Methodology for the Conversion of Tetramates to Pyroglutamates, and a Study of their Biological Activity

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

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Trinity 2018

Declaration

The thesis I am submitting is entirely my own work, except where I have acknowledged. I have clearly specified the presence of any Scheme, Figure, Table or any other materials with appropriate references.

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ABSTRACT

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Halima Bagum, St Cross College, University of Oxford

DPhil in Organic Chemistry, Trinity 2018

Highly functionalised pyroglutamates, molecules of interest for their biological uses and applications, are readily accessible from a bicyclic tetramic acid as a substrate for functionalisation at C3 and C4 of tetramic acid ring. These molecules have structural features common to pyroglutamate and pyrrolinone-containing natural products and this thesis particularly focuses on the development of novel routes to 3-substituted and 3,4-disubstituted pyroglutamic acid derivatives.

Chapter 1 represents an overview of antibacterial drug discovery and the need for the development of new antibiotics. It describes the importance of the pyroglutamate building block in natural product-inspired drug discovery. Preparation and application of 3-substituted pyroglutamate, pyrrolidinone, and pyroglutaminol derivatives have been extensively reviewed. Representative examples of lactam-derived natural products and their biological properties are also outlined.

Chapter 2 describes the synthetic strategy for the conversion of tetramates to pyrrolinones that allows stereospecific C3 arylation via Suzuki coupling. Conformationally constrained 3-aryl pyrrolidinone and pyroglutaminol derivatives are efficiently achievable from these newly developed 3-arylpyrrolinones under hydrogenation and *N*,*O*-acetal deprotection conditions, respectively. These synthetic routes permit the preparation of a large library of pyroglutamate derivatives. Alternatively, attempted Reformatsky conjugate addition conditions were unsuccessful for the C3 functionalisation of enones.

Chapter 3 effectively utilises the methodology developed in Chapter 2, for the synthesis of 3,4-disubstituted pyrrolinone and pyroglutamate derivatives. The use of an ethyl ester bicyclic tetramate or Weinreb amide did not work for the mesylation step as these tricarbonyls act as only a weak nucleophile and hence, further C4 functionalisation was thwarted.

Chapter 4 demonstrates a novel approach for the synthesis of bicyclic tetramic acids in a low-cost strategy using 2-methylpropanal as condensing reagent. The obtained tetramic acids are useful for a number of chemical transformations described in Chapter 2 and Chapter 3.

The synthesised compounds were tested for antibacterial activity against multidrug resistant pathogens and disappointingly, all of them showed very little or no activity.

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ABBREVIATIONS

1D	1-dimensional
2D	2-dimensional
Å	angstrom
Ac	acetyl
ACN	acetonitrile
anh.	anhydrous
APA	aminopenicillanic acid
aq.	aqueous
AQ	8-aminoquinoline
Ar	aromatic
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
^{n}Bu	n-butyl
^{t}Bu	*tert*-butyl
C	Celsius
Cbz	carboxybenzyl
CFU	colony-forming unit
COSY	correlation spectroscopy
CPAA	2-carboxypyrrolidine-3-acetic acid
CPME	cyclopentyl methyl ether
CT	chymotrypsin

d	day
DBU	1,8-diazabicycloundec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DDD	defined daily dose
DEAD	diethyl azodicarboxylate
DEPTQ	distortionless enhancement by polarization transfer with retention of quaternaries
DIBALH	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dppb	(diphenylphosphino)butane
dppf	(diphenylphosphino)ferrocene
E	*trans*
EA	ethyl acetate
EC or *E. coli*	*Escherichia coli*
EC_{50}	half maximal effective concentration

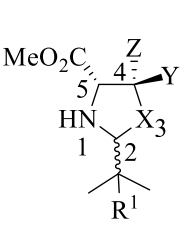
ee	enantiomeric excess
ent	enantiomer
epi	epimer
eq	equivalents
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FAB	fibroblast activation protein
FCC	flash column chromatography
FT-IR	fourier transform infra-red
GABA	gamma-amino butyric acid
Gly	glycine
h	hour
HCA	homocysteic acid
HCT-116	human colon cancer cell line
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single-quantum correlation
IR	infra-red
K	kelvin
KL	*Klebsiella pneumoniae*
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide

LRMS	low resolution mass spectroscopy
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHB	mueller-hinton broth
MIC	minimum inhibitory concentration
min	minute
m. p.	melting point
MRSA	methicillin resistant *Staphylococcus aureus*
Ms	methanesulfonyl
MW	molecular weight
n. a.	not active
NaHMDS	sodium bis(trimethylsilyl)amide
NMDA	*N*-methyl-D-aspartic acid
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
n. t.	not tested
PDC	pyridinium dichromate
PE	petroleum ether
PIFA	phenyliodine(III) bis(trifluoroacetate)
PKC	protein kinase C
ppm	parts per million

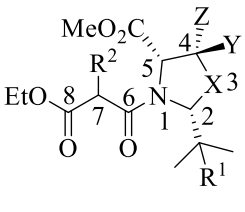
PS	*Pseudomonas aerogenosa*
Pyr	pyridine
quant.	quantitative
R_f	retention factor
rt	room temperature
SAR	structure activity relationship
sat.	saturated
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMSE	trimethylsilyl ethyl
Tol	toluene
Tr	triphenylmethyl
Ts	toluenesulfonyl
VT	variable temperature

NOMENCLATURE

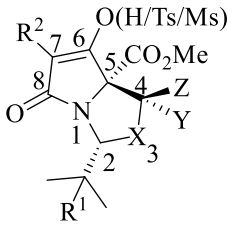
The following non-systematic numbering systems have been used throughout the thesis for oxazolidines/thiazolidines, *N*-acyl oxazolidines/thiazolidines, bicyclic tetramates/mesylates, pyrrolinones, pyrrolidinones and pyroglutaminols.



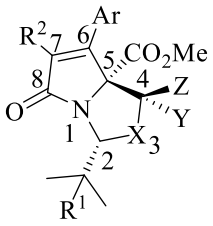
Oxazolidines/
Thiazolidines



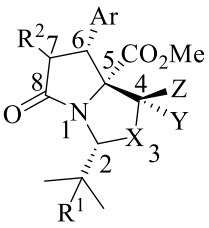
N-Acyloxazolidines/
N-Acylthiazolidines



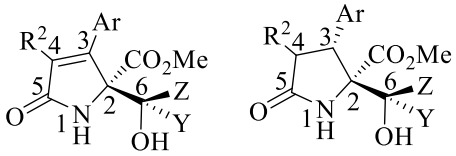
Bicyclic tetramic acids
/Tosylates/Mesylates



Pyrrolinones



Pyrrolidinones

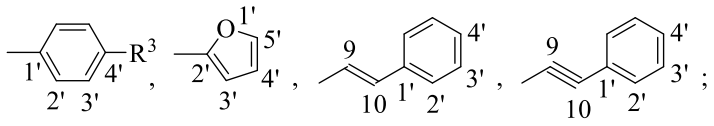
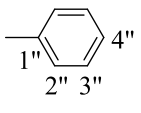


Pyroglutaminols

R^1 = H/Me, R^2 = H/Me/Ph

R^3 = OMe/H/Cl/CHO/CH_2OH/4-ClC_6H_4

L-Serine system : X = O, Y = H, Z = H
L-Threonine system : X = O, Y = H, Z = Me
L-*allo*-Threonine system : X = O, Y = Me, Z = H
L-Cysteine system : X = S/SO/SO_2, Y = H, Z = H

Ar =  Ph = 

Assignment of the ^1H and ^{13}C NMR signals in the experimental section follows these numbering systems, unless specified in the compound structure.

Nomenclature used for the bicyclic tetramates and pyroglutamates in this thesis is consistent with the nomenclature of related compounds published by the Moloney group. For naming pyroglutaminols, ChemDraw Professional 16.0 was used.

STEREOCHEMISTRY

For absolute stereochemistry, the Cahn-Ingold-Prelog convention has been used throughout the thesis to designate chiral centres as *R* and *S*. Alternatively, *E* and *Z* refer to the geometry of the double bonds. A ‘hashed wedged bond’ is used to denote a substituent placed behind the plane of the page and a ‘wedged bond’ is used to denote a substituent placed above the plane of the page. A wavy bond represents the presence of a mixture of diastereomers at that chiral centre.

The terms *cis* and *trans* describe the relative stereochemistry between C2 and C5 in oxazolidines, thiazolidines *N*-acyl oxazolidines, and *N*-acyl thiazolidines.

CHAPTER 1: INTRODUCTION

1.1 Antibacterial Drug Discovery

1.1.1 The History of Antibiotics

The first breakthrough in antimicrobial drug discovery was the treatment of malaria with the fully synthetic thiazine dye, methylene blue, reported by Guttmann and Ehrlich in 1891.[1] Later, Bertheim, Ehrlich and co-workers contributed to the discovery of the first antibacterial drug, salvarsan[2] (Figure 1.1), which was found to be effective for the treatment of syphilis.[3] Further investigation led to the discovery of the red dye, prontosil, and a number of sulfadrugs.[4] Noteworthy, the first two clinically used antibiotic classes were fully synthetic molecules.

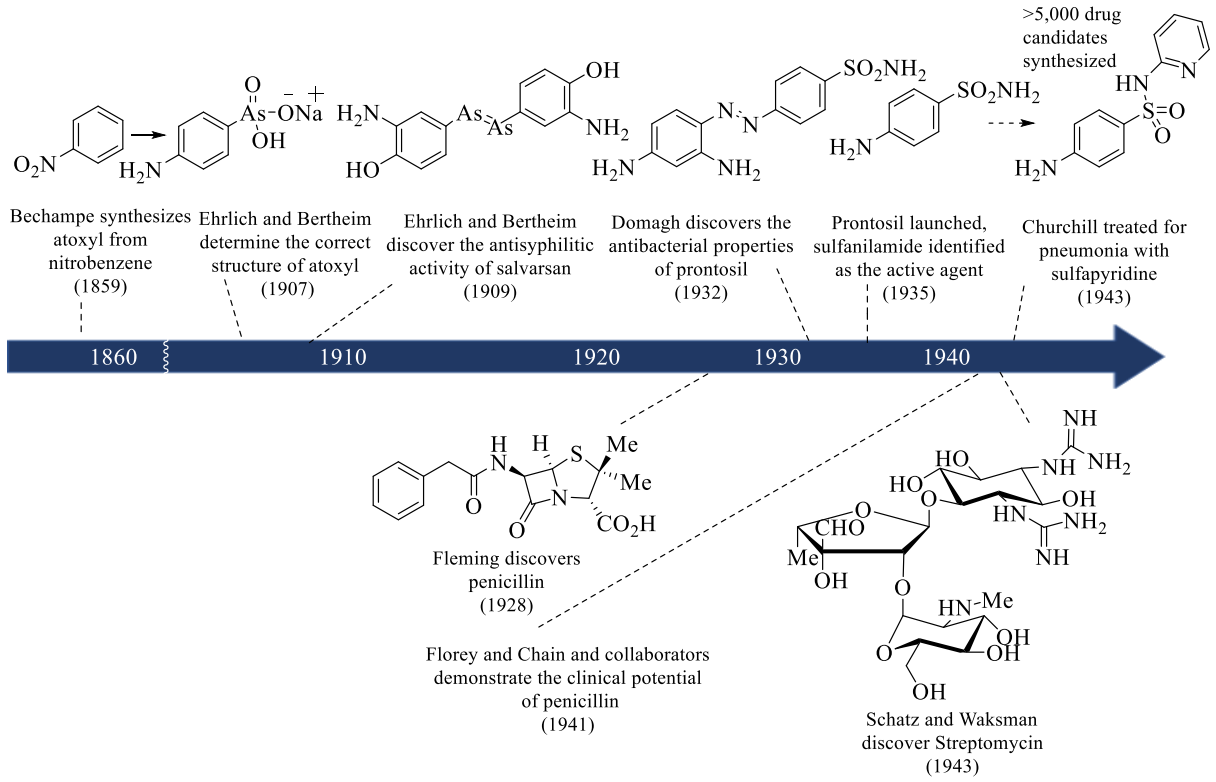


Figure 1.1: Early history of antibiotic drug discovery (*Angew. Chem. Int. Ed.* 2014, **53**, 8840-8869)

In 1928, the discovery of penicillin[5] was arguably the most exciting scientific development of the 20th century, which was isolated from the fungus *Penicillium chrysogenum* but the true significance of the discovery took another decade to realise. Further investigation revealed even crude or partially-purified penicillin had dramatic results against streptococcal[6] and staphylococcal infections.[7]

1.1.2 Different Classes of Antibacterials

According to large-scale manufacturing process, antibiotics can be categorised into three classes (Figure 1.2). This to some extent reflects their chronology of discovery and development.

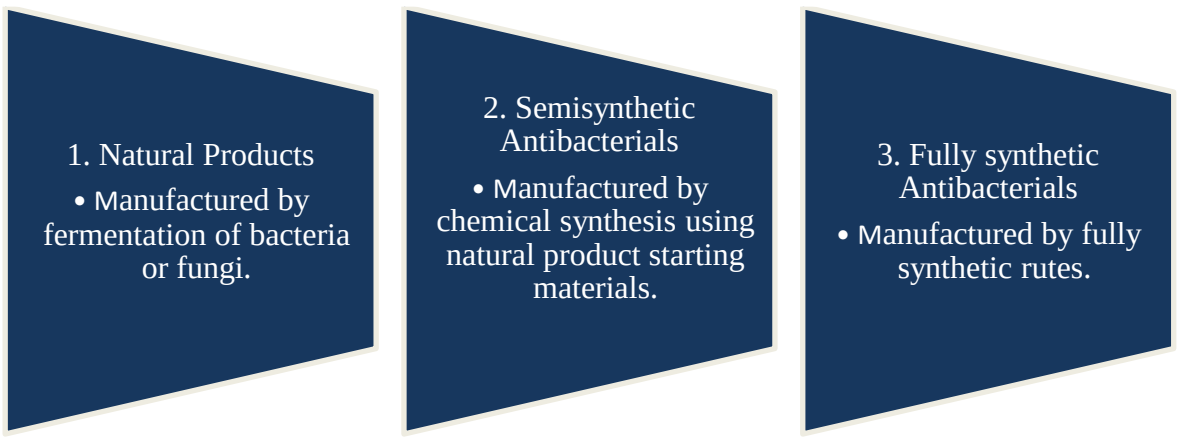


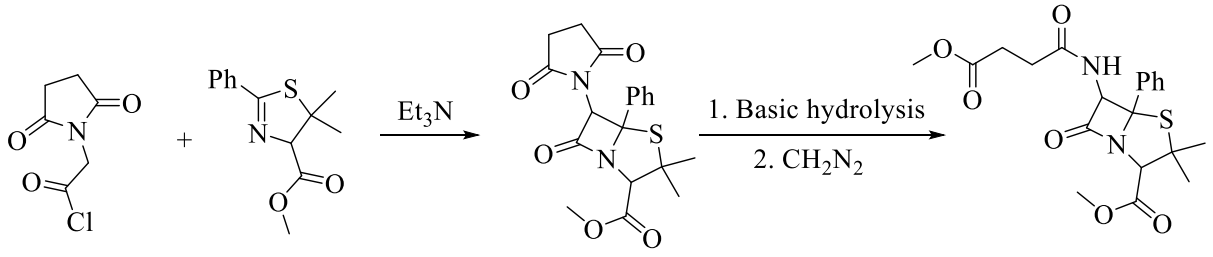
Figure 1.2: Three distinct categories of antibacterials (*Angew. Chem. Int. Ed.* 2014, **53**, 8840-8869)

In 1941, the British government exhorted American pharmaceutical companies to consider the mass production of penicillin by fermentation. Four chemical and pharmaceutical companies, including Pfizer, responded to this call for large-scale production of the therapeutic compound penicillin. In 1944, Pfizer opened the world's first large penicillin factory, soon after Jasper Cane and co-workers achieved a landmark advance by implementing their deep-tank fermentation techniques for the production of penicillin.[8]

Production began with a sterile culture of the *Penicillinium* bacteria, which was then propagated and moved to massive fermenter tanks containing microbe fodder, chiefly corn steep liquor, milk sugar, salts and minerals. The mould was allowed to grow for two to four days. Subsequently, penicillin was extracted from the broth, purified and bottled in sterile rooms to avoid contamination. Finally, the bottles were moved through a freezing apparatus and then into a vacuum drier to dehydrate the drug. This remarkable development made Pfizer the leading supplier of the drug during World War II. Later, the scientists improved the method that removed yellow impurities of the originally found penicillin. The crystallisation method yielded white penicillin, stable at ambient temperature and potent for two years. Pfizer applied the fermentation techniques to the manufacture of other antibiotics including streptomycin[9,10] and terramycin.[11]

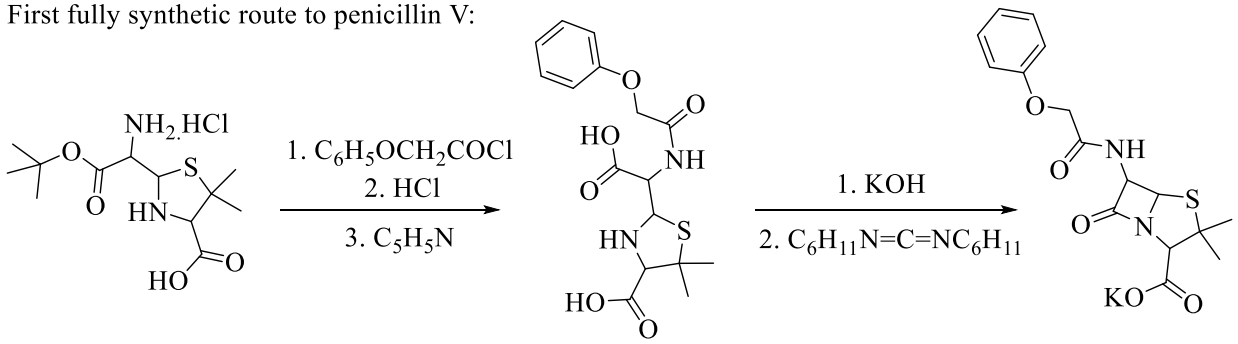
All efforts towards the development of a fully synthetic route towards penicillin failed during World War II.[12–16] John Sheehan solved the problem of finding fully synthetic pathways to penicillin. In 1950, Sheehan and co-workers[17] reported the total synthesis of methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate, a 5-phenylsubstituted penicillin derivative (Scheme 1.1). Although this analogue was inactive, this work was an important step forward. In 1955, Sheehan and Hess[18] invented an extremely mild method for the formation of amide bonds directly from the amine and carboxyl components, using carbodiimide reagents. This chemical transformation was the key step in the first fully synthetic route to a natural penicillin, penicillin V (phenoxymethylpenicillin).[19] A few years after this key discovery, Sheehan and Logan[20] reported the synthesis of 6-aminopenicillanic acid (6-APA) by both semisynthetic and synthetic routes. In the same year, Batchelor *et al.*[21] reported the isolation of 6-APA from penicillin fermentation broths and this then became the dominant precursor for the production of semisynthetic structural analogues of penicillin.

First fully synthetic route to penicillin derivative:



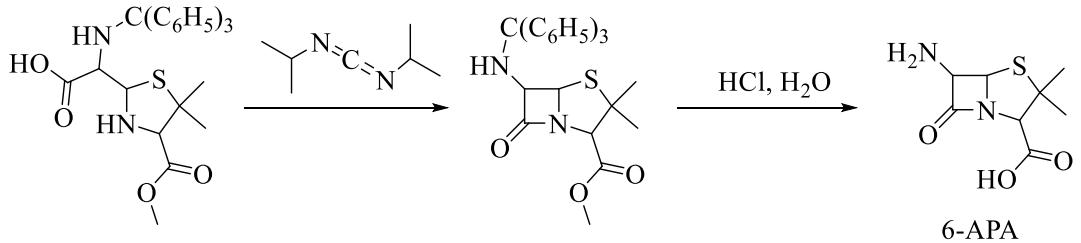
5-phenylsubstituted penicillin derivative

First fully synthetic route to penicillin V:



Penicillin V potassium (potassium phenoxymethylpenicillinate

Synthesis of 6-aminopenicillanic acid (6-APA):

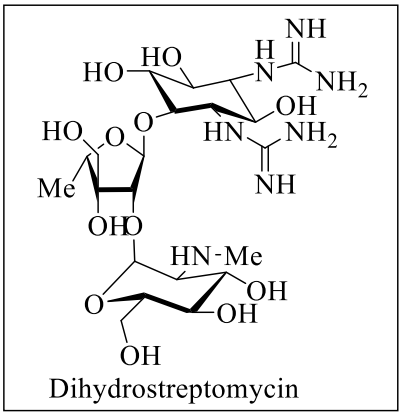


6-APA

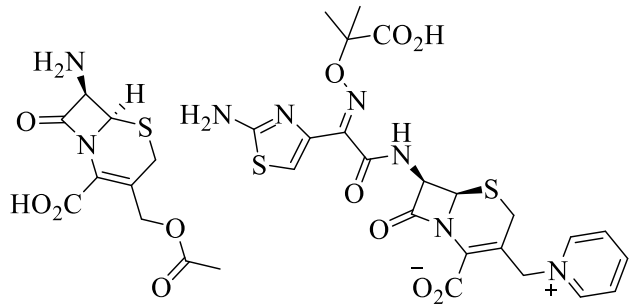
Prepared by both semisynthetic and fully synthetic routes, manufactured by fermentation

Scheme 1.1: Fully synthetic approaches to penicillin V and 6-aminopenicillanic acid[17,19,20]

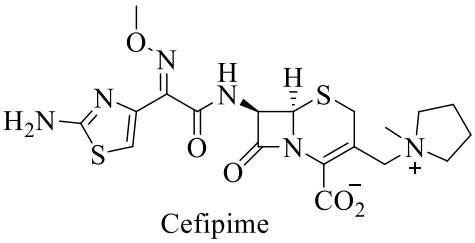
Semisynthesis became a key route in antibacterial drug discovery when dihydrostreptomycin,[22,23] a product found by catalytic hydrogenation of streptomycin, exhibited similar antibacterial properties with greater chemical stability. Using the semisynthetic approach, a broad-spectrum of β-lactam,[24–32] tetracycline[33–40] and macrolide[41–43] antibiotics (Figure 1.3) were then synthesised.



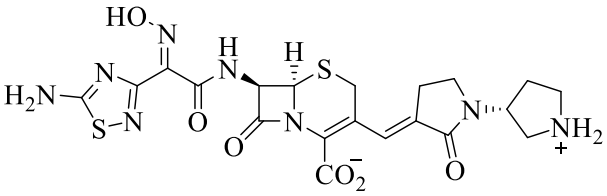
Dihydrostreptomycin



7-Aminocephalosporanic acid Ceftazidime

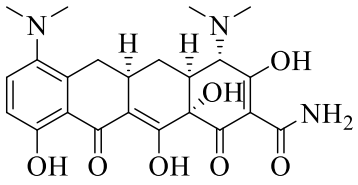


Cefipime

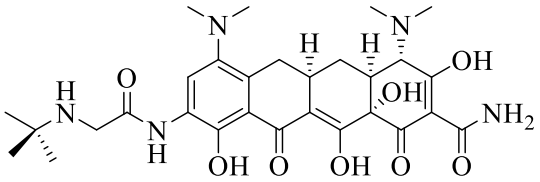


Ceftobiprole

(β-Lactam antibiotics)

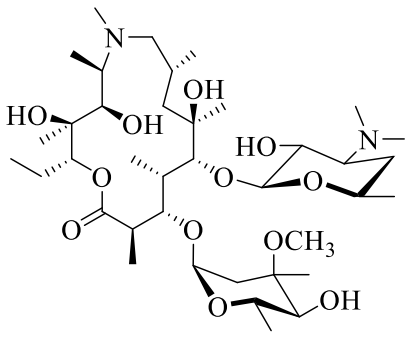


Minocycline

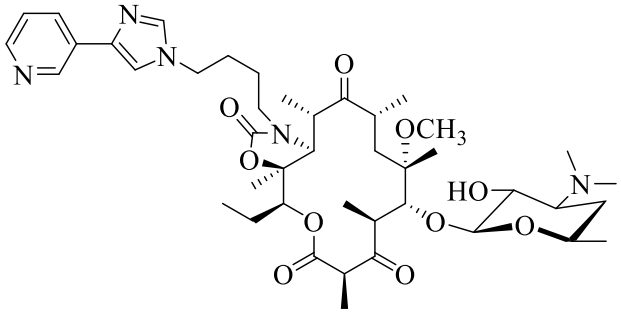


Tigecycline

(Tetracycline antibiotics)



Azithromycin



Telithromycin

(Macrolide antibiotics)

Figure 1.3: Some examples of antibacterial drug developed by semisynthetic approach

In addition to the continued widespread application of semisynthesis in the development of antibiotics, fully synthetic approaches led to a large number of drugs (Figure 1.4) including chloramphenicol,[44] metronidazole,[45] trimethoprim,[46,47] fosfomycin,[48–51] quinolines,[52–55] carbapenems[56–59] and oxazolidinones.[60–62]

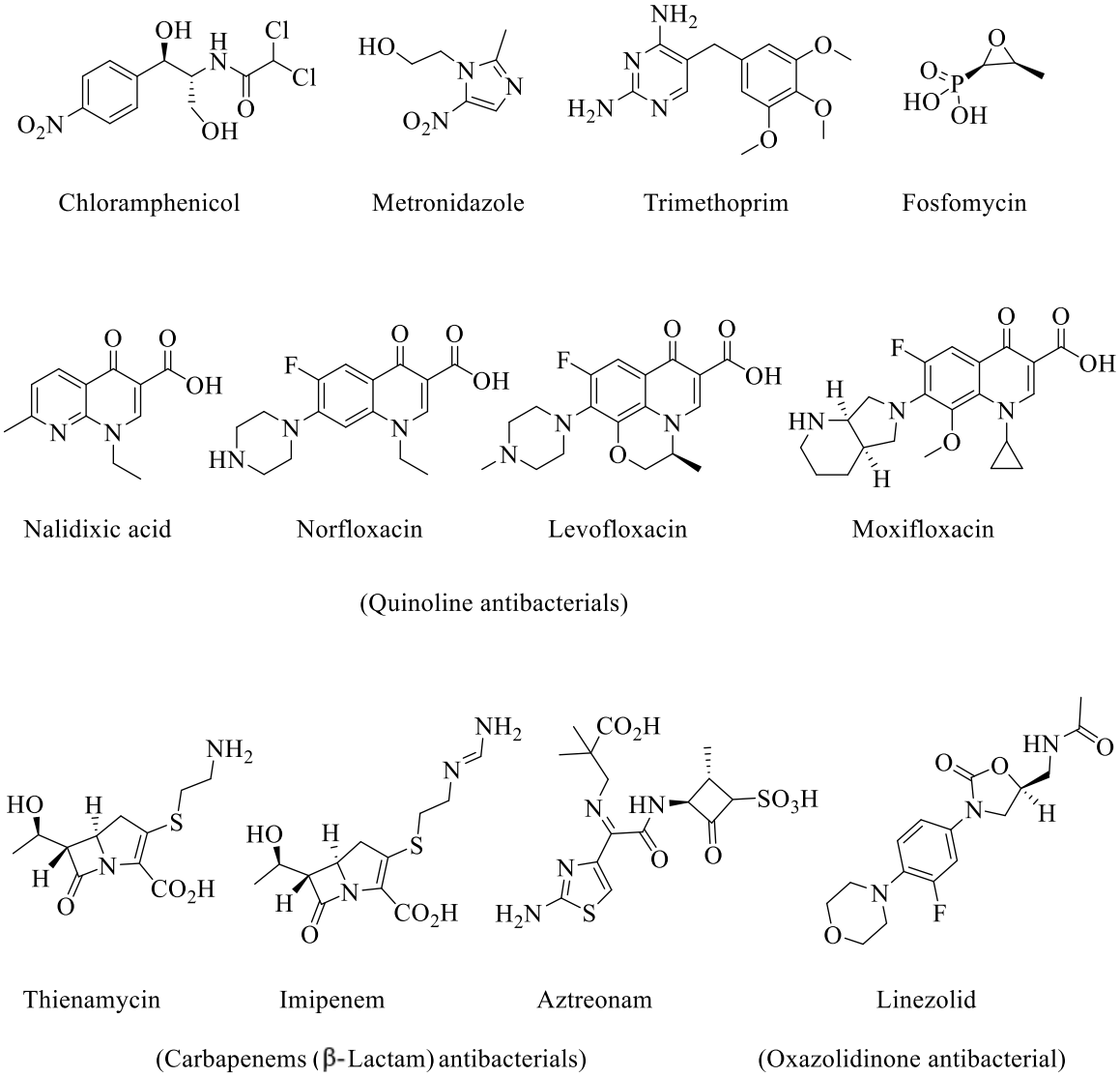


Figure 1.4: Some examples of fully synthetic antibacterials

1.1.3 Antibiotic Resistance

Unfortunately, many existing drugs are becoming less effective as a consequence of resistance in pathogenic bacteria. The phenomenon of antibacterial resistance is not new,

having been observed as early as 1940, when some bacteria had already acquired resistance to sulfa drugs.[63,64] Resistance, however, has now become much more widespread, and has increased to the stage that it is a global threat which will limit treatment options for patients. Antibiotic resistance results in part from high consumption, and a recent report[65] on antibiotic resistance shows an increase of global antibiotic consumption by 65% between 2000-2015 (Figure 1.5).

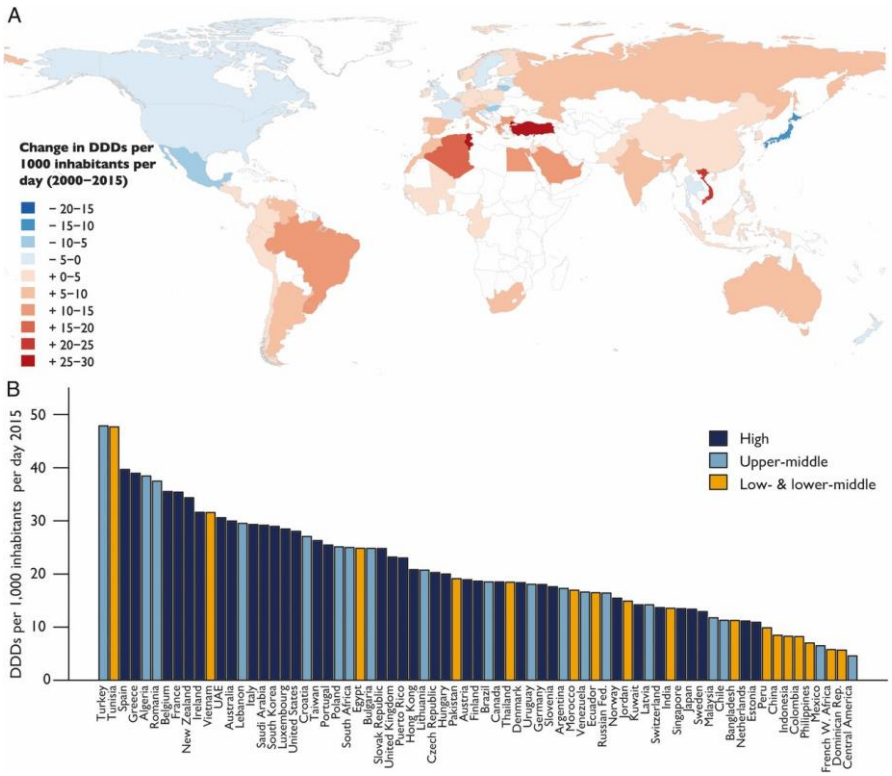


Figure 1.5: Global antibiotic consumption by country: 2000-2015. (A) Change in the national antibiotic consumption rate between 2000 to 2015 in DDDs per 1000 inhabitants per day. For Vietnam, Bangladesh, The Netherlands, and Croatia, change was calculated from 2005, and for Algeria from 2002 as data for those years from those countries were not available. (B) Antibiotic consumption rate by country for 2015 in DDDs per 1000 inhabitants per day. Source: IQVIA MIDAS, 2000-2015, IQVIA Inc. (www.pnas.org/cgi/doi/10.1073/pnas.1717295115; accessed on June 2018)

1.1.4 Modern Antibacterial Drug Discovery

The past and future of antibiotic drug discovery[66] can be illustrated as a timeline (Figure 1.6), showing the prevalent manoeuvres of each era. Most of the antibiotic drugs currently in use were discovered in the "Golden Era". Pharmacological and toxicological limitations and resistance to early antibiotics led to the development of next period of antibiotic drug discovery, the Medicinal Chemistry era.

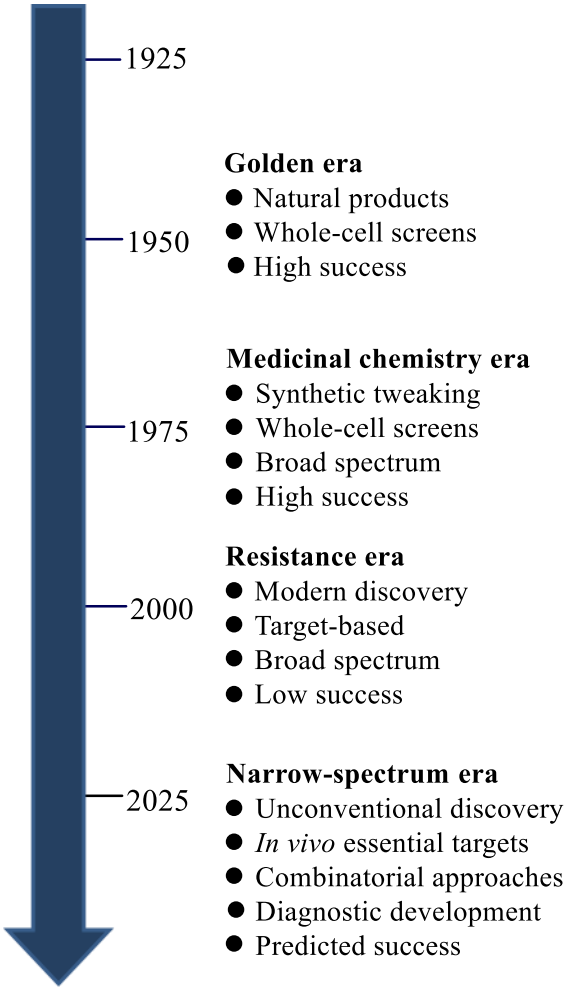


Figure 1.6: Models of antibiotic drug discovery and development (*Nature*, 2016, **529**, 336-343)

This involved the synthesis of derivatives of the natural scaffolds which had been found in the golden era of antibiotic discovery, and which contributed to the improved application of

antibiotics until the early 1990s. The emergence of new discovery methods then became essential due to the rise of antibiotic resistance. With the help of modern technology, a target-based approach was initiated, but no new antibacterial medicines have been found by this approach. When confronted with the increasing resistance in this era, the failure of the development of new antibiotics for more than two decades, coupled with over-prescription, has become a major concern. A careful investigation and understanding of antibiotics and their mode of action may now be required for the development of new medicines that will be able to tackle resistant bacteria.

1.2 Pyroglutamate as One of the Building Blocks for Drug Discovery

Proline chimeras **1**, that is mono-substituted prolines bearing a substituent on the pyrrolidine ring, have been synthesised as useful tools[67–70] in drug discovery (Figure 1.7), since they represent side-chain modifications of naturally occurring amino acids in which restriction of

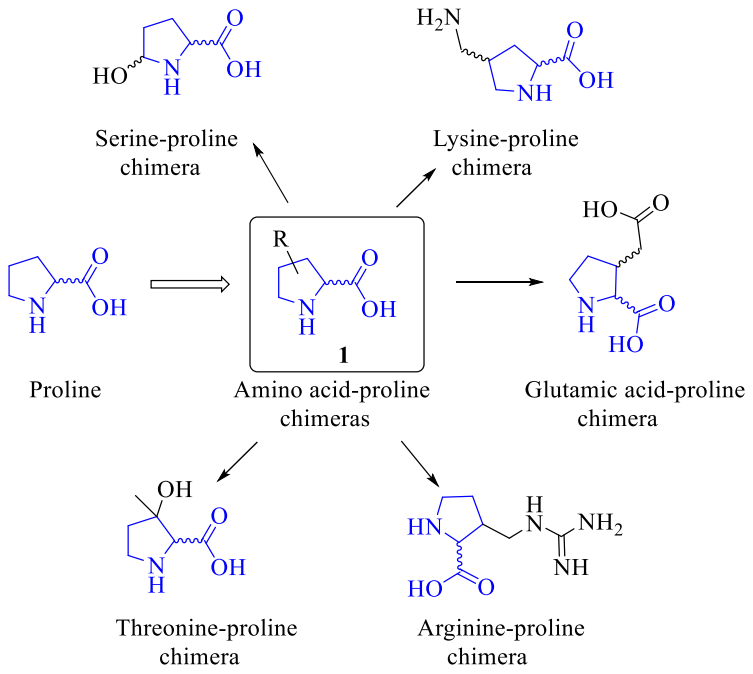


Figure 1.7: Representative amino acid-proline chimeras (*Heterocycles*, 2014, **89**(8), 1801-1825)

the conformational freedom for χ^1 and χ^2 can change the bio-activity of peptides which contain them. It has been demonstrated that a proline chimera can modify the folding of a peptides by inducing features like β-turns in the peptide backbone without changing recognition behaviour.[67]

Substituted pyroglutamic acids exhibit similar structural features to proline chimeras (Figure 1.8) and may be inserted into a bio-active peptide backbone, resulting in the modification of secondary structure and leading to improvement of interactions with the biological target.[70] For example, Tsai *et al.*[71] reported the use of 4-substituted pyroglutamate derivatives in the design and SAR studies of Fibroblast Activation Protein (FAP) inhibitors.

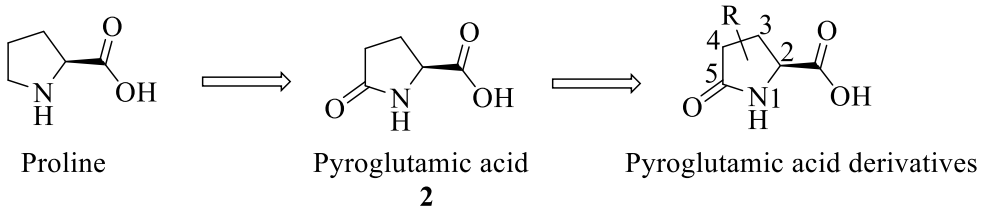


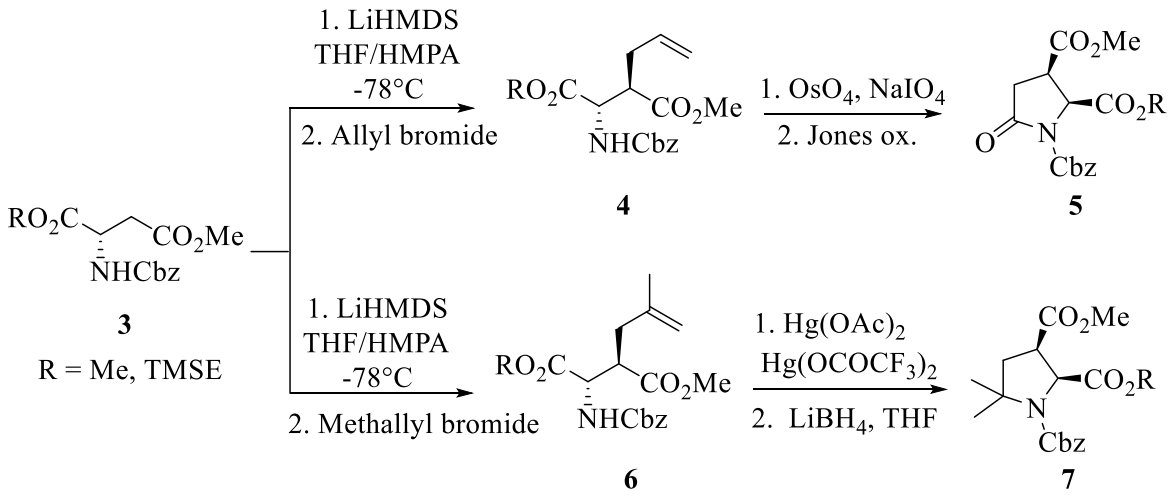
Figure 1.8: Schematic representation of pyroglutamic acid structure and its derivatives (*Heterocycles*, 2014, **89**(8), 1801-1825)

For this reason, the synthesis of pyroglutamic acid derivatives has attracted significant levels of interest, and some of the more important approaches are outlined below.

1.2.1 Synthesis of 3-Substituted Pyroglutamic Acid Derivatives

1.2.1.1 3-Substituted Pyrrolidines and Pyrrolidinones by Hanessian

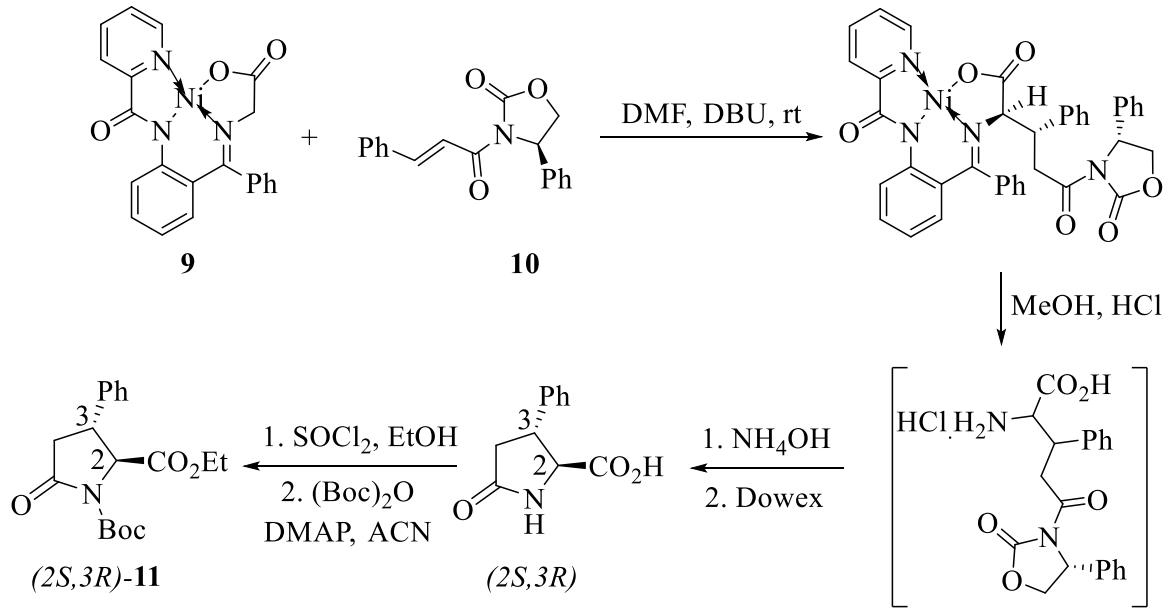
Hanessian and Margarita[72] reported the synthesis of 3-substituted pyrrolidines and pyrrolidinones by modifying the γ-unsaturated side-chain of allylated amino acid derivatives (Scheme 1.2). Pyrrolidinone **5** was prepared from the ester **3** by dihydroxylation and oxidation. Alternatively, cyclisation of **6** using $Hg(OAc)_2$ and demercuration of the resulting product yielded 5,5-dimethyl-pyrrolidine diester **7**.[73]



Scheme 1.2: Synthesis of 2,3-*cis*-substituted pyrrolidines and pyrrolidinones (*Heterocycles*, 2014, **89**(8), 1801-1825)

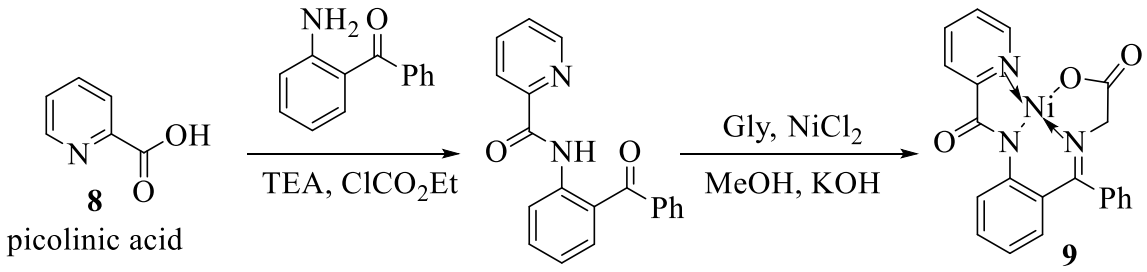
1.2.1.2 3-Phenylpyroglutamate via Asymmetric Michael Addition Reaction

A useful synthetic procedure in the synthesis of pyroglutamates was reported by Soloshonok *et al.*[74] which involves the reaction between the glycine Ni(II) complex **9** and oxazolidine-2-one **10** to yield enantiomerically pure 3-substituted pyroglutamate **11** (Scheme 1.3).



Scheme 1.3: Soloshonok *et al.*[74] methodology for the synthesis of 3-phenylpyroglutamate

Nickel complex **9** was easily prepared from the picolinic acid **8** as reported by Ueki *et al.* (Scheme 1.4).[75]

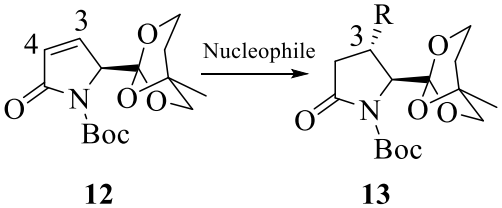


Scheme 1.4: Preparation of Ni complex[75]

1.2.1.3 Michael Addition to Unsaturated Orthopyroglutamate Derivative

The conjugated double bond in the 3,4-didehydro derivative of pyroglutamate facilitates nucleophilic attack at the 3-position. Oba *et al.*[76] described the stereoselective introduction of substituents at the 3-position of pyroglutamate derivatives via Michael addition to 2,7,8-trioxabicyclo [3.2.1] octane **12** (ABO ester) (Table 1.1).

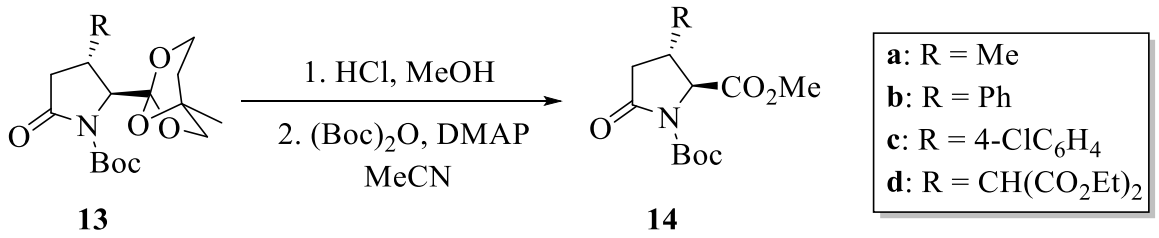
Table 1.1: Michael addition to unsaturated orthopyroglutamate **12**



12 **13**

SL	Reagent	R	Product
1	Me_2CuLi	Me	**13a**
2	$Ph_2CuMgBr$	Ph	**13b**
3	$(4\text{-}ClC_6H_4)_2CuMgBr$	$4\text{-}ClC_6H_4$	**13c**
4	$NaCH(CO_2Et)_2$	$CH(CO_2Et)_2$	**13d**

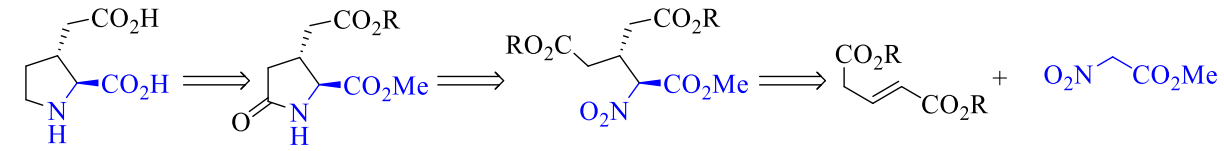
The ABO ester **13a-d** was converted to the methyl ester by HCl-promoted methanolysis followed by the reprotection of the amido group with a Boc group, yielding pyroglutamate derivatives **14a-d** in good yields (Scheme 1.5).[76]



13 **14**

Scheme 1.5: Synthesis of 3-substituted pyroglutamates[76]

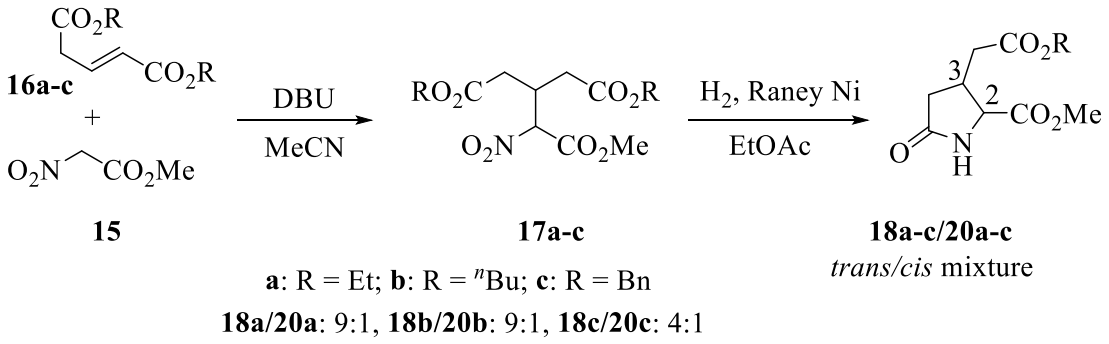
Felluga *et al.*[77] outlined the first chemoenzymatic synthesis of 2-carboxypyrrolidine-3-acetic acid (CPAA) **19** (Figure 1.9). They used a retrosynthetic approach in which pyroglutamate derivatives **18** were synthesised by conjugate addition of methyl nitroacetate **15** and the appropriate glutaconic diester **16** followed by cyclisation of intermediate **17**.



19 (+)-(*2S*,*3R*)-CPAA (*2S*,*3R*)-**18** **17** **16** **15**

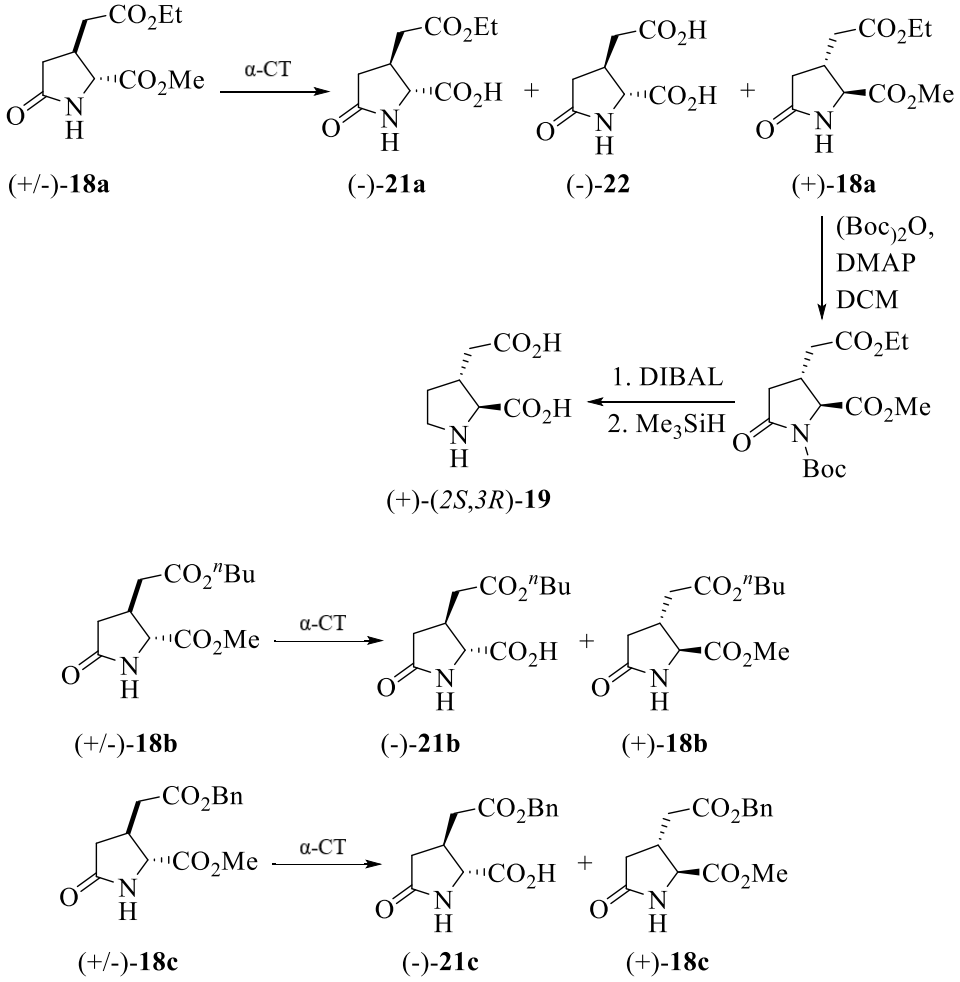
Figure 1.9: Retrosynthetic analysis for the synthesis of (+)-CPAA reported by Felluga *et al.*[77]

DBU-mediated addition of methyl nitroacetate **15** to the appropriate glutaconic diesters **16a-c** yielded the *trans* pyroglutamic acid derivatives **18a-c**, via the intermediate nitrotriesters **17a-c** (Scheme 1.6). The nitro group of **17a-c** was reduced by Raney nickel and followed by spontaneous cyclisation to lactams **18a-c** and **20a-c**. Unfortunately, this step was not completely diastereoselective and led to *trans/cis* mixtures of **18a-c** and **20a-c** in 9:1, 9:1 and 4:1 ratio, respectively.



Scheme 1.6: Synthesis of the racemic lactams as diastereomeric mixture[77]

The diester (*2S,3R*)-(+)-**18a** was converted to the target compound (*2S,3R*)-(+)-**19** by protection of the amidic nitrogen with a Boc group, followed by selective lactam carbonyl reduction (Scheme 1.7).



Scheme 1.7: Enzymatic hydrolysis and conversion to pyroglutamate derivative[77]

As the *trans*- and *cis*- diastereomers were not separable by FCC, each mixture was subjected to enzymatic resolution with the most selective hydrolytic enzyme being alpha-chymotrypsin (α-CT) (Table 1.2).

Table 1.2: Key results of the hydrolysis of mixtures of **18a-c** and **20a-c** with α- CT.[77]

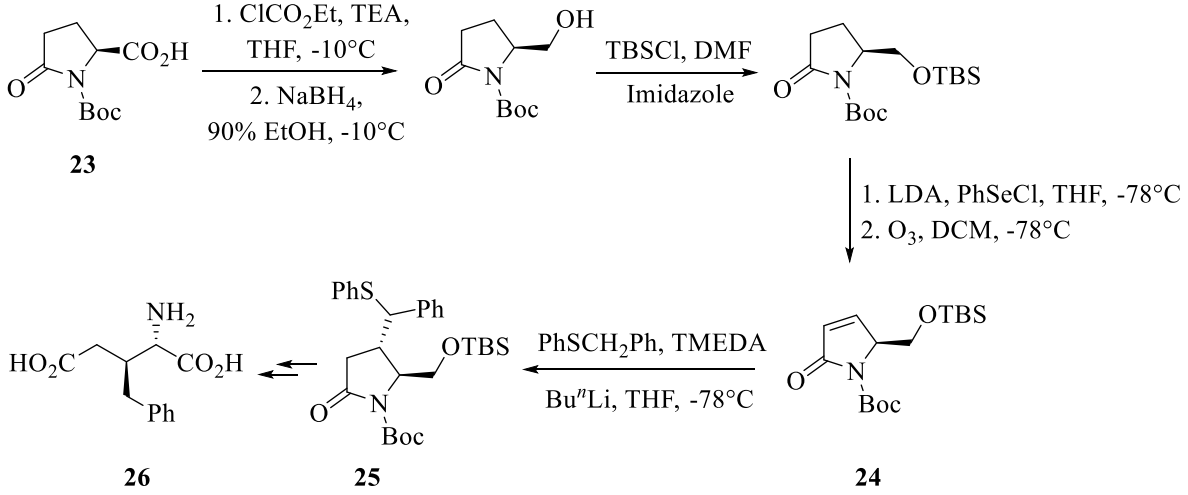
		Ca. 20% Conversion		**Ca. 80% Conversion**	
Substrate (relative ratio)	E	Time	Acid [ee %], (yield)	Time	Unreacted Ester [ee %], (yield)
18a + **20a** (9:1)	nd	10 min	(-)-**22** [65] (16)	30 min	(+)-**18a** [>99] (16)
18b + **20b** (9:1)	10	2 h	(-)-**21b** [72] (15)	8 h	(+)-**18b** [>99] (16)
18c	5	8 h	(-)-**21c** [61] (21)	36 h	(+)-**18c** [95] (22)

nd = not determined

1.2.2 Application of 3-Substituted Pyroglutamates and Pyroglutaminols

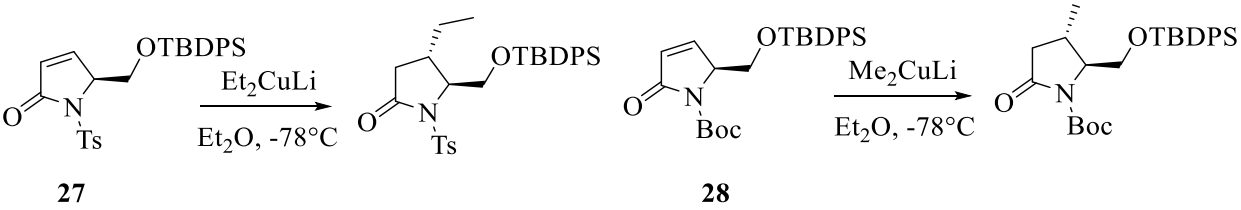
Pyroglutamate and its derivatives are widely used in asymmetric synthesis because of their easy modification and functionalisation at ring positions as well as side-chains. Some examples of the application of pyroglutamate derivatives are the synthesis of kainic acid derivatives, carbapenems, neurotransmitter, PKC modulators, antihypertensive and gastroprotective substances, and antibiotics.

Hashimoto *et al.*[78] reported the synthesis of an acyclic analogue of the kainoids to examine their neuroexcitatory activity. Michael addition of lithiated benzyl phenyl thioether to the α, β-unsaturated lactam **24** gave adduct **25**, which was transformed to (*2S,3S*)-3-benzylglutamic acid **26**, an acyclic analogue of kainoids, after several steps (Scheme 1.8). The lactam **24** was prepared from *N*-Boc-L-pyroglutamic acid **23** by a literature procedure.[79]



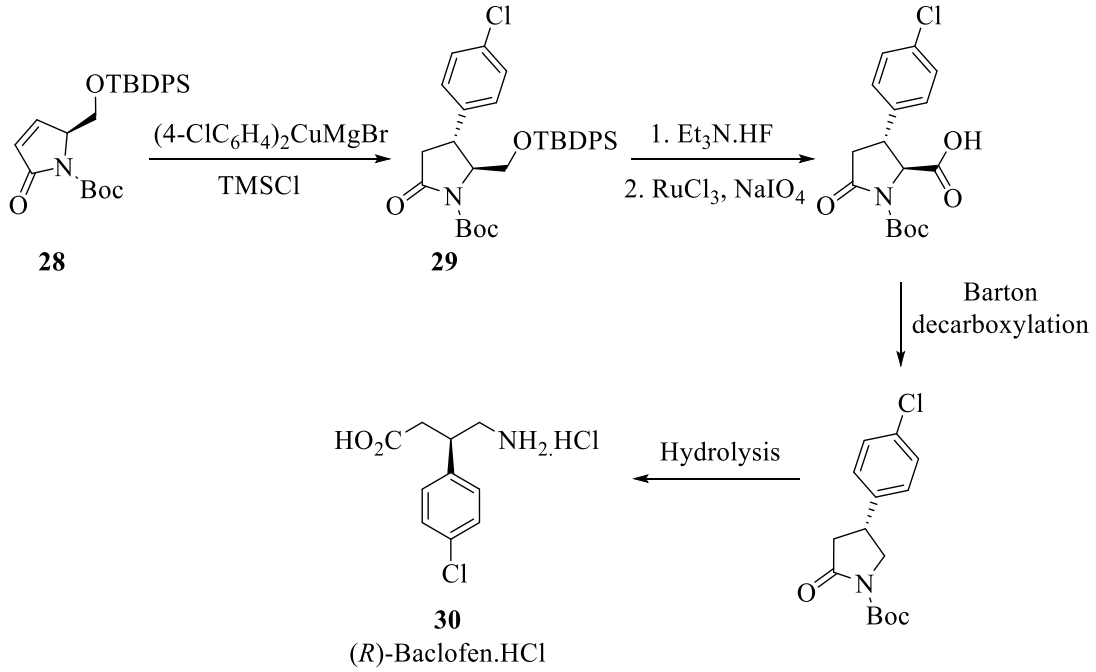
Scheme 1.8: Synthesis of (*2S,3S*)-3-benzylglutamic acid **26**, an acyclic analogue of kainoids[78,80]

The γ-lactam nucleus can be synthesised diastereoselectively via the Michael addition of lithium diethylcuprate to the *O*-silylated *N*-tosyldidehydropyroglutaminol **27**.[81] A similar transformation was reported by Woo[82] for *N*-Boc compound **28** (Scheme 1.9).



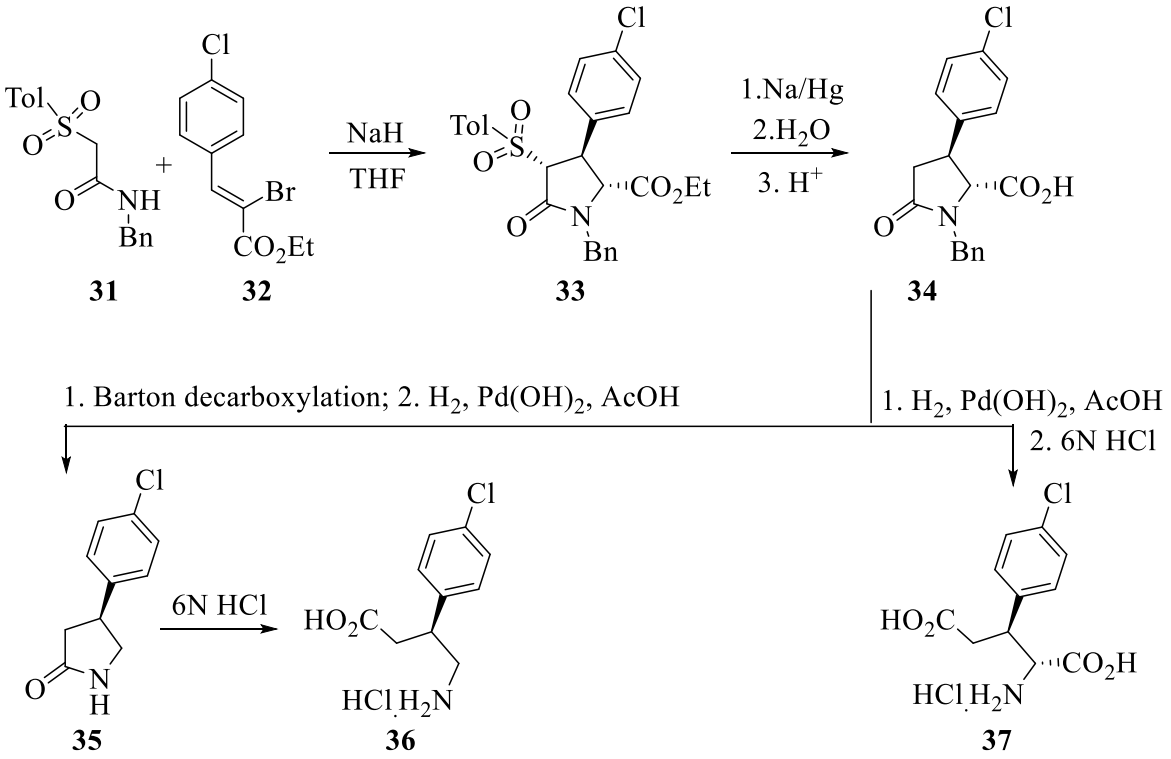
Scheme 1.9: Transformation of didehydropyroglutaminols[81,82]

The same strategy has been used for the preparation of (*R*)-baclofen, a derivative of the inhibitory neurotransmitter GABA. The synthesis started with a Michael addition using excess arylcuprate and trimethylsilyl chloride to yield lactam **29**. Oxidation and Barton decarboxylation transformed the compound **29** into a γ-lactam, which was then hydrolysed to desired compound, (*R*)-baclofen **30** (Scheme 1.10).[83]



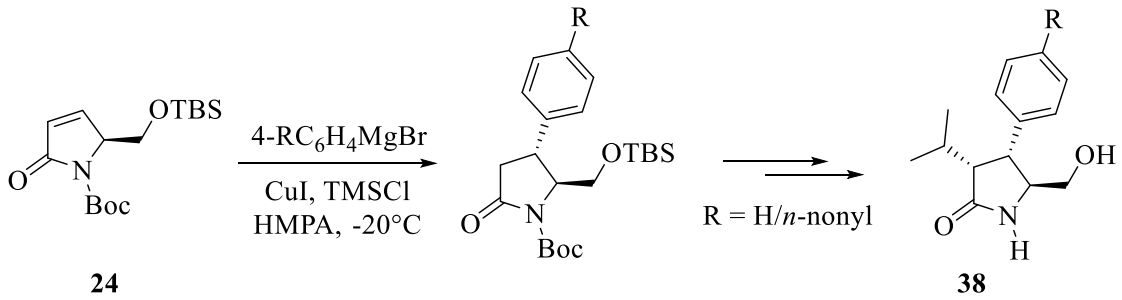
Scheme 1.10: Synthesis of (*R*)-baclofen via 3-arylpyroglutamic acid[83]

Baclofen was found to be a selective and therapeutically useful $GABA_B$ agonist.[84–86] Chlorpheg is a glutamic acid analogue having selective enhancement on the excitatory and depolarizing action of L-HCA on the neuron of amphibian and mammalian central nervous system.[87–89] Chang and co-workers[90] reported the use of a 3-arylpyroglutamic acid for the synthesis of baclofen and chlorpheg (Scheme 1.11). The stereo- and regioselective [3+2] annulation reaction of α-sulfonylacetamide **31** with (*Z*)-β-substituted α-bromoester **32** afforded single pyroglutamate isomers **33**, which were converted to acid **34** via desulfonation and hydrolysis. Application of Barton's decarboxylation procedure[91] followed by debenzylation yielded pyrrolidine-2-one **35**. Finally, hydrolysis of **35** by HCl afforded racemic baclofen hydrochloride **36**. To access chlorpheg **37**, acid **34** was directly subjected to debenzylation and hydrolysis.



Scheme 1.11: Synthesis of baclofen **36** and chlorpheg **37** via 3-arylpyroglutamic acid[90]

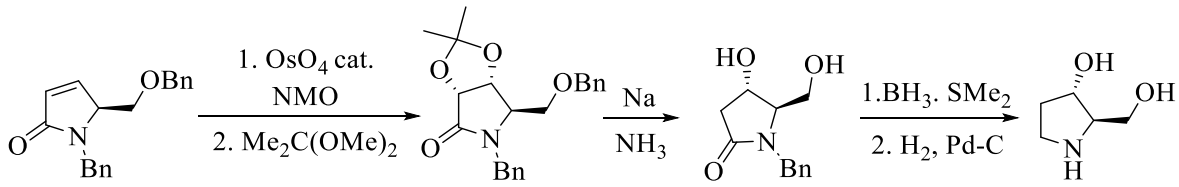
Qiao *et al*.[92] described the stereoselective synthesis of pyrrolidones **38**, which are very active as protein kinase C (PKC) modulators (Scheme 1.12).



Scheme 1.12: Synthesis of PKC modulators by Qiao *et al.*[92]

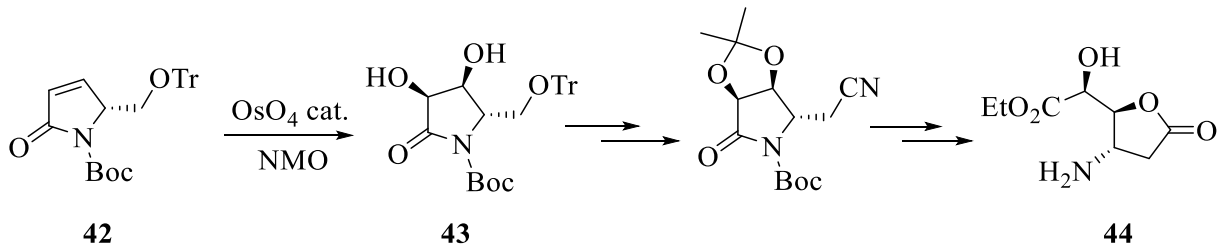
Pyrrolidinone and pyroglutaminol derivatives have importance for the synthesis of bio-active compounds. The dibenzyl-protected didehydroglutaminol **39** can be used as a precursor to prepare lactam **40** via dihydroxylation and reduction. Lactam **40** was transformed to

castanodiol hydrochloride **41** by reaction with borane followed by hydrogenation (Scheme 1.13).[93]



Scheme 1.13: Synthesis of (*2R,3S*)-3-hydroxy-2-hydroxymethylpyrrolidine **41**.

The (*R*)-pyroglutaminol derivative **42** has been used by Ikota *et al.*[94] for the synthesis of compound **44**, a precursor of (*2S,3S,4S*)-4-amino-2,3-dihydroxyhexanedioic acid which is a component of the gastroprotective substance AI-77-B.[95] The transformation starts by *cis*-hydroxylation of **42** to **43**, as a single diastereomer, which was transformed into the desired product **44** (Scheme 1.14).



Scheme 1.14: Synthesis of **44**, a precursor of (*2S,3S,4S*)-4-amino-2,3-dihydroxyhexanedioic acid derivative[94]

Yamada *et al.*[96] developed the methodology for an efficient asymmetric synthesis of the functionalised pyroglutamate scaffold **45** common to oxazolomycin A and neooxazolomycin (Figure 1.10).

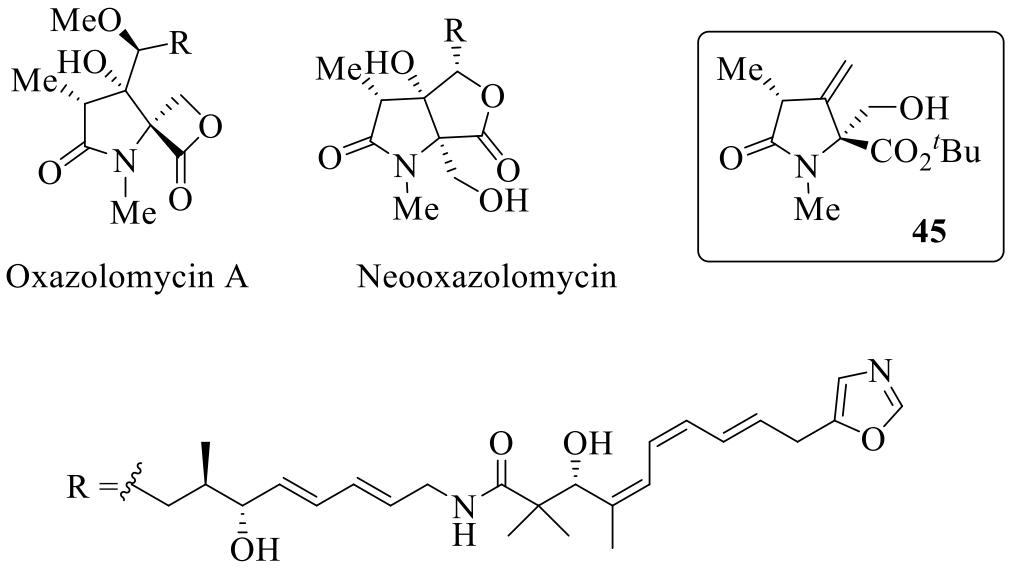
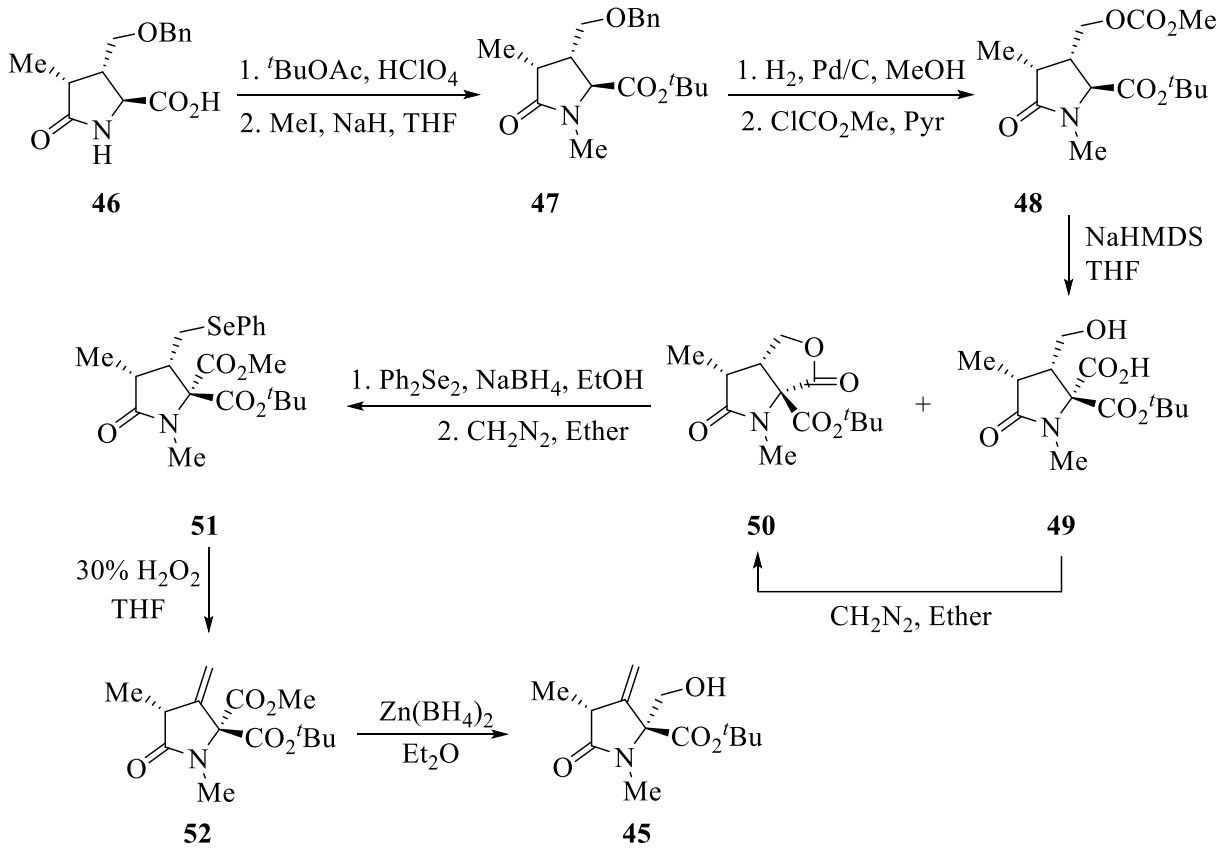


Figure 1.10: Structure of pyroglutamate scaffold **45** common to oxazolomycin A and neooxazolomycin (*Tetrahedron: Asymmetry*, 2008, **19**, 2789-2795)

The 3,4-disubstituted pyroglutamic acid **46**, after protection of carboxyl functional group as *tert*-butyl ester and subsequent *N*-methylation gave **47**, which upon the removal of the benzyl group at C3 followed by carboxymethylation of the resulting alcohol, delivered the carbonate **48** (Scheme 1.15). The treatment of **48** with NaHMDS afforded a mixture of γ-butyrolactone **50** and its hydrolysed product **49**. γ-Butyrolactone has been prepared as the only product via treatment of the mixture of **49** and **50** with diazomethane. Lactone ring opening results from phenylselenide attack to introduce a suitable leaving group at C3 and the resultant product was esterified to give diester **51**. In the following step, the leaving group could be removed using hydrogen peroxide. Finally, pyroglutamate scaffold **45** was accessed by reduction of the methyl ester with $Zn(BH_4)_2$.

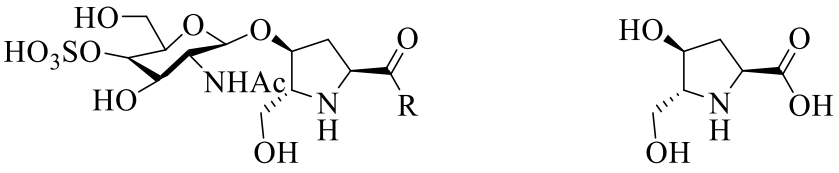


Scheme 1.15: Synthesis of pyroglutamate scaffold **45** common to oxazolomycin A and neooxazolomycin (*Tetrahedron: Asymmetry*, 2008, **19**, 2789-2795)

1.3 Some Examples of Lactam-Derived Natural Products

1.3.1 (-)-Bulgecinine

The microorganisms *Pseudomonas acidophila* and *Pseudomonas masoacidophila*[97] were found to produce a substance named bulgecin **53**, which induces bulge formation[98,99] in co-operation with β-lactam antibiotics (Figure 1.11). (-)-Bulgecinine **54** is a non-proteinogenic amino acid, and a common constituent of *O*-sulfonated glycopeptide bulgecins, found in the culture broth of the same organisms.[97]

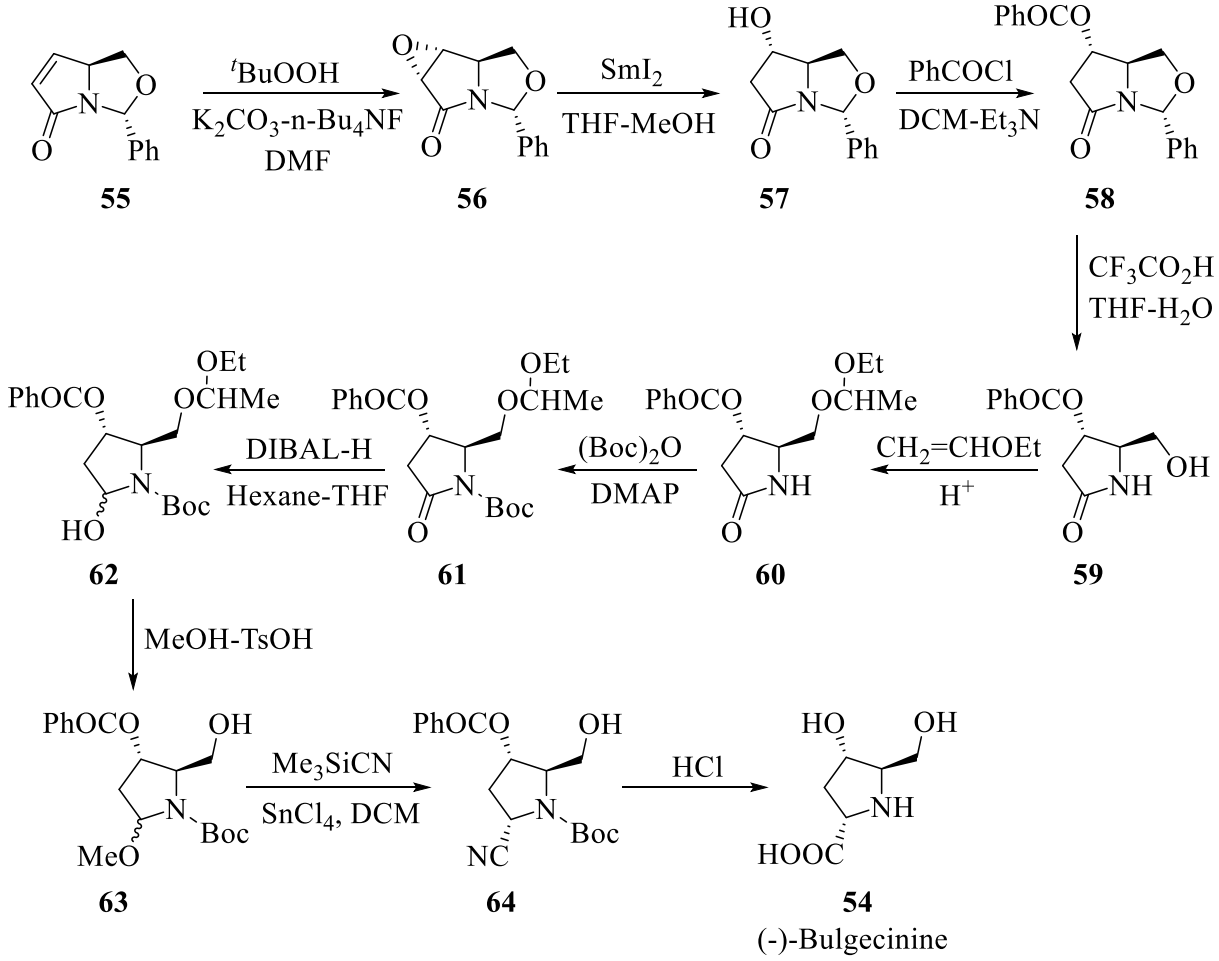


53
Bulgecin A: R = $NHCH_2CH_2SO_3H$
Bulgecin B: R = $NHCH_2CH_2CO_2H$
Bulgecin C: R = OH

54
(-)-Bulgecinine

Figure 1.11: Structure of bulgecin **53** and (-)-bulgencinine **54**

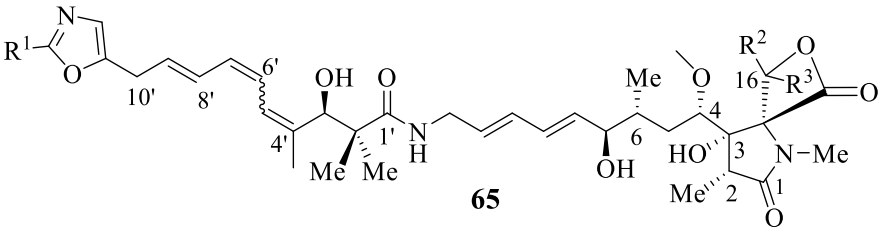
Panday *et al.*[100] reported the use of a pyroglutamate derivative for the synthesis of (-)-bulgecinine **54** (Scheme 1.16).



Scheme 1.16: Synthesis of (-)-bulgecinine **51** using pyroglutamate derivative[100]

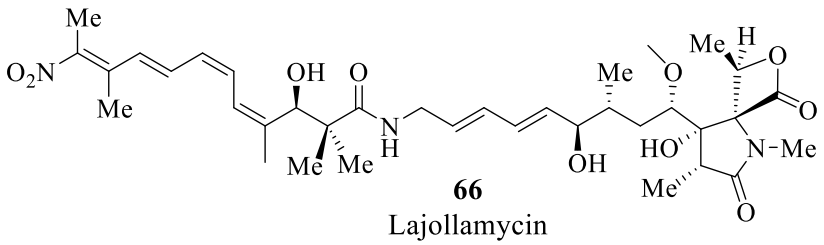
They started with bicyclic γ-lactam derivative **55**, which was converted to 6-hydroxy bicyclic derivative **57** via epoxidation and ring opening. The 6-hydroxy group was protected as the benzoate **58**, which, upon acidic hydrolysis with trifluoroacetic acid, afforded 4-benzyloxypyroglutaminol **59**. The hydroxyl group at C-5 was protected with ethyl vinyl ether prior to *N*-Boc protection of the free amine to give **61**. Selective partial reduction of the γ-lactam carbonyl of **61** with DIBAL-H followed by treatment with MeOH/HCl yielded α-methoxycarbamate **63** as mixture of diastereomers. Stereoselective nucleophilic addition of cyanide to α-methoxycarbamate **63** afforded nitrile **64**, which was hydrolysed with 6N HCl to give (-)-bulgecinine **54.**

1.3.2 Oxazolomycin



65

Oxazolomycin A	**a**: R^1 = H, R^2 = H, R^3 = H; 4'Z,6'Z,8'E
Oxazolomycin B	**b**: R^1 = H, R^2 = H, R^3 = H; 4'E,6'E,8'E
Oxazolomycin C	**c**: R^1 = H, R^2 = H, R^3 = H; 4'Z,6'E,8'E
16-Methyloxazolomycin	**d**: R^1 = H, R^2 = H, R^3 = Me; 4'Z,6'Z,8'E
Curromycin A	**e**: R^1 = Me, R^2 = H, R^3 = CH_2OMe; 4'Z,6'Z,8'E
Curromycin B	**f**: R^1 = Me, R^2 = H, R^3 = Me; 4'Z,6'Z,8'E
KSM-2690 B	**g**: R^1 = H, R^2 = Me, R^3 = H; 4'Z,6'Z,8'E
KSM-2690 C	**h**: R^1 = H, R^2 = Me, R^3 = H; 4'Z,6'E,8'E



66
Lajollamycin

Figure 1.12: Structure of oxazolomycin class of natural products (*Org. Biomol. Chem.*, 2012, **10**, 3472-3485).

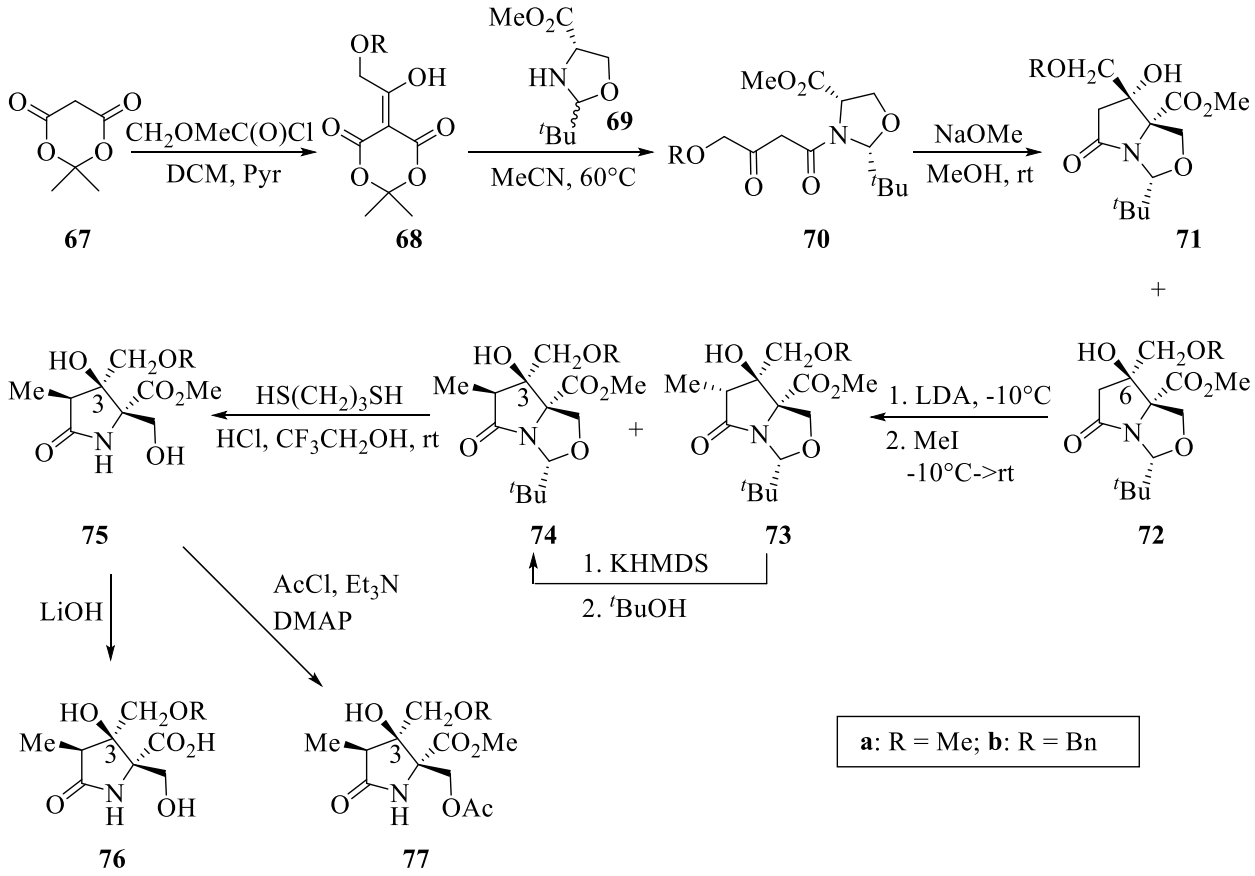
The oxazolomycin class of natural products (Figure 1.12), oxazolomycin A-C **65a-c**, 16-methyloxazolomycin **65d**, curromycin A-B **65e-f**, KSM2690 **65g-h** and lajollamycin **66**, are well-known for their structural features and wide range of biological activity.[101] For example, lajollamycin **66** shows antibacterial activity against drug-sensitive and drug-resistant micro-organisms (Table 1.3) and inhibits the growth of murine melanoma cell line B16-F10, with an EC_{50} of 9.6 µM.[102]

Table 1.3: Minimum inhibitory concentration (MIC) values for lajollamycin **66** against bacterial strains (*Journal of Natural Products*, 2005, **68**, 240-243)

SL	Microorganism	MIC (µg/mL)
1	*Staphylococcus aureus* - methicillin sensitive	4
2	*Staphylococcus aureus* – methicillin resistant	5
3	*Streptococcus pneumoniae* – penicillin sensitive	2
4	*Streptococcus pneumoniae* – penicillin resistant	1.5
5	*Enterococcus faecalis* – vancomycin sensitive	14
6	*Enterococcus faecium* – vancomycin resistant	20
7	*Escherichia coli - imp*	12

Angelov *et al.*[103] reported the synthesis of functionalised pyroglutamates, which are simpler mimics of the more complex spirolactam-lactone system of the oxazolomycins (Scheme 1.17). Acylation of Meldrum's acid **67** using methoxyacetyl chloride generated **68**, which was treated with oxazolidine **69** at 60 °C to give amide **70**. Intramolecular Aldol reaction of ketoamides **70** was achieved in presence of sodium methoxide and methanol, and the product was obtained as mixture of diastereomers **71** and **72** (major) among which the major one had correct relative stereochemistry for oxazolomycin.[103] *C*-Alkylation on **72** was

carried out using LDA and excess MeI, giving the products **73** (major) and **74** (minor). Fortunately, treatment of **73** with KHMDS followed by ^{t}BuOH yielded **74**, having the correct relative stereochemistry for oxazolomycins. Deprotection of **74** was carried out following Corey's procedure[104] to yield pyroglutaminols **75**.

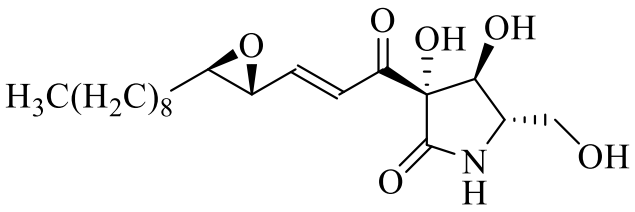


Scheme 1.17: Synthesis of mimics of the complex spirolactam-lactone system of the oxazolomycins via 6-substituted bicyclic pyroglutamates **72**.[103]

Ester hydrolysis of **75** gave corresponding acids **76**, with the correct relative configuration for the right-hand fragment of oxazolomycins. Similarly, successful acetylation was carried out on **75** yielding pyroglutamates of the type **77**. Of the compounds with correct relative configuration for the right-hand fragment of oxazolomycins, **75b** and **77b** were found to be active against *S. aureus*, and **74b**, **75a**, **75b**, **76a**, **77b** were active against *E. coli*.

1.3.3 Pramanicin

Paramanicin **78**, containing a highly functionalised pyroglutaminol moiety and functionalised fatty acid chain, was shown to exhibit antibacterial activity[105] against *Bacillus subtilis* with minimum inhibitory concentration (MIC) of 4μM.



78

Figure 1.13: Structure of pramanicin (*Org. Biomol. Chem*., 2017, **15**, 1889-1912)

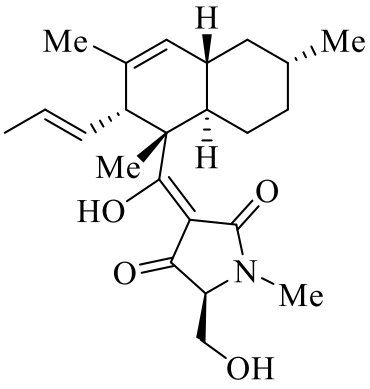
Microtiter dish broth dilution assays were used in determining antifungal activity. The results are shown in Table 1.4.

Table 1.4: Antimicrobial activity of Paramanicin **78** (*Tetrahedron*, 1994, **50**(6), 1675-1686)

SL NO	Organism	MIC of Pramanicin, µM
1	*Candida albicans*	20.0
2	*Candida parapsilosis*	4.0
3	*Candida tropicalis*	20.0
4	*Candida krusei*	>100.0
5	*Cryptococcus neoformans*	20.0
6	*Cryptococcus neoformans*	0.062
7	*Aspergillus fumigatus*	100.0

1.3.4 Equisetin

Equisetin[106–108] is an example of natural product class containing the 3-acyltetramic acid (2, 4-pyrrolidinone) core structure (Figure 1.14). It was isolated as a metabolite from the white mould *Fusarium hererosporum* by Hesseltine and co-workers in 1974,[109] which shows potent antibiotic activity and HIV inhibitory activity.

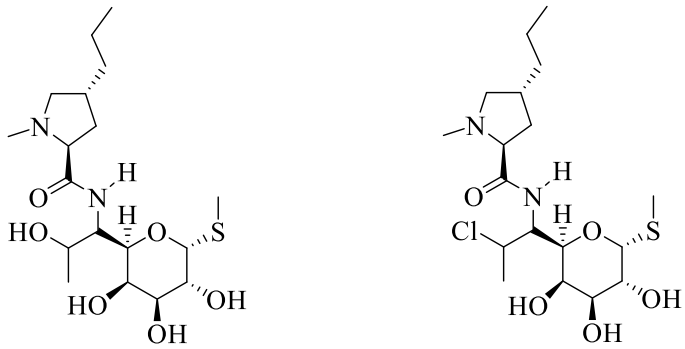


79

Figure 1.14: Structure of equisetin (*Chem. Commun*., 2005, 186-188)

1.3.5 Lincosamides

Lincosamides[110] are naturally occurring compounds, with a chemically distinct pyrrolidine core structure (Figure 1.15) and having wide range of biological activities. The first member of this family discovered was lincomycin **80**,[111] which was first introduced clinically in 1963. Lincomycin was shown to be clinically effective in a number of bacterial infections including *Staphylococcus osteitis*, infective dermatoses, and respiratory infections.[112] Excellent results were found in the treatment of penicillin-resistant infections, including penicillinase-producing *Staphylococcus pyogenes* in children.[113] Later, the original lincosamide antibiotic was superseded by a semi-synthetic drug clindamycin **81**, a derivative of lincomycin, because of its wide activity and better absorption behaviour after oral adminstration.[114]



80
Lincomycin

81
Clindamycin

Figure 1.15: Structure of Lincosamides (*J. Mol. Model*, 2012, **18**, 2727-2740)

The spectrum of activity for lincosamides includes staphylococci, penicillinase-producing strains, haemolytic streptococci, pneumococci, and *C. diptheriae* and the minimum inhibitory concentration for most strains of these compounds is usually less than 2 µg/mL.[113]

1.3.6 Lucentamycins

The lucentamycins[115–117] are a family of tripeptides produced by *Nocardiopsis lucentensis* (strain CNR-712) from the fermentation broth of a marine-derived actinomycete.[116]

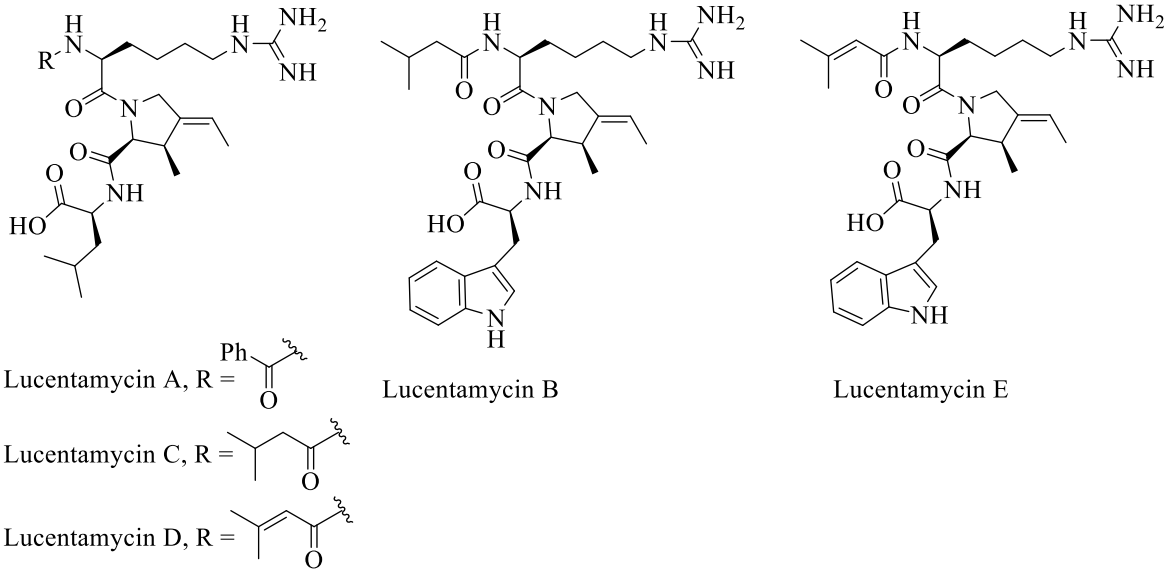


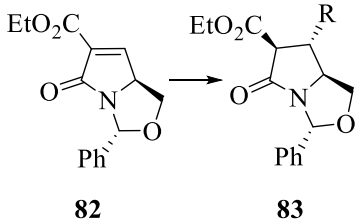
Figure 1.16: Structure of Lucentamycins (*J. Nat. Prod.*, 2012, **75**, 1648-1651)

They are structurally novel with 3-methyl-4-ethylideneproline unit (Figure 1.16) and show significant *in vitro* cytotoxicity against HCT-116 human colon carcinoma.[116]

1.4 Functionalised Pyrrolidinones: Moloney Group's Previous Work

The Moloney group has been interested in the development of methodology for the efficient synthesis of functionalised pyrrolidinones, since this class of compounds has potent biological activity and application in the synthesis of bio-active compounds.

