

Studies Towards and Total Synthesis of Pyrrolidinone Containing Natural Products

Léo B. Marx

Somerville College, University of Oxford

2014

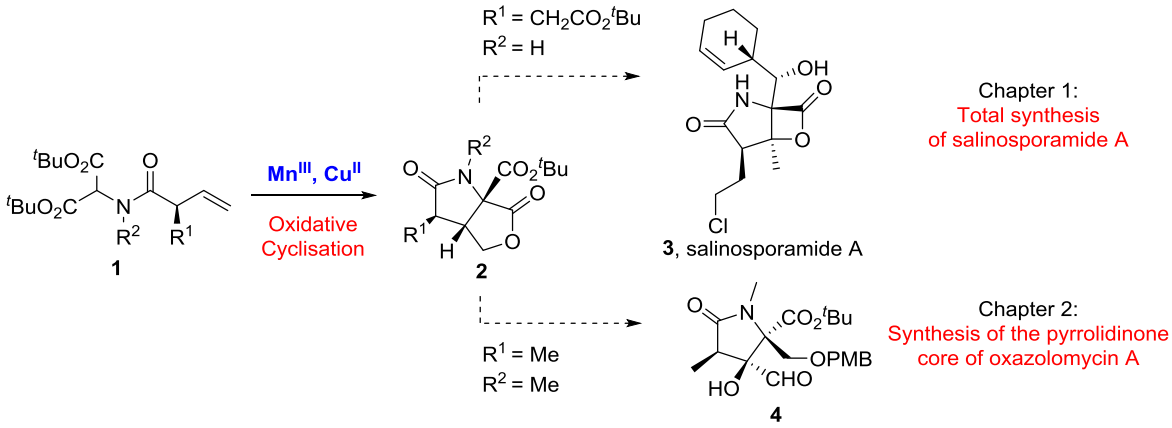
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

À la mémoire de ma grand-mère Monique Marx,

(In the memory of my grandmother Monique Marx)

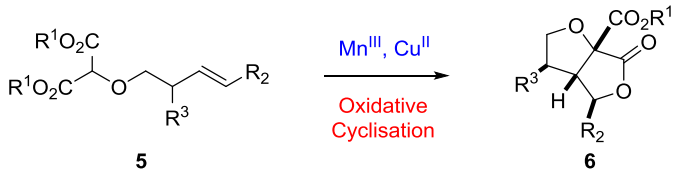
Abstract

Chapters 1 and **2** of this thesis focus on the application manganese(III) and copper(II)-mediated oxidative radical cyclisation of alkenyl amidomalonates **1** to the formation of pyrrolidinone-lactones **2** and their subsequent use in the total syntheses of highly bioactive pyrrolidinone-lactone containing natural products (**Scheme 1**). A novel concise total synthesis of (-)-salinosporamide A **3** based on the oxidative cyclisation previously developed in the group is presented in **chapter 1**. The second chapter discusses the work towards the pyrrolidinone core of the oxazolomycin family, which includes the synthesis of the advanced intermediate **4**. Each chapter contains its own introduction to set in context the presented results, which discusses the isolation and the biological activity of the two families of natural products. Previous synthetic work toward salinosporamide A and the oxazolomycin family achieved in the group and reported in the literature is also described in the introduction of each chapter.



Scheme 1 Synthetic work presented in chapter 1 and 2

The third chapter of the thesis succinctly presents the extension of the scope of the manganese(III) and copper(II)-mediated oxidative radical cyclisation reaction (**Scheme 2**). The optimisation, development and scope of the rapid access to fused THF-lactones **6** via the cyclisation of alkenyl oxymalonates **5** is described. Preliminary synthetic manipulations of the resultant bicyclic products **6** to study the application possibilities of the new reaction in future complex molecules syntheses are also presented.



Scheme 2 Extension of the scope of the manganese(III) and copper(II) cyclisation methodology in chapter 3

The final conclusion gives a summary of the results obtained and introduces the proposed future work that may arise from these three areas.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative work.

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Leo B. Marx

October 2014

Acknowledgements

I am very grateful to “The Robert Robinson University Trust Fund”, the EPSRC and Somerville College for having covered research and life expenses for the preparation of this D.Phil. thesis.

I would like to say “un grand merci” to my supervisor, Pr Jonathan Burton for having given me the opportunity to work in his research group and for having identified generous sources of funding. Additionally, I thank him for the enthusiastic educational and intellectual support he has given; along with his careful attention and valuable advice he provided during my D.Phil. studies. Pr Jonathan Burton also deserves a great acknowledgment for his fantastic macaroons and his remarkably tasty Burgundy beef.

I am also very grateful to Dr Emmanuel Demont (GSK), Mr Rino Bit (GSK) and Pr Serge Neunlist (University of Upper Alsace), who supported my application at the University of Oxford.

I would also like to thank Dr Anne-Caroline Chany, Dr Angus Logan, Sandra Ainsua Martinez and David Shepherd for patiently proof reading this thesis. It has been very pleasant to do chemistry in the Burton group and I am grateful to all my past and present lab mates for having created a stimulating and enjoyable working atmosphere. David, Anne-Caroline, Gus, Ling, Steven, Sandra, Wilfried, Bryony, James, Mareike, Ali, Hannah, Rhodri, Katie, Dave, Emma, Adam, Sania and Michael will only leave me good memories of these three years of intense work.

I would like to thank my Mum, Dad, Brother and Sister for all the good feelings they have shown during my time in Oxford. I particularly thank my brother Martin for all the administrative work he has done in my home country.

I finally thank Luana for strong love, attention and great support during my last two years in Oxford.

Contents

1 Total Synthesis of Salinosporamide A 1

1.1 Isolation of salinosporamide A 1

1.2 Biological activity 2

1.3 Proposed biosynthesis 4

1.4 Previous total syntheses of salinosporamide A and analogues 6

1.5 Aims and synthetic strategy 20

1.6 Problematic formation of amidomalonates 23

1.7 Alkenyl amidomalonate preparation and cyclisation 29

1.8 Lactone opening method with an equivalent of sodium phenyl selenide 31

1.9 Second generation route toward the cyclised pyrrolidinone-lactone 37

1.10 Reduction of carboxylic acid (+)-1.194 and subsequent alkene formation 43

1.11 Exploration of lactonisation possibilities 45

1.12 *tert*-Butyl ester alternatives 50

1.13 Acid carboxylic re-protection 51

1.14 Reductive cleavage of the phenyl selenium moiety 52

1.15 Oxidation, followed by the installation of the last stereocentres 52

1.16 PMB ester route 55

1.17 Final steps 57

1.18 NMR and characterisations 58

1.19 Summary and Conclusion 61

2 Studies Towards the Oxazolomycin Family 63

2.1 Introduction to the oxazolomycin family 63

2.2 Synthetic strategy and previous work in the Burton group 81

2.3 Asymmetric synthesis of alkenyl malonate 2.141 86

2.4 Oxidative radical cyclisation 91

2.5 Optimisation of the other steps 92

2.6 Further steps towards the core of oxazolomycin A 93

2.7 Preliminary studies on the installation of the side chain 107

2.8 Summary and conclusion 108

3 Extension of the Oxidative Cyclisation: Formation of Fused THF-Lactones 111

3.2 Experimental studies 113

4 General conclusion and future work 119

5 Experimental section 121

5.1 General Remarks 121

5.2 General procedures 122

5.3 Synthesis and compounds characterisation 123

6 References 217

7 Appendix 223

7.1 Selected spectra and HPLC traces 223

7.2 Selected results of ^{1}H NMR nOe and NOESY experiments 235

Selected abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
Ar	aryl
aq	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
Bop-Cl	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
b.p.	boiling point
BSA	bis(trimethylsilyl)acetamide
CAN	ceric ammonium nitrate
cat	catalytic
CbZ	carboxybenzyl
CHA	cyclohexenyl alanine
CoA	coenzyme A
COSY	correlation spectroscopy
d	day(s)
DBAD	dibenzyl azodicarboxylate
DBB	di-*tert*-butylbiphenyl
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DiBAl-H	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DiPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethylpyridin-4-amine
DME	dimethoxyethane

DMF	dimethyl formamide
DMS	dimethyl sulphide
DMP	Dess–Martin periodinane
DMPU	*N*,*N'*-dimethylpropylene urea
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	equivalent
ESI	electrospray ionisation
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
FC	flash chromatography
FI	field ionisation
FID	free induction decay
Fmoc	fluorenylmethyloxycarbonyl
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
IBX	2-iodoxybenzoic acid
IPA	isopropyl alcohol
IR	infrared
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
MEM	β-methoxyethoxymethyl ether
MOM	methoxymethyl ether
MS	mass spectroscopy, molecular sieves

min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NEM	4-*N*-ethylmorpholine
NIS	*N*-iodosuccinimide
NMI (4-NMI)	4-methylimidazole
NMO	*N*-methylmorpholine N-oxide
NMP	*N*-methyl-2-pyrrollidinone
NMR	nuclear magnetic resonance
nOe	nuclear overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PCP	peptidyl carrier protein
PE	petroleum ether b.p. 40–60 ° C
PE_{30-40}	petroleum ether b.p. 30–40 ° C
Ph	phenyl
PMB	para-methoxybenzyl
Piv	pivaloyl
PPY (or 4-PPY)	4-pyrrolidinopyridine
Py	pyridine
R_f	retention factor
RT	room temperature
SAM	S-adenosylmethionine
SAR	structure activity relationship
sat	saturated
SET	single electron transfer
T3P^{TM}	propylphosphonic anhydride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

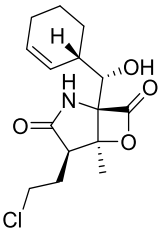
THF	tetrahydrofuran
THP	tetrahydropyranyl
Thr	threonine
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	4-methylbenzenesulfonyl
Tyr	tyrosine
UV	ultraviolet

1 Total Synthesis of Salinosporamide A

1.1 Isolation of salinosporamide A

Soil derived actinomycetes have been a very important source of naturally occurring microbial antibiotics,[1] and the effort to isolate new strains of widely distributed marine actinomycetes led to the discovery of salinosporamide A (**Figure 1.1**). The natural product was first discovered by Paul R. Jensen, and William Fenical as a bioactive metabolite of a marine bacterium of the genus *Salinospora tropica,*[2] which is part of the actinomycete group of bacteria. The strain CNB-392 of *Salinospora* bacteria was isolated from heat treated marine sediment of a mangrove environment in Chub Cay, the Bahamas. Crude extracts of the bacteria exhibited high cytotoxicity (see section **1.2**). Hence, the purification of these extracts was achieved by cytotoxicity-guided flash column chromatography followed by re-crystallisation, which gave (-)-salinosporamide A **(-)-1.1**.

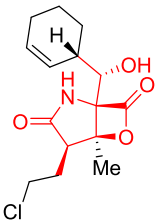
The molecular formula of salinosporamide A was obtained by HRMS experiments and the structure was solved by IR and extensive NMR experiments including the results of COSY, HMQC, and HMBC spectroscopy. X-ray crystallography confirmed the structure of the natural product and allowed the assignment of its absolute configuration.[2]



(-)-1.1, salinosporamide A

Figure 1.1 Structure of (-)-salinosporamide A

The structure of salinosporamide A is remarkably closed to the previously known proteasome inhibitor omuralide **(-)-1.2**. The two molecules display the same cis fused *γ*-lactam-β-lactone bicyclic core (**Figure 1.2**). Salinosporamide A bears a methyl group in place of a hydrogen atom at the junction of the two rings, and a cyclohexene group ring at the position of the *iso*-propyl group in omuralide. The four shared stereocentres of the two natural products have the same absolute configuration.



(-)-1.1, salinosporamide A



(-)-1.2, omuralide

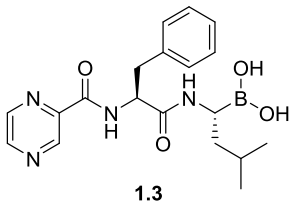
Figure 1.2 Structures of salinosporamide A and omuralide

In terms of biological activity, the presence of the chlorine atom on the structure of salinosporamide A gives the molecule a mechanistic advantage compared to the known proteasome inhibitor omuralide **(-)-1.2**. The extended mode of proteasome inhibition exhibited by salinosporamide A is presented in the next section.

1.2 Biological activity

The development of new anti-cancer therapies based on proteasome inhibition strategy has attracted considerable attention over the past decades.[3] The proteasome is a complex molecular machine that degrades and recycles denatured proteins. Polyubiquitination of denatured proteins is achieved by a series of kinases to signal degradation to the proteasome.[4] A protein needs to be marked with at least four ubiquitin units to be recognised by the proteasome.[5] As the proteasome plays an important role in most cellular process, it was questioned whether it would make a viable target to fight malignancies. The approach was reasonable as high proteasome activity is observed in cancer cells compared with healthy cells.[6]

The first proteasome inhibitor Bortezomib **1.3** (Velcade,™ **Figure 1.3**) was approved in the US in 2003 and in the EU in 2004.[7] US sales of Velcade™ for the year ending in October 2012, were $740 million mostly for the treatment of multiple myeloma. Adverse side effects associated with the molecule include peripheral neuropathy (nerve damages) in 30% of patients.[8]



1.3

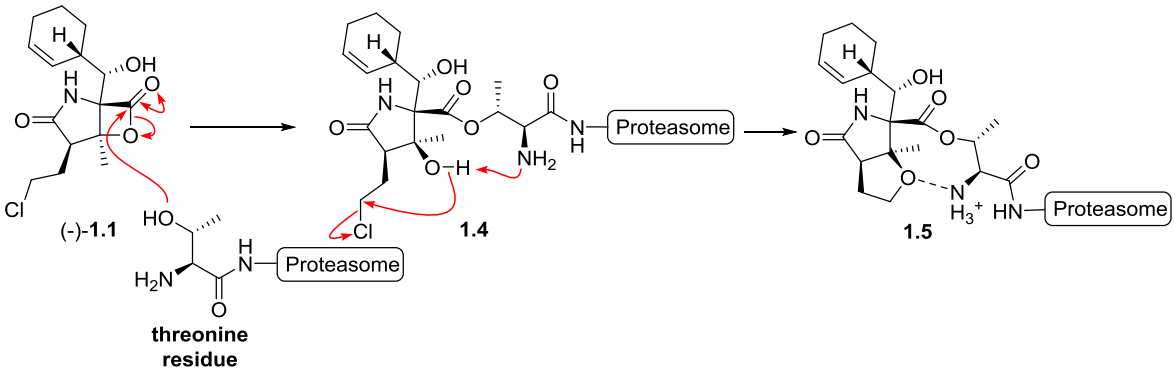
Figure 1.3 Bortezomib

As salinosporamide A displays the fused γ-lactam-β-lactone bicyclic core of omuralide **(-)-1.2**, which is a specific inhibitor of the 20S subunit of the proteasome, its activity was also tested against the 20S proteasome. Salinosporamide A was found to be 35 times more potent than omuralide **(-)-1.2** with an IC_{50} = 1.3 nmol.L^{-1} against this target.[2] Further tests showed that salinosporamide A displayed its highest cytotoxic properties against NCI-H226 non-small cell lung cancer, SF-539 CNS cancer, SK-MEL-

28 melanoma and MDA-MB-435 breast cancer (all IC_{50} < 10 ng.mL^{-1}) and HCT-116 human colon carcinoma (IC_{50} = 11 ng.mL^{-1}).[2]

Salinosporamide A (branded as Marizomib™ by Nereus Pharmaceuticals) is currently undergoing phase I clinical trials in patients with relapsed or relapsed/refractory multiple myeloma. Three other phase I clinical trials of Marizomib™ alone or in combination have been completed involving patients with non-small cell lung cancer, pancreatic cancer, melanoma, lymphoma, multiple myeloma, advanced malignancies and lymphomas.[9]

As with omuralide (-)-**1.2**, the β-lactone ring of salinosporamide A covalently binds to the N-terminus threonine residue in the binding pocket of the targeted 20S subunit of the proteasome. The relative rise in the affinity for the proteasome compared to omuralide **(-)-1.2**, may come from the ability of salinosporamide A to irreversibly form a THF ring **1.5** in the binding pocket of the receptor. The binding process starts with opening of the β-lactone ring by the threonine residue of the proteasome and is followed by intramolecular nucleophilic substitution of the chloride carried by the alcohol **1.4** (**Scheme 1.1**). This original mode of action was first postulated by Potts *et al.*[10]



Scheme 1.1 Covalent binding of salinosporamide A to the threonine residue, and subsequent THF formation catalysed by the N-terminal amine

X-ray studies have demonstrated the existence of the THF ring **1.5** in the binding pocket of the protein. The comparison of the activity of salinosporamide A with iodinated, brominated and de-halogenated analogues is consistent with this covalent binding mechanism.[11] **Figure 1.4** gives the key contact between the covalently bonded form **1.5** of (-)-salinosporamide A and the binding pocket of the 20S subunit of the proteasome inhibitor.[11]

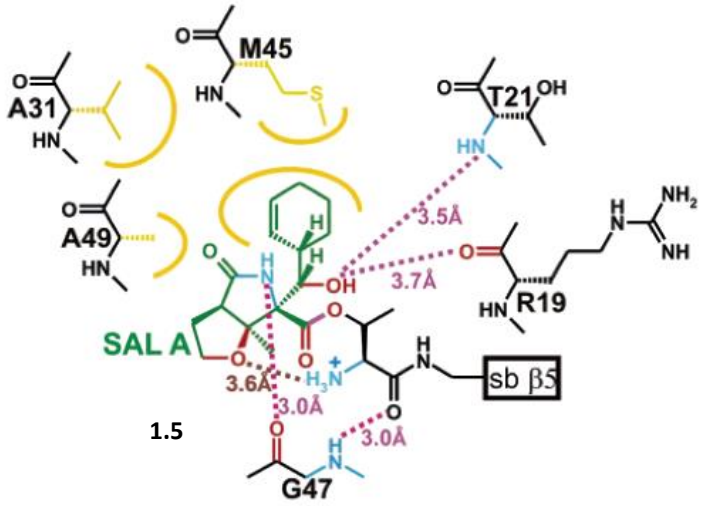
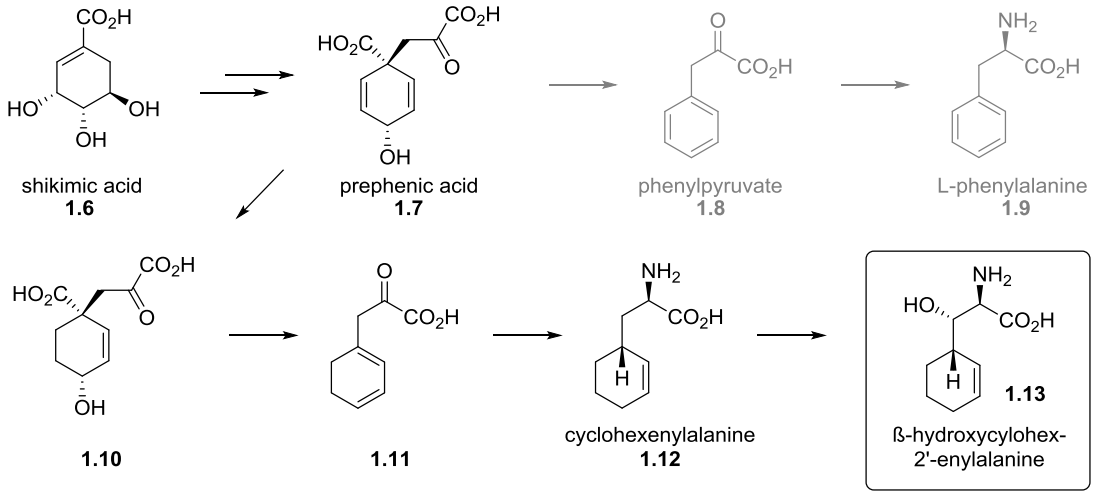


Figure 1.4 Key contacts between amino acids of the ligand binding site of the 20S proteasome core particle and the covalently bonded salinosporamide A unit 1.5.[11] Reprinted with permission from Groll, M.; Huber, R.; Potts, B. C. M. *J. Am. Chem. Soc.* 2006, *128*, 5136. Copyright 2014 American Chemical Society.

1.3 Proposed biosynthesis

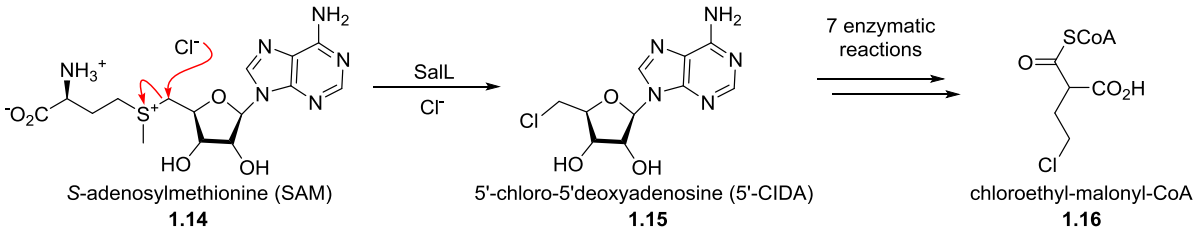
The study of an amplified sequence of a clone of the *sal* cluster of *Salinospora Tropica* strain CNB-440 led to the identification of 19 secondary metabolic gene clusters,[12] which were key in the elucidation of the different steps of the biosynthesis of salinosporamide A.

The study of the biosynthesis of salinosporamide A led to the interesting discovery of a novel non-proteinogenic amino acid residue **1.13** (β-hydroxycylohex-2'-enylalanine, **Scheme 1.2**).[13] The biosynthesis of the novel amino acid **1.13** would proceed *via* a shunt at the prephenic acid stage **1.7** of L-phenylalanine **1.9** amino acid biosynthesis. The pathway toward cyclohexenylalanine **1.12** was elucidated by studies of ^{13}C-labeled intermediates in *Salinospora tropica* strain CNB-476.[13] Bioinformatic analysis of the 41-kD salinosporamide gene cluster also displayed genes involved in the synthesis of cyclohexenylalanine **1.12** *via* the presumed shunt at the stage of prephenic acid **1.7**.[12] The first deviated step would be a reduction of **1.7** followed by a decarboxylative dehydration to give the corresponding diene **1.11**. Further reduction and amination would provide cyclohexenylalanine **1.7**, which would be oxidised to β-hydroxycyclohexenylalanine **1.13**.



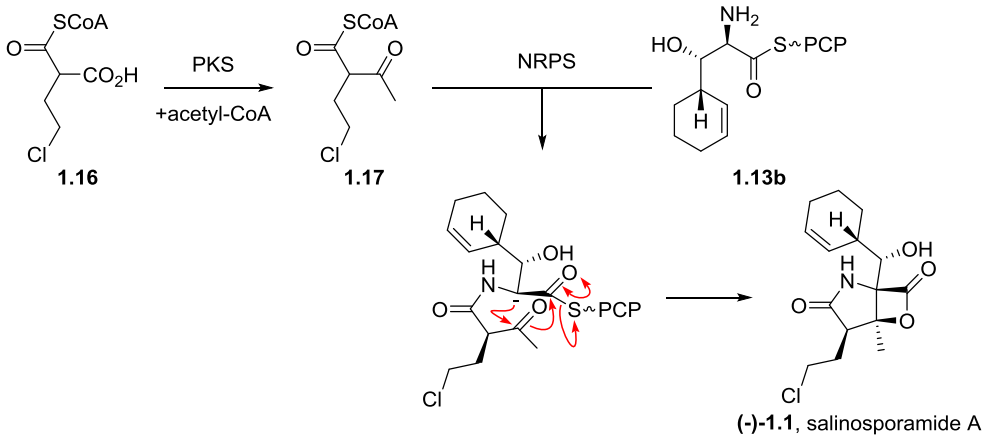
Scheme 1.2 Proposed biosynthesis of β-hydroxycylohex-2'-enylalanine via a shunt in the phenylalanine biosynthetic pathway.

The biosynthesis of the other main fragment chloroethylmalonyl-coenzyme A **1.16** of salinosporamide A has also been elucidated[14] using the analysis of the *sal* gene cluster. The substitution reaction on SAM **1.14** with a chloride anion occurs at a very early stage to give 5'-CIDA **1.15** (**Scheme 1.3**). A seven step sequence of enzymatic reactions would then transforms 5'-CIDA **1.15** into chloroethyl-malonyl-CoA **1.16**.[15]



Scheme 1.3 Biosynthesis of chloroethyl malonyl-CoA 1.16

Before the final assembly, 4-chloroethyl-malonyl-CoA **1.16** would undergo a condensation with acetyl-CoA (**Scheme 1.4**), which involves a polyketide synthase.[13] The new amino acid **1.13** would be transported by a peptidyl carrier protein (PCP) **1.13b** and the condensation with **1.17** would be achieved by a non-ribosomal peptide synthetase before final lactonisation, which would give salinosporamide A.



Scheme 1.4 Final assembly of salinosporamide A in the presumed biosynthetic pathway

The elucidation of *Salinospora tropica* genome sequence and the progress achieved in the understanding of the biosynthesis of salinosporamide A have paved the way for the engineered biosyntheses of salinosporamide A and highly potent analogues such as antiprotealide **1.18**.[16]

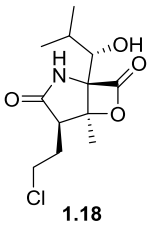


Figure 1.5 Antiprotealide, an omuralide-salinosporamide hybrid potent proteasome inhibitor

The promising biological activity of salinosporamide A has not only encouraged research in bio-engineering synthesis. The possibility of accessing salinosporamide A and its analogues by total synthesis has attracted the interest of many synthetic research groups.

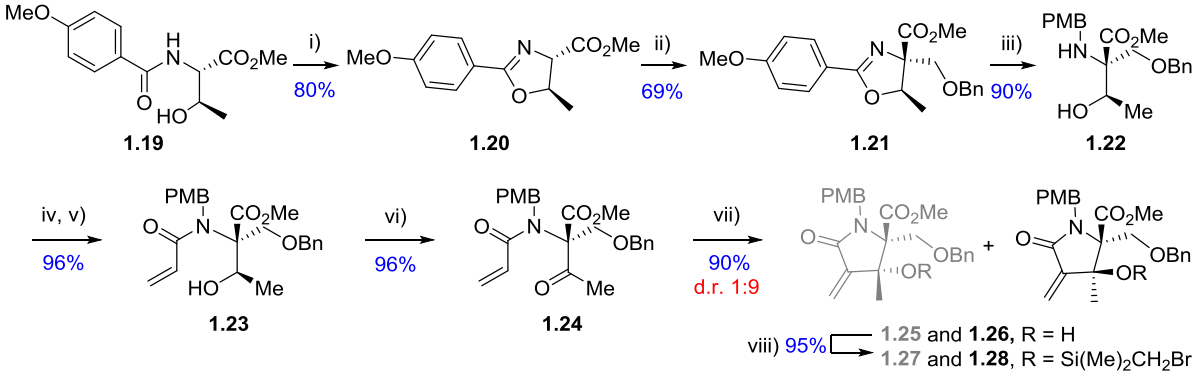
1.4 Previous total syntheses of salinosporamide A and analogues

The five contiguous tertiary, tertiary, quaternary, quaternary, tertiary stereocentres carried by the *cis* fused β-lactone-γ-lactam ring offers a challenging stereochemical array to synthetic chemists. A number of total syntheses of (-) and (±)-salinosporamide A have been reported. The synthesis of structurally related products such as omuralide **(-)-1.2** also raised considerable synthetic efforts. The need for new routes to deliver (-)-salinosporamide A remains important. Reported engineered biosynthesis yields the compound in moderate concentration (1 mg.L^{-1}) and requires further development.[16] New synthetic routes also offer handles for chemical diversification to further optimise biological and physical properties of the molecule. A total synthesis of omuralide**(-)-1.2**, has for example, been designed by Donohoe *et al.*[17] to introduce diversification at the position of the methyl group. The syntheses of (±) and (-)-salinosporamide A developed by Romo,[18,19] also allowed the delivery of active analogues such as (±)-cinnabaramide A (section **1.4.3**). Among the numerous

total syntheses of (-)-salinosporamide A, three syntheses are detailed in this introduction. The work of Corey and Reddy[20] has been selected as this is the first total synthesis of the natural product, which remains very efficient. The route developed by Danishefsky[21] is then presented in the introduction, as this work has motivated the Burton group in the use of fused γ-lactam-γ-lactones as key intermediates in the total synthesis presented in this thesis. The very short sequence to (-)-salinosporamide developed by Romo[18,19] has been selected and included in the introduction for its efficient biomimetic approach. The key steps of the other enantioselective syntheses of the natural product are described after the complete presentation of these 3 total syntheses.

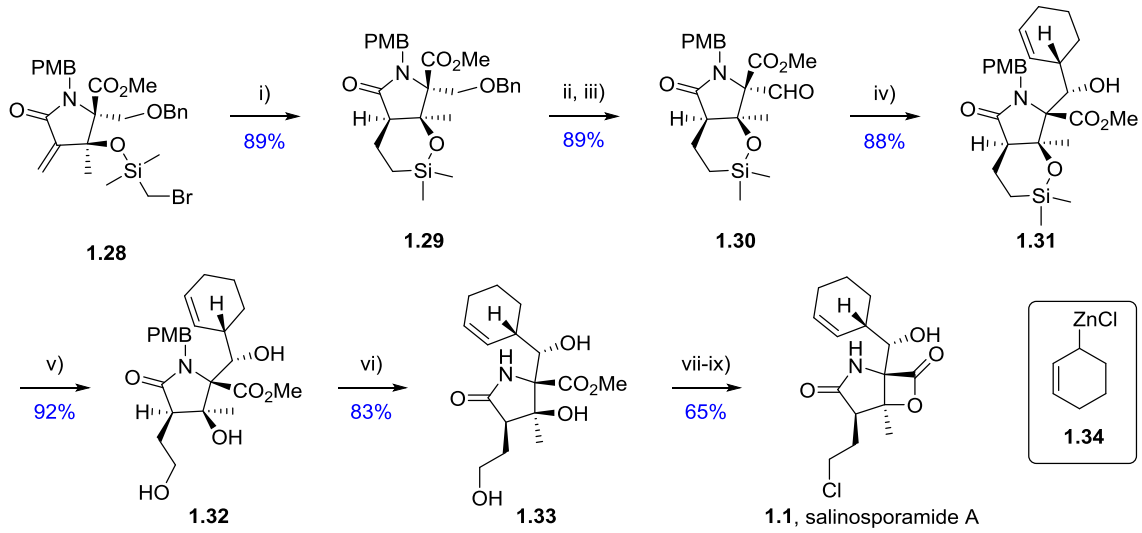
1.4.1 **Corey's total synthesis of (-)-salinosporamide A**

The first total synthesis of salinosporamide A was reported in 2004 by Corey and Reddy.[20] It is still one of the most concise asymmetric syntheses of the natural product, which was synthesised in 18 steps from (*S*)-threonine (**Scheme 1.5**). The protected (*S*)-threonine **1.19** was first cyclised to oxazoline **1.20** with *p*-TsOH. Subsequent deprotonation with LDA and alkylation, with chloromethyl benzyl ether approaching from the least hindered face of the enolate derived from **1.20,** gave the first quaternary stereocentre of oxazoline **1.21** stereoselectively. The PMB protected amine **1.22** was obtained by reduction of the oxazoline **1.21** with $NaBH_3CN$. After protection of the alcohol **1.22** with TMSCl, the amide coupling between the PMB amine **1.22** and acryloyl chloride followed by an acidic aqueous work-up, gave the acryl amide **1.23**. The hydroxy group of the latter was oxidised with DMP to form the ketone **1.24**. The subsequent intramolecular Baylis-Hillman reaction promoted by quinuclidine gave the mixture of products **1.25** and **1.26** in good yield and 1:9 d.r. at the formed quaternary centre. The first step after the cyclisation was a silylation reaction of the diasteromeric mixture of alcohol **1.25** and **1.26**, which gave the silyl ether **1.28** obtained as a single diastereoisomer after flash chromatography purification of the diasteromeric mixture of **1.27** and **1.28**.



Scheme 1.5 First steps of Corey's total synthesis of (-)-salinosporamide A[20]
Reagents and conditions i) *p*-TsOH, reflux, 12 h; ii) LDA, THF/HMPA, -78 °C, $ClCH_2OBn$, 4 h; iii) $NaBH_3CN$, AcOH, 40 °C, 12 h; iv) TMSCl, Et_2O, 23°C, 12 h; v) Acryloyl chloride, *i*-Pr_2NEt, DCM, 1 h, 0 °C then aq. HCl, Et_2O, 23 °C, 1 h; vi) DMP, 23 °C, 1 h; vii) Quinuclidine, DME, 0 °C, 30 min; viii) $BrCH_2SiMe_2Cl$, Et_3N, DMAP, DCM, 0 °C, 30 min.

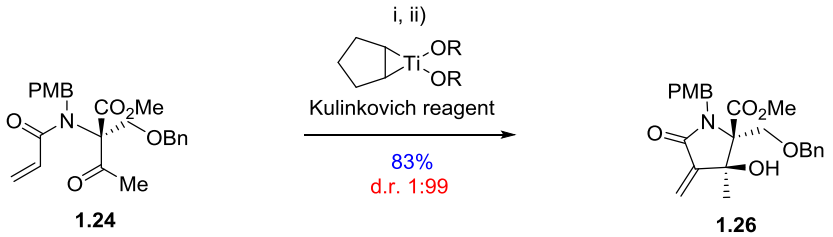
A 6-*endo* trig radical cyclisation was then performed with *n*-Bu_3SnH,[22] which installed another tertiary stereocentre on pyrrolidinone **1.29** (**Scheme 1.6**). Hydrogenolysis of the benzyl ether and the oxidation of the resultant alcohol with DMP gave the aldehyde **1.30**. The addition of the cyclohexenyl organozinc **1.34** into the aldehyde installed the last stereocentre of lactam **1.31** with a 20:1 d.r. A Tamao-Fleming oxidation of **1.31** gave triol **1.32**, and the PMB group protecting the lactam ring was removed with CAN to give **1.33**. After saponification of the methyl ester **1.33**, β-lactonisation of the corresponding triol acid was achieved with BOP-Cl, and the residual primary alcohol was chlorinated to give salinosporamide A in a 9.8% overall yield over an 18 step sequence starting from the natural amino acid (*S*)-threonine.



Scheme 1.6 Final steps of Corey's synthesis of (-)-salinosporamide A[20]

Reagents and conditions i) *n*-Bu_3SnH, AIBN, benzene, reflux, 8 h; ii) Pd-C, EtOH, H_2 (1 atm), 18 h; iii) DMP, 23 °C, 1 h; iv) **1.34**, THF, -78 °C, 5 h; v) KF, $KHCO_3$, H_2O_2, THF/MeOH (1:1), 23 °C, 18 h; vi) CAN, $MeCN/H_2O$ (3:1), 0 °C, 1 h, 83%; vii) 3.0 M aq. LiOH/THF (3:1), 5 °C, 4 days; viii) BOPCl, pyridine, DCM, 23 °C, 1 h; ix) Ph_3PCl_2, MeCN, pyridine, 23 °C, 1 h.

A year later Corey *et al.*[23] reported a quicker and more selective one pot procedure for the cyclisation of **1.24,** which involved the use of Kulinkovich reagent[24] formed by reaction of Ti(*i*-PrO)$_4$ with cyclopentylmagnesium chloride to give the corresponding cyclised α-titanamethyl species. Subsequent treatment with iodine, gave the corresponding α-iodomethyl, which underwent elimination to **1.26** after further treatment with NEt_3 in the same pot.

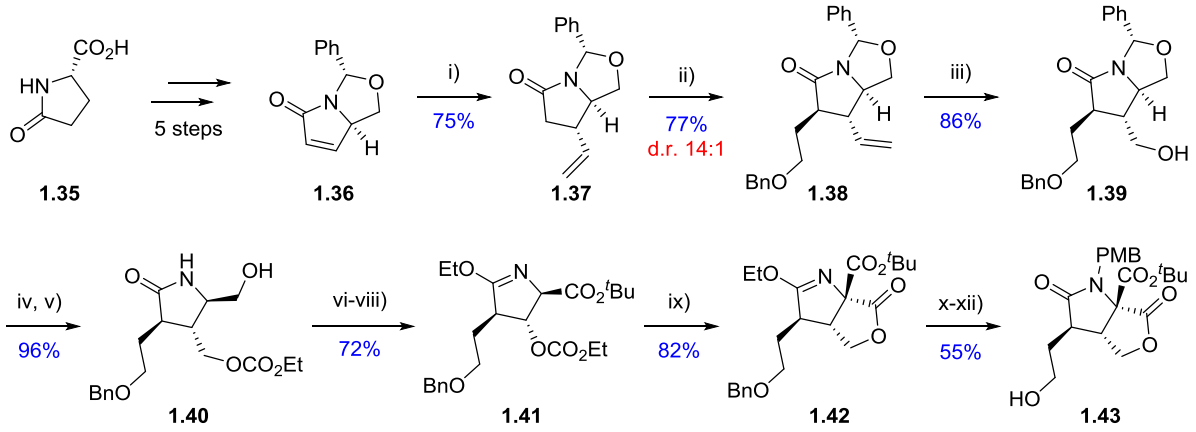


Scheme 1.7 More selective one pot cyclisation of 1.24[23]

Reagents and condition i) Ti(O*i*-Pr)$_4$ (4.0 eq), c-C_5H_9MgCl (7.0 eq), -40 °C, 30 min; then I_2, (5.0 eq), 2 h at -40 °C, 2 h at 0 °C; ii) NEt_3, RT, 30 min.

1.4.2 **Danishefsky's total synthesis of (-)-salinosporamide A**

Danishefsky disclosed his total synthesis[21] shortly after Corey. The synthesis starts from bicyclic enamide **1.36**, which can be reached in 5 known steps from pyroglutamic acid **1.35**.[25] The first step is a conjugate addition of divinyl cuprate to the convex face of the bicyclic lactam **1.36**, which gave the alkylated lactam **1.37** and installed a new stereocentre (**Scheme 1.8**). After deprotonation of lactam **1.37** with LDA, alkylation of the corresponding enolate with the required alkyl iodide approaching on the opposite face of the vinyl group, installed the side chain of **1.38** with a 14:1 d.r. Ozonolysis of the alkene **1.38** followed by a reductive work-up gave the alcohol **1.39**. The subsequent acylation of **1.39** to the corresponding ethyl carbonate, followed by hydrolysis of the *N'O*-acetal gave the hydroxymethyl substituted lactam-alcohol **1.40**. After oxidation of **1.40** to the corresponding acid carboxylic and subsequent esterification, the treatment of the resulting lactam-ester with Meerwein's reagent gave imidate **1.41**. Deprotonation of the imidate **1.41** with LiHMDS formed the lactone **1.42** and installed the first quaternary stereocentre of the molecule. The lactam functionality was then restored by an aqueous acidic treatment of imidate **1.42**. The PMB protection of the nitrogen atom of the resulting lactam and the subsequent benzyl ether hydrogenolysis provided the intermediate alcohol **1.43**.

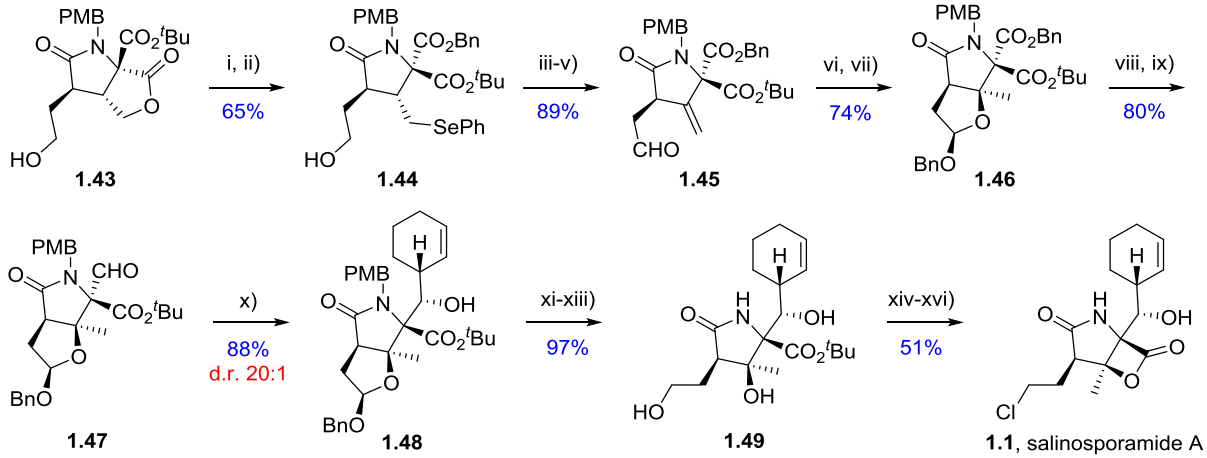


Scheme 1.8 First steps of Danishefsky's synthesis of (-)-salinosporamide A[21]

Reagents and conditions i) Vinylmagnesium bromide, TMSCl, CuI, THF, -78 °C; ii) $BnOCH_2CH_2I$, LDA, RT; iii) O_3, DCM/MeOH (3:1), -78 °C then $NaBH_4$, 0 °C; iv) $ClCO_2Et$, pyridine, RT; v) TfOH, THF/H_2O (9:1), RT; vi) Jones reagent, acetone, RT; vii) $Me_2NCH(O^tBu)_2$, PhMe, reflux; viii) Et_3OBF_4, K_2CO_3, DCM, RT; ix) LiHMDS, THF, -20 °C; x) aq. 1.0 M HCl and THF, 0 °C; xi) PMBCl, NaH, DMF, RT; xii) $Pd(OH)_2/C$, H_2, EtOH, RT.

The opening of the lactone **1.43** with an equivalent of the phenyl selenide anion followed by the benzylation of the so formed carboxylic acid gave the pyrrolidinone **1.44** that carries two differentiated esters (**Scheme 1.9**). The oxidative elimination of the phenyl selenium unit of **1.44** and the subsequent Dess-Martin oxidation gave the aldehyde **1.45**. The acetalisation of the aldehyde **1.45** with PhSeBr and $AgBF_4$ in the presence of benzyl alcohol followed by radical deselenylation gave the cyclic acetal **1.46**. The reduction of the benzyl ester of **1.46** followed by the Dess-Martin

oxidation of the corresponding alcohol generated the aldehyde **1.47**. The subsequent addition of the cyclohexenyl organozinc reagent **1.34** to the aldehyde **1.47** gave the alcohol **1.48** in high d.r. (> 20:1) and installed the last two stereocentres. The PMB group of the lactam **1.48** was then cleaved with CAN and the benzyl acetal group was opened under reductive conditions. The cleavage of the *tert*-butyl ester of the resulting lactam **1.49** was achieved with BCl_3, and the residual carboxylic acid was then subjected to the final lactonisation-chlorination sequence to give salinosporamide A.



Scheme 1.9 Late steps of Danishefsky and Endo's synthesis of (-)-salinosporamide A[21]

Reagents and conditions i) $(PhSe)_2$, $NaBH_4$, EtOH, 60 °C; ii) BnBr, K_2CO_3, DMF, RT; iii) 30% aq. H_2O_2, THF, RT; iv) Selenoxide heated in PhMe, 100 °C; v) DMP, DCM, RT; vi) PhSeBr, $AgBF_4$, BnOH, DCM, -20 to 0 °C; vii) AIBN, *n*-Bu_3SnH, PhMe, 100 °C; viii) $NaBH_4$, THF/EtOH (3:1), RT; ix) DMP, DCM, RT; x) Organozinc reagent **1.34**, THF, -78 °C, xi) CAN, MeCN/H_2O; xii) Na, liq. NH_3, -78 °C; xiii) $NaBH_4$, THF/H_2O (2:1), RT; xiv) BCl_3, DCM, 0 °C; xv) BOPCl, NEt_3, DCM, RT; xvi) Ph_3PCl_2, pyridine, MeCN, RT.

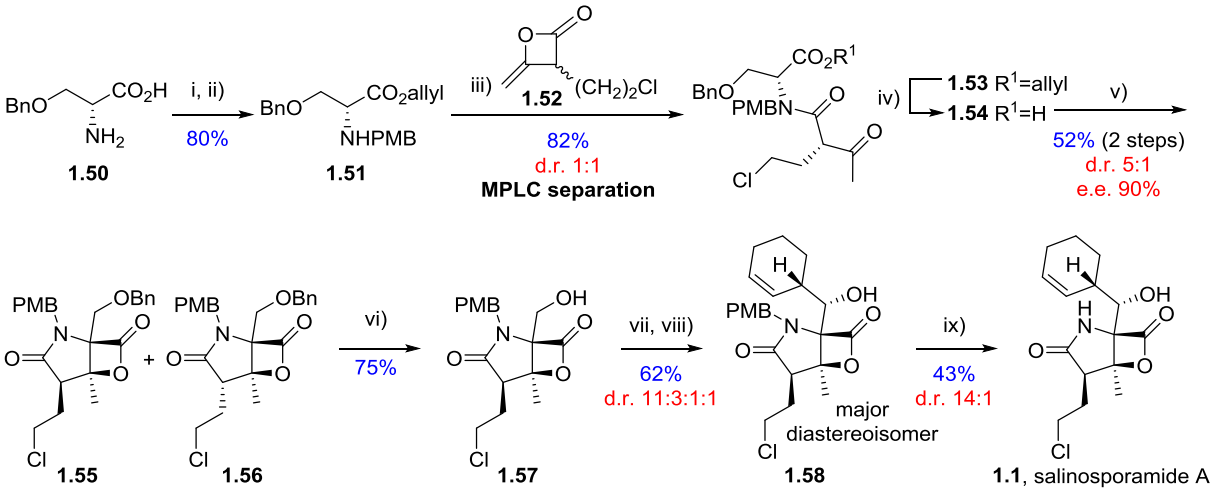
Danishefsky and Endo group achieved the total synthesis of (-)-salinosporamide A in 33 steps with and 1.8% overall yield, from (2*S*)-pyroglutamic acid.

1.4.3 **Romo's biomimetic synthesis of (-)-salinosporamide A**

The Romo group first reported a very concise total synthesis of (±)-salinosporamide A,[18] which was inspired by the biosynthesis of the natural product. A synthesis of enantiopure (-)-salinosporamide A based on the same strategy was later reported by the same group.[19]

The enantioselective synthesis starts with the coupling of N-PMB serine allyl ester **1.51** (made in two steps from benzyl serine **1.50)**, with the heteroketene dimer **1.52** prepared by heterodimerisation of acetyl chloride and 4-chlorobutanoyl chloride (**Scheme 1.10**). After MPLC separation of the 1:1 mixture of diastereoisomers of esters, the Pd-mediated deprotection of the single ester **1.53** gave the acid **1.54**. The bis-cyclisation of **1.54** provided the mixture of β-lactones **1.55** and **1.56** with 5:1 d.r. (mechanism detailed in the next scheme). After hydrogenolysis of the diastereomeric mixture of **1.55** and **1.56**, the resultant major alcohol **1.57** could be isolated as a single diastereoisomer after flash chromatography separation. The alcohol **1.57** was then oxidised under modified Mofatt

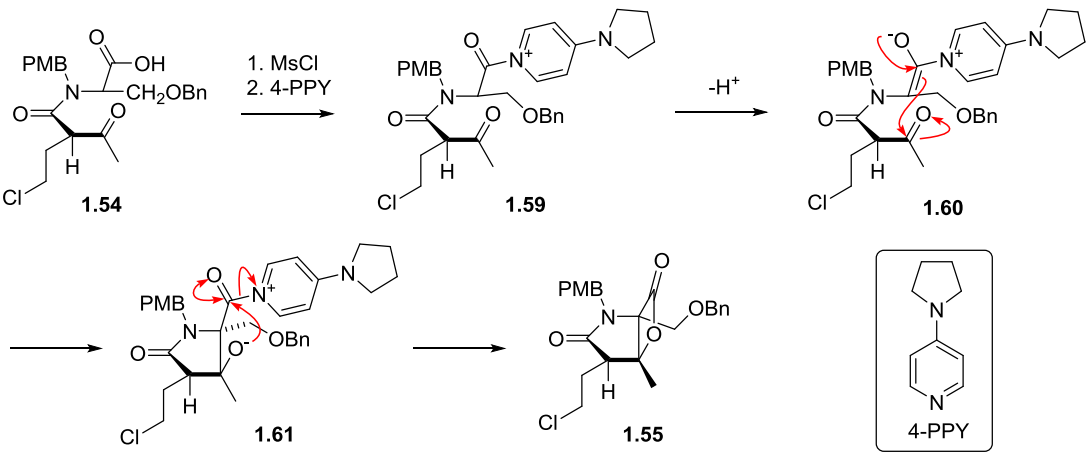
conditions and the corresponding aldehyde was submitted to the cyclohexenyl organozinc reagent **1.34** to give **1.58** in 11:3:3:1 d.r. After diastereoisomer separation, the final CAN deprotection gave salinosporamide A in 14:1 d.r.



Scheme 1.10 Romo's total synthesis of (-)-salinosporamide A[18]

Reagents and conditions i) *p*-anisaldehyde, MeOH, 0 °C, 8 h; $NaBH_4$, -10 °C, 10 h; ii) *p*-TsOH, allyl alcohol, PhH, 100 °C, 8 h; iii) DCE, 50 °C, µW, 2 h; iv) $Pd(PPh_3)_4$, morpholine; v) MsCl (1.5 eq), 4-PPy, PhMe, -10 °C, 6 h; vi) H_2, Pd/C, THF, RT; vii) EDCI, DMSO/PhMe, Cl_2CHCO_2H, RT, 5h; viii) Organozinc reagent **1.34**, THF, -78 °C, 4 h; ix) CAN, $MeCN/H_2O$, 0 °C, 6 h.

The proposed mechanism of the bis-cyclisation starts with the formation of the acyl mesylate **1.54**, which is converted into the corresponding acyl pyridinium ion **1.59**. Formation of the corresponding zwitterionic enolate **1.60** followed by intramolecular aldol reaction leads to the pyrrolidinone **1.61** (**Scheme 1.11**). The so formed alkoxide then cyclises to form the β-lactone **1.55**.



Scheme 1.11 Proposed mechanism for the bis-cyclisation[18]

The Romo group achieved the synthesis of (-)-salinosporamide A in a 9 step sequence from a natural amino acid. A similar sequence also delivered (±)-cinnabaramide A[18] **1.62a** and (-)-homosalinosporamide A[19] **1.62b** (**Figure 1.6**).



1.62a, cinnabaramide A **1.62b,** homosalniosporamide

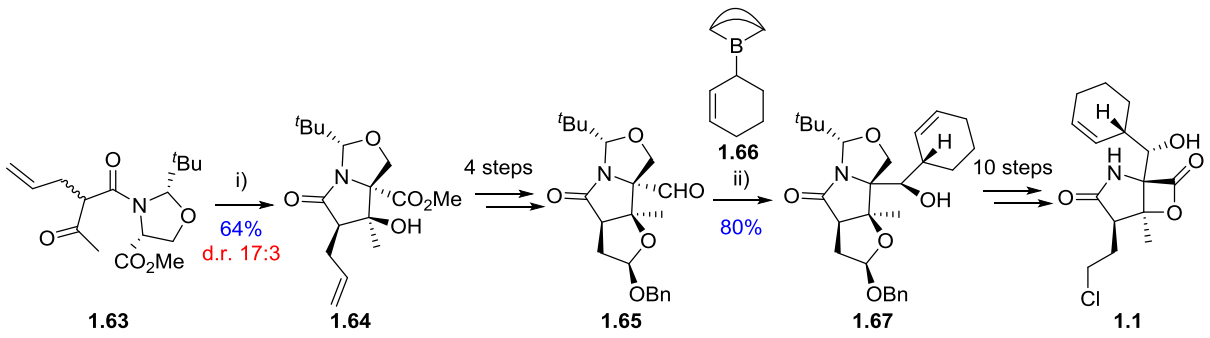
Figure 1.6 Cinnabaramide A and homosalinosporamide A

1.4.4 **Other enantioselective syntheses of (-)-salinosporamide A**

Five other total or very advanced formal syntheses of (-)-salinosporamide A have been reported. The key steps of these syntheses will be described in the following sub-sequences.

1.4.4.1 Nereus Pharmaceutical synthesis (Macherla *et al.*)[26]

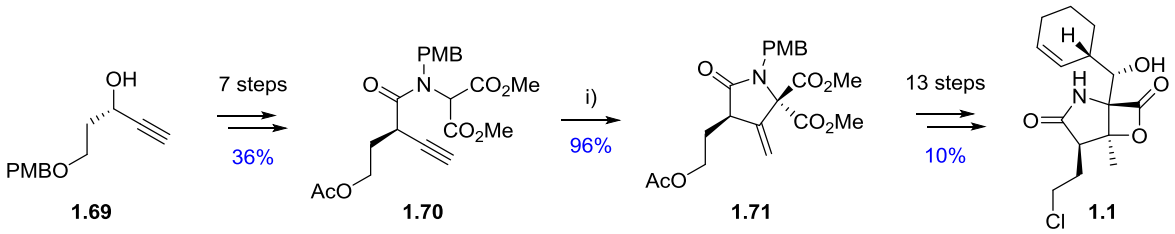
A strategic step in the total synthesis reported by Nereus Pharmaceuticals is an intra-molecular aldol reaction on the early intermediate **1.63** (**Scheme 1.12**). The functionalised bicyclic product **1.64** was then converted into the protected lactol aldehyde **1.65** in an undetailed 4 step sequence. Another important novel step in this synthesis was the addition of the allylboron reagent **1.66** to the aldehyde **1.65**. A series of standard transformation then allowed the conversion of the addition product **1.67** to salinosporamide A in 10 steps.



Scheme 1.12 Key steps in the total synthesis of (-)-salinosporamide A developed by Macherla *et al.*[26]
Reagents and conditions i) ^{t}BuOK, THF, RT, 15 min; ii) Allylboron **1.66**, THF, -78 °C to RT, 12 h.

1.4.4.2 Hatakeyama's total synthesis[27]

Hatakeyama applied a new indium-catalysed Conia-ene type reaction to a total synthesis of (-)-salinosporamide A. Their synthesis started from the propargyl alcohol **1.69**,[28] which was converted into the cyclisation substrate **1.70** in a 7 step sequence. The Conia-ene cyclisation proceeded in very high yield to give alkene **1.71** (**Scheme 1.13**). The further 13 steps toward (-)-salinosporamide A are closely related to the total synthesis developed by Danishefsky.

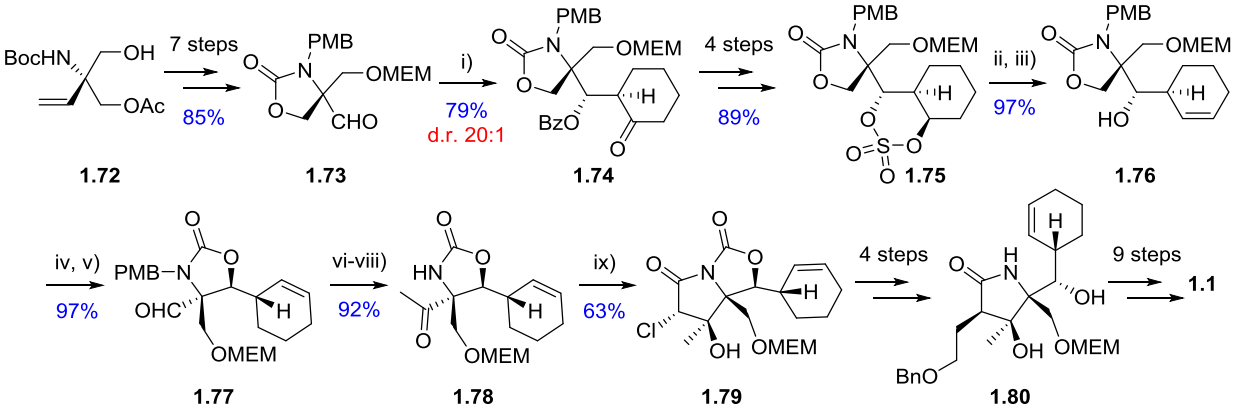


Scheme 1.13 Key Conia-Ene type cyclisation in the total synthesis of (-)-salinosporamide A developed by Hatakeyama *et al.*[27]

Reagents and conditions i) $In(OTf)_3$ (5 mol%), PhMe, 110 °C.

1.4.4.3 Omura's total synthesis[29]

The mono-acetylated diol **1.72** used as an early intermediate in this synthesis was obtained by the selective acetylation of the corresponding diol with a Lipase isolated from *Pseudomonas* sp. Then a seven step sequence allowed the formation of oxazolidinone aldehyde **1.73**, which underwent an aldol reaction with the lithium enolate of cyclohexanone to give the oxazolidinone **1.74**. After further synthetic manipulations, an elimination-deprotection sequence on sulfate **1.75** formed the cyclohexene **1.76**. Treatment of the alcohol **1.76** with a strong base promoted a rearrangement, which gave the aldehyde **1.77** after Swern oxidation. Addition of methyl magnesium bromide to aldehyde **1.77** followed by oxidation of the resulting alcohol and PMB deprotection gave the ketone **1.78**. N-acylation of **1.78** with chloroacetyl chloride followed by intramolecular aldol reaction gave **1.79**. Another undetailed 13 step sequence was required to reach salinosporamide A from **1.79**.



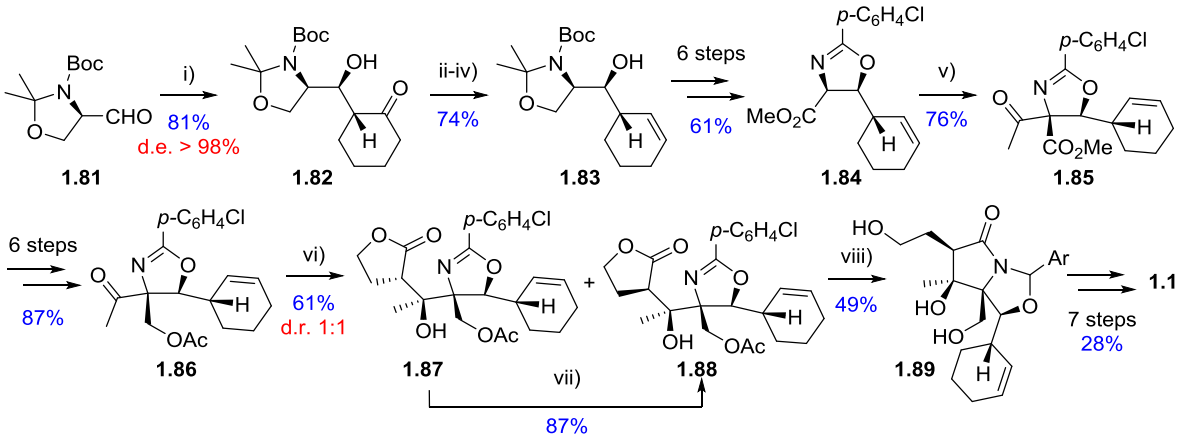
Scheme 1.14 Key steps in the total synthesis of (-)-salinosporamide A developed by Omura *et al.*[29]

Reagents and conditions i) LDA, cyclohexanone, THF, -78 °C then BzCl; ii) DBU, PhMe, 100 °C; iii) TsOH, dioxane, RT; iv) NaH, THF/EtOH, RT; v) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C; vi) MeMgBr, THF, -78 °C; vii) DMP, DCM, RT; viii) CAN, MeCN/H_2O, 0 °C; ix) LiHMDS, THF, -78 °C; then chloroacetyl chloride.

1.4.4.4 Iwabuchi's total synthesis[30]

The Iwabuchi synthesis starts with an aldol reaction between Garner's aldehyde[31] **1.81**, and cyclohexanone in the presence of D-proline, which gave the aldol **1.82** in excellent yield and diastereocontrol (**Scheme 1.15**). After TMS protection of the aldol product **1.82**, the enol triflate of

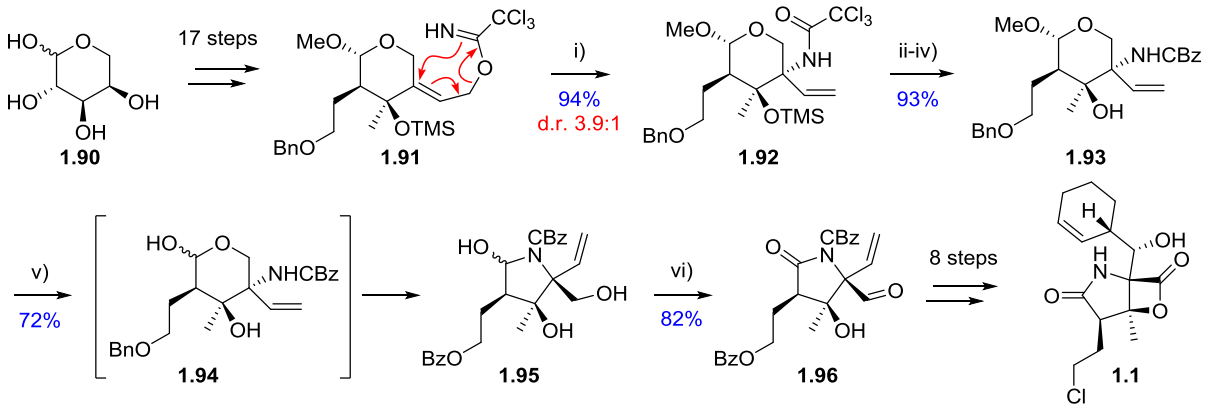
the residual ketone was formed and reduced with formic acid under palladium-catalysed conditions to give the alkene **1.83**. After an undetailed 6 step sequence, the anion of the oxazoline **1.84** was acetylated with acetyl chloride. Iwabuchi *et al.* had envisaged an aldol reaction of the formed ketone **1.85** with the enolate of γ-butyrolactone, unfortunately all attempts of the aldol reaction led to the undesired collapse of the tetrahedral intermediate by retro aldol, which gave **1.84**. An undetailed 6 step synthetic detour allowed the successful aldolisation of the acetate **1.86** under the Honda variant[32] of the Reformatsky conditions forming the product **1.87** and **1.88** in a 1:1 mixture of diastereoisomers. The undesired diastereoisomer **1.87** was isomerised in good yield to the required substrate **1.88**. The reduction of the oxazoline **1.88** eventually allowed the key formation of lactam **1.89**, which carries the 5 adjacent stereocentre of salinosporamide A. Further standard synthetic modifications of **1.89** allowed the synthesis of the targeted natural products in 7 additional steps.



Scheme 1.15 Key steps in the total synthesis of (-)-salinosporamide A developed by Iwabuchi *et al.*[30]
Reagents and conditions i) D-Proline (20 mol%), cyclohexanone (2.0 eq), $CHCl_3$/DMSO (3:1), 5 °C, 3 days; ii) TMSCl (2.0 eq), Et_3N (4.0 eq), DMAP (0.1 eq), DCM, 0 °C, 15 h; iii) KHMDS (1.3 eq), $PhNTf_2$ (1.1 eq), THF, -78 to -40 °C, 1 h; iv) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), HCO_2H (2.5 eq), *n*-Bu_3N (3.0 eq), DMF, 60 °C, 12 h; v) LDA (2.0 eq), THF, -78 °C; AcCl (3.0 eq), 15 min; vi) $(Ph_3P)_3RhCl$ (0.05 eq), α-bromo-γ-butyrolactone (4.0 eq), Et_2Zn (4.0 eq), THF, -20 °C, 3h; vii) DBU (1.0 eq), DCM, 0 °C, 12 h; viii) $NaBH_3CN$ (5.0 eq), AcOH/THF (2:1), 0 °C, 6 days.

1.4.4.5 Chida's total synthesis[33]

The total synthesis of (-)-salinosporamide developed by Chida *et al.* is based on a skeletal rearrangement of a pyranose derivative **1.93**, which was prepared from D-arabinose **1.90** in 21 steps including an Overmann rearrangement of the alkene **1.91**. After this rearrangement, the residual trichloroacetal group of the pyranose **1.92** was replaced by a Cbz group, and the silyl ether was cleaved to give the alcohol **1.93**. The skeletal rearrangement of the latter was best promoted with $Sc(OTf)_3$ in wet DCM. The resulting hemiaminal **1.95** could then be oxidised to the functionalised pyrrolidinone core of salinosporamide A **1.96**, which led to the natural product in 8 synthetic steps.

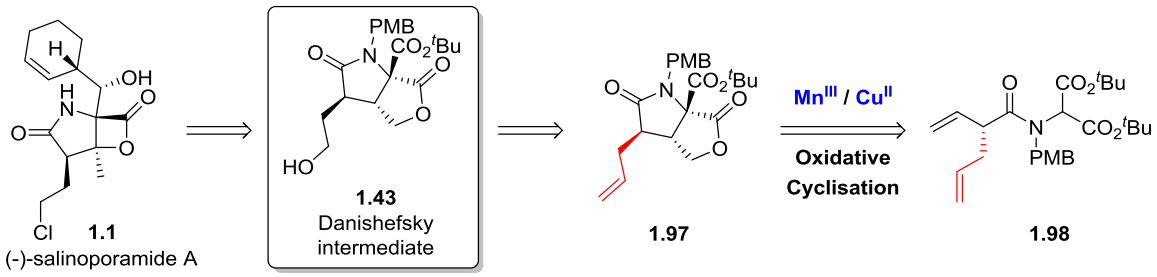


Scheme 1.16 Key steps in the total synthesis of (-)-salinosporamide A developed by Chida *et al.*[33]
Reagents and conditions i) Na_2CO_3, ^tBuPh, 170 °C in a sealed tube; ii) DiBAl-H, PhMe, -78 °C; iii) CbzCl, K_2CO_3, THF/H_2O, RT; iv) TBAF, THF, 0 °C; v) $Sc(OTf)_3$, DCM/H_2O (10:1), 40 °C; vi) CrO_3, H_2SO_4, acetone/H_2O, RT.

Two total syntheses of (±)-salinosporamide A have also been reported by Romo *et al.*[18] and Pattenden and co-workers.[34,35] Formal syntheses of (-) and (±)-salinosporamide A have also been achieved by Langlois *et al.,*[36] Lam *et al.,*[37] Chida *et al.,*[38] Tepe and Mosey,[39] Bode *et al.*[40] and Ling *et al.*[41] (Nereus Pharmaceuticals). Reviews containing synthetic route toward the natural product have also been released by Shibasaki *et al.*,[42] Moore *et al.,*[6] Potts *et al.*[43] and Markus *et al.*[4]

1.4.5 Burton group synthesis of pyrrolidinone-lactones, application to the formal synthesis of (-)-salinosporamide A[44]

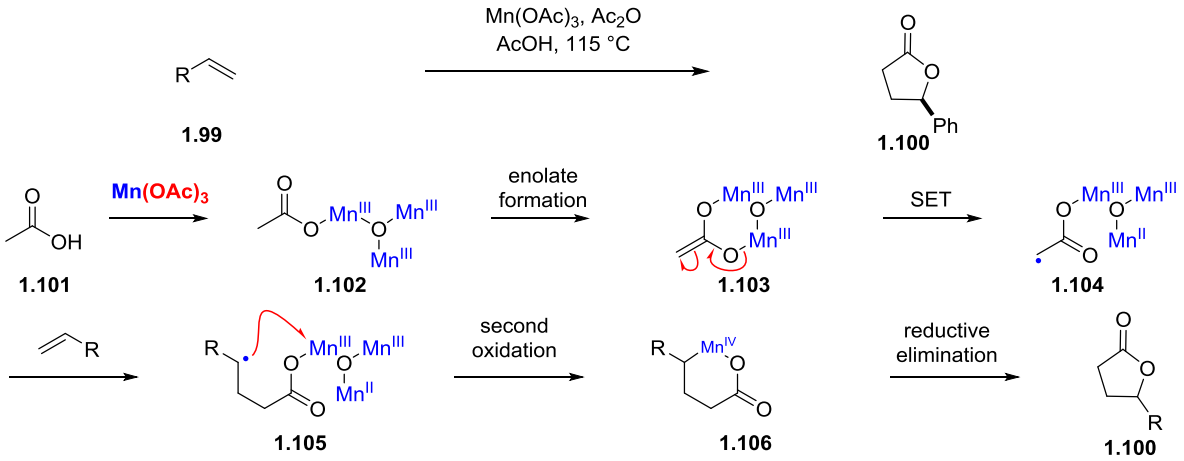
The Burton group recently reported the manganese(III) and copper(II)-mediated oxidative cyclisation of alkenyl amidomalonates to form fused pyrrolidinone-lactones.[44] The reaction was applied to an efficient synthesis of the fused pyrrolidinone-lactone **1.43,** which is an intermediate in Danishefsky's synthesis of salinosporamide A.[21]



Before presenting and detailing the scope of the reaction and its application to the formal synthesis of salinosporamide A, a brief overview of the use of manganese(III) in radical oxidative cyclisation is presented.

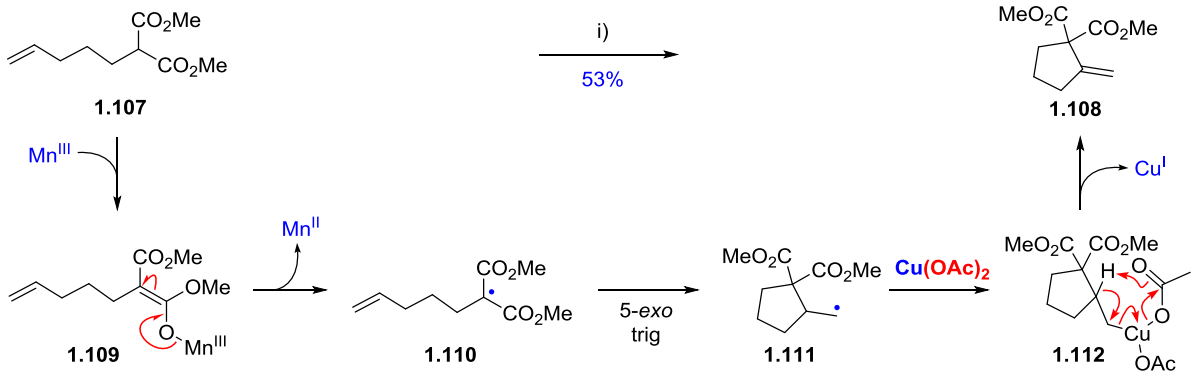
1.4.5.1 Manganese(III) and copper(II) in oxidative cyclisations

The first use of manganese(III) acetate in an oxidative cyclisation was reported in 1968 by Heiba *et al.*[45] and by Bush and Finkbeiner[46] for the lactonisation of a range alkenes **1.99** with acetic acid (**Scheme 1.17**). The likely mechanism proposed by Snider[47] begins with the formation of a manganese(III) enolate **1.103** followed by a single electron transfer to form the acetate radical **1.104**. The addition of the latter to an alkene **1.99** would form the secondary radical **1.105**, which would undergo a second oxidation with manganese(III) to form manganese(IV) species **1.106**. The lactone product **1.100** would then be formed by oxidative elimination of **1.106**. The overall process requires two equivalent of manganese(III) acetate as the radical **1.105** undergoes a second oxidation.



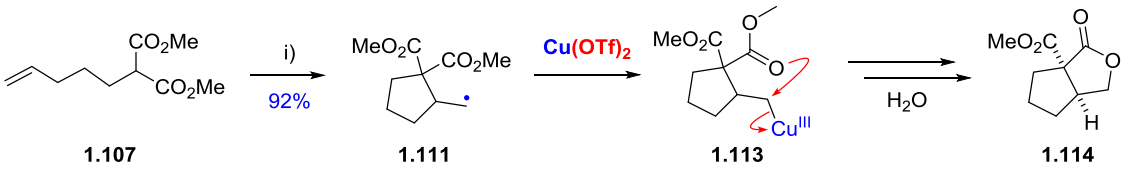
Scheme 1.17 Heiba *et al.*[45] and Bush Finkbeiner[46] lactonisation of alkenes in acetic acid in the presence of $Mn(OAc)_3$ and mechanism of the reaction proposed by Snider.[47]

The use of copper(II) salts as a co-oxidant with manganese(III) was studied by Heiba and Dessau,[48,49] who showed that copper(II) species were much faster oxidants for the second oxidation occurring during the oxidative cyclisation process. Snider *et al.* later developed an intramolecular mediated oxidative cyclisation of pentenyl malonate **1.107** using manganese(III) acetate and copper(II) acetate in DMSO (**Scheme 1.18**).[50,51] The mechanism for the reaction would also start with the formation of the manganese(III) enolate **1.109**, which would form malonate radical **1.110** via a single electron transfer. The latter would undergo a 5-*exo* trig cyclisation to form the second radical intermediate **1.111**. The second oxidation of the radical **1.111** by copper(II) acetate would form the copper(III) adduct **1.112**, which would fragment to the *exo*-alkene product **1.108**.[51] Using manganese(III) acetate and copper(II) acetate in AcOH, the reaction also gave **1.108** along with γ-lactone **1.114** as a by-product ouf the reaction.[50,51]



Scheme 1.18 Oxidative cyclisation developed by Snider *et al.*[50,51]
Reagents and conditions i) $Mn(OAc)_3$ (2.0 eq), $Cu(OAc)_2$ (1.0 eq), DMSO, 55 °C.

Based on this work and the results of Kochi and Jenkins[52] on the reaction of copper(II) salts with radicals, studies in the Burton group later re-examined the cyclisation of this type of alkenyl malonates and eventually allowed the formation of the cyclopentane-lactone **1.114** in high yield when the manganese(III)-mediated oxidative radical cyclisation was performed in the presence of copper(II) triflate as a co-oxidant in acetonitrile (**Scheme 1.19**).[53,54] Under these modified conditions, the copper(II) oxidation of the radical **1.111** gives the copper(III) adduct **1.113,** which reacts with the carbonyl group of the adjacent ester to form the lactone **1.114.** An undetailed range of fused cyclopentane-lactones was also synthesised in the group. [50,51]

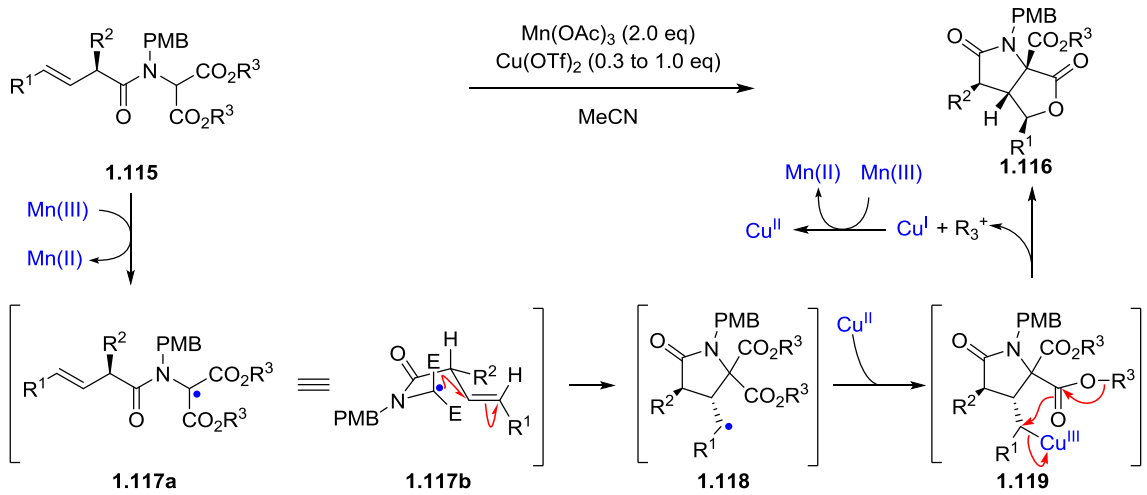


Scheme 1.19 Burton *et al.*[53] cyclisation of alkenyl amidomalonates
Reagents and conditions i) $Mn(OAc)_3$ (2.0 eq), $Cu(OTf)_2$ (1.0 eq), MeCN, 80 °C.

1.4.5.2 The oxidative cyclisation of alkenyl amidomalonate[44]

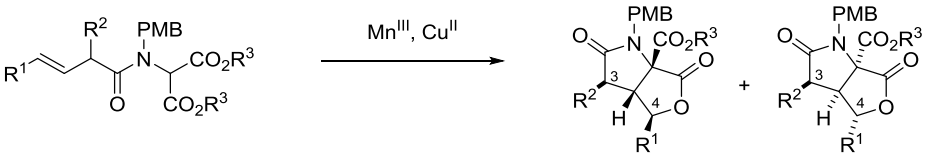
The manganese(III) and copper(II)-mediated oxidative radical cyclisation of alkenyl malonates for the formation of fused cyclopentane-lactones[53,54] has recently been extended to the cyclisation of alkenyl amidomalonates to give fused pyrrolidinone-lactones (**Scheme 1.20**).[44,55] The likely first step of the mechanism is the formation of the α-amido-radical **1.117a**, which also involves the formation of the manganese(III) enolate followed by a single electron transfer.[56] The α-amido-radical **1.117a** then reacts in a 5-*exo*-trig cyclisation to form the alkyl radical **1.118**. This result is in keeping with the Beckwith[57] and Houk[58] model, which rationalises the stereoselective cyclisation of 5-hexenyl radicals. With respect to the previous cyclisation of alkenyl amidomalonate, good predictions of the stereochemical outcome can be established using the Houk-Beckwith chair transition state model. However for alkenyl amidomalonates, a more realistic pre-transition state assembly is likely to be the

half chair like arrangement **1.117b**. When R^2 is alkyl, the depicted conformation of the radical **1.117b** allow minimising 1,3-allylic strain and 1,3-diaxial interactions.[58] The subsequent step is the oxidation of the alkyl radical **1.118** by a copper(II) species, which is a fast process.[52] The resulting copper(III) adduct **1.119** is sometimes represented as a simple secondary cation from which pyrrolidinone-lactone **1.116** is formed.



Scheme 1.20 **Manganese(III) and copper(II)-mediated oxidative radical cyclisation of alkenyl amidomalonates and proposed mechanism**

When R^1 is a phenyl group, the reaction tolerated a wide range of substituents R^2 at the allylic position (**Table 1.1**, entry 1 to 9). In these cases, the cyclisations are very efficient as the radical intermediate **1.118** is stabilised by the phenyl group. Alkyl, allyl, benzyl and alkyne substituents at the allylic position gave good yields and stereoselectivities. Only few terminal alkenes were originally tested in the reaction (entry 10 and 11), which gave lower yields but good levels of stereoselectivity.



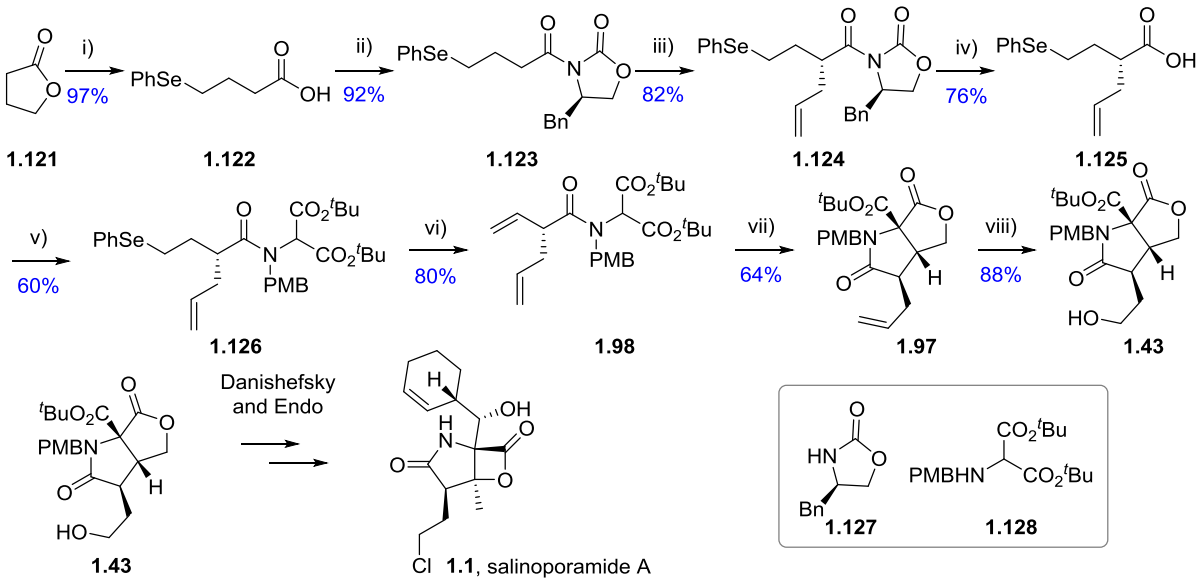
1.115 **1.116** **1.120**

Entry	R^1	R^2	R^3	Yield	Crude d.r.
1	Ph	H	Me	72%	14 :1*
2	Ph	Me	Me	84%	6.6:1*
3	Ph	Et	Me	76%	10.4:1*
4	Ph	*i*-Pr	Me	81%	> 25:1*
5	Ph	*n*-Bu	Me	65%	8.4:1*
6	Ph	$CH_2C{\equiv}H$	Me	76%	18:1*
7	Ph	Allyl	Me	74%	19:1*
8	Ph	Bn	Me	87%	11:1*
9	Ph	$(CH_2)_2OBn$	Me	70%	25:1*
10	H	Bn	^{t}Bu	52%	> 15:1*
11	H	Allyl	^{t}Bu	43%	> 15:1*

Table 1.1 Manganese (III) and copper(II)-mediated oxidative cyclisation of alkenyl amidomalonate substrates[44]
Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C.
*Refers to the mixture of diastereoisomers formed at C-3.

1.4.5.3 Previous formal synthesis of (-)-salinosporamide A[44]

The synthetic utility of this methodology has been demonstrated in the group by preliminary work towards (-)-salinosporamide A. A synthesis of the pyrrolidinone-lactone **1.43**, which is an intermediate in Danishefsky's total synthesis of (-)-salinosporamide A was achieved using the oxidative cyclisation of an alkenyl amidomalonate as a key step towards **1.43**. The formal synthesis starts with the opening of γ-butyrolactone with phenyl selenium anion,[59] which gave the carboxylic acid **1.122**. The acid could be converted in 2 steps to the substituted oxazolidinone **1.124** using an Evans' alkylation (**Scheme 1.21**).[60] After the cleavage of the auxiliary, the resulting carboxylic acid **1.125** was coupled with the amine **1.128** under Schotten-Baumann[61,62] conditions to give the amidomalonate **1.126**. The phenyl selenium moiety underwent an oxidative elimination to generate the second alkene group of the cyclisation substrate **1.98**. The cyclisation of the alkenyl amidomalonate **1.98** gave the required fused pyrrolidinone-lactone **1.97** with an excellent d.r. (> 20:1), which after ozonolysis and reductive work-up gave Danishefsky's advanced intermediate **1.43** in 8 steps and 19% yield from γ-butyrolactone.



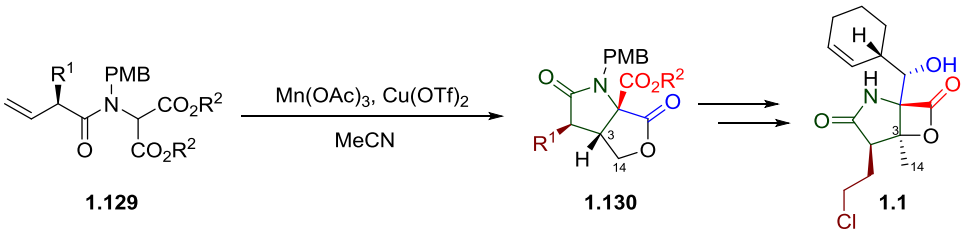
Scheme 1.21 Burton *et al.* formal synthesis of (-)-salinosporamide A[44]

Reagents and conditions i) $(PhSe)_2$, $NaBH_4$, DMF, 110 °C; ii) ^{t}BuCOCl, Et_3N, THF, -10 °C then **1.127**, LiCl; iii) NaHMDS, THF, -78 °C, then CH_2=$CHCH_2I$; iv) BnOLi, THF, then LiOH, H_2O/MeOH; v) $(COCl)_2$, DMF, DCM then **1.128**, DCM/aq. $NaHCO_3$; vi) *m*-CPBA, DCM, 15 °C to RT, then $(CH_3)_2S$, *i*-Pr_2NH, 40 °C; vii) $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OTf)_2$, MeCN, 40 °C, viii) O_3/O_2, DCM, -78 °C, then $NaBH_4$, MeOH.

1.5 Aims and synthetic strategy

Danishefsky and Endo had converted intermediate **1.43** into salinosporamide A in 15 steps. With encouraging results from the formal synthesis of salinosporamide A previously achieved in the group, it was decided to develop a new efficient total synthesis of (-)-salinosporamide A, based on the novel oxidative cyclisation of alkenyl amidomalonates. We aimed to improve on Danishefsky synthesis in term of step counts. Moreover, success in the total synthesis of this small stereochemically rich natural product would allow the synthesis of highly complex pyrrolidinone containing natural product using the oxidative radical cyclisation (**chapter 2**).

The development of our synthesis of (-)-salinosporamide A strongly relies on the stereochemical complexity that emerges during the radical oxidative cyclisation of an alkenyl amidomalonate such as **1.129**. The synthetic manipulation of the so formed pyrrolidinone-lactone **1.130** had to allow the efficient introduction of further functionality to complete the synthesis and preserve the structural features shared between a cyclised pyrrolidinone-lactone **1.130** and the natural product (**Scheme 1.22**). The first challenging feature to introduce was the cyclohexenyl group and the 2 adjacent upper tertiary stereocentres. The second challenge in our retro synthetic analysis was the introduction of the oxygen atom carried by the C-3 quaternary stereocentre of the natural product.

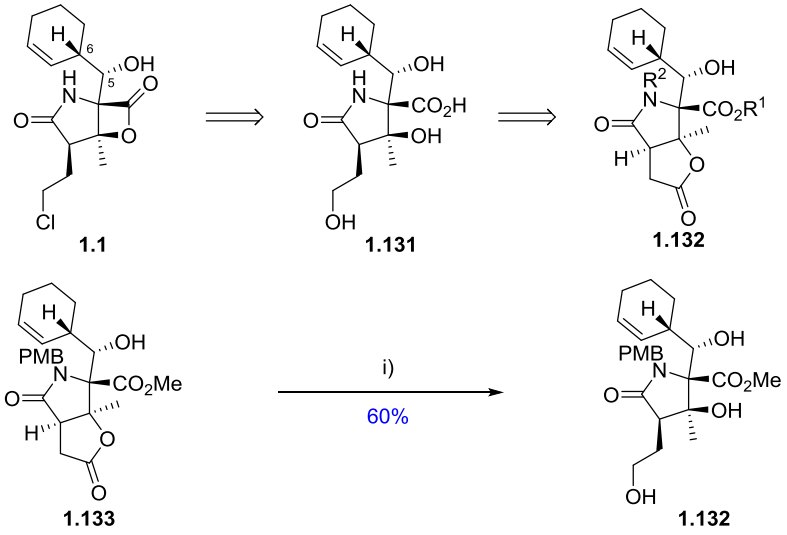


1.129 1.130 1.1

Scheme 1.22 Shared structural features between a cyclised pyrrolidinone-lactone and the targeted natural product

1.5.1 Retrosynthetic analysis of (-)-salinosporamide A

(-)-Salinosporamide A was reached by Corey *et al.*[20] after the lactonisation and chlorination of the carboxylic acid **1.131**. A similar strategy could be used for the end of our proposed synthesis. The carboxylic acid **1.131** would be obtained by the reduction of lactone **1.132** (**Scheme 1.23**). Danishefsky excluded the possibility of reaching an analogue of intermediate **1.132** as this lactone might not be readily differentiable from an ester group under reducing conditions required for the transformation.[21] But Lam *et al.* later reported a reasonable yield for the reduction of the similar substrate **1.133** in the presence of a methyl ester.[37] The reduction strategy of lactone **1.132** could therefore be viable if the appropriate alkyl group R^1 was used for the protection of the carboxyl unit carried by the lactam ring **1.132**.

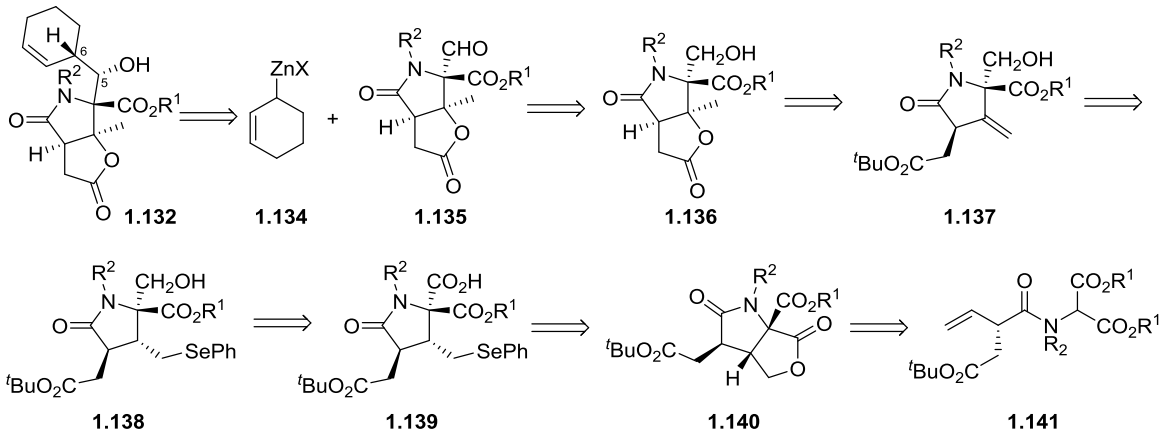


Scheme 1.23 Late step of the retrosynthetic analysis of (-)-salinosporamide A and reduction step in Lam *et al.* formal synthesis of (-)-salinosporamide A[37]

Reagents and conditions i) $NaBH_4$, (47.0 eq), MeOH, RT, 18 h.

The hydroxy functionality of the lactone **1.132** would emerge after the addition of the cyclohexenyl organozinc **1.134** into the aldehyde **1.135** generated by oxidation of the alcohol **1.136** (**Scheme 1.24**). This approach developed by Corey has been used in most syntheses of (-)-salinosporamide A to install stereocentres of lactam **1.132** at C-5 and C-6 position. The fused lactone functionality of the bicyclic molecule **1.136** would be introduced by intramolecular transition metal catalysed addition of

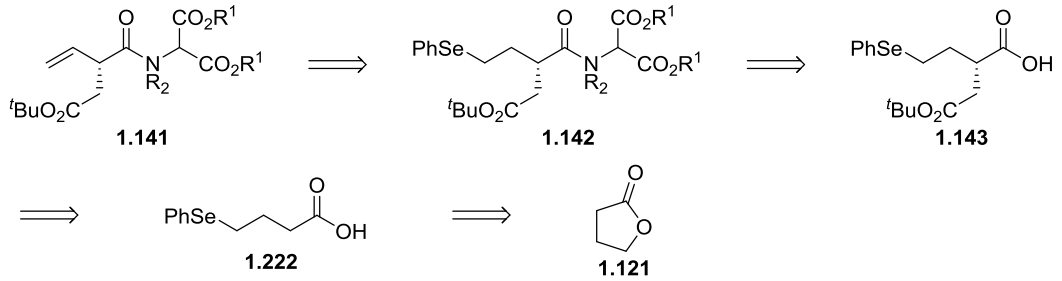
the *tert*-butyl ester (or corresponding carboxylic acid) onto the alkene of substrate **1.137**. Halo-lactonisations and seleno-lactonisations could be good alternatives but would require additional synthetic effort to obtain the methyl group of **1.138** from the resultant halogen or selenium moiety. The requisite *exo*-alkene functionality of lactam **1.137** would be installed by oxidative elimination of the phenyl selenium group of pyrrolidinone **1.138** after reduction of carboxylic acid **1.139**. Inspired by the work of Danishefsky and Endo,[21] the carboxylic acid carried by lactam **1.139** would be formed via the opening of the lactone **1.140** with an equivalent of the phenyl selenium anion. In keeping with the Beckwith-Houk model and following precedent in the group[44] (see **1.4.5.2**), the pyrrolidinone-lactone **1.140** would emerge in a favourable stereoselectivity from the manganese(III) and copper(II)-mediated oxidative cyclisation of the substrate **1.141**.



Scheme 1.24 Retrosynthetic analysis of (-)-salinosporamide A

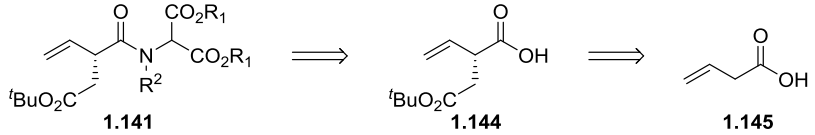
1.5.2 **Strategies for the cyclisation substrate**

Previous work in the group (see section **1.4.5**) suggested that the alkene functionality of the cyclisation substrate **1.141** could arise from an oxidative elimination of the phenyl selenium moiety of derivative **1.142** (**Scheme 1.25**), which would be obtained by amide coupling of the suitable amine and carboxylic acid **1.143**. Evans' alkylation of 4-(phenylselanyl)butanoic acid **1.222** would deliver the *tert*-butyl acetate side chain of **1.143** with the required configuration.



Scheme 1.25 Retrosynthetic analysis of the oxidative radical cyclisation substrate 1.141

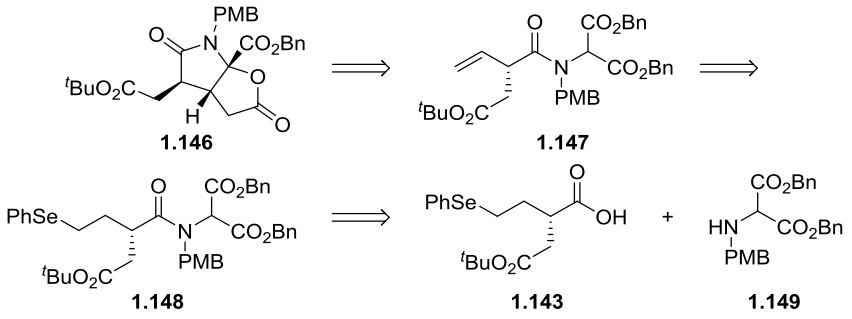
The direct manipulation of 3-butenoic acid had been investigated in the group.[63] It was shown that amide formation between a γ-δ unsaturated acid and an aminomalonate was problematic due to the conjugation of the double bond. The synthesis of the cyclisation substrate **1.141** by direct amide coupling of the butenoic acid derivative **1.144** with the suitable aminomalonate could nevertheless be re-examined (**Scheme 1.26**). The final sequence would be shortened by two steps, which correspond to the introduction and the oxidative elimination of the phenyl selenium moiety.



Scheme 1.26 Possible shorter route to the cyclisation substrate 1.141

1.6 Problematic formation of amidomalonates

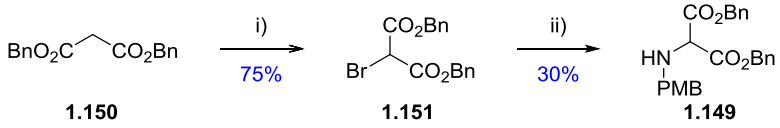
Preliminary work on this project focused on the preparation of the cyclisation substrate **1.147** in order to study the viability of the application of the radical oxidative cyclisation to the alkenyl amidomalonate **1.147**. The PMB protecting group carried by the amide nitrogen had proved to be well tolerated in previous cyclisation investigations,[21,44] moreover most previous syntheses of salinosporamide A used this protecting group. Therefore, the PMB group was chosen to protect the formed lactam **1.146** after the cyclisation step (**Scheme 1.27**). Previous manganese(III) and copper(II)-mediated oxidative radical cyclisations tolerated a wide range of malonate esters.[44] Benzyl groups were initially chosen for the side chain esters of the malonate **1.147**, as they were believed to be compatible with our synthetic strategy. The attempted synthesis of the precursor **1.148** of the cyclisation substrate by amide coupling between the carboxylic acid **1.143** and the amine **1.149** is presented in the following sections.



Scheme 1.27 Initial plans for the synthesis of the cyclisation substrate 1.147

1.6.1 **Synthesis of the amine 1.149**

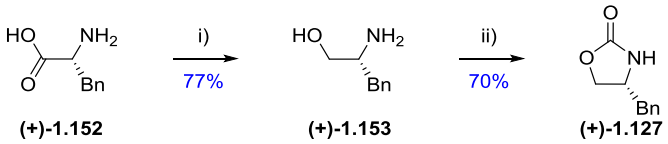
The first coupling partner (amine **1.149**) was prepared in a 2 step sequence from commercial dibenzyl malonate (**Scheme 1.28**). The initial step is the bromination of dibenzyl malonate anion using CBr_4 as source of bromine according to the procedure developed by Perreault and Spino.[64] The alkylation of PMB amine was not optimised as this route provided enough amine **1.149** (1.05 g) to test the amide coupling.



Scheme 1.28 Amine 1.149 preparation
Reagents and conditions i) DBU (1.00 eq), THF, 30 min then CBr_4, -78 °C, 6 h; ii) $PMBNH_2$ (2.00 eq), NEt_3 (2.00 eq), $CHCl_3$, 65 °C, 90 min.

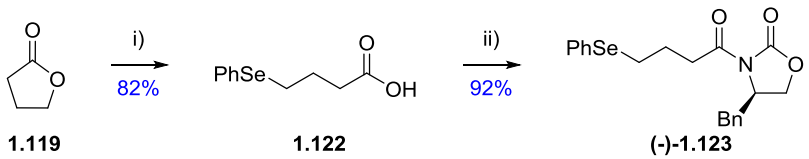
1.6.2 **Synthesis of the carboxylic acid 1.143 *via* Evans' alkylation**

The Evans' auxiliary was prepared in a 2 step sequence from (*R*)-phenylalanine (**Scheme 1.29**). The synthesis began with the reduction of the amino acid with $LiAlH_4$ using an anhydrous work-up[65] and was followed by the formation of the oxazolidinone ring with diethyl carbonate according to the procedure of Evans *et al.*[66]



Scheme 1.29 Evans' auxiliary preparation
Reagents and conditions i) $LiAlH_4$ (2.50 eq), THF, RT to 70 °C; ii) Diethyl carbonate (2.00 eq), K_2CO_3, 140 °C, 90 min

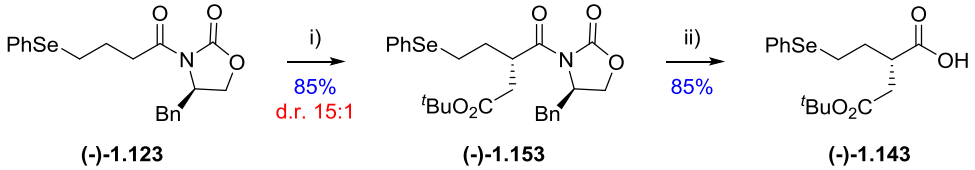
The required carboxylic acid **(-)-1.143** for the synthesis of the cyclisation substrate was prepared by Evan's alkylation of 4-(phenylselenyl)butanoic acid. The sequence starts with the opening of γ-butyrolactone with phenyl selenium anion using a procedure developed by Smith *et al.*[59] The so formed 4-(phenylselenyl)butanoic acid **1.122** was then coupled to Evans' auxiliary to afford the oxazolidinone **(-)-1.123** (**Scheme 1.30**).[60]



Scheme 1.30 Opening of γ-butyrolactone and coupling of the acid 1.122 with Evans' auxiliary
Reagents and conditions i) (PhSe)2 (0.6 eq), NaBH4 (1.3 eq), DMF, 100 °C, 5 min, then γ-butyrolactone (1.0 eq), 120 °C, 2 h; ii) NEt3 (1.2 eq), PivCl (1.1 eq), THF, -10 °C to RT, 1 h, then LiCl (1.1 eq), (*R*)-4-benzyloxazolidin-2-one (1.1 eq), RT, 3 h.

The alkylation of the sodium enolate of **(-)-1.123** with *tert*-butyl bromoacetate gave **(-)-1.153** in 15:1 crude d.r. (**Scheme 1.31**). The 2 diastereoisomers were separated by flash column chromatography.

The unusual conditions used for the cleavage of the auxiliary were developed and optimised for the preparation of the cyclisation substrate toward the core of oxazolomycin A, and are further discussed in the corresponding section (**2.3.2**). The cleavage starts with the substitution of the chiral auxiliary by BnOLi[60] followed by the saponification of the formed benzyl ester in the same pot to give the corresponding carboxylic acid **(-)-1.143** in good yield.



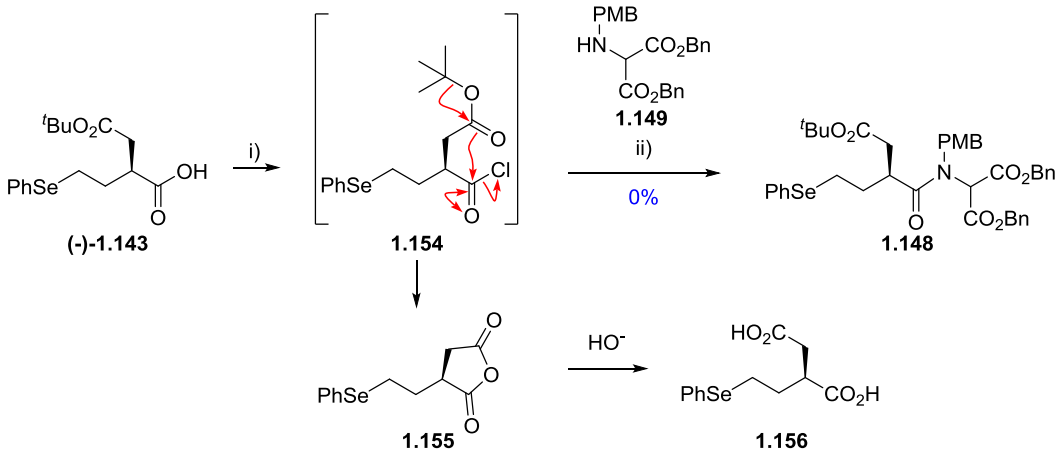
(-)-1.123 **(-)-1.153** **(-)-1.143**

Scheme 1.31 Evan's alkylation and cleavage of the chiral auxiliary
Reagents and conditions i) NaHMDS (1.5 eq), THF, -78 °C, 10 min, then $BrCH_2CO_2{}^tBu$ (3.0 eq), -78 °C, 30 min; ii) BnOH (1.5 eq), *n*-BuLi (1.2 eq), THF, 0 °C, 30 min; then **(-)-1.153** in THF, -78 °C to 0 °C, 3 h; then LiOH (5.0 eq), MeOH/H_2O/THF, 0 °C to RT, 12 h.

1.6.3 **Amide coupling attempts**

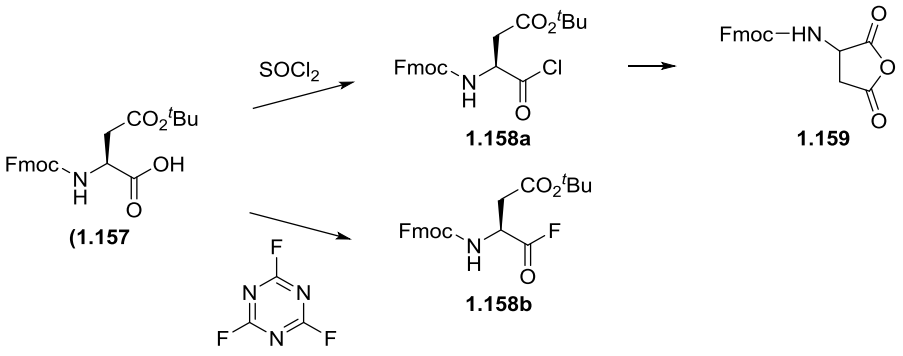
1.6.3.1 Schotten-Bauman conditions

Hatakeyama had previously reported the preparation of amidomalonates for the synthesis of the cyclisation substrates of the indium catalysed Conia-ene type cyclisation.[27] These amidomalonates could be formed by the coupling of aminomalonates and acyl chlorides under Schotten-Bauman[61,62] conditions. Such conditions were also used in the formal synthesis of salinosporamide A previously developed in the Burton group. Hence, a similar procedure was applied to the formation of the amide bond between carboxylic acid **(-)-1.143** and aminomalonate **1.149**. Exposure of the carboxylic acid **(-)-1.143** to oxalyl chloride followed by addition of the amine **1.149** did not give the desired amide product **1.148** (**Scheme 1.32**). Instead, the starting amine **1.149** was quantitatively recovered and the mass spectroscopy analysis of the reaction mixture indicated that the diacid **1.156** was formed ($[M-H]^-$ = 301). The reason for this failure is the formation of the succinic anhydride **1.155** by participation of the *tert*-butyl ester. Moreover this method was successfully used in the synthesis of the cyclisation substrate toward the core of oxazolomycin A, which does not carry any *tert*-butyl ester side chain (presented in section **2.3.2**).



Scheme 1.32 Attempt of amide coupling under Schotten-Bauman conditions
Reagents and conditions i) $(COCl)_2$ (1.5 eq), DMF (0.01 eq), dry DCM, 0 °C to RT, 45 min, evaporation; ii) Amine **1.149**, DCM/sat. aq. $NaHCO_3$, RT, 1 h.

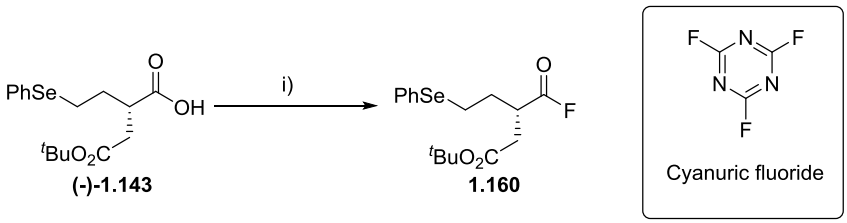
The formation of the succinic anhydride **1.155** from the acyl chloride **1.154** could not be avoided by formation of the acyl chloride at lower temperature or by decreasing the reaction time. The addition of a base (DIPEA) to increase the pH during the formation of the acyl chloride showed no improvement. Examples of formation of succinic anhydrides in the presence of a *tert*-butyl ester at the γ-position of the acyl chloride can be found in the literature.[67] Carpino reported that the presence of a *tert*-butyl ester at the γ-position of the acyl chloride **1.158a** led to the formation of succinic anhydride **1.159** (**Scheme 1.33**).[68] Carpino alternatively formed the acyl fluoride **1.158b** to safely promote the amide coupling of carboxylic acid **1.157** with different amines. Hence, further attempts focused on the formation of an acyl fluoride to achieve the formation of the amide bond of the substrate **1.148**.



Scheme 1.33 Carpino *et al.*[68] investigation on acyl halides bearing a *tert*-butyl ester at the γ-position.

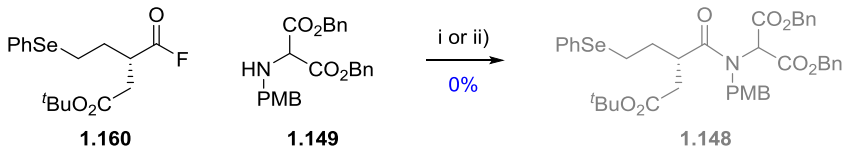
1.6.3.2 Use of acyl fluorides

The acyl fluoride **1.160** could be easily generated using a modified procedure developed by Carpino *et. al.*,[68] which involved the addition of cyanuric fluoride to the carboxylic acid **(-)-1.143** in DCM and pyridine (**Scheme 1.34**). The acyl fluoride proved to be stable to aqueous work-up.



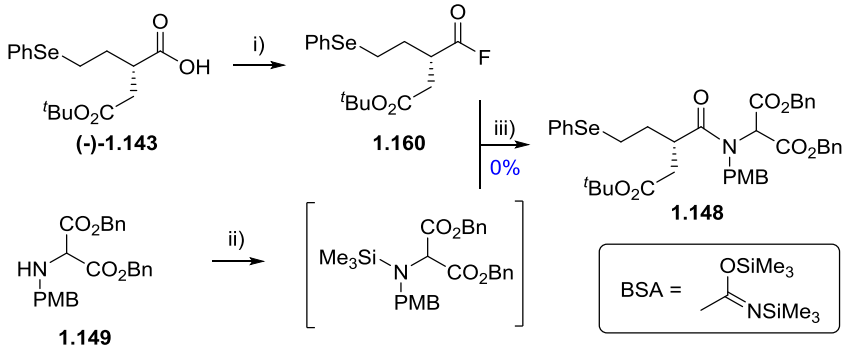
Scheme 1.34 Formation of acyl fluoride with cyanuric fluoride
Reagents and conditions i) Cyanuric fluoride (1.2 eq), pyridine, DCM, RT, 1 h

The IR spectrum of the crude reaction mixture showed a characteristic stretch of the C=O bond of the acyl fluoride bond at 1836 cm^{-1} (appendix **7.1.1**). This method was therefore reliable to produce acyl fluoride **1.160**. In a first attempt of achieving the amide coupling, a solution of amine **1.149** in DCM/pyridine was added to the crude acyl fluoride **1.160** following a known procedure used for a similar coupling.[69] After 24 h stirring, the amine **1.149** and the carboxylic acid **(-)-1.143** were recovered. The IR analysis of the crude of the reaction showed that the characteristic stretch at 1836 cm^{-1} of the acyl fluoride had disappeared. The same procedure at higher temperature (65 °C) in THF was also unsuccessful (**Scheme 1.35**).



Scheme 1.35 Unsuccessful coupling between acyl fluoride 1.160 and amine 1.149
Reagents and conditions i) DCM/pyridine, RT, 24 h; ii) THF/Pyridine, 65 °C, 12 h.

Kim *et al.* reported a reaction between highly congested *N*-silylamines with acyl fluorides.[70] A procedure using BSA as silylating agent for extremely hindered amines was tried on our system (**Scheme 1.36**).[71] Unfortunately this approach did not lead to the formation of the amide **1.148**



Scheme 1.36 Unsuccessful application of the procedure of Wenschuh *et al.*[71] for extremely hindered systems
Reagents and conditions i) Cyanuric fluoride (1.2 eq), pyridine, DCM, RT, 1 h; ii) BSA, DCM, 12 h iii) Solution of crude acyl fluoride (DCM) added to silylated amine reaction mixture.

Other more standard coupling conditions were also examined, although their chances of success were very limited due the high steric hindrance of the two coupling partners and the inductive deactivation of the amine.

1.6.3.3 Evaluation of other coupling agents

Several coupling reagents were evaluated for the amide coupling. The activation of the carboxylic acid **(-)-1.143** with MsCl (**Table 1.2,** entry 1), phosphorous reagents (entry 3 and 5), or DCC (entry 4) did not lead to the formation of the desired amide bond. Benzotriazole activation (entry 2 and 6) failed too. Further attempts of the formation of the acyl azide or mixed anhydride (entry 7 to 10) were unsuccessful. The recovery of starting materials was systematically observed.



(-)-1.143 1.149 1.148

Entry	Coupling agent	Base	Solvent	T (°C)	Time	Yield	Ref.
1	MsCl (1.0 eq)	4-NMI (2.5 eq)	DCM	RT	2 h	0%	[39]
2	TBTU (1.0 eq)	DIPEA (3.0 eq)	DMF	RT	12 h	0%	-
3	Bop-Cl (1.05 eq)	DIPEA (2.1 eq)	DCM	RT	12 h	0%	[36]
4	DCC (1.5 eq)	DIPEA (2.0 eq)	DCM	RT	12 h	0%	-
5	T3P (2.0 eq)	NEt_3 (3.0 eq)	DMF	RT	12 h	0%	[72]
6	HATU (1.1 eq)	DIPEA (2.0 eq)	DMF	50 °C	12 h	0%	-
7	DPPA (1.2 eq)	NEt_3 (2.0 eq)	DMF	0 °C to RT	12 h	0%	[73]
8	PivCl (1.1 eq)	NEt_3 (3.3 eq)	DCM	RT	2 h	0%	-
9	PivCl (1.1 eq)	NEt_3 (3.3 eq)	THF	65 °C	90 min	0%	-
10	PivCl (1.1 eq)	NEt_3 (3.3 eq)	PhMe	120 °C	12 h	0%	-

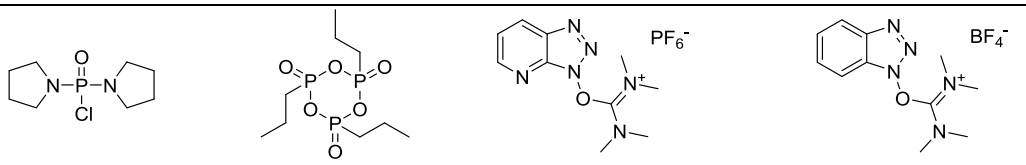
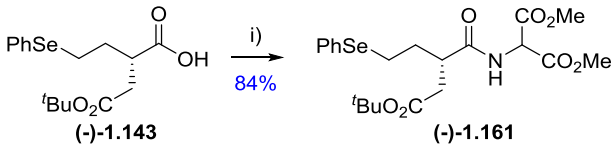


Table 1.2 Evaluation of other coupling agents for the problematic amide coupling

This amide bond could not be formed presumably because of the high steric hindrance of the two coupling partners and the poor nucleophilicity of the amine **1.149**. Further attempts presented in the next section focused on the use of less hindered amines, which do not carry the PMB side chain.

1.6.4 **Use of a different amine**

Commercial dimethyl aminomalonate was readily coupled to the carboxylic acid **(-)-1.143** at the first attempt (**Scheme 1.37**). The steric hindrance of the new amine partner was drastically reduced as the PMB group was absent and the benzyl esters of the malonate had been replaced by smaller methyl groups. The steric hindrance limitation tolerated by this amide coupling forced us to abandon the PMB protection of the nitrogen of the lactam ring formed in the following steps.

