN , rt; (d) DMAP (1.3 eq.), DCM, rt; (e) R^2CO_2H (1.1 eq.), DCC (1.1 eq.), DMAP (1.3 eq.), DCM, rt.

Taking inspiration from this approach, of interest was to synthesise C7-acetyltetramates derived from *allo*-phenylserine **125a**. As a result, tetramates **134a** were coupled with aromatic and aliphatic carboxylic acids using DCC and stoichiometric amounts of DMAP (1.3 eq.) and were left to react overnight at room temperature to form C7-acetyltetramates **161a-s** in acceptable yields (**Scheme 3.19**, **Table 3.12**). Electron-donating and electron-withdrawing groups were tolerated at the *para*-position of the aromatic ring system, with moderate yields being obtained in many cases. However, the yields dramatically decreased when introducing substituents at the *ortho*-position of the aromatic ring system. Moreover, when increasing the steric bulk around the carboxylic acid moiety such as when coupling tetramate **134a** with 1-naphthoic acid, 2,6-dichlorobenzoic acid, 2-chlorobenzoic acid and 9-

anthracenecarboxylic acid, either the products did not form or could not be isolated after chromatographic purification. It was assumed that this was due to the lack of access to the carboxylic acid moiety due to steric hinderance. Interestingly, the 2-thienyl substituent was obtained in poor yield although aliphatic substituents were obtained in moderate to good yields. Additionally, HMBC analysis was used to assign carbonyl peaks for the tetramate series (**Scheme 3.19**, **Table 3.12**). Additionally, NOESY studies suggested no epimerisation had occurred at any of the stereogenic centres after DCC/DMAP coupling (**Scheme 3.19**).



Scheme 3.19: Synthesis of C7-acyltetramates **161a-s** using DCC/DMAP coupling conditions.

Compound	R ¹	δ (ppm)						Yield (%)
		H2	H4	C6	C8	C9	C10	
161a		5.10	4.89	186.8	182.4	183.7	165.5	32
161b		5.08	4.87	186.9	182.6	183.6	165.6	26
161c		5.05	4.84	187.0	182.8	183.0	165.7	18
161d		5.09	4.88	186.9	182.2	182.2	165.3	39
161e		5.08	4.88	187.0	182.5	182.5	165.3	35
161f ^a		5.06	4.85	186.9	182.2	182.7	165.4	37
161g		5.07	4.88	n.d	n.d	n.d	165.1	30

161h		5.07	4.87	186.8	182.0	182.0	165.2	41
161i		5.06	4.84	186.7	182.5	183.5	165.5	44
161j		5.08	4.88	n.d	n.d	n.d	165.1	12
161k		5.06	4.84	186.6	182.7	183.5	165.5	17
161l		4.97	4.78	186.6	182.8	182.8	165.5	13
161m		5.02	4.84	187.4	179.3	181.9	164.8	37
161n		5.02	4.83	187.8	180.8	196.1	165.4	57
161o^b		4.99	4.79	188.3	180.2	191.7	165.3	44
161p^b		5.00	4.79	188.6	180.3	190.5	165.4	57
161q^b		4.98	4.79	188.3	179.9	188.5	165.3	51
161r		4.99	4.79	188.1	180.3	192.6	165.4	47
161s		4.99	4.80	188.1	180.2	192.1	165.3	41

Table 3.12: Key chemical shifts (δ) and yields of C7-acyltetramates **161a-s**; CDCl₃ solution, 400 MHz; ^a CDCl₃ solution, 500 MHz; ^b refers to the major **CD** tautomer; where n.d = not detected.

When purifying these tetramic acids through silica gel, they also picked up trace metal ions to give very broad resonances as shown in **Figure 3.17a**. When qualitatively looking at the NMR spectrum of metal-chelated C7-carboxamide **157a** (**Figure 3.16a**) in comparison to **161d** (**Figure 3.17a**), it was clear to see that C7-acyltetramates bound to metal ions with much higher affinity by looking at the line broadening

of the NMR peaks. In the case of carboxamidotetramate **157a**, discernible peaks were detected, however, looking at the NMR spectrum of acyltetramate **161d**, no discernible peaks could be assigned to a particular proton with any certainty. However, a simple acid wash with 10% citric acid solution (aq.) led to sharpened peaks, as shown in **Figure 3.17b**.

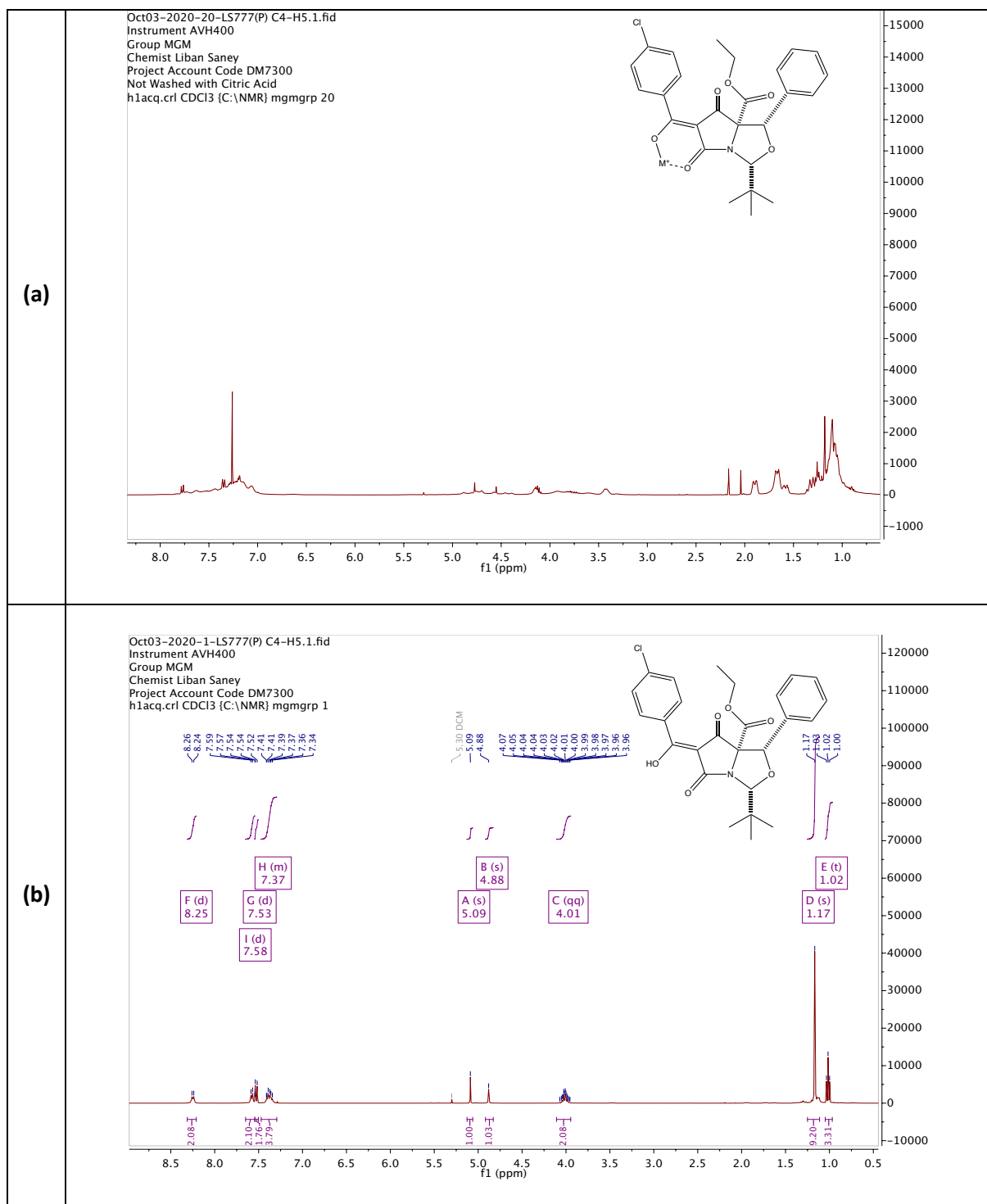


Figure 3.17: ¹H-NMR spectrum of C7-acyltetramate **161d** post-chromatographic purification, before (a) acid wash and (b) after 10% citric acid (aq.) wash; ^a CDCl₃ solution, 400 MHz.

Additionally, the products in all cases were obtained as a single tautomer **CD**, with the exception of **161o-q**, which was seen as a mixture of tautomers, in which the **CD** tautomer was the major tautomer. Tan *et al.* had demonstrated that the major tautomer for C7-acyltetramates **162-163** was the **CD** tautomer, as the C6-carbonyl peaks from the **AB** tautomer tended to be more downfield as a result of deshielding from hydrogen bond effects in comparison to the **CD** tautomer (**Figure 3.18**).^{39,43,64-65} By analogy, due to the very similar ¹³C-NMR carbonyl peaks obtained for this compound set with that of Tan *et al.*³⁹, it was assumed that the major tautomer for this compound set was **CD**.

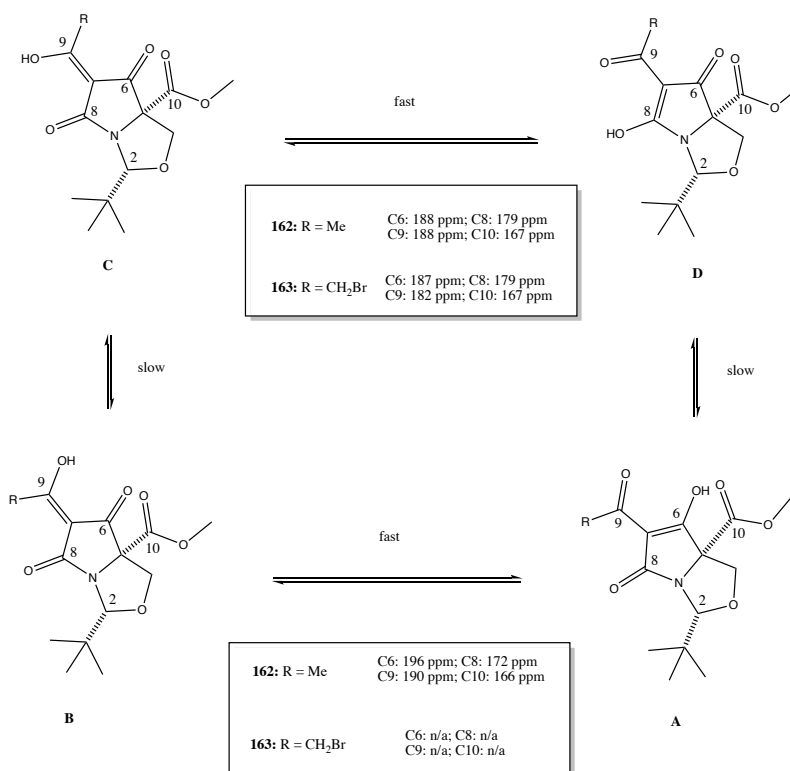
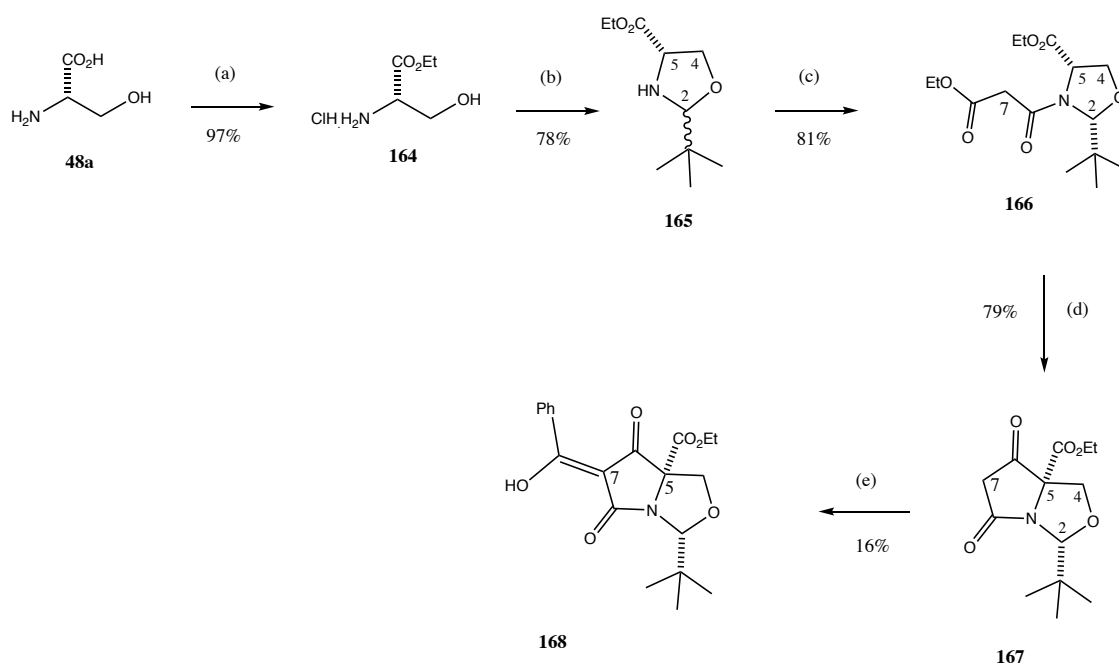


Figure 3.18: Tan *et al.* and Jeong *et al.* assignments of C7-acyltetramate tautomers **162** and **163** derived from the methyl ester of L-serine **8a**; CDCl₃ solution, 400 MHz.

Tan *et al.* and Jeong *et al.* had demonstrated that C7-acyltetramates derived from the methyl ester derivatives of L-serine **48a**, L-threonine **48b** and L-cysteine **48c** had to be washed with 10% HCl solution (aq.), or dilute HCl (aq.) after chromatographic purification on silica gel.^{39,43,65} However, this work has demonstrated that C7-acyltetramates **161a-s** derived from *allo*-phenylserine **125a** only required a mild acid wash, using 10% citric acid solution (aq.). Thus, of immediate interest was to study whether metal-

chelated C7-acyltetramic acids derived from L-serine **8a** required stronger acid washes or if they could also be washed with 10% citric acid solution (aq.) as well. This would enable examination as to whether the C4-phenyl substituent might contribute towards weakened metal-chelation across the tricarbonyl core and would allow for direct comparison between L-serine **8a** and *allo*-phenylserine **125a** derived C7-acyltetramates.

Shown in **Scheme 3.20** is the synthetic steps taken towards the synthesis of C7-acyltetramate **168** derived from L-serine **48a**, in which the ethyl ester hydrochloride salt **164** was formed to allow for direct comparison between the two systems. Moloney's synthetic methodology – outlined in **Scheme 1.1** – was followed. In the case of C7-acyltetramate **168**, only a mild acid wash in the form of 10% citric acid solution (aq.) was required to sharpen the NMR peaks post-chromatographic purification (**Figure 3.19**). Thus, no qualitative inference could be made as to whether the C4-phenyl substituents had a role in reducing metal-chelation across the tricarbonyl core.



Scheme 3.20: The synthesis of C7-acyltetramate **168** from L-serine **48a**; (a) EtOH, SOCl₂, 60°C, 3 h; (b) petroleum ether 40:60, pivaldehyde, Et₃N, >100°C, Dean-Stark, overnight; (c) ethyl malonyl chloride, pyridine, DCM, reflux, overnight; (d) KO^tBu, THF, reflux, 3 h; (e) benzoic acid, DCC, DMAP, DCM, rt, overnight.

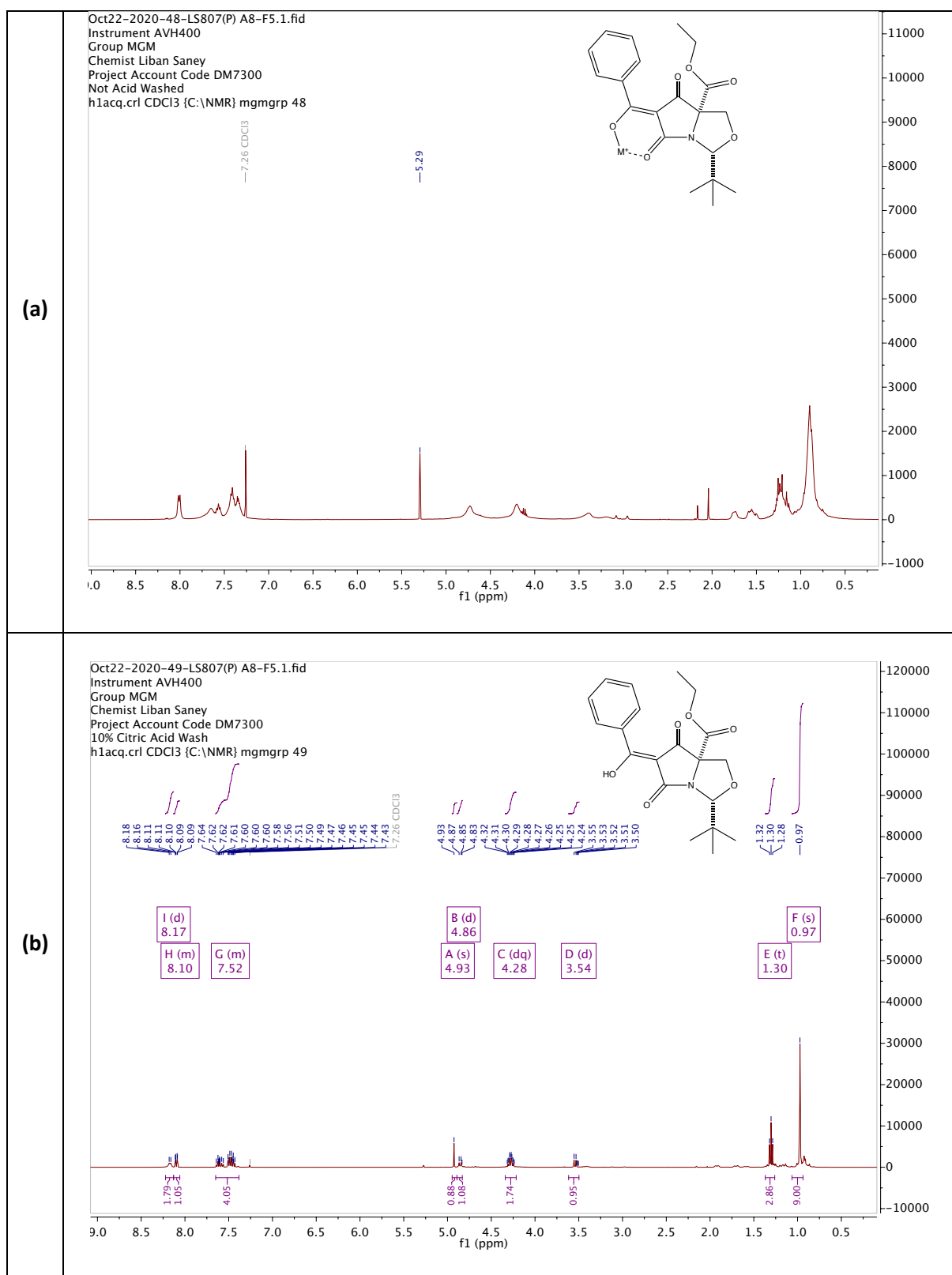
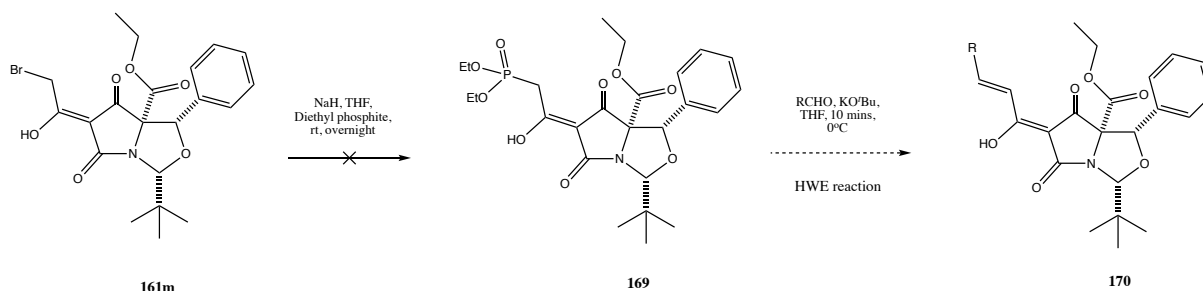


Figure 3.19: ¹H-NMR spectrum of C7-acyltetramate **168** post-chromatographic purification, before **(a)** acid wash and **(b)** after 10% citric acid (aq.) wash; CDCl₃ solution, 400 MHz.

As many natural product tetramates are part of the C3-acyltetramic acid class (**Chapter 1.5**), of interest was to develop a synthetic methodology to access this class of compounds **170** through the Horner-

Wadsworth-Emmons (HWE) reaction (**Scheme 3.21**). If this methodology could be extended to tetramate **161m**, a library of compounds could be tested for antibacterial activity. As a result, tetramate **161m** was reacted with sodium hydride and diethyl phosphite, however, phosphonate **169** was not formed or could not be isolated after purification.



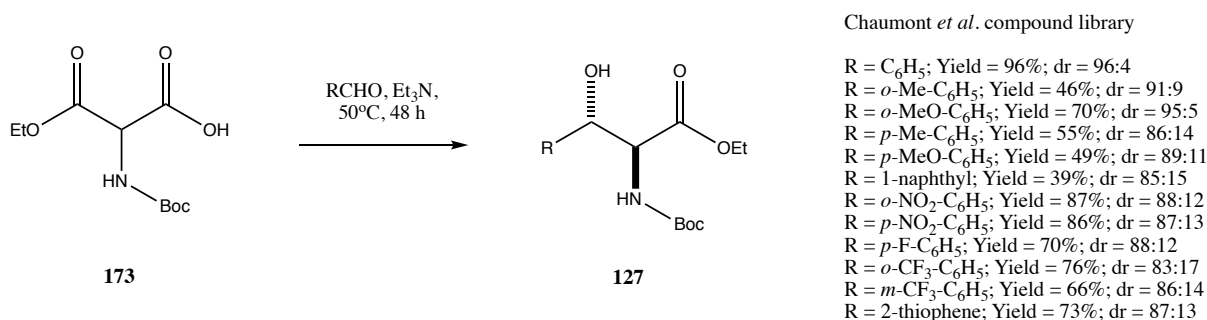
Scheme 3.21: Failed synthesis of phosphonate **169** from C7-acetyltetramate **161m**.

3.2.7: Alternative Synthesis of *erythro*-Phenylserine Derivatives

Although the synthesis of *allo*-phenylserine **125a-f** from β -oxoesters **122a-f** via Pd-C catalysed hydrogenation was very diastereoselective – where only a single product was obtained in most cases – it suffered from four major drawbacks. Firstly, all the β -oxoesters **122b-f** and oximes **123a-f** – with the exception of **122a** – had to be synthetically made. Secondly, a sizeable amount of Pd-C was required to convert the oximes **123a-f** to *allo*-phenylserines **125a-f**, and thirdly, the yields on average were only obtained in modest amounts. Additionally, chloro and bromo-substituted *allo*-phenylserine derivatives could react with Pd to form unwanted dehalogenated side-products.

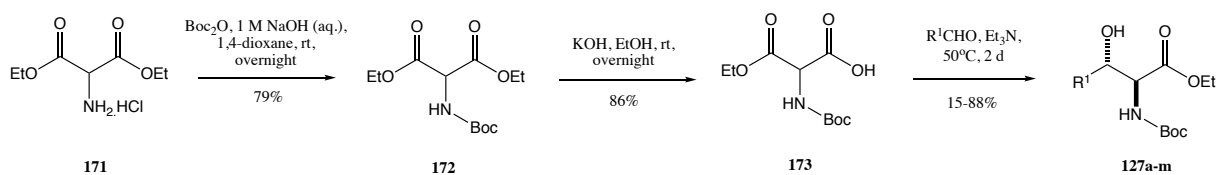
Of interest in the first instance was the synthesis of a diverse set of *allo*-phenylserine derivatives from commercially available, cheap starting materials. We took inspiration from the synthesis of Chaumont *et al.* of Boc-protected *allo*-phenylserine derivatives via a decarboxylative aldol reaction between the hemi-malonate derivative of diethyl (Boc-amino)malonate **173** and various aldehydes (**Scheme 3.22**).⁶⁶ This method had the advantage of utilising commercially available aldehydes to vary the substitution patterns around the aromatic ring system and could tolerate electron-withdrawing and electron-donating groups in addition to incorporating heterocycles as well.⁶⁶ These compounds could be

obtained in good yields, and in most cases were obtained with good diastereoselectivity – between 83:17/96:4 dr – in which the diastereomers could easily be separated by chromatographic purification.⁶⁶ In addition to this, the reaction conditions were very mild. Moreover, Chaumont *et al.* assigned the major aldol diastereomer in all cases to be the *erythro* isomer based on the single-crystal X-ray structure obtained for the 2-methoxyphenylserine derivative synthesised.⁶⁶



Scheme 3.22: Chaumont *et al.* synthesis of *allo*-phenylserine derivatives **127** derived from hemimalonate **173**.

The downside to this approach however, was that diethyl (Boc-amino)malonate **172** was surprisingly expensive to purchase, but could be synthesised by reacting diethyl aminomalonate hydrochloride **171** – which was very cheap to purchase – with Boc₂O (**Scheme 3.23**). As a result, we decided to try and reproduce the work of Chaumont *et al.* Firstly, Boc-protected *allo*-phenylserine **127a** was synthesised using the decarboxylative aldol methodology. The spectroscopic data was consistent with the work of Chaumont *et al.*⁶⁶ and the earlier synthesis of **127a** outlined in **Scheme 3.7**, which was also confirmed with a single-crystal X-ray structure – shown in **Figure 3.3**, *vide supra*. As a result – and due to the X-ray crystal structure of **127a** – it was assumed that the major aldol diastereomer for all compounds synthesised was the *erythro* isomer, as the NMR data set for the rest of the compound series was consistent with compound **127a** (**Table 3.13**), although the diastereomeric ratio for the compound synthesised was not calculated in this research. Many *ortho*, *meta* and *para*-substituted *allo*-phenylserine derivatives **127a-m** were synthesised to extend the synthetic methodology of providing easy access to C4-functionalised tetramates.

**Scheme 3.23:** Synthesis of Boc-protected-*allo*-phenylserine derivatives **127a-m**.

Compound	R ¹	δ (ppm)			J_{H2-H3} (Hz)	J_{H2-NH} (Hz)	Yield (%)
		H2	H3	NH			
127a		4.61	5.12	5.25	3.9	7.6	79
127b		4.65	5.16	5.30	3.7	7.3	64
127c		4.67	5.25	5.37	3.3	6.9	69
127d		4.69	5.25	5.36	3.7	7.2	62
127e		4.69	5.31	5.39	3.3	6.8	73
127f		4.69	5.19	5.31	3.8	7.5	69
127g		4.66	5.19	5.37	3.6	7.2	72
127h		4.64	5.17	5.37	3.6	7.2	70
127i		4.72	5.47	5.38	n.d. ^a	n.d. ^a	68
127j		4.73	5.31-5.48	5.31-5.48	n.d. ^a	n.d. ^a	88
127k		4.68	5.22	5.47	3.8	7.4	79
127l		4.75	5.48	5.39	n.d. ^a	n.d. ^a	51

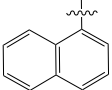
127m ^b		4.69	6.03	5.42	2.6	9.1	15

Table 3.13: Yields and key chemical shifts of Boc-protected-*allo*-phenylserines **127a-m**; CDCl₃ solvent, 400 MHz; ^a n.d = not determined due to a broad multiplet peak; ^b Data refers to the major rotamer.

Boc-protected-*allo*-phenylserine derivatives **127a-l** were deprotected using TFA and were stirred at room temperature for 2 h to furnish *allo*-phenylserines **174a-l** as the trifluoroacetate ammonium salts in quantitative yields (**Scheme 3.24**, **Table 3.14**). The exception was **127l**, which gave a complex mixture of side-products, thus was not used further. Moreover, **127m** was discontinued due to the low yield that was initially obtained.

Compound	R ¹	δ (ppm)					Yield (%)
		H2	H3	J_{H2-H3}	C2	C3	
174a	Ph	4.48	5.40	4.2	58.5	71.0	Quant.
174b	<i>p</i> -Br-C ₆ H ₄	4.48	5.38	3.9	58.3	70.4	Quant.
174c	<i>p</i> -CN-C ₆ H ₄	4.56	5.48	3.6	58.1	70.5	Quant.
174d	<i>p</i> -CF ₃ -C ₆ H ₄	4.57	5.51	3.7	58.3	70.5	Quant.
174e	<i>p</i> -NO ₂ -C ₆ H ₄	4.60	5.53	3.5	58.1	70.4	Quant.
174f	<i>m</i> -MeO-C ₆ H ₄	4.49	5.40	4.1	58.4	70.7	Quant.
174g	<i>m</i> -Cl-C ₆ H ₄	4.49	5.39	3.9	58.3	70.3	Quant.
174h	<i>m</i> -Br-C ₆ H ₄	4.49	5.40	3.8	58.3	70.3	Quant.
174i	<i>o</i> -F-C ₆ H ₄	4.54	5.59	3.7	57.0	66.3	Quant.
174j	<i>o</i> -Br-C ₆ H ₄	4.62	5.51	3.2	55.9	70.7	Quant.
174k	<i>m</i> -Pyridyl	4.69	5.64	2.7	57.5	68.2	Quant.

Table 3.14: Key chemical shifts, coupling constants and yields of amino esters **174a-k**; D₂O solvent, 400 MHz.

The *allo*-phenylserine derivatives **174a-k** were then reacted with pivaldehyde using the established protocols outlined in **Chapter 3.2.2**, to obtain oxazolidines **128a/128g-p** in good yields as a mixture of

diastereomers (**Scheme 3.24**, **Table 3.15**). The spectroscopic consistencies of oxazolidines **128a/128g-p** with that of **128a-f** derived from β -oxoesters **122a-f** again confirmed that the amino esters **174a-k** synthesised were indeed the *erythro* isomers (compare **Tables 3.5** with **3.15**). Moreover, the major and minor diastereomers of oxazolidines **128g-p** was assigned based upon the spectroscopic consistencies of oxazolidines **128a-f** which were derived from β -oxoesters **122a-f**.

Compound	R ¹	2,5- <i>cis</i> oxazolidine δ (ppm)				2,5- <i>trans</i> oxazolidine δ (ppm)				dr at the C2-position ^a	Yield (%) ^b
		H2	H4	H5	J_{H4-H5} (Hz)	H2	H4	H5	J_{H4-H5} (Hz)		
128a	Ph	4.15	4.98	4.09	9.0	4.94	5.23	4.22	7.4	5.6:1	57
128g	<i>p</i> -Br-C ₆ H ₄	4.20	5.00	4.15	9.0	4.98	5.24	4.28	7.3	5.7:1	82
128h	<i>p</i> -CN-C ₆ H ₄	4.23	5.07	4.21	9.1	5.01	5.29	4.34	7.4	4.6:1	74
128i	<i>p</i> -CF ₃ -C ₆ H ₄	4.23	5.10	4.20	9.0	5.02	5.32	4.33	7.3	5.3:1	85
128j	<i>p</i> -NO ₂ -C ₆ H ₄	4.25	5.13	4.24	9.1	5.03	5.35	4.37	7.4	4.6:1	61
128k	<i>m</i> -MeO-C ₆ H ₄	4.20	5.02	4.15	9.0	4.99	5.26	4.27	7.3	5.7:1	60
128l	<i>m</i> -Cl-C ₆ H ₄	4.13	4.94	4.09	9.1	4.94	5.18	4.22	7.4	4.6:1	78
128m	<i>m</i> -Br-C ₆ H ₄	4.13	4.93	4.08	8.9	4.92	5.17	4.22	7.4	3.8:1	80
128n	<i>o</i> -F-C ₆ H ₄	4.22	5.39	4.22	8.9	4.99	5.51	4.39	7.2	4.9:1	78
128o	<i>o</i> -Br-C ₆ H ₄	4.22	5.43	4.28	8.7	5.04	5.46	4.56	7.0	5.7:1	77
128p	<i>m</i> -Pyridyl	4.22	5.07	4.19	9.0	4.99	5.30	4.33	7.4	4.9:1	57

Table 3.15: Key chemical shifts (δ), coupling constants (J), diastereomeric ratio (dr) and yields of oxazolidines **128a/128g-p**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material where the major diastereomer was the 2,5-*cis* isomer; ^b Yields include both diastereomers.

These compounds were then *N*-acylated with ethyl malonyl chloride (**Scheme 3.24**) using the established protocols outlined in **Chapter 3.2.3** to obtain malonamides **129a/129g-p** in good yields as predominantly 1 diastereomer – consistent with that of malonamides **129a-f**. Due to the spectroscopic consistencies of **129a** observed with that of malonamide **129a** obtained from β -oxoester **122a**

(compare **Tables 3.6** with **3.16**), it was assumed that the malonamides synthesised **129g-p** from the hemi-malonate **173** had the same relative stereochemistry as malonamides **129a-f**. Additionally, NOESY studies also confirmed this to be the case also.

Compound	R ¹	δ (ppm)			$J_{\text{H4-H5}}$ (Hz)	Yield (%)
		H2	H4	H5		
129a	Ph	5.37	5.21	4.80	6.9	78
129g	<i>p</i> -Br-C ₆ H ₄	5.38	5.16	4.82	6.7	69
129h	<i>p</i> -CN-C ₆ H ₄	5.40	5.22	4.93	6.5	68
129i	<i>p</i> -CF ₃ -C ₆ H ₄	5.40	5.25	4.90	6.6	59
129j	<i>p</i> -NO ₂ -C ₆ H ₄	5.42	5.27	4.98	6.3	75
129k	<i>m</i> -MeO-C ₆ H ₄	5.38	5.18	4.80	6.9	68
129l	<i>m</i> -Cl-C ₆ H ₄	5.38	5.17	4.84	6.7	72
129m	<i>m</i> -Br-C ₆ H ₄	5.38	5.17	4.84	6.7	66
129n	<i>o</i> -F-C ₆ H ₄	5.39	5.33	4.93	6.3	61
129o	<i>o</i> -Br-C ₆ H ₄	5.40	5.33	5.15	6.5	54
129p	<i>m</i> -Pyridyl	5.39	5.22	4.89	6.6	68

Table 3.16: Key chemical shifts (δ) and coupling constants (J) of the major malonamide diastereomer including the yields of malonamides **129a/129g-p**; CDCl₃ solvent, 400 MHz.

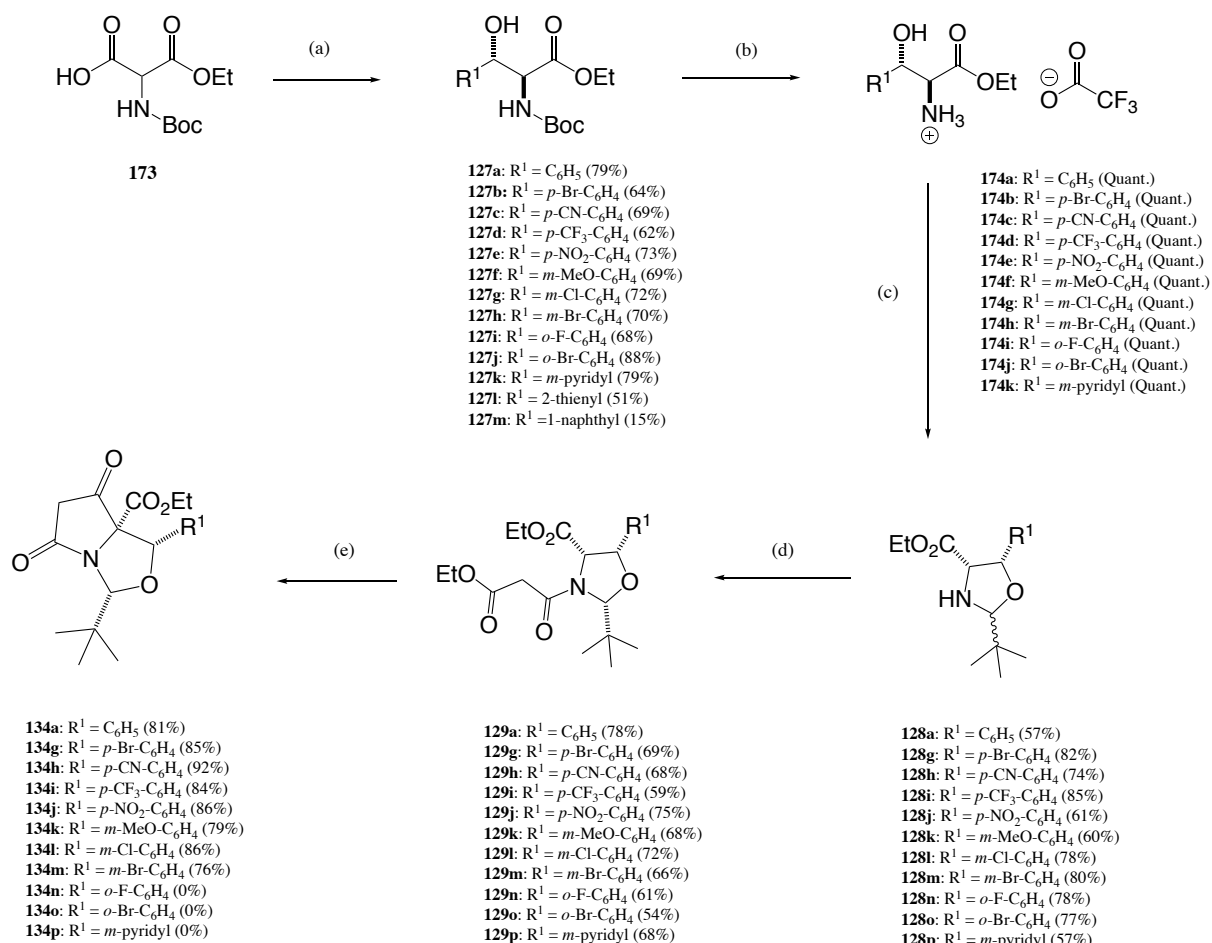
These malonamides **129a/g-p** were then reacted with DBU in THF overnight (**Scheme 3.24**) to form tetramates **134a/g-m** in good yields (**Table 3.17**). As tetramate **134a** had the same spectroscopic data as tetramate **134a** which was derived from β -oxoester **122a**, and that the NMR spectroscopic consistencies were apparent for the rest of the tetramate series (compare **Tables 3.9** with **3.17**) it was assumed that these tetramates had the same relative stereochemistry as tetramates **134a-f**, and NOESY analysis confirmed this to be the case also.

However, surprisingly, tetramate **134n** was formed as a very minor product, with an unidentified side-product being formed as the major product – chiefly detected in the NMR spectrum – and as a result

this material was discarded. Additionally, tetramate **134o** did not form at all. This had indicated that substituents attached at the *ortho*-position tended to have a detrimental impact on the Dieckmann cyclisation, however, it is not yet fully understood why this was the case. Additionally, the Dieckmann cyclisation of the 3-pyridyl substituent **129p** did not give the desired C7-unfunctionalised tetramate **134p** or the C7-ethyl ester tetramate arising from a different Dieckmann cyclisation pathway, in addition to any of its possible tautomers as well – as determined from the ¹H-NMR spectrum – however, the mass ion peak was detected. As a result, it was unclear as to which product was formed after the attempted Dieckmann cyclisation of malonamide **129p**.

Compound	R ¹	δ (ppm)				J_{H7-H7} (Hz)	Yield (%)
		H2	H4	H7	H7		
134a	Ph	5.16	4.96	3.79	3.22	20.5	81
134g	<i>p</i> -Br-C ₆ H ₄	5.16	4.88	3.81	3.23	20.7	85
134h	<i>p</i> -CN-C ₆ H ₄	5.19	4.95	3.84	3.26	20.8	92
134i	<i>p</i> -CF ₃ -C ₆ H ₄	5.20	4.97	3.84	3.26	20.7	84
134j	<i>p</i> -NO ₂ -C ₆ H ₄	5.21	4.99	3.86	3.28	20.9	86
134k	<i>m</i> -MeO-C ₆ H ₄	5.16	4.93	3.77	3.22	20.6	79
134l	<i>m</i> -Cl-C ₆ H ₄	5.16	4.90	3.82	3.23	20.7	86
134m	<i>m</i> -Br-C ₆ H ₄	5.16	4.89	3.82	3.22	20.6	76
134n	<i>o</i> -F-C ₆ H ₄	–	–	–	–	–	n.d. ^a
134o	<i>o</i> -Br-C ₆ H ₄	–	–	–	–	–	0
134p	<i>m</i> -Pyridyl	–	–	–	–	–	0

Table 3.17: Key chemical shifts (δ), coupling constants (J) and yields of tetramates **134a/134g-p**; CDCl₃ solvent, 400 MHz; ^a n.d = not determined as the compound was discarded.



Scheme 3.24: Expanded functionalisation of C4-aromatic tetramates **134a/134g-m** via the decarboxylative aldol reactions of hemimalonate **173**; (a) R¹CHO, Et₃N, 50°C, 2 d; (b) TFA, DCM, rt, 2 h; (c) petroleum ether 40:60, pivaldehyde, Et₃N, >100°C, Dean-Stark, overnight; (d) ethyl malonyl chloride, pyridine, DCM, reflux, overnight; (e) DBU, THF, rt, overnight.

3.3: Synthetic Methodologies Towards the Synthesis of the Clausenamide Family

Clausenamide **175a** is a densely functionalised pyrrolidinone natural product that was isolated from the Chinese herbal medicine, *Clausena lansium*.⁶⁷⁻⁷⁰ This compound has four chiral centres but was isolated as a racemate, however (-)-clausenamide **175a** was found to be a nootropic agent as it has long-term potentiation (LTP) enhancing capabilities in the hippocampus region of rats and is now undergoing clinical trials for potential use as a treatment against Alzheimer's disease.⁶⁹⁻⁷⁰ Moreover, (-)-clausenamide **175a** was found to be 5-10 times more potent than its enantiomer.⁶⁹ Additionally,

clausenamide **175a** was shown to have hepatoprotective properties against chemical toxins such as carbon tetrachloride and thioacetamide as well.⁶⁷ As clausenamide **175** has four chiral centres, it has a possible 16 stereoisomers and many family members have been isolated and/or synthesised – structures are shown in **Figure 3.20**.⁶⁷⁻⁷⁰ For example, (+)-*epi*-clausenamide **175h** is a non-natural diastereomer that has twice the LTP enhancement as (-)-clausenamide **175a** and the C3-deoxy analogue of (-)-*epi*-clausenamide **176** was found to be an inhibitor of 17- β -hydroxy-steroid dehydrogenase II (17- β -HSD-II) and could potentially find applications in preventing osteoporosis.⁷⁰ Described below is a very brief literature overview into the total synthesis of the clausenamide family.

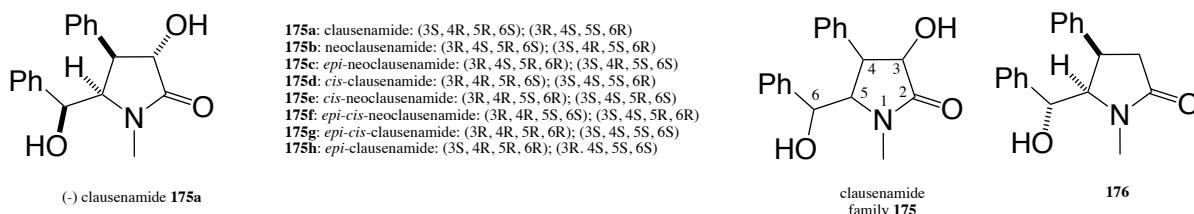
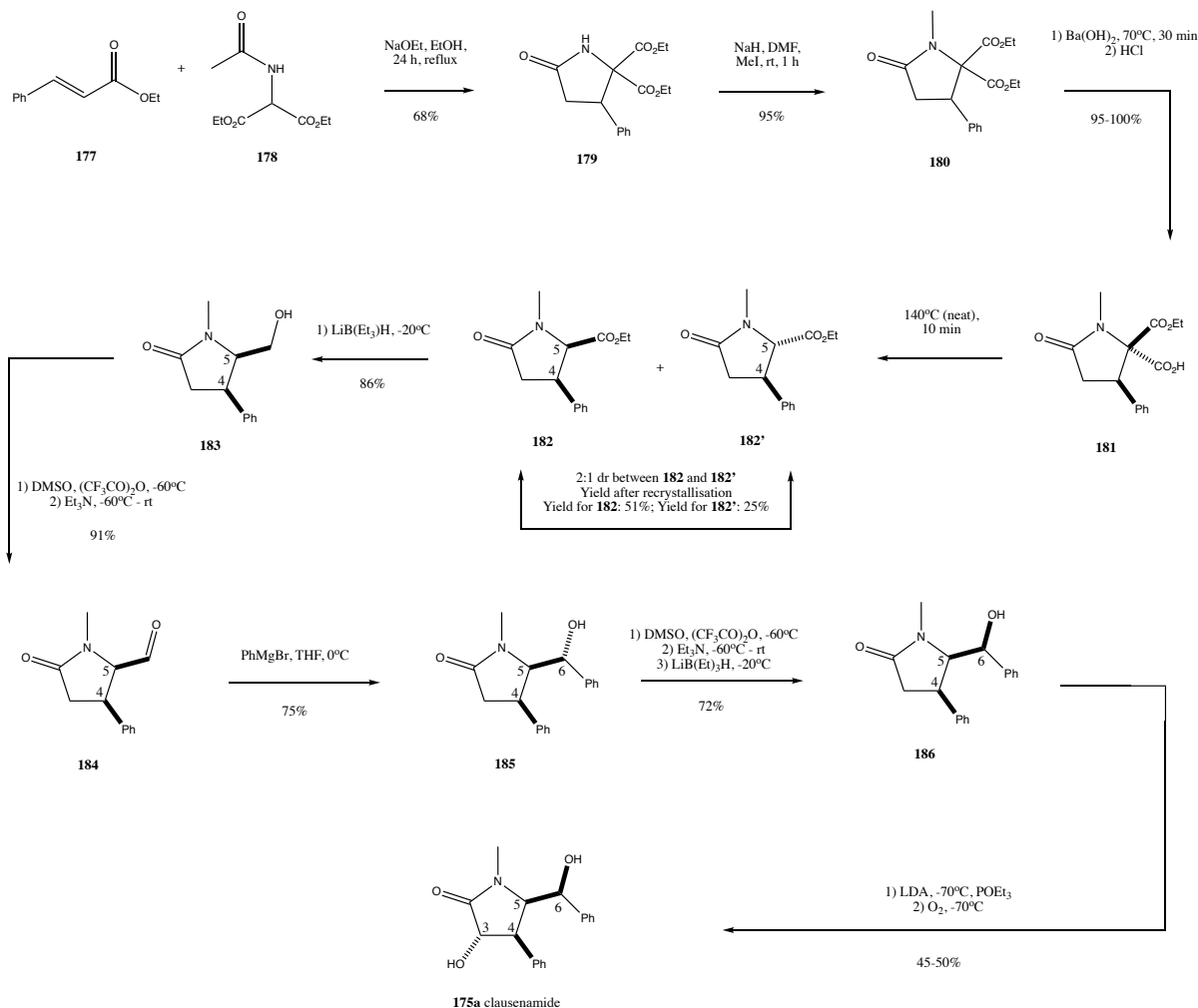


Figure 3.20: The clausenamide family **175a-h** and the C3-deoxy derivative of (-)-*epi*-clausenamide **176**.

3.3.1: Brief Literature Review on the Total Synthesis of the Clausenamide Family

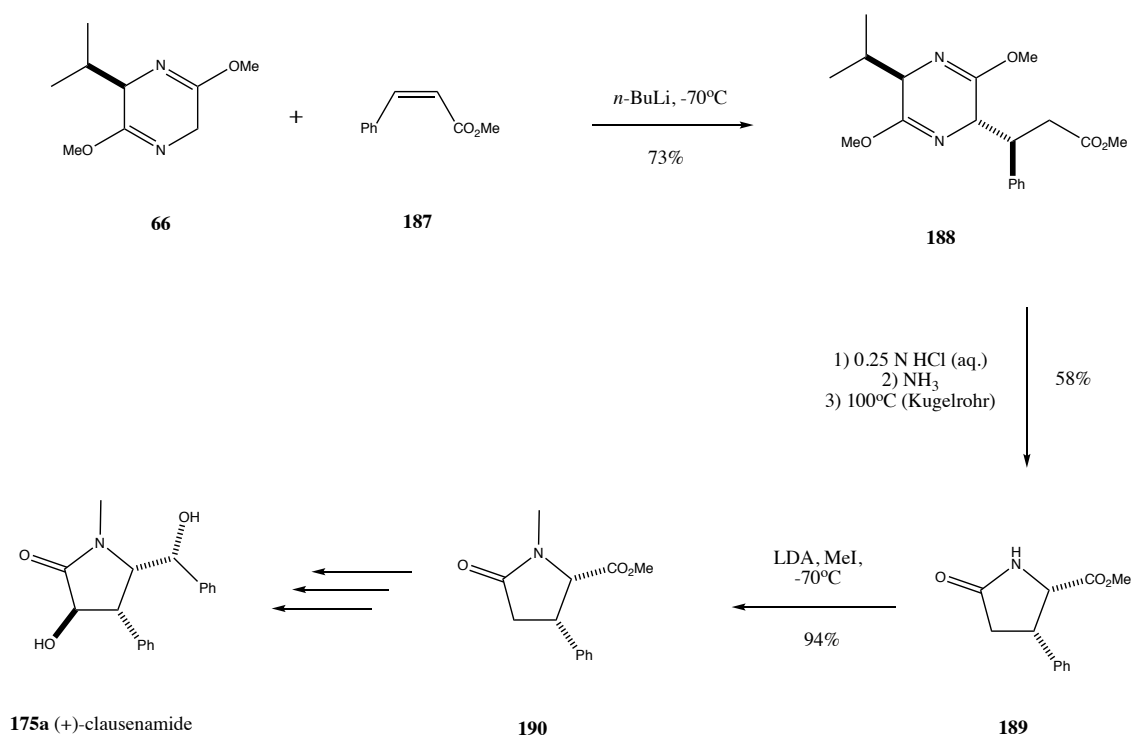
Hartwig *et al.* had developed one of the first diastereoselective total synthesis of clausenamide **175a** (**Scheme 3.25**).⁶⁷ The first step of their synthesis was the reaction between *trans*-ethyl cinnamate **177** and diethyl acetamidomalonate **178** to form pyrrolidinone **179** in good yield. Pyrrolidinone **179** was then *N*-methylated **180** using NaH and MeI and was subsequently reacted with Ba(OH)₂ to selectively hydrolyse the ethyl ester *trans* to the phenyl group to give carboxylic acid **181** in high yields. Compound **181** was then heated neat at 140°C to give a 2:1 mixture of pyrrolidinone esters **182** and **182'**, in which the esters could be separated by recrystallisation. Pyrrolidinone **182** was then reacted with Superhydride, LiEt₃H, to give 4,5-*cis*-alcohol **183** in 86% yield, which was then oxidised under Swern's conditions to form aldehyde **184** without epimerisation at the C5-position. Grignard addition using PhMgBr gave pyrrolidinone **185** in good yield and excellent diastereoselectivity, however, with the wrong C6-stereochemistry required in comparison to the natural product **175a**. Thus pyrrolidinone **185** was then oxidised and reduced to form pyrrolidinone **186** which had the correct C6-

stereochemistry. Pyrrolidinone **186** was then reacted with LDA, triethyl phosphite and oxygen at low temperatures to form clausenamide **175a** in the racemic form.



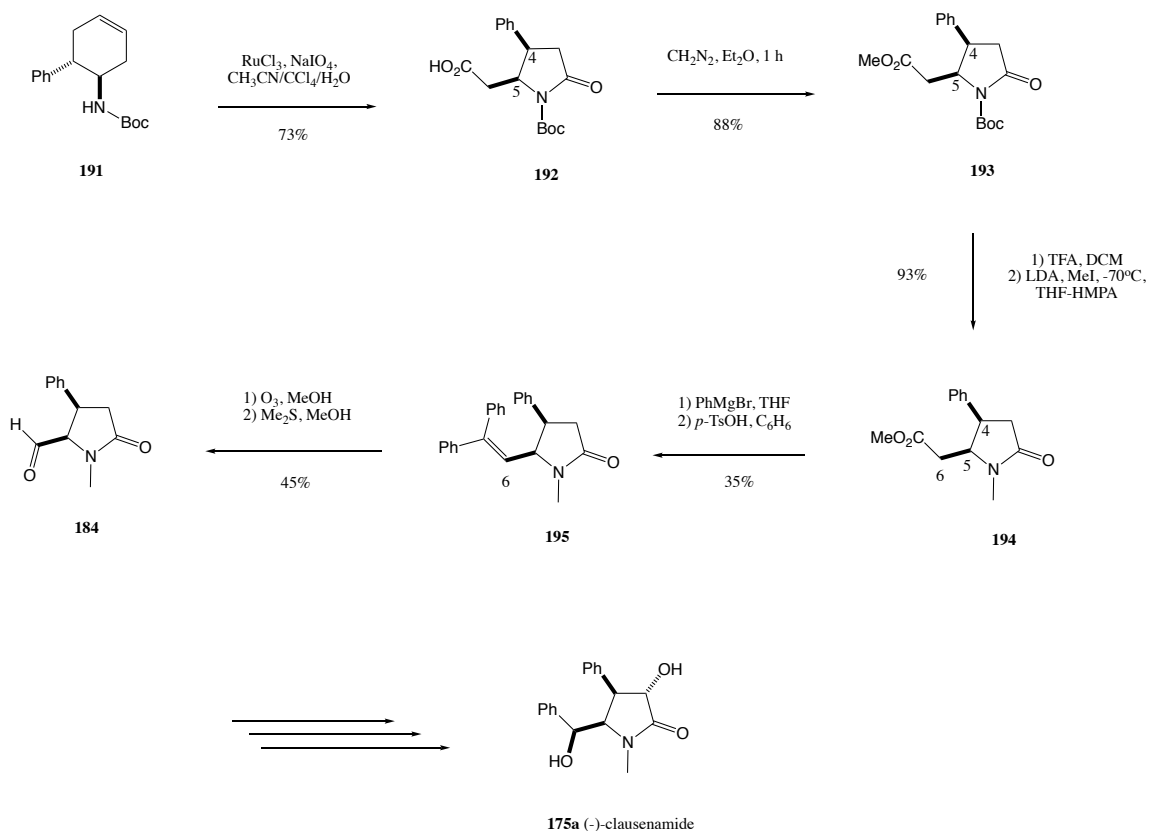
Scheme 3.25: Hartwig *et al.* racemic total synthesis of clausenamide **175a**.

Hartwig *et al.* also developed an enantioselective synthesis of (+)-clausenamide **175a** by reacting *cis*-methyl cinnamate **187** with Schöllkopf's bis-lactim ether reagent **66** at -70°C using *n*-BuLi to form optically pure pyrazine **188** in 73% yield as one of the key intermediates (**Scheme 3.26**).⁶⁷ Mild acid hydrolysis followed by neutralisation with NH_3 led to the formation of an optically active pyrrolidinone **189**, which was then subsequently *N*-methylated using LDA and MeI to form pyrrolidinone **190**. Following on from the synthetic methodology outlined in **Scheme 3.25**, pyrrolidinone **190** was converted to (+)-clausenamide **175a**.



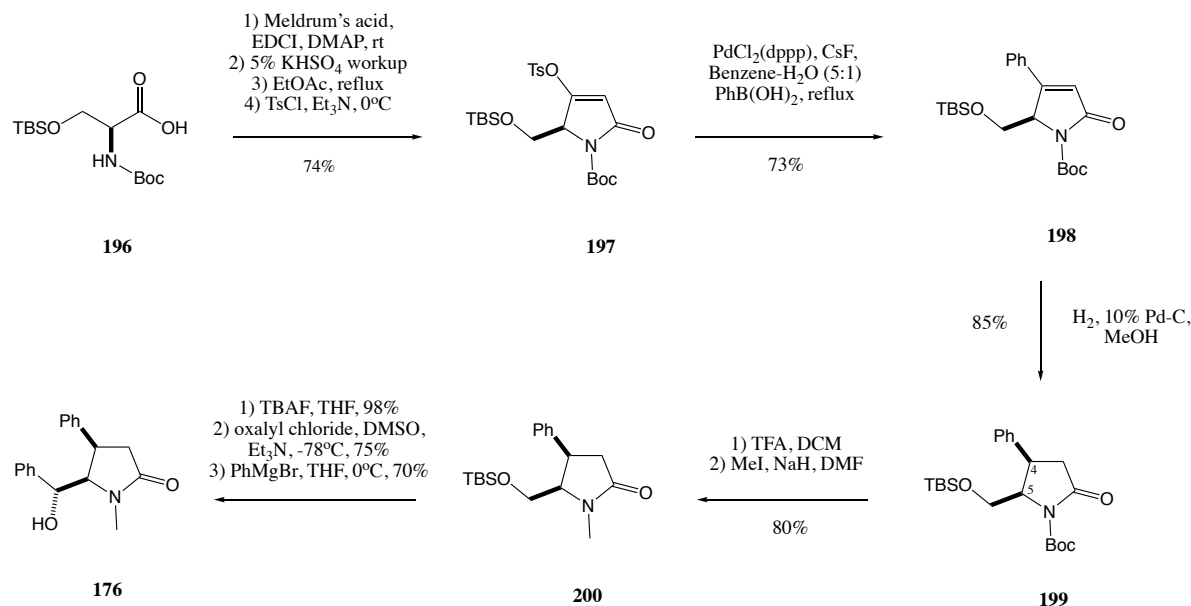
Scheme 3.26: Hartwig *et al.* enantioselective total synthesis of (+)-clausenamide **175a**.

Yakura *et al.* also accomplished a stereoselective total synthesis of (-)-clausenamide **175a** through the oxidation of an optically active multi-substituted cyclohexane derivative **191** to provide a key route towards 4,5-*cis*-pyrrolidinone **184** – an important precursor towards the synthesis of (-)-clausenamide **175a** (Scheme 3.27).⁶⁸ Firstly cyclohexane **191** was oxidised using $\text{RuCl}_3\text{-NaIO}_4$ in a $\text{CH}_3\text{CN-CCl}_4\text{-H}_2\text{O}$ solvent mixture to form 4,5-*cis*-pyrrolidinone **192**. The mechanism behind this reaction is through a periodate cleavage of cyclohexane **191** to form a dialdehyde which then cyclises to form a hydroxyaldehyde that subsequently gets oxidised *in-situ* to form pyrrolidinone **192**. Pyrrolidinone **192** was then esterified using diazomethane to form methyl ester **193**. The Boc-protecting group was then removed with TFA and then *N*-methylated using LDA and MeI to form pyrrolidinone **194**. Methyl ester **194** was then subjected to a double Grignard addition using PhMgBr , and then reacted with *p*-TsOH to form the acid-catalysed olefin product **195**. Ozonolysis cleavage of the alkene product **195** then produced aldehyde **184** in moderate yield. This was then transformed towards the natural product (-)-clausenamide **175a**.



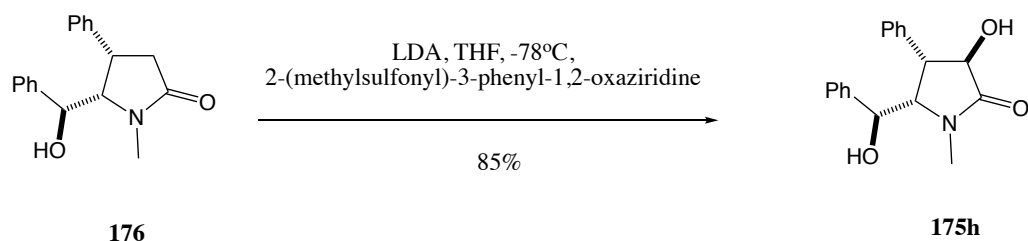
Scheme 3.27: Yakura *et al.* total synthesis of (-)-clausenamide **175a**.

And finally, Zhang *et al.* accomplished an enantioselective synthesis of (+)-*epi*-clausenamide **175h** and its C3-deoxy derivative **176** via a ‘scaffold hopping’ approach by converting a tetramate scaffold to a pyrroglutamate derivative.⁷⁰ **Scheme 3.28** shows the synthesis of the C3-deoxy analogue of (-)-*epi*-clausenamide **176**. This synthesis was achieved by reacting *N*-Boc-protected-*O*-silylated-L-serine **196** with Meldrum’s acid under EDCI/DMAP coupling conditions to form *O*-silyl protected tetramate, which was then subsequently reacted with TsCl to form tosylate **197** in 74% yield from L-serine **196**. Tetramate **197** was then reacted with phenylboronic acid under Suzuki-Miyaura cross-coupling conditions – using PdCl₂(dppp) and CsF – to furnish pyrrolidinone **198** in good yield. Pyrrolidinone **198** was then stereoselectively hydrogenated to form 4,5-*cis*-pyrrolidinone **199** and the Boc-protecting group was then removed with TFA and *N*-methylated using NaH and MeI to form pyrrolidinone **200**. The *O*-silyl protecting group was then removed with TBAF and then oxidised using Swern’s conditions to form an aldehyde, which was then reacted with a Grignard reagent, PhMgBr, to form the C3-deoxy analogue of (-)-*epi*-clausenamide **176**.



Scheme 3.28: Zhang *et al.* synthesis of C3-deoxy analogue of (-)-*epi*-clausenamide **176**.

Zhang *et al.* also accomplished the total synthesis of (+)-*epi*-clausenamide **175h**.⁷⁰ This was achieved by following the same synthetic procedure as outlined in **Scheme 3.28**, however, the D-form of serine **196** was used to provide the pre-requisite stereochemistry required across the pyrrolidinone core **176**. Pyrrolidinone **176** was then reacted with Davis' oxaziridine reagent to form (+)-*epi*-clausenamide **175h** in high yields (**Scheme 3.29**).

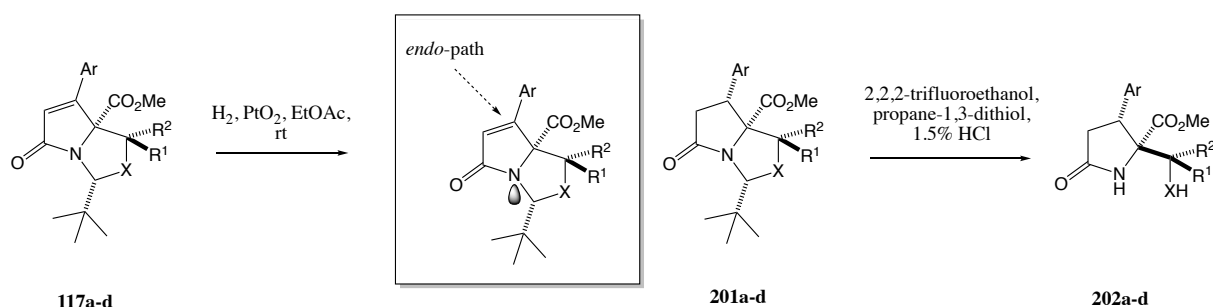


Scheme 3.29: Zhang *et al.* total synthesis of (+)-*epi*-clausenamide **175h**.

3.3.2: Rationale and Retrosynthetic Analysis Towards C3-Deoxy-Clausenamide

Intrigued by the 'scaffold hopping' approach as a synthetic methodology towards natural product synthesis as demonstrated by the work of Zhang *et al.*, of interest was to study whether this could be applicable to *allo*-phenylserine derived tetramic acids **134a**.⁷⁰ Bagum *et al.* had demonstrated that

bicyclic tetramates **11a-d** could be reacted with MsCl or TsCl to form mesylates **116a-d** or tosylates which could subsequently be reacted with substituted derivatives of phenylboronic acid to form pyroglutamates **201a-d** via the hydrogenation of the Suzuki products **117a-d** (Schemes 3.1 and 3.30).³⁵ The hydrogenation of the bicyclic lactam **117a-d** with PtO₂ was stereoselective and clearly preferred the *endo*-path, either due to the electrostatic repulsion of the nitrogen lone pair or due to the steric hinderance of the methyl ester and ^tBu groups.³⁵ *N,O/S*-acetal deprotection using Corey-Reichard's protocols produced the monocyclic pyrrolidinones **202a-d**.³⁵



Scheme 3.30: Bagum *et al.* synthetic methodology towards monocyclic pyrrolidinones **202a-d**.

Inspired by the 'scaffold hopping' approach, of interest was to look at tetramates **134a** which had a resemblance to the clausenamide family (Figure 3.21).

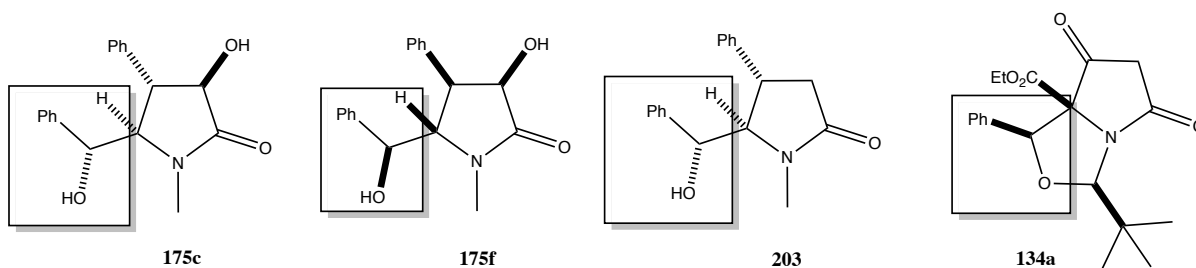


Figure 3.21: Structures of clausenamide compounds, **175c**, **175f**, **203** and bicyclic tetramate **134a** – with the rectangle highlighting the area of similarity.

Looking at the retrosynthetic analysis of pyrrolidinone **203** outlined in Figure 3.22, it was hypothesised that pyrrolidinone **203** could be synthesised from the *N,O*-acetal deprotection and subsequent *N*-methylation of pyrrolidinone **206**. Pyrrolidinone **206** could be synthesised from the hydrogenation,

saponification and subsequent decarboxylation of pyrrolidinone **205**. Suzuki coupling of mesylate **204** with phenylboronic acid can lead to the synthesis of **205**, and mesylate **204** can be synthesised from tetramate **134a**.

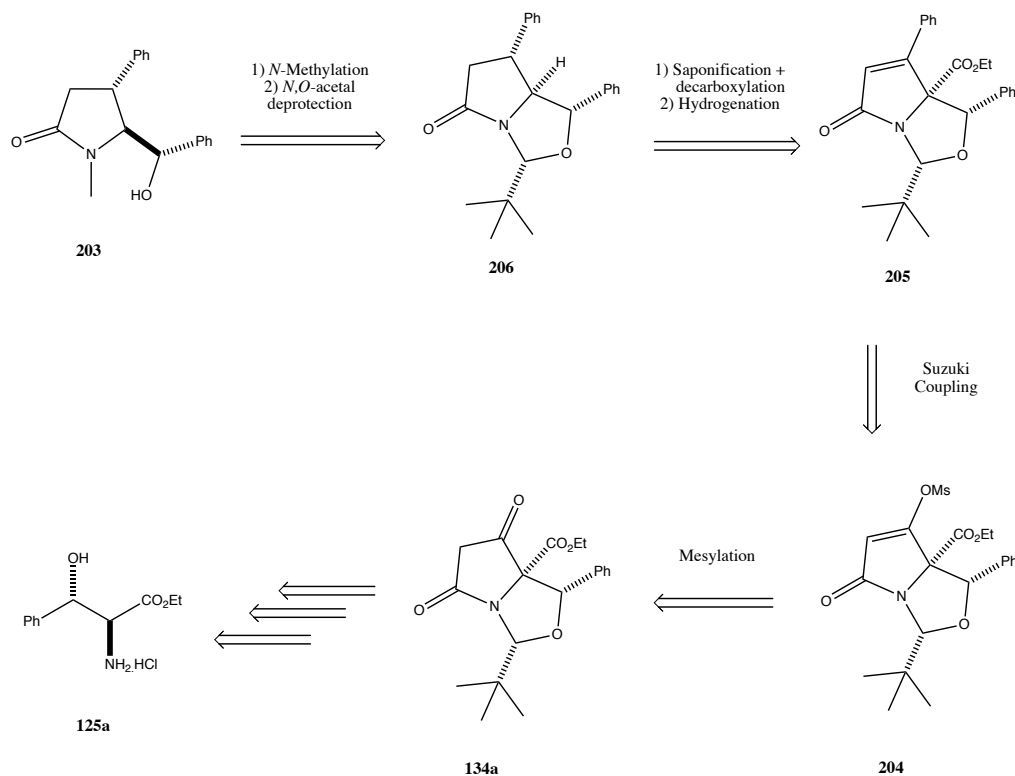


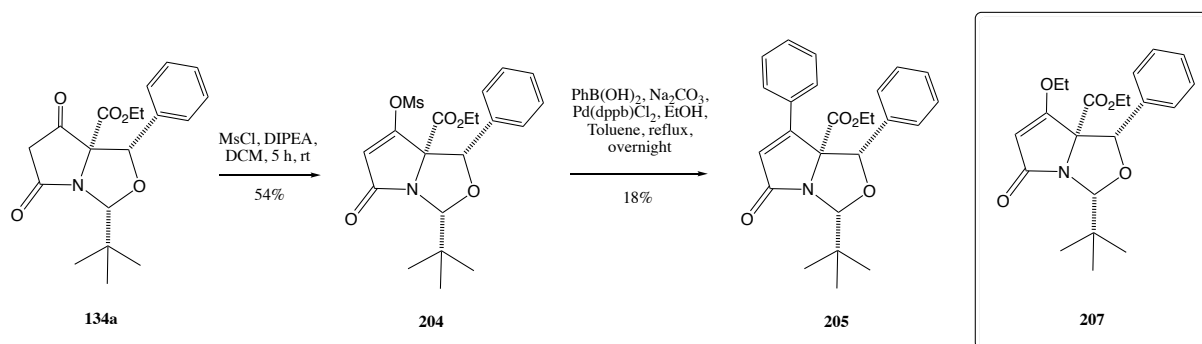
Figure 3.22: Retrosynthetic analysis towards the synthesis of C3-deoxy-clausenamide **203**.

3.3.3: Suzuki-Miyaura Cross-Coupling with Tetramic Acids

As a result, tetramate **134a** was reacted with MsCl under basic conditions to form mesylate **204**, using the reaction conditions of Bagum *et al.*³⁵, however, a maximum yield of 54% was achieved – similar to the maximum yield achieved by Bagum *et al.* (**Scheme 3.31**).³⁵ Mesylate **204** was stable to chromatographic purification and was easy to isolate, in addition to being stable in CDCl₃ solution for many months.

When mesylate **204** was then reacted with phenylboronic acid using the reaction conditions of Bagum *et al.*³⁵ – PdCl₂(dppb), Na₂CO₃ in a EtOH/toluene/H₂O solvent mixture – only a maximum yield of 18% was achieved for the Suzuki-Miyaura cross-coupling product **205**, in addition to the enol ether side-

product **207** that was not isolated but clearly detected in the mass spectrum of the crude product – and the formation of this side-product has been discussed in depth by Bagum *et al.*⁶³ Pyrrolidinone **205** could easily be isolated pure after chromatographic purification, however, the poor yields obtained for compound **205** significantly hampered the synthetic methodology towards the clausenamide family. Moreover, a lack of time did not permit us to optimise the reaction conditions to improve upon the maximum yield of the Suzuki-Miyaura cross-coupling reaction and as a result, this methodology was not investigated further.



Scheme 3.31: The synthesis of the Suzuki-Miyaura cross-coupling product **205** and the enol-ether side-product **207**.

3.4: Reduction of the Tetramate Bicyclic Core

Of interest was to investigate whether the ketone moiety of the tetramate core **134a** could be reduced diastereoselectively to produce novel hydroxylated pyrrolidinones **208**, which were similar to the core structure of the pseurotin natural product family that have vast biological activities, with an example being pseurotin A **209** which has antiparasitic, antioxidant, nematocidal, immunosuppressive and antibacterial activities amongst others.³¹ The similarities in the core structure of pyrrolidinone **208** and pseurotin A **209** was the phenyl ketone moiety and the hydroxyl group, highlighted with rectangles in **Figure 3.23**.

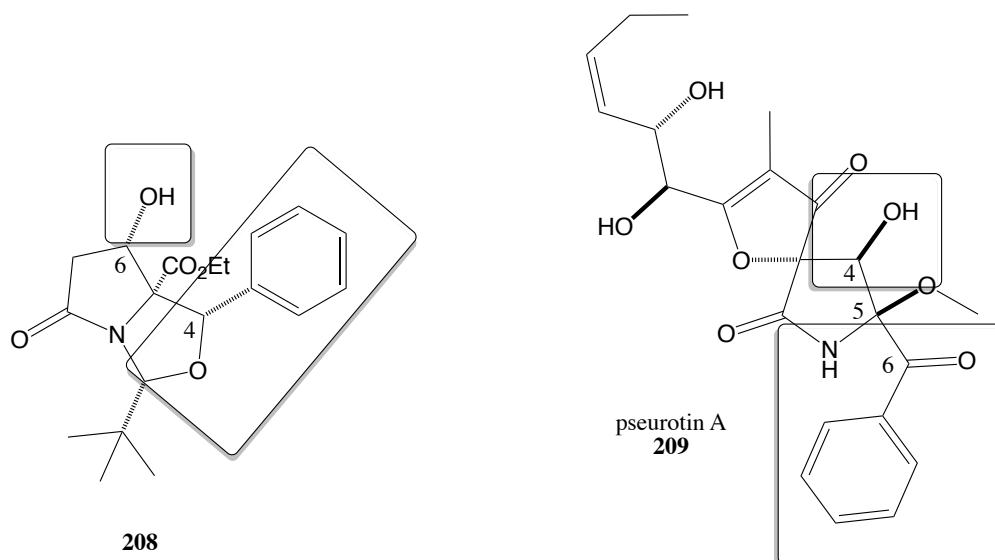
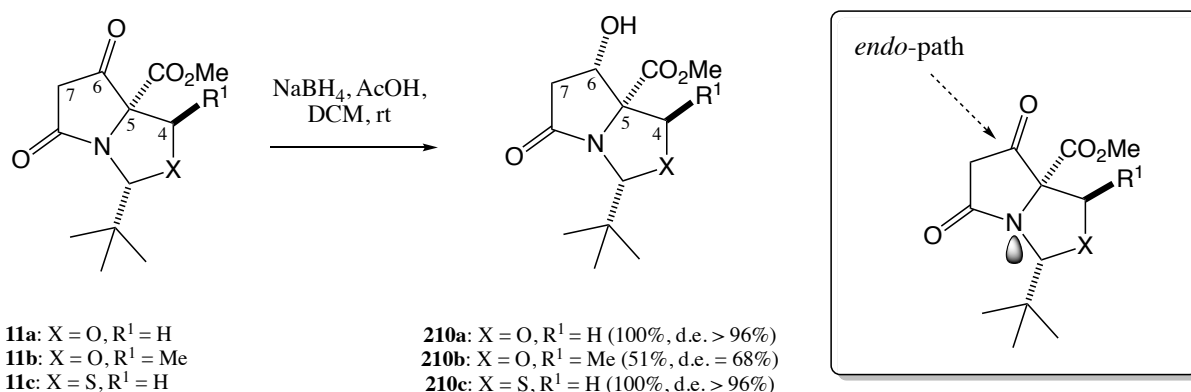


Figure 3.23: Structures of pyrrolidinone **208** and pseurotin A **209**.

3.4.1: Previous Work in the Moloney Group

Josa-Culleré *et al.* demonstrated that bicyclic tetramates **11a-c** derived from the methyl esters of L-serine **48a**, L-threonine **48b** and L-cysteine **48c** could be reduced with sodium acetoxyborohydride – which was generated *in-situ* – to give hydroxylated pyrrolidinones **210a-c** (Scheme 3.32).⁷¹ Although bicyclic tetramates **11a** and **11c** produced hydroxylated pyrrolidinones **210a** and **210c** diastereoselectively in quantitative yields – in which the diastereomeric excess (d.e.) was calculated to be over 96% – pyrrolidinone **210b** obtained from L-threonine **48b** was only obtained in 68% diastereomeric excess and in 51% yield.⁷¹ Additionally, tetramate **11b** required much longer reaction times – in which starting material was still present, even after a two-day reaction – whereas tetramates **11a** and **11c** only required 2 h to go to completion.⁷¹

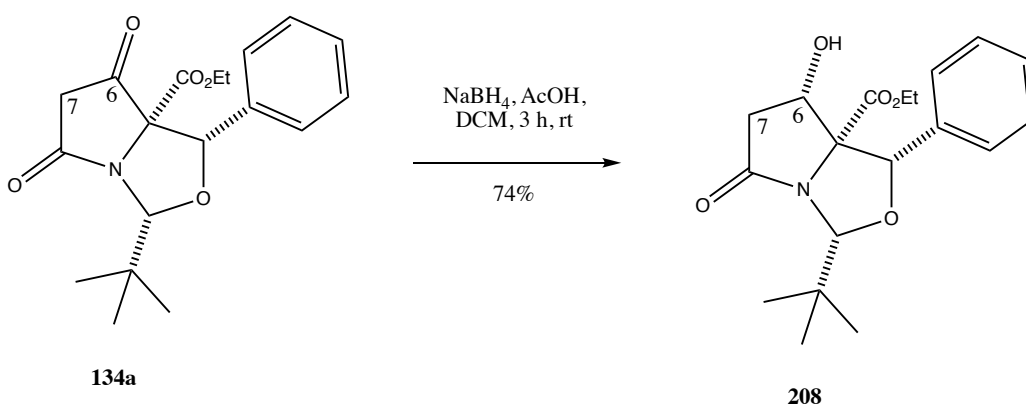
This indicated that the steric bulk at the C4-position of the bicyclic core via a methyl group could disrupt the diastereoselectivity and efficiency of the hydride addition.⁷¹ The diastereoselectivity of the hydride addition indicated that the *endo*-path was predominantly favoured to produce the *exo*-C6-hydroxylated pyrrolidines **210a-c** as the major products. This was possibly due to the methyl ester group at the C5-position sterically blocking access to the *exo*-attack or due to electrostatic repulsion from the nitrogen lone pair.⁷¹



Scheme 3.32: Reduction of tetramates **11a-c** with sodium acetoxyborohydride.

3.4.2: Reduction of the Tetramate Bicyclic Core

Due to the effect the C4-*endo*-methyl substituent **11b** has on the diastereoselectivity of the hydride addition, of interest was to study the effect the C4-*exo*-phenyl substituent **134a** might have on the hydride addition. Thus, tetramate **134a** was reacted with sodium acetoxyborohydride – generated *in-situ* – for 3 h, following the reaction conditions of Josa-Culleré *et al.*⁷¹ to form diastereoselective hydroxylated pyroglutamate **208** which was obtained in good yields and excellent diastereoselectivity – where its C6-epimer was not detected in the NMR spectrum (**Scheme 3.33**).



Scheme 3.33: Reduction of the tetramate core **134a** with sodium acetoxyborohydride.

The reaction was completed within 3 h, analogous to tetramates **11a/c** and this indicated that C4-functionalised bicyclic tetramates could be reduced diastereoselectively in high yields, so long as the C4-substituent was on the *exo*-face and not the *endo*-face of the bicyclic lactam – which was the case

for tetramate **11b**. The coupling constants for compound **208** at the C6 and C7-positions were very similar to that of pyrrolidinones **210a-c** (Table 3.18), and this indicated that pyrrolidinone **208** had the same relative stereochemistry as that of **210a-c**, and this was confirmed with a single-crystal X-ray structure of **208** (Figure 3.24).

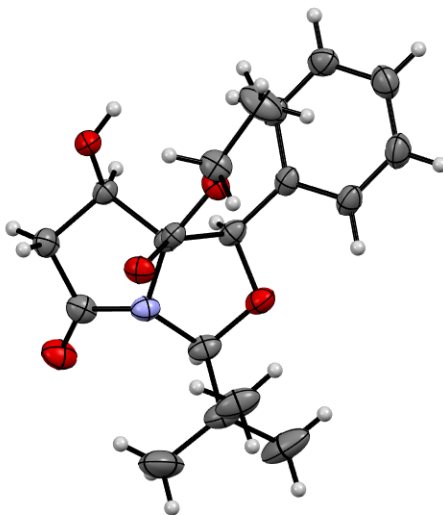


Figure 3.24: Single-crystal X-ray structure of C6-hydroxypyroglutamate **208**.

Compound	δ (ppm)						Yield (%)
	H6	H7	H7	$J_{\text{H6-H7}}$ (Hz)	$J_{\text{H6-H7}}$ (Hz)	$J_{\text{H7-H7}}$ (Hz)	
208	4.81	3.15	2.91	7.9	11.0	15.6	74
210a	4.56	3.15	2.81	8.0	10.5	15.5	100
210b	4.57-4.64	3.11	2.80	8.2	10.4	15.6	51
210c	4.43	2.98	2.74	8.0	10.5	15.5	100

Table 3.18: Key chemical shifts, coupling constants and yields of C6-hydroxylated pyrrolidinones **208** and **210a-c**. Data for **210a-c** was collected from *Synlett.*, 2016, **27**, 1677-1681.

3.5: Summary

This research has demonstrated that bicyclic tetramates **134** could be obtained from *erythro* phenylserine derivatives **125** and **174**. That the synthesis towards highly substituted tetramates **134** could be accomplished diastereoselectively and chemoselectively – in which the synthesis of malonamides **129** was obtained with excellent diastereoselectivity and the synthesis of tetramates **134**

was obtained chemoselectively. Due to the switch in chemoselectivity observed for the Dieckmann cyclisation, an extensive library of C7-carboxamides **157** could not be formed due to the poor yields obtained for C7-butyl ester tetramates **156**, however the synthesis of C7-acyltetramates **161** which had more resemblance to natural product tetramates could be synthesised in acceptable yields, enabling a compound library to be synthesised for antibacterial studies. Moreover, it has been shown that both C7-carboxamides **157** and C7-acyltetramates **161** can exist as a mixture of tautomers in solution and they also bind to metal ions after chromatographic purification, however a simple acid wash in the form of citric acid solution (aq.) is sufficient to remove metal ions from the tetramate core. Additionally, the bicyclic core **134** could be diastereoselectively reduced with sodium acetoxyborohydride to form hydroxylated pyroglutamates **208** in good yields. And finally, this project has demonstrated that C6-functionalised pyrrolidinones **205** could be synthesised via the Suzuki-Miyaura cross-coupling of C6-mesylates **204** with phenylboronic acid, albeit in poor yields, although with an extensive optimisation study, this yield could be improved upon further.

Chapter 4: Imidazolidine-Derived *N,N*-Bicyclic Tetramic Acids

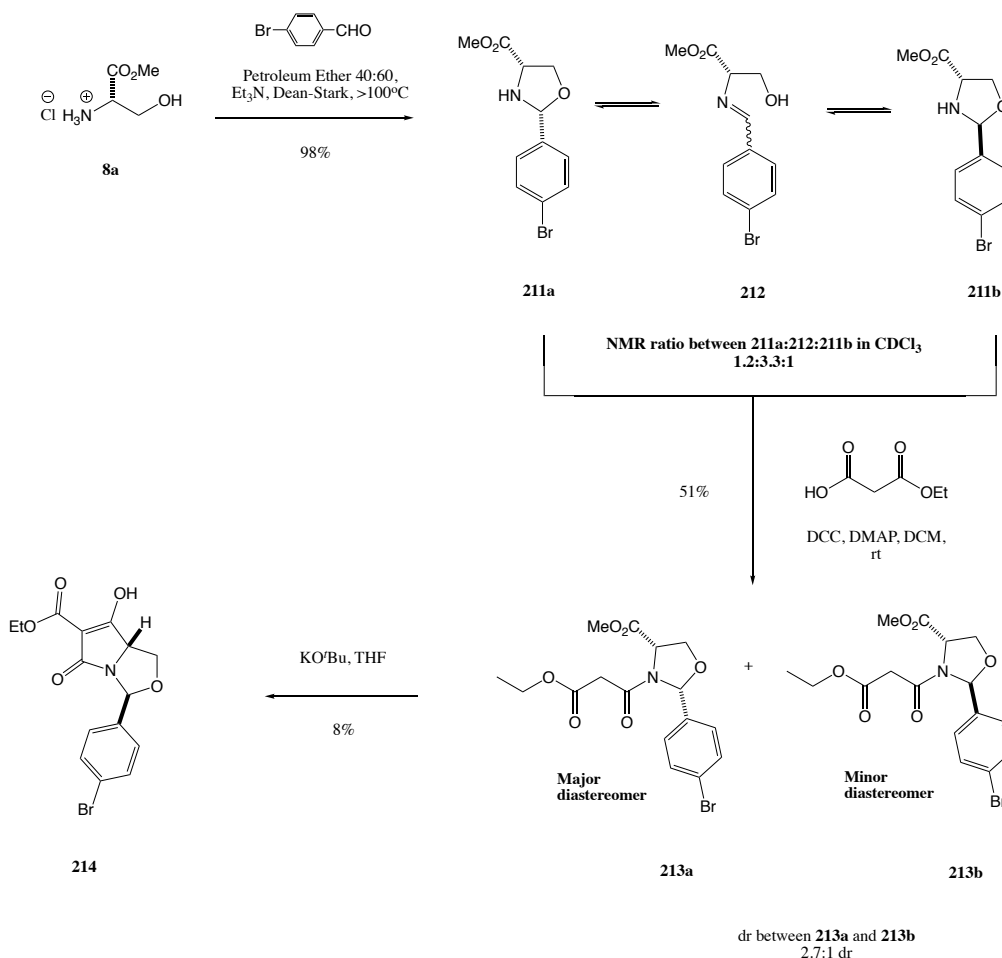
This chapter describes the various synthetic methodologies that were examined towards the synthesis of bicyclic tetramates that were functionalised at the C2-position while maintaining C4-aromatic functionalisation. Discussed firstly is the synthesis of *threo*-phenylserine-derived C2-functionalised tetramates (*N,O*-tetramates), in which the amino esters were condensed with aromatic aldehydes. Secondly, an attempted methodology for obtaining C2-functionalised tetramates (*N,S*-tetramates) using a thiazolidine template is also discussed via the synthesis of *allo/threo*-phenylcysteine derivatives. And lastly, imidazolidine-derived tetramic acids (or *N,N*-tetramates) – utilising a 1,3-dipolar cycloaddition – is discussed. Additionally, DFT calculations (conducted by Dr. Xiang Li) were carried out to understand the stereochemical outcomes of the diastereoselective synthesis of *N,N*-bicyclic tetramates.

4.1: Previous Work in the Moloney Group

Thus far, Dieckmann cyclisations have been limited to amino esters **82a-e**, **125a-f**, **174a-k** being condensed with pivaldehyde. Although the *tert*-butyl group was important for the control of the chemoselectivity, diastereoselectivity and stability of the products, in the case of medicinal chemistry however, it limited the ability to introduce chemical diversity at the C2-position. Of interest was to introduce various groups at the C2-position to permit adjustment of the physicochemical properties and to undertake a large SAR analysis to study the effect C2-functionalisation can have on antibacterial activity.

Panduwawala had demonstrated that L-serine methyl ester hydrochloride **8a** could be condensed with aromatic aldehydes to form unstable oxazolidines **211a-b** that were obtained as minor products, in addition to the ring-open imine **212** which was obtained as the major product – as detected in the NMR spectrum (**Scheme 4.1**).⁷² This was an interesting outcome as when L-serine methyl ester hydrochloride **8a** was condensed with pivaldehyde, oxazolidine **9a** was obtained exclusively in the ring-

closed form.³⁴⁻³⁵ This indicated that the planarity of the aromatic ring system at the C2-position compromises the stability of the oxazolidine ring, resulting in it being less favoured.⁷² However, it was theorised that the oxazolidine ring system could be 'locked' by reacting the secondary amine of the oxazolidine with ethyl hydrogen malonate using DCC/DMAP coupling conditions, thus driving the equilibrium between the oxazolidine **211a-b** and imine **212** towards the formation of the oxazolidine ring system.⁷² In this case, malonamides **213a-b** were obtained in 51% yield as a mixture of diastereomers, in which the 2,5-*cis* diastereomer was the major product (2.7:1 dr).⁷²



Scheme 4.1: The synthesis of bicyclic tetramate **214** from methyl ester hydrochloride **8a**.

It was believed that the 2,5-*cis* diastereomer was the more stable product as the substituents were in *pseudo*-equatorial positions, thus accounting for the diastereomeric preference.⁷² However, this result was in stark contrast to the *N*-acylation of oxazolidine **9a** that was condensed with pivaldehyde, in which malonamide **10a** was obtained mostly as a single 2,5-*cis* diastereomer (compare **Schemes 1.1**

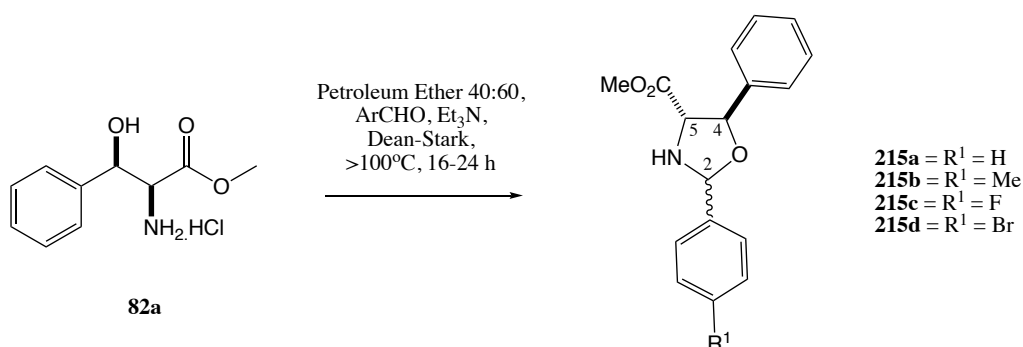
with **4.1**).³⁴⁻³⁵ The malonamide diastereomers **213a-b** were subjected to the Dieckmann cyclisation using KO^tBu, however, upon acidic workup of the reaction mixture, the product proved to be unstable.⁷² As a result, the crude mixture was directly purified on silica gel, and tetramate **214** was formed in 8% yield.⁷² Thus, it became apparent that the stability of these compounds was a significant drawback (**Scheme 4.1**) and that they were not suitable for the generation of compound libraries to be examined for possible antibacterial activity.^{44,72}

4.2: Synthesis of C2 and C4-Functionalised *N,O*-Bicyclic Tetramic Acids

It was not immediately obvious as to whether *threo*-phenylserine-derived tetramic acids could be functionalised at the C2-position and whether these bicyclic compounds would be stable enough to undertake a SAR analysis to assess for antibacterial activity. Thus, this was studied in detail.

4.2.1: Synthesis of Oxazolidines

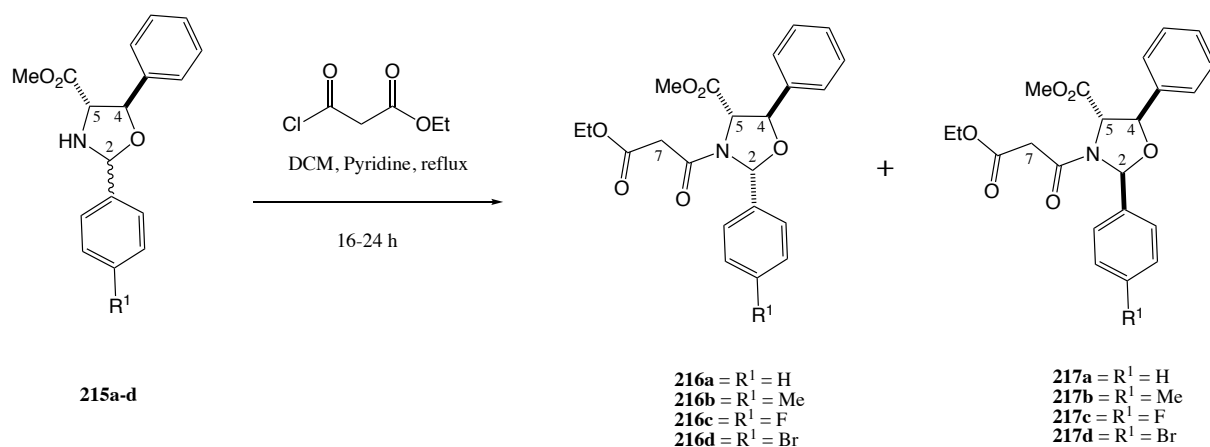
Threo-phenylserine methyl ester hydrochloride **82a** was condensed with benzaldehyde and *para*-substituted benzaldehydes to form oxazolidines **215a-d** using the established protocols outlined in **Chapters 2.2.2** and **3.2.2**. These compounds were not purified by column chromatography due to the possibility of retro-aldol decomposition occurring on silica gel as discussed by Lou *et al.*,⁵⁷ however excess aldehyde was always detected in the NMR spectra of the crude product, along with other unknown side-products, indicating poor conversion towards the desired products **215a-d**. As a result, yields were not determined at this stage and these oxazolidines **215a-d** were used in the crude form into the next reaction sequence.



Scheme 4.2: The synthesis of C2-functionalised oxazolidines **215a-d**.

4.2.2: Synthesis of *N*-Acylated Oxazolidines

Oxazolidines **215a-d** were then *N*-acylated under basic conditions to form malonamides **216a-d** and **217a-d** as roughly a 1:1 mixture of diastereomers at the C2-position (**Table 4.1**), with the 2,5-*cis* diastereomer **216a-d** being slightly more favoured than the 2,5-*trans* diastereomer **217a-d**. This was consistent with malonamides **86a-e/87a-e** that were derived from *threo*-phenylserine **82a-e** derivatives (compare **Tables 2.5** with **4.1**). When comparing the ^1H -NMR data for malonamides **216a-d/217a-d** with that of **86a-e/87a-e**, the H2 signals were invariably more downfield for malonamides **216a-d/217a-d**.



Scheme 4.3: The synthesis of malonamides **216a-d** and **217a-d** from oxazolidines **215a-d**.

Compound	2,5- <i>cis</i> diastereomer δ (ppm) ^a				Compound	2,5- <i>trans</i> diastereomer δ (ppm)				dr between 2,5- <i>cis/trans</i> ^b	Yield (%) ^c
	H2	H4	H5	$J_{\text{H4-H5}}$		H2	H4	H5	$J_{\text{H4-H5}}$		
216a	6.38	5.25	4.81	6.3	217a	6.30	5.18	4.64	8.1	1.6:1	14
216b	6.35	5.27	4.81	6.2	217b	6.28	5.17	4.63	8.2	1.1:1	43
216c	6.37	5.24	4.82	6.2	217c	6.32	5.18	4.65	8.0	1.1:1	49
216d	6.36	5.20	4.80	6.5	217d	6.29	5.18	4.64	8.0	1.6:1	25

Table 4.1: Key chemical shifts (δ), coupling constants (J) and diastereomeric ratio (dr) of 2,5-*cis/trans* malonamide diastereomers **216a-d/217a-d**; CDCl_3 solvent, 400 MHz; ^a Shown is the ^1H -NMR data for the major malonamide rotamer; ^b Determined from ^1H -NMR studies of the crude material; ^c Yield includes both diastereomers over two steps from amino ester **82a**.

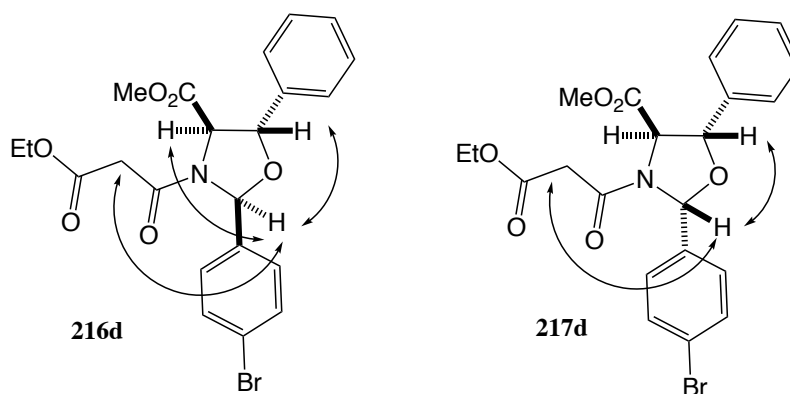


Figure 4.1: Relative stereochemistry of **216d** and **217d** assigned using nOe analysis.

nOe analysis was used to determine the relative stereochemistry for compounds **216a/d**, however this gave inconclusive results, but for compounds **217a/d**, this was more straightforward (**Figure 4.1**). However, the relative stereochemistry of malonamides **216a-d** and **217a-d** was confirmed from a single-crystal X-ray structure of compounds **216c** and **217c** (**Figure 4.2**). Based on these X-ray crystal structures and the similarities in the NMR data for the compound series (**Table 4.1**), it was assumed that the relative stereochemistry of malonamides **216a-d** and **217a-d** was that shown in **Figure 4.1**.

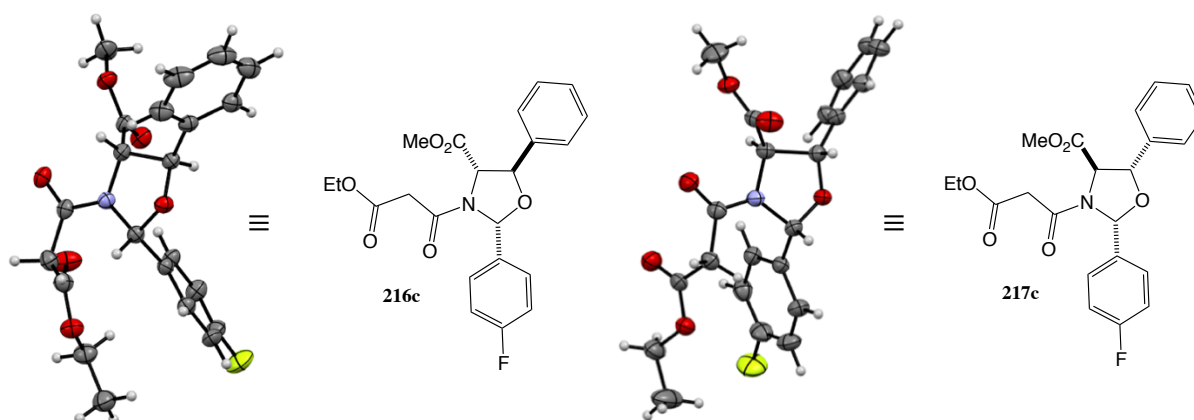


Figure 4.2: Single crystal X-ray structures of malonamides **216c** and **217c**.

Unlike the C2-*t*Bu series **86a-e/87a-e**, these malonamide diastereomers **216a-d/217a-d** were easier to separate by chromatographic purification and could be obtained in gram-scale quantities. Interestingly, however, the NMR spectra for malonamides **217a-d** in comparison to malonamides **87a-e** that had a *t*Bu substituent at the C2-position were very different. In the case of malonamides **217a-**

d, the NMR peaks were all sharp (**Figure 4.3**), but there was no presence of rotamers detected in the 2-D NOESY spectrum, whereas the NMR peaks for malonamides **87a-e** – particularly the oxazolidine ring protons – were very broad at room temperature but could be sharpened using low temperature VT-NMR experiments (compare **Figures 2.8** with **4.3**). The bulky ^tBu group at the C2-position for compounds **87a-e** was probably giving rise to this conformational dynamic, which was not seen for the planar aromatic ring substituents attached at the C2-position for malonamides **217a-d**. Moreover, it should be noted that malonamides **216a-d** existed as a pair of rotamers unlike **217a-d** (**Figure 4.4**). This was chiefly detected in the 2D-NOESY spectrum where various chemical exchange processes were detected that had the same sign as the diagonal peaks (red), whereas nOe cross peaks were of the opposite sign (blue). Additionally, 2,5-*cis* malonamides **10a-c** derived from the methyl ester derivatives of L-serine **48a**, L-threonine **48b** and L-cysteine **48c** have also been reported as a pair of rotamers as well.³⁵

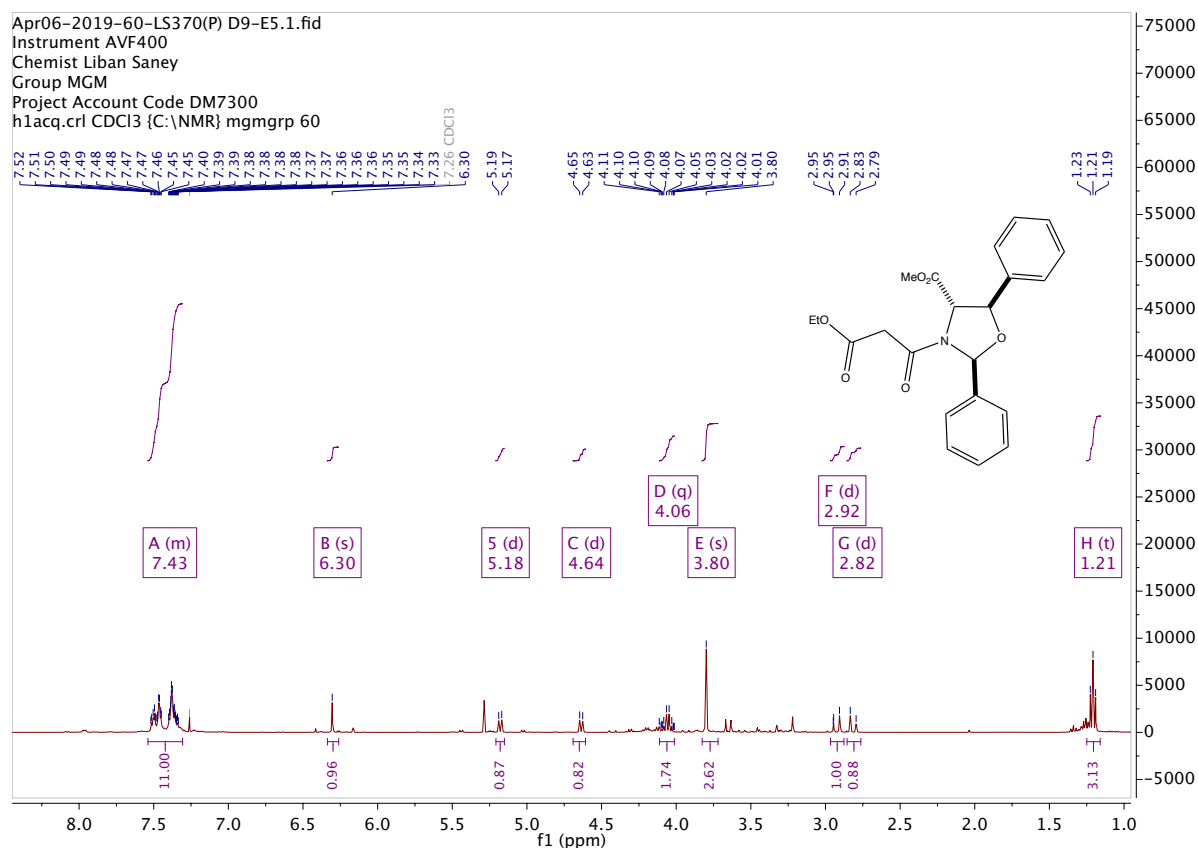


Figure 4.3: ¹H-NMR spectrum of malonamide **217a** at room temperature; CDCl₃ solvent, 400 MHz.

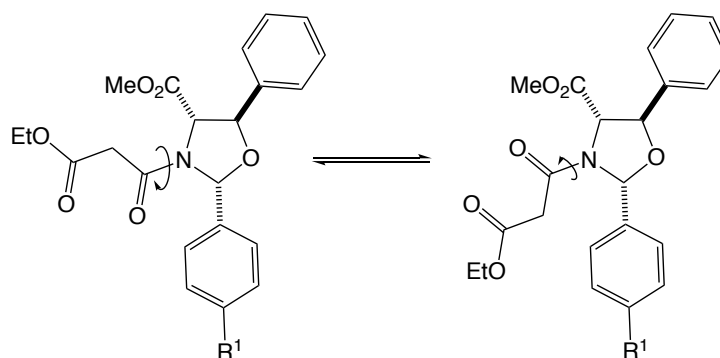
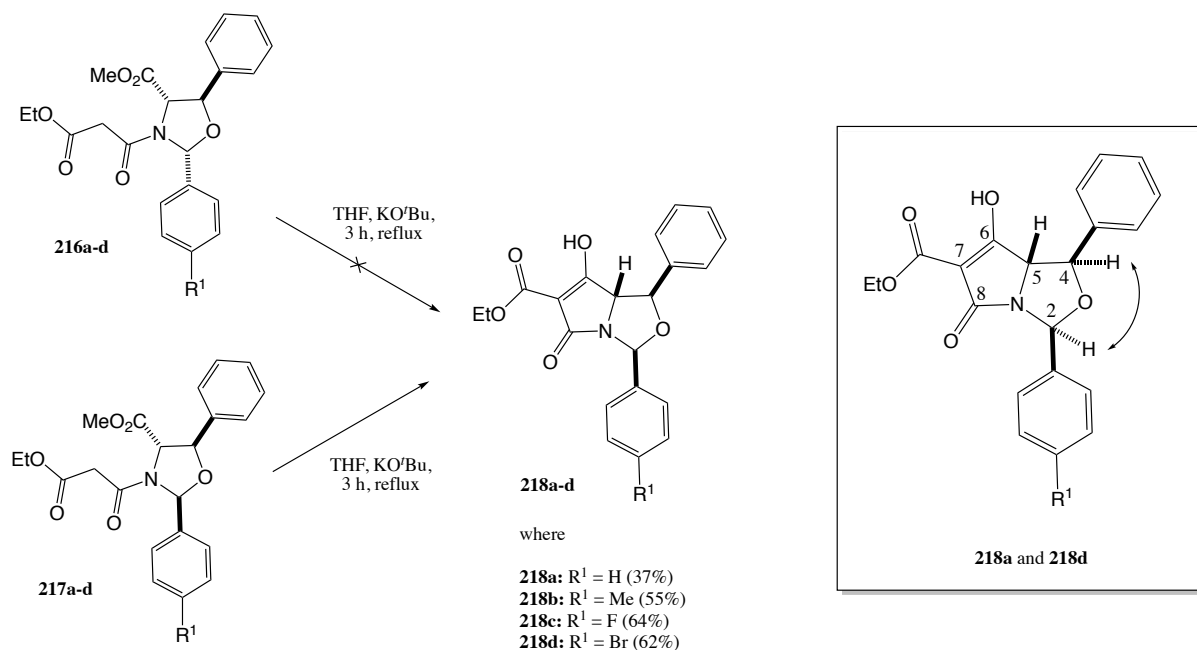


Figure 4.4: Rotameric exchange of malonamides **216a-d**.

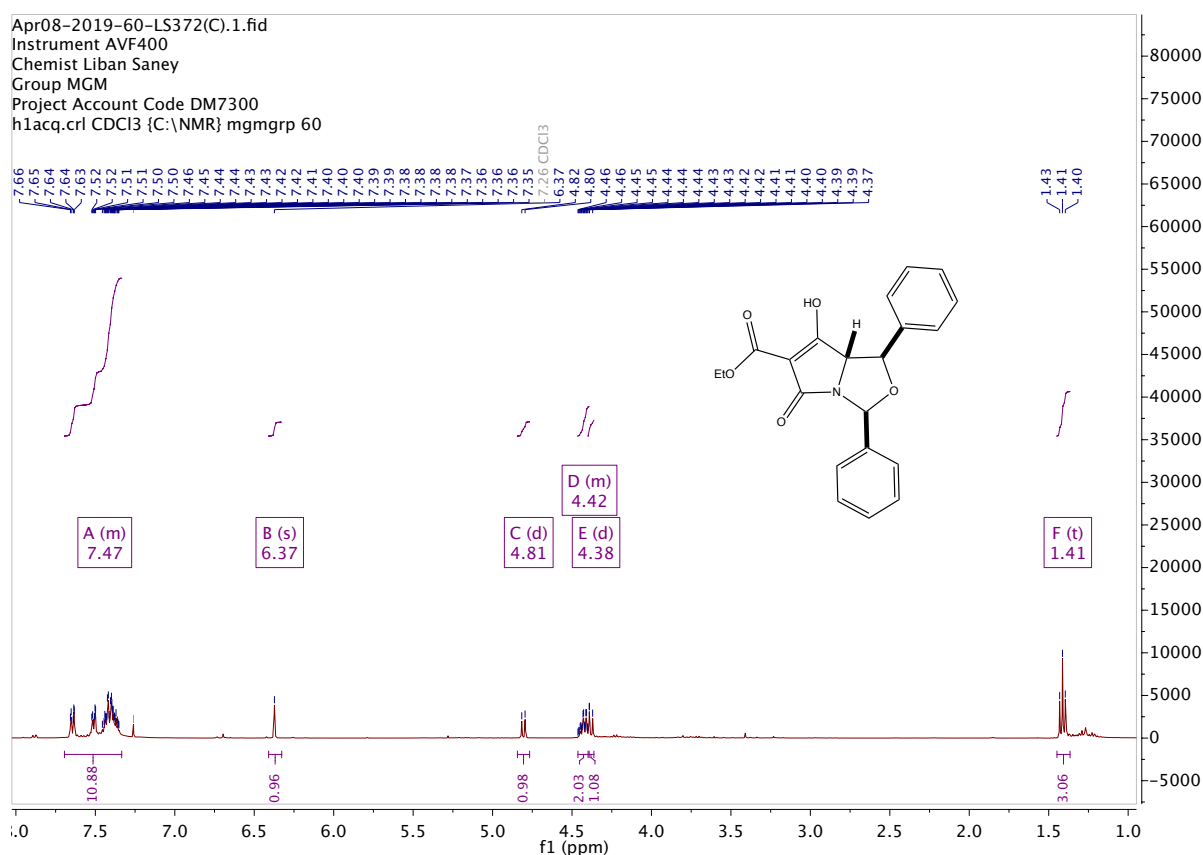
4.2.3: Synthesis of Tetramates

2,5-*cis* malonamides **216a/d** were subjected to the Dieckmann cyclisation using KO^tBu in THF (**Scheme 4.4**), but the ^1H -NMR spectrum of the crude material proved to be complex, indicating unknown side-products being formed. Additionally, none of the desired product was detected by mass spectroscopy. This was consistent with earlier findings that 2,5-*cis* malonamides **86a-e** were resistant to the Dieckmann cyclisation – and an in-depth discussion explaining the possible reasons is given in **Chapter 2.2.4**.

However, the 2,5-*trans* malonamides **217a-d** readily reacted with KO^tBu to give the desired tetramates **218a-d** in acceptable yields – typically between 37-64% – as the sole products (**Scheme 4.4**). These compounds were not purified on silica gel due to the problems encountered for tetramates **88a-e**, but the crude products were relatively pure by NMR analysis (**Figure 4.5**). The chemoselectivity of the Dieckmann cyclisation and the lack of diastereoselectivity of the *N*-acylation reaction of oxazolidines **215a-d** was consistent with that seen with the C2- ^tBu series for *threo*-phenylserine derived bicyclic tetramates **88a-e**. Additionally, the relative stereochemistry of tetramates **218a-d** was assigned using nOe spectroscopy (**Scheme 4.4**). The formation of tetramates **218a-d** was interesting as these tetramates **218a-d** proved to be stable after acidic workup and were obtained in acceptable yields in comparison to Panduwawala's attempt to obtain C2-functionalised tetramates **214** from L-serine **8a**. Moreover, the H2-signal for tetramates **218a-d** were invariably more downfield in comparison to the C2- ^tBu series **88a-e** (compare **Tables 2.6** with **4.2**).



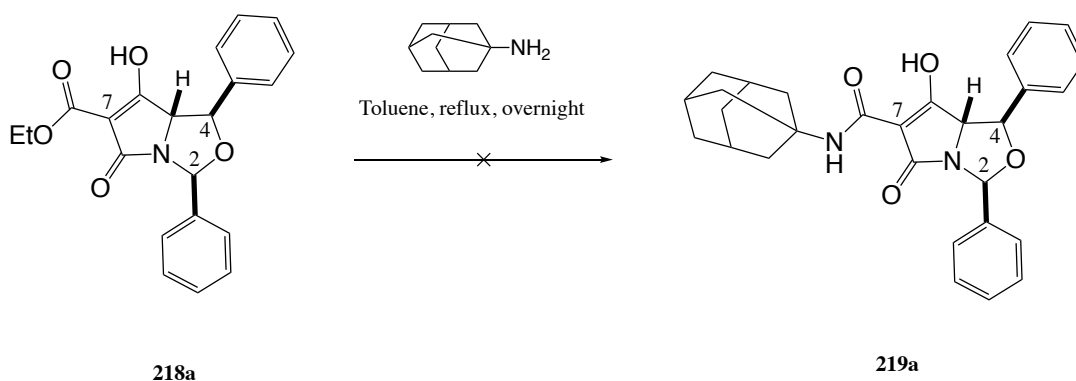
Scheme 4.4: The synthesis of tetramates **218a-d** from malonamides **217a-d** and the relative stereochemistry of tetramates **218a/d** assigned using nOe analysis.



Compound	R ¹	δ (ppm)				Yield (%)
		H2	H4	H5	J_{H4-H5} (Hz)	
218a	H	6.37	4.81	4.38	8.4	37
218b	Me	6.35	4.80	4.38	8.4	55
218c	F	6.32	4.80	4.37	8.4	64
218d	Br	6.30	4.80	4.35	8.4	62

Table 4.2: Key chemical shifts (δ), coupling constants (J) and yields of tetramates **218a-d**; CDCl₃ solvent, 400 MHz.

When tetramate **218a/d** was reacted with 1-adamantylamine using toluene as a solvent, the C7-carboxamide **219a/d** was not formed, and unidentified by-products were mostly obtained (**Scheme 4.5**). This nullified the synthetic approach towards making C2-functionalised tetramates from *threo*-phenylserine derivatives in which the C2, C4 and C7-substituents were all readily functionalised. Moreover, tetramates **218a-d** also proved to be very unstable, even in their solid form.



Scheme 4.5: The failed synthesis of C7-carboxamide **219a** from ethyl ester tetramate **218a**.

4.3: Attempted Synthesis of C2-Functionalised *N,S*-Bicyclic Tetramic Acids

It was theorised that the aryl substituents at the C2-position of tetramates **218a-d** compromised the stability of the *N,O*-hemiaminal, particularly when refluxing at high temperatures. However, thiazolidine templates are known to be approximately 10⁴ times more stable than oxazolidine derivatives due to the nucleophilicity of the sulphur lone pairs and the reduced steric strain of the sulphur atom in the ring system – thus aiding ring closure.⁴⁵ Thus, questions arose as to whether

thiazolidine-derived tetramic acids (also abbreviated as *N,S*-tetramates) of type **220** could be synthesised, in which the C2, C4 and C7-positions could all be readily functionalised in which the synthesis started with *threo*-phenylcysteine derivatives – as demonstrated by the retrosynthetic analysis shown in **Figure 4.6**.

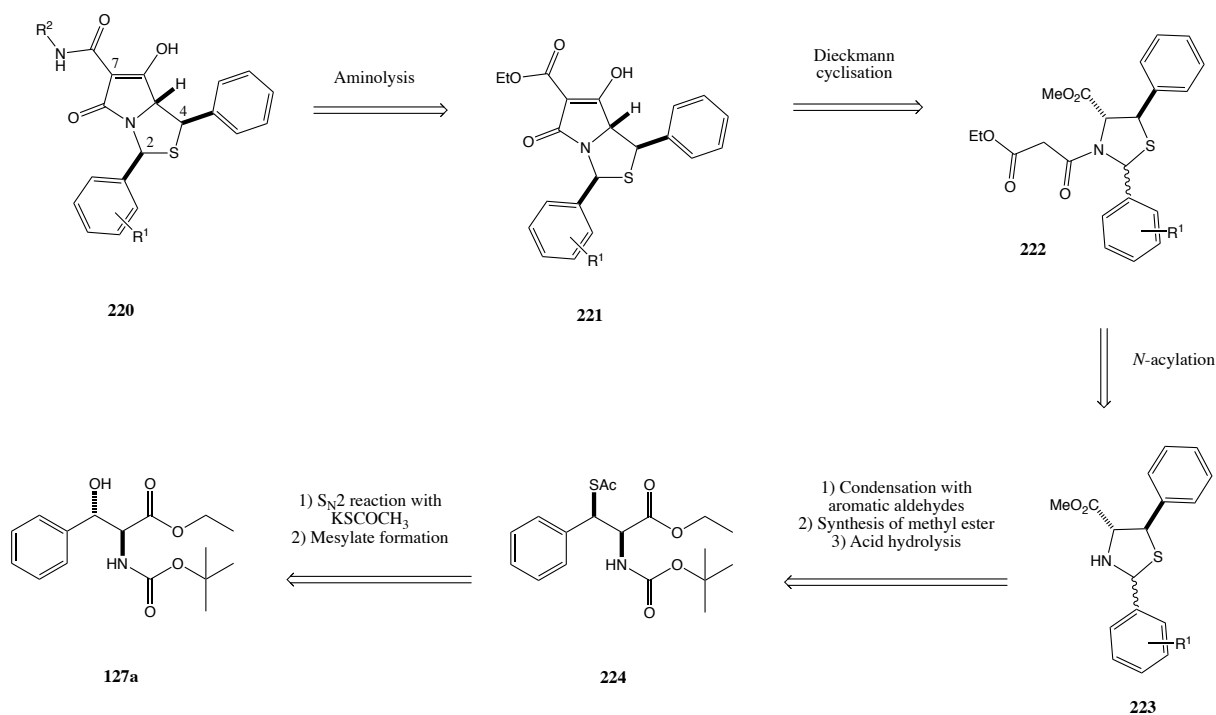
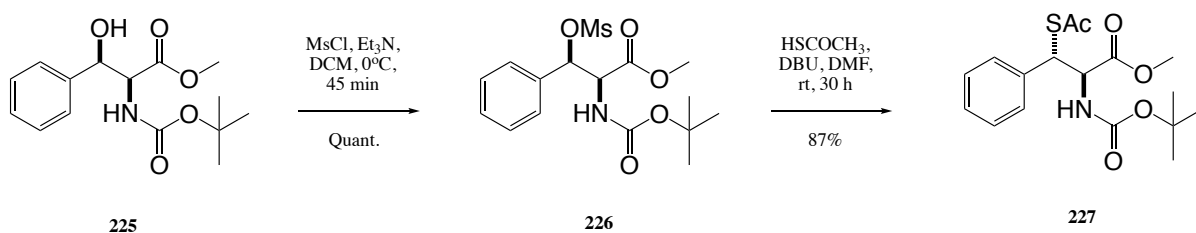


Figure 4.6: Retrosynthetic rationale towards the synthesis of multi-substituted tetramate **220**.

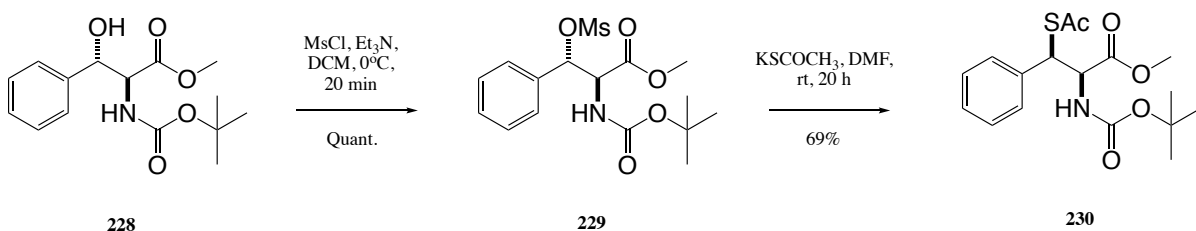
4.3.1: Literature Synthesis of *allo*/*threo*-Phenylcysteine

Lago *et al.* devised a stereoselective synthesis of *allo*-phenylcysteine via S_N2 reactions.⁷³ They achieved this by reacting Boc-protected *threo*-phenylserine **225** with mesyl chloride to form mesylate **226**, which was then subsequently reacted with thioacetic acid in DMF and DBU to form the *N,S*-protected *allo*-phenylcysteine **227** in 87% yield (**Scheme 4.6**).⁷³ However, the fact that this reaction explicitly required the use of the extremely malodorous thioacetic acid made this reaction extremely unappealing, and was not examined in this research.



Scheme 4.6: Lago *et al.* synthesis of *N,S*-protected *allo*-phenylcysteine **227**.

Lago *et al.* also synthesised *threo*-phenylcysteine by reacting Boc-protected *allo*-phenylserine **228** with mesyl chloride to form mesylate **229** in quantitative yields which was then subsequently reacted with potassium thioacetate to form *N,S*-protected *threo*-phenylcysteine **230** in good yield (**Scheme 4.7**).⁷³ As potassium thioacetate is an inorganic salt, it was believed that this would be a much better alternative than the malodorous thioacetic acid.

