TOWARDS THE SYNTHESIS OF NOVEL PROTEIN PHOSPHATASE INHIBITORS

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ABSTRACT

Protein phosphatases (PPases) are important enzymes which mediate dephosphorylation of proteins in eukaryotic cells. These enzymes are involved in a variety of cellular processes, and disruption of their activity has been shown to be involved in the development of diseases such as cancers and Alzheimer's. Protein phosphatase inhibitors (PPIs) have been used to regulate the activity of these enzymes, and hence, control the development of the cellular processes related to them. However, the lack of potent and selective readily accessible PPIs is a major obstacle to the understanding of these complex biological pathways, and the development of reliable synthetic routes towards new PPIs has therefore generated a significant amount of interest.

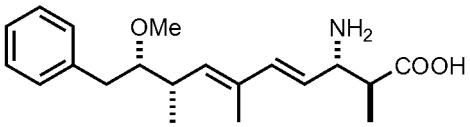
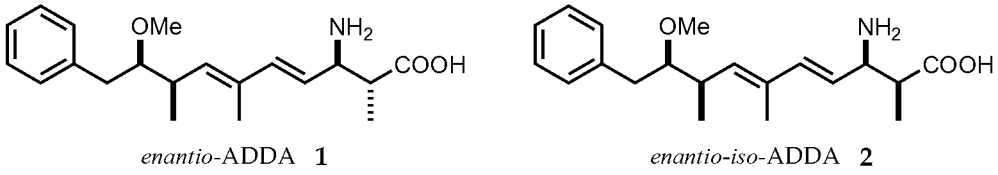


Figure 1. (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4*E*,6*E*-dienoic acid (ADDA).

Several naturally occurring PPIs possess the "ADDA" residue (**Figure 1**), which has been shown to be crucial for their inhibitory activity. We would like here to report the synthesis of "ADDA"-isoforms such as *enantio*-ADDA **1** and *enantio-iso*-ADDA **2** (**Scheme 1**) through a convergent approach taking advantage of cross-metathesis methodology, non-aldol aldol and aza-Claisen rearrangements, as well as β-lactam chemistry.



enantio-ADDA **1** *enantio-iso*-ADDA **2**

Scheme 1. *enantio*-ADDA and *enantio*-iso-ADDA residues.

We envisage using our synthetic approaches as a platform to generate a wide range of novel "ADDA"-containing analogues, which might lead to the discovery of potent and selective PPIs, which could be generated in multi-gram scale.

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Last but definitely not the least, I would like to thank my family, and more particularly Doris, my lover and mother of my daughter for making my life so complete, their endless support and love. Without her nothing would have ever been possible.

Finally, I would like to dedicate my thesis to my little daughter Melyssa, born in Glasgow the 08 / 06 / 2008.

AUTHOR'S DECLARATION

This thesis represents the original work of Sébastien MEIRIES unless explicitly stated otherwise in the text. The research was firstly carried out at the University of Dundee and was continued at the University of Glasgow in the Henderson Laboratory under the supervision of Dr Rudi MARQUEZ during the period of September 2005 to October 2008. Portions of the work described herein have been published elsewhere as listed below.

Convergent Synthesis of (2R,3R,8R,9R)-*N*-Boc-ADDA.

Sebastien Meiries and Rodolfo Marquez *J. Org. Chem.*, **2008**, *73*(13), 5015.

Synthesis of the Trichloroacetamide Derivative of *Enantio*-*iso*-ADDA Methyl Ester.

Sebastien Meiries, Andrew Parkin, and Rodolfo Marquez *Tetrahedron*, **2009**, *65*(15), 2951.

ABBREVIATIONS

AcOH	acetic acid
ADDA	(2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8,-trimethyl-10-phenyl-4,6-decadienoic acid
AIBN	2,2-azobisisobutyronitrile
Ala	alanine
aq.	aqueous
Arg	arginine
app	apparent
ATP	adenosine tri-phosphate
bd	broad doublet
Boc	*tert*-butoxycarbonyl
bs	broad singlet
bt	broad triplet
BuLi	butyllithium
°C	degree Celsius
cAMP	cyclic Adenosine Mono-Phosphate
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
CM	cross-metathesis
conc.	concentrated
COSY	correlation spectroscopy
d	doublet
D-(-)-DIPT	D-(-)-Diisopropyltartrate
DARPP32	Dopamine and cAMP-Regulated PhosPhoprotein of 32 kDa
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublet
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer

DIBAL-H	Diisobutylaluminiumhydride
DIEA	N,N'-Diisopropylethylamine (Hünig's base)
DIPEA	N,N'-Diisopropylethylamine (Hünig's base)
DME	1,2-Dimethoxyethane
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	Diphenyl phosphoryl azide
EC_{50}	concentration of a drug to inhibit 50% of growth
EI	electron impact ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalent
EI	electron impact
ES	electro spray
ESI	electro spray ionisation
FAB	fast atom bombardment
g	gram
GI	first generation Grubbs catalyst
GII	second generation Grubbs catalyst
Glu	glutamic acid
h	hours
HCl	hydrochloric acid
HGA	second generation Hoveyda-Grubbs analogue
HGII	second generation Hoveyda-Grubbs catalyst
HMBC	heteronuclear multiple bond correlation experiment
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphotriamide

HMQC	heteronuclear multiple-quantum coherence experiment
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
HWE	Horner-Wadsworth-Emmons
IC_{50}	inhibitory concentration 50.
IR	infra-red
*iso*ADDA	(2*R*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8,-trimethyl-10-phenyl-4,6-decadienoic acid
J	NMR spectra coupling constant
Kg	kilogram
KHMDS	potassium hexamethyldisilasane
Leu	leucine
LD_{50}'s	lethal dose 50
LDA	lithium diisopropylAmine
LHMDS	lithium hexamethyldisilasane
lit.	literature
LRMS	low resolution mass spectroscopy
m	multiplet
M	molar or metal
MCs	microcystins
Mdha	*N*-methyldehydroalanine
Mdhb	*N*-methyldehydrobutyrin
Me	methyl
MeAsp	β-methylaspartic acid
MeI	iodomethane
Mesyl	methanesulfonyl
mg	milligram
MHz	megahertz
mmol	millimole
mL	microlitre
MNNG	1-Methyl-3-nitro-1-nitrosoguanidine

M.p.	melting point
Ms	methanesulfonyl
NAA	non-aldol aldol (rearrangement)
N-Boc	*N*-*tert*-Butoxycarbonyl
n-BuLi	*n*-Butyllithium
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
N-TAC	*N*-trichloroacetamide
N-TBS	*N*-*tert*-Butylsilyl
OA	okadaic acid
PMB	*para*-Methoxy benzyl
PDC	Pyridinium dichromate
Ph	phenyl
PhH	benzene
PhMe	toluene
PKs	protein kinases
PPs	protein phosphatases
PPases	protein phosphatases
PPIs	protein phosphatase Inhibitors
PPP	protein phosphatase of type P (non Mg^{2+} dependent)
PPM	protein phosphatase of type M (Mg^{2+} dependent)
PTSA	*p*-toluene sulfonic acid
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q	quartet
RCM	ring closing metathesis
ROM	ring opening metathesis
rt	room temperature
s	seconds or singlet
SAR	structure-activity-relationship
Ser / Thr	serine / threonine

sat.	saturated
S_N1	nucleophilic primary substitution
S_N2	nucleophilic secondary substitution
t	*tert*
t	triplet
TBS	*tert*-Butyldimethylsilyl
TEA	triethylamine
TFA	trifluoro acetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	tautomycin
TMS	trimethylsilyl
THF	tetrahydrofuran
Tr	trityl or triphenylmethyl
trityl	triphenylmethyl
Ts	*para*-toluenesulfonyl
tosyl	*para*-toluenesulfonyl
UV	ultraviolet
v	very
vbs	very broad singulet
vbd	very broad doublet
µ	micro
µg	microgram
µL	microlitre
µmol	micromol
(±)	racemic
δ	NMR chemical shift
Å	Ångström
Δ	heating / reflux

INTRODUCTION

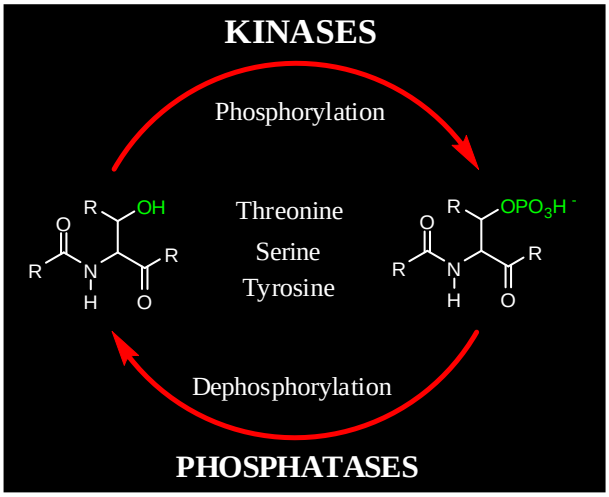
------- PART I – BIOLOGICAL INTRODUCTION -------

1 - THE PROTEIN PHOSPHATASES (PPase)[1]

1.1 – General introduction on PPases

1.1.1 The phosphorylation/dephosphorylation cycle

This reversible phosphorylation / dephosphorylation cycle (**Scheme 2**) is widely recognised as being critically involved in the regulation of countless eukaryotic cellular processes.[2] It is mediated by protein kinases (PKs), which catalyse the phosphorylation of hydroxyl-bearing amino acid in using ATP as a phosphoryl donor, and protein phosphatases (PPs) which regulate the dephosphorylation process.



Scheme 2. Reversible phosphorylation / dephosphorylation cycle.

Both phosphatases and kinases act in opposition to mediate the phosphorylation / dephosphorylation process, represented by the simplified cycle above (**Scheme 2**). This process can be considered as a molecular « on-off » switch that acts to selectively modulate the activity of a myriad of other cellular processes, and signalling pathways such as cell division, gene expression, glycogen synthesis, muscle contraction, and neurotransmission. Indeed, the addition or the removal of a phosphate group may activate or de-activate an enzyme, or enable a protein-protein interaction to occur, and thus represents one of the most important means by which eukaryotic cells communicate in the body. To reverse the regulatory effect, the phosphate can be removed on its own by hydrolysis, or by protein phosphatase-mediated dephosphorylation.

1.1.2 Classification of protein phosphatases

The phosphoprotein phosphatases represent a very broad family subdivided in five major subunits based upon their substrate specificity:

- Serine / threonine specific PPases
- Tyrosine-specific PPases
- Dual Specificity PPases
- Histidine PPases
- Lipid PPases

As part of this project, we are essentially interested in the synthesis of inhibitors of serine / threonine phosphatases. As such, the rest of the introduction will be focused around this specific class of PPases.

1.1.3 Classical disorders

The level of protein phosphorylation in cells is finely regulated by the complementary actions of protein kinases and protein phosphatases. This subtle balance is critical to maintaining both cellular and whole organism homeostasis, and even minor disturbance of this regulation process can lead to dramatic side effect on cell life. The abnormal phosphorylation levels have been shown to be narrowly linked to the development of cancers, diabetes, Alzheimer's and inflammatory diseases. A better understanding of the mechanism by which the PPs and PKs catalyse and finely regulate the level of phosphorylation would lead to major discovery, and would enable the design of new therapeutic treatments.

1.2 - Serine / threonine-specific protein phosphatases[3]

At least 99% of protein phosphorylation in eukaryotic cells occurs on serine and threonine residues.[4] Interestingly, while the human genome encodes an almost equal number of tyrosine kinases and tyrosine phosphatases (90 *vs* 107), there is a dramatic disparity between the number of serine / threonine kinases and phosphatases (428 *vs* 40).[5] Furthermore, the lack of selective protein phosphatases inhibitors available, which can be

used as biological probes,[6] have considerably limited the number of studies on the functions of serine / threonine protein phosphatases, by comparison with protein kinases.[6] For these reasons, protein phosphatases represents a very challenging and fascinating research area largely under explored.

1.2.1 Classification of Ser/Thr PPases

Ser / Thr phosphatases are metalloenzymes which dephosphorylate their phosphoserine and / or phosphothreonine-containing substrates in a single reaction step, using a metal-activated nucleophilic water molecule. They belong to the two major PPP and PPM (Mg^{2+}-dependent phosphatases) families of protein phosphatases, and are traditionally classified into several sub-families (PP1 to PP7), based upon fine and subtle characteristics such as their apparent sensitivity to inhibitors, their structural differences, and their *in vitro* substrate specificity.[1] These different sub-families of PPases are themselves subdivided into different types (A, B, C), which in turn can contain distinct isoforms of catalytic and regulatory subunits (ex: $\alpha 1$, $\alpha 2$, β, $\gamma 1$, $\gamma 2$, etc…):

- PP1
- PP2 (A, B*, C**)
- PP4
- PP5
- PP6
- PP7

*PP2B is also known as PP3, calcineurin and Ca^{2+} / calmodulin-dependent protein phosphatase

**PP2C is also known as ATP / Mg^{2+} -dependent protein phosphatase

More recently, the new relatives of PP1 (PPZ1, PPZ2, PPQ), PP2A (PPV, PPG) and PP2B (rdgC) have been included in addition to the newly characterised catalytic subunits of PP4 (over-expressed in human breast and lung tumors),[7] PP5, PP6 and PP7.

1.2.2 PP1 and PP2 protein phosphatases[3]

Although new catalytic subunits are regularly discovered, PP1 and PP2 subunits remain the most abundant, and generally account for most of the phosphoserine / threonine phosphatase activity in eukaryotic cells.[8] They are typically found as heterodimers made of different variable subunits inducing fine and subtle structural differences responsible

for imparting substrate specificity. Type-I phosphatases (PP1) preferentially dephosphorylate the β-subunit of phosphorylase kinase, whereas type-2 phosphatases (PP2) preferentially dephosphorylate their α-subunit. Furthermore, Type-I phosphatases are inhibited by two heat-stable proteins, termed inhibitor-1 (I-1 or I_1) and inhibitor-2 (I-2 or I_2), whereas type-2 phosphatases are insensitive to them. Type-2 phosphatases comprise three enzymes (PP2A, PP2B, and PP2C) that can be distinguished by their cation requirements. While PP2C belongs to the PPM family (Mg^{2+}-dependent phosphatases), and exhibit a relatively narrow specificity against a number of protein substrates, PP1, PP2A and PP2B all belong to the PPP family and exhibit broad specificities.

2 - INHIBITORS OF SER/THR PHOSPHATASES PP1 AND PP2A

Since the first appearance of PP1 in the literature in 1943,[9] more than 100 inhibitors, and targeting proteins,[5] have been reported. A large number of of them have been tested against PP1 and PP2A, which shed further light on the structures, functions and roles of PP1[10] and PP2A[11-13] in diverse processes. For instance, it is now known that PP1 activity is associated with abnormal calcium cycling, characteristic of experimental human heart failure.[14] Additionally, a growing body of evidence indicates that PP2A has complex inhibitory and stimulatory effects on hormone, and growth factor signalling,[4] and its activity is also believed to be a cause of the abnormal hyperphosporylation involved in Alzheimer's disease.[15] Inhibitors of PP1 and PP2A may represent attractive new therapeutic targets, and have consequently generated a growing interest. However, as their number is constantly increasing, notably through the use of modern technique such as virtual screening,[16] the list of PPase inhibitors will be here strictly limited to some of the most significant ones.

2.1 - Endogenous inhibitors

PP1 and PP2A can be potently inhibited *in vivo* by the action of endogenous phosphatase inhibitors such as Inhibitor-1 (I_1), Inhibitor-2 (I_2), dopamine, cAMP regulated phosphoprotein (DARPP-32), and nuclear inhibitor of protein phosphatase 1 (NIPP-1).[17]
The discovery of inhibitor-1 by Huang and Glinsmann in 1975 marked a turning point in the study of the protein phosphatases.[18] Inhibitor-1 (together with its homolog, DARPP-

32) was the first molecule discovered that was able to differentiate between the previously homologous PP1 and PP2A, and both have found great use *in vitro* as a result.[17] Until recently, no known endogenous inhibitors that specifically targeted PP2A had been identified. This view changed with the discovery of I_1^{PP2A} and I_2^{PP2A}, which have both been determined to specifically inhibit PP2A in mammalian tissues without affecting the activity of the other serine-threonine phosphatases.[15] Although the sequence of I_1^{PP2A} and I_2^{PP2A} has been determined, it is unknown whether they require phophorylation, or dephosphorylation to become activated.[17] Regulation of PP1 and PP2A has also been proved to occur indirectly through their activation and deactivation by cellular secondary messengers such as cAMP, ATP, and glucose.[17]

However, the use of endogenous inhibitors as effective PP1- and PP2A-specific inhibitors has been limited by their peptidic nature, which requires them to be microinjected directly into the cells under study. Thus, while such inhibitors may be mechanistically informative, they are also handicapped by the inherent shortcomings of peptides in general (i.e proteolytic degradation, poor membrane permeability, high molecular weight, and potential instability),[17] and so it can be seen that the old medicinal chemists credo of "peptides don't make good drugs" also extends to their use as *in vitro* inhibitors. The intrinsic deficiencies of using such endogenous phosphatase inhibitors as either biological probes or as potential drug leads have therefore prevented their widespread use. Hence, alternative inhibitors have had to be found in order for meaningful inhibition studies to be performed.

2.2 - Exogenous inhibitors of PP1 and PP2A

The difficulties posed by the use of the endogenous phosphatase inhibitors (quantity, stability, etc…) have been overcome by the use of small molecule inhibitors that are not compromised by the problems commonly associated with proteins.[17] Many naturally occurring structural scaffolds have been found to mimic small areas of the three-dimensional molecular surface presented by the endogenous protein inhibitors.[17] This has allowed researchers to identify a diverse range of natural products that possess potent inhibitory activity against the serine-threonine protein phosphatases over the last twenty years. However, unlike protein-based endogenous inhibitors, these small molecules are often non-selective, and have a tendancy to inhibit several classes of PPases at a time.[5]

2.2.1 Okadaic acid (OA)

This complex spirocycle, containing 16 stereocenters, was the first polyketide protein phosphatase inhibitor to be characterised (**Figure 2**). It was initially isolated from the marine sponges *Halichondria okadaii*, and *Halichondria melanodocia*, and was later proved to be produced by *Prorocentrum lima* too.[19] However, subsequent investigation demonstrated that sponges tend to accumulate certain species of marine plankton, which are the true source of OA.[17]

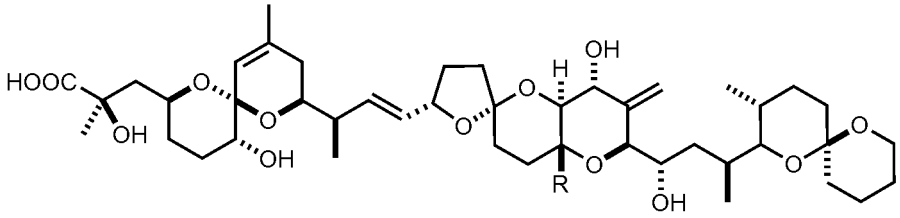


Figure 2. Okadaic Acid.

OA is known to be an important tumor promoter,[20] but also a potent and selective inhibitor of PP1 and PP2A (LD_{50} = 315 and 1.2 nM, respectively).[17,21,22] Even at high doses, PP2B is only weakly inhibited, while PP2C is apparently unaffected. Several naturally occurring congeners, consisting of slight structural modifications to the parent OA skeleton, have since been isolated and shown to be equipotent with OA.[17]

2.2.4 Calyculin A

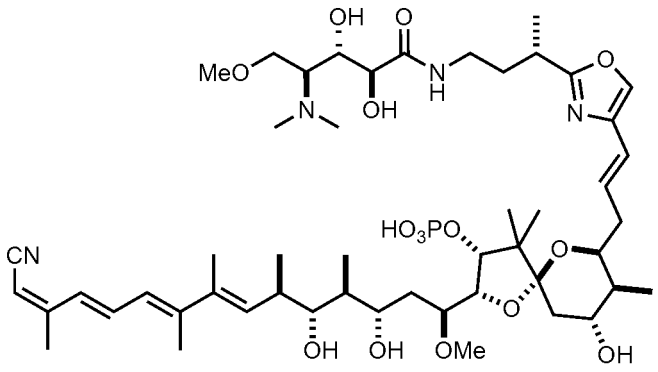


Figure 3. (-)-Calyculin.

Calyculin A is a sophisticated spirocyclic polyene that possesses 15 stereocenters and 5 (*E*)-double bonds (**Figure 3**). This octamethyl polyhydroxylated fatty acid, which was

isolated from several marine sponges, possesses similar phosphatase inhibition and tumour-promoting activities to OA.

2.2.5 Tautomycin and Tautomycetin

Tautomycin (**Figure 4**) possesses a simpler framework than either OA or calyculin, and contains 13 stereocentres. It was first isolated from the soil bacterium *Streptomyces spiroverticillus* in 1987, but it was not until 1993 that its structure was fully elucidated. It exhibits antifungal and hepatotoxic activity[17] at low concentrations, and inhibits PP1 (IC_{50} = 0.2 nM) and PP2A (IC_{50} = 1nM). As such, it is the only naturally-occurring small molecule inhibitor that is partially selective for PP1.

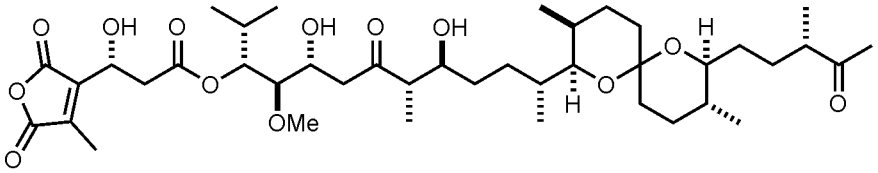


Figure 4. Tautomycin (TM).

Tautomycetin (**Figure 5**) is structurally related to tautomycin, but lacks the spiroketal moiety of the latter. This results in a simpler molecule to synthesize, as it contains only 8 stereogenic centres. It was isolated from *Streptomyces griseochromogenus*, and induces the same morphological changes in cells as observed for TM exposure, although data pertaining to its protein phosphatase inhibition characteristics has not been published.[17]

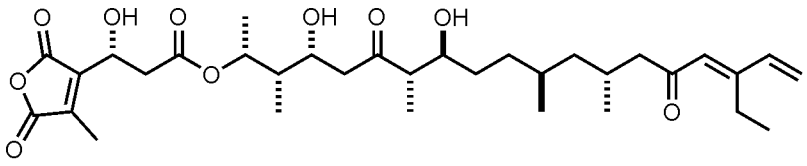


Figure 5. Tautomycetin.

2.2.6 Cantharidin

Cantharidin is a *meso*-symmetric molecule which is by far the simplest, and the most conformationnally rigid member of the PP inhibitors to date (**Figure 6**).

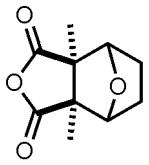


Figure 6. Cantharidin.

This *meso*-tricycle is a powerful vesicant, which was used in the 19th century to remove warts, although its high toxicity limited its general use. Indeed, human poisonings persist as a result of folklore surroundings its purported aphrodisiac and abortifacient properties.

2.2.7 Microcystins and Nodularins

The microcystins (**Figure 7**) are complex cyclic heptapeptides that are isolated from different *Mycrocystis* species of blue-green algae,[23] whereas the nodularins (**Figure 6**) are cyclic pentapeptides isolated from *Nodularia* species of algae.

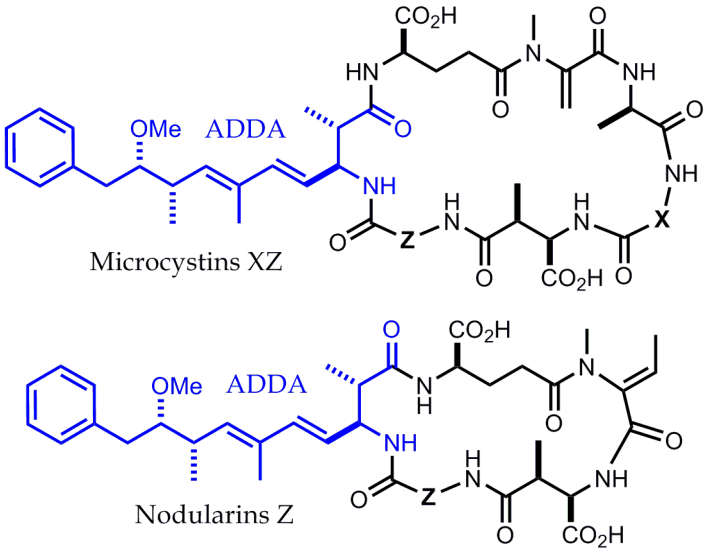


Figure 7. General Structures of Microcystins XZ and Nodularins Z.

Since their discovery, microcystins and nodularins have generated a lot of interest for biologists, ecologists, and chemists. They have been shown by a number of groups to possess potent inhibitory activity against PP1 and PP2A, but are also thought to be potent tumour promoters.[24] Conversely they have only weak inhibitory activity against PP2B, and no impact at all on PP2C.[6] They are the only known families of ADDA-containing

natural products (**Figure 7**) and represent therefore a major interest as part of this project and will then be discussed in further details in the next paragraphs.

2.2.8 General Overall Bilan

All of the natural products described above are collectively referred to as the Okadaic Acid-class of protein phosphatase inhibitors. They all exhibit competitive kinetics with okadaic acid, as do the endogenous protein inhibitors. The OA-class all inhibit PP1 and PP2A, and several members also affect PP4 and PP5. However PP2B (calcineurin) is only weakly inhibited, and PP2C remains unaffected. What is astonishing is that while all these inhibitors possess unrelated chemical structures, and come from very diverse origins, they all specifically and potently target the same protein phosphatases, supporting the contention that the phosphatases play an extremely important physiological role.

The use of exogenous small molecule inhibitors described above has been an invaluable tool for understanding specific signalling pathways, and has helped elucidate a wide range of protein phosphatase functions within the cell. However, althought the OA-class PPIs are fairly potent and selective inhibitors, they clearly also have numerous drawbacks. Their lack of specificity, their toxicity and their difficulty to be isolated and/or synthesised, clearly limit the quantity of material available for biological studies.

Such studies not only serve to increase our understanding of such complex biochemical pathways, but also uncover the potential for the development of novel drug therapies for a wide range of human and animal disorders. Thus, the development of more potent and highly selective phosphatase inhibitors has therefore become a priority for a number of research groups involved in the development of innovative therapies for the treatment of a range of illnesses as diverse as Alzeihmer's Disease and Cancer.

3 - ADDA-CONTAINING MICROCYSTINS & NODULARINS

The serine/threonine phosphatases are inhibited by a variety of natural toxins, including the microcystins and nodularins, which are the only ADDA-containing natural products (**Figure 7**). Since their isolation from their natural sources, they have generated a lot of

scientific work, which has demonstrated that these cyanotoxins possess high toxicity as well as strong inhibitory activity towards protein phosphatases inhibitors, both being closely related.

3.1 - The cyanobaterial origin[25]

3.1.1 Cyanobacteria

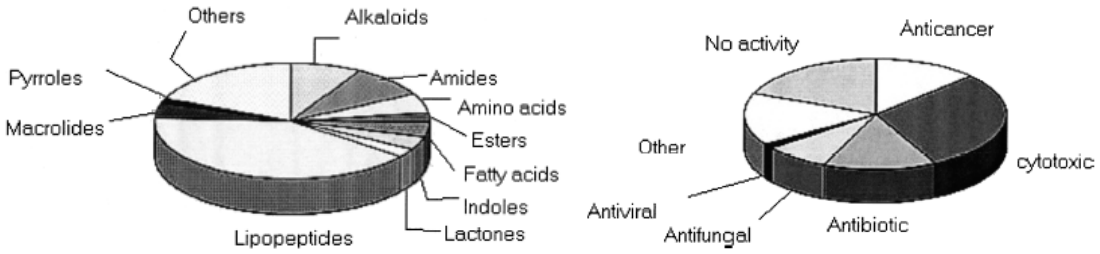
Cyanobacteria, also known as blue-green algae, are actually not true algae but rather photosynthetic bacteria that are believed to be among the first forms of life to exist on land. They are photosynthetic prokaryotes, and have been found to inhabit an extremely diverse range of habitats, ranging from sub-zero landscapes to hot deserts. They are capable of both aerobic and anaerobic photosynthesis, and utilise the enzyme nitrogenase to convert N_2 directly to ammonia, allowing them to undertake the fundamental metabolic process of nitrogen fixation with great efficiency. They also contain several photosynthetic pigments including chlorophyll-*a*, carotene, xanthophyll, blue *c*-phycocyanin, and red *c*-phycoerythrin, which translates into a wide range of colourful cyanobacterial waterblooms (**Figure 8**).

Figure 8. Blue-green and Red Cyanobacterial Waterblooms.

Many cyanobacterial species possess special gas vesicles which prevent them from developing vertically in a water column. In order to optimize their development, they spread horizontally, forming blooms at the surface of eutrophic slow-flowing waters during warm seasons (**Figure 8**). Their formation is a natural process linked to the climatic conditions as well as nitrogen- and/or phosphorous-containing nutrient levels, generally resulting from municipal wastewater discharge, and/or runoff from agricultural land.

Cyanobacterial waterblooms are found worldwide, and regularly cause animal poisoning, and pose risk to human health through the release of cyanotoxins.[26]

Despite their toxicity, cyanobacteria possess many attractive applications, and represent one of the main natural source of novel bioactive compounds (**Scheme 3**).[25,28]



Scheme 3. Types of chemical compounds isolated from marine Cyanobacteria and their reported biological activities.[25,28]

Cyanobacteria have also been recognized as an important source of vitamins and proteins. They represent a very inexpensive food supplement, and can be found in health food stores. Dried *Anthrospira* (*Spirulina*), for instance, is sold as a health food with annual sales estimated at US $ 40 million. Edible blue-green algae (*Nostoc*, *Spirulina* and *Aphanizomenon*) have a very quick development rate, and their ease of cultivation is currently helping solve problems of malnutrition in Africa. Interestingly, cyanobacteria have also been used in the production of green fuel (ethanol, H_2), and are the subject of active ongoing research.[27]

3.1.2 Cyanobacterial toxins[23]

The poisonous toxins produced by bloom-forming bacteria in the aquatic environment, are usually contained within the cyanobacterial cells. However, they may be released in fairly substantial quantities upon certain conditions, such as during cell lysis, and after cell death.[28] Cyanotoxins are conveniently categorised according to the main organs, cells, or physiological systems affected in animals, and *in vitro* toxicity studies: hepatotoxins, neurotoxins, cytotoxins, dermatotoxins, and irritant toxins (lipopolysaccharides). Although cyanotoxins have generated a significant amount of scientific interest, surprisingly, the biological role of these toxins within the cyanobacteria remains poorly understood, and represents an active research area.[29]

The overall toxicity of cyanobacterial extracts is commonly attributed to the microcystins[30,31] and nodularins,[32] which are considered to be the main toxic constituents produced by the algae. The hepatotoxicity of the microcystins and nodularins is closely related to their potent phosphatase inhibitory activity, which induces overall hyperphosphorylation of many cytosolic and cytoskeletal proteins, resulting in damage to cell structure and causing cytoskeletal disintegration. On the other hand, inactivation of protein phosphatases disturbs the normal balance of cell processes, resulting in cell proliferation and cancer production, or apoptosis and cell death. Hence, MCs detoxication of aquatic ecosystems by bacterial biodegradation have received a lot of interest, and certain strains of *Sphingomonas* sp. have proved to be effective.[33] However, although the toxicity of MCs is widely recognised, it should be noted that a recent study published by I. R. Falconer in 2007,[34] tends to moderate their role in the overall toxicity of cyanotoxins.

3.1.3 Health impacts of cyanotoxin poisoning[23]

Cyanobacterial toxins have been shown to be dangerous to humans, other mammals and invertebrates.[35] Contact with, or ingestion of, water containing cyanotoxins can cause skin irritation, allergic responses, blistering of mucosa, hay fever symptoms, diarrhoea, acute gastroenteritis, muscular pain, and acute liver and kidney damage.[36] They generally travel to the liver, *via* the bile acid transport system, where most of them get stored, though some toxins remain in the blood stream and may contaminate other tissue such as heart, lung, brain or kidney.[37] In the most severe cases of intoxication, the consumption of drinking water containing cyanotoxins leads to death resulting from severe disruption of hepatic liver function.

3.1.4 Historical human cyanotoxin poisoning[23]

The negative effects of cyanobacterial toxins on health have been observed and reported repeatedly over the years. Over a century ago, the first documented case of lethal intoxication by drinking water from an Australian freshwater lake heavily infested with cyanobacteria, was published.[38,17] However, the first recorded case of human illness resulting from cyanotoxin poisoning was not reported until an outbreak of gastroenteritis around Ohio in 1931.[35] In this outbreak, a massive *Microcystis* bloom caused illness in between 5,000 and 8,000 people who drank water originating from the Potomac river. The

methods used to treat drinking water at the time (precipitation, filtration and chlorination) were insufficient to remove the cyanotoxins.

In 1959, 12 people became ill after swimming in a Canadian lake contaminated by toxins from *Anabaena*. The affected people displayed symptoms such as headaches, nausea, muscular pain, and acute gastroenteritis. In 1989, 10 British soldiers became ill after swimming, and canoe-training in water with a heavy bloom of *Microcystis*. In Australia, a sickness known as Barcoo fever, which typically displays symptoms of diarrhoea and vomiting, is believed to be caused by the ingestion of cyanobacterial toxins. Cyanobacterial waterbloom toxicosis has been reported in both humans and animals, with mycrocystins being the most commonly implicated causative agent.

However, the most serious human poisoning episode of late occurred in February 1996, when 56 patients who underwent dialysis at the Kidney Disease Institute in Caruaru, north-east Brazil, died as a result of toxic hepatitis that was eventually attributed to *Microcystis* toxins present in the dialysis water.[39] Studies carried out in the People's Republic of China have shown a higher incidence of human hepatocellular carcinoma (primary liver cancer), and colorectal cancer in regions where the population uses surface water containing microcystins for drinking than in neighbouring areas where groundwater is apparently uncontaminated.[40,41]

Clearly, cyanobacterial toxins continue to pose a major risk to human health especially in areas of the world where surface water exists under conditions that are optimal for cyanobacterial blooms.

3.2 - The ADDA fragment

Microcystins and nodularins contain invariably the characteristic hydrophobic β-amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4*E*,6*E*-dienoic acid, often abbreviated as ADDA (**Figure 1**). The ADDA chain has not been found anywhere else other than in these two genera of toxins. This raises the prospect of using ADDA as marker for measuring the presence of microcystins and nodularins in environmental and clinical material, and thus determining the intoxication level.

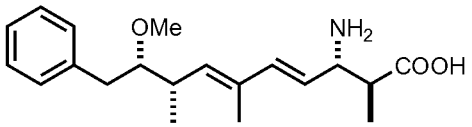


Figure 1. (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4*E*,6*E*-dienoic acid (ADDA).

3.2.1 Role of ADDA in bioactivity of MCs & nodularins

The ADDA residue plays a critical role in the bioactivity displayed by such cyanotoxins. Geometrical double-bond isomers of the (4*E*,6*E*)-1,3-diene do not exhibit biological activity, while additionally, ozonolysis or hydrogenation of the (4*E*,6*E*)-1,3-diene causes the microcystins and nodularins toxicity to cease.[34,42-44] Interestingly, MC analogues with modifications of the ADDA C_9 methyl ether, either as the corresponding hydroxyl[45] or acetylated[46] analogue, are fully active inhibitors.

It is worth mentioning that the ADDA chain, as its free amino acid form (**Figure 1**), and the remaining peptidic macrocycle of microcystins and nodularins are both non-toxic compounds. These two units are therefore complementary and both essential for potent bioactivity. However, although the peptidic macrocycle has been shown to be crucial for the bioactivity of MCs and nodularins, crystallographic studies of MCs and nodularins-protein phosphatase complexes show only a few binding interactions between the macrocyle and the enzymatic binding site (**Figure 9**). In **Figure 9**, the ADDA residue (in white) is situated deep in a pocket within the phosphatase, whereas half of the macrocyclic peptide (in orange) does not interact with the enzyme at all. These observations were also confirmed by extensive SAR studies, which demonstrated that ADDA analogues resulting from the replacement of peptidic macrocycles for smaller acyclic aminoacids, conserve significant inhibitory activity (SAR results will be further discussed in section 3).

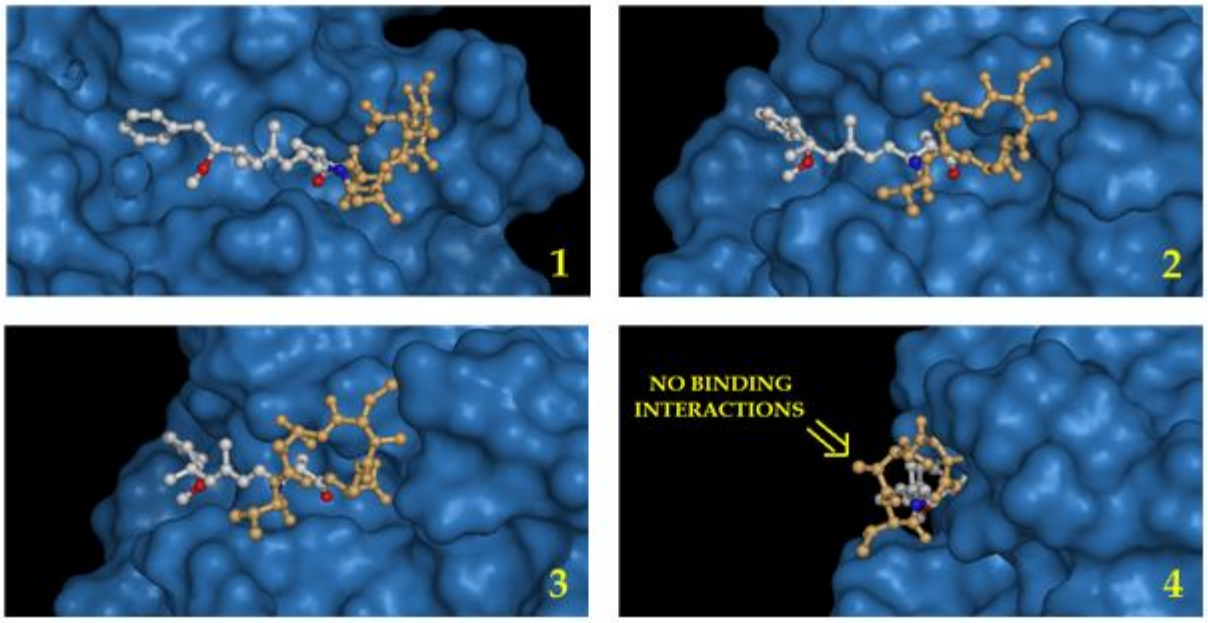


Figure 9. Binding interactions between motuporin and PP1.

3.2.2 Biosynthetic origin of ADDA

In addition to the structural and computational studies, several groups have investigated the (non-ribosomal) biosynthesis of these cyclic peptides, with particular emphasis on the amino acid ADDA. Rinehart conducted feeding experiments using isotopically labelled biological building blocks to determine the source of ADDA carbon atoms in nodularin.[47] Rinehart's work[47] suggested that ADDA is produced through a polyacetate pathway, in which a late intermediate is methylated, and dehydrated to form ADDA. A polypeptide chain is then built up from the C-terminus of ADDA, and cyclised to give either the microcystins or nodularins.

3.3 - The microcystins

The microcystins are the most abundant group of cyanotoxins[29] with more than 80 different mycrocystins identified to date,[48-52] from different genera of cyanobacteria. These cyanotoxins are known to be tumor promoters by inhibiting PP1 and PP2A, and are often reported as the most common and dangerous hepatotoxins.[53] These cyclic nonribosomal heptapeptide compounds (**Figure 10**) are named after the first genus from which they were isolated, *Microcystis aeruginosa*, and they can be obtained not only from *Microcystis*

spp., but also from *Anabaena*, *Nodularia*, *Nostoc*, *Oscillaria*, *Phanktotrix*, and *Umezakia*, all of which are also known to form waterblooms.

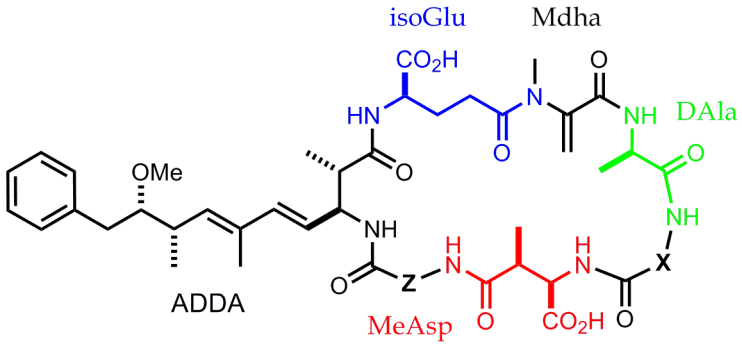


Figure 10. general structure of microcystins **XZ**.

Microcystins are most commonly represented in the literature by microcystin-LA and microcystin-LR variants (**Figure 15**) [the suffix identifies two variable L-amino acids found at two non-conserved positions in the macrocycle (e.g Leu and Arg in microcystin-LR)]. The general structure of these potent hepatotoxins is cyclo [-D-Ala-L-X-D-MeAsp-L-Z-ADDA-D-Glu-Mdha-] (**Figure 10**), which contains three D-aminoacids: Alanine (Ala), *erythro*-β-methylaspartic acid (MeAsp), glutamic acid (Glu), and two unusual amino acids: *N*-methyldehydroalanine (Mdha), and 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (ADDA). The two variable residues X and Z (**Figure 10**) can be occupied by a wide variety of L-amino acids with little effect on biological activity.[47] However, it should be noted that minor structural modifications have been detected in all seven amino acids units. Thus, a whole family of related heptapeptide cyanobacterial compounds exists through modification of amino acids.

3.4 - <u>The nodularins</u>

These cyclic pentapeptidic hepatotoxins (**Figure 11**) are closely related to microcystins, and are also known to be potent tumor promoters.[54] They have been isolated from the brackish water-dwelling filamentous cyanobacterium *Nodularia spumigena*,[55,56] and at least 10 variants have been reported to date.[57]

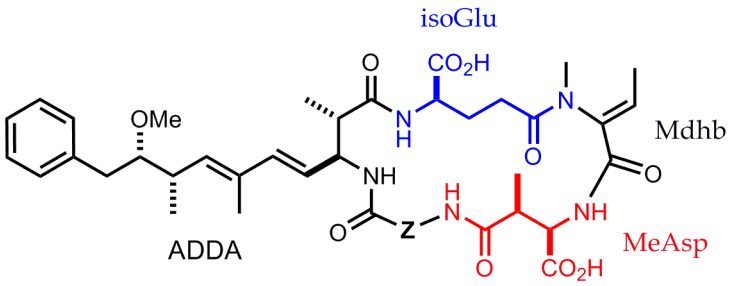


Figure 11. General Structure of Nodularins **Z**.

These cyclic pentapeptides are most commonly represented by the arginine variant nodularin-R, and bear a remarkable resemblance to the microcystins. They possess the ADDA subunit in addition to D-glutamate (D-Glu), L-araginine (Arg), D-β-methylaspartic acid (MeAsp) and D-*N*-methyl-dehydrobutyrin (Mdhb) (**Figure 11**). Structural variations characterised thus far include D-apartate nodularin, O-demethylAdda nodularin and L-valine nodularin (also known as nodularin-V or motuporin (**Figure 13**)). The lack of reliable and productive source of material is an obstacle for the accumulation of more information and very little is actually known about the biology of nodularins.

2.2.1 Motuporin

More recently, a major member of nodularins containing L-valine, and commonly named motuporin, was isolated from the marine sponge *Theonella swinhoei* collected from Papua New Guinea (**Figure 12**).[28] This discovery raised the possibility that cyanobacterial organism living in a symbiotic relationship with the marine sponge, may also account for this finding.[58] It has also been suggested that sponges and bivalves may accumulate cyanobacteria through filter feeding.

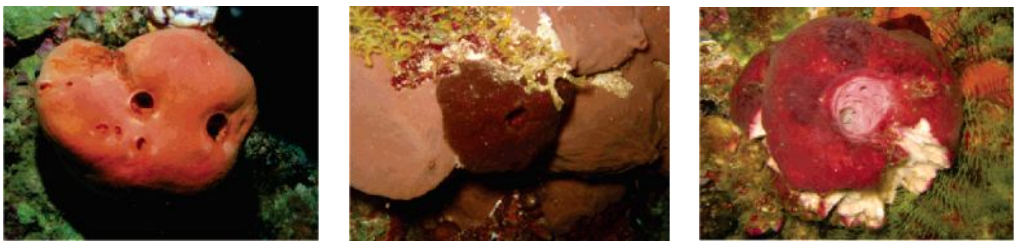


Figure 12. The three *Theonella swinhoei* phenotypes (with the kind permission of Prof. Phil Crews)[59]

This cyclic pentapeptide is one of the most potent PP1 inhibitors known, inhibiting at sub-nanomolar concentrations (IC_{50} < 1.0 nM), and showing strong *in vitro* cytotoxicity against a variety of human cancer cells. Motuporin shows remarkable resemblance with previous microcystins, as it contains the ADDA residue, but also an α,β-unsaturated amino acid N-methyldehydrobutyrine (N-MeΔBut or Mdhb), an isolinked D-glutamate, and a β–methyl D-aspartate (β-MeAsp or Masp) residue (**Figure 13**).

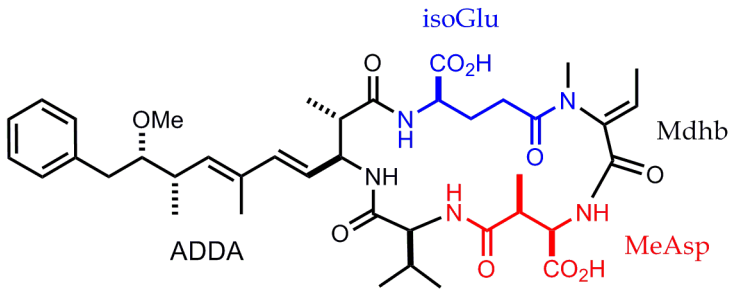
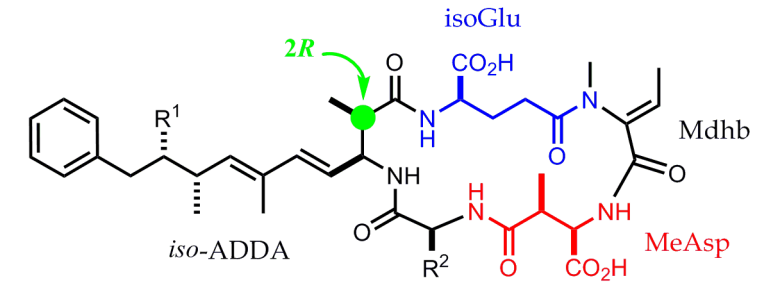


Figure 13. Motuporin (Nodularin-V).

Motuporin was isolated much later than other members of its class, and is derived from a much less readily accessible source. Consequently much of the information concerning its biology and chemistry is unknown.

2.2.2 Iso-motuporin

In 2007,[59] further investigations on the remarkably prolific Indo-Pacific *Theonella swinhoei* sponges (**Figure 12**), which had already originated motuporin,[28] shed further light on novel ADDA-containing analogues. Refinement of the observations published in 1998,[60] allowed isolating 15 natural compounds. 11 of them were already known such as motuporin, but more interestingly, 4 *iso*-motuporin analogues **A**, **B**, **C** and **D**, containing the (2*R*)-*iso*-ADDA residue, were identified (**Figure 14**).[59] Until now all the ADDA-containing inhibitors known, including microcystins, nodularins, and motuporin carried, with no exception, the (2*S*) stereochemistry (**Figure 13**).



(**A**) $R^1 = OCH_3$; $R^2 = CH(CH_3)_2$ (**B**) $R^1 = OCH3$; $R^2 = CH(CH_3)CH_2CH_3$

(**C**) $R^1 = OCH_3$; $R^2 = CH_2CH_3$ (**D**) $R^1 = H$; $R^2 = CH(CH_3)_2$

Figure 14. *iso*-motuporins **A**, **B**, **C** and **D**.

Due to the recent discovery, no biological or pharmaceutical work has been documented on ADDA isoforms, but their discovery reinforces the idea that more potent and selective PPIs can be generated from the chemical transformation of the ADDA chain.

4 - TOWARDS SIMPLIFIED ADDA-CONTAINING PPIs

Unlike PP2A which remains largely unknown, significant structural data has been accumulated about PP1 through the years.[43,61] The application of techniques such as Structure-Relation-Activity (SAR), and crystallographic studies of OA-class inhibitors with PP1 has provided major information regarding the chemical PPIs features required for binding interactions, and potent bioactivity (**Figure 15**).[62-66] The compilation of this information has led to the mapping of PP1, which has given crucial guidance for the modelling of novel PPIs,[67] which greatly inspired our own work.

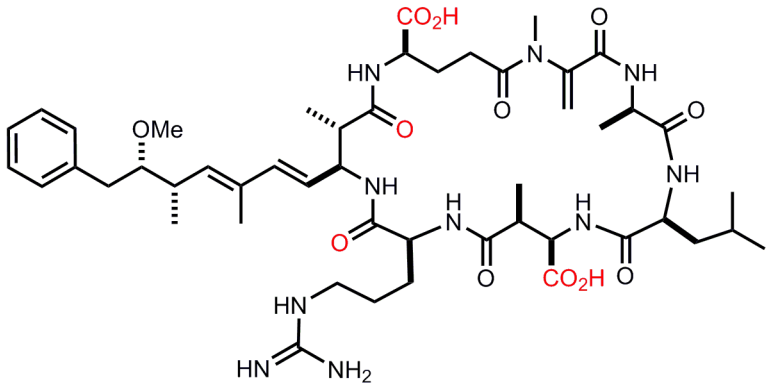


Figure 15. Microcystin-LR binding contacts necessary for interaction with PP1.

Despite the many naturally occurring PPIs that have been isolated, the number of substrates for available SAR studies has been restricted by the small quantities available through isolation, and by the limited types of chemical transformations that can be performed on the natural products themselves. Moreover, toxicity and bioactivity being considered as highly related, much of the biological data have been reported in the form of LD_{50}'s (general toxicity), and not IC_{50}'s (PP1/PP2A inhibition). Thus, the PP1/PP2A inhibition potency of many MCs is inferred from LD_{50} data, which obviously is only a crude estimate, and provides no information about the selectivity among the various phosphatases.

4.1 - First Structure-Activity-Relationship approach

The first approach taken to prepare MC and nodularin analogues has been to synthesize truncated or linear versions of the natural toxins by removing, or simplifying amino acid residues. Among the truncated derivatives, there have been two trains of thought. The first approach involved the replacement of ADDA with a simpler residue, while the second one started with ADDA, which is progressively extended in adding as little as necessary for binding.

The first reported attempt to make truncated MC analogues without ADDA, was by Abdel-Rahmen.[68] The Abdel-Rahmen group made three linear hexapeptides corresponding to three MCs they had isolated (MC-RR, MC-YM, and MC-LA). Compared to the respective natural products, these peptides had, in effect, excised ADDA, substituted Ala for Mdha, and substituted α-linked Arg for Masp. None of these compounds had any toxicity, implying (but not proving) that they are not PP1 or PP2A inhibitors.

Quinn has also reported a series of cyclic and acyclic analogues of the MCs and nodularins.[69,70] In all of the compounds, ADDA was substituted by either β-alanine or L-cysteine. The *iso*-linked D-Glu and β-methyl-D-aspartate were also replaced with D-glutamate or D-aspartate, along with other changes. Most of these analogues showed no inhibition of PP2A, with a few having IC_{50}'s in the low millimolar range (0.5 mM < IC_{50} < 10 mM). Of the four most active compounds, three were cyclic and one was linear, tending to prove that the macrocylic structure was important, but not essential for toxicity. Overall

however, the inhibitory activity of all of these analogues against PP2A was very poor and, no further analogues were designed.

Later, Chamberlin[67b,71] prepared, and tested a series of truncated analogues as small as possible that could conserve potent inhibitory activity. Chamberlin's approach, based on published crystallographic structures, demonstrated that the majority of the important contacts within the protein could be retained, even if most of the macrocycle was removed. However, it remained unclear how much of the parent structure could be excised without losing activity. Thus, Chamberlin decided to begin with the known, active tetrapeptide **3** (H_2N-ADDA-isoGlu-Mdha-Ala-OH) (**Figure 16**), and gradually build up the structure. The initial targets were AcNH-ADDA-isoGlu-NMe_2, AcNH-ADDA-D-Ala, and AcNH-ADDA-Gly.

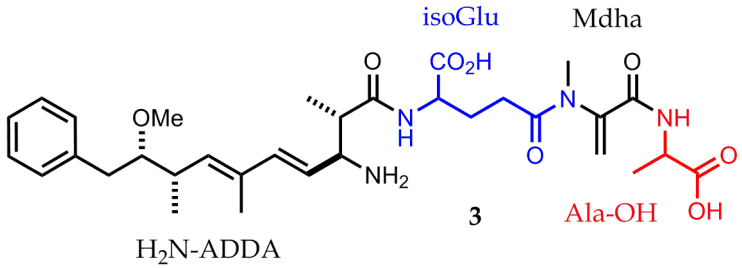
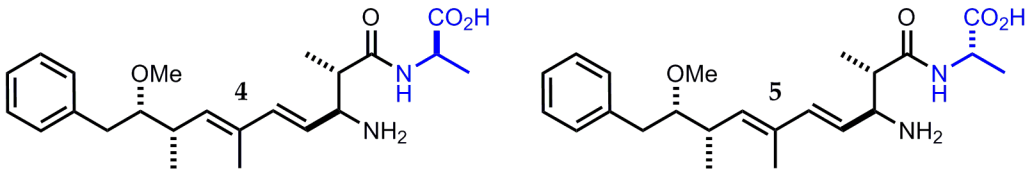


Figure 16. structure of tetrapeptide **3**.

Chamberlin's compounds were evaluated as inhibitors of the catalytic subunit of both PP1 and PP2A, and the results showed that all analogues retained inhibitory activity. However, the variants were several orders of magnitude less potent than the parent inhibitor, MC-LA, as well as tetrapeptide **3**. Nevertheless, the shortest peptide **4** (AcNH-ADDA-D-Ala), which bears the strongest resemblance to the parent compound of the analogues generated, retained high inhibitory potency (**Figure 17**). Interestingly, all derivatives showed partial selectivity for PP2A over PP1. The most PP2A selective, which is also the poorest inhibitor, was the "unnatural" L-alanine-containing variant **5**, while the D-alanine variant **4** was the most potent and least selective of the group (**Figure 17**).



IC_{50} (PP1 : PP2A) = 1.0 µM : 0.16 µM IC_{50} (PP1 : PP2A) = 170 µM : 7.8 µM

Figure 17. Respectively D-alanine variant **4** and L-alanine variant **5**.

The potency of the D-alanine containing variant was in the useful range, and this analogue has become the basis for the design, and synthesis of second-generation truncated MC analogues. These results demonstrated the importance of the stereochemistry for the bioactivity of ADDA-containing analogues, which reinforces our idea according to which ADDA-isoforms might lead to the discovery of more potent and selective PPIs.

4.2 - Second Structure-Activity-Relationship approach

The second approach to preparing MCs and nodularins analogues has been to synthesize "full-sized", but non-natural versions of the toxins containing specifically modified amino acids.

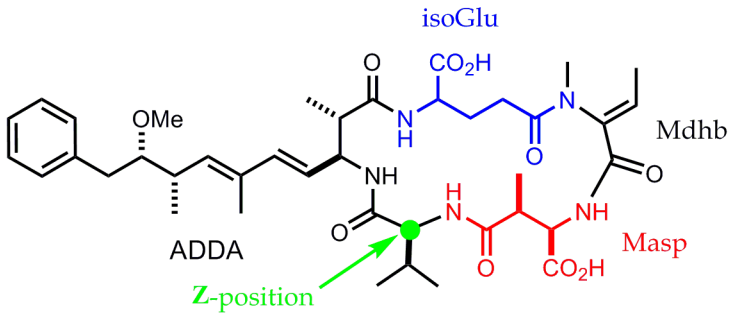


Figure **18**. motuporin (Nodularin-V).