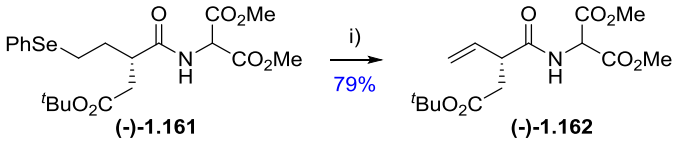


Scheme 1.37 Success of coupling with a less hindered aminomalonate
Reagents and conditions i) Dimethyl aminomalonate (1.15 eq), HATU (1.05 eq), DIPEA, (2.0 eq), DMF, 0 °C to RT, 2 h.

1.7 Alkenyl amidomalonate preparation and cyclisation

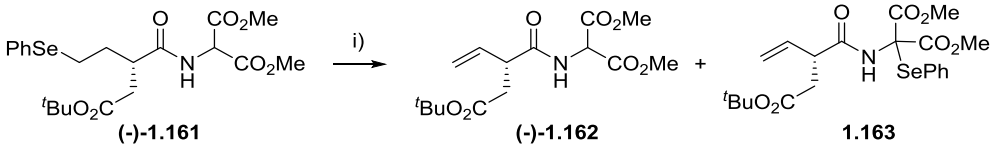
1.7.1 Phenyl selenium oxidative elimination

The alkene group of the first cyclisation substrate **(-)-1.162** was generated by the oxidative elimination of the phenyl selenium moiety of the amide **(-)-1.161**. The elimination conditions (**Scheme 1.38**) were investigated for the formation of the cyclisation substrate towards oxazolomycin A (section **2.3.2**). The optimal conditions for the oxidative elimination were based on a modification of the procedure developed by Kocienski *et al.*[74] In this modified protocol the crude selenoxide was heated in the absence of triethylamine.



Scheme 1.38 Oxidative elimination of the phenyl selenium group without NEt_3
Reagents and conditions i) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), MeOH/THF/Water (1:1:1); heat crude selenoxide in PhMe, 75 °C.

When the original basic conditions of Kocienski *et al.*[74] were initially applied to this substrate, the following mixture of products was obtained (**Scheme 1.39**).

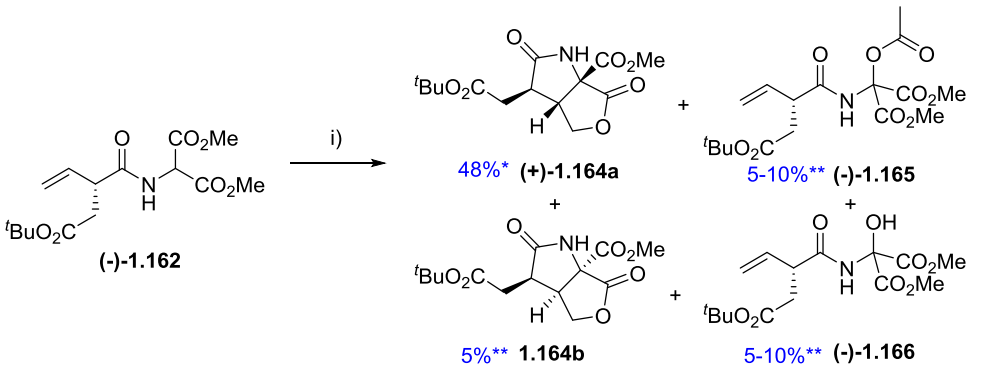


Scheme 1.39 Oxidative elimination of the phenyl selenium group with NEt_3
Reagents and conditions i) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), MeOH/THF/Water (1:1:1); heat crude selenoxide in PhMe/NEt_3 (10:1), 100 °C.

1.7.2 Oxidative radical pyrrolidinone-lactone formation

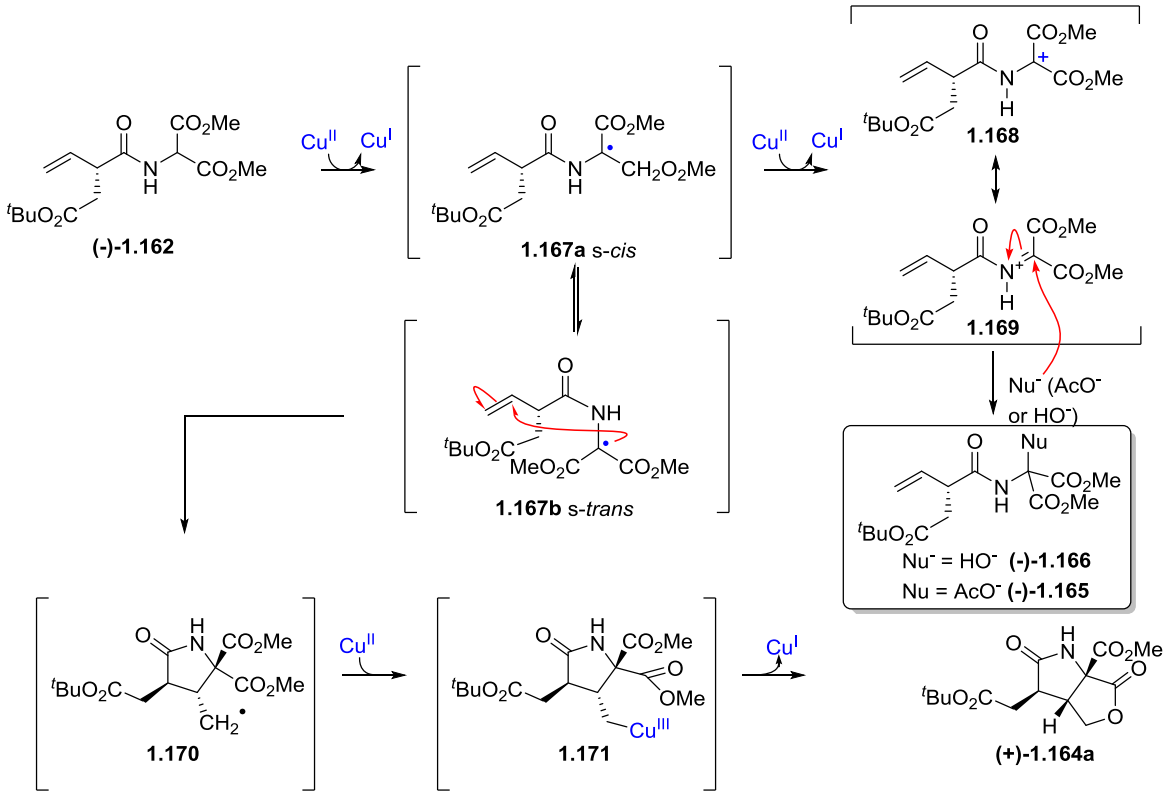
The alkenyl amidomalonate **(-)-1.162** was submitted to a typical manganese(III) and copper(II)-mediated oxidative radical cyclisation procedure developed in the group. The likelihood of success of the cyclisation was believed to be low as the previous studies[55] showed that the cyclisation of unprotected nitrogen substrates gave moderate and non-reproducible yields. However, the

cyclisation reaction proceeded in a 53% yield with an encouraging, favourable crude d.r. > 8:1 between the two *cis* fused bicyclic products **(+)-1.164a** and **1.164b**, which were separated by flash column chromatography (**Scheme 1.40**). The structure of the required major diastereoisomer **(+)-1.164a** was confirmed by ^{1}H NMR nOe experiments, the results of which are presented in the experimental section. Other oxidation side products (**(-)-1.165** and **(-)-1.166**) were also isolated. When the reaction temperature was decreased from 80 °C to 40 °C in an attempt to increase the stereoselectivity, the formation of side products **(-)-1.165** and **(-)-1.166** became predominant.



Scheme 1.40 Initial results of the radical cyclisation of alkenyl amidomalonate (-)-1.162
Reagents and conditions i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq), $Cu(OTf)_2$ (1.0 eq), MeCN, 80 °C, 4 h.

The formation of side products at low temperature may be explained by the energetic barrier that might exist between the s-*cis* form of radical **1.167a** and the s-*trans* productive form of the radical **1.167b**. At low temperature this barrier might not be overcome and the s-*cis* form, initially generated, might get oxidised by copper(II) before interconversion to the *s-trans* form and subsequent cyclisation. The copper (II) oxidation gives the intermediate iminium **1.169**, which can be trapped by AcO^- or HO^- to give side products **1.165** and **1.166** (**Scheme 1.41**).



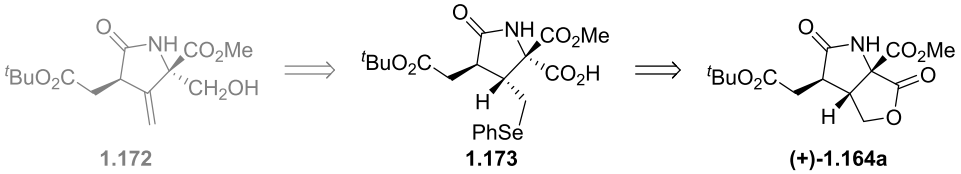
Scheme 1.41 Formation of side products through a new competitive pathway

The cyclisation was not further optimised at this stage as the alkenyl amidomalonate **(-)-1.162** was not used in the final route towards the natural product.

1.8 Lactone opening method with an equivalent of sodium phenyl selenide

1.8.1 Methyl ester selectivity issue

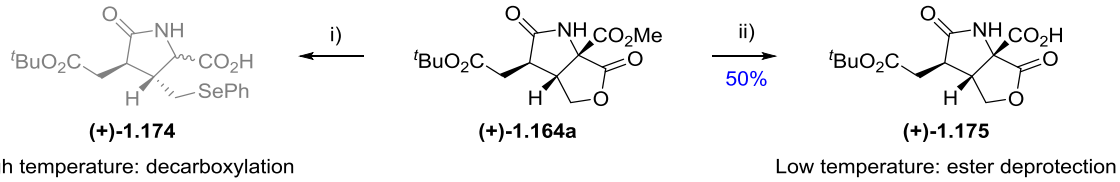
The lactone opening of the radical cyclisation product **(+)-1.164a** was required before reduction of the differentiated carboxylic acid **1.173** and oxidative elimination of the phenyl selenium group to reach the required alkene intermediate **1.172**.



Scheme 1.42 Required lactone opening

The opening of the lactone **(+)-1.164a** was trialled with an equivalent of the phenyl selenide anion generated by the treatment of $(PhSe)_2$ with $NaBH_4$. When this reaction was carried at high temperature (100 °C), the mass for the anion of the carboxylic acid **1.174** was detected by LRMS in the crude reaction mixture ($[M-H]^-$ = 412), which indicated that methyl ester removal, lactone opening and the decarboxylation of the opened product had occurred (**Scheme 1.43**). At lower

temperature, no product **1.172** of the lactone opening could be isolated as deprotection of the methyl ester solely occurred to form the undesired carboxylic acid **(+)-1.175.**



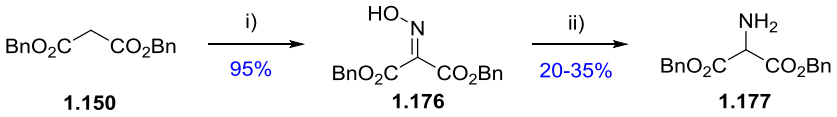
Scheme 1.43 Failure of phenyl selenium anion opening of lactone (+)-1.164a
Reagents and conditions i) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.0 eq), DMF, 100 °C then at 100 °C add lactone **(+)-1.164a** in DMF, 30 min; ii) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.0 eq), DMF, 100 °C then at 50 °C add lactone **(+)-1.164a** in DMF, 20 min.

New ester side chains were therefore considered to overcome the selectivity issue of the opening of the lactone **(+)-1.164a**. It was believed that bulkier benzyl or *tert*-butyl esters would be less likely to be cleaved by the phenyl selenium anion. Dibenzyl and *tert*-butyl ester analogues of the pyrrolidinone-lactone **(+)-1.164a** were then prepared in 2 steps from the carboxylic acid **(-)-1.143** and the corresponding aminomalonate. The synthesis of dibenzyl and *tert*-butyl aminomalonates is presented in the next section.

1.8.2 **Preparation of new aminomalonates for further lactone opening attempts**

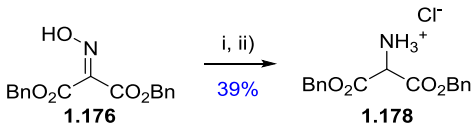
1.8.2.1 Dibenzyl aminomalonate hydrochloride

The preparation of this amine is reported in the literature[75] in a 2 step sequence from dibenzyl malonate. The formation of the oxime **1.176** proceeded in high yield. But the subsequent reduction proved difficult to achieve as it was difficult to control the quality of the Al/Hg amalgam prepared by immersing aluminium strips in a 2% aqueous solution of $HgCl_2$.



Scheme 1.44 Preparation of dibenzyl aminomalonate following the procedure of MacDonald *et al.*[75]
Reagents and conditions i) $NaNO_2$ (3.33 eq), dioxane/H_2O/AcOH (15:3:2), RT, 24 h; ii) Hg amalgamated aluminium strips, THF/H_2O, -30 °C to 50 °C.

To avoid the handling of highly toxic materials and waste, the use of other reducing conditions were examined. Standard conditions for the reduction of oximes, which involve heating with zinc dust and ammonium formate in MeOH were not tolerated by the benzyl esters of oxime **1.176**. Milder conditions[76] involving the use of $TiCl_3$, $NaBH_3CN$ and NH_4OAc in MeOH did not give the desired product and were therefore abandoned. Partial success was obtained by simply treating the oxime **1.177** with zinc dust in AcOH at room temperature (**Scheme 1.45**).[77]

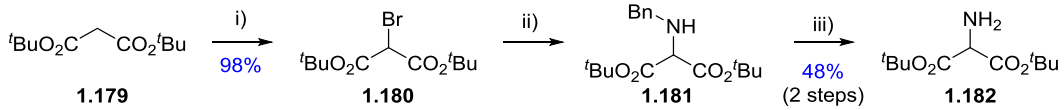


Scheme 1.45 Reduction of the oxime with zinc
Reagents and conditions i) Zn dust (3 x 1.5 eq), AcOH, RT, 2 h; ii) $HCl_{(g)}$, Et_2O.

Enough amine hydrochloride **1.178** (600 mg) was produced to test the following steps. The reduction conditions were never optimised as the amine hydrochloride **1.178** was not used in the final route.

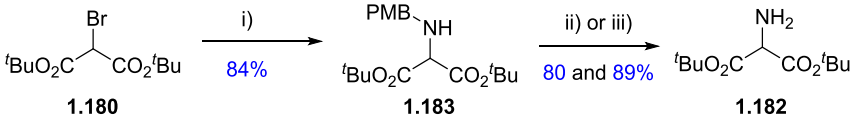
1.8.2.2 Synthesis of di *tert*-butyl aminomalonate

Di *tert*-butyl malonate was unreactive toward $NaNO_2$ used in the preparation of aminomalonate **1.178** and no improvement was observed when the oxime formation was attempted at higher temperature. The oxime route was abandoned for the synthesis of *tert*-butyl aminomalonate **1.182**. Instead, a 3 step sequence was developed to give the required amine (**Scheme 1.46**). Di *tert*-butyl bromomalonate **1.180** was first prepared by bromination of di *tert*-butyl malonate with CBr_4.[64] The modification of a known alkylation procedure developed for *N*-substituted benzylamine with diethyl bromomalonate[78] was applied to benzylamine and di-*tert* butyl bromomalonate **1.180**. Di *tert*-butyl aminomalonate **1.182** was obtained after transfer hydrogenation of the resulting aryl aminomalonate **1.181**.



Scheme 1.46 Initial synthesis of di *tert*-butyl aminomalonate
Reagents and conditions i) CBr_4 (1.0 eq), DBU (1.0 eq), THF, -78 °C, 2 h; ii) Benzylamine (2.0 eq), NEt_3 (2.0 eq), $CHCl_3$, 65 °C, 6 h; iii) NH_4HCO_2 (5.0 eq), Pd/C cat., EtOH, 60 to 80 °C, 1 h.

The moderate yield of the benzylamine alkylation was difficult to improve. During later scale up, the alkylation of 4-methoxybenzylamine under similar conditions was selected for its higher yield (Scheme **1.47**). In this case the PMB side chain was difficult to remove using ammonium formate and Pd/C for the transfer hydrogenation. When attempted on a large scale, the reaction required 25 equivalents of ammonium formate and two re-additions of Pd/C.[i] A safe and efficient hydrogenation procedure with $Pd(OH)_2/C$ eventually provided large amounts of *tert*-butyl aminomalonate.[79]



Scheme 1.47 Large scale route for the preparation of di *tert*-butyl aminomalonate
Reagents and conditions i) 4-methoxybenzylamine (2.0 eq), NEt_3 (2.0 eq), 65 °C, 10 h; ii) NH_4O_2C (5 x 5.0 eq), Pd/C cat., EtOH, 60 to 80 °C, 5 x 45 min; iii) H_2, $Pd(OH)_2/C$, MeOH, 12 h.

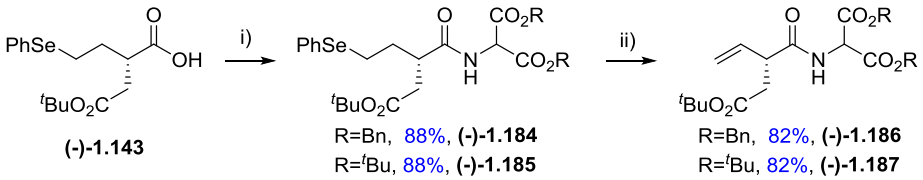
[i] Caution, in one experiment readdition of Pd/C to the transfer hydrogenation resulted in a fire.

With aminomalonates **1.178** and **1.182** in hand, further investigations of the opening possibilities of the corresponding ester analogues of bicyclic γ-lactones **(+)-1.164a** could be investigated.

1.8.3 **Lactone opening results and choice of the ester for the synthesis**

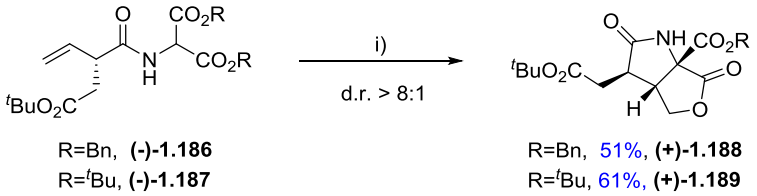
1.8.3.1 Preparation of the reaction substrate

The prepared amino malonates **1.178** and **1.182** were successfully coupled to the carboxylic acid **(-)-1.143** using HATU as coupling agent, which gave the cyclisation substrates bearing the new malonate esters in very good yields (**Scheme 1.48**).



Scheme 1.48 Amide coupling of new amines
Reagents and conditions i) Dialkyl aminomalonate (1.15 eq), HATU (1.05 eq), DIPEA, (2.0 eq), DMF, 0 °C to RT, 2 h; ii) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), MeOH/THF/Water (1:1:1); heat crude selenoxide in PhMe, 75 °C.

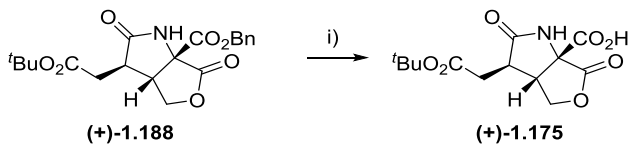
As expected the substrates carrying new malonate esters cyclised under the same conditions (**Scheme 1.49**). Further optimisation of the oxidative cyclisation is presented in section **1.9.3.2**.



Scheme 1.49 Manganese cyclisation of new esters
Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (2.0 eq), $Cu(OTf)_2$ (1.0 eq), MeCN, 80 °C.

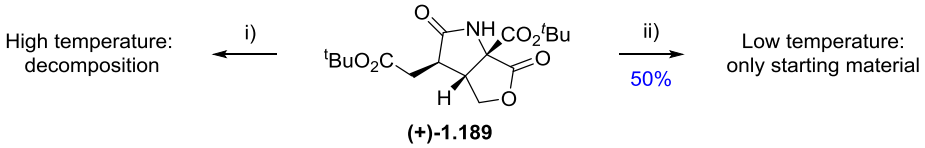
1.8.3.2 Attempts of opening the lactones **(+)-1.188** and **(+)-1.189**

The lactone opening conditions were then attempted on the two new substrates at 50 °C to avoid decarboxylation issues. The phenyl selenium anion reacted preferentially with the benzyl ester to give the carboxylic acid **(+)-1.175** as the major product, which was detected by NMR analysis of the crude reaction mixture (**Scheme 1.50**). The outcome of the reaction is the same as with the corresponding methyl ester **(+)-1.164a**.



Scheme 1.50 Unsuccessful attempt of the lactone opening in the presence of the benzyl ester
Reagents and conditions i) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.0 eq), DMF, 100 °C then at 50 °C add lactone **(+)-1.188** in DMF, 20 min.

Further investigation focused on the opening of the lactone carrying the *tert*-butyl ester side chain. In initial studies, $NaBH_4$ was used to generate the phenyl selenium anion from diphenyl diselenide (same conditions as **Scheme 1.43** and **Scheme 1.50**). A first attempt of the opening of the lactone **(+)-1.189** at high temperature (100 °C) led to decomposition. At lower temperature (50 °C) no reaction was observed, and starting material was recovered (**Scheme 1.51**).



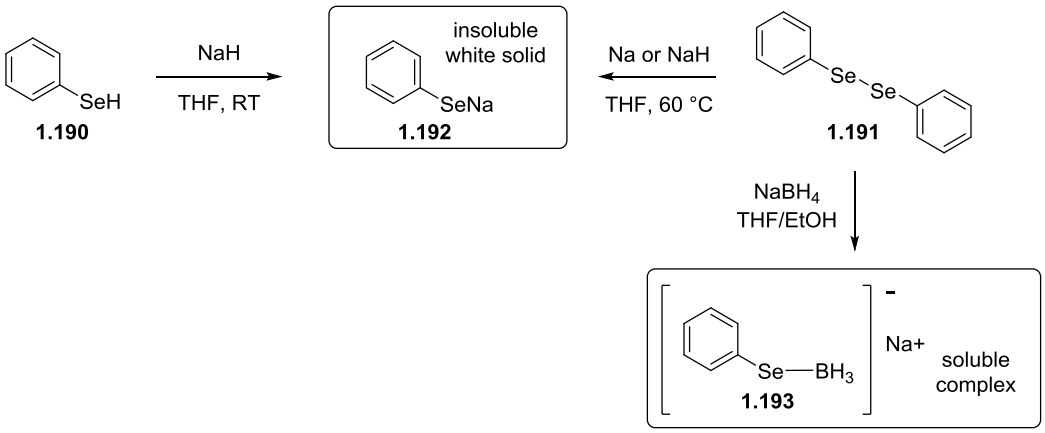
Scheme 1.51 Failure of the opening of lactone (+)-1.189 with phenyl selenium anion
Reagents and conditions i) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.0 eq), DMF, 100 °C then at 100 °C add lactone **(+)-1.189** in DMF, 30 min; ii) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.0 eq), DMF, 100 °C then at 50 °C add lactone **(+)-1.189** in DMF, 20 min.

The *tert*-butyl ester proved to be more resistant to the nucleophilicity of the phenyl selenium anion as no cleavage occurred at 50 °C. Unfortunately, the lactone was unreactive toward this nucleophile at this lower temperature. High temperature had to be avoided as it led to decarboxylation and decomposition of the starting material. Further investigation therefore focused on the development of the opening of the lactone **(+)-1.189** at room temperature.

1.8.3.3 Important classes of phenyl selenium anion

The success of the opening of lactone **(+)-1.189** with the phenyl selenium anion was vital for the planed synthesis. Our attention focused on Liotta's study,[80] which describes the existence of two classes of phenyl selenium anions.

When the phenyl selenide anion is generated from PhSeH and NaH or from $(PhSe)_2$ and Na, highly reactive sodium phenyl selenide **1.192** is obtained as an insoluble suspension in THF. [80] But when the phenyl selenide anion is generated from $(PhSe)_2$ and $NaBH_4$ the less reactive $PhSeNa{\cdot}BH_3$ **1.193** soluble complex is obtained (**Scheme 1.52**).[80]

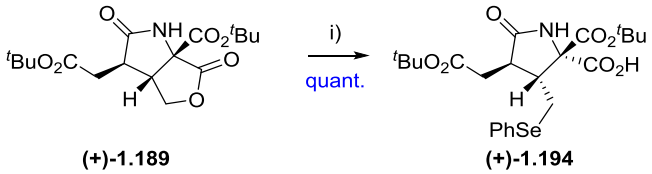


Scheme 1.52 Two classes of phenyl selenium anions reagents

As lactone **(+)-1.189** was decomposing at high temperature and not reacting at low temperature with the less reactive complex form PhSeNa·BH_3 **1.193**, it was envisaged that the highly reactive sodium phenyl selenide **1.192** could achieve the opening at low temperature.

1.8.3.4 Successful opening

A lactone opening procedure at room temperature using the highly reactive sodium phenyl selenide **1.192** was developed by Eustache *et al.*[81] The promising procedure was applied to the lactone **(+)-1.189.** PhSeNa **1.192** was prepared at 65 °C in THF by reduction of $(PhSe)_2$ with NaH. The subsequent addition of a solution of the lactone **(+)-1.189** and 18-crown-6 at low temperature yielded in 3 h the required carboxylic acid **(+)-1.194** without decarboxylation or side chain ester loss (**Scheme 1.53**).



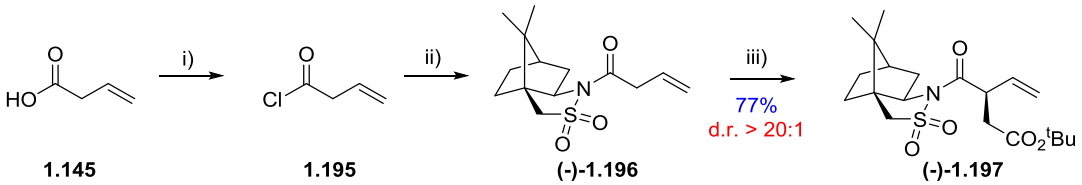
Scheme 1.53 Successful opening with the procedure developed Eustache *et al.*[81]
Reagents and conditions i) $(PhSe)_2$ (1.20 eq), NaH (2.40 eq), THF, 65 °C then add at 0 °C solution of lactone **(+)-1.189** and 18-crown-6 (0.25 eq) in THF; 0 °C to RT; 3 h.

After this success, the *tert*-butyl ester was selected to carry on the synthesis. In parallel of the progression on the front of the synthesis, the development of a shorter route toward the chosen cyclisation substrate bearing the di-*tert* butyl ester malonate **(-)-1.187** was started and is presented in the next section.

1.9 Second generation route toward the cyclised pyrrolidinone-lactone

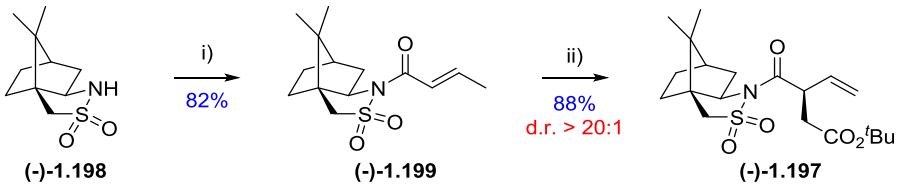
1.9.1 Oppolzer's alkylation

Direct manipulation of 3-butenoic acid derivatives would shorten the sequence to the cyclisation substrate and avoid the use of large amount of toxic selenium material at an early stage of the synthesis. Oppolzer *et al.* reported the highly stereoselective alkylation of the camphorsultam derivative of 3-butenoic acid **(-)-1.196** using benzyl bromide as the electrophile.[82] This procedure was followed using *tert*-butyl bromoacetate as the electrophile and gave the desired product **(-)-1.197** in good yield and excellent d.r. (**Scheme 1.54**).



Scheme 1.54 Oppolzer alkylation[82]
Reagents and conditions i) $SOCl_2$ (2.00 eq), neat, 60 °C; ii) (-)-camphorsultam, NaH 60%, PhMe, RT, 30 min then 3-butenoyl chloride, 0 °C to RT; iii) LiHMDS (1.15 eq), THF, -78 °C, 30 min; then $BrCH_2CO_2{}^tBu$ (3.00 eq), HMPA (3.00 eq), $(n\text{-}Bu)_4NI$ (0.10 eq), THF, -78 °C.

A deconjugative alkylation of (*R*)-(-)-(2-butenoyl)-2,10-camphorsultam **(-)-1.199** with MeI has also been reported.[83] Hence, it was planned to attempt this alkylation with *tert*-butyl bromoacetate to create a shorter route toward the alkylated product **(-)-1.197.** The new route starts with the condensation of commercial crotonyl chloride with inexpensive (-)-camphorsultam **(-)-1.198** (**Scheme 1.55**).[84] The subsequent deconjugative alkylation of substrate **(-)-1.199** proceeded in good yield and excellent d.r.



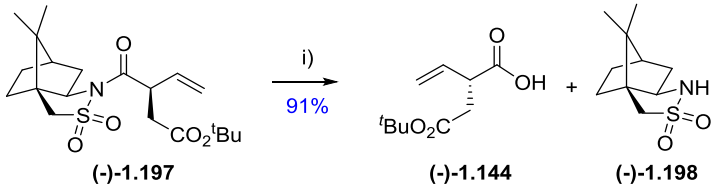
Scheme 1.55 Application of Batchelor *et al.* deconjugative alkylation[83]
Reagents and conditions i) NaH 60%, PhMe, RT, 45 min then crotonyl chloride, 0 °C to RT, 2 h; ii) HMPA (3.0 eq), LiHMDS (1.0 M in toluene, 1.50 eq), THF, -78 °C, 30 min; then $^tBuO_2CH_2Br$ (3.0 eq), THF, -78 °C, 7 h.

The alkylation product **(-)-1.197** was isolated in very good yield after re-crystallisation of the crude reaction from hexane. The minor diastereoisomer could not be detected by TLC and by proton NMR spectroscopy of the crude reaction mixture. The alkylation did not proceed without HMPA, which needed to be present during the deprotonation step of the conjugated alkene **(-)-1.199** with LiHMDS. Moreover, it was important to add the substrate **(-)-1.199** to the solution of base as the reversed

addition led to decomposition of the starting material. The removal of the chiral auxiliary from the alkylated product **(-)-1.197** had to be performed before the amide coupling was attempted.

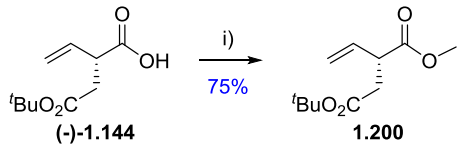
1.9.2 **Auxiliary cleavage and subsequent critical coupling**

The auxiliary was first cleaved with LiOH in THF/H_2O (5:1) at room temperature for 6 hours. HPLC enantiomeric excess measurement on the methyl ester derivatised from carboxylic acid **(-)-1.144** showed that the carboxylic acid **(-)-1.144** had partially racemised. The hydrolysis of the chiral auxiliary was eventually achieved with LiOH assisted by hydrogen peroxide, which decreased the reaction time to 10 min and buffers the pH (H_2O_2, pKa = 10.75) before quenching and acidification (**Scheme 1.56**). An acid-base extraction was not suitable for the purification of the crude mixture of carboxylic acid **(-)-1.144** and chiral auxiliary **(-)-1.198** as it led to a drop in enantiomeric excess. A trituration procedure in hexane[85] allowed the crystallisation of the undesired of the chiral auxiliary out of the mixture leaving the 90% pure acid **(-)-1.144** in solution in high enantiomeric excess.



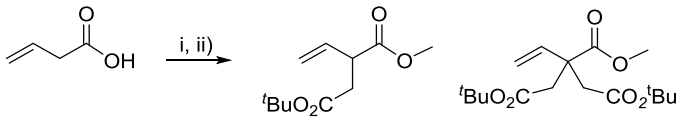
Scheme 1.56 Auxiliary cleavage
Reagents and conditions i) H_2O_2 30% (4.0 eq), LiOH (2.0 eq), THF/H_2O (3:2), 10 min.

The enantiomeric excess of the carboxylic acid **(-)-1.144** was measured after derivatisation with $TMSCHN_2$ to form the methyl ester **1.200** (**Scheme 1.57**).



Scheme 1.57 Esterification with $TMSCHN_2$
Reagents and conditions i) $TMSCHN_2$ (1.50 eq), Et_2O/MeOH (5:1), 5 min.

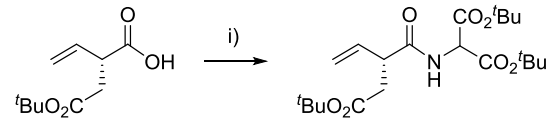
The e.e. of methyl ester **1.200** could then be measured by chiral HPLC against a racemic reference, which was prepared by the alkylation of 3-butenoic acid with *tert*-butyl bromoacetate. A significant amount of the dialkylated product was formed (**Scheme 1.58**). The treatment of the crude of the reaction with $TMSCHN_2$ allowed the isolation of enough mono-alkylated product **(±)-1.200** to develop a separation method by chiral HPLC. The two enantiomers of **(±)-1.200** were separated on an AD Chiralpak© column (hexane/IPA 9:1). The e.e. of the carboxylic acid **(-)-1.144** after derivatisation was 98.8%.



1.145 **(±)-1.200**, 7% **1.201**, 57%

Scheme 1.58 Preparation of racemic reference
Reagents and conditions i) LDA (3.0 eq), $BrCH_2CO_2{}^tBu$ (2.0 eq); ii) $TMSCHN_2$ (1.5 eq), Et_2O/MeOH (5:1), 5 min.

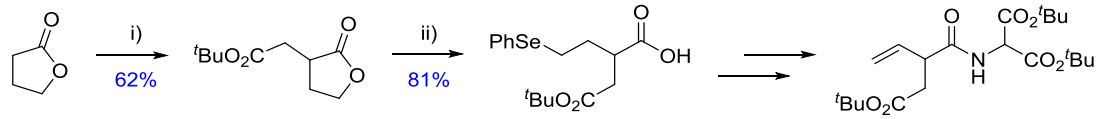
The amide coupling between the carboxylic acid **(-)-1.144** and the amine **1.182** was next investigated. The procedure presented in section **1.6.4** based on the use of HATU as a coupling agent and DIPEA as a base (pK_{aH} =10.6) was first trialled. Significant racemisation (e.e. = 74.6%) was observed under these coupling conditions (HATU/DIPEA), and another attempt using *N*-methylmorpholine as a weaker base (pK_{aH} = 7.7) did not show any improvement (**Scheme 1.59**). The use of HATU as a coupling agent was therefore abandoned.



(-)-1.144, e.e. 98.8% **(-)-1.187**, 58%, 74.6% e.e. (DIPEA)
63%, 72.0% e.e. (NEM)

Scheme 1.59 Partial racemisation during amide coupling with HATU
Reagents and conditions i) Di *tert*-butyl aminomalonate **1.182** (1.15 eq), HATU (1.05 eq), base (1.0 eq), DMF, 0 °C to RT, 2 h.

The enantiomeric excess of the amidomalonate **(-)-1.187** was measured after synthesis of the racemic reference amidomalonate **(±)-1.187**, which was prepared via alkylation of γ-butyrolactone (**Scheme 1.60**). The lithium enolate of γ-butyrolactone was first generated with LDA at -78 °C and treated with *tert*-butyl bromoacetate, which gave the lactone **(±)-1.201** in a reasonable yield. The formed lactone **(±)-1.201** was then opened with the borane complex of the phenyl selenium anion **1.193** at high temperature to give carboxylic acid **(±)-1.143**. The desired racemic alkenyl amidomalonate **(±)-1.187** was then prepared using the previously developed route on the enantiopure acid **(-)-1.143** (section **1.8.3.1**). A good separation of these two enantiomers was achieved on an HPLC instrument fitted with an AD Chiralpak© column (hexane/IPA 9:1). The HPLC trace is available in the appendix (section **7.1.8**)

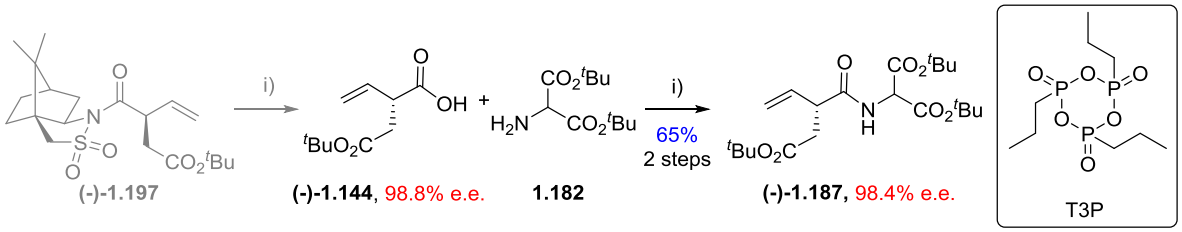


1.119 **(±)-1.201** **(±)-1.143** **(±)-1.187**

Scheme 1.60 Synthesis of the racemic reference (±)-1.187
Reagents and conditions LDA (1.1 eq), THF, -78 °C, 30 min then $BrCH_2CO_2{}^tBu$ (1.5 eq) -78 °C to RT, 90 min; ii) $(PhSe)_2$ (0.6 eq), $NaBH_4$ (1.4 eq), 100 °C, 10 min then add lactone **(±)-1.201** in DMF, 120 °C, 3 h.

The successful use of T3P (propylphosphonic anhydride) coupling agent in the presence of a mild base has been reported in an amide coupling prone to racemisation.[86] When applied to the coupling of carboxylic acid **(-)-1.144** and amine **1.182**, these conditions gave an encouraging 96% e.e. The

coupling was eventually performed at lower temperature (-40 °C, **Scheme 1.61**) to successfully achieve the formation of the amide bond in high e.e. on large scale (98.4%, HPLC trace is shown in the appendix, section **7.1.8**).



Scheme 1.61 Amide coupling with T3P
Reagents and conditions i) T3P (1.6 eq), pyridine/EtOAc, -40 °C to -10 °C, 6 h.

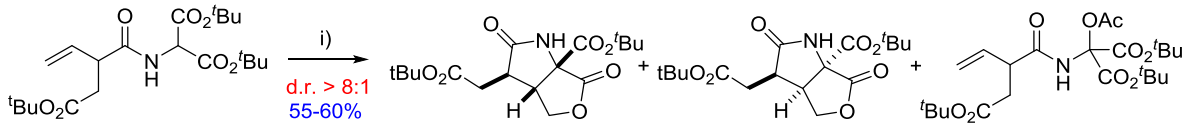
The yield is given over 2 steps from the substrate **(-)-1.197** because the purity of the starting carboxylic acid **(-)-1.144** was hard to evaluate as it contained some residual chiral auxiliary.

1.9.3 Cyclisation optimisation

Racemic alkenyl amidomalonate **(±)-1.187** was used to optimise the yield of the manganese(III) and copper(II)-mediated oxidative radical cyclisation step.

1.9.3.1 Initial results

When submitted to the initial cyclisation conditions using $Mn(OAc)_3{\cdot}2H_2O$ (2.0 eq) and $Cu(OTf)_2$ (1.0 eq) in MeCN at 80 °C, the total yield of lactones never exceeded 60% (typically 55-60%), the rest of the material mostly accounted for the formation of the side product **(±)-1.204** (rationalised in section **1.7.2**). In initial investigations, parameters such as concentration and $Cu(OTf)_2$ loading (0.2 to 1.0 eq) did not seem to have any influence on the formation of the main side product **(±)-1.204**. High stoichiometry of $Mn(OAc)_3{\cdot}2H_2O$ (3.0 eq) gave a slightly higher yield.

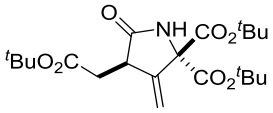


Scheme 1.62 Manganese(III) and copper(II) cyclisation under initial conditions
Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (2.0 or 3.0 eq), $Cu(OTf)_2$ (0.2 or 1.0 eq), MeCN, 80 °C, 90 min.

1.9.3.2 Study of the influence of water

In attempts of modifying the copper catalyst, $Cu(OTf)_2$ was replaced by the hygroscopic catalyst $Cu(BF_4)_2{\cdot}xH_2O$, the total yield appeared to be slightly higher (65%). When an older and much wetter batch of $Cu(BF_4)_2{\cdot}xH_2O$ was used, the reaction led to a higher total yield (69%). It was postulated that the presence of water could have a positive impact on the outcome of the reaction. Indeed studies of

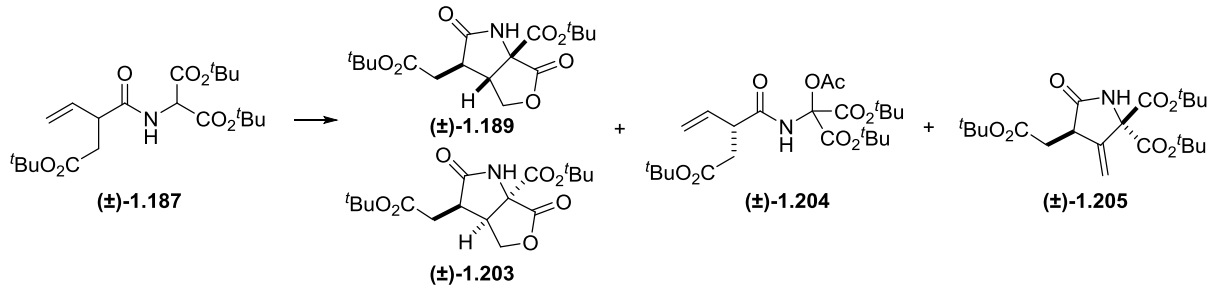
the influence of the water concentration showed that this parameter was important for the control of the formation of the oxidation side products **(±)-1.204**. It was also discovered in this study that the presence of water favoured the formation of a new *exo*-alkene side product **(±)-1.205** (Error! eference source not found.**)**.



(±)-1.205

Figure 1.7 New *exo*-alkene side product favoured by the addition of water

Five reactions with MeCN/H_2O ratios ranging from pure MeCN to MeCN/H_2O (50:5) were performed to examine the influence of the water concentration on the formation of the two side products. The proportions of the side products are given in molar percentage and result from the integration of the high field ^{1}H NMR (500 MHz) of the crude reaction mixtures (**Table 1.3**, column 3 to 5). The isolated yield (given in column 6), is the total yield of the two diastereoisomers **(±)-1.189** and **(±)-1.203**. In the absence of water (**Table 1.3**, entry 1), the reaction has only one side product which is the linear alkene **(±)-1.204**. The formation of the linear side product is minimised at high concentration of water, but in this case the formation of the *exo*-alkene **(±)-1.205** becomes important (**Table 1.3**, entry 5). Intermediate situations seem to give a good compromise in the total amount of formed side products **(±)-1.204** and **(±)-1.205** (**Table 1.3**, entry 2 to 4). The highest isolated yield (78%) was obtained for 50:3 MeCN/H_2O ratio (entry 4).



(±)-1.187 **(±)-1.189** **(±)-1.203** **(±)-1.204** **(±)-1.205**

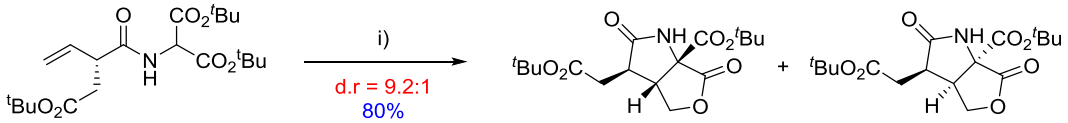
Entry	MeCN/H_2O	Lactones (crude)	(±)-1.204 (crude)	(±)-1.205 (crude)	Lactones (isol. yield)
1	50:0	89.5%	10.5%	0.0%	65%
2	50:1	93.2%	4.7%	2.1%	76%
3	50:2	95.2%	1.8%	3.0%	74%
4	50:3	94.8%	1.5%	4.7%	78%
5	50:5	93.1%	0.4%	6.5%	73%

Table 1.3 Isolated yields of the cyclisation products and NMR proportions (mol%) of product and side products, on 500 mg scale (C = 0.25 M).

Reagents and conditions $Mn(OAc)_3{\cdot}2H_2O$ (3.0 eq), $Cu(BF_4){\cdot}xH_2O$ (0.3 eq if x = 6), MeCN/H_2O (variable proportions), 105 °C, 30 min.

In this study, no correlation was observed between the stereochemical outcome of the cyclisation (d.r.) and the water concentration. For all reactions, the d.r. was in the 8.5:1–9.5:1 range. An example of the NMR determination of the proportions of the side product in the crude of the reaction is given in the appendix (section **7.1.3**).

MeCN/H_2O (50:3) solvent ratio gave the highest isolated yield (78%) and low proportions of side products. Hence, the ratio was kept for further scale up. On larger scale enantioenriched substrate was engaged in the reaction, which gave an 80% total isolated yield of the two diastereoisomers (**Scheme 1.63**). The crude d.r. (9.2:1) was determined by ^{1}H NMR (appendix **7.1.4**), the spectrum of the purified major diastereoisomer can also be found in the appendix (section **7.1.6**).



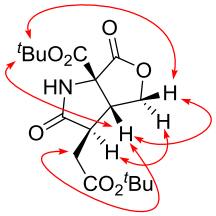
(-)-1.187 **(+)-1.189** **(-)-1.203**

Scheme 1.63 Optimised conditions for the manganese(III) and copper (II) oxidative radical cyclisation of the selected cyclisation product

Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (3.0 eq), $Cu(BF_4)_2{\cdot}xH_2O$ (0.3 eq if x=6), MeCN/H_2O (50:3), 105 °C, 30 min.

The structure of the major diastereoisomer was confirmed by ^{1}H NMR nOe experiments (**Scheme 1.64**). The three nOe interactions between the proton at the junction of the two cycles and the group of protons outside the bowl-shaped molecule confirmed the predicted stereochemistry.

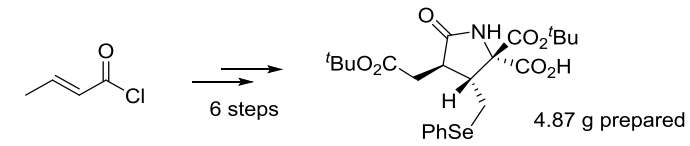
Key nOe interactions in $CDCl_3$



(-)-1.189

Scheme 1.64 Key nOe interactions of (-)-1.189

After the opening of the lactone ring, the new optimised route allowed the synthesis of the carboxylic acid **(+)-1.194** from crotonyl chloride in an efficient and scalable way (**Scheme 1.65**). This new route gave ample amount of enantiopure material required for the investigations of the subsequent synthetic steps.



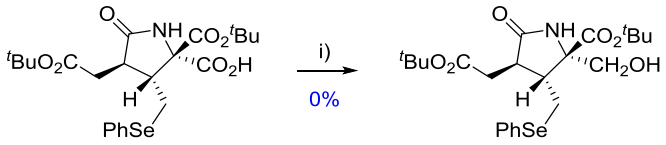
crotonyl chloride **(+)-1.194**

Scheme 1.65 Efficient route to the carboxylic acid (+)-1.194

1.10 Reduction of carboxylic acid (+)-1.194 and subsequent alkene formation

1.10.1 Initial attempts

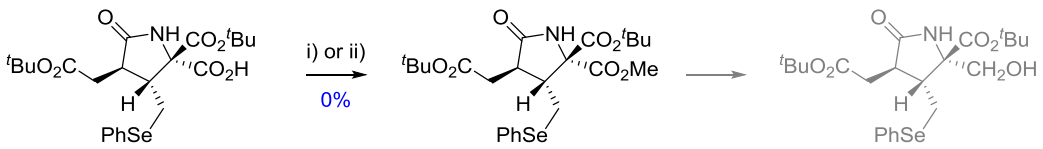
The reduction of the carboxylic acid **(+)-1.194** obtained after the opening of the lactone **(+)-1.189** was next investigated. Diverse reaction conditions were examined to perform this apparently simple step. Attempts at using $BH_3{\cdot}SMe_2$ as a reducing agent led to decomposition of the starting material, no trace of product could be found (**Scheme 1.66**). The reduction of pyrrolidinone to pyrrolidine at room temperature is reported in the literature with this reagent,[87] the use of borane derivatives was consequently excluded from further investigations.



(+)-1.194 **(-)-1.206**

Scheme 1.66 Initial attempt of the reduction of the carboxylic acid (+)-1.194
Reagents and conditions i) $BH_3{\cdot}SMe_2$, THF, 0 °C to RT, 1 h.

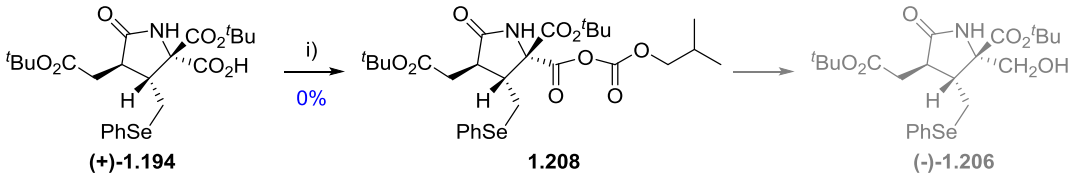
Methyl esters are readily reducible with $NaBH_4$. Hence, the possibility of forming the methyl ester of carboxylic acid **(+)-1.194** was examined (**Scheme 1.67**). Neither TMS-diazomethane, nor MeI/K_2CO_3 in DMF led to methyl esterification of carboxylic acid **(+)-1.194**. These results were surprising given that Danishefsky had esterified a closely related carboxylic acid (previously presented in **Scheme 1.9**).[21] The lack of reactivity of the carboxylic acid **(+)-1.194** toward reliable methyl esterification procedures is presumably due to the high steric hindrance around the carboxylic acid. The attempt at forming the methyl ester was thus, abandoned.



(+)-1.194 **1.207** **(-)-1.206**

Scheme 1.67 Attempts of the formation of the methyl ester 1.207
Reagents and conditions i) $TMSCHN_2$ (1.5 eq), Toluene/MeOH (5:1), 0 °C to RT, 1 h; ii) MeI (5.0 eq), K_2CO_3 (5.0 eq), DMF, RT, 12 h.

The activation of the carboxylic acid **(+)-1.194** to facilitate the reduction was then considered. Initially, the carboxylic acid **(+)-1.194** was treated in THF with isobutyl chloroformate to form the mixed acid/carbonic anhydride **1.208**, which was then treated *in situ* with $NaBH_4$ (**Scheme 1.68**).

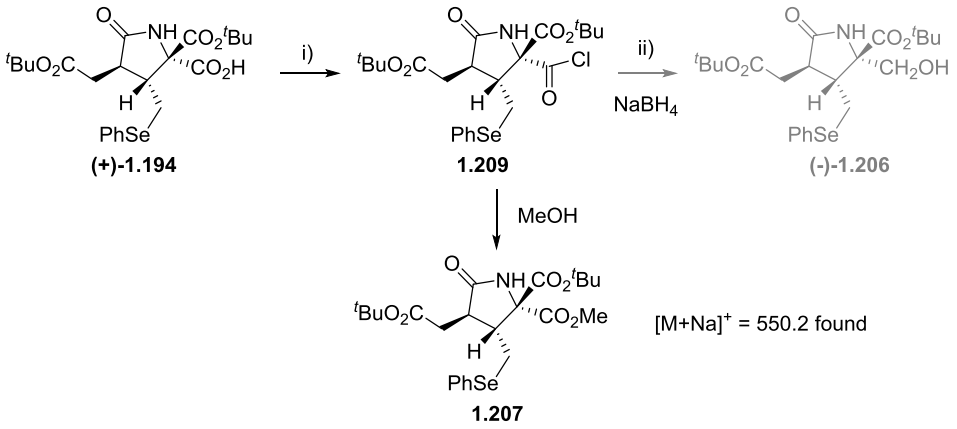


Scheme 1.68 Unsuccessful reduction of the carboxylic acid
Reagents and conditions i) Isobutyl chloroformate (1.10 eq), NEt_3 (1.10 eq), THF, 0 °C to RT, 1 h then add $NaBH_4$ (3.5 eq).

The approach was unsuccessful and led to the formation of several compounds observed by TLC analysis of the reaction mixture. It is unclear whether the intermediate **1.208** had been formed. Further attempt focused on the formation and the reduction of the acyl chloride of the carboxylic acid **(+)-1.194.**

1.10.2 **Successful reduction via formation of an acyl chloride and subsequent alkene formation**

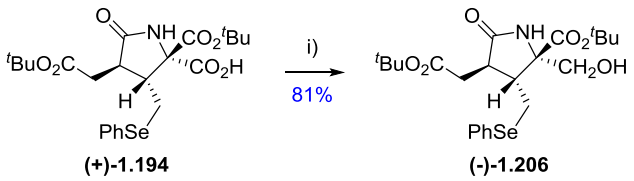
The carboxylic acid **(+)-1.194** was submitted to the Vilsmeier salt to generate the acyl chloride (**Scheme 1.69**). Subsequent treatment with excess $NaBH_4$ at -78 °C did not lead to the desired alcohol. However, the treatment of an aliquot of the reaction mixture with MeOH before the addition of $NaBH_4$, followed by positive LRMS analysis showed the mass corresponding to the methyl ester **1.207** ($[M+Na]^+$ = 550.2).



Scheme 1.69 Successful formation of the acyl chloride and failed subsequent reduction
Reagents and conditions i) $[Me_2N{=}CHCl]^+,Cl^-$ (2.0 eq), THF/MeCN (2:1), 1 h, RT; ii) $NaBH_4$ -78 °C to RT.

Despite the failure of the reduction step, the possibility of forming the acyl chloride **1.209** was encouraging. As boron reagents led to failures in every reduction attempt, the possibility of reducing the acyl chloride **1.209** with other reagents was investigated. $LiAl(O^tBu)_3H$ is capable of reducing acyl chlorides to aldehydes when used at -78 °C,[88] the use of an excess of this reagent at higher temperature was expected to drive the reduction process toward the formation of the desired alcohol **(-)-1.206**. In a first attempt, the acyl chloride was formed using the previous conditions and was treated *in situ* with a solution of $LiAl(O^tBu)_3H$ (5.0 eq) in THF at -78 °C. Successive aqueous acidic work-up on aliquots taken from the reaction mixture allowed the reaction to be monitored by ^1H

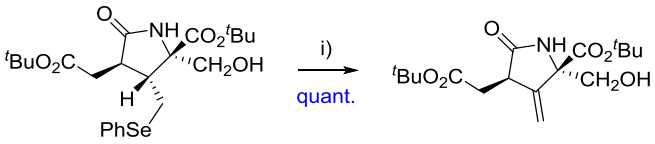
NMR analysis. The progressive conversion to the aldehyde and also the partial conversion toward another product, which was suspected to be the corresponding alcohol, could be observed. When the same process was repeated using a larger excess of $LiAl(O^tBu)_3H$ (10.0 eq) with slow warming to room temperature, complete conversion to the alcohol **(-)-1.206** occurred. The use of 8.0 eq of $LiAl(O^tBu)_3H$ on large scale gave the desired alcohol **(-)-1.206** in a good yield (**Scheme 1.70**).



(+)-1.194 **(-)-1.206**

Scheme 1.70 Final reduction
Reagents and conditions i) $[Me_2N{=}CHCl]^+,Cl^-$ (2.0 eq), THF/MeCN (3:2), 0 °C, 30 min; then add $LiAl(O^tBu)_3H$ (8.0 eq), THF, -78 °C to RT, 90 min.

The alkene **(-)-1.210** was formed by oxidative elimination of the phenyl selenium group of the lactam **(-)-1.206**. The reaction did not require any optimisation, as it proceeded in high yield when it was performed with $NaIO_4$ (**Scheme 1.71**).



(-)-1.206 **(-)-1.210**

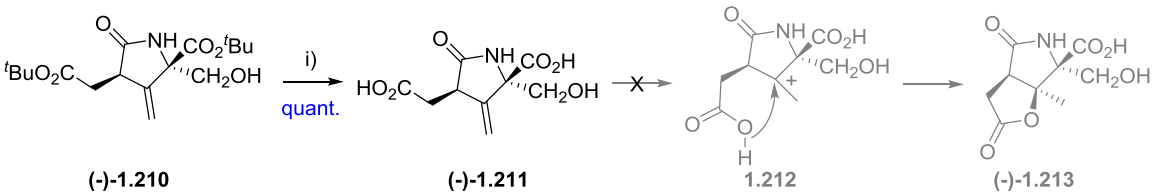
Scheme 1.71 Introduction of alkene functionality *via* the oxidative elimination of the phenyl selenium group
Reagents and conditions i) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), MeOH/THF/H_2O (1:1:1), RT, 45 min then $CHCl_3$, 75 °C, 60 min.

1.11 Exploration of lactonisation possibilities

The lactonisation of the alkene **(-)-1.210** is crucial in our strategy, as it installs the second adjacent quaternary stereocentres of (-)-salinosporamide A. A wide range of conditions had to be examined before success.

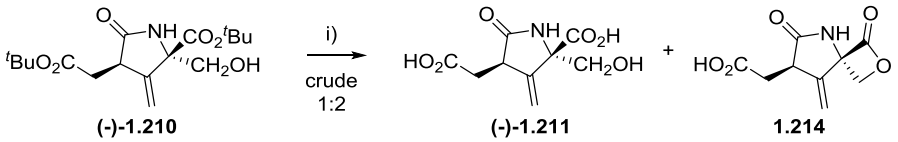
1.11.1 Alkene lactonisation promoted by Brønsted and Lewis acids

The treatment of alkene **(-)-1.210** with strong acids were tested to form the carbenium ion **1.212**, which was envisaged to react with the neighbouring carboxyl unit to form the desired γ-lactone **(-)-1.213** (**Scheme 1.72**). However, the use of TFA at room temperature in DCM only gave the corresponding diacid **(-)-1.211.**



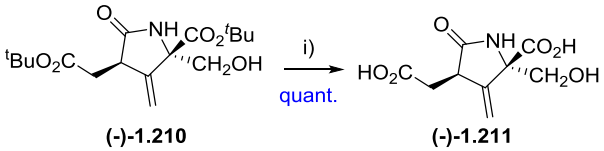
Scheme 1.72 Ester deprotection and unsuccessful subsequent lactonisation
Reagents and conditions i) TFA/DCM (1:1), RT, 2 h.

The same reaction was trialled at higher temperature in neat TFA (**Scheme 1.73**). The γ-lactone **(-)-1.213** was not formed; instead partial conversion to a product tentatively assigned as the spiro γ-lactam β-lactone fused ring system **1.214** was observed.



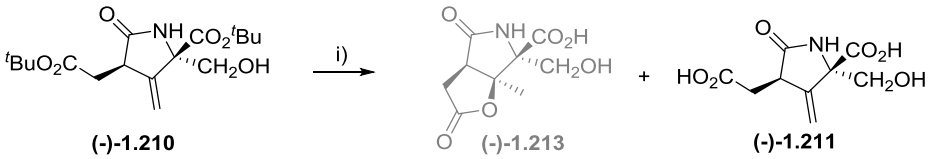
Scheme 1.73 First lactonisation attempt with TFA
Reagents and conditions i) TFA, 75, °C, 60 min

The analysis of the crude of the reaction NMR (appendix **7.1.2**) shows that the major product conserved the *exo*-alkene functionality but also presents two new doublets (4.81 ppm, 1H, *J* = 11.2 Hz and 4.70 ppm, 1H, *J* = 11.2 Hz), which would correspond to the γ-lactam-β-lactone **1.214**. When the reaction was repeated on a larger scale and left overnight to reach completion, the NMR analysis mostly showed decomposition. The treatment of the alkene **(-)-1.210** in dioxane by concentrated aqueous HCl also stops at the deprotection stage without further lactonisation (**Scheme 1.74**). Since the alkene **(-)-1.210** seemed unreactive toward strong Brønsted acids, other methods were then evaluated.



Scheme 1.74 Treatment of alkene (-)-1.210 with HCl
Reagents and conditions i) conc. aq. HCl/dioxane (1:2), RT, 12 h.

The use of $BF_3{\cdot}Et_2O$ complex for the lactonisation of γ-δ unsaturated *tert*-butyl ester has been reported.[89] It was thought that such conditions could be suitable for direct lactonisation of the diester alkene **(-)-1.210** (Scheme 1.75). Unfortunately these conditions also led to the formation of the diacid **(-)-1.211**, without any trace of the desired lactone.

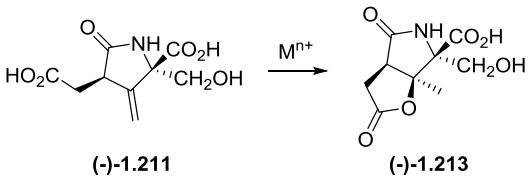


Scheme 1.75 Lactonisation attempt with $BF_3{\cdot}Et_2O$
Reagents and conditions i) $BF_3{\cdot}Et_2O$ (8.0 eq), MeCN/DCM (5:2), RT, 12 h.

The promotion of the lactonisation of alkene **(-)-1.210** with transition metals was therefore first examined as an alternative to previous failures. The use of halolactonisation or selenolactonisation was also appealing, but this type of strategy would add a dehalogenation or deselenylation step.

1.11.2 **Alkene lactonisation promoted by transition metals**

The use of transition metals to promote lactonisation of γ,δ-unsaturated carboxylic acids has been reported. Iron,[90] copper[91] and silver[92] metals have shown good precedents in the promotion of alkene lactonisations. Some of these reported conditions were tried on diacid alkene **(-)-1.211** without success (**Table 1.4**). The use of different transition metals at room temperature (**Table 1.4**, entry 1 to 3) only led to the recovery of the starting material. When the reaction was tried at higher temperatures with short reaction times in DCE, the starting material was again recovered (entry 4 to 6). Long reaction time at high temperature led to decomposition (entry 7). Halolactonisation conditions were then investigated for this system.



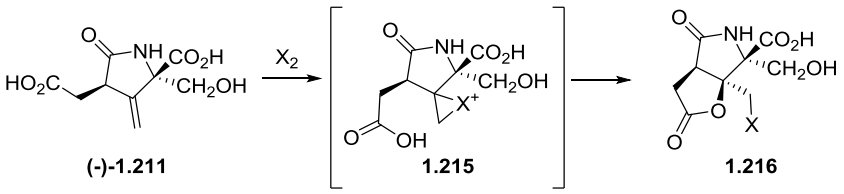
Entry	Metal a	Metal b	Solvent	T (°C)	t	Yield
1	Ag(OTf) 1.0 eq	-	MeCN	25	3 days	0%
2	$AgBF_4$ 1.0 eq	-	MeCN	25	3 days	0%
3	$Cu(OTf)_2$ 1.0 eq	-	MeCN	25	3 days	0%
4	Ag(OTf) 0.09	$FeCl_3$ 0.03 eq	DCE	83	1 h	0%
5	Ag(OTf) 0.1 eq	-	DCE	83	30 min	0%
6	$Cu(OTf)_2$ 0.1 eq	-	DCE	83	30 min	0%
7	$Cu(OTf)_2$ 0.1 eq	-	DCE	83	24 h	0%

Table 1.4 Unsuccessful attempts of transition metals catalysed lactonisation

1.11.3 **Alkene halolactonisation**

The electrophilic addition of di-halogens to alkenes can lead to the formation of reactive ionic species **1.215** (iodonium or bromonium), which can be opened intramolecularly to form the lactone ring. The conversion of γ,δ-unsaturated acids into halolactones is a widespread method to form

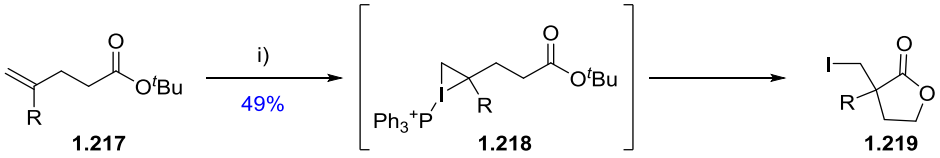
lactone rings,[93] but their use would add one step to the sequence corresponding to the removal of the residual halogen atom. During the initial investigations, standard iodolactonisation conditions were trialled (**Table 1.5,** entry 1 to 3). These conditions did not lead to the formation of the desired lactone. The addition of Ag(OTf) in the reaction showed a significant rate increase in reported iodolactonisations.[94] Such conditions were also trialled and did not provide the desired lactone (**Table 1.5**, entry 4).



Entry	Reagent 1	Reagent 2	Buffer	Solvent	T (°C)	t	Yield
1	I_2 (3.0 eq)	-	aq. NaHCO3	THF	0 to 25	12 h	0%
2	I_2 (6.0 eq)	-	aq. NaHCO3	THF	60	12 h	0%
3	I_2 (3.0 eq)	KI (5.0 eq)	aq. NaHCO3	H_2O	25	12 h	0%
4	I_2 (1.0 eq)	Ag(OTf) (1.0 eq)	-	MeCN	25	3 d	0%

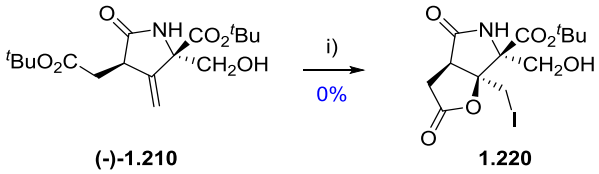
Table 1.5 Attempts of halolactonisation

Further literature investigations led to an interesting phosphine-catalysed iodolactonisation described by Ishihara *et al.* (**Scheme 1.76**).[95] The reaction proceeded by intramolecular reaction of the *tert*-butyl ester on the iodonium **1.218**.



Scheme 1.76 Phosphine-catalysed iodolactonisation of *tert*-butyl ester[95]
Reagents and conditions i) NIS (1.20 eq), Ph_3P (0.30 eq), PhMe, -40 °C to RT 12 h.

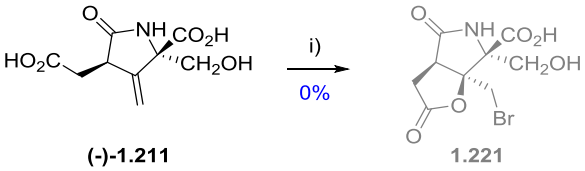
Such conditions were applied to alkene **(-)-1.210** carrying the two *tert*-butyl esters (**Scheme 1.77**), which again proved to be unreactive as the starting material was the only compound detected by proton NMR analysis of the crude reaction mixture.



Scheme 1.77 Failed attempt of direct lactonisation of the *tert*-butyl ester onto the alkene of substrate (-)-1.210
Reagents and conditions i) NIS (1.20 eq), Ph_3P (0.30 eq), PhMe, -40 °C to RT 12 h.

As alkenes **(-)-1.210** and **(-)-1.211** were unreactive under a wide range of iodolactonisation conditions, the use of bromine was then trialled in a bromolactonisation by addition of Br_2 to a

solution of diacid **(-)-1.211** in aqueous $NaHCO_3$.[96] The diacid was unreactive under these conditions too. Halolactonisations were therefore abandoned.



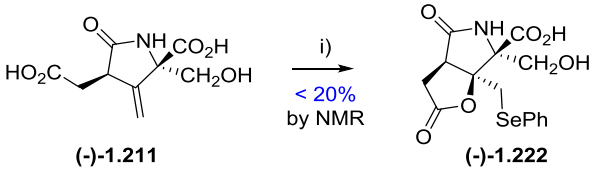
Scheme 1.78 Bromolactonisation attempt
Reagents and conditions i) Br_2 (1.2 eq), $NaHCO_3$ (2.5 eq), H_2O, RT, 12 h.

Last attempts focused on the use of an equivalent of the phenyl selenium cation "$PhSe^+$" appeared to promote the desired lactonisation of the unreactive *exo*-alkenes **(-)-1.210** and **(-)-1.211**. The activation of a similar alkene with "$PhSe^+$" is precedented by Danishefsky, as this activation allowed to promote an intramolecular acetalisation.[21]

1.11.4 **Selenolactonisation**

1.11.4.1 Initial attempt

In an initial attempt of selenolactonisation, diacid **(-)-1.211** was submitted to a known procedure using PhSeBr in Et_2O and MeOH (**Scheme 1.79**).[97] The ^1H NMR analysis of the crude reaction mixture indicated that the starting diacid partially reacted to form small quantities of the desired lactone **(-)-1.222**.

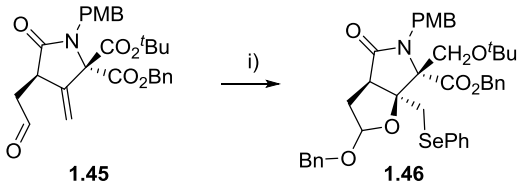


Scheme 1.79 First observation of the formation of the desired lactone ring
Reagents and conditions i) PhSeBr (1.0 eq), Et_2O/MeOH, -78 °C to RT, 3 h.

Since the initial lactonisation result was most encouraging, further attempts with a higher stoichiometry and longer reaction times were initially planned. However, different selenolactonisation conditions were also tested and led to more promising results.

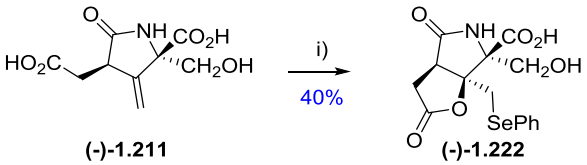
1.11.4.2 Danishefsky's acetalisation conditions

Danishefsky used PhSeBr and $AgBF_4$ to perform an acetalisation step toward (-)-salinosporamide A (**Scheme 1.80**).[21]



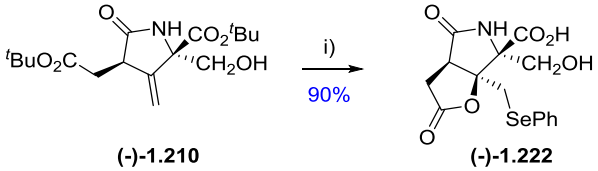
Scheme 1.80 Danishefsky[21] acetalisation *en route* to (-)-salinosporamide A
Reagents and conditions i) PhSeBr (4.0 eq), $AgBF_4$ (4.0 eq), BnOH (4.0 eq), DCM, -20 °C (30 min) to 0 °C (90 min).

Given the similarities between Danishefsky's intermediate **1.45** and the *exo*-alkene **(-)-1.211**, it was decided to test these conditions, which gave the required selenium derivative **(-)-1.211** (**Scheme 1.81**). The solvent system had to be modified as benzyl alcohol was not required. Moreover the diacid **(-)-1.211** used in this first attempt was insoluble in neat DCM. Therefore MeCN/DCM (1:1) was used as the solvent system of the reaction.



Scheme 1.81 Selenolactonisation of the diacid (-)-1.211
Reagents and conditions i) PhSeBr (4.0 eq), $AgBF_4$ (4.0 eq), DCM/MeCN (1:1), RT, 12 h.

The di *tert*-butyl ester **(-)-1.210** was also reactive under these conditions (**Scheme 1.82**). The second *tert*-butyl ester side chain was lost during the reaction. The reaction gave the fused γ-lactone-γ-lactam **(-)-1.222** in high yield.



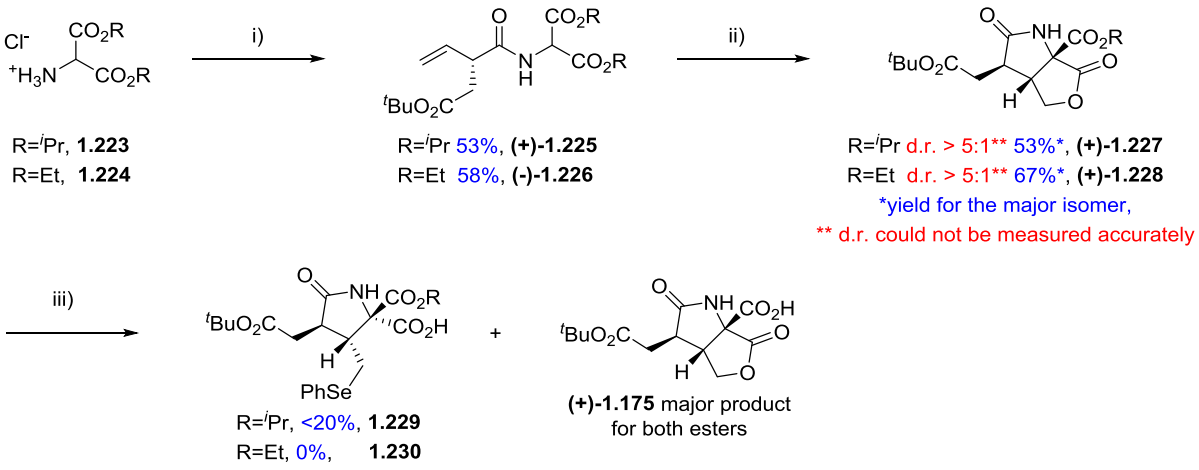
Scheme 1.82 Selenolactonisation of the diester (-)-1.211
Reagents and conditions i) PhSeBr (3.5 eq), $AgBF_4$ (2.5 eq), DCM/MeCN (1:1), RT, 7 h.

The loss of the *tert*-butyl ester could not be overcome. The use of different malonate esters were investigated in order to avoid the reprotection of the β-hydroxy acid **(-)-1.222**.

1.12 *tert*-Butyl ester alternatives

It was previously demonstrated that equivalents of the *exo*-alkene **(-)-1.210** bearing a methyl or benzyl side chain at the upper ester position would be impossible to synthesise as these ester groups could not resist the conditions of the selenium opening of their corresponding lactones **(+)-1.163** and **(+)-1.188** (section **1.8.1** and **1.8.3.2**). The ideal ester alternative therefore required three features: i) the compatibility with the oxidative cyclisation; ii) the resistance to selenium anion; iii) the resistance to the acidic conditions of the selenolactonisation. It was anticipated that an *iso*-propyl

ester would present these three properties. We were aware that the isopropyl ester would be difficult to remove at a late stage of the synthesis. Hence, the corresponding ethyl ester was also prepared, although its resistance to the phenyl selenium anion was considered lower.[80] The synthesis of the corresponding selenolactonisation substrates **1.229** and **1.230** could not be achieved as both esters **(+)-1.227** and **(+)-1.228** show low resistance to the phenyl selenium anion. The carboxylic acid **(+)-1.175** resulting from the cleavage of the two esters under the reaction conditions was the major product detected in the two crude reaction mixtures.

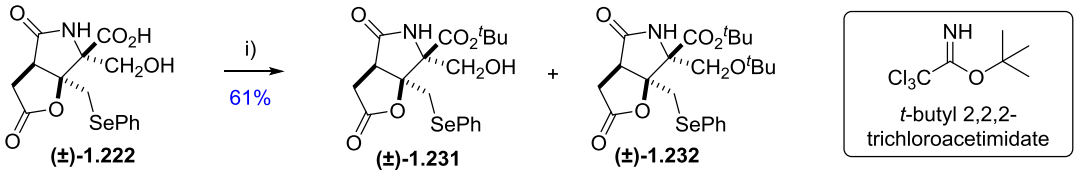


Scheme 1.83 Evaluation of alternative esters

Reagents and conditions i) Acid **(-)-1.144** (0.90 eq), T3P (2.0 eq), Pyridine (5.0 eq), -20 to -10 °C; ii) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq), $Cu(BF_4)_2 \cdot 6H_2O$ (0.30 eq), $MeCN/H_2O$, 85 °C, 45 min; iii) $(PhSe)_2$ (1.20 eq), NaH (2.40 eq), THF, 65 °C then add at 0 °C solution of lactone and 18-crown-6 (0.25 eq) in THF, 0 °C to RT; 3 h.

1.13 Carboxylic acid re-protection

A *tert*-butyl ester was initially chosen to re-protect the carboxylic acid **(-)-1.222**. A bulky protecting group was anticipated to increase the likelihood of success of the selective reduction of the lactone required in later steps. It would also be easily removed under acidic conditions at a late step of the synthesis. The protection of a carboxylic acid in presence of an alcohol at the β-position has been reported in high yield using *tert*-butyl 2,2,2-trichloroacetimidate.[98] The use of this reagent on racemic carboxylic acid **(±)-1.222**, led to moderate selectivity between the protection of the alcohol and the carboxylic acid; the yield of the protection never remained moderate (**Scheme 1.84**).

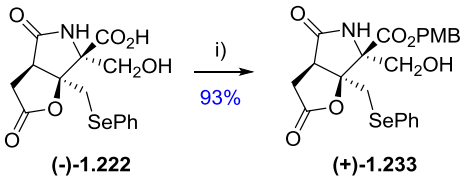


Scheme 1.84 Moderately selective protection of the carboxylic acid (±)-1.222 with *tert*-butyl 2,2,2-trichloroacetimidate

Reagents and conditions i) *tert*-butyl 2,2,2-trichloroacetimidate, Hexane/EtOAc (3:5), RT.

The selective protection of the carboxylic acid **(-)-1.222** was achieved with PMBCl (**Scheme 1.1**). The reaction proceeded in good yield in DMF in the presence of NaI and K_2CO_3.[99] The next 3 steps were

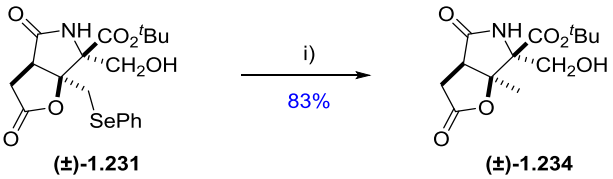
investigated and optimised on the racemic *tert*-butyl ester product **(±)-1.231**. The developed chemistry was then applied to the enantiopure PMB ester **(+)-1.233** and is presented in section **1.16.**



Scheme 1.85 Selective PMB protection of the carboxylic acid
Reagents and conditions i) PMBCl (3.0 eq), NaI (3.0 eq), K_2CO_3 (4.0 eq), DMF, 40 °C, 4 h.

1.14 Reductive cleavage of the phenyl selenium moiety

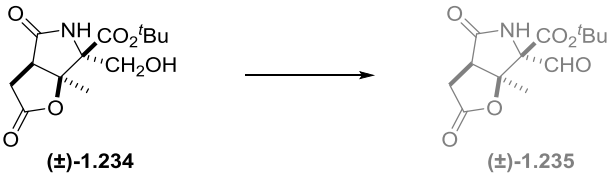
The deselenylation of lactam **(±)-1.231** was achieved by radical reduction with tri-butyl tin radical, generated at high temperature by decomposition of trace amounts of AIBN in the presence of *n*-Bu_3SnH (**Scheme 1.85**).[21]



Scheme 1.86 Deselenylation of (±)-1.231
Reagents and conditions i) *n*-Bu_3SnH (2.5 eq), AIBN (0.1 eq), PhMe (105 °C), 15 min.

1.15 Oxidation, followed by the installation of the last stereocentres

The oxidation of alcohol **(±)-1.234** to the corresponding aldehyde **(±)-1.235** was required at this stage to allow the addition of an organometallic reagent to install the cyclohexenyl side chain. Three different set of conditions were initially trialled for the oxidation of alcohol (**Table 1.6**). PCC show no reaction after 2 h (entry 3), and Py·SO_3 and DMP led to decomposition (entry 2 and 1).



Entry	Reagent 1	Base	Solvent	T (°C)	t	Yield
1	DMP (2.0 eq)	-	THF	0 to 25	1 h	0%
2	Py.SO_3 (4.0 eq)	DIPEA (6.0 eq)	DMSO/Pyridine	0	1 h	0%
3	PCC (1.5 eq)	-	DCM	25	2 h	0%

Table 1.6 Oxidation conditions

1.15.1 **NMR study of the Dess-Martin oxidation**

In order to understand the failure of the Dess-Martin oxidation, it was decided to carry the oxidation reaction in an NMR tube in DCM-d_2. Before the start of the reaction, the spectrometer was pre-shimmed with a solution of DMP (45.0 mg in DCM-d_2 0.75 mL).

The reaction was started by addition of DCM-d_2 (0.75 mL) to DMP (45 mg, 0.106 mmol) and alcohol **(±)-1.234** (15 mg, 0.053 mmol). The solution was immediately transferred into an NMR tube and a first 8 scans acquisition was runned before further shimming adjustments. Acquisitions were then run every 3-5 min over 1 hour.

Surprisingly, the NMR showed clean and complete conversion to the aldehyde in 40 min without decomposition over time. To simulate the effect of an aqueous work-up, water was added to the NMR tube which was shaken. When the layers had separated, the aqueous phase was removed from the tube and a new acquisition was run. This operation showed clear decomposition of the aldehyde **(±)-1.235** in the presence of water.

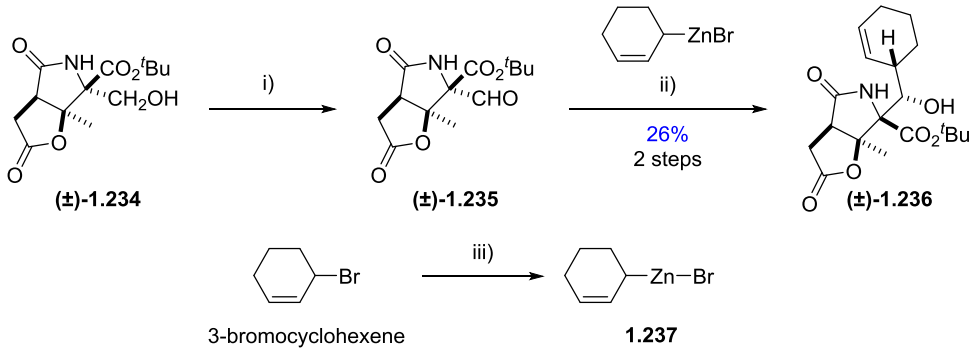
Further attempts were made to try to isolate the unstable aldehyde produced by the Dess-Martin oxidation without aqueous work up. Direct plugging of the reaction mixture on silica or basic alumina did not allow recovery of the aldehyde.

The use of a different oxidation procedure, which would not involve any aqueous work-up or column chromatography purification, was next envisaged.

1.15.2 **Use of IBX**

A purification-free alcohol oxidation to form the corresponding aldehydes or ketones, which involves the use of IBX as an oxidant at reflux temperature in EtOAc has been reported.[100] This protocol takes advantage of the insolubility of IBX and its residue in EtOAc at room temperature. All impurities can then be removed by filtration, which allows the recovery of the aldehyde by simple evaporation and without aqueous work-up.

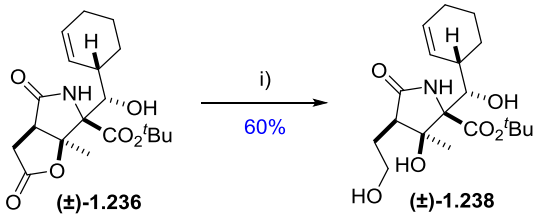
This IBX procedure was applied to the alcohol **(±)-1.234**, and the residual crude aldehyde **(±)-1.235** was readily treated with cyclohexene zinc reagent **1.237** to avoid possible decomposition of the aldehyde upon storage (**Scheme 1.87**). The isolated yield of the addition product **(±)-1.236** was low; in further attempts the NMR analysis of the intermediate aldehyde showed that oxidation of the starting alcohol was incomplete. (The cyclohexenyl organozinc **1.237** was prepared using Mulholland *et al.* procedure,[34] by treating 3-bromocyclohexene with zinc dust in THF).



Scheme 1.87 IBX oxidation followed by addition of 1.237 to the formed aldehyde (±)-1.235, and preparation of the organozinc reagent 1.237.[34]

Reagents and conditions i) IBX (3.0 eq), EtOAc, 80 °C, 3 h; ii) Cyclohexenyl organozinc **1.237** (3.0 eq), THF, -78 °C.

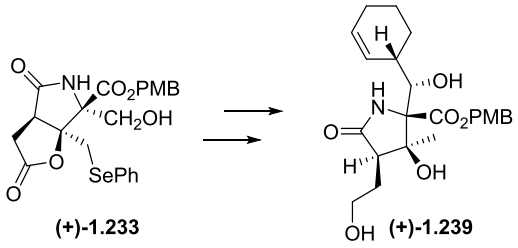
The oxidation and addition procedures were not further optimised on the *tert*-butyl ester **(±)-1.234**. One attempt of reduction of the racemic lactone **(±)-1.236** was trialled on the few milligrams of material left in hand. The reduction of a similar lactone ring to the corresponding diol, was reported by Lam *et al.*[37] In a similar reduction, 100 equivalents of $NaBH_4$ were used to achieve about 60% conversion to triol **(±)-1.238** (**Scheme 1.88**). 14% of starting material was also recycled.



Scheme 1.88 Reduction of lactone (±)-1.236

Reagents and conditions i) $NaBH_4$ (2 x 50.0 eq) added portionwise, MeOH, 2 x 90 min.

The last three steps were then tried on the PMB ester analogue **(+)-1.233** (**Scheme 1.89**), which was obtained in good yield in the protection reaction of the carboxylic acid **(-)-1.222** (previously presented in section **1.13**). The development of this route from **(+)-1.233** is presented in the next section.

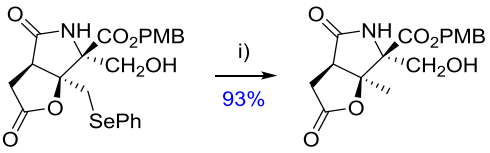


Scheme 1.89 Required steps toward (+)-1.239

1.16 PMB ester route

1.16.1 Reductive cleavage of the phenyl selenium moiety

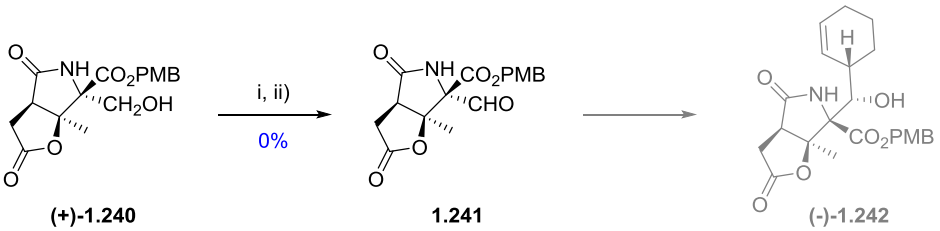
The reduction of the phenyl selenium moiety of the PMB substrate **(+)-1.233** with *n*-Bu_3SnH and AIBN proceeded in high yield (**Scheme 1.90**).



Scheme 1.90 Deselenylation of (+)-1.233
Reagents and conditions i) *n*-$BuSn_3H$ (2.5 eq), AIBN (0.1 eq), PhMe (100 °C), 45 min.

1.16.2 Alcohol oxidation and addition of the organozinc

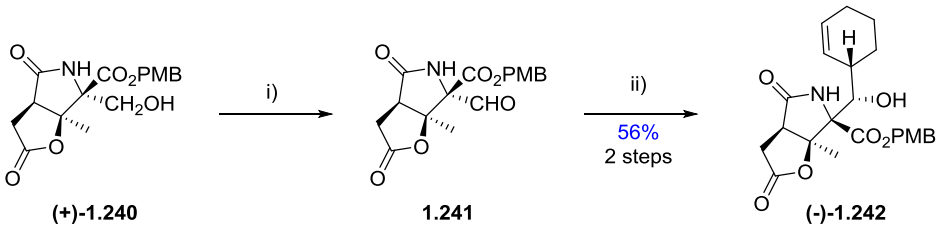
The oxidation with IBX followed by the addition of cyclohexenyl reagent **1.237** presented in section **1.15.2** could not be reproduced on alcohol **(+)-1.240** (**Scheme 1.91**). The NMR analysis of the crude intermediate aldehyde **1.241** indicated low conversion after 4 h. These conditions were abandoned in favour of a one pot oxidation addition procedure.



Scheme 1.91 Attempt of IBX oxidation followed by addition of cyclohexenyl reagent 1.237
Reagents and conditions i) IBX (3.0 eq), EtOAc, 80 °C, 4 h; ii) Organozinc reagent **1.137** (3.0 eq), THF, -78 °C, 2 h.

The Dess-Martin oxidation of alcohol **(+)-1.240** was also conducted in an NMR tube and monitored by ^{1}H NMR spectroscopy (as in section **1.15.1**). The study was performed in DCM-d_2 and also THF-d_8. In both solvent, clean conversion to the aldehyde was observed in less than 40 min.

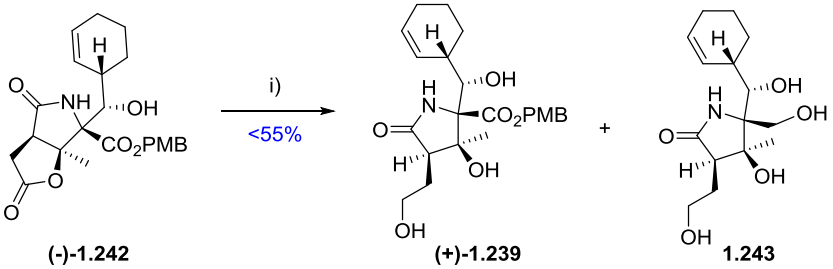
To overcome the decomposition of aldehyde **1.241** also occurring during the work-up, a one pot procedure was designed to add the organozinc reagent **1.237** to aldehyde **1.241**. The procedure started with the addition of DMP (2.0 eq) to the alcohol **(+)-1.240** in THF. After one hour stirring, the cyclohexenyl organozinc **1.237** reagent (10.0 eq) was added to the reaction mixture at low temperature (**Scheme 1.92**). Best yields were obtained with short reaction time. The organozinc reaction was therefore quenched after 10 min stirring at -78 °C. The desired product was isolated as a single diastereoisomer in a 56% yield over 2 steps on large scale (938 mg, 2.69 mmol).



Scheme 1.92 One pot DMP oxidation and addition of organozinc reagent 1.137 addition
Reagents and conditions i) DMP (2.0 eq), RT, THF, 75 min; ii) Organozinc reagent **1.137** (10.0 eq), THF, -78 °C, 15 min.

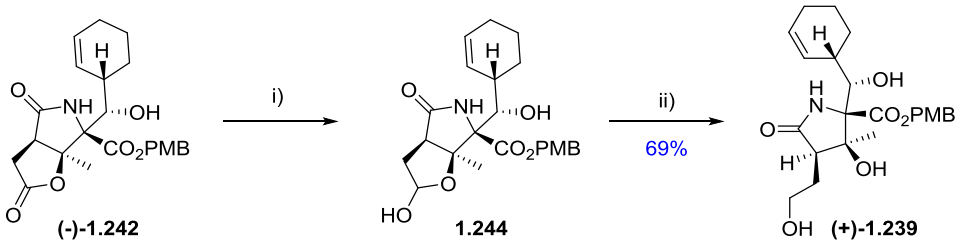
1.16.3 **Reduction of the lactone**

When the reduction of lactone **(-)-1.242** was attempted with a large excess of $NaBH_4$ (3 x 50 eq) in MeOH, the reaction did not reach completion (**Scheme 1.93**). Moreover the formation of a more polar side product was observed by TLC analysis, which was suspected to be the tetraol **1.243**.



Scheme 1.93 First attempt of reduction of lactone (-)-1.242 with a large excess of $NaBH_4$
i) $NaBH_4$ (3 x 50.0 eq) added portionwise, MeOH, 3 x 1 h.

The lactone **(-)-1.242** was then treated with $LiAl(O^tBu)_3H$ (-78 °C to RT), but no reaction was observed after 24 h stirring. The treatment of lactone **(-)-1.242** in THF with an excess of DiBAl-H at low temperature led to the rapid formation of the lactol **1.244** (**Scheme 1.94**). LRMS analysis of the reaction mixture indicated complete conversion in less than 20 min. The reaction was then quenched with MeOH and was treated by portionwise addition of $NaBH_4$ (50.0 eq). This one pot reduction using two reducing agents, led to the formation of triol **(+)-1.239** in satisfactory yield.



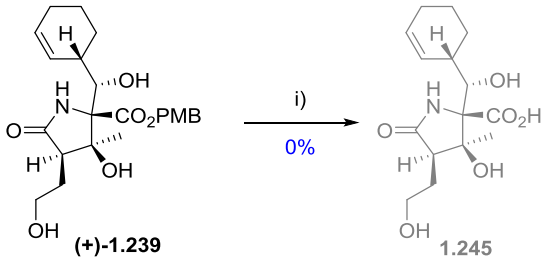
Scheme 1.94 One pot reduction of lactone (-)-1.242
Reagents and conditions i) DiBAl-H (6.0 eq), THF -10 °C, 15 min, then MeOH quench; ii) same pot: $NaBH_4$ (10 x 5.0 eq) every 10 min, MeOH/THF, RT, 30 min.

With enough material in hand, the deprotection, lactonisation, chlorination sequence toward the natural product could be tried.

1.17 Final steps

1.17.1 Deprotection of the PMB ester

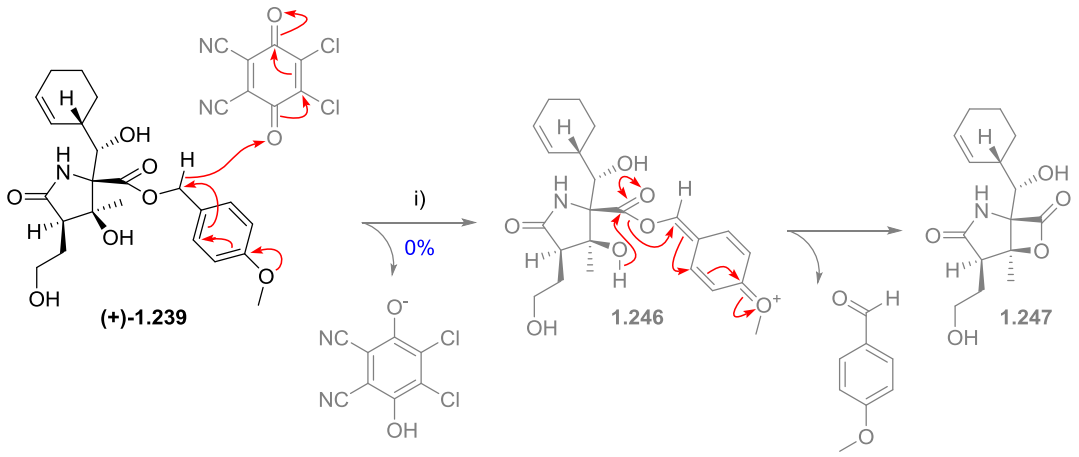
The use of TFA was first tried to achieve the PMB ester removal. But the bright purple reaction mixture decomposed to a brown solid upon evaporation of TFA.



Scheme 1.95 Failed attempt of TFA deprotection
Reagents and conditions i) TFA/DCM (1:1), 0 °C to RT, 75 min.

In a second attempt, excess TFA was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The extraction of the very polar carboxylic acid **1.245** from the reaction mixture proved difficult. After evaporation of EtOAc, the colourless crude turned brown upon drying under high vacuum. The use of TFA was abandoned and other conditions were investigated.

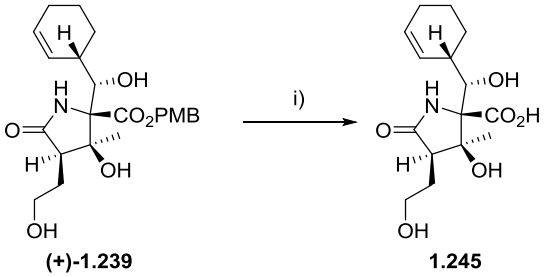
The use of DDQ for the deprotection was then considered as it was anticipated that the intermediate **1.246** after oxidation could react intra-molecularly to deliver lactone **1.247** (**Scheme 1.96**). Unfortunately this approach was unsuccessful as only starting material was recovered after 24 h of reaction.



Scheme 1.96 Unsuccessful deprotection-lactonisation sequence with DDQ
Reagents and conditions i) DDQ (1.5 eq), DCM, 24 h, RT.

The deprotection of the PMB ester was eventually achieved using BCl_3 in DCM. To avoid any aqueous work-up the reaction mixture was plugged through a short pad of silica after excess BCl_3 was

quenched with MeOH (**Scheme 1.97**). The low pH of the plugged mixture helped the elution of the extremely polar carboxylic acid **1.245** on silica.

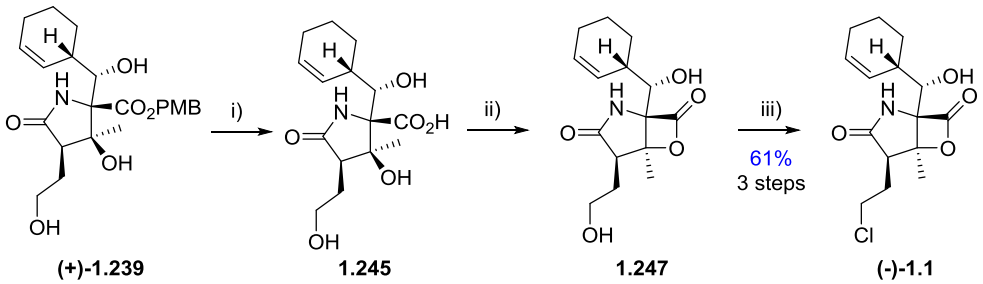


Scheme 1.97 Deprotection of carboxylic acid 1.245
Reagents and conditions i) BCl_3 (4.0 eq), DCM, 0 °C, 30 min.

The crude carboxylic acid **1.245** was directly taken through the next 2 steps without characterisation to avoid any possible decomposition.

1.17.2 **Lactonisation and chlorination: (-)-salinosporamide A**

After the PMB removal, the final sequence was achieved using Corey modified procedure[20] to form the β-lactone **1.247** (**Scheme 1.98**). Acidic work-up or silica column of the intermediate **1.247** led to partial decomposition and to a dramatic drop of the yield of the sequence. In the next attempt the reaction was washed with 10% brine, and the crude was readily taken through the final step without characterising the diol **1.247**. The chlorination of **1.247** gave (-)-salinosporamide A, which tolerated a rapid flash column chromatography.



Scheme 1.98 Final sequence of the total synthesis of (-)-salinosporamide A
Reagents and conditions i) BCl_3 (4.0 eq), DCM, 0 °C, 30 min; ii) BOPCl (1.50 eq), DCM/pyridine, RT, 2 h, then BOPCl (0.50 eq), RT, 1 h; iii) Ph_3PCl_2 (2.0 eq), MeCN/Pyridine, RT, 2 h.

1.18 NMR and characterisations

The proton and carbon NMR spectra of the natural product were acquired in deuterated pyridine (**Figure 1.8**). More than 30 mg of the natural product were prepared. Large quantities of key building blocks have been kept to allow possible future scale-up.

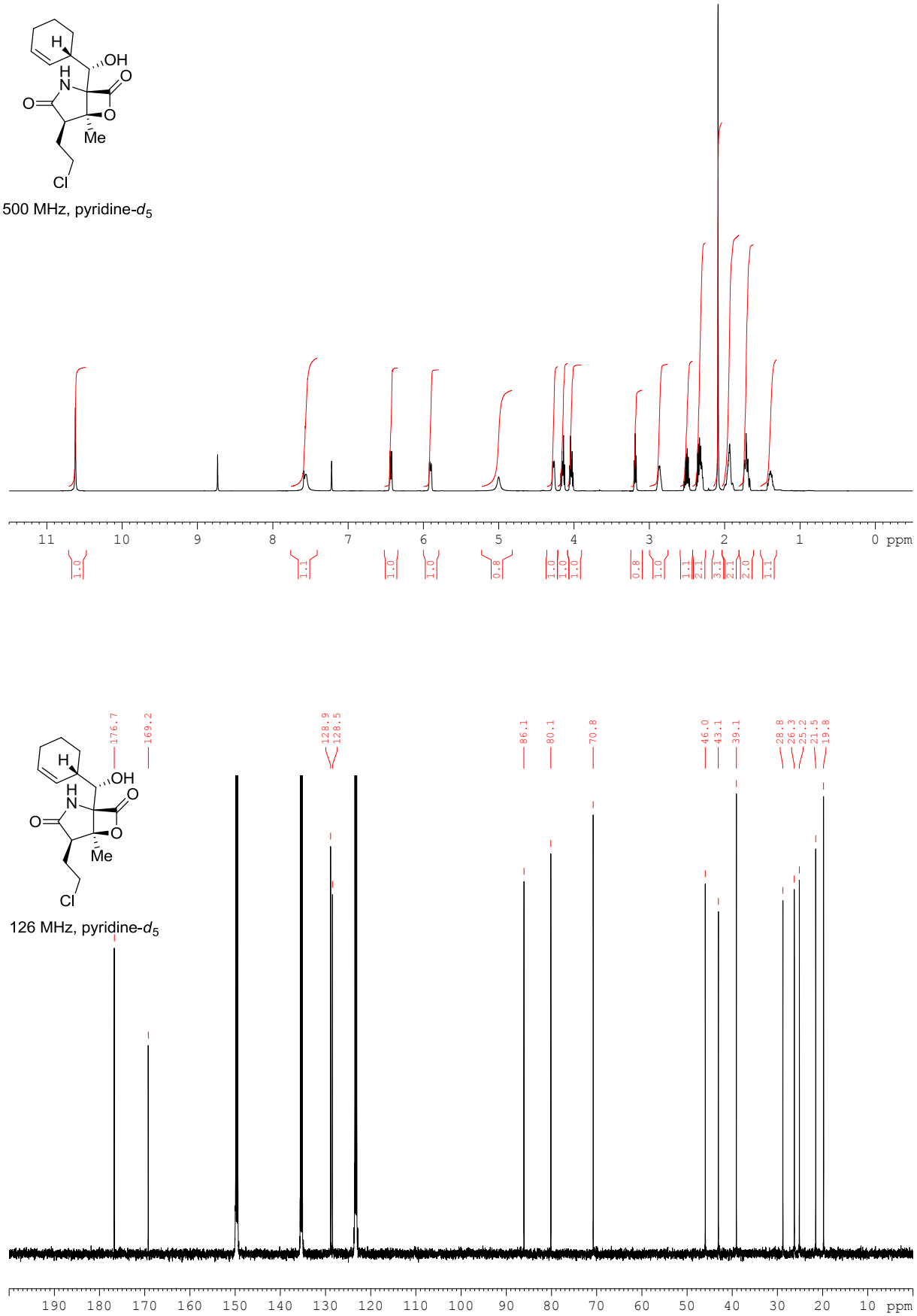
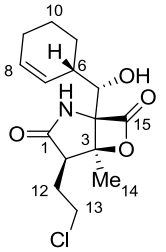


Figure 1.8 Proton and carbon NMR spectra of synthetic (-)-salinosporamide A in pyridine-d_5

The NMR data of the synthetic material were consistent with the isolation data.[2] One important shift between the two spectra was observed for the proton NMR signal of the proton OH group which is 2.68 ppm higher than synthetic salinosporamide A.



C no.[a]	δ_C[b] (isolation)	δ_C[c] (synthetic)	$\lvert\Delta\delta_c\rvert$	δ_H[d] *J* (isolation)	δ_H[e] *J* (synthetic)	$\lvert\Delta\delta_H\rvert$ $\lvert\Delta J\rvert$
1	176.4	176.7*	0.3			
2	46.2	46.0	0.2	3.17, t 7.0 Hz	3.19, t 7.3 Hz	0.02 0.3 Hz
3	86.1	86.2	0.0			
4	80.2	80.1	0.1			
5	70.9	70.8	0.1	4.24, d 9.0 Hz	4.27, d 8.2 Hz	0.03 0.8 Hz
6	39.2	39.1	0.1	2.85, m	2.87	0.02
7	128.4	128.5	0.1	6.42, d 9.6 Hz	6.45, d 10.4 Hz	0.03 0.8 Hz
8	128.8	128.9	0.1	5.88, m	5.90, m	0.02
9	25.3	25.2	0.1	1.91, m, 2H	1.95, m, 2H	0.04
10	21.7	21.5	0.2	a 1.66, m b 1.38, m	a 1.71, m b 1.39, m	0.05 0.01
11	26.5	26.3	0.2	a 2.37, m b 1.66, m	a 2.33, m b 1.71, m	0.04 0.05
12	29.0	28.8	0.2	a 2.48, m b 2.32, m	a 2.50, m b 2.33, m	0.02 0.01
13	43.2	43.1	0.1	a 4.14, m b 4.01, m	a 4.15, m b 4.04, m	0.01 0.03
14	20.0	19.8	0.2	2.07, s, 3H	2.09, s, 3H	0.02
15	169.0	169.2	0.2			
NH				10.60 br s	10.60 br s	0.02
OH				4.99 br s	7.67 br s	2.68

Table 7 Comparison with original isolation data.

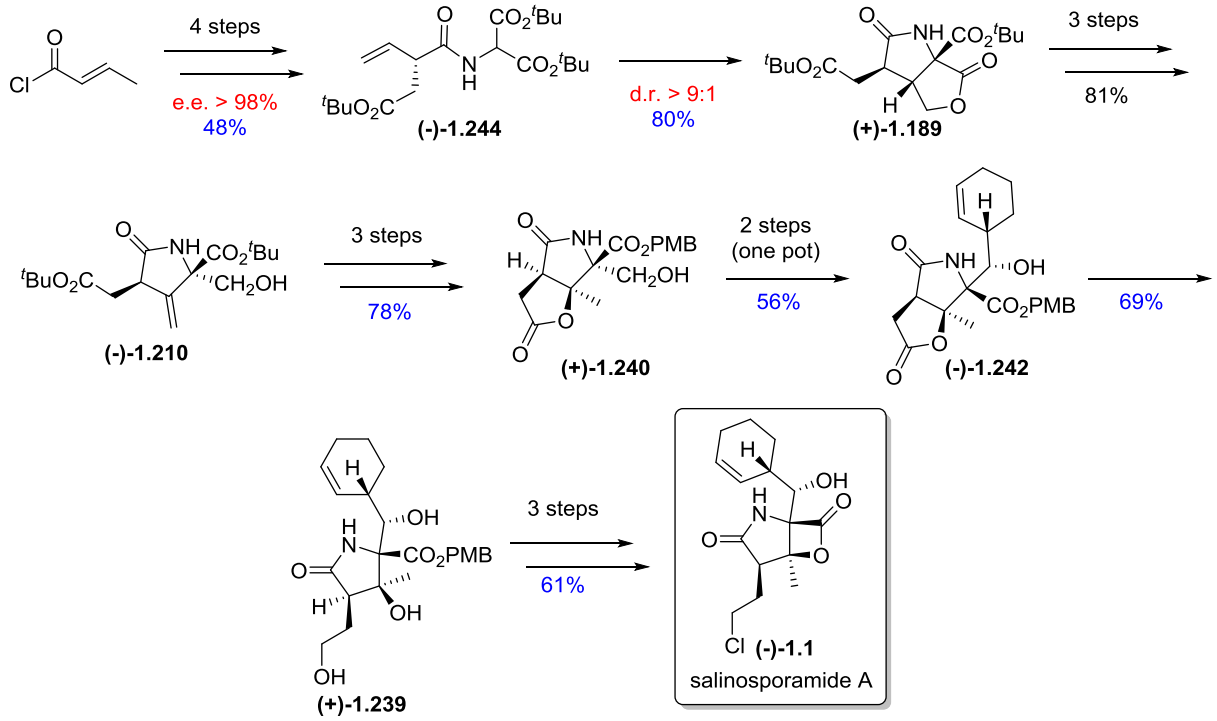
[a] Numbering taken from the original isolation paper; [b] unspecified frequency, pyridine-d_5; [c] 126 MHz, pyridine-d_5; [d] 300 MHz, pyridine-d_5; [e] 500 MHz, pyridine-d_5.

*Danishefsky and Corey reported δ_C = 176.9 ppm

Others characterisations were consistent with the isolation data: **m.p.** 175–178 °C (lit.[2] 168–170 °C); $[\alpha]_D^{20}$ -80.4 (c = 0.49, MeOH) (lit.[2] -72.98, c = 0.55, MeOH); ν_{max} (cm^{-1}) 1819 (C=O β-lactone), 1696 C=O) (lit.[2]1819 and 1702).

1.19 Summary and Conclusion

In summary our new total synthesis of salinosporamide A started from crotonyl chloride, which was transformed in a 4 step sequence into the cyclisation substrate **(-)-1.244** in high e.e. using a deconjugative alkylation and a subsequent amide coupling. The manganese(III) and copper(II)-mediated oxidative cyclisation developed in the group allowed the installation of the first quaternary centre of the key intermediate pyrrolidinone-lactone **(+)-1.189**. The latter was opened with sodium phenyl selenide, and the corresponding seleno carboxylic acid underwent a reduction and an oxidative elimination to give the key *exo*-alkene **(-)-1.210**. Selenolactonisation, reprotection of the carboxyl group affected by a loss of a *tert*-butyl ester and the radical reduction of the phenyl selenium unit gave the pyrrolidinone-lactone **(+)-1.240**. The alcohol **(+)-1.240** was oxidised to the corresponding aldehyde, which was treated in the same pot with an excess of organozinc reagent in order to install the tertiary alcohol carrying the cyclohexene side chain of the advanced intermediate **(-)-1.242**. The lactone **(-)-1.242** was then reduced to the corresponding triol **(+)-1.239**. After the PMB deprotection of the latter, the corresponding carboxylic acid was lactonised and chlorinated to give salinosporamide A. Many synthetic problems had to be overcome during this synthesis including a difficult amide coupling, the optimisation of the oxidative cyclisation under wet conditions, selectivity issues of the phenyl selenium anion, two problematic lactone and carboxylic acid reductions, one alcohol oxidation, and a lactonisation of an unreactive alkene.



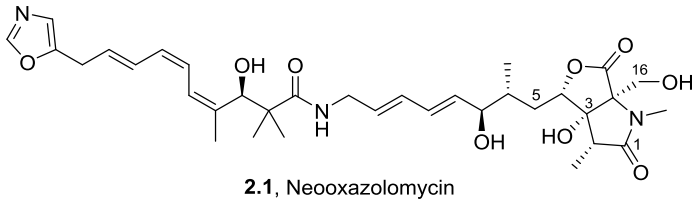
This work demonstrates the synthetic utility of the oxidative radical cyclisation of alkenyl amidomalonates by delivering a short sequence to the highly bioactive natural product (-)-salinosporamide A. The new synthesis may also offer opportunities for chemical diversification in possible SAR explorations. This novel sequence toward (-)-salinosporamide A also demonstrates that the total synthesis can be achieved without protection of the nitrogen atom of the lactam ring. The natural product was obtained in a 17 step sequence from crotonyl chloride with an overall 4.9% yield. The two other shortest sequence to (-)-salinosporamide A were reported by Corey (18 steps, 10.8% yield) and Romo (9 steps, 6.8% yield). The novel sequence therefore allows the synthesis of the natural product in a relatively efficient way.

2 Studies Towards the Oxazolomycin Family

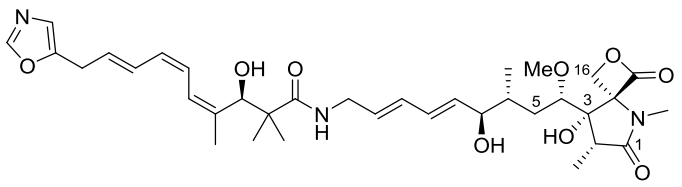
2.1 Introduction to the oxazolomycin family

2.1.1 **Isolation of the first two members**

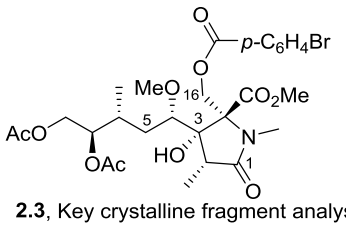
Neooxazolomycin **2.1** and oxazolomycin A **2.2** were simultaneously extracted 30 years ago by Uemura *et al.*[101,102] from the culture of a strain of the bacteria *Streptomyces* spp. (typically 15-20 mg from a 10 L culture). The purification of the crude fermentation extracts was achieved by silica column chromatography guided by *in vivo* activity testing against Ehrlich ascites tumour followed by HPLC. Elemental analysis and mass spectroscopy allowed the determination of the molecular formula. The structural elucidation of oxazolomycin A[101] and neooxazolomycin[102] (**Figure 2.1**) was achieved by X-ray analysis of derivatised key fragments such as **2.3** and by extensive 1D and 2D proton and carbon NMR, IR, UV and mass spectroscopy analysis of the two natural products and their fragments.



2.1, Neooxazolomycin



2.2, Oxazolomycin A



2.3, Key crystalline fragment analysed by X-ray (obtained by derivatisation and ozonolysis of oxazolomycin A)

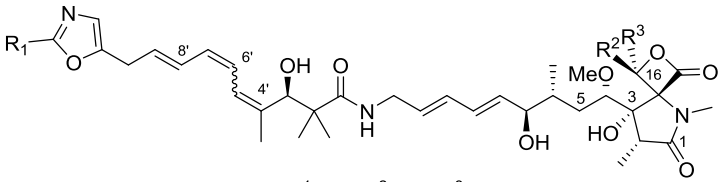
Figure 2.1 Structure of the parents members of the oxazolomycin family

Oxazolomycin A **2.2** and neooxazolomycin **2.1** have very similar structures. The left side chain, which starts at C_5 is identical in the two molecules and contains two secondary hydroxyl groups, a diene, an amide bond, a triene, and a terminal oxazole ring. The two natural products only differ in the organisation of the right-hand side bicyclic pyrrolidinone-lactones. Neooxazolomycin **2.1** displays a free hydroxyl group at C-16 and a γ-lactone ring is binding the C-4 oxygen atom and the carboxyl unit carried by the pyrrolidinone ring. The oxygen atom carried by C-4 in oxazolomycin A **2.2** is methylated and forms the corresponding ether, allowing the presence of a less favourable spiro fused β-lactone binding the oxygen atom at C-16 and the carboxyl unit attached to the pyrrolidinone.