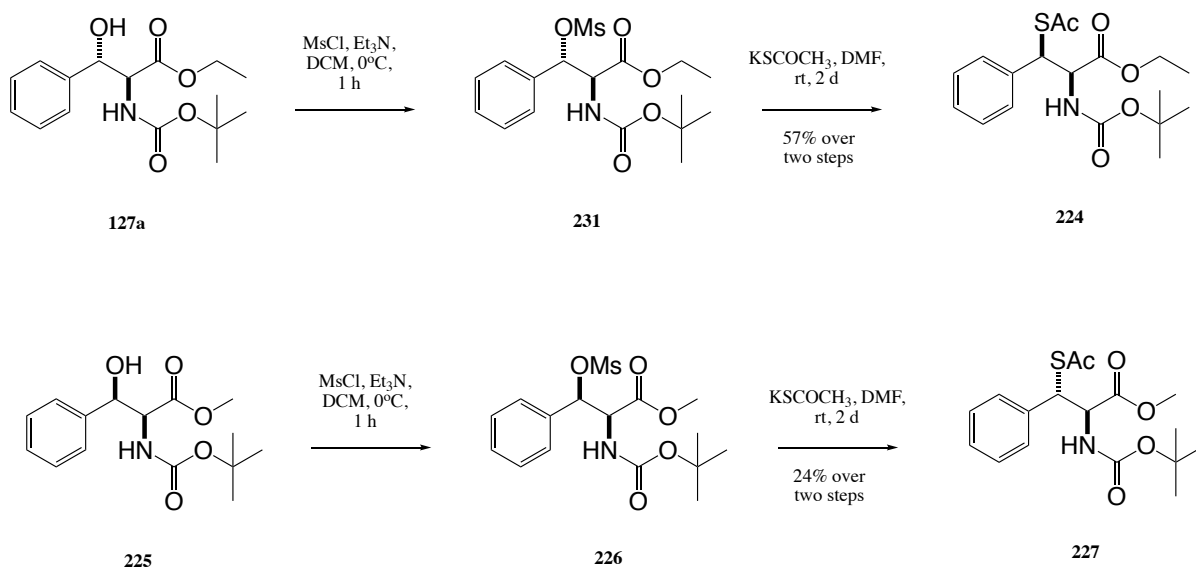


Scheme 4.7: Lago *et al.* synthesis of *N,S*-protected *threo*-phenylcysteine **230**.

4.3.2: Synthesis of *N,S*-Protected Phenylcysteine

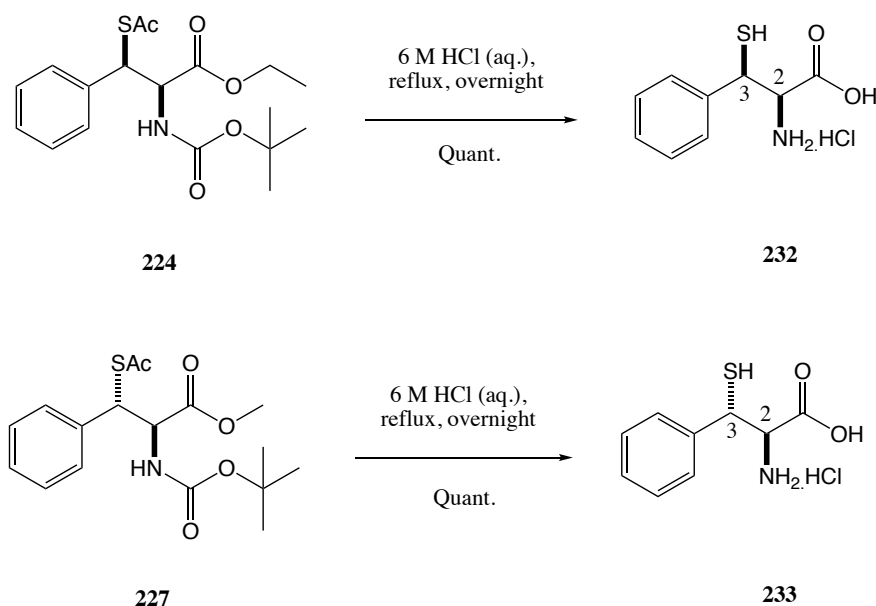
As a result, this research embarked upon the reproduction of the work of Lago *et al.* for the synthesis of *threo*-phenylcysteine. Thus, *allo*-phenylserine **127a** was reacted with mesyl chloride under basic conditions to form mesylate **231** in quantitative yields, although, **231** proved to be unstable – consistent with that reported in literature⁷³ – and was taken into the next reaction sequence in the crude form. Mesylate **231** was then reacted with potassium thioacetate to produce *N,S*-protected *threo*-phenylcysteine **224** in a maximum yield of 57% from phenylserine **127a**, however, the yields of these reactions varied substantially, and were typically formed between 15-30% (**Scheme 4.8**). Additionally, this reaction proved to be very malodorous in solution and thus, these two factors made

this synthetic methodology very unappealing. Moreover, Boc-protected *allo*-phenylcysteine **227** was also synthesised, however, even poorer yields were obtained from this synthesis (**Scheme 4.8**).



Scheme 4.8: Synthesis of *N,S*-protected-*threo*/allo-phenylcysteines **224** and **227** respectively.

The *N,S*-protected phenylcysteines **224** and **227** were then globally deprotected with 6 M HCl (aq.) to produce *threo*-phenylcysteine **232** and *allo*-phenylcysteine **233** in quantitative yields as their HCl salts (**Scheme 4.9**). The key chemical shifts and coupling constants are shown in **Table 4.3**.



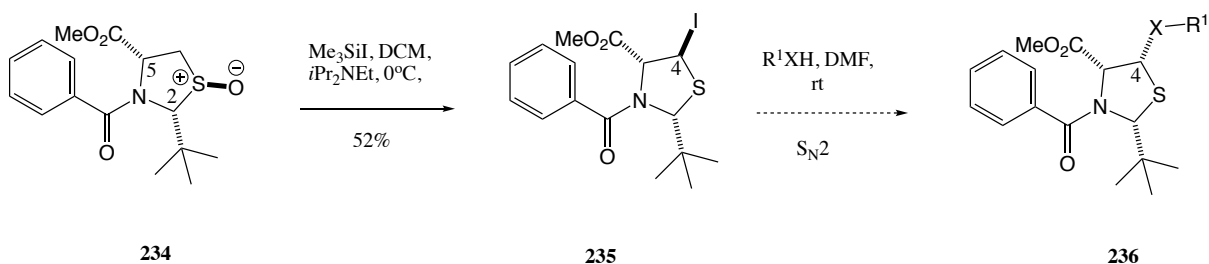
Scheme 4.9: Synthesis of *threo* and *allo*-phenylcysteine hydrochloride salt **232** and **233** respectively.

Compound	δ (ppm)					Yield (%)
	H2	H3	J_{H2-H3} (Hz)	C2	C3	
232	4.44	4.73	6.7	59.7	43.1	Quant.
233	4.38	4.74	6.2	60.1	42.3	Quant.

Table 4.3: Key chemical shifts, coupling constants and yields of *threo* and *allo*-phenylcysteine hydrochloride salt **232/233**; D₂O solvent, 400 MHz.

4.3.3: Alternative Methodology Towards C4-Functionalised Thiazolidines

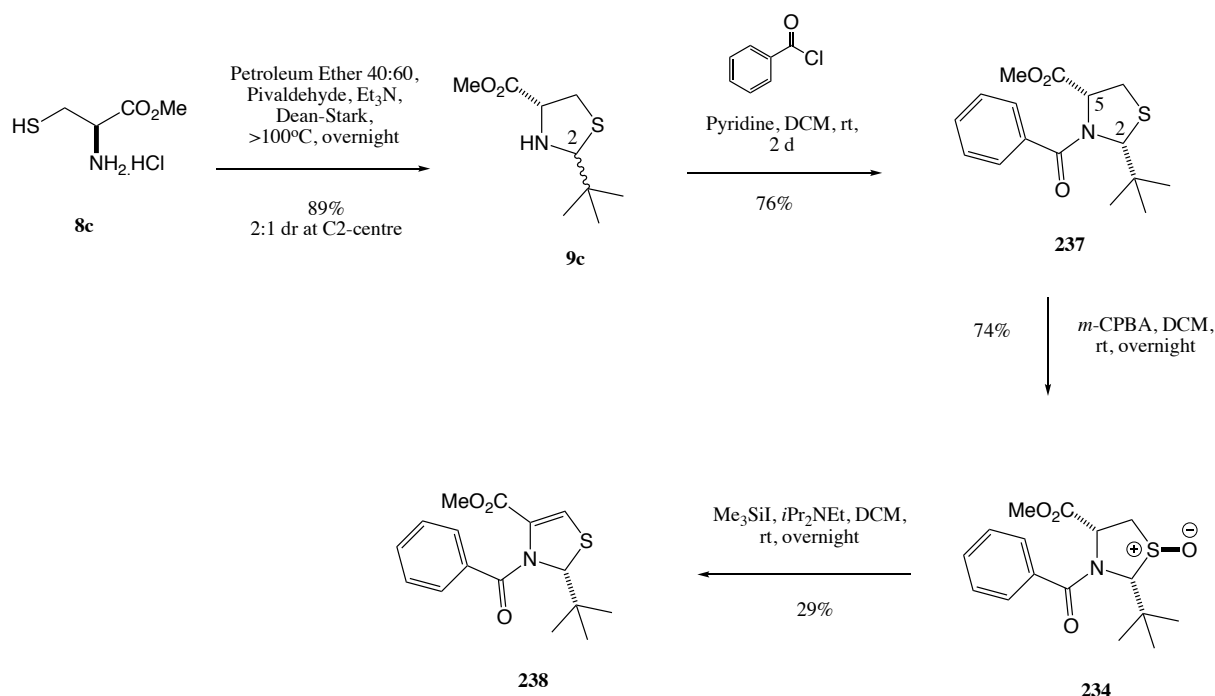
Due to the malodorous synthesis and low yields of *N,S*-protected-*threo*-phenylcysteine **224** from Boc-protected *allo*-phenylserine **127a**, of interest was a better methodology for the synthesis of C4-functionalised thiazolidine derivatives. Tokitoh *et al.*⁷⁴ synthesised C4-functionalised thiazolidines **235** via a silicon-Pummerer rearrangement of thiazolidine-S-oxides **234**. This had captured our attention, particularly as it enabled an iodine substituent to be attached at the C4-position, potentially allowing S_N2 reactions to take place, enabling compound libraries to be established at the C4-position of thiazolidines **236** (Scheme 4.10).



Scheme 4.10: Tokitoh *et al.* synthesis of C4-iodothiazolidine **235** from thiazolidine-S-oxide **234**.

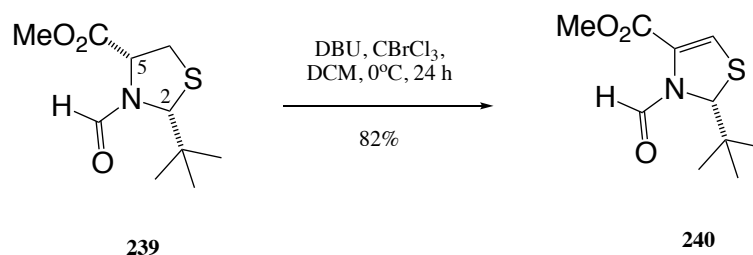
Thus, this research embarked upon the synthesis of thiazolidine-S-oxide **234**. Firstly, L-cysteine methyl ester hydrochloride **8c** was reacted with pivaldehyde to form thiazolidine **9c** in excellent yields as a mixture of diastereomers at the C2-position using the established protocols in Chapters 2.2.2 and 3.2.2 (Scheme 4.11).³⁵ Thiazolidine **9c** was then *N*-acylated with benzoyl chloride to form thiazolidine **237** as a single diastereomer – although the peaks in the NMR spectrum were very broad at room

temperature, which was attributed to rotameric effects. It was assumed that the relative stereochemistry was 2,5-*cis* based upon previous literature precedent for the *N*-acylation of thiazolidines.⁷⁴⁻⁷⁶ This compound **237** was then oxidised at room temperature with *m*-CPBA to form the sulfoxide **234** in good yield – although again, the NMR peaks were very broad at room temperature. However, when sulfoxide **234** was reacted with Me₃SiI at room temperature, instead of the literature reaction temperature of 0°C overnight, olefin **238** was obtained in 29% yield – tentatively assigned by NMR and mass spectroscopy – instead of the desired C4-iodothiazolidine **235**, along with an unknown side-product (**Scheme 4.11**).



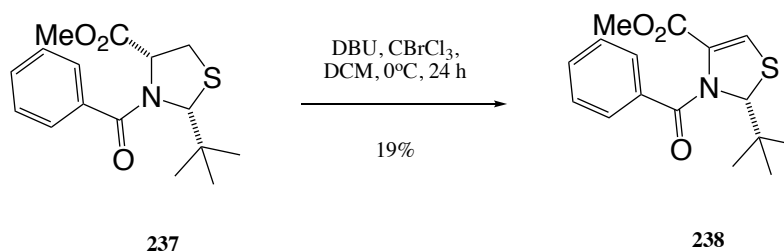
Scheme 4.11: The synthesis of olefin **238** from L-cysteine methyl ester hydrochloride **8c**.

It was believed that the olefin product **238** arose from elimination of the iodo-substituent from thiazolidine **235**. However, as this was a tentative assignment – in which there was no literature data to allow for comparison – we decided to synthesise olefin **238** via a different synthetic methodology. Gracia-Vitoria *et al.*⁷⁶ demonstrated that *N*-formyl thiazolidines **239** could be reacted with CBrCl₃ and DBU to form olefin **240** in excellent yields (**Scheme 4.12**).



Scheme 4.12: Gracia-Vitoria *et al.* synthesis of olefin **240**.

Thus *N*-benzoylated thiazolidine **237** was reacted with CBrCl_3 and DBU for 24 h at 0°C , following Gracia-Vitoria *et al.* synthesis to form olefin **238** in 19% yield (**Scheme 4.13**).⁷⁶ The NMR spectroscopic data in addition to the mass spectroscopic data was in agreement with the earlier synthesis of olefin **238** from **Scheme 4.11**, thus confirming that the alkene product was indeed formed.



Scheme 4.13: Synthesis of olefin **238** from *N*-benzoylated thiazolidine **237**.

Thus, due to the difficulties encountered towards functionalising the C4-position of thiazolidines either by means of making phenylcysteines from the mesylates of phenylserine or by introducing C4-functionality via the $\text{S}_{\text{N}}2$ reactions of C4-iodothiazolidines, there was a significant barrier towards functionalisation of the C4-position of thiazolidines. Additionally, due to a lack of synthetic methodologies that were available in literature,⁷⁷ in which the synthesis of C4-functionalised thiazolidine derivatives was relatively straightforward, rapid, diastereoselective and not malodorous, we discontinued with this approach towards making highly substituted tetramic acids from thiazolidine templates, in which the C2, C4 and C7-positions were all simultaneously functionalised. Additionally, it has recently been discovered that thiazolidine-derived tetramic acids of type **41** (**Chapter 1**) can be metabolised in the liver of rats as the sulphur atom is oxidised to either the sulfoxide or sulfone, again, making this approach less appealing.

4.4: Synthesis of C2 and C4-Functionalised *N,N*-Bicyclic Tetramic Acids

What has received little attention in the Moloney group was tetramic acids that were derived from imidazolidine scaffolds of type **241** (also abbreviated *N,N*-tetramates) (**Figure 4.7**). As thiazolidines are known to be more stable than oxazolidine derivatives,⁴⁵ questions arose as to where imidazolidine derivatives might fit in this spectrum. Additionally, due to the difficulties of introducing functionality within the thiazolidine template, of interest was the facile synthesis of imidazolidine-derived tetramic acids, which would allow functionality to be introduced at the C2, C4 and C7-positions. Moreover, these *N,N*-bicyclic tetramates would be a higher homologue of densely functionalised multi-substituted tetramic acids which could be readily amenable to an extensive SAR analysis to study for antibacterial activity.

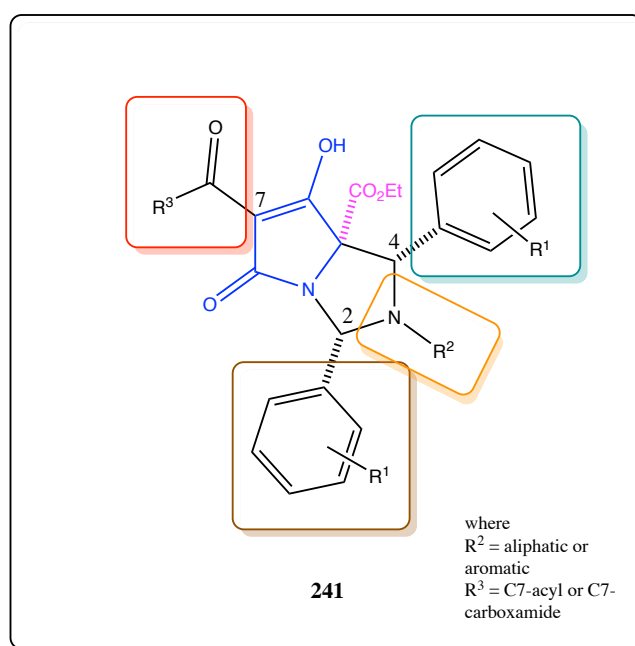
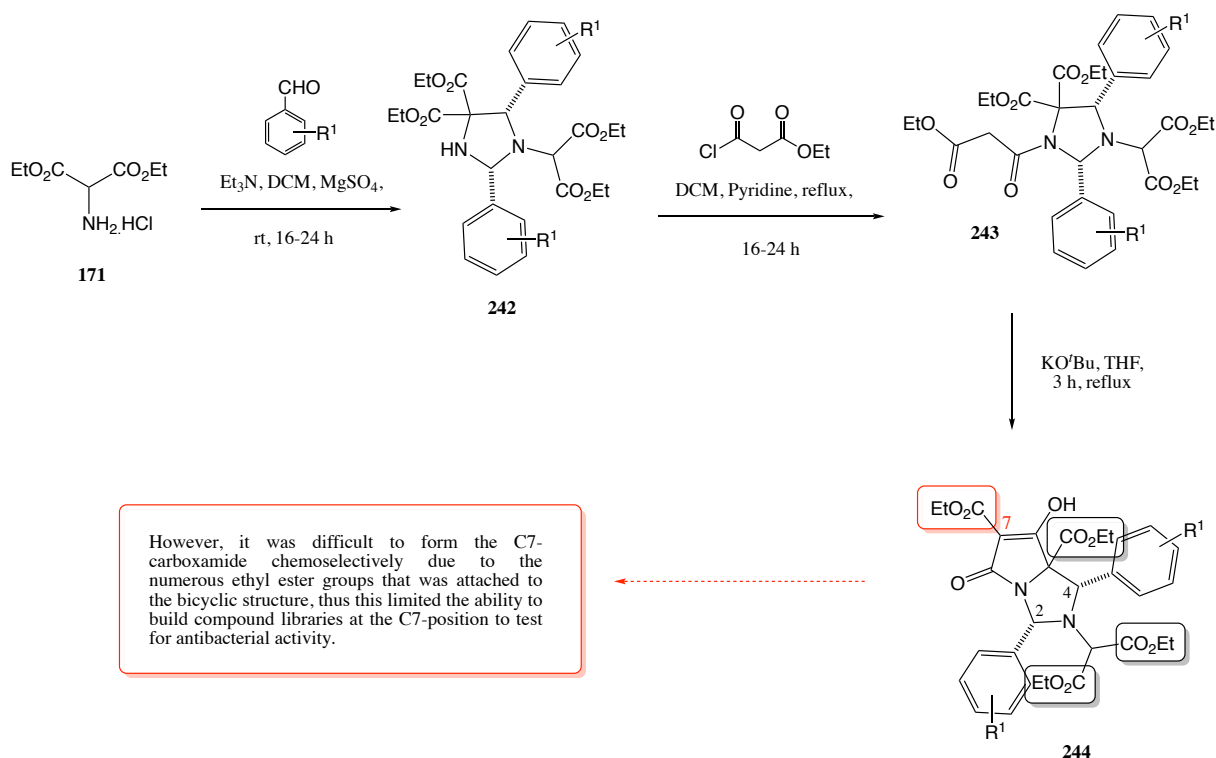


Figure 4.7: Imidazolidine-derived tetramic acids **241** of interest in this research project.

4.4.1: Previous Work in the Moloney Group

O'Shaughnessy had previously demonstrated that tetramates could be derived from imidazolidine scaffolds.⁷⁸ This was done by reacting diethyl aminomalonate hydrochloride **171** with substituted benzaldehydes to form C2 and C4-functionalised imidazolidine derivatives **242** in good yields and high diastereoselectivity (**Scheme 4.14**) via a 1,3-dipolar cycloaddition – this work has also been carried out

by other researchers such as Zhu *et al.*⁷⁹ These imidazolidines **242** were then *N*-acylated with ethyl malonyl chloride to form malonamides **243** in good yields which were then subjected to the Dieckmann cyclisation to form *N,N*-bicyclic tetramates **244**. Thus, this key piece of research demonstrated that imidazolidine-derived tetramic acids **244** could be synthesised in three synthetic steps in a diastereoselective fashion, whereby the C2 and C4-positions of the imidazolidine ring system could be functionalised with aromatic substituents. However, the main drawback to this synthesis was the numerous ethyl ester substituents that were attached to the bicyclic lactam **244**. Thus, it was not possible to chemoselectively form C7-carboxamides via aminolysis reactions to assess for antibacterial activity.



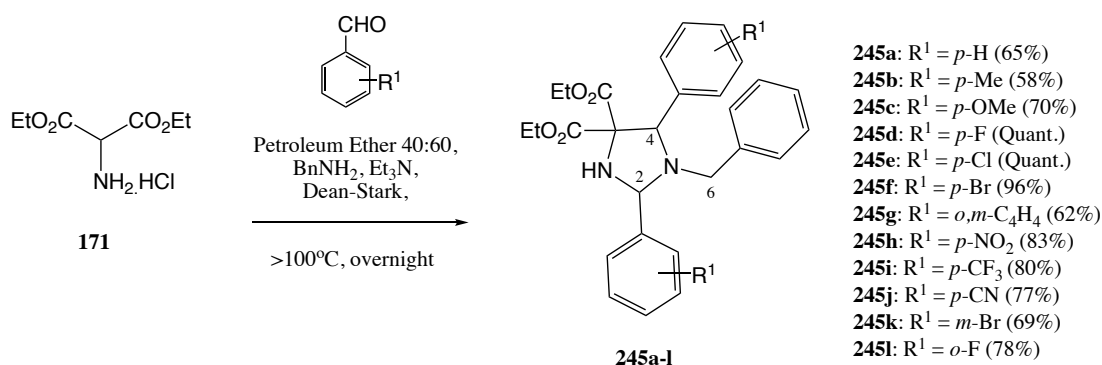
Scheme 4.14: O'Shaughnessy synthesis of *N,N*-bicyclic tetramates **244** from diethyl aminomalonate hydrochloride **171**.

4.4.2: Synthesis of Imidazolidines

Of interest was to remove the ethyl ester groups attached at the N3-position of the bicyclic core **244**, and to do so, the imidazolidine synthesis had to be modified. This research embarked upon a one-pot, three component 1,3-dipolar cycloaddition whereby diethyl aminomalonate hydrochloride **171**, 2 eq.

of substituted benzaldehydes and benzylamine were reacted under basic conditions and heated to more than 100°C in a Dean-Stark trap to form imidazolidines **245a-l** (**Scheme 4.15**) as either a single diastereomer or as a mixture of diastereomers (**Table 4.4, *vide infra***) – taking inspiration from the work of Nagao *et al.*⁸⁰

In the case of imidazolidine **245a**, a single crystal X-ray structure was obtained which confirmed the relative stereochemistry of the major diastereomer that was assigned by nOe studies – in which the relative stereochemistry was assigned to be 2,4-*cis* (**Figure 4.8**). Additionally, the spectroscopic data for **245a** matched literature data from the work of Nagao *et al.*⁸⁰ This enabled the spectroscopic data for the rest of the 2,4-*cis* imidazolidine series to be assigned based upon comparison with imidazolidine **245a** (**Table 4.4**). NMR data and the X-ray crystal structures of imidazolidines **245b**, **245e-f** also confirmed the presence of the 2,4-*trans* diastereomer (**Figure 4.8**).



Scheme 4.15: One-pot, three-component 1,3-dipolar cycloaddition towards the synthesis of imidazolidines **245a-l**.

While these imidazolidines **245a-l** could be purified by chromatographic purification, the diastereomers were often inseparable. It must also be noted that these compounds were surprisingly non-polar and often co-eluted with the aldehyde starting material and the imine side-product that was formed. Pleasingly however, these imidazolidines **245a-l** were stable to chromatographic purification, unlike the oxazolidine series. Interestingly, the electron-withdrawing substituents attached at the C2 and C4-positions were more downfield than the electron-donating substituents when looking at the

^1H -NMR data and additionally, the 2,4-*trans* diastereomers at the C2 and C4-positions were invariably more downfield compared with the 2,4-*cis* diastereomers (**Table 4.4**).

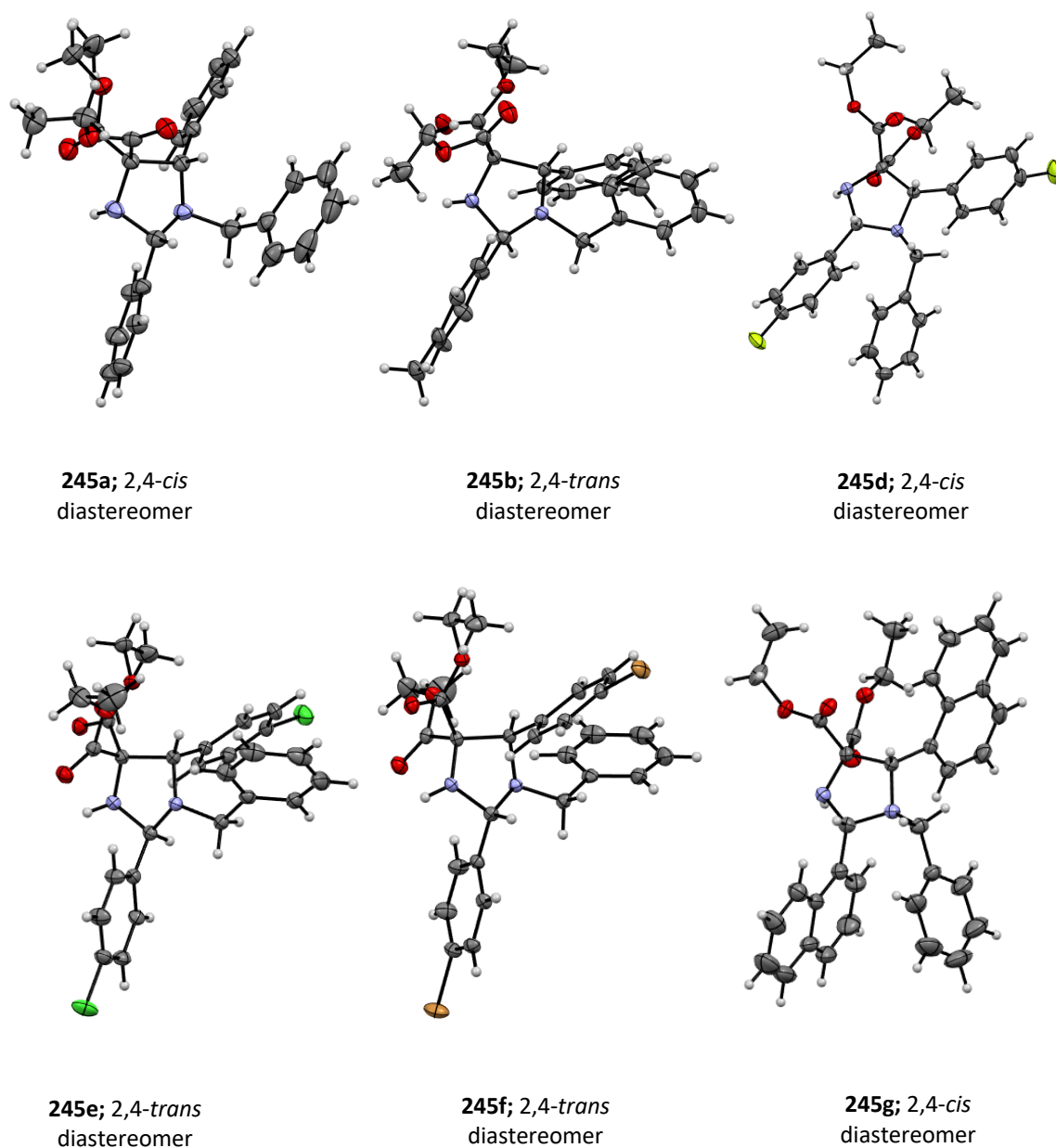


Figure 4.8: Single-crystal X-ray structures of imidazolidines **245a-b**, **245d-g**.

Interestingly, the methylene ethyl ester peaks were all distinctly diastereotopic in the ^1H -NMR spectra of the imidazolidine series **245a-l** (**Figure 4.9**).

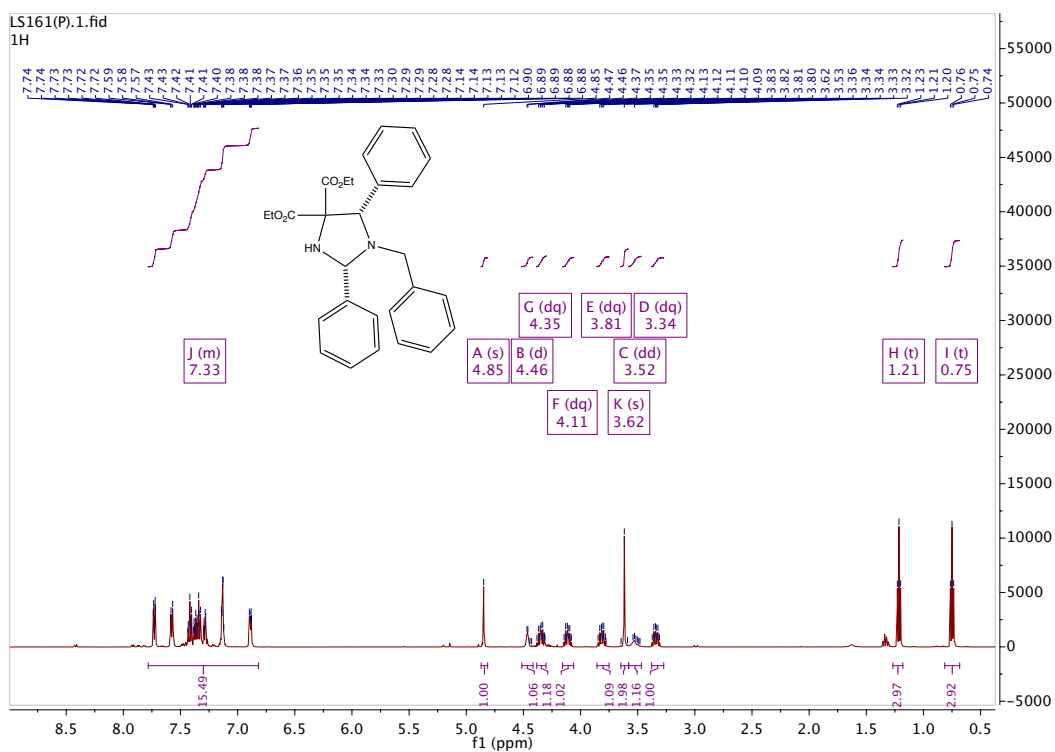


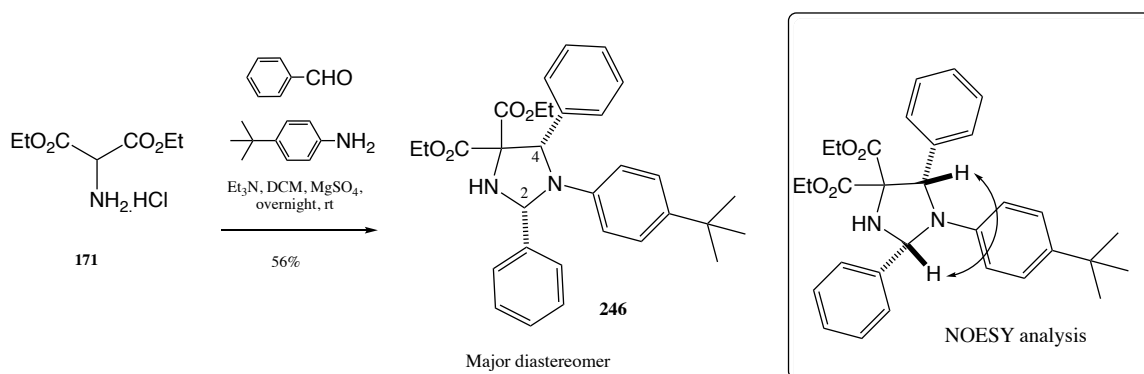
Figure 4.9: ^1H -NMR spectrum of 2,4-*cis* imidazolidine **245a**, showing the distinct diastereotopic methylene protons of the ethyl esters; CDCl_3 solution, 500 MHz.

Compound	R^1	2,4- <i>cis</i> diastereomer δ (ppm)					2,4- <i>trans</i> diastereomer δ (ppm)					dr between 2,4- <i>cis/trans</i> ^a	Yield (%) ^b
		H2	H4	H6	H6	$J_{\text{H6-H6}}$	H2	H4	H6	H6	$J_{\text{H6-H6}}$		
245a	<i>p</i> -H	4.46	4.85	3.62	n.d. ^c	n.d. ^c	5.19	5.14	2.98	3.50	14.2	2.3:1	65
245b	<i>p</i> -Me	4.41	4.76	3.58	n.d. ^c	n.d. ^c	5.10	5.07	2.95	3.46	14.2	1:1.9	58
245c	<i>p</i> -OMe	4.38	4.74	3.56	n.d. ^c	n.d. ^c	-	-	-	-	-	>94:6	70 ^d
245d	<i>p</i> -F	4.42	4.80	3.53	3.54	14.0	5.12	5.09	2.92	3.45	14.2	2.9:1	Quant.
245e	<i>p</i> -Cl	4.42	4.79	3.53	3.57	14.0	5.11	5.08	2.93	3.46	14.2	1:2.3	Quant.
245f	<i>p</i> -Br	4.42	4.78	3.53	3.58	14.0	5.10	5.07	2.94	3.46	14.3	1:2.6	96
245g	<i>o,m</i> -C ₄ H ₄	5.42	5.98	3.79	3.82	13.8	6.22	6.42	3.31	3.74	14.1	1:3	62
245h	<i>p</i> -NO ₂	4.62	4.97	3.55	3.59	13.6	5.33	5.25	2.95	3.48	14.3	1:1.1	83
245i	<i>p</i> -CF ₃	4.55	4.92	3.55	3.61	13.8	5.27	5.21	2.96	3.51	14.3	1:2.4	80
245j	<i>p</i> -CN	4.54	4.90	3.52	3.58	13.6	5.25	5.18	2.93	3.49	14.2	1.9:1	77
245k	<i>m</i> -Br	4.34	4.77	3.60	n.d. ^c	n.d. ^c	5.13	5.05	2.98	3.52	14.1	1:2.2	69
245l	<i>o</i> -F	4.92	5.30	3.63	n.d. ^c	n.d. ^c	-	-	-	-	-	>19:1	78 ^d

Table 4.4: Key chemical shifts, coupling constants, diastereomeric ratio (dr) and yields of imidazolidines **245a-l**; CDCl₃ solvent, 400 MHz; ^a Determined from ¹H-NMR studies of the crude material; ^b Yields include both diastereomers, however, at times, it was also contaminated with the imine side-product and aldehyde starting material; ^c n.d = not detected as the methylene benzyl protons were not diastereotopic; ^d Yield is only for a single diastereomer.

Thus, the modified synthesis towards making imidazolidine derivatives **245a-l** proved to be very successful, as the N3-substituents that had the ethyl esters **242** attached in the case of O'Shaughnessy's work could easily be replaced with a benzyl group. The mixture of diastereomers obtained was a concern, but it was hoped that after the *N*-acylation of these imidazolidines, that a single diastereomer – 2,4-*cis* – would predominantly form, based upon the work of Seebach *et al.*⁷⁵ – a termed which he coined the “*cis* effect” – and as a result, the mixture of diastereomers was taken into the next reaction sequence.

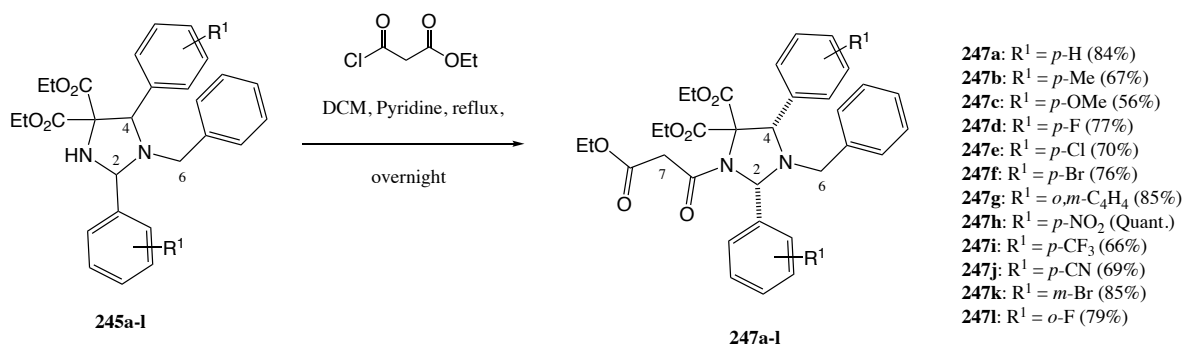
Additionally, Liu *et al.* had demonstrated that an aryl substituent could be attached at the N3-position, by reacting diethyl aminomalonate **171** with 2 eq. of substituted benzaldehydes and substituted anilines to form imidazolidines in good yields and good enantioselectivity, but moderate diastereoselectivity.⁸¹ Thus, as a model study and taking inspiration from the work of Liu *et al.*, diethyl aminomalonate **171** was reacted with 2 eq. of benzaldehyde and 4-*tert*-butylaniline under basic conditions to form 2,4-*cis* imidazolidine **246** in 56% yield with an acceptable level of diastereoselectivity observed (4:1 dr) – in which the NOESY analysis indicated the relative stereochemistry of the major diastereomer being the 2,4-*cis* diastereomer (**Scheme 4.16**). Additionally, it was shown that heating to more than 100°C in a Dean-Stark trap was not necessary for the cycloaddition reaction to occur and that using O'Shaughnessy's reaction conditions – in which the use of anhydrous MgSO₄ instead of a Dean-Stark apparatus – could enable these reactions to occur under milder reaction conditions.



Scheme 4.16: The synthesis and relative stereochemistry of imidazolidine **246**.

4.4.3: Synthesis of *N*-Acylated Imidazolidines

Imidazolidines **245a-l** were then *N*-acylated with ethyl malonyl chloride to form malonamides **247a-l** as single diastereomers in good to excellent yields (**Scheme 4.17**, **Table 4.5**). This was a pleasing outcome as this showed Seebach's "*cis* effect" could be applied to our work. Moreover, this methodology showed that 2,4-aryl substituted malonamides **247a-l** could be obtained diastereoselectively in 2 synthetic steps from commercially available, cheap starting materials, allowing ample scope for SAR analysis to take place to study the effect C2, C4 and N3-functionalisation can have on antibacterial activity.



Scheme 4.17: Synthesis and yields of malonamides **247a-l** from imidazolidines **245a-l**.

The relative stereochemistry of **247a-d**, **247f** and **247h** was established by nOe studies (**Figure 4.10**) and this was confirmed with various X-ray crystal structures of malonamides **247a**, **247c-d** and **247l** (**Figure 4.11**). As a result, it was assumed that the rest of the malonamide series had the same relative stereochemistry due to NMR spectroscopic consistencies (**Table 4.5**).

Compound	R ¹	δ (ppm)								Yield (%)
		H2	H4	H6	H6	J_{H6-H6}	H7	H7	J_{H7-H7}	
247a	<i>p</i> -H	5.37	4.42	3.63	3.49	14.9	2.89	2.64	15.7	84
247b	<i>p</i> -Me	5.29	4.34	3.63	3.46	14.9	2.91	2.63	15.7	67
247c	<i>p</i> -OMe	5.28	4.31	3.61	3.46	14.8	2.91	2.64	15.7	56
247d	<i>p</i> -F	5.36	4.39	3.58	3.49	14.8	2.87	2.68	15.7	77
247e	<i>p</i> -Cl	5.34	4.38	3.57	3.47	14.8	2.88	2.70	15.6	70
247f	<i>p</i> -Br	5.34	4.38	3.57	3.49	14.8	2.89	2.72	15.6	76
247g	<i>o,m</i> -C ₆ H ₄	6.50	5.55	3.67	3.47	14.9	2.86	2.55	15.8	85
247h	<i>p</i> -NO ₂	5.55	4.64	3.59	n.d. ^a	n.d. ^a	2.84	n.d. ^b	n.d. ^b	Quant.
247i	<i>p</i> -CF ₃	5.46	4.54	3.58	3.53	14.7	2.87	2.71	15.4	66
247j	<i>p</i> -CN	5.45	4.53	3.56	3.51	14.7	2.83	2.72	15.0	69
247k	<i>m</i> -Br	5.32	4.38	3.60	3.53	14.7	2.88	2.74	15.7	85
247l	<i>o</i> -F	5.89	4.85	3.58	n.d. ^a	n.d. ^a	3.04	2.72	15.8	79

Table 4.5: Key chemical shifts, coupling constants and yields of malonamides **247a-l**; CDCl₃ solvent, 400 MHz; ^a not detected as the benzyl methylene protons were not diastereotopic; ^b not determined due to a broad multiplet peak.

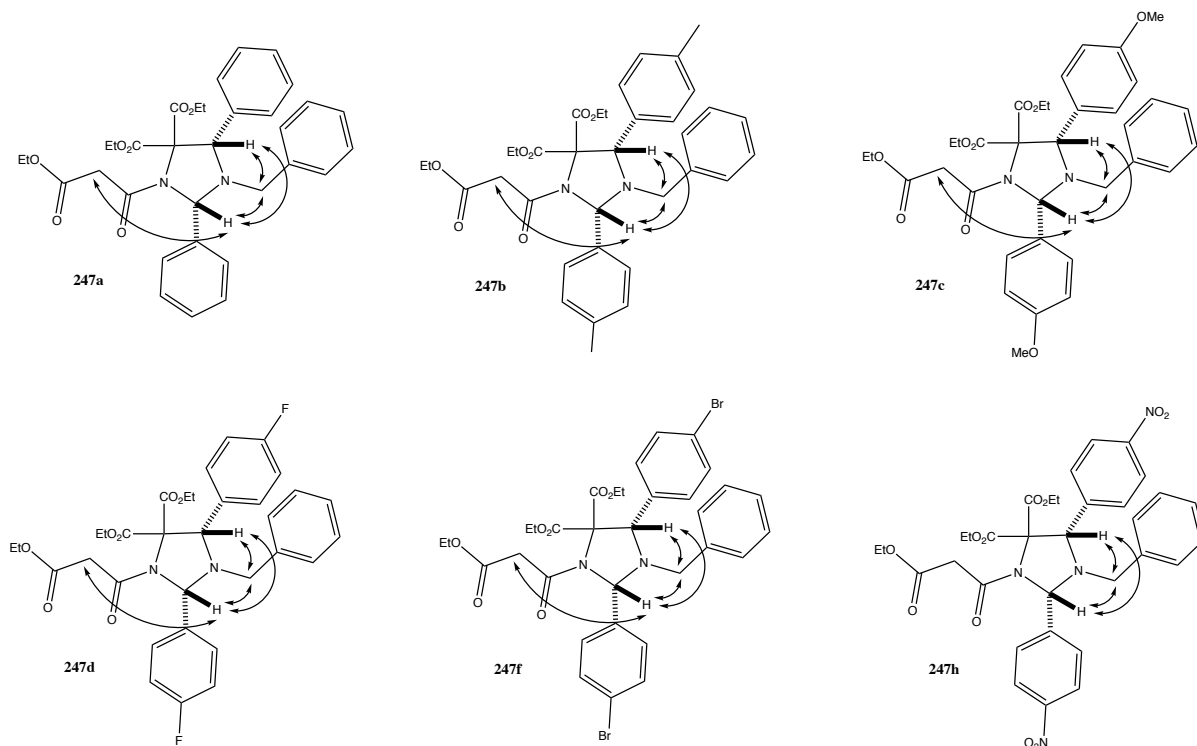


Figure 4.10: Relative stereochemistry of malonamides **247a-d**, **247f** and **247h**, assigned by nOe studies.

[illegible]

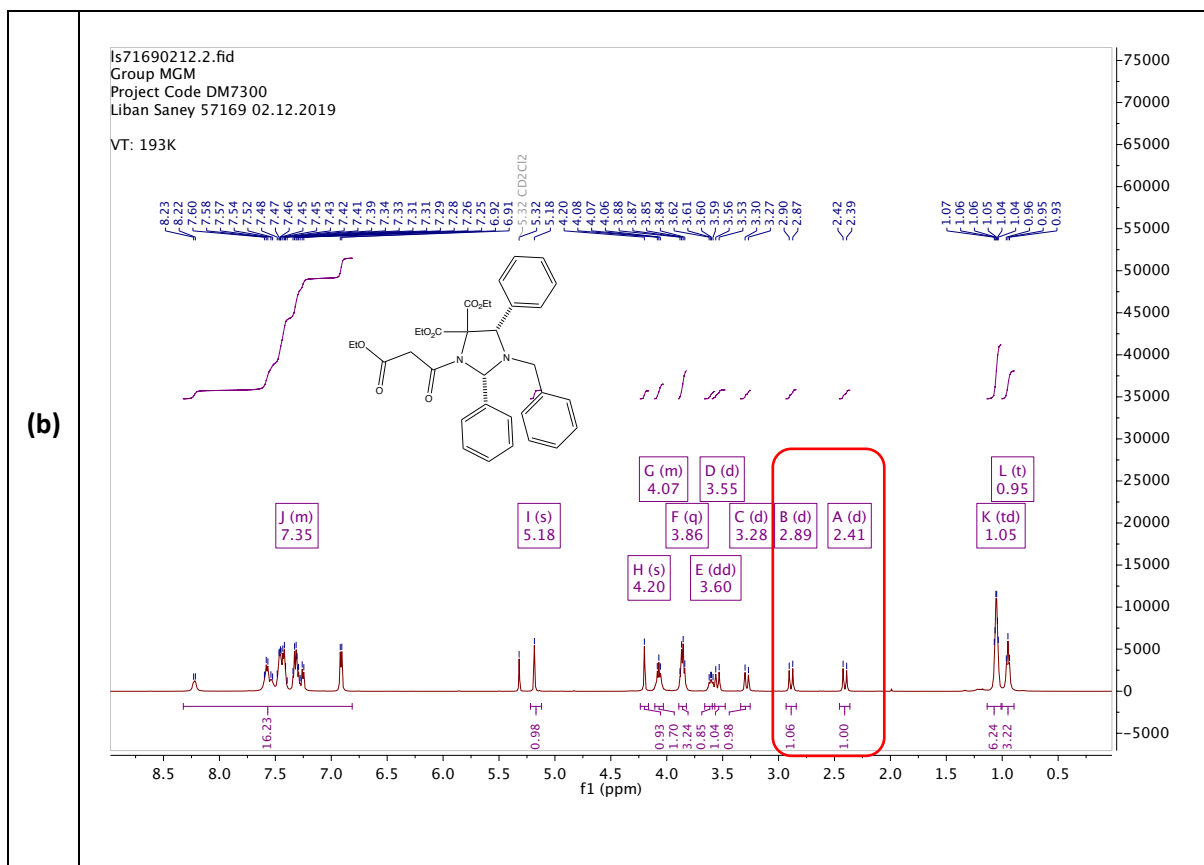


Figure 4.12: (a) ¹H-NMR spectrum of malonamide **247a** at room temperature; (b) ¹H-NMR spectrum of malonamide **247a** at 193K; with the red rectangle highlighting the diastereotopic H7-methylene protons of interest; CD₂Cl₂ solvent, 500 MHz.

Interestingly, there was an unusual NMR phenomenon that was observed in all the malonamide **247a**-I spectra. One of the diastereotopic methylene protons at the H7-position had a very broad doublet peak, whereas the other diastereotopic methylene proton had a sharp doublet peak at room temperature (**Figure 4.12a**). It was not a water-exchange effect since a D₂O-shake experiment showed no evidence of exchange. Surprisingly, electron-withdrawing or electron-donating substituents at the C2 and C4-positions affected the chemical shifts of the broad doublet peak, but in most cases, did not affect the chemical shift of the sharp doublet peak (compare compounds **247a** with **247f**, **247g** and **247i**; **Table 4.5**). As a result of this NMR observation, this may be a through space effect by the C2-aryl substituent which was within a 3.3-5.5 Å distance of the malonamide sidechain when considering the X-ray crystal structure of compound **247a** (**Figure 4.13**). However, it was shown that in the case of malonamide **247a**, use of low-temperature VT-NMR experiments (193 K) sharpened the broad doublet

peak that was observed at room temperature (**Figure 4.12b**). This had indicated that conformational dynamics was probably responsible for this broad doublet effect that was encountered throughout the malonamide series, however, as to why one methylene proton was more affected than the other proton has yet to be fully established.

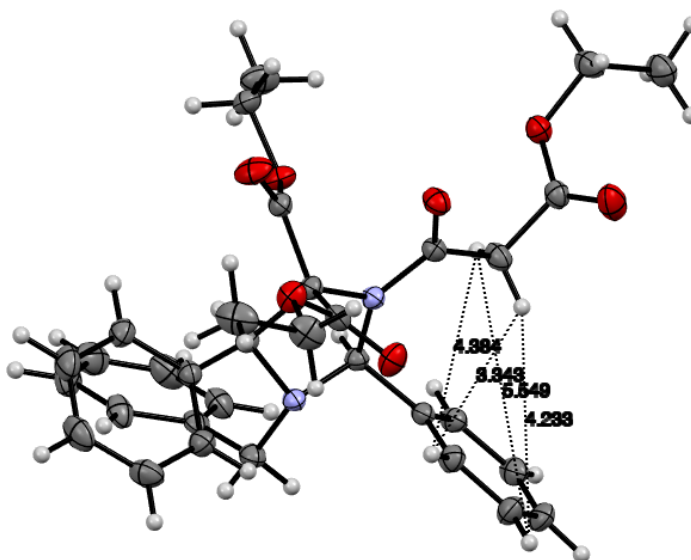


Figure 4.13: Single-crystal X-ray structure of malonamide **247a** – showing the distance in Å between the H7-methylene protons and the C2-aryl protons at the *ortho* and *meta*-positions.

Moreover, imidazolidine **246** was *N*-acylated with ethyl malonyl chloride to form malonamide **248** in 65% yield as a single diastereomer. The relative stereochemistry of **248** was confirmed from a single-crystal X-ray structure and showed a 2,4-*cis* relationship, consistent with the *N*-acylation of imidazolidines **245a-l** (**Figure 4.14**).

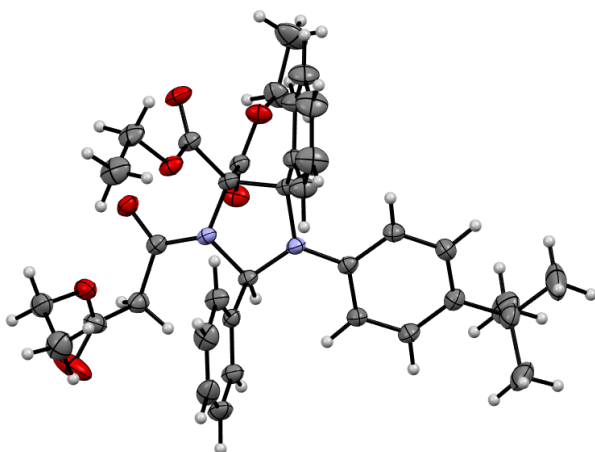


Figure 4.14: Single-crystal X-ray structure of malonamide **248**.

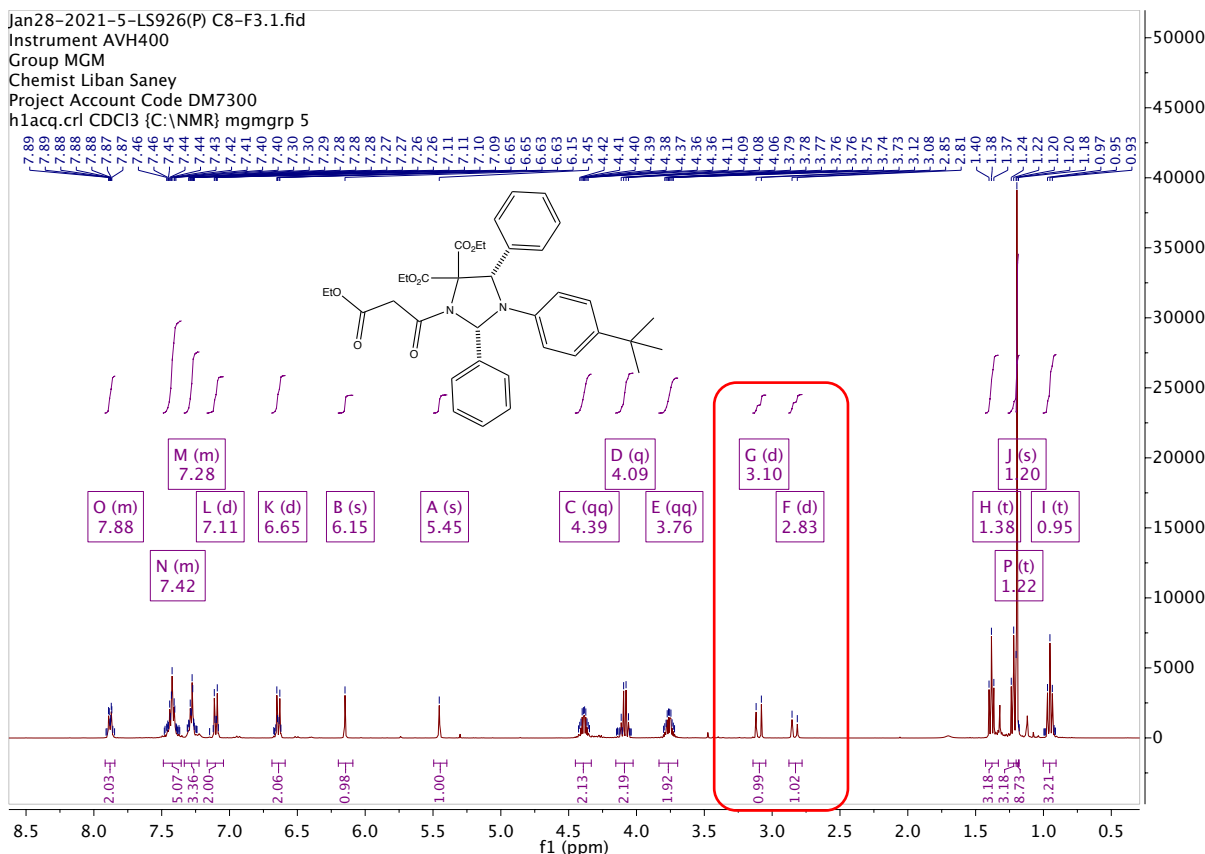


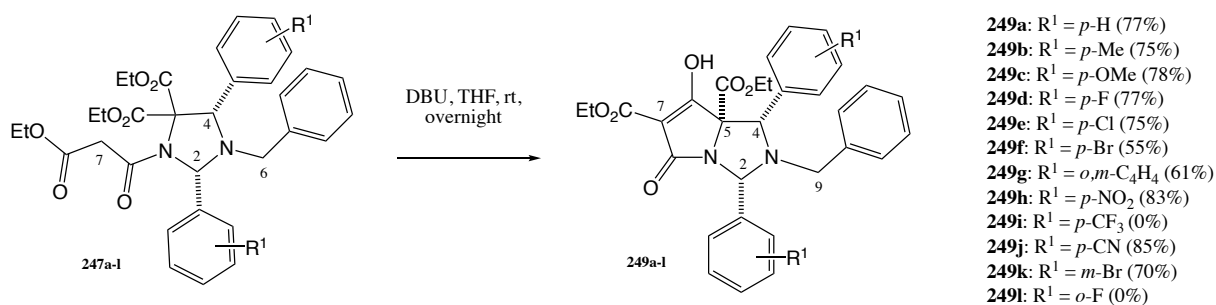
Figure 4.15: ^1H -NMR spectrum of malonamide **248** at room temperature; with the red rectangle highlighting the diastereotopic H7-methylene protons of interest; CDCl_3 solvent, 400 MHz.

Surprisingly, the NMR peaks for the methylene protons at the H7-position for **248** were both relatively sharp, which was in contrast to the benzyl malonamides **247a-i**, again suggesting that conformational dynamics and substituents attached around the periphery of the imidazolidine ring system at the C2, N3 and C4-positions could have a pronounced effect on the H7-protons (**Figure 4.15**).

4.4.4: Synthesis of Tetramates

Malonamides **247a-i** were subjected to the Dieckmann cyclisation using DBU in THF to form tetramates **249a-h**, **249j-k** in good yields with high levels of chemoselectivity observed – in which only a single diastereomer was isolated (**Scheme 4.18**). Electron-donating substituents were well-tolerated, however, some electron-withdrawing substituents gave no product, such as tetramates **249i** and **249l**. However, it was thought that this was due to the extraction process rather than the efficiency of the Dieckmann cyclisation – discussed in more detail below. Moreover, these compounds were not

purified by column chromatography as these compounds were found to be unstable in solution. The crude material was relatively pure by NMR analysis (**Figure 4.16**), although it should be noted that at times, minute quantities of the C7-decarboxylated material was also observed in the NMR spectrum over time, again indicating the instability of these systems in CDCl₃ solution – analogous to tetramates **88a-e** and **156a-f**.



Scheme 4.18: Synthesis of *N,N*-bicyclic tetramates **249a-h**, **249j-k** from malonamides **247a-l**.

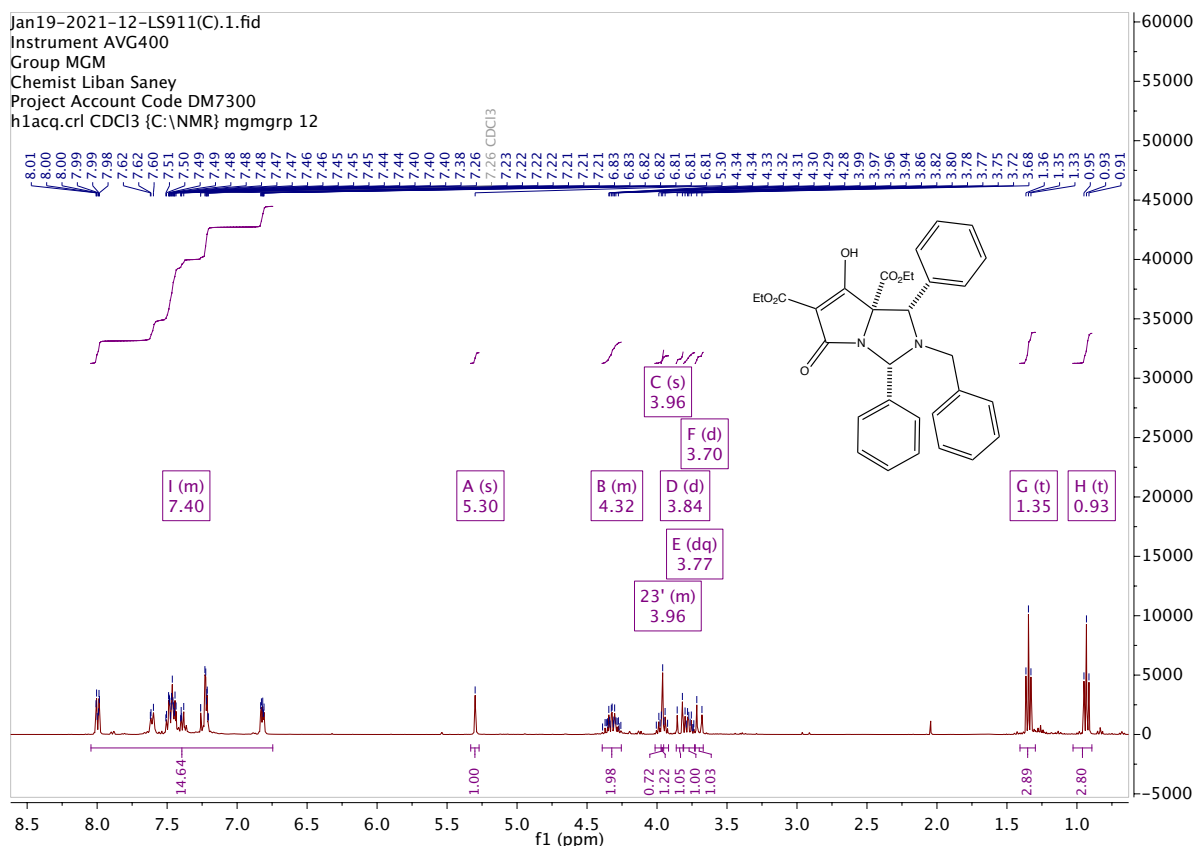


Figure 4.16: ¹H-NMR spectrum of tetramate **249a**, showing the relative purity of the crude material; CDCl₃ solution, 400 MHz.

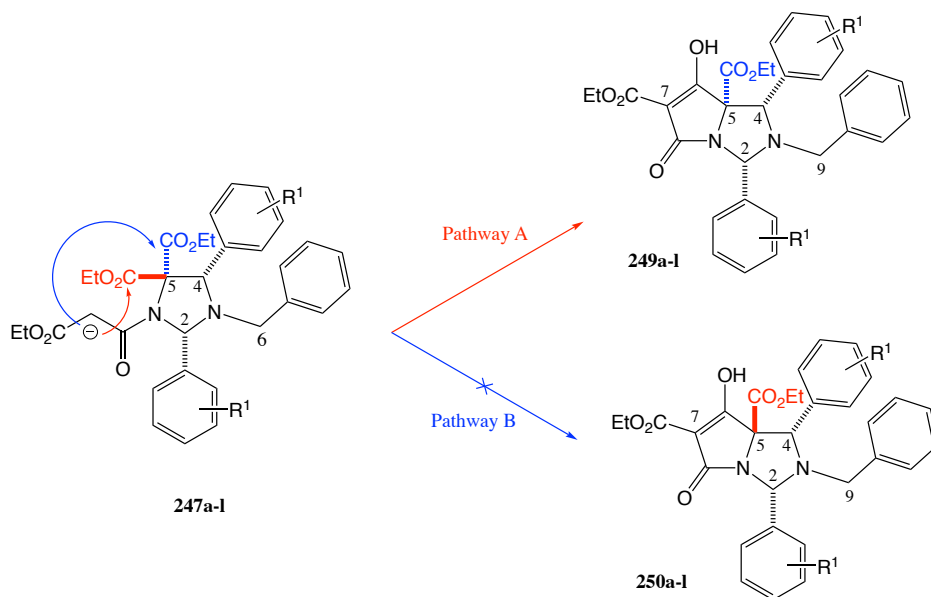
The relative stereochemistry – determined from nOe studies – showed a 2,4-*cis* relationship across the bicyclic core **249a-d**, indicating that no epimerisation had occurred at the C2 and C4-positions under basic conditions (**Figure 4.17**). Moreover, as the chemical shifts and coupling constants of **249a-d** were consistent with the rest of the tetramate series (**Table 4.6**), it was assumed that the remainder of the tetramate series had the same relative stereochemistry.

Compound	R ¹	δ (ppm)					Yield (%)
		H2	H4	H9	H9	J_{H9-H9}	
249a	<i>p</i> -H	5.30	3.96	3.84	3.70	14.8	77
249b	<i>p</i> -Me	5.25	3.90	3.85	3.69	14.7	75
249c	<i>p</i> -OMe	5.20	3.88	3.80	3.66	14.8	78
249d	<i>p</i> -F	5.26	3.93	3.77	3.67	14.6	77
249e	<i>p</i> -Cl	5.27	3.92	3.77	3.66	14.8	75
249f	<i>p</i> -Br	5.25	3.91	3.77	3.67	14.6	55
249g	<i>o,m</i> -C ₄ H ₄	6.25	4.91	3.81	3.52	14.7	61
249h	<i>p</i> -NO ₂	5.48	4.15	3.75	n.d. ^a	n.d. ^a	83
249i	<i>p</i> -CF ₃	-	-	-	-	-	0
249j	<i>p</i> -CN	5.39	4.05	3.72	n.d. ^a	n.d. ^a	85
249k	<i>m</i> -Br	5.18	3.84	3.71	3.63	14.7	70
249l	<i>o</i> -F	-	-	-	-	-	0

Table 4.6: Key chemical shifts, coupling constants and yields of tetramates **249a-l**; CDCl₃ solvent, 400 MHz; ^a n.d = not determined as the benzyl methylene protons were not diastereotopic.

Additionally, the C5-ethyl ester stereochemistry was tentatively assigned as being on the same face as the C2 and C4-aryl substituents (**Figure 4.17**), assuming the chemoselectivity of the Dieckmann cyclisation followed the same reaction pathway as the Dieckmann cyclisation of tetramates **134a-f**, where the C5-ethyl ester would be on the *exo*-face of the bicyclic lactam **249a-l** which would have

reduced steric strain within the bicyclic core in comparison to tetramates **250a-l** (**Scheme 4.19**). This was further supported with DFT calculations – shown in **Figure 4.19**, *vide infra*.



Scheme 4.19: Showing different reaction pathways towards bicyclic tetramates **249a-l** or **250a-l**.

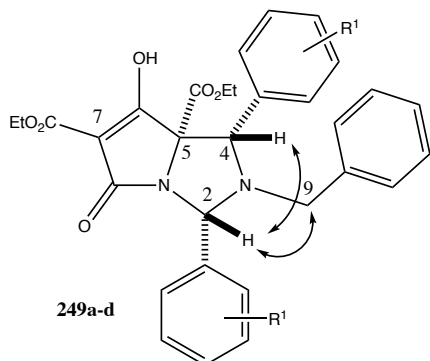
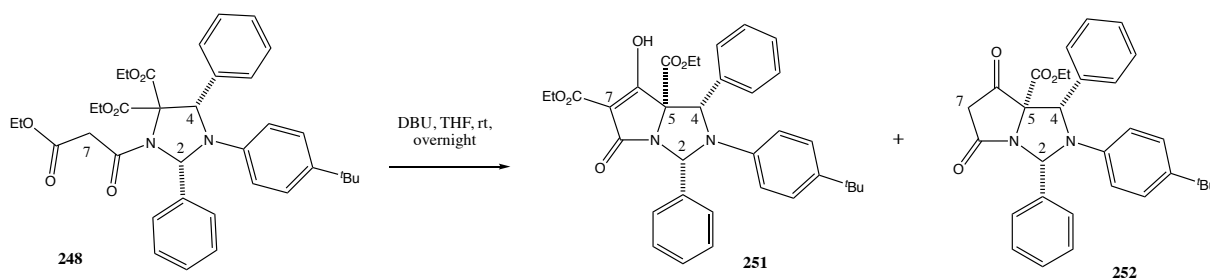


Figure 4.17: Relative stereochemistry of tetramates **249a-d** assigned by nOe analysis.

Additionally, malonamide **248** was subjected to the Dieckmann cyclisation, but the extraction process for this reaction was very complicated, and this was also the case for benzyl tetramates **249i/l**. Typically, when reacting malonamides with DBU in THF overnight, the reaction mixture would be cooled to 0°C and then separated between Et₂O and water. The aqueous layer – where the enolate product resides – would then be acidified to pH 1-2 and then extracted with EtOAc, dried over Na₂SO₄, filtered, and then the solvent would be evaporated under reduced pressure to obtain the desired tetramates. However, in the cases of tetramates **247i/l** and **248**, a white emulsion/suspension tended

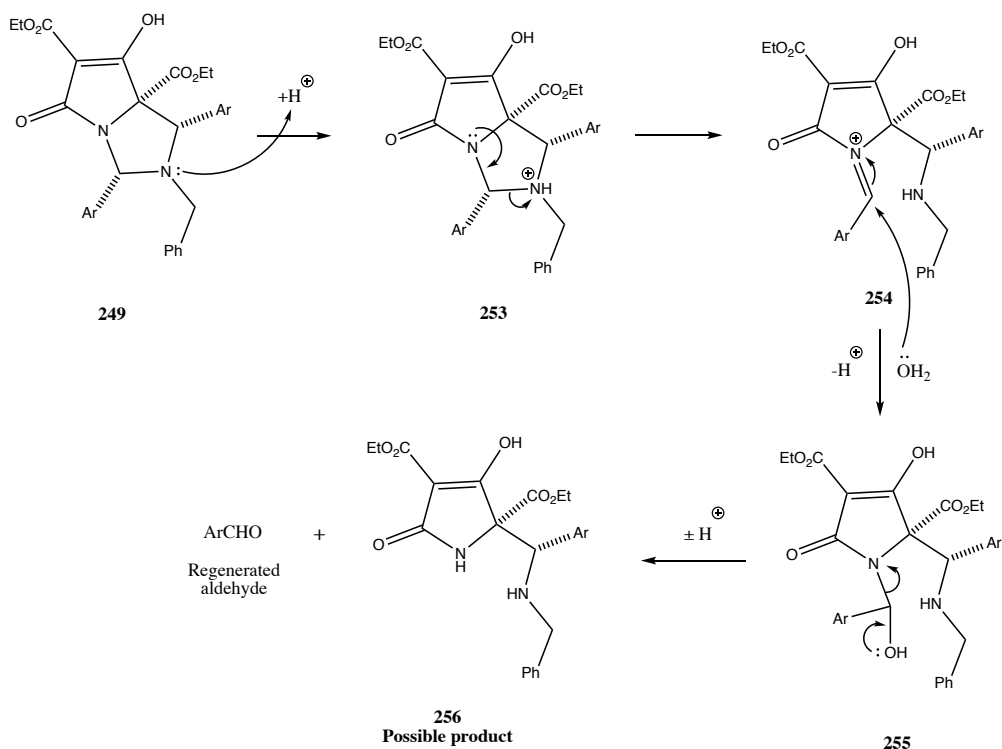
to form in the separatory funnel when adding Et₂O and water to the crude reaction mixture, hampering the extraction process severely. Nonetheless, tetramate **251** was obtained along with C7-decarboxylated tetramate **252** – as determined from ¹H-NMR studies and mass spectroscopy (**Scheme 4.20**). However, this material was not subjected to chromatographic purification and due to the mixture of products obtained, this material was discarded. However, this synthetic methodology did demonstrate that the N3-position could be varied if required.



Scheme 4.20: Synthesis of tetramates **251** and **252** from malonamide **248**.

Additionally, there was a question mark surrounding the stability of these bicyclic tetramates, as at times, a peak at > 9 ppm – indicative of an aldehyde – was detected in the NMR spectrum after the Dieckmann cyclisation, indicating that the *N,N*-aminal was not as stable as the *N,O*-hemiaminal that was initially condensed with pivaldehyde (**Scheme 4.21**). This had demonstrated that these *N,N*-bicyclic systems were perhaps not suitable for *in-vivo* administration in their current state, and that further work will be required to ascertain whether these *N,N*-aminals could be sufficiently stabilised for physiological applications.

It was believed that protonation at the N3-position of tetramates **249a-l** under acidic workup conditions, possibly led to the regeneration of the aldehyde starting material (**Scheme 4.21**). Introduction of an electron-withdrawing group at the N3-position, such as a 4-nitroaniline ring system **257a-b** might cause the lone pairs at the N3-position to delocalise into the aromatic ring system, thereby reducing its nucleophilicity and improving the stability of the *N,N*-aminal in acidic media (**Figure 4.18**), but this was not investigated.



Scheme 4.21: Possible mechanism explaining the instability of the *N,N*-aminal **249** in acidic solution that leads to the regeneration of the possible aldehyde peak detected in the ^1H -NMR spectrum.

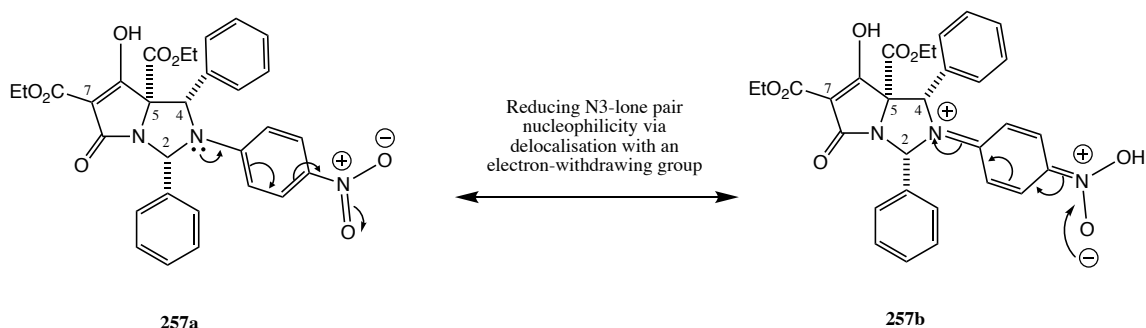


Figure 4.18: Electron-withdrawing substituents attached at the N3-position could possibly improve the stability of the *N,N*-aminal by reducing the nucleophilicity of the N3-amine.

4.4.5: Density Functional Theory (DFT) Calculations

Dr. Xiang Li conducted DFT calculations to determine computationally why only 1 diastereomer was isolated during the Dieckmann cyclisation, and which ester was chemoselectively attacked during the Dieckmann cyclisation to form tetramates **249** or **250** (**Scheme 4.19**) – taking into account the base and solvent used for the Dieckmann cyclisation.

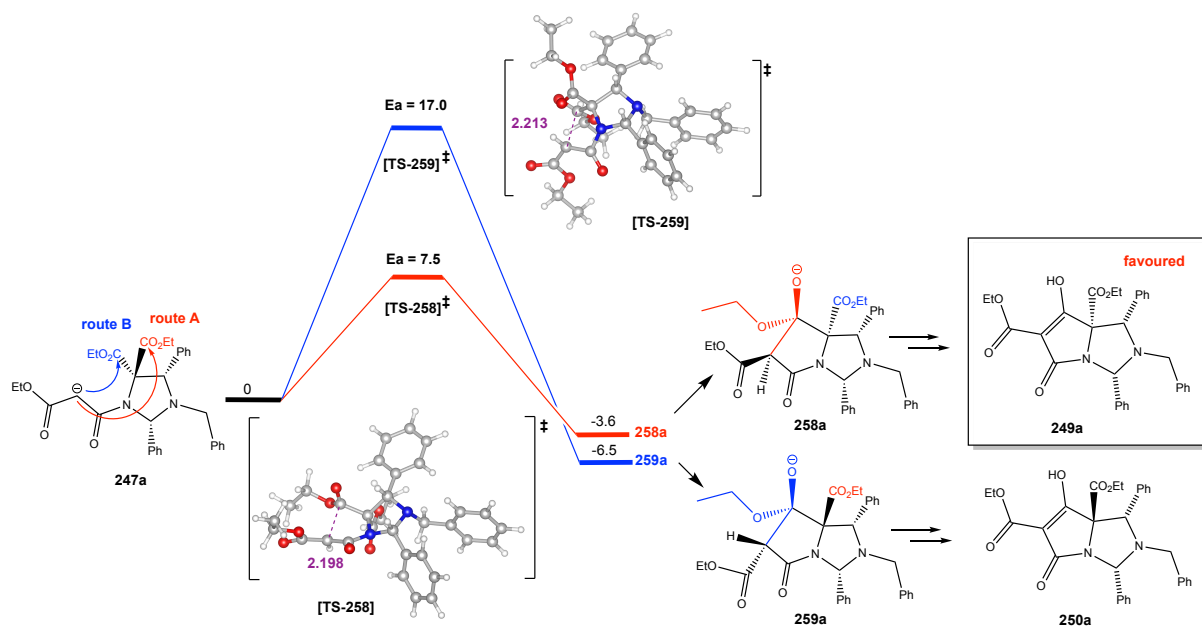
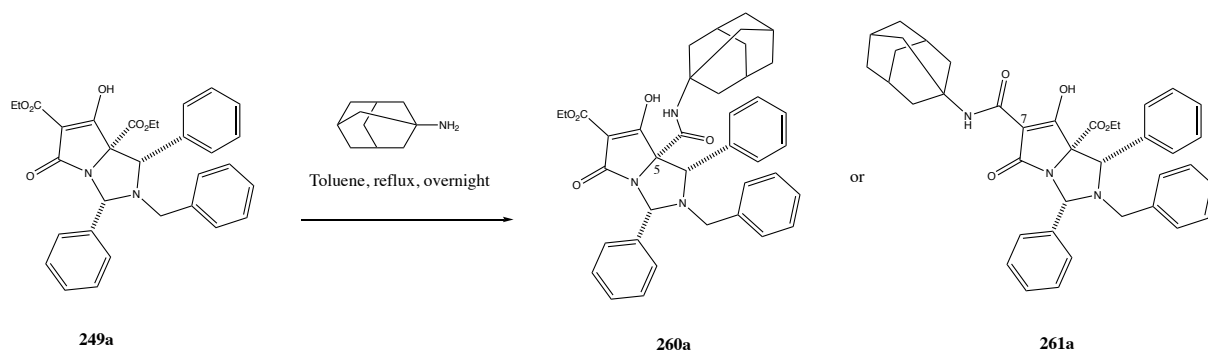


Figure 4.19: DFT calculated reaction energy profile for the Dieckmann cyclisation of malonamide **247a**, using B3LYP/6-31G(D)//B3LYP/6-311++g(D,P) level of theory with SMD solvation (THF) and zero-point energy correction. All energies are reported in kcal/mol and are referenced to the lowest energy carbanion generated after initial deprotonation.

DFT calculations showed that this reaction was principally governed by kinetics, in which the favoured reaction pathway (route A) – highlighted in red – had a considerably lower E_a than route B – highlighted in blue – typically about 9.5 kcal/mol (39.8 kJ/mol) (**Figure 4.19**), thus giving rise to its chemoselectivity and confirming what had been expected from previous Dieckmann cyclisations of tetramates derived from various amino acids used. Thus, as a result it was assumed that the C5-ethyl ester was on the same face as the C2 and C4-aryl substituents.

4.4.6: Synthesis of C7-Carboxamides and the Attempted Synthesis of C7-Acyltetramates

As the *N,N*-bicyclic tetramate core was in place, the next stage was to build compound libraries at the C7-position. It was assumed that the C7-ethyl ester would be chemoselectively attacked by the adamantylamine – similar to that observed for the aminolysis reactions of tetramates **156a-f** – but in practice, indiscriminate attack at both the C5 and C7-ethyl ester positions was observed to form either C5-**260a** and/or C7-**261a** carboxamides (**Scheme 4.22**).



Scheme 4.22: Synthesis of C5-**260a** and C7-**261a** carboxamides from *N,N*-bicyclic tetramate **249a**.

It was difficult to assign the structures of the carboxamide products by NMR analysis using NOESY or HMBC analysis, however, a very tentative assignment of the C5 and C7-carboxamides could be made based upon the ^1H -NMR spectrum of the *N,O*-bicyclic tetramic acids. When considering the ^1H -NMR spectra of C5-ethyl ester tetramates **134a-f** and C7-ethyl ester tetramates **88a-e**, the methylene protons of the C7-ethyl ester tetramates **88a-e** were more downfield at 4.40 ppm (**Figure 2.9**), whereas the methylene protons of the C5-ethyl ester tetramates **134a-f** were more upfield at 3.90 ppm (**Figure 3.13**). Thus, if the same holds true for tetramates **249**, and considering the ^1H -NMR spectrum shown in **Figure 4.16**, it was assumed that the C7-ethyl esters would be more downfield and the C5-ethyl esters would be more upfield for compounds **249**. Based upon this finding, it was possible to determine which ester was attacked by the adamantylamine based upon this assumption. As a result, **Figure 4.20a**, shows the ^1H -NMR spectrum of C5-carboxamide **260a** and **Figure 4.20b** shows the ^1H -NMR spectrum of C7-carboxamide **261a**.

As there were struggles introducing the C7-carboxamide into the bicyclic structure via aminolysis reactions through late-stage functionalisation, an alternative strategy through early-stage functionalisation was required. As a result, specific malonamides had to be synthesised in which the subsequent Dieckmann cyclisation would result in the formation of the C7-carboxamidotetramic acids directly. However, this approach would severely impact the ability to form compound libraries conveniently, as multistep synthesis would be required to make the desired malonamides separately.

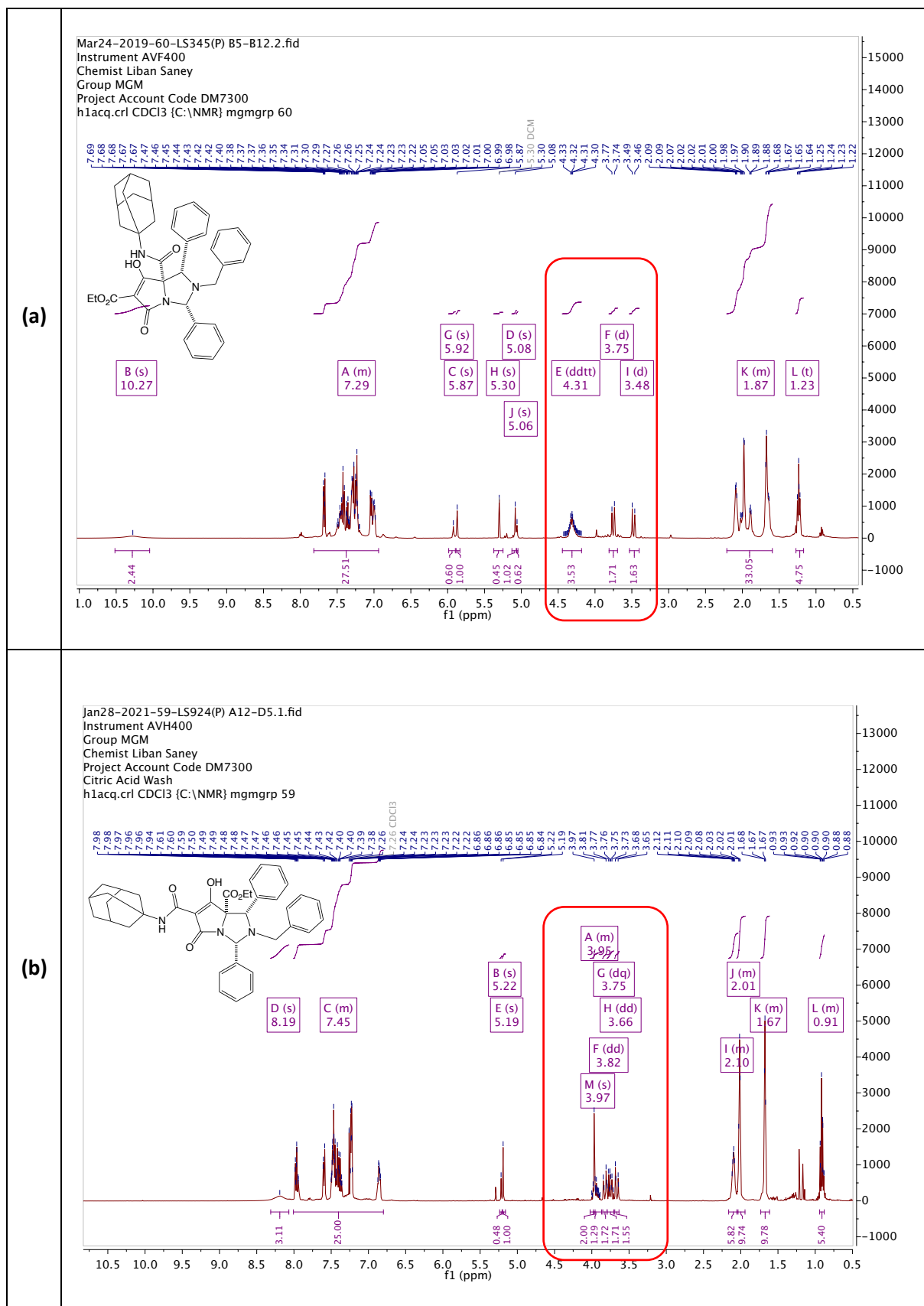
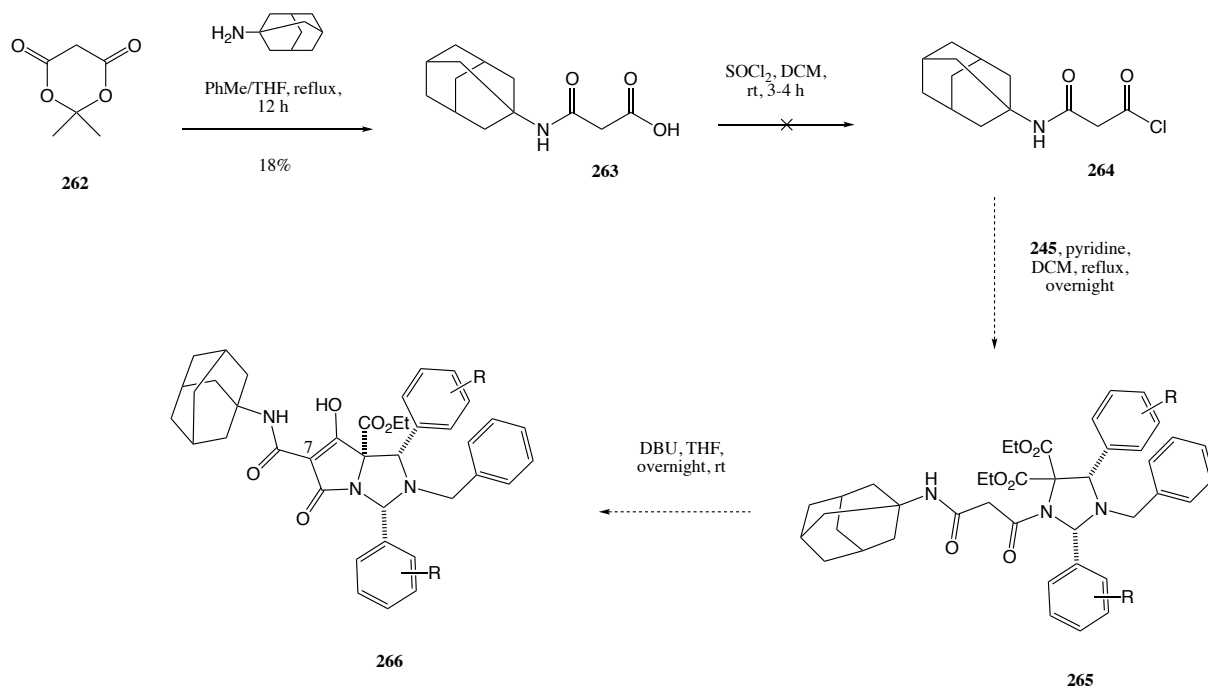


Figure 4.20: ^1H -NMR spectrum post-chromatographic purification after 10% citric acid (aq.) wash; with

(a) showing the ^1H -NMR spectrum of C5-carboxamide **260a** and (b) showing the ^1H -NMR spectrum of

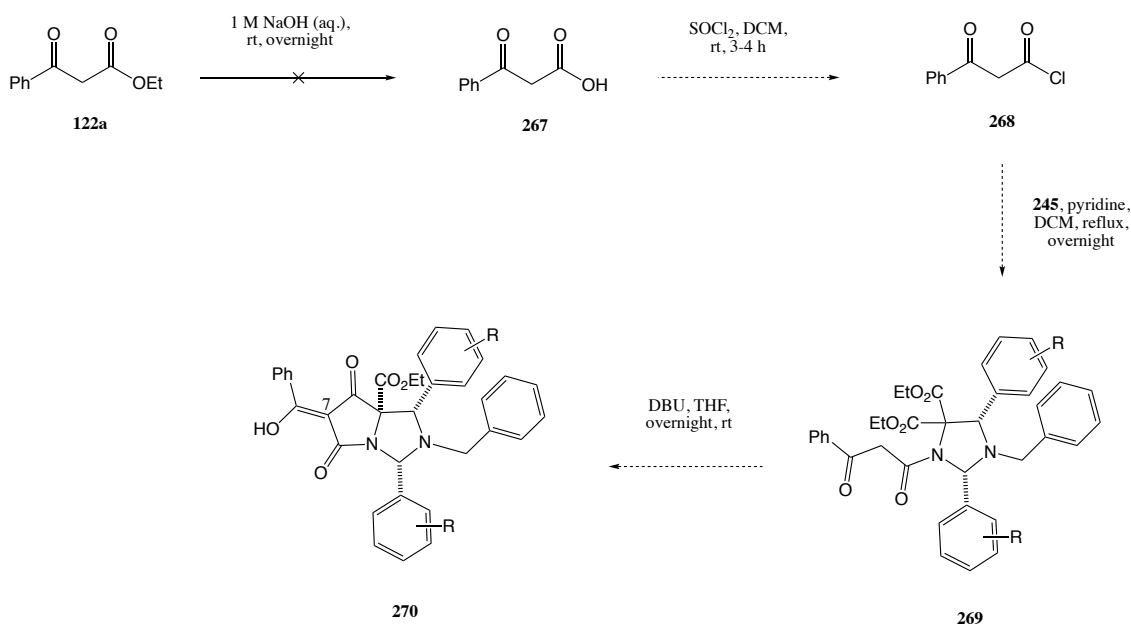
C7-carboxamide **261a**; with the red rectangle highlighting the area of interest within the ^1H -NMR spectrum, showing the differences between the two carboxamide products; CDCl_3 solvent, 400 MHz.

To test this theory however, acyl chloride **264** would be coupled to imidazolidines **245** to form malonamides of type **265**, which would then be subjected to the Dieckmann cyclisation to form C7-functionalised tetramates **266** (**Scheme 4.23**). Thus, carboxylic acid **263** was synthesised by reacting Meldrum's acid **262** with adamantylamine to form carboxylic acid **263** in poor yield (**Scheme 4.23**). However, when trying to form the acyl chloride **264** via reaction with thionyl chloride, the NMR spectrum of the crude material was very complicated – indicating the reaction did not work – and thus this approach to making C7-functionalised tetramates was not successful.



Scheme 4.23: Synthesis of carboxylic acid **263** and the attempted synthesis of acyl chloride **264**.

Due to the issues surrounding the synthesis of acyl chloride **264**, the acyl chloride derivative of β -ketoacid **268** was examined to access C7-acyltetramates **270**. As a result, the commercially available β -ketoester **122a** was reacted with 1 M NaOH solution (aq.), but again, the desired β -ketoacid **267** was not formed or was not stable (**Scheme 4.24**). As a result, this nullified the synthetic approach towards making C7-acyltetramates.



Scheme 4.24: Failed synthesis of β -ketoacid **267** towards the synthesis of C7-acyltetramate **270**.

4.5: Summary

This research has shown that bicyclic tetramates **218** functionalised at the C2-position could be obtained from *threo*-phenylserine **82a** in a chemoselective way – in which only one malonamide diastereomer cyclises to form tetramates **218** in acceptable yields. However, a C7-carboxamide library could not be formed, possibly due to the instability of the *N,O*-hemiaminal. As a result, attention was turned towards making *N,S*-tetramates **220** that were functionalised at the C2-position, however, the synthetic methodology towards the synthesis of *threo* and *allo*-phenylcysteine derivatives **232/233** hampered the synthetic methodology towards C2-functionalised tetramates **220**. Seeking an alternative, more streamlined approach towards making C2-functionalised tetramates, this research had demonstrated that bicyclic tetramates **249** could be synthesised diastereoselectively and chemoselectively from imidazolidine scaffolds **245**. Additionally, these compounds were obtained in good to excellent yields, could be obtained in gram-scale quantities and was obtained in 3 synthetic steps using cheap starting materials. Unfortunately, a C7-carboxamide compound library could not be formed due to the limited chemoselectivity seen towards the aminolysis reactions, thus limiting the ability to test these compounds for any antibacterial activity.

Chapter 5: Antibacterial Activity of Bicyclic Tetramic Acids

This chapter will examine the antibacterial activity of tetramic acids which were derived from *threo*-phenylserine derivatives (**Chapter 2**). Furthermore, the antibacterial activity of tetramic acids which were derived from *erythro*-phenylserine derivatives (**Chapter 3**) will also be explored. And finally, the antibacterial activity of tetramates derived from imidazolidine scaffolds (**Chapter 4**) will also be discussed. Additionally, the toxicity, the physicochemical properties and possible binding to human serum albumin (HSA) will also be examined.

5.1: Evaluation of Antibacterial Activity

All compounds assessed for antibacterial activity was determined using whole-cell screens, where MIC values were obtained using a broth dilution assay. The MIC data represents the lowest concentration of the compound required to inhibit visible growth of bacteria over a 24 h incubation period. Thus, lower MIC values indicate higher potency against pathogenic strains. However, a value of zero indicates no activity at all. The antibacterial activity of these compounds was assessed by the Oxford Antibiotic Group (OxAG) and these compounds were only tested for antibacterial activity against Gram (+) MRSA and Gram (-) *E. coli* strains. The extracts were tested in a primary 96 well plate-screening assay, according to SOP 0906. The substances were diluted in a Mueller-Hinter broth (MHB) assay for bacterial screening to a stock solution of 1000 µg/mL, serial diluted and overlaid with a microbe solution in a concentration of 10⁴ CFU/ml. The plates were incubated for a period of 24 h at 35°C.

5.2: Evaluation of Antibacterial Activity from Chapter 2

5.2.1: Antibacterial Activity of C7-Ethyl Ester Tetramates

Simple tetramic acids are devoid of antibacterial activity, such as tetramates **11a-c** and **12a-c** derived from the methyl esters of L-serine **8a**, L-threonine **8b** and L-cysteine **8c**, with activity in most cases exceeding 250 µg/ml.^{32-33,43,64-65,72,82} Tetramates **88a-b** also showed no activity against MRSA and *E. coli*, however, interestingly, there was some activity seen against MRSA for compounds **88c-e** with MIC

values ranging between 15.6-31.25 $\mu\text{g/ml}$ (**Figure 5.1**). This indicated that the added C4-aryl substitution within the core bicyclic system potentially affected the antibacterial activity, particularly when compared with L-serine, L-threonine and L-cysteine-derived tetramic acids **11a-c** and **12a-c**.³²⁻

33,43,72

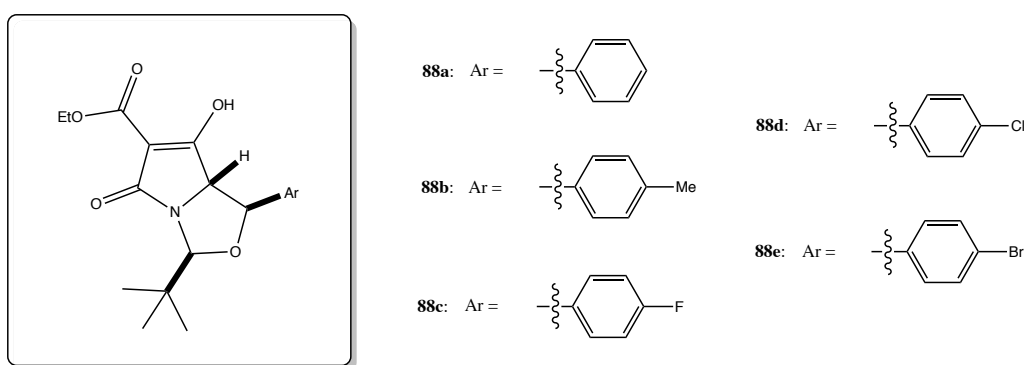
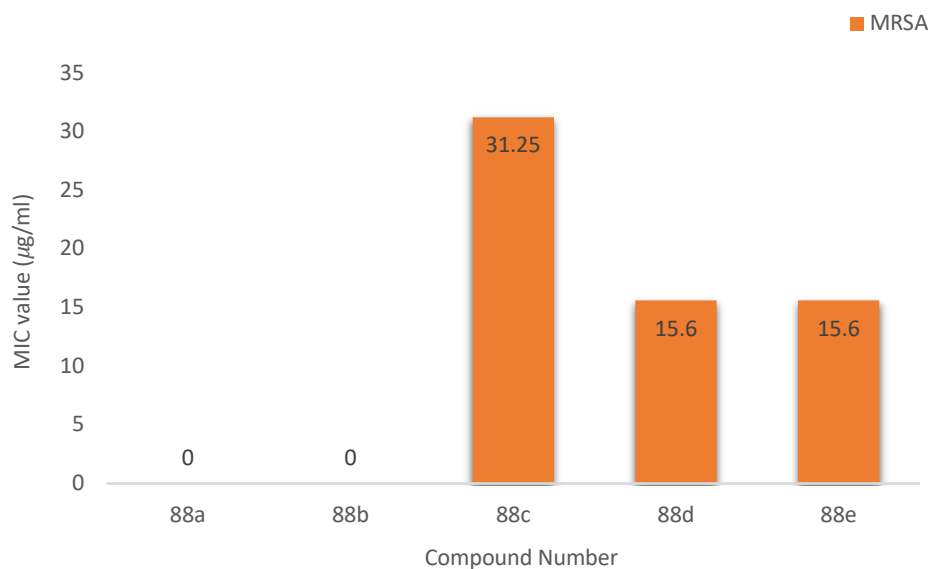


Figure 5.1: MIC values and chemical structures of C7-ethyl ester tetramates **88a-e** against MRSA.

5.2.2: Antibacterial Activity of C7-Carboxamides

Interestingly, when converting the C7-ethyl ester to a C7-aromatic carboxamide, good to excellent antibacterial activity was observed against MRSA, with activity ranging between 0.49-15.6 $\mu\text{g/ml}$, however, again, no activity was observed against *E. coli* (**Figure 5.2**). The Ph-substituent **111b** only exhibit modest antibacterial activity at 7.80 $\mu\text{g/ml}$, however, when adding substituents around the aromatic carboxamide, much better bioactivities were observed. In the case of single substitution

patterns at the *para*-position of the aromatic carboxamide, the *p*-Br **111c** and *p*-NO₂ **111d** substituents had MIC values of 3.90 µg/ml. The *p*-CF₃ substituent **111e** was tested for antibacterial activity as many marketed drugs tended to have a fluorine group attached which either better aided solubility, bioactivity or had a better pharmacokinetic/pharmacodynamic profile.⁸³ In this case, **111e** exhibited better antibacterial activity (MIC = 1.00 µg/ml) when compared with **111b-d**. In the case of adding more grease at the *para*-position of the aromatic carboxamide in the form of *p*-hexyl **111m** and *p*-cyclohexyl **111s**, it was interesting to note that the *p*-hexyl substituent had better activity (MIC = 0.49 µg/ml) than the *p*-cyclohexyl derivative (MIC = 1.00 µg/ml), indicating that the conformational flexibility of the hexyl group was better for bioactivity than the cyclohexyl derivative.

Moreover, of interest was to add substituents at the *ortho*-position of the aromatic ring system to see the effect this substitution pattern would have on antibacterial activity while maintaining *para*-substituted groups. When looking at compounds **111g-l**, it was clear to see that different groups were well-tolerated – such as a bulky *o*-Cl group **111h-i**, a small hydrophilic electron-withdrawing *o*-CF₃ group **111j** or an electron-donating *o*-Me group **111g/111k-l** – with activity ranging between 0.49-3.90 µg/ml. Interestingly when comparing **111h** with **111i** or comparing **111k** with **111l**, that the fluoro-substituents **111i** and **111l** had much better activities than their counterparts.

In the case of aliphatic carboxamides, the more grease that was attached at the C7-position, the more active the compound tended to be against MRSA (**Figure 5.3**). The nonyl **111q** and dodecyl **111r** substituents were far more active (MIC = 0.49 µg/ml) than the hexyl substituent **111p** (MIC = 3.90 µg/ml). The ^tBu substituent **111v** had comparable activity with the hexyl substituent **111p**, however, the Bn-analogue **111u** only exhibited modest bioactivity at 15.60 µg/ml. Interestingly, putting a more polar substituent at the C7-position in the form of a pyran **111t** compromised the antibacterial activity, with bioactivity only seen at concentrations above 125 µg/ml. This was consistent with Panduwawala *et al.*³³ and Jeong *et al.*⁴³ findings that polar substituents at the C7-position significantly worsens antibacterial activity for these bicyclic tetramates, however, in the case of **111d**, it was surprising that

there was good bioactivity seen, particularly as the C7-substituent was quite polar when considering the molecular surface area (MSA) and polar surface area (PSA) of **111d** in comparison to **111t** (see **Supporting Information** for the full physicochemical properties). Due to the instability – particularly when incubated for a period of 48 h – and conformational flexibility of these large straight-chained aliphatic carboxamides – particularly **111r** – of interest was looking at the activity of cyclohexyl **111n** and cycloheptyl **111o** substituents which would have conformationally well-defined pendants with the prerequisite grease required for good bioactivity. A MIC value of 1.00 $\mu\text{g/ml}$ was observed for both these compounds, thus having better activity than the hexyl substituent **111p**. However, although **111n-o** had good antibacterial activity, it was not as potent as the adamantyl substituent **111a**, which had a MIC value of 0.25 $\mu\text{g/ml}$, thus being the most potent compound synthesised in this library.

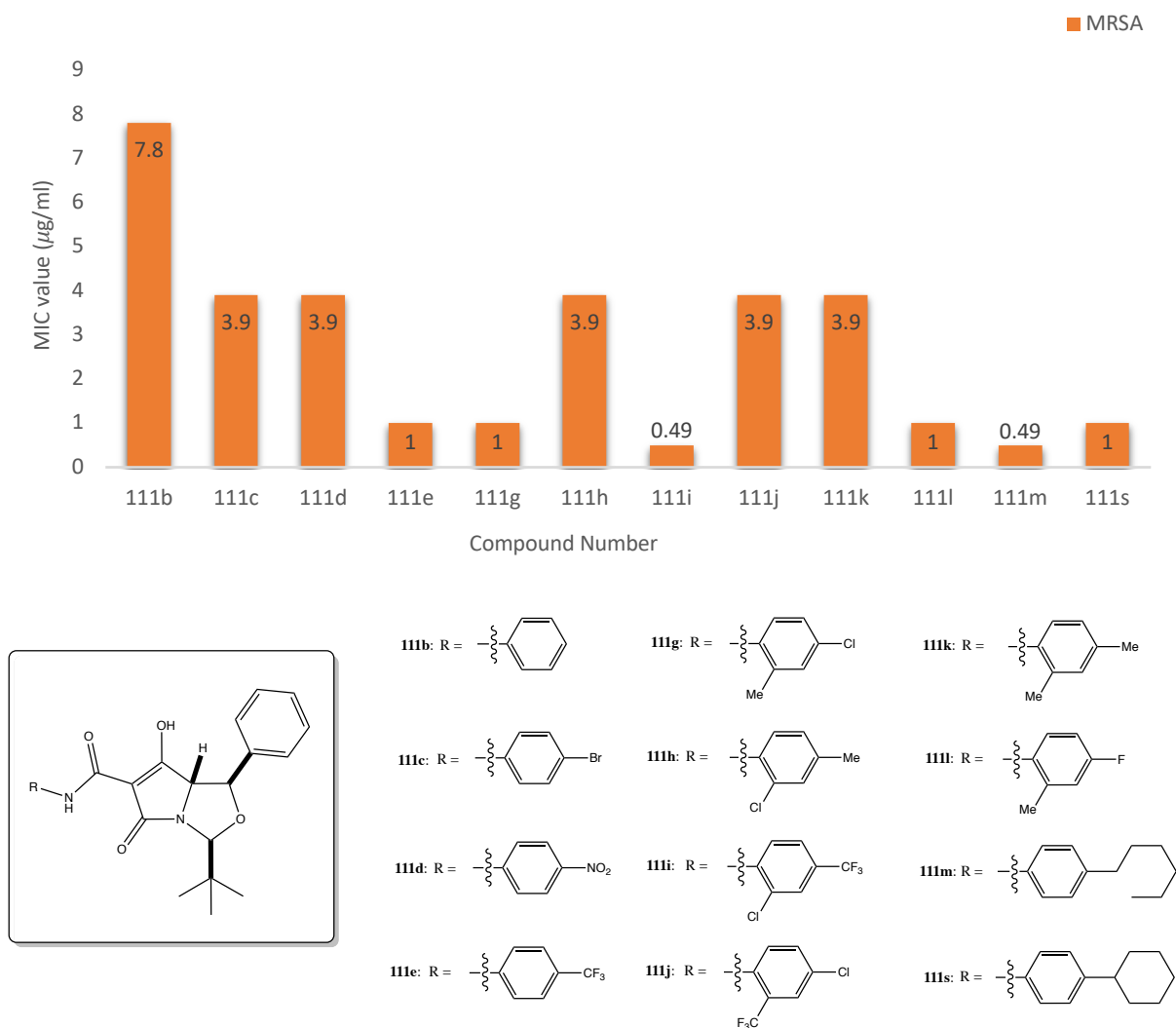


Figure 5.2: MIC values and chemical structures of C7-aromatic carboxamides **111b-e**, **111g-m** and **111s** against MRSA.

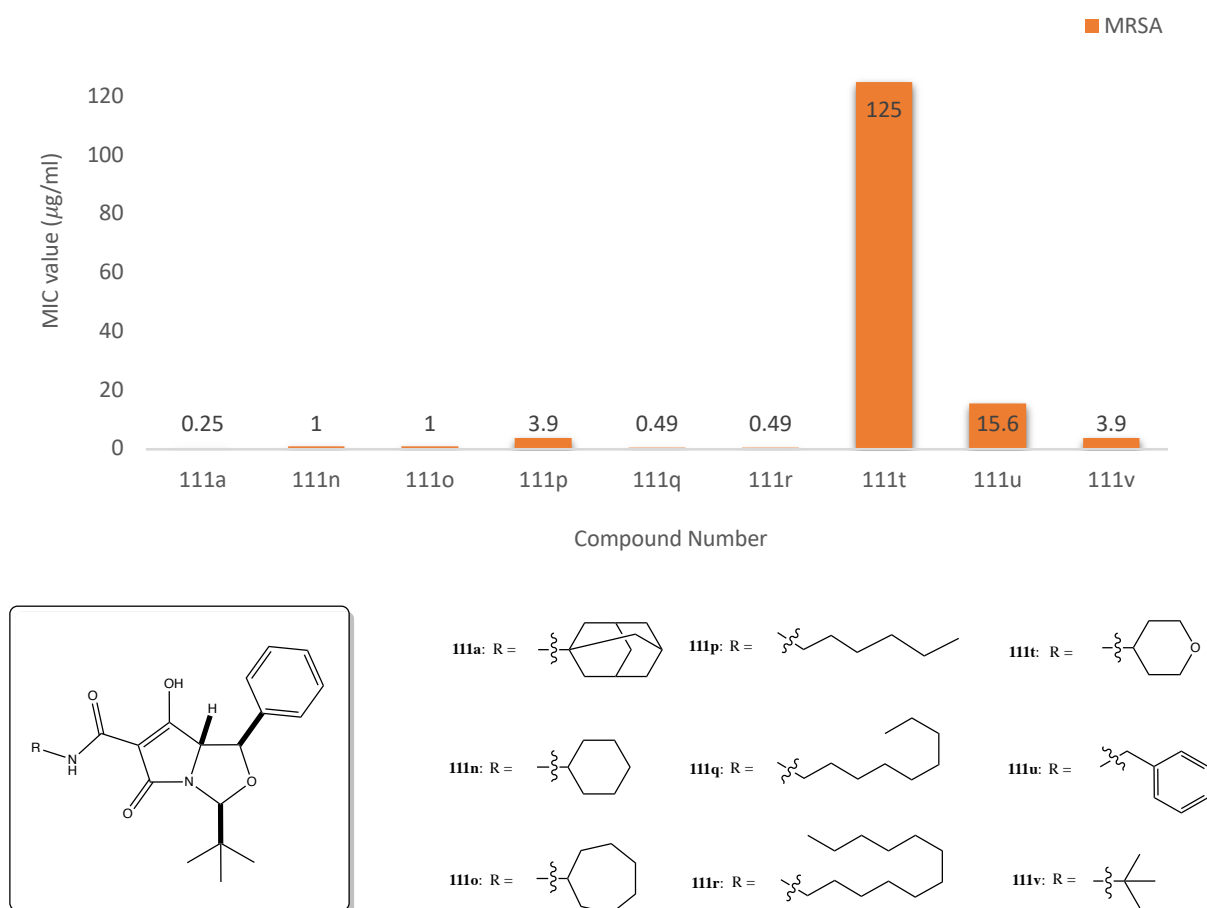


Figure 5.3: MIC values and chemical structures of C7-aliphatic carboxamides **111a**, **111n-r** and **111t-v** against MRSA.

As carboxamide **111a** was the most active compound in our C7-carboxamide series **111**, the C4-aromatic substituents in the tetramate core were varied with the C7-adamantylcarboxamide group being the constant factor (**Figure 5.4**). In the case of **112a**, the added grease at the *para*-position of the aromatic ring system in the form of a *p*-Me substituent worsened antibacterial activity (MIC = 3.90 μg/ml) when compared with **111a**. Additionally, the *p*-Cl substituent **114a** had a detrimental impact on the antibacterial activity (MIC = 7.80 μg/ml), however, the *p*-F **113a** and *p*-Br **115a** groups only had slightly worse activity when compared with **111a**, with activity typically observed at 1.00 μg/ml and 0.49 μg/ml respectively. Thus, it was clear to see that the C4-aromatic ring system had an impact on the antibacterial activity within these bicyclic systems. Additionally, compound **112b** had the same activity as **111g** at 1.00 μg/ml.

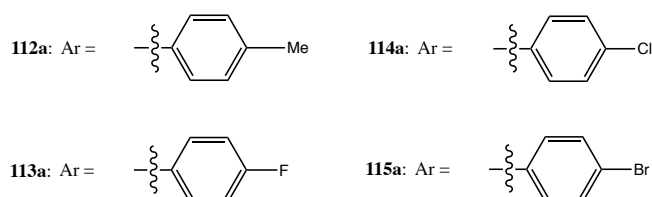
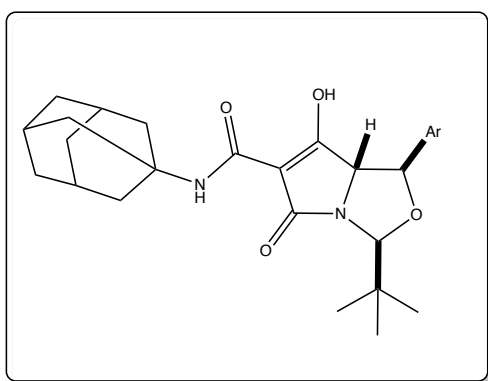
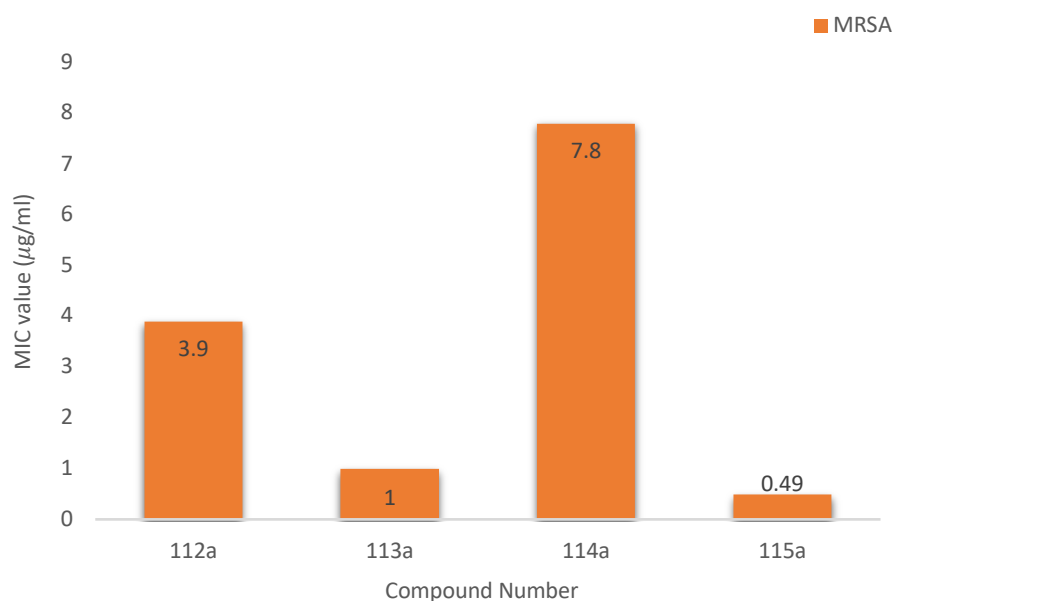


Figure 5.4: MIC values and chemical structures of C7-adamantylcarboxamides **112a**, **113a**, **114a** and **115a** against MRSA.

5.3: Evaluation of Antibacterial Activity from Chapter 3

5.3.1: Antibacterial Activity of C7-Unfunctionalised Tetramates

C7-Unfunctionalised tetramates **11a-c** derived from L-serine **8a**, L-threonine **8b** and L-cysteine **8c** have no intrinsic antibacterial activity against Gram (+) and Gram (-) bacteria. However, compounds **134a-f** showed appreciable activity against MRSA, with MIC values ranging between 7.8-15.6 μg/ml (**Figure 5.5**). This again indicated that the added C4-aromatic functionalisation within the core bicyclic system potentially affected the antibacterial activity, particularly when compared with tetramates **11a-c**. Additionally, the removal of the polar C7-ethyl ester group when compared with tetramates **88a-e**

brought about more potent antibacterial activity, although surprisingly, the difference in the aromatic substitution patterns at the *para*-position did not seem to affect the antibacterial activity of these tetramates, with the exception being **134b**. However, no activity was observed against *E. coli*.

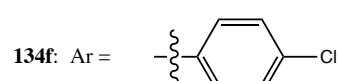
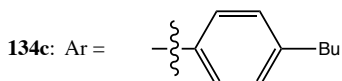
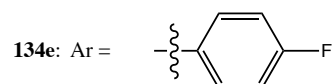
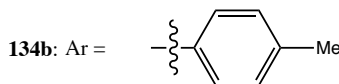
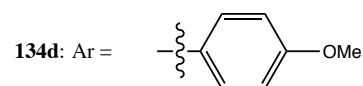
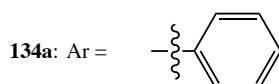
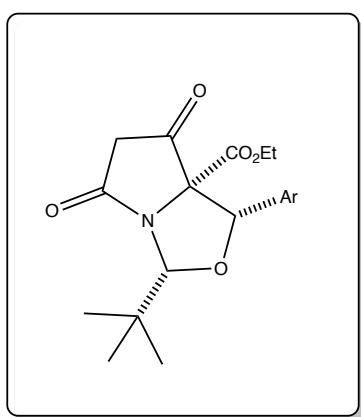
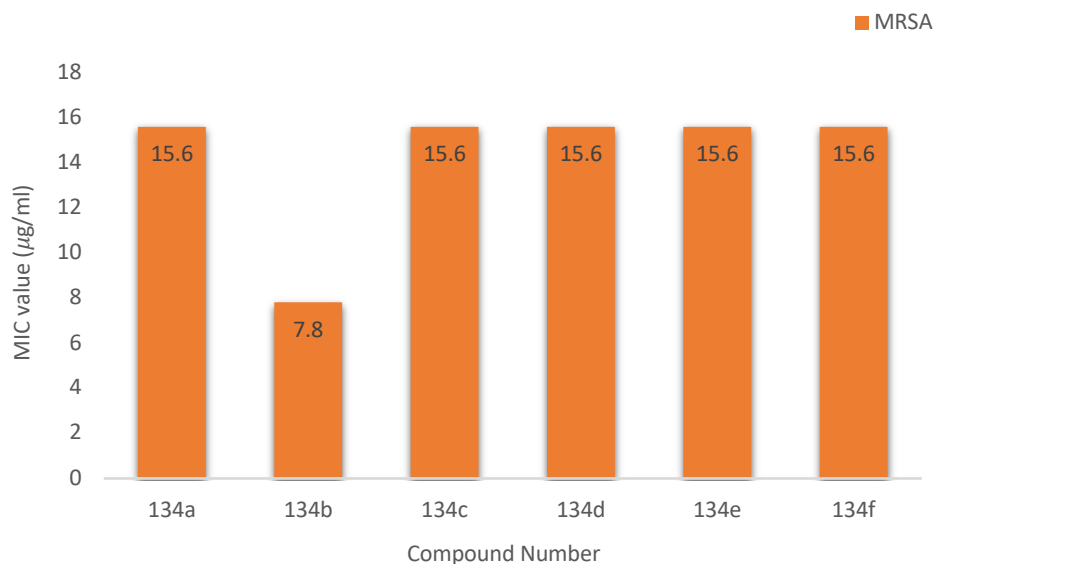


Figure 5.5: MIC values and chemical structures of C7-unfunctionalised tetramates **134a-f** against MRSA.

5.3.2: Antibacterial Activity of C7-Carboxamides

Converting the C7-unfunctionalised tetramates **134a-f** to the C7-carboxamides **157a-f** led to potent antibacterial activities against MRSA – similar to the C7-carboxamides **111-115**. Additionally, the introduction of a polar C5-ethyl ester group was well tolerated in relation to antibacterial activity. However, none of these compounds exhibited antibacterial activity against *E. coli*. The antibacterial activities for C7-carboxamides **157a-b**, **157d-f** was extremely potent against MRSA – with bioactivity

seen at concentrations of 0.25 $\mu\text{g/ml}$ – with the exception being tetramate **157c**, which had a MIC value of 3.9 $\mu\text{g/ml}$ (**Figure 5.6**). This indicated that the added grease at the *para*-position of the C4-aryl group can worsen bioactivity.

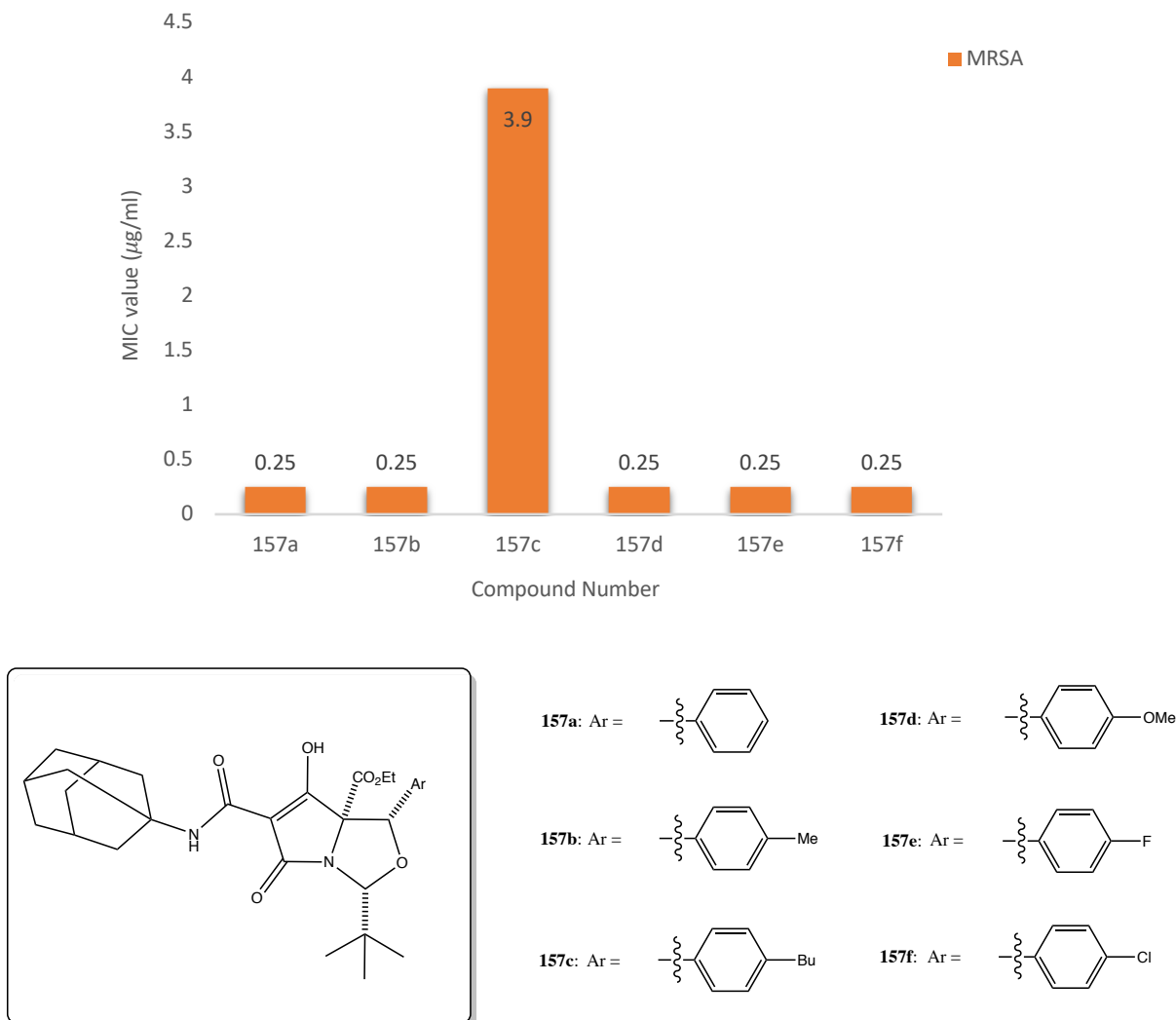


Figure 5.6: MIC values and chemical structures of C7-carboxamidotetramic acids **157a-f** against MRSA.

5.4: Evaluation of Antibacterial Activity from Chapter 4

5.4.1: Antibacterial Activity of C7-Ethyl Ester Tetramates

Analogous to C7-ethyl ester tetramates **88a-b**, C7-ethyl ester tetramates derived from imidazolidine scaffolds **249a**, **249c** and **249f** also showed no activity against MRSA and *E. coli*, however, there was some activity seen against MRSA for compounds **249b** and **249h** at concentrations of 31.25 $\mu\text{g/ml}$ (**Figure 5.7**). Again, this indicated that with appropriate functionalisation around the C2 and C4-

aromatic ring systems, that antibacterial activity can be restored within the core bicyclic structure for simple tetramic acids as seen in tetramates **88a-e**. However, an extensive library of C7-ethyl ester tetramates was not tested for antibacterial activity against MRSA or *E. coli*.