Toogood[72] used his synthesis of motuporin (**Figure 18**) as a platform for making analogues in which L-alanine replaced the Mdhb residue, *via* "chemical mutation" at specific positions.[72] This change was paired either with D- or L-valine at the variable position Z (**Figure 18**). The analogue **6** (**Figure 19**) with L-valine inhibited PP1 less potently than motuporin (IC_{50} motuporin = 1 nM). This observation makes sense given the natural variations at this position in both the nodularins and MCs appear to have little effect on toxicity. Similarly, analogue **7** (**Figure 19**), in wich D-valine is at the variable position also

retained nanomolar activity (IC_{50} 37.8 nM), reinforcing the idea that substantial structural variation is well-tolerated at this position.

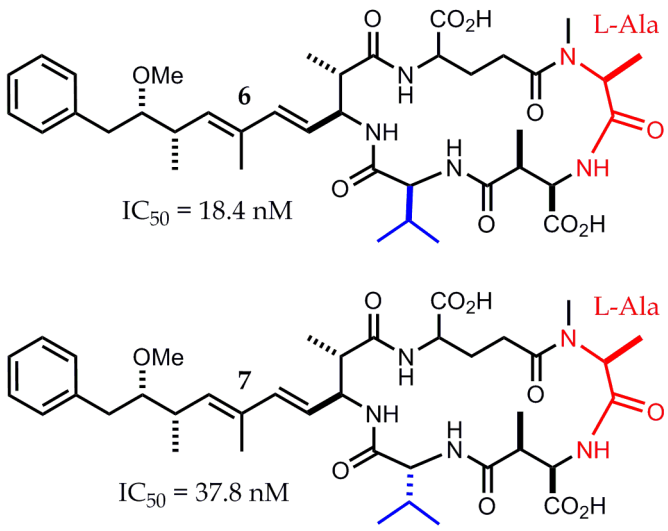


Figure 19. Full-sized variants **6** and **7** respectively.

The Chamberlin group has also made several "full-sized" non-natural variants of the MCs.[73] The goal, in this case, was not just to prepare new inhibitors for SAR studies, but especially to impart selectivity for PP1 over PP2A to these analogues, as the nodularins and MCs, for all of their variety, are essentially non-selective for PP1 *versus* PP2A. Gratifyingly, each of the compounds showed slightly better selectivity towards PP1, hence proving that chemical modifications can help direct the selectivity of MCs and nodularins towards PP1 or PP2A.

4.3 - Summary of Structure-Activity-Relationship results

The vast number of SAR experiments conducted on OA-class inhibitors over the past decades has allowed the accumulation of priceless information concerning the design of novel protein phosphatase inhibitors. McCluskey,[67c] published a very clear and concise review presenting a straightforward scale of the inhibitory activity of the key analogues generated for SAR studies. This scale gives a good overview of what must be kept in mind.

The SAR studies brought precious information, which confirmed that truncated or modified ADDA-containing inhibitors can retain potent bioactivity. These observations reinforced our idea according to which minor modifications of ADDA isoforms, would lead to the discovery of small inhibitors, possessing potent and selective inhibitory activity, but which could be synthesised in large amounts.

5 – OUR PROPOSED STRATEGY

As discussed so far, ADDA-containing protein phosphatase inhibitors have been generating an extraordinary amount of work through the past years. Despite the large number of promising results accumulated, as far as we know, no ADDA analogue combining potent inhibitory activity with high selectivity towards the different classes of PP has been developed yet.

We believe that isomeric ADDA-containing analogues might display unexpected and significant biological activities. It should be noted that, whereas many syntheses have been designed towards (2*S*,3*S*,8*S*,9*S*)-ADDA,[72,75-87] no work has been reported on the synthesis of enantiomeric ADDA, or any other isomeric forms. Hence, we decided to synthesise the *enantio*-ADDA chain through a novel convergent strategy, which can also be used to generate the naturally occurring (2*S*,3*S*,8*S*,9*S*)-ADDA isomer. We would also like to report the very first synthesis of *enantio*-*iso*-ADDA, which has been recently discovered as its *iso*-motuporin form.[59]

The final goal of this project will be the preparation of short ADDA analogues, which we hope will help in the development of novel, easy-to-make and potent PPIs, which will be used to extend our understanding of protein phosphatase pathways.

INTRODUCTION

------- PART II – CHEMICAL INTRODUCTION -------

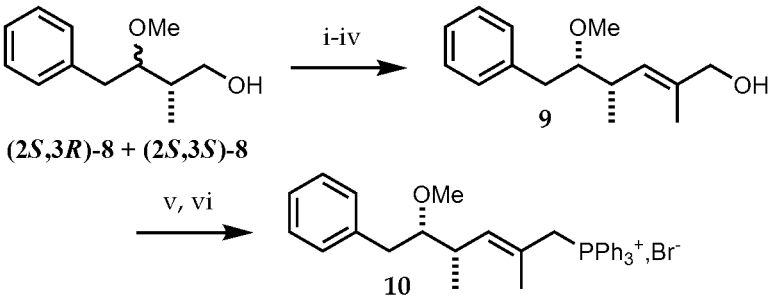
1 - PREVIOUS REPORTED SYNTHESES

The interesting biological properties of the MCs and nodularins have prompted a number of synthetic studies. Thus far, the synthesis of the unique amino acid ADDA has generated the most interest. Since the absolute stereochemistry of the aliphatic chain was elucidated,[32] 14 different syntheses have been reported.[72,74-86] The synthetic challenges include efficient selective formation of the (*E*,*E*)-diene, and the establishment of the four non-contiguous stereogenic centers in a reasonable number of steps.

1.1 - Rinehart's approach[74]

The first total synthesis of the (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8,-trimethyl-10-phenyl-4,6-decadienoic acid (ADDA) was reported by K. L. Rinehart in 1989.[74] The ADDA chain was prepared *via* a convergent synthesis involving purification by HPLC techniques to separate the different diastereoisomers generated.

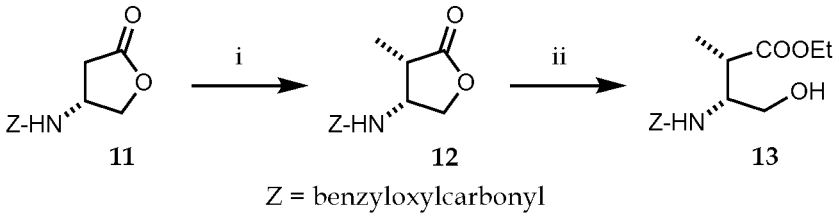
Rinehart's synthesis started from a diasteroisomeric mixture of alcohols **(2*S*,3*R*)-8** and **(2*S*,3*S*)-8**, which was used as a (1:1) mixture of diastereoisomers. A sequence including oxidation, Wittig olefination, and lithium aluminium hydride reduction afforded a diastereoisomeric mixture of allylic alcohol **9**. Separation by preparative HPLC allowed the isolation of the (4*S*,5*S*)-isomer **9**, which was then converted into the corresponding triphenylphosphonium bromide **10** in 35% overall yield and 6 steps in total (**Scheme 4**).



Reagents and conditions **i**, PDC, DCM; **ii**, $Ph_3P{=}C(CH_3)COOEt$, PhMe, 81% from **1**; **iii**, $LiAlH_4$, THF, 91%; **iv**, HPLC separation, 50%; **v**, PPh_3, CBr_4, MeCN; **vi**, PPh_3, MeCN, 94%.

Scheme 4. Synthesis of triphenylphosphonium bromide **10**.

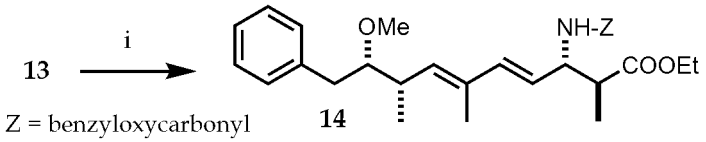
The synthesis of the amino acid partner began with the optically active γ-butyrolactone **11**, which was methylated to generate a (4:1) mixture of diastereoisomers, which could be separated by flash column chromatography. The minor diastereoisomer could be efficiently isomerised to the desired (2*S*,3*R*)-isomer **12** by heating it in a mixture of benzene/triethylamine over 2 days. The γ-butyrolactone **12** was then hydrolysed under basic conditions, and subsequently esterified to produce the ethyl ester **13** in 39% overall yield over the 2 steps (**Scheme 5**).



Reagents and conditions **i**, LDA, THF, -78 °C then MeI, 54%; **ii**, NaOH, MeOH then EtI, $KHCO_3$, DMF, 88%.

Scheme 5. Synthesis of the alcohol **13**.

Alcohol **13** was then oxidized to the corresponding aldehyde, which was coupled with phosphonium bromide **10** *via* a Wittig olefination, to give the protected ADDA chain **14** in 43% yield (from **13**) (**Scheme 6**). Although no details were given regarding the generation of undesired (*Z*)-isomers, their formation was confirmed, as expected, by further literature examples.[72,75,76,84,85]



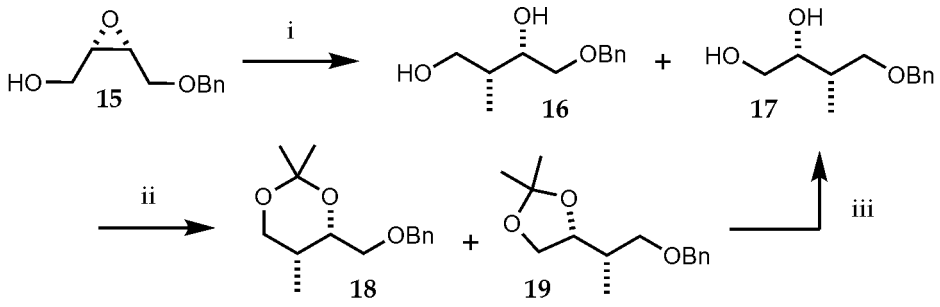
Reagents and conditions **i**, Swern, then **10**, DME, *n*-BuLi, 43% from **13**.

Scheme 6. Synthesis of the protected ADDA **14**.

Rinehart's 7 steps synthesis provided the ADDA derivative **14** in a respectable 17% overall yield, but also and above all, provided a useful platform from which further optimized synthesis were designed.

1.2 - Chakraborty's approach[75]

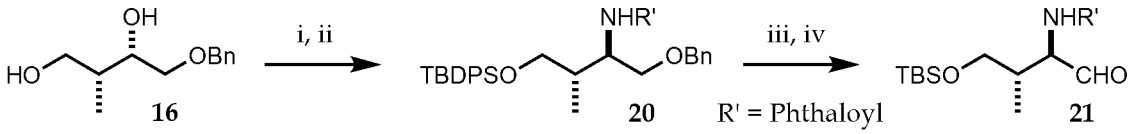
The second synthesis of the ADDA residue was proposed by T. K. Chakraborty in 1990.[75] A convergent approach, involving the coupling of two partners *via* a Wittig olefination was also utilised.[74] In Chakraborty's synthesis, both ADDA fragments originated from epoxide **15**, which was opened with Me_2CuLi to generate diols **16** and **17**. Both diols were ketal protected, and subsequently separated by flash column chromatography. Treatment of acetonides **18** and **19** in acidic conditions allowed re-generating diols **16** and **17** separately in 63% and 86% respectively over the three steps (**Scheme 8**).



Reagents and conditions **i**, a) Me_2CuLi, Et_2O, -40 °C or b) Me_3Al, DCM, 0 °C; **ii**, $Me_2C(OMe)_2$, PTSA; **iii**, Et_2O, HCl.

Scheme 8. Synthesis of diols **16** and **17**.

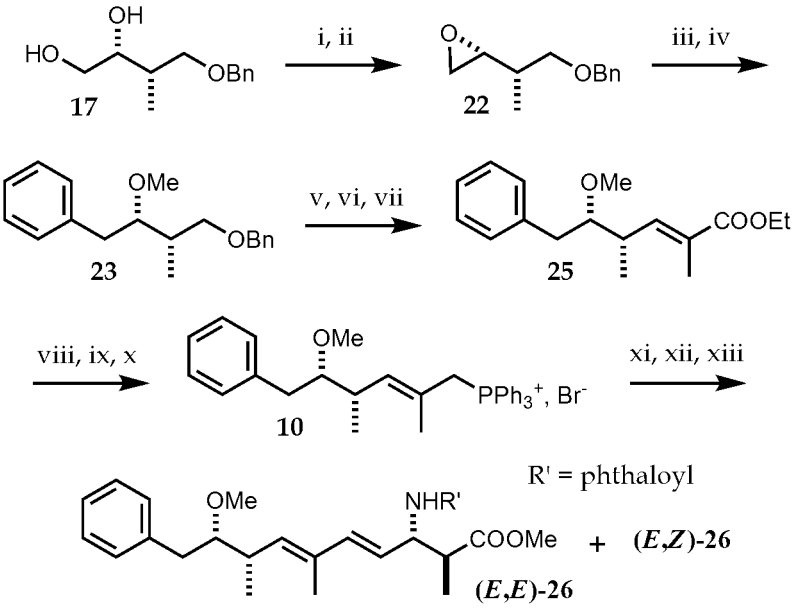
The synthesis of the amino partner **21** started from diol **16**, which was mono-protected. The remaining secondary alcohol was subjected to a Mitsunobu transformation, and the benzyl group of the protected alcohol **20** was removed. The resulting alcohol was oxidised to aldehyde **21**, which was isolated in 41% overall yield and 7 steps from epoxide **15** (**Scheme 9**).



Reagents and conditions **i**, ^{t}-$BuPh_2SiCl$, imidazole, DMF; **ii**, Phtalimide, DEAD, PPh_3, THF, 72% (2 steps); **iii**, Pd/C, H_2, EtOH; **iv**, Swern, 90% (2 steps).

Scheme 9. Synthesis of aldehyde **21**.

The synthesis of the aryl containing partner involved the use of diol **17**, which was regioselectively turned into the mono tosylate, and subsequently cyclised into the corresponding epoxide **22**. Addition of phenyl magnesium bromide onto the epoxide, followed by methylation of the resulting alcohol, led to the formation of ether **23**. Removal of the benzyl group, followed by a subsequent Swern oxidation, and a Wittig olefination, afforded the (*E*)-conjugated ester **25**, plus 8% of the (*Z*)-isomer (**Scheme 10**). The ester **25** was subsequently converted to the corresponding phosphonium salt **10** through a classical 3 steps sequence. Finally, the phosphonium salt was deprotonated, and then coupled to the aldehyde **21** *via* the same Wittig olefination used by Rinehart.[74] The *O*-TBS diene was deprotected, and the resulting alcohol was oxidised to the carboxylic acid, and quenched with diazomethane to form the methyl ester **26** (**Scheme 10**).



Reagents and conditions **i**,TsCl, pyridine; **ii**, MeONa, MeOH, 76% (2 steps); **iii**, PhMgBr, CuI, Et_2O; **iv**, NaH, MeI, THF, 80% (2 steps); **v**, Pd/C, H_2, EtOH; **vi**, Swern; **vii**, $Ph_3P{=}C(CH_3)COOEt$, PhH, 57% (3 steps); **viii**, DIBAL-H, DCM; **ix**, CBr_4, PPh_3, DCM; **x**, PPh_3, MeCN, 60% (3 steps); **xi**, *n*-BuLi then **7**, 39%; **xii**, HF-pyridine; **xiii**, Jones oxidation then CH_2N_2 (no yields provided).

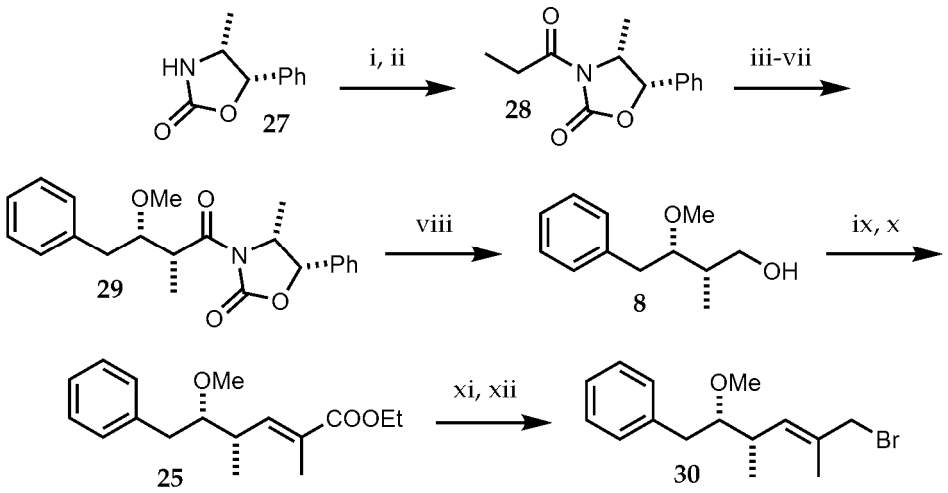
Scheme 10. Synthesis of ADDA derivative ***(E,E)*-26**.

It is worth noticing that the Wittig reaction provided the diene in 55% yield, and as a 7:3 mixture of isomers ***(E,E)*-26** and ***(E,Z)*-26**. The final ADDA methyl ester ***(E,E)*-26** was isolated in 7% overall yield over 20 steps in total.

1.3 - Beatty's approach[76]

V. F. Beatty's ADDA synthesis[76] is closely related to that of K. L. Rinehart.[74] Although parts of the synthesis were similar, the two coupling units were prepared in a stereocontrolled manner, and thus did not require the use of HPLC techniques to separate unwanted diastereoisomeric side products.

The synthesis of the left hand side partner took advantage of Evan's chiral oxazolidine template methodology to generate alcohol **8** as a single diastereoisomer. The rest of the synthesis was the same as proposed by Rinehart,[74] giving allylic bromide **30** in 11% overall yield (**Scheme 11**). Importantly, for the first time, Beatty[76] demonstrated the occurance of epimerisation during the Wittig olefination, resulting in the formation of small amount of undesired of C_4-epimerised (4*R*,5*S*)-ester from (4*S*,5*S*)-ester **25**. Furthermore, the same Wittig olefination also provide (4.5:1) (*E*)- and (*Z*)-isomeric mixture of ester **25**.

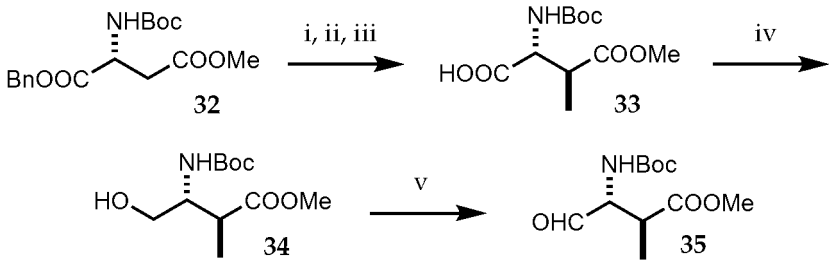


Reagents and conditions **i**, BuLi, THF; **ii**, EtCOCl, THF, 92%; **iii**, $Bu_2BOSO_2CF_3$, DIPEA, DCM; **iv**, DIPEA, DCM; **v**, phenylacetaldehyde; **vi**, H_2O_2, MeOH, 73%; **vii**, Me_3O^+,BF_4^-, proton sponge, 60%; **viii**, $LiBH_4$, 64%; **ix**, $Py.SO_3$, DMSO, 73%; **x**, $Ph_3P{=}C(CH_3)COOEt$, DMF, 70%; **xi**, DIBAL-H, THF, 94%; **xii**, PPh_3, CBr_4, Et_2O, 74%.

Scheme 11. Synthesis of allylic bromide **5**.

The synthesis of the right hand side unit started from the enantiomerically pure aspartic acid derivative **32**. Its non-diastereoselective methylation gave a (1:1.3) mixture of *erythro vs threo* diastereoisomers, where the major compound was the unwanted *threo*. The two isomers were separated, and the benzyl ester was cleaved to afford the carboxylic acid **33**.

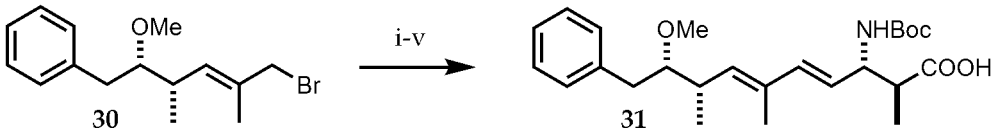
The acid **33** was reduced to the corresponding alcohol **34**, which was finally oxidized to the aldehyde **35** as a single diastereoisomer after 5 steps in 7% overall yield (from **32**) (**Scheme 12**).



Reagents and conditions **i**, LHMDS, THF, -78 °C; **ii**, MeI, THF; **iii**, H_2/Pd, MeOH; **iv**, BH_3·THF, MeOH, 0 °C; **v**, Py.SO_3, DMSO, TEA.

Scheme 12. Synthesis of aldehyde **35**.

Both partners were taken on crude, and coupled *via* the same Wittig olefination previously used by other workers.[74,75] The outcome of the reaction was proved to be a mixture of four geometric isomers. Purification by preparative TLC afforded the fully protected ADDA in a modest 30% yield, which was then converted to the *N*-Boc carboxylic acid **31** after 14 steps in total (**Scheme 13**).



Reagents and conditions **i**, PPh_3, PhH; **ii**, BuLi, THF; **iii**, **35**, THF, 0 °C; **iv**, NH_4Cl, 30%; **v**, NaOH, MeOH, 83%.

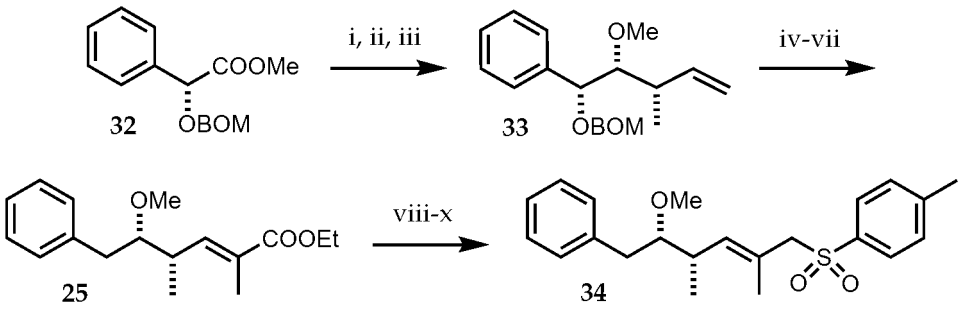
Scheme 13. Synthesis of *N*-Boc-ADDA **31**.

In spite of the very modest 2% overall yield, the work reported by V. F. Beatty[77] gave a large amount of precious information, which has been extremely useful for all future work realised on the ADDA chain.

1.4 - Schreiber's approach[77]

In 1995, S. L. Schreiber[77] reported a novel synthesis of the ADDA chain, together with the first total synthesis of motuporin. Schreiber designed a convergent and efficient approach, in which all of the motuporin stereocenters are derived from the chiral pool, and from either common amino acids or D-mandelic acid.

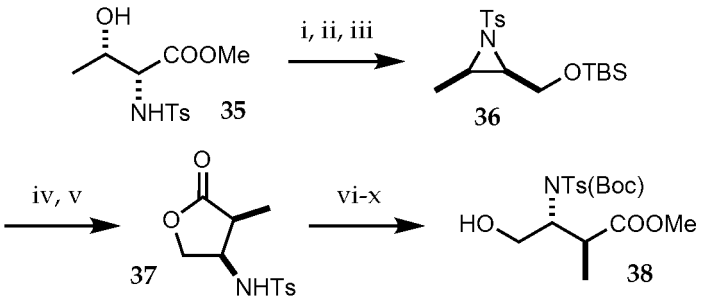
In the Schreiber's synthesis, all the stereocenters of the ADDA fragment were installed through a Lewis acid promoted crotylstannane addition to benzyloxymethyl-protected mandelaldehyde. No details were given regarding the diastereoselectivities of the crotylstannane addition, the removal of the benzyloxymethyl protecting group, or the problems encountered by previous workers on the selectivity of the Wittig olefination.[75,76] The chain was then elaborated by standard methods to give sulfone **34** in 10 steps, and an excellent 30% overall yield (from **32**) (**Scheme 14**).



Reagents and conditions **i**, DIBAL-H; **ii**, crotylstannane, $MgBr_2$, Et_2O, 74% (2 steps); **iii**, NaH, MeI, 98%; **iv**, OsO_4, NMO; **v**, H_2, Raney Ni, EtOH; **vi**, $NaIO_4$; **vii**, $Ph_3P{=}C(CH_3)COOEt$, 68% (4 steps); **viii**, $LiAlH_4$, 77%; **ix**, Ms_2O, pyridine; **x**, $Na(CH_3C_6H_4SO_2)$, Bu_4NBr, DME, 78% (2 steps).

Scheme 14. Synthesis of sulfone **34**.

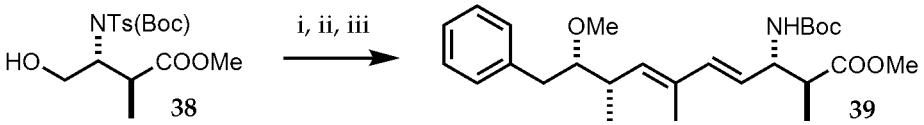
The synthesis of the aminoacid partner was inspired by Rinehart's work.[74] Protected D-threonine **35** was nicely converted to γ-butyrolactone **37** in five steps through the intermediate tosylaziridine **36**. The γ-butyrolactone **37** was the same used by Rinehart,[74] but this time, it was generated as a single enantiomer without requiring any HPLC purification. The lengthy process, due to the numerous protection/deprotection steps, yielded alcohol **38** in an excellent 60% overall yield over 10 steps (**Scheme 15**).



Reagents and conditions **i**, Ms_2O, pyridine; **ii**, $NaBH_4$, THF, EtOH; **iii**, TBSCl, DIEA, DMAP; **iv**, NaCN, DMSO; **v**, HCl, MeOH, 81% (2 steps); **vi**, $Ba(OH)_2$; **vii**, CH_2N_2; **viii**, TBSCl, DIEA, DMAP; **ix**, Boc_2O, DMAP; **x**, HCl, MeOH, 93% (5 steps).

Scheme 15. Synthesis of alcohol **38**.

A (*E*,*E*)-stereoselective diene-forming coupling was achieved through an alternative to the Wittig olefination[74-76] for the first time. A modified Julia coupling between sulfone **34** and the aldehyde resulting from the Swern oxidation of alcohol **38**, was followed by the treatment with sodium naphthalene, which gave protected ADDA **39**. Ester hydrolysis was conducted to give the carboxylic acid form, which was taken on crude to generate motuporin (nodularin-V) (**Scheme 16**).



Reagents and conditions **i**, Swern; **ii**, BuLi, THF, -78 °C then **34**; **iii**, NaNapthalene, THF -78 °C, 65% (3 steps).

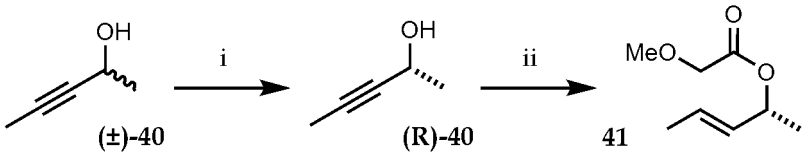
Scheme 16. Synthesis of *N*-Boc-ADDA methyl ester **39**.

Schreiber[77] reported the first synthesis of the ADDA chain involving an (*E*,*E*)-stereoselective coupling reaction. The ADDA derivative **39** was obtained as a single isomer after 23 steps in total, and in an excellent overall yield of 20%.

1.5 – Toogood's approach[78]

Toogood completed the enantioselective synthesis of *N*-Boc-ADDA,[78] using similar partners coupled through the same Wittig olefination, used previously by other groups.[74-76] However, each of the partners originated from a common precursor through a shorter approach.

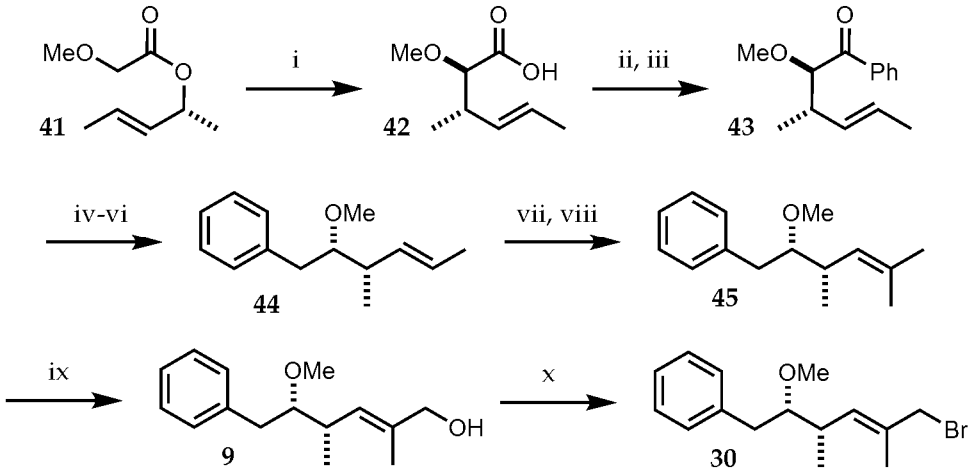
Toogood's synthesis began with the propargylic alcohol 3-pentyne-2-ol **(±)-40**, which was resolved to access the (*R*)-alcohol **(*R*)-40**, and the (*S*)-alcohol **(*S*)-40** separately. Each alkynol was reduced and esterified with methoxyacetyl chloride, providing *R*- and *S*-esters **41** (**Scheme 17**), which underwent an ester enolate Claisen rearrangement to yield both enantiomers of the acid **42** (**Scheme 18**).



Reagents and conditions **i**, resolution then Na, NH_3, Et_2O, 90%; **ii**, methoxyacetyl chloride, pyridine, DCM, 83%.

Scheme 17. Synthesis of ester **41**.

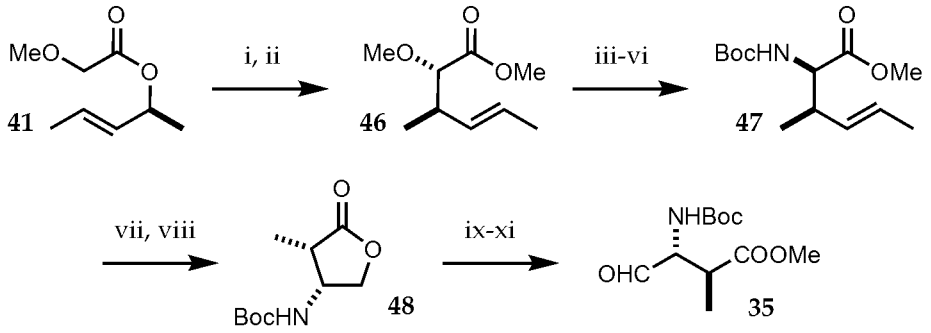
Synthesis of the aromatic-containing unit started from carboxylic acid **42**, which was initially converted to phenyl ketone **43**, which was in turn reduced to alkene **44**. Ozonolysis of the olefin **44**, followed by a Wittig olefination then produced the trisubstituted olefin **45**. The akene **45** was then oxidized regioselectively by selenium dioxide to give the (*E*)-allylic alcohol **9** exclusively. It is worth mentioning that if this sequence avoided the formation of the (*Z*)-double bond isomer, nothing was reported concerning the epimerization of the C_4 stereocenter observed by Beatty.[76] The alcohol **9** was finally converted into the corresponding bromide **30** after 7 steps, and 20% overall yield (from (*R*)-3-pentyne-2-ol **(*R*)-40**) (**Scheme 18**).



Reagents and conditions **i**, KHMDS, TMSCl, THF, 81%; **ii**, $Ph_2P(O)Cl$, $CH_3NH(OCH_3)$, THF, 95%; **iii**, PhMgBr, THF, 85%; **iv**, $NaBH_4$, 97%; **v**, PhOC(S)Cl, pyridine, DCM, 90%; **vi**, AIBN, nBu_3SnH, PhMe, 90%; **vii**, O_3, DMS, MeOH, 86%; **viii**, $Ph_3P{=}C(CH_3)_2$, THF, 80%; **ix**, SeO_2, EtOH then $NaBH_4$, 78%; **x**, PPh_3, CBr_4, Et_2O, 74%.

Scheme 18. Synthesis of allylic bromide **30**.

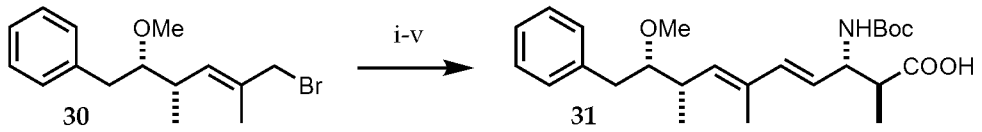
The synthesis of the amino partner started with methyl ether **41**, which was reacted with LiHMDS, followed by diazomethane to generate methoxyester **46**. The resulting ester **46** was converted to the *N*-Boc protected amine **47** through a 4 steps sequence involving the use of a Mitsunobu substitution, with inversion of configuration (**Scheme 19**). Reduction of ester **47**, followed by ozonolysis in methanol provided the lactone **48** in good yield. The lactone hydrolysis, followed by esterification of the resulting carboxylic acid, and Swern oxidation of the primary alcohol, generated the desired aldehyde **35** over a total of 6 steps, and in 10% overall yield (from (*S*)-3-pentyne-2-ol **(*S*)-40**) (**Scheme 19**). Other alternatives were also reported, leading to the same aldehyde **35** with similar ease and effectiveness.



Reagents and conditions **i**, LiHMDS, TMSCl, THF, 81%; **ii**, CH_2N_2, Et_2O, 100%; **iii**, BBr_3, DCM, 65%; **iv**, DEAD, DPPA, THF; **v**, PPh_3, H_2O, THF; **vi**, $(Boc)_2O$, 60% (3 steps); **vii**, $LiBH_4$, MeOH; **viii**, O_3, NaOH, MeOH, 63% (2 steps); **ix**, NaOH, MeOH, H_2O; **x**, CH_2N_2, DCM; **xi**, Swern, 68% (2steps).

Scheme 19. Synthesis of aldehyde **35**.

Finally, both allylic bromide **30** and the aldehyde **35** were coupled through the Wittig olefination sequence previously employed, and was followed by saponification of the methyl ester **31** (**Scheme 20**).



Reagents and conditions **i**, PPh_3, PhH; **ii**, BuLi, THF; **iii**, **14**, THF, 0 °C; **iv**, aq. NH_4Cl, 30%; **v**, NaOH, MeOH, 83%.

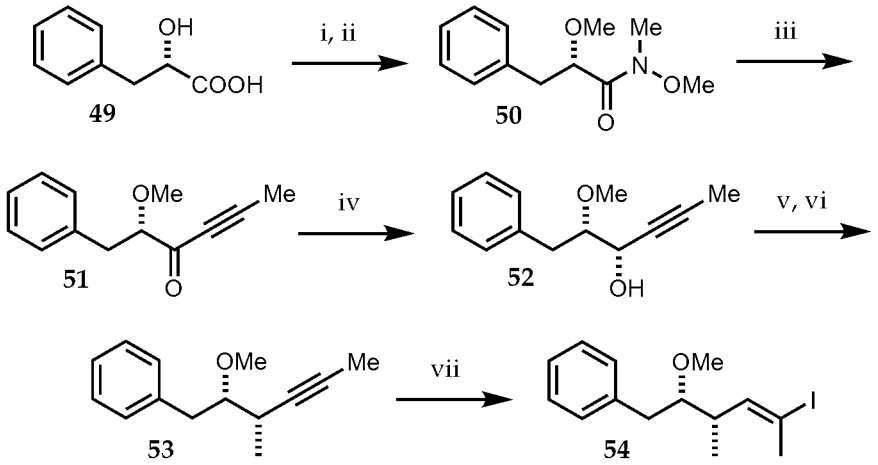
Scheme 20. Synthesis of the *N*-Boc-ADDA **31**

The *N*-Boc-ADDA **31** was successfully isolated after a total of 16 steps, and 3% overall yield (excluding the resolution of racemic 3-pentyne-2-ol **(±)-40**). It is worth noticing the inefficiency of the Wittig olefination[74-76,78] compared to the previously reported (*E*,*E*)-stereoselective Julia coupling.[77]

1.6 – Mann's approach[79]

The approach followed by A. Mann[79] in his convergent synthesis of the *N*-Boc-ADDA marked a turning point in the total synthesis history of the ADDA chain, as it was the first time that a palladium-catalysed coupling was employed to form the (*E*,*E*)-1,3-diene system selectively.

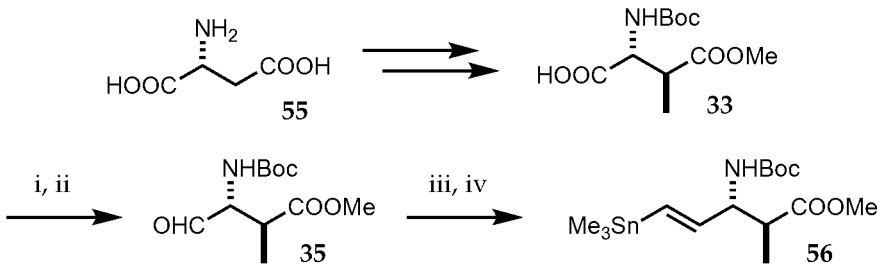
The synthesis of the aryl containing partner started from readily accessible (*S*)-phenyllactic acid **49**. Acid **49** was transformed into the Weinreb amide **50**, which was then converted into propargylic ketone **51** (**Scheme 21**). A *syn*-stereoselective reduction of ketone **51** was achieved in using K-Selectride to generate alcohol **52**. The resulting alcohol **52** was then turned into the corresponding bromoallene intermediate, which was reacted with MeCuCNLi to provide the desired alkyne **53**, plus 5% of undesired *trans*-diastereomer of **53**. After separation of the two isomers, alkyne **53** was subjected to a hydrozirconation, and quenched with iodine to generate selectively the (*E*)-iodide **54** after 7 steps, and in 17% overall yield (**Scheme 21**).



Reagents and conditions **i**, *N*,*O*-dimethylhydroxylamine·HCl, TEA, pyBOP, DCM, 81%; **ii**, MeI, Ag_2O, DMF, 88%; **iii**, MeC≡CLi, THF, -78 °C, 89%; **iv**, K-Selectride, THF, -100 °C, 72%; **v**, BuLi, LiBr, TsCl, THF, then CuBr·DMS, LiBr, -60 °C, 75%; **vi**, MeCuCNLi, THF, -78 °C, 72%; **vii**, $Cp_2ZrCl(H)$, PhH, 43 °C, then I_2 in CCl_4, 70%.

Scheme 21. Synthesis of iodoalkene **54**.

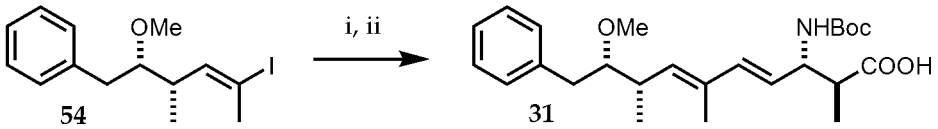
The synthesis of the amino partner began with acid **33**, which was accessed from the commercially available (*R*)-aspartic acid **55**. Acid **33** was converted to the corresponding ethylthioester, which was subsequently reduced to aldehyde **35**, in turn transformed into stannane **56**. The Stille partner **56** was thus obtained through a quick 4-step sequence in excellent 37% overall yield (from acid **33**) (**Scheme 22**).



Reagents and conditions **i**, EtSH, DCC, DMAP, DCM, 81%; **ii**, Et_3SiH, Pd/C, acetone, 82%; **iii**, CHI_3, $CrCl_2$, THF, 75%; **iv**, $(Me_3Sn)_2$, $Pd(PPh_3)_4$, THF, 74%.

Scheme 22. Synthesis of stannane **56**.

Vinyl iodide **54** and stannane **56** were coupled *via* a palladium-catalysed Stille coupling which provided the ADDA methyl ester derivative in a modest 58%, but with excellent (*E*,*E*)-regioselectivity (5% of the (*E*,*Z*)-isomer was still observed). A final saponification provided the carboxylic acid **31** over a total of 13 steps and 7% overall yield (**Scheme 23**).



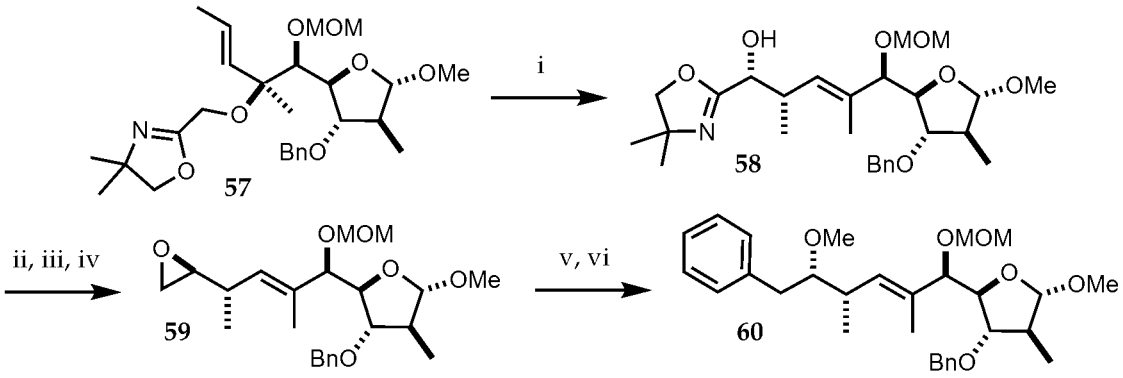
Reagents and conditions **i**, **56**, $PdCl_2(MeCN)_2$, DMF, 58%; **ii**, LiOH, DME, H_2O, 70%.

Scheme 23. Synthesis of *N*-Boc-ADDA **31**.

1.7 - Kallmerten's approach[80]

J. Kallmerten[80] reported the first linear asymmetric synthesis of *N*-trifluoroacetyl ADDA methyl ester **66** from the very inexpensive $_D$-glucose. This linear strategy had nothing in common with the previous reported ADDA syntheses, and took advantage of a [2,3] Wittig rearrangement to produce the ADDA chain as its *N*-trifluoroacetyl protected form.

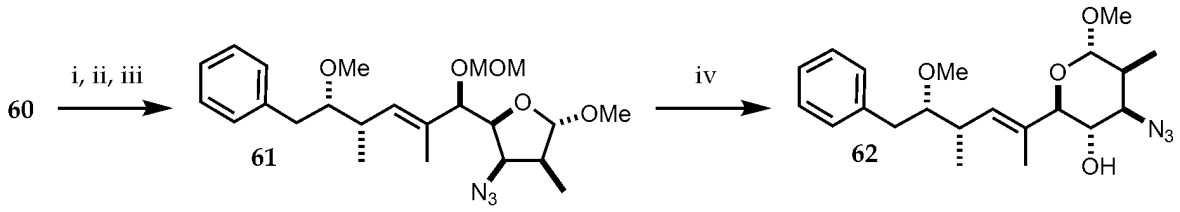
In Kallmerten's synthesis, the oxazoline **58** was accessed *via* the [2,3] Wittig rearrangement of the $_D$-glucose-derived tertiary ether **57**, made from D-glucose. Reductive cleavage of the oxazoline unit **58** afforded the corresponding diol, which underwent regioselective tosylation followed by base-induced cyclisation to furnish epoxide **59**. Introduction of the aryl subunit of ADDA was achieved by addition of phenyl Grignard reagent to **59** and *O*-methylation of the resulting alcohol yielded ether **60**, comprising the complete carbon framework of ADDA (**Scheme 24**).



Reagents and conditions **i**, BuLi, THF, -78 °C; **ii**, TFA, H_2O, THF then $LiAlH_4$; **iii**, TsCl, pyridine; **iv**, NaOH, MeOH, 83% (4 steps); **v**, PhMgBr, THF, 0 °C; **vi**, KH, MeI, DME, 83% (2 steps).

Scheme 24. Synthesis of ether **60**.

Deprotection of benzyl ether **60** afforded the corresponding alcohol, which was converted to the corresponding sensitive triflate, and treated with lithium azide in DMF to yield azide **61** (**Scheme 25**). Exposure of ether **61** to acidic methanol resulted in solvolytic cleavage of the methoxymethyl ether, followed by a thermodynamically driven furanose-to-pyranose conversion, which provided the anomeric pyranose **62** (**Scheme 25**) as the major component of a complex mixture of isomers.

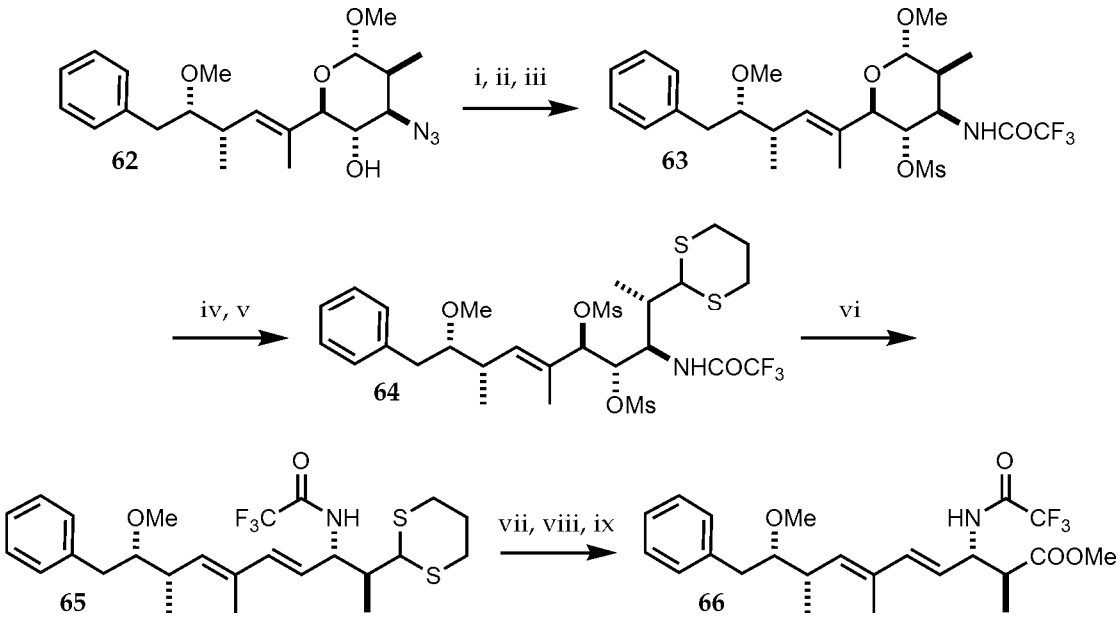


Reagents and conditions **i**, H_2, $Pd(OH)_2$, MeOH; **ii**, Tf_2O, pyridine, DCM, -20 °C; **iii**, LiN_3, DMF, 77% (3 steps); **iv**, HCl, MeOH, 50 °C.

Scheme 25. Synthesis of the alcohol **62**.

At this juncture, introduction of a halogen substituent at the C_4 position was necessary for the proposed *E*,*E*-diene-generating Vasella reductive halogenation. Despite of a broad variety of conditions attempted, the halogenated substrate could not be produced, forcing the authors to add additional steps to the 14-step approach initially envisaged.

In an alternative approach, the vicinal *bis*-mesylate **64** was prepared through a Lewis catalyzed thioketalization of mesylate **63**, to give the acyclic dithiane derivative, followed by mesylation of the remaining C_5 alcohol. Exposure of mesylate **64** to a THF solution of Na-anthracene, generated the desired (*E*,*E*)-diene **65** stereoselectively. Hydrolysis of the dithiane group yielded the corresponding aldehyde, which was then oxidised and esterified to the final ADDA methyl ester derivative **66** (**Scheme 26**) in 12% overall yield after 19 steps in total (from intermediate **57**).



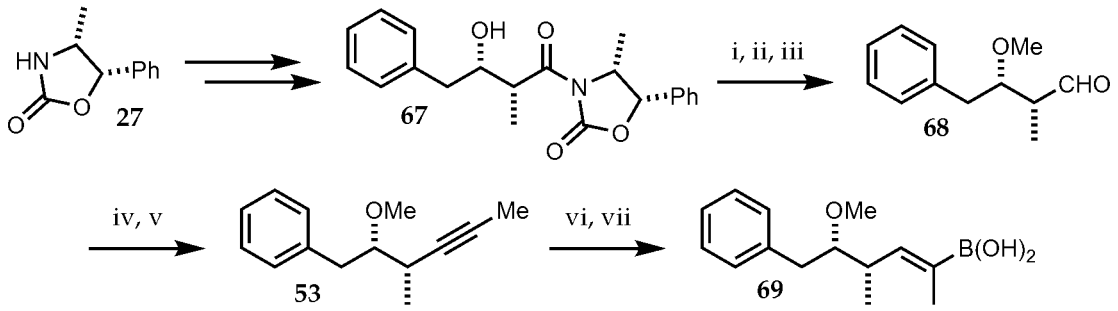
Reagents and conditions **i**, TFAA, pyridine; **ii**, H_2, Pd-C, EtOAc, 73% (2 steps); **iii**, MsCl, pyridine, 98%; **iv**, $BF_3.Et_2O$, $HS(CH_2)_3SH$, DCM; **v**, MsCl, pyridine, 45% (2 steps); **vi**, Na, anthracene, THF, 0 °C; **vii**, $AgNO_3$, MeCN, H_2O, 89%; **viii**, CrO_3, H_2SO_4, H_2O; **ix**, CH_2N_2, Et_2O, 0 °C, 91%.

Scheme 26. Synthesis of *N*-trifluoroacetyl ADDA methyl ester **66**.

1.8 - Chamberlin's approach[81]

In 1996, A. R. Chamberlin[81] reported the first total synthesis of Microcystin-LA including a new route towards the *N*-Boc-ADDA chain, involving a Suzuki coupling. This new convergent strategy was greatly inspired from the work described by A. Mann *et al.* in 1996.[79]

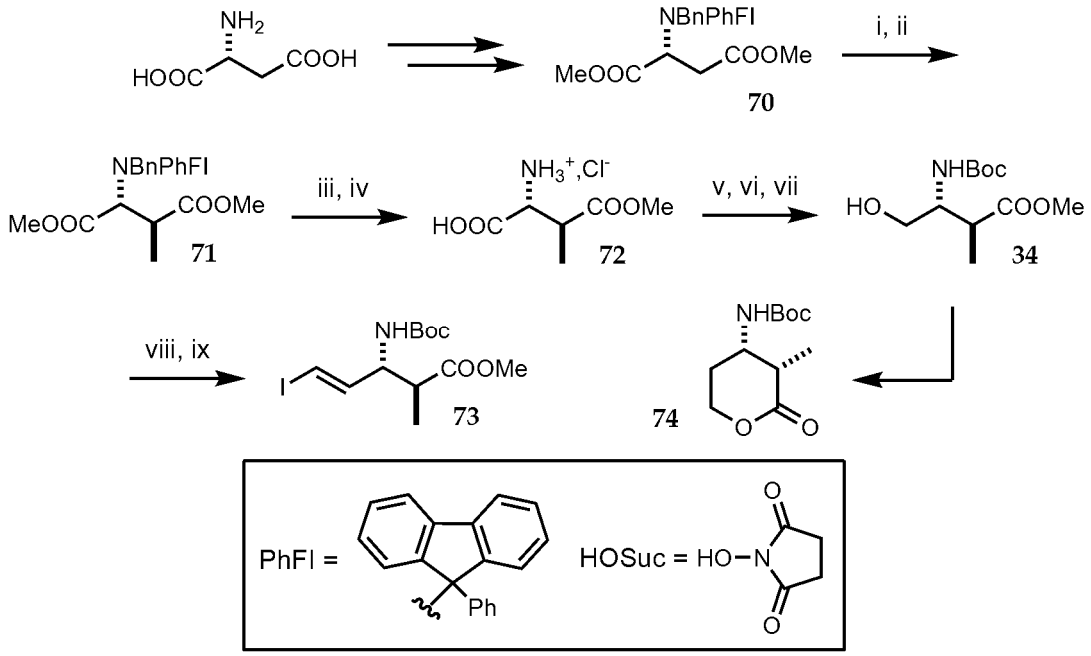
The synthesis of the aryl containing Suzuki partner began with the known Evans aldol product **67** originally synthesised by Beatty in 67% yield and 6 steps.[76] Conversion of the alcohol **67** into the Weinreb amide was followed by methyl ether formation, and reduction to the aldehyde **68** (**Scheme 27**). The resulting aldehyde **68** was readily converted into the methyl alkyne **53** *via* the Corey-Fuchs protocol, but the subsequent transformation of **53** into the requisite boronic acid **69** proved troublesome. Hydroboration of **53** followed by hydrolysis of the resulting dihaloborane gave an isomeric mixture of boronic acids, which were readily separated by chromatography. The unstable desired isomer **69** was prepared in 17% overall yield over 13 steps (from carbamate **27**) (**Scheme 27**).



Reagents and conditions **i**, $Me_2AlN(OMe)Me$, THF, 87%; **ii**, NaH, MeI, 95%; **iii**, DIBAL-H, 79%; **iv**, PPh_3, CBr_4; **v**, BuLi, MeI, 85% (2 steps); **vi**, $HBBr_2$; **vii**, aq. citrate buffer, 45% (2 steps).

Scheme 27. Synthesis of boronic acid **69**.

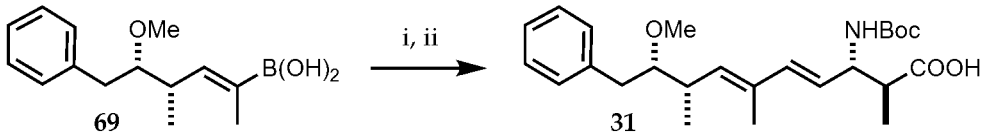
The synthesis of the second Suzuki coupling partner started from the benzyl / phenylfluorenyl protected dimethyl aspartate **70**, which had been obtained in three steps and 78% overall yield from commercially available D-aspartic acid. Compound **70** was then regio- and diastereoselectively methylated to give the *syn*-β-methyl diastereoisomer **71** exclusively. *N*-deprotection of the benzylphenylfluorenyl aspartate **71** produced the hydrochloride salt **72**, which was selectively saponified in nearly quantitative yield. *N*-Boc protection followed by ester formation, and *in situ* reduction led to the formation of alcohol **34**, which can lactonized spontaneously above -15°C to form lactone **74** (**Scheme 28**). Swern oxidation of alcohol **34** gave the epimerization-prone aldehyde intermediate, which was used immediately to generate the *trans* iodoalkene **73** exclusively *via* Takai's procedure. The synthesis of the iodoalkene **73** proved to be very tricky, but was successfully achieved in 26% overall yield and 11 linear steps (from D-aspartic acid) (**Scheme 28**).



Reagents and conditions **i**, LiHMDS; **ii**, MeI, 98% (2 steps); **iii**, H_2, Pd-C, TFA, 91%; **iv**, $CuCO_3$/$Cu(OH)_2$, 97%; **v**, $(Boc)_2O$, 98%; **vi**, DCC, HOSuc; **vii**, $NaBH_4$, 73% (2 steps); **viii**, Swern; **ix**, $CrCl_2$/CHI_3, THF/dioxane, 53% (2 steps).

Scheme 28. Synthesis of iodoalkene **73**.

Boronic acid **69** and iodoalkene **73** were reacted together, under the palladium-catalyzed Suzuki cross-coupling conditions. After a significant amount of optimization, the use of thallium ethoxide in the presence of water afforded the fully protected ADDA fragment, which was finally, saponified to the desired *N*-Boc-ADDA **31**, thus obtained in a satisfactory 12% overall yield after 26 steps in total (**Scheme 29**).



Reagents and conditions **i**, **73**, $Pd(PPh_3)_4$, TlOEt, H_2O, 82%; **ii**, LiOH, 88%.