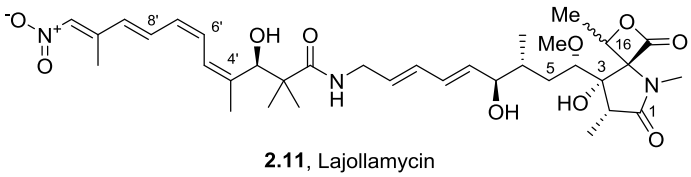
Several other members of the oxazolomycin family have been isolated since the discovery of the two parent members. Other natural products containing only the left hand-side fragments have also been isolated and are known as the Inthomycins. All these natural products are presented in the next paragraph. An excellent review on the members of the oxazolomycin family was published by Moloney *et al*.[103]

2.1.2 **Other oxazolomycins and the inthomycins**

Oxazolomycin B **2.4** (4'*E*, 6'*E*, 8'*E*) and oxazolomycin C **2.5** (4'*Z*, 6'*E*, 8'*E*) are two triene isomers of oxazolomycin A (4'*Z*, 6'*Z*, 8'*E*), which were isolated from a fermentation broth of *Streptomyces albus*[104] (**Figure 2.2**). The oxazole substituted curromycin A[105] **2.9** and curromycin B[106] **2.10** and the first C-16 methylisomer of oxazolomycin A (16-methyloxazolomycin **2.6**),[107,108] are produced by a strain of *Streptomyces hygroscopicus*. The second C-16 methylisomer of oxazolomycin A, KSM-2690B **2.7** and a C-16 methylisomer of oxazolomycin C, KSM-2690C **2.8** were also isolated from the bacterial strain *Streptomyces* sp. KSM2690.[109] The isolation of Lajollamycin, the most recent member of the oxazolomycin family was reported in 2005 by Nereus Pharmaceuticals.[110] The C-16 stereocentre of Lajollamycin was ambiguously reported as (*S*). A key nOe interaction reported by Potts *et al.*,[110] between the C-16 proton and the *N*-methyl group would suggests that C-16 is (*R*). Hence, it has been chosen not to depict the stereoconfiguration of the C-16 stereocentre of Lajollamycin.



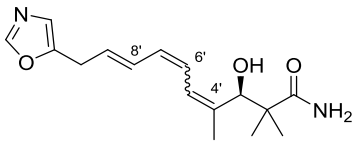
2.2, Oxazolomycin A : R^1 = H, R^2 = H, R^3 = H, 4'*Z*, 6'*Z*, 8'*E*
2.4, Oxazolomycin B : R^1 = H, R^2 = H, R^3 = H, 4'*E*, 6'*E*, 8'*E*
2.5, Oxazolomycin C : R^1 = H, R^2 = H, R^3 = H, 4'*Z*, 6'*E*, 8'*E*
2.6, 16-Methyloxazolomycin : R^1 = H, R^2 = H, R^3 = Me, 4'*Z*, 6'*Z*, 8'*E*
2.7, KSM2690-B : R^1 = H, R^2 = Me, R^3 = H, 4'*Z*, 6'*Z*, 8'*E*
2.8, KSM2690-C : R^1 = H, R^2 = Me, R^3 = H, 4'*Z*, 6'*E*, 8'*E*
2.9, Curromycin A : R^1 = Me, R^2 = CH_3OCH_2, R^3 = H, 4'*Z*, 6'*Z*, 8'*E*
2.10, Curromycin B : R^1 = Me, R^2 = H, R^3 = Me, 4'*Z*, 6'*Z*, 8'*E*



2.11, Lajollamycin

Figure 2.2 The other known members of the oxazolomycin family

Three natural products known as the inthomycins A, B and C (**2.11**, **2.12** and **2.13**) are direct fragments of the oxazolomycins A, B and C (**Figure 2.3**). They were isolated in the early 1990s by Omura *et al.*[111] and Henkel and Zeeck[112] a few years after the discovery of the parent members of the oxazolomycin family **2.1** and **2.2**.



2.11, Inthomycin A : 4'*Z*, 6'*Z*, 8'*E*
2.12, Inthomycin B : 4'*E*, 6'*E*, 8'*E*
2.13, Inthomycin C : 4'*Z*, 6'*E*, 8'*E*

Figure 2.3 The inthomycin family

2.1.3 **Biological activity**

2.1.3.1 Activity

All these natural products have been biologically evaluated, and the oxazolomycin family displayed a wide range of antibiotic, antiviral and antitumour activity with moderate toxicity in mice (LD_{50} = 10.6 $mg.kg^{-1}$ for oxazolomycin A).[103]

Tonew *et al.*[113] showed that the oxazolomycin A prevents the replication of herpes simplex type 1, vaccinia and influenza virus at high concentration (15.3 $\mu g.mL^{-1}$). In this study, the other members of the family did not display any significant antiviral activity against these three viruses (oxazolomycin B and C were unknown at that time). Curromycins A and B have also displayed anti-HIV properties in a study carried by Ohno *et. al.*[114] in 1994. The 50% effective concentrations (EC_{50}) of these molecules were respectively 2.5 and 5 $\mu g.mL^{-1}$ in HIV replication assays, which proved to be slightly more potent than the AZT reference. The study also demonstrated that the curromycins affect a late step in the virus replication cycle.

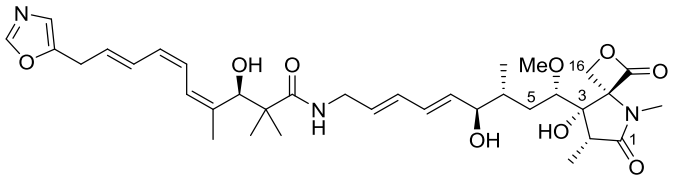
Few studies on the cytotoxic properties of the oxazolomycin family have been reported. The oxazolomycins (A, B and C) are not known to present further cytotoxic properties.[103] The close analogue 16-methyloxazolomycin proved potent against P388 leukaemia cells (IC_{50} = 0.23 $\mu g.mL^{-1}$) and against A-549 human lung adenocarcinoma cells (IC_{50} = 4.6 $\mu g.mL^{-1}$).[107] Curromycin A is cytotoxic against mouse B16 melanoma, P388 leukaemia and Friend leukaemia cells.[105] KSM2690-B and KSM2690-C have similar level potency against human bladder carcinoma T24 cell (IC_{50} = 10 $\mu g.mL^{-1}$).[109] Very small structural variations induce significant modification of the cytotoxic properties.[103] SAR explorations are therefore required in this area.

The oxazolomycins showed various antibiotic properties.[103] Oxazolomycin A displays specific activity against several strains of *Agrobacterium Tumefaciens*[104] (bacterial growth inhibition at few $\mu g.mL^{-1}$), which is responsible for the crown gall disease in plants. 16-Methyloxazolomycin showed activity (at 5-10 $\mu g.ml^{-1}$) against *Bacillus subtilis* 1069 and *Chlorella vulgaris* IFO15941.[107] Curromycin A also showed activity against *Bacillus subtilis.*[106] KSM2690-B displayed moderate activity (at 50 $\mu g.ml^{-1}$) against *Chlorella vulgaris* IFO15941 and against other Gram-positive bacteria including the resistant *Staphylococcus aureus* Smith strain.[109] Here again, small variations of the structure induce important changes in the antibiotic properties suggesting that the oxazolomycins and its analogues could become new probes in the discovery of antibiotics.[103]

Inthomycin A also displays some specific biological properties. The molecule was isolated in a search for cellulose biosynthesis inhibitors in a culture of *Streptomyces sp.* OM-5714, as cultures of this strain were known for their herbicidal properties.[111] In a screening of clinical drugs and natural products against epithelial tumour cells, inthomycin A was found to be an inhibitor of epithelial tumour cells and prostate cancer cells growth.[115]

2.1.3.2 Mode of action

The oxazolomycins were first considered as classic membranotropic antibiotics, which can also display antiviral activity by inhibiting the virus uncoating at an early stage of the virus life cycle.[103] But it was shown that oxazolomycin A inhibits a later stage of the influenza A replication cycle,[113] which suggested a new type of membranotropic mode of action for the dual antibiotic-antiviral activity.[103] Grafe *et al*.[113,116] studied in 1992 the behaviour of oxazolomycin A through an artificial lipid layer and demonstrated that oxazolomycin A is an effective protonophore at pH < 7.0 and conveys both monovalent cations and protons at pH > 7.5. Grafe *et al.* concluded that the ionophoric properties might be responsible for the antiviral, cytotoxic and antibiotic properties of oxazolomycin A. Due to a non-classical membranotropic mode of action of the oxazolomycins, the antibiotic properties of these molecules have raised a considerable interest.[103] Moloney *et al.*[117] suggested that the U-shape of the molecule caused by the *gem*-dimethyl amide could explain the atypical membranotropic antibiotic properties (**Figure 2.4**).



2.2, Oxazolomycin A

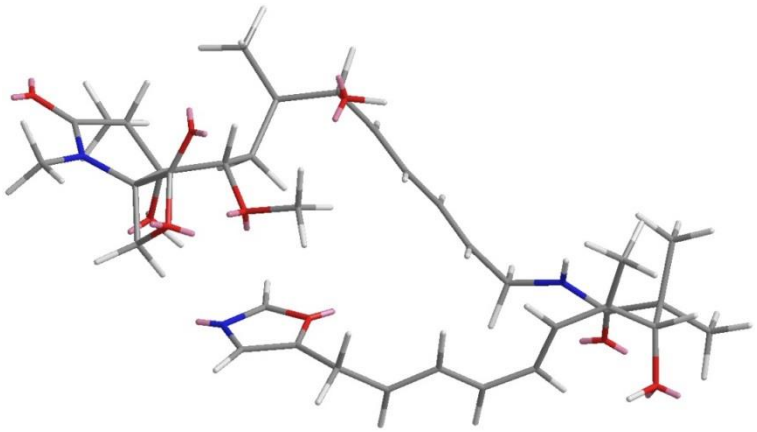
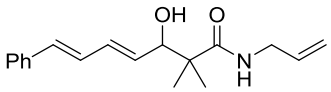


Figure 2.4 3D structure of oxazolomycin A after MM2 optimisation in ChemBio3D

In the study of the importance of this geometrical parameters Moloney *et al.* synthesised simpler analogues containing the gem-dimethyl amide, which showed potency against several bacterial strains (**Figure 2.5**).[117] For example the compound **2.14** has a minimum inhibitory concentration of 4 mg.mL^{-1} against *Staphylococcus aureus*, which remains 80 times higher than KSM-2690B. This concentration dropped to 0.5 mg.mL^{-1} for *Escherichia coli,* when the concentration for oxazolomycin A is 0.1 mg.mL^{-1}.



2.14

Figure 2.5 A simple active analogue synthesised by Moloney *et. al.,*[117] which contains oxazolomycin central pharmacophore

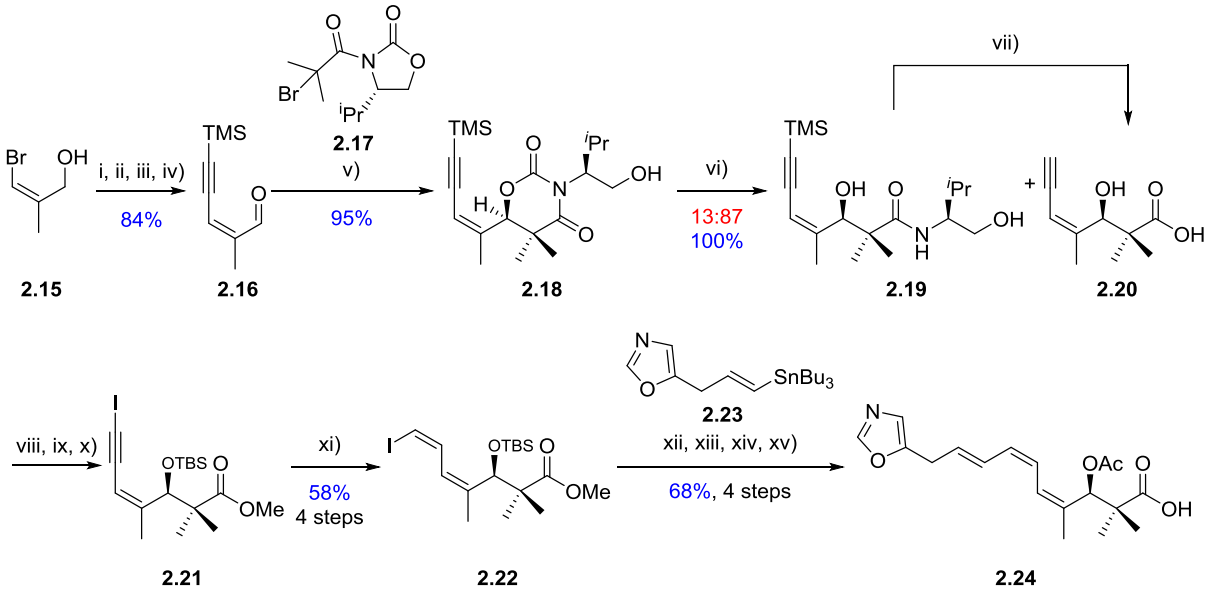
The relative activity of this simpler analogue suggests that the *gem*-dimethyl group plays an important role in the antibiotic properties of the oxazolomycin family. But the different activity characteristics of the inthomycins suggest that activity of the oxazolomycins should also be attributed to the pyrrolidinone-lactone ring. It is necessary to mention that some pyrrolidinones sharing substitution features of the oxazolomycins have also been found to display antibiotic properties against *Escherichia coli.* and *Staphylococcus aureus*.[118]

As most fragments of the oxazolomycins seem to have independent contribution to the activity of the molecule, the development of syntheses toward the natural product will be important for the future development of highly needed SAR studies.

2.1.4 **Former syntheses of neooxazolomycin**

2.1.4.1 Kende total synthesis of neooxazolomycin

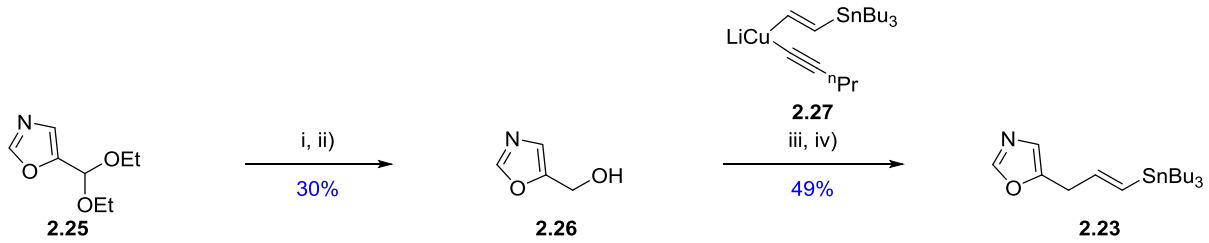
Kende *et al.*[119] reported the first total synthesis of a member of the oxazolomycin family in 1990. Their synthesis of the left-hand side *Z,Z,E* triene oxazole fragment starts from the known (*Z*)-3-bromo-2-methyl-2-propenol **2.15**,[120] which was *O*-silylated and engaged in a Sonagashira coupling reaction with TMS-acetylene. The coupling was followed by the de-silylation of the oxygen atom, and by the subsequent oxidation with basic MnO_2, which gave the aldehyde **2.16**. A diastereoselective Reformatsky type reaction between the bromo acyl oxazolidinone **2.17** and the aldehyde **2.16** followed by the intramolecular attack of the residual alkoxide on the carbonyl group formed the 3-oxazine-2,4 dione **2.18**. Next, removal of the chiral auxiliary with lithium hydroperoxide gave the carboxylic acid **2.20** along with 18% of the amide **2.19**, which upon treatment with aqueous LiOH was converted into the acid **2.20**. After an esterification of carboxylic acid **2.20** with diazomethane and subsequent *O*-silylation, the iodination of the corresponding alkyne gave the iodoalkyne **2.21**. The reduction of the latter with diimide gave the iodoalkene **2.22**, which was engaged in a Stille coupling with the oxazole stannane **2.23** and delivered after saponification the *Z,Z,E* oxazole triene acid fragment **2.24**.



Scheme 2.1 *Kende et al.* synthesis of the *Z,Z,E* oxazole triene fragment 2.24

Reagents and conditions i) TBSCl, imidazole, DMF, 0 °C, 5 min; ii) TMS-acetylene, $Pd(Ph_3P)_4$, CuI, *n*-$BuNH_2$, PhMe, RT, 18 h; iii) AcOH/THF/H_2O, RT, 18 h; iv) basic MnO_2, Hexane/DCM, RT, 2 h; v) $SnCl_2$, $LiAlH_4$, THF, RT, 20 min; then oxazolidinone **2.17** in THF, RT, 45 min; then aldehyde **2.16** in THF, RT, 16 h; vi) 30% aq. H_2O_2, LiOH, THF/H_2O, RT, 24 h; vii) LiOH, THF/MeOH/H_2O, RT, 24 h; viii) CH_2N_2, Et_2O, 0 °C; ix) TBSOTf, 2,6-lutidine, DCM, RT, 30 min; x) *n*-BuLi, THF, -78 °C, 1 h, then I_2 in THF, 1 h; xi) NH_2NH_2 (5 eq), $CuSO_4{\cdot}5H_2O$ (0.1 eq), 95% EtOH, RT, air (bubbled), 16 h; xii) Oxazole stannane **2.23**, 3 mol% $PdCl_2$-$(MeCN)_2$, DMF, RT, 91 h; xiii) 50% HF/MeCN, RT, 4 h; xiv) LiOH, THF/MeOH/H_2O, RT, 24 h, xv) Ac_2O, pyridine, 23 °C, 20 h.

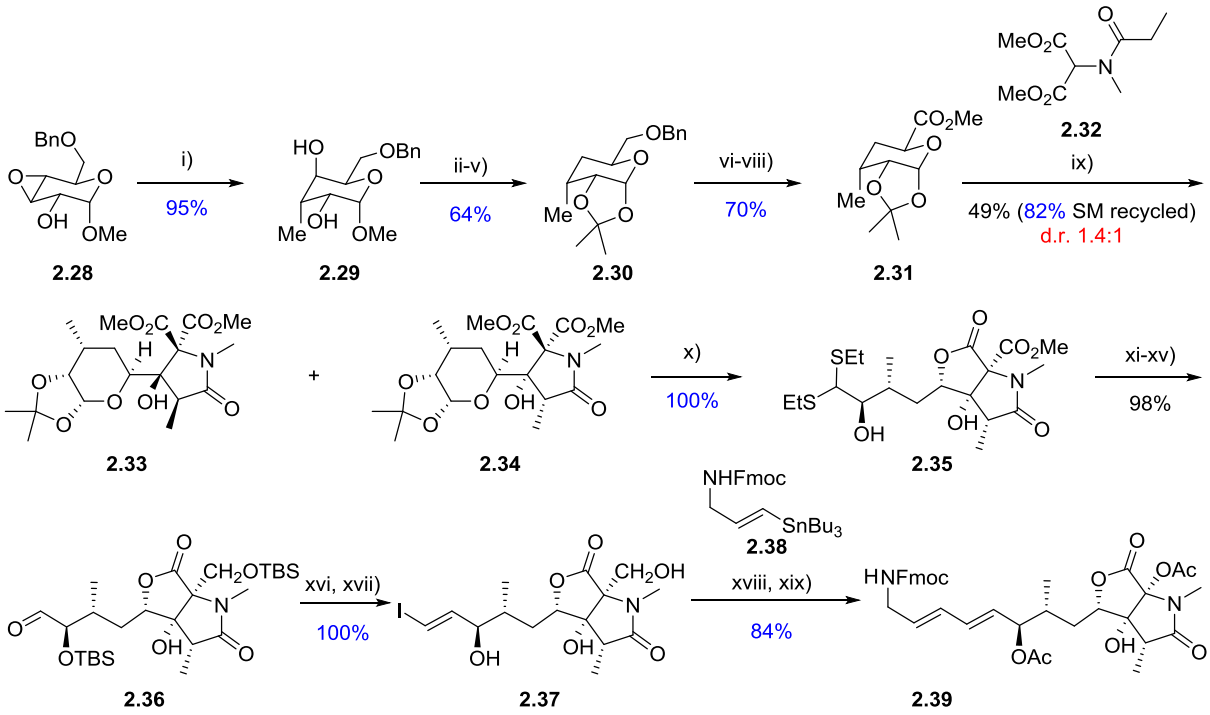
The oxazole stannane **2.23** was prepared from the reported acetal **2.25**,[121,122] which was hydrolysed and reduced to give the oxazole methanol **2.26**. The bromination of the alcohol followed by the immediate coupling of the unstable bromide to the cuprate **2.27** gave the required stannane **2.23**.



Scheme 2.2 Preparation of the oxazole stannane 2.23

Reagents and conditions i) conc. aq. HCl, THF/H_2O, RT; then sat. aq. $NaHCO_3$; then $NaBH_4$, 0 °C; ii) NBS, Ph_3P, THF, RT; iii) (*E*)-$Bu_3SnCH{=}CHSnBu_3$, *n*-BuLi, THF, -78 to -40 °C; then addition to CuC≡CPr, THF, -40 °C; addition to bromide, THF, -78 °C to -10 °C.

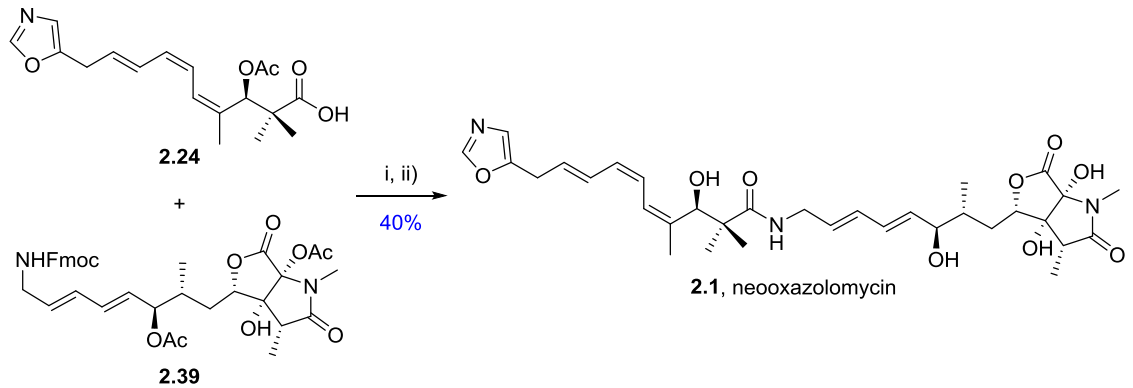
The synthesis of the right-hand side pyrrolidinone-lactone fragment **2.39** started from the reported anhydrogalactoside **2.28** (**Scheme 2.3)**.[121] The sequence begins with the *trans* diaxial opening of the epoxide **2.28** with excess dimethylmagnesium. The equatorial hydroxyl of the diol **2.29** was silylated and the axial hydroxyl was converted into the corresponding imidazole thiocarbamate, which underwent a radical reduction with *n*-Bu_3SnH. The subsequent TIPS deprotection with HF and the acetal formation with acetone gave the acetonide **2.30**. Hydrogenolytic debenzylation, followed by a 2 step oxidation and esterification with diazomethane gave the ester **2.31**. The addition of the dianion derived from **2.32** to the methyl ester of **2.31** generated the pyrrolidinones **2.33** and **2.34** in a 1.4:1 unfavourable d.r. Upon treatment with EtSH and HCl, the minor diastereoisomer **2.34** rearranged to the requisite fused pyrrolidinone-lactone **2.35**. The secondary alcohol of diol **2.35** was silylated, and after saponification of the methyl ester, the formed carboxylic acid was treated with the Vilsmeier salt to form the acyl chloride, which was reduced to the corresponding primary alcohol. The silylation of the resulting alcohol, and the subsequent deprotection of the thioacetal with $HgCl_2$ gave the aldehyde **2.36**. A Takai olefination of the aldehyde followed by de-silylation gave the requisite (*E*)-vinyl iodide **2.37**. A Stille coupling between the propenyl stannane reagent **2.38** and the (*E*)-vinyl iodide **2.37** and a final acetylation gave the diene **2.39**.



Scheme 2.3 Kende *et al.*[119] synthesis of the pyrrolidinone-lactone fragment

Reagents and conditions i) MeLi, MeMgCl, THF/Et_2O, RT, 16 h; ii) *i*-Pr_3SiOTf, 2,6-lutidine, THF, -78 °C to RT, 16 h; iii) $S=C(Im)_2$, DCE, heating; then *n*-Bu_3SnH, xylene, heating, 6 h; iv) *n*-Bu_4NF, THF, RT; v) $FeCl_2$, acetone, RT, 4 h; vi) H_2, $Pd(OH)_2$, MeOH, RT, 4 h; vii) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C to 0 °C, 1 h then $KMnO_4$, ^{t}BuOH/5% NaH_2PO_4, RT, 30 min; viii) CH_2N_2, Et_2O, 0 °C; ix) amidomalonate **2.32** (1.06 eq), ^{t}BuLi (2.12 eq), TMEDA (2.12 eq), THF, -78 °C, then addition to methyl ester **2.31** in THF, -78 °C; x) EtSH, conc. aq. HCl (cat); xi) TBSOTf, 2,6-lutidine, DCM, RT; xii) LiOH, THF/H_2O, RT, 1 h, then 1.0 M aq. HCl; xiii) $[Me_2N=CHCl]^+Cl^-$, MeCN/THF, 0 °C, 1 h then $NaBH_4$, DMF, -78 °C to RT, 16 h; xiv) TBSOTf, 2,6-lutidine, DCM, RT; xv) $HgCl_2$, $CaCO_3$, MeCN/H_2O, RT, 1 h; xvi) CHI_3, $CrCl_2$, THF, RT, 90 min; xvii) *n*-Bu_4NF, THF, RT; xviii) stannane **2.38**, $PdCl_2(MeCN)_2$ (5 mol%), DMF, RT, 24 h; xix) Ac_2O, pyridine, RT, 24 h.

The final coupling between the carboxylic acid of the *Z,Z,E* fragment **2.24** activated with BOP-Cl and a solution of Fmoc amine **2.38** pre-treated with DBU to liberate the reactive amine gave the triacetate of neooxazolomycin. The natural product **2.1** was obtained after a final deacetylation. Kende *et al.* achieved the elegant first total synthesis of neooxazolomycin in 23 chemical steps and 5% yield from the reported anhydrogalactoside **2.28**.[121]

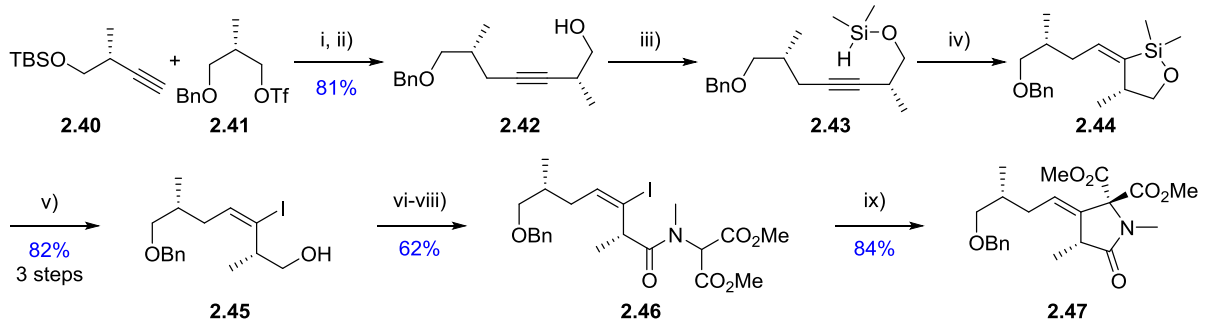


Scheme 2.4 Kende et al.[119] final coupling in the total synthesis of neooxazolomycin

Reagents and conditions i) Fmoc protected amine, DBU, DCM, RT, 30 min; then addition to the acid activated with BOP-Cl, Et_3N, DCM, RT, 3 ii) LiOH (10 eq), solvent is not given, RT, 30 min.

2.1.4.2 Hatakeyama total synthesis of neooxazolomycin

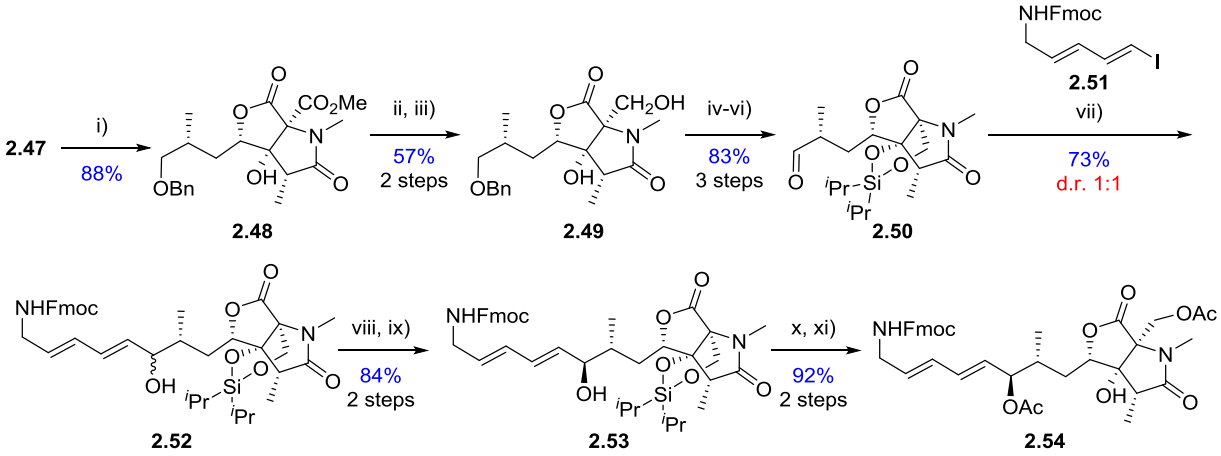
Hatakeyama *et al.*[123] reported their total synthesis of neooxazolomycin in 2007. The synthesis of the left-hand side *Z*,*Z*,*E* oxazole triene acid **2.24** is an optimisation of the synthesis developed by Kende *et al.*,[119] which is not presented in this section. The synthesis of the right-hand side pyrrolidinone-lactone fragment began with the coupling of the alkynyl lithium of the known alkyne **2.40**[124] with the known triflate **2.41**[125] (**Scheme 2.5**), which gave after deprotection of the silyl ether the alkynol **2.42**. The treatment of the alkynol **2.42** with 1,1,3,3-tetramethyldisilazane provided the substrate **2.43**, which underwent an intramolecular platinum-catalysed hydrosilylation. The resultant siloxane **2.44** was converted to the (*E*)-iodoalkene **2.45** using I_2 and CsF. After the oxidation of the alcohol **2.45** to the carboxylic acid, the corresponding acyl chloride was coupled to dimethyl 2-(methylamino)malonate, which gave the iodo enamidomalonate **2.46**. The latter underwent a palladium catalysed cyclisation, which stereoselectively formed the requisite pyrrolidinone alkene **2.47**.



Scheme 2.5 First steps of Hatakeyama *et al.*[123] synthesis of the pyrrolidinone-lactone fragment 2.54
Reagents and conditions i) *n*-BuLi, DMPU/THF, -78 °C; ii) TBAF, THF; iii) $(HMe_2Si)_2NH$ (1.1 eq), neat; iv) [Pt(dvds)] (0.3 mol%), THF; v) I_2 (1.0 eq), CsF (1.5 eq), DMF/MeOH (5:1); vi) H_2CrO_4, aq. acetone, -10 °C; vii) $SOCl_2$, DCM; viii) 2-(methylamino)malonate, PhMe, 0 °C; ix) $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), *n*-Bu_4NBr (1.0 eq), K_2CO_3 (4.0 eq), DMF/H_2O (9:1), 70 °C.

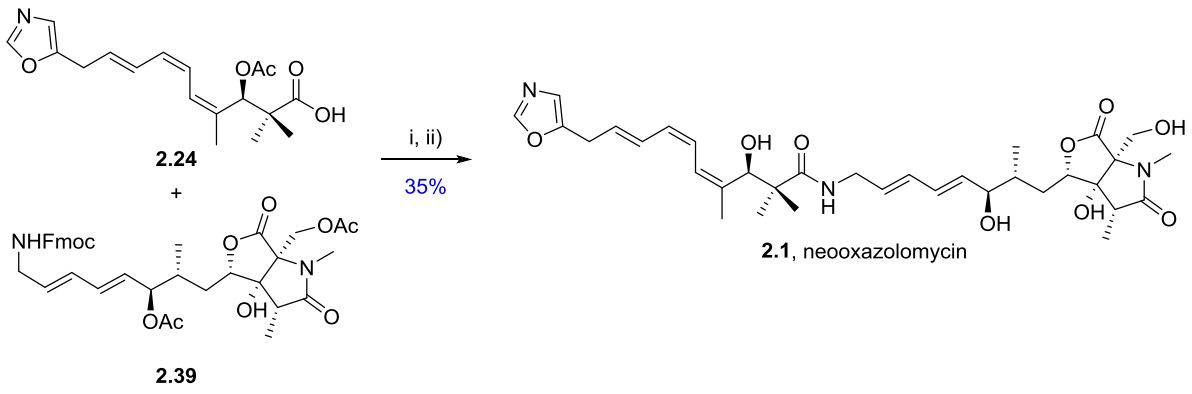
The alkene **2.47** was next dihydroxylated with OsO_4 and NMO, which gave the lactonised product **2.49** as a single diastereoisomer (**Scheme 2.6**). The surprising selectivity of this dihydroxylation may be explained by the presence of the benzyl group on the flexible side chain, which blocks one face of the alkene **2.47**. This feature was demonstrated by ^1H NMR nOe studies on the dihydroxylation substrates **2.47**, which showed key interactions between the methyl ester and the aromatic protons. After the saponification of the methyl ester **2.48**, and the reduction of the acyl chloride formed with the Vilsmeier salt, the so formed diol **2.49** was protected to give the corresponding dioxisilane, which was debenzylated and oxidised with DMP to the aldehyde **2.50**. A Nozaki-Hiyama-Kishi reaction between the iodo diene **2.51** and the aldehyde **2.50** gave the mixture of alcohols **2.52** with no diastereoselectivity. However, the re-oxidation of the diasteromeric mixture of alcohol **2.52** followed by selective reduction with L-Selectride gave **2.53** in high d.r. (30:1). The pyrrolidinone-lactone

fragment **2.54** was eventually isolated after deprotection of the silyl ether **2.53** and acetylation of the two secondary alcohols of the resultant triol.



Scheme 2.6 Late steps of Hatakeyama *et al.*[123] synthesis of the pyrrolidinone-lactone fragment 2.54
Reagents and conditions i) OsO_4 (0.4 eq), NMO (4 eq), THF/H_2O (3:1); ii) 4.0 M aq. LiOH, THF, then 1.0 M aq. HCl; iii) $[Me_2N{=}CHCl]^+Cl^-$, MeCN/THF (1:4), 0 °C, then $NaBH_4$, DMF, -78 °C to RT; iv) *i*-$Pr_2Si(OTf)_2$, 2,6-lutidine, DCE, reflux; v) H_2, Pd/C, MeOH; vi) DMP, DCM; vii) **2.51** (1.7 eq), $CrCl_2$ (4 eq), $NiCl_2$ (0.2 eq), THF/DMSO (3:1); viii) DMP, DCM; ix) L-selectride, THF, -78 °C; x) HF/pyridine/H_2O/MeCN (1:4:2:20), 0 °C; xi) Ac_2O, pyridine, 92%.

The final coupling between the (*Z,Z,E*)-fragment **2.24** and the Fmoc protected diacetate **2.39** was performed using Kende *et. al.*[119] conditions (**Scheme 2.7**). The total synthesis of oxazolomycin A developed by Hatakeyama *et al.* was achieved in 22 steps from the alkyne **2.40** and the triflate **2.41**.

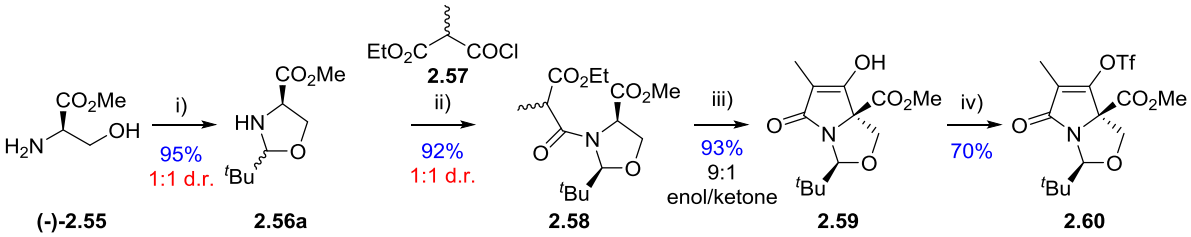


Scheme 2.7 Final coupling of Hatakeyama *et al.*[123] total synthesis of neooxazolomycin
Reagents and conditions i) Fmoc protected amine **2.39**, DBU, DCM; then add to the solution off acid treated with BOPCl, Et_3N, DCM; ii) LiOH (10 eq), THF/H2O (3:1), then 1.0 M aq. HCl.

2.1.4.3 Taylor formal synthesis of neooxazolomycin

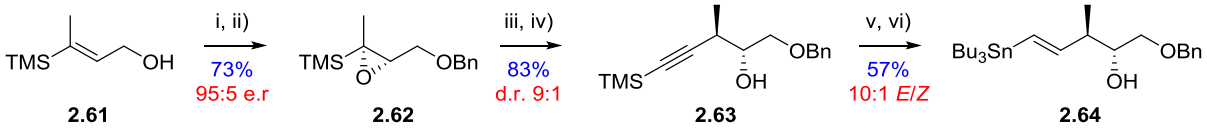
The formal synthesis of neooxazolomycin developed by Taylor *et al.*[126] was reported in 2005. It starts with a synthesis of enol triflate **2.60**, based on precedents from Moloney *et al.*[127] (section **2.1.6.1**). The synthesis starts from D-serine methyl ester, which was condensed with pivaldehyde to form the oxazolidine **2.56a** in 1:1 d.r. (**Scheme 2.8**). The subsequent coupling with malonyl chloride **2.57** then provided acyl oxazolidine **2.58** in 1:1 d.r. and 92% yield. The treatment of **2.58** under basic conditions

led to the formation of the most stable enol **2.59**, which was triflated to form the first cross coupling partner **2.60**.



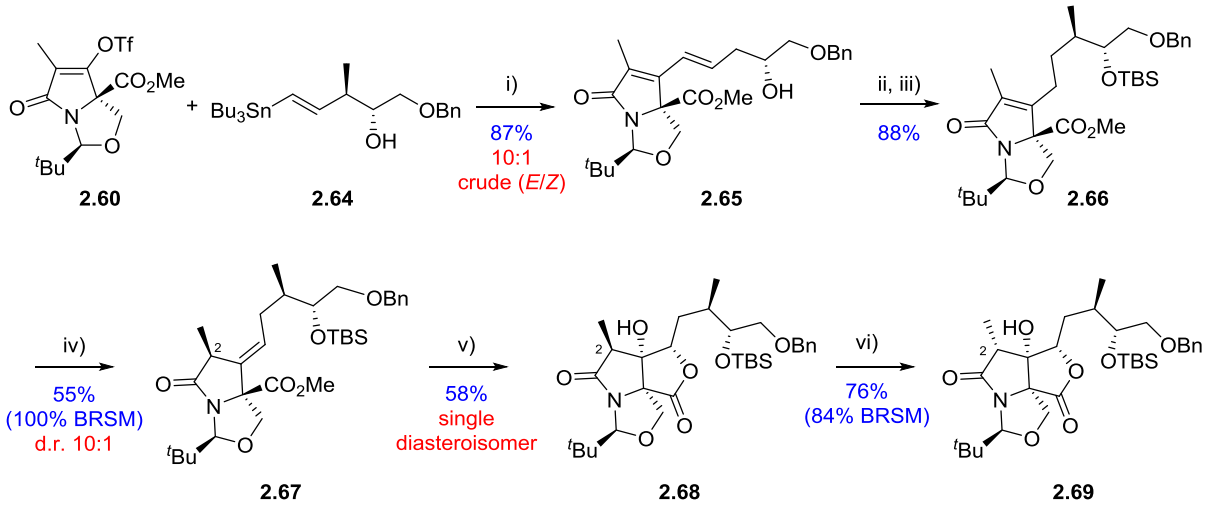
Scheme 2.8 Synthesis of the first cross coupling partner 2.60 in Taylor *et al.*[126] formal synthesis of neooxazolomycin
Reagents and conditions i) Pivaldehyde, NEt_3, pentane, RT; ii) Malonyl chloride **2.57**, DCM/Pyridine, RT; iii) KO^{t}Bu, ^{t}BuOH, heating; iv) Tf_2O (1.10 eq), DIPEA (1.10 eq), DCM, -50 °C.

The synthesis of the second cross coupling partner **2.64** started from the TMS allylic alcohol **2.61**, which was prepared according to a procedure developed by Denmark *et al.*[128] (**Scheme 2.9**) The subsequent Sharpless epoxidation gave the epoxide **2.62** in 95:5 e.r. after benzylation of the corresponding alcohol. Desilylation of **2.62** followed by the opening of the epoxide with lithium TMS acetylide in the presence of trimethylaluminium gave the alcohol **2.63** in 9:1 regioselectivity. Deprotection of the TMS alkyne **2.63** with TBAF followed by a radical hydrostannylation eventually gave the stannane **2.64** in a 10:1 *E*/*Z* mixture of isomers.



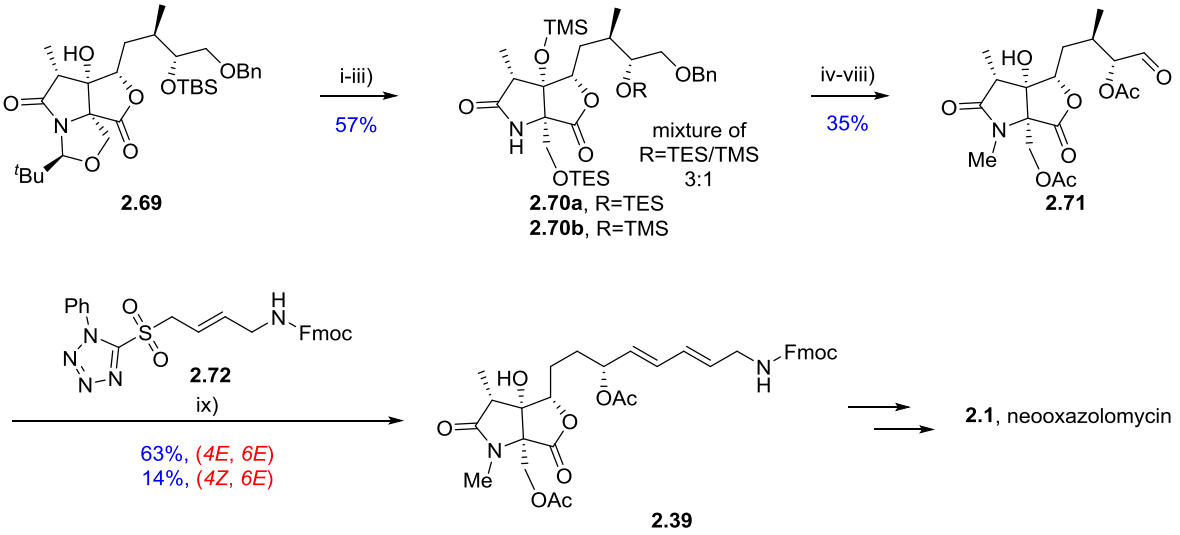
Scheme 2.9 Synthesis of the second cross coupling partner 2.64 in Taylor *et al.*[126] formal synthesis of neooxazolomycin
Reagents and conditions i) Ti(O*i*-Pr)$_4$, (+)-DIPT, TBHP, DCM, -20 °C, 21 h; ii) NaH, BnBr, THF, 0 °C to RT; iii) TBAF, THF, heating; iv) $AlMe_3$, lithium TMS acetylide, -78 °C to -40 °C; v) TBAF, THF, 0 °C, vi) Bu_3SnH, AIBN, 80 °C.

The Stille coupling between the enol triflate **2.60** and the stannane **2.64** formed the diene **2.65** in good yield and (*E*/*Z*) ratio (**Scheme 2.10**). The silylation of the alcohol **2.65** followed by an alkene reduction with diimide gave **2.66**. The subsequent deconjugation was achieved by the formation of the corresponding dienolate with KHMDS followed by reprotonation, which allowed the isolation of the *exo*-alkene **2.67**. A stoichiometric amount of osmium was required for the dihydroxylation of the alkene **2.67**, which was followed by spontaneous lactonisation to form the tri-cyclic lactone **2.68**. The required isomerisation of the methyl group at the α-position of the carbonyl group (C-2) gave the isomer **2.69** in good yield.



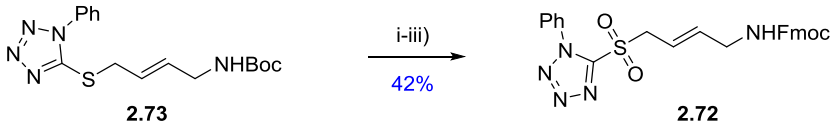
Scheme 2.10 Stille coupling of 2.60 and 2.64 and further steps in Taylor *et al.*[126] formal synthesis of neooxazolomycin
Reagents and conditions i) $Pd_2(dba)_3$ (10 mol%), P(2-Fur)$_3$ (40 mol%), DMF, 50 °C; ii) *p*-$TsNHNH_2$, KOAc, DME-H_2O; iii) TBSOTf, 2,6-lutidine, DCM, 10 °C; iv) KHMDS (2.0 eq), THF, -78 °C, 45 min; then H_2O quench; v) OsO_4 (1.05 eq), NMO (1.05 eq/day), 4:1 (^{t}BuOH/H_2O) RT, 6 d; vi) 10 mol% DBU, $CHCl_3$, RT.

The deprotection of the oxazolidine **2.69** under acidic conditions followed by reprotection of all hydroxy groups with TESOTf then TMSOTf gave the mixture of silyl ethers **2.70** in good yield (**Scheme 2.11**). N-methylation of lactam **2.70**, followed by complete desilylation and re-acetylation of the formed primary and secondary alcohols, hydrogenolysis of the benzyl ether and Dess-Martin oxidation of the resultant alcohol gave the aldehyde **2.71**. The final Julia-Kocienski coupling was achieved in good yield and reasonable (*E*/*Z*) selectivity to give Kende's advanced intermediate **2.39** toward neooxazolomycin **2.1**.



Scheme 2.11 Final steps of Taylor *et al.* [126] formal synthesis of neooxazolomycin
Reagents and conditions i) 1,2-Ethanedithiol, $HCl_{(g)}$, HFIP, RT; ii) TESOTf, 2,6-lutidine, DMF, RT; iii) TMSOTf, 2,6-lutidine, DCM, RT; iv) *n*-BuLi, MeI, THF, -78 °C to RT; v) $HCl_{(g)}$, CF_3CH_2OH, RT; vi) Ac_2O, pyridine, RT; vii) H_2, $Pd(OH)_2$, MeOH, RT; viii) DMP, DCM, RT; ix) NaHMDS, **2.72**, THF, -78 °C to RT.

The sulfone **2.72** used in the Kocienski coupling was obtained by deprotection, reprotection and oxidation of the known sulphide **2.73**.[129]

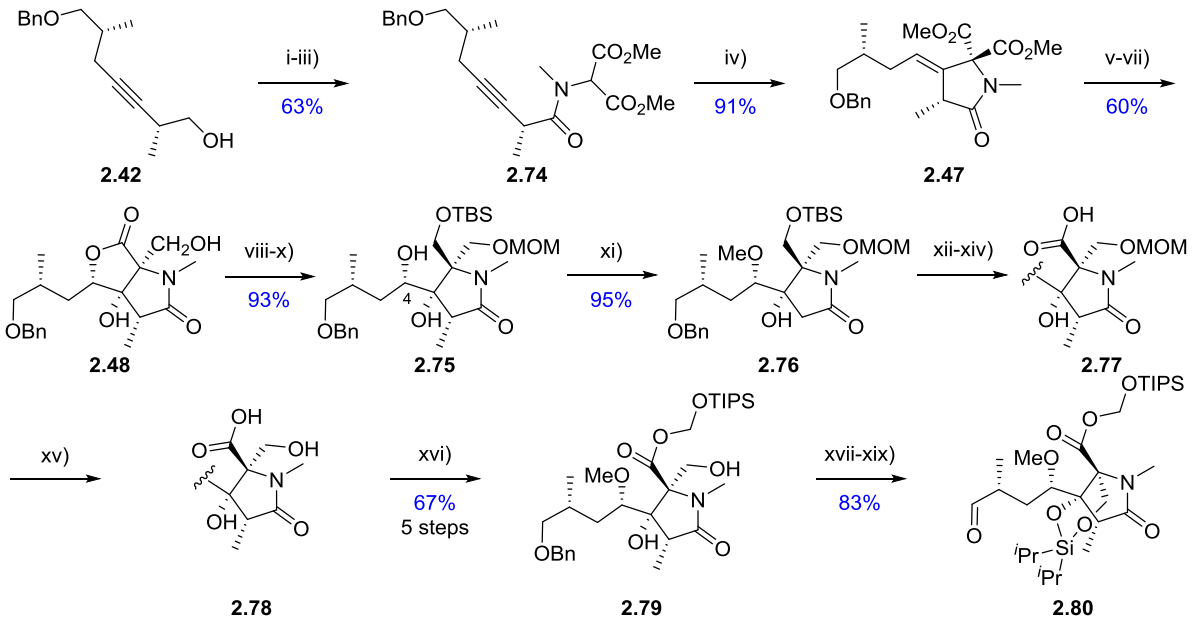


2.73 **2.72**

Scheme 2.12 Taylor *et al.*[126] preparation of the sulfone 2.72
Reagents and conditions i) TFA/DCM, RT; ii) FmocCl, $NaHCO_3$, THF/H_2O (2:1); H_2O_2; $Mo_7O_{24}(NH_4)_6$, EtOH, RT; iii) $Mo_7O_{24}(NH_4)_6$, H2O2, EtOH, RT.

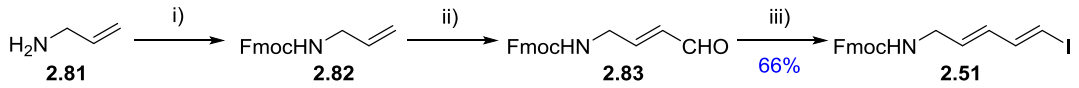
2.1.5 **Former total synthesis of oxazolomycin A**

Hatakeyama *et al.*[130] reported in 2011 the only known total synthesis of oxazolomycin A to date. The synthesis of the pyrrolidinone fragment started from the previously described alkynol **2.42**, which underwent an oxidation, followed by an amide coupling between the corresponding acyl chloride and 2-(methylamino)malonate (**Scheme 2.13**). The formed alkyne amidomalonate **2.74** was then cyclised using an Indium(III) catalysed Conia-ene type cyclisation, which gave the alkene pyrrolidinone **2.47**. The alkene **2.47** was transformed with the previously described 3 step sequence (see section **2.1.4.2**) into the pyrrolidinone diol **2.48**. MOM protection of the primary alcohol carried by **2.48**, followed by the reduction of the lactone ring and by the silylation of the formed primary alcohol, gave the pyrrolidinone diol **2.75**. The secondary hydroxyl group of pyrrolidinone **2.75** was methylated, which gave the ether **2.76**. The deprotection of the silyl ether **2.76**, and the subsequent Jones and Pinnick oxidation gave the carboxylic acid **2.77**. The cleavage of the MOM protecting group furnished the hydroxy acid **2.78**. The carboxylic acid was then protected to give the ester **2.79**. The subsequent protection of the remaining 1,3-diol to the dioxisilane, followed by the benzyl ether hydrogenolysis and the DMP oxidation of the resultant alcohol gave the aldehyde **2.80**.



Scheme 2.13 Hatakeyama *et al.*[130] synthesis of the pyrrolidinone fragment in the total synthesis of oxazolomycin A
Reagents and conditions i) H_2CrO_4, aq. acetone, 0 °C; ii) $SOCl_2$, DCM; iii) 2-(methylamino)malonate, PhMe; iv) $In(OTf)_3$ (5 mol%), DBU (4.4 mol%), PhMe, reflux; v) OsO_4 (0.4 eq), NMO (4.4 eq), THF/H_2O (3:1); vi) 4.0 M aq. LiOH, THF then 1.0 M aq. HCl; vii) $(COCl)_2$, DMF (cat.), DCM; then $NaBH_4$, THF/MeOH (9:1), -78 °C; viii) MOMCl, *i*-Pr_2EtN, DCM; ix) $NaBH_4$, THF/EtOH (1:1); x) TBSOTf, 2,6-lutidine, DCM, -78 °C; xi) Me_3OBF_4, proton sponge, 4 Å MS, DCM; xii) TBAF, THF; xiii) H_2CrO_4, aq. acetone, 0 °C; xiv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH-H_2O (5:1); xv) $ZrCl_4$ (0.3 eq), *i*-PrOH, reflux; xvi) *n*-$C_{12}H_{25}SCH_2OTIPS$, $CuBr_2$, *n*-Bu_4NBr, NEt_3, 4 Å MS, DCM; xvii) *i*-$Pr_2Si(OTf)_2$, 2,6-lutidine, DCE, reflux; xviii) H_2, $Pd(OH)_2$, EtOAc; xix) DMP, $NaHCO_3$, DCM.

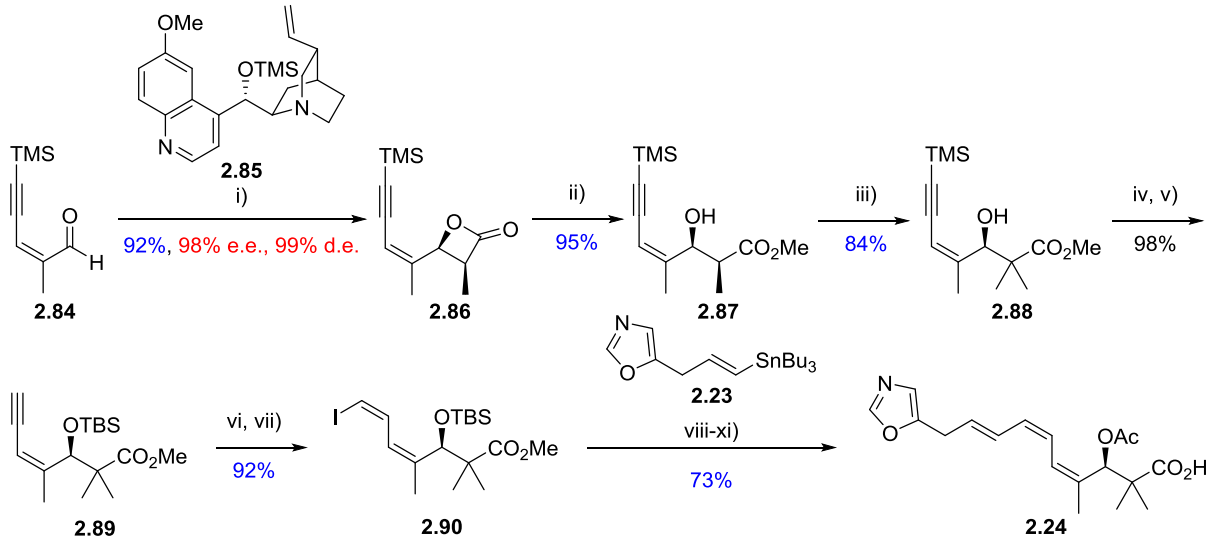
The middle fragment **2.51** was prepared in 3 steps from allyl amine **2.81**. The Fmoc allyl amine **2.82** was subjected to a cross metathesis reaction with acrolein, which gave the unsaturated aldehyde **2.83** (**Scheme 2.14**). The subsequent Takai olefination gave the iodo diene **2.51** as 8:1 *E*/*Z*-mixture, which could be isolated as single isomer after recrystallisation.



Scheme 2.14 Hatakeyama *et al.*[130] synthesis of the middle fragment in the total synthesis of oxazolomycin A
Reagents and conditions i) FmocCl, $NaHCO_3$, dioxane; ii) Acrolein, Hoveyda-Grubbs 2nd generation (5 mol%), DCM; iii) $CrCl_2$, CHI_3, THF.

The synthesis of the *Z*,*Z*,*E* oxazole triene acid fragment **2.24**, started from the aldehyde **2.84** readily available from propargyl alcohol (**Scheme 2.15**).[131] The asymmetric cyclocondensation of the aldehyde **2.84** with propanoyl chloride catalysed by the *Cinchona* alkaloid **2.85** gave the β-lactone **2.86** in high d.e. and e.e. The β-lactone ring was then opened with methanol and the corresponding lithium enolate of the formed methyl ester **2.87** was alkylated with methyl iodide, which gave the intermediate **2.88**. Desilylation, followed by TBS protection eventually offered a new access to the known intermediate alkyne **2.89**, which was treated with *n*-BuLi and I_2 to form after reduction the corresponding (*Z*)-iodo alkene **2.90**. The *Z*,*Z*,*E* triene was then obtained by Stille coupling between the oxazole stannane **2.23** and the (*Z*)-iodo alkene **2.90**. The final *Z*,*Z*,*E* oxazole triene acid fragment

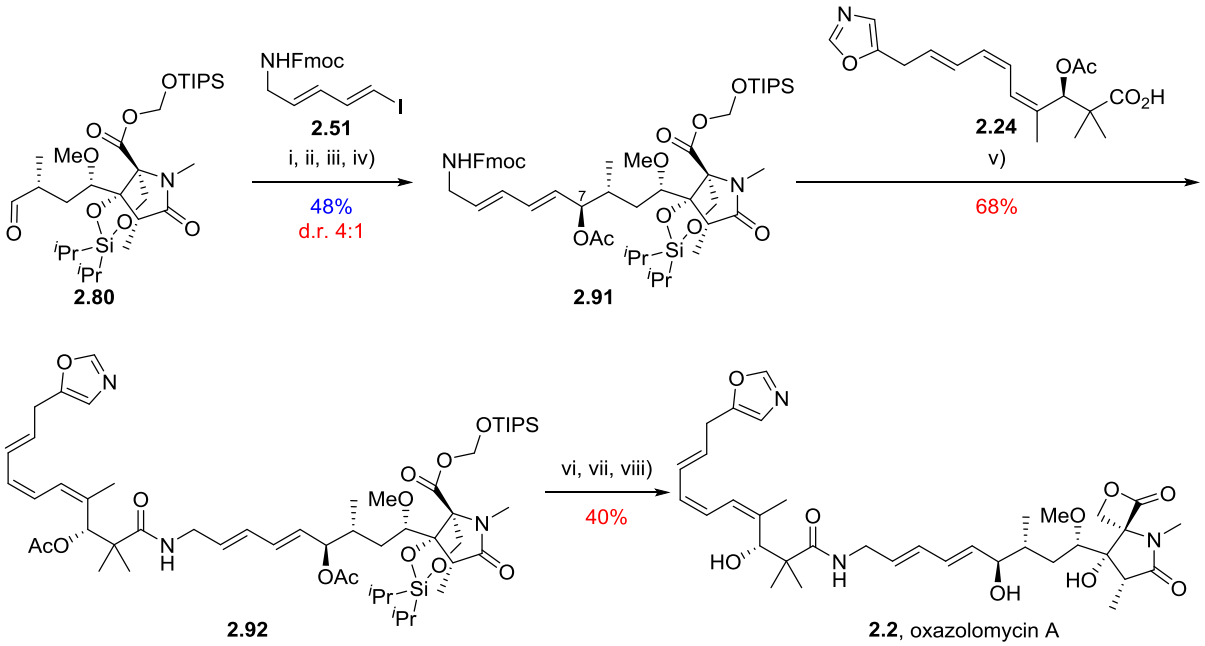
2.24 was eventually isolated after de-silylation of the silyl ether, saponification of the methyl ester and acetylation of the residual alcohol.



Scheme 2.15 Hatakeyama *et al.*[130] synthesis of the *Z,Z,E* oxazole triene acid fragment 2.24 in the total synthesis of oxazolomycin A

Reagents and conditions i) Alkaloid **2.85** (20 mol%), EtCOCl, $LiClO_4$, DIPEA, DCM/Et_2O, -78 °C; ii) NaOMe, MeOH; iii) LDA, MeI, THF, -20 °C; iv) NaOMe, MeOH; v) TBSOTf, 2,6-lutidine, DCM, 0 °C; vi) *n*-BuLi, I_2, THF, -78 °C; vii) *o*-$(NO_2)C_6H_4SO_2NHNH_2$, Et_3N, *i*-PrOH-THF (1:1); viii) Oxazole stannane **2.23**, $Pd(PPh_3)_4$, CuI (10 mol%), CsF (2 eq), DMF; ix) 47% HF, MeCN; x) LiOH, THF/H_2O (3:1); xi) Ac_2O, pyridine; then $NaHCO_3$, MeOH.

The final assembly started with a Nozaki-Hiyama-Kishi reaction between the right-hand side fragment **2.80** and the middle fragment **2.51** to give a 2:3 mixture of 7*R*:7*S* epimers of alcohol **2.91**, which was reversed to 4:1 by DMP re-oxidation and subsequent stereoselective reduction with L-Selectride (**Scheme 2.16**). After acetylation, the Fmoc pyrrolidinone fragment **2.91** was dissolved in DCM in the presence of DBU to release the free amine, which was coupled to the *Z,Z,E* oxazole triene acid **2.24** in the presence of BOP-Cl. De-silylation, deacetylation and β-lactonisation of the residual hydroxy acid with HATU eventually gave oxazolomycin A in 1.4% yield and 34 steps in the longest linear sequence from (*S*)-3-hydroxy-2-methylpropionate.[130]

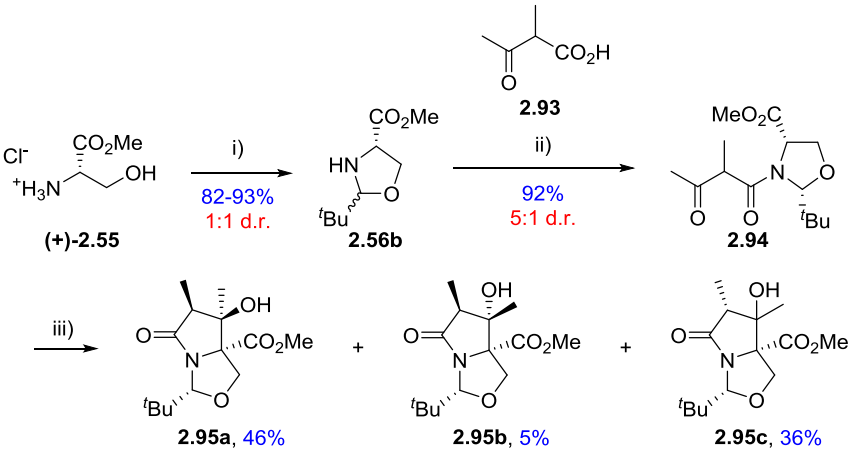


Scheme 2.16 Hatakeyama *et al.*[130] final assembly of oxazolomycin A
Reagents and conditions i) Iodo diene **2.51**, $NiCl_2$ (4 mol%), $CrCl_2$ (6 eq), THF-DMSO (3:1); ii) DMP, $NaHCO_3$, DCM; L-selectride, THF, -78 °C; iv) Ac_2O, pyridine; v) DBU, DCM; then add to acid **2.24** in the presence of BOPCl, NEt_3, DCM; vi) HF·Pyridine, THF; vii) LiOH, THF/H_2O then ion exchange resin viii) HATU, DIPEA, THF.

2.1.6 **Selected former syntheses of the lactam core of members of the oxazolomycin family**

2.1.6.1 Moloney early synthesis of the lactam core

Another early synthesis of the lactam core of the oxazolomycin family was reported by Moloney *et al.*[127] in 1996 (**Scheme 2.17**). The synthesis started with the reaction of L-serine methyl ester hydrochloride **(+)-2.55** with pivaldehyde according to the method of Seebach *et al.*[132] The acylation of the resulting oxazolidine **2.56b** with the acetoacid **2.93** then gave oxazolidine **2.94** in 1:5 cis/trans ratio. The treatment of the major *trans*-oxazolidine **2.94** with sodium methoxide lead to a mixture of three cyclisation products. The major isomer **2.95a** displays most of the structural elements of the γ-lactam core of the oxazolomycin family. In a recent study reported by the same group,[118] the strategy was applied to the synthesis and the evaluation of the antibacterial properties of a range of lactams derived from the core of the oxazolomycin family. This strategy was later applied in the previously described formal synthesis of neooxazolomycin developed by Taylor *et al.*[126]

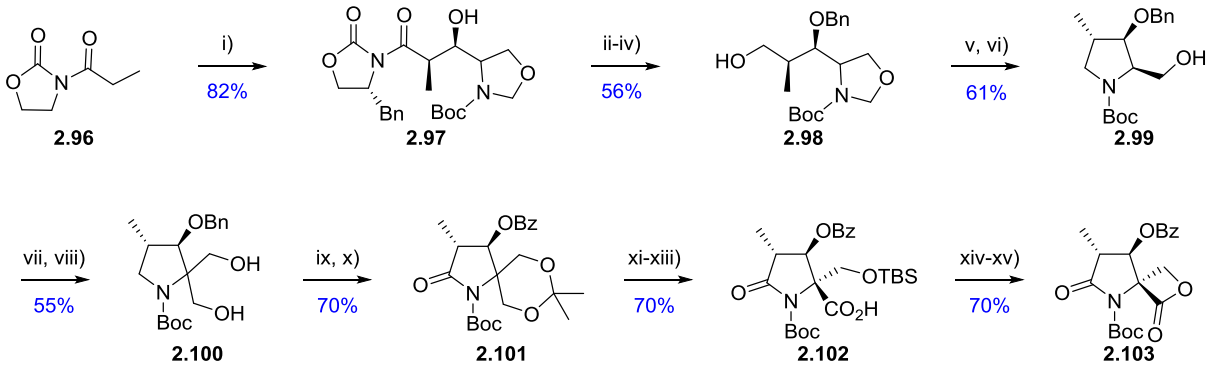


Scheme 2.17 Moloney *et al.*[127] early synthesis of the lactam core 2.95

Reagents and conditions i) Pivaldehyde, NEt_3, $PE_{30\text{-}40}$; ii) Acetoacid **2.93**, EDAC, DMAP, DCM; iii) NaOMe, MeOH, RT.

2.1.6.2 Mohapatra synthesis of the spiro fused pyrrolidinone-lactone core of oxazolomycin A

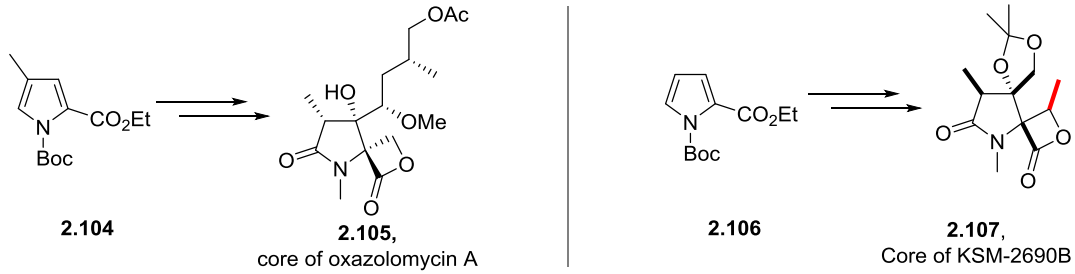
The synthesis of the spiro fused lactam-lactone core of oxazolomycin A **2.103** developed by Mohapatra *et al.*[133] started with an aldol reaction between oxazolidinone **2.96** and the corresponding Garner's aldehyde to give the aldol **2.97**. Subsequent reductive cleavage of the auxiliary, followed by TBS silylation of the formed primary hydroxyl, benzylation of the secondary hydroxyl and de-silylation gave the alcohol **2.98**. Tosylation of the alcohol **2.98** followed by acidic treatment promoted the intramolecular displacement of the formed tosylate, which gave pyrrolidine **2.99**. The oxidation of the residual primary alcohol, followed by aldolisation of the corresponding aldehyde with formaldehyde and *in situ* Cannizzaro reaction to reduce the aldol product gave the diol **2.100**. The formation of the acetonide of diol **2.100**, followed by ruthenium catalysed oxidation of the pyrrolidine ring gave the pyrrolidinone **2.101**. In this process, the undesired oxidation of the benzyl group to the corresponding ester could not be avoided. Deprotection of the acetonide **2.101**, followed by TBS mono-protection of the resultant diol on less hindered face and oxidation of the other hydroxyl group gave the carboxylic acid **2.102**. Final de-silylation and lactonisation gave the spiro bicyclic core of the oxazolomycin family **2.103**.



Scheme 2.18 Mohapatra *et al.*[133] synthesis of the spiro fused γ-lactam-β-lactone 2.103
Reagents and conditions i) Garner's aldehyde, $TiCl_4$, DIPEA, DCM, 0 °C, RT, ii) LiCl, $NaBH_4$, THF, EtOH/THF (2:1); RT; iii) TBSCl, NEt_3, DMAP (cat), DCM, RT; iv) NaH, BnBr, DMF, 0 °C; v) TsCl, NEt_3, DCM, RT; vi) *p*-TSA, MeOH, RT; vii) IBX, DMSO, THF, RT; viii) HCOH, aq. NaOH (2.0 M), THF/H_2O (2:1), RT; ix) 2,2-Dimethoxypropane, p-TSA, RT; x) $RuCl_3$, $NaIO_4$ (aq), EtOAc, RT; xi) *p*-TSA, MeOH, RT; xii) TBSCl, imidazole, DCM, RT; xiii) $RuCl_3$, $NaIO_4$ (aq), EtOAc, RT; xiv) AcOH, THF, H_2O, RT; xv) TPP, DEAD, THF, -78 °C.

2.1.6.3 Donohoe synthesis of the core of KSM2690-B

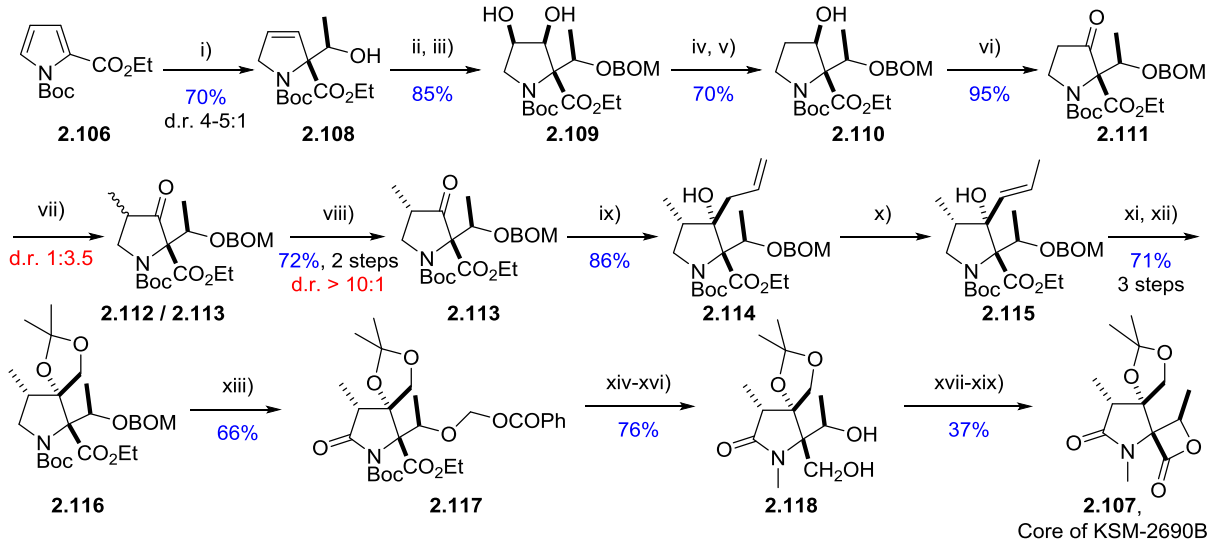
Donohoe et *al.* reported a synthesis of the core of oxazolomycin A in 2012,[134] after having disclosed the only synthesis of the synthetically more complex core of KSM-2690 B,[135] which carries an extra methyl group on the β-lactone (**Scheme 2.19**).



Scheme 2.19 Donohoe *et al.* syntheses of the pyrrolidinone-lactone cores of oxazolomycin A and KSM-2690 B

The synthesis of the racemic core of KSM-2690 B began with the ammonia free Birch reduction of the pyrrole **2.106**. In this process the intermediate dianion of the Birch reduction is quenched with (methoxyethyl)amine and gives the corresponding monoanion, which undergoes an aldol reaction after addition of acetaldehyde to form the aldol product **2.108**. After the protection of the alcohol **2.108**, the selective Sharpless dihydroxylation of the double bond from the anti-face of the carbon bearing the OBOM group gave the diol **2.109**. A Mitsunobu reaction then allowed the selective iodination of the less hindered hydroxyl group, which was then reduced with indium hydride to give mono alcohol **2.110**. The subsequent oxidation gave the ketone **2.111**, which was alkylated with NaHMDS and MeI in unfavourable 1:3.5 d.r. However good stereoselectivity could be obtained by treatment of the alkylated mixture of **2.112** and **2.113** with NaHMDS followed by the addition of a bulky phenol, which allowed the selective approach of this proton source from less hindered face

giving the alkylated ketone **2.113** in greater than 10:1 d.r. The addition of allyl magnesium bromide on the less hindered face of the ketone **2.113** gave tertiary alcohol **2.114** stereoselectively. The subsequent alkene isomerisation with Grubbs catalyst, followed by a reductive ozonolysis and a protection of the formed diol gave the acetonide **2.116**. The pyrrolidine **2.116** was then oxidised with catalytic $RuO_2 \cdot H_2O$ and $NaIO_4$ to give the pyrrolidinone **2.117** unavoidably oxidised at the benzylic position of the BOM group. Deprotection of the Boc group and of the oxidised BOM group, *N*-methylation and reduction of the ester then gave the diol **2.118**. The primary alcohol of the diol **2.118** underwent a selective oxidation to the corresponding aldehyde further oxidised to the carboxylic acid, which was then lactonised with TsCl to give the core of KSM2690-B **2.107**.

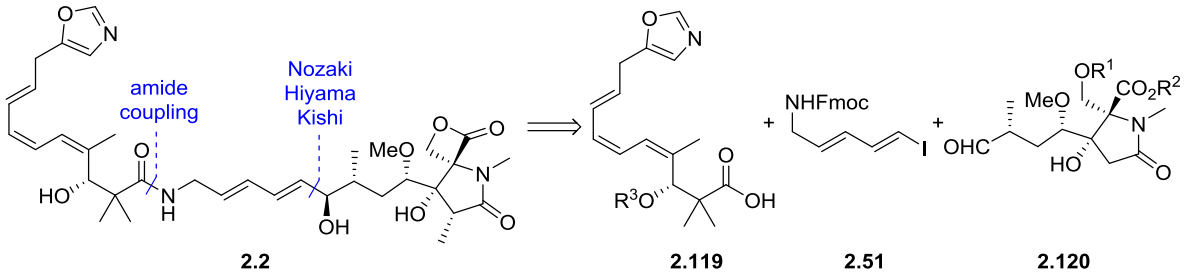


Scheme 2.20 Donohoe *et al.* synthesis of the racemic pyrrolidinone-β-lactone core of KSM-2690 B
Reagents and conditions i) LiDBB, THF, BMEA, -78 °C; ii) BOMCl, DIPEA, DCM; iii) $K_2OsO_4 \cdot 2H_2O$ (cat.), $K_3Fe(CN)_6$, K_2CO_3, quinuclidine, $^tBuOH/H_2O$ (9:1); iv) PPh_3, DBAD, THF, RT; then MeI reflux; v) $InCl_3$, $NaBH_4$, MeCN; vi) $(COCl)_2$, DMSO, DCM, Et_3N, -78 °C to RT; vii) NaHMDS, 15-crown-5, THF, -78 °C, then MeI; viii) NaHMDS, 15-crown-5, THF, -78 °C, then 2,6-di-*tert*-butylphenol; ix) Allylmagnesium bromide, Et_2O, -78 °C; x) Grubbs cat., CH_2=CHOTMS, PhMe, reflux; xi) O_3, DCM/MeOH, then $NaBH_4$; xii) CSA, 2,2-DMP; xiii) cat. $RuO_2 \cdot xH_2O$; aq. $NaIO_4$, EtOAC; xiv) $ZnBr_2$, DCM; xv) Cs_2CO_3, MeI; xvi) $LiBH_4$, Et_2O/MeOH; xvii) TEMPO, $PhI(OAc)_2$, DCM; xviii) $NaClO_2$, NaH_2PO_4, ^tBuOH, H_2O, 2-methyl-2-butene; xix) TsCl, pyridine-DCM, -5 to 0 °C.

2.2 Synthetic strategy and previous work in the Burton group

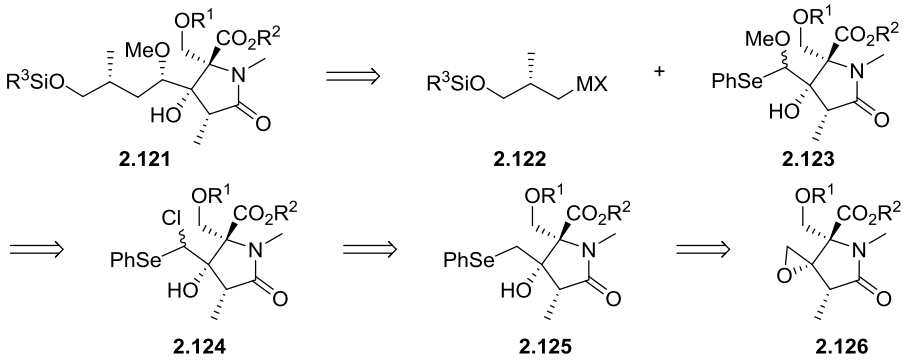
2.2.1 Retrosynthetic analysis

Our strategy is also based on the same disconnections used in the former total syntheses of oxazolomycin A and neooxazolomycin, as they will eventually allow the convergent synthesis of the natural products from three simpler fragments (**Scheme 2.21)**. The end of the total synthesis of oxazolomycin A developed by Hatakeyama *et al.*[130] is based on the assembly of fragments **2.119**, **2.51** and **2.120** *via* amide and Nozaki-Hiyama-Kishi coupling.



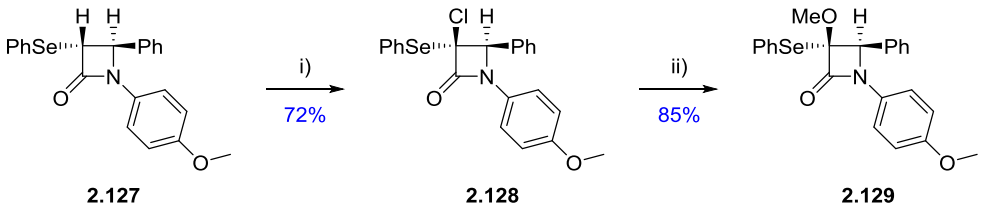
Scheme 2.21 Three main disconnections in former syntheses of the oxazolomycins

The aim of the work presented in this chapter is the development of a synthesis on equivalent of the right hand-side pyrrolidinone fragment **2.120** (**Scheme 2.22**). The equivalent fragment **2.121** would be formed during the reaction between an organometallic reagent such as **2.122** and the seleno lactam **2.123**. The methyl ether of **2.123** would be obtained by substitution of the chlorine atom of lactam **2.124**, which would be the product of a selenium Pummerer-like reaction of **2.125**.[136] The substrate of this reaction would be prepared by the opening of the epoxide **2.126** with an equivalent of the phenyl selenium anion.



Scheme 2.22 Key late disconnections for the formation of the intermediate 2.121

The possibility of reaching the selenium chloro lactam **2.124** and methoxy ether **2.123** via a selenium Pummerer-like reaction was inspired by the work of Bari *et al.*,[136] who synthesised the selenium substituted chloro-lactam **2.128** from selenium substituted lactam **2.127** in good yield (**Scheme 2.23**). In this study, the product of the Pummerer like reaction **2.128** was also converted to the methoxy ether **2.129**.

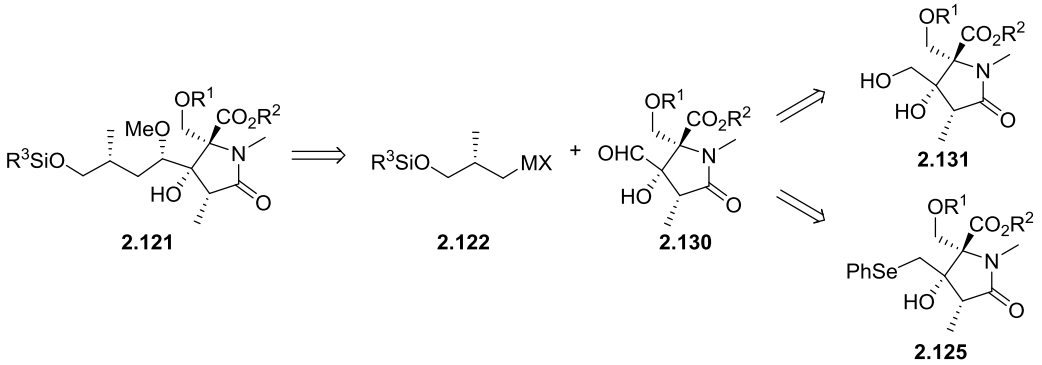


Scheme 2.23 Bari *et al.*[136] synthesis of seleno lactam 2.129

Reagents and conditions i) NCS, AIBN, CCl_4, reflux; ii) MeOH, $ZnCl_2$-SiO_2, $CHCl_3$, MS 3 Å, reflux.

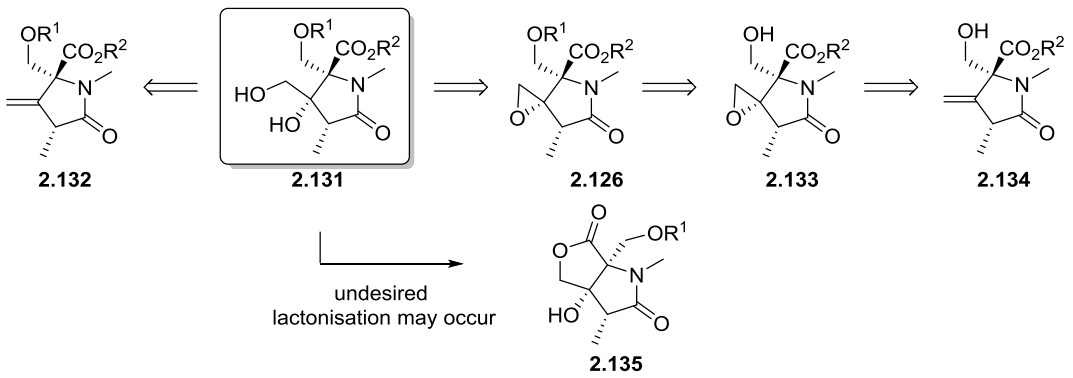
As our substrate **2.125** for the Pummerer-like reaction presented major differences from the original substrate **2.127**, the outcome of the Pummerer-like reaction remained uncertain. An alternative

approach was therefore considered in case of failure of the synthesis of methoxy ether **2.123**. The intermediate **2.121** would then be prepared by the addition of an organometallic reagent **2.122** to the corresponding aldehyde **2.130**, followed by the methylation of the corresponding alcohol (**Scheme 2.24**). The hydroxy aldehyde **2.130**, would be formed during the oxidation of the diol **2.131** or by a standard seleno-Pummerer reaction of the selenoxide of substrate **2.125**.



Scheme 2.24 Alternative synthetic approach for the formation of the fragment 2.121

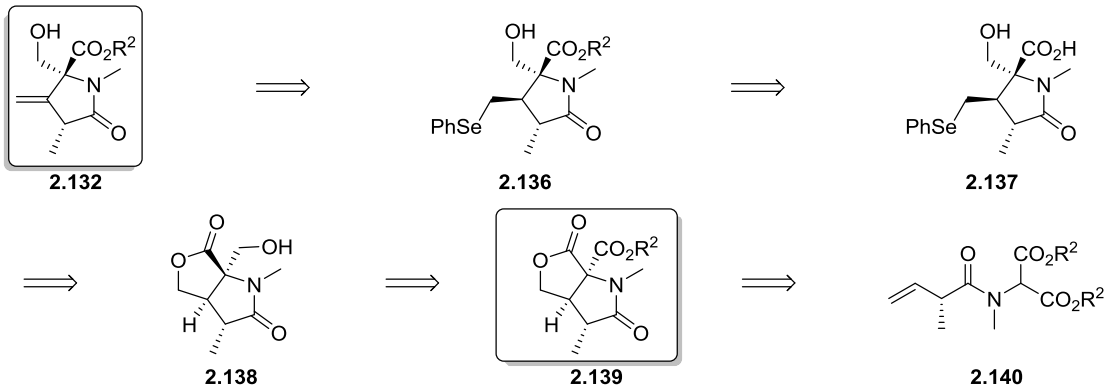
An obvious approach for the synthesis of the diol **2.131** would be the dihydroxylation of the alkene **2.132** (**Scheme 2.25**). The selectivity of the dihydroxylation may be difficult as the adjacent methyl group would disfavour the formation of the required diastereoisomer. If the use of the Sharpless asymmetric dihydroxylation failed to deliver the right selectivity, the required diol may be obtained by the opening of epoxide **2.126**, which would be formed by the directed epoxidation of homo allylic alcohol **2.134** with *m*-CPBA or ^{t}BuOOH and $VO(acac)_2$.[137] Precedents from Hatakeyama syntheses[123,130] led to anticipate a possible undesired cyclisation of the diol **2.131** to the lactone **2.135** (as previously presented in section **2.1.5** in **Scheme 2.13**). The use of a *tert*-butyl for the R^2 protecting group of the *tert*-butyl ester would decrease the probability of the undesired lactonisation.



Scheme 2.25 Two possible approaches for the formation of the diol 2.131

The alkene **2.132** was to be prepared from the bicyclic lactone-lactam **2.139**, which itself would be synthesised by manganese(III) and copper(II)-mediated oxidative cyclisation of the amidomalonate

2.140. A route between the oxidative cyclisation product **2.139** and the *exo*-alkene **2.132,** was developed (**Scheme 2.26**). The dual property of phenyl selenium species for the opening of lactone rings and the formation of alkenes was again a key feature in the development of this synthetic pathway. The *exo*-alkene functionality of the pyrrolidinone **2.132** would be generated by the oxidative elimination of the phenyl selenium group of the pyrrolidinone **2.136**, which would be obtained by the protection of the carboxylic acid **2.137**. The phenyl selenium moiety of the latter would be installed by opening of the lactone ring of the fused bicyclic pyrrolidinone **2.138** with sodium phenyl selenide. The alcohol functionality of the bicyclic pyrrolidinone **2.138** could be formed by reduction of the ester pyrrolidinone-lactone **2.139**, which would be obtained by the manganese(III) and copper(II)-mediated oxidative radical cyclisation of the alkenyl amidomalonate **2.140**.



Scheme 2.26 Synthetic strategy toward the key exo-alkene 2.132 from the fused pyrrolidinone-γ-lactone 2.140

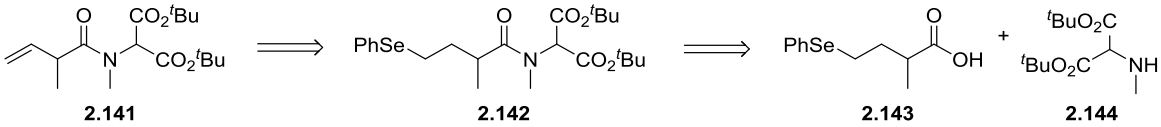
The synthetic studies toward the oxazolomycin family were initiated in the group by a postdoctoral researcher, who started the investigations of this strategy using racemic material.

2.2.2 **Previous work in the group toward the oxazolomycins**[ii]

2.2.2.1 Initial strategy for the synthesis of the cyclisation substrates and cyclisation results

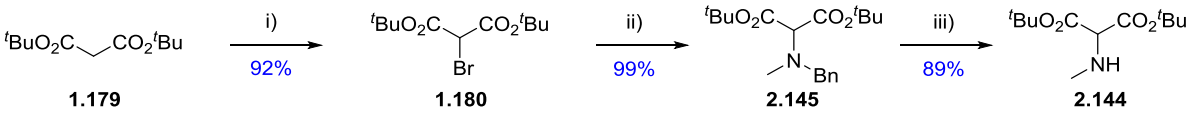
A route toward the key racemic cyclisation substrate **2.14** was initially developed by a post-doctoral co-worker. The alkenyl amidomalonate **2.141** was obtained by oxidative elimination of the selenium derivative **2.142**, avoiding possible isomerisation of the double bond during the amide bond formation. The selenide **2.142** could be obtained by amide coupling of carboxylic acid **2.143** and aminomalonate **2.144** (**Scheme 2.27**).

[ii] The work described in section **2.2.2** was conducted by Dr Wilfried Hess.



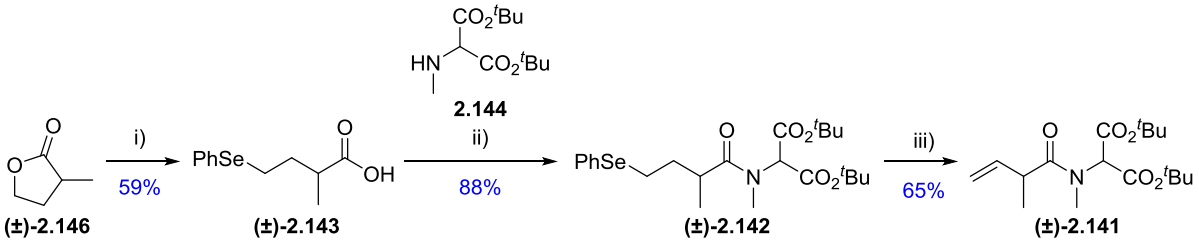
Scheme 2.27 Initial strategy for the synthesis of alkene amidomalonate 2.141

The aminomalonate **2.144** was synthesised in three steps from di-*tert*-butyl malonate. The first step was the bromination of di-*tert*-butyl malonate with CBr_4,[64] followed by the alkylation[78] of the corresponding bromomalonate **1.180** with benzyl methylamine (**Scheme 2.28**). The final hydrogenation of the aryl amine **2.145**, gave the clean methyl aminomalonate **2.144**.



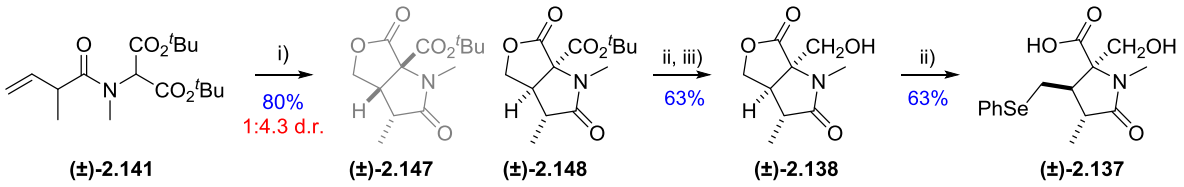
Scheme 2.28 Previously developed synthesis of aminomalonate 2.144
Reagents and conditions i) DBU (1.00 eq), CBr_4 (1.00 eq), THF, -78 °C, 2 h; ii) $BnNHCH_3$ (1.50 eq), NEt_3 (2.00 eq), $CHCl_3$, reflux, 15 h; (iii) H_2, Pd/C 5% (cat), MeOH, RT, 48 h.

In this approach, the carboxylic acid **(±)-2.143** required for the amide coupling with aminomalonate **2.144** was obtained by opening α-methyl-γ-butyrolactone **(±)-2.146** with the borane complex of phenyl selenium anion (**Scheme 2.29**). The coupling proceeded in good yield when an excess of carboxylic acid **(±)-2.143** was used for the reaction under Schotten-Baumann conditions.[61,62] The cyclisation substrate **(±)-2.141** was isolated after oxidative elimination of the phenyl selenium group of amidomalonate **(±)-2.142**.



Scheme 2.29 Previous synthesis of the racemic cyclisation substrate (±)-2.141
Reagents and conditions i) $(PhSe)_2$ (0.54 eq), $NaBH_4$ (1.22 eq), DMF, 100 °C, 5 min; then add solution of α-methyl-γ-butyrolactone in DMF, 120 °C, 2 h; ii) Acid **(±)-2.143** (1.20 eq), $(COCl)_2$ (1.1 eq), DMF (cat.), DCM, RT, 1 h; then add acyl chloride solution to solution of amine **2.144** (1.0 eq) in DCM/$NaHCO_3$ aq. solution, 1 h, RT; iii) *m*-CPBA (3.0 eq), -15 °C to RT, 1 h, then DMS (2.0 eq), DIPA, reflux 15 h.

The cyclisation of the alkenyl amidomalonate **(±)-2.141** with manganese(III) and copper(II) proceeded in good yield and satisfying d.r. (**Scheme 2.30**). The *tert*-butyl ester of the major pyrrolidinone-lactone **(±)-2.148** was then removed with TFA, and gave the corresponding carboxylic acid. The treatment of this carboxylic acid with the Vilsmeier salt, gave the acyl chloride, which was readily reduced with $NaBH_4$ according to the method of Fujisawa *et al.*,[138] to give the alcohol **(±)-2.138**. This bicyclic lactone **(±)-2.138** was opened with an equivalent of phenyl selenide anion to give the hydroxy acid **(±)-2.137**.

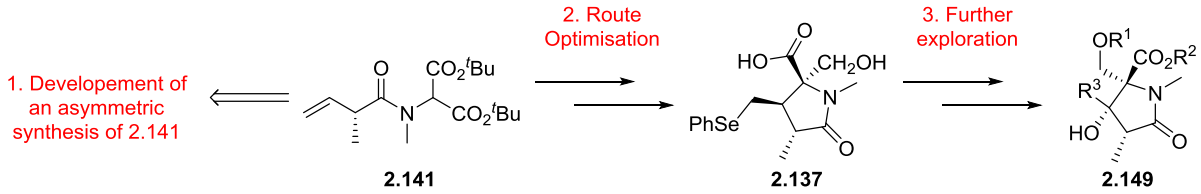


Scheme 2.30 Previous work toward the oxazolomycins

Reagents and conditions i) $Mn(OAc)_3 \cdot 2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 12 h, ii) TFA/DCM (1:1), RT, 12 h; then $[Me_2N{=}CHCl]^+,Cl^-$ in THF/MeCN, RT, 1 h; then $NaBH_4$ in DMF, -78 °C to RT, 15 h; iii) $NaBH_4$, $(PhSe)_2$, DMF, 100 °C, 5 min, then **(±)-2.138**, DMF, 100-120 °C, 2 h.

2.2.2.2 Project aims

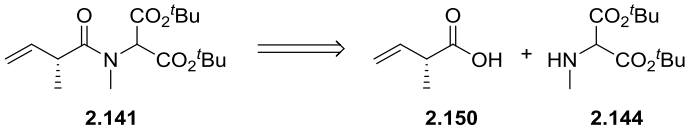
The results of this initial exploration toward the core of the oxazolomycin family demonstrated the viability of the synthetic strategy developed in the group. The development of an asymmetric route toward the cyclisation substrate **2.141** was the first aim of this research (**Scheme 2.31**). The optimisation of the d.r. of the oxidative cyclisation reaction and the improvement of the yield of the sequence toward hydroxy acid **2.137** would then make a new asymmetric route scalable for further synthetic explorations toward the core of the oxazolomycin family.



Scheme 2.31 Project aims

2.3 Asymmetric synthesis of alkenyl malonate 2.141

The most direct asymmetric synthesis of the alkenyl malonate **2.141** would be achieved by the amide bond formation between the amino malonate **2.144** and the enantiopure carboxylic acid **2.150** (**Scheme 2.32**).



Scheme 2.32 A direct approach to the cyclisation substrate 2.141

Reagents and conditions i) T3P (1.6 eq), pyridine/EtOAc, -40 °C to -10 °C, 6 h.

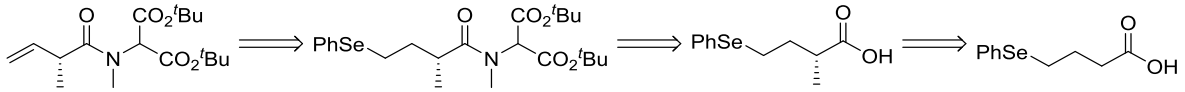
A similar amide coupling had proved to be difficult to optimise during the total synthesis of salinosporamide A due to epimerisation problems (see last chapter and **Scheme 2.33**).



(-)-1.144 98.8% e.e. **1.182** **(-)-1.187** 98.4% e.e.

Scheme 2.33 Successful coupling between a γ-δ unsaturated acid and an aminomalonate in the total synthesis of (-)-salinosporamide A

An alternative approach involving the use of selenium chemistry should be used in case of the failure of the coupling of the γ-δ unsaturated carboxylic acid **2.150**. The amide coupling of phenylselenyl butenoic acid with aminomalonates is precedented in the group and has been a reliable method to synthesise alkenyl amidomalonates.[44,63] The cyclisation substrate **2.141** would be formed by the oxidative elimination of the phenyl selenium group of the amide **2.142**, which would be prepared by the amide coupling between the aminomalonate **2.144** and the enantiomerically pure phenylselenyl butenoic acid **2.143** (**Scheme 2.34**). The carboxylic acid **2.143** would be prepared by Evans' alkylation of phenylselenyl butenoic acid **1.122** easily accessible from commercial butyrolactone and diphenyl diselenide.

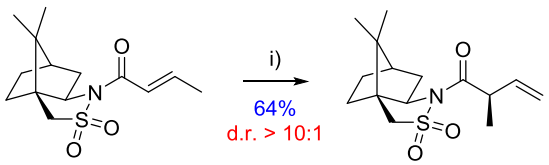


2.141 **2.142** **2.143** **1.122**

Scheme 2.34 Alternative approach to the cyclisation substrate 2.141

2.3.1 Attempt of coupling of the γ-δ unsaturated acid 2.150

The required γ-δ unsaturated carboxylic acid was prepared using the deconjugative alkylation of the enolate of crotonyl derivative **(-)-1.199**, which had been used for the total synthesis of (-)-salinosporamide A (section **1.9.1**). First attempts focused on trying to reproduce the procedure of Batchelor *et al.*[83] without carcinogenic HMPA (**Scheme 2.35**). When DMPU was used as an HMPA substitute[139] the alkylation proceed in good stereoselectivity (NMR analysis showed crude d.r. > 10:1). The alkylated product **(-)-2.151** was isolated as single diastereoisomer in 64% yield after two recrystallisations of the crude product from EtOAc/hexane (1:6).

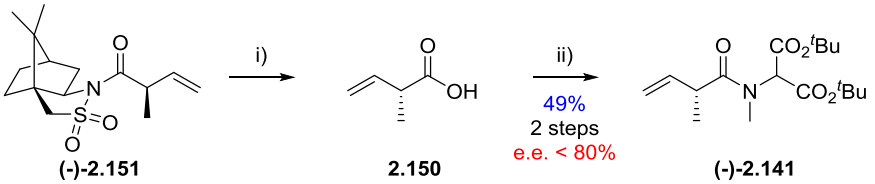


(-)-1.199 **(-)-2.151**

Scheme 2.35 HMPA free alkylation of the crotonyl derivative (-)-2.151

Reagents and conditions i) Add solution of **(-)-1.199** (1.00 eq) to LiHMDS 1.0 M in toluene (1.30 eq), DMPU (4.0 eq), THF, -78 °C, 15 min; then MeI (3.0 eq), THF, -78 °C, 15 h.

The subsequent cleavage of the Oppolzer chiral auxiliary was achieved using the procedure established in the previous chapter (LiOH and excess H_2O_2 in THF/H_2O). The crude carboxylic was then coupled to the methyl aminomalonate **2.144** (**Scheme 2.36**), which gave the desired alkene amidomalonate in moderate yield and only 80% e.e.

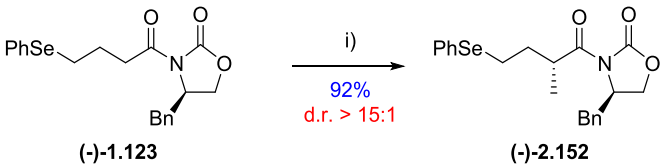


Scheme 2.36 Cleavage of the auxiliary and conditions for the amide coupling
Reagents and conditions i) LiOH (2.00 eq), H_2O_2 (4.00 eq), THF/H_2O (1:1), 0 °C, 15 min; ii) T3P (1.6 eq), aminomalonate **2.144**, pyridine, EtOAc, -40 °C, 4 h, -40 °C to -10 °C, 4 h.

T3P is a very good coupling agent for amide coupling prone to racemisation.[86] The moderate enantiomeric excess obtained in this particular case led us to anticipate that the coupling of the γ-δ unsaturated carboxylic acid **2.150** with the aminomalonate **2.144** would be difficult to improve. The previously described alternative strategy was therefore developed to synthesise the amidomalonate **(-)-2.141** in high enantiomeric excess.

2.3.2 **Phenylselenyl butenoic acid route**

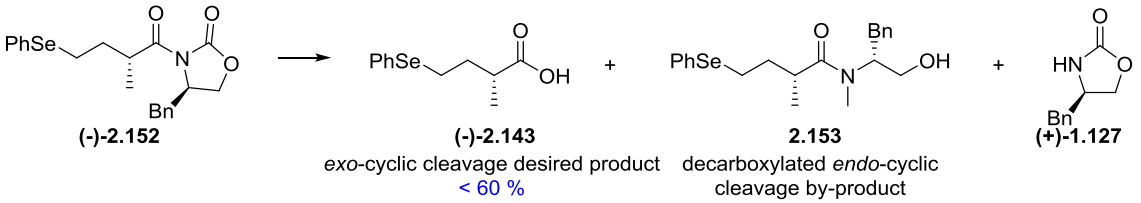
The synthesis of phenylselenium oxazolidinone **(-)-1.123** in two steps from butyrolactone was presented in the previous chapter (see section **1.6.2**). The alkylation of the sodium enolate of **(-)-1.123** with MeI gave **(-)-2.152** in an excellent yield and a good d.r. The traces of the minor diastereoisomer could be removed by careful purification (**Scheme 2.37**).



Scheme 2.37 Alkylation of phenyl selenium oxazolidinone (-)-2.152
Reagents and conditions i) NaHMDS in THF (2.0 M, 1.4 eq), -78 °C, 10 min; then MeI (3.0 eq), 3 h, -78 °C.

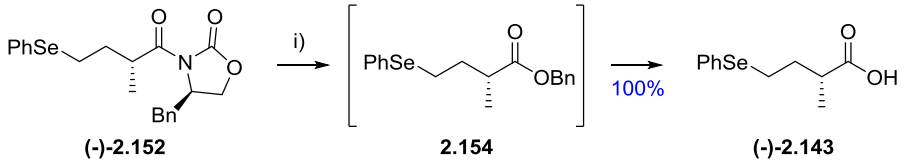
The cleavage of the oxazolidinone **(-)-2.152** proved problematic to form the carboxylic acid **(-)-2.143**. Many sources of hydroxides (LiOH, LiOOH, KOH and NaOH) were tested, but none of them gave yields over 60%. The ^{1}H NMR analysis of the crude reaction mixture systematically showed the existence of a side product, which could not be isolated after flash chromatography as it was discovered in a late scale-up that the side product eluted with auxiliary. Mass spectroscopy analysis of the mixture of the two products revealed a positive mass for the amide **2.153** ($[M+Na]^+$ = 414), whose structure was confirmed by careful ^{1}H NMR analysis of the mixture. The side product **2.153**

formed in the reaction probably results from the attack of a hydroxide ion on the carbonyl of the oxazolidinone ring.



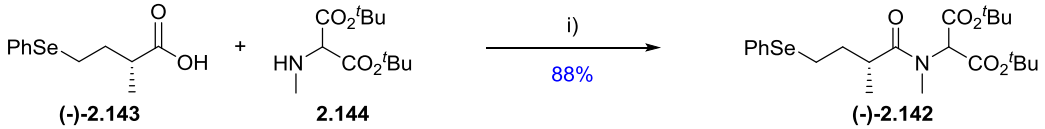
Scheme 2.38 Problematic cleavage of the auxiliary

A one pot procedure involving a selective substitution on the exo-carbonyl group by BnOLi[60] followed by saponification of the formed benzyl ester **2.154** with LiOH was successful (**Scheme 2.39**).



Scheme 2.39 Optimised cleavage of the auxiliary
Reagents and conditions i) BnOH (1.50 eq), *n*-BuLi (1.30 eq), THF, 0 °C, 30 min, then oxazolidinone **(-)-2.152** (1.00 eq) in THF, -78 °C to RT over 1 h, RT, 1 h then LiOH (15.0 eq), MeOH/H_2O/THF, 0°C to RT, 15 h.

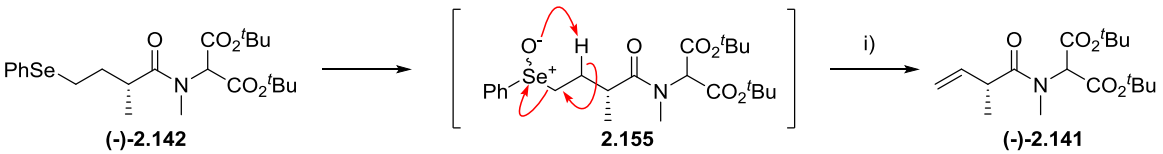
The amide bond was formed under Schotten-Bauman conditions[61,62] between the acyl chloride of carboxylic acid of **(-)-2.143** and the amine **2.144** (**Scheme 2.40**). When conditions from the racemic route were used, the reaction gave moderate yields (typically 50-70%). More careful attempts allowed isolation of the amidomalonate **(-)-2.142** in high yield, which could be obtained in a reproducible way when freshly purified amine **2.144**, and vacuum dried acyl chloride (freed from excess of oxalyl chloride) were engaged in the coupling procedure. The rapid addition of the solution of the acyl chloride to the biphasic mixture was also important to obtain a good yield for the coupling reaction. The enantiomeric excess of **(-)-2.142** (> 96%)**,** was measured against the racemic reference **(±)-2.143** provided by Dr Hess, HPLC traces are available in the appendix (section **7.1.12**).



Scheme 2.40 Amide coupling of aminomalonate 2.144 and phenylselenyl butenoic acid (-)-2.143
Reagents and conditions i) $(COCl)_2$ (1.50 eq), DMF (2 mol%), DCM, RT, 1 h then add to aminomalonate **2.144** in DCM/sat. aq. $NaHCO_3$ solution (1:1), RT, 30 min.

The oxidative elimination of the phenyl selenium with *m*-CPBA in the previously developed synthesis of the racemic alkene amidomalonate **(±)-2.141** and was reported in 65% yield. The reaction on the enantiopure substrate **(-)-2.142** gave a slightly lower yield (57%) under the same conditions. In order to optimise the yield, a promising oxidation procedure which involved a large excess of hydrogen peroxide was first attempted (**Table 1.1**).[21] No quenching operation was described in the procedure.

In order to develop a safe protocol for future scale-up, quenching agents were used (**Table 1.2**). An aqueous solution of Na_2SO_3 was first employed in the work-up of the selenoxide **2.155**, which caused partial reduction of the selenoxide back to the starting material before elimination to the corresponding alkene **(-)-2.141** occurred. A solution of $FeSO_4$ and citric acid was eventually used to quench the reaction. On small scale (422 mg) the reaction proceeded in good yield (83%). However on large scale (2.63 g), when the quenching solution was slowly added a runaway exotherm was observed after an induction period, and the yield dropped to 66%.

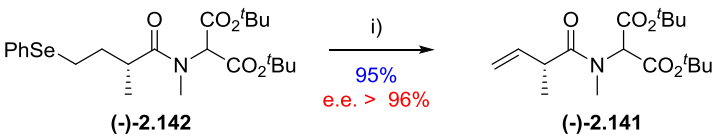


Quenching conditions	Scale	Yield
No quenching	50 mg	84%
Saturate Na_2SO_3	50 mg	72%
$FeSO_4$, citric acid	50 mg	84%
$FeSO_4$, citric acid	400 mg	83%
$FeSO_4$, citric acid	2.63 g	66%

Table 2.1 Oxidative elimination of the phenyl selenium group with H_2O_2

Reagents and conditions i) 30% aq. H_2O_2 (15.0 eq), THF, RT, 3 h; then workup with indicated solution; then reflux in DCM, 6 h.

In further attempts, $NaIO_4$ was used as the oxidising agent in a biphasic system between water and DCM.[140] Excess $NaIO_4$ could therefore be removed by simple aqueous work-up. But the oxidation appeared to be very slow and the low pH of the reaction (due to the unexpected acidity of bulk $NaIO_4$) led to the loss of the *tert*-butyl esters. Further attempts using $NaIO_4$ in a monophasic system[74] ($MeOH/THF/H_2O$, 1:1:1) in the presence of $NaHCO_3$ gave the selenoxide in 45 minutes at room temperature. Aqueous work-up gave the crude selenoxide **2.155** in a $CHCl_3$ solution, which was heated under reflux to give the desired alkene amidomalonate **(-)-2.241** in 95% yield after purification.

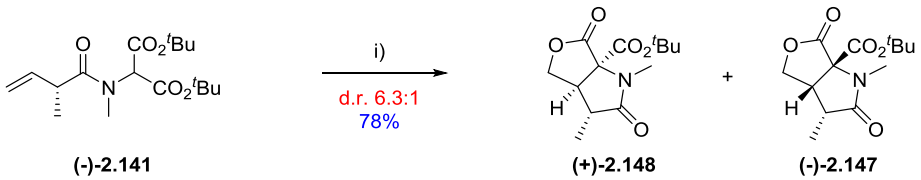


Scheme 2.41 Optimised selenium oxide elimination

Reagents and conditions i) $NaIO_4$ (4.0 eq), $NaHCO_3$ (4.0 eq), $MeOH/H_2O/THF$ (1:1:1), RT, 45 min; then work up $CHCl_3/H_2O$, heat organic layer under reflux (65 °C), 4 h.

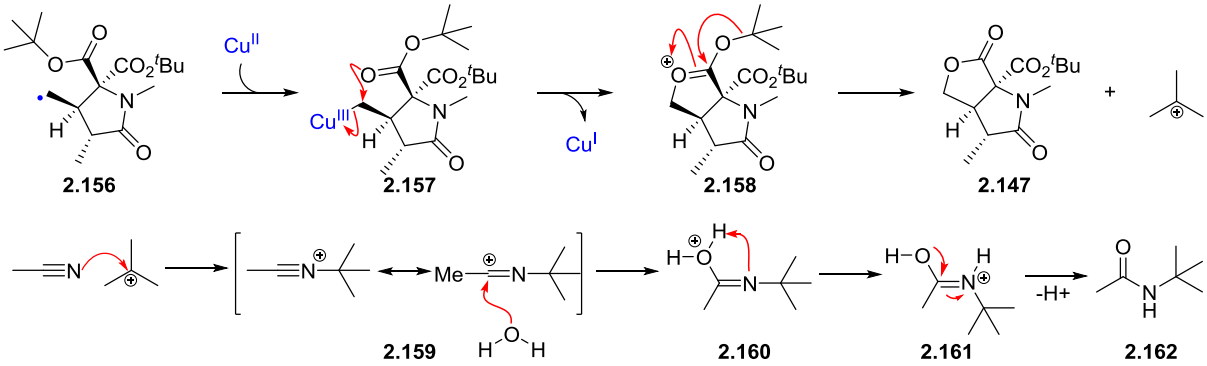
2.4 Oxidative radical cyclisation

The alkene amidomalonate **(-)-2.141** was submitted to the oxidative radical cyclisation reaction previously developed in the group.[44,55] The conditions used for the cyclisation in the racemic substrate gave similar good yields. The initial copper loading (1.0 eq) of the reaction was decreased (to 0.2 eq), with no effect on the yield of the reaction. The d.r. of the reaction could be raised from 4-5:1 to 6.3:1 by decreasing the temperature of the reaction from 40 °C to room temperature with almost complete conservation of the yield (**Scheme 2.42**). The cyclisation did not reach completion, when it was performed at 0 °C overnight.



Scheme 2.42 Optimised manganese(III) and copper(II)-mediated oxidative radical cyclisation
Reagents and conditions i) $Mn(OAc)_3 \cdot 2H_2O$ (2.00 eq), $Cu(OTf)_2$ (0.2 eq), MeCN, RT, 8 h.

The two diastereoisomers could be separated by flash column chromatography. The stereochemistry of the major diastereoisomer **(-)-2.248** was confirmed by ^{1}H NMR nOe experiments (see experimental part). A by-product contaminated the major diastereoisomer after flash chromatography purification. Most of it could be sublimed out of the samples under high vacuum (0.3 mmHg). ^{1}H NMR analysis and mass spectroscopy revealed that this compound was *tert*-butyl acetamide **2.162**, which is the product of the Ritter reaction between the *tert*-butyl carbocation (probably released during the *tert*-butyl ester lactonisation step in the oxidative cyclisation reaction) and a molecule of solvent (MeCN) (**Scheme 2.43**).

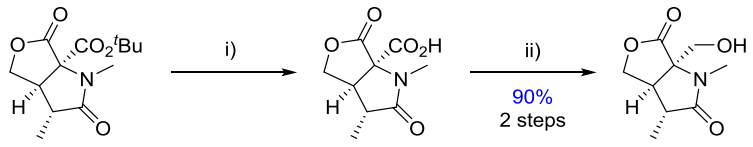


Scheme 2.43 Ritter reaction between the eliminated *tert*-butyl cation and a molecule of MeCN

2.5 Optimisation of the other steps

2.5.1 Hydrolysis of the ester and reduction

The *tert*-butyl ester of the major cyclisation product **(+)-2.147** was hydrolysed in TFA/DCM (1:1), which gave the intermediate carboxylic acid **2.163** in quantitative yield. The treatment of this carboxylic acid with the Vilsmeier salt in THF/MeCN gave the corresponding acyl chloride, which was readily reduced with $NaBH_4$ using Fujiswa conditions.[138] In initial attempts, the reaction typically gave yields around 60%, although the ^1H NMR analysis of the crude reaction mixture showed no significant impurity. TLC and mass spectroscopy analysis showed that a significant amount of the alcohol **(+)-2.138** remained in the aqueous phase after the work-up. To reduce the solubility of the product in the aqueous phase, the reaction solvents (THF/MeCN/DMF) were evaporated under reduced pressure before the work-up, during which the compound was extracted from a small amount of water saturated with NaCl. Eight extractions with EtOAc did not allow the complete recovery of the alcohol **(+)-2.138** from the aqueous phase. In further attempts, the reaction was quenched with aqueous HCl before evaporation to dryness (**Scheme 2.44**). The residue was dry loaded onto the final chromatography column without aqueous work-up. This procedure allowed the formation of **(+)-2.138** in 90% yield on 24.4 mmol scale.