Bailey and co-workers[118] reported the synthesis of functionalised pyroglutamates following methodology developed by Dyer.[119] They used a bicyclic lactam template **82** with C-7 ethoxycarbonyl activating group, which allowed effective conjugate addition, providing protection of amide and hydroxy functional groups in a single benzylidene protecting group (Scheme 1.18). Conjugate addition of triethyl methanetricarboxylate to acylated lactam **82**, prepared by literature procedure,[120] under phase transfer conditions[121] (Bu_4NHSO_4, K_2CO_3, anhydrous toluene at 60°C) gave the adduct **83a** as a single diastereomer (*6S,7S*).



82 **83**

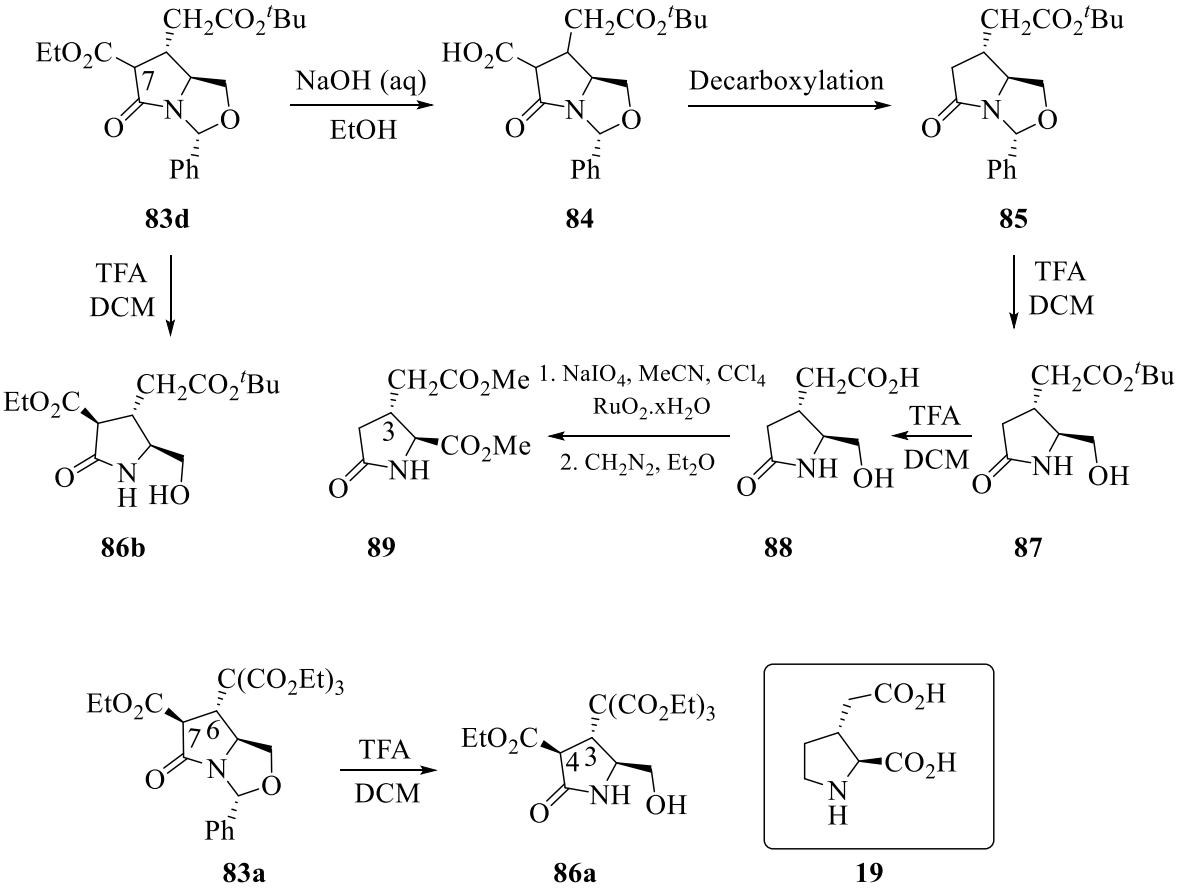
Product	Conditions	Diastereomeric ratio	Yield (%)
83a: R = $C(CO_2Et)_3$	A	1	60
83b: R = $CH(CN)CO_2Me$	B	1:1	54
83c: R = $CH(C(O)Me)CO_2Et$	C	1:1:4.5:4.5	72
83d: R = $CH_2CO_2{}^tBu$	D	1:5.5:43.5	77
83e: R = CH_2CO_2Et	E	Not determined	27
83f: R = $CH(Me)CO_2Me$	F	1:5:9:35	56
83g: R = $CH(Ph)CO_2Me$	G	1:17:17:74	53

Conditions: A = Bu_4NHSO_4, K_2CO_3; B = $NaNH_2$, DMPU, THF; C = $Ba(OH)_2$, EtOH; D = Zn, ultrasound, THF, DMPU, 30-35°C; E = Zn, ultrasound, dioxane, 35°C; F = Zn, ultrasound, THF, -5°C; G = Zn, ultrasound, THF, -10°C.

Scheme 1.18: Conjugate additions to acylated lactam **82**[120]

However, the reactions of methyl cyanoacetate and ethyl acetoacetate with lactam **82** gave an inseparable mixture of diastereoisomers **83b** and **83c**. Improved yields were observed by

changing the conditions to Reformatsky conditions,[122] and compounds **83d-g** were generated under these conditions. Carboxylic acid **84** was obtained by selective hydrolysis of the ethyl ester over the *tert*-butyl ester of **83d**, and subsequent decarboxylation[123] yielded compound **85** (Scheme 1.19). Finally, functionalised pyrrolidinones were achieved by *N*,*O*-acetal deprotection.

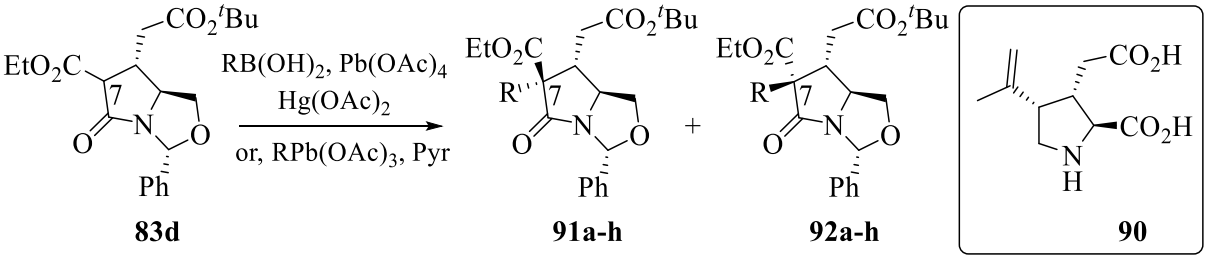


Scheme 1.19: Synthesis of 3-substituted pyroglutaminols and pyroglutamates **86a**, **86b** and **89** by Moloney group[118]

Treatment of lactam **83a** with TFA resulted in pyroglutaminol **86a**. The same conditions at even shorter reaction time gave pyrrolidinone **86b**. Treatment of **85** with TFA in DCM afforded pyroglutaminol **87**, which was reported as an intermediate[124] in the synthesis of (-)-(*2S*,*3R*)-2-carboxypyrrolidine-3-acetic acid (CPAA) **19**, an NMDA receptor agonist.[125]

Further treatment with TFA removed *tert*-butyl ester to yield **88**, which upon oxidation afforded 3-substituted pyroglutamate **89**.

In continuation of the works described above, Dyer and co-workers[126] investigated the ring functionalisation at C7 of esters **83a** and **83d**, in order to access conformationally constrained 4-aryl-5-oxo and 4-arylmethyl-5-oxo analogues of kainic acid **90** (Scheme 1.20).[119] Attempted ring functionalisation by arylation with phenyllead triacetate was found futile for adduct **83a**, whereas **83d** was used successfully to access desired kainoid analogues **99**. Compound **83d** was treated with aryllead reagents, which afforded products **91** and **92** as inseparable mixture of diastereomers.



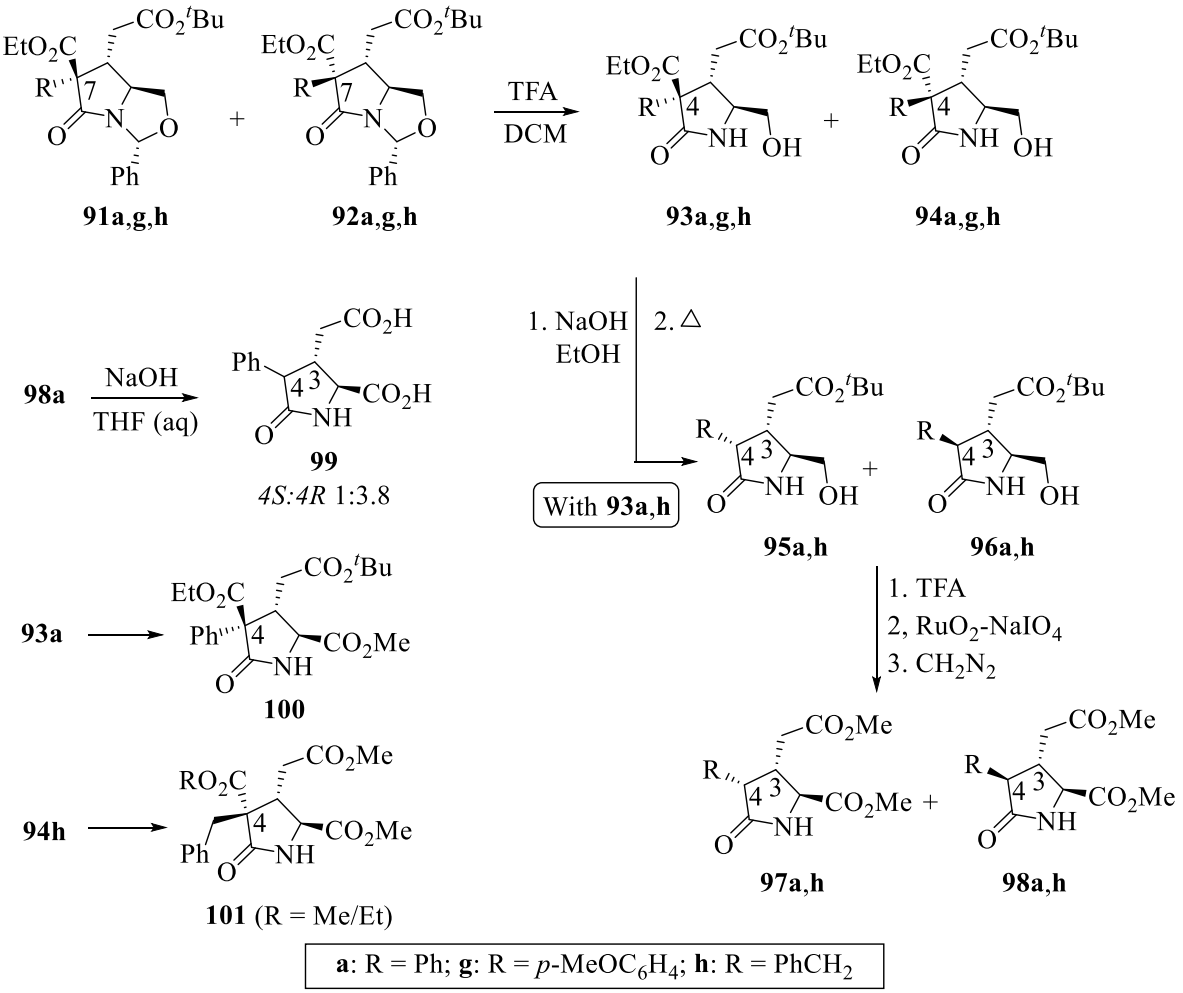
83d **91a-h** **92a-h** **90**

Product	Diasteriomeric ratio (91:92)	Yield (91, 92) (%)
a: R = Ph	2.4:1	61, 25
b: R = *o*-$MeOC_6H_4$	1.7:1	45, 27
c: R = *m*-$MeOC_6H_4$	4:1	67, 17
d: R = *p*-$MeOC_6H_4$	2.3:1	42, 18
e: R = *p*-$CF_3C_6H_4$	2.3:1	50, 22
f: R = *p*-BrC_6H_4	2.3:1	52, 22
g: R = *p*-$MeOC_6H_4$	2.3:1	26, 12
h: R = $PhCH_2$	1:12	34, 41

Scheme 1.20: Arylation and alkylations of lactam **83d**.

Deprotection of lactams **91a**,**g**,**h** and **92a**,**g**,**h** was performed with TFA in DCM, which gave diastereomerically pure alcohols **93** and **94** (Scheme 1.21). To remove the ethoxycarbonyl substituent at C7 position, hydrolysis and decarboxylation was performed on **93a**,**h**, resulting

in the diastereomers **95** and **96** with higher proportion of **95** having the desired kainic acid configuration.

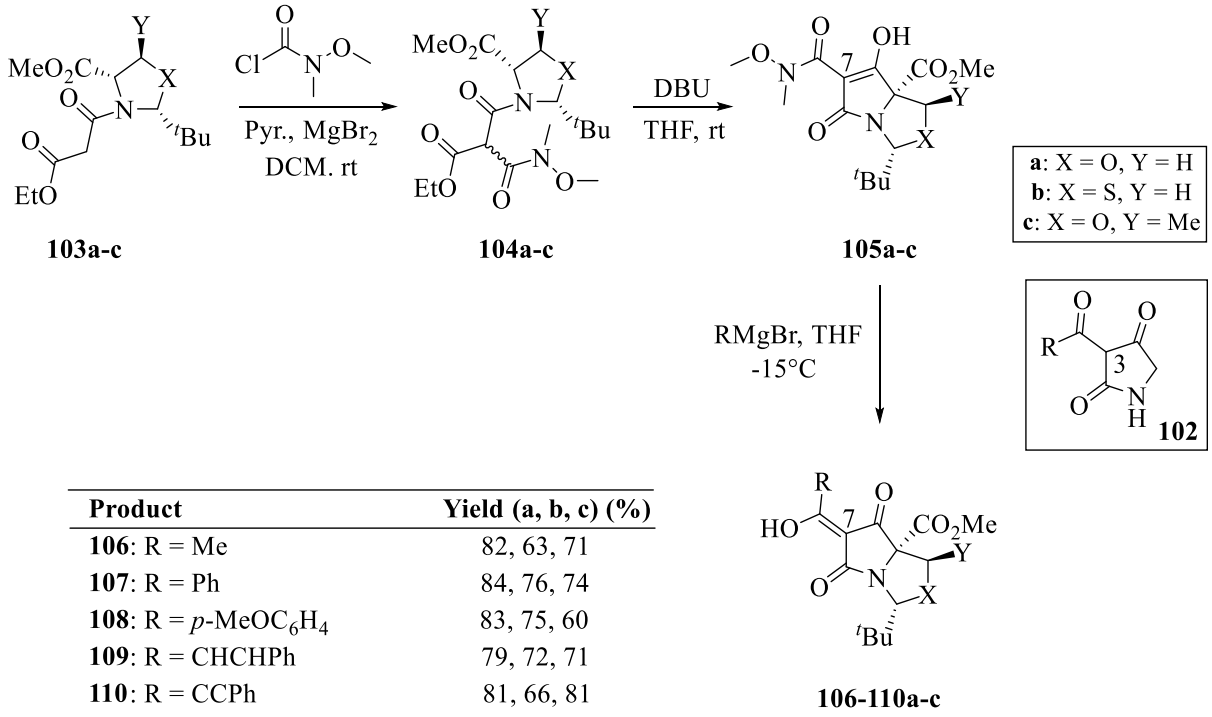


Scheme 1.21: Synthesis of 3,4-substituted pyroglutaminols and pyroglutamates by Moloney group[126]

Treatment of alcohols **95** and **96** with TFA removed the *tert*-butyl group and subsequent oxidation with ruthenium(IV) oxide/sodium periodate and methylation with diazomethane gave the expected diastereomers **97** and **98**. Hydrolysis of dimethyl ester **98a** with NaOH in aqueous THF afforded kainoid analogues **99** as a mixture of *4S* and *4R* isomers with *4R* as major isomer. Pyrrolidinone **93a** was converted to **100** via oxidation and esterification, while **94a** failed under the same conditions. Conversion of **94h** by hydrolysis, decarboxylation and

oxidation, as described for the conversion of **93** to **97**/**98**, gave an almost equal mixture of methyl ester and ethyl ester (at C4) **101** (Scheme 1.21).

Recently, the Moloney group has been interested in modification at C7 of bicyclic tetramate type **105**, leading to 3-acyl tetramic acid moiety **102**, found in natural products with antibacterial activities.[127–129] Josa-Cullere *et al.*[130] reported the use of Weinreb amides in the chemoselective formation and reaction of densely functionalised bicyclic tetramic acids **105** with Grignards (Scheme 1.22). Treatment of oxazolidine/thiazolidine[131] **103** with methoxy(methyl)carbamic chloride gave tricarbonyl compound **104**, which was then cyclised to Weinreb amide **105** using DBU/THF.

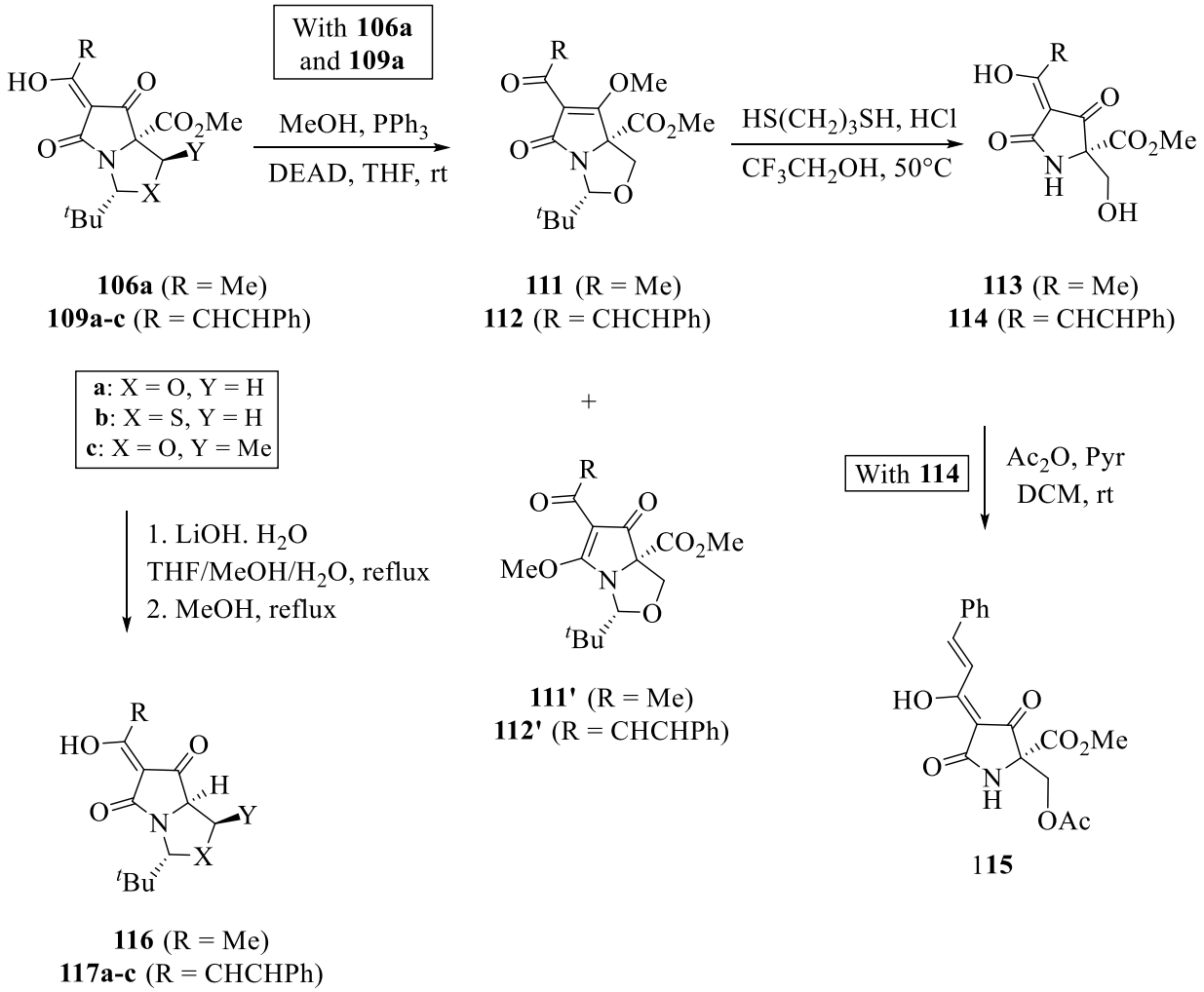


Product	Yield (a, b, c) (%)
106: R = Me	82, 63, 71
107: R = Ph	84, 76, 74
108: R = *p*-MeOC$_6$H$_4$	83, 75, 60
109: R = CHCHPh	79, 72, 71
110: R = CCPh	81, 66, 81

Scheme 1.22: Preparation and reaction of Weinreb amides[130]

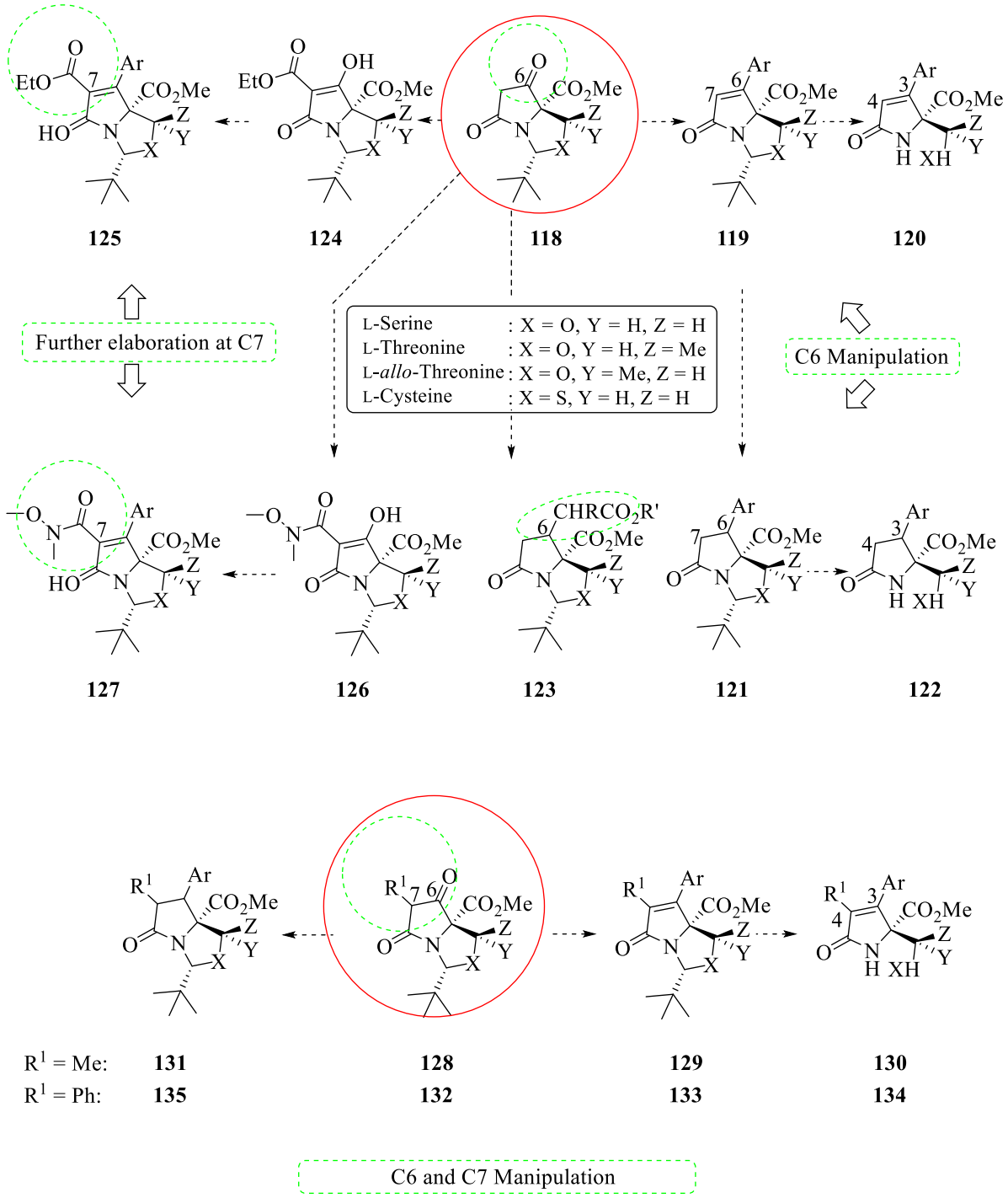
Attempted *N,O*-acetal deprotection was not successful for all of the synthesised compounds **106-110** with a variety of deprotection reagents.[130] These deprotected compounds were instead accessed by methylating **106a** and **109a** using Mitsunobu reaction conditions,[132]

which gave a mixture of enolates **111/112** and **111'/112'**, followed by treatment with propane-1,3-diol and 2,2,2-trifluroethanol at 50°C, resulting in the formation of deprotected alcohol **113** from **111** (Scheme 1.23). A similar conversion for **112** was found to be difficult at the purification stage of **114**, hence crude **114** was treated with an acylating reagent to isolate protected alcohol **115**. Decarboxylated products **116** and **117a-c** were prepared diastereoselectively via hydrolysis with excess LiOH and reflux in MeCN.



Scheme 1.23: *N,O*-Acetal deprotection and hydrolysis of **106a** and **109a-c** (*Eur. J. Org. Chem*, 2017, 7055-7059)

1.5 Aim of the Project



Scheme 1.24: Generalisable synthetic approaches towards C3 and C4 substituted pyroglutamates.

The aim of this project was to study and investigate the diverse functionalisation at C6 and C7 position of bicyclic tetramates (**118**, **128**, **132**) for the construction of highly functionalised, conformationally constrained pyroglutamates (**121**, **123**, **131, 135**), pyrrolinones (**119**, **125**, **127, 129**, **133**) and pyroglutaminol (**120, 122, 130, 134**) core units common to a variety of antibiotics (Scheme 1.24). To access the 3-substituted pyroglutamate, this research would focus on the use of tetramates **118** derived from L-serine, L-threonine, L-*allo*-threonine and L-cysteine oxazolidine/thiazolidine templates for further manipulation at C6 leading to 3-substituted pyroglutamates which are analogous to natural products.

Diversity could be introduced at the C7 position via ethyl ester tetramate **124** or Weinreb amide **126** with an aim to develop methodologies for the synthesis of bioactive molecules. Subsequent manipulation at both C6 an C7 would also be investigated via tetramates **128** and **132**. Finally, all the synthesised compounds would be tested for antibacterial activity.

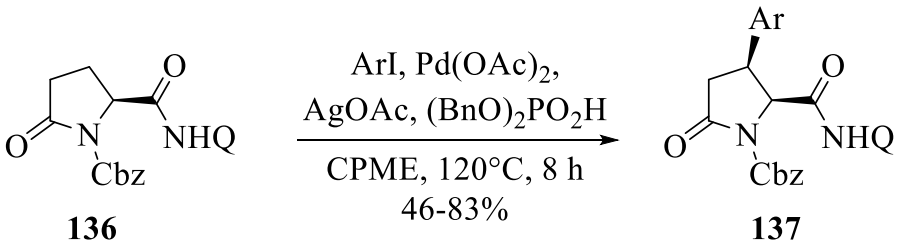
CHAPTER 2: STEREOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED PYROGLUTAMIC ACID DERIVATIVES

This Chapter describes the C6 functionalisation of the bicyclic tetramates **118**, derived from L-serine, L-threonine, L-*allo*-threonine and L-cysteine. The reaction conditions for Suzuki coupling and Reformatsky conjugate addition were applied to access 3-substituted pyroglutamates from tetramates. The feasibility, synthetic utility and scope of the process, and stereochemistry of the products are illustrated in this Chapter.

2.1 Introduction

2.1.1 Reported Syntheses of C3-Arylated Pyroglutamic Acid Derivatives

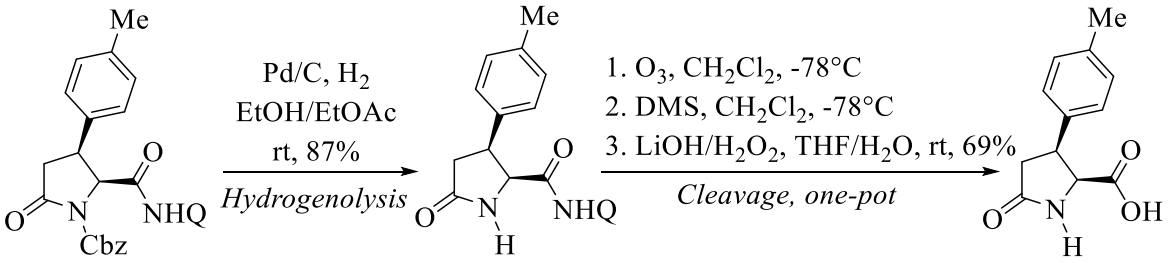
Earlier studies[76,90,92] on the synthesis of 3-substituted pyroglutamic acid derivatives required the 3,4-didehydroderivative of pyroglutamate, however, few reports are available describing C3-arylation. Recently, Verho and co-workers[133] reported the direct synthesis of C3-arylated pyroglutamic acid derivatives **137** via palladium (Pd) catalysed C-H arylation of substrate **136**, permitted by 8-aminoquinoline (8-AQ) as a directing group (Scheme 2.1).



Scheme 2.1: Pd catalysed C-H arylation by Verho and co-workers[133]

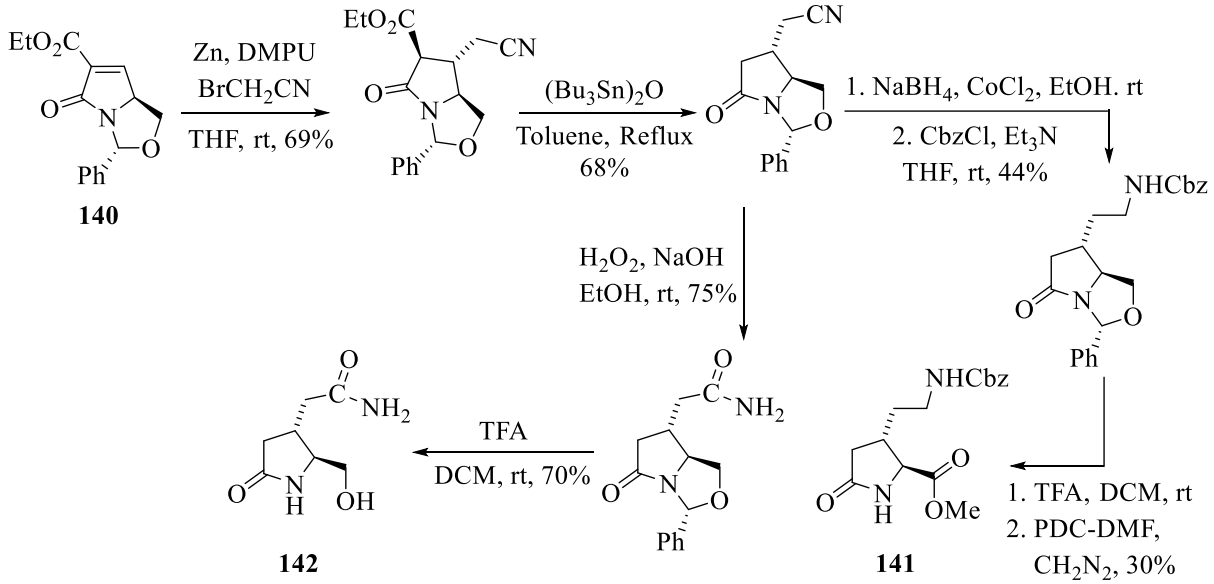
The reaction required the use of additive dibenzyl phosphate ($(BnO)_2PO_2H$) and the directing effects of 8-AQ facilitated the C-H arylation in a *cis*-fashion. The amino group was

deprotected by the removal of the Cbz group via Pd/C-catalysed hydrogenolysis of **137a**. The cleavage of the 8-AQ directing group was done using ozonolytic conditions and treatment with $LiOH/H_2O_2$ at room temperature to generate the C3-arylated pyroglutamic acid product **139** (Scheme 2.2).



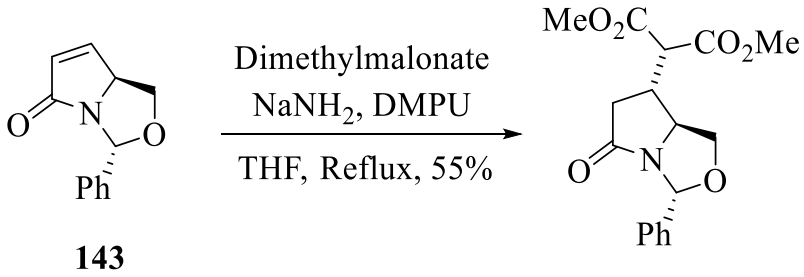
Scheme 2.2: Verho and co-workers[133] protocol for the synthesis of C3-arylpyroglutamic acid derivative **139** via hydrogenolysis and cleavage of **137a**.

2.1.2 Reported Syntheses of C3-Substituted Pyroglutamic Acid Derivatives via Conjugate Addition



Scheme 2.3: Synthesis of pyroglutamate **141** and pyroglutaminol **142** by Bentz *et al*.[134]

Bentz *et al.*[134] reported the use of Reformatsky conjugate addition of bromoacetonitrile to α,β-unsaturated lactam **140** to synthesise pyroglutamate **141** and pyroglutaminol **142** (Scheme 2.3). Similar conversions were examined by Bailey and co-workers[118] and effective conjugate addition to α,β-unsaturated lactam **143** was reported using Stefanofsky conditions[135] (Scheme 2.4).



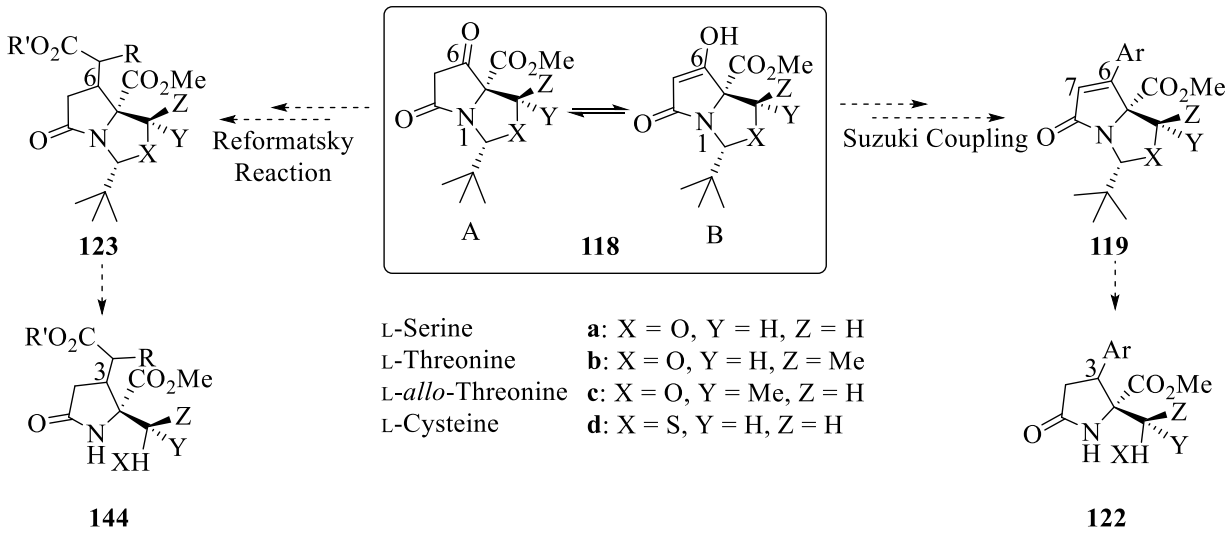
143

Scheme 2.4: Reported example for conjugate addition to α,β-unsaturated lactam **143**[118]

2.1.3 Synthetic Goals

As described in the Chapter 1, C3-substituted pyroglutamates are highly useful for a number of chemical transformations, and this application highlights the potential for the development of methodology to access such a system efficiently. Reported methodologies rely on Michael or Reformatsky type additions to an α,β-unsaturated lactam moiety or C(3)-H arylation of pyroglutamate in the presence of a directing group which limits their scope and synthetic utility.

The synthetic goal for this Chapter was to develop a more general methodology for the chemical transformation leading to C3-functionalised pyroglutamates and pyroglutaminols **122** and **144**, compounds of considerable interest for their utilisation and biological properties. Bicyclic tetramate scaffold **118** would be employed as a substrate, which could be a common precursor for the desired transformations via Suzuki-Miyaura cross-coupling or conjugate additions with functionalised reagents for further elaboration (Scheme 2.5).



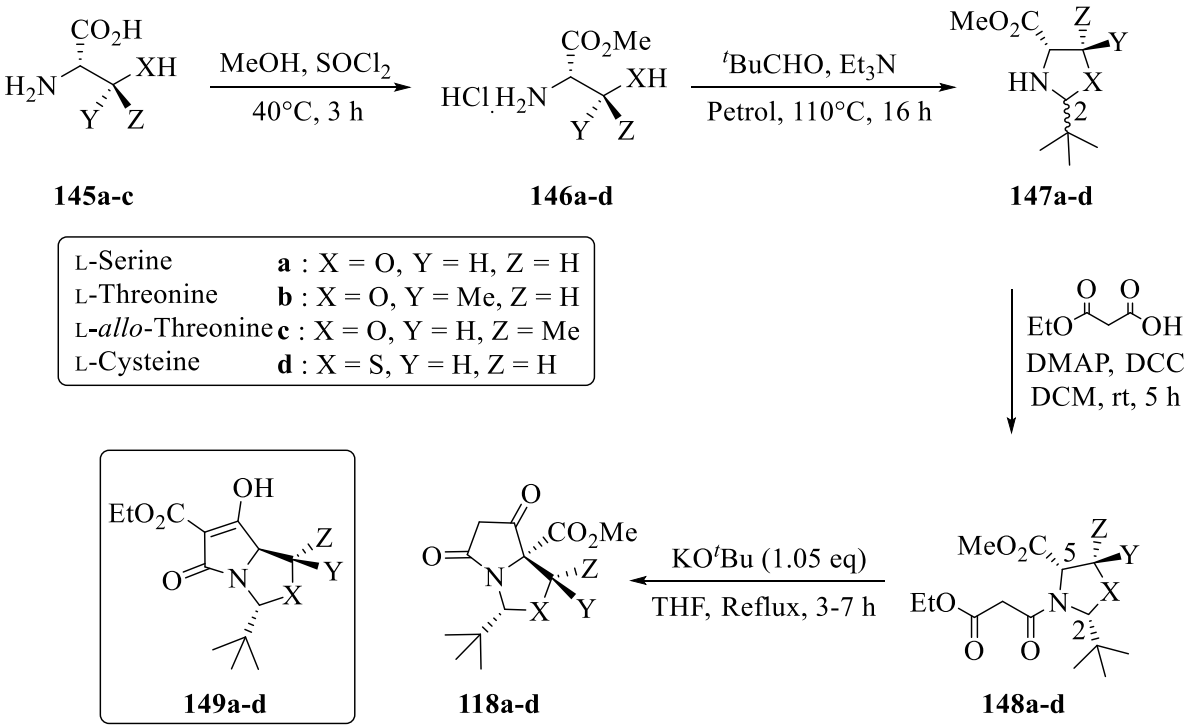
Scheme 2.5: Synthetic goals for Chapter 2

2.2 Synthesis of Bicyclic Tetramic Acids 118

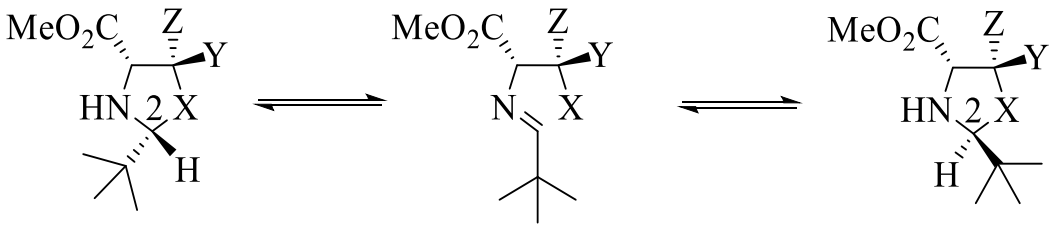
Firstly, methyl ester hydrochlorides of amino acids L-serine, L-threonine and L-*allo*-threonine **146a-c** were prepared from their respective amino acids **145a-c** adopting literature protocol (Scheme 2.6).[136] L-Cysteine methyl ester hydrochloride **146d** was used as consigned from the commercial supplier. The condensation reaction of methyl ester hydrochlorides **146a-d** with ^{t}BuCHO using Seebach's protocol[137] afforded a mixture of diastereomers for oxazolidines or thiazolidine **147a-d** in each case, with different ratios of *cis* and *trans* isomers. The oxazolidines **147a-c** and thiazolidine **147d** were then *N*-acylated using DCC coupling conditions[138] to produce malonamides **148a-d** mainly as the *cis*-2,5 diastereomers. Malonamides were found to exist as a mixture of rotamers, which has been discussed comprehensively in Section 2.2.1.

The preference of the *cis*-malonamides can be explained by the fact that **147a-d** exhibit ring-chain tautomerism[139,140] and can freely equilibrate as depicted in Scheme 2.7; presumably

the *cis*-isomer is more stable than *trans*-isomer, since the former places both groups pseudo equatorial.



Scheme 2.6: Synthetic route for tetramate templates **118a-d**



Scheme 2.7: Ring-chain tautomerism in **147a-d**

Jeong *et al.*[140] analysed this phenomenon scrupulously and proved although oxazolidines can equilibrate freely, *N*-acylation limits free rotation. For serine, the *cis*-2,5 diastereomer of malonamide **148a** was traced out to be more stable over the *trans*-2,5 diastereomer. In the *N*-acylated products **148**, *cis*-2,5 cannot convert to *trans*-2,5 via epimerisation at C2. They cyclise with different chemoselectivities to give **118** as a major product from the *cis* isomer and *ent*-**149** as a minor product from the *trans* isomer. Steric bulk deteriorates the 2,5-*cis*

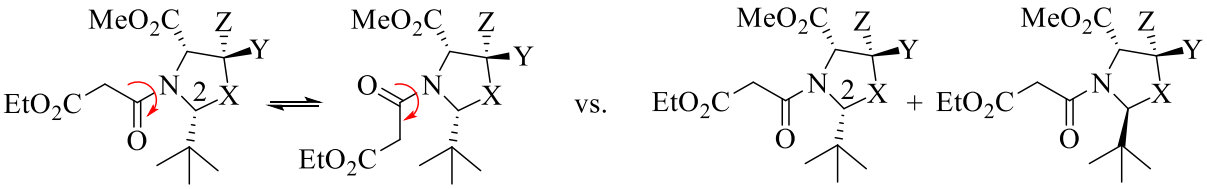
selectivity which was reflected in the experimental yield for malonamides **148b-c** derived from L-threonine and L-*allo*-threonine. Subsequent Dieckmann cyclisation[131] of *cis*-oxazolidines **148a-c** and thiazolidine **148d** in presence of potassium *tert*-butoxide furnished the envisaged bicyclic tetramates **118a-d**. In accordance with the literature,[131] the formation of ethyl ester tetramates **149a-d** (minor products) was also observed from 2,5-*trans*-malonamides, but only methyl ester tetramates **118a-d** of interest were isolated. Their stereochemistry was confirmed by NOE analysis. The key results for the synthesis of tetramates **118a-d** are summarised in Table 2.1. The low yield for malonamides originated from L-threonine and L-*allo*-threonine can be explained by the steric hindrance for the larger C(4)Me than smaller C(4)H for serine or cysteine-derived malonamides. Interestingly, $[\alpha]_D^{25}$ values were significantly lower for threonine systems.

Table 2.1: Key results for the synthesis of tetramate templates **118a-d**

Sl No	Systems	**147**		Yield of **148** (%)	Yield of **118** (%)	$[\alpha]_D^{25}$ of **118**
		1:5 *cis:trans*	Yield (%)			
1	**a**: X = O, Y = H, Z = H	1.4:1	86	80	75	+111.3 (*c* 1.2 in DCM)
2	**b**: X = O, Y = Me, Z = H	1.0:1	88	67	73	+41.3 (*c* 1.1 in DCM)
3	**c**: X = O, Y = H, Z = Me	2.5:1	71	66	75	+76.9 (*c* 1.0 in DCM)
4	**d**: X = S, Y = H, Z = H	1.5:1	95	78	74	+150.1 (*c* 1.0 in DCM)

2.2.1 C2 Epimerisation and Rotameric Behaviour of Malonamides: Rationalisation

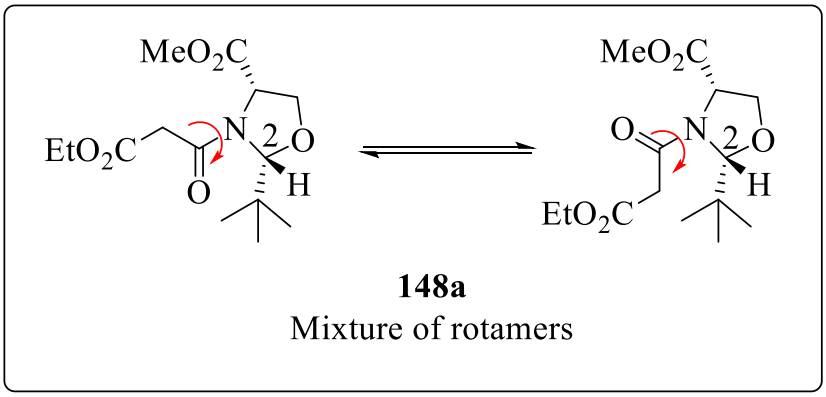
A mixture of two different species, even after careful column chromatography, was apparent in the ^{1}H NMR spectra of malonamides **148**. These mixtures could have been rotamers due to the presence of the *N*-protecting group or an inseparable mixture of diastereomers (Figure 2.1).



L-Serine	**a** : X = O, Y = H, Z = H
L-Threonine	**b** : X = O, Y = Me, Z = H
L-*allo*-Threonine	**c** : X = O, Y = H, Z = Me
L-Cysteine	**d** : X = S, Y = H, Z = H

Figure 2.1: Structure of rotamers and diastereomers for malonamides **148a-d**

The rate of rotameric exchange is fast and can be examined by using variable temperature (VT) ^{1}H NMR, 1D selective chemical exchange NMR experiment or 2D gradient NOE experiment. In the VT NMR experiment, ^{1}H signals from rotameric species would coalesce. On the other hand, proton signals for the rotameric species would exhibit similar behaviour in a 1D gradient NMR experiment or exchange peaks would appear in 2D gradient NOE experiment. Figure 2.2 symbolises the exchange peak for the H2 signals present in the ^{1}H NMR spectrum of **148a**. The 2D NOE **148c** exhibits similar exchange peak for H2 signal.



148a
Mixture of rotamers

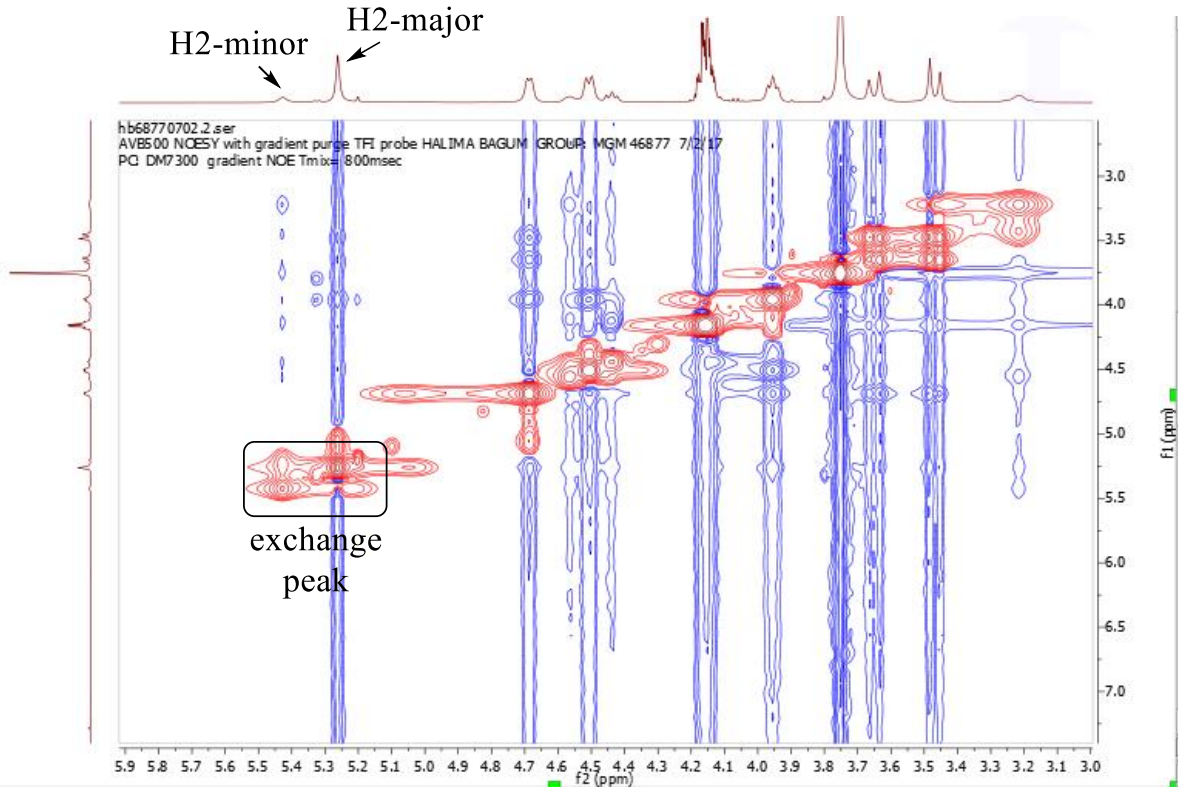


Figure 2.2: Rotameric species in 2D gradient NOE for malonamide **148a**

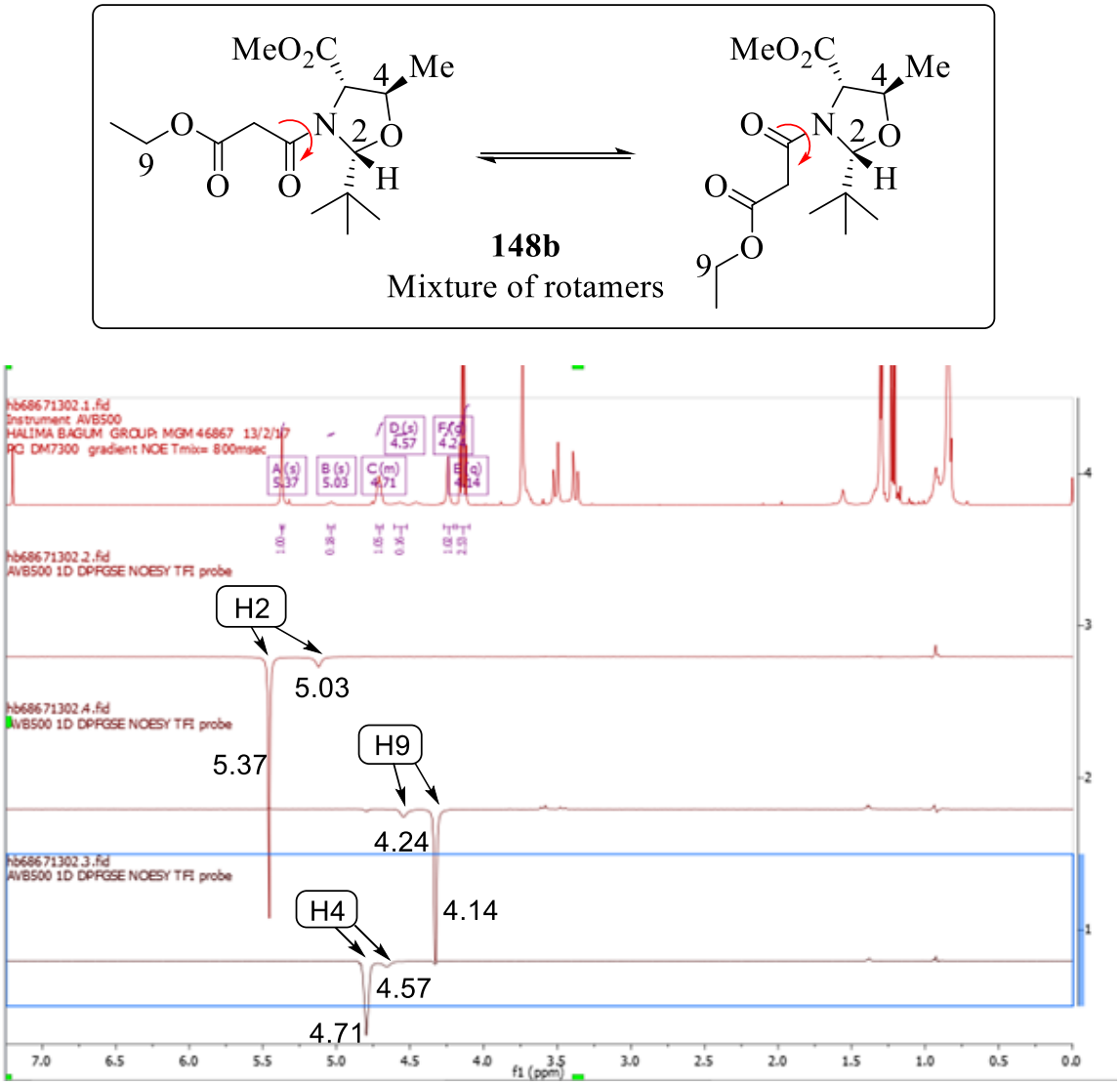
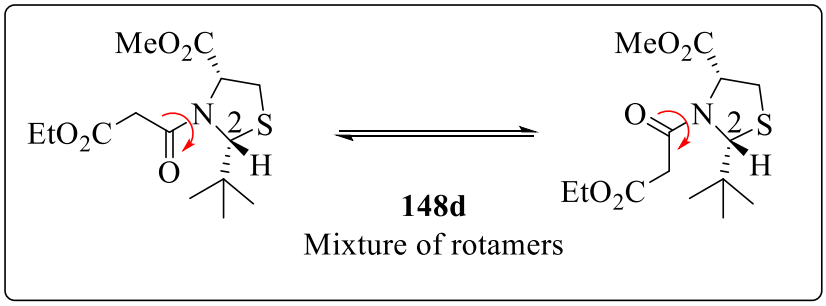


Figure 2.3: Rotameric species in 1D gradient NMR experiment for malonamide **148b**

Irradiation of the H2 peak at 5.37 ppm using 1D gradient NOE experiment represents two negative peaks at 5.37 ppm and 5.03 ppm. Similarly, selective irradiation at H4 at 4.71 ppm and H9 at 4.14 ppm show two negative peaks for each proton in the spectrum. These results imply the existence of minor rotameric species in the NMR spectrum of malonamide **148b** (Figure 2.3). The variable temperature (VT) ^{1}H NMR experiment for malonamide **148d** specifies the disappearance of ^{1}H signals for selected protons (Figure 2.4). At high temperature, rotation around C-N bond is faster which unites signals for rotameric protons and causes signal broadening in ^{1}H NMR spectrum.



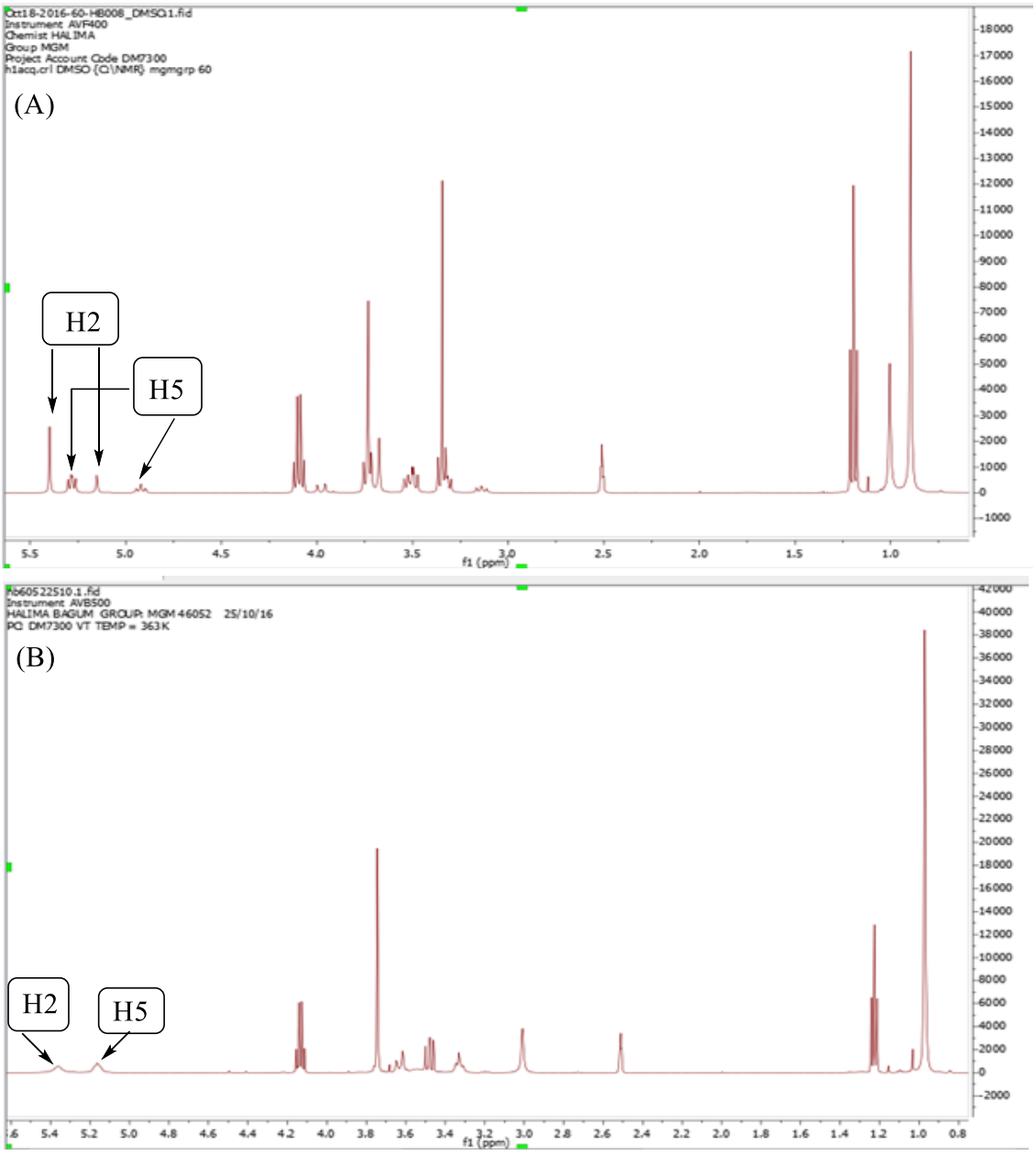
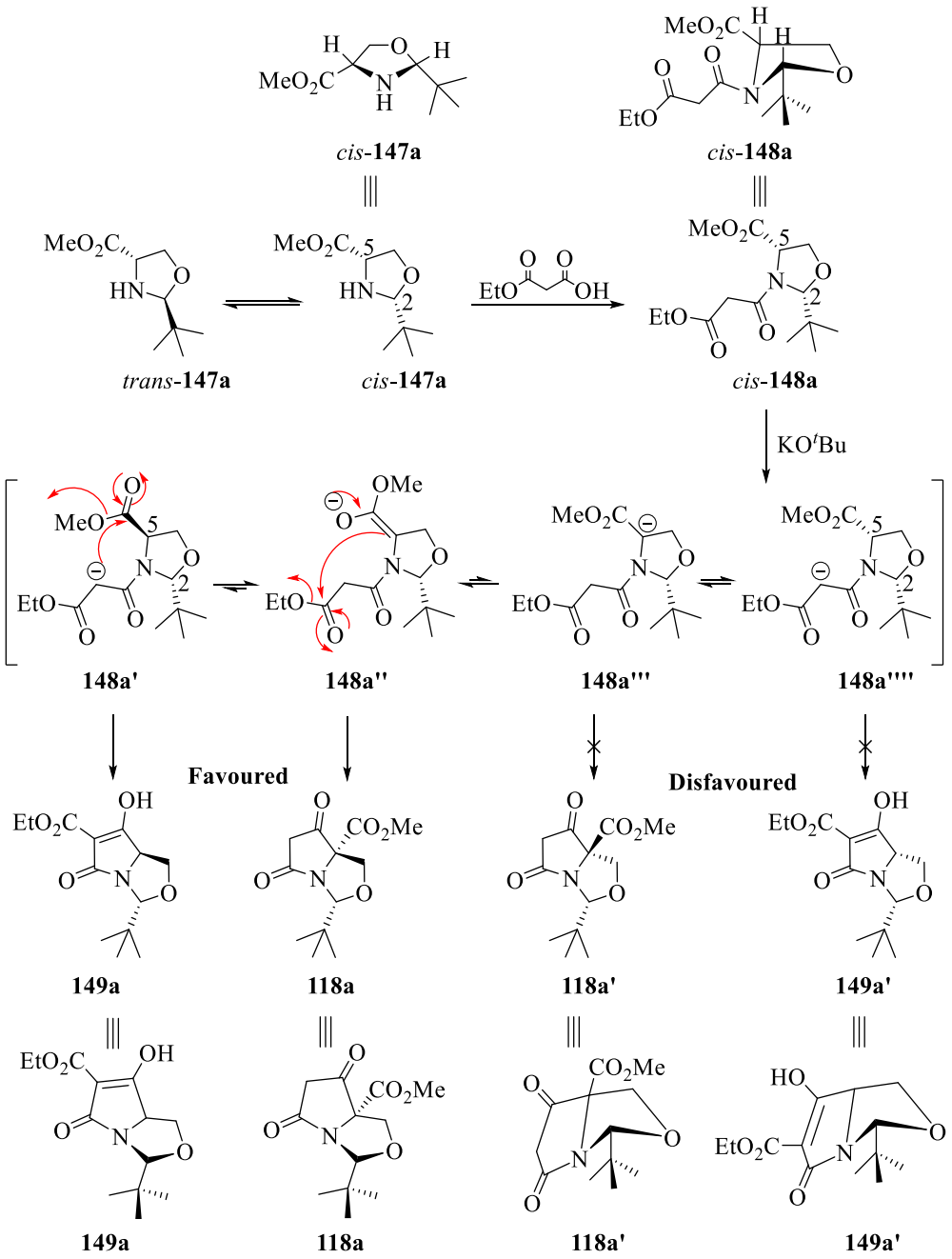


Figure 2.4: Variable temperature (VT) ^{1}H NMR spectrum for malonamide **148d** showing some broad signals at 363K; (A) ^{1}H NMR of **148d** in DMSO-d6 at 298K; (B) ^{1}H NMR of **148d** in DMSO-d6 at 363K

These experimental results clarify the rationalisation that the signals present in the NMR sample of *cis*-2,5 malonamides **148a-d** are not diastereomers but rotamers arising from the C-N single bond rotation as shown in Figure 2.1.

2.2.2 Regioselectivity and Diastereoselectivity in Dieckmann Cyclisation



Scheme 2.8: Mechanism and possible outcomes for the Dieckmann cyclisation[131,140]

Andrews and co-workers[131,138] have reported a comprehensive study on the regioselectivity, diastereoselectivity and enantioselectivity of the Dieckmann ring closure of *N*-acyl oxazolidines for the serine system (Scheme 2.8). The steric bulk from the *tert*-butyl group plays a pivotal role in the observed regioselectivity and diastereoselectivity in Dieckmann cyclisation. Deprotonation of *cis*-**148a** results in four possibilities for cyclisation among which only two are favoured as the bulky *tert*-butyl group is placed on the less hindered *exo*-face of the bicyclic system and consequently, the major product comes from the more stable enolate **148a''**. The other two structures, **148a'''** and **148a''''**, set the *tert*-butyl group in the more hindered *endo*-face of the bicyclic system and thereby cannot be formed. Jeong *et al*.[140] have examined the chemoselectivity in Dieckmann cyclisation. Seebach's substrate-controlling protocol 'Self Regeneration of Stereocentres'[137,141] allows this route to avoid racemization in the formation of chiral tetramates **118a** and **149a**. The optical purity of products was also examined by Andrews[131] and for **118a** the reported enantiomeric excess (ee) was >90%. Recently, Josa-Cullere *et al.*[142] reported the ee 96%, 100% and 100% for products **118a**, **118b**, and **118d**, respectively. These results clearly demonstrate that this three-step route to tetramate proceeds with regio- and chemoselectivity and develops tetramates **118** of excellent enantiomeric purity.

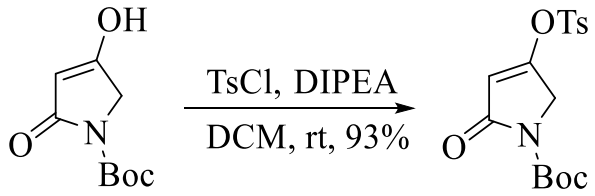
2.3 Towards Functionalisation at C6 of Tetramates: Part 1

It was a matter of great interest to introduce substituents at the C6 position of tetramates **118**, which could provide a route to access a library of 3-substituted pyrrolidinone and pyroglutamic acid derivatives. These analogues could be devised applying palladium-catalysed Suzuki-Miyaura cross-coupling reactions. In particular, tetramic acid **118** could exist as an equilibrium mixture of keto-enol tautomers in solution as shown in Scheme 2.5. The enolic structure B would enable a viable way for the synthesis of required substrate for

Suzuki coupling using reagents such as 4-toluenesulfonyl chloride (TsCl), methanesulfonyl chloride (MsCl) or trifluoromethanesulfonyl chloride/anhydride (TfCl/Tf_2O).

2.3.1 Synthesis of Tosylates

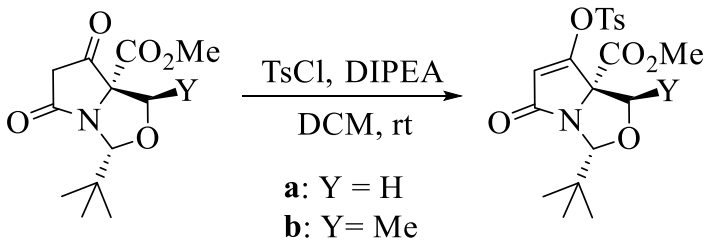
Li *et al.*[143] reported the preparation of tosylates from lactam-containing heterocycle **150** by using TsCl in presence of DIPEA (Scheme 2.9).



150 **151**

Scheme 2.9: Example for the synthesis of tosylate **151** reported by Li *et al.*[143]

With this reference, the conversion of tetramic acid **118** to its tosylate for the investigation of Suzuki coupling reactions was made. Treatment of **118a-b** with TsCl and DIPEA provided **152a-b** in good yields (Scheme 2.10).



118a-b **152a-b**

Scheme 2.10: Conversion of tetramates **118a-b** to **152a-b** tosylates

The formation of **152b** proceeded in a lower yield than **152a** (Table 2.2), which happened perhaps due to the steric effect of the additional methyl group placed *endo*-face of the bicyclic ring.

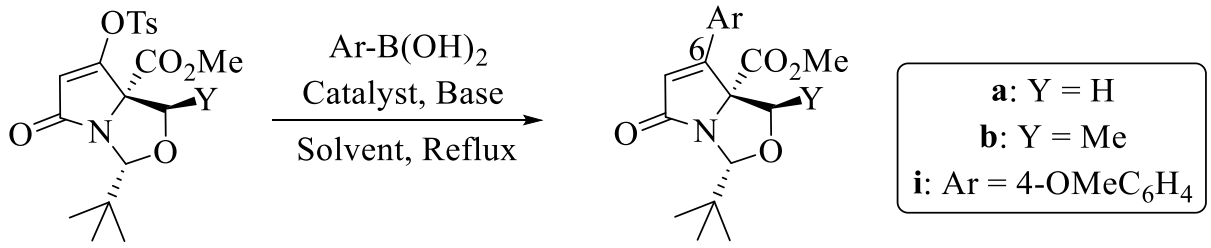
Table 2.2: Synthesis of tosylates from tetramate **118a-b**

Sl No	System	Entry	Y	Product	Yield (%)
1	L-Serine	**118a**	H	**152a**	78
2	L-Threonine	**118b**	Me	**152b**	57

2.3.2 Suzuki Coupling with Tosylates

With the tosylates **152a-b** in hand, the synthesis of C6-substituted analogues using boronic acids under Suzuki coupling conditions was examined (Table 2.3).

Table 2.3: Suzuki coupling reactions of tosylates **152a-b**



152a-b **119ai-bi**

Entry	Y	Ar	Conditions	Product (Yield)	Literature Method
152a	H	4-$OMeC_6H_4$	$PdCl_2$(dppf), Cs_2CO_3, THF/H_2O, 65°C, 6h	**119ai** (18%)	Yoon-Miller *et al.*[144]
152a	H	4-$OMeC_6H_4$	$NiCl_2(PPh_3)_2$, THF, rt, 15h	-	Kobayashi *et al.*[145]
152a	H	4-$OMeC_6H_4$	$NiCl_2(PPh_3)_2$, Cs_2CO_3, THF, 65°C, 15h	-	
152a	H	4-$OMeC_6H_4$	$PdCl_2$(dppb), Na_2CO_3, Toluene/EtOH, 110°C, 8h	**119ai** (56%)	Jones *et al.*[146]

Continued….

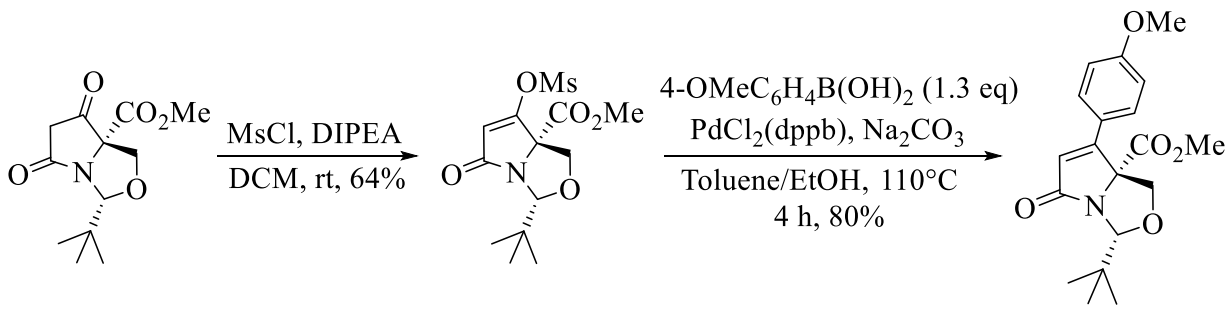
152a	H	Ph	$PdCl_2$(dppf), Cs_2CO_3, THF/H_2O, 65°C, 12h	-	Yoon-Miller *et al*.[144]
152a	H	4-BrC_6H_4	$PdCl_2$(dppf), Cs_2CO_3, THF/H_2O, 65°C, 12h	- (<1%)	”
152a	H	2-Thienyl	$PdCl_2$(dppf), Cs_2CO_3, THF/H_2O, 65°C, 12h	- (1%)	”
152b	Me	4-$OMeC_6H_4$	$PdCl_2$(dppb), Na_2CO_3, Toluene/EtOH, 110°C, 20h	**119bi** (<14%)	Jones *et al*.[146]

For tosylate **152a**, the maximum yield of 56% was obtained for coupling product **119ai**. Among the tested conditions, the catalyst [1,4-bis(diphenylphosphino)butane]palladium(II) chloride ($PdCl_2$(dppb)) was found to be the most apposite, and was prepared *in situ* from commercially available bis(benzonitrile)palladium(II) chloride ($PdCl_2(C_6H_5CN)_2$) and 1,4-bis(diphenylphosphino)butane ($(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$). Alternatively, the use of [1,1’-bis(diphenylphosphino)ferrocene]palladium(II) chloride ($PdCl_2$(dppf)) gave poor yields, and unidentified mixtures or no reaction at all for a number of boronic acids (Table 2.3). The coupling reaction using bis(triphenylphosphine)nickel(II) dichloride ($NiCl_2(PPh_3)_2$) as catalyst gave unreacted starting material. Tosylate **152b** resulted in less than 14% yield using ($PdCl_2$(dppb)) as a catalyst. Even after careful column chromatography, the spectrum showed unidentified signals along with the desired product.

Given the results obtained in Table 2.3, the next choice was coupling with a different substrate such as mesylate or triflate.

2.3.3 Synthesis of Serine-Derived Mesylate and Suzuki Coupling

In a diligent attempt to improve the yield for coupling products, mesylate **153a** was prepared from tetramic acid **118a** using exactly the same conditions[143] used for tosylate preparation (Scheme 2.11).



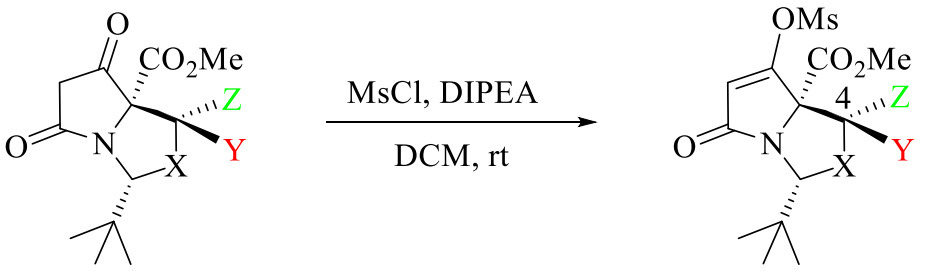
118a **153a** **119ai**

Scheme 2.11: Suzuki coupling of mesylate **153a**

Pleasingly, subsequent coupling with 4-methoxyphenyboronic acid using $PdCl_2$(dppb) catalyst furnished the desired product and the yield for **119ai** was increased from 56% to 80%.

2.3.4 Synthesis of Mesylates for L-Threonine, L-*allo*-Threonine, and L-Cysteine Systems

In order to study the coupling reactions for L-threonine, L-*allo*-threonine, and L-cysteine systems, the mesylates **153b-d** were synthesised from the respective tetramic acids **118b-d**. (Scheme 2.12). The L-threonine, L-*allo*-threonine systems would allow investigation of the effect of the C4 methyl group and its stereochemistry on coupling reactions, while the L-cysteine system would permit scrutiny of the feasibility and differences in reactivity between the *O*- and *S*-systems.



118b-d **153b-d**

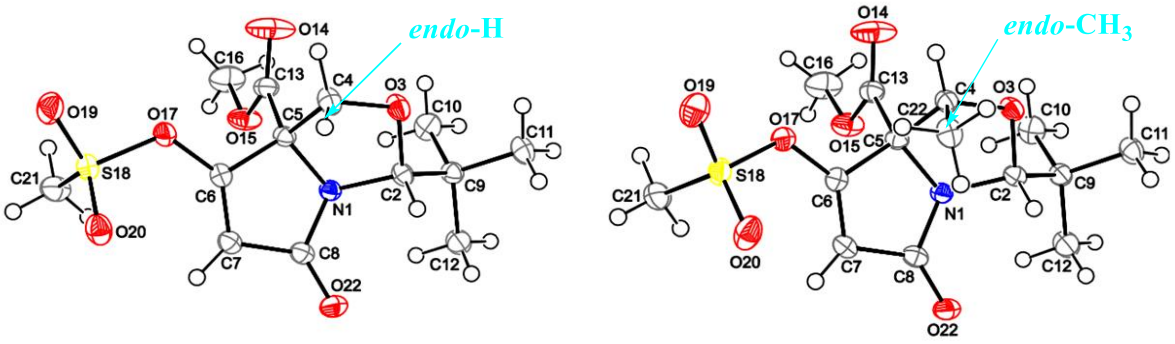
Scheme 2.12: Synthesis of mesylates **153b-d**

Table 2.4: Mesylation of tetramates **118** and characteristic chemical shifts for H4 (δ_{H4})

Sl No	System	Entry	X, Y, Z	Product	Yield (%)	δ_{H4} (ppm)
1	L-Serine	**118a**	O, H, H	**153a**	64	3.45, 4.74
2	L-Threonine	**118b**	O, Me, H	**153b**	25	5.01
3	L-*allo*-Threonine	**118c**	O, H, Me	**153c**	52	3.72
4	L-Cysteine	**118d**	S, H, H	**153d**	44	2.81, 3.60

Overall, yields for mesylates **153** were less compared to the tosylate analogue **152** (see Table 2.2). This can be explained by the formation of by-products from the rearrangement of mesylates under the reaction conditions. This outcome will be discussed briefly in Chapter 3. From the yields of mesylation reaction (Table 2.4), it was supposed that the stereochemistry at C4 is important for successful coupling reaction too. A significant change in chemical shift values was observed for C4 protons in ^{1}H NMR spectra of products **153a-c**, among which H4 of L-threonine was significantly deshielded in comparison to other *O*-systems. The three-dimensional structure of mesylates **153a** and **153b** was confirmed by X-ray crystallography (Figure 2.5). The non-planar shape of the bicyclic molecule positioned C(4)CH_3 group close to the periphery of C6 which could be the reason for poor yield of

mesylate **153b**. It was suspected that the stereochemistry of C(4) would influence coupling reactions for **153b-c**.



153a **153b**

Figure 2.5: X-Ray crystal structures of **153a** and **153b**

2.4 Suzuki-Miyaura Cross-Coupling Reactions

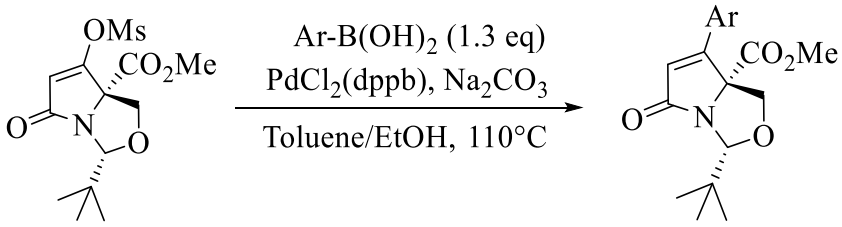
The Suzuki-Miyaura Cross-Coupling Reactions of **153a-d** were explored broadly with the optimal conditions established earlier (see Scheme 2.11). A range of commercially available arylboronic acids was selected which included electron rich, electron deficient and neutral systems.

2.4.1 L-Serine System

With the starting materials in hand, mesylate **153a** was treated with different boronic acids or boronic acid pinacol ester. The results are summarised in Table 2.5. Boronic acids were used for the synthesis of **119ai-avi**, and 2-phenyl-1-ethynylboronic acid pinacol ester was used for the preparation of **119avii**. The reactions were successful and furnished the corresponding substituted pyrrolidinones in acceptable yields, however, the coupling was less efficient for electron deficient systems and failed for 4-bromophenylboronic acid. Reaction times were calculated based on the total consumption of starting material (SM)

examined by thin layer chromatography (TLC). For **119avi**, TLC showed unreacted SM even after 48h.

Table 2.5: Suzuki coupling reactions for serine system



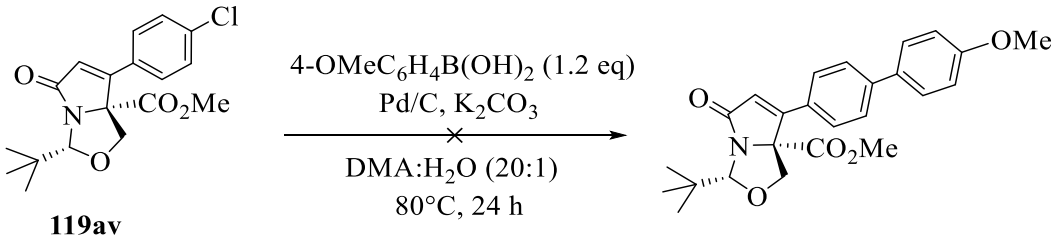
153a **119ai-avii**

Sl No	Entry	Ar	Reaction Time (h)	Product	Yields (%)
1	**153a**	**i**: 4-methoxyphenyl	4	**119ai**	80
2	**153a**	**ii**: phenyl	5	**119aii**	64
3	**153a**	**iii**: 2-furyl	12	**119aiii**	47
4	**153a**	**iv**: 4-formylphenyl	11	**119aiv**	28
5	**153a**	**v**: 4-chlorophenyl	7	**119av**	16 (49)[a]
6	**153a**	4-bromophenyl	overnight	-	-
7	**153a**	**vi**: *trans*-2-phenylvinyl	48	**119avi**	25
8	**153a**	**vii**: 2-phenyl-1-ethynyl	12	**119avii**	20

[a] 1.05 eq 4-chlorophenyl boronic acid

The adduct **119av** coupled further with excess boronic acid when treated with 1.3 equivalents (eq) of 4-chlorophenylboronic acid. Treatment of **153a** with 1.05 eq 4-chlorophenyl boronic acid allowed an improved yield for **119av**. In terms of purification, **119ai-av** were all easily purified by flash column chromatography with 25-30% ethyl acetate in petroleum ether. However, the rest of the products of this series, were purified with difficulty.

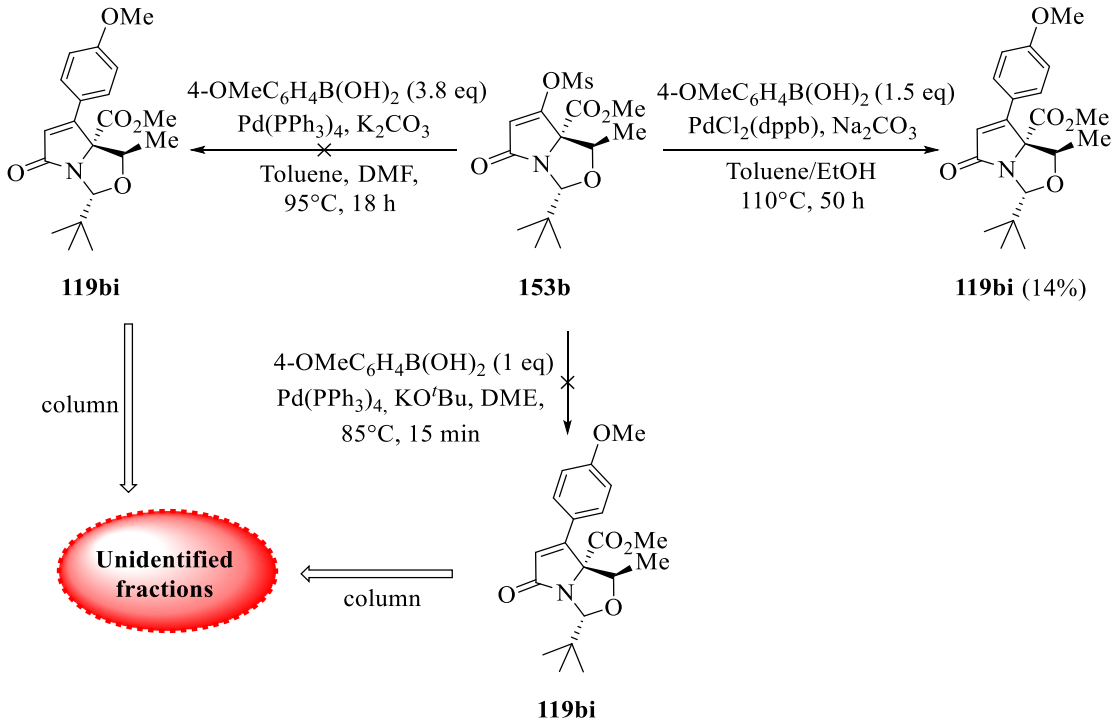
In an attempt at further coupling with 4-chlorophenyl adduct **119av**, LeBlond's coupling methodology[147] was examined but unreacted starting material was recovered (Scheme 2.13). This could be because ligandless, heterogeneous palladium is an unsuitable catalyst for this conversion.



Scheme 2.13: Attempted cross-coupling of **119av**

2.4.2 L-Threonine System

The coupling reaction of **153b** afforded a maximum yield of 14% for expected product **119bi** (Scheme 2.14).



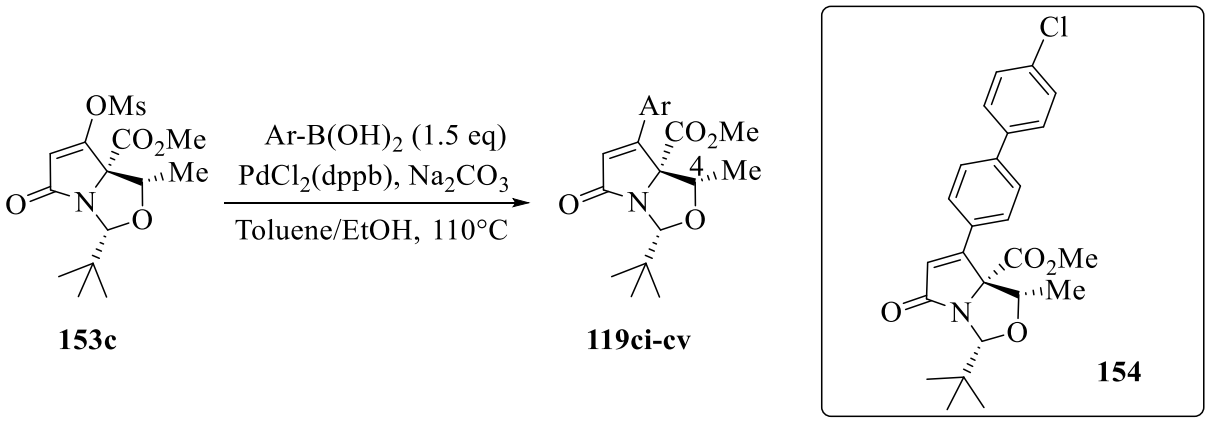
Scheme 2.14: Attempted Suzuki cross-coupling reactions of **153b**

The reaction seemed very slow and an increased quantity of boronic acid (1.5 eq) was used in this case. Though TLC showed unreacted starting material when treated with the previous coupling conditions, it was unfeasible to recover it. Interestingly, **119bi** prepared from **153b** was purified without any difficulty, which was troublesome when **152b** was the substrate for the same coupling reaction. Attempted Suzuki coupling reactions using the catalyst tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) by Zhang's conditions[148] or Gauler's conditions[149] generated a complex mixture. Unidentified fractions were isolated after column chromatography, notwithstanding that none of them were the expected product. Further conditions were not attempted, rather it was of interest to investigate the coupling for the L-*allo*-threonine system with the opposite stereochemistry at C4.

2.4.3 L-*allo*-Threonine System

Decision as to the use of the same conditions was embraced in order to compare the L-threonine and L-*allo*-threonine systems towards C6 functionalisation by Suzuki coupling reactions. Application of coupling conditions (as applied for successful coupling to **153b**) to mesylate **153c** delivered excellent yields, except for electron deficient systems (Table 2.6).

Table 2.6: Suzuki coupling reactions to **153c**



153c **119ci-cv**

Continued……

Sl No	Entry	Ar	Reaction Time (h)	Product	Yields (%)
1	**153c**	**i**: 4-methoxyphenyl	4	**119ci**	70
2	**153c**	**ii**: phenyl	4	**119cii**	80
3	**153c**	**iii**: 2-furyl	overnight	**119ciii**	28
4	**153c**	**iv**: 4-formylphenyl	28	**119civ**	36
5	**153c**	**v**: 4-chlorophenyl	4	**119cv**	71[a]
				154	5

[a] 1.05 eq 4-chlorophenyl boronic acid

This outcome demonstrated the steric interference of C4 substituent on the coupling. The reaction was more feasible for substrate **153c**, where the smaller H-atom was positioned towards the *endo*-face of the bicyclic core structure rather than larger *endo*-Me for L-threonine analogue **153b**.

2.4.4 Rationale for the Difference in Reactivity of Mesylates: *O*-system

To develop the rationale behind the difference in reactivity towards Suzuki coupling, firstly the potential energy relative to the most stable structure was generated, using Chem3D v.16, for substrates **153a-c** and coupling adducts analogous to each system (Table 2.7).

Table 2.7: MM2 energy for **153a-c** and 4-methoxyphenyl adducts **119ai-ci**

O-System	MM2 Energy Minimization (kcal/mol)		
	Substrate **153a-c**	4-$MeOC_6H_4$ Adduct **119ai-ci**	Difference
a: L-Serine	231.5618	47.3923	184.1695
b: L-Threonine	234.2661	49.0033	185.2628
c: L-*allo*-Threonine	234.6027	51.9781	182.6246

It was perceived from the relatively large difference in MM2 energy for the L-threonine system that the conversion to products is energetically less favorable. This could be one of the reasons for a poor yield of **119bi**.

Next, the X-ray crystal structures of the products were sought. Crystals were grown for 4-methoxyphenyl adducts **119ai-ci** obtained from L-serine, L-threonine, and L-*allo*-threonine derived mesylates **153a-c**. The X-ray crystal structures (Figure 2.6) were analyzed to gain an insight of their respective structures.

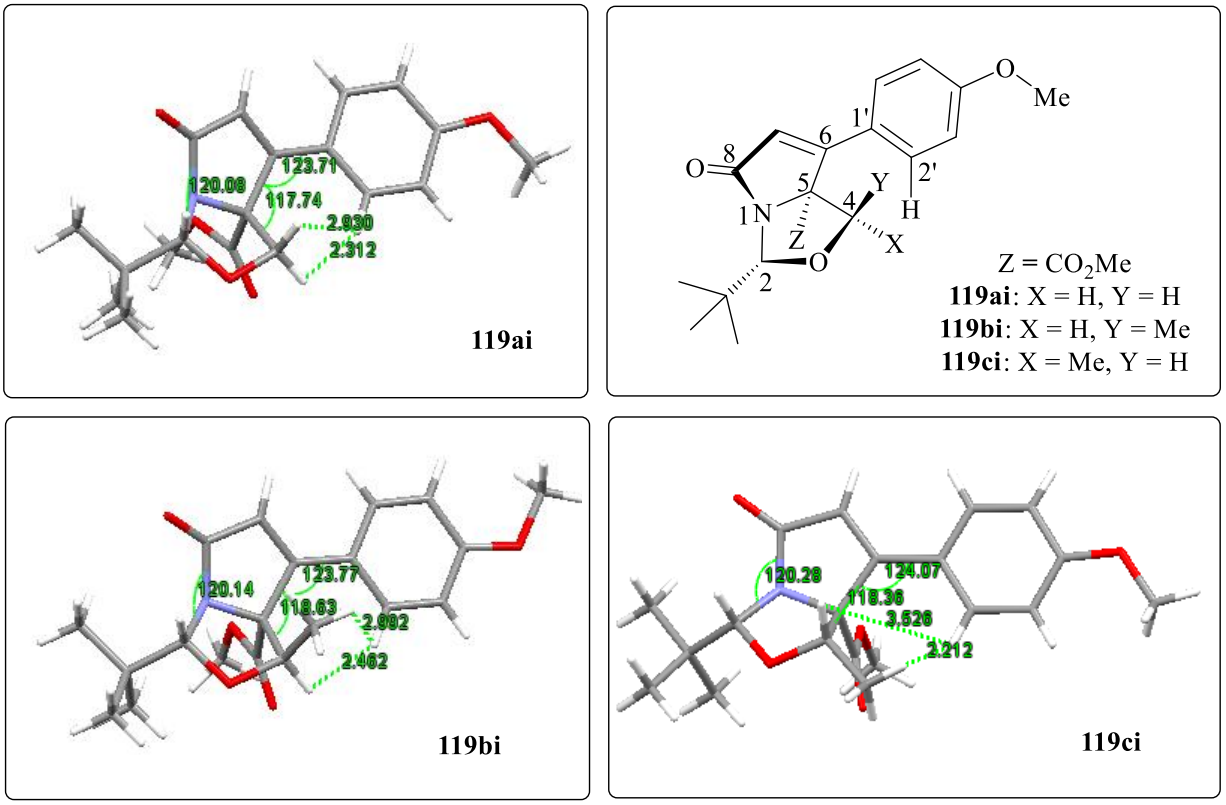


Figure 2.6: X-Ray crystal structures of **119ai, 119bi** and **119ci**

The software Mercury 3.10.1 was used for the measurement of bond lengths and bond angles. The C(1')-C(6)-C(5) and C(2)-N(1)-C(8) bond angles follow L-serine< L-threonine< L-*allo*-threonine for three systems, whereas the C(4)-C(5)-C(6) bond angle is relatively large for the L-threonine system (Table 2.8). The *endo*-Me group distorts the bicyclic core

structure for this system and likewise could account for relatively more steric hindrance compared to *endo*-H for the other two systems. Some representative bond lengths were also recorded from the crystal structure, these account relative distance from ArC2'.

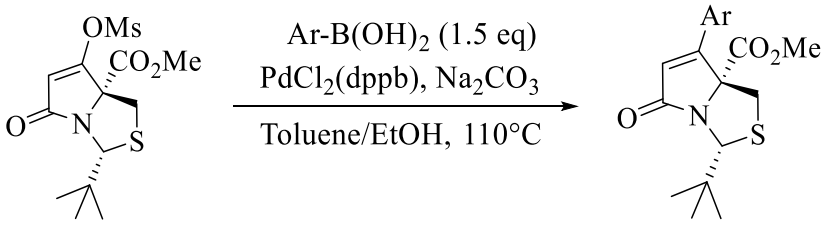
Table 2.8: Representative bond angles and bond lengths for coupling adducts **119ai-ci**

		***O*-Systems**					
		L-Serine a		**L-Threonine b**		**L-*allo*-Threonine c**	
		119ai		**119bi**		**119ci**	
Bond Angles [°]	C(1')-C(6)-C(5)	123.71		123.77		124.07	
	C(4)-C(5)-C(6)	117.74		118.63		118.36	
	C(2)-N(1)-C(8)	120.08		120.14		120.28	
Bond Lengths [A°]	Distance measured from C(2')H	*exo*-H	*endo*-H	*exo*-H	*endo*-Me(H)	*exo*-Me(H)	*endo*-H
		2.312	2.930	2.462	2.993	2.212	3.526

2.4.5 L-Cysteine System

With the mesylate **153d**, treatment with arylboronic acids implementing coupling conditions as applied for **153c** was successful and resulted in adducts **119di-dvii** in 15-62% yields (Table 2.9).

Table 2.9: Suzuki coupling reactions for cysteine system



153d **119di-dvii**

Continued…..

Sl No	Entry	Ar-B(OH)$_2$	Reaction Time (h)	Product	Yields (%)
1	**153d**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	3	**119di**	62
2	**153d**	**ii**: C$_6$H$_5$B(OH)$_2$	3	**119dii**	58
3	**153d**	**iii**: 2-furylboronic acid	20	**119diii**	22
4	**153d**	**iv**: 4-CHOC$_6$H$_4$B(OH)$_2$	overnight	**119div**	25
5	**153d**	**v**: 4-ClC$_6$H$_4$B(OH)$_2$	6	**119dv**	43[a]
6	**153d**	4-BrC$_6$H$_4$B(OH)$_2$	20	**-**	-
7	**153d**	**vi**: *trans*-2-phenylvinylboronic acid	24	**119dvi**	20
8	**153d**	**vii**: 2-phenyl-1-ethynylboronic acid pinacol ester	24	**119dvii**	15

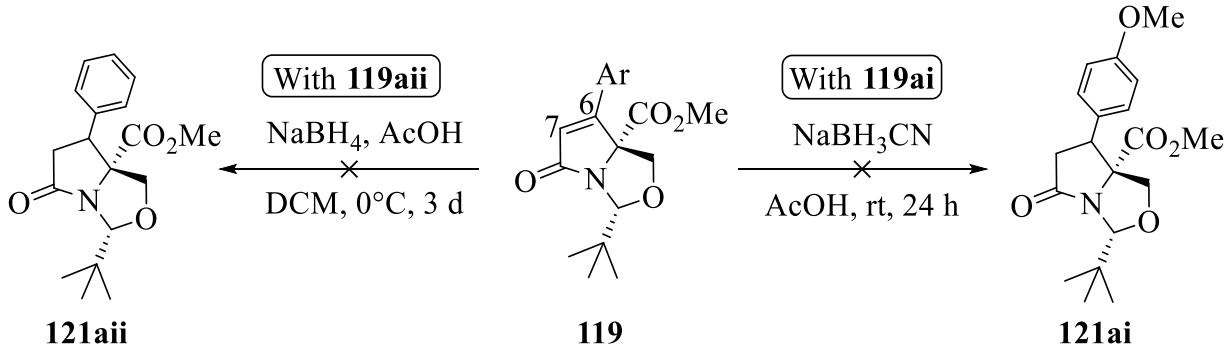
[a] 1.05 eq 4-chlorophenyl boronic acid

However, the formation of **119di-dvii** proceeded in lower yields than **119ai-avii** (see Table 2.5), and the lower yield was thought to be likely to happen due to the distortion of five-membered ring by the larger sulfur atom. Nevertheless, the overall coupling result and purification of adducts were consistent with the serine system. The use of 4-bromophenylboronic acid resulted a complex mixture, and the desired product was not observed by NMR or mass analysis. Unidentified fractions were isolated after flash column chromatography, however, none of them was the coupling product.

The 4-methoxyphenyl adducts **119ai-di** were easy to detect when monitoring the reaction as they were fluorescent under UV light, and eventuated isolation of products by flash column chromatography much easier.

2.5 Access to Pyrrolidinone and Pyroglutamate Derivatives

Having been able to synthesise a library of pyrrolinones **119a-d**, removal of the C6-C7 double bond was investigated to achieve a library of pyrrolidinones and pyroglutamates. The initial approach was reduction. Applying the conditions of Jouin and Castro[150] for the diastereoselective reduction of enone system, attempted reduction of **119aii** with $NaBH_4$ in AcOH was unsuccessful and resulted in quantitative recovery of starting material (Scheme 2.15).