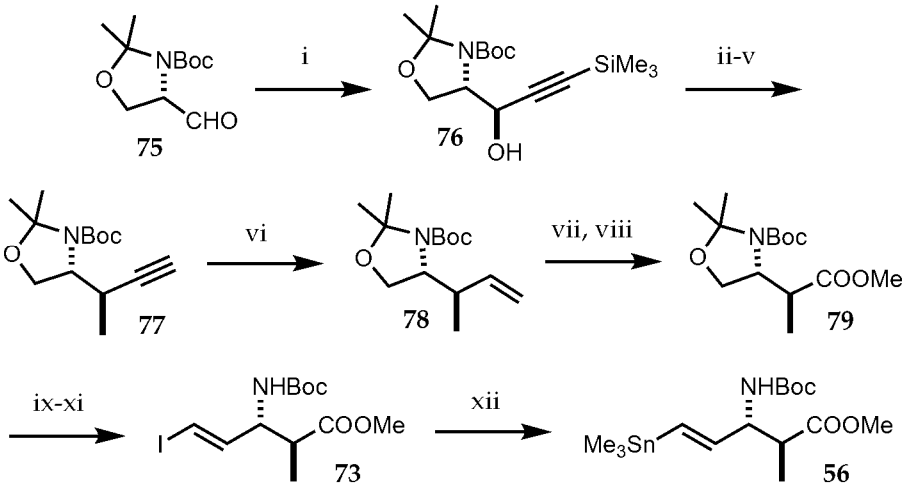
Scheme 29. Synthesis of *N*-Boc-ADDA **31**.

It should be noted that the total synthesis proposed by Chamberlin[81] was the most efficient ADDA synthesis reported at that time. Nevertheless, it involved numerous side reactions, as well as numerous unstable intermediates, which made the synthesis very complicated to reproduce and scale up.

1.9 - Mann's second approach[82]

In 1997, A. Mann[82] published an extension of his previous work published in 1996.[79] The only difference was the presentation of a novel strategy for the generation of the aminoacid partner.

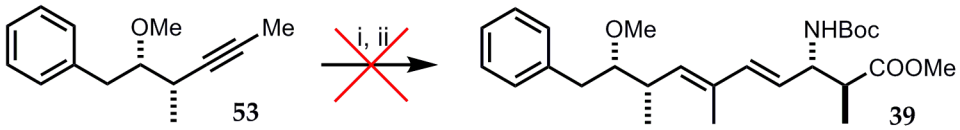
Mann's synthesis began with aldehyde **75**, originated from the (*S*)-serine, and was converted to the propargylic alcohol **76**, which was subsequently desilylated with TBAF. The resulting terminal alkyne was mesylated, and the corresponding mesylate was finally methylated to give the propargylic derivative **77** (**Scheme 30**). The terminal alkyne **77** was subsequently reduced to the corresponding olefin **78**, which was in turn oxidised, and then esterified to methyl ester **79**. Ring opening of the oxazolidine, followed by a Swern oxidation gave the aldehyde intermediate. The aldehyde was converted to the iodoalkene intermediate **73**, which could be cleanly transformed into the stannane **56** (6% yield over 12 steps from aldehyde 75) (**Scheme 30**).



Reagents and conditions **i**, $Me_3SiCCLi$, HMPT, THF, 85%; **ii**, TBAF, THF; **iii**, MsCl, TEA; **iv**, LiBr, CuBr·DMS, 38% (3 steps); **v**, MeMgBr, CuBr·DMS, LiBr, 80%; **vi**, H_2, $Pd/BaSO_4$, quinoline, 85%; **vii**, $RuCl_3$, aq. $NaIO_4$; **viii**, Me_3OBF_4, proton sponge, 61% (2 steps); **ix**, PPTS, EtOH; **x**, Swern, 85%; **xi**, CH_2I_2, $CrCl_2$, 75%; **xii**, $(Me_3Sn)_2$, $Pd(PPh_3)_4$, 74%.

Scheme 30. Synthesis of stannane **56**.

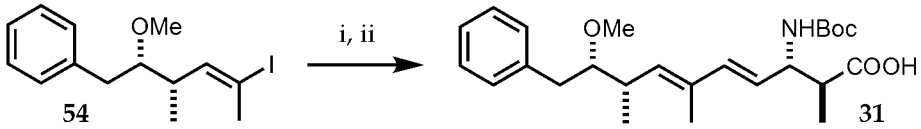
Mann initially attempted a Negishi coupling between alkyne **53** and iodoalkene **73**, which unfortunately failed to give the expected ADDA unit (**Scheme 31**).



Reagents and conditions **i**, Cp_2ZrClH, PhH; **ii**, **73**, $ZnCl_2$, various catalysts.

Scheme 31. Unsuccessful Negishi cross-coupling to ADDA derivative **39**.

The successful coupling was finally achieved by reverting to a Stille coupling between vinylstannane 5**6** and iodide **54**, as reported previously (**Scheme 32**).[79]



Reagents and conditions **i**, $PdCl_2(MeCN)_2$, **56**, DMF, 58%; **ii**, LiOH, DME, H_2O, 70%.

Scheme 32. Sucessful Stille coupling to *N*-Boc-ADDA **31**.

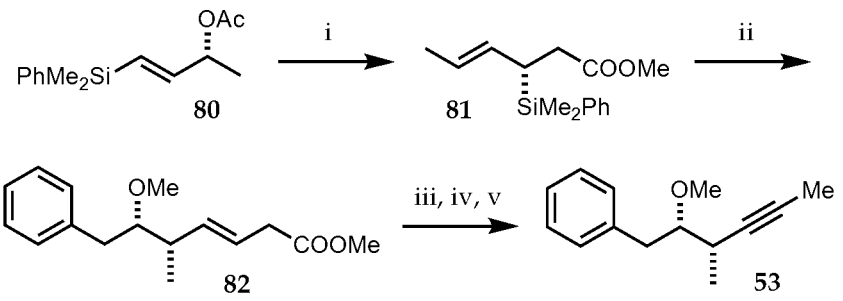
The second Mann's synthesis afforded the *N*-Boc-ADDA side chain **31** in a modest 3% overall yield over 13 steps (from compound **76**).

1.10 - Panek's approach[83,87]

In, 1997, J. S. Panek[83] reported a very efficient and sophisticated convergent synthesis of *N*-Boc-ADDA taking advantage of some of the previously reported approaches.[78,79,81] In 2002, he completed and published the total synthesis of (-)-motuporin[87] using the methodology initially developed in 1997.[83] A common precursor of chirality generated *via* Ireland-Claisen rearrangement,[88] was used to generate of both side of the ADDA chain, which were assembled through a palladium-mediated cross-coupling.

Panek's synthesis started with the acetate **80**, which was converted to the silane **81** through the use of the Ireland-Claisen rearrangement.[88] The condensation of silane (S)-**81** with phenylacetaldehyde dimethyl acetal afforded olefin **82** as a (10:1) diastereoisomeric mixture, which was then ozonolyzed, and converted to the corresponding dibromoolefin

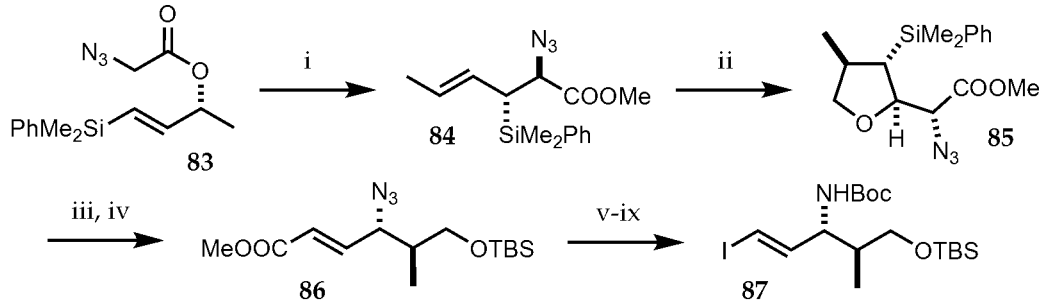
via a Corey-Fuchs reaction. Finally the dibromoolefin was treated with *n*-BuLi and iodomethane to give alkyne **53** in 58% overall yield after a 6 steps sequence (**Scheme 33**).



Reagents and conditions **i**, Ireland-Claisen rearrangement;[88] **ii**, phenyl acetaldehyde dimethyl acetal, $BF_3{\cdot}Et_2O$, -50 °C, 92%; **iii**, O_3, DMS; **iv**, CBr_4, PPh_3, 88% (2 steps); **v**, *n*BuLi, THF, then MeI, 98%.

Scheme 33. Synthesis of akyne **53**.

Silane **84** was prepared in 73% yield through a 3-step sequence involving the use of the Ireland-Claisen rearrangement. Treatment of silane **84** with trifluoroboron etherate produced the stereochemically pure tetrahydrofuran **85** as single product. Exposure of compound **85** to $SbCl_5$, followed by *O*-TBS protection led to the formation of ester **86**. Azide reduction, followed by *N*-Boc protection yielded the alkene intermediate, which was then ozonolysed and converted to the corresponding vinyl iodide **87** in 39% overall yield after 11 steps (**Scheme 34**).

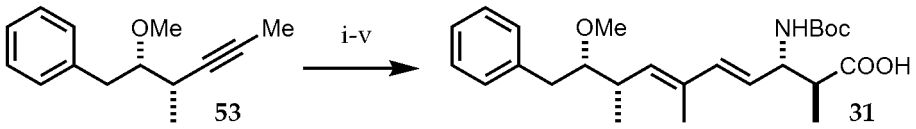


Reagents and conditions **i**, Ireland-Claisen rearrangement,[88] 73% (3 steps); **ii**, $BF_3{\cdot}Et_2O$, -50 °C, 91%; **iii**, $SbCl_5$, DCM, -50 °C, 96%; **iv**, TBSCl, imidazole, 99%; **v**, $SnCl_2$, MeOH, 0 °C; **vi**, $(Boc)_2O$, dioxane, aq. $NaHCO_3$, 84% (2 steps); **vii**, O_3, DMS; **viii**, $CrCl_2$ / CHI_3, THF, 74% (2 steps).

Scheme 34. Synthesis of iodoalkene **87**.

Unlike the results reported by Mann,[83] Panek reported a modified Negishi-type coupling which successfully linked the two alkyne **53** and iodoalkene **87** together. Mechanistically,

alkyne **53** was first converted regioselectively to the vinylzirconium intermediate, which was then transmetallated to the vinylzinc species. The intermediate vinylzinc was reacted with the vinyl iodide **87** through a Negishi coupling to yield the (*E*,*E*)-1,3-diene as a single isomer. TBAF deprotection followed by oxidation provided the carboxylic acid **31** in 28% overall yield after 21 steps in total (**Scheme 35**).

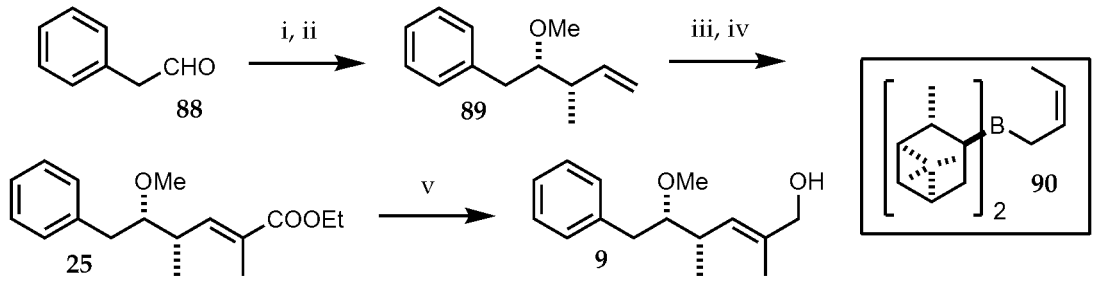


Reagents and conditions **i**, Cp_2ZrHCl, THF; **ii**, $ZnCl_2$, THF; **iii**, **87**, $Pd(PPh_3)_4$, 84% (3 steps); **iv**, TBAF, 99%; **v**, PDC, DMF, 86%.

Scheme 35. Synthesis of *N*-Boc-ADDA **31**.

1.11 - McCarthy's approach[84,89]

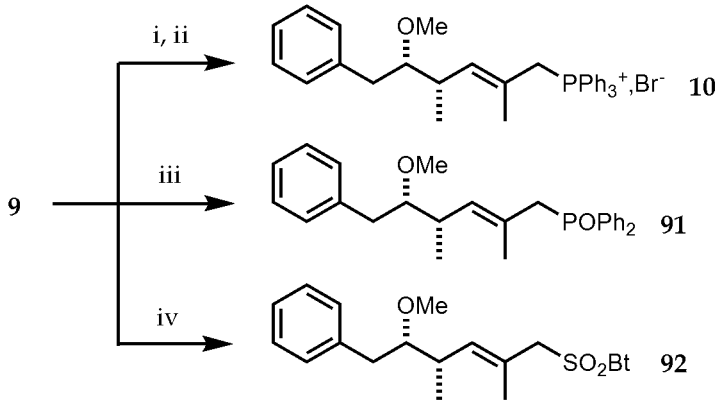
T. D. McCarthy[84,89] reported the synthesis of the ADDA chain using a convergent strategy based on some of the work initially developed by Rinehart and Beatty.[74,76] The synthesis of the aromatic-containing unit started with the diastereo- and enantioselective Brown crotylation of phenylacetaldehyde **88**, to generate the *syn*-homoallylic alcohol intermediate, which was then *O*-methylated to provide the alkene **89**. Ozonolytic cleavage of alkene **89**, followed by a Wittig olefination afforded the conjugated ester **25**, which was subjected to an 1,2-reduction giving the allylic alcohol **9** (**Scheme 36**). It is important to notice that conjugated ester **25** was obtained as the major isomer of a mixture containing some (*Z*)-isomer and C_4-epimer, as reported by Beatty.[76]



Reagents and conditions **i**, **90**, 95%; **ii**, NaH, MeI; **iii**, O_3 then PPh_3, 88% (3 steps); **iv**, $Ph_3PC{=}C(CH_3)COOEt$, 85%; **v**, $LiAlH_4$, 100%.

Scheme 36. Synthesis of allylic alcohol **9**.

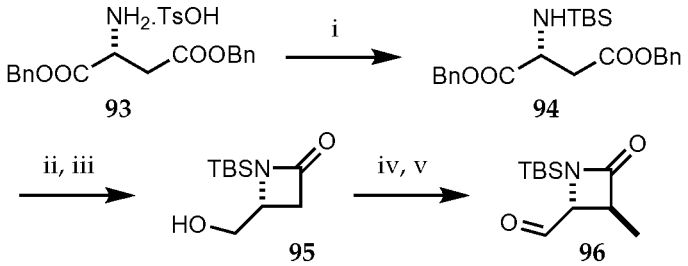
The allylic alcohol **9** was then converted to the three intermediates **10**, **91**, and **92** through the use of classical techniques. Intermediates **91** and **92** were isolated over 6 and 5 steps in excellent 37 and 55% overall yields respectively. The ylide **10** was generated *in situ*, and taken on crude into the Wittig olefination (**Scheme 37**).



Reagents and conditions **i**, CBr_4, PPh_3, 68%; **ii**, PPh_3; **iii**, $EtOPPh_2$, 73%; **iv**, BtSH, DEAD, PPh_3 then Oxone or H_2O_2, 73%.

Scheme 37. Synthesis of intermediates **10**, **91** and **92**.

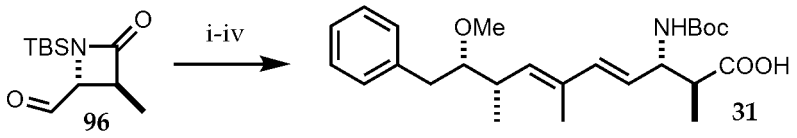
Although the synthetic sequence used to generate the aminoacid partner started, as many others,[76,79,81] with D-aspartic acid, the β-lactam framework was used for the very first time. The synthesis began with the *p*-toluenesulfonic acid salt of D-dibenzylaspartate **93**, which was *N*-TBS protected (**Scheme 38**). The resulting aminoester **94** was cyclised to the β-lactam by treatment with ^{t}BuMgCl. The crude β-lactam intermediate was reduced under mild conditions to give alcohol **95**, which was stereoselectively methylated, and then oxidised to the aldehyde **96**. This very short 5-step sequence gave multigram quantities of aldehyde **96** as a single diastereoisomer in a very good 26% overall yield (**Scheme 38**).



Reagents and conditions **i**, TBSCl, TEA, 90%; **ii**, ^{t}BuMgCl then NH_4Cl; **iii**, $NaBH_4$, LiBr, THF, H_2O, 55% (3 steps); **iv**, *n*-BuLi then MeI, 53% (from 8); **v**, Swern, 90%.

Scheme 38. Synthesis of aldehyde **96**.

McCarthy reported extensive studies on the couplings of **10**, **91**, and **92** intermediates with aldehyde **96**. Unfortunately the coupled products were obtained in poor to modest yields, and limited control of the double bond isomer geometry in all cases. The best results reported a 45% yield with an (3:1) (*E*/*Z)* ratio of diastereoisomers. The diene intermediate was *N*-TBS deprotected, and then was *N*-Boc re-protected to finally open the β-lactam ring, and isolate the *N*-Boc protected ADDA **31** after a total of 14 steps, and 11% overall yield (**Scheme 39**).



Reagents and conditions **i**, **92**, KHMDS; **ii**, KF, 45% (2 steps); **iii**, $(Boc)_2O$, TEA, 93%; **iv**, LiOH, THF, 86% (2 steps).

Scheme 39. Synthesis of *N*-Boc-ADDA **31**.

The route reported by McCarthy[84,89] presented the quickest, and the most efficient way to generate the two coupling units. Unfortunately, the inefficiency of the coupling reaction ruined the final overall yield of the total synthesis. Switching the Wittig-type termination of the project for the organometallic coupling described by Panek[83] would have significantly inproved the overall yield of the synthesis.

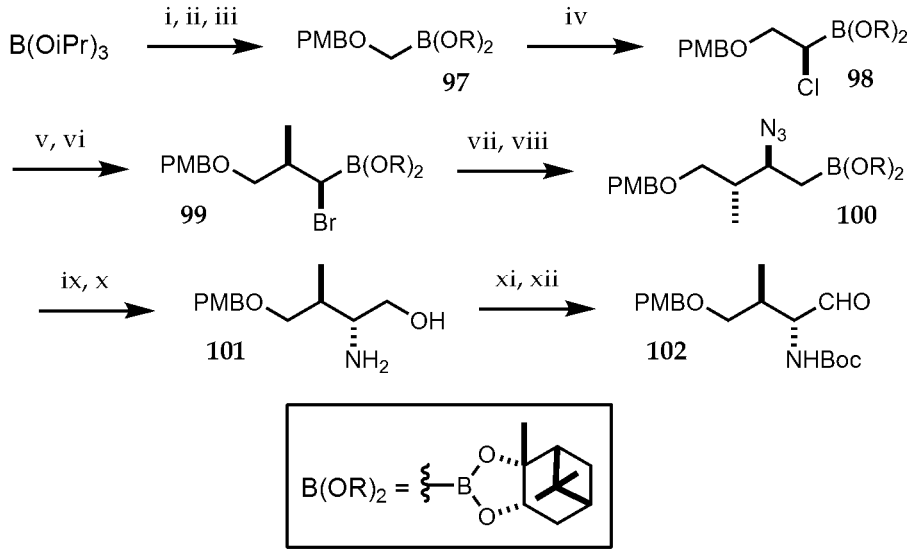
1.12 - Armstrong's approach[85]

R. W. Armstrong[85] reported the total synthesis of motuporin including an optimized synthesis of the ADDA chain based on a similar strategy to that used by McCarthy.[84,89]

The synthesis of the phenyl containing unit was prepared *via* the classical 6-step sequence in 32% overall yield (**Scheme 36**), using the methodology described by T. D. McCarthy.[84,89]

Armstrong's synthesis of the opposite amino partner began with the metalation of chloroiodomethane with *n*-butyllithium in the presence of triisopropyl borate to give diisopropyl chloromethylborate. The latter was transesterified with (+)-pinanediol, and the chloride was then displaced in S_N2 fashion with lithium *p*-methoxybenzyloxide in

THF, to produce protected alcohol **97** (**Scheme 40**). Chain extension of PMB-protected alcohol **97** by treatment with dichloromethyllithium, followed by addition of $ZnCl_2$ gave α-chloroborate ester **98** as a single diastereoisomer. Stereospecific displacement of the chloride with methylmagnesium chloride afforded the α-methyl borate ester, which was converted to the corresponding bromide **99**. The bromide was substituted cleanly *via* an S_N2 insertion of the azide unit providing azido borate **100**, which was then converted to aminoalcohol **101** *via* a borate oxidative cleavage and azide hydrogenation. A final *N*-Boc protection followed by a DMP oxidation yielded the aldehyde **102** in good 19% overall yield after 13 steps (**Scheme 40**).

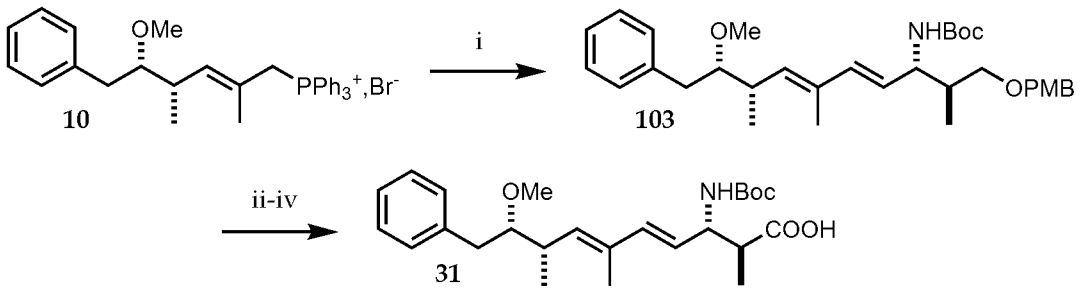


Reagents and conditions **i**, CH_2ICl, BuLi, THF, -78 °C; **ii**, (+)-Pinanediol, Et_2O; **iii**, LiOPMB, DMSO, THF, 62% (3 steps); **iv**, $LiCHCl_2$, -100 °C then $ZnCl_2$, 90%; **v**, MeMgCl, THF; **vi**, LDA, CH_2Br_2 then $ZnCl_2$, 87% (2 steps); **vii**, NaN_3, Aliquot 336, DCM, H_2O; **viii**, BuLi, CH_2ICl, THF, 74% (2 steps), **ix**, H_2O_2, THF then aq. NaOH; **x**, H_2, Pd/C, MeOH; **xi**, $(Boc)_2O$, DCM; **xii**, DMP, DCM, 54% (4 steps).

Scheme 40. Synthesis of aldehyde **102**.

The Wittig coupling between the two partners was extensively explored, but as experienced by other groups,[74-76,78,84,89] it could not provide efficient and selective (*E*,*E*)-diene formation. The best results were obtained *via* the known triphenylphosphonium salt **10**, which provided the (*E*,*E*)-diene **103** in 67% yield, plus 16% of its undesired (*Z*,*E*)-isomer. All attempts reported led to the formation of significant amounts of the (*E*,*Z*)-diene as well as a diastereoisomeric mixture (up to 1:1) stemming from the epimerisation of aldehyde **102** (**Scheme 40**). Cleavage of the *O*-PMB group caused the unwanted loss of the *N*-Boc protecting group under the reaction conditions. The resulting amine, was *N*-Boc

protected once again, and the free alcohol subsequently oxidized to yield *N*-Boc-ADDA **31** in a modest 8% overall yield after 24 steps in total (**Scheme 41**).



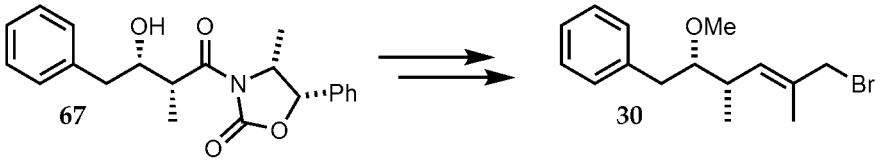
Reagents and conditions **i**, LDA, THF then **102**, 67%; **ii**, $BF_3{\cdot}Et_2O$, EtSH, DCM then $(Boc)_2O$, DCM; **iii**, DMP, DCM; **iv**, $NaClO_2$, 2-methyl-2-butene, ^{t}BuOH, H_2O, 60% (3 steps).

Scheme 41. Synthesis of the *N*-Boc-ADDA **31**.

1.13 - Toogood's second approach [72]

In 1999, P. L. Toogood achieved the total synthesis of motuporin, based on the strongest aspects of his previous work published in 1996.[78] The strategy developed in his previously published approach to ADDA was considered to be too long for scale-up purposes.

The synthesis of the aryl containing fragment employed the Evans aldol chemistry previously utilised by Rinehart and Beatty.[74,76] The allylic bromide **30** was isolated in 24% overall yield after 13 steps from phenylacetaldehyde, using the same methodology described by Toogood in his previous paper (**Schemes 11 & 42**).[78]

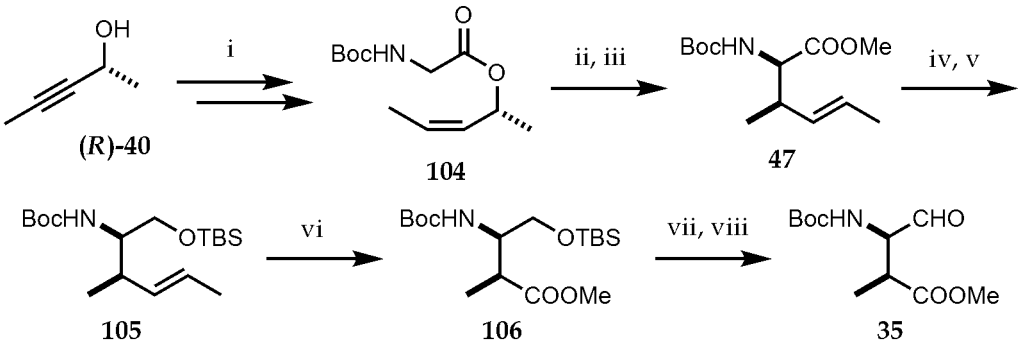


Reagents and conditions **(**refer to **Scheme 11**).

Scheme 42. Synthesis of allylic bromide **30**.[78]

In Toogood's synthesis, the amino unit was prepared from (*R*)-3-pentyn-2-ol **(*R*)-40** through a slightly modified version of the one previously reported.[78] Acylation of the alkynol with *N*-Boc-L-glycine under standard DCC conditions, followed by

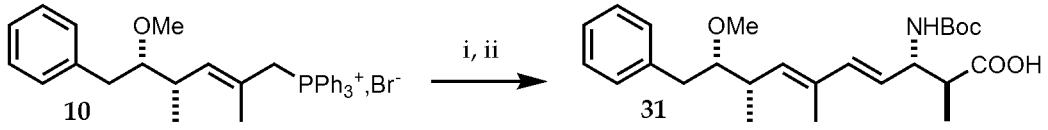
hydrogenation provided *cis*-olefin **104**. Then, treatment of alkene **104** with LDA, in the presence of zinc chloride, promoted a highly stereoselective Claisen rearrangement to the methyl ester **47** (**Scheme 43**). Reduction of ester **47** followed by *O*-TBS protection, and subsequent ozonolytic alkene cleavage in methanol yielded the methyl ester **106**. Removal of the TBS group, under extremely mild conditions, prevented lactonisation, and afforded the primary alcohol intermediate. The resulting alcohol was then oxidised to aldehyde **35** in excellent 40% overall yield after 9 steps (from (*R*)-3-pentyn-2-ol **(*R*)-40**) (**Scheme 43**).



Reagents and conditions **i**, a) *N*-Boc glycine, DCC, DMAP, 95%; b) H_2, Pd / $BaSO_4$ or $CaCO_3$, EtOAc, 91%; **ii**, LDA, -78 °C, $ZnCl_2$, 75%; **iii**, NaH, MeI, 95%; **iv**, $LiAlH_4$; **v**, TBSCl, 86% (2 steps); **vi**, O_3, NaOH, MeOH, 90%; **vii**, NBS; **viii**, Swern, 84% (2 steps).

Scheme 43. Synthesis of aldehyde **35**.

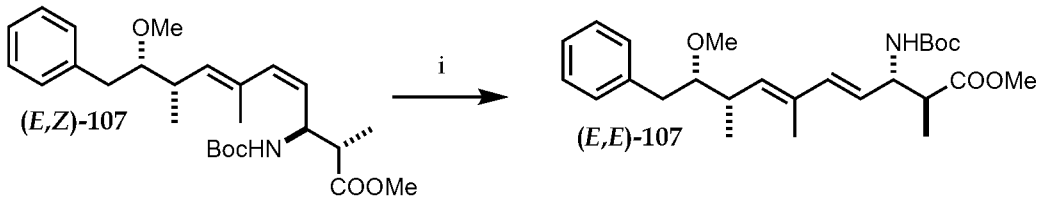
Toogood[72] ambitiously tried to apply modified ylide chemistry to the Wittig-type coupling reactions previously used in previously reported ADDA syntheses.[74-76,78,84,85,89] A number of derivatives, including phosphonates, phosphine oxides, phosphonium salts and alkylphosphoranes, were synthesized from allylic bromide **30**. Unfortunately, the best results were obtained, once again, through the use of triphenylphosphonium salt **10**, and no optimization of this olefination reaction could be achieved (**Scheme 44**).



Reagents and conditions **i**, *n*BuLi, 41%; **ii**, LiOH, 98%.

Scheme 44. Synthesis of *N*-Boc-ADDA **31**.

The Wittig olefination provided a (2:1) mixture of (*E*,*E*)- and (*E*,*Z*)-dienes in a poor 41% yield. Having failed to improve the reaction yield and selectivity, Toogood's efforts were focused on the isomerisation of the unwanted (*E*,*Z*)-isomer into the (*E*,*E*)-diene **107**, which was gratifyingly carried out in 51% yield through the use of light and iodine (**Scheme 45**). The (*E*,*E*)-diene methyl ester **107** was then saponified in nearly quantitative yield to provide the *N*-Boc-ADDA **31** in 10% overall yield over a 22 steps sequence.



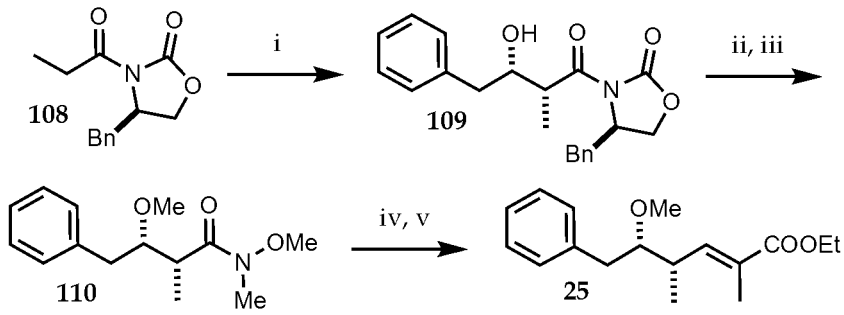
Reagents and conditions **i**, hυ, I_2, 51%.

Scheme 45. Isomerisation of (*Z*,*E*)-diene **107** to (*E*,*E*)-diene **107**.

1.14 - Rinehart's second approach [86]

The second linear and most efficient total synthesis of the *N*-Boc-ADDA chain **31** was proposed by Rinehart,[86] more than 10 years after his initial synthesis published in 1989.[74]

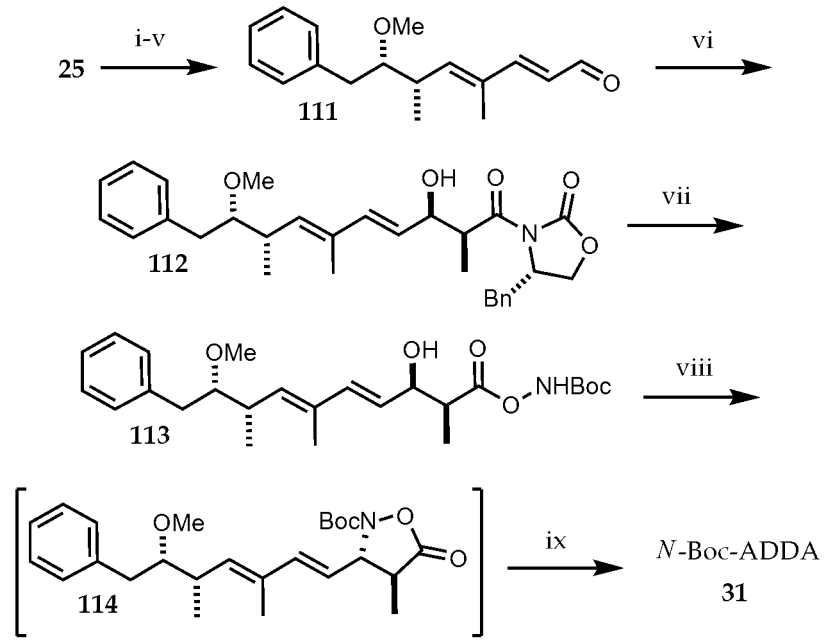
Rinehart's synthesis began with the use of the Evans aldol methodology used by Chamberlin[81] and Beatty[76] to generate amide **110**. The amide **110** was reacted with a stabilised ylide to provide (*E*)-conjugated ester **25** (**Scheme 46**). No information was given about the formation of any isomers of **25**, as reported by other workers.[76]



Reagents and conditions **i**, Bu_2BOTf, TEA, $PhCH_2CHO$, 99%; **ii**, $Me_2AlN(OMe)Me$; **iii**, NaH, MeI, 95% (2 steps); **iv**, DIBAL-H; **v**, $Ph_3P{=}C(CH_3)COOEt$), 86% (2 steps).

Scheme 46. Synthesis of (*E*)-conjugated ester **25**.

A second Dibal-H reduction of ester **25**, followed by oxidation of the resulting allylic alcohol, gave the aldehyde intermediate, which was subjected to a second Wittig olefination to generate the (*E*,*E*)-conjugated ester, completing the (*E*,*E*)-diene system of ADDA. Another Dibal-H reduction, followed by MnO_2 oxidation gave aldehyde **111**, which upon an Evans aldol reaction in the presence of the opposite enantiomer of the acylated oxazolidinone **108** yielded alcohol **112**. The treatment of oxazolidinone **112** with a mixture of NaH and *tert*-butyl-*N*-hydroxycarbamate gave *N*-Boc protected amine **113**. The synthesis of *N*-Boc-ADDA **31** was finally completed *via* a Mitsunobu cyclization followed by SmI_2 reduction in a "one-pot" process (**Scheme 47**).



Reagents and conditions **i**, DIBAL-H; **ii**, MnO_2, 97% (2 steps); **iii**, $Ph_3PCHCOOEt$, 96%; **iv**, DIBAL-H; **v**, MnO_2, 95% (2 steps); **vi**, ***(S)*-108**, Bu_2BOTf, TEA, 91%; **vii**, NaH, HONHBoc, 96%; **viii**, PPh_3, DEAD, **ix**, SmI_2, 64% (2 steps).

Scheme 47. Synthesis of *N*-Boc-ADDA **31**.

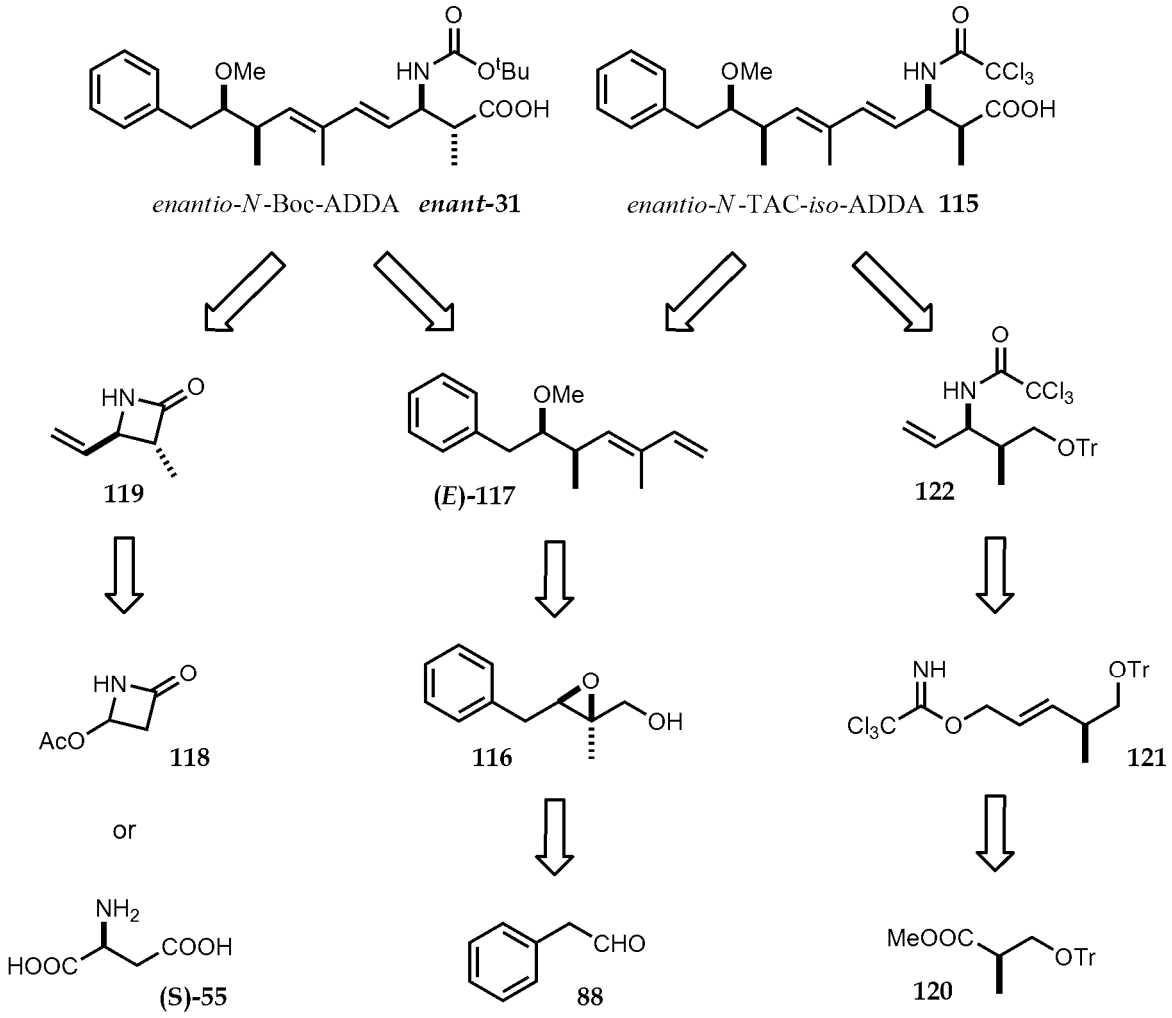
The Rinehart synthesis[86] yielded the *N*-Boc-ADDA chain in the best overall yield (40%) reported to this point, after only 13 linear steps from oxazolidinone **108**.

2 - OUR PROPOSED APPROACH

Many of the previously reported syntheses relied on similar strategies to prepare the ADDA residue. Although they presented a number of strong qualities, on the down side, they also contained major obstacles, which had to be taken into consideration to design an efficient new route towards ADDA. It is worth noticing that 8 of the 14 syntheses utilized the rather inefficient Wittig olefination to link the two coupling units, which generated the (*E*,*E*)-diene in low yield and with poor selectivity.[72,75-76,78,84,85,89] Moreover, the Wittig olefination required the use of the amino unit as an aldehyde, which was shown to be sensitive to epimerisation during its preparation,[72,81] but also under the coupling conditions,[85] leading to complex isomeric mixtures. Several groups have successfully overcome these problems by using linear syntheses,[80,86] or other coupling methodologies such as palladium-catalysed Stille[79] and Suzuki[81] reactions, or Julia olefination.[77] However, these alternatives generally involved the use of unstable material generated through toxic and costly processes, which were not suitable for scale-up.

2.1 – Cross-metathesis approach

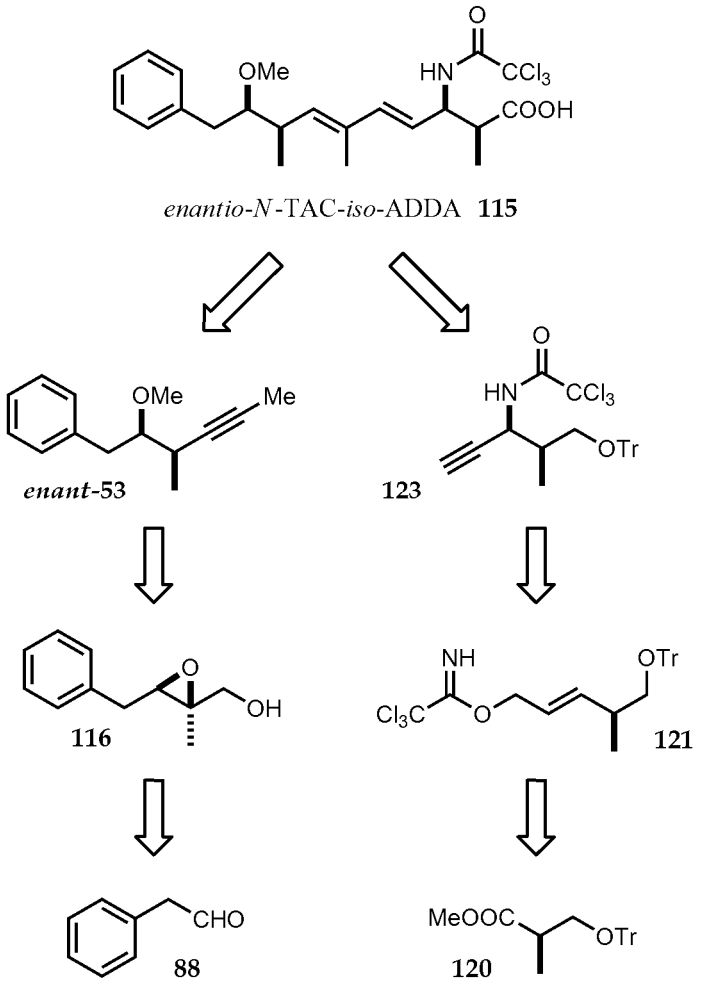
Chemically, the first goal of our approach was to find another method to assemble the two partners in by-passing the issues listed above. A cross-metathesis coupling methodology was envisaged, as it was known to be (*E*)-selective, and had not been employed to synthesise the ADDA framework before. Our proposed convergent synthesis towards *enantio*-ADDA, and *enantio-iso*-ADDA, involved the coupling of two cross-metathesis olefin partners, which were synthesised through the use of non-aldol aldol and aza-Claisen rearrangements, as well as β-lactam chemistry, as described below (**Scheme 48**).



Scheme 48. Retrosynthesis of *enantio-N*-Boc-ADDA ***enant*-31** and *enantio-N*-TAC-*iso*-ADDA **115**.

2.2 – Alkyne-alkyne coupling approach

Is should be noted that an alternative to the cross-metathesis methodology had also been envisaged through an alkyne-alkyne coupling (**Scheme 49**). Although opposite enantiomers of alkynes ***enant*-53** had already been synthesised in several previously reported ADDA syntheses,[79,81,83,87] the alkyne-alkyne coupling had never been utilised to construct the (*E*,*E*)-1,3-diene motif selectively.[90] With the prospect of using this coupling technique towards the synthesis of *enantio-N*-TAC-*iso*-ADDA **115**, the route presented below was attempted (**Scheme 49**). However the process was rapidly discontinued to the benefit of the cross-metathesis methodology.



Scheme 49. Retrosynthesis of *enantio*-*N*-TAC-*iso*-ADDA **115** involving an alkyne-alkyne coupling.

Despite the large amount of work accumulated over the past years, no ADDA-containing analogues combining potent inhibitory activities with high selectivities towards the different classes of PP have been developed yet. As an ultimate goal, we proposed to prepare small protein phosphatase inhibitors containing isomeric ADDA residue, such as *enantio*-ADDA and *enantio*-*iso*-ADDA, which might lead to the discovery of potent and selective inhibitory activity.

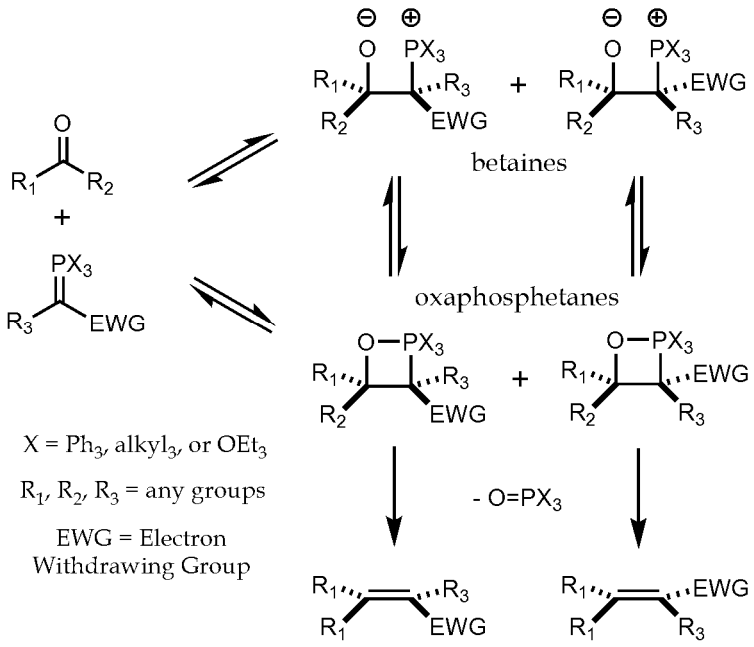
RESULTS & DISCUSSION

------- PART III – SYNTHESIS OF *ENANTIO*-ADDA CHAIN -------

1 – SYNTHESIS OF ARYL CONTAINING UNIT

1.1 - Initial methodology

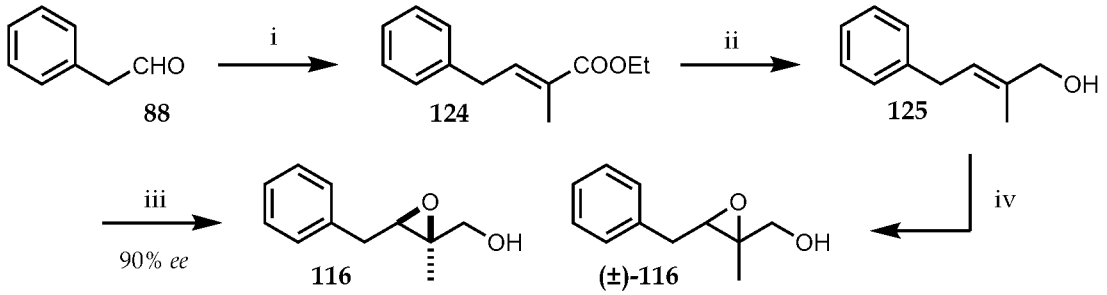
The synthesis of the aryl containing partner started with the treatment of commercially available phenylacetaldehyde **88** with 1-carbethoxyethylidene triphenylphosphorane (**Scheme 51**). Such stabilised ylide are well known for inducing regioselective formation of (*E*)-olefins in Wittig olefination,[91] and have been successfully used by many groups towards the synthesis of ADDA.[72,74,75,77,84-86,89] The Wittig olefination is a key reaction, which has been employed several times in our project. The intermediate oxaphosphetanes stemming from stabilised ylides have the ability to equilibrate, leading to the thermodynamic (*E*)-isomer, as shown in the mechanism below (**Scheme 50**). Although the Wittig olefination was discovered in 1954,[92] the existence and interconversion of betaine intermediates is still under debate as there is evidence that phosphonium ylides can react with carbonyl compounds *via* a [2+2] cycloaddition to directly form the oxaphosphetanes.[93]



Scheme 50. Mechanism of the Wittig olefination.

As expected, the conjugated ester **124** (**Scheme 51**) was obtained as a single double bond isomer, which was then reduced with lithium aluminium hydride to provide the allylic

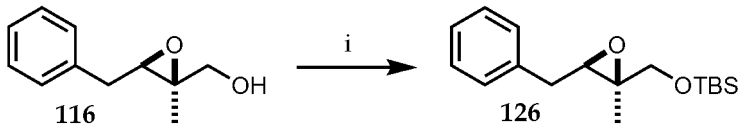
alcohol **125**. The (*E*)-double bond geometry of olefins **124** and **125** was confirmed by comparison of ^{1}H NMR chemical shifts with literature precedents.[74-78,84-86,89] The allylic alcohol **125** reacted under Sharpless Asymmetric Epoxydation conditions to afford the enantiomerically enriched epoxyalcohol **116** in very good yield and high enantiomeric excess. The preparation of the racemic epoxyalcohol **(±)-116** *via* a vanadium(III) acetyl acetonate-catalysed epoxidation, enabled the determination of the enantiomeric excess (90% *ee*) by chiral HPLC analysis (**Scheme 51**).



Reagents and conditions **i**, $Ph_3P{=}C(CH_3)COOEt$, benzene, Δ, 84%; **ii**, LAH, Et_2O, 90%; **iii**, *t*-BuOOH, Ti(O-*i*Pr)$_4$, D-(-)-DIPT, DCM, -30 °C, 95%, 90% *ee*; **iv**, V(acac)$_2$, *t*-BuOOH, toluene, rt, 1 h, 58%.

Scheme 51. Synthesis of epoxides **116** and **(±)-116**.

The epoxyalcohol **116** was then protected as the TBS silyl ether by treatment with TBSCl and imidazole in dimethylformamide to provide the compound **126** in excellent yield (**Scheme 52**).

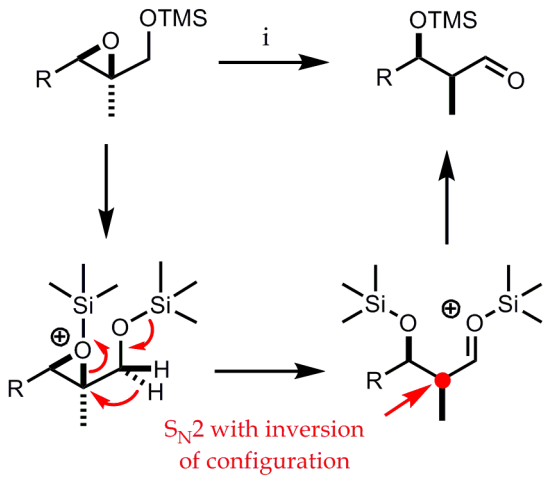


Reagents and conditions **i**, TBSCl, imidazole, DMF, rt, 2 h, 95%.

Scheme 52. Synthesis of the epoxide **126**.

With the TBS-protected epoxyalcohol **126** in hand, the non-aldol aldol (NAA) rearrangement was attempted for the first time. This reaction, under represented in the literature, and developed by M. E. Jung,[94] represents a very efficient way to generate aldol products *via* a non-aldol process. It only requires very mild conditions, and provides aldol products with excellent diastereoselectivity. As shown in the mechanism below (**Scheme**

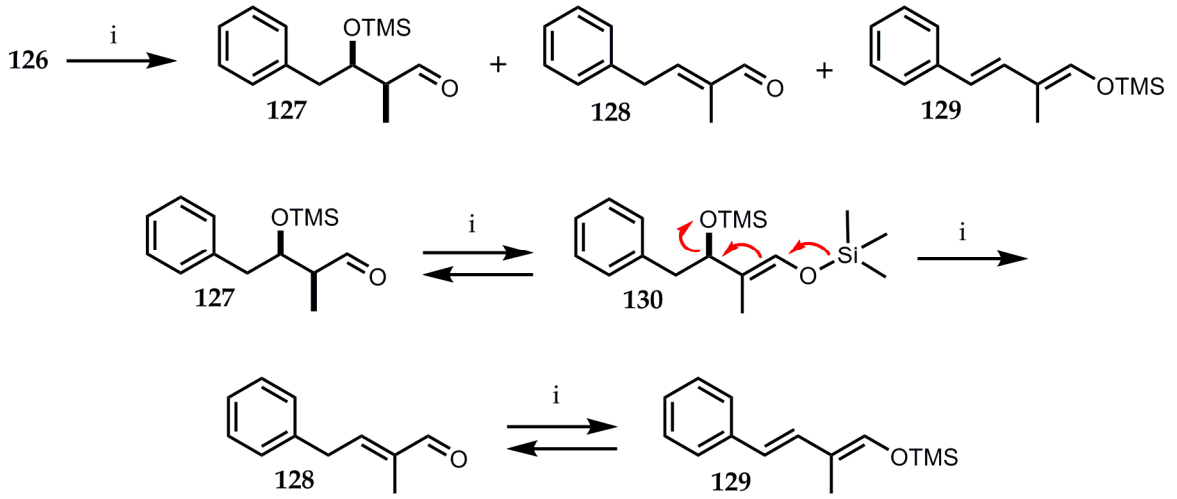
53), the diastereoselectivity of the reaction is a result of the exclusive departure of the H_{anti} to the breaking C-O bond of the epoxide. This hydride then attacks the adjacent stereocenter in a S_N2 fashion, resulting in an inversion of configuration of the stereocenter in α- of the carbonyl. The NAA rearrangement has also been successfully applied to secondary alcohols, and represents a very efficient route to ketones.[95]



Reagents and conditions **i**, TMSOTf, DIPEA, DCM, -78 °C then work-up.

Scheme 53. Mechanism of TMS-mediated non-aldol aldol rearrangement.

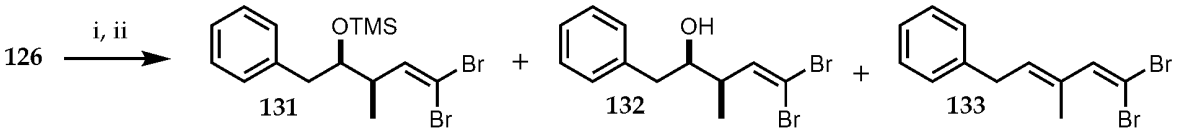
The rearrangement was first envisaged with TMSOTf and DIPEA, as shown above (**Scheme 53**), and provided the rearranged aldehyde **127** very quickly (**Scheme 54**). However, this aldehyde was proved to be unstable, and spontaneously degraded into the conjugated aldehyde **128** *via* β-elimination, resulting in the loss of stereochemistry (**Scheme 54**). Another side-product was also formed during the reaction, but it could not be isolated due to its great instability. Further experiments (isolation of silyl enol ether **135** in **Scheme 56**) demonstrated that the side product was in fact the TMS-enol ether **129** stemming from the aldehyde **128** (**Scheme 54**). Modifications of reaction time, temperature, and amounts of reagents did not give any better results.



Reagents and conditions **i**, TMSOTf, DIPEA, DCM, 20 min, -78 °C.

Scheme 54. TMS-mediated NAA rearrangement of epoxide **126**.

The aldehyde **127** was obtained in low yield and could not be purified due to its unstability. In order to by-pass this issue, the aldehyde **127** was taken on crude into the following reaction, which was, at that time, envisaged as a Corey-Fuchs olefination, with the prospect of the alkyne-alkyne coupling. Without any prior purification, the treatment of the crude aldehyde **127** under the Corey-Fuchs conditions provided the expected dibromoolefin **131** in poor yield, as a complex mixture of compounds (**Scheme 55**). The side dibromoolefin **133**, stemming from the olefination of the aldehyde **128**, was also isolated. In addition, during purification by flash column chromatography over neutralized silica gel, the desired dibromoolefin **131** partially degraded into the dibromoalkenol **132**, making the purification process troublesome (**Scheme 55**).



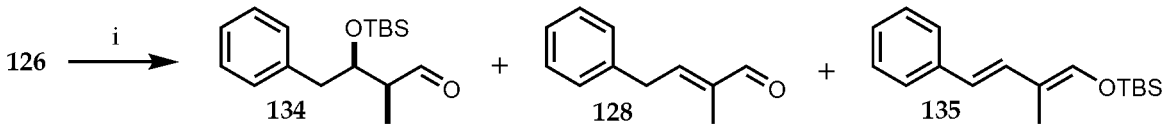
Reagents and conditions **i**, TMSOTf, DIPEA, DCM, -78 °C; **ii**, CBr_4, PPh_3, DCM, -78 °C.