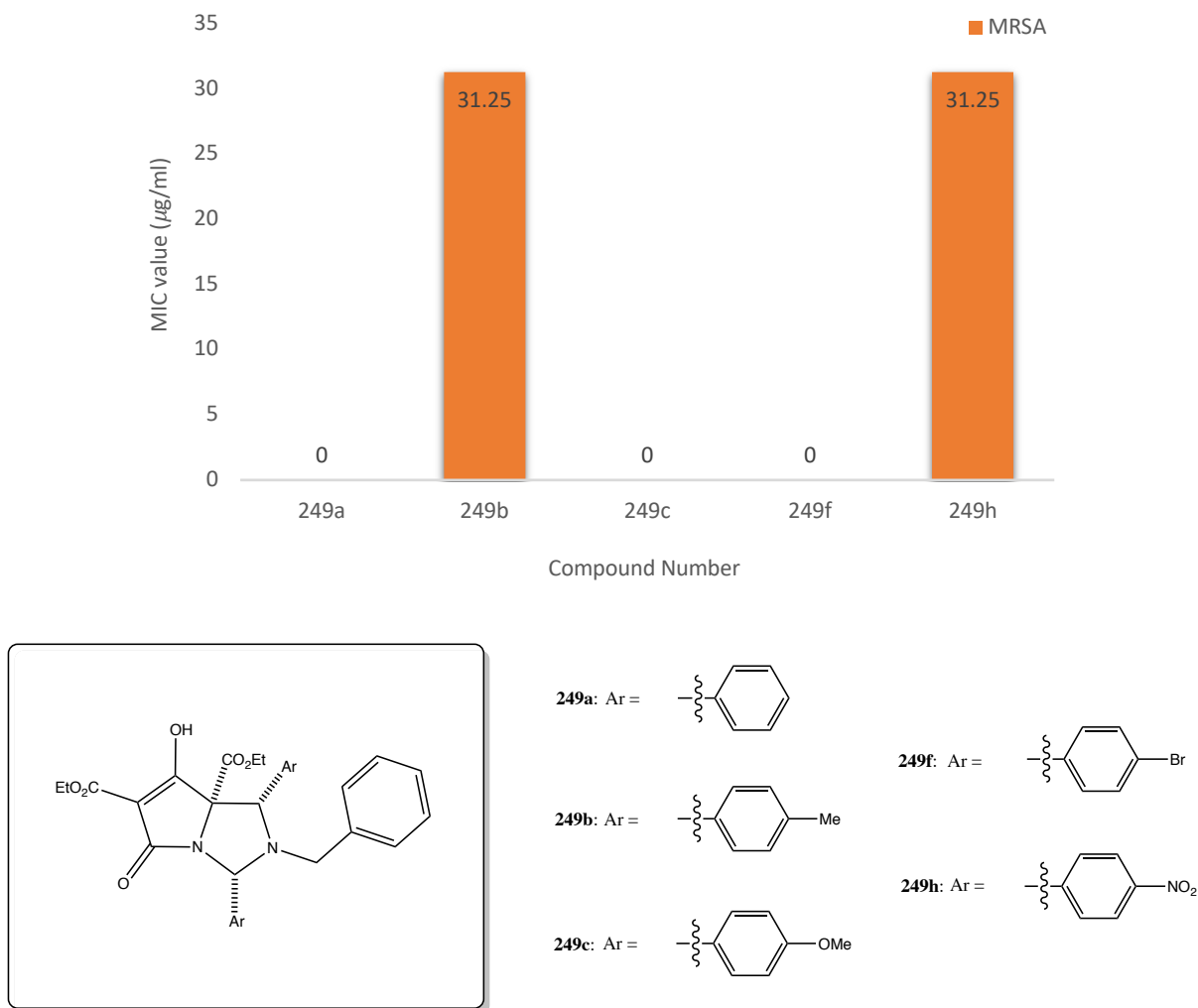


Figure 5.7: MIC values and chemical structures of C7-ethyl ester tetramates **249a-c**, **249f** and **249h** against MRSA.

5.4.2: Antibacterial Activity of C5 and C7-Carboxamides

The antibacterial activity of C5-carboxamide **260b** surprisingly showed good bioactivity against MRSA with activity seen at 3.9 µg/ml (**Figure 5.8**). This was a surprising outcome as this had shown that the formation of a C5-carboxamide can also potentially lead to potent antibacterial activity, particularly when compared with its ethyl ester counterpart **249b**. However, this research did not study in detail the role C5-carboxamides may have in relation to antibacterial activity.

Additionally, C7-carboxamides **261a-c** were tested for antibacterial activity against MRSA and *E. coli* (**Figure 5.8**). C7-carboxamide **261a** showed good antibacterial activity against MRSA with activity observed at 3.9 $\mu\text{g/ml}$, which again, demonstrated that the formation of a C7-carboxamide can lead to potent antibacterial activity, particularly when compared with its ethyl ester precursor **249a**. However, the activity of this compound **261a** was far less potent than that of the *N,O*-bicyclic tetramates **111a** and **157a**, which both had activities at 0.25 $\mu\text{g/ml}$. This had indicated that although the added C2-aromatic functionalisation and the introduction of an N3-benzyl substituent can be tolerated, this research has thus far shown a reduction in the potency of these compounds when compared with *N,O*-bicyclic tetramic acids.

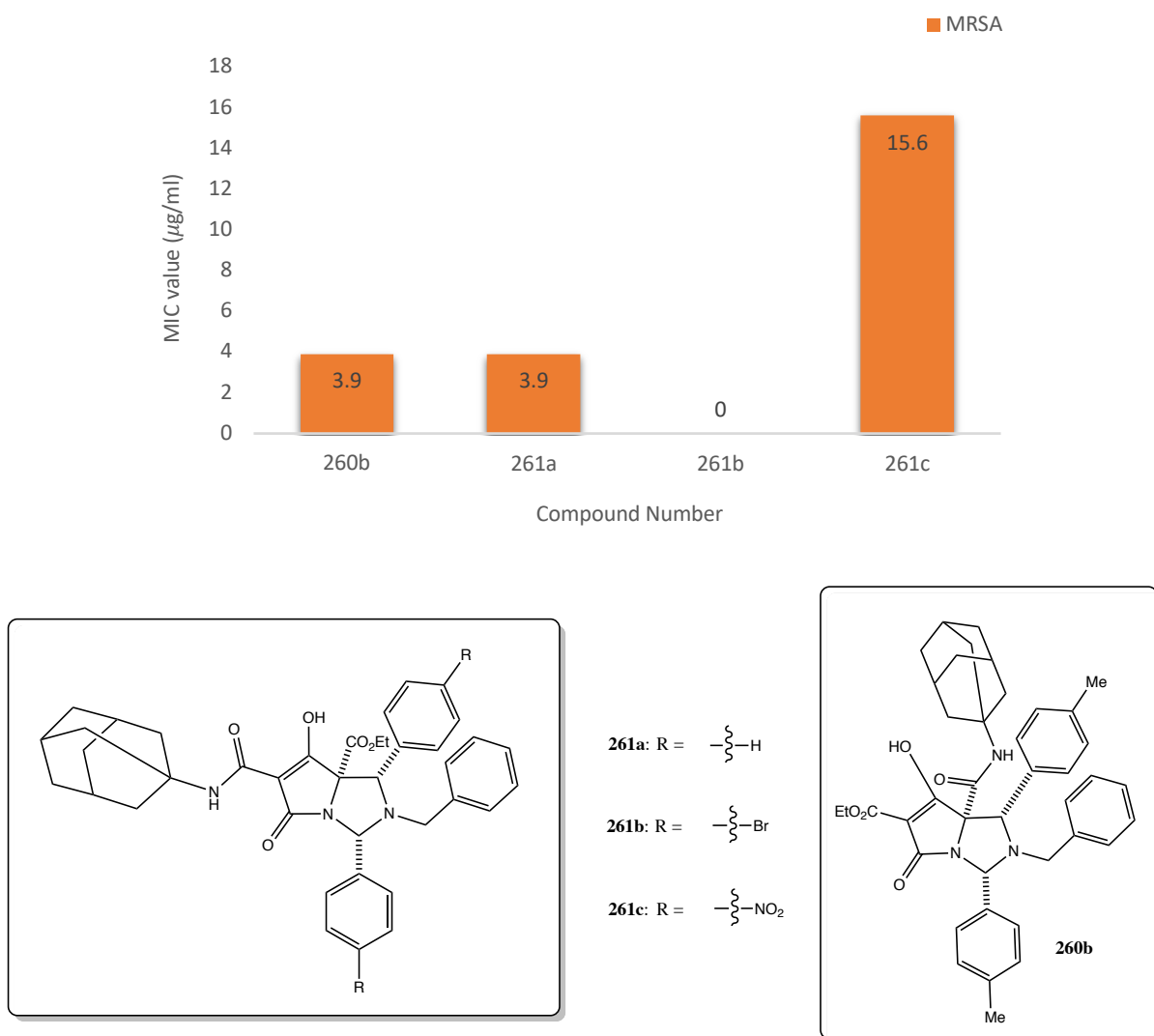


Figure 5.8: MIC values and chemical structures of C5-carboxamide **260b** and C7-carboxamides **261a-c** against MRSA.

Additionally, tetramate **261c** was far less potent than **261a**, with activity typically observed at 15.6 $\mu\text{g/ml}$, indicating that the introduction of a polar substituent in the form of a $-\text{NO}_2$ group at the *para*-position of the aromatic ring system can reduce antibacterial activity. Moreover, tetramate **261b** showed no antibacterial activity against MRSA, again, demonstrating the impact the substitution patterns around the aromatic ring system can have on antibacterial activity. Unsurprisingly, none of these carboxamides **260b** and **261a-c** were active against *E. coli*.

Future work will need to be carried out to form a library of C7-carboxamides derived from imidazolidine scaffolds, in which both the C2 and C4-aromatic ring substituents can be varied to develop an in-depth SAR analysis. Additionally, the N3-position of the bicyclic core also needs to be varied to study the role N3-substituents might have in relation to antibacterial activity. This SAR analysis will allow a more extensive study into the role imidazolidine-derived tetramic acids might have in relation to antibacterial activity by probing their physicochemical properties. Additionally, due to the ample scope for functionalisation at the C2, N3, C4, C5 and C7 positions, there is promise in examining these classes of compounds as future antibacterial therapeutics, with the proof-of-concept principle being demonstrated in this research.

5.5: Physicochemical Properties of Known Antibiotics, Natural Product

Tetramates and Bicyclic Tetramates with Antibacterial Activity

Antibiotics tend to work by targeting critical pathways that are essential to the survival of bacteria, however, only a few bacterial targets have been exploited in the drug discovery arena.⁸⁴⁻⁸⁵ The main bacterial targets are the disruption of cell wall biosynthesis (β -lactams and vancomycin), protein synthesis (tetracyclines, macrolides, aminoglycosides and oxazolidinones), RNA polymerase (rifamycin), nucleic acid synthesis (fluoroquinolones), folate biosynthesis (sulfonamides) and cell membranes (polymixins) (**Table 1.1** and **Figure 1.14**).⁸⁴⁻⁸⁵ These antibiotics however occupy very different chemical property space, and this is chiefly illustrated in their physicochemical properties.

5.5.1: Physicochemical Property Space of Known Antibiotics

It was Lipinski's seminal paper that brought attention to the role physicochemical properties might have in relation to the oral bioavailability of drugs and the possible attrition rates of drugs during both pre-clinical and clinical development.⁸⁶ Lipinski's work had demonstrated an "ideal" chemical space by considering the molecular weight (M_w), lipophilicity, hydrogen bond donors and hydrogen bond acceptors of drug compounds.⁸⁶ These parameters were dubbed Lipinski's rules or the rule of 5 (Ro5) and had a huge impact on drug discovery. The Ro5 argues that an orally bioactive compound tends to have less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, a M_w less than 500 g/mol and a $\text{Log}P$ not exceeding 5.⁸⁶

However, antibiotics have long disobeyed the Ro5, with many antibiotics falling outside these parameters, as they have to penetrate both the inner and outer membranes of prokaryotic cells.⁸⁶⁻⁸⁸ Typically, antibiotics have a $M_w > 500$ g/mol and tend to be more polar as well in comparison to other drug compounds (**Table 5.1**).⁸⁶⁻⁸⁸ Although, Lipinski himself stated that antibiotics typically fall outside these parameters,⁸⁶⁻⁸⁸ many small molecules screened by pharmaceutical companies tend to rigidly obey the Ro5, possibly accounting for the high attrition rates usually seen for finding new antibiotics. O'Shea and Moser conducted a review into antibacterial physicochemical property space, and this had shown many interesting outcomes. They had demonstrated that Gram (+) and Gram (-) antibacterials occupied very different chemical property space.⁸⁷ In the case of Gram (-) antibacterials, they tended to have much smaller M_w – with a cut-off point typically at ~ 600 g/mol in comparison to Gram (+) antibiotics that have a cut-off point at ~ 1900 g/mol.⁸⁷ Additionally, Gram (-) antibacterials were often less lipophilic and far more polar when considering their $\text{cLog}D_{7.4}$ and polar surface area (PSA) values⁸⁷ – shown in **Table 5.1**, **Figures 5.9** and **5.10**.

It was reasoned that the differences in the physicochemical property space for Gram (+) and Gram (-) antibacterials was due to the bacterial envelope of different bacteria (**Figure 1.14**). Gram (+) bacteria consists of an inner membrane that is made up of a hydrophobic phospholipid bilayer – which prevents

the penetration of hydrophilic small molecules – in addition to having a cell wall.⁸⁴ Gram (-) bacteria on the other hand, whilst also having an inner membrane and a cell wall layer, also have an added outer membrane that is made up of a lipopolysaccharide layer that is negatively charged. This layer stops large, hydrophobic compounds penetrating the outer membrane.⁸⁴ Moreover, the bacterial envelope for Gram (-) bacteria typically consists of MDR pumps that efflux out amphipathic compounds across the cell membrane, thus why it has been specifically hard to find new antibiotics for Gram (-) bacteria.⁸⁴

Mean physicochemical parameters	Gram (+) antibacterials	Gram (-) antibacterials
M _w (g/mol)	813	414
cLogP	2.1	-0.1
cLogD _{7.4}	-0.2	-2.8
PSA (Å ²)	243	165
rel. PSA (%)	30	42
H-donor	7.1	5.1
H-acceptor	16.3	9.4

Table 5.1: Mean physicochemical properties of Gram (+) and Gram (-) antibacterials; where M_w = molecular weight; cLogP = calculated partition coefficient between octanol and water; cLogD_{7.4} = calculated logarithm of the distribution coefficient at pH 7.4; PSA = calculated polar surface area; rel. PSA = relative polar surface area (derived from calculated polar surface area/calculated molecular surface area x 100); H-donor = hydrogen bond donor count; H-acceptor = hydrogen bond acceptor count. Adapted from *J. Med. Chem.*, 2008, **51**, 2871-2878.

Richter *et al.* further examined the physicochemical property space of small molecule antibacterials against *E. coli* and came up with the 'rules of permeation' for Gram (-) antibacterials.⁸⁹ They deduced that in addition to the analysis of O'Shea *et al.*,⁸⁷ that small molecules should generally have a rigid structure, have a low number of rotatable bonds and low globularity as well.⁸⁹ Additionally, they should typically be flat and possess a charged amino group (-NH₃⁺) in addition to being amphiphilic as well.⁸⁹ These criteria were considered good proponents for the development of small molecules that can permeate across the bacterial envelope of Gram (-) bacteria – using *E. coli* as a model.⁸⁹

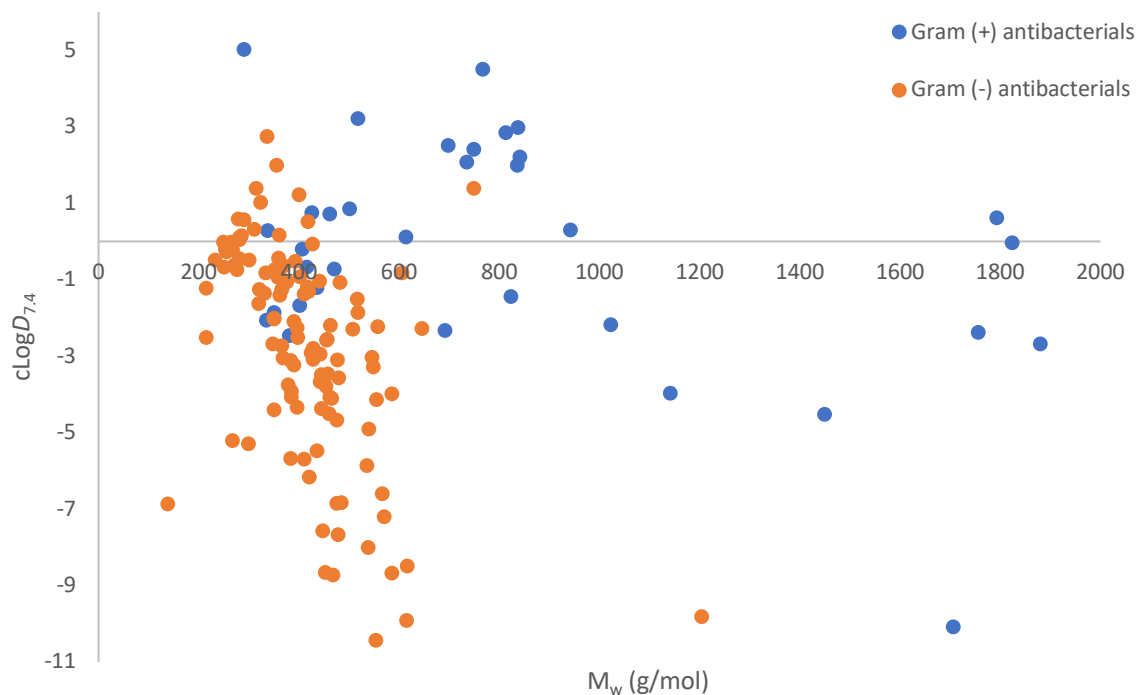


Figure 5.9: cLogD_{7.4} values plotted against M_w ; illustrating the chemical property space of Gram (+) antibacterials in comparison to Gram (-) antibacterials. Adapted from *J. Med. Chem.*, 2008, **51**, 2871-2878.

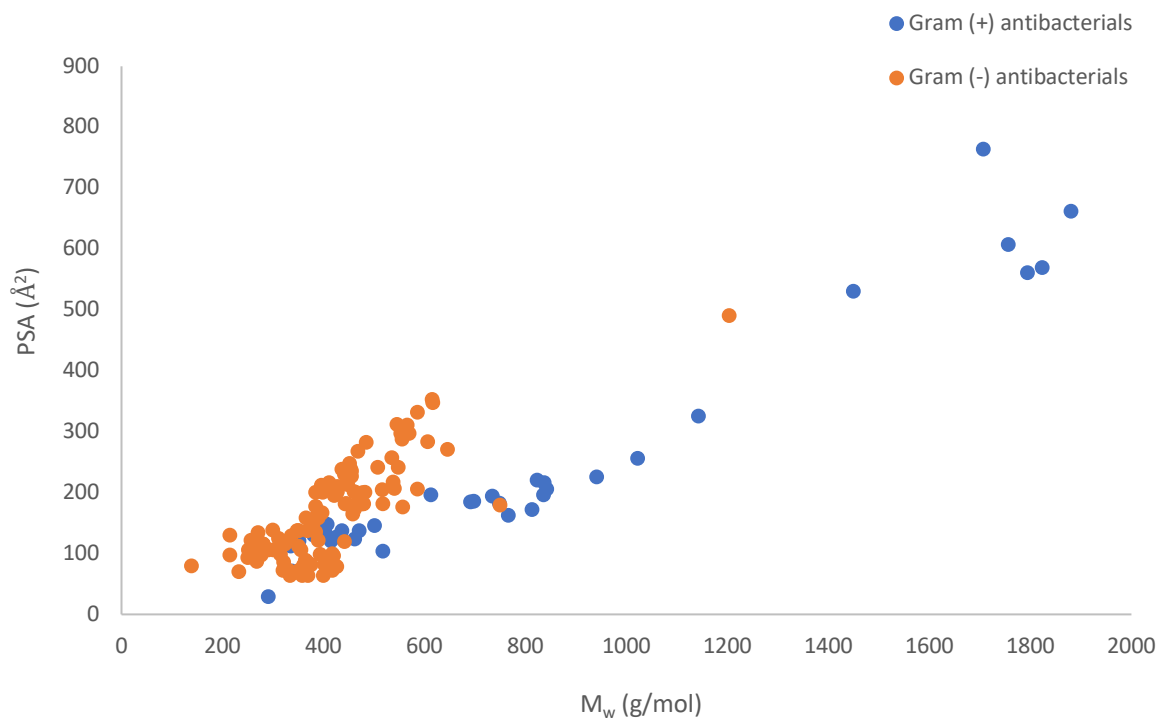


Figure 5.10: PSA values plotted against M_w ; illustrating the chemical property space of Gram (+) antibacterials in comparison to Gram (-) antibacterials. Adapted from *J. Med. Chem.*, 2008, **51**, 2871-2878.

Moreover, when looking at the physicochemical properties of each antibiotic class, they all occupied a very distinct chemical space (**Figure 5.11** and **Table 5.2**). The only antibiotic class that falls within the Ro5 was the sulfadruugs.⁸⁷ Moreover, the fluoroquinolones and oxazolidinones also occupied an area that was close to the chemical property space outlined within Lipinski's Ro5.⁸⁷ Additionally, as the fluoroquinolones are broad-spectrum antibiotics, they potentially represent a key chemical space that could be considered the 'optimum region' when developing novel antibacterial agents, particularly as they are orally bioavailable and have a good pharmacokinetic profile.⁸⁷ Gram (+) β -lactams fall just beneath the fluoroquinolone chemical property space as they are slightly more polar, however the Gram (-) β -lactams are in their own chemical space, as they are noticeably more polar – again illustrating the need for Gram (-) antibacterials to be more polar and hydrophilic to permeate through the bacterial envelope.⁸⁷ Tetracyclines are clustered closely to the Gram (-) β -lactams and are broad spectrum.⁸⁷ The aminoglycosides are Gram (-) antibiotics that occupy a unique chemical space, being extremely hydrophilic with $\text{cLogD}_{7.4} < -6$ and a $M_w > 500$ g/mol.⁸⁷ This is in stark contrast to the macrolides that are Gram (+) antibacterials that have a $M_w > 700$ g/mol and a $\text{cLogD}_{7.4} > 1$.⁸⁷

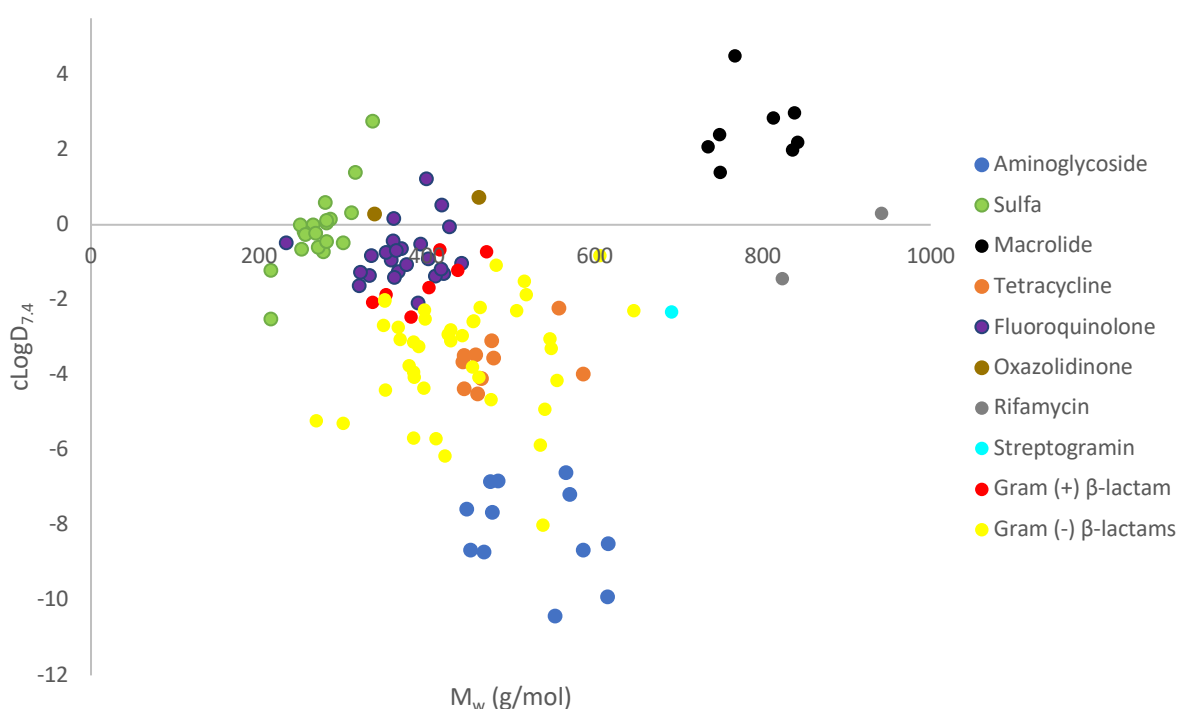


Figure 5.11: $\text{cLogD}_{7.4}$ plotted against M_w ; illustrating the distinct chemical property space for major antibiotic classes, excluding the glycopeptides. Adapted from *J. Med. Chem.*, 2008, **51**, 2871-2878.

Antibiotic Class	M _w (g/mol)	cLogP	cLogD _{7.4}	PSA (Å ²)	rel. PSA (%)	H-donor	H-acceptor
(Carba)penams	397	-3.0	-5.8	159	43	4.5	9
Penicillins	413	1.4	-2.4	149	39	2.8	8.5
Cephams	452	0.1	-3.0	210	51	4.1	10.8
Glycopeptides	1740	1.3	-1.8	586	37	22.8	37.2
Sulfa drugs	273	0.6	-0.1	112	45	3.1	6.2
Fluoroquinolones	371	1.3	-0.8	82	25	2.1	6.5
Tetracyclines	481	-0.7	-3.6	184	40	7.1	10.5
Aminoglycosides	526	-2.9	-8.1	279	54	14.8	15.4
Macrolides	790	3.5	2.6	189	23	3.6	15

Table 5.2: Average physicochemical properties of known antibiotics. Adapted from *J. Med. Chem.*, 2008, **51**, 2871-2878.

5.5.2: Physicochemical Property Space of Natural Product Tetramates with Antibacterial Activity

As discussed in **Chapter 1.5.1**, there are many natural product tetramates that exhibit antibacterial activity against many pathogenic species. The physicochemical property space of these natural products was compiled by Panduwawala *et al.*^{33,72} – as shown in **Table 5.3** below.

Natural Product Tetramates	M _w (g/mol)	cLogP	cLogD _{7.4}	PSA (Å ²)	MSA (Å ²)	rel. PSA (%)	H-donor	H-acceptor
Reutericyclin	349	5.21	1.68	74.7	578.3	12.9	1	4
Epicoccarine A	386	4.69	2.36	86.6	604.5	14.4	3	4
Vancoresmycin	1344	2.55	0.31	422.6	2174.4	19.4	17	22
Virgineone aglycone	588	6.59	3.34	144.2	983.4	14.7	5	7
Equisetin	376	3.03	0.44	77.8	589.0	13.2	2	4
Kibdelomycin	940	3.67	0.73	258.5	1282.5	20.2	6	12
Streptolydigin	601	2.09	-0.01	147.2	867.1	17.0	3	9

Table 5.3: Physicochemical properties of some natural product tetramates with antibacterial activity.

Adapted from *Org. Biomol. Chem.*, 2019, **17**, 5615-5632.

Natural product tetramates typically display Gram (+) antibacterial activity over Gram (-) antibacterial activity. When considering the physicochemical property space of many antibacterial natural product tetramates, some closely resembled the chemical property space of fluoroquinolones³³ – thus can be considered promising starting points for antibacterial drug development. Additionally, when analysing the chemoinformatic parameters of these natural products, they often occupied higher $c\text{Log}D_{7.4}$ values and were often less polar in comparison to known antibiotics, thus giving some explanation for the lack of activity observed against Gram (-) bacteria (compare **Figures 5.11** with **5.12**).

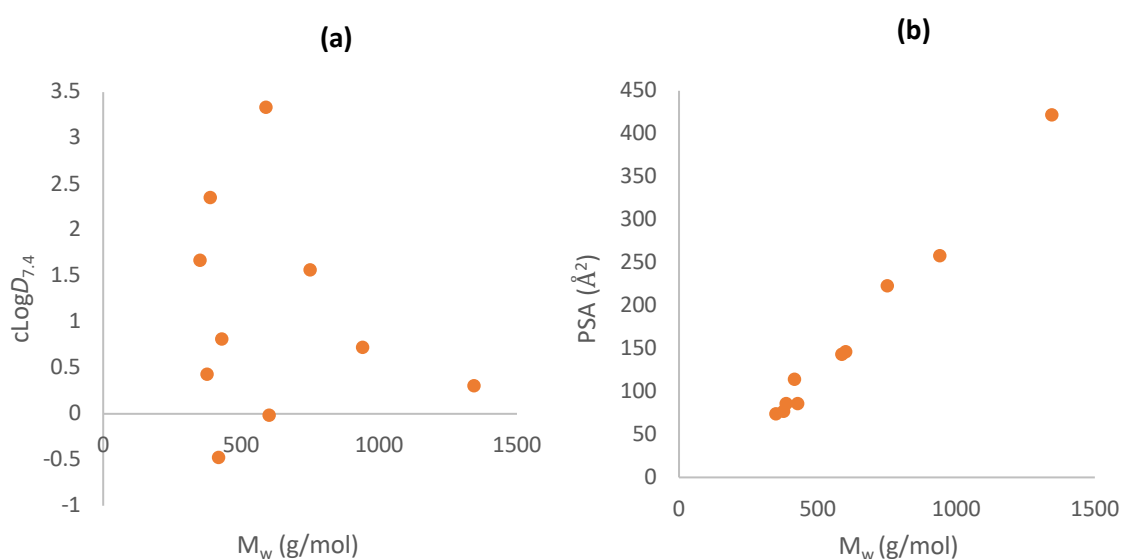


Figure 5.12: The physicochemical properties of natural product tetramates; where **(a)** shows $c\text{Log}D_{7.4}$ plotted against M_w and **(b)** shows PSA plotted against M_w .

5.5.3: Physicochemical Property Space of Bicyclic Tetramates

The physicochemical property space of bicyclic tetramates synthesised in this research is as follows; $345 < M_w < 790$ g/mol; $1.7 < c\text{Log}P < 8.5$; $9.6 < \text{rel-PSA} < 22.3\%$; with many bioactive compounds being within the Ro5 – potentially demonstrating that these compounds might be orally bioavailable (**Figures 5.13** and **5.14**, also see **Supporting Information** for full physicochemical properties of tetramates synthesised). Additionally, when considering the physicochemical property space, these compounds tended to have much higher $c\text{Log}P$ values and were generally more lipophilic than Gram (-) antibacterials, thus possibly explaining the lack of activity observed against Gram (-) *E. coli* bacteria. Moreover, when considering **Figures 5.14a-b**, it was clear to see that increasing lipophilicity

corresponded to higher potency against MRSA. Additionally, the most potent compounds – shown in red, gold and yellow – occupied a narrow region of chemical space, with $c\text{LogP}$ values ranging between $3.4 < c\text{LogP} < 6.6$ and MSA values ranging between $587 < \text{MSA} < 818 \text{ \AA}^2$. Additionally, **Figure 5.14b** also showed a cut-off point at which an increase in rel. PSA $> 14\%$ led to a marked reduction in potency.

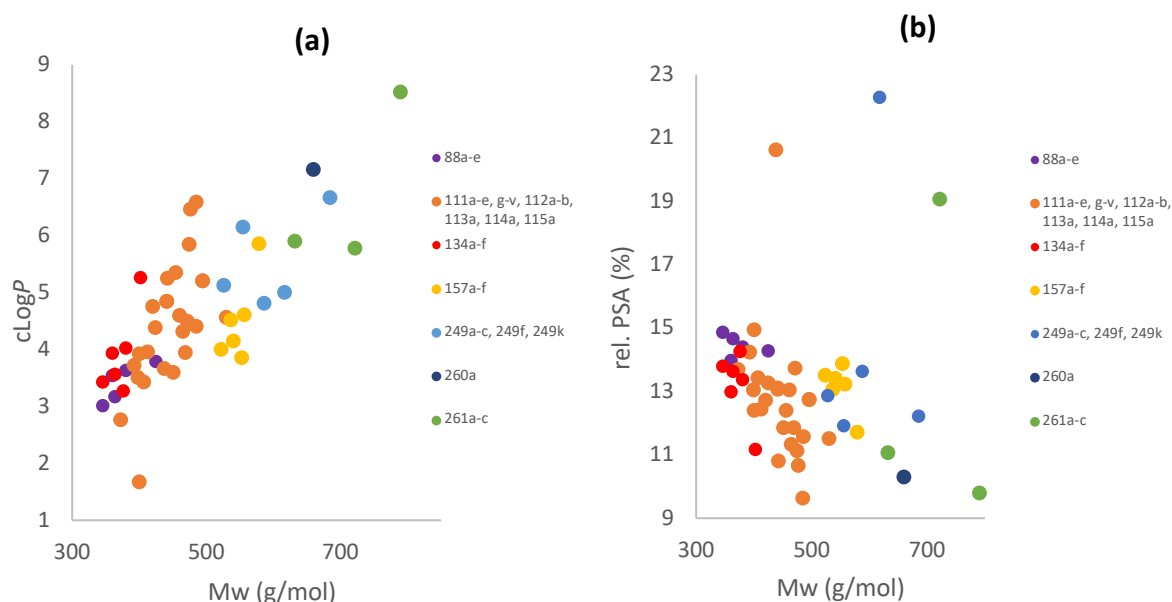


Figure 5.13: Physicochemical property space of each tetramate class synthesised; where (a) shows $c\text{LogP}$ plotted against M_w and (b) shows rel. PSA plotted against M_w ; where $c\text{LogP}$, MSA and PSA were calculated using Marvin (19.9.0), 2019, ChemAxon.

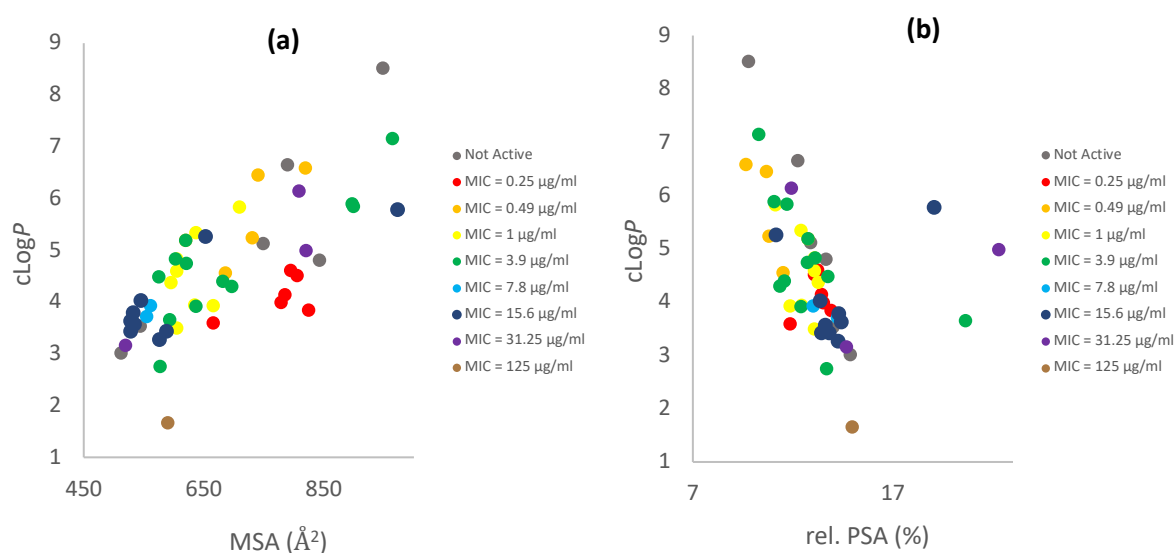


Figure 5.14: Demonstrating how potency against MRSA correlates with the physicochemical properties; where (a) shows $c\text{LogP}$ plotted against MSA and (b) shows $c\text{LogP}$ plotted against rel. PSA; where $c\text{LogP}$, MSA and PSA were calculated using Marvin (19.9.0), 2019, ChemAxon.

Figure 5.15 shows the region in chemical space these bicyclic tetramates occupied in relation to known antibiotic classes. These bicyclic tetramates were significantly more lipophilic and less polar than other antibiotic classes, thus future work will need to be carried out to make these classes of compounds more polar and hydrophilic, which might contribute to broader-spectrum activity.

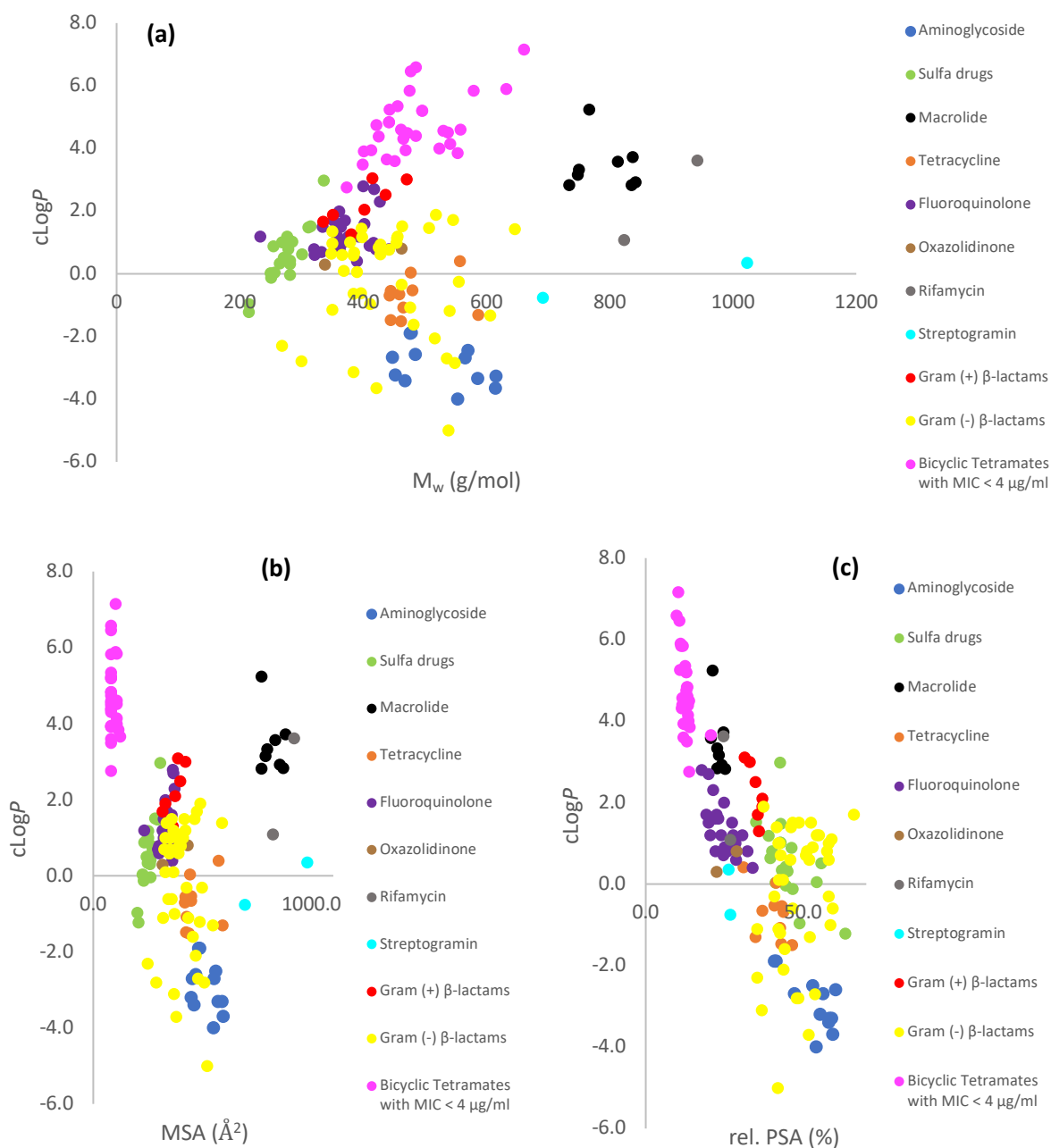
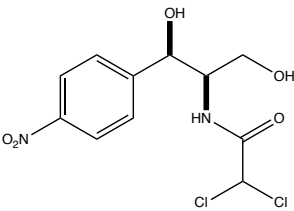
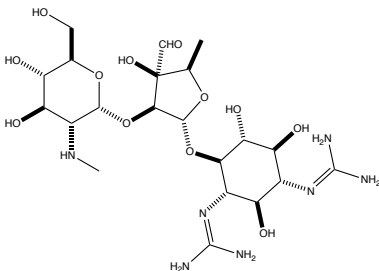
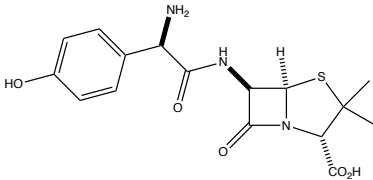
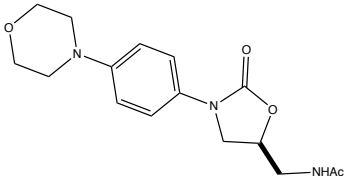
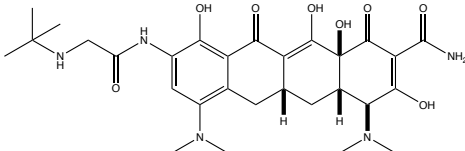


Figure 5.15: Chemical property space of bicyclic tetramates in comparison to known antibiotics. **(a)** shows cLogP plotted against M_w ; **(b)** shows cLogP plotted against MSA; **(c)** shows cLogP plotted against rel. PSA; where cLogP, MSA and PSA for tetramates were calculated using Marvin (19.9.0), 2019, ChemAxon. The remaining data was collected from *J. Med. Chem.*, 2008, **51**, 2871-2878.

Additionally, the potency of these compounds was comparable to known antibiotics as shown in **Table 5.4**, demonstrating the promise these compounds may have as being a new antibiotic class.

Antibiotic Class	Antibiotic	Structure	MIC ₅₀ value against <i>S. aureus</i> (μg/ml)
Amphenicol	Chloramphenicol		8
Aminoglycoside	Streptomycin		2
β-lactam	Amoxicillin		2
Oxazolidinone	Linezolid		2
Tetracycline	Tigecycline		0.25

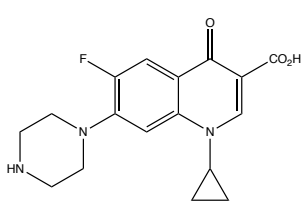
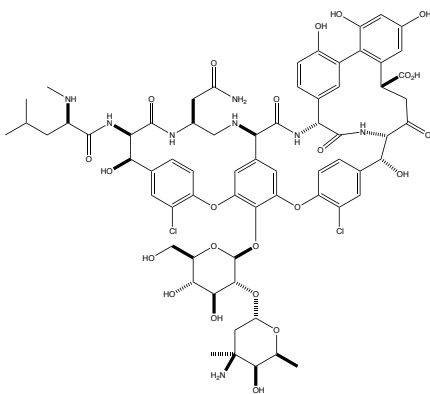
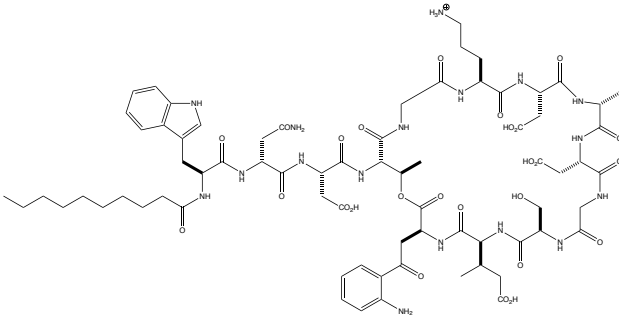
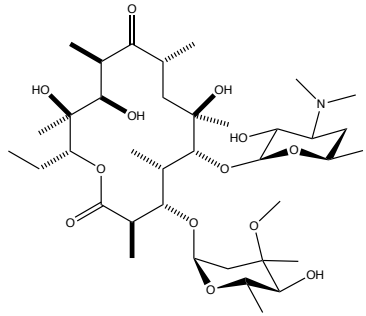
Fluoroquinolone	Ciprofloxacin		0.25
Glycopeptide	Vancomycin		0.5
Lipopeptide	Daptomycin		0.25
Macrolide	Erythromycin		0.25

Table 5.4: Known antibiotic classes and their MIC₅₀ values against *S. aureus*; where MIC₅₀ is the minimum concentration needed to inhibit 50% of bacteria. Data collected from *J. Med. Chem.*, 2008, **51**, 2871-2878.

5.6 Toxicity of Bicyclic Tetramates

Moreover, the selectivity of these compounds for prokaryotic cells over mammalian cells was analysed by considering their cytotoxicity against Hela, heK-293, CaCo and MDCK human cell lines. Additionally, the therapeutic ratio was estimated using the Hela cell line (EC_{50} Hela cell line / MIC (*S. aureus*)) (**Table 5.5**).

Compound	Cell lines EC_{50} ($\mu\text{g/ml}$)				MIC (<i>S. aureus</i>) ($\mu\text{g/ml}$)	Selected therapeutic ratio using Hela cell lines
	Hela	heK-293	CaCo	MDCK		
88c	31.3	62.5	62.5	62.5	31.3	1
88d	31.3	31.3	31.3	62.5	15.6	2
88e	31.3	62.5	62.5	62.5	15.6	2
111a	7.8	31.3	15.6	7.8	0.3	26
134a	15.6	31.3	62.5	31.3	15.6	1
134b	15.6	15.6	31.3	31.3	7.8	2
134c	7.8	3.9	31.3	15.6	15.6	0.5
134d	15.6	31.3	62.5	31.3	15.6	1
134e	15.6	31.3	62.5	31.3	15.6	1
134f	15.6	15.6	31.3	31.3	15.6	1
157a	15.6	15.6	31.3	31.3	0.3	52
157b	15.6	15.6	31.3	31.3	0.3	52
157c	15.6	31.3	31.3	62.5	3.9	4
157d	7.8	15.6	7.8	31.3	0.3	26
157e	7.8	15.6	15.6	31.3	0.3	26
157f	7.8	7.8	15.6	15.6	0.3	26
249b	31.3	31.3	62.5	31.3	31.3	1
249f	31.3	31.3	62.5	31.3	31.3	1
260b	15.6	62.5	125.0	62.5	3.9	4
261a	31.3	62.5	62.5	62.5	3.9	8
261c	62.5	62.5	62.5	125.0	15.6	4

Table 5.5: Determining cytotoxicity by evaluating the EC_{50} values against various cell lines and determining selectivity for bacteria over human cell lines by measuring the therapeutic ratio.

In the case of C7-ethyl ester tetramates **88c-e**, the therapeutic ratio was between 1-2, demonstrating a lack of selectivity against Hela cell lines and *S. aureus*, although this was mainly due to these compounds not being potent against MRSA. Additionally, carboxamide **111a** was 26-fold more selective for bacteria over Hela cell lines, showing excellent compromise between high potency and low toxicity (**Table 5.5**) – this was particularly important as antibacterial drug candidates should have >10-fold higher antibacterial activity over cytotoxicity.⁹⁰ Similar to C7-ethyl ester tetramates **88c-e**, C5-ethyl ester tetramates **134a-f** showed a lack of selectivity, although again, this was mainly due to the lack of potency observed against MRSA. Interestingly however, carboxamides **157a-b** showed even more selectivity for bacteria, with a therapeutic ratio of 52 being measured – thus indicating that the C5-ethyl esters reduce toxicity even further, particularly when compared with **111a**. Carboxamides **157d-f** showed the same selectivity as **111a**, however **157c** showed slightly poorer selectivity. Imidazolidine-derived tetramic acids **249b/f**, **260b** and **261a/c**, although were less potent against MRSA, were also significantly less toxic against various cell lines, indicating that there might be promise in developing these classes of compounds in the future. Brown *et al.*⁹¹ demonstrated that high lipophilicity correlated with increased cytotoxicity, however, these bicyclic tetramates, although being quite lipophilic, were generally non-toxic.

5.7: Activity in the Presence of Metal Ions and Human Serum Albumin

When carboxamides **111-115** were tested in the presence of blood, the activity for most of these compounds plummeted, with 15/26 carboxamides only showing activity at concentrations >124 µg/ml. However, the remaining 11 carboxamides were active at concentrations between 31.25-62.5 µg/ml. Although this was not an ideal outcome, this was still somewhat a promising result as findings from Jeong *et al.*⁴³ and Zhang *et al.*⁹² had demonstrated that C3-acyl/carboxamidotetramic acids showed in most cases, either partial or total loss of efficacy when tested in the presence of blood. This had indicated that the added C4-aryl functionalisation had some effect on the antibacterial efficacy when tested in the presence of blood. As tetramic acids are well-known metal-chelators and siderophores,⁹³⁻

⁹⁴ of interest was to investigate whether the loss of activity was due to metal-chelation or plasma protein binding (PPB), specifically with human serum albumin (HSA).^{33,43}

5.7.1: Activity in the Presence of Metal Ions

In this protocol, bicyclic tetramates **111a** and **157a-f** were tested against MRSA using a broth dilution assay, and this was used as a standard or a blank. Then these compounds were tested against MRSA together with the same ion concentration as that found in blood to see the effect metal ions may have on the MIC values. In the case of carboxamide **111a**, the activity was slightly improved when tested in the presence of metal ions – with the activity increasing from 0.49 $\mu\text{g/ml}$ to 0.24 $\mu\text{g/ml}$ (**Table 5.6**). In the case of carboxamides **157a-f**, metal ions had no measurable effect on the antibacterial activity of these bicyclic tetramates (**Table 5.6**).

5.7.2: Activity in the Presence of Human Serum Albumin

Panduawala *et al.*³³ and Jeong *et al.*⁴³ had demonstrated that carboxamidotetramic acids typically lost their antibacterial activity when tested in the presence of HSA. As HSA is one of the principal protein components within plasma – with a blood concentration of 700 μM – of interest was to study the role HSA might have in relation to antibiotic efficacy, as binding to HSA could lead to a reduction in the free drug concentration in blood.⁷² To test the role HSA had in relation to antibacterial activity, bicyclic tetramates **111a** and **157a-f** were tested against MRSA using a broth dilution assay, and this was used as a standard or a blank. Then these compounds were tested against MRSA in the presence of 1/3 the serum albumin concentration as that found in human blood. In the case of carboxamides **111a**, **157a-b**, **157d** and **157f**, the activity dropped 16-fold, and in the case of **157e**, activity reduced 33-fold. However, compound **157c** only showed a 4-fold decrease in antibacterial activity (**Table 5.6**). Although the antibacterial activity only reduced 4-fold, it was clear to see that the MIC value was shifted to higher concentrations when compared with the rest of the C7-carboxamide series. This was an interesting outcome as this compound **157c** was the most lipophilic in the carboxamide series **157a-f** (see **Supporting Information** for the calculated physicochemical properties of bicyclic tetramates).

Compound	MIC value ($\mu\text{g/ml}$) against MRSA	Experiment
111a	0.49	Blank
	0.24	With metal ions
	7.81	With HSA
157a	0.24	Blank
	0.24	With metal ions
	3.91	With HSA
157b	0.24	Blank
	0.24	With metal ions
	3.91	With HSA
157c	3.91	Blank
	3.91	With metal ions
	15.63	With HSA
157d	0.24	Blank
	0.24	With metal ions
	3.91	With HSA
157e	0.12	Blank
	0.12	With metal ions
	3.91	With HSA
157f	0.24	Blank
	0.24	With metal ions
	3.91	With HSA

Table 5.6: Antibacterial activity in the presence of metal ions and HSA.

Thus, these results indicated possible binding to HSA due to the MIC values being shifted to higher concentrations when tested in the presence of HSA, however it was not determined whether this was due to non-specific hydrophobic interactions or site-specific interactions with plasma protein. However, there is a possibility that the loss of efficacy in HSA might be attributable to non-specific hydrophobic interactions, particularly when considering the high lipophilicity of these bicyclic tetramates – as seen in the carboxamide series **157a-f**. As a result, this issue could be rectified via

adjusting the physicochemical parameters. Additionally, AstraZeneca published a review into their antibiotic drug discovery programme, in which they analysed the physicochemical parameters of their compound libraries and deduced that PPB strongly correlated with increased hydrophobicity.⁹¹

5.8: Summary

In the case of *N,O*-bicyclic tetramates, it has been demonstrated that C7-ethyl ester tetramates **88a-e** showed either no antibacterial activity or had weak antibacterial activity against MRSA. Moreover C7-unfunctionalised tetramates **134a-f** had appreciable activity against MRSA. Interestingly, conversion to the C7-carboxamides **111-115** and **157** led to much improved antibacterial activity (**Figure 5.16**). Additionally, it was shown that the use of a large, bulky, hydrophobic carboxamide pendant at the C7-position led to more potent antibacterial activity, with the most active compounds (shown in **Figure 5.17**) being comparable with known antibiotics (**Table 5.4**). However, the use of a more polar substituent at the C7-position compromised bioactivity. All the compounds screened showed no antibacterial activity against *E. coli*. This could be due to the fact that these compounds were effluxed out of bacterial cell membranes or were not polar enough to penetrate the bacterial envelope.

Additionally, it was shown that the C7-adamantylcarboxamidotetramic acids **111a**, **157a-f** were very selective for bacteria over mammalian cells, with the polar C5-ethyl esters in the case of **157** potentially reducing toxicity even further (**Figure 5.16**). Many of the compounds synthesised were within the Ro5 (shown in the **Supporting Information** Section), indicating that these compounds might have 'drug-like' properties, in which they might be orally bioavailable and have a good ADMET profile, however, as stated above, the physicochemical parameters of these compounds need to be fine-tuned to make these compounds have reduced lipophilicity and increased polarity, which might contribute to broader spectrum activity against Gram (-) bacteria. Moreover, these compounds occupied a distinct chemical property space different from that occupied by other known antibiotics, with the most potent compounds occupying these parameters; $399 < M_w < 557$; $2.7 < cLogP < 6.6$; $587 < MSA < 818 \text{ \AA}^2$; $9.6 < \text{rel. PSA} < 20.6\%$.

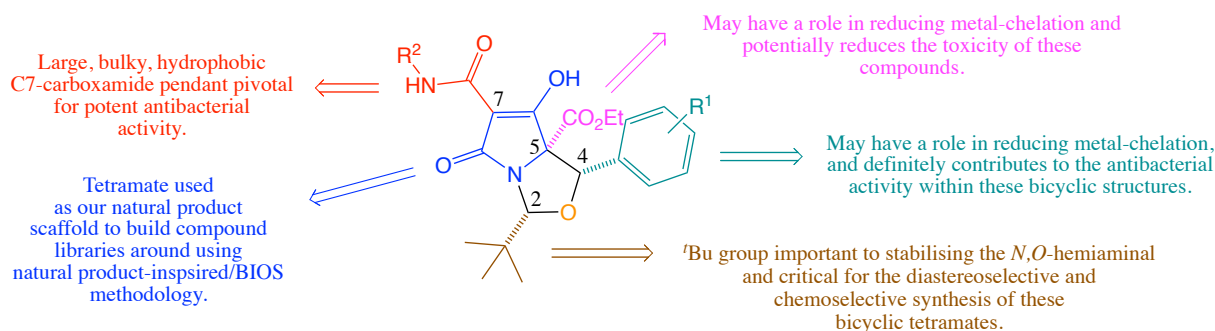
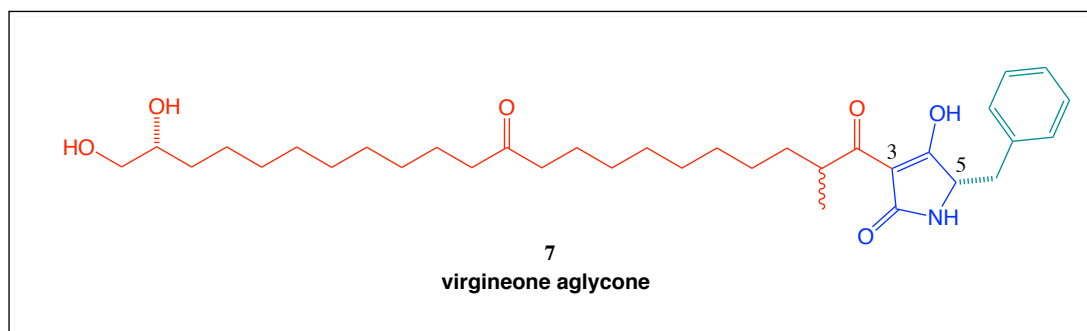


Figure 5.16: Overview of the chemical components necessary for potent antibacterial activity against MRSA, derived from an in-depth SAR analysis of the *N,O*-bicyclic tetramates.

The synthesis of these compounds was generally straightforward, cost-efficient and could be prepared in gram-scale quantities. Additionally, although the mode of action for these compounds have not yet been determined, Panduwawala *et al.* and Jeong *et al.* had demonstrated that similar bicyclic tetramates have shown modes of action against RNAP and UPPS – with UPPS being a novel mode of action that targets bacterial fatty acid synthesis that is important for cell wall biosynthesis – thus there being a low chance for resistance to occur rapidly, particularly as many of these systems have dual modes of action.^{33,43} Panduwawala *et al.* had also demonstrated that these classes of compounds are chemically stable in that they do not react with nucleophiles such as L-cysteine,³³ and were found not to initiate hemolysis.⁴³

Unfortunately, these compounds suffered from PPB, leading to the MIC values being shifted to higher concentrations when tested in the presence of HSA or blood, although it is possible that this could be rectified by adjusting the physicochemical parameters of these bicyclic tetramates. Alternatively,

instead of *in-vivo* use, these antibacterials agents might find applications in topical use, such as treating for acute skin and skin structure infections, ear infections or respiratory infections which are often caused by Gram (+) bacteria.

Considering the physicochemical properties, potency and toxicity of these compounds, some of the most promising candidates for further optimisation were **111a** and **111i** which all complied with the Ro5. Additionally, although compounds **115a**, **157a-b**, **157d-f** had a $M_w > 500$ g/mol, they could also be considered excellent candidates for optimisation as well (**Figure 5.17**).

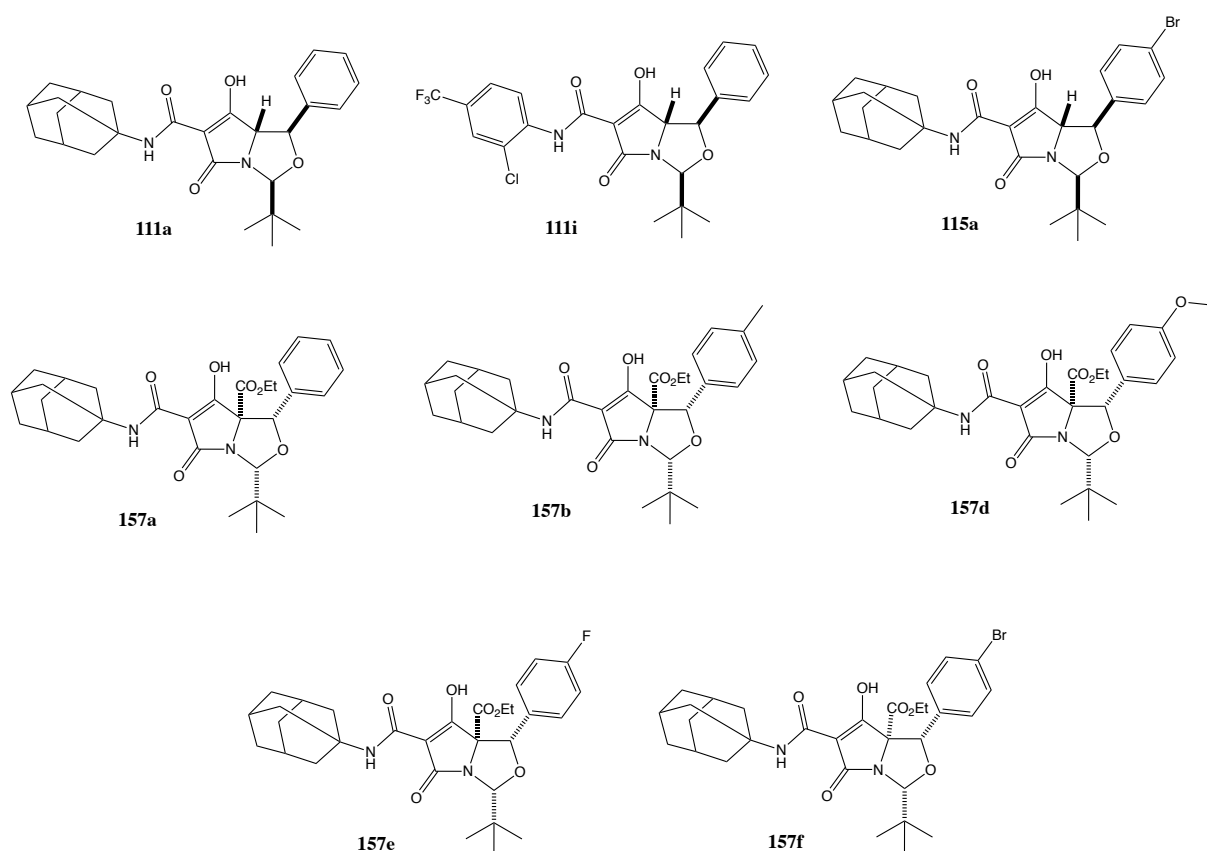


Figure 5.17: Most promising compounds for future development.

Additionally, it was demonstrated that in the case of imidazolidine-derived tetramic acids, that C2-aryl functionalisation can be tolerated, although with reduced bioactivity observed against MRSA. Additionally, the toxicity profile of **260b**, **261a**, **261c** demonstrated that these compounds were far less toxic than their *N,O*-bicyclic counterparts. The synthesis of these compounds was relatively

straightforward and diastereoselective, however, further studies are required to examine the stability of these *N,N*-aminals. Additionally, an in-depth SAR analysis would be required to assess the promise these compounds might have as being future antibacterial therapeutics, with ample scope for the physicochemical parameters to be adjusted at the C2, C4 and N3-positions. However, the proof-of-concept principle has been demonstrated that these classes of compounds might have promise as being future therapeutics.

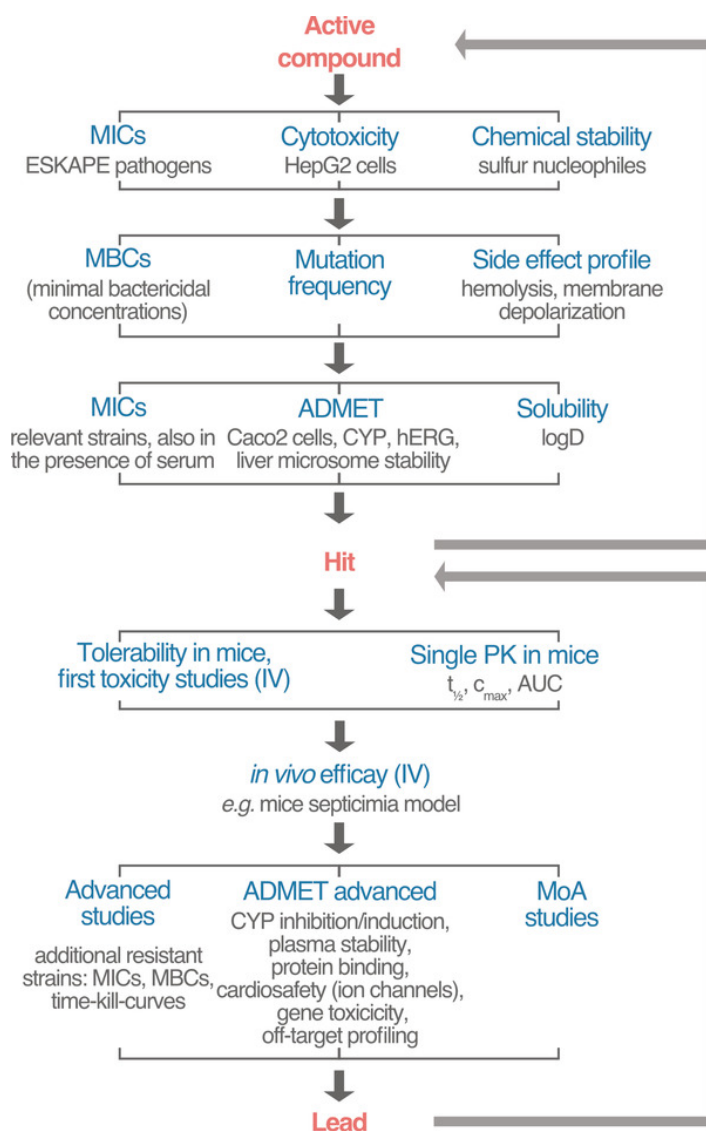


Figure 5.18: Diagram showing the drug discovery process for developing novel antibiotics; where CYP = cytochrome P450; hERG channel = human ether-a-go-go related gene; LogD = distribution coefficient; IV = intravenous; PK = pharmacokinetics; $t_{1/2}$ = elimination half-life; c_{max} = maximal concentration of drug; AUC = area under the curve; MoA = mode of action. Copyright (2018) Wiley. Used with

permission from M. Lakemeyer, W. Zhao, F.A. Mandl, P. Hammann and S.A. Sieber, Thinking Outside the Box – Novel Antibacterials to Tackle the Resistance Crisis, *Angew. Chem. Int. Ed.*, Wiley-VCH.

Thus, this research has demonstrated that natural products should once again be considered for antibacterial drug discovery. Interestingly, the use of natural product-inspired/BIOS drug discovery was hugely successful, with many of the simpler analogues of virgineone aglycone **7** being more potent than the natural product itself. Additionally, these compounds have well-defined 3-D templates and were densely functionalised, possibly allowing ‘escape from flatland’.⁹⁵ Hence, this research has demonstrated the potential these compounds may have as being a new antibiotic class, where an active compound in the form of virgineone aglycone **7** has nearly been converted to a hit compound through the drug discovery process outlined in **Figure 5.18**; with the last step being the need to rectify the issue of serum-binding to allow *in-vivo* studies to take place in mice.

Chapter 6: Experimental Section

6.1: General Methods

Overnight reaction refers to reactions occurring between 15-24 h. All reagents were obtained from commercial sources and was used without further purification. Anhydrous solvents were dried by pre-storing them over activated 3 Å molecular sieves before being passed through an activated alumina column on a solvent tower under N₂ pressure. Solvents were evaporated at 40°C under reduced pressure on a Büchi R-114 rotatory evaporator attached to a Vacuubrand CVC2 pump and a pressure control system, with the exception of water, which was evaporated between 70-80°C.

Analytical thin-layer chromatography (TLC) was carried out on Merck aluminium foil backed sheets precoated with 0.2 mm Kielselgel 60 F₂₅₄. The eluent used is specified in each case. The spots were visualised by UV irradiation ($\lambda=254$ nm) and by staining with KMnO₄ solution followed by heating. Retention factors (R_f) are quoted to the nearest 0.01. Flash column chromatography was performed on Kielselgel 60 silica gel (230-400 mesh particle size).

Melting points were measured using a Stuart Scientific SMP1 melting point instrument and are uncorrected.

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with an attached Pike Miracle attenuated total reflectance (ATR) module. Absorption maxima ($\nu_{\max}$) are reported in wavenumbers (cm⁻¹) and only selected peaks are reported.

¹H-NMR spectra were recorded at 200 MHz, 400 MHz and 500 MHz, ¹³C-NMR spectra were recorded at 101 MHz or 126 MHz and ¹⁹F-NMR spectra were recorded at 377 MHz or 471 MHz using either a Bruker DPX200, AVIIIHD 400 and AVIIIHD 500. Chemical shifts (δ_H , δ_F and δ_C) are reported in parts per million (ppm) upfield from TMS and are referenced to the residual solvent peak (in some cases, it was

not possible to reference the chloroform peak in the ^1H -NMR spectra due to it being obscured by aromatic protons). Coupling constants (J) are quoted in Hertz (Hz). Data is reported in this format: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = double doublet, dt = double triplet, dq = double quartet, m = multiplet, br = broad and app = apparent), coupling constant, and assignment. Two-dimensional COSY, HSQC, HMBC and NOESY experiments were recorded at 400 MHz and 500 MHz and nOe experiments were recorded at 500 MHz. Assignments of the spectra were made with ^1H , COSY, HSQC, HMBC, ^{13}C and DEPT-135 experiments and stereochemistry were assigned on the basis of nOe, NOESY or X-ray crystallography.

Low resolution mass spectra (m/z) were recorded on an Agilent 6120 spectrometer or a Waters LCT Premier XE spectrometer using electrospray ionisation (ESI). Selected peaks are reported in Daltons and their intensities given as percentages of the base peak. High resolution mass spectra (HRMS) were recorded on a Bruker microTOF (ESI) or on an Agilent 7200 Q-TOF (EI or CI).

Crystals for X-ray crystallography were grown from slow vapour diffusion of petroleum ether 40:60 into a solution of compound dissolved in minimal EtOAc at room temperature. Low temperature⁹⁶ single-crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer. Raw frame data were collected and reduced using CrysAlisPro and the structures were solved using 'Superflip'⁹⁷ before refinement with CRYSTALS⁹⁸.

6.2: Experimental Section for Chapter 2

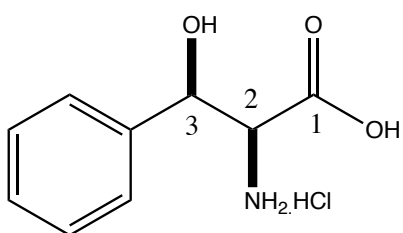
General procedure for the synthesis of *threo*-phenylserines:⁵²

Method A: To a stirring solution of 3 M NaOH (aq.) (1.5 eq.) at rt was added glycine (1.0 eq.) and the solution was stirred for 10 min. Benzaldehyde (2.1 eq.) was added and the solution was stirred until a solid condensation cake formed. The solid was broken apart after 48-72 h at rt and 3 M HCl (aq.) was added to acidify the solution to pH 1 and the mixture was stirred until the solid was consumed to give a clear solution. The solution was separated between Et₂O and water and the aqueous layer was

reduced to dryness *in-vacuo* to give β -arylserine **81a** as a HCl salt that was contaminated with NaCl and was used without further purification.

Method B: To a stirring solution of 3 M KOH (eth.) (1.5 eq.) at rt was added glycine (1.0 eq.) and the solution was stirred for 10 min (glycine tended to be sparingly soluble in ethanolic solution). Aldehyde (2.1 eq.) was then added, and the solution was stirred until a condensation cake formed. The solid was broken apart after 48-72 h at rt and 3 M HCl (aq.) was added to acidify the solution to pH 1 and the mixture was stirred until the solid was consumed to give a clear solution. The solution was separated between Et₂O and water and the aqueous layer was reduced to dryness *in-vacuo* to give β -arylserines **81a-e** as HCl salts that were contaminated with KCl and was used without further purification.

(2S*,3R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid hydrochloride salt 81a



Method A: Yield (9.12 g, Quantitative, contaminated with NaCl);

Off-white solid; m.p. 159-163°C (lit.⁵² 150-152°C); $\nu_{\max}/\text{cm}^{-1}$ 3033

(O-H/N-H), 1725 (C=O); Diastereomeric ratio between

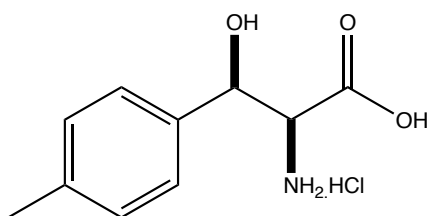
threo:erythro 93:7; $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 4.07 (1H, d, $J=4.1$ Hz,

H2), 5.37 (1H, d, $J=4.0$ Hz, H3), 7.28-7.51 (5H, m, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 60.2 (C2), 71.0 (C3),

125.9 (Ar-C), 128.7 (Ar-C), 129.0 (Ar-C), 138.6 (Ar-C), 171.4 (C1); LRMS (ESI⁻) m/z : 180.1 ([M - H]⁻ 96%);

HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₉H₁₀NO₃, 180.0666, found 180.0659.

(2S*,3R*)-2-Amino-3-hydroxy-3-(4-methylphenyl)propanoic acid hydrochloride salt 81b



Method B: Yield (10.55 g, Quantitative, contaminated with KCl);

Off-white solid; m.p. 165-169°C; $\nu_{\max}/\text{cm}^{-1}$ 3331 (O-H), 3038 (N-

H), 1734 (C=O); Diastereomeric ratio between *threo:erythro*

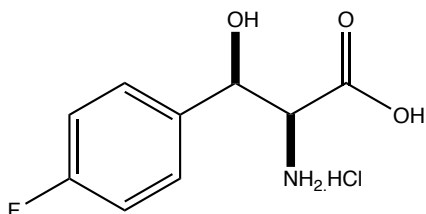
19:1; $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 2.37 (3H, s, CH₃), 4.26 (1H, d, $J=4.2$

Hz, H2), 5.40 (1H, d, $J=4.2$ Hz, H3), 7.34 (2H, d, $J=8.2$ Hz, Ar-H), 7.40 (2H, d, $J=8.1$ Hz, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101

MHz, D₂O) 20.3 (CH₃), 59.4 (C2), 70.6 (C3), 125.9 (Ar-C), 129.6 (Ar-C), 135.1 (Ar-C), 139.2 (Ar-C), 170.3

(C1); LRMS (ESI⁺) m/z : 234.1 ([M + K]⁺ 55%), 391.2 ([2M + H]⁺ 21%), 429.2 ([2M + K]⁺ 100%); LRMS (ESI⁻) m/z : 194.1 ([M - H]⁻ 97%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₀H₁₄NO₃, 196.0968, found 196.0970.

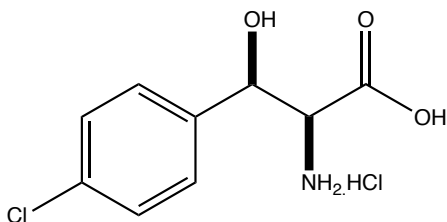
(2S*,3R*)-2-Amino-3-hydroxy-3-(4-fluorophenyl)propanoic acid hydrochloride salt 81c



Method B: Yield (3.61 g, 76%, contaminated with KCl); Off-white solid; m.p. 167-170°C (lit.⁹⁹ 162-164°C); $\nu_{\max}/\text{cm}^{-1}$ 3324 (O-H), 2892 (N-H), 1735 (C=O); Diastereomeric ratio between *threo*:*erythro* 84:16; $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 4.10 (1H, d, $J=4.3$

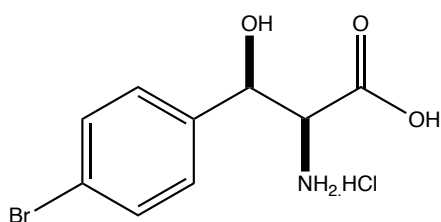
Hz, H2), 5.35 (1H, d, $J=4.2$ Hz, H3), 7.17 (2H, m, Ar-H), 7.43 (2H, m, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 59.8 (C2), 70.4 (C3), 115.7 (d, $J=21.9$ Hz, Ar-C), 127.8 (d, $J=8.6$ Hz, Ar-C), 134.4 (d, $J=2.9$ Hz, Ar-C), 162.5 (d, $J=244.3$ Hz, Ar-C), 170.8 (C1); $\delta_{\text{F}}(\text{Threo})$ (377 MHz, D₂O) -114.19; LRMS (ESI⁺) m/z : 238.1 ([M + K]⁺ 58%), 437.1 ([2M + K]⁺ 95%); LRMS (ESI⁻) m/z : 198.0 ([M - H]⁻ 95%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₉H₁₁NO₃F, 200.0717, found 200.0720.

(2S*,3R*)-2-Amino-3-hydroxy-3-(4-chlorophenyl)propanoic acid hydrochloride salt 81d



Method B: Yield (6.98 g, 68%, contaminated with KCl); Off-white solid; m.p. 171-176°C; $\nu_{\max}/\text{cm}^{-1}$ 3316 (O-H), 3064 (N-H), 1733 (C=O); Diastereomeric ratio between *threo*:*erythro* 9:1; $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 4.22 (1H, d, $J=4.0$ Hz, H2), 5.39 (1H, d,

$J=4.0$ Hz, H3), 7.42 (2H, d, $J=8.7$ Hz, Ar-H), 7.46 (2H, d, $J=8.7$ Hz, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 59.2 (C2), 70.1 (C3), 127.5 (Ar-C), 129.0 (Ar-C), 133.9 (Ar-C), 136.9 (Ar-C), 170.2 (C1); LRMS (ESI⁻) m/z : 214.0 ([M³⁵ - H]⁻ 97%), 216.0 ([M³⁷ - H]⁻ 32%); HRMS (ESI⁻) m/z : [M³⁵ - H]⁻ calcd. for C₉H₉NO₃Cl, 214.0276, found 214.0273; [M³⁷ - H]⁻ calcd. for C₉H₉NO₃Cl, 216.0247, found 216.0243.

(2*S,3*R**)-2-Amino-3-hydroxy-3-(4-bromophenyl)propanoic acid hydrochloride salt **81e****

Method B: Yield (6.33 g, Quantitative, contaminated with KCl);

Off-white solid; m.p. 190-193°C; $\nu_{\max}/\text{cm}^{-1}$ 3324 (O-H), 3031 (N-H), 1740 (C=O); Diastereomeric ratio between *threo*:*erythro*

94:6; δ_{H} (*Threo*) (400 MHz, D₂O) 4.28 (1H, d, $J=3.9$ Hz, H2), 5.38

(1H, d, $J=3.8$ Hz, H3), 7.34 (2H, d, $J=8.6$ Hz, Ar-H), 7.58 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (*Threo*) (101 MHz, D₂O)

58.8 (C2), 69.9 (C3), 122.2 (Ar-C), 127.8 (Ar-C), 132.0 (Ar-C), 137.1 (Ar-C), 169.7 (C1); LRMS (ESI⁺) m/z :

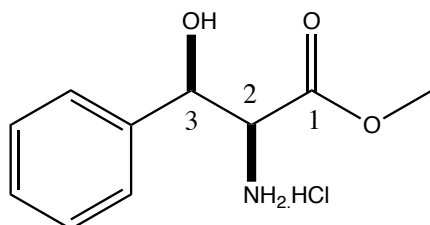
260.0 ([M⁷⁹ + H]⁺ 42%), 262.0 ([M⁸¹ + H]⁺ 41%); LRMS (ESI⁻) m/z : 258.0 ([M⁷⁹ - H]⁻ 97%), 260.0 ([M⁸¹ -

H]⁻ 97%); HRMS (ESI⁺) m/z : [M⁷⁹ + H]⁺ calcd. for C₉H₁₁NO₃Br, 259.9917, found 259.9919; [M⁸¹ + H]⁺ calcd.

for C₉H₁₁NO₃Br, 261.9896, found 261.9898.

General procedure for the synthesis of amino ester hydrochlorides:⁵³

SOCl₂ (1.2 eq.) was added dropwise to a stirring solution of amino acid **81a-e** (1.0 eq.) in MeOH or EtOH at 0°C and left to stir for 15 mins at this temperature. The mixture was then refluxed overnight. The reaction was then stopped and left to cool to rt and then the solvent was evaporated under reduced pressure to give the methyl/ethyl ester hydrochloride salt **82a-f** and was used without further purification.

Methyl (2*S,3*R**)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride salt **82a****

Yield (9.31 g, 96%, contaminated with NaCl); Off-white/cream

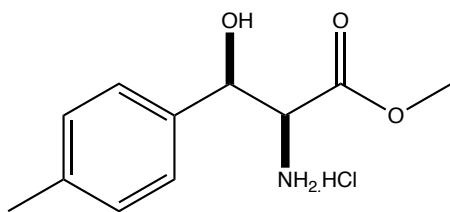
solid; m.p. 168-171°C (lit.¹⁰⁰ 179-180°C); $\nu_{\max}/\text{cm}^{-1}$ 3321 (O-H), 2997 (N-H), 1744 (C=O); δ_{H} (*Threo*) (400 MHz, D₂O) 3.79 (3H, s,

OCH₃), 4.37 (1H, d, $J=4.0$ Hz, H2), 5.40 (1H, d, $J=4.0$ Hz, H3), 7.22-

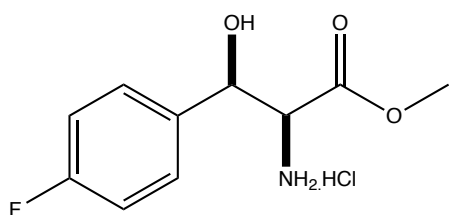
7.46 (5H, m, Ar-H); δ_{C} (*Threo*) (101 MHz, D₂O) 53.7 (OCH₃), 59.0 (C2), 70.5 (C3), 125.8 (Ar-C), 129.0 (Ar-C),

129.1 (Ar-C), 137.5 (Ar-C), 168.5 (C1); LRMS (ESI⁺) m/z : 196.1 ([M + H]⁺ 18%), 218.1 ([M + Na]⁺ 9%),

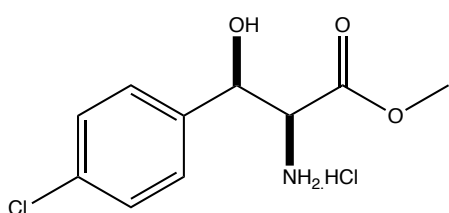
391.2 ([2M + H]⁺ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₀H₁₄NO₃, 196.0968, found 196.0971.

Methyl (2*S,3*R**)-2-amino-3-hydroxy-3-(4-methylphenyl)propanoate hydrochloride salt 82b**

Yield (10.86 g, 98%, contaminated with KCl); Off-white/cream solid; m.p. 180-183°C; $\nu_{\max}/\text{cm}^{-1}$ 3347 (O-H), 3014 (N-H), 2913 (C-H), 1758 (C=O); $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 2.41 (3H, s, CH₃), 3.90 (3H, s, OCH₃), 4.46 (1H, d, $J=4.5$ Hz, H₂), 5.44 (1H, d, $J=4.5$ Hz, H₃), 7.38 (2H, d, $J=8.1$ Hz, Ar-H), 7.42 (2H, d, $J=8.3$ Hz, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 20.4 (CH₃), 53.8 (OCH₃), 59.1 (C₂), 70.6 (C₃), 126.0 (Ar-C), 129.7 (Ar-C), 134.6 (Ar-C), 139.4 (Ar-C), 168.6 (C₁); LRMS (ESI⁺) m/z : 248.1 ([M + K]⁺ 39%), 419.2 ([2M + H]⁺ 100%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₁H₁₅NO₃Na, 232.0944, found 232.0947.

Methyl (2*S,3*R**)-2-amino-3-hydroxy-3-(4-fluorophenyl)propanoate hydrochloride salt 82c**

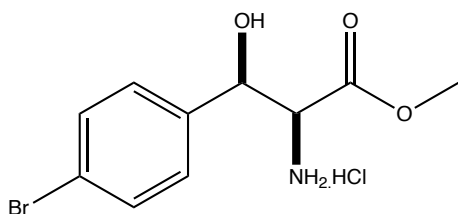
Yield (1.16 g, 97%, contaminated with KCl); Off-white/cream solid; m.p. 167-169°C; $\nu_{\max}/\text{cm}^{-1}$ 3313 (O-H), 3002 (N-H), 2910 (C-H), 1744 (C=O); $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 3.85 (3H, s, OCH₃), 4.43 (1H, d, $J=4.1$ Hz, H₂), 5.45 (1H, d, $J=4.1$ Hz, H₃), 7.21 (2H, app. t, $J=8.9$ Hz, Ar-H), 7.49 (2H, dd, $J=5.4$ Hz, 8.6 Hz, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 53.8 (OCH₃), 59.0 (C₂), 70.0 (C₃), 115.9 (d, $J=21.8$ Hz, Ar-C), 127.9 (d, $J=8.5$ Hz, Ar-C), 133.5 (d, $J=3.0$ Hz, Ar-C), 162.6 (d, $J=244.7$ Hz, Ar-C), 168.5 (C₁); $\delta_{\text{F}}(\text{Threo})$ (377 MHz, D₂O) -113.73; LRMS (ESI⁺) m/z : 252.1 ([M + K]⁺ 41%), 427.2 ([2M + H]⁺ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₀H₁₃NO₃F, 214.0874, found 214.0885.

Methyl (2*S,3*R**)-2-amino-3-hydroxy-3-(4-chlorophenyl)propanoate hydrochloride salt 82d**

Yield (7.08 g, Quantitative, contaminated with KCl); Off-white/cream solid; m.p. 184-186°C; $\nu_{\max}/\text{cm}^{-1}$ 3319 (O-H), 2998 (N-H), 2912 (C-H), 1744 (C=O); $\delta_{\text{H}}(\text{Threo})$ (400 MHz, D₂O) 3.87 (3H, s, OCH₃), 4.46 (1H, d, $J=4.2$ Hz, H₂), 5.46 (1H, d, $J=4.2$ Hz, H₃), 7.47 (2H, d, $J=8.7$ Hz, Ar-H), 7.51 (2H, d, $J=8.9$ Hz, Ar-H); $\delta_{\text{C}}(\text{Threo})$ (101 MHz, D₂O) 53.9 (OCH₃), 58.9 (C₂), 70.0 (C₃), 127.6 (Ar-C), 129.1 (Ar-C), 134.1 (Ar-C), 136.4 (Ar-C), 168.5 (C₁); LRMS (ESI⁺) m/z :

268.0 ($[M^{35} + K]^+$ 41%), 270.0 ($[M^{37} + K]^+$ 15%); HRMS (ESI⁺) m/z : $[M^{35} + H]^+$ calcd. for $C_{10}H_{13}NO_3Cl$, 230.0578, found 230.0579; $[M^{37} + H]^+$ calcd. for $C_{10}H_{13}NO_3Cl$, 232.0549, found 232.0550.

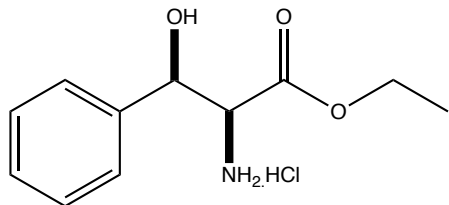
Methyl (2*S,3*R**)-2-amino-3-hydroxy-3-(4-bromophenyl)propanoate hydrochloride salt 82e**



Yield (12.02 g, Quantitative, contaminated with KCl); Off-white/cream solid; m.p. 175-177°C; ν_{max}/cm^{-1} 3316 (O-H), 2997 (N-H), 2908 (C-H), 1743 (C=O); δ_H (Threo) (400 MHz, D_2O) 3.83 (3H, s, OCH_3), 4.41 (1H, d, $J=4.1$ Hz, H2), 5.40 (1H, d, $J=4.1$

Hz, H3), 7.37 (2H, d, $J=8.4$ Hz, Ar-H), 7.62 (2H, d, $J=8.5$ Hz, Ar-H); δ_C (Threo) (101 MHz, D_2O) 53.8 (OCH_3), 58.8 (C2), 70.0 (C3), 122.3 (Ar-C), 127.9 (Ar-C), 132.0 (Ar-C), 136.8 (Ar-C), 168.4 (C1); LRMS (ESI⁺) m/z : 274.0 ($[M^{79} + H]^+$ 42%), 276.0 ($[M^{81} + H]^+$ 43%), 547.0 ($[2M^{79} + H]^+$ 82%), 549.0 ($[2M^{79+81} + H]^+$ 100%), 551.0 ($[2M^{81} + H]^+$ 66%); HRMS (ESI⁺) m/z : $[M^{79} + H]^+$ calcd. for $C_{10}H_{13}NO_3Br$, 274.0073, found 274.0073; $[M^{81} + H]^+$ calcd. for $C_{10}H_{13}NO_3Br$, 276.0053, found 276.0053.

Ethyl (2*S,3*R**)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride salt 82f**



Yield (2.31 g, Quantitative, contaminated with NaCl); Off-white/cream solid; m.p. 120-123°C (lit.¹⁰¹ 183-184°C); ν_{max}/cm^{-1} 3287 (O-H), 2983 (N-H), 2910 (C-H), 1742 (C=O); δ_H (Threo) (400 MHz, D_2O) 1.27 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.32 (2H, q, $J=7.2$

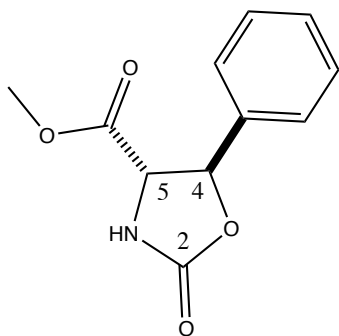
Hz, OCH_2CH_3), 4.43 (1H, d, $J=4.6$ Hz, H2), 5.45 (1H, d, $J=4.6$ Hz, H3), 7.32-7.55 (5H, m, Ar-H); δ_C (Threo) (101 MHz, D_2O) 13.1 (OCH_2CH_3), 59.1 (C2), 63.8 (OCH_2CH_3), 70.8 (C3), 126.1 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-C), 137.8 (Ar-C), 168.1 (C1); LRMS (ESI⁺) m/z : 232.0 ($[M + Na]^+$ 31%); HRMS (ESI⁺) m/z : $[M + H]^+$ calcd. for $C_{11}H_{16}NO_3$, 210.1125, found 210.1126.

General procedure for the synthesis of oxazolidinone.¹⁰²

Methyl ester hydrochloride salt ($\pm$) **82a** (1.0 eq.) was suspended in THF and triethylamine (1.2 eq.) was added, and the solution was stirred at rt for 5 mins. CDI (1.8 eq.) was then added, and the solution was

stirred overnight at rt. The mixture was then quenched with sat. NH_4Cl (aq.), extracted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered, reduced *in-vacuo* and then purified by flash column chromatography to furnish oxazolidinone ($\pm$) **83**.

Methyl (4*S,5*R**)-2-oxo-5-phenyloxazolidine-4-carboxylate **83****



Yield (58 mg, 30%); Colourless oil; R_f (50% EtOAc in Pet. Ether 40:60)

0.33; $\nu_{\text{max}}/\text{cm}^{-1}$ 3274 (N-H), 1751 (C=O); δ_{H} (400 MHz, CDCl_3) 3.84 (3H, s, OCH₃), 4.31 (1H, dd, $J=0.7$ Hz, 5.0 Hz, H5), 5.63 (1H, d, $J=5.0$ Hz, H4),

6.88 (1H, br s, NH), 7.36-7.43 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 53.3

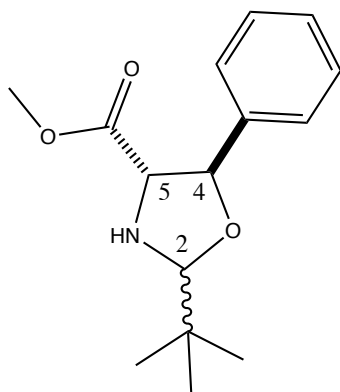
(OCH₃), 61.5 (C5), 79.5 (C4), 125.5 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-C),

138.1 (Ar-C), 158.6 (C2), 170.3 (C=O); LRMS (ESI⁺) m/z : 244.0 ($[\text{M} + \text{Na}]^+$

97%), 465.2 ($[\text{2M} + \text{Na}]^+$ 28%); HRMS (ESI⁺) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{Na}$, 244.0580, found 244.0582.

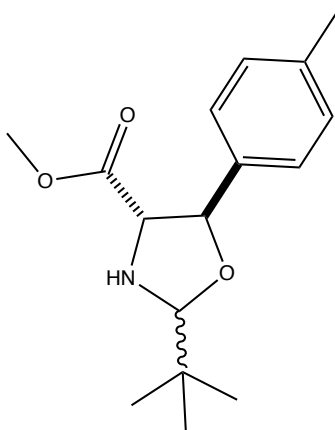
General procedure for the synthesis of oxazolidines:³⁴⁻³⁵

Methyl ester hydrochloride salt ($\pm$) **82a-e** or ethyl ester hydrochloride salt ($\pm$) **82f** (1.0 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2 eq.) and trimethylacetaldehyde (1.1 eq.) was added to this reaction mixture and was heated to more than 100°C with continuous removal of water using a Dean-Stark apparatus overnight. The precipitate was then filtered and washed with Et₂O. The combined filtrates were concentrated under reduced pressure to yield the desired products **84a-f** and was used without further purification.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-phenyloxazolidine-4-carboxylate 84a**

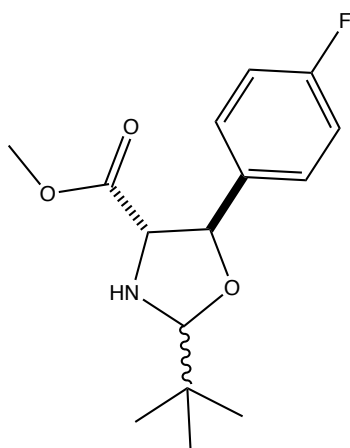
Yield (472 mg, 82%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3337 (N-H), 2956 (C-H), 2907 (C-H), 2871 (C-H), 1739 (C=O); 1.1:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.98 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.63 (1H, d, $J=6.6$ Hz, H5), 3.68 (3H, s, OCH_3), 4.42 (1H, s, H2), 4.74 (1H, d, $J=6.6$ Hz, H4), 7.16-7.34 (5H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 1.00 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.73 (3H, s, OCH_3), 3.77 (1H, d, $J=7.0$ Hz,

H5), 4.42 (1H, s, H2), 4.67 (1H, d, $J=7.0$ Hz, H4), 7.16-7.34 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 25.3 and 25.4 ($(\text{CH}_3)_3$), 33.7 and 34.5 ($\text{C}(\text{CH}_3)_3$), 52.5 and 52.7 (OCH_3), 67.4 and 68.7 (C5), 81.4 and 82.4 (C4), 99.4 and 100.3 (C2), 125.8 and 126.2 (Ar-C), 127.9 and 128.2 (Ar-C), 128.6 and 128.7 (Ar-C), 139.8 and 141.3 (Ar-C), 172.0 and 172.8 (C=O); LRMS (ESI^+) m/z : 264.1 ($[\text{M} + \text{H}]^+$ 55%), 286.1 ($[\text{M} + \text{Na}]^+$ 60%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_3$, 264.1594, found 264.1595.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-methylphenyl)oxazolidine-4-carboxylate 84b**

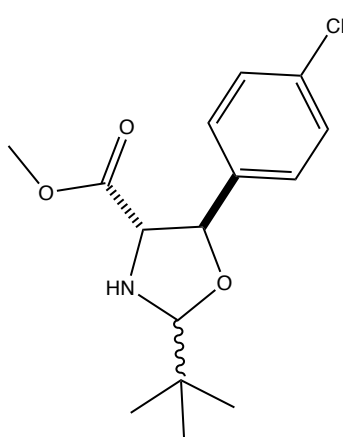
Yield (461 mg, 81%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3338 (N-H), 2956 (C-H), 2908 (C-H), 2870 (C-H), 1740 (C=O); 1.1:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.96 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.27 (3H, s, CH_3), 3.61 (1H, d, $J=6.7$ Hz, H5), 3.67 (3H, s, OCH_3), 4.41 (1H, s, H2), 4.69 (1H, d, $J=6.7$ Hz, H4), 7.07-7.21 (4H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.27 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 3.77 (1H, d, $J=7.0$ Hz, H5), 4.41 (1H, s, H2), 4.63 (1H, d, $J=7.0$ Hz,

H4), 7.07-7.21 (4H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 21.3 and 21.3 (CH_3), 25.3 and 25.4 ($(\text{CH}_3)_3$), 33.8 and 34.6 ($\text{C}(\text{CH}_3)_3$), 52.4 and 52.6 (OCH_3), 67.4 and 68.7 (C5), 81.5 and 82.5 (C4), 99.3 and 100.1 (C2), 125.8 and 126.2 (Ar-C), 129.3 and 129.4 (Ar-C), 136.8 and 137.6 (Ar-C), 137.9 and 138.3 (Ar-C), 172.0 and 172.9 (C=O); LRMS (ESI^+) m/z : 278.2 ($[\text{M} + \text{H}]^+$ 12%), 300.1 ($[\text{M} + \text{Na}]^+$ 8%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{24}\text{NO}_3$, 278.1751, found 278.1751.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-fluorophenyl)oxazolidine-4-carboxylate 84c**

Yield (4.72 g, 70%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3335 (N-H), 2957 (C-H), 2907 (C-H), 2872 (C-H), 1740 (C=O); 1.1:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.96 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.58 (1H, d, $J=6.7$ Hz, H5), 3.68 (3H, s, OCH_3), 4.41 (1H, s, H2), 4.70 (1H, d, $J=6.7$ Hz, H4), 6.89-7.00 (2H, m, Ar-H), 7.15-7.31 (2H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.70 (1H, obscured by OCH_3 peak, H5), 3.72 (3H, s, OCH_3), 4.40 (1H, br s, H2),

4.62 (1H, d, $J=7.0$ Hz, H4), 6.89-7.00 (2H, m, Ar-H), 7.15-7.31 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 25.2 and 25.3 ($(\text{CH}_3)_3$), 33.7 and 34.5 ($\text{C}(\text{CH}_3)_3$), 52.5 and 52.7 (OCH_3), 67.3 and 68.8 (C5), 80.8 and 81.9 (C4), 99.3 and 100.2 (C2), 115.5 (d, $J=21.5$ Hz, Ar-C) and 115.5 (d, $J=21.8$ Hz, Ar-C), 127.5 (d, $J=8.2$ Hz, Ar-C) and 127.9 (d, $J=8.4$ Hz, Ar-C), 135.5 (d, $J=3.1$ Hz, Ar-C) and 137.0 (d, $J=3.1$ Hz, Ar-C), 162.4 (d, $J=245.6$ Hz, Ar-C) and 162.6 (d, $J=245.9$ Hz, Ar-C), 171.7 and 172.6 (C=O); δ_{F} (377 MHz, CDCl_3) -114.16, -114.78; LRMS (ESI^+) m/z : 282.1 ($[\text{M} + \text{H}]^+$ 22%), 304.2 ($[\text{M} + \text{Na}]^+$ 6%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{F}$, 282.1500, found 282.1501.

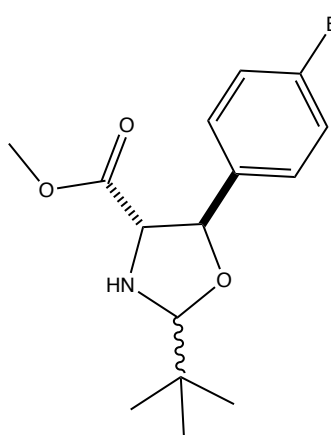
Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-chlorophenyl)oxazolidine-4-carboxylate 84d**

Yield (354 mg, 62%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3335 (N-H), 2956 (C-H), 2908 (C-H), 2871 (C-H), 1741 (C=O); 1.2:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.96 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.58 (1H, d, $J=6.6$ Hz, H5), 3.69 (3H, s, OCH_3), 4.41 (1H, s, H2), 4.70 (1H, d, $J=6.6$ Hz, H4), 7.16-7.29 (4H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.71 (1H, d, $J=7.2$ Hz, H5), 3.73 (3H, s, OCH_3), 4.39 (1H, br s, H2), 4.62 (1H, d, $J=7.0$ Hz, H4), 7.16-7.29 (4H, m,

Ar-H); δ_{C} (101 MHz, CDCl_3) 25.3 and 25.3 ($(\text{CH}_3)_3$), 33.7 and 34.5 ($\text{C}(\text{CH}_3)_3$), 52.6 and 52.8 (OCH_3), 67.3 and 68.7 (C5), 80.7 and 81.7 (C4), 99.4 and 100.3 (C2), 127.2 and 127.6 (Ar-C), 128.7 and 128.8 (Ar-C), 133.6 and 133.9 (Ar-C), 138.3 and 139.8 (Ar-C), 171.6 and 172.5 (C=O); LRMS (ESI^+) m/z : 298.0 ($[\text{M}^{35} +$

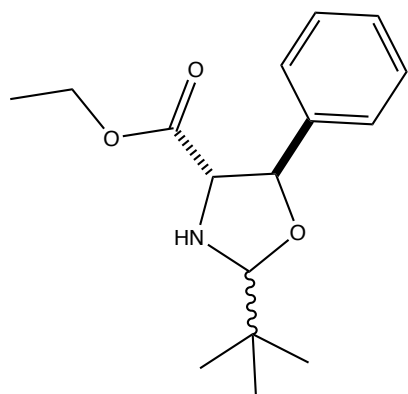
$\text{H}]^+$ 28%), 300.1 ($[\text{M}^{37} + \text{H}]^+$ 9%); HRMS (ESI⁺) m/z : $[\text{M}^{35} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{Cl}$, 298.1204, found 298.1205; $[\text{M}^{37} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{Cl}$, 300.1175, found 300.1175.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-bromophenyl)oxazolidine-4-carboxylate 84e**



Yield (385 mg, 69%); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3332 (N-H), 2956 (C-H), 2907 (C-H), 2871 (C-H), 1740 (C=O); 1.2:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.96 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.58 (1H, d, $J=6.6$ Hz, H5), 3.69 (3H, s, OCH_3), 4.41 (1H, s, H2), 4.69 (1H, d, $J=6.6$ Hz, H4), 7.14-7.21 (2H, m, Ar-H), 7.34-7.42 (2H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.71 (1H, obscured by OCH_3 peak, H5), 3.73 (3H, s, OCH_3), 4.38 (1H, br s, H2), 4.60 (1H, d, $J=6.9$ Hz, H4), 7.14-7.21 (2H, m, Ar-H), 7.34-7.42 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 25.3 and 25.3 ($(\text{CH}_3)_3$), 33.7 and 34.5 ($\text{C}(\text{CH}_3)_3$), 52.6 and 52.8 (OCH_3), 67.3 and 68.7 (C5), 80.7 and 81.7 (C4), 99.5 and 100.4 (C2), 121.7 and 122.0 (Ar-C), 127.5 and 127.9 (Ar-C), 131.7 and 131.8 (Ar-C), 138.9 and 140.4 (Ar-C), 171.6 and 172.5 (C=O); LRMS (ESI⁺) m/z : 342.0 ($[\text{M}^{79} + \text{H}]^+$ 19%), 344.0 ($[\text{M}^{81} + \text{H}]^+$ 19%); HRMS (ESI⁺) m/z : $[\text{M}^{79} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{Br}$, 342.0699, found 342.0699; $[\text{M}^{81} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{Br}$, 344.0679, found 344.0679.

Ethyl (4*S,5*R**)-2-(*tert*-butyl)-5-phenyloxazolidine-4-carboxylate 84f**



Yield (1.70 g, 77%); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3332 (N-H), 2958 (C-H), 2907 (C-H), 2871 (C-H), 1734 (C=O); 1.6:1 mixture of diastereomers at the C2-position; δ_{H} (2,5-*trans* diastereomer) (400 MHz, CDCl_3) 0.98 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.18 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.59 (1H, d, $J=6.8$ Hz, H5), 4.17 (2H, m, OCH_2CH_3), 4.44 (1H, s, H2), 4.71 (1H, d, $J=6.8$ Hz, H4), 7.19-7.34 (5H, m, Ar-H); δ_{H} (2,5-*cis* diastereomer) (400 MHz, CDCl_3) 1.00 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.21 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.74 (1H, d, $J=6.9$ Hz, H5), 4.17 (2H, m, OCH_2CH_3), 4.43 (1H, s, H2), 4.66 (1H, d, $J=6.9$ Hz, H4), 7.19-7.34 (5H, m, Ar-H); δ_{C} (101 MHz,

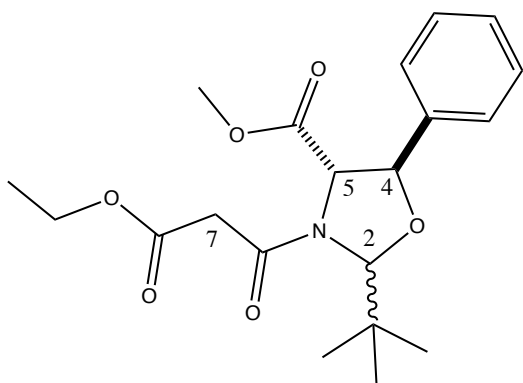
CDCl₃) 14.3 and 14.3 (OCH₂CH₃), 25.3 and 25.4 ((CH₃)₃), 33.8 and 34.6 (C(CH₃)₃), 61.5 and 61.8 (OCH₂CH₃), 67.4 and 68.7 (C5), 81.6 and 82.7 (C4), 99.4 and 100.2 (C2), 125.8 and 126.3 (Ar-C), 127.9 and 128.2 (Ar-C), 128.5 and 128.6 (Ar-C), 139.8 and 141.4 (Ar-C), 171.5 and 172.3 (C=O); LRMS (ESI⁺) *m/z*: 278.2 ([M + H]⁺ 35%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₁₆H₂₄NO₃, 278.1751, found 278.1751.

General procedure for the synthesis of *N*-acylated oxazolidines:³⁴⁻³⁵

Method A: To a stirring solution of oxazolidine (**±**) **84a-b** (1.0 eq.) in anhydrous DCM was added DMAP (0.05 eq.) and DCC (1.05 eq.). The mixture was cooled to 0°C and ethyl hydrogen malonate (1.05 eq.) was added. The mixture was stirred at 0°C for 30 min and then stirred at rt overnight. A white precipitate was formed, which was filtered and washed with DCM. The combined filtrates were concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated oxazolidines **86a-b**.

Method B: To a stirring solution of oxazolidine (**±**) **84a-f** (1.0 eq.) in anhydrous DCM at 0°C was added ethyl malonyl chloride (1.1 eq.) and pyridine (1.2 eq.) dropwise. The mixture was stirred at 0°C for 10-20 min and then refluxed overnight. The mixture was then washed with sat. NH₄Cl (aq.), sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated oxazolidines **86a-f/87a-e**.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-phenyloxazolidine-4-carboxylate **86a and 87a****

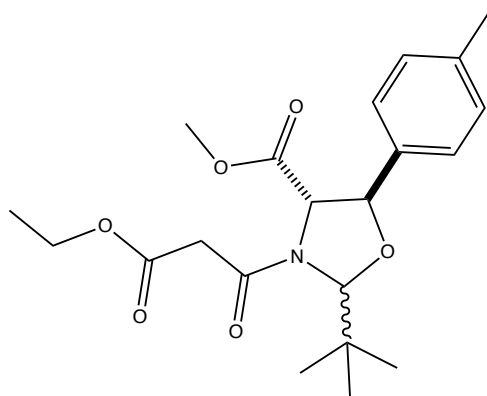


Method B: Yield (3.74 g, 81%); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.48 (**86a**) and 0.25 (**87a**); $\nu_{\text{max}}/\text{cm}^{-1}$ (**86a**) 2958 (C-H), 1742 (C=O), 1675 (C=O); 65:35 diastereomeric ratio between (**±**) **86a** and (**±**) **87a**; δ_{H} (**86a**) (400 MHz, CDCl₃) 0.98 (9H, s, C(CH₃)₃), 1.15 (3H, br t, *J*=6.4 Hz, OCH₂CH₃), 3.41 (1H, d, *J*=15.4 Hz, H7), 3.47

(1H, d, *J*=15.4 Hz, H7), 3.84 (3H, s, OCH₃), 4.05 (2H, m, OCH₂CH₃), 4.59 (1H, d, *J*=4.2 Hz, H5), 5.69 (1H,

d, $J=4.1$ Hz, H4), 5.77 (1H, s, H2), 7.26-7.37 (5H, m, Ar-H); δ_{C} (**86a**) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 25.9 ($(\text{CH}_3)_3$), 38.4 ($\text{C}(\text{CH}_3)_3$), 42.8 (C7), 53.2 (OCH_3), 61.7 (OCH_2CH_3), 66.9 (C5), 81.7 (C4), 98.0 (C2), 125.8 (Ar-C), 128.6 (Ar-C), 128.9 (Ar-C), 140.3 (Ar-C), 166.8 ($\text{C}=\text{O}$), 167.0 ($\text{C}=\text{O}$), 170.1 ($\text{C}=\text{O}$); δ_{H} (**87a**) (203K, Major conformer) (500 MHz, CD_2Cl_2) 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.27 (3H, br m, OCH_2CH_3), 3.50 (2H, m, H7), 3.73 (3H, s, OCH_3), 4.00 (1H, d, $J=9.0$ Hz, H5), 4.17 (2H, m, OCH_2CH_3), 5.14 (1H, d, $J=9.2$ Hz, H4), 5.36 (1H, s, H2), 7.38-7.43 (5H, m, Ar-H); δ_{C} (**87a**) (203K, Major conformer) (126 MHz, CD_2Cl_2) 13.8 (OCH_2CH_3), 25.2 ($(\text{CH}_3)_3$), 39.1 ($\text{C}(\text{CH}_3)_3$), 41.7 (C7), 53.1 (OCH_3), 61.7 (OCH_2CH_3), 64.9 (C5), 82.2 (C4), 96.1 (C2), 125.6 (Ar-C), 128.7 (Ar-C), 128.7 (Ar-C), 135.4 (Ar-C), 163.9 ($\text{C}=\text{O}$), 166.8 ($\text{C}=\text{O}$), 167.7 ($\text{C}=\text{O}$); LRMS (**86a**) (ESI^+) m/z : 400.2 ($[\text{M} + \text{Na}]^+$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{28}\text{NO}_6$, 378.1911, found 378.1904.

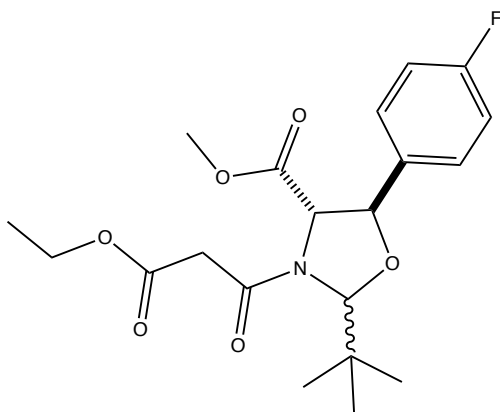
Methyl (4*S,5*R**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-methylphenyl)oxazolidine-4-carboxylate **86b** and **87b****



Method B: Yield (3.45 g, 67%); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.53 (**86b**) and 0.45 (**87b**); $\nu_{\text{max}}/\text{cm}^{-1}$ (**86b**) 2958 (C-H), 1740 ($\text{C}=\text{O}$), 1675 ($\text{C}=\text{O}$); 59:41 diastereomeric ratio between ($\pm$) **86b** and ($\pm$) **87b**; δ_{H} (**86b**) (400 MHz, CDCl_3) 1.00 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.19 (3H, br t, $J=7.1$ Hz, OCH_2CH_3), 2.35 (3H, s, CH_3), 3.46 (2H, m, H7), 3.85 (3H, s, OCH_3), 4.09 (2H, m, OCH_2CH_3), 4.58 (1H, d, $J=4.3$ Hz, H5), 5.65 (1H, d, $J=4.3$ Hz, H4), 5.76 (1H, s, H2), 7.18 (2H, d, $J=7.9$ Hz, Ar-H), 7.26 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (**86b**) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 21.3 (CH_3), 25.9 ($(\text{CH}_3)_3$), 38.4 ($\text{C}(\text{CH}_3)_3$), 42.8 (C7), 53.1 (OCH_3), 61.7 (OCH_2CH_3), 67.0 (C5), 81.7 (C4), 97.9 (C2), 125.8 (Ar-C), 129.6 (Ar-C), 137.2 (Ar-C), 138.4 (Ar-C), 166.9 ($\text{C}=\text{O}$), 167.0 ($\text{C}=\text{O}$), 170.1 ($\text{C}=\text{O}$); δ_{H} (**87b**) (203K, Major conformer) (500 MHz, CD_2Cl_2) 0.98 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.23 (3H, br t, $J=7.0$ Hz, OCH_2CH_3), 2.31 (3H, s, CH_3), 3.43 (2H, m, H7), 3.66 (3H, s, OCH_3), 3.93 (1H, d, $J=9.2$ Hz, H5), 4.11 (2H, m, OCH_2CH_3), 5.03 (1H, d, $J=9.2$ Hz, H4), 5.28 (1H, s, H2), 7.18 (2H, d, $J=7.9$ Hz, Ar-H), 7.22 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (**87b**) (203K, Major conformer) (126 MHz, CD_2Cl_2) 13.8 (OCH_2CH_3), 21.0 (CH_3), 25.2 ($(\text{CH}_3)_3$), 39.1 ($\text{C}(\text{CH}_3)_3$), 41.7 (C7), 53.1 (OCH_3), 61.7 (OCH_2CH_3), 65.0 (C5), 82.3 (C4), 96.0 (C2), 125.7 (Ar-C), 129.3 (Ar-C), 132.2 (Ar-C), 138.9

(Ar-C), 163.9 (C=O), 166.8 (C=O), 167.6 (C=O); LRMS_(86b) (ESI⁺) m/z : 414.2 ([M + Na]⁺ 95%); LRMS_(87b) (ESI⁺) m/z : 414.2 ([M + Na]⁺ 96%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₁H₂₉NO₆Na, 414.1887, found 414.1886.

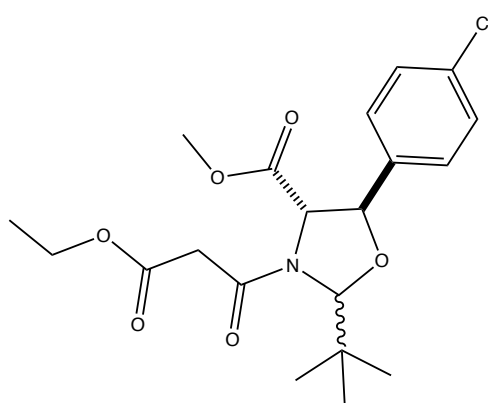
Methyl (4S*,5R*)-2-(tert-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-fluorophenyl)oxazolidine-4-carboxylate 86c and 87c



Method B: Yield (3.90 g, 60%); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.55_(86c) and 0.38_(87c); $\nu_{\max}/\text{cm}^{-1}$ _(86c) 2959 (C-H), 1743 (C=O), 1675 (C=O); 59:41 diastereomeric ratio between (**±**) **86c** and (**±**) **87c**; δ_{H} _(86c) (400 MHz, CDCl₃) 0.98 (9H, s, C(CH₃)₃), 1.18 (3H, br t, $J=7.2$ Hz, OCH₂CH₃), 3.42 (1H, d, $J=15.5$ Hz, H7), 3.49 (1H, d,

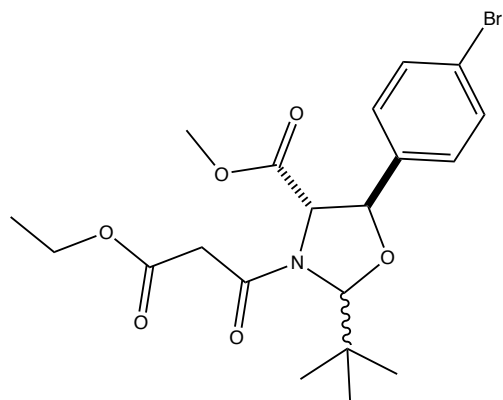
$J=15.4$ Hz, H7), 3.85 (3H, s, OCH₃), 4.07 (2H, m, OCH₂CH₃), 4.57 (1H, d, $J=4.4$ Hz, H5), 5.66 (1H, d, $J=4.4$ Hz, H4), 5.77 (1H, s, H2), 7.06 (2H, app. t, $J=8.6$ Hz, Ar-H), 7.37 (2H, dd, $J=5.3$ Hz, 8.5 Hz, Ar-H); δ_{C} _(86c) (126 MHz, CDCl₃) 14.1 (OCH₂CH₃), 25.9 ((CH₃)₃), 38.4 (C(CH₃)₃), 42.7 (C7), 53.3 (OCH₃), 61.8 (OCH₂CH₃), 66.8 (C5), 81.3 (C4), 98.0 (C2), 115.8 (d, $J=21.6$ Hz, Ar-C), 127.8 (d, $J=8.4$ Hz, Ar-C), 136.1 (d, $J=3.2$ Hz, Ar-C), 162.8 (d, $J=247.1$ Hz, Ar-C), 166.9 (C=O), 167.0 (C=O), 170.0 (C=O); δ_{F} _(86c) (471 MHz, CDCl₃) -113.43; δ_{H} _(87c) (203K, Major conformer) (500 MHz, CD₂Cl₂) 0.96 (9H, s, C(CH₃)₃), 1.21 (3H, br t, $J=7.0$ Hz, OCH₂CH₃), 3.36 (1H, d, $J=15.9$ Hz, H7), 3.49 (1H, d, $J=15.9$ Hz, H7), 3.65 (3H, s, OCH₃), 3.91 (1H, d, $J=9.2$ Hz, H5), 4.09 (2H, m, OCH₂CH₃), 5.05 (1H, d, $J=9.2$ Hz, H4), 5.27 (1H, s, H2), 7.06 (2H, app. t, $J=8.5$ Hz, Ar-H), 7.32 (2H, m, Ar-H); δ_{C} _(87c) (213K, Major conformer) (126 MHz, CD₂Cl₂) 13.8 (OCH₂CH₃), 25.2 ((CH₃)₃), 39.1 (C(CH₃)₃), 41.7 (C7), 53.2 (OCH₃), 61.8 (OCH₂CH₃), 65.0 (C5), 81.7 (C4), 96.1 (C2), 115.7 (d, $J=21.5$ Hz, Ar-C), 127.8 (d, $J=8.3$ Hz, Ar-C), 131.3 (Ar-C), 162.5 (d, $J=246.2$ Hz, Ar-C), 164.1 (C=O), 166.8 (C=O), 167.6 (C=O); δ_{F} _(87c) (213K, Major conformer) (471 MHz, CD₂Cl₂) -113.38; LRMS_(86c) (ESI⁺) m/z : 418.2 ([M + Na]⁺ 96%); LRMS_(87c) (ESI⁺) m/z : 418.2 ([M + Na]⁺ 97%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₀H₂₆NO₆FNa, 418.1636, found 418.1635.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-chlorophenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate **86d** and **87d****



Method B: Yield (4.66 g, 76%); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.50 (**86d**) and 0.38 (**87d**); $\nu_{\max}/\text{cm}^{-1}$ (**86d**) 2959 (C-H), 1744 (C=O), 1671 (C=O); 60:40 diastereomeric ratio between ($\pm$) **86d** and ($\pm$) **87d**; δ_H (**86d**) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.17 (3H, br t, $J=6.5$ Hz, OCH_2CH_3), 3.42 (1H, br d, $J=15.6$ Hz, H7), 3.50 (1H, d, $J=15.2$ Hz, H7), 3.85 (3H, s, OCH_3), 4.07 (2H, m, OCH_2CH_3), 4.62 (1H, d, $J=4.0$ Hz, H5), 5.68 (1H, d, $J=3.7$ Hz, H4), 5.75 (1H, s, H2), 7.34 (4H, s, Ar-H); δ_C **86d** (101 MHz, CDCl_3) 13.9 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 38.1 ($\text{C}(\text{CH}_3)_3$), 42.5 (C7), 53.0 (OCH_3), 61.5 (OCH_2CH_3), 66.5 (C5), 80.9 (C4), 97.7 (C2), 127.1 (Ar-C), 128.8 (Ar-C), 134.1 (Ar-C), 138.8 (Ar-C), 166.7 (C=O), 166.8 (C=O), 169.7 (C=O); δ_H (**87d**) (203K, Major conformer) (500 MHz, CD_2Cl_2) 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.21 (3H, br m, OCH_2CH_3), 3.44 (1H, d, $J=15.6$ Hz, H7), 3.50 (1H, d, $J=15.8$ Hz, H7), 3.68 (3H, s, OCH_3), 3.91 (1H, d, $J=9.2$ Hz, H5), 4.10 (2H, m, OCH_2CH_3), 5.07 (1H, d, $J=9.2$ Hz, H4), 5.29 (1H, s, H2), 7.28 (2H, d, $J=8.5$ Hz, Ar-H), 7.34 (2H, m, Ar-H); δ_C (**87d**) (203K, Major conformer) (126 MHz, CD_2Cl_2) 13.7 (OCH_2CH_3), 25.1 ($(\text{CH}_3)_3$), 39.0 ($\text{C}(\text{CH}_3)_3$), 41.6 (C7), 53.2 (OCH_3), 61.8 (OCH_2CH_3), 64.8 (C5), 81.5 (C4), 96.1 (C2), 127.1 (Ar-C), 128.7 (Ar-C), 133.9 (Ar-C), 134.0 (Ar-C), 163.9 (C=O), 166.8 (C=O), 167.5 (C=O); LRMS (**86d**) (ESI^+) m/z : 412.1 ($[\text{M}^{35} + \text{H}]^+$ 79%), 414.2 ($[\text{M}^{37} + \text{H}]^+$ 67%); LRMS (**87d**) (ESI^+) m/z : 434.2 ($[\text{M}^{35} + \text{Na}]^+$ 98%), 436.2 ($[\text{M}^{37} + \text{Na}]^+$ 69%); HRMS (ESI^+) m/z : $[\text{M}^{35} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{Cl}$, 412.1521, found 412.1521; $[\text{M}^{37} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{Cl}$, 414.1492, found 414.1492.