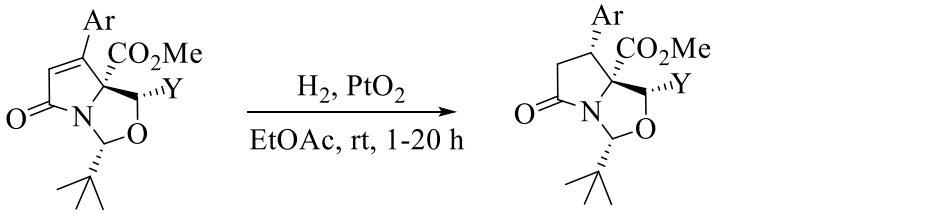
Scheme 2.15: Attempted reduction of the C6-C7 double bond of **119**

As another option, Pinheiro's conditions[151] were used for the reduction of **119ai** with $NaBH_3CN$ in AcOH and similarly, the starting material was recovered quantitatively. Milne *et al.*[152] reported the similar conversion by means of hydrogenation using PtO_2 as a catalyst. Inspired by this literature, attention was turned to pursue hydrogenation reactions on pyrrolinone **119**.

2.5.1 Hydrogenation: *O*-System

The treatment of **119ai-av** with hydrogen at atmospheric pressure and PtO_2 catalyst efficiently furnished desired products **121ai-av** (Scheme 2.16). Following these thriving conversions, hydrogenation of **119ci-cv** under the same reaction conditions provided

pyrrolidinone or pyroglutamate derivatives **121ci-cv**. Hydrogenation reactions were completed within 1-6 hours for different substrates except for **119aiv**, which resulted in a mixture of **121aiv** and **155**, identified by LRMS analysis. It was assumed that the hydrogenation of C6-C7 double bond was significantly slower compared to the reduction of aldehyde functional group.



119ai-av
119ci-cv

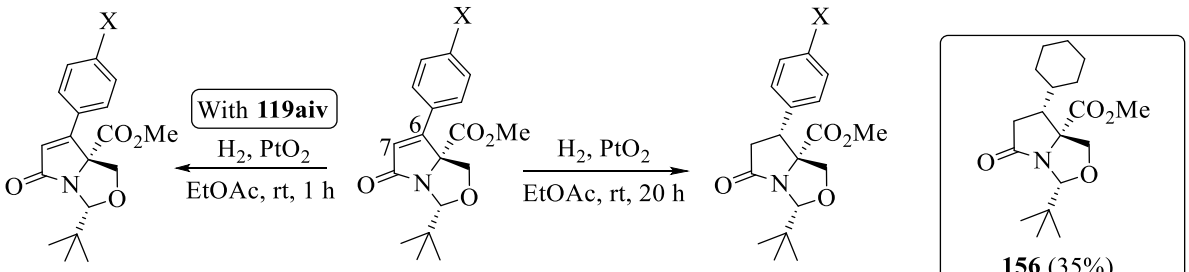
121ai-av
121ci-cv

a: Y = H
c: Y = Me

Products	121a (%)	121c (%)
i : Ar = 4-OMeC_6H_4	98	71
ii : Ar = C_6H_5	88	94
iii : Ar = 2-furyl	28	67
iv : Ar = 4-$OHCH_2C_6H_4$	76	79
v : Ar = 4-ClC_6H_4	33	84

Scheme 2.16: Hydrogenation of pyrrolinones **119** in L-serine and L-*allo*-threonine systems

This reaction was monitored carefully and after 1 h an additional spot appeared strong on TLC. Starting material was consumed completely (by TLC) after 20 h and resulted in **121aiv** (Scheme 2.17).



155: X = CH_2OH (49%)

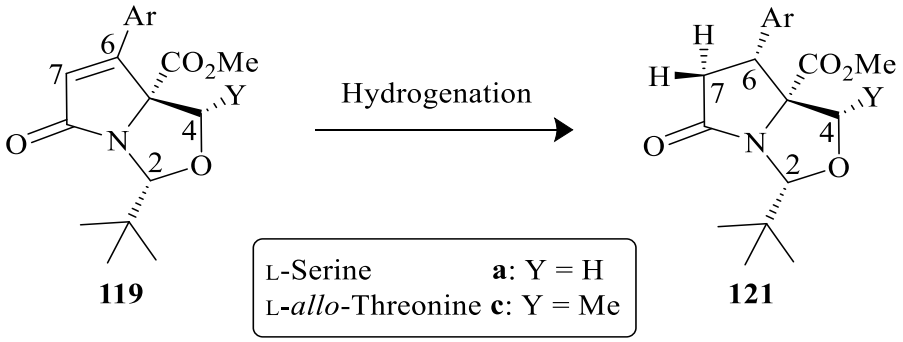
119aiv: X = CHO
119av : X = Cl

121aiv: X = CH_2OH (76%)
121av : X = Cl (33%)

Scheme 2.17: Hydrogenation of **119aiv-av**

Interestingly, when the hydrogenation reaction was run for 1 h, it was possible to isolate 49% of **155** as inferred from LRMS analysis. The poor yields for **121aiii** and **121av** can be elucidated by the formation of by-products resulting from the hydrogenation of aromatic rings, which was detected in LRMS analysis (not shown for **121aiii**). The pyrrolidinone **156** was secured from **119av** under the reaction conditions by hydrogenolysis of the C-Cl bond and successive hydrogenation of aromatic ring. A more careful experiment could avoid the hydrogenation of aromatic rings which was discovered in the synthesis of similar analogues (**121ciii** and **121cv**) for the L-*allo*-threonine system. The high stereoselectivity was observed in all cases of the hydrogenation reactions. The stereochemistry of pyroglutamates **121ai-av** and **121ci-cv** were assigned by NOE analysis (Table 2.10).

Table 2.10: NOESY analysis of products **121ai-av** and **121ci-cv**



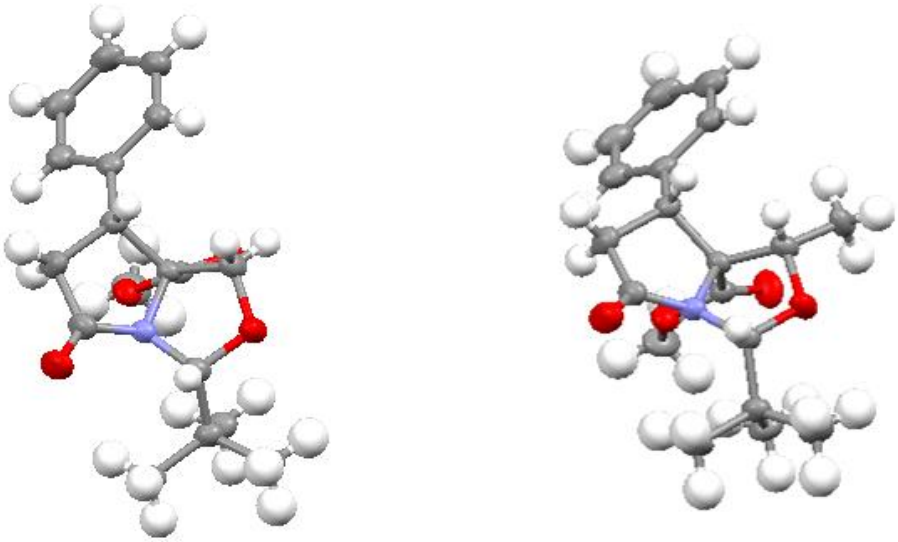
119 **121**

Sl No	Ar in 121	Products	Selected NOEs
1	**i**: 4-$OMeC_6H_4$	**121ai**	*endo*-H4-H6, *endo*-H4-H2, CO_2Me-ArH, *exo*-H7-^{t}Bu
		121ci	H4-H2, C(4)CH_3-ArH
2	**ii**: phenyl	**121aii**	*endo*-H4-H6, *endo*-H4-H2, CO_2Me-ArH, *exo*-H4-ArH
		121cii	H4-H2, H4-H6, *exo*-H7-H6
3	**iii**: 2-furyl	**121aiii**	*endo*-H4-H6, *endo*-H7-H2, *exo*-H7-ArH,
		121ciii	H4-H6, H4-H2

Continued….

4	**iv**: 4-	**121aiv**	*exo*-H7-ArH, *endo*-H7-H6
	$CH_2OHC_6H_4$	**121civ**	H4-H6, H4-H2, CO_2Me-ArH
5	**v**: 4-ClC_6H_4	**121av**	*exo*-H7-ArH, *endo*-H7-H6, *exo*-H4-ArH, CO_2Me-^{t}Bu
	cyclohexyl	**156**	*endo*-H4-H6, *exo*-H4-cyclohehexylH, *exo*-H7-^{t}Bu
	v: 4-ClC_6H_4	**121cv**	*exo*-H7-H6, H4-H2, H4-H6

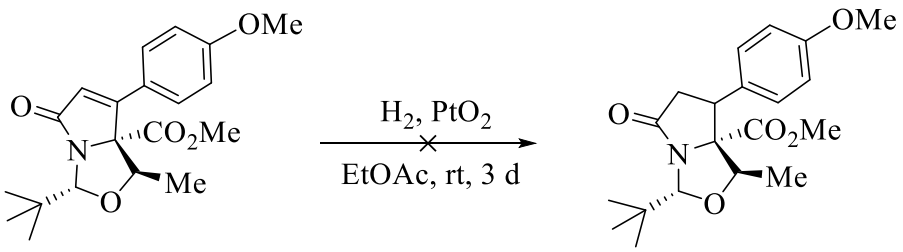
The relative configuration of hydrogenated products was further confirmed by X-ray crystal structures of **121aii** and **121cii (**Figure 2.7).



121aii **121cii**

Figure 2.7: X-Ray crystal structure of **121aii** and **121cii** (Ellipsoid Style)

Conversely, hydrogenation of **119bi** was attempted which was unsuccessful and unreacted starting material was recovered quantitatively (Scheme 2.18). This abortive result confirms convincingly the considerable steric obstruction of the C4-methyl group in L-threonine system.



119bi **121bi**

Scheme 2.18: Unsuccessful hydrogenation reaction in L-threonine system

2.5.2 Stereoselectivity in the Hydrogenation Reaction

The stereoselective hydrogenation is understandable since the bicyclic core is not planar as confirmed by the X-ray crystal structure of related compounds (see Figure 2.6). The bulky *tert*-butyl group, methyl ester and the lone pair of electrons on nitrogen atom are located on the *exo*-face of the bicyclic template which facilitate binding of the catalyst surface at the *endo*-face (Figure 2.8). The lack of reactivity of **119bi** for hydrogenation reaction is also manifestly reasonable. In L-threonine derived adduct **119bi**, the methyl group is located to the *endo*-face which is bulky compared to hydrogen for the other two systems and the *exo*-face is already hindered. The steric impact thwarts binding at the catalyst surface from either up or down side of the bicyclic core in the L-threonine system.

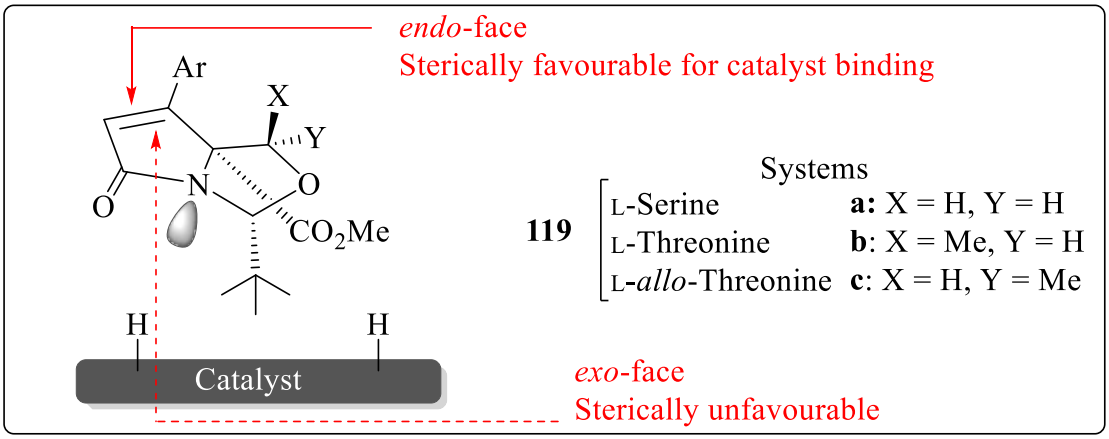
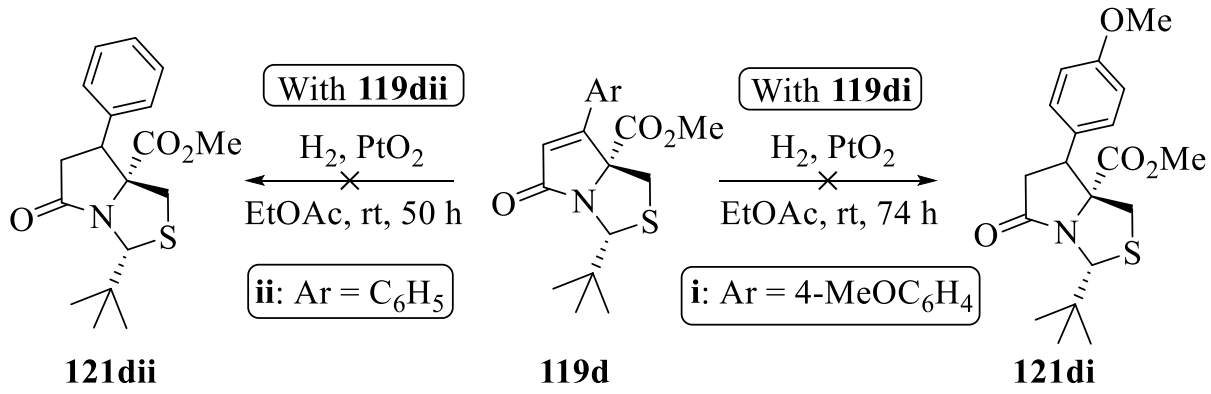


Figure 2.8: Catalyst binding pathways for hydrogenation in *O*-system

2.5.3 Hydrogenation: *S*-System

The same conditions with H_2 and PtO_2 catalyst were applied for the hydrogenation of **119d** (Scheme 2.19), but unfortunately this reaction was not successful. Although LRMS analysis of reaction mixtures after around 40 hours witnessed peaks for **121di** or **121dii**, the NMR spectrum for crude material did not show signals for expected product. Flash column chromatography was attempted for **121di**, but only unreacted starting material was recovered. It was surmised that the lone pairs on sulfur poisoned and deactivated the Pt catalyst.



Scheme 2.19: Attempted hydrogenation reactions for **119di-dii**

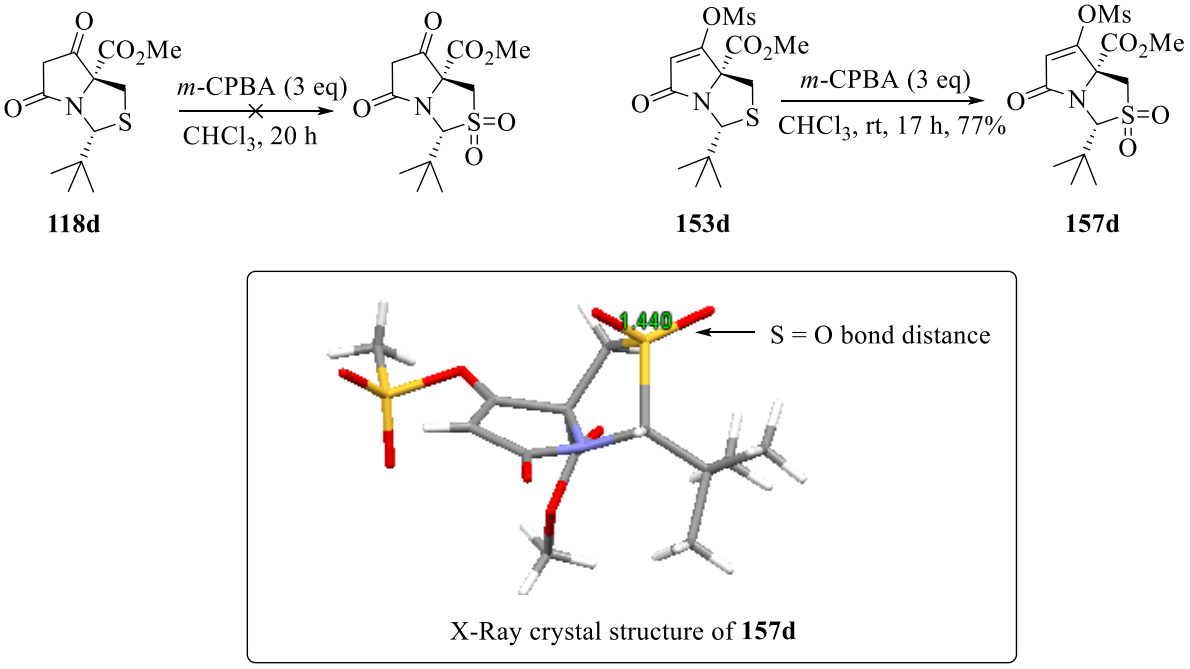
2.6 Exploration of Cysteine-Derived Pyroglutamates

It was an insatiable interest to investigate the hydrogenation of sulfone analogues which no longer have lone pair electrons on sulfur. This could facilitate hydrogenation and accordingly could give access to pyrrolidinone derivatives for the *S*-system.

2.6.1 Preparation of Sulfone Analogues

Keith *et al.*[153] reported the conversion of the sulfur to sulfone system in lactams by using *m*-chloroperbenzoic acid (*m*-CPBA). Firstly, tetramate **118d** was treated with *m*-CPBA at room

temperature (Scheme 2.20). Attempted oxidation resulted in poor yields for crude materials. Although LRMS analysis strongly suggested product formation, it was not possible to identify product signals in NMR analysis of the crude mixture, nor isolate sulfone from **118d**. The reason can be interpreted by the high polarity of product which prevented its isolation on silica. Secondly, it was assumed the difficulty could be avoided if the conversion commenced from mesylate **153d**. The application of *m*-CPBA oxidation to **153d** furnished expected product **157d** in 77% yield. The formation of sulfone **157d** was confirmed by single-crystal X-ray diffraction analysis.

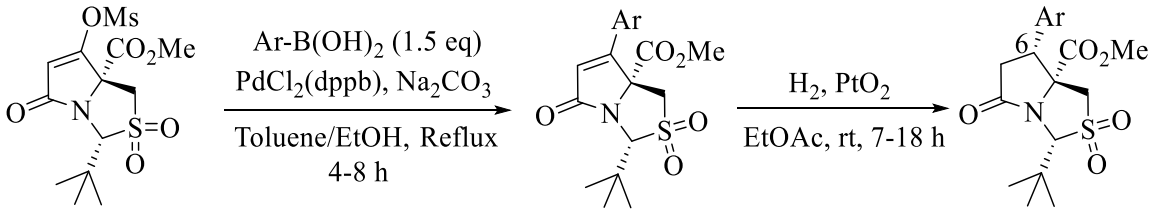


Scheme 2.20: Synthesis and X-ray crystal structure of cysteine derived sulfone **157d**

The sulfone **157d** was treated exerting the optimal conditions for Suzuki coupling (Table 2.11). Interestingly, the yields for sulfone adducts **158di-dv** were consistent with the *S*-analogues **119di-dv**, which reflected the tremendous effectiveness of coupling in a highly constrained and functionalised system. With mesylate **157d**, the formation of by-product **160** was also observed for the Suzuki coupling with 4-chlorophenylboronic acid. Finally, the adducts **158di-dv** were subjected to hydrogenation and pleasingly this time hydrogenation

proceeded diastereoselectively for all sulfone analogues. The highly functionalised pyroglutamate derivatives **159di-dv** were achieved in satisfactory yields. The low yield for **159diii** could be reasoned by the formation of dearomatized by-product (not shown here). The key results for the Suzuki coupling and hydrogenation reactions, and representative values for **158di-dv** and **159di-dv** are summarised in Table 2.11.

Table 2.11: Key results from Suzuki coupling of sulfone **157d** and subsequent hydrogenation



157d **158di-dv** **159di-dv**

Sl No	Ar	Products, Yield	δ_{H6} (ppm)	δ_{H7} (ppm)	$[\alpha]_D^{25}$ (*c* 1.0 in DCM)
1	**i**: 4-OMeC_6H_4	**158di**, 56%	-	6.52	+129.2
	i: 4-OMeC_6H_4	**159di**, 83%	3.79	2.57, 3.26	-87.6
2	**ii**: C_6H_5	**158dii**, 53%	-	6.65	+132.3
	ii: C_6H_5	**159dii**, 82%	3.84	2.60, 3.32	-89.8
3	**iii**: 2-furyl	**158diii**, 20%	-	6.47	+88.3
	iii: 2-furyl	**159diii**, 37%	3.90	2.62, 3.18	-65.1
4	**iv**: 4-CHOC_6H_4	**158div**, 26%	-	6.80	+103.0
	iv: 4-CH_2OHC_6H_4	**159div**, 54%	3.82	2.54, 3.29	-72.7
5	**v**: 4-ClC_6H_4	**158dv**, 48%	-	6.65	+105.4
	4'-Cl[1,1'-C_6H_4]	**160**, 8%	-	6.70	+70.2
	v: 4-ClC_6H_4	**159dv**, 77%	3.81	2.60, 3.26	-65.1

The stereochemistry of the newly formed chiral centre C6 was assigned by NOESY analysis which conveyed a strong NOE among *endo*-H4-H6-H2 for all synthesised products in this series. The relative stereochemistry was further confirmed by the X-ray crystal structure of **159dv** (Figure 2.9).

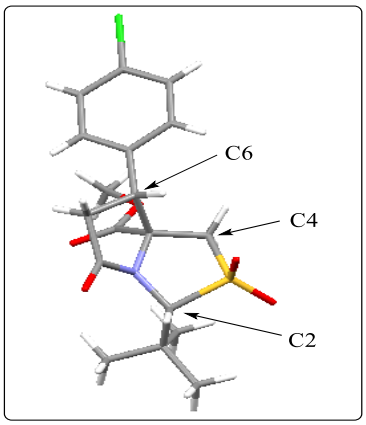
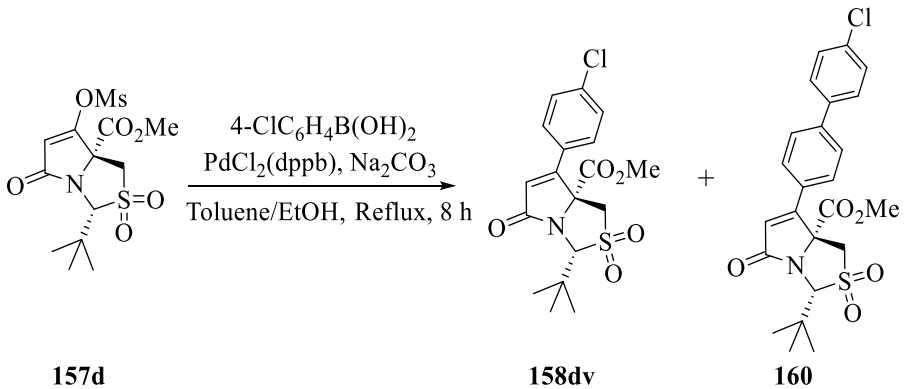


Figure 2.9: X-Ray crystal structure of **159dv** (Capped Sticks style)

Of interest, Suzuki coupling of **157d** was tested with different numbers of equivalents of 4-chlorophenylboronic acids which gave increased yields of adduct **160** for higher quantities of boronic acid (Scheme 2.21).



157d **158dv** **160**

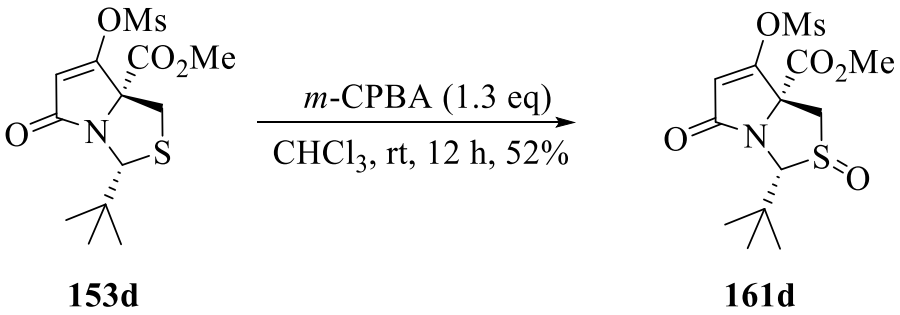
157d: 4-$ClC_6H_4B(OH)_2$	**158dv,** Yield	**160,**Yield
1:1.05	**48%**	8%
1:1.50	31%	10%
1:2.05	31%	**16%**

Scheme 2.21: Effect of the increased equivalent of boronic acid on Suzuki coupling

The reaction condition were not optimised for the achievement of maximum yield for **160**. However, this experiment presented an indication of the usefulness of this process to further coupling with other boronic acids.

2.6.2 Preparation of Sulfoxide Analogues

Given the successful hydrogenation of **158di-dv**, it was decided to synthesise sulfoxide analogues to further inspect the poisoning effect of lone pair electrons on the sulfur atom in hydrogenation reactions. For the preparation of sulfoxide, the mesylate **153d** was subjected to oxidation with a limited amount of *m*-CPBA. Among the attempted conditions, entry 2 produced sulfoxide **161d** in a maximum yield of 52% (Scheme 2.22).



153d **161d**

Sl No	**153d**:*m*-CPBA	**161d**, Yield
1	1:1.0	34% (+ 19% unreacted **153d**)
2	1:1.3	52%
3	1:1.5	39% (+ sulfone **157d**)

Scheme 2.22: Optimisation of reaction conditions for the synthesis of cysteine derived sulfoxide **161d**

The reaction proceeded with a high degree of stereoselectivity to yield a single diastereomer of **161d**. The structure was determined by X-ray crystallography, in which the chiral sulfoxide group was positioned towards the *endo*-face of the bicyclic ring system (**A**, Figure

2.10). The bulky *tert*-butyl group and bicyclic core structure played a pivotal role in the diastereoselectivity observed during the preparation of **161d**.

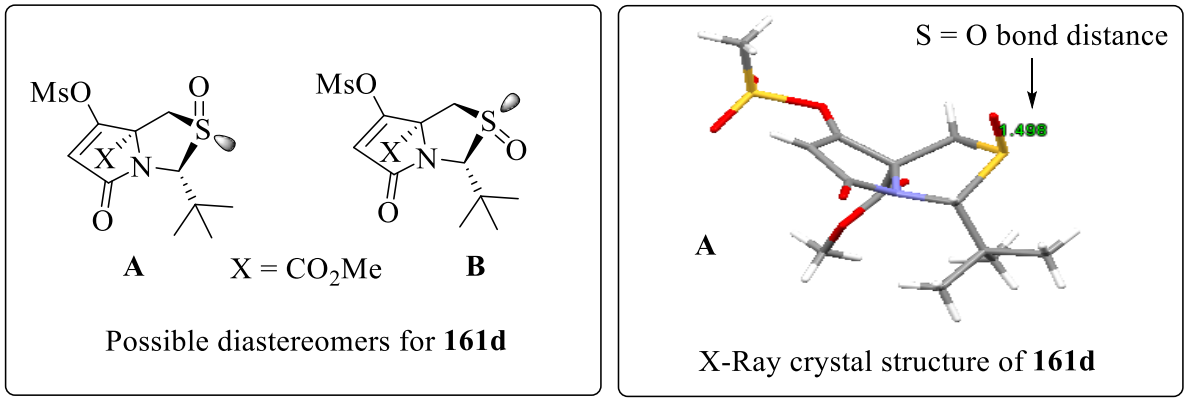
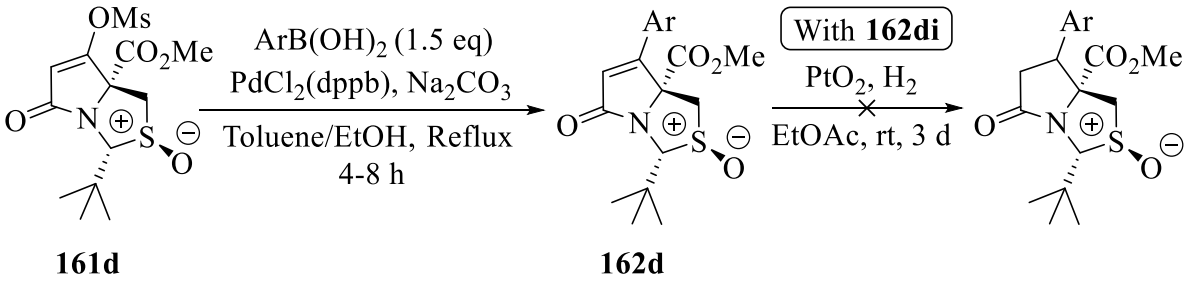


Figure 2.10: Structure determination of chiral sulfoxide **161d**

Suzuki coupling of sulfoxide **161d** with boronic acids offered the adducts **162d** but less efficiently (Scheme 2.23). It was suspected that the *endo*-face suffered from more steric hindrance caused by the *endo*-sulfoxide positioned close to C6. The steric effect can be evidenced by the comparison of S=O bond distance which is 1.440 Å in **157d** (see Scheme 2.20) and 1.498 Å in **161d** as measured from the X-ray crystal structures (Figure 2.10).



161d **162d**

Products	Yield
162di : Ar = 4-$MeOC_6H_4$	18%
162dii : Ar = C_6H_5	18%
162dv : Ar = 4-ClC_6H_4	8%

Scheme 2.23: Suzuki coupling and attempted hydrogenation of sulfoxide

The structure of sulfoxide adduct **162di** was confirmed by the X-ray crystal structure (Figure 2.11).

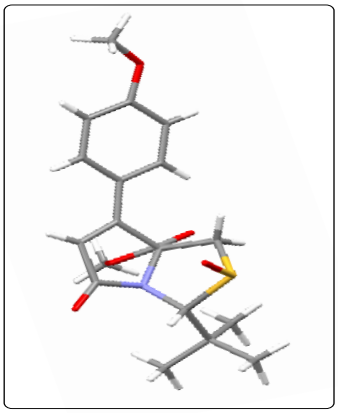


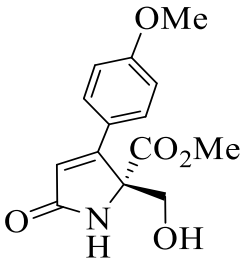
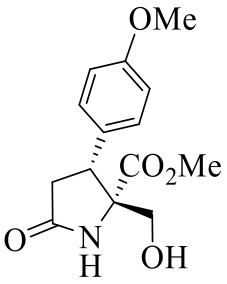
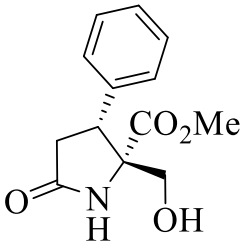
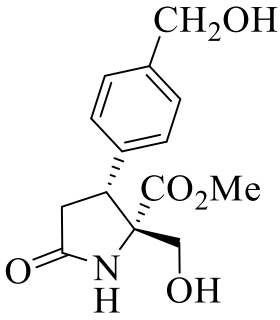
Figure 2.11: X-Ray crystal structure of **162di** (Capped Sticks style)

Attempted hydrogenation of **162di** resulted in quantitative recovery of starting material (Scheme 2.23). This unproductive result was coherent with the previous assumption that the lone pair electrons on sulfur was poisoning the catalyst and deactivated the hydrogenation reaction.

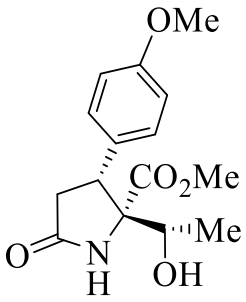
2.7 *N,O*-Acetal Deprotection

Having prepared a diverse library of C3-arylated (considering lactam ring) pyrrolinone, pyrrolidinone, and pyroglutamate derivatives, it was of paramount importance to extend their synthetic utility. Application of Corey-Reichard protocol[104] to representative analogues efficiently removed the *N,O*-protecting group (Table 2.12). Pyrrolinone, pyrrolidinone or pyroglutamate derivatives were treated with 1,3-propanedithiol and 1.5% HCl in 2,2,2-trifluoroethanol, which resulted in direct access to highly functionalised 3-arylpyrrolinone **163** and 3-aryl pyrrolidinones/pyroglutamates/pyroglutaminols **164-167**. However, hydrolysis of the *N,S*-protecting group was not effective following the same conditions.

Table 2.12: *N,O*-Acetal deprotection (condition: propane-1,3-dithiol, 1.5% solution of HCl in CF_3CH_2OH, rt, 30-36 h)

Sl No	Propane-1,3-dithiol	Entry	Product	Yield (%)
1	2.1 eq	**119ai**	**163** 	94
2	2.3 eq	**121ai**	**164** 	80
3	2.3 eq	**121aii**	**165** 	79
4	2.3 eq	**121aiv**	**166** 	90

Continued.....

5	2.3 eq	**121ci**	**167**		81
6	2.3 eq	**119dv**	-	-	Unreacted SM recovered

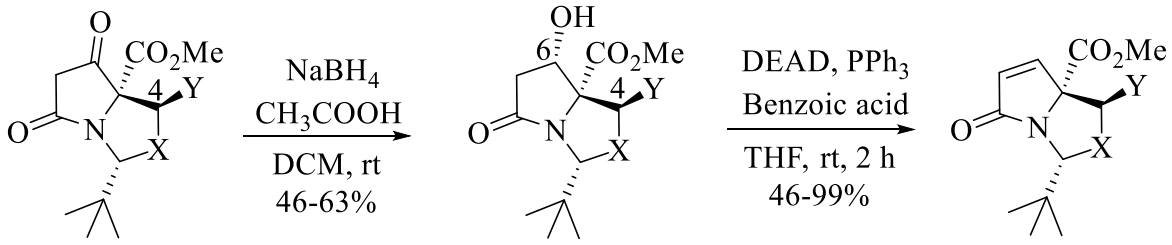
SM = starting material

2.8 Towards Functionalisation at C6 of Tetramates: Part 2

It was of interest to see if an ester functionality could be introduced at C6 of tetramates **118**, which would allow further elaboration at C6 and would access a range of C3-substituted pyroglutamates.

2.8.1 Preparation of Unsaturated Lactam

Josa-Cullere *et al.*[142] reported the diastereoselective reduction of bicyclic tetramates **118**, derived from serine, threonine, and cysteine. Stereoselective reduction of tetramates **118** with $NaBH_4$ and acetic acid furnished alcohols **168** (Scheme 2.24).



118 **168** **169**

Scheme 2.24: Reduction of tetramic acids **118** (**a**: X = O, Y = H; **b**: X = O, Y = Me; **d**: X = S, Y = H)

In accordance with literature, C6 epimers were not noticed. The alcohols **168a-b,d** were converted to alkene **169a-b,d** following a literature procedure.[142] The conversions were efficient for serine and cysteine systems. For **168b** and **169b**, yields were low which can be explained by the steric effect exerted by the C4-Me group (Table 2.13).

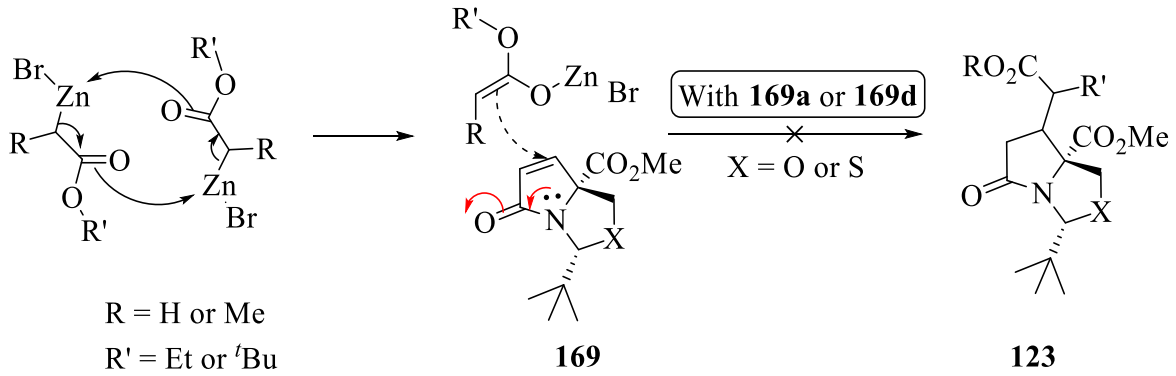
Table 2.13: The conversion of tetramic acid **118** to enone **169**

	Sl No	Entry	Reduction 168, Yield (%)	Formation of Alkene 169, Yield (%)
a: X = O, Y = H	1	**118a**	96	99
b: X = O, Y = Me	2	**118b**	46	49
d: X = S, Y = H	3	**118d**	84	98

2.8.2 Attempted C6-Functionalisation by Conjugate Addition

In the light of the possibility of conjugate addition, it was expected that enamide of the type **169** would be useful as a substrate for Reformatsky conjugate addition.

Application of Bentz's conditions[134] to **169a** or **169d** with ethyl bromoacetate resulted quantitative recovery of starting material (Scheme 2.25).



Scheme 2.25: Attempted Reformatsky conjugate additions

Alternatively, attempted conjugate additions of **169a** with ethyl bromoacetate or *tert*-butyl-2-bromopropanoate using a literature protocol[154] were also unsuccessful. These abortive results suggested forcibly that the enamide **169** is not activated enough to attack intermediate zinc enolates for Reformatsky conjugate addition. Delocalisation of the N-lone pair electrons, as indicated by the red arrow, could be the prime reason for this inactivity. The results are summarised in Table 2.14.

Table 2.14: Attempted Reformatsky conjugate additions

Sl No	Entry	Reagents Reaction Conditions	Comment
1	**169a**	Ethyl bromoacetate DMPU, I_2, Zn, THF, rt, 24 h	**169a** recovered
2	**169a**	Ethyl bromoacetate I_2, Zn, THF, reflux, 18 h	**169a** recovered
3	**169d**	Ethyl bromoacetate DMPU, I_2, Zn, THF, rt, 24 h	Ethyl bromoacetate recovered
4	**169a**	*tert*-Butyl 2-bromopropanoate I_2, Zn, THF, reflux, 18 h	**169a** recovered

2.9 Antibacterial Screening

The synthesised compounds were tested for antibacterial activity against following Gram-negative and Gram-positive bacteria:

1. *Escherichia coli* (EC 34)
2. *Klebsiella pneumoniae* (KL 18)

3. *Pseudomonas aerogenosa* (PS 23)
4. Methicillin resistant *Staphylococcus aureus* (MRSA 1)
5. Methicillin resistant *Staphylococcus aureus* (MRSA 2)

Disappointingly, all of them showed very little or no activity (Table 2.15). The test method is provided in Appendix D.

Table 2.15: MIC values for the screening of compounds synthesised in Chapter 2 against several pathogens

Sl No	Compound	Gram-negative bacteria			Gram-positive bacteria	
		EC 34	KL 18	PS 23	MRSA 1	MRSA 2
1	**119ai**	n. a.	n. a.	n. a.	n. a.	n. a.
2	**119aii**	n. a.	n. a.	n. a.	n. a.	n. a.
3	**119aiii**	n. a.	n. a.	n. a.	n. a.	n. a.
4	**119aiv**	n. a.	n. a.	n. a.	n. a.	n. a.
5	**119av**	n. a.	n. a.	n. a.	n. a.	n. a.
6	**119avi**	n. a.	n. a.	n. a.	n. a.	n. a.
7	**119avii**	n. a.	n. a.	n. a.	n. a.	n. a.
8	**119bi**	n. a.	n. a.	n. a.	n. a.	n. a.
9	**119ci**	n. a.	n. a.	n. a.	n. a.	n. a.
10	**119cii**	n. a.	n. a.	n. a.	n. a.	n. a.
11	**119ciii**	n. a.	n. a.	n. a.	n. a.	n. a.
12	**119civ**	n. a.	n. a.	n. a.	31.25 µg/mL	15.63 µg/mL
13	**119cv**	n. a.	n. a.	n. a.	n. a.	n. a.
14	**154**	n. a.	n. a.	n. a.	n. a.	n. a.

Continued….

15	**119di**	n. a.	n. a.	n. a.	n. a.	n. a.
16	**119dii**	n. a.	n. a.	n. a.	n. a.	n. a.
17	**119diii**	n. a.	n. a.	n. a.	n. a.	n. a.
18	**119div**	n. a.	n. a.	n. a.	15.63 µg/mL	15.63 µg/mL
19	**119dv**	n. a.	n. a.	n. a.	n. a.	n. a.
20	**119dvi**	n. a.	n. a.	n. a.	n. a.	n. a.
21	**119dvii**	n. a.	n. a.	n. a.	n. a.	n. a.
22	**121ai**	n. a.	n. a.	n. a.	n. a.	62.00 µg/mL
23	**121aii**	n. a.	n. a.	n. a.	n. a.	n. a.
24	**121aiii**	n. a.	n. a.	n. a.	n. a.	n. a.
25	**121aiv**	n. a.	n. a.	n. a.	n. a.	n. a.
26	**121av**	n. a.	n. a.	n. a.	n. a.	n. a.
27	**121ci**	n. a.	n. a.	n. a.	n. a.	n. a.
28	**121cii**	n. a.	n. a.	n. a.	n. a.	n. a.
29	**121ciii**	n. a.	n. a.	n. a.	n. a.	n. a.
30	**121civ**	n. a.	n. a.	n. a.	n. a.	n. a.
31	**121cv**	n. a.	n. a.	n. a.	n. a.	n. a.
32	**155**	n. a.	n. a.	n. a.	n. a.	n. a.
33	**156**	n. a.	n. a.	n. a.	n. a.	n. a.
34	**158di**	n. a.	n. a.	n. a.	n. a.	n. a.
35	**158dii**	n. a.	n. a.	n. a.	n. a.	n. a.
36	**158diii**	n. a.	n. a.	n. a.	n. a.	n. a.
37	**158div**	n. a.	n. a.	n. a.	n. a.	n. a.
38	**158dv**	n. a.	n. a.	n. a.	n. a.	n. a.

Continued….

39	**159di**	n. a.	n. a.	n. a.	n. a.	n. a.
40	**159dii**	n. a.	n. a.	n. a.	n. a.	n. a.
41	**159diii**	n. a.	n. a.	n. a.	n. a.	n. a.
42	**159div**	n. a.	n. a.	n. a.	n. a.	n. a.
43	**159dv**	n. a.	n. a.	n. a.	n. a.	n. a.
44	**160**	n. a.	n. a.	n. a.	n. a.	n. a.
45	**162di**	n. a.	n. a.	n. a.	n. a.	n. a.
46	**162dii**	n. a.	n. a.	n. a.	n. a.	n. a.
47	**162dv**	n. a.	n. a.	n. a.	n. a.	31.25 µg/mL
48	**163**	n. a.	n. a.	n. a.	n. a.	n. a.
49	**164**	n. a.	n. a.	n. a.	n. a.	n. a.
50	**165**	n. a.	n. a.	n. a.	n. a.	n. a.
51	**166**	n. a.	n. a.	n. a.	n. a.	n. a.
52	**167**	n. a.	n. a.	n. a.	n. a.	n. a.

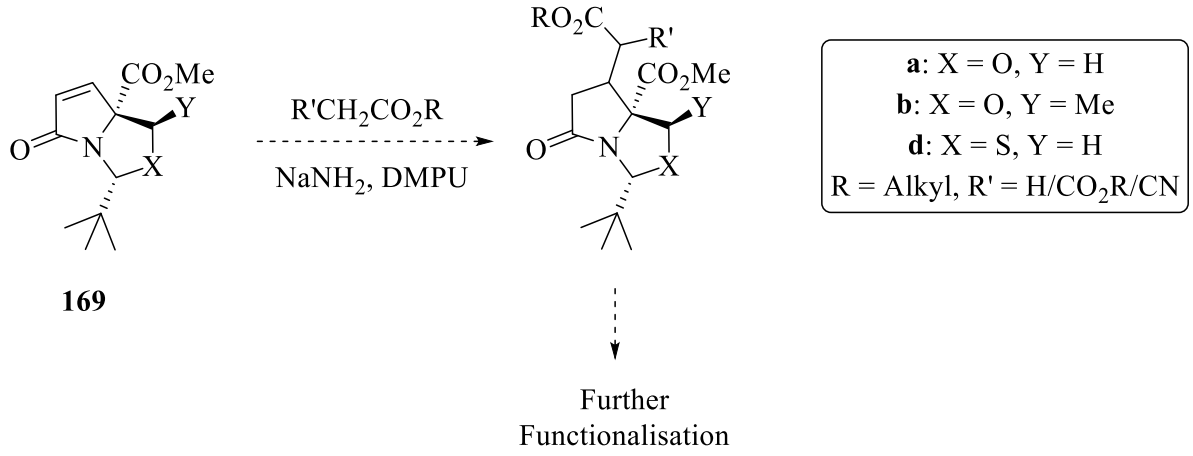
n. a. = not active

2.10 Summary and Future Works

An efficient methodology was developed for the conversion of tetramates to pyroglutamic acid derivatives. The required bicyclic tetramates were prepared using the literature protocol. It was shown that the C6 position of bicyclic tetramates derived from L-serine, L-threonine, L-*allo*-threonine, and L-cysteine can be arylated applying Suzuki coupling conditions with different boronic acids. An extensive library of 6-aryl pyrrolinones was synthesised. However, coupling was less efficient for the L-threonine system because of the steric hindrance caused by the *endo*-methyl group.

The synthetic utility of the established method was explored conveniently by the removal of the C6-C7 double bond via highly stereoselective hydrogenation of pyrrolinones, with exceptions in the L-threonine and L-cysteine systems. L-Threonine-derived 4-methoxyphenyl adduct was found to be unreactive towards hydrogenation or sodium borohydride reduction, again because of the steric hindrance in both faces of the bicyclic tetramate core. For the *S*-system, removal C6-C7 of the double bond by hydrogenation reaction was not possible, notwithstanding that synthesis of sulfone analogues allowed hydrogenation for this system. The lone pair on sulfur poisoned the PtO_2 catalyst, which was further scrutinised by the examination of hydrogenation for sulfoxide analogues. Interestingly, a single diastereomer was obtained for sulfoxide. The bulky *tert*-butyl group played vital role in the stereoselectivity for a number of chemical transformations.

The generated C6-arylated pyrrolinones, pyrrolidinones or pyroglutamates were efficiently converted to 3-arylpyroglutaminols by *N,O*-acetal deprotection. This conversion permitted remarkable access from tetramates to highly functionalised derivatives of 3-arylpyrrolinone, 3-arylpyroglutamate, 3-arylpyrrolidinone, and 3-arylpyroglutaminol. However, the same conditions did not function at all for the *S*-system and further experiment could be required for removing *tert*-butyl protecting group in the *S*-system. Attempted Reformatsky conjugate addition conditions were unsuccessful for the enone. Stefanofsky conditions[135] could be the other option for the introduction of ester functionalities at the C6 position.



Scheme 2.26: Proposed future work for Chapter 2

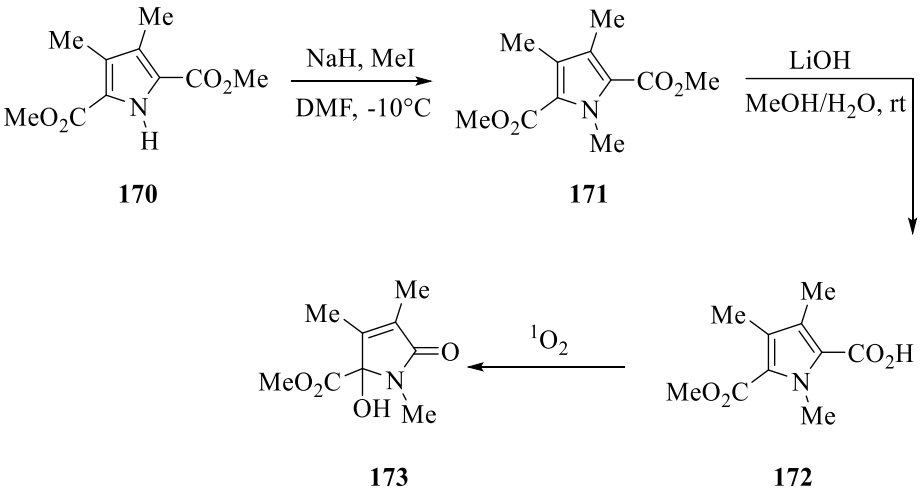
CHAPTER 3: A FACILE ROUTE TO 3,4-DISUBSTITUTED PYRROLINONES AND PYRROLIDINONES

3,4-Disubstituted pyrrolinones and pyrrolidinones are remarkable for their broad diversity of biological activities e.g. oxazolomycin (see Section 1.3.2) and pramanicin (see Section 1.3.3) exhibit antibacterial activities;[102,105,155] kainic acid is a potent neuroexcitatory agonist.[156,157] The development of a novel route for the synthesis of 3-arylpyroglutamic acid derivatives has been already discussed in Chapter 2. The current Chapter describes the use of the same methodology for the straightforward preparation of 3,4-disubstituted pyrrolinone, pyrrolidinone, and pyroglutamate derivatives. In addition, this Chapter describes the difficulties encountered for the attempted elaborations for C7 functionalities via ring systems substituted with ethyl esters or Weinreb amides.

3.1 Introduction

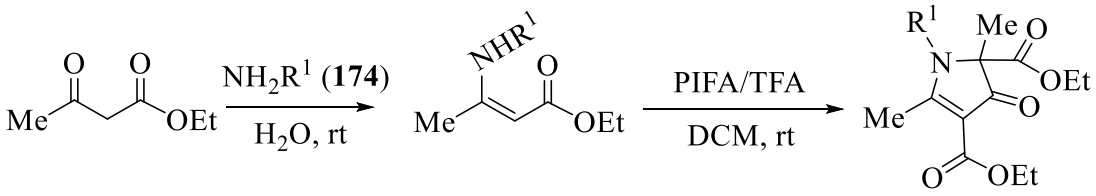
3.1.1 Previous Work for the Preparation of 3,4-Disubstituted Pyrrolinones

Boger and Baldino[158] reported the synthesis of 3,4-dimethyl pyrrolinones **173** via singlet oxygen ($^1O_2$) addition to 5-(methoxycarbonyl)pyrrole-2-carboxylic acid **172** (Scheme 3.1).



Scheme 3.1: Preparation of 3,4-dimethyl pyrrolinones **173** reported by Boger and Baldino[158]

The carboxylic acid **172** was developed by the treatment of 2,5-bis(methoxycarbonyl)-3,4-dimethylpyrrole **170** with MeI and subsequent mono-hydrolysis of resulting diester **171**. While this is a short approach to substituted pyrrolinones, it does not have the capacity to allow easy substituent variation. As an alternative, the Moloney group previously explored access to 3,4-disubstituted pyroglutamic acid derivatives via Reformatsky conjugate addition to bicyclic acylated lactam **82** (see Scheme 1.18, Chapter 1).[118] Furthermore, Huang and co-workers[159] described the synthesis of 3,4-disubstituted pyrrolinone derivatives **177a-b** via phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated cyclisation of enaminones **176a-b** which were easily obtained from 1,3-dicarbonyl compound **175** and amines **174a-b** (Scheme 3.2).



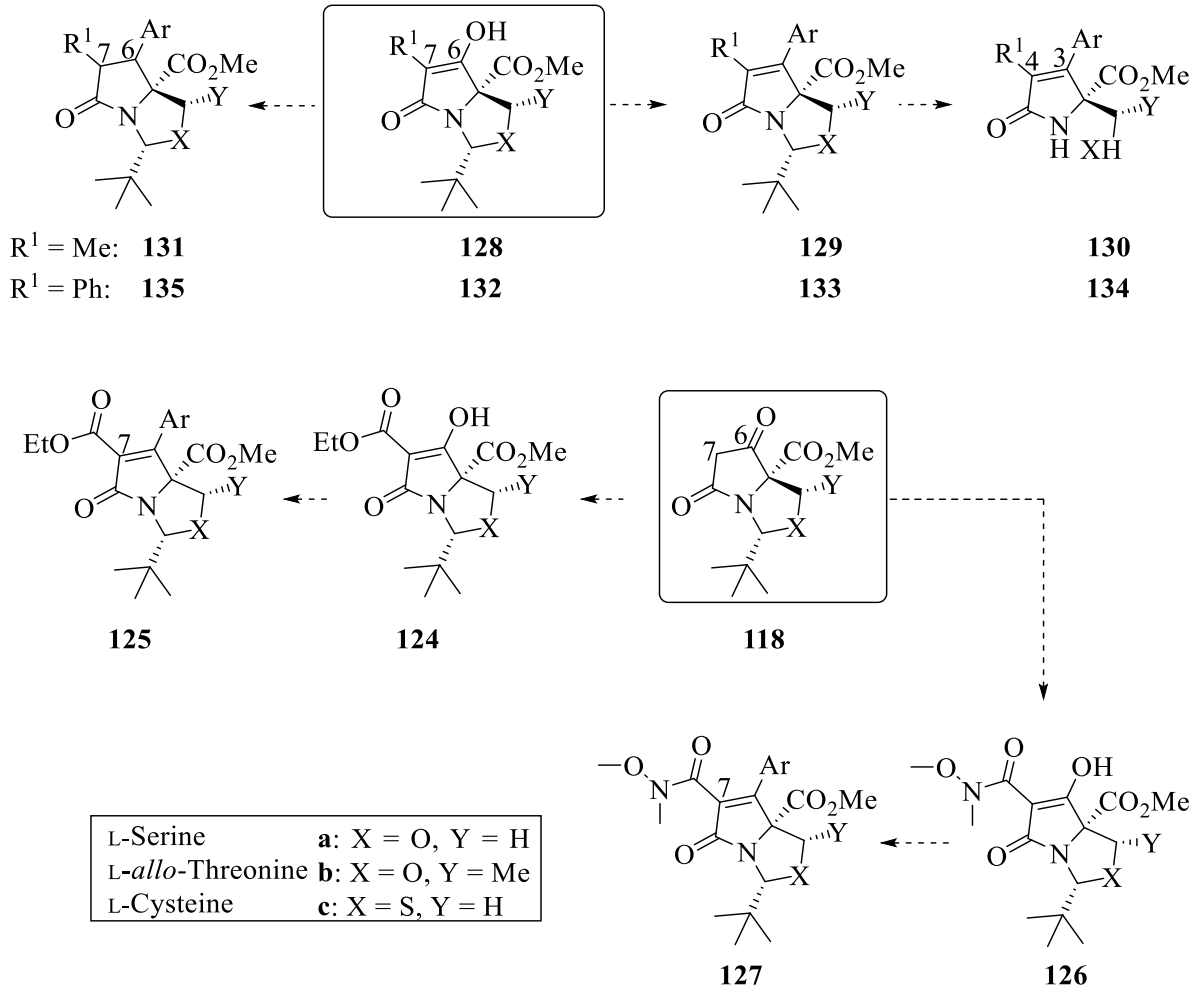
Entry	R^1	177, Yield
176a	Me	59%
176b	Bn	68%

Scheme 3.2: Synthesis of 3,4-disubstituted pyrrolinone derivatives **177a-b** by Huang and co-workers[159]

The preparation of 3,4-disubstituted pyrrolinones or pyroglutamic acid derivatives has been less studied, and only a few examples have been reported, which are outlined in this section (Scheme 3.1 and 3.2). However, no examples have been documented for the preparation of 3,4-diaryl or 3-aryl-4-methyl pyrrolinones or pyroglutamic acid derivatives. This encouraged the study and development of an efficient route to access these derivatives.

3.1.2 Synthetic Goals

The bicyclic tetramic acids **128** and **132** would be used as substrates for conversions leading to exceptionally functionalised derivatives (Scheme 3.3), and it was envisaged that mesylation and subsequent Suzuki coupling could afford a compatible route for the synthesis of highly functionalised 6,7-disubstituted bicyclic compounds **129** and **133**.



Scheme 3.3: Synthetic goals for Chapter 3

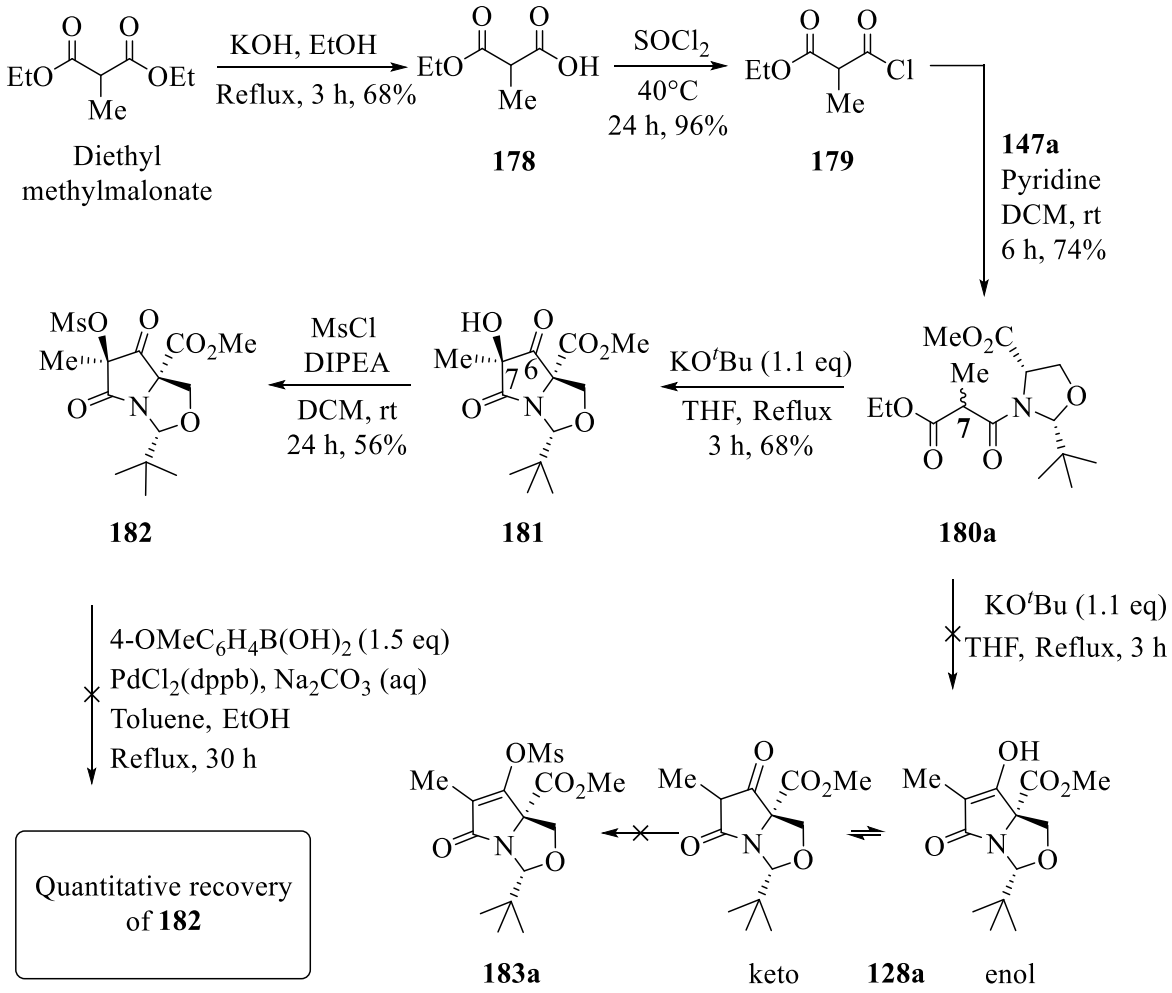
The coupling reactions which were chosen used 4-methoxyphenylboronic acid, phenylboronic acid, and 4-chlorophenylboronic acid, as these were found to be most effective for coupling with bicyclic mesylates **118** over other tested boronic acids (Chapter 2). Further treatment under hydrogenation conditions or *N*,*O*-acetal deprotection would

allow access to pyroglutamate derivatives **131** and **135** or highly functionalised pyroglutaminols **130** and **134**, respectively. The effect of further functionalisation would be investigated at C7 via ethyl ester tetramic acids **124** or Weinreb amides **126**. Because of the difficulties encountered for the L-threonine system, arising from unfavourable steric effects (see Chapter 2), the present Chapter will focus on L-serine (**a**), L-*allo*-threonine (**b**), and L-cysteine (**c**) -derived systems.

3.2 Towards C6 and C7 Functionalisation

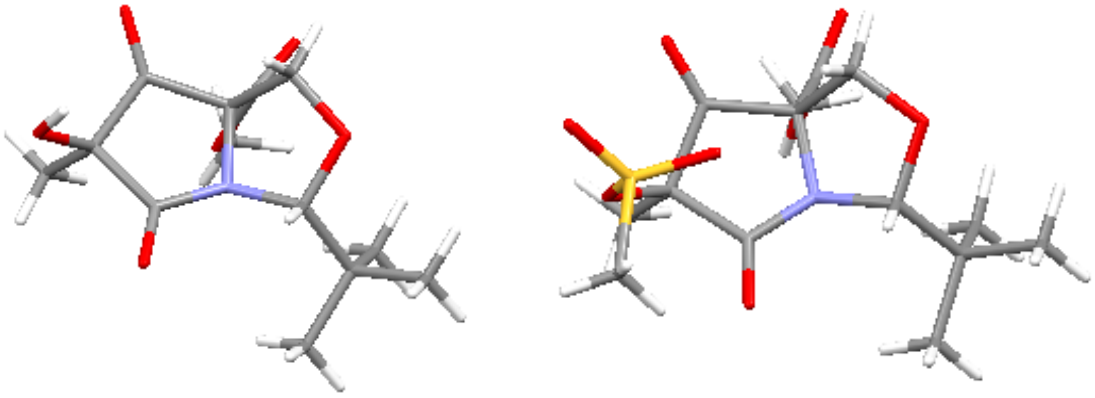
Following the success of C6 functionalisation of tetramic acids **118** described in Chapter 2, it was of interest to examine the similar conversions on the 7-methyltetramic acid **128**. The tetramic acid **128** exists as its enol tautomer and this was expected to facilitate the formation of its mesylate. Successive coupling and hydrogenation would permit the simpler route for the synthesis of pyroglutamate core unit **45** common to oxazolomycin and neooxazolomycin (see Figure 1.10, Chapter 1).

Danieli and coworkers[160] methodology was used for the conversion of diethyl methylmalonate to mono-acid **178** via basic hydrolysis and the treatment of **178** with thionyl chloride afforded acid chloride **179** (Scheme 3.4). Malonyl chloride **179** was then treated with serine-derived oxazolidine **147a** and pyridine to furnish *N*-acylated oxazolidine **180a** as a mixture of C7-epimers. The structure of **180a** was assigned in accordance with the reported work by Andrews *et al.*[131] Cyclisation of **180a**, under basic conditions using potassium *tert*-butoxide in THF, gave exclusively **181** instead of the desired tetramate **128a**. From the initial NMR analysis, it was thought the product **128a** (enol) had been formed, but the real outcome became evident when LRMS and HRMS analysis showed the presence of an additional oxygen atom in the molecular formula, consistent with structures **181** and its mesylated product **182**.



Scheme 3.4: Attempted C6 and C7 functionalisation for serine system

Finally, the structures of **181** and **182** were confirmed by single-crystal X-ray diffraction analysis (Figure 3.1). It was suspected that the tetramate **128a** that was formed first and subsequently oxidized to **181**. The phenomenon of auto-oxidation in C7-methyl tetramate **128a** had been earlier observed by Andrews and co-workers,[161] although interestingly auto-oxidation in that case had been slower, and led to the equivalent oxidation product only as a minor species. The attempted Suzuki coupling of **182** with 4-methoxyphenylboronic acid, sought before the correct structure had been made, resulted in quantitative recovery of starting material which was evident and consistent with the known lower reactivity of sp^3 centres in Suzuki processes.



181 **182**

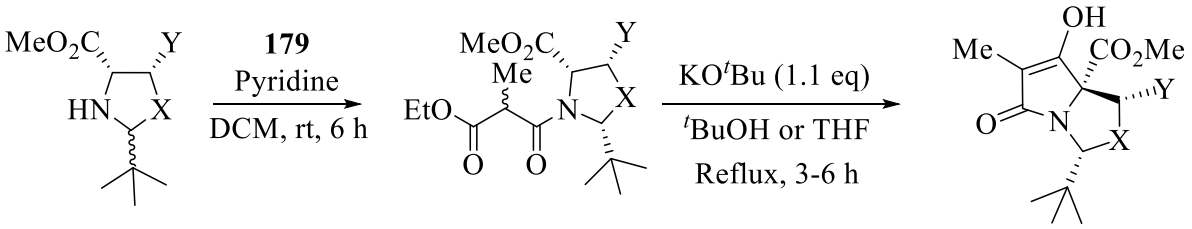
Figure 3.1: X-Ray crystal structure of **181** and **182** (Capped Sticks style)

Later, cyclisation of **180a** and mesylation of **128a** in quick succession, which would avoid aerial oxidation, was followed to achieve the desired mesylate **183a** (Section 3.3 and 3.4).

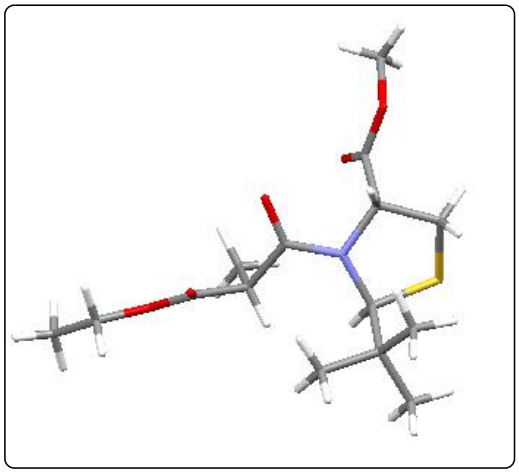
3.3 C6 and C7 Functionalised Pyrrolinones: Part 1

3.3.1 Synthesis of Bicyclic Tetramic Acids 128: C7-Me Derivatives

The oxazolidines **147** were produced via condensation of the respective amino acid and pivaldehyde using Seebach's protocol[162] (see Scheme 2.6, Chapter 2). Andrews and co-workers[138] discussed the synthesis of **128a** via basic conditions using potassium *tert*-butoxide in *tert*-butanol. The reported result was successfully reproduced and **128a** was obtained as a mixture of keto-enol tautomers. The alternative tetramates **128b-c** were also prepared applying the same conditions[138] and were found to exist as the enolic tautomers (Scheme 3.5) by NMR analysis. The malonamides **180a-b** were found to be an inseparable mixture of C7 epimers, whereas cysteine-derived malonamides were separable C2 epimers (**180c** and **180c'**). The malonamides **180b-c** were secured exclusively as the *cis*-2,5 diastereomer with the *7R* epimer as major, which was assigned by NOE analysis (Figure 3.2), whereas **180a** was characterised according to literature.[138]

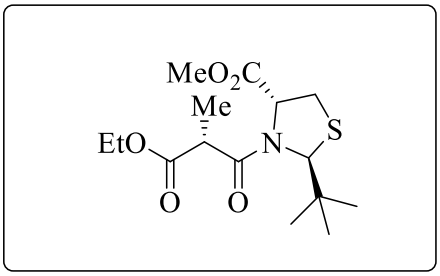


147a-c **180a-c** **128a-c**



X-ray crystal structure of **180c'**

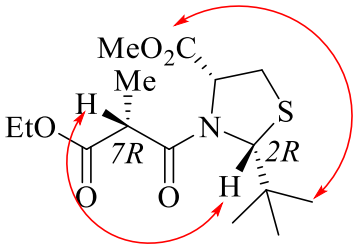
L-Serine **a**: X = O, Y = H
L-*allo*-Threonine **b**: X = O, Y = Me
L-Cysteine **c**: X = S, Y = H



180c', 27% (Minor)

Scheme 3.5: Preparation of C7-Me Tetramates **128a-c**

180b (Major) C7 Epimers **180b'** (Minor)



180c (Major)

Figure 3.2: NOE analysis for **180b-c**

For the L-cysteine system, the *7R* epimer of *trans*-2,5 diastereomer **180c'** was isolated as a minor product, and its structure was determined by X-ray crystal analysis (Scheme 3.5). This result indicated that a *trans*-2,5 diastereomer which was epimeric on the side chain could also be formed during the acylation of **147a-b** but it was impossible to detect or isolate the corresponding analogues for **180a-b**. Since the *cis*- and *trans*-2,5 diastereomers of malonamide cyclise with different chemoselectivities,[140] cyclisation of **180a-c** would result enantiomerically pure **128a-c**. The results for *N*-acylation and Dieckmann cyclisation are summarised in Table 3.1.

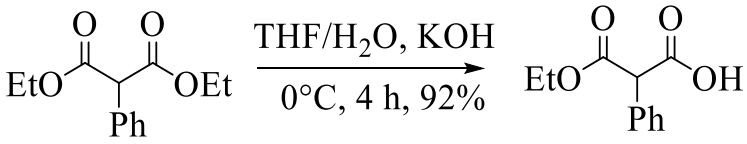
Table 3.1: The preparation of malonamides **180a-c** and tetramates **128a-c**

Sl No	Systems	Malonamides 180, Yield (%), Ratio		Tetramates 128	
		***cis*-2,5**	***trans*-2,5**	**Solvent**	**Yield**
1	L-Serine, **a**	74 (*7R*:*7S*, 2.2:1.0)	-	^{t}BuOH	82%
2	L-*allo*-Threonine, **b**	86 (*7R*:*7S*, 2.1:1.0)	-	^{t}BuOH	67%
3	L-Cysteine, **c**	71 (*7R*), 2.5	27 (*7R*), 1.0	THF	84%

3.3.2 Synthesis of Bicyclic Tetramic Acids 132: C7-Ph Derivatives

Initially, monohydrolysis of diethylphenyl malonate was performed via Danieli's protocol[160] which gave only 6% of mono-acid **184** (Table 3.2). Niwayama and co-workers[163,164] reported the selective monohydrolysis of diethylphenyl malonate but unfortunately this conversion was not reproducible using identical conditions with KOH or NaOH. The starting material was recovered almost exclusively in both cases. The reaction was repeated using increased base equivalent. Among the tested conditions, the use of 93 equivalents of 0.25 M aqueous Na_2CO_3 solution furnished mono-acid **184** in 92% yield.

Table 3.2: Reaction conditions tested for the preparation of mono-acid **184**



Diethylphenyl malonate **184**

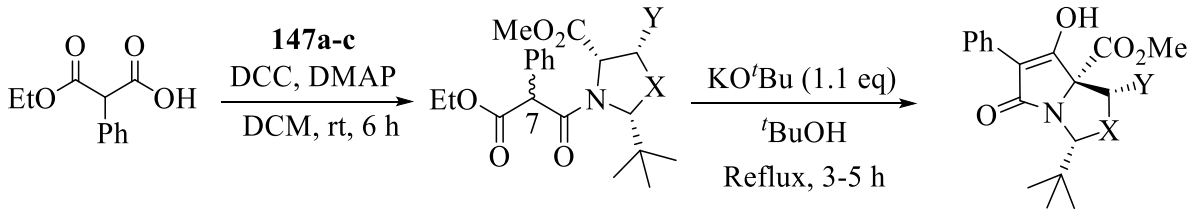
Sl No	Reaction Conditions	Yield of 184	Comments
1	KOH (1 eq), EtOH, reflux, 24 h	6%	57% SM recovered
2	KOH (1.2 eq of 0.25 M aq sol) THF:H_2O (10:1), 0°C, 28 h	-	Quantitative recovery of SM
3	NaOH (1.2 eq of 0.25 M aq sol) THF:H_2O (1:10), 0°C, 5 h	7%	82% SM recovered
4	KOH (120 eq of 0.25 M aq sol) THF:H_2O (10:1), 0°C, 2 h	69%	Diacid formed
5	KOH (93 eq of 0.25 M aq sol) THF:H_2O (10:1), 0°C, 2 h	86%	10% SM recovered
6	KOH (93 eq of 0.25 M aq sol) THF:H_2O (10:1), 0°C, 4 h	92%	-

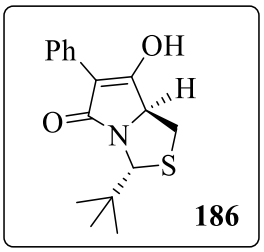
SM = starting material

Oxazolidines or thiazolidine **147**, prepared from the respective amino acid and pivaldehyde as detailed in Section 2.2, were acylated by DCC coupling[138] with ethyl α-phenylmalonic acid **184** to give malonamides **185a-c** predominantly as their *cis*-2,5 diastereomers (*7S*) (Table 3.3). The *trans*-2,5 diastereomer was detected as only a minor isomer for the malonamide derived from L-*allo*-threonine. The C2 stereochemistry for malonamides **185a-c** was assigned confidently by NOE analysis, whereas C7 stereochemistry was undetermined

as all of them showed an NOE between H5 and H7. Moreover, the presence of rotameric species, confirmed by 2D NOE gradient, made the assignment more complicated. Finally, crystals were grown from solid diastereomers and the stereochemistry of all diastereomers was then confirmed by analyzing their NOE spectrum in combination with the X-ray crystal structure (Figure 3.3). With the malonamides **185a-c** in hand, Dieckmann cyclisation[131] under basic conditions provided the formation of tetramic acids **132a-c** (Table 3.3).

Table 3.3: Preparation of malonamides **185a-c** and tetramic acids **132a-c**



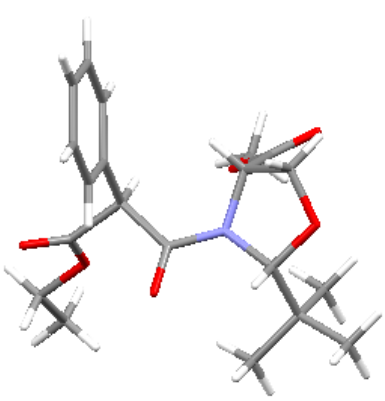


L-Serine **a**: X = O, Y = H
L-*allo*-Threonine **b**: X = O, Y = Me
L-Cysteine **c**: X = S, Y = H

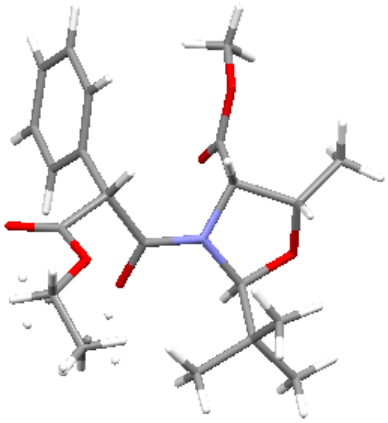
Sl No	Systems	Malonamide 185, Yield (%), Ratio		Tetramate 132	
		cis-2,5	*trans*-2,5	Solvent	Yield
1	L-Serine, **a**	88 (*7R*:*7S*, 1.0:2.0)	-	^{t}BuOH	82%
2	L-*allo*-Threonine, **b**	95 (*7R*:*7S*, 1.6:2.0) +	*7R*, 1.0	^{t}BuOH	70%
3	L-Cysteine, **c**	85 (*7R*:*7S*, 1.0:1.8)	-	^{t}BuOH	73%

For L-serine and L-*allo*-threonine systems, the desired tetramic acids **132a-b** were obtained. However, the L-cysteine system resulted an inseparable mixture of three different compounds, among which the desired tetramate **132c** was predominant. The formation of

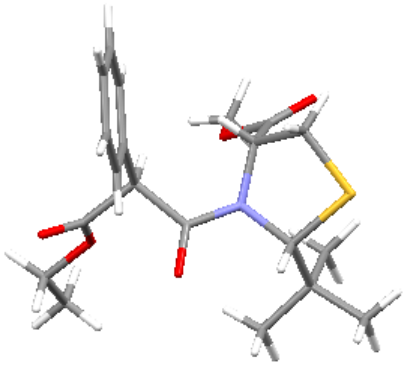
decarboxylated tetramate **186** was detected by ^{1}H NMR analysis and the third compound was not assigned as it showed very weak signals. Notably, the proton signal for methyl ester was absent for this minor compound.



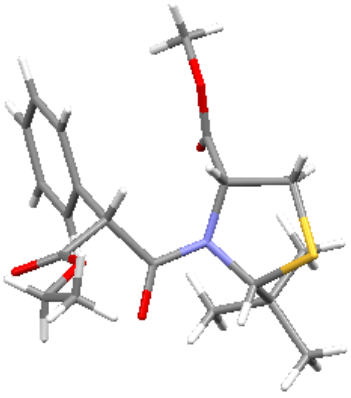
185a Major (*2R,7S*)



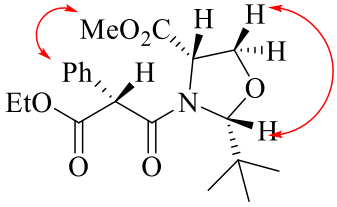
185b'' Minor (*2S,7R*)



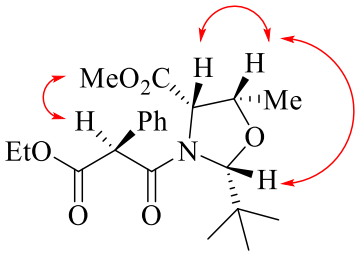
185c Major (*2R,7S*)



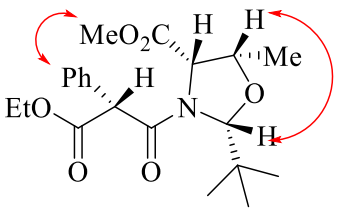
185c' Minor (*2R,7R*)



185a' Minor (*2R,7R*)



185b Major (*2R,7S*)



185b' (*2R,7R*)

Figure 3.3: The stereochemistry of malonamides **185** determined by NOE analysis and X-ray crystal structure

The stereochemistry of tetramic acids **132a-c** and **186** was assigned by NOE analysis (Figure 3.4).

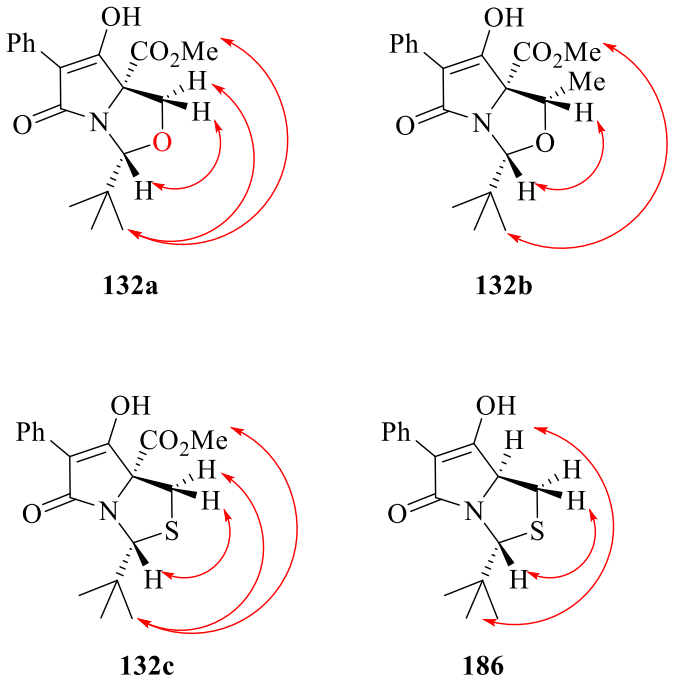


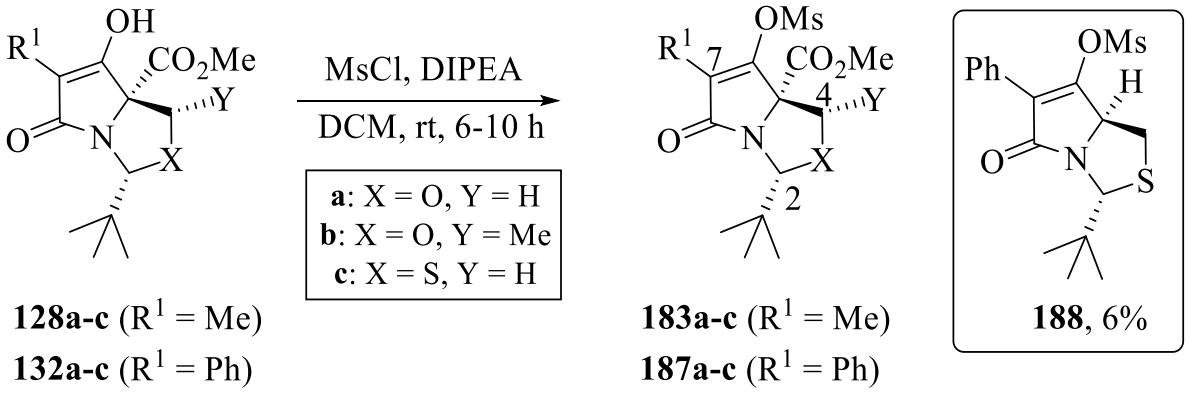
Figure 3.4: NOE analysis for bicyclic tetramic acids **132a-c** and **186**

3.4 Mesylation Reactions

Tetramic acids **128a-c** and **132a-c** were subjected to mesylation with methanesulfonyl chloride and *N*,*N*-diisopropylethylamine to furnish mesylates **183a-c** and **187a-c** in good to excellent yields (Table 3.4). Interestingly, the relevant mesylate **187c** and decarboxylated mesylate **188** were separable by flash column chromatography but were produced from an inseparable mixture of tetramates **132c** and **186**. The C7-Me/Ph derivatives **183a-c** and **187a-c** were prepared with improved yields compared to the analogous mesylates **153** (see Table 2.4, Chapter 2), and this might arise from the preferred enolic structure for tetramates **128** and **132**. For C7-Me derivatives **183a-c, 183b** was found in excellent yields compared to other two systems, **183a** and **183c**. The slightly lower yield for **183a** could be explained by the fact that the starting material **128a** was prone to auto-oxidation and the reason for lower

yields in the *S*-system could be the shape of the larger sulfur atom which caused steric hindrance in the bicyclic system.

Table 3.4: Mesylation of tetramic acids **128a-c** and **132a-c**



128a-c (R^1 = Me)
132a-c (R^1 = Ph)

183a-c (R^1 = Me)
187a-c (R^1 = Ph)

188, 6%

Sl No	Systems	C7-Me Derivatives **183, Yield**	C7-Ph Derivatives **187, Yield**
1	L-Serine, **a**	71%	71%
2	L-*allo*-Threonine, **b**	89%	64%
3	L-Cysteine, **c**	65%	64%

The structure of mesylate **183a** was confirmed by X-ray crystal structure (Figure 3.5).

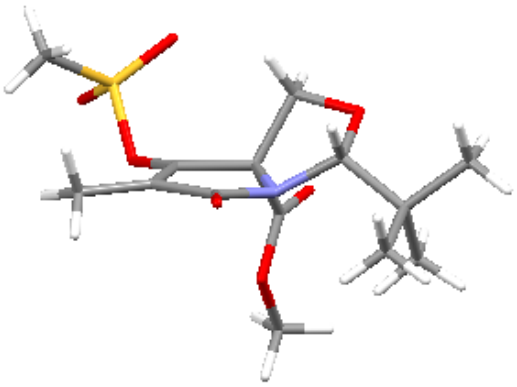


Figure 3.5: X-Ray crystal structure of **183a**

3.4.1 Isomerisation in Mesylates

The ^{1}H NMR analysis of most of the crude mesylates displayed a mixture of two compounds. Careful column chromatography allowed the isolation of by-products **189** and **190-191** and MS analysis identified them as isomers of the mesylates **183a** and **187b-c**, respectively. It was initially suspected that they were stereoisomers formed via slow C2 epimerisation under the basic reaction conditions. However, a large difference in chemical shift values was observed in ^{1}H NMR and ^{13}C NMR analysis (Table 3.5), and the H2 of **189** and **190-191** was deshielded by 0.39-0.43 ppm compared to **183a** and **187b-c**. The difference in chemical shift between *endo*-H4 and *exo*-H4 was significantly larger for products **183a** and **187c** than by-products **189** and **191**. Interestingly, a considerable difference in the chemical shift was noticed for aromatic protons. The δ_C C7 value was remarkably high in mesylates **183a** and **187b-c** compared to the other isomers **189-191**.

Table 3.5: Representative chemical shifts of products from the mesylation reactions

Sl No	Tetramic Acids	Products, Yield	Chemical Shifts δ (ppm)				
			H2	H4		ArH	C7
				H_A, H_B	Δ_{HB-HA}		
1	**128a**	**183a**, 63%	4.65	3.45, 4.74	1.29	-	125.6
		189, 7%	5.05	3.91, 4.73	0.82	-	79.1
2	**132b**	**187b**, 64%	4.71	3.87, -	-	7.32-7.38, 7.57	126.8
		190, 5%	5.10	4.19, -	-	7.36-7.42, 7.71-7.79	80.1
3	**132c**	**187c**, 64%	5.00	2.98, 3.73	0.75	7.31-7.41, 7.60-7.67	124.9
		191, 9%	5.43	3.25, 3.67	0.42	7.36-7.45, 7.80-7.85	82.8

Eventually, crystals were successfully generated for by-product **189** to reveal the structure, in which rearrangement of the mesylate functional group had occurred (Figure 3.6). The spectroscopic analysis of **190-191** was consistent to that of **189** which indicated that they also formed by rearrangement of respective mesylates **187b-c**, respectively.

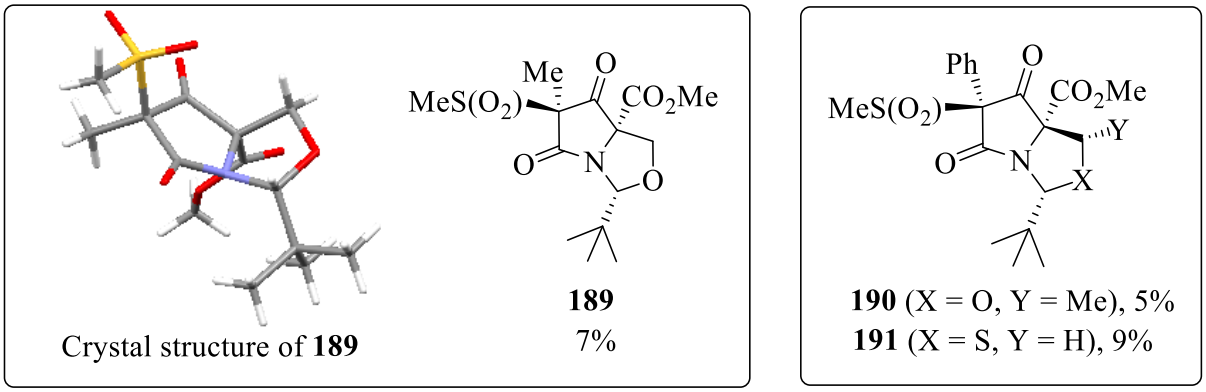
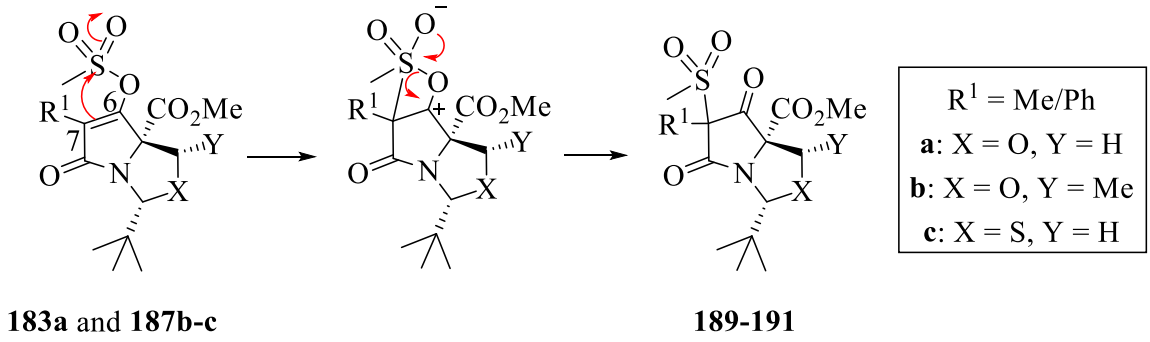


Figure 3.6: Isomerisation in mesylates

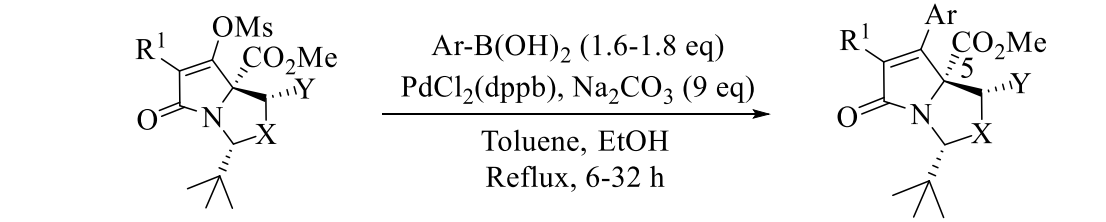
It was hypothesised that the mesylates **183a** and **187b-c** were formed first which isomerized slowly to sulfones **189** and **190-191**, respectively, via nucleophilic attack of π-electrons (C6=C7) which facilitated SO_2Me group to move to the C7 (Scheme 3.6). However, no precedent for this process could be found in the literature. This isomerisation could account for the lower yield of mesylates in general.



Scheme 3.6: Proposed mechanism for the isomerisation of **183a** and **187b-c**

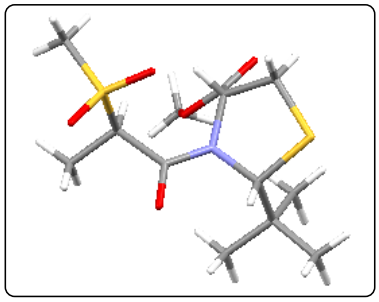
3.5 Suzuki-Miyaura Cross-Coupling

Treatment of mesylates **183a-c** and **187a-c** with boronic acids in the presence of $PdCl_2$(dppb) catalyst furnished the coupling adducts **129a-c** and **133a-c** (Scheme 3.7). In most cases, the coupling reactions of **183a-c** and **187a-c** were found to be much slower than those of **153** (see Section 2.4). A number of coupling reactions occurred with the formation of by-products **192-196**. The structure of **192** was determined by single crystal X-ray diffraction analysis while that of **193-196** was assigned by spectroscopic analysis.



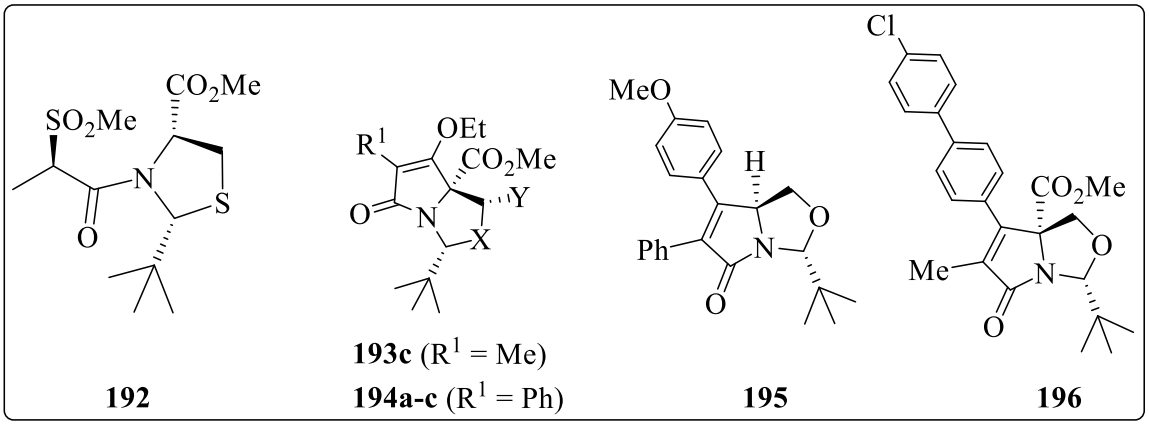
R^1 = Me: **183a-c** — **129a-c**

R^1 = Ph: **187a-c** — **133a-c**



X-ray crystal structure of **192**

L-Serine **a**: X = O, Y = H
L-*allo*-Threonine **b**: X = O, Y = Me
L-Cysteine **c**: X = S, Y = H



192 — **193c** (R^1 = Me), **194a-c** (R^1 = Ph) — **195** — **196**

Scheme 3.7: Suzuki Coupling of mesylates **183a-c** and **187a-c**

The steric bulk at C7 could be considered for the lower coupling efficiency in this system. Hence, for the L-serine system, the yields were comparatively poorer for 7-phenyl derivatives **133ai-aiii** than for the 7-methyl derivatives **129ai-aiii** (Table 3.6).

Table 3.6: Suzuki Coupling of mesylates **183a-c** and **187a-c**

Sl No	Systems		Entry	Ar-B(OH)$_2$	Product, Yield	
1	L-Serine	R^1 = Me	**183a**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**129ai**, 32%	
				ii: C$_6$H$_5$B(OH)$_2$	**129aii**, 33%	
				iii:[a] 4-ClC$_6$H$_4$B(OH)$_2$	**129aiii**, 38%, **196**, 5%	
		R^1 = Ph	**187a**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**133ai**, 9%	**194a**, 4-5%
				ii: C$_6$H$_5$B(OH)$_2$	**133aii**, 9%	
				iii:[a] 4-ClC$_6$H$_4$B(OH)$_2$	**133aiii**, 5%	
2	L-*allo*-Threonine	R^1 = Me	**183b**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**129bi**, 9%	
		R^1 = Ph	**187b**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**133bi**, <2%	**194b**, 7%
3	L-Cysteine	R^1 = Me	**183c**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**129ci**, 23%; **192**, 2%	**193c**, 3%
				ii: C$_6$H$_5$B(OH)$_2$	**129cii**, 23%	
				iii:[a] 4-ClC$_6$H$_4$B(OH)$_2$	**129ciii**, 21%	
		R^1 = Ph	**187c**	**i**: 4-MeOC$_6$H$_4$B(OH)$_2$	**133ci**, 23%	**194c**, 5%
				ii: C$_6$H$_5$B(OH)$_2$	**133cii**, 17%	
				iii:[a] 4-ClC$_6$H$_4$B(OH)$_2$	**133ciii**, 9%	

[a] 1.05 eq 4-ClC$_6$H$_4$B(OH)$_2$

Prolonged reaction time resulted in decarboxylated adduct **195** during the formation of **133ai**. The L-*allo*-threonine system, which experienced an additional steric effect from the

C4-methyl group, gave even poorer yields for coupling adducts **129bi** and **133bi**. However, the results for **129ci-ciii** and **133ci-ciii** were similar and could be due to the presence of larger sulfur atom that flattens the bicyclic core.

The structures of the coupling products were confirmed by X-ray crystal structure of representative adducts **129ai**, **133ai**, and **133ci** (Figure 3.7).