Scheme 55. TMS-mediated NAA rearrangement of epoxide **126** followed by Corey-Fuchs reaction.

As the alcohol **132** was a key intermediate towards the generation of the methoxyolefin **137**, its formation *via* the preceding synthetic sequence (**Scheme 55**) was tried and optimized. The final reaction mixture, stemming from the NAA rearrangement (**Scheme**

55), was treated with a number of reagents such as TBAF, HF.pyridine, and silica gel / methanol, which unfortunately, all failed to give the alcohol **132**.

To overcome the stability problems induced by the use of the trimethyl silyl protecting group, the non-aldol aldol rearrangement of epoxide **126** was performed using TBSOTf. The reaction was much more difficult to monitor by TLC analysis, and required a much longer reaction time (3 h at -40 °C). However, the rearrangement worked well, and provided the desired aldelyde **134** as a single diastereoisomer in 70% yield (**Scheme 56**). The formation of the conjugated adduct **128** was still observed, but its formation was greatly reduced. Another side product, which had a similar TLC profile as the one observed during the TMSOTf rearrangement (silyl enol ether **129**), was also formed during the reaction. This compound was ultimately isolated, and fully characterised as the TBS-enol ether **135** stemming from the aldehyde **128** (**Scheme 56**).

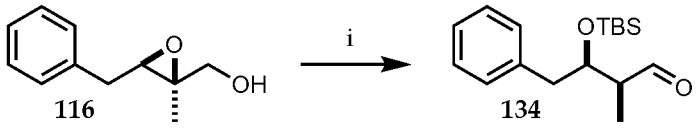


Reagents and conditions **i**, TBSOTf, DIPEA, DCM, -45 °C, 70% (**134**).

Scheme 56. TBS-mediated NAA rearrangement of epoxide **126**.

It is worth noting that, unlike the TMS-enol ether **129**, the TBS-enol ether **135** was very stable and could easily be isolated without observable decomposition by flash chromatography. However, under mass spectrometry conditions, the silyl enol ether **135** could not be observed entirely and decomposed to the aldehyde **128** instead. It should be noted that these very mild conditions (TBSOTf and DIPEA) might offer an efficient route towards series of useful TBS-enol ethers from epoxyalcohols.

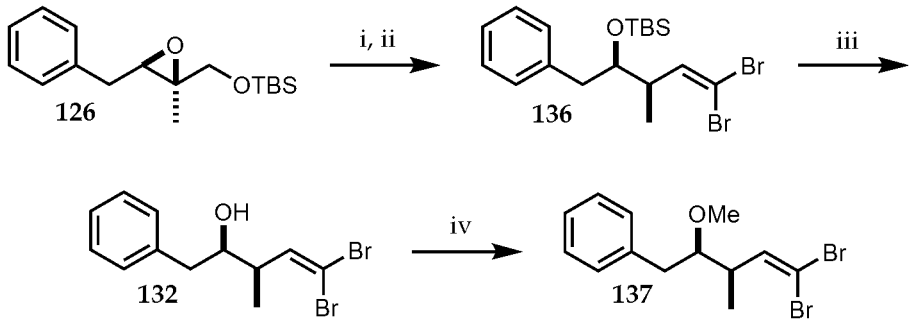
Interestingly, the aldehyde **134** was also successfully generated directly from the epoxyalcohol **116** with a better yield, and thus saved a step in the synthesis (**Scheme 57**).



Reagents and conditions **i**, TBSOTf, DIPEA, DCM, -60 to -20 °C, 77%.

Scheme 57. TBS-mediated NAA rearrangement of epoxide **116**.

The TBS-protected aldol **134** proved to be fairly fragile upon storage and underwent partial decomposition. However, it could easily be purified by rapid flash column chromatography. Alternatively, the aldehyde **134** was usually taken on crude or semi-pure in the subsequent Corey-Fuchs olefination to provide the dibromoolefin **136** in good yield. The TBS group was then cleaved off, and the resulting alcohol **132** was methylated to afford dibromoolefin **137** in low yield (**Scheme 58**). The data of olefin **137** were in full agreement with those of the opposite enantiomer previously reported in the literature,[81,83,87] confirming the *syn*-stereochemistry of compound **137**, and by extension the structures of the previously generated intermediates **127**, **132** and **134**.



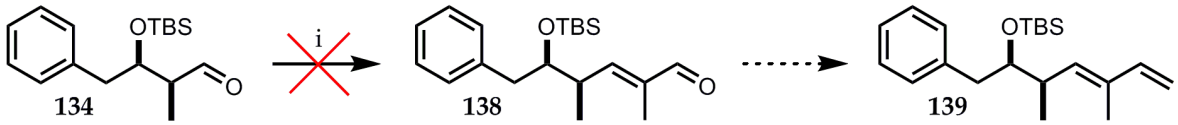
Reagents and conditions **i**, TBSOTf, DIPEA, DCM, -50 °C; **ii**, CBr_4, PPh_3, DCM, -78 °C, 67% (2 steps); **iii**, TBAF, THF, 81%; **iv**, NaH, MeI, THF, 0 °C, 43%.

Scheme 58. Synthesis of dibromoolefin **137**.

Meanwhile, the synthesis of the opposite amino partner (section *1.4.2*), conducted in parallel, failed to give satisfactory results. The approach involving the conversion of dibromoolefin **137** to alkyne ***enant*-53** (**Scheme 49**) with the prospect of a later alkyne-alkyne coupling, was consequently abandoned to the benefit of the cross-metathesis methodology.

1.2 - Synthesis of the aromatic containing CM partner

As part of our new approach, the freshly purified TBS-protected aldol **134** had to be converted into a suitable diene for the CM coupling reaction. Initially, aldehyde **134** was subjected to a Wittig olefination by treatment with readily accessible stabilised ylide 2-(triphenylphosphoranylidene)propionaldehyde. Unfortunately, several attempts all failed to generate the desired aldehyde **138**, precursor of diene **(*E*)-139** (**Scheme 59**).

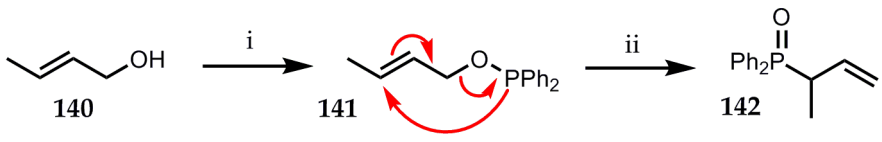


Reagents and conditions **i**, $Ph_3P=C(CH_3)CHO$, various conditions.

Scheme 59. Synthesis of aldehyde **138**.

The TBS-protected diene **134** was instead obtained through a Horner-Wadsworth-Emmons (HWE) olefination. Although being a well recognized method for the regioselective synthesis of (*E*,*E*)-1,3-dienes[96,97] *via* the use of readily accessible 1-methylallyldiphenylphosphine oxide **142**,[98] this method remains under-represented in organic synthesis (**Scheme 62**).

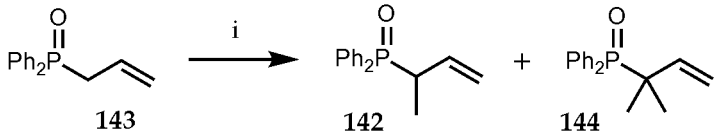
The required phosphine oxide **142**[98] was accessed *via* two different and easily scalable methods (**Scheme 60 & 61**). In the first one, the inexpensive and readily available crotyl alcohol **140** and diphenylphoshine chloride were reacted together, and the resulting crude mixture was then thermally rearranged (**Scheme 60**).[98] The pure phosphine oxide **142** was then obtained in multi-gram quantities after a subsequent purification by flash column chromatography. This purification method appeared to be much more straightforward than the classical recrystallisation technique used in previous work.[98]



Reagents and conditions **i**, PPh_2Cl, pyridine, Et_2O; **ii**, thermal rearrangement at 130°C, 20% (2 steps).

Scheme 60. Synthesis of 1-methylallyldiphenylphosphine oxide **142** from crotyl alcohol **140**.

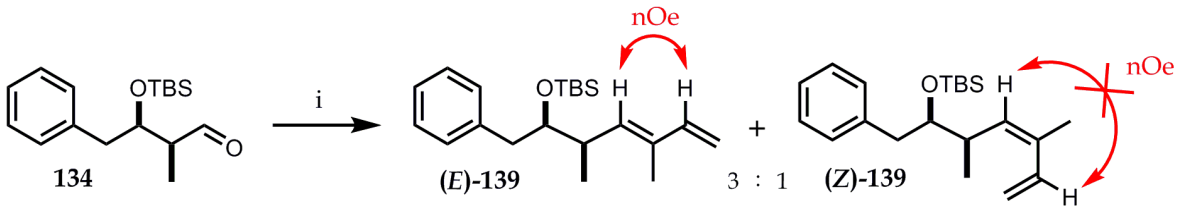
The second method started with commercially available allyldiphenylphosphine oxide **143** which was methylated by treatment with *n*-BuLi and iodomethane. The desired methylated phosphine oxide **142** was obtained with comparable ease, but greater efficiency than in the first route. Nevertheless, it required a trickier purification by flash column chromatography due to the formation of the unwanted dimethylated phosphine oxide **144** (**Scheme 61**). However, residual amount of the over-methylated by-product **144** were not considered as a problem for the WHE, as it could not be deprotonated during the reaction process.



Reagents and conditions **i**, *n*-BuLi, THF, -78 °C then MeI, 85% (**142**), 15% (**144**).

Scheme 61. Synthesis of 1-methylallyldiphenylphosphine oxide **142** from commercially available allyldiphenylphosphine oxide **143**.

As described by previous workers,[96,97] the Horner-Wadsworth-Emmons olefination provided the expected 1,3-diene **i**n good yield, but as a (3:1) mixture of (*E*)- and (*Z*)-isomers **(*E*)-139** and **(*Z*)-139** (**Scheme 62**). The double bond geometry of each isomer was corroborated through nOe and NOESY analyses and by comparison with NMR data reported in the literature.[96,97]

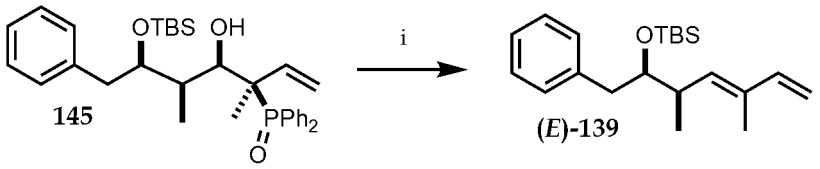


Reagents and conditions **i**, *n*-BuLi, HMPA, THF, -78 °C then **142**, 73%, (E / Z 3:1).

Scheme 62. Synthesis of dienes **(*E*)-139** and **(*Z*)-139** *via* a HWE olefination.

Numerous conditions were explored in order to improve the (*E* / *Z*) ratio between coumponds **(*E*)-139** and **(*Z*)-139**. The use of lower temperatures (< -78 °C) afforded a slightly better (*E* / *Z*) ratio, but also dramatically affected the yield which dropped below 30%. Interestingly, the reaction performed at -100 °C in anhydrous diethyl ether enabled

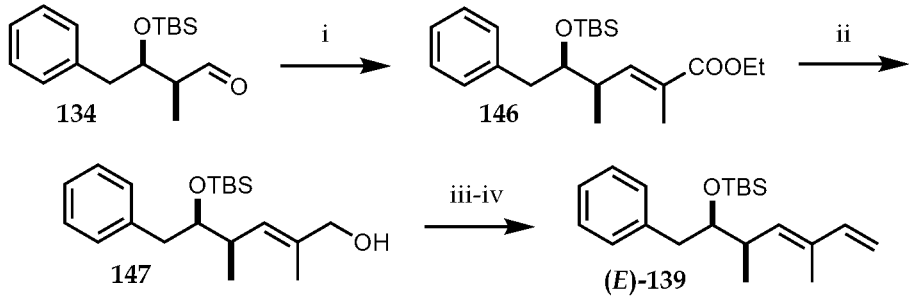
the isolation of the non-eliminated phosphinyl alcohol intermediate **145** as a white crystalline solid (**Scheme 63**). Unfortunately, crystallographic analysis failed to provide precious structural information about these potentially useful intermediates, which have never been isolated, and characterized before. Thus, the stereochemistry of both newly created stereocenters could not be experimentally determined, and was therefore deduced from the Felkin-Ahn model. Treatment of phosphinyl alcohol **145** with *n*-BuLi at -78 °C afforded the diene **(*E*)-139** as a single (*E*)-isomer exclusively (**Scheme 63**). However, this route was not extensively explored, due to lack of time.



Reagents and conditions **i**, *n*-BuLi, THF, -78 °C, 71%, (E) only.

Scheme 63. Synthesis of diene **(*E*)-139** from phosphinyl alcohol **145**.

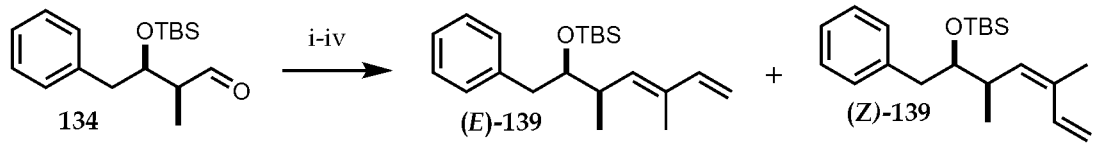
It is important to mention that the HWE process, although leading efficiently to the desired diene, was highly temperamental. After many unsuccessful attempts, which resulted in the waste of considerable amount of aldehyde **134**, the more classic, but robust initial approach, previously used by Rinehart,[86] was envisaged to bring more material through. The aldehyde **134** was olefinated through a Wittig olefination, and the (*E*)-conjugated ethyl ester **146** was then reduced into the allylic alcohol **147**. A subsequent MnO_2 oxidation, followed by a second Wittig olefination provided the *O*-TBS protected diene **(*E*)-139** as a single diastereoisomer (**Scheme 64**).



Reagents and conditions **i**, $Ph_3P{=}C(CH_3)COOEt$, DCM, Δ, 2 days, 54%, (*E*) only; **ii**, LAH, Et_2O, -78 °C, 91%; **iii**, MnO_2, DCM, rt, 1 h; **iv**, Ph_3CH_2I, LiHMDS, DCM, -78°C to rt, overnight, 60 %, (*E*) only.

Scheme 64. Synthesis of diene **(*E*)-139** *via* a Wittig olefination.

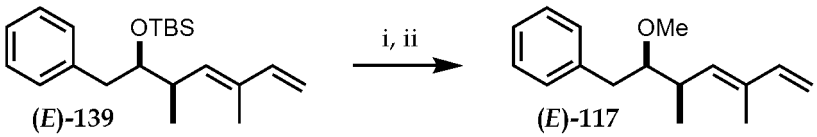
This process was chosen to provide the (*E*)-isomer **(*E*)-139** exclusively, requiring no separation by flash chromatography of the (*E*)- and (*Z*)-isomers. Surprisingly, although the first microscale trials were very satisfying, for unclear reasons, scale-up of the process gave an unwanted (3:1) inseparable mixture of (*E*) and (*Z*)-isomers of ester **146** (**Scheme 64**). However, unlike described by Beatty[76] who encountered the same issue, the use of different solvents did not help change the (*E*/*Z*) ratio. The isomeric mixture of **146** was taken on crude to the next steps, and both double bond isomers **(*E*)-139** and **(*Z*)-139** were separated by flash column chromatography after the diene-forming reaction.



Reagents and conditions **i**, $Ph_3P{=}C(CH_3)COOEt$, DCM, Δ, 2 days; **ii**, LAH, Et_2O, -78 °C; **iii**, MnO_2, DCM, rt, 1 h; **iv**, Ph_3CH_2I, LiHMDS, DCM, -78°C to rt, overnight, 45 % (4 steps), (*E*/*Z*) (3:1).

Scheme 65. Synthesis of dienes **(*E*)-139** and **(*Z*)-139**.

Isomers **(*E*)-139** and **(*Z*)-139** were usually separated by flash column chromatography at this point. However, it should be noted that the diene isomers have also been successfully separated by flash column chromatography (silica gel, 70% toluene in 40 - 60 petroleum ether) as their methyl ethers **(*E*)-117** and **(*Z*)-117.** Unlike the situation described in the literature,[97] purification of the (*E*)- and (*Z*)-isomeric mixture of diene **139** by flash column chromatography over silica gel coated with $AgNO_3$ was shown to be ineffective for the separation. TBS-deprotection was performed by treatment of **(*E*)-139** with TBAF under anhydrous conditions, and the resulting crude alcohol was then immediately methylated, without prior purification, to give final diene **(*E*)-117** in good overall yield (**Scheme 66**).



Reagents and conditions **i**, TBAF, THF; **ii**, KH, MeI, 92% (2 steps).

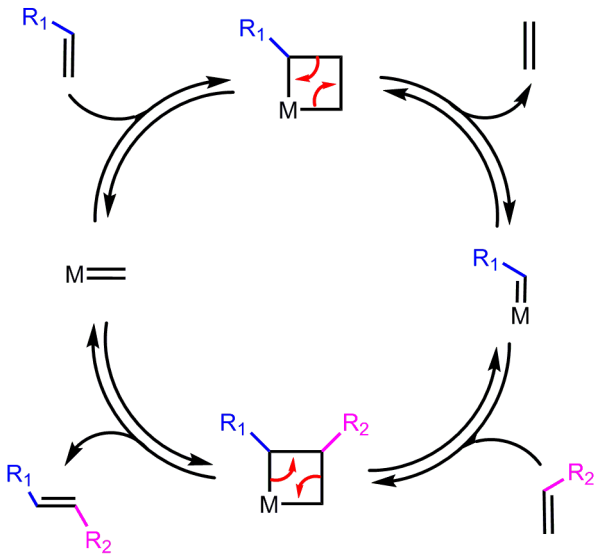
Scheme 66. Synthesis of diene **(*E*)-117**.

2 - SYNTHESIS OF THE AMINO UNIT

2.1 - Cross-metathesis methodology

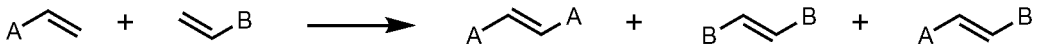
2.1.1 General information on cross-metathesis

Olefin cross-metatheses are metal-catalysed coupling reactions leading to the formation of dimeric olefins *via* the fine balance of successive subtle thermodynamic equilibria. Cross-metatheses are known to be preferentially (*E*)-double bond forming reactions, but the global regioselectivity of the CM reaction is poorly understood, and is still the subject of intense ongoing research. The mechanism proposed by Chauvin and Hérisson,[99] *via* the formation of metallocyclobutane intermediates is the most widely accepted (**Scheme 67**).



Scheme 67. Widely accepted cross-metathesis mechanism.[99]

In recent years, olefin cross-metathesis has emerged as a powerful and convenient synthetic technique in organic chemistry. However, the use of CM as a general synthetic method has been limited by the lack of predictability in product selectivity and stereoselectivity. Cross-metathesis reactions are governed by the statistical formation of three possible dimers, separately available as their (*E*)- and (*Z*)-double bond isomers (**Scheme 68**). Two of them result from the homodimerization of each starting olefin with itself, while the third dimer is the heterodimeric product formed by the coupling of both starting olefins to one another.



1	:	1	25%	25%	50%
2	:	1	17%	17%	66%
4	:	1	10%	10%	80%
10	:	1	4.5%	4.5%	91%
20	:	1	2.5%	2.5%	95%

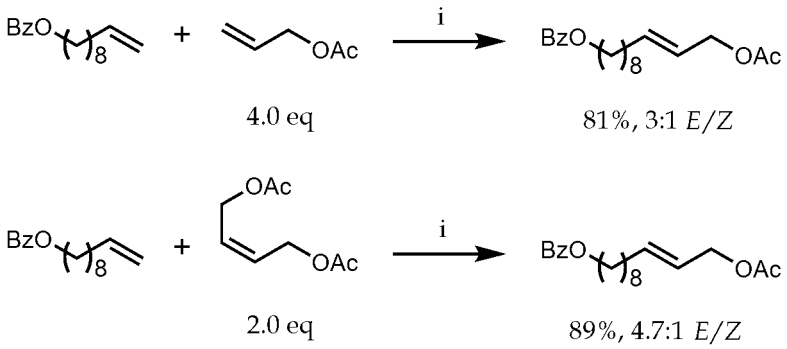
Scheme 68. Statistical distribution of Cross-Metathesis dimers.[100]

The outcomes of non-selective cross-metathesis reactions obey to statistical distribution (**Scheme 68**), and result in the formation of complex mixture of products, that are generally difficult to separate.[100] Such CM reactions, producing the desired heterodimer AB in a maximum of 50% yield, and tangled up with a complex mixture of side products, do not represent an attractive coupling tool for organic chemists. This is the reason why many scientists have focused their efforts onto the control of CM selectivity.[100]

Playing with the ratio between starting olefins[100] is one of the few options which can be employed to direct CM selectivity. Using one of the two starting olefins in large excess can afford the desired heterodimer with very good conversion (> 95%) (**Scheme 68**). However, at least one of the two olefins has to be cheaply accessible, as it is common to use more than ten equivalents of one partner over the other. The choice of the olefin to use in excess is closely related to the ability of each olefin partner to undergo homodimerization, and as a result can be tricky to determine. Thus, the most valuable partner will be the one to use in excess sometimes, making the cross-metathesis of two sophisticated and elaborated partners unthinkable.

The addition rate of the CM partner can also help direct the selectivity of cross-metathesis reactions. The olefin having the strongest ability to homodimerize can be added very slowly to the other olefin in solution with the catalyst, through the use of a syringe pump. Although this process can help improve the conversion towards the heterodimer, it usually requires the two olefins to have very different reactivity.

Finally, different modifications of the reaction conditions such as solvent, temperature, or the use of additives such as Lewis acids[101] can also help increase the reactivity of partners in certain CM reactions. Alternatively, the use of olefin partners as their homodimers (**Scheme 69**),[102] the addition of the catalyst neat or in solution, or the use of *vacuum*[102a] during the reaction to remove ethylene from the catalyst, thus helping drive the equilibrium to the right, are also factors which have to be taken into consideration. Although the effects of these factors on CM efficiency cannot be predicted, very time-consuming screening of such parameters can nevertheless give significant results.



Reagents and conditions **i**, first generation Grubbs catalyst (5 mol%), DCM, 40 °C, 12 h.

Scheme 69. Effect of symmetric olefin partner on cross-metathesis.[102a]

As the choice of the CM catalysts and olefin partners is absolutely crucial for the CM selectivity, it will be discussed in details in the next sections (**II-2.1.2** and **II-2.1.3**).

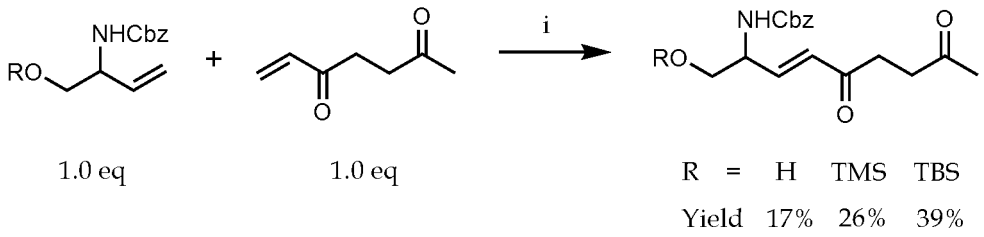
2.1.2 Choice of cross-metathesis allylic amino alkene partner[100]

The choice of CM partners is by far the most important factor to be controlled in order to guarantee successful selective CM. Although being fairly unpredictable, two major features can be finely modified to direct the CM selectivity:

- Steric effects

The steric hindrance of each partner does affect their ability to undergo homodimerzation, and directly favours or disfavours the heterodimerization. Two different olefins A and B will tend to dimerize according to the statistical distribution discussed earlier (**Scheme 68**). However, if the olefin A is made more hindered, this will reduce its propensity to

homodimerize with itself, and will consequently increase its probability to heterodimerize with B. Nevertheless, if the olefin A is made too hindered, the opposite olefin B will prefer homodimerize with itself rather than heterodimerize. For instance, the incorporation of additional bulky groups, such as protecting groups, can facilitate important geometrical modifications of a CM partner, affecting its propensity to homodimerize, and making its double bond more or less accessible for the coupling reaction (**Scheme 70**).



Reagents and conditions **i**, second generation Grubbs catalyst (5 mol%), DCM, 40 °C, 24 h.

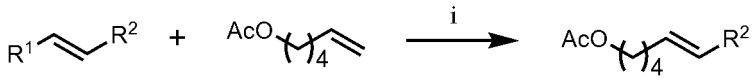
Scheme 70. Effect of protecting groups on cross-metathesis.[102b]

- Electronic effects

The idea that two olefins possessing opposite electronic properties are more likely to heterodimerize, is widely accepted in metathesis. That is to say that an electron withdrawing olefin has more chance to heterodimerize with an electron rich olefin. Despite the fact that this common magnet-like principle is in total contradiction with homodimerization, which can be observed in very high yields sometimes, it remains a reliable scheme to use for the design of efficient CM couplings.

It is difficult to accurately predict how the complex interplay of steric and electronic factors will determine the ability of various sets of olefins to participate in selective CM. In order to make this point clearer, R. H. Grubbs[100] published a general model based, notably, on the ability of different class of olefins to homodimerize. It represents an interesting empirical tool for the prediction of competitive CM couplings, involving notably polyalkene partners with several competing C=C double bonds. However, it appeared to be rather limited by the number of substrates and catalysts listed, and in fact, did not help us find the optimal conditions in our case.

Cross-metathesis is a very powerful tool which can be employed to couple most types of olefin. However, to do so, it can require a significant amount of work to screen all the possible conditions. However, due to the lack of predictability in CM selectivity, this time-consuming screening remains the only real way to significantly improve the efficiency of CM couplings, as illustrated below (**Scheme 71**).

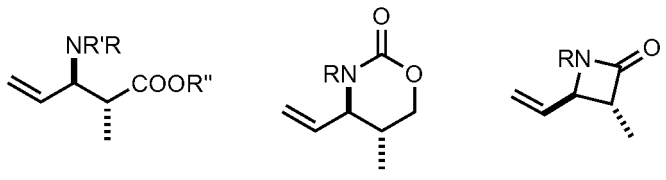


eq.	R^1	R^2	Yield	*E/Z*
1.0	H	CHO	62%	>20:1
1.0	Me	CHO	95%	>20:1
2.0	H	COOEt	98%	>20:1
2.0	Me	COOEt	50%	>20:1

Reagents and conditions **i**, second generation Grubbs catalyst (5 mol%), DCM, 40 °C, 12 h.

Scheme 71. Effect of alkene substitution on cross-metathesis.[102a]

The use of 1,3-dienes as metathesis partners is known from the literature,[103-107] and several groups have reported their use in metathesis couplings with allylic ethers,[103,106,107] or allylic alcohols.[105] However, the CM coupling of 1,3-dienes with allylic amines have never been reported before, and thus represented an opportunity to extend the scope of cross metathesis methodology. As a result, an important screening of conditions such as, CM partners, catalysts, solvents, and many other parameters was necessary to establish suitable CM conditions. It was first crucial to reduce the large choice of amino CM partners to a limited number of frameworks structurally similar to successful CM partners reported in the literature (**Figure 20**).[108-114]



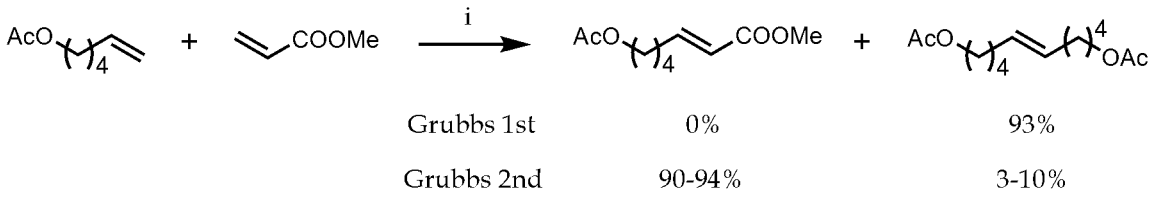
R and R' = H or any protecting groups

Figure 20. Possible frameworks for Cross-Metathesis coupling.

According to the preliminary results, the β-lactam scaffold appeared as one of the best candidates. It had already been used in cross-metatheses with success,[113] and offered an internal protection of both amino and carboxylic groups masked as the β-lactam scaffold. As presented in McCarthy's work,[84,89] once coupled to the diene, the lactam could easily be cleaved in one step, and thus liberates both amine and carboxylic acid functions required in the final ADDA structure. Furthermore, the relative *trans*-stereochemistry, required in the final ADDA chain, had been demonstrated to be relatively easy to control through β-lactam chemistry.[84,89]

2.1.3 Choice of cross-metathesis catalysts

The selection of appropriate CM catalysts represents a difficult task which can have dramatic effects on the outcome of the coupling reaction, as illustrated below (**Scheme 72**).



Reagents and conditions **i**, CM catalyst (3-5 mol%), DCM, 40 °C, 12 h.

Scheme 72. Effect of catalyst on CM selectivity.[102a]

Since the discovery of the cross-metathesis coupling reaction in the 1950s, the development of CM catalysts has become a very intense and productive area of research. Among the numerous catalysts designed, more than a dozen are now commercially available.[115] Nevertheless they remain fairly expensive to use and so focusing our attention on the most promising candidates, was consequently considered as crucial. Moreover, it should be noted that metathesis catalysts have generally low activity in cross-metathesis and require then to be used in fairly large amounts (> 30 mol%). This is due to the lack of enthalpic driving force in cross-metathesis unlike in Ring Closing Metathesis (RCM) (formation of favoured 5 or 6-membered ring) or Ring-Opening Metathesis (ROM) (ring-strain release). This obstacle has widely participated to the under-representation of CM compared with RCM or ROM.

In addition to the general model published by Grubbs,[100] a review published in 2007[115] appeared to be extremely helpful for the selection of the five most adapted CM catalysts, listed below (**Figure 21**):

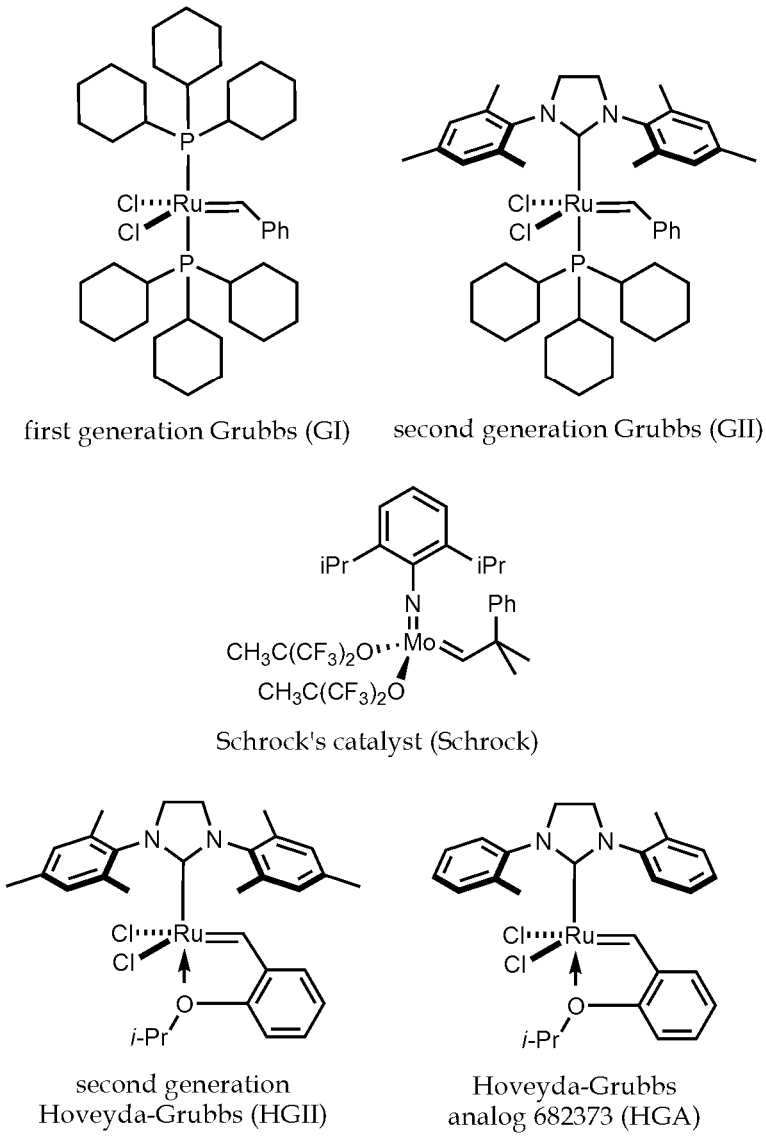


Figure 21. Most promising selected CM catalysts.[115]

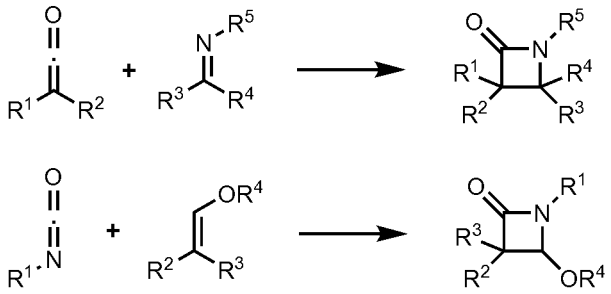
The selection was based upon their price, their ability to catalyse cross-metathesis rather than other types of metathesis (RCM, ROM), their ability to catalyse CM of hindered olefins, and their reactivity at low temperatures.

2.2 - Synthesis of β–lactam CM partner

2.2.1 Brief overview on β–lactam chemistry

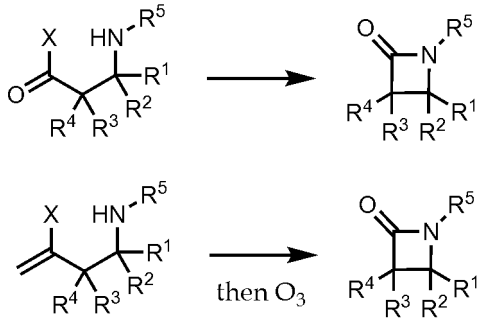
The chemistry related to the synthesis of β-lactams has generated a lot of interest since the discovery of penicillin and other β-lactam-containing antibiotics, and is frequently represented in the literature by two majors synthetic routes, presented below:

- [2+2] cycloadditions (**Scheme 73**)[116]



Scheme 73. Synthesis of β-lactam *via* [2+2] cycloadditions.[116]

- Nucleophilic cyclisations (**Scheme 74**)[117]



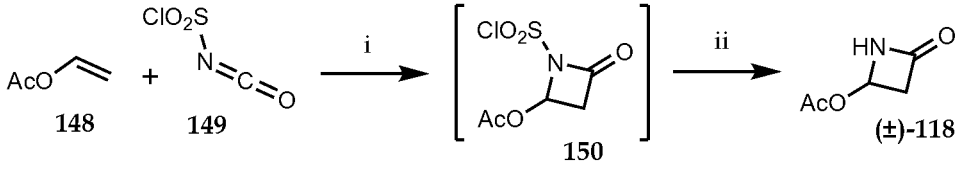
Scheme 74. Synthesis of β-lactam *via* nucleophilic cyclisations.[117]

Many other methods, such as catalysed C-H insertion,[118] are known to synthesise β-lactams. However, they are not as widely reported as the two methods exposed above (**Schemes 73 & 74**). These well-known approaches can also be found in many different

variants, involving ketene precursors such as acyl chlorides or diazo-compounds, to name a few.[119]

2.2.2 *Synthesis of β-lactam* **(±)-119**

Before embarking on an enantioselective synthesis, it was first decided to focus on the preparation of the racemic β–lactam, which could allow the isolation of the *enantio*-ADDA, and its diasteromeric analogue simultaneously. The synthesis started with the [2+2] cycloaddition of vinyl acetate **148** and chlorosulfonyl isocyanate **149**, which afforded the known acetoxy azetidinone **(±)-118** in good yield compared with literature precedents.[120] This highly scalable reaction allowed the preparation of large amounts of lactam **(±)-118** in an inexpensive manner (**Scheme 75**). The low yield obtained was essentially due to the non-trivial work-up required to cleave the chlorosulfonyl moiety of the intermediate **150** to access the azetidinone **(±)-118**. Indeed, the chlorosulfonyl cleavage, which must be carried out at low temperature in pre-cooled glassware, releases one equivalent of hydrochloric acid and one equivalent of sulphuric acid. Although the majority of the acids were neutralized during the buffered work-up, the remaining acidic traces, and the elevation of the temperature induced the rapid decomposition of the β-lactam unit.

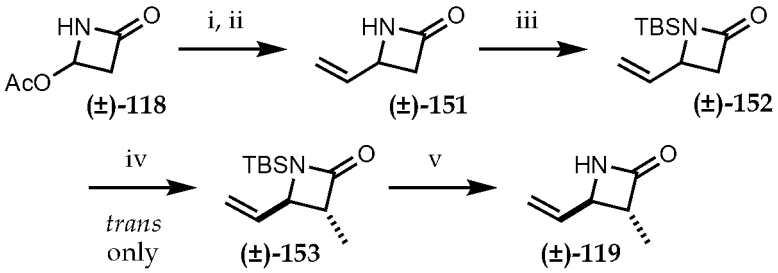


Reagents and conditions **i**, neat, 0 °C, 1 h; ii, $NaHCO_3$, Na_2SO_3, water, ice, 0 °C, 24% (2 steps).

Scheme 75. Synthesis of acetoxy azetidinone **(±)-118**.

The reaction required no purification to afford the unstable acetoxyazetidinone **(±)-118** in very good purity. The azetidinone **(±)-118** was then immediately converted into the vinyl azetidinone **(±)-151** by treatment of the phenyl sulfone intermediate with vinyl magnesium bromide at -78 °C, as described in the literature.[120ab] The lactam **(±)-151** was then protected as *N*-TBS azetidinone **(±)-152** in quantitative yield, and an extra methyl group was incorporated α-position to the carbonyl group by treatment of azetidinone **(±)-152** with *n*-BuLi and methyl iodide. The resulting methylated vinyl azetidinone **(±)-153**

was thus obtained in good yield with the desired *trans*-relationship exclusively. The *N*-TBS azetidinone **(±)-153** was finally deprotected to yield the final *trans*-β-lactam **(±)-119** (**Scheme 76**).



Reagents and conditions **i**, $PhSO_2Na$, water, Δ, 20 min; **ii**, CH_2=CHMgBr, THF, -78 °C, 90%; **iii**, TBSOTf, DCM, rt, 10 min, 98%; **iv**, *n*-BuLi, THF, -78 °C, then MeI, 78%, *trans* only; **v**, KF, MeOH, 0 °C, 87%.

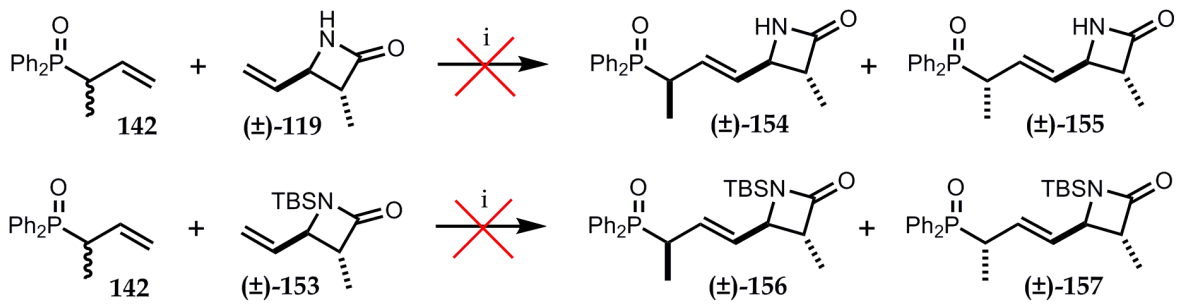
Scheme 76. Synthesis of *trans*-azetidinone **(±)-119**.

3 – THE CROSS-METATHESIS COUPLING

3.1 – First attempts

Although extensive work have been reported to better understand and predict cross-metathesis selectivity,[100] the screening of a broad range of conditions appeared necessary. With both the left and right hand side ADDA fragments in hands, the first CM test reactions could be attempted. However, before embarking on the initial cross-metathesis methodology, it was first decided to take advantage of the successful Horner-Wadsworths-Emmons olefination used to construct the diene **(*E*)-139** (**Scheme 62**). The idea was to turn the lactams **(±)-119** and **(±)-153** into the corresponding allylic phosphine oxides **(±)-154**, **(±)-155**, **(±)-156**, and **(±)-157** through a cross-metathesis reaction (**Scheme 77**). Surprisingly, cross-metathesis of phosphine oxides are barely represented in the literature,[121,122] and a wide number of conditions was screened to find the best coupling conditions. A broad variety of conditions involving the use of different CM catalysts (GI, GII, HGII, 10 - 20 mol%), in different solvents (dichloromethane and toluene), and in the presence of titanium isopropoxide. Unfortunately, the coupling of racemic 1-

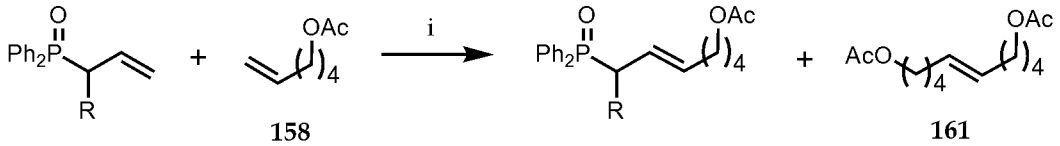
methylallyldiphenylphosphine oxide **142** with lactams **(±)-119** and **(±)-153**, proved fruitless, as it did not give even a trace of the expected heterodimer (**Scheme 77**).



Reagents and conditions **i**, various conditions (see text).

Scheme 77. Failed CM with between phosphine oxide **142** and β-lactams **(±)-119** and **(±)-153**.

Our attention was then drawn on literature precedents, which reported the use of allyldiphenylphosphine oxide **143** as a successful cross-metathesis partner.[121,122] It was first decided to compare the reactivity of both phosphine oxides **142** and **143** with one another and thus determine the effect of the extra methyl group on the CM reactions. The previously reported methodology,[122] involving the use of hexenylacetate **158**, was rigorously followed as described, and reliably reproduced for both phosphine oxides (**Scheme 78**). The comparison brought precious information, highlighting the fact that the extra methyl caused dramatic effects on the CM selectivity (**Scheme 78**).



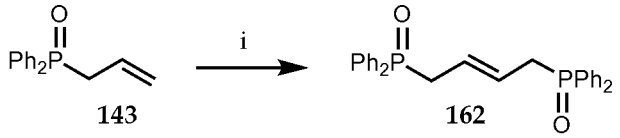
142	R = Me	3.3 eq	**159**	R = Me	52%	54%
143	R = H	3.1 eq	**160**	R = H	84%	38%

Reagents and conditions **i**, Second generation Grubbs catalyst (6 mol%), DCM, Δ, 24 h.

Scheme 78. Comparison of CM abilities of phosphine oxides **142** and **143**.

It should be noted that, although the formation of traces quantities of (*Z*)-isomers of olefins **159**, **160**, and **161** were expected, as described in the literature,[122] this could not be confirmed by NMR analyses as the NMR signals of the side-products traces were mostly

unresolved. The phosphine oxide **143** was thus proved to be a much better CM partner than the 1-methylallyldiphenylphosphine oxide **142** (**Scheme 78**). CM test reactions were continued, and were all re-attempted with the allyldiphenylphosphine oxide **143**. Among the numerous conditions employed, it should also be noted that the use of symmetrical (*E*)-allyldiphenylphosphine oxide homodimer **162** (**Scheme 79**), obtained through the method reported by V. Gouverneur,[122] as CM partner, or the addition of Ti(O-*i*Pr)$_4$ did not give any better results.

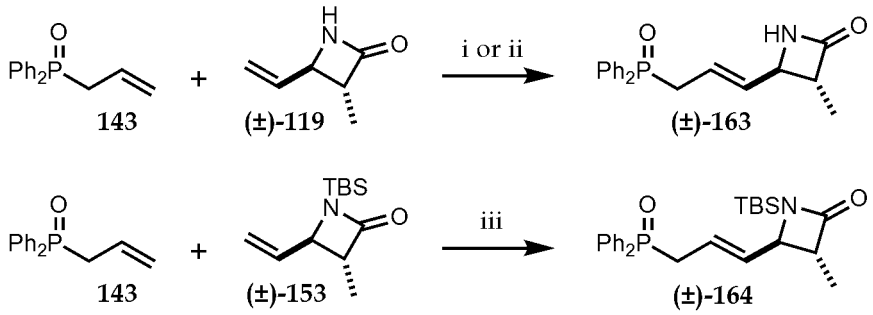


143 162

Reagents and conditions **i**, Second generation Grubbs catalyst (2 mol%), DCM, Δ, 24 h.

Scheme 79. Homodimerization of allyldiphenylphosphine oxide **162**.

After a significant amount of optimization, the first promising results were obtained in toluene, at 80 °C, with either second generation Grubbs catalyst or second generation Hoveyda-Grubbs catalyst. Interestingly, the choice of β-lactam CM partner appeared important for the cross-metathesis efficiency (**Scheme 80**). Indeed, unprotected azetidinone **(±)-119** was shown to undergo heterodimerization with phosphine oxide **142** in a much better yield than *N*-TBS protected azetidinone **(±)-153** (**Scheme 80**), which was since considered as a poor CM partner, and discarded from the future CM screenings. Traces of side products were also observed by NMR but could not be identified as they were mainly unresolved. Hence, the existence of the (*Z*)-isomers of **(±)-163** and **(±)-164** heterodimers could not be demonstrated.



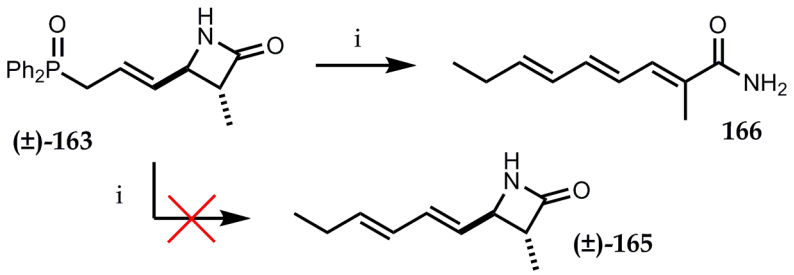
143 (±)-119 (±)-163

143 (±)-153 (±)-164

Reagents and conditions **i**, Second generation Grubbs catalyst (19 mol%), toluene, 65 to 80 °C, 38 h, 69%; **ii**, Second generation Hoveyda-Grubbs catalyst (31 mol%), toluene, 80 °C, 13 h, 78%; **iii**, Second generation Hoveyda-Grubbs catalyst (10 mol%), toluene, 80 °C, 33 h, 31%.

Scheme 80. Heterodimersation of phosphine oxides **(±)-163** and **(±)-164**.

Both very polar heterodimers **(±)-163** and **(±)-164** were isolated after difficult purifications by flash chromatography, and pure phosphine oxide **(±)-163** was taken into HWE coupling. The phosphine oxide **(±)-163** was treated with *n*-BuLi, and then with freshly distilled propionaldehyde in using the same methodology previously utilised to generate the dienes **(*E*)-139** and **(*Z*)-139** *via* the Horner-Wadsworths-Emmons olefination (**Scheme 62** & **81**). Unfortunately, the expected but unwanted side β-elimination followed by the opening of the lactam occurred, in place of the staighforward olefination designed to provide diene **(±)-165**. Another attempt, with catalytic amount of *n*-BuLi gave the same unwanted triene **166** (**Scheme 81**), and the process was consequently abandoned without trying the reaction with *N*-TBS protected hetrodimer **(±)-164**. The CM reactions seen above (**Scheme 80**) were therefore not optimized. The major (*E*,*E*,*E*)-geometry of the triene was deduced from NMR analyses reported in the literature for equivalent trienes.[123]



Reagents and conditions **i**, *n*-BuLi, HMPA, THF, -78 °C, the EtCHO, -78 °C to rt, overnight, 66%.

Scheme 81. Unsuccessful synthesis of diene **(±)-165** through HWE olefination.

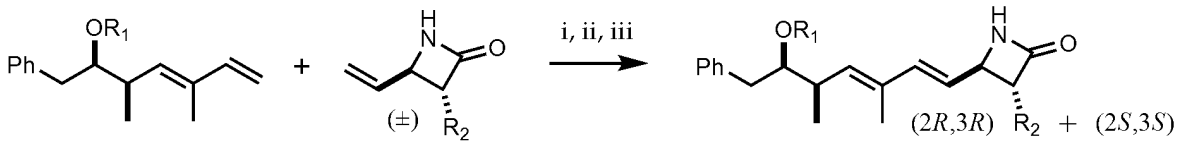
It worth mentioning that the CM / HWE-sequence developed (**Scheme 80 & 81**), offers a novel interesting route to valuable polyenes commonly found in the literature.[123] After failing to form the (*E*,*E*)-1,3-diene, the initial CM strategy was then re-envisaged, and the CM / HWE approach was left aside.

3.2 – Towards the successful metathesis

The statistical distribution of olefins (**Scheme 68**) can be significantly modified for cross-metatheses involving polyalkenes possessing several competitive C=C double bonds. The

competition between the double bonds tends to increase the risk of forming undesired cross-dimers. This is one of the reasons why cross-metathesis of polyalkenes remains fairly under represented in the literature.

In order to find the best cross-metathesis partners among all the olefin intermediates generated so far, a straightforward screening was operated. On one hand, the CM abilities of OMe-diene **(*E*)-117** were compared with those of *O*-TBS diene **(*E*)-139**, in coupling them separately to β-lactam **(±)-119.** And, on the other hand, the CM abilities of lactam **(±)-119** and those of lactam **(±)-151** were also compared in coupling them separately to diene **(*E*)-139**. Thus, we expected to be able to determine, and better understand the effects of the TBS and methoxy groups on the reactivity of the dienes **(*E*)-117** and **(*E*)-139**, as well as the effects of the extra methyl group of β-lactam **(±)-119** compared with non-methylated β-lactam **(±)-151** (**Scheme 82**).



(*E*)-139	R_1 = TBS	**(±)-119**	R_2 = Me	cond. i	37% (*E*) only	**167** and	**168**
(*E*)-117	R_1 = Me	**(±)-119**	R_2 = Me	cond. ii	37% (*E*) only	**169** and	**170**
(*E*)-117	R_1 = Me	**(±)-151**	R_2 = H	cond. iii	11% (*E*) only	**171** and	**172**

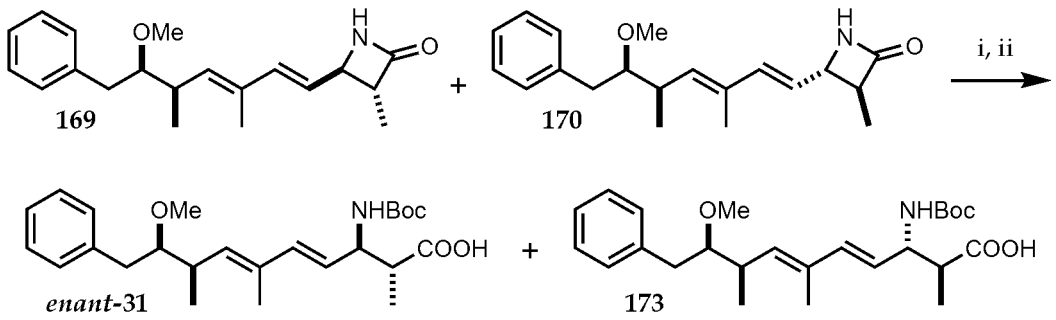
Reagents and conditions **i**, HGII (11 mol%), toluene, Δ, 2 days, 37%; **ii**, HGII (16 mol%), toluene, Δ, overnight, 37%; **iii**, HGII (10 mol%), DCM, Δ, 10 h, 11%.

Scheme 82. First successful cross-metatheses between diene and β-lactam units.

After trying many CM reactions under various conditions (solvents, temperatures and catalysts), interesting results were obtained. The coupling of diene **(*E*)-139** with β-lactam **(±)-119** using second generation Hoveyda-Grubbs catalyst, in toluene, at reflux, provided heterodimers **167** and **168** with a modest but encouraging 37% yield (**Scheme 82**). The same CM conditions were then applied to methoxy diene **(*E*)-117**, and provided heterodimers **169** and **170** with the same efficiency. Finally, the CM coupling of diene **(*E*)-117** with β-lactam **(±)-151** yielded dienes **171** and **172** in very low yield (**Scheme 82**).

Interestingly, the preliminary results obtained showed that, unlike for the dienes **(*E*)-117** and **(*E*)-139**, which had almost identical CM abilities, the presence of the additional methyl of β-lactam **(±)-119**, compared with **(±)-151**, dramatically reduced the efficiency of the coupling metathesis. Based on these observations, the azetidinone **(±)-119** was considered as the best CM partner, and our future efforts were essentially focused on the optimisation of its CM coupling with diene **(*E*)-117**.

Before optimising the CM reaction, the inseparable heterodimers **169** and **170** were *N*-Boc protected by treatment with triethylamine, DMAP, and $(Boc)_2O$, and the resulting *N*-Boc protected lactam intermediates were subsequently opened by addition of lithium hydroxide, as described by McCarthy.[84,89] The sequence provided the final *N*-Boc carboxylic acids ***enant*-31** and **173**, which matched with the data previously reported for the opposite enantiomer (**Scheme 83**).[72,76-79,81-89]

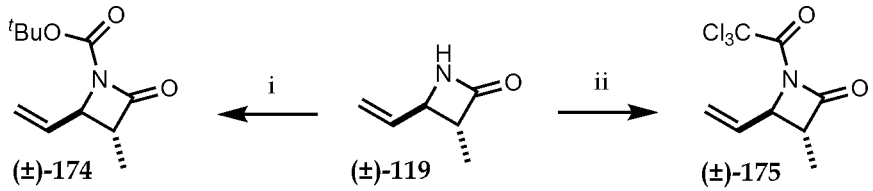


Reagents and conditions **i**, $(Boc)_2O$, DMAP, TEA, DCM, rt, overnight, 70%; **ii**, LiOH, THF, rt, 23 h, 85%.

Scheme 83. Synthesis of *enantio*-*N*-Boc-ADDA ***enant*-31** and the ADDA isoform **173**.

3.3 – Optimisation of the coupling

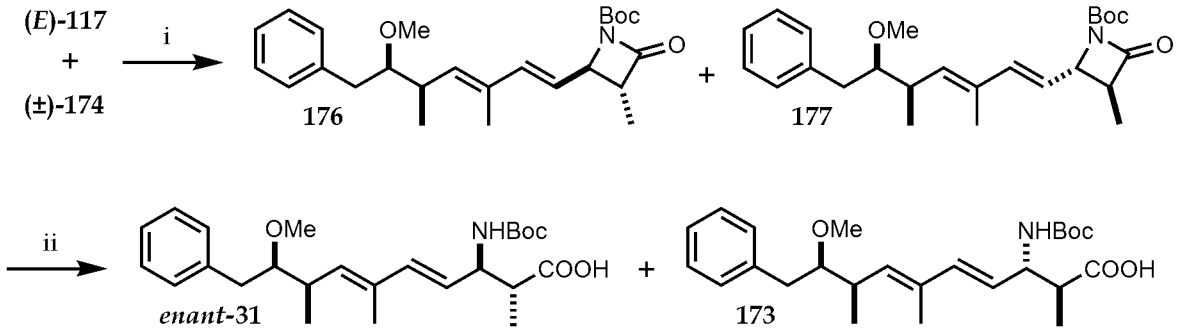
A large number of modifications were envisaged to optimize the actual cross-metathesis of the β-lactam **(±)-119** and the diene **(*E*)-117** (**Scheme 82**). The use of a suitable nitrogen protecting group was envisaged to make the azetidinone **(±)-119** more hindered, and less electron rich in taking some of the electron density away from the nitrogen. In order to do this, the *N*-Boc and *N*-TAC protecting groups appeared as the most judicious options, and both racemic *N*-protected β-lactams **(±)-174** and **(±)-175** were generated from the unprotected azetidinone **(±)-119** in quantitative yield (**Scheme 84**).