Methyl (4*S,5*R**)-2-(*tert*-butyl)-5-(4-bromophenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate **86e** and **87e****



Method B: Yield (8.53 g, 88%); Pale yellow oil; R_f (30%

EtOAc in Pet. Ether 40:60) 0.50 (**86e**) and 0.40 (**87e**); $\nu_{\max}/\text{cm}^{-1}$

¹ (**86e**) 2958 (C-H), 1743 (C=O), 1675 (C=O); 60:40

diastereomeric ratio between (**±**) **86e** and (**±**) **87e**; δ_H (**86e**)

(400 MHz, CDCl_3) 0.98 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.17 (3H, br t, $J=7.2$ Hz, OCH_2CH_3), 3.42 (1H, d, $J=15.4$ Hz, H7), 3.49 (1H,

d, $J=15.3$ Hz, H7), 3.86 (3H, s, OCH_3), 4.07 (2H, m,

OCH_2CH_3), 4.58 (1H, d, $J=4.2$ Hz, H5), 5.66 (1H, d, $J=4.1$ Hz, H4), 5.76 (1H, s, H2), 7.27 (2H, d, $J=8.4$ Hz,

Ar-H), 7.50 (2H, d, $J=8.4$ Hz, Ar-H); δ_C (**86e**) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 25.9 ($(\text{CH}_3)_3$), 38.4 ($\text{C}(\text{CH}_3)_3$),

42.8 (C7), 53.3 (OCH_3), 61.8 (OCH_2CH_3), 66.7 (C5), 81.2 (C4), 98.0 (C2), 122.6 (Ar-C), 127.6 (Ar-C), 132.0

(Ar-C), 139.4 (Ar-C), 166.9 (C=O), 166.9 (C=O), 169.9 (C=O); δ_H (**87e**) (193K, Major conformer) (500 MHz, CD_2Cl_2)

0.93 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.19 (3H, m, OCH_2CH_3), 3.43 (1H, d, $J=15.1$ Hz, H7), 3.48 (1H, d, $J=16.5$ Hz, H7),

3.66 (3H, s, OCH_3), 3.89 (1H, d, $J=9.2$ Hz, H5), 4.07 (2H, m, OCH_2CH_3), 5.04 (1H, d, $J=9.1$ Hz, H4), 5.27

(1H, s, H2), 7.21 (2H, d, $J=8.1$ Hz, Ar-H), 7.48 (2H, d, $J=8.3$ Hz, Ar-H); δ_C (**87e**) (193K, Major conformer) (126 MHz,

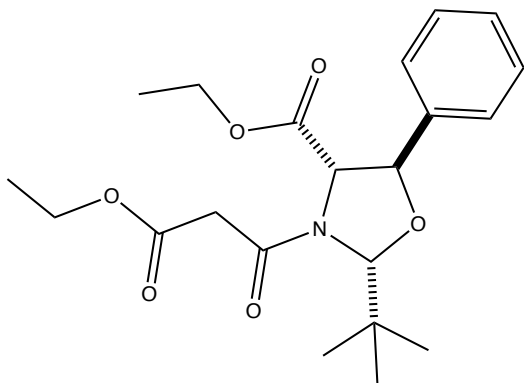
CD_2Cl_2) 13.6 (OCH_2CH_3), 25.0 ($(\text{CH}_3)_3$), 38.9 ($\text{C}(\text{CH}_3)_3$), 41.4 (C7), 53.2 (OCH_3), 61.7 (OCH_2CH_3), 64.6 (C5),

81.4 (C4), 96.0 (C2), 122.2 (Ar-C), 127.3 (Ar-C), 131.5 (Ar-C), 134.4 (Ar-C), 163.9 (C=O), 166.8 (C=O),

167.4 (C=O); LRMS (**86e**) (ESI^+) m/z : 478.0 ($[\text{M}^{79} + \text{Na}]^+$ 96%), 480.0 ($[\text{M}^{81} + \text{Na}]^+$ 89%); LRMS (**87e**) (ESI^+)

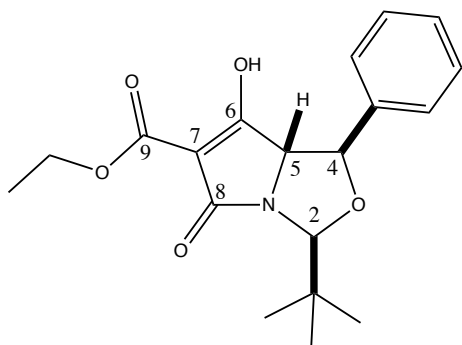
m/z : 478.0 ($[\text{M}^{79} + \text{Na}]^+$ 94%), 480.0 ($[\text{M}^{81} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{H}]^+$ calcd. for

$\text{C}_{20}\text{H}_{27}\text{NO}_6\text{Br}$, 456.1016, found 456.1016; $[\text{M}^{81} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{Br}$, 458.0996, found 458.0993.

Ethyl (2*R,4*S**,5*R**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-phenyloxazolidine-4-carboxylate****86f**Method B: Yield 34% (771 mg); Pale yellow oil; R_f (20%EtOAc in Pet. Ether 40:60) 0.43; $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H),1741 (C=O), 1675 (C=O); δ_H (400 MHz, CDCl_3) 0.99 (9H,s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.34 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.42 (1H, d, $J=15.5$ Hz, H7), 3.47(1H, d, $J=15.5$ Hz, H7), 4.04 (2H, m, OCH_2CH_3), 4.30 (2H,m, OCH_2CH_3), 4.55 (1H, d, $J=4.3$ Hz, H5), 5.67 (1H, d, $J=4.4$ Hz, H4), 5.78 (1H, s, H2), 7.26–7.38 (5H, m,Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 14.2 (OCH_2CH_3), 25.9 ($(\text{CH}_3)_3$), 38.4 ($\text{C}(\text{CH}_3)_3$), 42.7 (C7), 61.7(OCH_2CH_3), 62.5 (OCH_2CH_3), 67.0 (C5), 81.9 (C4), 98.0 (C2), 125.8 (Ar-C), 128.6 (Ar-C), 128.9 (Ar-C),140.4 (Ar-C), 166.9 (C=O), 167.0 (C=O), 169.6 (C=O); LRMS (ESI^+) m/z : 414.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS(ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{21}\text{H}_{30}\text{NO}_6$, 392.2068, found 392.2064.**General procedure for the synthesis of tetramates:**³⁴⁻³⁵

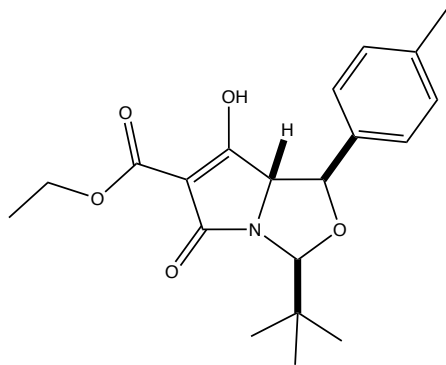
To a solution of malonamide (**±**) **87a-e** (1.0 eq.) in anhydrous THF was added potassium *tert*-butoxide (1.1 eq.). The mixture was heated at reflux for 3 h or refluxed overnight. Then the reaction mixture was cooled, separated between Et_2O and water and the aqueous layer was acidified to pH 1 using 3 M HCl (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to obtain ethyl ester tetramates **88a-e** and was used without further purification.

Ethyl (1*R,3*S**,7*aS**)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 88a**



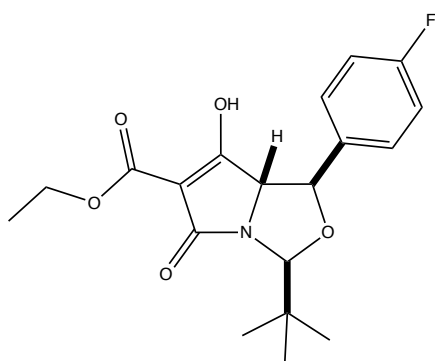
Yield (88 mg, 80%); Yellow solid; m.p. 85-89°C; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1711 (C=O), 1656 (C=O), 1616 (C=C); δ_{H} (400 MHz, CDCl_3) 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.36 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.17 (1H, d, $J=8.5$ Hz, H5), 4.36 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.53 (1H, d, $J=8.4$ Hz, H4), 4.99 (1H, s, H2), 7.32-7.49 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 24.9 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 61.7 (OCH_2CH_3), 67.9 (C5), 80.9 (C4), 94.9 (C2), 99.8 (C7), 126.2 (Ar-C), 128.7 (Ar-C), 128.8 (Ar-C), 135.8 (Ar-C), 167.1 (C9), 171.4 (C8), 185.3 (C6); LRMS (ESI^+) m/z : 368.2 ($[\text{M} + \text{Na}]^+$ 95%); LRMS (ESI^-) m/z : 344.1 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_5\text{Na}$, 368.1468, found 368.1469.

Ethyl (1*R,3*S**,7*aS**)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-(4-methylphenyl)-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 88b**



Yield (401 mg, 79%); Orange solid; m.p. 91-95°C; $\nu_{\max}/\text{cm}^{-1}$ 2969 (C-H), 1716 (C=O), 1658 (C=O), 1617 (C=C); δ_{H} (400 MHz, CDCl_3) 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.40 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.37 (3H, s, CH_3), 4.17 (1H, d, $J=8.5$ Hz, H5), 4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.51 (1H, d, $J=8.5$ Hz, H4), 5.00 (1H, s, H2), 7.21 (2H, d, $J=7.9$ Hz, Ar-H), 7.38 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 21.4 (CH_3), 25.1 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 61.8 (OCH_2CH_3), 68.1 (C5), 81.2 (C4), 95.2 (C2), 99.9 (C7), 126.4 (Ar-C), 129.5 (Ar-C), 133.0 (Ar-C), 138.9 (Ar-C), 167.5 (C9), 171.6 (C8), 185.7 (C6); LRMS (ESI^+) m/z : 382.2 ($[\text{M} + \text{Na}]^+$ 96%); LRMS (ESI^-) m/z : 358.1 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{20}\text{H}_{24}\text{NO}_5$, 358.1660, found 358.1657.

Ethyl (1*R,3*S**,7*aS**)-3-(*tert*-butyl)-1-(4-fluorophenyl)-7-hydroxy-5-oxo-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 88c**



Yield (228 mg, 60%); Red solid; m.p. 97-100°C; $\nu_{\max}/\text{cm}^{-1}$ 2969

(C-H), 1715 (C=O), 1658 (C=O), 1617 (C=C); δ_{H} (500 MHz, CDCl_3)

1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.40 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.16 (1H,

d, $J=8.4$ Hz, H5), 4.40 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.54 (1H, d,

$J=8.4$ Hz, H4), 5.00 (1H, s, H2), 7.10 (2H, app. t, $J=8.6$ Hz, Ar-H),

7.48 (2H, dd, $J=5.4$ Hz, 8.6 Hz, Ar-H); δ_{C} (126 MHz, CDCl_3) 14.3

(OCH_2CH_3), 25.1 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3), 68.0 (C5), 80.6 (C4), 95.2 (C2), 100.3 (C7),

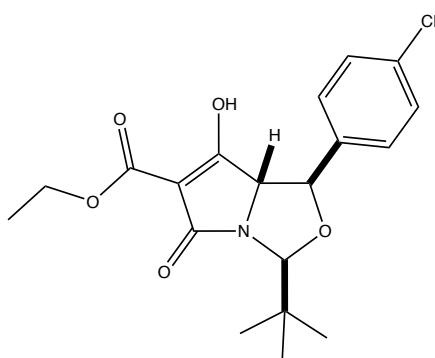
115.9 (d, $J=21.7$ Hz, Ar-C), 128.2 (d, $J=8.2$ Hz, Ar-C), 131.8 (d, $J=3.2$ Hz, Ar-C), 163.1 (d, $J=247.7$ Hz, Ar-

C), 167.4 (C9), 171.1 (C8), 185.4 (C6); δ_{F} (377 MHz, CDCl_3) -112.73; LRMS (ESI^+) m/z : 386.2 ($[\text{M} + \text{Na}]^+$

96%); LRMS (ESI^-) m/z : 362.1 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{F}$, 362.1409,

found 362.1408.

Ethyl (1*R,3*S**,7*aS**)-3-(*tert*-butyl)-1-(4-chlorophenyl)-7-hydroxy-5-oxo-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 88d**



Yield (236 mg, 74%); Red foamy solid; m.p. 99-105°C; $\nu_{\max}/\text{cm}^{-1}$

2969 (C-H), 1719 (C=O), 1662 (C=O), 1619 (C=C); δ_{H} (400 MHz,

CDCl_3) 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.40 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.14

(1H, d, $J=8.4$ Hz, H5), 4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.54 (1H,

d, $J=8.4$ Hz, H4), 5.01 (1H, s, H2), 7.38 (2H, d, $J=8.6$ Hz, Ar-H),

7.44 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3),

25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3), 67.9 (C5), 80.4 (C4), 95.3 (C2), 127.7 (Ar-C), 129.1 (Ar-C),

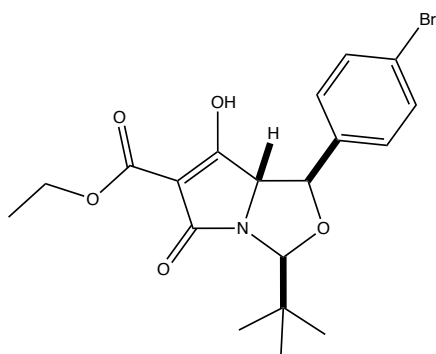
134.5 (Ar-C), 134.8 (Ar-C), 167.4 (C9), 172.4 (C8), 185.3 (C6); LRMS (ESI^+) m/z : 402.2 ($[\text{M}^{35} + \text{Na}]^+$ 91%),

404.2 ($[\text{M}^{37} + \text{Na}]^+$ 46%); LRMS (ESI^-) m/z : 378.0 ($[\text{M}^{35} - \text{H}]^-$ 97%), 380.0 ($[\text{M}^{37} - \text{H}]^-$ 34%); HRMS (ESI^-)

m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$, 378.1114, found 378.1113; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$,

380.1085, found 380.1084.

Ethyl (1*R,3*S**,7*aS**)-3-(*tert*-butyl)-1-(4-bromophenyl)-7-hydroxy-5-oxo-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 88e**



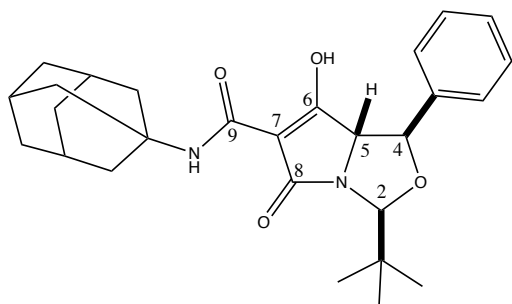
Yield (808 mg, 78%); Red foamy solid; m.p. 95-97°C; $\nu_{\max}/\text{cm}^{-1}$ 2968 (C-H), 1716 (C=O), 1618 (C=C); δ_{H} (400 MHz, CDCl_3) 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.39 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.13 (1H, d, $J=8.4$ Hz, H5), 4.39 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.52 (1H, d, $J=8.4$ Hz, H4), 5.00 (1H, s, H2), 7.38 (2H, d, $J=8.4$ Hz, Ar-H), 7.53 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 25.0

((CH_3)₃), 36.2 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3), 67.7 (C5), 80.4 (C4), 95.2 (C2), 100.3 (C7), 123.0 (Ar-C), 128.0 (Ar-C), 132.0 (Ar-C), 135.1 (Ar-C), 167.4 (C9), 171.1 (C8), 185.2 (C6); LRMS (ESI^-) m/z : 422.0 ($[\text{M}^{79} - \text{H}]^-$ 94%), 424.0 ($[\text{M}^{81} - \text{H}]^-$ 97%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 422.0609, found 422.0613; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 424.0588, found 424.0591.

General procedure for the synthesis of C7-carboxamidotetramic acids:^{33,43}

To a solution of ethyl ester tetramic acids ($\pm$) **88a-e** (1.0 eq.) in anhydrous toluene was added an aliphatic or aromatic amine (1.2-1.5 eq.). The mixture was heated at reflux overnight. Then the reaction mixture was evaporated *in-vacuo* and purified by flash column chromatography to yield tetramates that were chelated with metals. The tetramates were then redissolved in DCM, washed with 10% citric acid solution (aq.), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the desired C7-carboxamides.

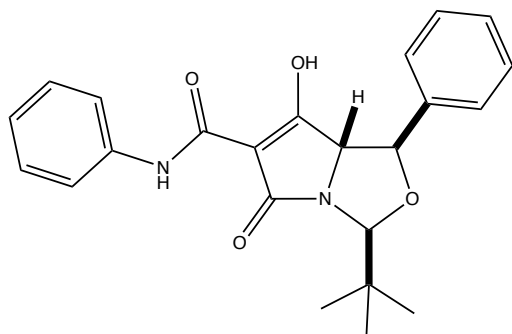
(1*R,3*S**,7*aS**)-N-(Adamantan-1-yl)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111a**



Yield (3.32 g, 55%); Brown foamy solid; m.p. 130-135°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.33; $\nu_{\max}/\text{cm}^{-1}$ 2909 (C-H), 2852 (C-H), 1692 (C=O), 1645 (C=O); AB:CD=80:20; δ_{H} (400 MHz, CDCl_3) 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.07 (9H, s,

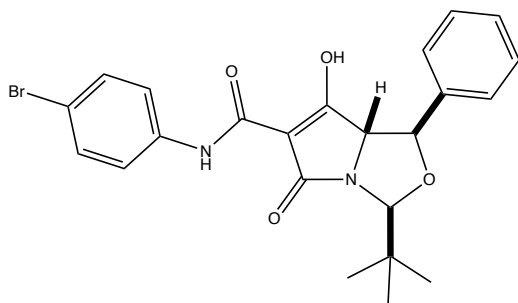
$\text{C}(\text{CH}_3)_3$, AB), 1.71 (6H, br m, Adamantyl- CH_2), 2.08 (6H, br m, Adamantyl- CH_2), 2.12 (3H, br m, Adamantyl-CH), 3.90 (1H, d, $J=8.8$ Hz, H5, CD), 4.12 (1H, d, $J=8.7$ Hz, H5, AB), 4.58 (1H, d, $J=8.6$ Hz, H4, AB), 4.61 (1H, d, $J=8.9$ Hz, H4, CD), 4.97 (1H, s, H2, AB), 4.99 (1H, s, H2, CD), 7.35-7.54 (5H, m, Ar-H), 9.00 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 25.1 ($(\text{CH}_3)_3$), 29.5 (Adamantyl-C), 36.0 (Adamantyl-C, CD), 36.2 ($\text{C}(\text{CH}_3)_3$), 36.3 (Adamantyl-C, AB), 41.8 (Adamantyl-C), 53.1 (Adamantyl-C, AB), 54.6 (Adamantyl-C, CD), 69.4 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.9 (C2, AB), 94.9 (C2, CD), 97.0 (C7), 126.4 (Ar-C, AB), 126.5 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 128.8 (Ar-C, AB), 136.4 (Ar-C), 166.3 (C9, AB), 167.1 (C9, CD), 175.1 (C8, AB), 181.3 (C8, CD), 186.9 (C6, AB), 190.5 (C6, CD); LRMS (ESI^-) m/z : 449.2 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_4$, 449.2446, found 449.2443.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-5-oxo-*N*,1-diphenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111b**



Yield (109 mg, 42%); Brown foamy solid; m.p. 75-79°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.30; $\nu_{\text{max}}/\text{cm}^{-1}$ 3281 (O-H), 2960 (C-H), 1695 (C=O), 1650 (C=O), 1599 (C=C); AB:CD=99:1; δ_{H} (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.27 (1H, d, $J=8.5$ Hz, H5), 4.63 (1H, d, $J=8.5$ Hz, H4), 5.02 (1H, s, H2), 7.07-7.61 (10H, m, Ar-H), 9.16 (1H, br s, NH/OH), 9.41 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.1 (C4), 94.9 (C2), 100.0 (C7), 120.5 (Ar-C), 125.2 (Ar-C), 126.4 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 129.3 (Ar-C), 135.8 (Ar-C), 136.6 (Ar-C), 164.1 (C9), 174.4 (C8), 184.0 (C6); LRMS (ESI^-) m/z : 391.1 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_4$, 391.1663, found 391.1662.

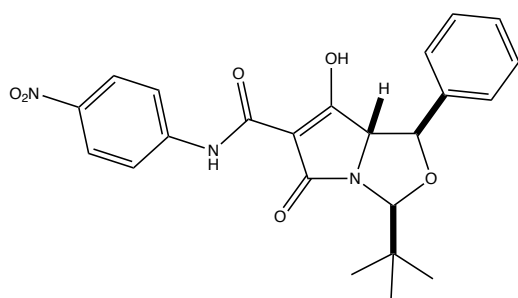
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-bromophenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111c**



Yield (122 mg, 42%); Orange foamy solid; m.p. 91-94°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.13; $\nu_{\max}/\text{cm}^{-1}$ 3271 (O-H), 2962 (C-H), 1692 (C=O), 1633 (C=O), 1593 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.27 (1H, d, $J=8.5$ Hz, H5), 4.61 (1H, d, $J=8.5$ Hz, H4), 5.01

(1H, s, H2), 7.38-7.53 (9H, m, Ar-H), 9.44 (1H, br s, NH/OH), 10.27 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.1 (C4), 94.9 (C2), 100.1 (C7), 117.8 (Ar-C), 121.8 (Ar-C), 126.3 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 132.3 (Ar-C), 135.7 (Ar-C), 135.8 (Ar-C), 164.0 (C9), 174.2 (C8), 183.7 (C6); LRMS (ESI^-) m/z : 469.0 ($[\text{M}^{79} - \text{H}]^-$ 11%), 471.0 ($[\text{M}^{81} - \text{H}]^-$ 11%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4\text{Br}$, 469.0768, found 469.0770; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4\text{Br}$, 471.0748, found 471.0749.

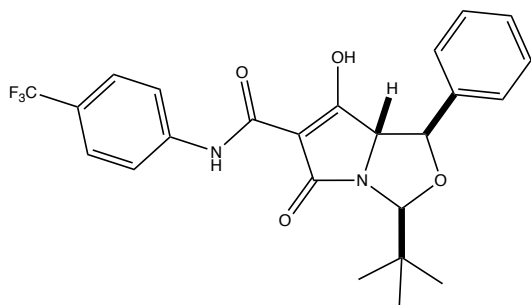
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-*N*-(4-nitrophenyl)-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111d**



Yield (41 mg, 15%); Dark brown foamy solid; m.p. 175-179°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.13; $\nu_{\max}/\text{cm}^{-1}$ 2963 (C-H), 1694 (C=O), 1632 (C=O), 1595 (C=C), 1511 (N-O); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.31 (1H, d, $J=8.5$ Hz, H5), 4.64 (1H, d, $J=8.5$ Hz,

H4), 5.02 (1H, s, H2), 7.38-7.54 (5H, m, Ar-H), 7.78 (2H, d, $J=8.8$ Hz, Ar-H), 8.23 (2H, d, $J=8.9$ Hz, Ar-H), 9.82 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.1 (C4), 94.9 (C2), 100.3 (C7), 119.8 (Ar-C), 125.3 (Ar-C), 126.4 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 135.5 (Ar-C), 142.6 (Ar-C), 144.1 (Ar-C), 164.3 (C9), 174.0 (C8), 184.0 (C6); LRMS (ESI^-) m/z : 436.0 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_6$, 436.1514, found 436.1512.

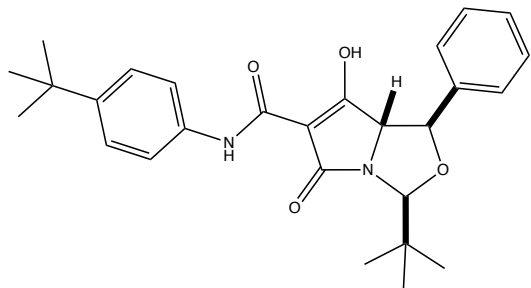
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-5-oxo-1-phenyl-*N*-(4-(trifluoromethyl)phenyl)-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111e**



Yield (109 mg, 38%); Red oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.15; $\nu_{\max}/\text{cm}^{-1}$ 3270 (O-H), 2963 (C-H), 1698 (C=O), 1655 (C=O), 1636 (C=O), 1605 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.30 (1H, d, $J=8.6$ Hz, H5), 4.63 (1H, d, $J=8.5$ Hz, H4),

5.02 (1H, s, H2), 7.33-7.54 (5H, m, Ar-H), 7.61 (2H, d, $J=8.6$ Hz, Ar-H), 7.74 (2H, d, $J=8.4$ Hz, Ar-H), 9.61 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.1 (C4), 94.9 (C2), 100.2 (C7), 120.0 (Ar-C), 126.4 (Ar-C), 126.6 (q, $J=3.7$ Hz, Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 135.6 (Ar-C), 139.8 (Ar-C), 164.3 (C9), 174.2 (C8), 183.9 (C6); δ_F (377 MHz, CDCl_3) -62.18; LRMS (ESI^-) m/z : 459.0 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4\text{F}_3$, 459.1537, found 459.1540.

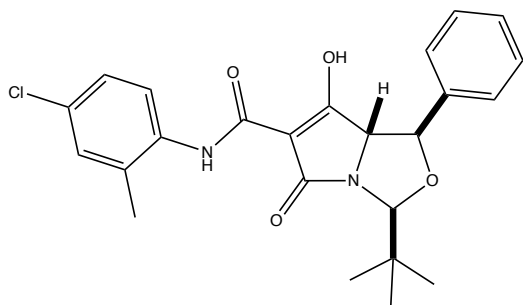
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-(*tert*-butyl)phenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111f**



Yield (96 mg, 27%); Red/brown solid; m.p. 89-94°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.75; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1694 (C=O), 1646 (C=O), 1601 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 0.98 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.18 (9H, s, Ar- $\text{C}(\text{CH}_3)_3$), 4.00 (1H, br m, H5), 4.44 (1H, d, $J=8.5$ Hz, H4),

4.90 (1H, s, H2), 7.12-7.46 (9H, m, Ar-H), 9.50 (1H, br s, NH/OH), 9.93 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 31.4 (Ar- $(\text{CH}_3)_3$), 34.4 (Ar- $\text{C}(\text{CH}_3)_3$), 36.1 ($\text{C}(\text{CH}_3)_3$), 69.1 (C5), 80.9 (C4), 94.8 (C2), 98.7 (C7), 120.3 (Ar-C), 126.0 (Ar-C), 126.2 (Ar-C), 126.4 (Ar-C), 128.7 (Ar-C), 134.1 (Ar-C), 136.1 (Ar-C), 147.8 (Ar-C), 164.1 (C9), 175.4 (C8), 185.1 (C6); LRMS (ESI^-) m/z : 447.2 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_4$, 447.2289, found 447.2289.

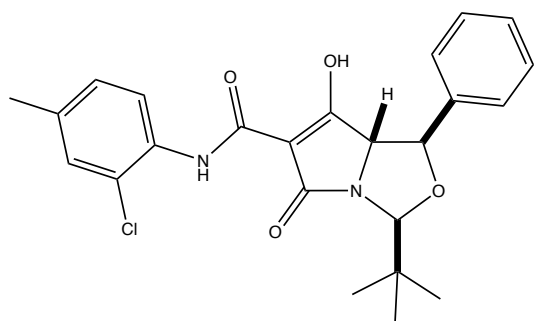
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-chloro-2-methylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111g**



Yield (109 mg, 40%); Brown foamy solid; m.p. 101-105°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.18; $\nu_{\max}/\text{cm}^{-1}$ 3270 (O-H), 2961 (C-H), 1694 (C=O), 1634 (C=O), 1587 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.36 (3H, s, CH_3), 4.27 (1H, d, $J=8.5$ Hz, H5),

4.63 (1H, d, $J=8.4$ Hz, H4), 5.03 (1H, s, H2), 7.17-7.19 (2H, m, Ar-H), 7.37-7.54 (5H, m, Ar-H), 8.02 (1H, d, $J=8.4$ Hz, Ar-H), 9.18 (1H, br s, NH/OH), 9.42 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 17.8 (CH_3), 25.0 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.0 (C4), 94.7 (C2), 100.2 (C7), 122.9 (Ar-C), 126.3 (Ar-C), 126.8 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 130.2 (Ar-C), 130.3 (Ar-C), 130.5 (Ar-C), 133.5 (Ar-C), 135.8 (Ar-C), 163.9 (C9), 174.4 (C8), 183.6 (C6); LRMS (ESI^-) m/z : 439.1 ($[\text{M}^{35} - \text{H}]^-$ 36%), 441.1 ($[\text{M}^{37} - \text{H}]^-$ 15%); HRMS (ESI^-) m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{Cl}$, 439.1430, found 439.1427; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{Cl}$, 441.1401, found 441.1393.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(2-chloro-4-methylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111h**

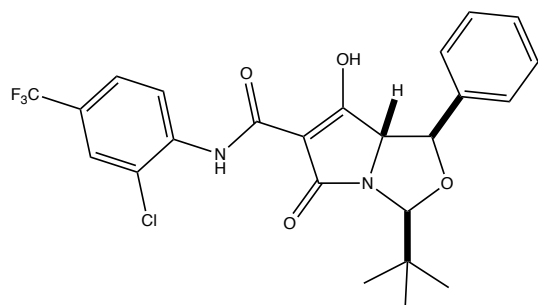


Yield (141 mg, 44%); Brown foamy solid; m.p. 104-107°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 1699 (C=O), 1649 (C=O), 1631 (C=O), 1609 (C=O), 1593 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.32 (3H, s, CH_3), 4.27 (1H, d, $J=8.4$

Hz, H5), 4.63 (1H, d, $J=8.4$ Hz, H4), 5.06 (1H, s, H2), 7.08 (1H, d, $J=8.3$ Hz, Ar-H), 7.24-7.54 (6H, m, Ar-H), 8.20 (1H, d, $J=8.3$ Hz, Ar-H), 9.85 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 20.8 (CH_3), 25.1 ($(\text{CH}_3)_3$), 36.3 ($\text{C}(\text{CH}_3)_3$), 68.7 (C5), 81.1 (C4), 94.8 (C2), 100.4 (C7), 122.1 (Ar-C), 124.0 (Ar-C), 126.4 (Ar-C), 128.3 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 129.9 (Ar-C), 131.2 (Ar-C), 135.8 (Ar-C), 135.9 (Ar-C), 164.2 (C9), 174.0 (C8), 183.9 (C6); LRMS (ESI^-) m/z : 439.0 ($[\text{M}^{35} - \text{H}]^-$ 97%), 441.1 ($[\text{M}^{37} - \text{H}]^-$ 28%); HRMS (ESI^-) m/z : $[\text{M}^{35}$

– H]⁺ calcd. for C₂₄H₂₄N₂O₄Cl, 439.1430, found 439.1434; [M³⁷ – H]⁺ calcd. for C₂₄H₂₄N₂O₄Cl, 441.1401, found 441.1404.

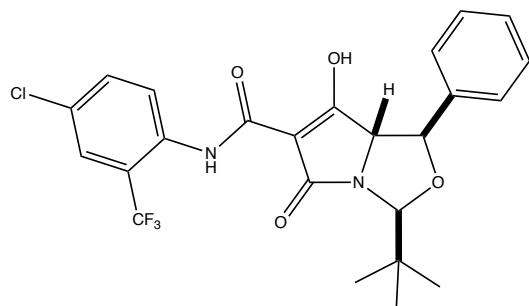
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111*i***



Yield (77 mg, 21%); Red foamy solid; m.p. 93-97°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.15; ν_{max}/cm⁻¹ 2963 (C-H), 1701 (C=O), 1658 (C=O), 1633 (C=O), 1594 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl₃) 1.11 (9H, s, C(CH₃)₃), 4.31 (1H, d, *J*=8.5 Hz, H5), 4.64 (1H, d, *J*=8.5 Hz, H4),

5.07 (1H, s, H2), 7.34-7.70 (7H, m, Ar-H), 8.59 (1H, d, *J*=8.7 Hz, Ar-H), 10.19 (1H, br s, NH/OH); δ_C (101 MHz, CDCl₃) 25.1 ((CH₃)₃), 36.3 (C(CH₃)₃), 68.7 (C5), 81.2 (C4), 94.9 (C2), 100.6 (C7), 121.6 (Ar-C), 123.8 (Ar-C), 124.9 (q, *J*=3.7 Hz, Ar-C), 126.4 (Ar-C), 126.7 (q, *J*=3.7 Hz, Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 129.6 (Ar-C), 135.7 (Ar-C), 137.1 (Ar-C), 164.5 (C9), 173.8 (C8), 184.0 (C6); δ_F (377 MHz, CDCl₃) -62.35; LRMS (ESI⁺) *m/z*: 493.0 ([M³⁵ – H]⁺ 100%), 495.0 ([M³⁷ – H]⁺ 39%); HRMS (ESI⁺) *m/z*: [M³⁵ – H]⁺ calcd. for C₂₄H₂₁N₂O₄F₃Cl, 493.1147, found 493.1152; [M³⁷ – H]⁺ calcd. for C₂₄H₂₁N₂O₄F₃Cl, 495.1118, found 495.1122.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-chloro-2-(trifluoromethyl)phenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111*j***

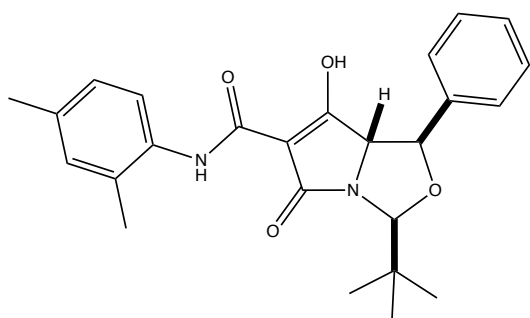


Yield (139 mg, 43%); Orange foamy solid; m.p. 107-111°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.15; ν_{max}/cm⁻¹ 3270 (O-H), 2964 (C-H), 1701 (C=O), 1633 (C=O), 1590 (C=C); AB:CD=99:1; δ_H (400 MHz, CDCl₃) 1.10 (9H, s, C(CH₃)₃), 4.28 (1H, d, *J*=8.5 Hz, H5), 4.64 (1H, d, *J*=8.4 Hz,

H4), 5.06 (1H, s, H2), 7.37-7.65 (7H, m, Ar-H), 8.20 (1H, d, *J*=8.9 Hz, Ar-H), 9.16 (1H, br s, NH/OH), 9.83 (1H, br s, NH/OH); δ_C (101 MHz, CDCl₃) 25.1 ((CH₃)₃), 36.3 (C(CH₃)₃), 68.6 (C5), 81.1 (C4), 94.8 (C2), 100.2

(C7), 125.8 (Ar-C), 126.1 (Ar-C), 126.4 (Ar-C), 126.6-126.7 (m, Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 129.5-129.6 (m, Ar-C), 132.6 (Ar-C), 132.8 (Ar-C), 135.8 (Ar-C), 164.5 (C9), 173.7 (C8), 183.8 (C6); δ_F (377 MHz, $CDCl_3$) -61.31; LRMS (ESI^-) m/z : 493.0 ($[M^{35} - H]^-$ 97%), 495.0 ($[M^{37} - H]^-$ 34%); HRMS (ESI^-) m/z : $[M^{35} - H]^-$ calcd. for $C_{24}H_{21}N_2O_4F_3Cl$, 493.1147, found 493.1149; $[M^{37} - H]^-$ calcd. for $C_{24}H_{21}N_2O_4F_3Cl$, 495.1118, found 495.1119.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(2,4-dimethylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111k**



Yield (102 mg, 41%); Yellow foamy solid; m.p. 77-81°C;

R_f (50% EtOAc in Pet. Ether 40:60) 0.45; ν_{max}/cm^{-1} 2968

(C-H), 1694 (C=O), 1648 (C=O), 1633 (C=O), 1603 (C=C);

AB:CD=99:1; δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s, $C(CH_3)_3$),

2.32 (3H, s, CH_3), 2.36 (3H, s, CH_3), 4.27 (1H, d, $J=8.5$ Hz,

H5), 4.65 (1H, d, $J=8.5$ Hz, H4), 5.05 (1H, s, H2), 7.04 (2H, m, Ar-H), 7.37-7.46 (3H, m, Ar-H), 7.53-7.56

(2H, m, Ar-H), 7.85 (1H, d, $J=8.7$ Hz, Ar-H), 8.14 (1H, br s, NH/OH), 9.29 (1H, br s, NH/OH); δ_C (101 MHz,

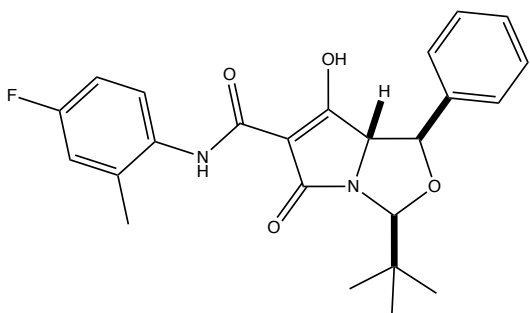
$CDCl_3$) 17.9 (CH_3), 21.1 (CH_3), 25.1 ($(CH_3)_3$), 36.3 ($C(CH_3)_3$), 68.8 (C5), 81.0 (C4), 94.8 (C2), 99.9 (C7),

122.3 (Ar-C), 126.4 (Ar-C), 127.4 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 129.0 (Ar-C), 131.4 (Ar-C), 132.1 (Ar-

C), 135.3 (Ar-C), 136.0 (Ar-C), 164.2 (C9), 174.5 (C8), 184.2 (C6); LRMS (ESI^-) m/z : 419.1 ($[M - H]^-$ 95%);

HRMS (ESI^+) m/z : $[M + H]^+$ calcd. for $C_{25}H_{29}N_2O_4$, 421.2122, found 421.2125.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-fluoro-2-methylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111l**



Yield (131 mg, 51%); Red/brown foamy solid; m.p. 65-

69°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.45; ν_{max}/cm^{-1}

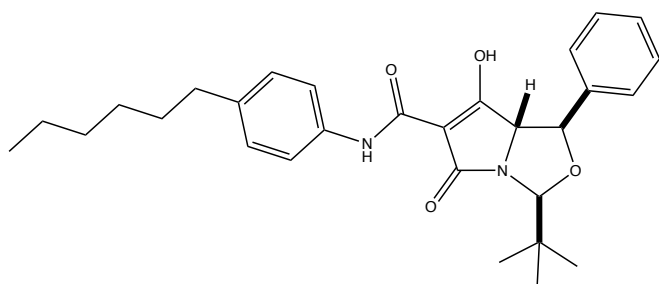
3292 (O-H), 2961 (C-H), 1693 (C=O), 1632 (C=O), 1558

(C=C); AB:CD=99:1; δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s,

$C(CH_3)_3$), 2.37 (3H, s, CH_3), 4.27 (1H, d, $J=8.5$ Hz, H5),

4.64 (1H, d, $J=8.5$ Hz, H4), 5.04 (1H, s, H2), 6.90-6.95 (2H, m, Ar-H), 7.37-7.56 (5H, m, Ar-H), 7.95 (1H, dd, $J=5.3$ Hz, 8.6 Hz, Ar-H), 9.17 (1H, br s, NH/OH), 9.33 (1H, br s, NH/OH); δ_c (101 MHz, $CDCl_3$) 18.1 (CH_3), 25.0 ($(CH_3)_3$), 36.2 ($C(CH_3)_3$), 68.7 (C5), 81.0 (C4), 94.7 (C2), 100.0 (C7), 113.3 (d, $J=22.2$ Hz, Ar-C), 117.3 (d, $J=22.4$ Hz, Ar-C), 123.8 (d, $J=8.3$ Hz, Ar-C), 126.3 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 130.7 (d, $J=3.0$ Hz, Ar-C), 131.5 (d, $J=8.0$ Hz, Ar-C), 135.8 (Ar-C), 159.9 (d, $J=244.7$ Hz, Ar-C), 164.0 (C9), 174.4 (C8), 183.8 (C6); δ_f (377 MHz, $CDCl_3$) -116.90; LRMS (ESI⁻) m/z : 423.1 ($[M - H]^-$ 95%); HRMS (ESI⁻) m/z : $[M - H]^-$ calcd. for $C_{24}H_{24}N_2O_4F$, 423.1726, found 423.1726.

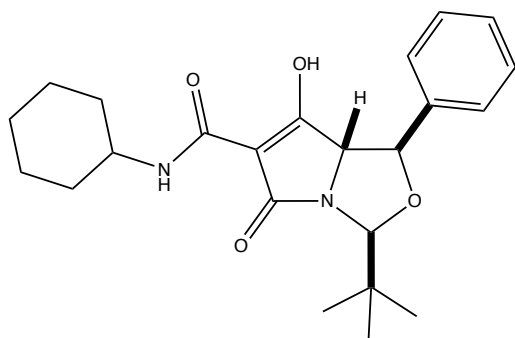
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-hexylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111m**



Yield (66 mg, 18%); Orange oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.65; ν_{max}/cm^{-1} 3280 (O-H), 2957 (C-H), 2928 (C-H), 2857 (C-H), 1697 (C=O), 1649 (C=O), 1605 (C=C); AB:CD=99:1; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t,

$J=6.6$ Hz, Alkyl- CH_3), 1.11 (9H, s, $C(CH_3)_3$), 1.26-1.33 (6H, br s, Alkyl- CH_2), 1.59 (2H, qn, $J=7.4$ Hz, Alkyl- CH_2), 2.58 (2H, t, $J=7.7$ Hz, Alkyl- CH_2), 4.26 (1H, d, $J=8.5$ Hz, H5), 4.62 (1H, d, $J=8.5$ Hz, H4), 5.02 (1H, s, H2), 7.17 (2H, d, $J=8.1$ Hz, Ar-H), 7.37-7.45 (3H, m, Ar-H), 7.49 (2H, d, $J=8.1$ Hz, Ar-H), 7.53 (2H, d, $J=8.3$ Hz, Ar-H), 8.54 (1H, br s, NH/OH), 9.34 (1H, br s, NH/OH); δ_c (101 MHz, $CDCl_3$) 14.3 (Alkyl-C), 22.8 (Alkyl-C), 25.1 ($(CH_3)_3$), 29.1 (Alkyl-C), 31.6 (Alkyl-C), 31.9 (Alkyl-C), 35.6 (Alkyl-C), 36.2 ($C(CH_3)_3$), 68.8 (C5), 81.1 (C4), 94.9 (C2), 99.8 (C7), 120.5 (Ar-C), 126.4 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 134.1 (Ar-C), 135.9 (Ar-C), 140.1 (Ar-C), 164.0 (C9), 174.4 (C8), 184.1 (C6); LRMS (ESI⁻) m/z : 475.1 ($[M - H]^-$ 96%); HRMS (ESI⁻) m/z : $[M - H]^-$ calcd. for $C_{29}H_{35}N_2O_4$, 475.2602, found 475.2605.

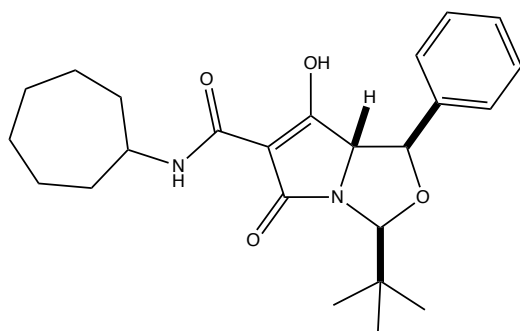
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-cyclohexyl-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111n**



Yield (159 mg, 45%); Red/purple foamy solid; m.p. 94-97°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.20; $\nu_{\max}/\text{cm}^{-1}$ 2932 (C-H), 2856 (C-H), 1697 (C=O), 1648 (C=O); AB:CD=82:18; δ_H (400 MHz, CDCl_3) 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$, AB), 1.14-1.96 (10H, br m, Cyclohexyl- CH_2), 3.80-3.89 (1H, br m, Cyclohexyl-CH),

3.90 (1H, d, $J=8.9$ Hz, H5, CD), 4.15 (1H, d, $J=8.6$ Hz, H5, AB), 4.58 (1H, d, $J=8.6$ Hz, H4, AB), 4.61 (1H, d, $J=9.0$ Hz, H4, CD), 4.97 (1H, s, H2, AB), 4.99 (1H, s, H2, CD), 7.34-7.56 (5H, m, Ar-H), 10.51 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 24.7 (Cyclohexyl-C), 25.0 ($(\text{CH}_3)_3$), 25.4 (Cyclohexyl-C), 32.8 (Cyclohexyl-C), 32.9 (Cyclohexyl-C), 36.1 ($\text{C}(\text{CH}_3)_3$, CD), 36.2 ($\text{C}(\text{CH}_3)_3$, AB), 48.0 (Cyclohexyl-C, AB), 49.6 (Cyclohexyl-C, CD), 69.2 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.8 (C2, AB), 94.9 (C2, CD), 97.2 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 136.2 (Ar-C, AB), 137.1 (Ar-C, CD), 165.5 (C9, AB), 166.0 (C9, CD), 174.9 (C8, AB), 181.0 (C8, CD), 186.1 (C6, AB), 190.6 (C6, CD); LRMS (ESI^-) m/z : 397.2 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : calcd. $[\text{M} - \text{H}]^-$ for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_4$, 397.2133, found 397.2127.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-cycloheptyl-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111o**

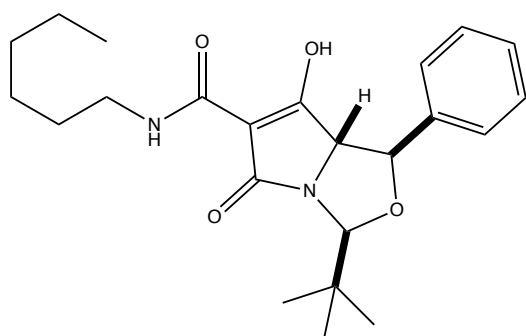


Yield (140 mg, 24%); Brown foamy solid; m.p. 59-64°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.20; $\nu_{\max}/\text{cm}^{-1}$ 2929 (C-H), 2858 (C-H), 1695 (C=O), 1645 (C=O); AB:CD=83:17; δ_H (400 MHz, CDCl_3) 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$, AB), 1.48-2.05 (12H, br m, Cycloheptyl- CH_2), 3.90 (1H, d, $J=8.8$ Hz, H5, CD), 4.06 (1H, m, Cycloheptyl-CH), 4.15 (1H, d, $J=8.5$ Hz, H5, AB), 4.58 (1H, d, $J=8.6$ Hz, H4, AB), 4.61 (1H, d, $J=9.0$ Hz, H4, CD), 4.97 (1H, s, H2, AB), 4.99 (1H, s,

4.99 (1H, s, H2, CD), 7.34-7.56 (5H, m, Ar-H), 10.51 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 24.7 (Cycloheptyl-C), 25.0 ($(\text{CH}_3)_3$), 25.4 (Cycloheptyl-C), 32.8 (Cycloheptyl-C), 32.9 (Cycloheptyl-C), 36.1 ($\text{C}(\text{CH}_3)_3$, CD), 36.2 ($\text{C}(\text{CH}_3)_3$, AB), 48.0 (Cycloheptyl-C, AB), 49.6 (Cycloheptyl-C, CD), 69.2 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.8 (C2, AB), 94.9 (C2, CD), 97.2 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 136.2 (Ar-C, AB), 137.1 (Ar-C, CD), 165.5 (C9, AB), 166.0 (C9, CD), 174.9 (C8, AB), 181.0 (C8, CD), 186.1 (C6, AB), 190.6 (C6, CD); LRMS (ESI^-) m/z : 397.2 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : calcd. $[\text{M} - \text{H}]^-$ for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_4$, 397.2283, found 397.2275.

H₂, CD), 7.33-7.57 (5H, m, Ar-H), 10.73 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 24.0 (Cycloheptyl-C, AB), 24.1 (Cycloheptyl-C, CD), 25.0 ((CH₃)₃), 27.9 (Cycloheptyl-C, CD), 28.1 (Cycloheptyl-C, AB), 34.9 (Cycloheptyl-C), 35.0 (Cycloheptyl-C), 36.1 (C(CH₃)₃, CD), 36.2 (C(CH₃)₃, AB), 50.2 (Cycloheptyl-C, AB), 50.8 (Cycloheptyl-C, CD), 69.2 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.8 (C2, AB), 94.9 (C2, CD), 97.2 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 136.2 (Ar-C, AB), 137.1 (Ar-C, CD), 165.2 (C9, AB), 165.7 (C9, CD), 174.9 (C8, AB), 181.0 (C8, CD), 186.1 (C6, AB), 190.6 (C6, CD); LRMS (ESI⁻) m/z : 411.1 ([M - H]⁻ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₄H₃₃N₂O₄, 413.2435, found 413.2432.

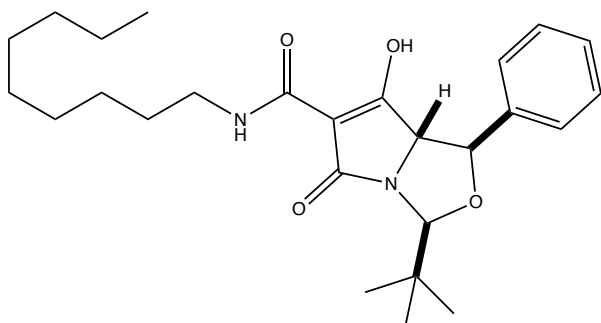
(1R*,3S*,7aS*)-3-(tert-Butyl)-N-hexyl-7-hydroxy-5-oxo-1-phenyl-5,7a-dihydro-1H,3H-pyrrolo[1,2-c]oxazole-6-carboxamide 111p



Yield (65 mg, 19%); Orange oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 3339 (O-H), 2957 (C-H), 2930 (C-H), 2860 (C-H), 1697 (C=O), 1649 (C=O); AB:CD=82:18; δ_H (400 MHz, CDCl₃) 0.90 (3H, t, J =6.7 Hz, Alkyl-CH₃), 1.07 (9H, s, C(CH₃)₃), 1.21-1.40 (6H, br m,

Alkyl-CH₂), 1.52-1.68 (2H, br m, Alkyl-CH₂), 3.36 (2H, q, J =6.8 Hz, Alkyl-CH₂), 3.90 (1H, d, J =8.9 Hz, H5, CD), 4.16 (1H, d, J =8.5 Hz, H5, AB), 4.58 (1H, d, J =8.4 Hz, H4, AB), 4.61 (1H, obscured by H4/AB peak, CD), 4.97 (1H, s, H2, AB), 5.00 (1H, s, H2, CD), 7.34-7.55 (5H, m, Ar-H), 10.00 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 14.2 (Alkyl-C), 22.6 (Alkyl-C), 25.0 ((CH₃)₃), 26.6 (Alkyl-C), 29.5 (Alkyl-C), 31.5 (Alkyl-C), 36.2 (C(CH₃)₃), 39.0 (Alkyl-C), 69.2 (C5, AB), 72.5 (C5, CD), 79.6 (C4, CD), 80.8 (C4, AB), 94.8 (C2, AB), 95.0 (C2, CD), 97.7 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 128.9 (Ar-C, AB), 129.2 (Ar-C, CD), 136.2 (Ar-C, AB), 137.0 (Ar-C, CD), 166.3 (C9, AB), 167.0 (C9, CD), 174.8 (C8, AB), 181.0 (C8, CD), 185.6 (C6, AB), 188.4 (C6, CD); LRMS (ESI⁻) m/z : 399.2 ([M - H]⁻ 97%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₂₃H₃₁N₂O₄, 399.2289, found 399.2282.

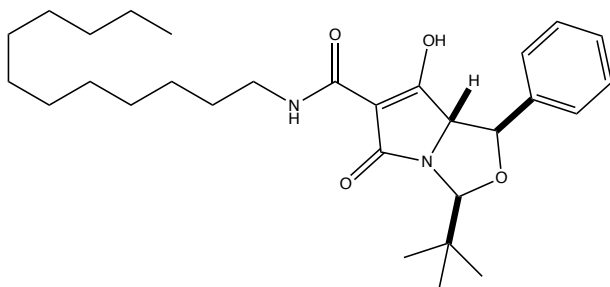
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-*N*-nonyl-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111q**



Yield (104 mg, 40%); Orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.43; $\nu_{\max}/\text{cm}^{-1}$ 2956 (C-H), 2925 (C-H), 2855 (C-H), 1696 (C=O), 1648 (C=O); AB:CD=99:1; δ_H (400 MHz, CDCl_3) 0.88 (3H, t, $J=7.0$ Hz, Alkyl- CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.19-

1.37 (12H, br m, Alkyl- CH_2), 1.58 (2H, m, Alkyl- CH_2), 3.37 (2H, m, Alkyl- CH_2), 4.17 (1H, m, H5), 4.58 (1H, d, $J=8.6$ Hz, H4), 4.97 (1H, s, H2), 7.33-7.53 (5H, m, Ar-H), 10.58 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 14.2 (Alkyl-C), 22.8 (Alkyl-C), 25.0 ($(\text{CH}_3)_3$), 26.9 (Alkyl-C), 29.3-29.5 (Alkyl-C), 31.9 (Alkyl-C), 36.2 ($\text{C}(\text{CH}_3)_3$), 39.0 (Alkyl-C), 69.2 (C5), 80.8 (C4), 94.8 (C2), 97.6 (C7), 126.3 (Ar-C), 128.8 (Ar-C), 136.2 (Ar-C), 166.3 (C9), 174.8 (C8), 185.6 (C6); LRMS (ESI^-) m/z : 441.2 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{39}\text{N}_2\text{O}_4$, 443.2904, found 443.2901.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-dodecyl-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111r**

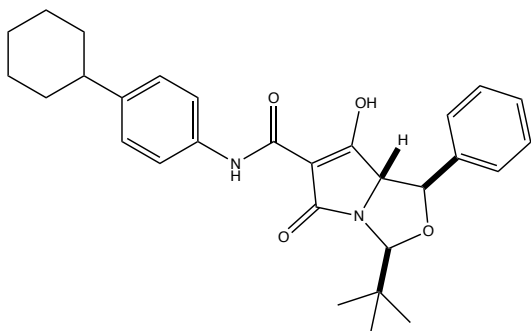


Yield (163 mg, 57%); Orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 2924 (C-H), 2854 (C-H), 1697 (C=O), 1648 (C=O); AB:CD=84:16; δ_H (400 MHz, CDCl_3) 0.88 (3H, t, $J=6.7$ Hz, Alkyl- CH_3), 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$, CD),

1.07 (9H, s, $\text{C}(\text{CH}_3)_3$, AB), 1.21-1.37 (18H, br m, Alkyl- CH_2), 1.54-1.64 (2H, m, Alkyl- CH_2), 3.36 (2H, m, Alkyl- CH_2), 3.90 (1H, d, $J=8.9$ Hz, H5, CD), 4.16 (1H, d, $J=8.6$ Hz, H5, AB), 4.58 (1H, d, $J=8.5$ Hz, H4, AB), 4.60 (1H, obscured by H4/AB peak, H4, CD), 4.97 (1H, s, H2, AB), 5.00 (1H, s, H2, CD), 7.32-7.56 (5H, m, Ar-H), 10.51 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 14.3 (Alkyl-C), 22.8 (Alkyl-C), 25.0 ($(\text{CH}_3)_3$, AB), 25.1 ($(\text{CH}_3)_3$, CD), 27.0 (Alkyl-C, AB), 27.0 (Alkyl-C, CD), 29.4-29.8 (Alkyl-C), 32.0 (Alkyl-C), 36.1 ($\text{C}(\text{CH}_3)_3$, CD), 36.2 ($\text{C}(\text{CH}_3)_3$, AB), 38.9 (Alkyl-C, CD), 39.0 (Alkyl-C, AB), 69.2 (C5, AB), 72.5 (C5, CD), 79.6 (C4, CD), 80.8

(C4, AB), 94.8 (C2, AB), 95.0 (C2, CD), 97.7 (C7), 126.3 (Ar-C, AB), 126.5 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 129.4 (Ar-C, CD), 136.2 (Ar-C, AB), 137.0 (Ar-C, CD), 166.3 (C9, AB), 167.0 (C9, CD), 174.8 (C8, AB), 180.4 (C8, CD), 185.6 (C6, AB), 190.7 (C6, CD); LRMS (ESI⁻) m/z : 483.3 ([M - H]⁻ 97%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₂₉H₄₃N₂O₄, 483.3228, found 483.3234.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-cyclohexylphenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111s**



Yield (113 mg, 25%); Brown foamy solid; m.p. 97-101°C;

R_f (50% EtOAc in Pet. Ether 40:60) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 3272

(O-H), 2925 (C-H), 2852 (C-H), 1697 (C=O), 1649 (C=O),

1604 (C=C); AB:CD=99:1; δ_{H} (400 MHz, CDCl₃) 1.11 (9H,

s, C(CH₃)₃), 1.21-1.42 (6H, br m, Cyclohexyl-CH₂), 1.73-

1.88 (4H, br m, Cyclohexyl-CH₂), 2.48 (1H, br m,

Cyclohexyl-CH), 4.26 (1H, d, J =8.5 Hz, H5), 4.63 (1H, d, J =8.5 Hz, H4), 5.02 (1H, s, H2), 7.19-7.54 (9H, m,

Ar-H), 9.32 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl₃) 25.1 ((CH₃)₃), 26.3 (Cyclohexyl-C), 27.0 (Cyclohexyl-

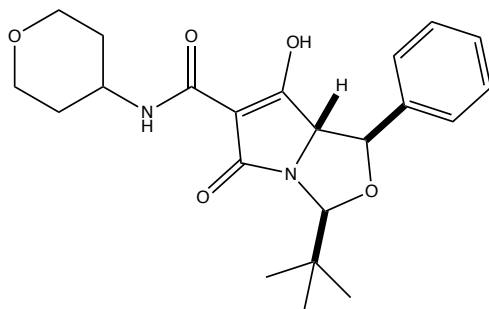
C), 34.6 (Cyclohexyl-C), 36.2 (C(CH₃)₃), 44.2 (Cyclohexyl-C), 68.8 (C5), 81.0 (C4), 94.9 (C2), 99.8 (C7),

120.6 (Ar-C), 126.4 (Ar-C), 127.6 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 134.2 (Ar-C), 135.9 (Ar-C), 145.3 (Ar-

C), 164.0 (C9), 174.4 (C8), 184.1 (C6); LRMS (ESI⁻) m/z : 473.1 ([M - H]⁻ 100%); HRMS (ESI⁻) m/z : [M - H]⁻

calcd. for C₂₉H₃₃N₂O₄, 473.2446, found 473.2449.

(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-5-oxo-1-phenyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111t**



Yield (96 mg, 31%); Brown/orange foamy solid; m.p. 100-

103°C; R_f (100% EtOAc) 0.10; $\nu_{\max}/\text{cm}^{-1}$ 3324 (O-H), 2960 (C-

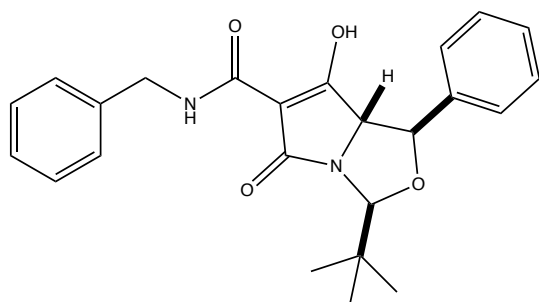
H), 2849 (C-H), 1692 (C=O), 1645 (C=O); AB:CD=88:12; δ_{H}

(400 MHz, CDCl₃) 1.06 (9H, s, C(CH₃)₃, CD), 1.07 (9H, s,

C(CH₃)₃, AB), 1.55-1.68 (2H, br m, Pyran-CH₂), 1.87-1.97

(2H, br m, Pyran-CH₂), 3.50 (2H, br m, Pyran-CH₂), 3.92 (1H, d, $J=8.9$ Hz, H5, CD), 3.98 (2H, br m, Pyran-CH₂), 4.08 (1H, m, Pyran-CH), 4.19 (1H, d, $J=8.6$ Hz, H5, AB), 4.58 (1H, d, $J=8.6$ Hz, H4, AB), 4.62 (1H, d, $J=9.0$ Hz, H4, CD), 4.97 (1H, s, H2, AB), 4.99 (1H, s, H2, CD), 7.33-7.56 (5H, m, Ar-H), 10.51 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 25.0 ((CH₃)₃, AB), 25.1 ((CH₃)₃, CD), 32.7 (Pyran-C, CD), 32.8 (Pyran-C, AB), 32.9 (Pyran-C, AB), 36.1 (C(CH₃)₃, CD), 36.2 (C(CH₃)₃, AB), 45.3 (Pyran-C, AB), 47.0 (Pyran-C, CD), 66.4 (Pyran-C, CD), 66.6 (Pyran-C, AB), 69.0 (C5, AB), 72.6 (C5, CD), 79.5 (C4, CD), 80.9 (C4, AB), 94.9 (C2, AB), 95.0 (C2, CD), 98.5 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.9 (Ar-C, AB), 128.9 (Ar-C, AB), 136.1 (Ar-C, AB), 136.9 (Ar-C, CD), 165.6 (C9, AB), 166.4 (C9, CD), 174.6 (C8, AB), 181.1 (C8, CD), 184.9 (C6, AB), 190.6 (C6, CD); LRMS (ESI⁻) m/z : 399.1 ([M - H]⁻ 96%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₂₂H₂₇N₂O₅, 399.1926, found 399.1925.

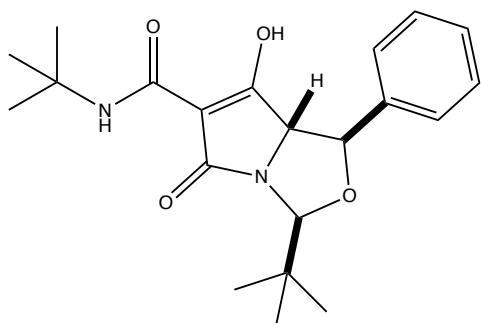
(1*R,3*S**,7*aS**)-*N*-Benzyl-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111u**



Yield (98 mg, 33%); Orange oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.20; $\nu_{\max}/\text{cm}^{-1}$ 3326 (O-H), 2967 (C-H), 1695 (C=O), 1647 (C=O); AB:CD=99:1; δ_H (400 MHz, CDCl₃) 1.07 (9H, s, C(CH₃)₃), 4.20 (1H, d, $J=8.5$ Hz, H5), 4.56 (2H, br dd, $J=1.7$ Hz, 6.2 Hz, NHCH₂), 4.59 (1H, d,

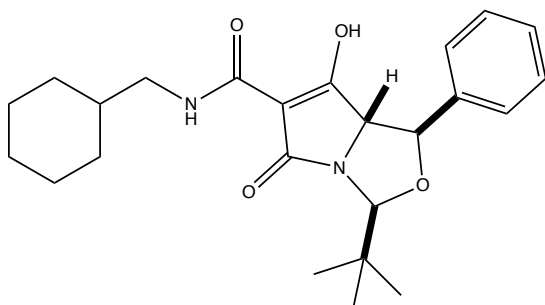
$J=8.6$ Hz, H4), 4.96 (1H, s, H2), 7.30-7.53 (10H, m, Ar-H), 7.86 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 25.0 ((CH₃)₃), 36.2 (C(CH₃)₃), 42.8 (NHCH₂), 68.9 (C5), 80.9 (C4), 94.8 (C2), 98.8 (C7), 126.3 (Ar-C), 127.9 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 136.0 (Ar-C), 137.1 (Ar-C), 166.0 (C9), 174.5 (C8), 184.6 (C6); LRMS (ESI⁻) m/z : 405.1 ([M - H]⁻ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₄H₂₇N₂O₄, 407.1965, found 407.1967.

(1*R,3*S**,7*aS**)-N,3-Di-*tert*-butyl-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111v**



Yield (92 mg, 41%); Orange oil; *R_f* (50% EtOAc in Pet. Ether 40:60) 0.63; $\nu_{\max}/\text{cm}^{-1}$ 3323 (O-H), 2968 (C-H), 1697 (C=O), 1649 (C=O), 1623 (C=C); AB:CD=82:18; δ_{H} (400 MHz, CDCl_3) 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$, AB), 1.44 (9H, s, $\text{NHC}(\text{CH}_3)_3$, AB), 1.47 (9H, s, $\text{NHC}(\text{CH}_3)_3$, CD), 3.91 (1H, d, $J=8.8$ Hz, H5, CD), 4.13 (1H, d, $J=8.6$ Hz, H5, AB), 4.58 (1H, d, $J=8.6$ Hz, H4, AB), 4.61 (1H, d, $J=8.9$ Hz, H4, CD), 4.96 (1H, s, H2, AB), 4.99 (1H, s, H2, CD), 7.36-7.57 (5H, m, Ar-H), 9.40 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 25.1 ($(\text{CH}_3)_3$), 29.0 ($\text{NC}(\text{CH}_3)_3$, AB), 29.3 ($\text{NC}(\text{CH}_3)_3$, CD), 36.2 ($\text{C}(\text{CH}_3)_3$, CD), 36.2 ($\text{C}(\text{CH}_3)_3$, AB), 52.3 ($\text{NHC}(\text{CH}_3)_3$, AB), 53.8 ($\text{NHC}(\text{CH}_3)_3$, CD), 69.3 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.8 (C2, AB), 94.9 (C2, CD), 97.3 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 128.7 (Ar-C, CD), 128.8 (Ar-C, AB), 136.3 (Ar-C, AB), 137.1 (Ar-C, CD), 166.3 (C9, AB), 167.2 (C9, CD), 175.1 (C8, AB), 181.2 (C8, CD), 186.5 (C6, AB), 190.5 (C6, CD); LRMS (ESI^-) m/z : 371.1 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4$, 373.2122, found 373.2124.

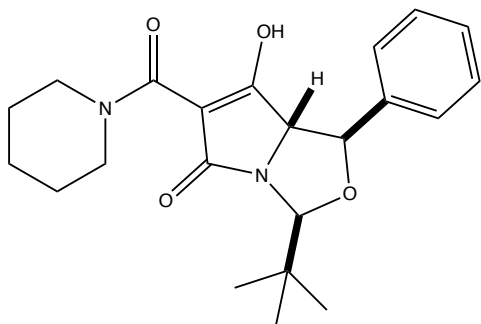
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-N-(cyclohexylmethyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 111w**



Yield (96 mg, 37%); Red/orange oil; *R_f* (50% EtOAc in Pet. Ether 40:60) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 3337 (O-H), 2925 (C-H), 2853 (C-H), 1696 (C=O), 1648 (C=O); AB:CD=99:1; δ_{H} (400 MHz, CDCl_3) 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.13-1.30 (4H, br m, Cyclohexyl- CH_2), 1.65-1.78 (7H, br m, Cyclohexyl- CH_2 , CH), 3.10-3.28 (2H, m, NHCH_2), 4.16 (1H, d, $J=8.5$ Hz, H5), 4.58 (1H, d, $J=8.5$ Hz, H4), 4.98 (1H, s, H2), 7.33-7.61 (5H, m, Ar-H), 10.61 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 25.8 (Cyclohexyl-C), 26.3 (Cyclohexyl-C), 30.8 (Cyclohexyl-C), 36.2 ($\text{C}(\text{CH}_3)_3$), 37.9 (Cyclohexyl-C), 45.0 (NCH_2), 69.2 (C5), 80.7 (C4), 94.8 (C2), 97.6 (C7), 126.3 (Ar-C), 128.8 (Ar-C), 136.2 (Ar-C), 166.3 (C9),

174.8 (C8), 185.6 (C6); LRMS (ESI⁻) m/z : 411.1 ([M - H]⁻ 96%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₄H₃₃N₂O₄, 413.2435, found 413.2433.

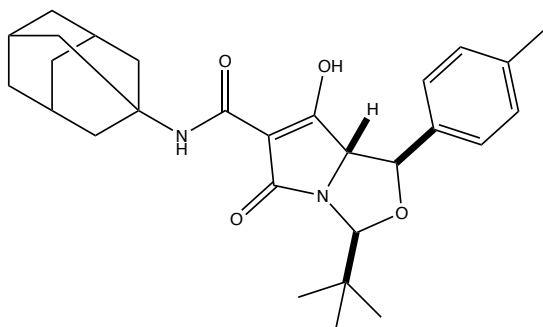
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-7-hydroxy-1-phenyl-6-(piperidine-1-carbonyl)-1,7*a*-dihydro-3*H*,5*H*-pyrrolo[1,2-*c*]oxazol-5-one 111x**



Yield (38 mg, 16%); Orange oil; R_f (20% MeOH in EtOAc) 0.68; $\nu_{\max}/\text{cm}^{-1}$ 3038 (O-H), 2938 (C-H), 2861 (C-H), 1697 (C=O), 1636 (C=O), 1571 (C=C); AB:CD=99:1; δ_{H} (500 MHz, CDCl₃) 1.06 (9H, s, C(CH₃)₃), 1.69 (6H, br s, Piperidine-CH₂), 3.53 (2H, br m, Piperidine-CH₂), 3.80 (1H, br s, OH), 4.00 (1H,

br d, $J=8.6$ Hz, H5), 4.58 (1H, d, $J=8.6$ Hz, H4), 5.04 (1H, s, H2), 7.31-7.57 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 24.3 (Piperidine-C), 25.2 ((CH₃)₃), 26.4 (Piperidine-C), 36.3 (C(CH₃)₃), 43.2 (Piperidine-C), 47.6 (Piperidine-C), 70.1 (C5), 80.4 (C4), 95.2 (C2), 126.6 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 137.1 (Ar-C), 165.4 (C=O), 166.1 (C=O); LRMS (ESI⁻) m/z : 383.1 ([M - H]⁻ 96%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₂H₂₉N₂O₄, 385.2122, found 385.2125.

(1*R,3*S**,7*aS**)-N-(Adamantan-1-yl)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-(*p*-tolyl)-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 112a**

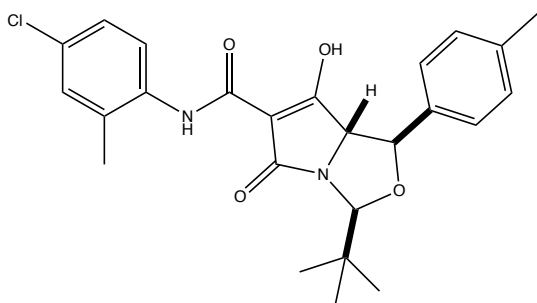


Yield (70 mg, 52%); Brown foamy solid; m.p. 124-127°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.83; $\nu_{\max}/\text{cm}^{-1}$ 3312 (O-H), 2909 (C-H), 2852 (C-H), 1695 (C=O), 1647 (C=O); AB:CD=80:20; δ_{H} (400 MHz, CDCl₃) 1.05 (9H, s, C(CH₃)₃, CD), 1.06 (9H, s, C(CH₃)₃, AB), 1.70

(6H, br m, Adamantyl-CH₂), 2.07 (6H, br m, Adamantyl-CH₂), 2.12 (3H, br s, Adamantyl-CH), 2.35 (3H, s, CH₃, CD) 2.36 (3H, s, CH₃, AB), 3.88 (1H, d, $J=8.8$ Hz, H5, CD), 4.10 (1H, d, $J=8.6$ Hz, H5, AB), 4.53 (1H, d, $J=8.6$ Hz, H4, AB), 4.57 (1H, d, $J=8.9$ Hz, H4, CD), 4.94 (1H, s, H2, AB), 4.97 (1H, s, H2, CD), 7.21 (2H, d, $J=7.9$ Hz, Ar-H), 7.40 (2H, d, $J=8.0$ Hz, Ar-H), 9.92 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl₃) 21.4 (CH₃),

25.1 ((CH₃)₃), 29.4 (Adamantyl-C, CD), 29.5 (Adamantyl-C, AB), 36.0 (Adamantyl-C, CD), 36.2 (C(CH₃)₃), 36.2 (Adamantyl-C, AB), 41.7 (Adamantyl-C, AB), 42.7 (Adamantyl-C, CD), 53.0 (Adamantyl-C, AB), 54.5 (Adamantyl-C, CD), 69.3 (C5, AB), 72.5 (C5, CD), 79.5 (C4, CD), 80.7 (C4, AB), 94.8 (C2, AB), 94.8 (C2, CD), 97.2 (C7), 126.3 (Ar-C, AB), 126.4 (Ar-C, CD), 129.4 (Ar-C, CD), 129.5 (Ar-C, AB), 133.3 (Ar-C, AB), 134.1 (Ar-C, CD), 138.1 (Ar-C, CD), 138.6 (Ar-C, AB), 166.2 (C9, AB), 167.0 (C9, CD), 175.1 (C8, AB), 181.2 (C8, CD), 186.6 (C6, AB), 190.5 (C6, CD); LRMS (ESI⁻) *m/z*: 463.2 ([M - H]⁻ 97%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₂₈H₃₇N₂O₄, 465.2748, found 465.2748.

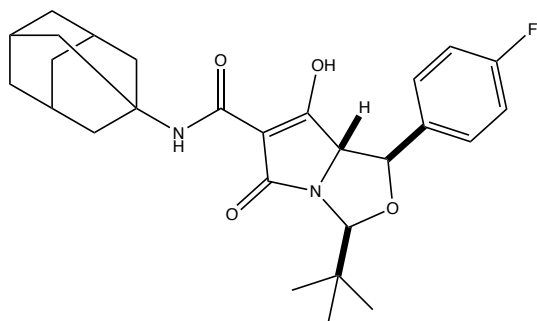
(1*R,3*S**,7*aS**)-3-(*tert*-Butyl)-*N*-(4-chloro-2-methylphenyl)-7-hydroxy-5-oxo-1-(*p*-tolyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 112b**



Yield (24 mg, 7%); Red oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 3272 (O-H), 2960 (C-H), 1694 (C=O), 1635 (C=O); AB:CD=99:1; δ_{H} (400 MHz, CDCl₃) 1.10 (9H, s, C(CH₃)₃), 2.37 (3H, s, CH₃), 2.38 (3H, s, CH₃), 4.27 (1H, d, *J*=8.5 Hz, H5), 4.59 (1H, d, *J*=8.5 Hz, H4),

5.01 (1H, s, H2), 7.19 (2H, m, Ar-H), 7.23 (2H, d, *J*=7.9 Hz, Ar-H), 7.41 (2H, d, *J*=7.9 Hz, Ar-H), 8.01 (1H, d, *J*=8.3 Hz, Ar-H), 9.40 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl₃) 17.9 (CH₃), 21.4 (CH₃), 25.1 ((CH₃)₃), 36.2 (C(CH₃)₃), 68.8 (C5), 81.2 (C4), 94.8 (C2), 100.3 (C7), 123.0 (Ar-C), 126.4 (Ar-C), 126.8 (Ar-C), 129.6 (Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 132.8 (Ar-C), 133.6 (Ar-C), 139.0 (Ar-C), 164.1 (C9), 174.4 (C8), 183.8 (C6); LRMS (ESI⁻) *m/z*: 453.1 ([M³⁵ - H]⁻ 96%), 455.1 ([M³⁷ - H]⁻ 34%); HRMS (ESI⁻) *m/z*: [M³⁵ - H]⁻ calcd. for C₂₅H₂₆N₂O₄Cl, 453.1587, found 453.1587; [M³⁷ - H]⁻ calcd. for C₂₅H₂₆N₂O₄Cl, 455.1557, found 455.1549.

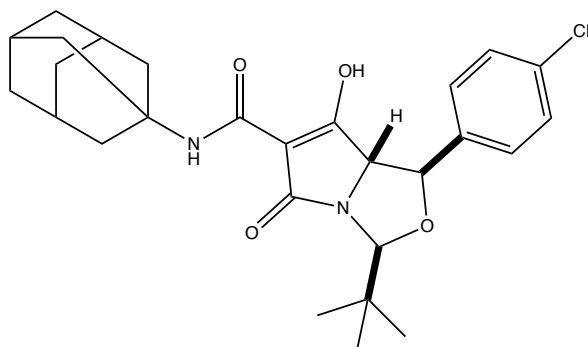
(1*R,3*S**,7*aS**)-N-(Adamantan-1-yl)-3-(*tert*-butyl)-1-(4-fluorophenyl)-7-hydroxy-5-oxo-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 113a**



Yield (182 mg, 70%); Brown foamy solid; m.p. 126-128°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 2909 (C-H), 2852 (C-H), 1693 (C=O), 1646 (C=O), 1625 (C=C); AB:CD=78:22; δ_H (400 MHz, CDCl_3) 1.03 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$, AB), 1.69 (6H, br m,

Adamantyl- CH_2), 2.06 (6H, br m, Adamantyl- CH_2), 2.10 (3H, br m, Adamantyl-CH), 3.83 (1H, br d, $J=8.7$ Hz, H5, CD), 4.04 (1H, br d, $J=8.8$ Hz, H5, AB), 4.53 (1H, br d, $J=8.9$ Hz, H4, AB), 4.57 (1H, br d, $J=9.3$ Hz, H4, CD), 4.94 (1H, s, H2, AB), 4.97 (1H, s, H2, CD), 7.03-7.09 (2H, m, Ar-H), 7.42 (1H, br s, NH/OH), 7.47-7.55 (2H, m, Ar-H), 12.22 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 25.0 ($(\text{CH}_3)_3$), 29.4 (Adamantyl-C), 36.0 (Adamantyl-C, CD), 36.1 ($\text{C}(\text{CH}_3)_3$), 36.2 (Adamantyl-C, AB), 41.4 (Adamantyl-C, CD), 41.7 (Adamantyl-C, AB), 53.1 (Adamantyl-C, AB), 54.6 (Adamantyl-C, CD), 69.4 (C5, AB), 72.3 (C5, CD), 78.9 (C4, CD), 80.0 (C4, AB), 94.9 (C2, AB), 94.9 (C2, CD), 96.5 (C7), 115.5 (d, $J=21.5$ Hz, Ar-C, CD), 115.7 (d, $J=21.3$ Hz, Ar-C, AB), 128.1 (d, $J=8.4$ Hz, Ar-C, AB), 128.2 (obscured by Ar-C/AB, Ar-C, CD), 132.2 (Ar-C, AB), 133.0 (Ar-C, CD), 162.7 (d, $J=246.3$ Hz, Ar-C, CD), 162.9 (d, $J=247.2$ Hz, Ar-C, AB), 166.2 (C9, AB), 167.0 (C9, CD), 175.1 (C8, AB), 181.1 (C8, CD), 187.1 (C6, AB), 190.4 (C6, CD); δ_F (377 MHz, CDCl_3) -113.18 (AB), -113.97 (CD); LRMS (ESI⁻) m/z : 467.1 ($[\text{M} - \text{H}]^-$ 94%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_4\text{F}$, 467.2352, found 467.2352.

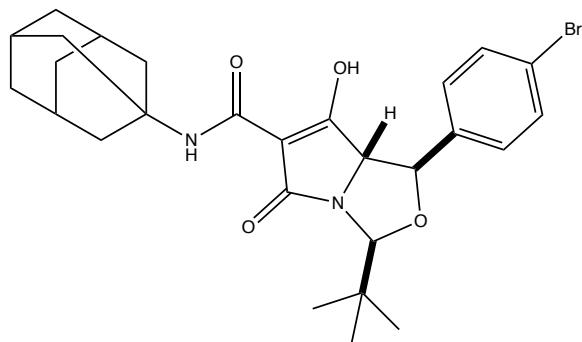
(1*R,3*S**,7*aS**)-N-(Adamantan-1-yl)-3-(*tert*-butyl)-1-(4-chlorophenyl)-7-hydroxy-5-oxo-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 114a**



Yield (155 mg, 44%); Brown/red foamy solid; m.p. 107-110°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.48; $\nu_{\max}/\text{cm}^{-1}$ 2909 (C-H), 2852 (C-H), 1693 (C=O), 1647 (C=O); AB:CD=76:24; δ_H (400 MHz, CDCl_3) 1.03 (9H, s, $\text{C}(\text{CH}_3)_3$, CD), 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$, AB),

1.70 (6H, br m, Adamantyl-CH₂), 2.07 (6H, br m, Adamantyl-CH₂), 2.13 (3H, br m, Adamantyl-CH), 3.84 (1H, d, *J*=8.9 Hz, H5, CD), 4.04 (1H, d, *J*=8.6 Hz, H5, AB), 4.55 (1H, d, *J*=8.6 Hz, H4, AB), 4.58 (1H, d, *J*=8.9 Hz, H4, CD), 4.96 (1H, s, H2, AB), 4.99 (1H, s, H2, CD), 7.37 (2H, d, *J*=8.6 Hz, Ar-H), 7.42 (1H, br s, NH/OH), 7.47 (2H, d, *J*=8.5 Hz, Ar-H), 10.29 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 25.0 ((CH₃)₃), 29.4 (Adamantyl-C, CD), 29.5 (Adamantyl-C, AB), 36.0 (Adamantyl-C, CD), 36.2 (C(CH₃)₃), 36.2 (Adamantyl-C, AB), 41.7 (Adamantyl-C), 53.2 (Adamantyl-C, AB), 54.6 (Adamantyl-C, CD), 69.4 (C5, AB), 72.3 (C5, CD), 78.7 (C4, CD), 79.9 (C4, AB), 94.9 (C2, AB), 95.0 (C2, CD), 96.3 (C7), 127.7 (Ar-C, AB), 127.8 (Ar-C, CD), 128.9 (Ar-C, CD), 129.0 (Ar-C, AB), 134.1 (Ar-C, CD), 134.6 (Ar-C, AB), 135.0 (Ar-C, AB), 135.8 (Ar-C, CD), 166.3 (C9, AB), 167.0 (C9, CD), 175.1 (C8, AB), 181.1 (C8, CD), 187.3 (C6, AB), 190.3 (C6, CD); LRMS (ESI⁻) *m/z*: 483.1 ([M³⁵ - H]⁻ 100%), 485.1 ([M³⁷ - H]⁻ 41%); HRMS (ESI⁺) *m/z*: [M³⁵ + H]⁺ calcd. for C₂₇H₃₄N₂O₄Cl, 485.2207, found 485.2203; [M³⁷ + H]⁺ calcd. for C₂₇H₃₄N₂O₄Cl, 487.2178, found 487.2171.

(1*R,3*S**,7*aS**)-N-(Adamantan-1-yl)-1-(4-bromophenyl)-3-(*tert*-butyl)-7-hydroxy-5-oxo-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxamide 115a**



Yield (156 mg, 49%); Brown foamy solid; m.p. 107-108°C; *R_f* (50% EtOAc in Pet. Ether 40:60) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 3311 (O-H), 2909 (C-H), 2852 (C-H), 1697 (C=O), 1649 (C=O), 1626 (C=C); AB:CD=77:23; δ_H (400 MHz, CDCl₃) 1.02 (9H, s, C(CH₃)₃, CD), 1.04 (9H, s, C(CH₃)₃, AB), 1.69 (6H, br m, Adamantyl-CH₂),

2.06 (6H, br m, Adamantyl-CH₂), 2.12 (3H, br m, Adamantyl-CH), 3.83 (1H, d, *J*=8.9 Hz, H5, CD), 4.03 (1H, d, *J*=8.6 Hz, H5, AB), 4.53 (1H, d, *J*=8.7 Hz, H4, AB), 4.56 (1H, d, *J*=9.2 Hz, H4, CD), 4.95 (1H, s, H2, AB), 4.98 (1H, s, H2, CD), 7.39-7.53 (4H, m, Ar-H), 10.17 (1H, br s, NH/OH); δ_c (101 MHz, CDCl₃) 25.0 ((CH₃)₃), 29.4 (Adamantyl-C, AB), 29.5 (Adamantyl-C, CD), 36.0 (Adamantyl-C, CD), 36.2 (C(CH₃)₃), 36.2 (Adamantyl-C, AB), 41.5 (Adamantyl-C, CD), 41.7 (Adamantyl-C, AB), 53.2 (Adamantyl-C, AB), 54.6 (Adamantyl-C, CD), 69.3 (C5, AB), 72.2 (C5, CD), 78.7 (C4, CD), 79.8 (C4, AB), 94.9 (C2, AB), 95.0 (C2, CD), 96.3 (C7), 122.3 (Ar-C, CD), 122.7 (Ar-C, AB), 128.0 (Ar-C, AB), 128.1 (Ar-C, CD), 131.8 (Ar-C, CD),

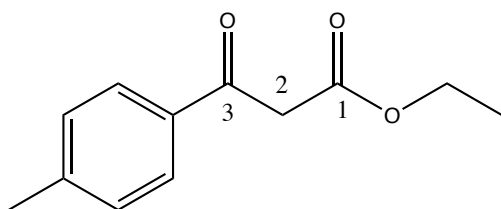
132.0 (Ar-C, AB), 135.5 (Ar-C, AB), 136.3 (Ar-C, CD), 166.3 (C9, AB), 166.9 (C9, CD), 175.1 (C8, AB), 181.1 (C8, CD), 187.3 (C6, AB), 190.3 (C6, CD); LRMS (ESI⁻) m/z : 527.0 ([M⁷⁹ - H]⁻ 96%), 529.0 ([M⁸¹ - H]⁻ 92%); HRMS (ESI⁻) m/z : [M⁷⁹ - H]⁻ calcd. for C₂₇H₃₂N₂O₄Br, 527.1551, found 527.1555; [M⁸¹ - H]⁻ C₂₇H₃₂N₂O₄Br, 529.1531, found 529.1537.

6.3: Experimental Section for Chapter 3

General procedure for the synthesis of β -oxoesters:⁶⁰

Ethyl potassium malonate (1.9 eq.) was dissolved in MeCN and cooled to 0°C in an ice/water bath. MgCl₂ (2.5 eq.) was added and the flask was put under N₂ atmosphere. Et₃N (3 eq.) was then added dropwise and the solution was left to stir at rt for 2 h, where a white slurry formed. The flask was re-cooled to 0°C and the acyl chloride (1 eq.) was added dropwise, followed by an additional amount of Et₃N (0.5 eq.) and the solution was stirred overnight at rt. MeCN was then subsequently removed *in-vacuo*. The concentrate was cooled to 0°C and added to it was toluene and 12 % HCl solution (aq.) carefully, and the mixture was left to stir at rt for 20 min. The mixture was then transferred to a separatory funnel, where the organic layer was washed with 12 % HCl solution (aq.), water and brine, dried over Na₂SO₄, filtered and the solvent was removed *in-vacuo* to obtain the desired β -oxoesters **122b-g** as a mixture of keto-enol tautomers and was used without further purification.

Ethyl 3-oxo-3-(*p*-tolyl)propanoate **122b**

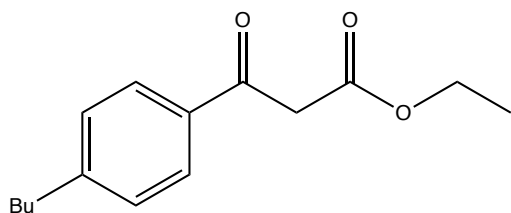


Yield (3.03 g, Quantitative); Red oil; $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1738 (C=O), 1682 (C=O); Keto:enol tautomers=5.5:1; δ_{H} (Major keto tautomer) (400 MHz, CDCl₃) 1.26 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.42 (3H, s, CH₃), 3.97 (2H, s, H₂), 4.22 (2H, q,

$J=7.2$ Hz, OCH₂CH₃), 7.28 (2H, d, $J=8.1$ Hz, Ar-H), 7.85 (2H, d, $J=8.3$ Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl₃) 14.2 (OCH₂CH₃), 21.8 (CH₃), 46.1 (C2), 61.6 (OCH₂CH₃), 128.8 (Ar-C), 129.6 (Ar-C), 133.7 (Ar-C), 144.8 (Ar-C), 167.8 (C1), 192.3 (C3); δ_{H} (Minor enol tautomer) (400 MHz, CDCl₃) 1.34 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.39 (3H, s, CH₃), 4.27 (2H, m, OCH₂CH₃), 5.64 (1H, s, H₂), 7.28-8.00 (4H, m, Ar-H), 12.59 (1H,

s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl_3) 14.4 (OCH_2CH_3), 21.9 (CH_3), 60.3 (OCH_2CH_3), 86.8 (C2), 129.3 (Ar-C), 130.3 (Ar-C), 133.7 (Ar-C), 144.6 (Ar-C), 171.5 (C=O), 173.4 (C=O); LRMS (ESI^+) m/z : 229.0 ($[\text{M} + \text{Na}]^+$ 9%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}$, 229.0835, found 229.0837.

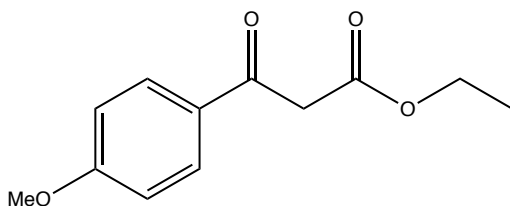
Ethyl 3-(4-butylphenyl)-3-oxopropanoate 122c



Yield (3.49 g, Quantitative); Orange/red oil that solidified on standing to a semi-solid; $\nu_{\text{max}}/\text{cm}^{-1}$ 2958 (C-H), 2932 (C-H), 2861 (C-H), 1740 (C=O), 1685 (C=O); Keto:enol tautomers=2.8:1; δ_{H} (Major keto tautomer) (400 MHz, CDCl_3) 0.94

(3H, m, CH_2CH_3), 1.26 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.36 (2H, m, CH_2CH_3), 1.62 (2H, m, CH_2CH_2), 2.67 (2H, m, CH_2CH_2), 3.97 (2H, s, H2), 4.22 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.28 (2H, d, $J=8.3$ Hz, Ar-H), 7.86 (2H, d, $J=8.3$ Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl_3) 14.0 (CH_2CH_3), 14.2 (OCH_2CH_3), 22.4 (CH_2CH_3), 33.3 (CH_2CH_2), 35.8 (CH_2CH_2), 46.1 (C2), 61.6 (OCH_2CH_3), 128.8 (Ar-C), 128.9 (Ar-C), 133.9 (Ar-C), 149.7 (Ar-C), 167.8 (C1), 192.3 (C3); δ_{H} (Minor enol tautomer) (400 MHz, CDCl_3) 0.94 (3H, m, CH_2CH_3), 1.26 (3H, m, OCH_2CH_3), 1.36 (2H, m, CH_2CH_3), 1.62 (2H, m, CH_2CH_2), 2.67 (2H, m, CH_2CH_2), 4.28 (2H, m, OCH_2CH_3), 5.64 (1H, s, H2), 7.23-8.04 (4H, m, Ar-H), 12.58 (1H, s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl_3) 14.0 (CH_2CH_3), 14.2 (OCH_2CH_3), 22.4 (CH_2CH_3), 33.4 (CH_2CH_2), 35.9 (CH_2CH_2), 60.3 (OCH_2CH_3), 86.8 (C2), 128.7 (Ar-C), 130.4 (Ar-C), 133.9 (Ar-C), 149.6 (Ar-C), 171.6 (C=O), 173.4 (C=O); LRMS (ESI^+) m/z : 271.2 ($[\text{M} + \text{Na}]^+$ 95%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Na}$, 271.1305, found 271.1304.

Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate 122d

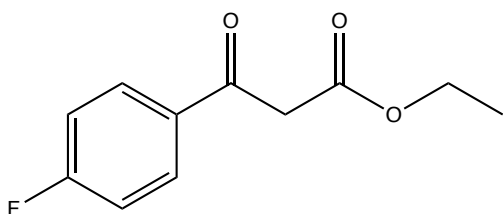


Yield (3.27 g, Quantitative); Orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2981 (C-H), 1736 (C=O), 1676 (C=O); Keto:enol tautomers=13:1; δ_{H} (Major keto tautomer) (400 MHz, CDCl_3) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.86 (3H, s, OCH_3), 3.93 (2H, s, H2), 4.19 (2H,

q, $J=7.1$ Hz, OCH_2CH_3), 6.93 (2H, d, $J=8.9$ Hz, Ar-H), 7.91 (2H, d, $J=8.9$ Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 45.9 (C2), 55.6 (OCH_3), 61.5 (OCH_2CH_3), 114.0 (Ar-C), 129.2 (Ar-C), 131.0

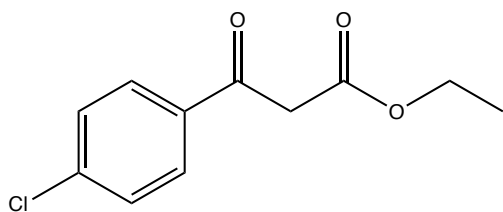
(Ar-C), 164.1 (Ar-C), 167.9 (C1), 191.1 (C3); δ_{H} (Minor enol tautomer) (400 MHz, CDCl_3) 1.31 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.86 (3H, s, OCH_3), 4.25 (2H, m, OCH_2CH_3), 5.56 (1H, s, H2), 6.93-8.05 (4H, m, Ar-H), 12.62 (1H, s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl_3) 14.4 (OCH_2CH_3), 55.6 (OCH_3), 60.3 (OCH_2CH_3), 85.8 (C2), 113.8 (Ar-C), 129.2 (Ar-C), 131.2 (Ar-C), 162.2 (Ar-C), 171.5 (C=O), 173.5 (C=O); LRMS (ESI^+) m/z : 245.0 ($[\text{M} + \text{Na}]^+$ 72%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{Na}$, 245.0784, found 245.0785.

Ethyl 3-(4-fluorophenyl)-3-oxopropanoate 122e



Yield (1.73 g, Quantitative); Orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2985 (C-H), 1736 (C=O), 1686 (C=O); Keto:enol tautomers=4.9:1; δ_{H} (Major keto tautomer) (400 MHz, CDCl_3) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.95 (2H, s, H2), 4.20 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.14 (2H, app t, $J=8.9$ Hz, Ar-H), 7.97 (2H, dd, $J=5.3$ Hz, 8.9 Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 46.1 (C2), 61.7 (OCH_2CH_3), 116.1 (d, $J=21.6$ Hz, Ar-C), 131.4 (d, $J=9.5$ Hz, Ar-C), 132.6 (d, $J=3.1$ Hz, Ar-C), 166.4 (d, $J=255.9$ Hz, Ar-C), 167.4 (C1), 191.0 (C3); δ_{F} (Major keto tautomer) (377 MHz, CDCl_3) -103.93; δ_{H} (Minor enol tautomer) (400 MHz, CDCl_3) 1.32 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.26 (2H, m, OCH_2CH_3), 5.59 (1H, s, H2), 7.06-8.10 (4H, m, Ar-H), 12.60 (1H, s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl_3) 14.4 (OCH_2CH_3), 60.5 (OCH_2CH_3), 87.3 (C2), 115.8 (d, $J=21.6$ Hz, Ar-C), 128.3 (d, $J=8.8$ Hz, Ar-C), 132.6 (Ar-C), 166.4 (Ar-C), 170.5 (C=O), 173.2 (C=O); δ_{F} (Minor enol tautomer) (377 MHz, CDCl_3) -108.52; LRMS (ESI^+) m/z : 233.0 ($[\text{M} + \text{Na}]^+$ 65%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{11}\text{H}_{11}\text{O}_3\text{FNa}$, 233.0584, found 233.0585.

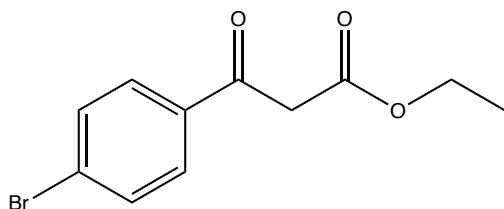
Ethyl 3-(4-chlorophenyl)-3-oxopropanoate 122f



Yield (1.78 g, Quantitative); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2983 (C-H), 1737 (C=O), 1687 (C=O); Keto:enol tautomers=3.2:1; δ_{H} (Major keto tautomer) (400 MHz, CDCl_3) 1.18 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.88 (2H, s, H2), 4.13 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.38 (2H, d, $J=8.6$ Hz, Ar-H), 7.81 (2H, d, $J=8.7$ Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl_3)

14.2 (OCH₂CH₃), 46.1 (C2), 61.7 (OCH₂CH₃), 129.2 (Ar-C), 130.1 (Ar-C), 134.5 (Ar-C), 140.4 (Ar-C), 167.3 (C1), 191.4 (C3); δ_{H} (Minor enol tautomer) (400 MHz, CDCl₃) 1.26 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.19 (2H, m, OCH₂CH₃), 5.56 (1H, s, H2), 7.31-7.81 (4H, m, Ar-H), 12.50 (1H, s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl₃) 14.4 (OCH₂CH₃), 60.6 (OCH₂CH₃), 87.8 (C2), 127.5 (Ar-C), 128.9 (Ar-C), 134.5 (Ar-C), 140.4 (Ar-C), 170.2 (C=O), 173.2 (C=O); LRMS (ESI⁺) m/z : 249.0 ([M³⁵ + Na]⁺ 82%), 251.0 ([M³⁷ + Na]⁺ 26%); HRMS (ESI⁺) m/z : [M³⁵ + Na]⁺ calcd. for C₁₁H₁₁O₃ClNa, 249.0289, found 249.0291; [M³⁷ + Na]⁺ calcd. for C₁₁H₁₁O₃ClNa, 251.0259, found 251.0261.

Ethyl 3-(4-bromophenyl)-3-oxopropanoate **122g**



Yield (2.96 g, 91%); Orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2983 (C-H), 1739 (C=O), 1687 (C=O); Keto:enol=2.7:1 tautomers; δ_{H} (Major keto tautomer) (400 MHz, CDCl₃) 1.25 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.95 (2H, s, H2), 4.20 (2H, q, $J=7.1$ Hz, OCH₂CH₃), 7.62 (2H, d, $J=8.6$ Hz, Ar-H), 7.80 (2H, d, $J=8.6$ Hz, Ar-H); δ_{C} (Major keto tautomer) (101 MHz, CDCl₃) 14.2 (OCH₂CH₃), 46.1 (C2), 61.7 (OCH₂CH₃), 129.2 (Ar-C), 130.1 (Ar-C), 132.2 (Ar-C), 134.9 (Ar-C), 167.3 (C1), 191.6 (C3); δ_{H} (Minor enol tautomer) (400 MHz, CDCl₃) 1.33 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.26 (2H, m, OCH₂CH₃), 5.63 (1H, s, H2), 7.53-7.81 (4H, m, Ar-H), 12.55 (1H, s, OH); δ_{C} (Minor enol tautomer) (101 MHz, CDCl₃) 14.4 (OCH₂CH₃), 60.6 (OCH₂CH₃), 87.9 (C2), 127.7 (Ar-C), 129.2 (Ar-C), 131.9 (Ar-C), 134.9 (Ar-C), 170.3 (C=O), 173.2 (C=O); LRMS (ESI⁺) m/z : 293.0 ([M⁷⁹ + Na]⁺ 30%), 295.0 ([M⁸¹ + Na]⁺ 27%); HRMS (ESI⁺) m/z : [M⁷⁹ + Na]⁺ calcd. for C₁₁H₁₁O₃BrNa, 292.9784, found 292.9784; [M⁸¹ + Na]⁺ calcd. for C₁₁H₁₁O₃BrNa, 294.9763, found 294.9764.

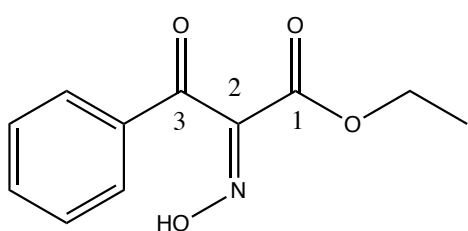
General procedure for the synthesis of oximes:⁶¹

Method A: To a stirred solution of ethyl benzoylacetate **122a** (1 eq.) dissolved in glacial acetic acid at 0 °C was added a solution of sodium nitrite (1.2-1.3 eq.) in water dropwise to ensure the temperature of the reaction medium did not rise above 10 °C. After stirring for 30 minutes at rt, the product started to precipitate out and the solution was poured into water and stirred for a further 10 mins. The product

was filtered off via vacuum filtration, washed with water and dried *in-vacuo* to give a white solid **123a** and was used without further purification.

Method B: To a stirred solution of substituted β -oxoesters **122b-g** (1 eq.) dissolved in glacial acetic acid at 0°C was added a solution of sodium nitrite (1.5 eq.) in water dropwise to ensure the temperature of the reaction medium did not rise above 10°C. The reaction was then left to stir at rt for 3 h or left to stir overnight at rt, and then glacial acetic acid was evaporated *in-vacuo*. Then added to the residue was DCM and H₂O and this mixture was left to stir for 10-20 min at rt (where a white/cream suspension might form). The layers were then separated using a separatory funnel, and the organic layer was washed successively with water, NaHCO₃ (aq.) (very cautiously) and brine, dried over Na₂SO₄, filtered, and the solvent was removed *in-vacuo* to obtain the desired oxime **123b-g** and was used without further purification.

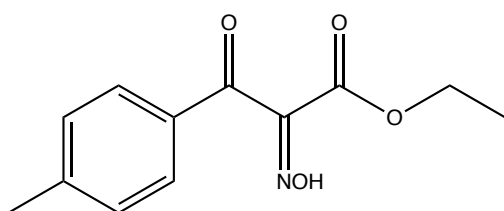
Ethyl (*E*)-2-(hydroxyimino)-3-oxo-3-phenylpropanoate **123a**



Method A: Yield (16.19 g, 71%); White solid; m.p. 144-147°C (lit.¹⁰³ 121-122°C); 21:1 mixture of *E/Z* isomers; $\nu_{\max}/\text{cm}^{-1}$ 3325 (O-H), 2987 (C-H), 1721 (C=O), 1679 (C=O), 1596 (C=N);

δ_{H} (Major *E*-isomer) (400 MHz, CDCl₃) 1.20 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 4.26 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 7.41-8.00 (5H, m, Ar-H), 10.62 (1H, br s, OH); δ_{C} (Major *E*-isomer) (101 MHz, CDCl₃) 13.9 (OCH₂CH₃), 62.8 (OCH₂CH₃), 129.2 (Ar-C), 129.3 (Ar-C), 134.3 (Ar-C), 134.9 (Ar-C), 149.6 (C2), 161.0 (C1), 190.3 (C3); LRMS (ESI⁺) *m/z*: 244.0 ([M + Na]⁺ 100%); LRMS (ESI⁻) *m/z*: 220.0 ([M - H]⁻ 98%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₁₁H₁₁NO₄Na, 244.0580, found 244.0581.

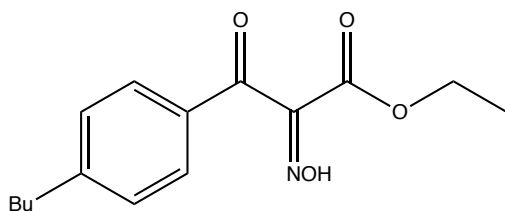
Ethyl 2-(hydroxyimino)-3-oxo-3-(*p*-tolyl)propanoate **123b**



Method B: Yield (2.47 g, 73%); Light brown solid; m.p. 133-136°C; 17:1 mixture of *E/Z* isomers; $\nu_{\max}/\text{cm}^{-1}$ 3312 (O-H), 2985 (C-H), 1721 (C=O), 1678 (C=O), 1605 (C=N); δ_{H} (Major isomer) (400 MHz, CDCl₃) 1.26 (3H, t, *J*=7.1 Hz,

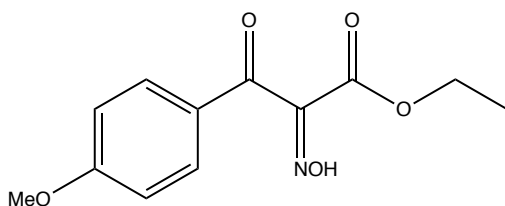
OCH₂CH₃), 2.43 (3H, s, CH₃), 4.30 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 7.31 (2H, d, *J*=8.3 Hz, Ar-H), 7.78 (2H, d, *J*=8.3 Hz, Ar-H); δ_{C} (Major isomer) (101 MHz, CDCl₃) 14.0 (OCH₂CH₃), 22.0 (CH₃), 62.7 (OCH₂CH₃), 129.5 (Ar-C), 129.9 (Ar-C), 132.0 (Ar-C), 146.2 (Ar-C), 149.8 (C2), 160.8 (C1), 189.5 (C3); LRMS (ESI⁻) *m/z*: 234.1 ([M - H]⁻ 98%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₁₂H₁₃NO₄Na, 258.0737, found 258.0738.

Ethyl 3-(4-butylphenyl)-2-(hydroxyimino)-3-oxopropanoate 123c

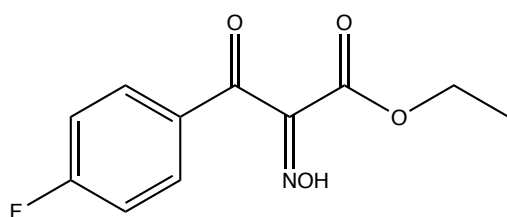


Method B: Yield (3.19 g, 83%); Thick orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3256 (O-H), 2958 (C-H), 2932 (C-H), 2861 (C-H), 1724 (C=O), 1680 (C=O), 1605 (C=N); 3.8:1 mixture of *E/Z* isomers; δ_{H} (Major isomer) (400 MHz, CDCl₃) 0.94 (3H, m, CH₂CH₃), 1.28 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.37 (2H, m, CH₂CH₃), 1.62 (2H, m, CH₂CH₂), 2.68 (2H, m, CH₂CH₂), 4.33 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 7.30 (2H, d, *J*=8.4 Hz, Ar-H), 7.79 (2H, d, *J*=8.3 Hz, Ar-H); δ_{C} (Major isomer) (101 MHz, CDCl₃) 14.0 (CH₂CH₃), 14.1 (OCH₂CH₃), 22.4 (CH₂CH₃), 33.2 (CH₂CH₂), 36.0 (CH₂CH₂), 62.7 (OCH₂CH₃), 129.2 (Ar-C), 129.5 (Ar-C), 132.1 (Ar-C), 149.4 (Ar-C), 150.9 (C2), 161.3 (C1), 189.6 (C3); LRMS (ESI⁺) *m/z*: 300.1 ([M + Na]⁺ 52%); LRMS (ESI⁻) *m/z*: 276.1 ([M - H]⁻ 96%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₁₅H₁₈NO₄, 276.1241, found 276.1240.

Ethyl 2-(hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate 123d



Method B: Yield (3.39 g, 93%); Orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3307 (O-H), 2984 (C-H), 1719 (C=O), 1668 (C=O), 1594 (C=N); 5.7:1 mixture of *E/Z* isomers; δ_{H} (Major isomer) (400 MHz, CDCl₃) 1.23 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.87 (3H, s, OCH₃), 4.28 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 6.96 (2H, d, *J*=8.9 Hz, Ar-H), 7.83 (2H, d, *J*=8.9 Hz, Ar-H), 9.99 (1H, br s, OH); δ_{C} (Major isomer) (101 MHz, CDCl₃) 14.0 (OCH₂CH₃), 55.8 (OCH₃), 62.7 (OCH₂CH₃), 114.5 (Ar-C), 127.6 (Ar-C), 131.9 (Ar-C), 150.0 (C2), 161.0 (C1), 165.0 (Ar-C), 188.4 (C3); LRMS (ESI⁺) *m/z*: 274.1 ([M + Na]⁺ 24%); LRMS (ESI⁻) *m/z*: 250.1 ([M - H]⁻ 97%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₁₂H₁₂NO₅, 250.0721, found 250.0722.

Ethyl 3-(4-fluorophenyl)-2-(hydroxyimino)-3-oxopropanoate 123e

Method B: Yield (2.72 g, 73%); Yellow solid; m.p. 144-

147°C; 3.6:1 mixture of *E/Z* isomers; $\nu_{\max}/\text{cm}^{-1}$ 3307 (O-H),

2987 (C-H), 1723 (C=O), 1678 (C=O), 1597 (C=N); δ_{H} (Major

isomer) (400 MHz, CDCl_3) 1.23 (3H, t, $J=7.1$ Hz, OCH_2CH_3),

4.29 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.18 (2H, app t, $J=8.9$ Hz, Ar-H), 7.89 (2H, dd, $J=5.3$ Hz, 8.8 Hz, Ar-H);

δ_{C} (Major isomer) (101 MHz, CDCl_3) 14.0 (OCH_2CH_3), 62.9 (OCH_2CH_3), 116.6 (d, $J=22.3$ Hz, Ar-C), 130.9 (d,

$J=2.6$ Hz, Ar-C), 132.1 (d, $J=10.0$ Hz, Ar-C), 149.5 (C2), 160.9 (C1), 166.8 (d, $J=257.6$ Hz, Ar-C), 188.6 (C3);

δ_{F} (Major isomer) (377 MHz, CDCl_3) -101.67; δ_{H} (Minor isomer) (400 MHz, CDCl_3) 1.35 (3H, t, $J=7.2$ Hz, OCH_2CH_3),

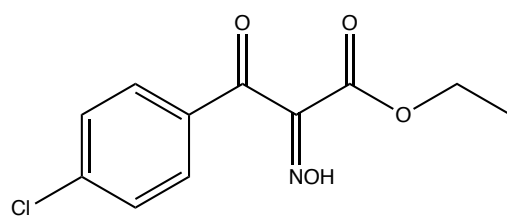
4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.09-8.08 (4H, m, Ar-H); δ_{C} (Minor isomer) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3),

62.8 (OCH_2CH_3), 115.8 (d, $J=21.7$ Hz, Ar-C), 130.9 (Ar-C), 133.4 (d, $J=9.5$ Hz, Ar-C), 149.8 (C2), 161.6 (C1),

165.5 (d, $J=256.7$ Hz, Ar-C), 185.6 (C3); δ_{F} (Minor isomer) (377 MHz, CDCl_3) -103.40; LRMS (ESI^+) m/z : 262.0

($[\text{M} + \text{Na}]^+$ 27%); LRMS (ESI^-) m/z : 238.0 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{11}\text{H}_9\text{NO}_4\text{F}$,

238.0521, found 238.0521.

Ethyl 3-(4-chlorophenyl)-2-(hydroxyimino)-3-oxopropanoate 123f

Method B: Yield (2.31 g, 78%); Off-white solid; m.p. 148-

150°C; 3:1 mixture of *E/Z* isomers; $\nu_{\max}/\text{cm}^{-1}$ 3291 (O-H),

2986 (C-H), 1725 (C=O), 1681 (C=O), 1588 (C=N); δ_{H} (Major

isomer) (400 MHz, CDCl_3) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3),

4.29 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.48 (2H, d, $J=8.6$ Hz, Ar-H), 7.80 (2H, d, $J=8.6$ Hz, Ar-H); δ_{C} (Major isomer)

(101 MHz, CDCl_3) 14.0 (OCH_2CH_3), 62.9 (OCH_2CH_3), 129.6 (Ar-C), 130.6 (Ar-C), 132.7 (Ar-C), 141.5 (Ar-

C), 149.4 (C2), 160.8 (C1), 189.0 (C3); δ_{H} (Minor isomer) (400 MHz, CDCl_3) 1.35 (3H, t, $J=7.1$ Hz, OCH_2CH_3),

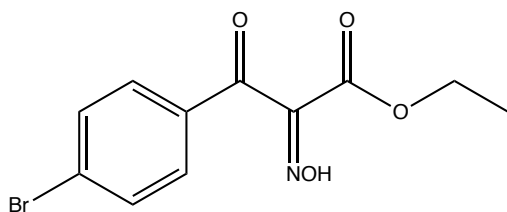
4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.42 (2H, d, $J=8.6$ Hz, Ar-H), 7.95 (2H, d, $J=8.7$ Hz, Ar-H); δ_{C} (Minor isomer)

(101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 62.8 (OCH_2CH_3), 128.9 (Ar-C), 132.0 (Ar-C), 133.6 (Ar-C), 140.6 (Ar-

C), 149.8 (C2), 161.5 (C1), 186.0 (C3); LRMS (ESI^+) m/z : 278.0 ($[\text{M}^{35} + \text{Na}]^+$ 32%), 280.0 ($[\text{M}^{37} + \text{Na}]^+$ 10%);

LRMS (ESI⁻) m/z : 254.0 ([M³⁵ – H]⁻ 98%), 255.9 ([M³⁷ – H]⁻ 31%); HRMS (ESI⁻) m/z : [M³⁵ – H]⁻ calcd. for C₁₁H₉NO₄Cl, 254.0226, found 254.0226; [M³⁷ – H]⁻ calcd. for C₁₁H₉NO₄Cl, 256.0197, found 256.0196.

Ethyl 3-(4-bromophenyl)-2-(hydroxyimino)-3-oxopropanoate **123g**

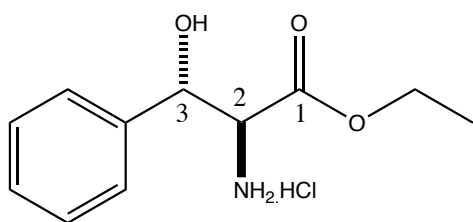


Method B: Yield (2.77 g, 86%); Off-white solid; m.p. 141-144°C; 3.5:1 mixture of *E/Z* isomers; $\nu_{\max}/\text{cm}^{-1}$ 3336 (O-H), 2986 (C-H), 1721 (C=O), 1682 (C=O), 1585 (C=N); δ_{H} (Major isomer) (400 MHz, CDCl₃) 1.24 (3H, t, J =7.1 Hz, OCH₂CH₃),

4.29 (2H, q, J =7.1 Hz, OCH₂CH₃), 7.65 (2H, d, J =8.6 Hz, Ar-H), 7.72 (2H, d, J =8.6 Hz, Ar-H), 10.12 (1H, br s, OH); δ_{C} (Major isomer) (101 MHz, CDCl₃) 14.0 (OCH₂CH₃), 62.9 (OCH₂CH₃), 130.4 (Ar-C), 130.7 (Ar-C), 132.6 (Ar-C), 133.1 (Ar-C), 149.4 (C2), 160.7 (C1), 189.2 (C3); δ_{H} (Minor isomer) (400 MHz, CDCl₃) 1.35 (3H, t, J =7.1 Hz, OCH₂CH₃), 4.40 (2H, q, J =7.2 Hz, OCH₂CH₃), 7.58 (2H, d, J =8.7 Hz, Ar-H), 7.86 (2H, d, J =8.6 Hz, Ar-H); δ_{C} (Minor isomer) (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 62.8 (OCH₂CH₃), 130.4 (Ar-C), 131.9 (Ar-C), 132.0 (Ar-C), 133.1 (Ar-C), 149.7 (C2), 161.5 (C1), 186.2 (C3); LRMS (ESI⁻) m/z : 297.9 ([M⁷⁹ – H]⁻ 92%), 299.9 ([M⁸¹ – H]⁻ 96%); HRMS (ESI⁻) m/z : [M⁷⁹ – H]⁻ calcd. for C₁₁H₉NO₄Br, 297.9720, found 297.9719; [M⁸¹ – H]⁻ calcd. for C₁₁H₉NO₄Br, 299.9699, found 299.9698.

General procedure for the synthesis of *erythro*-phenylserine:⁵⁸⁻⁵⁹

A solution of oxime **123a-g** (1 eq.) dissolved in EtOH and concentrated HCl was hydrogenated in the presence of 10% Pd-C under ambient pressure and temperature for a period of 1-3 d. The reaction mixture was then diluted with water and Pd-C was filtered off x4 under vacuum filtration. The filtrate was then separated between Et₂O and H₂O and the aqueous layer was concentrated under reduced pressure to give the desired *allo*-phenylserine as a hydrochloride salt **125a-f** and was used without further purification.

Ethyl (2*S,3*S**)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride salt 125a**

Yield (3.58 g, 75%); Off-white solid; m.p. 197-201°C (lit.⁵⁸

176°C); $\nu_{\max}/\text{cm}^{-1}$ 3311 (N-H/O-H), 3136 (N-H/O-H), 2990 (C-

H), 2868 (C-H), 1743 (C=O); δ_{H} (400 MHz, D₂O) 1.12 (3H, t,

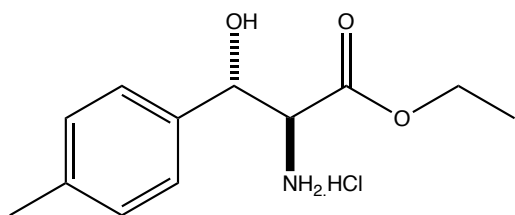
$J=7.2$ Hz, OCH₂CH₃), 4.15 (2H, dq, $J=2.2$ Hz, 7.2 Hz, OCH₂CH₃),

4.44 (1H, d, $J=4.2$ Hz, H₂), 5.36 (1H, d, $J=4.1$ Hz, H₃), 7.34-7.46 (5H, m, Ar-H); δ_{C} (101 MHz, D₂O) 13.0

(OCH₂CH₃), 58.5 (C₂), 63.5 (OCH₂CH₃), 70.9 (C₃), 125.9 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 136.9 (Ar-C),

167.4 (C₁); LRMS (ESI⁺) m/z : 210.4 ([M + H]⁺ 7%), 419.7 ([2M + H]⁺ 97%); HRMS (ESI⁺) m/z : [M + H]⁺

calcd. for C₁₁H₁₆NO₃, 210.1125, found 210.1128.

Ethyl (2*S,3*S**)-2-amino-3-hydroxy-3-(*p*-tolyl)propanoate hydrochloride salt 125b**

Yield (735 mg, 27%); Off-white solid; m.p. 171-173°C;

$\nu_{\max}/\text{cm}^{-1}$ 3307 (N-H/O-H), 3134 (N-H/O-H), 2989 (C-H),

2908 (C-H), 2863 (C-H), 1745 (C=O); δ_{H} (400 MHz, D₂O)

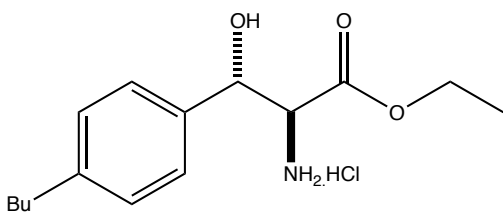
1.19 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.36 (3H, s, CH₃), 4.22

(2H, dq, $J=2.4$ Hz, 7.1 Hz, OCH₂CH₃), 4.46 (1H, d, $J=4.2$ Hz, H₂), 5.38 (1H, d, $J=4.1$ Hz, H₃), 7.29-7.34 (4H,

m, Ar-H); δ_{C} (101 MHz, D₂O) 13.0 (OCH₂CH₃), 20.2 (CH₃), 58.5 (C₂), 63.6 (OCH₂CH₃), 70.8 (C₃), 126.0 (Ar-

C), 129.4 (Ar-C), 133.9 (Ar-C), 139.4 (Ar-C), 167.5 (C₁); LRMS (ESI⁺) m/z : 246.0 ([M + Na]⁺ 15%); HRMS

(ESI⁺) m/z : [M + H]⁺ calcd. for C₁₂H₁₈NO₃, 224.1281, found 224.1282.

Ethyl (2*S,3*S**)-2-amino-3-(4-butylphenyl)-3-hydroxypropanoate hydrochloride salt 125c**

Yield (2.51 g, 72%); Brown gummy semi-solid; $\nu_{\max}/\text{cm}^{-1}$

3318 (N-H/O-H), 3135 (N-H/O-H), 2954 (C-H), 2927 (C-H),

2859 (C-H), 1747 (C=O); δ_{H} (400 MHz, MeOD) 0.92 (3H, m,

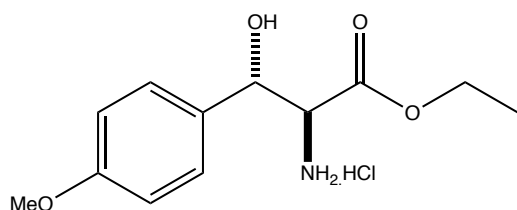
CH₂CH₃), 1.12 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.35 (2H, m,

CH₂CH₃), 1.59 (2H, m, CH₂CH₂), 2.62 (2H, m, CH₂CH₂), 4.12 (2H, q, $J=7.1$ Hz, OCH₂CH₃), 4.31 (1H, d, $J=3.7$

Hz, H₂), 5.27 (1H, d, $J=3.8$ Hz, H₃), 7.20 (2H, d, $J=7.9$ Hz, Ar-H), 7.30 (2H, d, $J=8.0$ Hz, Ar-H); δ_{C} (101 MHz,

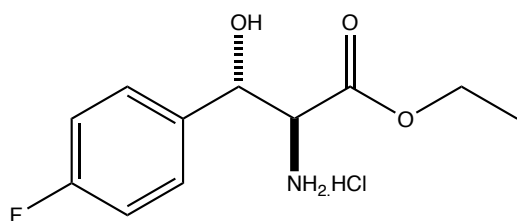
MeOD) 14.2 (CH₃CH₂), 14.2 (OCH₂CH₃), 23.2 (CH₂CH₃), 34.8 (CH₂CH₂), 36.2 (CH₂CH₂), 60.0 (C2), 63.3 (OCH₂CH₃), 72.1 (C3), 127.2 (Ar-C), 129.5 (Ar-C), 136.9 (Ar-C), 144.3 (Ar-C), 167.9 (C1); LRMS (ESI⁺) *m/z*: 266.2 ([M + H]⁺ 15%), 288.2 ([M + Na]⁺ 9%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₁₅H₂₄NO₃, 266.1751, found 266.1751.