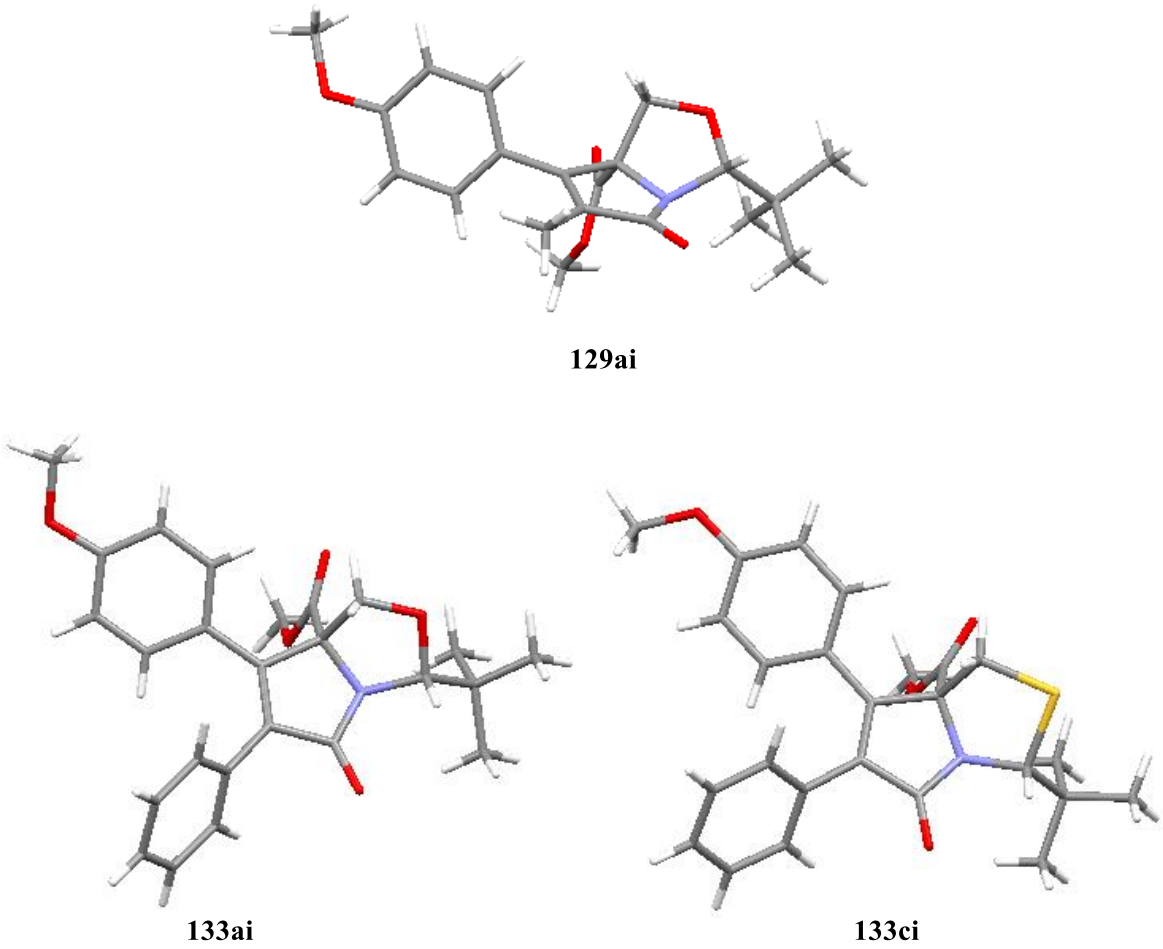
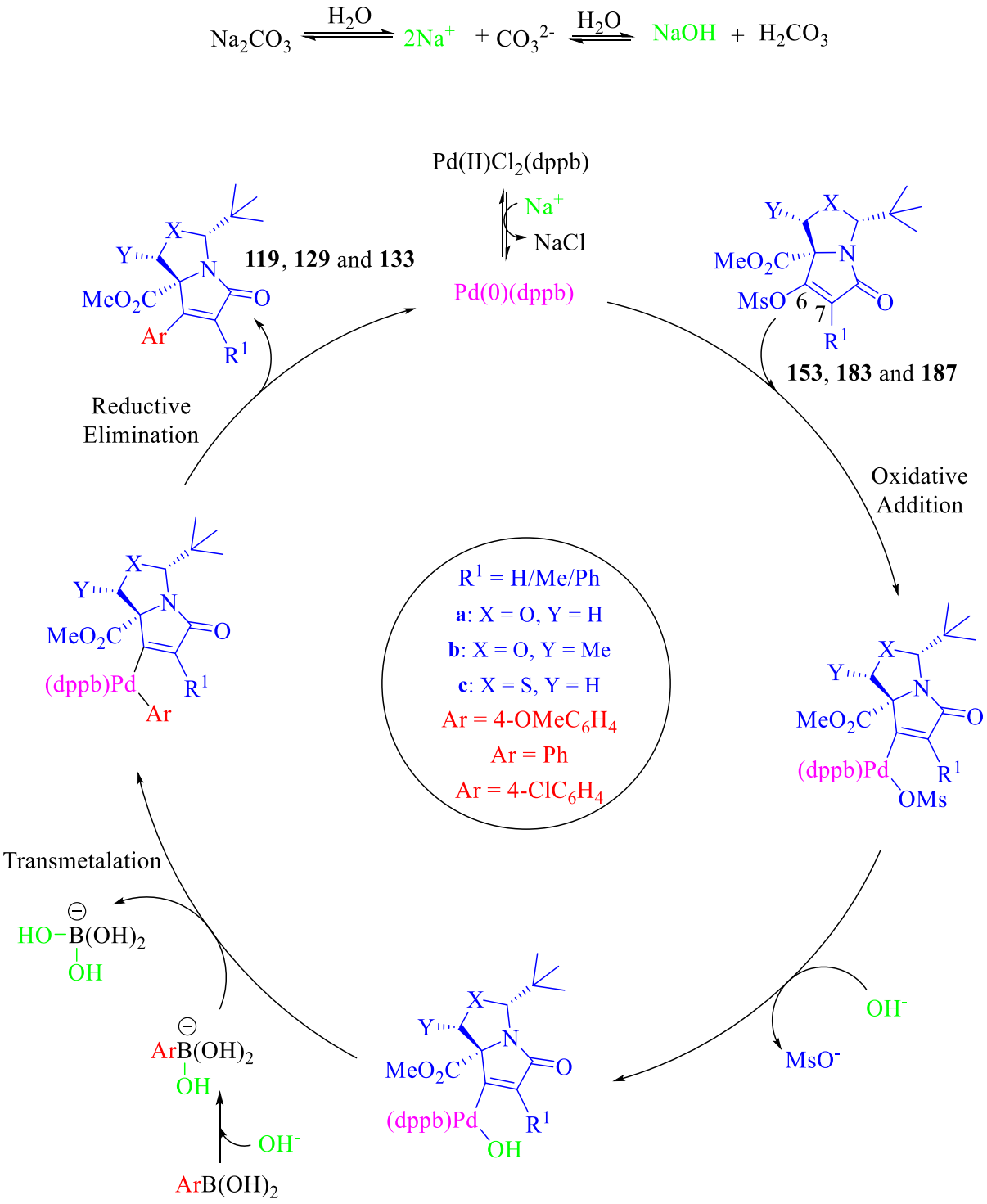


Figure 3.7: X-Ray crystal structure of **129ai**, **133ai**, and **133ci** (Capped Sticks Style)

The lower reactivity of C7-substituted mesylates **183a-c** and **187a-c** was understandable as the bulky Me or Ph group at the adjacent C7 position triggered more steric hindrance than a H atom (in **153**) for the oxidative addition at C6 (Scheme 3.8). Similarly, the C7-substituent

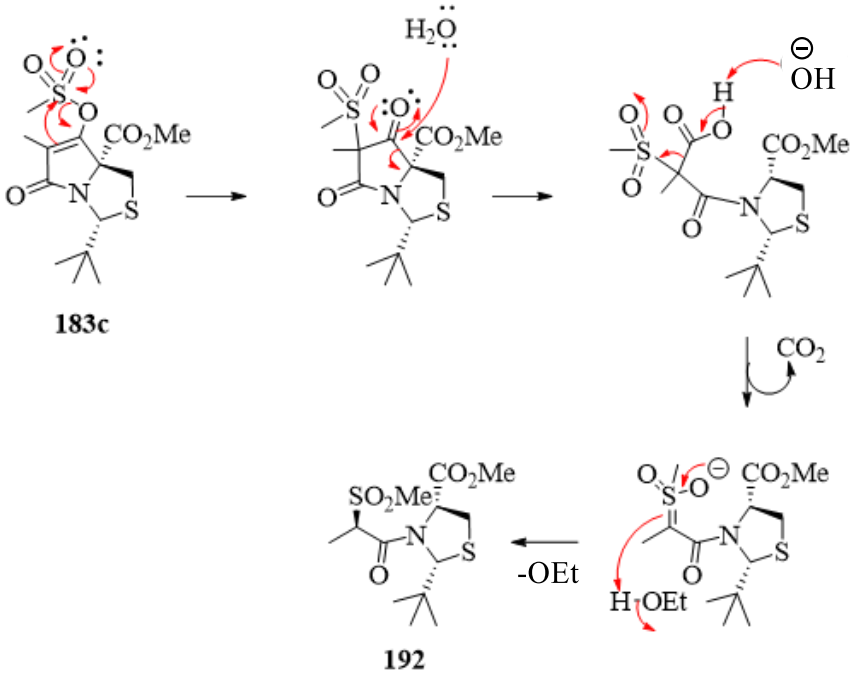
could thwart the transmetallation and participate in slowing down the overall coupling process.



Scheme 3.8: Proposed mechanism for the Suzuki coupling of **153**, **183a-c** and **187a-c**

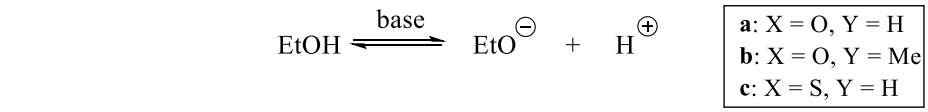
3.5.1 Proposed Explanation for By-products 192, 193c, and 194a-c

The formation of **192** can be resolved by the rearrangement, ring opening, and decarboxylation of the starting material **183c** (Scheme 3.9).

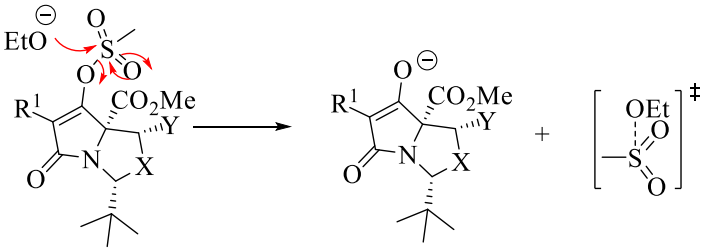


Scheme 3.9: Proposed mechanism for the formation of **192**

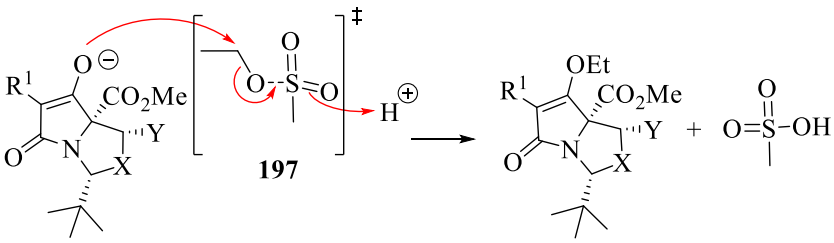
Interestingly, the solvent EtOH was found to react with the mesylates **183** and **187**, introducing in ethers of the type **193c** and **194a-c**. For L-*allo*-threonine system the coupling was very slow which enabled preferential formation of **194b** (see Table 3.6). Initially, it was perceived that a base-initiated concerted displacement[165] might result in formation of the ethers **193c** and **194a-c** (Mechanism 1a, Scheme 3.10), in which the ethyl ether arose by alkylation with *in situ* generated ethyl mesylate **197**. Alternatively, a direct addition-elimination displacement of the mesylate by ethanol could also be possible (Mechanism 1b, Scheme 3.10).



Mechanism 1a

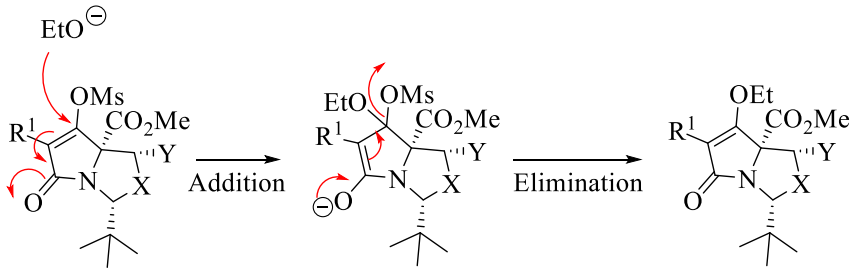


183c (R^1 = Me) and **187a-c** (R^1 = Ph) **197**



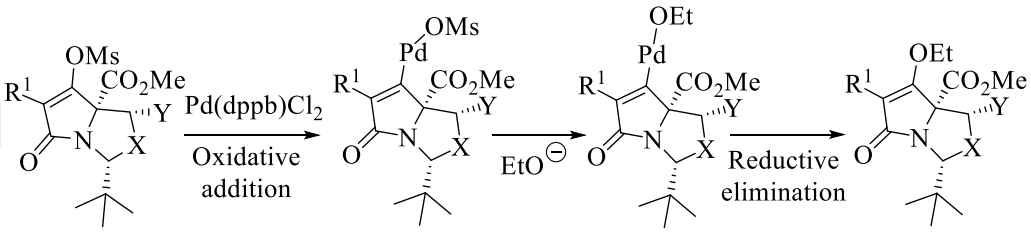
193c (R^1 = Me) and **194a-c** (R^1 = Ph)

Mechanism 1b



183c (R^1 = Me) and **187a-c** (R^1 = Ph) **193c** (R^1 = Me) and **194a-c** (R^1 = Ph)

Mechanism 2



183c (R^1 = Me) and **187a-c** (R^1 = Ph) **193c** (R^1 = Me) and **194a-c** (R^1 = Ph)

Scheme 3.10: Proposed mechanism for the formation of **193c** and **194a-c**

To investigate the reaction mechanism, **187a** was treated with Na_2CO_3 and EtOH but this gave quantitative recovery of starting material **187a** (Table 3.7). Therefore, ether formation could not take place in the absence of palladium catalyst and boronic acid. This result disproved Mechanism 1a and 1b. However, the reaction of **187a** with Na_2CO_3 and EtOH in presence of $Pd(dppb)Cl_2$ afforded only 4% of ether **194a** in addition to majority of unreacted starting material **187a**. It was hypothesised that the reaction occurred by consecutive oxidative addition and reductive elimination (Mechanism 2, Scheme 3.10). Moreover, the effect of the catalytic amount of boronic acid was tested which resulted coupling adduct **133ai** as a major product with ether by-product **194a** and unreacted starting material. These outcomes clarified that mesylates **183** and **187** reacted with solvent EtOH because of the slow coupling caused by C7 substituents.

Table 3.7: Reactions tested for the plausible mechanism of **194a**

Sl No	Entry	Conditions	Results	Remarks
1	**187a**	Na_2CO_3, EtOH, Toluene Reflux, 15 h	Quantitative recovery of SM	Did not proceed via mechanism 1
2		$Pd(dppb)Cl_2$, Na_2CO_3, Toluene, EtOH, Reflux, 15 h	**194a**, 4% + SM	Proceeded via mechanism 2
3		4-$MeOC_6H_4B(OH)_2$ (0.3 eq) $Pd(dppb)Cl_2$, Na_2CO_3, Toluene, EtOH, Reflux, 24 h	**194a**, 3% + **133ai**, 4% + SM	Boronic acid did not play any role for the formation of ethers

SM = starting material

3.5.2 Base Effect on the Suzuki Coupling of the Bulky Mesylates

Of interest was study of the effect of base on the Suzuki coupling of bulky mesylates **187** and **183** as this could accelerate the coupling process and could offer better results for

coupling. The coupling of the representative mesylates **187a**, **183a**, **187b**, **187c**, and **183c** was examined with 4-methoxyphenylboronic acid (i) or phenylboronic acid (ii) under basic conditions using different stoichiometric amount of base (Table 3.8). In most of the cases, the reaction proceeded in a shorter time with improved yields (marked green, Table 3.8) compared to the previously used basic condition (marked red, Table 3.8). Among the tested conditions, the use of 18 eq base allowed better results for coupling of **187a**, **183a**, and **187b** with 4-methoxyphenylboronic acid.

Table 3.8: Effect of the base on the Suzuki coupling of representative mesylates **187** and **183**

Systems and SL No		Na_2CO_3 (1M aq solution)	Entry	Reaction time	Yield	
					Product	By-product
O-System	1	9 eq	**187a**	24h	**133ai**, 9%	**194a**, 7%
	2	13 eq		24h	**133ai**, 25%	**194a**, 9%
	3	16 eq		20h	**133ai**, 19%	**194a**, 7%
	4	18 eq		24h	**133ai**, 30%	**194a**, 4%
	5	21 eq		15h	**133ai**, 26%	**194a**, 11%
	6	25 eq		19h	**133ai**, 12%	**194a**, 6%
	7	30 eq		15h	**133ai**, 8%	**194a**, 17%
	8	9 eq	**183a**	30h	**129ai**, 32%	Unpredicted impurity
	9	18 eq		15h	**129ai**, 54%	-
	10	9 eq	**187b**	43h	133bi, <2%	194b, 7%
	11	18 eq		17h	**133bi**, 7%	**194b**, 1%

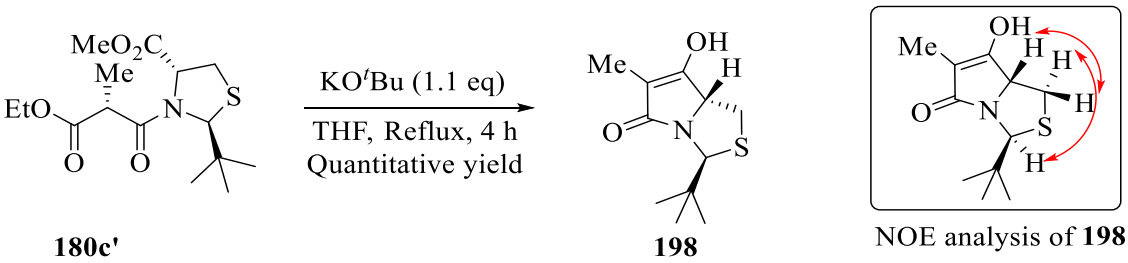
Continued…..

S-System	12	9 eq	**187c**	24h	**133ci**, 23%	**194c**, 5%
	13	18 eq		13h	**133ci**, 8%	**194c**, 3%
	14	9 eq		24h	**133cii**, 17%	**194c**, 5%
	15	15.5 eq		12h	**133cii**, 56%	-
	16	9 eq	**183c**	24h	**129ci**, 23%	**193**, 3%
	17	18 eq		13h	**129ci**, 2%	**193**, 3%

Interestingly, the impurity at the same R_f value for the C7-Me system (entry 8, Table 3.8) disappeared when 18 eq of base was used and the purification of **129ai** was much easier (entry 9, Table 3.8). For the *S*-system, the results were inconsistent and the use of 18 eq base gave poorer yields. The optimal base equivalent was 15.5 for coupling of **187c** with phenylboronic acid permitting a maximum yield of 56% (entry 15, Table 3.8).

3.5.3 The Study of *trans*-2,5 Diastereomer 180c'

Dieckmann ring closure of **180c'** was attempted separately and this resulted in decarboxylated tetramate **198** in quantitative yield (Scheme 3.11).



180c' **198** NOE analysis of **198**

Scheme 3.11: Dieckmann cyclisation of **180c'**

The ^{1}H NMR analysis for the crude product clearly showed the absence of the methyl ester signal (Figure 3.8). Moreover, LRMS analysis displayed both $[M+H]^+$ and $[M-H]^-$ peak for

198, which was further confirmed by HRMS analysis. The product was analyzed in MeOD and DMSO, and found essentially pure by NMR spectroscopy.

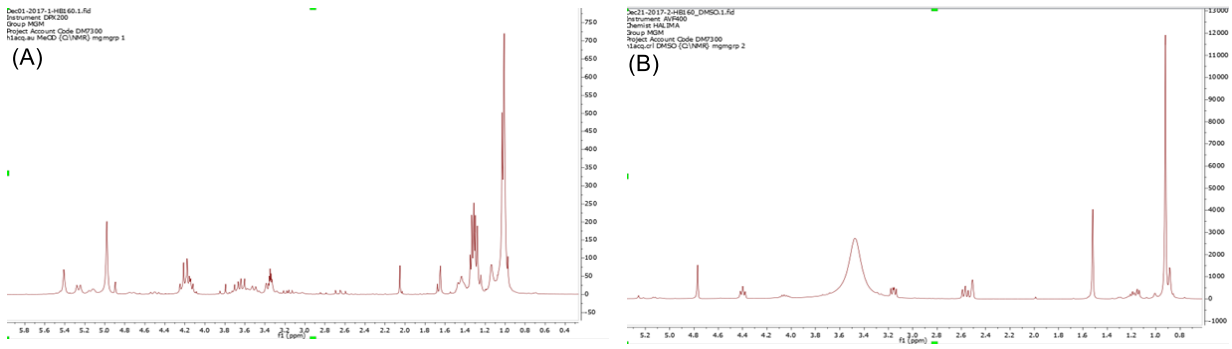
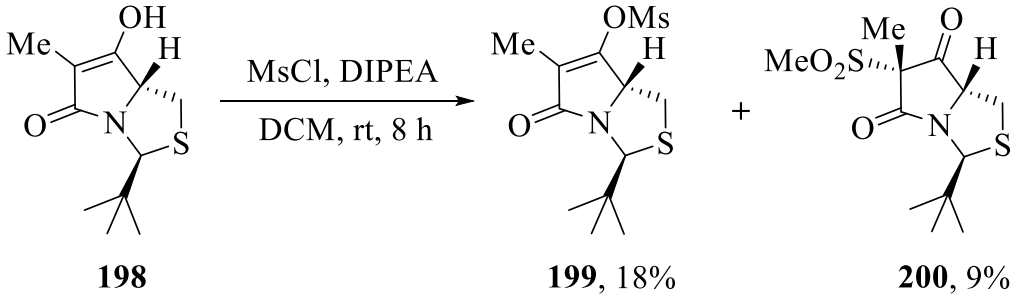


Figure 3.8: ^{1}H NMR analysis of **198**. (A) crude **198** in MeOD; (B) crude **198** in DMSO-d_6

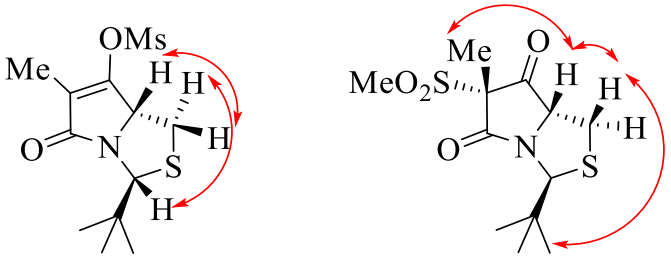
It was suspected that the *trans*-2,5 diastereomer **180c'** cyclised to give ent-**128c** and subsequent decarboxylation of ent-**128c** resulted in formation of **198**. Notably, alternative cyclisation[140] leading to an ethyl ester like **149** (see Chapter 2, Scheme 2.6) was not observed in MS or NMR analysis for the 7-Me system. Mesylation of **198** provided a complex mixture of products among which the mesylate **199** and by-product **200** were isolated in 18% and 9% yields, respectively, by careful flash column chromatography (Scheme 3.12).



198 **199**, 18% **200**, 9%

Scheme 3.12: Mesylation reaction of **198**

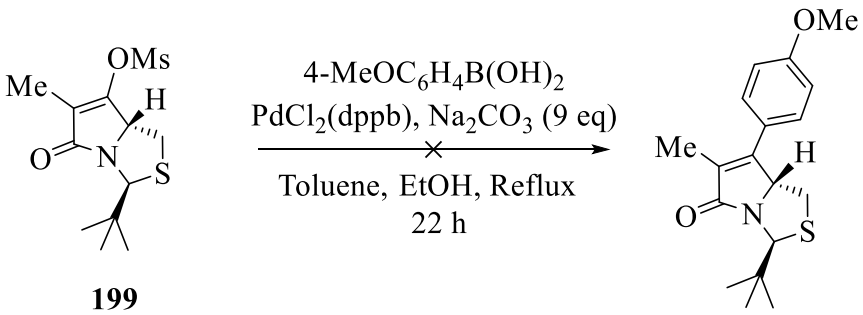
The by-product **200** was formed via isomerisation of **199** and the chemical shift δ_H 3.05 ppm was consistent with the SO_2Me chemical shift in **189** (δ_H 3.12 ppm). The stereochemistry of **199** and **200** was again confirmed by NOE analysis (Figure 3.9).



199 **200**

Figure 3.9: NOE Analysis of **199** and **200**

Coupling of **199** with 4-methoxyphenylboronic acid was unsuccessful (Scheme 3.13) and generated a complex mixture. Three fractions were isolated by flash column chromatography, but none of them were coupling adduct. A significant amount of unreacted starting material (40%) was recovered from the reaction mixture.



199

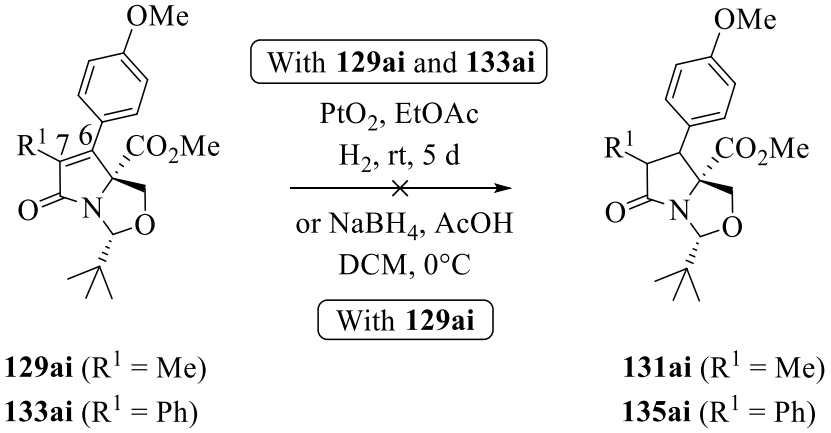
Scheme 3.13: Attempted Suzuki coupling of **199**

The surprising results for the coupling of **199** and **222b**, in which the difference with the latter system is the bicyclic core structure and *N*,*S*-protecting group might indicate an unfavourable steric effect for **199** (for **222b** coupling see entry 2, Table 4.4 in Chapter 4).

However, it was interpreted that *trans*-2,5 diastereomer **180c'** was not as effective as the *cis*-2,5 diastereomer **180c** for the series of reactions studied (see Section 3.3.1, 3.4 and 3.5).

3.6 Removal of the C6, C7 double Bond

Having been able to couple at C6, it was of interest to reduce the double bond between C7 and C6 to prepare 6,7-disubstituted analogues of pyroglutamates **131** and **135**. Attempted reduction of **129ai** using $NaBH_4$/AcOH or hydrogenation in presence of PtO_2 catalyst delivered quantitative recovery of the starting material (Scheme 3.14).



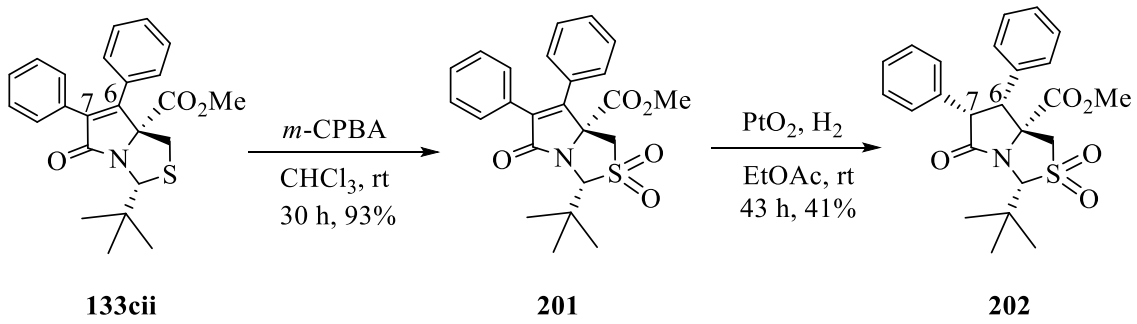
129ai (R^1 = Me)
133ai (R^1 = Ph)

131ai (R^1 = Me)
135ai (R^1 = Ph)

Scheme 3.14: Attempted reductions of **129ai** and **133ai**

Hydrogenation of **133ai** was also attempted to access compound **135ai**. Unfortunately, this reaction was also unsuccessful and gave quantitative recovery of starting material **133ai**. These results suggested that C7-Me/Ph caused steric hindrance leading to failure of the reductions.

As described in Section 2.5.3, preparation of **131** could not be achieved via direct hydrogenation in the *S*-system, as the lone pair on sulfur deactivates the catalyst. The sulfone **201** was prepared by the reaction of **133cii** with *m*-CPBA (Scheme 3.15). Successive catalytic hydrogenation furnished pyrrolidinone **202** in 40% yield with the recovery of 51% of unreacted starting material **201**.



133cii **201** **202**

Scheme 3.15: Preparation and hydrogenation of sulfone **201**

The successful access from pyrrolinone **201** to pyrrolidinone **202** in the *S*-system, which was unsuccessful in *O*-system (see Scheme 3.14), can be explained by the presence of the larger sulfur atom. The sulfur atom could flatten the bicyclic core structure which permited access for the catalyst surface to bind (A, Figure 3.10). However, the reaction was very slow which was evident from the reaction time and the recovery of unreacted starting material. Qu and co-workers[166] reported the metal binding behaviour of sulfoxides and sulfones with various ions including Pt^{4+}. Likewise, the sulfone could partly facilitate the hydrogenation of pyrrolidinone **201** through binding with platinum (B, Figure 3.10).

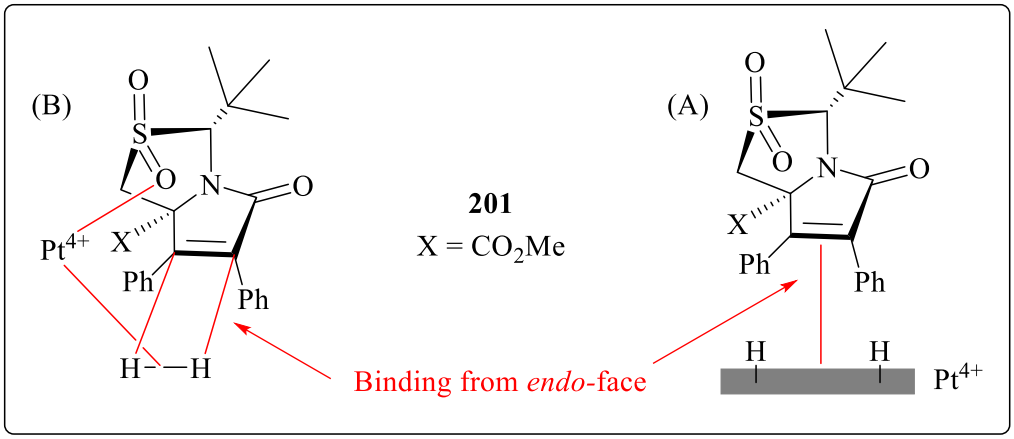
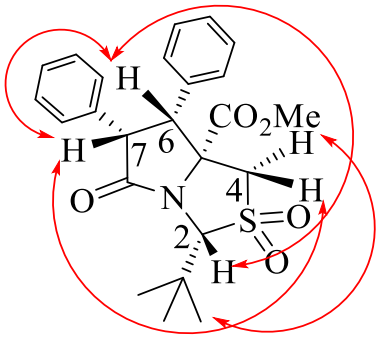


Figure 3.10: Possible mechanisms for the hydrogenation of sulfone **201**. (A) Direct binding of platinum with double bond; (B) Hydrogenation via binding of sulfone with platinum (Pt^{4+})

The stereochemistry of the newly formed chiral centres C6 and C7 was assigned by NOE analysis (Figure 3.11). The NOE showed enhancement between H6-H7, H2-H6, and *endo*-H4-H7 which confirmed the stereochemistry of **202**. This hydrogenation result was consistent with the hydrogenation of similar analogues discussed in Section 2.6.1.

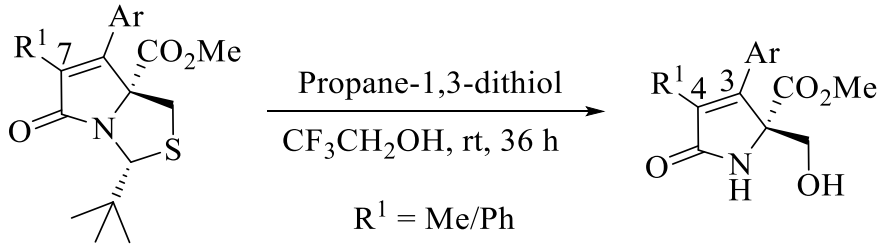


202

Figure 3.11: NOE analysis of **202**

3.7 *N,O*-Acetal Deprotection

N,O-Acetal deprotection of **129ai-aiii** proceeded efficiently applying the Corey-Reichard protocol[104] (Scheme 3.16). The conversion was slow when compared to previous reactions (see Table 2.12) and total consumption of starting material was observed while using excess propane-1,3-dithiol (4.0 eq) and a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol. This reaction privided access from pyrrolinone **129ai-aiii** to 3,4-disubstituted pyroglutaminol or pyroglutamate derivatives **203-205** for C7-Me bicyclic pyroglutamate systems.



129ai-aiii **203-205**

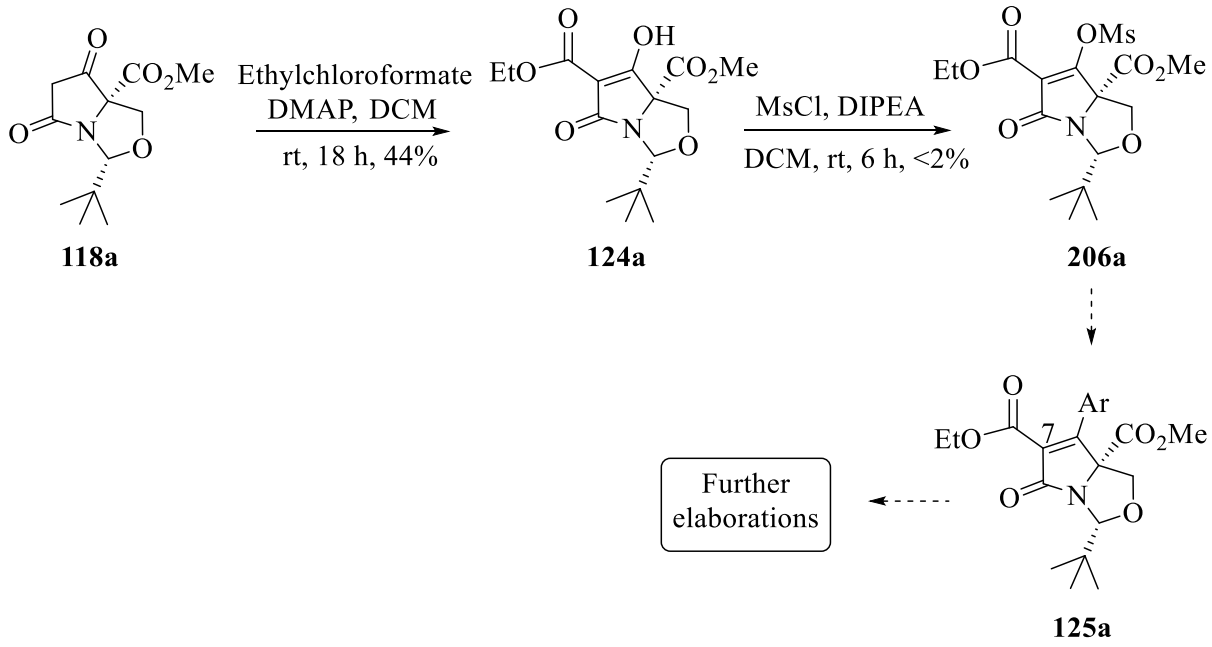
Ar	Starting Material	Product	Yield (%)
4-$OMeC_6H_4$	**129ai** (R^1 =Me)	**203**	99
Ph	**129aii** (R^1 =Me)	**204**	90
4-ClC_6H_4	**129aiii** (R^1 =Me)	**205**	89
4-$OMeC_6H_4$	**133ai** (R^1 =Ph)	**-**	-

Scheme 3.16: *N,O*-Acetal deprotection of **129ai-aiii**

Alternatively, *N,O*-acetal deprotection for the C7-Ph bicyclic pyroglutamate system was attempted with **133ai** but showed no detectable (by LRMS) product formation at room temperature, however, gave a complex mixture when heated at 50 °C. Careful column chromatography resulted the recovery of 17% of unreacted starting material but other fractions were unrecognized as ^{1}H NMR spectra had few signals and LRMS analysis did not show the desired product.

3.8 C6 and C7 Functionalised Pyrrolinones: Part 2

An alternative route for the synthesis of 3,4-disubstituted pyrrolinones would be to use the ethyl ester tetramic acid **124a** which could allow further elaborations via an ethyl ester functional group. Josa-Cullere[167] described the preparation of ethyl ester **124a** using ethyl chloroformate. The treatment of tetramic acid **118a** with ethyl chloroformate and DMAP provided ethyl ester **124a** in 44% yield (Scheme 3.17).



Scheme 3.17: Preparation of ethyl ester **124a** and its mesylation reaction

Then, mesylation was attempted via previously used method with MsCl and DIPEA but this gave less than 2% yield (Table 3.9). The use of Gilfillan methodology[168] with MsCl and Et_3N also resulted in unreacted starting material even after 3 days. Likewise, attempted mesylation following Kobayashi protocol[145] with MsCl and NaH was also unsuccessful.

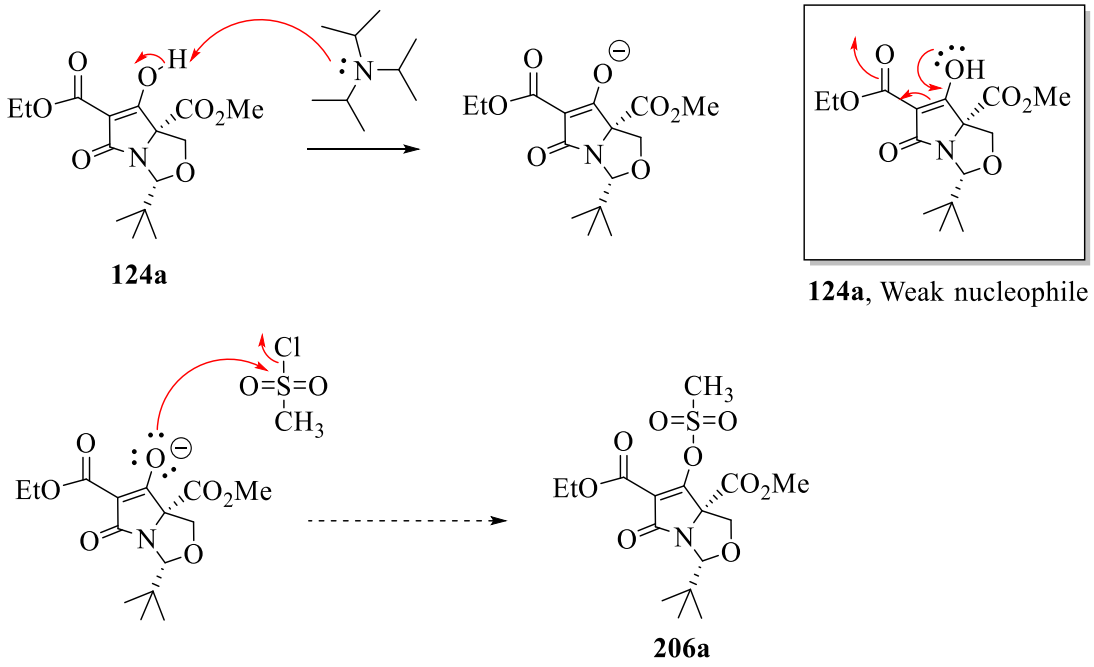
Table 3.9: Attempted conditions for mesylation reaction of **124a**

Sl No	Tested conditions	Product 206a, Yield (%)	Comment
1	MsCl, DIPEA, DCM, rt, 6 h	<2	Unreacted SM
2	MsCl, ET_3N, DCM, rt, 3 d	-	No reaction
3	MsCl, NaH, THF, 3 d	-	No reaction

SM = starting material

The lack of reactivity of ethyl ester tetramate **124a** towards mesylation can be explained by the very weak nucleophilicity of the highly resonance stabilised enolate (Scheme 3.18). The

lone pair of electrons on the hydroxyl functional group are not available due to the extensive delocalisation of electrons in the tricarbonyl system in **124a**.



Scheme 3.18: Mesylation mechanism and explanation for the lack of reactivity of ethyl ester tetramate **124a**

A further attempt to prepare 6,7-disubstituted pyrrolinones **127** through Weinreb amides **126** was made (Figure 3.12).

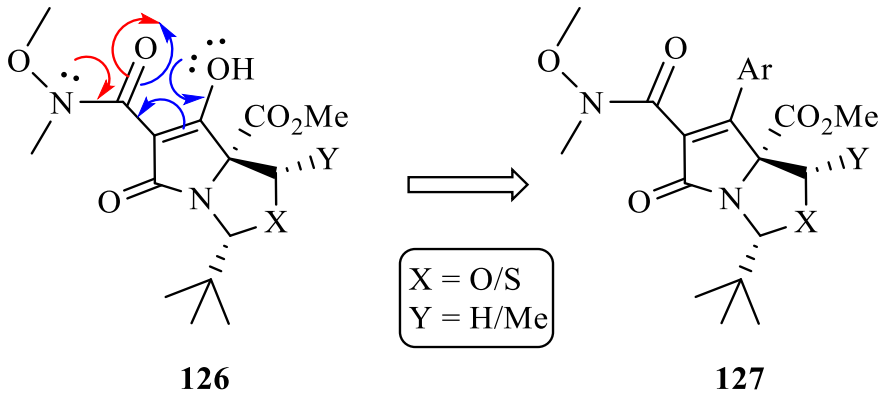
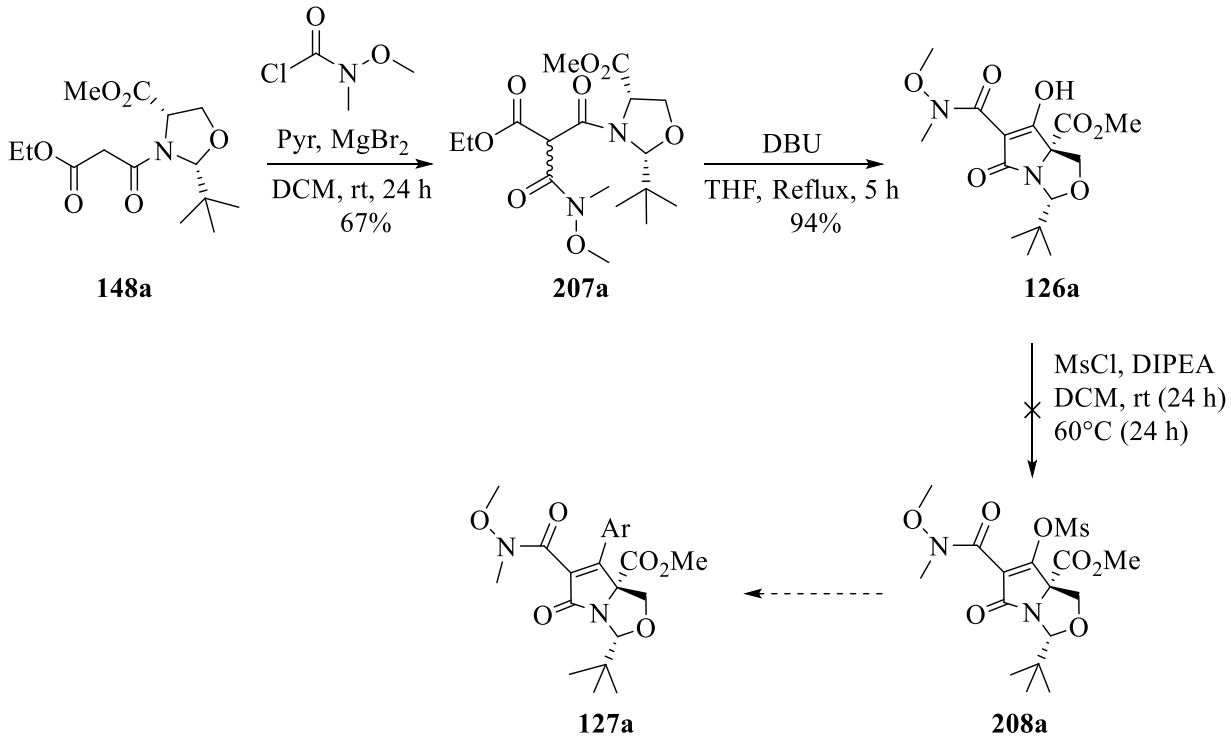


Figure 3.12: Hypothesis for the retention of nucleophilicity of the OH group in **126**

The nitrogen lone pair electron could delocalise with C=O in *N*-methoxy-*N*-methylcarbamoyl functionality (red arrow) which could prevent the delocalisation of hydroxyl oxygen lone pair electrons (blue arrow) (Figure 3.11), and this might improve their reactivity leading to 3,4-disubstituted pyrrolinone derivatives. Josa-Cullere *et al.*[169] reported the preparation of Weinreb amide **126a** via tricarbonyl **207a**. The oxazolidine **148a** was synthesised as described in Section 2.2. Treatment of **148a** with *N*-methoxy-*N*-methylcarbamoyl chloride gave **207a**, which on cyclisation using DBU resulted in the desired Weinreb amide **126a** (Scheme 3.19). Attempted mesylation with MsCl and DIPEA showed no detectable conversion by TLC. LRMS analysis showed the unreacted starting material **126a** peak and no peak was observed for the desired mesylate **208a**. This could be due to the stability of the highly conjugated tricarbonyl system or steric hindrance by a larger group at the adjacent carbon.



Scheme 3.19: Preparation of Weinreb amide **126a** and attempted mesylation reaction

3.9 Antibacterial Screening

Some of the pyrrolinone and pyroglutaminol derivatives were tested for antibacterial activity against Gram-negative and Gram-positive bacteria and all of them showed very little or no activity (Table 3.10). The test method is provided in Appendix D.

Table 3.10: MIC values for the screening of representative compounds synthesised in Chapter 3 against several pathogens

Sl No	Compound	Gram-negative bacteria			Gram-positive bacteria	
		EC 34	KL 18	PS 23	MRSA 1	MRSA 2
1	**129ai**	n. a.	n. a.	n. a.	n. a.	n. a.
2	**129aii**	n. a.	n. a.	n. a.	n. a.	n. a.
3	**129aiii**	n. a.	n. a.	n. a.	n. a.	n. a.
4	**129bi**	n. a.	n. a.	n. a.	n. a.	n. a.
5	**129ci**	n. a.	n. t.	n. t.	n. a.	-
6	**129cii**	n. a.	n. t.	n. t.	n. a.	-
7	**129ciii**	n. a.	n. t.	n. t.	n. a.	-
8	**203**	n. a.	n. a.	n. a.	n. a.	n. a.
9	**204**	n. a.	n. a.	n. a.	n. a.	125.00 µg/mL
10	**205**	n. a.	n. a.	n. a.	n. a.	125.00 µg/mL

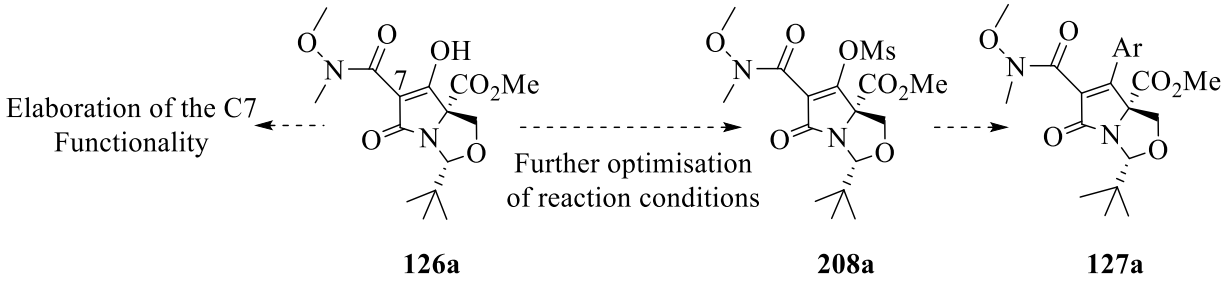
n. a. = not active; n. t. = not tested

3.10 Summary and Future Works

A facile route has been developed for the synthesis of 3,4-disubstituted pyrrolinones. The C7-Me/Ph bicyclic tetramates were prepared via literature methodology. The mesylates were used as a suitable substrate for Suzuki coupling. It was demonstrated that the coupling of 7-substituted bicyclic mesylates with arylboronic acids took place efficiently. This remarkable process enabled preparation of a library of 3,4-disubstituted highly functionalised pyrrolinone derivatives. Although the application of coupling conditions as described in Chapter 2 resulted maximum 33% yield for coupling adducts, a base effect study allowed improved yields of up to 56%.

Catalytic hydrogenation provided access from 3,4-disubstituted pyrrolinone to 3,4-disubstituted pyrrolidinone derivatives for the *S*-system. The *O*-system was unreactive to this conversion as both faces of the bicyclic core were hindered by a number of functionalities which was comparatively easier for the *S*-system due to the ring flattening effect by the larger sulfur atom.

N,*O*-Acetal deprotection of C7-Me derivatives provided access to the desired 3,4-disubstituted pyroglutamate and pyroglutaminol derivatives. Unfortunately, attempted *N*,*O*-acetal deprotection of the C7-Ph derivative was unsuccessful. This could be the steric or electronic effect of C7-phenyl group and requires further optimisation of reaction conditions.



126a **208a** **127a**

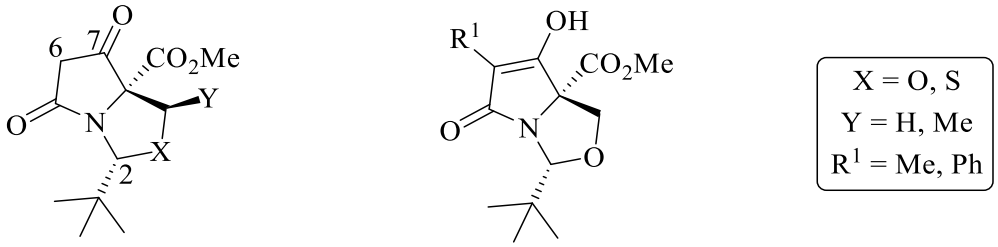
Scheme 3.20: Proposed future work for Chapter 3

CHAPTER 4: SYNTHESIS AND REACTIONS OF A NOVEL BICYCLIC TETRAMATE MOTIF

This Chapter describes the use of 2-methylpropanal as an alternative to the previously used condensing reagent 2,2-dimethylpropanal to develop an economical route to novel bicyclic tetramic acids derived from L-serine and L-cysteine. The feasibility of using this newly developed tetramate has been investigated for the representative chemical transformations described in Chapter 2 and 3.

4.1 Synthetic Goals

The Moloney group explored the preparation of bicyclic methyl ester tetramic acids **118**, **128** and **132** which enabled access to a library of C6 and C7 functionalised derivatives of pyroglutamates (Figure 4.1).[131,138,140,170]



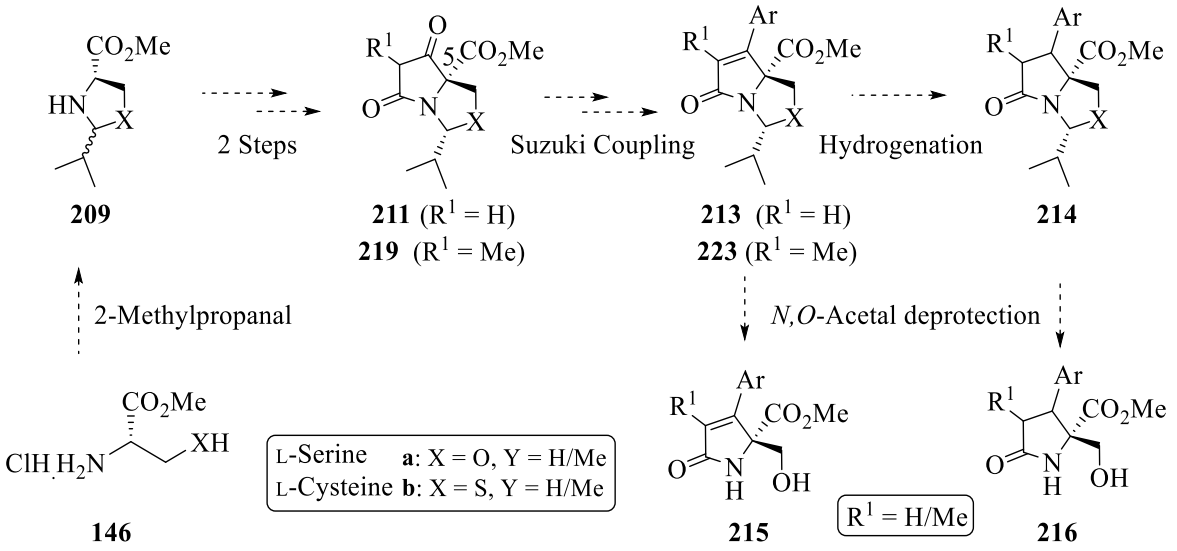
118 **128** and **132**

Figure 4.1: Methyl ester tetramate templates developed by Moloney group[131,138,140,170]

In pyroglutamate library generation so far, the *tert*-butyl group had been used as a common protecting group for amide and hydroxyl/thiol functional groups, as it was easy to introduce and to remove as well, although the required starting material, pivaldehyde was expensive. However, methyl ester tetramate library synthesis with diversity at C2 had not been explored before, and it was of interest to replace the *tert*-butyl group by an isopropyl group as this might have similar synthetic characteristics. This study became necessary because during

2017, the global supply of pivaldehyde became uncertain and it was not clear that reliability of supply would return. Thus, study of the ease of the synthesis and application of the tetramate core with an isopropyl protecting group for the amide and alcohol/thiol functionalities was initiated.

Methyl ester hydrochlorides of the amino acids L-serine and L-cysteine **146a** and **146b** were used as substrates (Scheme 4.1). The treatment of **146** with 2-methylpropanal could give condensation in a similar fashion to the previously used 2,2-dimethylpropanal (pivaldehyde) to furnish oxazolidine **209a** or thiazolidine **209b**. DCC coupling and Dieckmann cyclisation could afford the novel methyl ester tetramates **211** or **219** having isopropyl NH and OH/SH protecting group.

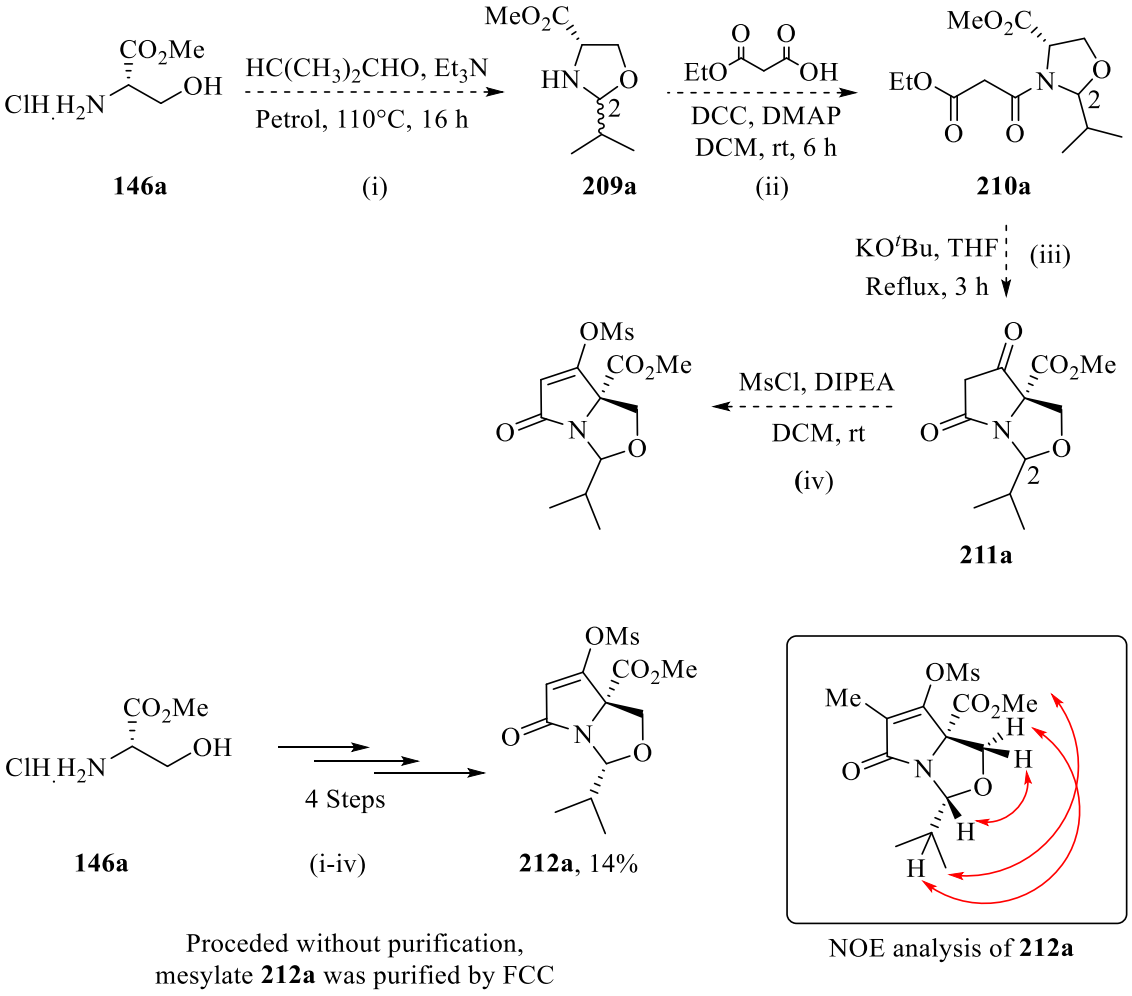


Scheme 4.1: Synthetic goals for Chapter 4

For the reasons postulated by Seebach,[141] the malonamides would ensure the regeneration of same stereochemistry at C5 in bicyclic tetramates **211** and **219**, and the control of chemoselectivity[140] in cyclisation of *cis*-2,5 diastereomer would be a safeguard for the enantiopurity of tetramates **211** and **219**. The synthetic utility, scoping and stereochemistry of all the synthesised products will be discussed in this chapter.

4.2 Preparation and Application of the L-Serine Derived Tetramate

Following the Seebach protocol,[137] L-serine methyl ester hydrochloride **146a** was heated with 2-methylpropanal/triethylamine to furnish oxazolidine **209a** (Scheme 4.2), obtained as a mixture of diastereomers.



Scheme 4.2: Attempted (i) condensation, (ii) DCC coupling, (iii) Dieckmann cyclisation, and (iv) mesylation reactions

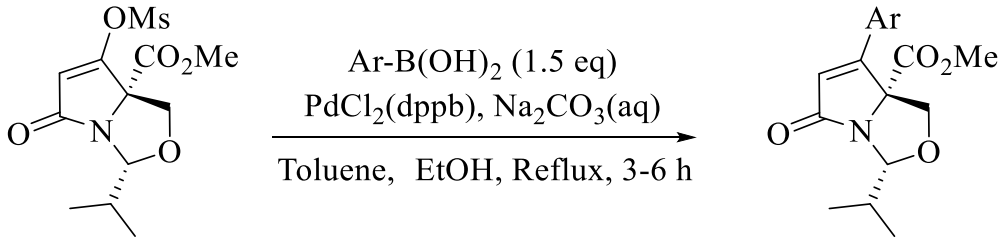
Attempted flash column chromatography was not fruitful as most of the compound stuck onto silica. However, LRMS and ^{1}H NMR analysis of the crude mixture indicated the presence of **209a**. The condensation reaction was then repeated and the resulting crude **209a** was *N*-acylated via DCC coupling.[138] The LRMS analysis of the resulting mixture showed

the peak for malonamide **210a** but again attempted purification by column chromatography was unsuccessful and malonamide **210a** stuck on the silica. The NMR spectrum of the crude product showed only a few detectable signals for the expected product, along with other unpredictable signals. The application of Dieckmann cyclisation conditions[138] to the crude malonamide **210a** resulted in formation of the desired tetramate **211a** but it was not possible to isolate the product. In fact, all the synthesised products **209a**-**211a**, which could be detected by LRMS and ^{1}H NMR analysis of crude mixtures, were found to stick with silica and could not be eluted. Finally, it was decided to demonstrate the conversions (i-iv) without purification in each step. The treatment of crude **211a** with MsCl/DIPEA furnished 14% of desired mesylate **212a**. The structure of **212a** was determined by NMR, MS, and NOE analysis (Scheme 4.2).

4.2.1 C6 Functionalisation via Suzuki Coupling

With mesylate **212a** in hand, Suzuki coupling with 1.5 eq of aryl boronic acid resulted pyrrolinone derivatives **213ai-aiii**, with 40-47% isolated yield (Table 4.1). The low yield could be due to the affinity of products to silica, as observed before during the purification of intermediates **209a**-**211a**.

Table 4.1: Suzuki coupling of **212a** with arylboronic acids



212a **213a**

Continued.....

Sl No	Entry	Ar	Reaction Time (h)	Product	Yields (%)
1	**212a**	**i**: 4-methoxyphenyl	6	**213ai**	47
2	**212a**	**ii**: phenyl	6	**213aii**	45
3	**212a**	**iii**:[a] 4-chlorophenyl	3	**213aiii**	40

[a] 4-chlorophenylboronic acid: 1.05 eq

The coupling results were consistent with those of **153a** (see Table 2.5, Chapter 2), excluding the yields. For example, the 4-methoxyphenyl adduct **213ai** was easy to detect when monitoring the reaction as it was fluorescent under UV light and made isolation of product by flash column chromatography much easier. The structures of the coupling adducts **213ai-aiii** were determined by NMR, LRMS, and HRMS analysis and further confirmed by the X-ray crystal structure of **213aii** (Figure 4.2).

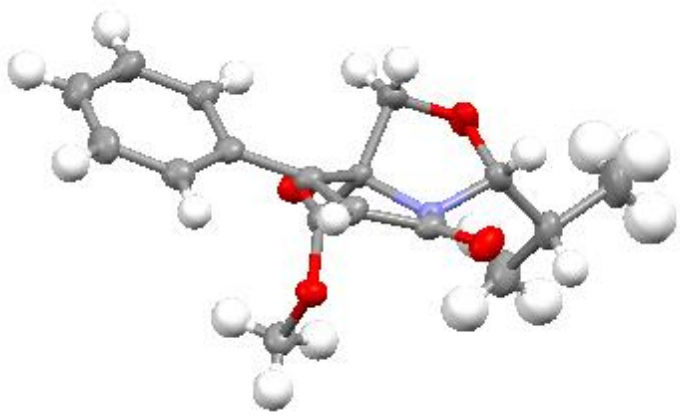
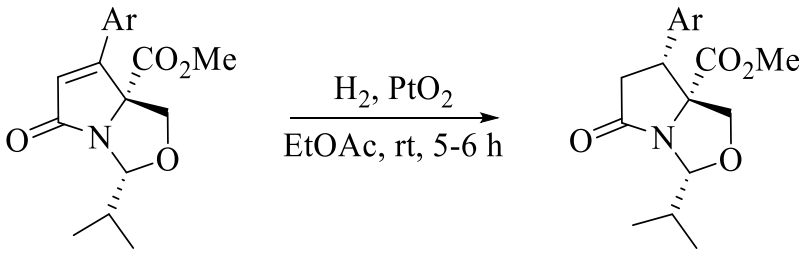


Figure 4.2: X-Ray crystal structure of **213aii** (Ellipsoid Style)

4.2.2 Access to Pyrrolidinone Derivatives via Hydrogenation

Treatment of pyrrolinones **213ai-aiii** with H_2/PtO_2 furnished pyrrolidinone or pyroglutamic acid derivatives **214ai-aiii** in high yields (Table 4.2). The isolation of products **214ai-aiii** by flash column chromatography on this occasion was much easier.

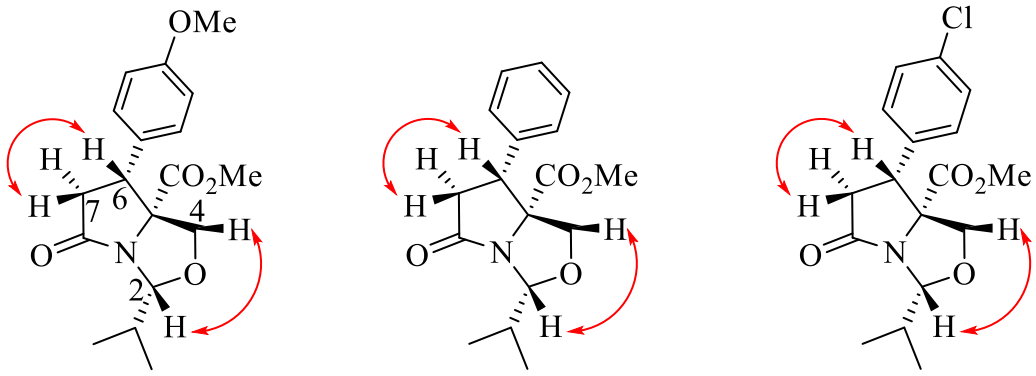
Table 4.2: Hydrogenation of **213ai-aiii**



213a **214a**

Sl No	Entry	Ar	Reaction Time (h)	Product	Yields (%)
1	**213ai**	**i**: 4-methoxyphenyl	6	**214ai**	82
2	**213aii**	**ii**: phenyl	5	**214aii**	75
3	**213aiii**	**iii**: 4-chlorophenyl	6	**214aiii**	85

The stereochemistry of the pyrrolidinones **214ai-aiii** was assigned by NOE analysis, and all of them showed a strong NOE between *endo*-H4-H2 and *endo*-H7-H6 (Figure 4.3). The stereochemistry of the newly formed chiral centres C6 and C7 was found to be in accord with the reduced analogues in the *tert*-butyl system (see Scheme 2.16, Chapter 2).



214ai **214aii** **214aiii**

Figure 4.3: NOE analysis of **214ai-aiii**

The stereochemistry of the pyrrolidinones was further confirmed by the X-ray crystal structure of **214aii** (Figure 4.4).

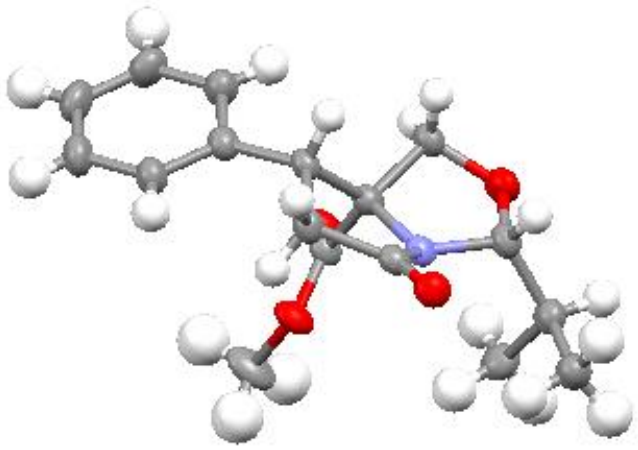
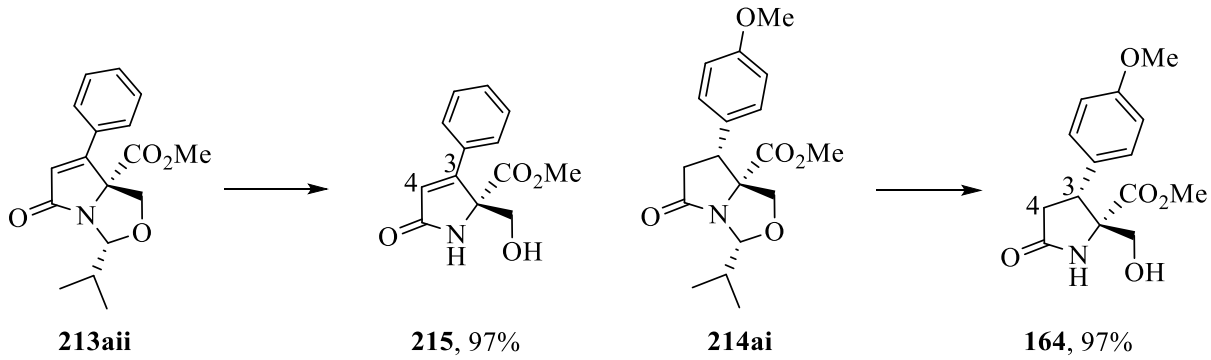


Figure 4.4: X-Ray crystal structure of **214aii** (Ellipsoid Style)

4.2.3 *N,O*-Acetal Deprotection

With the pyrrolinones **213ai-aiii** and pyrrolidinones **214ai-aiii** in hand, it was of consequent interest to elaborate the synthetic utility by the removal of isopropyl protecting group. The representative compounds **213aii** and **214ai** were subjected to *N,O*-acetal deprotection via Corey-Reichard protocol[104] (Scheme 4.3).



Scheme 4.3: *N,O*-Acetal Deprotection of **213aii** and **214ai** (reaction condition: propane-1,3-dithiol (2.3 eq), 1.5% solution of HCl in CF_3CH_2OH, rt, 18-22 h)

This chemical transformation allowed efficient access to 3-arylpyrrolinone **215**, 3-arylpyrrolidinone, 3-arylpyroglutamate, or 3-arylpyroglutaminol derivative **164** in 97% yield. Previously, the pyroglutaminol **164** (see Table 2.12, Chapter 2) was prepared from **121ai** with 80% yield. This result demonstrated the significance of the isopropyl protecting group over the *tert*-butyl protecting group, but also might explain the recurrent problem with chromatographic purification – that is, the isopropyl system may be much more susceptible to acidic hydrolysis, and if this occurred during chromatography, elution would be problematic.

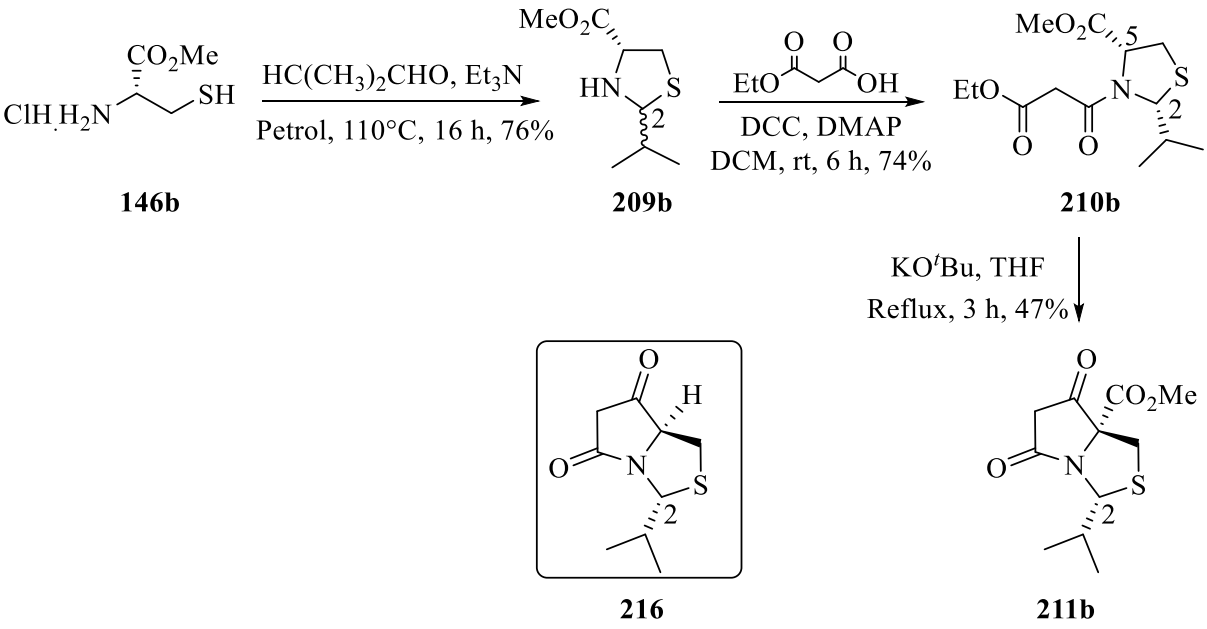
Following the difficulties encountered with the serine-derived oxazolidine, malonamide, and tetramates, further elaboration for the preparation of 3,4-disubstituted pyroglutamate derivatives was halted in this system.

4.3 Preparation and Application of L-Cysteine Derived Tetramate: I

4.3.1 Synthesis of Tetramate with Isopropyl Amide and Thiol Protecting Group

Commercial L-cysteine methyl ester hydrochloride **146b** produced a 2:1 mixture of diastereomers **209b** when refluxed with 2-methylpropanal and Et_3N following Seebach's protocol (Scheme 4.4).[162] The thiazolidine **209b** was purified by flash column chromatography (FCC) but it was not possible to separate the C2 epimers. *N*-Acylation of this mixture of thiazolidine **209b** via DCC coupling[138] furnished predominantly *cis*-2,5 diastereomer **210b** with 81% yield. The *trans*-2,5 diastereomer of **210b** was also detected in ^{1}H NMR spectrum of the crude product but only *cis*-2,5 diastereomer **210b** was isolated by FCC. The preference for *cis*-2,5 diastereomer can be explained by the ring-chain tautomerism,[139,140] probably the equatorial position of two bigger substituents making it the more stable isomer. Subsequent Dieckmann cyclisation following Andrew's protocol[138] gave bicyclic tetramates **211b** and **216** with an isopropyl protecting group for amide and thiol

functionalities. The tetramates **211b** and **216** were found to be nearly an inseparable mixture and the major tetramate **211b** was isolated only for characterisation.

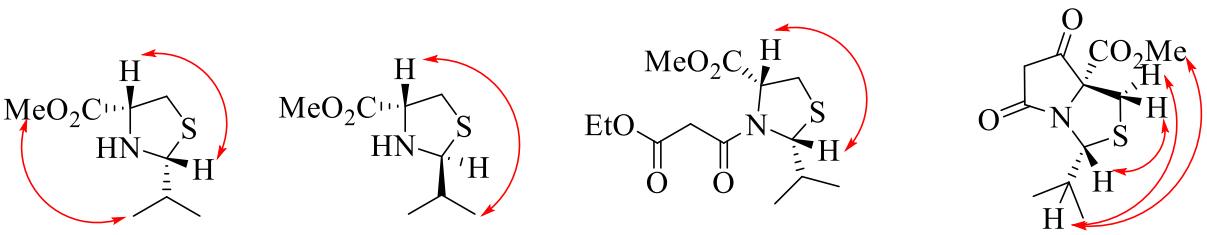


146b **209b** **210b** **216** **211b**

Scheme 4.4: Preparation of cysteine derived bicyclic tetramate **211b** with isopropyl NH/SH-protecting group

4.3.2 Stereochemical Assignment

The stereochemistries of the thiazolidine **209b**, malonamide **210b**, and tetramate **211b** were assigned by NOE analysis (Figure 4.5).



209b (Major) **209b'** (Minor) **210b** **211b**

Figure 4.5: NOE analysis of thiazolidine **209b**, malonamide **210b**, and tetramate **211b**

For tetramate by-product **216**, the stereochemistry was determined by the NOE analysis of mesylate derivative **217** which will be presented in the following section.

The *cis*-2,5 malonamide **210b** was found to exist as a mixture of rotamers detected by a 1D gradient selective NOE NMR experiment (Figure 4.6). Selective irradiation of signal at 4.69 ppm in 1D gradient NOE experiment provided a spectrum (B) with two negative signals at 4.69 ppm and 5.32 ppm. This experiment revealed the rotameric exchange in *cis*-2,5 malonamide **210b**.

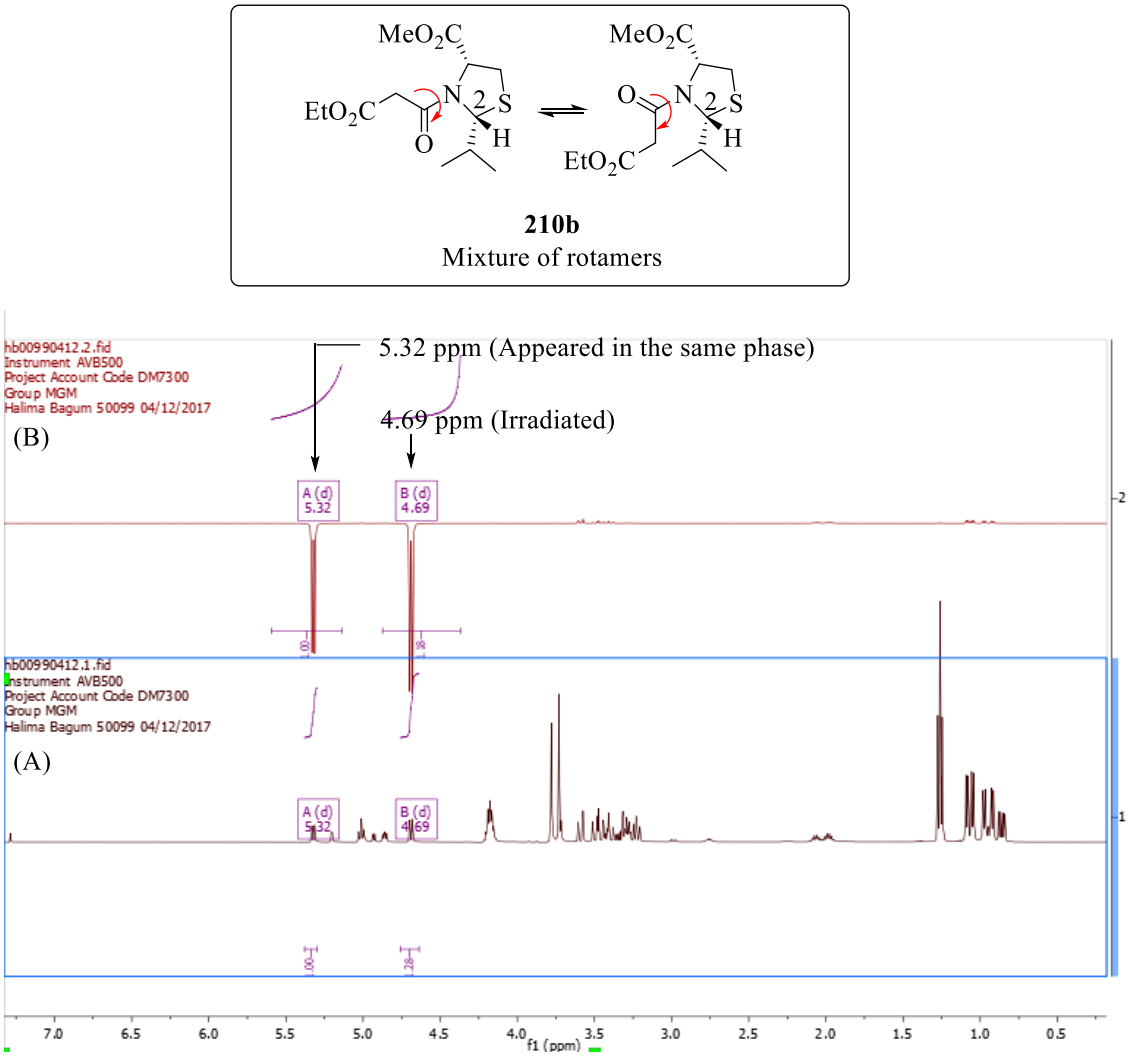
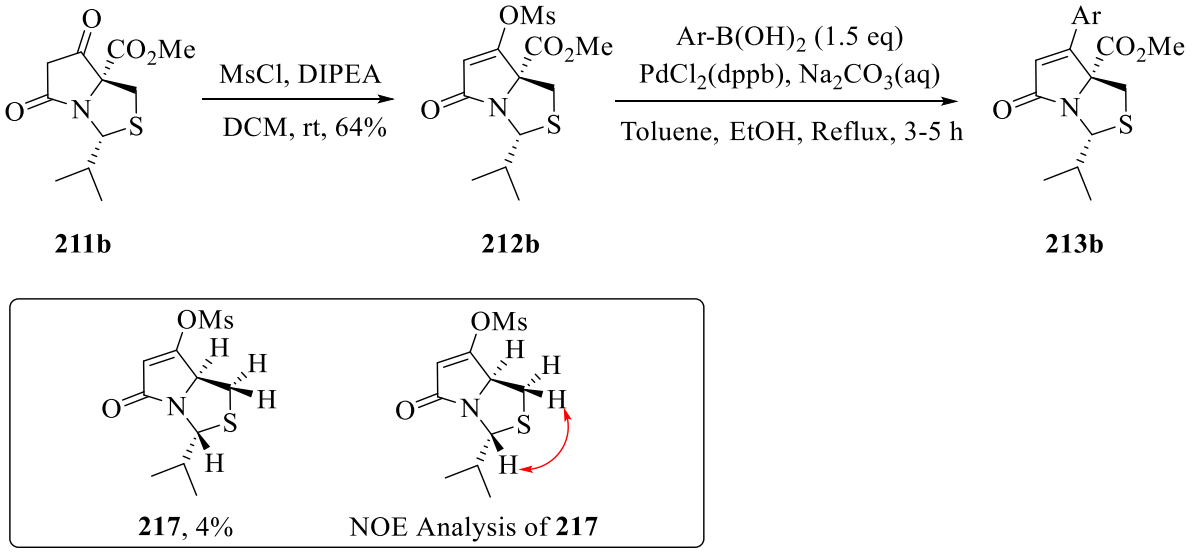


Figure 4.6: (A) ^{1}H NMR of *cis*-2,5 malonamide **210b**; (B) 1D gradient NOE showing selective irradiation at H2

4.3.3 Application of the Bicyclic Tetramate 211b

As a convenient substrate for Suzuki coupling, mesylate **212b** was synthesised from **211b** and MsCl/DIPEA (Scheme 4.5). The mesylate **212b** was produced with improved yield compared to the *tert*-butyl system (see Section 2.3.4, Chapter 2). The decarboxylated mesylate **217** was isolated in 4% yield. The stereochemistry of **217** was determined by NOE analysis which also demonstrated the stereochemistry of tetramate by-product **216**. The Suzuki coupling of **212b** with boronic acids provided pyrrolinones **213bi-biii** effectively, in 41-72% yields (Table 4.3).



Scheme 4.5: C6 Functionalisation of bicyclic teramate **211b** in the isopropyl system

Table 4.3: Suzuki coupling of mesylate **212b**

Sl No	Entry	Ar	Reaction Time (h)	Product	Yields (%)
1	**212b**	**i**: 4-methoxyphenyl	3	**213bi**	72
2	**212b**	**ii**: phenyl	3	**213bii**	74
3	**212b**	**iii**: 4-chlorophenyl[a]	5	**213biii**	41

[a] 4-chlorophenylboronic acid: 1.05 eq

The pyrrolinones **213bi-biii** were obtained in better yields compared to *O*-analogues **213ai-aiii** (see Table 4.1) and purification was much more convenient for the *S*-analogues. The poor yield of coupling adduct **213biii** was due to the tendency of further coupling with 4-chlorophenylboronic acid, detected in ^{1}H NMR of the crude product. The structure of pyrrolinones was confirmed by the X-ray crystal structure of representative compound **213bii** (Figure 4.7).

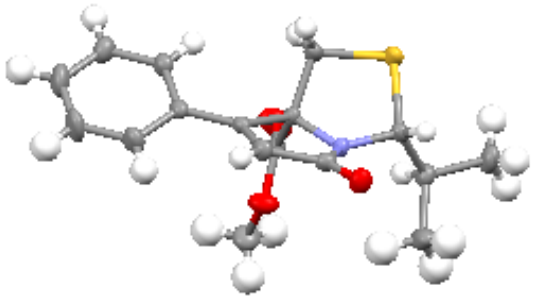


Figure 4.7: X-Ray crystal structure of **213bii**

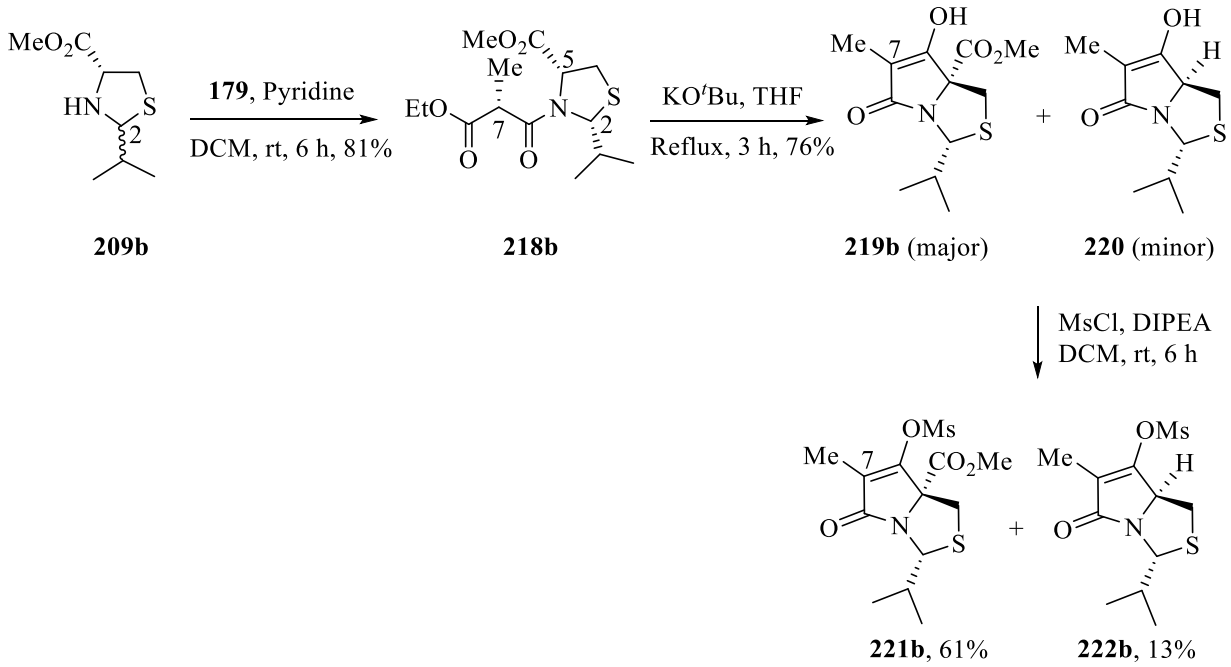
4.4 Preparation and Application of L-Cysteine Derived Tetramate: II

Following the remarkable success in the synthesis of bicyclic teramate motif **211b** and access to C3-arylpyrrolinone derivatives, it was of interest to investigate the preparation and reactions of C7-methyl bicyclic tetramate with an isopropyl NH and SH-protecting group. This would permit access to 3-aryl-4-methylpyrrolinone derivatives.

4.4.1 Synthesis of C7-Me Tetramate with Isopropyl Protecting Group

Alternative C7-methyl tetramate **219b** was developed following the methodology reported by Andrews and co-workers.[138] The thiazolidine **209b** was *N*-acylated by ethyl α-methylmalonyl chloride **179** and pyridine to furnish *cis*-2,5 malonamide **218b** (Scheme 4.6). The *trans*-2,5 malonamide was also formed as a minor product but only *cis*-2,5 malonamide **218b** was isolated. Dieckmann cyclisation under basic condition resulted in C7-methyl

tetramates **219b** and **220b** which were inseparable at this stage. The treatment of this mixture with MsCl/DIPEA gave mesylates **221b** and **222b** in 61% and 13% isolated yield, respectively. The structures of these novel compounds were determined by NMR and MS analysis.



Scheme 4.6: Synthesis of C7-Me Tetramic acid **221b** with isopropyl NH and SH-protecting group and subsequent mesylation

4.4.2 Stereochemistry of Intermediates

The *cis*-2,5 malonamide **218b** was found as a mixture of C7 epimers with *7R* as a major one and 1D gradient NMR spectropscopy showed the presence of rotameric exchange (Figure 4.8). The stereochemistry of the major malonamide analogue **218b** was assigned confidently by NOE analysis (Figure 4.9). The stereochemistry of the major tetramic acid **219b** was determined by NOE analysis, whereas that of minor was assigned by NOE analysis of mesylate derivative **222b**. The stereochemistry of major mesylate **221b** was also confirmed by NOE analysis.

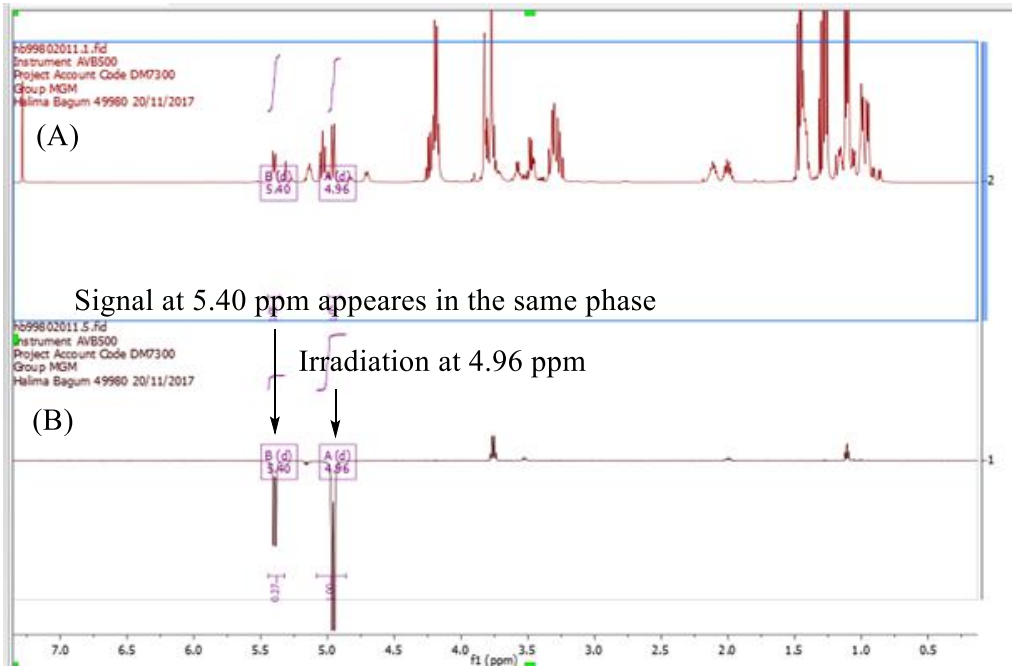


Figure 4.8: (A) ^{1}H NMR of *cis*-2,5 malonamide **218b**; (B) 1D gradient NOE showing selective irradiation at H2

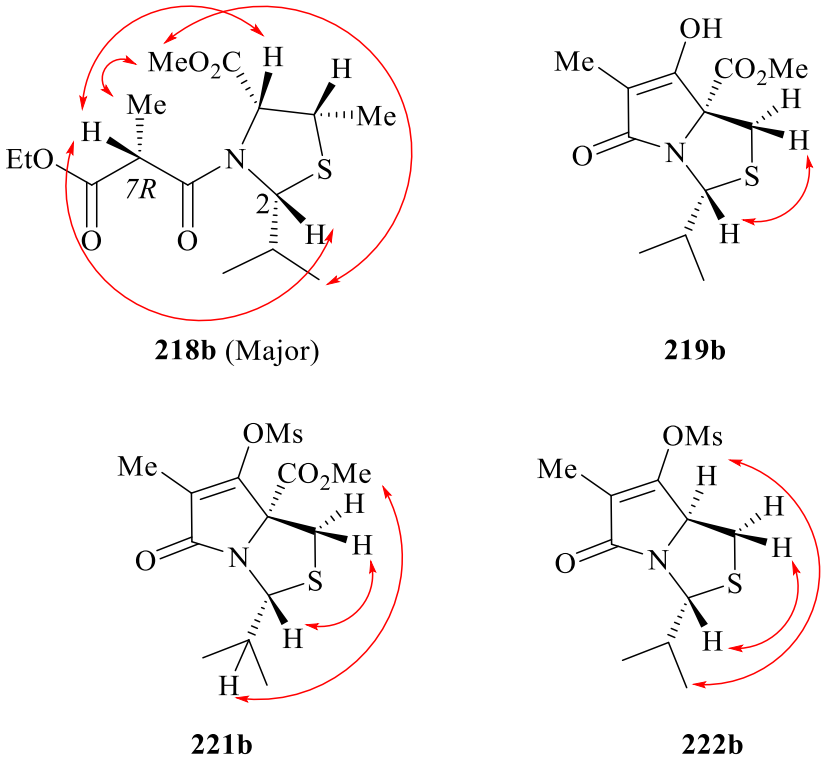
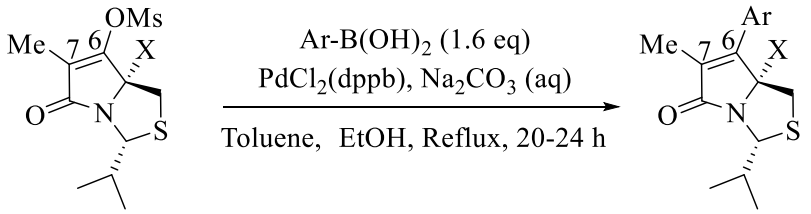


Figure 4.9: NOE Analysis of malonamide **218b**, tetramic acid **219b**, and mesylates **221b** and **222b**

4.4.3 C6 Functionalisation of C7-Me Bicyclic Tetramate via Suzuki Coupling

The Suzuki coupling reactions of mesylates **221b** and **222b** with arylboronic acids furnished the desired coupling adducts **223bi-biii** and **224bi** (Table 4.4). However, the reaction was much slower and gave a poor yield, which could be due to the presence of C7-methyl group as explained in Section 3.5 (see Chapter 3). The effect of steric bulk at adjacent carbon can also be interpreted with the improved yield for adduct **224bi**. The yields of the products could be improved by using optimal basic conditions as discussed in Section 3.5.2 (see Chapter 3).

Table 4.4: Suzuki coupling of mesylate **221b** and **222b**



221b (X = CO_2Me)
222b (X = H)

223b (X = CO_2Me)
224b (X = H)

Sl No	Entry	X	Ar	Reaction Time	Product	Yields
1	**221b**	CO_2Me	**i**: 4-methoxyphenyl	24h	**223bi**	13%
2	**222b**	H	**i**: 4-methoxyphenyl	24h	**224bi**	32%
3	**221b**	CO_2Me	**ii**: phenyl	20h	**223bii**	12%
4	**221b**	CO_2Me	**iii**: 4-chlorophenyl[a]	24h	**223biii**	11%

[a] 4-chlorophenylboronic acid: 1.05 eq

4.5 Antibacterial Screening

Some of the representative pyrrolinone derivatives were tested for antibacterial activity against Gram-negative and Gram-positive bacteria and all of them showed no activity (Table 4.5). The test method is provided in Appendix D.

Table 4.5: MIC values for the screening of representative compounds synthesised in Chapter 4 against several pathogens

Sl No	Compound	Gram-negative bacteria			Gram-positive bacteria
		EC 34	KL 18	PS 23	MRSA
1	**213ai**	n. a.	n. t.	n. t.	n. a.
2	**213aii**	n. a.	n. t.	n. t.	n. a.
3	**213aiii**	n. a.	n. t.	n. t.	n. a.
4	**213bi**	n. a.	n. t.	n. t.	n. a.
5	**213bii**	n. a.	n. t.	n. t.	n. a.
6	**213biii**	n. a.	n. t.	n. t.	n. a.
7	**223bi**	n. a.	n. t.	n. t.	n. a.
8	**223bii**	n. a.	n. t.	n. t.	n. a.
9	**223biii**	n. a.	n. t.	n. t.	n. a.
10	**224bi**	n. a.	n. t.	n. t.	n. a.

n. a. = not active; n. t. = not tested

4.6 Summary and Future Works

In this Chapter, it was demonstrated that a new class of tetramic acid with an isopropyl amide and alcohol/thiol protecting group can be prepared in a cost-effective way using 2-methylpropanal as the condensing reagent.

Although serine-derived intermediates and tetramate were found to be retained during silica purification, the application of this tetramate was useful. The successful C6 functionalisation furnished 3-arylpyrrolinone derivatives. Subsequent hydrogenation allowed access to 3-arylpyrrolidinone derivatives in high yields. Moreover, the modification of the tetramate core via efficient *N,O*-acetal deprotection gave an excellent result and 3-arylpyroglutaminol derivatives were prepared by this chemical transformation. Further elaboration of this system was thwarted by the prevention of isolation of some of the intermediates on silica. Most importantly, this route manifested that the densely functionalised 3-arylpyroglutaminol or 3-arylpyroglutamic acid derivatives can be prepared via a bicyclic tetramate with the *tert*-butyl NH/OH protecting group (see Chapter 2) or bicyclic tetramate with isopropyl NH/OH protecting group; the former is very easy to handle but the latter is much cheaper.

The cysteine-derived bicyclic tetramates with isopropyl NH/SH protecting group behaved in a similar fashion to bicyclic tetramates with a *tert*-butyl NH/SH protecting group. A library of 3-arylpyrrolinone and 3-aryl-4-methylpyrrolinone derivatives were prepared using the novel tetramate.

In short, a novel approach was developed for the tetramic and pyroglutamic acid derivatives. The aryl group was introduced late in the synthesis via Suzuki-Miyaura cross-coupling. The implementation of this strategy has the potential to provide a ready access to 3-arylpyrrolinones, 3-arylpyrrolidinones, 3-arylpyroglutaminols, 3-arylpyroglutamates and 3-aryl-4-methylpyrrolinone derivatives in a low-cost strategy.

The investigation was significant and revealed that cysteine-derived bicyclic tetramates with isopropyl NH/OH protecting group essentially can be an alternative to bicyclic tetramates with a *tert*-butyl NH/OH protecting group for further elaborations.

CHAPTER 5: EXPERIMENTAL

5.1 General Techniques

Reactions were conducted in oven-dried glassware and under an inert atmosphere of nitrogen. Starting materials were obtained from Sigma Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem or Acros Organics and used without further purification. Reaction times were recorded in minutes (min), hours (h) and days (d). Light petroleum ether of boiling point 40-60 °C was used as purchased from commercial suppliers. Solvents were evaporated at 40 °C under reduced pressure on a Büchi R-210 and RE 111 rotary evaporator attached to a Vacuubrand CVC2 pump and pressure control system.

Analytical thin-layer chromatography (TLC) was performed on Merck aluminium foil backed sheets precoated with 0.2 mm Kielselgel 60 F_{254}. The eluents are specified for each reaction. Ultraviolet light (254 nm) and potassium permanganate were used to visualize the spots. Flash column chromatography was performed on Kielselgel 60 silica gel (230-400 mesh particle size). The eluents are specified for each column.

NMR spectra were recorded on Bruker DPX200 (200 MHz), AVF400 (400 MHz), AVG400 (400 MHz), AVH400 (400 MHz), AVB500 (500 MHz), AVC500 (500 MHz) and AVX500 (500 MHz). ^{1}H NMR spectra were recorded at 400/500 MHz and data are reported as follows: chemical shifts (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dq = doublet of quartet, h = heptet and m = multiplet), coupling constant, nucleus). ^{13}C NMR spectra were recorded at 100/125 MHz with proton decoupling. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent peak for ^{1}H NMR spectra and deuterated solvent peak for ^{13}C NMR spectra, downfield from TMS. Coupling constants (*J*) are reported in Hertz (Hz). Assignments of the spectra have been

made using ^{1}H, ^{13}C, DEPTQ, COSY, HSQC and confirmation of stereochemistry was made using NOESY and X-ray crystallography. For X-ray crystallography, crystals were grown from slow vapour diffusion of petroleum ether into a solution of the sample at room temperature.

Infrared (IR) spectra were recorded by using Attenuated Total Reflection (ATR) sampling technique in a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Only selected peaks are reported.

Low Resolution Mass Spectra (m/z) were recorded by Fison Platform spectrometer using Electrospray Ionisation (ESI). The selected peaks are reported in Daltons and their intensities are given as percentages of the base peak. High Resolution Mass Spectra (HRMS) were recorded using a Bruker microTOF (ESI) instrument by the internal service at the Department of Chemistry, University of Oxford.

Optical rotations were measured with Perkin-Elmer 241 polarimeter at 25 °C. The wavelength of light was 589 nm and path length 1 dm. Concentrations (*c*) are given in g/100 mL and specific rotations in 10^{-1} deg cm^2 g^{-1}.

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

In the cases where products exist as a mixture of diastereomers, rotamers or tautomers, the ratio was calculated from ^{1}H NMR spectrum of mixtures.

Screening of novel compounds was performed against selected multidrug-resistant pathogens by Oxford Antibiotic Group, Austria. The compounds were tested in a primary 96 well plates screening assay, according to SOP 0906. The compounds were diluted in “MHB” for bacterial screening to a stock solution of 1000µg/mL, serial diluted and overlaid with a

microbe solution in a concentration of 10^4 CFU/mL. The plates were incubated at 35 °C for 24 hours.

5.2 Experimental for Chapter 2

5.2.1 Synthesis of Methyl Ester Hydrochloride: General Method A[136]

$SOCl_2$ (1.5 eq) was added dropwise to stirring anhydrous MeOH (2 M) at 0 °C, followed by L-amino acid (1 eq) portion-wise. The mixture was heated to 40 °C and stirred at this temperature for 3 h. The solvent was then evaporated under reduced pressure to give methyl ester hydrochlorides **146a-c**.