Reagents and conditions **i**, $(Boc)_2O$, DMAP, TEA, DCM, rt, overnight, 100%; **ii**, $Cl_3CC(O)Cl$, TEA, DCM, -78 °C, 10 min, 100%.

Scheme 84. Synthesis of *N*-Boc and *N*-TAC protected β-lactams **(±)-174** and **(±)-175**.

McCarthy demonstrated that *N*-Boc protection was essential for the LiOH-based lactam hydrolysis,[84,89] and for this reason, the *N*-Boc protected lactam **(±)-174** was preferably engaged into the CM coupling. Gratifyingly, the *N*-Boc heterodimer was obtained as the (*E*,*E*)-isomer exclusively, in a much better yield, and the subsequent opening of the lactam *via* addition of lithium hydroxide was acheived in quantitative yield (**Scheme 85**). The spectral data of the final *N*-Boc carboxylic acid ***enant*-31** matched with the data previously reported for the opposite enantiomer.[72,76-79,81-89]



Reagents and conditions **i**, HGII (21 mol%), toluene, Δ, 22 h, 67%; **ii**, LiOH, THF, rt, 23 h, 85%.

Scheme 85. Synthesis of *enantio*-*N*-Boc-ADDA ***enant*-31** and the ADDA isoform **173**.

As a consequence of the satisfactory results obtained for the CM of diene **(*E*)-117** and *N*-Boc protected lactam **(±)-174**, the fragile *N*-TAC protected lactam **(±)-175** was finally not utilised.

4 – COMPARISON OF COLLECTED DATA

The final mixture of inseparable diastereoisomers ***enant*-31** and **173** was fully characterised and the collected data, including ^{1}H, ^{13}C NMRs and $[\alpha]_D$, was thoroughly compared with the data available in the literature.[72,76-79,81-89] Against the odds, the similarity was just astonishing. The obtained isomeric mixture had the same physical and spectral data as the *N*-Boc-ADDA chain reported in the literature.[72,76-79,81-89] To explain these observations, three possible theories were proposed:

1) Both diastereoisomers ***enant*-31** and **173** had exactly the same properties and consequently appeared to be identical;
2) A diastereoselective cross-metathesis was achieved, as is documented in the literature, *via* the use of chiral CM catalysts;[124]
3) The unwanted isomer **173** decomposed at some point during the reaction or the purification process.

4.1 – First investigations

The *N*-Boc lactam 176 and 177 showed two distinct , but very close set of signals by ^{1}H and ^{13}C NMRs. However, this difference completely disappeared in the final *N*-Boc acid *enant*-31, showing only one set of NMR signals, and a very similar optical rotation ($[\alpha]^{23}_D$ +15.1, (c = 1.0, $CHCl_3$)) to the one of the opposite enantiomer reported in the literature ($[\alpha]^{22}_D$ -15.1, (c = 1.0, $CHCl_3$)[76]) and ($[\alpha]^{23}_D$ -15.7, (c = 1.0, $CHCl_3$)[79]). To explain these observations the existence of two blocked rotamers was postulated, as illustrated below (Figure 22).

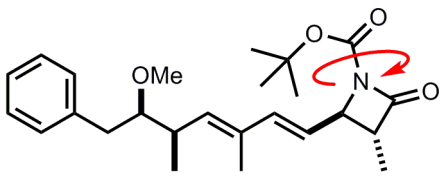


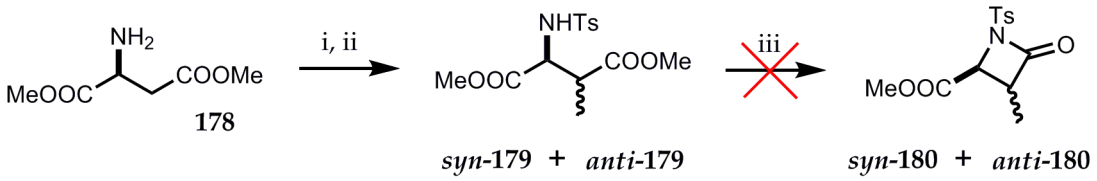
Figure 22. Possible barrier originating two rotamers from *N*-Boc lactam **176**.

In order to probe the existence of potential conformers, high temperature ^{1}H NMR experiments (C_6D_6, 20 to 80 °C) of the isomeric mixture of *N*-Boc protected lactams **176**

and **177** were carried out. The two sets of signals were expected to merge into one, but unfortunately these experiments did not provide any conclusive evidence regarding the presence, or not, of rotamers. As the ^{1}H and ^{13}C NMR of the lactams **176** and **177** showed very distinct chemical shifts, their separation using chiral HPLC was first attempted. However, independently on the columns and the conditions used, a single sharp peak was only observed. A HPLC separation of the isomeric mixture of acids ***enant*-31** and **173** was then attempted. However, neither HPLC in reverse phase, nor chiral HPLC in normal phase enabled the observation of two peaks either. Despite using various columns and conditions, a single sharp peak was always observed, suggesting the presence of two rotamers resulting from a diastereoselective CM. However, the synthesis of the enantiomerically pure lactam **174**, appeared necessary to formally demonstrate the presence of a single diastereoisomer beyond a doubt.

4.2 – Synthesis of optically pure lactam **174**

A large number of methods have been reported for the synthesis of enantiomerically pure lactams.[125,84,89] They can either be generated through enzymatic[125a] or crystallographic[125b] resolution methods, using chiral reagents or catalysts,[125c] or be generated from the chiral pool.[84,89] The documented cyclisation of 3-methylaspartic acid derivatives[84,89] was initially investigated, to obtain optically pure β–lactams. The well-known diastereoselective methylation was used to prepare the trans-methylated aspartate exclusively, as described in the literature.[126] However, in our hands this methylation was proved troublesome (**Scheme 86**), resulting in a mixture of diastereoisomers ***syn*-179** and ***anti*-179**, as described by Chamberlin.[81] Furthermore, the mixture could not be cyclised into the β–lactams ***syn*-180** and ***anti*-180** (**Scheme 86**).



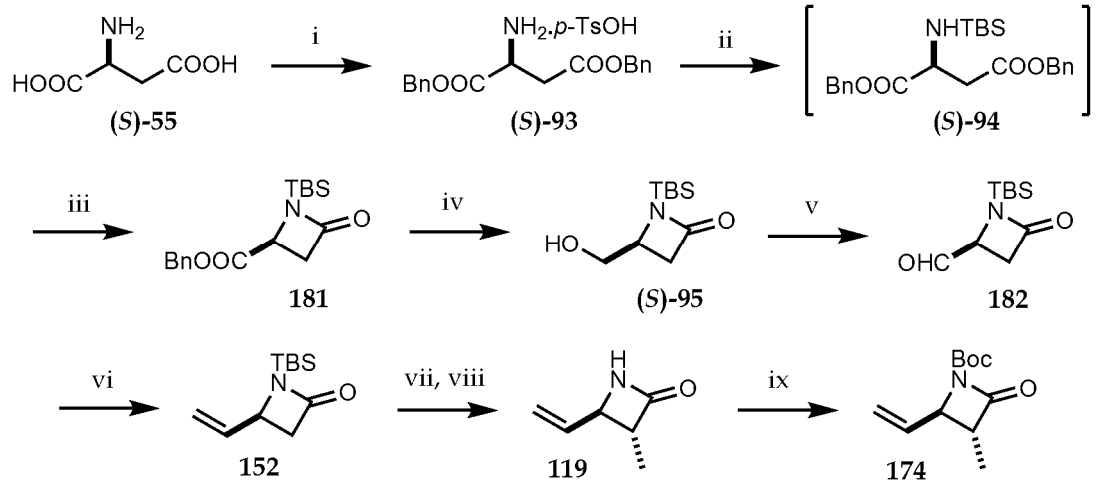
Reagents and conditions **i**, TsCl, TEA, rt, 24 h, THF; **ii**, KHMDS, THF, -78 °C then MeI, -78 °C to rt, 45%, (1:3) *syn* / *anti*; **iii**, *t*BuMgCl, Et_2O.

Scheme 86. Unsuccessful route to optically pure azetidinone ***anti*-180**.

The issue was finally overcome thanks to methodology described by McCarthy,[84,89] which was also based on the same type of cyclisation to produce the 4-membered ring (**Scheme 87**). The main difference was the use of benzyl esters in place of methyl esters. This better leaving group greatly facilitated the cyclisation process, but on the down side, made the purification steps more difficult, as benzyl alcohol was liberated in place of methanol. Initially, the procedure was rigorously followed as described by McCarthy.[84,89] However, the instability of crude *N*-TBS aspartic ester **(*S*)-94** towards extensive manipulations, as well as the racemisation at many stages, rapidly appeared as major problems. After repeating the McCarthy's β-lactam synthesis[84,89] several times, obtaining partial to total racemisation along the way, the whole procedure was modified to insure the formation of the final *N*-Boc protected β-lactam as a single enantiomer (**Scheme 87**).

The readily accessible and enantiomerically pure (*S*)-aspartic acid **(*S*)-55** was firstly dibenzylated. The resulting benzyl diester **(*S*)-93** was then *N*-TBS protected to give the fragile and unstable intermediate **(*S*)-94**, which was used immediately in the cyclisation reaction (**Scheme 87**). The resulting lactam **181** was then gently reduced by treatment with $NaBH_4$ and LiBr with control of the temperature, yielding the alcohol **(*S*)-95** in modest yield. The Swern oxidation, which represented one of the most sensitive steps regarding epimerisation, was performed by addition of triethylamine at -78 °C and led to optically pure aldehyde **182**. However, as demonstrated later, this reaction should have been operated with DIPEA to suppress completely any risk of racemisation (Section **IV-2.3.3**).

The resulting aldehyde **182** was first olefinated with Ph_3CH_2I and LiHMDS, but the procedure led to the total decomposition. Alternatively, the treatment of aldehyde **182** with Petasis reagent allowed the preparation of vinyl lactam **152** with complete conversion as observed by NMR analyses. However, vinyl lactam **152** was isolated in very low yield as it decomposed during the purification by flash column chromatography over neutralised silica. This decomposition was completely unexpected as this purification process had previously been used with excellent success, with exactly the same conditions to provide the racemic vinyl lactam **(±)-152** in nearly quantitative yield. The degradation was thought to be a result of the action of silica and Petasis derivatives combined together.



Reagents and conditions **i**, BnOH, p-TsOH, Δ, 6 h; **ii**, TBSCl, TEA, DMAP, DCM, rt, overnight; **iii**, *t*BuMgCl, Et_2O, -78 °C to rt, overnight; **iv**, $NaBH_4$, LiBr, water, THF, < 28 °C, 9% (4 steps); **v**, $(COCl)_2$, DMSO, TEA, DCM, -78 °C; **vi**, Petasis reagent, THF, Δ, 2.5 h, 22% (2 steps); **vii**, *n*-BuLi, THF, -78 °C, then MeI, 78%, *trans* only; **viii**, KF, MeOH, 0 °C, 55% (2 steps); **ix**, $(Boc)_2O$, DMAP, TEA, DCM, rt, overnight, 65%.

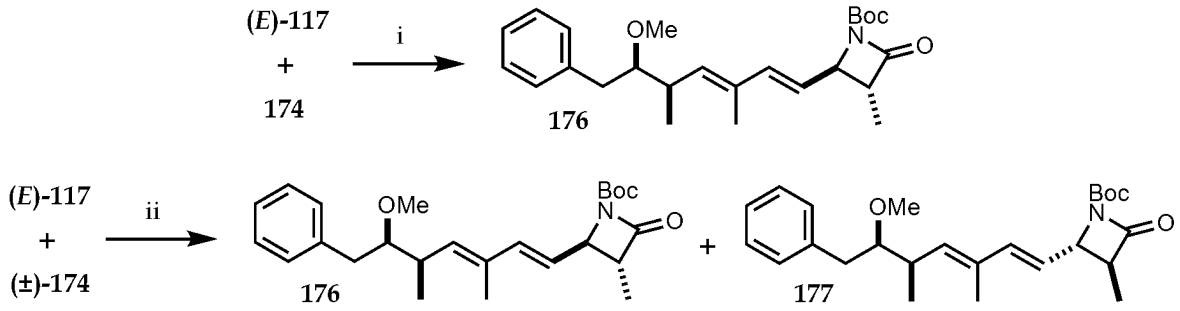
Scheme 87. Synthesis of the optically pure azetidinone **174**.

The next part of the synthesis was achieved following the same conditions previously described for the synthesis of racemic lactam **(±)-174** (**Scheme 76** & **84**), which provided the enantiopure *N*-Boc lactam **174** in modest to good yield. Comparison of HPLC traces of optically pure lactam **174** with its racemic version **(±)-174** allowed the determination of an excellent enantiomeric excess (*ee* = 98%). Although, the new method ensured the formation of the final *N*-Boc protected β-lactam as a single enantiomer, the synthesis of lactam **174** was completed in very low yields. The lack of time prevented us from optimising the whole process.

4.3 – Coupling toward enantiopure *N*-Boc-ADDA chain

To compare the results in a rigorous and scientific manner, the final cross metathesis couplings were set up in parallel, and performed under strictly identical conditions with enantiopure *N*-Boc lactam **174** and the racemic *N*-Boc lactam **(±)-174** obtained from the [2+2] cycloaddition. Both *N*-Boc lactam sets were coupled to diene **(*E*)-117** using the same methodology as before, which provided the (*E*,*E*)-*N*-Boc heterodimers **176** and [**176** + **177**] exclusively in similar yields (**Scheme 88**). At this stage, the difference between the two sets of (*E*,*E*)-heterodimers **176** and [**176** + **177**] was clearly visible by NMR analyses. This formally proved that compound **176**, obtained from the CM coupling of the diene **(*E*)-117**

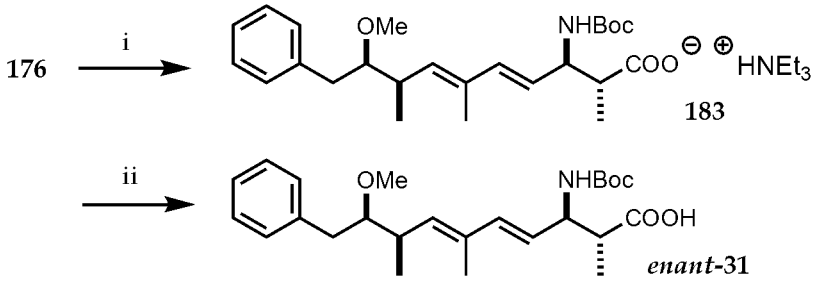
with the racemic lactam **(±)-174** (Section **III-3.2**) was definitely not a mixture of two rotamers, but only a mixture of two diastereoisomers [**176** + **177**]. Thus, the diastereoselective metathesis theory was formally disproved, but not the one involving potential decomposition of the undesired diastereoisomer **177**, which was still realistic.



Reagents and conditions **i**, HGII (20 mol%), toluene, Δ, 14 h, 61%; ii, HGII (20 mol%), toluene, Δ, 14 h, 69%

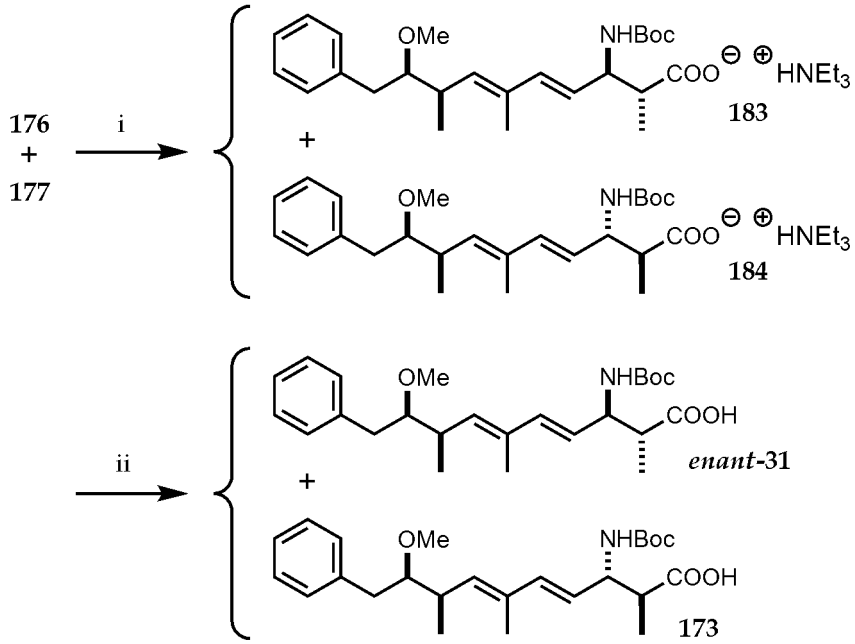
Scheme 88. Synthesis of heterofimers **176** and [**176**+**177**].

Both sets of *N*-Boc protected lactams **176** and [**176** + **177**] were brought to the carboxylic acid stage, by treatment with LiOH (**Scheme 89** & **90**). Purification of the resulting isomeric mixture of acids ***enant*-31** and **173** by flash column chromatography over neutralised silica gel with triethylamine, provided the unwanted ammonium salts **183** and [**183** + **184**], which interestingly presented significant differences by NMR analysies, revealing clearly the presence of both diastereoisomers. A quick acidic work-up of the ammonium salts cleanly generated the free carboxylic acids ***enant*-31** and [***enant*-31** + **173**] (**Schemes 89** & **90**).



Reagents and conditions **i**, LiOH, THF, rt, 90 min, triethylamine, 94%; ii, acidic work-up, 90%

Scheme 89. Synthesis of enantiomerically pure *enantio-N*-Boc-ADDA ***enant*-31**.



Reagents and conditions **i**, LiOH, THF, rt, 90 min, triethylamine, 90%; ii, acidic work-up, 88%

Scheme 90. Synthesis of diastereoisomeric mixture of acids ***enant*-31** and **173**.

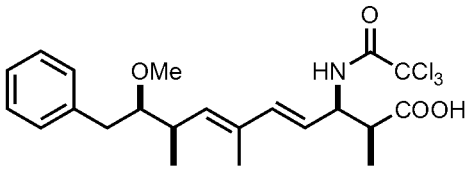
More interestingly, at this point, the two sets of acids ***enant*-31** and [***enant*-31**+**173**] became impossible to differenciate by ^{1}H or ^{13}C NMR, as it was the case before (Section **III-3.2**). The spectral differences between both diastereoisomers ***enant*-31** and **173** were almost impossible to observe. A very large expansion of the NMR data was necessary to reveal a couple of very close doubled signals, which could not have been seen without a fine comparison with the enantiomerically pure carboxylic acid ***enant*-31**. These observations finally confirmed that both diastereoisomers ***enant*-31** and **173** had almost identical physical and spectral properties, and that no decomposition of the undesired diastereoisomer **173** had occurred. Importantly, the $[\alpha]_D$ of enantiopure *enantio*-*N*-Boc-ADDA chain ***enant*-31** obtained ($[\alpha]^{26}_D$ +23.8, (c = 1.0, $CHCl_3$)) did not match very well with the literature ($[\alpha]_D$ -19, (c = 0.0547, $CHCl_3$)[85] and ($[\alpha]_D$ -13.3, (c = 0.73, $CHCl_3$)[72]). Strangely, the optical rotations extracted from the literature[85,72] were closer to the optical rotation of the diastereoisomeric mixture [***enant*-31**+**173**] than the actual enantiomerically pure *enantio*-*N*-Boc-ADDA ***enant*-31**, casting doubt on the authenticity of some of the data previously reported in the literature.

5 – BRIEF CONCLUSION

The synthesis of the *enantio*-*N*-Boc-ADDA ***enant*-31** was successfully completed, and the first part of our work was published in 2008.[127] Our investigations demonstrated that cross-metathesis was an efficient (*E*,*E*)-selective technique to construct the ADDA framework. But more importantly, our results filled the gap caused by the lack of data in the literature (expansion of NMR spectra, and optical rotations), and illustrated the real complexity of such an apparently simple compound as the ADDA chain.

RESULTS & DISCUSSION

------- PART IV – SYNTHESIS OF *ENANTIO-ISO*-ADDA CHAIN -------



enantio-N-TAC-*iso*-ADDA **115**

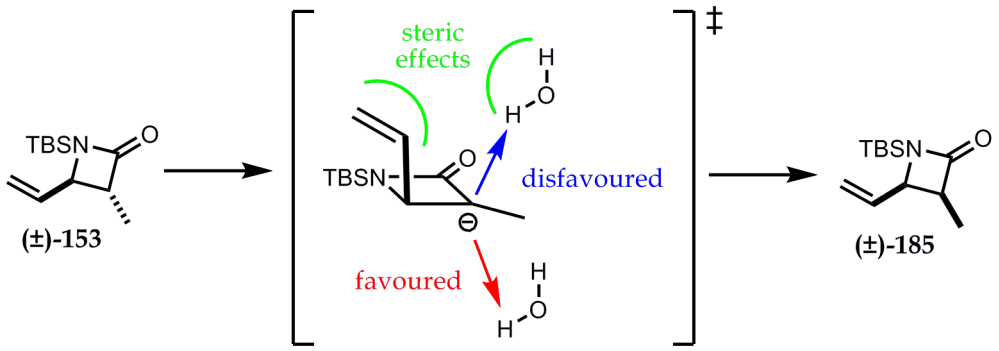
Figure 23. *enantio-N*-TAC-*iso*-ADDA **115**

The synthesis of *enantio-N*-TAC-*iso*-ADDA chain **115** (**Figure 23**) was carried out in parallel with the synthesis of the *enantio-N*-Boc-ADDA ***enant*-31**. Well before the previous cross-metathesis was made to work, the initial approach was envisaged through an alkyne-alkyne organometallic coupling (Section **III-2.2**), which had never been used to generate the ADDA framework. However, this strategy was rapidly discarded as the required aldehyde intermediate could not be generated (see section 1.2.2). In the meantime, the cross-metathesis methodology utilised to synthesise *enantio-N*-Boc-ADDA ***enant*-31** gave the first promising results, and was therefore considered as a better approach towards *enantio-N*-TAC-*iso*-ADDA **115** (**Figure 23**). The convergent synthesis of *enantio-N*-TAC-*iso*-ADDA **115** employed the same diene **(*E*)-117**, which was prepared through the same process presented earlier (section **1.1** and **1.2**, **Schemes 51**, **57**, **62**, **66**). Consequently, the next part of the discussion will essentially focus on the synthesis of the right hand side CM amino-partner.

1 – SYNTHESIS OF THE AMINO UNIT

1.1 – Epimerisation of *trans*- β-lactam **(±)-153** to *cis*- β-lactam **(±)-185**

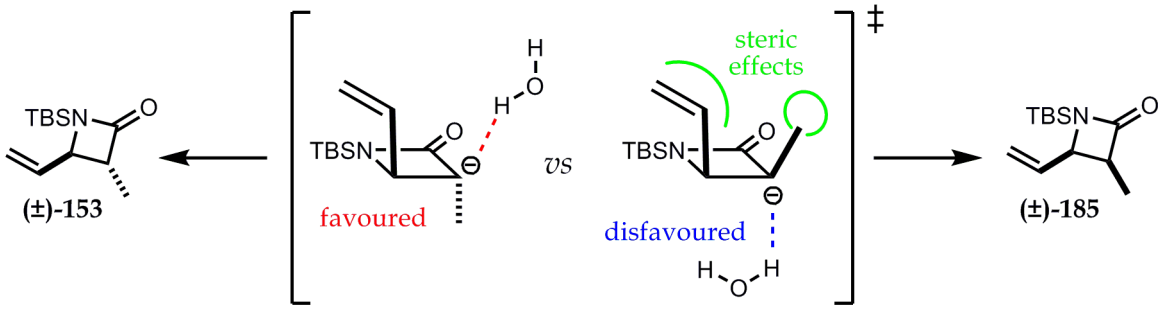
It was first tried to take advantage of the β-lactam chemistry developed earlier (section *4.3.1*) to generate the *cis*-relationship required in the *iso*-ADDA framework. To acheive this goal, the isomerisation of racemic *N*-TBS protected β-lactam **(±)-153** to racemic *cis*-lactam **(±)-185**, was envisaged through the mechanism presented below (**Scheme 91**).



Reagents and conditions **i**, *n*-BuLi, THF, -78 °C then H_2O, -78 °C to rt.

Scheme 91. First isomerisation mechanism of *trans*-azetidinone **(±)-153**.

However, treatment of the *N*-TBS β-lactam **(±)-153** with *n*-BuLi followed by quenching with water did not form any of the epimerized lactam **(±)-185**. The proposed mechanism was consequently re-envisaged to account for these observations, as presented below (**Scheme 92**).



Reagents and conditions **i**, *n*-BuLi, THF, -78 °C then H_2O, -78 °C to rt.

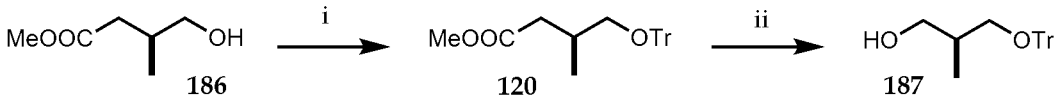
Scheme 92. Second isomerisation mechanism of *trans*-azetidinone **(±)-153**.

However, it should be noted that quenching with deuterated water did not produce observable disappearance of the proton in α-position of the carbonyl under any conditions, putting a serious doubt on the actual formation of the anion.

1.2 – Synthesis of trichloroacetamide **122**

As *cis*-β-lactam **(±)-185** could not be prepared, a different approach was designed to access the required *cis*-stereochemistry present in the *enantio-iso*-ADDA. The synthesis started

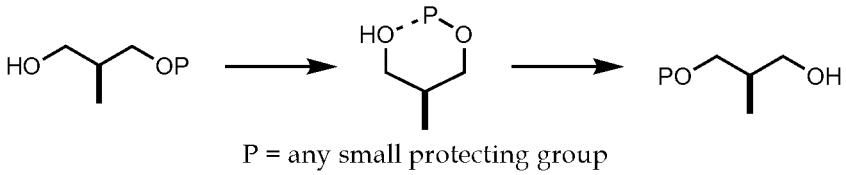
with the readily available and enantiomerically pure propionate **186**, which was trityl-protected, and subsequently reduced to the alcohol **187** (**Scheme 93**).



Reagents and conditions **i**, TrCl, TEA, DCM, 0°C to rt, overnight, 100%; ii, LAH, Et_2O, -30 °C to rt, overnight, 97%.

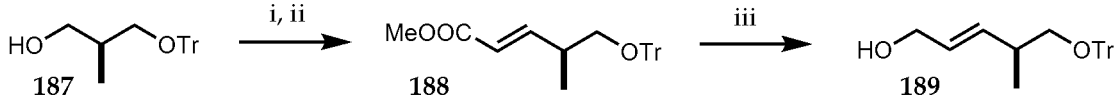
Scheme 93. Synthesis of the diol **187**.

This protecting group was thought to be bulky enough to reduce the risk of racemisation of the mono-protected diol **187**, by protecting group migration between both hydroxyls of diol **187** (**Scheme 94**). The other reason for the choice of trityl protecting group was to improve the diastereoselectivity of the aza-Claisen rearrangement (**Schemes 43** & **44**), as discussed later in this paragraph.



Scheme 94. Racemisation of a monoprotected diol by protecting group migration.

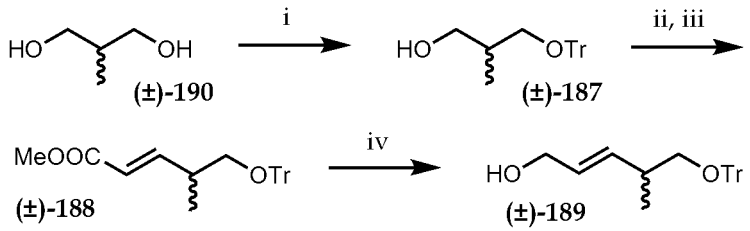
The alcohol **187** was oxidised to the aldehyde intermediate, which was subsequently olefinated to give the conjugated methyl ester **188** through a Wittig olefination. The (*E*)-double bond isomer was obtained exclusively, as corroborated by NMR analysis,[128] and the ester was reduced to the allylic alcohol **189** by treatment with Dibal-H (**Scheme 95**).



Reagents and conditions **i**, $(COCl)_2$, DMSO, TEA, DCM, -78 °C; ii, $Ph_3P{=}C(CH_3)COOMe$, DCM, Δ, 3 days, 90% (2 steps); iii, Dibal-H, Et_2O, 0 °C, 2 h, 78%.

Scheme 95. Synthesis of the allylic alcohol **189**.

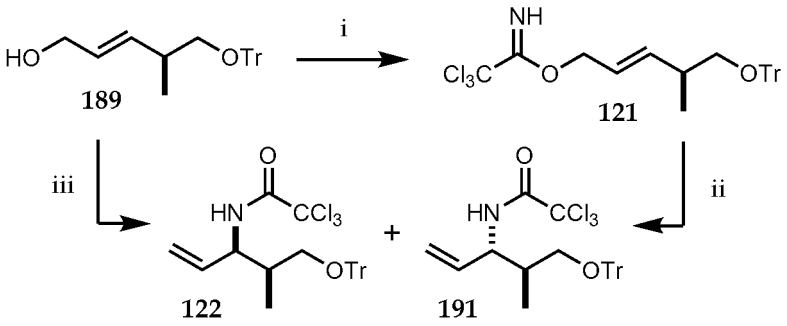
As the intermediates **188**, **189**, **121** and **122** (**Schemes 95** & **97**) possessed optical rotation close to zero, the enantiomeric excess of allylic alcohol **189** was measured by chiral HPLC, to confirm that no racemisation occurred during the synthesis. The migration of the trityl group (**Scheme 94**), the triethylamine-based Swern oxidation (see Section **IV-2.3.3** for further details), or the Wittig olefination, as described by Beatty,[76] were all likely to cause epimerisation. The racemic allylic alcohol **(±)-189** was prepared through the chemistry developed above (**Scheme 95**) from the readily accessible symmetrical diol **190** (**Scheme 96**). The comparison of the HPLC traces of both allylic alcohols **189** and **(±)-189** confirmed that no epimerization occurred during the synthesis of **189** (*ee* = 98%) (**Schemes 93** & **95**).



Reagents and conditions **i**, TrCl, TEA, rt, 2 days, 88%; **ii**, $(COCl)_2$, DMSO, TEA, DCM, -78 °C; **iii**, $Ph_3P{=}C(CH_3)COOMe$, DCM, Δ, 3 days, 87% (2 steps); **iv**, Dibal-H, Et_2O, 0 °C, 2 h, 42%.

Scheme 96. Synthesis of racemic allylic alcohol **(±)-189**.

The alcohol **189** was then converted to the trichloroacetimidate **121** by treatment with trichloroacetonitrile under basic conditions (**Scheme 97**). The trichloroacetimidate **121** was subjected to a palladium-catalysed aza-Claisen rearrangement, which was attempted using various conditions in order to improve the diastereoisomeric ratio of trichloroacetamides **122** and **191**. The best results were obtained in dry dichloromethane with *p*-benzoquinone, and trichloroacetamides **122** and **191** were obtained in a (4:1) diastereoisomeric ratio (**Scheme 97**). A one-pot version was also developed and proved to be extremely efficient. Nevertheless, it is worth mentioning that the one-pot procedure required the use of twice as much palladium catalyst and *p*-benzoquinone as the classical two-step protocol (**Scheme 97**).



Reagents and conditions **i**, Cl_3CCN, DBU, DCM, -78 °C, 3 h, 97%; **ii**, $PdCl_2(MeCN)_2$, *p*-benzoquinone, DCM, rt 24 h, 89%, **122**/**191** (4:1); **iii**, $PdCl_2(MeCN)_2$, *p*-benzoquinone, DCM, rt, 24 h, 95% (2 steps), **122**/**191** (4:1).

Scheme 97. Synthesis of trichloroacetamides **122** and **191**.

Both trichloroacetamides **122** and **191** were easily separable by recrystallisation, which allowed structural data to be obtained by X-Ray crystallography, and thus confirmed the *syn*-stereochemistry of the major desired diastereoisomer **122** (**Figure 24**). It is worth noting that minor *anti*-isomer **191** could have potentially been used to generate the ADDA chain *via* a subsequent CM coupling with the opposite enantiomer of the diene **(*E*)-117**.

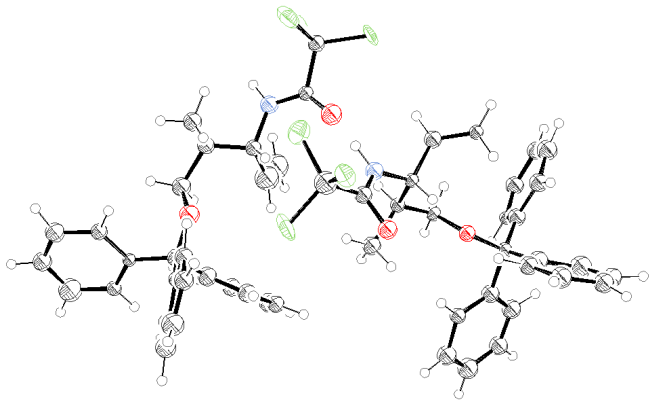
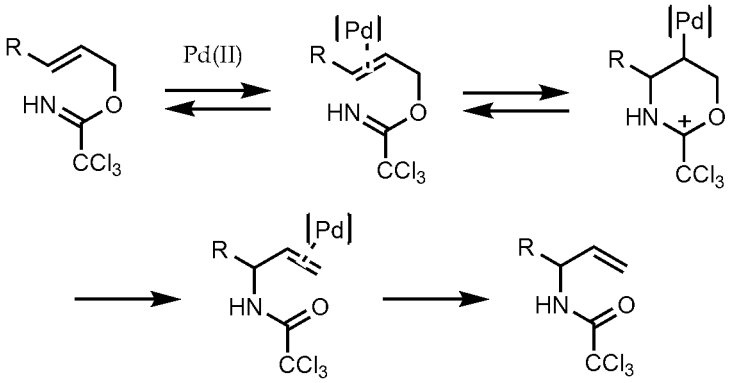


Figure 24. Crystal structure of the dimeric allylic amine **122**.

1.3 – <u>The aza-Claisen rearrangement</u>

The Aza-Claisen rearrangement, commonly known as the Overman rearrangement, is a thermal or metal-catalysed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides (**Scheme 98**). Since its first development by Overman,[129] the reaction has found widespread use in synthetic organic chemistry to generate allylic

amines.[130] Like other [3,3]-sigmatropic rearrangements, the reaction pathway progresses *via* a concerted suprafacial pathway involving a highly ordered chair-like transition state.[131] The metal-catalysed reaction follows a stepwise pathway involving intramolecular amino palladation of the alkene followed by reductive elimination to generate the amide products (**Scheme 98**).

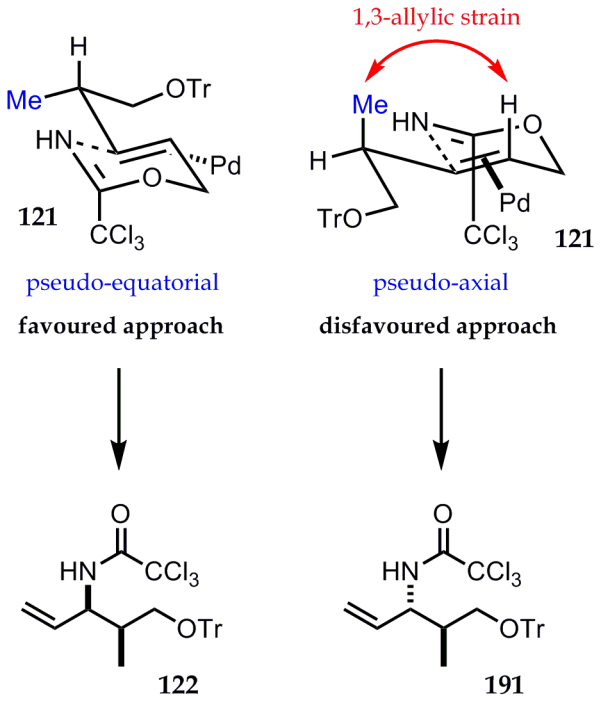


Scheme 98. General palladium-mediated aza-Claisen rearrangement.

The palladium(II)-catalysed version of this reaction is carried out under extremely mild conditions allowing the isolation of products in high yields and excellent regio- and stereoselectivities.[131] However, the mechanism by which the diasteroselectivity of aza-Claisen rearrangement of allylic trichloroacetimidates can be explained is still under debate, and some results are contradictory.[130b,132] The diastereoselectivity appears to be influenced by steric bulk, but also by chelation between the substrate and the palladium(II) catalyst.[130b,132] In these cases both effects probably participate together to give the diastereoselectivity observed in our rearrangement reaction, and several assumptions can be made to explain the observed (4:1) ratio of *syn*- and *anti*-diasteroisomers **122** and **191**.

The biggest steric effects are due to the trityl group, causing the thricloroacetimidate **121** to adopt a zig-zag geometry which places the trityl group as far as possible from the rest of the chain. However, the diastereocontrol of the reaction will be essentially dictated by the small difference of size between the competing substituents directly attached to the allylic carbon; that is to say the CH_3 and the CH_2O groups. As the carbon-oxygen bond is longer than a carbon-carbon bond, it is possible to considerate the methyl group as the bulkier of the two, although the difference is not massive. On the other hand, the 1,3-

allylic strain caused by the methyl group has to be taken into account as shown in **Scheme 99** and discussed by Sutherland.[130e] Thus, sterics will direct the palladium to the face opposite to the methyl group. The nitrogen should then insert to the opposite face of the bulky [palladium + ligands], forming the *syn*-trichloroacetamide **122** as the major isomer.



Scheme 99. Proposed explanation of aza-Claisen diastereoselectivity.

The diastereoselectivity observed in our example could also be explained through a chelation controlled transition state between the oxygen and the palladium, as described by Sutherland.[130b,130e] However, the presence of the trityl group is likely to prevent this chelation from taking place, and further investigations would be required to completely explain the diastereoselectivity observed in this aza-Claisen rearrangement.

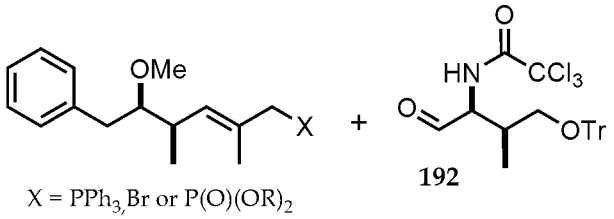
It is also worth mentioning that the diasteroselectivity of our rearrangement reaction could be optimised through the use of chiral catalyst, as was shown in some literature examples.[130a,133]

1.4 - The initial alkyne-alkyne approach

1.2.1 Possible coupling methods available

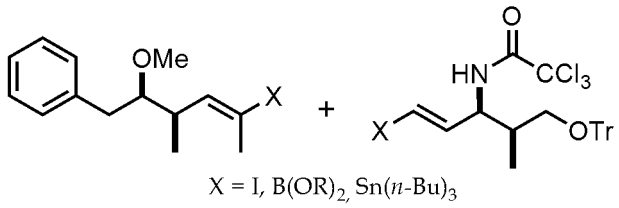
While the cross-metathesis methodology was being investigated to complete the synthesis of the *enantio*-ADDA chain ***enant*-31**, an alkyne-alkyne coupling technique (**Scheme 102**) was also taken into consideration in parallel to form the 1,3-(*E,E*)-diene of the ADDA scaffold. However, a significant number of methods were also available, as listed below:

- Wittig and Horner-Wadsworth-Emmons olefination (**Scheme 100**)[72,74-78,84,85,89]



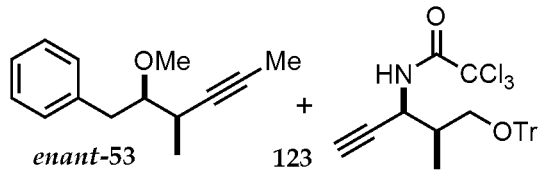
Scheme 100. Wittig-type couplings.[72,74-78,84,85,89]

- Stille, Sonogashira, Suzuki and Negishi couplings (**Scheme 101**)[79,81-83,87]



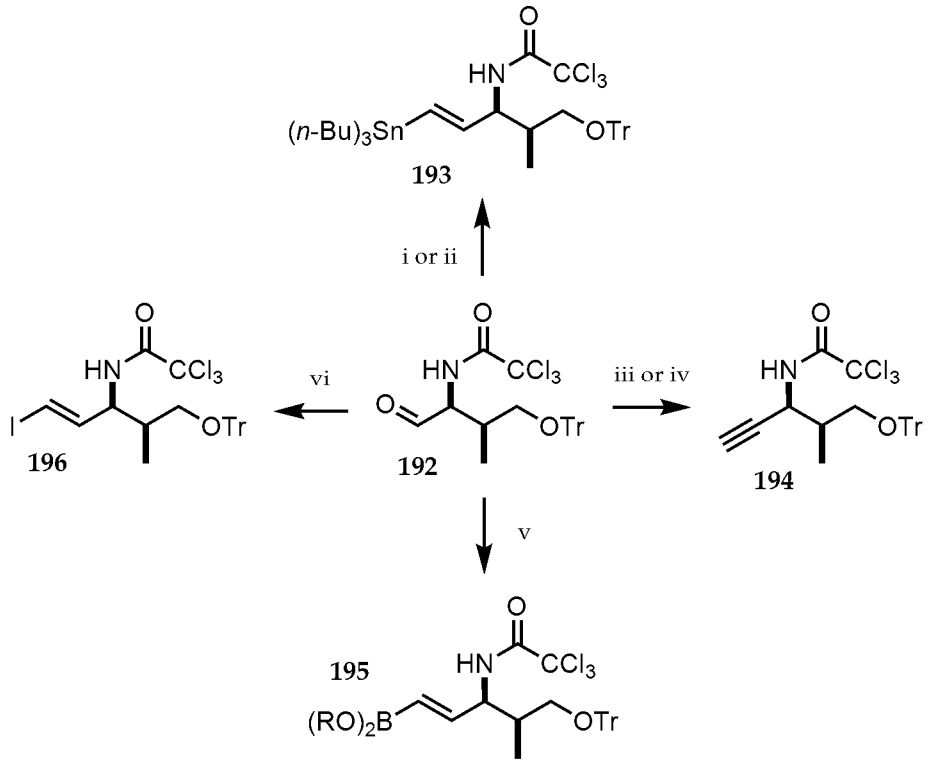
Scheme 101. Palladium-catalysed couplings.[79,81-83,87]

- Alkyne-alkyne titanium catalysed couplings (**Scheme 102**)[90]



Scheme 102. alkyne-alkyne coupling.

Alkyne-alkyne coupling (**Scheme 102**),[90] which had never been used to construct the ADDA side chain, represented an attractive route to access the *enantio-iso*-ADDA, and was preferably proposed for our novel approach. However, the efficient organometallic couplings listed above (**Schemes 100** & **101**) were also envisaged as they had already proved to lead successfully to the ADDA framework in the literature.[72,74-79,81-85,89] All of these coupling methods had one thing in common, as they all required the aldehyde intermediate **192**, accessible from olefin **122** (**Scheme 103**).



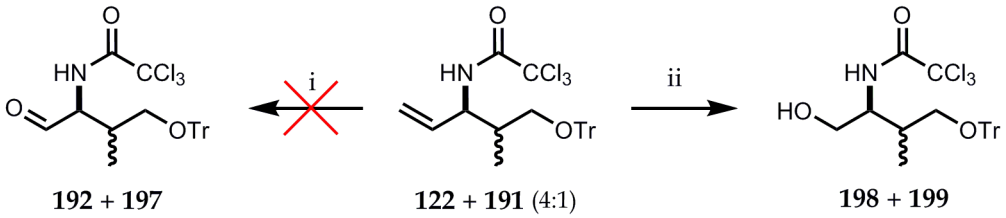
Reagents and conditions **i**, $CrCl_2$, *n*-$Bu_3SnCHBr_2$, LiI, THF, DMF; **ii**, CHI_3, $CrCl_2$, THF then (*n*-$Bu_3Sn)_2$, $Pd(PPh_3)_4$; **iii**, $TMSCHN_2$, *n*-BuLi, THF; **iv**, Corey-Fuchs conditions; **v**, $CrCl_2$, THF, $Cl_2CHB(OR)_2$, LiI; **vi**, CHI_3, $CrCl_2$, THF.

Scheme 103. General method for the convertion of aldehyde **192** into suitable organometallic coupling partners.

*1.2.2 Synthesis of aldehyde **192***

The first route was envisaged through ozonolytic cleavage of the double bond of olefin **122** (**Scheme 104**). In order to find the best conditions without consuming too much of the precious trichloroacetamide **122**, test reactions were all carried out on the (4:1) mixture of diastereoisomers **122** and **191**. Treatment of olefins **122** and **191** with ozone, induced the

complete disappearance of starting material according to TLC analyses, nevertheless no traces of expected aldehydes **192** and **197** were detected by NMR. A large number of condition modifications (solvents, concentration, reaction time) failed to give the desired aldehydes **192** and **197**, and alternatively the crude ozonolyzed mixture previously quenched with triphenylphosphine oxide, showing no aldehyde signals by NMR, was taken on crude to the following reaction. However, not surprisingly, no desired compounds were retrieved either. The aldehyde was presumably formed, but was too unstable to be isolated. To prove the formation of the aldehyde, a stream of argon was bubbled through the final bluish mixture of ozonolysed olefins **122** and **191**, and the coulourless mixture was subsequently quenched with $NaBH_4$ without any prior work-up. After purification by flash column chromatography, the alcohols **198** and **199** were isolated in poor yield, thus demonstrating that the unstable aldehydes **192** and **197** were actually well formed during the process (**Scheme 104**).



Reagents and conditions **i**, O_3, EtOH, DCM, -78 °C, 75 min then DMS or PPh_3; **ii**, O_3, EtOH, DCM, -78 °C, 75 min then $NaBH_4$, -78 °C to rt, 20 h, 31%, syn / anti (4:1).

Scheme 104. Evidence of the formation of aldehydes **192** and **197**.

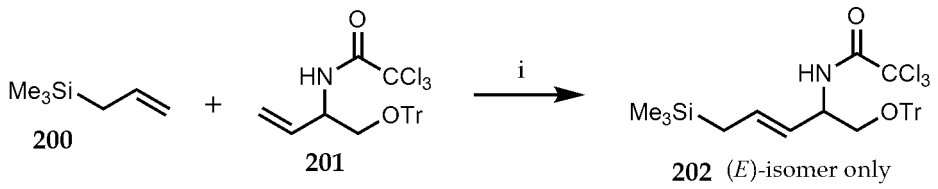
Alternatives to ozonolytic cleavage, such as the use of $NaIO_4$ to cleave a 1,2-diol,[134] were first envisaged, before it was decided to focus our attention on the ambitious cross-metathesis, which appeared as a better approach.

2 – FIRST CROSS-METATHESIS COUPLINGS

Unlike other couplings which require additional synthetic steps to prepare suitable partners, cross-metathesis only requires alkene functions, which are present in the final heterodimer. As a result, cross-metathesis methodology represented the most direct way

to link the ADDA aromatic containing unit to olefin **122**, without changing its already optimized synthesis.

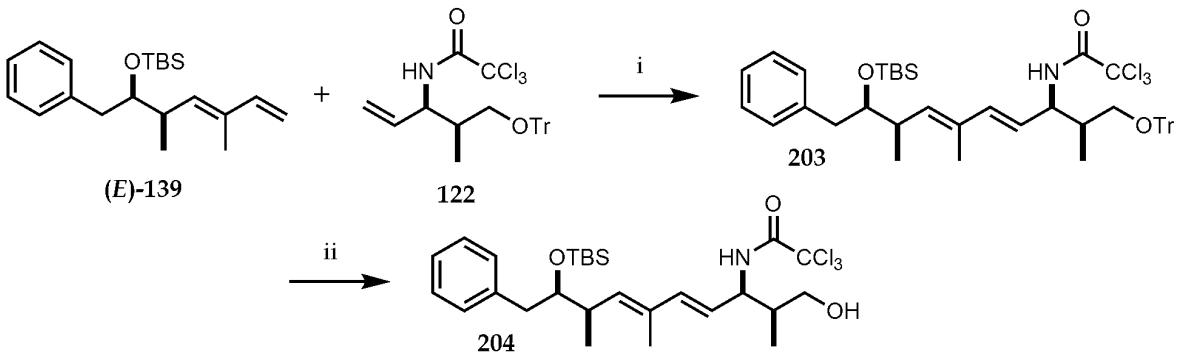
2.1 – First investigations towards cross-metathesis of trichloroacetamide **122**



Reagents and conditions **i**, Schrock's catalyst (10 mol%), DCM, 40 °C, 16 h, 98%.

Scheme 105. Use of *N*-TAC and *O*-Tr protected allylic amine in cross-metathesis.[135]

A successful cross-metathesis reaction published by Blechert (**Scheme 105**),[135] and using a very similar trichloroacetamide **201** to ours **122**, was reproduced between a (3:1) isomeric mixture of diene **(*E*)-139** and **(*Z*)-139** and a (4:1) isomeric mixture of trichloroacetamides **122** and **191** (**Scheme 106** *only the major diastereoisomers are drawn*). The CM couplings were performed using similar reaction conditions to those described by Blechert,[135] but also using the same conditions developed for our previous successful metathesis reactions.



Reagents and conditions **i**, GII (12 mol%), DCM, Δ, 1 h; **ii**, silica, 15% (2 steps).

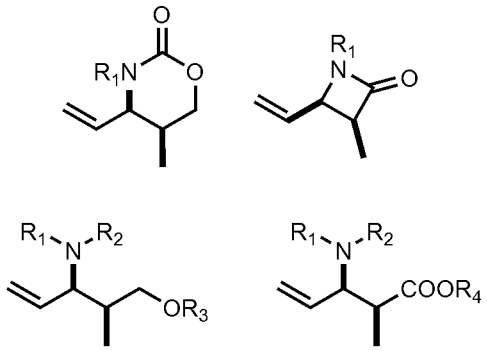
Scheme 106. First cross-metathesis between diene **(*E*)-139** and acyclic allylic amine **122**.

Unfortunately, the semi-pure heterodimer **203** (mixture of isomers) could only be isolated in very small quantities using the CM conditions described above (**Scheme 106**). A second purification by flash column chromatography caused the complete loss of the trityl protecting group, and afforded alcohol **204** (mixture of isomers) (**Scheme 106**). As a result,

the trityl-protected heterodimer **203** was only characterized by ^{1}H NMR and LRMS. The reaction was re-attempted under the same conditions, but failed to give the heterodimer **203**. Although the reaction appeared rather temperamental and ineffective, these first results were rather encouraging, and extensive modifications, such as the transformation of the trichloroacetimidate **122**, were envisaged.

2.2 – Proposed modifications of trichloroacetamide **122**

A large number of possibilities were available to modify the steric hindrance and the electronics of the trichloroacetamide **122**. This number was limited to four general structures (**Figure 25**), which were retained for their properties, but also for their relative ease of synthesise from the trichloroacetamide **122**.



R_1, R_2, R_3, R_4 = H or any protecting groups

Figure 25. General structure of possible CM partners originated from trichloroacetamide **122**.

With a dozen of CM analogues (including various protecting groups) to test with 5 different commercially available catalysts, under different conditions, at least 60 cross-metathesis reactions would have been necessary to screen all combinations. For obvious time and economical reasons, selection was refined, based on the empirical observations listed below:

1) Hindered allylic amine containing trichloroacetamide and trityl groups were shown undergo CM couplings in excellent yield and very high (*E*)-selectivity (**Scheme 105**).[135] However, the tricloroacetamide **201** was coupled to rather small allylic trimethylsilane **200**, used in a large excess. In our case, these protecting groups were suspected of making

the olefin **122** too hindered and less reactive. Consequently the use of one of these two protecting groups at a time was preferred.

2) It has been established as a "dogma" that efficient metathesis reactions are suppressed in the presence of basic amines due to their ability to coordinate to metal-alkylidene complexes and to interfere unproductively with catalytic activity.[136] For this reason, fully unprotected amines were discarded from our screening.

3) Synthesis of the β-lactam from the trichloroacetamide **122** would have added far too many steps to the synthesis to be realistic, and it was therefore not considered as a suitable CM partner this time.

As a result of the application of the empirical criteria listed above, the modifications were limited to the following most promising structures (**Figure 26**):

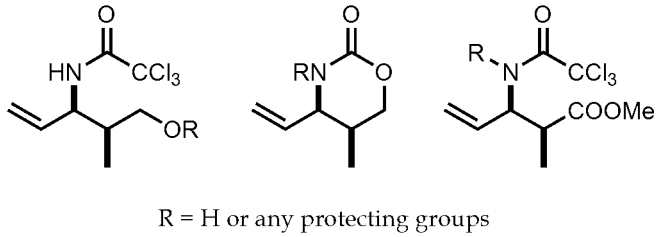


Figure 26. Selected structure of CM partners originated from trichloroacetamide **122**.

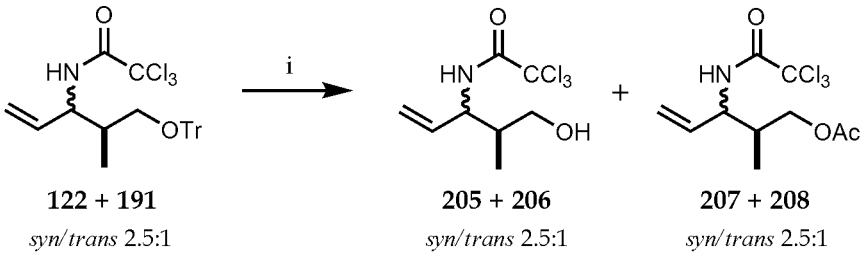
The strategy was to synthesise analogues of the compounds listed above (**Figure 26**), and try to couple them with the diene **(*E*)-117**, using the same conditions as employed in the previous successful metathesis reactions. The candidates giving the best results were then subjected to optimisation.

2.3 – Synthesis of modified trichloroacetamide **122** analogues

*2.3.1 Synthesis of alcohol **205***

A number of conditions (aq. conc. HCl, TFA, TFAA, amberlyst, $CuSO_4$) failed to cleave the trityl group, until the use of *p*-TsOH enabled the isolation of a multi-gram quantity of the desired alcohol **205** in modest yield. Although being extensively used at the start, this scalable process required a very tricky purification, and a more efficient alternative was sought. Treatment of an isomeric mixture of trityl-protected trichloroacetamides **122** and

191 with a freshly made sat. solution of HCl in ethyl acetate yielded alcohols **205** and **206** in modest yield (**Scheme 107**). Although the process was much cleaner than the *p*-TsOH-mediated trityl-deprotection reaction, undesired acetates **207** and **208** resulting from the transesterification, were also formed in low yield during the reaction.

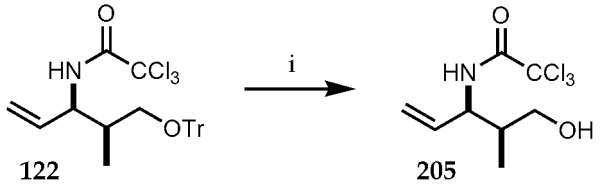


122 + 191 *syn/trans* 2.5:1 | **205 + 206** *syn/trans* 2.5:1 | **207 + 208** *syn/trans* 2.5:1

Reagents and conditions **i**, HCl in EtOAc, DCM, rt, 30 min, 47% **122** / **191** (2.5:1), 8% **207** / **208** (2.5:1).

Scheme 107. Trityl removal with HCl in ethyl acetate.

Finally, the reaction was significantly optimized through the use of anhydrous hydrochloric acid in diethyl ether, which provided the clean alcohol **205** in quantitative yield from trichloroacetamide **122** (**Scheme 108**).



122 **205**

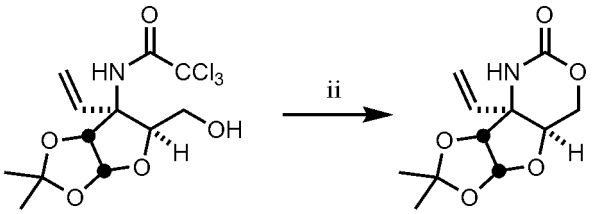
Reagents and conditions **i**, HCl in Et_2O, DCM, rt, 1 h, 100%.