Ethyl (2*S,3*S**)-2-amino-3-hydroxy-3-(4-methoxyphenyl)propanoate hydrochloride salt 125d**

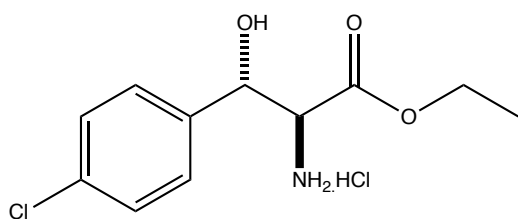


Yield (2.19 g, 67%); Off-white solid; m.p. 172-175°C (lit.⁵⁹ 167-170°C); $\nu_{\max}/\text{cm}^{-1}$ 3325 (N-H/O-H), 3134 (N-H/O-H), 2906 (C-H), 2865 (C-H), 1740 (C=O); δ_{H} (400 MHz, D₂O) 1.19 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 3.86 (3H, s, OCH₃), 4.22 (2H, dq, *J*=1.7 Hz, 7.2 Hz, OCH₂CH₃), 4.46 (1H, d, *J*=4.3 Hz, H2), 5.37 (1H, d, *J*=4.4 Hz, H3), 7.07 (2H, d, *J*=8.8 Hz, Ar-H), 7.37 (2H, d, *J*=8.6 Hz, Ar-H); δ_{C} (101 MHz, D₂O) 13.1 (OCH₂CH₃), 55.4 (OCH₃), 58.5 (C2), 63.5 (OCH₂CH₃), 70.6 (C3), 114.3 (Ar-C), 127.5 (Ar-C), 129.5 (Ar-C), 159.2 (Ar-C), 167.5 (C1); LRMS (ESI⁺) *m/z*: 240.1 ([M + H]⁺ 11%), 479.2 ([2M + H]⁺ 74%), 501.2 ([2M + Na]⁺ 37%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₁₂H₁₈NO₄, 240.1230, found 240.1232.

Ethyl (2*S,3*S**)-2-amino-3-(4-fluorophenyl)-3-hydroxypropanoate hydrochloride salt 125e**



Yield (1.00 g, 66%); Off-white solid; m.p. 155-161°C; $\nu_{\max}/\text{cm}^{-1}$ 3325 (N-H/O-H), 3138 (N-H/O-H), 2908 (C-H), 2868 (C-H), 1739 (C=O); δ_{H} (400 MHz, D₂O) 1.19 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 4.23 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 4.50 (1H, d, *J*=4.1 Hz, H2), 5.43 (1H, d, *J*=4.1 Hz, H3), 7.23 (2H, app. t, *J*=8.8 Hz, Ar-H), 7.44 (2H, dd, *J*=5.2 Hz, 8.5 Hz, Ar-H); δ_{C} (101 MHz, D₂O) 13.0 (OCH₂CH₃), 58.5 (C2), 63.6 (OCH₂CH₃), 70.4 (C3), 115.7 (d, *J*=21.9 Hz, Ar-C), 128.0 (d, *J*=8.6 Hz, Ar-C), 133.1 (d, *J*=3.0 Hz, Ar-C), 162.7 (d, *J*=244.7 Hz, Ar-C), 167.4 (C1); δ_{F} (376 MHz, D₂O) -113.80; LRMS (ESI⁺) *m/z*: 228.1 ([M + H]⁺ 49%), 250.1 ([M + Na]⁺ 20%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₁₁H₁₅NO₃F, 228.1030, found 228.1030.

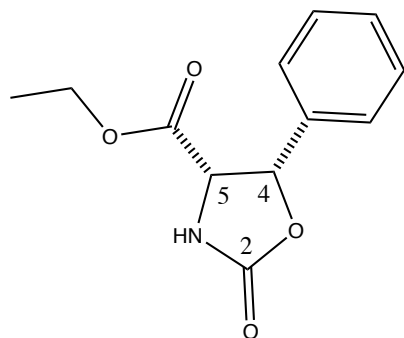
Ethyl (2S*,3S*)-2-amino-3-(4-chlorophenyl)-3-hydroxypropanoate hydrochloride salt 125f

Yield (728 mg, 45%, contaminated with an unidentified impurity); Off-white solid; m.p. 180-182°C (lit.¹⁰⁴ 168-170°C); $\nu_{\max}/\text{cm}^{-1}$ 3319 (N-H/O-H), 3140 (N-H/O-H), 2906 (C-H), 2862 (C-H), 1738 (C=O); δ_{H} (400 MHz, D₂O) 1.16

(3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.21 (2H, m, OCH₂CH₃), 4.51 (1H, d, $J=4.0$ Hz, H2), 5.42 (1H, d, $J=3.8$ Hz, H3), 7.40 (2H, d, $J=8.5$ Hz, Ar-H), 7.50 (2H, d, $J=8.6$ Hz, Ar-H); δ_{C} (101 MHz, D₂O) 13.0 (OCH₂CH₃), 58.3 (C2), 63.6 (OCH₂CH₃), 70.4 (C3), 127.5 (Ar-C), 128.8 (Ar-C), 134.0 (Ar-C), 136.0 (Ar-C), 167.3 (C1); LRMS (ESI⁺) m/z : 266.1 ([M³⁵ + Na]⁺ 4%); HRMS (ESI⁺) m/z : [M³⁵ + H]⁺ calcd. for C₁₁H₁₅NO₃Cl, 244.0735, found 244.0736; [M³⁷ + H]⁺ calcd. for C₁₁H₁₅NO₃Cl, 246.0705, found 246.0707.

General procedure for the synthesis of oxazolidinone:^{62,102}

Ethyl ester hydrochloride **125a** (1.0 eq.) was suspended in THF and triethylamine (1.2 eq.) was added and stirred at rt for 5 mins and 1,1'-carbonyldiimidazole (CDI) (1.8 eq.) was then added and the solution was stirred overnight at rt. The reaction mixture was then quenched with sat. NH₄Cl (aq.), extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in-vacuo* to furnish oxazolidinone **126**.

Ethyl (4S*,5S*)-2-oxo-5-phenyloxazolidine-4-carboxylate 126

Yield (316 mg, Quantitative); Colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 1747 (C=O); δ_{H} (400 MHz, CDCl₃) 0.79 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 3.60 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH₂CH₃), 3.76 (1H, m, OCH₂CH₃), 4.66 (1H, d, $J=9.1$ Hz, H5), 5.83 (1H, d, $J=9.1$ Hz, H4), 6.39 (1H, br s, NH), 7.29-7.42 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 60.0 (C5), 61.8 (OCH₂CH₃), 79.4 (C4), 126.5 (Ar-C), 128.5 (Ar-C), 129.4 (Ar-

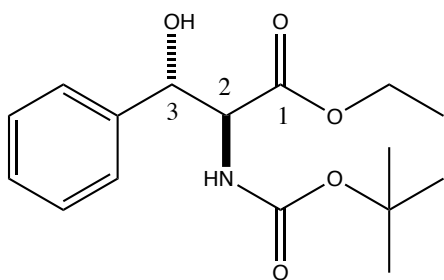
C), 134.2 (Ar-C), 159.1 (C2), 168.7 (C=O); LRMS (ESI⁺) m/z : 258.0 ([M + Na]⁺ 57%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₂H₁₃NO₄Na, 258.0737, found 258.0738.

General procedure for the synthesis of Boc-protected amino esters:⁶⁶

Method A: Amino ester **125a** (1 eq.) was suspended in DCM and cooled to 0°C. Et₃N (1.1 eq.) and Boc₂O (1.1-1.2 eq.) was added dropwise at 0°C. The reaction mixture was then heated to reflux overnight. The mixture was then left to cool to rt and then washed with sat. NH₄Cl (aq.), brine, dried over MgSO₄, filtered and the solvent was evaporated *in-vacuo*. The reaction mixture was then purified by flash column chromatography to obtain the desired product **127a**.

Method B: Boc-protected hemimalonate **173** (1 eq.), Et₃N (1 eq.) and aldehyde (oil) (4 eq.) was stirred at 50°C for 48 h under an atmosphere of N₂ (caution should be taken due to the internal build-up of CO₂). The reaction mixture was then directly purified by flash column chromatography to obtain the desired product.

Method C: Boc-protected hemimalonate **173** (1 eq.), Et₃N (1 eq.) and aldehyde (solid) (4 eq.) dissolved in THF (3 M) was stirred at 50°C for 48 h under an atmosphere of N₂ (caution should be taken due to the internal build-up of CO₂). The reaction mixture was then directly purified by flash column chromatography to obtain the desired product.

Ethyl (2S*,3S*)-2-((tert-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate 127a

Method A: Yield (1.80 g, 75%); Method B: Yield (3.39 g, 79%);

White solid; m.p. 110-115°C (lit.¹⁰⁵ 88-89°C); R_f (30% EtOAc in

Pet. Ether 40:60) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 3438 (O-H), 2980 (C-H), 1710

(C=O); δ_{H} (400 MHz, CDCl₃) 1.11 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.36

(9H, s, C(CH₃)₃), 3.98 (1H, br s, OH), 4.06 (2H, q, $J=7.2$ Hz,

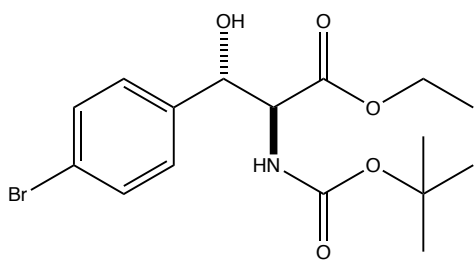
OCH₂CH₃), 4.61 (1H, br dd, $J=3.9$ Hz, 7.9 Hz, H₂), 5.12 (1H, br m, H₃), 5.25 (1H, br d, $J=7.6$ Hz, NH), 7.19-

7.26 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 28.4 ((CH₃)₃), 59.9 (C₂), 61.8 (OCH₂CH₃), 75.2

(C₃), 80.7 (C(CH₃)₃), 126.2 (Ar-C), 128.1 (Ar-C), 128.3 (Ar-C), 139.4 (Ar-C), 156.5 (C=O), 169.9 (C₁); LRMS

(ESI⁺) m/z : 332.2 ([M + Na]⁺ 95%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₆H₂₃NO₅Na, 332.1468, found

332.1468.

Ethyl (2*S,3*S**)-3-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate 127b**

Method C: Yield (1.01 g, 64%); White solid; m.p. 136-140°C

(lit.¹⁰⁵ 123-124°C); R_f (30% EtOAc in Pet. Ether 40:60) 0.48;

$\nu_{\max}/\text{cm}^{-1}$ 3426 (O-H), 2980 (C-H), 1696 (C=O); δ_H (400 MHz,

CDCl_3) 1.22 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$),

4.16 (2H, m, OCH_2CH_3), 4.65 (1H, br dd, $J=3.7$ Hz, 7.3 Hz, H2),

5.16 (1H, br d, $J=3.7$ Hz, H3), 5.30 (1H, br m, NH), 7.15 (2H, d, $J=8.1$ Hz, Ar-H), 7.45 (2H, d, $J=8.3$ Hz, Ar-

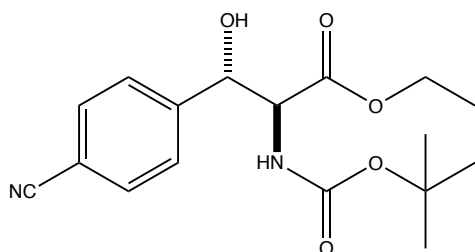
H); δ_C (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 59.9 (C2), 62.1 (OCH_2CH_3), 74.9 (C3), 81.0

($\text{C}(\text{CH}_3)_3$), 122.0 (Ar-C), 128.0 (Ar-C), 131.4 (Ar-C), 138.6 (Ar-C), 156.7 (C=O), 169.6 (C1); LRMS (ESI⁺)

m/z : 410.0 ($[\text{M}^{79} + \text{Na}]^+$ 95%), 412.0 ($[\text{M}^{81} + \text{Na}]^+$ 86%); HRMS (ESI⁺) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for

$\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 410.0574, found 410.0573; $[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 412.0554, found

412.0551.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-(4-cyanophenyl)-3-hydroxypropanoate 127c**

Method C: Yield (930 mg, 69%); Pale yellow oil that solidified

overnight to a white solid; m.p. 109-113°C; R_f (30% EtOAc in

Pet. Ether 40:60) 0.40; $\nu_{\max}/\text{cm}^{-1}$ 3432 (O-H), 2981 (C-H),

2229 ($\text{C}\equiv\text{N}$), 1696 (C=O); δ_H (400 MHz, CDCl_3) 1.20 (3H, t,

$J=7.1$ Hz, OCH_2CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.16 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.40 (1H, br s, OH), 4.67 (1H,

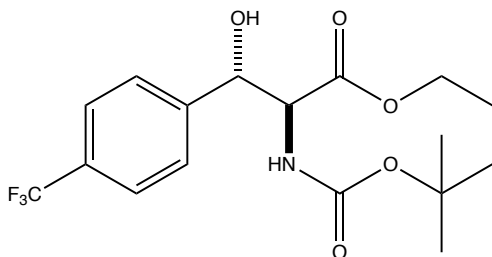
br dd, $J=3.5$ Hz, 7.0 Hz, H2), 5.25 (1H, br d, $J=3.3$ Hz, H3), 5.37 (1H, br d, $J=6.9$ Hz, NH), 7.41 (2H, d, $J=8.0$

Hz, Ar-H), 7.62 (2H, d, $J=8.3$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.3 ($(\text{CH}_3)_3$), 60.0 (C2), 62.2

(OCH_2CH_3), 74.9 (C3), 81.2 ($\text{C}(\text{CH}_3)_3$), 111.8 ($\text{C}\equiv\text{N}$), 118.8 (Ar-C), 127.1 (Ar-C), 132.1 (Ar-C), 145.1 (Ar-C),

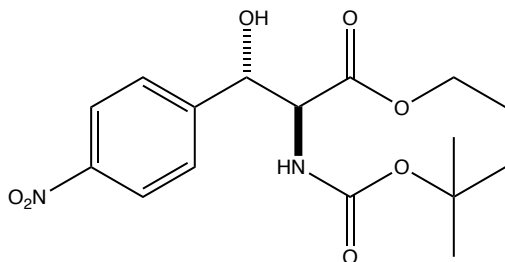
156.6 (C=O), 169.2 (C1); LRMS (ESI⁺) m/z : 357.2 ($[\text{M} + \text{Na}]^+$ 10%); HRMS (ESI⁺) m/z : $[\text{M} + \text{Na}]^+$ calcd. for

$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5\text{Na}$, 357.1421, found 357.1421.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate****127d**

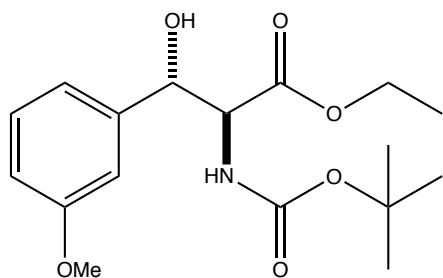
Method B: Yield (1.09 g, 62%); Pale yellow oil that solidified to a white solid overnight; m.p. 111-115°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.53; $\nu_{\max}/\text{cm}^{-1}$ 3430 (O-H), 2982 (C-H), 1692 (C=O); δ_H (400 MHz, CDCl_3) 1.18 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.15 (2H, q, $J=7.1$ Hz,

OCH_2CH_3), 4.69 (1H, br dd, $J=3.7$ Hz, 7.6 Hz, H2), 5.25 (1H, br d, $J=3.5$ Hz, H3), 5.36 (1H, br d, $J=7.2$ Hz, NH), 7.40 (2H, d, $J=8.1$ Hz, Ar-H), 7.58 (2H, d, $J=8.1$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.3 ($(\text{CH}_3)_3$), 59.9 (C2), 62.1 (OCH_2CH_3), 74.9 (C3), 81.1 ($\text{C}(\text{CH}_3)_3$), 124.2 (q, $J=272.3$ Hz, CF_3), 125.2 (q, $J=3.8$ Hz, Ar-C), 126.7 (Ar-C), 130.3 (q, $J=32.4$ Hz, Ar-C), 143.7 (Ar-C), 156.6 (C=O), 169.5 (C1); δ_F (376 MHz, CDCl_3) -62.57; LRMS (ESI^+) m/z : 400.2 ($[\text{M} + \text{Na}]^+$ 52%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{17}\text{H}_{22}\text{F}_3\text{NO}_5\text{Na}$, 400.1342, found 400.1343.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)propanoate 127e**

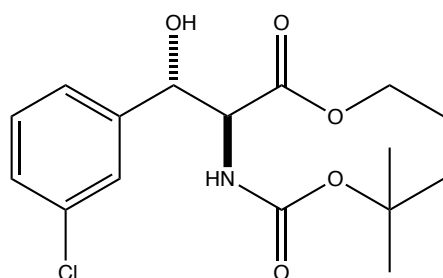
Method C: Yield (1.15 g, 73%); Pale yellow solid; m.p. 117-120°C (lit.¹⁰⁵ 108°C); R_f (30% EtOAc in Pet. Ether 40:60) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 3416 (O-H), 2981 (C-H), 1735 (C=O), 1694 (C=O), 1520 (N-O); δ_H (400 MHz, CDCl_3) 1.21 (3H, t, $J=6.9$ Hz, OCH_2CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.18 (2H, q, $J=7.1$ Hz,

OCH_2CH_3), 4.69 (1H, br dd, $J=3.5$ Hz, 7.0 Hz, H2), 5.31 (1H, br d, $J=3.3$ Hz, H3), 5.39 (1H, br d, $J=6.8$ Hz, NH), 7.47 (2H, d, $J=8.4$ Hz, Ar-H), 8.18 (2H, d, $J=8.8$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 28.3 ($(\text{CH}_3)_3$), 60.0 (C2), 62.3 (OCH_2CH_3), 74.9 (C3), 81.3 ($\text{C}(\text{CH}_3)_3$), 123.5 (Ar-C), 127.2 (Ar-C), 147.1 (Ar-C), 147.7 (Ar-C), 156.7 (C=O), 169.1 (C1); LRMS (ESI^+) m/z : 377.0 ($[\text{M} + \text{Na}]^+$ 9%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_7\text{Na}$, 377.1319, found 377.1318.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(3-methoxyphenyl)propanoate 127f**

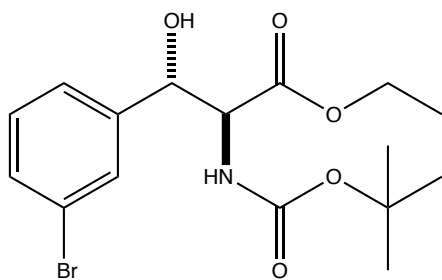
Method B: Yield (995 mg, 69%); White solid; m.p. 108-110°C; R_f (50% EtOAc in Pet. Ether 40:60) 0.70; $\nu_{\max}/\text{cm}^{-1}$ 3435 (O-H), 2979 (C-H), 1701 (C=O); δ_H (400 MHz, CDCl_3) 1.22 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.80 (3H, s, OCH_3), 4.02 (1H, br s, OH), 4.17 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.69 (1H, br dd, $J=3.8$

Hz, 7.9 Hz, H2), 5.19 (1H, br m, H3), 5.31 (1H, br d, $J=7.5$ Hz, NH), 6.81-6.85 (3H, m, Ar-H), 7.22-7.28 (1H, m, Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 55.3 (OCH_3), 59.9 (C2), 61.9 (OCH_2CH_3), 75.1 (C3), 80.8 ($\text{C}(\text{CH}_3)_3$), 111.8 (Ar-C), 113.7 (Ar-C), 118.5 (Ar-C), 129.4 (Ar-C), 141.1 (Ar-C), 156.6 (C=O), 159.8 (Ar-C), 169.9 (C1); LRMS (ESI^+) m/z : 362.2 ($[\text{M} + \text{Na}]^+$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_6\text{Na}$, 362.1574, found 362.1573.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-3-hydroxypropanoate 127g**

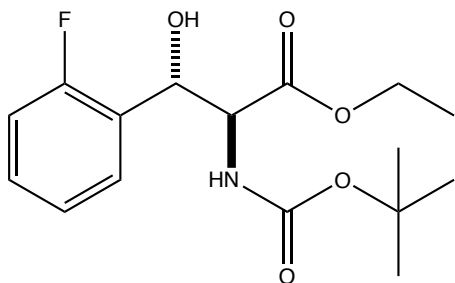
Method B: Yield (1.07 g, 72%); Pale yellow oil that solidified to a white solid overnight; m.p. 56-60°C; R_f (40% EtOAc in Pet. Ether 40:60) 0.75; $\nu_{\max}/\text{cm}^{-1}$ 3427 (O-H), 2980 (C-H), 1694 (C=O); δ_H (400 MHz, CDCl_3) 1.22 (3H, t, $J=7.0$ Hz, OCH_2CH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.17 (2H, dq, $J=1.8$ Hz, 7.4 Hz, OCH_2CH_3), 4.66

(1H, br dd, $J=3.6$ Hz, 7.4 Hz, H2), 5.19 (1H, br d, $J=3.6$ Hz, H3), 5.37 (1H, br d, $J=7.2$ Hz, NH), 7.15 (1H, m, Ar-H), 7.25-7.27 (2H, m, Ar-H), 7.30 (1H, m, Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 60.0 (C2), 62.1 (OCH_2CH_3), 74.9 (C3), 81.1 ($\text{C}(\text{CH}_3)_3$), 124.4 (Ar-C), 126.6 (Ar-C), 128.2 (Ar-C), 129.6 (Ar-C), 134.4 (Ar-C), 141.7 (Ar-C), 156.7 (C=O), 169.5 (C1); LRMS (ESI^+) m/z : 366.0 ($[\text{M}^{35} + \text{Na}]^+$ 96%), 368.0 ($[\text{M}^{37} + \text{Na}]^+$ 39%); HRMS (ESI^+) m/z : $[\text{M}^{35} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{ClNa}$, 366.1079, found 366.1079; $[\text{M}^{37} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{ClNa}$, 368.1050, found 368.1050.

Ethyl (2S*,3S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-bromophenyl)-3-hydroxypropanoate 127h

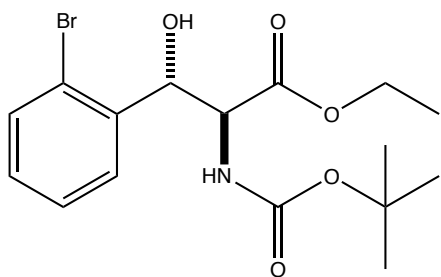
Method B: Yield (1.15 g, 70%); Colourless oil that solidified to a white solid overnight; m.p. 83-87°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 3424 (O-H), 2979 (C-H), 1692 (C=O); δ_H (400 MHz, CDCl_3) 1.21 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.15 (2H, m, OCH_2CH_3), 4.64 (1H, br dd, $J=3.6$ Hz, 7.4

Hz, H2), 5.17 (1H, br d, $J=3.6$ Hz, H3), 5.37 (1H, br d, $J=7.2$ Hz, NH), 7.18-7.19 (2H, m, Ar-H), 7.39-7.41 (1H, m, Ar-H), 7.44 (1H, m, Ar-H); δ_C (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 60.0 (C2), 62.1 (OCH_2CH_3), 74.8 (C3), 81.0 ($\text{C}(\text{CH}_3)_3$), 122.5 (Ar-C), 124.8 (Ar-C), 129.5 (Ar-C), 129.9 (Ar-C), 131.1 (Ar-C), 141.9 (Ar-C), 156.6 (C=O), 169.5 (C1); LRMS (ESI^+) m/z : 410.0 ($[\text{M}^{79} + \text{Na}]^+$ 96%), 412.0 ($[\text{M}^{81} + \text{Na}]^+$ 89%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 410.0574, found 410.0573; $[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 412.0554, found 412.0551.

Ethyl (2S*,3S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-fluorophenyl)-3-hydroxypropanoate 127i

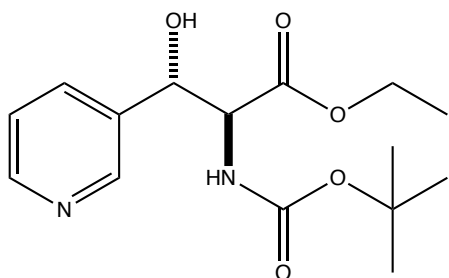
Method B: Yield (933 mg, 68%); Colourless oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 3430 (O-H), 2980 (C-H), 1716 (C=O), 1696 (C=O); δ_H (400 MHz, CDCl_3) 1.21 (3H, t, $J=7.0$ Hz, OCH_2CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.15 (2H, m, OCH_2CH_3), 4.72 (1H, br m, H2), 5.38 (1H, br m, NH), 5.47 (1H, br m, H3),

7.00 (1H, m, Ar-H), 7.15 (1H, dt, $J=1.2$ Hz, 7.6 Hz, Ar-H), 7.27 (1H, m, Ar-H), 7.44 (1H, dt, $J=1.8$ Hz, 7.6 Hz, Ar-H); δ_C (101 MHz, CDCl_3) 14.0 (OCH_2CH_3), 28.3 ($(\text{CH}_3)_3$), 59.3 (C2), 62.1 (OCH_2CH_3), 70.2 (C3), 80.8 ($\text{C}(\text{CH}_3)_3$), 115.1 (d, $J=22.0$ Hz, Ar-C), 124.2 (d, $J=3.5$ Hz, Ar-C), 126.7 (d, $J=13.6$ Hz, Ar-C), 128.3 (Ar-C), 129.6 (d, $J=8.3$ Hz, Ar-C), 156.7 (C=O), 159.7 (d, $J=245.0$ Hz, Ar-C), 169.8 (C1); δ_F (376 MHz, CDCl_3) -117.84; LRMS (ESI^+) m/z : 350.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{FNa}$, 350.1374, found 350.1375.

Ethyl (2*S,3*S**)-3-(2-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate 127j**

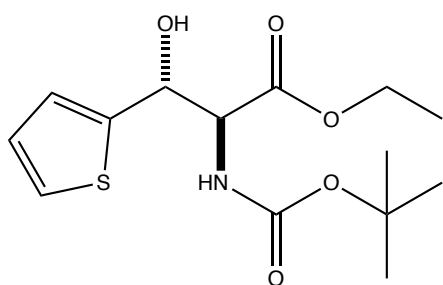
Method B: Yield (1.43 g, 88%); Colourless oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.33; $\nu_{\max}/\text{cm}^{-1}$ 3428 (O-H), 2979 (C-H), 1717 (C=O), 1695 (C=O); δ_{H} (400 MHz, CDCl_3) 1.09 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.78 (1H, br s, OH), 3.97-4.30 (2H, m, OCH_2CH_3), 4.73 (1H, br m, H2), 5.31-5.48 (2H, br m, NH,

H3), 7.15 (1H, dt, $J=1.8$ Hz, 7.7 Hz, Ar-H), 7.32 (1H, dt, $J=1.3$ Hz, 7.6 Hz, Ar-H), 7.49 (1H, dd, $J=1.7$ Hz, 7.8 Hz, Ar-H), 7.52 (1H, dd, $J=1.3$ Hz, 8.0 Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.9 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 58.1 (C2), 61.7 (OCH_2CH_3), 73.9 (C3), 80.6 ($\text{C}(\text{CH}_3)_3$), 122.4 (Ar-C), 127.5 (Ar-C), 128.5 (Ar-C), 129.6 (Ar-C), 132.8 (Ar-C), 138.9 (Ar-C), 155.7 (C=O), 170.4 (C1); LRMS (ESI^+) m/z : 410.0 ($[\text{M}^{79} + \text{Na}]^+$ 97%), 412.0 ($[\text{M}^{81} + \text{Na}]^+$ 95%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 410.0574, found 410.0575; $[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{BrNa}$, 412.0554, found 412.0554.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(pyridin-3-yl)propanoate 127k**

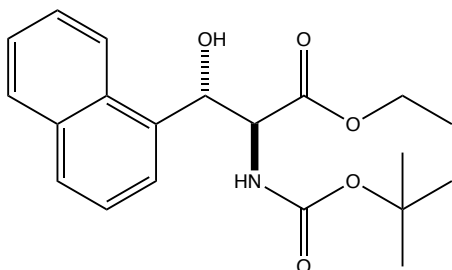
Method B: Yield (2.09 g, 79%); Colourless oil; R_f (100% EtOAc) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 3348 (O-H), 2980 (C-H), 1738 (C=O), 1709 (C=O); δ_{H} (400 MHz, CDCl_3) 1.20 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.16 (2H, m, OCH_2CH_3), 4.68 (1H, br dd, $J=3.9$ Hz, 7.4 Hz, H2), 4.95 (1H, br s, OH), 5.22 (1H, br d, $J=3.8$

Hz, H3), 5.47 (1H, br d, $J=7.4$ Hz, NH), 7.27 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 8.48 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 28.3 ($(\text{CH}_3)_3$), 59.9 (C2), 62.1 (OCH_2CH_3), 73.4 (C3), 81.0 ($\text{C}(\text{CH}_3)_3$), 123.3 (Ar-C), 134.4 (Ar-C), 135.5 (Ar-C), 148.0 (Ar-C), 149.1 (Ar-C), 156.5 (C=O), 169.5 (C1); LRMS (ESI^+) m/z : 311.2 ($[\text{M} + \text{H}]^+$ 36%), 333.2 ($[\text{M} + \text{Na}]^+$ 8%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_5$, 311.1601, found 311.1600.

Ethyl (2*S,3*R**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(thiophen-2-yl)propanoate 127l**

Method B: Yield (651 mg, 51%); White solid; m.p. 79-83°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.23; $\nu_{\max}/\text{cm}^{-1}$ 3430 (O-H), 2979 (C-H), 1702 (C=O); δ_H (400 MHz, CDCl_3) 1.25 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.46 (1H, br d, $J=5.9$ Hz, OH), 4.75 (1H, br m, H2),

5.39 (1H, br m, NH), 5.48 (1H, br m, H3), 6.88 (1H, m, Ar-H), 6.96 (1H, dd, $J=3.5$ Hz, 5.1 Hz, Ar-H), 7.25 (1H, dd, $J=1.2$ Hz, 5.1 Hz, Ar-H); δ_C (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 59.8 (C2), 62.2 (OCH_2CH_3), 72.2 (C3), 81.1 ($\text{C}(\text{CH}_3)_3$), 124.4 (Ar-C), 125.3 (Ar-C), 126.8 (Ar-C), 143.0 (Ar-C), 157.0 (C=O), 169.3 (C1); LRMS (ESI^+) m/z : 338.2 ($[\text{M} + \text{Na}]^+$ 98%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_5\text{SNa}$, 338.1033, found 338.1035.

Ethyl (2*S,3*S**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(naphthalen-1-yl)propanoate 127m**

Method B: Yield (261 mg, 15%); Yellow oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.18; $\nu_{\max}/\text{cm}^{-1}$ 3433 (O-H), 2979 (C-H), 1696 (C=O); Presence of rotamers; δ_H (400 MHz, CDCl_3) 0.95/1.27 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.27/1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.94/4.27 (2H, m, OCH_2CH_3), 4.69 (1H, dd, $J=2.6$ Hz, 9.2 Hz,

H2)/4.81 (1H, br dd, $J=3.9$ Hz, 7.6 Hz, H2), 5.42 (1H, br d, $J=9.1$ Hz, NH)/5.54 (1H, br d, $J=7.8$ Hz, NH), 5.90 (1H, br s, H3)/6.03 (1H, br d, $J=3.3$ Hz, H3), 7.44-8.17 (7H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.8/14.3 (OCH_2CH_3), 28.3/28.4 ($(\text{CH}_3)_3$), 58.6/58.9 (C2), 61.5/61.9 (OCH_2CH_3), 70.8/71.7 (C3), 80.0/80.5 ($\text{C}(\text{CH}_3)_3$), 122.3-135.6 (Ar-C), 155.8 (C=O), 170.2/171.3 (C1); LRMS (ESI^+) m/z : 382.2 ($[\text{M} + \text{Na}]^+$ 95%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_5\text{Na}$, 382.1625, found 382.1624.

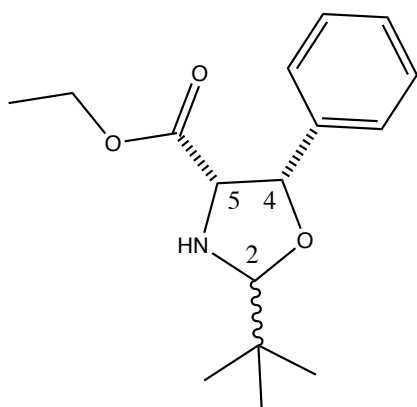
General procedure for the synthesis of oxazolidines:³⁴⁻³⁵

Method A: Amino ester **125a-f** (1.0 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2 eq.) and trimethylacetaldehyde (1.1 eq.) was added. The reaction mixture was

heated overnight to more than 100°C with continuous removal of water using a Dean-Stark apparatus. The white/brown precipitate was then filtered and washed with Et₂O. The combined filtrates were concentrated under reduced pressure to furnish a diastereomeric mixture of oxazolidines **128a-f** and was used without further purification.

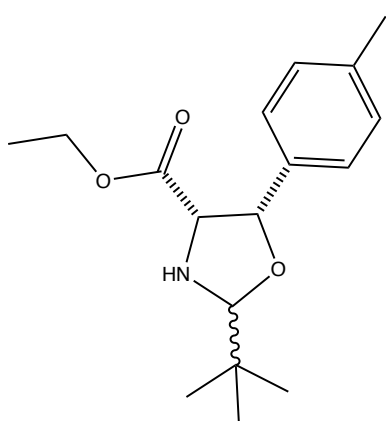
Method B: Amino ester **171a-k** (1.0 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2 eq.) and trimethylacetaldehyde (1.1 eq.) was added. The reaction mixture was heated overnight to more than 100°C with continuous removal of water using a Dean-Stark apparatus. The reaction mixture was then washed with brine, and the organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to furnish a diastereomeric mixture of oxazolidines **128g-p** and was used without further purification.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-phenyloxazolidine-4-carboxylate **128a****

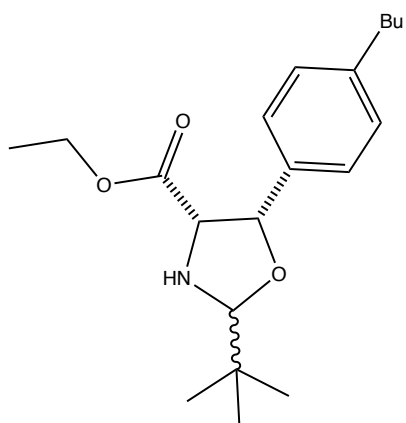


Method A: Yield (1.62 g, 81%); Method B: Yield (1.36 g, 57%); Pale yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2958 (C-H), 2872 (C-H), 1734 (C=O); 5.6:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.70 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.08 (9H, s, C(CH₃)₃), 2.72 (1H, br s, NH), 3.35 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 3.62 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH₂CH₃), 4.09 (1H, d, $J=8.9$ Hz, H5), 4.15 (1H, s, H2), 4.98 (1H, d, $J=9.0$ Hz, H4), 7.11-

7.29 (5H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 61.2 (OCH₂CH₃), 65.7 (C5), 80.5 (C4), 99.0 (C2), 127.1 (Ar-C), 128.1 (Ar-C), 128.2 (Ar-C), 138.3 (Ar-C), 170.9 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.83 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 0.91 (9H, s, C(CH₃)₃), 2.72 (1H, br s, NH), 3.53 (1H, m, OCH₂CH₃), 3.73 (1H, m, OCH₂CH₃), 4.22 (1H, d, $J=7.4$ Hz, H5), 4.94 (1H, s, H2), 5.23 (1H, d, $J=7.3$ Hz, H4), 7.11-7.29 (5H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 25.2 ((CH₃)₃), 36.5 (C(CH₃)₃), 61.0 (OCH₂CH₃), 65.6 (C5), 81.3 (C4), 101.5 (C2), 126.3-139.2 (Ar-C), 170.3 (C=O); LRMS (ESI⁺) m/z : 278.2 ([M + H]⁺ 77%), 300.2 ([M + Na]⁺ 76%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₆H₂₄NO₃, 278.1751, found 278.1749.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(*p*-tolyl)oxazolidine-4-carboxylate 128b**

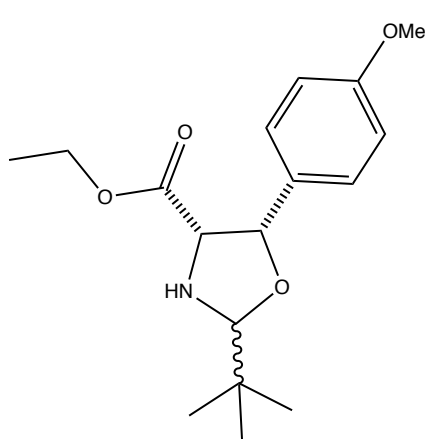
Method A: Yield (766 mg, 97%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3306 (N-H), 2958 (C-H), 2871 (C-H), 1735 (C=O); 3.7:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.78 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.29 (3H, s, CH_3), 3.47 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.70 (1H, m, OCH_2CH_3), 4.13 (1H, d, $J=9.0$ Hz, H5), 4.20 (1H, s, H2), 5.02 (1H, d, $J=9.0$ Hz, H4), 7.08 (2H, m, Ar-H), 7.14 (2H, d, $J=8.2$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 21.2 (CH_3), 25.7 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.2 (OCH_2CH_3), 65.6 (C5), 80.5 (C4), 98.9 (C2), 127.0 (Ar-C), 128.7 (Ar-C), 135.3 (Ar-C), 137.9 (Ar-C), 171.0 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.93 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.29 (3H, s, CH_3), 3.65 (1H, m, OCH_2CH_3), 3.82 (1H, m, OCH_2CH_3), 4.26 (1H, d, $J=7.3$ Hz, H5), 4.99 (1H, s, H2), 5.26 (1H, d, $J=7.3$ Hz, H4), 7.08 (2H, m, Ar-H), 7.14 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 21.2 (CH_3), 25.2 ($(\text{CH}_3)_3$), 36.5 ($\text{C}(\text{CH}_3)_3$), 61.0 (OCH_2CH_3), 65.6 (C5), 81.2 (C4), 101.4 (C2), 126.2 (Ar-C), 128.8 (Ar-C), 136.2 (Ar-C), 137.6 (Ar-C), 170.4 (C=O); LRMS (ESI^+) m/z : 292.2 ($[\text{M} + \text{H}]^+$ 20%), 314.2 ($[\text{M} + \text{Na}]^+$ 20%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_3$, 292.1907, found 292.1906.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(4-butylphenyl)oxazolidine-4-carboxylate 128c**

Method A: Yield (2.51 g, 90%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2957 (C-H), 2931 (C-H), 2871 (C-H), 1735 (C=O); 5.3:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.75 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 0.90 (3H, m, CH_3CH_2), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (2H, m, CH_2CH_3), 1.56 (2H, m, CH_2CH_2), 2.56 (2H, t, $J=7.6$ Hz, CH_2CH_2), 3.07 (1H, br s, NH), 3.43 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.69 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.17 (1H, d, $J=9.0$ Hz, H5), 4.21 (1H, s, H2), 5.04 (1H, d, $J=9.0$ Hz, H4), 7.09 (2H, d, $J=8.1$ Hz, Ar-H), 7.17 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.0 (CH_3CH_2), 22.3 (CH_2CH_3),

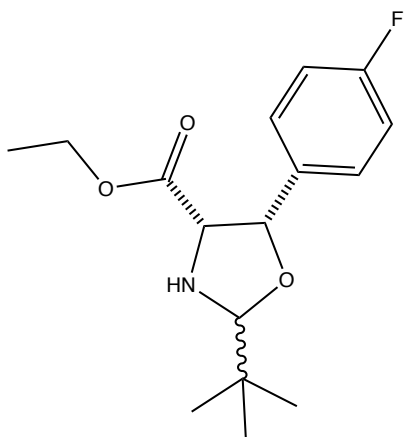
25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 33.8 (CH₂CH₂), 35.4 (CH₂CH₂), 61.2 (OCH₂CH₃), 65.4 (C5), 80.6 (C4), 98.7 (C2), 127.0 (Ar-C), 128.1 (Ar-C), 135.4 (Ar-C), 143.0 (Ar-C), 171.0 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.90 (6H, m, CH₃CH₂, OCH₂CH₃), 0.97 (9H, s, C(CH₃)₃), 1.31 (2H, m, CH₂CH₃), 1.56 (2H, m, CH₂CH₂), 2.56 (2H, m, CH₂CH₂), 3.07 (1H, br s, NH), 3.69 (1H, m, OCH₂CH₃), 3.79 (1H, m, OCH₂CH₃), 4.27 (1H, d, $J=7.4$ Hz, H5), 4.99 (1H, s, H2), 5.26 (1H, d, $J=7.4$ Hz, H4), 7.09 (2H, m, Ar-H), 7.17 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.0 (CH₃CH₂), 22.4 (CH₂CH₃), 25.1 ((CH₃)₃), 33.5 (CH₂CH₂), 35.8 (CH₂CH₂), 36.5 (C(CH₃)₃), 60.9 (OCH₂CH₃), 65.6 (C5), 81.3 (C4), 101.3 (C2), 126.2 (Ar-C), 128.2 (Ar-C), 136.4 (Ar-C), 142.7 (Ar-C), 170.4 (C=O); LRMS (ESI⁺) m/z : 356.2 ([M + Na]⁺ 9%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₀H₃₂NO₃, 334.2377, found 334.2376.

Ethyl (4S*,5S*)-2-(tert-butyl)-5-(4-methoxyphenyl)oxazolidine-4-carboxylate 128d

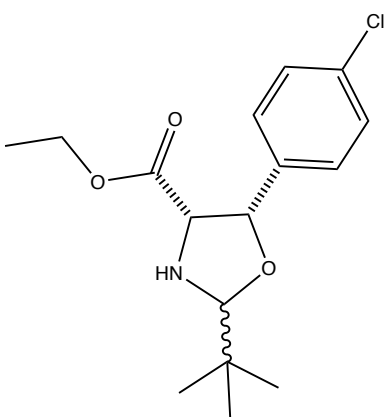


Method A: Yield (2.22 g, 97%); Orange oil; ν_{max} /cm⁻¹ 3306 (N-H), 2958 (C-H), 2907 (C-H), 2872 (C-H), 1734 (C=O); 3.9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.82 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.14 (9H, s, C(CH₃)₃), 3.50 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 3.72 (1H, m, OCH₂CH₃), 3.77 (3H, s, OCH₃), 4.13 (1H, d, $J=9.0$ Hz, H5), 4.19 (1H, s, H2), 5.02 (1H, d, $J=8.9$ Hz, H4), 6.82 (2H, d, $J=8.8$ Hz, Ar-H), 7.19 (2H, d,

$J=8.7$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.3 (C(CH₃)₃), 55.4 (OCH₃), 61.1 (OCH₂CH₃), 65.6 (C5), 80.1 (C4), 98.8 (C2), 113.5 (Ar-C), 128.2 (Ar-C), 130.5 (Ar-C), 159.6 (Ar-C), 171.0 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.95 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 0.98 (9H, s, C(CH₃)₃), 3.50 (1H, m, OCH₂CH₃), 3.72 (1H, m, OCH₂CH₃), 3.77 (3H, s, OCH₃), 4.25 (1H, d, $J=7.3$ Hz, H5), 4.99 (1H, s, H2), 5.26 (1H, d, $J=7.3$ Hz, H4), 6.82 (2H, m, Ar-H), 7.13 (2H, d, $J=8.6$ Hz, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.9 (OCH₂CH₃), 25.1 ((CH₃)₃), 36.5 (C(CH₃)₃), 55.3 (OCH₃), 61.0 (OCH₂CH₃), 65.6 (C5), 81.0 (C4), 101.3 (C2), 113.5 (Ar-C), 127.5 (Ar-C), 131.3 (Ar-C), 159.4 (Ar-C), 170.4 (C=O); LRMS (ESI⁺) m/z : 330.2 ([M + Na]⁺ 35%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₇H₂₆NO₄, 308.1856, found 308.1855.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(4-fluorophenyl)oxazolidine-4-carboxylate 128e**

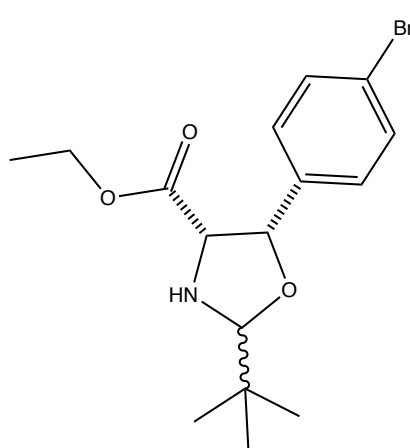
Method A: Yield (993 mg, 89%); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2979 (C-H), 2908 (C-H), 2874 (C-H), 1735 (C=O); 4.8:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.76 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.81 (1H, br s, NH), 3.43 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 3.68 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 4.07 (1H, d, $J=9.0$ Hz, H5), 4.13 (1H, s, H2), 4.97 (1H, d, $J=9.0$ Hz, H4), 6.91 (2H, app t, $J=8.6$ Hz, Ar-H), 7.18 (2H, dd, $J=5.5$ Hz, 8.7 Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.3 (OCH_2CH_3), 65.6 (C5), 79.8 (C4), 99.1 (C2), 115.0 (d, $J=21.5$ Hz, Ar-C), 128.7 (d, $J=8.2$ Hz, Ar-C), 134.2 (d, $J=3.1$ Hz, Ar-C), 162.7 (d, $J=246.2$ Hz, Ar-C), 170.8 (C=O); δ_{F} (Major diastereomer) (376 MHz, CDCl_3) -114.17; δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.87 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.81 (1H, br s, NH), 3.58 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 3.76 (1H, m, OCH_2CH_3), 4.21 (1H, d, $J=7.4$ Hz, H5), 4.92 (1H, s, H2), 5.20 (1H, d, $J=7.3$ Hz, H4), 6.91 (2H, m, Ar-H), 7.18 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.9 (OCH_2CH_3), 25.1 ($(\text{CH}_3)_3$), 36.5 ($\text{C}(\text{CH}_3)_3$), 61.1 (OCH_2CH_3), 65.6 (C5), 80.7 (C4), 101.5 (C2), 115.1 (d, $J=21.5$ Hz, Ar-C), 128.0 (d, $J=8.1$ Hz, Ar-C), 135.1 (d, $J=3.1$ Hz, Ar-C), 162.6 (d, $J=246.4$, Ar-C), 170.3 (C=O); δ_{F} (Minor diastereomer) (376 MHz, CDCl_3) -114.54; LRMS (ESI^+) m/z : 296.2 ($[\text{M} + \text{H}]^+$ 24%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{F}$, 296.1657, found 296.1656.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(4-chlorophenyl)oxazolidine-4-carboxylate 128f**

Method A: Yield (1.58 g, 85%); Orange oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3306 (N-H), 2960 (C-H), 2907 (C-H), 2872 (C-H), 1735 (C=O); 5.6:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.84 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.51 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.76 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.16 (1H, d, $J=9.1$ Hz, H5), 4.21 (1H, s, H2), 5.03 (1H, d, $J=9.1$ Hz, H4), 7.22 (2H, m, Ar-H), 7.27 (2H, m, Ar-H); δ_{C} (Major diastereomer)

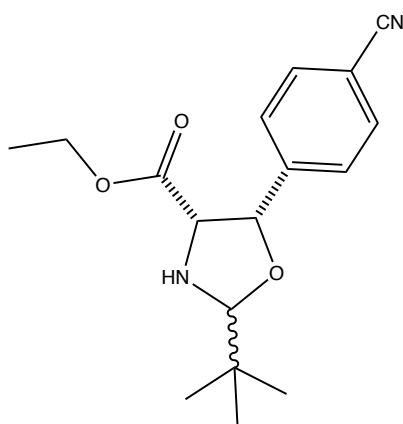
(101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 61.4 (OCH₂CH₃), 65.6 (C5), 79.8 (C4), 99.2 (C2), 128.2 (Ar-C), 128.4 (Ar-C), 134.0 (Ar-C), 137.0 (Ar-C), 170.7 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.95 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 0.98 (9H, s, C(CH₃)₃), 3.43 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 3.68 (1H, m, OCH₂CH₃), 4.29 (1H, d, $J=7.4$ Hz, H5), 4.99 (1H, s, H2), 5.26 (1H, d, $J=7.3$ Hz, H4), 7.22 (2H, m, Ar-H), 7.27 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.9 (OCH₂CH₃), 25.1 ((CH₃)₃), 36.5 (C(CH₃)₃), 61.2 (OCH₂CH₃), 65.6 (C5), 80.7 (C4), 101.6 (C2), 127.7 (Ar-C), 128.1 (Ar-C), 133.8 (Ar-C), 137.8 (Ar-C), 170.2 (C=O); LRMS (ESI⁺) m/z : 312.2 ([M³⁵ + H]⁺ 34%); HRMS (ESI⁺) m/z : [M³⁵ + H]⁺ calcd. for C₁₆H₂₃NO₃Cl, 312.1361, found 312.1361; [M³⁷ + H]⁺ calcd. for C₁₆H₂₃NO₃Cl, 314.1332, found 314.1333.

Ethyl (4*S,5*S**)-5-(4-bromophenyl)-2-(*tert*-butyl)oxazolidine-4-carboxylate 128g**

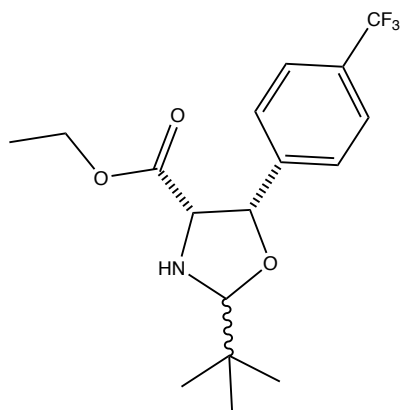


Method B: Yield (735 mg, 82%); Pale yellow oil; ν_{max} /cm⁻¹ 3309 (N-H), 2959 (C-H), 2907 (C-H), 2872 (C-H), 1736 (C=O); 5.7:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.84 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.13 (9H, s, C(CH₃)₃), 2.80 (1H, br s, NH), 3.51 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.75 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH₂CH₃), 4.15 (1H, d, $J=9.0$ Hz, H5), 4.20 (1H, s, H2), 5.00 (1H, d, $J=9.0$ Hz, H4), 7.15 (2H, d, $J=8.3$ Hz, Ar-H),

7.41 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 61.4 (OCH₂CH₃), 65.6 (C5), 79.9 (C4), 99.2 (C2), 122.1 (Ar-C), 128.8 (Ar-C), 131.2 (Ar-C), 137.5 (Ar-C), 170.7 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.95 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 0.97 (9H, s, C(CH₃)₃), 2.80 (1H, br s, NH), 3.66 (1H, m, OCH₂CH₃), 3.84 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 4.28 (1H, d, $J=7.3$ Hz, H5), 4.98 (1H, s, H2), 5.24 (1H, d, $J=7.4$ Hz, H4), 7.09 (2H, d, $J=8.2$ Hz, Ar-H), 7.41 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.9 (OCH₂CH₃), 25.1 ((CH₃)₃), 36.5 (C(CH₃)₃), 61.2 (OCH₂CH₃), 65.6 (C5), 80.7 (C4), 101.6 (C2), 121.9 (Ar-C), 128.1 (Ar-C), 131.3 (Ar-C), 138.4 (Ar-C), 170.2 (C=O); LRMS (ESI⁺) m/z : 356.0 ([M⁷⁹ + H]⁺ 46%), 358.0 ([M⁸¹ + H]⁺ 42%), 378.2 ([M⁷⁹ + Na]⁺ 27%), 380.2 ([M⁸¹ + Na]⁺ 25%); HRMS (ESI⁺) m/z : [M⁷⁹ + H]⁺ calcd. for C₁₆H₂₃NO₃Br, 356.0856, found 356.0854; [M⁸¹ + H]⁺ calcd. for C₁₆H₂₃NO₃Br, 358.0835, found 358.0833.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(4-cyanophenyl)oxazolidine-4-carboxylate 128h**

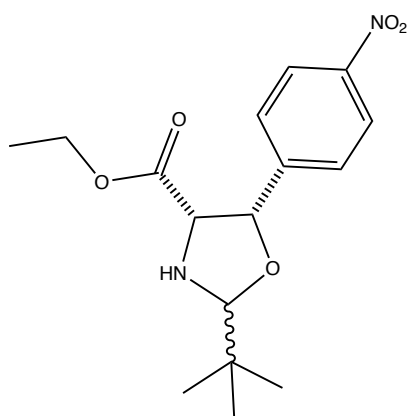
Method B: Yield (638 mg, 74%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3308 (N-H), 2961 (C-H), 2907 (C-H), 2873 (C-H), 2229 (C $\equiv$ N), 1734 (C=O); 4.6:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.82 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.13 (9H, s, C(CH₃)₃), 3.46 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.74 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 4.21 (1H, d, $J=9.1$ Hz, H5), 4.23 (1H, s, H2), 5.07 (1H, d, $J=9.0$ Hz, H4), 7.40 (2H, d, $J=8.3$ Hz, Ar-H), 7.58 (2H, d, $J=8.4$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 61.5 (OCH₂CH₃), 65.6 (C5), 79.7 (C4), 99.6 (C2), 112.0 (C $\equiv$ N), 118.7 (Ar-C), 127.8 (Ar-C), 131.9 (Ar-C), 143.9 (Ar-C), 170.3 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.92 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 0.98 (9H, s, C(CH₃)₃), 3.62 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.82 (1H, m, OCH₂CH₃), 4.34 (1H, d, $J=7.4$ Hz, H5), 5.01 (1H, s, H2), 5.29 (1H, d, $J=7.4$ Hz, H4), 7.35 (2H, d, $J=8.2$ Hz, Ar-H), 7.64 (2H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.9 (OCH₂CH₃), 25.1 ((CH₃)₃), 36.3 (C(CH₃)₃), 61.2 (OCH₂CH₃), 65.6 (C5), 80.6 (C4), 101.9 (C2), 111.8 (C $\equiv$ N), 118.7 (Ar-C), 127.2 (Ar-C), 132.0 (Ar-C), 144.8 (Ar-C), 169.9 (C=O); LRMS (ESI⁺) m/z : 303.2 ([M + H]⁺ 95%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₇H₂₃N₂O₃ 303.1703, found 303.1703.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(4-(trifluoromethyl)phenyl)oxazolidine-4-carboxylate 128i**

Method B: Yield (770 mg, 85%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3309 (N-H), 2961 (C-H), 2909 (C-H), 2874 (C-H), 1736 (C=O); 5.3:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.76 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.15 (9H, s, C(CH₃)₃), 3.46 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.70 (1H, m, OCH₂CH₃), 4.20 (1H, d, $J=9.0$ Hz, H5), 4.23 (1H, s, H2), 5.10 (1H, d, $J=9.0$ Hz, H4), 7.40 (2H, d, $J=8.5$ Hz, Ar-H), 7.56 (2H, d, $J=8.2$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 25.7 ((CH₃)₃), 33.4 (C(CH₃)₃), 61.4 (OCH₂CH₃), 65.6 (C5), 79.9

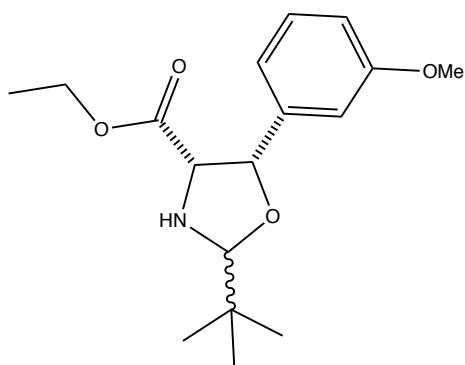
(C4), 99.4 (C2), 125.0 (q, $J=3.7$ Hz, Ar-C), 127.5 (Ar-C), 130.5 (q, $J=32.4$ Hz, Ar-C), 142.5 (Ar-C), 170.6 (C=O); δ_F (Major diastereomer) (376 MHz, $CDCl_3$) -62.70; δ_H (Minor diastereomer) (400 MHz, $CDCl_3$) 0.87 (3H, m, OCH_2CH_3), 0.99 (9H, s, $C(CH_3)_3$), 3.61 (1H, m, OCH_2CH_3), 3.79 (1H, m, OCH_2CH_3), 4.33 (1H, d, $J=7.3$ Hz, H5), 5.02 (1H, s, H2), 5.32 (1H, d, $J=7.4$ Hz, H4), 7.35 (2H, m, Ar-H), 7.47 (2H, m, Ar-H); δ_C (Minor diastereomer) (101 MHz, $CDCl_3$) 13.7 (OCH_2CH_3), 25.1 ($(CH_3)_3$), 36.4 ($C(CH_3)_3$), 61.2 (OCH_2CH_3), 65.7 (C5), 80.7 (C4), 101.8 (C2), 126.4 (Ar-C), 126.8 (Ar-C), 130.5 (Ar-C), 143.4 (Ar-C), 170.1 (C=O); δ_F (Minor diastereomer) (376 MHz, $CDCl_3$) -62.61; LRMS (ESI⁺) m/z : 346.2 ($[M + H]^+$ 82%), 368.2 ($[M + Na]^+$ 24%); HRMS (ESI⁺) m/z : $[M + H]^+$ calcd. for $C_{17}H_{23}NO_3F_3$, 346.1625, found 346.1623.

Ethyl (4S*,5S*)-2-(tert-butyl)-5-(4-nitrophenyl)oxazolidine-4-carboxylate 128j



Method B: Yield (602 mg, 61%); Orange oil; ν_{max}/cm^{-1} 3305 (N-H), 2961 (C-H), 2908 (C-H), 2873 (C-H), 1736 (C=O), 1523 (N-O); 4.6:1 mixture of diastereomers at the C2-position; δ_H (Major diastereomer) (400 MHz, $CDCl_3$) 0.83 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.15 (9H, s, $C(CH_3)_3$), 3.47 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.75 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.24 (1H, d, $J=9.1$ Hz, H5), 4.25 (1H, s, H2), 5.13 (1H, d, $J=9.1$ Hz, H4), 7.46 (2H, d, $J=8.6$ Hz, Ar-H), 8.16 (2H, d, $J=8.8$

Hz, Ar-H); δ_C (Major diastereomer) (101 MHz, $CDCl_3$) 13.7 (OCH_2CH_3), 25.7 ($(CH_3)_3$), 33.4 ($C(CH_3)_3$), 61.5 (OCH_2CH_3), 65.7 (C5), 79.5 (C4), 99.7 (C2), 123.3 (Ar-C), 127.9 (Ar-C), 145.9 (Ar-C), 147.8 (Ar-C), 170.3 (C=O); δ_H (Minor diastereomer) (400 MHz, $CDCl_3$) 0.94 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.99 (9H, s, $C(CH_3)_3$), 3.64 (1H, dq, $J=7.2$ Hz, 10.9 Hz, OCH_2CH_3), 3.84 (1H, m, OCH_2CH_3), 4.37 (1H, d, $J=7.4$ Hz, H5), 5.03 (1H, s, H2), 5.35 (1H, d, $J=7.4$ Hz, H4), 7.41 (2H, d, $J=8.4$ Hz, Ar-H), 8.16 (2H, m, Ar-H); δ_C (Minor diastereomer) (101 MHz, $CDCl_3$) 13.9 (OCH_2CH_3), 25.1 ($(CH_3)_3$), 36.4 ($C(CH_3)_3$), 61.3 (OCH_2CH_3), 65.7 (C5), 80.4 (C4), 102.0 (C2), 123.4 (Ar-C), 127.3 (Ar-C), 146.8 (Ar-C), 147.7 (Ar-C), 169.9 (C=O); LRMS (ESI⁺) m/z : 323.2 ($[M + H]^+$ 100%); HRMS (ESI⁺) m/z : $[M + H]^+$ calcd. for $C_{16}H_{23}N_2O_5$, 323.1601, found 323.1600.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(3-methoxyphenyl)oxazolidine-4-carboxylate 128k**

Method B: Yield (568 mg, 60%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3307 (N-H), 2958 (C-H), 2907 (C-H), 2872 (C-H), 1735 (C=O); 5.7:1

mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer)

(400 MHz, CDCl_3) 0.81 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.14 (9H, s,

$\text{C}(\text{CH}_3)_3$), 2.76 (1H, br s, NH), 3.50 (1H, dq, $J=7.1$ Hz, 10.8 Hz,

OCH_2CH_3), 3.72 (1H, m, OCH_2CH_3), 3.77 (3H, s, OCH_3), 4.15

(1H, d, $J=9.0$ Hz, H5), 4.20 (1H, s, H2), 5.02 (1H, d, $J=9.0$ Hz, H4), 6.78 (1H, m, Ar-H), 6.84 (2H, m, Ar-H),

7.18 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.8 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 55.3

(OCH_3), 61.2 (OCH_2CH_3), 65.7 (C5), 80.4 (C4), 99.1 (C2), 112.4 (Ar-C), 114.0 (Ar-C), 119.5 (Ar-C), 129.1

(Ar-C), 140.0 (Ar-C), 159.5 (Ar-C), 170.8 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.94 (3H, t, $J=7.1$ Hz,

OCH_2CH_3), 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.76 (1H, br s, NH), 3.72 (1H, m, OCH_2CH_3), 3.77 (3H, s, OCH_3), 3.80 (1H,

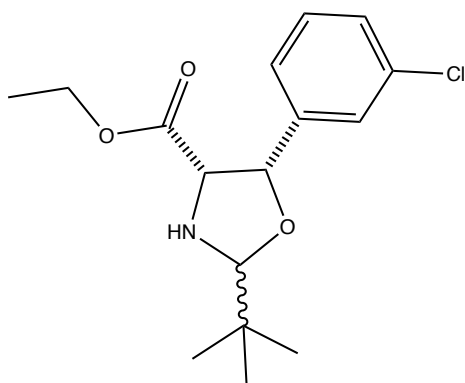
m, OCH_2CH_3), 4.27 (1H, d, $J=7.3$ Hz, H5), 4.99 (1H, s, H2), 5.26 (1H, d, $J=7.3$ Hz, H4), 6.78 (1H, m, Ar-H),

6.84 (2H, m, Ar-H), 7.18 (1H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 25.2 ($(\text{CH}_3)_3$),

36.5 ($\text{C}(\text{CH}_3)_3$), 55.3 (OCH_3), 61.0 (OCH_2CH_3), 65.6 (C5), 81.2 (C4), 101.5 (C2), 112.1 (Ar-C), 113.3 (Ar-C),

118.7 (Ar-C), 129.2 (Ar-C), 140.9 (Ar-C), 159.6 (Ar-C), 170.3 (C=O); LRMS (ESI⁺) m/z : 308.2 ($[\text{M} + \text{H}]^+$

57%), 330.2 ($[\text{M} + \text{Na}]^+$ 75%); HRMS (ESI⁺) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_4$, 308.1856, found 308.1856.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(3-chlorophenyl)oxazolidine-4-carboxylate 128l**

Method B: Yield (689 mg, 78%); Pale yellow oil; $\nu_{\max}/\text{cm}^{-1}$

3308 (N-H), 2960 (C-H), 2907 (C-H), 2873 (C-H), 1736 (C=O);

4.6:1 mixture of diastereomers at the C2-position; δ_{H} (Major

diastereomer) (400 MHz, CDCl_3) 0.79 (3H, t, $J=7.1$ Hz, OCH_2CH_3),

1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.71 (1H, br s, NH), 3.46 (1H, dq, $J=7.2$

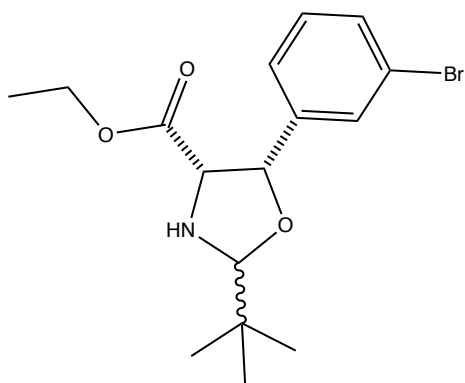
Hz, 10.7 Hz, OCH_2CH_3), 3.69 (1H, dq, $J=7.1$ Hz, 10.8 Hz,

OCH_2CH_3), 4.09 (1H, d, $J=9.1$ Hz, H5), 4.13 (1H, s, H2), 4.94 (1H, d, $J=9.1$ Hz, H4), 7.08-7.24 (4H, m, Ar-

H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.8 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.4 (OCH_2CH_3),

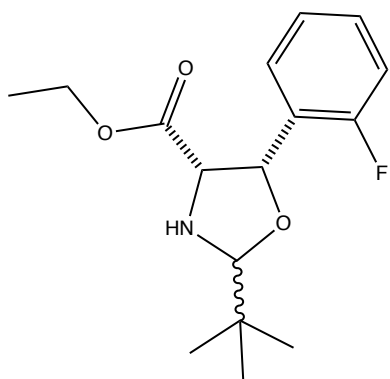
65.7 (C5), 79.7 (C4), 99.4 (C2), 125.1 (Ar-C), 127.3 (Ar-C), 128.3 (Ar-C), 129.4 (Ar-C), 134.0 (Ar-C), 140.6 (Ar-C), 170.6 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.90 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.71 (1H, br s, NH), 3.63 (1H, m, OCH_2CH_3), 3.78 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.22 (1H, d, $J=7.4$ Hz, H5), 4.94 (1H, s, H2), 5.18 (1H, d, $J=7.3$ Hz, H4), 7.08-7.24 (4H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 25.2 ($(\text{CH}_3)_3$), 36.5 ($\text{C}(\text{CH}_3)_3$), 61.2 (OCH_2CH_3), 65.6 (C5), 80.6 (C4), 101.7 (C2), 124.5 (Ar-C), 126.5 (Ar-C), 128.1 (Ar-C), 129.5 (Ar-C), 134.2 (Ar-C), 141.4 (Ar-C), 170.1 (C=O); LRMS (ESI^+) m/z : 312.0 ($[\text{M}^{35} + \text{H}]^+$ 97%), 314.2 ($[\text{M}^{37} + \text{H}]^+$ 28%); HRMS (ESI^+) m/z : $[\text{M}^{35} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Cl}$, 312.1361, found 312.1362; $[\text{M}^{37} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Cl}$, 314.1332, found 314.1334.

Ethyl (4S*,5S*)-5-(3-bromophenyl)-2-(tert-butyl)oxazolidine-4-carboxylate 128m

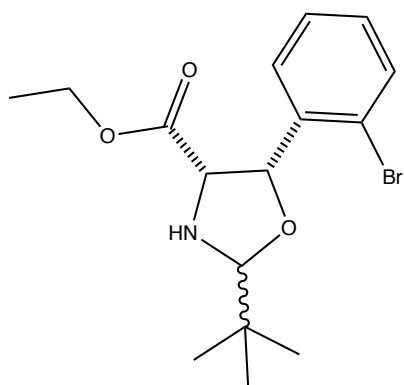


Method B: Yield (797 mg, 80%); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3307 (N-H), 2959 (C-H), 2906 (C-H), 2872 (C-H), 1734 (C=O); 3.8:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.81 (1H, br s, NH), 3.47 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.69 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.08

(1H, d, $J=8.9$ Hz, H5), 4.13 (1H, s, H2), 4.93 (1H, d, $J=8.9$ Hz, H4), 7.07-7.43 (4H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.8 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.4 (OCH_2CH_3), 65.7 (C5), 79.7 (C4), 99.4 (C2), 122.1 (Ar-C), 125.6 (Ar-C), 129.7 (Ar-C), 130.2 (Ar-C), 131.2 (Ar-C), 140.9 (Ar-C), 170.5 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.90 (3H, m, OCH_2CH_3), 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.81 (1H, br s, NH), 3.58 (1H, m, OCH_2CH_3), 3.78 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.22 (1H, d, $J=7.4$ Hz, H5), 4.92 (1H, s, H2), 5.17 (1H, d, $J=7.3$ Hz, H4), 7.07-7.43 (4H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.9 (OCH_2CH_3), 25.2 ($(\text{CH}_3)_3$), 36.5 ($\text{C}(\text{CH}_3)_3$), 61.3 (OCH_2CH_3), 65.7 (C5), 80.5 (C4), 101.7 (C2), 122.1-141.7 (Ar-C), 170.1 (C=O); LRMS (ESI^+) m/z : 356.0 ($[\text{M}^{79} + \text{H}]^+$ 83%), 358.0 ($[\text{M}^{81} + \text{H}]^+$ 77%), 378.0 ($[\text{M}^{79} + \text{Na}]^+$ 69%), 380.0 ($[\text{M}^{81} + \text{Na}]^+$ 69%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Br}$, 356.0856, found 356.0860; $[\text{M}^{81} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Br}$, 358.0836, found 358.0839.

Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(2-fluorophenyl)oxazolidine-4-carboxylate 128n**

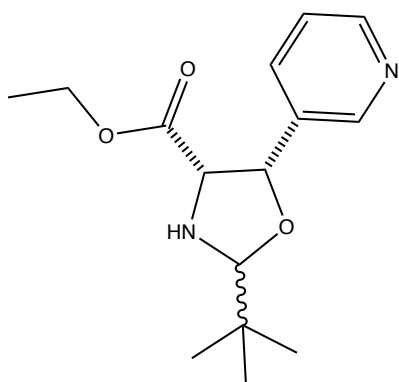
Method B: Yield (648 mg, 78%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3307 (N-H), 2960 (C-H), 2907 (C-H), 2873 (C-H), 1735 (C=O); 4.9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.82 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.47 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 3.74 (1H, m, OCH_2CH_3), 4.22 (1H, d, $J=8.9$ Hz, H5), 4.22 (1H, s, H2), 5.39 (1H, d, $J=8.9$ Hz, H4), 6.99 (1H, m, Ar-H), 7.08 (1H, m, Ar-H), 7.22 (1H, m, Ar-H), 7.36 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.3 (OCH_2CH_3), 64.5 (C5), 73.8 (d, $J=4.5$ Hz, C4), 99.0 (C2), 114.8 (d, $J=21.3$ Hz, Ar-C), 124.1 (d, $J=3.4$ Hz, Ar-C), 125.7 (d, $J=12.6$ Hz, Ar-C), 127.8 (d, $J=3.7$ Hz, Ar-C), 129.4 (d, $J=8.2$ Hz, Ar-C), 160.4 (d, $J=247.4$ Hz, Ar-C), 171.1 (C=O); δ_{F} (Major diastereomer) (376 MHz, CDCl_3) -118.03; δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.87 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.62 (1H, m, OCH_2CH_3), 3.78 (1H, m, OCH_2CH_3), 4.39 (1H, d, $J=7.2$ Hz, H5), 4.99 (1H, s, H2), 5.51 (1H, d, $J=7.2$ Hz, H4), 6.99 (1H, m, Ar-H), 7.08 (1H, m, Ar-H), 7.22 (1H, m, Ar-H), 7.36 (1H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.1 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 61.0 (OCH_2CH_3), 64.8 (C5), 75.4 (d, $J=4.1$ Hz, C4), 101.1 (C2), 114.8 (d, $J=21.5$ Hz, Ar-C), 124.1 (Ar-C), 125.7 (Ar-C), 127.8 (Ar-C), 129.4 (Ar-C), 160.1 (d, $J=246.2$ Hz, Ar-C), 170.7 (C=O); δ_{F} (Minor diastereomer) (376 MHz, CDCl_3) -117.59; LRMS (ESI^+) m/z : 296.1 ($[\text{M} + \text{H}]^+$ 98%), 318.1 ($[\text{M} + \text{Na}]^+$ 33%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{F}$, 296.1656, found 296.1655.

Ethyl (4*S,5*S**)-5-(2-bromophenyl)-2-(*tert*-butyl)oxazolidine-4-carboxylate 128o**

Method B: Yield (993 mg, 77%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3305 (N-H), 2959 (C-H), 2906 (C-H), 2872 (C-H), 1733 (C=O); 5.7:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.15 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.24 (1H, br s, NH), 3.43 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.71 (1H, dq, $J=7.2$ Hz, 10.6 Hz, OCH_2CH_3), 4.22 (1H, s, H2), 4.28 (1H, d, $J=8.7$

Hz, H5), 5.43 (1H, d, $J=8.6$ Hz, H4), 7.11 (1H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.39 (1H, m, Ar-H), 7.49 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 25.8 ($(\text{CH}_3)_3$), 33.5 ($\text{C}(\text{CH}_3)_3$), 61.4 (OCH_2CH_3), 63.7 (C5), 79.5 (C4), 99.0 (C2), 123.3 (Ar-C), 127.4 (Ar-C), 128.0 (Ar-C), 129.3 (Ar-C), 132.2 (Ar-C), 137.6 (Ar-C), 171.3 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 1.02 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.06 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.24 (1H, br s, NH), 3.54 (1H, m, OCH_2CH_3), 3.71 (1H, m, OCH_2CH_3), 4.56 (1H, d, $J=7.0$ Hz, H5), 5.04 (1H, s, H2), 5.46 (1H, d, $J=7.1$ Hz, H4), 7.11 (1H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.39 (1H, m, Ar-H), 7.49 (1H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.1 ($(\text{CH}_3)_3$), 35.4 ($\text{C}(\text{CH}_3)_3$), 60.8 (OCH_2CH_3), 64.1 (C5), 80.6 (C4), 101.0 (C2), 122.7 (Ar-C), 127.5 (Ar-C), 128.2 (Ar-C), 129.2 (Ar-C), 132.2 (Ar-C), 138.1 (Ar-C), 170.8 (C=O); LRMS (ESI^+) m/z : 356.0 ($[\text{M}^{79} + \text{H}]^+$ 7%), 358.0 ($[\text{M}^{81} + \text{H}]^+$ 7%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Br}$, 356.0856, found 356.0858; $[\text{M}^{81} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Br}$, 358.0835, found 358.0838.

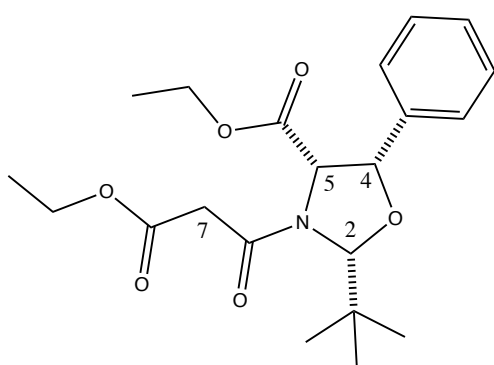
Ethyl (4*S,5*S**)-2-(*tert*-butyl)-5-(pyridin-3-yl)oxazolidine-4-carboxylate 128p**



Method B: Yield (1.11 g, 57%); Yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3306 (N-H), 2959 (C-H), 2907 (C-H), 2873 (C-H), 1734 (C=O); 4.9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.05 (1H, br s, NH), 3.50 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.73 (1H, dq, $J=7.0$ Hz, 10.7 Hz, OCH_2CH_3), 4.19 (1H, d, $J=9.0$ Hz, H5), 4.22 (1H, s, H2), 5.07 (1H, d, $J=9.0$ Hz, H4), 7.22 (1H, m, Ar-H), 7.30 (1H, m, Ar-H), 7.60 (1H, m, Ar-H), 8.52 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 33.4 ($\text{C}(\text{CH}_3)_3$), 61.4 (OCH_2CH_3), 65.7 (C5), 78.1 (C4), 99.5 (C2), 123.2 (Ar-C), 134.3 (Ar-C), 134.5 (Ar-C), 148.8 (Ar-C), 149.5 (Ar-C), 170.5 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.91 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.05 (1H, br s, NH), 3.65 (1H, m, OCH_2CH_3), 3.81 (1H, m, OCH_2CH_3), 4.33 (1H, d, $J=7.4$ Hz, H5), 4.99 (1H, s, H2), 5.30 (1H, d, $J=7.6$ Hz, H4), 7.10-8.52 (4H, m, Ar-H); LRMS (ESI^+) m/z : 279.2 ($[\text{M} + \text{H}]^+$ 96%), 301.2 ($[\text{M} + \text{Na}]^+$ 78%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_3$, 279.1703, found 279.1704.

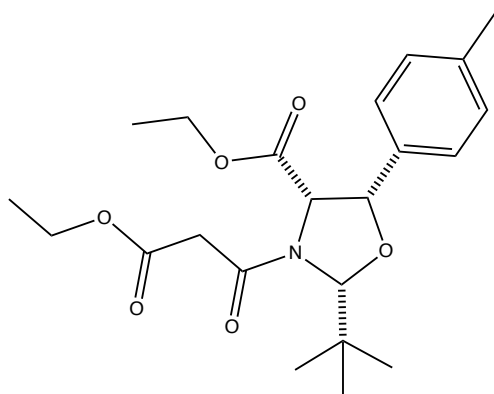
General procedure for the synthesis of malonamides:³⁴

To a stirring solution of oxazolidine **128a-p** (1.0 eq.) in anhydrous DCM at 0°C was added ethyl malonyl chloride (1.1 eq.) and pyridine (1.2 eq.) dropwise. The mixture was stirred at 0°C for 10-20 min and then refluxed overnight. The mixture was then left to cool to rt, washed with sat. NH₄Cl (aq.), sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated oxazolidines **129a-p**.

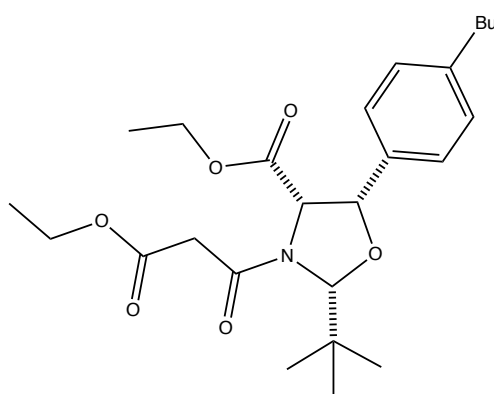
Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-phenyloxazolidine-4-carboxylate****129a**

Yield (2.95 g, 80%); Yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.58; $\nu_{\text{max}}/\text{cm}^{-1}$ 2981 (C-H), 1739 (C=O), 1679 (C=O); 11.5:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.79 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.14 (9H, s, C(CH₃)₃), 1.31 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 3.41 (1H, d, $J=15.3$ Hz, H7), 3.48 (1H, d, $J=15.4$ Hz, H7), 3.66 (1H,

dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.80 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH₂CH₃), 4.21 (2H, m, OCH₂CH₃), 4.80 (1H, br d, $J=6.9$ Hz, H5), 5.21 (1H, d, $J=6.9$ Hz, H4), 5.37 (1H, s, H2), 7.31-7.39 (5H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.9 ((CH₃)₃), 37.5 (C(CH₃)₃), 44.0 (C7), 61.3 (OCH₂CH₃), 61.9 (OCH₂CH₃), 64.6 (C5), 80.5 (C4), 97.1 (C2), 126.5 (Ar-C), 128.4 (Ar-C), 128.6 (Ar-C), 135.1 (Ar-C), 167.4 (C=O), 168.1 (C=O), 168.1 (C=O); LRMS (ESI⁺) m/z : 414.2 ([M + Na]⁺ 93%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₁H₂₉NO₆Na, 414.1887, found 414.1884.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(*p*-tolyl)oxazolidine-4-carboxylate****129b**

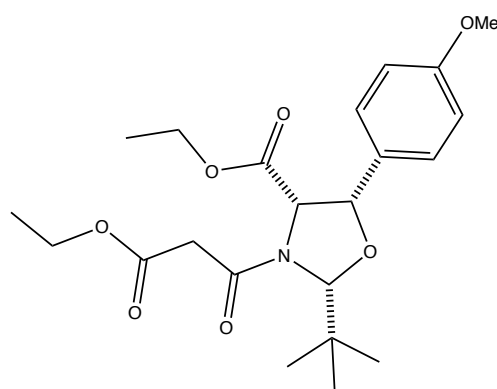
Yield (1.02 g, Quantitative); Red oil; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1741 (C=O), 1680 (C=O); 9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.82 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.15 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 2.35 (3H, s, CH_3), 3.42 (1H, d, $J=15.4$ Hz, H7), 3.47 (1H, d, $J=15.4$ Hz, H7), 3.71 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.82 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.22 (2H, m, OCH_2CH_3), 4.77 (1H, br d, $J=6.9$ Hz, H5), 5.18 (1H, d, $J=6.9$ Hz, H4), 5.36 (1H, s, H2), 7.15 (2H, d, $J=7.9$ Hz, Ar-H), 7.26 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.2 (OCH_2CH_3), 21.3 (CH_3), 27.0 ($(\text{CH}_3)_3$), 37.5 ($\text{C}(\text{CH}_3)_3$), 44.0 (C7), 61.2 (OCH_2CH_3), 61.9 (OCH_2CH_3), 64.6 (C5), 80.5 (C4), 97.1 (C2), 126.5 (Ar-C), 129.0 (Ar-C), 132.0 (Ar-C), 138.4 (Ar-C), 167.4 (C=O), 168.1 (C=O), 168.1 (C=O); LRMS (ESI^+) m/z : 428.2 ($[\text{M} + \text{Na}]^+$ 64%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_6\text{Na}$, 428.2044, found 428.2043.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-5-(4-butylphenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129c**

Yield (1.94 g, 60%); Yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.60; $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2932 (C-H), 2872 (C-H), 1743 (C=O), 1681 (C=O); 9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.79 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.92 (3H, t, $J=7.3$ Hz, CH_3CH_2), 1.15 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.32 (5H, m, CH_2CH_3 , OCH_2CH_3), 1.57 (2H, m, CH_2CH_2), 2.60 (2H, m, CH_2CH_2), 3.42 (1H, d, $J=15.4$ Hz, H7), 3.46 (1H, d, $J=15.3$ Hz, H7), 3.67 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 3.81 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.23 (2H, m, OCH_2CH_3), 4.77 (1H, br d, $J=7.0$ Hz, H5), 5.19 (1H, d, $J=6.9$ Hz, H4), 5.37 (1H, s, H2), 7.16 (2H, d, $J=8.2$ Hz, Ar-H), 7.28 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.0 (CH_3CH_2), 14.2

(OCH₂CH₃), 22.4 (CH₂CH₃), 27.0 ((CH₃)₃), 33.8 (CH₂CH₂), 35.5 (CH₂CH₂), 37.5 (C(CH₃)₃), 44.1 (C7), 61.2 (OCH₂CH₃), 61.9 (OCH₂CH₃), 64.7 (C5), 80.6 (C4), 97.1 (C2), 126.5 (Ar-C), 128.4 (Ar-C), 132.2 (Ar-C), 143.5 (Ar-C), 167.4 (C=O), 168.1 (C=O), 168.2 (C=O); LRMS (ESI⁺) *m/z*: 470.2 ([M + Na]⁺ 13%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₅H₃₇NO₆Na, 470.2513, found 470.2513.

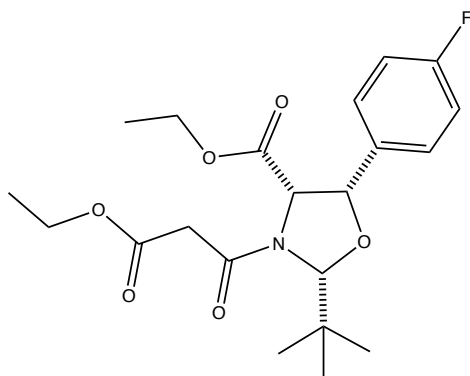
Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-methoxyphenyl)oxazolidine-4-carboxylate 129d**



Yield (3.13 g, Quantitative); Red oil; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1742 (C=O), 1679 (C=O); 9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.86 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.15 (9H, s, C(CH₃)₃), 1.31 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.42 (1H, d, *J*=15.3 Hz, H7), 3.46 (1H, d, *J*=15.3 Hz, H7), 3.72 (1H, dq, *J*=7.2 Hz, 10.8 Hz,

OCH₂CH₃), 3.80 (3H, s, OCH₃), 3.86 (1H, m, OCH₂CH₃), 4.22 (2H, m, OCH₂CH₃), 4.75 (1H, br d, *J*=7.0 Hz, H5), 5.17 (1H, d, *J*=6.9 Hz, H4), 5.36 (1H, s, H2), 6.88 (2H, d, *J*=8.7 Hz, Ar-H), 7.30 (2H, d, *J*=8.5 Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.9 ((CH₃)₃), 37.5 (C(CH₃)₃), 44.0 (C7), 55.4 (OCH₃), 61.2 (OCH₂CH₃), 61.9 (OCH₂CH₃), 64.7 (C5), 80.3 (C4), 97.0 (C2), 113.7 (Ar-C), 127.0 (Ar-C), 127.8 (Ar-C), 159.9 (Ar-C), 167.3 (C=O), 168.1 (C=O), 168.2 (C=O); LRMS (ESI⁺) *m/z*: 444.2 ([M + Na]⁺ 43%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₂H₃₁NO₇Na, 444.1993, found 444.1992.

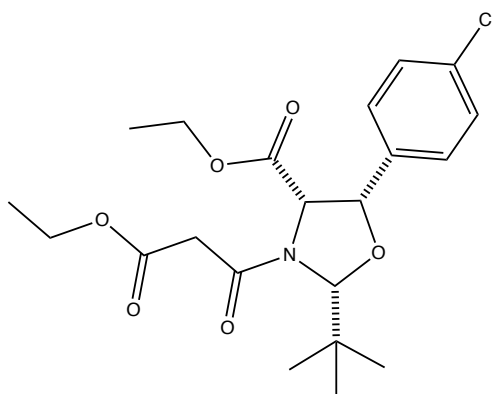
Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-fluorophenyl)oxazolidine-4-carboxylate 129e**



Yield (1.05 g, 37%); Yellow oil; *R_f* (30% EtOAc in Pet. Ether 40:60) 0.53; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1740 (C=O), 1679 (C=O); 9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.86 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.12 (9H, s, C(CH₃)₃), 1.30 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 3.42

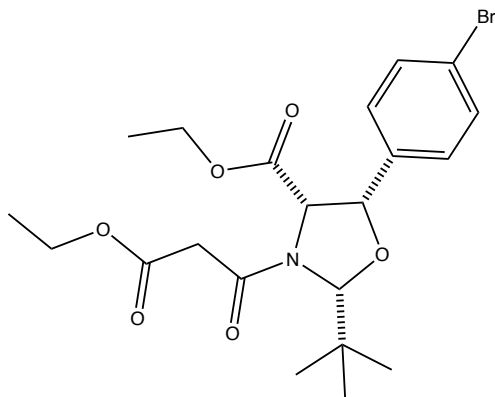
(1H, d, $J=15.4$ Hz, H7), 3.48 (1H, d, $J=15.3$ Hz, H7), 3.72 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH₂CH₃), 3.83 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 4.21 (2H, m, OCH₂CH₃), 4.79 (1H, br d, $J=6.8$ Hz, H5), 5.18 (1H, d, $J=6.8$ Hz, H4), 5.36 (1H, s, H2), 7.04 (2H, app t, $J=8.7$ Hz, Ar-H), 7.36 (2H, dd, $J=5.3$ Hz, 8.6 Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.9 ((CH₃)₃), 37.5 (C(CH₃)₃), 44.0 (C7), 61.4 (OCH₂CH₃), 62.0 (OCH₂CH₃), 64.4 (C5), 79.9 (C4), 97.1 (C2), 115.3 (d, $J=22.0$ Hz, Ar-C), 128.3 (d, $J=8.4$ Hz, Ar-C), 131.0 (d, $J=3.2$ Hz, Ar-C), 163.2 (d, $J=247.1$ Hz, Ar-C), 167.5 (C=O), 168.0 (C=O), 168.1 (C=O); δ_{F} (Major diastereomer) (377 MHz, CDCl₃) -113.30; LRMS (ESI⁺) m/z : 432.2 ([M + Na]⁺ 97%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₁H₂₈NO₆FNa, 432.1793, found 432.1791.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-5-(4-chlorophenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129f**



Yield (1.61 g, 76%); Yellow oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.20; ν_{max} /cm⁻¹ 2980 (C-H), 1740 (C=O), 1678 (C=O); 9:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.86 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.11 (9H, s, C(CH₃)₃), 1.30 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.43 (1H, d, $J=15.3$ Hz, H7), 3.50 (1H, d, $J=15.3$ Hz, H7), 3.79 (2H, m, OCH₂CH₃), 4.22 (2H, m, OCH₂CH₃), 4.81 (1H, br d, $J=6.8$ Hz, H5), 5.17 (1H, d, $J=6.7$ Hz, H4), 5.37 (1H, s, H2), 7.32 (4H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.8 ((CH₃)₃), 37.5 (C(CH₃)₃), 43.9 (C7), 61.4 (OCH₂CH₃), 62.0 (OCH₂CH₃), 64.2 (C5), 79.8 (C4), 97.1 (C2), 127.9 (Ar-C), 128.5 (Ar-C), 133.8 (Ar-C), 134.4 (Ar-C), 167.5 (C=O), 167.8 (C=O), 168.1 (C=O); LRMS (ESI⁺) m/z : 448.2 ([M³⁵ + Na]⁺ 65%), 450.2 ([M³⁷ + Na]⁺ 19%); HRMS (ESI⁺) m/z : [M³⁵ + Na]⁺ calcd. for C₂₁H₂₈NO₆ClNa, 448.1497, found 448.1498; [M³⁷ + Na]⁺ calcd. for C₂₁H₂₈NO₆ClNa, 450.1470, found 450.1468.

Ethyl (2*R,4*S**,5*S**)-5-(4-bromophenyl)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129g**



Yield (648 mg, 69%); Yellow oil; R_f (30% EtOAc in Pet.

Ether 40:60) 0.55; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 1741 (C=O), 1679

(C=O); 91:9 mixture of diastereomers at the C2-position;

δ_H (Major diastereomer) (400 MHz, CDCl_3) 0.88 (3H, t, $J=7.2$ Hz,

OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.1$ Hz,

OCH_2CH_3), 3.43 (1H, d, $J=15.3$ Hz, H7), 3.52 (1H, d, $J=15.3$

Hz, H7), 3.76 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 3.85

(1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.23 (2H, m, OCH_2CH_3), 4.82 (1H, br d, $J=6.7$ Hz, H5), 5.16 (1H, d,

$J=6.7$ Hz, H4), 5.38 (1H, s, H2), 7.27 (2H, d, $J=8.4$ Hz, Ar-H), 7.49 (2H, d, $J=8.4$ Hz, Ar-H); δ_C (Major diastereomer)

(101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 14.2 (OCH_2CH_3), 26.8 ($(\text{CH}_3)_3$), 37.5 ($\text{C}(\text{CH}_3)_3$), 43.9 (C7), 61.4

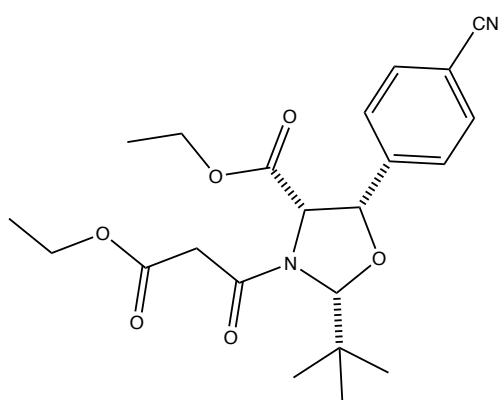
(OCH_2CH_3), 62.0 (OCH_2CH_3), 64.1 (C5), 79.8 (C4), 97.1 (C2), 122.5 (Ar-C), 128.2 (Ar-C), 131.5 (Ar-C),

134.3 (Ar-C), 167.5 (C=O), 167.8 (C=O), 168.1 (C=O); LRMS (ESI^+) m/z : 492.0 ($[\text{M}^{79} + \text{Na}]^+$ 97%), 494.0

($[\text{M}^{81} + \text{Na}]^+$ 81%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{28}\text{NO}_6\text{BrNa}$, 492.0992, found 492.0994;

$[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{28}\text{NO}_6\text{BrNa}$, 494.0973, found 494.0974.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-5-(4-cyanophenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129h**



Yield (568 mg, 68%); Yellow oil; R_f (30% EtOAc in Pet. Ether

40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 2229 ($\text{C}\equiv\text{N}$), 1740 (C=O),

1678 (C=O); 9:1 mixture of diastereomers at the C2-

position; δ_H (Major diastereomer) (400 MHz, CDCl_3) 0.88 (3H, t,

$J=7.1$ Hz, OCH_2CH_3), 1.09 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.1$

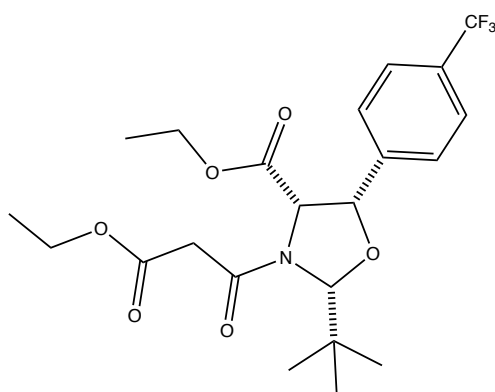
Hz, OCH_2CH_3), 3.46 (1H, d, $J=15.3$ Hz, H7), 3.59 (1H, d,

$J=15.3$ Hz, H7), 3.77 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.86 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3),

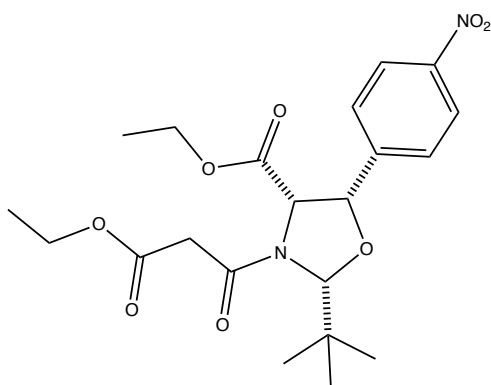
4.23 (2H, m, OCH_2CH_3), 4.93 (1H, br d, $J=6.5$ Hz, H5), 5.22 (1H, d, $J=6.4$ Hz, H4), 5.40 (1H, s, H2), 7.51

(2H, d, $J=8.0$ Hz, Ar-H), 7.65 (2H, d, $J=8.4$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 26.6 ($(\text{CH}_3)_3$), 37.4 ($\text{C}(\text{CH}_3)_3$), 43.8 (C7), 61.6 (OCH_2CH_3), 62.0 (OCH_2CH_3), 63.6 (C5), 79.4 (C4), 97.1 (C2), 112.2 (Ar-C), 118.6 ($\text{C}\equiv\text{N}$), 127.2 (Ar-C), 132.1 (Ar-C), 140.8 (Ar-C), 167.5 ($\text{C}=\text{O}$), 167.6 ($\text{C}=\text{O}$), 168.1 ($\text{C}=\text{O}$); LRMS (ESI^+) m/z : 439.0 ($[\text{M} + \text{Na}]^+$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_6\text{Na}$, 439.1840, found 439.1837.

Ethyl

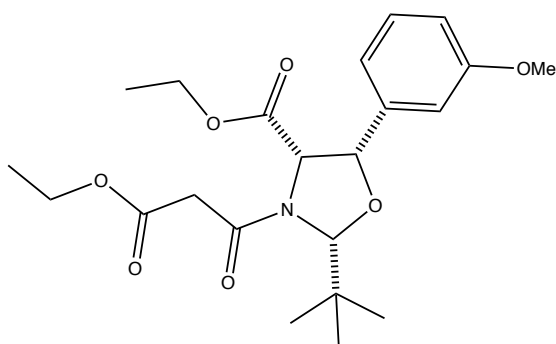
(2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-****(trifluoromethyl)phenyl)oxazolidine-4-carboxylate 129i**Yield (562 mg, 59%); Pale yellow oil; R_f (30% EtOAc in Pet.Ether 40:60) 0.50; $\nu_{\text{max}}/\text{cm}^{-1}$ 2982 (C-H), 1741 ($\text{C}=\text{O}$), 1679($\text{C}=\text{O}$); 93:7 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.45 (1H, d, $J=15.3$ Hz, H7), 3.55 (1H, d, $J=15.3$ Hz, H7), 3.72 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 3.82 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.23 (2H,m, OCH_2CH_3), 4.90 (1H, d, $J=6.6$ Hz, H5), 5.25 (1H, d, $J=6.6$ Hz, H4), 5.40 (1H, s, H2), 7.52 (2H, d, $J=8.5$ Hz, Ar-H), 7.63 (2H, d, $J=8.2$ Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.2(OCH_2CH_3), 26.8 ($(\text{CH}_3)_3$), 37.5 ($\text{C}(\text{CH}_3)_3$), 43.9 (C7), 61.5 (OCH_2CH_3), 62.0 (OCH_2CH_3), 64.0 (C5), 79.7 (C4),97.2 (C2), 125.3 (q, $J=3.8$ Hz, Ar-C), 126.9 (Ar-C), 130.8 (d, $J=32.6$ Hz, Ar-C), 139.4 (Ar-C), 167.6 ($\text{C}=\text{O}$),167.7 ($\text{C}=\text{O}$), 168.1 ($\text{C}=\text{O}$); δ_{F} (Major diastereomer) (376 MHz, CDCl_3) -62.68; LRMS (ESI^+) m/z : 482.2 ($[\text{M} + \text{Na}]^+$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{28}\text{NO}_6\text{F}_3\text{Na}$, 482.1761, found 482.1758.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(4-nitrophenyl)oxazolidine-4-carboxylate 129j**



Yield (582 mg, 75%); Yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.33; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 1739 (C=O), 1678 (C=O), 1524 (N-O); 9:1 mixture of diastereomers at the C2-position; δ_H (Major diastereomer) (400 MHz, CDCl_3) 0.90 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.09 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.47 (1H, d, $J=15.3$ Hz, H7), 3.63 (1H, d, $J=15.3$ Hz, H7), 3.78 (1H, dq, $J=7.2$ Hz, 10.9 Hz, OCH_2CH_3), 3.87 (1H, m, OCH_2CH_3), 4.23 (2H, m, OCH_2CH_3), 4.98 (1H, br d, $J=6.3$ Hz, H5), 5.27 (1H, d, $J=6.3$ Hz, H4), 5.42 (1H, s, H2), 7.57 (2H, d, $J=8.5$ Hz, Ar-H), 8.22 (2H, d, $J=8.7$ Hz, Ar-H); δ_C (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 26.6 ($(\text{CH}_3)_3$), 37.4 ($\text{C}(\text{CH}_3)_3$), 43.7 (C7), 61.6 (OCH_2CH_3), 62.1 (OCH_2CH_3), 63.5 (C5), 79.2 (C4), 97.1 (C2), 123.5 (Ar-C), 127.3 (Ar-C), 142.8 (Ar-C), 147.9 (Ar-C), 167.4 (C=O), 167.7 (C=O), 168.1 (C=O); LRMS (ESI^+) m/z : 459.2 ($[\text{M} + \text{Na}]^+$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_8\text{Na}$, 459.1738, found 459.1736.

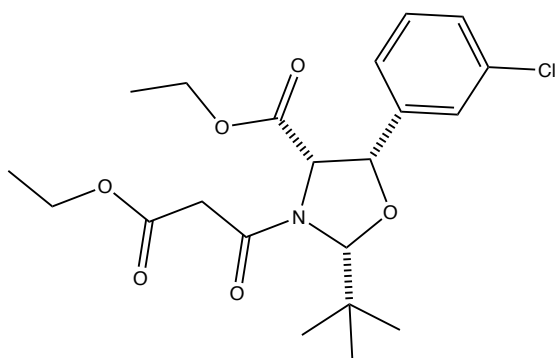
Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(3-methoxyphenyl)oxazolidine-4-carboxylate 129k**



Yield (533 mg, 68%); Yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.55; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 1741 (C=O), 1679 (C=O); 89:11 mixture of diastereomers at the C2-position; δ_H (Major diastereomer) (400 MHz, CDCl_3) 0.84 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.15 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.42 (1H, d, $J=15.3$ Hz, H7), 3.49 (1H, d, $J=15.3$ Hz, H7), 3.72 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.82 (1H, m, OCH_2CH_3), 4.22 (2H, m, OCH_2CH_3), 4.80 (1H, br d, $J=6.9$ Hz, H5), 5.18 (1H, d, $J=6.8$ Hz, H4), 5.38 (1H, s, H2), 6.86 (1H, m, Ar-H), 6.96 (2H, m, Ar-H), 7.26 (1H, m, Ar-H); δ_C (Major diastereomer) (101 MHz, CDCl_3) 13.6

(OCH₂CH₃), 14.2 (OCH₂CH₃), 27.0 ((CH₃)₃), 37.5 (C(CH₃)₃), 44.0 (C7), 55.4 (OCH₃), 61.3 (OCH₂CH₃), 61.9 (OCH₂CH₃), 64.5 (C5), 80.4 (C4), 97.1 (C2), 112.2 (Ar-C), 114.0 (Ar-C), 118.9 (Ar-C), 129.4 (Ar-C), 136.7 (Ar-C), 159.7 (Ar-C), 167.4 (C=O), 168.1 (C=O), 168.1 (C=O); LRMS (ESI⁺) *m/z*: 422.2 ([M + H]⁺ 75%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₂H₃₁NO₇Na, 444.1993, found 444.1991.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-5-(3-chlorophenyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129I**



Yield (650 mg, 72%); Off-white solid; m.p. 118-121°C;

R_f (30% EtOAc in Pet. Ether 40:60) 0.63; *v*_{max}/cm⁻¹

2980 (C-H), 1740 (C=O), 1678 (C=O); 9:1 mixture of

diastereomers at the C2-position; δ_{H} (Major diastereomer)

(400 MHz, CDCl₃) 0.87 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 1.13

(9H, s, C(CH₃)₃), 1.31 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 3.43

(1H, d, *J*=15.4 Hz, H7), 3.53 (1H, d, *J*=15.3 Hz, H7), 3.77 (1H, dq, *J*=7.1 Hz, 10.8 Hz, OCH₂CH₃), 3.86 (1H,

dq, *J*=7.2 Hz, 10.8 Hz, OCH₂CH₃), 4.24 (2H, m, OCH₂CH₃), 4.84 (1H, br d, *J*=6.7 Hz, H5), 5.17 (1H, d, *J*=6.7

Hz, H4), 5.38 (1H, s, H2), 7.26-7.31 (3H, m, Ar-H), 7.38 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃)

13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.8 ((CH₃)₃), 37.5 (C(CH₃)₃), 43.9 (C7), 61.4 (OCH₂CH₃), 62.0

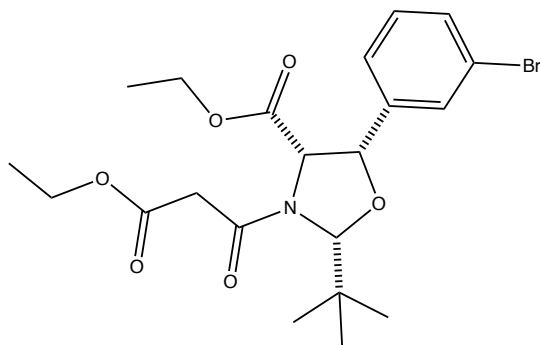
(OCH₂CH₃), 64.2 (C5), 79.7 (C4), 97.1 (C2), 124.7 (Ar-C), 126.7 (Ar-C), 128.7 (Ar-C), 129.6 (Ar-C), 134.4

(Ar-C), 137.3 (Ar-C), 167.5 (C=O), 167.8 (C=O), 168.1 (C=O); LRMS (ESI⁺) *m/z*: 448.2 ([M³⁵ + Na]⁺ 96%),

450.2 ([M³⁷ + Na]⁺ 30%); HRMS (ESI⁺) *m/z*: [M³⁵ + Na]⁺ calcd. for C₂₁H₂₈NO₆ClNa, 448.1497, found

448.1498; [M³⁷ + Na]⁺ C₂₁H₂₈NO₆ClNa, 450.1470, found 450.1468.

Ethyl (2*R,4*S**,5*S**)-5-(3-bromophenyl)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129m**



Yield (698 mg, 66%); Off-white solid; m.p. 121-124°C;

R_f (30% EtOAc in Pet. Ether 40:60) 0.58; $\nu_{\max}/\text{cm}^{-1}$ 2980

(C-H), 1738 (C=O), 1678 (C=O); 89:11 mixture of

diastereomers at the C2-position; δ_H (Major diastereomer)

(400 MHz, CDCl_3) 0.88 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.13

(9H, s, $\text{C}(\text{CH}_3)_3$), 1.32 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.44

(1H, d, $J=15.3$ Hz, H7), 3.53 (1H, d, $J=15.3$ Hz, H7), 3.77 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.86 (1H,

dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.23 (2H, m, OCH_2CH_3), 4.84 (1H, d, $J=6.7$ Hz, H5), 5.17 (1H, d, $J=6.7$

Hz, H4), 5.38 (1H, s, H2), 7.23 (1H, m, Ar-H), 7.32 (1H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.53 (1H, m, Ar-H);

δ_C (Major diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 14.2 (OCH_2CH_3), 26.8 ($(\text{CH}_3)_3$), 37.5 ($\text{C}(\text{CH}_3)_3$), 43.9

(C7), 61.4 (OCH_2CH_3), 62.0 (OCH_2CH_3), 64.2 (C5), 79.6 (C4), 97.1 (C2), 122.4 (Ar-C), 125.2 (Ar-C), 129.6

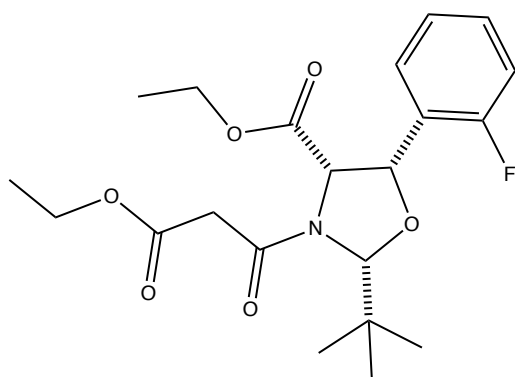
(Ar-C), 129.9 (Ar-C), 131.6 (Ar-C), 137.6 (Ar-C), 167.5 (C=O), 167.8 (C=O), 168.1 (C=O); LRMS (ESI^+) m/z :

492.0 ($[\text{M}^{79} + \text{Na}]^+$ 91%), 494.0 ($[\text{M}^{81} + \text{Na}]^+$ 94%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for

$\text{C}_{21}\text{H}_{28}\text{NO}_6\text{BrNa}$, 492.0992, found 492.0992; $[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{28}\text{NO}_6\text{BrNa}$, 494.0971, found

494.0971.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(2-fluorophenyl)oxazolidine-4-carboxylate 129n**



Yield (512 mg, 61%); Off-white solid; m.p. 66-69°C; R_f

(30% EtOAc in Pet. Ether 40:60) 0.80; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-

H), 1743 (C=O), 1680 (C=O); 92:8 mixture of

diastereomers at the C2-position; δ_H (Major diastereomer) (400

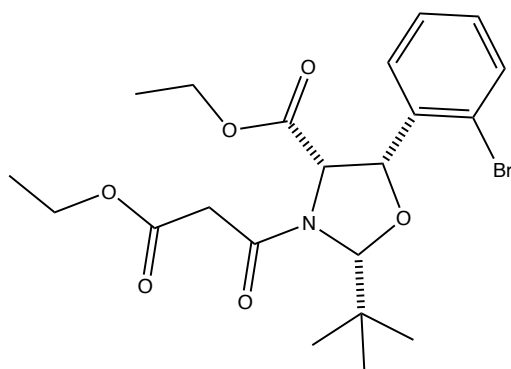
MHz, CDCl_3) 0.85 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.10 (9H, s,

$\text{C}(\text{CH}_3)_3$), 1.30 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.46 (1H, d,

$J=15.4$ Hz, H7), 3.60 (1H, d, $J=15.4$ Hz, H7), 3.81 (2H, m, OCH_2CH_3), 4.23 (2H, dq, $J=4.2$ Hz, 7.1 Hz,

OCH₂CH₃), 4.93 (1H, br d, *J*=6.3 Hz, H5), 5.33 (1H, d, *J*=6.3 Hz, H4), 5.39 (1H, s, H2), 7.03 (1H, m, Ar-H), 7.17 (1H, dt, *J*=1.2 Hz, 7.6 Hz, Ar-H), 7.31 (1H, m, Ar-H), 7.57 (1H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 26.7 ((CH₃)₃), 37.4 (C(CH₃)₃), 43.9 (C7), 61.3 (OCH₂CH₃), 62.0 (OCH₂CH₃), 62.6 (d, *J*=1.7 Hz, C5), 74.8 (d, *J*=3.8 Hz, C4), 96.5 (C2), 114.7 (d, *J*=20.5 Hz, Ar-C), 123.3 (d, *J*=13.6 Hz, Ar-C), 124.3 (d, *J*=3.3 Hz, Ar-C), 127.3 (d, *J*=3.9 Hz, Ar-C), 129.7 (d, *J*=8.2 Hz, Ar-C), 159.8 (d, *J*=245.4 Hz, Ar-C), 167.2 (C=O), 167.8 (C=O), 168.2 (C=O); δ_{F} (Major diastereomer) (377 MHz, CDCl₃) -117.95; LRMS (ESI⁺) *m/z*: 432.2 ([M + Na]⁺ 96%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₁H₂₈NO₆FNa, 432.1793, found 432.1792.

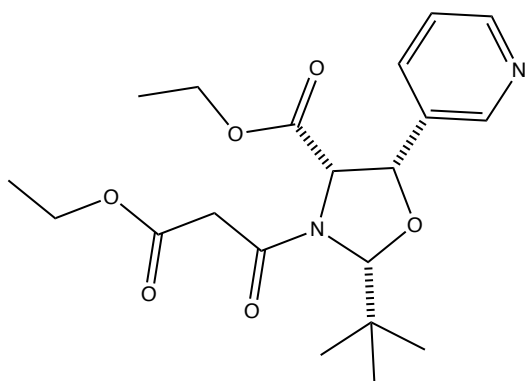
Ethyl (2*R,4*S**,5*S**)-5-(2-bromophenyl)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 129o**



Yield (707 mg, 54%); White solid; m.p. 135-139°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.73; ν_{max} /cm⁻¹ 2979 (C-H), 1743 (C=O), 1680 (C=O); >95:5 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.81 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 1.12 (9H, s, C(CH₃)₃), 1.31 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.46 (1H, d, *J*=15.5 Hz, H7),

3.56 (1H, d, *J*=15.4 Hz, H7), 3.72 (1H, dq, *J*=7.2 Hz, 10.7 Hz, OCH₂CH₃), 3.81 (1H, dq, *J*=7.2 Hz, 10.8 Hz, OCH₂CH₃), 4.23 (2H, dq, *J*=1.0 Hz, 7.2 Hz, OCH₂CH₃), 5.15 (1H, br d, *J*=6.5 Hz, H5), 5.33 (1H, d, *J*=6.5 Hz, H4), 5.40 (1H, s, H2), 7.20 (1H, dt, *J*=1.7 Hz, 7.7 Hz, Ar-H), 7.34 (1H, dt, *J*=1.3 Hz, 7.6 Hz, Ar-H), 7.54 (1H, dd, *J*=1.2 Hz, 8.0 Hz, Ar-H), 7.63 (1H, ddd, *J*=0.7 Hz, 1.7 Hz, 7.8 Hz, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.3 (OCH₂CH₃), 26.8 ((CH₃)₃), 37.5 (C(CH₃)₃), 44.0 (C7), 61.3 (OCH₂CH₃), 61.8 (C5), 62.0 (OCH₂CH₃), 79.6 (C4), 96.5 (C2), 122.2 (Ar-C), 127.5 (Ar-C), 128.1 (Ar-C), 129.8 (Ar-C), 132.3 (Ar-C), 135.4 (Ar-C), 167.2 (C=O), 167.8 (C=O), 168.3 (C=O); LRMS (ESI⁺) *m/z*: 492.0 ([M⁷⁹ + Na]⁺ 89%), 494.0 ([M⁸¹ + Na]⁺ 96%); HRMS (ESI⁺) *m/z*: [M⁷⁹ + Na]⁺ calcd. for C₂₁H₂₈NO₆BrNa, 492.0992, found 492.0992; [M⁸¹ + Na]⁺ calcd. for C₂₁H₂₈NO₆BrNa, 494.0973, found 494.0971.

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)-5-(pyridin-3-yl)oxazolidine-4-carboxylate **129p****

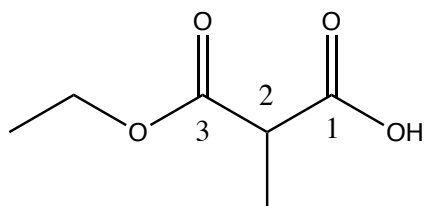


Yield (1.05 g, 68%); Yellow oil; R_f (70% EtOAc in Pet. Ether 40:60) 0.23; $\nu_{\max}/\text{cm}^{-1}$ 2979 (C-H), 1739 (C=O), 1676 (C=O); 82:18 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.85 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.10 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.44 (1H, d, $J=15.4$ Hz, H7), 3.56 (1H,

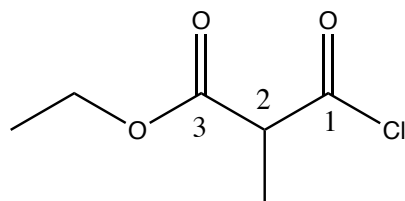
d, $J=15.4$ Hz, H7), 3.76 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.85 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.21 (2H, m, OCH_2CH_3), 4.89 (1H, br d, $J=6.6$ Hz, H5), 5.22 (1H, d, $J=6.6$ Hz, H4), 5.39 (1H, s, H2), 7.30 (1H, m, Ar-H), 7.74 (1H, m, Ar-H), 8.58 (2H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 26.7 ($(\text{CH}_3)_3$), 37.4 ($\text{C}(\text{CH}_3)_3$), 43.9 (C7), 61.5 (OCH_2CH_3), 62.0 (OCH_2CH_3), 63.9 (C5), 78.3 (C4), 97.1 (C2), 123.3 (Ar-C), 131.3 (Ar-C), 134.3 (Ar-C), 148.1 (Ar-C), 149.6 (Ar-C), 167.5 (C=O), 167.7 (C=O), 168.1 (C=O); LRMS (ESI^+) m/z : 393.2 ($[\text{M} + \text{H}]^+$ 96%), 415.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_6$, 393.2020, found 393.2020.

General procedure for the monosaponification of diethyl methyl malonate and the formation of the acyl chloride.⁶³

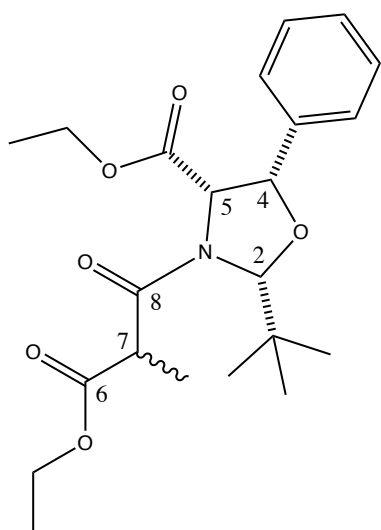
Added dropwise to a stirring 1 M KOH solution (1 eq.) (eth.) at 0°C was diethyl methyl malonate (1 eq.) and this reaction mixture was refluxed for 2 h. The reaction mixture was then filtered and concentrated to give a white solid. Water was then added to the concentrate and acidified to pH 3 using 3 M HCl solution (aq.) and extracted with Et_2O . The organic layer was washed with brine, dried over Na_2SO_4 , filtered and evaporated *in-vacuo* to obtain carboxylic acid **130'** as a colourless oil and was used without further purification. SOCl_2 (2 eq.) was added dropwise to a solution of monoethyl methyl malonate **130'** (1 eq.) at 0°C and this solution was then stirred for 3.5 h at 50°C. This solution was then concentrated *in-vacuo* to obtain the acyl chloride **130** as a yellow/orange oil and was used without further purification.

3-Ethoxy-2-methyl-3-oxopropanoic acid 130'

Yield (5.38 g, 71%); Colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 3187 (O-H), 2988 (C-H), 1714 (C=O); δ_{H} (400 MHz, CDCl_3) 1.26 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.43 (3H, d, $J=7.3$ Hz, CH_3), 3.46 (1H, q, $J=7.3$ Hz, H2), 4.20 (2H, dq, $J=0.8$ Hz, 7.2 Hz, OCH_2CH_3), 9.52 (1H, br s, OH); δ_{C} (101 MHz, CDCl_3) 13.7 (CH_3), 14.1 (OCH_2CH_3), 46.1 (C2), 61.9 (OCH_2CH_3), 170.0 (C=O), 175.8 (C=O); LRMS (ESI^+) m/z : 147.0 ($[\text{M} + \text{H}]^+$ 14%), 168.9 ($[\text{M} + \text{Na}]^+$ 22%), 185.0 ($[\text{M} + \text{K}]^+$ 64%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_6\text{H}_{10}\text{O}_4\text{Na}$, 169.0471, found 169.0472.

Ethyl 3-chloro-2-methyl-3-oxopropanoate 130

Yield (5.64 g, 93%); Yellow oil; δ_{H} (400 MHz, CDCl_3) 1.30 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.52 (3H, d, $J=7.2$ Hz, CH_3), 3.84 (1H, q, $J=7.2$ Hz, H2), 4.25 (2H, dq, $J=2.8$ Hz, 7.1 Hz, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 14.0 (CH_3), 14.2 (OCH_2CH_3), 57.2 (C2), 62.4 (OCH_2CH_3), 167.6 (C=O), 170.8 (C=O).

Ethyl (2*R,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-2-methyl-3-oxopropanoyl)-5-phenyloxazolidine-4-carboxylate 131**

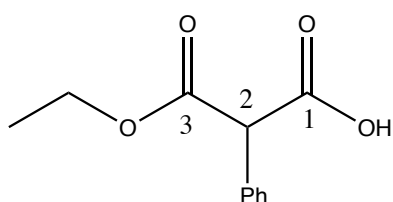
Yield (1.79 g, 76%); Pale green oil that crystallised overnight; R_f (20% EtOAc in Pet. Ether 40:60) 0.58 (Minor diastereomer), 0.35 (Major diastereomer); $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1740 (C=O), 1682 (C=O); 1.8:1 mixture of diastereomers at the C7-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 0.79 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.32 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.43 (3H, d, $J=7.0$ Hz, CH_3), 3.50 (1H, q, $J=7.0$ Hz, H7), 3.68 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.80 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.23 (2H, dq, $J=4.7$ Hz, 7.1 Hz, OCH_2CH_3), 4.99 (1H, d, $J=6.8$ Hz, H5), 5.19 (1H, d, $J=6.8$ Hz, H4), 5.41 (1H, s, H2), 7.31-7.39 (5H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.3 (CH_3), 14.7 (OCH_2CH_3), 26.9 ($(\text{CH}_3)_3$), 37.4 ($\text{C}(\text{CH}_3)_3$),

46.8 (C7), 61.2 (OCH₂CH₃), 61.8 (OCH₂CH₃), 64.4 (C5), 80.5 (C4), 96.7 (C2), 126.5 (Ar-C), 128.3 (Ar-C), 128.6 (Ar-C), 135.2 (Ar-C), 168.4 (C=O), 170.1 (C=O), 172.7 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.77 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.16 (9H, s, C(CH₃)₃), 1.24 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.42 (3H, d, $J=7.0$ Hz, CH₃), 3.49 (1H, br s, H7), 3.60 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 3.76 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH₂CH₃), 4.12 (2H, dq, $J=5.5$ Hz, 7.2 Hz, OCH₂CH₃), 4.63 (1H, br s, H5), 5.17 (1H, d, $J=7.0$ Hz, H4), 5.39 (1H, s, H2), 7.30-7.39 (5H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 13.5 (OCH₂CH₃), 14.1 (CH₃), 27.0 ((CH₃)₃), 37.7 (C(CH₃)₃), 47.3 (C7), 61.0 (OCH₂CH₃), 61.7 (OCH₂CH₃), 65.0 (C5), 80.8 (C4), 97.2 (C2), 126.6 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 134.9 (Ar-C), 167.7 (C=O), 170.0 (C=O), 172.0 (C=O); LRMS (ESI⁺ (Major diastereomer)) m/z : 428.2 ([M + Na]⁺ 83%); LRMS (ESI⁺ (Minor diastereomer)) m/z : 428.2 ([M + Na]⁺ 95%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₂H₃₁NO₆Na, 428.2044, found 428.2041.

General procedure for the monosaponification of diethyl phenyl malonate and the formation of the acyl chloride malonate:¹⁰⁶

A solution of diethyl phenyl malonate (1 eq.) in EtOH (0.7 M) was cooled to 0°C and KOH (1 eq.) was added and left to stir at this temperature for 30 mins. The mixture was then stirred at rt for 5 h and then left in the fridge overnight. The reaction mixture was then concentrated *in-vacuo* and the residue was dissolved in H₂O and extracted with Et₂O. The aqueous layer was then acidified to pH 1-2, extracted with Et₂O and the organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated *in-vacuo* to obtain carboxylic acid **132'** as a white solid and was used without further purification. To a solution of monoethyl phenyl malonate **132'** (1 eq.) in DCM (0.34 M) was added SOCl₂ (2 eq.) dropwise at 0°C and this solution was then refluxed for 3 h. This solution was then concentrated *in-vacuo* to obtain acyl chloride **132** as a crude yellow oil and was used without further purification.