5.2.2 Synthesis of Oxazolidine and Thiazolidine Compounds: General Method B[131,137]

The ester hydrochloride of the L-amino acid **146a-d** (1.0 eq) was suspended in petroleum ether. Triethylamine (1.5 eq) and trimethylacetaldehyde (1.2 eq) were then added. The mixture was heated at reflux with continuous removal of water using a Dean-Stark apparatus for 18 h. The white precipitate was then filtered and washed with Et_2O. The combined filtrates were concentrated under reduced pressure to furnish the oxazolidines or thiazolidine **147a-d**.

5.2.3 *N*-Acylation of Oxazolidine and Thiazolidine Compounds: General Method C[131]

DMAP (0.05 eq) and DCC (1.05 eq) were added to a solution of oxazolidine or thiazolidine **147a-d** (1.0 eq) in anhydrous DCM. The mixture was cooled to 0 °C and ethyl malonate (1.05 eq) was added. The reaction mixture was then stirred 30 min at 0 °C and 5 h at room temperature. A white precipitate was formed, which was filtered and washed with DCM. The combined filtrates were concentrated *in vacuo* and purified by flash column chromatography to give the required *N*-acyl oxazolidines or thiazolidine **148a-d**.

5.2.4 Dieckmann Cyclisation: General Method D[131]

To a solution of *N*-acyl oxazolidine or thiazolidine **148a-d** (1.0 eq) in anhydrous THF was added potassium *tert*-butoxide (1.05 eq). The mixture was heated at reflux for 3 h. The reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the methyl ester tetramic acids **118a-d**.

5.2.5 Synthesis of Tosylate/Mesylate: General Method E[143]

Tetramic acid **118** (1.0 eq) was dissolved in DCM under nitrogen atmosphere. *p*-Toluenesulfonyl chloride or methanesulfonyl chloride (1 eq) and DIPEA (2 eq) were added to this solution. The resulting mixture was stirred for 2-6 h at room temperature until total consumption of the starting material. The reaction mixture was washed with 5% HCl, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel using ethyl acetate:petroleum ether as eluants to give tosylates **152a-b** or mesylates **153a-d**.

5.2.6 Attempted Methods for Suzuki Coupling

Procedure 1:[144] Tosylate/mesylate (1.0 eq) and boronic acid (1.2 eq) were dissolved in THF (0.1 M). $Pd(dppf)Cl_2$ (5 mol%) and a solution of Cs_2CO_3 (3.0 eq) in water (1/10 THF) was added subsequently to this solution. The reaction mixture was then stirred at room temperature for 40 minutes and refluxed until total consumption of the starting material. After completion, the reaction mixture was filtered through Celite and washed with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried over

anhydrous sodium sulfate and concentrated *in vacuo* to give crude material, which was purified by flash column chromatography.

Procedure 2:[145] To a suspension of the boronic acid (227 mg, 1.5 mmol) and the $NiCl_2(PPh_3)_2$ (24 mg, 0.04 mmol) in THF (10 mL) was added tosylate (153 mg, 0.37 mmol) in THF (0.1 M). The reaction mixture was stirred at room temperature or refluxed for 15 h and quenched using saturated sodium bicarbonate. The product was extracted with EtOAc, the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude material, which was purified by flash column chromatography.

***Procedure 3*: General Method F**[146]

A mixture of 1,4-bis(diphenylphosphino)butane (0.06 eq) and bis(benzonitrile)palladium(II) chloride (0.05 eq) in dry toluene was stirred at room temperature under nitrogen atmosphere for 30 minutes to form a creamy orange slurry of [1,4-bis(diphenylphosphino)butane] palladium(II) chloride. Tosylate/mesylate (1.0 eq), boronic acid (1.05-1.8 eq), ethanol (7.0 eq), 1 M aqueous sodium carbonate solution (9-18 eq) and dry toluene were added to the catalyst and the mixture was refluxed for 3-30 hours. After cooling, water was added, and the mixture was diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried and evaporated *in vacuo* to find the crude product, which was then purified to achieve **119ai-avii**, **119bi**, **119ci-cv**, **119di-dvii**, **158di-dv**, **162di-dii**, and **162dv** by flash column chromatography.

Procedure 4:[147] To a solution of aryl chloride (1.0 eq) in DMA:water (20/1) was added Pd/C (5 mol%), 4-methoxyphenylboronic acid (1.2 eq), and K_2CO_3 (2.0 eq) under a N_2 atmosphere. The reaction mixture was degassed and allowed to stir at 80 °C. The catalyst was filtered, washed with acetonitrile, and evaporated to find crude material, which was then purified by flash column chromatography.

Procedure 5:[148] A mixture of tosylate (1.0 eq) and tetrakis(triphenylphosphine)palladium(0) (0.05 eq) in DME was degassed and then stirred with gentle heating until it turned into a clear solution. 4-Methoxyphenylboronic acid (1.0 eq) and potassium *tert*-butoxide (2.0 eq) in *tert*-butyl alcohol (2.0 M) were then added. The reaction mixture was degassed again and refluxed at 95 °C for 15 minutes under N_2 atmosphere. The reaction mixture was filtered through Celite and washed with DCM. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography.

Procedure 6:[149] The mesylate (1.0 eq) was dissolved in a mixture of dry DMF and toluene. To this solution was added K_2CO_3 (7.6 eq), tetrakis(triphenylphosphine)palladium(0) (10 mol%) and 4-methoxyphenylboronic acid (3.8 eq). The reaction mixture was heated at 95 °C for 18 h under N_2 atmosphere. After being cooled to room temperature, water was added, and the solution was extracted with DCM. The organic layer was washed with water, dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography.

5.2.7 Attempted Methods for Reduction of C6-C7 double bond

Procedure 1:[150] To a solution of **119aii** (58 mg, 0.18 mmol) in DCM (1 mL) and AcOH (0.1 mL) at 0 °C was added $NaBH_4$ (14 mg, 0.38 mmol) portion wise. The reaction mixture was stirred at 0 °C for 6 h and then at room temperature for 30 h, after which time the mixture was quenched with water. The layers were separated, and the aqueous phase was extracted with DCM. The combined organic phase was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure which resulted recovery of starting material.

Procedure 2:[151] To a solution of **119ai** (62 mg, 0.18 mmol) in AcOH (1.3 mL) at 0 °C was added portion wise $NaBH_3CN$ (225 mg, 3.6 mmol) slowly. The reaction mixture was cooled

to 0°C, 2M NaOH was added cautiously and the mixture was extracted with ethyl ether to separate the organic layer, dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The starting material was recovered finally.

***Procedure 3*:**

General Method G: Hydrogenation[171]

To a solution of α,β-unsaturated lactam (1 eq) in EtOAc (0.05 M), platinum(IV) oxide (0.15 eq) was added. The reaction mixture was stirred at room temperature under H_2 atmosphere for 1-48 h, filtered through Celite, evaporated under reduced pressure, and then purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as eluents to give pure pyrrolidinones **121ai-av**, **121ci-cv**, and **159di-dv**.

5.2.8 Preparation of sulfone and sulfoxide: General Method H[153]

A solution of cysteine-derived mesylate **153d** (1 eq) in $CHCl_3$ (0.086 M) was cooled to 0°C. A solution of *m*-chloroperbenzoic acid (1.3-3.0 eq) in $CHCl_3$ (0.15 M) was added dropwise. The reaction mixture was stirred at room temperature for 12-17 hours. After completion, the mixture was poured into EtOAc (0.01 M) and the resultant solution was washed with sat. aq. solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to get crude sulfone or sulfoxide. The sulfone **157d** or sulfoxide **161d** was purified by flash column chromatography using 35-40% EtOAc in petroleum ether.

5.2.9 *N,O*-Acetal deprotection:[104] General Method I

Under a nitrogen atmosphere, the pyrrolinone or pyrrolidinone (1 eq) was treated with propane-1,3-dithiol (2.1-4.0 eq) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol. The solution was stirred at room temperature for 24-36 h or at 50 °C

for 12-17 h. The reaction mixture was concentrated *in vacuo,* the crude residue was dissolved in MeOH, washed with petroleum ether and concentrated under reduced pressure to give *N,O*-acetal deprotected amides **163-167**.

5.2.10 Preparation of α,β-Unsaturated Lactam: General Method J[142]

To a solution of alcohol **168a-b,d** (1.0 eq), triphenylphosphine (4.0 eq) and benzoic acid (1.05 eq) in anhydrous THF was added, dropwise, a solution of diethyl azodicarboxylate (1.7 eq) in anhydrous THF. The mixture was stirred at room temperature for 2-3 h, poured into a 0.05 M aqueous solution of NaH_2PO_4, extracted with EtOAc, dried over anhydrous Na_2SO_4 and evaporated *in vacuo.* Purification by flash column chromatography (petroleum ether:EtOAc, 9:1) gave alkene **169a-b,d**.

5.2.11 Attempted Reformatsky Conjugate Additions

Activation of Zinc:[134] Zinc powder was activated by shaking with a saturated solution of NH_4Cl for 5 min, followed by washing with H_2O, EtOH, Et_2O and then drying under high vacuum at room temperature for 3 h.

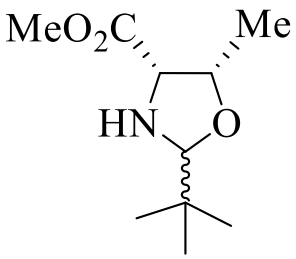
Method 1:[134] Under a nitrogen atmosphere, iodine (0.25 eq) and ethyl bromoacetate (3 eq) were added to activated Zn powder (10 eq) in THF. The mixture was sonicated for 15 min at 35-40°C. After cooling to 0°C, DMPU (15 eq) was added followed by a solution of unsaturated bicyclic lactam **169a** or **169d** (1 eq) in THF. The mixture was quickly brought to 40 °C and the mixture was sonicated at that temperature for 15 minutes. The reaction mixture was stirred at room temperature. Quenching of the mixture was carried out with sat. solution of NH_4Cl and then EtOAc was added to the residue. The aqueous phase was extracted three times with EtOAc and the combined organic phases were washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/Petrol:40/60).

Method 2:[154] To activated Zn powder (5 eq) in THF under a nitrogen atmosphere were added a few crystals of iodine, followed by ester (3 eq). The mixture was sonicated at 35-40 °C for 15 min. With stirring, unsaturated bicyclic lactam **169a** (1 eq) was added and the mixture was sonicated for 15 min at 35-40°C. After 18 h at reflux, the mixture was quenched with sat. solution of NH_4Cl and then EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo.* The crude material was purified by flash column chromatography (EtOAc-Petrol (40/60)).

(*2R,4S,5S*)- and (*2S,4S,5S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 147c

According to general method B, L-*allo*-threonine methyl ester hydrochloride **146c** (2.96 g, 17.5 mmol) was reacted with triethylamine (3.65 mL, 26.2 mmol) and trimethylacetaldehyde (2.27 mL, 20.9 mmol).

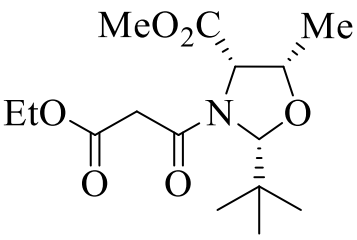


Yield 71% (2.5 g); colourless oil; 2.5:1 mixture of diastereomers; R_f (50% EtOAc in DCM) 0.60; ν_{max}/cm^{-1} 3313 (N-H), 2956 (C-H), 2872 (C-H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) major isomer (*2R*): 0.94 (9H, s, $C(CH_3)_3$), 1.01 (3H, d, *J* 6.4, $C(4)CH_3$), 2.49 (1H, br s, NH), 3.70 (3H, s, CO_2CH_3), 3.88-3.92 (1H, m, C(5)H), 4.02 (1H, s, C(2)H), 4.16 (1H, dq, *J* 8.2, 6.4, C(4)H); minor isomer (*2S*): 0.82 (9H, s, $C(CH_3)_3$), 1.00 (3H, d, *J* 6.4, $C(4)CH_3$), 2.49 (1H, br, NH), 3.68 (3H, s, CO_2CH_3), 3.88-3.92 (1H, m, C(5)H), 4.28-4.39 (1H, m, C(4)H), 4.54 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) major isomer (*2R*): 16.8 ($C(4)\underline{C}H_3$), 25.3 ($C(\underline{C}H_3)_3$), 32.8 ($\underline{C}(CH_3)_3$), 52.1 ($O\underline{C}H_3$), 63.3 (C(5)), 73.4 (C(4)), 98.5 (C(2)), 171.7 ($\underline{C}O_2CH_3$); minor isomer (*2S*): 16.0 ($C(4)\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_3$), 35.7

(C(CH$_3$)$_3$), 52.0 (OCH$_3$), 63.2 (C(5)), 74.6 (C(4)), 98.1 (C(2)), 171.8 (CO$_2$CH$_3$); m/z ([ESI]$^+$) 202.2 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 202.1438, $C_{10}H_{20}NO_3$ ([M+H]$^+$) requires 202.1438.

_(2R,4S,5S)_-2-(_tert_-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 148c

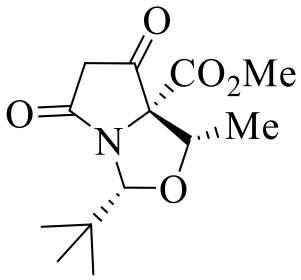
According to general method C, oxazolidine **147c** (3.5 g, 17.4 mmol), DCC (3.77 g, 18.3 mmol), and DMAP (106 mg, 0.9 mmol) was reacted with ethyl hydrogen malonate (2.15 mL, 18.3 mmol) in DCM.



Yield 66% (1.83 g); colourless oil; R_f (40% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$ -50.3 (*c* 1.0 in DCM); ν_{max}/cm-1 2981 (C-H), 2958 (C-H), 1743 (C=O), 1677 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, C(CH$_3$)$_3$), 1.21 (3H, t, *J* 7.2, C(10)CH$_3$), 1.35 (3H, d, *J* 6.4, C(4)CH$_3$), 3.33 (1H, d, *J* 15.3, C(7)H$_A$H$_B$), 3.42 (1H, d, *J* 15.3, C(7)H$_A$H$_B$), 3.70 (3H, s, CO$_2$CH$_3$), 4.08-4.18 (3H, m, C(9)H$_2$ + C(4)H), 4.44 (1H, d, *J* 6.6, C(5)H), 5.13 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.1 (C(10)), 15.4 (C(4)CH$_3$), 26.3 (C(CH$_3$)$_3$), 36.9 (C(CH$_3$)$_3$), 43.7 (C(7)), 52.0 (CO$_2$CH$_3$), 61.7 (C(9)), 62.8 (C(5)), 74.9 (C(4)), 96.5 (C(2)), 167.4 (C(8)), 167.8 (CO$_2$CH$_3$), 168.9 (C(6)); m/z ([ESI]$^+$) 338.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 316.1746, $C_{15}H_{26}NO_6$ ([M+H]$^+$) requires 316.1755.

_(2R,4S,5R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-6,8-dioxobicyclo [3.3.0]-octane, 118c

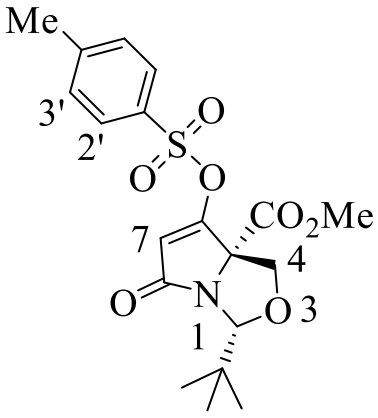
According to general method D, malonamide **148c** (1.84 g, 5.8 mmol) was refluxed with potassium *tert*-butoxide (685 mg, 6.1 mmol) in THF (0.2 M).



Yield 75% (1.17 g); yellow solid, m. p. 118-120; R_f (20% MeOH in EtOAc) 0.38; $[\alpha]_D^{25}$ +76.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2872 (C-H), 1755 (C=O), 1723 (C=O), 1623 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (9H, s, $C(CH_3)_3$), 1.60 (3H, d, *J* 6.5, $C(4)CH_3$), 3.07 (1H, d, *J* 21.2, $C(7)\underline{H}_A H_B$), 3.65 (1H, d, *J* 21.2, $C(7)H_A\underline{H}_B$), 3.71 (3H, s, CO_2CH_3), 3.75 (1H, q, *J* 6.5, C(4)H), 4.90 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.6 ($C(4)\underline{C}H_3$), 25.0 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 45.1 (C(7)), 52.9 ($CO_2\underline{C}H_3$), 76.6 (C(4)), 80.1 (C(5)), 96.8 (C(2)), 165.7 ($\underline{C}O_2CH_3$), 172.6 (C(8)), 198.3 (C(6)); m/z ($[ESI]^+$) 270.2 ($[M+H]^+$, 80%), 292.1 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 270.1336, $C_{13}H_{20}NO_5$ ($[M+H]^+$) requires 270.1336.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-tosyloxybicyclo[3.3.0]-oct-6-ene, 152a**

According to general method E, tetramic acid **118a** (2.37 g, 9.3 mmol) was reacted with TsCl (1.77 g, 9.3 mmol) and DIPEA (3.2 mL, 18.6 mmol) in DCM (0.1 M).

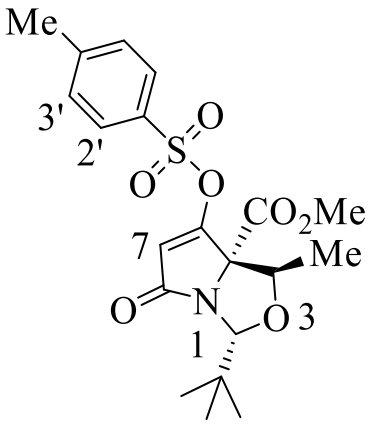


Yield 78% (2.97 g); white solid, m. p. 144-148°C; R_f (20% EA in PE) 0.26; $[\alpha]_D^{25}$ +72.9 (*c* 1.3 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2873 (C-H), 1723 (C=O), 1629 (C=O); δ_H (400 MHz, $CDCl_3$): 0.78 (9H, s, $C(CH_3)_3$), 2.43 (3H, s, Ar-$C\underline{H}_3$), 3.21 (1H, d, *J* 8.6, $C(4)\underline{H}_A H_B$), 3.50 (3H, s, CO_2CH_3), 4.58 (1H, s, C(2)H), 4.63 (1H, d, *J* 8.6, $C(4)H_A\underline{H}_B$), 5.77 (1H, s, C(7)H), 7.35 (2H, d, *J* 8.6, C(3')H), 7.74 (2H, d, *J* 8.6, C(2')H); δ_C (100 MHz, $CDCl_3$): 21.9 (Ar-$\underline{C}H_3$), 24.6 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 69.4 (C(4)), 75.0 (C(5)), 96.9 (C(2)), 107.5 (C(7)), 128.7 (C(2')), 130.3 (C(3')), 130.8 (C(4')), 147.2 (C(1')), 163.6 ($\underline{C}O_2CH_3$),

166.8 (C(8)), 175.6 (C(6)); m/z ([ESI]$^+$) 410.2 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 410.1277, $C_{19}H_{24}NO_7S$ ([M+H]$^+$) requires 410.1268.

***(2R,4R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-tosyloxy bicyclo[3.3.0]-oct-6-ene, 152b**

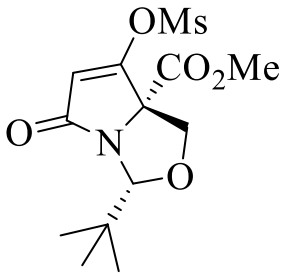
According to general method E, tetramic acid **118b** (56.0 mg, 0.2 mmol) was reacted with TsCl (40.0 mg, 0.2 mmol) and DIPEA (0.07 mL, 0.4 mmol) in DCM (0.1 M).



Yield 57% (50 mg); Colourless oil; R_f (20% EA in PE) 0.35; $[\alpha]_D^{25}$ +79.4 (*c* 1.1 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2874 (C-H), 1720 (C=O), 1627 (C=O); δ_H (400 MHz, $CDCl_3$): 0.76 (9H, s, $C(CH_3)_3$), 0.85 (3H, d, *J* 6.8, C(4)CH_3), 2.43 (3H, s, Ar$C\underline{H}_3$), 3.45 (3H, s, CO_2CH_3), 4.66 (1H, s, C(2)H), 4.94 (1H, q, *J* 6.8, C(4)H), 5.84 (1H, s, C(7)H), 7.35 (2H, d, *J* 8.2, C(3')H), 7.75 (2H, d, *J* 8.4, C(2')H); δ_C (100 MHz, $CDCl_3$): 14.3 (C(4)$\underline{C}H_3$), 21.9 (Ar-$\underline{C}H_3$), 24.6 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 73.5 (C(4)), 78.1 (C(5)), 94.0 (C(2)), 107.7 (C(7)), 128.7 (C(2')), 130.3 (C(3')), 130.8 (C(4')), 147.2 (C(1')), 161.9 ($\underline{C}O_2CH_3$), 167.3 (C(8)), 175.4 (C(6)); m/z ([ESI]$^+$) 424.2 ([M+H]$^+$, 60%), 446.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 424.1419, $C_{20}H_{26}O_7NS$ ([M+H]$^+$) requires 424.1425.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 153a**

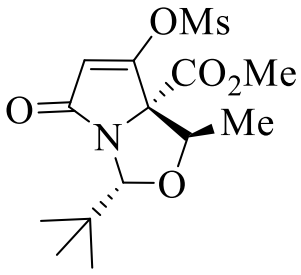
According to general method E, tetramic acid **118a** (6.83 g, 26.8 mmol) was reacted with MsCl (2.1 mL, 26.8 mmol) and DIPEA (9.3 mL, 53.6 mmol) in DCM (0.1 M).



Yield 64% (5.7 g); white solid, m. p. 186-188°C; R_f (50% EA in PE) 0.50; $[\alpha]_D^{25}$ +144.3 (*c* 1.1 in DCM); ν_{max}/cm^{-1} 2980 (C-H), 2885 (C-H), 1721 (C=O), 1632 (C=O); δ_H (400 MHz, $CDCl_3$): 0.85 (9H, s, $C(CH_3)_3$), 3.17 (3H, s, $OSO_2C\underline{H}_3$), 3.45 (1H, d, *J* 8.6, C(4)$\underline{H}_A$$H_B$), 3.76 (3H, s, CO_2CH_3), 3.67 (1H, s, C(2)H), 4.75 (1H, d, *J* 8.6, C(4)$H_A\underline{H}_B$), 5.86 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 23.6 ($C(\underline{C}H_3)_3$), 34.2 ($\underline{C}(CH_3)_3$), 37.2 (OSO_2CH_3), 52.5 ($CO_2\underline{C}H_3$), 68.5 (C(4)), 74.0 (C(5)), 96.0 (C(2)), 107.0 (C(7)), 161.9 ($\underline{C}O_2CH_3$), 166.3 (C(8)), 174.2 (C(6)); m/z ($[ESI]^+$) 356.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 356.0774, $C_{13}H_{19}NNaO_7S$ ($[M+Na]^+$) requires 356.0774.

***(2R,4R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 153b**

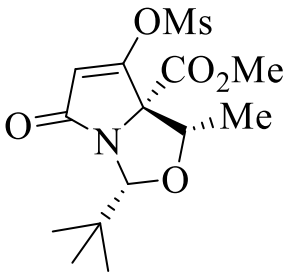
According to general method E, tetramic acid **118b** (3.45 g, 12.8 mmol) was reacted with MsCl (0.99 mL, 12.8 mmol) and DIPEA (4.45 mL, 25.6 mmol) in DCM (0.1 M).



Yield 25% (1.1 g); white solid, m. p. 138-140°C; R_f (40% EA in PE) 0.38; $[\alpha]_D^{25}$ +150.0 (*c* 1.1 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 2875 (C-H), 1720 (C=O), 1629 (C=O); δ_H (400 MHz, $CDCl_3$): 0.82 (9H, s, $C(CH_3)_3$), 1.01 (3H, d, *J* 6.7, C(4)CH_3), 3.17 (3H, s, $OSO_2C\underline{H}_3$), 3.75 (3H, s, CO_2CH_3), 4.73 (1H, s, C(2)H), 5.01 (1H, q, *J* 6.7, C(4)H), 5.90 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 14.6 (C(4)$\underline{C}H_3$), 24.6 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 38.2 ($OSO_2\underline{C}H_3$), 53.5 ($CO_2\underline{C}H_3$), 73.6 (C(4)), 78.1 (C(5)), 94.1 (C(2)), 108.6 (C(7)), 161.4 ($\underline{C}O_2CH_3$), 167.7 (C(8)), 175.0 (C(6)); m/z ($[ESI]^+$) 348.2 ($[M+H]^+$), 370.0 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 370.0918, $C_{14}H_{21}NNaO_7S$ ($[M+Na]^+$) requires 370.0931.

***(2R,4S,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 153c**

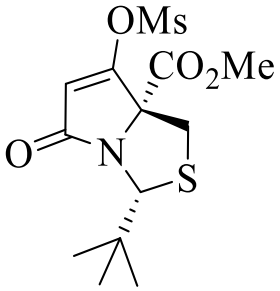
According to general method E, tetramic acid **118c** (478 mg, 1.8 mmol) was reacted with MsCl (0.14 mL, 1.8 mmol) and DIPEA (0.62 mL, 3.6 mmol) in DCM (0.1 M).



Yield 52% (320 mg); white solid, m. p. 88-90°C; R_f (40% EA in PE) 0.35; $[\alpha]_D^{25}$ +71.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2980 (C-H), 2884 (C-H), 1719 (C=O), 1630 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (9H, s, $C(CH_3)_3$), 1.58 (3H, d, *J* 6.5, C(4)CH_3), 3.19 (3H, s, $OSO_2C\underline{H}_3$), 3.71 (3H, s, CO_2CH_3), 3.72 (1H, q, *J* 6.5, C(4)H), 4.61 (1H, s, C(2)H), 5.83 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 14.7 (C(4)$\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.0 ($\underline{C}(CH_3)_3$), 38.0 ($OSO_2\underline{C}H_3$), 52.7 ($CO_2\underline{C}H_3$), 75.1 (C(5)), 79.5 (C(4)), 96.8 (C(2)), 107.3 (C(7)), 163.9 ($\underline{C}O_2CH_3$), 166.1 (C(8)), 175.8 (C(6)); m/z ($[ESI]^+$) 348.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 348.1110, $C_{14}H_{22}NO_7S$ ($[M+H]^+$) requires 348.1112.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-((methylsulfonyl)oxy)-5-methoxycarbonyl-8-oxa-3-thiabicyclo [3.3.0]-oct-6-ene, 153d**

According to general method E, tetramic acid **118d** (5.54 g, 20.4 mmol) was reacted with MsCl (1.58 mL, 20.4 mmol) and DIPEA (7.11 mL, 40.8 mmol) in DCM (0.1 M).

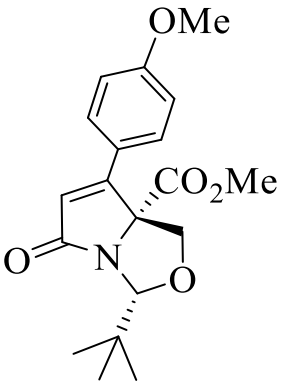


Yield 44% (3.16 g); white solid, m. p. 140-142°C; R_f (50% EA in PE) 0.48; $[\alpha]_D^{25}$ +232.3 (*c* 1.2 in DCM); ν_{max}/cm^{-1} 3010 (C-H), 2960 (C-H), 1714 (C=O), 1639 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 2.81 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.20 (3H, s, $OSO_2C\underline{H}_3$), 3.60 (1H, d, *J* 11.2, C(4)$H_A\underline{H_B}$), 3.78 (3H, s, CO_2CH_3), 4.91 (1H, s, C(2)H), 5.79 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 33.0 (C(4)), 36.8

($\underline{C}(CH_3)_3$), 38.2 ($OSO_2\underline{C}H_3$), 53.6 ($CO_2\underline{C}H_3$), 71.5 (C(2)), 79.6 (C(5)), 105.5 (C(7)), 162.7 ($\underline{C}O_2CH_3$), 167.3 (C(8)), 173.1 (C(6)); m/z ($[ESI]^+$) 372.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 350.0724, $C_{13}H_{20}NO_6S_2$ ($[M+H]^+$) requires 350.0727.

_(2R,5S)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 119ai

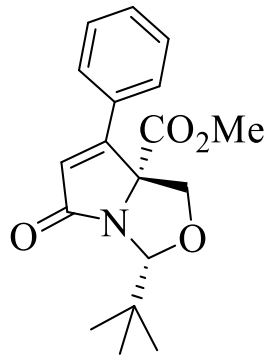
According to general method F, mesylate **153a** (623 mg, 1.9 mmol) was reacted with 4-methoxyphenylboronic acid (369 mg, 2.4 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.8 mL, 16.6 mmol) in ethanol (0.8 mL, 13.1 mmol) and toluene (15 mL) for 4 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (48 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (35 mg, 0.1 mmol) in toluene (3 mL).



Yield 80% (513 mg); white solid, m. p. 136-138°C; R_f (50% EA in PE) 0.58; $[\alpha]_D^{25}$ +155.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1742 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 3.41 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.57 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.68 (1H, s, C(2)H), 5.05 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.19 (1H, s, C(7)H), 6.86 (2H, d, *J* 9.0, C(3')H), 7.31 (2H, d, *J* 9.0, C(2')H); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 70.4 (C(4)), 77.4 (C(5)), 96.3 (C(2)), 114.7 (C(3')), 119.1 (C(7)), 122.5 (C(1')), 128.7 (C(2')), 159.2 (C(6)), 161.9 (C(4')), 170.0 ($\underline{C}O_2CH_3$), 177.8 (C(8)); m/z ($[ESI]^+$) 346.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 346.1642, $C_{19}H_{24}NO_5$ ($[M+H]^+$) requires 346.1649.

(2R,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo[3.3.0]-oct-6-ene, 119aii

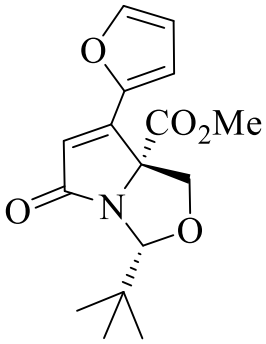
According to general method F, mesylate **153a** (741 mg, 2.2 mmol) was reacted with phenylboronic acid (351 mg, 2.9 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (2.1 mL, 20.0 mmol) in ethanol (0.9 mL, 15.5 mmol) and toluene (15 mL) for 5 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (57 mg, 0.13 mmol) and $(C_6H_5CN)_2PdCl_2$ (43 mg, 0.1 mmol) in toluene (3 mL).



Yield 64% (300 mg); white solid, m. p. 162-164°C; R_f (20% EA in PE) 0.25; $[\alpha]_D^{25}$ +153.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2866 (C-H), 1742 (C=O), 1699 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 3.44 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.57 (3H, s, CO_2CH_3), 4.70 (1H, s, C(2)H), 5.08 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.33 (1H, s, C(7)H), 7.36 (5H, s, ArH); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 70.4 (C(4)), 77.4 (C(5)), 96.3 (C(2)), 121.6 (C(7)), 126.9-131.2 (ArC), 159.5 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 177.4 (C(8)); m/z ($[ESI]^+$) 316.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 316.1543, $C_{18}H_{22}NO_4$ ($[M+H]^+$) requires 316.1543.

(2R,5S)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 119aiii

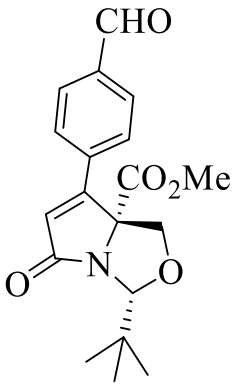
According to general method F, mesylate **153a** (513 mg, 1.5 mmol) was reacted with 2-furylboronic acid (206 mg, 1.8 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.47 mL, 13.8 mmol) in ethanol (0.62 mL, 10.8 mmol) and toluene (15 mL) for 12 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (39 mg, 0.09 mmol) and $(C_6H_5CN)_2PdCl_2$ (29 mg, 0.08 mmol) in toluene (3 mL).



Yield 47% (219 mg); yellow solid, m. p. 98-102°C; R_f (30% EA in PE) 0.43; $[\alpha]_D^{25}$ +47.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2871 (C-H), 1711 (C=O), 1627 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 3.33 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.64 (3H, s, CO_2CH_3), 4.67 (1H, s, C(2)H), 4.92 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 6.15 (1H, s, C(7)H), 6.43 (1H, dd, *J* 3.6, 1.8, C(3')H), 6.59 (1H, d, *J* 3.6, C(4')H). 7.49 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 75.9 (C(5)), 96.7 (C(2)), 112.7 (C(3')), 113.8 (C(4')), 118.1 (C(7)), 145.9 (C(5')), 146.1 (C(2')), 147.8 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 177.6 (C(8)); m/z ($[ESI]^+$) 328.0 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 306.1336, $C_{16}H_{20}O_5N$ ($[M+H]^+$) requires 306.1336.

_(2R,5S)_-1-Aza-2-(_tert_-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 119aiv

According to general method F, mesylate **153a** (676 mg, 2.0 mmol) was reacted with 4-formylphenylboronic acid (396 mg, 2.6 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.9 mL, 18.3 mmol) in ethanol (0.82 mL, 14.2 mmol) and toluene (15 mL) for 11 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (39.0 mg, 0.09 mmol) and $(C_6H_5CN)_2PdCl_2$ (29 mg, 0.08 mmol) in toluene (3 mL).

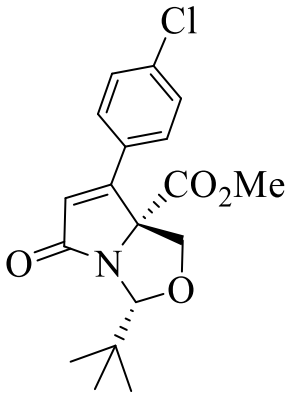


Yield 28% (194 mg); white solid, m. p. 154-158°C; R_f (10% EA in DCM) 0.46; $[\alpha]_D^{25}$ +119.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2871 (C-H), 1743 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 3.47 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.58 (3H, s, CO_2CH_3), 4.72 (1H, s, C(2)H), 5.10 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.47 (1H, s, C(7)H), 7.53 (2H, d, *J* 8.6, C(2')H), 7.88 (2H, d, *J* 8.6, C(3')H). 9.98 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.4 ($CO_2\underline{C}H_3$), 70.4 (C(4)), 77.4

(C(5)), 96.5 (C(2)), 124.4 (C(7)), 127.5 (C(2')), 130.4 (C(3')), 135.1 (C(4')), 137.6 (C(1')), 157.8 (C(6)), 169.4 ($\underline{C}O_2CH_3$), 176.6 (C(8)), 191.1 (CHO); m/z ($[ESI]^+$) 344.2 ($[M+H]^+$, 30%), 366.2 ($[M+Na]^+$, 50%); HRMS ($[ESI]^+$) found 366.1309, $C_{19}H_{21}O_5NNa$ ($[M+Na]^+$) requires 366.1312.

***(2R,5S)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 119av**

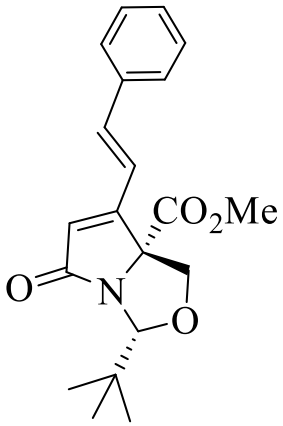
According to general method F, mesylate **153a** (676 mg, 2.0 mmol) was reacted with 4-chlorophenylboronic acid (201 mg, 0.6 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.6 mL, 5.4 mmol) in ethanol (0.24 mL, 4.2 mmol) and toluene (15 mL) for 7 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (15 mg, 0.04 mmol) and $(C_6H_5CN)_2PdCl_2$ (11.5 mg, 0.03 mmol) in toluene (2 mL).



Yield 49% (103 mg); white solid, m. p. 168-172°C; R_f (20% EA in PE) 0.32; $[\alpha]_D^{25}$ +133.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1743 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 3.42 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.57 (3H, s, CO_2CH_3), 4.69 (1H, s, C(2)H), 5.05 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.32 (1H, s, C(7)H), 7.29 (2H, d, *J* 8.9, C(2')H), 7.33 (2H, d, *J* 8.9, C(3')H); δ_C (100 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 77.4 (C(5)), 96.4 (C(2)), 122.1 (C(7)), 128.2 (C(2')), 128.3 (C(4')), 129.7 (C(3')), 137.4 (C(1')), 158.1 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 177.0 (C(8)); m/z ($[ESI]^+$) 372.0 ($[M+Na]^+$, ^{35}Cl, 100%), 374.0 ($[M+Na]^+$, ^{37}Cl, 25%); HRMS ($[ESI]^+$) found 372.0970, $C_{18}H_{20}O_4NClNa$ ($[M+Na]^+$, ^{35}Cl) requires 372.0973.

(2R,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-((*E*)-styryl)bicyclo [3.3.0]-oct-6-ene, 119avi

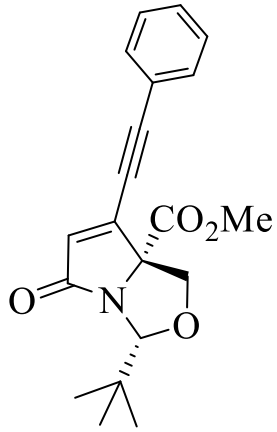
According to general method F, mesylate **153a** (101 mg, 0.3 mmol) was reacted with *trans*-2-phenylvinylboronic acid (67 mg, 0.45 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.3 mL, 2.7 mmol) in ethanol (0.12 mL, 2.1 mmol) and toluene (10 mL) for 48 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (7.7 mg, 0.018 mmol) and $(C_6H_5CN)_2PdCl_2$ (5.8 mg, 0.015 mmol) in toluene (1 mL).



Yield 25% (26 mg); yellow solid, m. p. 218-220°C; R_f (30% EA in PE) 0.45; $[\alpha]_D^{25}$ +6.4 (*c* 0.9 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 1742 (C=O), 1707 (C=O); δ_H (500 MHz, $CDCl_3$): 0.98 (9H, s, $C(CH_3)_3$), 3.44 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.77 (3H, s, CO_2CH_3), 4.76 (1H, s, C(2)H), 5.08 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 6.09 (1H, s, C(7)H), 6.84 (1H, d, *J* 16.7, C(10)H), 6.94 (1H, d, *J* 16.7, C(9)H), 7.36-7.53 (5H, m, ArH); δ_C (125 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.1 (C(4)), 76.7 (C(5)), 96.3 (C(2)), 119.2 (C(10)), 123.8 (C(7)), 127.5-135.1 (ArC), 137.4 (C(9)), 157.3 (C(6)), 170.1 ($\underline{C}O_2CH_3$), 177.6 (C(8)); m/z ($[ESI]^+$) 342.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 342.1699, $C_{20}H_{24}NO_4$ ($[M+H]^+$) requires 342.1700.

(2R,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-(phenylethynyl)bicyclo [3.3.0]-oct-6-ene, 119avii

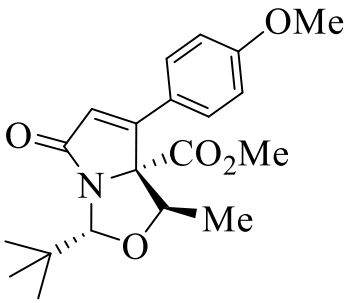
According to general method F, mesylate **153a** (276 mg, 0.83 mmol) was reacted with 2-phenyl-1-ethynylboronic acid (303 mg, 1.33 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.8 mL, 7.5 mmol) in ethanol (0.34 mL, 5.8 mmol) and toluene (13 mL) for 12 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (21 mg, 0.05 mmol) and $(C_6H_5CN)_2PdCl_2$ (16 mg, 0.04 mmol) in toluene (1 mL).



Yield 20% (55.0 mg); yellow sticky material; R_f (20% EA in PE) 0.32; $[\alpha]_D^{25}$ +11.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2871 (C-H), 1748 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 3.36 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.73 (3H, s, CO_2CH_3), 4.68 (1H, s, C(2)H), 4.85 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 6.16 (1H, s, C(7)H), 7.25-7.45 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.4 (C(4)), 78.9 (C(5)), 79.5 (C(9)), 97.4 (C(2)), 105.2 (C(10)), 120.9, 128.6, 130.3, 132.2 (ArC), 129.4 (C(7)), 141.9 (C(6)), 168.3 ($\underline{C}O_2CH_3$), 177.3 (C(8)); m/z ($[ESI]^+$) 362.2 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 362.1362, $C_{20}H_{21}NNaO_4$ ($[M+Na]^+$) requires 362.1363.

***(2R,4R,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 119bi**

According to general method F, mesylate **153b** (106.0 mg, 0.3 mmol) was reacted with 4-methoxyphenylboronic acid (60 mg, 0.4 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.3 mL, 2.8 mmol) in ethanol (0.13 mL, 2.2 mmol) and toluene (10 mL) for 50 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.0 mg, 0.018 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.0 mg, 0.015 mmol) in toluene (1 mL).

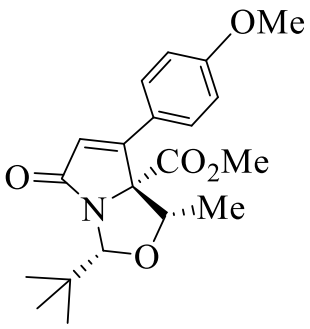


Yield 14% (15 mg); white solid, m. p. 150-152°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ +193.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2872 (C-H), 1743 (C=O), 1707 (C=O); δ_H (500 MHz, $CDCl_3$): 0.95 (9H, s, $C(CH_3)_3$), 0.96 (3H, d, *J* 6.6, C(4)CH_3), 3.65 (3H, s, CO_2CH_3), 3.86 (3H, s, OCH_3), 4.83 (1H, s, C(2)H), 5.40 (1H, q, *J* 6.6, C(4)H), 6.35 (1H, s, C(7)H), 6.95 (2H, d, *J* 8.9, C(3')H), 7.41 (2H, d, *J* 8.9, C(2')H); δ_C (125 MHz, $CDCl_3$): 14.0 (C(4)$\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 35.3

($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 74.3 (C(4)), 80.3 (C(5)), 93.3 (C(2)), 114.7 (C(3')), 120.2 (C(7)), 122.3 (C(1')), 128.7 (C(2')), 157.3 (C(6)), 161.8 (C(4')), 170.4 ($\underline{C}O_2CH_3$), 177.3 (C(8)); m/z ([ESI]$^+$) 360.2 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 360.1808 $C_{20}H_{26}NO_5$ ([M+H]$^+$) requires 360.1806.

***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 119ci**

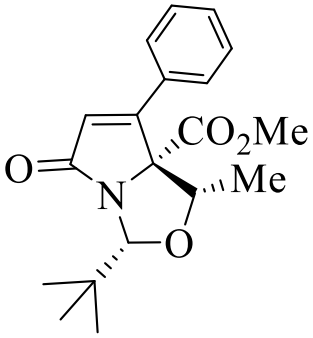
According to general method F, mesylate **153c** (264.0 mg, 0.73 mmol) was reacted with 4-methoxyphenylboronic acid (166 mg, 1.1 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.7 mL, 6.6 mmol) in ethanol (0.3 mL, 5.1 mmol) and toluene (13 mL) for 4 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (18.7 mg, 0.043 mmol) and $(C_6H_5CN)_2PdCl_2$ (14.0 mg, 0.037 mmol) in toluene (2 mL).



Yield 70% (183 mg); white solid, m. p. 174-176°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ -86.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2870 (C-H), 1710 (C=O), 1607 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.71 (3H, d, *J* 6.6, C(4)CH_3), 3.51 (1H, q, *J* 6.6, C(4)H), 3.61 (3H, s, CO_2CH_3), 3.78 (3H, s, OCH_3), 4.67 (1H, s, C(2)H), 6.23 (1H, s, C(7)H), 6.86 (2H, d, *J* 9.0, C(3')H), 7.37 (2H, d, *J* 9.0, C(2')H); δ_C (100 MHz, $CDCl_3$): 14.7 (C(4)$\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 52.5 ($CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 76.7 (C(5)), 80.3 (C(4)), 95.9 (C(2)), 114.5 (C(3')), 119.9 (C(7)), 122.9 (C(1')), 128.5 (C(2')), 159.0 (C(4')), 161.6 (C(6)), 169.4 ($\underline{C}O_2CH_3$), 178.0 (C(8)); m/z ([ESI]$^+$) 360.2 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 360.1803 $C_{20}H_{26}NO_5$ ([M+H]$^+$) requires 360.1806.

(2R,4S,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0]-oct-6-ene, 119cii

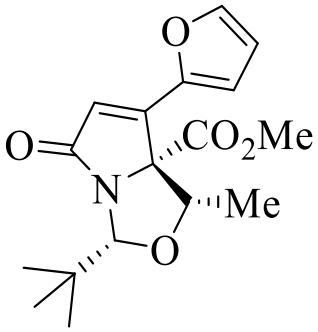
According to general method F, mesylate **153c** (92.0 mg, 0.26 mmol) was reacted with phenylboronic acid (48 mg, 0.39 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 4 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (7 mg, 0.0156 mmol) and $(C_6H_5CN)_2PdCl_2$ (5 mg, 0.013 mmol) in toluene (1 mL).



Yield 80% (70.0 mg); white solid, m. p. 110-112°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25}$ -25.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2869 (C-H), 1748 (C=O), 1710 (C=O); δ_H (500 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 1.78 (3H, d, *J* 6.5, C(4)CH_3), 3.63 (1H, q, *J* 6.5, C(4)H), 3.71 (3H, s, CO_2CH_3), 4.77 (1H, s, C(2)H), 6.44 (1H, s, C(7)H), 7.38-7.53 (5H, m, ArH); δ_C (125 MHz, $CDCl_3$): 14.7 (C(4)$\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 52.6 ($CO_2\underline{C}H_3$), 76.8 (C(5)), 80.2 (C(4)), 96.0 (C(2)), 122.6 (C(7)), 126.8-130.8 (ArC), 159.5 (C(6)), 169.0 ($\underline{C}O_2CH_3$), 177.6 (C(8)); m/z ($[ESI]^+$) 352.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 352.1513, $C_{19}H_{23}NNaO_4$ ($[M+Na]^+$) requires 352.1519.

(2R,4S,5S)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo[3.3.0]-oct-6-ene, 119ciii

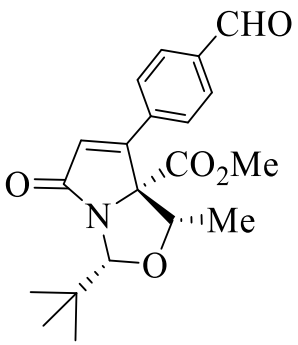
According to general method F, mesylate **153c** (116.0 mg, 0.33 mmol) was reacted with 2-furylboronic acid (56.0 mg, 0.5 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.31 mL, 3.0 mmol) in ethanol (0.14 mL, 2.3 mmol) and toluene (10 mL) for overnight. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.5 mg, 0.02 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.4 mg, 0.017 mmol) in toluene (1 mL).



Yield 28% (30.0 mg); yellow solid, m. p. 38-40°C; R_f (20% EA in PE) 0.27; $[\alpha]_D^{25}$ -10.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 2871 (C-H), 1749 (C=O), 1711 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.73 (3H, d, *J* 6.6, C(4)$\underline{C}H_3$), 3.52 (1H, q, *J*, 6.6, C(4)H), 3.59 (3H, s, CO_2CH_3), 4.68 (1H, s, C(2)H), 6.18 (1H, s, C(7)H), 6.44 (1H, dd, *J* 3.6, 1.8, C(3')H), 6.67 (1H, d, *J* 3.6, C(4')H). 7.49 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 14.4 (C(4)C$\underline{H}_3$), 25.0 (C($\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 52.5 ($CO_2\underline{C}H_3$), 75.7 (C(5)), 80.6 (C(4)), 96.2 (C(2)), 112.6 (C(3')), 113.7 (C(4')), 118.7 (C(7)), 145.5 (C(5')), 146.3 (C(2')), 148.1 (C(6)), 168.6 ($\underline{C}O_2CH_3$), 177.8 (C(8)); m/z ($[ESI]^+$) 320.2 ($[M+H]^+$, 60%), 342.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 320.1483, $C_{17}H_{22}O_5N$ ($[M+H]^+$) requires 320.1493.

***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo [3.3.0]-oct-6-ene, 119civ**

According to general method F, mesylate **153c** (118 mg, 0.34 mmol) was reacted with 4-formylphenylboronic acid (76.5 mg, 0.51 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.32 mL, 3.06 mmol) in ethanol (0.14 mL, 2.38 mmol) and toluene (10 mL) for 28 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.7 mg, 0.02 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.5 mg, 0.017 mmol) in toluene (1 mL).

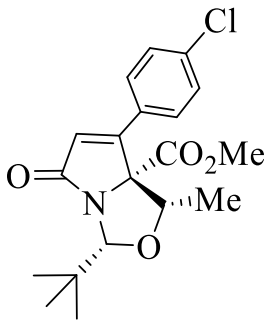


Yield 36% (44 mg); white solid, m. p. 82-84°C; R_f (40% EA in PE) 0.44; $[\alpha]_D^{25}$ -71.0 (*c* 1.0 DCM); ν_{max}/cm^{-1} 2980 (C-H), 2870 (C-H), 1748 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.69 (3H, d, *J*, 6.5, C(4)CH_3), 3.56 (1H, q, *J*, 6.5, C(4)H), 3.64 (3H, s, CO_2CH_3), 4.69 (1H, s, C(2)H), 6.48 (1H, s, C(7)H), 7.56 (2H, d, *J* 8.4, C(2')H), 7.87 (2H, d, *J* 8.4, C(3')H). 9.98 (1H, s, CHO); δ_C (100

MHz, $CDCl_3$): 14.8 (C(4)$\underline{C}H_3$), 25.0 (C($\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 76.9 (C(5)), 80.1 (C(4)), 96.1 (C(2)), 125.4 (C(7)), 127.3 (C(2')), 130.2 (C(3')), 135.8 (C(4')), 137.3 (C(1')), 157.8 (C(6)), 168.7 ($\underline{C}O_2CH_3$), 176.7 (C(8)), 191.1 (CHO); m/z ($[ESI]^+$) 358.2 ($[M+H]^+$, 90%); HRMS ($[ESI]^+$) found 358.1650, $C_{20}H_{24}O_5N$ requires ($[M+H]^+$) 358.1649.

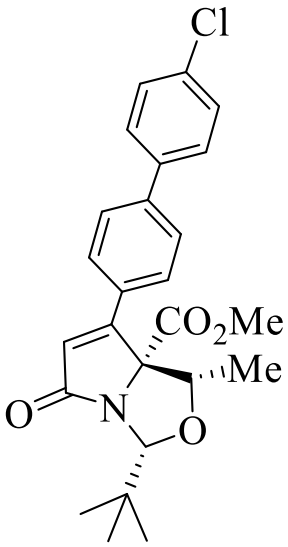
***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 119cv**

According to general method F, mesylate **153c** (122 mg, 0.35 mmol) was reacted with 4-chlorophenylboronic acid (58 mg, 0.37 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.33 mL, 3.15 mmol) in ethanol (0.14 mL, 2.45 mmol) and toluene (10 mL) for 4 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (9.0 mg, 0.021 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.7 mg, 0.018 mmol) in toluene (1 mL).



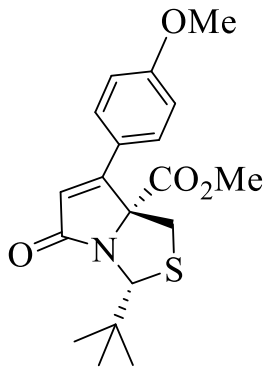
Yield 71% (90.0 mg); white solid, m. p. 128-130°C; R_f (20% EA in PE) 0.40; $[\alpha]_D^{25}$ -51.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2977 (C-H), 2870 (C-H), 1748 (C=O), 1711 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.68 (3H, d, *J* 6.5, C(4)CH_3), 3.52 (1H, q, *J* 6.5, C(4)H), 3.62 (3H, s, CO_2CH_3), 4.67 (1H, s, C(2)H), 6.34 (1H, s, C(7)H), 7.33 (4H, s, ArH); δ_C (100 MHz, $CDCl_3$): 14.7 (C(4)$\underline{C}H_3$), 25.0 (C($\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 76.7 (C(5)), 80.2 (C(4)), 96.0 (C(2)), 123.0 (C(7)), 128.0-137.0 (ArC), 158.0 (C(6)), 168.9 ($\underline{C}O_2CH_3$), 177.2 (C(8)); m/z ($[ESI]^+$) 364.2 ($[M+H]^+$, ^{35}Cl, 50%), 366.2 ($[M+H]^+$, ^{37}Cl, 15%); HRMS ($[ESI]^+$) found 364.1307, $C_{19}H_{23}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 364.1310.

***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-6-(4'-chloro-[1,1'-biphenyl]-4-yl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 154**



By-product from **119cv**; Yield 5% (15 mg); white solid, m. p. 148-150°C; R_f (20% EA in PE) 0.35; $[\alpha]_D^{25}$ -56.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 1748 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.73 (3H, d, *J* 6.5, $C(4)CH_3$), 3.55 (1H, q, *J* 6.5, C(4)H), 3.64 (3H, s, CO_2CH_3), 4.69 (1H, s, C(2)H), 6.40 (1H, s, C(7)H), 7.34-7.57 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.8 ($C(4)\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 80.3 (C(4)), 96.0 (C(2)), 122.5 (C(7)), 127.4-142.3 (ArC), 158.7 (C(6)), 169.1 ($\underline{C}O_2CH_3$), 177.5 (C(8)); m/z ($[ESI]^-$) 338.8 ($[M-H]^-$, ^{35}Cl, 40%),]$^-$) 340.8 ($[M-H]^-$, ^{37}Cl, 30%); HRMS ($[ESI]^+$) found 440.1610, $C_{25}H_{27}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 440.1623.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene, 119di**



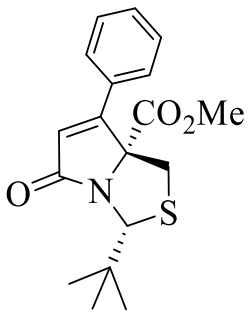
According to general method F, mesylate **153d** (117 mg, 0.33 mmol) was reacted with 4-methoxyphenylboronic acid (75 mg, 0.49 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.3 mL, 2.97 mmol) in ethanol (0.13 mL, 2.31 mmol) and toluene (13 mL) for 3 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.4 mg, 0.02 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.4 mg, 0.02 mmol) in toluene (1 mL).

Yield 62% (75 mg); yellow solid, m. p. 50-52°C; R_f (30% EA in PE) 0.38; $[\alpha]_D^{25}$ +276.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3040 (C-H), 2954 (C-H), 2906 (C-H), 1703 (C=O), 1644 (C=O); δ_H

(400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 2.78 (1H, d, *J* 11.0, C(4)$\underline{H_A}H_B$), 3.58 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.89 (1H, d, *J* 11.0, C(4)$H_A\underline{H_B}$), 4.92 (1H, s, C(2)H), 6.14 (1H, s, C(7)H), 6.85 (2H, d, *J* 8.9, C(3')H), 7.39 (2H, d, *J* 8.9, C(2')H); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.6 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 70.6 (C(2)), 81.9 (C(5)), 114.7 (C(3')), 117.6 (C(7)), 122.4 (C(1')), 128.5 (C(2')), 158.8 (C(4')), 161.7 (C(6)), 170.1 ($\underline{C}O_2CH_3$), 175.3 (C(8)); m/z ($[ESI]^+$) 362.2 ($[M+H]^+$, 100%), 384.2 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 362.1417, $C_{19}H_{24}O_4NS$ ($[M+H]^+$) requires 362.1421.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene, 119dii**

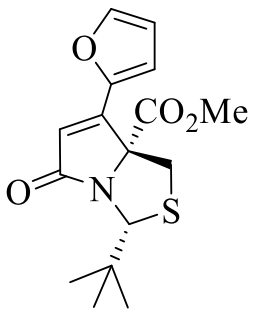
According to general method F, mesylate **153d** (361 mg, 1.03 mmol) was reacted with phenylboronic acid (188 mg, 1.55 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.98 mL, 9.27 mmol) in ethanol (0.42 mL, 7.21 mmol) and toluene (13 mL) for 3 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (31.5 mg, 0.074 mmol) and $(C_6H_5CN)_2PdCl_2$ (19.7 mg, 0.052 mmol) in toluene (2 mL).



Yield 58% (200 mg); white solid, m. p. 128-130°C; R_f (40% EA in PE) 0.60; $[\alpha]_D^{25}$ +266.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2980 (C-H), 2904 (C-H), 1745 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 2.81 (1H, d, *J* 11.0, C(4)$\underline{H_A}H_B$), 3.58 (3H, s, CO_2CH_3), 3.90 (1H, d, *J* 11.0, C(4)$H_A\underline{H_B}$), 4.93 (1H, s, C(2)H), 6.28 (1H, s, C(7)H), 7.32-7.45 (5H, s, ArH); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.6 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.6 (C(2)), 82.0 (C(5)), 120.1 (C(7)), 126.8-130.9 (ArC), 159.1 (C(6)), 169.8 ($\underline{C}O_2CH_3$), 174.9 (C(8)); m/z ($[ESI]^+$) 332.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 332.1311, $C_{18}H_{22}NO_3S$ ($[M+H]^+$) requires 332.1315.

(2R,5R)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene, 119diii

According to general method F, mesylate **153d** (240 mg, 0.69 mmol) was reacted with 2-furylboronic acid (116 mg, 1.04 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.66 mL, 6.21 mmol) in ethanol (0.3 mL, 4.83 mmol) and toluene (12 mL) for 20 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (17.7 mg, 0.04 mmol) and $(C_6H_5CN)_2PdCl_2$ (13.2 mg, 0.03 mmol) in toluene (2 mL).

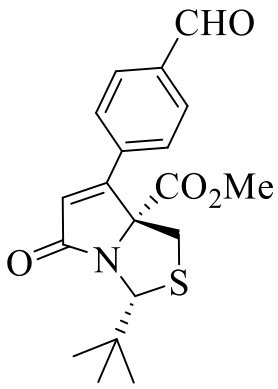


Yield 22% (35 mg); white solid, m. p. 118-120°C; R_f (40% EA in PE) 0.49; $[\alpha]_D^{25}$ +179.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C-H), 2869 (C-H), 1745 (C=O), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 2.69 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.64 (3H, s, CO_2CH_3), 3.77 (1H, d, *J* 11.1, C(4)$H_A\underline{H_B}$), 4.90 (1H, s, C(2)H), 6.10 (1H, s, C(7)H), 6.43 (1H, dd, *J* 3.6, 1.8, C(3')H), 6.60 (1H, d, *J* 3.6, C(4')H). 7.49 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.5 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 71.1 (C(2)), 80.4 (C(5)), 112.6 (C(3')), 113.3 (C(4')), 116.4 (C(7)), 145.7 (C(5')), 145.8 (C(2')), 148.1 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 175.0 (C(8)); m/z ($[ESI]^+$) 322.2 ($[M+H]^+$, 90%), 344.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 322.1102, $C_{16}H_{20}O_4NS$ ($[M+H]^+$) requires 322.1108.

(2R,5R)-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene, 119div

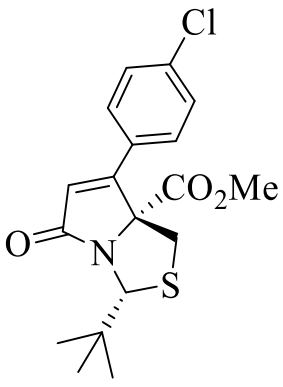
According to general method F, mesylate **153d** (617 mg, 1.77 mmol) was reacted with 4-formylphenylboronic acid (398 mg, 2.66 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.69 mL, 15.93 mmol) in ethanol (0.72 mL, 12.4 mmol) and toluene (15 mL) for

overnight. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (45 mg, 0.106 mmol) and $(C_6H_5CN)_2PdCl_2$ (34 mg, 0.088 mmol) in toluene (3 mL).



Yield 25% (135 mg); yellow solid, m. p. 148-150°C; R_f (40% EA in PE) 0.40; $[\alpha]_D^{25}$ +203.1 (*c* 1.0 DCM); ν_{max}/cm^{-1} 2956 (C-H), 2842 (C-H), 1745 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$): 0.94 (9H, s, $C(CH_3)_3$), 2.83 (1H, d, *J* 11.0, C(4)$\underline{H_A}H_B$), 3.60 (3H, s, CO_2CH_3), 3.92 (1H, d, *J* 11.0, C(4)$H_A\underline{H_B}$), 4.95 (1H, s, C(2)H), 6.41 (1H, s, C(7)H), 7.60 (2H, d, *J* 8.4, C(2')H), 7.87 (2H, d, *J* 8.4, C(3')H), 9.98 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.4 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 53.4 ($CO_2\underline{C}H_3$), 70.8 (C(2)), 81.9 (C(5)), 122.9 (C(7)), 127.4 (C(2')), 130.4 (C(3')), 135.1 (C(4')), 137.4 (C(1')), 157.4 (C(6)), 169.5 ($\underline{C}O_2CH_3$), 174.1 (C(8)), 191.1 (CHO); m/z ($[ESI]^+$) 360.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 360.1263, $C_{19}H_{22}O_4NS$ ($[M+H]^+$) requires 360.1264.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene, 119dv**



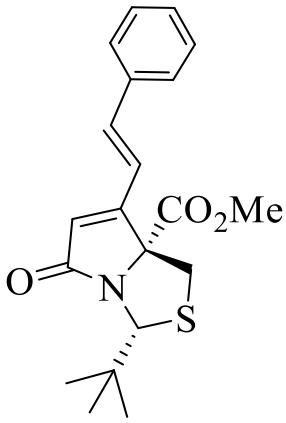
According to general method F, mesylate **153d** (584 mg, 1.67 mmol) was reacted with 4-chlorophenylboronic acid (274 mg, 1.75 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.6 mL, 15.0 mmol) in ethanol (0.68 mL, 11.7 mmol) and toluene (15 mL) for 6 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (42 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (32 mg, 0.08 mmol) in toluene (3 mL).

Yield 43% (265 mg); white solid, m. p. 165-167°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25}$ +276.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3091 (C-H), 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O);

δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 2.79 (1H, d, *J* 11.0, C(4)$\underline{H_A}H_B$), 3.59 (3H, s, CO_2CH_3), 3.87 (1H, d, *J* 11.0, C(4)$H_A\underline{H_B}$), 4.92 (1H, s, C(2)H), 6.26 (1H, s, C(7)H), 7.32 (2H, d, *J* 8.8, C(2')H), 7.38 (2H, d, *J* 8.8, C(3')H); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.5 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.7 (C(2)), 81.9 (C(5)), 120.5 (C(7)), 128.1 (C(3')), 128.3 (C(4')), 129.6 (C(2')), 137.1 (C(1')), 157.7 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 174.5 (C(8)); m/z ($[ESI]^+$) 366.0 ($[M+H]^+$, ^{35}Cl, 20%), 368.2 ($[M+H]^+$, ^{37}Cl, 15%), 388.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 388.0739, $C_{18}H_{20}O_3NClSNa$ ($[M+Na]^+$, ^{35}Cl) requires 372.0745.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-((*E*)-styryl)-3-thiabicyclo [3.3.0]-oct-6-ene, 119dvi**

According to general method F, mesylate **153d** (463 mg, 1.33 mmol) was reacted with *trans*-2-phenylvinylboronic acid (294 mg, 2.0 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.26 mL, 12.0 mmol) in ethanol (0.54 mL, 9.3 mmol) and toluene (15 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (34 mg, 0.08 mmol) and $(C_6H_5CN)_2PdCl_2$ (25.4 mg, 0.07 mmol) in toluene (2 mL).

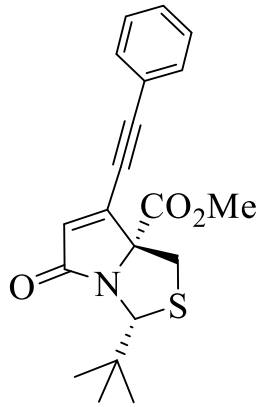


Yield 20% (95 mg); yellow sticky material; R_f (30% EA in PE) 0.40; $[\alpha]_D^{25}$ +126.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 1744 (C=O), 1703 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 2.70 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.67 (3H, s, CO_2CH_3), 3.83 (1H, d, *J* 11.1, C(4)$H_A\underline{H_B}$), 4.89 (1H, s, C(2)H), 5.94 (1H, s, C(7)H), 6.76 (1H, d, *J* 16.7, C(10)H), 6.86 (1H, d, *J* 16.7, C(9)H), 7.27-7.43 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.2 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 70.9 (C(2)), 81.4 (C(5)), 118.6 (C(10)), 121.8 (C(7)), 127.4-135.2 (ArC), 136.9

(C(9)), 157.1 (C(6)), 170.0 ($\underline{C}O_2CH_3$), 175.1 (C(8)); m/z ($[ESI]^+$) 358.2 ($[M+H]^+$, 20%); HRMS ($[ESI]^+$) found 358.1471, $C_{20}H_{24}NO_3S$ ($[M+H]^+$) requires 358.1471.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-(phenylethynyl)-3-thiabicyclo [3.3.0]-oct-6-ene, 119dvii**

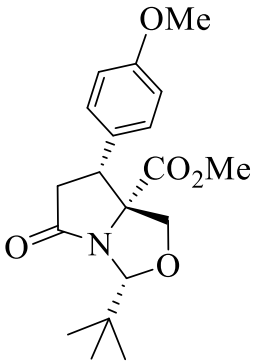
According to general method F, mesylate **153d** (203 mg, 0.58 mmol) was reacted with 2-phenyl-1-ethynylboronic acid (198 mg, 0.87 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.55 mL, 5.22 mmol) in ethanol (0.24 mL, 4.06 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (15 mg, 0.035 mmol) and $(C_6H_5CN)_2PdCl_2$ (11 mg, 0.03 mmol) in toluene (1 mL).



Yield 15% (30 mg); yellow sticky material. R_f (30% EA in PE) 0.50; $[\alpha]_D^{25}$ +84.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C-H), 1749 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 2.72 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.73 (3H, s, CO_2CH_3), 3.73 (1H, d, *J* 11.2, C(4)$H_A\underline{H_B}$), 4.90 (1H, s, C(2)H), 6.09 (1H, s, C(7)H), 7.27-7.46 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 34.0 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 53.4 ($CO_2\underline{C}H_3$), 72.1 (C(2)), 79.3 (C(5)), 83.5 (C(9)), 104.7 (C(10)), 127.4 (C(7)), 120.9, 128.6-132.2 (ArC), 142.4 (C(6)), 168.3 ($\underline{C}O_2CH_3$), 174.8 (C(8)); m/z ($[ESI]^+$) 356.0 ($[M+H]^+$, 10%), 378.2 ($[M+Na]^+$, 15%); HRMS (ESI^+) found 356.1312, $C_{20}H_{22}NO_3S$ ($[M+H]^+$) requires 356.1315.

_(2R,5S,6R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo[3.3.0]-octane, 121ai

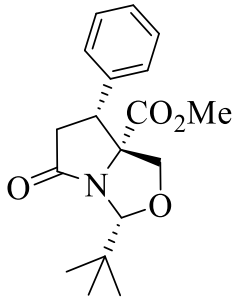
According to general method G, pyrrolinone **119ai** (51 mg, 0.15 mmol) was hydrogenated for 8 h using platinum(IV) oxide (5 mg, 0.02 mmol) in EtOAc (7 mL) to afford pyrrolidinone **121ai**.



Yield 98% (50 mg); white solid, m. p. 118-120°C; R_f (40% EA in PE) 0.46; $[\alpha]_D^{25}$ -40.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2907 (C-H), 2872 (C-H), 1742 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.81 (9H, s, $C(CH_3)_3$), 2.63 (1H, dd, *J* 15.2, 7.5, C(7)$\underline{H_A}H_B$), 3.31 (3H, s, CO_2CH_3), 3.53 (1H, dd, *J* 15.2, 13.8, C(7)$H_A\underline{H_B}$), 3.69 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.72 (3H, s, OCH_3), 3.73-3.77 (1H, m, C(6)H), 4.86 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 4.91 (1H, s, C(2)H), 6.78 (2H, d, *J* 8.8, C(3')H), 6.97 (2H, d, *J* 8.8, C(2')H); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 36.2 ($\underline{C}(CH_3)_3$), 39.3 (C(7)), 49.9 (C(6)), 52.1 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 74.7 (C(4)), 77.3 (C(5)), 96.1 (C(2)), 114.0 (C(3')), 126.8 (C(1')), 128.6 (C(2')), 159.3 (C(4')), 170.3 ($\underline{C}O_2CH_3$), 176.2 (C(8)); m/z ($[ESI]^+$) 348.2 ($[M+H]^+$, 15%), 370.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 348.1801, $C_{19}H_{26}NO_5$ ($[M+H]^+$) requires 348.1806.

_(2R,5S,6R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0]-octane, 121aii

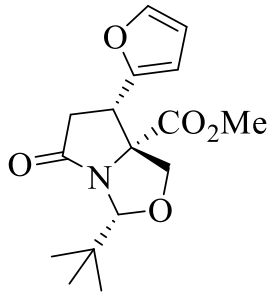
According to general method G, pyrrolinone **119aii** (105 mg, 0.33 mmol) was hydrogenated for 7 h using platinum(IV) oxide (11 mg, 0.05 mmol) in EtOAc (10 mL) to afford pyrrolidinone **121aii**.



Yield 88% (93 mg); white solid, m. p. 180-186°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25}$ -42.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 2872 (C-H), 1743 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 0.82 (9H, s, $C(CH_3)_3$), 2.66 (1H, dd, *J* 15.2, 7.5, C(7)$\underline{H_A}H_B$), 3.27 (3H, s, CO_2CH_3), 3.58 (1H, dd, *J* 15.2, 13.6, C(7)$H_A\underline{H_B}$), 3.73 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.80 (1H, dd, *J* 13.6, 7.5, C(6)H), 4.88 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 4.92 (1H, s, C(2)H), 7.03-7.28 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 24.9 ($C(\underline{C}H_3)_3$), 36.2 ($\underline{C}(CH_3)_3$), 38.9 (C(7)), 50.5 (C(6)), 52.0 ($CO_2\underline{C}H_3$), 74.7 (C(4)), 77.2 (C(5)), 96.1 (C(2)), 127.5-135.0 (ArC), 170.2 ($\underline{C}O_2CH_3$), 176.1 (C(8)); m/z ($[ESI]^+$) 318.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 318.1701, $C_{18}H_{24}NO_4$ ($[M+H]^+$) requires 318.1700.

***(2R,5S,6S)*-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] -octane, 121aiii**

According to general method G, pyrrolinone **119aiii** (43 mg, 0.14 mmol) was hydrogenated for 18 h using platinum(IV) oxide (4.8 mg, 0.021 mmol) in EtOAc (7 mL) to afford pyrrolidinone **121aiii**.

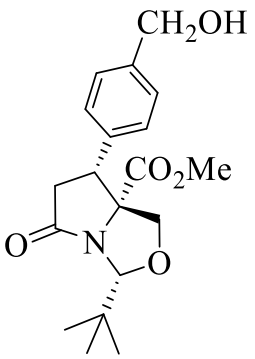


Yield 28% (12 mg); white solid, m. p. 140-146°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ -6.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2872 (C-H), 1744 (C=O), 1719 (C=O); δ_H (500 MHz, $CDCl_3$): 0.82 (9H, s, $C(CH_3)_3$), 2.68 (1H, dd, *J* 15.5, 7.8, C(7)$\underline{H_A}H_B$), 3.42 (1H, dd, *J* 15.5, 13.6, C(7)$H_A\underline{H_B}$), 3.45 (3H, s, CO_2CH_3), 3.70 (1H, d, *J* 8.8, C(4)$\underline{H_A}H_B$), 3.75 (1H, dd, *J* 13.6, 7.8, C(6)H), 4.84 (1H, d, *J* 8.8, C(4)$H_A\underline{H_B}$), 4.89 (1H, s, C(2)H), 6.09 (1H, d, *J* 3.3, C(3')H), 6.25 (1H, dd, *J* 3.3, 1.8, C(4')H). 7.28 (1H, d, *J* 1.8, C(5')H); δ_C (125 MHz, $CDCl_3$): 23.8 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 37.7 (C(7)), 43.4 (C(6)), 51.4 ($CO_2\underline{C}H_3$), 73.4 (C(4)), 75.0 (C(5)), 95.3 (C(2)), 106.6 (C(3')), 109.4 (C(4')), 141.8

(C(5')), 148.9 (C(2')), 169.2 ($\underline{C}O_2CH_3$), 174.5 (C(8)); m/z ($[ESI]^+$) 308.2 ($[M+H]^+$, 25%), 330.2 ($[M+Na]^+$, 85%); HRMS ($[ESI]^+$) found 308.1493, $C_{16}H_{22}NO_5$ ($[M+H]^+$) requires 308.1493.

***(2R,5S,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-octane, 121aiv**

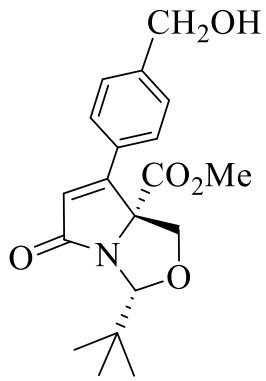
According to general method G, hydrogenation (reaction time: 20 h) of pyrrolinone **119aiv** (51.0 mg, 0.148 mmol) using platinum(IV) oxide (5 mg, 0.02 mmol) in EtOAc (7 mL) gave 4-(hydroxymethyl)phenyl pyrrolidinone derivative **121aiv**.



Yield 76% (39.5 mg); white solid, m. p. 108-112°C; R_f (40% EA in PE) 0.18; $[\alpha]_D^{25}$ -30.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3429 (O-H), 2958 (C-H), 2872 (C-H), 1743 (C=O), 1714 (C=O); δ_H (400 MHz, $CDCl_3$): 0.81 (9H, s, $C(CH_3)_3$), 1.97 (1H, s, OH), 2.60 (1H, dd, *J* 15.2, 7.5, C(7)$\underline{H_A}H_B$), 3.30 (3H, s, CO_2CH_3), 3.55 (1H, dd, *J* 15.2, 13.5, C(7)$H_A\underline{H_B}$), 3.72 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.77 (1H, dd, *J* 13.5, 7.5, C(6)H), 4.61 (2H, s, $C\underline{H_2}OH$), 4.87 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 4.90 (1H, s, C(2)H), 7.03 (2H, d, *J* 8.0, C(2')H), 7.26 (2H, d, *J* 8.0, C(3')H); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 36.1 ($\underline{C}(CH_3)_3$), 39.0 (C(7)), 50.2 (C(6)), 52.1 ($CO_2\underline{C}H_3$), 64.6 ($\underline{C}H_2OH$), 74.7 (C(4)), 77.1 (C(5)), 96.1 (C(2)), 127.1 (C(3')), 127.6 (C(2')), 134.2 (C(1')), 141.0 (C(4')), 170.2 ($\underline{C}O_2CH_3$), 176.2 (C(8)); m/z ($[ESI]^+$) 348.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 348.1804, $C_{19}H_{26}O_5N$ ($[M+H]^+$) requires 348.1806.

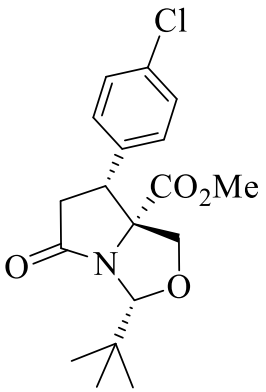
***(2R,5S)*-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 155**

According to general method G, hydrogenation (reaction time: 1 h) of (4-formylphenyl) pyrrolinone derivative **119aiv** (51 mg, 0.148 mmol) using PtO_2 (5 mg, 0.02 mmol) in EtOAc (7 mL) afforded 4-(hydroxymethyl)phenyl pyrrolinone derivative **155**.



Yield 49% (25 mg); white solid, m. p. 166-172°C; R_f (40% EA in PE) 0.14; $[\alpha]_D^{25}$ +122.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3440 (O-H), 2957 (C-H), 2871 (C-H), 1744 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 3.40 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.56 (3H, s, CO_2CH_3), 4.67 (2H, s, $C\underline{H_2}OH$), 4.68 (1H, s, C(2)H), 5.06 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.28 (1H, s, C(7)H), 7.33 (2H, d, *J* 8.8, C(2')H), 7.35 (2H, d, *J* 8.8, C(3')H); δ_C (100 MHz, $CDCl_3$): 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 64.5 ($\underline{C}H_2OH$), 70.4 (C(4)), 77.4 (C(5)), 96.3 (C(2)), 121.4 (C(7)), 127.1 (C(2')), 127.6 (C(3')), 129.0 (C(1')), 144.4 (C(4')), 159.2 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 177.5 (C(8)); m/z ($[ESI]^+$) 346.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 368.1466, $C_{19}H_{23}O_5NNa$ ($[M+Na]^+$) requires 368.1468.

***(2R,5S,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 121av**

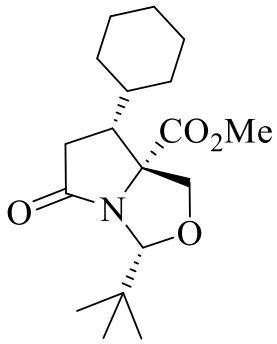


According to general method G, pyrrolinone **119av** (60 mg, 0.17 mmol) was hydrogenated for 8 h using platinum(IV) oxide (6.0 mg, 0.03 mmol) in EtOAc (7 mL) to afford pyrrolidinone **121av**.

Yield 33% (20 mg); white solid, m. p. 128-130°C; R_f (30% EA in PE) 0.44; $[\alpha]_D^{25}$ -43.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 2871 (C-H),

1742 (C=O), 1715 (C=O); δ_H (500 MHz, $CDCl_3$): 0.81 (9H, s, $C(CH_3)_3$), 2.66 (1H, dd, *J* 15.2, 7.6, C(7)$\underline{H_A}H_B$), 3.32 (3H, s, CO_2CH_3), 3.52 (1H, dd, *J* 15.2, 13.7, C(7)$H_A\underline{H_B}$), 3.71 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.75 (1H, dd, *J* 13.7, 7.6, C(6)H), 4.87 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 4.91 (1H, s, C(2)H), 6.99 (2H, d, *J* 8.4, C(2')H), 7.24 (2H, d, *J* 8.4, C(3')H); δ_C (125 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 36.2 ($\underline{C}(CH_3)_3$), 39.0 (C(7)), 49.8 (C(6)), 52.2 ($CO_2\underline{C}H_3$), 74.6 (C(4)), 77.0 (C(5)), 96.2 (C(2)), 128.9-134.1 (ArC), 170.1 ($\underline{C}O_2CH_3$), 175.7 (C(8)); m/z ($[ESI]^+$) 352.2 ($[M+H]^+$, ^{35}Cl, 15%), 354.2 ($[M+H]^+$, ^{37}Cl, 5%); HRMS ($[ESI]^+$) found 352.1312, $C_{18}H_{23}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 352.1310.

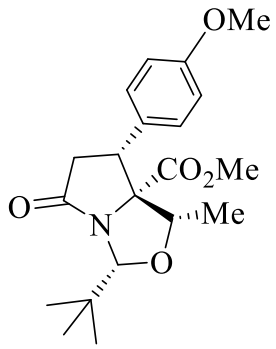
***(2R,5S,6R)*-1-Aza-2-(*tert*-butyl)-6-cyclohexyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 156**



Hydrogenolysis and hydrogenation product from **121av**. Yield 35% (19 mg); white solid, m. p. 72-82°C; R_f (30% EA in PE) 0.58; $[\alpha]_D^{25}$ +51.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2930 (C-H), 2856 (C-H), 1741 (C=O), 1716 (C=O); δ_H (500 MHz, $CDCl_3$): 0.79 (9H, s, $C(CH_3)_3$), 0.99-1.69 (11H, m, cyclohexyl), 2.06-2.16 (1H, m, C(6)H), 2.42 (1H, dd, *J* 15.2, 7.4, C(7)$\underline{H_A}H_B$), 2.79-2.90 (1H, m, C(7)$H_A\underline{H_B}$)), 3.42 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.72 (3H, s, CO_2CH_3), 4.76 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 4.80 (1H, s, C(2)H); δ_C (125 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 25.6-31.9, 38.5 (cyclohexyl), 36.2 ($\underline{C}(CH_3)_3$), 39.9 (C(7)), 52.3 ($CO_2\underline{C}H_3$), 53.3 (C(6)), 74.8 (C(4)), 75.7 (C(5)), 95.3 (C(2)), 171.6 ($\underline{C}O_2CH_3$), 176.3 (C(8)); m/z ($[ESI]^+$) 324.2 ($[M+H]^+$, 100%), 346.2 ($[M+Na]^+$, 45%); HRMS ($[ESI]^+$) found 324.2170, $C_{18}H_{30}NO_4$ ($[M+H]^+$) requires 324.2169.

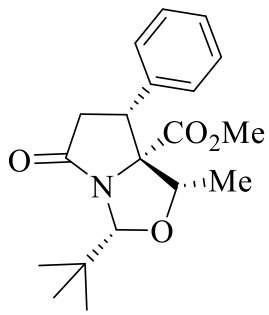
***(2R,4S,5S,6R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 121ci**

According to general method G, pyrrolinone **119ai** (52 mg, 0.144 mmol) was hydrogenated for 4 h with platinum(IV) oxide (5.0 mg, 0.022 mmol) in EtOAc (8 mL) to afford pyrrolidinone **121ci**.



Yield 71% (37 mg); white solid, m. p. 92-94°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ -70.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2977 (C-H), 2870 (C-H), 1749 (C=O), 1712 (C=O); δ_H (400 MHz, $CDCl_3$): 0.83 (9H, s, $C(CH_3)_3$), 1.53 (3H, d, *J* 6.6, C(4)CH_3), 2.63 (1H, dd, *J* 15.5, 7.8, C(7)$\underline{H_A}H_B$), 3.34 (3H, s, CO_2CH_3), 3.46 (1H, dd, *J* 15.5, 13.5, C(7)$H_A\underline{H_B}$), 3.62 (1H, dd, *J* 13.5, 7.8, C(6)H), 3.72 (3H, s, OCH_3), 3.90 (1H, q, *J* 6.6, C(4)H), 4.81 (1H, s, C(2)H), 6.79 (2H, d, *J* 8.8, C(3')H), 7.04 (2H, d, *J* 8.8, C(2')H); δ_C (100 MHz, $CDCl_3$): 15.4 (C(4)$\underline{C}H_3$), 25.0 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 40.2 (C(7)), 49.4 (C(6)), 51.4 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 77.2 (C(5)), 84.2 (C(4)), 94.3 (C(2)), 114.0 (C(3')), 127.1 (C(1')), 129.0 (C(2')), 159.4 (C(4')), 169.3 ($\underline{C}O_2CH_3$), 176.0 (C(8)); m/z ($[ESI]^+$) 362.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 362.1960, $C_{20}H_{28}NO_5$ ($[M+H]^+$) requires 362.1962.

***(2R,4S,5S,6R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0]-octane, 121cii**



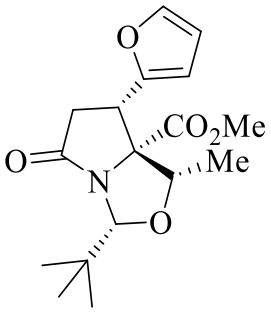
According to general method G, pyrrolinone **119aii** (137 mg, 0.41 mmol) was hydrogenated for 4 h with platinum(IV) oxide (14 mg, 0.06 mmol) in EtOAc (15 mL) to afford pyrrolidinone **121cii**.

Yield 94% (129 mg); white solid, m. p. 88-90°C; R_f (20% EA in PE) 0.25; $[\alpha]_D^{25}$ -29.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2977 (C-H), 2957 (C-H), 2870 (C-H), 1747

(C=O), 1714 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$), 1.54 (3H, d, *J* 6.5, $C(4)CH_3$), 2.66 (1H, dd, *J* 15.5, 7.8, $C(7)\underline{H_A}H_B$), 3.30 (3H, s, CO_2CH_3), 3.50 (1H, dd, *J* 15.5, 13.4, $C(7)H_A\underline{H_B}$), 3.67 (1H, dd, *J* 13.4, 7.8, C(6)H), 3.93 (1H, q, *J* 6.5, C(4)H), 4.82 (1H, s, C(2)H), 7.09-7.29 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 15.4 ($C(4)\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 39.9 (C(7)), 50.1 (C(6)), 51.4 ($CO_2\underline{C}H_3$), 77.3 (C(5)), 84.3 (C(4)), 94.4 (C(2)), 127.9-135.3 (ArC), 169.1 ($\underline{C}O_2CH_3$), 176.0 (C(8)); m/z ($[ESI]^+$) 332.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 332.1853, $C_{19}H_{26}NO_4$ ($[M+H]^+$) requires 332.1856.

***(2R,4S,5S,6S)*-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo[3.3.0]-octane, 121ciii**

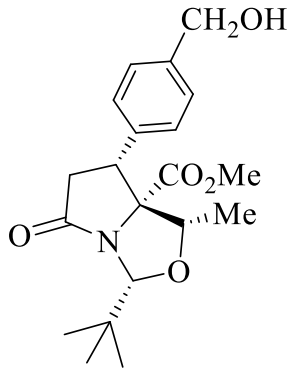
According to general method G, pyrrolinone **119aiii** (78 mg, 0.24 mmol) was hydrogenated for 8h with platinum(IV) oxide (8.0 mg, 0.037 mmol) in EtOAc (10 mL) to afford pyrrolidinone **121ciii**.



Yield 67% (52 mg); white solid, m. p. 83-85°C; R_f (20% EA in PE) 0.21; $[\alpha]_D^{25}$ -14.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2978 (C-H), 2958 (C-H), 2871 (C-H), 1747 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.83 (9H, s, $C(CH_3)_3$), 1.61 (3H, d, *J* 6.6, $C(4)\underline{C}H_3$), 2.68 (1H, dd, *J* 15.5, 7.9, $C(7)\underline{H_A}H_B$), 3.32-3.38 (1H, m, $C(7)H_A\underline{H_B}$), 3.41 (3H, s, CO_2CH_3), 3.65 (1H, dd, *J* 13.5, 7.9, C(6)H), 3.86 (1H, q, *J*, 6.6, C(4)H), 4.80 (1H, s, C(2)H), 6.08 (1H, d, *J* 3.3, C(3')H), 6.25 (1H, dd, *J* 3.3, 1.8, C(4')H), 7.30 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 14.5 ($C(4)C\underline{H_3}$), 25.0 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 39.2 (C(7)), 43.4 (C(6)), 51.7 ($CO_2\underline{C}H_3$), 76.1 (C(5)), 84.1 (C(4)), 94.7 (C(2)), 107.5 (C(3')), 110.4 (C(4')), 142.8 (C(5')), 150.3 (C(2')), 169.1 ($\underline{C}O_2CH_3$), 175.1 (C(8)); m/z ($[ESI]^+$) 322.2 ($[M+H]^+$, 100%), 344.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 322.1649, $C_{17}H_{24}O_5N$ ($[M+H]^+$) requires 322.1649.

***(2R,4S,5S,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 121civ**

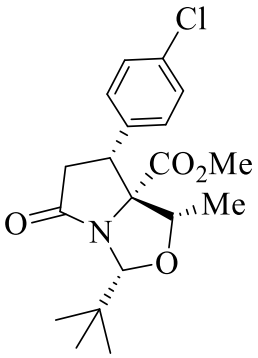
According to general method G, pyrrolinone **119aiv** (55.6 mg, 0.155 mmol) was hydrogenated for 6 h with platinum(IV) oxide (5.3 mg, 0.02 mmol) in EtOAc (8 mL) to afford pyrrolidinone **121civ**.



Yield 79% (44 mg); white solid, m. p. 128-130°C; R_f (60% EA in PE) 0.28; $[\alpha]_D^{25}$ -39.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3409 (O-H), 2957 (C-H), 2871 (C-H), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$), 1.53 (3H, d, *J* 6.5, C(4)CH_3), 1.75 (1H, br s, OH), 2.61 (1H, dd, *J* 15.4, 7.7, C(7)$\underline{H_A}H_B$), 3.33 (3H, s, CO_2CH_3), 3.48 (1H, dd, *J* 15.4, 13.5, C(7)$H_A\underline{H_B}$), 3.65 (1H, dd, *J* 13.5, 7.7, C(6)H), 3.92 (1H, q, *J* 6.5, C(4)H), 4.62 (2H, s, $C\underline{H_2}OH$), 4.82 (1H, s, C(2)H), 7.11 (2H, d, *J* 7.9, C(2')H), 7.28 (2H, d, *J* 7.9, C(3')H); δ_C (100 MHz, $CDCl_3$): 15.4 (C(4)$\underline{C}H_3$), 25.0 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 40.0 (C(7)), 49.9 (C(6)), 51.4 ($CO_2\underline{C}H_3$), 64.7 ($\underline{C}H_2OH$), 77.1 (C(5)), 84.3 (C(4)), 94.4 (C(2)), 127.1 (C(3')), 128.1 (C(2')), 134.6 (C(1')), 141.1 (C(4')), 169.1 ($\underline{C}O_2CH_3$), 175.9 (C(8)); m/z ($[ESI]^+$) 384.2 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 384.1782, $C_{20}H_{27}NO_5Na$ ($[M+Na]^+$) requires 384.1781.

***(2R,4S,5S,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 121cv**

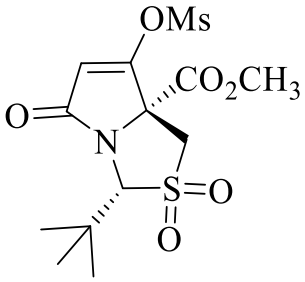
According to general method G, pyrrolinone **119av** (79 mg, 0.22 mmol) was hydrogenated for 4 h with platinum(IV) oxide (7.4 mg, 0.03 mmol) in EtOAc (10 mL) to furnish pyrrolidinone **121cv**.



Yield 84% (66 mg); white solid, m. p. 132-134°C; R_f (20% EA in PE) 0.23; $[\alpha]_D^{25}$ -32.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2870 (C-H), 1712 (C=O); δ_H (400 MHz, $CDCl_3$): 0.83 (9H, s, $C(CH_3)_3$), 1.53 (3H, d, *J* 6.5, C(4)CH_3), 2.65 (1H, dd, *J* 15.5, 7.8, C(7)$\underline{H_A}H_B$), 3.34 (3H, s, CO_2CH_3), 3.44 (1H, dd, *J* 15.5, 13.4, C(7)$H_A\underline{H_B}$), 3.63 (1H, dd, *J* 13.4, 7.8, C(6)H), 3.91 (1H, q, *J* 6.5, C(4)H), 4.81 (1H, s, C(2)H), 7.06 (2H, d, *J* 8.3, C(2')H), 7.25 (2H, d, *J* 8.3, C(3')H); δ_C (100 MHz, $CDCl_3$): 15.4 (C(4)$\underline{C}H_3$), 25.0 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 40.0 (C(7)), 49.3 (C(6)), 51.5 ($CO_2\underline{C}H_3$), 84.2 (C(4)), 94.4 (C(2)), 128.9 (C(3')), 129.2 (C(2')), 133.9 (C(4')), 134.2 (C(1')), 169.0 ($\underline{C}O_2CH_3$), 175.6 (C(8)); m/z ($[ESI]^+$) 388.2 ($[M+Na]^+$, ^{35}Cl, 20%), 390.2 ($[M+Na]^+$, ^{37}Cl, 5%); HRMS ($[ESI]^+$) found 388.1283, $C_{19}H_{24}NO_4ClNa$ ($[M+Na]^+$, ^{35}Cl) requires 388.1286.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-((methylsulfonyl)oxy)-5-methoxycarbonyl-8-oxa-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 157d**

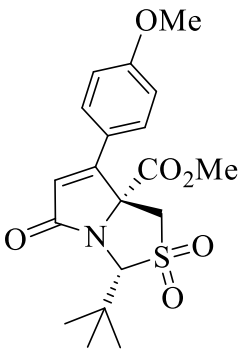
According to general method H, of **153d** (203 mg, 0.58 mmol) in $CHCl_3$ (7 mL) was reacted with *m*-chloroperbenzoic acid (300 mg, 1.74 mmol) in $CHCl_3$ (4 mL) to prepare **157d**.



Yield 77% (171 mg); white solid, m. p. 104-106°C; R_f (60% EA in PE) 0.50; $[\alpha]_D^{25}$ +109.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3022 (C-H), 2965 (C-H), 1730 (C=O), 1638 (C=O); δ_H (400 MHz, $CDCl_3$): 1.07 (9H, s, $C(CH_3)_3$), 3.24 (3H, s, $OSO_2C\underline{H}_3$), 3.36 (1H, d, *J* 14.2, C(4)$\underline{H_A}H_B$), 3.81 (3H, s, CO_2CH_3), 3.95 (1H, d, *J* 14.2, C(4)$H_A\underline{H_B}$), 4.60 (1H, s, C(2)H), 6.16 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 38.7 (SO_2CH_3), 50.9 (C(4)), 54.7 ($CO_2\underline{C}H_3$), 70.1 (C(5)), 81.9 (C(2)), 107.7 (C(7)), 163.7 ($\underline{C}O_2CH_3$), 166.6 (C(8)), 173.5 (C(6)); m/z ($[ESI]^+$) 382.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 382.0628, $C_{13}H_{20}NO_8S_2$ ($[M+H]^+$) requires 382.0625.

(2R,5R)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 158di

According to general method F, mesylate **157d** (105 mg, 0.27 mmol) was reacted with 4-methoxyphenylboronic acid (63 mg, 0.4 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.25 mL, 2.43 mmol) in ethanol (0.11 mL, 1.89 mmol) and toluene (12 mL) for 4 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (7.0 mg, 0.02 mmol) and $(C_6H_5CN)_2PdCl_2$ (5.0 mg, 0.01 mmol) in toluene (1 mL).

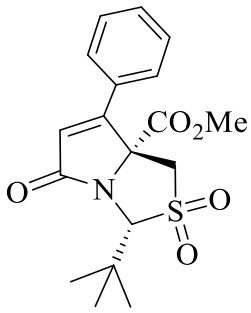


Yield 56% (60 mg); colourless oil; R_f (40% EA in PE) 0.30; $[\alpha]_D^{25}$ +129.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 1746 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 1.10 (9H, s, $C(CH_3)_3$), 3.32 (1H, d, *J* 13.5, C(4)$\underline{H_A}H_B$), 3.64 (3H, s, CO_2CH_3), 3.79 (3H, s, OCH_3), 4.44 (1H, d, *J* 13.5, C(4)$H_A\underline{H_B}$), 4.64 (1H, s, C(2)H), 6.52 (1H, s, C(7)H), 6.87 (2H, d, *J* 9.0, C(3')H), 7.37 (2H, d, *J* 9.0, C(2')H); δ_C (100 MHz, $CDCl_3$): 26.3 ($C(\underline{C}H_3)_3$), 35.5 ($\underline{C}(CH_3)_3$), 54.2, 54.3 (C(4), $CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 71.5 (C(5)), 81.3 (C(2)), 114.9 (C(3')), 118.3 (C(7)), 121.2 (C(1')), 128.8 (C(2')), 160.4 (C(4')), 162.2 (C(6)), 169.4 ($\underline{C}O_2CH_3$), 175.1 (C(8)); m/z ($[ESI]^+$) 394.2 ($[M+H]^+$, 100%), 416.2 ($[M+Na]^+$, 95%); HRMS ($[ESI]^+$) found 416.1137, $C_{19}H_{23}O_6NNaS$ ($[M+Na]^+$) requires 416.1138.

(2R,5R)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 158dii

According to general method F, mesylate **157d** (300 mg, 0.78 mmol) was reacted with phenylboronic acid (144 mg, 1.18 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.7 mL, 7.02 mmol) in ethanol (0.32 mL, 5.46 mmol) and toluene (13 mL) for 5 h. $PdCl_2$(dppb)

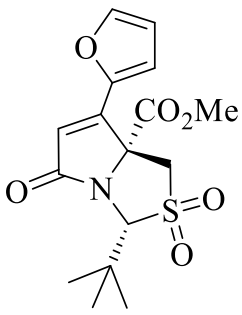
was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (20 mg, 0.047 mmol) and $(C_6H_5CN)_2PdCl_2$ (15 mg, 0.04 mmol) in toluene (2 mL).



Yield 53% (150 mg); white solid, m. p. 175-177°C; R_f (40% EA in PE) 0.34; $[\alpha]_D^{25}$ +132.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 1748 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 1.10 (9H, s, $C(CH_3)_3$), 3.32 (1H, d, *J* 13.5, C(4)$\underline{H_A}H_B$), 3.64 (3H, s, CO_2CH_3), 4.45 (1H, d, *J* 13.5, C(4)$H_A\underline{H_B}$), 4.64 (1H, s, C(2)H), 6.65 (1H, s, C(7)H), 7.35-7.45 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.3 ($C(\underline{C}H_3)_3$), 35.6 ($\underline{C}(CH_3)_3$), 54.2 (C(4), $CO_2\underline{C}H_3$), 71.7 (C(5)), 81.5 (C(2)), 121.0 (C(7)), 127.0-131.7 (ArC), 160.7 (C(6)), 169.0 ($\underline{C}O_2CH_3$), 174.7 (C(8)); m/z ($[ESI]^+$) 364.2 ($[M+H]^+$, 100%), 486.0 ($[M+Na]^+$, 95%); HRMS ($[ESI]^+$) found 364.1218, $C_{18}H_{22}O_5NS$ $[M+H]^+$) requires 364.1213.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 158diii**

According to general method F, mesylate **157d** (540 mg, 1.42 mmol) was reacted with 2-furylboronic acid (238 mg, 2.13 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.35 mL, 12.8 mmol) in ethanol (0.58 mL, 9.94 mmol) and toluene (15 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (36 mg, 0.085 mmol) and $(C_6H_5CN)_2PdCl_2$ (27 mg, 0.07 mmol) in toluene (3 mL).