Scheme 108. Trityl removal with HCl in diethyl ether.

*2.3.2 Synthesis of carbamates **209** and **213***

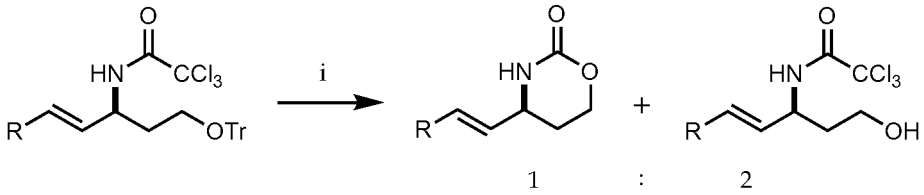
2.3.2.1 – Through internal cyclisation

The preparation of carbamate **209** was initially envisaged to be accomplished by nucleophilic cyclisation of the free hydroxyl onto the trichloroacetamide moiety. As illustrated below, this efficient and rapid process is well-reported in the literature[137] for the generation of five-membered cyclic carbamates[137] and six-membered cyclic carbamates,[138] (**Schemes 109** & **110**).



Reagents and conditions **i**, Na_2CO_3, DMF, 40 min, Δ, 93%.

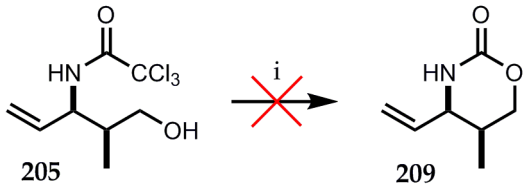
Scheme 109. Synthesis of 6-membered carbamate.[138b]



Reagents and conditions **i**, 88% HCOOH, no further details provided.

Scheme 110. Synthesis of 6-membered carbamate.[138c]

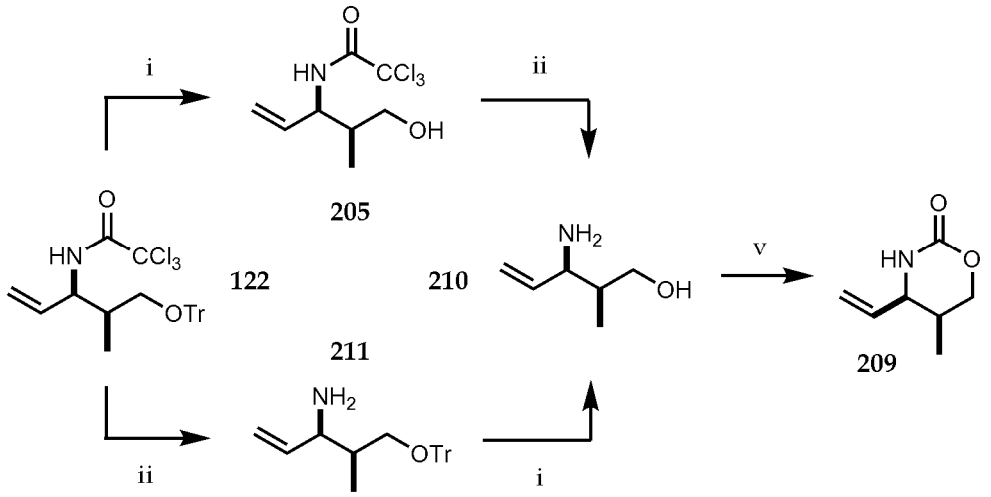
However, application of the reported conditions[137,138] to alcohol **205** all failed to give the desired carbamate **209**, and resulted in no reaction and/or partial decomposition instead (**Scheme 111**). Various acidic and basic conditions including the use of DBU, KHMDS, TMSOTf, *n*BuLi and *t*BuOK were also unsuccessful to give the desired carbamate **209**.



Scheme 111. Unsuccesful cyclisation of alcohol **205** to carbamate **209**

2.3.2.2 – Through external cyclisation

A classical alternative, using triphosgene, was finally proposed to access the unprotected carbamate **209** from the free aminoalcohol **210**. The preparation of the aminoalcohol **210** was envisaged from the transformation of trichloroacetamide **122** *via* two possible routes (**Scheme 112**). The first approach started with the deprotection of the trityl-protected alcohol **122** followed by the cleavage of its trichloroacetamide group, whereas the second method proceeded the other way round (**Scheme 112**).

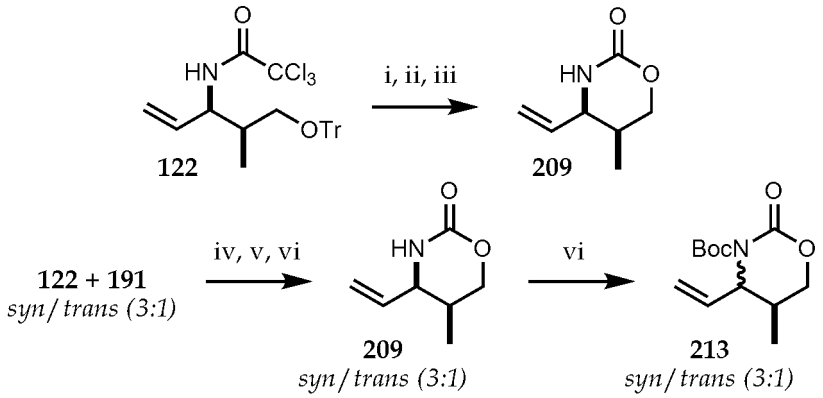


Reagents and conditions **i**, *p*-TsOH, EtOH; **ii**, KOH, iPrOH.

Scheme 112. General procedures to free aminoalcohol **210**.

The bottom pathway was proved to be much more efficient than the top one, and was consequently preferred (**Scheme 112**). However, the volatility of the unprotected aminoalcohol **210**, and the uncontrolled formation of unidentified side products from time to time, made both routes highly temperamental.

Trichloroacetamide **122** was deprotected to give the amine **211**, which was subsequently treated with potassium hydroxide to provide the volatile aminoalcohol **210**, in poor to modest yield (**Scheme 112**). The resulting crude aminoalcohol **210** was then converted to the 6-membered carbamate **209**, in modest yield, by treatment with triphosgene (**Scheme 113**). As the first metathesis reaction (section 3.3) had been significantly optimised *via* the *N*-Boc protection of lactam **(±)-119**, it was also decided to convert the free carbamate **209** to its *N*-Boc protected version. It should be noted that, unlike carbamate **209**, which was also generated as a single diastereoisomer, carbamate **213** was generated as a (3:1) diastereoisomeric mixture only, as it was originated from a (3:1) isomeric mixture of trichloroacteamides **122** and **191** (**Scheme 113**).



Reagents and conditions **i**, KOH, iPrOH, Δ, 3 h; **ii**, *p*-TsOH, EtOH, overnight; **iii**, triphosgene, DBU, rt, 2 h, 18% (3 steps); **iv**, KOH, iPrOH, Δ, 2 h; **v**, *p*-TsOH, EtOH, rt, overnight; **vi**, triphosgene, DBU, rt, 2 h, 21% (3 steps); **vii**, $(Boc)_2O$, DMAP, TEA, DCM, rt, overnight, 81%.

Scheme 113. Synthesis of carbamates **209** and **213**.

Interestingly, primary NMR and mass spectrometry analyses (LRMS), suggested the formation of orthoacid **212** as an important side product, resulting from the treatment of trichloroacetamide **122** with potassium hydroxide (**Figure 27**). Against the odds, this very unclean by-product, stemming from the nucleophilic substitution of the chlorines by hydroxyl groups, proved to be fairly stable. However, the purification of the side product appeared impossible, and thus its structure could not be confirmed.

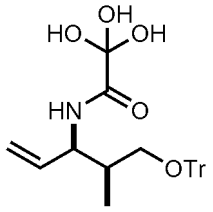
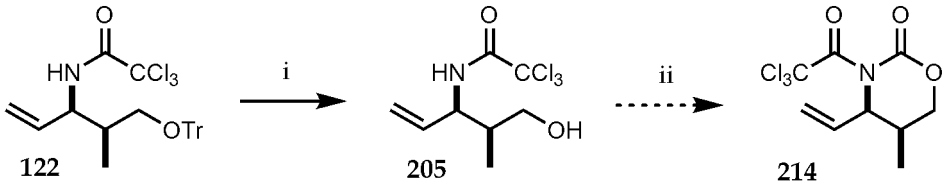


Figure 27. Undesired orthoacid **212**.

As it will be discussed later (sections *2.4.1 & 2.4.2*) the use of carbamates **209** and **213** as CM partners gave disappointing results, and as a result, their synthesis was abandoned, and left unoptimized. Hence, the following interesting alternative, involving an internal nucleophilic cyclisation of the hydroxyl onto the trichloroacetamide carbonyl was not utilised (**Scheme 114**).

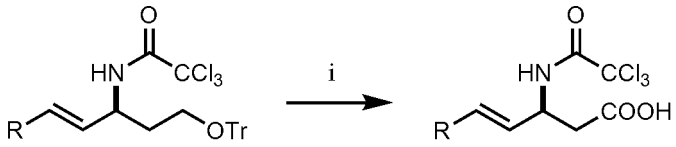


Reagents and conditions **i**, HCl in Et_2O, 100%; **ii**, triphosgene, DBU, DCM.

Scheme 114. Synthesis of *N*-TAC carbamate **214**.

*2.3.3 Synthesis of ester **221***

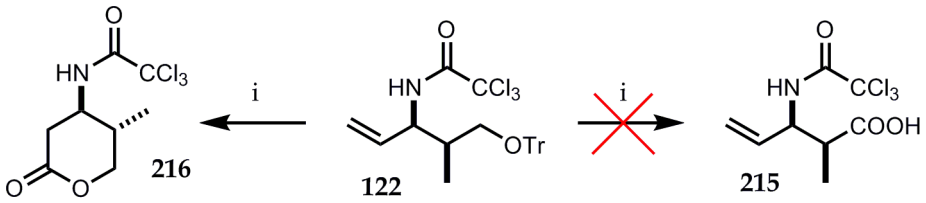
A very clever one-pot procedure reported by P. J. Walsh[138c] was firstly utilised to convert tritylated alcohols to carboxylic acids, which are essential intermediates to the synthesis of esters (**Scheme 115**). The procedure consisted in using the Jones oxidation to cleave the trityl group off chemoselectively, and oxidise the resulting alcohol to the carboxylic acid in one-pot (**Scheme 115**).



Reagents and conditions **i**, Jones oxidation conditions, 85-95%.

Scheme 115. One-pot synthesis of carboxylic acids from trityl-protected alcohols.

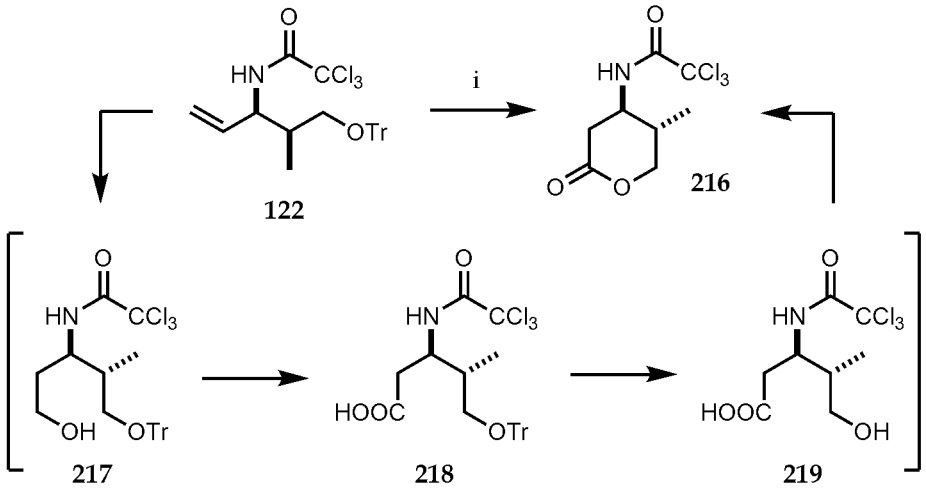
Although the substrates utilised were very similar to ours (olefin **122**), in our hands, the application of this procedure, under several conditions, failed to give the desired carboxylic acid **215** from the tritylated alcohol **122** (**Scheme 116**). Very surprisingly this reaction afforded traces of unwanted lactone **216** as a single diastereoisomer (**Scheme 116**). The data of lactone **216** was compared with a similar lactone **74** (**Scheme 28**), which had already been reported as a side product in the Mann's ADDA synthesis in 1997.[82] It should be noticed that this unoptimised reaction might represent an attractive novel one-pot route, involving four transformations, to the synthesis of protected aminolactones.



Reagents and conditions **i**,CrO_3, H_2SO_4, H_2O, acetone, DCM, rt, overnight, 3% **216**.

Scheme 116. One-pot synthesis to acid **215** and lactone **216**.

A mechanism (**Scheme 117**) involving an anti-Markovnikov addition of the hydroxyl group to the double bond of the olefin **122** was suggested to account for the formation of the lactone **216**.



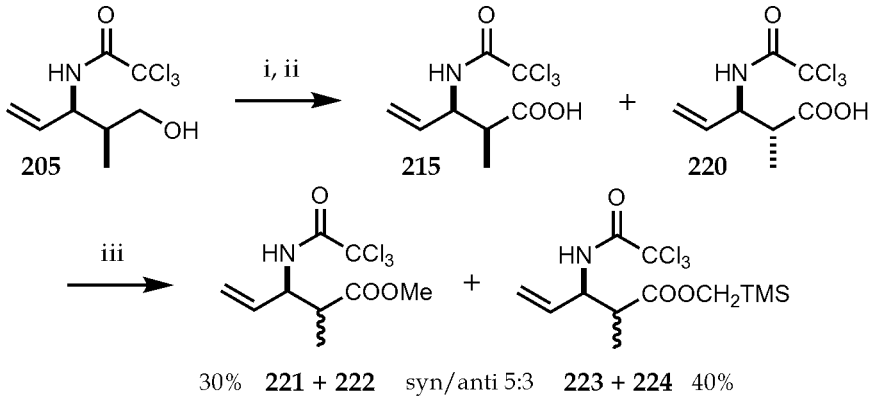
Reagents and conditions **i**,CrO_3, H_2SO_4, H_2O, acetone, DCM, rt, overnight, 3% **216**.

Scheme 117. Proposed mechanism of the synthesis of aminolactone **216**.

In order to reduce the addition and the oxidation of the hydroxyl group on the double-bond, the deprotection of the trityl group was first operated. The Jones oxidation was then carried out on the alcohol **205**, but this still surprisingly gave the unwanted lactone **216**, casting a serious doubt on the proposed mechanism above (**Scheme 117**).

Another attempt using PDC, previously successfully utilised for the synthesis of ADDA,[83,87] did not give access to the carboxylic acid **215** either. Further investigation of the literature revealed that PtO_2 was often considered as a reliable alternative to resistant oxidations of primary alcohols to carboxylic acids.[137a] However, due to technical difficulties involved in this procedure, a more classical and straightforward alternative was envisaged.

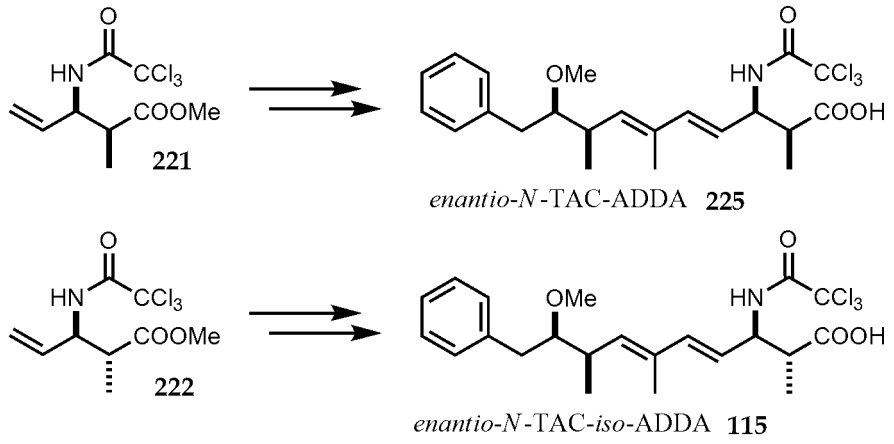
Instead, the trichloroacetamide **122** was trityl-deprotected using anhydrous acidic conditions to give the primary alcohol **205**, which was then oxidised to carboxylic acid **215** *via* a Swern oxidation, immediately followed by Pinnick oxidation (**Scheme 118**). Interestingly, the original Swern oxidation procedure, involving the use of anhydrous triethylamine, epimerized the aldehyde intermediate, yielding an inseparable diastereoisomeric mixture of acids **215** and **220** in a (5:3) ratio, which could either be purified or, as was more commonly preferred, used into the following esterification reaction without any further purification (**Scheme 118**). It is important to mention that both diastereoisomers **215** and **220** could not be separated through reverse phase HPLC techniques. The esterification was first attempted with a commercially available solution of TMS-diazomethane, which provided a (5:3) mixture of methyl esters **221** and **222**, as well as an unwanted (5:3) mixture of TMS-methyl esters **223** and **224** (**Scheme 118**).



Reagents and conditions **i**, $(COCl)_2$, DMSO, TEA, DCM, -78°C; **ii**, *t*BuOH, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, rt, overnight, 96% *syn*/*anti* (5:3) (2 steps); **iii**, $TMSCH_2N_2$, Et_2O, rt, overnight, 27% (**221** + **222**), 42% (**223** + **224**).

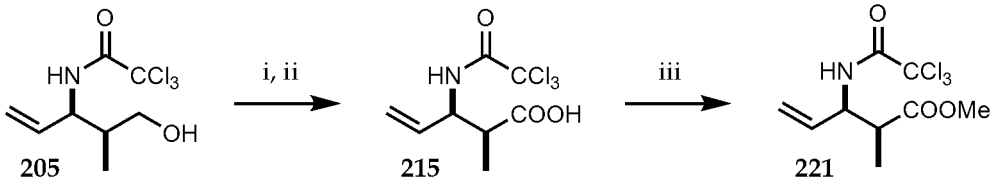
Scheme 118. Synthesis of methyl esters **221** and **222**.

Surprisingly, the silicon-carbon bond was stronger than expected, and a number of conditions (KF, TBAF, HF.pyridine) all failed to cleave the TMS group off. Saponification of the esters **223** and **224** did not give any satisfactory results either. After a subsequent purification by flash column chromatography, the methyl esters **221** and **222** were easily isolated in poor yield, and both diastereosisomers were successfully separated by reverse phase semi-preparative HPLC. This epimerisation afforded a platform from which the two major ADDA isoforms, *enantio*-*N*-TAC-ADDA **225** and *enantio*-*N*-TAC-*iso*-ADDA **115**, could be easily accessed *via* the same synthesis (**Scheme 119**).



Scheme 119. Generation of *enantio-N*-TAC-ADDA **225** and *enantio-N*-TAC-*iso*-ADDA **115** from methyl esters **221** and **222**.

To prevent the epimerisation from occurring, the primary alcohol was alternatively oxidised with commercially available Dess-Martin periodinane, which is well-known to suppress undesirable epimerisations often observed during triethylamine-based Swern oxidations.[139] The Dess-Martin oxidation easily led to the final methyl ester **221** in pretty good yield as a unique *syn*-diasteroisomer. However, the use of DMP induced the formation of aromatic side products, like iodobenzoic acid, which made the purification of the final methyl ester **221** or the prior intermediates, extremely difficult. This is the reason why the Swern oxidation was alternatively operated with DIPEA (**Scheme 120**), which is also known to limit or suppress the epimerisation risk.[139] The DIPEA-based process thus cleanly provided the carboxylic acid **215** in excellent yield, and as a single diasteroisomer, which was not purified but converted straight into the methyl ester **221** by treatment with diazomethane, generated *in situ* from MNNG (**Scheme 120**). This sequence afforded the final methyl ester **221** in very good yield and no epimerisation at all, and this procedure was therefore used to generate the desired diastereoisomer **221** selectively.



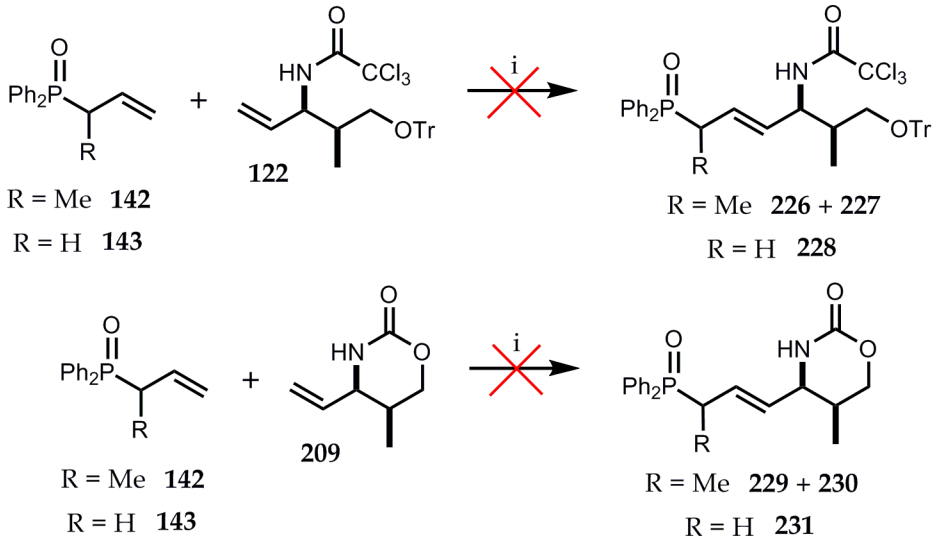
Reagents and conditions **i**, $(COCl)_2$, DMSO, DIPEA, DCM, -78°C; **ii**, *t*BuOH, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, rt, 1 h, **iii**, CH_2N_2, Et_2O, 30 min, then AcOH, 69% (3 steps).

Scheme 120. Synthesis of methyl ester **221** as a single diastereoisomer.

2.4 - Towards the successful cross coupling

2.4.1 CM/HWE coupling sequence

The coupling methodology between the aromatic-containing unit and the amino partner was first envisaged using the HWE olefination previously employed to synthesise diene **(*E*)-139** (**Scheme 62**). The methodology was the same used for the synthesis of phosphine oxides **(±)-154** to **(±)-157** (**Scheme 77**). The preparation of phosphine oxides **226** to **231** was attempted under various cross-metathesis coupling conditions, utilising the phosphine oxides **142** and **143** with the allylic amines **122** and **209**, which were the only partners available at that time. It should be noted that test CM couplings were all attempted in toluene, at room temperature, and were then allowed to warm up slowly to 110 °C. Althought different ratio of CM partners, various CM catalysts, and additives such as titanium isopropoxide were employed, none of the conditions allowed successful preparation of the heterodimers listed below (**Scheme 121**).



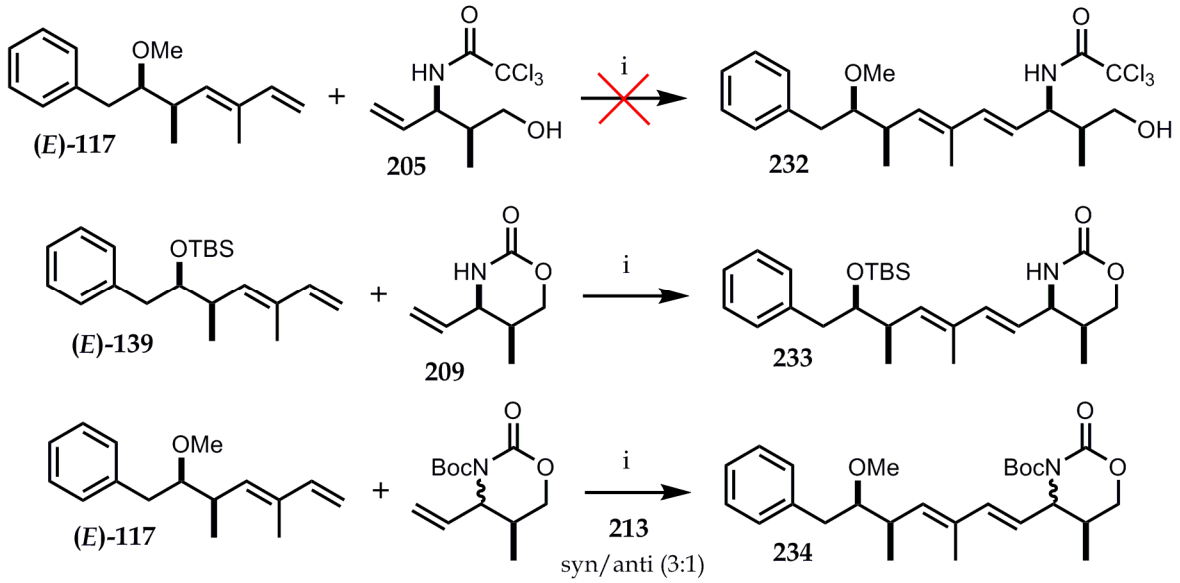
Reagents and conditions **i**, various conditions, 0%.

Scheme 121. Unsuccessful cross-metathesis towards the synthesis of heterodimers **226** to **231**.

2.4.2 Cross-metathesis of 1,3-dienes with allylic amines

As a result of the previous disappointing results, the initial cross metathesis was attempted. The first coupling reactions were tried with compounds **205**, **209**, and **213** (as a

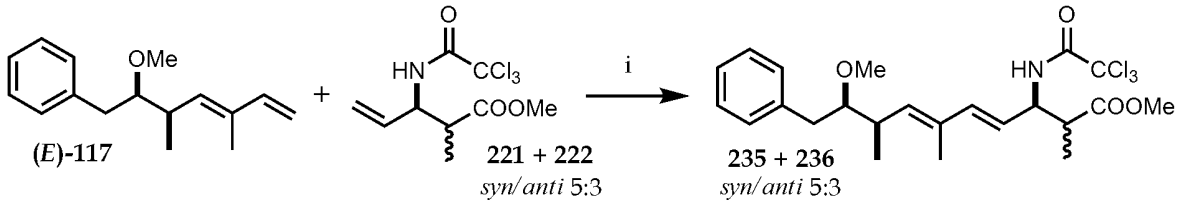
(3:1) mixture of *syn*- and *trans*-**213** isomers) with either dienes **(*E*)-117** and **(*E*)-139**, using second generation Hoveyda-Grubbs catalysts, in toluene at reflux (**Scheme 122**). Unfortunately none of them led to efficient coupling. The alcohol **205** did not give any heterodimer **232** at all, unlike the carbamates **209** and **213**, which led to traces of heterodimers **233** and **234**, according to preliminary analyses (**233** was not detected by mass spectroscopy, HMRS **234** (FAB) observed $(M+Na)^+$ 466.2563, calculated for $C_{26}H_{37}NO_5Na$ 466.2569). However due to the microscale used in these test CM reactions, the compounds **233** and **234** could not possibly be isolated and characterized.



Reagents and conditions **i**, HGII, toluene, Δ.

Scheme 122. Synthesis of CM heterodimers **232**, **233**, and **234**.

Further modifications of the CM conditions did not help improve the yields, and therefore, the final derivative **221** became the focus of attention. The advantage of using the ester **221** was pretty obvious, as it required minimal transformation to access the ADDA framework, once coupled to the diene **(*E*)-117**. The CM coupling was first tried with a (5:3) isomeric mixture of methyl esters **221** and **222** using the second generation Hoveyda-Grubbs catalyst, in toluene at reflux. The first micro-scale attempts were pretty disappointing but encouraging, so the process was repeated and scaled up to provide the heterodimers **235** and **236** in 20% yield (**Scheme 123**).

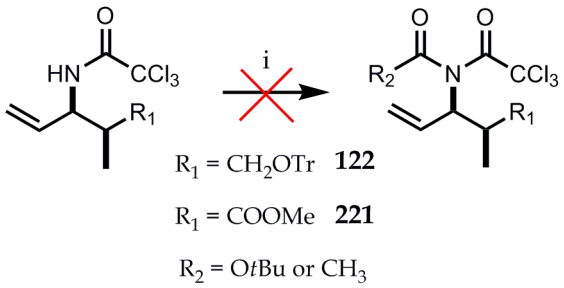


Reagents and conditions **i**, HGII (21 mol%), toluene, Δ, 24 h, 20%.

Scheme 123. Synthesis of CM heterodimers **235** and **236**.

*2.4.3 Optimisation of CM coupling with ester **221***

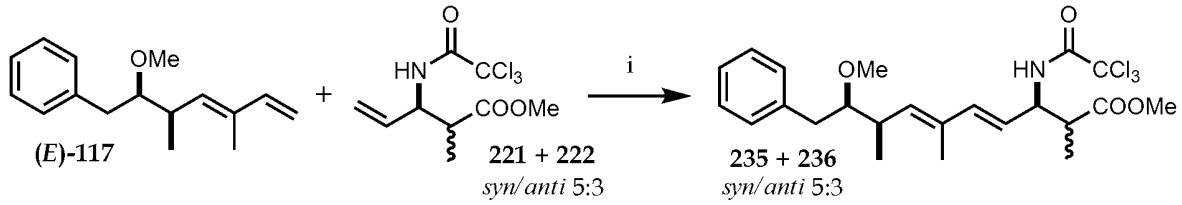
Although the yield of the cross-metathesis products was very poor, the ester **221** was by far the best CM coupling partner tested for the synthesis of *enantio-iso*-ADDA chain. The optimization through the use of a fully protected tertiary amine was first envisaged, as basic amines are known to reduce metathesis catalyst reactivity.[136] Furthermore, the full protection of the β-lactam **119** nitrogen as its *N*-Boc equivalent **174** had previously been shown to improve the reactivity of CM partners (Section **III-3.3**). The *N*-Boc and *N*-Ac protecting groups were selected, and diverse protection conditions were tested on both ester **221** and trityl-protected alcohol **122** (**Scheme 124**) through the use of various base such as TEA, DMAP, KH, and *n*BuLi followed by addition of $(Boc)_2O$ or freshly distilled acetic anhydride at different temperatures. Although the protection of trichloroacetamide appeared relatively straightforward at first sight,[140] none of the conditions screened led to the fully protected amines. The delocalisation of the nitrogen lone pair, in addition to the steric hindrance of *N*-TAC protected amines **221** and **122** were assumed to make the protection difficult.



Scheme 124. Unsucessful *N*-Ac and *N*-Boc protections of trichloroacetamide **122** and **221**.

In all cases (entries **1** to **7**), the starting amine remained always unreacted, although traces of decomposition products were generally detected too. However, the screening illustrated the stability and the resistance of the trichloroacetamides **122** and **221** towards such harsh conditions.

The *N*-protection option was given up, and a different approach was attempted. Trichloroacetamide group removal, or preparation of esters analogues (such as *t*-butyl or benzyl esters), were both realistic options. However, it was initially preferred to start with the modification of the conditions (solvents, temperature, additives, etc) previously employed (**Scheme 123**). To acheive this goal, a wide range of anhydrous solvents, including toluene, DCM, DCE, THF, acetonitrile and diethyl ether, were used, with the second generation Hoveyda-Grubbs catalyst, and under reflux to couple the diene **(*E*)-117** with a (5:3) diastereoisomeric mixture of methyl esters **221** and **222** (**Scheme 125**). Gratifyingly, the coupling performed in anhydrous THF quickly showed significant promising changes by TLC and NMR analysis, compared with the other test reactions. This reaction was reliably repeated, and scaled up to confirm the formation of the heterodimers **235** and **236** in excellent yield and total (*E*,*E*) selectivity (**Scheme 125**).



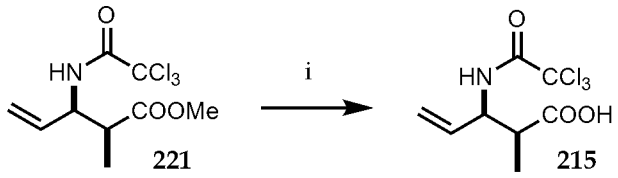
Reagents and conditions **i**, HGII (21 mol%), THF, Δ, 24 h, 90%.

Scheme 125. Optimisation of CM leading to *enantio*-*N*-TAC-*iso*-ADDA methyl ester **235** and *enantio*-*N*-TAC-ADDA methyl ester **236**.

The cross-coupling was then successfully repeated with each single diastereoisomer **221** and **222** separately, and provided the heterodimers **235** and **236** separately in comparable efficiency. Both heterodimers were obtained as single (*E*,*E*)-double bond isomers, and were fully characterised.

The preparation of the final *enantio*-*N*-TAC-*iso*-ADDA chain **115**, as its carboxylic acid form, was then proposed through the mild saponification of the methyl ester **235** by treatment with LiOH. This reaction, never reported before in the presence of *N*-TAC

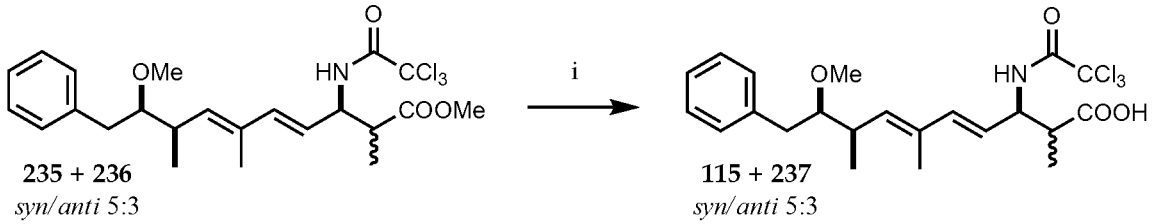
protecting group, was rather ambitious as both the ester and the trichloroacetimidate moieties are sensitive to base. In addition, the substrate was expected to be potentially sensitive to epimerisation of the stereocentre next to the methyl ester function. The reaction was firstly attempted with the methyl ester **221**, which provided the carboxylic acid **215** with an exceptional 95% yield, and without epimerization (**Scheme 126**). To the best of our knowledge, this was the first efficient and chemoselective saponification of *N*-TAC protected esters, and should contribute to expanding the scope of *N*-TAC protecting groups in organic chemistry.



Reagents and conditions **i**, LiOH, THF, rt, 1 h, 95%.

Scheme 126. Saponification of methyl ester **221** to carboxylic acid **215**.

The same procedure was then successfully applied to the (5:3) isomeric mixture of heterodimers **235** and **236**, to give the expected carboxylic acids **115** and **237** in a good 71% yield (**Scheme 127**).



Reagents and conditions **i**, LiOH, THF, 1 h, 95%.

Scheme 127. Synthesis of *enantio*-*N*-TAC-*iso*-ADDA **115** and *enantio*-*N*-TAC-ADDA **237**.

The synthesis of the *enantio*-*N*-TAC-*iso*-ADDA was published as the synthesis of its methyl ester derivative **235**, and consequently, the saponification was not repeated on each diasteroisomer **235** and **236** separately.

2.5 – Isolation of CM homodimers

The remaining fractions, free of desired heterodimers, resulting from previous purifications of CM reactions were combined, and purified to recover some precious starting olefins, but also to isolate any residual traces of undesired dimers. Among the significant number of CM olefins used, these purifications allowed the isolation of milligram quantities of homodimers **238**, **(±)-239**, **(±)-240*E*** and **(±)-240*Z*** only (**Figure 28**). Unlike the olefin **180**, which was observed as two isomers (presumably *E* and *Z*), **238**, **(±)-239** have been isolated as their single (*E*)-double bond isomers. Although the presence of traces of (*Z*)-isomer of olefins **238**, **(±)-239** was suspected, it could not be confirmed, as the majority of impurity NMR signals were unresolved.

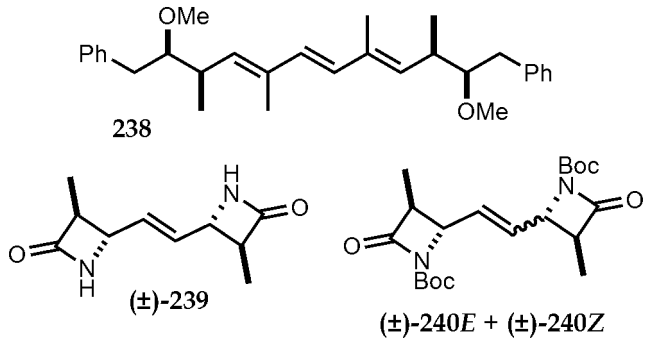


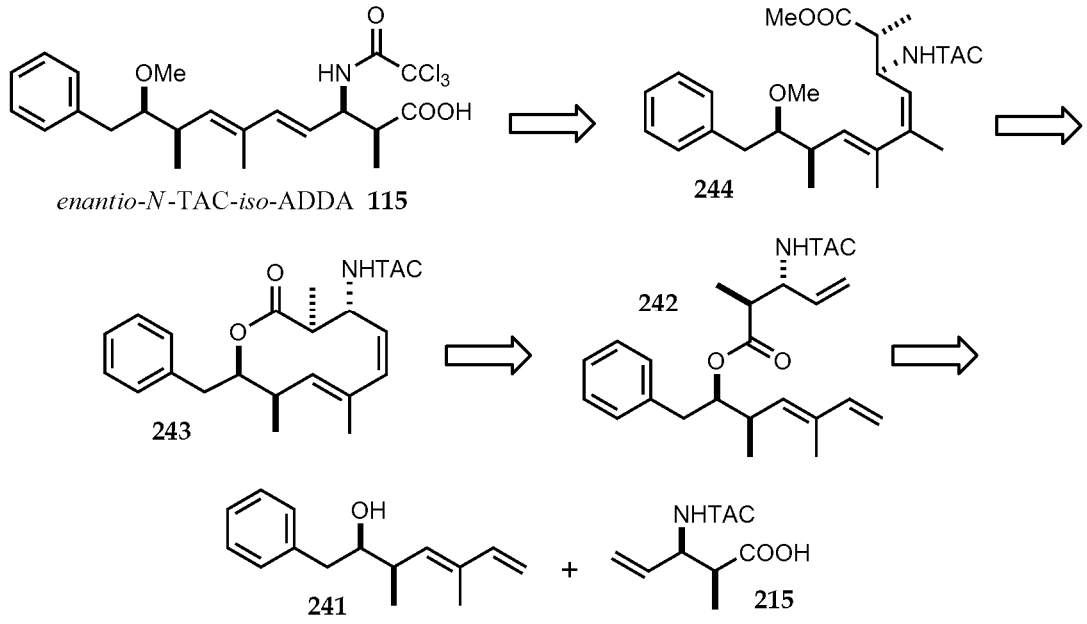
Figure 28. CM homodimers isolated and characterised.

3 – BRIEF CONCLUSION

The synthesis of *enantio*-*N*-TAC-*iso*-ADDA methyl ester **235** was successfully completed and published in the literature.[127] It represents the first synthesis of the *iso*-ADDA framework, as well as a useful platform from which new protein phosphatase inhibitors containing *iso*-ADDA residue, might be synthesised, and subsequently biologically tested. Our approach demonstrated once again the efficiency of cross-metathesis chemistry, which should extend its scope as a superb tool for carbon-carbon coupling method. The chemistry developed should be easily scaled up, and utilised to generate the *enantio*-*N*-TAC-*iso*-ADDA **115** and *enantio*-*N*-TAC-ADDA **237** though the same approach, and on multigram scale.

4 – RING CLOSING METATHESIS ALTERNATIVE

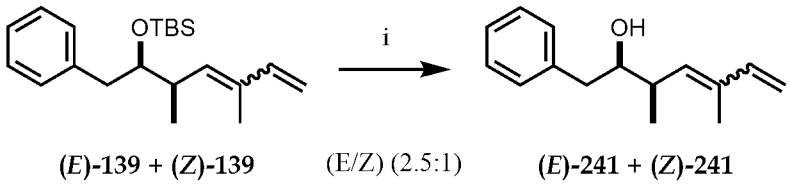
Before the cross-metathesis methodology was proved to work, the synthesis of ester **242** from carboxylic acid **215** and dienol **241**, followed by a ring closing metathesis (RCM), was thought to be an alternative route towards the synthesis of *enantio*-*N*-TAC-*iso*-ADDA **115** (**Scheme 128**). A subsequent opening of the 10-membered ring, followed with the isomerisation of the (*E*,*Z*)-double bond isomer to the (*E*,*E*)-isomer, as described by Toogood,[72] would have then been used to isolate the *enantio*-*iso*-ADDA **115** (**Scheme 128**).



Scheme 128. RCM alternative towards *enantio*-*N*-TAC-*iso*-ADDA **115**.

As the cross-metathesis methodology was subsequently shown to lead successfully to both isomeric ADDA ***enant*-31** and **115**, the RCM alternative was rapidly considered irrelevant. However, it represented a synthetic challenge that we proposed to investigate. Although the generation of rings *via* RCM is now a well known technique, the generation of 10-membered rings has already been demonstrated to be a disfavoured process, due to entropy and inherent ring strain,[141] and only a very few RCM reactions have been reported to give this ring size.[141] In addition, the synthesis of 10-membered rings containing the (*E*,*Z*)-1,3-diene motif has not been acheived to date, although these frameworks are present in natural products.[142] These features made this synthetic target a very ambitious and challenging project to us.

The (2.5:1) isomeric mixture of alcohol **(*E*)-241** and **(*Z*)-241** was prepared from the treatment of a (2.5:1) isomeric mixture of TBS-protected dienes **(*E*)-139** and **(*Z*)-139** with TBAF (**Scheme 129**).

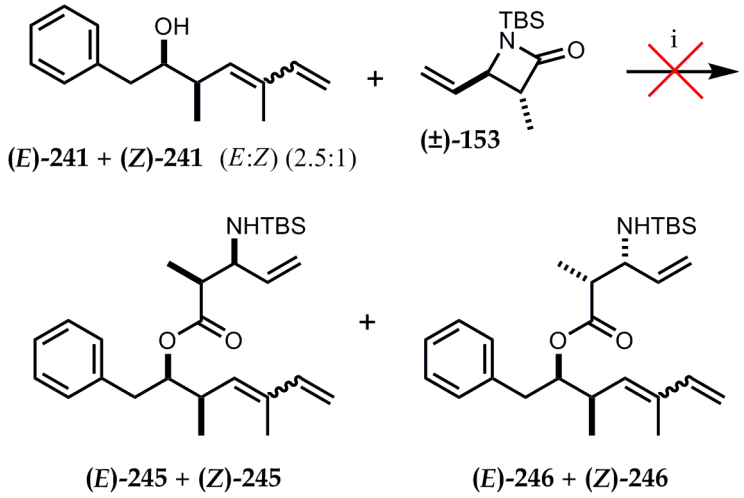


Reagents and conditions **i**, TBAF, THF, rt, 15 min, 95%.

Scheme 129. Synthesis of dienols **(*E*)-241** and **(*Z*)-241**.

However, the two isomers **(*E*)-241** and **(*Z*)-241** were not separated, and the mixture was used directly into the first RCM test reactions. The reason for this was to determine whether or not the RCM of one of the double bond isomers was favoured over the other.

A nucleophilic esterification between the isomeric mixture of dienols **(*E*)-241** and **(*Z*)-241**, and the racemic lactam **(±)-153**, was initially attempted to form the ester linkage (**Scheme 130**). Unfortunately, even after a long reaction time no coupling product was observed.

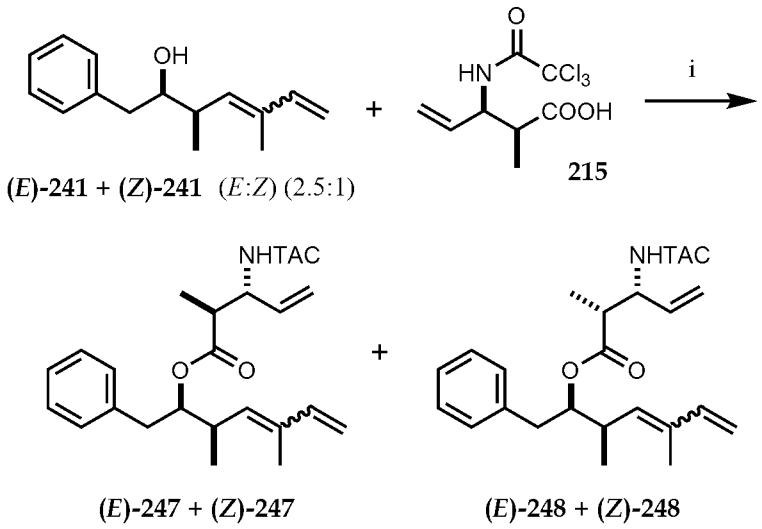


Reagents and conditions **i**, MeMgBr, THF, -78 °C to rt, overnight.

Scheme 130. Unsuccessful synthesis of trienes **245** and **246**.

The firstly suggested coupling between dienols **(*E*)-241** and **(*Z*)-241** and carboxylic acid **215** (**Scheme 128**), was then attempted through the Yamaguchi procedure. Gratifyingly,

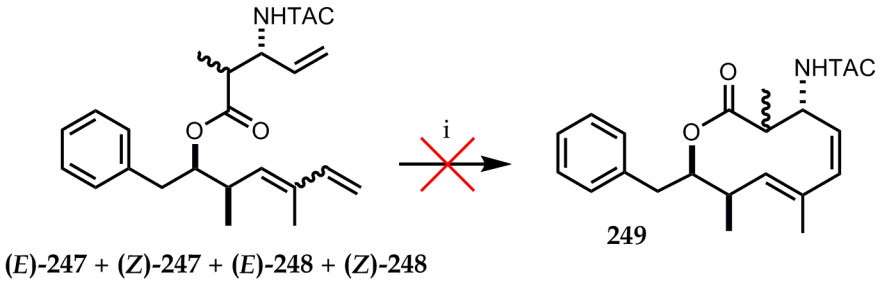
the reaction gave the esters **(*E*)-247** and **(*Z*)-247** in good yield, but as a complex mixture of isomers, resulting from the potential epimerisation of the stereocentre next to the carbonyl of the anhydride intermediate, as was previously observed for the epimerization of acid **215** (Section **IV-2.3.3**) (**Scheme 131**).



Reagents and conditions **i**, 2,4,6-trichlorobenzoyl chloride, DMAP, DIPEA, THF, toluene, rt, 2 h, 78%.

Scheme 131. Synthesis of triene **247** and **248**.

The (*E*)- and (*Z*)-isomeric mixture of esters **247** and **248** was treated with second generation Hoveyda-Grubbs catalyst in tetrahydrofuran, at reflux, but only starting material was observed. A last attempt, in toluene, at reflux, fully consumed the starting ester, and yielded a crude oil possessing a very complex NMR profile. Unfortunately, none of the isomeric macrocycle **249** was detected by mass spectrometry (**Scheme 132**).



Reagents and conditions **i**, HGII (20 mol%), THF or toluene, Δ, 24 h.

Scheme 132. Unsuccessful synthesis of 10-membered ring diene **249**.

Due to lack of time, the whole process was not further investigated, and the structure of the undesired isomers generated under the Yamaguchi esterification (**Scheme 131**) could not be determined in time. However, the preliminary results tend to confirm that 10-membered rings containing the (*E*,*Z*)-1,3-diene cannot be accessed easily through the employed RCM methodology.

CONCLUSION

Enantio-*N*-Boc-ADDA chain ***enant*-31** has been successfully synthesised in modest yield,[127] but due to the recent discoveries made through the use of enantiomerically pure β-lactam **174**, the whole synthesis needs to be optimized. Conversely, the efficient convergent synthesis of *enantio*-*N*-TAC-*iso*-ADDA methyl ester **235** has already been well optimised. Our approach allowed the isolation of the aromatic containing fragment **(*E*)-117** in 28% overall yield in 7 steps, while the synthesis of the amino containing unit **221** was obtained in 36% yield over 10 synthetic steps. Our approach, terminated through the use of a successful cross-metathesis coupling, which enabled the isolation of *enantio*-*N*-TAC-*iso*-ADDA methyl ester **235** in 25% overall yield after 18 steps from commercially available starting material. Hence, ranking our approach among the best syntheses towards the ADDA scaffold reported to date. However, our results are by no means comparable to the Rinehart's linear synthesis, which yielded the ADDA chain in an excellent 40% overall yield in 13 steps.

However, more importantly, we demonstrated the importance of cross-metathesis methodology as a key technique for the generation of (*E*,*E*)-1,3-diene motif, in good yield and with total (*E*)-selectivity. The results obtained have extended the scope of cross-metathesis methodology beyond the synthesis of ADDA, in coupling efficiently 1,3-dienes with allylic amines, which are both electron rich olefins. Moreover it is also worth noticing that CM couplings were achieved with almost equimolar ratio between CM partners, thus by-passing the classical CM distribution discussed in section **III-2.1.1**. Additionally, low amounts of catalysts (< 10 mol%) were required, with preliminary evidence that smaller loadings (< 5 mol%) do not dramatically affect the coupling reaction.

Both syntheses of *enantio*-*N*-Boc-ADDA ***enant*-31** and *enantio*-*N*-TAC-*iso*-ADDA **115** involve the use of stable intermediates made through robust and reliable chemistry. Every single intermediate (except aldehyde **134**) was shown to be stable upon storage at room temperature, and was often taken on crude to the following reaction. It should also be noted that distillation techniques (*via* Kugelrohr apparatus) could be employed as an alternative to rather difficult purification by flash column chromatography for multi-gram scale cross-metathesis reactions. These qualities should offer the opportunity to scale-up

the synthetic process, and prepare multi-gram quantities of both ADDA isoforms in little amount of time. Hence, the next part of the project, which is the synthesis of isomeric ADDA-containing analogues, should be now possible from this synthetic platform. Furthermore, it is worth mentioning that access to multi-gram quantities of *enantio*-ADDA **1** and *enantio-iso*-ADDA **2** might allow the use of high throughput screening techniques to prepare and test a broad range of ADDA-containing analogues.

The synthesis and biological test of such ADDA-containing analogues might give a better understanding of the bioactivity related to the ADDA profile. As an ultimate goal, our research might lead to the discovery of potent and selective novel ADDA-containing protein phosphatase inhibitors, which might help elucidate biological pathways, and access new drug therapies.

EXPERIMENTAL PART

1 – GENERAL INFORMATION

1.1 – General procedure and material

All reactions were performed under inert argon atmosphere unless otherwise stated. Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, and toluene were purified through a solvent purification system. All reagents were used as received and the solvents were evaporated under reduced pressure at 60 °C, unless otherwise stated. Flash column chromatography was performed using silica gel (Silica Gel 60, 40-63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica. The plates were visualised by the quenching of UV fluorescence (λ_{max}254nm) and/or by staining with, anisaldehyde, potassium permanganate, phosphomolybdic acid or iodine followed by heating.

It is important to mention that the vast majority of test reactions, were in a first instance operated with isomeric mixtures of starting olefins such as compounds **122** and **191 (4:1)**, **(*E*)-139** and **(*Z*)-139** (3:1) or **(*E*)-117** and **(*Z*)-117** (3:1). In these cases, it resulted in the isolation of complex isomeric mixtures of heterodimers where only the major heterodimers formed were identified, characterized and reported in the experimental part. However, every successful reaction necessary to the synthesis of final *enantio*-*N*-Boc-ADDA ***enant*-31** and *enantio*-*N*-TAC-*iso*-ADDA **115** was optimized, reproduced, and then scaled-up in using diastereo- and enantiomerically pure starting material.

1.2 – Characterisations & data collection

Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were respectively recorded at 400MHz and 100MHz on Bruker AV 400 and DPX 400. Chemical shifts (δ) are reported in parts per million (ppm), and are referenced to the residual solvent peak, which is generally deuterochloroform (^{1}H-δ 7.26 and ^{13}C-δ 77.0 ppm), unless otherwise stated. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad, vb = very broad, app = apparent), and (3) coupling constant (*J*) quoted in Hertz.

Optical rotations were determined as solutions in chloroform, irradiating wwith the sodium D line (λ = 589 nm) using an JASCO DIP-370 digital polarimeter. $[\alpha]_D$ values are given in units 10^{-1} degcm^{2}g^{-1}.

Infrared (IR) spectra were recorded on JASCO FTIR 410 spectrometer, as thin films on NaCl plates, and in the range 4000-600 cm^{-1}. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

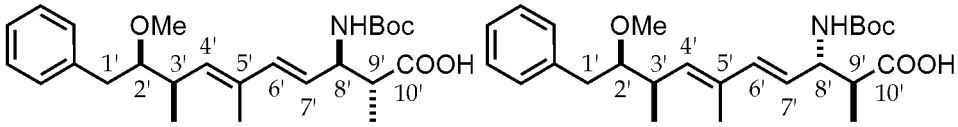
Mass spectra and accurate mass measurements were obtained by fast atom bombardment (FAB), electrospray ionisation (ES), electronical impact (EI) or chemical ionization (CI), on JEOL JMS-700 spectrometer operating at a resolution of 15000 full widths at half height.

Melting points were determined using a Mel-Temp II melting point apparatus.

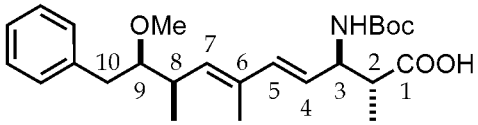
1.3 - Crystallographic data collection

X-ray data for trichloroacetamide **122** were collected at 100 K on a Rigaku R-Axis RAPID Image Plate diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ = 0.71069 Å) radiation Data reduction was carried out using CrystalClear software version 1.4.0 [CRYSTALCLEAR 1.4.0. Rigaku, 9009 New Trails Dr., The Woodlands, Texas 77381, USA, 1998]. The structures was solved by direct methods using the program SHELXS [SHELXS86. Sheldrick, G.M. (1986). Program for the solution of crystal structures. Univ. of Göttingen, Germany] and refined using full-matrix least-squares refinement on F ($I > 2\sigma_I$) using CRYSTALS [Betteridge, P.W.; Carruthers, J.R.; Cooper, R.I.; Prout, K.; Watkin, D.J. *J. Appl. Cryst.*, **2003**, *36*, 1487]. All non-hydrogen atoms were refined anisotropically. H atoms were placed in geometrically calculated positions and refined as riding groups, except for the atoms involved in hydrogen bonding, which were located on a difference map in each case, and their positions allowed to refine. CCDC 699929 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The Cif is supplied as Electronic Supplementary Information.

2 - PROCEDURES & DATA

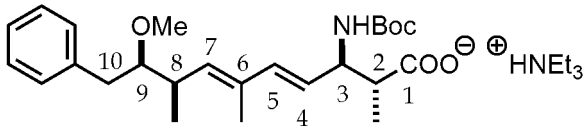


(2*R*,3*R*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (*enantio*-*N*-Boc-ADDA), *enant*-31 and (2*S*,3*S*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, 173. ***First procedure yielding the carboxylic acids in quantitative yield:*** A solution of a (1:1) diastereoisomeric mixture of *N*-Boc protected lactams **176** and **177** (1:1, 55 mg, 130 µmol) in THF (3 mL) was treated with an aq. solution of LiOH (1.0 M, 600 µL, 600 µmol) at room temperature. The reaction was stirred at room temperature until completion (5 h), and then quenched by the sequential addition of water (2.4 mL) and glacial acetic acid (0.3 mL). The resulting mixture was extracted with diethyl ether (3 x 20 mL), and the combined organic phases were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a yellow oil (70 mg) which was purified by flash chromatography (silica gel, 0-10% methanol in dichloromethane) to give *enantio*-*N*-Boc-ADDA ***enant*-31** and **173** (1:1) as a clear and very viscous light yellowish oil (58 mg, 100%).