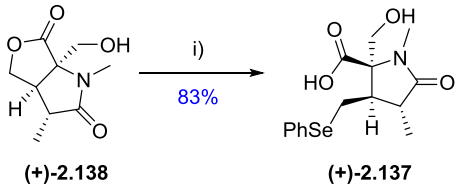
(+)-2.148 **2.163** **(+)-2.138**

Scheme 2.44 Optimised hydrolysis and reduction of the *tert*-butyl ester
Reagents and conditions i) TFA/DCM (1:1), 0 °C to RT, 20 h; ii) $[Me_2N{=}CHCl]^+,Cl^-$ (2.10 eq) in THF/MeCN (3:2), 0 °C to RT, 1 h then $NaBH_4$ (2.10 eq) in DMF, -78 °C to RT, 2 h.

2.5.2 Opening of the lactone ring

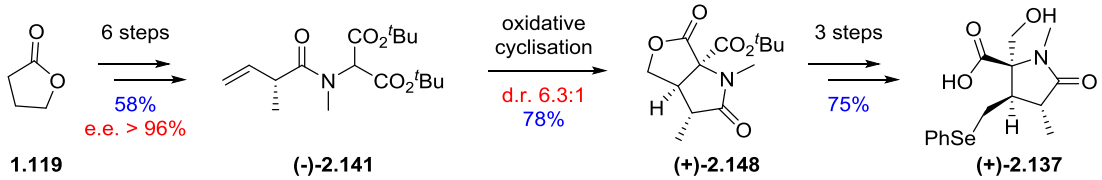
The last known step reproduced from the previous racemic sequence was the opening of the lactone **(+)-2.238** with the phenyl selenide anion. The phenyl selenide anion equivalent was prepared by heating yellow $(PhSe)_2$ and $NaBH_4$ at 100 °C before the addition of the lactone **(+)-2.238**. The initial procedure developed by Hess involved the use of 1.32 eq of $NaBH_4$ for the reduction of 0.6 eq of $(PhSe)_2$, which forms the borane complex of the phenyl selenium anion. The procedure only gave yields around 65%. It was anticipated that the excess of $NaBH_4$, could degrade the starting material by the possible reduction of the lactone or lactam ring. A solution of $NaBH_4$ in DMF was therefore added slowly to a solution of $(PhSe)_2$ in DMF at 100 °C until complete reduction of $(PhSe)_2$ indicated by the disappearance of the bright yellow colour of $(PhSe)_2$. The complete reduction of $(PhSe)_2$

typically required 0.7 eq of $NaBH_4$. When the addition of $NaBH_4$ was completed, heating was maintained for 10 min to allow the decomposition of excess $NaBH_4$, before the addition of the lactone solution (**Scheme 2.45**). This procedure modification along with the replacement of the aqueous work-up by a direct dry loading of the residue obtained after evaporation of the reaction to dryness on the final column allowed an increase of the 65% initial yield to 83%.



Scheme 2.45 Optimised opening of the lactone ring
Reagents and conditions i) $(PhSe)_2$ (0.60 eq), $NaBH_4$ (0.70 eq), DMF, 100 °C, 10 min; then add lactone **(+)-2.138** in DMF, 110 °C, 2 h.

The key hydroxy acid **(+)-2.137** (6.43 g, 18.1 mmol) was produced in 29% yield through a 10 steps sequence from γ-butyrolactone **1.119** (**Scheme 2.46**).

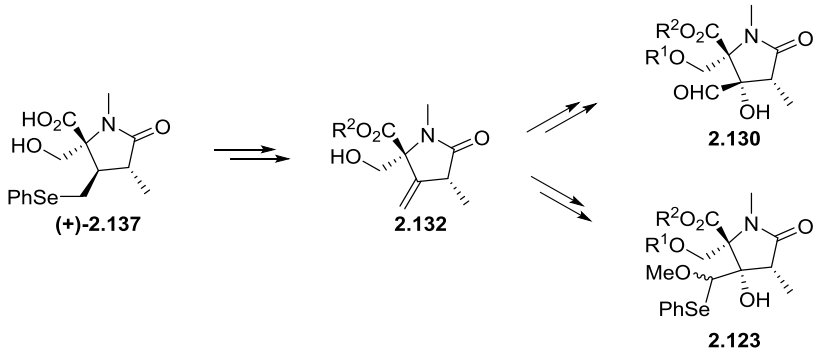


Scheme 2.46 Route summary to the key hydroxy acid (+)-2.137

The optimised enantioselective route to the key hydroxy acid **(+)-2.137** allowed novel synthetic exploration toward the pyrrolidinone core of the oxazolomycin family.

2.6 Further steps towards the core of oxazolomycin A

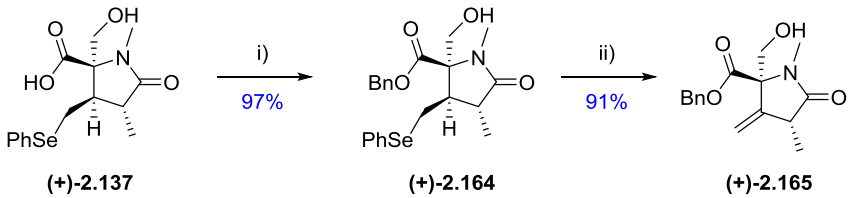
The aim of these further steps is to develop the route between the hydroxy acid **(+)-2.137** and the key lactam alcohol **2.130** or **2.123** following our strategy presented in section **2.2.1** and summarised below (**Scheme 2.47**). The next two key steps would be the protection of the carboxylic acid **(+)-2.137**, followed by an oxidative elimination of the phenyl selenium unit to isolate the key intermediate *exo*-alkene **2.132.**



Scheme 2.47 Previously presented strategy

2.6.1 Use of a benzyl ester for the protection of the β-hydroxy acid (+)-2.137

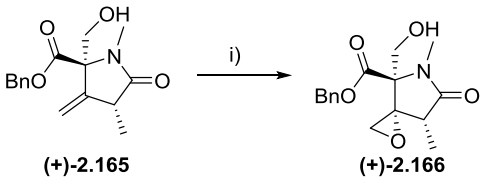
The oxidative elimination of the phenyl selenium moiety was made after the protection of the hydroxy acid **(+)-2.137** with benzyl bromide (**Scheme 2.48**). Oxidation of the selenium unit was achieved using $NaIO_4$ conditions that were previously presented.[74]



Scheme 2.48 Benzyl esterification and oxidation of the phenyl selenium group
Reagents and conditions i) BnBr (2.5 eq), K_2CO_3 (5.0 eq), DMF, RT, 1 h; ii) $NaIO_4$ (3.0 eq), $NaHCO_3$ (3.0 eq), MeOH/THF/H_2O, RT, 15 min, then aqueous work-up, heat 80 °C, PhMe/NEt_3 (10:1), 15 min.

2.6.1.1 Epoxidation attempt

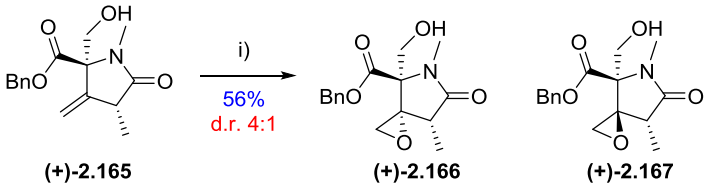
The directed epoxidation of the homoallylic *exo*-alkene **(+)-2.165** was then attempted. The $VO(acac)_2$/^{t}BuOOH system seemed ideal to install the required epoxide on the face of the alcohol group. When the conditions of Takashi *et al.*[137] were applied to the alkene **(+)-2.165**, the epoxidation proceed with complete selectivity but also formed an unidentified impurity which was inseparable from the epoxide (**Scheme 2.49**).



Scheme 2.49 Directed epoxidation with $VO(acac)_2$
Reagents and conditions i) ^{t}BuOOH (3.00 eq) added over 6 h, $VO(acac)_2$ (2.0 eq), DCM, 0 °C, then add more $VO(acac)_2$ (2.00 eq) and ^{t}BuOOH (3.00 eq) over 6 h, 0 °C.

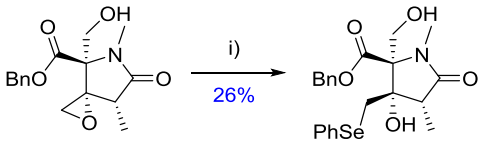
Since no clean epoxide could be isolated from the vanadium epoxidation, the *exo*-alkene **(+)-2.165** was treated with *m*-CPBA, which gave a mixture of the epoxides in a favourable 4:1 d.r. (**Scheme 2.50**). The reaction was stopped after 4 days as it had not reached completion. The relative

structures of the two epoxides were assigned by comparison of the ^{1}H NMR nOe interactions between the epoxide protons and the methyl group protons. The results of these two nOe experiments are available in the experimental part.



Scheme 2.50 Epoxidation of the *exo*-alkene (+)-2.165
Reagents and conditions i) *m*-CPBA (5.00 eq), DCM, 40 °C, 4 days.

The opening of the epoxide **(+)-2.167** with a phenyl selenium anion equivalent to obtain the Pummerer substrate **(+)-2.168** was then trialled (**Scheme 2.51**). The reaction gave a mixture of products; only limited amount of the required diol **(+)-2.168** could be isolated after purification. The cleavage of the benzyl ester might have been a side reaction.

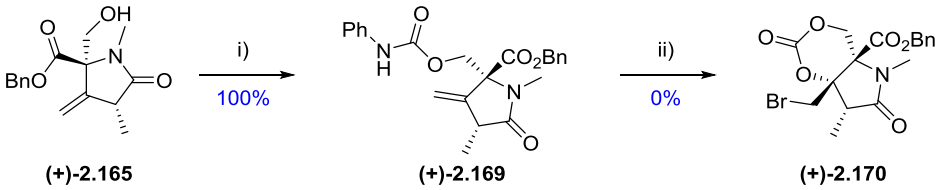


Scheme 2.51 First attempt of epoxide opening
Reactions and conditions i) $(PhSe)_2$ (1.00 eq) and $NaBH_4$ (1.00 eq), DMF, 100 °C, 5 min, then epoxide (1.00 eq), RT, 30 min.

The use of a benzyl ester for the protection of the carboxylic acid **(+)-2.137** was abandoned. A *tert*-butyl ester was preferred for its resistance toward the phenyl selenium anion. The corresponding esterification reaction is presented in section **2.6.2**. The remainder of benzyl ester **(+)-2.165** was used in the investigation of an alternative carbonate cyclisation briefly presented in the following paragraph.

2.6.1.2 Attempt of the formation of a cyclic carbonate

The attempt of intramolecular cyclisation of the carbamate **(+)-2.165** onto its alkene group was inspired by precedents from Baran *et al.*[141] and from our synthesis of salinosporamide A. The formation of the bromo carbonate **(+)-2.170** would have installed the second quaternary stereocentre carrying the required oxygen atom. The residual bromine atom may have also offered a possible handle to introduce the side chain of the natural product. Unfortunately, the carbamate alkene **(+)-2.169** was unreactive to NBS used to promote the cyclisation. The conditions used for the selenolactonisation in section **1.11.4.2** did not allow the formation of the the phenyl selenium equivalent of **(+)-2.170.**



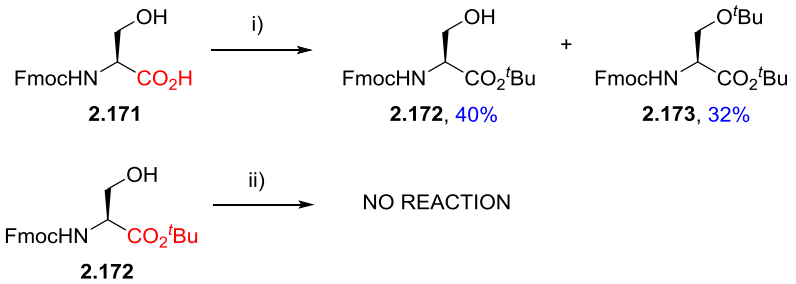
(+)-2.165 (+)-2.169 (+)-2.170

Scheme 2.52 Attempt of the formation of a cyclic carbonate (+)-2.170

Reagents and conditions i) Phenyl isocyanate (1.00 eq), NEt_3 (1.00 eq), DCM, RT, 20 min; ii) NBS (2.00 eq), DCM, RT, 6 h.

2.6.2 Use of a *tert*-butyl ester for the protection of the β-hydroxy acid (+)-2.137

The presence of a *tert*-butyl ester group protecting the carboxylic acid **(+)-2.137** would make the carboxyl unit ideally resistant toward nucleophiles used during the opening of the corresponding epoxide. The *tert*-butyl esterification of a β-hydroxy acid was tried during the development of the synthesis of (-)-salinosporamide A and is reported in moderate yield in the previous chapter (section **1.13**). The reaction with *tert*-butyl 2,2,2-trichloroacetimidate had given poor results as *tert*-butyl esterification took place in moderate selectivity over both etherification and esterification of the primary β-hydroxy group. Thierry *et. al.*[142] studied the *tert*-butyl esterification of *N*-protected amino acids with *tert*-butyl 2,2,2-trichloroacetimidate. In this study, when Fmoc-Tyr-OH **2.171** was treated with *tert*-butyl 2,2,2-trichloroacetimidate (1.5 eq), a mixture of the desired mono-alkylated (ester) Fmoc-Tyr-O^{t}Bu **2.172** and of the dialkylated (ester-ether) product **2.173** was obtained. More interestingly, when the mono-alkylated (ester) Fmoc-Tyr-O^{t}Bu **2.172** was submitted to similar reaction conditions, no etherification happened. The author suggested that the etherification required the presence of the carboxylic acid to proceed.



2.171 **2.172**, 40% **2.173**, 32%

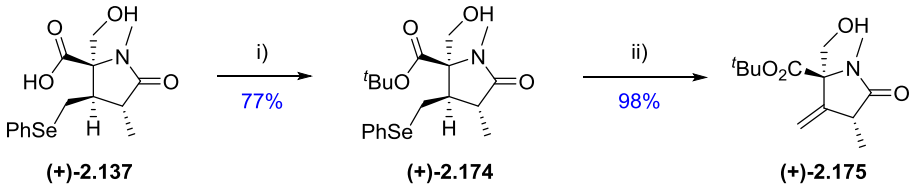
2.172

Scheme 2.53 Summary of Thierry *et. al.* results

Reagents and conditions i) *tert*-butyl 2,2,2-trichloroacetimidate (1.50 eq), DCM, RT, 12 h; ii) *tert*-butyl 2,2,2-trichloroacetimidate (6.00 eq), DCM, RT, 72h.

If the catalytic process of the alcohol etherification by the carboxylic acid is an intramolecular process, the use of another catalyst that increases the rate of the esterification should therefore increase the selectivity of the esterification. $BF_3{\cdot}Et_2O$ is sometime used as a catalyst for the formation of *tert*-butyl ester with 2,2,2-trichloroacetimidate.[143] One full equivalent of $BF_3{\cdot}Et_2O$ was therefore used in the esterification of hydroxy acid **(+)-2.137**, (**Scheme 2.54**). This approach was successful as

the ester **(+)-2.174** was isolated in 77% yield. No optimisation was required for the subsequent oxidative elimination, which proceeded in quantitative yield.

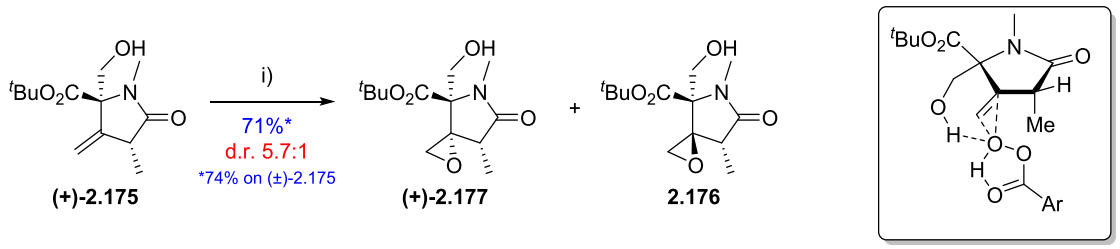


Scheme 2.54 Successful *tert*-butyl esterification of hydroxy acid (+)-2.137, and oxidative elimination of the phenyl selenium group

Reagents and conditions i) *tert*-butyl 2,2,2-trichloroacetimidate (3.00 eq), $BF_3{\cdot}Et_2O$ (1.00 eq), THF, 0 °C to RT, 3 h; ii) $NaIO_4$ (5.00 eq), $NaHCO_3$ (5.00 eq), THF/MeOH/H_2O (1:1:1), RT, 40 min; work-up then reflux in $CHCl_3$, 3 h.

2.6.3 Epoxidation of the *exo*-alkene and opening attempts

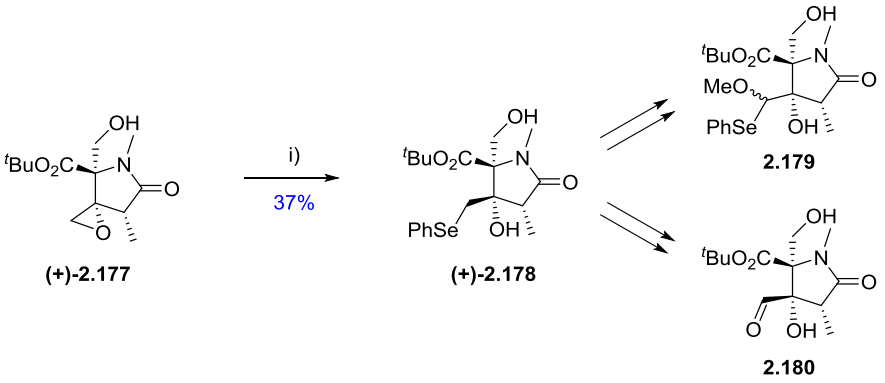
The epoxidation of the alkene **(+)-2.175** was performed with *m*-CPBA. The reaction is very slow at room temperature but gave a good facial selectivity, and reached completion when five equivalents of *m*-CPBA are used (**Scheme 2.55**). The two diastereoisomers **(+)-2.176** and **(+)-2.177** formed in 5.7:1 favourable ratio were easily separated by flash column chromatography and their respective stereoconfiguration was assigned by ^{1}H NMR nOe experiments. The results of these experiments are available in the Experimental. The selectivity of the reaction might be explained by the stabilisation offered by the bonding between the hydroxyl group and the oxygen atom when the *m*-CPBA molecule approaches the alkene on the methyl group face.



Scheme 2.55 Epoxidation of the alkene (+)-2.175

Reagents and conditions i) *m*-CPBA (5.00 eq), DCM, RT, 84 h.

The opening of the epoxide **(+)-2.177** with a phenyl selenium anion equivalent to obtain the selenium substrate **(+)-2.178** was to be achieved to test the selenium Pummerer-like reactions that could deliver the key intermediates **2.179** or **2.180** (**Scheme 2.56**). The reaction of phenyl selenium anion was performed following the modified procedure of Wolf *et al.*[144] The opening of the epoxide **(+)-2.177** did not require reflux conditions used in the followed procedure as full conversion was obtained by warming the reaction to room temperature. The recovery of the product was low as the very polar diol **(+)-2.178** streaked on the chromatography column.

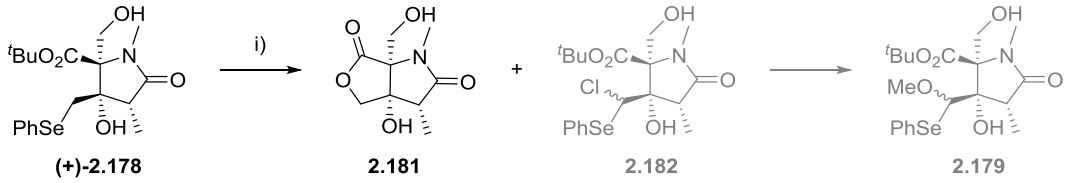


Scheme 2.56 Opening of the epoxide (+)-2.177 with selenium anion in order to develop a Pummerer reaction
Reagents and conditions i) $(PhSe)_2$ (0.60 eq), $NaBH_4$ (1.10 eq), EtOH/THF, 70 °C, 10 min; then add epoxide **(+)-2.177** at -20 °C to RT, 1 h.

2.6.4 **Selenium Pummerer reaction**

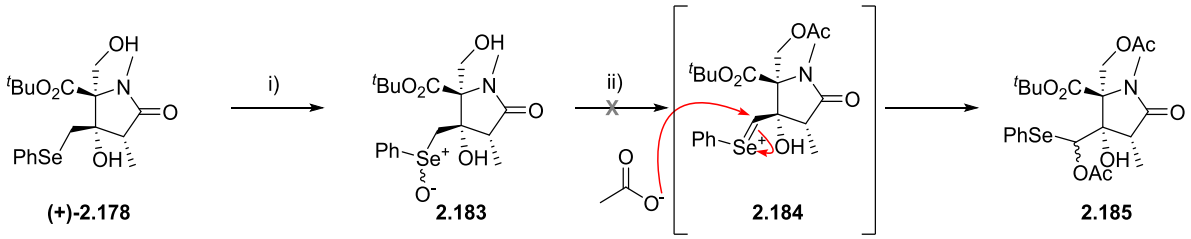
2.6.4.1 Attempt of formation of the key intermediate **2.179**

The chlorination conditions via a selenium Pummerer-like reaction developed by Bari *et al.*[136] previously presented (section **2.2.1**, **Scheme 2.23**) were tested on the substrate **(+)-2.175** (**Scheme 2.57**). The reaction did not give any chlorinated product **2.182**. Instead, the formation of the major bicyclic pyrrolidinone-lactone product **2.181** was observed by ^{1}H NMR and mass-spectroscopy analysis ($[M+Na]^+$ = 238) of the crude reaction mixture.



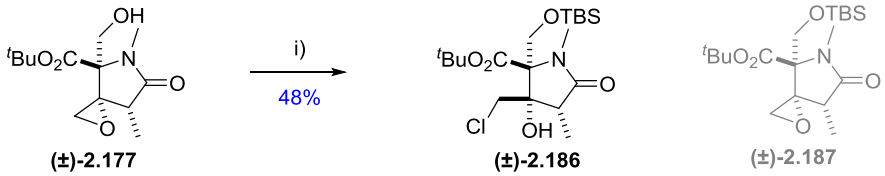
Scheme 2.57 Chlorination attempt using Bari *et al.*[136] procedure
Reagents and conditions i) NCS (1.10 eq), AIBN (0.10 eq), CCl_4, reflux.

It was alternatively attempted to form the hydroxyl aldehyde **(+)-2.180** using available selenium derivative **(+)-2.178** in a more usual type of Pummerer reaction.[145] The initial step in this process was the clean and quantitative formation of the crude mixture of selenoxides **2.183**. The Pummerer reaction of this crude mixture was tried in neat Ac_2O in the presence of NaOAc following precedents from Urabe *et al.*[146] The monitoring of the reaction by TLC and mass spectroscopy was difficult as acetylation occured on the primary alcohol (**Scheme 2.58**). The reaction gave a mixture of products. It remains unclear whether the Pummerer reaction occurred on this substrate.



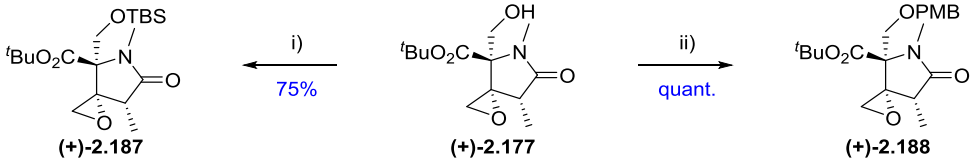
Scheme 2.58 First attempt of Pummerer reaction acetylation on selenoxide 2.183
Reagents and conditions i) $NaIO_4$ (5.00 eq), $NaHCO_3$ (5.00 eq), THF/MeOH/H_2O (1:1:1), RT, 1 h; ii) Ac_2O (50.0 eq), NaOAc (10.0 eq), 100 °C, 4 h.

The second step of the Pummerer reaction would be much easier to monitor if the primary hydroxyl group could be protected. The primary alcohol of the epoxide **(±)-2.177** was unreactive toward TBSCl, and the opening of the epoxide with a chlorine atom occurred at higher temperature, which predominantly gave the product **(±)-2.186.**



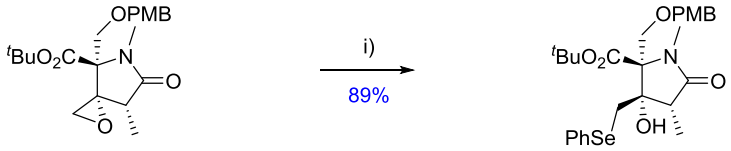
Scheme 2.59 Unsuccessful attempt of protecting the epoxide (±)-2.177
Reagents and conditions i) TBSCl (1.3 eq), Imidazole (1.5 eq), DMAP (0.15 eq), RT, 16 h, then more TBSCl (1.3 eq), Imidazole (1.5 eq), 60 °C, 2 h.

The use of an excess of TBSOTf eventually allowed the silylation of the alcohol of epoxide **(+)-2.177** to give **(+)-2.187** (**Scheme 2.60**). The introduction of a PMB protecting group was also simultaneously studied. The protection could be quantitatively achieved with 4-methoxybenzyl-2,2,2-trichloroacetimidate in the presence of catalytic TfOH.



Scheme 2.60 Protection of the primary alcohol of epoxide (+)-2.177
Reagents and conditions i) TBSOTf (2.00 eq), 2,6-lutidine (4.00 eq), DCM, 0 °C, 30 min; ii) 4-methoxybenzyl-2,2,2-trichloroacetimidate (2 x 2.50 eq), TfOH (2 x 2.50 mol%), Et_2O, RT, 2 x 15 min.

The epoxide **(+)-2.188** was then opened with the phenyl selenium anion using previously described conditions (**Scheme 2.61**). The flash column chromatography purification of the crude reaction could be easily achieved and gave the alcohol **(+)-2.189** in good yield.

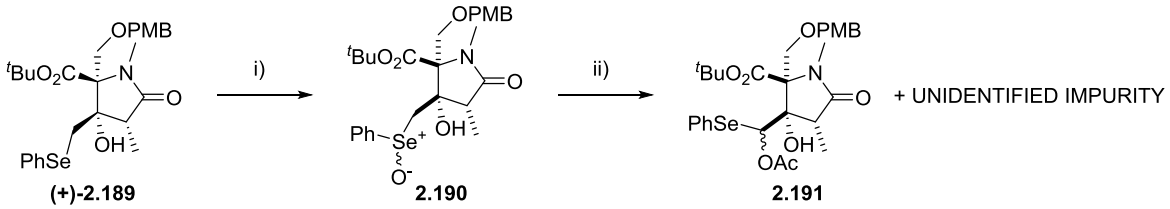


(+)-2.188 (+)-2.189

Scheme 2.61 Opening of the epoxide (+)-2.188

Reagents and conditions i) $(PhSe)_2$ (0.75 eq), $NaBH_4$ (1.50 eq), EtOH/THF, 70 °C, 10 min then add epoxide **(+)-2.188**, -20 °C to RT, 1 h.

The α-seleno alcohol **(+)-2.189** was then cleanly oxidised to the selenoxide **2.190**. The subsequent Pummerer reaction of the crude mixture of selenoxides **2.190** was attempted at 100 °C in neat Ac_2O in the presence of NaOAc.[146] The mass spectroscopy monitoring of the reaction showed the formation of Pummerer product **2.191** ($[M+Na]^+$ = 630, **Scheme 2.62**), and the formation of an unknown major side product ($[M+H]^+$ = 450, $[M+Na]^+$ = 472, no selenium pattern). The ^1H NMR analysis of the crude reaction mixture showed a complex mixture of products.

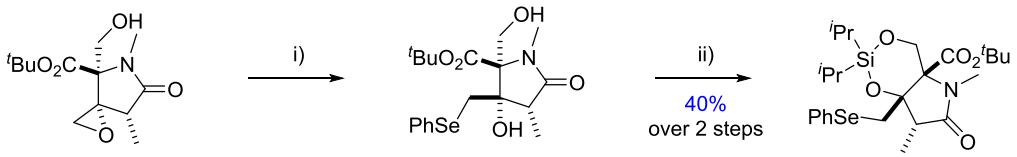


(+)-2.189 2.190 2.191

Scheme 2.62 Second attempt of the selenium Pummerer reaction

Reagents and conditions i) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), THF/MeOH/H_2O (1:1:1), RT, 1 h; ii) Ac_2O (50.0 eq), NaOAc (10.0 eq), 100 °C, 2 h.

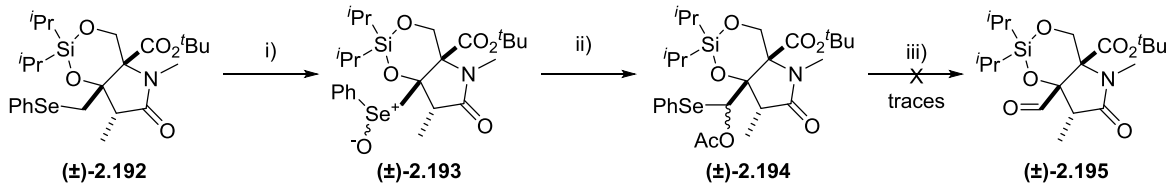
No precedents for selenium Pummerer reaction at the α-position of a free hydroxyl group could be found. The use of dioxisilane protecting group for the 1,3-diol **(±)-2.178** would allow engaging the fully protected substrate **(±)-2.192** in the Pummerer reaction. The previously described opening of the epoxide **(±)-2.177** was performed on racemic starting material. In order to avoid the low recovery of the streaking diol, the column was first eluted with a low polarity solvent to wash excess of selenium species and further elutions with MeOH in EtOAc were all combined. The mass recovery of the diol **(±)-2.178** was much higher, but the proton NMR analysis of the diol **(±)-2.178** indicated the presence of a minor unknown impurity (approximately 15 mol%). This batch was converted to the corresponding dioxisilane **(±)-2.192** with diisopropylsilyl bis(trifluoromethanesulfonate) according to the modified procedure of Hatakeyama *et al.*[130] (**Scheme 2.63**). The protection reaction did not reach completion, and several side products were detected by TLC. The overall yield after flash column chromatography purification was moderate (40%).



(±)-2.177 **(±)-2.178** **(±)-2.192**

Scheme 2.63 Second attempt of the opening of the epoxide (±)-2.177 and protection of the diol (±)-2.178
Reagents and conditions i) $(PhSe)_2$ (0.60 eq), $NaBH_4$ (1.10 eq), EtOH/THF, 70 °C, 10 min then add epoxide **(±)-2.177** -20 °C to RT, 1 h ii) *i*-$Pr_2Si(OTf)_2$ (3.30 eq), 2,6-lutidine (10.0 eq), RT to reflux, 45 min.

The compound **(±)-2.192** was then submitted to the oxidation/Pummerer reaction sequence, which produced a mixture of the Pummerer product **(±)-2.194** and some minor impurities. The crude reaction product **(±)-2.194**, was then hydrolysed with MeOH and K_2CO_3 in an unsuccessful attempt of the formation of the aldehyde **(±)-2.195**. The NMR and mass spectroscopy analysis of the crude reaction showed the formation of a mixture of products. Only trace amount of the required aldehyde could be identified in the NMR spectra (**Scheme 2.64**).



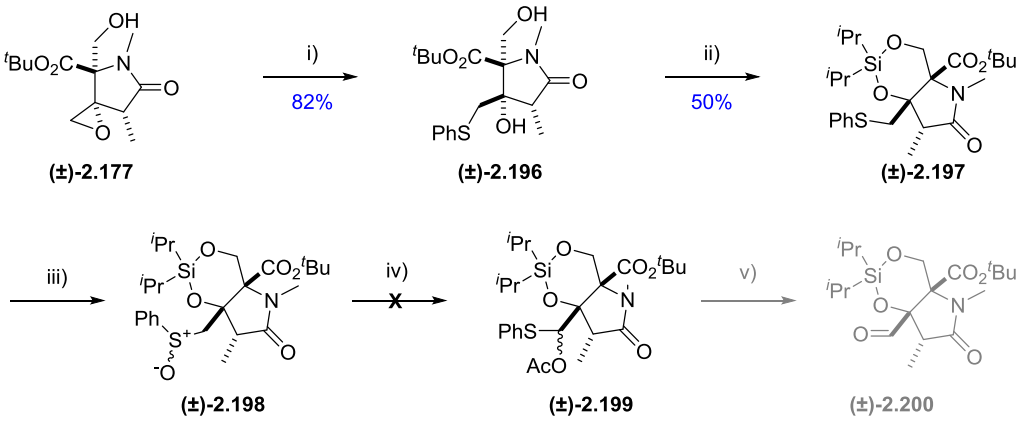
(±)-2.192 **(±)-2.193** **(±)-2.194** **(±)-2.195**

Scheme 2.64 Last attempt of the phenylselenium Pummerer reaction
Reagents and conditions i) $NaIO_4$ (5.0 eq), $NaHCO_3$ (5.0 eq), THF/MeOH/H_2O (1:1:1), RT, 1 h; ii) Ac_2O (50.0 eq), NaOAc (10.0 eq), 100 °C, 45 min, iii) K_2CO_3 (5.0 eq), MeOH, RT 12 h.

Given the low success of the selenium Pummerer reactions, a last attempt of a sulfur Pummerer reaction was carried before other strategies to synthesise the required aldehyde were considered.

2.6.5 **Sulfur Pummerer attempt**

The epoxide **(±)-2.177** was opened with sodium benzenethiolate in THF, and the formed diol was protected as a dioxisilane. The sulfur derivative **(±)-2.196** was oxidised with *m*-CPBA to give the sulfoxide, which was treated in the same pot with Ac_2O and NaOAc according to the modified procedure of Magnus et *al.*[147] The Pummerer reaction did not proceed at 100 °C and further heating at 150 °C led to decomposition of the mixture to a black oil.



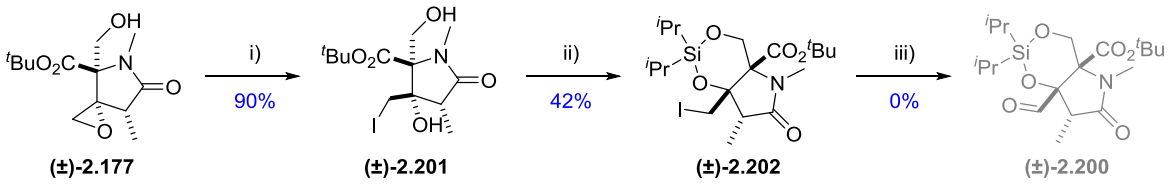
Scheme 2.65 Sulfur Pummerer attempt
Reagents and conditions i) PhSH (1.40 eq), NaH (1.35 eq), THF, 0 °C, 10 min; then add solution of epoxide, 15 min, 0 °C; ii) *i*-$Pr_2Si(OTf)_2$ (5.00 eq), 2,6-lutidine, DCE, RT to reflux; iii) *m*-CPBA (1.05 eq), -78 °C to RT; iv) NaOAc (2.0 eq), Ac_2O, 100 °C to 150 °C.

The selenium and sulfur Pummerer routes were abandoned and the use of other nucleophiles for the opening of the epoxide **(+)-2.177** was investigated in order to reach the a β-hydroxy aldehyde such as **2.180** or **2.200**.

2.6.6 **Investigation of the opening possibilities of other epoxide**

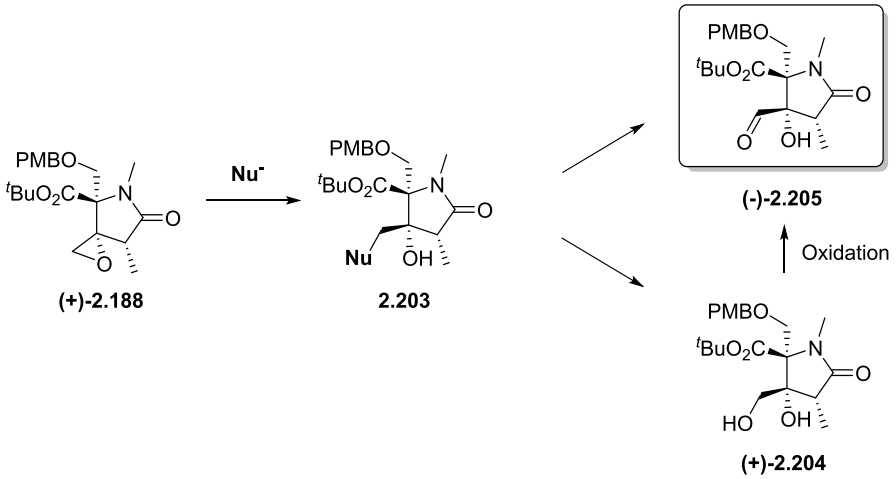
2.6.6.1 Opening with potassium iodide

The opening of the epoxide **(±)-2.177** was also achieved with potassium iodide and gave the iodo diol **(±)-2.201**, which was protected as the dioxisilane **(±)-2.202** (**Scheme 2.66**). It was first envisaged that the latter could be used in a Kornblum oxidation[148,149] to form the aldehyde **(±)-2.200**. For aliphatic iodide substrates the reaction typically requires heating above 100 °C. Sorensen *et al.*[150] reported the use of DMDO to convert an α-iodo ketone to the 1,2-diketone at room temperature. This alternative reaction was therefore preferred for the conversion of the iodide **(±)-2.202** to the aldehyde **(±) 2.200**. The reaction did not lead to the formation of the required product **(±)-2.200**. The starting material was instead converted to an unidentified product. The ^{1}H NMR analysis of the isolated product indicated the absence of aldehyde functionality and of the dioxisilane protecting group.



Scheme 2.66 Opening of the epoxide (±)-2.177 with KI and attempt of the formation of the aldehyde(±)-2.200
Reagents and conditions i) KI (10.0 eq), THF/AcOH/H_2O (8:4:1), THF/AcOH/H_2O, 65 °C, 3 h; ii) *i*-$Pr_2Si(OTf)_2$ (7.50 eq), 2,6-lutidine (15.0 eq), DCE, RT to 80 °C, 45 min, iii) DMDO 0.05 M (2.50 eq), DCM, RT, 3 h.

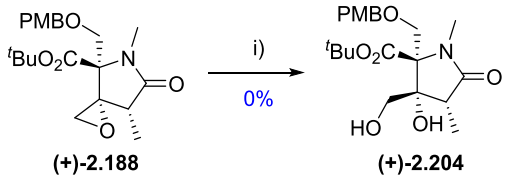
Other nucleophiles were also tested to open the epoxide **(+)-2.188** and form a precursor of the diol **(+)-2.204** or the hydroxy aldehyde **(-)-2.205** (**Scheme 2.67**). In this strategy the upper hydroxy group of the starting material can be protected as the PMB ether **(+)-2.188** as drawn in the scheme, or as the TBS **(+)-2.187** equivalent, which was also synthesised.



Scheme 2.67 Strategy to convert epoxide (+)-2.204 to the key hydroxy aldehyde (-)-2.205

2.6.6.2 Opening of the epoxide with sodium hydroxide and sodium acetate

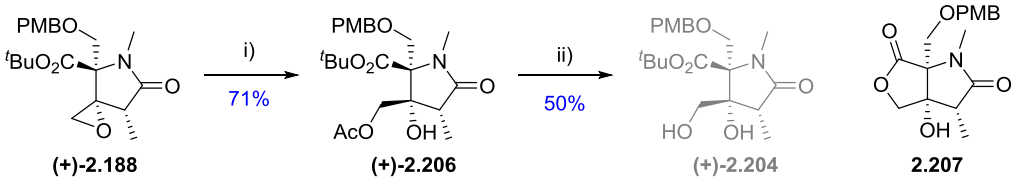
The formation of the diol **(+)-2.204** *via* the direct opening of the epoxide **(+)-2.188** was first investigated. It was anticipated that the *tert*-butyl ester would be incompatible with strong acids and the use of basic conditions was therefore investigated. The epoxide **(+)-2.188** showed no reactivity toward sodium hydroxide at low temperature. Furthermore the epoxide **(+)-2.188** decomposed to a mixture of several products at high temperature in dioxane in the presence of aqueous NaOH (**Scheme 2.68**). One major product could be isolated after FC purification in 20% yield. The structure was not elucidated, but proton NMR analysis showed that the loss of the *tert*-butyl ester and the PMB group had occurred.



Scheme 2.68 Unsuccessful attempt of epoxide opening with NaOH
Reagents and conditions i) 1.0 M aq. NaOH / dioxane (1:1), 80 °C, 4 h.

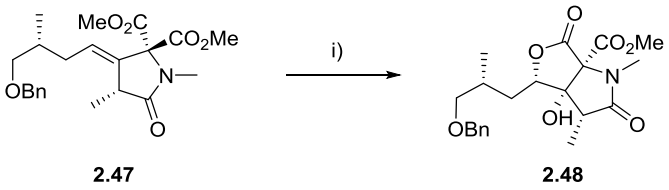
The use of sodium hydroxide was abandoned, and the opening was instead tried with sodium acetate, which would allow the formation of the required diol after hydrolysis of the residual acetate. The opening was first tried in presence of the TBS protecting the upper oxygen atom of the epoxide **(+)-2.187,** but the silicon ether did not resist sodium acetate at high temperature. The epoxide substrate **(+)-2.188** bearing the PMB protecting could be opened with sodium acetate in DMSO and

acetic acid (**Scheme 2.69**).[151] The subsequent hydrolysis of the acetate group under basic conditions did not form the required diol **(+)-2.204** as a problematic lactonisation occurred to form the side product **2.207**.



Scheme 2.69 Opening of the epoxide (+)-2.188 with sodium acetate and unsuccessful hydrolysis
Reagents and conditions i) NaOAc (10.0 eq), AcOH (50.0 eq), DMSO, 85 °C, 20 h; ii) K_2CO_3 (0.50 eq), MeOH, RT, 30 min.

Hatakeyama *et al.* reported in their precedent total synthesis of Neooxazolomycin[123] a similar spontaneous lactonisation reaction in the dihydroxylation reaction of alkene **2.47** (**Scheme 2.70**).

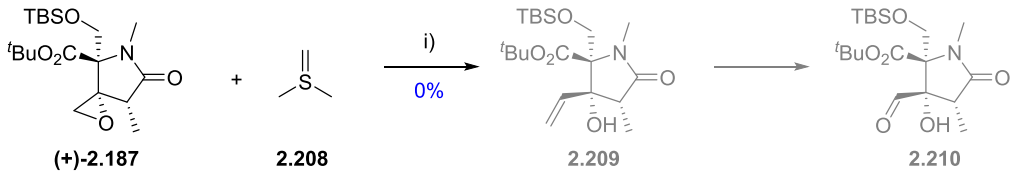


Scheme 2.70 Spontaneous lactonisation in Hatakeyama total synthesis of Neooxazolomycin
Reagents and conditions i) OsO_4 (0.4 eq), NMO (4 eq), THF/H_2O (3:1)

The protecting *tert*-butyl ester had been selected for its resistance toward problematic nucleophilic attack on the protected carboxyl group, but did not prevent the formation of the undesired lactone **2.207** under these basic conditions. The stability of the diol **(+)-2.204** under neutral conditions remained unknown at this stage. Hence, the formation of the diol under non-basic conditions was to be tested and is presented in sections **2.6.6.4** and **2.6.7**. The following section presents an attempt of the formation of the required aldehyde from a non-alcoxy intermediate.

2.6.6.3 Opening of the epoxide with a sulfur ylide

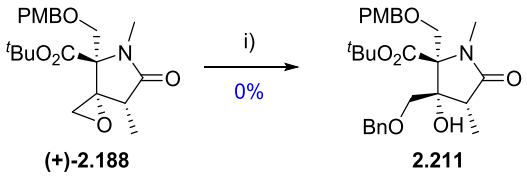
An ideal nucleophile for the opening of the epoxide **(+)-2.187** would allow the formation of a non-alkoxy precursor of the hydroxy aldehyde **2.210** to prevent any lactonisation event. The use of the sulfur ylid **2.208** to open the epoxide **(+)-2.187** was therefore attempted in order to form the terminal alkene **2.209**, which would then undergo an ozonolysis to form the hydroxy aldehyde **2.210** (**Scheme 2.71**). The reaction conditions led to the decomposition of the starting material to a mixture of products, and these conditions were therefore abandoned.



Scheme 2.71 Unsuccessful opening of the epoxide (+)-2.187 with a sulfur ylid
Reagents and conditions i) $[Me_3S]^+,I^-$ (4.0 eq), *n*-BuLi (4.0 eq), THF, -10 °C; then add epoxide **(+)-2.187** in THF, -10 °C to RT.

2.6.6.4 Opening with benzyl alcoholate

In one of the last attempts, the anion of benzyl alcohol was used to open the epoxide **(+)-2.188** in order to generate the diol under non-basic conditions *via* the hydrogenolysis of the resulting benzyl ether **2.211** (**Scheme 2.72**). This approach proved unsuccessful as decomposition of the starting material also occurred.

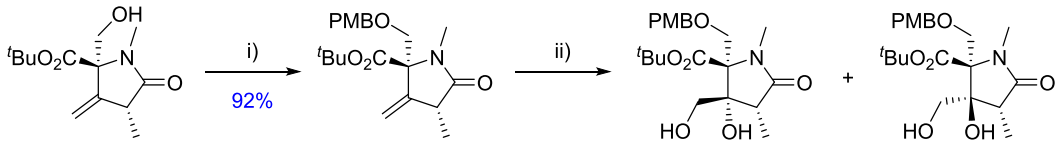


Scheme 2.72 Unsuccessful opening of the epoxide (+)-2.188 with the anion of benzyl alcohol
Reagents and conditions i) BnOH (3.00 eq), *n*-BuLi (1.50 eq), THF, 0 °C, then add solution of epoxide **(+)-2.188** in THF, 0 °C to RT, 30 min.

As the epoxide opening strategies did not allow to reach the diol **(+)-2.204** or the corresponding hydroxy aldehyde **(-)-2.205**, dihydroxylation conditions were tried to form the diol under non-basic conditions.

2.6.7 **Dihydroxylation of alkene (+)-2.175 and subsequent oxidation**

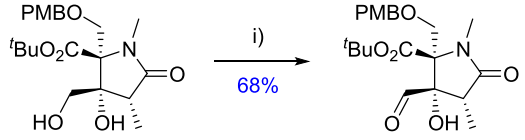
The epoxidation of the alkene **(+)-2.175** had been initially chosen over a possible dihydroxylation as the corresponding homo allylic alcohol directs the approach of the oxidising agent on the face hindered by the adjacent methyl group. The dihydroxylation was anticipated to be less selective, as the hydroxy group would not favour the approach of OsO_4 on the bulkiest face of the alkene. The simple dihydroxylation with OsO_4 and NMO used by Hatakeyama[123] may allow the formation of the diol **(+)-2.204** in a diastereoselective mixture. The stability of the required diastereoisomer of the diol **(+)-2.204** under non-basic conditions would eventually be assessed. After protection of the alcohol **(+)-2.175**, the resulting alkene **(+)-2.212** was submitted to dihydroxylation conditions used by Hatakeyama, and gave a mixture of the two diols **(+)-2.204** and **(-)-2.213** with almost no selectivity (**Scheme 2.73**). The two diols were stable as no lactonisation was detected, and the flash column chromatography purification allowed the separation of the mixture of diols. The relative structure of the diastereoisomers was determined by nOe experiments, which results are presented in the Experimental.



(+)-2.175 **(+)-2.212** **(+)-2.204**, 43% **(-)-2.213**, 34%

Scheme 2.73 Dihydroxylation of the alkene (+)-2.212
Reagents and conditions i) 4-methoxybenzyl-2,2,2-trichloroacetimidate (2 x 2.50 eq), TfOH (2 x 10 mol%), RT, Et_2O, 2 x 15 min, RT; ii) OsO_4 (20.0 mol%), NMO (5.00 eq), ^{t}BuOH/H_2O/THF (1:2:4), RT, 60 h.

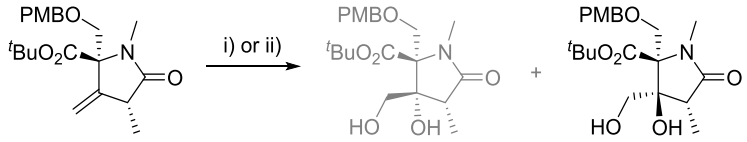
The diol **(+)-2.204** was then oxidised with DMP to form the key β-hydroxy aldehyde **(-)-2.205** (**Scheme 2.74**), which is our most advanced intermediate toward the oxazolomycin family. It contains the fully functionalised pyrrolidinone core of the oxazolomycin family. The aldehyde functionality will allow the introduction of the side chain in order to complete a total synthesis of the natural product.



(+)-2.204 **(-)-2.205**

Scheme 2.74 Oxidation of the diol (+)-2.204
Reagents and conditions i) DMP (1.50 eq), DCM, RT, 72 h.

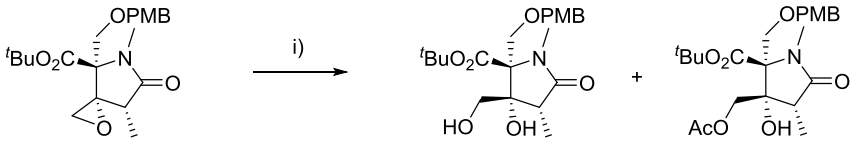
It was now established that the diol **(+)-2.204** was stable and highly useful for the synthesis as its oxidation could lead to aldehyde **(-)-2.205**. In order to develop a selective route toward the diol **(+) 2.204,** the dihydroxylation was repeated under similar conditions adding $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ to the two reaction mixtures (**Scheme 2.75**). Unfortunately, NMR analysis of the two reaction crudes indicated that both ligands lead to the clean and exclusive formation of the undesired diol **(-)-2.213**.



(+)-2.212 **(+)-2.204** **(-)-2.213**

Scheme 2.75 Dihydroxylation of the alkene (+)-2.212
Reagents and conditions i) OsO_4 (10.0 mol%), $(DHQ)_2PHAL$ (20.0 mol%), NMO (5.00 eq), ^{t}BuOH/H_2O/THF (1:2:4), RT, 72 h; ii) OsO_4 (10.0 mol%), $(DHQD)_2PHAL$ (20.0 mol%), NMO (5.00 eq), ^{t}BuOH/H_2O/THF (1:2:4), RT, 72 h.

Following precedents from Barua,[152] a very last synthetic effort therefore focused on the re-investigation of the opening of the epoxide **(+)-2.188** with $NaNO_2$ to form the diol **(+)-2.204**. In a first attempt, only a small amount of diol **(+)-2.204** was isolated (about 10%). The major product of the reaction is the product of the opening of the epoxide by acetic acid **(+)-2.206**. The use of another acid to carry the reaction might allow the isolation of the required diol **(+)-2.204** in future attempts. Time constraints did not allow further investigation of this type of conditions for the opening of **(+)-2.188**.

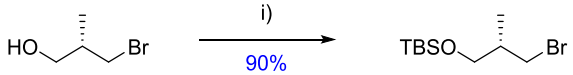


(+)-2.188 **(+)-2.204**, 10% **(+)-2.206**

Scheme 2.76 Attempt of opening the epoxide (-)-2.188 with $NaNO_2$
Reagents and conditions i) $NaNO_2$ (2.00 eq), H_2O/AcOH (4:1) RT, 16 h, then more $NaNO_2$ (2.00 eq) 80 °C, 12 h.

2.7 Preliminary studies on the installation of the side chain

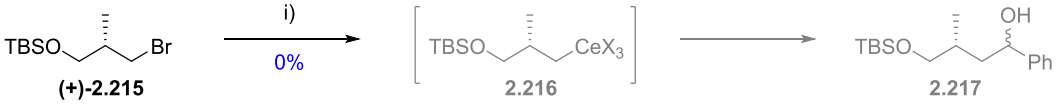
To install a first segment of the side chain of the natural product, the addition of an organometallic reagent to the aldehyde **(-)-2.205** was investigated. The required starting alkyl bromide **(+)-2.215** was obtained in one silylation step[153] from commercially available alcohol **(+)-2.214** (**Scheme 2.77**).



(+)-2.214 **(+)-2.215**

Scheme 2.77 Silylation of the commercial alcohol (+)-2.214
Reagents and conditions i) TBSCl (1.30 eq), imidazole (1.50 eq), 0 °C to RT.

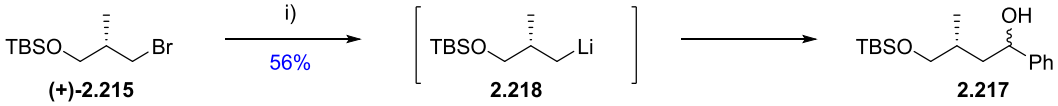
It was initially attempted to form the corresponding organocerium reagent of the alkyl bromide **(+)-2.215** by transmetallation of the organolithium reagent following the procedure used by Donohoe *et al.*[134] for the installation of the side chain on a pyrrolidine-aldehyde intermediate *en route* to the core of oxazolomycin A. The addition of a solution of benzaldehyde to the organocerium solution in a test reaction did not form any addition product (**Scheme 2.78**). At this stage it remained unclear whether the lithiation and the transmetallation occurred.



(+)-2.215 **2.216** **2.217**

Scheme 2.78 Attempt of the formation of the organocerium reagent 2.216 and test reaction with benzaldehyde
Reagents and conditions i) ^{t}BuLi (2.05 eq), -78 °C, 20 min; then anhydrous $CeCl_3$ (2.05 eq), -78 °C to -30 °C, 1 h; then benzaldehyde (1.00 eq).

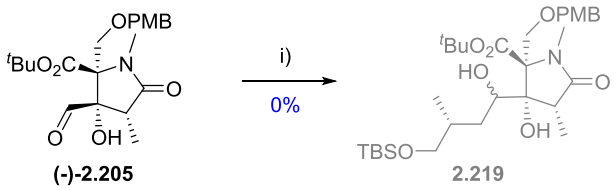
The lithiation step was therefore tested (**Scheme 2.79**), and the formed organolithium **2.218** was successfully added to benzaldehyde.



(+)-2.215 **2.218** **2.217**

Scheme 2.79 Formation of the organolithium reagent 2.218 and test reaction with benzaldehyde
Reagents and conditions i) ^{t}BuLi (2.05 eq), -78 °C, 10 min; then benzaldehyde (1.00 eq) in THF, -78 °C to 0 °C.

The lithium reagent **2.218** was then reacted with the pyrrolidinone aldehyde **(-)-2.205** (**Scheme 2.80**), which lead to decomposition of the starting material into two major unidentifiable products.

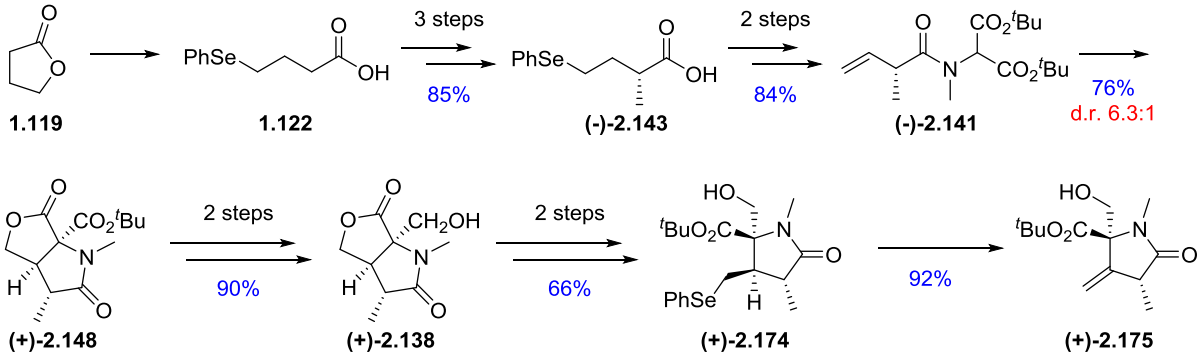


Scheme 2.80 Attempt of the addition of the organolithium to the aldehyde (-)-2.205
Reagents and conditions i) Add ^{t}BuLi in hexanes (6.00 eq) to alkyl bromide **(+)-2.215** (3.00 eq), -78 °C; then add solution of aldehyde **(-)-2.205** (1.0 eq) in THF -78 °C, 45 min.

The study of the addition of organometallic reagents to the hydroxy aldehyde **(-)-2.205** was limited by time constraints and low quantities of aldehyde synthesised *via* the non-selective dihydroxylation.

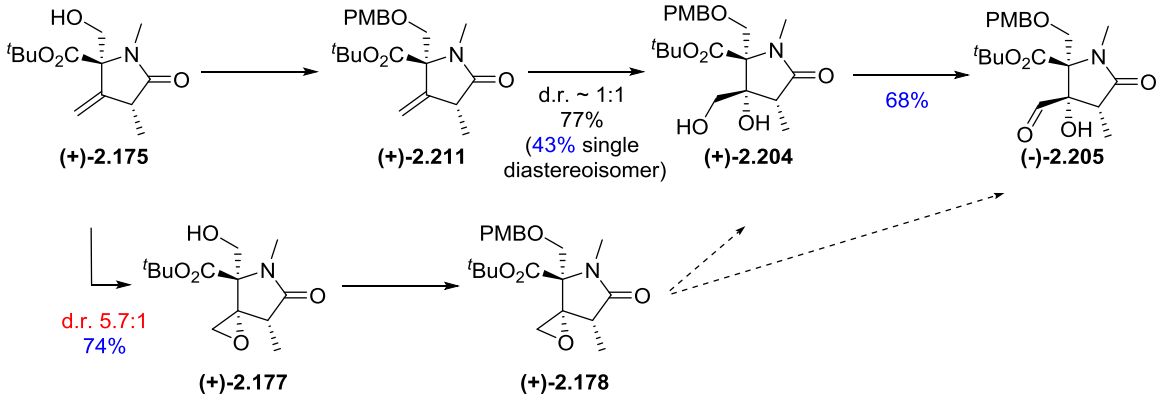
2.8 Summary and conclusion

Based on the optimisation and extension of previous synthetic work in the group on racemic material, a new enantioselective synthesis of the functionalised pyrrolidinone core of oxazolomycin A was synthesised from γ-butyrolactone. The sequence started with the opening of the lactone with a phenyl selenium anion equivalent to obtain the corresponding carboxylic acid, which underwent an Evan's alkylation to form the enantiopure carboxylic acid **(-)-2.143**. The coupling of the latter with the corresponding aminomalonate, followed by the oxidative elimination of the phenyl selenium group gave the cyclisation substrate **(-)-2.141** in greater than 96% e.e. The optimisation of the manganese(III) and copper(II)-mediated oxidative cyclisation allowed the formation of the fused pyrrolidinone-lactone **(+)-2.148** in good yield and stereoselectivity. The yield of the following ester deprotection and reduction sequence applied on the cyclisation product **(+)-2.148** was greatly improved. The opening of the resulting lactone alcohol **(+)-2.138** with an equivalent of phenyl selenium anion was also optimised, and the subsequent selective *tert*-butyl esterification of the formed carboxylic acid gave the new pyrrolidinone **(+)-2.174**, which underwent an oxidative elimination to give the key *exo*-alkene **(+)-2.175**. The latter was synthesised in 11 steps and 30% yield from γ-butyrolactone.



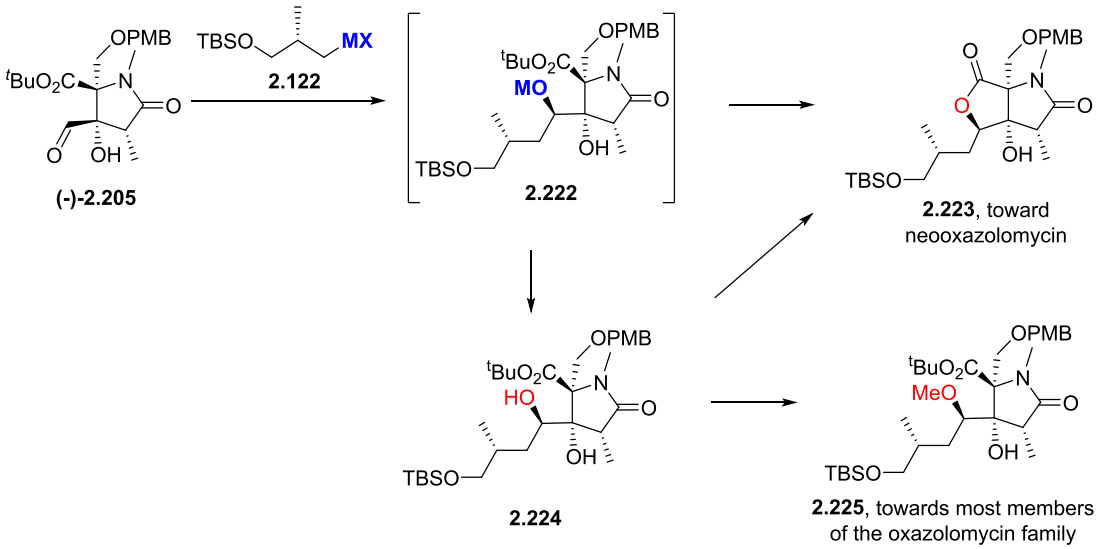
Scheme 2.81 Route summary to key *exo*-alkene (+)-2.175

It was demonstrated that the alkene **(-)-2.175** is a valuable intermediate for the preparation of the key β-hydroxy aldehyde **(-)-2.205**. A first non-selective dihydroxylation also proved the stability of the diol **(+)-2.204**, which could be oxidised to the aldehyde **(-)-2.205**. Further attempts of directing the epoxidation were unsuccessful. The last synthetic efforts of this PhD focused on the opening of the epoxide **(-)-2.188**, in order to develop a more selective route between the *exo*-alkene **(+)-2.175** and the key hydroxy aldehyde **(-)-2.205**.



Scheme 2.82 Need for a more selective route between the *exo*-alkene (+)-2.175 and the aldehyde (-)-2.205

The addition of an organometallic reagent to the aldehyde **(-)-2.205** to install the side chain in a novel total synthesis of a member of the oxazolomycin family will be explored in the group. A spontaneous lactonisation during this process may compromise the efficient access to the spiro fused pyrrolidinone-β-lactone core of oxazolomycin A (**Scheme 2.83**). But this possible lactonisation would provide the fused pyrrolidinone-γ-lactone **2.225**, which could still be used in a total synthesis of neooxazolomycin.

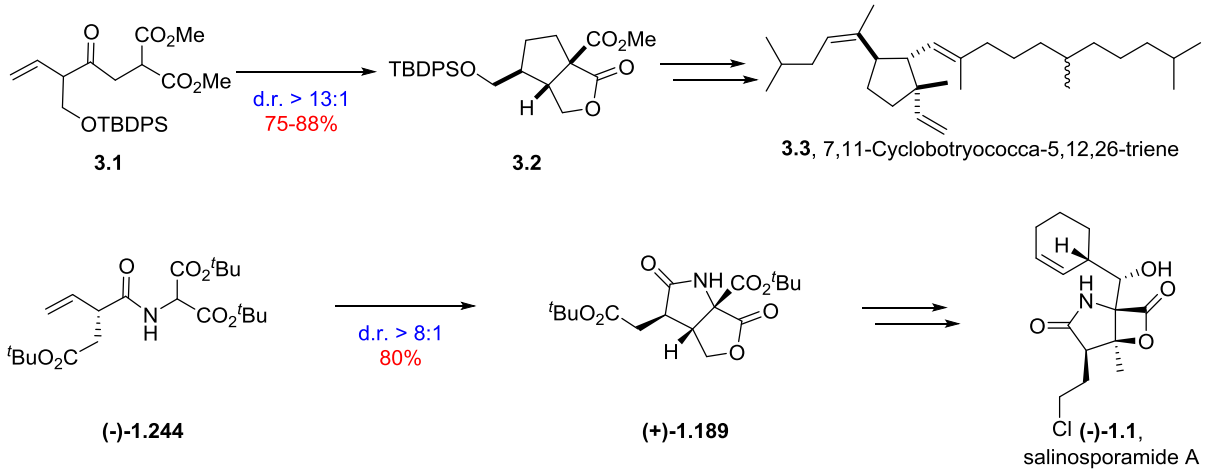


Scheme 2.83 Future challenges toward the oxazolomycin family

3 Extension of the Oxidative Cyclisation: Formation of Fused THF-Lactones

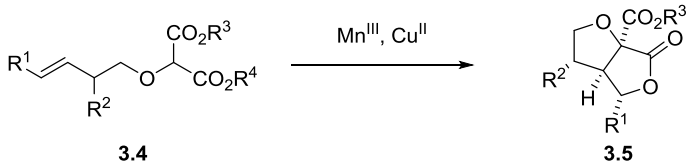
3.1.1 Motivations and aims

The manganese(III) and copper(II)-mediated oxidative cyclisation of alkenyl malonates and alkenyl amidomalonates for the respective formation of fused cyclopentane-lactones[53] and pyrrolidinone-lactones[44] proved to be an efficient reaction to build the structural complexity in several total syntheses of natural products. For example, in the group the two types of oxidative cyclisations were used in efficient total syntheses of complex natural products (**Scheme 3.1**) such as cyclobotryococcatriene[154] and salinosporamide A (**Chapter 1**).



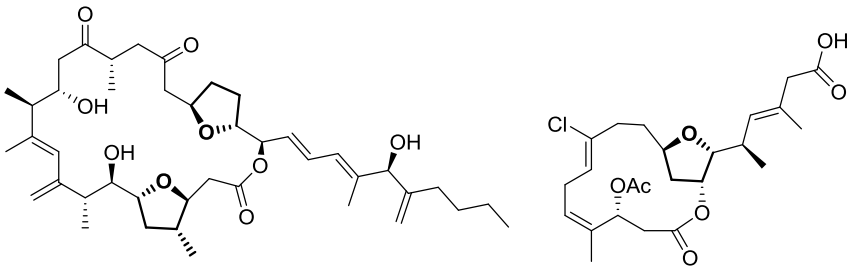
Scheme 3.1 Examples of the application of the oxidative cyclisation reaction of alkenyl malonates and amidomalonates

The possibility of extending the manganese(III) and copper(II)-mediated oxidative cyclisation to alkenyl oxymalonate **3.4** substrates would allow the formation of fused THF-lactone bicycles **3.5** (**Scheme 3.2**).



Scheme 3.2 Extension of the manganese(III) and copper(II) oxidative cyclisation

Chemical modification of fused THF-lactones might find applications in new syntheses of a variety of complex THF-containing natural molecules such as amphidinolide C[155] **3.5** and haterumalide NA **3.6**.[156]



3.5, Amphidinolide C

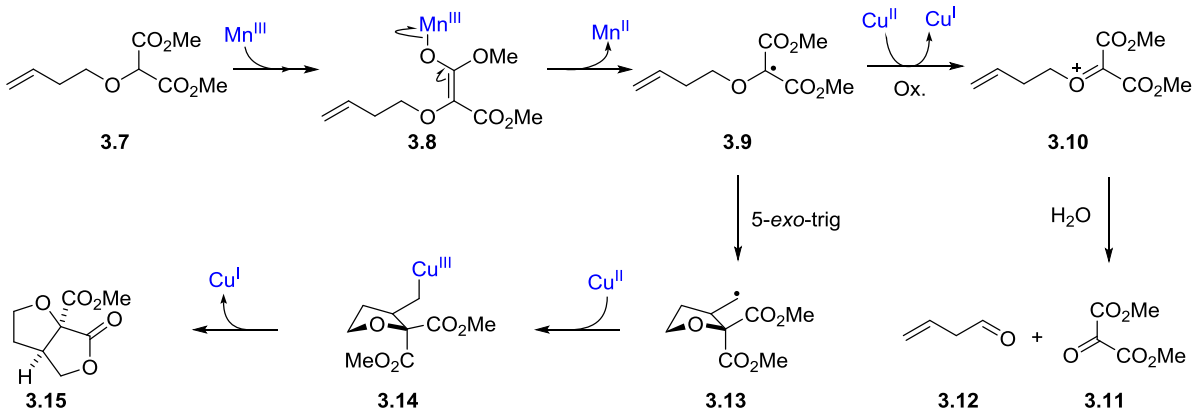
3.6, Haterumalide NA

Scheme 3.3 Possible natural product targets for the application of the methodology

Some results presented in this chapter, were obtained by Dr Anne-Caroline Chany, a postdoctoral researcher in the Burton group who originally proposed development of the extension of the oxidative cyclisation reaction to the formation of fused THF-lactone rings. For consistency purposes, the totality of the results obtained in tandem will be presented, but the experimental part of this thesis does not include the reactions performed by Chany. In the following section Chany's contributions are systematically made explicit.

3.1.2 **Mechanistic considerations**

The first step of this new cyclisation would be a single electron transfer from the malonate **3.7** to a manganese(III) species, which is likely to proceed via the formation of the manganese(III) enolate[157] **3.8** (**Scheme 3.4**). The so formed radical **3.9**, was anticipated to be stabilised by the captodative effect.[158] It was assumed that the high stability of the linear radical **3.9** may compromise the outcome of the cyclisation. If the cyclising radical is too stable, the cyclisation to **3.13** may be inefficient and bimolecular side reaction such as the copper(II) oxidation of the linear radical **3.9** to the oxonium species **3.10** may predominate. The existence of this type of side reactions would be indicated by the formation of side products such as ketomalonate **3.11** and aldehyde **3.12**.

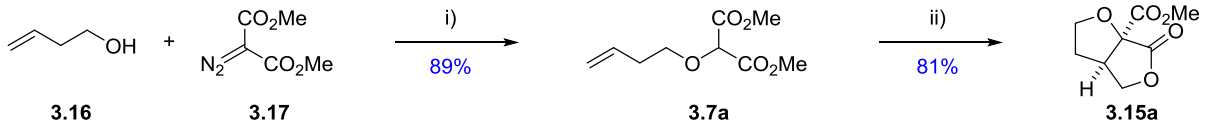


Scheme 3.4 Possible competitive decomposition via Cu^{II} oxidation of the stable captodative radical

3.2 Experimental studies

3.2.1 Preliminary attempts[iii]

The first reaction was attempted on the alkenyl oxymalonate **3.7a**, which was prepared by OH insertion[27] of the alcohol **3.16** with the diazomalonate[159] **3.17** catalysed by $Rh_2(OAc)_4$ in very good yield (**Scheme 3.5**). The cyclisation substrate **3.7a** was submitted to the standard oxidative cyclisation reaction used for the cyclisation of the alkenyl amidomalonate.[44] The expected fused THF-lactone **3.15** was isolated in good yield at 40 °C and 80 °C (respectively 81% and 78%). At room temperature the reaction did not reach completion after 12 h.



3.16 3.17 3.7a 3.15a

Scheme 3.5 Formation of the alkenyl oxymalonate 3.7a, by A.-C. Chany
Reagents and conditions i) $Rh_2(OAc)_4$ (0.5 mol%), benzene, 60 °C, 2 h; ii) $Mn(OAc)_3 \cdot 2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 6 h.

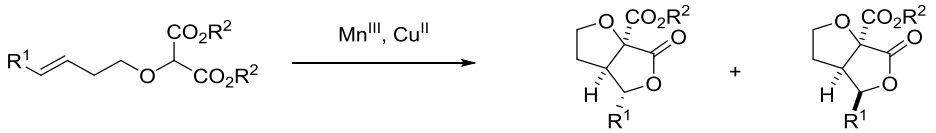
The positive preliminary results led us to keep this set of conditions for the study of the scope of the reaction. Performing the reaction at 40 °C would assure the best compromise between conversion and diastereoselectivity in the presence of side chains on the alkenyl moiety of the cyclisation substrate. Control experiments conducted by Dr Chany also indicated that both manganese(III) and copper(II) were required for efficient cyclisation of substrate **3.7a**.

3.2.2 Scope of the reaction

3.2.2.1 Linear substrates[iii]

In the amidomalonate series, cyclisation substrates carrying phenyl-substituted alkenes or *tert*-butyl malonates cyclised very efficiently. The oxymalonate analogues were therefore prepared from their corresponding commercial alcohol and submitted to the previous cyclisation conditions. An alkyl (ethyl) side chain was also tested (**Table 3.1**). The cyclisation on the terminal alkenes of the di *tert*-butyl and dimethyl malonates **3.7a** and **3.7b** both proceeded in good yields (entries 1 and 2). The corresponding phenyl substituted alkenes **3.7c** and **3.7d** respectively bearing the di *tert*-butyl and dimethyl malonates cyclised in very good d.r. and satisfying yield (entries 3 and 4).

[iii] Work done by Dr Anne-Caroline Chany

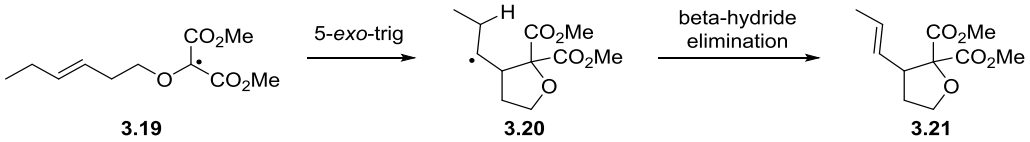


3.7 3.15 3.18

Entry	Substrate	R^1	R^2	Yield	Crude d.r.
1	**3.7a**	H	Me	81%	-
2	**3.7b**	H	^{t}Bu	83%	-
3	**3.7c**	Ph	Me	72%	12:1
4	**3.7d**	Ph	^{t}Bu	62%	14:1
5	**3.7e**	Et	Me	50%	2:1

Table 3.1 Cyclisation of linear substrates, by A.-C. Chany.
Reagents and conditions i) $Mn(OAc)_3 \cdot 2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 6 h.

Lower yields were obtained when the alkene **3.7e** carrying an alkyl (ethyl) side chains was cyclised (**Table 3.1,** entry 5). In keeping with previous results in the all carbon series,[160] the non-stabilised secondary radicals **3.20** gave the alkene by product **3.21** (**Scheme 3.6**).



3.19 3.20 3.21

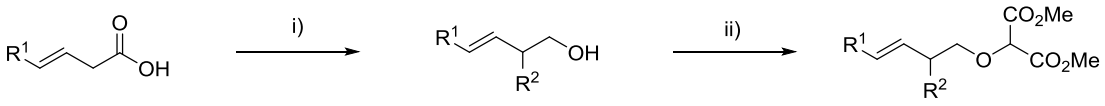
Scheme 3.6 Undesired β-hydride elimination on alkyl side chains

As methyl and *tert*-butyl malonates behaved similarly under these reaction conditions, only dimethyl malonates containing cyclisation substrates were used in the following studies of the scope of the reaction. The lower yield and selectivity of the ethyl alkene led to exclude this type of substrate in further studies.

3.2.2.2 Substitution at the allylic position[iv]

Varying the allylic position in the amidomalonate series was well tolerated in the presence of terminal and phenyl substituted alkenes (see section **1.4.5.2**, **Table 1.1**).[44] We envisaged the cyclisation of six linear substrates **3.24a** to **3.24f** substituted at the allylic position of the terminal or of the phenyl substituted alkenes. Four substrates **3.24a** to **3.24d** carrying alkyl side chains were prepared in a one pot alkylation-reduction sequence of 3-butenoic acid **1.145** or *trans*-styrylacetic acid **3.22**, followed by the rhodium-catalysed insertion of the formed alcohols on dimethyl diazomalonate (**Scheme 3.7**).

[iv] Work done by the author



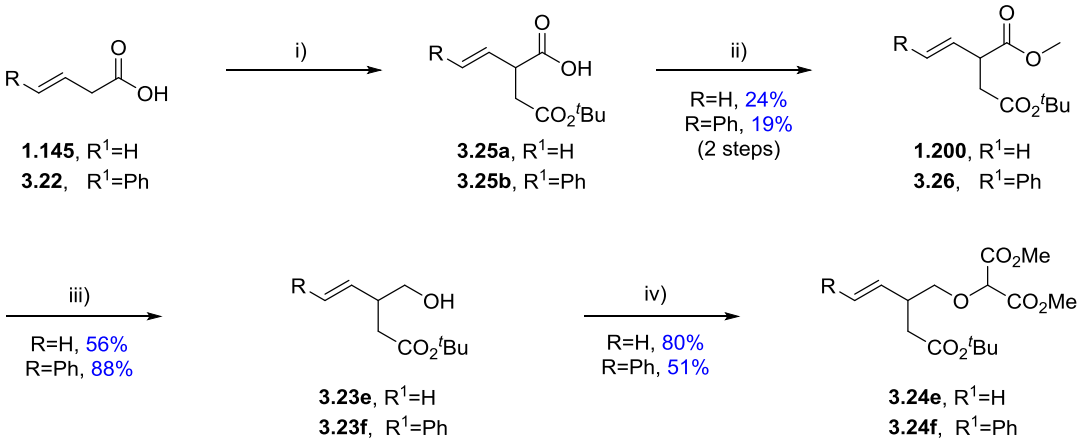
1.145, R^1=H
1.145, R^1=Ph
3.22, R^1=H
3.22, R^1=Ph

3.23a, R^1=H, R^2=Me, commercial
3.23b, R^1=Ph, R^2=Me, 30%
3.23c, R^1=H,R^2=^{i}Pr, 48%
3.23d, R^1=Ph, R^2=^{i}Pr, 46%

3.24a, 32%
3.24b, 55%
3.24c, 61%
3.24d, 74%

Scheme 3.7 Preparation of cyclisation substrates 3.24a to 3.24d
Reagents and conditions i) *n*-BuLi (2.20 eq), alkyl halide (3.00 eq), THF -78 °C to RT, various reaction times; then add $LiAlH_4$ (1.75 eq), 0 °C, 30 min; ii) Dimethyl diazomalonate (1.05 eq), $Rh_2(OAc)_4$ (0.5 mol%), benzene, 60 °C, 2 h.

Two other substrates **3.24e** and **3.24f** carrying *tert*-butyl ester side chains were prepared according to a similar strategy, but the reduction was conducted after the esterification of the alkylated acids **3.25a** and **3.25b** in order to facilitate the selective reduction of the formed methyl esters over the *tert*-butyl esters carried by **1.200** and **3.26b** (**Scheme 3.8**).



1.145, R^1=H
3.22, R^1=Ph

3.25a, R^1=H
3.25b, R^1=Ph

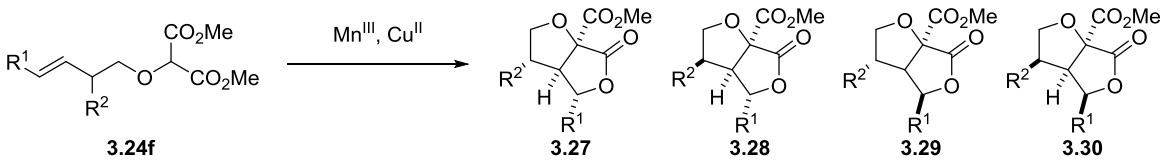
1.200, R^1=H
3.26, R^1=Ph

3.23e, R^1=H
3.23f, R^1=Ph

3.24e, R^1=H
3.24f, R^1=Ph

Scheme 3.8 Preparation of cyclisation substrates 3.24e and 3.24f
Reagents and conditions i) *n*-BuLi (2.20 eq), *tert*-butyl bromoacetate (3.00 eq), THF -78 °C to RT, 8 h; ii) MeI (2.50 eq), K_2CO_3 (3.00 eq), DMF, 4 h, RT; iii) $NaBH_4$ (4 x 5.00 eq), THF/MeOH (1:1), RT, 4 x 30 min; iv) Dimethyl diazomalonate (1.05 eq), $Rh_2(OAc)_4$ (0.5 mol%), benzene, 60 °C, 2 h.

The cyclisation of the six substituted alkenyl oxymalonate **3.24a** to **3.24f** using the previous conditions gave the corresponding major bicyclic THF-lactones **3.27a** to **3.27f** with good d.r. and satisfying yields (**Table 3.2**).



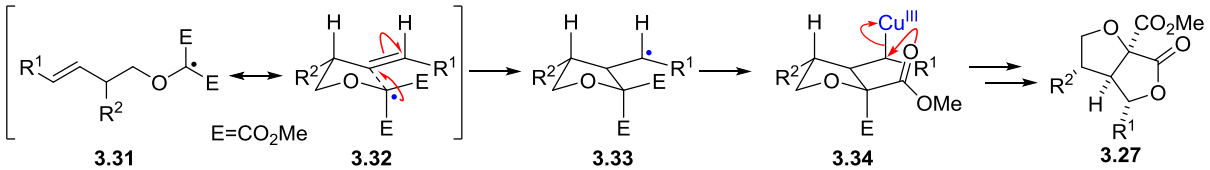
Entry	Substrate	R^1	R^2	Yield	Crude d.r.
1	3.24a	H	Me	73%*	3.0:1*
2	3.24b	Ph	Me	92%	4.6:1:0:0
3	3.24c	H	*i*-Pr	73%	22:1
4	3.24d	Ph	*i*-Pr	92%	28:1:0:0
5	3.24e	H	$CH_2CO_2{}^tBu$	76%	3.6:1
6	3.24f	Ph	$CH_2CO_2{}^tBu$	69%	6.7:1:0.7:0.4**

Table 3.2 Cyclisation of substrates alkylated at the allylic position of the alkene
Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 6 h.
*Isolated in 63% yield and 2.7:1 d.r. with the corresponding di-*tert* butyl malonate. ** The respective stereochemistry of the three minor diastereoisomers was not assigned and their respective ratio is given in a random order.

The stereochemistry of the major diastereoisomers **3.24b** to **3.24f** (entries 2, 3, 4, 5 and 6) was confirmed by nOe experiments (appendix **7.2**), and the stereochemistry of the major diastereoisomer **3.24a** (entry 1) was assigned by analogy to **3.24c** (entry 3).

There is no possible ambiguity for the stereochemistry of the minor diastereoisomers **3.28a**, **3.28c** and **3.28e** (entries 1, 3 and 5) as in each case only one other *cis*-fused diastereoisomer exists. The stereochemistry of the minor diastereoisomer **3.28b** (isolated from the reaction of entry 2) was assigned by 2D NOESY NMR (appendix **7.2.2**), and the stereochemistry of the minor diastereoisomer **3.28d** (entry 4) was assigned by analogy. The three minor diastereoisomers **3.28f**, **3.29f** and **3.30f** (detected by NMR analysis of the crude reaction, entry 6) could not be separated and their relative stereochemistry was therefore not assigned.

The cyclisation of the phenyl substituted alkenes and terminal alkene **3.24a** and **3.24b** in the presence of small methyl side chains is less selective than the cyclisation of the corresponding substrates **3.24c** and **3.24d**, which carry larger *iso*-propyl side chain (**Table 3.2**, entry 1 to 4). These results are in keeping with the Beckwith[57] and Houk[58] model, which predicts that the R^2 substituent occupies the equatorial position of the transition state **3.32** to minimise the 1,3-allylic strain (**Scheme 3.9**).

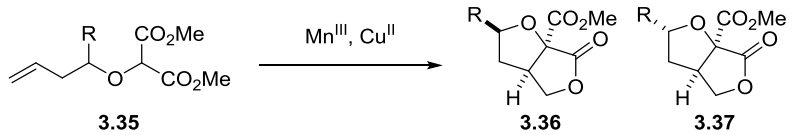


Scheme 3.9 Beckwith and Houk-like transition state used to predict the stereochemical outcome of cyclisation presented in Table 3.2

The NMR analysis of the crude of the cyclisation of **3.24f** (entry 6), shows a mixture of four products, indicating that the two others diastereoisomers **3.29f** and **3.30f** might have also been formed. The particular behaviour of the substrate **3.24f** carrying the $CH_2CO_2{}^tBu$ side chains in the cyclisation remains unexplained. The overall selectivity of the cyclisation of $CH_2CO_2{}^tBu$ substituted substrates **3.24e** and **3.24f** (entries 5 and 6) is an intermediate situation between the selectivity of the cyclisation of substrates **3.24a** and **3.24b** (entries 1 and 2), which carry less bulky methyl groups, and the selectivity of the cyclisation of the substrates **3.24c** and **3.24d** (entries 3 and 4), which carry bulkier *iso*-propyl groups.

3.2.2.3 Substitution at the homoallylic position[v]

The substitution at the homoallylic position of the terminal alkene was studied on four cyclisation substrates, which were prepared from commercial alcohols. The cyclisation of these substrates was a bit slower and required overnight reaction, but proceeded in good d.r. and excellent yield (**Table 3.3**). The size of the side chains at the homoallylic positions of the cyclisation substrates **3.35a** to **3.35d** did not have a significant effect on the stereoselectivity of the reaction. The predominant formation of products **3.36a** to **3.36d** is also in accordance with the Beckwith[57] and Houk[58] model. The structures of all major diastereoisomers were confirmed by nOe or NOESY experiments.



3.35 3.36 3.37

1	**3.35a**	Me	96%	6.1:1
2	**3.35b**	*i*-Pr	94%	5.7:1
3	**3.35c**	Ph	80%	7.5:1
4	**3.35d**	$CH{=}CH_2$	86%	5.0:1

Table 3.3 Cyclisation of substrates substituted at the homoallylic position of the alkene
Reagents and conditions i) $Mn(OAc)_3{\cdot}2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 15 h.

3.2.2.4 Preparation of more elaborated substrates[vi]

A route between the lactone **3.15b** and the elaborated cyclisation substrate was designed, based on the work achieved during the derivatisation of the cyclisation products toward salinosporamide A and oxazolomycin. Under previously developed conditions, the lactone **3.15b** could be easily opened with the phenyl selenium anion to give the carboxylic acid **3.38**. The formation and reduction of the corresponding acyl chloride gave the alcohol **3.39** in good yield. Next, the oxidative elimination of the phenyl selenium unit of **3.39** gave the exo-*alkene* **3.40**. The free hydroxy group of *exo*-alkene **3.40**

[v] Work done by Dr Anne-Caroline Chany
[vi] Work done by the author

was then engaged in the rhodium-catalysed insertion with dimethyl diazomalonate to form the more elaborate cyclisation substrate **3.41**. The latter was submitted to the manganese(III) and copper(II)-mediated oxidative cyclisation conditions with the hope of forming the fused tri-cyclic THF-THF-lactone **3.43**. The cyclisation was unsuccessful, as the NMR analysis of the crude of the reaction indicated the formation of a mixture of products probably containing the predominant 6-*endo* cyclisation product **3.42**.

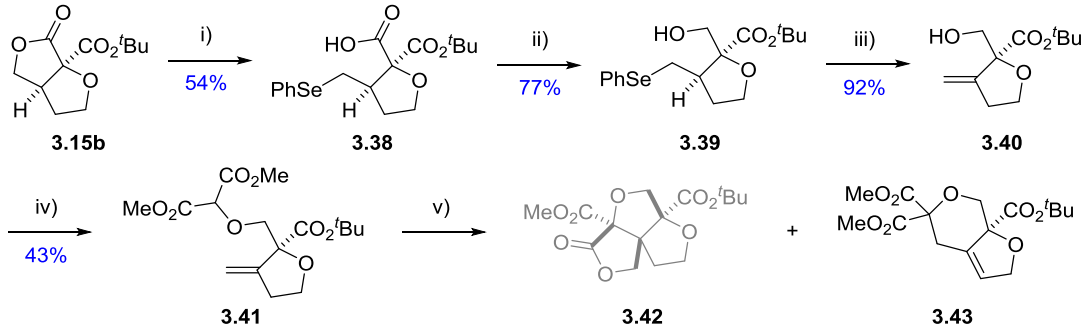


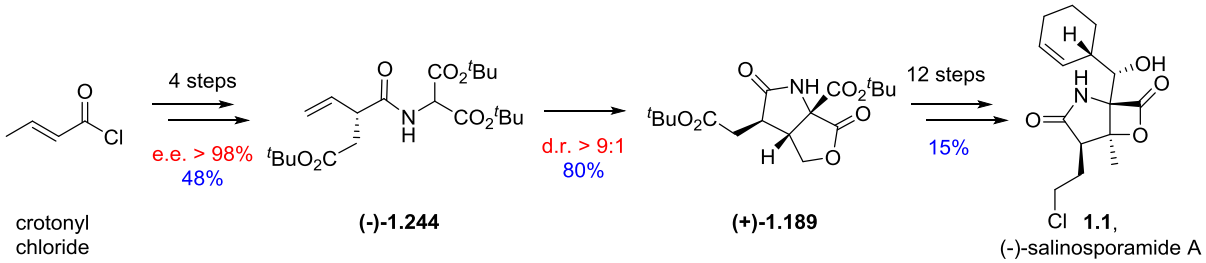
Figure 3.1 Modifications of the THF-lactone 3.7b towards more elaborated cyclisations
Reagents and conditions i) $(PhSe)_2$ (1.20 eq), NaH (2.00 eq), THF, 65 °C, 90 min; then add THF-lactone **3.7b**, 0 °C to RT, 90 min; ii) $[Me_2N{=}CHCl]^+,Cl^-$ (2.00 eq), THF/MeCN (1:1), 20 min, 0 °C; then $LiAl(O^tBu)_3H$ (10.0 eq) in THF, -78 °C to RT, 90 min; iii) $NaIO_4$ (5.00 eq), $NaHCO_3$ (5.00 eq), $THF/H_2O/MeOH$ (1:1:1), RT, 30 min; then heat under reflux in $CHCl_3$, 65 °C, 2 h; iv) Dimethyl diazomalonate (1.05 eq), $Rh_2(OAc)_4$ (0.5 mol%), PhH, 60 °C, 2 h; v) $Mn(OAc)_3{\cdot}2H_2O$ (2.00 eq), $Cu(OTf)_2$ (1.00 eq), MeCN, 40 °C, 18 h.

3.2.3 **Summary and conclusion**

The manganese(III) and copper(II)-mediated oxidative cyclisation was successfully extended to a wide range of alkenyl oxymalonates allowing the formation of fused THF-lactone rings. As anticipated different malonate esters were tolerated in the cyclisation, and complex substrates presenting a range of chemical substitution at different positions can be used in the reaction. Synthetic handles such as alkyl, alkene, esters and alkyl groups may allow the future application of the reaction to new total syntheses of complex molecules.

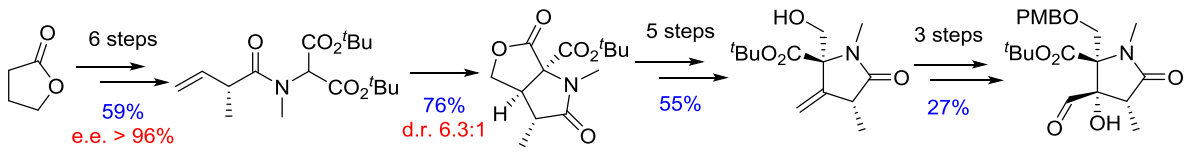
4 General conclusion and future work

The manganese(III) and copper(II)-mediated oxidative cyclisation previously developed in the group was applied to a new efficient total synthesis of (-)-salinosporamide A, which was achieved in 17 steps and 5% yield from crotonyl chloride and the Oppolzer auxiliary **(-)-1.198** (**Scheme 4.1**). The synthetic route is now being applied to the development of new potential proteasome inhibitors in the group.



Scheme 4.1 Efficient oxidative radical cyclisation in the novel total synthesis of (-)-salinosporamide A

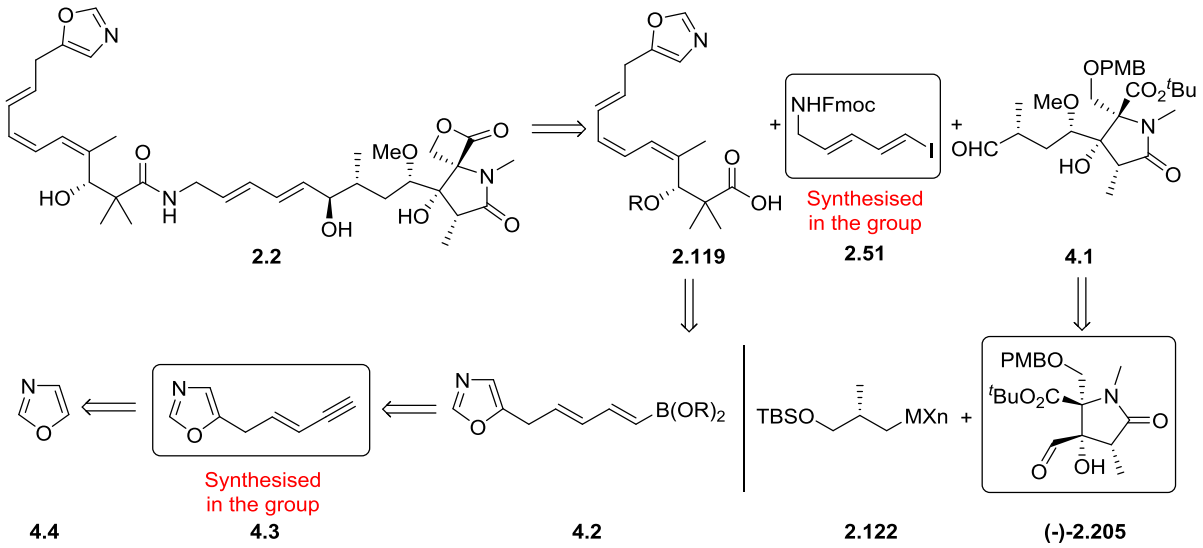
The development of a new efficient enantioselective route toward the key cyclisation substrate **(-)-2.141** for the synthesis of oxazolomycin, was achieved in good e.e. (**Scheme 4.2**). After having optimised the cyclisation of the alkenyl amidomalonate **(-)-2.141**, the reduction of the ester of **(+)-2.148** and the subsequent lactone opening, two new steps allowed the formation of the *exo*-alkene **(+)-2.175** in a 12 steps sequence and 21% yield from γ-butyrolactone**.** The yield of the last 3 steps toward the key α-hydroxy aldehyde **(-)-2.205** of this sequence remains moderate as the dihydroxylation of alkene **(+)-2.175** was non-selective. However, recent preliminary re-exploration of the opening of the epoxide selectively obtained from alkene **(+)-2.175** may give new opportunities toward a scalable and efficient synthesis of key intermediate aldehyde **(-)-2.205**.



Scheme 4.2 The efficient synthesis of the pyrrolidinone core of the oxazolomycin family

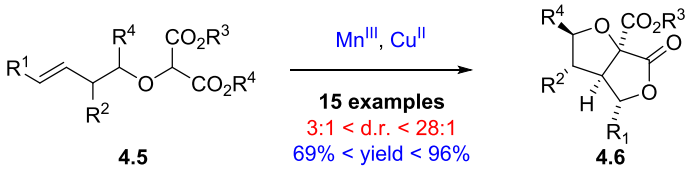
The future work in the group will first focus on the addition of an organometallic reagent to install the side chain of the natural product (**Scheme 4.3**) in order to achieve the synthesis of the right hand side fragment **4.1**. Key preliminary studies of the synthesis of the two others fragments have also been recently started within the group.[161] Syntheses of the middle fragment **2.51** and of the intermediate **4.3** *en route* to the key acid **2.119** have been achieved. The conversion of the alkyne **4.3**

to corresponding boron species **4.2** will be vital for the synthesis of this acid, which will be the last fragment needed for the final assembly of oxazolomycin A and neooxazolomycin.



Scheme 4.3 One possible strategy to reach oxazolomycin A from intermediates synthesised in the Burton group

The work toward the total synthesis of two families of pyrrolidinone containing natural product demonstrated the synthetic utility of the oxidative cyclisation of alkenyl amidomalonates. This success motivated the extension of the oxidative cyclisation to alkenyl oxymalonates **4.5**, which gave rapid access to a range of substituted fused THF-lactone bicycles **4.6** (**Scheme 4.4**).



Scheme 4.4 Novel oxidative cyclisation of alkenyl oxymalonates

The synthesis of substituted fused lactone-lactones **4.8** based on the cyclisation of alkenoyl oxymalonates **4.7** is currently being developed by Chany. The two new synthetic methodologies may give new routes to THF and lactone containing bioactive natural products.



Scheme 4.5 Oxidative cyclisation of alkenoyl oxymalonate

5 Experimental section

5.1 General Remarks

NMR spectra were recorded on Bruker AV400, AVII500, and DRX500 spectrometers. Proton and carbon chemical shifts (δ_H, δ_C) are quoted in ppm and referenced to tetramethylsilane with residual protonated solvent as internal standard. When the residual solvent peak was detectable, proton and carbon spectra were referenced to the solvent chemical shift established by Gottlieb *et al.*[162] Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and combinations thereof. Coupling constants (*J*) are given in Hz and rounded to nearest 0.1 Hz. For diastereotopic protons, no particular stereochemistry is implied.

Mass spectra (low resolution) were recorded on a Micromass ZMD (ES). High resolution spectra were recorded by the Mass Spectrometry service at the Chemical Research Laboratory, University of Oxford using a Bruker Daltronics microTOF (ES) or a Micromass GCT (FI). *m/z* values are reported in Daltons with their percentage abundance and, where known, the relevant fragment ions in parentheses. High resolution values are calculated to 4 d.p. from the molecular formula, all found values being within 5 ppm tolerance.

Infrared spectra were recorded on a Bruker Tensor 27 equipped with a diamond ATR. Absorption maxima (ν_{max}) are described as s (strong), m (medium), w (weak), and br (broad) and are quoted in wavenumbers (cm^{-1}).

Optical rotations were recorded using an Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (*l*) using the sodium D line (589 nm).

HPLC analysis was undertaken on an Agilent 1200 with DAD, equipped with ChiralPak™ AD-H column.

Melting points of solids obtained after evaporation of chromatography solvents were measured on a Leica Galen III compound microscope and are given uncorrected. When recrystallisations were carried, resultant solids obtained from indicated solvent systems were used for the measurement.

TLC was performed on Merck DC-Alufolien 60 F_{254} 0.2 mm precoated plates and visualised using an acidic vanillin or basic potassium permanganate dip. Retention factors ($\mathbf{R_f}$) are reported with the

solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 40–63 μm, pore diameter 60 Å) and the solvent system used is recorded in parentheses.

All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen and employing standard techniques for handling air-sensitive materials. Solvents and commercially available reagents were dried and purified before use, as appropriate. In particular DCM and THF were distilled from CaH_2 and stored over 3 Å molecular sieves. 'PE' refers to the fraction of light petroleum ether boiling in the range 40–60 °C unless otherwise stated. All water used experimentally was Millipore filtered. The aqueous solution of pH 2 sulfate buffer was prepared by dissolving $NaHSO_4$ (213 g, 1.50 mol) and conc. H_2SO_4 (28.0 mL, 0.500 mol) in water (1.00 L). The aqueous solution of pH 3 citric acid buffer was prepared by dissolving citric acid (192 g, 1.00 mol) and NaOH (20.0 g, 0.500 mol) in water (2.00 L).

5.2 General procedures

General procedure 1: Amide coupling with HATU

To a solution of acid (1.00 eq), free amine or amine·HCl salt (1.15 eq) and DIPEA (2.00 eq for free amine or 3.00 eq for amine·HCl) in dry DMF (5 mL/1 mmol of acid) at 0 °C, was added HATU (1.05 eq) portionwise (100 mg per portion added every 20 seconds). The reaction was stirred at 0 °C under nitrogen for 5 min and then for two hours at RT. The reaction was quenched with pH 2 sulfate buffer (0.5 mL/1 mmol of acid). The residue was diluted with EtOAc (15 mL/mmol of acid) and the organic phase was washed with a solution of pH 2 sulfate buffer/H_2O (1:1, 20 mL/mmol of acid) followed by a saturated aqueous solution of $NaHCO_3$ (10 mL/mmol of acid). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC using an EtOAc/PE solvent system, which gave an $\mathbf{R_f}$ for the product between 0.3 and 0.5.

General procedure 2: Rh(II)-catalysed OH-insertion on diazomalonate

To a solution of alcohol (1.00 eq) in benzene (0.30 M) were added diazomalonate (1.05 eq) and $Rh_2(OAc)_4$ (0.5 mol%). The reaction mixture was heated at 60 °C for 2 h. After cooling to RT, the solvent was evaporated, which gave the crude product. The residue was purified by FC using the indicated solvent system.

General procedure 3: one pot alkylation-reduction of 3-enoic acids

To a solution of 3-enoic acid derivative (1.00 eq) in THF (0.40 M) at -78 °C was added a solution of *n*-BuLi in hexanes (2.5 M, 2.20 eq) over 30 sec/mmol added. The mixture was stirred at -78 °C and the

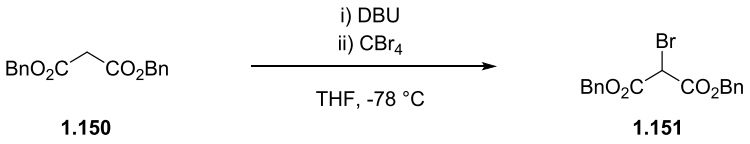
corresponding alkyl halide (3.00 eq) was added over 20 sec/mmol added. After 5 min stirring the reaction was warmed to RT outside the cooling bath and stirred at this temperature for the indicated period. The reaction mixture was then cooled to 0 °C and $LiAlH_4$ (1.75 eq) was added portionwise (about 1 mmol every 20 seconds). The reaction mixture was stirred at this temperature for 30 min before careful addition of an aqueous solution of HCl (2.0 M, 175 eq). During the addition, Et_2O (2 initial volumes of THF) was also progressively added to maintain good stirring. The mixture was then vigorously stirred for 30 min and the layers were separated. The aqueous layer was extracted with more Et_2O (1 initial volume of THF). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and carefully evaporated (given the volatility of some alcohols). The residue was purified by FC using the indicated solvent system.

General procedure 4: radical oxidative cyclisation of alkenyl oxymalonates

Copper(II) triflate (1.00 eq) and manganese(III) acetate dihydrate (2.00 eq) were placed under vacuum and heated to 40 °C (unless otherwise specified) for 10 minutes. The reaction vessel was then backfilled with N_2. A solution of alkenyl oxymalonate (1.00 eq) in MeCN (0.15 M) was then added rapidly and the solution stirred for 6 h. After cooling to RT, a saturated solution of aqueous NH_4Cl and water (1:1) were added and the reaction mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum, which gave the crude product. The residue was purified by FC using the indicated solvent system.

5.3 Synthesis and compounds characterisation

Dibenzyl 2-bromomalonate

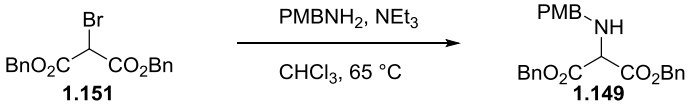


1.150 **1.151**

According to the modified procedure of Perreault *et al.*,[64] DBU (2.97 g, 19.5 mmol) was slowly added to dibenzyl malonate **1.150** (6.54 g, 19.5 mmol) in dry THF (160 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and was then cooled to -78 °C. CBr_4 (6.46 g, 19.5 mmol) was then added in one portion. The reaction mixture was stirred at -78 °C for 6 h and was quenched by slow addition of an aqueous saturated solution of NH_4Cl (60 mL) and water (20 mL). The mixture was warmed to RT, the organic layer was separated and washed with brine (50 mL). The combined aqueous layers were extracted with DCM (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by FC (1:14 EtOAc/PE), which gave the title compound **1.151** as a colourless oil (5.30 g, 14.6 mmol, 75%). $\mathbf{R_f}$ 0.63

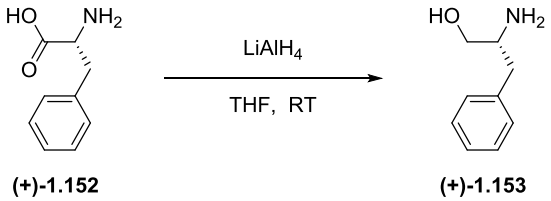
(1:9 EtOAc/PE); δ_H (400 MHz, $CDCl_3$) 7.39–7.31 (m, 10H, Ar*H*), 5.24 (s, 4H, CH_2Ph), 4.94 (1H, s, CHBr); δ_C (100 MHz, CDCl3) 164.3 (2 x *C*=O), 134.5 (2 x *Ar*), 128.7 (2 x *Ar*), 128.7 (2 x *Ar*), 128.3 (2 x *Ar*), 68.7 (2 x *C*H_2Ph), 42.5 (*C*HBr); ν_{max} 1739 (s, C=O), 1230 (s), 1136 (s, C-O), 738 (m, Ar), 695 (w); m/z (ESI$^+$): 385 and 387; ([M+Na]$^+$, 100%); HRMS found 385.0041 and 387.0022, $C_{17}H_{15}BrNaO_4$ requires 385.0046 and 387.0026.

Dibenzyl 2-((4-methoxybenzyl)amino)malonate, 1.149



According to the modified procedure of Hess *et al.*,[78] a mixture of dibenzyl 2-bromomalonate **1.151** (2.99 g, 8.23 mmol), NEt_3 (2.30 mL, 16.5 mmol) and 4-methoxybenzylamine (2.10 mL, 16.5 mmol) was heated under reflux (65 °C) in $CHCl_3$ (80 mL) for 90 min. The reaction mixture was cooled to RT, and DCM (40 mL) and H_2O (80 mL) were added. The aqueous layer was extracted with more DCM (2 × 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:7 EtOAc/PE), which gave the title compound **1.149** as a yellow oil (1.05 g, 2.51 mmol, 30%). R_f 0.51 (1:9 EtOAc/PE); δ_H (400 MHz, $CDCl_3$) 7.40–7.26 (10H, m, Ar*H*), 7.23–7.18 (2H, m, Ar*H*), 6.85–6.82 (2H, m, Ar*H*), 5.17 (s, 4H, CH_2Ph), 4.70 (1H, s, N*H*), 3.80 (3H, s, CH_3), 4.17 (1H, s, C*H*), 3.74 (2H, s, CH_2Ar); δ_C (100 MHz, $CDCl_3$) 168.3 (2 x *C*=O), 158.9 (*Ar*), 135.1 (*Ar*), 130.6 (*Ar*), 129.70 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 128.3 (*Ar*), 127.6 (*Ar*), 127.0 (*Ar*), 113.8 (*Ar*), 67.4 (*C*H_2Ph), 63.9 (s, *C*H), 55.2 (*C*H_2PMB), 50.9 (*C*H_3); ν_{max} 2955 (w, C-H), 1735 (s, C=O), 1512 (m), 1247 (s), 1213 (m), 1173 (m), 1031 (w), 738 (m), 687 (m); **m/z** (ESI$^+$) 861 ([2M+Na]$^+$, 100%), 420 ([M+H]$^+$, 90%); HRMS found 442.1610, $C_{25}H_{26}NNaO_5$ requires 442.1625.

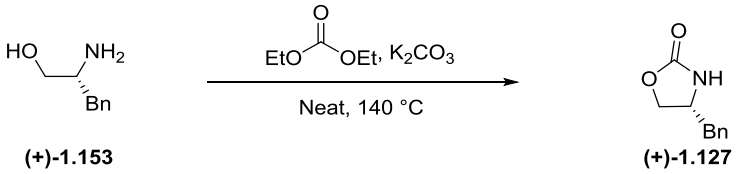
(*R*)-2-Amino-3-phenylpropan-1-ol, (+)-1.153



According to the modified procedure of Granander *et al.*,[163] in a dry 3 neck flask fitted with a condenser and a mechanical stirrer containing a suspension of $LiAlH_4$ (17.2 g, 452.5 mmol) in dry THF (400 mL) at RT, was added (*R*)-phenylalanine **(+)-1.152** (29.9 g, 181 mmol) portionwise over 40 min. The reaction mixture was then heated under reflux (72 °C) for 1 h and cooled to 0 °C. The reaction was quenched by slow addition of H_2O in THF (25 mL in 200 mL) over 40 min. An aqueous solution of NaOH (2.0 M, 15 mL) and H_2O (30 mL) were added to the mixture, which was stirred overnight at RT.

The white suspension was filtered through Celite,™ which was eluted with THF (200 mL) and DCM (2 × 250 mL). The eluent was dried ($MgSO_4$), filtered and evaporated to give a yellow solid which was recrystallised from EtOAc. The title compound **(+)-1.153** was isolated as a light yellow solid (21.0 g, 139 mmol, 77%). $\mathbf{R_f}$ 0.25 (1:5:100 conc. aq. NH_3/MeOH/EtOAc); **m.p.** 86–89 °C (lit. 88–90 °C); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.36-7.15 (m, 5 H, Ar*H*), 3.64 (1H, dd, *J* = 10.8, 3.9, HOCH*H'*), 3.40 (1H, dd, *J* = 10.8, 7.3, HOC*H*H'), 3.11 (1H, dddd, *J* = 8.8, 7.3, 5.2, 3.9, C*H*NH_2), 2.80 (1H, dd, *J* = 13.5, 5.2, PhCH*H'*), 2.52 (1H, dd, *J* = 13.5, 8.8, PhC*H*H'); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +20.4 (c = 1.00, EtOH), lit. +22.8 (c = 1.00, EtOH). *Data are in accordance with the literature.*[164,165]

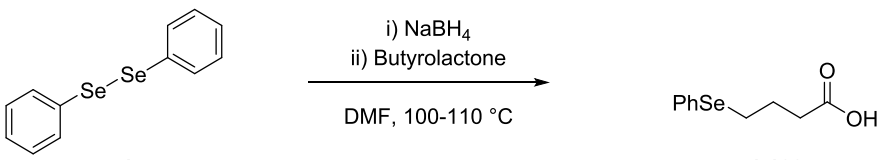
(*R*)-4-Benzyloxazolidin-2-one, (+)-1.127



(+)-1.153 **(+)-1.127**

According to the modified procedure of Evans *et al.*,[165] a flask containing a mixture of (*R*)-2-amino-3-phenylpropan-1-ol **(+)-1.153** (21.0 g, 139 mmol), diethyl carbonate (32.8 g, 278 mmol) and K_2CO_3 (1.92 g, 13.9 mmol) was equipped for distillation, and was heated at 140 °C until no more EtOH could be distilled out of the reaction (90 min). The mixture was then cooled down to RT, diluted with EtOAc (200 mL) and was washed with water (200 mL). The aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered and evaporated. The residue was re-crystallised from EtOAc/Hexane, which gave the title compound **(+)-1.127** as a white solid (17.2 g, 97.1 mmol, 70%). $\mathbf{R_f}$ 0.28 (1:1 EtOAc/PE); **m.p.** 86–87 °C (lit. 80–89 °C); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +64.1 (c = 1.00 in $CHCl_3$, lit. +59.1, c = 1.18); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.38–7.31 (2H, m, Ar*H*), 7.31–7.25 (1H, m, Ar*H*), 7.22–7.15 (2H, m, Ar*H*), 4.45 (1H, dd, *J* = 8.2, 8.2, OCH*H'*), 4.16 (1H, dd, *J* = 8.2, 5.6, OC*H*H'), 4.13–4.05 (1H, m, C*H*NH), 2.92-2.85 (2H, m, PhC*HH'*); $\boldsymbol{\delta_H}$ (100 MHz, $CDCl_3$) 159.4(*C*=O), 135.9 (*Ar*), 129.0 (*Ar*), 129.0 (*Ar*), 127.3 (*Ar*), 69.6 (CH_2O), 53.8 (*C*HN), 41.4 ($PhCH_2$); *Data are in accordance with the literature.*[166]

4-(Phenylselanyl)butanoic acid, 1.122

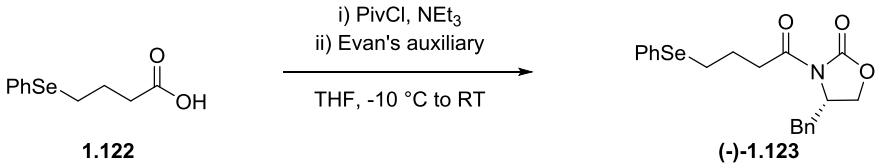


5.1 **1.122**

According to the modified procedure of Smith *et al.*,[59] $NaBH_4$ (3.95 g, 105 mmol) was added portionwise to $(PhSe)_2$ **5.1** (14.3 g, 45.9 mmol) in dry degassed DMF (250 mL). The reaction mixture

was heated at 100 °C for 5 min and γ-butyrolactone (7.31 g, 85.0 mmol) in dry degassed DMF (40 mL) was added. The reaction mixture was then stirred at 120 °C for 2 h and cooled to RT. An aqueous solution of NaOH (2.0 M, 200 mL) was then added and the mixture was concentrated under reduced pressure to V = 100 mL. H_2O (250 mL) and EtOAc (250 mL) were added, and the layers were separated. The organic layer was extracted with an aqueous solution of NaOH (2.0 M, 2 × 250 mL). The combined aqueous layers were acidified at 0 °C with a concentrated aqueous solution of HCl to pH < 2, and the suspension was extracted with EtOAc (3 × 200 mL). The combined organic extracts were successively washed with an aqueous solution of NH_4Cl (2.0 M, 200 mL), H_2O (500 mL, then 2 × 250 mL) and brine (200 mL). The organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow solid, which was recrystallised from Et_2O/hexane to give the title compound **1.122** as yellow crystals (17.0 g, 69.8 mmol, 82%). $\mathbf{R_f}$ 0.25 (1:2:97 AcOH/MeOH/DCM); **m.p.** 55–63 °C (lit. 60–62 °C); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.53–7.47 (2H, m, Ar*H*), 7.31–7.22 (3H, m, Ar*H*), 2.96 (2H, t, *J* = 7.3, PhSeCH_2), 2.52 (2H, t, *J* = 7.3, CH_2CO$_2$H), 2.02 (2H, dd, *J* = 7.3, 7.3, CH$_2$CH_2CH$_2$); $\boldsymbol{\delta_C}$ (100 MHz, CDCl3) 179.3 (*C*=O), 132.8 (*Ar*), 129.7 (*Ar*), 129.1 (*Ar*), 127.0 (*Ar*), 33.6 (*C*H$_2$), 26.8 (*C*H$_2$), 24.9 (*C*H$_2$); *Data are in accordance with the literature.*[167]

(*R*)-4-Benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one, (-)-1.123

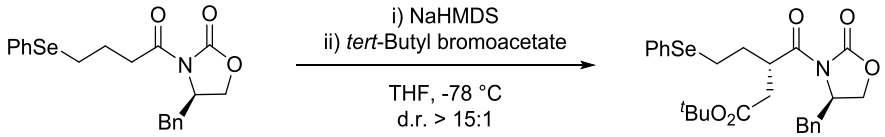


1.122 **(-)-1.123**

To a solution of 4-(phenylselanyl)butanoic acid **1.122** (17.0 g, 69.8 mmol) in dry THF (300 mL) at -10 °C was added NEt_3 (26.1 mL, 188 mmol) and PivCl (9.44 mL, 76.8 mmol). The mixture was stirred at RT for 1 h. LiCl (3.57 g, 76.8 mmol) and (*R*)-4-benzyloxazolidin-2-one (18.2 g, 76.8 mmol) were successively added and the reaction was stirred at RT for 3 h. A saturated aqueous solution of $NaHCO_3$ (100 mL) and H_2O (400 mL) were added and the mixture was extracted with EtOAc (1 x 400 mL, 1 x 250 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by FC (1:5 to 1:3 EtOAc/PE), which gave the title compound **(-)-1.123** as a colourless oil (25.7 g, 64.0 mmol, 92%). $\mathbf{R_f}$ 0.31 (1:3 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -16.9 (c = 1.00, DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.57–7.49 (2H, m, Ar*H*), 7.38–7.17 (8H, m, Ar*H*), 4.64 (1H, dddd, *J* = 9.7, 6.8, 3.3, 3.3, NC*H*), 4.23–4.15 (2H, m, C(O)OCC*HH'*), 3.28 (1H, dd, *J* = 13.3, 3.3, PhCH*H'*), 3.13–3.05 (2H, m, CH$_2$CH_2C(O)N), 3.01 (2H, t, *J* = 7.3, PhSeCH_2), 2.75 (1H, dd, *J* = 13.3, 9.7, PhC*H*H'), 2.14–2.06 (2H, tt, *J* = 7.3, 7.3, CH$_2$CH_2CH$_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.3 (CH$_2$*C*(O)), 153.4 (N*C*(O)O), 135.2 (*Ar*), 132.7 (*Ar*), 130.0 (*Ar*), 129.4 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 127.4 (*Ar*), 126.9 (*Ar*), 66.2 (C(O)O*C*H$_2$), 55.1 (PhCH$_2$*C*H), 37.8 (PhCH$_2$), 35.3 (*C*H$_2$(CO)N), 26.9 (PhSe*C*H$_2$), 24.6 (CH$_2$*C*H$_2$CH$_2$);

ν_{max} 2922 (w, C-H), 1779 (s, C=O), 1698 (s, C=O amide); **m/z** (ESI^+) 426 ($[M+Na]^+$, 100%), 829 ($[2M+Na]^+$, 58%); HRMS found 426.0574, $C_{20}H_{21}NNaO_3{}^{80}Se$ requires 426.0579.