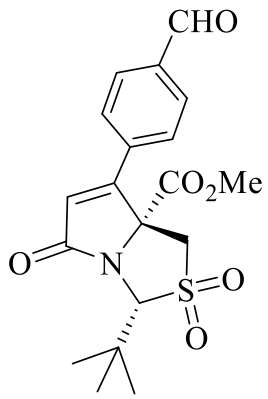


Yield 20% (100 mg); yellow solid, m. p. 130-132°C; R_f (40% EA in PE) 0.37; $[\alpha]_D^{25}$ +88.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 1748 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 1.10 (9H, s, $C(CH_3)_3$), 3.30 (1H, d, *J* 13.8, C(4)$\underline{H_A}H_B$), 3.69 (3H, s, CO_2CH_3), 4.30 (1H, d, *J* 13.8, C(4)$H_A\underline{H_B}$), 4.61 (1H, s, C(2)H), 6.42-6.55 (2H, m, C(7)H + C(3')H), 6.66 (1H, d, *J* 3.6, C(4')H), 7.54 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 26.3

(C($\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.9 (C(4)), 54.3 ($CO_2\underline{C}H_3$), 70.2 (C(5)), 81.6 (C(2)), 112.9 (C(7)), 114.5 (C(4')), 117.5 (C(3')), 145.0 (C(5')), 146.5 (C(2')), 149.6 (C(6)), 168.9 ($\underline{C}O_2CH_3$), 175.0 (C(8)); m/z ($[ESI]^+$) 354.0 ($[M+H]^+$, 45%), 376.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 354.1006, $C_{16}H_{20}O_6NS$ ($[M+H]^+$) requires 354.1006.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 158div**

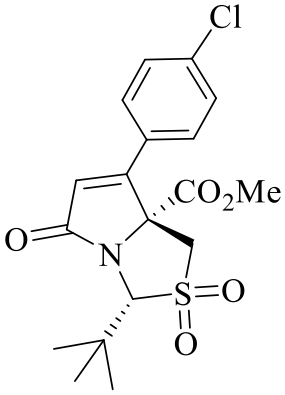
According to general method F, mesylate **157d** (500 mg, 1.31 mmol) was reacted with 4-formylphenylboronic acid (295 mg, 1.97 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.25 mL, 11.8 mmol) in ethanol (0.54 mL, 9.17 mmol) and toluene (15 mL) for 8 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (34 mg, 0.08 mmol) and $(C_6H_5CN)_2PdCl_2$ (25 mg, 0.07 mmol) in toluene (3 mL).



Yield 26% (135 mg); white solid, m. p. 138-140°C; R_f (40% EA in PE) 0.30; $[\alpha]_D^{25}$ +103.0 (*c* 1.0 DCM); ν_{max}/cm^{-1} 2961 (C-H), 1747 (C=O), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 1.11 (9H, s, $C(CH_3)_3$), 3.34 (1H, d, *J* 13.6 Hz, C(4)$\underline{H_A}H_B$), 3.66 (3H, s, CO_2CH_3), 4.47 (1H, d, *J* 13.6, C(4)$H_A\underline{H_B}$), 4.66 (1H, s, C(2)H), 6.80 (1H, s, C(7)H), 7.59 (2H, d, *J* 8.4, C(2')H), 7.90 (2H, d, *J* 8.4, C(3')H). 9.99 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$): 26.3 (C($\underline{C}H_3)_3$), 35.6 ($\underline{C}(CH_3)_3$), 54.0 (C(4)), 54.4 ($CO_2\underline{C}H_3$), 71.7 (C(5)), 81.6 (C(2)), 123.7 (C(7)), 127.6 (C(2')), 130.5 (C(3')), 133.9 (C(4')), 137.9 (C(1')), 159.0 (C(6)), 168.8 ($\underline{C}O_2CH_3$), 174.1 (C(8)), 190.9 (CHO); m/z ($[ESI]^+$) 392.0 ($[M+H]^+$,100%), 414.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 392.1161, $C_{19}H_{22}O_6NS$ requires ($[M+H]^+$) 392.1162.

(2R,5R)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 158dv

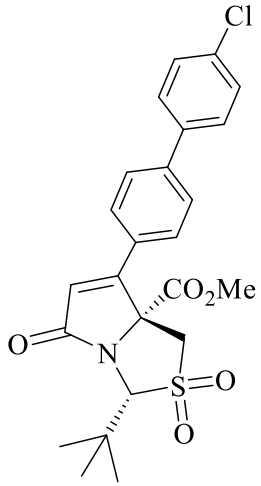
According to general method F, mesylate **157d** (100 mg, 0.26 mmol) was reacted with 4-chlorophenylboronic acid (42.6 mg, 0.27 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 8 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (6.6 mg, 0.016 mmol) and $(C_6H_5CN)_2PdCl_2$ (5 mg, 0.013 mmol) in toluene (1 mL).



Yield 48% (45 mg); white solid, m. p. 50-52°C; R_f (20% EA in PE) 0.20; $[\alpha]_D^{25}$ +105.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 1747 (C=O), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 1.10 (9H, s, $C(CH_3)_3$), 3.30 (1H, d, *J* 13.4, C(4)$\underline{H_A}H_B$), 3.65 (3H, s, CO_2CH_3), 4.43 (1H, d, *J* 13.4, C(4)$H_A\underline{H_B}$), 4.65 (1H, s, C(2)H), 6.65 (1H, s, C(7)H), 7.36 (4H, s, ArH); δ_C (100 MHz, $CDCl_3$): 26.3 ($C(\underline{C}H_3)_3$), 35.5 ($\underline{C}(CH_3)_3$), 54.0 (C(4)), 54.4 ($CO_2\underline{C}H_3$), 71.6 (C(5)), 81.5 (C(2)), 121.4 (C(7)), 127.2-138.0 (ArC), 159.3 (C(6)), 169.0 ($\underline{C}O_2CH_3$), 174.5 (C(8)); m/z ($[ESI]^+$) 398.0 ($[M+H]^+$, ^{35}Cl, 100%), 400.2 ($[M+H]^+$, ^{37}Cl, 40%), 420.0 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 398.0822, $C_{18}H_{21}O_5NClS$ ($[M+H]^+$, ^{35}Cl) requires 398.0823.

(2R,5R)-1-Aza-2-(*tert*-butyl)-6-(4'-chloro-[1,1'-biphenyl]-4-yl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 160

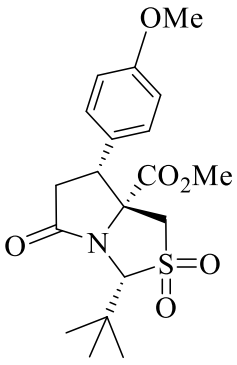
According to general method F, mesylate **157d** (100 mg, 0.26 mmol) was reacted with 4-chlorophenylboronic acid (83.3 mg, 0.53 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 8 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (6.6 mg, 0.016 mmol) and $(C_6H_5CN)_2PdCl_2$ (5 mg, 0.013 mmol) in toluene (1 mL).



Yield 16% (20 mg); white solid, m.p. 86-88°C; R_f (20% EA in PE) 0.12; $[\alpha]_D^{25}$ +70.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2923 (C-H), 1747 (C=O), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 1.12 (9H, s, $C(CH_3)_3$), 3.35 (1H, d, *J* 13.6, C(4)$\underline{H_A}H_B$), 3.67 (3H, s, CO_2CH_3), 4.48 (1H, d, *J* 13.6, C(4)$H_A\underline{H_B}$), 4.67 (1H, s, C(2)H), 6.70 (1H, s, C(7)H), 7.35-7.60 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 35.6 ($\underline{C}(CH_3)_3$), 54.2 (C(4)), 54.3 ($CO_2\underline{C}H_3$), 71.6 (C(5)), 81.5 (C(2)), 120.8 (C(7)), 127.6-143.1 (ArC), 160.0 (C(6)), 169.2 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 474.0 ($[M+H]^+$, ^{35}Cl , 40%), 476.0 ($[M+H]^+$, ^{37}Cl , 15%); HRMS ($[ESI]^+$) found 474.1135, $C_{24}H_{25}O_5NClS$ ($[M+H]^+$, ^{35}Cl) requires 474.1137.

***(2R,5R,6R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 159di**

According to general method G, pyrrolinone **158di** (24 mg, 0.06 mmol) was hydrogenated for 24 h with platinum(IV) oxide (2.0 mg, 0.009 mmol) in EtOAc (7 mL) to afford pyrrolidinone **159di**.

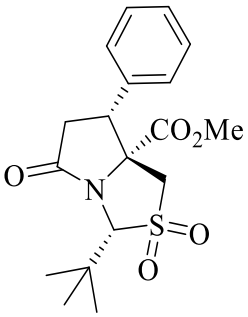


Yield 83% (20 mg); white solid, m. p. 209-211°C; R_f (40% EA in PE) 0.35; $[\alpha]_D^{25}$ -87.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 1722 (C=O), 1613 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.57 (1H, dd, *J* 16.1, 7.6, C(7)$\underline{H_A}H_B$), 3.26 (1H, dd, *J* 16.1, 13.7, C(7)$H_A\underline{H_B}$), 3.38-3.45 (4H, m, ($CO_2C\underline{H_3}$ + C(4)$\underline{H_A}H_B$)), 3.63 (1H, d, *J* 14.6, C(4)$H_A\underline{H_B}$), 3.74 (3H, s, OCH_3), 3.79 (1H, dd, *J* 13.7, 7.6, C(6)H), 4.65 (1H, s, C(2)H), 6.82 (2H, d, *J* 8.7, C(3')H), 7.07 (2H, d, *J* 8.7, C(2')H); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 34.4 (C(7)), 35.4 ($\underline{C}(CH_3)_3$), 52.8 (C(6)), 53.1 ($CO_2\underline{C}H_3$), 53.9 (C(4)), 55.3 ($O\underline{C}H_3$), 71.7 (C(5)), 81.0 (C(2)), 114.5 (C(3')), 125.2 (C(1')), 128.6 (C(2')), 160.1 (C(4')), 169.9

($\underline{C}O_2CH_3$), 176.4 (C(8)); m/z ([ESI]$^+$) 396.2 ([M+H]$^+$, 35%), 418.2 ([M+Na]$^+$, 65%); HRMS ([ESI]$^+$) found 396.1479, $C_{19}H_{26}NO_6S$ ([M+H]$^+$) requires 396.1486.

***(2R,5R,6R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 159dii**

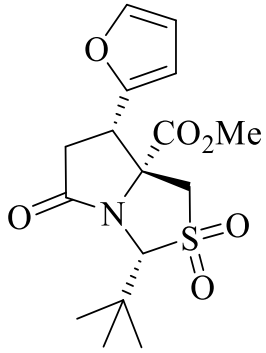
According to general method G, pyrrolinone **158dii** (68 mg, 0.19 mmol) was hydrogenated for 7 h with platinum(IV) oxide (6.4 mg, 0.03 mmol) in EtOAc (10 mL) to afford pyrrolidinone **159dii**.



Yield 82% (56 mg); white solid, m. p. 218-220°C; R_f (40% EA in PE) 0.43; $[\alpha]_D^{25}$ -89.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2967 (C-H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.60 (1H, dd, *J* 16.1, 7.6, C(7)$\underline{H_A}H_B$), 3.32 (1H, dd, *J* 16.1, 13.6, C(7)$H_A\underline{H_B}$), 3.39 (3H, s, CO_2CH_3), 3.47 (1H, d, *J* 14.6, C(4)$\underline{H_A}H_B$), 3.63 (1H, d, *J* 14.6, C(4)$H_A\underline{H_B}$), 3.84 (1H, dd, *J* 13.6, 7.6, C(6)H), 4.66 (1H, s, C(2)H), 7.13-7.33 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 34.1 (C(7)), 35.4 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 53.3 (C(6), 53.8 (C(4)), 71.7 (C(5)), 80.9 (C(2)), 127.4-133.4 (ArC), 169.8 ($\underline{C}O_2CH_3$), 176.4 (C(8)); m/z ([ESI]$^+$) 366.2 ([M+H]$^+$, 60%), 388.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 366.1371, $C_{18}H_{24}NO_5S$ ([M+H]$^+$) requires 366.1370.

***(2R,5R,6S)*-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 159diii**

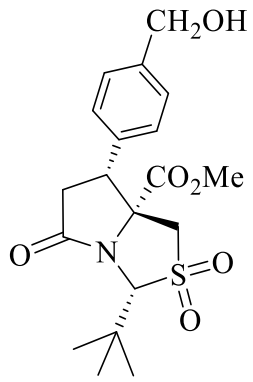
According to general method G, pyrrolinone **158diii** (41 mg, 0.116 mmol) was hydrogenated with platinum(IV) oxide (3.9 mg, 0.017 mmol) in EtOAc (7 mL) for 8 h to afford pyrrolidinone **159diii**.



Yield 37% (15 mg); white solid, m. p. 170-172°C; R_f (30% EA in PE) 0.22; $[\alpha]_D^{25}$ -65.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.62 (1H, dd, *J* 16.1, 7.7, C(7)$\underline{H_A}H_B$), 3.18 (1H, dd, *J* 16.1, 13.6, C(7)$H_A\underline{H_B}$), 3.52 (3H, s, CO_2CH_3), 3.57 (1H, d, *J* 14.7, C(4)$\underline{H_A}H_B$), 3.68 (1H, d, *J* 14.7, C(4)$H_A\underline{H_B}$), 3.90 (1H, dd, *J* 13.6, 7.7, C(6)H), 4.59 (1H, s, C(2)H), 6.18 (1H, d, *J* 3.3, C(3')H), 6.28 (1H, dd, *J* 3.3, 1.9, C(4')H), 7.34 (1H, d, *J* 1.8, C(5')H); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 33.4 (C(7)), 35.4 ($\underline{C}(CH_3)_3$), 47.0 (C(6)), 53.5 ($CO_2\underline{C}H_3$), 53.9 (C(4)), 70.3 (C(5)), 80.9 (C(2)), 108.5 (C(3')), 110.6 (C(4')), 143.5 (C(5')), 148.3 (C(2')), 169.7 ($\underline{C}O_2CH_3$), 175.8 (C(8)); m/z ($[ESI]^+$) 356.0 ($[M+H]^+$, 100%), 378.0 ($[M+Na]^+$, 50%); HRMS ($[ESI]^+$) found 356.1162, $C_{16}H_{22}O_6NS$ ($[M+H]^+$) requires 356.1162.

***(2R,5R,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 159div**

According to general method G, pyrrolinone **158div** (65 mg, 0.17 mmol) was hydrogenated with platinum(IV) oxide (5.6 mg, 0.02 mmol) in EtOAc (8 mL) for 18 h to afford pyrrolidinone **159div**.

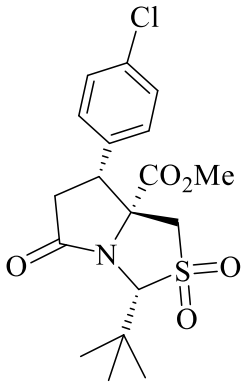


Yield 54% (35 mg); white solid, m. p. 168-170°C; R_f (60% EA in PE) 0.30; $[\alpha]_D^{25}$ -72.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3464 (O-H), 2980 (C-H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.54 (1H, dd, *J* 16.2, 7.6, C(7)$\underline{H_A}H_B$), 3.29 (1H, dd, *J* 16.2, 13.7, C(7)$H_A\underline{H_B}$), 3.43 (3H, s, CO_2CH_3), 3.44 (1H, d, *J* 14.7, C(4)$\underline{H_A}H_B$), 3.62 (1H, d, *J* 14.7, C(4)$H_A\underline{H_B}$), 3.82 (1H, dd, *J* 13.7, 7.6, C(6)H), 4.64-4.66 (3H, m, $C\underline{H_2}OH$ + C(2)H), 7.14 (2H, d, *J* 8.2, C(2')H), 7.32 (2H, d, *J* 8.2, C(3')H); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 34.3 (C(7)), 35.4 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 53.2 (C(6)), 53.8

(C(4)), 64.6 (C(2)), 71.6 (C(5)), 81.0 ($\underline{C}H_2OH$), 127.5 (C(3')), 127.6 (C(2')), 132.6 (C(1')), 142.0 (C(4')), 169.8 ($\underline{C}O_2CH_3$), 176.4 (C(8)); m/z ($[ESI]^+$) 396.2 ($[M+H]^+$, 100%), 418.2 ($[M+H]^+$, 45%); HRMS ($[ESI]^+$) found 396.1475, $C_{19}H_{26}O_6NS$ ($[M+H]^+$) requires 396.1475.

***(2R,5R,6R)*-1-Aza-2-(*tert*-butyl)-6-(4-cholorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 159dv**

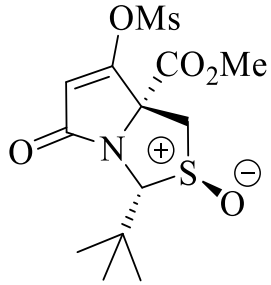
According to general method G, pyrrolinone **158dv** (124 mg, 0.30 mmol) was hydrogenated for 6 h with platinum(IV) oxide (10.6 mg, 0.05 mmol) in EtOAc (15 mL) to afford pyrrolidinone **159dv**.



Yield 77% (96 mg); white solid, m. p. 164-166°C; R_f (20% EA in PE) 0.20; $[\alpha]_D^{25}$ -65.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.60 (1H, dd, *J* 16.1, 7.6, C(7)$\underline{H_A}H_B$), 3.26 (1H, dd, *J* 16.1, 13.7, C(7)$H_A\underline{H_B}$), 3.40-3.45 (4H, m, CO_2CH_3 + C(4)$\underline{H_A}H_B$), 3.64 (1H, d, *J* 14.6, C(4)$H_A\underline{H_B}$), 3.77-3.85 (1H, m, C(6)H), 4.65 (1H, s, C(2)H), 7.10 (2H, d, *J* 8.5, C(2')H), 7.27 (2H, d, *J* 8.5, C(3')H); δ_C (100 MHz, $CDCl_3$): 26.2 ($C(\underline{C}H_3)_3$), 34.2 (C(7)), 35.4 ($\underline{C}(CH_3)_3$), 52.6 (C(6)), 53.2 ($CO_2\underline{C}H_3$), 53.7 (C(4)), 71.5 (C(5)), 80.9 (C(2)), 128.8 (C(2')), 129.4 (C(3')), 132.0 (C(4')), 135.1 (C(1')), 169.7 ($\underline{C}O_2CH_3$), 176.0 (C(8)); m/z ($[ESI]^+$) 422.0 ($[M+Na]^+$, ^{35}Cl, 50%), 424.0 ($[M+Na]^+$, ^{37}Cl, 10%); HRMS ($[ESI]^+$) found 400.0978, $C_{18}H_{23}ClNO_5S$ ($[M+H]^+$, ^{35}Cl) requires 400.0980.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3-oxide, 161d**

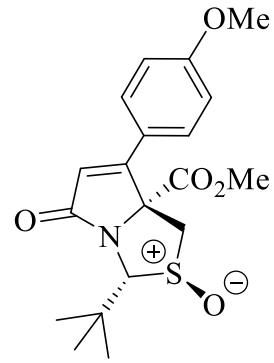
According to general method H, of **153d** (2.09 g, 5.98 mmol) in $CHCl_3$ (70 mL) was reacted with *m*-chloroperbenzoic acid (1.34 g, 7.77 mmol) in $CHCl_3$ (50 mL) to furnish **161d**.



Yield 52% (1.13 g); white solid, m. p. 160-162°C; R_f (50% EA in PE) 0.15; $[\alpha]_D^{25}$ +138.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2965 (C-H), 2935 (C-H), 1723 (C=O), 1637 (C=O); δ_H (400 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 3.13 (1H, d, *J* 14.4, C(4)$\underline{H_A}H_B$), 3.23 (3H, s, $OSO_2C\underline{H}_3$), 3.78 (3H, s, CO_2CH_3), 3.97 (1H, d, *J* 14.4, C(4)$H_A\underline{H_B}$), 4.70 (1H, s, C(2)H), 5.98 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 27.2 ($C(\underline{C}H_3)_3$), 34.7 ($\underline{C}(CH_3)_3$), 38.5 (OSO_2CH_3), 53.4 (C(4)), 54.4 ($CO_2\underline{C}H_3$), 78.5 (C(5)), 94.6 (C(2)), 105.8 (C(7)), 164.6 ($\underline{C}O_2CH_3$), 167.6 (C(8)), 174.6 (C(6)); m/z ($[ESI]^+$) 366.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 366.0678, $C_{13}H_{20}NO_7S_2$ ($[M+H]^+$) requires 366.0676.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3-oxide, 162di**

According to general method F, mesylate **161d** (227 mg, 0.62 mmol) was reacted with 4-methoxyphenylboronic acid (141.6 mg, 0.93 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.6 mL, 5.58 mmol) in ethanol (0.25 mL, 4.34 mmol) and toluene (10 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (15.8 mg, 0.037 mmol) and $(C_6H_5CN)_2PdCl_2$ (12 mg, 0.031 mmol) in toluene (2 mL).

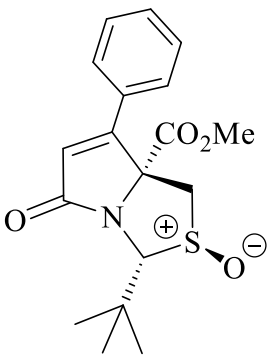


Yield 18% (41 mg); white solid, m. p. 154-156°C; R_f (60% EA in PE) 0.20; $[\alpha]_D^{25}$ +243.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 1739 (C=O), 1706 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.96 (1H, d, *J* 13.3, C(4)$\underline{H_A}H_B$), 3.61 (3H, s, CO_2CH_3), 3.79 (3H, s, OCH_3), 4.50-4.55 (2H, m, C(4)$H_A\underline{H_B}$+ C(2)H), 6.36 (1H, s, C(7)H), 6.87 (2H, d, *J* 8.3, C(3')H), 7.37 (2H, d, *J* 8.3, C(2')H); δ_C (100 MHz, $CDCl_3$): 27.2 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 53.9 ($CO_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 56.5 (C(4)), 79.3 (C(5)), 92.7 (C(2)), 114.8 (C(3')), 117.2 (C(7)), 121.8 (C(1')), 128.6 (C(2')), 159.8 (C(6)), 162.0 (C(4')),

170.5 ($\underline{C}O_2CH_3$), 175.8 (C(8)); m/z ([ESI]$^+$) 378.2 ([M+H]$^+$, 100%), 400.2 ([M+Na]$^+$, 60%); HRMS ([ESI]$^+$) found 378.1365, $C_{19}H_{24}O_5NS$ ([M+H]$^+$) requires 378.1370.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3-oxide, 162dii**

According to general method F, mesylate **161d** (360 mg, 0.98 mmol) was reacted with phenylboronic acid (180 mg, 1.48 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.93 mL, 8.82 mmol) in ethanol (0.4 mL, 6.89 mmol) and toluene (12 mL) for 18 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (25 mg, 0.06 mmol) and $(C_6H_5CN)_2PdCl_2$ (19 mg, 0.05 mmol) in toluene (3 mL).

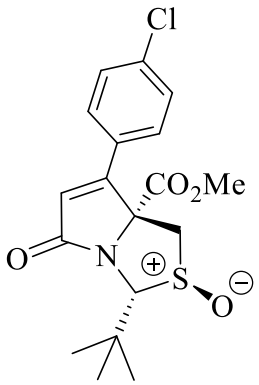


Yield 18% (61 mg); white solid, m. p. 154-156°C; R_f (60% EA in PE) 0.16; $[\alpha]_D^{25}$ +219.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 1740 (C=O), 1711 (C=O); δ_H (400 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 2.96 (1H, d, *J* 13.2, C(4)$\underline{H_A}H_B$), 3.61 (3H, s, CO_2CH_3), 4.52-4.57 (2H, m, C(4)$H_A\underline{H_B}$+ C(2)H), 6.50 (1H, s, C(7)H), 7.38-7.41 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 27.2 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 54.0 ($CO_2\underline{C}H_3$), 56.4 (C(4)), 79.3 (C(5)), 92.8 (C(2)), 119.8 (C(7)), 126.7-131.3 (ArC), 160.0 (C(6)), 170.2 ($\underline{C}O_2CH_3$), 175.4 (C(8)); m/z ([ESI]$^+$) 348.0 ([M+H]$^+$, 40%), 370.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 348.1261, $C_{18}H_{22}O_4NS$ [M+H]$^+$) requires 348.1264.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3-oxide, 162diii**

According to general method F, mesylate **161d** (360 mg, 0.98 mmol) was reacted with 4-chlorophenylboronic acid (162 mg, 1.48 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.93 mL, 8.82 mmol) in ethanol (0.4 mL, 6.89 mmol) and toluene (12 mL) for 18 h.

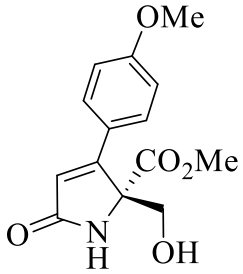
$PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (25 mg, 0.06 mmol) and $(C_6H_5CN)_2PdCl_2$ (19 mg, 0.05 mmol) in toluene (3 mL).



Yield 8% (30 mg); colourless oil; R_f (40% EA in PE) 0.20; $[\alpha]_D^{25}$ +209.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 1713 (C=O); δ_H (500 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 2.92 (1H, d, *J* 13.3, C(4)$\underline{H_A}H_B$), 3.58 (3H, s, CO_2CH_3), 4.46 (1H, d, *J* 13.3, C(4)$H_A\underline{H_B}$), 4.53 (1H, s, C(2)H), 6.44 (1H, s, C(7)H), 7.31 (4H, s, ArH); δ_C (125 MHz, $CDCl_3$): 27.2 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 54.1 ($CO_2\underline{C}H_3$), 56.2 (C(4)), 79.4 (C(5)), 93.0 (C(2)), 120.3 (C(7)), 128.0-137.6 (ArC), 158.8 (C(6)), 170.1 ($\underline{C}O_2CH_3$), 175.2 (C(8)); m/z ($[ESI]^+$) 404.0 ($[M+Na]^+$, ^{35}Cl, 70%), 406.0 ($[M+Na]^+$, ^{37}Cl, 25%); HRMS ($[ESI]^+$) found 382.0873, $C_{18}H_{21}O_4NClS$ $[M+H]^+$, ^{35}Cl) requires 382.0874.

Methyl (*S*)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate, 163

According to general method I, the bicyclic pyrrolidinone derivative **119ai** (100 mg, 0.29 mmol) was treated with propane-1,3-dithiol (0.06 mL, 0.61 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (4.84 mL) to develop pyroglutaminol derivative **163**.

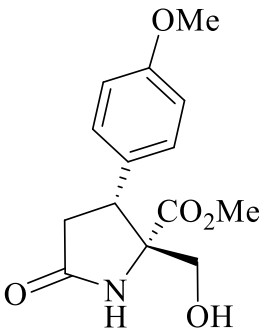


Yield 94% (75 mg); yellow solid, m. p. 99-101°C; ν_{max}/cm^{-1} 3245 (O-H), 2955 (C-H), 2840 (C-H), 1731 (C=O), 1691 (C=O); δ_H (400 MHz, MeOD): 3.64 (3H, s, $CO_2C\underline{H_3}$), 3.73 (3H, s, OCH_3), 3.85 (1H, d, *J* 11.7, C(6)$\underline{H_A}H_B$), 4.16 (1H, d, *J* 11.7, C(6)$H_A\underline{H_B}$), 6.29 (1H, s, C(4)H), 6.87 (2H, d, *J* 8.9, C(3')H), 7.43 (2H, d, *J* 8.9, C(2')H); δ_C (100 MHz, MeOD): 52.2 ($CO_2\underline{C}H_3$), 54.5 ($O\underline{C}H_3$), 62.9 (C(6)), 72.4 (C(2)), 114.0 (C(3')), 120.7 (C(1')), 123.3 (C(4)), 128.6 (C(2')), 158.0 (C(4')), 160.4 (C(3)), 161.4 ($\underline{C}O_2CH_3$), 170.0 (C(5)); m/z

([ESI]$^+$) 300.0 ([M+Na]$^+$, 80%); HRMS ([ESI]$^+$) found 300.0842, $C_{14}H_{15}NaNO_5$ ([M+Na]$^+$) requires 300.0842.

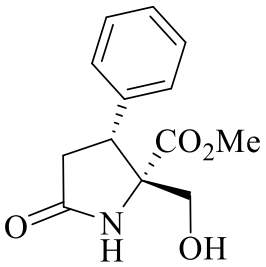
Methyl (2*S*,3*R*)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, 164

According to general method I, the bicyclic pyrrolinone derivative **121ai** (15 mg, 0.04 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.1 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (0.7 mL) to develop pyroglutaminol derivative **164**.



From **121ai**: Yield 80% (12 mg); colourless oil; $[\alpha]_D^{25}$ -74.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3273 (O-H), 2952 (C-H), 2839 (C-H), 1736 (C=O), 1687 (C=O); δ_H (400 MHz, MeOD): 2.56 (1H, dd, *J* 17.1, 8.0, C(4)$\underline{H_A}H_B$), 2.69 (1H, dd, *J* 17.1, 9.0, C(4)$H_A\underline{H_B}$), 3.22 (3H, s, $CO_2C\underline{H_3}$), 3.56 (1H, t, *J* 8.3, C(3)H), 3.66-3.70 (4H, m, OCH_3 + C(6)$\underline{H_A}H_B$), 3.88 (1H, d, *J* 11.5, C(6)$H_A\underline{H_B}$), 6.76 (2H, d, *J* 8.5, C(3')H), 7.02 (2H, d, *J* 8.5, C(2')H); δ_C (100 MHz, MeOD): 36.8 (C(4)), 44.3 (C(3)), 51.0 ($CO_2\underline{C}H_3$), 54.3 ($O\underline{C}H_3$), 64.5 (C(6)), 73.2 (C(2)), 113.4 (C(3')), 128.7 (C(2')), 130.1 (C(1')), 159.3 (C(4')), 171.1 ($\underline{C}O_2CH_3$), 178.6 (C(5)); m/z ([ESI]$^+$) 302.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 302.0999, $C_{14}H_{17}NO_5Na$ ([M+Na]$^+$) requires 302.0999.

Methyl (2*S*,3*R*)-2-(hydroxymethyl)-5-oxo-3-phenylpyrrolidine-2-carboxylate, 165



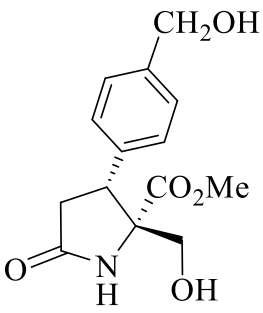
According to general method I, the bicyclic pyrrolinone derivative **121aii** (45 mg, 0.14 mmol) was treated with propane-1,3-dithiol (0.03 mL, 0.33 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (2.33 mL) to develop pyroglutaminol

derivative **165**.

Yield 79% (32 mg); colourless oil; $[\alpha]_D^{25}$ -81.8 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3280 (O-H), 2951 (C-H), 1736 (C=O), 1689 (C=O); δ_H (400 MHz, MeOD): 2.70 (1H, dd, *J* 17.1, 7.2, C(4)$\underline{H_A}H_B$), 2.85 (1H, dd, *J* 17.1, 9.1, C(4)$H_A\underline{H_B}$), 3.28 (3H, s, $CO_2\underline{C}H_3$), 3.73 (1H, dd, *J* 9.1, 7.2, C(3)H), 3.82 (1H, d, *J* 11.5, C(6)$\underline{H_A}H_B$), 4.00 (1H, d, *J* 11.5, C(6)$H_A\underline{H_B}$), 7.06-7.43 (5H, m, ArH); δ_C (100 MHz, MeOD): 36.9 (C(4)), 45.0 (C(3)), 51.0 ($CO_2\underline{C}H_3$), 64.7 (C(6)), 73.2 (C(2)), 127.4-138.6 (ArC), 171.0 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 250.0 $([M+H])^+$, 25%), 272.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 272.0894, $C_{14}H_{15}NO_4Na$ ($[M+Na]^+$) requires 272.0893.

Methyl (2*S*,3*R*)-2-(hydroxymethyl)-3-(4-(hydroxymethyl)phenyl)-5-oxopyrrolidine-2-carboxylate, 166

According to general method I, the bicyclic pyrrolinone derivative **121aiv** (12 mg, 0.03 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.08 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (0.5 mL) to develop pyroglutaminol derivative **166**.

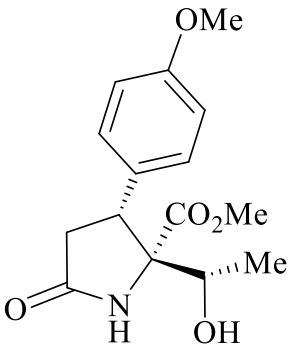


Yield 90% (9.0 mg); colourless oil; $[\alpha]_D^{25}$ -56.5 (*c* 0.9 in MeOH); ν_{max}/cm^{-1} 3308 (O-H), 2951 (C-H), 2875 (C-H), 1735 (C=O), 1686 (C=O); δ_H (400 MHz, MeOD): 2.58 (1H, dd, *J* 17.1, 7.4, C(4)$\underline{H_A}H_B$), 2.72 (1H, dd, *J* 17.1, 9.0, C(4)$H_A\underline{H_B}$), 3.19 (3H, s, $CO_2C\underline{H_3}$), 3.62 (1H, dd, *J* 9.0, 7.4, C(3)H), 3.70 (1H, d, *J* 11.5, C(6)$\underline{H_A}H_B$), 3.88 (1H, d, *J* 11.5, C(6)$H_A\underline{H_B}$), 4.48 (2H, s, $C\underline{H_2}OH$), 7.08 (2H, d, *J* 8.2, C(2')H), 7.21 (2H, d, *J* 8.3, C(3')H); δ_C (100 MHz, MeOD): 36.9 (C(4)), 44.7 (C(3)), 51.0 ($CO_2\underline{C}H_3$), 63.3 ($\underline{C}H_2OH$), 64.6 (C(6)), 73.2 (C(2)), 126.7 (C(3')), 127.6 (C(2')), 137.5 (C(1')), 141.0 (C(4')), 171.0

($\underline{C}O_2CH_3$), 178.5 (C(8)); m/z ([ESI]$^+$) 302.1 ([M+Na]$^+$, 35%); HRMS ([ESI]$^+$) found 302.1000, $C_{14}H_{17}NO_5Na$ ([M+Na]$^+$) requires 302.0999.

Methyl (2*S*,3*R*)-2-((*S*)-1-hydroxyethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, 167

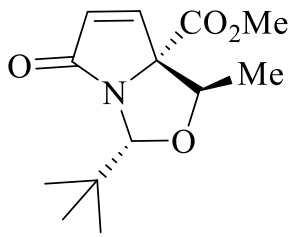
According to general method I, the bicyclic pyrrolinone derivative **121ci** (21 mg, 0.06 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.13 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.0 mL) to develop pyroglutaminol derivative **167**.



Yield 81% (12 mg); white solid, m. p. 171-173°C; $[\alpha]_D^{25}$ -41.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3250 (O-H), 2980 (C-H), 2952 (C-H), 1737 (C=O), 1687 (C=O); δ_H (400 MHz, MeOD): 0.99 (3H, d, *J* 6.4, C(6)$\underline{C}H_3$), 2.26 (1H, dd, *J* 17.0, 4.1, C(4)$\underline{H_A}H_B$), 2.91 (1H, dd, *J* 17.0, 9.4, C(4)$H_A\underline{H_B}$), 3.12 (3H, s, $CO_2C\underline{H_3}$), 3.66 (3H, s, OCH_3), 3.71 (1H, dd, *J* 9.4, 4.1, C(3)H), 4.15 (1H, q, *J* 6.4, C(6)H), 6.73 (2H, d, *J* 8.7, C(3')H), 6.99 (2H, d, *J* 8.7, C(2')H); δ_C (100 MHz, MeOD): 17.2 (C(6)CH_3), 38.6 (C(4)), 46.0 (C(3)), 50.8 ($CO_2\underline{C}H_3$), 54.2 ($O\underline{C}H_3$), 70.1 (C(6)), 76.7 (C(2)), 113.3 (C(3')), 128.6 (C(2')), 133.0 (C(1')), 159.0 (C(4')), 171.0 ($\underline{C}O_2CH_3$), 179.6 (C(5)); m/z ([ESI]$^+$) 294.0 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 294.1337, $C_{15}H_{20}NO_5$ ([M+H]$^+$) requires 294.1336.

***(2R,4R,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 169b**

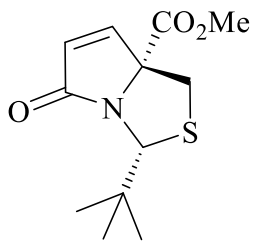
According to general method J, alcohol **168b** (22 mg, 0.08 mmol) was reacted with triphenylphosphine (84 mg, 0.32 mmol), benzoic acid (10 mg, 0.084 mmol) and diethyl azodicarboxylate (0.02 mL, 0.14 mmol) in anhydrous THF (0.1 M) to prepare alkene **169b**.



Yield 49% (10 mg); white solid, m. p. 84-88°C; R_f (20% EtOAc in DCM) 0.68; $[\alpha]_D^{25}$ +309.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2873 (C-H), 1745 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84-0.86 (12H, m, C(4)CH_3 + C$(CH_3)_3$), 3.69 (3H, s, CO_2CH_3), 4.66 (1H, s, C(2)H), 4.98 (1H, q, *J* 6.8, C(4)H), 6.12 (1H, d, *J* 5.7, C(6)H), 6.84 (1H, d, *J* 5.7, C(7)H); δ_C (100 MHz, $CDCl_3$): 15.6 (C(4)$\underline{C}H_3$), 24.9 (C($\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 74.5 (C(4)), 80.7 (C(5)), 93.9 (C(2)), 130.5 (C(6)), 145.5 (C(7)), 169.8 ($\underline{C}O_2CH_3$), 177.2 (C(8)); m/z ($[ESI]^+$) 276.1 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 254.1387, $C_{13}H_{20}NO_4$ ($[M+H]^+$) requires 254.1387.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene, 169d**

According to general method J, alcohol **168d** (120 mg, 0.44 mmol) was reacted with triphenylphosphine (462 mg, 1.76 mmol), benzoic acid (56.4 mg, 0.46 mmol) and diethyl azodicarboxylate (0.12 mL, 0.75 mmol) in anhydrous THF (0.1 M) to prepare alkene **169d**.



Yield 98% (110 mg); white solid, m. p. 106-108°C; R_f (20% EtOAc in DCM) 0.73; $[\alpha]_D^{25}$ +296.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 1745 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, C$(CH_3)_3$), 2.60 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.59 (1H, d, *J* 11.2, C(4)$H_A\underline{H_B}$), 3.70 (3H, s, CO_2CH_3), 4.84 (1H, s, C(2)H), 6.01 (1H, d, *J* 5.8, C(6)H), 6.96 (1H, d, *J* 5.8, C(7)H); δ_C (100 MHz, $CDCl_3$): 26.8 (C($\underline{C}H_3)_3$), 34.0 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 71.6 (C(2)), 82.4 (C(5)), 127.6 (C(6)), 147.1 (C(7)), 169.2 ($\underline{C}O_2CH_3$), 175.2 (C(8)); m/z ($[ESI]^+$) 278.0 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 256.1002, $C_{12}H_{18}NO_3S$ ($[M+H]^+$) requires 256.1002.

5.3 Experimental for Chapter 3

5.3.1 Synthesis of Oxazolidine and Thiazolidine Compounds[131,137] 147a-c

General Method A-B: See Section 5.2.1-5.2.2

5.3.2 Preparation of Oxazolidine and Thiazolidine Compounds 180a-c: General Method K[131]

To a solution of oxazolidine/thiazolidine **147a-c** (0.5 eq) and dry pyridine (1.04 eq) in anhydrous DCM, a solution of ethyl α-methylmalonyl chloride **179** (1 eq) in anhydrous DCM was added at 0°C. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 6 h. It was then washed with sat. aq. NH_4Cl and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude *N*-acyl oxazolidine/thiazolidine was purified by flash column chromatography (20%-35% EtOAc in petroleum ether) to yield **180a-c** as a mixture of diastereomers 7*R* (major) and 7*S* (minor).

5.3.3 Preparation of Oxazolidine and Thiazolidine Compounds 185a-c: General method L[131]

DMAP (0.07 eq) and DCC (1.1 eq) were added to a solution of oxazolidine or thiazolidine **147a-c** (1.0 eq) in anhydrous DCM. The mixture was cooled to 0 °C and ethyl α-phenyl malonic acid (1.1 eq) was added. Then the reaction mixture was stirred 30 min at 0 °C and 6 h at room temperature. A white precipitate was formed, which was filtered and washed with DCM. The combined filtrates were concentrated *in vacuo* and purified by flash column chromatography to give the required *N*-acyl oxazolidines or thiazolidine **185a-c**.

5.3.4 Dieckmann Cyclisation: General Method M[131,138]

To a solution of *N*-acyl oxazolidine or thiazolidine **180a-c**, **185a-c** or **180c'** (1.0 eq) in anhydrous ^{t}BuOH or THF (0.1 M) was added potassium *tert*-butoxide (1.09-1.10 eq). The mixture was heated at reflux for 3-6 h. Then the reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give the tetramic acids **128a-c**, **132a-c** and **198**.

5.3.5 Synthesis of 183a-c, 187a-c and 199: Mesylation Reaction

General Method E: See Section 5.2.5

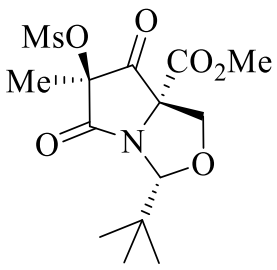
5.3.6 Preparation of 129ai-aiii, 129bi, 129ci-ciii, 133ai-aiii, 133bi and 133ci-ciii: Suzuki-Miyaura Cross-Coupling

General Method F: See Section 5.2.6

5.3.7 Synthesis of 203-205: *N,O*-Acetal deprotection

General Method I: See Section 5.2.9

(2R,5R,7S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-7-methyl-7-((methylsulfonyl)oxy)-3-oxa-6, 8-dioxobicyclo [3.3.0]-octane, 182



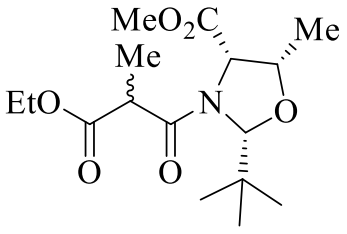
According to general method E, tetramate **181** (132 mg, 0.49 mmol) was reacted with MsCl (0.04 mL, 0.49 mmol) and DIPEA (0.17 mL, 0.98 mmol) in DCM (0.1 M).

Yield 56% (100 mg); white solid, m. p. 115-117°C; R_f (40% EA in

PE) 0.40; $[\alpha]_D^{25}$ +53.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2908 (C-H), 1795 (C=O), 1733 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (9H, s, $C(CH_3)_3$), 1.80 (3H, s, $C(7)CH_3$), 3.18 (3H, s, $OSO_2C\underline{H}_3$), 3.78 (3H, s, CO_2CH_3), 3.89 (1H, d, *J* 8.5, $C(4)\underline{H}_AH_B$), 4.78 (1H, d, *J* 8.5, $C(4)H_A\underline{H}_B$), 5.02 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 21.3 ($C(7)\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 41.0 (SO_2CH_3), 54.0 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 77.6 (C(5)), 84.7 (C(7)), 99.6 (C(2)), 166.4 ($\underline{C}O_2CH_3$), 172.7 (C(8)), 197.1 (C(6)); m/z ($[ESI]^+$) 386.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 364.1066, $C_{14}H_{22}NO_8S$ ($[M+H]^+$) requires 364.1067.

(2*R*,4*S*,5*S*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-methylacetyl)- and (2*R*, 4S, 5*S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 180b and 180b'

According to general method K, oxazolidine **147b** (690 mg, 3.43 mmol) was reacted with dry pyridine (0.57 mL, 7.1 mmol) and malonyl chloride **179** (1.1 g, 6.85 mmol) in anhydrous DCM (12 mL). The crude product was purified by flash column chromatography (20%-35% EtOAc in petroleum ether) to give *N*-acyl oxazolidine as a 2.1:1 mixture of diastereomers **180b** and **180b'**, which were separated only for characterisation.

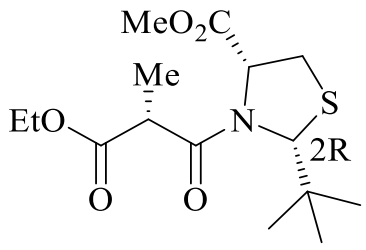


Yield 86% (968 mg); mixture of diastereomers, which were only separated for characterisation. Major isomer (**180b**): Colourless oil; R_f (30% EtOAc in Petrol) 0.38; $[\alpha]_D^{25}$ -76.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2986 (C-H), 2873 (C-H), 1755 (C=O), 1676 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.35 (3H, d, *J* 6.9, $C(7)CH_3$), 1.37 (3H, d, *J* 6.4, $C(4)C\underline{H}_3$), 3.44 (1H, q, *J* 6.9, C(7)H), 3.71 (3H, s, CO_2CH_3), 4.07-4.19 (3H, m, $C(9)H_2$ + C(4)H), 4.64 (1H, d, *J* 6.4, C(5)H), 5.17 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 14.1 (C(10)), 14.6, 15.5 ($C(7)\underline{C}H_3$ + $C(4)\underline{C}H_3$), 26.3 ($C(\underline{C}H_3)_3$), 36.8 ($\underline{C}(CH_3)_3$), 46.4 (C(7)), 52.1 ($CO_2\underline{C}H_3$), 61.6 (C(9)), 62.7 (C(5)), 74.9

(C(4)), 96.2 (C(2)), 169.3, 170.0, 172.3 (C(6)), $\underline{C}O_2CH_3$, C(8)); m/z (ESI$^+$) 352.0 ([M+Na]$^+$, 25%); HRMS ([ESI]$^+$) found 330.1910, $C_{16}H_{28}NO_6$ ([M+H]$^+$) requires 330.1911. Minor isomer (**180b'**): Colourless oil; R_f (30% EtOAc in Petrol) 0.25; ν_{max}/cm^{-1} 2986 (C-H), 2874 (C-H), 1755 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$), 1.31 (6H, t, *J* 7.2, $C(7)CH_3$ + $C(4)CH_3$), 3.35-3.46 (1H, m, C(7)H), 3.69 (3H, s, CO_2CH_3), 4.01-4.19 (3H, m, $C(9)H_2$ + C(4)H), 4.28-4.37 (1H, m, C(5)H), 5.15 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 13.4 ($C(7)\underline{C}H_3$), 14.0 (C(10)), 15.4 ($C(4)\underline{C}H_3$), 26.4 ($C(\underline{C}H_3)_3$), 37.1 ($\underline{C}(CH_3)_3$), 46.8 (C(7)), 51.9 ($CO_2\underline{C}H_3$), 61.6, 63.4 (C(4), C(9)), 75.0 (C(5)), 96.7 (C(2)), 168.7, 170.0, 171.7 (C(6)), $\underline{C}O_2CH_3$, C(8)); m/z (ESI$^+$) 352.0 ([M+Na]$^+$, 20%); HRMS ([ESI]$^+$) found 330.1909, $C_{16}H_{28}NO_6$ ([M+H]$^+$) requires 330.1911.

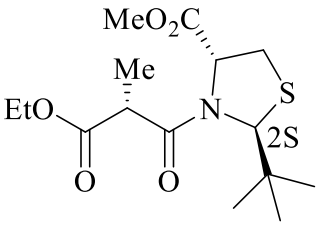
(*2R,5R*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine, 180c and (*2S,5R*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine, 180c'

According to general method K, thiazolidine **147c** (700 mg, 3.5 mmol) was reacted with dry pyridine (0.6 mL, 7.35 mmol) and malonyl chloride **179** (1.15 g, 7 mmol) in anhydrous DCM (20 mL). The crude *N*-acyl thiazolidine was purified by flash column chromatography (20%-35% EtOAc in petroleum ether) to yield **180** as a 2.5:1 mixture of diastereomers 2*R* (**c**) and 2*S* (**c'**). Major isomer **180c** was assigned by NOE correlations and minor isomer **180c'** was assigned by X-ray crystallography.



Major isomer (**180c**): Yield 71% (808 mg); colourless oil; mixture of rotamers; R_f (30% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ -105.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2981 (C-H), 1746 (C=O), 1664 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95, 1.02 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.37 (3H, d, *J* 6.9, $C(7)C\underline{H}_3$), 3.15-3.30 (2H, m,

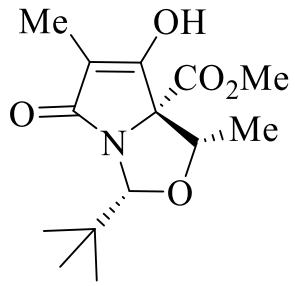
C(4)H_AH_B), 3.70, 3.73 (3H, s, CO_2CH_3), 3.87 (1H, q, *J* 6.9, C(7)H), 4.10 (2H, q, *J* 7.1 $CO_2CH_2CH_3$), 4.70, 4.96 (1H, t, *J* 9.5, C(5)H), 5.02, 5.52 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 12.8, 13.5 (C(7)CH_3), 14.0, 14.1 ($CO_2CH_2CH_3$), 26.9, 27.0 (C(CH_3)$_3$), 32.9, 33.8 (C(4)), 39.6, 39.8 (C(CH_3)$_3$), 44.3, 44.9 (C(7)), 52.5, 52.9 (CO_2CH_3), 61.5, 61.7 ($CO_2CH_2CH_3$), 63.9, 64.6 (C(5)), 73.2, 73.8 (C(2)), 169.6-171.2 (NCO, CO_2CH_3, CO_2Et); m/z (ESI$^+$) 332.2 ([M+H]$^+$, 10%), 354.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 354.1349, $C_{15}H_{25}NO_5SNa$ ([M+Na]$^+$) requires 354.1346.



Minor isomer (**180c'**): Yield 27% (307 mg); white solid, m. p. 82-84°C; mixture of rotamers; R_f (30% EtOAc in Petrol) 0.30; $[\alpha]_D^{25}$ -22.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 1744 (C=O), 1678 (C=O), 1652 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90, 1.02 (9H, s, C(CH_3)$_3$), 1.24-1.28 (3H, m, $CO_2CH_2CH_3$), 1.38 (3H, d, *J* 7.1, C(7)CH_3), 2.90, 3.12 (1H, d, *J* 12.2, C(4)H_AH_B), 3.43-3.51 (1H, m, C(4)H_AH_B), 3.65, 3.74 (3H, s, CO_2CH_3), 3.83-3.96 (1H, m, C(7)H), 4.09-4.26 (2H, m, $CO_2CH_2CH_3$), 4.65-4.73 (1H, m, C(5)H), 4.76, 5.40 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 13.6, 13.8 (C(7)CH_3), 13.9, 14.1 ($CO_2CH_2CH_3$), 27.2 (C(CH_3)$_3$), 34.1 (C(4)), 35.5 (C(CH_3)$_3$), 45.3, 46.5 (C(7)), 52.4, 53.1 (CO_2CH_3), 61.3, 63.3 ($CO_2CH_2CH_3$), 65.4, 67.3 (C(5)), 72.2, 73.9 (C(2)), 167.6-171.2 (NCO, CO_2CH_3, CO_2Et); m/z ([ESI]$^+$) 354.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 354.1341, $C_{15}H_{25}NO_5SNa$ ([M+Na]$^+$) requires 354.1346.

***(2R,4S,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-4,7-dimethyl-3-oxa-8-oxobicyclo[3.3.0] oct-6-ene, 128b**

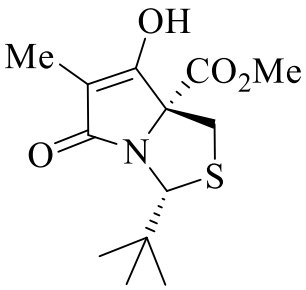
According to general method M, malonamide **180b** (853 mg, 2.6 mmol) was reacted with KO^{t}Bu (319 mg, 2.85 mmol) in ^{t}BuOH (0.2 M) to furnish tetramic acid **128b**.



Yield 67% (494 mg); white solid, m. p. 168-170°C; R_f (EtOAc) 0.30; $[\alpha]_D^{25}$ +96.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3420 (O-H), 2958 (C-H), 2871 (C-H), 1755 (C=O), 1649 (C=O); δ_H (400 MHz, MeOD): 0.81 (9H, s, $C(CH_3)_3$, 1.52-1.57 (6H, m, ($C(7)CH_3$ + $C(4)CH_3$)), 3.50 (1H, q, *J* 6.5, C(4)H), 3.60 (3H, s, CO_2CH_3), 4.45 (1H, s, C(2)H); δ_C (100 MHz, MeOD): 4.8 (C(7)$\underline{C}H_3$), 13.6 (C(4)$\underline{C}H_3$), 24.2 ($C(\underline{C}H_3)_3$), 34.5 ($\underline{C}(CH_3)_3$), 51.2 ($CO_2\underline{C}H_3$), 73.7 (C(5)), 79.8 (C(4)), 95.8 (C(2)), 102.1 (C(7)), 167.8 ($\underline{C}O_2CH_3$), 169.4 (C(8)), 181.7 (C(6)); m/z ($[ESI]^+$) 284.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 284.1492, $C_{14}H_{22}NO_5$ ($[M+H]^+$) requires 284.1493.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane, 128c**

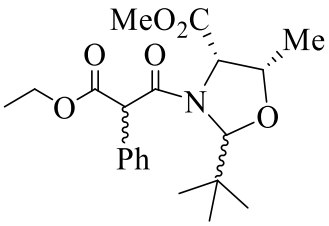
According to general method M, malonamide **180c** (5.38 g, 16.2 mmol) was reacted with KO^{t}Bu (2.0 g, 17.8 mmol) in THF (0.2 M) to furnish tetramic acid **128c**.



Yield 84% (3.9 g); white solid, m. p. 148-150°C; $[\alpha]_D^{25}$ +291.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3366 (O-H), 2956 (C-H), 1751 (C=O), 1650 (C=O); δ_H (400 MHz, MeOD): 0.95 (9H, s, $C(CH_3)_3$), 1.66 (3H, s, $C(7)CH_3$), 2.80 (1H, d, *J* 11.2, $C(4)\underline{H_A}H_B$), 3.68 (1H, d, *J* 11.2, $C(4)H_A\underline{H_B}$), 3.78 (3H, s, CO_2CH_3), 4.88 (1H, s, C(2)H); δ_C (100 MHz, MeOD): 4.8 (C(7)$\underline{C}H_3$), 25.6 ($C(\underline{C}H_3)_3$), 32.6 (C(4)), 36.3 ($\underline{C}(CH_3)_3$), 52.1 ($CO_2\underline{C}H_3$), 71.2 (C(2)), 79.1 (C(5)), 100.0 (C(7)), 168.6 ($\underline{C}O_2CH_3$), 169.2 (C(8)), 179.4 (C(6)); m/z ($[ESI]^+$) 286.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 286.1105, $C_{13}H_{20}NO_4S$ ($[M+H]^+$) requires 286.1108.

(*2R,4S,5S*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine (185b), (*2R,4S,5S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine (185b') and (*2S,4S,5S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine (185b'')

According to general method L, oxazolidine **147b** (870 mg, 4.3 mmol), DCC (969 mg, 4.7 mmol), and DMAP (37 mg, 0.3 mmol) was reacted with ethyl α-phenyl malonic acid **184** (990 mg, 4.7 mmol) in DCM (43 mL). The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether) to afford *N*-acyl oxazolidine as a 2:1.6:1 mixture of diastereomers **185b**, **185b'** and **185b''**. The stereochemistry of **185b** and **185b'** was assigned by NOE correlations and that of minor isomer **185b''** was determined by X-ray crystallography.

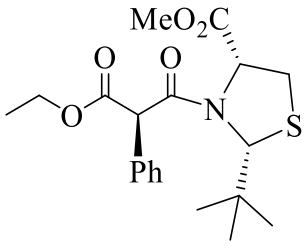


Yield 95% (1.61 g); 2:1.6:1 mixture of diastereomers; colourless oil; minor isomer **185b''** is solid for which m. p. is 84-86°C. R_f (20% EtOAc in Petrol) 0.19+0.25+0.28; isomers were separated only for characterisation. Major isomer **185b**: $[\alpha]_D^{25}$ +25.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2984 (C-H), 2958 (C-H), 2872 (C-H), 1754 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, $C(10)H_3$), 1.22 (3H, d, *J* 6.4, $C(4)CH_3$), 3.75 (3H, s, CO_2CH_3), 3.81 (1H, q, *J* 6.4, C(4)H), 4.04-4.23 (3H, m, (C(5)H + $C(9)H_2$), 4.58 (1H, s, (C(7)H), 5.11 (1H, s, C(2)H), 7.25-7.33 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.0 (C(10)), 15.3 (C(4)$\underline{C}H_3$), 26.4 (C($\underline{C}H_3)_3$), 37.1 ($\underline{C}(CH_3)_3$), 52.1 ($CO_2\underline{C}H_3$), 59.1 (C(7)), 61.8 (C(9)), 62.2 (C(5)), 74.8 (C(4)), 96.7 (C(2)), 128.5-131.9 (ArC), 168.2 (N$\underline{C}$=O), 168.9 ($\underline{C}O_2CH_3$), 169.3 (CO_2Et); m/z ($[ESI]^+$) 392.2 ($[M+H]^+$, 50%); HRMS ($[ES]I^+$) found 392.2061, $C_{21}H_{30}NO_6$ ($[M+H]^+$) requires 392.2068. Diastereomer **185b'**: $[\alpha]_D^{25}$ -46.0 (*c* 1.0

in DCM); ν_{max}/cm^{-1} 2985 (C-H), 2957 (C-H), 2873 (C-H), 1751 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, C(10)$\underline{H}_3$), 1.28 (3H, d, *J* 6.4, C(4)C$\underline{H}_3$), 3.50 (3H, s, CO_2CH_3), 4.08-4.21 (3H, m, $C(9)H_2$ + C(4)H), 4.51 (1H, d, *J* 6.4, C(5)H), 4.68 (1H, s, C(7)H), 5.18 (1H, s, C(2)H), 7.24-7.30 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.1 (C(10)), 15.2 (C(4)$\underline{C}H_3$), 26.4 ($C(\underline{C}H_3)_3$), 37.0 ($\underline{C}(CH_3)_3$), 51.8 ($CO_2\underline{C}H_3$), 59.2 (C(7)), 61.9 (C(9)), 63.5 (C(5)), 75.1 (C(4)), 96.9 (C(2)), 128.1-133.1 (ArC), 168.3 (N$\underline{C}$=O), 168.6 ($\underline{C}O_2CH_3$), 170.5 (CO_2Et); m/z ($[ESI]^+$) 392.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 392.2069, $C_{21}H_{30}NO_6$ ($[M+H]^+$) requires 392.2068.

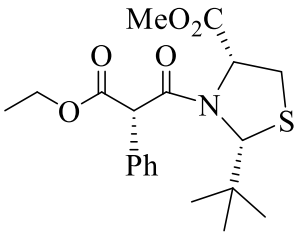
(*2R,5R*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-phenylacetyl)- and (*2R,5R*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-phenylacetyl)-5-methoxycarbonyl-1,3-thiazolidine, 185c and 185c'

According to general method L, oxazolidine **147c** (4.0 g, 19.6 mmol), DCC (4.4 g, 21.6 mmol), and DMAP (167 mg, 1.37 mmol) was reacted with ethyl α-phenyl malonic acid **184** (4.5 g, 21.6 mmol) in DCM (196 mL). The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether) to afford *N*-acyl oxazolidine as a 1.8:1 mixture of diastereomers **185c** and **185c'** with 85% (6.57 g) yield, which were separated only for characterisation. The structure of diastereomers **185c** and **185c'** was confirmed by X-ray crystallography.



Major isomer **185c** (major rotamer A, minor rotamer B): white solid, m. p. 78-80°C; R_f (20% EtOAc in Petrol) 0.23; $[\alpha]_D^{25}$-46.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2871 (C-H), 1750 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, $C(CH_3)_3$ **A**), 1.06 (9H, s, $C(CH_3)_3$ **B**), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.00 (1H, dd, *J* 11.9, 8.5, C(4)$\underline{H}_AH_B$, **A**), 3.11 (1H, d, *J* 12.1, C(4)$\underline{H}_AH_B$ **B**), 3.23 (1H, dd, *J* 11.8, 6.9, C(4)$H_A\underline{H}_B$ **A**), 3.50 (1H, dd,

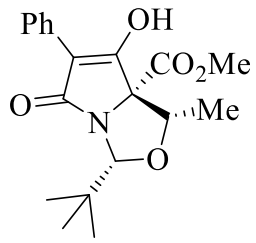
J 12.4, 7.1, C(4)$H_A\underline{H}_B$ **B**), 3.64 (3H, s, CO_2CH_3 **B**), 3.81 (3H, s, CO_2CH_3 **A**), 4.08-4.21 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.60 (1H, t, *J* 7.8, C(5)H **A**), 4.64 (1H, s, C(7)H **A**), 5.10 (1H, s, C(7)H **B**), 5.40 (1H, s, C(2)H **B**), 5.52 (1H, s, C(2)H **A**), 7.22-7.32 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.0 ($CO_2CH_2\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 33.9 (C(4)), 39.5 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 57.7 (<u>C</u>HPh), 61.8 ($CO_2\underline{C}H_2CH_3$), 63.4 (C(5)), 73.2 (C(2)), 128.2-132.7 (ArC), 168.2 (N<u>C</u>=O), 168.4 (CO_2Et), 171.0 ($\underline{C}O_2CH_3$).



Minor isomer **185c'** (major rotamer C, minor rotamer D): white solid, m. p. 72-74°C; R_f (20% EtOAc in Petrol) 0.18; $[\alpha]_D^{25}$ -94.1.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2872 (C-H), 1751 (C=O), 1657 (C=O); δ_H (400 MHz, $CDCl_3$): 0.85 (9H, s, $C(CH_3)_3$ **C**), 1.07 (9H, s, $C(CH_3)_3$ **D**), 1.19 (3H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$), 2.98-3.33 (2H, m, C(4)H_2), 3.57 (3H, s, CO_2CH_3 **C**), 3.71 (3H, s, CO_2CH_3 **D**), 4.11-4.18 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.59 (1H, s, C(5)H **D**), 4.61 (1H, s, C(2)H **D**), 4.73 (1H, s, C(7)H **C**), 4.96 (1H, s, C(7)H **D**), 5.04 (1H, s, C(5)H **C**), 5.58 (1H, C(2)H **C**), 7.26-7.38 (5H, s, ArH); δ_C (100 MHz, $CDCl_3$): 14.1 ($CO_2CH_2\underline{C}H_3$), 26.9, 27.3 ($C(\underline{C}H_3)_3$), 32.8, 34.5 (C(4)), 39.4, 41.2 ($\underline{C}(CH_3)_3$), 52.6, 52.8 ($CO_2\underline{C}H_3$), 56.8, 57.6 (<u>C</u>HPh), 61.7, 62.1 ($CO_2\underline{C}H_2CH_3$), 64.3, 64.5 (C(5)), 73.6, 73.7 (C(2)), 128.1-133.3 (ArC), 168.3 (N<u>C</u>=O), 170.6 (CO_2Et), 170.9 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 394.1 ($[M+H]^+$, 65%), 416.2 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 394.1691, $C_{20}H_{28}NO_5S$ ($[M+H]^+$) requires 394.1683.

***(2R,4S,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-7-phenylbicyclo [3.3.0]oct-6-ene, 132b**

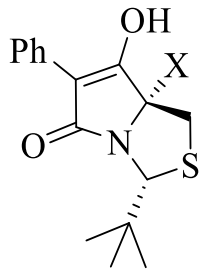
According to general method M, KO^{t}Bu (452 mg, 4.0 mmol) was reacted with a solution of oxazolidine (1.45 g, 3.7 mmol) in ^{t}BuOH (0.1 M). The crude product was purified by flash column chromatography to yield desired tetramic acid **132b**.



Yield 70% (899 mg); white solid, m. p. 160-162°C; R_f (10% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +26.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3329 (O-H), 2958 (C-H), 2871 (C-H), 1757 (C=O), 1685 (C=O); δ_H (400 MHz, MeOD): 0.86 (9H, s, $C(CH_3)_3$), 1.63 (3H, d, *J* 6.5, $C(4)CH_3$), 3.66 (3H, s, CO_2CH_3), 3.70 (1H, q, *J* 6.5, C(4)H), 4.58 (1H, s, C(2)H), 7.16-7.51 (5H, m, ArH); δ_C (100 MHz, MeOD): 13.7 ($C(4)\underline{C}H_3$), 24.3 ($C(\underline{C}H_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 51.5 ($CO_2\underline{C}H_3$), 73.7 (C(5)), 79.9 (C(4)), 96.2 (C(2)), 107.4 (C(7)), 127.1-129.7 (ArC), 167.6 ($\underline{C}O_2CH_3$), 169.4 (C(8)), 179.5 (C(6)); m/z ($[ESI]^+$) 346.1 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 346.1646, $C_{19}H_{24}NO_5$ ($[M+H]^+$) requires 346.1649.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0]oct-6-ene, 132c and *(2R,5S)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-8-oxo-7-phenyl-3-thiabicyclo [3.3.0]oct-6-ene, 186**

According to general method M, KO^{t}Bu (1.73 g, 14.17 mmol) was reacted with a solution of oxazolidine (5.12 g, 13.0 mmol) in ^{t}BuOH (87 mL). The crude product was purified by flash column chromatography which resulted in an inseparable mixture of tetramic acids **132c** and **186**.

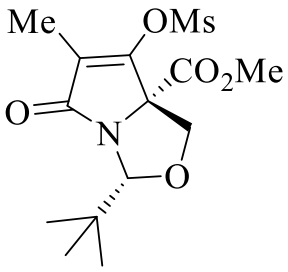


Yield 73% (3.3 g); 8:1 mixture of **132c** (X = CO_2Me) and **186** (X = H); white solid; R_f (10% MeOH in EtOAc) 0.20 + 0.23; ν_{max}/cm^{-1} 3284 (O-H), 3057 (C-H), 2955 (C-H), 1750 (C=O), 1649 (C=O), 1600 (C=O); **132c**: δ_H (400 MHz, MeOD): 0.91 (9H, s, $C(CH_3)_3$,), 2.71 (1H, d, *J* 11.3, $C(4)\underline{H_A}H_B$), 3.55 (1H, d, *J* 11.3, $C(4)H_A\underline{H_B}$), 3.72 (3H, s, CO_2CH_3), 4.86 (1H, s, C(2)H), 7.19-7.54 (ArH); δ_C (100 MHz, MeOD): 26.7 ($C(\underline{C}H_3)_3$), 33.7 (C(4)), 36.8 ($\underline{C}(CH_3)_3$), 53.4 ($CO_2\underline{C}H_3$), 72.0 (C(2)), 78.5 (C(5)), 106.5 (C(7)), 127.9-129.1 (ArC), 166.1 (C(8)), 169.2

($\underline{C}O_2CH_3$), 175.7 (C(6)); m/z ([ESI]$^+$) 348.1 ([M+H]$^+$, 50%), 370.1 ([M+Na]$^+$, 45%); HRMS ([ESI]$^+$) found 346.1117, $C_{18}H_{20}NO_4S$ ([M-H]$^-$) requires 346.1119.

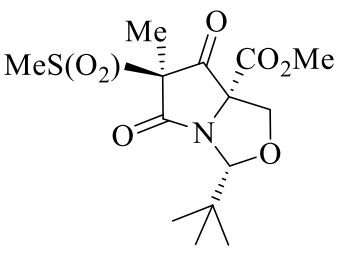
_(2R,5R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 183a

According to general method E (see Section 5.2.5), reaction of tetramic acid **128a** (4.6 g, 17.04 mmol) with MsCl (1.32 mL, 17.04 mmol) and DIPEA (5.9 mL, 34.08 mmol) in DCM (0.1 M) resulted in mesylate **183a**.



Yield 71% (4.2 g); white solid, m. p. 85-87°C; R_f (40% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$+130.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2873 (C-H), 1719 (C=O), 1685 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 1.84 (3H, s, C(7)CH_3), 3.19 (3H, s, OSO_2CH_3), 3.45 (1H, d, *J* 8.9, C(4)$\underline{H_A}H_B$), 3.73 (3H, s, CO_2CH_3), 4.65 (1H, s, C(2)H), 4.74 (1H, d, *J* 8.9, C(4)$H_A\underline{H_B}$); δ_C (100 MHz, $CDCl_3$): 8.2 (C(7)CH_3), 24.7 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 39.2 (OSO_2CH_3), 53.4 (CO_2CH_3), 70.8 (C(4)), 74.5 (C(5)), 96.6 (C(2)), 125.6 (C(7)), 155.5 (CO_2CH_3), 168.0 (C(8)), 175.4 (C(6)); m/z ([ESI]$^+$) 348.0 ([M+H]$^+$, 100%), 370.0 ([M+Na]$^+$, 90%); HRMS ([ESI]$^+$) found 348.1111, $C_{14}H_{22}NO_7S$ ([M+H]$^+$) requires 348.1112.

_(2S,5R,7S)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-7-methyl-7-(methylsulfonyl)-3-oxa-6,8-dioxobicyclo [3.3.0] octane, 189

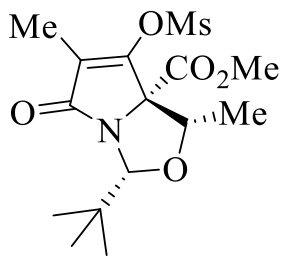


By-product from **183a**: Yield 7% (39 mg); white solid, m. p. 120-122°C; R_f (40% EtOAc in Petrol) 0.39; $[\alpha]_D^{25}$ +82.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2878 (C-H), 1754 (C=O), 1721 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 1.83 (3H,

s, C(7)CH_3), 3.12 (3H, s, SO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.91 (1H, d, *J* 8.6, C(4)$\underline{H_A}H_B$), 4.73 (1H, d, *J* 8.6, C(4)$H_A\underline{H_B}$), 5.05 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 18.0 (C(7)CH_3), 24.7 (C$(CH_3)_3$), 35.4 (C$(CH_3)_3$), 38.4 (SO_2CH_3), 54.0 (CO_2CH_3), 67.2 (C(4)), 73.7 (C(5)), 79.1 (C(7)), 100.1 (C(2)), 166.7 (CO_2CH_3), 171.5 (C(8)), 195.1 (C(6)); m/z ($[ESI]^+$) 370.1 ($[M+Na]^+$, 40%); HRMS ($[ESI]^+$) found 370.0931, $C_{14}H_{21}NO_7SNa$ ($[M+Na]^+$) requires 370.0931.

***(2R,4S,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4, 7-dimethyl-6-((methylsulfonyl)-oxy)-3-oxa-8-oxobicyclo[3.3.0] oct-6-ene, 183b**

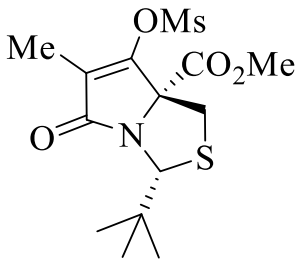
According to general method E (see Section 5.2.5), reaction of tetramic acid **128b** (400 mg, 1.4 mmol) with MsCl (0.11 mL, 1.4 mmol) and DIPEA (0.5 mL, 2.8 mmol) in DCM (0.1 M) resulted in mesylate **183b**.



Yield 89% (456 mg); white solid, m. p. 92-94°C; R_f (20% EtOAc in Petrol) 0.22; $[\alpha]_D^{25}$ +115.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2873 (C-H), 1700 (C=O), 1683 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, C$(CH_3)_3$), 1.55 (3H, d, *J* 6.4, C(4)CH_3), 1.86 (3H, s, C(7)CH_3), 3.24 (3H, s, OSO_2CH_3), 3.65-3.69 (4H, m, (C(4)H + CO_2CH_3)), 4.60 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.9 (C(7)$\underline{C}H_3$), 15.3 (C(4)$\underline{C}H_3$), 25.2 (C($\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 39.6 ($OSO_2\underline{C}H_3$), 52.6 ($CO_2\underline{C}H_3$), 74.4 (C(5)), 80.1 (C(4)), 96.4 (C(2)), 124.1 (C(7)), 156.2 ($\underline{C}O_2CH_3$), 166.8 (C(8)), 175.9 (C(6)); m/z ($[ESI]^+$) 362.2 ($[M+H]^+$, 50%), 384.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 362.1268, $C_{15}H_{24}NO_7S$ ($[M+H]^+$) requires 362.1268.

_(2R,5R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 183c

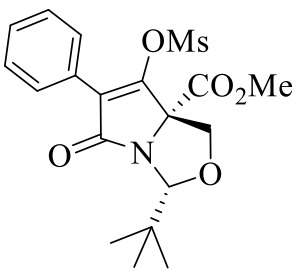
According to general method E (see Section 5.2.5), reaction of tetramic acid **128c** (546 mg, 1.9 mmol) with MsCl (0.15 mL, 1.9 mmol) and DIPEA (0.61 mL, 3.8 mmol) in DCM (0.1 M) resulted in mesylate **183c**.



Yield 65% (449 mg); colourless oil; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +198.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3020 (C-H), 2956 (C-H), 1749 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.84 (3H, s, C(7)CH_3), 2.79 (1H, d, *J* 11.3, C(4)$\underline{H_A}H_B$), 3.20 (3H, s, OSO_2CH_3), 3.60 (1H, d, *J* 11.3, C(4)$H_A\underline{H_B}$), 3.73 (3H, s, CO_2CH_3), 4.89 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.7 (C(7)$\underline{C}H_3$), 26.7 ($C(\underline{C}H_3)_3$), 33.6 (C(4)), 36.8 ($\underline{C}(CH_3)_3$), 39.5 (OSO_2CH_3), 53.4 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 79.2 (C(5)), 122.7 (C(7)), 155.5 ($\underline{C}O_2CH_3$), 168.1 (C(8)), 173.7 (C(6)); m/z ($[ESI]^+$) 386.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 364.0886, $C_{14}H_{22}NO_6S_2$ ($[M+H]^+$) requires 364.0883.

_(2R,5R)_-1-Aza-2-(_tert_-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 187a

According to general method E (see Section 5.2.5), reaction of tetramic acid **132a** (5.69 g, 17.17 mmol) with MsCl (1.33 mL, 17.17 mmol) and DIPEA (5.98 mL, 34.34 mmol) in DCM (0.1 M) resulted in mesylate **187a**.

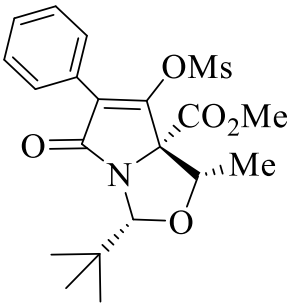


Yield 71% (5.0 g); colourless oil; R_f (30% EtOAc in Petrol) 0.30; $[\alpha]_D^{25}$ +164.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 2874 (C-H), 1751 (C=O), 1720 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 3.00 (3H, s, OSO_2CH_3), 3.62 (1H, d, *J* 9.1, C(4)$\underline{H_A}H_B$),

3.77 (3H, s, CO_2CH_3), 4.77 (1H, s, C(2)H), 4.86 (1H, d, *J* 9.1, C(4)$H_A\underline{H_B}$), 7.30-7.40 (3H, m, C(3'')H + C(4'')H)), 7.73 (2H, dd, *J* 8.0, 1.7, C(2'')H); δ_C (100 MHz, $CDCl_3$): 24.8 (C($\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 39.6 (OSO_2CH_3), 53.6 ($CO_2\underline{C}H_3$), 71.2 (C(4)), 74.3 (C(5)), 96.8 (C(2)), 126.6 (C(7)), 127.0-130.0 (ArC), 155.0 ($\underline{C}O_2CH_3$), 167.8 (C(8)), 173.4 (C(6)); m/z ($[ESI]^+$) 410.1 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 432.1088, $C_{19}H_{23}NO_7SNa$ ($[M+Na]^+$) requires 432.1087.

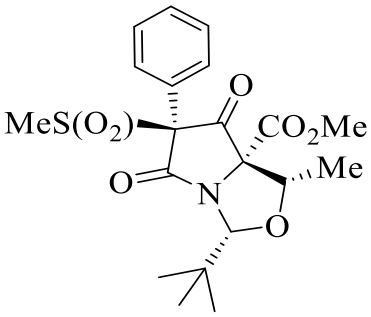
***(2R,4S,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 187b**

According to general method E (see Section 5.2.5), reaction of tetramic acid **132b** (1.27 g, 3.7 mmol) with MsCl (0.28 mL, 3.7 mmol) and DIPEA (1.29 mL, 7.4 mmol) in DCM (0.1 M) resulted in mesylate **187b**.



Yield 64% (1.0 g); colourless oil; R_f (30% EtOAc in Petrol) 0.33; $[\alpha]_D^{25}$ +52.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2873 (C-H), 1752 (C=O), 1719 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.67 (3H, d, *J* 6.4, C(4)CH_3), 2.87 (3H, s, OSO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.87 (1H, q, *J* 6.4, C(4)H), 4.71 (1H, s, C(2)H), 7.32-7.38 (3H, m, (C(3'')H + C(4'')H)), 7.56-7.60 (2H, m, C(2'')H); δ_C (100 MHz, $CDCl_3$): 15.4 (C(4)CH_3), 25.2 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 40.6 (OSO_2CH_3), 52.8 (CO_2CH_3), 74.5 (C(5)), 80.2 (C(4)), 96.4 (C(2)), 126.8 (C(7)), 127.3-129.9 (ArC), 156.8 ($\underline{C}O_2CH_3$), 166.3 (C(8)), 173.9 (C(6)); m/z ($[ESI]^+$) 424.2 ($[M+H]^+$, 20%), 446.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 424.1419, $C_{20}H_{26}NO_7S$ ($[M+H]^+$) requires 424.1425.

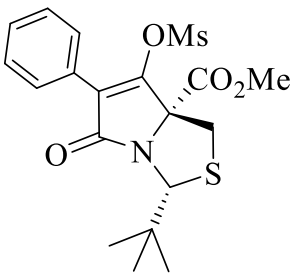
***(2S,4S,5R,7S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-7-(methylsulfonyl)-3-oxa-6, 8-dioxo-7-phenylbicyclo[3.3.0] oct-6-ene, 190**



By-product from **187b**: Yield 5% (73 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +27.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 2875 (C-H), 1758 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 1.62 (3H, d, *J* 6.5, $C(4)CH_3$), 2.88 (3H, s, SO_2CH_3), 3.30 (3H, s, CO_2CH_3), 4.19 (1H, q, *J* 6.5, C(4)H), 5.10 (1H, s, C(2)H), 7.36-7.42 (3H, m, C(3'')H + C(4'')H), 7.71-7.79 (2H, m, C(2'')H); δ_C (100 MHz, $CDCl_3$): 14.3 ($C(4)CH_3$), 25.2 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 38.5 (SO_2CH_3), 52.7 (CO_2CH_3), 76.3 (C(4)), 78.3 (C(5)), 80.1 (C(7)), 98.5 (C(2)), 127.6-130.4 (ArC), 164.6 ($\underline{C}O_2CH_3$), 169.8 (C(8)), 192.1 (C(6)); m/z ($[ESI]^+$) 446.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 446.1238, $C_{20}H_{25}NO_7SNa$ ($[M+Na]^+$) requires 446.1234.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-7-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 187c**

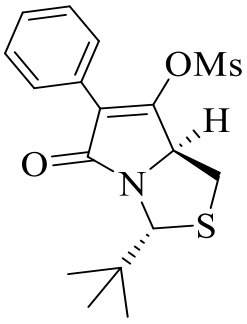
According to general method E (see Section 5.2.5), reaction of tetramic acid **132c** (3.7 g, 10.6 mmol) with MsCl (0.82 mL, 10.6 mmol) and DIPEA (3.7 mL, 21.2 mmol) in DCM (0.1 M) resulted in mesylate **187c**.



Yield 64% (2.9 g); white solid, m. p. 110-112°C; R_f (30% EtOAc in Petrol) 0.31; $[\alpha]_D^{25}$ +229.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C-H), 2935 (C-H), 1750 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, $C(CH_3)_3$), 2.98 (4H, d, *J* 11.9, (OSO_2CH_3 + $C(4)\underline{H_A}H_B$)), 3.73 (1H, d, *J* 11.5, $C(4)H_A\underline{H_B}$), 3.78 (3H, s, CO_2CH_3), 5.00 (1H, s, C(2)H), 7.31-7.41 (3H, m, (C(3'')H + C(4'')H)), 7.60-7.67 (2H, m, C(2'')H); δ_C (100 MHz, $CDCl_3$): 26.7

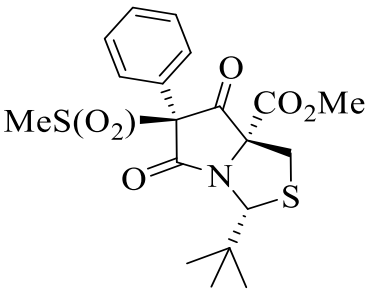
($C(\underline{C}H_3)_3$), 33.9 (C(4)), 37.0 (OSO_2CH_3), 40.1 ($\underline{C}(CH_3)_3$), 53.6 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 79.1 (C(5)), 124.9 (C(7)), 127.2-129.9 (ArC), 155.5 ($\underline{C}O_2CH_3$), 167.7 (C(8)), 171.6 (C(6)); m/z ($[ESI]^+$) 448.1 ($[M+Na]^+$, 75%); HRMS ($[ESI]^+$) found 448.0860, $C_{19}H_{23}NO_6S_2Na$ ($[M+Na]^+$) requires 448.0859.

***(2R,5S)*-1-Aza-2-(*tert*-butyl)-6-((methylsulfonyl)oxy)-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 188**



By-product from **187c**: Yield 6% (23 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.34; $[\alpha]_D^{25}$ +62.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 2934 (C-H), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 2.74 (1H, t, *J* 10.3, C(4)$\underline{H_A}H_B$), 2.98 (3H, s, OSO_2CH_3), 3.16-3.24 (1H, m, C(4)$H_A\underline{H_B}$), 4.90 (1H, dd, *J* 10.0, 6.1, C(5)H), 5.01 (1H, s, C(2)H), 7.30-7.39 (3H, m, C(3'')H + C(4'')H), 7.63-7.69 (2H, m, C(2'')H); δ_C (100 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 32.9 (C(4)), 37.5 (OSO_2CH_3), 39.3 ($C(CH_3)_3$), 66.6 (C(5)), 69.1 (C(2)), 121.8 (C(7)), 127.6-129.4 (ArC), 156.5 (C(8)), 169.7 (C(6)); m/z ($[ESI]^+$) 368.1 ($[M+H]^+$, 65%); HRMS ($[ESI]^+$) found 368.0985, $C_{17}H_{22}NO_4S_2$ ($[M+H]^+$) requires 368.0985.

***(2S,5R,7S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-7-(methylsulfonyl)-6,8-dioxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 191**

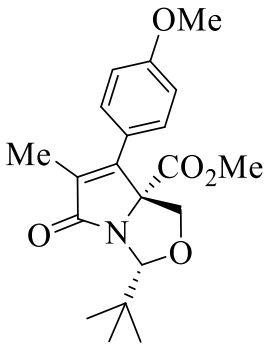


By-product from **187c**: Yield 9% (400 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +72.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2935 (C-H), 1753 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 2.88 (3H, s, SO_2CH_3), 3.25 (1H, d, *J* 11.1, C(4)$\underline{H_A}H_B$), 3.40 (3H, s, CO_2CH_3), 3.67 (1H, d, *J* 11.1, C(4)$H_A\underline{H_B}$), 5.43 (1H, s, C(2)H), 7.36-7.45 (3H, m,

(C(3'')H + C(4'')H)), 7.80-7.85 (2H, m, C(2'')H); δ_C (100 MHz, $CDCl_3$): 26.6 (C($\underline{C}H_3)_3$), 33.1 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 38.4 (SO_2CH_3), 53.6 ($CO_2\underline{C}H_3$), 74.6 (C(2)), 78.4 (C(5)), 82.8 (C(7)), 127.5-130.3 (ArC), 166.0 ($\underline{C}O_2CH_3$), 168.2 (C(8)), 193.1 (C(6)); m/z ($[ESI]^+$) 448.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 426.1034, $C_{19}H_{24}NO_6S_2$ ($[M+H]^+$) requires 426.1040.

***(2R,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 129ai**

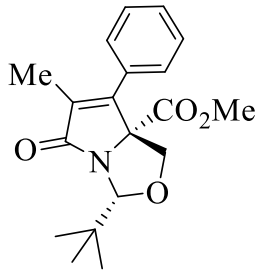
According to general method F (see Section 5.2.6), mesylate **183a** (141 mg, 0.41 mmol) was reacted with 4-methoxyphenylboronic acid (93 mg, 0.74 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.8 mL, 7.38 mmol) in ethanol (0.17 mL, 2.87 mmol) and toluene (12 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (10.5 mg, 0.025 mmol) and $(C_6H_5CN)_2PdCl_2$ (7.9 mg, 0.021 mmol) in toluene (2 mL).



Yield 54% (78 mg); white solid, m. p. 148-150°C; R_f (20% EtOAc in Petrol) 0.32; $[\alpha]_D^{25}$ +270.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1744 (C=O), 1606 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.98 (3H, s, C(7)CH_3), 3.43 (1H, d, *J* 8.1, C(4)$\underline{H_A}H_B$), 3.49 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.70 (1H, s, C(2)H), 5.04 (1H, d, *J* 8.1, C(4)$H_A\underline{H_B}$), 6.88 (2H, d, *J* 8.5, C(3')H), 7.16 (2H, d, *J* 8.5, C(2')H); δ_C (100 MHz, $CDCl_3$): 10.7 (C(7)$\underline{C}H_3$), 24.8 (C($\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 55.4 ($O\underline{C}H_3$), 71.0 (C(4)), 77.2 (C(5)), 96.4 (C(2)), 114.4 (C(3')), 123.5 (C(7)), 129.8 (C(2')), 129.8 (C(1')), 151.6 (C(6)), 160.5 (C(4')), 170.0 ($\underline{C}O_2CH_3$), 179.0 (C(8)); m/z ($[ESI]^+$) 360.2 ($[M+H]^+$, 40%), 382.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 360.1807, $C_{20}H_{26}NO_5$ ($[M+H]^+$) requires 360.1806.

(2R,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] oct-6-ene, 129aii

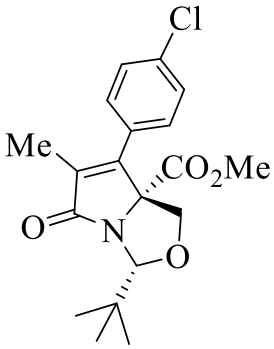
According to general method F (see Section 5.2.6), mesylate **183a** (600 mg, 1.73 mmol) was reacted with phenylboronic acid (337 mg, 2.76 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.65 mL, 15.6 mmol) in ethanol (0.71 mL, 12.11 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (44 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (33 mg, 0.086 mmol) in toluene (3 mL).



Yield 33% (190 mg); white solid, m. p. 134-136°C; R_f (20% EtOAc in Petrol) 0.42; $[\alpha]_D^{25}$ +250.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1745 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.97 (3H, s, C(7)CH_3), 3.46 (1H, d, *J* 8.2, C(4)$\underline{H_A}H_B$), 3.49 (3H, s, CO_2CH_3), 4.72 (1H, s, C(2)H), 5.03 (1H, d, *J* 8.2, C(4)$H_A\underline{H_B}$), 7.13-7.40 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.6 (C(7)$\underline{C}H_3$), 24.8 (C($\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 71.0 (C(4)), 77.3 (C(5)), 96.5 (C(2)), 128.1-131.8 (C(7) + ArC), 151.9 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 178.7 (C(8)); m/z ($[ESI]^+$) 352.2 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 352.1518, $C_{19}H_{23}NO_4Na$ ($[M+Na]^+$) requires 352.1519.

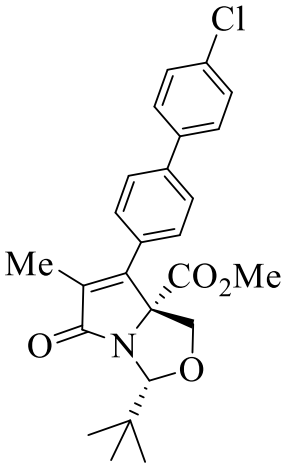
(2R,5S)-1-Aza-2-(*tert*-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 129aiii

According to general method F (see Section 5.2.6), mesylate **183a** (600 mg, 1.73 mmol) was reacted with 4-chlorophenylboronic acid (283 mg, 1.81 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.65 mL, 15.6 mmol) in ethanol (0.71 mL, 12.11 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (44 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (33 mg, 0.086 mmol) in toluene (3 mL).



Yield 38% (237 mg); white solid, m. p. 120-122°C; R_f (20% EtOAc in Petrol) 0.50; $[\alpha]_D^{25}$ +225.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1745 (C=O), 1594 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.96 (3H, s, $C(7)CH_3$), 3.44 (1H, d, *J* 8.1, $C(4)\underline{H_A}H_B$), 3.51 (3H, s, CO_2CH_3), 4.71 (1H, s, C(2)H), 5.00 (1H, d, *J* 8.1, $C(4)H_A\underline{H_B}$), 7.11 (2H, d, *J* 8.3, C(2')H), 7.34 (2H, d, *J* 8.3, C(3')H); δ_C (100 MHz, $CDCl_3$): 10.6 ($C(7)\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 70.9 (C(4)), 77.2 (C(5)), 96.5 (C(2)), 129.3 (C(2')), 129.4 (C(3')), 129.5 (C(7)), 132.4 (C(4')), 135.9 (C(1')), 150.5 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 178.3 (C(8)); m/z ($[ESI]^+$) 386.2 ($[M+Na]^+$, ^{35}Cl, 10%); HRMS ($[ESI]^+$) found 386.1127, $C_{19}H_{22}ClNO_4Na$ ($[M+Na]^+$, ^{35}Cl) requires 386.1130.

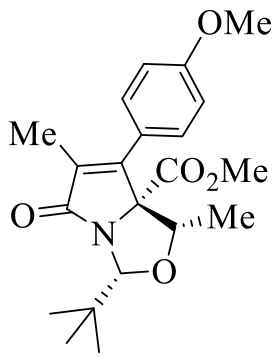
***(2R,5S)*-1-Aza-2-(*tert*-butyl)-6-(4'-chloro-[1,1'-biphenyl]-4-yl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 196**



By-product from **129aiii**: Yield 5% (36 mg); white solid, m. p. 110-112°C; R_f (20% EtOAc in Petrol) 0.40; $[\alpha]_D^{25}$ +166.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2869 (C-H), 1745 (C=O), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 2.02 (3H, s, $C(7)CH_3$), 3.48 (1H, d, *J* 8.1, $C(4)\underline{H_A}H_B$), 3.52 (3H, s, CO_2CH_3), 4.73 (1H, s, C(2)H), 5.07 (1H, d, *J* 8.1, $C(4)H_A\underline{H_B}$), 7.25-7.56 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.8 ($C(7)\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 71.0 (C(4)), 77.2 (C(5)), 96.5 (C(2)), 127.4-141.2 (ArC + C(7)), 151.3 (C(6)), 169.8 ($\underline{C}O_2CH_3$), 178.6 (C(8)); m/z ($[ESI]^+$) 440.2 ($[M+H]^+$, ^{35}Cl, 90%), 442.2 ($[M+H]^+$, ^{37}Cl, 70%); HRMS ($[ESI]^+$) found 440.1623, $C_{25}H_{27}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 440.1623.

***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4,7-dimethyl-8-oxo-3-oxabicyclo [3.3.0] oct-6-ene, 129bi**

According to general method F (see Section 5.2.6), mesylate **183b** (116 mg, 0.32 mmol) was reacted with 4-methoxyphenylboronic acid (78 mg, 0.51 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.3 mL, 2.88 mmol) in ethanol (0.3 mL, 2.88 mmol) and toluene (10 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.0 mg, 0.019 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.0 mg, 0.016 mmol) in toluene (1 mL).

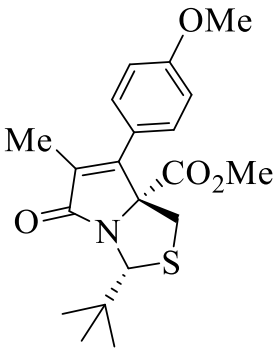


Yield 9% (11 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$ -13.7 (*c* 0.7 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 2934 (C-H), 1748 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.47 (1H, d, *J* 6.5, C(4)CH_3), 1.83 (3H, s, C(7)CH_3), 3.54 (1H, q, *J* 6.5, C(4)H), 3.62 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.64 (1H, s, C(2)H), 6.87 (2H, d, *J* 8.5, C(3')H), 7.03 (2H, d, *J* 8.5, C(2')H); δ_C (100 MHz, $CDCl_3$): 10.5 (C(7)$\underline{C}H_3$), 15.1 (C(4)$\underline{C}H_3$), 25.1 (C($\underline{C}H_3$)$_3$), 35.2 ($\underline{C}(CH_3)_3$), 52.1 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 77.2 (C(5)), 80.2 (C(4)), 95.7 (C(2)), 114.3 (C(3')), 124.1 (C(7)), 129.1 (C(2')), 132.3 (C(1')), 152.9 (C(6)), 160.1 (C(4')), 169.0 ($\underline{C}O_2CH_3$), 178.9 (C(8)); m/z ($[ESI]^+$) 374.2 ($[M+H]^+$, 90%), 382.2 ($[M+Na]^+$, 80%); HRMS ($[ESI]^+$) found 374.1964, $C_{21}H_{28}NO_5$ ($[M+H]^+$) requires 374.1962.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 129ci**

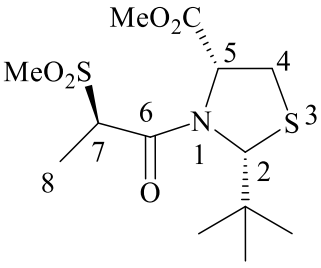
According to general method F (see Section 5.2.6), mesylate **183c** (395 mg, 1.08 mmol) was reacted with 4-methoxyphenylboronic acid (263 mg, 1.73 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.03 mL, 9.72 mmol) in ethanol (0.44 mL, 7.56 mmol) and toluene (13

mL) for overnight. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (28.0 mg, 0.065 mmol) and $(C_6H_5CN)_2PdCl_2$ (21.0 mg, 0.054 mmol) in toluene (2 mL).



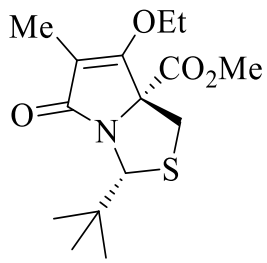
Yield 23% (95 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.28; $[\alpha]_D^{25}$ +289.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C-H), 2839 (C-H), 1745 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.89 (3H, s, C(7)CH_3), 2.81 (1H, d, *J* 10.8, C(4)$\underline{H_A}H_B$), 3.52 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.81 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 4.95 (1H, s, C(2)H), 6.86 (2H, d, *J* 8.5, C(3')H), 7.17 (2H, d, *J* 8.5, C(2')H); δ_C (100 MHz, $CDCl_3$): 10.6 (C(7)$\underline{C}H_3$), 26.7 ($C(\underline{C}H_3)_3$), 34.9 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 71.0 (C(2)), 82.3 (C(5)), 114.3 (C(3')), 123.5 (C(7)), 128.9 (C(1')), 129.5 (C(2')), 151.9 (C(6)), 160.3 (C(4')), 169.9 ($\underline{C}O_2CH_3$), 176.5 (C(8)); m/z ($[ESI]^+$) 376.2 ($[M+H]^+$, 100%), 398.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 376.1577, $C_{20}H_{26}NO_4S$ ($[M+H]^+$) requires 376.1577.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-1-((*R*)-2-(methylsulfonyl)propanoyl)-1,3-thiazolidine, 192**



By-product from **129ci**: Yield 2% (9 mg); yellow solid, m. p. 108-110°C; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +63.4 (*c* 0.7 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 1747 (C=O), 1655 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.65 (3H, d, *J* 6.9, C(8)H_3), 2.92 (3H, s, SO_2CH_3), 3.34-3.42 (2H, m, C(4)H_2), 3.77 (3H, s, CO_2CH_3), 3.95 (1H, q, *J* 6.9, C(7)H), 5.37 (1H, dd, *J* 8.7, 7.1, C(5)H), 5.52 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.9 (C(8)), 26.9 ($C(\underline{C}H_3)_3$), 33.3 (C(4)), 36.8 ($SO_2\underline{C}H_3$), 39.5 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 63.3 (C(7)), 63.7 (C(5)), 72.9 (C(2)), 167.5 ($\underline{C}O_2CH_3$), 170.9 (C(6)); m/z ($[ESI]^+$) 338.1 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 338.1091, $C_{13}H_{24}NO_5S_2$ ($[M+H]^+$) requires 338.1090.

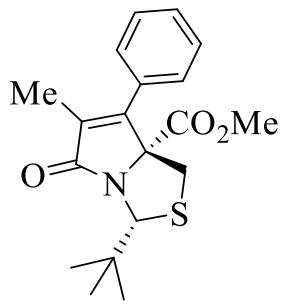
***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-ethoxy-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 193c**



By-product from **129ci**: Yield 3% (11 mg); yellow semi-solid; R_f (20% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +124.2 (*c* 0.8 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2933 (C-H), 1749 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 1.24 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 1.84 (3H, s, $C(7)C\underline{H}_3$), 2.65 (1H, d, *J* 11.1, $C(4)\underline{H}_AH_B$), 3.59 (1H, d, *J* 11.1, $C(4)H_A\underline{H}_B$), 3.70 (3H, s, CO_2CH_3), 4.21-4.30 (2H, m, $OC\underline{H}_2CH_3$), 4.87 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.6 ($C(7)\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 26.5 ($C(\underline{C}H_3)_3$), 33.9 (C(4)), 36.7 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 67.5 ($O\underline{C}H_2CH_3$), 71.8 (C(2)), 79.0 (C(5)), 101.6 (C(7)), 166.6 ($\underline{C}O_2CH_3$), 169.3 (C(8)), 177.9 (C(6)); m/z ($[ESI]^+$) 314.1 ($[M+H]^+$, 45%); HRMS ($[ESI]^+$) found 314.1421, $C_{15}H_{24}NO_4S$ ($[M+H]^+$) requires 314.1421.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)- 5-methoxycarbonyl-7-methyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 129cii**

According to general method F (see Section 5.2.6), mesylate **183c** (309 mg, 0.85 mmol) was reacted with phenylboronic acid (166 mg, 1.36 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.81 mL, 7.65 mmol) in ethanol (0.34 mL, 5.95 mmol) and toluene (13 mL) for 12 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (21.7 mg, 0.051 mmol) and $(C_6H_5CN)_2PdCl_2$ (16.3 mg, 0.043 mmol) in toluene (2 mL).