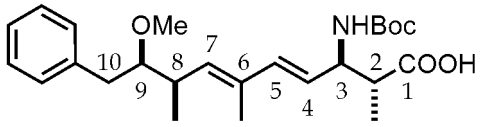


(2*R*,3*R*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (*enantio*-*N*-Boc-ADDA chain) *enant*-31: A solution of the single diastereoisomer **176** (40 mg, 97 µmol) in THF (2.2 mL) was treated with LiOH (1.0 M aq, 450 µL, 450 µmol) at room temperature. After stirring the reaction for 90 min, water (1.7 mL) was added and the solution was acidified by addition of glacial acetic acid (0.2 mL), before being extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to give a viscous yellow oil (61 mg). Purification by flash column chromatography (silica gel, 0.5% TEA, 0-10% methanol in dichloromethane) gave the triethylammonium salt of *enantio*-*N*-Boc-ADDA **183** contaminated with an slight excess of triethylamine, as a clear and very viscous light yellowish oil (49 mg, 94%) which could be fully characterised. The pure triethylammonium salt was dissolved in chloroform (50 mL) and was washed with

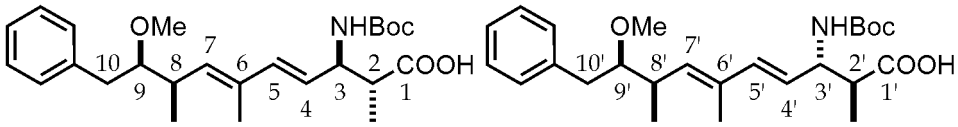
acidic water (10 mL of H_2O + 1.0 mL of 1.0 M HCl) to regenerate the carboxylic acid ***enant*-31**. The organic layer was then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. This quick work up afforded the single diastereoisomer of the free *enantio-N*-Boc-ADDA ***enant*-31** as a very viscous colourless clear oil (38 mg, 90%).



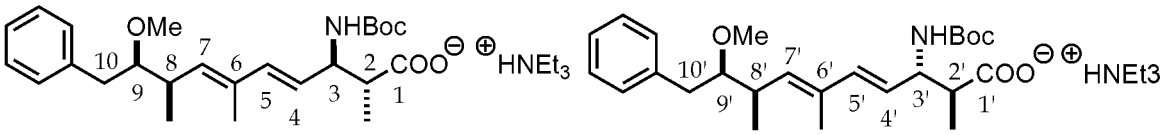
183. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 6.5 Hz, 8-CCH_3), 1.20 (9H, t, *J* = 7.3 Hz, 3 x CH_3), 1.20 (3H, hidden m, 2-CCH_3), 1.43 (3H, s, $OC(CH_3)_3$), 1.58 (3H, s, 6-CCH_3), 2.56 (2H, m, 8-CH + 2-CH), 2.64 (1H, dd, *J* = 14.0, 7.5 Hz, 10-CH), 2.78 (1H, dd, *J* = 13.9, 4.1 Hz, 10-CH'), 2.98 (6H, q, *J* = 7.3 Hz, 3 x CH_2), 3.15 (1H, m, 9-CH), 3.20 (3H, s, OCH_3), 4.22 (1H, appbs, 3-CH), 5.32 (1H, d, *J* = 9.7 Hz, 7-CH), 5.54 (1H, unresolved dd, *J* = 14.7, 3.6 Hz, 4-CH), 6.09 (1H, bs, NH), 6.16 (1H, d, *J* = 15.7 Hz, 5-CH), 7.16-7.26 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 8.3 ($(NCH_2CH_3)_3$), 12.7 (6-CCH_3), 15.5 (2-CCH_3), 16.3 (8-CCH_3), 28.4 ($OC(CH_3)_3$), 36.6 (8-CH), 38.2 (10-CH_2), 44.8 ($(NCH_2CH_3)_3$), 44.9 (2-CH), 54.9 (3-CH), 58.6 (OCH_3), 78.6 ($OC(CH_3)_3$), 86.9 (9-CH), 125.8 (4-CH), 127.3 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 132.7 (6-C_{IV}), 134.7 (7-CH), 134.8 (5-CH), 139.3 (ArC_{IV}), 156.5 (HNCOO), 180.0 (10-C=O); $[\alpha]^{26}_D$ +23.2, (c = 1.0, $CHCl_3$);



***enant*-31.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.7 Hz, 8-CCH_3), 1.25 (3H, d, *J* = 7.4 Hz, 2-CCH_3), 1.45 (3H, s, $OC(CH_3)_3$), 1.61 (3H, s, 6-CCH_3), 2.60 (1H, m, 8-CH), 2.67 (1H, dd, *J* = 13.9, 7.5 Hz, 10-CH), 2.77 (1H, m, 2-CH), 2.79 (2H, dd, *J* = 13.9, 4.5 Hz, 10-CH'), 3.19 (1H, m, 9-CH), 3.23 (3H, s, OCH_3), 4.39 (1H, appbs, 3-CH), 5.25 (1H, bs, NH), 5.39 (1H, d, *J* = 9.8 Hz, 7-CH), 5.48 (1H, dd, *J* = 15.7, 6.1 Hz, 4-CH), 6.20 (1H, d, *J* = 15.6 Hz, 5-CH), 7.17-7.29 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (6-CCH_3), 14.6 (2-CCH_3), 16.2 (8-CCH_3), 28.4 ($OC(CH_3)_3$), 36.7 (8-CH), 38.3 (10-CH_2), 44.1 (2-CH), 54.1 (3-CH), 58.6 (OCH_3), 79.8 ($OC(CH_3)_3$), 87.0 (9-CH), 125.1 (4-CH), 125.9 ($ArCH_{para}$), 128.2 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 132.5 (6-C_{IV}), 135.9 (7-CH), 136.5 (5-CH), 139.4 (ArC_{IV}), 155.5 (HNCOO), 179.4 (10-COOH); $[\alpha]^{26}_D$ +23.8, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3334, 3029, 2972, 2929, 2605, 2534, 1709, 1169, 740, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 432.2749, calculated for $C_{25}H_{38}O_5N$ 432.2750. Data was in full agreement with the one of the opposite enantiomer.[72,74-86]

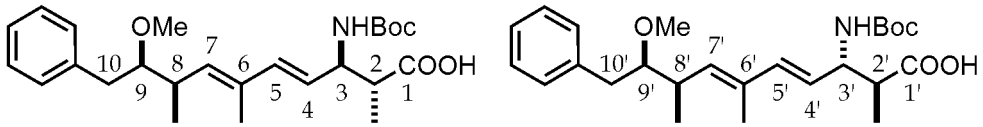


(2*R*,3*R*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (*enantio*-*N*-Boc-ADDA chain) *enant*-31, and (2*S*,3*S*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, 173: A solution of a (1:1) mixture of diastereoisomers **176** and **177** (50 mg, 120 µmol) in THF (2.5 mL) was treated with LiOH (1.0 M aq, 500 µL, 500 µmol) at room temperature. After stirring the reaction for 90 min, water (2.0 mL) was added and the solution was acidified by addition of glacial acetic acid (25 µL), before being extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to give a viscous yellow oil (72 mg). Purification by flash column chromatography (silica gel, 0.5% TEA, 0-10% methanol in dichloromethane) gave the triethylammonium carboxylate salts **183** and **184** as a clear and very viscous light yellowish oil (58 mg, 90%) which could be fully characterised. The pure triethylammonium salts **183** and **184** were dissolved in chloroform (50 mL) and were washed with acidic water (10 mL of H_2O + 1.0 mL of 1.0M HCl) to regenerate the carboxylic acids ***enant*-31** and **173**. The organic layer was then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the inseparable diastereoisomeric mixture of carboxylic acids ***enant*-31** and **173** as a very viscous colourless clear oil (46 mg, 88%).

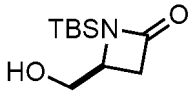


183 and **184.** ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 and 0.99 (6H, 2 x d, *J* = 6.6 Hz, 8-CCH_3 + 8'-CCH_3), 1.19 (18H, t, *J* = 7.3 Hz, 3 x CH_3 + 3 x CH_3'), 1.19 (6H, hidden m, 2-CCH_3 + 2'-CCH_3), 1.42 (6H, s, $OC(CH_3)_3$ + $OC(CH_3)_3$'), 1.57 and 1.58 (6H, 2 x d, *J* = 0.9 Hz, 6-CCH_3 + 6'-CCH_3), 2.56 (4H, m, 8-CH + 8'-CH + 2-CH + 2'-CH), 2.64 (2H, dd, *J* = 14.0, 7.5 Hz, 10-CH + 10'-CH), 2.78 (2H, 2 x unresolved dd, *J* = 13.9 Hz, 10-CH" + 10'-CH"), 2.97 (12H, q, *J* = 7.3 Hz, 3 x CH_2 + 3 x CH_2'), 3.14 (2H, m, 9-CH + 9'-CH), 3.19 and 3.20 (6H, 2 x s, OCH_3 + OCH_3'), 4.20 (2H, appbs, 3-CH + 3'-CH), 5.31 (2H, d, *J* = 9.7 Hz, 7-CH + 7'-CH), 5.54 (1H, bd, *J* = 14.8 Hz, 4-CH + 4'-CH), 6.16 (2H, hidden, NH), 6.16 and 6.17 (2H, 2 x d, *J* = 15.5 Hz, 5-CH + 5'-CH), 7.15-7.26 (10H, m, ArH + ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 8.4 ($(NCH_2CH_3)_3$ + $(NCH_2CH_3)_3$'), 12.7 (6-CCH_3 + 6'-CCH_3), 15.6 (2 peaks, 2-CCH_3 + 2'-CCH_3), 16.3 and 16.4 (8-

CCH_3 + 8'-CCH_3), 28.4 ($OC(CH_3)_3$), 36.6 and 36.7 (8-CH + 8'-CH), 38.2 (10-CH_2 + 10'-CH_2), 44.8 (($NCH_2CH_3)_3$), 45.0 and 45.1 (2-CH + 2'-CH), 54.9 and 55.0 (3-CH + 3'-CH), 58.6 (OCH_3 + OCH_3'), 78.5 ($OC(CH_3)_3$ + $OC(CH_3)_3$'), 86.9 and 87.0 (9-CH + 9'CH), 125.8 (4-CH + 4'CH), 127.6 (2 peaks, $ArCH_{para}$ + $ArCH_{para}$'), 128.1 ($ArCH_{ortho}$ + $ArCH_{ortho}$'), 129.4 (2 peaks, $ArCH_{meta}$ + $ArCH_{meta}$'), 132.8 (2 peaks, 6-C_{IV} + 6-C_{IV}'), 134.5 (7-CH + 7'-CH), 134.7 (5-CH + 5'-CH), 139.3 and 139.4 (ArC_{IV} + ArC_{IV}'), 156.0 (2 peaks, HNCOO + HNCOO'), 180.2 (10-C=O + 10'-C=O); $[\alpha]^{26}_D$ +15.8, (c = 1.0, $CHCl_3$);



***enant*-31** and **173.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 and 1.04 (6H, 2 x d, *J* = 6.7 Hz, 8-CCH_3 + 8'-CCH_3), 1.25 (6H, d, *J* = 7.4 Hz, 2-CCH_3 + 2'-CCH_3), 1.45 (6H, s, $OC(CH_3)_3$ + $OC(CH_3)_3$'), 1.61 (6H, s, 6-CCH_3 + 6'-CCH_3), 2.60 (2H, m, 8-CH + 8'-CH), 2.70 (2H, dd, *J* = 14.0, 7.4 Hz, 10-CH + 10'-CH), 2.67 (2H, 2 x dd, *J* = 13.9, 7.5 and 14.0, 7.6 Hz, 10-CH + 10'-CH), 2.74 (2H, m, 2-CH + 2'-CH), 2.80 (2H, 2 x unresolved dd, *J* = 13.9, 3.8 Hz, 10-CH" + 10'-CH"), 3.19 (2H, m, 9-CH, 9'-CH), 3.23 (6H, s, OCH_3 + OCH_3'), 4.39 (2H, appbs, 3-CH + 3'-CH), 5.25 (2H, bs, NH + NH'), 5.39 (2H, d, *J* = 9.8 Hz, 7-CH + 7'-CH), 5.48 (2H, dd, *J* = 15.7, 6.1 Hz, 4-CH + 4'-CH), 6.20 (2H, 2 x d, *J* = 15.6 Hz, 5-CH + 5'-CH), 7.17-7.29 (10H, m, ArH + ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (6-CCH_3 + 6'-CCH_3), 14.5 (2-CCH_3 + 2'-CCH_3), 16.2 (8-CCH_3 + 8'-CCH_3), 28.3 ($OC(CH_3)_3$ + $OC(CH_3)_3$'), 36.6 (2 peaks, 8-CH + 8'-CH), 38.2 (2 peaks, 10-CH_2 + 10'-CH_2), 44.1 (2-CH + 2'-CH), 54.4 (3-CH + 3'CH), 58.6 (OCH_3 + OCH_3'), 79.5 ($OC(CH_3)_3$ + $OC(CH_3)_3$'), 87.0 (2 peaks, 9-CH + 9'-CH), 125.1 (4-CH + 4'-CH), 125.9 ($ArCH_{para}$ + $ArCH_{para}$'), 128.1 ($ArCH_{ortho}$ + $ArCH_{ortho}$'), 129.4 ($ArCH_{meta}$ + $ArCH_{meta}$'), 132.5 (6-C_{IV} + 6-C_{IV}'), 135.9 (7-CH + 7'-CH), 136.5 (5-CH + 5'-CH), 139.3 (ArC_{IV} + ArC_{IV}'), 155.7 (HNCOO + HNCOO'), 179.9 (10-COOH + 10'-COOH); $[\alpha]^{26}_D$ +19.3, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3334, 3029, 2972, 2929, 2605, 2534, 1709, 1169, 740, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 432.2749, calculated for $C_{25}H_{38}O_5N$ 432.2750.



(4*S*)-*N*-(*tert*-Butyldimethylsilyl)-4-(hydroxymethyl)azetidinone, (*S*)-95: A suspension of (L)-aspartic acid **(*S*)-55** (16.5 g, 124 mmol) in regular toluene (600 mL) was treated with benzyl alcohol (124 mL, 1.20 mol) and *p*-toluenesulfonic acid (25.8 g, 136 mmol). The mixture was refluxed under vigorous stirring until no more water was formed in the

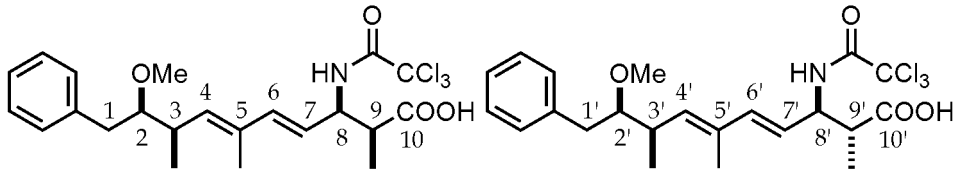
Dean-Stark apparatus (6 h). The half of the solvent was then evaporated under reduced pressure and 40-60 petroleum ether was then added until no more white solid precipitated. The suspension was filtered, and the white solid was dissolved in chloroform (1 L). The new resulting suspension was filtered one more time to provide a clear filtrate containing the final benzyl ester free of any starting reagents. The solvents were evaporated under vacuum to afford the benzyl ester **(*S*)-93** (35.6 g) in good purity as a white solid, which was used into the next step without any further purification. The ^{1}H and ^{13}C NMRs data agreed with those reported in the literature.[146]

A solution of crude benzyl ester **(*S*)-93** (35.6 g) in dry dichloromethane (400 mL) was treated with DMAP (8.9 g, 72 mmol) and a solution of TBSCl (13.8 g, 92 mmol) in anhydrous dichloromethane (50 mL). The mixture was then treated by the dropwise addition of a solution of anhydrous triethylamine (12.8 ml, 92 mmol) in anhydrous dichloromethane (50 mL) over 40 min at room temperature. The mixture was stirred overnight, the majority of the solvent was evaporated off under vacuum, and 40-60 petroleum ether was added to the resulting mixture to precipitate the ammonium and pyridinium salts, which were discarded after filtration. The filtrate was concentrated under reduced pressure (< 40 °C) to afford the crude *N*-TBS protected amine **(*S*)-94** (33.3 g) as a viscous and colourless clear oil, which was also used into the next reaction without any further purification. The ^{1}H and ^{13}C NMRs data agreed with those reported in the literature.[147]

A portion of crude *N*-TBS protected amine **(*S*)-94** (14.1 g) was dissolved in anhydrous diethyl ether (600 mL), cooled down to -78 °C and treated by the slow addition of ^{t}BuMgCl (15 mL, 2.0 M in diethyl ether, 30 mmol) over 10 min. The reaction mixture was then slowly allowed to warm up to room temperature, and was stirred overnight before being quenched by addition of methanol (20 mL). The mixture was filtrated through Celite, which was thoroughly washed with diethyl ether (600 mL), and the half of the solvent was removed *in vacuo* (< 45 °C). The resulting organic solution (~ 600 mL) was then washed with water (3 x 250 mL), and the organic layer was dried over anhydrous sodium sulfate. Evaporation of the diethyl ether under reduced pressure (< 45 °C) yielded the crude azetidinone **181** (11.0 g) as a viscous yellow to orange oil. Although the crude could be used into the next reaction without any further purification, removal of the equivalent of benzyl alcohol liberated during the cyclisation was readily acheived by flash column chromatography (silica gel, 1% TEA, 20-50% ethyl acetate in 40-60 petroleum ether). The semi-pure azetidinone **181** (3.09 g) was isolated as a viscous yellowish clear oil, which was

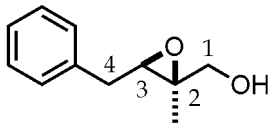
used into the next reaction without any further purification. The ^{1}H and ^{13}C NMRs data agreed with those reported in the literature.[147]

A suspension of sodium borohydride (480 mg, 12.7 mmol) in tetrahydrofuran (30 mL) and an aq. solution of lithium bromide (1.1 g, 13 mmol) in water (7.2 mL) were placed in the same dropping funnel, and added dropwise over a period of 40 min to a solution of the semi-pure lactam **181** (3.09 g) in tetrahydrofuran (30 mL) at such a rate that the internal temperature did not rise above 28 °C. The mixture was then stirred at room temperature until completion as indicated by TLC analysis. The reaction was quenched with a sat. aq. solution of ammonium chloride (30 mL), and the aqueous layer was extracted with ethyl acetate (2 x 60 mL) and dichloromethane (60 mL). The phases were separated, and the organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude yellow viscous oil (3.07 g) was then purified by flash chromatography (silica gel, 0.5% TEA, 20-40% ethyl acetate in 40-60 petroleum ether) to afford the pure alcohol **(*S*)-95** (1.03 g, 9% over 4 steps) as a viscous yellowish clear oil. The ^{1}H and ^{13}C NMRs data agreed with those reported for the opposite enantiomer.[148] $[\alpha]^{25}_{D}$ -72.0, (c = 1.0, $CHCl_3$).



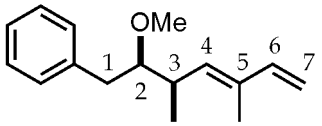
(2*S*,3*R*,4*E*,6*E*,8*R*,9*R*)-9-Methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoic acid (*enantio-iso-N*-TAC-ADDA), 115 and **(2*R*,3*R*,4*E*,6*E*,8*R*,9*R*)-9-Methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoic acid, 237.** A solution of a (1:1) mixture of methyl esters **235** and **236** (85 mg, 173 µmol) in tetrahydrofuran (2.0 mL) was treated with an aq. solution of lithium hydroxide (1.5 mL, 1.0 M, 1.5 mmol) at room temperature. The reaction was left overnight under vigorous stirring, and was subsequently quenched by addition of an aq. solution of HCl (1.0 M, 1.8 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 5 mL) and ethyl acetate (10 mL). The organic fractions were combined, and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure, and the resulting very viscous orange oil (72 mg) was purified by flash column chromatography (silica gel, 80% ethyl acetate in 40-60 petroleum spirit). The pure mixture of carboxylic acids **115** and **237** was obtained as an extremely

viscous and clear yellowish oil (59 mg, 71%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 and 1.04 (6H, 2 x d, *J* = 6.7 and 6.8 Hz, 3-CCH_3 + 3'-CCH_3), 1.26 and 1.34 (6H, 2 x d, *J* = 7.2 Hz, 9-CCH_3 + 9'-CCH_3), 1.62 (6H, 2 x d, *J* = 1.2 Hz, 5-CCH_3 + 5'-CCH_3), 2.62 (2H, m, 3-CH + 3'-CH), 2.67 and 2.70 (2H, 2 x dd, *J* = 7.6, 3.5 and 7.5, 3.5 Hz, 1-CH + 1'-CH), 2.79 (2H, 2 x dd, *J* = 14.0, 4.7 Hz, 1-CH" + 1'-CH"), 2.92 (2H, m, 9-CH + 9'-CH), 3.21 (2H, m, 2-CH + 2'-CH), 3.24 and 3.25 (6H, 2 x s, OCH_3 + OCH_3'), 4.62 (2H, m, 8-CH + 8-CH'), 5.41-5.51 (4H, m, 7-CH + 7'-CH + 4-CH + 4'-CH), 6.27 and 6.30 (2H, 2 x d, *J* = 15.3 and 15.4 Hz, 6-CH + 6'-CH), 7.17-7.28 (10H, m, ArH + ArH'), 7.62 and 7.80 (2H, bd, *J* = 8.8 and 8.9 Hz, NH + NH'), 9.58 (2H, vbs, OH + OH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (5-C*C*H_3 + 5'-C*C*H_3), 13.6 and 15.2, (9-CCH_3 + 9'-CCH_3), 16.1 (3-CCH_3 + 3'-CCH_3), 36.7 (3-CH + 3'-CH), 38.2 (1-CH_2 + 1'-CH_2), 42.8 and 43.3 (9-CH + 9'-CH), 55.1 and 55.4 (8-CH + 8'-CH), 58.6 (2 peaks, OCH_3 + OCH_3'), 86.9 and 87.0 (2-CH + 2'-CH), 92.7 and 92.8 (CCl_3 + C'Cl_3), 120.0 and 122.6 (4-CH + 4'-CH), 126.0 ($ArCH_{para}$ + $ArCH'_{para}$), 128.2 ($ArCH_{ortho}$ + $ArCH'_{ortho}$), 129.3 ($ArCH_{meta}$ + $ArCH'_{meta}$), 132.2 (5-C_{IV}), 137.3 and 138.1 (7-CH + 7'-CH), 137.6 and 140.0 (6-CH + 6'-CH), 139.2 (ArC_{IV}), 160.9 and 161.7 (Cl_3CC=O + Cl_3CC'=O), 178.4 and 179.5 (10-C=O + 10'-C=O).



((2*R*,3*R*)-3-Benzyl-2-methyloxiran-2-yl)methanol, 116. To flame-dried 4 Å molecular sieves (32 g in powder) in a round bottom flask was added dry dichloromethane (250 mL), followed by freshly distilled D(-)-DIPT (13.55 mL, 14.95 g, 63.80 mmol). After cooling to -30 °C, freshly distilled $Ti(OiPr)_4$ (17.82 mL, 17.11 g, 60.19 mmol) was added, and the reaction was allowed to stir at -30 °C for 30 min. After the addition of *t*-BuOOH (5.5 M in decanes, 64.0 mL, 352 mmol) at -25 °C, the solution was left to stir for a further hour at -30 °C before being treated with a solution of alcohol **125** (27.7 g, 171 mmol) in anhydrous dichloromethane (250 mL). The reaction was stirred 1 h at -30 °C, then allowed to warm up slowly to room temperature overnight, before being quenched by addition of water (800 mL) followed by an aq. solution of sodium hydroxide (30%) sat. with NaCl (175 mL total volume). The resultant milky mixture was filtered through cotton wool and sand (2 kg), and then washed with diethyl ether (1000 mL) and dichloromethane (1000 mL). The phases were separated and the aqueous layer was washed with dichloromethane (250 mL). The organic extracts were combined, dried over anhydrous sodium sulfate and concentrated under vacuum to afford a viscous oil (51.3 g). Purification of the resulting

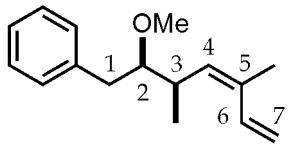
crude residue by flash column chromatography (silica gel, 30% ethyl acetate in 40-60 petroleum ether) afforded the pure desired epoxide **116** (28.7 g, 95%, *ee* = 90%) as a clear and colourless viscous oil. The enantiomeric excess was determined through HPLC analysis with a Chiracel IB column using hexanes:*iso*propanol (99:1) at a flow rate of 0.75 mL/min (retention time (2*R*,3*R*) = 28.85 min; (2*S*,3*S*) = 25.55 min). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.45 (3H, s, CH_3), 2.06 (1H, bs, OH), 2.90 (1H, dd, *J* = 14.7, 6.2 Hz, 4-CH), 3.00 (1H, dd, *J* = 14.7, 6.4 Hz, 4-CH'), 3.33 (1H, t, *J* = 6.3 Hz, 3-CH), 3.61 (1H, d, *J* = 12.3 Hz, 1-CH), 3.73 (1H, d, *J* = 12.3 Hz, 1-CH'), 7.26-7.38 (5H, m, ArCH); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.5 (CH_3), 34.7 (4-CH_2), 60.3 (3-CH), 61.4 (2-C_{IV}), 65.3 (1-CH_2), 126.7 ($ArCH_{para}$), 128.7 ($ArCH_{ortho}$), 128.8 ($ArCH_{meta}$), 137.6 (ArC_{IV}); $[\alpha]^{25}_D$ +23.2, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (EI) observed M^+ 178.0995, calculated for $C_{11}H_{14}O_2$ 178.0994.



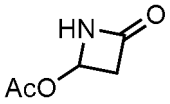
((2*R*,3*R*,4*E*)-2-Methoxy-3,5-dimethylhepta-4,6-dienyl)benzene, (*E*)-117. A solution of *O*-TBS protected diene **(*E*)-139** (544 mg, 1.65 mmol) in anhydrous THF (30 mL) was transferred into a round bottom flask containing flame-activated powdered 4 Å molecular sieves (2 g). The suspension was treated with tetrabutylammonium fluoride (1.0 M in THF, 4.90 mL, 4.90 mmol), and the resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (15 min). The mixture was quenched with water (40 mL), and then extracted with ethyl acetate (2 x 20 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and the solvents were removed under vacuum. The resulting brown oil (447 mg) was then taken on crude to the next reaction without any further purification.

Neat KH (1.2 g, 30 mmol) was mixed with anhydrous THF (90 mL), and the resulting suspension was treated with the crude dienol at 0 °C. The reaction mixture was then stirred under argon at 0 °C for 20 min, and iodomethane (1.60 mL, 3.65 g, 25.7 mmol) was incorporated after having been filtered through a small pad of basic alumina. The solution was then allowed to slowly warm up to room temperature, and the reaction was stirred at room temperature until completion as indicated by TLC analysis (2 h). The reaction was carefully quenched by the slow addition of a sat. aq. solution of $NaHCO_3$ (70 mL), the phases were separated, and the aqueous layer was extracted with diethyl ether (30 mL).

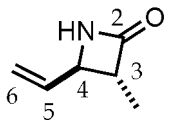
The organic extract was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude yellow oil (433 mg) obtained was then purified by flash column chromatography (silica gel, 70% toluene in 40-60 petroleum ether) to afford diene **(*E*)-117** as a colourless and clear viscous oil (347 mg, 91% over 2 steps). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 6.7 Hz, 3-CCH_3), 1.65 (3H, d, *J* = 1.2 Hz, 5-CCH_3), 2.57-2.66 (1H, m, 3-CH), 2.70 (1H, dd, *J* = 13.9, 7.4 Hz, 1-CH), 2.83 (1H, dd, *J* = 13.9, 4.5 Hz, 1-CH'), 3.19-3.23 (1H, m, 2-CH), 3.24 (3H, s, OCH_3), 4.97 (1H, d, *J* = 10.7 Hz, 7-CH), 5.11 (2H, dd, *J* = 17.4, 0.3 Hz, 7-CH'), 5.41 (1H, d, *J* = 9.8 Hz, 4-CH), 6.38 (1H, ddd, *J* = 17.4, 10.6, 0.6 Hz, 6-CH), 7.17-7.30 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 11.9 (5-$C\!CH_3$), 16.2 (3-$C\!CH_3$), 36.6 (3-CH), 38.2 (1-CH_2), 58.6 (OCH_3), 86.9 (2-CH), 111.1 (7-CH_2), 125.9 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 133.7 (5-C_{IV}), 135.8 (4-CH), 139.4 (ArC_{IV}), 141.6 (6-CH); $[\alpha]^{25}_{D}$ -2.6, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3027, 2955, 2928, 2871, 1454, 1096, 700 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 231.1745, calculated for $C_{16}H_{23}O$ 231.1749.



The procedure employed for the synthesis of **(*E*)-117**, was repeated on a (3:1) mixture of TBS 1,3-dienes **(*E*)-139** and **(*Z*)-139**, and provided a mixture of methoxy 1,3-dienes **(*E*)-117** and **(*Z*)-117** in identical yields. Both diastereoisomers were then successfully separated by flash chromatography (silica gel, 70% toluene in 40-60 petroleum spirit), and the methoxy 1,3-diene **(*Z*)-117** was isolated as a colourless clear viscous oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.9 Hz, 3-CCH_3), 1.74 (3H, d, *J* = 1.2 Hz, 5-CCH_3), 2.63 (1H, dd, *J* = 13.7, 5.9 Hz, 1-CH), 2.71 (1H, m, 3-CH), 2.83 (1H, dd, *J* = 13.7, 7.2 Hz, 1-CH'), 3.31 (1H, m, 2-CH), 3.32 (3H, s, OCH_3), 5.00 (1H, d, *J* = 10.7 Hz, 7-CH), 5.15 (2H, dd, *J* = 17.4, 0.3 Hz, 7-CH'), 5.57 (1H, d, *J* = 9.7 Hz, 4-CH), 6.46 (1H, ddd, *J* = 17.4, 10.7, 0.5 Hz, 6-CH), 7.19-7.32 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 11.9 (5-$C\!CH_3$), 16.9 (3-$C\!CH_3$), 35.5 (3-CH), 38.1 (1-CH_2), 58.5 (OCH_3), 86.8 (2-CH), 110.8 (7-CH_2), 125.9 ($ArCH_{para}$), 128.2 ($ArCH_{ortho}$), 129.3 ($ArCH_{meta}$), 134.2 (5-C_{IV}), 134.3 (4-CH), 139.4 (ArC_{IV}), 141.7 (6-CH); $[\alpha]^{25}_{D}$ -4.2, (c = 1.0, $CHCl_3$). IR (thin film) ν_{max} = 3032, 2966, 2930, 2865, 1455, 1101, 699 cm^{-1}.

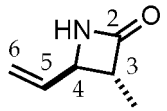


4-Acetoxyazetidinone, (±)-118. Freshly distilled vinyl acetate **148** (286 mL, 267 g, 3.10 mol) was treated with chlorosulfonyl isocyanate **149** (50.0 mL, 81.3 g, 574 mmol) at 0 °C. The reaction was followed by ^{1}H NMR, and the maximum conversion was obtained after 1 h, when the reaction mixture started to turn yellow. The reaction was then cooled down to -78 °C, and cannulated into a 2 L conical flask containing a previously made mixture of sodium bicarbonate (130 g, 1.54 mol), sodium sulfite (90 g, 710 mmol), ice (250 g, 13.9 mol) and water (250 g, 13,9 mol). The transfer was made in an air vessel which was imperatively kept below 0 °C throughout the transfer, and the mixture was stirred until the bubbling ceased (1 h), before being poured into a separating funnel. The phases were separated, and the organic layer was extracted with water (5 x 150 mL). The combined aqueous extracts were extracted with dichloromethane (3 x 150 mL) followed by saturation of the aqueous phase with sodium chloride. The saturated aqueous solution was then extracted with dichloromethane (2 x 150 mL) and ethyl acetate (150 mL). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated (< 30 °C) under reduced pressure to give the desired azetidinone **(±)-118** as a viscous light yellow oil, which was shown pure by ^{1}H NMR analysis, and was used in the next step without any further purification (17.8 g, 24%). Data fully agreed with those reported in the literature.[145]



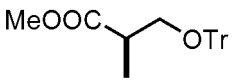
(±)-(3*R*,4*R*)-3-Methyl-4-vinylazetidin-2-one, (±)-119. A solution of *N*-TBS protected vinylazetidinone **(±)-153** (8.78 g, 39.0 mmol) in methanol (300 mL) was treated by the slow addition of potassium fluoride (4.22 g, 72.6 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and the solvent was evaporated under reduced pressure to yield a crude orange/brown oil (5.57 g), which was purified by flash column chromatography (silica gel, 50% ethyl acetate in 40-60 petroleum ether) to afford the pure desired azetidinone **(±)-119** as a clear, colourless and slightly viscous oil (3.77 g, 87%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.34 (3H, d, J = 7.4 Hz, CH_3), 2.92 (1H, qdd, J = 7.4, 2.3, 1.0 Hz, 3-CH), 3.72 (1H, dm, J = 7.2 Hz, 4-CH), 5.17 (1H, dappt, J = 10.2, 0.9 Hz, 6-CH), 5.30 (1H, dappt, J =

17.1, 1.0 Hz, 6-CH'), 5.92 (1H, ddd, J = 17.1, 10.2, 7.1 Hz, 5-CH), 6.12 (1H, s, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (CH_3), 53.3 (3-CH), 58.2 (4-CH), 116.9 (6-CH_2), 137.1 (5-CH), 171.3 (2-C=O); IR (thin film) ν_{max} = 3471, 3253, 3087, 3008, 2968, 2931, 2873, 1750, 1644, 1176, 926 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 112.0760, calculated for $C_6H_{10}ON$ 112.0762.



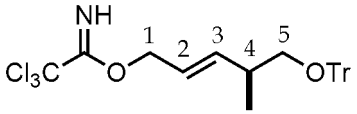
(3*R*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-methyl-4-vinylazetidin-2-one, 119: The *N*-TBS protected azetidinone **152** (92 mg, 430 µmol) was dissolved in dry tetrahydrofuran (10 mL), and the solution was cooled down to -78 °C. *n*-BuLi (2.0 M, 600 µL, 600 µmol) was then incorporated slowly, and the mixture was stirred for 10 min at -78 °C, before adding iodomethane (150 µL, 2.41 mmol) through a short pad of basic alumina. The reaction was stirred for a further 10 min and then worked up by adding methanol (300 µL) followed by a sat. aq. solution of ammonium chloride (3.5 mL) at -78 °C. The mixture was then filtered through a pad of Celite, washed with diethyl ether (200 mL), and concentrated *in vacuo* to afford a yellow oil as the crude azetidinone **153** (196 mg), which was then used into the next reaction without any further purification.

The crude *N*-TBS protected vinylazetidinone **153** (196 mg) was dissolved in methanol (5 mL) and the solution was cooled down to 0 °C. Potassium fluoride (75 mg, 1.3 mmol) was slowly added to the reaction, which was stirred for 10 min. The solvent was evaporated under reduced pressure, and the crude residue (131 mg) was purified by flash column chromatography (silica gel, 30% ethyl acetate in 40-60 petroleum ether) to afford the pure desired azetidinone **119** as a clear, colourless and slightly viscous oil (27 mg, 55% over 2 steps). Data were in full agreement with those reported for the racemic azetidinone **(±)-119** $[\alpha]^{29}_D$ +6.2, (c = 1.0, $CHCl_3$).



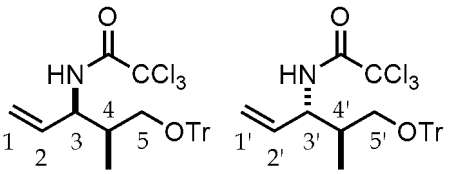
(*R*)-(-)-3-Trityloxy-2-methylpropionate, 120. To a solution of (*R*)-(-)-3-hydroxy-2-methylpropionate **186** (91.0 mg, 0.77 mmol) in anhydrous dichloromethane (5 mL) was added anhydrous triethylamine (170 µL, 1.22 mmol) at room temperature. After stirring the mixture at room temperature for 5 min, the solution was cooled down to 0 °C and a previously prepared solution of tritylchloride (279 mg, 1.00 mmol) in dry dichloromethane

(1 mL) was added slowly. The reaction was allowed to warm up to room temperature, and stirred overnight. The mixture was then quenched by the addition of a sat. aq. solution of ammonium chloride (4 mL), and extracted with dichloromethane (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum to afford a sticky yellowish oil (324 mg). Purification by flash column chromatography (silica gel, 1% TEA, elution gradient 0-20% ethyl acetate in 40-60 petroleum ether) yielded the pure trityl-protected ester **120** as a sticky, clear and colourless oil (277 mg, 100%), which tends to form white crystals upon storage. For multigram scales the ester **120** was taken on crude in the next reaction without any purification. The spectroscopic data was in full agreement with the one reported in the literature.[143] $[\alpha]^{25}_{D}$ –19.7, (c = 1.0, $CHCl_3$).



(*4S,2E*)-5-Trityloxy-4-methylpent-2-enyl 2,2,2-trichloroacetimidate, 121. To a -78 °C solution of allylic alcohol **189** (73.2 mg, 204 µmol) in anhydrous dichloromethane (5 mL) was added trichloroacetonitrile (30 µL, 0.3 mmol) and DBU (6.2 µL, 40 µmol). The mixture was slowly allowed to warm up to room temperature, where it was stirred under argon until completion as indicated by TLC analysis (3 h). The reaction was quenched by addition of water (5 mL), and diluted with diethyl ether (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The organic extracts were combined, and dried over anhydrous sodium sulfate before being concentrated under vacuum to afford a crude yellowish oil (121 mg). Purification of the oily residue by flash column chromatography (silica gel, 1% TEA, elution gradient 0-5% ethyl acetate in 40-60 petroleum ether) afforded the desired trichloroacetimidate **121** (99 mg, 97%) as a sticky colourless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.8 Hz, CH_3), 2.53 (1H, appsept, *J* = 6.5 Hz, 4-CH), 2.99 (1H, dd, *J* = 8.7, 6.2 Hz, 5-CH), 3.03 (1H, dd, *J* = 8.7, 6.7 Hz, 5-CH'), 4.78 (2H, d, *J* = 6.1 Hz, 1-CH_2), 5.72 (1H, dtd, *J* = 15.6, 6.1, 0.9 Hz, 2-CH), 5.88 (1H, bdd, *J* = 15.6, 7.0 Hz, 3-CH), 7.21-7.46 (15H, m, ArH), 8.29 (1H, s, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 16.8 (CH_3), 37.1 (3-CH), 67.8 (5-CH_2), 69.9 (1-CH_2), 86.2 ($OCPh_3$), 91.5 (CCl_3), 122.6 (2-CH), 126.8 ($ArCH_{para}$), 127.7 ($ArCH_{ortho}$), 128.7 ($ArCH_{meta}$), 139.3 (3-CH), 144.2 (ArC_{IV}), 162.6 (C=N); $[\alpha]^{24.5}_{D}$ -1.4, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3342,

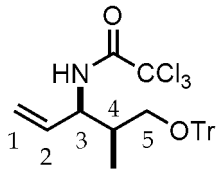
3087, 3059, 3023, 2961, 2926, 2871, 1661, 1490, 1448, 1307, 1290, 1218, 1073, 974, 797, 763, 707, 649 cm^{-1}.



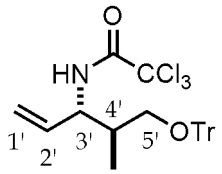
2,2,2-Trichloro-*N*-((*3R,4S*)-5-trityloxy-4-methylpent-1-en-3-yl)acetamide, 122; and 2,2,2-Trichloro-*N*-((*3R,4R*)-5-trityloxy-4-methylpent-1-en-3-yl)acetamide, 191. A solution of trichloroacetimidate **121** (9.84 g, 19.6 mmol) in anhydrous dichloromethane (435 mL) was treated with *p*-benzoquinone (3.12 g, 28.9 mmol) and *bis*(acetonitrile)dichloropalladium (II) (460 mg, 1.77 mmol, 9.1 mol%). The reaction was stirred at room temperature until TLC analysis indicated completion (24 h). An initial filtration of the reaction mixture through a short pad of silica was then used to remove the main colouring agent, and the silica pad was subsequently flushed with diethyl ether and the combined organic flushes were concentrated to afford crude residue that was purified by flash column chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40-60 petroleum ether) to afford the desired terminal alkenes **122** and **191** as a mixture of two *syn*- and *anti*-diastereoisomers (4:1) (8.71 g, 89%) as a very viscous and clear light brown oil. The two diastereoisomers **122** and **191** were separated successfully by recrystallisation (ethanol:40-60 petroleum ether) to afford **122** as a white powder.

***One-pot procedure**:* To a 0 °C solution of allylic alcohol **189** (812 mg, 2.27 mmol) in anhydrous dichloromethane (50 mL) was added DBU (67 µL, 0.4 mmol) followed by trichloroacetonitrile (320 µL, 3.19 mmol). The reaction was then allowed to warm up to room temperature, where it was stirred until completion as indicated by TLC analysis (2 h). *p*-Benzoquinone (315 mg, 2.91 mmol) and *bis*(acetonitrile)dichloropalladium (II) (63 mg, 0.24 mmol, 10.7 mol%) were then quickly incorporated into the reaction at the same time, and the reaction was stirred under argon for 5 h. At this time, extra *p*-benzoquinone (158 mg, 1.46 mmol) and *bis*(acetonitrile)dichloropalladium (II) (47 mg, 0.18 mmol, 8.0 mol%) were incorporated, and the reaction was stirred at room temperature for 2 days, before the reaction mixture was filtered through a pad of silica gel, which was then flushed with diethyl ether. Evaporation under reduced pressure of the organic solvent afforded a crude dark brown oil (1.46 g), which was purified by flash column chromatography (silica gel,

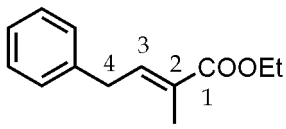
1% TEA, 10% ethyl acetate in 40-60 petroleum ether) to provide the expected terminal alkenes **122** and **191** (1.08 g, 95% over two steps) as a viscous and clear light brown oil. As in the two-pot procedure, the pure terminal alkenes **122** and **191** were obtained as a (4:1) mixture of *syn*- and *anti*-diastereoisomers, which could be separated by recrystallisation to afford **122** as a white powder (ethanol:40-60 petroleum ether).



122. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.82 (3H, d, *J* = 7.2 Hz, CH_3), 2.12 (1H, m, 4-CH), 3.12 (1H, t, *J* = 9.8 Hz, 5-CH), 3.26 (1H, dd, *J* = 10.0, 4.0 Hz, 5-CH'), 4.43 (1H, m, 3-CH), 5.12 (1H, appdt, *J* = 10.4, 1.2 Hz, 1-CH), 5.14 (1H, appdt, *J* = 17.1, 1.3 Hz, 1-CH'), 5.52 (1H, ddd, *J* = 17.0, 10.4, 6.1 Hz, 2-CH), 7.23-7.45 (15H, m, ArH), 7.76 (1H, d, *J* = 8.1 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.4 (CH_3), 36.7 (4-CH), 57.2 (3-CH), 65.9 (5-CH_2), 87.9 ($OCPh_3$), 92.8 (CCl_3), 117.8 (1-CH_2), 127.2 ($ArCH_{para}$), 127.9 ($ArCH_{ortho}$), 128.7 ($ArCH_{meta}$), 132.4 (2-CH), 143.3 (ArC_{IV}), 161.1 (C=O); $[\alpha]^{24}_D$ -1.6, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3368, 3086, 3058, 3022, 2967, 2927, 2883, 1706, 1492, 1448, 1218, 1036, 821, 759, 707, 633 cm^{-1}; M.p. 140 °C.

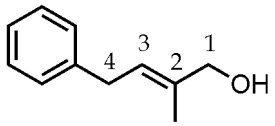


191. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.24 (3H, d, *J* = 7.1 Hz, CH_3), 2.00 (1H, m, 4-CH), 3.12 (1H, t, *J* = 9.8 Hz, 5-CH), 3.26 (1H, dd, *J* = 10.0, 4.0 Hz, 5-CH'), 4.43 (1H, m, 3-CH), 4.98 (1H, brd, *J* = 10.2 Hz, 1-CH), 5.01 (1H, d, *J* = 17.0 Hz, 1-CH'), 5.49 (1H, partially masked dd, *J* = 17.0, 10.2 Hz, 2-CH), 7.23-7.46 (15H, m, ArH), 7.59 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.9 (CH_3), 36.8 (4-CH), 57.5 (3-CH), 64.2 (5-CH_2), 87.4 ($OCPh_3$), 92.7 (CCl_3), 116.0 (1-CH_2), 127.1 ($ArCH_{para}$), 127.9 ($ArCH_{ortho}$), 128.7 ($ArCH_{meta}$), 135.0 (2-CH), 143.2 (ArC_{IV}), 161.7 (C=O).



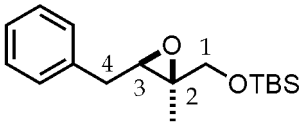
(*E*)-Ethyl 2-methyl-4-phenylbut-2-enoate, 124. To a stirred solution of commercially available phenylacetaldehyde **88** (6.05 g, 504 mmol) in dry benzene (120 mL) was added (1-ethoxycarbonylethylidene)-triphenylphosphorane (23.9 g, 660 mmol), and the resultant

solution was refluxed overnight. The reaction mixture was concentrated under reduced pressure, and the resultant yellow oily residue was washed with 40-60 petroleum ether (150 mL) to crush out triphenylphosphine oxide. The suspension was filtered and the solid was washed with 40-60 petroleum ether four more times (4 x 150 mL). The combined washings were then concentrated under vacuum to give a crude residue (9.34 g), which was purified by flash column chromatography (silica gel, 1-2% diethyl ether in petroleum ether) to afford (*E*)-Ethyl 2-methyl-4-phenylbut-2-enoate **124** (8.64 g, 84%) as a clear and colourless viscous oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.32 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.00 (3H, appq, *J* = 1.4 Hz, 2-CCH_3), 3.57 (2H, d, *J* = 7.6 Hz, 4-CH_2), 4.23 (2H, q, *J* = 7.1 Hz, OCH_2), 6.96 (1H, tq, *J* = 7.6, 1.4 Hz, 3-CH), 7.22-7.37 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.6 (2CCH_3), 14.3 (CH_2CH_3), 34.9 (4-CH_2), 60.6 (OCH_2), 126.4 ($ArCH_{para}$), 128.5 (2-C_{IV}), 128.6 ($ArCH_{meta}$), 128.7 ($ArCH_{ortho}$), 139.1 (ArC_{IV}), 140.0 (3-CH), 168.1 (1-C=O); IR (thin film) ν_{max} = 3029, 2981, 2932, 1710, 1255, 742, 699 cm^{-1}; HRMS (EI) observed M^+ 204.1152, calculated for $C_{13}H_{16}O_2$ 204.1150.

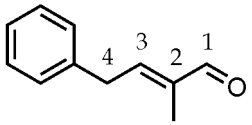


(*E*)-2-Methyl-4-phenylbut-2-en-1-ol, 125. To a stirred solution of (*E*)-Ethyl 2-methyl-4-phenylbut-2-enoate 124 (2.11 g, 10.3 mmol) in anhydrous diethyl ether (40 mL) was added $LiAlH_4$ dropwise (1.0 M in hexanes, 10.0 mL, 10.0 mmol) at 0 °C. The reaction was allowed to warm up to room temperature until completion as indicated by TLC (4 h). The reaction mixture was quenched at 0 °C by addition of water (2 mL) and aq. sodium hydroxide (20%, 1 mL). The work-up was continued by the further addition of water (40 mL) and aq. sodium hydroxide (20%, 20 mL). The mixture was stirred for 30 min after which, the mineral solid precipitate was filtrated, and washed with diethyl ether (120 mL). The organic extracts were dried over anhydrous sodium sulfate, and concentrated under vacuum to give a crude residue (1.71 g). Flash column chromatography (silica gel, 60% diethyl ether in 40-60 petroleum ether) provided the desired alcohol **125** (1.51 g, 90%) as a clear and colourless viscous oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.80 (3H, s, CH_3), 1.98 (1H, bs, OH), 3.42 (2H, d, *J* = 7.4 Hz, 4-CH_2), 4.04 (2H, s, 1-CH_2), 5.64 (1H, tq, *J* = 7.4, 1.4 Hz, 3-CH), 7.23-7.33 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.8 (CH_3), 33.9 (4-CH_2), 68.6 (1-CH_2), 124.6 (3-CH), 126.0 ($ArCH_{para}$), 128.4 ($ArCH_{meta}$), 128.6 ($ArCH_{ortho}$), 135.7 (2-C_{IV}), 141.0 (ArC_{IV}); IR (thin film) ν_{max} = 3324, 3027, 2915, 2860, 1493, 1453, 1016, 741, 698 cm^{-1};

HRMS (EI) observed M^+ 162.1043, calculated for $C_{11}H_{14}O$ 162.1045. Data was in full agreement with the one reported in the literature.[149]

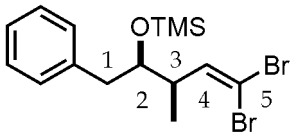


(((2*R*,3*R*)-3-Benzyl-2-methyloxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane, 126. A solution of epoxide **116** (207 mg, 1.16 mmol) in anhydrous *N,N*-dimethylformamide (6 mL) was treated with imidazole (237 mg, 3.48 mmol), and stirred until homogeneous. The reaction mixture was treated with TBSCl (277 mg, 1.84 mmol), and stirred under argon until completion as indicated by TLC analysis (2 h). The reaction was quenched by the addition of a (1:1) mixture of diethyl ether / water (14 mL total volume). The mixture was then slightly acidified by addition of aq. HCl (1.0 M, 1.5 mL) before the two phases were separated. The organic extracts were washed with water (10 mL) and brine (10 mL) after which, the combined ether extracts were then dried over anhydrous sodium sulfate, and subsequently concentrated under vacuum to yield a dark yellow crude oil (331 mg). Flash column chromatography (silica gel, 30% ethyl acetate in hexane) gave the desired silyl protected epoxide **126** (325 mg, 95%) as a clear and colourless viscous oil. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.03 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), δ 1.36 (3H, s, 2-CH_3), 2.78 (1H, dd, *J* = 14.8, 6.7 Hz, 4-CH), 2.93 (1H, dd, *J* = 14.8, 6.0 Hz, 4-CH'), 3.09 (1H, appt, *J* = 6.3 Hz, 3-CH), 3.52 (1H, d, *J* = 11.1 Hz, 1-CH), 3.57 (1H, d, *J* = 11.1 Hz, 1-CH'), 7.18-7.28 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -5.4 ($SiCH_3$), 14.4 (2-CCH_3), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 34.7 (4-CH_2), 61.2 (3-CH), 61.3 (2-C_{IV}), 68.0 (1-CH_2), 126.5 ($ArCH_{para}$), 128.6 ($ArCH_{ortho}$), 128.7 ($ArCH_{meta}$), 137.8 (ArC_{IV}); $[\alpha]^{25}_D$ -2.5, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 2929, 2857, 1689, 1471, 1461, 1255, 1096, 837 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 293.1935, calculated for $C_{17}H_{29}O_2Si$ 293.1937.



(*E*)-2-Methyl-4-phenylbut-2-enal, 128. The procedures employed for the synthesis of aldehydes **127** and **134** produced small variable amounts of conjugated aldehyde **128** as a side product, which could be isolated after a subsequent purification by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum ether). ^{1}H

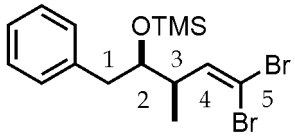
NMR (400MHz, $CDCl_3$) δ 1.88 (3H, s, CH_3), 3.70 (2H, d, J = 7.4 Hz, 4-CH_2), 6.65 (1H, td, J = 7.4, 0.9 Hz, 3-CH), 7.19-7.36 (5H, m, ArH), 9.44 (1H, s, 1-CHO); ^{13}C NMR (100MHz, $CDCl_3$) δ 9.4 (2-CCH_3), 35.2 (4-CH_2), 126.7 ($ArCH_{para}$), 128.5 ($ArCH_{meta}$), 128.8 ($ArCH_{ortho}$), 138.2 (2-C_{IV}), 139.5 (ArC_{IV}), 152.2 (3-CH), 195.1 (1-CH=O); IR (thin film) ν_{max} = 3063, 3028, 2957, 2926, 2854, 2818, 2715, 1686, 1644, 1494, 1454, 1072, 1005, 752, 699; HRMS (CI) observed $(M+H)^+$ 161.0966, calculated for $C_{11}H_{13}O$ 161.0969. Data was in full agreement with the one reported in the literature.[149c,150]



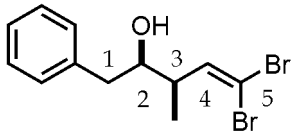
((2*R*,3*R*)-5,5-Dibromo-3-methyl-1-phenylpent-4-en-2-yloxy)trimethylsilane, 131. A -78 °C solution of epoxide **126** (202 mg, 691 µmol) and DIPEA (271 mg, 365 µL, 2.10 mmol) in anhydrous dichloromethane (20 mL) was treated by addition of TMSOTf (467 mg, 380 µL, 2.10 mmol). After being stirred for 10 min at -78 °C, the reaction was poured into a separating funnel containing a (1:1) mixture of diethyl ether and $NaHPO_4$ (1.0 M, 100 mL in total). The phases were thoroughly mixed up, and subsequently separated. The organic layer was then washed with an additional portion of water (50 mL), isolated and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave the crude aldehyde **127** (387 mg) as a single diastereoisomer.

A -78 °C solution of carbon tetrabromide (348 mg, 1.05 mmol) in anhydrous dichloromethane (5 mL) was slowly treated by the slow addition of a solution of triphenylphosphine (468 mg, 1.78 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 30 min at -78 °C before being treated with a previously prepared solution of crude aldehyde **127** (289 mg) in dry dichloromethane (5 mL). The mixture was stirred, and allowed to slowly warm up to room temperature overnight after which, the reaction was quenched and worked-up by addition of 40-60 petroleum spirit (3 x 100 mL) followed each time by filtration. The filtrates were combined, and concentrated *in vacuo* to provide a crude viscous and colourless oil (256 mg). NMR analysis proved the crude to be a (3:1) mixture of the TMS-protected alkenol **131** and free alkenol **132**. Purification by flash column chromatography (silica gel, 1% TEA, 100% 40-60 petroleum spirit) gave the pure TMS-protected alkenol **131** (68 mg, 24%) and free alkenol **132** (71 mg, 31%) both as viscous, clear and colourless oils. The conjugated dibromoolefin **133** (13 mg, 6%), formed during

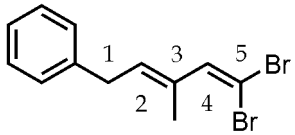
the process as a minor side product, could also be isolated by flash column chromatography (silica gel, 1% TEA, 100% 40-60 petroleum spirit).



131. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.10 (9H, s, $Si(CH_3)_3$), 1.07 (3H, d, J = 6.8 Hz, 3-CCH_3), 2.52 (1H, m, 3-CH), 2.67 (1H, dd, J = 13.5, 8.1 Hz, 1-CH), 2.79 (1H, dd, J = 13.5, 4.8 Hz, 1-CH'), 3.83 (1H, dt, J = 8.1, 4.8 Hz, 2-CH), 6.32 (1H, d, J = 9.5 Hz, 4-CH), 7.17-7.31 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 0.0 ($Si(CH_3)_3$), 13.7 (3-CCH_3), 41.8 (1-CH_2), 43.6 (3-CH), 76.3 (2-CH), 88.3 (5-C_{IV}), 126.3 ($ArCH_{para}$), 128.3 ($ArCH_{meta}$), 129.6 ($ArCH_{ortho}$), 138.8 (ArC_{IV}), 141.9 (4-CH); $[\alpha]^{23}_D$ -7.0, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3085, 3064, 3028, 2957, 2875, 1622, 1604, 1496, 1455, 1366, 1251, 1216, 1107, 1019, 932, 886, 841, 750, 699 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 404.9888, calculated for $C_{15}H_{23}OSi^{79}Br_2$ 404.9885.

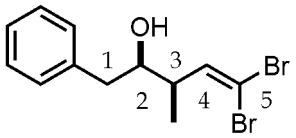


(*2R,3R*)-5,5-Dibromo-3-methyl-1-phenylpent-4-en-2-ol, 132. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.8 Hz, CH_3), 1.64 (1H, vbs, OH), 2.60 (1H, m, 3-CH), 2.65 (1H, dd, J = 13.8, 9.5 Hz, 1-CH), 2.87 (1H, dd, J = 13.7, 3.5 Hz, 1-CH'), 3.74 (1H, ddd, J = 9.4, 5.8, 3.5 Hz, 2-CH), 6.43 (1H, d, J = 9.6 Hz, 4-CH), 7.21-7.35 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.9 (CH_3), 41.5 (1-CH_2), 43.8 (3-CH), 74.7 (2-CH), 89.0 (5-C_{IV}), 126.7 ($ArCH_{para}$), 128.7 ($ArCH_{meta}$), 129.3 ($ArCH_{ortho}$), 138.0 (ArC_{IV}), 141.0 (4-CH); $[\alpha]^{22}_D$ -12.8, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3550, 3422, 3085, 3059, 3027, 2973, 2928, 2875, 1724, 1603, 1495, 1454, 1371, 1261, 1214, 1093, 1076, 1032, 989, 850, 822783, 746, 700 cm^{-1}; HRMS (CI) observed $(M-OH)^+$ 314.9365, calculated for $C_{12}H_{13}{}^{79}Br_2$ 314.9384.