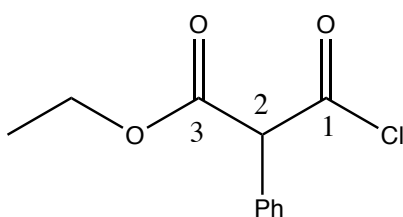
3-Ethoxy-3-oxo-2-phenylpropanoic acid 132'



Yield (1.54 g, 35%); Colourless oil that solidified on standing; m.p. 80-85°C (lit.¹⁰⁷ 76-77°C); ν_{max} /cm⁻¹ 3172 (O-H), 2985 (C-H), 1715 (C=O); δ_{H} (400 MHz, CDCl₃) 1.26 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.23

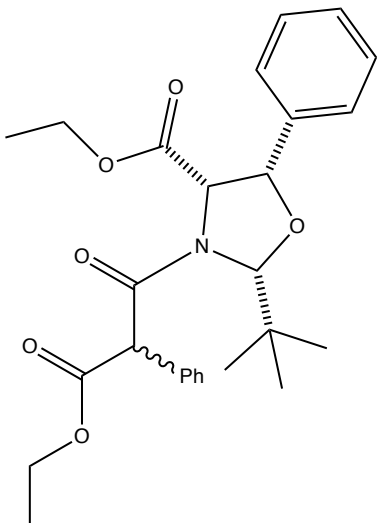
(2H, m, OCH₂CH₃), 4.65 (1H, s, H₂), 7.34-7.42 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 14.0 (OCH₂CH₃), 57.7 (C₂), 62.3 (OCH₂CH₃), 128.5 (Ar-C), 128.8 (Ar-C), 129.3 (Ar-C), 132.4 (Ar-C), 168.4 (C=O), 172.8 (C=O); LRMS (ESI⁺) m/z : 231.0 ([M + Na] 100%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₁H₁₂O₄Na, 231.0628, found 231.0629.

Ethyl 3-chloro-3-oxo-2-phenylpropanoate 132



Yield (1.42 g, 93%); Yellow oil; δ_{H} (400 MHz, CDCl₃) 1.30 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.27 (2H, m, OCH₂CH₃), 5.02 (1H, s, H₂), 7.36-7.43 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 14.0 (OCH₂CH₃), 62.8 (OCH₂CH₃), 68.4 (C₂), 129.2 (Ar-C), 129.3 (Ar-C), 129.5 (Ar-C), 130.8 (Ar-C), 165.9 (C=O), 168.7 (C=O).

Ethyl (2*R**,4*S**,5*S**)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxo-2-phenylpropanoyl)-5-phenyloxazolidine-4-carboxylate 133



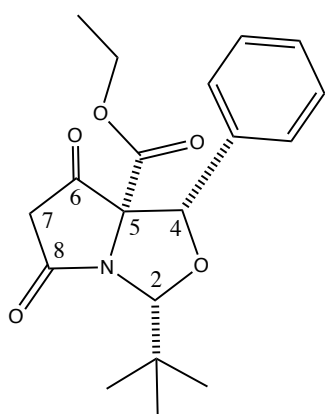
Yield (2.00 g, 70%); Pale green oil that crystallised overnight; R_f (20% EtOAc in Pet. Ether 40:60) 0.58_(Minor diastereomer) and 0.45_(Major diastereomer); $\nu_{\text{max}}/\text{cm}^{-1}$ 2980 (C-H), 1753 (C=O), 1675 (C=O); 1.7:1 mixture of diastereomers at the C7-position; δ_{H} (Major diastereomer) (400 MHz, CDCl₃) 0.72 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.07 (9H, s, C(CH₃)₃), 1.31 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.45 (1H, m, OCH₂CH₃), 3.59 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 4.26 (2H, m, OCH₂CH₃), 4.77 (1H, s, H₇), 4.84 (1H, d, $J=6.9$ Hz, H₅), 5.22 (1H, br d, $J=6.9$ Hz, H₄), 5.44 (1H, s, H₂), 7.26-7.36 (10H, m, Ar-H); δ_{C} (Major diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.3 (OCH₂CH₃), 27.1 ((CH₃)₃), 37.6 (C(CH₃)₃), 59.6 (C₇), 61.0 (OCH₂CH₃), 62.1 (OCH₂CH₃), 65.1 (C₅), 80.8 (C₄), 97.3 (C₂), 126.5 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 129.9 (Ar-C), 133.0 (Ar-C), 134.9 (Ar-C), 167.5 (C=O), 168.4 (C=O), 171.0 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl₃) 0.86 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.19 (9H, s, C(CH₃)₃), 1.27 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.72 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 3.86

(1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 4.17 (2H, m, OCH₂CH₃), 4.59 (1H, d, $J=6.9$ Hz, H5), 4.66 (1H, s, H7) 4.89 (1H, d, $J=6.9$ Hz, H4), 5.36 (1H, s, H2), 7.19-7.50 (10H, m, Ar-H); δ_{C} (Minor diastereomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 14.1 (OCH₂CH₃), 27.0 ((CH₃)₃), 37.7 (C(CH₃)₃), 59.4 (C7), 61.2 (OCH₂CH₃), 62.0 (OCH₂CH₃), 63.8 (C5), 80.4 (C4), 97.2 (C2), 126.5-134.9 (Ar-C), 167.9 (C=O), 168.2 (C=O), 169.6 (C=O); LRMS (ESI⁺ (Major diastereomer)) m/z : 490.2 ([M + Na]⁺ 96%); LRMS (ESI⁺ (Minor diastereomer)) m/z : 490.2 ([M + Na]⁺ 94%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₇H₃₃NO₆Na, 490.2200, found 490.2197.

General procedure for the synthesis of C7-unfunctionalised tetramates:⁴¹

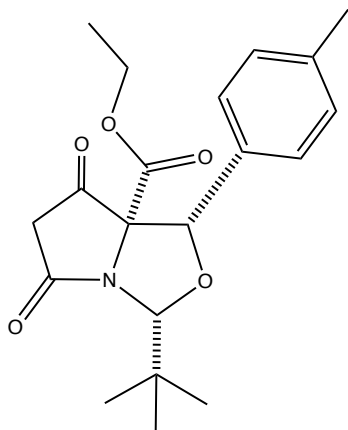
To a solution of *N*-acylated oxazolidine **129a-p**, **131** and **133** (1.0 eq.) in anhydrous THF was added DBU (1.1-1.2 eq.). The mixture was stirred overnight at rt. The reaction mixture was then cooled to 0°C, diluted with water, and partitioned between Et₂O and water and the aqueous layer was acidified to pH 1-2 using 3 M HCl solution (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the desired tetramates **134a-m**, **141** and **142** and was used without further purification.

Ethyl (1*S**,3*R**,7*aR**)-3-(*tert*-butyl)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **134a**



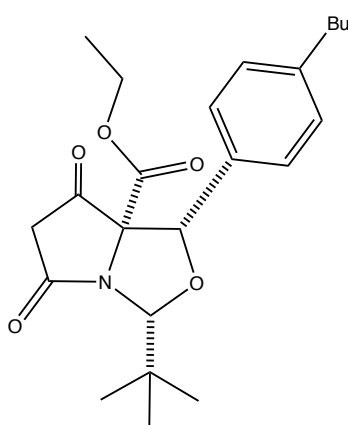
Yield (2.45 g, 94%); Red oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2962 (C-H), 1720 (C=O), 1622 (C=O); δ_{H} (400 MHz, CDCl₃) 0.91 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.09 (9H, s, C(CH₃)₃), 3.22 (1H, d, $J=20.5$ Hz, H7), 3.79 (1H, dd, $J=0.9$ Hz, 20.5 Hz, H7), 3.90 (2H, m, OCH₂CH₃), 4.96 (1H, s, H4), 5.16 (1H, d, $J=0.9$ Hz, H2), 7.32-7.56 (5H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 25.7 ((CH₃)₃), 36.0 (C(CH₃)₃), 46.1 (C7), 62.4 (OCH₂CH₃), 80.4 (C4), 81.7 (C5), 96.9 (C2), 126.5 (Ar-C), 128.1 (Ar-C), 128.3 (Ar-C), 134.4 (Ar-C), 165.0 (C=O), 172.0 (C8), 198.1 (C6); LRMS (ESI⁻) m/z : 344.1 ([M - H]⁻ 97%); LRMS (ESI⁺) m/z : 368.2 ([M + Na]⁺ 100%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₉H₂₃NO₅Na, 368.1468, found 368.1470.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-5,7-dioxo-1-(*p*-tolyl)dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134b**



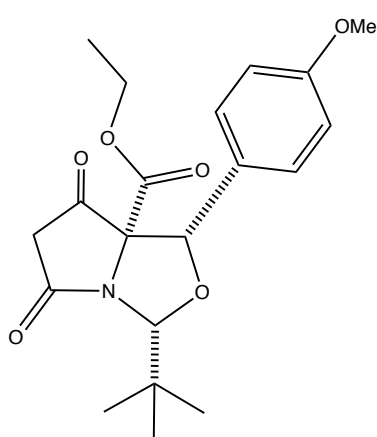
Yield (663 mg, 79%); Red oil; $\nu_{\max}/\text{cm}^{-1}$ 2976 (C-H), 1722 (C=O), 1620 (C=O); δ_{H} (400 MHz, CDCl_3) 0.95 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.35 (3H, s, CH₃), 3.22 (1H, d, $J=20.6$ Hz, H7), 3.78 (1H, dd, $J=0.9$ Hz, 20.6 Hz, H7), 3.91 (2H, m, OCH_2CH_3), 4.92 (1H, s, H4), 5.15 (1H, d, $J=0.8$ Hz, H2), 7.17 (2H, d, $J=7.9$ Hz, Ar-H), 7.42 (2H, d, $J=8.0$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 21.4 (CH₃), 25.7 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.1 (C7), 62.4 (OCH_2CH_3), 80.6 (C4), 81.6 (C5), 96.9 (C2), 126.5 (Ar-C), 128.7 (Ar-C), 131.3 (Ar-C), 138.1 (Ar-C), 164.9 (C=O), 172.3 (C8), 198.1 (C6); LRMS (ESI^-) m/z : 358.1 ($[\text{M} - \text{H}]^-$ 100%); LRMS (ESI^+) m/z : 382.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{20}\text{H}_{24}\text{NO}_5$, 358.1649, found 358.1658.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-butylphenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134c**



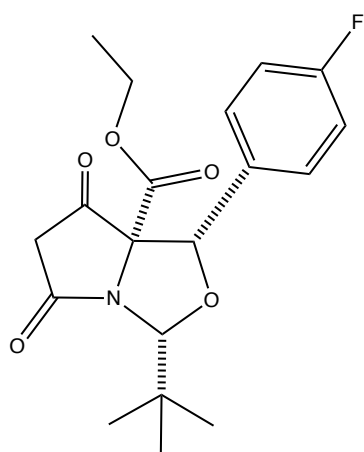
Yield (1.05 g, 78%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2931 (C-H), 2872 (C-H), 1721 (C=O), 1614 (C=O); δ_{H} (400 MHz, CDCl_3) 0.93 (6H, m, CH_3CH_2 , OCH_2CH_3), 1.10 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.34 (2H, m, CH_2CH_3), 1.60 (2H, m, CH_2CH_2), 2.62 (2H, m, CH_2CH_2), 3.23 (1H, d, $J=20.6$ Hz, H7), 3.79 (1H, dd, $J=1.0$ Hz, 20.5 Hz, H7), 3.91 (2H, m, OCH_2CH_3), 4.94 (1H, s, H4), 5.16 (1H, d, $J=0.9$ Hz, H2), 7.18 (2H, d, $J=8.2$ Hz, Ar-H), 7.45 (2H, d, $J=8.0$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.1 (CH_3CH_2), 22.4 (CH_2CH_2), 25.7 ($(\text{CH}_3)_3$), 33.7 (CH_2CH_2), 35.5 (CH_2CH_2), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.2 (C7), 62.3 (OCH_2CH_3), 80.7 (C4), 81.8 (C5), 97.0 (C2), 126.5 (Ar-C), 128.1 (Ar-C), 131.5 (Ar-C), 143.1 (Ar-C), 165.0 (C=O), 172.1 (C8), 198.1 (C6); LRMS (ESI^-) m/z : 400.2 ($[\text{M} - \text{H}]^-$ 100%); LRMS (ESI^+) m/z : 424.2 ($[\text{M} + \text{Na}]^+$ 51%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{23}\text{H}_{30}\text{NO}_5$, 400.2119, found 400.2125.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-methoxyphenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134d**



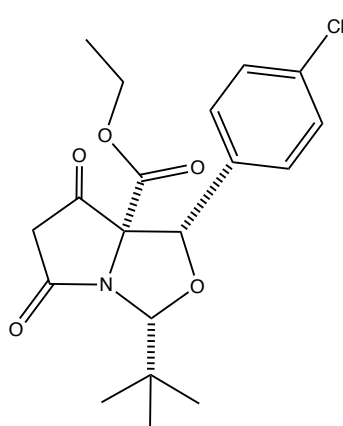
Yield (2.18 g, 80%); Red oil; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1722 (C=O), 1615 (C=O); δ_{H} (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.09 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.22 (1H, d, $J=20.5$ Hz, H7), 3.80 (1H, dd, $J=0.9$ Hz, 20.5 Hz, H7), 3.82 (3H, s, OCH_3), 3.93 (2H, m, OCH_2CH_3), 4.91 (1H, s, H4), 5.15 (1H, d, $J=0.8$ Hz, H2), 6.91 (2H, d, $J=8.8$ Hz, Ar-H), 7.46 (2H, d, $J=8.8$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.1 (C7), 55.4 (OCH_3), 62.4 (OCH_2CH_3), 80.5 (C4), 81.6 (C5), 96.9 (C2), 113.5 (Ar-C), 126.2 (Ar-C), 127.9 (Ar-C), 159.7 (Ar-C), 164.9 (C=O), 172.1 (C8), 198.2 (C6); LRMS (ESI^-) m/z : 374.1 ($[\text{M} - \text{H}]^-$ 100%); LRMS (ESI^+) m/z : 398.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{20}\text{H}_{24}\text{NO}_6$, 374.1598, found 374.1606.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-fluorophenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134e**



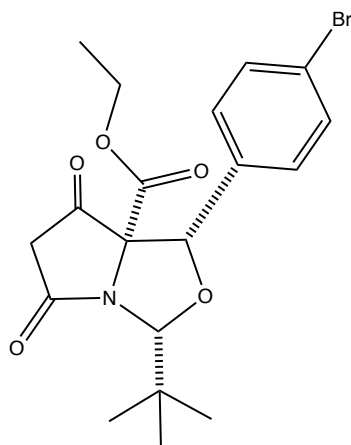
Yield (723 mg, 82%); Orange oil; $\nu_{\max}/\text{cm}^{-1}$ 2963 (C-H), 1720 (C=O), 1606 (C=O); δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.22 (1H, d, $J=20.6$ Hz, H7), 3.80 (1H, d, $J=20.6$ Hz, H7), 3.94 (2H, m, OCH_2CH_3), 4.92 (1H, s, H4), 5.16 (1H, s, H2), 7.06 (2H, app t, $J=8.6$ Hz, Ar-H), 7.53 (2H, dd, $J=5.4$ Hz, 8.4 Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.1 (C7), 62.5 (OCH_2CH_3), 79.9 (C4), 81.4 (C5), 96.9 (C2), 115.0 (d, $J=21.6$ Hz, Ar-C), 128.3 (d, $J=8.2$ Hz, Ar-C), 130.1 (d, $J=3.3$ Hz, Ar-C), 163.1 (d, $J=246.7$ Hz, Ar-C), 164.9 (C=O), 172.1 (C8), 198.2 (C6); δ_{F} (377 MHz, CDCl_3) -113.84; LRMS (ESI^-) m/z : 362.1 ($[\text{M} - \text{H}]^-$ 98%); LRMS (ESI^+) m/z : 386.0 ($[\text{M} + \text{Na}]^+$ 38%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{F}$, 362.1398, found 362.1408.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-chlorophenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134f**



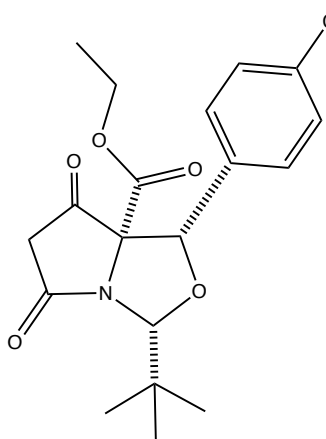
Yield (1.19 g, 86%); Orange oil; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1720 (C=O), 1622 (C=O); δ_{H} (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.23 (1H, d, $J=20.7$ Hz, H7), 3.80 (1H, dd, $J=0.9$ Hz, 20.7 Hz, H7), 3.95 (2H, m, OCH_2CH_3), 4.90 (1H, s, H4), 5.16 (1H, d, $J=0.9$ Hz, H2), 7.34 (2H, d, $J=8.5$ Hz, Ar-H), 7.49 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.0 (C7), 62.6 (OCH_2CH_3), 79.7 (C4), 81.3 (C5), 96.9 (C2), 127.9 (Ar-C), 128.3 (Ar-C), 133.0 (Ar-C), 134.1 (Ar-C), 164.8 (C=O), 172.0 (C8), 198.2 (C6); LRMS (ESI^-) m/z : 378.0 ($[\text{M}^{35} - \text{H}]^-$ 100%), 380.1 ($[\text{M}^{37} - \text{H}]^-$ 36%); LRMS (ESI^+) m/z : 402.0 ($[\text{M}^{35} + \text{Na}]^+$ 40%), 404.0 ($[\text{M}^{37} + \text{Na}]^+$ 7%); HRMS (ESI^-) m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$, 378.1103, found 378.1112; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$, 380.1074, found 380.1083.

Ethyl (1*S,3*R**,7*aR**)-1-(4-bromophenyl)-3-(*tert*-butyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134g**



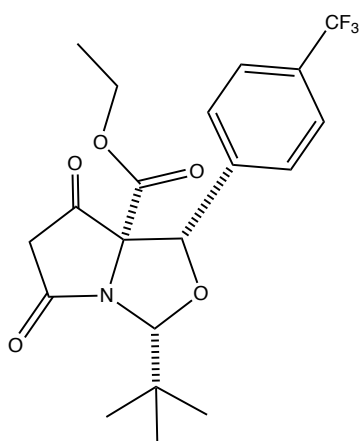
Yield (468 mg, 85%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2973 (C-H), 1721 (C=O), 1623 (C=O); δ_{H} (400 MHz, CDCl_3) 0.99 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.23 (1H, d, $J=20.7$ Hz, H7), 3.81 (1H, dd, $J=0.8$ Hz, 20.7 Hz, H7), 3.95 (2H, m, OCH_2CH_3), 4.88 (1H, s, H4), 5.16 (1H, d, $J=0.8$ Hz, H2), 7.44 (2H, d, $J=8.6$ Hz, Ar-H), 7.50 (2H, d, $J=8.6$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.0 (C7), 62.6 (OCH_2CH_3), 79.8 (C4), 81.2 (C5), 96.9 (C2), 122.3 (Ar-C), 128.3 (Ar-C), 131.2 (Ar-C), 133.5 (Ar-C), 164.9 (C=O), 172.0 (C8), 198.2 (C6); LRMS (ESI^-) m/z : 422.0 ($[\text{M}^{79} - \text{H}]^-$ 100%), 424.0 ($[\text{M}^{81} - \text{H}]^-$ 100%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 422.0609, found 422.0604; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 424.0589, found 424.0584.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-cyanophenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134h**



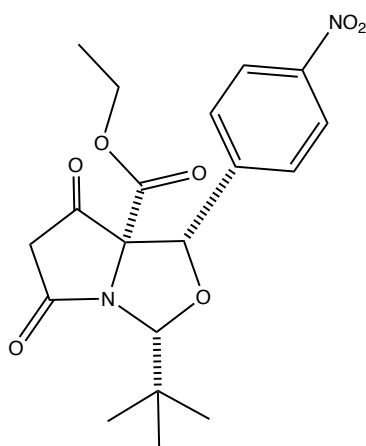
Yield (405 mg, 92%); Yellow oil that solidified overnight; m.p. 164–168°C; $\nu_{\max}/\text{cm}^{-1}$ 2973 (C-H), 2229 (C≡N), 1722 (C=O), 1612 (C=O); δ_{H} (400 MHz, CDCl₃) 1.00 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.04 (9H, s, C(CH₃)₃), 3.26 (1H, d, $J=20.9$ Hz, H7), 3.84 (1H, dd, $J=0.7$ Hz, 20.8 Hz, H7), 3.97 (2H, dq, $J=4.1$ Hz, 7.1 Hz, OCH₂CH₃), 4.95 (1H, s, H4), 5.19 (1H, d, $J=0.8$ Hz, H2), 7.66 (2H, d, $J=8.8$ Hz, Ar-H), 7.70 (2H, d, $J=8.3$ Hz, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.4 ((CH₃)₃), 36.0 (C(CH₃)₃), 45.8 (C7), 62.8 (OCH₂CH₃), 79.1 (C4), 80.9 (C5), 96.8 (C2), 111.9 (Ar-C), 118.8 (C≡N), 127.2 (Ar-C), 131.9 (Ar-C), 139.9 (Ar-C), 164.7 (C=O), 171.9 (C8), 198.2 (C6); LRMS (ESI⁻) m/z : 369.1 ([M – H]⁻ 97%); HRMS (ESI⁻) m/z : [M – H]⁻ calcd. for C₂₀H₂₁N₂O₅, 369.1456, found 369.1451.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-5,7-dioxo-1-(4-(trifluoromethyl)phenyl)dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134i**



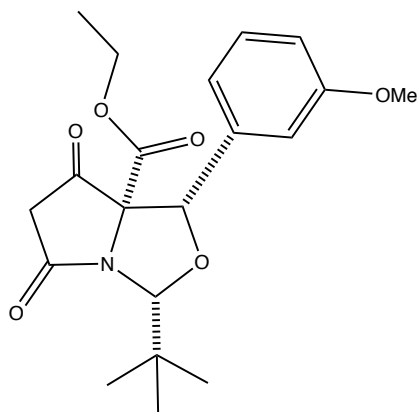
Yield (401 mg, 84%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2974 (C-H), 1724 (C=O), 1622 (C=O); δ_{H} (400 MHz, CDCl₃) 0.95 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.07 (9H, s, C(CH₃)₃), 3.26 (1H, d, $J=20.7$ Hz, H7), 3.84 (1H, dd, $J=0.7$ Hz, 20.7 Hz, H7), 3.93 (2H, m, OCH₂CH₃), 4.97 (1H, s, H4), 5.20 (1H, d, $J=0.8$ Hz, H2), 7.63 (2H, d, $J=8.3$ Hz, Ar-H), 7.70 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 25.5 ((CH₃)₃), 36.0 (C(CH₃)₃), 46.0 (C7), 62.7 (OCH₂CH₃), 79.5 (C4), 81.2 (C5), 96.9 (C2), 125.0 (q, $J=3.8$ Hz, Ar-C), 126.9 (Ar-C), 130.4 (Ar-C), 138.6 (Ar-C), 164.9 (C=O), 171.9 (C8), 198.2 (C6); δ_{F} (376 MHz, CDCl₃) -62.61; LRMS (ESI⁻) m/z : 412.1 ([M – H]⁻ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₀H₂₃NO₅F₃, 414.1523, found 414.1522.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(4-nitrophenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134j**



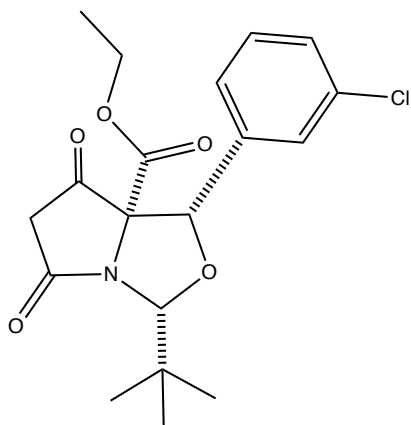
Yield (410 mg, 86%); Orange foamy solid; m.p. 182-185°C; $\nu_{\max}/\text{cm}^{-1}$ 2974 (C-H), 1723 (C=O), 1606 (C=O), 1523 (N-O); δ_{H} (400 MHz, CDCl_3) 1.02 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.28 (1H, d, $J=20.9$ Hz, H7), 3.86 (1H, dd, $J=0.6$ Hz, 20.9 Hz, H7), 3.98 (2H, dq, $J=2.2$ Hz, 7.1 Hz, OCH_2CH_3), 4.99 (1H, s, H4), 5.21 (1H, d, $J=0.8$ Hz, H2), 7.76 (2H, d, $J=9.0$ Hz, Ar-H), 8.23 (2H, d, $J=9.0$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 45.8 (C7), 62.8 (OCH_2CH_3), 79.0 (C4), 80.9 (C5), 96.9 (C2), 123.3 (Ar-C), 127.4 (Ar-C), 141.9 (Ar-C), 147.7 (Ar-C), 164.7 (C=O), 172.0 (C8), 198.2 (C6); LRMS (ESI^-) m/z : 389.1 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_7$, 391.1500, found 391.1501.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(3-methoxyphenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134k**



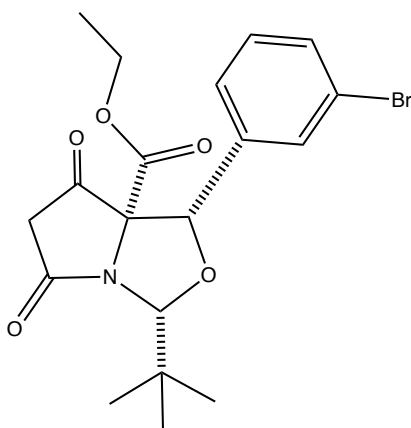
Yield (355 mg, 79%); Orange oil; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1721 (C=O), 1606 (C=O); δ_{H} (400 MHz, CDCl_3) 0.94 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.22 (1H, d, $J=20.6$ Hz, H7), 3.77 (1H, m, H7), 3.82 (3H, s, OCH_3), 3.92 (2H, m, OCH_2CH_3), 4.93 (1H, s, H4), 5.16 (1H, d, $J=0.8$ Hz, H2), 6.86 (1H, m, Ar-H), 7.14 (2H, m, Ar-H), 7.29 (1H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.2 (C7), 55.3 (OCH_3), 62.4 (OCH_2CH_3), 80.2 (C4), 81.7 (C5), 96.9 (C2), 112.3 (Ar-C), 113.7 (Ar-C), 118.9 (Ar-C), 129.2 (Ar-C), 136.0 (Ar-C), 159.4 (Ar-C), 165.0 (C=O), 172.0 (C8), 198.0 (C6); LRMS (ESI^-) m/z : 374.1 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{20}\text{H}_{24}\text{NO}_6$, 374.1609, found 374.1605.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-1-(3-chlorophenyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134l**



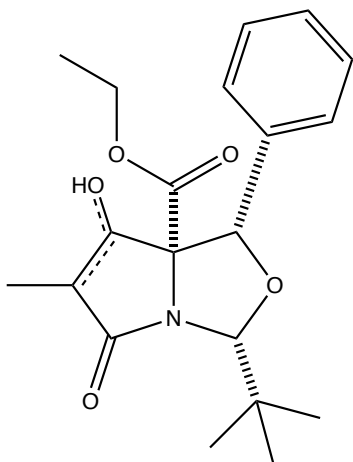
Yield (446 mg, 86%); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 2909 (C-H), 2874 (C-H), 1719 (C=O), 1657 (C=O); δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.23 (1H, d, $J=20.6$ Hz, H7), 3.82 (1H, dd, $J=0.8$ Hz, 20.7 Hz, H7), 3.95 (2H, m, OCH_2CH_3), 4.90 (1H, s, H4), 5.16 (1H, d, $J=0.9$ Hz, H2), 7.30 (2H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.55 (1H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.0 (C7), 62.6 (OCH_2CH_3), 79.5 (C4), 81.3 (C5), 96.9 (C2), 124.8 (Ar-C), 126.7 (Ar-C), 128.4 (Ar-C), 129.4 (Ar-C), 134.1 (Ar-C), 136.6 (Ar-C), 164.9 (C=O), 171.9 (C8), 198.1 (C6); LRMS (ESI^-) m/z : 378.1 ($[\text{M}^{35} - \text{H}]^-$ 47%), 380.1 ($[\text{M}^{37} - \text{H}]^-$ 15%); HRMS (ESI^-) m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$, 378.1114, found 378.1106; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$, 380.1085, found 380.1076.

Ethyl (1*S,3*R**,7*aR**)-1-(3-bromophenyl)-3-(*tert*-butyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 134m**



Yield (432 mg, 76%); Orange oil; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 2908 (C-H), 2873 (C-H), 1718 (C=O), 1657 (C=O); δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.22 (1H, d, $J=20.6$ Hz, H7), 3.82 (1H, dd, $J=0.6$ Hz, 20.5 Hz, H7), 3.95 (2H, m, OCH_2CH_3), 4.89 (1H, s, H4), 5.16 (1H, d, $J=0.8$ Hz, H2), 7.24 (1H, m, Ar-H), 7.47 (2H, m, Ar-H), 7.70 (1H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 46.0 (C7), 62.6 (OCH_2CH_3), 79.4 (C4), 81.3 (C5), 96.9 (C2), 122.2 (Ar-C), 125.2 (Ar-C), 129.6 (Ar-C), 129.6 (Ar-C), 131.3 (Ar-C), 136.8 (Ar-C), 164.9 (C=O), 171.9 (C8), 198.0 (C6); LRMS (ESI^-) m/z : 422.1 ($[\text{M}^{79} - \text{H}]^-$ 31%), 424.1 ($[\text{M}^{81} - \text{H}]^-$ 35%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 422.0609, found 422.0606; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Br}$, 424.0589, found 424.0585.

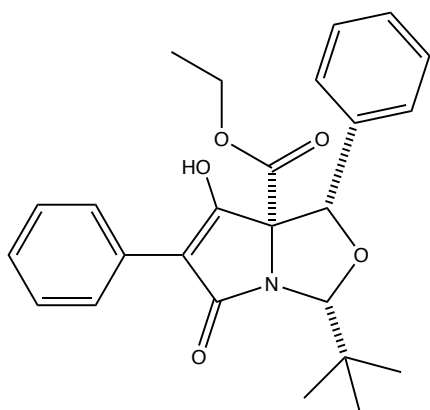
Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-7-hydroxy-6-methyl-5-oxo-1-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 141**



Yield (1.57 g, 62%); Off-white solid; $\nu_{\text{max}}/\text{cm}^{-1}$ 2963 (C-H), 1758 (C=O), 1658 (C=O), 1623 (C=C); 38:35:27 enol:keto_(major):keto_(minor) tautomers; δ_{H} (400 MHz, CDCl_3) 0.85 (3H, t, $J=7.1\text{ Hz}$, OCH_2CH_3 -keto_(minor)), 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$ -keto_(minor+major)), 1.14 (3H, t, $J=7.1\text{ Hz}$, OCH_2CH_3 , underneath $\text{C}(\text{CH}_3)_3$ peak-keto_(major)), 1.16 (9H, s, $\text{C}(\text{CH}_3)_3$ -enol), 1.28 (3H, t, $J=7.1\text{ Hz}$, OCH_2CH_3 -enol), 1.32 (3H, d, $J=7.2\text{ Hz}$, CH_3 -keto_(minor)), 1.44 (3H, d, $J=7.3\text{ Hz}$, CH_3 -keto_(major)), 1.74 (3H, s, CH_3 -enol), 3.46 (1H, q, $J=7.3\text{ Hz}$, $\text{H}7$ -keto_(major)),

3.69 (1H, dq, $J=1.0\text{ Hz}$, 7.2 Hz, $\text{H}7$ -keto_(minor)), 3.81 (1H, m, OCH_2CH_3 -keto_(minor)), 3.88 (1H, m, OCH_2CH_3 -keto_(minor)), 3.96 (1H, dq, $J=7.2\text{ Hz}$, 10.9 Hz, OCH_2CH_3 -keto_(major)), 4.07 (1H, dq, $J=7.1\text{ Hz}$, 10.8 Hz, OCH_2CH_3 -keto_(major)), 4.21 (2H, dq, $J=0.6\text{ Hz}$, 7.1 Hz, OCH_2CH_3), 4.69 (1H, s, $\text{H}4$ -keto_(major)), 4.80 (1H, s, $\text{H}2$ -keto_(major)), 4.89 (1H, s, $\text{H}4$ -keto_(minor)), 5.12 (1H, d, $J=1.0\text{ Hz}$, $\text{H}2$ -keto_(minor)), 7.28-7.60 (10H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 6.3 (CH_3 -enol), 7.3 (CH_3 -keto_(minor)), 13.5 (OCH_2CH_3), 13.7 (CH_3 -keto_(major)), 13.8 (OCH_2CH_3), 14.1 (OCH_2CH_3), 25.8 ($(\text{CH}_3)_3$), 26.2 ($(\text{CH}_3)_3$), 35.5 ($\text{C}(\text{CH}_3)_3$), 36.1 ($\text{C}(\text{CH}_3)_3$), 45.9 ($\text{C}7$ -keto_(major)), 50.5 ($\text{C}7$ -keto_(minor)), 61.8 (OCH_2CH_3), 62.3 (OCH_2CH_3), 62.9 (OCH_2CH_3), 76.0 (C5), 80.7 (C5), 81.0 ($\text{C}4$ -keto_(minor)), 86.1 ($\text{C}4$ -keto_(major)), 97.0 ($\text{C}2$ -keto_(minor)), 97.8 ($\text{C}2$ -keto_(major)), 105.6 ($\text{C}7$ -enol), 126.3 (Ar-C), 126.6 (Ar-C), 128.1 (Ar-C), 128.4 (Ar-C), 128.6 (Ar-C), 129.0 (Ar-C), 134.5 (Ar-C), 134.8 (Ar-C), 165.1 (C=O), 166.3 (C=O), 168.7 (C=O), 170.2 (C=O), 174.6 (C=O), 174.9 (C=O), 180.9 ($\text{C}6$ -enol), 200.6 ($\text{C}6$ -keto); LRMS (ESI^+) m/z : 382.2 ($[\text{M} + \text{Na}]^+$ 77%); LRMS (ESI^-) m/z : 358.1 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{26}\text{NO}_5$, 360.1805, found 360.1806.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1,6-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **142****

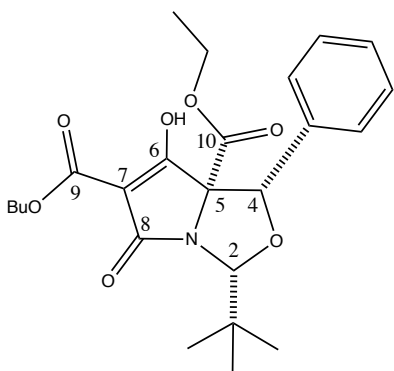


Yield (103 mg, 10%); Pale-yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 2976 (C-H), 1703 (C=O), 1648 (C=O), 1600 (C=C); δ_{H} (400 MHz, CDCl_3) 1.22 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.26 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.14 (2H, m, OCH_2CH_3), 4.84 (1H, s, H4), 4.93 (1H, s, H2), 7.30-7.47 (8H, m, Ar-H), 8.00 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 26.4 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 63.3 (OCH_2CH_3), 75.4 (C5), 86.6 (C4), 98.6 (C2), 107.7 (C7), 126.2 (Ar-C), 127.7 (Ar-C), 128.0 (Ar-C), 128.3 (Ar-C), 128.8 (Ar-C), 129.4 (Ar-C), 134.5 (Ar-C), 165.7 (C=O), 169.1 (C8), 178.4 (C6); LRMS (ESI⁻) m/z : 420.1 ($[\text{M} - \text{H}]^-$ 94%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{25}\text{H}_{26}\text{NO}_5$, 420.1816, found 420.1820.

General procedure for the synthesis of C7-butyl ester tetramic acids:⁴³

To a solution of tetramate **134a-f** (1.0 eq.) in anhydrous DCM was added DMAP (1.2 eq.) and butyl chloroformate (1.2 eq.) and the reaction mixture was refluxed overnight. The reaction mixture was then washed with 2 M HCl (aq.), brine, dried over Na_2SO_4 , filtered and concentrated *in-vacuo* and subsequently purified by flash column chromatography to obtain metal-chelated tetramic acids. The tetramic acids were then re-dissolved in EtOAc, washed with 10% citric acid solution (aq.), dried over Na_2SO_4 , filtered, and evaporated *in-vacuo* to obtain C7-butyl ester tetramic acids **156a-f**.

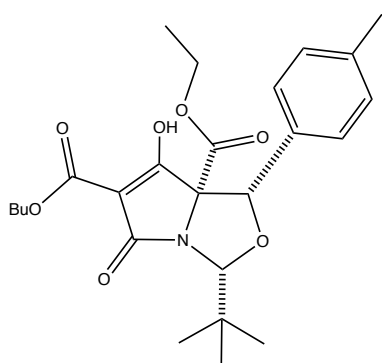
6-Butyl 7*a*-ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6,7*a*(5*H*)-dicarboxylate **156a****



Yield (603 mg, 26%); Red oil; R_f (100% EtOAc) 0.48; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1730 (C=O), 1626 (C=O); δ_{H} (400 MHz, CDCl_3) 0.98 (6H, m, CH_2CH_3 , OCH_2CH_3), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.47 (2H, m, CH_2CH_3), 1.78 (2H, m, OCH_2CH_2), 3.96 (2H, m, OCH_2CH_3), 4.37 (2H, m, OCH_2CH_2), 4.81 (1H, s, H4), 4.91 (1H, s, H2), 7.33-7.55 (5H, m, Ar-H); δ_{C} (101

MHz, CDCl₃) 13.7 (OCH₂CH₃), 13.8 (CH₂CH₃), 19.2 (CH₂CH₃), 25.5 ((CH₃)₃), 30.6 (OCH₂CH₂), 35.6 (C(CH₃)₃), 62.2 (OCH₂CH₃), 66.0 (OCH₂CH₂), 74.9 (C5), 82.9 (C4), 97.1 (C2), 100.4 (C7), 126.5 (Ar-C), 128.0 (Ar-C), 128.3 (Ar-C), 134.6 (Ar-C), 164.5 (C10), 167.5 (C9), 172.1 (C8), 184.9 (C6); LRMS (ESI⁻) *m/z*: 444.1 ([M - H]⁻ 100%); LRMS (ESI⁺) *m/z*: 468.2 ([M + Na]⁺ 95%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₂₄H₃₀NO₇, 444.2028, found 444.2027.

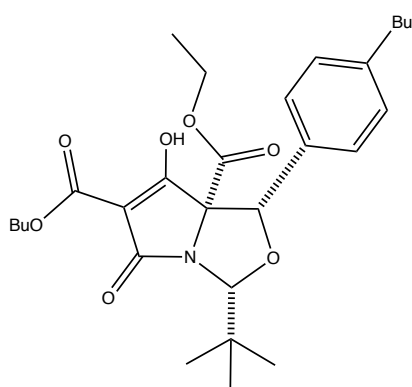
6-Butyl 7a-ethyl (1S*,3R*,7aR*)-3-(tert-butyl)-7-hydroxy-5-oxo-1-(p-tolyl)-1H,3H-pyrrolo[1,2-c]oxazole-6,7a(5H)-dicarboxylate 156b



Yield (138 mg, 17%); Orange oil; R_f (100% EtOAc) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1732 (C=O), 1657 (C=O), 1626 (C=C); δ_{H} (400 MHz, CDCl₃) 0.97 (3H, t, *J*=7.4 Hz, OCH₂CH₃), 1.03 (3H, m, CH₂CH₃), 1.07 (9H, s, C(CH₃)₃), 1.47 (2H, m, CH₂CH₃), 1.78 (2H, m, OCH₂CH₂), 2.36 (3H, s, CH₃), 3.98 (2H, m, OCH₂CH₃), 4.37 (2H, m, OCH₂CH₂), 4.77 (1H, s, H4), 4.90 (1H, s, H2), 7.18 (2H, d, *J*=7.9 Hz, Ar-H), 7.41 (2H, d, *J*=8.0 Hz,

Ar-H); δ_{C} (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 13.8 (CH₂CH₃), 19.2 (CH₂CH₃), 21.4 (CH₃), 25.6 ((CH₃)₃), 30.6 (OCH₂CH₂), 35.6 (C(CH₃)₃), 62.2 (OCH₂CH₃), 66.0 (OCH₂CH₂), 83.1 (C4), 97.0 (C2), 126.5 (Ar-C), 128.7 (Ar-C), 131.4 (Ar-C), 138.0 (Ar-C), 164.5 (C10), 167.6 (C9), 172.2 (C8), 185.0 (C6); LRMS (ESI⁻) *m/z*: 458.1 ([M - H]⁻ 94%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₂₅H₃₂NO₇, 458.2173, found 458.2185.

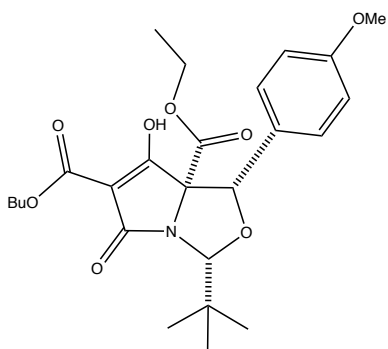
6-Butyl 7a-ethyl (1S*,3R*,7aR*)-3-(tert-butyl)-1-(4-butylphenyl)-7-hydroxy-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-6,7a(5H)-dicarboxylate 156c



Yield (117 mg, 10%); Orange oil; R_f (70% EtOAc in Pet. Ether 40:60) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2932 (C-H), 2872 (C-H), 1732 (C=O), 1657 (C=O), 1627 (C=C); δ_{H} (400 MHz, CDCl₃) 0.90-1.02 (9H, m, CH₂CH₃, CH₂CH₃, OCH₂CH₃), 1.08 (9H, s, C(CH₃)₃), 1.35 (2H, m, CH₂CH₃), 1.47 (2H, m, CH₂CH₃), 1.60 (2H, m, CH₂CH₃), 1.77 (2H, m, OCH₂CH₂), 2.62 (2H, m, CH₂CH₂), 3.95 (2H, m, OCH₂CH₃), 4.36 (2H,

m, OCH₂CH₂), 4.78 (1H, s, H₄), 4.89 (1H, s, H₂), 7.18 (2H, d, *J*=8.2 Hz, Ar-H), 7.43 (2H, d, *J*=8.0 Hz, Ar-H); δ_c (101 MHz, CDCl₃) 13.6 (CH₂CH₃), 13.8 (OCH₂CH₃), 14.0 (CH₂CH₃), 19.1 (CH₂CH₃), 22.4 (CH₂CH₃), 25.5 ((CH₃)₃), 30.6 (OCH₂CH₂), 33.6 (CH₂CH₂), 35.5 (CH₂CH₂), 35.5 (C(CH₃)₃), 62.1 (OCH₂CH₃), 65.9 (OCH₂CH₂), 82.9 (C₄), 97.0 (C₂), 126.4 (Ar-C), 128.0 (Ar-C), 131.6 (Ar-C), 143.0 (Ar-C), 164.5 (C₁₀), 167.6 (C₉), 172.1 (C₈), 184.9 (C₆); LRMS (ESI⁻) *m/z*: 500.2 ([M - H]⁻ 96%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₂₈H₃₈NO₇, 500.2643, found 500.2655.

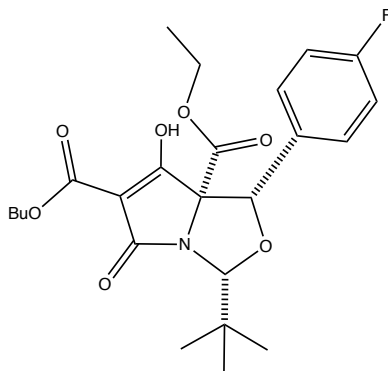
6-Butyl 7a-ethyl (1S*,3R*,7aR*)-3-(tert-butyl)-7-hydroxy-1-(4-methoxyphenyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-6,7a(5H)-dicarboxylate 156d



Yield (490 mg, 19%); Red oil; R_f (100% EtOAc) 0.40; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1731 (C=O), 1658 (C=O), 1617 (C=C); δ_H (400 MHz, CDCl₃) 0.97 (3H, t, *J*=7.4 Hz, OCH₂CH₃), 1.03 (3H, m, CH₂CH₃), 1.07 (9H, s, C(CH₃)₃), 1.46 (2H, m, CH₂CH₃), 1.77 (2H, m, OCH₂CH₂), 3.81 (3H, s, OCH₃), 3.98 (2H, m, OCH₂CH₃), 4.36 (2H, m, OCH₂CH₂), 4.75 (1H, s,

H₄), 4.89 (1H, s, H₂), 6.90 (2H, d, *J*=8.8 Hz, Ar-H), 7.44 (2H, d, *J*=8.7 Hz, Ar-H); δ_c (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 13.8 (CH₂CH₃), 19.2 (CH₂CH₃), 25.6 ((CH₃)₃), 30.6 (OCH₂CH₂), 35.6 (C(CH₃)₃), 55.4 (OCH₃), 62.2 (OCH₂CH₃), 66.0 (OCH₂CH₂), 80.5 (C₅), 83.0 (C₄), 97.1 (C₂), 113.4 (Ar-C), 126.4 (Ar-C), 127.9 (Ar-C), 159.6 (Ar-C), 164.5 (C₁₀), 167.5 (C₉), 172.2 (C₈), 185.0 (C₆); LRMS (ESI⁻) *m/z*: 474.2 ([M - H]⁻ 95%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₂₅H₃₂NO₈, 474.2133, found 474.2134.

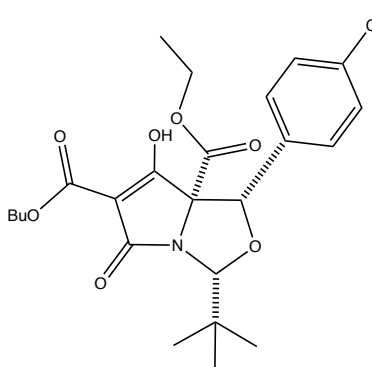
6-Butyl 7a-ethyl (1S*,3R*,7aR*)-3-(tert-butyl)-1-(4-fluorophenyl)-7-hydroxy-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-6,7a(5H)-dicarboxylate 156e



Yield (238 mg, 27%); Red oil; R_f (70% EtOAc in Pet. Ether 40:60) 0.23; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1733 (C=O), 1658 (C=O), 1628 (C=C); δ_H (400 MHz, CDCl₃) 0.97 (3H, t, *J*=7.4 Hz, OCH₂CH₃), 1.04 (3H, t, *J*=7.2 Hz, CH₂CH₃), 1.06 (9H, s, C(CH₃)₃), 1.47 (2H, m, CH₂CH₃), 1.77 (2H, m, OCH₂CH₂), 3.99 (2H, m, OCH₂CH₃), 4.36 (2H, m, OCH₂CH₂), 4.76

(1H, s, H4), 4.91 (1H, s, H2), 7.06 (2H, app t, $J=8.7$ Hz, Ar-H), 7.51 (2H, dd, $J=5.4$ Hz, 8.4 Hz, Ar-H); δ_c (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 13.8 (CH₂CH₃), 19.2 (CH₂CH₃), 25.5 ((CH₃)₃), 30.6 (OCH₂CH₂), 35.6 (C(CH₃)₃), 62.3 (OCH₂CH₃), 66.0 (OCH₂CH₂), 82.2 (C4), 97.1 (C2), 115.0 (d, $J=21.7$ Hz, Ar-C), 128.3 (d, $J=8.1$ Hz, Ar-C), 130.4 (d, $J=3.2$ Hz, Ar-C), 162.7 (d, $J=246.6$ Hz, Ar-C), 164.6 (C10), 167.7 (C9), 172.0 (C8), 184.8 (C6); δ_f (377 MHz, CDCl₃) -113.88; LRMS (ESI⁻) m/z : 462.1 ([M - H]⁻ 95%).

6-Butyl 7a-ethyl (1S*,3R*,7aR*)-3-(tert-butyl)-1-(4-chlorophenyl)-7-hydroxy-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-6,7a(5H)-dicarboxylate 156f



Yield (151 mg, 11%); Orange oil; R_f (70% EtOAc in Pet. Ether 40:60)

0.25; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1733 (C=O), 1658 (C=O), 1628 (C=C); δ_H

(400 MHz, CDCl₃) 0.97 (3H, t, $J=7.4$ Hz, OCH₂CH₃), 1.03 (3H, m,

CH₂CH₃), 1.06 (9H, s, C(CH₃)₃), 1.47 (2H, m, CH₂CH₃), 1.78 (2H, m,

OCH₂CH₂), 4.00 (2H, m, OCH₂CH₃), 4.37 (2H, m, OCH₂CH₂), 4.75 (1H,

s, H4), 4.91 (1H, s, H2), 7.35 (2H, d, $J=8.6$ Hz, Ar-H), 7.48 (2H, d, $J=8.3$

Hz, Ar-H); δ_c (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 13.8 (CH₂CH₃), 19.2 (CH₂CH₃), 25.5 ((CH₃)₃), 30.6

(OCH₂CH₂), 35.6 (C(CH₃)₃), 62.4 (OCH₂CH₃), 66.1 (OCH₂CH₂), 82.2 (C4), 97.1 (C2), 127.9 (Ar-C), 128.2 (Ar-

C), 133.1 (Ar-C), 134.1 (Ar-C), 164.4 (C10), 170.9 (C8), 184.6 (C6); LRMS (ESI⁻) m/z : 478.0 ([M³⁵ - H]⁻

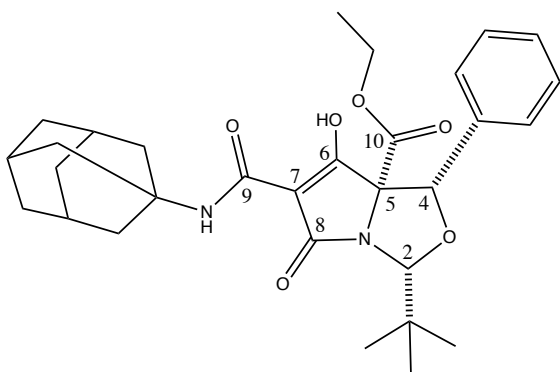
88%), 480.0 ([M³⁷ - H]⁻ 32%); HRMS (ESI⁻) m/z : [M³⁵ - H]⁻ calcd. for C₂₄H₂₉NO₇Cl, 478.1638, found

478.1638; [M³⁷ - H]⁻ calcd. for C₂₄H₂₉NO₇Cl, 480.1613, found 480.1603.

General procedure for the synthesis of C7-carboxamidotetramic acids:^{33,43}

To a solution of C7-butyl ester tetramic acids **156a-f** (1.0 eq.) in anhydrous toluene was added 1-adamantylamine (1.2 eq.). The mixture was heated at reflux overnight. Then the reaction mixture was left to cool to rt, and the solvent was evaporated *in-vacuo* and the concentrate was purified by flash column chromatography to yield tetramates that were chelated with metals. The tetramates were then redissolved in DCM, washed with 10% citric acid solution (aq.), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the desired carboxamides **157a-f**.

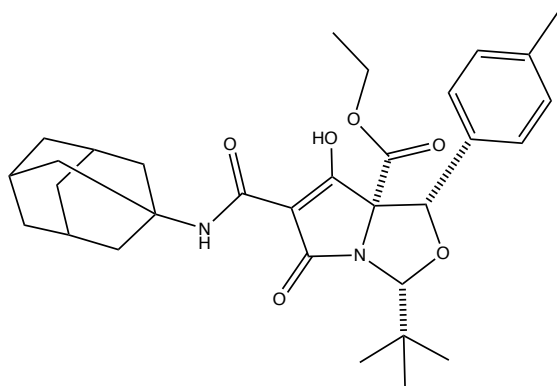
Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 157a**



Yield (242 mg, 42%); Brown foamy solid; m.p. 108-111°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.40; $\nu_{\max}/\text{cm}^{-1}$ 3307 (O-H), 2910 (C-H), 2853 (C-H), 1738 (C=O), 1697 (C=O), 1652 (C=O), 1627 (C=C); AB:CD 54:46 by δ_H -NMR; δ_H (400 MHz, CDCl_3) 0.93 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.96 (3H, t, $J=6.5$ Hz, OCH_2CH_3),

1.08 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.72 (6H, br s, Adamantyl- CH_2), 2.10 (6H, m, Adamantyl- CH_2), 2.15 (3H, br s, Adamantyl-CH), 3.93 (2H, m, OCH_2CH_3), 4.80 (1H, s, H4), 4.80 (1H, s, H4), 4.87 (1H, s, H2), 4.88 (1H, s, H2), 7.29-7.38 (3H, m, Ar-H), 7.54-7.58 (2H, m, Ar-H), 7.67 (1H, br s, NH/OH), 7.98 (1H, br s, NH/OH), 8.59 (2H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 13.7 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 25.5 ($(\text{CH}_3)_3$), 29.5 (Adamantyl-C), 35.5 ($\text{C}(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 41.8 (Adamantyl-C), 54.1 (Adamantyl-C), 54.9 (Adamantyl-C), 61.6 (OCH_2CH_3), 61.9 (OCH_2CH_3), 77.3 (C5), 79.1 (C5), 81.1 (C4), 82.0 (C4), 85.7 (C7), 92.5 (C7), 96.5 (C2), 96.7 (C2), 126.4 (Ar-C), 126.4 (Ar-C), 127.7 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 135.3 (Ar-C), 135.8 (Ar-C), 165.5 (C10), 166.2 (C10), 166.9 (C9), 167.3 (C9), 176.9 (C8), 182.6 (C8), 188.0 (C6), 189.4 (C6); LRMS (ESI^-) m/z : 521.2 ($[\text{M} - \text{H}]^-$ 100%); LRMS (ESI^+) m/z : 545.2 ($[\text{M} + \text{Na}]^+$ 94%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_6$, 521.2657, found 521.2655.

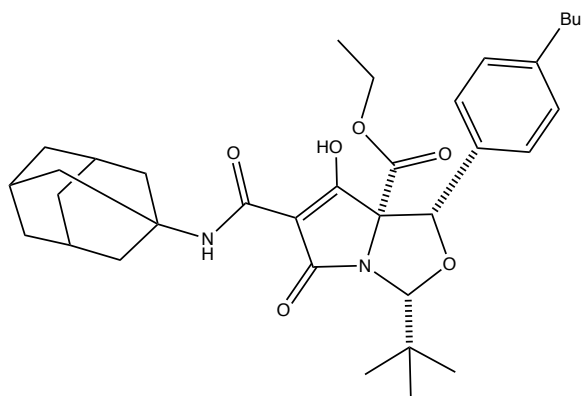
Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-(*p*-tolyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 157b**



Yield (76 mg, 49%); Brown foamy solid; m.p. 115-120°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.68; $\nu_{\max}/\text{cm}^{-1}$ 3309 (O-H), 2910 (C-H), 2853 (C-H), 1738 (C=O), 1694 (C=O), 1651 (C=O), 1625 (C=C); AB:CD 58:42 by δ_{H} -NMR; δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.00 (3H, t, $J=7.2$ Hz, OCH_2CH_3),

1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.72 (6H, br s, Adamantyl- CH_2), 2.09 (6H, m, Adamantyl- CH_2), 2.15 (3H, br s, Adamantyl-CH), 2.35 (3H, s, CH_3), 3.95 (2H, m, OCH_2CH_3), 4.75 (1H, s, H4), 4.85 (1H, s, H2), 4.86 (1H, s, H2), 7.15-7.18 (2H, m, Ar-H), 7.42-7.45 (2H, m, Ar-H), 7.66 (1H, br s, NH/OH), 7.97 (1H, br s, NH/OH), 9.96 (2H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 21.4 (CH_3), 25.4 ($(\text{CH}_3)_3$), 25.5 ($(\text{CH}_3)_3$), 29.4 (Adamantyl-C), 35.4 ($\text{C}(\text{CH}_3)_3$), 35.5 ($\text{C}(\text{CH}_3)_3$), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.6 (Adamantyl-C), 41.7 (Adamantyl-C), 54.0 (Adamantyl-C), 54.8 (Adamantyl-C), 61.5 (OCH_2CH_3), 61.8 (OCH_2CH_3), 79.0 (C5), 81.1 (C4), 82.1 (C4), 85.6 (C7), 92.7 (C7), 96.4 (C2), 96.6 (C2), 126.3 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 132.1 (Ar-C), 132.7 (Ar-C), 137.2 (Ar-C), 137.5 (Ar-C), 165.3 (C10), 166.0 (C10), 166.8 (C9), 167.2 (C9), 176.8 (C8), 182.6 (C8), 187.9 (C6), 189.1 (C6); LRMS (ESI^-) m/z : 535.2 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{31}\text{H}_{39}\text{N}_2\text{O}_6$, 535.2803, found 535.2816.

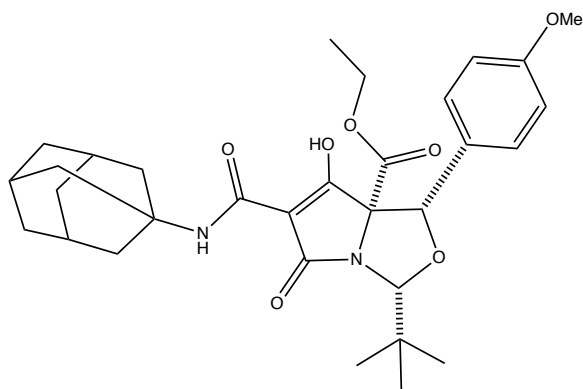
Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-1-(4-butylphenyl)-7-hydroxy-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 157c**



Yield (47 mg, 35%); Brown foamy solid; m.p. 84-90°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.65; $\nu_{\max}/\text{cm}^{-1}$ 3309 (O-H), 2956 (C-H), 2911 (C-H), 2854 (C-H), 1738 (C=O), 1698 (C=O), 1651 (C=O), 1627 (C=C); AB:CD 58:42 by δ_{H} -NMR; δ_{H} (400 MHz, CDCl_3) 0.90-0.98 (6H, m, CH_2CH_3 , OCH_2CH_3), 1.08 (9H, s,

$\text{C}(\text{CH}_3)_3$, 1.33 (2H, m, CH_2CH_3), 1.59 (2H, m, CH_2CH_2), 1.72 (6H, br s, Adamantyl- CH_2), 2.09 (6H, m, Adamantyl- CH_2), 2.15 (3H, br s, Adamantyl-CH), 2.61 (2H, t, $J=7.7$ Hz, CH_2CH_2), 3.94 (2H, m, OCH_2CH_3), 4.76 (1H, s, H4), 4.77 (1H, s, H4), 4.85 (1H, s, H2), 4.85 (1H, s, H2), 7.15-7.18 (2H, m, Ar-H), 7.43-7.46 (2H, m, Ar-H), 7.65 (1H, br s, NH/OH), 7.98 (1H, br s, NH/OH), 9.78 (2H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 13.7 (OCH_2CH_3), 14.1 (CH_2CH_3), 22.4 (CH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 25.6 ($(\text{CH}_3)_3$), 29.5 (Adamantyl-C), 33.7 (CH_2CH_2), 33.8 (CH_2CH_2), 35.5 ($\text{C}(\text{CH}_3)_3$), 35.5 (CH_2CH_2), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 41.7 (Adamantyl-C), 54.0 (Adamantyl-C), 54.8 (Adamantyl-C), 61.5 (OCH_2CH_3), 61.8 (OCH_2CH_3), 77.3 (C5), 79.2 (C5), 81.3 (C4), 82.2 (C4), 85.6 (C7), 92.8 (C7), 96.5 (C2), 96.7 (C2), 126.3 (Ar-C), 126.4 (Ar-C), 127.9 (Ar-C), 128.0 (Ar-C), 132.4 (Ar-C), 132.9 (Ar-C), 142.4 (Ar-C), 142.6 (Ar-C), 165.4 (C10), 166.1 (C10), 166.8 (C9), 167.2 (C9), 176.9 (C8), 182.6 (C8), 187.9 (C6), 189.2 (C6); LRMS (ESI⁻) m/z : 577.3 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{34}\text{H}_{45}\text{N}_2\text{O}_6$, 577.3283, found 577.3279.

Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-7-hydroxy-1-(4-methoxyphenyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 157d**

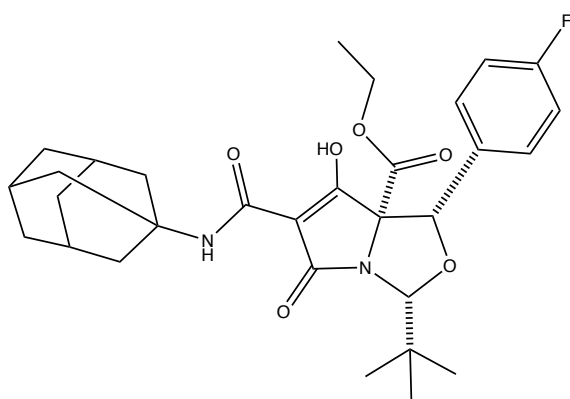


Yield (142 mg, 26%); Brown foamy solid; m.p. 108-111°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.45; $\nu_{\text{max}}/\text{cm}^{-1}$ 3310 (O-H), 2910 (C-H), 2853 (C-H), 1736 (C=O), 1696 (C=O), 1651 (C=O), 1624 (C=C); AB:CD 55:45 by δ_{H} -NMR; δ_{H} (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.01 (3H, t, $J=7.1$ Hz, OCH_2CH_3),

1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.71 (6H, br s, Adamantyl- CH_2), 2.09 (6H, m, Adamantyl- CH_2), 2.15 (3H, br s, Adamantyl-CH), 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.96 (2H, m, OCH_2CH_3), 4.73 (1H, s, H4), 4.74 (1H, s, H4), 4.84 (1H, s, H2), 4.85 (1H, s, H2), 6.88-6.91 (2H, m, Ar-H), 7.08 (2H, br s, NH/OH), 7.44-7.48 (2H, m, Ar-H), 7.65 (1H, br s, NH/OH), 7.96 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 25.6 ($(\text{CH}_3)_3$), 29.5 (Adamantyl-C), 35.5 ($\text{C}(\text{CH}_3)_3$), 35.5 ($\text{C}(\text{CH}_3)_3$), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 41.7 (Adamantyl-C), 54.1 (Adamantyl-C), 54.9 (Adamantyl-C), 55.4

(OCH₃), 61.6 (OCH₂CH₃), 61.9 (OCH₂CH₃), 79.0 (C5), 81.1 (C4), 82.0 (C4), 85.6 (C7), 92.7 (C7), 96.5 (C2), 96.7 (C2), 113.3 (Ar-C), 113.4 (Ar-C), 127.2 (Ar-C), 127.7 (Ar-C), 159.2 (Ar-C), 159.4 (Ar-C), 165.4 (C10), 166.1 (C10), 166.8 (C9), 167.2 (C9), 176.9 (C8), 182.7 (C8), 188.0 (C6), 189.3 (C6); LRMS (ESI⁻) *m/z*: 551.2 ([M – H]⁻ 95%); HRMS (ESI⁻) *m/z*: [M – H]⁻ calcd. for C₃₁H₃₉N₂O₇, 551.2752, found 551.2768.

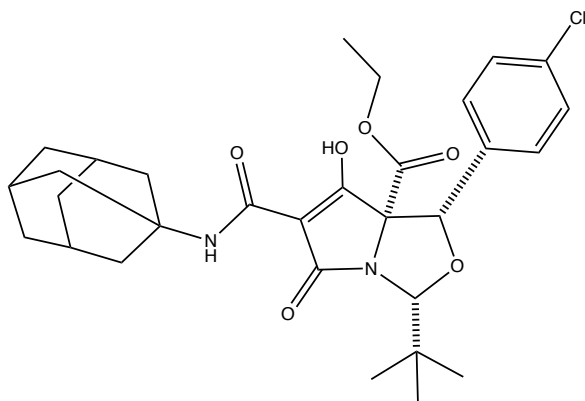
Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-1-(4-fluorophenyl)-7-hydroxy-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 157e**



Yield (151 mg, 54%); Brown foamy solid; m.p. 98-102°C; *R_f* (30% EtOAc in Pet. Ether 40:60) 0.68; $\nu_{\text{max}}/\text{cm}^{-1}$ 3305 (O-H), 2911 (C-H), 2854 (C-H), 1739 (C=O), 1697 (C=O), 1653 (C=O), 1628 (C=C); AB:CD 53:47 by δ_{F} -NMR; δ_{H} (400 MHz, CDCl₃) 1.00 (3H, m, OCH₂CH₃), 1.06 (9H, s, C(CH₃)₃), 1.72 (6H, br s,

Adamantyl-CH₂), 2.09 (6H, m, Adamantyl-CH₂), 2.15 (3H, br s, Adamantyl-CH), 3.95 (2H, m, OCH₂CH₃), 4.75 (1H, s, H4), 4.86 (1H, s, H2), 7.05 (2H, app t, *J*=8.6 Hz, Ar-H), 7.53 (2H, m, Ar-H), 7.70 (1H, br s, NH/OH), 7.98 (1H, br s, NH/OH); δ_{C} (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 25.4 ((CH₃)₃), 29.5 (Adamantyl-C), 35.5 (C(CH₃)₃), 35.5 (C(CH₃)₃), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 54.3 (Adamantyl-C), 55.0 (Adamantyl-C), 61.7 (OCH₂CH₃), 61.9 (OCH₂CH₃), 78.8 (C5), 80.5 (C4), 81.3 (C4), 85.6 (C7), 91.9 (C7), 96.5 (C2), 96.7 (C2), 114.7 (d, *J*=21.0 Hz, Ar-C), 114.9 (d, *J*=21.5 Hz, Ar-C), 128.1 (d, *J*=8.2 Hz, Ar-C), 131.1 (d, *J*=3.0 Hz, Ar-C), 131.6 (d, *J*=3.0 Hz, Ar-C), 162.5 (d, *J*=245.8 Hz, Ar-C), 165.5 (C10), 166.1 (C10), 166.9 (C9), 167.2 (C9), 176.9 (C8), 182.5 (C8), 187.9 (C6), 189.7 (C6); δ_{F} (377 MHz, CDCl₃) -114.56, -114.97; LRMS (ESI⁻) *m/z*: 539.2 ([M – H]⁻ 83%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₀H₃₈N₂O₆F, 541.2708, found 541.2707.

Ethyl (1*S,3*R**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-3-(*tert*-butyl)-1-(4-chlorophenyl)-7-hydroxy-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **157f****

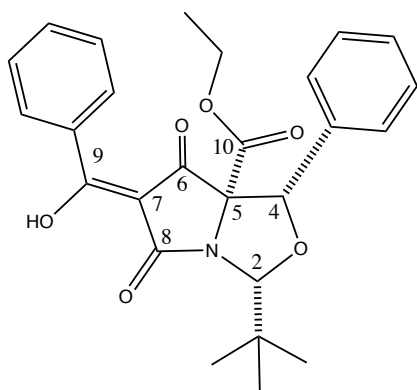


Yield (93 mg, 60%); Brown foamy solid; m.p. 131-135°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.63; $\nu_{\max}/\text{cm}^{-1}$ 3309 (O-H), 2911 (C-H), 2853 (C-H), 1757 (C=O), 1740 (C=O), 1697 (C=O), 1628 (C=C); AB:CD 55:45 by δ_H -NMR; δ_H (400 MHz, CDCl_3) 0.97-1.03 (6H, m, OCH_2CH_3), 1.05 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.72 (6H, br s, Adamantyl- CH_2), 2.09 (6H, m, Adamantyl- CH_2), 2.16 (3H, br s, Adamantyl-CH), 3.96 (2H, m, OCH_2CH_3), 4.74 (1H, s, H4), 4.86 (1H, s, H2), 4.87 (1H, s, H2), 7.31-7.34 (2H, m, Ar-H), 7.49-7.53 (2H, m, Ar-H), 7.71 (1H, br s, NH/OH), 7.95 (1H, br s, NH/OH); δ_C (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 25.4 ($(\text{CH}_3)_3$), 29.4 (Adamantyl-C), 35.5 ($\text{C}(\text{CH}_3)_3$), 35.5 ($\text{C}(\text{CH}_3)_3$), 36.0 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 41.7 (Adamantyl-C), 54.3 (Adamantyl-C), 55.0 (Adamantyl-C), 61.8 (OCH_2CH_3), 62.0 (OCH_2CH_3), 77.1 (C5), 78.7 (C5), 80.4 (C4), 81.2 (C4), 85.6 (C7), 91.7 (C7), 96.5 (C2), 96.6 (C2), 127.8 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 128.1 (Ar-C), 133.4 (Ar-C), 133.7 (Ar-C), 134.0 (Ar-C), 134.4 (Ar-C), 165.5 (C10), 166.1 (C10), 166.9 (C9), 167.2 (C9), 176.9 (C8), 182.5 (C8), 187.9 (C6), 189.8 (C6); LRMS (ESI⁻) m/z : 555.2 ($[\text{M}^{35} - \text{H}]^-$ 97%), 557.2 ($[\text{M}^{37} - \text{H}]^-$ 36%); HRMS (ESI⁻) m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_6\text{Cl}$, 555.2267, found 555.2275; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_6\text{Cl}$, 557.2247, found 557.2241.

General procedure for the synthesis of C7-acyltetramates:^{39,43,64-65}

To a stirring solution of tetramic acid **134a** (1 eq.) in DCM was added DCC (1.1 eq.) and DMAP (1.3 eq.). The solution was cooled to 0°C and the respective carboxylic acid (1.1 eq.) was added portion wise. The reaction mixture was then left to stir at rt overnight. The suspension was then filtered, and the filtrate was concentrated *in-vacuo*. The concentrate was then purified by flash column chromatography to obtain metal-chelated tetramic acids which were then re-dissolved in DCM, washed with 10% citric acid solution (aq.), dried over Na_2SO_4 , filtered, and then concentrated *in-vacuo* to obtain the desired product **161a-s**.

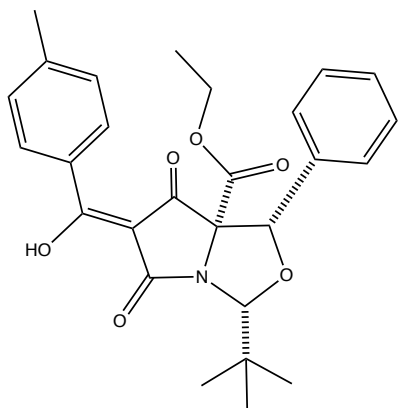
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(phenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161a**



Yield (131 mg, 32%); Red oil; R_f (100% EtOAc) 0.48; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1760 (C=O), 1712 (C=O), 1652 (C=O), 1592 (C=C); δ_H (400 MHz, CDCl_3) 1.02 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.17 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.02 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.89 (1H, s, H4), 5.10 (1H, s, H2), 7.36 (3H, m, Ar-H), 7.57 (4H, m, Ar-H), 7.68 (1H, m, Ar-H), 8.24 (2H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3),

25.5 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 61.9 (OCH_2CH_3), 78.0 (C5), 80.9 (C4), 97.2 (C2), 100.3 (C7), 126.5 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.5 (Ar-C), 130.3 (Ar-C), 131.1 (Ar-C), 134.8 (Ar-C), 134.9 (Ar-C), 165.5 (C10), 182.4 (C8), 183.7 (C9), 186.8 (C6); LRMS (ESI^-) m/z : 448.1 ($[\text{M} - \text{H}]^-$ 94%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{26}\text{NO}_6$, 448.1766, found 448.1758.

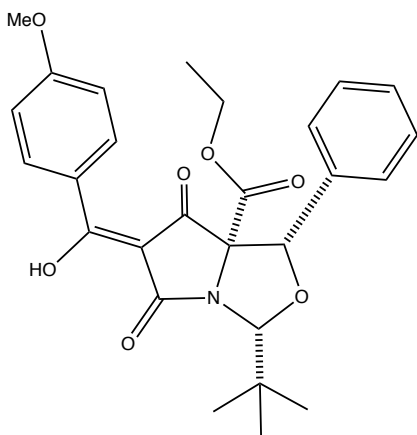
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(*p*-tolyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161b**



Yield (112 mg, 26%); Orange oil; R_f (100% EtOAc) 0.58; $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1761 (C=O), 1737 (C=O), 1710 (C=O), 1651 (C=O), 1588 (C=C); δ_H (400 MHz, CDCl_3) 1.02 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.16 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.48 (3H, s, CH_3), 4.01 (2H, dq, $J=2.0$ Hz, 7.2 Hz, OCH_2CH_3), 4.87 (1H, s, H4), 5.08 (1H, s, H2), 7.31-7.42 (5H, m, Ar-H), 7.58 (2H, d, $J=7.4$ Hz, Ar-H), 8.18 (2H, d, $J=7.9$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 22.1 (CH_3), 25.5 ($(\text{CH}_3)_3$), 35.6

($\text{C}(\text{CH}_3)_3$), 61.9 (OCH_2CH_3), 77.9 (C5), 81.0 (C4), 97.2 (C2), 99.9 (C7), 126.5 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.4 (Ar-C), 129.2 (Ar-C), 130.5 (Ar-C), 135.0 (Ar-C), 146.4 (Ar-C), 165.6 (C10), 182.6 (C8), 183.6 (C9), 186.9 (C6); LRMS (ESI^-) m/z : 462.1 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{28}\text{NO}_6$, 462.1922, found 462.1914.

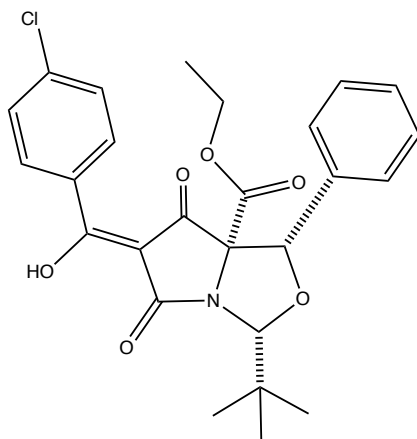
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(4-methoxyphenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161c**



Yield (89 mg, 18%); Orange solid/oil; R_f (100% EtOAc) 0.53; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1759 (C=O), 1736 (C=O), 1705 (C=O), 1650 (C=O), 1584 (C=C); δ_H (400 MHz, CDCl_3) 0.99 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.90 (3H, s, OCH_3), 3.98 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.84 (1H, s, H4), 5.05 (1H, s, H2), 7.00 (2H, d, $J=9.0$ Hz, Ar-H), 7.28-7.37 (3H, m, Ar-H), 7.57 (2H, m, Ar-H), 8.35 (2H, d, $J=9.0$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.5

((CH_3)₃), 35.6 ($\text{C}(\text{CH}_3)_3$), 55.7 (OCH_3), 61.9 (OCH_2CH_3), 77.8 (C5), 81.1 (C4), 97.2 (C2), 99.2 (C7), 114.0 (Ar-C), 126.6 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 133.2 (Ar-C), 135.1 (Ar-C), 165.4 (Ar-C), 165.7 (C10), 182.8 (C8), 183.0 (C9), 187.0 (C6); LRMS (ESI^-) m/z : 478.1 ($[\text{M} - \text{H}]^-$ 51%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{28}\text{NO}_7$, 478.1871, found 478.1861.

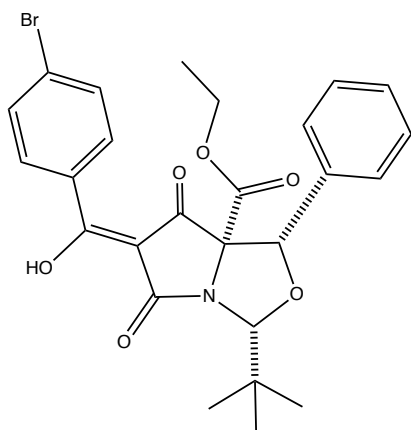
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-((4-chlorophenyl)(hydroxy)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161d**



Yield (206 mg, 39%); Red solid; m.p. 42-47°C; R_f (100% EtOAc) 0.45; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1710 (C=O), 1652 (C=O), 1588 (C=C); δ_H (400 MHz, CDCl_3) 1.02 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.17 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.01 (2H, m, OCH_2CH_3), 4.88 (1H, s, H4), 5.09 (1H, s, H2), 7.33-7.41 (3H, m, Ar-H), 7.53 (2H, d, $J=8.7$ Hz, Ar-H), 7.58 (2H, d, $J=7.4$ Hz, Ar-H), 8.25 (2H, d, $J=8.2$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.5 ((CH_3)₃), 35.6 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3),

77.9 (C5), 81.0 (C4), 97.3 (C2), 100.4 (C7), 126.5 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 128.9 (Ar-C), 129.4 (Ar-C), 131.7 (Ar-C), 134.8 (Ar-C), 141.3 (Ar-C), 165.3 (C10), 182.2 (C8), 182.2 (C9), 186.9 (C6); LRMS (ESI^-) m/z : 482.1 ($[\text{M}^{35} - \text{H}]^-$ 100%), 484.1 ($[\text{M}^{37} - \text{H}]^-$ 36%); HRMS (ESI^-) m/z : $[\text{M}^{35} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Cl}$, 482.1365, found 482.1369; $[\text{M}^{37} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Cl}$, 484.1340, found 484.1344.

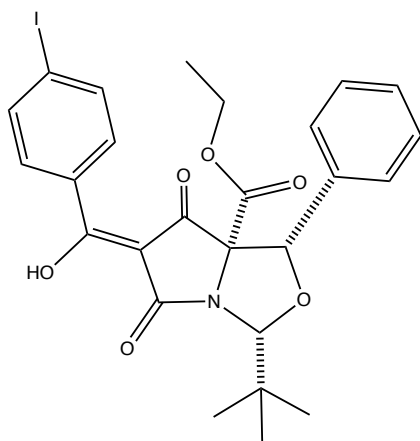
Ethyl (1*S,3*R**,7*aR**,*Z*)-6-((4-bromophenyl)(hydroxy)methylene)-3-(*tert*-butyl)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161e**



Yield (181 mg, 35%); Orange solid; m.p. 43-48°C; R_f (100% EtOAc) 0.55; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1759 (C=O), 1735 (C=O), 1711 (C=O), 1651 (C=O), 1586 (C=C); δ_H (400 MHz, CDCl_3) 1.01 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.16 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.01 (2H, m, OCH_2CH_3), 4.88 (1H, s, H4), 5.08 (1H, s, H2), 7.34-7.41 (3H, m, Ar-H), 7.57 (2H, d, $J=7.3$ Hz, Ar-H), 7.69 (2H, d, $J=8.7$ Hz, Ar-H), 8.15 (2H, d, $J=8.5$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$),

62.0 (OCH_2CH_3), 77.9 (C5), 81.0 (C4), 97.3 (C2), 126.5 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 129.9 (Ar-C), 130.2 (Ar-C), 131.8 (Ar-C), 131.9 (Ar-C), 134.8 (Ar-C), 165.3 (C10), 182.5 (C8), 182.5 (C9), 187.0 (C6); LRMS (ESI^-) m/z : 526.0 ($[\text{M}^{79} - \text{H}]^-$ 95%), 528.0 ($[\text{M}^{81} - \text{H}]^-$ 97%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Br}$, 526.0860, found 526.0863; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Br}$, 528.0847, found 528.0844.

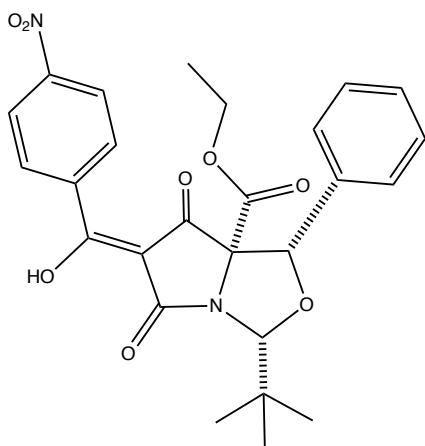
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(4-iodophenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161f**



Yield (224 mg, 37%); Pink foamy solid/oil; R_f (100% EtOAc) 0.65; $\nu_{\max}/\text{cm}^{-1}$ 3320 (O-H), 2932 (C-H), 2855 (C-H), 1760 (C=O), 1713 (C=O), 1653 (C=O), 1584 (C=C); δ_H (500 MHz, CDCl_3) 0.98 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.97 (2H, dq, $J=2.5$ Hz, 7.2 Hz, OCH_2CH_3), 4.85 (1H, s, H4), 5.06 (1H, s, H2), 7.29-7.39 (3H, m, Ar-H), 7.52 (2H, d, $J=8.6$ Hz, Ar-H), 7.89 (2H, d, $J=8.5$ Hz, Ar-H), 7.94 (2H, d, $J=8.5$ Hz, Ar-H); δ_C (126 MHz, CDCl_3) 13.7

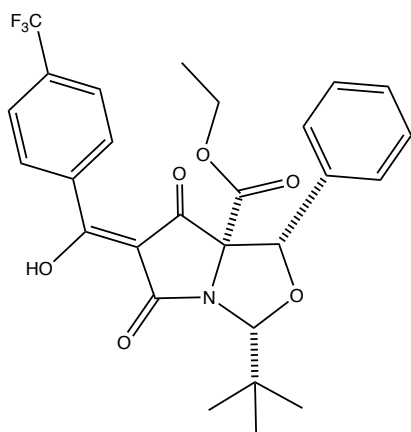
(OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 62.1 (OCH_2CH_3), 78.1 (C5), 81.0 (C4), 97.3 (C2), 100.6 (Ar-C), 103.3 (C7), 126.5 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 131.4 (Ar-C), 134.8 (Ar-C), 138.0 (Ar-C), 165.4 (C10), 182.2 (C8), 182.7 (C9), 186.9 (C6); LRMS (ESI^-) m/z : 574.0 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{I}$, 574.0732, found 574.0723.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(4-nitrophenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161g**



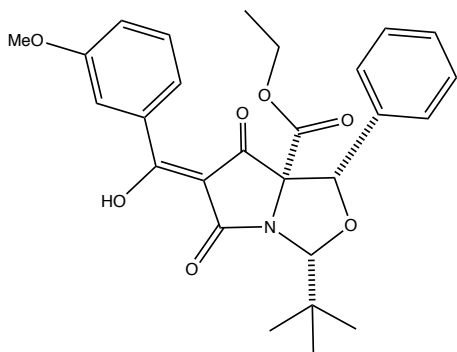
Yield (159 mg, 30%); Red oil/solid; m.p. 160-164°C; R_f (100% EtOAc) 0.60; $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1716 (C=O), 1654 (C=O), 1612 (C=O), 1568 (C=C); δ_H (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.98 (2H, dq, $J=3.9$ Hz, 7.1 Hz, OCH_2CH_3), 4.88 (1H, s, H4), 5.07 (1H, s, H2), 7.31-7.37 (3H, m, Ar-H), 7.52 (2H, d, $J=7.2$ Hz, Ar-H), 8.34 (4H, s, Ar-H), 11.38 (1H, br s, OH); δ_C (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 62.2 (OCH_2CH_3), 78.1 (C5), 81.0 (C4), 97.5 (C2), 123.4 (Ar-C), 126.4 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 131.3 (Ar-C), 134.5 (Ar-C), 136.5 (Ar-C), 150.9 (Ar-C), 165.1 (C10); LRMS (ESI^-) m/z : 493.1 ($[\text{M} - \text{H}]^-$ 94%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_8$, 493.1616, found 493.1609.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(4-(trifluoromethyl)phenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161h**



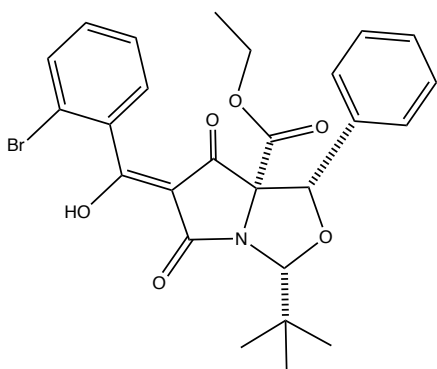
Yield (190 mg, 41%); Orange oil; R_f (100% EtOAc) 0.63; $\nu_{\max}/\text{cm}^{-1}$ 2963 (C-H), 1715 (C=O), 1653 (C=O), 1596 (C=C); δ_H (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.99 (2H, m, OCH_2CH_3), 4.87 (1H, s, H4), 5.07 (1H, s, H2), 7.32-7.38 (3H, m, Ar-H), 7.54 (2H, d, $J=8.0$ Hz, Ar-H), 7.79 (2H, d, $J=8.3$ Hz, Ar-H), 8.30 (2H, d, $J=8.2$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 62.1 (OCH_2CH_3), 78.1 (C5), 81.0 (C4), 97.4 (C2), 125.4 (q, $J=3.7$ Hz, Ar-C), 126.5 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 130.6 (Ar-C), 134.7 (Ar-C), 165.2 (C10), 182.0 (C8), 182.0 (C9), 186.8 (C6); δ_F (376 MHz, CDCl_3) -63.36; LRMS (ESI^-) m/z : 516.1 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{25}\text{NO}_6\text{F}_3$, 516.1639, found 516.1628.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(3-methoxyphenyl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161i**



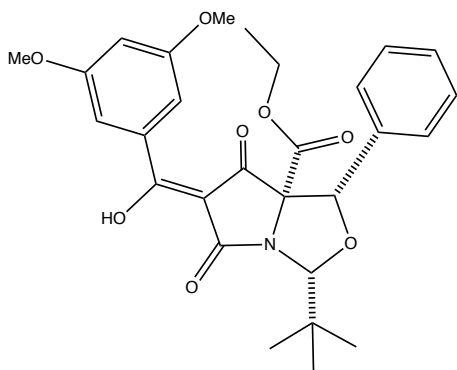
Yield (198 mg, 44%); Orange oil; R_f (100% EtOAc) 0.45; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1760 (C=O), 1734 (C=O), 1711 (C=O), 1653 (C=O), 1592 (C=C); δ_H (400 MHz, CDCl_3) 1.00 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.88 (3H, s, OCH_3), 3.99 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.84 (1H, s, H4), 5.06 (1H, s, H2), 7.20 (1H, ddd, $J=1.0$ Hz, 2.6 Hz, 8.3 Hz, Ar-H), 7.28-7.39 (3H, m, Ar-H), 7.43 (1H, t, $J=8.0$ Hz, Ar-H), 7.55 (2H, d, $J=7.3$ Hz, Ar-H), 7.80 (1H, m, Ar-H), 7.85 (1H, d, $J=7.8$ Hz, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 55.6 (OCH_3), 61.9 (OCH_2CH_3), 77.9 (C5), 80.9 (C4), 97.2 (C2), 100.3 (C7), 114.6 (Ar-C), 121.4 (Ar-C), 122.8 (Ar-C), 126.6 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 129.5 (Ar-C), 132.3 (Ar-C), 134.9 (Ar-C), 159.5 (Ar-C), 165.5 (C10), 182.5 (C8), 183.5 (C9), 186.7 (C6); LRMS (ESI^-) m/z : 478.1 ($[\text{M} - \text{H}]^-$ 96%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{27}\text{H}_{28}\text{NO}_7$, 478.1871, found 478.1867.

Ethyl (1*S,3*R**,7*aR**,*Z*)-6-((2-bromophenyl)(hydroxy)methylene)-3-(*tert*-butyl)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161j**



Yield (84 mg, 12%); Orange oil; R_f (100% EtOAc) 0.70; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1761 (C=O), 1725 (C=O), 1656 (C=O), 1606 (C=C); δ_H (400 MHz, CDCl_3) 0.96 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.94 (2H, dq, $J=1.2$ Hz, 7.1 Hz, OCH_2CH_3), 4.88 (1H, s, H4), 5.08 (1H, s, H2), 7.29-7.53 (8H, m, Ar-H), 7.70 (1H, dd, $J=1.3$ Hz, 7.8 Hz, Ar-H), 11.40 (1H, br s, OH); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3), 80.7 (C4), 97.2 (C2), 126.4 (Ar-C), 127.4 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 130.4 (Ar-C), 133.0 (Ar-C), 133.6 (Ar-C), 134.8 (Ar-C), 165.1 (C10); LRMS (ESI^-) m/z : 526.0 ($[\text{M}^{79} - \text{H}]^-$ 93%), 528.0 ($[\text{M}^{81} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Br}$, 526.0860, found 526.0863; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{Br}$, 528.0841, found 528.0844.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-((3,5-dimethoxyphenyl)(hydroxy)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161k**



Yield (77 mg, 17%); Orange oil; R_f (100% EtOAc) 0.45; $\nu_{\max}/\text{cm}^{-1}$

^{12961} (C-H), 1760 (C=O), 1736 (C=O), 1711 (C=O), 1653 (C=O),

1562 (C=C); δ_H (400 MHz, CDCl_3) 1.01 (3H, t, $J=7.2$ Hz,

OCH_2CH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.86 (6H, s, OCH_3 , OCH_3), 3.99

(2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.84 (1H, s, H4), 5.06 (1H, s, H2),

6.75 (1H, t, $J=2.3$ Hz, Ar-H), 7.28-7.60 (7H, m, Ar-H); δ_C (101

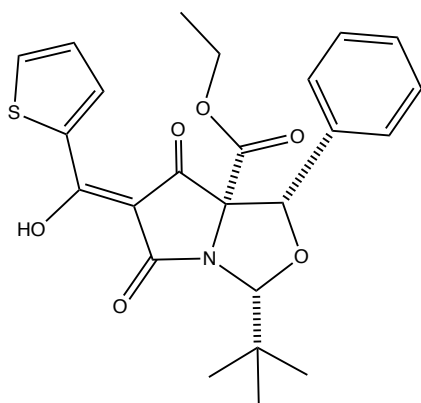
MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 55.8 (OCH_3), 61.9 (OCH_2CH_3), 77.8 (C5), 81.0

(C4), 97.2 (C2), 100.4 (C7), 107.8 (Ar-C), 107.9 (Ar-C), 126.6 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 132.8 (Ar-

C), 134.9 (Ar-C), 160.6 (Ar-C), 165.5 (C10), 182.7 (C8), 183.5 (C9), 186.6 (C6); LRMS (ESI^-) m/z : 508.1

($[\text{M} - \text{H}]^-$ 45%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{28}\text{H}_{30}\text{NO}_8$, 508.1977, found 508.1968.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(hydroxy(thiophen-2-yl)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161l**



Yield (57 mg, 13%); Yellow foamy solid; m.p. 80-84°C; R_f (100%

EtOAc) 0.60; $\nu_{\max}/\text{cm}^{-1}$ 3400 (O-H), 2974 (C-H), 2934 (C-H), 1758

(C=O), 1736 (C=O), 1704 (C=O), 1652 (C=O), 1558 (C=C); δ_H (400

MHz, CDCl_3) 0.90 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$),

3.89 (2H, m, OCH_2CH_3), 4.78 (1H, s, H4), 4.97 (1H, s, H2), 7.20 (1H,

dd, $J=4.1$ Hz, 4.9 Hz, Ar-H), 7.22-7.32 (3H, m, Ar-H), 7.49 (2H, m,

Ar-H), 7.82 (1H, dd, $J=1.1$ Hz, 4.9 Hz, Ar-H), 9.19 (1H, dd, $J=1.2$ Hz, 4.1 Hz, Ar-H); δ_C (101 MHz, CDCl_3)

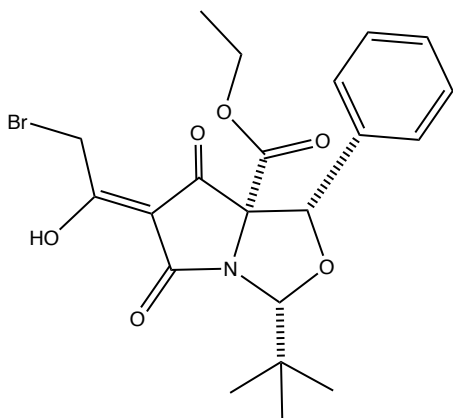
13.7 (OCH_2CH_3), 25.5 ($(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 62.0 (OCH_2CH_3), 81.2 (C4), 97.3 (C2), 126.5 (Ar-C), 126.6

(Ar-C), 127.9 (Ar-C), 128.0 (Ar-C), 129.3 (Ar-C), 135.0 (Ar-C), 137.6 (Ar-C), 138.6 (Ar-C), 165.5 (C10),

182.8 (C8), 182.8 (C9), 186.6 (C6); LRMS (ESI^-) m/z : 454.1 ($[\text{M} - \text{H}]^-$ 26%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$

calcd. for $\text{C}_{24}\text{H}_{24}\text{NO}_6\text{S}$, 454.1330, found 454.1320.

Ethyl (1*S,3*R**,7*aR**,*Z*)-6-(2-bromo-1-hydroxyethylidene)-3-(*tert*-butyl)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161m**

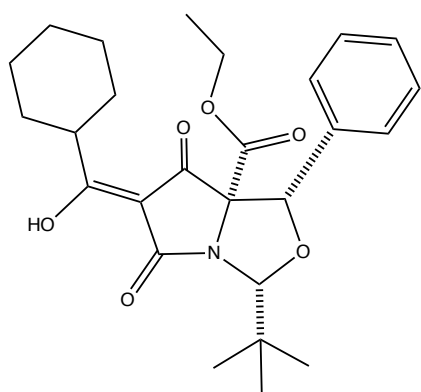


Yield (1.45 g, 37%); Orange semi-solid; R_f (100% EtOAc) 0.70;

$\nu_{\max}/\text{cm}^{-1}$ 3305 (O-H), 2962 (C-H), 1721 (C=O), 1664 (C=O), 1606 (C=C); δ_H (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.10 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.95 (2H, dq, $J=4.3$ Hz, 6.8 Hz, OCH_2CH_3), 4.41 (1H, d, $J=10.8$ Hz, CH_2Br), 4.50 (1H, d, $J=10.9$ Hz, CH_2Br), 4.84 (1H, s, H4), 5.02 (1H, s, H2), 7.31-7.40 (3H, m, Ar-H), 7.52 (2H, d, $J=7.1$ Hz, Ar-H), 9.10 (1H, br s, OH); δ_C (101

MHz, CDCl_3) 13.6 (OCH_2CH_3), 23.5 (CH_2Br), 25.4 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 62.2 (OCH_2CH_3), 79.1 (C5), 80.7 (C4), 97.3 (C2), 102.1 (C7), 126.4 (Ar-C), 128.0 (Ar-C), 128.2 (Ar-C), 134.5 (Ar-C), 164.8 (C10), 179.3 (C8), 181.9 (C9), 187.4 (C6); LRMS (ESI^-) m/z : 464.0 ($[\text{M}^{79} - \text{H}]^-$ 93%), 466.0 ($[\text{M}^{81} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : $[\text{M}^{79} - \text{H}]^-$ calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_6\text{Br}$, 464.0703, found 464.0706; $[\text{M}^{81} - \text{H}]^-$ calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_6\text{Br}$, 466.0684, found 466.0686.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(cyclohexyl(hydroxy)methylene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161n**

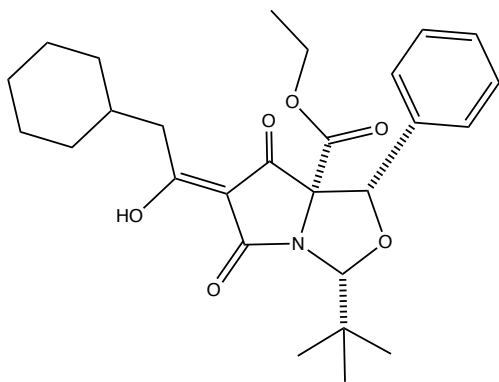


Yield (295 mg, 57%); Orange oil; R_f (100% EtOAc) 0.55; $\nu_{\max}/\text{cm}^{-1}$ 2934 (C-H), 1760 (C=O), 1711 (C=O), 1653 (C=O), 1591 (C=C); δ_H (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.25-1.98 (10H, m, Cyclohexyl- CH_2), 3.50 (1H, m, Cyclohexyl-H), 3.98 (2H, m, OCH_2CH_3), 4.83 (1H, s, H4), 5.02 (1H, s, H2), 7.33-7.42 (3H, m, Ar-H), 7.58 (2H, d, $J=7.1$ Hz, Ar-H), 11.99

(1H, br s, OH); δ_C (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 25.3 ($(\text{CH}_3)_3$), 25.3 (Cyclohexyl-C), 25.6 (Cyclohexyl-C), 28.4 (Cyclohexyl-C), 35.4 ($\text{C}(\text{CH}_3)_3$), 41.3 (Cyclohexyl-C), 61.7 (OCH_2CH_3), 78.6 (C5), 80.6 (C4), 96.8 (C2), 100.1 (C7), 126.3 (Ar-C), 127.7 (Ar-C), 127.8 (Ar-C), 135.0 (Ar-C), 165.4 (C10), 180.8 (C8), 187.8

(C6), 196.1 (C9); LRMS (ESI⁻) m/z : 454.2 ([M – H]⁻ 96%); HRMS (ESI⁻) m/z : [M – H]⁻ calcd. for C₂₆H₃₂NO₆, 454.2235, found 454.2227.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(2-cyclohexyl-1-hydroxyethylidene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161o**



Yield (219 mg, 44%); Orange oil; R_f (100% EtOAc) 0.43;

$\nu_{\max}/\text{cm}^{-1}$ 2926 (C-H), 2853 (C-H), 1763 (C=O), 1717 (C=O),

1655 (C=O), 1598 (C=C); AB:CD 22:78 by δ_{H} -NMR; δ_{H} (Major

Tautomer) (400 MHz, CDCl₃) 0.96 (3H, t, J =7.1 Hz, OCH₂CH₃),

1.09 (9H, s, C(CH₃)₃), 1.11-1.33 (6H, m, Cyclohexyl-CH₂),

1.60-1.93 (5H, m, Cyclohexyl-CH₂, CH), 2.71 (1H, dd, J =6.9

Hz, 13.0 Hz, CH₂-Cyclohexyl), 2.96 (1H, dd, J =7.3 Hz, 13.0 Hz, CH₂-Cyclohexyl), 3.94 (2H, dq, J =2.6 Hz,

7.1 Hz, OCH₂CH₃), 4.79 (1H, s, H₄), 4.99 (1H, s, H₂), 7.29-7.39 (3H, m, Ar-H), 7.54 (2H, m, Ar-H); δ_{C} (Major

Tautomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 25.4 ((CH₃)₃), 26.1 (Cyclohexyl-C), 26.1 (Cyclohexyl-C), 32.9

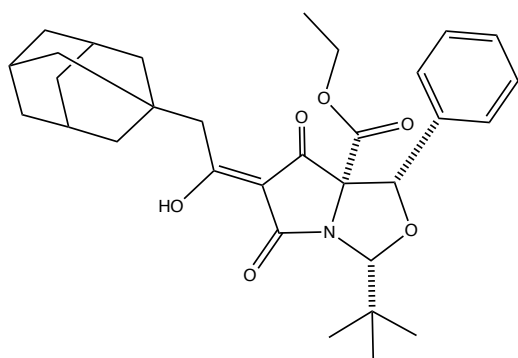
(Cyclohexyl-C), 33.2 (Cyclohexyl-C), 33.8 (Cyclohexyl-C), 35.5 (C(CH₃)₃), 36.9 (Cyclohexyl-C), 40.4 (CH₂-

Cyclohexyl), 61.8 (OCH₂CH₃), 78.7 (C₅), 80.6 (C₄), 96.9 (C₂), 102.5 (C₇), 126.4 (Ar-C), 127.8 (Ar-C), 127.9

(Ar-C), 134.9 (Ar-C), 165.3 (C₁₀), 180.2 (C₈), 188.3 (C₆), 191.7 (C₉); LRMS (ESI⁻) m/z : 468.2 ([M – H]⁻

96%); HRMS (ESI⁻) m/z : [M – H]⁻ calcd. for C₂₇H₃₄NO₆, 468.2392, found 468.2383.

Ethyl (1*S,3*R**,7*aR**,*Z*)-6-(2-(adamantan-1-yl)-1-hydroxyethylidene)-3-(*tert*-butyl)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161p**



Yield (276 mg, 57%); Yellow foamy solid; m.p. 68-72°C;

R_f (100% EtOAc) 0.30; $\nu_{\max}/\text{cm}^{-1}$ 3400 (O-H), 2904 (C-H),

2850 (C-H), 1763 (C=O), 1717 (C=O), 1653 (C=O), 1598

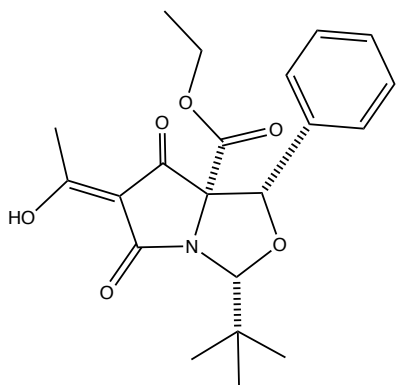
(C=C); AB:CD 15:85 by δ_{H} -NMR; δ_{H} (Major Tautomer) (400 MHz,

CDCl₃) 0.97 (3H, t, J =7.1 Hz, OCH₂CH₃), 1.08 (9H, s,

C(CH₃)₃), 1.65-1.70 (12H, m, Adamantyl-CH₂), 1.95-1.98

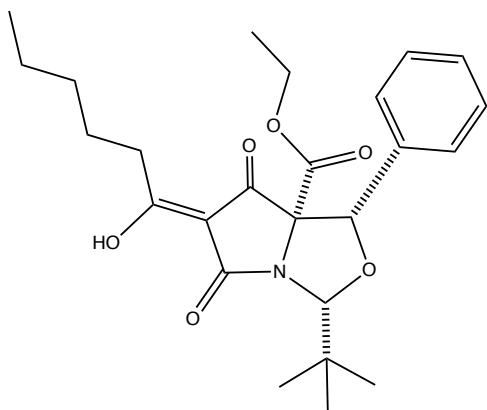
(3H, m, Adamantyl-CH), 2.48 (1H, d, $J=11.7$ Hz, CH₂-Adamantyl), 3.00 (1H, d, $J=11.7$ Hz, CH₂-Adamantyl), 3.94 (2H, m, OCH₂CH₃), 4.79 (1H, s, H₄), 5.00 (1H, s, H₂), 7.29-7.39 (3H, m, Ar-H), 7.53 (2H, m, Ar-H); δ_{C} (Major Tautomer) (101 MHz, CDCl₃) 13.7 (OCH₂CH₃), 25.4 ((CH₃)₃), 29.0 (Adamantyl-C), 35.6 (C(CH₃)₃), 36.7 (Adamantyl-C), 42.6 (Adamantyl-C), 46.5 (CH₂-Adamantyl), 49.4 (Adamantyl-C), 61.8 (OCH₂CH₃), 78.5 (C₅), 80.7 (C₄), 96.9 (C₂), 103.5 (C₇), 126.4 (Ar-C), 127.9 (Ar-C), 128.0 (Ar-C), 134.9 (Ar-C), 165.4 (C₁₀), 180.3 (C₈), 188.6 (C₆), 190.5 (C₉); LRMS (ESI⁻) m/z : 520.2 ([M - H]⁻ 96%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₃₁H₃₈NO₆, 520.2705, found 520.2695.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(1-hydroxyethylidene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161q**



Yield (174 mg, 51%); Yellow oil; R_f (100% EtOAc) 0.18; $\nu_{\text{max}}/\text{cm}^{-1}$ 2961 (C-H), 1762 (C=O), 1718 (C=O), 1656 (C=O), 1602 (C=C); AB:CD 21:79 by δ_{H} -NMR; δ_{H} (Major Tautomer) (400 MHz, CDCl₃) 0.96 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.09 (9H, s, C(CH₃)₃), 2.54 (3H, s, CH₃), 3.94 (2H, m, OCH₂CH₃), 4.79 (1H, s, H₄), 4.98 (1H, s, H₂), 7.29-7.38 (3H, m, Ar-H), 7.52 (2H, m, Ar-H), 12.22 (1H, br s, OH); δ_{C} (Major Tautomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 20.1 (CH₃), 25.4 ((CH₃)₃), 35.5 (C(CH₃)₃), 61.9 (OCH₂CH₃), 78.9 (C₅), 80.7 (C₄), 96.9 (C₂), 102.3 (C₇), 126.4 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 134.9 (Ar-C), 165.3 (C₁₀), 179.9 (C₈), 188.3 (C₆), 188.5 (C₉); LRMS (ESI⁻) m/z : 386.1 ([M - H]⁻ 96%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₂₁H₂₄NO₆, 386.1609, found 386.1602.

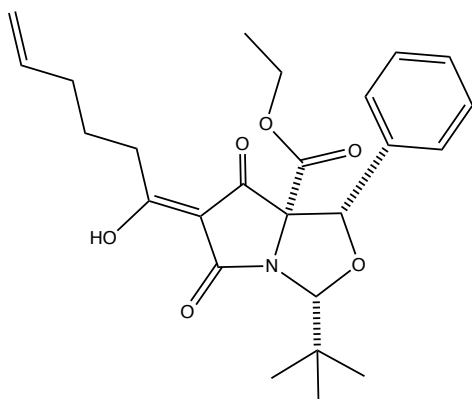
Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(1-hydroxyhexylidene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161r**



Yield (227 mg, 47%); Orange oil; R_f (100% EtOAc) 0.48; $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2934 (C-H), 2872 (C-H), 1763 (C=O), 1738 (C=O), 1718 (C=O), 1656 (C=O), 1600 (C=C); δ_H (Major Tautomer) (400 MHz, CDCl_3) 0.91 (3H, t, $J=7.0$ Hz, Hexyl- CH_3), 0.96 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.09 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.32-1.42 (4H, m, Hexyl- CH_2), 1.73 (2H, qn, $J=7.4$ Hz, Hexyl- CH_2),

2.86 (1H, dt, $J=7.6$ Hz, 14.3 Hz, Hexyl- CH_2), 2.98 (1H, dt, $J=7.6$ Hz, 13.8 Hz, Hexyl- CH_2), 3.94 (2H, dq, $J=2.4$ Hz, 7.2 Hz, OCH_2CH_3), 4.79 (1H, s, H4), 4.99 (1H, s, H2), 7.31-7.39 (3H, m, Ar-H), 7.53 (2H, m, Ar-H); δ_C (Major Tautomer) (101 MHz, CDCl_3) 13.6 (Hexyl- CH_3), 13.9 (OCH_2CH_3), 22.4 (Hexyl- CH_2), 25.4 ($(\text{CH}_3)_3$), 25.7 (Hexyl- CH_2), 31.4 (Hexyl- CH_2), 33.1 (Hexyl- CH_2), 35.5 ($\text{C}(\text{CH}_3)_3$), 61.8 (OCH_2CH_3), 78.7 (C5), 80.7 (C4), 96.9 (C2), 101.7 (C7), 126.4 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 134.9 (Ar-C), 165.4 (C10), 180.3 (C8), 188.1 (C6), 192.6 (C9); LRMS (ESI^-) m/z : 442.1 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{25}\text{H}_{32}\text{NO}_6$, 442.2235, found 442.2230.

Ethyl (1*S,3*R**,7*aR**,*Z*)-3-(*tert*-butyl)-6-(1-hydroxyhex-5-en-1-ylidene)-5,7-dioxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate 161s**



Yield (188 mg, 41%); Red oil; R_f (100% EtOAc) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 2974 (C-H), 2960 (C-H), 2935 (C-H), 1762 (C=O), 1718 (C=O), 1656 (C=O), 1600 (C=C); δ_H (Major Tautomer) (400 MHz, CDCl_3) 0.96 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.09 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.83 (2H, qn, $J=7.5$ Hz, Hexenyl- CH_2), 2.18 (2H, q, $J=7.4$ Hz, Hexenyl- CH_2), 2.89 (1H, dt, $J=7.6$ Hz, 14.4 Hz, Hexenyl- CH_2),

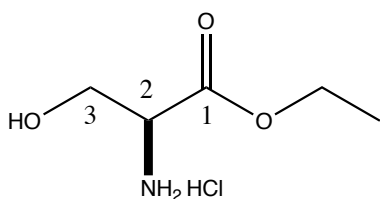
2.99 (1H, dt, $J=7.6$ Hz, 15.0 Hz, Hexenyl- CH_2), 3.94 (2H, dq, $J=3.2$ Hz, 7.1 Hz, OCH_2CH_3), 4.80 (1H, s, H4), 4.99 (1H, s, H2), 5.04 (2H, m, $\text{CH}_2=\text{CH}$), 5.81 (1H, ddt, $J=6.7$ Hz, 10.2 Hz, 17.0 Hz, $\text{CH}_2=\text{CH}$), 7.30-7.39 (3H, m, Ar-H), 7.53 (2H, m, Ar-H); δ_C (Major Tautomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 25.4

(Hexenyl-CH₂), 32.6 (Hexenyl-CH₂), 33.2 (Hexenyl-CH₂), 35.5 (C(CH₃)₃), 61.9 (OCH₂CH₃), 78.7 (C5), 80.7 (C4), 96.9 (C2), 101.8 (C7), 115.9 (CH₂=CH), 126.4 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 134.9 (Ar-C), 137.3 (CH₂=CH), 165.3 (C10), 180.2 (C8), 188.1 (C6), 192.1 (C9); LRMS (ESI⁻) *m/z*: 440.1 ([M - H]⁻ 100%); HRMS (ESI⁻) *m/z*: [M - H]⁻ calcd. for C₂₅H₃₀NO₆, 440.2079, found 440.2075.

General procedure for the synthesis of amino ester hydrochlorides:^{35,53}

SOCl₂ (1.2 eq.) was added dropwise to a stirring solution of amino acid **48a** (1.0 eq.) in EtOH (0.3 M) at 0°C and left to stir for 15 mins at this temperature. Then the reaction mixture was stirred at 60°C for 3 h. The reaction was then stopped and left to cool to rt and then the solvent was evaporated under reduced pressure to give the ethyl ester hydrochloride salt **164** which was used without further purification.

Ethyl L-serinate hydrochloride **164**



Yield (3.12 g, 97%); White solid; m.p. 127-130°C (lit. 130-132°C);

$\nu_{\max}/\text{cm}^{-1}$ 3384 (O-H), 2876 (N-H), 1735 (C=O); δ_{H} (400 MHz, D₂O)

1.36 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 4.07 (1H, dd, *J*=3.5 Hz, 12.5 Hz, H3),

4.16 (1H, dd, *J*=4.3 Hz, 12.5 Hz, H3), 4.31 (1H, dd, *J*=3.4 Hz, 4.3 Hz,

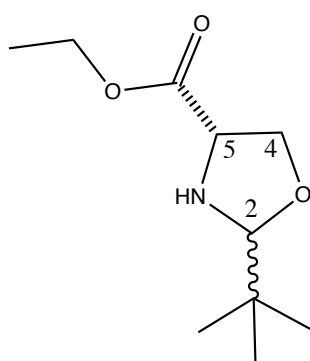
H2), 4.38 (2H, dq, *J*=2.2 Hz, 7.2 Hz, OCH₂CH₃); δ_{C} (101 MHz, D₂O) 13.2 (OCH₂CH₃), 54.8 (C2), 59.3 (C3),

63.8 (OCH₂CH₃), 168.5 (C1); LRMS (ESI⁺) *m/z*: 134.0 ([M + H]⁺ 100%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd.

for C₅H₁₂NO₃, 134.0812, found 134.0811.

General procedure for the synthesis of oxazolidines:³⁴⁻³⁵

Amino ester **164** (1.0 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2 eq.) and trimethylacetaldehyde (1.1 eq.) was added. The mixture was heated overnight to more than 100°C with continuous removal of water using a Dean-Stark apparatus. The white precipitate was then filtered and washed with Et₂O. The combined filtrates were concentrated under reduced pressure to furnish a diastereomeric mixture of oxazolidines **165** which was used without further purification.

Ethyl (4S)-2-(*tert*-butyl)oxazolidine-4-carboxylate 165

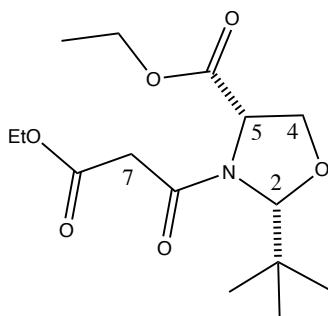
Yield (2.81 g, 78%); Colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 3312 (N-H), 2959 (C-H), 2872 (C-H), 1737 (C=O); 1.7:1 mixture of diastereomers at the C2-position; δ_{H}

(Major diastereomer) (400 MHz, CDCl_3) 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.28 (3H, m, OCH_2CH_3), 2.44 (1H, br s, NH), 3.72 (1H, dd, $J=4.6$ Hz, 6.9 Hz, H4), 3.86-3.96 (2H, m, H4, H5), 4.08 (1H, s, H2), 4.21 (2H, m, OCH_2CH_3); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 33.3 ($\text{C}(\text{CH}_3)_3$),

59.8 (C5), 61.7 (OCH_2CH_3), 68.5 (C4), 100.1 (C2), 172.6 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.28 (3H, m, OCH_2CH_3), 2.44 (1H, br s, NH), 3.68 (1H, m, H4), 3.86-3.96 (1H, m, H5), 4.12 (1H, dd, $J=7.3$ Hz, 8.0 Hz, H4), 4.21 (2H, m, OCH_2CH_3), 4.35 (1H, s, H2); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 25.0 ($(\text{CH}_3)_3$), 34.8 ($\text{C}(\text{CH}_3)_3$), 59.6 (C5), 61.5 (OCH_2CH_3), 69.3 (C4), 99.4 (C2), 172.8 (C=O); LRMS (ESI^+) m/z : 202.2 ($[\text{M} + \text{H}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{20}\text{NO}_3$, 202.1438, found 202.1439.

General procedure for the synthesis of malonamides:³⁴

To a stirring solution of oxazolidine ($\pm$) **165** (1.0 eq.) in DCM at 0°C was added ethyl malonyl chloride (1.1 eq.) and pyridine (1.2 eq.) dropwise. The mixture was stirred at 0°C for 10-20 min and then refluxed overnight. The mixture was then washed with sat. NH_4Cl (aq.), sat. NaHCO_3 (aq.), brine, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated oxazolidine **166**.

Ethyl (2*R*,4*S*)-2-(*tert*-butyl)-3-(3-ethoxy-3-oxopropanoyl)oxazolidine-4-carboxylate 166

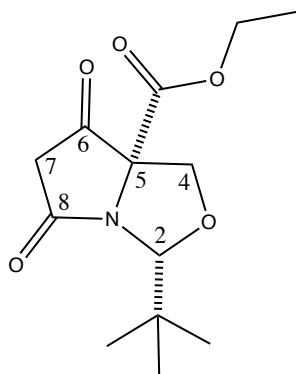
Yield (3.54 g, 81%); Orange oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.30; $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 1739 (C=O), 1673 (C=O); >19:1 mixture of diastereomers at the C2-position and a 6.7:1 rotameric mixture; δ_{H} (Major rotamer) (400 MHz, CDCl_3) 0.89 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.28 (6H, m, OCH_2CH_3), 3.49 (1H, d, $J=15.3$ Hz, H7), 3.67 (1H, br d, $J=15.5$ Hz, H7), 4.00

(1H, m, H4), 4.20 (4H, m, OCH₂CH₃, OCH₂CH₃), 4.52 (1H, m, H4), 4.67 (1H, m, H5), 5.29 (1H, s, H2); δ_c (Major rotamer) (101 MHz, CDCl₃) 14.2 (OCH₂CH₃, OCH₂CH₃), 25.8 ((CH₃)₃), 37.5 (C(CH₃)₃), 43.1 (C7), 59.7 (C5), 61.8 (OCH₂CH₃), 62.2 (OCH₂CH₃), 67.9 (C4), 96.9 (C2), 167.6 (C=O, C=O), 169.6 (C=O); LRMS (ESI⁺) m/z : 338.2 ([M + Na]⁺ 96%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₅H₂₅NO₆Na, 338.1574, found 338.1574.

General procedure for the synthesis of tetramates:³⁴⁻³⁵

To a solution of malonamide (**±**) **166** (1.0 eq.) in anhydrous THF was added potassium *tert*-butoxide (1.1 eq.). The mixture was heated at reflux for 3 h. Then the reaction mixture was cooled, separated between Et₂O and water and the aqueous layer was acidified to pH 1 using 3 M HCl solution (aq.) and extracted with EtOAc. The organic layer was washed with 1 M NaH₂PO₄ (aq.) solution, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to obtain tetramate **167** which was used without further purification.

Ethyl (3*R*,7*aR*)-3-(*tert*-butyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **167**



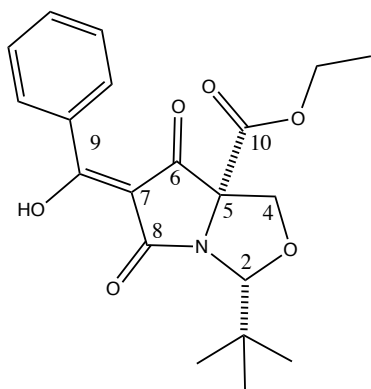
Yield (2.31 g, 79%); Yellow solid; m.p. 125-130°C; $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1741 (C=O), 1648 (C=O); δ_H (400 MHz, CDCl₃) 0.89 (9H, s, C(CH₃)₃), 1.29 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.15 (1H, d, $J=21.1$ Hz, H7), 3.62 (1H, d, $J=9.0$ Hz, H4), 3.72 (1H, dd, $J=0.8$ Hz, 21.1 Hz, H7), 4.27 (2H, m, OCH₂CH₃), 4.77 (1H, d, $J=9.0$ Hz, H4), 5.06 (1H, d, $J=0.8$ Hz, H2); δ_c (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 24.8 ((CH₃)₃), 35.7 (C(CH₃)₃), 44.9 (C7), 63.4 (OCH₂CH₃), 68.0 (C4), 80.8 (C5),

98.4 (C2), 166.5 (C=O), 172.7 (C8), 198.6 (C6); LRMS (ESI⁺) m/z : 270.1 ([M + H]⁺ 30%), 292.0 ([M + Na]⁺ 100%); LRMS (ESI⁻) m/z : 268.1 ([M - H]⁻ 97%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₃H₂₀NO₅, 270.1336, found 270.1336.

General procedure for the synthesis of C7-acyltetramates:^{39,43,64-65}

To a stirring solution of tetramic acid **167** (1 eq.) in DCM was added DCC (1.1 eq.) and DMAP (1.3 eq.). The solution was cooled to 0°C and benzoic acid (1.1 eq.) was added portion wise. The reaction mixture was then left to stir at rt overnight. The suspension was filtered, and the filtrate was concentrated *in-vacuo*. The concentrate was then purified by flash column chromatography to obtain metal-chelated tetramic acids which were then re-dissolved in DCM, washed with 10% citric acid solution (aq.), dried over Na₂SO₄, filtered, and then concentrated *in-vacuo* to obtain the desired product **168**.

Ethyl (3*R*,7*aR*,*Z*)-3-(*tert*-butyl)-6-(hydroxy(phenyl)methylene)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **168**

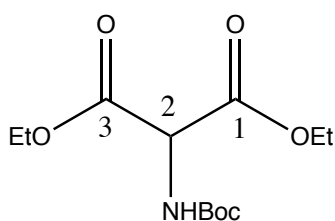


Yield (161 mg, 16%); Red oil; *R*_f (100% EtOAc) 0.40; δ_H (400 MHz, CDCl₃) 0.97 (9H, s, C(CH₃)₃), 1.30 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 3.54 (1H, d, *J*=8.9 Hz, H₄), 4.28 (2H, dq, *J*=3.1 Hz, 7.2 Hz, OCH₂CH₃), 4.86 (1H, d, *J*=8.9 Hz, H₄), 4.93 (1H, s, H₂), 7.50 (2H, d, *J*=7.9 Hz, Ar-H), 7.56-7.64 (1H, m, Ar-H), 8.17 (2H, d, *J*=7.8 Hz, Ar-H); δ_C (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 24.9 ((CH₃)₃), 35.3 (C(CH₃)₃), 62.9 (OCH₂CH₃), 68.6 (C₄),

98.8 (C₂), 128.4 (Ar-C), 130.2 (Ar-C), 133.6 (Ar-C), 134.8 (Ar-C), 167.2 (C₁₀), 182.7 (C₈), 183.6 (C₉), 186.7 (C₆).

General procedure for the synthesis of Boc-protected diethylaminomalonate:¹⁰⁸

Diethyl aminomalonate.HCl **171** (1 eq.) was dissolved in 1,4-dioxane (1.2 M) and cooled to 0°C. 1 M NaOH solution (aq.) (1 eq.) was added to this reaction mixture dropwise. Boc₂O (1.1 eq.) in 1,4-dioxane (2.4 M) was subsequently added dropwise at 0°C and the mixture was left to stir at rt overnight. 1,4-Dioxane was then evaporated *in-vacuo* and added to this reaction mixture was EtOAc. After phase separation, the organic layer was washed with 1 M HCl solution (aq.), dried over Na₂SO₄, filtered and the solvent was removed *in-vacuo* and the crude product was purified by flash column chromatography to yield the desired Boc-protected malonate **172** as a colourless oil.

Diethyl 2-((*tert*-butoxycarbonyl)amino)malonate **172**

Yield (5.11 g, 79%); Colourless oil; R_f (20% EtOAc in Pet. Ether 40:60)

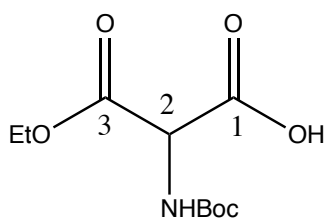
0.45; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1742 (C=O), 1715 (C=O); δ_H (400 MHz, CDCl_3)

1.27 (6H, t, $J=7.1$ Hz, OCH_2CH_3 , OCH_2CH_3), 1.43 (9H, s, $(\text{CH}_3)_3$), 4.24 (4H, m, OCH_2CH_3 , OCH_2CH_3), 4.92 (1H, d, $J=7.7$ Hz, H2), 5.54 (1H, br s, NH);

LRMS (ESI^+) m/z : 298.0 ($[\text{M} + \text{Na}]^+$ 75%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{12}\text{H}_{21}\text{NO}_6\text{Na}$, 298.1261, found 298.1263.