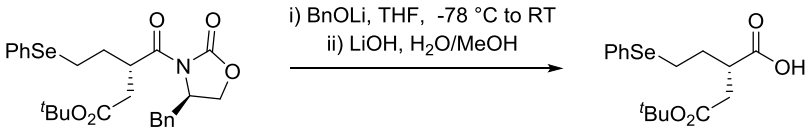
(*R*)-*tert*-Butyl 3-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-(phenylselanyl)pentanoate, (-)-1.153



(-)-1.123 **(-)-1.153**

To a stirred solution of (*R*)-4-benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one **(-)-1.123** (7.32 g, 18.2 mmol) in THF (180 mL) at -78 °C, was added NaHMDS in THF (2.0 M, 12.8 mL, 25.5 mmol) dropwise over 10 min. After stirring for 10 min, *tert*-butyl bromoacetate (8.06 mL, 54.6 mmol) was added dropwise over 10 min and the reaction was stirred for a further 45 min. A saturated aqueous solution of $NaHCO_3$ (200 mL) was added, and the reaction was warmed to RT. The mixture was extracted with EtOAc (1 × 200 mL, then 2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:7 EtOAc/PE), which gave the title compound **(-)-1.153** as a colourless oil (8.01 g, 15.5 mmol, 85%). **R_f** 0.44 (1:7 EtOAc/PE); $[\alpha]_D^{20}$ -36.5 (c = 1.00, $CHCl_3$); **δ_H** (400 MHz, $CDCl_3$) 7.50–7.48 (2H, m, Ar*H*), 7.37–7.31 (2H, m, Ar*H*), 7.30–7.20 (6H, m, Ar*H*), 4.65–4.61 (1H, m, NC*H*Bn), 4.27–4.21 (1H, m, *H*C(CO)N), 4.16–4.12 (2H, m, CO_2CHH'), 3.32 (1H, dd, *J* = 13.4, 3.5, C*H*H'Ph), 2.90-2.96 (2H, m, $PhSeCH_2$), 2.80 (1H, dd, *J* = 16.5, 10.5, C*H*H'$CO_2{}^tBu$), 2.74 (1H, dd, *J* = 13.4, 9.9, CH*H'*Ph), 2.48 (1H, dd, *J* = 16.5, 4.6, CH*H'*$CO_2{}^tBu$), 2.12–2.08 (1H, m, $PhSeCH_2CHH'$), 1.88 (1H, dddd, *J* = 13.6, 9.6, 6.7, 6.7, $PhSeCH_2CHH'$), 1.43 (9H, s, $OC(CH_3)_3$); **δ_C** (100 MHz, $CDCl_3$) 174.7 (*C*=O), 170.9 (*C*=O ester), 153.0 (*C*=O oxazolidinone), 135.6 (*Ar*), 132.6 (*Ar*), 129.7 (*Ar*), 129.5 (*Ar*), 129.1 (*Ar*), 128.9 (*Ar*), 127.2 (*Ar*), 127.0 (*Ar*), 81.0 ($OC(CH_3)_3$), 66.0 (CO_2CH_2), 55.0 (N*C*H), 39.9 (*C*HC=O), 37.5 (CH_2Ph), 36.9 ($CH_2CO_2{}^tBu$), 32.4 ($PhSeCH_2CH_2$), 28.0 ($OC(CH_3)_3$), 24.3 ($PhSeCH_2$); **ν_{max}** 2978 (w, C-H), 1779 (s, C=O oxazolidinone), 1725 (m, C=O ester), 1695 (m, C=O), 1391 (m), 1156 (m, C-O), 737.5m (Ar); **m/z** (ESI^+) 1057 ($[2M+Na]^+$, 100%), 540 ($[M+Na]^+$, 55%); HRMS found 540.1258, $C_{26}H_{31}NNaO_5{}^{80}Se$ requires 540.1261.

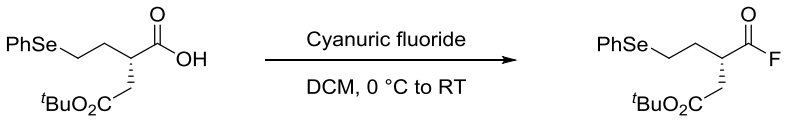
(*R*)-4-(*tert*-Butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid, (-)-1.143



(-)-1.153 **(-)-1.143**

To a nitrogen sparged solution of BnOH (1.61 mL, 15.6 mmol) in THF (160 mL) at 0 °C was added dropwise *n*-BuLi solution in hexane (2.5 M, 5.00 mL, 12.4 mmol). The mixture was stirred at 0 °C for 45 min and then cooled to -78 °C. (*R*)-*tert*-Butyl 3-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-(phenylselanyl)pentanoate **(-)-1.153** (5.65 g, 10.4 mmol) in THF (40 mL) was added dropwise at -60 °C. The reaction mixture was then warmed to RT over three hours. A solution of LiOH (2.18 g, 51.9 mmol) in H_2O/MeOH (1:1, 160 mL) was added at 0 °C via cannula over 5 min. The reaction mixture was stirred at RT for 16 h. THF and MeOH were evaporated under reduced pressure, and then an aqueous solution of pH 2 sulfate buffer (100 mL) was slowly added at 0 °C. The mixture was treated with concentrated HCl dropwise until pH 2. The white emulsion was extracted with EtOAc (3 × 125mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:1 EtOAc/PE) to give a mixture of benzyl alcohol and product which was co-evaporated several times with H_2O/MeOH (1:1, 5 × 70 mL) and gave the title compound **(-)-1.143** as a light yellow oil (3.16 g, 8.84 mmol, 85%). Further washing of the column with EtOAc allowed Evans' auxiliary to be recycled. $\mathbf{R_f}$ 0.19 (1:99 AcOH/DCM); $[\alpha]_D^{20}$ -14.9 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.46 (2H m, Ar*H*), 7.30–7.22 (3H, m, Ar*H*), 2.99–2.91 (3H, m, PhSeC*HH'* and C*H*CO_2H), 2.61 (1H, dd, *J* = 16.5, 5.6, C*H*H'$CO_2{}^t$Bu), 2.40 (1H, dd, *J* = 16.5, 8.6, CH*H'*$CO_2{}^t$Bu), 2.11–2.05 (1H, m, PhSeCH_2C*H*H'), 1.91–1.85 (1H, m, PhSeCH_2CH*H'*), 1.42, (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 180.4 (*C*=O acid), 170.6 (*C*=O ester), 132.8 (*Ar*), 129.1 (2 × *Ar*), 127.1 (*Ar*), 81.3 (O*C*(CH_3)$_3$), 41.3 (*C*HCO_2H), 36.8 (*C*$H_2CO_2{}^t$Bu), 31.9 (PhSeCH_2*C*H_2), 28.0 (OC(*C*H_3)$_3$), 24.6 (PhSe*C*H_2); $\boldsymbol{\nu_{max}}$ 2978 (br, C-H and OH acid), 1729 (s, C=O ester), 1707 (s, C=O acid), 1368 (s), 1154s (C-O), 737 (w, Ar); **m/z** (ESI^-) 357 ($[M-H]^-$, 100%); HRMS found 381.0569 ($[M+Na]^+$), $C_{16}H_{22}NaO_4Se$ requires 381.0576.

(*tert*-Butyl (*R*)-3-(fluorocarbonyl)-5-(phenylselanyl)pentanoate, 1.160

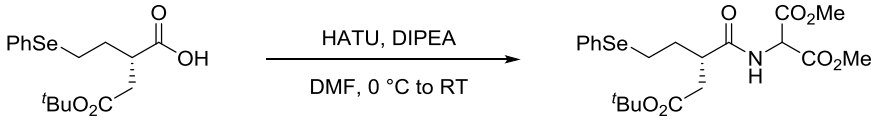


(-)-1.143 **1.160**

According to the modified procedure of Han *et al.*,[69] cyanuric fluoric (20.0 mg, 0.148 mmol) was added to a solution of (*R*)-4-(tert-Butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid **(-)-1.143** (20.0 mg, 0.0560 mmol) in dry DCM (0.4 mL) at 0 °C. The mixture was stirred at RT for 45 min and

was diluted with DCM (1.5 mL). The organic phase was rapidly washed with ice-water (1.5 mL) and dried on Na_2SO_4, filtered and evaporated, which gave the crude acyl fluoride **1.160**. ν_{max} 1836 (s).

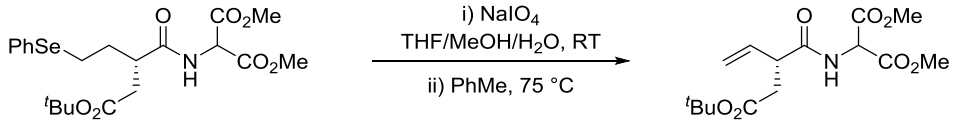
(*R*)-Dimethyl 2-(4-(tert-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate, (-)-1.161



(-)-1.143 **(-)-1.161**

The title compound was prepared from (*R*)-4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid **(-)-1.143** (680 mg, 1.80 mmol) and dimethyl aminomalonate (336 mg, 3.81 mmol) according to general procedure 1 and was purified by FC (1:3 EtOAc/PE). The title compound **(-)-1.161** was isolated as a colourless oil (775 mg, 1.59 mmol, 84%). $\mathbf{R_f}$ 0.67 (3:7 EtOAc/PE); $[\alpha]_D^{20}$ -33.3 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.53–7.48 (2H, m, Ar*H*), 7.30–7.20 (3H, m, Ar*H*), 6.88 (1H, d, *J* = 6.6, N*H*), 5.15 (1H, d, *J* = 6.6, NC*H*), 3.81 (3H, s, OCH_3), 3.05–2.82 (3H, m, PhSeCH_2 and *H*C(CO)N), 3.75 (3H, s, OCH_3), 2.63 (1H, dd, *J* = 16.8, 9.1, C*H*H'$CO_2{}^t$Bu), 2.30 (1H, dd, *J* = 16.8, 5.1, CH*H*'$CO_2{}^t$Bu), 2.08 (1H, dddd, *J* = 13.5, 8.6, 8.6, 5.1, PhSeCH$_2$C*H*H'), 1.75 (1H, dddd, *J* = 13.5, 8.1, 8.1, 5.1, PhSeCH$_2$CH*H*'), 1.40 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.7 (*C*=O), 171.0 (*C*=O), 166.5 (*C*=O), 166.3 (*C*=O), 132.7 (*Ar*), 129.6 (*Ar*), 129.1 (*Ar*), 127.0 (*Ar*), 81.1 (O*C*(CH$_3$)$_3$), 56.3 (N*C*H), 53.4 (O*C*H$_3$), 53.4 (O*C*H$_3$), 37.8 (*C*H$_2$CO$_2{}^t$Bu), 32.3 (PhSeCH$_2$*C*H$_2$), 28.0 (OC(*C*H$_3$)$_3$), 24.8 (PhSe*C*H$_2$); $\boldsymbol{\nu_{max}}$ 3326 (br, N-H), 2971 (w, C-H), 1745 (s, C=O), 1680 (m, C=O), 1157 (s, C-O), 739 (w, Ar); **m/z** (ESI$^+$) 510 ([M+Na]$^+$, 100%); HRMS found 510.1010, $C_{21}H_{29}NNaO_7Se$ requires 510.1003.

(*R*)-Dimethyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate, (-)-1.162

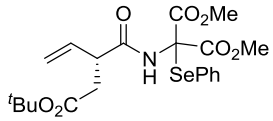


(-)-1.161 **(-)-1.162**

According to the modified procedure of Kocienski *et al.*,[74] $NaIO_4$ (262 mg, 1.23 mmol) was added to a stirred mixture of $NaHCO_3$ (104 mg, 1.23 mmol) and (*R*)-dimethyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate **(-)-1.161** (200 mg, 0.410 mmol) in MeOH/THF/H_2O (1:1:1, 12 mL) at RT under air. Stirring was continued at RT for 15 min. H_2O (20 mL) and DCM (25 mL) were added and the mixture was stirred vigorously before being filtered through a Celite™ pad, which was eluted with DCM (2 × 10 mL). The aqueous layer was extracted with DCM (2 × 10 mL), the combined organic extracts were dried (Na_2SO_4), filtered and quickly evaporated under reduced pressure. The crude selenoxide ([M+Na]$^+$ 526) was dissolved in degassed toluene and heated at 75 °C

for 25 min. The reaction mixture was then cooled to RT and was evaporated under reduced pressure. The residue was purified by FC (1:3 EtOAc/PE), which gave the title compound **(-)-1.162** as a colourless oil (116 mg, 0.352 mmol, 79%). $\mathbf{R_f}$ 0.61 (3:7 EtOAc/PE); $[\alpha]_D^{20}$ -42.9 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.77 (d, *J* = 6.7, N*H*), 5.87 (1H, ddd, *J* = 17.1, 10.2, 7.5, CH=C*H*H'), 5.32 (1H, dd, *J* = 17.1, 1.0, CH=CH*H'*), 5.27 (1H, dd, *J* = 10.2, 1.0, C*H*=CHH'), 5.16 (1H, d, J = 6.7, NC*H*), 3.81 (6H, s, 2 x OCH_3), 3.43 (1H, ddd, *J* = 7.5, 7.5, 7.5 Hz, *H*C(CO)N), 2.80 (1H, dd, *J* = 16.5, 7.5, C*H*H'$CO_2{}^t$Bu), 2.45 (1H, dd, *J* = 16.5, 7.5, CH*H'*$CO_2{}^t$Bu), 1.42 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.8 (*C*=O), 170.7 (*C*=O), 166.5 (*C*=O), 166.5 (*C*=O), 134.9 (*C*H=CH_2), 119.3 (CH=*C*H_2), 80.9 (O*C*(CH_3)$_3$), 56.2 (N*C*H), 54.0 (O*C*H_3), 53.4 (O*C*H_3), 46.8 (H*C*(CO)N), 37.0 (*C*$H_2CO_2{}^t$Bu), 28.0 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 3328 (br, N-H), 2979 (w, C-H), 1733 (C=O esters), 1684m (C=O amide), 1157 (s, C-O); **m/z** (ESI$^+$) 352 ([M+Na]$^+$, 100%); HRMS found 352.1358, $C_{15}H_{23}NNaO_7$ requires 352.1367.

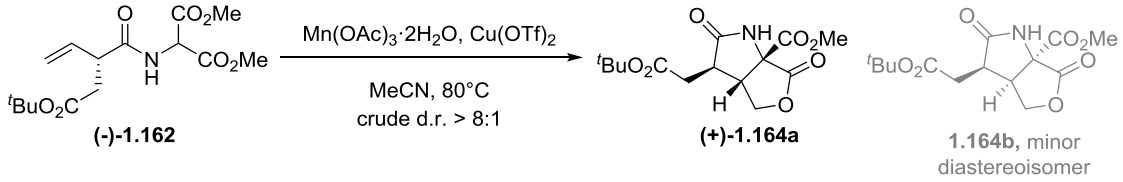
Dimethyl (*R*)-2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)-2-(phenylselanyl)malonate, 1.163



1.163

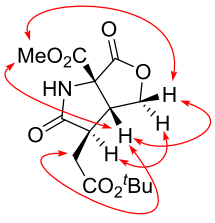
The title compound **1.163** is a side product, which was obtained when the previous phenyl selenium oxidative elimination of **(-)-1.161** was attempted in the presence of NEt_3 during the elimination step according to the un-modified procedure of Kocienski *et al.*[74] $\mathbf{R_f}$ 0.79 (3:7 EtOAc/PE); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.54–7.49 (2H, m, Ar*H*), 7.47–7.41 (1H, m, Ar*H*), 7.37–7.27 (2H, m, Ar*H*), 5.62 (1H, ddd, *J* = 17.0, 10.1, 8.8, C*H*=CHH'), 5.17 (1H, d, *J* = 10.1, CH=C*H*H'), 5.15 (1H, d, *J* = 17.0, CH=CH*H'*), 3.83 (3H, s, CO_2CH_3), 3.82 (3H, s, CO_2CH_3), 3.25 (1H, m, C*H*(CO)N), 2.81 (1H, dd, *J* = 16.2, 6.6, C*H*H'$CO_2{}^t$Bu), 2.36 (1H, dd, *J* = 16.2, 7.3, CH*H'*$CO_2{}^t$Bu), 1.43 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (126 MHz, $CDCl_3$) 170.8 (*C*=O), 169.9 (*C*=O), 166.8 (*C*=O), 166.6 (*C*=O), 139.6 (*Ar*), 134.5 (*C*H=CH), 130.2 (*Ar*), 129.2 (*Ar*), 126.5 (*Ar*), 119.9 (CH=*C*H), 81.0 (C_{quat}), 64.5 (C_{quat}), 54.1 (2 x OCH_3), 47.3 (*C*H(CO)N), 36.9 (*C*$H_2CO_2{}^t$Bu), 28.2 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 2979 (w, C-H), 1733 (s, C=O), 1689 (m, C=O), 1485 (m), 1247 (s), 1153 (m), 746 (w); **m/z** (ESI$^+$) 508 ([M+Na]$^+$, 100%); HRMS found 508.0839, $C_{21}H_{27}NNaO_7{}^{80}Se$ requires 508.0846.

(+)-(3*R*,3a*R*,6a*R*)-Methyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate, (+)-1.164a



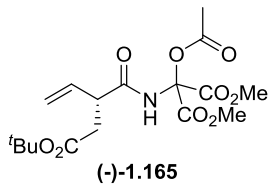
A solution of (*R*)-dimethyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate (211 mg, 0.610 mmol) **(-)-1.162** in nitrogen sparged MeCN (8 + 1 mL rinse) was added to $Mn(OAc)_3{\cdot}2H_2O$ (327 mg, 1.22 mmol) and $Cu(OTf)_2$ (131 mg, 0.610 mmol) in a 2 necked flask fitted with a condenser under argon at 80 °C. The reaction mixture was stirred for 4 h, and was then cooled to RT. The mixture was filtered through a silica pad eluted with EtOAc. The solvent was then evaporated and the residue was purified by FC (7:3 EtOAc/PE, then EtOAc) which gave the title compound **(+)-1.164a** as a white solid (0.295 mmol, 92.2 mg, 48%) and the two by-products described below. The NMR analysis of the crude of the reaction indicated presence of minor diastereoisomer **1.164b** (d.r. > 8:1), which could not be isolated in a pure form after FC. *Characterisation is given for* **(+)-1.164a**. $\mathbf{R_f}$ 0.69 (Et_2O); **m.p.** 85–87 °C; $[\alpha]_D^{20}$ +15.0 (c = 1.00, $CHCl_3$); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 6.65 (s, 1H, N*H*), 4.77 (1H, dd, *J* = 9.7, 6.9, CHC*H*H'O), 4.61 (1H, dd, *J* = 9.7, 2.1, CHCH*H'*O), 3.89 (3H, s, OCH_3), 3.21 (1H, ddd, *J* = 6.9, 6.9, 2.1, CHC*H*CHH'O), 2.95 (1H, dd, *J* = 17.4, 3.3, C*H*H'$CO_2{}^t$Bu), 2.81 (1H, ddd, *J* = 10.2, 6.9, 3.3, C*H*CHH'$CO_2{}^t$Bu), 2.47 (1H, dd, *J* = 17.4, 10.2, CH*H'*$CO_2{}^t$Bu), 1.44 (9H, s, OC(CH_3)$_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 174.9 (*C*=O), 171.4 (*C*=O), 170.6 (*C*=O), 167.5 (*C*=O), 81.9 (O*C*(CH_3)$_3$), 72.2 (CH*C*H_2O), 66.3 (C_{quat}), 54.0 (O*C*H_3), 46.7 (CH*C*HCH$_2$O), 43.8 (*C*HCH$_2$$CO_2{}^t$Bu), 36.1 (*C*$H_2$$CO_2{}^t$Bu), 28.0 (OC(*C*$H_3$)$_3$); $\mathbf{\nu_{max}}$ 2980 (m, C-H), 1784 (s, C=O), 1720 (s, C=O), 1156 (m, C-O); HRMS (FI) found 313.1161, $C_{14}H_{19}NO_7$ requires 313.1175.

Key nOe interactions in $CDCl_3$



(+)-1.164a

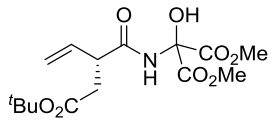
(*R*)-Dimethyl 2-acetoxy-2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate, (-)-1.165



(-)-1.165

The title compound **(-)-1.165** was isolated as a by-product of the former cyclisation reaction (12.3 mg, no yield given as most product was discarded with impure fractions). $\mathbf{R_f}$ 0.65 (1:3 EtOAc/PE); $[\alpha]_D^{20}$ -38.2 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.70 (1H, s, N*H*), 5.79–5.85 (1H, m, C*H*=CHH'), 5.33 (1H, d, *J* = 16.9, CH=C*H*H'), 5.27 (1H, d, *J* = 9.9, CH=CH*H'*), 3.82 (6H, s, OCH_3), 3.39–3.33 (1H, m, C*H*(CO)N), 2.77 (1H, dd, *J* = 16.7, 7.6, C*H*H'$CO_2{}^t$Bu), 2.45 (1H, dd, *J* = 16.7, 6.1, CH*H'*$CO_2{}^t$Bu), 2.17 (3H, s, O(CO)CH_3), 1.42 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.6 (*C*=O), 170.4 (*C*=O), 170.0 (*C*=O), 164.0 (*C*=O), 163.9 (*C*=O), 134.2 (*C*H=CH_2), 119.7 (CH=*C*H_2), 81.6 (C_{quat}), 81.0 (C_{quat}), 54.2 (2 x OCH_3), 46.6 (*C*H(CO)N), 36.8 (*C*$H_2CO_2{}^t$Bu), 28.0 (OC(*C*H_3)$_3$), 20.8 (O(CO)*C*H_3); $\boldsymbol{\nu_{max}}$ 3341 (br, NH), 1767 (s, C=O), 1746 (m, C=O), 1728 (m, C=O), 1669 (m, C=O amide), 1243 (s, C-O), 1155 (m, C-O), 1059 (m); **m/z** (ESI^+) 410 ($[M+Na]^+$, 100%); HRMS found 410.1414, $C_{17}H_{25}NNaO_9$ requires 410.1422.

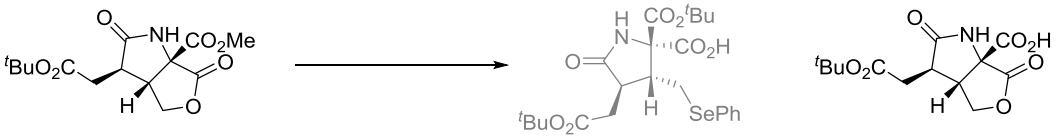
(*R*)-Dimethyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)-2-hydroxymalonate, (-)-1.166



(-)-1.166

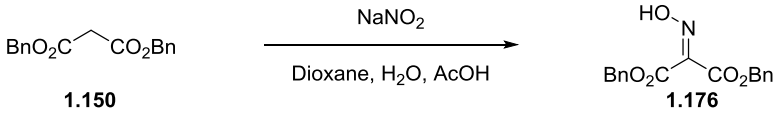
The title compound **(-)-1.166** was isolated as a by-product of the former cyclisation reaction (no yield given as most product was discarded with impure fractions). $\mathbf{R_f}$ 0.40 (3:7 EtOAc/PE); $[\alpha]_D^{20}$ -46.8 (c = 0.5 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.60 (1H, s, N*H*), 5.86 (1H, ddd, *J* = 16.2, 10.0, 7.0, C*H*=CHH'), 5.32 (1H, d, *J* = 16.2, CH=C*H*H'), 5.27 (1H, d, *J* = 10.0, CH=CH*H'*), 5.05 (1H, s, O*H*), 3.85 (6H, s, OCH_3), 3.40 (1H, ddd, *J* = 7.0, 7.0, 7.0, C*H*(CO)N), 2.78 (1H, dd, *J* = 16.5, 7.0, C*H*H'$CO_2{}^t$Bu), 2.44 (1H, dd, *J* = 16.5, 7.0, CH*H'*$CO_2{}^t$Bu), 1.43 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.4 (*C*=O), 170.5 (2 x *C*=O), 167.2 (*C*=O), 134.5 (*C*H=CH_2), 119.5 (CH=*C*H_2), 81.1 (O*C*(CH_3)$_3$), 79.8 (N*C*-OH), 54.2 (2 × OCH_3), 46.8 (*C*H(CO)N), 36.8 (*C*$H_2CO_2{}^t$Bu), 28.0 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 3386 (br, O-H), 2680 (w, C-H), 1752 (s, C=O), 1728 (s, C=O), 1690 (s, C=O), 1293 (m), 1245 (m), 1154 (s, C-O); **m/z** (ESI^+) 368 ($[M+Na]^+$, 100%); HRMS found 368.1314 $C_{15}H_{23}NNaO_8$ requires 368.1316.

(3*R*,3a*R*,6a*R*)-3-(2-(*tert*-Butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylic acid, (+)-1.175



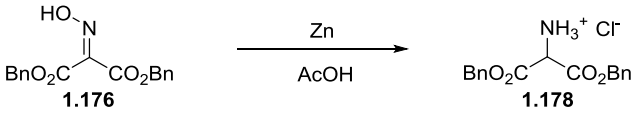
The title compound **(+)-1.175** was isolated as a white solid when it was attempted to open the lactone ring of **(+)-1.164a** with phenyl selenide anion. **m.p.** decomposed at T > 150 °C; $[\alpha]_D^{20}$ +31.4 (c = 0.5 in MeOH); δ_H (500 MHz, MeOD-d_4) 4.75 (dd, *J* = 9.1, 6.6, CHCHC*H*H'O), 4.51 (1H, dd, *J* = 9.1, 1.3, CHCHCH*H'*O), 3.18–3.12 (1H, m, C*H*), 2.85–2.79 (1H, m, C*H*), 2.82 (1H, dd, *J* = 17.7, 3.8, C*H*H'$CO_2{}^t$Bu), 2.52 (1H, dd, *J* = 17.7, 10.1, CH*H'*$CO_2{}^t$Bu), 1.48 (9H, s, OC(CH_3)$_3$); δ_C (126 MHz, MeOD-d_4) 178.6 (*C*=O), 177.3 (*C*=O), 172.6 (2 x *C*=O), 82.4 (*C*(CH_3)$_3$), 73.1 (*C*HH'O), 49.3 (*C*H, under solvent peak), 45.6 (*C*H), 36.8 (*C*$H_2CO_2{}^t$Bu), 28.0 (OC(*C*H_3)$_3$); ν_{max} 3257 (br, O-H), 2979 (w, C-H), 1772 (m, C=O), 1717 (s, C=O), 1656 (s, C=O), 1367 (s, m), 1157 (s, C-O); **m/z** (ESI^-) 298 ([M-H]$^-$, 100%); HRMS found 298.0933, $C_{13}H_{16}NO_7$ requires 298.0932.

Dibenzyl 2-(hydroxyimino)malonate, 1.176[75]



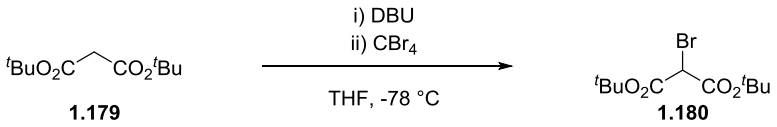
According to the modified procedure of MacDonald *et al.*,[75] $NaNO_2$ (2.99 g, 35.2 mmol) was added in one portion to a solution of dibenzyl malonate **1.150** (10.6 mmol, 3.00 g) in dioxane (30 mL), H_2O (6 mL) and AcOH (4 mL). The reaction mixture was stirred for 36 h at RT. The reaction was diluted with H_2O (60 mL) and quenched by the addition of a saturated aqueous solution of $NaHCO_3$ until gas evolution ceased. The mixture was then extracted with diethyl ether (3 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (3:7 EtOAc/PE), which gave the title compound **1.176** as a white solid (3.34 g, 10.0 mmol, 95%). R_f 0.36 (1:3 EtOAc/PE); **m.p.** 56-60 °C; δ_H (400 MHz, $CDCl_3$) 10.44 (1H, br, OH), 7.38–7.30 (10H, m, Ar*H*), 5.29 (2H, s, CH_2), 5.35 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 160.3 (*C*=O), 159.8 (*C*=O), 143.8 (*C*=N), 134.4 (*Ar*), 128.7 (*Ar*), 123.4 (*Ar*), 128.4 (*Ar*), 68.1 (*C*H_2), 68.0 (*C*H_2); ν_{max} 3327 (br, O-H), 1740 (s, C=O), 1266 (m), 1094 (s, C-O), 1023 (s), 747 (m), 696 (s); ***m/z*** (ESI^+) 336 ([M+Na]$^+$, 100%); HRMS 336.0838, $C_{17}H_{15}NNaO_5$ requires 336.0842.

Dibenzyl 2-aminomalonate hydrochloride,[77] 1.178



According to the modified procedure of Hasimoto *et al.*,[77] a vigorously stirred solution of dibenzyl 2-(hydroxyimino)malonate **1.176** (1.50 g, 4.40 mmol) in acetic acid (21 mL) was sparged with nitrogen for 10 min and then zinc dust (893 mg, 13.7 mmol) was added. After 45 min two more portions of zinc dust (446 mg each, 6.85 mmol) were added at 45 min intervals after the first addition. 30 min after the last addition the reaction was filtered through a Celite™ pad which was eluted with AcOH (35 mL). The filtrate was concentrated under reduced pressure to V = 10 mL and diluted in H_2O (200 mL). Sodium carbonate was added portionwise until gas evolution ceased. The mixture was then extracted with diethyl ether (3 × 60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to V = 25 mL. Dry HCl (from the dropwise addition of concentrated H_2SO_4 on solid NaCl) was bubbled through solution for 20 min during which time a white precipitate formed. The solid was filtered, washed with Et_2O (5 mL) and recovered from the filter by dissolution in MeOH. After evaporation of MeOH under reduced pressure, the title compound **1.178** was isolated as a white solid (1.71 mmol, 575 mg, 39%). **R_f** 0.58 (3:7 EtOAc/PE); **m.p.** 109–115 °C; **δ_H** (400 MHz, DMSO-d_6) 9.35 (3H, br, NH_3Cl), 7.38–7.32 (10H, m, Ar*H*), 5.30–5.20 (5H, m, C*H* and 2 × CH_2); **δ_C** (100 MHz, DMSO-d_6) 164.5 (2 x *C*=O), 135.5 (*Ar*), 129.3 (*Ar*), 129.1 (*Ar*), 129.1 (*Ar*), 69.0 (2 × CH_2), 55.7 (*C*H); **ν_{max}** 2803 (m, C-H), 1763 (s, C=O), 1276 (s), 736 (s); **m/z** (ESI$^+$) 322 ([M-H+Na]$^+$, 100%); HRMS found 322.1045, $C_{17}H_{17}NNaO_4$ requires 322.1050.

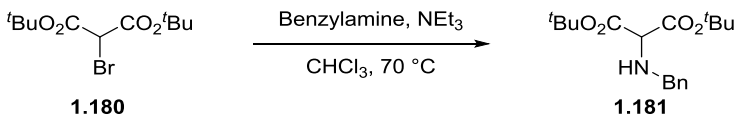
Di-*tert*-butyl 2-bromomalonate,[64] 1.179



According to the modified procedure of Perreault *et al.*,[64] DBU (7.61 g, 50.0 mmol) was slowly added to di-*tert*-butyl malonate **1.179** (10.8 g, 50.0 mmol) in dry THF (400 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then cooled to -78 °C. CBr_4 (16.6 g, 50.0 mmol) was then added in one portion. The reaction mixture was stirred at -78 °C for 2 h and was quenched by slow addition of an aqueous saturated solution of NH_4Cl (160 mL) and water (40 mL). The mixture was warmed to RT, the organic layer was separated and washed with brine (100 mL). The combined aqueous layers were extracted with DCM (2 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was fractionally distilled under reduced pressure (0.3–0.5 mmHg, 85–95 °C), which gave the title compound **1.180** as a colourless oil (14.3 g,

48.6 mmol, 98%). **R_f** 0.41 (1:20 EtOAc/PE); **δ_H** (400 MHz, $CDCl_3$) 4.67 (1H, s, C*H*Br), 1.25 (18H, s, OC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 163.6 (*C*=O), 83.9 (*C*(CH_3)$_3$), 45.64 (*C*HBr), 27.7 (OC(*C*H_3)$_3$); **m/z** (ES^+) 317 and 319 ($[M+Na]^+$, 100%). *Data are consistent with literature values*.[168]

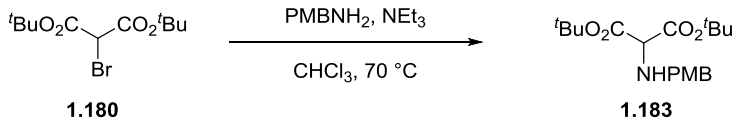
Di-*tert*-butyl 2-(benzylamino)malonate, 1.181



1.180 **1.181**

According to the modified procedure of Hess *et al.,*[78] a mixture of di-*tert*-butyl 2-bromomalonate **1.180** (500 mg, 1.69 mmol), NEt_3 (0.47 mL, 3.39 mmol) and benzylamine (0.370 mL, 3.39 mmol) in $CHCl_3$ (5 mL) was sparged for 5 min with N_2. The reaction mixture was then heated under reflux (70 °C) for 6 h. DCM (5 mL) was added and the mixture was washed with H_2O (5 mL) and brine (5 mL). The combined aqueous layers were extracted with more DCM (5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue **1.181** was purified by FC (1:14 EtOAc/PE), which gave the title compound as an orange oil (348 mg, 1.08 mmol, 64%). **R_f** 0.56 (14:1 EtOAc/PE); **δ_H** (400 MHz, $CDCl_3$) 7.38-7.29 (4H, m, Ar*H*), 7.29–7.23 (1H, m, Ar*H*), 3.86 (1H, s, C*H*), 3.80 (2H, s, CH_2), 2.27 (1H, br, N*H*), 1.48 (18H, s, OC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 167.9 (2 x *C*=O), 139.1 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 127.2 (*Ar*), 82.1 (2 x O*C*(CH_3)$_3$), 65.4 (*C*H), 51.4 (*C*H_2), 28.1 (2 x OC(*C*H_3)$_3$); **ν_{max}** 2978 (w, C-H), 1753 (m, C=O), 1730 (s, C=O), 1136 (s, C-O), 731 (w), 689 (w); **m/z** (ESI^+) 322 ($[M+H]^+$, 100%); HRMS found 322.2006, $C_{18}H_{28}NO_4$ requires 322.2013.

Di-*tert*-butyl 2-((4-methoxybenzyl)amino)malonate, 1.183

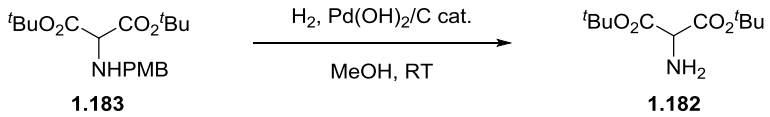


1.180 **1.183**

According to the modified procedure of Hess *et al.,*[78] a solution of 4-methoxybenzylamine (13.9 mL, 107 mmol), NEt_3 (14.8 mL, 107 mmol) and di-*tert*-butyl 2-bromomalonate **1.180** (15.7 g, 53.3 mmol) in $CHCl_3$ (250 mL) was sparged with nitrogen for 10 min and then heated at 70 °C under argon for 10 h. The reaction mixture was cooled to RT, then washed with water (180 mL) and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:6 to 1:4 $Et_2O/PE_{30\text{-}40}$), which gave the title compound **1.183** as a yellow oil (15.7 g, 44.8 mmol, 84%); **R_f** 0.38 (1:6 EtOAc/PE); **δ_H** NMR (400 MHz, $CDCl_3$) 7.29–7.25 (2H, m, Ar*H*), 6.88–6.84 (2H, m, Ar*H*), 3.84 (1H, s, NC*H*), 3.80 (3H, s, OCH_3), 3.73 (2H, s, ArCH_2), 1.47 (18H, s, OC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 167.9 (*C*=O), 158.8 (*Ar*), 131.2 (*Ar*), 129.7 (*Ar*), 113.8 (*Ar*), 82.1 (*C*(CH_3)$_3$), 65.5 (*C*H($CO_2{}^tBu$)$_2$), 55.3 (OCH_3), 50.8 (Ar*C*H_2), 27.9 (C(*C*H_3)$_3$); **ν_{max}** 3339 (w,

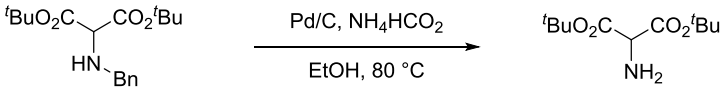
N-H), 2979 (w, C-H), 1732 (s, C=O ester); **m/z** (ESI+) 353 ([M+H]$^+$, 100%), 374 ([M+Na]$^+$, 30%); HRMS found 374.1924, $C_{19}H_{29}NNaO_5$ requires 374.1938.

Di-*tert*-butyl 2-aminomalonate, 1.182



1.183 **1.182**

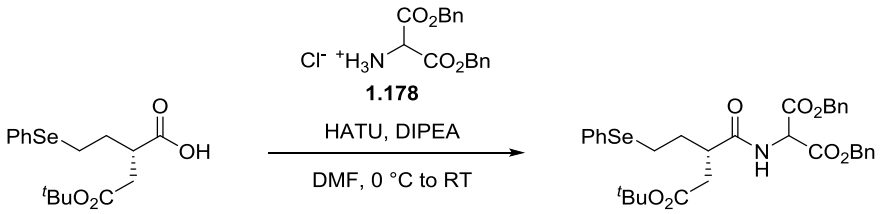
$Pd(OH)_2$ (20% on activated carbon, 1.00 g) was added to a nitrogen purged solution di-*tert*-butyl 2-((4-methoxybenzyl)amino)malonate **1.183** (10.4 g, 29.5 mmol) in MeOH (120 mL). The stirred solution was purged with nitrogen. The atmosphere was then replaced with hydrogen. The reaction was vigorously stirred for 12 h under hydrogen (balloon pressure). The reaction was then backfilled with N_2 and the mixture was filtered through a Celite™ pad, which was further eluted with MeOH (2 x 30 mL). The filtrate was then evaporated and the residue was purified by FC (short column, 1:2 to 1:0 Et_2O/PE), which gave the title compound **1.182** as a colourless oil (6.40 g, 26.1 mmol, 89%). $\mathbf{R_f}$ 0.65 (3:1 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.94 (s, 1H, C*H*), 1.81 (2H, br, NH_2), 1.46 (18H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.1 (*C*=O), 82.4 (*C*(CH$_3$)$_3$), 60.1 (*C*H), 28.0 (OC(*C*H$_3$)$_3$); $\boldsymbol{\nu_{max}}$ 2979 (w, C-H), 1732 (s, C=O), 1142 (s, C-O), 848 (w); **m/z** (ESI$^+$) 254 ([M+Na]$^+$, 100%); HRMS found 254.1363, $C_{11}H_{21}NNaO_4$ requires 254.1363.



1.181 **1.182**

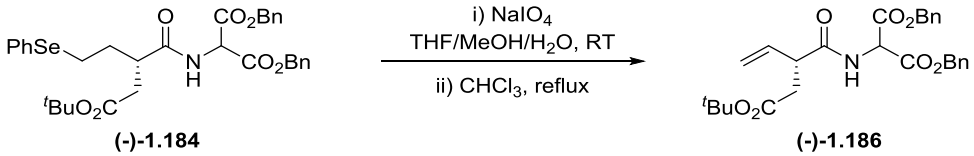
A mixture of ammonium formate (0.31 g, 5.0 mmol) and di-*tert*-butyl 2-(benzylamino)malonate **1.181** (318 mg, 0.988 mmol) in EtOH (7 mL) was purged with argon. Pd/C 10% w/w (32.0 mg) was then added, and the reaction mixture was heated under reflux (80 °C) for one hour. The reaction was cooled to RT, and filtered through a Celite™ pad, eluting with EtOH. The filtrate was evaporated and the residue was purified by FC (7:3 EtOAc/PE) to give the title compound as a colourless oil **1.182** (190 mg, 0.774 mmol, 75%). *Characterisation is given with previous preparation.*

(*R*)-Dibenzyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate, (-)-1.184



The title compound **(-)-1.184** was prepared from (*R*)-4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid **(-)-1.143** (350 mg, 0.980 mmol) and dibenzyl 2-aminomalonate hydrochloride (362 mg, 1.08 mmol) according to general procedure 1 and was purified by FC (1:5 EtOAc/PE). The title compound **(-)-1.184** was isolated as a white solid (553 mg, 0.865 mmol, 88%). $\mathbf{R_f}$ 0.77 (DCM); **m.p.** 52–55 °C; $[\alpha]_D^{20}$ -27.5 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.47 (2H, m, Ar*H*), 7.35–7.30 (6H, m, Ar*H*), 7.29–7.18 (7H, m, Ar*H*), 6.92 (1H, d, *J* = 6.6, N*H*), 5.25–5.12 (5H, m, NC*H* and 2 x OC*HH'*Ph), 3.01–2.81 (3H, m, PhSeCH_2 and C*H*(CO)N), 2.62 (1H, dd, *J* = 16.7, 9.1, C*H*H'$CO_2{}^t$Bu), 2.28 (1H, dd, *J* = 16.7, 5.1, CH*H'*$CO_2{}^t$Bu), 2.08 (1H, dddd, *J* = 13.4, 10.0, 8.6, 5.1, PhSeCH_2C*H*H'), 1.74 (1H, dddd, *J* = 13.4, 8.1, 8.1, 5.1, PhSeCH_2CH*H'*), 1.40 (s, 9H, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.7 (*C*=O), 171.0 (*C*=O), 165.8 (*C*=O), 165.7 (*C*=O), 134.7 (*Ar*), 134.6 (*Ar*), 132.7 (*Ar*), 129.6 (*Ar*), 129.1 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 128.3 (*Ar*), 128.3 (*Ar*), 126.9 (*Ar*), 81.1 (O*C*(CH_3)$_3$), 68.2 (*C*H_2Ph), 68.1 (*C*H_2Ph), 41.8 (*C*H(CO)N), 56.7 (NCH), 37.8 (*C*$H_2CO_2{}^t$Bu), 32.2 (PhSeCH_2*C*H_2), 28.0 (OC(*C*H_3)$_3$), 24.8 (PhSe*C*H_2); $\boldsymbol{\nu_{max}}$ 3355 (br, NH), 2931 (w, C-H), 1760 (s, C=O), 1731 (s, C=O), 1680 (m, C=O amide), 1156 (s, C-O), 738 (m, Ar), 696 (w); **m/z** (ESI^+) this compound showed no detectable ionization.

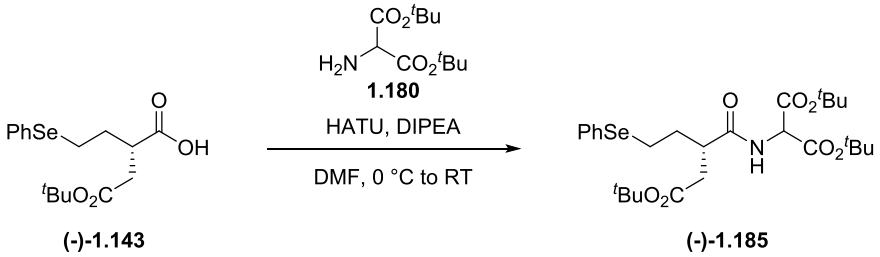
(*R*)-Dibenzyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate, (-)-1.186



To a stirred mixture of (*R*)-dibenzyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate **(-)-1.184** (399 mg, 0.625 mmol) and $NaHCO_3$ (263 mg, 3.13 mmol) in MeOH/H_2O/THF (1:1:1, 12 mL), was added $NaIO_4$ (669 mg, 3.13 mmol) portionwise over 3 min. The reaction mixture was stirred for 15 min. H_2O (20 mL) and DCM (20 mL) were added, and this mixture was stirred for 5 min and was filtered through a Celite™ pad, which was eluted with DCM (2 x 15 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and quickly evaporated under reduced pressure. The crude selenoxide (**m/z** (ESI^+) $[M+Na]^+$ 678) was then dissolved in $CHCl_3$ (40 mL)

and the solution was sparged with nitrogen before being heated under reflux (65 °C) for 45 min. The reaction mixture was cooled to RT and evaporated under reduced pressure; the residue was purified by FC (1:7 EtOAc/PE), which gave the title compound **(-)-1.186** as colourless oil (248 mg, 0.515 mmol, 82%). $\mathbf{R_f}$ 0.18 (9:1 EtOAc/PE); $[\alpha]_D^{20}$-33.9 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.37–7.30 (5H, m, Ar*H*), 7.30–7.23 (5H, m, Ar*H*), 6.79 (1H, d, *J* = 6.7, N*H*), 5.85 (1H, ddd, *J* = 17.2, 10.1, 8.5, C*H*=CHH'), 5.35–5.10 (7H, m, 2 × C*HH'*Ph, NC*H* and CH=C*HH'*), 3.43 (1H, ddd, *J* = 8.5, 7.0, 7.0, C*H*(CO)N), 2.80 (1H, dd, *J* = 13.4, 7.0, C*H*H'$CO_2{}^t$Bu), 2.43 (1H, dd, *J* = 13.4, 7.0, CH*H'*$CO_2{}^t$Bu), 1.42 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.8 (*C*=O), 170.8 (*C*=O), 165.8 (*C*=O malonate), 134.9 (*C*H=CH_2), 134.6 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.3 (*Ar*), 128.2 (*Ar*), 119.4 (CH=*C*H_2), 80.9 (O*C*$(CH_3)_3$), 68.2 (*C*H_2Ph), 68.2 (*C*H_2Ph), 56.6 (N*C*H), 46.9 (*C*H(CO)N), 37.0 (*C*$H_2CO_2{}^t$Bu), 28.0 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 3439 (br, N-H), 2979 (w, C-H), 1733 (s, C=O), 1683 (m, C=O), 1155 (s, C-O), 749 (w, Ar), 698 (w); **m/z** (ESI$^+$) 504 ([M+Na]$^+$, 100%); HRMS found 504.1984, $C_{27}H_{31}NNaO_7$ requires 504.1993.

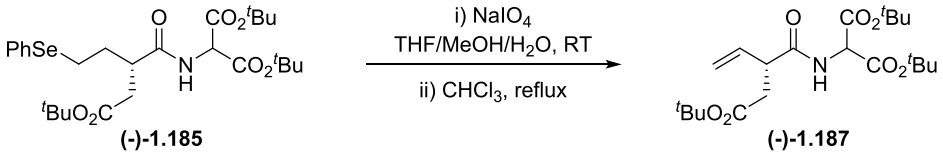
(*R*)-Di-*tert*-butyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate, (-)-1.185



The title compound was prepared from (*R*)-4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid **(-)-1.143** (3.17 g, 8.9 mmol) and di-*tert*-butyl 2-aminomalonate **1.182** (2.36 g, 10.2 mmol) according to general procedure 1. The crude product was purified by FC (1:7 EtOAc/PE). The title compound **(-)-1.185** was isolated as a colourless oil (4.45 g, 7.80 mmol, 88%). $\mathbf{R_f}$ 0.49 (1:7 EtOAc/PE); $[\alpha]_D^{20}$ -10.2 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.47 (m, 2H, Ar*H*), 7.27–7.20 (m, 3H, Ar*H*), 6.75 (1H, d, *J* = 6.6, N*H*), 4.88 (1H, d, *J* = 6.6, (CO)NC*H*), 3.01 (1H, ddd, *J* = 12.4, 8.6, 5.0, PhSeC*H*H'), 2.93–2.85 (2H, m, C*H*(CO)N and PhSeCH*H'*), 2.64 (1H, dd, *J* = 16.7, 8.9, C*H*H'$CO_2{}^t$Bu), 2.28 (1H, dd, *J* = 16.7, 5.6, CH*H'*$CO_2{}^t$Bu), 2.07 (1H, m, PhSeCH_2*C*HH'), 1.75 (1H, dddd, *J* = 13.7, 8.6, 7.8, 4.9, PhSeCH_2*C*HH'), 1.48 (9H, s, OC(CH_3)$_3$), 1.40 (9H, s, OC(CH_3)$_3$), 1.47 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.3 (*C*=O), 171.0 (*C*=O), 165.3 (*C*=O), 165.2 (*C*=O), 132.6 (*Ar*), 129.6 (*Ar*), 129.1 (*Ar*), 126.8 (*Ar*), 83.2 (O*C*$(CH_3)_3$), 83.0 (O*C*$(CH_3)_3$), 81.0 (O*C*$(CH_3)_3$), 58.0 (NH*C*H), 42.0 (*C*H(CO)NH), 37.8 (*C*$H_2CO_2{}^t$Bu), 32.4 (PhSeCH_2*C*H_2), 28.0 (OC(*C*H_3)$_3$), 27.8 (2 × OC(*C*H_3)$_3$), 24.8 (PhSe*C*H_2); $\boldsymbol{\nu_{max}}$ 2979 (w, C-H), 1749 (m, C=O), 1730 (s, C=O), 1680 (m, C=O), 1145 (s, C-O), 737 (w, Ar); **m/z** (ESI$^+$) 594 ([M+Na]$^+$, 20%); HRMS found 594.1935, $C_{27}H_{41}NNaO_7{}^{80}Se$ requires 594.1942.

The racemic title compound **(±)-1.185** was prepared with the same procedure using (±)-4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid **(±)-1.143** (10.3 g, 28.8 mmol) and di-*tert*-butyl 2-aminomalonate (7.32 g, 31.7 mmol), which gave the racemic title compound as a colourless oil (14.6 g, 25.6 mmol, 89%).

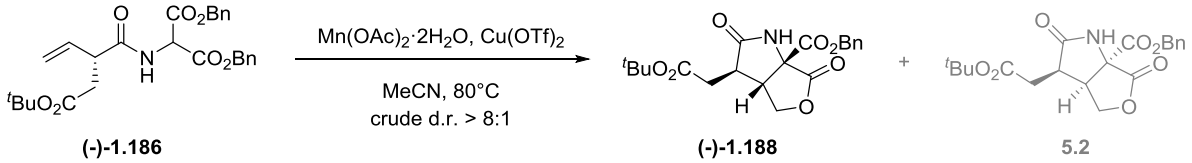
(*R*)-di-*tert*-Butyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate



To a solution of (*R*)-di-*tert*-butyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate **(-)-1.185** (295 mg, 0.520 mmol) and $NaHCO_3$ (218 mg, 2.60 mmol) in MeOH/H_2O/THF (1:1:1, 10 mL), was added $NaIO_4$ (556 mg, 2.60 mmol) portionwise over 3 min. The reaction mixture was stirred for 15 min. H_2O (20 mL) and DCM (20 mL) were added, this mixture was stirred for 5 min and was filtered through a Celite™ pad, which was eluted with DCM. The organic layer was separated and the aqueous layer was extracted with more DCM (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude selenoxide was dissolved in $CHCl_3$ (40 mL) and the solution was sparged with nitrogen before being heated under reflux (66 °C) for 45 min. The reaction mixture was cooled to RT, evaporated, and the residue was purified by FC (1:8 EtOAc/PE), which gave title compound **(-)-1.187** as colourless oil (248 mg, 0.515 mmol, 82%). *Characterisation is given with the alternative preparation (second generation synthesis).* For this batch: **e.e**. 82% (ChiralPak AD-H, 10% IPA in hexane, 0.40 mL/min; $\mathbf{t_{R\text{-}minor}}$ = 13.38 min, $\mathbf{t_{R\text{-}minor}}$ = 14.63 min).

The racemic title compound was also prepared on a larger scale: $NaIO_4$ (23.3 g) was added portionwise to a solution of (±)-di-*tert*-butyl 2-(4-(*tert*-butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanamido)malonate **(±)-1.185** (14.6 g, 25.3 mmol) and $NaHCO_3$ (10.6 g, 126 mmol) in MeOH/H_2O/THF (1:1:1, 375 mL) at RT. The mixture was stirred for 30 min and $CHCl_3$ (450 mL) was added. The mixture was filtered through Celite™, which was then eluted with $CHCl_3$ (100 mL). The mixture was washed with water (150 mL). The aqueous layer was extracted with more $CHCl_3$ (2 x 100 mL). The combined organic extract were dried (Na_2SO_4), filtered and heated under reflux (66 °C) for 3 h. The solvent was then evaporated and the residue was purified by FC (1:13 to 1:5 EtOAc/PE), which gave the racemic title compound **(±)-1.187** (10.0 g, 20.4 mmol, 81%).

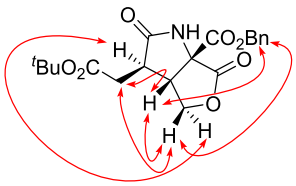
(+)-(3*R*,3a*R*,6a*S*)-Benzyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate, (-)-1.188



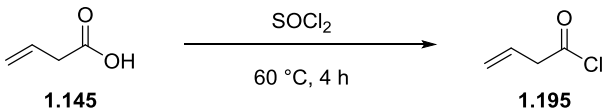
(-)-1.186 **(-)-1.188** 5.2

A solution of (*R*)-dibenzyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate **(-)-1.186** (189 mg, 0.547 mmol) in MeCN (12 + 2 mL) was added to $Mn(OAc)_3{\cdot}2H_2O$ (293 mg, 1.09 mmol) and $Cu(OTf)_2$ (198 mg, 0.547 mmol) under argon at 80 °C. The reaction mixture was stirred for 4 h and cooled to RT. The reaction mixture was plugged through a silica pad, which was eluted with EtOAc. The solvent was then evaporated and the residue was purified by FC (1:1 to 2:1 Et_2O/PE), which gave the title compound as a colourless oil (0.281 mmol, 88 mg, 51%). The minor diastereoisomer was isolated in a mixture of side products. Characterisation is given for the major diastereoisomer **(-)-1.188**. $\mathbf{R_f}$ 0.41 (2:1 Et_2O/PE); $[\alpha]_D^{20}$ +20.2 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.41–7.36 (3H, m, Ar*H*), 7.35–7.30 (2H, m, Ar*H*), 6.62 (1H, br, N*H*), 5.31 (1H, d, *J* = 12.0, C*H*H'Ph), 5.26 (1H, d, *J* = 12.0, CH*H'*Ph), 4.71 (1H, dd, *J* = 9.8, 7.0, CHC*H*H'O), 4.57 (1H, dd, *J* = 9.8, 2.0, CHCH*H'*O), 3.17 (1H, ddd, *J* = 7.0, 7.0, 2.0, C*H*CHH'O), 2.91 (1H, dd, *J* = 17.3, 3.2, CHC*H*H'$CO_2{}^t$Bu), 2.78 (1H, ddd, *J* = 10.1, 7.0, 3.2, C*H*$CH_2CO_2{}^t$Bu), 2.44 (1H, dd, *J* = 17.3, 10.1, CHCH*H'*$CO_2{}^t$Bu), 1.43 (s, 9H, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (126 MHz, $CDCl_3$) 174.8 (*C*=O), 171.3 (*C*=O), 170.4 (*C*=O), 166.9 (*C*=O), 134.0 (*Ar*), 129.0 (*Ar*), 128.9 (*Ar*), 128.3 (*Ar*), 81.9 (C_{quat}), 72.1 (CH_2O), 68.9 (CH_2Ph), 66.3 (C_{quat}), 46.7 (*C*HCH_2O), 43.7 (*C*H$CH_2CO_2{}^t$Bu), 35.9 ($CH_2CO_2{}^t$Bu), 28.0 (OC(CH_3)$_3$); $\boldsymbol{\nu_{max}}$ 2974 (w, C-H), 1784 (m, C=O), 1720 (s, C=O), 1155 (s, C-O), 747 (w, Ar); **m/z** (ESI^+) 412 ($[M+Na]^+$, 100%); HRMS found 412.1357, $C_{20}H_{23}NO_7$ $[M+Na]^+$ requires 412.1367.

Key nOe interactions in $CDCl_3$



But-3-enoyl chloride[169]

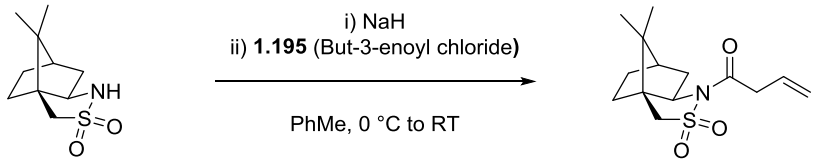


1.145 **1.195**

According to the procedure of Xu et al.,[169] a mixture of but-3-enoic acid **1.145** (4.30 mL, 50.0 mmol) and $SOCl_2$ (7.30 mL, 100 mmol) was heated at 60 °C for 4 h. The mixture was purified by fractional distillation, which gave the title compound **1.195** as a colourless oil (4.85 g, 46.6 mmol, 93%).

b.p. 50 °C (at 60 mmHg), lit.[170] 40 °C (at 50 mmHg); δ_H (400 MHz, $CDCl_3$) 5.91 (1H, ddd, J = 17.0, 10.2, 6.9, CH=CHH'), 5.32 (1H, dd, *J* = 10.2, 1.1, CH=CHH'), 5.28 (1H, d, *J* = 17.0, 1.1, CH=CHH'), 3.63 (2H, d, *J* = 6.9, CH_2(CO)); δ_C (100 MHz, $CDCl_3$) 171.9 (C=O), 127.8 ($CH=CH_2$), 121.2 ($CH=CH_2$), 51.0 (CH_2(CO)); ν_{max} 1796, (s, C=O), 990 (m), 736 (m). IR data is in accordance with the literature.[170]

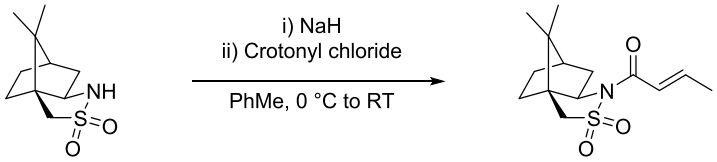
1-((3a*S*,6*R*,7a*R*)-8,8-Ddimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[*c*]isothiazol-1(4H)-yl)but-3-en-1-one,



(-)-1.198 **(-)-1.196**

According to the modified procedure of Liang *et al.*,[84] NaH (60% dispersion in mineral oil, 155 mg, 3.88 mmol) was added portionwise over 2 min to a vigorously stirred solution of (1*S*)-(-)-2,10-camphorsultam **(-)-1.198** (667 mg, 3.10 mmol) in toluene (15 mL) at 0 °C. The reaction was warmed to RT and stirred for 30 min. The mixture was then cooled to 0 °C and but-3-enoyl chloride **1.195** (0.460 mL, 5.80 mmol) in PhMe (3.0 mL) was added over 5 min. The reaction was then warmed to RT. After 2 hours stirring, the reaction was quenched by the slow addition of an aqueous solution of HCl (1.0 M, 30 mL). The mixture was extracted with EtOAc (2 x 25 mL), and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:7 to 1:3 EtOAc/PE), which gave the title compound **(-)-1.196** as a colourless oil (280 mg, 0.989 mmol, 32%), which crystallised upon storage at -20 °C. R_f 0.83 (3:7 EtOAc/PE); **m.p.** 70–73 °C, lit.[171] 67–69 °C; $[\alpha]_D^{20}$-105.2 (c = 1.00, $CHCl_3$), lit.[171] -105.9 (c = 0.51 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.95 (1H, dddd, *J* = 13.7, 12.0, 10.0, 6.9, C*H*=CHH'), 5.23 (1H, m, CH=C*H*H'), 5.19 (1H, m, CH*H'*), 3.87 (1H, dd, *J* = 7.8, 5.1, C*H*N), 3.51 (2H, C*HH'*(CO)), 3.50 (1H, d, *J* = 13.9, C*H*H'SO_2), 3.45 (1H, d, *J* = 13.9 CH*H'*SO_2), 2.18–2.09 (1H, m, NCHC*H*H'), 2.07 (1H, dd, *J* = 13.9, 7.8, NCHCH*H'*), 1.98–1.83 (2H, m, C*H*H'C*H*H'), 1.46–1.29 (3H, m, CH*H'*CH*H'* and $CHC_{quat}(CH_3)_2$), 1.15 (3H, s, CH_3), 0.97 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.9 (*C*=O), 129.6 (*C*H=CH_2), 119.4 (CH=*C*H_2), 65.4 (*C*HNH), 53.1 (CH_2SO_2), 48.6 (C_{quat}), 47.9 (C_{quat}), 44.8 ($CHC_{quat}(CH_3)_2$), 40.2 (CH_2(CO)), 38.5 (CH_2CHNH), 33.0 (CH_2CH_2), 26.6 (CH_2CH_2), 20.9 (CH_3), 20.0 (CH_3); ν_{max} 2960 (w, C-H), 1697 (s, C=O), 1329 (s), 1235 (m); **m/z** (ESI$^+$) 306.1 ([M+Na]$^+$, 100%); HRMS found 306.1141, $C_{14}H_{21}NNaO_3S$ requires 306.1134. The data is in accordance with the literature.[171]

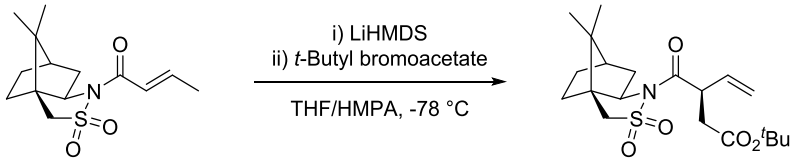
(*E*)-1-((3aS,6R)-8,8-Dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazol-1-yl)but-2-en-1-one, (-)-1.199



(-)-1.198 **(-)-1.199**

According to the modified procedure of Liang *et al.*,[84] NaH (60% dispersion in mineral oil, 3.36 g, 82.3 mmol) was added portionwise over 2 min to a vigorously stirred solution of (1*S*)-(−)-2,10-camphorsultam **(-)-1.198** (14.2 g, 65.9 mmol) in PhMe (350 mL) at 0 °C. The reaction was warmed to RT and stirred for 45 min. The mixture was then cooled to 0 °C and crotonyl chloride (7.9 mL, 82 mmol) was added over 15 min. The mixture was then warmed to RT and after 2 h stirring the reaction was quenched by slow addition of an aqueous solution HCl solution (1.0 M, 350 mL). The mixture was extracted with EtOAc (350 mL), and the organic layer was further washed with a saturated aqueous solution of $NaHCO_3$ (2 x 150 mL). The combined aqueous extracts were treated with several portions of Na_2CO_3 until gas evolution ceased. This solution was further extracted with EtOAc (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was recrystallised overnight at -20 °C from EtOAc/Hexane (1:5), which gave the title compound **(-)-1.199** as a white solid (14.1 g, 49.8 mmol, 76%). The mother liquor was concentrated under reduced pressure and was purified by FC (5:1 PE/EtOAc) to give another batch of white solid (1.15 g, 4.06 mmol, 6%). $\mathbf{R_f}$ 0.79 (7:3 EtOAc/PE); **m.p.** (recrystallised batch) 176−180 °C (lit. 180−183 °C) ; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -98.4 (c = 1.00, $CHCl_3$, lit.[84] +99.9, c = 1.00, $CHCl_3$, opposite enantiomer); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.09 (1H, dq, *J* = 14.5, 6.9, CH=C*H*-CH_3), 6.58 (1H, dd, *J* = 14.5, 1.3, C*H*=CH-CH_3), 3.93 (1H, dd, *J* = 7.6, 5.4, C*H*N), 3.51 (1H, d, *J* = 13.9, C*H*H'SO_2), 3.44 (1H, d, *J* = 13.9, CH*H*'SO_2), 2.17–2.10 (1H, m, C*H*H'CHN), 2.08 (1H, dd, *J* = 13.9, 7.6, CH*H*'CHN), 1.93 (3H, dd, *J* = 6.9, 1.3, CHCH_3), 1.91–1.84 (3H, m, C*H*$C_{quat}(CH_3)_2$ and C*H*H'CHH'C'$_{quat}$ and CHH'C*H*H'C'$_{quat}$), 1.46–1.31 (2H, m, CH*H*'CHH'C'$_{quat}$ and CHH'CH*H*'C'$_{quat}$), 1.17 (3H, s, C$H_3$$C_{quat}$), 0.97 (3H, s, C$H_3$'$C_{quat}$); $\boldsymbol{\delta_c}$ (126 MHz, $CDCl_3$) 164.1 (*C*=O), 146.2 (CH=*C*H-CH_3), 122.4 (*C*H=CH-CH_3), 65.2 (*C*-N), 53.3 (CH_2SO_2), 48.6 (C_{quat}), 47.9 (C_{quat}), 44.8 ($CHC_{quat}(CH_3)_2$), 38.6 (*C*H_2CHN), 33.0 (*C*$H_2$$CH_2$$C_{quat}$), 26.6 ($CH_2$*C*$H_2$$C_{quat}$), 20.9 (*C*$H_3$), 20.0 (*C*$H_3$), 18.5 (CH*C*$H_3$); **m/z** ($ESI^+$) 284 ($[M+H]^+$, 65%), 306 ($[M+Na]^+$, 100%). *Data are consistent with literature values*.[84]

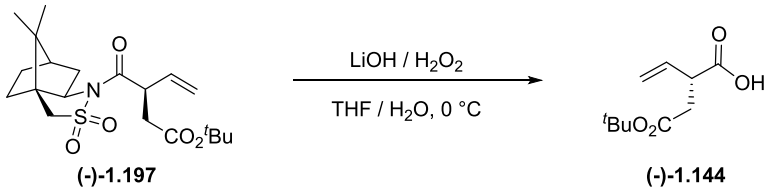
(3*S*)-*tert*-Butyl 3-((3aS,6R)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)pentanoate, (-)-1.197



(-)-1.199 **(-)-1.197**

According to the modified procedure of Oppolzer *et al.*,[82] a solution of (*E*)-1-((3aS,6R)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazol-1-yl)but-2-en-1-one **(-)-1.199** (13.5 g, 47.6 mmol) in THF (110 + 5 mL rinse) was added dropwise over 40 min to a mixture of LiHMDS in toluene (1.0 M, 72 mL, 72 mmol) and HMPA (25 mL) in THF (80 mL) at -78 °C. The mixture was stirred for 30 min and *tert*-butyl bromoacetate (27.9 g, 143 mmol) was added dropwise over 30 min. After 7 h stirring at -78 °C, the reaction mixture was quenched by slow addition of pH 2 sulfate buffer solution (350 mL), and was then warmed to RT. The mixture was extracted with EtOAc (600 mL). The organic layer was washed with water (500 mL) and brine (200 mL). The organic layer was then dried (Na_2SO_4), filtered and evaporated. The residual white solid was recrystallised from hexane; which gave the title compound **(-)-1.197** as a 95% pure by weight white solid (17.5 g, 41.9 mmol, 88%). Minor impurity is residual HMPA. A small amount of compound was re-purified by FC (6:1 EtOAc/PE) for analytical purposes. $\mathbf{R_f}$ 0.53 (6:1 EtOAc/PE); **m.p.** 128–135 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -63.0 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 5.90 (1H, ddd, *J* = 17.5, 10.3, 7.8, CHH'=C*H*), 5.27 (1H, d, *J* = 17.5, C*H*H'=CH), 5.21 (1H, d, *J* = 10.3, CH*H'*=CH), 4.07 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 3.90 (1H, dd, *J* = 7.9, 5.2, C*H*N), 3.51 (1H, d, *J* = 13.8, C*H*H'SO_2), 3.43 (1H, d, *J* = 13.8, CH*H'*SO_2), 2.86 (1H, dd, *J* = 15.0, 8.7, CHC*H*H'$CO_2{}^t$Bu), 2.50 (1H, dd, *J* = 15.0, 5.2, CHCH*H'*$CO_2{}^t$Bu), 2.22–2.14 (1H, m, C*H*H'CHN), 2.04 (1H, dd, *J* = 13.9, 7.9 CH*H'*CHN), 1.94–1.84 (3H, m, C*H*$C_{quat}(CH_3)_2$ and C*H*H'CHH'C'$_{quat}$ and CHH'C*H*H'C'$_{quat}$), 1.48–1.30 (11H, m, OC(CH_3)$_3$ and CH*H'*CHH'C'$_{quat}$ and CHH'CH*H'*C'$_{quat}$); $\boldsymbol{\delta_c}$ (100 MHz, $CDCl_3$) 172.0 (*C*=O), 170.1 (*C*=O), 133.8 (CH_2=*C*H), 118.5 (CH_2=C), 81.0 (*C*$(CH_3)_3$), 65.5 (*C*HN), 53.2 (CH_2SO_2), 48.6 (C_{quat}), 47.9 (C_{quat}), 45.7 (*C*H(CO)), 44.7 (*C*H$C_{quat}(CH_3)_2$), 39.0 ($CH_2CO_2{}^t$Bu), 38.2 (CH_2CHN), 33.0 ($CH_2CHCH_2SO_2$), 28.1 (OC(CH_3)$_3$), 26.6 ($CH_2CH_2C_{quat}$), 20.7 (CH_3), 20.1 (CH_3); $\boldsymbol{\nu_{max}}$ 2963 (w, C-H), 1729 (s, C=O), 1691 (s, C=O), 1331 (s, SO_2), 1216 (s, SO_2), 1154 (s); **m/z** (ESI^+) 398 ($[M+H]^+$, 20%), 420 ($[M+Na]^+$, 100%); HRMS found 420.1802, $C_{20}H_{31}NNaO_5S$ requires 420.1815.

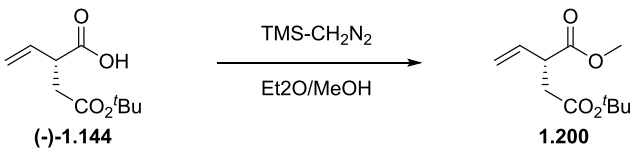
(*R*)-2-(2-(*tert*-Butoxy)-2-oxoethyl)but-3-enoic acid, (-)-1.144



(-)-1.197 (-)-1.144

A solution of LiOH·H_2O (1.85 g, 44.0 mmol) and aqueous H_2O_2 30% (8.8 mL, 88 mmol) in H_2O (35 mL) was added to (3*S*)-*tert*-butyl 3-((3aS,6R)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)pentanoate **(-)-1.197** (9.21 g, 22 mmol) in THF/H_2O (4:1, 165 mL) over 3 min at 0 °C. The reaction mixture was stirred for 10 min and an aqueous solution of $Na_2S_2O_8$ solution (2.4 M, 45 mL) was added over 3 min. The mixture was stirred at 0 °C for 3 min and then quenched by slow addition of pH 3 citric buffer (250 mL). The mixture was extracted with Et_2O (1 x 250 mL, 1 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was triturated with hexane (30 mL) for 10 min. The precipitated chiral auxiliary **(-)-1.198** was removed by filtration through cotton wool, and the solid was washed with more hexane (4 x 10 mL). The filtrate was evaporated under reduced pressure, which gave the title compound **(-)-1.144** as a 90% pure colourless oil (4.56 g, 20.5 mmol, 91%). Minor impurity is residual chiral auxiliary. A small amount of compound was re-purified by FC (1:6 EtOAc/PE) for analytical purposes. $\mathbf{R_f}$ is not given as compound streaks in solvent systems tested; $[\alpha]_D^{20}$ -32.5 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.87 (1H, ddd, *J* = 17.4, 10.2, 7.8, CHH'=C*H*), 5.24 (1H, d, *J* = 17.4 C*H*H'=CH), 5.21 (1H, d, *J* = 10.2, CH*H'*=CH), 3.50 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 2.76 (1H, dd, *J* = 16.7, 8.7, C*H*H'$CO_2{}^t$Bu), 2.50 (1H, dd, *J* = 16.7, 5.7, CH*H'*$CO_2{}^t$Bu), 1.43 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_c}$ (100 MHz, $CDCl_3$) 178.6 (*C*=O), 170.6 (*C*=O), 133.8 (CH_2=*C*H), 118.5 (*C*H_2=CH), 81.4 (C_{quat}), 45.6 (*C*HCH$_2CO_2{}^t$Bu), 37.0 (*C*$H_2CO_2{}^t$Bu), 28.1 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 2981 (w, C-H), 1731 (s, C=O), 1709 (s, C=O), 1369 (w), 1155 (s); **m/z** (ESI$^-$) 199 ([M-H]$^-$, 100%); HRMS found 199.0868, $C_{10}H_{15}O_4$ requires 199.0976.

4-(*tert*-Butyl) 1-methyl (*R*)-2-vinylsuccinate

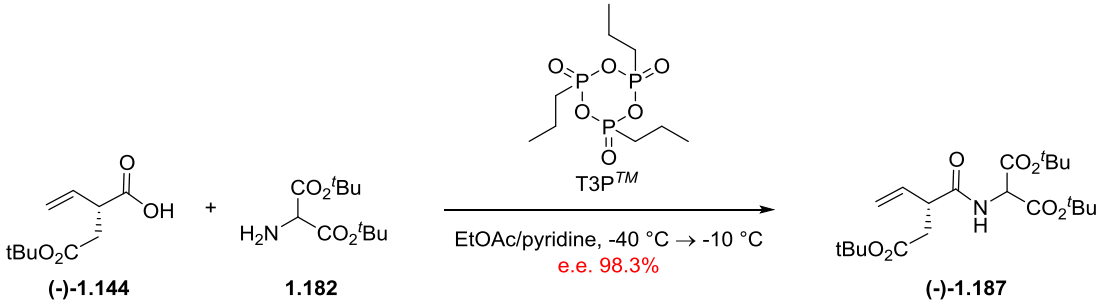


(-)-1.144 1.200

To a solution of crude (*R*)-2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enoic acid **(-)-1.144** (15.0 mg, 0.0750 mmol) in Et_2O/MeOH (4:1, 0.375 mL) at 0 °C was added TMS-CHN_2 in Et_2O (2.0 M, 57 µL, 0.114 mmol) dropwise. The mixture was stirred at RT for 15 min and 2 drops of AcOH were added. The solvent was evaporated and the residue was purified by FC (Et_2O/$PE_{30\text{-}40}$ 1:1), which gave the title compound

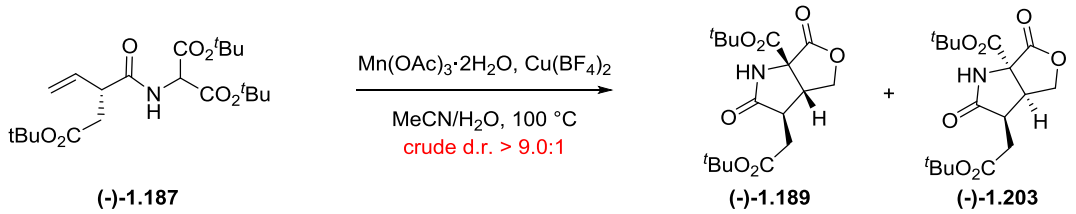
as a colourless oil (12.0 mg, 0.0560 mmol, 75%). *Characterisation for this compound is given with an alternative preparation.*

(*R*)-Di-*tert*-butyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate



According to the modified procedure of Dunetz *et al.*,[86] to a solution of (*R*)-2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enoic acid (4.40 g, 22.0 mmol) in EtOAc (21 mL) at -10 °C were successively added pyridine (9 mL) and di-*tert*-butyl 2-aminomalonate **1.182** (6.10 g, 26.4 mmol). The vigorously stirred mixture was then cooled to -40 °C and propane phosphonic acid anhydride (50% in EtOAc, 21 mL, 35 mmol) was added dropwise over 30 min. The reaction mixture was warmed to -10 °C over 6 h (+5 °C every 60 min). The reaction was stirred at this temperature for 30 min and was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL) and water (100 mL). The mixture was extracted with EtOAc (1 x 150 mL, 2 x 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:8 to 1:6 EtOAc/PE), which gave the title compound **(-)-1.187** as a colourless oil (6.05 g, 14.4 mmol, 65% over 2 steps). $\mathbf{R_f}$ 0.49 (1:6 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -38.5 (c = 1.00, $CHCl_3$); **e.e** 98.3% (ChiralPak AD-H, 10% IPA in hexane, 0.40 mL/min; $\mathbf{t_{R\text{-}minor}}$ 13.38 min, $\mathbf{t_{R\text{-}major}}$ = 14.63 min; HPLC traces are available in the appendix); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.67 (1H, d, *J* = 6.7, N*H*), 5.89 (1H, ddd, *J* = 17.2, 10.2, 7.0, C*H*=CHH'), 5.33 (1H, dd, *J* = 17.2, 1.0, CH=C*H*H'), 5.28 (1H, dd, *J* = 10.2, 1.0, CH=CH*H'*), 4.89 (1H, d, *J* = 6.7, (CO)NC*H*), 3.42 (1H, ddd, *J* = 7.0, 7.0, 7.0, C*H*(CO)N), 2.83 (1H, dd, *J* = 16.3, 7.0, C*H*H'$CO_2{}^t$Bu), 2.45 (1H, dd, *J* = 16.3, 7.0, CH*H'*$CO_2{}^t$Bu), 1.49 (9H, s, OC(CH_3)$_3$), 1.48 (9H, s, OC(CH_3)$_3$), 1.43 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.5 (*C*=O), 170.9 (*C*=O), 165.5 (*C*=O), 165.4 (*C*=O), 135.3 (CH_2=*C*H), 119.3 (*C*H_2=CH), 83.3 (O*C*(CH_3)$_3$), 83.3 (O*C*(CH_3)$_3$), 80.9 (O*C*(CH_3)$_3$), 58.0 (NCH), 47.1 (*C*H(CO)NH), 37.1 (*C*$H_2CO_2{}^t$Bu), 28.2 (OC(*C*H_3)$_3$), 27.9 (2 × OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 2980 (w, C-H), 1752 (m, C=O), 1733 (s, C=O), 1684 (m, C=O), 1394 (m), 1251 (m), 1149 (s, C-O), 845 (w); **m/z** (ESI^+) 436 ([M+Na]$^+$, 100%); HRMS found 436.2297, $C_{21}H_{35}NNaO_7$ requires 436.2306.

(3*R*,3a*R*,6a*S*)-*tert*-Butyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate, (-)-1.189

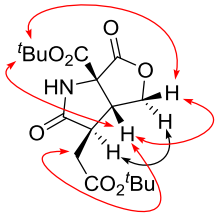


(-)-1.187 (-)-1.189 (-)-1.203

This first procedure was applied when the positive influence of water was discovered. The final optimised conditions are given at the end of this page. In an oil bath at 100 °C, a boiling solution of enamido malonate **(-)-1.187** in nitrogen sparged MeCN/H_2O (9:1, 53 mL) under argon was treated by simultaneous and quick addition of $Mn(OAc)_3{\cdot}2H_2O$ (11.5 g, 43.1 mmol) and $Cu(BF_4)_2{\cdot}xH_2O$ (1.49 g, 4.31 mmol if x = 6). The reaction mixture was stirred vigorously for 40 min at 100 °C and was then cooled to RT. The brown suspension was plugged through a one inch silica pad (rinsing flask with 3 x 10 mL of H_2O/EtOAc 1:1, all rinsing liquids were loaded on the pad). The pad was eluted with EtOAc, the solvent was evaporated and the residue was purified by FC (2:1 Et_2O/Pentane), which gave the title compound as a white solid (3.42 g, 9.62 mmol, 67%) and its minor diastereoisomer **(-)-1.203** (0.34 g, 0.95 mmol, 7%) contaminated by *exo*-alkene **1.205**. $\mathbf{R_f}$ 0.40 (Et_2O/$PE_{30\text{-}40}$ 2:1); $[\alpha]_D^{20}$ +17.8 (c = 1.00, $CHCl_3$); **m.p**. 147–151 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.68 (1H, s, NH), 4.69 (1H, dd, *J* = 9.6, 7.0, CHC*H*H'O), 4.58 (1H, dd, *J* = 9.6, 1.7, CHCH*H*'O), 3.12 (1H, ddd, *J* = 7.0, 7.0 1.7, C*H*CHH'O), 2.94 (1H, dd, *J* = 17.2, 3.2, C*H*H'$CO_2{}^t$Bu), 2.78 (1H, ddd, *J* = 10.4, 7.0, 3.2, C*H*CHH'$CO_2{}^t$Bu), 2.47 (1H, dd, *J* = 17.2, 10.4, CH*H*'$CO_2{}^t$Bu), 1.51 (9H, s, OC(C*H*$_3$)$_3$), 1.41 (9H, s, OC(*C*H_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.1 (*C*=O), 172.1 (*C*=O), 170.1 (*C*=O), 166.0 (*C*=O), 85.6 (C_{quat}), 81.9 (C_{quat}), 72.1 (CH_2O), 66.9 (C_{quat}), 47.1 (*C*HCH_2O), 44.0 (*C*$HCH_2CO_2{}^t$Bu), 36.2 ($CH_2CO_2{}^t$Bu), 28.2 (C(*C*H_3)$_3$), 27.9 (C(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 2980 (w, C-H), 1782 (m, C=O), 1717 (s, C=O), 1151 (s, C-O); **m/z** (ESI^+) 378 ($[M+Na]^+$, 100%); HRMS found 378.1512, $C_{17}H_{25}NNaO_7$ requires 378.1523.

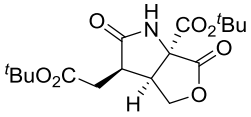
After complete optimisation of the H_2O/MeCN ratio, the reaction was performed according to the same procedure on a 82% e.e. batch of (*R*)-di-*tert*-butyl 2-(2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate **(-)-1.187** (4.06 g, 9.82 mmol) using $MnOAc_3{\cdot}2H_2O$ (7.89 g, 29.5 mmol) and $CuBF_4{\cdot}xH_2O$ (1.01 g, 0.295 mmol if x = 6) in MeCN/H_2O (50:3), which gave the major diastereoisomer **(-)-1.189** (2.48 g, 6.97 mmol, 71%) and the minor diastereoisomer **(-)-1.203** (325 mg, 0.914 mmol, 9%).

Key nOe interactions in $CDCl_3$



(-)-1.189

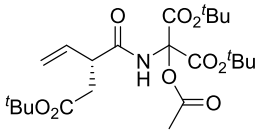
(3*R*,3a*S*,6a*R*)-*tert*-Butyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate, (-)-1.203



(-)-1.203

The minor diastereoisomer was isolated as a by-product during the optimisation of the of the manganese(III) and copper(II)-mediated cyclisation of **(-)-1.187**. $\mathbf{R_f}$ 0.44 (Et_2O/PE 2:1); $[\alpha]_D^{20}$ 64.1 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.06 (1H, br, N*H*), 4.55 (1H, dd, *J* = 9.8, 8.6, OC*H*H'), 4.17 (1H, dd, *J* = 9.8, 6.3, OCH*H'*), 3.70 (1H, ddd, *J* = 15.0, 8.7, 6.3, OCH_2CH), 3.10 (1H, m, $CHCH_2CO_2{}^tBu$), 2.90 (1H, dd, *J* = 17.7, 3.9, $CHH'CO_2{}^tBu$), 2.34 (1H, *J* = 11.7, $CHH'CO_2{}^tBu$), 1.50 (9H, s, $OC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.5 (C=O), 173.3 (C=O), 170.8 (C=O), 166.4 (C=O), 85.3 ($OC(CH_3)_3$), 82.0 ($OC(CH_3)_3$), 67.5 (CH_2), 67.0 (C_{quat}), 42.7 ($CHCH_2CO_2{}^tBu$), 39.8 (OCH_2CH), 32.3 ($CH_2CO_2{}^tBu$), 28.1 ($OC(CH_3)_3$), 27.9 ($OC(CH_3)_3$); $\boldsymbol{\nu_{max}}$ 2980 (w, C-H), 1784 (m, C=O), 1714 (s, C=O), 1244 (m, C=O), 1148 (s, C=O), 731 (m); **m/z** (ESI^+) 378 ($[M+Na]^+$, 100%); HRMS found 378.1512, $C_{17}H_{25}NNaO_7$ requires 378.1523.

di-*tert*-Butyl (*R*)-2-acetoxy-2-(2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate, (-)-1.204

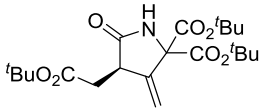


(-)-1.204

The compound was isolated as a by-product during the optimisation of the of the manganese(III) and copper(II)-mediated cyclisation of **(-)-1.204**. $\mathbf{R_f}$ 0.58 (Et_2O/PE 2:1); $[\alpha]_D^{20}$ -32.2 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.62 (1H, br, N*H*), 5.81 (1H, ddd, *J* = 17.1, 10.0, 8.3, C*H*=CHH'), 5.30 (1H, d, *J* = 17.1, CH=C*H*H'), 5.26 (1H, d, *J* = 10.0, CH=CH*H'*), 3.35 (1H, dd, *J* = 7.0, 7.0, $CHCHH'CO_2{}^tBu$), 2.79 (1H, dd, *J* = 16.6, 7.0, $CHH'CO_2{}^tBu$), 2.41 (1H, dd, *J* = 16.6, 7.0, $CHH'CO_2{}^tBu$), 2.14 (3H, s, $(CO)CH_3$), 1.46 (9H, s, $OC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 1.41 (9H, s, $OC(CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 170.9 (*C*=O), 170.6

(*C*=O), 169.9 (*C*=O), 162.3 (*C*=O), 162.0 (*C*=O), 134.7 (*C*H=CH$_2$), 119.5 (CH=*C*H$_2$), 84.4 (C_{quat}), 84.2 (C_{quat}), 80.9 (C_{quat}), 46.9 (*C*HCH$_2$CO2^{t}Bu), 36.9 (*C*H$_2$CO$_2$^{t}Bu), 28.2 (OC(*C*H$_3$)$_3$), 27.7 (2 x OC(*C*H$_3$)$_3$), 20.9 ((CO)*C*H$_3$); **ν_{max}** 2979 (w, C-H), 1758 (s, C=O), 1699 (m, C=O), 1248 (m), 1150 (s), 1058 (w), 842 (s); **m/z** (ESI$^+$) 494.3 ([M+Na]$^+$, 100%); HRMS found 494.2359, $C_{23}H_{37}NNaO_9$ requires 494.2361.

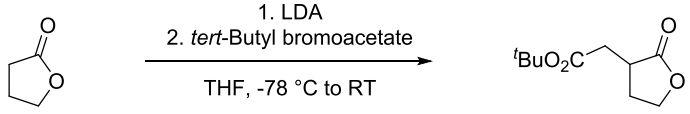
Di-*tert*-butyl (*R*)-4-(2-(*tert*-butoxy)-2-oxoethyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate, (-)-1.205



(-)-1.205

The compound was isolated as a by-product of the manganese(III) and copper(II)-mediated cyclisation of **(-)-1.205** as a colourless oil. **R_f** 0.46 (Et$_2$O/PE 2:1); **δ_H** (400 MHz, CDCl$_3$) 6.37 (1H, s, NH), 5.75 (1H, d, *J* = 2.6, =C*H*H'), 5.40 (1H, d, *J* = 2.6, =CH*H'*), 3.39 (1H, ddd, *J* = 7.1, 4.7, 2.6, C*H*CHH'CO$_2$^{t}Bu), 2.72 (1H, dd, *J* = 16.4, 4.7, C*H*H'CO$_2$^{t}Bu), 2.42 (1H, dd, *J* = 16.4, 7.1, CH*H'*CO$_2$^{t}Bu), 1.51–1.41 (27H, m, 3 x OC(C*H$_3$*)$_3$); **δ_C** (100 MHz, CDCl$_3$); 175.5 (*C*=O), 170.1 (*C*=O), 166.3 (*C*=O), 165.7 (*C*=O), 140.6 (*C*=CH$_2$), 114.6 (C=*C*H$_2$), 83.8 (C_{quat}), 83.8 (C_{quat}), 81.3 (C_{quat}), 71.8 (C_{quat}), 41.8 (*C*H), 36.3 (*C*H), 28.1 (2 x OC(*C*H$_3$)$_3$), 27.9 (OC(*C*H$_3$)$_3$); **ν_{max}** 2978 (w, C-H), 1714 (s, C=O), 1250 (m), 1145 (s), 845 (s); **m/z** (ESI$^+$) 434.3 ([M+Na]$^+$, 100%); HRMS found 434.2140, $C_{21}H_{33}NNaO_7$ requires 434.2149.

(±)-*tert*-Butyl 2-(2-oxotetrahydrofuran-3-yl)acetate, (±)-1.201

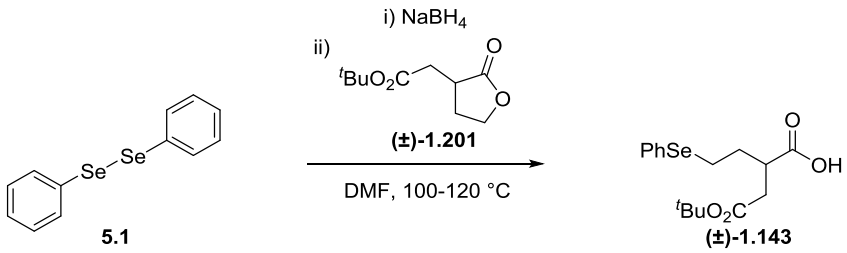


1.199 **(±)-1.201**

To a solution of DIPA (6.42 g, 58.1 mmol) in THF (50 mL) at -78 °C was added a solution of *n*-BuLi in hexanes (1.6 M, 43.6 mL, 69.7 mmol) dropwise over 15 min. The mixture was stirred for 20 min and *tert*-butyl bromoacetate (17.0 g, 87.2 mmol) was added dropwise over 10 min and the reaction was warmed to RT over 3 h. The reaction was quenched by addition of a saturated aqueous solution of NH$_4$Cl (30 mL) and H$_2$O (10 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and evaporated. The residue was purified by FC (1:1 Et$_2$O/PE$_{30\text{-}40}$), which gave the title compound **(±)-1.201** as a colourless oil (7.22 g, 36.1 mmol, 62%). **R_f** 0.40 (1:2 EtOAc/PE); **δ_H** (400 MHz, CDCl$_3$) 4.40 (1H, ddd, *J* = 9.0, 9.0, 2.2, OC*H*H'), 4.23 (1H, ddd, *J* = 10.3, 9.0, 6.7, OCH*H'*), 2.91 (1H, dddd, *J* = 11.1, 9.0, 9.0, 4.0, C*H*), 2.81 (1H, dd, 16.9, 4.0, ^{t}BuO$_2$CC*H*H'), 2.53 (1H, m, OCH$_2$C*H*H'), 2.47 (1H, dd, 16.9, 9.0, ^{t}BuO$_2$CCH*H'*), 2.05 (1H, m, OCH$_2$CH*H'*), 1.46 (9H, s, OC(C*H$_3$*)$_3$); **δ_C** (100 MHz, CDCl$_3$) 178.4 (*C*=O), 170.4 (*C*=O), 81.5 (O*C*(CH$_3$)), 66.6 (O*C*H$_2$), 36.1 (*C*H), 35.9

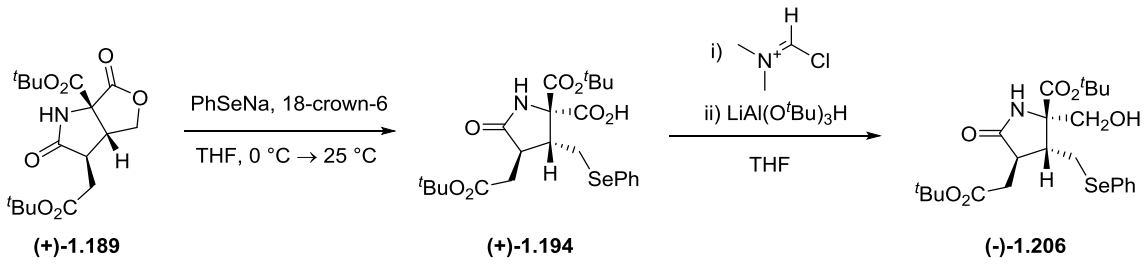
($CH_2CO_2{}^tBu$), 28.6 (OCH_2CH_2), 28.1 ($OC(CH_3)$); **ν_{max}** 2979 (w, C-H), 1769 (s, C=O), 1724 (s, C=O), 1368 (m), 1146 (s), 1023 (m); **m/z** (ESI^+) 223 ($[M+Na]^+$, 100%); HRMS found 223.0938, $C_{10}H_{16}NaO_4$ requires 223.0941.

(±)-4-(*tert*-Butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid, (±)-1.143



To a solution of $(PhSe)_2$ (6.76 g, 21.6 mmol) in degassed DMF (140 mL) was added $NaBH_4$ (1.90 g, 50.5 mmol) in one portion. The mixture was heated at 100 °C for 10 min under argon. A solution of (±)-*tert*-butyl 2-(2-oxotetrahydrofuran-3-yl)acetate **(±)-1.201** (7.22 g, 36.1 mmol) in DMF (30 mL) was added at this temperature. The reaction was stirred for 3 h at 120 °C and cooled to RT. An aqueous solution of pH 2 sulfate buffer (125 mL) and water (125 mL) were successively added. The mixture was extracted with EtOAc (1 x 250 mL, 2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:13 EtOAc/PE until all bright yellow $(PhSe)_2$ ran out of the column, then 1:1 EtOAc/PE), which gave the title compound **(±)-1.143** as a colourless oil containing 18% DMF (12.7 g, 35.5 mmol, 81%). *Characterisation is given for the enantioenriched form of the title compound.*

(2*S*,3*R*,4*R*)-*tert*-Butyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate



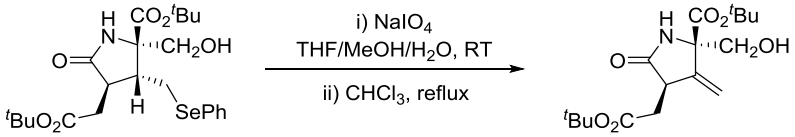
According to the modified procedure of Eustache *et al.*,[81] NaH (60% dispersion in oil, 811 mg, 20.2 mmol) was added to a solution of $(PhSe)_2$ (3.16 g, 10.1 mmol) in degassed THF (16 mL) under argon at RT. The mixture was stirred vigorously stirred for 90 min at 65 °C and was cooled to 0 °C. A solution of (3*R*,3a*R*,6a*S*)-*tert*-butyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate **(+)-1.189** (3.00 g, 8.45 mmol) and 18-crown-6 (558 mg, 2.11 mmol) in THF (25 + 3 mL) was added over 1 min. The reaction mixture was stirred under argon for 3 h at RT. It was

then quenched by successive addition of MeOH (5 mL) and H_2O (5 mL). DCM (150 mL) was added and the mixture was extracted with aqueous NaOH (0.1 M, 1 x 150 mL and 2 x 75 mL). The combined aqueous extracts were slowly acidified at 0 °C with pH 2 sulfate buffer solution (200 mL). The acidified aqueous layer was then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated, which gave the crude carboxylic acid **(+)-1.194** (4.87 g) as a white solid; $\mathbf{R_f}$ 0.73 (1:5:40 AcOH/MeOH/EtOAc); **m.p**. 152–158 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +1.6 (c = 1.00, MeOH); $\boldsymbol{\delta_H}$ (400 MHz, MeOD-d_4) 7.56 (2H, dd, *J* = 8.0, 1.3, ArH), 7.31–7.17 (3H, m, Ar*H*), 3.72 (1H, dd, *J* = 12.3, 2.1, C*H*H'Se), 3.10–2.98 (1H, m, C*H*CHH'Se), 2.95–2.83 (2H, m, CH*H'*Se and C*H*H'$CO_2{}^t$Bu), 2.76 (1H, dd, *J* = 17.2, 4.6, CH*H'*$CO_2{}^t$Bu), 2.73–2.66 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 1.46 (9H, s, OC(CH_3)$_3$), 1.33 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, MeOD-d_4) 179.7 (*C*=O), 172.2 (2 x *C*=O), 171.4 (*C*=O), 133.1 (*Ar*), 131.2 (*Ar*), 130.2 (*Ar*), 127.8 (*Ar*), 83.0 (*C*$(CH_3)_3$), 82.0 (*C*$(CH_3)_3$), 74.6 (C_{quat}), 46.2 (*C*$H_2CO_2{}^t$Bu), 44.2 (*C*H_2Se), 36.6 (*C*$H_2CO_2{}^t$Bu), 29.7 (*C*H_2Se), 28.3 (C(*C*$H_3)_3$), 28.2 (C(*C*$H_3)_3$); $\boldsymbol{\nu_{max}}$ 3283 (br, O-H), 2979 (w, C-H), 1723 (s, C=O), 1695 (s, C=O), 1618 (s, C=O), 1368 (m), 1155 (s), 735 (w); HRMS (FI and ESI^-) showed no detectable ionisation.

To a solution of DMF (1.31 mL, 16.9 mmol) in dry DCM (65 mL) at 0 °C was added oxalyl chloride (4.6 mL, 51 mmol) over 5 min. The reaction was stirred for 30 minutes at RT and all volatiles were removed under reduced pressure. The residual white salt was dried under high vacuum for a further 20 min before being re-dissolved in THF (65 mL) and MeCN (45 mL). A solution of the crude carboxylic acid **(+)-1.194** (4.87 g) in THF (40 + 10 mL) was then added over 10 min at 0 °C. The reaction was stirred at 0 °C for 30 minutes and then cooled to -78 °C. $LiAl(O^tBu)_3H$ (17.2 g, 67.6 mmol) in THF (115 mL) was added via cannula over 15 min. The reaction mixture was stirred for 10 min at -78 °C and then allowed to warm to RT. After 90 min, the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl (75 mL), water (75 mL) and a saturated aqueous solution of Rochelle's salt (300 mL). After 3 h stirring, the mixture was extracted with EtOAc (1 x 200 mL, 2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (EtOAc), which gave the title compound **(-)-1.206** as a colourless solid (3.40 g, 6.82 mmol, 81% over 2 steps). $\mathbf{R_f}$ 0.66 (EtOAc); **m.p.** 30–35 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -59.2 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.54–7.50 (2H, m, Ar*H*), 7.28–7.22 (3H, m, Ar*H*), 7.11 (1H, s, N*H*), 3.90 (1H, s, O*H*) 3.89 (1H, dd, *J* = 17.6, 7.6, C*H*H'OH), 3.81 (1H, m, CH*H'*OH), 3.52 (1H, dd, *J* = 12.3, 4.3, C*H*H'Se), 3.14 (1H, dd, *J* = 12.3, 10.2, CH*H'*Se), 2.89 (1H, dd, *J* = 16.2, 4.1, C*H*H'$CO_2{}^t$Bu), 2.80 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 2.76 (1H, dd, *J* = 16.2, 5.0, CH*H'*$CO_2{}^t$Bu), 2.67 (1H, td, *J* = 10.2, 4.3, C*H*CHH'Se); $\boldsymbol{\delta_c}$ (126 MHz, $CDCl_3$) 177.8 (*C*=O), 170.9 (*C*=O), 170.6 (*C*=O), 130.0 (*Ar*), 129.7 (*Ar*), 129.3 (*Ar*), 127.3 (*Ar*), 83.0 (O*C*$(CH_3)_3$), 81.0 (O*C*$(CH_3)_3$), 68.4 (C_{quat}), 64.2 (*C*H_2OH), 45.4 (*C*H), 45.2 (*C*H), 36.1 (*C*$H_2CO_2{}^t$Bu), 28.2 (OC(*C*$H_3)_3$), 27.9 (OC(*C*$H_3)_3$), 27.2 (*C*H_2Se); $\boldsymbol{\nu_{max}}$ 3356 (br, O-H), 2979 (w, C-H), 1767 (m, C=O), 1724 (s, C=O), 1700

(s, C=O), 1369 (w), 1154 (s), 739 (w); **m/z** (ESI$^+$) 522.1 ([M+Na]$^+$, 100%); HRMS found 522.1358, $C_{23}H_{33}NNaO_6{}^{80}Se$ requires 522.1367.

(2*S*,4*R*)-*tert*-Butyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate, (-)-1.210



(-)-1.206 **(-)-1.210**

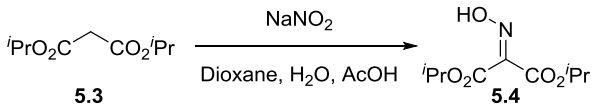
According to the modified procedure of Kocienski *et al.*,[74] $NaIO_4$ (7.92 g, 31.2 mmol) was added portionwise over 3 min to a mixture of (2*S*,3*R*,4*R*)-*tert*-butyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate **(-)-1.206** (3.40 g, 6.23 mmol) and $NaHCO_3$ (2.62 g, 31.2 mmol) in MeOH/H_2O/THF (1:1:1, 135 mL) at 25 °C. The reaction mixture was stirred under air at 25 °C for 45 min. H_2O (150 mL) and $CHCl_3$ (150 mL) were then added and stirring was continued for 5 min. The whole mixture was filtered through Celite,^{TM} and the Celite^{TM} pad was eluted with $CHCl_3$ (2 x 35 mL). The layers were separated and the aqueous phase was re-extracted with $CHCl_3$ (2 x 70 mL). The combined organic extracts were dried (Na_2SO_4), filtered, sparged with argon (5 min) and heated under reflux at 75 °C for 60 min. The mixture was cooled to RT, concentrated under reduced pressure and the residue was purified by FC (1:1 EtOAc/PE 3 CV, then 1:50 MeOH/EtOAc 4 CV), which gave the title compound **(-)-1.210** as a white solid (2.13 g, 6.23 mmol, 100%). $\mathbf{R_f}$ 0.60 (EtOAc); **m.p.** 158–167 °C; $[\alpha]_D^{20}$-32.5 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.51 (1H, br, N*H*), 5.46 (1H, dd, *J* = 3.0, 0.5, CH*H'*=C), 5.24 (1H, dd, *J* = 2.3, 0.5, C*H*H'=C), 4.09 (1H, d, *J* = 11.1, C*H*H'OH), 3.64 (1H, d, *J* = 11.1, CH*H'*OH), 3.41 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 2.82 (1H, dd, *J* = 16.7, 4.6, C*H*H'$CO_2{}^t$Bu), 2.57 (1H, dd, *J* = 16.7, 8.1, CH*H'*$CO_2{}^t$Bu), 1.49 (9H, s, OC(CH_3)$_3$), 1.43 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$) 176.9 (*C*=O), 170.5 (*C*=O), 169.4 (*C*=O), 144.1 (CH_2=*C*), 111.3 (*C*H_2=C), 83.1 (*C*$(CH_3)_3$), 81.3 (*C*$(CH_3)_3$), 71.0 (C_{quat}), 68.7 (*C*H_2OH), 42.6 (*C*H), 36.8 (*C*$H_2CO_2{}^t$Bu), 28.1 (C(*C*H_3)$_3$), 27.9 (C(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 3339 (br, O-H), 2978 (w, C-H), 1725 (s, C=O), 1710 (s, C=O), 1660 (m, C=O), 1368 (m), 1152(s), 845 (w); **m/z** (ESI$^+$) 364 ([M+Na]$^+$, 100%); HRMS found 364.1727, $C_{17}H_{27}NNaO_6$ requires 364.1731.

(2*S*,4*R*)-4-(carboxymethyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylic acid, (-)-1.211



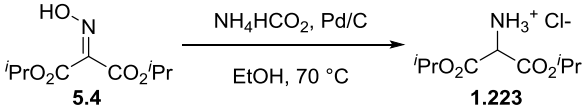
To a solution of (2*S*,4*R*)-*tert*-butyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate **(-)-1.210** (102 mg, 0.300 mmol) in DCM (1.00 mL) at 0 °C, was added TFA (1.00 mL) over 5 min. The reaction mixture was stirred for 15 h at RT and the solvent was evaporated. The residue was co-evaporated with toluene (3 x 3 mL), which gave the title compound **(-)-1.211** as a white solid (70.0 mg, 0.300 mmol, quant.). $\mathbf{R_f}$ not measure as compounds streaked in tested solvent system; **m.p.** 28–32 °C; $[\alpha]_D^{20}$-3.7 (c = 1.00, MeOH); $\mathbf{\delta_H}$ (400 MHz, MeOD-d_4) 5.47 (1H, s, C_{quat}=C*H*H'), 5.24 (1H, s, C_{quat}=CH*H'*), 3.91 (1H, d, *J* = 11.1, C*H*H'OH), 3.69 (1H, d, *J* = 11.1, CH*H'*OH), 3.39 (1H, m, C*H*(CO)), 2.77 (1H, dd, *J* = 16.3, 3.9, C*H*H'$CO_2{}^t$Bu), 2.56 (1H, dd, *J* = 16.3, 7.3, CH*H'*$CO_2{}^t$Bu); $\mathbf{\delta_c}$ (100 MHz, MeOD-d_4) 179.0 (*C*=O), 175.3 (*C*=O), 175.1 (*C*=O), 146.9 (C_{quat}=CH_2), 111.0 (C_{quat}=*C*H_2), 68.9 (*C*H_2OH), 43.3 (*C*H$CH_2CO_2{}^t$Bu), 36.5 (*C*$H_2CO_2{}^t$Bu); $\mathbf{\nu_{max}}$ 3225 (br, O-H), 1706 (s, C=O), 1654 (m, C=O), 1406 (w) 1229 (m).

Diisopropyl 2-(hydroxyimino)malonate, 5.4



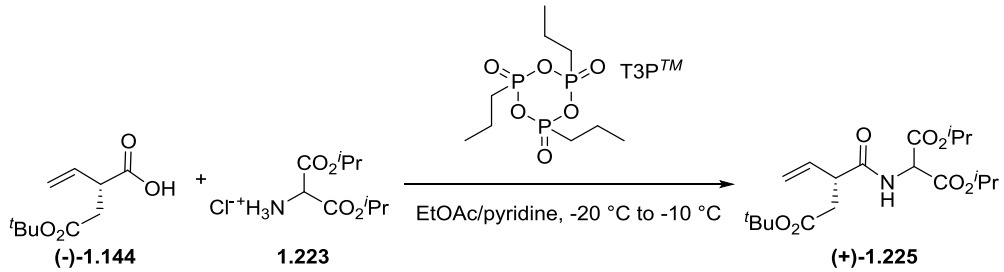
To a solution of diisopropyl malonate (10.0 g, 53.2 mmol) in dioxane (100 mL) at RT were successively added H_2O (21 mL), AcOH (14 mL) and $NaNO_2$ (12.2 g, 177 mmol). The reaction mixture was heated at 60 °C for 150 min and more $NaNO_2$ (12.2, 177 mmol) was added at RT. The mixture was further heated for 60 min at 60 °C and a third portion of $NaNO_2$ (12.2 g, 177 mmol) was added. The mixture was heated again (60 °C, 60 min), cooled to RT and diluted with Et_2O (350 mL), and washed with water (350 mL) and a saturated aqueous solution of $NaHCO_3$ (2 x 350 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated, which gave the crude title compound as a yellow oil (11.5 g, 53.2 mmol, quant.). $\mathbf{R_f}$ 0.44 (1:1, Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 10.47–10.31 (1H, br, O-H), 5.26 (1H, sept, *J* = 6.1, C*H*), 5.18 (1H, sept, *J* = 6.4, C*H*), 1.34 (6H, d, *J* = 6.1 CH(CH_3)$_2$), 1.31 (6H, d, *J* = 6.4, CH(CH_3)$_2$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 160.4 (*C*=O), 159.6 (*C*=O), 144.8 (*C*=N), 70.8 (*C*H), 67.2 (*C*H), 21.7 (2 x (CH_3)$_2$); $\mathbf{\nu_{max}}$ 3338 (br, O-H), 2958 (w, C-H), 1736 (s, C=O), 1719 (s, C=O), 1183 (s), 1084 (s), 1011 (s); **m/z** (ESI$^+$) 240.1 ([M+Na]$^+$, 100%); HRMS found 240.0843, $C_9H_{15}NNaO_5$ requires 240.0842.

Diisopropyl aminomalonate hydrochloride, 1.223



To a nitrogen purged solution of the crude diisopropyl 2-(hydroxyimino)malonate **5.4** (11.5 g, 53.2 mmol) and ammonium formate (33.0 g, 533 mmol) in EtOH (180 mL) was added Pd/C 10% (1.15 g). The reaction mixture was then heated at 70 °C for 45 min and cooled to RT. The mixture was then filtered through Celite^{TM} and evaporated. The residue was dissolved in Et_2O (350 mL) and the solution was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and sparged with dry HCl for one hour. The white precipitate was filtered and washed with Et_2O (25 mL) and dried *in vacuo*, which gave the title compound **1.223** as a white solid (6.80 g, 23.4 mmol, 53%). $\mathbf{R_f}$ 0.21 (free amine, 2:3 Et_2O/PE); **m.p.** decomposed at T > 140 °C; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 9.35–9.05 (3H, br, NH_3Cl), 5.02 (2H, sept, J = 6.0, CHCH$_3$), 4.88 (1H, s, NCH), 1.25 (6H, d, J = 6.0, 2 x CH$_3$), 1.21 (6H, J = 6.0, 2 x CH$_3$); $\boldsymbol{\delta_C}$ (100 MHz, DMSO-d_6) 164.2 (2 x C=O), 71.8 (2 x CH(CH$_3$)$_2$), 55.7 (NCH), 22.1 (2 x CH$_3$), 22.0 (2 x CH$_3$); $\boldsymbol{\nu_{max}}$ 2983 (w, C-H), 1732 (s, C=O), 1260 (m), 1175 (s), 1101 (s), 979 (w); **m/z** (ESI$^+$) 204.1 ([M+Na]$^+$, 100%); HRMS found 204.12288, $C_9H_{18}NO_4$ requires 204.1230.