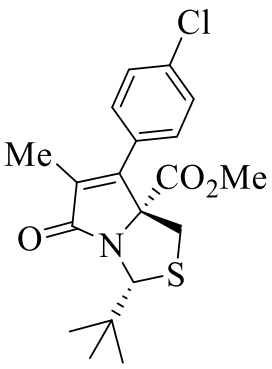


Yield 23% (68 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.50; $[\alpha]_D^{25}$ +325.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 2869 (C-H), 1746 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.94 (9H, s, $C(CH_3)_3$), 1.87 (3H, s, $C(7)CH_3$), 2.83 (1H, d, *J* 10.8, $C(4)\underline{H}_AH_B$),

3.53 (3H, s, CO_2CH_3), 3.77 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 4.95 (1H, s, C(2)H), 7.15-7.36 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.4 (C(7)$\underline{C}H_3$), 26.7 (C($\underline{C}H_3)_3$), 34.7 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 71.2 (C(2)), 82.4 (C(5)), 127.9-131.3 (ArC + C(7)), 152.2 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 176.2 (C(8)); m/z ($[ESI]^+$) 346.2 ($[M+H]^+$, 100%), 368.2 ($[M+Na]^+$, 80%); HRMS ($[ESI]^+$) found 346.1471, $C_{19}H_{24}NO_3S$ ($[M+H]^+$) requires 346.1471.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 129ciii**

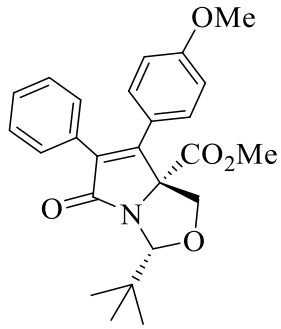
According to general method F (see Section 5.2.6), mesylate **183c** (380 mg, 1.04 mmol) was reacted with 4-chlorophenylboronic acid (172 mg, 1.09 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.99 mL, 9.36 mmol) in ethanol (0.43 mL, 7.28 mmol) and toluene (13 mL) for 12 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (26.7 mg, 0.0624 mmol) and $(C_6H_5CN)_2PdCl_2$ (20.0 mg, 0.052 mmol) in toluene (2 mL).



Yield 21% (84 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.44; $[\alpha]_D^{25}$ +261.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C-H), 2871 (C-H), 1746 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.86 (3H, s, C(7)CH_3), 2.80 (1H, d, *J* 10.8, C(4)$\underline{H_A}H_B$), 3.54 (3H, s, CO_2CH_3), 3.75 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 4.94 (1H, s, C(2)H), 7.12 (2H, d, *J* 8.5, C(2')H), 7.33 (2H, d, *J* 8.5, C(3')H); δ_C (100 MHz, $CDCl_3$): 10.4 (C(7)$\underline{C}H_3$), 26.7 (C($\underline{C}H_3)_3$), 34.7 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 71.2 (C(2)), 82.2 (C(5)), 129.3 (C(2') + C(3')), 129.6 (C(7)), 131.0 (C(4')), 135.7 (C(1')), 150.8 (C(6)), 169.4 ($\underline{C}O_2CH_3$), 175.8 (C(8)); m/z ($[ESI]^+$) 380.0 ($[M+H]^+$, ^{35}Cl, 100%), 382.0 ($[M+H]^+$, ^{37}Cl, 40%), 402.0 ($[M+Na]^+$, ^{35}Cl, 40%); HRMS ($[ESI]^+$) found 380.1082, $C_{19}H_{23}ClNO_3S$ ($[M+H]^+$, ^{35}Cl) requires 380.1082.

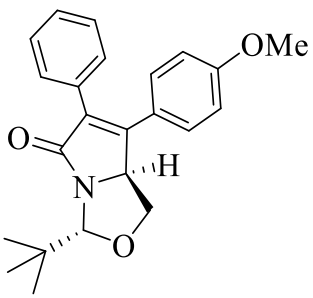
(2R,5S)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 133ai

According to general method F (see Section 5.2.6), mesylate **187a** (261 mg, 0.63 mmol) was reacted with 4-methoxyphenylboronic acid (172 mg, 1.13 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.2 mL, 11.34 mmol) in ethanol (0.26 mL, 4.41 mmol) and toluene (13 mL) 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.1 mg, 0.038 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.2 mg, 0.0315 mmol) in toluene (3 mL).



Yield 30% (81 mg); white solid, m. p. 134-136°C; R_f (30% EtOAc in Petrol) 0.40; $[\alpha]_D^{25}$ +150.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1746 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 3.51 (3H, s, CO_2CH_3), 3.59 (1H, d, *J* 8.1, C(4)$\underline{H_A}H_B$), 3.72 (3H, s, OCH_3), 4.78 (1H, s, C(2)H), 5.12 (1H, d, *J* 8.1, C(4)$H_A\underline{H_B}$), 6.72 (2H, d, *J* 8.9, C(3')H), 7.01 (2H, d, *J* 8.5, C(2')H), 7.22-7.34 (5H, m, C(7)ArH); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 71.1 (C(4)), 77.1 (C(5)), 96.9 (C(2)), 114.3-152.2 (ArC + C(7)), 160.8 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 177.4 (C(8)); m/z ($[ESI]^+$) 422.2 ($[M+H]^+$, 50%); HRMS ($[ES]I^+$) found 444.1776, $C_{25}H_{27}NO_5Na$ ($[M+Na]^+$) requires 444.1781.

(2R,5S)-1-Aza-2-(*tert*-butyl)-6-(4-methoxyphenyl)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 195

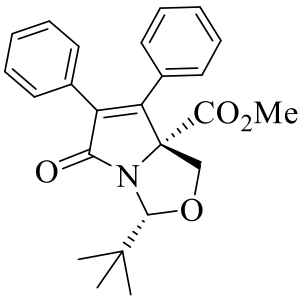


By-product from **133a**: Colourless oil; R_f (20% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ -21.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2869 (C-H), 1699 (C=O), 1606 (C=O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 3.30 (1H, dd, *J* 9.6, 8.0, C(4)$\underline{H_A}H_B$), 3.73 (3H, s, OCH_3), 4.33 (1H, dd, *J* 8.0, 6.2, C(4)$H_A\underline{H_B}$), 4.75 (1H, dd, *J* 9.6, 6.2, C(5)H), 4.87 (1H, s,

C(2)H), 6.73 (2H, d, *J* 8.9, C(3')H), 7.15 (2H, d, *J* 8.9, C(2')H), 7.23-7.38 (5H, m, C(7)ArH); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 36.0 ($\underline{C}(CH_3)_3$), 55.3 ($CO_2\underline{C}H_3$), 65.1 (C(5)), 70.0 (C(4)), 94.7 (C(2)), 114.3-151.6 (ArC + C(7)), 160.7 (C(6)), 176.4 (C(8)); m/z ($[ESI]^+$) 464.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 364.1908, $C_{23}H_{26}NO_3$ ($[M+H]^+$) requires 364.1907.

***(2R,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6,7-diphenylbicyclo [3.3.0] oct-6-ene, 133aii**

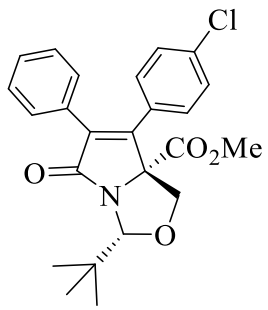
According to general method F (see Section 5.2.6), mesylate **187a** (525 mg, 1.28 mmol) was reacted with phenylboronic acid (250 mg, 2.05 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.22 mL, 11.52 mmol) in ethanol (0.52 mL, 8.96 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (32.7 mg, 0.077 mmol) and $(C_6H_5CN)_2PdCl_2$ (24.5 mg, 0.064 mmol) in toluene (3 mL).



Yield 9% (46 mg); white solid, m. p. 158-160°C; R_f (30% EtOAc in Petrol) 0.38; $[\alpha]_D^{25}$ +152.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1747 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 3.50 (3H, s, CO_2CH_3), 3.62 (1H, d, *J* 8.2, $C(4)\underline{H_A}H_B$), 4.80 (1H, s, C(2)H), 5.10 (1H, d, *J* 8.2, $C(4)H_A\underline{H_B}$), 7.00-7.34 (10H, m, (C(6)Ph + C(7)Ph)); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 71.0 (C(4)), 77.3 (C(5)), 97.1 (C(2)), 128.8 (C(7)), 115.3-133.8 (ArC), 152.4 (C(6)), 169.4 ($\underline{C}O_2CH_3$), 177.1 (C(8)); m/z ($[ESI]^+$) 392.2 ($[M+H]^+$, 10%), 414.2 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 392.1856, $C_{24}H_{26}NO_4$ ($[M+H]^+$) requires 392.1856.

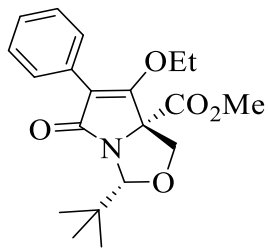
(2R,5S)-1-Aza-2-(*tert*-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 133aiii

According to general method F (see Section 5.2.6), mesylate **187a** (536 mg, 1.3 mmol) was reacted with 4-chlorophenylboronic acid (215 mg, 1.364 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.2 mL, 11.7 mmol) in ethanol (0.5 mL, 9.1 mmol) and toluene (13 mL) for 16 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (33.0 mg, 0.078 mmol) and $(C_6H_5CN)_2PdCl_2$ (25.0 mg, 0.065 mmol) in toluene (3 mL).



Yield 5% (28 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.53; $[\alpha]_D^{25}$ +124.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1747 (C=O), 1711 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 3.52 (3H, s, CO_2CH_3), 3.60 (1H, d, *J* 8.1, C(4)$\underline{H_A}H_B$), 4.79 (1H, s, C(2)H), 5.08 (1H, d, *J* 8.1, C(4)$H_A\underline{H_B}$), 6.99 (2H, d, *J* 8.6, C(2')H), 7.20 (2H, d, *J* 8.6, C(3')H), 7.24-7.30 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 71.0 (C(4)), 77.1 (C(5)), 97.1 (C(2)), 129.1 (C(7)), 128.5-136.1 (ArC), 150.9 (C(6)), 169.3 ($\underline{C}O_2CH_3$), 176.7 (C(8)); m/z ($[ESI]^+$) 426.2 ($[M+H]^+$, ^{35}Cl, 70%), 428.2 ($[M+H]^+$, ^{37}Cl, 35%), 448.1 ($[M+Na]^+$, ^{35}Cl, 60%), 450.1 ($[M+Na]^+$, ^{37}Cl, 30%); HRMS ($[ESI]^+$) found 426.1465, $C_{24}H_{25}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 426.1467.

(2R,5R)-1-Aza-2-(*tert*-butyl)-6-ethoxy-5-methoxycarbonyl-3-oxa-8-oxo-7-phenylbicyclo [3.3.0] oct-6-ene, 194a

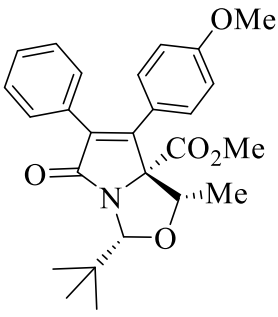


By-product from **133ai-aiii**: Yield 4-5% (23 mg); colourless oil; R_f (20% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ +142.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1747 (C=O), 1708 (C=O); δ_H (400 MHz,

$CDCl_3$): 0.87 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 3.48 (1H, d, *J* 8.4, $C(4)\underline{H}_A H_B$), 3.75 (3H, s, CO_2CH_3), 3.78 (1H, dd, *J* 9.8, 7.0, $OC\underline{H}_A H_B CH_3$), 4.00 (1H, dd, *J* 9.8, 7.0, $OCH_A\underline{H}_B CH_3$), 4.71 (1H, s, C(2)H), 4.85 (1H, d, *J* 8.4, $C(4)H_A\underline{H}_B$), 7.23-7.50 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 15.0 ($OCH_2\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 53.3 ($CO_2\underline{C}H_3$), 69.1 ($O\underline{C}H_2CH_3$), 70.0 (C(4)), 74.0 (C(5)), 97.0 (C(2)), 111.0 (C(7)), 128.1-129.9 (ArC), 167.6 ($\underline{C}O_2CH_3$), 169.2 (C(8)), 177.7 (C(6)); m/z ($[ESI]^+$) 360.2 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 360.1806, $C_{20}H_{26}NO_5$ ($[M+H]^+$) requires 360.1806.

***(2R,4S,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-Methyl-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 133bi**

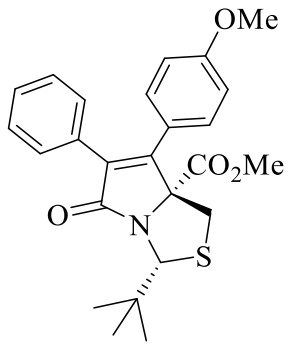
According to general method F (see Section 5.2.6), mesylate **187b** (230 mg, 0.54 mmol) was reacted with 4-methoxyphenylboronic acid (89 mg, 0.58 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.0 mL, 9.32 mmol) in ethanol (0.22 mL, 3.78 mmol) and toluene (13 mL) for 17 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (13.8 mg, 0.032 mmol) and $(C_6H_5CN)_2PdCl_2$ (10.3 mg, 0.027 mmol) in toluene (1 mL).



Yield 7% (17 mg); yellow semi-solid; R_f (20% EtOAc in Petrol) 0.42; $[\alpha]_D^{25}$ +4.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2870 (C-H), 1749 (C=O), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.53 (3H, d, *J* 6.5, $C(4)CH_3$), 3.66 (3H, s, CO_2CH_3), 3.67-3.71 (1H, m, C(4)H), 3.73 (3H, s, OCH_3), 4.76 (1H, s, C(2)H), 6.75 (2H, d, *J* 8.8, C(3')H), 6.96 (2H, d, *J* 8.8, C(2')H), 7.18-7.37 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 15.2 ($C(4)\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.3 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 80.3 (C(4)), 92.1 (C(5)), 96.0 (C(2)), 114.3-133.6 (ArC + C(7)), 160.3 (C(6)), 168.8 ($\underline{C}O_2CH_3$), 176.9 (C(8)); m/z ($[ESI]^+$) 458.2 ($[M+Na]^+$, 70%); HRMS ($[ESI]^+$) found 458.1941, $C_{26}H_{29}NO_5Na$ ($[M+Na]^+$) requires 458.1938.

(2R,5R)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 133ci

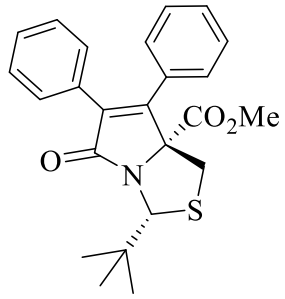
According to general method F (see Section 5.2.6), mesylate **187c** (303 mg, 0.71 mmol) was reacted with 4-methoxyphenylboronic acid (195 mg, 1.28 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.67 mL, 6.4 mmol) in ethanol (0.3 mL, 4.97 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (18.1 mg, 0.043 mmol) and $(C_6H_5CN)_2PdCl_2$ (13.6 mg, 0.035 mmol) in toluene (2 mL).



Yield 23% (72 mg); white solid, m. p. 152-154°C; R_f (20% EtOAc in Petrol) 0.36; $[\alpha]_D^{25}$ +313.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 2906 (C-H), 1745 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 2.94 (1H, d, *J* 10.8, C(4)$\underline{H_A}H_B$), 3.54 (3H, s, CO_2CH_3), 3.72 (3H, s, OCH_3), 3.87 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 5.03 (1H, s, C(2)H), 6.72 (2H, d, *J* 8.8, C(3')H), 7.05 (2H, d, *J* 8.8, C(2')H), 7.19-7.32 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 26.7 ($C(\underline{C}H_3)_3$), 34.9 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 71.6 (C(2)), 82.0 (C(5)), 123.4 (C(7)), 114.3, 128.3-152.4 (ArC), 160.5 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 174.8 (C(8)); m/z ($[ESI]^+$) 438.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 438.1725, $C_{25}H_{28}NO_4S$ ($[M+H]^+$) requires 438.1734.

(2R,5R)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6,7-diphenyl-3-thiabicyclo [3.3.0] oct-6-ene, 133cii

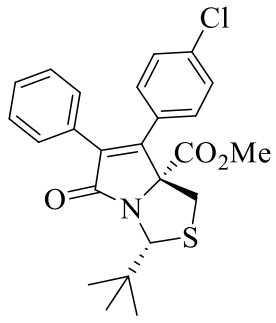
According to general method F (see Section 5.2.6), mesylate **187c** (624 mg, 1.46 mmol) was reacted with phenylboronic acid (462 mg, 3.8 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (2.4 mL, 22.63 mmol) in ethanol (0.59 mL, 10.2 mmol) and toluene (15 mL) for 18 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (37.5 mg, 0.088 mmol) and $(C_6H_5CN)_2PdCl_2$ (28.1 mg, 0.073 mmol) in toluene (2 mL).



Yield 56% (222 mg); white solid, m. p. 180-182°C; R_f (20% EtOAc in Petrol) 0.46; $[\alpha]_D^{25}$ +321.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 2906 (C-H), 1747 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.98 (9H, s, $C(CH_3)_3$), 2.96 (1H, d, *J* 10.8, C(4)$\underline{H_A}H_B$), 3.55 (3H, s, CO_2CH_3), 3.83 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 5.04 (1H, s, C(2)H), 7.04-7.33 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.8 ($C(\underline{C}H_3)_3$), 34.8 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 82.2 (C(5)), 128.7 (C(7)), 128.2, 128.3, 129.0-132.1 (ArC), 152.7 (C(6)), 169.3 ($\underline{C}O_2CH_3$), 174.5 (C(8)); m/z ($[ESI]^+$) 408.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 408.1626, $C_{24}H_{26}NO_3S$ ($[M+H]^+$) requires 408.1628.

_(2R,5R)_-1-Aza-2-(_tert_-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 133ciii

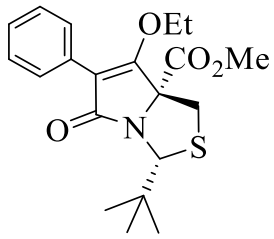
According to general method F (see Section 5.2.6), mesylate **187c** (624 mg, 1.46 mmol) was reacted with 4-chlorophenylboronic acid (240 mg, 1.53 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (2.4 mL, 22.63 mmol) in ethanol (0.59 mL, 10.2 mmol) and toluene (15 mL) for 6 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (37.5 mg, 0.088 mmol) and $(C_6H_5CN)_2PdCl_2$ (28.1 mg, 0.073 mmol) in toluene (2 mL).



Yield 9% (59 mg); white solid, m. p. 128-130°C; R_f (20% EtOAc in Petrol) 0.60; $[\alpha]_D^{25}$ +262.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 2829 (C-H), 1747 (C=O), 1706 (C=O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 2.94 (1H, d, *J* 10.8, C(4)$\underline{H_A}H_B$), 3.56 (3H, s, CO_2CH_3), 3.82 (1H, d, *J* 10.8, C(4)$H_A\underline{H_B}$), 5.03 (1H, s, C(2)H), 7.02 (2H, d, *J* 8.6, C(2')H), 7.18-7.29 (7H, m, (C(3')H + C(7)Ph)); δ_C (100 MHz, $CDCl_3$): 26.7 ($C(\underline{C}H_3)_3$), 34.8 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 82.0 (C(5)), 128.4-135.8 (ArC + C(7)), 151.1 (C(6)), 169.2 ($\underline{C}O_2CH_3$), 174.2 (C(8)); m/z ($[ESI]^+$) 442.2

([M+H]$^+$, ^{35}Cl, 45%), 444.2 ([M+H]$^+$, ^{37}Cl, 20%), 464.0 ([M+Na]$^+$, ^{35}Cl, 100%), 466.0 ([M+Na]$^+$, ^{37}Cl, 40%); HRMS ([ESI]$^+$) found 442.1239, $C_{24}H_{25}ClNO_3S$ ([M+H]$^+$, ^{35}Cl) requires 442.1238.

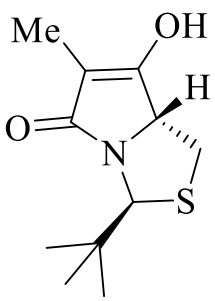
***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-ethoxy-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 194c**



By-product from **133ci-133ciii**: Yield 5% (13 mg); yellow oil; R_f (20% EtOAc in Petrol) 0.39; $[\alpha]_D^{25}$ +195.2 (*c* 0.9 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2931 (C-H), 1749 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.07 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 2.82 (1H, d, *J* 11.1, C(4)$\underline{H}_AH_B$), 3.69 (1H, d, *J* 11.1, C(4)$H_A\underline{H}_B$), 3.75 (3H, s, CO_2CH_3), 3.79 (1H, dd, *J* 10.1, 7.0, $OC\underline{H}_AH_BCH_3$), 3.94 (1H, dd, *J* 10.1, 7.0, $OCH_A\underline{H}_BCH_3$), 4.96 (1H, s, C(2)H), 7.23-7.39 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 13.9 ($OCH_2\underline{C}H_3$), 25.5 ($C(\underline{C}H_3)_3$), 33.0 (C(4)), 35.8 ($\underline{C}(CH_3)_3$), 52.1 ($CO_2\underline{C}H_3$), 68.1 ($O\underline{C}H_2CH_3$), 71.1 (C(2)), 77.9 (C(5)), 107.3 (C(7)), 127.0-129.2 (ArC), 166.4 ($\underline{C}O_2CH_3$), 168.1 (C(8)), 174.9 (C(6)); m/z ([ESI]$^+$) 376.2 ([M+H]$^+$, 55%); HRMS ([ESI]$^+$) found 376.1580, $C_{20}H_{26}NO_4S$ ([M+H]$^+$) requires 376.1577.

***(2S,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane, 198**

According to general method M, KO^{t}Bu (260 mg, 2.1 mmol) was reacted with a solution of thiazolidine **180c'** (700 mg, 2.31 mmol) in THF (0.2 M) which gave tetramic acid **198**.

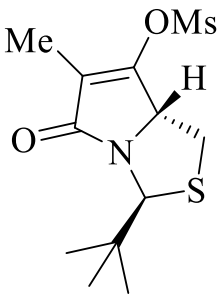


Quantitative yield (543 mg); white solid, m. p. 191-193°C; $[\alpha]_D^{25}$ -200.7 (*c* 1.0 in DMSO-d_6); δ_H (400 MHz, DMSO-d_6): 0.92 (9H, s, $C(CH_3)_3$), 1.52 (3H, s, C(7)CH_3), 2.57 (1H, dd, *J* 10.6, 8.9, C(4)$\underline{H}_AH_B$), 3.16 (1H, dd, *J* 10.6, 6.9, C(4)$H_A\underline{H}_B$), 4.40 (1H, t, *J* 7.9, C(5)H), 4.77 (1H, s, C(2)H); δ_C (100 MHz, DMSO-d_6): 6.6 (C(7)$\underline{C}H_3$), 26.6 ($C(\underline{C}H_3)_3$), 32.8

(C(4)), 37.4 (C(CH$_3$)$_3$), 66.9 (C(5)), 69.6 (C(2)), 99.2 (C(7)), 169.2 (C(8)), 176.7 (C(6)); m/z ([ESI]$^+$) 226.1 ([M-H]$^-$, 100%); HRMS ([ESI]$^+$) found 226.0905, $C_{11}H_{16}NO_2S$ ([M-H]$^-$) requires 226.0907.

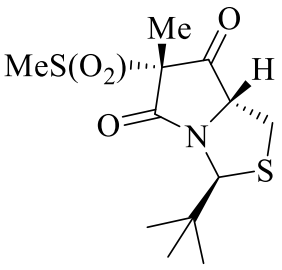
***(2S,5R)*-1-Aza-2-(*tert*-butyl)-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 199**

According to general method E (see Section 5.2.5), reaction of tetramic acid **198** (551 mg, 1.9 mmol) with MsCl (0.15 mL, 1.9 mmol) and DIPEA (0.66 mL, 3.8 mmol) in DCM (0.1 M) resulted mesylate **199**



Yield 18% (104 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.32; $[\alpha]_D^{25}$ -203.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2967 (C-H), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, C(CH$_3$)$_3$), 1.77 (3H, s, C(7)CH$_3$), 2.59 (1H, dd, *J* 10.7, 10.0, C(4)H$_A$H$_B$), 3.08 (1H, dd, *J* 10.7, 6.0, C(4)H$_A$H$_B$), 3.21 (3H, s, OSO$_2$CH$_3$), 4.65-4.73 (1H, m, C(5)H), 4.90 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 6.7 (C(7)CH$_3$), 25.3 (C(CH$_3$)$_3$), 31.6 (C(4)), 36.4 (C(CH$_3$)$_3$), 38.0 (OSO$_2$CH$_3$), 65.9 (C(5)), 67.9 (C(2)), 120.0 (C(7)), 155.4 (C(8)), 170.4 (C(6)); m/z ([ESI]$^+$) 306.0 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 306.0828, $C_{12}H_{20}NO_4S_2$ ([M+H]$^+$) requires 306.0828.

***(2S,5R,7R)*-1-Aza-2-(*tert*-butyl)-7-methyl-7-(methylsulfonyl)-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 200**

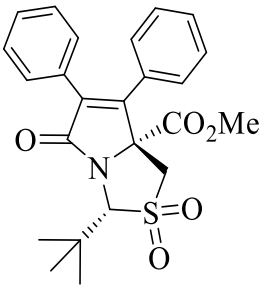


By-product from **199**: Yield 9% (52 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.40; δ_H (400 MHz, $CDCl_3$): 1.08 (9H, s, C(CH$_3$)$_3$), 1.72 (3H, s, C(7)CH$_3$), 2.88 (1H, t, *J* 10.1, C(4)H$_A$H$_B$), 3.05 (3H, s, SO$_2$CH$_3$), 3.28-3.35 (1H, m, C(4)H$_A$H$_B$), 4.83 (1H, dd, *J* 9.5, 7.5,

C(5)H), 5.33 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.1 (C(7)$\underline{C}H_3$), 26.2 (C($\underline{C}H_3)_3$), 32.6 (C(4)), 37.5 ($\underline{C}(CH_3)_3$), 38.7 (SO_2CH_3), 71.2 (C(2)).

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxa-6,7-diphenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 201**

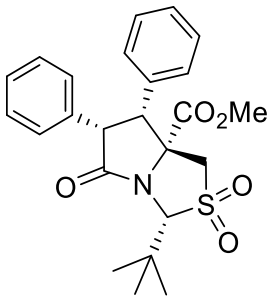
A solution of **133ci** (148 mg, 0.36 mmol) in $CHCl_3$ (4.0 mL) was cooled to 0 °C and the solution of *m*-chloroperbenzoic acid (188 mg, 1.08 mmol) in $CHCl_3$ (7 mL) was added dropwise to this solution. The reaction mixture was stirred at room temperature for 30 h. After completion, the mixture was poured into EtOAc (30 mL) and the resultant solution was washed with sat. aq. solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain crude sulfone. Purification by flash column chromatography using 20% EtOAc in Petroleum ether gave sulfone **201**.



Yield 93% (149 mg); white solid, m. p. 62-64°C; R_f (20% EA in PE) 0.30; $[\alpha]_D^{25}$ +163.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2980 (C-H), 2913 (C-H), 1750 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 1.15 (9H, s, $C(CH_3)_3$), 3.32 (1H, d, *J* 13.4, C(4)$\underline{H_A}H_B$), 3.65 (3H, s, CO_2CH_3), 4.30 (1H, d, *J* 13.4, C(4)$H_A\underline{H_B}$), 4.77 (1H, s, C(2)H), 7.02-7.35 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.4 (C($\underline{C}H_3)_3$), 35.9 ($\underline{C}(CH_3)_3$), 53.9 ($CO_2\underline{C}H_3$), 54.2 (C(4)), 72.1 (C(5)), 82.6 (C(2)), 128.2-130.7 (ArC), 133.6 (C(7)), 154.1 (C(6)), 168.1 ($\underline{C}O_2CH_3$), 174.4 (C(8)); m/z ($[ESI]^+$) 462.1 ($[M+Na]^+$, 45%); HRMS ($[ESI]^+$) found 462.1342, $C_{24}H_{25}O_5NSNa$ ($[M+Na]^+$) requires 462.1346.

***(2R,6R,7S,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6,7-diphenyl-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 202**

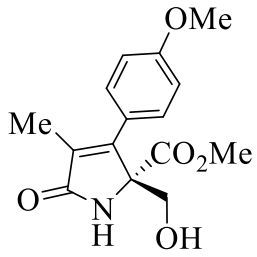
To a solution of α,β-unsaturated lactam **201** (29 mg, 0.065 mmol) in EtOAc (10 mL), platinum(IV) oxide (2.2 mg, 0.00975 mmol) was added. The reaction mixture was stirred at room temperature under H_2 atmosphere for 43 h, filtered through Celite, evaporated under reduced pressure, and then purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as eluents resulted pure product **202**.



Yield 41% (12 mg); white solid; m. p. 55°C. R_f (20% EA in PE) 0.28; $[\alpha]_D^{25}$ +11.7 (*c* 0.5 in DCM); ν_{max}/cm^{-1} 2980 (C-H), 2970 (C-H), 1748 (C=O), 1720 (C=O); δ_H (500 MHz, $CDCl_3$): 1.27 (9H, s, $C(CH_3)_3$), 3.42 (3H, s, CO_2CH_3), 3.44 (1H, d, *J* 14.7, C(4)$\underline{H_A}H_B$), 3.68 (1H, d, *J* 14.7, C(4)$H_A\underline{H_B}$), 4.14 (1H, d, *J* 10.7, C(7)H), 4.36 (1H, d, *J* 10.7, C(6)H), 4.99 (1H, s, C(2)H), 6.51-7.30 (10H, m, ArH); δ_C (125 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 52.6, 52.7 (C(6), $CO_2\underline{C}H_3$), 55.3 (C(4)), 58.1 (C(7)), 71.9 (C(5)), 82.0 (C(2)), 127.6-134.6 (ArC), 170.6 ($\underline{C}O_2CH_3$), 178.7 (C(8)); m/z ($[ESI]^+$) 442.2 ($[M+H]^+$, 10%); HRMS (ESI^+) found 442.1682, $C_{24}H_{28}O_5NS$ $[M+H]^+$) requires 442.1683.

Methyl(*S*)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-4-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate, 203

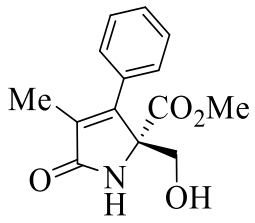
According to general method I (see Section 5.2.9), pyrrolinone **129ai** (34 mg, 0.0946 mmol) was treated with propane-1,3-dithiol (0.04 mL, 0.38 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.58 mL). Successive workup gave *N,O*-acetal deprotected amide **203**.



Yield 99% (27 mg); colourless oil; $[\alpha]_D^{25}$ +20.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3349 (O-H), 2954 (C-H), 2840 (C-H), 1737 (C=O), 1691 (C=O); δ_H (500 MHz, MeOD): 1.80 (3H, s, C(4)C$\underline{H}_3$), 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.77 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 3.84 (3H, s, OCH_3), 4.10 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.00 (2H, d, *J* 8.8, C(3')H), 7.13 (2H, d, *J* 8.8, C(2')H); δ_C (125 MHz, MeOD): 8.5 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 54.4 ($O\underline{C}H_3$), 62.4 (C(6)), 72.4 (C(2)), 113.7 (C(3')), 124.1 (C(4)), 129.4 (C(2')), 132.2 (C(1')), 151.1 (C(3)), 160.2 (C(4')), 169.7 ($\underline{C}O_2CH_3$), 175.6 (C(5)); m/z ($[ESI]^+$) 292.0 ($[M+H]^+$, 100%), 314.0 ($[M+Na]^+$, 80%); HRMS (ESI^+) found 292.1180, $C_{15}H_{18}NO_5$ ($[M+H]^+$) requires 292.1180.

Methyl(*S*)-2-(hydroxymethyl)-4-methyl-5-oxo-3-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate, 204

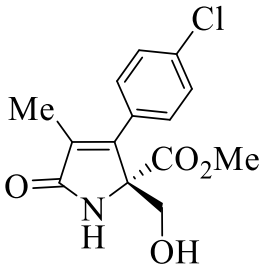
According to general method I (see Section 5.2.9), pyrrolinone **129aii** (44 mg, 0.13 mmol) was treated with propane-1,3-dithiol (0.05 mL, 0.52 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (2.17 mL). Successive workup gave *N*,*O*-acetal deprotected amide **204**.



Yield 90% (31 mg); yellow oil; $[\alpha]_D^{25}$ +32.5 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3306 (O-H), 2953 (C-H), 2925 (C-H), 1738 (C=O), 1695 (C=O); δ_H (500 MHz, MeOD): 1.78 (3H, s, C(4)CH_3), 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.78 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 4.09 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.18-7.46 (5H, m, ArH); δ_C (125 MHz, MeOD): 8.3 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 62.4 (C(6)), 72.6 (C(2)), 128.0-132.2 (ArC + C(4)), 151.2 (C(3)), 169.4 ($\underline{C}O_2CH_3$), 175.4 (C(5)); m/z ($[ESI]^+$) 262.0 ($[M+H]^+$, 100%), 284.0 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 262.1074, $C_{14}H_{16}NO_4$ ($[M+H]^+$) requires 262.1074.

Methyl(*S*)-3-(4-chlorophenyl)-2-(hydroxymethyl)-4-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate, 205

According to general method I (see Section 5.2.9), pyrrolinone **129aiii** (41 mg, 0.11 mmol) was treated with propane-1,3-dithiol (0.04 mL, 0.44 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.8 mL). Successive workup gave *N*,*O*-acetal deprotected amide **205**.



Yield 89% (29.8 mg); colourless oil; $[\alpha]_D^{25}$ +36.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3343 (O-H), 2953 (C-H), 2855 (C-H), 1738 (C=O), 1695 (C=O); δ_H (500 MHz, MeOD): 1.78 (3H, s, C(4)CH_3), 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.80 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 4.07 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.19 (2H, d, *J* 8.5, C(2')H), 7.47 (2H, d, *J* 8.5, C(3')H); δ_C (125 MHz, MeOD): 8.3 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 62.2 (C(6)), 72.6 (C(2)), 128.5 (C(3')), 128.9 (C(4)), 129.7 (C(2')), 130.9 (C(4')), 134.6 (C(1')), 149.8 (C(3)), 169.3 ($\underline{C}O_2CH_3$), 175.0 (C(5)); m/z ($[ESI]^+$) 296.0 ($[M+H]^+$, ^{35}Cl, 100%), 298.0 ($[M+H]^+$, ^{37}Cl, 40%), 318.0 ($[M+Na]^+$, ^{35}Cl, 20%), 320.0 ($[M+Na]^+$, ^{37}Cl, 10%); HRMS ($[ESI]^+$) found 296.0684, $C_{14}H_{15}ClNO_4$ ($[M+H]^+$, ^{35}Cl) requires 296.0684.

5.4 Experimental for Chapter 4

5.4.1 Synthesis of Methyl Ester Hydrochlorides 146a

General Method A: See Section 5.2.1

5.4.2 Synthesis of Oxazolidine and Thiazolidine Compounds 209a-b

General Method B: See Section 5.2.2

5.4.3 Preparation of Malonamides 210a-b

General Method C: See Section 5.2.3

5.4.4 Synthesis of Malonamide 218b

General Method K: See Section 5.3.2

5.4.5 Dieckmann Cyclisation of Oxazolidine and Thiazolidine Compounds 210a-b and 218b

General Method D: See Section 5.2.4

5.4.6 Synthesis of 212a-b and 221b: Mesylation Reaction

General method E: See Section 5.2.5

5.4.7 Preparation of 213ai-aiii, 213bi-biii, 223bi-biii and 224bi: Suzuki-Miyaura Cross-Coupling

General method F: See Section 5.2.6

5.4.8 Synthesis of 214ai-aiii: Hydrogenation

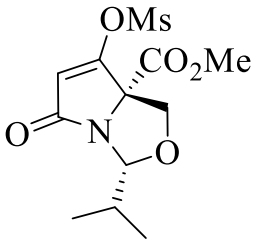
General Method G: See Section 5.2.7

5.4.9 Preparation of 215 and 164: *N, O*-Acetal deprotection

General Method I: See Section 5.2.9

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0] oct-6-ene, 212a**

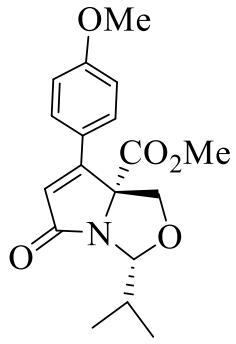
The mesylate **212a** was prepared following general methods A, B, D and E successively without purification of products in each step of the reactions.



Yield: 14%; yellow semi-solid; R_f (40% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +55.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2932 (C-H), 1745 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (6H, dd, *J* 8.2, 6.8 ($CH(C\underline{H}_3)_2$), 1.78 (1H, dq, *J* 13.4, 6.8, $C\underline{H}(CH_3)_2$), 3.19 (3H, s, OSO_2CH_3), 3.58 (1H, d, *J* 8.8, C(4)$\underline{H_A}H_B$), 3.77 (3H, s, CO_2CH_3), 4.63 (1H, d, *J* 8.8, C(4)$H_A\underline{H_B}$), 4.81 (1H, d, *J* 6.3, C(2)H), 5.86 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 17.2 ($CH(\underline{C}H_3)_2$), 32.7 ($\underline{C}H(CH_3)_2$), 38.3 ($OSO_2\underline{C}H_3$), 53.7 ($CO_2\underline{C}H_3$), 69.3 (C(4)), 74.6 (C(5)), 94.8 (C(2)), 108.2 (C(7)), 163.2 ($\underline{C}O_2CH_3$), 167.4 (C(8)), 175.1 (C(6)); m/z ($[ESI]^+$) 320.0 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 320.0799, $C_{12}H_{18}NO_7S$ ($[M+H]^+$) requires 320.0799.

***(2R,5S)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 213ai**

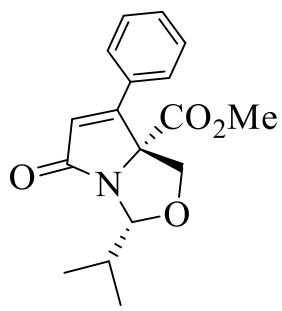
According to general method F (see Section 5.2.6), mesylate **212a** (210 mg, 0.66 mmol) was reacted with 4-methoxyphenylboronic acid (150 mg, 0.98 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.62 mL, 5.94 mmol) in ethanol (0.27 mL, 4.62 mmol) and toluene (12 mL) for 6 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.9 mg, 0.04 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.6 mg, 0.022 mmol) in toluene (2 mL).



Yield 47% (102 mg); yellow solid, m. p. 90-92°C; R_f (30% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +138.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (6H, dd, *J* 8.9, 6.8, HC($C\underline{H}_3$)$_2$), 1.80 (1H, dq, *J* 6.8, 5.6, ($\underline{H}C(CH_3)_2$), 3.48 (1H, d, *J* 8.3, C(4)$\underline{H_A}H_B$), 3.59 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.84 (1H, d, *J* 5.6, C(2)H), 5.02 (1H, d, *J* 8.3, C(4)$H_A\underline{H_B}$), 6.19 (1H, s, C(7)H), 6.86 (2H, d, *J* 8.9, C(3')H), 7.31 (2H, d, *J* 8.9, C(2')H); δ_C (100 MHz, $CDCl_3$): 17.1, 17.1 (HC($\underline{C}H_3$)$_2$), 33.2 (H$\underline{C}$(CH$_3$)$_2$), 53.3 ($CO_2\underline{C}H_3$), 55.5 (OCH_3), 70.3 (C(4)), 76.8 (C(5)), 93.5 (C(2)), 114.7 (C(3')), 119.0 (C(7)), 122.5 (C(1')), 128.8 (C(2')), 159.3 (C(6)), 161.9 (C(4')), 170.1 ($\underline{C}O_2CH_3$), 177.5 (C(8)); m/z ($[ESI]^+$) 332.1 ($[M+H]^+$, 30%); HRMS ($[ESI]^+$) found 332.1493, $C_{18}H_{22}NO_5$ ($[M+H]^+$) requires 332.1493.

***(2R,5S)*-1-Aza-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] oct-6-ene, 213aii**

According to general method F (see Section 5.2.6), mesylate **212a** (206 mg, 0.65 mmol) was reacted with phenylboronic acid (119 mg, 0.98 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.62 mL, 5.85 mmol) in ethanol (0.26 mL, 4.55 mmol) and toluene (13 mL) for 6 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.6 mg, 0.04 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.3 mg, 0.033 mmol) in toluene (2 mL).

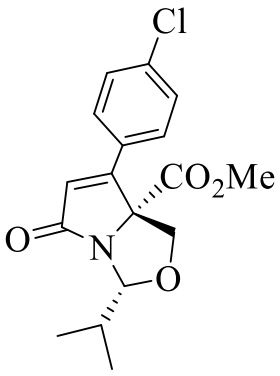


Yield 45% (87 mg); white solid, m. p. 110-112°C; R_f (30% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$ +136.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2965 (C-H), 2875 (C-H), 1743 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (6H, dd, *J* 9.5, 6.8, HC($C\underline{H}_3$)$_2$), 1.81 (1H, dq, *J* 6.8, 5.6, $\underline{H}C(CH_3)_2$), 3.50 (1H, d, *J* 8.4, C(4)$\underline{H_A}H_B$), 3.59 (3H, s, CO_2CH_3), 4.85 (1H, d, *J* 5.6, C(2)H), 5.04 (1H, d, *J* 8.4, C(4)$H_A\underline{H_B}$), 6.33 (1H, s, C(7)H), 7.35-7.39 (5H, m, ArH); δ_C

(100 MHz, $CDCl_3$): 17.1, 17.1 ($HC(\underline{C}H_3)_2$), 33.2 ($H\underline{C}(CH_3)_2$), 53.3 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 76.9 (C(5)), 93.5 (C(2)), 121.5 (C(7)), 127.0-131.2 (ArC), 159.6 (C(6)), 169.8 ($\underline{C}O_2CH_3$), 177.0 (C(8)); m/z ($[ESI]^+$) 302.1 ($[M+H]^+$, 30%); HRMS ($[ESI]^+$) found 324.1171, $C_{17}H_{19}NO_4Na$ ($[M+Na]^+$) requires 324.1206.

***(2R,5S)*-1-Aza-6-(4-chloroyphenyl)-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 213aiii**

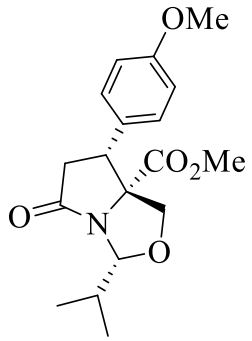
According to general method F (see Section 5.2.6), mesylate **212a** (202 mg, 0.63 mmol) was reacted with 4-chlorophenylboronic acid (104 mg, 0.66 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.6 mL, 5.67 mmol) in ethanol (0.25 mL, 4.41 mmol) and toluene (12 mL) for 3 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.0 mg, 0.038 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.0 mg, 0.032 mmol) in toluene (2 mL).



Yield 40% (84 mg); white solid, m. p. 120-122°C; R_f (30% EtOAc in Petrol) 0.42; $[\alpha]_D^{25}$ +125.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2969 (C-H), 2876 (C-H), 1742 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (6H, dd, *J* 9.6, 6.8, $HC(C\underline{H}_3)_2$), 1.80 (1H, dq, *J* 6.8, 5.6, ($\underline{H}C(CH_3)_2$), 3.49 (1H, d, *J* 8.4, C(4)$\underline{H}_A$H$_B$), 3.60 (3H, s, CO_2CH_3), 4.85 (1H, d, *J* 5.6, C(2)H), 5.01 (1H, d, *J* 8.4, C(4)H$_A\underline{H}_B$), 6.32 (1H, s, C(7)H), 7.29 (2H, d, *J* 8.8, C(2')H), 7.34 (2H, d, *J* 8.8, C(3')H); δ_C (100 MHz, $CDCl_3$): 17.1, 17.1 ($HC(\underline{C}H_3)_2$), 33.2 ($H\underline{C}(CH_3)_2$), 53.5 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 76.8 (C(5)), 93.6 (C(2)), 122.0 (C(7)), 128.3 (C(2')), 128.3 (C(4')), 129.7 (C(3')), 137.4 (C(1')), 158.2 (C(6)), 169.7 ($\underline{C}O_2CH_3$), 176.6 (C(8)); m/z ($[ESI]^+$) 336.1 ($[M+H]^+$, ^{35}Cl, 25%), 338.1 ($[M+H]^+$, ^{37}Cl, 10%); HRMS ($[ESI]^+$) found 358.0812, $C_{17}H_{18}ClNO_4Na$ ($[M+Na]^+$, ^{35}Cl) requires 358.0817.

***(2R,5S,6R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo [3.3.0] octane, 214ai**

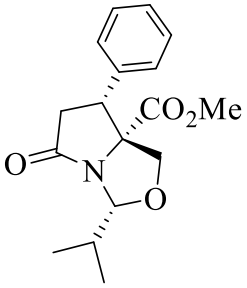
According to general method G (see Section 5.2.7), the hydrogenation reaction of α,β-unsaturated lactam **213ai** (72 mg, 0.21 mmol) in presence of platinum(IV) oxide (7.4 mg, 0.03 mmol) under a H_2 atmosphere for 6 h afforded pyrrolidinone **214ai**.



Yield 82% (59 mg); white semi-solid; R_f (30% EtOAc in Petrol) 0.22; $[\alpha]_D^{25}$ -52.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2875 (C-H), 1742 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (6H, dd, *J* 15.1, 6.8, $HC(C\underline{H}_3)_2$), 1.69 (1H, dq, *J* 13.9, 6.8, $\underline{H}C(CH_3)_2$), 2.66 (1H, dd, *J* 15.8, 7.8, C(7)$\underline{H_A}H_B$), 3.31 (3H, s, CO_2CH_3), 3.41 (1H, dd, *J* 15.8, 13.0, C(7)$H_A\underline{H_B}$), 3.68-3.76 (5H, m, C(6)H + OCH_3 + C(4)$\underline{H_A}H_B$), 4.69 (1H, d, *J* 8.6, C(4)$H_A\underline{H_B}$), 5.00 (1H, d, *J* 6.5, C(2)H), 6.78 (2H, d, *J* 8.8, C(3')H), 6.99 (2H, d, *J* 8.8, C(2')H); δ_C (100 MHz, $CDCl_3$): 16.8, 17.5 ($HC(\underline{C}H_3)_2$), 32.4 ($H\underline{C}(CH_3)_2$), 39.3 (C(7)), 49.5 (C(6)), 52.2 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 73.8 (C(4)), 76.7 (C(5)), 93.3 (C(2)), 114.0 (C(3')), 127.2 (C(1')), 128.6 (C(2')), 159.3 (C(4')), 170.6 ($\underline{C}O_2CH_3$), 175.9 (C(8)); m/z ($[ESI]^+$) 334.2 ($[M+H]^+$, 35%); HRMS ($[ESI]^+$) found 334.1649, $C_{18}H_{24}NO_5$ ($[M+H]^+$) requires 334.1649.

***(2R,5S,6R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] octane, 214aii**

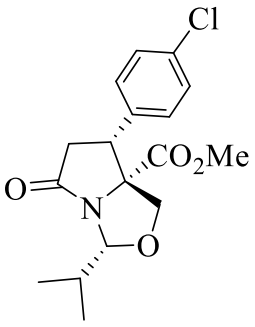
According to general method G (see Section 5.2.7), the hydrogenation reaction of α,β-unsaturated lactam **213aii** (52 mg, 0.17 mmol) in presence of platinum(IV) oxide (5.9 mg, 0.025 mmol) under a H_2 atmosphere for 5 h afforded pyrrolidinone **214aii**.



Yield 75% (39 mg); white solid, m. p. 76-78°C; R_f (30% EtOAc in Petrol) 0.28; $[\alpha]_D^{25}$ -46.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2875 (C-H), 1742 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (6H, dd, *J* 16.2, 6.8, HC($C\underline{H}_3$)$_2$), 1.70 (1H, dq, *J* 13.4, 6.8, $\underline{H}C(CH_3)_2$), 2.69 (1H, dd, *J* 15.8, 7.9, C(7)$\underline{H}_AH_B$), 3.27 (3H, s, CO_2CH_3), 3.46 (1H, dd, *J* 15.8, 12.8, C(7)$H_A\underline{H}_B$), 3.70-3.85 (2H, m, (C(4)$\underline{H}_AH_B$ + C(6)H)), 4.71 (1H, d, *J* 8.7, C(4)$H_A\underline{H}_B$), 5.01 (1H, d, *J* 6.5, C(2)H), 7.05-7.29 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 16.7, 17.5 (HC($\underline{C}H_3$)$_2$), 32.4 ($H\underline{C}(CH_3)_2$), 39.1 (C(7)), 50.0 (C(6)), 52.1 ($CO_2\underline{C}H_3$), 74.0 (C(4)), 76.6 (C(5)), 93.2 (C(2)), 127.5-135.4 (ArC), 170.5 ($\underline{C}O_2CH_3$), 175.8 (C(8)); m/z ($[ESI]^+$) 304.1 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 304.1543, $C_{17}H_{22}NO_4$ ($[M+H]^+$) requires 304.1543.

***(2R,5S,6R)*-1-Aza-6-(4-chlorophenyl)-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] octane, 214aiii**

According to general method G (see Section 5.2.7), the hydrogenation reaction of α,β-unsaturated lactam **213aiii** (43 mg, 0.12 mmol) in presence of platinum(IV) oxide (4.3 mg, 0.02 mmol) under a H_2 atmosphere for 6 h afforded pyrrolidinone **214aiii**.

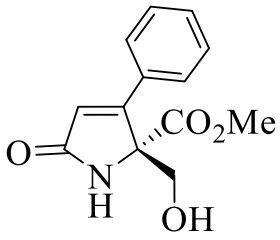


Yield 85% (37 mg); white solid, m. p. 90-92°C; R_f (30% EtOAc in Petrol) 0.27; $[\alpha]_D^{25}$ -49.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2876 (C-H), 1742 (C=O), 1714 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (6H, dd, *J* 15.2, 6.8 HC($C\underline{H}_3$)$_2$), 1.69 (1H, dq, *J* 13.4, 6.8, $\underline{H}C(CH_3)_2$), 2.69 (1H, dd, *J* 15.8, 7.8, C(7)$\underline{H}_AH_B$), 3.32 (3H, s, CO_2CH_3), 3.40 (1H, dd, *J* 15.8, 12.8, C(7)$H_A\underline{H}_B$), 3.68-3.79 (2H, m, C(4)$\underline{H}_AH_B$ + C(6)H), 4.70 (1H, d, *J* 8.8, C(4)$H_A\underline{H}_B$), 5.00 (1H, d, *J* 6.5, C(2)H), 7.01 (2H, d, *J* 8.5, C(2')H), 7.24 (2H, d, *J* 8.5, C(3')H); δ_C (100 MHz, $CDCl_3$): 16.8, 17.5 (HC($\underline{C}H_3$)$_2$), 32.4 ($H\underline{C}(CH_3)_2$), 39.2 (C(7)), 49.5 (C(6)), 52.3 ($CO_2\underline{C}H_3$), 73.9 (C(4)), 76.4 (C(5)), 93.3 (C(2)), 128.7-134.0 (ArC), 170.4

($\underline{C}O_2CH_3$), 175.4 (C(8)); m/z ([ESI]$^+$) 338.1 ([M+H]$^+$, ^{35}Cl, 35%), 340.1 ([M+H]$^+$, ^{37}Cl, 25%); HRMS ([ESI]$^+$) found 338.1154, $C_{17}H_{21}NO_4Cl$ ([M+H]$^+$, ^{35}Cl) requires 338.1154.

Methyl(*S*)-2-(hydroxymethyl)-5-oxo-3-phenyl-2,5-dihydro-1H-pyrrole-2-carboxylate, 215

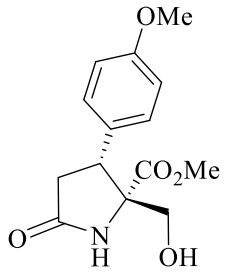
According to general method I, the bicyclic pyrrolinone derivative **213aii** (14 mg, 0.046 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.1 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (0.76 mL) to develop pyroglutaminol derivative **215**.



Yield 97% (12 mg); colourless oil; ν_{max}/cm^{-1} 3361 (O-H), 2953 (C-H), 2927 (C-H), 1796 (C=O); δ_H (500 MHz, MeOD): 3.76 (3H, s, $CO_2C\underline{H}_3$), 3.98 (1H, d, *J* 11.8, C(6)$\underline{H_A}H_B$), 4.25 (1H, d, *J* 11.8, C(6)$H_A\underline{H_B}$), 6.49 (1H, s, C(4)H), 7.42-7.58 (5H, m, ArH); δ_C (125 MHz, MeOD): 52.2 ($CO_2\underline{C}H_3$), 62.6 (C(6)), 72.7 (C(2)), 123.4 (C(4)), 127.0-131.1 (ArC + C(3)), 158.4 ($\underline{C}O_2CH_3$), 169.7 (C(5)); m/z ([ESI]$^+$) 248.1 ([M+H]$^+$, 35%); HRMS ([ESI]$^+$) found 248.0918, $C_{13}H_{14}NO_4$ ([M+H]$^+$) requires 248.0917.

Methyl (*2S,3R*)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, 164

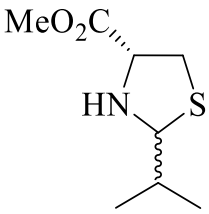
According to general method I, the bicyclic pyrrolidinone derivative **214ai** (22 mg, 0.065 mmol) was treated with propane-1,3-dithiol (0.015 mL, 0.15 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.1 mL) to develop pyroglutaminol derivative **164**.



From **214ai**: Yield 97% (18 mg); colourless oil; $[\alpha]_D^{25}$ -70.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3384 (O-H), 2953 (C-H), 1678 (C=O), 1614 (C=O); δ_H (400 MHz, MeOD): 2.56 (1H, dd, *J* 17.1, 7.6, C(4)$\underline{H_A}H_B$), 2.69 (1H, dd, *J* 17.1, 9.0, C(4)$H_A\underline{H_B}$), 3.22 (3H, s, $CO_2C\underline{H_3}$), 3.56 (1H, dd, *J* 9.1, 7.6, C(3)H), 3.66-3.70 (4H, m, (OCH_3 + C(6)$\underline{H_A}H_B$)), 3.88 (1H, d, *J* 11.5, C(6)$H_A\underline{H_B}$), 6.76 (2H, d, *J* 8.8, C(3')H), 7.02 (2H, d, *J* 8.8, C(2')H); δ_C (100 MHz, MeOD): 36.9 (C(4)), 44.3 (C(3)), 51.0 ($CO_2\underline{C}H_3$), 54.3 ($O\underline{C}H_3$), 64.5 (C(6)), 73.2 (C(2)), 113.4 (C(3')), 128.7 (C(2')), 130.2 (C(1')), 159.3 (C(4')), 171.2 ($\underline{C}O_2CH_3$), 178.6 (C(5)); m/z ([ESI]$^+$) 280.2 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 302.0998, $C_{14}H_{17}NO_5Na$ ([M+Na]$^+$) requires 302.0999.

(*2R*,*5R*)- and (*2S*,*5R*)-2-(Isopropyl)-5-methoxycarbonyl-1,3-thiazolidine, 209b

According to general method B (see Section 5.2.2), reaction of L-cysteine methyl ester hydrochloride **146b** (2.0 g, 11.65 mmol) with 2-methylpropanal (1.27 mL, 14.0 mmol) and Et_3N (2.4 mL, 17.47 mmol) in petrol (60 mL) furnished thiazolidine **209b**.

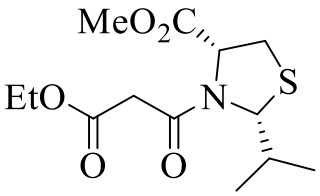


Yield 76% (1.68 g); colourless oil; 2:1 mixture of diastereomers; R_f (30% EtOAc in Petrol) 0.40; ν_{max}/cm^{-1} 3295 (N-H), 2958 (C-H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) major isomer (*2R*): 1.10 (6H, dd, *J* 19.7, 6.7, $CH(C\underline{H_3})_2$), 1.99 (1H, h, *J* 6.7, $C\underline{H}(CH_3)_2$), 2.21 (1H, br s, NH), 2.76 (1H, dd, *J* 10.6, 9.2, C(4)$\underline{H_A}H_B$), 3.28 (1H, dd, *J* 10.1, 6.9, C(4)$H_A\underline{H_B}$), 3.78 (3H, s, CO_2CH_3), 3.82 (1H, dd, *J* 9.6, 7.1, C(5)H), 4.36 (1H, d, *J* 7.2, C(2)H); minor isomer (*2S*): 0.97-1.03 (6H, m, $CH(C\underline{H_3})_2$), 1.80 (1H, h, *J* 6.8, $CH(C\underline{H_3})_2$), 2.21 (1H, br s, NH), 3.01 (1H, dd, *J* 10.6, 6.2, C(4)$\underline{H_A}H_B$), 3.18 (1H, dd, *J* 10.6, 6.7, C(4)$H_A\underline{H_B}$), 3.77 (3H, s, CO_2CH_3), 4.10 (1H, t, *J* 6.5, C(5)H), 4.44 (1H, d, *J* 7.7, C(2)H); δ_C (100 MHz, $CDCl_3$) major isomer (*2R*): 20.3, 20.7 ($CH(\underline{C}H_3)_2$), 33.6 ($\underline{C}H(CH_3)_2$), 37.5 (C(4)), 52.5 ($CO_2\underline{C}H_3$), 65.4 (C(5)), 78.0 (C(2)), 171.8 ($\underline{C}O_2CH_3$); minor isomer (*2S*): 19.7, 20.5 ($CH(\underline{C}H_3)_2$), 35.1 ($\underline{C}H(CH_3)_2$), 37.3 (C(4)), 52.5

($CO_2\underline{C}H_3$), 64.4 (C(5)), 76.8 (C(2)), 172.2 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 190.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 190.0893, $C_8H_{16}NO_2S$ ($[M+H]^+$) requires 190.0896.

(*2R*,*5R*)-2-Isopropyl-1-ethoxycarbonylacetyl-5-methoxycarbonyl-1,3-thiazolidine, 210b

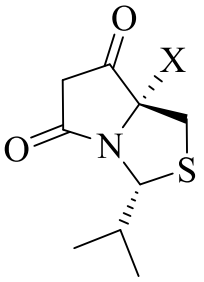
According to general method C (see Section 5.2.3), *N*-acyl thiazolidine **210b** was prepared from thiazolidine **209b** (2.19 g, 11.6 mmol), DCC (2.5 g, 12.18 mmol), DMAP (70 mg, 0.6 mmol), and ethyl hydrogen malonate (1.44 mL, 12.18 mmol) in DCM (50 mL).



Yield 74% (2.58 g); colourless oil; 1:1.5 mixture of rotamers (major **A**, minor **B**); R_f (40% EtOAc in Petrol) 0.28; ν_{max}/cm^{-1} 2960 (C-H), 2873 (C-H), 1743 (C=O), 1658 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (6H, dd, *J* 21.5, 6.7, $CH(C\underline{H}_3)_2$ **B**), 1.02 (6H, dd, *J* 14.4, 6.7 $CH(C\underline{H}_3)_2$ **A**), 1.22 (6H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$ (**A**+**B**)), 1.89-1.97 (1H, m, $C\underline{H}(CH_3)_2$ **A**), 1.99-2.06 (1H, m, $C\underline{H}(CH_3)_2$ **B**), 3.19-3.38 (4H, m, C(4)$\underline{H}_A\underline{H}_B$ (**A**+**B**)), 3.42 (2H, d, *J* 15.4, C(7)$\underline{H}_AH_B$ (**A**+**B**)), 3.55 (2H, d, *J* 15.3, C(7)$H_A\underline{H}_B$ (**A**+**B**)), 3.69 (3H, s, CO_2CH_3 **B**), 3.74 (3H, s, CO_2CH_3 **A**), 4.10-4.17 (4H, m, $CO_2C\underline{H}_2CH_3$ (**A**+**B**)), 4.64 (1H, d, *J* 8.7, C(2)H **A**), 4.78-4.85 (1H, m, C(5)H **B**), 4.96 (1H, t, *J* 8.6, C(5)H **A**), 5.28 (1H, d, *J* 8.7, C(2)H **B**); δ_C (100 MHz, $CDCl_3$): 14.1 ($CO_2CH_2\underline{C}H_3$ (**A**+**B**)), 18.8, 19.9 ($CH(\underline{C}H_3)_2$ **B**), 19.1, 20.2 ($CH(\underline{C}H_3)_2$ **A**), 31.8 (C(4) **A**), 32.8 (C(4) **B**), 33.9 ($\underline{C}H(CH_3)_2$ **B**), 35.2 ($\underline{C}H(CH_3)_2$ **A**), 42.0 (C(7) **A**), 42.6 (C(7) **B**), 52.6 ($CO_2\underline{C}H_3$ **A**), 53.0 ($CO_2\underline{C}H_3$ **B**), 61.7 ($CO_2\underline{C}H_2CH_3$ (**A**+**B**)), 62.6 (C(5) **A**), 63.1 (C(5) **B**), 70.7 (C(2) **B**), 71.9 (C(2) **A**), 165.0 (C(6) **A**), 165.3 (C(6) **B**), 166.7 ($\underline{C}O_2Et$ **A**), 167.1 (CO_2Et **B**), 170.5 ($\underline{C}O_2CH_3$ **B**), 170.7 ($\underline{C}O_2CH_3$ **B**); m/z ($[ESI]^+$) 326.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 326.1030, $C_{13}H_{21}NO_5SNa$ ($[M+Na]^+$) requires 326.1033.

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6,8-dioxo-3-thiabicyclo [3.3.0]octane, 211b**

According to general method D (see Section 5.2.4), **211b** was synthesised via Dieckman cyclisation of **210b** (2.39 g, 7.87 mmol) under basic condition (KO^{t}Bu, 928 mg, 8.27 mmol) in THF (0.2 M). The decarboxylated tetramic acid **216** was found as a nearly inseparable minor compound. **211b** was separated only for characterisation.

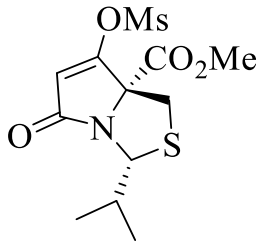


211b: X = CO_2Me
216: X = H

211b: Yield 47% (1.24 g); yellow solid, m. p. 82-84°C; $[\alpha]_D^{25}$ +134.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2872 (C-H), 1782 (C=O), 1746 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (3H, d, *J* 6.6, CH(C$\underline{H}_3$)(CH_3)), 1.02 (3H, d, *J* 6.6, CH(CH_3)(C$\underline{H}_3$)), 1.62 (1H, dq, *J* 10.0, 6.6, C$\underline{H}$(CH_3)$_2$), 2.97 (1H, d, *J* 11.2, C(4)$\underline{H_A}H_B$), 3.12 (1H, d, *J* 21.6, C(7)$\underline{H_A}H_B$), 3.47 (1H, d, *J* 21.6, C(7)$H_A\underline{H_B}$), 3.75 (1H, d, *J* 11.2, C(4)$H_A\underline{H_B}$), 3.78 (3H, s, CO_2CH_3), 5.04 (1H, d, *J* 10.0, C(2)H); δ_C (100 MHz, $CDCl_3$): 19.3, 20.0 (CH(C$\underline{H}_3$)$_2$), 34.8 (C(4)), 36.6 (C$\underline{H}$(CH_3)$_2$), 42.6 (C(7)), 54.0 ($CO_2C\underline{H}_3$), 68.5 (C(2)), 83.3 (C(5)), 166.9 (C$\underline{O}_2CH_3$), 168.8 (C(8)), 198.4 (C(6)); m/z ($[ESI]^+$) 258.0 ($[M+H]^+$, 100%), 280.0 ($[M+Na]^+$, 70%); HRMS ($[ESI]^+$) found 258.0795, $C_{11}H_{16}NO_4S$ ($[M+H]^+$) requires 258.0795.

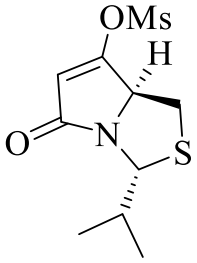
***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 212b and *(2R,5S)*-1-Aza-2-isopropyl-6-((methylsulfonyl)-oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 217**

According to general method E (see Section 5.2.5), treatment of tetramic acids (**211b + 216**) (1.19 g, 4.64 mmol) with MsCl (0.36 mL, 4.64 mmol) and DIPEA (1.6 mL, 9.28) in DCM afforded desired mesylates **212b** and **217**.



212b

Yield 64% (990 mg); white solid, m. p. 96-98°C; R_f (40% EtOAc in Petrol) 0.29; $[\alpha]_D^{25}$ +187.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C-H), 2935 (C-H), 1750 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (3H, d, *J* 6.6, CH(C<u>H</u>$_3$)(CH$_3$)), 0.97 (3H, d, *J* 6.6, CH(CH$_3$)(C<u>H</u>$_3$)), 1.76 (1H, dq, *J* 9.4, 6.6, C<u>H</u>(CH$_3$)$_2$), 2.89 (1H, d, *J* 11.2, C(4)<u>H$_A$</u>H$_B$), 3.20 (3H, s, OSO_2CH_3), 3.64 (1H, d, *J* 11.2, C(4)H$_A$<u>H$_B$</u>), 3.78 (3H, s, CO_2CH_3), 4.72 (1H, d, *J* 9.4, C(2)H), 5.79 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 19.4, 19.9 (CH(<u>C</u>H$_3$)$_2$), 34.0 (C(4)), 36.4 (<u>C</u>H(CH$_3$)$_2$), 38.3 (OSO_2<u>C</u>H$_3$), 53.9 (CO_2<u>C</u>H$_3$), 67.3 (C(2)), 78.7 (C(5)), 106.7 (C(7)), 161.6 (<u>C</u>O$_2$CH$_3$), 167.4 (C(8)), 171.5 (C(6)); m/z ($[ESI]^+$) 336.0 ($[M+H]^+$, 90%), 358.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 336.0570, $C_{12}H_{18}NO_6S_2$ ($[M+H]^+$) requires 336.0581.



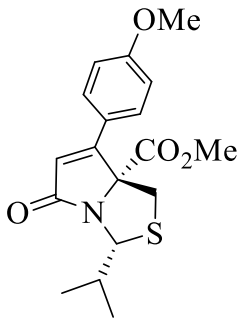
217

Yield 4% (37 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.22; $[\alpha]_D^{25}$ +21.1 (*c* 0.2 in DCM); ν_{max}/cm^{-1} 2964 (C-H), 2873 (C-H), 1700 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91-0.99 (6H, m, CH(C<u>H</u>$_3$)$_2$), 1.89 (1H, h, *J* 6.7, C<u>H</u>(CH$_3$)$_2$), 2.69 (1H, dd, *J* 10.7, 9.6, C(4)<u>H$_A$</u>H$_B$), 3.05 (1H, dd, *J* 10.7, 6.3, C(4)H$_A$<u>H$_B$</u>), 3.22 (3H, s, OSO_2CH_3), 4.59 (1H, dd, *J* 9.6, 6.3, C(5)H), 4.87 (1H, d, *J* 7.1, C(2)H), 5.67 (1H, s, C(7)H); δ_C (100 MHz, $CDCl_3$): 18.8, 19.4 (CH(<u>C</u>H$_3$)$_2$), 32.2 (C(4)), 36.0 (<u>C</u>H(CH$_3$)$_2$), 38.5 (OSO_2<u>C</u>H$_3$), 65.5 (C(2)), 67.0 (C(5)), 106.6 (C(7)), 163.1 (C(8)), 171.0 (C(6)); m/z ($[ESI]^+$) 278.1 ($[M+H]^+$, 40%), 300.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 278.0516, $C_{10}H_{16}NO_4S_2$ ($[M+H]^+$) requires 278.0515.

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 213bi**

According to general method F (see Section 5.2.6), mesylate **212b** (70 mg, 0.21 mmol) was reacted with 4-methoxyphenylboronic acid (48 mg, 0.315 mmol), $PdCl_2$(dppb), 1 M aqueous

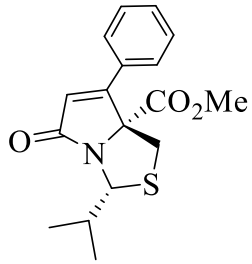
Na_2CO_3 solution (0.2 mL, 1.89 mmol) in ethanol (0.08 mL, 1.47 mmol) and toluene (10 mL) for 3 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (5.3 mg, 0.013 mmol) and $(C_6H_5CN)_2PdCl_2$ (4.0 mg, 0.011 mmol) in toluene (1 mL).



Yield 72% (52 mg); colourless oil; R_f (30% EtOAc in Petrol) 0.28; $[\alpha]_D^{25}$ +269.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2870 (C-H), 1742 (C=O), 1701 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (3H, d, *J* 6.6, HC(C<u>H</u>$_3$)(CH_3)), 1.00 (3H, d, *J* 6.6, HC(CH_3)(C<u>H</u>$_3$)), 1.71 (1H, dq, *J* 16.2, 6.6, <u>H</u>C(CH_3)$_2$), 2.86 (1H, d, *J* 10.8, C(4)<u>H$_A$</u>H$_B$), 3.62 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.98 (1H, d, *J* 10.8, C(4)H$_A$<u>H$_B$</u>), 4.74 (1H, d, *J* 9.5, C(2)H), 6.15 (1H, s, C(7)H), 6.86 (2H, d, *J* 9.0, C(3')H), 7.42 (2H, d, *J* 9.0, C(2')H); δ_C (100 MHz, $CDCl_3$): 19.5, 19.9 (HC(<u>C</u>H$_3$)$_2$), 35.3 (C(4)), 37.3 (H<u>C</u>(CH_3)$_2$), 53.4 (CO_2<u>C</u>H$_3$), 55.5 (OCH_3), 65.7 (C(2)), 80.6 (C(5)), 114.6 (C(3')), 118.0 (C(7)), 122.3 (C(1')), 128.7 (C(2')), 157.6 (C(6)), 161.7 (C(4')), 170.2 (<u>C</u>O_2CH_3), 173.2 (C(8)); m/z ($[ESI]^+$) 348.2 ($[M+H]^+$, 40%), 370.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 348.1264, $C_{18}H_{22}NO_4S$ ($[M+H]^+$) requires 348.1264.

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 213bii**

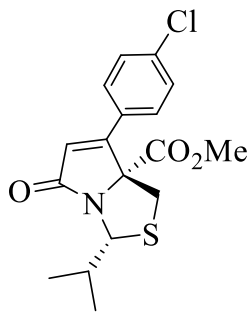
According to general method F (see Section 5.2.6), mesylate **212b** (70 mg, 0.21 mmol) was reacted with phenylboronic acid (38 mg, 0.315 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.2 mL, 1.89 mmol) in ethanol (0.08 mL, 1.47 mmol) and toluene (10 mL) for 3 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (5.3 mg, 0.013 mmol) and $(C_6H_5CN)_2PdCl_2$ (4.0 mg, 0.011 mmol) in toluene (1 mL).



Yield 74% (49 mg); white solid, m. p. 116-118°C; R_f (30% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ +250.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2871 (C-H), 1743 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (3H, d, *J* 6.6, HC(C<u>H</u>$_3$)(CH$_3$)), 1.01 (3H, d, *J* 6.6, HC(CH$_3$)(C<u>H</u>$_3$)), 1.73 (1H, dq, *J* 13.7, 6.6, <u>H</u>C(CH$_3$)$_2$), 2.89 (1H, d, *J* 10.8, C(4)<u>H$_A$</u>H$_B$), 3.62 (3H, s, CO_2CH_3), 4.00 (1H, d, *J* 10.8, C(4)H$_A$<u>H$_B$</u>), 4.76 (1H, d, *J* 9.6, C(2)H), 6.29 (1H, s, C(7)H), 7.33-7.49 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 19.5, 19.9 (HC(<u>C</u>H$_3$)$_2$), 35.2 (C(4)), 37.3 (H<u>C</u>(CH$_3$)$_2$), 53.4 (CO_2<u>C</u>H$_3$), 65.7 (C(2)), 80.7 (C(5)), 120.6 (C(7)), 127.0-130.9 (ArC), 157.9 (C(6)), 169.9 (<u>C</u>O$_2$CH$_3$), 172.8 (C(8)); m/z ($[ESI]^+$) 318.0 ($[M+H]^+$, 90%), 340.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 318.1158, $C_{17}H_{20}NO_3S$ ($[M+H]^+$) requires 318.1158.

***(2R,5R)*-1-Aza-6-(4-cholorophenyl)-2-isopropyl-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 213biii**

According to general method F (see Section 5.2.6), mesylate **212b** (70 mg, 0.21 mmol) was reacted with 4-chlorophenylboronic acid (34.5 mg, 0.22 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.2 mL, 1.89 mmol) in ethanol (0.08 mL, 1.47 mmol) and toluene (10 mL) for 5 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (5.3 mg, 0.013 mmol) and $(C_6H_5CN)_2PdCl_2$ (4.0 mg, 0.011 mmol) in toluene (1 mL).

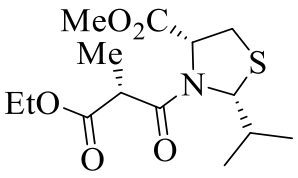


Yield 41% (30 mg); colourless oil; R_f (30% EtOAc in Petrol) 0.53; $[\alpha]_D^{25}$ +230.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2956 (C-H), 2870 (C-H), 1746 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (3H, d, *J* 6.6, HC(C<u>H</u>$_3$)(CH$_3$)), 1.01 (3H, d, *J* 6.6, HC(CH$_3$)(C<u>H</u>$_3$)), 1.72 (1H, dq, *J* 9.7, 6.6, <u>H</u>C(CH$_3$)$_2$), 2.87 (1H, d, *J* 10.8, C(4)<u>H$_A$</u>H$_B$), 3.63 (3H, s, CO_2CH_3), 3.96 (1H, d, *J* 10.8, C(4)H$_A$<u>H$_B$</u>), 4.75 (1H, d, *J* 9.7, C(2)H), 6.27 (1H, s, C(7)H), 7.33 (2H, d, *J* 8.6, C(2')H), 7.40 (2H, d, *J* 8.6, C(3')H); δ_C (100 MHz, $CDCl_3$): 19.5, 19.9

(HC($\underline{C}$H$_3$)$_2$), 35.2 (C(4)), 37.3 (H$\underline{C}$(CH$_3$)$_2$), 53.5 (CO$_2\underline{C}$H$_3$), 65.7 (C(2)), 80.7 (C(5)), 121.1 (C(7)), 128.2 (C(4')), 128.3 (C(3')), 129.6 (C(2')), 137.2 (C(1')), 156.5 (C(6)), 169.8 ($\underline{C}$O$_2$CH$_3$), 172.4 (C(8)); m/z ([ESI]$^+$) 352.0 ([M+H]$^+$, ^{35}Cl, 80%), 354.0 ([M+H]$^+$, ^{37}Cl, 25%), 374.0 ([M+Na]$^+$, ^{35}Cl, 40%); HRMS ([ESI]$^+$) found 352.0770, $C_{17}H_{19}ClNO_3S$ ([M+H]$^+$, ^{35}Cl) requires 352.0769.

(*2R*,*5R*)-1-((*R*)-1-Ethoxycarbonyl-1-methylacetyl)-2-(isopropyl)-5-methoxycarbonyl-1,3-thiazolidine, 218b

According to general method K (see Section 5.3.2), thiazolidine **209b** (1.35 g, 7.1 mmol) was reacted with dry pyridine (0.6 mL, 7.4 mmol) and malonyl chloride **179** (2.3 mL, 14.2 mmol) in DCM (50 mL). Purification of crude product by flash column chromatography (20% EtOAc in petroleum ether) yielded *N*-acyl thiazolidine **218b** as a mixture of diastereomers and their rotamers. Only *7R* (major) was isolated.

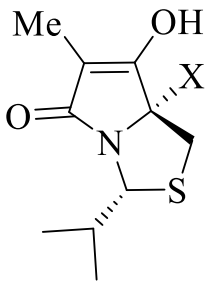


Yield 81% (1.82 g); colourless oil; mixture of rotamers; R_f (40% EtOAc in Petrol) 0.43; $[\alpha]_D^{25}$ -114.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2874 (C-H), 1742 (C=O), 1654 (C=O); δ_H (400 MHz, CDCl$_3$): 0.89 (6H, dd, *J* 15.7, 6.4, CH(C$\underline{H}_3$)$_2$), 1.01-1.04 (6H, m, CH(C$\underline{H}_3$)$_2$), 1.20 (6H, t, *J* 7.2, C(10)H$_3$), 1.37 (6H, dt, *J* 7.6, 4.3, C(7)CH$_3$), 1.88-1.95 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.99-2.06 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.13-3.30 (4H, m, C(4)$\underline{H}_A\underline{H}_B$), 3.35-3.44 (1H, m, C(7)H), 3.45-3.54 (1H, m, C(7)H), 3.69 (3H, s, CO$_2$CH$_3$), 3.74 (3H, s, CO$_2$CH$_3$), 4.08-4.14 (4H, m, C(9)$\underline{H}_2$), 4.88 (1H, d, *J* 9.2, C(2)H), 4.95 (1H, t, *J* 8.7, C(5)H), 4.04-4.09 (1H, m, C(5)H), 5.31 (1H, d, *J* 8.3, C(2)H); δ_C (100 MHz, CDCl$_3$): 13.7 (C(7)$\underline{C}$H$_3$), 14.0, 14.1 (C(10)), 18.7-20.1 (CH($\underline{C}$H$_3$)$_2$), 31.8, 32.5 (C(4)), 33.8, 35.2 ($\underline{C}$H(CH$_3$)$_2$), 44.3, 45.7 (C(7)), 52.6, 53.0 (CO$_2\underline{C}$H$_3$), 61.6, 61.7 (C(9)), 62.8, 62.8 (C(5)), 70.6, 71.3 (C(2)), 168.5-173.4 (C(6),

$\underline{C}O_2CH_3$, C(8)); m/z ([ESI]$^+$) 318.2 ([M+H]$^+$, 50%), 340.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 318.1368, $C_{14}H_{24}NO_5S$ ([M+H]$^+$) requires 318.1370.

_(2R,5R)_-1-Aza-6-hydroxy 2-(isopropyl)-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane (219b) and _(2R,5S)_-1-Aza-6-hydroxy 2-(isopropyl)-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane (220b)

According to general method D (see Section 5.2.4), reaction of *N*-acyl thiazolidine **218b** (4.2 g, 13.2 mmol) with KO^{t}Bu (1.6 g, 14.5 mmol) in THF (0.2 M) gave inseparable mixture of tetramic acids **219b** and **220**.

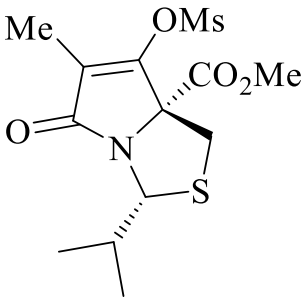


219b (**A**): X = CO_2Me
220b (**B**): X = H

Yield 76% (2.7 g); white solid; inseparable mixture of A and B (2.3:1); ν_{max}/cm^{-1} 3377 (O-H), 2960 (C-H), 2930 (C-H), 2872 (C-H), 1750 (C=O), 1647 (C=O); δ_H (400 MHz, MeOD): 0.81-0.95 (6H, m, CH(C$\underline{H}_3$)$_2$, (**A**+**B**)), 1.51 (3H, s, C(7)CH$_3$, **B**), 1.55 (3H, s, C(7)CH$_3$, **A**), 1.62-1.72 (1H, m, C$\underline{H}$(CH$_3$)$_2$, **A**), 1.77-1.84 (1H, m, C$\underline{H}$(CH$_3$)$_2$, **B**), 2.52-2.60 (1H, m, C(4)$\underline{H_A}H_B$, **B**), 2.77 (1H, d, *J* 11.4, C(4)$\underline{H_A}H_B$, **A**), 3.06 (1H, dd, *J* 10.8, 6.8, C(4)$H_A\underline{H_B}$, **B**), 3.63 (1H, d, *J* 11.4, C(4)$H_A\underline{H_B}$, **A**), 3.68 (3H, s, CO_2CH_3, **A**), 4.35 (1H, t, *J* 7.7, C(5)H, **B**), 4.57 (1H, d, *J* 9.4, C(2)H, **A**), 4.69 (1H, d, *J* 7.3, C(2)H, **B**); δ_C (100 MHz, MeOD): 4.5 (C(7)$\underline{C}H_3$, **B**), 4.8 (C(7)$\underline{C}H_3$, **A**), 18.0, 18.5 (CH($\underline{C}H_3$)$_2$, **B**), 18.4, 19.0 (CH($\underline{C}H_3$)$_2$, **A**), 31.6 (C(4), **B**), 33.2 (C(4), **A**), 35.7 ($\underline{C}$H(CH$_3$)$_2$, **B**), 36.1 ($\underline{C}$H(CH$_3$)$_2$, **A**), 52.3 ($CO_2\underline{C}H_3$, **A**), 65.7 (C(2), **B**), 66.0 (C(5), **B**), 67.2 (C(2), **A**), 77.9 (C(5), **A**), 100.1 (C(7), **B**), 100.7 (C(7), **A**), 167.8 ($\underline{C}O_2CH_3$, **A**), 169.2 (C(8), **A**), 169.5 (C(8), **B**), 178.1 (C(6), **A**); m/z ([ESI]$^+$) 214.0 ([M+H]$^+$, **B**, 100%), 272.0 ([M+H]$^+$, **A**, 30%), 294.0 ([M+Na]$^+$, **A**, 75%); HRMS ([ESI]$^+$)**A** found 272.0951, $C_{12}H_{18}NO_4S$ ([M+H]$^+$) requires 272.0951; HRMS ([ESI]$^+$)**B** found 214.0896, $C_{10}H_{16}NO_2S$ ([M+H]$^+$) requires 214.0896.

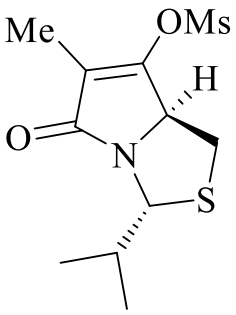
***(2R,5R)*-1-Aza-2-(isopropyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene (221b) and *(2R,5S)*-1-Aza-2-isopropyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene (222b)**

According to general method E (see Section 5.2.5), tetramic acids (**219b + 220b**, 2.32 g, 8.55 mmol) was reacted with MsCl (0.66 mL, 8.55 mmol) and DIPEA (2.9 mL, 17.1 mmol) in DCM (85 mL). Purification by flash column chromatography (20-30% EtOAc in petroleum ether) furnished isolated mesylates **221b** and **222b**.



221b

Yield 61% (1.82 g); colourless oil; 8:1 mixture of **221b** and undetermined compound; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +235.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2935 (C-H), 1747 (C=O), 1713 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (3H, d, *J* 6.6, CH(C$\underline{H}_3$)), 1.02 (3H, d, *J* 6.6, CH(C$\underline{H}_3$)), 1.78-1.84 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.85 (3H, s, C(7)CH$_3$), 2.84 (1H, d, *J* 11.1, C(4)$\underline{H_A}H_B$), 3.23 (3H, s, OSO$_2$CH$_3$), 3.58 (1H, d, *J* 11.1, C(4)H$_A\underline{H_B}$), 3.76 (3H, s, CO$_2$CH$_3$), 4.70 (1H, s, *J* 9.7, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.6 (C(7)$\underline{C}$H$_3$), 19.6, 20.2 (CH($\underline{C}$H$_3$)$_2$), 35.2 (C(4)), 36.9 ($\underline{C}$H(CH$_3$)$_2$), 39.5 (OSO$_2$CH$_3$), 53.7 (CO$_2\underline{C}$H$_3$), 66.8 (C(2)), 78.2 (C(5)), 124.0 (C(7)), 154.0 ($\underline{C}$O$_2$CH$_3$), 168.4 (C(8)), 171.4 (C(6)); m/z ($[ESI]^+$) 372.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 372.0547, $C_{13}H_{19}NNaO_6S_2$ ($[M+Na]^+$) requires 372.0546.



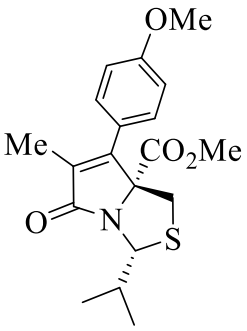
222b

Yield 13% (180 mg); colourless oil; R_f (40% EtOAc in Petrol) 0.27; $[\alpha]_D^{25}$ +179.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2963 (C-H), 2930 (C-H), 1700 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (6H, t, *J* 6.2, CH(C$\underline{H}_3$)$_2$), 1.77 (3H, s, C(7)CH$_3$), 1.85-1.95 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.62 (1H, t, *J* 10.3, C(4)$\underline{H_A}H_B$), 3.09 (1H, dd, *J* 10.7, 6.1, C(4)H$_A\underline{H_B}$), 3.22 (3H, s, OSO$_2$CH$_3$), 4.66-4.75 (1H, m, C(5)H), 4.86 (1H, d, *J* 7.1, C(2)H); δ_C

(100 MHz, $CDCl_3$): 7.7 (C(7)$\underline{C}H_3$), 18.8, 19.5 (CH($\underline{C}H_3$)$_2$), 32.7 (C(4)), 36.1 ($\underline{C}H(CH_3)_2$), 39.0 ($OSO_2\underline{C}H_3$), 65.2 (C(2)), 66.2 (C(5)), 121.5 (C(7)), 156.3 (C(8)), 171.1 (C(6)); m/z ($[ESI]^+$) 292.0 ($[M+H]^+$, 100%), 314.0 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 292.0671, $C_{11}H_{18}NO_4S_2$ ($[M+H]^+$) requires 292.0672.

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 223bi**

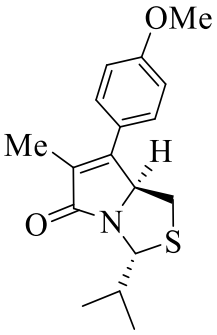
According to general method F (see Section 5.2.6), mesylate **221b** (295 mg, 0.84 mmol) was reacted with 4-methoxyphenylboronic acid (205 mg, 1.35 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.8 mL, 7.56 mmol) in ethanol (0.34 mL, 5.88 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (21.0 mg, 0.05 mmol) and $(C_6H_5CN)_2PdCl_2$ (16.0 mg, 0.04 mmol) in toluene (2 mL).



Yield 13% (40 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.55; $[\alpha]_D^{25}$ +353.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2840 (C-H), 1744 (C=O), 1703 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (3H, d, *J* 6.6, HC($C\underline{H}_3$)(CH_3)), 1.03 (3H, d, *J* 6.6, HC(CH_3)($C\underline{H}_3$)), 1.67-1.79 (1H, m, $\underline{H}C(CH_3)_2$), 1.91 (3H, s, C(7)CH_3), 2.86 (1H, d, *J* 10.6, C(4)$\underline{H_A}H_B$), 3.56 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.86 (1H, d, *J* 10.6, C(4)$H_A\underline{H_B}$), 4.76 (1H, d, *J* 9.5, C(2)H), 6.87 (2H, d, *J* 8.9, C(3')H), 7.19 (2H, d, *J* 8.9, C(2')H); δ_C (100 MHz, $CDCl_3$): 10.7 (C(7)$\underline{C}H_3$), 19.6, 20.1 (HC($\underline{C}H_3$)$_2$), 35.9 (C(4)), 37.3 (H$\underline{C}$(CH_3)$_2$), 53.0 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 65.9 (C(2)), 81.1 (C(5)), 114.2 (C(3')), 123.5 (C(7)), 129.4 (C(1')), 129.6 (C(2')), 150.2 (C(6)), 160.3 (C(4')), 170.0 ($\underline{C}O_2CH_3$), 174.2 (C(8)); m/z ($[ESI]^+$) 362.2 ($[M+H]^+$, 100%), 384.2 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 362.1417, $C_{19}H_{24}NO_4S$ ($[M+H]^+$) requires 362.1421.

***(2R,5S)*-1-Aza-2-isopropyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 224bi**

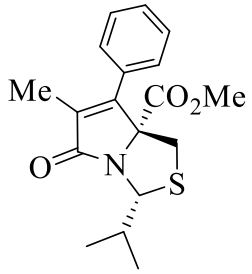
According to general method F (see Section 5.2.6), mesylate **222b** (104 mg, 0.36 mmol) was reacted with 4-methoxyphenylboronic acid (87 mg, 0.57 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (0.34 mL, 3.24 mmol) in ethanol (0.15 mL, 2.52 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (9.0 mg, 0.021 mmol) and $(C_6H_5CN)_2PdCl_2$ (7.0 mg, 0.018 mmol) in toluene (1 mL).



Yield 32% (35 mg); colourless oil; R_f (30% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ +100.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C-H), 2929 (C-H), 1688 (C=O); δ_H (400 MHz, $CDCl_3$): 0.99 (6H, t, *J* 6.4, $CH(C\underline{H}_3)_2$), 1.91-2.01 (4H, m, $C\underline{H}(CH_3)_2$ + $C(7)CH_3$), 2.41 (1H, t, *J* 10.4, $C(4)\underline{H}_A H_B$), 2.97 (1H, dd, *J* 10.6, 6.0, $C(4)H_A\underline{H}_B$), 3.78 (3H, s, OCH_3), 4.87-4.94 (2H, m, (C(2)H + C(5)H)), 6.90 (2H, d, *J* 8.5, C(3')H), 7.33 (2H, d, *J* 8.5, C(2')H); δ_C (100 MHz, $CDCl_3$): 10.7 ($C(7)\underline{C}H_3$), 18.9, 19.5 ($CH(\underline{C}H_3)_2$), 34.0 (C(4)), 36.4 ($\underline{C}H(CH_3)_2$), 55.4 ($O\underline{C}H_3$), 65.1 (C(2)), 68.6 (C(5)), 114.4 (C(3')), 125.3 (C(7)), 127.3 (C(1')), 129.1 (C(2')), 149.7 (C(6)), 160.2 (C(4')), 174.2 (C(8)); m/z ($[ESI]^+$) 304.1 ($[M+H]^+$, 10%), 326.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 304.1366, $C_{17}H_{22}NO_2S$ ($[M+H]^+$) requires 304.1366.

***(2R,5R)*-1-Aza-2-isopropyl-5-methoxycarbonyl-7-methyl-8-oxo-6-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 223bii**

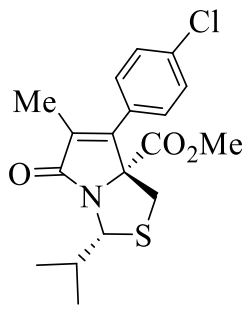
According to general method F (see Section 5.2.6), mesylate **221b** (503 mg, 1.44 mmol) was reacted with phenylboronic acid (280 mg, 2.3 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.37 mL, 12.96 mmol) in ethanol (0.58 mL, 10.08 mmol) and toluene (13 mL) for 20 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (36.8 mg, 0.0864 mmol) and $(C_6H_5CN)_2PdCl_2$ (27.6 mg, 0.072 mmol) in toluene (3 mL).



Yield 12% (55 mg); colourless oil; R_f (40% EtOAc in Petrol) 0.64; $[\alpha]_D^{25}$ +338.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2927(C-H), 1745 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (3H, d, *J* 6.6, HC(C<u>H</u>$_3$)(CH_3)), 1.04 (3H, d, *J* 6.6, HC(CH_3)(C<u>H</u>$_3$)), 1.76 (1H, dq, *J* 9.4, 6.6, (<u>H</u>C(CH_3)$_2$), 1.88 (3H, s, C(7)CH_3), 2.89 (1H, d, *J* 10.6, C(4)<u>H$_A$</u>H$_B$), 3.56 (3H, s, CO_2CH_3), 3.82 (1H, d, *J* 10.6, C(4)H$_A$<u>H$_B$</u>), 4.76 (1H, d, *J* 9.4, C(2)H), 7.19-7.38 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.5 (C(7)<u>C</u>H_3), 19.6, 20.1 (HC(<u>C</u>H_3)$_2$), 35.8 (C(4)), 37.3 (H<u>C</u>(CH_3)$_2$), 53.0 (CO_2<u>C</u>H_3), 66.0 (C(2)), 81.3 (C(5)), 128.0-131.2 (ArC+C(7)), 150.6 (C(6)), 169.7 (<u>C</u>O_2CH_3), 173.9 (C(8)); m/z ($[ESI]^+$) 332.2 ($[M+H]^+$, 20%), 354.0 ($[M+Na]^+$, 25%); HRMS ($[ESI]^+$) found 332.1315, $C_{18}H_{22}NO_3S$ ($[M+H]^+$) requires 332.1315.

***(2R,5R)*-1-Aza-6-(4-cholorophenyl)-2-isopropyl-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 223biii**

According to general method F (see Section 5.2.6), mesylate **221b** (570 mg, 1.63 mmol) was reacted with 4-chlorophenylboronic acid (267 mg, 1.71 mmol), $PdCl_2$(dppb), 1 M aqueous Na_2CO_3 solution (1.55 mL, 14.67 mmol) in ethanol (0.66 mL, 11.41 mmol) and toluene (13 mL) for 24 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (42.0 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (31.0 mg, 0.08 mmol) in toluene (3 mL).



Yield 11% (67 mg); white solid, m. p. 76-78°C; R_f (40% EtOAc in Petrol) 0.57; $[\alpha]_D^{25}$ +341.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2871 (C-H), 1744 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (3H, d, *J* 6.6, HC(C<u>H</u>$_3$)(CH_3)), 1.03 (3H, d, *J* 6.6, HC(CH_3)(C<u>H</u>$_3$)), 1.75 (1H, dq, *J* 9.7, 6.6, <u>H</u>C(CH_3)$_2$), 1.87 (3H, s, C(7)CH_3), 2.86 (1H, d, *J* 10.6, C(4)<u>H$_A$</u>H$_B$), 3.57 (3H, s, CO_2CH_3), 3.79 (1H, d, *J* 10.6, C(4)H$_A$<u>H$_B$</u>), 4.75 (1H, d, *J* 9.7, C(2)H), 7.14 (2H, d, *J* 8.7, C(2')H), 7.34 (2H, d, *J* 8.7, C(3')H); δ_C (100 MHz, $CDCl_3$): 10.5

(C(7)$\underline{C}H_3$), 19.6, 20.1 (HC($\underline{C}H_3$)$_2$), 35.8 (C(4)), 37.3 (H$\underline{C}$(CH$_3$)$_2$), 53.1 ($CO_2\underline{C}H_3$), 66.0 (C(2)), 81.2 (C(5)), 129.2 (C(3')), 129.4 (C(2')), 129.6 (C(7)), 131.8 (C(4')), 135.6 (C(1')), 149.1 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 173.5 (C(8)); m/z ([ESI]$^+$) 366.0 ([M+H]$^+$, ^{35}Cl, 100%), 368.0 ([M+H]$^+$, ^{37}Cl, 40%), 388.0 ([M+Na]$^+$, ^{35}Cl, 50%); HRMS ([ESI]$^+$) found 366.0924, $C_{18}H_{21}ClNO_3S$ ([M+H]$^+$, ^{35}Cl) requires 366.0925.

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APPENDICES

APPENDIX A: SYNTHESIS AND CHARACTERISATION OF REPORTED COMPOUNDS

APPENDIX B: X-RAY CRYSTALLOGRAPHY DATA

APPENDIX C: NOE CORRELATIONS

APPENDIX D: TEST METHOD FOR BIOASSAY

APPENDIX A: SYNTHESIS AND CHARACTERISATION OF REPORTED COMPOUNDS

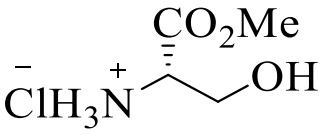
The synthesis and characterisation of previously reported compounds are presented here.

Synthesis of Methyl Ester Hydrochloride:[1] General Method A

$SOCl_2$ (1.5 eq) was added dropwise to stirring anhydrous MeOH (2 M) at 0°C, followed by L-amino acid (1 eq) portion-wise. The mixture was heated to 40°C and stirred at this temperature for 3 h. The solvent was then evaporated under reduced pressure to give methyl ester hydrogen chlorides **146a-c**.

L-Serine methyl ester hydrochloride,[2] 146a

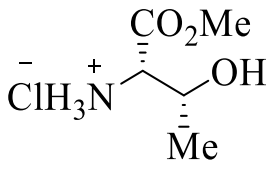
According to general method A, L-serine (5.0 g, 47.6 mmol) was reacted with MeOH (2.0 M) and $SOCl_2$ (5.2 mL, 71.4 mmol).



Yield 99% (7.31 g); white solid, m. p. 168-176°C (lit.[2] m. p. 163.1°C); $[\alpha]_D^{25}$ +3.5 (*c* 1.2 in EtOH); ν_{max}/cm^{-1} 3338 (O-H), 3020 (N-H), 2925 (C-H), 1746 (C=O); δ_H (400 MHz, D_2O) 3.76 (3H, s, CO_2CH_3), 3.91 (1H, dd, *J* 12.5, 3.4, $C\underline{H}_AH_BOH$), 4.01 (1H, dd, *J* 12.6, 4.2, $CH_A\underline{H}_BOH$), 4.19 (1H, dd, *J* 4.2, 3.4, $C\underline{H}NH_2$); δ_C (100 MHz, D_2O) 53.7 ($CO_2\underline{C}H_3$), 54.7 ($\underline{C}HNH_2$), 59.2 ($\underline{C}H_2$), 168.9 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 120.1 ($[M\text{-}Cl]^+$, 100%); HRMS ($[ESI]^+$) found 120.0656, $C_4H_{10}NO_3^+$ ($[M\text{-}Cl]^+$) requires 120.0655.