General procedure for the monosaponification of Boc-protected diethylaminomalonate:⁶⁶

A solution of 4.5 M KOH (1 eq.) (aq.) was added dropwise to a solution of diethyl (Boc-amino)malonate **172** (1 eq.) in ethanol (0.45 M) at 0°C . The reaction mixture was allowed to warm up to rt and stirred for 15 h. Ethanol was then evaporated *in-vacuo*, and Et_2O was added to the reaction mixture and this was transferred to a separatory funnel. The aqueous layer was then acidified to pH 1 with 1 M HCl solution (aq.), then extracted with EtOAc. The organic layer was then washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed *in-vacuo* to obtain the carboxylic acid **173** as a colourless oil and was used without further purification.

2-((*tert*-butoxycarbonyl)amino)-3-ethoxy-3-oxopropanoic acid **173**

Yield (3.89 g, 86%); Colourless oil that solidified to a white solid; m.p 83-

86°C (lit.¹⁰⁹ 98-99 $^\circ\text{C}$); $\nu_{\max}/\text{cm}^{-1}$ 3309 (O-H), 2981 (C-H), 1720 (C=O), 1669 (C=O); 1:1 mixture of rotamers; δ_H (400 MHz, CDCl_3) 1.31 (3H, t, $J=7.1$ Hz,

OCH_2CH_3), 1.43/1.44 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.26/4.26 (2H, m, OCH_2CH_3), 4.77

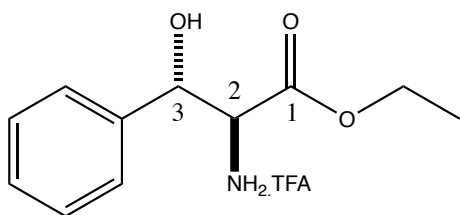
(1H, d, $J=5.0$ Hz, H2)/4.98 (1H, d, $J=7.5$ Hz, H2), 5.65 (1H, d, $J=7.5$ Hz, NH)/7.59 (1H, d, $J=5.1$ Hz, NH), 8.73 (1H, br s, OH); δ_C (101 MHz, CDCl_3) 14.1/14.2 (OCH_2CH_3), 28.3/28.3 ($(\text{CH}_3)_3$), 57.5/58.8 (C2),

62.5/63.0 (OCH_2CH_3), 81.4/82.8 ($\text{C}(\text{CH}_3)_3$), 155.4/156.6 (C=O), 166.7/166.7 (C=O), 168.4/169.6 (C=O);

LRMS (ESI^+) m/z : 270.0 ($[\text{M} + \text{Na}]^+$ 29%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}_6\text{Na}$, 270.0948, found 270.0948.

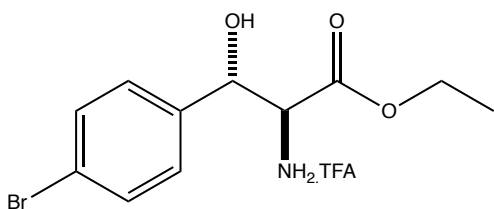
General procedure for the deprotection of Boc-protected amino esters:⁶⁶

To a solution of Boc-protected amino ester **127** (1 eq.) dissolved in DCM was added TFA (4 eq.) at 0°C under an atmosphere of N₂. The reaction mixture was then stirred at rt for 2 h, and then concentrated *in-vacuo* to obtain the deprotected amino ester as a trifluoroacetate ammonium salt **174** and was used without further purification.

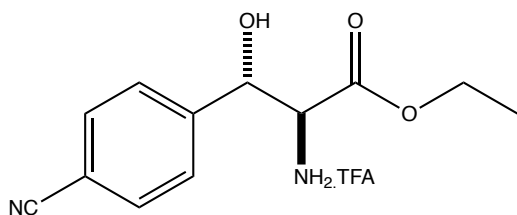
Ethyl (2S*,3S*)-2-amino-3-hydroxy-3-phenylpropanoate trifluoroacetic acid **174a**

Yield (2.82 g, Quantitative); Thick orange oil; δ_{H} (400 MHz, D₂O) 1.16 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.20 (2H, dq, $J=2.0$ Hz, 7.2 Hz, OCH₂CH₃), 4.48 (1H, d, $J=4.2$ Hz, H₂), 5.40 (1H, d, $J=4.2$ Hz, H₃), 7.39-7.50 (5H, m, Ar-H); δ_{C} (101 MHz, D₂O) 13.0

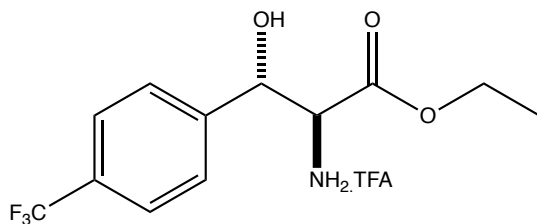
(OCH₂CH₃), 58.5 (C₂), 63.6 (OCH₂CH₃), 71.0 (C₃), 126.0 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 137.1 (Ar-C), 167.5 (C₁); LRMS (ESI⁺) m/z : 210.2 ([M + H]⁺ 6%), 232.2 ([M + Na]⁺ 13%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₁H₁₆NO₃, 210.1125, found 210.1127.

Ethyl (2S*,3S*)-2-amino-3-(4-bromophenyl)-3-hydroxypropanoate trifluoroacetic acid **174b**

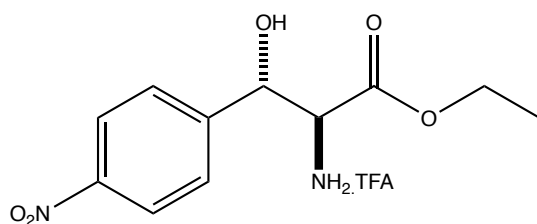
Yield (1.22 g, Quantitative); Pale yellow oil that solidified to a beige solid; m.p. 130-134°C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3140 (O-H), 2902 (N-H), 1741 (C=O); δ_{H} (400 MHz, D₂O) 1.13 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 4.18 (2H, dq, $J=2.5$ Hz, 7.1 Hz, OCH₂CH₃), 4.48 (1H, d, $J=3.9$ Hz, H₂), 5.38 (1H, d, $J=4.0$ Hz, H₃), 7.32 (2H, d, $J=8.4$ Hz, Ar-H), 7.64 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, D₂O) 13.0 (OCH₂CH₃), 58.3 (C₂), 63.6 (OCH₂CH₃), 70.4 (C₃), 122.2 (Ar-C), 127.8 (Ar-C), 131.8 (Ar-C), 136.6 (Ar-C), 167.3 (C₁); LRMS (ESI⁺) m/z : 288.1 ([M⁷⁹ + H]⁺ 95%), 290.1 ([M⁸¹ + H]⁺ 92%); HRMS (ESI⁺) m/z : [M⁷⁹ + H]⁺ calcd. for C₁₁H₁₅NO₃Br, 288.0230, found 288.0231; [M⁸¹ + H]⁺ calcd. for C₁₁H₁₅NO₃Br, 290.0209, found 290.0210.

Ethyl (2*S,3*S**)-2-amino-3-(4-cyanophenyl)-3-hydroxypropanoate trifluoroacetic acid 174c**

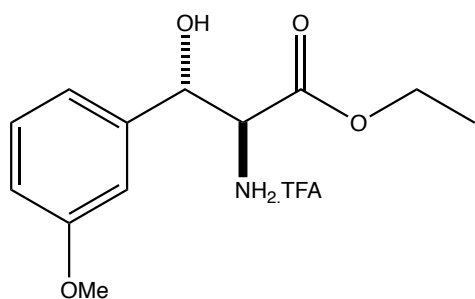
Yield (1.11 g, Quantitative); Light brown oil that solidified to a beige solid; m.p. 150-153°C; $\nu_{\max}/\text{cm}^{-1}$ 3342 (O-H), 2988 (N-H), 2233 (C≡N), 1748 (C=O); δ_{H} (400 MHz, D₂O) 1.07 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 4.15 (2H, dq, $J=3.3$ Hz, 7.2 Hz, OCH₂CH₃), 4.56 (1H, d, $J=3.6$ Hz, H₂), 5.48 (1H, d, $J=3.6$ Hz, H₃), 7.59 (2H, d, $J=8.1$ Hz, Ar-H), 7.85 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, D₂O) 12.9 (OCH₂CH₃), 58.1 (C₂), 63.5 (OCH₂CH₃), 70.5 (C₃), 111.2 (C≡N), 119.4 (Ar-C), 126.6 (Ar-C), 132.8 (Ar-C), 143.5 (Ar-C), 167.1 (C₁); LRMS (ESI⁺) m/z : 235.1 ([M + H]⁺ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₂H₁₅N₂O₃, 235.1077, found 235.1078.

Ethyl (2*S,3*S**)-2-amino-3-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate trifluoroacetic acid 174d**

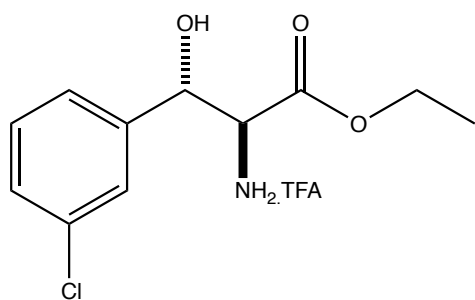
Yield (1.17 g, Quantitative); Yellow oil that solidified to a beige solid; m.p. 124-127°C; $\nu_{\max}/\text{cm}^{-1}$ 3130 (O-H), 2910 (N-H), 1740 (C=O); δ_{H} (400 MHz, D₂O) 1.10 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 4.17 (2H, dq, $J=4.0$ Hz, 7.2 Hz, OCH₂CH₃), 4.57 (1H, d, $J=3.7$ Hz, H₂), 5.51 (1H, d, $J=3.7$ Hz, H₃), 7.61 (2H, d, $J=8.1$ Hz, Ar-H), 7.81 (2H, d, $J=8.3$ Hz, Ar-H); δ_{C} (101 MHz, D₂O) 12.9 (OCH₂CH₃), 58.3 (C₂), 63.5 (OCH₂CH₃), 70.5 (C₃), 125.7 (q, $J=3.6$ Hz, Ar-C), 126.4 (Ar-C), 130.2 (q, $J=32.2$ Hz, Ar-C), 141.8 (Ar-C), 167.2 (C₁); δ_{F} (376 MHz, D₂O) -62.39; LRMS (ESI⁺) m/z : 278.1 ([M + H]⁺ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₂H₁₅NO₃F₃, 278.0999, found 278.0998.

Ethyl (2S*,3S*)-2-amino-3-hydroxy-3-(4-nitrophenyl)propanoate trifluoroacetic acid 174e

Yield (1.35 g, Quantitative); Yellow oil that solidified to a brown solid; m.p. 142-145°C; $\nu_{\max}/\text{cm}^{-1}$ 3336 (O-H), 2946 (N-H), 1747 (C=O), 1518 (N-O); δ_{H} (400 MHz, D_2O) 1.06 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 4.15 (2H, m, OCH_2CH_3), 4.60 (1H, d, $J=3.5$ Hz, H2), 5.53 (1H, d, $J=3.5$ Hz, H3), 7.66 (2H, d, $J=9.0$ Hz, Ar-H), 8.31 (2H, d, $J=8.9$ Hz, Ar-H); δ_{C} (101 MHz, D_2O) 12.9 (OCH_2CH_3), 58.1 (C2), 63.6 (OCH_2CH_3), 70.4 (C3), 123.9 (Ar-C), 127.0 (Ar-C), 145.5 (Ar-C), 147.7 (Ar-C), 167.0 (C1); LRMS (ESI^+) m/z : 255.1 ($[\text{M} + \text{H}]^+$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_5$, 255.0975, found 255.0975.

Ethyl (2S*,3S*)-2-amino-3-hydroxy-3-(3-methoxyphenyl)propanoate trifluoroacetic acid 174f

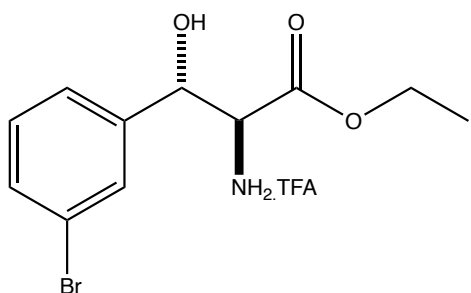
Yield (1.19 g, Quantitative); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3424 (O-H), 2943 (N-H), 1738 (C=O); δ_{H} (400 MHz, D_2O) 1.16 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.86 (3H, s, OCH_3), 4.21 (2H, m, OCH_2CH_3), 4.49 (1H, d, $J=4.1$ Hz, H2), 5.40 (1H, d, $J=4.0$ Hz, H3), 7.00-7.06 (3H, m, Ar-H), 7.43 (1H, t, $J=7.9$ Hz, Ar-H); δ_{C} (101 MHz, D_2O) 13.0 (OCH_2CH_3), 55.4 (OCH_3), 58.4 (C2), 63.5 (OCH_2CH_3), 70.7 (C3), 111.7 (Ar-C), 114.3 (Ar-C), 118.6 (Ar-C), 130.3 (Ar-C), 139.0 (Ar-C), 159.2 (Ar-C), 167.4 (C1); LRMS (ESI^+) m/z : 262.0 ($[\text{M} + \text{Na}]^+$ 21%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_4$, 240.1230, found 240.1232.

Ethyl (2S*,3S*)-2-amino-3-(3-chlorophenyl)-3-hydroxypropanoate trifluoroacetic acid 174g

Yield (1.19 g, Quantitative); Yellow oil that solidified to an off-white solid; m.p. 80-83°C; $\nu_{\max}/\text{cm}^{-1}$ 3450 (O-H), 2989 (N-H), 1741 (C=O); δ_{H} (400 MHz, D_2O) 1.13 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 4.18 (2H, m, OCH_2CH_3), 4.49 (1H, d, $J=3.9$ Hz, H2), 5.39 (1H, d, $J=3.9$ Hz, H3), 7.30-7.45 (4H, m, Ar-H); δ_{C} (101 MHz, D_2O) 13.0 (OCH_2CH_3), 58.3 (d, $J=4.8$ Hz, C2), 63.6 (OCH_2CH_3), 70.3 (d, $J=5.6$ Hz, C3), 124.3 (Ar-C),

125.9 (Ar-C), 128.8 (Ar-C), 130.3 (Ar-C), 134.1 (Ar-C), 139.6 (Ar-C), 167.2 (C1); LRMS (ESI⁺) m/z : 244.1 ([M³⁵ + H]⁺ 75%), 246.1 ([M³⁷ + H]⁺ 67%); HRMS (ESI⁺) m/z : [M³⁵ + H]⁺ calcd. for C₁₁H₁₅NO₃Cl, 244.0735, found 244.0736; [M³⁷ + H]⁺ calcd. for C₁₁H₁₅NO₃Cl, 246.0705, found 246.0707.

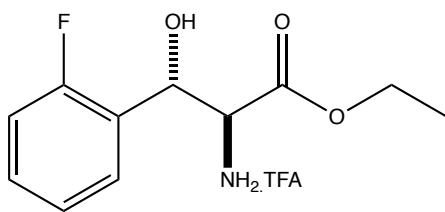
Ethyl (2S*,3S*)-2-amino-3-(3-bromophenyl)-3-hydroxypropanoate trifluoroacetic acid 174h



Yield (1.19 g, Quantitative); Off-white semi-solid; $\nu_{\max}/\text{cm}^{-1}$ 3163 (O-H), 2871 (N-H), 1749 (C=O); δ_{H} (400 MHz, D₂O) 1.14 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 4.19 (2H, m, OCH₂CH₃), 4.49 (1H, d, $J=3.8$ Hz, H2), 5.40 (1H, d, $J=3.8$ Hz, H3), 7.34-7.41 (2H, m, Ar-H), 7.56-7.63 (2H, m, Ar-H); δ_{C} (101 MHz, D₂O) 13.0

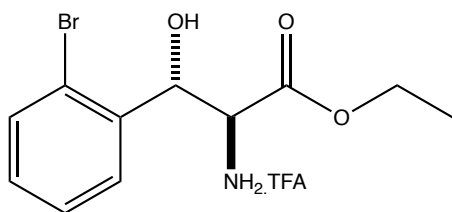
(OCH₂CH₃), 58.3 (C2), 63.6 (OCH₂CH₃), 70.3 (C3), 122.2 (Ar-C), 124.8 (Ar-C), 128.9 (Ar-C), 130.6 (Ar-C), 131.8 (Ar-C), 139.9 (Ar-C), 167.2 (C1); LRMS (ESI⁺) m/z : 288.0 ([M⁷⁹ + H]⁺ 100%), 290.1 ([M⁸¹ + H]⁺ 100%); HRMS (ESI⁺) m/z : [M⁷⁹ + H]⁺ calcd. for C₁₁H₁₅NO₃Br, 288.0230, found 288.0230; [M⁸¹ + H]⁺ calcd. for C₁₁H₁₅NO₃Br, 290.0209, found 290.0209.

Ethyl (2S*,3S*)-2-amino-3-(2-fluorophenyl)-3-hydroxypropanoate trifluoroacetic acid 174i

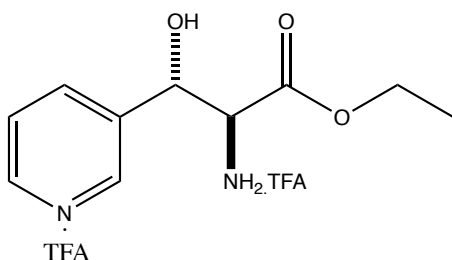


Yield (1.12 g, Quantitative); Yellow oil that solidified to a light orange solid; m.p. 127-130°C; $\nu_{\max}/\text{cm}^{-1}$ 3558 (O-H), 2907 (N-H), 1733 (C=O); δ_{H} (400 MHz, D₂O) 1.10 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 4.16 (2H, dq, $J=0.8$ Hz, 7.2 Hz, OCH₂CH₃), 4.54 (1H,

d, $J=3.7$ Hz, H2), 5.59 (1H, d, $J=3.7$ Hz, H3), 7.21 (1H, m, Ar-H), 7.32 (1H, dt, $J=1.2$ Hz, 7.6 Hz, Ar-H), 7.48 (1H, m, Ar-H), 7.54 (1H, m, Ar-H); δ_{C} (101 MHz, D₂O) 12.9 (OCH₂CH₃), 57.0 (d, $J=2.1$ Hz, C2), 63.5 (OCH₂CH₃), 66.3 (d, $J=2.0$ Hz, C3), 115.4 (d, $J=21.1$ Hz, Ar-C), 124.7 (d, $J=8.0$ Hz, Ar-C), 124.7 (d, $J=8.8$ Hz, Ar-C), 127.6 (d, $J=3.9$ Hz, Ar-C), 130.8 (d, $J=8.6$ Hz, Ar-C), 159.4 (d, $J=244.2$ Hz, Ar-C), 167.4 (C1); δ_{F} (376 MHz, D₂O) -118.29; LRMS (ESI⁺) m/z : 228.1 ([M + H]⁺ 100%), 250.1 ([M + Na]⁺ 59%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₁₁H₁₅NO₃F, 228.1030, found 228.1030.

Ethyl (2S*,3S*)-2-amino-3-(2-bromophenyl)-3-hydroxypropanoate trifluoroacetic acid 174j

Yield (1.61 g, Quantitative); Yellow oil that solidified to an off-white solid; m.p. 65-70°C; $\nu_{\max}/\text{cm}^{-1}$ 3502 (O-H), 2982 (N-H), 1732 (C=O); δ_{H} (400 MHz, D_2O) 1.02 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 4.09 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.62 (1H, d, $J=3.2$ Hz, H2), 5.51 (1H, d, $J=3.2$ Hz, H3), 7.33 (1H, dt, $J=1.9$ Hz, 7.7 Hz, Ar-H), 7.48 (1H, dt, $J=1.3$ Hz, 7.6 Hz, Ar-H), 7.55 (1H, dd, $J=1.8$ Hz, 7.9 Hz, Ar-H), 7.68 (1H, dd, $J=1.2$ Hz, 8.0 Hz, Ar-H); δ_{C} (101 MHz, D_2O) 12.9 (OCH_2CH_3), 55.9 (C2), 63.4 (OCH_2CH_3), 70.7 (C3), 120.8 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 130.4 (Ar-C), 132.8 (Ar-C), 137.0 (Ar-C), 167.3 (C1); LRMS (ESI^+) m/z : 288.0 ($[\text{M}^{79} + \text{H}]^+$ 63%), 290.0 ($[\text{M}^{81} + \text{H}]^+$ 63%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{Br}$, 288.0230, found 288.0229; $[\text{M}^{81} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{Br}$, 290.0209, found 290.0208.

Ethyl (2S*,3S*)-2-amino-3-hydroxy-3-(pyridin-3-yl)propanoate trifluoroacetic acid 174k

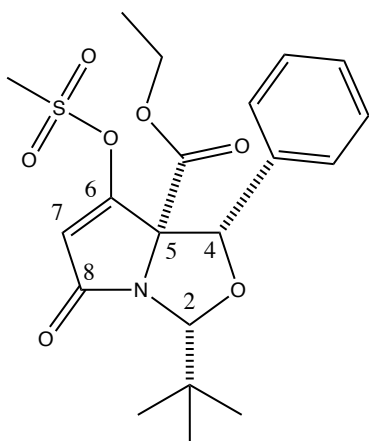
Yield (3.30 g, Quantitative); Yellow semi-solid; $\nu_{\max}/\text{cm}^{-1}$ 3076 (O-H), 2988 (N-H), 1742 (C=O); δ_{H} (400 MHz, D_2O) 1.02 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.14 (2H, m, OCH_2CH_3), 4.69 (1H, d, $J=2.7$ Hz, H2), 5.64 (1H, d, $J=2.7$ Hz, H3), 8.16 (1H, m, Ar-H), 8.68 (1H, m, Ar-H), 8.82 (1H, m, Ar-H), 8.91 (1H, m, Ar-H); δ_{C} (101 MHz, D_2O) 12.9 (OCH_2CH_3), 57.5 (C2), 63.7 (OCH_2CH_3), 68.2 (C3), 127.2 (Ar-C), 139.0 (Ar-C), 140.1 (Ar-C), 140.9 (Ar-C), 144.5 (Ar-C), 166.4 (C1); LRMS (ESI^+) m/z : 211.1 ($[\text{M} + \text{H}]^+$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3$, 211.1077, found 211.1079.

General procedure for the mesylation of tetramates:³⁵

Tetramate **134a** (1 eq.) was dissolved in anhydrous DCM under an atmosphere of N_2 . The mixture was cooled to 0°C and MsCl (1 eq.) and DIPEA (2 eq.) were added to this reaction mixture dropwise. The resulting mixture was stirred for 5 h at rt. The reaction mixture was then washed with 10% HCl solution (aq.), sat. NaHCO_3 (aq.) and brine, dried over Na_2SO_4 , filtered and the solvent was evaporated *in-vacuo*.

and the residue was purified by flash column chromatography to give the desired mesylate product **204**.

Ethyl (1*S,3*R**,7*aR**)-3-(*tert*-butyl)-7-((methylsulfonyl)oxy)-5-oxo-1-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **204****



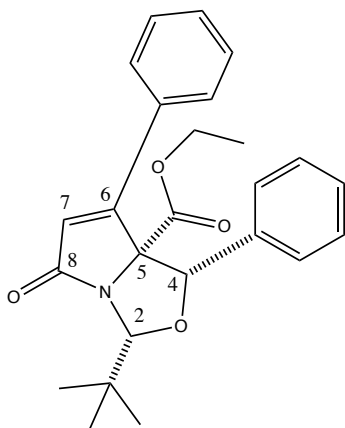
Yield (920 mg, 54%); Yellow oil that solidified to a semi-solid; R_f (50 % EtOAc in Pet. Ether 40:60) 0.83; $\nu_{\max}/\text{cm}^{-1}$ 2972 (C-H), 1722 (C=O), 1629 (C=C); δ_H (400 MHz, CDCl_3) 1.02 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.23 (3H, s, SO_2CH_3), 3.97 (2H, m, OCH_2CH_3), 4.84 (1H, s, H4), 4.88 (1H, s, H2), 6.03 (1H, s, H7), 7.33-7.39 (3H, m, Ar-H), 7.50 (2H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 25.6 ($(\text{CH}_3)_3$), 35.6 ($\text{C}(\text{CH}_3)_3$), 38.3 (SO_2CH_3), 62.3 (OCH_2CH_3), 76.5 (C5), 83.7 (C4), 96.9

(C2), 107.7 (C7), 126.7 (Ar-C), 128.0 (Ar-C), 128.5 (Ar-C), 134.2 (Ar-C), 164.3 (C=O), 165.3 (C8), 176.0 (C6); LRMS (ESI^+) m/z : 446.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_7\text{SNa}$, 446.1244, found 446.1234.

General procedure for the Suzuki-Miyaura Cross-Coupling:³⁵

A mixture of 1,4-bis-(diphenylphosphino)butane (0.06 eq.) and bis(benzonitrile)-palladium (II) chloride (0.05 eq.) in dry toluene (0.03 M) was stirred at rt under a N_2 atmosphere for 30 min to form 1,4-bis(diphenylphosphino)butane-palladium (II) chloride $[\text{Pd}(\text{dppb})\text{Cl}_2]$ as a creamy orange slurry. Mesylate **204** (1 eq.), phenylboronic acid (1.2 eq.), ethanol (7 eq.), 10 M Na_2CO_3 solution (aq.) (15 eq.) and dry toluene was added. The reaction mixture was left to reflux overnight. After cooling, water was added, and the reaction mixture was diluted with EtOAc and there was phase separation using a separatory funnel. The organic layer was then filtered exhaustively under vacuum filtration. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated *in-vacuo* and purified by flash column chromatography to obtain the Suzuki-Miyaura cross-coupling product **205**.

Ethyl (1*S,3*R**,7*aS**)-3-(*tert*-butyl)-5-oxo-1,7-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **205****

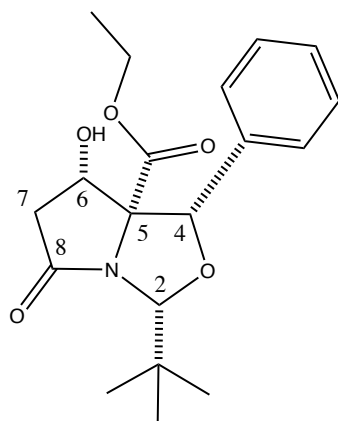


Yield (149 mg, 18%); White solid; m.p. 155-158°C; R_f (20 % EtOAc in Pet. Ether 40:60) 0.53; $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1750 (C=O), 1708 (C=O); δ_H (400 MHz, CDCl_3) 0.95 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.03 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.96 (2H, dq, $J=1.0$ Hz, 7.2 Hz, OCH_2CH_3), 4.47 (1H, s, H4), 4.87 (1H, s, H2), 6.47 (1H, s, H7), 7.06-7.32 (10H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 25.4 ($(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 61.8 (OCH_2CH_3), 78.0 (C5), 85.9 (C4), 95.8 (C2), 122.2 (C7), 127.1 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 129.6 (Ar-C), 130.1 (Ar-C), 131.0 (Ar-C), 133.7 (Ar-C), 160.0 (C6), 167.8 (C=O), 177.9 (C8); LRMS (ESI^+) m/z : 428.2 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_4\text{Na}$, 428.1832, found 428.1829.

General procedure for the reduction of tetramates:⁷¹

NaBH_4 (2.2 eq.) was added portion wise at 0°C to a solution of tetramic acid **134a** (1 eq.) which was dissolved in acetic acid (9 eq.) and anhydrous DCM. The reaction mixture was stirred at 0°C for 15 min and then at rt for 3 h. The reaction mixture was cautiously quenched with sat. NaHCO_3 (aq.), washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in-vacuo* to obtain alcohol **208**.

Ethyl (1*S,3*R**,7*S**,7*aS**)-3-(*tert*-butyl)-7-hydroxy-5-oxo-1-phenyldihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7*a*(5*H*)-carboxylate **208****



Yield (383 mg, 74%); Yellow solid; m.p. 58-61°C; $\nu_{\max}/\text{cm}^{-1}$ 3411 (O-H), 2975 (C-H), 2961 (C-H), 1710 (C=O); δ_H (400 MHz, CDCl_3) 0.95 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.03 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.91 (1H, dd, $J=7.9$ Hz, 15.6 Hz, H7), 3.15 (1H, ddd, $J=0.9$ Hz, 11.0 Hz, 15.6 Hz, H7), 3.96 (2H, dq, $J=3.8$ Hz, 7.2 Hz, OCH_2CH_3), 4.81 (1H, dd, $J=7.9$ Hz, 11.0 Hz, H6), 4.86 (1H, s, H4), 5.00 (1H, d, $J=0.8$ Hz, H2), 7.28-7.44 (5H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 25.7 ($(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 44.3 (C7), 61.5

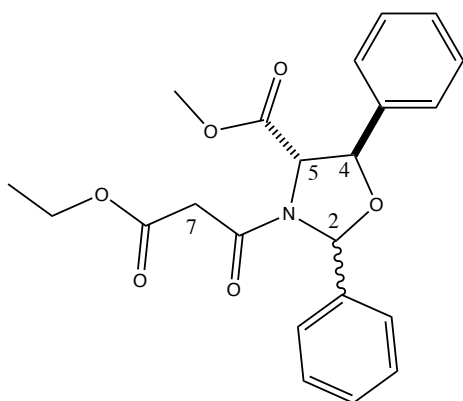
(OCH₂CH₃), 74.4 (C6), 77.9 (C5), 86.7 (C4), 95.4 (C2), 125.5 (Ar-C), 128.0 (Ar-C), 128.2 (Ar-C), 135.8 (Ar-C), 169.2 (C=O), 174.6 (C8); LRMS (ESI⁺) *m/z*: 370.2 ([M + Na]⁺ 90%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₁₉H₂₅NO₅Na, 370.1625, found 370.1626.

6.4: Experimental Section for Chapter 4

General procedure for the synthesis of oxazolidines and malonamides:³⁴⁻³⁵

Methyl ester hydrochloride salt **82a** (1 eq.) was suspended in petroleum ether 40:60. The reaction mixture was cooled to 0°C and triethylamine (1.2 eq.) and aromatic aldehyde (1.1 eq.) was added, and the mixture was heated overnight to more than 100°C with continuous removal of water using a Dean-Stark apparatus. The white/brown precipitate was then filtered and washed with Et₂O. The combined filtrates were then concentrated under reduced pressure to furnish the desired oxazolidines **215a-d** as a mixture of diastereomers and was taken on crude into the next reaction sequence. To a stirring solution of oxazolidine **215a-d** (1.0 eq.) in anhydrous DCM at 0°C was added ethyl malonyl chloride (1.1 eq.) and pyridine (1.2 eq.) dropwise. The mixture was stirred at 0°C for 10-20 min and then refluxed overnight. The mixture was then washed with sat. NH₄Cl (aq.), sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated oxazolidines **216a-d** and **217a-d**.

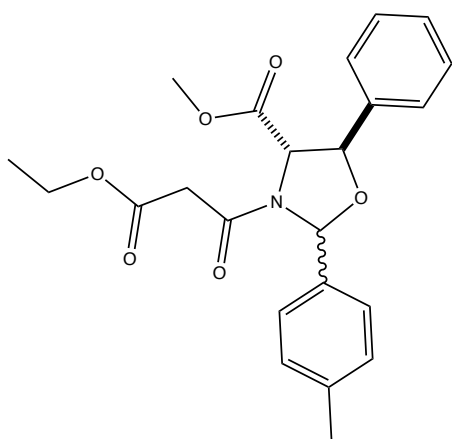
Methyl (4*S**,5*R**)-3-(3-ethoxy-3-oxopropanoyl)-2,5-diphenyloxazolidine-4-carboxylate **216a/217a**



Yield (486 mg, 14% over two steps from **82a**); Yellow oil; *R_f* (30% EtOAc in Pet. Ether 40:60) 0.35(**216a**) and 0.18(**217a**); *v*_{max}/cm⁻¹ 2933 (C-H), 1742 (C=O), 1663 (C=O); 1.6:1 diastereomeric ratio at the C2-position; **216a** had a mixture of rotamers; δ_{H} (**216a**, Major rotamer) (400 MHz, CDCl₃) 1.23 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.13 (1H, d, *J*=15.6 Hz, H7), 3.16 (1H, d, *J*=15.6 Hz, H7), 3.81 (3H, s, OCH₃), 4.12 (2H, dq, *J*=2.0 Hz, 7.1 Hz, OCH₂CH₃), 4.81 (1H, d, *J*=6.3 Hz, H5), 5.25 (1H, d, *J*=6.3 Hz, H4), 6.38 (1H, s, H2), 7.38-7.81 (10H, m, Ar-H); δ_{C} (**216a**, Major rotamer) (101 MHz, CDCl₃)

14.1 (OCH₂CH₃), 42.2 (C7), 52.9 (OCH₃), 61.7 (OCH₂CH₃), 64.8 (C5), 80.7 (C4), 90.6 (C2), 126.6 (Ar-C), 127.9 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 129.2 (Ar-C), 130.1 (Ar-C), 136.3 (Ar-C), 136.9 (Ar-C), 164.2 (C=O), 166.5 (C=O), 169.8 (C=O); δ_{H} (217a) (400 MHz, CDCl₃) 1.21 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.82 (1H, d, $J=15.7$ Hz, H7), 2.92 (1H, d, $J=15.7$ Hz, H7), 3.80 (3H, s, OCH₃), 4.06 (2H, q, $J=7.2$ Hz, OCH₂CH₃), 4.64 (1H, d, $J=8.1$ Hz, H5), 5.18 (1H, d, $J=8.1$ Hz, H4), 6.30 (1H, s, H2), 7.31-7.54 (10H, m, Ar-H); δ_{C} (217a) (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 42.3 (C7), 52.8 (OCH₃), 61.5 (OCH₂CH₃), 66.8 (C5), 82.2 (C4), 91.6 (C2), 126.4 (Ar-C), 128.3 (Ar-C), 128.9 (Ar-C), 129.2 (Ar-C), 129.4 (Ar-C), 130.7 (Ar-C), 136.1 (Ar-C), 136.8 (Ar-C); 164.2 (C=O), 166.5 (C=O), 169.8 (C=O); LRMS (216a) (ESI⁺) m/z : 420.0 ([M + Na]⁺ 95%); LRMS (217a) (ESI⁺) m/z : 420.0 ([M + Na]⁺ 95%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₂₂H₂₃NO₆Na, 420.1418, found 420.1418.

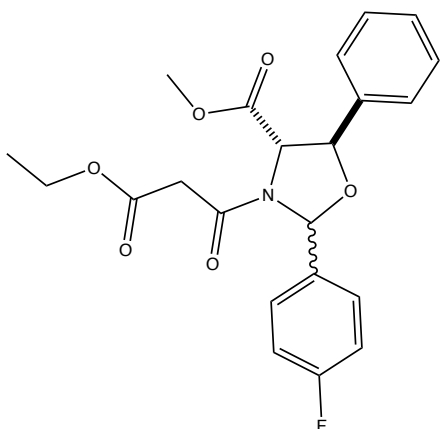
Methyl (4S*,5R*)-3-(3-ethoxy-3-oxopropanoyl)-5-phenyl-2-(*p*-tolyl)oxazolidine-4-carboxylate
216b/217b



Yield (2.32 g, 43% over two steps from **82a**); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.35(216b) and 0.20(217b); $\nu_{\text{max}}/\text{cm}^{-1}$ 2985 (C-H), 1742 (C=O), 1662 (C=O); 1.1:1 diastereomeric ratio at the C2-position; **216b** had a mixture of rotamers; δ_{H} (216b, Major rotamer) (400 MHz, CDCl₃) 1.23 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 2.40 (3H, s, CH₃), 3.13 (1H, d, $J=15.6$ Hz, H7), 3.18 (1H, d, $J=15.6$ Hz, H7), 3.82 (3H, s, OCH₃), 4.14 (2H, q, $J=7.1$ Hz, OCH₂CH₃), 4.81 (1H, d, $J=6.2$ Hz, H5), 5.27 (1H, d, $J=6.2$ Hz, H4), 6.35 (1H, s, H2), 7.27-7.70 (9H, m, Ar-H); δ_{C} (216b, Major rotamer) (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 21.4 (CH₃), 42.2 (C7), 52.8 (OCH₃), 61.7 (OCH₂CH₃), 64.8 (C5), 80.6 (C4), 90.5 (C2), 126.6 (Ar-C), 127.9 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 129.8 (Ar-C), 133.9 (Ar-C), 136.4 (Ar-C), 140.1 (Ar-C), 164.2 (C=O), 166.6 (C=O), 169.8 (C=O); δ_{H} (217b) (400 MHz, CDCl₃) 1.23 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 2.40 (3H, s, CH₃), 2.84 (1H, d, $J=15.7$ Hz, H7), 2.94 (1H, d, $J=15.7$ Hz, H7), 3.81 (3H, s, OCH₃), 4.08 (2H, q, $J=7.2$ Hz, OCH₂CH₃), 4.63 (1H, d, $J=8.2$ Hz, H5), 5.17 (1H, d, $J=8.2$ Hz, H4), 6.28 (1H, s, H2), 7.26-7.42 (9H, m, Ar-H); δ_{C} (217b) (101 MHz, CDCl₃) 14.1

(OCH₂CH₃), 21.5 (CH₃), 42.3 (C7), 52.8 (OCH₃), 61.4 (OCH₂CH₃), 66.8 (C5), 82.1 (C4), 91.5 (C2), 126.4 (Ar-C), 128.2 (Ar-C), 128.9 (Ar-C), 129.2 (Ar-C), 130.1 (Ar-C), 133.8 (Ar-C), 136.2 (Ar-C), 140.9 (Ar-C), 163.9 (C=O), 166.4 (C=O), 169.6 (C=O); LRMS (_{216b}) (ESI⁺) *m/z*: 412.7 ([M + H]⁺ 40%); LRMS (_{217b}) (ESI⁺) *m/z*: 412.7 ([M + H]⁺ 50%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₃H₂₅NO₆Na, 434.1574, found 434.1572.

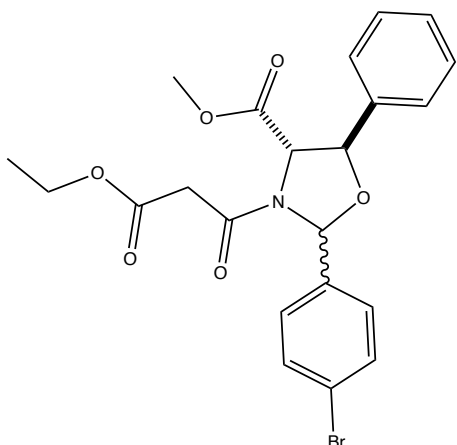
Methyl (4*S,5*R**)-3-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)-5-phenyloxazolidine-4-carboxylate 216c/217c**



Yield (2.66 g, 49% over two steps from **82a**); Orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.30(_{216c}) and 0.10(_{217c}); *v*_{max}/cm⁻¹ 2986 (C-H), 1743 (C=O), 1662 (C=O); 1.1:1 diastereomeric ratio at the C2-position; **216c** had a mixture of rotamers; δ_{H} (_{216c}, Major rotamer) (400 MHz, CDCl₃) 1.23 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 3.14 (1H, d, *J*=15.5 Hz, H7), 3.15 (1H, d, *J*=15.5 Hz, H7), 3.82 (3H, s, OCH₃), 4.14 (2H, m, OCH₂CH₃), 4.82 (1H, d, *J*=6.2 Hz, H5), 5.24

(1H, d, *J*=6.2 Hz, H4), 6.37 (1H, s, H2), 7.05-7.84 (9H, m, Ar-H); δ_{C} (_{216c}, Major rotamer) (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 42.2 (C7), 52.9 (OCH₃), 61.8 (OCH₂CH₃), 64.7 (C5), 80.7 (C4), 89.9 (C2), 116.2 (d, *J*=22.0 Hz, Ar-C), 126.6 (Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 130.1 (d, *J*=8.4 Hz, Ar-C), 132.8 (d, *J*=3.1 Hz, Ar-C), 136.2 (Ar-C), 163.8 (d, *J*=249.7 Hz, Ar-C), 164.1 (C=O), 166.4 (C=O), 169.9 (C=O); δ_{F} (_{216c}) (377 MHz, CDCl₃) -110.93; δ_{H} (_{217c}) (400 MHz, CDCl₃) 1.22 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 2.86 (1H, d, *J*=15.6 Hz, H7), 2.94 (1H, d, *J*=15.6 Hz, H7), 3.81 (3H, s, OCH₃), 4.07 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 4.65 (1H, d, *J*=8.0 Hz, H5), 5.18 (1H, d, *J*=8.0 Hz, H4), 6.32 (1H, s, H2), 7.14-7.53 (9H, m, Ar-H); δ_{C} (_{217c}) (101 MHz, CDCl₃) 14.1 (OCH₂CH₃), 42.3 (C7), 52.9 (OCH₃), 61.6 (OCH₂CH₃), 66.7 (C5), 82.1 (C4), 90.8 (C2), 116.5 (d, *J*=21.6 Hz, Ar-C), 126.4 (Ar-C), 128.9 (Ar-C), 129.3 (Ar-C), 130.3 (d, *J*=8.6 Hz, Ar-C), 132.7 (d, *J*=3.0 Hz, Ar-C), 136.0 (Ar-C), 163.8 (C=O), 163.9 (d, *J*=250.6 Hz, Ar-C), 166.2 (C=O), 169.5 (C=O); δ_{F} (_{217c}) (377 MHz, CDCl₃) -109.52; LRMS (_{216c}) (ESI⁺) *m/z*: 416.6 ([M + H]⁺ 85%); HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd. for C₂₂H₂₂NO₆FNa, 438.1323, found 438.1322.

Methyl (4*S,5*R**)-2-(4-bromophenyl)-3-(3-ethoxy-3-oxopropanoyl)-5-phenyloxazolidine-4-carboxylate **216d/217d****



Yield (1.55 g, 25% over two steps from **82a**); Orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.28_(216d) and 0.13_(217d); $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1744 (C=O), 1664 (C=O); 1.6:1 diastereomeric ratio at the C2-position; **216d** had a mixture of rotamers; δ_H (**216d**, Major rotamer) (400 MHz, CDCl_3) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.16 (2H, s, H7), 3.81 (3H, s, OCH_3), 4.14 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.80 (1H, d, $J=6.5$ Hz, H5), 5.20 (1H,

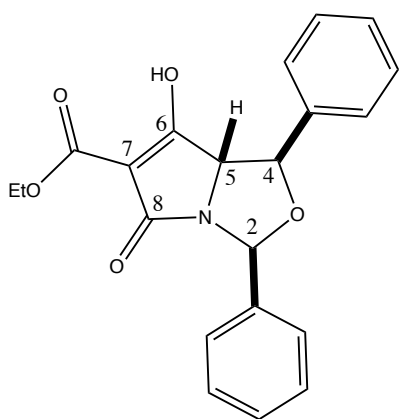
d, $J=6.5$ Hz, H4), 6.36 (1H, s, H2), 7.33-7.71 (9H, m, Ar-H); δ_C (**216d**, Major rotamer) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 42.2 (C7), 52.9 (OCH_3), 61.9 (OCH_2CH_3), 64.7 (C5), 80.9 (C4), 89.9 (C2), 124.5 (Ar-C), 126.3 (Ar-C), 126.6 (Ar-C), 129.0 (Ar-C), 129.7 (Ar-C), 132.4 (Ar-C), 135.9 (Ar-C), 136.0 (Ar-C), 164.0 (C=O), 166.4 (C=O), 169.8 (C=O); δ_H (**217d**) (400 MHz, CDCl_3) 1.22 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.87 (1H, d, $J=15.6$ Hz, H7), 2.95 (1H, d, $J=15.5$ Hz, H7), 3.81 (3H, s, OCH_3), 4.08 (2H, dq, $J=1.5$ Hz, 7.2 Hz, OCH_2CH_3), 4.64 (1H, d, $J=8.0$ Hz, H5), 5.18 (1H, d, $J=8.0$ Hz, H4), 6.29 (1H, s, H2), 7.33-7.89 (9H, m, Ar-H); δ_C (**217d**) (101 MHz, CDCl_3) 14.1 (OCH_2CH_3), 42.3 (C7), 52.9 (OCH_3), 61.6 (OCH_2CH_3), 66.7 (C5), 82.3 (C4), 90.9 (C2), 125.0 (Ar-C), 126.3 (Ar-C), 128.9 (Ar-C), 129.3 (Ar-C), 129.9 (Ar-C), 132.6 (Ar-C), 135.9 (Ar-C), 136.0 (Ar-C), 163.7 (C=O), 166.1 (C=O), 169.5 (C=O); LRMS (**216d**) (ESI^+) m/z : 498.0 ($[\text{M}^{79} + \text{Na}]^+$ 95%), 500.0 ($[\text{M}^{81} + \text{Na}]^+$ 97%); LRMS (**217d**) (ESI^+) m/z : 498.0 ($[\text{M}^{79} + \text{Na}]^+$ 94%), 500.0 ($[\text{M}^{81} + \text{Na}]^+$ 95%); HRMS (ESI^+) m/z : $[\text{M}^{79} + \text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}_6\text{BrNa}$, 498.0523, found 498.0522; $[\text{M}^{81} + \text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}_6\text{BrNa}$, 500.0504, found 500.0502.

General procedure for the synthesis of tetramates:³⁴⁻³⁵

To a solution of malonamide **217a-d** (1.0 eq.) in anhydrous THF was added potassium *tert*-butoxide (1.1 eq.). The mixture was heated at reflux for 3 h. Then the reaction mixture was left to cool and then separated between Et_2O and water and the aqueous layer was acidified to pH 1-2 using 3 M HCl solution (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 ,

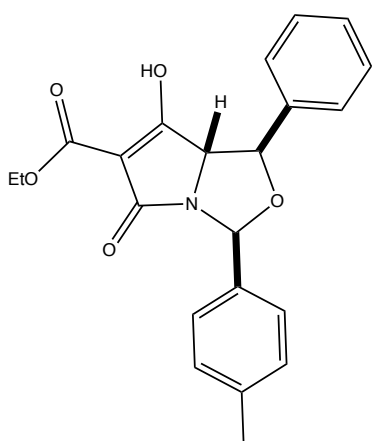
filtered and concentrated under reduced pressure to obtain the desired ethyl ester tetramates **218a-d** and was used without further purification.

Ethyl (1*R,3*S**,7*aS**)-7-hydroxy-5-oxo-1,3-diphenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate **218a****



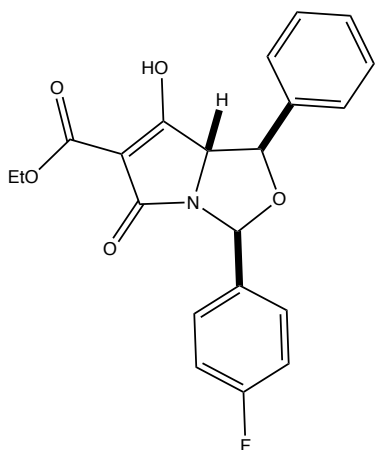
Yield (57 mg, 37%); Orange oil; $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1700 (C=O), 1661 (C=O), 1614 (C=C); δ_{H} (400 MHz, CDCl_3) 1.41 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.38 (1H, d, $J=8.4$ Hz, H5), 4.42 (2H, m, OCH_2CH_3), 4.81 (1H, d, $J=8.3$ Hz, H4), 6.37 (1H, s, H2), 7.36-7.66 (10H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.2 (OCH_2CH_3), 62.0 (OCH_2CH_3), 67.4 (C5), 81.8 (C4), 88.2 (C2), 100.1 (C7), 126.3 (Ar-C), 126.6 (Ar-C), 128.6 (Ar-C), 128.8 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 135.7 (Ar-C), 139.0 (Ar-C), 167.3 (C=O), 175.2 (C8), 185.7 (C6); LRMS (ESI⁻) m/z : 364.0 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{21}\text{H}_{18}\text{NO}_5$, 364.1191, found 364.1195.

Ethyl (1*R,3*S**,7*aS**)-7-hydroxy-5-oxo-1-phenyl-3-(*p*-tolyl)-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate **218b****



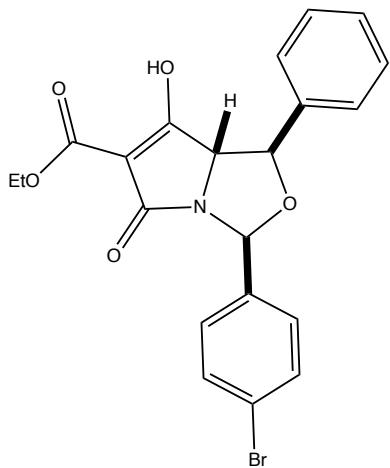
Yield (567 mg, 55%); Orange oil; δ_{H} (400 MHz, CDCl_3) 1.42 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.39 (3H, s, CH_3), 4.38 (1H, d, $J=8.4$ Hz, H5), 4.43 (2H, m, OCH_2CH_3), 4.80 (1H, d, $J=8.3$ Hz, H4), 6.35 (1H, s, H2), 7.23-7.54 (9H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 21.3 (CH_3), 62.0 (OCH_2CH_3), 67.5 (C5), 81.8 (C4), 88.3 (C2), 126.3 (Ar-C), 126.6 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 129.3 (Ar-C), 135.8 (Ar-C), 136.2 (Ar-C), 138.6 (Ar-C), 167.4 (C=O), 175.3 (C8), 185.7 (C6).

Ethyl (1*R,3*S**,7*aS**)-3-(4-fluorophenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 218c**



Yield (643 mg, 64%); Yellow foamy solid; m.p. 53-58°C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3245 (O-H), 2984 (C-H), 1700 (C=O), 1657 (C=O), 1607 (C=C); δ_{H} (400 MHz, CDCl_3) 1.41 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.37 (1H, d, $J=8.3$ Hz, H5), 4.42 (2H, m, OCH_2CH_3), 4.80 (1H, d, $J=8.4$ Hz, H4), 6.32 (1H, s, H2), 7.10 (2H, app t, $J=8.7$ Hz, Ar-H), 7.34-7.50 (5H, m, Ar-H), 7.61 (2H, dd, $J=5.4$ Hz, 8.5 Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 62.1 (OCH_2CH_3), 67.4 (C5), 81.8 (C4), 87.8 (C2), 115.5 (d, $J=21.8$ Hz, Ar-C), 126.6 (Ar-C), 128.3 (d, $J=8.4$ Hz, Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 134.9 (d, $J=3.1$ Hz, Ar-C), 135.6 (Ar-C), 163.1 (d, $J=247.0$ Hz, Ar-C), 167.3 (C=O), 185.8 (C6); δ_{F} (377 MHz, CDCl_3) -113.28.

Ethyl (1*R,3*S**,7*aS**)-3-(4-bromophenyl)-7-hydroxy-5-oxo-1-phenyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate 218d**



Yield (488 mg, 62%); Red semi-solid/oil; δ_{H} (400 MHz, CDCl_3) 1.41 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.35 (1H, d, $J=8.4$ Hz, H5), 4.42 (2H, m, OCH_2CH_3), 4.80 (1H, d, $J=8.4$ Hz, H4), 6.30 (1H, s, H2), 7.40-7.56 (9H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 14.3 (OCH_2CH_3), 62.1 (OCH_2CH_3), 67.3 (C5), 81.9 (C4), 87.7 (C2), 100.2 (C7), 122.9 (Ar-C), 126.6 (Ar-C), 128.1 (Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 131.7 (Ar-C), 135.5 (Ar-C), 138.1 (Ar-C), 167.3 (C=O), 171.2 (C8), 185.7 (C6); LRMS (ESI⁻) m/z :

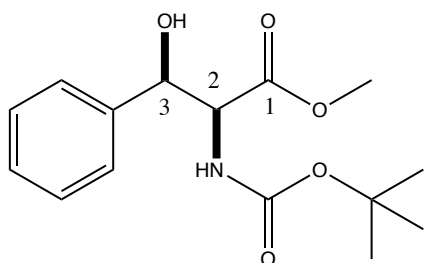
441.9 ($[\text{M}^{79} - \text{H}]^-$ 95%), 443.9 ($[\text{M}^{81} - \text{H}]^-$ 97%).

General procedure for the Boc-protection of *threo*-phenylserine:¹¹⁰

To a stirring solution of *threo*-phenylserine **82a** (1.0 eq.) suspended in DCM at 0°C was added $(\text{Boc})_2\text{O}$ (1.3 eq.) and Et_3N (1.4 eq.) and the solution was stirred for 10 min at this temperature. The solution was then stirred overnight at rt and then the crude mixture was washed with sat. NH_4Cl (aq.), brine,

dried over Na₂SO₄, filtered, concentrated *in-vacuo* and then purified by flash column chromatography to yield the desired product **225**.

Methyl (2*S,3*R**)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate **225****



Yield (1.54 g, 42%); Yellow oil; R_f (30% EtOAc in Pet. Ether 40:60)

0.30; $\nu_{\max}/\text{cm}^{-1}$ 3426 (O-H), 2979 (C-H), 1717 (C=O), 1693 (C=O);

δ_{H} (400 MHz, CDCl₃) 1.33 (9H, br s, C(CH₃)₃), 3.18 (1H, br s, OH),

3.75 (3H, s, OCH₃), 4.53 (1H, br m, H₂), 5.23 (1H, br m, H₃), 5.40

(1H, br d, $J=9.2$ Hz, NH), 7.28-7.38 (5H, m, Ar-H); δ_{C} (101 MHz,

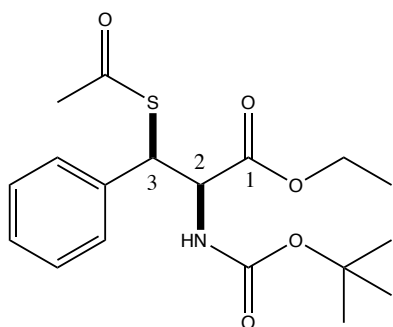
CDCl₃) 28.3 ((CH₃)₃), 52.6 (OCH₃), 59.6 (C₂), 73.9 (C₃), 80.2 (C(CH₃)₃), 126.1 (Ar-C), 128.1 (Ar-C), 128.4

(Ar-C), 140.0 (Ar-C), 155.7 (C=O), 171.5 (C₁); LRMS (ESI⁺) m/z : 318.2 ([M + Na]⁺ 97%); HRMS (ESI⁺) m/z :

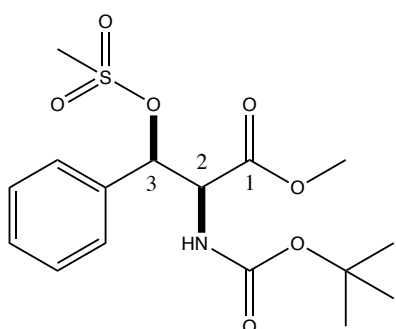
[M + Na]⁺ calcd. for C₁₅H₂₁NO₅Na, 318.1312, found 318.1312.

General procedure for the mesylation and subsequent thioacetylation of Boc-protected *allo*/*threo*-phenylserine:⁷³

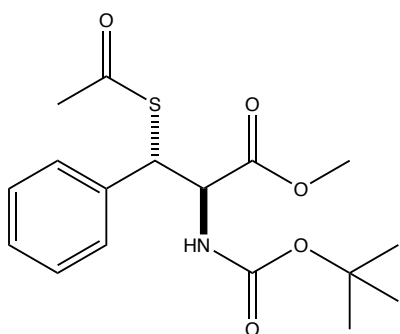
To a solution of Boc-protected *allo*/*threo*-phenylserine **127a/225** (1.0 eq.) in DCM at 0°C was added MsCl or Ms₂O (1.1-1.2 eq.) and Et₃N (1.2-2 eq.) dropwise and left to stir at 0°C for 1 h. Then the solution was quenched with dilute HCl solution (aq.) and extracted with DCM. The organic layer was washed with sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered and concentrated *in-vacuo* at 15-20°C to obtain a foamy white solid/pale-yellow oil which was then taken on crude into the next reaction sequence immediately (Caution: this compound is extremely unstable when left overnight at rt or heated). To this white foamy solid/pale yellow oil was added dry DMF and KSAc (2-3 eq.) and stirred at rt over 1-2 d. This solution was then partitioned between H₂O and DCM, and the organic layer was washed with H₂O (x5), dried over Na₂SO₄, filtered, concentrated *in-vacuo* and then purified by flash column chromatography to yield the *N,S*-protected phenylcysteine products **224/227**.

Ethyl (2*R,3*R**)-3-(acetylthio)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate 224**

Yield (1.53 g, 57% over two steps from **127a**); Red/purple oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.55; $\nu_{\max}/\text{cm}^{-1}$ 3367 (C-S), 2979 (C-H), 1699 (C=O); δ_H (400 MHz, CDCl_3) 1.07 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.41 (9H, br s, $\text{C}(\text{CH}_3)_3$), 2.32 (3H, s, CH_3), 4.02 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.72 (1H, br m, H2), 4.99 (1H, br d, $J=7.2$ Hz, H3), 5.26 (1H, br d, $J=9.6$ Hz, NH), 7.25-7.30 (5H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.9 (OCH_2CH_3), 28.4 ($(\text{CH}_3)_3$), 30.5 (CH_3), 50.6 (C3), 58.3 (C2), 61.7 (OCH_2CH_3), 80.3 ($\text{C}(\text{CH}_3)_3$), 128.2 (Ar-C), 128.5 (Ar-C), 128.8 (Ar-C), 137.8 (Ar-C), 155.3 (C=O), 170.4 (C1), 194.0 (C=O); LRMS (ESI^+) m/z : 390.2 ($[\text{M} + \text{Na}]^+$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_5\text{SNa}$, 390.1346, found 390.1346.

Methyl (2*S,3*R**)-2-((*tert*-butoxycarbonyl)amino)-3-((methylsulfonyl)oxy)-3-phenylpropanoate 226**

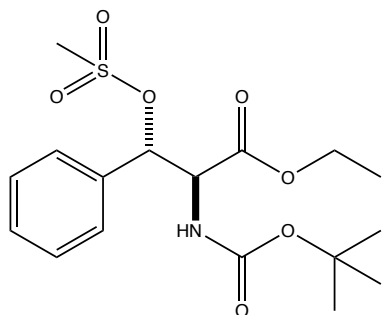
Yield (3.81 g, Quantitative); Light-green oil; (400 MHz, CDCl_3) 1.34 (9H, br s, $\text{C}(\text{CH}_3)_3$), 2.82 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.75 (1H, br dd, $J=3.5$ Hz, 9.7 Hz, H2), 5.37 (1H, br d, $J=9.6$ Hz, NH), 6.00 (1H, br d, $J=3.4$ Hz, H3), 7.28-7.41 (5H, s, Ar-H); LRMS (ESI^+) m/z : 396.0 ($[\text{M} + \text{Na}]^+$ 43%).

Methyl (2*R,3*S**)-3-(acetylthio)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate 227**

Yield (525 mg, 24% over two steps from **225**); Red/purple oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 3361 (C-S), 2978 (C-H), 1746 (C=O), 1699 (C=O); δ_H (400 MHz, CDCl_3) 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.34 (3H, s, CH_3), 3.69 (3H, s, OCH_3), 4.92 (1H, br dd, $J=5.0$ Hz, 9.7 Hz, H2), 5.06 (1H, br d, $J=9.8$ Hz, NH), 5.14 (1H, br d, $J=4.9$ Hz, H3), 7.25-7.32 (5H, m, Ar-H); δ_C (101 MHz, CDCl_3) 28.4 ($(\text{CH}_3)_3$), 30.6 (CH_3), 50.1 (C3), 52.5 (OCH_3),

57.5 (C2), 80.4 (C(CH₃)₃), 128.4 (Ar-C), 128.8 (Ar-C), 129.8 (Ar-C), 136.7 (Ar-C), 155.4 (C=O), 170.4 (C1), 193.7 (C=O); LRMS (ESI⁺) m/z : 376.6 ([M + Na]⁺ 46%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₇H₂₃NO₅Na, 376.1189, found 376.1189.

Ethyl (2S*,3S*)-2-((*tert*-butoxycarbonyl)amino)-3-((methylsulfonyl)oxy)-3-phenylpropanoate 231



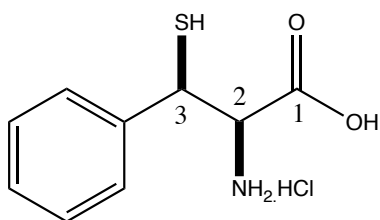
Yield (1.77 g, Quantitative); Yellow oil; $\nu_{\max}/\text{cm}^{-1}$ 3371 (C-S), 2981 (C-H), 1740 (C=O), 1715 (C=O), 1366 (S=O); δ_{H} (400 MHz, CDCl₃) 1.20 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.40 (9H, s, C(CH₃)₃), 2.92 (3H, br s, CH₃), 4.15 (2H, m, OCH₂CH₃), 4.83 (1H, br dd, $J=5.0$ Hz, 8.9 Hz, H₂), 5.23 (1H, br m, NH), 5.92 (1H, br d, $J=5.0$ Hz, H₃), 7.28-7.39 (5H, s, Ar-H);

LRMS (ESI⁺) m/z : 410.0 ([M + Na]⁺ 38%); HRMS (ESI⁺) m/z : [M + Na]⁺ calcd. for C₁₇H₂₅NO₇Na, 410.1244, found 410.1244.

General procedure for the synthesis of *allo*/*threo*-phenylcysteine hydrochloride salt:

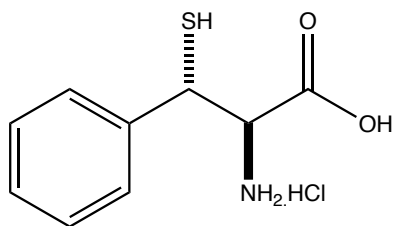
6 M HCl solution (aq.) was added to *allo*/*threo*-thioacylated-Boc-protected amino ester **224/227** (1.0 eq.) and heated to reflux overnight. The solution was then left to cool to rt, separated between Et₂O and water, and the aqueous layer was concentrated *in-vacuo* to obtain a crude yellow/green solid and was used without further purification.

(2R*,3R*)-2-Amino-3-mercapto-3-phenylpropanoic acid hydrochloride salt 232



Yield (230 mg, Quantitative); Green solid; m.p. 200-206°C (lit.¹¹¹ 196-197°C); $\nu_{\max}/\text{cm}^{-1}$ 3027 (C-S), 2955 (N-H), 2901 (C-H), 2465 (S-H), 1727 (C=O); δ_{H} (400 MHz, D₂O) 4.44 (1H, d, $J=6.7$ Hz, H₂), 4.73 (1H, d, $J=6.7$ Hz, H₃), 7.40-7.47 (5H, m, Ar-H); δ_{C} (101 MHz, D₂O) 43.1

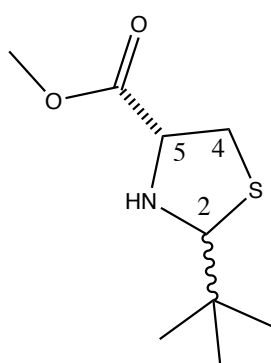
(C3), 59.7 (C2), 127.4 (Ar-C), 128.9 (Ar-C), 129.3 (Ar-C), 137.6 (Ar-C), 169.9 (C1); LRMS (ESI⁺) m/z : 198.3 ([M + H]⁺ 28%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₉H₁₂NO₂S, 198.0583, found 198.0585.

(2*R,3*S**)-2-Amino-3-mercapto-3-phenylpropanoic acid hydrochloride salt 233**

Yield (126 mg, Quantitative); Yellow solid; δ_{H} (400 MHz, D_2O) 4.38 (1H, d, $J=6.2$ Hz, H2), 4.74 (1H, underneath D_2O peak, H3), 7.42-7.46 (5H, m, Ar-H); δ_{C} (101 MHz, D_2O) 42.3 (C3), 60.1 (C2), 127.8 (Ar-C), 129.1 (Ar-C), 129.3 (Ar-C), 136.3 (Ar-C); LRMS (ESI⁻) m/z : 196.1 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_9\text{H}_{10}\text{NO}_2\text{S}$, 196.0427, found 196.0436.

General procedure for the synthesis of thiazolidines:³⁵

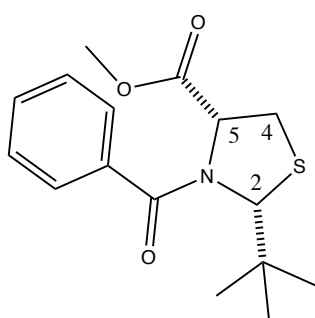
L-Cysteine methyl ester hydrochloride salt **8c** (1 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2 eq.) and trimethylacetaldehyde (1.1 eq.) was added dropwise and the mixture was then heated to more than 100°C with continuous removal of water using a Dean-Stark apparatus overnight. The white precipitate was then filtered and washed with Et_2O . The combined filtrates were then concentrated under reduced pressure to furnish the desired thiazolidine **9c** which was used without further purification.

Methyl (4*R*)-2-(*tert*-butyl)thiazolidine-4-carboxylate 9c

Yield (2.12 g, 89%); Colourless oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3319 (N-H), 2954 (C-H), 2906 (C-H), 2868 (C-H), 1741 (C=O); 2:1 mixture of diastereomers at the C2-position; δ_{H} (Major diastereomer) (400 MHz, CDCl_3) 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.31 (1H, br s, NH), 2.67 (1H, dd, $J=9.7$ Hz, 10.2 Hz, H4), 3.25 (1H, dd, $J=6.7$ Hz, 10.2 Hz, H4), 3.77 (3H, s, OCH_3), 3.80 (1H, dd, $J=6.7$ Hz, 9.7 Hz, H5), 4.45 (1H, s, H2); δ_{C} (Major diastereomer) (101 MHz, CDCl_3) 27.1 ($(\text{CH}_3)_3$), 34.1 ($\text{C}(\text{CH}_3)_3$), 37.6 (C4), 52.6 (OCH_3), 65.6 (C5), 82.0 (C2), 172.0 (C=O); δ_{H} (Minor diastereomer) (400 MHz, CDCl_3) 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.31 (1H, br s, NH), 3.01 (1H, dd, $J=5.6$ Hz, 10.6 Hz, H4), 3.11 (1H, dd, $J=6.4$ Hz, 10.6 Hz, H4), 3.74 (3H, s, OCH_3), 4.13 (1H, m, H5), 4.52 (1H, s, H2); δ_{C} (Minor diastereomer) (101 MHz, CDCl_3) 26.7 ($(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 37.2 (C4), 52.5 (OCH_3), 65.2 (C5), 79.9 (C2), 172.6 (C=O); LRMS (ESI⁺) m/z : 204.0 ($[\text{M} + \text{H}]^+$ 100%); HRMS (ESI⁺) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_9\text{H}_{18}\text{NO}_2\text{S}$, 204.1053, found 204.1054.

General procedure for the *N*-benzoyl-protection of thiazolidines:⁷⁴

To a stirring solution of thiazolidine **9c** (1.0 eq.) in DCM at 0°C was added benzoyl chloride (1.1 eq.) and pyridine (1.1 eq.) and the solution was stirred for 10 min at this temperature. The solution was then stirred at rt for 2 days, and the crude mixture was then washed with sat. NH₄Cl (aq.), sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated *in-vacuo* and then purified by flash column chromatography to yield the desired product **237**.

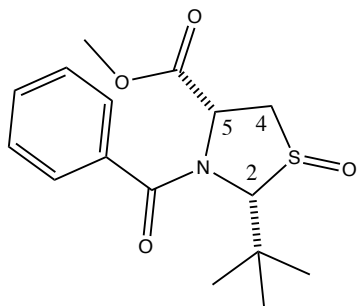
Methyl (2*R*,4*R*)-3-benzoyl-2-(*tert*-butyl)thiazolidine-4-carboxylate **237**

Yield (2.41 g, 76%); Thick colourless oil; *R*_f (20% EtOAc in Pet. Ether 40:60) 0.55; $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (C-H), 1750 (C=O), 1657 (C=O); 1.7:1 mixture of rotamers; δ_{H} (233K) (500 MHz, CD₂Cl₂) 0.74/1.02 (9H, s, C(CH₃)₃), 3.08 (1H, dd, *J*=7.5 Hz, 11.7 Hz, H4)/3.27 (1H, m, H4), 3.62/3.77 (3H, s, OCH₃), 4.65 (1H, dd, *J*=5.3 Hz, 7.4 Hz, H5)/5.06 (1H, app t., *J*=9.6 Hz, H5), 5.13/5.73

(1H, s, H2), 7.35-7.48 (5H, m, Ar-H); δ_{C} (233K) (126 MHz, CD₂Cl₂) 26.5/26.6 ((CH₃)₃), 33.1/33.6 (C4), 38.4/39.7 (C(CH₃)₃), 52.7/52.8 (OCH₃), 63.8/66.1 (C5), 72.5/74.4 (C2), 126.6/126.7 (Ar-C), 128.4/128.5 (Ar-C), 129.7/130.0 (Ar-C), 136.1/136.5 (Ar-C), 170.4/171.0 (C=O), 170.8/173.2 (C=O); LRMS (ESI⁺) *m/z*: 308.0 ([M + H]⁺ 13%), 330.0 ([M + Na]⁺ 100%), 346.0 ([M + K]⁺ 61%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₁₆H₂₂NO₃S, 308.1315, found 308.1315.

General procedure for the oxidation of *N*-benzoyl protected thiazolidines:^{74,76}

To a stirring solution of *N*-benzoyl protected thiazolidine **237** (1.0 eq.) in dry DCM at rt was added slowly *m*-CPBA (1.2 eq.) portion wise and the solution was stirred at this temperature overnight. The solution was then quenched with sat. NaHCO₃ (aq.), and then washed with sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated *in-vacuo* and purified by flash column chromatography to yield the desired sulfoxide **234**.

Methyl (2*R*,4*R*)-3-benzoyl-2-(*tert*-butyl)thiazolidine-4-carboxylate 1-oxide **234**

Yield (904 mg, 74%); Thick colourless oil; R_f (100% EtOAc) 0.45;

$\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 1752 (C=O), 1659 (C=O), 1050 (S=O); 1.4:1

mixture of rotamers; δ_H (233K) (500 MHz, CD_2Cl_2) 0.80/1.11 (9H, s,

$\text{C}(\text{CH}_3)_3$), 3.16 (1H, dd, $J=9.3$ Hz, 14.8 Hz, H4)/3.28 (1H, dd, $J=9.6$ Hz,

14.9 Hz, H4), 3.49 (1H, ddd, $J=2.1$ Hz, 8.5 Hz, 14.8 Hz, H4)/3.62 (1H,

ddd, $J=1.6$ Hz, 9.1 Hz, 15.0 Hz, H4), 3.57/3.80 (3H, s, OCH_3), 4.94 (1H, app. t, $J=8.9$ Hz, H5)/5.57 (1H, m,

underneath H2 peak, H5), 5.13/5.57 (1H, s, H2), 7.32-7.45 (5H, m, Ar-H); δ_C (233K) (126 MHz, CD_2Cl_2)

27.3/27.4 ($(\text{CH}_3)_3$), 35.4/35.4 ($\text{C}(\text{CH}_3)_3$), 52.0/53.2 (C4), 53.1 (OCH_3), 60.9/62.6 (C5), 92.8/92.9 (C2),

125.9/127.6 (Ar-C), 128.6/128.6 (Ar-C), 129.9/129.9 (Ar-C), 135.0/135.7 (Ar-C), 170.5/171.5 (C=O),

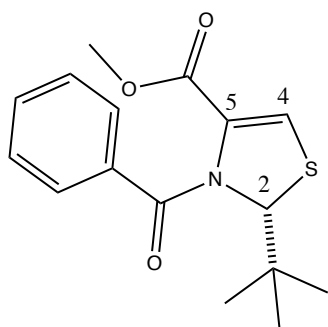
172.7/174.2 (C=O); LRMS (ESI^+) m/z : 346.0 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for

$\text{C}_{16}\text{H}_{21}\text{NO}_4\text{SNa}$, 346.1084, found 346.1086.

General procedure for the synthesis of olefin **238:**^{74,76}

Method A: To a stirring solution of *N*-benzoyl-protected thiazolidine-*S*-oxide **234** (1.0 eq.) in anhydrous DCM at 0°C was added DIPEA (1.2 eq.) and trimethylsilyl chloride (1.2 eq.) and this solution was stirred at this temperature for 30 mins and then the solution was stirred at rt overnight. The solution was then washed with sat. NH_4Cl (aq.), brine, dried over Na_2SO_4 , filtered, concentrated *in-vacuo* and purified by flash column chromatography to yield the alkenic thiazolidine **238**.

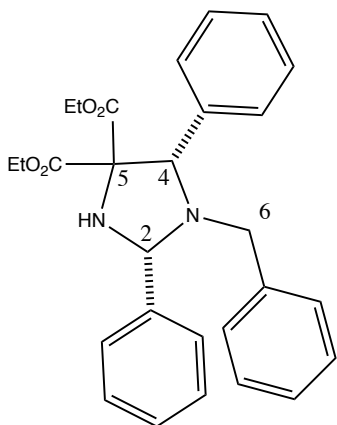
Method B: To a solution of *N*-benzoyl-protected thiazolidine **237** (1.0 eq.) in DCM at 0°C was added DBU (1.8 eq.) and CBrCl_3 (1.3 eq.). The reaction was stirred at 0°C overnight, in which the solution turned from pale yellow to orange to dark red overnight. To the solution was then added sat. NaHCO_3 (aq.) at the same volume as DCM at 0°C and the mixture was left to warm to rt. The two layers were separated, and the aqueous phase was extracted with DCM (x3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in-vacuo*. The concentrate was then purified by flash column chromatography to obtain the alkenic thiazolidine **238**.

Methyl (*R*)-3-benzoyl-2-(*tert*-butyl)-2,3-dihydrothiazole-4-carboxylate **238**

Method A: Yield (169 mg, 29%); Method B: Yield (459 mg, 19%); Pale yellow oil that solidified to a white solid overnight; m.p. 125-129°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.70; $\nu_{\max}/\text{cm}^{-1}$ 2966 (C-H), 1721 (C=O), 1662 (C=O) 1573 (C=C); δ_H (400 MHz, CDCl_3) 1.02 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.22 (3H, s, OCH_3), 5.92 (1H, d, $J=0.8$ Hz, H2), 7.01 (1H, d, $J=0.8$ Hz, H4), 7.32-7.45 (5H, m, Ar-H); δ_C (101 MHz, CDCl_3) 24.9 ($(\text{CH}_3)_3$), 39.5 ($\text{C}(\text{CH}_3)_3$), 51.7 (OCH_3), 79.8 (C2), 127.3 (Ar-C), 127.6 (C4), 128.3 (Ar-C), 130.5 (Ar-C), 136.3 (Ar-C), 159.8 (C=O), 171.0 (C=O); LRMS (ESI^+) m/z : 328.0 ($[\text{M} + \text{Na}]^+$ 96%); HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{SNa}$, 328.0978, found 328.0979.

General procedure for the synthesis of Imidazolidine:^{34-35,80-81}

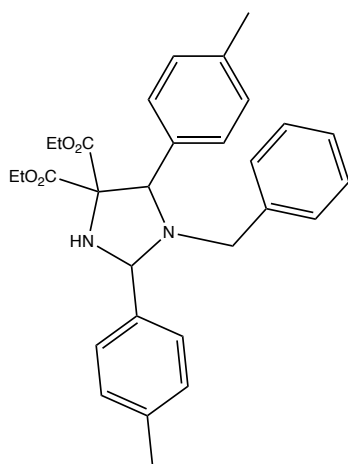
Diethyl aminomalonate hydrochloride salt **171** (1.0 eq.) was suspended in petroleum ether 40:60 and cooled to 0°C. Triethylamine (1.2-1.4 eq.), aldehyde (2.1-2.5 eq.) and amine (1.0-1.2 eq.) were added dropwise, and the mixture was then heated to more than 100°C with continuous removal of water using a Dean-Stark apparatus for 16-24 h. The white/brown precipitate was then filtered and washed with Et_2O . The combined filtrates were then concentrated under reduced pressure and then purified by flash column chromatography to yield the desired imidazolidines **245a-l** and **246**.

Diethyl (2*R,5*S**)-1-benzyl-2,5-diphenylimidazolidine-4,4-dicarboxylate **245a****

Yield (1.64 g, 65%); White solid; m.p. 145-147°C (lit.⁸⁰ 147°C); R_f (20% EtOAc in Pet. Ether 40:60) 0.63; $\nu_{\max}/\text{cm}^{-1}$ 3307 (N-H), 3063 (C-H), 3030 (C-H), 2985 (C-H), 1728 (C=O); 2.3:1 mixture of 2,4-*cis/trans* diastereomers; δ_H (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.72 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.19 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.32 (1H, dq, $J=7.2$ Hz, 10.6 Hz, OCH_2CH_3), 3.52 (1H, br s, H1 or NH), 3.59 (2H, s, H6), 3.79 (1H, m, OCH_2CH_3), 4.09 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.32 (1H, dq, $J=7.2$

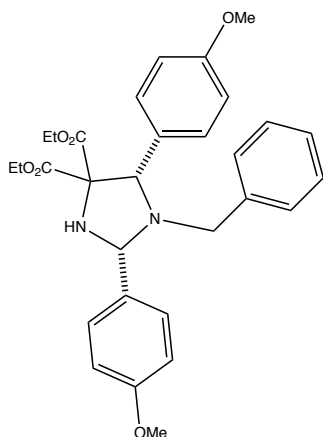
Hz, 10.7 Hz, OCH₂CH₃), 4.44 (1H, br s, H₂), 4.83 (1H, s, H₄), 6.87 (2H, m, Ar-H), 7.10-7.47 (9H, m, Ar-H), 7.56 (2H, m, Ar-H), 7.71 (2H, m, Ar-H); δ_c (2,4-*cis* diastereomer) (101 MHz, CDCl₃) 13.4 (OCH₂CH₃), 14.0 (OCH₂CH₃), 52.0 (C₆), 61.8 (OCH₂CH₃), 62.1 (OCH₂CH₃), 69.6 (C₄), 75.8 (C₅), 79.9 (C₂), 127.0 (Ar-C), 127.8-127.9 (Ar-C), 128.2 (Ar-C), 128.7 (Ar-C), 129.0 (Ar-C), 130.1 (Ar-C), 134.8 (Ar-C), 138.2 (Ar-C), 138.9 (Ar-C), 169.7 (C=O), 170.2 (C=O); LRMS (ESI⁺) *m/z*: 459.2 ([M + H]⁺ 100%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₂₈H₃₁N₂O₄, 459.2278, found 459.2272.

Diethyl 1-benzyl-2,5-bis(4-methylphenyl)imidazolidine-4,4-dicarboxylate 245b



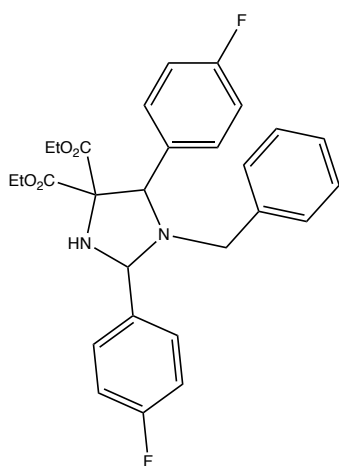
Yield (3.13 g, 58%); Light green oil; R_f (10% EtOAc in Pet. Ether 40:60) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1729 (C=O); 1:1.9 mixture of 2,4-*cis*/*trans* diastereomers; δ_H (2,4-*cis* diastereomer) (400 MHz, CDCl₃) 0.74 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.18 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 2.35 (3H, s, CH₃), 2.38 (3H, s, CH₃), 3.37 (1H, dq, *J*=7.1 Hz, 10.6 Hz, OCH₂CH₃), 3.52 (1H, br s, H₁ or NH), 3.58 (2H, s, H₆), 3.80 (1H, m, OCH₂CH₃), 4.08 (1H, m, OCH₂CH₃), 4.30 (1H, m, OCH₂CH₃), 4.41 (1H, m, H₂), 4.76 (1H, s, H₄), 6.86-7.80

(13H, m, Ar-H); δ_C (2,4-*cis* diastereomer) (101 MHz, CDCl₃) 13.3 (OCH₂CH₃), 14.0 (OCH₂CH₃), 21.3 (CH₃), 21.4 (CH₃), 51.3 (C₆), 61.8 (OCH₂CH₃), 62.1 (OCH₂CH₃), 68.9 (C₄), 75.7 (C₅), 79.2 (C₂), 126.8-138.7 (Ar-C), 169.9 (C=O), 170.3 (C=O); δ_H (2,4-*trans* diastereomer) (400 MHz, CDCl₃) 0.74 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.32 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 2.34 (6H, s, CH₃, CH₃), 2.95 (1H, d, *J*=14.2 Hz, H₆), 3.46 (1H, d, *J*=14.2 Hz, H₆), 3.80 (2H, m, OCH₂CH₃), 4.30 (1H, m, OCH₂CH₃), 4.38 (1H, m, OCH₂CH₃), 5.07 (1H, s, H₄), 5.10 (1H, br s, H₂), 6.86-7.80 (13H, m, Ar-H); δ_C (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.3 (OCH₂CH₃), 21.3 (CH₃), 21.3 (CH₃), 49.4 (C₆), 61.7 (OCH₂CH₃), 62.4 (OCH₂CH₃), 67.3 (C₄), 75.9 (C₅), 79.3 (C₂), 126.8-138.7 (Ar-C), 168.8 (C=O), 171.0 (C=O); LRMS (ESI⁺) *m/z*: 487.2 ([M + H]⁺ 100%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₀H₃₅O₄N₂, 487.2591, found 487.2586.

Diethyl (2*R,5*S**)-1-benzyl-2,5-bis(4-methoxyphenyl)imidazolidine-4,4-dicarboxylate 245c**

Yield (2.02 g, 70%); Light green oil; R_f (10% EtOAc in Pet. Ether 40:60) 0.23; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1729 (C=O), 1610 (N-H); >94:6 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.79 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.19 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.41 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.56 (2H, s, H6), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.85 (1H, m, OCH_2CH_3), 4.08 (1H, m, OCH_2CH_3), 4.31 (1H, m, OCH_2CH_3), 4.38 (1H, s, H2), 4.74 (1H, s, H4), 6.85-7.86 (13H, m, Ar-H); δ_{C}

(2,4-*cis* diastereomer) (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.0 (OCH_2CH_3), 51.6 (C6), 55.4 (OCH_3), 55.5 (OCH_3), 60.5 (OCH_2CH_3), 61.8 (OCH_2CH_3), 68.8 (C4), 75.5 (C5), 79.1 (C2), 113.7 (Ar-C), 114.1 (Ar-C), 127.0 (Ar-C), 127.8 (Ar-C), 129.9-130.1 (Ar-C), 131.1 (Ar-C), 132.1 (Ar-C), 134.9 (Ar-C), 159.4 (Ar-C), 160.1 (Ar-C), 169.9 (C=O), 170.3 (C=O); LRMS (ESI^+) m/z : 519.2 ($[\text{M} + \text{H}]^+$ 71%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{30}\text{H}_{35}\text{O}_6\text{N}_2$, 519.2490, found 519.2488.

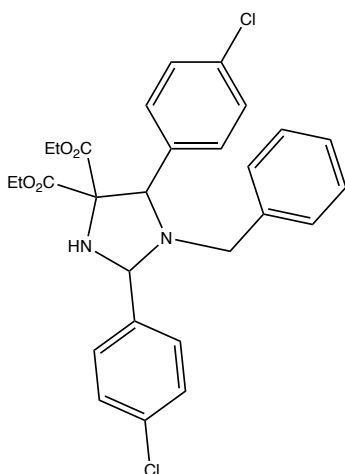
Diethyl 1-benzyl-2,5-bis(4-fluorophenyl)imidazolidine-4,4-dicarboxylate 245d

Yield (6.07 g, Quantitative); Light green oil; R_f (10% EtOAc in Pet. Ether 40:60) 0.30; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 1729 (C=O), 1603 (N-H); 2.9:1 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.78 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.19 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.40 (1H, m, OCH_2CH_3), 3.53 (1H, d, $J=14.0$ Hz, H6), 3.54 (1H, d, $J=14.0$ Hz, H6), 3.81 (1H, m, OCH_2CH_3), 4.09 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.31 (1H, m, OCH_2CH_3), 4.42 (1H, br d, $J=9.8$ Hz, H2), 4.80 (1H, s, H4), 6.80-7.91

(13H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl_3) 13.4 (OCH_2CH_3), 14.0 (OCH_2CH_3), 52.7 (C6), 62.0 (OCH_2CH_3), 62.3 (OCH_2CH_3), 69.5 (C4), 75.7 (C5), 79.8 (C2), 114.9-139.3 (Ar-C), 162.6 (d, $J=246.3$ Hz, Ar-C), 163.2 (d, $J=247.1$ Hz, Ar-C), 169.6 (C=O), 170.0 (C=O); δ_{H} (2,4-*trans* diastereomer) (400 MHz, CDCl_3) 0.78 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.29 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.92 (1H, d, $J=14.2$ Hz, H6), 3.45 (1H, d, $J=14.3$ Hz, H6), 3.82 (2H, m, OCH_2CH_3), 4.32 (2H, m, OCH_2CH_3), 5.09 (1H, s, H4), 5.12 (1H, s, H2), 6.80-7.91

(13H, m, Ar-H); δ_c (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.2 (OCH₂CH₃), 49.6 (C6), 61.9 (OCH₂CH₃), 62.5 (OCH₂CH₃), 66.9 (C4), 75.7 (C5), 78.7 (C2), 114.9-139.3 (Ar-C), 162.7 (d, $J=246.8$ Hz, Ar-C), 163.0 (d, $J=246.7$ Hz, Ar-C), 168.6 (C=O), 170.7 (C=O); LRMS (ESI⁺) m/z : 517.2 ([M + Na]⁺ 6%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₂₈H₂₉O₄N₂F₂, 495.2101, found 495.2089.

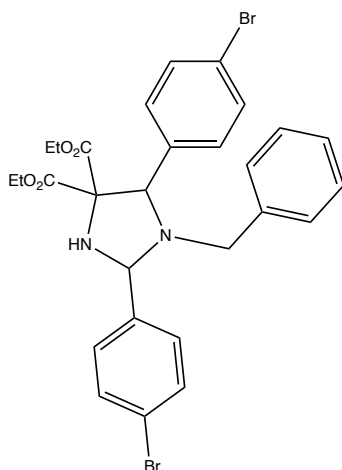
Diethyl 1-benzyl-2,5-bis(4-chlorophenyl)imidazolidine-4,4-dicarboxylate 245e



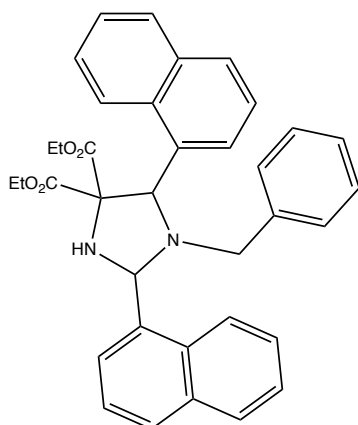
Yield (2.53 g, Quantitative); Colourless oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.65 and 0.78; $\nu_{\max}/\text{cm}^{-1}$ 3304 (N-H), 2983 (C-H), 1730 (C=O);

1:2.3 mixture of 2,4-*cis/trans* diastereomers; δ_H (2,4-*cis* diastereomer) (400 MHz, CDCl₃) 0.79 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.20 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.42 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH₂CH₃), 3.53 (1H, d, $J=14.0$ Hz, H6), 3.57 (1H, d, $J=14.0$ Hz, H6), 3.84 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH₂CH₃), 4.11 (1H, m, OCH₂CH₃), 4.32 (1H, m, OCH₂CH₃), 4.42 (1H, br s, H2), 4.79 (1H, s, H4), 6.80-7.62 (13H, m, Ar-H); δ_c (2,4-*cis* diastereomer) (101

MHz, CDCl₃) 13.4 (OCH₂CH₃), 14.0 (OCH₂CH₃), 52.7 (C6), 62.1 (OCH₂CH₃), 62.4 (OCH₂CH₃), 69.4 (C4), 75.7 (C5), 79.8 (C2), 127.3 (Ar-C), 128.0 (Ar-C), 128.4 (Ar-C), 129.0 (Ar-C), 130.0 (Ar-C), 130.1 (Ar-C), 130.3 (Ar-C), 133.7 (Ar-C), 134.8 (Ar-C), 134.8 (Ar-C), 136.7 (Ar-C), 137.5 (Ar-C), 169.5 (C=O), 170.0 (C=O); δ_H (2,4-*trans* diastereomer) (400 MHz, CDCl₃) 0.80 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.30 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.93 (1H, d, $J=14.2$ Hz, H6), 3.46 (1H, d, $J=14.3$ Hz, H6), 3.82 (2H, m, OCH₂CH₃), 4.33 (2H, m, OCH₂CH₃), 5.08 (1H, s, H4), 5.11 (1H, br s, H2), 7.10-7.85 (13H, m, Ar-H); δ_c (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 49.7 (C6), 62.0 (OCH₂CH₃), 62.6 (OCH₂CH₃), 67.0 (C4), 75.7 (C5), 78.7 (C2), 127.2-139.5 (Ar-C), 168.6 (C=O), 170.6 (C=O); LRMS (ESI⁺) m/z : 527.1 ([M³⁵⁺³⁵ + H]⁺ 100%), 529.1 ([M³⁵⁺³⁷ + H]⁺ 90%), 531.1 ([M³⁷⁺³⁷ + H]⁺ 40%); HRMS (ESI⁺) m/z : [M³⁵⁺³⁵ + H]⁺ calcd. for C₂₈H₂₉O₄N₂Cl₂, 527.1475, found 527.1488; [M³⁵⁺³⁷ + H]⁺ calcd. for C₂₈H₂₉O₄N₂Cl₂, 529.1448, found 529.1462; [M³⁷⁺³⁷ + H]⁺ calcd. for C₂₈H₂₉O₄N₂Cl₂, 531.1428, found 531.1424.

Diethyl 1-benzyl-2,5-bis(4-bromophenyl)imidazolidine-4,4-dicarboxylate 245f

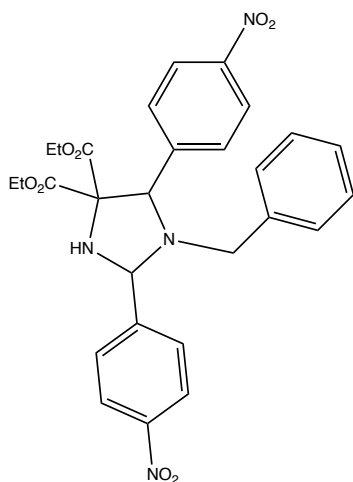
Yield (6.57 g, 96%); Light green oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.38 and 0.35; $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 1729 (C=O), 1645 (N-H); 1:2.6 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.21 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.46 (1H, m, OCH_2CH_3), 3.53 (1H, d, $J=14.0$ Hz, H6), 3.58 (1H, d, $J=13.9$ Hz, H6), 3.83 (1H, m, OCH_2CH_3), 4.12 (1H, m, OCH_2CH_3), 4.32 (1H, m, OCH_2CH_3), 4.42 (1H, br m, H2), 4.78 (1H, s, H4), 6.81-7.77 (13H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl_3) 13.4 (OCH_2CH_3), 14.0 (OCH_2CH_3), 52.6 (C6), 62.1 (OCH_2CH_3), 62.4 (OCH_2CH_3), 69.5 (C4), 75.7 (C5), 79.8 (C2), 121.8-140.0 (Ar-C), 169.5 (C=O), 169.9 (C=O); δ_{H} (2,4-*trans* diastereomer) (400 MHz, CDCl_3) 0.80 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.31 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.94 (1H, d, $J=14.3$ Hz, H6), 3.46 (1H, d, $J=14.3$ Hz, H6), 3.83 (2H, m, OCH_2CH_3), 4.32 (2H, m, OCH_2CH_3), 5.07 (1H, s, H4), 5.10 (1H, br s, H2), 6.81-7.77 (13H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 14.2 (OCH_2CH_3), 49.7 (C6), 62.0 (OCH_2CH_3), 62.6 (OCH_2CH_3), 67.0 (C4), 75.7 (C5), 78.8 (C2), 121.8-140.0 (Ar-C), 168.5 (C=O), 170.6 (C=O); LRMS (ESI^+) m/z : 615.8 ($[\text{M}^{79+79} + \text{H}]^+$ 60%), 617.8 ($[\text{M}^{79+81} + \text{H}]^+$ 100%), 619.8 ($[\text{M}^{81+81} + \text{H}]^+$ 62%); HRMS (ESI^+) m/z : $[\text{M}^{79+79} + \text{H}]^+$ calcd. for $\text{C}_{28}\text{H}_{29}\text{O}_4\text{N}_2\text{Br}_2$, 615.0500, found 615.0481; $[\text{M}^{79+81} + \text{H}]^+$ calcd. for $\text{C}_{28}\text{H}_{29}\text{O}_4\text{N}_2\text{Br}_2$, 617.0479, found 617.0464; $[\text{M}^{81+81} + \text{H}]^+$ calcd. for $\text{C}_{28}\text{H}_{29}\text{O}_4\text{N}_2\text{Br}_2$, 619.0459, found 619.0442.

Diethyl 1-benzyl-2,5-di(naphthalen-1-yl)imidazolidine-4,4-dicarboxylate 245g

Yield (1.65 g, 62%); Foamy white solid; m.p. 65-68°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.63 and 0.53; $\nu_{\max}/\text{cm}^{-1}$ 3299 (N-H), 3060 (C-H), 2982 (C-H), 1728 (C=O); 1:3 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.20 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.27 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.84 (1H, dq, $J=7.2$ Hz, 10.6 Hz, OCH_2CH_3), 3.47 (1H, m, OCH_2CH_3), 3.79 (1H, m, H6), 3.82 (1H, d, $J=13.8$ Hz, H6), 4.22 (1H, m, OCH_2CH_3), 4.41 (1H, dq, $J=7.1$ Hz, 10.6 Hz, OCH_2CH_3), 5.42 (1H,

d, $J=11.3$ Hz, H2), 5.98 (1H, s, H4), 6.80-8.57 (19H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl_3) 12.9 (OCH_2CH_3), 14.0 (OCH_2CH_3), 50.8 (C6), 61.5 (OCH_2CH_3), 62.3 (OCH_2CH_3), 63.8 (C4), 76.4 (C2), 123.6-138.7 (Ar-C), 168.3 (C=O), 170.8 (C=O); δ_{H} (2,4-*trans* diastereomer) (400 MHz, CDCl_3) 0.26 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.11 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.31 (1H, d, $J=14.1$ Hz, H6), 3.47 (2H, m, OCH_2CH_3), 3.58 (1H, br s, NH), 3.74 (1H, d, $J=14.1$ Hz, H6), 4.22 (2H, m, OCH_2CH_3), 6.22 (1H, s, H2), 6.42 (1H, s, H4), 6.80-8.57 (19H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl_3) 12.6 (OCH_2CH_3), 14.1 (OCH_2CH_3), 53.3 (C6), 61.2 (C4), 61.6 (OCH_2CH_3), 62.2 (OCH_2CH_3), 76.5 (C2), 123.6-138.7 (Ar-C), 168.6 (C=O), 170.4 (C=O); LRMS (ESI⁺) m/z : 559.2 ($[\text{M} + \text{H}]^+$ 100%); HRMS (ESI⁺) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{36}\text{H}_{35}\text{N}_2\text{O}_4$, 559.2591, found 559.2587.

Diethyl 1-benzyl-2,5-bis(4-nitrophenyl)imidazolidine-4,4-dicarboxylate 245h



Yield (4.33 g, 83%); Yellow oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.30

and 0.20; $\nu_{\text{max}}/\text{cm}^{-1}$ 3310 (N-H), 2983 (C-H), 1731 (C=O), 1603 (N-H);

1:1.1 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400

MHz, CDCl_3) 0.76 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.23 (3H, t, $J=7.2$ Hz,

OCH_2CH_3), 3.37 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 3.48 (1H, br s,

NH), 3.55 (1H, d, $J=13.6$ Hz, H6), 3.59 (1H, d, $J=13.6$ Hz, H6), 3.84 (1H,

dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.16 (1H, dq, $J=7.1$ Hz, 10.6 Hz,

OCH_2CH_3), 4.36 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.62 (1H, br s,

H2), 4.97 (1H, s, H4), 6.81 (2H, m, Ar-H), 7.03 (3H, m, Ar-H), 7.69 (2H, d, $J=8.7$ Hz, Ar-H), 7.82 (2H, d,

$J=8.6$ Hz, Ar-H), 8.14 (2H, d, $J=8.8$ Hz, Ar-H), 8.20 (2H, d, $J=8.8$ Hz, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz,

CDCl_3) 13.5 (OCH_2CH_3), 14.0 (OCH_2CH_3), 54.5 (C6), 62.6 (OCH_2CH_3), 62.6 (OCH_2CH_3), 70.5 (C4), 76.1 (C5),

80.7 (C2), 123.3 (Ar-C), 123.9 (Ar-C), 127.7 (Ar-C), 128.1 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C),

134.8 (Ar-C), 145.9 (Ar-C), 146.0 (Ar-C), 147.7 (Ar-C), 148.5 (Ar-C), 168.9 (C=O), 169.5 (C=O); δ_{H} (2,4-*trans*

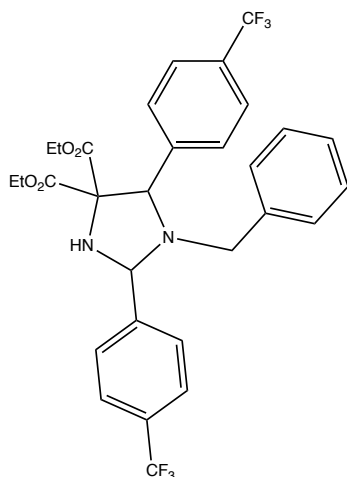
diastereomer) (400 MHz, CDCl_3) 0.76 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 2.95 (1H,

d, $J=14.3$ Hz, H6), 3.48 (1H, m, H6), 3.85 (2H, m, OCH_2CH_3), 4.33 (2H, m, OCH_2CH_3), 5.25 (1H, s, H4), 5.33

(1H, d, $J=5.1$ Hz, H2), 6.79-8.46 (13H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl_3) 13.6 (OCH_2CH_3),

14.2 (OCH₂CH₃), 50.1 (C₆), 62.4 (OCH₂CH₃), 62.9 (OCH₂CH₃), 67.2 (C₄), 75.7 (C₅), 78.4 (C₂), 123.3-148.5 (Ar-C), 168.2 (C=O), 170.0 (C=O); LRMS (ESI⁺) *m/z*: 548.2 ([M]⁺ 6%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₂₈H₂₉O₈N₄, 549.1980, found 549.1977.

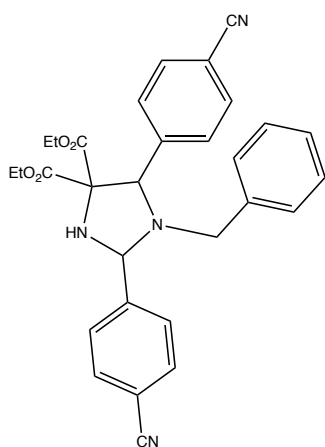
Diethyl 1-benzyl-2,5-bis(4-(trifluoromethyl)phenyl)imidazolidine-4,4-dicarboxylate 245i



Yield (2.25 g, 80%, contaminated with side-products); Colourless oil; R_f (20% EtOAc in Pet. Ether 40:60) 0.78 and 0.53; $\nu_{\max}/\text{cm}^{-1}$ 2986 (C-H), 1732 (C=O), 1620 (N-H); 1:2.4 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl₃) 0.76 (3H, m, OCH₂CH₃), 1.22 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.55 (1H, d, *J*=14.1 Hz, H₆), 3.55 (1H, m, OCH₂CH₃), 3.61 (1H, d, *J*=13.8 Hz, H₆), 3.80 (1H, m, OCH₂CH₃), 4.16 (1H, m, OCH₂CH₃), 4.35 (1H, m, OCH₂CH₃), 4.55 (1H, s, H₂), 4.92 (1H, s, H₄),

6.80-8.04 (13H, m, Ar-H); δ_{H} (2,4-*trans* diastereomer) (400 MHz, CDCl₃) 0.75 (3H, m, OCH₂CH₃), 1.32 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 2.96 (1H, d, *J*=14.3 Hz, H₆), 3.51 (1H, d, *J*=14.3 Hz, H₆), 3.80 (2H, m, OCH₂CH₃), 4.35 (2H, m, OCH₂CH₃), 5.21 (1H, s, H₄), 5.27 (1H, s, H₂), 6.80-8.04 (13H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.4 (OCH₂CH₃), 14.2 (OCH₂CH₃), 49.9 (C₆), 62.2 (OCH₂CH₃), 62.7 (OCH₂CH₃), 67.3 (C₄), 75.9 (C₅), 78.8 (C₂), 122.8-144.9 (Ar-C), 168.5 (C=O), 170.4 (C=O); LRMS (ESI⁺) *m/z*: 594.2 ([M]⁺ 30%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₀H₂₉O₄N₂F₆, 595.2026, found 595.2021.

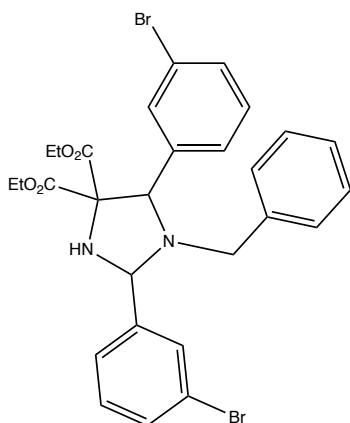
Diethyl 1-benzyl-2,5-bis(4-cyanophenyl)imidazolidine-4,4-dicarboxylate 245j



Yield (945 mg, 77%); White crystals/colourless oil; m.p. 55-58°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.20 and 0.13; $\nu_{\max}/\text{cm}^{-1}$ 3327 (N-H), 2984 (C-H), 2228 (C≡N), 1730 (C=O), 1609 (N-H); 1.9:1 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl₃) 0.77 (3H, m, OCH₂CH₃), 1.22 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 3.36 (1H, dq, *J*=7.2 Hz, 10.7 Hz, OCH₂CH₃), 3.52 (1H, d, *J*=13.6 Hz, H₆), 3.58 (1H, d, *J*=13.6 Hz, H₆), 3.85 (1H, m, OCH₂CH₃), 4.15 (1H, dq, *J*=7.1 Hz, 10.7 Hz, OCH₂CH₃), 4.34 (1H, m,

OCH₂CH₃), 4.54 (1H, br d, $J=9.8$ Hz, H₂), 4.90 (1H, s, H₄), 6.78-7.77 (13H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl₃) 13.4 (OCH₂CH₃), 14.0 (OCH₂CH₃), 54.3 (C₆), 62.5 (OCH₂CH₃), 62.6 (OCH₂CH₃), 70.6 (C₄), 76.0 (C₅), 80.9 (C₂), 111.8-146.0 (Ar-C), 169.0 (C=O), 169.5 (C=O); δ_{H} (2,4-*trans* diastereomer) (400 MHz, CDCl₃) 0.78 (3H, m, OCH₂CH₃), 1.29 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.93 (1H, d, $J=14.3$ Hz, H₆), 3.49 (1H, d, $J=14.2$ Hz, H₆), 3.84 (2H, m, OCH₂CH₃), 4.34 (2H, m, OCH₂CH₃), 5.18 (1H, s, H₄), 5.25 (1H, br d, $J=5.0$ Hz, H₂), 6.78-7.77 (13H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.2 (OCH₂CH₃), 50.1 (C₆), 62.3 (OCH₂CH₃), 62.8 (OCH₂CH₃), 67.4 (C₄), 75.7 (C₅), 78.7 (C₂), 111.8-146.0 (Ar-C), 168.3 (C=O), 170.1 (C=O); LRMS (ESI⁺) m/z : 509.2 ([M + H]⁺ 68%); HRMS (ESI⁺) m/z : [M – H][–] calcd. for C₃₀H₂₇O₄N₄, 507.2027, found 507.2025.

Diethyl 1-benzyl-2,5-bis(3-bromophenyl)imidazolidine-4,4-dicarboxylate 245k



Yield (1.01 g, 69%); Colourless oil; R_f (20% EtOAc in Pet. Ether 40:60)

0.50; ν_{max} /cm^{–1} 3315 (N-H), 2982 (C-H), 1730 (C=O); 1:2.2 mixture of

2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl₃) 0.85

(3H, m, OCH₂CH₃), 1.22 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.45 (1H, m,

OCH₂CH₃), 3.60 (2H, m, H₆), 3.84 (1H, m, OCH₂CH₃), 4.12 (1H, dq, $J=7.1$

Hz, 10.7 Hz, OCH₂CH₃), 4.34 (1H, m, OCH₂CH₃), 4.34 (1H, underneath

OCH₂CH₃ peaks, H₂), 4.77 (1H, s, H₄), 6.85-7.80 (13H, m, Ar-H); δ_{C} (2,4-

cis diastereomer) (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.0 (OCH₂CH₃), 53.2 (C₆), 62.2 (OCH₂CH₃), 62.4

(OCH₂CH₃), 69.8 (C₄), 75.8 (C₅), 80.2 (C₂), 122.5-143.5 (Ar-C), 169.2 (C=O), 169.8 (C=O); δ_{H} (2,4-*trans*

diastereomer) (400 MHz, CDCl₃) 0.80 (3H, m, OCH₂CH₃), 1.32 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.98 (1H, d, $J=14.1$

Hz, H₆), 3.52 (1H, d, $J=14.1$ Hz, H₆), 3.84 (2H, m, OCH₂CH₃), 4.34 (2H, m, OCH₂CH₃), 5.05 (1H, s, H₄),

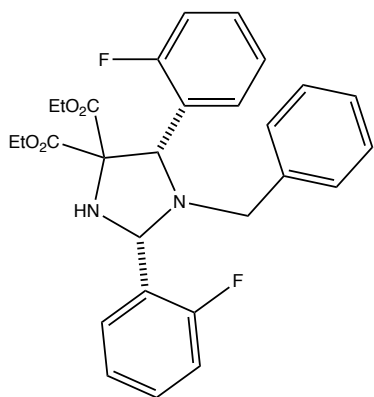
5.13 (1H, br d, $J=3.2$ Hz, H₂), 6.85-7.80 (13H, m, Ar-H); δ_{C} (2,4-*trans* diastereomer) (101 MHz, CDCl₃) 13.5

(OCH₂CH₃), 14.2 (OCH₂CH₃), 50.0 (C₆), 62.1 (OCH₂CH₃), 62.7 (OCH₂CH₃), 67.3 (C₄), 75.8 (C₅), 78.9 (C₂),

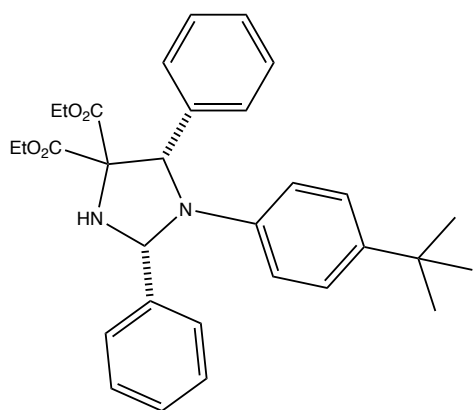
122.5-143.5 (Ar-C), 168.5 (C=O), 170.4 (C=O); LRMS (ESI⁺) m/z : 616.0 ([M⁷⁹⁺⁸¹]⁺ 29%); HRMS (ESI⁺) m/z :

[M⁷⁹⁺⁷⁹ – H][–] calcd. for C₂₈H₂₇O₄N₂Br₂, 613.0332, found 613.0330; [M⁷⁹⁺⁸¹ – H][–] calcd. for C₂₈H₂₇O₄N₂Br₂,

615.0313, found 615.0320; [M⁸¹⁺⁸¹ – H][–] calcd. for C₂₈H₂₇O₄N₂Br₂, 617.0297, found 617.0452.

Diethyl (2*R,5*S**)-1-benzyl-2,5-bis(2-fluorophenyl)imidazolidine-4,4-dicarboxylate 245I**

Yield (922 mg, 78%); Pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.68; $\nu_{\max}/\text{cm}^{-1}$ 3306 (N-H), 2983 (C-H), 1732 (C=O), 1616 (N-H); >19:1 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.81 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.39 (1H, br s, OCH_2CH_3), 3.63 (2H, s, H6), 3.68 (1H, br d, $J=9.3$ Hz, NH), 3.81 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.18 (1H, m, OCH_2CH_3), 4.37 (1H, dq, $J=7.2$ Hz, 10.8 Hz, OCH_2CH_3), 4.92 (1H, br d, $J=10.2$ Hz, H2), 5.30 (1H, br s, H4), 6.90-7.90 (13H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl_3) 13.4 (OCH_2CH_3), 14.0 (OCH_2CH_3), 54.5 (C6), 62.1 (OCH_2CH_3), 62.3 (OCH_2CH_3), 73.9 (d, $J=3.4$ Hz, C2), 76.0 (C5), 114.9 (d, $J=21.9$ Hz, Ar-C), 115.7 (d, $J=21.8$ Hz, Ar-C), 123.8 (d, $J=3.5$ Hz, Ar-C), 124.7 (d, $J=3.5$ Hz, Ar-C), 125.8 (d, $J=11.5$ Hz, Ar-C), 126.7 (d, $J=12.1$ Hz, Ar-C), 127.0 (Ar-C), 127.8 (Ar-C), 129.1-129.2 (Ar-C), 129.6 (Ar-C), 130.4 (d, $J=8.4$ Hz, Ar-C), 161.5 (d, $J=248.8$ Hz, Ar-C), 162.1 (d, $J=248.9$ Hz, Ar-C), 168.7 (C=O), 169.4 (C=O); δ_{F} (2,4-*cis* diastereomer) (377 MHz, CDCl_3) -116.95, -118.74; LRMS (ESI^+) m/z : 495.2 ($[\text{M} + \text{H}]^+$ 100%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{28}\text{H}_{29}\text{O}_4\text{N}_2\text{F}_2$, 495.2090, found 495.2086.

Diethyl (2*R,5*S**)-1-(4-(*tert*-butyl)phenyl)-2,5-diphenylimidazolidine-4,4-dicarboxylate 246**

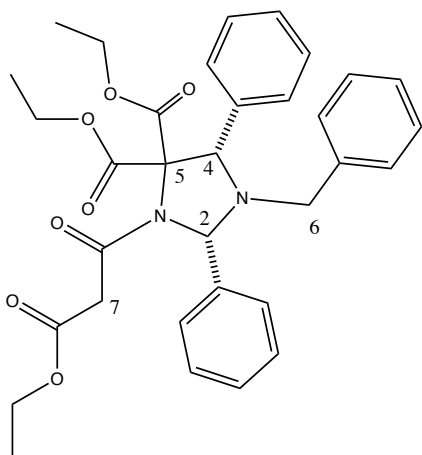
Yield (4.47 g, 56%); Yellow solid; m.p. 61-63°C; R_f (20% EtOAc in Pet. Ether 40:60) 0.68; $\nu_{\max}/\text{cm}^{-1}$ 3314 (N-H), 2962 (C-H), 1734 (C=O), 1614 (N-H); 4:1 mixture of 2,4-*cis/trans* diastereomers; δ_{H} (2,4-*cis* diastereomer) (400 MHz, CDCl_3) 0.94 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.20 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.28 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.54 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.62 (1H, d, $J=11.0$ Hz, NH), 3.81 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.24 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.41 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 5.36 (1H, br d, $J=10.8$ Hz, H2), 5.63 (1H, s, H4), 6.46 (2H, d, $J=8.9$ Hz, Ar-H), 7.08 (2H, d, $J=8.9$ Hz, Ar-H), 7.26-7.45 (6H, m, Ar-H), 7.58 (2H, m, Ar-H), 7.69 (2H, m, Ar-H); δ_{C} (2,4-*cis* diastereomer) (101 MHz, CDCl_3) 13.6

(OCH₂CH₃), 14.1 (OCH₂CH₃), 31.5 ((CH₃)₃), 33.9 (C(CH₃)₃), 62.2 (OCH₂CH₃), 62.6 (OCH₂CH₃), 70.7 (C4), 77.2 (C5), 78.6 (C2), 114.8 (Ar-C), 125.6 (Ar-C), 127.4 (Ar-C), 128.3 (Ar-C), 128.5 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 139.1 (Ar-C), 140.6 (Ar-C), 141.3 (Ar-C), 144.4 (Ar-C), 166.8 (C=O), 169.2 (C=O); LRMS (ESI⁺) *m/z*: 500.2 ([M]⁺ 35%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₁H₃₇N₂O₄, 501.2748, found 501.2737.

General procedure for the synthesis of *N*-acylated imidazolidines:

To a stirring solution of imidazolidine **245a-I** and **246** (1.0 eq.) in anhydrous DCM at 0°C was added ethyl malonyl chloride (1.05-1.1 eq.) and pyridine (1.1-1.2 eq.) dropwise. The mixture was stirred at 0°C for 10-20 min and then refluxed overnight. The mixture was then washed with sat. NH₄Cl (aq.), sat. NaHCO₃ (aq.), brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography to give *N*-acylated imidazolidines **247a-I** and **248**.

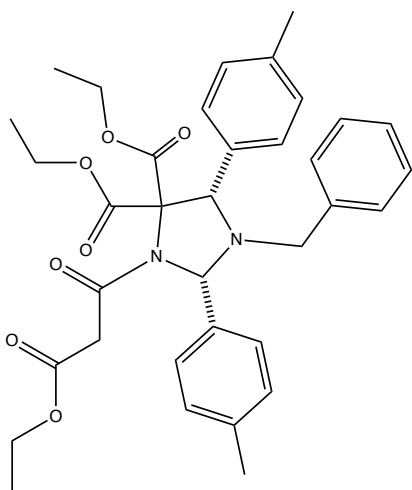
Diethyl (2*S**,5*S**)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-diphenylimidazolidine-4,4-dicarboxylate **247a**



Yield (1.63 g, 84%); Thick sticky colourless oil that crystallised overnight; *R_f* (30% EtOAc in Pet. Ether 40:60) 0.30; *v*_{max}/cm⁻¹ 2982 (C-H), 1740 (C=O), 1661 (C=O); δ_H (400 MHz, CDCl₃) 0.93 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 1.18 (6H, m, OCH₂CH₃, OCH₂CH₃), 2.64 (1H, br d, *J*=15.7 Hz, H7), 2.89 (1H, d, *J*=15.7 Hz, H7), 3.49 (1H, d, *J*=14.9 Hz, H6), 3.63 (1H, d, *J*=14.9 Hz, H6), 3.69 (1H, m, OCH₂CH₃), 3.95 (1H, dq, *J*=7.1 Hz, 10.6 Hz, OCH₂CH₃), 4.03 (2H, q, *J*=7.1 Hz, OCH₂CH₃), 4.21 (2H, dq, *J*=1.1 Hz, 7.2 Hz, OCH₂CH₃), 4.42 (1H, s, H4), 5.37 (1H, s, H2), 6.89 (2H, m, Ar-H), 7.20 (3H, m, Ar-H), 7.30-7.48 (8H, m, Ar-H), 7.91 (2H, m, Ar-H); δ_C (101 MHz, CDCl₃) 13.5 (OCH₂CH₃), 14.0 (OCH₂CH₃), 14.1 (OCH₂CH₃), 42.8 (C7), 50.2 (C6), 60.4 (OCH₂CH₃), 61.2 (OCH₂CH₃), 61.8 (OCH₂CH₃), 70.7 (C4), 75.4 (C5), 79.2 (C2), 127.6 (Ar-C), 128.2 (Ar-C), 128.4 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 129.8 (Ar-C), 130.0 (Ar-C), 130.2 (Ar-C), 133.6 (Ar-C), 134.4 (Ar-C), 138.7 (Ar-C),

165.3 (C=O), 165.4 (C=O), 166.6 (C=O), 166.9 (C=O); LRMS (ESI⁺) m/z : 573.2 ([M + H]⁺ 55%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₃₃H₃₇N₂O₇, 573.2595, found 573.2594.

Diethyl (2S*,5S*)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis-(4-methylphenyl)imidazolidine-4,4-dicarboxylate 247b



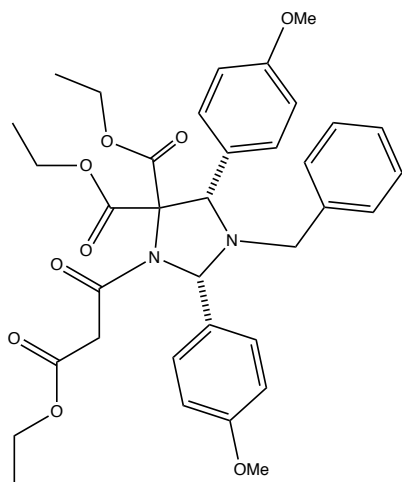
Yield (5.58 g, 67%); Thick sticky orange oil; R_f (50% EtOAc in Pet.

Ether 40:60) 0.63; $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1743 (C=O), 1663 (C=O);

δ_{H} (400 MHz, CDCl₃) 0.97 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.17 (6H, m, OCH₂CH₃, OCH₂CH₃), 2.37 (3H, s, CH₃), 2.42 (3H, s, CH₃), 2.63 (1H, br d, $J=15.7$ Hz, H7), 2.91 (1H, d, $J=15.7$ Hz, H7), 3.46 (1H, d, $J=14.9$ Hz, H6), 3.63 (1H, d, $J=14.9$ Hz, H6), 3.74 (1H, dq, $J=7.0$ Hz, 10.6 Hz, OCH₂CH₃), 3.95 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH₂CH₃), 4.03 (2H, q, $J=7.1$ Hz, OCH₂CH₃), 4.19 (2H, dq, $J=1.9$ Hz, 7.1 Hz, OCH₂CH₃),

4.34 (1H, s, H4), 5.29 (1H, s, H2), 6.91 (2H, m, Ar-H), 7.11-7.38 (9H, m, Ar-H), 7.79 (2H, d, $J=7.6$ Hz, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.0 (OCH₂CH₃), 14.1 (OCH₂CH₃), 21.3 (CH₃), 21.5 (CH₃), 42.9 (C7), 49.5 (C6), 61.1 (OCH₂CH₃), 61.7 (OCH₂CH₃), 61.9 (OCH₂CH₃), 70.0 (C4), 75.1 (C5), 78.5 (C2), 127.5 (Ar-C), 128.2 (Ar-C), 129.1 (Ar-C), 129.7 (Ar-C), 130.1-130.2 (Ar-C), 131.2 (Ar-C), 133.3 (Ar-C), 135.5 (Ar-C), 138.7 (Ar-C), 139.8 (Ar-C), 165.3 (C=O), 165.4 (C=O), 166.7 (C=O), 166.9 (C=O); LRMS (ESI⁺) m/z : 601.3 ([M + H]⁺ 60%), 623.2 ([M + Na]⁺ 100%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₃₅H₄₁N₂O₇, 601.2908, found 601.2906.

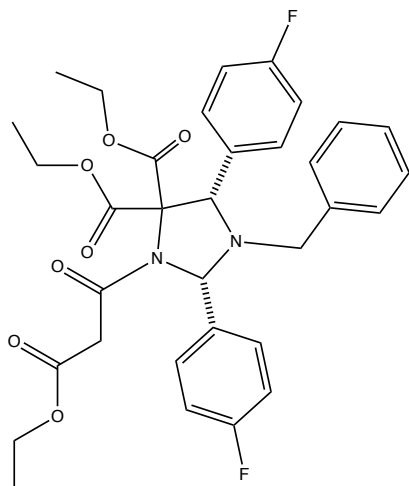
Diethyl (2S*,5S*)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis-(4-methoxyphenyl)imidazolidine-4,4-dicarboxylate 247c



Yield (3.07 g, 56%); Thick sticky orange oil that crystallised overnight; R_f (50% EtOAc in Pet. Ether 40:60) 0.50; $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1742 (C=O), 1659 (C=O); δ_H (400 MHz, CDCl_3) 1.00 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.18 (6H, m, OCH_2CH_3 , OCH_2CH_3), 2.64 (1H, br d, $J=15.7$ Hz, H7), 2.91 (1H, d, $J=15.6$ Hz, H7), 3.46 (1H, d, $J=14.8$ Hz, H6), 3.61 (1H, d, $J=15.1$ Hz, H6), 3.77 (1H, m, OCH_2CH_3), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.97 (1H, m, OCH_2CH_3), 4.04 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.19 (2H, dq, $J=1.3$ Hz, 7.1 Hz, OCH_2CH_3),

4.31 (1H, s, H4), 5.28 (1H, s, H2), 6.85-7.84 (13H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 49.8 (C6), 55.4 (OCH_3), 55.4 (OCH_3), 61.2 (OCH_2CH_3), 61.8 (OCH_2CH_3), 61.9 (OCH_2CH_3), 69.8 (C4), 75.1 (C5), 78.4 (C2), 113.8 (Ar-C), 114.3 (Ar-C), 126.1 (Ar-C), 127.5 (Ar-C), 128.2 (Ar-C), 129.3 (Ar-C), 130.1 (Ar-C), 130.4 (Ar-C), 131.5 (Ar-C), 133.6 (Ar-C), 160.1 (Ar-C), 160.6 (Ar-C), 165.3 (C=O), 165.6 (C=O), 166.8 (C=O), 167.0 (C=O); LRMS (ESI^+) m/z : 655.2 ($[\text{M} + \text{Na}]^+$ 63%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{35}\text{H}_{41}\text{N}_2\text{O}_9$, 633.2807, found 633.2798.