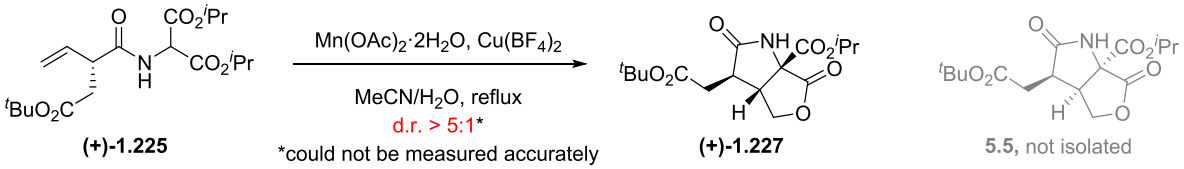
Diethyl (*R*)-2-(2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate, (+)-1.225



According to the modified procedure of Dunetz *et al.,*[86] T3P™ (50% in EtOAc, 4.78 mL, 8.04 mmol) was added dropwise over 15 min to a mixture of diisopropyl aminomalonate hydrochloride **1.223** (1.05 g, 4.42 mmol) and (*R*)-2-(2-(*tert*-Butoxy)-2-oxoethyl)but-3-enoic acid (804 mg, 4.02 mmol) in EtOAc (4.8 mL) and pyridine (1.60 mL, 20.2 mmol) keeping the internal temperature below -20 °C. The reaction mixture was warmed to -10 °C over 1 h and was stirred at this temperature for 2 h. An aqueous solution of pH 2 sulfate buffer (20 mL) was then added and the temperature was raised to RT. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:7 EtOAc/PE), which gave the title compound **(+)-1.225** as a colourless oil (821 mg, 2.13 mmol, 53%). $\mathbf{R_f}$ 0.47 (1:7 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +15.0 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.73 (1H, J = 6.6, NHCH), 5.86

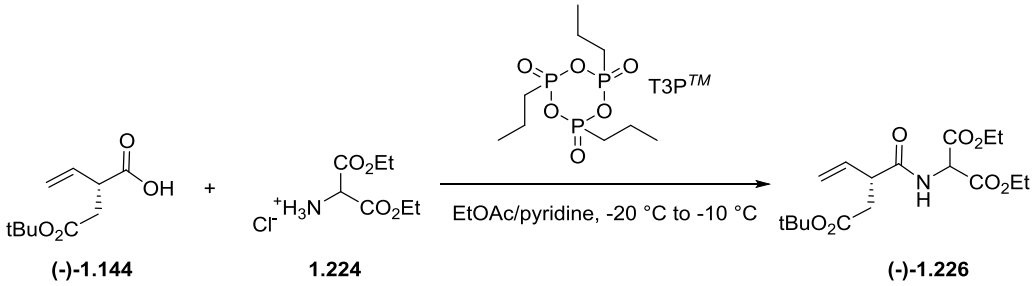
(1H, ddd, *J* = 17.2, 10.3, 8.6, C*H*=CHH'), 5.30 (1H, d, *J* = 17.2, CH=C*H*H'), 5.25 (1H, d, *J* = 10.3, CH=CH*H'*), 5.13–5.02 (2H, m, 2 x C*H*(CH_3)$_2$), 5.01 (1H, d, *J* = 6.60, NHC*H*), 3.42 (1H, m, C*H*CHH'$CO_2{}^t$Bu), 2.80 (1H, dd, *J* = 16.4, 7.3, C*H*H'$CO_2{}^t$Bu), 2.43 (1H, dd, *J* = 16.4, 7.1, CH*H'*$CO_2{}^t$Bu), 1.41 (9H, s, OC(CH_3)$_3$), 1.28 (3H, d, *J* = 6.4, CHCH_3), 1.27 (3H, d, *J* = 6.4, CHCH_3), 1.24 (3H, d, *J* = 6.1, CHCH_3), 1.23 (3H, d, *J* = 6.1, CHCH_3); **δ$_C$** (100 MHz, $CDCl_3$) 171.7 (C=O), 170.9 (C=O), 165.8 (2 x C=O), 135.1 (*C*H=CH_2), 119.3 (CH=*C*H_2), 80.9 (*C*$_{quat}$), 70.5 (2 x O*C*H(CH_3)$_2$), 57.0 (*C*HNH), 47.0 (*C*HCHH'), 37.1 (*C*$H_2CO_2{}^t$Bu), 28.1 (OC(*C*H_3)$_3$), 21.6 (2 x *C*H_3), 21.5 (2 x *C*H_3); **ν$_{max}$** 2982 (w, C-H), 1731 (s, C=O), 1684 (m, C=O), 1506 (w), 1368 (w), 1244 (m), 1153 (s), 1101 (s), 912 (w); **m/z** (ESI$^+$) 408.2 ([M+Na]$^+$, 100%); HRMS found 408.1979, $C_{19}H_{31}NNaO_7$ requires 408.1993.

(+)-Isopropyl (3*R*,3a*R*,6a*S*)-3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxotetrahydro-1*H*-furo[3,4-*b*]pyrrole-6a(6*H*)-carboxylate, (+)-1.227



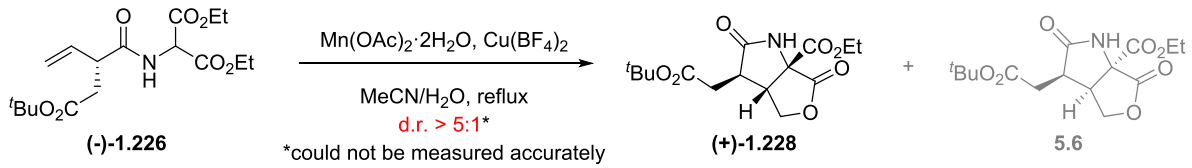
To a boiling solution of diethyl (*R*)-2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate **(+)-1.225** (802 mg, 2.08 mmol) in nitrogen sparged MeCN/H_2O (9:1, 8 mL) under argon, were added simultaneously and quickly $Mn(OAc)_3{\cdot}2H_2O$ (1.67 g, 6.24 mmol) and $Cu(BF_4){\cdot}xH_2O$ (251 mg, 0.624 mmol, if x = 6). The reaction mixture was vigorously stirred under reflux for 2 h and was then cooled to RT. An aqueous solution of pH 2 sulfate buffer was added (15 mL), and stirring was maintained for 15 min. The mixture was extracted with EtOAc (2 x 15 mL). The reaction vessel was rinsed by simultaneously stirring more aqueous pH 2 sulfate buffer solution (15 mL) and EtOAc (15 mL). The combined organic extracts and organic rinsing solution were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (Et_2O/Pentane 2:1 to 7:3), which gave the title major diastereoisomer **(+)-1.227** as a colourless oil (421 mg, 1.23 mmol, 59%). **R$_f$** 0.47 (7:3 Et_2O/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ +12.9 (c = 1.00, $CHCl_3$); **δ$_H$** (400 MHz, $CDCl_3$) 6.80–6.72 (1H, br, N*H*), 5.16 (1H, sept, *J* = 6.1, C*H*(CH_3)$_2$), 4.73 (1H, dd, *J* = 9.5, 7.0, (CO)OC*H*H'), 4.60 (1H, dd, *J* = 9.5, 2.0, (CO)OCH*H'*), 3.16 (1H, ddd, *J* = 7.0, 7.0, 2.0, (CO)OCHH'C*H*), 2.94 (1H, dd, *J* = 17.4, 3.3, ^{t}BuO(CO)C*H*H'), 2.80 (1H, ddd, *J* = 10.0, 7.0, 3.3, N(CO)C*H*), 2.46 (1H, dd, *J* = 17.4, 10.0, ^{t}BuO(CO)CH*H'*), 1.44 (9H, s, OC(CH_3)$_3$), 1.32 (3H, d, *J* = 6.1, CHCH_3), 1.30 (3H, d, *J* = 6.1, CHCH_3); **δ$_C$** (100 MHz, $CDCl_3$) 175.0 (*C*=O), 171.8 (*C*=O), 170.7 (*C*=O), 168.7 (*C*=O), 82.0 (*C*$_{quat}$), 72.2 ((CO)O*C*H_2), 72.0 (O*C*H(CH_3)$_2$), 66.5 (*C*$_{quat}$), 47.0 ((CO)OCH_2*C*H), 43.9 (N(CO)*C*H), 36.2 (^{t}BuO(CO)*C*H_2), 28.2 (OC(*C*H_3)$_3$), 21.7 (CH*C*H_3), 21.6 (CH*C*H_3); **ν$_{max}$** 2982 (w, C-H), 1784 (m, C=O), 1719 (s, C=O), 1274 (w), 1155 (s), 1104 (w), 1017 (w); **m/z** (ESI$^+$) 364.2 ([M+Na]$^+$, 100%); HRMS found 364.1355, $C_{16}H_{23}NNaO_7$ requires 364.1367.

Diethyl (*R*)-2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate, (-)-1.226



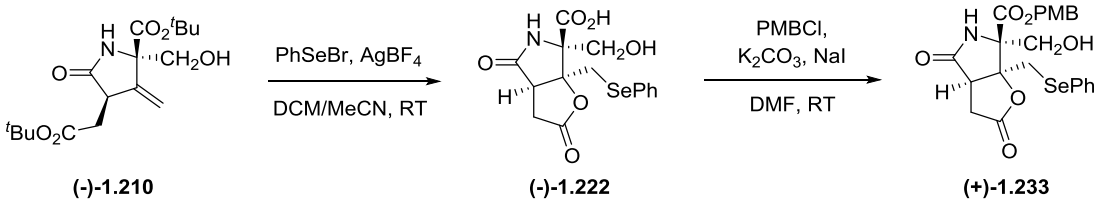
According to the modified procedure of Dunetz *et al.,*[86] T3P™ (50% in EtOAc, 3.65 mL, 6.14 mmol) was added dropwise over 15 min to a mixture of diethyl aminomalonate hydrochloride **1.224** (715 mg, 3.38 mmol), pyridine (1.24 mL, 15.4 mmol) and (*R*)-2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enoic acid **(-)-1.144** (615 mg, 3.07 mmol) in EtOAc (3.0 mL) keeping the internal temperature below -20 °C. The reaction mixture was warmed up to -10 °C over 1 h and was stirred at this temperature for 30 min. An aqueous solution of pH 2 sulfate buffer (20 mL) was then added and the temperature was raised to RT. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:4 EtOAc/PE), which gave the title compound **(-)-1.226** as a colourless oil (632 mg, 1.77 mmol, 58%). $\mathbf{R_f}$ 0.44 (1:4 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -42.3 (c = 1.00, $CHCl_3$) (the enantiomeric excess was not measured for this substrate); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.76 (1H, d, *J* = 6.7, N*H*), 5.87 (1H, ddd, *J* = 17.1, 10.1, 8.6, C*H*=CHH'), 5.31 (1H, dt, *J* = 17.1, 1.1, CH=C*H*H'), 5.26 (1H, d, *J* = 10.1, CH=CH*H'*), 5.10 (1H, d, *J* = 6.7, C*H*NH), 4.33–4.17 (4H, m, 2 x $CO_2CH_2CH_3$), 3.43 (1H, dd, *J* = 7.0, 7.0, C*H*(CO)NH), 2.80 (1H, dd, *J* = 16.5, 7.0, C*H*H'$CO_2{}^t$Bu), 2.44 (1H, dd, *J* = 16.5, 7.0, CH*H*'$CO_2{}^t$Bu), 1.42 (9H, s, OC(CH_3)$_3$), 1.28 (6H, dd, *J* = 7.1, 3.2, 2 x $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.9 (*C*=O), 170.9 (*C*=O), 166.2 (2 x *C*=O), 135.1 (*C*H=CH_2), 119.3 (CH=*C*H_2), 81.0 (C_{quat}), 62.7 (1 x $CO_2CH_2CH_3$), 62.7 (1 x $CO_2CH_2CH_3$), 56.7 (*C*HNH), 47.0 (*C*H(CO)NH), 37.1 ($CH_2CO_2{}^t$Bu), 28.2 OC(CH_3)$_3$), 14.1 (2 x $CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ 3341 (br and w, N-H), 2981 (w, C-H), 1732 (s, C=O), 1683 (m, C=O), 1154 (m); **m/z** (ESI^+) 380 ($[M+Na]^+$, 100%); HRMS found 380.1680, $C_{17}H_{27}NNaO_7$ requires 380.1680.

Ethyl (3*R*,3a*R*,6a*R*)-3-(2-(*tert*-butoxy)-2-oxoethyl)-2,6-dioxotetrahydro-1H-furo[3,4-*b*]pyrrole-6a(6*H*)-carboxylate, (+)-1.228



To a vigorously stirred boiling solution of diethyl (*R*)-2-(2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido)malonate **(-)-1.226** (615 mg, 1.72 mmol) in MeCN/H_2O (9:1), was rapidly added a solid mixture of $Mn(OAc)_3{\cdot}2H_2O$ (1.38 g, 5.16 mmol) and $Cu(BF_4)_2{\cdot}xH_2O$ (210 mg, 0.516 mmol if x = 6). The reaction mixture was stirred at 85 °C for 45 min. After cooling to RT, an aqueous solution of pH 2 sulfate buffer (40 mL) and EtOAc (40 mL) were added and the mixture was stirred for 5 min. The layers were separated and the aqueous phase was further extracted with (EtOAc 1 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (Et_2O/Pentane 2:1), which gave the major title diastereoisomer **(+)-1.275** as a colourless oil (380 mg, 1.16 mmol, 67%). $\mathbf{R_f}$ 0.47 (Et_2O); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +15.0 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.75 (1H, dd, *J* = 9.5, 7.0, CO_2CHH'), 4.61 (1H, dd, *J* = 9.5, 1.9, CO_2CHH' lactone), 4.33 (2H, q, *J* = 7.1, $CO_2CH_2CH_3$), 3.19 (1H, ddd, *J* = 7.0, 7.0, 1.9, $CO_2CHH'CH$ lactone), 2.94 (1H, dd, *J* = 17.5, 3.3, $CHH'CO_2{}^tBu$), 2.81 (1H, ddd, *J* = 10.3, 7.0, 3.3, $CHCHH'CO_2{}^tBu$), 2.46 (1H, dd, *J* = 17.5, 10.3, $CHH'CO_2{}^tBu$), 1.44 (9H, s, $OC(CH_3)_3$), 1.33 (3H, t, *J* = 7.1, OCH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.1 (*C*=O), 171.7 (*C*=O), 170.8 (*C*=O), 167.2 (*C*=O), 82.0 (C_{quat}), 72.2 (OCH_2 lactone), 66.5 (C_{quat}), 63.6 (OCH_2CH_3), 47.0 (CO_2CH_2CH lactone), 44.0 ($CHCH_2CO_2{}^tBu$), 36.2 ($CH_2CO_2{}^tBu$), 28.2 ($OC(CH_3)_3$), 14.1 (OCH_2CH_3); $\boldsymbol{\nu_{max}}$ 2981 (w, C-H), 1783 (m, C=O), 1715 (s, C=O), 1154 (s), 1022 (w), 733; **m/z** (ESI^+) 350.1 ($[M+Na]^+$, 100%); HRMS found 350.1198, $C_{15}H_{21}NNaO_7$ requires 350.1210.

(3a*R*,6*R*,6a*S*)-4-Methoxybenzyl 6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate, (+)-1.233



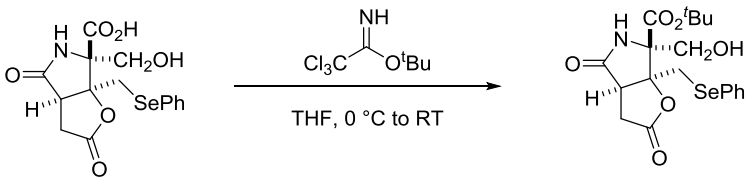
(-)-1.210 **(-)-1.222** **(+)-1.233**

According to the modified procedure of Danishefsky *et al.*,[21] PhSeBr (5.15 g, 21.8 mmol) and $AgBF_4$ (3.03 g, 15.6 mmol) were successively and rapidly added to a vigorously stirred solution of (2S,4R)-tert-Butyl-4-(2-(tert-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate **(-)-1.210** (2.13 g, 6.23 mmol) in degassed DCM/MeCN (1:1, 115 mL) under argon. The reaction mixture was stirred at RT for 7 h. Et_2O (200 mL) and pH 2 sulfate buffer (200 mL) were added to the mixture. The aqueous phase was saturated with NaCl and further extracted (EtOAc 8 x 70 mL). The combined organic layers were extracted with aq. NaOH (0.5 M, 1 x 100 mL, 1 x 50 mL). The aqueous extract were treated at 0 °C with a solution of pH 2 sulfate buffer (75 mL) followed by dropwise addition of an aqueous solution of concentrated HCl until pH = 2. The cloudy suspension was extracted with EtOAc (1 x 150 mL, 8 x 70 mL). The combined organic extracts were dried

(Na_2SO_4), filtered and evaporated, which gave the crude carboxylic acid (2.16 g, 5.60 mmol, 90%) **(-)-1.222**. **R_f** 0.53 (1:20:80 AcOH/MeOH/EtOAc); **δ_H** (400 MHz, DMSO-d_6) 7.59–7.52 (2H, m, ArH), 7.33–7.21 (3H, m, ArH), 4.10 (1H, d, *J* = 13.7, C*H*H'SePh), 3.97 (1H, d, *J* = 11.5, C*H*H'OH), 3.83 (1H, d, *J* = 13.7, CH*H*'SePh), 3.44 (1H, m, CH*H*'OH), 2.93 (1H, dd, *J* = 17.9, 9.9, O(CO)C*H*H'), 2.77 (1H, d, *J* = 9.9, N(CO)C*H*), 2.42 (1H, d, *J* = 17.9, O(CO)CH*H*'); **δ_C** (126 MHz, DMSO-d_6) 174.7 (*C*=O), 173.2 (*C*=O), 170.3 (*C*=O), 130.8 (*Ar*), 130.6 (*Ar*), 129.3 (*Ar*), 126.8 (*Ar*), 91.8 (C_{quat}), 73.5 (C_{quat}), 64.5 (CH_2OH), 47.8 (N(*C*O)CH), 33.3 (O(CO)CH_2), 31.6 (CH_2SePh); **ν_{max}** 3293 (br, O-H), 1781 (m, C=O), 1701 (s, C=O), 1160 (m), 739(w); **m/z** (ESI^-) 384 ($[M-H]^-$, 100%); HRMS found 383.9985, $C_{15}H_{14}NNO_6{}^{80}Se$ requires 383.9993.

A solution of the crude carboxylic acid **(-)-1.222** (2.16 g), K_2CO_3 (3.45 g, 24.7 mmol) and PMBCl (2.5 mL, 18.9 mmol) in DMF (20 mL) was treated with NaI (3.45 g, 18.9 mmol) at RT. The reaction mixture was then heated at 40 °C for 4 h. The reaction mixture was cooled to RT, diluted with EtOAc (150 mL) and washed with water (3 x 100 mL) and brine (1 x 100 mL). The organic extract was dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:80:20 MeOH/EtOAc/PE), which gave the title compound **(+)-1.233** as a white solid (2.31 g, 5.26 mmol, 84% over 2 steps). **R_f** 0.33 (EtOAc); **m.p.** 67–71 °C; $[\alpha]_D^{20}$ +10.9 (c = 1.00, $CHCl_3$); **δ_H** (500 MHz, $CDCl_3$) 7.65 (1H, s, N*H*), 7.52–7.45 (2H, m, Ar*H*), 7.28–7.22 (3H, m, Ar*H*), 7.20 (2H, d, *J* = 8.2, Ar*H*), 6.86 (2H, d, *J* = 8.2, Ar*H*), 5.14 (1H, d, *J* = 11.9, C*H*H'Ar), 5.06 (1H, d, *J* = 11.9, CH*H*'Ar), 4.16 (1H, m, OH), 4.02 (1H, dd, *J* = 12.3, 7.0, C*H*H'OH), 3.79 (3H, s, OCH_3), 3.74 (1H, dd, *J* = 12.3, 4.7, CH*H*'OH), 3.74 (s, 2H, C*HH*'Se), 3.13 (1H, dd, *J* = 18.1, 10.0, O(CO)C*H*H'), 2.94 (1H, d, *J* = 10.0, N(CO)C*H*), 2.67 (1H, d, *J* = 18.1, O(CO)CH*H*'); **δ_c** (100 MHz, $CDCl_3$) 173.5 (*C*=O), 167.5 (*C*=O), 160.1 (*C*=O), 132.2 (*Ar*), 130.4 (*Ar*), 129.7 (*Ar*), 129.5 (*Ar*), 127.9 (*Ar*), 126.6 (*Ar*), 114.2 (*Ar*), 90.7 (C_{quat}), 74.3 (C_{quat}), 68.5 (CH_2OH), 64.0 (CH_2Ar), 55.4 (OCH_3), 48.0 (*C*H), 33.4 (CH_2 lactone), 31.8 (CH_2Se); **ν_{max}** 3316 (br, OH), 1788 (m, C=O), 1730 (m, C=O), 1709 (s, C=O), 1245 (s), 734 (m); **m/z** (ESI^+) 528 ($[M+Na]^+$, 100%); HRMS found 528.0529, $C_{19}H_{23}NNaO_6{}^{80}Se$ requires 528.0532.

(±)-*tert*-Butyl (3a*R*,6*R*,6a*S*)-6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate, (±)-1.231

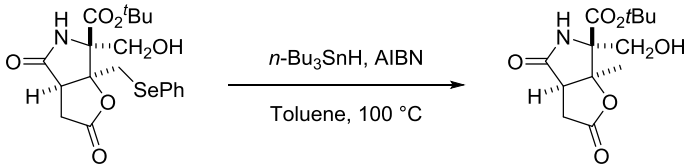


(±)-1.222 **(±)-1.231**

According to the modified procedure of Knerr *et al.*,[98] a solution *tert*-butyl 2,2,2-trichloroacetimidate (800 mg, 3.39 mmol) in hexane (3 mL) was added dropwise over 5 min to a solution of (±)-

(3a*R*,6*R*,6a*S*)-6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2H-furo[2,3-c]pyrrole-6-carboxylic acid **(±)-1.222** (435 mg, 1.13 mmol) in EtOAc (5 mL) at RT. The mixture was stirred for 12 h and was then concentrated under reduced pressure. The residue was purified by FC (3:2 to 1:0 EtOAc/PE), which gave the title compound **(±)-1.231** as a white solid (264 mg, 0.687 mmol, 61%). **R_f** 0.34 (EtOAc); **m.p.** 182–186 °C; **δ_H** (500 MHz, $CDCl_3$) 7.61–7.56 (2H, m, Ar*H*), 7.45 (1H, br, O*H*), 7.31–7.27 (3H, m, Ar*H*), 4.03 (1H, d, *J* = 12.3, C*H*H'OH), 3.76 (1H, d, *J* = 13.9, C*H*H'Se), 3.71 (1H, d, *J* = 12.3, CH*H'*OH), 3.70 (1H, d, *J* = 13.9, CH*H'*Se), 3.18 (1H, dd, *J* = 18.3, 10.4, O(CO)C*H*H'), 2.97 (1H, d, *J* = 10.3, N(O)C*H*), 2.74 (1H, d, *J* = 18.3, O(CO)CH*H'*), 1.42 (9H, s, $OC(CH_3)_3$); **δ_C** (126 MHz, $CDCl_3$) 175.7 (*C*=O), 173.5 (*C*=O), 166.4 (*C*=O), 132.8 (*Ar*), 129.6 (*Ar*), 129.6 (*Ar*), 128.0 (*Ar*), 90.6 (C_{quat}), 84.8 (C_{quat}), 74.3 (C_{quat}), 64.2 (CH_2OH), 48.3 (N(CO)*C*H), 33.5 (O(CO)*C*H_2), 32.5 (CH_2Se), 28.0 ($OC(CH_3)_3$); **ν_{max}** 3296 (br, O-H), 2979 (w, C-H), 1787 (m, C=O), 1708 (s, C=O), 1370 (w), 1151 (s), 734 (m); **m/z** (ESI^+) 464 ($[M+Na]^+$, 100%); HRMS found 464.0573, $C_{19}H_{23}NNaO_6{}^{80}Se$ requires 464.0584.

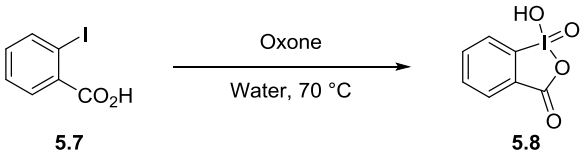
(±)-*tert*-Butyl (3a*R*,6*R*,6a*S*)-6-(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate, (±)-1.234



(±)-1.231 **(±)-1.234**

According to the modified procedure of Endo et al.,[21] *n*-Bu_3SnH (0.66 mL, 2.44 mmol) was added to a mixture of *tert*-butyl (3a*R*,6*R*,6a*S*)-6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate **(±)-1.231** (430 mg, 0.976 mmol) and AIBN (16 mg) in nitrogen sparged toluene (4.3 mL). The reaction was then heated at 100 °C for 15 min, and cooled to RT. The reaction mixture was filtered through a silica/K_2CO_3 plug,[172] using (4:1 EtOAc/PE, then 1:19 MeOH/EtOAc), which gave the title compound **(±)-1.234** as a white solid (230 mg, 0.806 mmol, 83%). **R_f** 0.37 (MeOH/EtOAc 1:19); **m.p.** 160–165 °C; **δ_H** (500 MHz, MeOD-*d*$_4$) 3.96 (1H, d, *J* = 11.4, C*H*H'OH), 3.72 (1H, d, *J* = 11.4, CH*H'*OH), 3.08 (1H, d, *J* = 9.7, O(CO)C*H*H'), 3.01 (1H, dd, *J* = 17.8, 9.7, O(CO)CH*H'*), 2.69 (1H, d, *J* = 17.8, O(CO)CHH'C*H*), 1.71 (9H, s, $OC(CH_3)_3$), 1.51 (3H, s, $C_{quat}CH_3$); **δ_C** (126 MHz, MeOD-*d4*) 176.9 (*C*=O), 175.4 (*C*=O), 168.2 (*C*=O), 91.8 (C_{quat}), 84.4 (C_{quat}), 74.5 (C_{quat}), 64.8 (CH_2OH), 49.8 (O(CO)CH_2*C*H), 31.3 (O(CO)CH_2), 28.2 ($OC(CH_3)_3$), 19.3 ($C_{quat}CH_3$); **ν_{max}** 3316 (br, O-H), 2981 (w, C-H), 1788 (m, C=O), 1710 (s, C=O), 1370 (w), 1154 (m), 733 (w); **m/z** (ESI^+) 308 ($[M+Na]^+$, 100%); HRMS found 308.1099, $C_{13}H_{19}NNaO_6$ requires 308.1105.

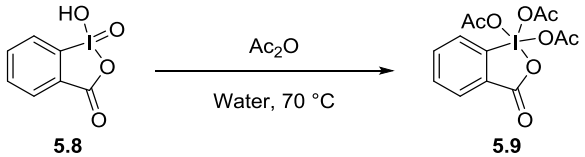
IBX,[173] 5.7



5.7 **5.8**

According to the procedure of Frigerio *et al.*,[173] iodobenzoic acid **5.7** (5.00 g, 20.0 mmol) was added to a solution of oxone (37.2 g, 61.0 mmol) in water (200 mL). The mixture was heated at 70 °C for one hour and then cooled in an ice bath, which allowed crystallisation of IBX **5.8**. After 30 min, the solid was filtered and washed with water (6 x 10 mL) and acetone (2 x 10 mL). The white solid was dried *in vacuo*, which gave IBX (4.50 g, 16.1 mmol, 80%).

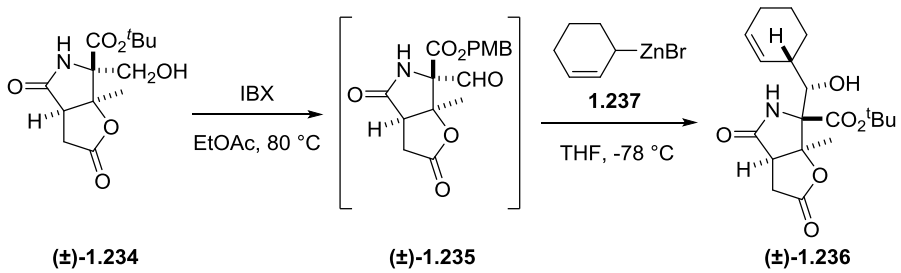
Dess-Martin Periodinane,[174] 5.9



5.8 **5.9**

According to the procedure of Boeckman *et. al.,*[174] a suspension of IBX **5.8** (4.00 g, 14.2 mmol) in AcOH (6.8 mL) and Ac_2O (13.6 mL) was sparged with argon for 10 minutes. The mixture was then warmed to 85 °C over 1 h, and stirred at this temperature until complete dissolution of the white suspension (30 min). The reaction mixture was slowly cooled down to RT. After 4 h, the residual precipitate was filtered under nitrogen and washed with Et_2O (3 x 10 mL). The white solid was dried *in vacuo,* which gave DMP **5.9** (4.65 g, 11.0 mmol, 77%).

(±)-*tert*-Butyl (3a*R*,6*R*,6a*S*)-6-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate, (±)-1.236



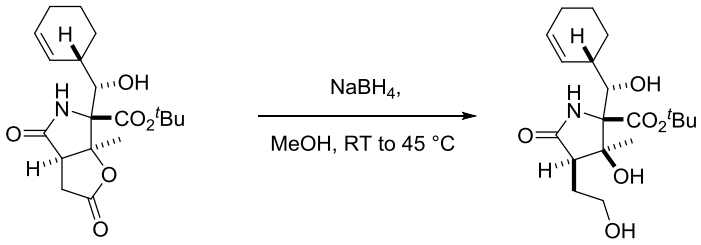
(±)-1.234 **(±)-1.235** **(±)-1.236**

According to the modified procedure of More *et al.,*[100] an RB flask was charged with IBX (249 mg, 0.888 mmol) and *tert*-butyl (3a*R*,6*R*,6a*S*)-6-(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate **(±)-1.234** (89.5 mg, 0.296 mmol) before EtOAc was added (2 mL). The mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to 15 °C, and was then allowed to stand at this temperature for 30 min. The precipitate was filtered through a short Celite

pad, which was further eluted with EtOAc (1.0 mL). The filtrate was evaporated under reduced pressure, which gave the crude aldehyde **(±)-1.235**.

According to the modified procedure of Mulholland *et al.*,[34] cyclohexenyl bromide (102 µL, 0.888 mmol) was added dropwise to a vigorously stirred suspension of freshly activated zinc powder[175] (69.7 mg, 1.07 mmol) in THF (1.8 mL) at 0 °C under argon. The mixture was stirred at RT for 1 h and was then cooled to -78 °C. The crude aldehyde **(±)-1.235** was dissolved in THF (0.4 mL + 0.2 mL rinse) and was added dropwise over 5 min to the solution of organozinc **1.237**. After 2 h stirring at -78 °C, the reaction was quenched by slow addition of a saturated aqueous solution of NH_4Cl (3 mL). The mixture was warmed to RT, and was extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified FC (3:1 EtOAc/PE), which gave the title compound **(±)-1.236** as a white solid (28 mg, 0.077 mmol, 26%). $\mathbf{R_f}$ 0.57 (EtOAc); **m.p.** decomposed at T > 220 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.54–7.36 (1H, br, NH), 6.09–6.02 (1H, m, C*H*=CH), 5.67–5.59 (1H, m, CH=C*H*), 4.07–3.96 (1H, br, C*H*OH), 3.08 (1H, d, *J* = 8.8, O(CO)CHH'*CH*), 2.88 (1H, d, *J* = 18.3, O(CO)C*H*H'), 2.75 (1H, dd, *J* = 18.3, 9.4, O(CO)CH*H'*), 2.34–2.27 (1H, br, C*H*CHOH), 2.27–2.09 (1H, br, O*H*), 2.06–1.97 (2H, m, C*HH'* cyclohexene), 1.82–1.65 (5H, m, CH_3 and 2 x C*H*H' cyclohexene), 1.65–1.47 (2H, m, 2 x CH*H'* cyclohexene), 1.52 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.6 (*C*=O), 173.2 (*C*=O), 166.9 (*C*=O), 135.5 (*C*H=CH), 123.3 (CH=*C*H), 91.9 (C_{quat}), 84.3 (C_{quat}), 75.8 (CHOH), 48.4 (O(CO)CH_2*C*H), 37.3 (*C*HCHOH), 30.6 (O(CO)CH_2), 29.1 (CH_2 cyclohexene), 28.0 (OC(CH_3)$_3$), 24.9 (*C*H_2 cyclohexene), 20.5 (*C*H_2 cyclohexene), 19.7 (CH_3); $\boldsymbol{\nu_{max}}$ 3794 (br, O-H), 2933 (w, C-H), 1784 (m, C=O), 1706 (s, C=O), 1150 (m), 913 (w), 730 (m); **m/z** (ESI^+) 388 ($[M+Na]^+$, 100%); HRMS found 388.1737, $C_{19}H_{27}NNaO_6$ requires 388.1731.

(±)-*tert*-Butyl (2*R*,3*S*,4*R*)-2-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxopyrrolidine-2-carboxylate, (±)-1.238

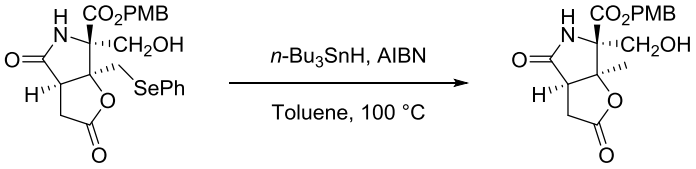


(±)-1.236 **(±)-1.238**

According to the modified procedure of Lam *et al.*,[37] $NaBH_4$ (120 mg, 3.15 mmol) was added in 6 portions over 30 min to a solution of *tert*-butyl (3a*R*,6*R*,6a*S*)-6-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate **(±)-1.236** (23.0 mg, 0.0630 mmol) in MeOH (1 mL). The reaction mixture was stirred for 90 min at RT, and the reaction mixture was diluted with MeOH (1 mL) and heated to 45 °C before addition of more $NaBH_4$

(120 mg, 3.15 mmol) in 6 portions over 30 min. The reaction mixture was stirred at 45 °C for 90 min, and was cooled to 0 °C. A solution of pH 2 sulfate buffer (10 mL) was added, and the mixture stirred for 10 min. The mixture was then extracted with EtOAc (1 x 10 mL, 2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:49 MeOH/EtOAc), which gave starting material (4.0 mg, 0.011 mmol, 17%) and the title compound **(±)-1.238** as a white solid (14.0 mg, 0.0379 mmol, 60%). $\mathbf{R_f}$ 0.27 (EtOAc); $\mathbf{\delta_H}$ (500 MHz, MeOD-d_4) 5.85–5.75 (2H, m, C*H*=C*H*), 3.98 (1H, d, *J* = 4.4, C*H*OH), 3.73 (2H, t, *J* = 6.3, CH_2OH), 2.87 (1H, dd, *J* = 8.8, 4.4, C*H*CH_2CH_2OH), 2.29–2.19 (1H, br, C*H*CHOH), 2.07–1.91 (2H, br, C*HH'*CH=CH), 1.90–1.66 (5H, m, 5 x ½ CH_2), 1.64–1.56 (1H, m, ½ CH_2), 1.58 (3H, s, CH_3), 1.51 (9H, s, OC(CH_3)$_3$); $\mathbf{\delta_C}$ (126 MHz, MeOD-*d4*) 181.3 (*C*=O), 170.7 (*C*=O), 130.8 (*C*H=CH), 127.9 (CH=*C*H), 83.7 (C_{quat}), 82.5 (C_{quat}), 78.9 (C_{quat}), 76.6 (*C*HOH), 62.2 (*C*H_2OH), 51.3 (*C*HCH_2CH_2OH), 40.3 (*C*HCHOH), 29.5 (*C*H_2), 28.3 (OC(*C*H_3)$_3$), 27.9 (*C*H_2), 26.0 (*C*H_2), 22.8 (*C*H_2), 20.4 (*C*H_3); $\mathbf{\nu_{max}}$ 3288 (s and br, O-H), 2929 (w, C-H), 1710 (s, C=O), 1668 (m, C=O), 1370 (w), 1288 (w), 1155 (s), 843 (w); **m/z** (ESI^+) 392 ($[M+Na]^+$, 100%); HRMS found 392.2040, $C_{19}H_{31}NNaO_6$ requires 392.2044.

(+)-(3a*R*,6*R*,6a*S*)-4-Methoxybenzyl 6-(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate, (+)-1.240

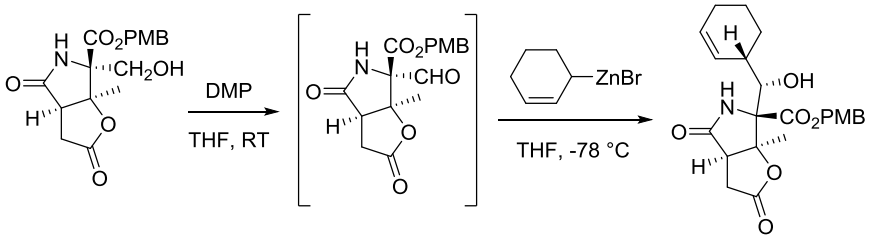


(+)-1.233 **(+)-1.240**

According to the modified procedure of Danishefsky *et al.,*[21] to a solution of AIBN (49.0 mg, 0.297 mmol) and 4-methoxybenzyl (3a*R*,6R,6a*S*)-6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate **(+)-1.233** (1.50 g, 2.97 mmol) was added *n*-Bu_3SnH (2.0 mL, 7.4 mmol). The reaction flask was submerged in a pre-heated oil bath (100 °C) and stirred at this temperature for 45 min. The reaction mixture was cooled to RT and was then plugged through a silica pad (1:1 EtOAc/PE 3 CV then 1:20 MeOH/EtOAc 10 CV), which gave the title compound **(+)-1.240** as a white solid (963 mg, 2.76 mmol, 93%). $\mathbf{R_f}$ 0.53 (EtOAc/MeOH 20:1); **m.p.** 184–191 °C; $[\alpha]_D^{20}$ +72.1 (c = 1.00, MeOH); $\mathbf{\delta_H}$ (500 MHz, DMSO-d_6) 7.33 (2H, d, *J* = 8.7, Ar*H*), 6.93 (2H, d, *J* = 8.7, Ar*H*), 5.50 (1H, dd, *J* = 5.0, 5.0, CHH'O*H*), 5.14 (1H, d, *J* = 12.2, C*H*H'Ar), 5.09 (1H, d, *J* = 12.2, CH*H'*Ar), 3.78 (1H, dd, *J* = 10.9, 5.0, C*H*H'OH), 3.75 (3H, s, OCH_3), 3.61 (1H, dd, *J* = 10.9, 5.0, CH*H'*OH), 3.07 (1H, dd, *J* = 17.8, 9.5, C*H*H'(CO)O), 2.96 (1H, d, *J* = 9.5, N(CO)C*H*), 2.49 (1H, d, *J* = 17.8, C*H*H'(CO)O), 1.58 (3H, s, $C_{quat}CH_3$); $\mathbf{\delta_C}$ (126 MHz, DMSO-d_6) 173.8 (*C*=O), 173.7 (*C*=O), 168.1 (*C*=O), 159.2 (*Ar*), 129.6 (*Ar*), 127.4 (*Ar*), 113.8 (*Ar*), 89.8 (C_{quat}), 72.3 (C_{quat}), 66.5 (*C*H_2Ar), 63.3 (*C*H_2OH), 55.1

(OCH_3), 47.4 (*C*H), 30.3 (*C*H_2 lactone), 18.6 ($C_{quat}CH_3$); **ν_{max}** 3329 (br, OH), 1785 (m, C=O), 1741 (m, C=O), 1709 (m, C=O), 1516 (w), 1246 (m); **m/z** (ESI^+) 372 ($[M+Na]^+$, 100%); HRMS found 372.1057, $C_{17}H_{19}NNaO_7$ requires 372.1054.

(-)-(3a*R*,6*R*,6a*S*)-4-Methoxybenzyl 6-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate

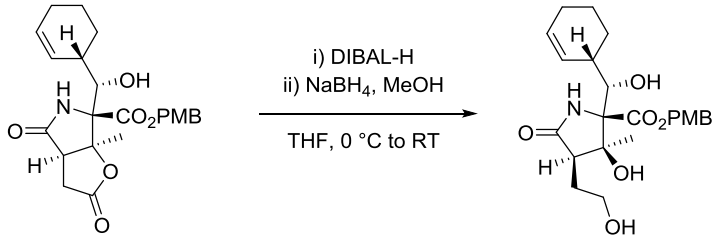


(+)-1.240 **1.241** **(-)-1.242**

According to the modified procedure of Mulholland *et Al.*,[34] 3-bromocyclohexene (3.1 mL, 26.9 mmol) was added dropwise over 5 min to a vigorously stirred suspension of activated zinc dust[175] (2.11 g, 32.2 mmol) in degassed THF (39 mL) under argon at 0 °C . This mixture was stirred for 90 min. In the meantime, degassed THF (28 mL) was then added to DMP (2.28 g, 5.38 mmol) and (3a*R*,6*R*,6a*S*)-4-Methoxybenzyl 6-(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate **(+)-1.240** (938 mg, 2.69 mmol) at RT. The mixture was stirred for 75 min and was added to the cyclohex-2-en-1-ylzinc(II) bromide solution at -78 °C over 10 min. The reaction mixture was stirred for 10 min at -78 °C and was quenched by addition of a saturated aqueous solution of NH_4Cl (40 mL) and water (10 mL). The stirred mixture warmed to RT and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified two times by FC (4:1 EtOAc/PE), which gave the title compound **(-)-1.242** as a white solid (645 mg, 1.50 mmol, 56% over 2 steps). **m.p.** 79–85 °C; $[\alpha]_D^{20}$ -22.9 (c = 1.00, $CHCl_3$); **e.e.** 98.4%; (HPLC chiralpak AD-H column 30% IPA/Hexane); **δ_H** (500 MHz, $CDCl_3$); 7.34–7.29 (2H, m, ArH), 6.94 (1H, br, N*H*), 6.90–6.86 (2H, m, ArH), 6.00 (1H, ddd, *J* = 10.0, 5.1, 3.6 C*H*=CH), 5.57 (1H, dd, *J* = 10.0, 2.0, CH=C*H*), 5.26 (1H, d, 11.8, C*H*H'Ar), 5.11 (1H, d, 11.8, CH*H*'Ar), 3.99 (1H, s, CHOH), 3.80 (3H, s, OCH_3), 3.07 (1H, d, *J* = 9.3, N(CO)C*H*), 2.89 (1H, d, *J* = 18.3, C*H*H'(CO)O), 2.75 (1H, dd, *J* = 18.3, 9.3, CH*H*'(CO)O), 2.44–2.24 (1H, br, OH), 2.08–2.01 (1H, m, C*H*CHOH), 2.00–1.85 (2H, m, C*HH*' cyclohexene), 1.76 (3H, s, $C_{quat}CH_3$), 1.68–1.59 (1H, m, C*H*H' cyclohexene), 1.50–1.28 (m, 3H, CH*H*' cyclohexene and C*HH*' cyclohexene); **δ_c** (126 MHz, $CDCl_3$) 175.3 (*C*=O), 173.0 (*C*=O), 168.0 (*C*=0), 160.2 (*Ar*), 135.2 (*C*H alkene), 130.9 (*Ar*), 126.8 (*Ar*), 123.4 (*C*H alkene), 114.2 (*Ar*), 91.9 (C_{quat}), 75.7 (*C*HOH), 75.5 (C_{quat}), 68.1 (CH_2PMB), 55.4 (OCH_3), 48.3 (*C*H lactone), 37.5 (*C*HCHOH), 30.5 (CH_2 lactone), 28.3 (CH_2 cyclohexene), 24.9 (CH_2 cyclohexene), 20.5 (CH_2 cyclohexene), 19.7 (CH_3); **ν_{max}**

3310 (br, O-H), 2929 (w, C-H), 1786 (m, C=O), 1709 (s, C=O), 1246 (s), 731 (w); **m/z** (ESI^+) 452 ($[M+Na]^+$, 100%); HRMS found 452.1672, $C_{23}H_{27}NNaO_7$ requires 452.1680.

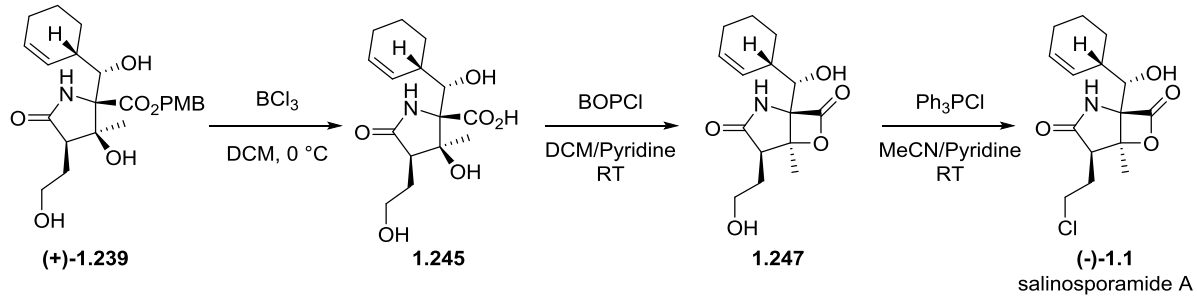
(+)-(2*R*,3*S*,4*R*)-4-Methoxybenzyl 2-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxopyrrolidine-2-carboxylate, (+)-1.239



(-)-1.242 **(+)-1.239**

To a solution of lactone **(-)-1.242** (200 mg, 0.466 mmol) in THF (8.0 mL) at -10 °C, was added DiBAl-H in hexanes (1.0 M, 2.80 mL, 2.80 mmol) over 5 min. This mixture was stirred for 15 min at -10 °C and was treated with MeOH (15 mL). The mixture was stirred for 5 min at RT and $NaBH_4$ (880 mg, 21.2 mmol) was added in 10 portions every 10 min. The mixture was stirred for 30 min and was quenched with a saturated aqueous solution of NH_4Cl (20 mL). EtOAc (120 mL), water (40 mL) and a saturated aqueous solution of Rochelle's salt (100 mL) were also added and the mixture was vigorously stirred for 6 hours. The Organic layer was separated and the aqueous layer was extracted with more EtOAc (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:50 MeOH/EtOAc), which gave the title compound **(+)-1.239** as a white solid (139 mg, 0.76 mmol, 69%). $\mathbf{R_f}$ 0.31 (EtOAc); **m.p.** 93–96 °C; $[\alpha]_D^{20}$ +72.1 (c = 1.00, MeOH); $\boldsymbol{\delta_H}$ (500 MHz, MeOD-d_4) 7.39–7.34 (2H, m, Ar*H*), 7.93–7.88 (2H, m, Ar*H*), 5.76–5.70 (2H, m, C*H*=C*H*), 2.24 (1H, d, *J* = 11.0, C*H*H'Ar), 5.05 (1H, d, *J* = 11.0, CH*H'*Ar), 3.91 (1H, d, *J* = 5.0, C*H*OH), 3.79 (3H, s, OCH_3), 3.73 (1H, t, *J* = 6.3, CH_2OH), 2.89 (1H, dd, *J* = 8.6, 4.5, N(CO)C*H*), 2.03–1.94 (1H, m, C*H*CHOH), 1.93–1.86 (2H, m, CHH'CHH'C*HH'*CH=CH), 1.86–1.80 (1H, m, C*H*H'CH_2OH), 1.78–1.68 (1H, m, CH*H'*CH_2OH), 1.63–1.56 (1H, m, CHH'C*H*H'CHH'CH=CH), 1.57 (3H, s, $C_{quat}CH_3$), 1.47–1.37 (1H, m, C*H*H'CHH'CHH'CH=CH), 1.36–1.25 (1H, m, CHH'CH*H'*CHH'CH=CH), 1.23–1.10 (1H, m, CH*H'*CHH'CHH'CH=CH); $\boldsymbol{\delta_H}$ (126 MHz, MeOD-d_4) 181.3 (*C*=O), 171.8 (*C*=O), 161.4 (*Ar*), 132.0 (*Ar*), 130.5 (*C*H=CH), 128.8 (Ar), 128.1 (CH=*C*H), 114.9 (*Ar*), 82.6 (C_{quat}), 78.9 (C_{quat}), 76.6 (*C*HOH), 68.0 (CH_2Ar), 62.1 (CH_2OH), 55.7 (OCH_3), 50.9 (N(CO)*C*H), 40.4 (*C*HCHOH), 28.4 ($CH_2CH_2CH_2$CH=CH), 27.8 (CH_2CH_2OH), 25.9 ($CH_2CH_2CH_2$CH=CH), 22.9 ($CH_2CH_2CH_2$CH=CH), 20.4 ($C_{quat}CH_3$); $\boldsymbol{\nu_{max}}$ 3298 (br, OH), 2934 (w, C-H), 1716 (m, C=O), 1684 (m, C=O), 1247 (s), 824 (w); **m/z** (ESI^+) 434 ($[M+H]^+$, 100%), 456 ($[M+Na]^+$, 30%); HRMS found 456.2006, $C_{23}H_{31}NNaO_7$ requires 456.1993.

(-)-Salinosporamide A, (-)-1.1



(+)-1.239 **1.245** **1.247** **(-)-1.1** salinosporamide A

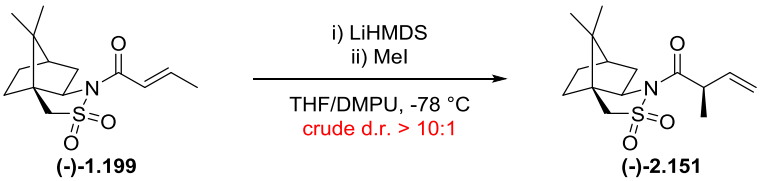
To a solution of (+)-(2*R*,3*S*,4*R*)-4-methoxybenzyl 2-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxopyrrolidine-2-carboxylate **(+)-1.239** (75.0 mg, 0.173 mmol) in DCM (3.5 mL) at 0 °C was added BCl_3 in DCM (1.0 M, 0.69 mL, 0.69 mmol) over 5 min. The reaction mixture was stirred at this temperature for 30 min and was quenched with MeOH (0.2 mL). The mixture plugged through a 1 inch long silica pad (1:20 MeOH/DCM 4 CV, then 1:4 MeOH/DCM 4 CV), which gave crude carboxylic acid **1.245** (54.2 mg).

To a solution of readily prepared crude carboxylic acid **1.245** (54.2 mg) in DCM (1 mL) and pyridine (0.5 mL) at RT, was added BOPCl (66.2 mg, 0.216 mmol) in one portion. The reaction was stirred for 2 h and another portion of BOPCl (21.0 mg, 0.0720 mmol) was added. After one hour stirring all volatiles were quickly removed under reduced pressure and the residue was diluted in EtOAc (10 mL) and washed with 10% aq. NaCl (10 mL). The aqueous layer was re-extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to give crude β-lactone **1.247** (50.7mg).

To a solution of crude β-lactone **1.247** (50.7 mg) in MeCN (0.35 mL) and pyridine (0.35 mL) at RT under argon was added Ph_3PCl_2 (115.4 mg, 0.346 mmol) in one portion. The mixture was stirred for two hours and quenched with H_2O (0.05 mL). All volatiles were removed quickly and the residue was diluted in EtOAc (10 mL) and washed with 10% aq. NaCl (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. FC purification (3:2 EtOAc/Hexane) of the residue gave (-)-salinosporamide A **(-)-1.1** as a white solid (33.0 mg, 0.105 mmol, 61% over 3 steps). $\mathbf{R_f}$ 0.59 (EtOAc/Hexane, 1:1), **m.p.** 175–178 °C (lit.[2] 168–170 °C); $[\alpha]_D^{20}$ -80.4 (c = 0.49, MeOH) (lit.[2] -72.98, c = 0.55, MeOH); $\boldsymbol{\delta_H}$ (500 MHz, C_6D_5N) 10.65–10.60 (1H, br, NH), 7.67–7.45 (1H, br, OH), 6.45 (1H, d, *J* = 10.2, CH-C*H*=CH-CH_2), 5.95–5.86 (1H, m, CH-CH=C*H*-CH_2), 4.27 (1H, d, *J* = 9.0, CHOH), 4.21–4.10 (1H, m, C*H*H'Cl), 4.08–3.99 (1H, m, CH*H'*Cl), 3.19 (1H, t, *J* = 7.0, N(CO)C*H*), 2.93–2.81 (1H, m, C*H*OH), 2.57–2.44 (1H, m, C*H*H'CHH'Cl), 2.41–2.26 (2H, m, CH*H'*CHH'Cl and C*H*H'CHH'CHH'CH=C), 2.09 (s, 3H, CH_3), 2.04–1.86 (2H, m, C*HH'*CH=CH), 1.78–1.64 (2H, m, C*H*H'CHH'CH=CH and CH*H'*CHH'CHH'CH=CH), 1.46–1.33 (1H, m, CH*H'*CHH'CH=CH); $\boldsymbol{\delta_C}$ (500

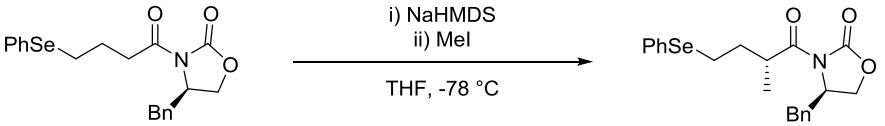
MHz, C_6D_5N) 176.7 (*C*=O), 169.2 (*C*=O), 128.9 (CH_2–*C*H=CH), 128.5 (CH_2–CH=*C*H), 86.1 (C_{quat}), 80.1 (C_{quat}), 70.8 (*C*HOH), 46.0 (N(CO)*C*H), 43.1 (*C*H_2Cl), 39.1 (*C*HCHOH), 28. (*C*H_2CH_2Cl), 26.3 (*C*$H_2CH_2CH_2CH$=CH), 25.2 (CH_2CH=CH), 21.5 (CH_2*C*H_2CH_2CH=CH), 19.8 (CH_3); **ν_{max}** 3395 (w, O-H), 1819 (m, C=O), 1696 (s, C=O), 1025 (w) 833 (m); **m/z** (ESI^+) 336 ([M+Na]$^+$, 100%); HRMS found 336.0978, $C_{15}H_{20}{}^{35}ClNNaO_4$ requires 336.0973. Data are in accordance with the literature.[2]

(*R*)-1-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-methylbut-3-en-1-one, (-)-2.151



According to the modified procedure of Batchelor *et al.*[83] A solution of (*E*)-1-((3a*S,*6*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazol-1-yl)but-2-en-1-one **(-)-1.199** (3.00 g, 10.6 mmol) in THF (12 mL) was added over 40 min to a mixture of LiHMDS 1.0 M in toluene (13.8 mL, 13.8 mmol), DMPU (5.10 mL, 42.4 mmol) and THF (9 mL) at -78 °C. The reaction was stirred for 15 min, and MeI (1.98 mL, 31.8 mmol) in THF (6.0 mL) was added dropwise over 10 min. The reaction mixture was stirred for 12 h at -78 °C. A saturated aqueous solution of NH_4Cl (25 mL) was then added and the mixture was warmed to RT. Water (75 mL) and EtOAc (100 mL) were added and the aqueous layer was separated. The organic phase was washed with brine (75 mL), dried (Na_2SO_4), filtered and evaporated. The solid residue was recrystallised at -20 °C overnight (EtOAc/Hexane 1:6), which gave the desired product **(-)-2.251** (2.02 g, 6.79 mmol, 64%). **R_f** 0.63 (1:4 EtOAc/PE); **m.p.** 170–172 °C; lit. 168-70; $[\alpha]_D^{20}$ -106.0 (c = 1.00, $CHCl_3$) lit. +104.8 (opposite enantiomer, c = 0.53, DCM); **δ_H** (400 MHz, $CDCl_3$) 5.97 (1H, ddd, *J* = 17.4, 10.3, 7.3, CHH'=C*H*), 5.20 (1H, dt, *J* = 17.4, 1.1, C*H*H'=CH), 5.13 (1H, dt, *J* = 10.3, 1.1, CH*H'*=CH), 3.88 (1H, t, *J* = 6.4, NC*H*), 3.84–3.73 (1H, m, C*H*CH_3), 3.51 (1H, d, *J* = 13.8, C*H*H'SO_2), 3.44 (1H, d, *J* = 13.8, CH*H'*SO_2), 2.09–2.03 (2H, m, NCHC*HH'*), 1.97–1.82 (3H, m, C*H*H'-C*H*H' and CH_2CHCH_2), 1.44–1.30 (5H, m, CH*H'*-CH*H'* and CHCH_3), 1.16 (3H, s, $C_{quat}CH_3$), 0.97 (3H, s, $C_{quat}CH_3$); **δ_C** (100 MHz, $CDCl_3$) 174.3 (*C*=O), 136.4 (CH_2=*C*H), 116.7 (*C*H_2=CH), 65.3 (NCH), 53.2 (*C*H_2SO_2), 48.5 (C_{quat}), 47.9 (C_{quat}), 44.7 (CH_2CHCH_2), 44.1 (*C*HCH_3), 38.5 (NCH*C*H_2), 33.0 (*C*H_2-CH_2), 26.5 (CH_2-*C*H_2), 21.0 ($C_{quat}CH_3$), 20.0 ($C_{quat}CH_3$), 19.0 (CH*C*H_3); **ν_{max}** 2948 (w, C-H), 1683 (s, C=O), 1322 (m), 1222 (s), 1136 (m), 1063 (m), 918 (w), 766 (w); **m/z** (ESI^+) 320.1 ([M+Na]$^+$, 100%), 298 ([M+H]$^+$, 30%); HRMS found 298.14681, $C_{15}H_{24}NSO_3$ requires 298.14714. The data are in accordance with the literature.[83,176]

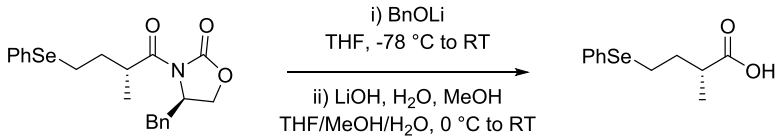
(*R*)-4-Benzyl-3-((*R*)-2-methyl-4-(phenylselanyl)butanoyl)oxazolidin-2-one, (-)-2.152



(-)-1.123 **(-)-2.152**

To a solution of (*R*)-4-benzyl-2-oxooxazolidin-3-yl 4-(phenylselanyl)butanoate (18.9 g, 47.0 mmol) in dry THF **(-)-1.123** (450 mL) at -78 °C was added NaHMDS in THF (2.0 M, 32.9 mL, 65.8 mmol) over 15 min. The reaction was stirred at this temperature for 10 min. Methyl iodide (8.80 mL, 141 mmol) was then added over 5 min. The reaction mixture was stirred for 3 h and quenched with a saturated solution of aqueous NH_4Cl (200 mL) and water (100 mL). The mixture was then warmed to RT and the layers were separated. The organic phase was washed with brine (150 mL), and the combined aqueous layers were re-extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude was purified by FC (1:9 to 1:4 EtOAc/PE), which gave the title compound as a pale yellow oil **(-)-2.152** (17.9 g, 43.0 mmol, 92%). $\mathbf{R_f}$ 0.36 (1:7 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -85.9 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.46 (2H, m, Ar*H*), 7.37–7.18 (8H, m, Ar*H*), 4.65–4.58 (1H, m, CO_2CH_2CH), 4.16 (2H, d, *J* = 5.3, CO_2CH_2CH), 3.90–3.79 (1H, m, $CHCH_3$), 3.23 (1H, dd, *J* = 13.3, 3.2, PhC*H*H'), 2.90 (1H, ddd, *J* = 12.2, 9.3, 5.9, SeC*H*H´), 2.88 (1H, ddd, *J* = 12.2, 8.9, 6.5, SeCH*H´*), 2.76 (1H, dd, *J* = 13.3, 9.5, PhCH*H'*), 2.23 (1H, dddd, *J* = 13.5, 8.9, 8.0, 5.9, $SeCH_2CH$H´), 1.81 (1H, dddd, *J* = 13.5, 9.3, 6.5, 5.9, $SeCH_2CH$H´), 1.24 (3H, d, *J* = 7.0, $CHCH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.1 (*C*=O), 152.9 (*C*=O), 132.5 (*Ar*), 135.2 (*Ar*), 130.1 (*Ar*), 129.4 (*Ar*), 129.1 (*Ar*), 128.9 (*Ar*), 127.4 (*Ar*), 126.8 (*Ar*), 66.0 (OCH_2), 55.2 (N*C*H), 38.0 ($PhCH_2$), 37.9 (CH_3CH), 33.7 ($SeCH_2CH_2$), 25.1 ($SeCH_2$), 17.5 (CH_3); $\boldsymbol{\nu_{max}}$ 2975 (w, C-H), 1774 (s, C=O oxazolidinone), 1692 (s, C=O), 1384 (m, Ar), 1212 (m, C-O), 734 (m, Ar); **m/z** (ESI^+) 440 ($[M+Na]^+$, 100%), 857 ($[2M+Na]^+$, 57%); HRMS found 440.0743, $C_{21}H_{23}NNaO_3{}^{80}Se$ requires 440.0736.

(*R*)-2-Methyl-4-(phenylselanyl)butanoic acid, (-)-2.143

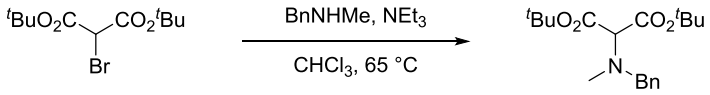


(-)-2.152 **(-)-2.143**

According to the modified procedure of Carrick *et al.*,[177] *n*-BuLi in hexanes (2.5 M, 22.4 mL, 55.9 mmol) was added over 5 min to benzyl alcohol (6.68 mL, 64.5 mmol) in dry degassed THF (60 mL) at 0 °C. The reaction mixture was stirred for 30 min, and then cooled to -78 °C. (*R*)-4-benzyl-3-((*R*)-2-methyl-4-(phenylselanyl)butanoyl)oxazolidin-2-one **(-)-2.152** (17.9 g, 43.0 mmol) in dry degassed THF (200 mL) was added via cannula over 15 min. The reaction was then slowly warmed to

RT and stirred for 60 min. A solution of LiOH (16.8 g, 700 mmol) in MeOH/H_2O (1:1, 400 mL) was then added at 0 °C. The mixture was warmed to RT and was stirred for 12 h. Water (200 mL) and Et_2O (400 mL) were added. The layers were separated and the organic phase was extracted with an aqueous solution of NaOH (0.5 M, 1 x 400 mL, 1 x 150 mL). The combined aqueous layers were vigorously stirred at 0 °C, and an aqueous solution of concentrated HCl was added dropwise until pH < 2. The aqueous phase was extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Excess benzyl alcohol was removed from the crude by co-evaporation with H_2O/MeOH (1:1, 5 x 100 mL) and then with toluene (1 x 100 mL), which gave the title carboxylic acid **(-)-2.143** as a pale oil (11.1 g, 43.0 mmol, 100%). $\mathbf{R_f}$ 0.27 (0.5:2.0:97.5 AcOH/MeOH/DCM); $[\alpha]_D^{20}$ -12.1 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.48 (m, 2 H, Ar*H*), 7.32–7.23 (m, 3H, Ar*H*), 2.96 (1H, ddd, *J* = 12.2, 9.0, 6.5, SeC*H*H'), 2.92 (1H, ddd, *J* = 12.2, 8.7, 6.4, SeCH*H'*), 2.73–2.62 (1H, m, C*H*CH_3), 2.10 (1H, dddd, *J* = 15.0, 8.7, 7.9, 6.5, CH_2CHH'CH), 1.80 (1H, dddd, *J* = 15.0, 9.0, 6.4, 6.4, CH_2CH*H'*CH), 1.20 (3H, d, *J* = 7.2, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 181.9 (*C*=*O*), 132.7 (*Ar*), 129.8 (*Ar*), 129.1 (*Ar*), 127.0 (*Ar*), 39.2 (*C*H), 33.7 ($SeCH_2CH_2$), 25.0 ($SeCH_2$), 6.7 (CH_3); $\boldsymbol{\nu_{max}}$ 2974 (w, C-H), 2900 (br, O-H carboxylic acid), 1701 (s, C=O), 1235 (m, C-O), 735 (m); **m/z** (ESI^-) 257 ($[M-H]^-$, 100%), (ES^+) 281 ($[M+Na]^+$, 100%); HRMS found 257.0086, $C_{11}H_{13}O_2Se$ requires 257.0087.

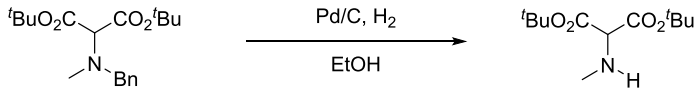
Di-*tert*-butyl 2-(benzyl(methyl)amino)malonate, 2.145



1.180 **2.145**

According to the modified procedure of Hess *et al.*,[78] di-*tert*-butyl 2-bromomalonate **1.180** (14.3 g, 48.6 mmol), *N*-benzylmethylamine (9.40 mL, 73.0 mmol) and NEt_3 (13.5 mL, 97.0 mmol) were heated under reflux (65 °C) in $CHCl_3$ (150 mL) for 15 h. The reaction mixture was then cooled to RT, H_2O (150 mL) was added and the layers were separated. The organic phase was washed with brine (100 mL) and the combined aqueous layers were extracted with DCM (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a brown oil. The residue was purified by FC (1:20 to 1:10 EtOAc/PE), which gave the title compound **2.145** as a colourless oil (15.3 g, 45.6 mmol, 94%). $\mathbf{R_f}$ 0.34 (1:2 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.42 (2H, d, *J* = 7.1, Ar*H*), 7.32 (2H, dd, *J* = 7.1, 7.0, Ar*H*), 7.26 (1H, d, *J* = 7.0, Ar*H*), 3.97 (1H, s, C*H*N), 3.82 (2H, s, CH_2Ph), 2.45 (3H, s, NCH_3), 1.51 (18H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 167.1 (2 × *C*=O), 139.1 (*Ar*), 128.9 (*Ar*), 128.2 (*Ar*), 127.1 (*Ar*), 81.9 (N*C*H), 70.6 (2 x O*C*(CH_3)$_3$, 58.5 (CH_2), 39.5 (CH_3), 28.1 (2 × OC(CH_3)$_3$); **m/z** (ESI^+) 326.2 ($[M+H]^+$, 40%), 358 ($[M+Na]^+$, 59%), 693 ($[2M+Na]^+$, 100%); HRMS found 358.1988, $C_{19}H_{29}NNaO_4^+$ requires 358.1989.

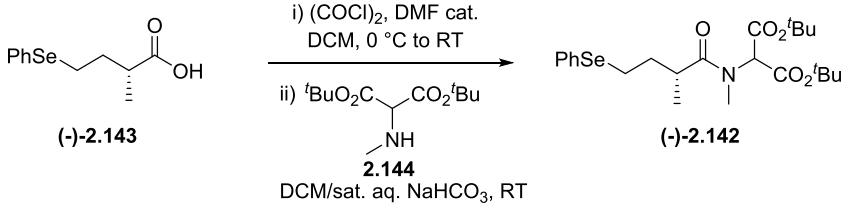
Di-*tert*-butyl 2-(methylamino)malonate, 2.144



2.145 **2.144**

A mixture of di-*tert*-butyl 2-(benzyl(methyl)amino)malonate (42.7 mmol, 14.3 g) and wet Pd/C 10% by weight (715 mg) in EtOH (150 mL) was stirred under hydrogen (balloon pressure) for 36 h. The reaction mixture was filtered through Celite, which was eluted with EtOH (3 x 75 mL). The solvent was then evaporated under reduced pressure. The residue was purified by FC (1:9 to 1:4 EtOAc/PE), which gave the title compound **2.144** as a yellow oil (8.27 g, 33.7 mmol, 79%). $\mathbf{R_f}$ 0.42 (1:1 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.73 (s, 1H, NC*H*), 2.44 (s, 3H, NCH_3), 1.48 (s, 18H, OC(CH_3)$_3$); $\boldsymbol{\delta_c}$ (100 MHz, $CDCl_3$) 167.7 (2 x *C*=O), 82.2 (2 x O*C*(CH$_3$)$_3$), 68.0 (*C*H), 34.1 (N*C*H$_3$), 27.9 (2 x OC(*C*H$_3$)$_3$); $\boldsymbol{\nu_{max}}$ 2979(w, C-H), 1731 (s, C=O), 1140 (s, C-O); **m/z** (ESI$^+$) 246 ([M+H]$^+$, 100%), 268 ([M+Na]$^+$, 70%); HRMS found 246.1709, $C_{12}H_{25}NO_4^+$ requires 246.1700.

(*R*)-Di-*tert*-butyl 2-(N,2-dimethyl-4-(phenylselanyl)butanamido)malonate, (-)-2.142

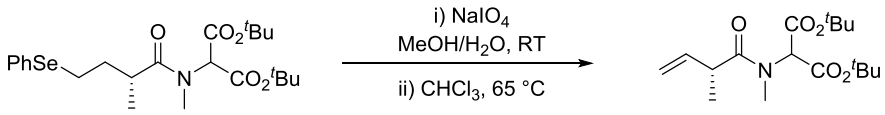


(-)-2.143 **2.144** **(-)-2.142**

To a stirred solution of (*R*)-2-methyl-4-(phenylselanyl)butanoic acid **(-)-2.143** (11.1 g, 43.0 mmol) and DMF (66 µL, 0.86 mmol) in dry DCM (125 mL), was added $(COCl)_2$ (5.53 mL, 64.5 mmol) dropwise at 0 °C. The mixture was stirred at RT for until gas evolution completely ceased (about one hour). All volatiles were evaporated under reduced pressure and the flask was backfilled with nitrogen. The residue was re-dissolved in dry DCM (125 mL) and this solution was quickly added to di-*tert*-butyl 2-(methylamino)malonate **2.144** (45.2 mmol, 11.1 g) in a vigorously stirred biphasic mixture of DCM (125 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL) at RT. After 30 min, the organic layer was separated from the aqueous phase, which was extracted with DCM (2 × 125 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:10 EtOAc/PE), which gave the title compound **(-)-2.142** as a colourless oil, which crystallised at -20 °C to give a white solid (18.4 g, 37.9 mmol, 88%). $\mathbf{R_f}$ 0.39 (1:12 EtOAc/PE); **m.p.** 46–49 °C; $[\alpha]_D^{20}$ -26.5 (c = 1.00 in $CHCl_3$); NMR showed mixture of 2 rotamers (ratio 6:1), data is only given for the major

one : δ_H (400 MHz, $CDCl_3$) 7.51–7.46 (2H, m, Ar*H*), 7.29–7.20 (3H, m, Ar*H*), 5.79 (1H, s, C*H*N), 3.13 (3H, s, NCH_3), 3.08–2.94 (2H, m, SeCH_2), 2.89–2.80 (1H, m, C*H*CH_3), 2.22–2.10 (1H, m, $SeCH_2CHH'CH$), 1.78–1.69 (1H, m, $SeCH_2CHH'CH$), 1.49 (9H, s, C(CH_3)$_3$), 1.47 (9H, s, C(CH_3)$_3$), 1.14 (3H, d, *J* = 6.8, CHCH_3); δ_C (100 MHz, $CDCl_3$) 176.5 (*C*=O), 165.9 (*C*=O), 165.8 (*C*=O), 132.4 (*Ar*), 130.0 (*Ar*), 129.1 (*Ar*), 126.8 (*Ar*), 82.8 (2 × O*C*(CH$_3$)$_3$), 61.4 (N*C*H), 35.2 (*C*HCH$_3$), 33.9 ($SeCH_2CH_2$), 33.4 (NCH_3), 27.9 (2 × OC(*C*H$_3$)$_3$), 25.4 (Se*C*H$_2$), 17.0 (*C*H$_3$CH); ν_{max} 2978 (m, C-H), 1733 (s, C=O ester), 1653 (s, C=O amide), 1478 (m, Ar), 1394 (m), 1257 (m), 1143 (s, C-O), 738 (w); **m/z** (ESI$^+$) 508 ([M+Na]$^+$, 100%), 993 ([2M+Na]$^+$, 57%), (ESI$^-$) 484 ([M-H]$^-$, 100%); HRMS found 508.1578, $C_{23}H_{35}NNaO_5{}^{80}Se$ requires 508.1574.

(*R*)-Di-*tert*-butyl 2-(N,2-dimethylbut-3-enamido)malonate, (-)-2.141



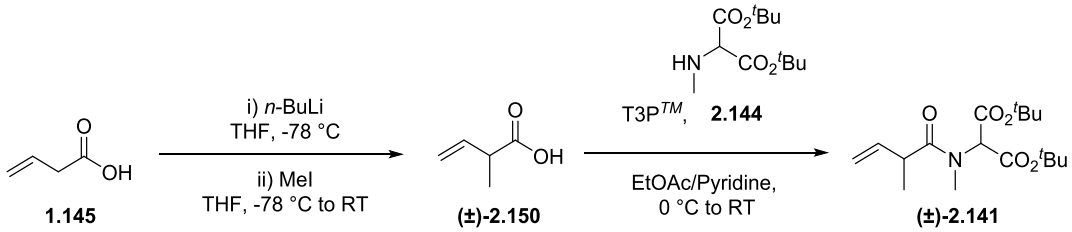
(-)-2.142 **(-)-2.141**

The first batch of the title compound was prepared according to the modified procedure of Danishefsky *et al.*[21] : H_2O_2 in water (30%, 1.3 mL, 13.1 mmol) was added to (*R*)-di-*tert*-butyl 2-(N,2-dimethylbut-3-enamido)malonate **(-)-2.142** (422 mg, 0.870 mmol) in THF at RT (13 mL). The reaction was stirred for 3 h, and quenched at 0 °C with a solution of $FeSO_4$ (3.30 g) and CiH (1.03 g) in water (5 mL) dropwise. The mixture was then stirred for 30 min at RT. After dilution with water (50 mL), the mixture was extracted with DCM (2 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and heated under reflux for 12 h. The residue was purified by FC (1:12 to 1:6 EtOAc/PE), which gave the title **(-)-2.141** compound as a colourless oil (0.237 g, 0.724 mmol, 83%). On larger scale (2.63 g, 4.40 mmol), the quenching led to a strong exotherm when the reaction was warmed to RT, and the yield drop to 66%. The procedure was not re-attempted.

According to the modified procedure of Kocienski *et al.*,[74] $NaIO_4$ (31.6 g, 148 mmol) was added portionwise over 5 min to a stirred mixture of (*R*)-di-*tert*-butyl 2-(*N*,2-dimethyl-4-(phenylselanyl)butanamido)malonate **(-)-2.142** (18.4 g, 36.8 mmol) and $NaHCO_3$ (12.4 g, 148 mmol) in MeOH/THF/H_2O (1:1:1, 600 mL) at RT. The reaction mixture was stirred under air for 45 min. $CHCl_3$ (250 mL) was added and the mixture was stirred vigorously for 5 min. The all mixture was filtered through Celite, which was then eluted with $CHCl_3$ (2 × 75 mL). The mixture was washed with water (200 mL). The aqueous layer was extracted with more $CHCl_3$ (2 × 100 mL) and the combined organic extracts were dried (Na_2SO_4) and filtered. The crude selenoxide solution was heated under reflux at 65 °C for 4 h. The reaction was cooled to RT and the solvent was removed under reduced pressure. The residue was purified by FC (1:12 to 1:6 EtOAc/PE), which gave the title compound **(-)-2.141** as a

colourless oil (11.9 g, 34.9 mmol, 95%). **R_f** 0.48 (1:12 EtOAc/PE); $[\alpha]_D^{20}$ -18.5 (c = 1.00, $CHCl_3$); **e.e** (HPLC Chiralpak AD-H column 10% IPA/hexane) > 96%; **δ_H** (400 MHz, $CDCl_3$) mixture of rotamers (ratio 6:1); 5.86 (1H, ddd, *J* = 17.4, 10.4, 6.8, HH'C=C*H*), 5.81 (1H, s, NC*H*), 5.15–5.00 (2H, m, *HH*'C=CH), 3.43/3.28 (1H, *dq*, *J* = 6.8, 6.8, C*H*CH_3), 3.11/2.97 (3H, s, NCH_3), 1.47 (9H, s, OC(CH_3)$_3$), 1.46 (9H, s, OC(CH_3)$_3$), 1.24 (3H, d, *J* = 6.8, CHCH_3); **δ_C** (100 MHz, $CDCl_3$) 174.6 (*C*=O), 166.0 (*C*=O), 165.8 (*C*=O), 137.5 (CH_2=*C*H), 115.7 (*C*H_2=CH), 82.8 (2 × $CO_2C(CH_3)_3$), 61.4 (N*C*H(CO_2tBu)$_2$), 40.7 (CO*C*HCH_3), 33.2 (N*C*H_3), 27.9 (2 × OC(*C*H_3)$_3$), 17.6 (*C*H_3CH); **ν_{max}** 2979 (s, C-H), 1734 (s, C=O ester), 1659 (m, C=O amide), 1458 (w), 1394 (w), 1370 (m), 1255 (m), 1143 (s, C-O ester), 918 (w, C-H alkene); **m/z** (ESI^+) 350 ([M+Na]$^+$, 64%), 677 ([2M+Na]$^+$, 100%), (ESI^-) 326 ([M-H]$^-$, 100%); HRMS found 350.1943, $C_{17}H_{29}NNaO_5$ requires 350.1938.

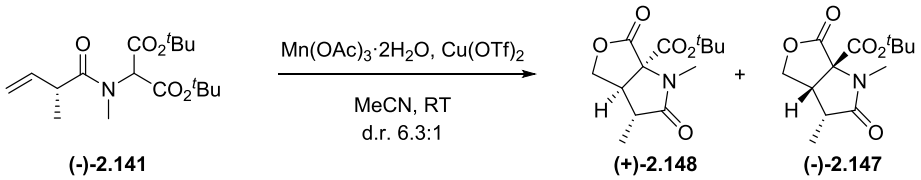
(±)-Di-*tert*-butyl 2-(N,2-dimethylbut-3-enamido)malonate, (±)-2.141



To a vigorously stirred solution of vinylacetic acid **1.145** (6.72 mL, 79 mmol) in THF (150 mL), was added a solution *n*-BuLi in hexanes (2.5 M, 66.4 mL, 166 mmol) at -78 °C. After 10 min stirring, MeI (237 mmol, 14.8 mL) The reaction mixture was warmed to RT over 2 h, and stirred at this temperature for 2 h. Et_2O (150 mL) and an aqueous solution of NaOH (0.5 M, 200 mL) were added at 0 °C. The aqueous phase was separated and acidified at 0 °C with a solution of concentrated HCl solution until pH < 2. The aqueous phase was then extracted with Et_2O (2 x 200 mL), the combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was distilled under reduced pressure, which gave an inseparable mixture of starting material **1.145** and carboxylic acid **(±)-2.141**. **b.p.** (mixture) 70 °C (1.2 mmHg).

To the mixture of acids **1.145** and **(±)-2.141** (7.16 g) and 1-(*tert*-butyl) 3-butyl 2-(methylamino)malonate (15.0 g, 65 mmol) at 0 °C in EtOAc (60 mL) and pyridine (25 mL) was added T3P solution (50% in EtOAC, 58.0 mL, 97.5 mmol). The reaction mixture was stirred for 1 h at this temperature and 3 h at RT, before dilution with EtOAc (250 mL). The mixture was washed with an aqueous solution of saturated $NaHCO_3$ (250 mL), water (100 mL) and 10% brine (100 mL). The solvent was evaporated and the residue was purified by FC (1:9 EtOAc/PE), which gave the title compound **(±)-2.141** as colourless oil (7.01 g, 21.4 mmol, 27%). *The characterisation is given the preparation of the enantioenriched compound.*

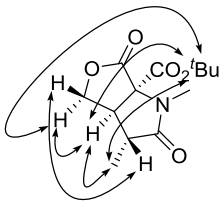
(+)-(3*R*,3a*R*,6a*S*-*tert*-Butyl 1,3-dimethyl-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylate, (+)-2.148



(-)-2.141 (+)-2.148 (-)-2.147

According to the modified procedure of Sprague *et al.,*[160] $Mn(OAc)_3{\cdot}2H_2O$ (19.5 g, 72.8 mmol) and $Cu(OTf)_2$ (2.62 mg, 7.28 mmol) were quickly and simultaneously added to a solution of (*R*)-di-*tert*-butyl 2-(N,2-dimethylbut-3-enamido)malonate **(-)-2.141** (11.9 g, 36.4 mmol) in nitrogen sparged MeCN (190 mL, un-dried) under argon atmosphere at RT. The reaction mixture was stirred at RT for 8 h. Water (200 mL) and a saturated aqueous solution of NH_4Cl (100 mL) were added and the mixture was extracted with DCM (1 x 400 mL, 1 x 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:1 Et_2O/Pentane), which gave the two diastereoisomers. The title major diastereoisomer **(+)-2.148** was isolated as a colourless sticky gum contaminated with 19% *N*-(tert-butyl)acetamide (8.10 g equivalent to 6.56 g of pure compound, 24.4 mmol, 67%). $\mathbf{R_f}$ 0.22 (1:1 EtOAc/PE); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ +89.5 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.66 (1H, dd, *J* = 9.2, 8.2, OC*H*H'CH), 4.11 (1H, dd, *J* = 9.2, 4.6, OCH*H'*CH), 3.04 (3H, s, NCH_3), 2.88 (1H, ddd, *J* = 12.1, 8.2, 4.6, OCHH'C*H*), 2.44 (1H, dq, *J* = 12.1, 7.3, C*H*CH_3), 1.51 (9H, s, OC(CH_3)$_3$), 1.27 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_H}$ (400 MHz, MeOD-d_4) 4.70 (1H, dd, *J* = 9.6, 8.1, OC*H*H'CH), 4.22 (1H, dd, *J* = 9.6, 4.5, OCH*H'*CH), 3.05 (1H, ddd, *J* = 8.1, 4.5, 4.5, OCH_2CH), 2.99 (3H, s, NCH_3), 2.56 (1H, qd, *J* = 7.3, 4.5, C*H*CH_3), 1.52 (9H, s, OC(CH_3)$_3$), 1.24 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.7 (*C*=O), 170.3 (*C*=O), 166.5 (*C*=O), 85.2 (O*C*(CH$_3$)$_3$), 71.2 (OCH_2), 70.5 (C_{quat}), 47.2 (OCH_2CH), 41.8 (*C*HCH_3), 28.0 (OC(*C*H$_3$)$_3$), 27.7 (NCH$_3$), 16.4 (CH*C*H$_3$); $\boldsymbol{\nu_{max}}$ 2979 (w, C-H), 1780 (m, C=O), 1748 (m, C=O), 1708 (s, C=O), 1370 (m), 1260 (m), 1140 (m), 1044 (w), 836 (w); **m/z** (ESI$^+$) 292 ([M+Na]$^+$, 26%), 561 ([2M+Na]$^+$, 100%); HRMS found 292.1161, $C_{13}H_{19}NNaO_5$ requires 292.1155.

Key nOe interactions in MeOD
(major diastereoisomer)

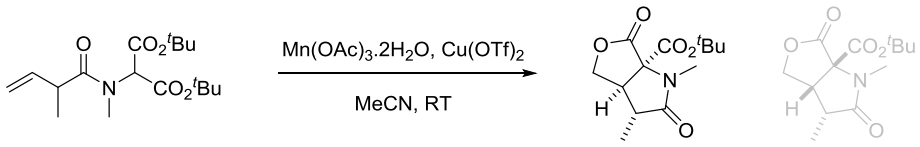


(-)-2.148

The minor diastereoisomer **(-)-2.147** was isolated as a white solid (1.05 g, 3.90 mmol, 10.7%). $\mathbf{R_f}$ 0.25 (1:1 EtOAc/PE); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$-72.1 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.50 (1H, dd, *J* = 10.0, 8.0, OC*H*H'CH), 4.15 (1H, dd, *J* = 10.0, 8.0, OCH*H'*CH), 3.39 (1H, ddd, *J* = 15.5, 8.0, 8.0, OCH_2CH), 2.99 (3H,

s, NCH_3), 2.75 (1H, dq, *J* = 15.5, 7.3, C*H*CH$_3$), 1.51 (9H, s, OC(CH_3)$_3$), 1.20 (3H, d, *J* = 7.3, CHCH_3); **δ$_C$** (100 MHz, $CDCl_3$) 175.1 (*C*=O lactam), 169.8 (*C*=O lactone), 166.1 (C=O ester), 84.9 (O*C*(CH$_3$)$_3$), 70.2 (OCH$_2$), 67.2 (C_{quat}), 43.4 (OCH$_2$*C*H), 37.1 (*C*HCH$_3$), 27.9 (OC(*C*H$_3$)$_3$), 27.5 (N-*C*H$_3$), 10.6 (CH*C*H$_3$); **ν$_{max}$** 2979 (w, C-H), 1782 (m, C=O), 1740 (m, C=O), 1710 (m, C=O), 1432 (s), 1258 (m), 1149 (m, C-O), 1036 (w), 992 (w), 836 (w); **m/z** (ESI$^+$) 292 ([M+Na]$^+$, 85%), 561 ([2M+Na]$^+$, 100%); HRMS found 292.1159, $C_{13}H_{19}NNaO_5$ requires 292.1155.

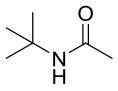
(±)-(3*R*,3a*R*,6a*S*-*tert*-Butyl 1,3-dimethyl-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylate, (±)-2.148



(±)-2.141 **(±)-2.148** (±)-2.147

The title compound **(±)-2.148** was prepared according to the previous procedure, using (±)-di-*tert*-butyl 2-(N,2-dimethylbut-3-enamido)malonate **(±)-2.141** (6.98 g, 21.4 mmol). The lactone **(±)-2.148** was obtained as a sticky solid contaminated with 13% N-(tert-butyl)acetamide (total mass 4.40 g equivalent to 3.83 g of pure compound, 14.2 mmol, 67%). *The characterisation is given for the enantioenriched material.*

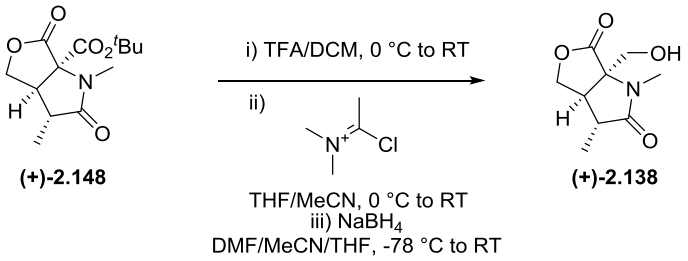
N-(*tert*-Butyl)acetamide, 2.162



2.162

The title compound **2.162** was isolated as a side product of the previous oxidative radical cyclisation, which partially sublimed out of the reaction crude as a white solid upon drying at RT under high vacuum (1 mmHg). **δ$_H$** (400 MHz, $CDCl_3$) 5.65–5.15 (1H, br, N*H*), 1.91 (3H, s, CH_3), 1.33 (9H, s, C(CH_3)$_3$); **δ$_C$** (100 MHz, $CDCl_3$) 169.7 (*C*=O), 51.3 (C_{quat}), 28.9 (C(CH_3)$_3$), 24.6 (*C*H$_3$); **m/z** (ESI$^+$) 253 ([2M+Na]$^+$, 100%), 139 ([M+Na]$^+$, 65%). NMR data is in accordance with the literature.[178]

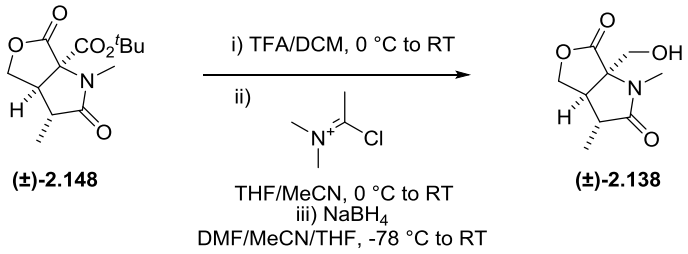
(+)-(3*R*,3a*R*,6a*R*)-6a-(Hydroxymethyl)-1,3-dimethyldihydro-1*H*-furo[3,4-*b*]pyrrole-2,6(3H,6aH)-dione, (+)-2.138



To a solution of (3*R*,3a*R*,6a*R*)-*tert*-butyl 1,3-dimethyl-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate **(+)-2.148** (6.56 g, 24.4 mmol) in DCM (50 mL) at 0 °C, was added TFA (50 mL). The reaction was stirred at RT for 20 h. The solvent was removed under reduced pressure and the residue was co-evaporated from toluene (3 x 10 mL), which gave the crude carboxylic acid **2.163** as a grey solid.

To a vigorously stirred solution of DMF (4.00 mL, 51.2 mmol) in dry DCM (80 mL) at 0 °C was slowly added $(COCl)_2$ (13.3 mL, 154 mmol). The mixture was stirred at RT for 30 min and all volatiles were removed under reduced pressure. The flask was backfilled with nitrogen and the white residual salt was dissolved in THF/MeCN (166 mL, 3:2). The crude carboxylic acid **2.163** was dissolved in THF (160 mL, heating at 50 °C and sonification required). The solution of carboxylic acid was added via cannula over 10 min to the Vilsmeier salt solution at 0 °C. The reaction mixture was then stirred at RT for one hour and cooled to -78 °C. A freshly prepared solution of $NaBH_4$ (3.75 g, 51.2 mmol) in DMF (60 mL) was added slowly over 10 min. After complete addition the reaction mixture was stirred for 15 min, warmed to RT and stirred for 2 h. A solution of aqueous HCl (6.0 M, 85 mL) was carefully added at 0 °C. The mixture was stirred for 20 min at RT, the solvent was then evaporated under reduced pressure and the residue was dissolved in MeOH (200 mL), dry loaded onto silica (40 g) and purified by FC (1:4 to 1:0 EtOAc/PE), which gave the title compound **(+)-2.138** as light yellow oil contaminated by DMF 24% by weight (5.74 g equivalent to 4.36 g of pure compound, 21.9 mmol, 90% over 2 steps). $\mathbf{R_f}$ 0.51 (EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +56.0 (c = 1.00, MeOH); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.64 (1H, dd, *J* = 9.5, 8.3, OC*H*H'CH), 4.12 (1H, dd, *J* = 9.5, 4.3, OCH*H*'CH), 4.00 (1H, dd, *J* = 11.1, 5.1, C*H*H'OH), 3.85 (1H, dd, *J* = 11.1, 2.3, CH*H*'OH), 2.93 (3H, s, NCH_3), 2.92–2.88 (1H, m, OCHH'C*H*), 2.48 (1H, qd, *J* = 7.3, 4.8, C*H*CH_3), 2.32 (1H, br, O*H*), 1.35 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.3 (*C*=O), 174.0 (*C*=O), 72.0 (CH_2), 68.3 (C_{quat}), 61.4 (CH_2), 43.2 (*C*H), 42.7 (*C*H), 26.1 (NCH_3), 16.7 (CH_3); $\boldsymbol{\nu_{max}}$ 1764 (m, C=O), 1668 (m, C=O), 1390 (m), 1207 (m), 1035 (m), 977 (s); **m/z** (ESI^+) 222 ($[M+Na]^+$, 85%), 421 ($[2M+Na]^+$, 80%); HRMS 222.0736, $C_9H_{13}NNaO_4$ requires 222.0737.

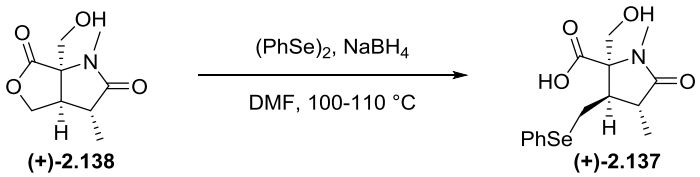
(±)-(3*R*,3a*R*,6a*R*)-6a-(Hydroxymethyl)-1,3-dimethyldihydro-1*H*-furo[3,4-*b*]pyrrole-2,6(3H,6aH)-dione, (±)-2.138



(±)-2.148 (±)-2.138

The title compound **(±)-2.138** was prepared using the previous procedure, starting from (±)-(3*R*,3a*R*,6a*S*-*tert*-vutyl 1,3-dimethyl-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylate **(±)-2.148** (3.83 g, 14.2 mmol), and was obtained as a colourless oil containing contaminated with DMF 16% by weight (3.36 g equivalent to 2.72 g of pure compound, 13.7 mmol, 96%). *The characterisation is given for the enantioenriched material.*

(+)-(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid, (+)-2.137

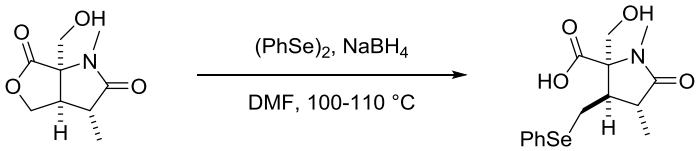


(+)-2.138 (+)-2.137

According to the modified procedure of Smith *et al.*,[59] a solution of $NaBH_4$ (815 mg, 21.9 mmol) in nitrogen sparged DMF (35 mL) was added slowly (5 mL/min) to $(PhSe)_2$ (4.10 g, 13.4 mmol) in nitrogen sparged DMF (145 mL) at 100 °C under argon until the yellow colour disappeared (only 25 mL of solution was added over 5 min). The addition was then stopped and this mixture was stirred at 100 °C for 10 min, and (3*R*,3a*R*,6a*R*)-6*a*-(hydroxymethyl)-1,3-dimethyldihydro-1*H*-furo[3,4-*b*]pyrrole-2,6(3H,6*a*H)-dione **(+)-2.138** (4.36 g, 21.9 mmol) in nitrogen sparged DMF (80 + 20 mL rinse) was added rapidly via cannula. The reaction was then heated at 110 °C for 2 h and was then quenched at RT with a solution of pH 2 sulfate buffer (5 mL). The solvent was evaporated, and the residue was dry loaded on silica to be purified on a short silica column (1:1 to 1:0 EtOAc/PE, then 1:20 to 1:9 MeOH/EtOAc), which gave the title compound **(+)-2.137** as a colourless oil containing 17% DMF by weight (7.75 g equivalent to 6.43 g of pure compound, 18.1 mmol, 83%). $\mathbf{R}_f$ 0.14 (1:10:90, AcOH/MeOH/DCM); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +35.5 (c = 1.00 in MeOH); $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz, MeOD-d_4) 7.55–7.50 (2H, m, Ar*H*), 7.31–7.21 (3H, m, Ar*H*), 3.95 (1H, d, *J* = 12.4, C*H*H'OH), 3.92 (1H, d, *J* = 12.4, CH*H'*OH), 3.31–3.27 (1H, m, PhSeC*H*H'), 2.98 (1H, dd, *J* = 11.9, 8.8, PhSeCH*H'*), 2.77 (s, 3 H, NCH_3), 2.39–2.35

(2H, m, C*H*CH$_3$ and C*H*CH$_2$), 1.23 (3H, d, *J* = 6.6, CHC*H*$_3$); **δ$_c$** (100 MHz, MeOD-*d4*) 179.2 (2 × *C*=O), 132.5 (*Ar*), 130.9 (*Ar*), 129.2 (*Ar*), 127.0 (*Ar*), 61.3 (*C*H$_2$O), 55.0 (weak, *C$_{quat}$*), 44.5 (*C*H), 43.1 (*C*H), 28.4 (Se*C*H$_2$ or N*C*H$_3$), 26.5 (Se*C*H$_2$ or N*C*H$_3$), 16.1 (CH*C*H$_3$); **ν$_{max}$** 3392 (br, OH) 1658 (s, C=O) 1598 (s), 1398 (m), 736 (m); **m/z** (ESI$^-$) 356 ([M-H]$^-$, 100%), 713 ([2M-H]$^-$, 30%); HRMS found 356.0407, $C_{15}H_{18}NO_4{}^{80}Se$ requires 356.0407.

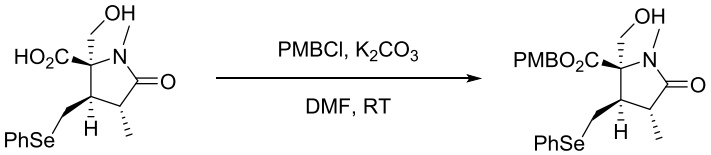
(±)-(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid, (±)-2.138



(±)-2.137 **(±)-2.138**

The title compound **(±)-2.137** was prepared according to the previous procedure, using (±)-(3*R*,3a*R*,6a*R*)-6a-(hydroxymethyl)-1,3-dimethyldihydro-1*H*-furo[3,4-*b*]pyrrole-2,6(3H,6aH)-dione **(±)-2.138** (2.72 g, 13.7 mmol), and was obtained as a colourless oil containing with 9% DMF by weight (4.78 g equivalent to 4.35 g of pure compound, 12.2 mmol, 89%). *The characterisation is given for the enantioenriched material.*

(+)-4-methoxybenzyl (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, 5.5

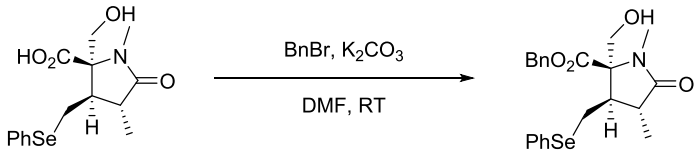


(+)-2.137 **(+)-5.10**

To a stirred mixture of K_2CO_3 (194 mg, 1.40 mmol) and (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid **(+)-2.137** (179 mg, 0.500 mmol) in DMF (3.0 mL), was added PMBCl (95 µL, 0.70 mmol). The mixture was stirred for 24 h and more K_2CO_3 (194 mg, 1.40 mmol) and PMBCl (95 µL, 0.70 mmol) were added. After 12 h stirring, the mixture was diluted with EtOAc (20 mL) and washed with 10% brine (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:1 to 1:0 EtOAc/PE), which gave the title compound **5.5** as a white solid (194 mg, 0.407 mmol, 81%); **R$_f$** 0.38 (1:1 EtOAc/PE); **m.p**. = 84–87 °C; $[\alpha]_D^{20}$ +52.4 (c = 0.50, $CHCl_3$); **δ$_H$** (400 MHz, $CDCl_3$) 7.43–7.37 (2H, m, Ar*H*), 7.32–7.24 (5H, m, Ar*H*), 6.91–6.84 (2H, d, *J* = 8.6, Ar*H*), 5.22 (1H, d, *J* = 11.6, OC*H*H'Ar), 5.11 (1H, d, *J* = 11.6, OCH*H*'Ar), 4.03 (1H, dd, *J* = 12.4, 5.1, C*H*H'OH), 3.91 (1H, dd, *J* = 12.4, 8.3, CH*H*'OH), 3.81 (3H, s, OCH_3), 2.90 (1H, dd, *J* = 12.6, 5.9, C*H*H'Se),

2.76 (3H, s, NCH_3), 2.67 (1H, dd, *J* = 12.6, 7.6, CH*H'*Se), 2.30 (1H, m, C*H*CH_3), 2.20 (1H, ddd, *J* = 9.9, 7.6, 5.9, C*H*CHH'Se), 2.02 (1H, dd, *J* = 8.3, 5.3, O*H*), 1.22 (3H, d, *J* = 7.1, CHCH_3); **δ_C** (100 MHz, $CDCl_3$) 177.5 (*C*=O), 170.8 (*C*=O), 160.1 (*Ar*), 132.8 (*Ar*), 130.8 (*Ar*), 129.9 (*Ar*), 129.4 (*Ar*), 127.4 (*Ar*), 127.0 (*Ar*), 114.2 (*Ar*), 72.6 (C_{quat}), 67.5 (OCH_2Ar), 62.9 (CH_2OH), 55.4 (OCH_3), 45.1 (*C*H), 41.9 (*C*H), 27.3 (NCH_3), 27.0 (CH_2Se), 16.1 (CHCH_3); **ν_{max}** 3385 (br, O-H), 2932 (w, C-H), 1731 (m, C=O), 1677 (s, C=O), 1515 (m), 1247 (m), 1031 (w), 740 (w); **m/z** (ESI^+) 915 ([2M+Na]$^+$, 100%), 470 ([M+Na]$^+$, 90%); HRMS found 470.0830, $C_{22}H_{25}NNaO_4{}^{80}Se$ requires 470.0842.

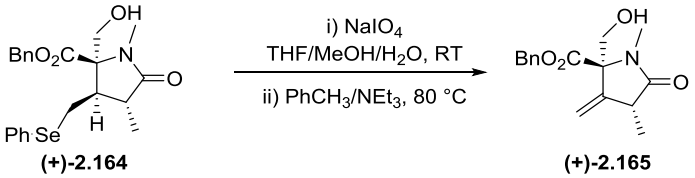
(+)-(2*R*,3*R*,4*R*)-Benzyl 2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (+)-2.164



(+)-2.137 **(+)-2.164**

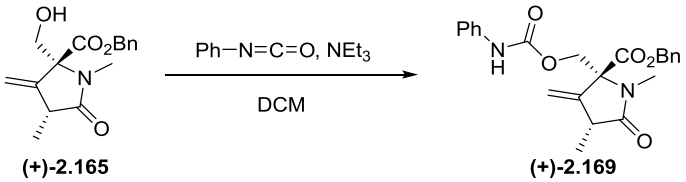
According to the procedure of Endo et al.,[21] benzyl bromide (5.1 mmol, 0.60 mL) was added dropwise to a stirred mixture K_2CO_3 (1.40 g, 10.2 mmol) and (2R,3R,4R)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid **(+)-2.137** (980 mg, 2.04 mmol) in DMF (10 mL). The reaction mixture was stirred at RT for 60 min, which was then concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and H_2O (50 mL), and the aqueous phase was separated. The organic layer was then washed with brine (30 mL). The combined aqueous layers were extracted with more EtOAc (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated, which gave the title compound **(+)-2.164** as a white solid (880 mg, 1.97 mmol, 97%). **R_f** 0.24 (3:2 EtOAc/PE); **m.p**. = 118–125 °C; $[\alpha]_D^{20}$ +45.6 (c = 1.00, $CHCl_3$). **δ_H** (400 MHz, $CDCl_3$) 7.43–7.39 (2H, m, Ar*H*), 7.38–7.33 (4H, m, Ar*H*), 7.29–7.25 (4H, m, Ar*H*), 5.26 (1H, d, *J* = 12.0, PhC*H*H'), 5.18 (1H, d, *J* = 12.0, PhCH*H'*), 4.04 (1H, dd, *J* = 12.4, 5.0, C*H*H'OH), 3.92 (1H, dd, *J* = 12.4, 8.0, CH*H'*OH), 2.90 (1H, dd, *J* = 12.6, 6.0, PhSeC*H*H'), 2.77 (3H, s, NCH_3), 2.70 (1H, dd, *J* = 12.6, 7.7, PhSeCH*H'*), 2.33 (1H, dq, *J* = 10.1, 7.0, CHC*H*CH_3), 2.20 (1H, ddd, *J* = 10.1, 7.7, 6.0, C*H*$CHCH_3$), 1.96 (1H, dd, *J* = 8.0, 5.0, OH), 1.22 (3H, d, *J* = 7.0, CH_3CH); **δ_C** (100 MHz, $CDCl_3$) 177.3 (*C*=O), 170.6 (*C*=O), 134.7 (*Ar*), 132.8 (*Ar*), 129.7 (*Ar*), 129.3 (*Ar*), 128.9 (*Ar*), 128.8 (*Ar*), 128.8 (*Ar*), 127.4 (*Ar*), 72.6 (C_{quat}), 67.6 (OCH_2Ph), 62.8 (CH_2OH), 45.1 (*C*H$CHCH_3$), 41.8 (*C*HCH_3), 27.2 (NCH_3), 27.0 (PhSeCH_2), 16.0 (s, *C*H_3); **ν_{max}** 3392 (br, OH), 1733 (m, C=O), 1677 (s, C=O), 1210 (w), 739(w); **m/z** (ESI^+) 500 ([M+Na]$^+$, 100%); HRMS found 500.0947, $C_{23}H_{27}NNaO_5{}^{80}Se$ requires 500.0947.

(+)-(2*R*,4*R*)-Benzyl 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate, (+)-2.165



To a stirred solution of (2*R*,3*R*,4*R*)-benzyl 2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate **(+)-2.164** (875 mg, 1.96 mmol) in MeOH (15 mL), THF (15 mL) and H_2O (20 mL) at RT, was added $NaHCO_3$ (0.490 g, 5.88 mmol) followed by $NaIO_4$ (1.25 g, 5.88 mmol). The reaction was stirred at RT for 15 min, and then DCM (100 mL) and H_2O (100 mL) were added. The mixture was stirred vigorously for 5 min before being filtered through a Celite™ pad eluted with DCM (2 x 20 mL). The organic layer was then decanted off and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was then rapidly evaporated under reduced pressure and the residual selenoxide was dissolved in $PhCH_3$ (35 mL) and NEt_3 (3.5 mL). The selenoxide solution was purged with nitrogen, and was heated at 80 °C for 15 min. The mixture was then cooled to RT, and was poured on a solution of aqueous pH 2 sulfate buffer (100 mL) and extracted with DCM (1 × 150 mL, then 2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:1 EtOAc/PE), which gave the title compound **(+)-2.165** as a white solid (518 mg, 1.79 mmol, 91%). $\mathbf{R_f}$ 0.19 (EtOAc/PE 3:2); **m.p.** = 82–85 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +82.1 (c = 1.00, $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40–7.33 (3H, m, Ar*H*), 7.31–7.28 (2H, m, Ar*H*), 5.37 (1H, dd, *J* = 2.8, 1.0, C*H*H'=C), 5.26 (1H, dd, *J* = 2.8, 1.0, CH*H'*=C), 5.22 (1H, d, *J* = 12.3, PhC*H*H'), 5.16 (1H, d, *J* = 12.3, PhCH*H'*), 4.12 (1H, dd, *J* = 12.5, 6.7, C*H*H'OH), 3.98 (1H, dd, *J* = 12.5, 6.7, CH*H'*OH), 3.10 (1H, qdd, *J* = 7.4, 2.8, 2.8, C*H*CH_3), 2.98 (3H, s, NCH_3), 1.93 (1H, dd, 6.7, 6.7, OH), 1.31 (1H, d, *J* = 7.4, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.3 (*C*=O), 169.8 (*C*=O), 145.0 (CH_2=*C*), 134.9 (*Ar*), 128.7 (*Ar*), 128.6 (*Ar*), 128.1 (*Ar*), 110.6 (CH_2=C), 73.6 (C_{quat}), 67.6 (Ph*C*H_2O), 64.3 (*C*H_2OH), 39.9 (*C*HCH_3), 27.1 (NCH_3), 15.9 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 3392 (br, OH), 1738 (m, C=O ester), 1687 (s, C=O lactam), 1659 (m), 1622 (m), 1022 (w); **m/z** (ESI^+) 601 ($[2M+Na]^+$, 100%), 312 ($[M+Na]^+$, 57%); HRMS found 312.1195, $C_{19}H_{19}NNaO_4$ requires 312.1206.

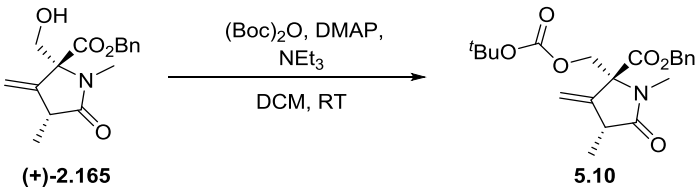
(+)-Benzyl (2*R*,4*R*)-1,4-dimethyl-3-methylene-5-oxo-2-(((phenylcarbamoyl)oxy)methyl)pyrrolidine-2-carboxylate, (+)-2.169



(+)-2.165 **(+)-2.169**

To a mixture of (+)-(2*R*,4*R*)-benzyl 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.165** (150 mg, 0.520 mmol) and NEt_3 (90 µL, 0.52 mmol) in dry DCM (1 mL) was added phenyl isocyanate (70 µL, 0.52 mmol) over 1 min. The reaction mixture was stirred at RT for 20 min and was diluted with EtOAc (7 mL). The mixture was washed with an aqueous solution of pH 2 sulfate buffer (7 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:3 EtOAc/PE), which gave the title compound **(+)-2.169** as a white solid (217 mg, 0.520 mmol, quant.). $\mathbf{R_f}$ 0.46 (2:3 EtOAc/PE); $[\alpha]_D^{20}$ +23.4 (c = 1.00, $CHCl_3$); **m.p.** 129–132 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.49–7.25 (9H, m, Ar*H*), 7.11–7.04 (1H, m, Ar*H*), 7.04–6.94 (1H, br, N*H*), 5.46 (1H, dd, *J* = 2.9, 1.2, =C*H*H'), 5.27 (1H, dd, *J* = 2.3, 1.2, CH*H'*), 5.24 (1H, d, *J* = 12.2, OC*H*H'Ph), 5.18 (1H, d, *J* = 12.2, OCH*H'*Ph), 4.76 (1H, d, *J* = 12.2, NCO_2CHH'), 4.57 (1H, d, *J* = 12.2, NCO_2CHH'), 3.18–3.05 (1H, m, C*H*CH_3), 2.86 (3H, s, NCH_3), 1.43–1.15 (3H, d and br, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.2 (*C*=O), 168.8 (*C*=O), 144.3 (Ar or *C*=CH_2), 137.5 (*Ar*), 134.8 (*Ar*), 129.2 (*Ar*), 128.9 (*Ar*), 128.4 (*Ar*), 123.9 (*Ar*), 118.9 (*Ar*), 111.4 (C=*C*H_2), 72.1 (C_{quat}), 68.0 (O*C*H_2Ph), 64.0 (NCO_2CH_2), 39.8 (*C*H), 26.9 (*C*H), 16.1 (*C*HCH_3); $\boldsymbol{\nu_{max}}$ 1736 (m, C=O), 1692 (s, C=O), 1212 (s), 1061 (w), 750 (s), 694 (m); **m/z** (ESI^+) 431 ($[M+Na]^+$, 80%); HRMS found 431.15643 $C_{23}H_{24}N_2NaO_5$ requires 431.15774.

Benzyl (2*R*,4*R*)-2-(((*tert*-Butoxycarbonyl)oxy)methyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate, (-)-5.6

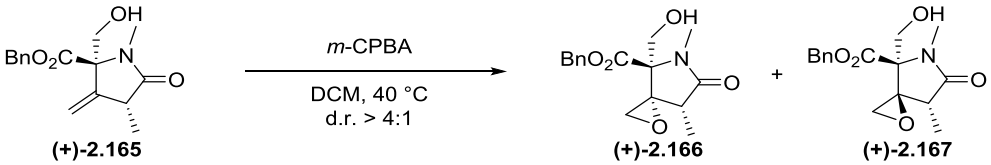


(+)-2.165 **5.10**

To a mixture of 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.165** (50 mg, 0.173 mmol), Boc_2O (75.5 mg, 0.346 mmol), DMAP (42.3 mg, 0.43 mg) were successively added DCM (0.6 mL) and NEt_3 (48 µL, 0.35 mmol). The reaction mixture was stirred for 12 h at RT, and was diluted with EtOAc (5 mL). The mixture was washed an aqueous solution of NH_4Cl (2.0 M, 5 mL). The aqueous layer was extracted with more EtOAc (5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:4 EtOAc/PE),

which gave the title compound **(-)-5.6** as a colourless oil (51.8 mg, 0.133 mmol, 77%); $\mathbf{R_f}$ 0.32 (1:4 EtOAc/PE); $[\alpha]_D^{20}$ -4.0 (c = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.40–7.25 (5H, m, Ar*H*), 5.39 (1H, dd, *J* = 2.5, 1.2, =C*H*H'), 5.25 (1H, dd, *J* = 2.5, 1.2, =CH*H'*), 5.23 (1H, d, *J* = 12.5, OC*H*H'Ph), 5.17 (1H, d, *J* = 12.5, OCH*H'*Ph), 4.59 (1H, d, *J* = 12.1, (CO)OC*H*H'), 4.51 (1H, d, *J* = 12.1, (CO)OCH*H'*), 3.08 (1H, m, C*H*CH_3), 2.83 (3H, s, NCH_3), 1.44 (9H, s, OC(CH_3)$_3$), 1.33 (3H, d, *J* = 7.3, CHCH_3); δ_C (100 MHz, $CDCl_3$) 176.3 (*C*=O), 168.8 (*C*=O), 153.1 (*C*=O), 144.6 (C_{quat}=CH_2), 134.5 (*Ar*), 128.8 (*Ar*), 128.3 (*Ar*), 111.3 (=*C*H_2), 82.9 (C_{quat}), 72.2 (C_{quat}), 68.0 (O*C*H_2Ph), 65.9 ((CO)O*C*H_2), 39.9 (*C*HCH$_3$), 27.8 (OC(*C*H$_3$)$_3$), 27.7 (NCH$_3$), 16.4 (CH*C*H$_3$); ν_{max} 2979 (C-H, w), 1743 (s, C=O), 1706 (s, C=O), 1278 (m), 1253 (m), 1159 (m); **m/z** (ESI$^+$) 412 ([M+Na]$^+$, 100%), 390 ([M+H]$^+$, 20%); HRMS found 412.17191 $C_{21}H_{27}NNaO_7$ requires 412.17306.

(+)-(3*S*,4*S*,7*R*)-Benzyl 4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate, (+)-2.166

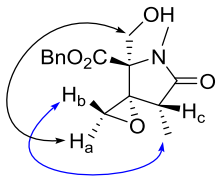


To a solution of (2*R*,4*R*)-benzyl 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.165** (126 mg, 0.435 mmol) in dry DCM (2.5 mL), was added a solution of *m*-CPBA in DCM (0.37 M, 0.56 mmol, 1.5 mL). The reaction mixture was stirred at 40 °C, and more *m*-CPBA solution (0.37 M, 1.30 mmol, 3.5 mL) was added over 48 h with a syringe pump. TLC (7:3 EtOAc/PE) showed incomplete conversion, another portion of *m*-CPBA (100 mg) was added and the reaction was heated for 24 h. An aqueous solution of saturated Na_2SO_3 (5 mL) was then added to the reaction mixture at 0 °C, which was stirred for 15 min. A solution of aqueous NaOH (1.0 M, 10 mL) and DCM (5 mL) were added, the layers were separated and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:1 EtOAc/PE), which gave the two separated diastereoisomers **(+)-2.166** and **(+)-2.167**. The title epoxide **(+)-2.166** was isolated as a sticky gum (60.7 mg, 0.199 mmol, 46%). $\mathbf{R_f}$ 0.50 (7:3 EtOAc/PE); **m.p**. = 82–85 °C; $[\alpha]_D^{20}$ +73.0 (c = 1.00 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.41–7.35 (3H, m, Ar*H*), 7.32–7.26 (2H, m, Ar*H*), 5.19 (2H, s, OCH_2Ph), 3.81 (2H, s, CH_2OH), 3.02 (1H, d, *J* = 3.8, C*H*H' epoxide), 2.91 (1H, s, NCH_3), 2.87 (1H, q, *J* = 7.5, C*H*CH$_3$), 2.80 (1H, d, *J* = 3.8, *CH*H' epoxide), 2.23 (1H, t, *J* = 7.7, O-*H*), 1.00 (3H, d, *J* = 7.5, CHCH_3); δ_C (100 MHz, $CDCl_3$) 175.0 (*C*=O), 169.3 (*C*=O), 134.6 (*Ar*), 128.9 (*Ar*), 128.8 (*Ar*), 128.3 (*Ar*), 70.7 (C_{quat}), 67.8 (OCH_2Ph), 62.4 (C_{quat}), 58.6 (*C*H_2OH), 46.5 (*C*H_2 epoxide), 37.2 (*C*HCH$_3$), 26.9 (NCH$_3$), 8.1 (CH*C*H$_3$); ν_{max} 3393 (br, O-H), 1738 (s, C=O ester),

1683 (s, C=O lactam), 1217 (m); **m/z** (ESI$^+$) 633 ([2M+Na]$^+$, 100%), 328 ([M+Na]$^+$, 69%) HRMS found 328.1152, $C_{16}H_{19}NNaO_5$ requires 328.1155.