L-Threonine methyl ester hydrochloride,[3] 146b

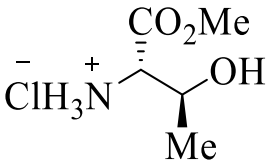
According to general method A, L-threonine (5.0 g, 41.9 mmol) was reacted with MeOH (2.0 M) and $SOCl_2$ (4.6 mL, 62.9 mmol).



Yield 100% (7.1 g); colourless oil; $[\alpha]_D^{25}$ -5.7 (*c* 1.2 in EtOH); ν_{max}/cm^{-1} 3356 (O-H), 2974 (C-H), 1746 (C=O); δ_H (400 MHz, D_2O) 1.31 (3H, d, *J* 6.6, CH_3), 3.83 (3H, s, OCH_3), 4.09 (1H, d, *J* 3.8, C<u>H</u>CO), 4.40 (1H, qd, *J* 6.6, 3.8, C<u>H</u>OH); δ_C (100 MHz, D_2O) 18.7 (<u>C</u>H_3), 53.6 (O<u>C</u>H_3), 58.3 (<u>C</u>HCO), 65.2 (<u>C</u>HOH), 169.2 (<u>C</u>O_2CH_3); m/z ($[ESI]^+$) 134.1 ($[M\text{-}Cl]^+$, 100%); HRMS ($[ESI]^+$) found 134.0810, $C_5H_{12}NO_3^+$ ($[M\text{-}Cl]^+$) requires 134.0812.

L-*allo*-Threonine methyl ester hydrochloride,[4] 146c

According to general method A, L-*allo*-threonine (500 mg, 4.2 mmol) was reacted with MeOH (2.0 M) and $SOCl_2$ (4.6 mL, 6.3 mmol).



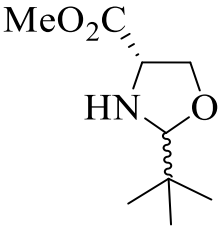
Yield 100% (710 mg); white solid, m. p. 62-64°C (lit.[4] 95-97°C); $[\alpha]_D^{25}$ +23.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3357 (O-H), 2980 (C-H), 2920 (C-H), 1739 (C=O); δ_H (400 MHz, D_2O) 1.20 (3H, d, *J* 6.6, CH_3), 3.76 (3H, s, CO_2CH_3), 4.11 (1H, d, *J* 3.4, C<u>H</u>NH_2), 4.24 (1H, qd, *J* 6.6, 3.4, C<u>H</u>OH); δ_C (100 MHz, D_2O) 17.6 (<u>C</u>H_3), 53.5 (O<u>C</u>H_3), 57.9 (<u>C</u>HCO), 65.5 (<u>C</u>HOH), 168.3 (<u>C</u>O_2CH_3); m/z ($[ESI]^+$) 134.2 ($[M\text{-}Cl]^+$, 40%); HRMS ($[ESI]^+$) found 134.8111, $C_5H_{12}NO_3^+$ ($[M\text{-}Cl]^+$) requires 134.0812.

Synthesis of Oxazolidine and Thiazolidine Compounds:[5,6] General Method B

The ester hydrogen chloride of the L-amino acid **146** (1.0 eq) was suspended in petroleum ether (50-100 mL). Triethylamine (1.5 eq) and trimethylacetaldehyde (1.2 eq) were then added. The mixture was heated at reflux with continuous removal of water using a Dean-Stark apparatus for 18 h. The white precipitate was then filtered and washed with Et_2O. The combined filtrates were concentrated under reduced pressure to furnish the oxazolidines or thiazolidine **147**.

(*2R,5S*)- and (*2S,5S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-1,3-oxazolidine,[6] 147a

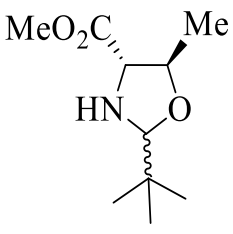
According to general method B, L-serine methyl ester hydrochloride **146a** (7.4 g, 47.5 mmol) was reacted with triethylamine (9.9 mL, 71.2 mmol) and $(CH_3)_3CCHO$ (6.2 mL, 57 mmol).



Yield 86% (7.6 g); yellow oil; 1.4:1 mixture of diastereomers; R_f (85% EtOAc in DCM) 0.60; ν_{max}/cm^{-1} 3316 (N-H), 2957 (C-H), 2871 (C-H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) major isomer (*2R*): 0.95 (9H, s, $C(CH_3)_3$), 2.48 (1H, br s, NH), 3.64-3.67 (1H, m, C(4)$\underline{H_A}H_B$), 3.72 (3H, s, CO_2CH_3), 3.84-3.88 (2H, m, (C(4)$H_A\underline{H_B}$) + (C(5)H)), 4.04 (1H, s, C(2)H); minor isomer (*2S*): 0.87 (9H, s, $C(CH_3)_3$), 2.48 (1H, br s, NH), 3.67-3.69 (1H, m, C(4)$\underline{H_A}H_B$), 3.70 (3H, s, CO_2CH_3), 3.89-3.93 (1H, m, C(5)H), 4.07 (1H, dd, *J* 8.0, 7.3, C(4)$H_A\underline{H_B}$), 4.28 (1H, s C(2)H); δ_C (100 MHz, $CDCl_3$) major isomer (*2R*): 25.2 ($C(\underline{C}H_3)_3$), 33.2 ($\underline{C}(CH_3)_3$), 52.5 ($CO_2\underline{C}H_3$), 59.6 (C(5)), 68.3 (C(4)), 99.9 (C(2)), 172.9 ($\underline{C}O_2CH_3$); minor isomer (*2S*): 24.9 ($C(\underline{C}H_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 52.4 ($CO_2\underline{C}H_3$), 59.4 (C(5)), 68.9 (C(4)), 99.2 (C(2)), 173.1 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 188.1 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 188.1282, $C_9H_{18}NO_3$ ($[M+H]^+$) requires 188.1281.

(*2R,4R,5S*)- and (*2S,4R,5S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine,[7] 147b

According to general method B, L-threonine methyl ester hydrochloride **146b** (9.7 g, 57.2 mmol) was reacted with triethylamine (11.96 mL, 85.8 mmol) and trimethylacetaldehyde (7.46 mL, 68.6 mmol).

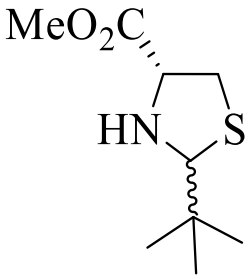


Yield 88% (10.1 g); yellow oil; 1:1 mixture of diastereomers; R_f (50% EtOAc in DCM) 0.62; ν_{max}/cm^{-1} 3341 (N-H), 2957 (C-H), 2870 (C-H), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) isomer (*2R*): 0.96 (9H, s, $C(CH_3)_3$),

1.31 (3H, d, *J* 6.0, C(4)CH_3), 2.67 (1H, br s, NH), 3.34 (1H, d, *J* 7.2, C(5)H), 3.75 (3H, s, CO_2CH_3), 3.78-3.85 (1H, m, C(4)H), 4.27 (1H, s, C(2)H); isomer (*2S*): 0.88 (9H, s, $C(CH_3)_3$), 1.35 (3H, d, *J* 6.0, C(4)CH_3), 2.67 (1H, br, NH), 3.45 (1H, d, *J* 7.2, C(5)H), 3.74 (3H, s, CO_2CH_3), 3.78-3.85 (1H, m, C(4)H), 4.36 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) isomer (*2R*): 19.9 (C(4)$\underline{C}H_3$), 25.2 ($C(\underline{C}H_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 52.4 ($O\underline{C}H_3$), 65.7 (C(5)), 76.2 (C(4)), 98.2 (C(2)), 171.9 ($\underline{C}O_2CH_3$); isomer (*2S*): 18.9 (C(4)$\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 33.5 ($\underline{C}(CH_3)_3$), 52.3 ($O\underline{C}H_3$), 67.1 (C(5)), 77.3 (C(4)), 98.8 (C(2)), 172.7 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 202.1 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 202.1438, $C_{10}H_{20}NO_3$ ($[M+H]^+$) requires 202.1438.

(*2R*,*5S*)- and (*2S*,*5S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-1,3-thiazolidine,[8,9] 147d

According to general method B, L-cysteine methyl ester hydrochloride **146d** (5.0 g, 29.1 mmol) was reacted with triethylamine (6.09 mL, 43.7 mmol) and trimethylacetaldehyde (3.8 mL, 35.0 mmol).



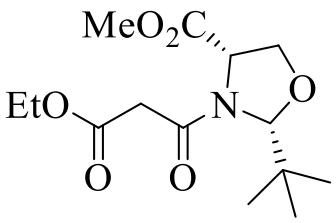
Yield 95% (5.62 g); yellow oil; 1.5:1 mixture of diastereomers; R_f (75% EtOAc in DCM) 0.58; ν_{max}/cm^{-1} 3317 (N-H), 2954 (C-H), 2868 (C-H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) major isomer (*2R*): 1.01 (9H, s, $C(CH_3)_3$), 2.19 (1H, br s, NH), 2.62 (1H, t, *J* 10.0, C(4)$\underline{H_A}H_B$), 3.20 (1H, dd, *J* 10.2, 6.4, C(4)$H_A\underline{H_B}$), 3.72 (3H, s, CO_2CH_3), 4.72-3.78 (1H, m, C(5)H), 4.40 (1H, s, C(2)H); minor isomer (*2S*): 0.92 (9H, s, $C(CH_3)_3$), 2.19 (1H, br s, NH), 2.96 (1H, dd, *J* 10.6, 5.6, C(4)$\underline{H_A}H_B$), 3.05 (1H, dd, *J* 10.2, 6.4, C(4)$H_A\underline{H_B}$), 3.69 (3H, s, CO_2CH_3), 4.08 (1H, dd, *J* 6.3, 5.6, C(5)H), 4.47 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) major isomer (*2R*): 27.0 ($C(\underline{C}H_3)_3$), 34.0 ($\underline{C}(CH_3)_3$), 37.5 (C(4)), 52.5 ($CO_2\underline{C}H_3$), 65.5 (C(5)), 81.9 (C(2)), 171.9 ($\underline{C}O_2CH_3$); minor isomer (*2S*): 26.6 ($C(\underline{C}H_3)_3$), 35.9 ($\underline{C}(CH_3)_3$), 37.1 (C(4)), 52.5 ($CO_2\underline{C}H_3$), 65.1 (C(5)), 79.9 (C(2)), 172.5 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 204.1 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 204.1055, $C_9H_{18}NO_2S$ ($[M+H]^+$) requires 204.1053.

_N_-Acylation of Oxazolidine and Thiazolidine Compounds:[5] General Method C

DMAP (0.05 eq) and DCC (1.05 eq) were added to a solution of oxazolidine or thiazolidine **147** (1.0 eq) in anhydrous DCM. The mixture was cooled to 0°C and ethyl hydrogen malonate (1.05 eq) was added. The reaction mixture was stirred 30 min at 0°C and 5-6 h at room temperature. A white precipitate was formed, which was filtered and washed with DCM. The combined filtrates were concentrated *in vacuo* and purified by flash column chromatography to give the required *N*-acyl oxazolidines or thiazolidine **148**.

***(2R,5S)*-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-1,3-oxazolidine,[5] 148a**

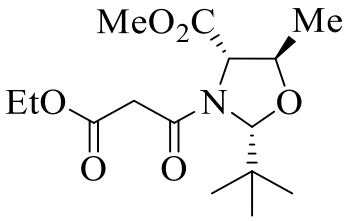
According to general method C, oxazolidine **147a** (10.6 g, 56.5 mmol), DCC (12.2 g, 59.3 mmol), and DMAP (345 mg, 2.8 mmol) was reacted with ethyl hydrogen malonate (7.0 mL, 59.3 mmol) in DCM.



Yield 80% (13.6 g); colourless oil; R_f (10% EtOAc in DCM) 0.52; $[\alpha]_D^{25}$ -62.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 1741 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$): 0.83 (9H, s, $C(CH_3)_3$), 1.23 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 3.46 (1H, d, *J* 15.5, $C(7)\underline{H}_AH_B$), 3.65 (1H, d, *J* 15.5, $C(7)H_A\underline{H}_B$), 3.74 (3H, s, CO_2CH_3), 3.89-4.06 (1H, m, $C(4)\underline{H}_AH_B$), 4.14 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 4.42-4.53 (1H, m, $C(4)H_A\underline{H}_B$), 4.60-4.68 (1H, m, C(5)H), 5.22 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 13.9 ($OCH_2\underline{C}H_3$), 25.4 ($C(\underline{C}H_3)_3$), 37.1 ($\underline{C}(CH_3)_3$), 42.9 (C(7)), 52.6 ($CO_2\underline{C}H_3$), 59.3 (C(5)), 61.4 ($O\underline{C}H_2CH_3$), 67.5 (C(4)), 96.4 (C(2)), 167.4 (C(8)), 167.6 ($\underline{C}O_2CH_3$), 169.8 (C(6)); m/z ($[ESI]^+$) 302.2 ($[M+H]^+$, 55%), 324.1 ($[M+Na]^+$, 65%); HRMS ($[ESI]^+$) found 302.1594, $C_{14}H_{24}NO_6$ requires ($[M+H]^+$) 302.1598.

***(2R,4R,5S)*-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-4-methyl-1,3-oxazolidine,[7] 148b**

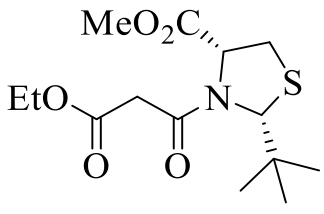
According to general method C, oxazolidine **147b** (9.95 g, 49.4 mmol), DCC (10.7 g, 51.9 mmol), and DMAP (302 mg, 2.5 mmol) was reacted with ethyl hydrogen malonate (6.12 mL, 51.9 mmol) in DCM.



Yield 67% (10.5 g); yellow oil; R_f (10% EtOAc in DCM) 0.42; $[\alpha]_D^{25}$ -37.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2977 (C-H), 2958 (C-H), 1741 (C=O), 1669 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$), 1.22 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.30 (3H, d, *J* 6.0, $C(4)CH_3$), 3.38 (1H, d, *J* 15.4, $C(7)\underline{H}_AH_B$), 3.52 (1H, d, *J* 15.4, $C(7)H_A\underline{H}_B$), 3.74 (3H, s, CO_2CH_3), 4.14 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 4.23-4.27 (1H, m, C(5)H), 4.68-4.75 (1H, m, C(4)H), 5.37 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 20.1 ($C(4)CH_3$), 25.8 ($C(\underline{C}H_3)_3$), 37.9 ($\underline{C}(CH_3)_3$), 42.9 (C(7)), 52.9 ($CO_2\underline{C}H_3$), 61.7 ($O\underline{C}H_2CH_3$), 65.5 (C(5)), 76.1 (C(4)), 96.2 (C(2)), 167.3, 167.4 (C(6), C(8)), 170.0 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 316.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 316.1752, $C_{15}H_{26}NO_6$ ($[M+H]^+$) requires 316.1755.

***(2R,5R)*-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-1,3-thiazolidine,[10] 148d**

According to general method C, thiazolidine **147d** (5.54 g, 27.3 mmol), DCC (5.9 g, 28.6 mmol), and DMAP (167 mg, 1.4 mmol) was reacted with ethyl hydrogen malonate (3.38 mL, 28.6 mmol) in DCM.



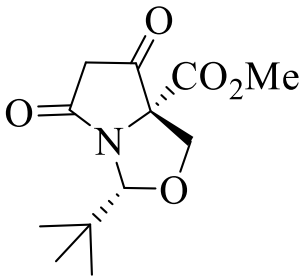
Yield 78% (5.88 g); colourless oil; R_f (10% EtOAc in DCM) 0.71; $[\alpha]_D^{25}$ -102.5 (*c* 1.0 in $CHCl_3$); 1.5:1 mixture of rotamers, major **A** and minor **B**; ν_{max}/cm^{-1} 2958 (C-H), 1740 (C=O), 1664 (C=O); δ_H

(400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$ **A**), 1.01 (9H, s, $C(CH_3)_3$ **B**), 1.22 (3H, t, *J* 7.1, $CH_2C\underline{H}_3$), 3.21-3.52 (4H, m, ($C(4)H_AH_B$ + $C(7)H_AH_B$)), 3.70 (3H, s, CO_2CH_3 **B**), 3.75 (3H, s, CO_2CH_3 **A**), 4.14 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 4.74 (1H, s, C(2)H **B**), 4.83 (1H, t, *J* 8.0, C(5)H **A**), 5.05 (1H, t, *J* 9.5, C(5)H **B**), 5.48 (1H, s, C(2)H **A**); δ_C (100 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$ **A**), 27.2 ($C(\underline{C}H_3)_3$ **B**), 32.9 (C(4) **B**), 34.2 (C(4) **A**), 39.4 ($\underline{C}(CH_3)_3$ **A**), 40.1 ($\underline{C}(CH_3)_3$ **B**), 42.4 (C(7)), 52.5 ($CO_2\underline{C}H_3$ **B**), 53.0 ($CO_2\underline{C}H_3$ **A**), 61.6 ($O\underline{C}H_2CH_3$ **B**), 61.7 ($O\underline{C}H_2CH_3$ **A**), 64.2 (C(5)), 73.3 (C(2) **A**), 74.7 (C(2) **B**), 166.8, 167.0 (C(8), $\underline{C}O_2CH_3$), 170.6 (C(6) **B**), 170.8 (C(6) **A**); m/z (ESI^+) 318.1 ($[M+H]^+$, 100%); HRMS (ESI^+) found 318.1367, $C_{14}H_{24}NO_5S$ ($[M+H]^+$) requires 318.1370.

Dieckmann Cyclisation:[5] General Method D

To a solution of *N*-acyl oxazolidine or thiazolidine **148** (1.0 eq) in anhydrous THF was added potassium *tert*-butoxide (1.05 eq). The mixture was heated at reflux for 3 h. The reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the methyl ester tetramic acids **118**.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-6,8-dioxobicyclo[3.3.0]-octane,[10] 118a**



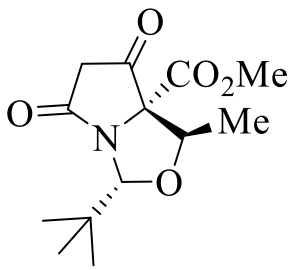
According to general method D, malonamide **148a** (7.06 g, 23.4 mmol) was refluxed with potassium *tert*-butoxide (2.76 g, 24.6 mmol) in THF (0.2 M).

Yield 75% (4.49 g); yellow solid, m. p. 118-120°C (lit.[10] m. p. 131-133°C); R_f (25% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +111.3 (*c* 1.2 in DCM); ν_{max}/cm^{-1} 2960 (C-H),

1747 (C=O), 1724 (C=O), 1621 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$), 3.11 (1H, d, *J* 21.2, C(7)$\underline{H_A}H_B$), 3.56 (1H, d, *J* 9.0, C(4)$\underline{H_A}H_B$), 3.68 (1H, d, *J* 21.2, C(7)$H_A\underline{H_B}$), 3.76 (3H, s, CO_2CH_3), 4.73 (1H, d, *J* 9.0, C(4)$H_A\underline{H_B}$), 5.01 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 24.7 (C($\underline{C}H_3)_3$), 35.6 ($\underline{C}(CH_3)_3$), 44.8 (C(7)), 53.7 ($CO_2\underline{C}H_3$), 67.9 (C(4)), 80.5 (C(5)), 98.3 (C(2)), 166.9 ($\underline{C}O_2CH_3$), 172.3 (C(8)), 198.3 (C(6)); m/z ($[ESI]^-$) 254.1 ($[M-H]^-$, 100%); HRMS ($[ESI]^-$) found 254.1032, $C_{12}H_{16}NO_5$ ($[M-H]^-$) requires 254.1034.

***(2R,4R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-6,8 dioxobicyclo [3.3.0]-octane,[10] 118b**

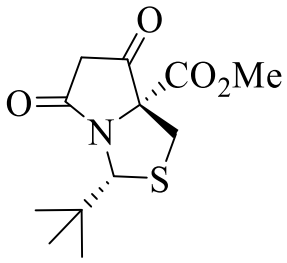
According to general method D, malonamide **148b** (5.23 g, 16.6 mmol) was refluxed with potassium *tert*-butoxide (1.95 g, 17.4 mmol) in THF (0.2 M).



Yield 73% (3.25 g); yellow solid, m. p. 134-136°C (lit.[10] m. p. 132-134°C); R_f (20% MeOH in EtOAc) 0.38; $[\alpha]_D^{25}$ +41.3 (*c* 1.1 in DCM); ν_{max}/cm^{-1} 2960 (C-H), 2874 (C-H), 1782 (C=O), 1749 (C=O), 1617 (C=O); δ_H (400 MHz, $CDCl_3$): 0.83 (9H, s, $C(CH_3)_3$), 0.98 (3H, d, *J* 6.7, $C(4)CH_3$), 3.08 (1H, d, *J* 21.7, C(7)$\underline{H_A}H_B$), 3.58 (1H, d, *J* 21.7, C(7)$H_A\underline{H_B}$), 3.74 (3H, s, CO_2CH_3), 5.02 (1H, q, *J* 6.7, C(4)H), 5.05 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 15.1 (C(4)$\underline{C}H_3$), 24.7 (C($\underline{C}H_3)_3$), 35.5 ($\underline{C}(CH_3)_3$), 45.1 (C(7)), 53.6 ($CO_2\underline{C}H_3$), 75.0 (C(4)), 83.6 (C(5)), 95.9 (C(2)), 167.1 ($\underline{C}O_2CH_3$), 172.9 (C(8)), 199.4 (C(6)); m/z ($[ESI]^+$) 270.1 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 270.1336, $C_{13}H_{20}NO_5$ ($[M+H]^+$) requires 270.1336.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6,8-dioxo-3-thiabicyclo[3.3.0]-octane,[10] 118d**

According to general method D, malonamide **148d** (5.81 g, 18.3 mmol) was refluxed with potassium *tert*-butoxide (2.16 g, 19.2 mmol) in THF (0.2 M).

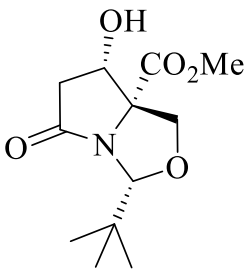


Yield 74% (3.7 g); yellow solid, m. p. 114-116 (lit.[10] m. p. 114-116°C); R_f (25% MeOH in EtOAc) 0.38; $[\alpha]_D^{25}$ +150.1 (c 1.0 in DCM); ν_{max}/cm^{-1} 2957 (C-H), 1748 (C=O), 1714 (C=O), 1626 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 2.95 (1H, d, *J* 11.6, C(4)$\underline{H_A}H_B$), 3.07 (1H, d, *J* 21.5, C(7)$\underline{H_A}H_B$), 3.56 (1H, d, *J* 21.5, C(7)$H_A\underline{H_B}$), 3.72 (1H, d, *J* 11.6, C(4)$H_A\underline{H_B}$), 3.76 (3H, s, CO_2CH_3), 5.26 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 33.8 (C(4)), 37.2 ($\underline{C}(CH_3)_3$), 42.9 (C(7)), 53.9 ($CO_2\underline{C}H_3$), 73.7 (C(2)), 84.9 (C(5)), 167.1 ($\underline{C}O_2CH_3$), 170.6 (C(8)), 199.5 (C(6)); m/z ([ESI]$^-$) 270.1 ([M-H]$^-$, 100%); HRMS ([ESI]$^+$) found 272.0951, $C_{12}H_{18}NO_4S$ ([M+H]$^+$) requires 272.0951.

5.2.10 Reduction of Tetramic acids:[11] General Method N

At 0°C, $NaBH_4$ (2.2 eq) was added portion-wise to a solution of tetramic acid **118** (1.0 eq) and acetic acid (9.0 eq) in anhydrous DCM. The reaction mixture was stirred for 15 min at 0°C and then at room temperature until starting material disappeared by TLC (typically 2-3 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give the product alcohol **168**.

***(2R,5R,6S)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-octane,[10] 168a**



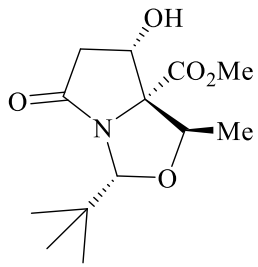
According to general method N, tetramic acid **118a** (74 mg, 0.29 mmol) was reduced by $NaBH_4$ (24 mg, 0.64 mmol) /acetic acid (0.15 mL, 2.7 mmol) in anhydrous DCM (0.1 M) to afford alcohol **168a**.

Yield 96% (48 mg); white solid, m. p. 146-148 (lit.[10] m. p. 146-148°C); R_f (50% EtOAc in DCM) 0.32; $[\alpha]_D^{25}$ +77.8 (*c* 1.2 in DCM); ν_{max}/cm^{-1} 3400 (O-H), 2958 (C-

H), 1692 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 2.82 (1H, dd, *J* 15.8, 8.0 Hz, C(7)$\underline{H_A}H_B$), 3.14 (1H, dd, *J* 15.8, 10.7, C(7)$H_A\underline{H_B}$), 3.55 (1H, d, *J* 8.8, C(4)$\underline{H_A}H_B$), 3.82 (3H, s, CO_2CH_3), 4.55 (1H, dd, *J* 10.7, 8.0, C(6)H), 4.87 (1H, s, C(2)H), 4.89 (1H, d, *J* 8.8, C(4)$H_A\underline{H_B}$); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 36.1 ($\underline{C}(CH_3)_3$), 43.1 (C(7)), 52.8 ($CO_2\underline{C}H_3$), 73.6, 73.7 (C(4), C(6)), 77.4 (C(5)), 96.3 (C(2)), 170.7 ($\underline{C}O_2CH_3$), 174.8 (C(8)); m/z ($[ESI]^+$) 258.1 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 258.1336, $C_{12}H_{20}NO_5$ ($[M+H]^+$) requires 258.1336.

***(2R,4R,5S,6S)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxy carbonyl-4-methyl-3-oxa-8-oxobicyclo[3.3.0]-octane,[10] 168b**

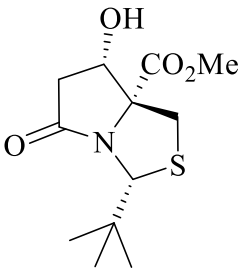
According to general method N, tetramic acid **118b** (390 mg, 1.45 mmol) was reduced by $NaBH_4$ (120 mg, 3.19 mmol) /acetic acid (0.74 mL, 13.05 mmol) in anhydrous DCM (0.1 M) to afford alcohol **168b**.



Yield 46% (110 mg); colourless semi-solid; $[\alpha]_D^{25}$ +35.3 (*c* 1.0 in DCM); R_f (50% EtOAc in DCM) 0.32; ν_{max}/cm^{-1} 3401 (O-H), 2959 (C-H), 2873 (C-H), 1745 (C=O), 1693 (C=O); δ_H (400 MHz, $CDCl_3$): 0.80 (9H, s, $C(CH_3)_3$), 1.18 (3H, d, *J* 6.6, C(4)CH_3), 2.72 (1H, dd, *J* 15.8, 8.1, C(7)$\underline{H_A}H_B$), 3.06 (1H, dd, *J* 15.8, 10.4, C(7)$H_A\underline{H_B}$), 3.75 (3H, s, CO_2CH_3), 4.52-4.59 (1H, m, C(6)H), 4.77 (1H, s, C(2)H), 4.94 (1H, q, *J* 6.6, C(4)H); δ_C (100 MHz, $CDCl_3$): 16.0 (C(4)$\underline{C}H_3$), 25.0 ($C(\underline{C}H_3)_3$), 36.3 ($\underline{C}(CH_3)_3$), 42.8 (C(7)), 52.6 ($CO_2\underline{C}H_3$), 69.5 (C(6)), 75.4 (C(4)), 79.2 (C(5)), 93.9 (C(2)), 171.4 ($\underline{C}O_2CH_3$), 175.0 (C(8)); m/z ($[ESI]^+$) 272.2 ($[M+H]^+$, 60%), 294.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 272.1491, $C_{13}H_{22}NO_5$ ($[M+H]^+$) requires 272.1493.

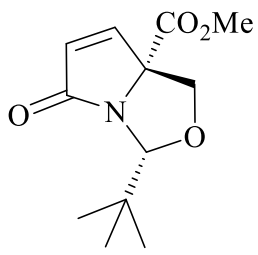
***(2R,5R,6S)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane,[10] 168d**

According to general method N, tetramic acid **118d** (107 mg, 0.39 mmol) was reduced by $NaBH_4$ (33 mg, 0.87 mmol)/acetic acid (0.2 mL, 3.5 mmol) in anhydrous DCM (0.1 M) to afford alcohol **168d**.



Yield 84% (90 mg); white solid, m. p. 160-162 (lit.[10] m. p. 75-77°C); R_f (50% EtOAc in Petrol) 0.44; $[\alpha]_D^{25}$ +20.5 (*c* 1.2 in DCM); ν_{max}/cm^{-1} 3368 (O-H), 2956 (C-H), 1743 (C=O), 1685 (C=O); δ_H (400 MHz, $CDCl_3$): 0.85 (9H, s, $C(CH_3)_3$), 2.65 (1H, dd, *J* 15.9, 7.9, C(7)$\underline{H_A}H_B$), 2.93 (1H, dd, *J* 15.9, 10.7, C(7)$H_A\underline{H_B}$), 3.00 (1H, d, *J* 11.9, C(4)$\underline{H_A}H_B$), 3.77 (3H, s, CO_2CH_3), 3.82 (1H, d, *J* 11.9, C(4)$H_A\underline{H_B}$), 4.37 (1H, dd, *J* 10.7, 7.9, C(6)H), 4.95 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 26.5 ($C(\underline{C}H_3)_3$), 37.9 ($\underline{C}(CH_3)_3$), 38.4 (C(4)), 40.7 (C(7)), 53.0 ($CO_2\underline{C}H_3$), 72.6 (C(2)), 76.5 (C(6)), 82.1 (C(5)), 171.2 ($\underline{C}O_2CH_3$), 174.2 (C(8)); m/z ($[ESI]^+$) 274.1 ($[M+H]^+$, 60%); HRMS ($[ESI]^+$) found 274.1107, $C_{12}H_{20}NO_4S$ ($[M+H]^+$) requires 274.1108.

***(2R,5S)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene,[10] 169a**

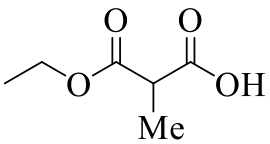


To a solution of alcohol **168a** (470 mg, 1.83 mmol), triphenylphosphine (1.92 g, 7.32 mmol), and benzoic acid (235 mg, 1.92 mmol) in anhydrous THF was added, dropwise, a solution of diethyl azodicarboxylate (0.5 mL, 3.1 mmol) in anhydrous THF (0.1 M). The mixture was stirred at room temperature for 2-3 h, poured into a 0.05 M aqueous solution of NaH_2PO_4, extracted with EtOAc, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Purification by flash column chromatography (petroleum ether:EtOAc, 9:1) gave alkene **169a**.

Yield 99% (434 mg); white solid, m. p. 60-62°C (lit.[10] m. p. 77-79°C); R_f (20% EtOAc in DCM) 0.65; $[\alpha]_D^{25}$ +249.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C-H), 2871 (C-H), 1745 (C=O), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 3.24 (1H, d, *J* 8.5, C(4)$\underline{H_A}H_B$), 3.70 (3H, s, CO_2CH_3), 4.63 (1H, s, C(2)H), 4.72 (1H, d, *J* 8.5, C(4)$H_A\underline{H_B}$), 6.10 (1H, d, *J* 5.7, C(6)H), 7.03 (1H, d, *J* 5.7, C(7)H); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 70.8 (C(4)), 77.9 (C(5)), 97.0 (C(2)), 129.9 (C(6)), 146.6 (C(7)), 169.2 ($\underline{C}O_2CH_3$), 177.7 (C(8)); m/z ($[ESI]^+$) 262.1 ($[M+Na]^+$, 25%); HRMS ($[ESI]^+$) found 240.1130, $C_{12}H_{18}NO_4$ ($[M+H]^+$) requires 240.1230.

Ethyl α-methylmalonic acid,[12] 178

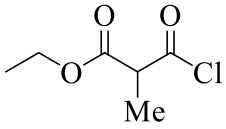
Diethyl methylmalonate (9.0 mL, 53 mmol) was added to a solution of KOH (2.99 g, 53.3 mmol) in EtOH (55 mL) at 0°C and stirred at room temperature for 24 h or refluxed for 90 min. The resulting mixture was filtered and concentrated to give white solid. Water was then added, acidified the solution with HCl (pH 3.0) and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired mono-acid, **178**.



Yield 68% (5.28 g); colourless oil; ν_{max}/cm^{-1} 3183 (O-H), 2989 (C-H), 2947 (C-H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.1, C(5)H_3), 1.38 (3H, d, *J* 7.3, C(2)CH_3), 3.42 (1H, q, *J* 7.3, C(2)H), 4.15 (2H, q, *J* 7.1, C(4)H_2), 11.35 (1H, s, COOH); δ_C (100 MHz, $CDCl_3$): 13.4 (C(2)$\underline{C}H_3$), 13.9 (C(5)), 46.0 (C(2)), 61.7 (C(4)), 169.9 (C(3)), 176.0 (C(1)); m/z ($[ESI]^+$) 147.0 ($[M+H]^+$, 90%), 169.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 147.0653, $C_6H_{11}O_4$ ($[M+H]^+$) requires 147.0652.

Ethyl α-methylmalonyl chloride,[12] **179**

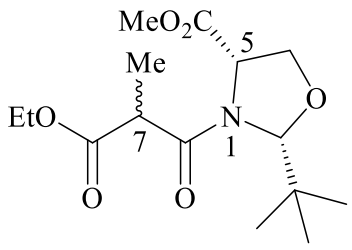
Thionyl chloride (4.76 mL, 65.2 mmol) was added dropwise to the mono-acid **178** (4.77 g, 32.6 mmol) at 0°C and the reaction mixture was stirred at 40°C for overnight. The excess thionyl chloride was removed *in vacuo* to give the acid chloride, which was used directly in the next step.



Yield 96% (5.15 g); orange oil; ν_{max}/cm^{-1} 2988 (C-H), 2945 (C-H), 1789 (C=O), 1736 (C=O); δ_H (400 MHz, $CDCl_3$): 1.24 (3H, t, *J* 7.1, C(5)H_3), 1.46 (3H, d, *J* 7.2, C(2)CH_3), 3.78 (1H, q, *J* 7.2, C(2)H), 4.19 (2H, q, *J* 7.1, C(4)H_2); δ_C (100 MHz, $CDCl_3$): 13.9 (C(5)), 14.0 (C(2)$\underline{C}H_3$), 57.0 (C(2)), 62.3 (C(4)), 167.5 (C(3)), 170.8 (C(1)).

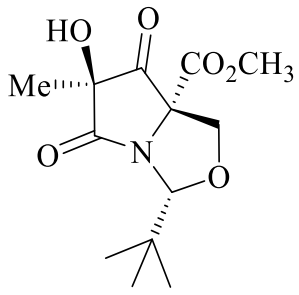
(*2R*,*5S*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-methylacetyl)- and (*2R*,*5S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine,[5] **180a and 180a'**

To a solution of oxazolidine/thiazolidine **147a** (2.32 g, 12.4 mmol) and dry pyridine (2.02 mL, 25.77 mmol) in anhydrous DCM (66 mL), a solution of malonyl chloride **179** (4.08 g, 24.8 mmol) in anhydrous DCM was added at 0°C. The resulting mixture was stirred at 0°C for 30 min and at room temperature for 6 h. It was then washed with sat. aq. NH_4Cl and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20%-35% EtOAc in petroleum ether) to give *N*-acyl oxazolidine as a 2.2:1 mixture of diastereomers **180a** and **180a'**. Isomers were characterized by comparison with reported assignment by M. D. Andrews *et al*.[5]



Yield 74% (5.01 g); yellow oil; 2.2:1 mixture of diastereomers. R_f (40% EtOAc in Petrol) 0.65+0.51; ν_{max}/cm^{-1} 2959 (C-H), 1745 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) major isomer (**180a**): 0.86 (9H, s, $C(CH_3)_3$), 1.22-1.24 (3H, m, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, d, *J* 7.2, $C(7)C\underline{H}_3$), 3.62 (1H, q, *J* 7.0, C(7)H), 3.71 (3H, s, CO_2CH_3), 3.89-3.96 (1H, m, $C(4)\underline{H}_AH_B$), 4.13-4.18 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.43-4.51 (2H, m, $C(4)H_A\underline{H}_B$ + C(5)H), 5.29 (1H, s, C(2)H); minor isomer (**180a'**): 0.81 (9H, s, $C(CH_3)_3$), 1.18 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, d, *J* 6.9, $C(7)C\underline{H}_3$), 3.52 (1H, q, *J* 6.9, C(7)H), 3.74 (3H, s, CO_2CH_3), 3.86-3.95 (1H, m, $C(4)\underline{H}_AH_B$), 4.10 (2H, q, *J* 7.1 $CO_2C\underline{H}_2CH_3$), 4.51 (1H, d, *J* 8.8, $C(4)H_A\underline{H}_B$), 4.86 (1H, d, *J* 6.8, C(5)H), 5.28 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) major isomer (**180a**): 13.7 ($CO_2CH_2\underline{C}H_3$), 14.1 ($CH\underline{C}H_3$), 25.6 ($C(\underline{C}H_3)_3$), 37.6 ($\underline{C}(CH_3)_3$), 45.7 ($\underline{C}HCH_3$), 52.7 ($CO_2\underline{C}H_3$), 59.4 (C(5)), 61.7 ($CO_2\underline{C}H_2CH_3$), 68.1 (C(4)), 96.7 (C(2)), 169.1, 170.3, 171.6 ($N\underline{C}O$, $\underline{C}O_2CH_3$, CO_2Et); minor isomer (**180a'**): 14.0 ($CO_2CH_2\underline{C}H_3$), 14.4 ($CH\underline{C}H_3$), 25.5 ($C(\underline{C}H_3)_3$), 37.2 ($\underline{C}(CH_3)_3$), 45.8 ($\underline{C}HCH_3$), 52.9 ($CO_2\underline{C}H_3$), 59.4 (C(5)), 61.7 ($CO_2\underline{C}H_2CH_3$), 67.5 (C(4)), 96.4 (C(2)), 170.1, 170.2 ($N\underline{C}O$, $\underline{C}O_2CH_3$), 171.9 (CO_2Et); m/z (ESI^+) 338.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 316.1750, $C_{15}H_{26}NO_6$ ($[M+H]^+$) requires 316.1755.

***(2R,5R,7S)*-1-Aza-2-(*tert*-butyl)-7-hydroxy-5-methoxycarbonyl-7-methyl-3-oxa-6,8-dioxobicyclo[3.3.0]-octane,[5] 181**



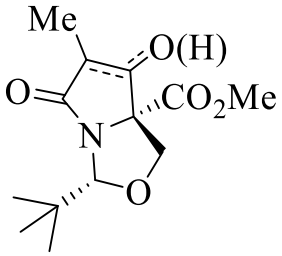
According to general method D, malonamide **180a** (2.45 g, 7.78 mmol) was refluxed with potassium *tert*-butoxide (961 mg, 8.56 mmol) in anhydrous THF (0.2 M).

Yield 68% (1.42 g); white solid, m. p. 158-160°C (lit.[5] m. p. 188-191°C); R_f (40% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +65.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3424 (O-H), 2964 (C-H), 1784 (C=O), 1742 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s,

$C(CH_3)_3$), 1.67 ($C(7)CH_3$), 3.56 (1H, d, *J* 8.9, $C(4)\underline{H_A}H_B$), 3.77 (3H, s, CO_2CH_3), 4.78 (1H, d, *J* 8.9, $C(4)H_A\underline{H_B}$), 5.00 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 23.8 ($C(7)\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.8 ($CO_2\underline{C}H_3$), 69.6 (C(4)), 77.3 (C(5)), 77.5 (C(7)), 99.0 (C(2)), 166.4 ($\underline{C}O_2CH_3$), 177.8 (C(8)), 200.8 (C(6)); m/z ($[ESI]^+$) 286.1 ($[M+H]^+$, 75%), 308.0 ($[M+Na]^+$); HRMS ($[ESI]^+$) found 286.1286, $C_{13}H_{20}NO_6$ ($[M+H]^+$) requires 286.1285.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-7-methyl-3-oxa-6,8-dioxobicyclo [3.3.0]octane,[5] 128a**

To a solution of *N*-acyl oxazolidine **180a** (1.42 g, 4.5 mmol) in anhydrous ^{t}BuOH (0.2 M) was added potassium *tert*-butoxide (555 mg, 4.9 mmol). The mixture was heated at reflux for 4 h. The reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the tetramic acids **128a**.



Yield 82% (1.0 g); white solid, m. p. 135-137°C (lit.[5] m.p. 94-100°C); 1:2 mixture of keto-enol tautomers. R_f (10% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +80.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3298 (O-H), 2963 (C-H), 2876 (C-H), 1790 (C=O), 1733 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$ (keto+enol)), 1.22 (3H, d, *J* 7.2, $C(7)CH_3$ (keto)), 1.63 (3H, s, $C(7)CH_3$ (enol)), 3.35 (1H, d, *J* 8.5, $C(4)\underline{H_A}H_B$ (enol)), 3.49 (1H, d, *J* 9.4, $C(4)\underline{H_A}H_B$ (keto)), 3.65 (1H, q, J 7.2, C(7)H (keto)), 3.71 (3H, s, CO_2CH_3 (enol)), 3.76 (3H, s, CO_2CH_3 (keto)), 4.59 (1H, s, C(2)H (enol)), 4.71-4.82 (2H, m, $C(4)H_A\underline{H_B}$ (keto+enol)), 4.99 (1H, s, C(2)H (keto)); δ_C (100 MHz, $CDCl_3$): 6.3 ($C(7)\underline{C}H_3$ (keto)), 7.6 ($C(7)\underline{C}H_3$ (enol)), 24.6 ($C(\underline{C}H_3)_3$ (enol)), 24.7 ($C(\underline{C}H_3)_3$ (keto)), 35.1 ($\underline{C}(CH_3)_3$ (enol)), 35.6 ($\underline{C}(CH_3)_3$ (keto)), 49.4 (C(7) keto), 53.1 ($CO_2\underline{C}H_3$ (keto)), 53.8 ($CO_2\underline{C}H_3$ (enol)), 68.3 (C(4) enol), 69.9 (C(4) keto), 74.2 (C(5) (enol)), 79.1 (C(5) (keto)),

96.6 (C(2) (keto)), 98.0 (C(2) (enol)), 103.9 (C(7) (enol)), 166.9 ($\underline{C}O_2CH_3$ (enol)), 168.0 ($\underline{C}O_2CH_3$ (keto)), 169.2 (C(8) (keto)), 175.4 (C(8) (enol)), 181.5 (C(6) (enol)), 201.1 (C(6) (keto)); m/z ($[ESI]^+$) 270.2 ($[M+H]^+$, 60%), 292.0 ($[M+Na]^+$); HRMS ($[ESI]^+$) found 270.1333, $C_{13}H_{20}NO_5$ ($[M+H]^+$) requires 270.1336.

Monohydrolysis of Diethyl Phenyl Malonate: Attempted Methods

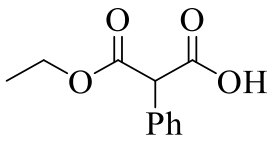
Method 1:[13] Water was added to a solution of diethyl phenyl malonate (1 eq) in THF (1/10 of water). The reaction mixture was cooled to 0°C and 0.25 M aqueous solution of KOH (1.2 eq) was added dropwise. On stirring the reaction mixture for 5 h followed by acidification with 1 M HCl at 0°C (pH 2), saturation with NaCl, extraction with EtOAc, drying over Na_2SO_4 provided colourless extract which was concentrated *in vacuo* to yield crude mono-ester. The crude product was purified by flash column chromatography.

Method 2:[12] Diethyl phenyl malonate (1 eq) was added to a solution of KOH (1 eq) in EtOH (55 mL) at 0°C and stirred at room temperature for 24 h or refluxed for 90 min. The resulting mixture was filtered and concentrated to give white solid. Water was then added, acidified the solution with HCl (pH 3.0) and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

Method 3:[14] Water was added to a solution of diethyl phenyl malonate (1 eq) in THF (1/10 of water). The reaction mixture was cooled to 0°C and 0.25 M aqueous solution of KOH/NaOH (1.2 eq) was added dropwise. On stirring the reaction mixture for 5 h followed by acidification with 1 M HCl at 0°C (pH 2), saturation with NaCl, extraction with EtOAc, drying over Na_2SO_4 resulted in colourless extract which was concentrated *in vacuo* to yield crude mono-ester. The crude product was purified by flash column chromatography.

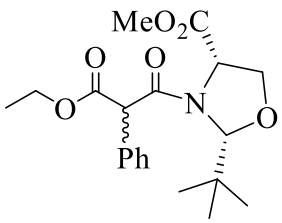
Ethyl α-phenylmalonic acid,[13] 184

According to general method 1[13] reaction of diethyl phenyl malonate (3.28 g, 13.88 mmol) in 0.6 M THF/ 0.06 M water (1/10) and 0.25 M aqueous solution of KOH (72.2 mL) furnished desired mono-ester.



Yield 92% (2.65 g); white solid, m. p. 65-67°C (Lit.[13] m. p. 74°C); R_f (EtOAc) 0.13; ν_{max}/cm^{-1} 3284 (O-H), 3065 (C-H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$): 1.19 (3H, t, *J* 7.1, C(5)H_3), 4.08-4.23 (2H, m, C(4)H_2), 4.57 (1H, s, C(2)H), 7.23-7.35 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.0 (C(5)), 57.4 (C(2)), 62.3 (C(4)), 128.5-132.2 (ArC), 168.4 (C(3)), 173.0 (C(1)); m/z ($[ESI]^+$) 231.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 231.0628, $C_{11}H_{12}O_4Na$ ($[M+Na]^+$) requires 231.0628.

(*2R,5S*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-phenylacetyl)- and (*2R,5S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine,[15,16] 185a and 185a'



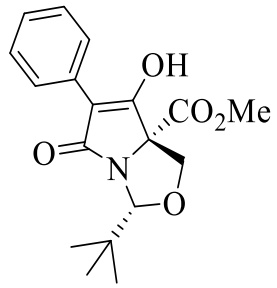
According to general method C, oxazolidine **147a** (410 mg, 2.2 mmol), DCC (497 mg, 2.4 mmol), and DMAP (19 mg, 0.15 mmol) was reacted with ethyl α-phenyl malonic acid **184** (499 mg, 2.4 mmol) in DCM (22 mL). The crude product was purified by flash column chromatography (20%-25% EtOAc in petroleum ether) to afford *N*-acyl oxazolidine as a 2:1 mixture of diastereomers **185a** and **185a'**. The structure of major isomer **185a** was confirmed by X-ray crystallography.

Yield 88% (726 mg); 2:1 mixture of diastereomers; R_f (20% EtOAc in petrol) 0.18+0.27; only major isomer was separated for characterisation, stereochemistry was confirmed by single-

crystal X-ray crystallography. Major isomer (**185a**): white solid, m. p. 86-88°C (lit.[15] 119-122°C); $[\alpha]_D^{25}$ +34.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C-H), 2874 (C-H), 1747 (C=O), 1673 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 1.20 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.51 (1H, dd, *J* 9.2, 7.1, C(4)$\underline{H}_AH_B$), 3.78 (3H, s, CO_2CH_3), 4.08-4.26 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.28-4.37 (2H, m, (C(4)$H_A\underline{H}_B$ + C(5)H)), 4.94 (1H, s, C$\underline{H}$Ph), 5.25 (1H, s, C(2)H), 7.26-7.34 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.1 ($CO_2CH_2\underline{C}H_3$), 25.6 ($C(\underline{C}H_3)_3$), 37.5 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 58.3 ($\underline{C}$HPh), 58.7 (C(5)), 61.7 ($CO_2\underline{C}H_2CH_3$), 67.6 (C(4)), 96.8 (C(2)), 128.5-132.1 (ArC), 168.4 (N$\underline{C}$=O), 169.0 ($\underline{C}O_2CH_3$), 169.9 (CO_2Et); m/z ($[ESI]^+$) 378.2 ($[M+H]^+$, 55%); HRMS ($[ESI]^+$) found 400.1723, $C_{20}H_{27}NO_6Na$ ($[M+Na]^+$) requires 400.1731.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-3-oxa-8-oxo-7-phenylbicyclo [3.3.0]oct-6-ene,[15] 132a**

To a solution of *N*-acyl oxazolidine **185a** (684 mg, 1.81 mmol) in anhydrous ^{t}BuOH (0.1 M) was added potassium *tert*-butoxide (221 mg, 1.97 mmol). The mixture was heated at reflux for 3-6 h. The reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the tetramic acid **132a**.

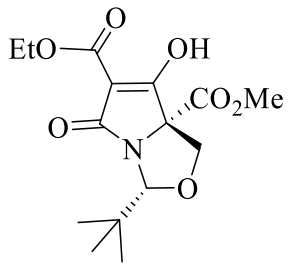


Yield 82% (495 mg); white solid, m. p. 160-162°C (lit.[15] m. p. 72-77°C); R_f (10% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +89.4 (*c* 0.9 in MeOH); ν_{max}/cm^{-1} 3485 (O-H), 2957 (C-H), 2871 (C-H), 1750 (C=O), 1650 (C=O); δ_H (400 MHz, MeOD): 0.82 (9H, s, $C(CH_3)_3$), 3.39 (1H, d, *J* 8.4, C(4)$\underline{H}_AH_B$), 3.64 (3H, s, CO_2CH_3), 4.61 (1H, s, C(2)H), 4.67 (1H, d, *J* 8.4, C(4)$H_A\underline{H}_B$), 6.90-6.99 (1H, m, C(4'')H), 7.14 (2H, t, *J* 7.8, C(3'')H), 7.81 (2H, d, *J* 7.0, C(2'')H); δ_C (100 MHz, MeOD): 24.1 ($C(\underline{C}H_3)_3$), 34.9 ($\underline{C}(CH_3)_3$), 51.8 ($CO_2\underline{C}H_3$), 69.5 (C(4)), 76.2 (C(5)), 96.9

(C(2)), 99.0 (C(7)), 124.2 (C(4'')), 126.2 (C(2'')), 127.2 (C(3'')), 133.7 (C(1'')), 171.2 ($\underline{C}O_2CH_3$), 181.3 (C(8)), 183.2 (C(6)); m/z ($[ESI]^+$) 332.1 ($[M+H]^+$, 30%), 354.1 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 354.1314, $C_{18}H_{21}NO_5Na$ ($[M+Na]^+$) requires 354.1312.

***(2R,5R)*-1-Aza-2-(*tert*-butyl)-7-ethoxycarbonyl-6-hydroxy-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene,[17] 124a**

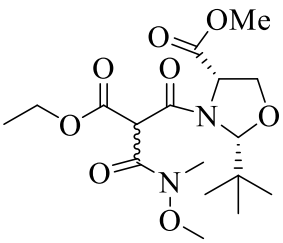
Ethyl chloroformate (0.22 mL, 2.35 mmol) was added to a solution of tetramic acid **118a** (500 mg, 1.96 mmol) and DMAP (527 mg, 4.3 mmol) in anhydrous DCM (39 mL). The reaction mixture was stirred for 24 h at room temperature and then concentrated under reduced pressure. EtOAc was added to the resulting mixture and extracted the organic layer with 1 M aqueous NaH_2PO_4. 2 M aqueous HCl was used to acidify the aqueous layer and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired product **124a**.



Yield 44% (280 mg); orange solid, m. p. 61-63°C (lit.[17] 62°C); R_f (20% MeOH in EtOAc) 0.51; $[\alpha]_D^{25}$ +93.1 (c 1.0, DCM); ν_{max}/cm^{-1} 3438 (O-H), 2959 (C-H), 2872 (C-H), 1693 (C=O), 1633 (C=O); δ_H (400 MHz, MeOD): 0.78 (9H, s, $C(CH_3)_3$), 1.20 (3H, t, *J* 7.1, $C\underline{H}_3CH_2O$), 3.30 (1H, d, *J* 8.5 Hz, $C(4)\underline{H}_A H_B$), 3.62 (3H, s, CO_2CH_3), 4.13 (2H, q, *J* 7.1, $CH_3C\underline{H}_2O$), 4.58-4.62 (2H, m, ($C(4)H_A\underline{H}_B$ + C(2)H)); δ_C (400 MHz, MeOD): 13.6 ($\underline{C}H_3CH_2O$), 24.1 ($C(\underline{C}H_3)_3$), 34.8 ($\underline{C}(CH_3)_3$), 51.8 ($CO_2\underline{C}H_3$), 59.2 ($CH_3\underline{C}H_2O$), 68.6 (C(4)), 76.8 (C(5)), 97.5 (C(2)), 167.1 ($\underline{C}O_2Me$), 170.1 ($\underline{C}O_2Et$), 181.8 (C(8)), 189.8 (C(6)); m/z ($[ESI]^+$) 350.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 350.1209, $C_{15}H_{21}O_7NNa$ requires ($[M+Na]^+$) 350.1210.

(*2R,5S*)-2-(*tert*-Butyl)-1-((*R*)-1-ethoxycarbonyl-1-(methoxy(methyl)carbamoyl))acetyl-5-methoxycarbonyl-1,3-oxazolidine and (*2R, 5S*)-2-(*tert*-Butyl)-1-((*S*)-1-ethoxycarbonyl-1-(methoxy(methyl)carbamoyl))acetyl-5-methoxycarbonyl-1,3-oxazolidine,[17,18] **207a and 207a'**

To a solution of *N*-acyl oxazolidine **148a** (1.64 g, 5.44 mmol) in anhydrous DCM (0.5 M), magnesium bromide (1.5 g, 8.16 mmol) and dry pyridine (0.66 mL, 8.16 mmol) were added dropwise at 0°C. The resulting mixture was stirred at 0°C for 15 min and a solution of methoxy(methyl)carbamic chloride (1.0 g, 8.17 mmol) in anhydrous DCM was added dropwise. The reaction mixture was stirred at room temperature for 24 h and then acidified with 2 M aq. HCl at 0°C. The aqueous phase was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get crude product, which was then purified by flash column chromatography to yield tricarbonyl oxazolidine **207**.

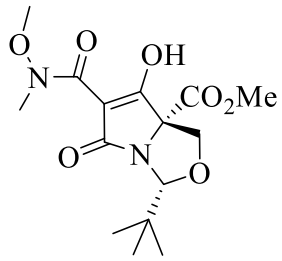


Yield 67% (1.42 g); colourless oil; 1.5:1 mixture of diastereomers; R_f (80% EtOAc in PE) 0.45 + 0.50; ν_{max}/cm^{-1} 2958 (C-H), 2908 (C-H), 2876 (C-H), 1746 (C=O), 1680 (C=O); δ_H (400 MHz, $CDCl_3$) Major diastereomer: 0.84 (9H, s, $C(CH_3)_3$), 1.24 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 3.15 (3H, s, NCH_3), 3.62 (3H, s, $NOCH_3$), 3.71 (3H, s, $CO_2\underline{C}H_3$), 3.82-3.91 (1H, m, C(4)$\underline{H}_AH_B$), 4.22 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 4.44-4.49 (2H, m, (C(4)$H_A\underline{H}_B$ + C(5)H)), 4.88 (1H, s, C(7)H), 5.30 (1H, s, C(2)H); Minor diastereomer: 0.84 (9H, s, $C(CH_3)_3$), 1.23 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 3.17 (3H, s, NCH_3), 3.68 (3H, s, $NOCH_3$), 3.72 (3H, s, $CO_2\underline{C}H_3$), 3.82-3.91 (1H, m, C(4)$\underline{H}_AH_B$), 4.22 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 4.32-4.37 (1H, m, C(5)H), 4.44-4.49 (1H, m, C(4)$H_A\underline{H}_B$), 4.96 (1H, s, C(7)H), 5.26 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) Major diastereomer: 14.0 ($OCH_2\underline{C}H_3$), 25.5 ($C(\underline{C}H_3)_3$), 32.5 (NCH_3), 37.3 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 58.7 (C(7)), 59.4 (C(5)), 61.2 ($NOCH_3$), 62.0 ($O\underline{C}H_2CH_3$), 67.7 (C(4)), 96.8 (C(2)),

164.9 ($\underline{C}O_2CH_2CH_3$), 165.6 ($\underline{C}ON$), 165.9 (C(8)), 169.6 ($\underline{C}O_2CH_3$); Minor diastereomer: 14.0 ($OCH_2\underline{C}H_3$), 25.5 ($C(\underline{C}H_3)_3$), 32.8 (NCH_3), 37.1 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 58.3 (C(7)), 59.3 (C(5)), 61.6 ($NOCH_3$), 62.4 ($O\underline{C}H_2CH_3$), 67.6 (C(4)), 97.0 (C(2)), 164.9 ($\underline{C}O_2CH_2CH_3$), 165.5 ($\underline{C}ON$), 165.7 (C(8)), 169.6 ($\underline{C}O_2CH_3$); m/z ($[ESI]^+$) 411.2 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 389.1919, $C_{17}H_{29}N_2O_8$ requires ($[M+H]^+$) 389.1918.

(*2R*,*5R*)-1-Aza-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-7-(methoxy(methyl)-carbamoyl)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene,[18] 126a

To a solution of tricarbonyl oxazolidine **207a** (912 mg, 2.35 mmol) in anhydrous THF (0.2 M), 1,8-diazabicycloundec-7-ene (0.38 mL, 2.58 mmol) was added. The mixture was stirred at room temperature for 24 h. The resulting reaction mixture was then cooled to 0°C, diluted with water and partitioned between Et_2O and water. The aqueous layer was acidified with 2 M aq. HCl, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get Weinreb amide **126a**.



Yield 94% (757 mg); orange solid, m. p. 108-110°C (lit.[17] m. p. 100-102°C); R_f (20% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +115.3 (*c* 1.1 in DCM); ν_{max}/cm^{-1} 3486 (O-H), 2958 (C-H), 2871 (C-H), 1749 (C=O), 1706 (C=O), 1655 (C=O), 1601 (C=C); δ_H (400 MHz, MeOD): 0.86 (9H, s, $C(CH_3)_3$), 3.42-3.47 (4H, m, ($C(4)\underline{H_A}H_B$ + NCH_3)), 3.73 (3H, s, CO_2CH_3), 3.74 (3H, s, $NOCH_3$), 4.72 (1H, s, C(2)H), 4.78 (1H, d, *J* 8.8, $C(4)H_A\underline{H_B}$); δ_C (100 MHz, MeOD): 24.7 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 62.2 ($NOCH_3$), 68.9 (C(4)), 76.0 (C(5)), 98.0 (C(2)), 166.4 (C(9)), 167.9 (CO_2Me); m/z ($[ESI]^+$) 343.2 ($[M+H]^+$, 60%), 365.2 ($[M+Na]^+$, 35%); HRMS ($[ESI]^+$) found 343.1505, $C_{15}H_{23}N_2O_7$ ($[M+H]^+$) requires 343.1506.

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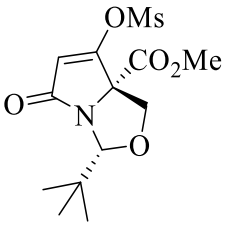
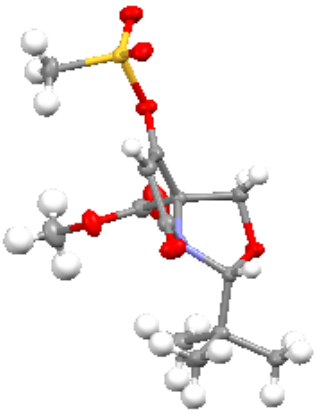
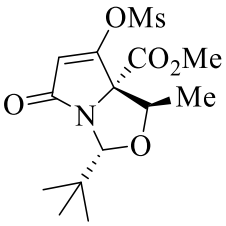
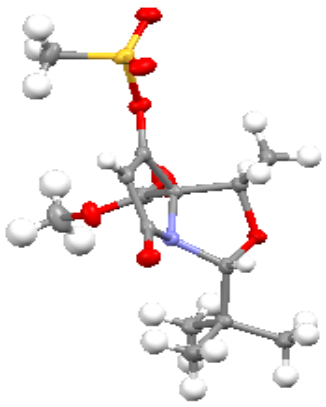
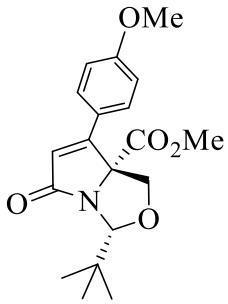
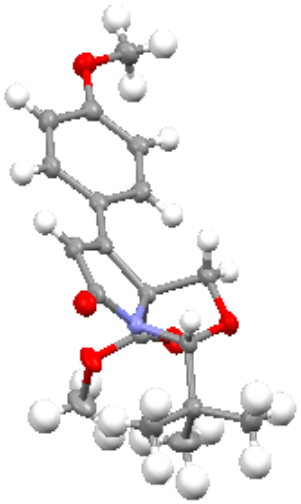
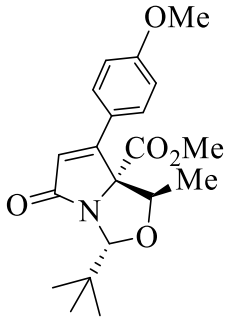
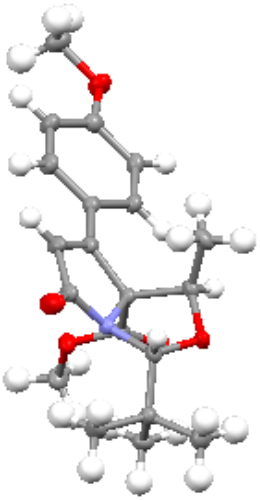
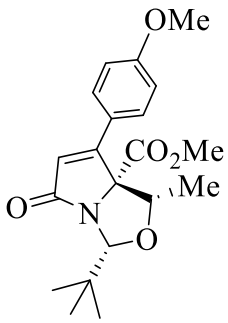
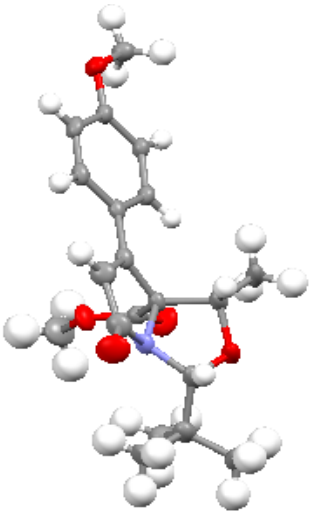
APPENDIX B: X-RAY CRYSTALLOGRAPHY DATA

X-Ray crystal structures of the compounds (Table B.1) were determined by the Oxford Chemistry Crystallography Service. The software Mercury v3.10.1 was used to produce Ellipsoid representations of the crystal structures. The data for crystal structures are provided separately on the CD.

Table B.1: X-Ray crystal structures and respective file names

Sl No	Compound	Structure	Crystal Structure (Ellipsoid Style)	File Name
1	**153a**			6662
2	**153b**			6661

Continued….

3	**119ai**			6728
4	**119bi**			6729
5	**119ci**			6730

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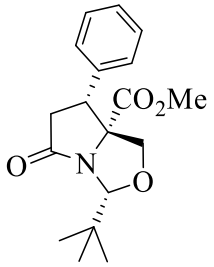
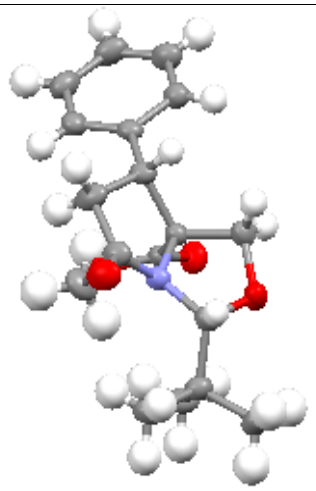
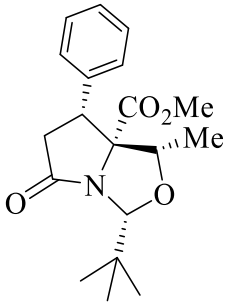
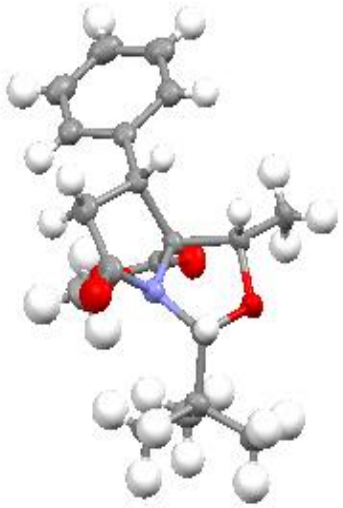
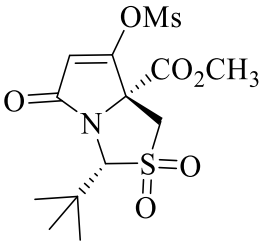
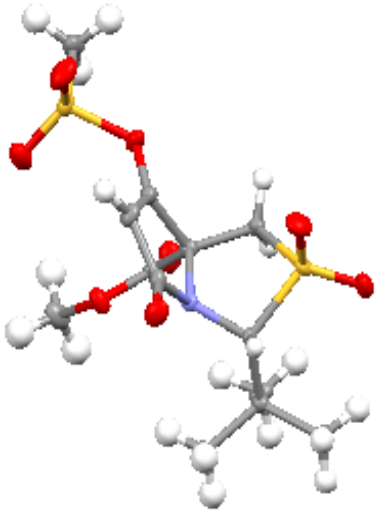
6	**121aii**			6810
7	**121cii**			6828
8	**157d**			6744

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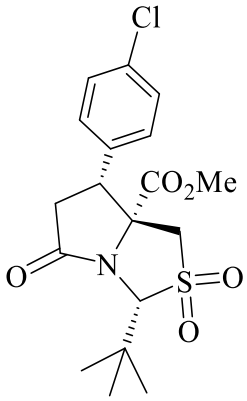
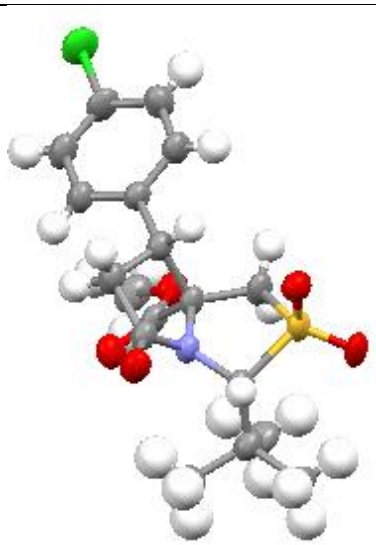
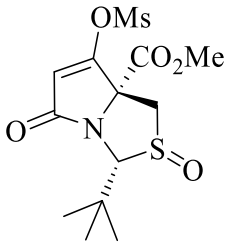
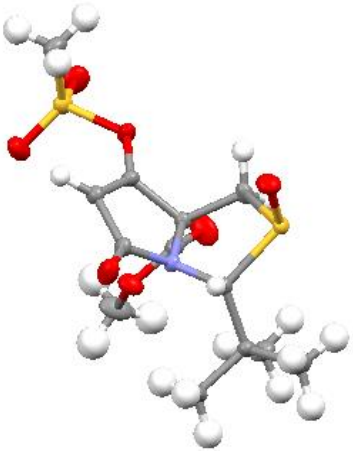
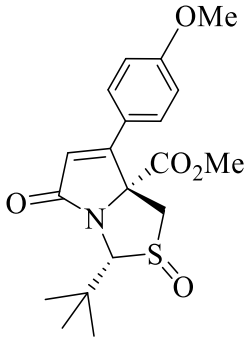
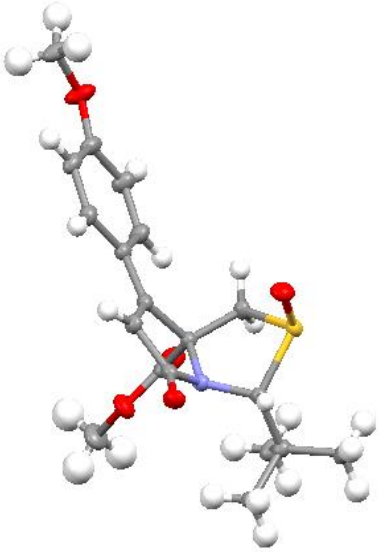
9	**159dv**			6805
10	**161d**			6785
11	**162di**			6807

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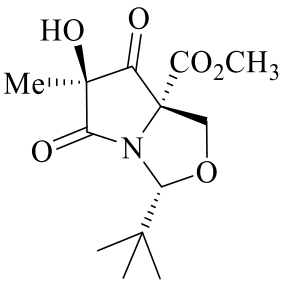
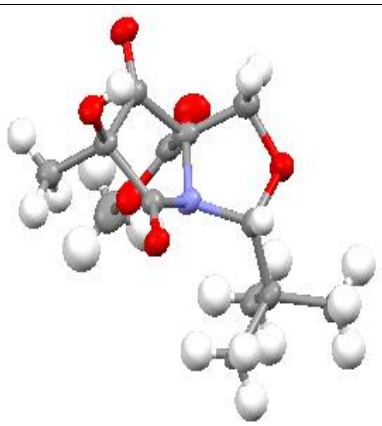
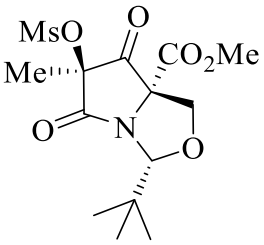
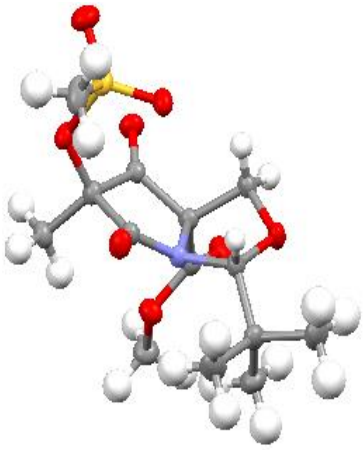
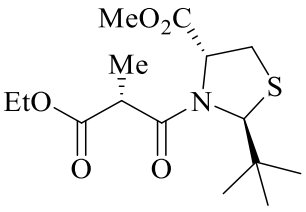
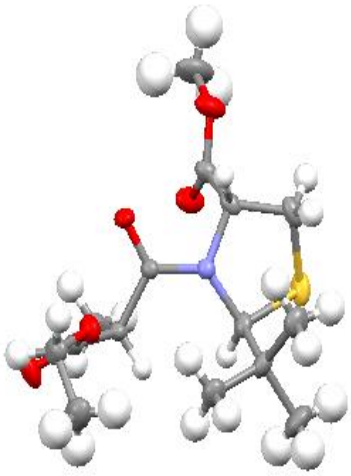
12	**181**			6758
13	**182**			6745
14	**180c'**			6842
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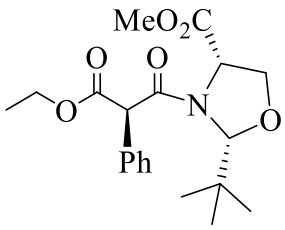
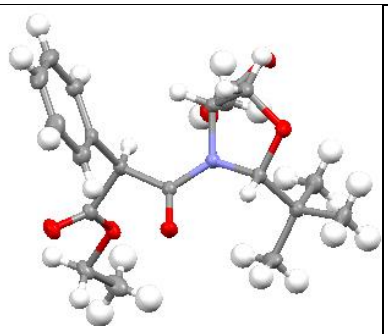
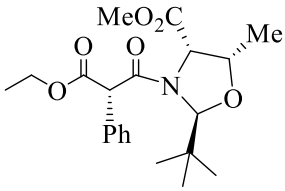
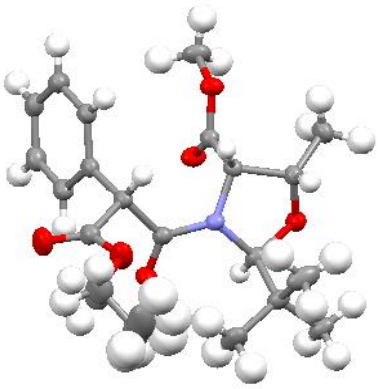
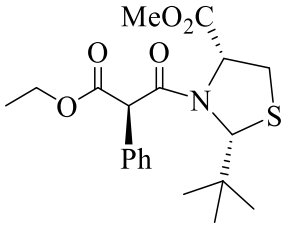
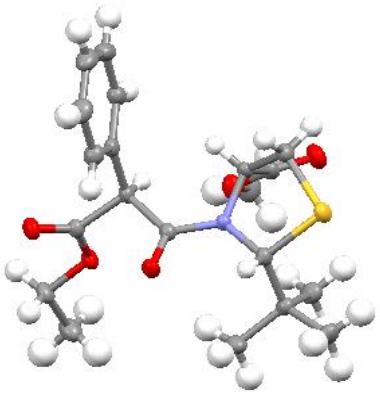
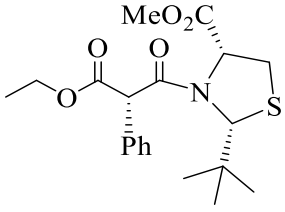
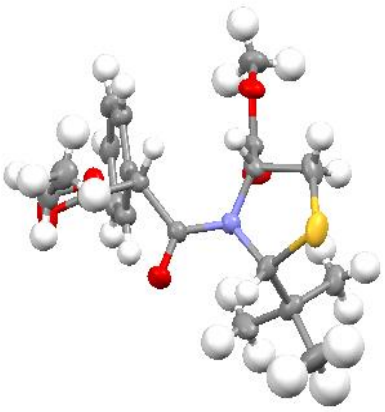
15	**185a**			6930
16	**185b''**			6931
17	**185c**			6935
18	**185c'**			6958

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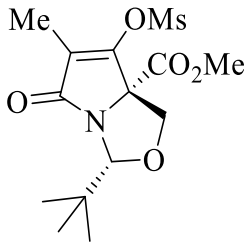
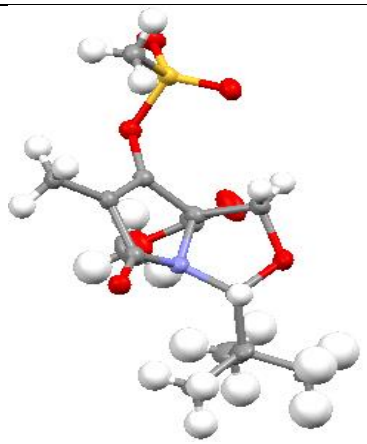
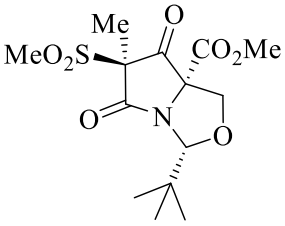
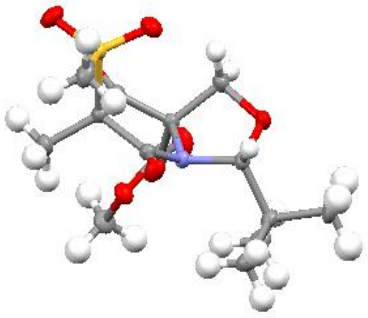
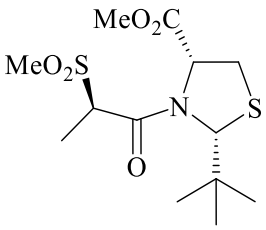
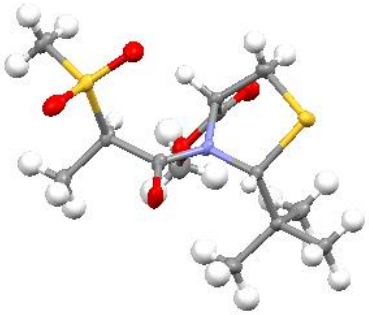
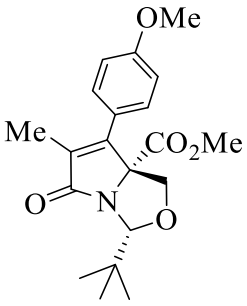
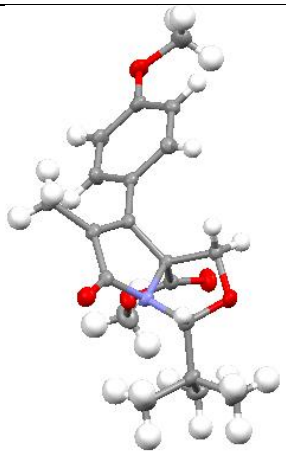
19	**183a**			6784
20	**189**			6985
21	**192**			6956
22	**129ai**			6806
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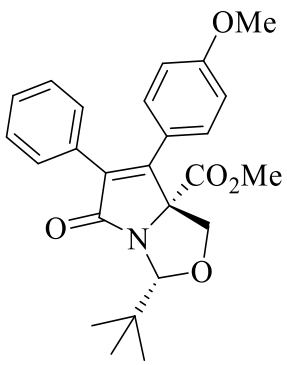
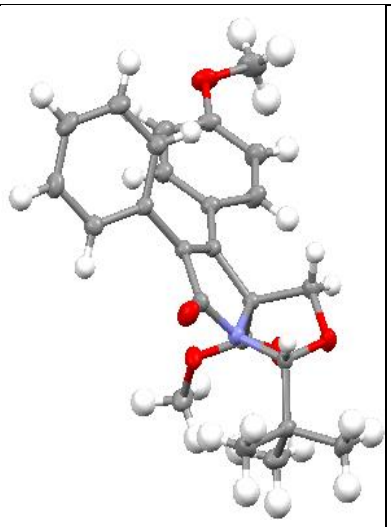
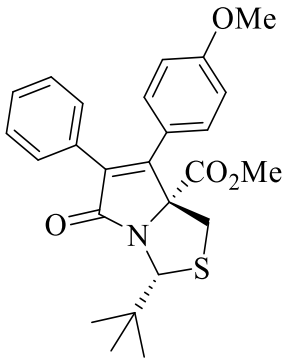
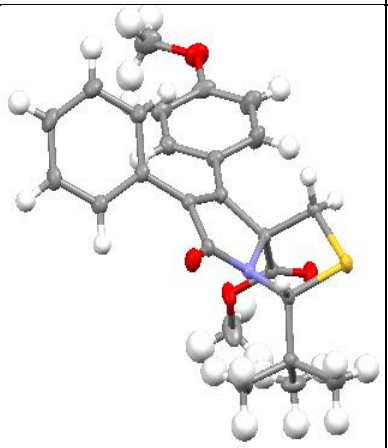
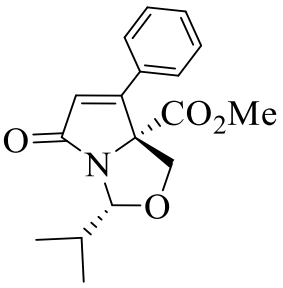
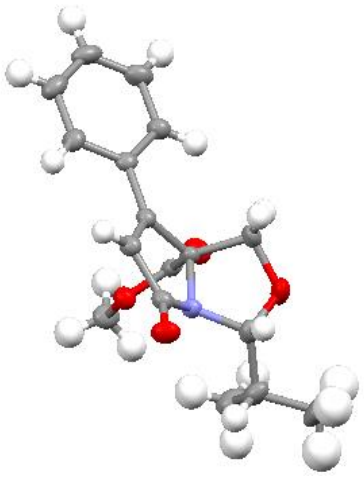
23	**133ai**			6964
24	**133ci**			6954
25	**213aii**			6903

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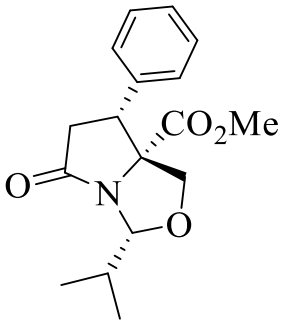
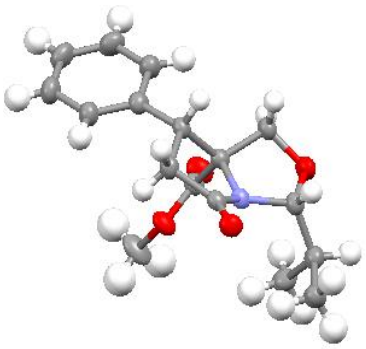
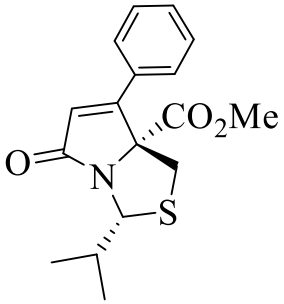
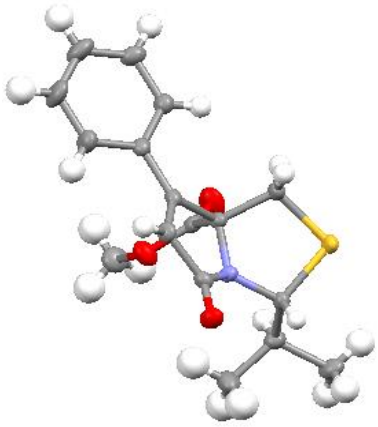
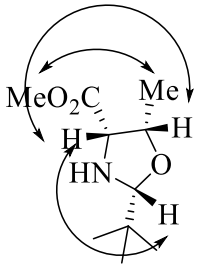
26	**214aii**			6932
27	**213bii**			6902

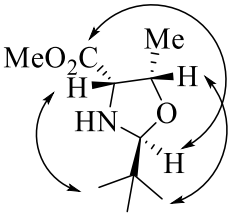
APPENDIX C: NOE CORRELATIONS

NOE experiments were conducted on Bruker AVB 500, AVC 500 or AVX 500 (500 MHz). Figure C.1, C.2 and C.3 show the NOE correlations used to determine stereochemistry of compounds in Chapter 2, 3, and 4, respectively.

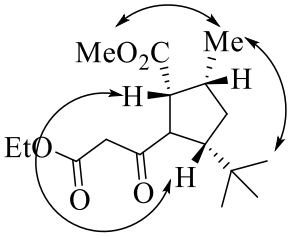
NOE Correlations for Compounds in Chapter 2:



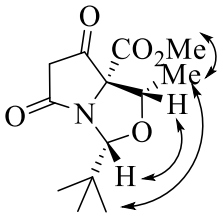
147c



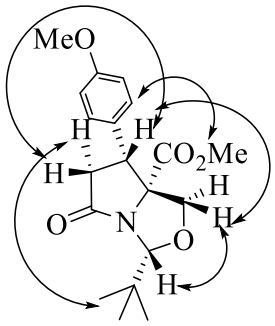
147c'



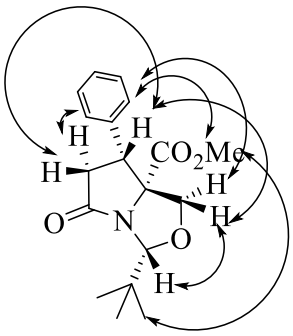
148c



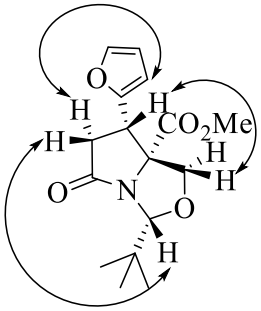
118c



121ai



121aii



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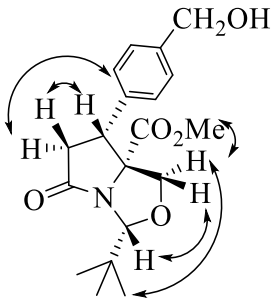

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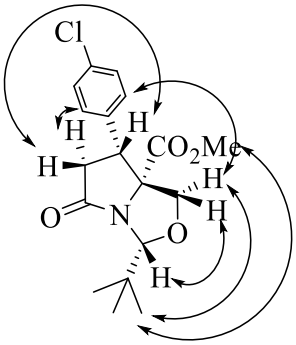

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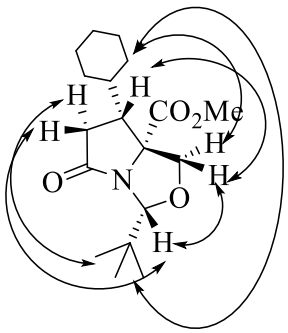

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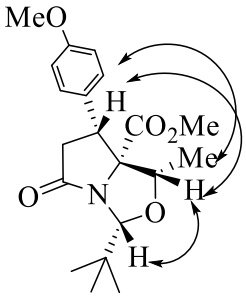

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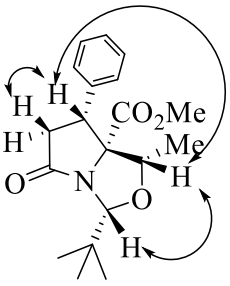

121cii

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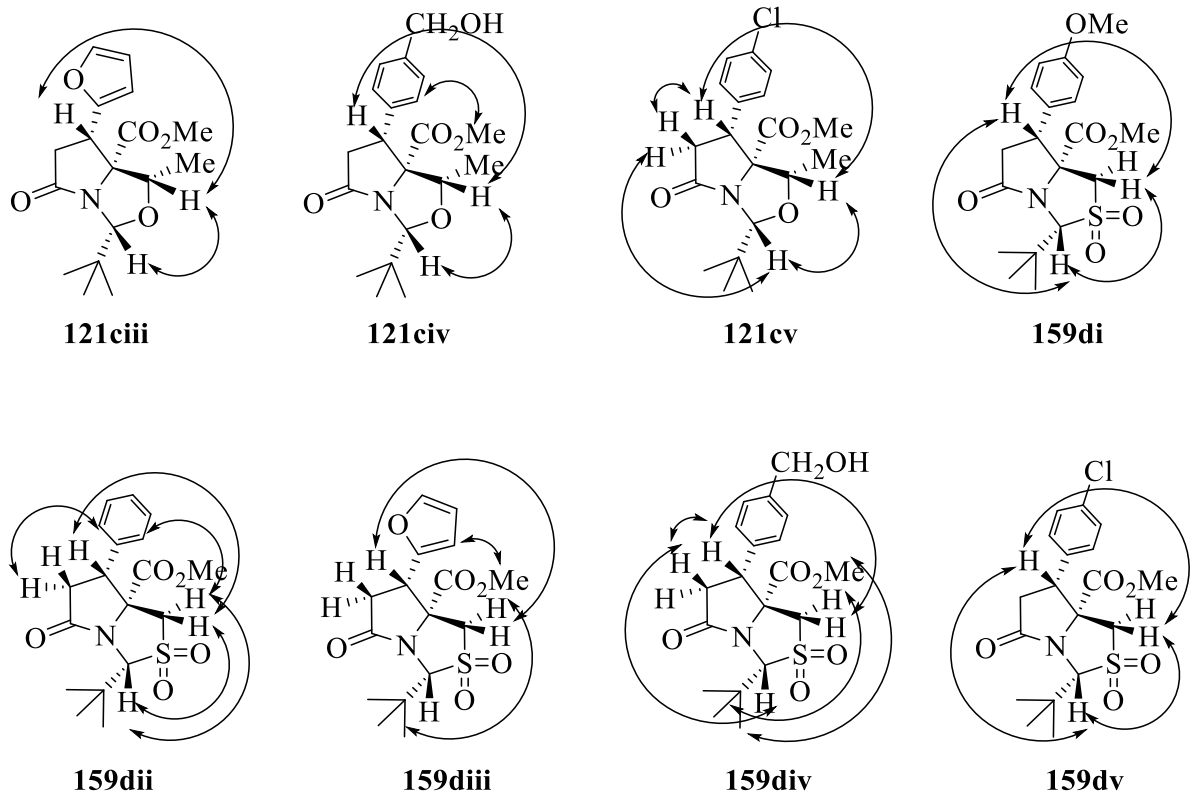
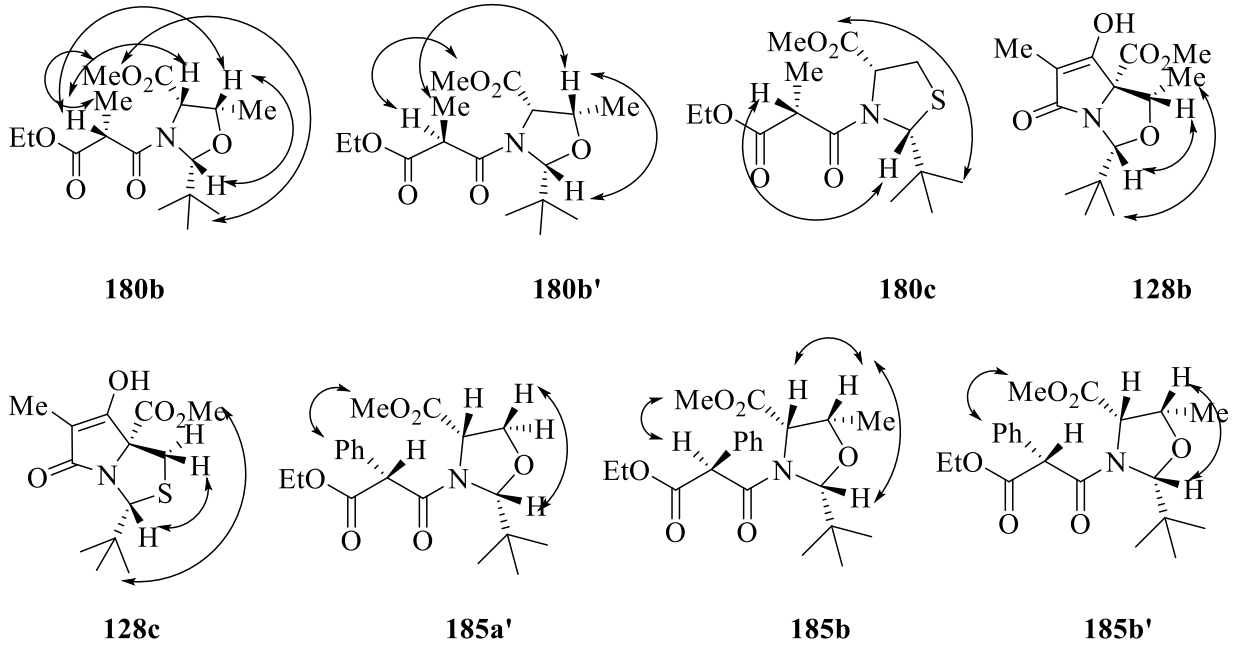


Figure C.1: NOE correlations for compounds in Chapter 2

NOE Correlations for Compounds in Chapter 3:



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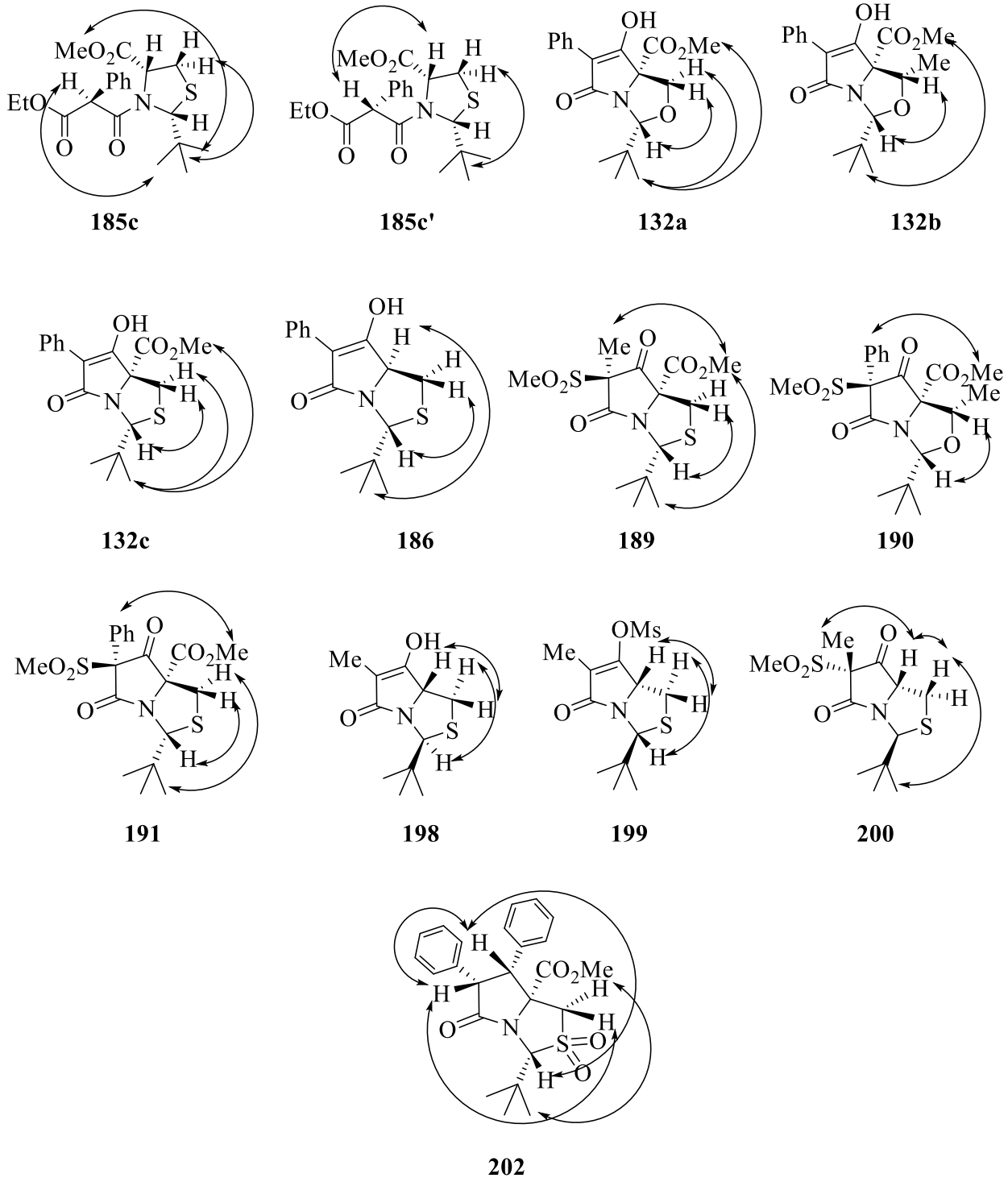

Figure C.2: NOE correlations for compounds in Chapter 3

NOE Correlations for Compounds in Chapter 4:

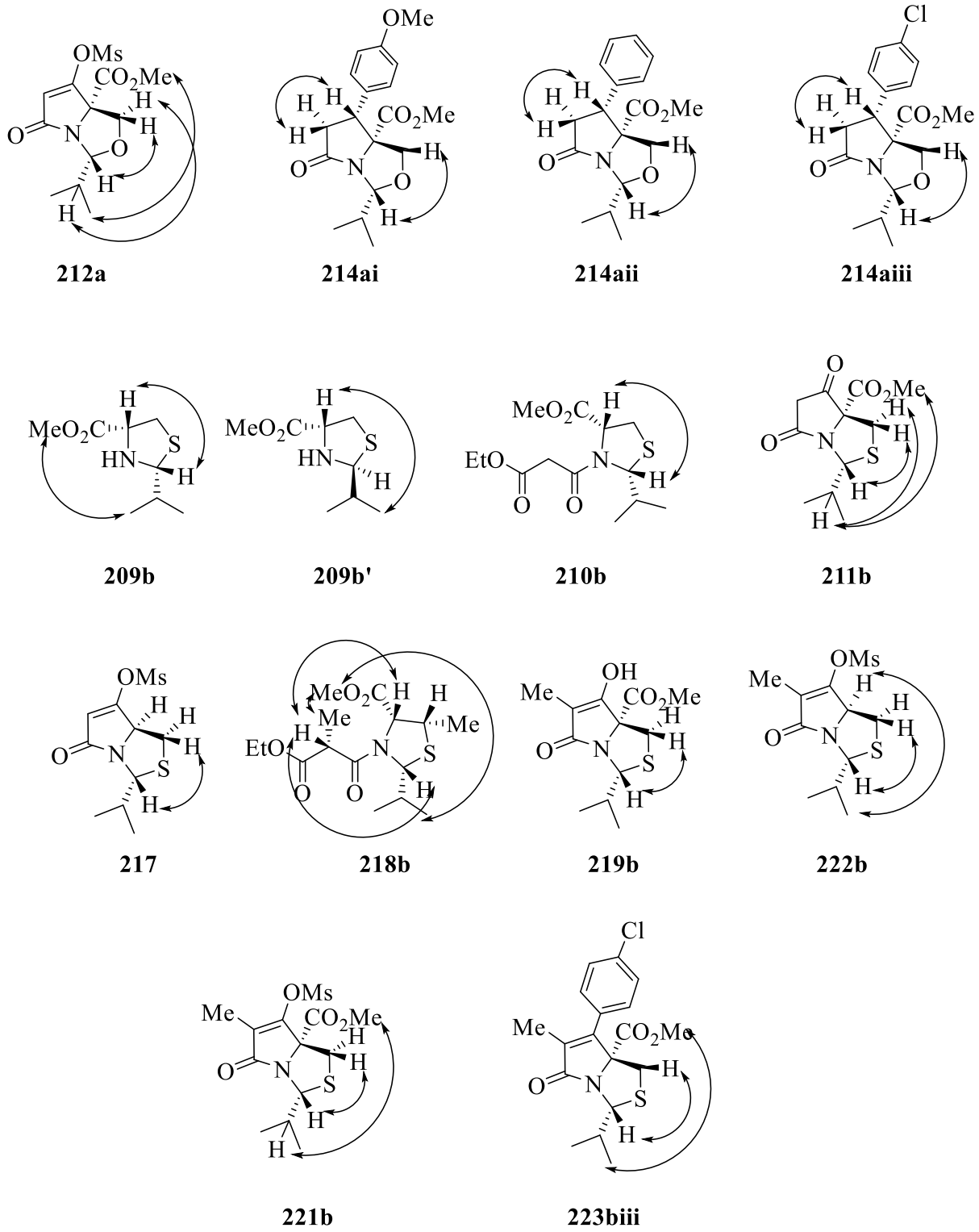

Figure C.3: NOE correlations for compounds in Chapter 4

APPENDIX D: TEST METHOD FOR BIOASSAY

Screening of novel compounds was performed against selected multidrug-resistant pathogens by Oxford Antibiotic Group, Austria. The compounds were tested in a primary 96 well plates screening assay, according to SOP 0906. The compounds were diluted in “MHB” for bacterial screening to a stock solution of 1000µg/mL, serial diluted and overlaid with a microbe solution in a concentration of 10^4 CFU/mL. The plates were incubated at 35°C for 24 hours.

MIC values were assessed by visual inspection of optical density, with complete bacterial lysis inhibition by a clear saturation of the solution.