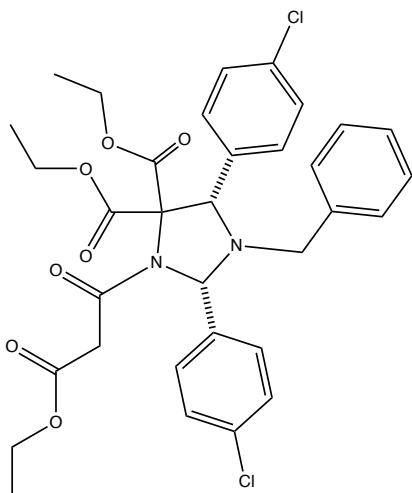
Diethyl (2S*,5S*)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis(4-fluorophenyl)imidazolidine-4,4-dicarboxylate 247d



Yield (5.78 g, 77%); Thick sticky yellow oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.73; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 1740 (C=O), 1662 (C=O); δ_H (400 MHz, CDCl_3) 0.98 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.17 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.21 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.68 (1H, br d, $J=15.7$ Hz, H7), 2.87 (1H, d, $J=15.6$ Hz, H7), 3.49 (1H, d, $J=14.8$ Hz, H6), 3.58 (1H, d, $J=14.8$ Hz, H6), 3.74 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 3.97 (1H, m, OCH_2CH_3), 4.05 (2H, m, OCH_2CH_3), 4.22 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.39 (1H, s, H4), 5.36 (1H, s, H2),

6.84 (2H, m, Ar-H), 7.02-7.28 (7H, m, Ar-H), 7.40 (2H, m, Ar-H), 7.87 (2H, m, Ar-H); δ_c (101 MHz, $CDCl_3$) 13.7 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 50.8 (C6), 61.3 (OCH_2CH_3), 62.0 (OCH_2CH_3), 62.2 (OCH_2CH_3), 70.3 (C4), 75.3 (C5), 78.8 (C2), 115.4 (d, $J=21.5$ Hz, Ar-C), 116.0 (br d, $J=22.0$ Hz, Ar-C), 127.7 (Ar-C), 128.3 (Ar-C), 129.8 (Ar-C), 130.0 (d, $J=3.1$ Hz, Ar-C), 130.8 (Ar-C), 132.0 (d, $J=8.3$ Hz, Ar-C), 133.6 (Ar-C), 134.6 (d, $J=3.2$ Hz, Ar-C), 163.1 (d, $J=247.8$ Hz, Ar-C), 163.5 (d, $J=249.7$ Hz, Ar-C), 165.2 (C=O), 165.5 (C=O), 166.4 (C=O), 166.8 (C=O); δ_F (377 MHz, $CDCl_3$) -110.97, -112.77; LRMS (ESI^+) m/z : 631.2 ($[M + Na]^+$ 95%); HRMS (ESI^+) m/z : $[M + H]^+$ calcd. for $C_{33}H_{35}N_2O_7F_2$, 609.2407, found 609.2410.

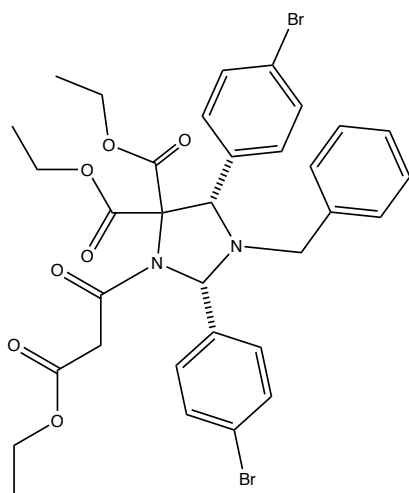
Diethyl (2S*,5S*)-1-benzyl-2,5-bis(4-chlorophenyl)-3-(3-ethoxy-3-oxopropanoyl)imidazolidine-4,4-dicarboxylate 247e



Yield (1.57 g, 70%); Thick sticky pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.33; ν_{max}/cm^{-1} 2983 (C-H), 1742 (C=O), 1665 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.18 (6H, m, OCH_2CH_3 , OCH_2CH_3), 2.70 (1H, br d, $J=15.8$ Hz, H7), 2.88 (1H, d, $J=15.6$ Hz, H7), 3.47 (1H, d, $J=14.8$ Hz, H6), 3.57 (1H, d, $J=14.8$ Hz, H6), 3.74 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 3.96 (1H, m, OCH_2CH_3), 4.03 (2H, dq, $J=1.3$ Hz, 7.2 Hz, OCH_2CH_3), 4.21 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.38 (1H, s, H4), 5.34 (1H, s, H2), 6.83

(2H, m, Ar-H), 7.17-7.22 (3H, m, Ar-H), 7.34 (4H, m, Ar-H), 7.40 (2H, d, $J=8.6$ Hz, Ar-H), 7.80 (2H, d, $J=8.4$ Hz, Ar-H); δ_c (101 MHz, $CDCl_3$) 13.6 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 50.9 (C6), 61.4 (OCH_2CH_3), 62.1 (OCH_2CH_3), 62.4 (OCH_2CH_3), 70.4 (C4), 75.3 (C5), 78.8 (C2), 127.8 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 129.3 (Ar-C), 129.9 (Ar-C), 130.5 (Ar-C), 131.5 (Ar-C), 133.0 (Ar-C), 133.4 (Ar-C), 134.9 (Ar-C), 137.3 (Ar-C), 165.1 (C=O), 166.4 (C=O), 166.8 (C=O); LRMS (ESI^+) m/z : 663.1 ($[M^{35+35} + Na]^+$ 100%), 665.1 ($[M^{35+37} + Na]^+$ 83%), 667.1 ($[M^{37+37} + Na]^+$ 28%); HRMS (ESI^+) m/z : $[M^{35+35} + Na]^+$ calcd. for $C_{33}H_{34}N_2O_7Cl_2Na$, 663.1635, found 663.1633; $[M^{35+37} + Na]^+$ calcd. for $C_{33}H_{34}N_2O_7Cl_2Na$, 665.1613, found 665.1599; $[M^{37+37} + Na]^+$ calcd. for $C_{33}H_{34}N_2O_7Cl_2Na$, 667.1603, found 667.1555.

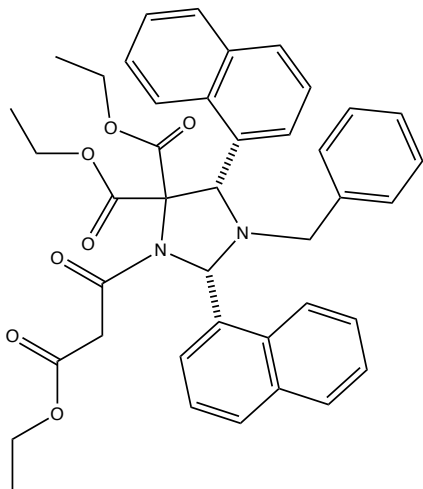
Diethyl (2*S,5*S**)-1-benzyl-2,5-bis(4-bromophenyl)-3-(3-ethoxy-3-oxopropanoyl)imidazolidine-4,4-dicarboxylate **247f****



Yield (5.82 g, 76%); Thick sticky orange oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.75; $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1739 (C=O), 1663 (C=O); δ_H (400 MHz, CDCl_3) 0.99 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.19 (6H, m, OCH_2CH_3 , OCH_2CH_3), 2.72 (1H, br d, $J=15.1$ Hz, H7), 2.89 (1H, d, $J=15.6$ Hz, H7), 3.49 (1H, d, $J=14.8$ Hz, H6), 3.57 (1H, d, $J=14.8$ Hz, H6), 3.75 (1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.97 (1H, m, OCH_2CH_3), 4.04 (2H, dq, $J=1.4$ Hz, 7.1 Hz, OCH_2CH_3), 4.22 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.38 (1H, s, H4), 5.34 (1H, s, H2), 6.84 (2H, m,

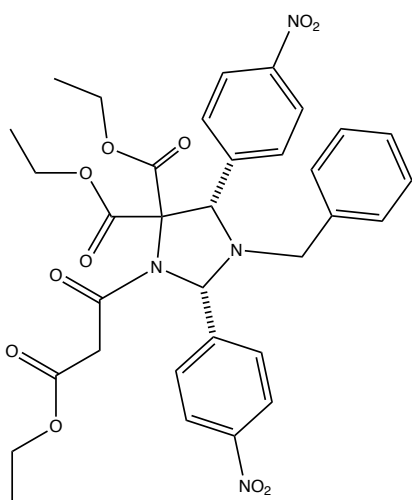
Ar-H), 7.18-7.22 (3H, m, Ar-H), 7.29 (2H, m, Ar-H), 7.50 (2H, d, $J=8.7$ Hz, Ar-H), 7.56 (2H, d, $J=8.5$ Hz, Ar-H), 7.74 (2H, d, $J=8.4$ Hz, Ar-H); δ_c (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 50.9 (C6), 61.4 (OCH_2CH_3), 62.1 (OCH_2CH_3), 62.3 (OCH_2CH_3), 70.5 (C4), 75.2 (C5), 78.9 (C2), 123.1 (Ar-C), 124.0 (Ar-C), 127.8 (Ar-C), 128.4 (Ar-C), 129.8 (Ar-C), 130.7 (Ar-C), 131.7 (Ar-C), 131.8 (Ar-C), 132.2 (Ar-C), 133.4 (Ar-C), 133.5 (Ar-C), 137.9 (Ar-C), 165.0 (C=O), 165.4 (C=O), 166.3 (C=O), 166.8 (C=O); LRMS (ESI^+) m/z : 751.0 ($[\text{M}^{79+79} + \text{Na}]^+$ 47%), 753.0 ($[\text{M}^{79+81} + \text{Na}]^+$ 98%), 755.0 ($[\text{M}^{81+81} + \text{Na}]^+$ 49%); HRMS (ESI^+) m/z : $[\text{M}^{79+79} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 729.0806, found 729.0800; $[\text{M}^{79+81} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 731.0785, found 731.0778; $[\text{M}^{81+81} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 733.0765, found 733.0761.

Diethyl (2*S,5*S**)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-di(naphthalen-1-yl)imidazolidine-4,4-dicarboxylate 247g**



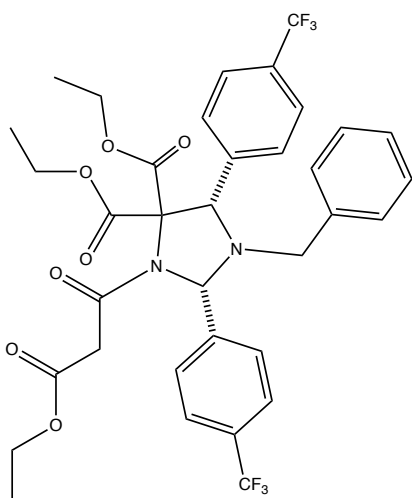
Yield (1.61 g, 85%); Light yellow foamy solid; m.p. 75-78°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 3061 (C-H), 2983 (C-H), 1740 (C=O), 1659 (C=O); δ_H (400 MHz, CDCl_3) 0.65 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.06 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.16 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 2.55 (1H, br d, $J=15.8$ Hz, H7), 2.86 (1H, d, $J=15.8$ Hz, H7), 3.41 (1H, m, OCH_2CH_3), 3.47 (1H, d, $J=14.7$ Hz, H6), 3.67 (1H, d, $J=14.9$ Hz, H6), 3.92 (3H, m, OCH_2CH_3 , OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 5.55 (1H, s, H4), 6.50 (1H, s, H2), 6.57-8.82 (19H, m, Ar-H); δ_c (101 MHz, CDCl_3) 13.3 (OCH_2CH_3), 13.9 (OCH_2CH_3), 13.9 (OCH_2CH_3), 42.3 (C7), 51.9 (C6), 61.1 (OCH_2CH_3), 61.6 (OCH_2CH_3), 62.5 (OCH_2CH_3), 66.6 (C4), 73.7 (C2), 76.1 (C5), 121.8-134.4 (Ar-C), 165.5 (C=O), 165.7 (C=O), 166.7 (C=O), 168.2 (C=O); LRMS (ESI⁻) m/z : 672.1 ($[\text{M}]^-$ 100%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{41}\text{H}_{39}\text{N}_2\text{O}_7$, 671.2763, found 671.2776.

Diethyl (2*S,5*S**)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis(4-nitrophenyl)imidazolidine-4,4-dicarboxylate 247h**



Yield (1.68 g, Quantitative); Yellow foamy solid; m.p. 69-72°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.08; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 1739 (C=O), 1666 (C=O); δ_H (400 MHz, CDCl_3) 0.99 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.18 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.29 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.84 (2H, br m, H7), 3.59 (2H, s, H6), 3.77 (1H, dq, $J=7.2$ Hz, 10.9 Hz, OCH_2CH_3), 4.03 (3H, m, OCH_2CH_3 , OCH_2CH_3), 4.31 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.64 (1H, s, H4), 5.55 (1H, s, H2), 6.82 (2H, m, Ar-H), 7.15 (3H, m, Ar-H), 7.64 (2H, d, $J=8.3$ Hz, Ar-H), 8.01 (2H, d, $J=8.8$ Hz, Ar-H), 8.23 (4H, m, Ar-H); δ_c (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 52.9 (C6), 61.6 (OCH_2CH_3), 62.5 (OCH_2CH_3), 63.0 (OCH_2CH_3), 71.6 (C4), 75.6 (C5),

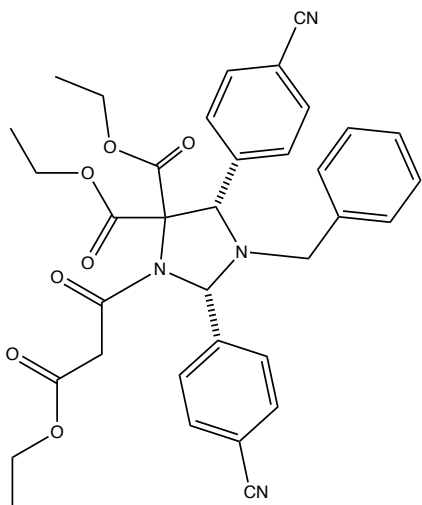
79.6 (C2), 123.5 (Ar-C), 123.9 (Ar-C), 128.1 (Ar-C), 128.5 (Ar-C), 129.5 (Ar-C), 130.1 (Ar-C), 130.9 (Ar-C), 133.4 (Ar-C), 141.9 (Ar-C), 146.1 (Ar-C), 148.4 (Ar-C), 148.6 (Ar-C), 164.9 (C=O), 165.2 (C=O), 165.9 (C=O), 166.6 (C=O); LRMS (ESI⁺) *m/z*: 685.2 ([M + Na]⁺ 95%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₃H₃₅N₄O₁₁, 663.2297, found 663.2289.

Diethyl**(2*S**,5*S**)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis(4-(trifluoromethyl)phenyl)imidazolidine-4,4-dicarboxylate 247i**

Yield (1.19 g, 66%); Thick sticky orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.30; ν_{max} /cm⁻¹ 2986 (C-H), 1742 (C=O), 1667 (C=O); δ_{H} (400 MHz, CDCl₃) 0.91 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 1.16 (3H, t, *J*=7.1 Hz, OCH₂CH₃), 1.24 (3H, t, *J*=7.2 Hz, OCH₂CH₃), 2.71 (1H, br m, H7), 2.87 (1H, d, *J*=15.4 Hz, H7), 3.53 (1H, d, *J*=14.7 Hz, H6), 3.58 (1H, d, *J*=14.7 Hz, H6), 3.70 (1H, m, OCH₂CH₃), 3.94 (1H, m, OCH₂CH₃), 4.02 (2H, dq, *J*=3.1 Hz, 7.1 Hz, OCH₂CH₃), 4.25 (2H, q, *J*=7.2 Hz, OCH₂CH₃), 4.54 (1H, s, H4), 5.46 (1H, s, H2), 6.82 (2H, m,

Ar-H), 7.15 (3H, m, Ar-H), 7.56 (2H, d, *J*=8.2 Hz, Ar-H), 7.64 (4H, m, Ar-H), 7.97 (2H, d, *J*=7.9 Hz, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.4 (OCH₂CH₃), 14.0 (OCH₂CH₃), 14.1 (OCH₂CH₃), 42.9 (C7), 52.0 (C6), 61.5 (OCH₂CH₃), 62.2 (OCH₂CH₃), 62.6 (OCH₂CH₃), 71.2 (C4), 75.5 (C5), 79.5 (C2), 125.4 (q, *J*=3.5 Hz, Ar-C), 125.9 (Ar-C), 127.9 (Ar-C), 128.4 (Ar-C), 129.5 (Ar-C), 129.6 (Ar-C), 130.5 (Ar-C), 131.2 (Ar-C), 131.5 (Ar-C), 133.4 (Ar-C), 138.8 (Ar-C), 143.0 (Ar-C), 165.0 (C=O), 165.3 (C=O), 166.2 (C=O), 166.8 (C=O); δ_{F} (377 MHz, CDCl₃) -62.74, -62.80; LRMS (ESI⁺) *m/z*: 709.2 ([M + H]⁺ 8%); LRMS (ESI⁻) *m/z*: 707.2 ([M - H]⁻ 95%); HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd. for C₃₅H₃₅N₂O₇F₆, 709.2343, found 709.2337.

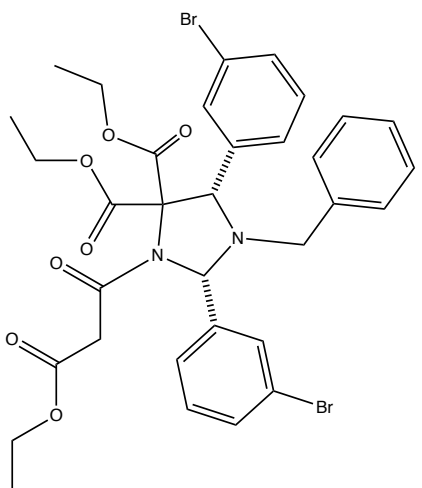
Diethyl (2S*,5S*)-1-benzyl-2,5-bis(4-cyanophenyl)-3-(3-ethoxy-3-oxopropanoyl)imidazolidine-4,4-dicarboxylate 247j



Yield (682 mg, 69%); White crystals/colourless oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.33; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 2229 (C $\equiv$ N), 1743 (C=O), 1667 (C=O); δ_H (400 MHz, CDCl₃) 0.94 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.17 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.24 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.72 (1H, br m, H7), 2.83 (1H, d, $J=15.0$ Hz, H7), 3.51 (1H, d, $J=14.9$ Hz, H6), 3.56 (1H, d, $J=14.7$ Hz, H6), 3.70 (1H, dq, $J=7.1$ Hz, 10.6 Hz, OCH₂CH₃), 3.96 (1H, m, OCH₂CH₃), 4.03 (2H, dq, $J=1.0$ Hz, 7.2 Hz, OCH₂CH₃), 4.26 (2H, q, $J=7.1$ Hz, OCH₂CH₃),

4.53 (1H, s, H4), 5.45 (1H, s, H2), 6.77 (2H, m, Ar-H), 7.14 (3H, m, Ar-H), 7.54 (2H, d, $J=8.0$ Hz, Ar-H), 7.65 (4H, m, Ar-H), 7.92 (2H, d, $J=8.0$ Hz, Ar-H); δ_C (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.0 (OCH₂CH₃), 14.1 (OCH₂CH₃), 42.8 (C7), 52.7 (C6), 61.6 (OCH₂CH₃), 62.4 (OCH₂CH₃), 62.9 (OCH₂CH₃), 71.7 (C4), 75.5 (C5), 79.8 (C2), 113.0 (C $\equiv$ N), 118.4 (Ar-C), 128.1 (Ar-C), 128.5 (Ar-C), 129.5 (Ar-C), 129.9 (Ar-C), 130.7 (Ar-C), 132.2 (Ar-C), 132.6 (Ar-C), 133.4 (Ar-C), 140.0 (Ar-C), 144.2 (Ar-C), 164.9 (C=O), 165.3 (C=O), 166.0 (C=O), 166.6 (C=O); LRMS (ESI⁺) m/z : 623.2 ([M + H]⁺ 17%); LRMS (ESI⁻) m/z : 621.2 ([M - H]⁻ 94%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₃₅H₃₅N₄O₇, 623.2500, found 623.2495.

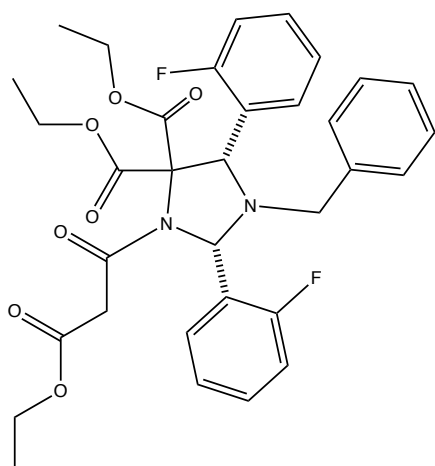
Diethyl (2S*,5S*)-1-benzyl-2,5-bis(3-bromophenyl)-3-(3-ethoxy-3-oxopropanoyl)imidazolidine-4,4-dicarboxylate 247k



Yield (887 mg, 85%); Thick sticky pale yellow oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.28; $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1742 (C=O), 1666 (C=O); δ_H (400 MHz, CDCl₃) 1.09 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.19 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.24 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 2.74 (1H, br m, H7), 2.88 (1H, d, $J=15.7$ Hz, H7), 3.53 (1H, d, $J=14.7$ Hz, H6), 3.60 (1H, d, $J=14.7$ Hz, H6), 3.85 (1H, m, OCH₂CH₃), 3.99 (1H, m, OCH₂CH₃), 4.06 (2H, dq, $J=0.9$ Hz, 7.1 Hz, OCH₂CH₃), 4.24 (2H,

dq, $J=2.5$ Hz, 7.1 Hz, OCH_2CH_3), 4.38 (1H, s, H4), 5.32 (1H, s, H2), 6.86 (2H, m, Ar-H), 7.18-7.38 (7H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.81 (1H, d, $J=7.7$ Hz, Ar-H), 7.93 (1H, m, Ar-H); δ_c (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 14.0 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.9 (C7), 51.6 (C6), 61.4 (OCH_2CH_3), 62.2 (OCH_2CH_3), 62.5 (OCH_2CH_3), 70.8 (C4), 75.3 (C5), 79.2 (C2), 122.6 (Ar-C), 123.0 (Ar-C), 127.9 (Ar-C), 128.4 (Ar-C), 128.8 (Ar-C), 129.7 (Ar-C), 130.1 (Ar-C), 130.6 (Ar-C), 132.2 (Ar-C), 133.0 (Ar-C), 133.6 (Ar-C), 136.8 (Ar-C), 141.1 (Ar-C), 165.1 (C=O), 166.4 (C=O), 166.7 (C=O); LRMS (ESI^-) m/z : 727.0 ($[\text{M}^{79+79} - \text{H}]^-$ 52%), 729.0 ($[\text{M}^{79+81} - \text{H}]^-$ 100%), 731.0 ($[\text{M}^{81+81} - \text{H}]^-$ 57%); HRMS (ESI^+) m/z : $[\text{M}^{79+79} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 729.0806, found 729.0804; $[\text{M}^{79+81} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 731.0787, found 731.0783; $[\text{M}^{81+81} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{Br}_2$, 733.0774, found 733.0765.

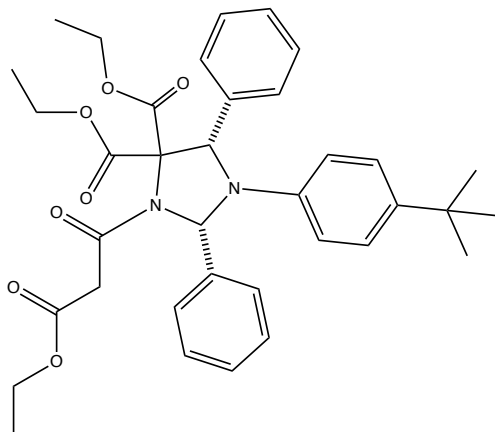
Diethyl (2S*,5S*)-1-benzyl-3-(3-ethoxy-3-oxopropanoyl)-2,5-bis(2-fluorophenyl)imidazolidine-4,4-dicarboxylate 247I



Yield (791 mg, 79%); Thick sticky orange oil; R_f (30% EtOAc in Pet. Ether 40:60) 0.30; $\nu_{\text{max}}/\text{cm}^{-1}$ 2985 (C-H), 1744 (C=O), 1668 (C=O); δ_H (400 MHz, CDCl_3) 0.93 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.18 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.20 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.72 (1H, br d, $J=15.8$ Hz, H7), 3.04 (1H, d, $J=15.8$ Hz, H7), 3.58 (2H, s, H6), 3.66 (2H, br m, OCH_2CH_3), 4.04 (2H, dq, $J=1.5$ Hz, 7.1 Hz, OCH_2CH_3), 4.20 (2H, m, OCH_2CH_3), 4.85 (1H, s, H4), 5.89 (1H, s,

H2), 6.91-8.32 (13H, m, Ar-H); δ_c (101 MHz, CDCl_3) 13.6 (OCH_2CH_3), 13.9 (OCH_2CH_3), 14.1 (OCH_2CH_3), 42.0 (C7), 52.1 (C6), 61.3 (OCH_2CH_3), 62.0 (OCH_2CH_3), 62.3 (OCH_2CH_3), 63.6 (C4), 71.6 (C2), 74.8 (C5), 115.2 (d, $J=21.8$ Hz, Ar-C), 115.7 (d, $J=21.9$ Hz, Ar-C), 122.2 (d, $J=12.1$ Hz, Ar-C), 124.2 (d, $J=3.5$ Hz, Ar-C), 125.6 (Ar-C), 126.1 (d, $J=8.9$ Hz, Ar-C), 127.6 (Ar-C), 128.2 (Ar-C), 129.1 (Ar-C), 129.6 (Ar-C), 130.4 (d, $J=8.3$ Hz, Ar-C), 131.5 (d, $J=9.3$ Hz, Ar-C), 131.9 (Ar-C), 133.4 (Ar-C), 161.3 (d, $J=247.1$ Hz, Ar-C), 161.9 (d, $J=248.4$ Hz, Ar-C), 165.0 (C=O), 165.6 (C=O), 166.2 (C=O), 166.3 (C=O); δ_F (377 MHz, CDCl_3) -117.03, -119.42; LRMS (ESI^-) m/z : 607.2 ($[\text{M} - \text{H}]^-$ 45%); LRMS (ESI^+) m/z : 609.2 ($[\text{M} + \text{H}]^+$ 13%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_7\text{F}_2$, 609.2407, found 609.2402.

Diethyl (2*S,5*S**)-1-(4-(*tert*-butyl)phenyl)-3-(3-ethoxy-3-oxopropanoyl)-2,5-diphenylimidazolidine-4,4-dicarboxylate **248****



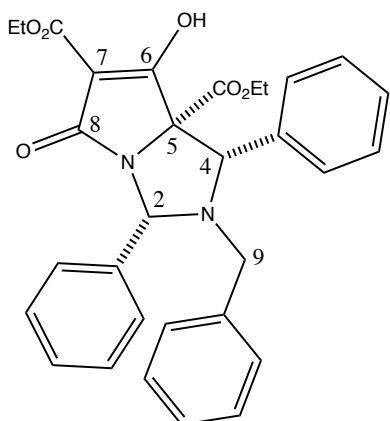
Yield (571 mg, 65%); Yellow foamy solid; m.p. 52-55°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.40; $\nu_{\max}/\text{cm}^{-1}$ 2963 (C-H), 1742 (C=O), 1669 (C=O); δ_H (400 MHz, CDCl_3) 0.95 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.20 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.22 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.38 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.83 (1H, br d, $J=15.5$ Hz, H7), 3.10 (1H, d, $J=15.5$ Hz, H7), 3.76 (2H, m, OCH_2CH_3), 4.09 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.39 (2H, m,

OCH_2CH_3), 5.45 (1H, s, H4), 6.15 (1H, s, H2), 6.65 (2H, d, $J=8.8$ Hz, Ar-H), 7.11 (2H, d, $J=8.8$ Hz, Ar-H), 7.28 (3H, m, Ar-H), 7.42 (5H, m, Ar-H), 7.88 (2H, m, Ar-H); δ_C (101 MHz, CDCl_3) 13.5 (OCH_2CH_3), 14.2 (OCH_2CH_3), 31.4 ($(\text{CH}_3)_3$), 34.1 ($\text{C}(\text{CH}_3)_3$), 43.0 (C7), 61.4 (OCH_2CH_3), 62.0 (OCH_2CH_3), 62.8 (OCH_2CH_3), 71.4 (C4), 76.3 (C5), 80.6 (C2), 118.7 (Ar-C), 125.8 (Ar-C), 127.9 (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 128.9 (Ar-C), 129.6 (Ar-C), 129.8 (Ar-C), 136.7 (Ar-C), 140.0 (Ar-C), 141.7 (Ar-C), 144.8 (Ar-C), 165.1 (C=O), 165.5 (C=O), 166.4 (C=O), 167.6 (C=O); LRMS (ESI^+) m/z : 615.3 ($[\text{M} + \text{H}]^+$ 25%), 637.2 ($[\text{M} + \text{Na}]^+$ 54%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{36}\text{H}_{43}\text{N}_2\text{O}_7$, 615.3065, found 615.3066.

General procedure for the synthesis of imidazolidine-derived tetramates:⁴¹

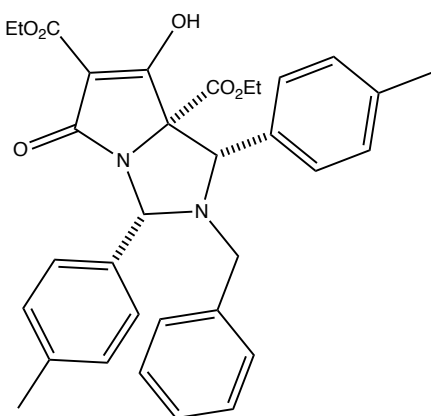
To a solution of *N*-acylated imidazolidines **247a-l** (1.0 eq.) in anhydrous THF was added DBU (1.1-1.2 eq.). The mixture was stirred overnight at rt. The reaction mixture was then cooled to 0°C, diluted with water, and partitioned between Et_2O and water and the aqueous layer was acidified to pH 1-2 using 3 M HCl solution (aq.) and extracted with EtOAc. The organic layer was washed with brine, then dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the desired tetramates **249a-l**, which was then used without further purification.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-7-hydroxy-5-oxo-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249a**



Yield (2.12 g, 77%); Yellow foamy solid; m.p. 70-74°C; $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1718 (C=O), 1656 (C=O), 1614 (C=C); δ_{H} (500 MHz, CDCl_3) 0.93 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.35 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.70 (1H, d, $J=14.9$ Hz, H9), 3.78 (1H, dq, $J=7.2$ Hz, 10.5 Hz, OCH_2CH_3), 3.84 (1H, d, $J=14.8$ Hz, H9), 3.96 (1H, m, OCH_2CH_3), 3.96 (1H, s, H4), 4.33 (2H, m, OCH_2CH_3), 5.30 (1H, s, H2), 6.82 (2H, m, Ar-H), 7.22 (3H, m, Ar-H), 7.37-7.51 (6H, m, Ar-H), 7.61 (2H, d, $J=7.5$ Hz, Ar-H), 8.00 (2H, d, $J=7.1$ Hz, Ar-H); δ_{C} (126 MHz, CDCl_3) 13.6 (OCH_2CH_3), 14.2 (OCH_2CH_3), 50.1 (C9), 62.0 (OCH_2CH_3), 62.3 (OCH_2CH_3), 69.8 (C4), 75.7 (C5), 76.4 (C2), 127.9 (Ar-C), 128.5 (Ar-C), 128.5 (Ar-C), 128.8 (Ar-C), 128.8 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-C), 129.4 (Ar-C), 130.5 (Ar-C), 132.5 (Ar-C), 133.7 (Ar-C), 138.4 (Ar-C), 164.7 (C=O), 167.6 (C=O), 185.2 (C6); LRMS (ESI^+) m/z : 549.2 ($[\text{M} + \text{Na}]^+$ 35%); LRMS (ESI^-) m/z : 525.2 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_6$, 527.2177, found 527.2179.

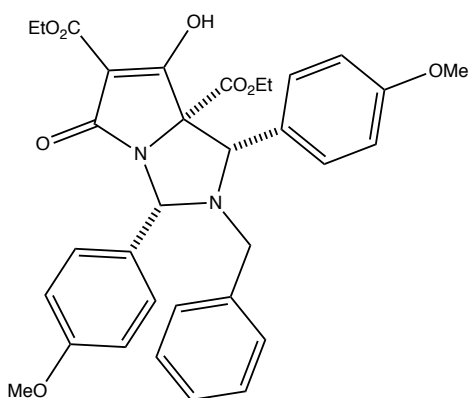
Diethyl (1*S,3*S**,7*aR**)-2-benzyl-7-hydroxy-5-oxo-1,3-di-*p*-tolyl-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249b**



Yield (3.76 g, 75%); Yellow foamy solid; m.p. 91-97°C; $\nu_{\max}/\text{cm}^{-1}$ 2982 (C-H), 1723 (C=O), 1656 (C=O), 1614 (C=C); δ_{H} (400 MHz, CDCl_3) 1.00 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.35 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 2.42 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.69 (1H, d, $J=14.7$ Hz, H9), 3.85 (1H, m, H9), 3.85 (1H, m, OCH_2CH_3), 3.90 (1H, s, H4), 4.01 (1H, dq, $J=7.1$ Hz, 10.7 Hz, OCH_2CH_3), 4.32 (2H, m, OCH_2CH_3), 5.25 (1H, s, H2), 6.83 (2H, m, Ar-H), 7.22-7.36 (7H, m, Ar-H), 7.49 (2H, d, $J=7.7$ Hz, Ar-H), 7.90 (2H, d, $J=8.1$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 21.4 (CH_3), 21.4 (CH_3), 49.5 (C9), 61.8 (OCH_2CH_3), 62.3 (OCH_2CH_3), 69.4 (C4), 76.0 (C2),

127.8 (Ar-C), 128.4 (Ar-C), 129.0 (Ar-C), 129.1 (Ar-C), 129.3 (Ar-C), 129.5 (Ar-C), 130.5 (Ar-C), 132.3 (Ar-C), 135.3 (Ar-C), 138.4 (Ar-C), 139.0 (Ar-C), 164.8 (C=O), 167.5 (C=O), 185.3 (C6); LRMS (ESI⁻) m/z : 553.2 ([M - H]⁻ 97%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₃₃H₃₃N₂O₆, 553.2344, found 553.2339.

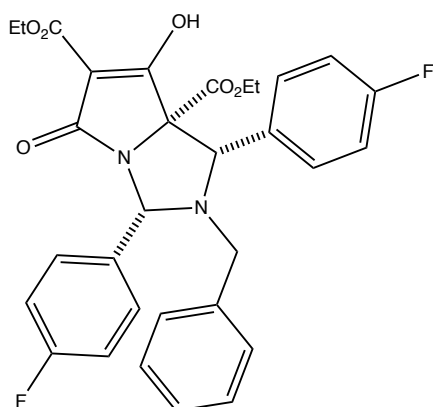
Diethyl (1*S,3*S**,7*aR**)-2-benzyl-7-hydroxy-1,3-bis(4-methoxyphenyl)-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249c**



Yield (2.17 g, 78%); Yellow sticky solid/oil; m.p. 81-85°C;

$\nu_{\text{max}}/\text{cm}^{-1}$ 2980 (C-H), 1736 (C=O), 1685 (C=O), 1600 (C=C); δ_{H} (400 MHz, CDCl₃) 1.01 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.34 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.66 (1H, d, $J=14.8$ Hz, H9), 3.80 (1H, d, $J=14.3$ Hz, H9), 3.83 (1H, m, OCH₂CH₃), 3.85 (3H, s, OCH₃), 3.88 (4H, m, OCH₃, H4), 4.01 (1H, m, OCH₂CH₃), 4.30 (2H, m, OCH₂CH₃), 5.20 (1H, s, H2), 6.80 (2H, m, Ar-H), 6.98-7.02 (4H, m, Ar-H), 7.19-7.25 (3H, m, Ar-H), 7.50 (2H, d, $J=8.2$ Hz, Ar-H), 7.91 (2H, d, $J=8.7$ Hz, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 14.2 (OCH₂CH₃), 49.5 (C9), 55.4 (OCH₃), 61.8 (OCH₂CH₃), 62.3 (OCH₂CH₃), 69.2 (C4), 75.7 (C5), 76.0 (C2), 113.8 (Ar-C), 114.2 (Ar-C), 125.4 (Ar-C), 127.8 (Ar-C), 128.4 (Ar-C), 130.2 (Ar-C), 130.5 (Ar-C), 130.7 (Ar-C), 132.1 (Ar-C), 132.4 (Ar-C), 160.0 (Ar-C), 160.2 (Ar-C), 165.0 (C=O), 167.5 (C=O), 185.4 (C6); LRMS (ESI⁻) m/z : 585.2 ([M - H]⁻ 96%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₃₃H₃₃N₂O₈, 585.2231, found 585.2243.

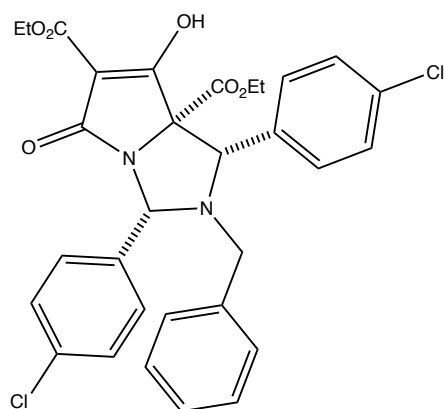
Diethyl (1*S,3*S**,7*aR**)-2-benzyl-1,3-bis(4-fluorophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249d**



Yield (3.94 g, 77%); Yellow foamy solid; m.p. 95-99°C; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 1723 (C=O), 1658 (C=O), 1606 (C=C); δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.35 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.67 (1H, d, $J=14.6$ Hz, H9), 3.77 (1H, d, $J=14.6$ Hz, H9), 3.82 (1H, m, OCH_2CH_3), 3.93 (1H, s, H4), 3.97 (1H, dq, $J=7.3$ Hz, 10.9 Hz, OCH_2CH_3), 4.33 (2H, m, OCH_2CH_3), 5.26 (1H, s, H2), 6.79 (2H, m, Ar-H), 7.08-7.26 (7H, m, Ar-H), 7.57 (2H, m, Ar-H),

7.94 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 50.4 (C9), 62.0 (OCH_2CH_3), 62.4 (OCH_2CH_3), 69.2 (C4), 76.0 (C2), 115.3 (d, $J=21.3$ Hz, Ar-C), 115.9 (d, $J=21.5$ Hz, Ar-C), 128.1 (Ar-C), 128.6 (Ar-C), 129.3 (d, $J=3.3$ Hz, Ar-C), 130.3 (Ar-C), 130.8 (Ar-C), 131.1 (d, $J=8.1$ Hz, Ar-C), 132.3 (Ar-C), 134.1 (Ar-C), 163.1 (d, $J=246.6$ Hz, Ar-C), 163.2 (d, $J=248.2$ Hz, Ar-C), 164.7 (C=O), 167.5 (C=O), 185.1 (C6); δ_{F} (377 MHz, CDCl_3) -112.18, -113.71; LRMS (ESI⁻) m/z : 561.1 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{31}\text{H}_{27}\text{N}_2\text{O}_6\text{F}_2$, 561.1843, found 561.1832.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-1,3-bis(4-chlorophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249e**

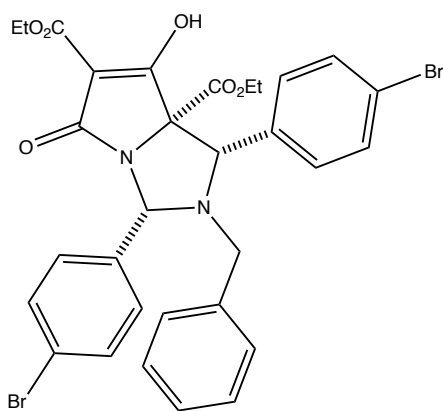


Yield (1.06 g, 75%); Yellow foamy solid; m.p. 88-91°C; $\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1746 (C=O), 1721 (C=O), 1658 (C=O), 1616 (C=C); δ_{H} (400 MHz, CDCl_3) 0.97 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.35 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.66 (1H, d, $J=14.6$ Hz, H9), 3.77 (1H, d, $J=14.8$ Hz, H9), 3.82 (1H, m, OCH_2CH_3), 3.92 (1H, s, H4), 3.98 (1H, m, OCH_2CH_3), 4.32 (2H, m, OCH_2CH_3), 5.27 (1H, s, H2), 6.79 (2H, m, Ar-H), 7.23 (3H, m, Ar-H), 7.41 (2H, d, $J=8.5$ Hz, Ar-H),

7.46 (2H, d, $J=8.6$ Hz, Ar-H), 7.52 (2H, d, $J=8.2$ Hz, Ar-H), 7.88 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 50.6 (C9), 62.0 (OCH_2CH_3), 62.5 (OCH_2CH_3), 69.3 (C4), 75.5 (C5), 75.9

(C2), 128.1 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-C), 129.1 (Ar-C), 130.3 (Ar-C), 130.7 (Ar-C), 132.3 (Ar-C), 134.5 (Ar-C), 135.1 (Ar-C), 137.0 (Ar-C), 164.7 (C=O), 167.4 (C=O), 185.2 (C6); LRMS (ESI⁻) m/z : 593.0 ([M³⁵⁺³⁵ - H]⁻ 100%), 595.0 ([M³⁵⁺³⁷ - H]⁻ 69%), 597.1 ([M³⁷⁺³⁷ - H]⁻ 22%); HRMS (ESI⁺) m/z : [M³⁵⁺³⁵ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Cl₂, 595.1397, found 595.1399; [M³⁵⁺³⁷ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Cl₂, 597.1373, found 597.1362; [M³⁷⁺³⁷ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Cl₂, 599.1360, found 599.1323.

Diethyl (1S*,3S*,7aR*)-2-benzyl-1,3-bis(4-bromophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1H-pyrrolo[1,2-c]imidazole-6,7a(5H)-dicarboxylate 249f



Yield (2.95 g, 55%); Yellow foamy solid; m.p. 85-90°C; $\nu_{\max}/\text{cm}^{-1}$

2983 (C-H), 1745 (C=O), 1721 (C=O), 1658 (C=O), 1616 (C=C);

δ_{H} (400 MHz, CDCl₃) 0.96 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.35 (3H,

t, $J=7.1$ Hz, OCH₂CH₃), 3.67 (1H, d, $J=14.6$ Hz, H₉), 3.77 (1H, d,

$J=14.7$ Hz, H₉), 3.82 (1H, m, OCH₂CH₃), 3.91 (1H, s, H₄), 3.97

(1H, m, OCH₂CH₃), 4.34 (2H, m, OCH₂CH₃), 5.25 (1H, s, H₂), 6.79

(2H, m, Ar-H), 7.23 (3H, m, Ar-H), 7.47 (2H, d, $J=8.1$ Hz, Ar-H),

7.56 (2H, d, $J=8.4$ Hz, Ar-H), 7.62 (2H, d, $J=8.7$ Hz, Ar-H), 7.82 (2H, d, $J=8.5$ Hz, Ar-H); δ_{C} (101 MHz, CDCl₃)

13.7 (OCH₂CH₃), 14.2 (OCH₂CH₃), 50.6 (C₉), 62.1 (OCH₂CH₃), 62.5 (OCH₂CH₃), 69.4 (C₄), 75.3 (C₅), 75.9

(C₂), 122.8 (Ar-C), 123.3 (Ar-C), 128.2 (Ar-C), 128.7 (Ar-C), 130.3 (Ar-C), 130.7 (Ar-C), 131.0 (Ar-C), 131.6

(Ar-C), 132.1 (Ar-C), 132.6 (Ar-C), 137.4 (Ar-C), 164.4 (C=O), 167.4 (C=O), 169.2 (C=O), 184.9 (C₆); LRMS

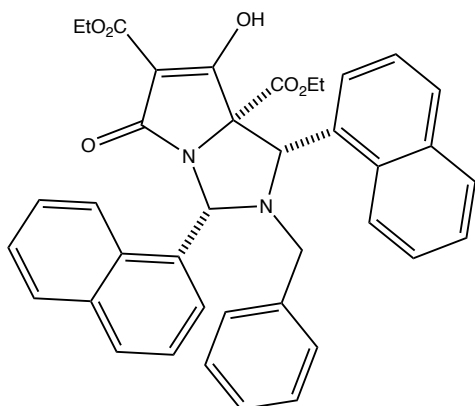
(ESI⁻) m/z : 681.0 ([M⁷⁹⁺⁷⁹ - H]⁻ 46%), 683.0 ([M⁷⁹⁺⁸¹ - H]⁻ 95%), 685.0 ([M⁸¹⁺⁸¹ - H]⁻ 51%); HRMS (ESI⁻)

m/z : [M⁷⁹⁺⁷⁹ - H]⁻ calcd. for C₃₁H₂₇N₂O₆Br₂, 681.0241, found 681.0242; [M⁷⁹⁺⁸¹ - H]⁻ calcd. for

C₃₁H₂₇N₂O₆Br₂, 683.0221, found 683.0225; [M⁸¹⁺⁸¹ - H]⁻ calcd. for C₃₁H₂₇N₂O₆Br₂, 685.0200, found

685.0996.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-7-hydroxy-1,3-di(naphthalen-1-yl)-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249g**

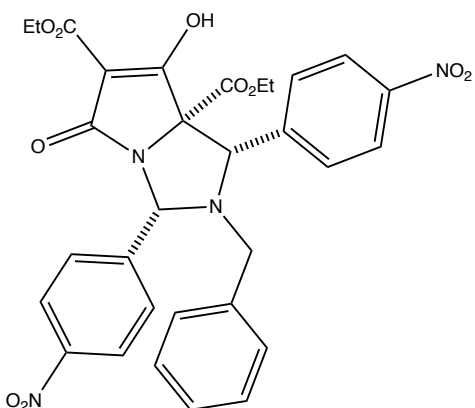


Yield (851 mg, 61%); Yellow foamy solid; m.p. 108-111°C;

$\nu_{\max}/\text{cm}^{-1}$ 3055 (C-H), 2982 (C-H), 1746 (C=O), 1721 (C=O), 1656 (C=O), 1618 (C=C); δ_{H} (400 MHz, CDCl_3) 0.89 (3H, br m, OCH_2CH_3), 1.34 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.52 (1H, d, $J=14.7$ Hz, H9), 3.81 (2H, m, OCH_2CH_3 , H9), 4.03 (1H, m, OCH_2CH_3), 4.35 (2H, m, OCH_2CH_3), 4.91 (1H, s, H4), 6.25 (1H, s, H2), 6.55-9.04 (19H, m, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.6

(OCH_2CH_3), 14.3 (OCH_2CH_3), 50.1 (C9), 61.8 (OCH_2CH_3), 62.3 (OCH_2CH_3), 64.7 (C4), 71.3 (C2), 123.0-136.8 (Ar-C), 167.4 (C=O); LRMS (ESI^-) m/z : 625.2 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{39}\text{H}_{35}\text{N}_2\text{O}_6$, 627.2490, found 627.2495.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-7-hydroxy-1,3-bis(4-nitrophenyl)-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249h**

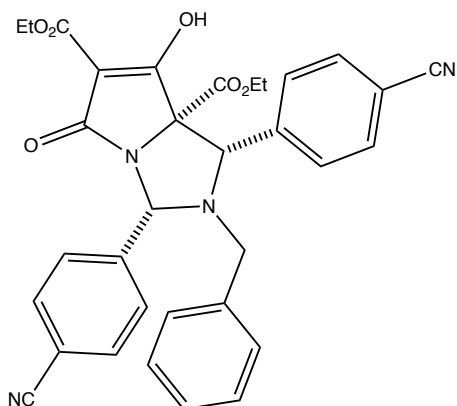


Yield (1.24 g, 83%); Orange foamy solid; m.p. 125-128°C;

$\nu_{\max}/\text{cm}^{-1}$ 1723 (C=O), 1608 (C=C); δ_{H} (400 MHz, CDCl_3) 0.90 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.39 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 3.75 (3H, m, OCH_2CH_3 , H9), 3.95 (1H, dq, $J=7.1$ Hz, 10.8 Hz, OCH_2CH_3), 4.15 (1H, s, H4), 4.39 (2H, m, OCH_2CH_3), 5.48 (1H, s, H2), 6.83 (2H, m, Ar-H), 7.21 (3H, m, Ar-H), 7.83 (2H, d, $J=8.4$ Hz, Ar-H), 8.05 (2H, d, $J=8.8$ Hz, Ar-H), 8.25 (2H, d,

$J=8.8$ Hz, Ar-H), 8.36 (2H, d, $J=9.0$ Hz, Ar-H); δ_{C} (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 14.2 (OCH_2CH_3), 52.9 (C9), 62.4 (OCH_2CH_3), 62.8 (OCH_2CH_3), 70.1 (C4), 75.2 (C5), 76.1 (C2), 123.6 (Ar-C), 124.0 (Ar-C), 128.5 (Ar-C), 128.9 (Ar-C), 129.9 (Ar-C), 130.0 (Ar-C), 130.2 (Ar-C), 132.3 (Ar-C), 140.9 (Ar-C), 148.1 (Ar-C), 148.6 (Ar-C), 163.9 (C=O), 167.3 (C=O), 184.6 (C6); LRMS (ESI^-) m/z : 615.1 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{31}\text{H}_{27}\text{N}_4\text{O}_{10}$, 615.1733, found 615.1732.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-1,3-bis(4-cyanophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249j**

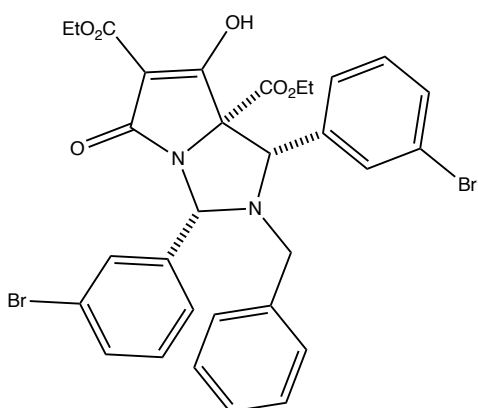


Yield (509 mg, 85%); Pale orange oil that solidified overnight;

m.p. 79-83°C; $\nu_{\max}/\text{cm}^{-1}$ 2984 (C-H), 2229 (C≡N), 1749 (C=O), 1713 (C=O), 1660 (C=O), 1610 (C=C); δ_{H} (400 MHz, CDCl₃) 0.88 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 1.37 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.72 (2H, s, H₉), 3.77-3.99 (2H, m, OCH₂CH₃), 4.05 (1H, s, H₄), 4.36 (2H, m, OCH₂CH₃), 5.39 (1H, s, H₂), 6.79 (2H, m, Ar-H), 7.21 (3H, m, Ar-H), 7.68 (2H, m, Ar-H), 7.72 (2H, m, Ar-H), 7.78

(2H, m, Ar-H), 7.98 (2H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.6 (OCH₂CH₃), 14.2 (OCH₂CH₃), 52.6 (C₉), 62.3 (OCH₂CH₃), 62.7 (OCH₂CH₃), 70.2 (C₄), 76.3 (C₂), 112.4 (C≡N), 113.2 (C≡N), 118.4 (Ar-C), 118.9 (Ar-C), 128.5 (Ar-C), 128.8 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C), 130.2 (Ar-C), 132.2 (Ar-C), 132.3 (Ar-C), 132.6 (Ar-C), 139.2 (Ar-C), 143.8 (Ar-C), 167.3 (C=O), 184.6 (C₆); LRMS (ESI⁻) m/z : 575.2 ([M - H]⁻ 96%); HRMS (ESI⁺) m/z : [M + H]⁺ calcd. for C₃₃H₂₉N₄O₆, 577.2082, found 577.2080.

Diethyl (1*S,3*S**,7*aR**)-2-benzyl-1,3-bis(3-bromophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-6,7*a*(5*H*)-dicarboxylate 249k**



Yield (560 mg, 70%); Yellow foamy solid; m.p. 81-84°C;

$\nu_{\max}/\text{cm}^{-1}$ 2983 (C-H), 1747 (C=O), 1720 (C=O), 1658 (C=O), 1617 (C=C); δ_{H} (400 MHz, CDCl₃) 0.97 (3H, t, $J=7.2$ Hz, OCH₂CH₃), 1.28 (3H, t, $J=7.1$ Hz, OCH₂CH₃), 3.63 (1H, d, $J=14.7$ Hz, H₉), 3.71 (1H, d, $J=14.6$ Hz, H₉), 3.79 (1H, m, OCH₂CH₃), 3.84 (1H, s, H₄), 3.94 (1H, m, OCH₂CH₃), 4.26 (2H, m, OCH₂CH₃), 5.18 (1H, s, H₂), 6.75 (2H, m, Ar-H), 7.15-7.31

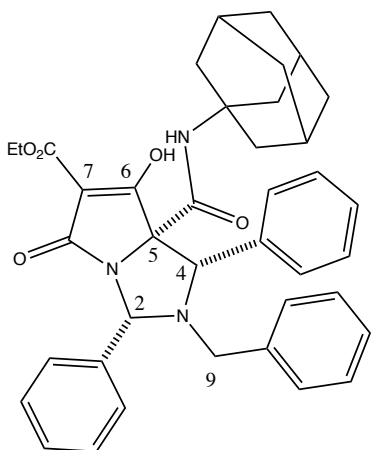
(6H, m, Ar-H), 7.42 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.78 (1H, m, Ar-H), 8.00 (1H, m, Ar-H); δ_{C} (101 MHz, CDCl₃) 13.8 (OCH₂CH₃), 14.2 (OCH₂CH₃), 51.2 (C₉), 62.1 (OCH₂CH₃), 62.7 (OCH₂CH₃), 69.5 (C₄), 75.4 (C₅), 76.1 (C₂), 122.5 (Ar-C), 123.0 (Ar-C), 128.0 (Ar-C), 128.2 (Ar-C), 128.7 (Ar-C), 130.0 (Ar-C),

130.3 (Ar-C), 130.4 (Ar-C), 131.9 (Ar-C), 132.1 (Ar-C), 132.3 (Ar-C), 132.4 (Ar-C), 136.0 (Ar-C), 140.8 (Ar-C), 164.4 (C=O), 167.3 (C=O), 185.0 (C6); LRMS (ESI⁻) m/z : 681.0 ([M⁷⁹⁺⁷⁹ - H]⁻ 49%), 683.0 ([M⁷⁹⁺⁸¹ - H]⁻ 97%), 685.0 ([M⁸¹⁺⁸¹ - H]⁻ 51%); HRMS (ESI⁺) m/z : [M⁷⁹⁺⁷⁹ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Br₂, 683.0374, found 683.0392; [M⁷⁹⁺⁸¹ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Br₂, 685.0355, found 685.0364; [M⁸¹⁺⁸¹ + H]⁺ calcd. for C₃₁H₂₉N₂O₆Br₂, 687.0341, found 687.0342.

General procedure for the synthesis of C5 and C7-carboxamidotetramic acids:^{33,43}

To a solution of tetramic acids **249a-b**, **249f**, **249k** (1.0 eq.) in anhydrous toluene was added 1-adamantylamine (1.2 eq.). The mixture was heated at reflux overnight. Then the reaction mixture was concentrated *in-vacuo* and purified by flash column chromatography to yield tetramates that were chelated with metals. The product was then redissolved in DCM, washed with 10% citric acid solution (aq.), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the desired carboxamides **260a-b**, **261a-c**.

Ethyl (1S*,3S*,7aR*)-7a-(adamantan-1-ylcarbamoyl)-2-benzyl-7-hydroxy-5-oxo-1,3-diphenyl-2,3,5,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carboxylate **260a**

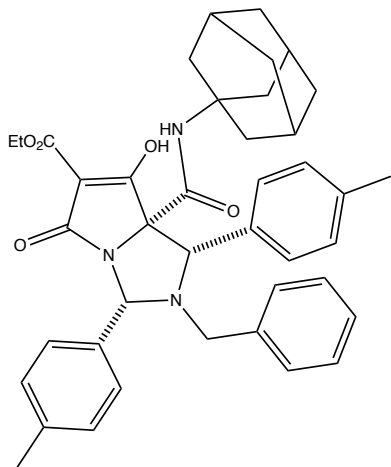


Yield (56 mg, 21%); Orange oil; R_f (50% EtOAc in Pet. Ether 40:60) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 2910 (C-H), 2852 (C-H), 1743 (C=O), 1689 (C=O), 1626 (C=C); AB:CD 62:38 by δ_{H} -NMR; δ_{H} (Major tautomer) (400 MHz, CDCl₃) 1.23 (3H, t, $J=7.0$ Hz, OCH₂CH₃), 1.64-1.68 (6H, br m, Adamantyl-CH₂), 1.88-2.02 (6H, br m, Adamantyl-CH₂), 2.08 (3H, br m, Adamantyl-H), 3.48 (1H, d, $J=13.7$ Hz, H₉), 3.75 (1H, d, $J=13.6$ Hz, H₉), 4.31 (2H, m, OCH₂CH₃), 5.08 (1H, s, H₄), 5.87 (1H, s, H₂), 6.99 (2H, m, Ar-H), 7.04

(2H, m, Ar-H), 7.20-7.50 (9H, m, Ar-H), 7.68 (2H, m, Ar-H), 10.27 (1H, br s, NH/OH); δ_{C} (Major tautomer) (101 MHz, CDCl₃) 14.2 (OCH₂CH₃), 29.3 (Adamantyl-C), 36.1 (Adamantyl-C), 41.6 (Adamantyl-C), 49.9 (C₉), 53.5 (Adamantyl-C), 62.9 (OCH₂CH₃), 65.4 (C₄), 77.7 (C₂), 79.2 (C₅), 95.3 (C₇), 127.1 (Ar-C), 128.1 (Ar-C), 128.2 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 134.8

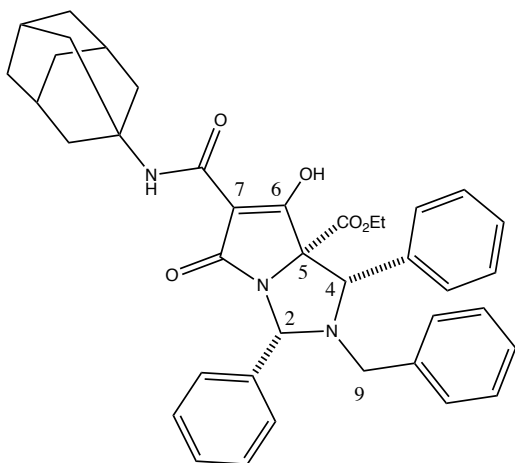
(Ar-C), 137.5 (Ar-C), 139.6 (Ar-C), 165.9 (C=O), 168.1 (C=O), 174.0 (C=O), 186.5 (C6); LRMS (ESI⁻) m/z : 630.2 ([M - H]⁻ 95%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₃₉H₄₀N₃O₅, 630.2973, found 630.2967.

Ethyl (1*S,3*S**,7*aR**)-7a-(adamantan-1-ylcarbamoyl)-2-benzyl-7-hydroxy-5-oxo-1,3-di-*p*-tolyl-2,3,5,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate 260b**



Yield (300 mg, 36%); Brown foamy solid; m.p. 108-111°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.68; $\nu_{\max}/\text{cm}^{-1}$ 3308 (O-H), 2909 (C-H), 2852 (C-H), 1742 (C=O), 1686 (C=O), 1625 (C=C); AB:CD 69:31 by δ_{H} -NMR; δ_{H} (Major tautomer) (400 MHz, CDCl₃) 1.25 (3H, t, J =7.1 Hz, OCH₂CH₃), 1.66-1.68 (6H, br m, Adamantyl-CH₂), 1.97-2.01 (6H, br m, Adamantyl-CH₂), 2.09 (3H, br s, Adamantyl-CH), 2.33 (3H, s, CH₃), 2.36 (3H, s, CH₃), 3.40 (1H, d, J =13.7 Hz, H₉), 3.69 (1H, d, J =13.7 Hz, H₉), 4.31 (2H, m, OCH₂CH₃), 5.01 (1H, s, H₄), 5.77 (1H, s, H₂), 6.70 (1H, br s, NH/OH), 6.85 (2H, d, J =7.5 Hz, Ar-H), 7.04 (2H, d, J =7.2 Hz, Ar-H), 7.08 (2H, d, J =7.7 Hz, Ar-H), 7.20-7.25 (5H, m, Ar-H), 7.44 (1H, br s, NH/OH), 7.53 (2H, d, J =8.1 Hz, Ar-H); δ_{C} (Major tautomer) (101 MHz, CDCl₃) 14.2 (OCH₂CH₃), 21.3 (CH₃), 21.3 (CH₃), 29.4 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 49.9 (C₉), 53.4 (Adamantyl-C), 62.8 (OCH₂CH₃), 65.1 (C₄), 77.4 (C₂), 79.2 (C₅), 96.0 (C₇), 127.1 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 128.4 (Ar-C), 129.0 (Ar-C), 129.2 (Ar-C), 129.3 (Ar-C), 136.6 (Ar-C), 138.6 (Ar-C), 166.0 (C=O), 168.2 (C=O), 186.1 (C₆); LRMS (ESI⁻) m/z : 658.2 ([M - H]⁻ 97%); HRMS (ESI⁻) m/z : [M - H]⁻ calcd. for C₄₁H₄₄N₃O₅, 658.3286, found 658.3295.

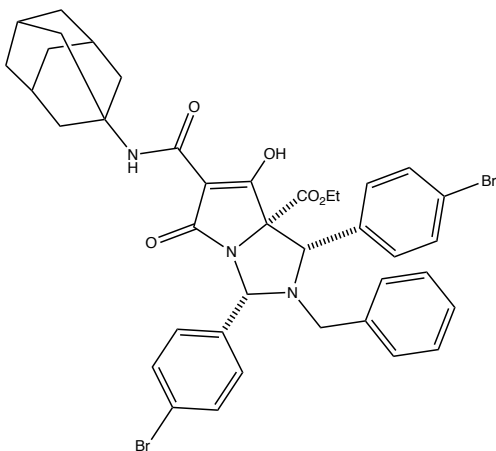
Ethyl (1*S,3*S**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-2-benzyl-7-hydroxy-5-oxo-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-7*a*(5*H*)-carboxylate 261a**



Yield (365 mg, 31%); Yellow foamy solid; m.p. 105-108°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.85; $\nu_{\max}/\text{cm}^{-1}$ 3310 (O-H), 2909 (C-H), 2852 (C-H), 1743 (C=O), 1692 (C=O), 1625 (C=C); AB:CD 67:33 by δ_{H} -NMR; δ_{H} (Major tautomer) (400 MHz, CDCl_3) 0.92 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 1.67-1.68 (6H, br m, Adamantyl- CH_2), 2.01-2.11 (9H, br m, Adamantyl- CH_2 , CH), 3.66 (1H, d, $J=14.7$ Hz, H9), 3.75

(1H, dq, $J=7.2$ Hz, 10.7 Hz, OCH_2CH_3), 3.82 (1H, d, $J=14.7$ Hz, H9), 3.95 (1H, m, OCH_2CH_3), 3.97 (1H, s, H4), 5.19 (1H, s, H2), 6.77 (2H, m, Ar-H), 7.23 (3H, m, Ar-H), 7.36-7.50 (6H, m, Ar-H), 7.60 (2H, d, $J=7.5$ Hz, Ar-H), 7.97 (2H, m, Ar-H); δ_{C} (Major tautomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 29.4 (Adamantyl-C), 36.1 (Adamantyl-C), 41.7 (Adamantyl-C), 50.1 (C9), 53.4 (Adamantyl-C), 62.0 (OCH_2CH_3), 69.3 (C4), 76.6 (C2), 79.2 (C5), 94.5 (C7), 127.6-139.1 (Ar-C), 165.3 (C=O), 166.5 (C=O), 174.9 (C=O), 187.6 (C6); LRMS (ESI⁻) m/z : 630.3 ($[\text{M} - \text{H}]^-$ 97%); HRMS (ESI⁻) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{39}\text{H}_{40}\text{N}_3\text{O}_5$, 630.2963, found 630.2980.

Ethyl (1*S,3*S**,7*aR**)-6-(adamantan-1-ylcarbamoyl)-2-benzyl-1,3-bis(4-bromophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-7*a*(5*H*)-carboxylate 261b**

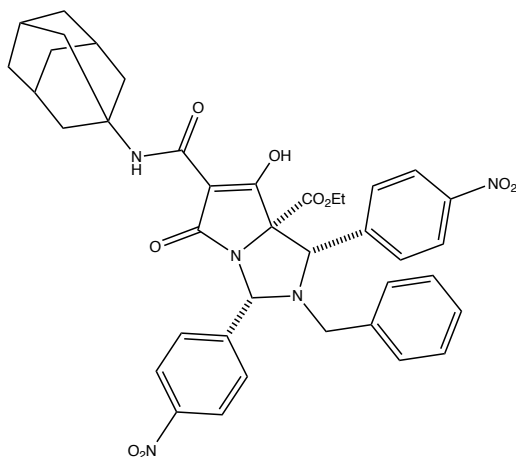


Yield (221 mg, 38%); Orange foamy solid; m.p. 129-133°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.90; $\nu_{\max}/\text{cm}^{-1}$ 3309 (O-H), 2910 (C-H), 2852 (C-H), 1744 (C=O), 1693 (C=O), 1627 (C=C); AB:CD 60:40 by δ_{H} -NMR; δ_{H} (Major tautomer) (400 MHz, CDCl_3) 0.95 (3H, t, $J=6.9$ Hz, OCH_2CH_3), 1.67-1.69 (6H, br s, Adamantyl- CH_2), 2.01-2.03 (6H, br s, Adamantyl- CH_2), 2.11 (3H, br s, Adamantyl-CH), 3.65 (1H, d, $J=14.6$ Hz, H9), 3.74-

3.83 (2H, m, OCH_2CH_3 , H9), 3.92 (1H, s, H4), 3.97 (1H, m, OCH_2CH_3), 5.15 (1H, s, H2), 6.83 (2H, m, Ar-H), 7.23 (2H, m, Ar-H), 7.45 (3H, m, Ar-H), 7.57 (2H, d, $J=8.4$ Hz, Ar-H), 7.61 (2H, m, Ar-H), 7.79 (2H, m,

Ar-H); δ_c (Major tautomer) (101 MHz, CDCl_3) 13.7 (OCH_2CH_3), 29.4 (Adamantyl-C), 36.1 (Adamantyl-C), 41.6 (Adamantyl-C), 50.7 (C9), 53.8 (Adamantyl-C), 62.2 (OCH_2CH_3), 68.9 (C4), 76.2 (C2), 93.3 (C7), 122.8-138.1 (Ar-C), 165.1 (C=O), 166.6 (C=O), 174.8 (C=O), 188.2 (C6); LRMS (ESI^-) m/z : $[\text{M}^{79+79} - \text{H}]^-$ 45%), 788.0 ($[\text{M}^{79+81} - \text{H}]^-$ 100%), 790.0 ($[\text{M}^{81+81} - \text{H}]^-$ 55%); HRMS (ESI^-) m/z : $[\text{M}^{79+79} - \text{H}]^-$ calcd. for $\text{C}_{39}\text{H}_{38}\text{N}_3\text{O}_5\text{Br}_2$, 786.1173, found 786.1187; $[\text{M}^{79+81} - \text{H}]^-$ calcd. for $\text{C}_{39}\text{H}_{38}\text{N}_3\text{O}_5\text{Br}_2$, 788.1156, found 788.1167; $[\text{M}^{81+81} - \text{H}]^-$ calcd. for $\text{C}_{39}\text{H}_{38}\text{N}_3\text{O}_5\text{Br}_2$, 790.1145, found 790.1151.

Ethyl (1S*,3S*,7aR*)-6-(adamantan-1-ylcarbamoyl)-2-benzyl-7-hydroxy-1,3-bis(4-nitrophenyl)-5-oxo-2,3-dihydro-1H-pyrrolo[1,2-c]imidazole-7a(5H)-carboxylate 261c



Yield (305 mg, 37%); Brown solid; m.p. 156-160°C; R_f (30% EtOAc in Pet. Ether 40:60) 0.58; $\nu_{\text{max}}/\text{cm}^{-1}$ 3307 (O-H), 2911 (C-H), 2852 (C-H), 1742 (C=O), 1693 (C=O), 1629 (C=C); AB:CD 58:42 by δ_{H} -NMR; δ_{H} (Major tautomer) (400 MHz, CDCl_3) 0.88 (3H, m, OCH_2CH_3), 1.66-1.70 (6H, br m, Adamantyl- CH_2), 2.04-2.06 (6H, br m, Adamantyl- CH_2), 2.14 (3H, br s, Adamantyl-CH), 3.71-3.81 (3H, m,

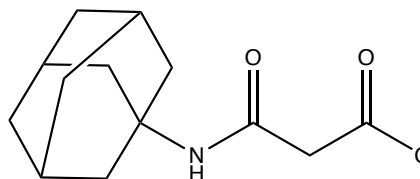
OCH_2CH_3 , H9), 3.95 (1H, m, OCH_2CH_3), 4.14 (1H, s, H4), 5.39 (1H, s, H2), 6.86 (2H, m, Ar-H), 7.19 (3H, m, Ar-H), 7.53 (1H, br s, NH/OH), 7.80 (2H, d, $J=8.7$ Hz, Ar-H), 7.98 (2H, m, Ar-H), 8.22 (2H, d, $J=8.7$ Hz, Ar-H), 8.33 (2H, d, $J=8.7$ Hz, Ar-H); δ_c (Major tautomer) (101 MHz, CDCl_3) 13.8 (OCH_2CH_3), 29.4 (Adamantyl-C), 36.0 (Adamantyl-C), 41.7 (Adamantyl-C), 53.4 (C9), 54.4 (Adamantyl-C), 62.4 (OCH_2CH_3), 69.7 (C4), 76.6 (C2), 90.9 (C7), 123.5-148.3 (Ar-C), 164.8 (C=O), 166.8 (C=O), 174.6 (C=O), 189.2 (C6); LRMS (ESI^-) m/z : 720.0 ($[\text{M} - \text{H}]^-$ 98%); HRMS (ESI^-) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{39}\text{H}_{38}\text{N}_5\text{O}_9$, 720.2675, found 720.2679.

General procedure for the synthesis of carboxylic acid:

Meldrum's acid **262** (1 eq.) was dissolved in toluene (0.7 M) and MeCN (0.7 M). 1-Adamantylamine (2 eq.) was added and the reaction mixture was heated to 80°C for 12 h. After allowing the reaction mixture to cool to rt, the reaction mixture was concentrated under reduced pressure. Added to the

concentrate was sat. NaHCO_3 (aq.) and EtOAc and this reaction mixture was transferred to a separatory funnel. The aqueous layer was then acidified to pH 1-2 using 3 M HCl solution (aq.) and extracted with EtOAc. The organic layer was then dried over Na_2SO_4 , filtered and concentrated *in-vacuo* to obtain a white solid **263** which was used without further purification.

3-(Adamantan-1-ylamino)-3-oxopropanoic acid **263**



Yield (345 mg, 18%, contaminated with an unknown impurity);

White solid; $\nu_{\text{max}}/\text{cm}^{-1}$ 3338 (O-H), 2909 (C-H), 2846 (C-H), 1752

(C=O), 1709 (C=O); δ_{H} (400 MHz, CDCl_3) 1.69 (6H, br m,

Adamantyl- CH_2), 2.01 (6H, br m, Adamantyl- CH_2), 2.11 (3H, br s, Adamantyl-CH), 3.24 (2H, s, CH_2), 6.02

(1H, br s, NH/OH); δ_{C} (101 MHz, CDCl_3) 29.5 (Adamantyl-C), 36.3 (Adamantyl-C), 38.8 (CH_2), 41.4

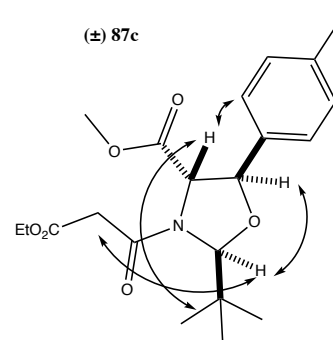
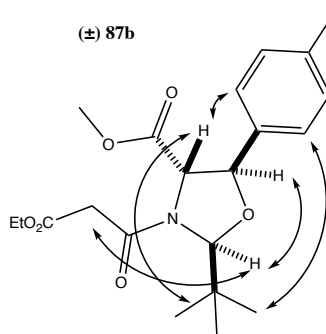
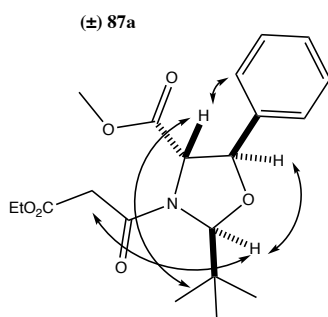
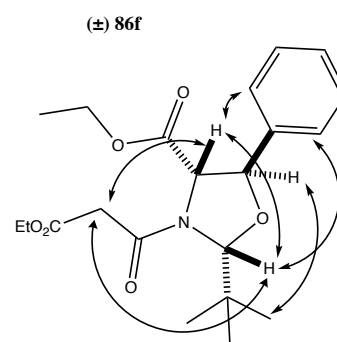
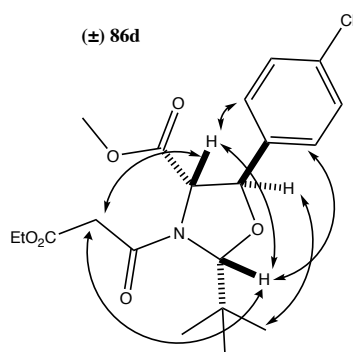
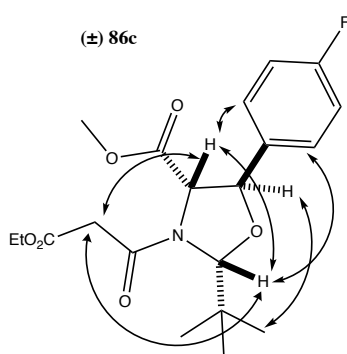
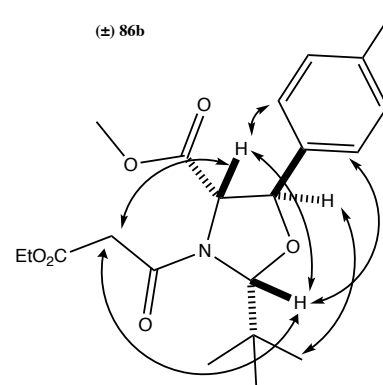
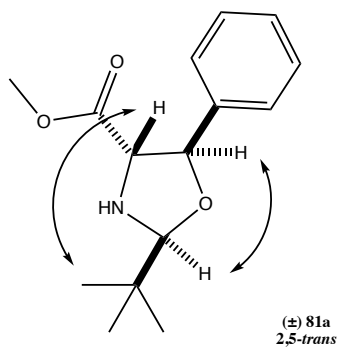
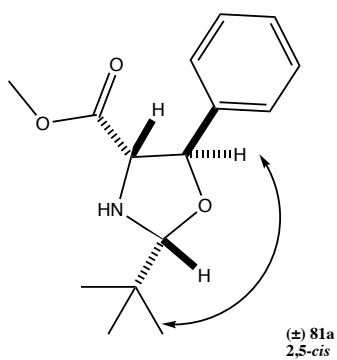
(Adamantyl-C), 53.7 (Adamantyl-C), 163.0 (C=O), 168.4 (C=O); LRMS (ESI)⁺ m/z : 238.2 ($[\text{M} + \text{H}]^+$ 96%),

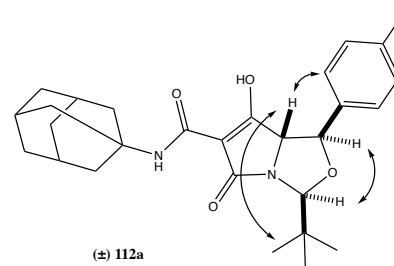
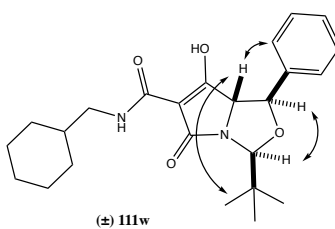
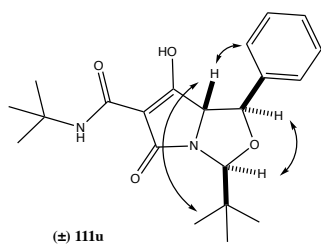
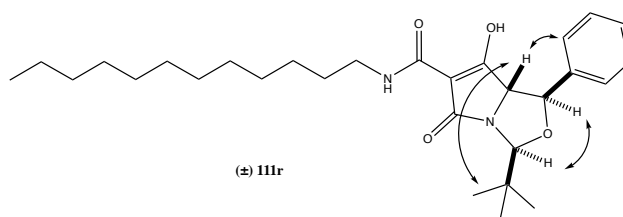
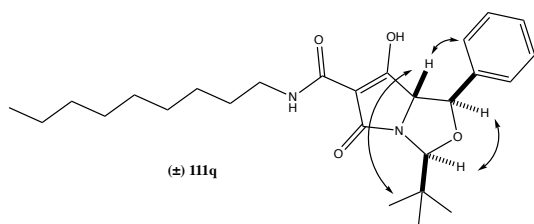
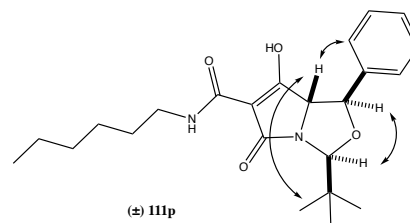
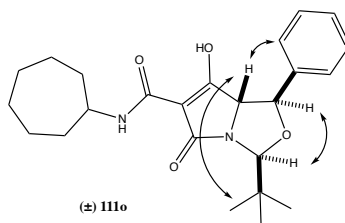
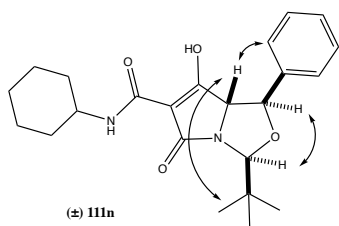
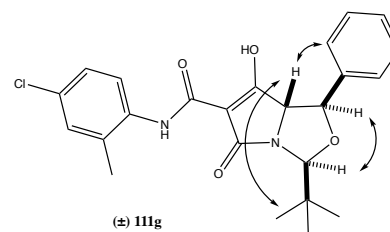
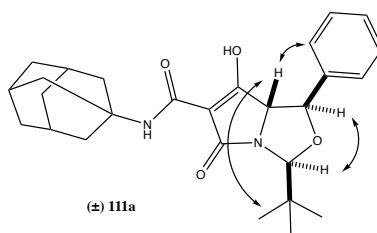
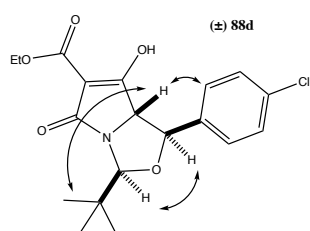
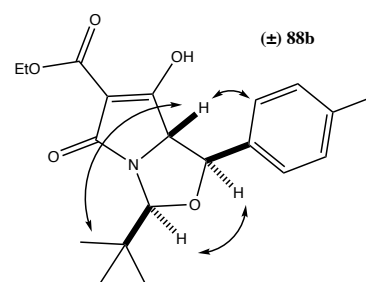
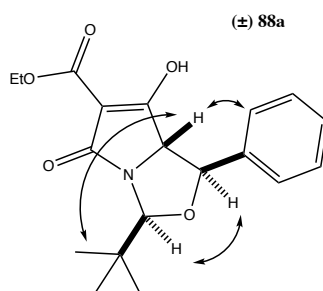
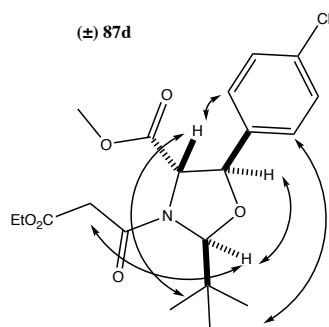
260.1 ($[\text{M} + \text{Na}]^+$ 96%); LRMS (ESI)⁻ m/z : 236.1 ($[\text{M} - \text{H}]^-$ 95%); HRMS (ESI)⁺ m/z : $[\text{M} + \text{H}]^+$ calcd. for

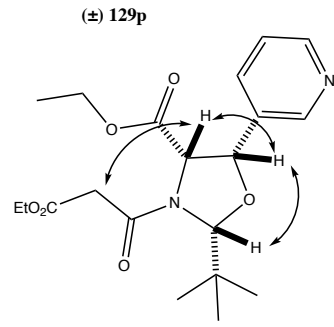
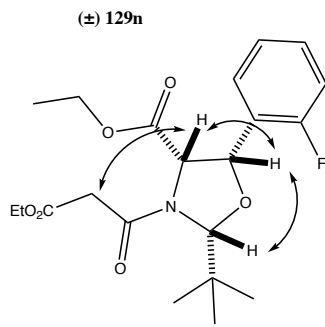
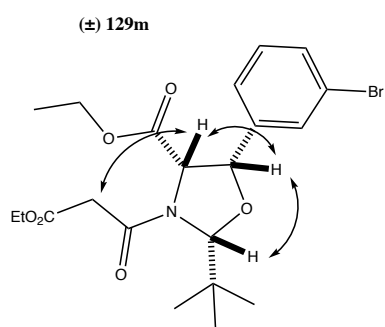
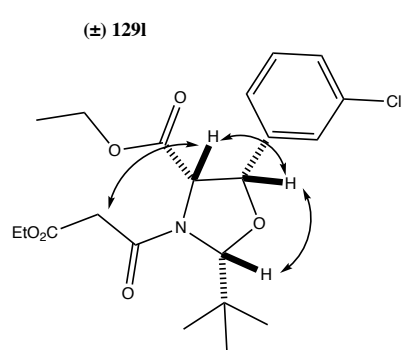
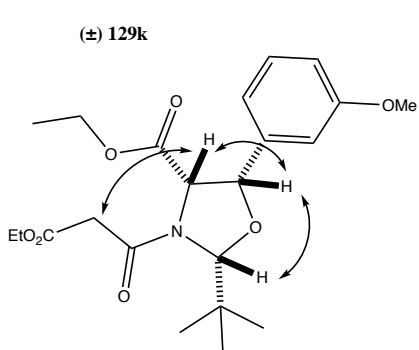
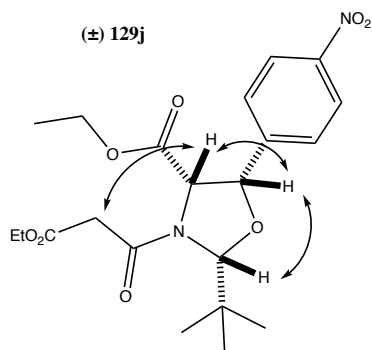
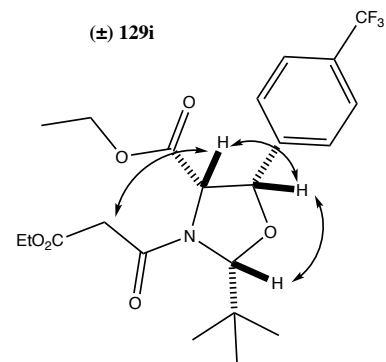
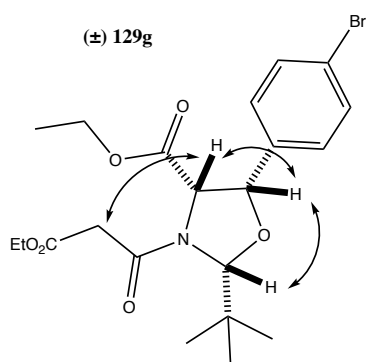
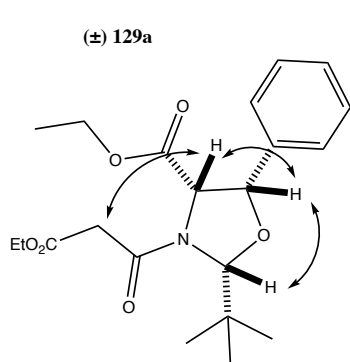
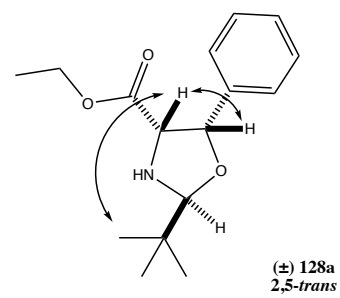
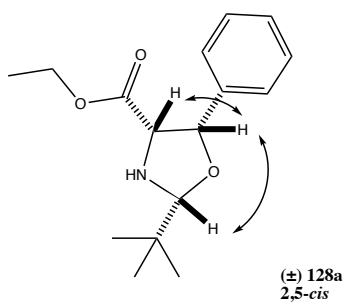
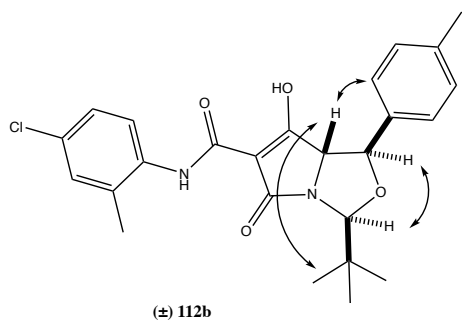
$\text{C}_{13}\text{H}_{20}\text{O}_3\text{N}$, 238.1438, found 238.1439.

Appendices

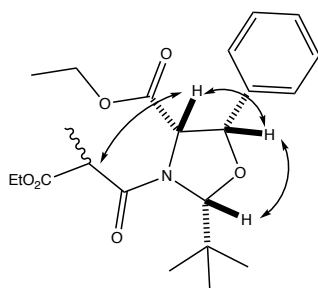
nOe, NOESY and ROESY Interactions



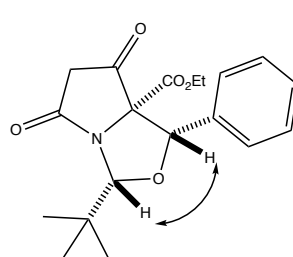




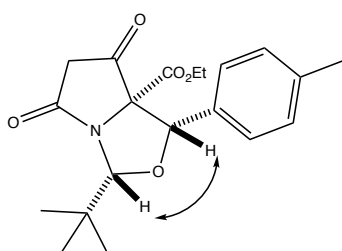
(±) 131



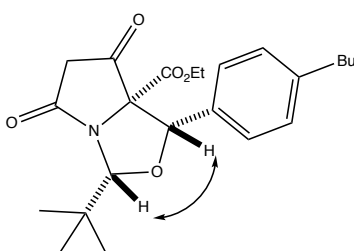
(±) 134a



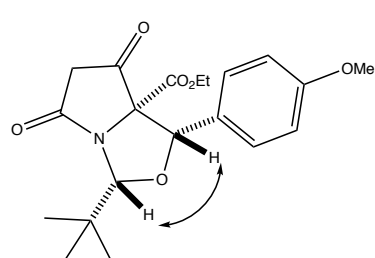
(±) 134b



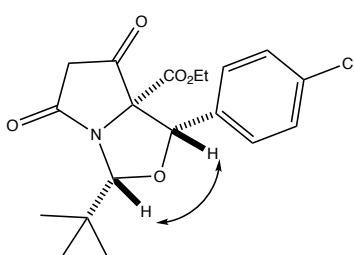
(±) 134c



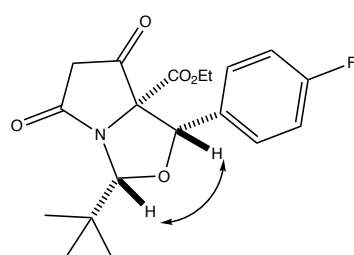
(±) 134d



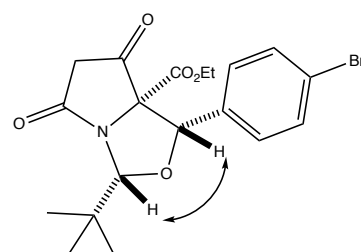
(±) 134e



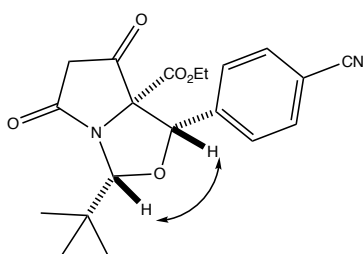
(±) 134f



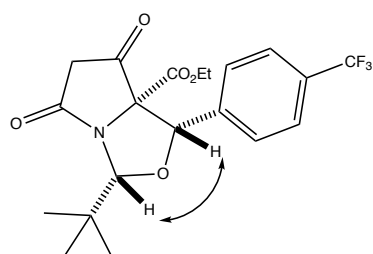
(±) 134g



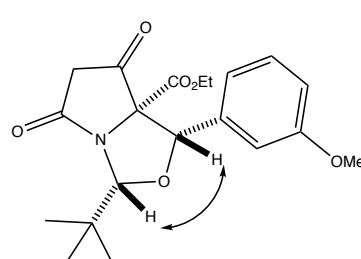
(±) 134h



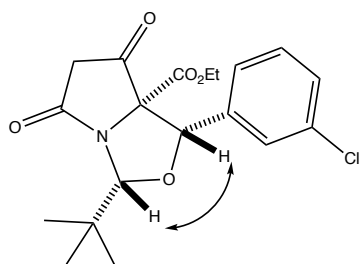
(±) 134i



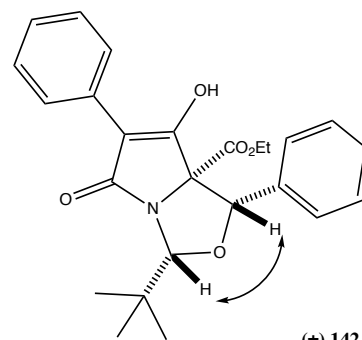
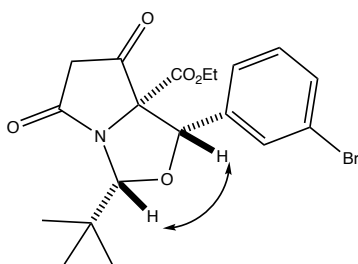
(±) 134k



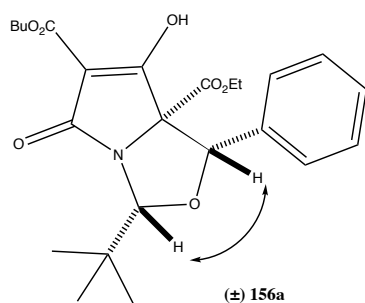
(±) 134l



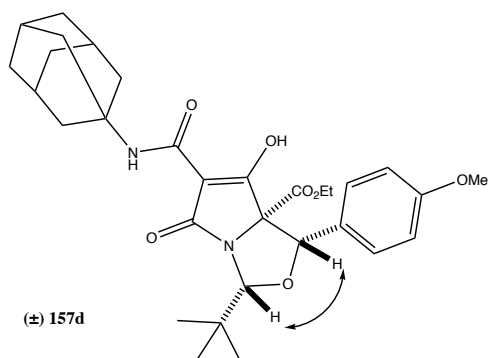
(±) 134m



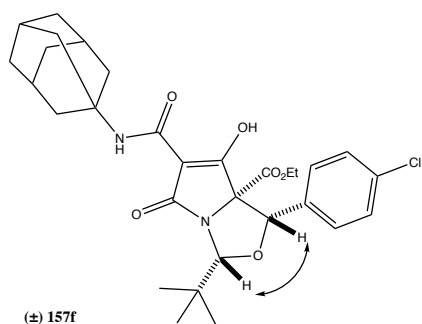
(±) 142



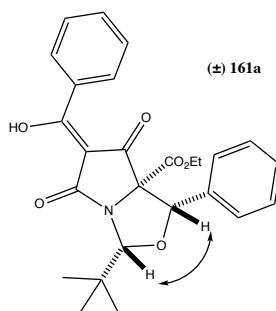
(±) 156a



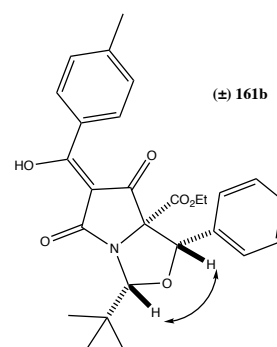
(±) 157d



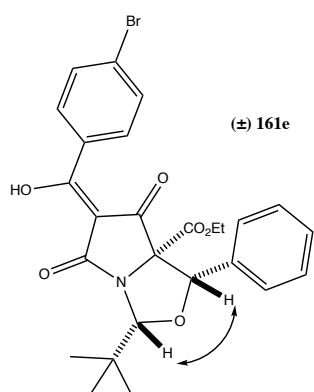
(±) 157f



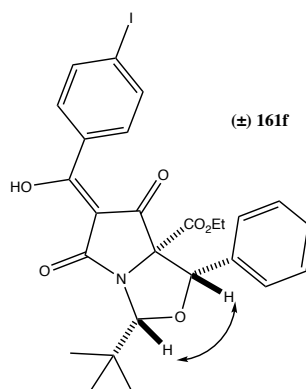
(±) 161a



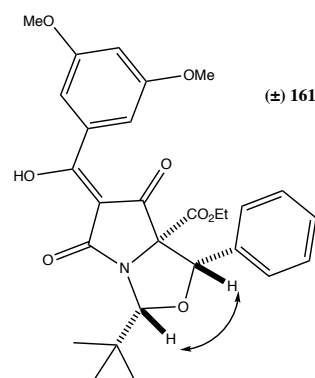
(±) 161b



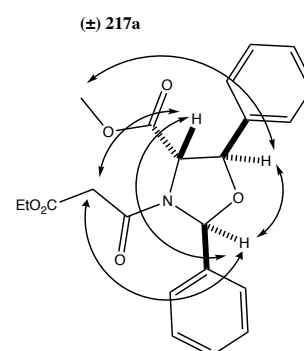
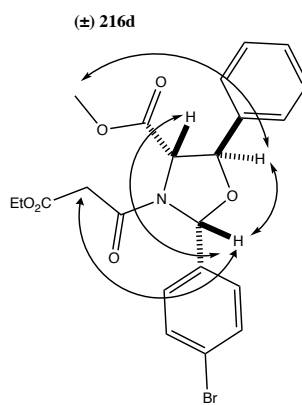
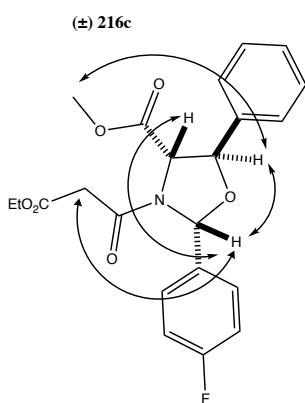
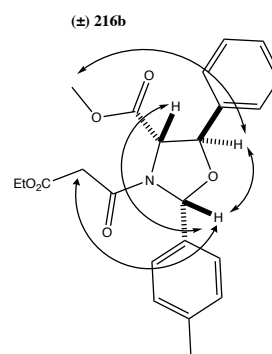
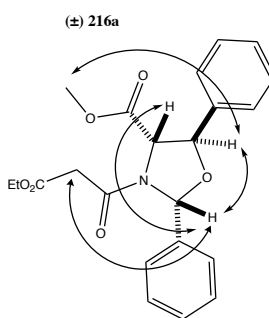
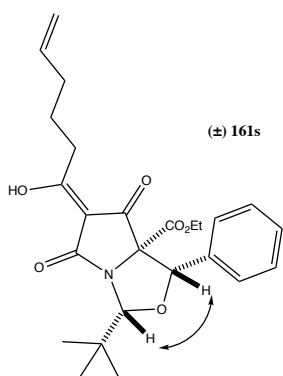
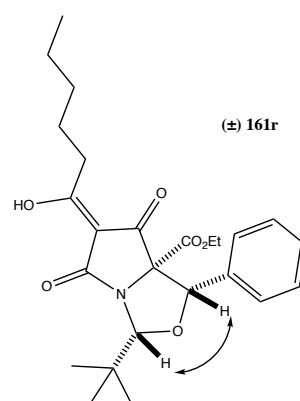
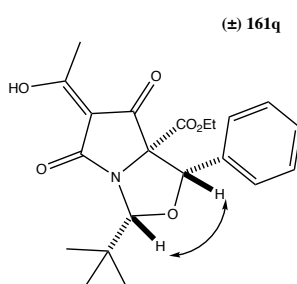
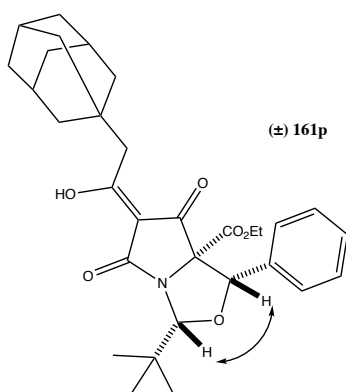
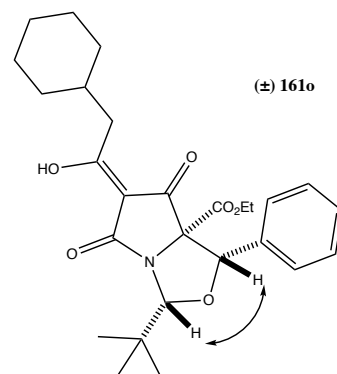
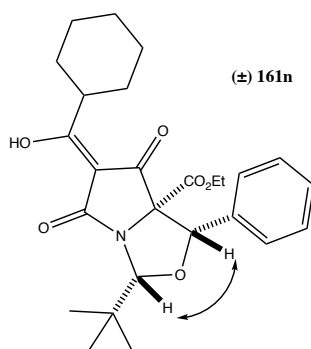
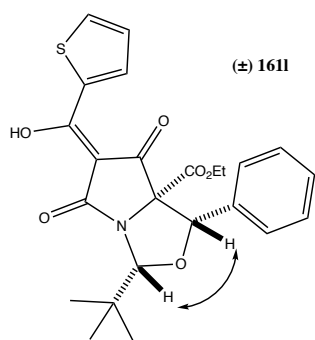
(±) 161e

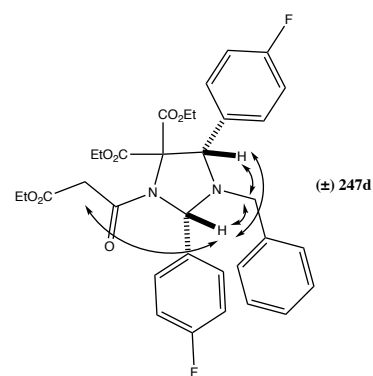
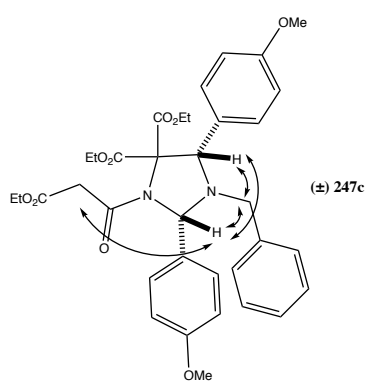
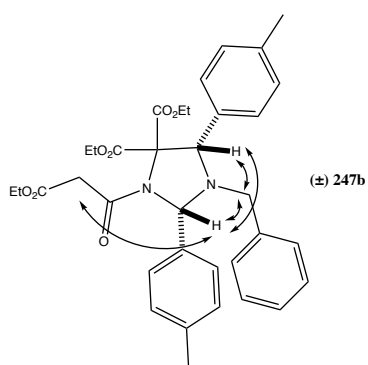
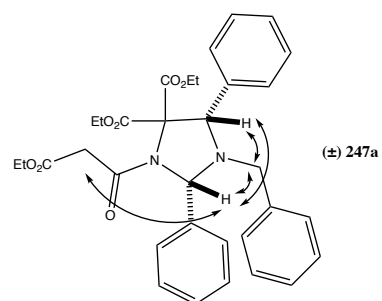
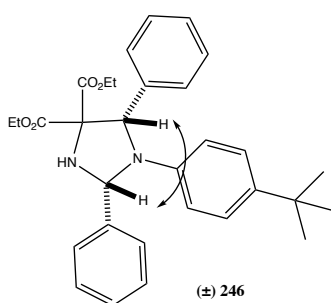
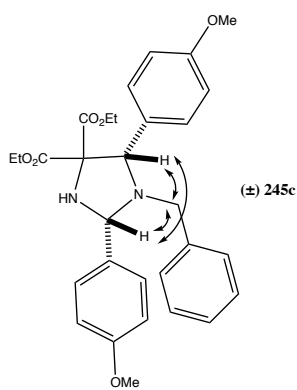
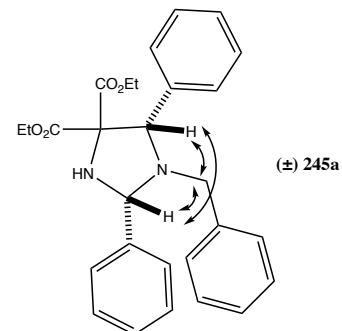
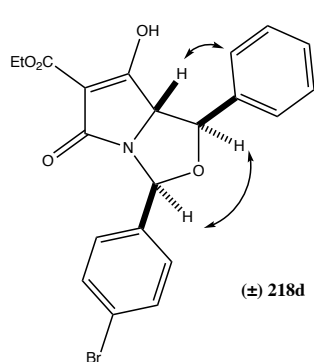
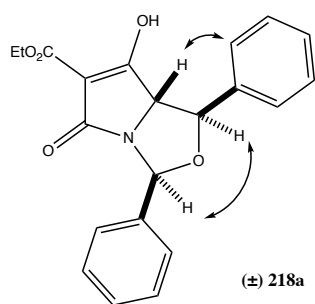
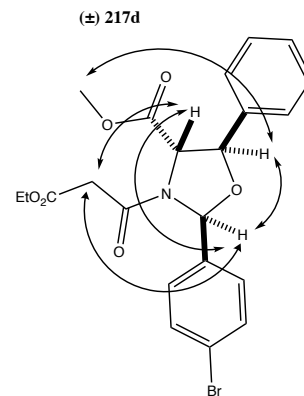
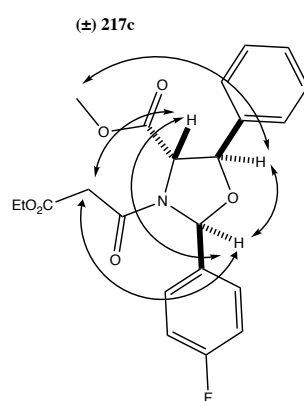
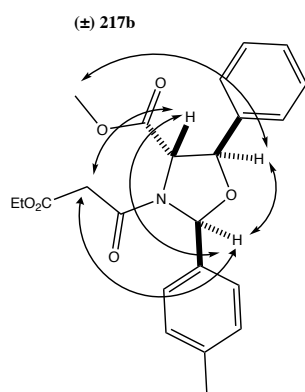


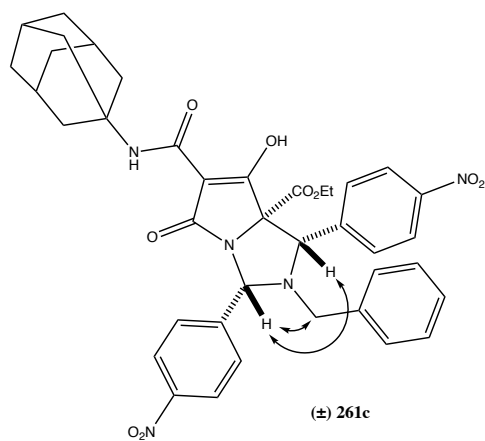
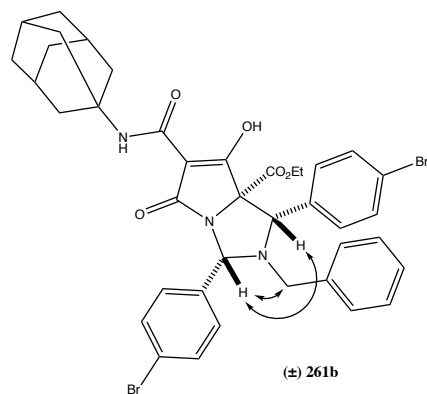
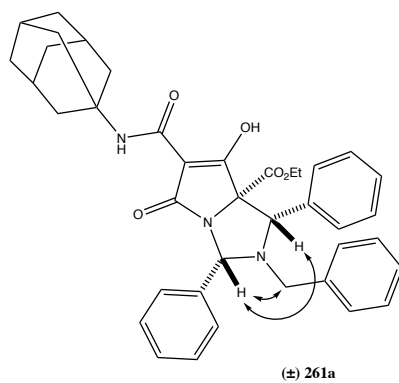
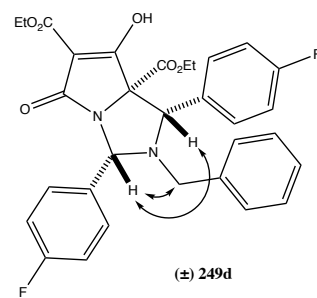
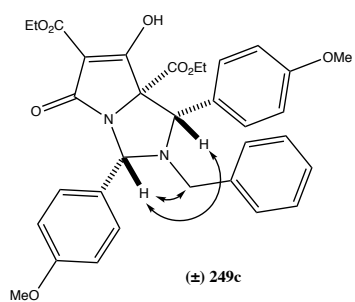
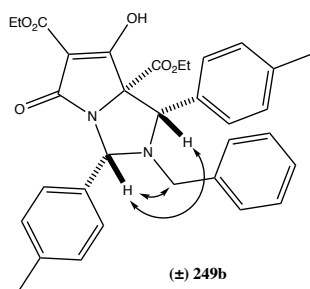
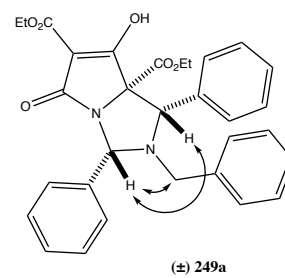
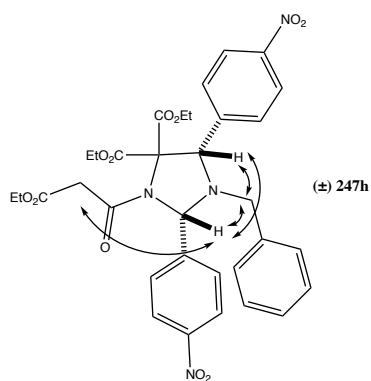
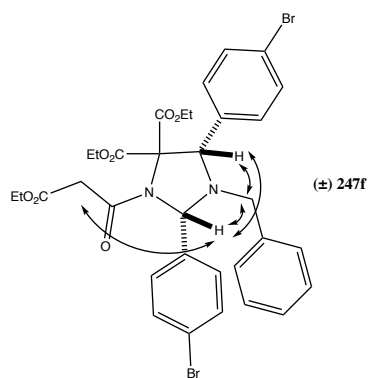
(±) 161f



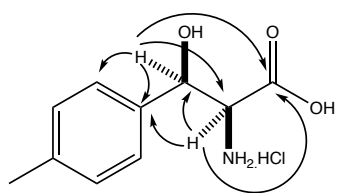
(±) 161k



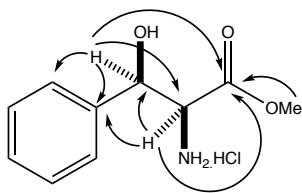




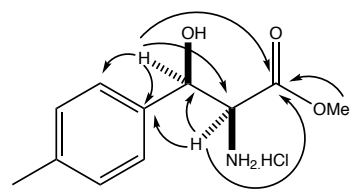
HMBC Interactions



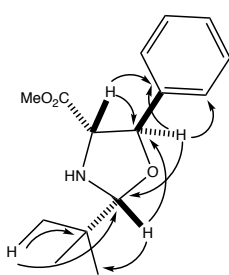
(±) 81b



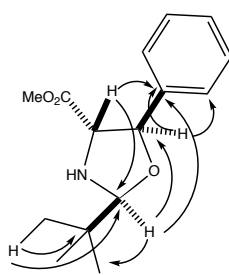
(±) 82a



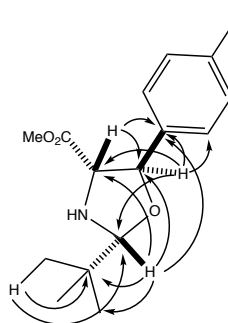
(±) 82b



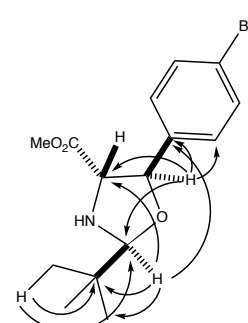
(±) 2,5-cis 84a



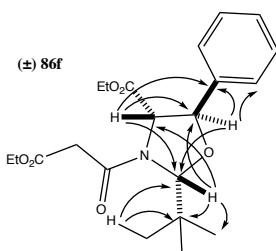
(±) 2,5-trans 84a



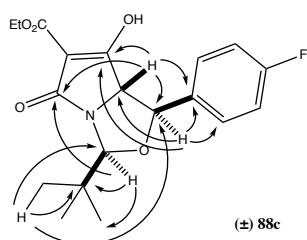
(±) 2,5-cis 84e



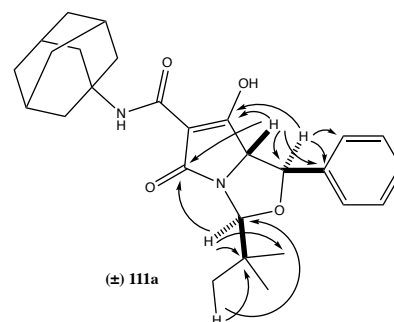
(±) 2,5-trans 84e



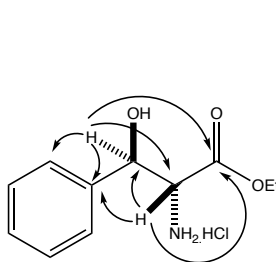
(±) 86f



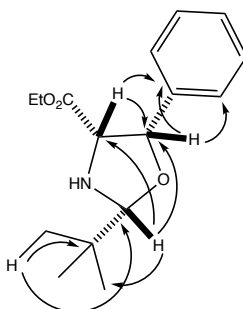
(±) 88c



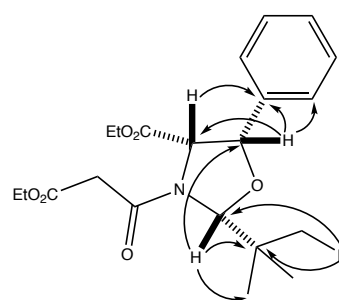
(±) 111a



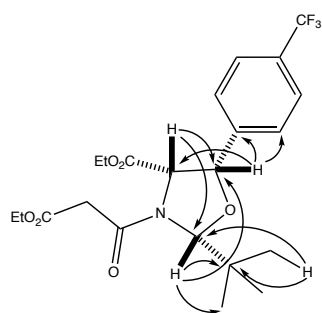
(±) 125a



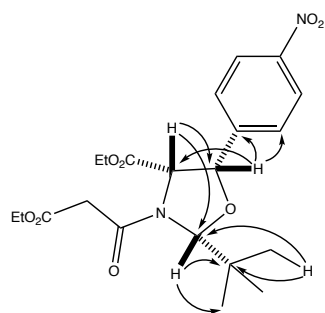
(±) 2,5-cis 128a



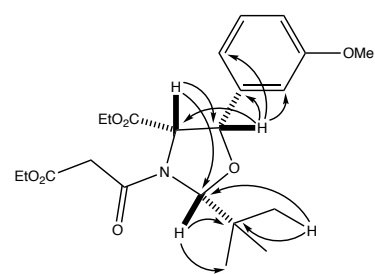
(±) 129a



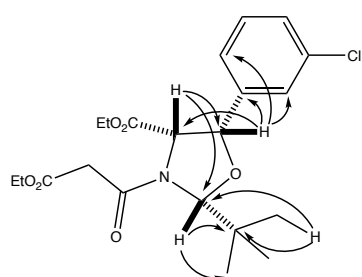
(±) 129i



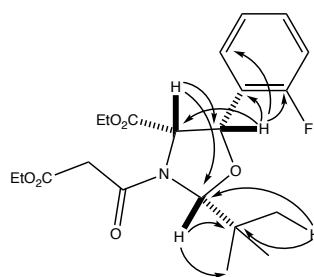
(±) 129g



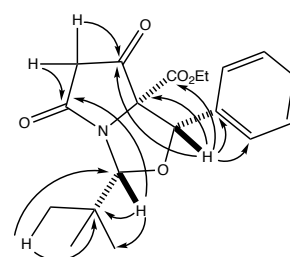
(±) 129k



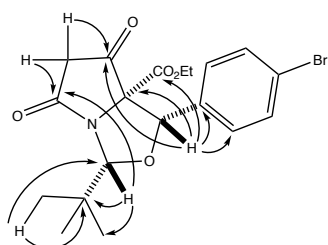
(±) 129l



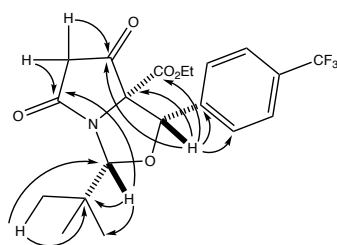
(±) 129n



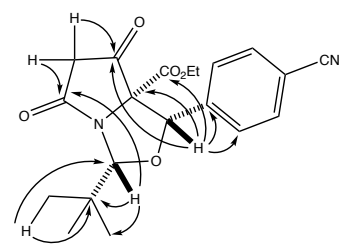
(±) 134a



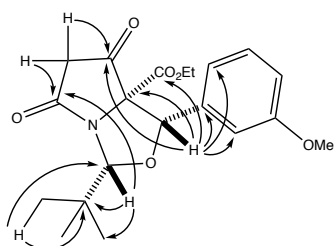
(±) 134g



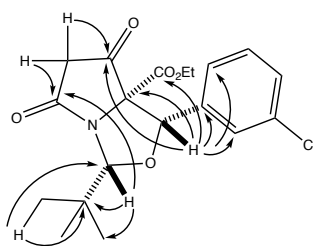
(±) 134i



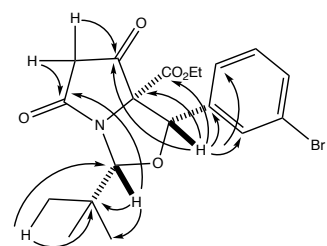
(±) 134h



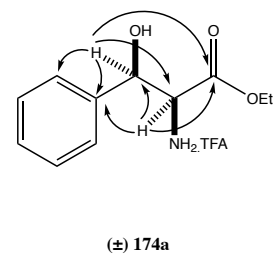
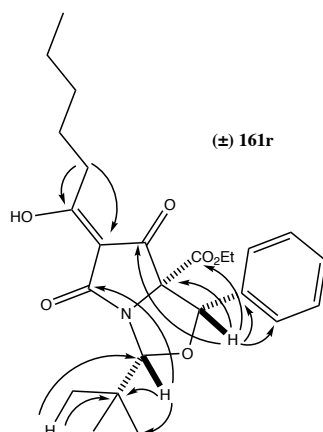
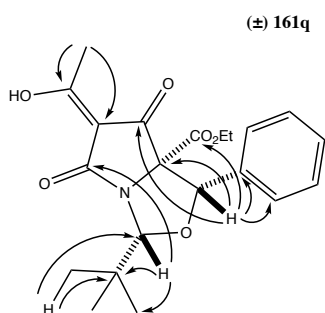
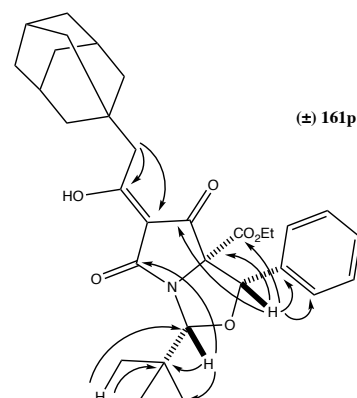
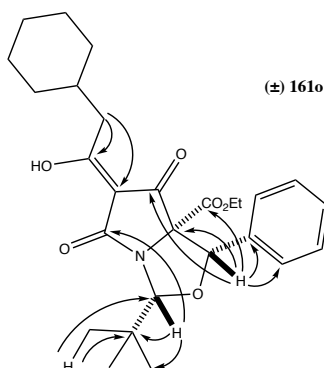
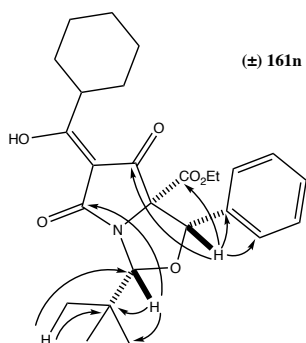
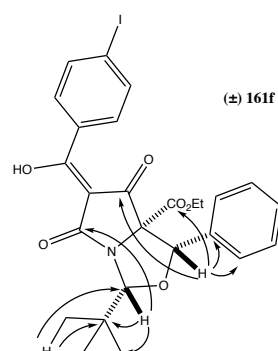
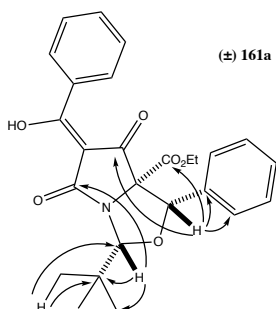
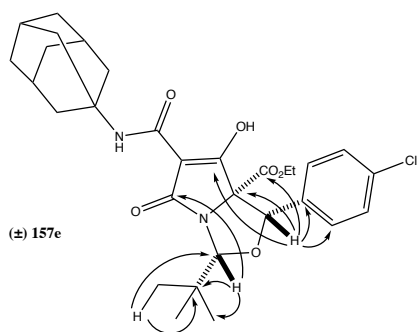
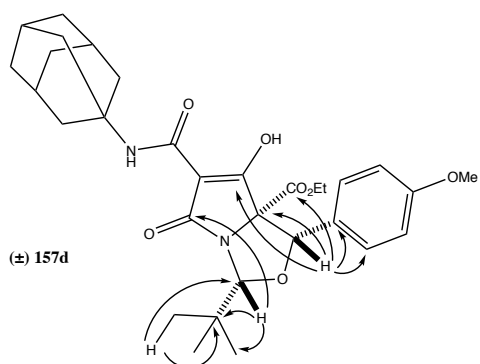
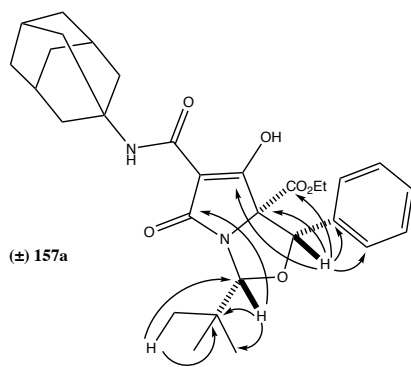
(±) 134k

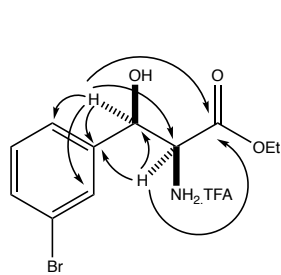


(±) 134l

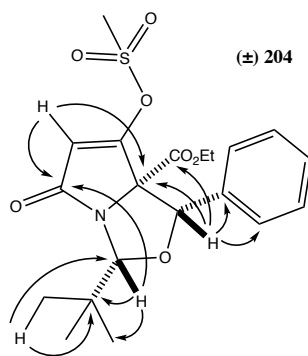


(±) 134m

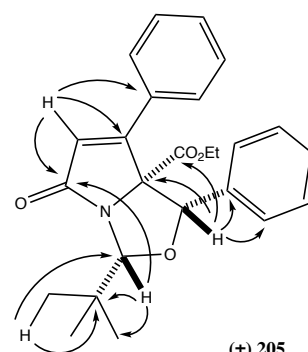




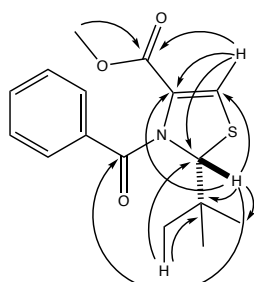
(±) 174h



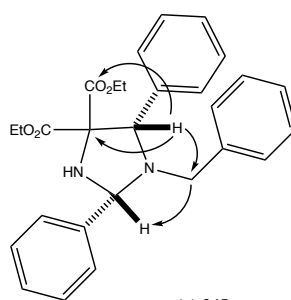
(±) 204



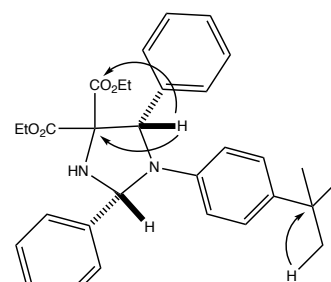
(±) 205



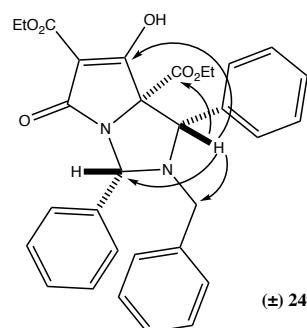
238



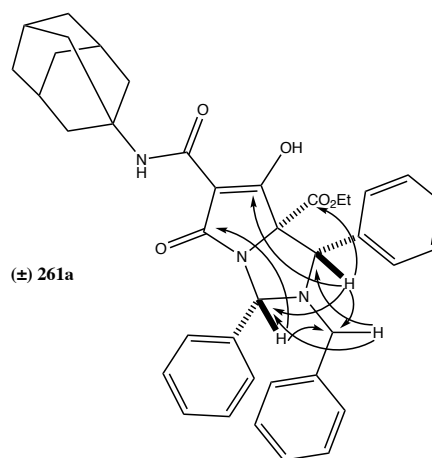
(±) 245a



(±) 246



(±) 249a



(±) 261a

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