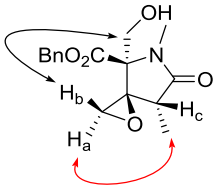
The minor diastereoisomer was isolated as a white solid **(+)-2.167** (12.6 mg, 0.041 mmol, 9.5%). $\mathbf{R_f}$ 0.31 (7:3 EtOAc/PE); **m.p.** = 117–120 °C; $[\alpha]_D^{20}$ +50.3 (c = 1.00 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ar*H*), 5.24 (1H, d, *J* = 12.1, OC*H*H'Ph), 5.17 (1H, d, *J* = 12.1, OCH*H'*Ph), 3.97 (1H, d, *J* = 12.5, C*H*H'OH), 3.90 (1H, d, *J* = 12.5, CH*H'*OH), 3.13 (1H, d, *J* = 3.8, C*H*H' epoxide), 3.05 (1H, d, *J* = 3.8, CH*H'* epoxide), 2.84 (3H, s, NCH_3), 2.72 (1H, q, *J* = 7.5, C*H*CH$_3$), 1.19 (3H, d, *J* = 7.5, CHCH_3); δ_C (100 MHz, $CDCl_3$) 175.8 (*C*=O), 167.7 (*C*=O), 134.8 (*Ar*), 128.7 (*Ar*), 128.6 (*Ar*), 128.3 (*Ar*), 77.2 (C_{quat}), 72.0 (C_{quat}), 67.7 (O*C*H$_2$Ph), 60.4 (*C*H$_2$OH), 49.0 (*C*H$_2$ epoxide), 39.7 (*C*HCH$_3$), 27.1 (N*C*H$_3$), 12.9 (CH*C*H$_3$); ν_{max} 3369 (br, OH), 1742 (s, C=O), 1680 (s, C=o), 1230 (m); **m/z** (ESI$^+$) 633 ([2M+Na]$^+$, 100%), 328 ([M+Na]$^+$, 70%); HRMS 328.1150, $C_{16}H_{19}NNaO_5$ requires 328.1155.

Key nOe interactions in $CDCl_3$
(+)-2.166, major diastereoisomer



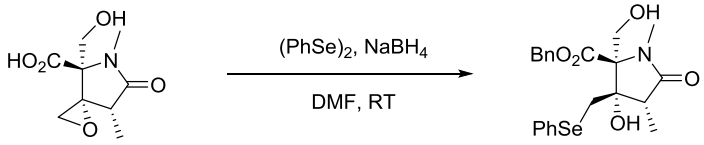
CH_3 - H_b : 0.5%
(CH_3 - H_c : 1.7 %)
ratio : 0.29

Key nOe interactions in $CDCl_3$
(+)-2.167, minor diastereoisomer



CH_3 - H_a : 1.0 %
(CH_3 - H_c : 1.8 %)
ratio : 0.56

(+)-(2*S*,3*S*,4*R*)-Benzyl 3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, 2.168

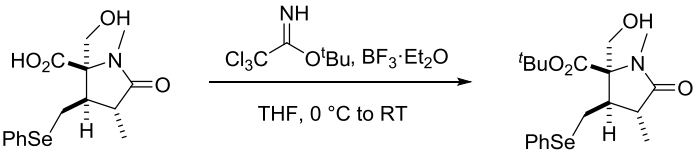


(+)-2.166 **2.168**

Diphenyl diselenide (10.3 mg, 2.06 µmol) was quickly warmed to 100 °C under argon in nitrogen sparged dry DMF (0.6 mL) and 0.1 mL of solution $NaBH_4$ in DMF was added (The solution was prepared by dissolving 15 mg of $NaBH_4$ in 1 mL of DMF). The colourless mixture was heated for 5 min before being cooled to RT and added to (3*S*,4*S*,7*R*)-benzyl 4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.166** (10.1 mg, 2.06 µmol) in dry degassed DMF (0.3 mL) at RT under argon. The reaction mixture was stirred for 2 h at RT and was quenched with a few drops of a solution of pH 2 sulfate buffer. All volatiles were removed *in vacuo*, the residue was dissolved in MeOH to be dry loaded on silica and purified by FC (EtOAc to 1:19 MeOH/EtOAc) and re-

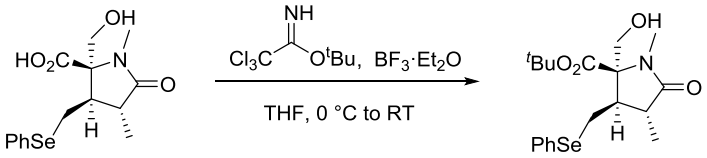
purified by FC (1:10 MeOH/Et_2O), which gave the title compound **2.168** as a colourless sticky oil (4.0 mg, 0.9 µmol, 26%). $\mathbf{R_f}$ 0.49 (Et_2O); $\mathbf{\delta_H}$ (500 MHz, $CDCl_3$) 7.41–7.32 (7H, m, Ar*H*), 7.31–7.23 (3H, m, Ar*H*), 5.26 (1H, d, *J* = 12.0, OC*H*H'Ph), 5.17 (1H, d, *J* = 12.0, OCH*H'*Ph), 4.33 (1H, dd, *J* = 12.9, 3.5, C*H*H'OH), 3.98 (1H, dd, *J* = 12.9, 10.2, CH*H'*OH), 3.37 (1H, s, $C_{quat}O\mathit{H}$), 3.13 (1H, d, *J* = 13.0, PhSeC*H*H'), 2.95 (1H, d, *J* = 13.0, PhSeCH*H'*), 2.88 (1H, dd, *J* = 10.2, 3.5, $CH_2O\mathit{H}$), 2.83 (3H, s, $NC\mathit{H_3}$), 2.46 (1H, q, *J* = 7.4, C*H*CH_3), 1.14 (3H, d, *J* = 7.4, CHC$\mathit{H_3}$); $\mathbf{\delta_C}$ (126 MHz, $CDCl_3$) 175.5 (*C*=O), 170.4 (C=O), 134.3 (*Ar*), 132.6 (*Ar*), 129.8 (*Ar*), 129.5 (*Ar*), 129.1 (*Ar*), 128.9 (*Ar*), 127.9 (*Ar*), 78.9 (C_{quat}), 74.9 (C_{quat}), 67.9 (OCH_2Ph), 61.1 (CH_2OH), 45.5 ($CHCH_3$), 37.6 (PhSeCH_2), 27.1 (NCH_3), 9.0 ($CHCH_3$); $\mathbf{\nu_{max}}$ 3340 (br, OH), 2929 (w, C-H), 1734 (m, C=O), 1679 (s, C=O), 1218 (m, C-O), 1065 (w), 741 (w), 694 (w); **m/z** (ESI^+) 486 ($[M+Na]^+$, 100%); HRMS found 486.0788, $C_{22}H_{25}NNaO_5{}^{80}Se$ requires 486.0791.

(±)-*tert*-Butyl (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (±)-2.174



According to the modified procedure of Long *et al.*,[143] *tert*-butyl 2,2,2-trichloroacetimidate (6.98 mL, 36.6 mmol) was added over 1 min followed by $BF_3{\cdot}Et_2O$ (1.49 mL, 12.2 mmol) over 5 min to a solution of (±)-(2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid) **(±)-2.137** (4.35 g, 12.2 mmol) in THF (90 mL) at 0 °C. The mixture was stirred at RT for 3 h. The solution was then carefully quenched with an aqueous solution of saturated $NaHCO_3$ (100 mL). After addition of Et_2O (100 mL), the aqueous layer was separated and re-extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was evaporated and the residue was purified by FC (1:1 to 3:1 EtOAc/PE), which gave the title compound **(±)-2.174** as a white solid (4.02 g, 9.76 mmol, 80%). All characterisations are consistent with the enantiopure material (next compound). *The characterisation is given for the enantioenriched compound (next procedure).*

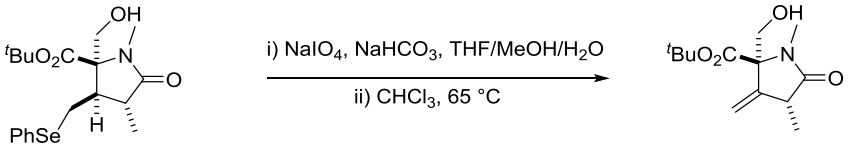
(+)-tert-Butyl (2R,3R,4R)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (+)-2.174



(+)-2.137 **(+)-2.174**

The title compound **(+)-2.174** was prepared according to the previous procedure, using (*+*)-(2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid) **(+)-2.137** (3.39 g, 12.5 mmol) and was obtained as a white solid (3.98 g, 9.65 mmol, 77%). $\mathbf{R_f}$ 0.28 (1:1 EtOAc/PE); **m.p.** = 131–133 °C; $[\alpha]_D^{20}$ +44.5 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.53–7.45 (2H, m, Ar*H*), 7.32–7.24 (3H, m, Ar*H*), 3.99 (1H, d, *J* = 12.5, C*H*H'OH), 3.88 (1H, d, *J* = 12.5, CH*H'*OH), 3.10 (1H, dd, *J* = 12.6, 6.1, C*H*H'Se), 2.88 (1H, d, *J* = 12.6, 8.1, CH*H'*Se), 2.78 (3H, s, NCH_3), 2.44 (1H, br, OH), 2.32 (1H, m, C*H*CH_3), 2.23 (1H, m, C*H*CH_2Se), 1.47 (9H, s, OC(CH_3)$_3$), 1.19 (3H, d, *J* = 7.1, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 177.6 (*C*=O), 170.0 (*C*=O), 132.9 (*Ar*), 130.0 (*Ar*), 129.4 (*Ar*), 127.5 (*Ar*), 83.8 (C_{quat}), 72.8 (C_{quat}), 63.2 (CH_2OH), 45.1 (*C*HCH_3), 42.4 (*C*HCH_2Se), 28.2 (OC(CH_3)$_3$), 27.4 (*C*H_2Se), 27.3 (NCH_3), 16.4 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 3384 (br O-H), 2930 (w, C-H), 1725 (m, C=O), 1674 (s, C=O), 1156 (s), 737 (m), 692 (w); **m/z** (ESI$^+$) 414 ([M+H]$^+$, 100%), 436 ([M+Na]$^+$, 80%); HRMS found 436.1001, $C_{19}H_{27}NNaO_4{}^{80}Se$ requires 436.0998.

(±)-*tert*-Butyl (2*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate, (±)-2.175

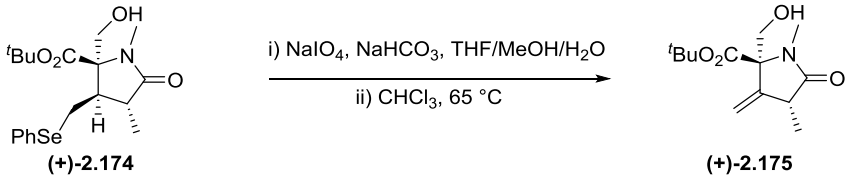


(±)-2.174 **(±)-2.175**

According to the modified procedure of Kocienski *et al.*,[74] a solution of (±)-*tert*-butyl (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate **(±)-2.174** (5.03 g, 12.2 mmol) and $NaHCO_3$ (5.12 g, 61.0 mmol) in THF/MeOH/H_2O (1:1:1, 240 mL) was added $NaIO_4$ (13.0 g, 61.0 mmol) over 5 min in 10 portions. The mixture was stirred at RT for 40 min. Water (300 mL) and $CHCl_3$ (300 mL) were then added and the bi-phasic mixture was filtered through a short plug of Celite,^{TM} which was further eluted with chloroform (100 mL). The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered and refluxed at 65 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by FC (1:3 to 3:1 EtOAc/PE), which gave the title compound

(±)-2.175 as a white solid (2.44 g, 9.56 mmol, 98%). All characterisations are consistent with enantiopure material (next compound).

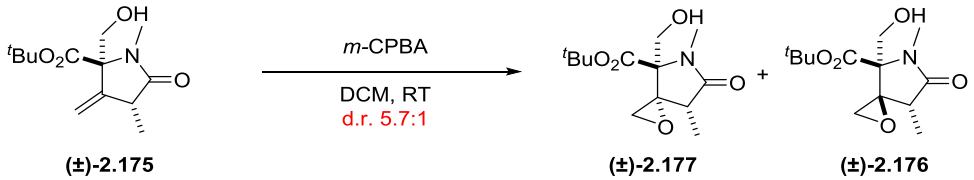
(+)-*tert*-Butyl (2*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate, (+)-2.175



(+)-2.174 **(+)-2.175**

The title compound **(+)-2.175** was prepared using the previous procedure, starting from (+)-*tert*-Butyl (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate **(+)-2.174** (3.98 g, 9.65 mmol) and was obtained as a white solid (2.47 g, 9.65 mmol, 100%). $\mathbf{R_f}$ 0.28 (3:2 EtOAc/PE); **m.p.** = 107–109 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +93.5 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.34 (1H, dd, *J* = 2.7, 0.7, C=C*H*H'), 5.22 (1H, dd, *J* = 2.7, 0.5, C=CH*H'*), 4.04 (1H, d, *J* = 12.5, C*H*H'OH), 3.90 (1H, d, *J* = 12.5, CH*H'*OH), 3.05 (1H, m, C*H*CH_3), 2.87 (3H, s, NCH_3), 1.41 (9H, $CO_2C(CH_3)_3$), 1.27 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.5 (*C*=O), 169.1 (*C*=O), 145.8 (*C*=CH_2), 109.9 (C=*C*H_2), 83.1 (C_{quat}), 74.1 (C_{quat}), 64.3 (*C*H_2OH), 40.1 (*C*HCH$_3$), 27.9 ($CO_2C(CH_3)_3$), 27.1 (NCH_3), 16.1 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 3392 (br, O-H), 1730 (m, C=O), 1685 (s, C=O), 1657 (m, C=O), 1159 (s), 1012 (m), 839 (w); **m/z** (ESI^+) 278 ($[M+Na]^+$, 100%), 256 ($[M+H]^+$, 45%); HRMS found 278.1667, $C_{13}H_{21}NNaO_4$ requires 278.1363.

(±)-*tert*-Butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate, (±)-2.177

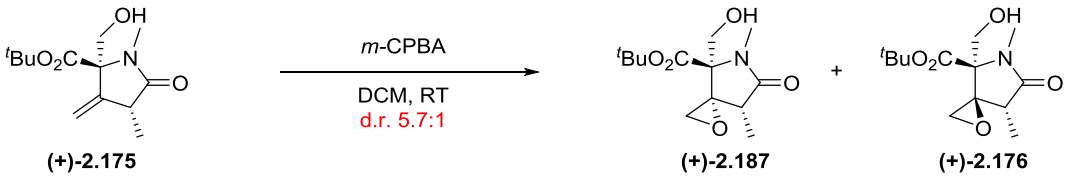


(±)-2.175 **(±)-2.177** **(±)-2.176**

The following procedure was performed using racemic starting material: To a solution of (±)-*tert*-butyl (2*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(±)-2.175** (2.44 g, 9.57 mmol) in DCM (40 mL) was added purified *m*-CPBA[179] (8.26 g, 47.9 mmol) in one portion. The reaction was stirred for 84 h. The stirred mixture was then cooled to 0 °C and treated with a saturated aqueous solution of $NaHCO_3$ (40 mL) and then with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL). EtOAc (150 mL) was added, the layers were separated and the organic phase was washed with a half saturated aqueous solution of $NaHCO_3$ (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (7:3 to 1:0 EtOAc/PE), which gave the major epoxide **(±)-2.177** as a white solid (1.64 g, 6.05 mmol, 63%) and the minor epoxide

(±)-2.176 as a colourless oil (0.288 g, 1.06 mmol, 11%). All characterisations are consistent with the enantiopure materials (next compounds).

(+)-*tert*-Butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate, (+)-2.177



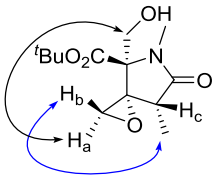
(+)-2.175 **(+)-2.187** **(+)-2.176**

The title epoxide was prepared using the previous procedure, starting from (+)-*tert*-butyl (2*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.175** (671 mg, 2.63 mmol). The major and minor epoxides **(+)-2.176** and **(+)-2.177** were respectively obtained as a white solid (426 mg, 1.57 mmol, 60%) and a colourless oil (78.1 mg, 0.288 mmol, 11%).

Characterisation for the major epoxide **(+)-2.176**: $\mathbf{R_f}$ 0.43 (3:2 EtOAc/PE); **m.p.** = 113–116 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +78.0 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.77 (1H, d, *J* = 13.2, C*H*H'OH), 3.72 (1H, d, *J* = 13.2, CH*H'*OH), 3.10 (1H, d, *J* = 3.9, C*H*H' epoxide), 2.91 (4H, m, NCH_3 and CH*H'* epoxide), 2.87 (1H, q, *J* = 7.3, C*H*CH_3), 1.44 (9H, s, OC(CH_3)$_3$), 0.99 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_H}$ (400 MHz, acetone-d_6) 3.79 (1H, dd, *J* = 13.4, 8.2, C*H*H'OH), 3.68 (1H, dd, *J* = 13.4, 3.8, CH*H'*OH), 3.65 (1H, br, O*H*), 3.10 (1H, d, *J* = 4.2, C*H*H' epoxide), 2.94 (1H, d, *J* = 4.2, CH*H'* epoxide), 2.88 (3H, s, NCH_3), 2.78 (1H, q, *J* = 7.3, C*H*CH_3), 1.47 (9H, s, CO_2C(CH_3)$_3$), 0.89 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.3 (C=O), 168.5 (C=O) 83.9 (C_{quat}), 71.0 (C_{quat}), 62.7 (C_{quat}), 58.8 (CH_2OH), 46.6 (CH_2 epoxide), 37.5 ($CHCH_3$), 28.1 (OC(CH_3)$_3$), 26.9 (NCH_3), 8.3 (CHCH_3); $\boldsymbol{\nu_{max}}$ 3413 (br, O-H), 2979 (w, C-H), 1731 (m, C=O), 1685 (s, C=O), 1159 (m); **m/z** (ESI$^+$) 272 ([M+H]$^+$, 100%), 294 ([M+Na]$^+$, 70%); HRMS found 294.1314, $C_{13}H_{21}NNaO_5$ requires 294.1312.

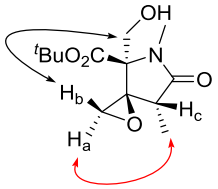
Partial characterisation for the minor epoxide **(+)-2.177**: $\mathbf{R_f}$ 0.17 (3:2 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.90 (1H, d, *J* = 12.6, C*H*H'OH), 3.82 (1H, d, *J* = 12.6, CH*H'*OH), 3.15 (1H, d, *J* = 3.9, C*H*H' epoxide), 3.02 (1H, d, *J* = 3.9, CH*H'* epoxide), 2.87 (3H, s, NCH_3), 2.72 (1H, q, *J* = 7.6, C*H*CH_3), 1.47 (9H, s, OC(CH_3)$_3$), 1.18 (3H, d, *J* = 7.6, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.0 (C=O), 167.2 (C=O) 83.9 (C_{quat}), 71.7 (C_{quat}), 64.0 (C_{quat}), 60.7 (CH_2OH), 49.2 (CH_2 epoxide), 39.8 ($CHCH_3$), 28.2 (OC(CH_3)$_3$), 27.2 (NCH_3), 13.0 (CHCH_3).

Key nOe interactions in d_6-acteone
(+)-2.177 major diastereoisomer



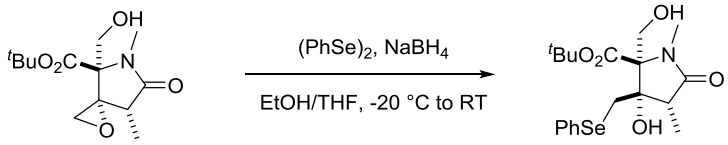
CH_3 - H_b : 0.33 %
(CH_3 - H_c : 1.47 %)
ratio : 0.22

Key nOe interactions in $CDCl_3$
(+)-2.176 minor diastereoisomer



CH_3 - H_a : 1.37 %
(CH_3 - H_c : 3.26 %)
ratio : 0.42

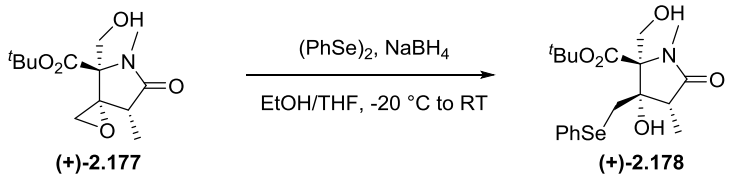
(±)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (±)-2.178



(±)-2.177 **(±)-2.178**

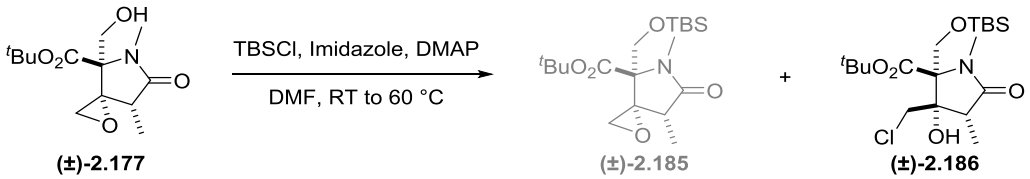
According to the modified procedure of Wolf *et al.,*[144] $NaBH_4$ (30.9 mg, 0.830 mmol) was added to a solution of diphenyl diselenide (173 mg, 0.554 mmol) in nitrogen sparged THF/EtOH (1:1, 2 mL) at RT. The reaction mixture was heated at 70 °C for 10 min and then cooled to -20 °C. A solution of (±)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(±)-2.177** (200 mg, 0.738 mmol) in degassed THF/EtOH (1:1, 1 mL + 0.4 mL rinse) was then added to the mixture over 2 min. The mixture was then warmed to RT and the progress monitor by mass spectrometry (product and starting material have same $\mathbf{R_f}$). After stirring for one hour, the reaction mixture was quenched with a solution of pH 2 sulfate buffer (8.0 mL), which was then extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified through a short silica column, which was eluted with 1:4 EtOAc/PE until the excess of diphenyl diselenide ran out of the column (bright yellow band on silica). The column was then washed with 1:49 MeOH/EtOAc (8 CV). All polar fractions were combined (the product streaks on the column and stains very weakly in $KMnO_4$ or vanillin solutions). The solvent was then evaporated, which gave a mixture of the title compound **(±)-2.178** and of an unknown impurity (356 mg, yield is given over 2 steps after protection of the diol). All characterisations are given for enantiopure material (next compound).

(+)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (+)-2.178



The title compound **(+)-2.178** was prepared using the previous procedure and double FC purification (2:3 to 3:2 EtOAc/PE), starting from (+)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.177** (50.0 mg, 0.184 mmol) and was obtained as a white solid (46 mg, 0.067 mmol, 37%). $\mathbf{R_f}$ 0.37 (7:3 EtOAc/PE); **m.p.** = 144–147 °C; $[\alpha]_D^{20}$ +70.1 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.56–7.50 (2H, m, ArH), 7.32–7.27 (3H, m, ArH), 4.31 (1H, dd, *J* = 12.8, 3.2, C*H*H'OH), 3.95 (1H, dd, *J* = 12.8, 10.0, CH*H*'OH), 3.45 (1H, s, C_{quat}OH), 3.38 (1H, d, *J* = 13.0, C*H*H'Se), 3.20 (1H, d, *J* = 13.0, CH*H*'Se), 2.94 (1H, dd, *J* = 10.0, 3.2, CHH'O*H*), 2.83 (3H, s, NCH_3), 2.48 (1H, q, *J* = 7.3, C*H*CH_3), 1.47 (9H, s, OC(CH_3)$_3$), 1.22 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.9 (*C*=O), 169.6 (*C*=O), 132.7 (*Ar*), 129.7 (2x*Ar*), 127.9 (*Ar*), 82.2 (C_{quat}), 75.8 (C_{quat}), 75.4 (C_{quat}), 61.3 (CH_2OH), 46.0 (*C*HCH_3), 38.2 (CH_2Se), 28.1 (OC(CH_3)$_3$), 27.2 (NCH_3), 9.2 (*C*HCH_3); $\boldsymbol{\nu_{max}}$ 3324 (br, O-H), 2997 (w, C-H), 1725 (m, C=O), 1677 (s, C=O), 1155 (m), 738 (w); **m/z** (ESI^+) 430.1 ($[M+H]^+$, 100%), 452.1 ($[M+Na]^+$, 80%); HRMS found 452.0955, $C_{19}H_{27}NNaO_5{}^{80}Se$ requires 452.0948.

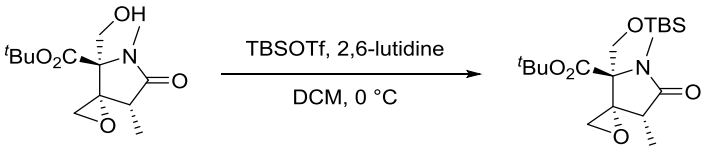
(±)-*tert*-Butyl (2*S*,3*S*,4*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(chloromethyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (±)-2.186



To a solution of (±)-*tert*-Butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(±)-2.177** (20.0 mg, 0.0740 mmol), imidazole (14.5 mg, in 0.111 mmol) and DMAP (1.4 mg, 0.011 mmol) in DMF (0.3 mL), was added TBSCl (14.5 mg, 0.0962 mmol) and the mixture was stirred for 16 h at RT. More TBSCl (14.5 mg, 0.0962 mmol) and imidazole (14.5 mg, in 0.111 mmol) were then added and the mixture was heated at 60 °C. The mixture was then cooled to RT, and a saturated aqueous solution of NH_4Cl (1 mL) and water (2 mL) were added. The mixture was extracted with EtOAc (2 x 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:3 to 3:1 EtOAc/PE), which gave the title compound **(±)-2.186** as a colourless oil (15 mg, 0.036 mmol, 48%). $\mathbf{R_f}$ 0.48 (3:7 EtOAc/PE); $\boldsymbol{\delta_H}$ (400

MHz, $CDCl_3$) 4.63 (1H, s, O*H*), 4.49 (1H, d, *J* = 11.5, C*H*H'OH), 4.05 (1H, d, *J* = 11.5, CH*H'*OH), 3.73 (1H, d, *J* = 11.5, C*H*H'Cl), 3.69 (1H, d, *J* = 11.5, CH*H'*Cl), 2.79 (3H, s, NCH_3), 2.54 (1H, q, *J* = 7.2, C*H*CH_3), 1.48 (9H, s, OC(CH_3)$_3$), 1.21 (3H, d, *J* = 7.2, CHCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.16 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3); **δ_H** (100 MHz, $CDCl_3$); 175.8 (*C*=O), 168.2 (*C*=O), 84.2 (C_{quat}), 79.1 (C_{quat}), 74.3 (C_{quat}), 62.0 (O*C*H_2), 49.0 (*C*H_2Cl), 44.9 (*C*HCH_3), 28.0 (OC(*C*H_3)$_3$), 26.8 (N*C*H_3), 25.8 (SiC(*C*H_3)$_3$), 18.1 (SiC_{quat}), 8.8 (CH*C*H_3), -5.6 (Si*C*H_3), -5.7 (Si*C*H_3); **ν_{max}** 3340 (br, O-H), 2931 (w, C-H), 1730 (m, C=O), 1683 (s, C=O), 1251 (w), 837 (m); **m/z** (ESI^+) 444 and 446 ($[M+Na]^+$, 100% and 30%); HRMS found 444.1951 and 446.1930, $C_{19}H_{36}ClNNaO_5Si$ requires 444.1943 and 446.1916.

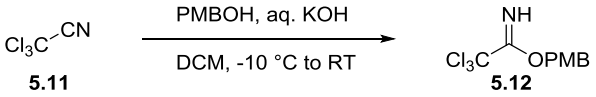
(+)-*tert*-Butyl (3*S*,4*S*,7*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate, (+)-2.187



(+)-2.177 **(+)-2.187**

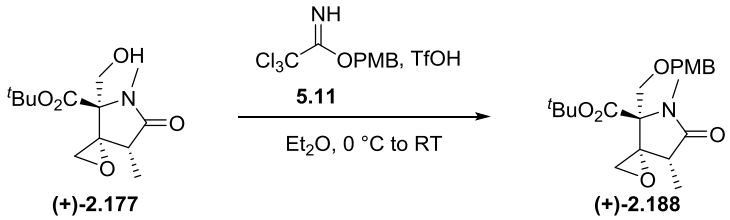
To a solution of (+)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(hydroxymethyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.177** (100 mg, 0.369 mmol) and 2,6-lutidine (170 µL, 1.48 mmol) in DCM (2.0 mL) at 0 °C was added TBSOTf (133 µL, 0.738 mmol) dropwise over 3 min. The reaction mixture was stirred for 30 min and was then quenched by addition of water (5 mL). An aqueous solution of pH 2 sulfate buffer was then added (5 mL) and the mixture was extracted with DCM (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by FC (2:3 EtOAc/PE), which gave the title compound **(+)-2.187** as a pale yellow oil (106 mg, 0.275 mmol, 75%). **R_f** 0.40 (1:4 EtOAc/PE); $[\alpha]_D^{20}$ +34.7 (c = 1.00 in $CHCl_3$); **δ_H** (400 MHz, $CDCl_3$) 3.77 (1H, dd, *J* = 10.8, C*H*H'OTBS), 3.69 (1H, dd, *J* = 10.8, CH*H'*OTBS), 3.04 (1H, d, *J* = 4.5, C*H*H' epoxide), 2.94 (3H, s, NCH_3), 2.76 (1H, d, *J* = 4.5, CH*H'* epoxide), 2.74 (1H, q, *J* = 7.5, C*H*CH_3), 1.44 (9H, s, CO_2(CH_3)$_3$), 0.99 (3H, d, *J* = 7.5, CHCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, Si*C*H_3), 0.05 (3H, s, Si*C*H_3); **δ_C** (100 MHz, $CDCl_3$) 175.3 (*C*=O), 168.7 (*C*=O), 83.1 (C_{quat}), 71.5 (C_{quat}), 62.0 (C_{quat}), 61.8 (*C*H_2OTBS), 46.9 (*C*H_2 epoxide), 37.7 (C*H*CH_3), 28.1 ($C_{quat}CO_2$(CH_3)$_3$), 27.8 (N*C*H_3), 25.9 (SiC(*C*H_3)$_3$), 18.2 (SiC_{quat}), 8.7 (CH*C*H_3), -5.6 (Si*C*H_3), -5.7 (Si*C*H_3); **ν_{max}** 2932 (w), 1725 (m, C=O), 1704 (s, C=O), 1159 (m), 837 (s), 779 (m); **m/z** (ESI^+) 386.2 ($[M+H]^+$, 100%), 408.2 ($[M+Na]^+$, 80%); HRMS found 408.2182, $C_{19}H_{35}NNaO_5Si$ requires 408.2177.

4-Methoxybenzyl-2,2,2-trichloroacetimidate, 5.12



According to the procedure of Patil *et. al.,*[180] to a stirred solution of 4-methoxybenzyl alcohol (2.00 g, 14.5 mmol) in DCM (20 mL), was added a solution of aqueous KOH (50%) and tetrabutylammonium hydrogen sulfate (30.0 mg, 0.0883 mmol). The stirred mixture was cooled at -10 °C and trichloroacetonitrile **5.11** (1.74 mL, 17.4 mmol) was added dropwise to the mixture. After 45 min stirring, the reaction mixture was warmed to RT and stirred for 1 h. The layers were then separated (the top layer is the organic phase), and the aqueous phase was extracted with more DCM (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by Kugelrohr distillation, which gave the title compound **5.12** as a colourless oil (3.44 g, 12.2 mmol, 84%). **b.p** (180 °C, 0.4 mmHg); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.49–8.26 (1H, br, N*H*), 7.38 (2H, d, *J* = 8.8, Ar*H*), 6.92 (2H, d, *J* = 8.8, Ar*H*), 5.29 (2H, s, CH_2), 3.83 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 162.8 (*C*=NH), 159.8 (*Ar*), 129.9 (*Ar*), 127.6 (*Ar*), 114.0 (*Ar*), 70.8 (*C*H_2), 55.4 (*C*H_3). Data are in accordance with the literature.[181]

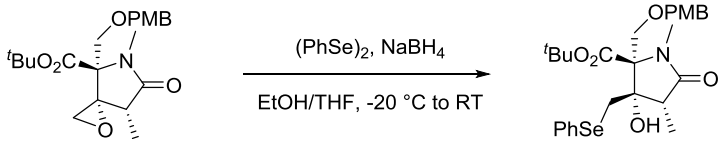
(+)-*tert*-Butyl (3*S*,4*S*,7*R*)-4-(((4-methoxybenzyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate, (+)-2.188



To a solution of (+)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.177** (100 mg, 0.369 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (261 mg, 0.923 mmol) in Et_2O (4.0 mL) at RT, was added a freshly prepared solution of TfOH in Et_2O (0.1 M, 90 µL, 9 µmol) dropwise. The reaction mixture was stirred at RT for 20 min. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and water (5 mL). The mixture was then extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried, filtered and the solvent was evaporated. The residue was purified by FC (1:4 to 2:3 EtOAc/PE), which gave the title compound **(+)-2.188** as a colourless oil (158 mg, 0.369 mmol, quantitative). $\mathbf{R_f}$ 0.24 (3:7 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +15.0 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.20 (2H, d, *J* = 8.6, Ar), 6.85 (2H, d, *J* = 8.6, Ar), 4.46 (1H, *J* = 11.6, C*H*H'Ar), 4.42 (1H, d, *J* = 11.6 CH*H'*Ar), 3.79 (3H, s, OCH_3), 3.58 (1H, d, *J* = 10.3, C*H*H'OPMB), 3.52 (1H, d, *J* = 10.3, CH*H'*OPMB), 3.06 (1H, d, *J*

= 4.4, C*H*H' epoxide), 2.92 (3H, s, NCH_3), 2.78 (1H, d, *J* = 4.4, CH*H'* epoxide), 2.75 (1H, q, *J* = 7.4, C*H*CH$_3$), 1.93 (9H, s, OC(CH_3)$_3$), 0.99 (3H, d, *J* = 7.4, CHCH_3); **δ$_C$** (100 MHz, $CDCl_3$) 175.1 (*C*=O), 168.5 (*C*=O), 159.3 (*Ar*), 129.9 (*Ar*), 129.2 (*Ar*), 113.9 (*Ar*), 83.2 (C_{quat}), 73.5 (*C*H$_2$Ar), 70.8 (C_{quat}), 68.3 (*C*H$_2$OPMB), 62.2 (C_{quat}), 55.4 (OCH_3), 47.0 (*C*H$_2$ epoxide), 37.6 (*C*HCH$_3$), 28.1 (OC(CH_3)$_3$), 27.7 (NCH_3), 8.7 (CH*C*H$_3$); **ν$_{max}$** 2936 (w, C-H), 1733 (m, C=O), 1702 (s, C=O), 1247 (s), 1159 (m), 820 (w); **m/z** (ESI$^+$) 414 ([M+Na]$^+$, 100%), 392 ([M+H]$^+$, 35%); HRMS found 414.1896, $C_{21}H_{29}NNaO_6$ requires 414.1887.

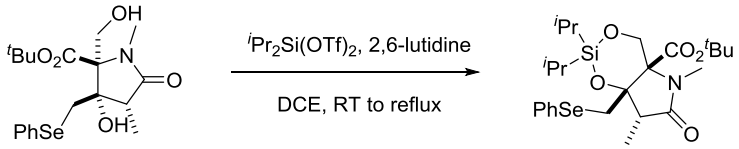
(+)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate, (+)-2.189



(+)-2.188 **(+)-2.189**

To a solution diphenyl diselenide (50.1 mg, 0.128 mmol) at RT in nitrogen sparged THF/EtOH (1:1, 2 mL) was added $NaBH_4$ (7.1 mg, 0.19 mmol). The reaction mixture was then heated at 70 °C for 10 min and then cooled to -20 °C. A solution of (+)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.188** (30.0 mg, 0.0960 mmol) in degassed THF/EtOH (1:1, 0.3 mL + 0.2 mL rinse) was then added to the mixture over 1 min. The reaction mixture was warmed to RT and the progress of the reaction was monitored by mass spectrometry (product and starting material have close **R$_f$**). After one hour stirring at RT, the reaction mixture was quenched with a solution of pH 2 sulfate buffer (1.0 mL), which was then extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:4 to 1:1 EtOAc/PE), which gave the title compound **(+)-2.189** as a white solid (62.3 mg, 0.113 mmol, 89%). **R$_f$** 0.41 (1:1 EtOAc/PE); **m.p.** 106–108 °C; $[\alpha]_D^{20}$ +36.0 (c = 1.00 in $CHCl_3$); **δ$_H$** (400 MHz, $CDCl_3$) 7.56–7.50 (2H, m, Ar*H*), 7.28–7.19 (5H, m, Ar*H*), 6.87 (2H, d, *J* = 8.6, Ar*H*), 4.55 (1H, d, *J* = 11.4, OC*H*H'Ar), 4.48 (1H, d, *J* = 11.4, OCH*H'Ar*), 4.31 (1H, d, *J* = 10.8, OC*H*H'C_{quat}), 4.15 (1H, s, O*H*), 3.89 (1H, d, *J* = 10.8, OCH*H'*C_{quat}), 3.79 (3H, s, OCH_3), 3.30 (1H, d, *J* = 12.7, C*H*H'Se), 3.18 (1H, d, *J* = 12.7, CH*H'*Se), 2.75 (3H, s, NCH_3), 2.51 (1H, q, *J* = 7.3, C*H*CH$_3$), 1.43 (9H, s, OC(CH_3)$_3$), 1.21 (3H, d, *J* = 7.3, CHCH_3); **δ$_C$** (100 MHz, $CDCl_3$) 175.9 (*C*=O), 168.6 (*C*=O), 159.7 (*Ar*), 132.6 (*Ar*), 131.5 (*Ar*), 129.8 (*Ar*), 129.3 (*Ar*), 128.7 (*Ar*), 127.2 (*Ar*), 114.1 (*Ar*), 84.0 (C_{quat}), 78.9 (C_{quat}), 75.3 (C_{quat}), 73.7 (O*C*H$_2$Ar), 68.2 (O*C*H$_2$$C_{quat}$), 55.4 (OC$H_3$), 46.2 (*C*HCH$_3$), 37.2 (*C*H$_2$Se), 28.0 (OC(*C*H$_3$)$_3$), 27.1 (NC$H_3$), 9.1 (*C*HCH$_3$); **ν$_{max}$** 3351 (br, OH), 2937 (w, C-H), 1726 (m, C=O), 1681 (s, C=O), 1248 (s, C=O), 1157 (m), 842 (w), 736 (m); **m/z** (ESI$^+$) 572.2 ([M+Na]$^+$, 100%), 550.2 ([M+H]$^+$, 35%); HRMS found 572.1537, $C_{27}H_{35}NNaO_6{}^{80}Se$ requires 572.1524.

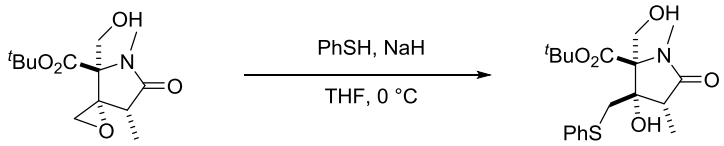
(±)-*tert*-Butyl (4aS,7R,7aS)-2,2-diisopropyl-5,7-dimethyl-6-oxo-7a-((phenylselanyl)methyl)tetrahydro-[1,3,2]dioxasilino[5,4-*b*]pyrrole-4a(4*H*)-carboxylate, (±)-2.192



(±)-2.178 (±)-2.192

To a solution of (±)-*tert*-butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate **(±)-2.178** (356 mg) in DCE (7.4 mL) at RT was added 2,6-lutidine (0.866 mL, 7.38 mmol) followed by diisopropylsilyl bis(trifluoromethanesulfonate) (0.717 mL, 2.44 mmol). The reaction was then heated under reflux at 80 °C for 45 min. The reaction mixture was diluted with EtOAc (40 mL) and was washed with a solution pH 2 sulfate buffer (30 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified two times by FC (EtOAc/PE 1:7, second column EtOAc/DCM 1:10), which gave the title compound **(±)-2.192** as a colourless oil (158 mg, 0.291 mmol, 40% over 2 steps). $\mathbf{R_f}$ 0.50 (1:4 EtOAc/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.51–7.45 (2H, m, Ar*H*), 7.29–7.21 (3H, m, Ar*H*), 4.66 (1H, d, *J* = 13.5, OC*H*H'), 4.08 (1H, d, *J* = 13.5, OCH*H'*), 3.48 (1H, d, *J* = 12.2, C*H*H'Se), 3.16 (1H, d, *J* = 12.2, CH*H'*Se), 2.81 (3H, s, NCH_3), 2.69 (1H, q, *J* = 7.2, (CO)C*H*CH_3), 1.43 (9H, s, OC(CH_3)$_3$), 1.27 (3H, *J* = 7.2, (CO)CHCH_3), 1.11–1.02 (7H, m, 2 x SiCH(CH_3) and SiC*H*(CH_3)$_2$)), 0.98 (3H, d, *J* = 5.1, SiCHCH_3), 0.96 (3H, d, *J* = 4.9, SiCHCH_3), 0.90–0.77 (1H, m, Si*CH*CH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 176.7 (*C*=O), 168.6 (*C*=O), 132.4 (*Ar*), 131.5 (*Ar*), 129.3 (*Ar*), 127.1 (*Ar*), 84.2 (C_{quat}), 81.5 (C_{quat}), 73.7 (C_{quat}), 60.0 (OCH_2), 46.5 ((CO)*C*HCH_3), 36.0 (*C*H_2Se), 28.0 (OC(CH_3)$_3$), 26.3 (NCH_3), 17.2 (SiCH*C*H_3), 17.1 (SiCH*C*H_3), 16.9 (SiCH*C*H_3), 16.8 (SiCH*C*H_3), 13.7 (Si*C*H), 13.6 (Si*C*H), 9.0 ((CO)CH*C*H_3); $\mathbf{\nu_{max}}$ 2943 (w, C-H), 1705 (s, C=O), 1154 (m), 1029 (m), 1007 (m), 733 (m), 691 (s); **m/z** (ESI^+) 542.2 ($[M+H]^+$, 100%), 558.2 ($[M+Na]^+$, 20%); HRMS found 542.18195, $C_{25}H_{40}NO_5Si^{80}Se$ requires 542.18355.

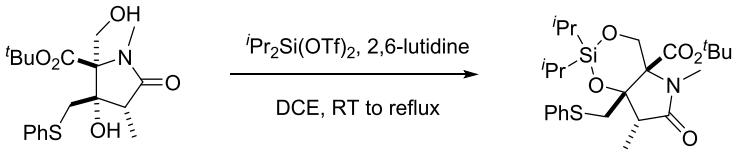
(±)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylthio)methyl)pyrrolidine-2-carboxylate, (±)-2.196



(±)-2.177 **(±)-2.196**

To a solution of thiophenol (27 µL, 0.26 mmol) at 0 °C, was added NaH 60% dispersion in mineral oil (14.2 mg, 0.250 mmol). The mixture was stirred for 10 min at 0 °C and a solution of (±)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(±)-2.177** (50.0 mg, 0.185 mmol) in THF (0.6 mL + 0.2 mL rinse) was added over 1 min at this temperature. Stirring was maintained for 15 minutes and the reaction was quenched by the addition of brine (5 mL). The mixture was extracted with EtOAc (3 x 5 mL). The combined organic extract were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:1 EtOAc/PE), which gave the title compound **(±)-2.196** as a colourless oil (58.1 mg, 0.152 mmol, 82%). $\mathbf{R_f}$ 0.48 (EtOAc/PE, 2:3); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.42–7.37 (2H, m, Ar*H*), 7.36–7.29 (2H, m, Ar*H*), 7.28– 7.22 (1H, m, Ar*H*), 4.34 (1H, d, *J* = 12.3, C*H*H'OH), 3.98 (1H, dd, *J* = 12.3, 5.1, CH*H'*OH), 3.66 (1H, s, O*H*), 3.41 (1H, d, *J* = 13.7, C*H*H'S), 3.25 (1H, d, *J* = 13.7, CH*H'*S), 3.11 (1H, br, O*H*), 2.83 (3H, s, NCH_3), 2.52 (1H, q, *J* = 7.3, C*H*CH_3), 1.49 (9H, s, OC(CH_3)$_3$), 1.24 (3H, d, *J* = 7.3, CHCH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 175.9 (*C*=O), 169.5 (*C*=O), 136.0 (*Ar*), 129.9 (*Ar*), 129.5 (*Ar*), 127.3 (*Ar*), 84.3 (C_{quat}), 79.2 (C_{quat}), 75.2 (C_{quat}), 61.3 (O*C*H_2), 45.7 (*C*HCH$_3$), 43.7 (*C*H_2S), 28.1 (OC(*C*H_3)$_3$), 27.2 (N*C*H_3), 9.1 (*C*HCH$_3$); $\mathbf{\nu_{max}}$ 3336 (br, O-H), 2978 (w, C-H), 1725 (m, C=O), 1677 (s, C=O), 1154 (m), 739 (w); **m/z** (ESI$^+$) 404.1 ([M+Na]$^+$, 100%), 382.1 ([M+H]$^+$, 70%); HRMS found 404.14917 $C_{19}H_{27}NO_5SNa$ requires 404.15021.

(±)-tert-*Butyl* (4a*S*,7*R*,7a*S*)-2,2-diisopropyl-5,7-dimethyl-6-oxo-7a-((phenylthio)methyl)tetrahydro-[1,3,2]dioxasilino[5,4-*b*]pyrrole-4a(4*H*)-carboxylate, (±)-2.197

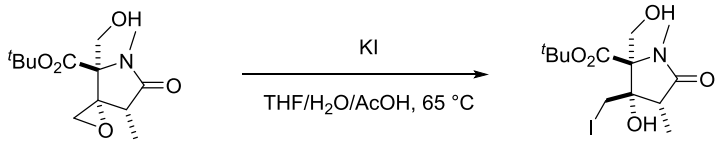


(±)-2.196 **(±)-2.197**

To a solution of (±)-*tert*-butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxo-3-((phenylthio)methyl)pyrrolidine-2-carboxylate **(±)-2.196** (58.4 mg, 0.153 mmol) in DCE (1.4 mL) at RT, was added 2,6-lutidine (270 µL, 2.29 mmol) followed by diisopropylsilyl bis(trifluoromethanesulfonate) (225 µL, 0.765 mmol). The reaction was then heated at 80 °C for 45

min, cooled to RT and transferred into a separating funnel containing a solution of pH 2 sulfate buffer (20 mL). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified two times by FC (EtOAc/DCM 1:24), which gave the title compound **(±)-2.197** as a colourless oil (38.1 mg, 0.0772 mmol, 50%). The characterisation is given for racemic material. $\mathbf{R_f}$ 0.66 (EtOAc/DCM 1:24); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.36–7.32 (2H, m, Ar*H*), 7.32–7.25 (2H, m, Ar*H*), 7.22–7.16 (1H, m, Ar*H*), 4.68 (1H, d, *J* = 13.5, C*H*H'OH), 4.10 (1H, d, *J* = 13.5, CH*H'*OH), 3.41 (1H, d, *J* = 13.2, C*H*H'S), 3.30 (1H, d, *J* = 13.2, CH*H'*S), 2.82 (3H, s, NCH_3), 2.69 (1H, q, *J* = 7.3, C*H*CH_3), 1.45 (9H, s, OC(CH_3)$_3$), 1.23 (3H, d, *J* = 7.3, CHCH_3), 1.15–1.03 (7H, m, 2 x SiCHCH_3 and SiCH), 0.98 (3H, d, *J* = 7.1, SiCHCH_3), 0.96 (3H, d, *J* = 7.1, SiCHCH_3), 0.90–0.78 (1H, m, Si*H*); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 176.6 (*C*=O), 168.5 (*C*=O), 137.3 (*Ar*), 129.4 (*Ar*), 129.2 (*Ar*), 126.4 (*Ar*), 84.2 (C_{quat}), 81.7 (C_{quat}), 73.5 (C_{quat}), 60.2 (*C*H_2OH), 46.0 (*C*HCH_3), 42.2 (*C*H_2S), 28.1 (OC(*C*H_3)$_3$), 26.3 (NCH_3), 17.2 (SiCH*C*H_3), 17.1 (SiCH*C*H_3), 16.9 (SiCH*C*H_3), 16.8 (SiCH*C*H_3), 13.7 (Si*C*H), 13.6 (Si*C*H), 8.6 (CH*C*H_3); $\mathbf{\nu_{max}}$ 2943 (w, C-H), 1725 (m, C=O), 1709 (s, C=O), 1155 (m), 1041 (s), 691 (m); **m/z** (ESI^+) 516.3 ([M+Na]$^+$, 100%), 494.2 ([M+H]$^+$, 85%); HRMS found 516.22065 $C_{25}H_{39}NO_5SNaSi$ requires 516.22104.

(±)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-3-(iodomethyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (±)-2.201

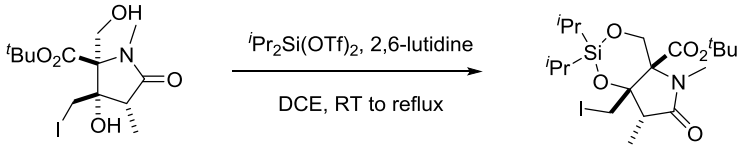


(±)-2.177 **(±)-2.201**

According to the procedure of Li *et al.*[182] KI (614 mg, 3.69 mmol) was added in one portion to a solution of (±)-*tert*-butyl (3S,4S,7R)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(±)-2.177** (100 mg, 0.369 mmol) in THF (1.5 mL), AcOH (0.75 mL) and H_2O (0.2 mL). The mixture was heated at 65 °C for 3 h. The reaction was then cooled to RT and a saturated aqueous solution of $NaHCO_3$ (20 mL) was slowly added. The mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (3:2 EtOAc/PE), which gave the title compound **(±)-2.201** as colourless oil (133 mg, 0.333 mmol, 90%). $\mathbf{R_f}$ 0.48 (3:2 EtOAc/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 4.44 (1H, dd, *J* = 12.9, 4.4, C*H*H'OH), 3.95 (1H, dd, *J* = 12.9, 8.6, CH*H'*OH), 3.76 (1H, s, C_{quat}O*H*), 3.51 (1H, d, *J* = 10.8, C*H*H'I), 3.42 (1H, d, *J* = 10.8, CH*H'*I), 3.27 (1H, dd, *J* = 8.6, 4.4, CH_2O*H*), 2.81 (3H, s, NCH_3), 2.58 (1H, q, J = 7.3, C*H*CH_3), 1.50 (9H, s, OC(CH_3)$_3$), 1.29 (1H, d, *J* = 7.3, CHCH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 175.8 (*C*=O), 169.1 (*C*=O), 84.6 (C_{quat}), 77.1 (C_{quat}), 74.7 (C_{quat}), 61.2 (*C*H_2OH), 46.2 (*C*HCH_3), 28.1 (OCH_3), 27.2 (NCH_3), 12.5 (*C*H_2I), 9.9 (CH*C*H_3); $\mathbf{\nu_{max}}$ 3311 (br, O-H), 2978 (w, C-H), 1724 (m, C=O), 1677 (s, C=O),

1155 (m), 990 (w); **m/z** (ESI$^+$) 422 ([M+Na]$^+$, 100%), 400 ([M+H]$^+$, 60%); HRMS found 422.04236, $C_{13}H_{22}NO_5NINa$ requires 422.04349.

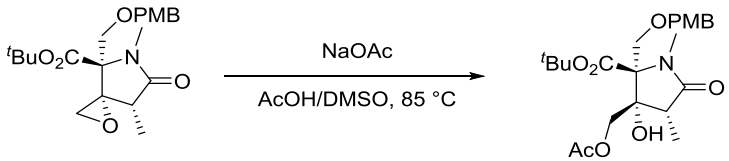
(±)-*tert*-Butyl (4a*S*,7*R*,7a*S*)-7a-(iodomethyl)-2,2-diisopropyl-5,7-dimethyl-6-oxotetrahydro-[1,3,2]dioxasilino[5,4-*b*]pyrrole-4a(4*H*)-carboxylate, 2.207



(±)-2.201 **2.207**

To a solution of (±)-*tert*-butyl (2*S*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)-3-(iodomethyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (133 mg, 0.333 mmol) in DCE (4.0 mL) were successively added 2,6-lutidine (0.580 mL, 4.99 mmol) and diisopropylsilyl bis(trifluoromethanesulfonate) (0.490 mL, 2.44 mmol). The reaction was then heated under reflux at 80 °C for 45 min. The reaction was cooled to RT and was added to a solution of pH 2 sulfate buffer (20 mL). The mixture was extracted with DCM (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified two times by FC (EtOAc/DCM 1:24), which gave the title compound as a colourless oil (71.5 mg, 0.140 mmol, 42%). The characterisation is given for racemic material. $\mathbf{R_f}$ 0.40 (1:24 EtOAc/DCM); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 4.68 (1H, d, *J* = 13.4, OC*H*H'), 4.04 (1H, d, *J* = 13.4, OCH*H'*), 3.45 (1H, d, *J* = 11.0, C*H*H'I), 3.41 (1H, d, *J* = 11.0, CH*H'*I), 2.80 (3H, s, NCH_3), 2.66 (1H, q, *J* = 7.3, (CO)C*H*CH_3), 1.49 (9H, s, OC(CH_3)$_3$), 1.29 (3H, d, *J* = 7.3, (CO)CHCH_3), 1.23–1.15 (1H, m, SiC*H*), 1.14 (3H, d, *J* = 5.4, SiCHCH_3), 1.13 (3H, d, *J* = 6.3, SiCHCH_3), 0.98 (3H, d, *J* = 7.6, SiCHCH_3), 0.96 (3H, d, *J* = 7.6, SiCHCH_3), 0.90–0.78 (1H, m, SiC*H*); $\boldsymbol{\delta_C}$ (126 MHz, $CDCl_3$) 176.0 (*C*=O), 168.3 (*C*=O), 84.4 (C_{quat}), 78.7 (C_{quat}), 73.1 (C_{quat}), 59.8 (OCH_2), 46.5 (*C*HCH_3), 28.1 (OC(*C*H_3)$_3$), 26.2 (NCH_3), 17.2 (SiCH*C*H_3), 17.2 (SiCH*C*H_3), 16.9 (SiCH*C*H_3), 16.8 (SiCH*C*H_3), 13.9 (Si*C*H), 13.7 (Si*C*H), 9.5 (*C*H_2I), 8.8 (*C*HCH_3); $\boldsymbol{\nu_{max}}$ 2944 (w, C-H), 1708 (s, C=O), 1156 (m), 1033 (m), 817 (w), 698 (w); **m/z** (ESI$^+$) 512 ([M+H]$^+$, 100%), 534 ([M+Na]$^+$, 60%); HRMS found 534.11259, $C_{19}H_{34}NO_5NINaSi$ requires 534.11431.

(+)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-(acetoxymethyl)-3-hydroxy-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (±)-2.206

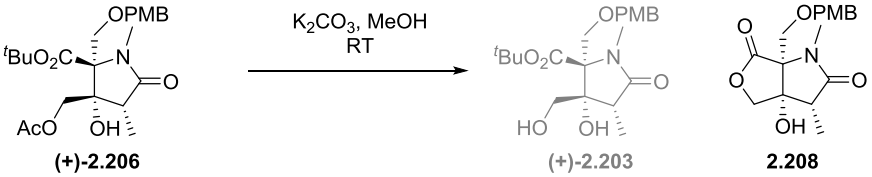


(+)-2.188 **(+)-2.206**

To a solution of (+)-*tert*-butyl (3*S*,4*S*,7*R*)-4-(((4-methoxybenzyl)oxy)methyl)-5,7-dimethyl-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate **(+)-2.188** (158 mg, 0.369 mmol) in AcOH (1.05 mL) and

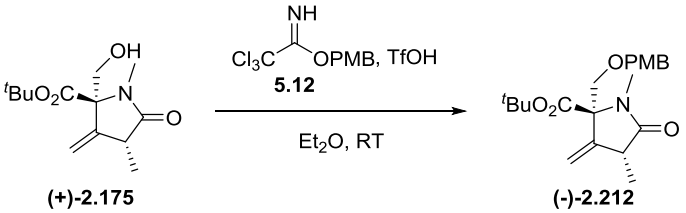
DMSO (1.05 mL), was added NaOAc (303 mg, 3.69 mmol). The reaction mixture was stirred at 85 °C for 20 h and was then cooled to RT. EtOAc (20 mL) was added and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (1 x 20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (7:3 EtOAc/PE), which gave the title compound **(+)-2.206** as a colourless oil (118 mg, 0.261 mmol, 71%). $\mathbf{R_f}$ 0.45 (7:3 EtOAc/PE), $[\alpha]_D^{20}$ +16.4 (c = 1.00 in $CHCl_3$), $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.23 (2H, d, *J* = 8.8, Ar*H*), 6.88 (2H, d, *J* = 8.8, Ar*H*), 4.54 (1H, d, *J* = 11.5, OC*H*H'), 4.49 (1H, d, *J* = 11.5, OCH*H'*), 4.26 (1H, s, O*H*), 4.18 (1H, d, *J* = 12.0, OC*H*H'Ar), 4.15 (1H, d, *J* = 12.0, OCH*H'*Ar), 3.80 (5H, m, OCH_3, C*H*H'OPMB and CH*H'*OPMB), 2.74 (3H, s, NCH_3), 2.46 (1H, q, *J* = 7.3, C*H*CH_3), 2.04 (3H, s, (CO)CH_3), 1.43 (9H, s, OC(CH_3)$_3$), 1.16 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.8 (*C*=O), 170.7 (*C*=O), 168.0 (*C*=O), 159.8 (*Ar*), 129.9 (*Ar*), 128.4 (*Ar*), 114.2 (*Ar*), 84.0 (C_{quat}), 78.6 (C_{quat}), 73.7 (C_{quat}), 73.7 (CH_2Ar), 67.8 (OCH_2), 67.2 (OCH_2), 55.4 (OCH_3), 43.5 (*C*HCH_3), 28.0 (OC(*C*H_3)$_3$), 26.8 (N*C*H_3), 20.9 ((CO)*C*H_3), 8.6 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 3378 (br, O-H), 2679 (w, C-H), 1730 (s, C=O), 1683 (s, C=O), 1245 (s), 1036 (m), 732 (w); **m/z** (ESI^+) 474.2 ($[M+Na]^+$, 100%), 452.2 ($[M+H]^+$, 35%); HRMS found 474.20900, $C_{23}H_{33}NNaO_8$ requires 474.20984.

(3*R*,3a*S*,6a*S*)-3a-hydroxy-6a-(((4-methoxybenzyl)oxy)methyl)-1,3-dimethyltetrahydro-6H-furo[3,4-b]pyrrole-2,6(3H)-dione, 2.208



The undesired title compound **2.208** was obtained when (+)-*tert*-butyl (2*S*,3*S*,4*R*)-3-(acetoxymethyl)-3-hydroxy-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate **(+)-2.206** (9.9 mg, 0.022 mmol) was stirred for 30 min in MeOH (0.2 mL) at RT in the presence of K_2CO_3 (1.5 mg, 0.011 mmol). The mixture was plugged through a containing silica gel (EtOAc/PE 7:3), which gave the crude product **2.208** (4.0 mg, 0.011 mmol, 50%). Only proton NMR is given for the title side product. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.22 (2H, d, *J* = 8.7, Ar*H*), 6.91 (2H, d, *J* = 8.7, Ar*H*), 4.57 (1H, d, *J* = 11.5, C*H*H'), 4.48 (1H, d, *J* = 11.5, CH*H'*), 4.37 (1H, d, *J* = 10.0, C'*H*H'), 4.21 (1H, d, *J* = 10.0, C'H*H'*), 3.87 (1H, d, *J* = 10.0, C''*H*H'), 3.83 (3H, s, OCH_3), 3.80 (1H, d, *J* = 10.0, C''H*H'*), 2.82 (3H, s, NCH_3), 2.59 (3H, q, *J* = 7.5, C*H*CH_3), 1.26 (3H, d, *J* = 7.5, CHCH_3).

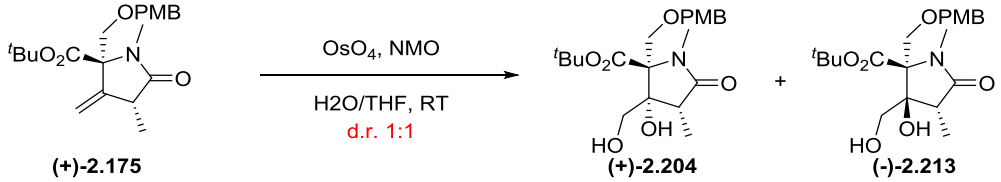
(+)-*tert*-Butyl (2*R*,4*R*)-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate



To a solution of (+)-*tert*-butyl (2*R*,4*R*)-2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.175** (200 mg, 0.783 mmol) in Et_2O (15 mL) at RT, were successively added 4-methoxybenzyl-2,2,2-trichloroacetimidate **5.12** (553 mg, 1.96 mol) and a freshly prepared solution of TfOH in Et_2O (0.1 M, 78 µL, 7.8 µmol). After 15 min stirring, more 4-methoxybenzyl-2,2,2-trichloroacetimidate (553 mg, 1.96 mol) were added followed by more TfOH solution in Et_2O (0.1 M, 78 µL, 7.8 µmol). The mixture was stirred for 15 min, diluted with EtOAc (50 mL) and then washed with a solution of pH 2 sulfate buffer (50 mL), followed by a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by FC (1:4 to 1:3 EtOAc/PE), which gave the title compound **(+)-2.212** as a colourless oil (270 mg, 0.719 mmol, 92%). $\mathbf{R_f}$ 0.33 (3:7 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +16.2 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.19 (2H, d, *J* = 8.5, Ar*H*), 6.86 (2H, d, *J* = 8.5, Ar*H*), 5.30 (1H, d, *J* = 2.3, =C*H*H'), 5.16 (1H, d, *J* = 2.3, =CH*H'*), 4.45 (2H, s, OC*HH'*Ar), 3.86 (1H, d, *J* = 10.2, C*H*H'OPMB), 3.80 (3H, s, OCH_3), 3.67 (1H, d, *J* = 10.2, CH*H'*OPMB), 3.05 (1H, m, C*H*CH_3), 2.84 (3H, s, NCH_3), 1.43 (9H, s, OC(CH_3)$_3$), 1.30 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.2 (*C*=O), 168.7 (*C*=O), 159.4 (*Ar*), 146.4 (*Ar*), 129.8 (*C*=CH_2), 129.3 (*Ar*), 113.9 (*Ar*), 109.3 (=*C*H_2), 82.7 (C_{quat}), 73.3 (OCH_2Ar), 71.6 (*C*H_2OPMB), 55.4 (O*C*H_3), 40.1 (*C*HCH_3), 27.9 (OC(*C*H_3)$_3$), 27.2 (N*C*H_3), 16.5 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 2976 (w, C-H), 1732 (m, C=O), 1701 (s, C=O), 1661 (w, C=O), 1513 (m), 1247 (s), 819 (w), 731 (w); **m/z** (ESI^+) 376.2 ($[M+H]^+$, 100%), 398.2 ($[M+Na]^+$, 80%); HRMS found 398.19275 $C_{21}H_{29}NO_5Na$ requires 398.19379.

(+)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-3-(hydroxymethyl)-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (+)-2.204

(-)-*tert*-Butyl (2*S*,3*R*,4*R*)-3-hydroxy-3-(hydroxymethyl)-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (-)-2.213



(+)-2.175 (+)-2.204 (-)-2.213

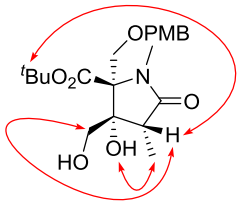
According to the modified procedure of Eto *et al.*,[130] a solution of OsO_4 in ^{t}BuOH (0.10 M, 0.88 mL, 0.088 mmol) was added to a solution of (+)-*tert*-butyl (2*R*,4*R*)-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **(+)-2.212** (165 mg, 0.440 mmol) and NMO (259 mg, 2.20 mmol) in THF (2.4 mL) and water (1.8 mL) at RT. After stirring for 60 h, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and water (5 mL). The mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:24 MeOH/DCM), which gave the first title diastereoisomer **(+)-2.204** as a pale yellow oil (77.7 mg, 0.190 mmol, 43%) and the second title diastereoisomer **(-)-2.213** as a white solid (61.0 mg, 0.149 mmol, 34%).

Characterisation for the first diastereoisomer **(+)-2.204**: $\mathbf{R_f}$ 0.33 (1:19 MeOH/DCM); $[\boldsymbol{\alpha}]_D^{20}$ +10.2 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, C_6D_6) 7.05 (2H, d, *J* = 8.5, Ar*H*), 6.74 (2H, d, *J* = 8.5, Ar*H*), 4.15 (1H, d, *J* = 11.4, OC*H*H'Ar), 4.10 (1H, d, *J* = 11.4, OCH*H'*Ar), 3.91 (1H, d, *J* = 10.1, C_{quat}C*H*H'OPMB), 3.86 (1H, d, *J* = 10.1, C_{quat}CH*H'*OPMB), 3.73 (1H, s, C_{quat}O*H*), 3.61 (1H, dd, *J* = 12.0, 5.4, C*H*H'OH), 3.51 (1H, dd, *J* = 12.0, 8.2, CH*H'*OH), 3.27 (3H, s, OCH_3), 2.85 (3H, s, NCH_3), 2.64 (1H, dd, *J* = 8.2, 5.4, CHH'O*H*), 2.38 (1H, q, 7.1, C*H*CH_3), 1.32 (3H, d, *J* = 7.1, CHCH_3), 1.21 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (126 MHz, C_6D_6) 175.4 (*C*=O), 169.8 (*C*=O), 160.1 (*Ar*), 129.7 (*Ar*), 128.3 (*Ar*), 114.3 (*Ar*), 82.8 (C_{quat}), 80.0 (C_{quat}), 75.0 (C_{quat}),73.6 (OCH_2Ar), 70.2 ($C_{quat}CH_2$OPMB), 65.7 (CH_2OH), 54.8 (OCH_3), 42.9 (*C*HCH_3), 27.7 (OC(*C*H_3)$_3$), 27.3 (N*C*H_3), 8.8 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 3389 (br, O-H), 2976 (w, C-H), 1729 (m, C=O), 1673 (s, C=O), 1514 (w), 1249 (s), 1165 (m), 1085 (m), 1034 (m), 823 (w), 733 (w); **m/z** (ESI$^+$) 432 ([M+Na]$^+$, 100%), 410 ([M+H]$^+$, 35%); HRMS found 432.19801 $C_{21}H_{31}NNaO_7$ requires 432.19927.

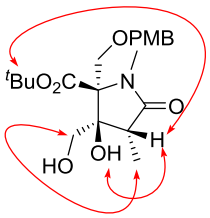
Characterisation for the second diastereoisomer **(-)-2.213**: $\mathbf{R_f}$ 0.29 (1:19 MeOH/DCM); $[\boldsymbol{\alpha}]_D^{20}$ -0.3 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, C_6D_6) 7.06 (2H, d, *J* = 8.4, Ar*H*), 6.75 (2H, d, *J* = 8.4, Ar*H*), 4.13 (1H, d, *J* = 11.5, OC*H*H'Ar), 4.07 (1H, d, *J* = 11.5, OCH*H'*Ar), 3.95 (1H, s, C_{quat}O*H*), 3.87–3.81 (2H, m, C_{quat}*C*H*H'*OPMB and C*H*H'OH), 3.69–3.60 (2H, m, C_{quat}CH*H'*OPMB and CH*H'*OH), 3.29 (3H, s, OCH_3), 3.20–3.13 (1H, m, CHH'O*H*), 2.96 (3H, s, NCH_3), 2.91 (1H, q, *J* = 7.1, C*H*CH_3), 1.42 (3H, d, *J* = 7.1,

CHC*H*$_3$), 1.34 (9H, s, OC(C*H*$_3$)$_3$); **δ$_C$** (126 MHz, C_6D_6) 176.5 (*C*=O), 168.9 (*C*=O), 160.1 (*Ar*), 129.8 (*Ar*), 129.3 (*Ar*), 114.3 (*Ar*), 82.6 (C_{quat}), 79.3 (C_{quat}), 76.1 (C_{quat}), 73.5 (O*C*H$_2$Ar), 67.6 (C_{quat}*C*H$_2$OPMB), 63.1 (*C*H$_2$OH), 54.8 (O*C*H$_3$), 46.7 (*C*HCH$_3$), 28.0 (OC(*C*H$_3$)$_3$), 27.8 (N*C*H$_3$), 10.6 (CH*C*H$_3$); **ν$_{max}$** 3389 (br, O-H), 2977 (w, C-H), 1729 (m, C=O), 1673 (s, C=O), 1514 (w), 1249 (s), 1165 (m), 1085 (m), 1034 (m), 823 (w), 733 (w); **m/z** (ESI$^+$) 432 ([M+Na]$^+$, 100%), 410 ([M+H]$^+$, 35%); HRMS found 432.19802 $C_{21}H_{31}NNaO_7$ requires 432.19927.

Key nOe interactions in C_6D_6
(+)-2.204



Key nOe interactions in C_6D_6
(-)-2.213



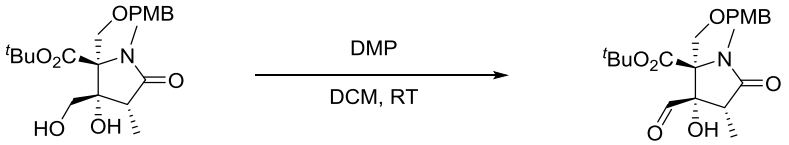
(*S*)-(3-bromo-2-methylpropoxy)(tert-butyl)dimethylsilane,[153] (+)-2.215



(+)-2.214 **(+)-2.215**

According to the modified procedure of Nicolaou *et al.*,[153] TBSCl (449 mg, 2.98 mmol) and imidazole (234 mg, 3.44 mmol) were successively added to a solution of (*S*)-3-bromo-2-methyl-1-propanol (351 mg, 2.29 mmol) **(+)-2.214** in DMF (2.3 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirring was maintained for 30 min. The reaction was then diluted with Et$_2$O (15 mL) and was transferred to a separating funnel containing hexane (15 mL). The mixture was washed with a solution of aqueous HCl (1.0 M, 15 mL) and a mixture of saturated brine/water (1:1, 10 mL). The organic layer was dried (MgSO$_4$), filtered and evaporated. The residue was purified by FC (1:99 Et$_2$O/Pentane), which gave the title compound **(+)-2.215** as a colourless oil (548 mg, 2.05 mmol, 90%). **R$_f$** 0.63 (1:99 Et$_2$O/PE); $[\alpha]_D^{20}$ +10.6 (c = 1.00 in DCM), *lit.*[183] $[\alpha]_D^{27}$ +11.0 (c = 1.42 in DCM); **δ$_H$** (400 MHz, $CDCl_3$) 3.58 (1H, dd, *J* = 10.0, 5.0, C*H*H'OTBS), 3.53–3.48 (2H, m, C*HH'*Br), 3.45 (1H, dd, *J* = 10.0, 5.5, CH*H'*OTBS), 2.04–1.92 (1H, m, *C*HCH$_3$), 0.99 (3H, d, *J* = 6.9, *CH*CH$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.07 (6H, s, Si(C*H*$_3$)$_2$); **δ$_C$** (100 MHz, $CDCl_3$) 66.5 (*C*H$_2$OTBS), 38.2 (*C*H$_2$Br), 37.9 (*C*HCH$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 18.4 (C_{quat}), 15.6 (CH*C*H$_3$), -5.3 Si(*C*H$_3$)$_2$; **ν$_{max}$** 2956 (m C-H), 1858 (m, C-H), 1256 (m), 1098 (s), 836 (s), 776 (s). The *data are in accordance with the literature.*[183]

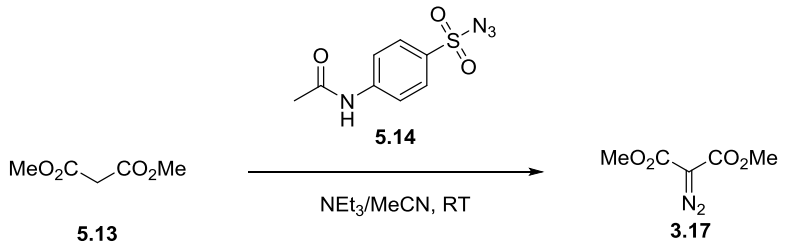
(-)-*tert*-Butyl (2*S*,3*S*,4*R*)-3-formyl-3-hydroxy-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate, (-)-2.205



(+)-2.204 **(-)-2.205**

To a solution of (+)-*tert*-butyl (2*S*,3*S*,4*R*)-3-hydroxy-3-(hydroxymethyl)-2-(((4-methoxybenzyl)oxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate **(+)-2.204** (74.9 mg, 0.183 mmol) in DCM (1.8 mL) at RT, was added DMP (116 mg, 0.275 mmol). The mixture was stirred for 72 h and was then diluted with DCM (20 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and the aqueous phase was extracted with more DCM (10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was rapidly purified through a short silica column (1:1 EtOAc/PE), which gave the title compound **(-)-2.205** as a colourless oil (50.5 mg, 0.125 mmol, 68%). $\mathbf{R_f}$ 0.40 (1:1 EtOAc/PE); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -11.8 (c = 1.00 in $CHCl_3$); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 9.58 (1H, s, *H*C=O), 7.20 (2H, d, *J* = 8.5, Ar*H*), 6.88 (2H, d, *J* = 8.5, Ar*H*), 4.48 (1H, d, *J* = 11.4, OC*H*H'Ar), 4.45 (1H, d, *J* = 11.4, OCH*H'*Ar), 3.87 (1H, d, *J* = 10.0, OC*H*H'C_{quat}), 3.87 (3H, s, OCH_3), 3.77 (1H, d, *J* = 10.0, OCH*H'*C_{quat}), 2.92 (3H, s, NCH_3), 2.87 (1H, q, *J* = 7.3, C*H*CH_3), 1.45 (9H, s, OC(CH_3)$_3$), 1.03 (3H, d, *J* = 7.3, CHCH_3); $\boldsymbol{\delta_C}$ (126 MHz, $CDCl_3$) 197.9 (H*C*=O), 174.1 (*C*=O), 167.7 (*C*=O), 159.6 (*Ar*), 129.5 (*Ar*), 129.1 (*Ar*), 114.0 (*Ar*), 84.5 (C_{quat}), 83.3 (C_{quat}), 74.5 (C_{quat}), 73.7 (OCH_2Ar), 70.0 (OCH_2C_{quat}), 55.4 (OCH_3), 41.7 (*C*HCH_3), 28.1 (OC(*C*H_3)$_3$), 27.8 (NCH_3), 7.5 (CH*C*H_3); $\boldsymbol{\nu_{max}}$ 2937 (w, C-H), 1737 (s, C=O), 1684 (s, C=O), 1514 (m), 1370 (w), 1249 (s), 1159 (m), 1033 (m), 839 (w); **m/z** (ESI^+) 462.2 ($[M+MeOH+Na]^+$, 100%), 430 ($[M+Na]^+$, 15%), 408 ($[M+H]^+$, 3%); HRMS found 430.18249 $C_{21}H_{29}NNaO_7$ requires 432.18362.

(±)-Dimethyl 2-diazomalonate, 3.17

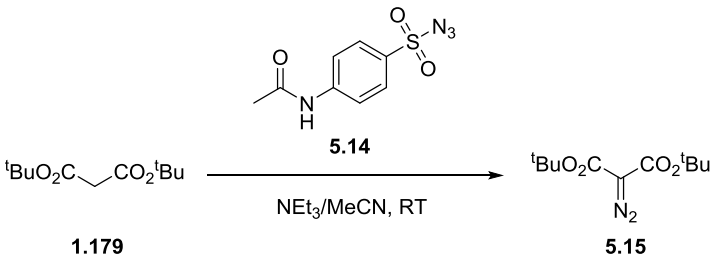


5.13 **3.17**

According to the procedure Baum *et al.*,[159] NEt_3 (22.0 mL) was added to a solution of dimethylmalonate **5.13** (6.00 mL, 52.5 mmol) and p-acetamidobenzensulfonyl azide **5.14** (2.90 g, 53.8 mmol) in MeCN (130 mL). The solution was allowed to warm to RT and the reaction mixture was stirred for 24 h. The solvent was then evaporated under reduced pressured and the residue was

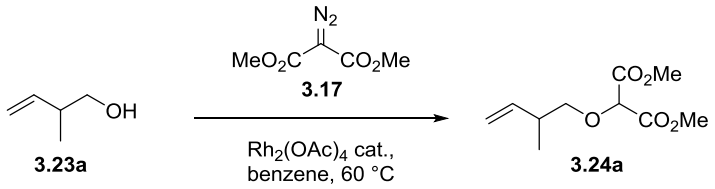
triturated with Et_2O/PE (1:1) and filtered. The solvent was evaporated under reduced pressured. The crude product was then purified by FC ($PE_{40\text{-}60}$/Et_2O 4:1 to 2:1), which gave the title compound **3.17** as a yellow oil (6.30 g, 40.0 mmol, 76 %). $\mathbf{R_f}$ 0.49 (EtOAc/PE 1:1); $\mathbf{\delta_H}$ ($CDCl_3$, 400 MHz) 3.83 (6H, s, CO_2Me), $\mathbf{\delta_C}$ ($CDCl_3$, 100 MHz) 161.4 (2 x C=O), 52.5 (2 x OC*H*$_3$); $\mathbf{\nu_{max}}$ 2133 (s, C=N_2), 1735 (s, C=O); **m/z** (ESI^+) 159 ($[M+H]^+$, 9%), 339 ($[2M+Na]^+$, 100 %). Data are in accordance with the literature.[184]

(±)-Di-*tert*-butyl 2-diazomalonate, 5.15



According to the procedure Baum *et al.*,[159] NEt_3 (10.0 mL) was added to a solution of di-tert-butyl malonate **1.179** (5.38 mL, 24 mmol) and p-acetamidobenzensulfonyl azide **5.14** (6.34 g, 26.4 mmol) in acetonitrile (55 mL) at 0 °C. The solution was allowed to warm to RT and stirred for 72 h. The solvent was then evaporated under reduced pressured and the residue was triturated with Et_2O/PE (1:1), filtered and evaporated. The crude product was then purified by flash chromatography (PE/Et_2O 4:1 to 2:1), which gave the title compounds **5.15** as a yellow oil (5.40 g, 22.3 mmol, 93%). $\mathbf{R_f}$ 0.73 (EtOAc/PE 2:3); $\mathbf{\delta_H}$ ($CDCl_3$, 400 MHz) 1.47 (18H, s, $OC(CH_3)_3$); $\mathbf{\delta_C}$ ($CDCl_3$, 100 MHz) 160.4 (2 × C=O), 82.8 (C_{quat}), 28.3 ($OC(CH_3)_3$); **m/z** (ESI^+) 507.3 ($[2M+Na]^+$, 100 %). Data are in accordance with the literature.[185]

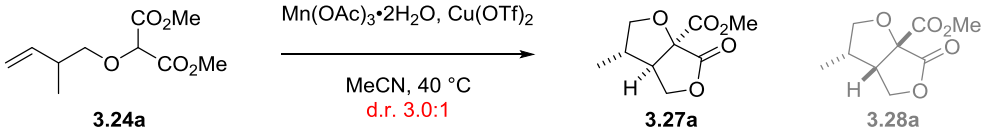
(±)-Dimethyl 2-((2-methylbut-3-en-1-yl)oxy)malonate, 3.24a



The title compound was prepared according to general procedure 4 using 2-methylbut-3-en-1-ol **3.23a** (258 mg, 3.00 mmol) and dimethyl 2-diazomalonate **3.17** (501 mg, 3.15 mmol). FC purification (1:4 Et_2O/$PE_{30\text{-}40}$) gave the title compound **3.24a** as a colourless oil (216 mg, 0.957 mmol, 32%). $\mathbf{R_f}$ 0.36 (3:7 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 5.78 (1H, dd, *J* = 17.3, 10.4, 7.0, CH_2=C*H*), 5.08 (1H, d, *J* = 17.3, C*H*H'=CH_2), 5.03 (1H, d, *J* = 10.4, CH*H'*=CH_2), 4.51 (1H, s, OC*H*(CO_2CH_3)$_2$), 3.80 (6H, s, (CO_2CH_3)$_2$), 3.51 (1H, dq, *J* = 8.9, 7.0, CHC*H*H'O), 3.41 (1H, dd, *J* = 8.9, 7.0, CHCH*H'*O), 2.60–2.51 (1H, m, C*H*CH_3), 1.05 (3H, d, *J* = 7.0); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 167.1 (*C*=O), 140.3 (CH_2=*C*H), 114.9 (*C*H_2=CH), 79.3 (O*C*H), 79.1 (O*C*H_2), 53.0 (2 x CO_2*C*H_3), 37.6 (*C*HCH_3), 16.4 (CH*C*H_3); $\mathbf{\nu_{max}}$ 2958 (w, C-H), 1744 (s, C=O), 1200 (m),

1128 (s), 1026 (m), 917 (w); **m/z** (ESI$^+$) 239 ([M+Na]$^+$, 100%), 455 ([2M+Na]$^+$, 11%); HRMS found 239.0894, $C_{10}H_{16}NaO_5$ requires 239.0890.

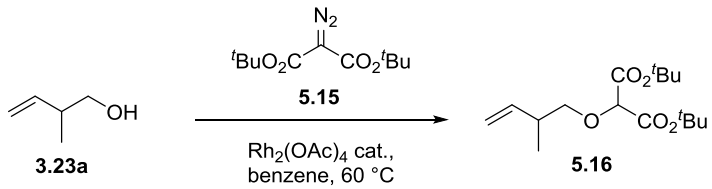
(±)-Methyl (3*R*,3a*S*,6a*R*)-3-methyl-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.24a



3.24a **3.27a** **3.28a**

The title compound was prepared according to the general procedure 4 using dimethyl 2-((2-methylbut-3-en-1-yl)oxy)malonate **3.24a** (55 mg, 0.254 mmol). Flash Chromatography purification ($PE_{30\text{-}40}$/Et_2O 1:2 to 1:4) gave the mixture of the two diastereoisomers (37 mg, 0.185 mmol, 73%). A second purification ($PE_{30\text{-}40}$/Et_2O 1:2 to 1:4) gave the clean major diastereoisomer **3.27a**. Characterisation is given for the major diastereoisomer only. $\mathbf{R_f}$ 0.38 (4:1 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 4.56 (1H, dd, *J* = 9.7, 6.8, CO_2CHH'), 4.25 (1H, dd, *J* = 9.7, 1.8, CO_2CHH'), 4.18 (1H, dd, *J* = 8.6, 6.6, OC*H*H'), 3.83 (3H, s, CO_2CH_3), 3.74 (1H, dd, *J* = 8.6, 8.6, OCH*H'*), 2.82 (1H, ddd, *J* = 6.8, 6.8, 1.8, $CO_2CHH'CH$), 2.37–2.24 (1H, m, CH_2CHCH_3), 1.12 (3H, d, *J* = 6.9, $CHCH_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 172.0 (*C*=O), 168.6 (*C*=O), 86.7 (C_{quat}), 77.3 (OCH_2CHCH_3), 69.5 (CO_2CH_2CH), 53.3 (CO_2CH_3), 53.1 (CO_2CH_2CH), 41.1 (CH_2CHCH_3), 15.4 (CH_2CHCH_3); $\mathbf{\nu_{max}}$ 2962 (w, C-H), 1778 (s, C=O), 1760 (s, C=O), 1728 (m, C=O), 1194 (m); **m/z** (ESI$^+$) 201.1 ([M+H]$^+$, 20%), 223.1 ([M+Na]$^+$, 50%), 423.1 ([2M+Na]$^+$, 100%); HRMS found 223.0578, $C_9H_{12}NaO_5$ requires 223.0577.

(±)-di-*tert*-Butyl 2-((2-methylbut-3-en-1-yl)oxy)malonate, 5.16

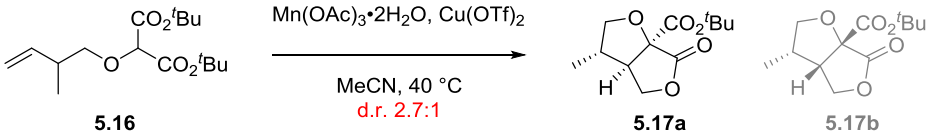


3.23a **5.16**

The title compound was prepared according to general procedure 2 using 2-methylbut-3-en-1-ol **3.23a** (258 mg, 3.00 mmol) and di-*tert*-butyl 2-diazomalonate **5.15** (763 mg, 3.15 mmol). FC purification (1:9 Et_2O/$PE_{30\text{-}40}$) gave the title compound **5.16** as a colourless oil (340 mg, 1.13 mmol, 38%). $\mathbf{R_f}$ 0.27 (3:7 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 5.80 (1H, dd, *J* = 17.2, 10.4, 6.6, CH_2=C*H*), 5.08 (1H, d, *J* = 17.2, C*H*H'=CH), 5.03 (1H, d, *J* = 10.4, CH*H'*=CH), 4.23 (1H, s, $OCH(CO_2C(CH_3)_3)_2$), 3.50 (1H, dd, *J* = 8.8, 6.1, CHC*H*H'O), 3.38 (1H, dd, *J* = 8.8, 7.3, CHCH*H'*O), 2.59–2.48 (1H, m, $CHCH_3$), 1.49 (9H, s, $OC(CH_3)_3$), 1.06 (3H, d, *J* = 7.0, $CHCH_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 166.0 (2 x *C*=O), 140.6 (CH_2=*C*H), 114.6 (CH_2=CH), 82.6 (2 x C_{quat}), 80.6 (O*C*H), 75.6 (CH_2O), 37.7 ($CHCH_3$), 28.1 ($OC(CH_3)_3$) 16.5 ($CHCH_3$); $\mathbf{\nu_{max}}$

2979 (w, C-H), 1738 (s, C=O), 1394 (w), 1249 (w), 1139 (s), 848 (w); **m/z** (ESI$^+$) 323 ([M+Na]$^+$, 100%), 623 ([2M+Na]$^+$, 33%); HRMS found 323.1835, $C_{16}H_{28}NaO_5$ requires 323.1839.

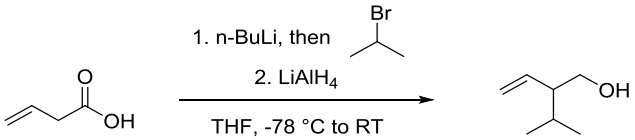
(±)-*tert*-Butyl (3*R*,3a*S*,6a*S*)-3-methyl-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 5.17a



5.16 **5.17a** 5.17b

The title compound was prepared according to general procedure 4 using di-*tert*-butyl 2-((2-methylbut-3-en-1-yl)oxy)malonate **5.16** (90.1 mg, 0.300 mmol). FC purification (Et_2O/$PE_{30\text{-}40}$ 2:1) gave the product as a white solid (12.1 mg, 0.050 mmol, 17%) and a mixture of the two diastereoisomers (33.6 mg, 0.139 mmol, 46%). Characterisation is given for the major diastereoisomer **5.17a** only. $\mathbf{R_f}$ 0.55 (Et_2O); **m.p.** not given, decomposition observed at T > 115 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.49 (1H, dd, *J* = 9.4, 6.9, $CO_2CHH'CH$), 4.22 (1H, dd, *J* = 9.4, 1.7, $CO_2CHH'CH$), 4.17 (1H, dd, *J* = 8.8, 6.9, $OCHH'CHCH_3$), 3.71 (1H, dd, *J* = 8.8, 8.8, $OCHH'CHCH_3$), 2.73 (1H, ddd, *J* = 8.1, 6.9, 1.7, CO_2CH_2CH), 2.34–2.20 (1H, m, OCH_2CHCH_3), 1.49 (9H, s, $OC(CH_3)_3$), 1.12 (3H, d, *J* = 6.6, $CHCH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.6 (*C*=O), 167.0 (*C*=O), 86.9 (C_{quat}), 84.2 (C_{quat}), 77.4 (OCH_2CHCH_3), 69.5 (CO_2CH_2CH), 53.4 (CO_2CH_2CH), 41.0 ($CHCH_3$), 28.0 ($CO_2C(CH_3)_3$), 15.3 ($CHCH_3$); $\boldsymbol{\nu_{max}}$ 2981 (w, C-H), 1771 (m, C=O), 1748 (s, C=O), 1147 (m), 842 (s); **m/z** (ESI$^+$) 265.1 ([M+Na]$^+$, 55%), 507.0 ([2M+Na]$^+$, 100%); HRMS found 265.1058, $C_{12}H_{18}NaO_5$ requires 265.1046.

(±)-2-Isopropylbut-3-en-1-ol, 3.23c

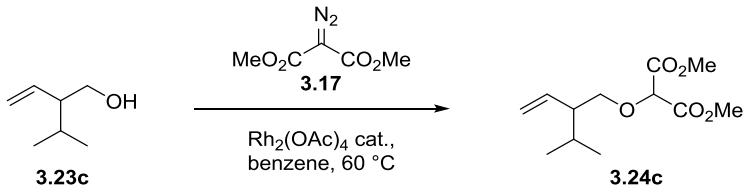


1.145 **3.23c**

The title compound was prepared according to general procedure 3 using vinyl acetic acid **1.145** (1.00 g, 11.7 mmol) and 2-bromopropane (3.30 mL, 35.1 mmol). The stirring period at RT was 6 h. FC purification (3:7 Et_2O/$PE_{30\text{-}40}$) gave the title compound **3.23c** as a colourless oil (635 mg, 5.56 mmol, 48%). $\mathbf{R_f}$ 0.32 (3:7 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.65 (1H, ddd, *J* = 17.1, 10.3, 9.3, CH_2=C*H*), 5.23 (1H, dd, *J* = 10.3, 2.4, C*H*H'=CH), 5.15 (1H, ddd, *J* = 17.1, 2.4, 0.5, CH*H'*=CH), 3.70 (1H, dd, *J* = 10.5, 4.9, C*H*H'OH), 3.47 (1H, dd, *J* = 10.5, 9.1, CH*H'*OH), 2.08–1.99 (1H, m, C*H*CH_2OH), 1.69 (1H, m, C*H*$(CH_3)_2$), 0.94 (3H, d, *J* = 6.9, $CHCH_3$), 0.89 (3H, d, *J* = 6.9, $CHCH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.3 (CH_2=*C*H), 118.5

(CH_2), 63.9 (CH_2OH), 53.9 ($CHCH_2$), 28.7 ($CH(CH_3)_2$), 20.9 (CH_3), 19.7 (CH_3); ν_{max} 3335 (br, O-H), 2958 (m, C-H), 1044 (m), 913 (s); **m/z** (ESI^+) compound showed no detectable ionisation.

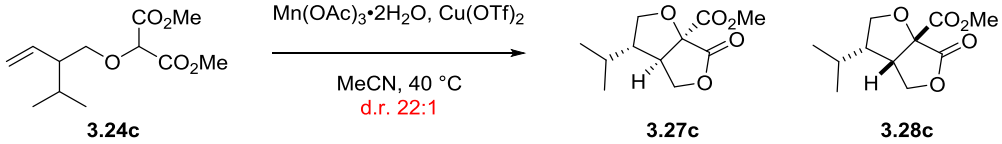
(±)-Dimethyl 2-((2-isopropylbut-3-en-1-yl)oxy)malonate, 3.24c



3.23c **3.24c**

The title compound was prepared according to general procedure 2 using 2-isopropylbut-3-en-1-ol **3.23c** (343 mg, 3.0 mmol) and dimethyl 2-diazomalonate (501 mg, 3.15 mmol). FC purification (1:9 $Et_2O/PE_{30\text{-}40}$) gave the title compound **3.24c** as a colourless oil (590 mg, 1.84 mmol, 61%). $\mathbf{R_f}$ 0.20 (1:9 Et_2O/PE); δ_H (400 MHz, $CDCl_3$) 5.69 (1H, ddd, *J* = 17.1, 10.5, 9.1, CH_2=*C*H), 5.13 (1H, dd, *J* = 10.5, 2.0, C*H*H'=CH), 5.09 (1H, dd, *J* = 17.1, 2.0, CH*H'*=CH), 4.52 (1H, s, OC*H*), 3.82 (6H, s, CO_2CH_3), 3.63 (1H, dd, *J* = 9.1, 6.6, C*H*H'O), 3.59 (1H, dd, *J* = 9.1, 6.6, CH*H'*O), 2.31–2.21 (1H, m, C*H*CH(CH_3)$_2$), 1.88 (1H, m, C*H*(CH_3)$_2$), 0.93 (3H, d, *J* = 6.6, CHCH_3), 0.86 (3H, d, *J* = 6.6, CHCH_3); δ_C (100 MHz, $CDCl_3$) 167.2 (*C*=O), 167.1 (*C*=O), 137.0 (CH_2=*C*H), 117.3 (CH_2=CH), 79.3 (O*C*H), 73.2 (OCH_2), 52.9 (CO_2CH_3), 49.9 (*C*HCH(CH_3)$_2$), 28.1 (*C*H(CH_3)$_2$), 20.8 (CH*C*H_3), 18.4 (CH*C*H_3); ν_{max} 2958 (w, C-H), 1746 (s, C=O), 1129 (m), 1028 (m), 917 (w); **m/z** (ESI^+) 267.1 ($[M+Na]^+$, 100%), 511.0 ($[2M+Na]^+$, 20%); HRMS found 267.1205 $C_{12}H_{20}NaO_5$ requires 267.1203.[186]

(±)-*tert*-Butyl (3*R*,3a*S*,6a*S*)-3-isopropyl-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6H)-carboxylate, 3.27c

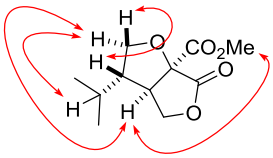


3.24c **3.27c** **3.28c**

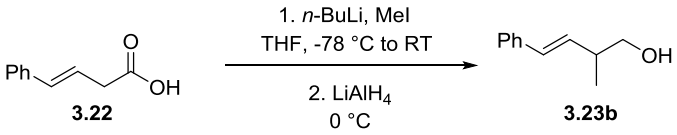
The title compound was prepared according to the general procedure 4 using dimethyl 2-((2-isopropylbut-3-en-1-yl)oxy)malonate **3.24c** (70.0 mg, 0.287 mmol). Flash Chromatography purification ($PE_{30\text{-}40}/Et_2O$ 2:3) gave the title compound **3.27c** in a 26:1 mixture of diastereoisomers as a colourless oil (48 mg, 0.211 mmol, 73%). $\mathbf{R_f}$ 0.50 (7:3 $Et_2O/PE_{30\text{-}40}$); δ_H (400 MHz, $CDCl_3$) 4.52 (1H, dd, *J* = 9.5, 7.0, CO_2CHH'), 4.22 (1H, dd, *J* = 9.5, 1.7, CO_2CH*H'*), 4.19 (1H, dd, *J* = 8.8, 7.3, C*H*H'O), 3.80 (3H, s, OCH_3), 3.79 (1H, m, CH*H'*O), 2.90 (1H, ddd, *J* = 7.0, 7.0, 1.7, CO_2CH_2CH), 1.97 (1H, m, C*H*CH(CH_3)$_2$), 1.60 (1H, qqd, *J* = 6.7, 6.7, 2.2, C*H*(CH_3)$_2$), 0.91 (3H, d, *J* = 6.7, CHCH_3), 0.84 (3H, d, *J* = 6.7, CHCH_3); δ_C (100 MHz, $CDCl_3$) 172.0 (*C*=O), 168.8 (*C*=O), 87.1 (C_{quat}), 75.6 (OCH_2), 70.7 (CO_2CH_2), 54.0 (*C*HCH(CH_3)$_2$), 53.3 (OCH_3), 50.4 (CO_2CH_2CH), 30.9 (C*H*(CH_3)$_2$), 21.4 (CH*C*H_3), 21.2 (CH*C*H_3); ν_{max} 2960

(w, C-H), 1783 (s, C=O), 1762 (m, C=O), 1730 (w, C=O), 1028 (m); **m/z** (ESI$^+$) 251.0 ([M+Na]$^+$, 100%), 479.0 ([2M+Na]$^+$, 80%); HRMS found 251.0892 $C_{11}H_{16}NaO_5$ requires 251.0890.

Key nOe interactions
3.27c

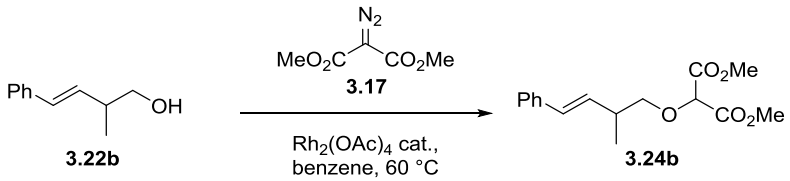


(±)-(*E*)-2-Methyl-4-phenylbut-3-en-1-ol, 3.22b



The title compound was prepared according to general procedure 3 using *trans*-styrylacetic acid **3.22** (1.00 g, 6.17 mmol) and iodomethane (1.18 mL, 3.00 eq). The stirring period at RT was one hour. FC purification ($Et_2O/PE_{30\text{-}40}$ 2:3) gave the title compound **3.22b** as an orange oil (302 mg, 1.86 mmol, 30%). $\mathbf{R_f}$ 0.52 (1:1 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 Hz, $CDCl_3$) 7.40–7.35 (2H, m, Ar*H*), 7.34–7.27 (2H, m, Ar*H*), 7.25–7.19 (1H, m, Ar*H*), 6.49 (1H, d, *J* = 15.9, Ar-C*H*=CH), 6.10 (1H, dd, *J* = 15.9, 8.1, Ar-CH=C*H*), 3.60 (1H, dd, *J* = 10.6, 5.6, C*H*H'OH), 3.52 (1H, dd, *J* = 10.6, 7.6, CH*H'*OH), 2.61–2.48 (1H, m, C*H*CH_3), 1.11 (1H, d, *J* = 6.6, CHC*H*$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.3 (Ar-CH=*C*H), 132.6 (Ar-*C*H=CH), 131.1 (*Ar*), 128.7 (*Ar*), 127.4 (*Ar*), 126.3 (*Ar*), 67.5 (CH_2), 40.3 (*C*HCH_3), 16.6 (CH_3); $\boldsymbol{\nu_{max}}$ 3342 (br, O-H), 2960 (w, C-H), 1031 (m), 476 (s), 693 (s); **m/z** (ESI$^+$) 185.1 ([M+Na]$^+$, 100%). Data are in accordance with the literature.[187]

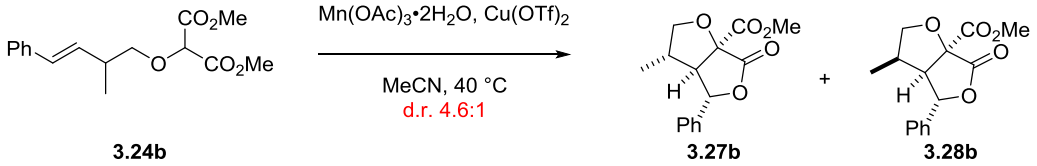
(±)-Dimethyl (*E*)-2-((2-methyl-4-phenylbut-3-en-1-yl)oxy)malonate, 3.24b



The title compound was prepared according to general procedure 2 using (*E*)-2-Methyl-4-phenylbut-3-en-1-ol **3.22b** (286 mg, 1.76 mmol) and dimethyl 2-diazomalonate **3.17** (294 mg, 1.85 mmol). FC purification (1:3 $Et_2O/PE_{30\text{-}40}$) gave the title compound **3.24b** as a colourless oil (285 mg, 0.975 mmol, 55%); $\boldsymbol{\delta_H}$ (400 Hz, $CDCl_3$) 7.37–7.32 (2H, m, Ar*H*), 7.32–7.26 (2H, m, Ar*H*), 7.23–7.17 (1H, m, Ar*H*), 6.45 (1H, d, *J* = 16.0, Ar-C*H*=CH), 6.16 (1H, dd, *J* = 16.0, 6.20, Ar-CH=C*H*), 4.54 (1H, s, OC*H*$(CO_2Me)_2$), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.59 (1H, dd, *J* = 9.4, 6.1, C*H*H'OCH), 3.51 (1H, dd, *J* = 9.4, 7.1, CH*H'*OCH), 2.80–2.67 (1H, m, C*H*CH_3), 1.16 (1H, d, *J* = 6.9, CHCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 167.1 (C=O), 167.1 (C=O), 137.6 (Ar-CH=*C*H), 132.0 (Ar-*C*H=CH), 130.2 (*Ar*), 128.6 (*Ar*), 127.3 (*Ar*), 126.3 (*Ar*), 79.4

(O*C*H(CO$_2$Me)$_2$), 76.3 (*C*H$_2$-O-CH), 53.0 (CO$_2$*C*H$_3$), 37.2 (C*H*CH$_3$), 17.0 (CHC*H*$_3$); **ν$_{max}$** 2957 (w, C-H), 1764 (m, C=O), 1746 (s, C=O), 1139 (m), 1028 (w), 750 (w), 695 (w); **m/z** (ESI$^+$) 315.1 ([M+Na]$^+$, 100%); HRMS found 315.1203, $C_{16}H_{20}NaO_5$ requires 315.1203.

(±)-Methyl (3*R*,3a*S*,4*R*,6a*R*)-3-methyl-6-oxo-4-phenyltetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.27b

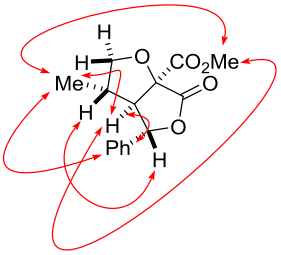


3.24b **3.27b** **3.28b**

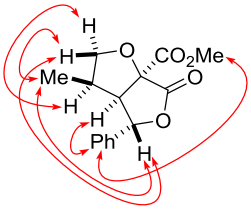
The title compound **3.27b** was prepared according to the general procedure 4 using dimethyl (*E*)-2-((2-methyl-4-phenylbut-3-en-1-yl)oxy)malonate **3.24b** (75 mg, 0.257 mmol). Flash Chromatography purification (PE/Et$_2$O 2:3) gave the product as a mixture of two diastereoisomers (65 mg, 0.236 mmol, 92%). A second purification (PE/Et$_2$O 2:3) gave the clean major diastereoisomer **3.27b** and a small amount of the clean minor diastereoisomer **3.28b** (3.0 mg).

Major diastereoisomer **3.27b**: **R$_f$** 0.24 (2:3 Et$_2$O/PE); **δ$_H$** (500 MHz, CDCl$_3$) 7.46–7.50 (3H, m, Ar*H*), 7.40–7.34 (2H, m, Ar*H*), 5.26 (1H, d, *J* = 4.7, C*H*Ph), 4.29 (1H, dd, *J* = 9.1, 6.0, OC*H*H'), 3.97 (1H, *J* = 9.1, 4.7, OCH*H'*), 3.78 (3H, s, CO$_2$C*H*$_3$), 2.96 (1H, dd, *J* = 4.1, 4.1, PhCHC*H*), 2.55 (1H, m, C*H*CH$_3$), 1.15 (3H, d, *J* = 6.9, CHC*H*$_3$); **δ$_C$** (126 MHz, CDCl$_3$) 171.4 (*C*=O), 169.0 (*C*=O), 138.6 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 122.5 (*Ar*), 87.5 (*C*$_{quat}$), 84.5 (PhCH), 66.0 (*C*H$_2$), 61.4 (PhCH*C*H), 53.4 (O*C*H$_3$), 41.2 (*C*HCH$_3$), 17.5 (CH*C*H$_3$); **ν$_{max}$** 2959 (w, C-H), 1780 (s, C=O), 1732 (s, C=O), 725 (w), 699 (w); **m/z** (ESI$^+$) 299 ([M+Na]$^+$, 100%), 575 ([2M+Na]$^+$, 75%); HRMS found 299.0886, $C_{15}H_{16}NaO_5$ requires 299.0890.

NMR analysis of the minor diastereoisomer **3.28b**: **δ$_H$** (500 MHz, CDCl$_3$) 7.33–7.22 (5H, m, ArH), 5.30 (1H, d, *J* = 6.2, C*H*Ph), 4.26 (1H, dd, *J* = 8.7, 7.3, OC*H*H'), 3.72 (3H, s, OCH$_3$), 3.63 (1H, dd, *J* = 10.7, 8.7, OCH*H'*), 3.24 (1H, dd, *J* = 7.1, 6.2, C*H*CHPh), 2.63–2.52 (1H, m, C*H*CH$_3$), 1.05 (3H, d, *J* = 6.9, CHCH$_3$); **δ$_C$** (126 MHz, CDCl$_3$) 171.2 (*C*=O), 168.7 (*C*=O), 138.7 (*Ar*), 129.2 (*Ar*), 129.2 (*Ar*), 126.5 (*Ar*), 88.4 (*C*$_{quat}$), 79.3, 75.8, 57.4, 53.5 (O*C*H$_3$), 36.9 (*C*HCH$_3$), 10.9 (CH*C*H$_3$).

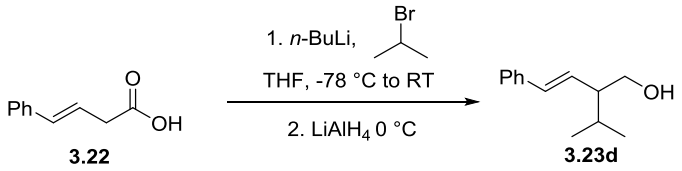


Major diastereoisomer **3.27b**
Key nOe interactions



Minor diastereoisomer **3.28b**
Key NOESY interactions

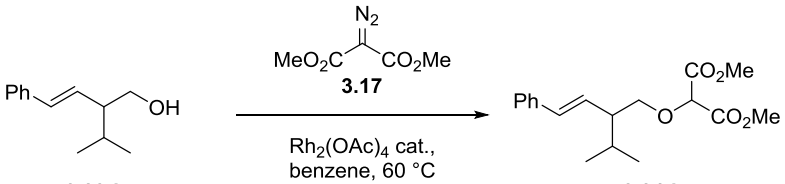
(±)-(*E*)-2-isopropyl-4-phenylbut-3-en-1-ol, 3.23d



3.22 **3.23d**

The title compound was prepared according to general procedure 3 using *trans*-styrylacetic acid **3.22** (1.50 g, 9.25 mmol) and 2-bromopropane (2.77 mL, 3.0 eq). The stirring period at RT was 3 h. Two successive FC purifications (1:3 $Et_2O/PE_{30\text{-}40}$) gave the title compound **3.23d** as a colourless oil (540 mg, 2.84 mmol, 46%). $\mathbf{R_f}$ 0.27 (1:3 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 Hz, $CDCl_3$) 7.42–7.38 (2H, m, Ar*H*), 7.36–7.30 (2H, m, Ar*H*), 7.26–7.22 (1H, m, Ar*H*), 6.50 (1H, d, *J* = 15.8, Ar-C*H*=CH), 6.05 (1H, dd, *J* = 15.8, 9.3, Ar-CH=C*H*), 3.76 (1H, dd, *J* = 10.7, 4.9, C*H*H'OH), 3.56 (1H, dd, *J* = 10.7, 9.1, CH*H'*OH), 2.25–2.14 (1H, m, C*H*CH$(CH_3)_2$), 1.84–1.72 (1H, m, CHC*H*$(CH_3)_2$), 0.97 (3H, d, *J* = 6.9, CH_3), 0.84 (3H, d, *J* = 6.9, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.2 (Ar-*C*H=CH), 133.6 (Ar-CH=*C*H), 129.8 (*Ar*), 128.7 (*Ar*), 127.5 (*Ar*), 126.3 (*Ar*), 64.4 (*C*H_2OH), 53.1 (C*H*CH$(CH_3)_2$), 29.3 (CHC*H*$(CH_3)_2$), 21.1 (*C*H_3), 19.8 (*C*H_3); $\boldsymbol{\nu_{max}}$ 3349 (br, OH), 2957 (m, C-H), 967 (m), 746 (s, =C-H), 693 (s, =C-H); **m/z** (ESI^+) 213.1 ($[M+Na]^+$, 100%); HRMS found 213.1248, $C_{13}H_{18}NaO$ requires 213.1250. Data are in accordance with the literature.[188]

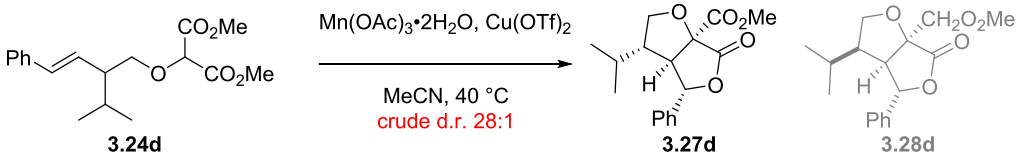
(±)-Dimethyl (*E*)-2-((2-isopropyl-4-phenylbut-3-en-1-yl)oxy)malonate, 3.24d



3.23d **3.24d**

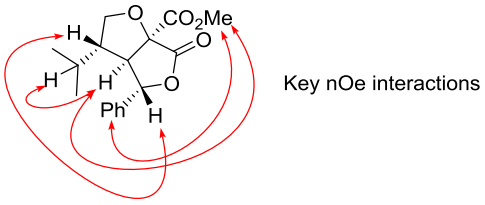
The title compound **3.24d** as was prepared according to general procedure 2 using (*E*)-2-isopropyl-4-phenylbut-3-en-1-ol **3.23d** (476 mg, 2.50 mmol) and dimethyl 2-diazomalonate **3.17** (418 mg, 2.63 mmol). FC purification (1:4 to 1:3 $Et_2O/PE_{30\text{-}40}$) gave the title compound **3.24d** as a colourless oil (590 mg, 1.84 mmol, 74%). $\mathbf{R_f}$ 0.38 (3:7 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40–7.30 (2H, m, Ar*H*), 7.28–7.21 (2H, m, Ar*H*), 7.20–7.16 (1H, m, Ar*H*), 6.44 (1H, d, *J* = 15.8, Ar-C*H*=CH), 6.09 (1H, dd, *J* = 15.8, 9.2, Ar-CH=C*H*), 4.52 (1H, s, OC*H*$(CO_2Me)_2$), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.70 (1H, dd, *J* = 6.4, 2.9, C*H*H'OCH), 3.65 (1H, dd, *J* = 9.3, 6.4, CH*H'*OCH), 2.46–2.36 (1H, m, C*H*CH$(CH_3)_2$), 1.97 (1H, m, C*H*$(CH_3)_2$), 0.96 (3H, d, *J* = 6.8, CH_3), 0.91 (3H, d, *J* = 6.8, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 167.2 (*C*=O), 167.1 (*C*=O), 137.7 (Ar-*C*H=CH), 132.5 (Ar-CH=*C*H), 128.9 (*Ar*), 128.6 (*Ar*), 127.2 (*Ar*), 126.3 (*Ar*), 79.4 (CH_2O*C*H), 73.4 (*C*H_2OCH), 52.9 (O*C*H_3), 49.4 (*C*HCH$(CH_3)_2$), 28.7 (CH*C*H$(CH_3)_2$), 21.0 (*C*H_3), 18.7 (*C*H_3); $\boldsymbol{\nu_{max}}$ 2957 (w, C-H), 1748 (s, C=O), 1139 (m), 749 (w, =C-H), 695 (w, =C-H); **m/z** (ESI^+) 343.1 ($[M+Na]^+$, 100%); HRMS found 343.1531, $C_{18}H_{24}NaO_5$ requires 343.1516.

(±)-*tert*-Butyl (3*R*,3a*S*,4*R*,6a*S*)-3-isopropyl-6-oxo-4-phenyltetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.27d



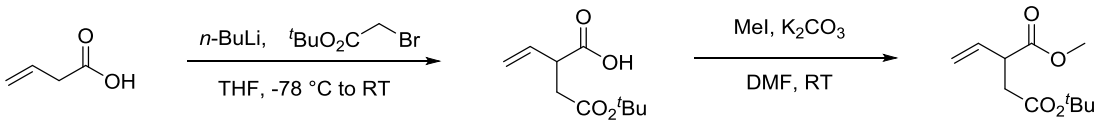
3.24d **3.27d** **3.28d**

The title compound **3.27d** was prepared according to the general procedure 4 using dimethyl (*E*)-2-((2-isopropyl-4-phenylbut-3-en-1-yl)oxy)malonate **3.24d** (84.0 mg, 0.260 mmol). Flash Chromatography purification (PE/Et_2O 2:3) gave the title compound **3.27d** in 25:1 d.r. mixture of diastereoisomer (73.0 mg, 0.240 mmol, 92%). $\mathbf{R_f}$ 0.24 (2:3 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.44–7.34 (5H, m, Ar*H*), 5.28 (1H, d, *J* = 4.7, C*H*Ph), 4.33 (1H, dd, *J* = 9.1, 7.3, OC*H*H'), 4.02 (1H, *J* = 7.3, 3.3, OCH*H'*), 3.78 (3H, s, CO_2CH_3), 3.11 (1H, dd, *J* = 4.7, 4.7, PhCHC*H*), 2.23 (1H, m, C*H*CH$(CH_3)_2$), 1.60 (1H, m, C*H*$(CH_3)_2$), 0.88 (3H, d, *J* = 6.6, CHCH_3), 0.83 (3H, d, *J* = 6.6, CHCH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 170.9 (*C*=O), 169.2 (*C*=O), 138.2 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 126.1 (*Ar*), 88.3 (C_{quat}), 86.2 (*C*HPh), 75.2 (OCH_2), 58.1 (PhCHC*H*), 55.2 (*C*HCH$(CH_3)_2$), 53.3 (CO_2CH_3), 30.4 (*C*H$(CH_3)_2$), 21.4 (CH*C*H_3), 21.0 (CH*C*H_3); $\mathbf{\nu_{max}}$ 2959 (w, C-H), 1782 (s, C=O), 1760 (m, C=O), 1731 (w, C=O), (699, =C-H); **m/z** (ESI$^+$) 327.1 ([M+Na]$^+$, 100%), 631.3 ([2M+Na]$^+$, 80%); HRMS found 327.1212 $C_{17}H_{20}NaO_5$ requires 327.1203.



Key nOe interactions

(±)-4-(*tert*-Butyl) 1-methyl 2-vinylsuccinate, 1.200

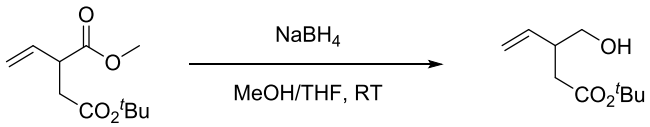


1.145 **3.25a** **1.200**

To a solution of 3-butenoic acid **1.145** (0.796 mL, 9.25 mmol) in THF (24 mL) at -78 °C was added a solution of *n*-BuLi in hexanes (2.5 M, 8.14 mL, 20.4 mmol) over 5 min. The mixture was stirred for 10 min and *tert*-butyl bromoacetate (4.1 mL, 28 mmol) was added over 5 min. The reaction was warmed to RT outside the cooling bath and stirred for 8 h. The mixture was quenched at 0° C with aq. NaOH (0.5 M, 40 mL), Et_2O was added (40 mL). The layers were separated and the organic phase was extracted with more aq. NaOH (0.5 M, 20 mL). The combined aqueous layers were treated with pH 2 sulfate buffer (15 mL) and acidified by dropwise addition of a concentrated aqueous solution of HCl until pH 2. The aqueous phase was then extracted with Et_2O (3 x 30 mL). The combined layers were

dried (Na_2SO_4), filtered and evaporated to give the crude carboxylic acid **3.25a** (2.16 g). The residual oil was dissolved in dry DMF and treated upon stirring at RT with K_2CO_3 (3.83 g, 27.8 mmol) and MeI (1.43 mL, 23.1 mmol). The reaction was stirred for 4 h at RT and was then diluted with Et_2O (50 mL) and pentane (50 mL). The mixture was washed with H_2O (2 x 100 mL) and brine (50 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (1:9 $Et_2O/PE_{30\text{-}40}$), which gave the title compound **1.200** as a colourless oil (473 mg, 2.21 mmol, 24%). $\mathbf{R_f}$ 0.48 (1:6 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 5.84 (1H, ddd, *J* = 16.1, 10.0, 7.6, CH_2=*C*H), 5.20 (1H, ddd, *J* = 16.1, 2.1, 1.0, C*H*H'=CH), 5.16 (1H, ddd, *J* = 7.6, 2.1, 1.0, CH*H'*=CH), 3.70 (3H, s, OCH_3), 3.48 (1H, m, C*H*CH_2), 2.76 (1H, dd, *J* = 16.4, 8.8, C*H*H'$CO_2{}^t$Bu), 2.47 (1H, dd, *J* = 16.4, 6.1, CH*H'*$CO_2{}^t$Bu), 1.42 (9H, OC(CH_3)$_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 173.4 (*C*=O), 170.6 (*C*=O), 134.4 (CH_2=*C*H), 117.9 (*C*H_2=CH), 81.1 (C_{quat}), 52.3 (O*C*H_3), 45.8 (*C*H), 37.3 (*C*H_2), 28.2 (OC(*C*H_3)$_3$); $\mathbf{\nu_{max}}$ 2980 (w, C-H), 1730 (s, C=O), 1150 (s), 924 (w, =C-H), 845 (w, =C-H); **m/z** (ESI^+) 237.1 ($[M+Na]^+$, 100%), 451.2 ($[2M+Na]^+$, 20%); HRMS found 237.1102 $C_{11}H_{18}NaO_4$ requires 237.1097.

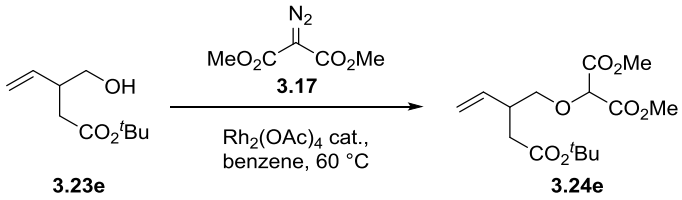
(±)-*tert*-Butyl 3-(hydroxymethyl)pent-4-enoate, 3.23e



3.26a **3.23e**

To a vigorously stirred solution of 4-(*tert*-butyl) 1-methyl 2-vinylsuccinate **3.26a** (457 mg, 2.13 mmol) in THF/MeOH (1:1, 15 mL) at RT, was added every 30 min $NaBH_4$ (4 additions, each addition: 457 mg, 10.7 mmol) and the reaction was stirred for another hour. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and water was added (20 mL). The mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:3 $Et_2O/PE_{30\text{-}40}$), which gave the title compound **3.23e** as a colourless oil (224 mg, 1.20 mmol, 56%); $\mathbf{R_f}$ 0.30 (2:3 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 5.70 (1H, ddd, *J* = 17.0, 10.5, 7.8, CH_2=C*H*), 5.16 (2H, m, C*HH'*=CH), 3.56 (2H, d, *J* = 6.1, CH_2OH), 2.71 (1H, m, C*H*(CH_2)$_2$), 2.40 (1H, dd, *J* = 15.0, 6.6, C*H*H'$CO_2{}^t$Bu), 2.29 (1H, dd, *J* = 15.0, 7.6, CH*H'*$CO_2{}^t$Bu), 1.43 (9H, s, OC(CH_3)$_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 177.1 (*C*=O), 138.0 (CH_2=*C*H), 117.2 (*C*H_2=CH), 80.9 (C_{quat}), 65.4 (*C*H_2OH), 43.0 (C*H*), 37.5 (*C*$H_2CO_2{}^t$Bu), 28.2 (OC(*C*H_3)$_3$); $\mathbf{\nu_{max}}$ 3428 (Br, O-H), 2979 (w, C-H), 1727 (s, C=O), 1368 (w), 1153 (s), 918 (=C-H), 842 (=C-H); **m/z** (ESI^+) 209.1 ($[M+Na]^+$, 100%), 395.3 ($[2M+Na]^+$, 15%); HRMS found 209.1158 $C_{10}H_{18}NaO_3$ requires 209.1148.

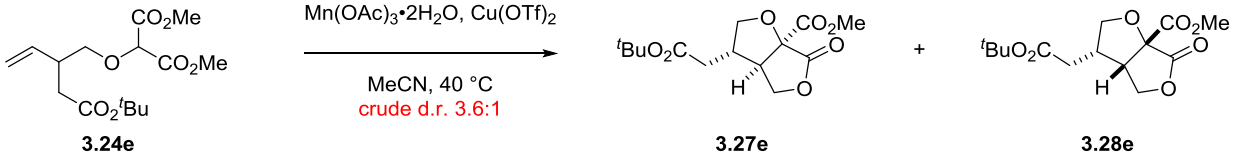
(±)-Dimethyl 2-((2-(2-(tert-butoxy)-2-oxoethyl)but-3-en-1-yl)oxy)malonate, 3.24e



3.23e **3.24e**

The title compound was prepared according to general procedure 2 using *tert*-butyl 3-(hydroxymethyl)pent-4-enoate **3.23e** (210 mg, 0.800 mmol) and dimethyl 2-diazomalonate **3.17e** (134 mg, 0.840 mmol). FC purification (1:3 to 1:2 $Et_2O/PE_{30\text{-}40}$) gave the title compound **3.24e** product as a colourless oil (217 mg, 0.639 mmol, 80%); $\mathbf{R_f}$ 0.38 (1:2 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.65, (1H, ddd, *J* = 17.3, 10.3, 7.6, CH_2=C*H*), 5.09 (1H, ddd, *J* = 17.3, 1.2, 1.2, C*H*H'=CH), 5.05 (1H, ddd, *J* = 10.3, 1.2, 1.2, CH*H'*=CH), 4.45 (1H, s, OC*H*), 3.74 (6H, s, 2 x OCH_3), 3.55 (1H, dd, *J* = 9.1, 5.9, OC*H*H'), 3.45 (1H, dd, *J* = 9.1, 7.1, OCH*H'*), 2.82 (1H, m, C*H*$(CH_2)_2$), 2.51 (1H, dd, *J* = 15.4, 5.6, C*H*H'$CO_2{}^t$Bu), 2.20 (1H, dd, *J* = 15.4, 8.6, CH*H'*$CO_2{}^t$Bu), 1.36 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.5 (*C*=O), 166.9 (2 x *C*=O), 137.3 (CH_2=*C*H), 116.8 (*C*H_2=CH), 80.5 (C_{quat}), 79.2 (O*C*H), 73.8 (O*C*H_2), 53.0 (O*C*H_3), 40.2 (*C*H$(CH_2)_2$), 37.3 (*C*$H_2CO_2{}^t$Bu), 28.2 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 2979 (w, C-H) 1740 (C=O), 1727 (s, C=O), 1243 (m), 1138 (s), 1027 (m), 921 (w, =C-H); **m/z** (ESI^+) 339.1 ($[M+Na]^+$, 100%); HRMS found 339.1413 $C_{15}H_{24}NaO_7$ requires 339.1414.

(±)-Methyl (3*R*,3a*S*,6a*R*)-3-(2-(*tert*-butoxy)-2-oxoethyl)-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.27e

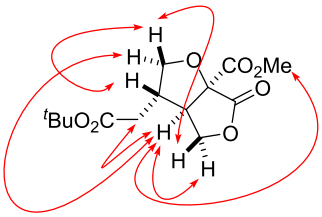


3.24e **3.27e** **3.28e**

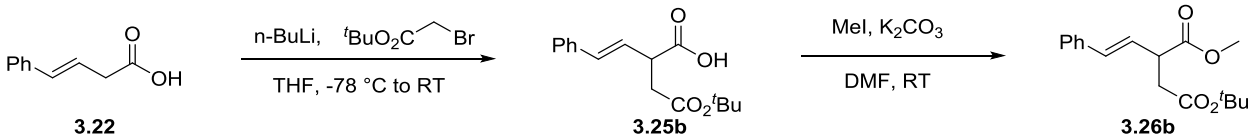
The title compound was prepared according to general procedure 4 using dimethyl 2-((2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-en-1-yl)oxy)malonate **3.24e** (94.9 mg, 0.300 mmol). FC purification (4:1 $Et_2O/PE_{30\text{-}40}$) gave an inseparable mixture (3.6:1) of the two diastereoisomers (68.0 mg, 0.226 mmol, 76%) as a white solid. For analytical purposes, two successive recrystallisations from EtOAc/Hexane (1:4) gave the title compound **3.27e** in higher diasteromeric purity (12:1, 42 mg). Characterisation was performed on the recrystallised mixture and is given for the major diastereoisomer **3.27e** only. $\mathbf{R_f}$ 0.59 (4:1 Et_2O/PE); **m.p.** 98–99 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.54 (1H, dd, *J* = 9.8, 7.1, CO_2C*H*H'), 4.33 (1H, dd, *J* = 9.8, 2.5, CO_2CH*H'*), 4.17 (1H, dd, *J* = 9.1, 6.9, OC*H*H'), 3.80 (1H, dd, *J* = 9.1, 4.6, OCH*H'*), 3.80 (3H, s, OCH_3), 2.94 (1H, ddd, *J* = 7.1, 7.1, 2.5, CO_2CH_2C*H*), 2.55 (1H, m, C*H*$CH_2CO_2{}^t$Bu), 2.41 (1H,

dd, *J* = 16.4, 6.6, C*H*H'$CO_2{}^t$Bu), 2.29 (1H, dd, *J* = 16.4, 8.3, CH*H'*$CO_2{}^t$Bu), 1.38 (9H, s, OC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 171.7 (*C*=O), 170.6 (*C*=O), 168.5 (*C*=O), 86.9 (C_{quat}), 81.8 (C_{quat}), 75.5 (OCH_2), 70.6 (CO_2CH_2), 53.5 (OCH_3), 51.3 (CO_2CH_2CH), 43.1 ($CHCH_2CO_2{}^t$Bu), 37.4 ($CH_2CO_2{}^t$Bu), 28.2 (OC(CH_3)$_3$); **ν_{max}** 2980 (w, C-H), 1783 (s, C=O), 1763 (m, C=O), 1724 (s, C=O), 1256 (m), 1155 (s); **m/z** (ESI^+) 323.1 ($[M+Na]^+$, 100%), 623.2 ($[2M+Na]^+$, 35%); HRMS found 323.1099 $C_{14}H_{20}NaO_7$ requires 323.1101.

Key nOe interactions
3.27e



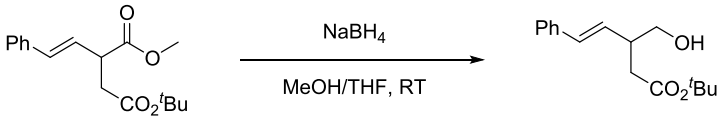
(±)-4-(*tert*-Butyl) 1-methyl (*E*)-2-styrylsuccinate, 3.26b



To a solution of *trans*-styrylacetic acid **3.22** (1.50 g, 9.25 mmol) in THF (24 mL) at -78 °C was added a solution of n-BuLi in hexanes (2.5 M, 8.14 mL, 20.4 mmol) over 5 min. The mixture was stirred for 10 min and *tert*-butyl bromoacetate (4.1 mL, 28 mmol) was added over 5 min. The reaction mixture was warmed to RT outside the cooling bath and stirred for 3 h. The mixture was quenched at 0° C with an aqueous solution of NaOH (0.5 M, 40 mL), Et_2O was added (40 mL). Layers were separated and the organic phase was extracted with more aqueous solution of NaOH (0.5 M, 20 mL). The combined aqueous layers were treated with pH 2 sulfate buffer (15 mL) and acidified by dropwise addition of a concentrated aqueous solution of HCl until pH 2. The aqueous phase was then extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to give the crude carboxylic acid **3.25b** (3.07 g). The residual oil was dissolved in dry DMF and treated upon stirring at RT with K_2CO_3 (3.83 g, 27.8 mmol) and MeI (1.43 mL, 23.1 mmol). The reaction was stirred for 16 h at RT and was then diluted with EtOAc (50 mL) and PE (50 mL). The mixture was washed with H_2O (2 x 100 mL) and brine (50 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified 2 times by FC (9:1 $PE_{30\text{-}40}/Et_2O$), which gave the title compound **3.26b** as a colourless oil (520 mg, 1.79 mmol, 19% over 2 steps). **R_f** 0.32 (1:8 Et_2O/PE); **δ_H** (400 MHz, $CDCl_3$) 7.36–7.28 (4H, m, Ar*H*), 7.27–7.20 (1H, m, Ar*H*), 6.53 (1H, d, *J* = 15.9, PhC*H*=CH), 6.18 (1H, d, *J* = 15.9, 8.6, PhCH=C*H*), 3.73 (3H, s, CO_2CH_3), 3.64 (1H, ddd, *J* = 8.6, 8.6, 6.0, C*H*CH_2), 2.86 (1H, *J* = 16.4, 8.6, C*H*H'), 2.56 (1H, dd, *J* = 16.4, 6.0, CH*H'*), 1.6 (9H, s, OC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 173.5 (*C*=O), 170.6 (*C*=O), 136.6 (*Ar*), 133.1 (PhCH=CH),

128.7 (*Ar*), 127.9 (*Ar*), 126.5 (*Ar*), 125.7 (PhCH=C*H*), 81.2 (C_{quat}), 52.3 (CH_3), 45.4 (*C*H), 37.8 (CH_2), 28.2 ($OC(CH_3)_3$); **ν_{max}** 2978 (w, C-H), 1729 (s, C=O), 1254 (w), 1148 (s), 745 (w, =C-H), 694 (w, =C-H); **m/z** (ESI^+) 313.1 ($[M+Na]^+$, 100%); HRMS found 313.1417 $C_{17}H_{22}NaO_4$ requires 313.1410.

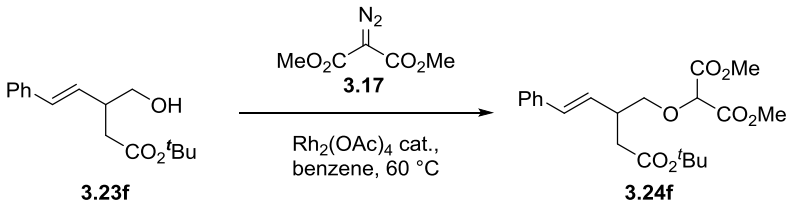
(±)-*tert*-Butyl (*E*)-3-(hydroxymethyl)-5-phenylpent-4-enoate, 3.23f



3.26b **3.23f**

To a solution 4-(*tert*-butyl) 1-methyl (*E*)-2-styrylsuccinate **3.26b** (418 mg, 1.44 mmol) in THF/MeOH (1:1, 10 mL) was added $NaBH_4$ (272 mg) in three portions. The reaction mixture was stirred for 30 min and quench with an aqueous solution of NH_4Cl (2.0 M, 30 mL), the mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:1 $Et_2O/PE_{30\text{-}40}$), which gave the title compound **3.23f** as colourless oil (334 mg, 1.27 mmol, 88%); **R_f** 0.38 (1:1 $Et_2O/PE_{30\text{-}40}$); **δ_H** (400 MHz, $CDCl_3$) 7.37–7.27 (4H, m, Ar*H*), 7.25–7.18 (1H, m, Ar*H*), 6.52 (1H, d, *J* = 16.0, PhC*H*=CH), 6.08 (1H, dd, *J* = 16.0, 8.5, PhCH=C*H*), 3.65 (2H, d, *J* = 5.9, CH_2OH), 2.94–2.84 (1H, m, C*H*), 2.50 (1H, dd, *J* = 14.9, 6.6, C*H*H'$CO_2{}^t$Bu), 2.37 (1H, dd, *J* = 14.9, 7.6, CH*H*'$CO_2{}^t$Bu), 1.99 (1H, br, OH), 1.43 (9H, s, $OC(CH_3)_3$); **δ_C** (100 MHz, $CDCl_3$) 172.0 (*C*=O), 137.0 (*Ar*), 132.4 (PhCH=CH), 129.4 (PhCH=*C*H), 128.7 (*Ar*), 127.6 (*Ar*), 126.3 (*Ar*), 80.9 (C_{quat}), 65.7 (CH_2OH), 42.7 (*C*H), 38.0 (C$H_2CO_2{}^t$Bu), 28.2 ($OC(CH_3)_3$); **ν_{max}** 3248 (br, OH), 2978 (w, C-H), 1724 (m, C=O), 1148 (s), 748 (w, =C-H); **m/z** (ESI^+) 285.1 ($[M+Na]^+$, 100%); HRMS found 285.1460 $C_{16}H_{22}NaO_3$ requires 285.1461.

(±)-Dimethyl (*E*)-2-((2-(2-(*tert*-butoxy)-2-oxoethyl)-4-phenylbut-3-en-1-yl)oxy)malonate, 3.24f

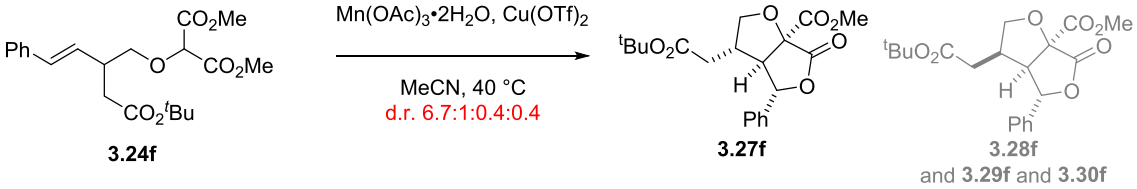


3.23f **3.24f**

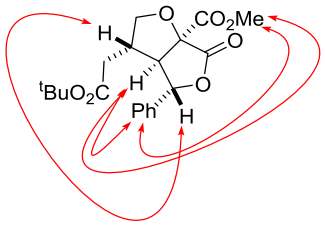
The title compound was prepared according to general procedure 2 using *tert*-butyl (*E*)-3-(hydroxymethyl)-5-phenylpent-4-enoate **3.23f** (370 mg, 1.42 mmol) and dimethyl 2-diazomalonate **3.17** (237 mg, 1.49 mmol). FC purification (1:3 $Et_2O/PE_{30\text{-}40}$) gave the desired product as a colourless oil (284 mg, 0.724 mmol, 51%). **R_f** 0.42 (2:3 Et_2O/PE); **δ_H** (400 MHz, $CDCl_3$) 7.37–7.25 (4H, m, Ar*H*), 7.25–7.16 (1H, m, Ar*H*), 6.50 (1H, d, *J* = 16.0, PhC*H*=CH), 6.11 (1H, dd, *J* = 16.0, 8.3, PhCH=C*H*), 4.54 (1H, s, OC*H*), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.69 (1H, dd, *J* = 9.1, 5.6, C*H*H'O), 3.60 (1H, dd, *J* =

9.1, 5.6, CH*H'*O), 3.05 (1H, m, C*H*CH$_2$), 2.67 (1H, dd, *J* = 15.2, 5.4, C*H*H'CO$_2$^{t}Bu), 2.36 (1H, dd, *J* = 15.2, 8.8, CH*H'*CO$_2$^{t}Bu), 1.40 (9H, s, OC(C*H*$_3$)$_3$); **δ$_C$** (100 MHz, CDCl$_3$) 171.4 (*C*=O), 166.9 (2 x *C*=O), 137.1 (*Ar*), 131.9 (PhCH=CH), 128.7 (PhCH=*C*H), 128.5 (*Ar*), 127.4 (*Ar*), 126.3 (*Ar*), 80.5 (*C$_{quat}$*), 79.1 (O*C*H), 73.9 (O*C*H$_2$), 52.9 (O*C*H$_3$), 39.8 (*C*H(CH$_2$)$_2$), 37.8 (*C*H$_2$CO$_2$^{t}Bu), 28.1 (OC(*C*H$_3$)$_3$); **ν$_{max}$** 2977 (w, C-H), 1747 (s, C=O), 1723 (s, C=O), 1240 (m), 1149 (s), 751 (w, =C-H); **m/z** (ESI$^+$) 415 ([M+Na]$^+$, 100%); HRMS found 415.1732 $C_{21}H_{28}NaO_7$ requires 415.1727.

(±)-Methyl (3*R*,3a*S*,4*R*,6a*R*)-3-(2-(*tert*-butoxy)-2-oxoethyl)-6-oxo-4-phenyltetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.27f



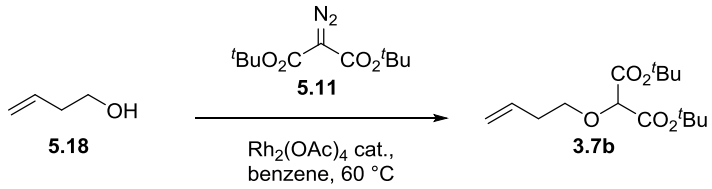
The title compound was prepared according to the general procedure 4 using dimethyl (*E*)-2-((2-(2-(*tert*-butoxy)-2-oxoethyl)-4-phenylbut-3-en-1-yl)oxy)malonate **3.24f** (62 mg, 0.158 mmol). Flash Chromatography purification (PE$_{30-40}$/Et$_2$O 3:2) gave the desired product as a colourless oil (41 mg, 0.109 mmol, 69%) as a mixture of diastereoisomers. For analytical purposes, a second purification gave the clean major diastereoisomer **3.27f**. **R$_f$** 0.32 (2:3 Et$_2$O/PE); **δ$_H$** (400 MHz, CDCl$_3$) 7.44–7.32 (5H, m, Ar*H*), 5.36 (1H, d, *J* = 4.8, PhC*H*), 4.30 (1H, dd, *J* = 9.3, 6.1, OC*H*H'), 4.05 (1H, dd, *J* = 9.3, 4.0, OCH*H'*), 3.79 (3H, s, OC*H*$_3$), 3.04 (1H, dd, *J* = 4.8, 3.0, CHC*H*CH), 2.86 (1H, m, C*H*CH$_2$CO$_2$^{t}Bu), 2.46 (1H, dd, *J* = 16.4, 7.6, C*H*H'CO$_2$^{t}Bu), 2.33 (1H, dd, *J* = 16.4, 7.6, CH*H'*CO$_2$^{t}Bu), 1.36 (9H, s, OC(C*H*$_3$)$_3$); **δ$_C$** (100 MHz, CDCl$_3$) 171.1 (*C*=O), 170.5 (*C*=O), 168.7 (*C*=O), 138.5 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 125.8 (*Ar*), 87.6 (*C$_{quat}$*), 84.6 (PhCH), 81.7 (*C$_{quat}$*), 75.2 (O*C*H$_2$), 59.4 (CH*C*HCH), 53.5 (O*C*H$_3$), 43.0 (*C*HCH$_2$CO$_2$^{t}Bu), 38.0 (*C*H$_2$CO$_2$^{t}Bu), 28.1 (OC(*C*H$_3$)$_3$); **ν$_{max}$** 2978 (w, C-H), 1783 (s, C=O), 1761 (m, C=O), 1722 (m, C=O), 1152 (s), 726 (w, =C-H); **m/z** (ESI$^+$) 399.1 ([M+Na]$^+$, 100%); HRMS found 399.1421 $C_{20}H_{24}NaO_7$ requires 399.1414.



Key nOe interactions

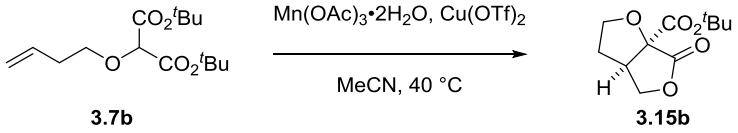
3.27f

(±)-di-*tert*-Butyl 2-(but-3-en-1-yloxy)malonate, 3.7b



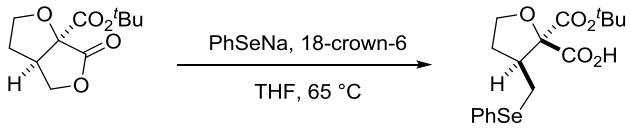
The title compound **3.7b** was prepared according to general procedure 2 using 3-buten-1-ol **5.14** (0.86 mL, 10 mmol) and di-*tert*-butyl 2-diazomalonate **5.11** (2.54 g, 10.5 mmol). FC purification (1:9 Et_2O/PE) gave the title compound **3.7b** as a colourless oil (1.91 g, 6.66 mmol, 66%); $\mathbf{R_f}$ 0.37 (1:9 Et_2O/PE); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 5.78 (1H, ddd, *J* = 17.1, 10.3, 7.0, CH_2=C*H*), 5.04 (1H, ddt, *J* = 17.1, 2.0, 1.3, C*H*H'=CH), 4.99 (1H, ddt, *J* = 10.3, 2.0, 1.3, CH*H'*=CH), 4.19 (1H, s, OC*H*), 3.55 (1H, t, *J* = 7.0, OCH_2), 2.36 (2H, dddd, *J* = 7.0, 7.0, 1.3, 1.3, =CHCH_2), 1.42 (9H, OC(CH_3)$_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 166.0 (*C*=O), 134.6 (CH_2=*C*H), 116.9 (*C*H_2=CH), 82.7 (C_{quat}), 80.4 (O*C*H), 70.4 (O*C*H_2), 34.0 (=CH-*C*H_2), 28.0 (OC(*C*H_3)$_3$); $\mathbf{\nu_{max}}$ 2980 (w, C-H), 1758 (m, C=O), 1737 (s, C=O), 1394 (w), 1248 (m), 1137 (s), 848 (=C-H); **m/z** (ESI$^+$) 309 ([M+Na]$^+$, 100%), 595 ([2M+Na]$^+$, 29%); HRMS found 309.1674 $C_{15}H_{26}NaO_5$ requires 309.1672.

(±)-*tert*-Butyl (3a*S*,6a*S*)-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate, 3.15b



The title compound was prepared according to general procedure 4 using di-*tert*-butyl 2-(but-3-en-1-yloxy)malonate **3.7b** (1.28 g, 4.46 mmol). FC purification (1:1 EtOAc/PE) gave the title compound **3.15b** as a white solid (841 mg, 3.69 mmol, 83%). $\mathbf{R_f}$ 0.38 (1:1 EtOAc/PE); **m.p.** 116–118 °C; $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 4.54 (1H, dd, *J* = 9.5, 6.8, CO_2C*H*H'), 4.21 (1H, dd, *J* = 9.5, 2.3, CO_2CH*H'*), 4.11 (1H, ddd, *J* = 8.8, 6.8, 6.8, OC*H*H'), 4.05 (1H, ddd, *J* = 8.8, 6.8, 5.9, OCH*H'*), 3.22 (1H, dddd, *J* = 9.0, 6.8, 6.8, 2.3, CH_2C*H*CH_2), 2.38 (1H, dddd, *J* = 9.0, 6.8, 6.8, 5.9, OCH_2C*H*H'), 1.92 (1H, dddd, *J* = 9.0, 9.0, 6.8, 6.8, OCH_2CH*H'*), 1.49 (9H, s, OC(*C*H_3)$_3$); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 172.4 (*C*=O), 166.7 (*C*=O), 86.8 (C_{quat}), 84.2 (C_{quat}), 70.8 (CO_2*C*H_2), 45.6 (*C*H), 33.0 (OCH_2*C*H_2), 28.0 (OC(*C*H_3)$_3$); $\mathbf{\nu_{max}}$ 2986 (w, C-H), 1767 (m, C=O), 1748 (s, C=O), 1158 (m), 1116 (s); **m/z** (ESI$^+$) 251.1 ([M+Na]$^+$, 100%), 479.2 ([2M+Na]$^+$, 34%); HRMS found 251.0901 $C_{11}H_{16}NaO_5$ requires 251.0890.

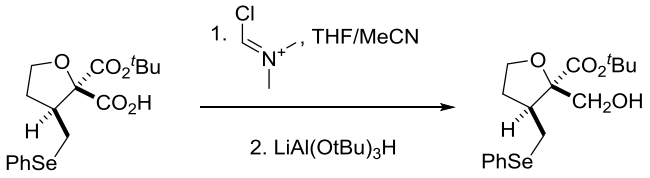
(±)-(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)-3-((phenylselanyl)methyl)tetrahydrofuran-2-carboxylic acid, 3.38



3.15b **3.38**

To $(PhSe)_2$ (749 mg, 2.40 mmol) and NaH (60% dispersion, 160 mg, 4.00 mmol) was added nitrogen sparged THF (4.1 mL) at RT under argon. The mixture was then stirred at 65 °C for 90 min. The mixture was cooled to 0 °C and a solution of *tert*-butyl (3a*S*,6a*S*)-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate **3.15b** (456 mg, 2.00 mmol) and 18-crown-6 (132 mg, 0.50 mmol) in nitrogen sparged THF (4 mL) was added to the mixture. The mixture was then stirred at RT for 90 min. An aqueous solution of NaOH (0.5 M, 15 mL) and Et_2O (15 mL) were then carefully added. The organic layer was extracted with more aqueous solution of NaOH (0.5 M, 2 x 10 mL). A solution of pH 2 sulfate buffer (10 mL) followed by a concentrated aqueous solution of HCl were added until pH 2. The aqueous layer was then extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude title compound **3.38** as a yellow oil (416 mg, 1.07 mmol, 54%). $\mathbf{R_f}$ is not given as compounds streaks even in the presence of AcOH; (0.416 mg, 1.07 mmol, 54%); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.12–8.50 (1H, br, CO_2*H*), 7.56–7.50 (2H, m, Ar*H*), 7.32–7.24 (3H, m, Ar*H*), 4.22 (1H, ddd, *J* = 8.3, 8.3, 3.4, OC*H*H'), 3.96 (1H, ddd, *J* = 8.3, 8.3, 8.3, OCH*H'*), 3.39 (1H, dd, *J* = 12.2, 3.4, C*H*H'Se), 3.07–2.96 (1H, m, C*H*CH_2Se), 2.71 (1H, dd, *J* = 12.2, 12.2, CH*H'*Se), 2.40–2.30 (1H, m, OCH_2C*H*H'), 2.00–1.90 (1H, m, OCH_2CH*H'*), 1.45 (1H, s, $OC(CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.2 (*C*=O), 167.8 (*C*=O), 132.9 (*Ar*), 129.5 (*Ar*), 129.4 (*Ar*), 127.3 (*Ar*), 88.8 (C_{quat}), 83.9 (C_{quat}), 69.1 (OCH_2), 46.8 (*C*H), 31.9 (OCH_2CH_2), 27.8 ($OC(CH_3)_3$), 27.6 (CH_2Se); $\boldsymbol{\nu_{max}}$ 3200 (br, CO_2-H), 2979 (w, C-H), 1734 (s, C=O), 1158 (m), 1122 (m), 737 (m); **m/z** (ESI^+) 409 ($[M+Na]^+$, 100%), 793 ($[2M+Na]^+$, 34%); HRMS found 431.0359 ($[M-H+2Na]^+$) $C_{17}H_{21}Na_2O_5{}^{80}Se$ requires 431.0345.

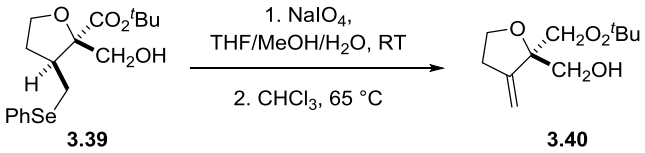
(±)-*tert*-Butyl (2*S*,3*R*)-2-(hydroxymethyl)-3-((phenylselanyl)methyl)tetrahydrofuran-2-carboxylate, 3.39



3.38 **3.39**

To a solution of DMF (96 µL, 1.24 mmol) in DCM (14 mL) was added oxalyl chloride dropwise (0.32 mL, 3.72 mmol) at RT. The mixture was stirred for 20 min and all volatiles were removed. The residual salt was dissolved in dry THF/MeCN (1:1, 15 mL). A solution of (2*S*,3*R*)-2-(*tert*-butoxycarbonyl)-3-((phenylselanyl)methyl)tetrahydrofuran-2-carboxylic acid **3.38** (239 mg, 0.620 mmol) was added over 2 min at 0 °C. The mixture was stirred for 20 min and cooled to -78 °C. A solution of $LiAl(O^tBu)_3H$ in THF (1.0 M, 6.2 mL, 6.2 mmol) was added over 5 min. The mixture was warmed to RT outside the cooling bath, and stirred at RT for 90 min. Water (20 mL), a saturated aqueous solution of NH_4Cl (20 mL), a saturated aqueous solution of Rochelle salt (20 mL) and EtOAc (50 mL) were successively added. The mixture was vigorously stirred for two hours and the layers were separated. The aqueous layer was extracted with more EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by FC (2:3 EtOAc/PE), which gave the title compound **3.39** as a colourless oil (176 mg, 0.474 mmol, 77%). $\mathbf{R_f}$ 0.34 (2:3 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.55–7.48 (2H, m, Ar*H*), 7.31–7.22 (3H, m, Ar*H*), 4.08 (1H, ddd, *J* = 10.3, 8.0, 2.2, OC*H*H'), 3.90 (1H, ddd, *J* = 10.3, 9.0, 6.0, OCH*H'*), 3.77 (2H, s, CH_2OH), 3.35 (1H, dd, *J* = 12.0, 3.7, C*H*H'Se), 2.90 (1H, dd, *J* = 12.0, 12.0, CH*H'*Se), 2.54 (1H, dddd, *J* = 12.0, 10.0, 7.5, 3.7, C*H*), 2.30 (1H, dddd, *J* = 12.5. 7.5, 6.0, 2.2, OCH_2CHH'), 2.24 (1H, br, O*H*), 1.78 (1H, dddd, *J* = 12.5, 10.0, 9.0, 8.0, OCH_2CHH'), 1.40 (9H, s, $OC(CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 177.2 (*C*=O), 133.0 (*Ar*), 129.6 (*Ar*), 129.3 (*Ar*), 127.3 (*Ar*), 86.7 (C_{quat}), 82.1 (C_{quat}), 68.0 (OCH_2), 63.8 (CH_2OH), 46.6 (*C*H), 33.6 (OCH_2CH_2), 28.0 ($OC(CH_3)_3$), 27.7 (CH_2Se); $\boldsymbol{\nu_{max}}$ 3468 (br, O-H), 2976 (w, C-H), 1742 (s, C=O), 1368 (m), 1148 (s), 1036 (s), 737 (s); **m/z** (ESI^+) 395 ($[M+Na]^+$, 100%), 767 ($[2M+Na]^+$, 8%); HRMS found 395.0740 $C_{17}H_{24}NaO_4Se$ requires 395.0733.

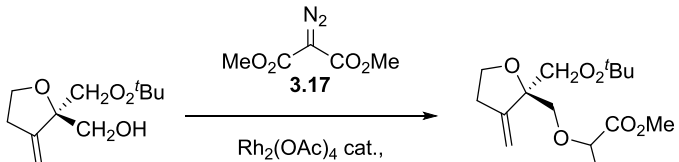
(±)-*tert*-Butyl 2-(hydroxymethyl)-3-methylenetetrahydrofuran-2-carboxylate, 3.40



3.39 **3.40**

To a vigorously stirred solution of *tert*-butyl (2*S*,3*R*)-2-(hydroxymethyl)-3-((phenylselanyl)methyl)tetrahydrofuran-2-carboxylate **3.39** (218 mg, 0.588 mmol) in THF/MeOH/H_2O (1:1:1, 12 mL) at RT were added successively $NaHCO_3$ (198 mg, 2.85 mmol) and $NaIO_4$ (503 mg, 2.85, mmol). The mixture was stirred for 30 min. Water (35 mL) and $CHCl_3$ (20 mL) were added. Stirring was continued for 5 min and the mixture was filtered through Celite,™ which was further eluted with $CHCl_3$ (15 mL). The layers were separated and the aqueous phase was extracted with more $CHCl_3$ (20 mL). The combined organic layers were dried (Na_2SO_4), filtered and refluxed for 2 h at 65 °C. Solvent was evaporated and the residue was purified by FC (2:3 to 3:2 Et_2O/PE), which gave the title compound **3.40** as a colourless oil (116 mg, 0.541 mmol, 92%); $\mathbf{R_f}$ 0.40 (3:2 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.22 (1H, dd, *J* = 2.2, 2.2, C*H*H'=C), 5.19 (1H, dd, *J* = 2.2, 2.2, CH*H'*=C), 4.10 (2H, t, *J* = 7.0, OCH_2), 3.90 (1H, d, *J* = 11.5, C*H*H'OH), 3.68 (1H, d, *J* = 11.5, CH*H'*OH), 2.65 (1H, tdd, *J* = 7.0, 2.2, 2.2, OCH$_2$CH_2), 2.13 (1H, br, O*H*), 1.47 (1H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 170.6 (*C*=O), 147.5 (CH_2=*C*), 108.4 (*C*H_2=C), 87.2 (*C*$_{quat}$), 82.2 (*C*$_{quat}$), 68.1 (O*C*H_2), 67.0 (*C*H_2OH), 33.3 (*C*H), 28.0 (OC(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ 3468 (br, O-H), 2977 (w, C-H), 1725 (s, C=O), 1163 (s), 1031 (s), 899 (w), 846 (w); **m/z** (ESI$^+$) 237 ([M+Na]$^+$, 47%), 451 ([2M+Na]$^+$, 100%); HRMS found 237.1102 $C_{11}H_{18}NaO_4$ requires 237.1097.

(±)-Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methylenetetrahydrofuran-2-yl)methoxy)malonate, 3.41



3.40 **3.41**

The title compound was prepared according to general procedure 2 using *tert*-Butyl 2-(hydroxymethyl)-3-methylenetetrahydrofuran-2-carboxylate **3.40** (406 mg, 0.495 mmol) and dimethyl 2-diazomalonate (126 mg, 0.520 mmol). FC purification (1:1 Et_2O/$PE_{30\text{-}40}$) gave the product as a colourless oil (82.3 mg, 0.239 mmol, 43%); $\mathbf{R_f}$ 0.34 (1:1 Et_2O/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.20 (1H, dd, *J* = 2.2, 2.2, C*H*H'=C), 5.19 (1H, dd, *J* = 2.2, 2.2, CH*H'*=C), 4.84 (1H, s, OCH), 4.08 (1H, ddd, *J* = 12.5, 8.5, 4.4, OC*H*H'CH_2), 4.05 (1H, ddd, *J* = 8.5, 8.5, 7.1, OCH*H'*CH_2), 4.01 (1H, d, *J* = 11.3, OC*H*H'C$_{quat}$), 3.83 (1H, d, *J* = 11.3, OCH*H'*C$_{quat}$), 3.77 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.72–2.53 (2H, m, OCH_2CHH'), 1.46 (9H, s, OC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 167.0 (*C*=O), 167.0 (C=O) 147.6 (CH_2=*C*),

108.7 (*C*H_2=C), 87.1 (C_{quat}), 82.2 (C_{quat}), 79.8 (O*C*H), 75.0 (*C*H_2OH), 68.2 (O*C*$H_2$$CH_2$), 52.9 (O*C*$H_3$), 32.9 (O$CH_2$*C*$H_2$), 27.9 (OC($CH_3$)$_3$); **$\nu_{max}$** 2957 (w, C-H), 1742 (s, C=O), 1240 (m), 1163 (s), 1101 (m), 1031 (m), 904 (w), 846 (w); **m/z** (ESI$^+$) 367.0 ([M+Na]$^+$, 100%), 711.0 ([2M+Na]$^+$, 25%); HRMS found 367.1370 $C_{16}H_{24}NaO_8$ requires 367.1363.

6 References

(1) Mincer, T. J.; Jensen, P. R.; Kauffman, C. A.; Fenical, W. *Appl. Environ. Microbiol.* **2002**, 5005.
(2) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355.
(3) Corey, E. J.; Li, W.-D. Z.; Nagamitsu, T.; Fenteany, G. *Tetrahedron* **1999**, *55*, 3305.
(4) Rentsch, A.; Landsberg, D.; Brodmann, T.; Bülow, L.; Girbig, A.-K.; Kalesse, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5450.
(5) Piotrowski, J.; Beal, R.; Hoffman, L.; Wilkinson, K. D.; Cohen, R. E.; Pickart, C. M. *J. Biol. Chem.* **1997**, *272*, 23712.
(6) Gulder, T. A. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9346.
(7) Cavo, M. *Current Hematologic Malignancy Reports* **2007**, *2*, 128.
(8) Pour, L.; Adam, Z.; Buresova, L.; Krejci, M.; Krivanova, A.; Sandecka, V.; Zahradova, L.; Buchler, T.; Vorlicek, J.; Hajek, R. *Clin. Lymphoma Myeloma Leuk.* **2009**, *9*, 151.
(9) Millward, M. *Invest. New Drugs* **2012**, *30*.
(10) Macherla, V. R.; Mitchell, S. S.; Manam, R. R.; Reed, K. A.; Chao, T.-H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P. R.; Fenical, W. F.; Neuteboom, S. T. C.; Lam, K. S.; Palladino, M. A.; Potts, B. C. M. *J. Med. Chem.* **2005**, *48*, 3684.
(11) Groll, M.; Huber, R.; Potts, B. C. M. *J. Am. Chem. Soc.* **2006**, *128*, 5136.
(12) Udwary, D. W.; Zeigler, L.; Asolkar, R. N.; Singan, V.; Lapidus, A.; Fenical, W.; Jensen, P. R.; Moore, B. S. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 10376.
(13) Beer, L. L.; Moore, B. S. *Org. Lett.* **2007**, *9*, 845.
(14) Eustáquio, A. S.; McGlinchey, R. P.; Liu, Y.; Hazzard, C.; Beer, L. L.; Florova, G.; Alhamadsheh, M. M.; Lechner, A.; Kale, A. J.; Kobayashi, Y.; Reynolds, K. A.; Moore, B. S. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 12295.
(15) Huang, F.; Haydock, S. F.; Spiteller, D.; Mironenko, T.; Li, T.-L.; O'Hagan, D.; Leadlay, P. F.; Spencer, J. B. *Chem. Biol.* **2006**, *13*, 475.
(16) McGlinchey, R. P.; Nett, M.; Eustáquio, A. S.; Asolkar, R. N.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc.* **2008**, *130*, 7822.
(17) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293.
(18) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143.
(19) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803.
(20) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230.
(21) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298.
(22) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.
(23) Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699.
(24) Kulinkovich, O. G. *Chem. Rev. (Washington, DC)* **2003**, *103*, 2597.
(25) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.
(26) Ling, T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M. *Org. Lett.* **2007**, *9*, 2289.
(27) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244.
(28) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153.
(29) Fukuda, T.; Sugiyama, K.; Arima, S.; Harigaya, Y.; Nagamitsu, T.; Omura, S. *Org. Lett.* **2008**, *10*, 4239.
(30) Sato, Y.; Fukuda, H.; Tomizawa, M.; Masaki, T.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Heterocycles* **2010**, *81*, 2239.
(31) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, *1994*, 31.

(32) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549.
(33) Kaiya, Y.; Hasegawa, J.-i.; Momose, T.; Sato, T.; Chida, N. *Chem. Asian J.* **2011**, *6*, 209.
(34) Mulholland, N. P.; Pattenden, G.; Walters, I. A. S. *Org. Biomol. Chem.* **2008**, *6*, 2782.
(35) Mulholland, N. P.; Pattenden, G.; Walters, I. A. S. *Org. Biomol. Chem.* **2006**, *4*, 2845.
(36) Caubert, V.; Massé, J.; Retailleau, P.; Langlois, N. *Tetrahedron Lett.* **2007**, *48*, 381.
(37) Villanueva Margalef, I.; Rupnicki, L.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7896.
(38) Momose, T.; Kaiya, Y.; Hasegawa, J.-i.; Sato, T.; Chida, N. *Synthesis* **2009**, *2009*, 2983.
(39) Mosey, R. A.; Tepe, J. J. *Tetrahedron Lett.* **2009**, *50*, 295.
(40) Struble, J. R.; Bode, J. W. *Tetrahedron* **2009**, *65*, 4957.
(41) Ling, T.; Potts, B. C.; Macherla, V. R. *J. Org. Chem.* **2010**, *75*, 3882.
(42) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20.
(43) Potts, B. C.; Lam, K. S. *Marine Drugs* **2010**, *8*, 835.
(44) Logan, A. W. J.; Sprague, S. J.; Foster, R. W.; Marx, L. B.; Garzya, V.; Hallside, M. S.; Thompson, A. L.; Burton, J. W. *Org. Lett.* **2014**, *16*, 4078.
(45) Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 5905.
(46) Bush, J. B.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903.
(47) Snider, B. B. *Tetrahedron* **2009**, *65*, 10738.
(48) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524.
(49) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 2888.
(50) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544.
(51) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217.
(52) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.
(53) Powell, L. H.; Docherty, P. H.; Hulcoop, D. G.; Kemmitt, P. D.; Burton, J. W. *Chem. Commun.* **2008**, 2559.
(54) Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W. *Org. Lett.* **2012**, *14*, 2940.
(55) Sprague, S. J. Dphil Thesis, University of Oxford, 2010.
(56) Snider, B. B. *Chem. Rev. (Washington, DC)* **1996**, *96*, 339.
(57) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
(58) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
(59) Scarborough, R. M.; Toder, B. H.; Smith, A. B. *J. Am. Chem. Soc.* **1980**, *102*, 3904.
(60) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(61) Schotten, C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2544.
(62) Baumann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3218.
(63) Curry, L.; Hallside, M. S.; Powell, L. H.; Sprague, S. J.; Burton, J. W. *Tetrahedron* **2009**, *65*, 10882.
(64) Perreault, S.; Spino, C. *Org. Lett.* **2006**, *8*, 4385.
(65) Micovic, V.; Mihailovic, M. *J. Org. Chem.* **1953**, *18*, 1190.
(66) Evans, D. A.; Gage, R. G. *Org. Synth.* **1990**, *68*, 77.
(67) Barlaam, B.; Bird, T. G.; Lambert-van der Brempt, C.; Campbell, D.; Foster, S. J.; Maciewicz, R. *J. Med. Chem.* **1999**, *42*, 4890.
(68) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.
(69) Kim, Y.-A.; Han, S.-Y. *ChemInform* **2001**, *32*, no.
(70) Kim, H.-O.; Gardner, B.; Kahn, M. *Tetrahedron Lett.* **1995**, *36*, 6013.
(71) Wenschuh, H.; Beyermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L. A. *Tetrahedron Lett.* **1996**, *37*, 5483.
(72) Wissmann, H.; Kleiner, H.-J. *Angew. Chem.* **1980**, *92*, 129.
(73) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(74) Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797.
(75) MacDonald, S. A.; Willson, C. G.; Chorev, M.; Vernacchia, F. S.; Goodman, M. *J. Med. Chem.* **1980**, *23*, 413.

(76) Leeds, J. P.; Kirst, H. A. *Synth. Commun.* **1988**, *18*, 777.
(77) Hashimoto, N.; Kuritani, M.; Toukai, N.; Takeda Chemical Industries, Ltd., Japan: 1976; Vol. US3941823 A.
(78) Hess, W.; Burton, J. W. *Chem. Eur. J.* **2010**, *16*, 12303.
(79) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765.
(80) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.
(81) Rodeschini, V.; Boiteau, J.-G.; Van de Weghe, P.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2003**, *69*, 357.
(82) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.
(83) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R.; Jones, S. D.; Murdoch, R. *Tetrahedron* **1994**, *50*, 809.
(84) Liang, B.; Carroll, P. J.; Joullié, M. M. *Org. Lett.* **2000**, *2*, 4157.
(85) Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron* **2002**, *58*, 7275.
(86) Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13*, 5048.
(87) Welch, K. D.; Smith, P. L.; Keller, A. P.; Myers, W. H.; Sabat, M.; Harman, W. D. *Organometallics* **2006**, *25*, 5067.
(88) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1956**, *78*, 252.
(89) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 2946.
(90) Komeyama, K.; Mieno, Y.; Yukawa, S.; Morimoto, T.; Takaki, K. *Chem. Lett.* **2007**, *36*, 752.
(91) Adrio, L. A.; Quek, L. S.; Taylor, J. G.; Kuok Hii, K. *Tetrahedron* **2009**, *65*, 10334.
(92) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553.
(93) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.
(94) Delle Monache, G.; Misiti, D.; Salvatore, P.; Zappia, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1137.
(95) Sakakura, A.; Shomi, G.; Shomi, A.; Ishihara, K. *Heterocycles* **2010**, *82*.
(96) Paquette, L. A.; Gardlik, J. M.; Johnson, L. K.; McCullough, K. J. *J. Am. Chem. Soc.* **1980**, *102*, 5026.
(97) Khokhar, S. S.; Wirth, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 631.
(98) Knerr, P. J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 7648.
(99) Seko, T.; Kato, M.; Kohno, H.; Ono, S.; Hashimura, K.; Takimizu, H.; Nakai, K.; Maegawa, H.; Katsube, N.; Toda, M. *Bioorg. Med. Chem.* **2003**, *11*, 1901.
(100) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.
(101) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073.
(102) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1077.
(103) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang , Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.
(104) Kanzaki, H.; Wada, K.-i.; Nitoda, T.; Kawazu, K. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 438.
(105) Ogura, M.; Nakayma, H.; Furihatam, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot. (Tokyo)* **1985**, *38*, 669.
(106) Ogura, M.; Nakayama, H.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1985**, *49*, 1909.
(107) Ryu, G.; Hwang, S.; Kim, S.-K. *J. Antibiot. (Tokyo)* **1997**, *50*, 1064.
(108) Ryu, G.; Kim, S.-K. *J. Antibiot. (Tokyo)* **1999**, *52*, 193.
(109) Otani, T.; Yoshida, K.-C.; Kubota, H.; Kawai, S.; Ito, S.; Hori, H.; Ishiyama, T.; Oki, T. *J. Antibiot. (Tokyo)* **2000**, *12*.
(110) Manam, R. R.; Teisan, S.; White, D. J.; Nicholson, B.; Grodberg, J.; Neuteboom, S. T. C.; Lam, K. S.; Mosca, D. A.; Lloyd, G. K.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 240.
(111) Omura, S.; Tanaka, Y.; Kanaya, I.; Shinose, M.; Takahashi, Y. *J Antibiot (Tokyo)* **1990**, *43*, 1034.
(112) Henkel, T.; Zeeck, A. *Liebigs Ann. Chem.* **1991**, *1991*, 367.

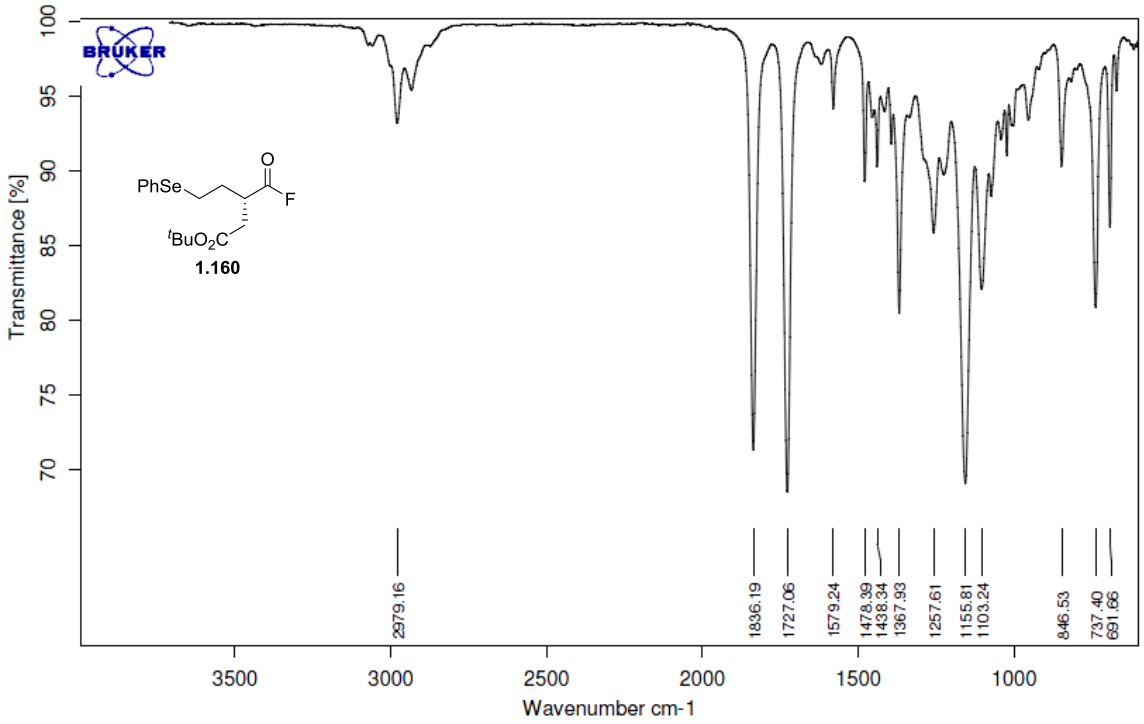
(113) Tonew, E.; Tonew, M.; Grafe, U. *Acta Virol.* **1992**, *36*, 166.
(114) Nakamura, M.; Honma, H.; Kamada, M.; Ohno, T.; Kunimoto, S.; Ikeda, Y.; Kondo, S.; Takeuchi, T. *J. Antibiot. (Tokyo)* **1994**, *47*, 616.
(115) Kawada, M.; Yoshimoto, Y.; Minamiguchi, K.; Kumagai, H.; Someno, T.; Masuda, T.; Ishizuka, M.; Ikeda, D. *Anticancer Res.* **2004**, *24*, 1561.
(116) Grigorjev, P.; Schlegel, R.; Grafe, U. *Pharmazie* **1992**, *47*, 707.
(117) Bagwell, C. L.; Moloney, M. G.; Thompson, A. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4081.
(118) Angelov, P.; Chau, Y. K. S.; Fryer, P. J.; Moloney, M. G.; Thompson, A. L.; Trippier, P. C. *Org. Biomol. Chem.* **2012**, *10*, 3472.
(119) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070.
(120) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.
(121) Buchanan, J. G.; Fletcher, R. *J. Chem. Soc.* **1965**, 6316.
(122) Schöllkopf, U.; Schröder, R. *Angewandte Chemie International Edition in English* **1971**, *10*, 333.
(123) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703.
(124) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618.
(125) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angewandte Chemie International Edition in English* **1995**, *34*, 793.
(126) Bastin, R.; Dale, J. W.; Edwards, M. G.; Papillon, J. P. N.; Webb, M. R.; Taylor, R. J. K. *Tetrahedron* **2011**, *67*, 10026.
(127) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, *1996*, 612.
(128) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168.
(129) Bastin, R.; Liron, M.; Taylor, R. J. K. *Synlett* **2008**, *2008*, 2183.
(130) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*, 5398.
(131) Kiyotsuka, Y.; Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 2725.
(132) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.
(133) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031.
(134) Donohoe, T. J.; O'Riordan, T. J. C.; Peifer, M.; Jones, C. R.; Miles, T. J. *Org. Lett.* **2012**, *14*, 5460.
(135) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421.
(136) Bhalla, A.; Venugopalan, P.; Bhasin, K. K.; Bari, S. S. *Tetrahedron* **2007**, *63*, 3195.
(137) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(138) Tamotsu, F.; Toshiki, M.; Toshio, S. *Chem. Lett.* **1983**, *12*, 835.
(139) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
(140) Burton, J. W. D.Phil. Thesis, University of Cambridge, 1997.
(141) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.
(142) Thierry, J.; Yue, C.; Potier, P. *Tetrahedron Lett.* **1998**, *39*, 1557.
(143) Song, Y.-L.; Tan, J.; Luo, X.-M.; Long, Y.-Q. *Org. Biomol. Chem.* **2006**, *4*, 659.
(144) Sadek, S. A.; Shaw, S. M.; Kessler, W. V.; Wolf, G. C. *J. Org. Chem.* **1981**, *46*, 3259.
(145) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282.
(146) Urabe, D.; Yamaguchi, H.; Someya, A.; Inoue, M. *Org. Lett.* **2012**, *14*, 3842.
(147) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.
(148) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.
(149) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.
(150) Siler, D. A.; Mighion, J. D.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5332.

(151) Haseltine, J. N.; Paz Cabal, M.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850.
(152) Boruwa, J.; Borah, J. C.; Gogoi, S.; Barua, N. C. *Tetrahedron Lett.* **2005**, *46*, 1743.
(153) Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V.; Scarpelli, R.; Pereira, M. M. A.; Bollbuck, B.; Bigot, A.; Werschkun, B.; Winssinger, N. *Chem. Eur. J.* **2000**, *6*, 2783.
(154) Davies, J. J.; Krulle, T. M.; Burton, J. W. *Org. Lett.* **2010**, *12*, 2738.
(155) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev. (Washington, DC)* **2013**, *113*, 4567.
(156) Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309.
(157) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.
(158) Stella, L.; Harvey, J. N. In *Radicals in Organic Synthesis*; Wiley-VCH Verlag GmbH: 2008, p 360.
(159) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(160) Docherty, P. H. Dphil Thesis, University of Oxford, 2008.
(161) Overy, A. Part II Thesis, University of Oxford, 2014.
(162) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.
(163) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717.
(164) Rozwadowska, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1615.
(165) Quagliato, D. A.; Andrae, P. M.; Matelan, E. M. *J. Org. Chem.* **2000**, *65*, 5037.
(166) Iwama, S.; Katsumura, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3363.
(167) Detty, M. R.; Wood, G. P. *J. Org. Chem.* **1980**, *45*, 80.
(168) Gleicher, G. J.; Mahiou, B.; Aretakis, A. J. *J. Org. Chem.* **1989**, *54*, 308.
(169) Xu, X.-D.; Zhang, X.-Z.; Wang, B.; Cheng, S.-X.; Zhuo, R.-X.; Wang, Z.-C. *Colloids Surf., B.* **2007**, *59*, 158.
(170) Marson, C. M.; Grabowska, U.; Fallah, A.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994**, *59*, 291.
(171) Raczko, J.; Achmatowicz, M.; Kwiatkowski, P.; Chapuis, C.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1027.
(172) Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010**, *46*, 6335.
(173) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
(174) Boeckman, R. K. J.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 696.
(175) Smith, C. R. *Synlett* **2009**, 1522.
(176) Cooksey, J. P. *Org. Biomol. Chem.* **2013**, *11*, 5117.
(177) Carrick, J. D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 769.
(178) Kalkhambkar, R. G.; Waters, S. N.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 867.
(179) Aggarwal, V. K.; Gultekin, Z.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771.
(180) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.
(181) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795.
(182) Ji, L.; Zhang, D.-f.; Zhao, Q.; Hu, S.-m.; Qian, C.; Chen, X.-Z. *Tetrahedron* **2013**, *69*, 7031.
(183) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998.
(184) Ciganek, E. *J. Org. Chem.* **1965**, *30*, 4366.
(185) Harned, A. M.; Sherrill, W. M.; Flynn, D. L.; Hanson, P. R. *Tetrahedron* **2005**, *61*, 12093.
(186) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997.
(187) Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* **2004**, *2004*, 2151.
(188) Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R.; Aparicio-Lara, S. *Synthesis* **2001**, *2001*, 1149.

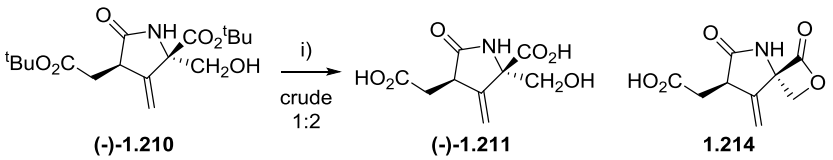
7 Appendix

7.1 Selected spectra and HPLC traces

7.1.1 IR spectra of acyl fluoride 1.160



7.1.2 NMR spectra of the reaction of the exo alkene (-)-1.210 in warm TFA



(-)-1.210 **(-)-1.211** **1.214**

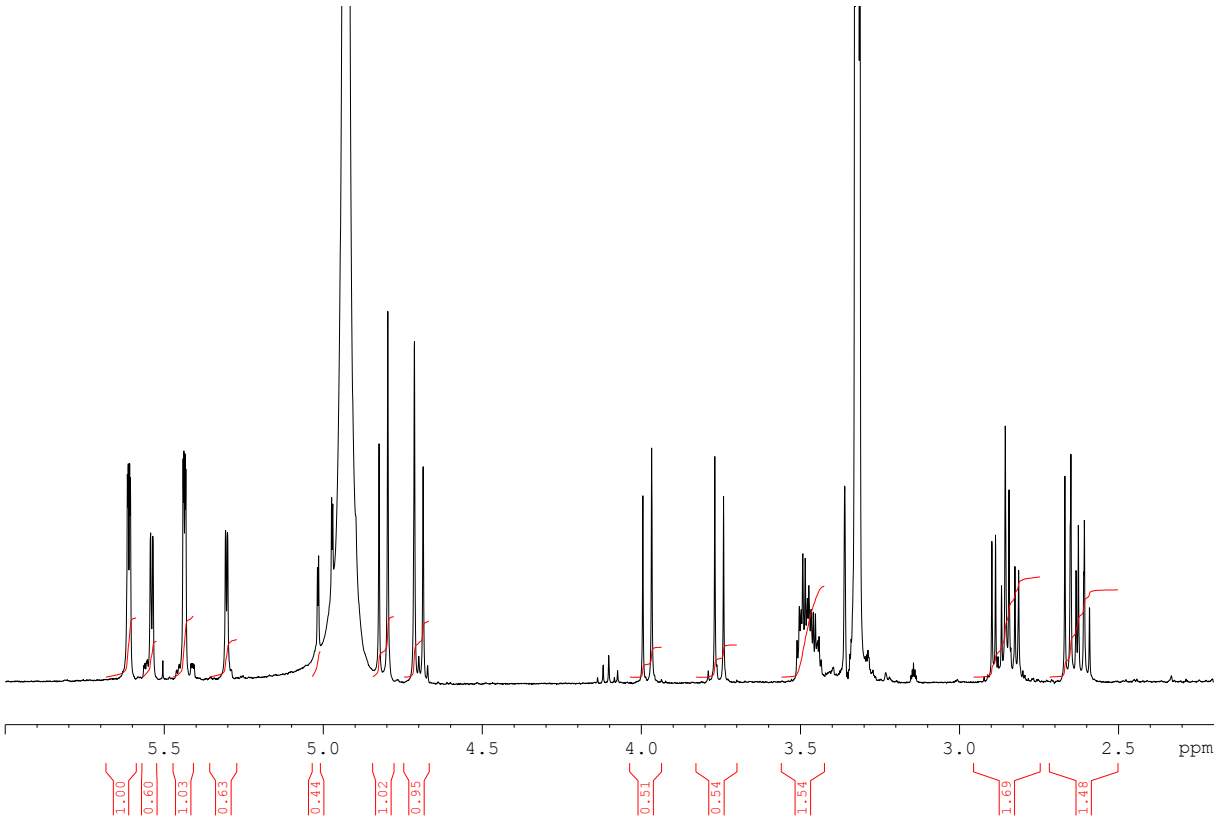


Figure 7.1 NMR spectra after the reaction of the exo alkene (-)-1.210 in warm TFA
Reagents and conditions i) TFA, 75 °C, 60 min

7.1.3 **Example of NMR determination of the proportion of side product during the cyclisation of (±)-1.187**

The integration of the multiplet (4.62–4.57 ppm) corresponds to the sum of the integration of one lactone proton of the minor diastereoisomer and one lactone proton of the major diastereoisomer (spectra available in **7.1.6**). The integration of the doublet at 5.77 ppm corresponds to the integration of the *exo*-alkene side product **(±)-1.205** and the integration of the mutiplet (5.93–5.77 ppm) corresponds to the integration of the side products of the linear alkene.

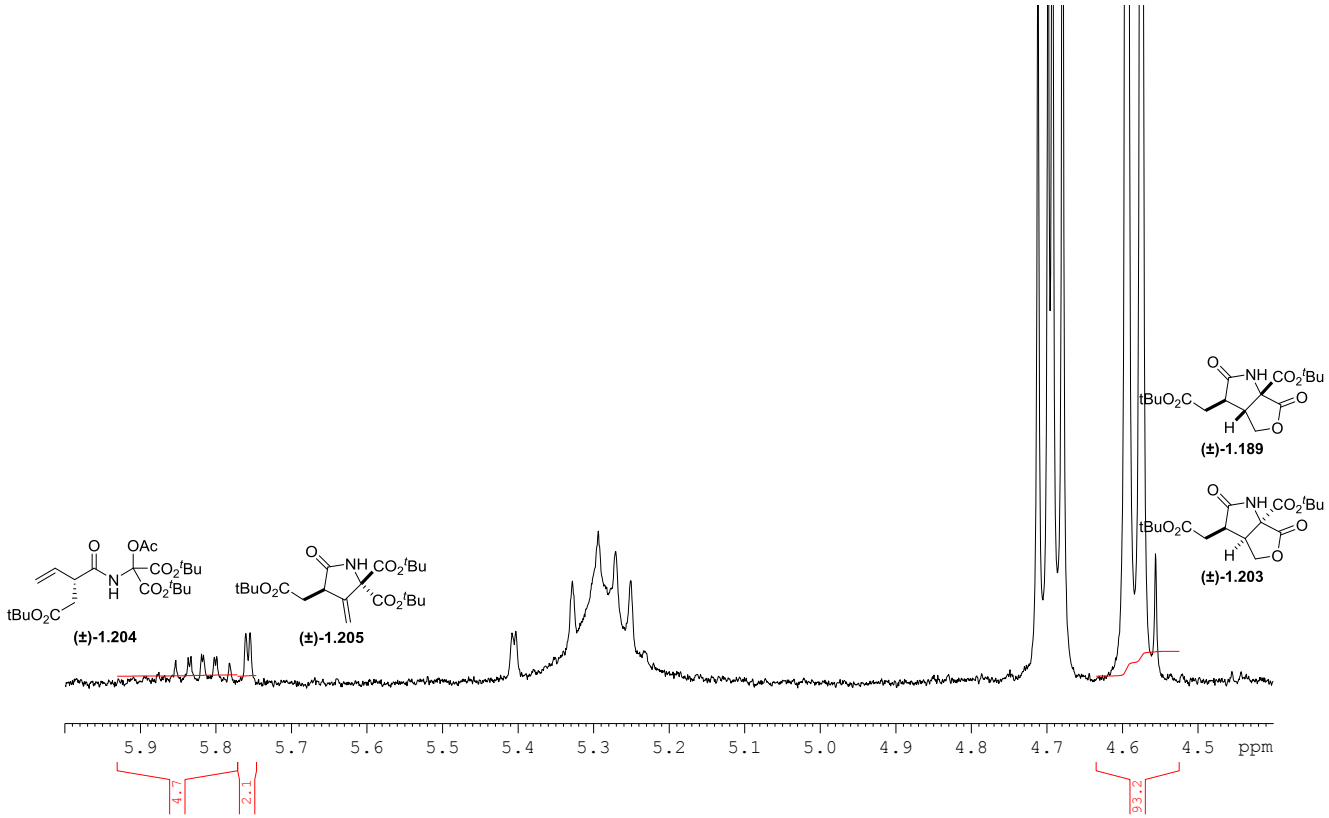


Figure 7.2 Example of determination (H_2O 2%) of the proportion of (±)-1.204, (±)-1.205 and (±)-1.189 and (±)-1.203 in the crude of the reaction.

7.1.4 NMR determination of the crude d.r. of the oxidative cyclisation of (-)-1.187

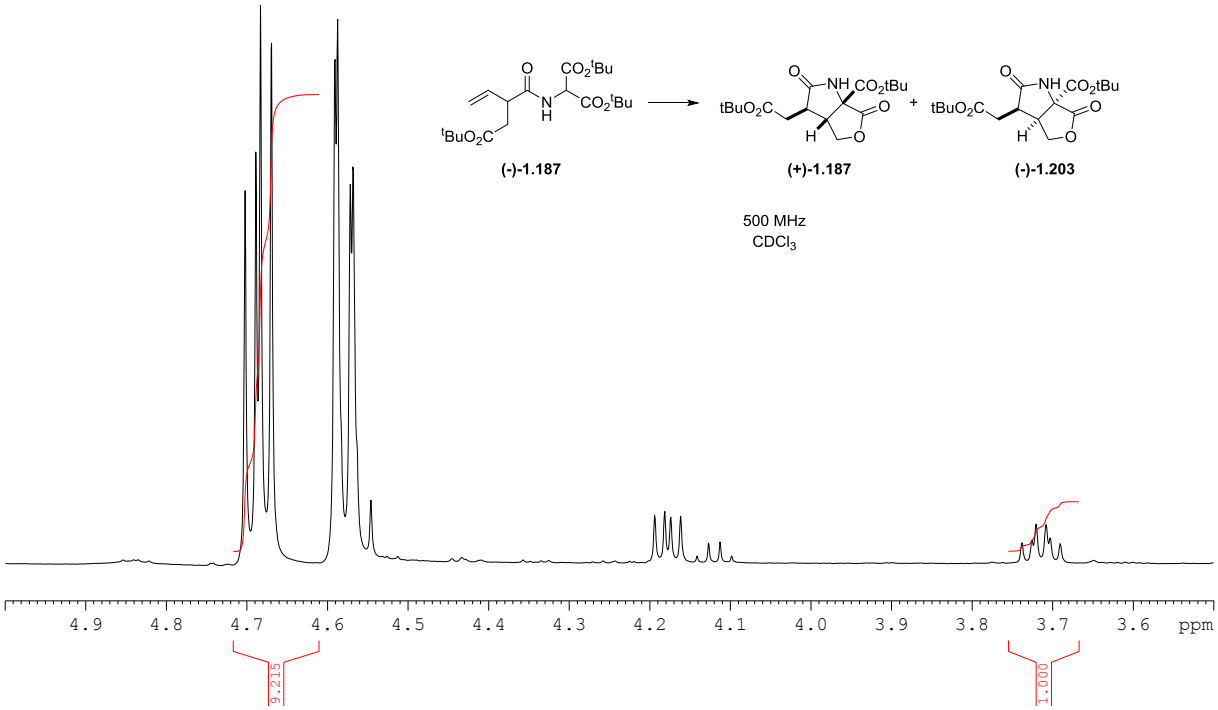
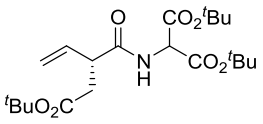
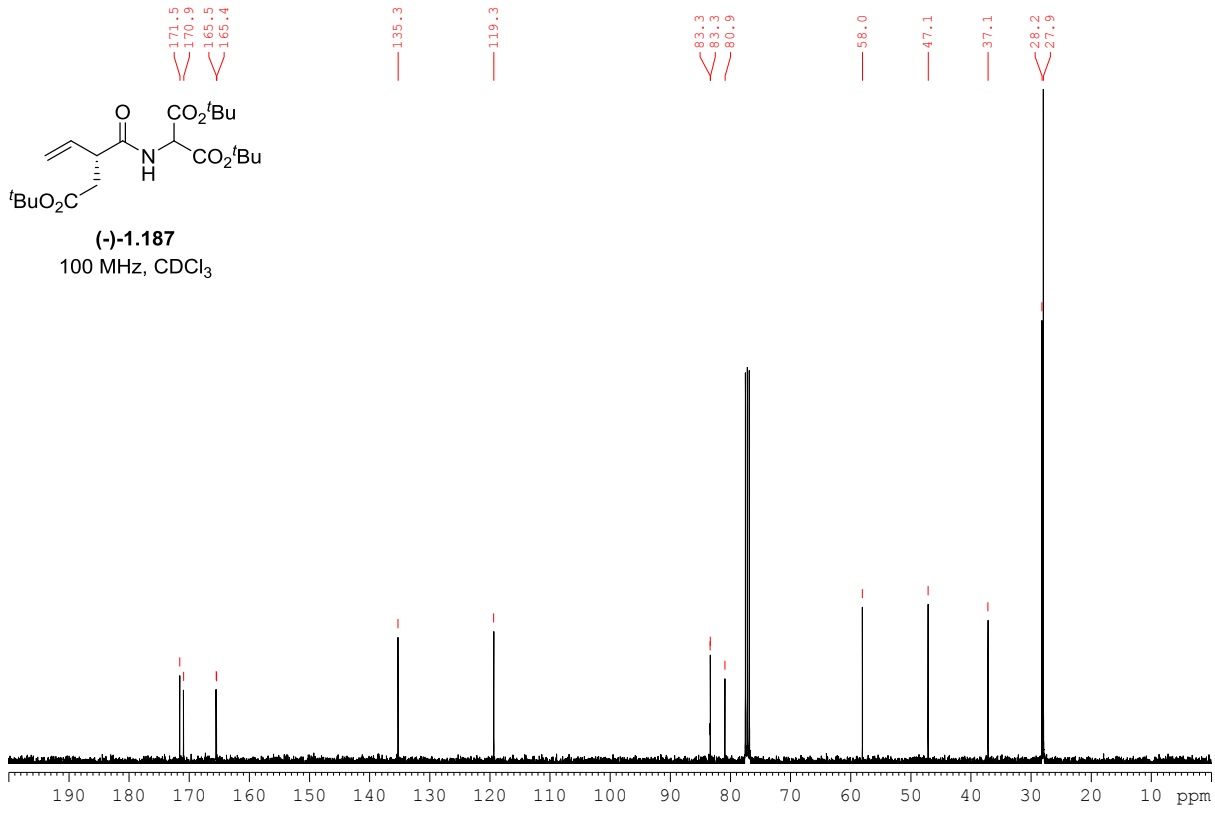


Figure 7.3 Determination of the d.r. of the cyclisation reaction of (-)-1.187

7.1.5 **Spectra for compound (-)-1.187**

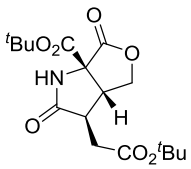


(-)-1.187
400 MHz, $CDCl_3$



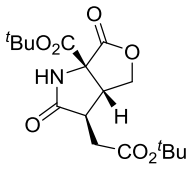
(-)-1.187
100 MHz, $CDCl_3$

7.1.6 **Spectra for compound (+)-1.189**



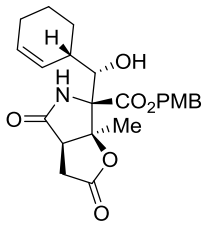
(+)-1.189
400 MHz, $CDCl_3$



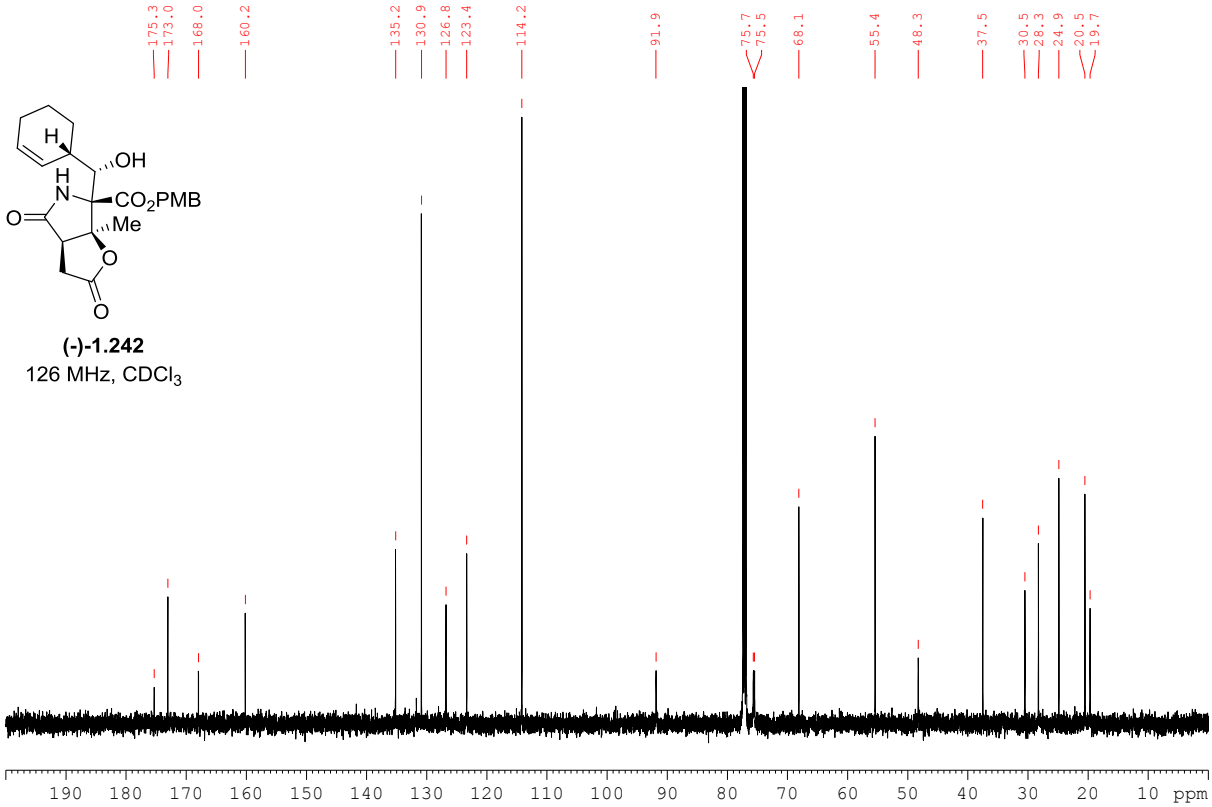


(+)-1.189
100 MHz, $CDCl_3$

7.1.7 Spectra for compound (-)-1.242

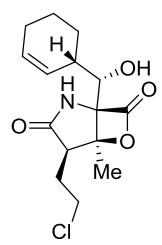


(-)-1.242
500 MHz, $CDCl_3$

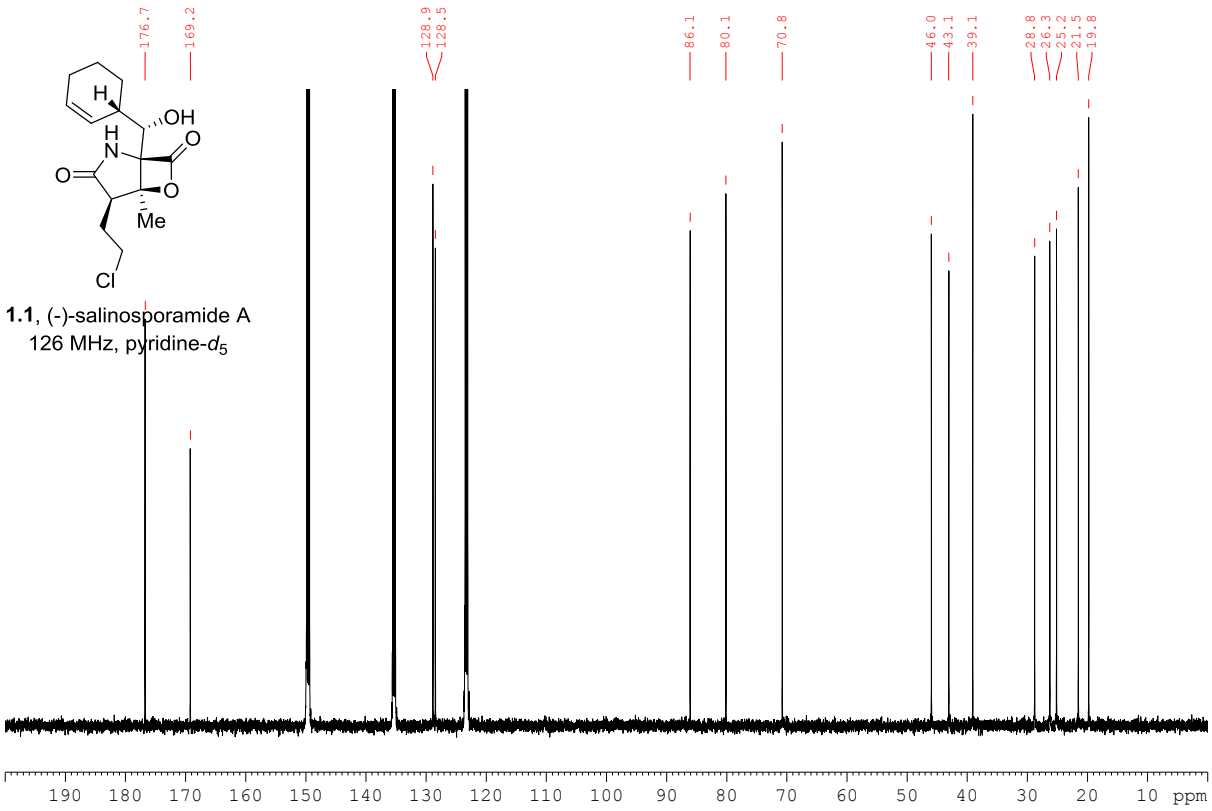


(-)-1.242
126 MHz, $CDCl_3$

Spectra for **1.1,** (-)-salinosporamide A



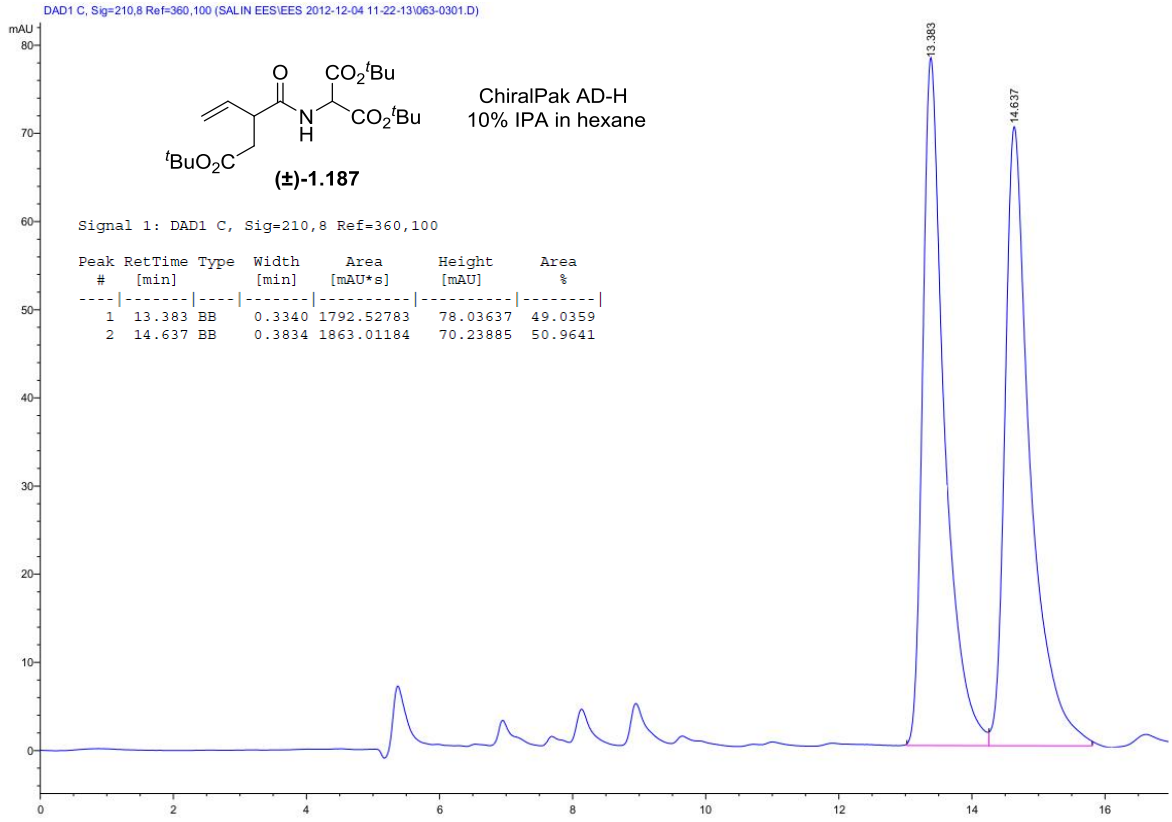
1.1, (-)-salinosporamide A
500 MHz, pyridine-d_5



1.1, (-)-salinosporamide A
126 MHz, pyridine-d_5

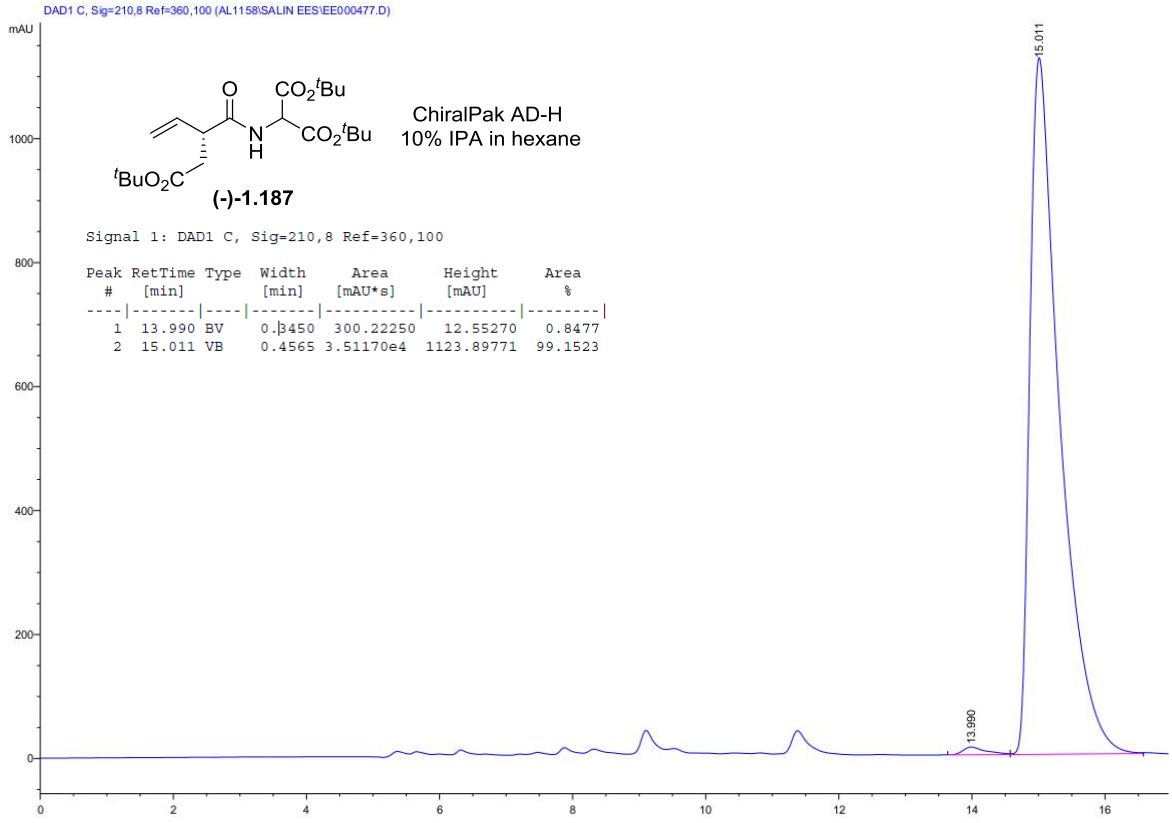
Figure 7.4

7.1.8 **HPLC traces for compound (-)-1.187**



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

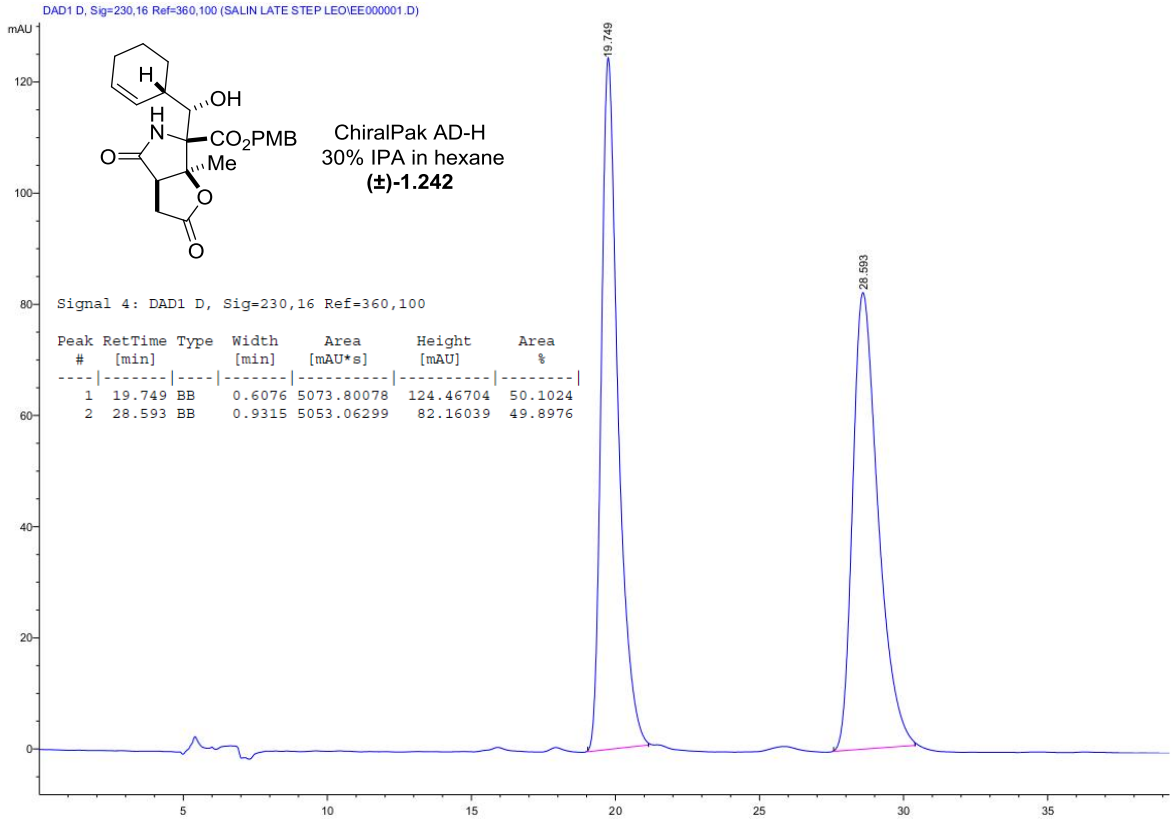
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.383	BB	0.3340	1792.52783	78.03637	49.0359
2	14.637	BB	0.3834	1863.01184	70.23885	50.9641



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

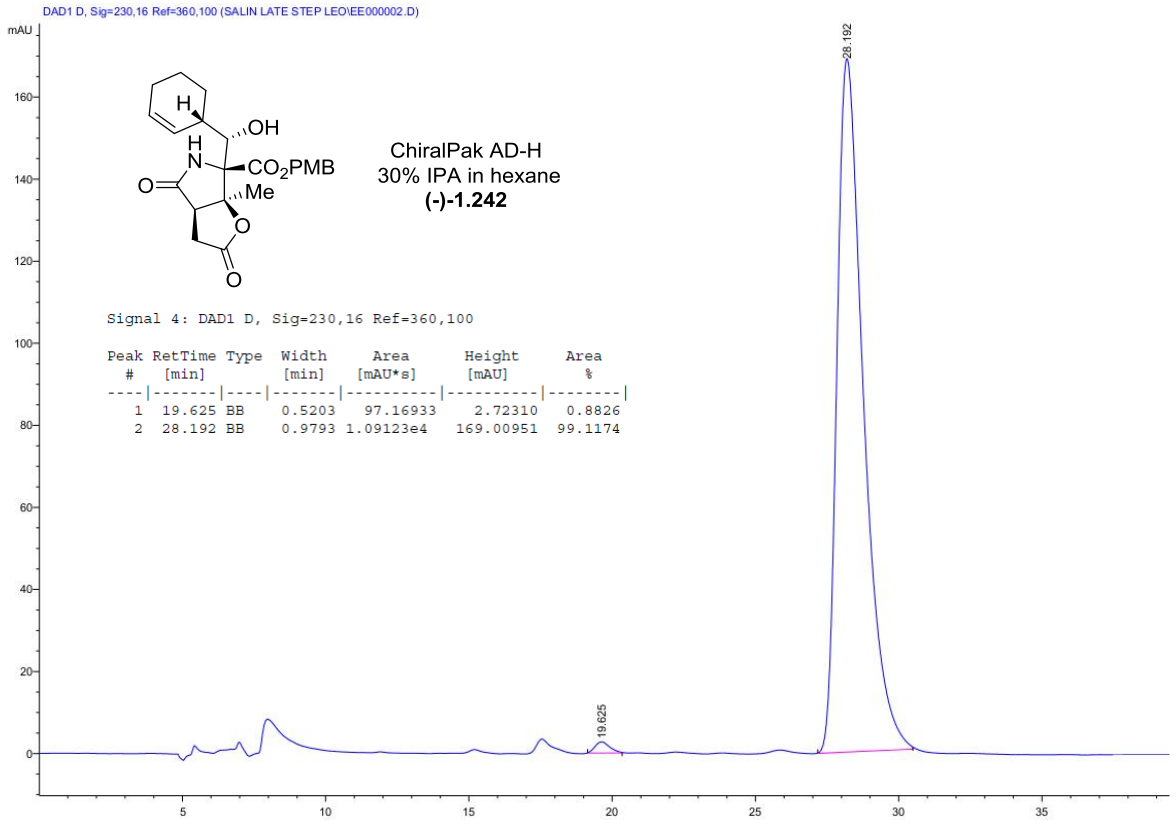
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.990	BV	0.3450	300.22250	12.55270	0.8477
2	15.011	VB	0.4565	3.51170e4	1123.89771	99.1523

7.1.9 **HPLC traces for compound (±)-1.242 and (-)-1.242**



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.749	BB	0.6076	5073.80078	124.46704	50.1024
2	28.593	BB	0.9315	5053.06299	82.16039	49.8976

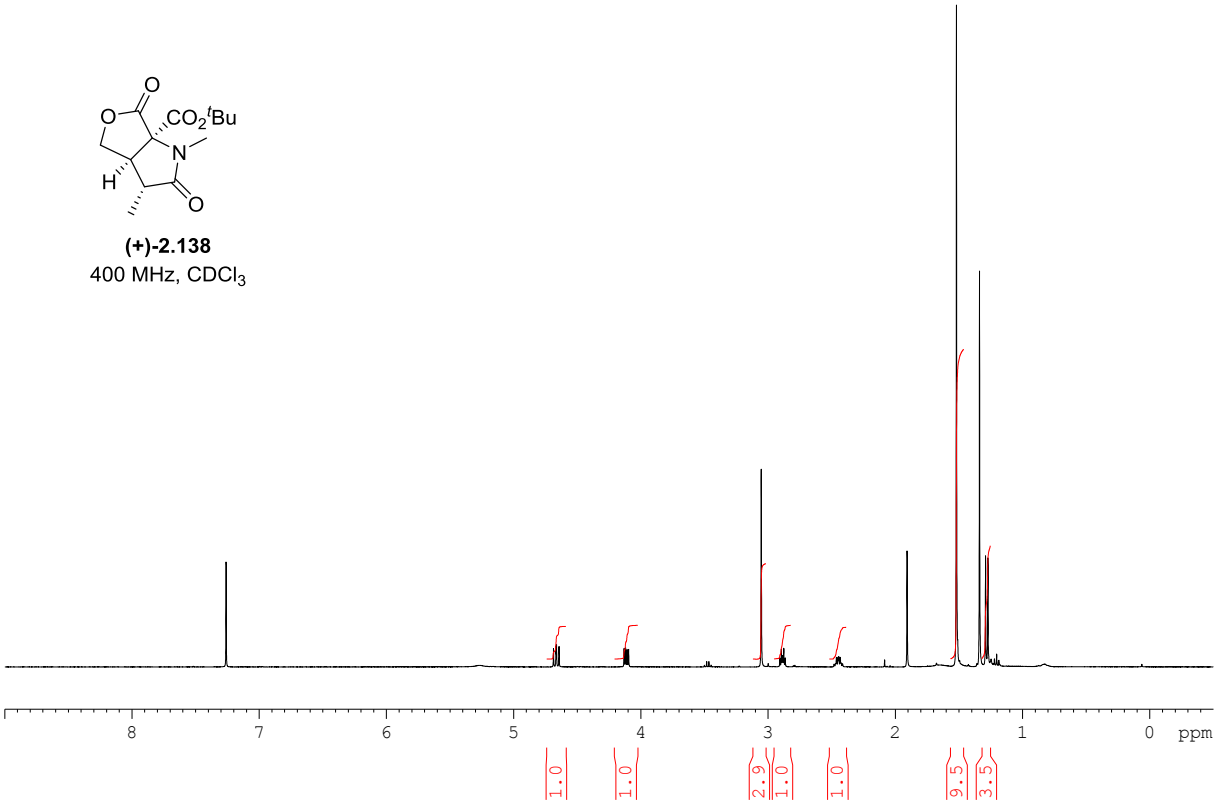


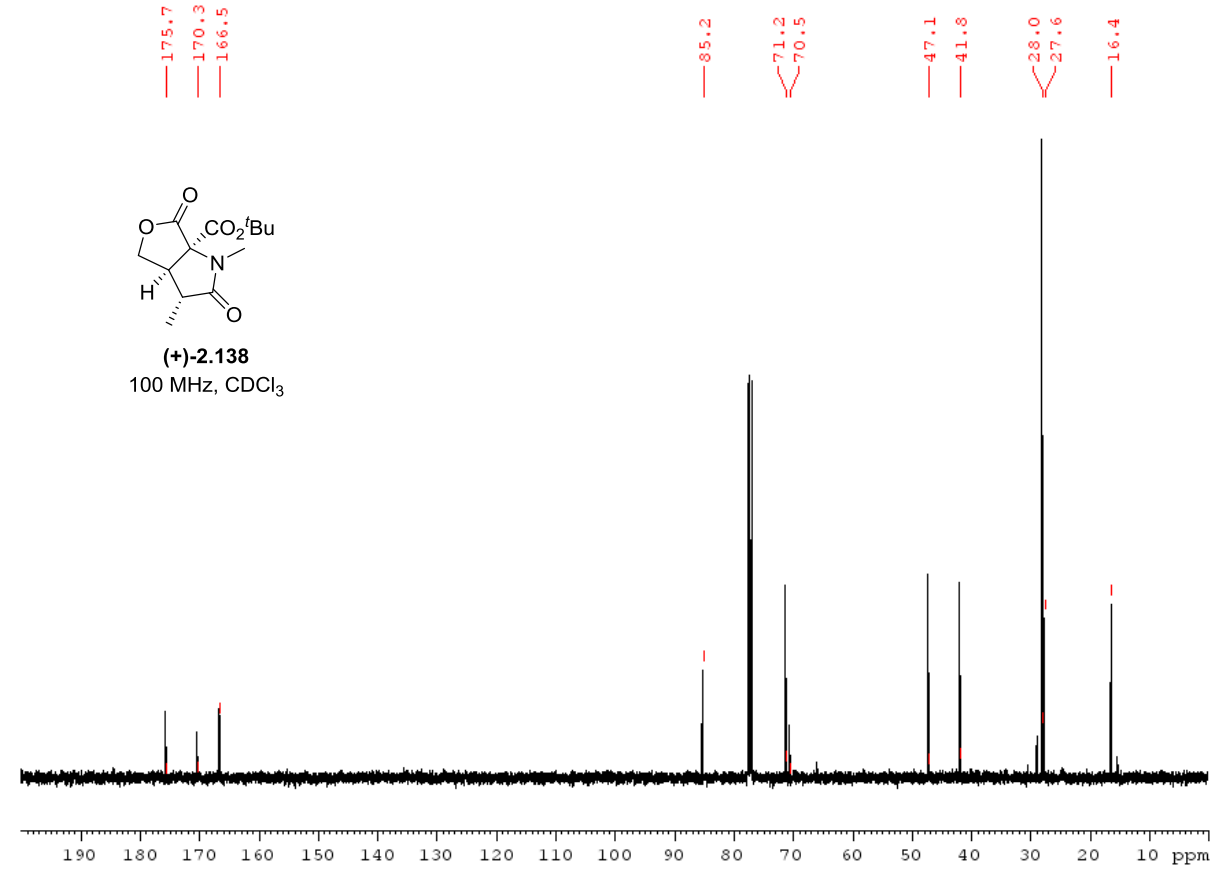
Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.625	BB	0.5203	97.16933	2.72310	0.8826
2	28.192	BB	0.9793	1.09123e4	169.00951	99.1174

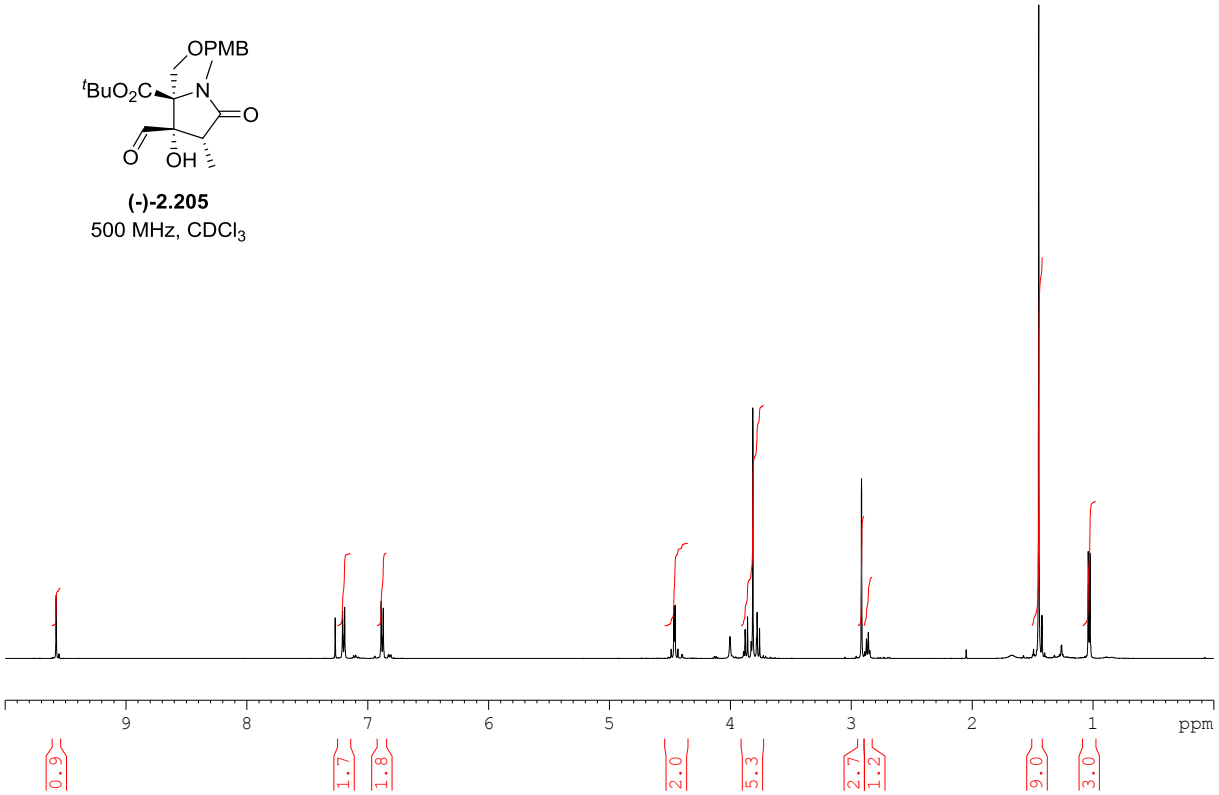
.

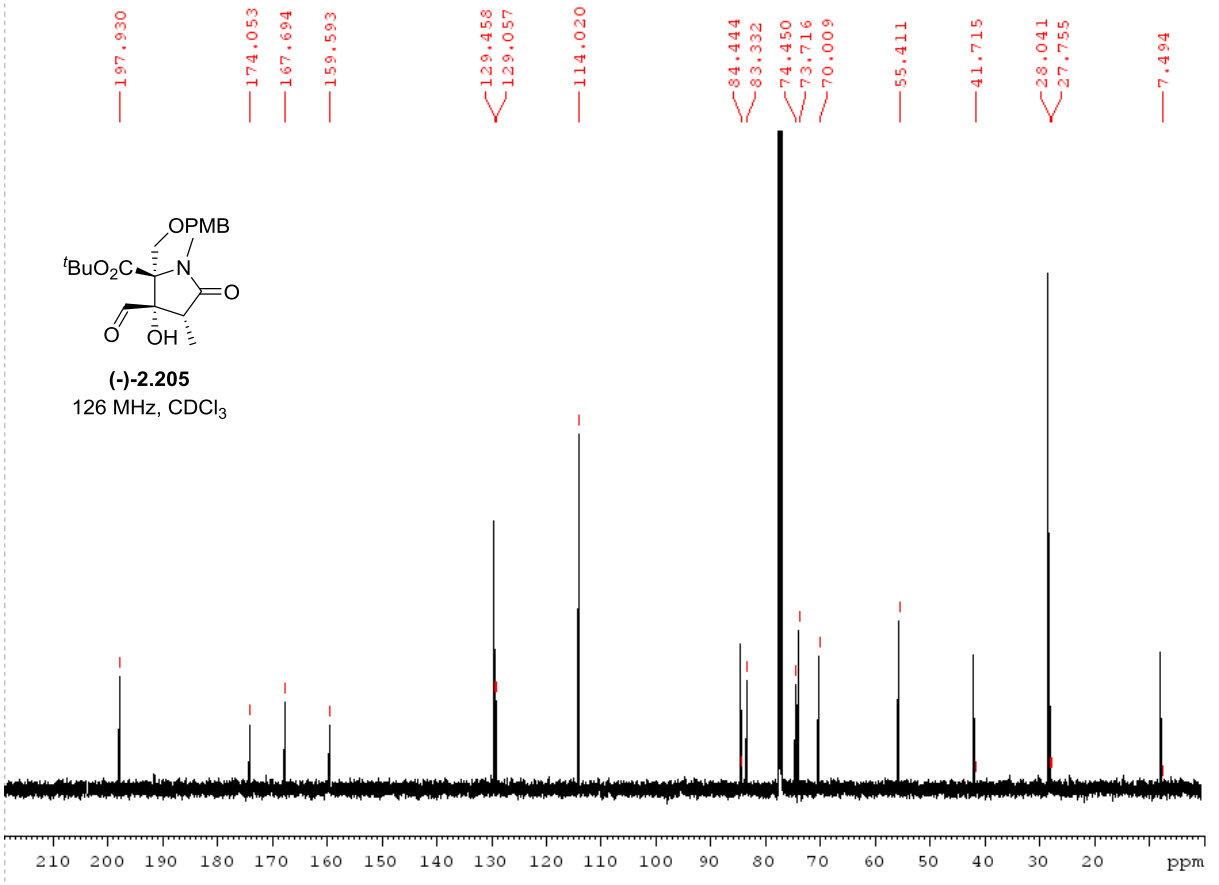
7.1.10 **Spectra for compound (+)-2.138**



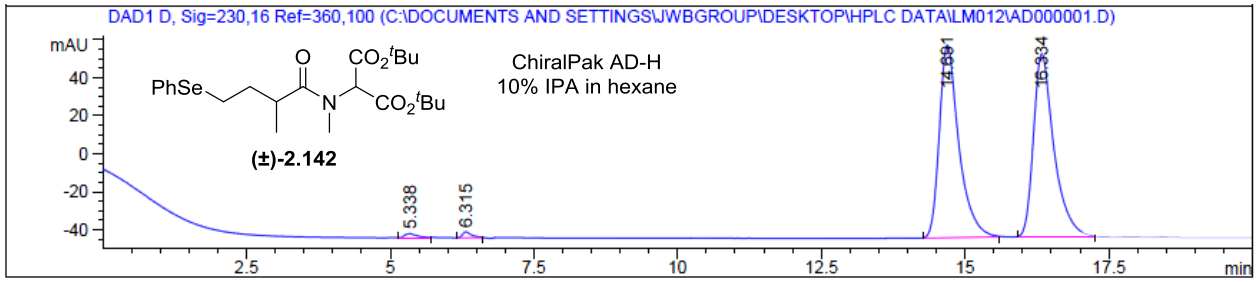


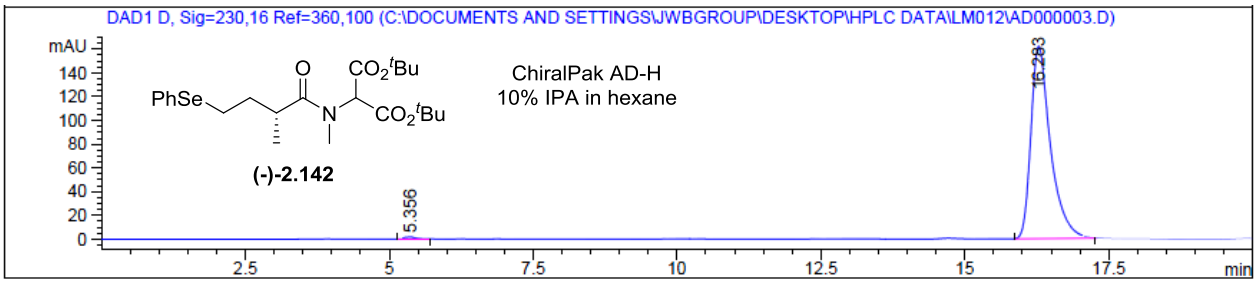
7.1.11 **Spectra for compound (-)-2.205**





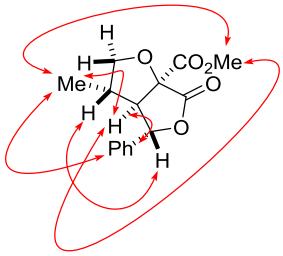
7.1.12 HPLC traces for compound (±)-2.142 and (+)-2.142



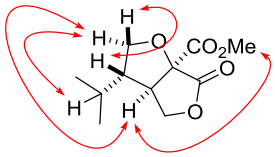


7.2 Selected results of ^{1}H NMR nOe and NOESY experiments

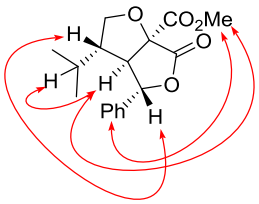
7.2.1 nOe interactions for compound 3.24b to 3.24f and



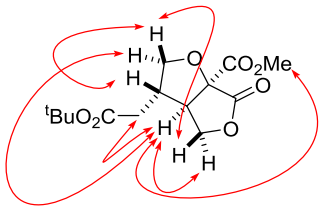
3.24b



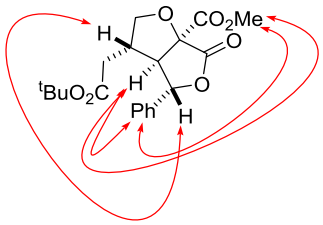
3.24c



3.24d

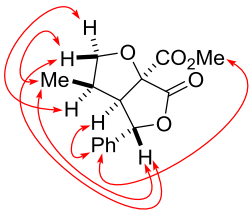


3.24e



3.24f

7.2.2 **NOESY interactions for compound 3.28b**



3.28b