(*E*)-(5,5-Dibromo-3-methylpenta-2,4-dienyl)benzene, 133. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.99 (3H, d, J = 0.8 Hz, CH_3), 3.46 (2H, d, J = 7.5 Hz, 1-CH_2), 5.84 (1H, tappqn, J = 7.5, 1.3 Hz, 2-CH), 6.99 (1H, s, 4-CH), 7.19-7.33 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.4 (CH_3), 34.3 (1-CH_2), 86.4 (5-C_{IV}), 126.1 ($ArCH_{para}$), 128.4 ($ArCH_{meta}$), 128.5 ($ArCH_{ortho}$), 132.4 (3-C_{IV}), 133.5 (2-CH), 139.8 (ArC_{IV}), 140.5 (4-CH); IR (thin film) ν_{max} = 3085, 3062, 3027,

2954, 2926, 2855, 1603, 1495, 1453, 1264, 831, 773, 739, 698 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 314.9342, calculated for $C_{12}H_{13}{}^{79}Br_2$ 314.9384.



(*2R,3R*)-5,5-Dibromo-3-methyl-1-phenylpent-4-en-2-ol, 132. ***Procedure A:*** A solution of TMS-protected alcohol **131** (65.3 mg, 160 µmol) in anhydrous tetrahydrofuran (5 mL) was treated with TBAF (176 µL, 1.0 M in THF, 176 µmol) at room temperature. The mixture quickly turned orange, and was left 3 h under stirring and argon. An additional portion of TBAF (64 µL, 1.0 M in THF, 64 µmol) was incorporated and the reaction was stirred for an extra 1 h. The reaction mixture was diluted with ethyl acetate (10 mL), and quenched with a sat. aq. solution of sodium chloride (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic fractions were combined, and dried over anhydrous magnesium sulphate, before being concentrated under reduced pressure to give the crude alcohol **132** as a viscous yellow oil (56 mg). Purification by flash chromatography (silica gel, 100% 40-60 petroleum spirit) afforded the pure alcohol **132** as a viscous yellow oil (17 mg, 32%).

Procedure B: A -78 °C solution of TBS-protected epoxyalcohol **126** (371 mg, 1.27 mmol) and DIPEA (492 mg, 663 µL, 3.81 mmol) in anhydrous dichloromethane (45 mL) was treated with TMSOTf (847 mg, 689 µL, 3.81 mmol). After being stirred 15 min at -78 °C, the reaction was poured into a separating funnel containing a 1:1 mixture of diethyl ether and $NaHPO_4$ (1.0 M, 100 mL in total). The phases were thoroughly mixed up, and subsequently separated. The organic layer was then washed with an additional portion of water (50 mL), isolated, and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave the crude aldehyde **134** (458 mg) as a single diastereoisomer.

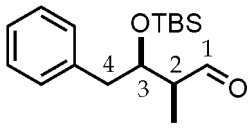
A -78 °C solution of carbon tetrabromide (682 mg, 2.06 mmol) in anhydrous dichloromethane (12 mL) was slowly treated by the slow addition of a solution of triphenylphosphine (954 mg, 3.64 mmol) in dichloromethane (12 mL). The reaction mixture was stirred for 30 min at -78 °C, before a previously prepared solution of crude aldehyde **134** (458 mg) in dry dichloromethane (12 mL) was added. The resulting reaction mixture was then allowed to slowly warm up to room temperature, and was then quenched by the sequential addition of 40-60 petroleum spirit (3 x 300 mL), followed each

time by an appropriate filtration. Evaporation of the solvent *in vacuo* provided a crude oil (406 mg), which was used in the next step without further purification.

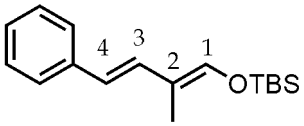
A fraction of the crude oil (270 mg) was dissolved in anhydrous tetrahydrofuran (8 mL), and the resulting solution was treated at room temperature by addition of anhydrous pyridine (1.05 g, 1.07 mL, 13.2 mmol) followed by a solution of hydrogen fluoride pyridine (158 mg, 144 µL, 7.91 mmol, 70% HF). The mixture was stirred at room temperature for 2.5 h, and was quenched by the dropwise and careful addition of a sat. aq. solution of sodium bicarbonate (55 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL) and dichloromethane (100 mL). The obtained organic phases were washed with an acidic sat. aq. solution of sodium chloride (50 mL + 3.4 mL of HCl 1.0 M), and subsequently separated. The combined organic layers were dried over anhydrous magnesium sulphate, and evaporation of the solvents under vacuum provided the crude alcohol **132** as a viscous oil (269 mg). Purification by flash column chromatography (silica gel, 0-10% ethyl acetate in 40-60 petroleum spirit) yielded the pure alcohol **132** as a clear, and colourless viscous oil (98 mg, 23% over 3 steps).

Procedure C: A solution of TBS-protected alcohol **126** (497 mg, 1.11 mmol) in anhydrous tetrahydrofuran (30 mL) was treated by addition of TBAF (1.66 mL, 1.0 M in THF, 1.66 mmol) at room temperature. The mixture quickly turned orange, and was stirred under argon overnight. The reaction mixture was diluted with ethyl acetate (50 mL), and quenched by adding a sat. aq. solution of sodium chloride (50 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL), before the organic fractions were combined, and dried over anhydrous magnesium sulfate. Evaporation of the solvents under reduced pressure gave the crude alcohol as a sticky orange oil (860 mg), which was purified through an initial flash column chromatography (silica gel, 0-5% ethyl acetate in 40-60 petroleum spirit). A second purification of the resulting semi-pure product by flash column chromatography (silica, 40% ethyl acetate in 40-60 petroleum spirit) afforded the pure alcohol **132** as a viscous yellow oil (301 mg, 81%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.8 Hz, CH_3), 1.64 (1H, vbs, OH), 2.60 (1H, m, 3-CH), 2.65 (1H, dd, J = 13.8, 9.5 Hz, 1-CH), 2.87 (1H, dd, J = 13.7, 3.5 Hz, 1-CH'), 3.74 (1H, ddd, J = 9.4, 5.8, 3.5 Hz, 2-CH), 6.43 (1H, d, J = 9.6 Hz, 4-CH), 7.21-7.35 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.9 (CH_3), 41.5 (1-CH_2), 43.8 (3-CH), 74.7 (2-CH), 89.0 (5-C_{IV}), 126.7 ($ArCH_{para}$), 128.7 ($ArCH_{meta}$), 129.3 ($ArCH_{ortho}$), 138.0 (ArC_{IV}), 141.0 (4-CH); $[\alpha]^{22}_D$ -12.8, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3550, 3422, 3085, 3059, 3027, 2973, 2928, 2875,

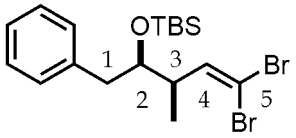
1724, 1603, 1495, 1454, 1371, 1261, 1214, 1093, 1076, 1032, 989, 850, 822783, 746, 700 cm^{-1}; HRMS (CI) observed $(M\text{-}OH)^+$ 314.9365, calculated for $C_{12}H_{13}{}^{79}Br_2$ 314.9384.



(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-phenylbutanal, 134. A -78 °C solution of epoxyalcohol **126** (1.35 g, 4.60 mmol) in anhydrous dichloromethane (125 mL) was sequentially treated with anhydrous DIPEA (2.42 mL, 1.80 g, 13.9 mmol) and TBSOTf (3.19 mL, 3.67 g, 13.9 mmol). The mixture was then slowly allowed to warm up to -45 °C and stirred until completion as indicated by TLC analysis (3 h). The cold mixture was then cooled down once again to -78 °C, before being poured into a separating funnel containing a (1:1) mixture of diethyl ether and 1.0 M aq. solution of $NaHPO_4$ (100 mL total volume). The phases were separated, and the organic layer was then successively washed with water (2 x 50 mL) and aq. solution of $NaHPO_4$ (1.0 M, 50 mL). The combined aqueous fractions were extracted with diethyl ether (20 mL), and the organic extracts were combined, and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to provide a light yellow crude oil (3.25 g), which was purified by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum ether) to afford the pure aldehyde **134** as a clear and colourless viscous oil (948 mg, 70%). The aldehyde proved unstable standing, and it could not be stored for any periods of time without decomposition was observed. The purification by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum ether) also allowed the isolation of aldehyde **128** (mg, 8%) and silyl enol ether **135** (mg, 4%) as minor side-products. ^1H NMR (400MHz, $CDCl_3$) δ -0.14 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.15 (3H, d, J = 7.0 Hz, 2-CCH_3), 2.35 (1H, qd, J = 6.9, 3.0 Hz, 2-CH), 2.80 (2H, d, J = 7.0 Hz, 4-CH_2), 4.39 (1H, td, J = 7.0, 3.0 Hz, 3-CH), 7.16-7.32 (5H, m, ArH), 9.70 (1H, bs, 1-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.9 ($SiCH_3$), -4.7 ($SiCH_3$), 7.3 (2-CCH_3), 18.0 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 41.2 (4-CH_2), 50.5 (2-CH), 73.2 (3-CH), 126.6 ($ArCH_{para}$), 128.5 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 138.0 (ArC_{IV}), 204.9 (1-C=O); $[\alpha]^{25}{}_D$ +37.0, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3028, 2954, 2929, 2710, 1727, 1254, 1104, 1032, 837, 777, 700 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 293.1938, calculated for $C_{17}H_{29}O_2Si$ 293.1937.



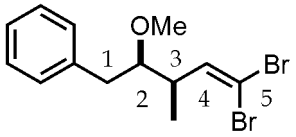
***tert*-Butyldimethyl((1*E*,3*E*)-2-methyl-4-phenylbuta-1,3-dienyloxy)silane, 135.** The procedures employed for the synthesis of aldehyde **127** and **134** produced small variable amounts of conjugated aldehyde **128** as a side product, which could be isolated after a subsequent purification by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum ether). ^{1}H NMR (400MHz, $CDCl_3$) δ 0.59 (6H, s, $Si(CH_3)_2$), 0.98 (9H, s, $SiC(CH_3)_3$), 1.87 (3H, d, *J* = 1.2 Hz, 2-CCH_3), 6.39 (1H, d, *J* = 15.9 Hz, 4-CH), 6.60 (1H, s, 1-CH), 6.76 (1H, d, *J* = 15.9 Hz, 3-CH), 7.15-7.41 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -5.3 ($Si(CH_3)_2$), 9.4 (2-CCH_3), 18.3 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 118.3 (2-C_{IV}), 123.4 (4-CH), 125.6 (3-CH), 126.2 ($ArCH_{para}$), 128.5 ($ArCH_{meta}$), 129.7($ArCH_{ortho}$), 138.5 (ArC_{IV}), 142.7 (1-CH); IR (thin film) ν_{max} = 3060, 3027, 2957, 2930, 2886, 2858, 1631, 1253, 1173, 840 cm^{-1}; LRMS (ESI) observed $(M+H)^+$ 274.20 and LRMS (CI) observed $(M+H)^+$ 161.2.



***tert*-Butyl((2*R*,3*R*)-5,5-dibromo-3-methyl-1-phenylpent-4-en-2-yloxy)dimethylsilane, 136.** A -78 °C solution of epoxide **126** (197 mg, 674 µmol) and DIPEA (261 mg, 352 µL, 2.02 mmol) in anhydrous dichloromethane (15 mL) was treated with TBSOTf (534 mg, 464 µL, 2.02 mmol). The mixture was slowly allowed to warm up to -50 °C, and was stirred until completion as indicated by TLC analysis (3 h). The reaction was then cooled down to -78 °C before being poured into a separating funnel containing a (1:1) mixture of diethyl ether and an aq. solution of $NaHPO_4$ (1.0 M, 100 mL total volume). The phases were thoroughly mixed up, and subsequently separated, before the organic layer was washed with an additional portion of water (50 mL). The phases were separated, and the organic fraction was isolated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the crude aldehyde **134** (289 mg) as a single diastereoisomer.

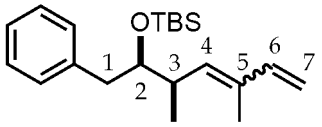
A -78 °C solution of carbon tetrabromide (378 mg, 1.14 mmol) in anhydrous dichloromethane (5 mL) was slowly treated with the slow addition of a solution of triphenylphosphine (549 mg, 2.09 mmol) in dichloromethane (5 mL). The reaction mixture was stirred 30 min at -78 °C before being treated with a previously made solution of crude

aldehyde **134** (289 mg) in dry dichloromethane (5 mL). The -78 °C reaction mixture was then allowed to slowly warm up to room temperature overnight, and the mixture was then quenched by the sequential addition of 40-60 petroleum spirit (3 x 100 mL), followed each time by an appropriate filtration. Evaporation of solvent *in vacuo* provided the crude dibromoolefin **136** (256 mg) as a viscous colourless oil, which was purified by flash column chromatography (silica gel, 1% TEA, 100% hexane) to yield the pure olefin **136** (202 mg, 67% over 2 steps) as a viscous, clear and colourless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.14 (3H, s, $SiCH_3$), -0.11 (3H, s, $SiCH_3$), -0.97 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, J = 6.9 Hz, 3-CCH_3), 2.54 (1H, m, 3-CH), 2.81 (1H, dd, J = 13.6, 6.9 Hz, 1-CH), 2.86 (1H, dd, J = 13.6, 6.8 Hz, 1-CH'), 3.99 (1H, td, J = 6.7, 3.5 Hz, 2-CH), 6.43 (1H, d, J = 9.3 Hz, 4-CH), 7.24-7.38 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.9 (CH_3), -4.7 (CH_3), 12.6 (3-CCH_3), 18.1 ($SiC(CH_3)_3$, 25.9 ($SiC(CH_3)_3$), 41.4 (1-CH_2), 42.4 (3-CH), 75.5 (2-CH), 87.9 (5-C_{IV}), 126.3 ($ArCH_{para}$), 128.3 ($ArCH_{meta}$), 129.5 ($ArCH_{ortho}$), 138.4 (ArC_{IV}), 142.3 (4-CH); $[\alpha]^{23}_D$ +4.1, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3028, 2954, 2929, 2885, 2856, 1471, 1461, 1255, 1102, 1022, 836, 775, 760, 700 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 447.0328, calculated for $C_{18}H_{29}OSi^{79}Br_2$ 447.0354.

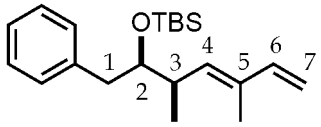


((2*R*,3*R*)-5,5-Dibromo-2-methoxy-3-methylpent-4-enyl)benzene, 137. A solution of alcohol **132** (63.5 mg, 189 µmol) in a 2:1 mixture of anhydrous tetrahydrofuran and dimethylformamide (0.8 mL + 0.4 mL) was cooled down to 0 °C, and was then treated with iodomethane (117 µL, 1.89 mmol) previously filtered trough basic alumina. The reaction mixture was then treated with the addition of sodium hydride (23 mg, 60% in oil, 575 µmol), and was stirred for 5 h at 0 °C. The mixture was then carefully poured into a mixture of ice, water (25 mL in total), and ethyl acetate (50 mL). The phases were separated, and the organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave the crude dibromoolefin **137** as a yellow to orange viscous oil (68 mg). Three purifications by flash column chromatography (silica gel, 15% ethyl acetate in 40-60 petroleum spirit) (silica gel, 1% ethyl acetate in 40-60 petroleum spirit) (silica gel, 50% dichloromethane in hexane) were necessary to isolate the pure methoxydibromoolefin **137** as a clear and colourless viscous oil (28 mg, 43%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.07 (3H, d, J = 6.9 Hz, 3-CCH_3), 2.59 (1H, m, 3-CH), 2.74 (1H, dd,

J = 13.9, 5.6 Hz, 1-CH), 2.82 (1H, dd, J = 13.9, 7.2 Hz, 1-CH'), 3.26 (3H, s, OCH_3), 3.31 (1H, m, 2-CH), 6.37 (1H, d, J = 9.5 Hz, 4-CH), 7.21-7.32 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.7 (CH_3), 37.9 (1-CH_2), 41.6 (3-CH), 58.6 (OCH_3), 85.0 (2-CH), 88.6 (5-C_{IV}), 126.2 ($ArCH_{para}$), 128.4 ($ArCH_{meta}$), 129.3 ($ArCH_{ortho}$), 138.6 (ArC_{IV}), 141.2 (4-CH); $[\alpha]^{21}_D$ -3.3, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3088, 3062, 3025, 2961, 2926, 2875, 2852, 2826, 1737, 1600, 1495, 1455, 1357, 1261, 1102, 1030, 787, 743, 699 cm^{-1}; HRMS (CI) observed $(M\text{-}OMe)^+$ 314.9370, calculated for $C_{12}H_{13}{}^{79}Br_2$ 314.9384; HRMS (CI) observed $(M+H)^+$ 346.9641, calculated for $C_{13}H_{17}O^{79}Br_2$ 346.9646. The spectroscopic data was in full agreement with this of the opposite enantiomer reported in the literature.[81,83,87]

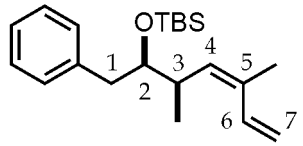


***tert*-Butyl((2*R*,3*R*,4*E*)-3,5-dimethyl-1-phenylhepta-4,6-dien-2-yloxy)dimethylsilane, (*E*)-139 and *tert*-Butyl((2*R*,3*R*,4*Z*)-3,5-dimethyl-1-phenylhepta-4,6-dien-2-yloxy)dimethylsilane, (*Z*)-139.** A -78 °C solution of phosphine oxide **142** (1.20 g, 4.68 mmol) in anhydrous THF (16 mL) was treated with the dropwise addition of *n*-butyl lithium (2.5 M in hexanes, 1.8 ml, 4.5 mmol). The reaction was stirred for 20 min at -78 °C before a solution of freshly distilled HMPA (1.65 mL, 1.70 g, 9.48 mmol) in dry THF (5 mL) was incorporated. A solution of aldehyde **134** (913 mg, 3.11 mmol) in anhydrous THF (5 mL) was then added dropwise, and the reaction mixture was stirred at -78 °C until completion as indicated by TLC analysis (15 min). The reaction was quenched with water (20 mL), and the two phases were separated. The organic layer was sequentially washed with water (2 x 20 mL), and sat. aq. solution of LiBr (2 x 20 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a viscous yellow oil (1.69 g), which was then purified by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum ether) to afford 565 mg of the pure *O*-TBS protected diene **(*E*)-139** and 188 mg of the minor diene **(*Z*)-139** as colourless, clear and viscous oils (753 mg, 73% overall yield).

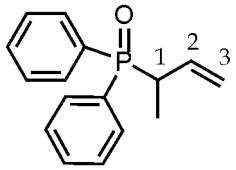


(*E*)-139. ^1H NMR (400MHz, $CDCl_3$) δ -0.26 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, J = 6.8 Hz, 3-CCH_3), 1.56 (3H, d, J = 1.2 Hz, 5-CCH_3), 2.45-2.54 (1H,

m, 3-CH), 2.69 (1H, dd, *J* = 13.6, 6.4 Hz, 1-CH), 2.82 (1H, dd, *J* = 13.6, 6.0 Hz, 1-CH'), 3.78 (1H, appq, *J* = 6.2 Hz, 2-CH), 4.93 (1H, d, *J* = 10.8 Hz, 7-CH), 5.07 (1H, d, *J* = 17.4 Hz, 7-CH'), 5.42 (1H, d, *J* = 9.7 Hz, 4-CH), 6.34 (1H, ddd, *J* = 17.4, 10.7, 0.4 Hz, 6-CH), 7.15 -7.28 (5H, m, ArCH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$), -4.5 ($SiCH_3$), 11.8 (5-CCH_3), 15.2 (3-CCH_3), 18.1 (Si*C*$(CH_3)_3$), 25.9 (SiC(*C*$H_3)_3$), 37.1 (3-CH), 41.7 (1-CH_2), 77.3 (2-CH), 110.7 (7-CH_2), 126.0 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.7 ($ArCH_{meta}$), 132.9 (5-C_{IV}), 136.9 (ArC_{IV}), 139.1 (4-CH), 141.8 (6-CH); $[\alpha]^{20}_D$ +23.0, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3027, 2956, 2928, 2856, 1254, 1100, 1085, 835, 774, 699 cm^{-1}.



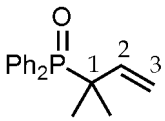
(*Z*)-139. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.15 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, *J* = 6.8 Hz, 3-CCH_3), 1.68 (3H, s, 5-CCH_3), 2.51-2.56 (1H, m, 3-CH), 2.65 (2H, dd, *J* = 8.4, 1.3 Hz, 1-CH2), 3.76-3.80 (1H, m, 2-CH), 4.96 (1H, d, *J* = 10.7 Hz, 7-CH), 5.11 (1H, d, *J* = 17.4 Hz, 7-CH'), 5.58 (1H, d, *J* = 9.6 Hz, 4-CH), 6.44 (1H, dd, *J* = 17.4, 10.7 Hz, 6-CH), 7.06-7.28 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$), -4.6 ($SiCH_3$), 12.1 (5-CCH_3), 16.9 (3-CCH_3), 18.1 (Si*C*$(CH_3)_3$), 25.9 (SiC(*C*$H_3)_3$), 37.2 (3-CH), 41.3 (1-CH_2), 77.4 (2-CH), 110.7 (7-CH_2), 126.0 ($ArCH_{para}$), 128.2 ($ArCH_{ortho}$), 129.7 ($ArCH_{meta}$), 133.9 (5-C_{IV}), 134.8 136.9 (ArC_{IV}), 139.4 (4-CH), 142.0 (6-CH); $[\alpha]^{25}_D$ -11.8, (c = 1.0, $CHCl_3$). IR (thin film) ν_{max} = 3027, 2956, 2928, 2856, 1254, 1100, 1085, 835, 774, 699 cm^{-1}.



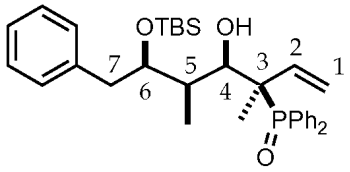
1-Methylallyldiphenylphosphine oxide, 142. ***Procedure A:*** A solution of diphenylphosphine chloride (6.20 g, 5.19 mL, 28.1 mmol) in anhydrous diethyl ether (30 mL) was added slowly at 0 °C to a stirred solution of crotyl alcohol **140** (2.01 g, 27.7 mmol) and anhydrous pyridine (5.1 mL, 64.8 mmol) in dry diethyl ether (15 mL). After stirring the reaction for 1 h, the resulting suspension was filtered, and the filtrate was evaporated under reduced pressure. The crude oil (8.86 g) was then heated at 130 °C for 1 h under argon. Diethyl ether (2 x 250 mL) was added to the crude resulting oil under vigorous stirring, leaving a black sticky residue at the bottom of the flask. The ethereal layer was isolated, and concentrated under reduced pressure to give a brown sticky oil, which was

purified by flash column chromatography (silica gel, 100% ethyl acetate) to obtain the pure phosphine oxide **142** as a white powder (1.44 g, 20%).

Procedure B: A -78 °C solution of commercially available allyldiphenylphosphine oxide **143** (5.64 g, 23.3 mmol) in anhydrous tetrahydrofuran (120 mL) was treated with the slow addition of *n*-BuLi (10.2 mL, 2.5 M in hexanes, 25.6 mmol). The mixture immediately turned dark red, and was stirred for 20 min at -78 °C before iodomethane (16.4 g, 7.20 mL, 116 mmol) was incorporated into the reaction through a short pad of basic alumina. The reaction was stirred under argon for 2 h at -78 °C, and then quenched by the careful addition of water (100 mL). Dichloromethane (100 mL) and additional water (100 mL) were added, and the resulting mixture was stirred vigorously overnight. The phases were separated, and the organic layer was dried over anhydrous sodium sulfate, and then concentrated *in vacuo*. The resulting crude oil (6.35 g) was purified by flash column chromatography (silica gel, 100 % ethyl acetate) to afford the desired phosphine oxide **142** (5.1 g, 85%) contaminated with 1,1-Dimethylallyldiphenylphosphine oxide **144** (1.0 g, 15%) as a white powder. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.27 (3H, dd, $J_{H\text{-}P}$ = 16.1 Hz, J = 7.1 Hz, CH_3), 3.18 (1H, appdqn, $J_{H\text{-}P}$ = 11.6 Hz, J = 7.2 Hz, 1-CH), 5.03 (1H, dd, J = 17.3 Hz, $J_{H\text{-}P}$ = 4.6 Hz, 3-CH), 5.08 (1H, dd, J = 10.5 Hz, $J_{H\text{-}P}$ = 3.6 Hz, 3-CH'), 5.82 (1H, m, 2-CH), 7.39-7.49 (6H, m, ArH_{meta} + ArH_{para}), 7.73-7.80 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.5 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH_3), 38.6 (d, $J_{C\text{-}P}$ = 68.9 Hz, 1-CH), 118.2 (d, $J_{C\text{-}P}$ = 11.2 Hz, 3-CH_2), 128.2 (d, $J_{C\text{-}P}$ = 11.5 Hz, $ArCH_{meta}$), 128.5 (d, $J_{C\text{-}P}$ = 11.4 Hz, $ArCH_{meta}$), 131.1 (d, $J_{C\text{-}P}$ = 8.6 Hz, $ArCH_{ortho}$), 131.3 (d, $J_{C\text{-}P}$ = 8.5 Hz, $ArCH_{ortho}$), 131.5 (d, $J_{C\text{-}P}$ = 96.6 Hz, ArC_{IV}), 131.5 (d, $J_{C\text{-}P}$ = 2.7 Hz, $ArCH_{para}$), 131.5 (d, $J_{C\text{-}P}$ = 2.7 Hz, $ArCH_{para}$), 131.9 (d, $J_{C\text{-}P}$ = 94.8 Hz, ArC_{IV}), 134.0 (d, $J_{C\text{-}P}$ = 6.7 Hz, 2-CH); M.p. 85 °C. Data was in full agreement with the one reported in the literature.[151]

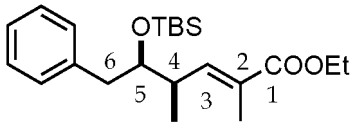


^{1}H NMR (400MHz, $CDCl_3$) δ 1.30 (6H, d, $J_{H\text{-}P}$ = 14.7 Hz, 2 x CH_3), 5.08 (1H, partially hidden m, 3-CH), 5.22 (1H, ddd, J = 10.7, 0.9 Hz, $J_{H\text{-}P}$ = 3.7 Hz, 3-CH'), 5.95 (1H, ddd, J = 17.4, 10.7 Hz, $J_{H\text{-}P}$ = 4.9 Hz, 2-CH), 7.39-7.49 (6H, hidden m, ArH_{meta} + ArH_{para}), 7.89-7.94 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.6 (d, $J_{C\text{-}P}$ = 0.9 Hz, 2 x CH_3), 40.9 (d, $J_{C\text{-}P}$ = 67.9 Hz, 1-CH), 115.6 (d, $J_{C\text{-}P}$ = 10.3 Hz, 3-CH_2), 128.0 (d, $J_{C\text{-}P}$ = 11.1 Hz, $ArCH_{meta}$), 131.5 (d, $J_{C\text{-}P}$ = 2.8 Hz, $ArCH_{para}$), 132.2 (d, $J_{C\text{-}P}$ = 8.0 Hz, $ArCH_{ortho}$), ArC_{IV} and 2-CH unresolved;



(3*R*,4*S*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-3-(diphenylphosphoryl)-3,5-dimethyl-7-phenylhept-1-en-4-ol, 145. A -78 °C solution of phosphine oxide **142** (6.08 g, 23.7 mmol) in anhydrous diethyl ether (400 mL) was treated by addition of *n*-BuLi (11.1 mL, 2.3 M in hexanes, 25.5 mmol). The dark red reaction mixture was stirred for 1 h at -78 °C before being treated with freshly distilled hexamethylphosphoramide (9.58 g, 9.3 mL, 53.5 mmol). The reaction was stirred for 15 min at -78 °C, and was then cooled down to -100 °C. At this temperature, a -78 °C solution of aldehyde **134** (4.48 g, 15.3 mmol) in anhydrous diethyl ether (200 mL) was cannulated into the reaction, and the resulting mixture was stirred for a further 30 min at -100 °C. The reaction was quenched at -100 °C by addition of water (11.5 mL), and then allowed to warm up to room temperature. The phases were separated and the organic layer was washed with water (2 x 115 mL), followed by a sat. aq. LiBr solution (2 x 115 mL). The combined aqueous layers were finally extracted with diethyl ether (300 mL), and the combined organic fractions were concentrated under reduced pressure to yield to a crude viscous oil (8.05 g). Purification by flash column chromatography (silica, 1% TEA, 0-30% ethyl acetate in 40-60 petroleum spirit) enabled the isolation of the pure TBS-protected dienol **139** as a 3:1 mixture of **(*E*)-139** and **(*Z*)-139** double-bond isomers (1.18 g, 23%) as well as the phosphinyl alcohol **145** as a white solid (445 mg, 5%). It should be noted that the side product **145** failed to diffract during crystallographic assays. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.75 (3H, s, $SiCH_3$), -0.26 (3H, s, $SiCH_3$), 0.59 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, J = 7.1 Hz, 5-CCH_3), 1.37 (3H, d, $J_{H\text{-}P}$ = 16.3 Hz, 3-CCH_3), 1.70 (1H, m, 5-CH), 2.60 (1H, dd, J = 13.9, 8.9 Hz, 7-CH), 2.97 (1H, dd, J = 13.9, 3.0 Hz, 7-CH'), 3.49 (1H, m, 6-CH), 4.51 (1H, d, J = 10.3 Hz, 4-CH), 5.17 (1H, ddd, J = 17.5, 0.8 Hz, $J_{H\text{-}P}$ = 5.3 Hz, 1-CH), 5.31 (1H, ddd, J = 10.8, 0.9 Hz, $J_{H\text{-}P}$ = 4.8 Hz, 1-CH'), 5.61 (1H, ddd, J = 17.5, 10.8 Hz, $J_{H\text{-}P}$ = 4.9 Hz, 2-CH), 5.70 (1H, bs, OH), 7.05-7.21 (6H, m, ArH_{meta} + ArH_{para} (Ph_2PO)), 7.45-7.58 (4H, m, ArH_{ortho} (Ph_2PO)), 7.95-8.06 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -6.0 ($SiCH_3$), -4.5 ($SiCH_3$), 11.7 (d, $J_{C\text{-}P}$ = 13.8 Hz, 3-CCH_3), (5-CCH_3 was not observed), 17.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 39.3 (7-CH_2), 39.4 (d, $J_{C\text{-}P}$ = 10.4 Hz, 5-CH), 49.2 (d, $J_{C\text{-}P}$ = 64.3 Hz, 3-C_{IV}), 69.1 (d, $J_{C\text{-}P}$ = 3.7 Hz, 4-CH), 78.5 (6-CH), 117.5 (d, $J_{C\text{-}P}$ = 11.2 Hz, 1-CH_2), 125.6 ($ArCH_{para}$), 127.8 ($ArCH_{ortho}$), 128.2 (d, $J_{C\text{-}P}$ = 11.2 Hz), 128.5 (d, $J_{C\text{-}P}$ = 11.2 Hz), 130.0 (d, $J_{C\text{-}P}$ = 92.5 Hz, ArC_{IV} (Ph_2PO)), 130.0 ($ArCH_{meta}$), 130.3 (d, $J_{C\text{-}P}$ = 91.3 Hz,

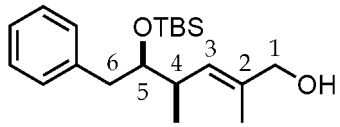
ArC_{IV} (Ph_2PO)), 131.9 (d, J_{C-P} = 2.6 Hz), 132.0 (d, J_{C-P} = 2.7 Hz), 132.2 (d, J_{C-P} = 7.3 Hz), 132.4 (d, J_{C-P} = 8.2 Hz), 138.2 (d, J_{C-P} = 3.5 Hz, 2-CH), 140.4 (ArC_{IV});(*) $[\alpha]^{25}_D$ +56.7, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3333, 3060, 2956, 2928, 2885, 2856, 1437, 1256, 1153, 1111, 1065, 930, 834, 698 cm^{-1}; HRMS (FAB) observed $(M+H)^+$ 549.2957, calculated for $C_{33}H_{46}O_3SiP$ 549.2954. (*) The J_{P-H} couplings for the ^1H and ^{13}C NMRs are consistent with J_{P-H} couplings reported in the literature.[152]



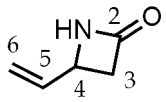
(4*R*,5*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-6-phenylhex-2-enoate, 146. A -78 °C solution of epoxyalcohol **126** (604 mg, 2.07 mmol) in anhydrous dichloromethane (125 mL) was sequentially treated with anhydrous DIPEA (1.41 mL, 1.04 g, 8.04 mmol) and TBSOTf (1.92 mL, 2.19 g, 8.27 mmol). The mixture was then slowly allowed to warm up to -40 °C, and stirred until completion as indicated by TLC analysis (4.5 h). The cold mixture was then cooled down once again to -78 °C, before being poured into a separating funnel containing a (1:1) mixture of diethyl ether and 1.0 M aq. solution of $NaHPO_4$ (40 mL total volume). The phases were separated, and the organic layer was then successively washed with water (2 x 20 mL) and aq. solution of $NaHPO_4$ (1.0 M, 2 x 20 mL). The combined aqueous fractions were extracted with diethyl ether (20 mL), and the organic extracts were combined, and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to provide a light yellow crude oil (701 mg), which was used immediately into the next reaction without any further purification.

A fraction of the crude oil (141 mg) was dissolved in anhydrous dichloromethane (5 mL), and the resulting solution was treated with (1-ethoxycarbonylethylidene)-triphenylphosphorane (290 mg, 80.4 mmol). The reaction mixture was refluxed for 2 days before being cooled down to room temperature, and quenched by addition of 40-60 petroleum ether (50 mL). The precipitate formed was filtered out and the process was repeated until no further phosphine oxide could be forced out of solution. Subsequent evaporation of the organic filtrates provided a very sticky orange oil (208 mg), which could be used without any further purification in the next step. Purification by flash column chromatography (silica gel, 1% TEA, 0-50% dichloromethane in 40-60 petroleum ether) yielded the pure ethyl ester **146** (84 mg, 54% over two steps) as an extremely viscous colourless oil. ^1H NMR (400MHz, $CDCl_3$) δ -0.11 (3H, s, CH_3), 0.10 (3H, s, CH_3), 0.98 (9H, s,

$SiC(CH_3)_3$), 1.13 (3H, d, *J* = 6.8 Hz, 4-CC*H*$_3$), 1.38 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.73 (3H, d, *J* = 1.4 Hz, 2-CCH_3), 2.57 (1H, m, 4-CH), 2.83 (1H, dd, *J* = 13.6, 6.3 Hz, 6-CH), 2.91 (1H, dd, *J* = 13.6, 6.6 Hz, 6-CH'), 3.92 (1H, td, *J* = 6.4, 4.2 Hz, 5-CH), 4.25 (1H, dq, *J* = 7.2, 7.1 Hz, OC*H*CH_3), 4.26 (1H, dq, *J* = 7.2, 7.1 Hz, OC*H*'CH_3) 6.81 (1H, dq, *J* = 10.1, 1.4 Hz, 3-CH), 7.24-7.38 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$), -4.7 ($SiCH_3$), 12.3 (2-CCH_3), 13.9 (4-CH_3), 14.3 (OCH_2CH_3), 18.1 (Si*C*$(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 37.4 (4-CH), 41.6 (6-CH_2), 60.4 (OCH_2), 76.4 (5-CH), 126.2 ($ArCH_{para}$), 126.7 (2-C_{IV}), 128.2 ($ArCH_{ortho}$), 129.6 ($ArCH_{meta}$), 138.6 (ArC_{IV}), 145.4 (3-CH), 168.2 (1-C=O); $[\alpha]^{23}_D$ +32.9, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3027, 2956, 2929, 2898, 2857, 1712, 1462, 1366, 1254, 1082, 1032, 837, 776 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 377.2509, calculated for $C_{22}H_{37}O_3Si$ 377.2512.

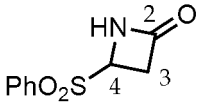


(4*R*,5*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-6-phenylhex-2-en-1-ol, 147. A solution of ester **146** (1.54 g, 4.09 mmol) in anhydrous diethyl ether (100 mL) was cooled down to -78 °C, and treated with a solution of LAH (10.0 mL, 1.0 M in diethyl ether, 10.0 mmol). The reaction was stirred for 30 min at -78 °C, and was then quenched by the careful addition of ethyl acetate (10 mL). The thick mixture was subsequently washed with water (3 x 100 mL), and the organic layer was dried over anhydrous sodium sulfate. Concentration under reduced pressure provided the crude alcohol **147** as a viscous oil (1.55 g). Purification by flash column chromatography (silica, 1% TEA, 10% ethyl acetate in 40-60 petroleum spirit) yielded the pure alcohol **147** as a clear and colourless viscous oil (1.25 g, 91%). ^{1}H NMR (400MHz, $CDCl_3$) δ -0.15 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.96 (9H, s, $SiC(CH_3)_3$), 1.07 (3H, d, *J* = 6.8 Hz, 4-CC*H*$_3$), 1.31 (1H, bt, *J* = 5.7 Hz, OH), 1.58 (3H, d, *J* = 1.2 Hz, 2-CCH_3), 2.51 (1H, m, 4-CH), 2.80 (1H, dd, *J* = 13.6, 6.4 Hz, 6-CH), 2.89 (1H, dd, *J* = 13.6, 6.2 Hz, 6-CH'), 3.85 (1H, td, *J* = 6.2, 5.0 Hz, 5-CH), 4.03 (2H, d, *J* = 4.7 Hz, 1-C*H*$_2$), 5.40 (1H, dq, *J* = 9.7, 1.2 Hz, 3-CH), 7.24-7.36 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$), -4.5 ($SiCH_3$), 13.7 (2-CCH_3), 15.6 (4-CCH_3), 18.1 (Si*C*$(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 36.9 (4-CH), 41.7 (6-CH_2), 69.0 (1-CH_2), 77.4 (5-CH), 126.0 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.7 ($ArCH_{meta}$), 129.8 (3-CH), 133.8 (2-C_{IV}), 139.3 (ArC_{IV}); $[\alpha]^{22}_D$ +8.1, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3324, 3028, 2956, 2928, 2857, 1471, 1461, 1254, 1081, 1056, 1041, 1006, 835, 774, 699 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 377.2402, calculated for $C_{20}H_{35}O_2Si$ 335.2406.

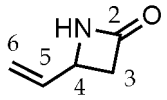


(±)-4-Vinylazetidin-2-one, (±)-151. Acetoxyazetidinone **(±)-118** (27.1 g, 210 mmol) was dissolved in water (110 mL), treated with sodium phenyl sulfinate (35.0 g, 213 mmol), and the mixture was refluxed for 20 min. The yellow reaction mixture was then cooled down to room temperature, and was then extracted with dichloromethane (5 x 150 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the pure sulfone intermediate as a white powder (36.6 g, 173 mmol, 82%), which was used in the next reaction without any further purification.

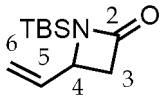
A -78 °C solution of sulfone (36.6 g, 172 mmol) in anhydrous THF (620 mL) was treated with vinyl magnesium bromide (1.0 M in THF, 426 mL, 426 mmol), and the reaction was vigorously stirred at -78 °C for 30 min. The mixture was allowed to warm up to 0 °C, and was stirred for a further 50 min. The reaction was then warmed up to room temperature and stirred for 2 h, before being quenched with a sat. aq. solution of ammonium chloride (185 mL), and stirred for 15 min. The crude mixture was then filtered through cotton wool, the two resulting phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 500 mL). The combined organic extracts were collected, dried over anhydrous sodium sulfate, and the solvents were evaporated under vacuum to give a crude orange/brown oil. The crude product was purified by flash column chromatography (silica gel, 50% ethyl acetate in 40-60 petroleum ether) to give the pure vinylazetidinone **(±)-151** as a colourless and slightly viscous oil (15.0 g, 90%).



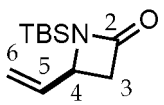
^{1}H NMR (400MHz, $CDCl_3$) δ 3.22 (1H, dd, J = 15.5, 2.3 Hz, 3-CH), 3.31 (1H, dd, J = 15.5, 5.0 Hz, 3-CH'), 4.73 (1H, dd, J = 5.0, 2.3 Hz, 4-CH), 6.47 (1H, bs, NH), 7.62-7.66 (2H, m, ArH_{meta}), 7.73-7.78 (1H, m, ArH_{para}) 7.93-7.96 (2H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 41.6 (3-CH_2), 64.8 (4-CH), 129.3 ($ArCH_{ortho}$), 129.7 ($ArCH_{meta}$), 134.6 (ArC_{IV}), 135.0 ($ArCH_{para}$), 164.4 (2-C=O); IR (thin film) ν_{max} = 3490, 3253, 3017, 2923, 2852, 1769, 1313, 1148 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 212.0374, calculated for $C_9H_{10}O_3NS$ 212.0381; M.p. 157 °C. Data was in full agreement with the one reported in the literature.[153]



(±)-151. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.67 (1H, dq, *J* = 14.8, 1.3 Hz, 3-CH), 3.17 (1H, ddd, *J* = 14.8, 5.2, 2.0 Hz, 3-CH'), 4.07-4.11 (1H, m, 4-CH), 5.14 (1H, dt, *J* = 10.2, 0.9 Hz, 6-CH), 5.28 (1H, dt, *J* = 17.0, 1.0 Hz, 6-CH'), 5.88 (1H, ddd, *J* = 17.0, 10.2, 7.0 Hz, 5-CH), 6.68 (1H, s, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 44.9 (4-CH), 49.4 (3-CH_2), 116.9 (6-CH_2), 137.5 (5-CH), 168.1 (2-C=O); IR (thin film) ν_{max} = 3471, 3263, 2986, 2924, 1761 cm^{-1}; LRMS (CI) $(M+H)^+$ 98.18 (100%). Data was in full agreement with the one reported in the literature.[154]



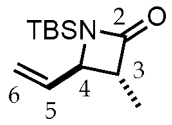
(±)-1-(*tert*-Butyldimethylsilyl)-4-vinylazetidin-2-one, (±)-152. A solution of vinylazetidinone **(±)-151** (100 mg, 1.03 mmol) in dry dichloromethane (10 mL) was treated with triethylamine (215 µL, 156 µg, 1.54 mmol) and TBSOTf (409 mg, 336 µL, 1.55 mmol) at room temperature. The reaction mixture was stirred for 10 min, and the solvent was evaporated under reduced pressure. The resulting crude orange oil was immediately purified by flash column chromatography (silica gel, 10% ethyl acetate in 40-60 petroleum ether) to afford the desired *N*-TBS protected azetidinone **(±)-152** as a clear, colourless and slightly viscous oil (215 mg, 98%). ^{1}H NMR (400MHz, $CDCl_3$) δ 0.17 (3H, s, $SiCH_3$), 0.21 (3H, s, $SiCH_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 2.75 (1H, dd, *J* = 15.4, 2.8 Hz, 3-CH), 3.29 (1H, dd, *J* = 15.4, 5.6 Hz, 3-CH'), 3.99 (1H, ddd, *J* = 8.8, 5.6, 2.8 Hz, 4-CH), 5.16 (1H, dd, *J* = 10.0, 0.8 Hz, 6-CH), 5.27 (1H, dq, *J* = 17.1, 0.7 Hz, 6-CH'), 5.84 (1H, ddd, *J* = 17.1, 10.1, 8.9 Hz, 5-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ -5.7 ($SiCH_3$), -5.5 ($SiCH_3$), 18.9 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 45.4 (3-CH_2), 51.7 (4-CH), 117.5 (6-CH2), 139.7 (5-CH), 172.3 (2-C=O); IR (thin film) ν_{max} = 3475, 3084, 2954, 2929, 2858, 1749 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 212.1468, calculated for $C_{11}H_{22}ONSi$ 212.1471.



(*S*)-1-(*tert*-Butyldimethylsilyl)-4-vinylazetidin-2-one, 152. A -78 °C solution of oxalyl chloride (220 µL, 2.56 mmol) in anhydrous dichloromethane (8 mL) was treated with the slow addition of anhydrous dimethylsulfoxide (335 µL, 4.72 mmol), and the resulting mixture was stirred for 30 min under argon. A solution of alcohol **(*S*)-95** (424 mg, 1.97

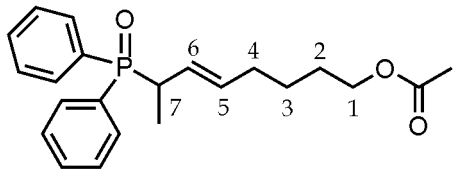
mmol) in dry dichloromethane (15 mL) was then added slowly at -78 °C, and the mixture was stirred for a further 30 min at -78 °C. Anhydrous triethylamine (600 µL, 4.31 mmol) was then incorporated slowly, and the reaction was allowed to warm up to room temperature over 1 h. The reaction was then quenched by addition of a sat. aq. solution of ammonium chloride (15 mL), followed by water (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated under vacuum to afford the crude aldehyde **182** as a viscous orange oil (430 mg). The crude aldehyde, proved to be clean by ^{1}H NMR, was then used into the next reaction without any further purification.

A solution of the crude aldehyde **182** (430 mg) in anhydrous tetrahydrofuran (15 mL) was treated with a solution of Petasis's reagent in toluene (11 mL, 10 g, 2.4 mmol). The mixture was refluxed for 2.5 h under argon before being worked up by addition of 40-60 petroleum ether (100 mL) to precipitate the titanium derivatives. After a subsequent filtration, the filtrate was concentrated under reduced pressure to give a viscous orange oil (965 mg). This oil was then purified by flash column chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40-60 petroleum ether) to afford the pure vinyl azetidinone **152** (92 mg, 22%) as a viscous yellow oil. Unfortunately, the compound **152** proved to be unstable to the purification conditions. Data were in full agreement with those reported for the racemic azetidinone **(±)-152**. $[\alpha]^{25}_D$ -16.0, (c = 1.0, $CHCl_3$).



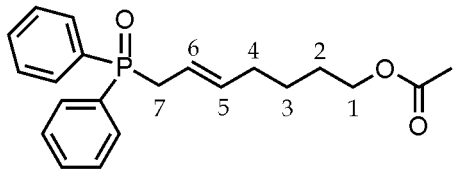
(±)-(3*R*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-methyl-4-vinylazetidin-2-one, (±)-153. A -78 °C solution of *N*-TBS protected azetidinone **(±)-152** (7.73 g, 36.4 mmol) in anhydrous THF (400 mL) was treated with the slow addition of *n*-BuLi (2.5 M, 28.4 mL, 710 mmol). The reaction was stirred for 10 min at -78 °C, and was then quenched by addition of iodomethane (7.52 mL, 17.2 g, 121 mmol) previously filtered through a short pad of basic alumina. The reaction mixture was stirred at -78 °C for a further 10 min and then worked up by the sequential addition of methanol (12.9 mL), and sat. aq. solution of ammonium chloride (169 mL). The crude mixture was then filtered through a pad of Celite and washed with diethyl ether (400 mL). The solvent was removed under vacuum, and the crude yellow oil (16.97 g) was purified by flash column chromatography (silica gel, 10% ethyl acetate in 40-60 petroleum ether) to provide the pure methylated azetidinone **(±)-153**

as a clear, colourless and slightly viscous oil (6.43 g, 78%). ^{1}H NMR (400MHz, $CDCl_3$) δ 0.14 (3H, s, $SiCH_3$), 0.21 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.28 (3H, d, J = 7.4 Hz, 3-CCH_3), 2.88 (1H, qd, J = 7.4, 2.5 Hz, 3-CH), 3.56 (1H, dd, J = 8.9, 2.5 Hz, 4-CH), 5.13 (1H, dd, J = 10.1, 1.0 Hz, 6-CH), 5.24 (1H, dq, J = 17.6, 0.6 Hz, 6-CH'), 5.82 (1H, ddd, J = 17.6, 10.1, 8.9 Hz, 5-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ -5.6 ($SiCH_3$), -5.5 ($SiCH_3$), 13.2 (3-CCH_3), 18.3 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 53.2 (3-CH), 60.7 (4-CH), 117.3 (6-CH_2), 139.2 (5-CH), 176.1 (2-C=O); IR (thin film) ν_{max} = 3474, 3084, 2958, 2929, 2858, 1744 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 226.1626, calculated for $C_{12}H_{24}ONSi$ 226.1627.

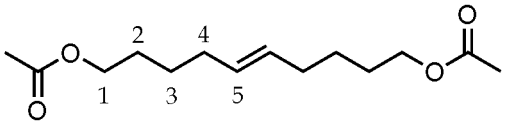


(±)-(*E*)-7-(Diphenylphosphoryl)oct-5-enyl acetate, 159. Second generation Grubbs catalyst (24 mg, 28 µmol, 6 mol%) was added to a solution of 1-methylallyldiphenylphosphine oxide **142** (120 mg, 468 µmol) and hexenyl acetate **158** (250 µL, 221 mg, 1.55 mmol) in anhydrous dichloromethane (2.0 mL). The reaction was refluxed for 24 h, and cooled down to room temperature before the solvent was evaporated under reduced pressure. The resulting dark residue (391 mg) was purified by flash chromatography (silica gel, 100% ethyl acetate) to afford the heterodimer **159** (90 mg, 52%), and the starting phosphine oxide **142** (20 mg) as an inseparable mixture. The semi-pure homodimer **161** was also isolated as a slightly viscous, clear and colourless oil (215 mg, 54%). Both olefins **159** and **161** were obtained as their (*E*)-double bond isomer almost exclusively, with traces of side-products which could not be formally attributed to the (*Z*)-isomers, as their NMR signals were mostly unresolved. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.24 (2H, m, 3-CH_2), 1.25 (3H, dd, J_{H-P} = 16.2 Hz, J = 7.1 Hz, 7-CCH_3), 1.35 (2H, m, 2-CH_2), 1.91 (2H, m, 4-CH_2), 2.00 (3H, s, $OOCCH_3$), 3.11 (2H, appdqn or m, 7-CH), 3.90 (2H, t, J = 6.6 Hz, 1-CH_2), 5.39 (2H, m, 5-CH + 6-CH), 7.38-7.47 (6H, m, ArH_{meta} + ArH_{para}), 7.70-7.80 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.3 (d, J_{C-P} = 3.4 Hz, 7-CCH_3), 20.9 ($OOCCH_3$), 25.3 (d, J_{C-P} = 3.0 Hz, 3-CH_2), 27.6 (2-CH_2), 32.0 (d, J_{C-P} = 1.9 Hz, 4-CH_2), 37.7 (d, J_{C-P} = 69.5 Hz, 7-CH_2), 64.2 (1-CH_2), 126.1 (d, J_{C-P} = 7.0 Hz, 5-CH), 128.1 (d, J_{C-P} = 11.3 Hz, $ArCH_{meta}$), 128.4 (d, J_{C-P} = 11.2 Hz, $ArCH_{meta}$), 131.1 (d, J_{C-P} = 8.6 Hz, $ArCH_{ortho}$), 131.4 (partially hidden d, J_{C-P} = 8.6 Hz, $ArCH_{ortho}$), 131.5 (d, J_{C-P} = 96.6 Hz, ArC_{IV}), 131.5 (d, J_{C-P} = 2.7 Hz, $ArCH_{para}$), 131.5 (d, J_{C-P} = 2.7 Hz, $ArCH_{para}$), 131.9 (d, J_{C-P} = 94.8 Hz, ArC_{IV}), 134.0 (d, J_{C-P} = 11.5 Hz, 6-CH), 171.0

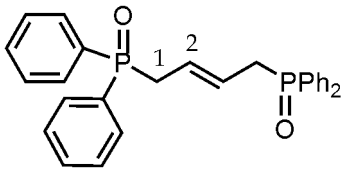
(C=O); IR (thin film) ν_{max} = 3423, 3055, 2973, 2932, 2875, 2852, 1735, 1637, 1438, 1372, 1245, 1183, 1119, 1046, 721, 692 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 371.1782, calculated for $C_{22}H_{28}O_3P$ 371.1776.



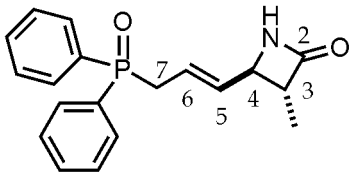
(*E*)-7-(Diphenylphosphoryl)hept-5-enyl acetate, 160.[122] Second generation Grubbs catalyst (24 mg, 28 µmol, 6 mol%) was added to a solution of allyldiphenylphosphine oxide **143** (120 mg, 495 µmol) and hexenyl acetate **158** (250 µL, 221 mg, 1.55 mmol) in anhydrous dichloromethane (2.0 mL). The reaction was refluxed for 24 h before it was cooled down to room temperature, and the solvent was evaporated under reduced pressure. The dark residue (395 mg) was purified by flash column chromatography (silica gel, 30% ethyl acetate in 40-60 petroleum ether) to give the heterodimer **160** as a very viscous black oil (183 mg) as well as the unclean homodimer **161** as a slightly viscous, clear and colourless oil (191 mg). Further purification by flash column chromatography of the heterodimer **160** (silica gel, 0-100% ethyl acetate in chloroform) and the homodimer **161** (silica gel, 100% chloroform) gave the analytically pure heterodimer **160** (148 mg, 84%), and an improved sample of homodimer **161** (150 mg, 38%). Both olefins **159** and **161** were obtained as their (*E*)-double bond isomer almost exclusively, with traces of side-products which could not be formally attributed to the (*Z*)-isomers, as their NMR signals were mostly unresolved. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.22 (2H, qn, J = 7.5 Hz, 3-CH_2), 1.38 (2H, m, 2-CH_2), 1.91 (2H, m, 4-CH_2), 1.97 (3H, s, $OOCCH_3$), 3.03 (2H, dd, J = 14.1, 5.8 Hz, 7-CH_2), 3.90 (2H, t, J = 6.6 Hz, 1-CH_2), 5.41 (2H, m, 5-CH + 6-CH), 7.38-7.48 (6H, m, ArH_{meta} + ArH_{para}), 7.65-7.72 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.8 (CH_3), 25.1 (d, J_{C-P} = 3.1 Hz, 3-CH_2), 27.6 (2-CH_2), 31.9 (d, J_{C-P} = 2.1 Hz, 4-CH_2), 34.6 (d, J_{C-P} = 69.4 Hz, 7-CH_2), 64.1 (1-CH_2), 118.5 (d, J_{C-P} = 9.2 Hz, 5-CH), 128.3 (d, J_{C-P} = 11.6 Hz, $ArCH_{meta}$), 130.8 (d, J_{C-P} = 9.1 Hz, $ArCH_{ortho}$), 131.5 (d, J_{C-P} = 2.7 Hz, $ArCH_{para}$), 132.4 (d, J_{C-P} = 98.3 Hz, ArC_{IV}), 136.5 (d, J_{C-P} = 11.8 Hz, 6-CH), 170.9 (C=O); IR (thin film) ν_{max} = 3437, 3056, 2937, 2858, 2218, 1735, 1438, 1388, 1366, 1244, 1185, 1120, 1043, 970, 730, 718, 696 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 357.1624, calculated for $C_{21}H_{26}O_3P$ 357.1620.



(*E*)-Dec-5-ene-1,10-diyl diacetate, 161.[122] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.37 (2H, appqn, J = 7.5 Hz, 3-CH_2), 1.58 (2H, appqn, J = 7.0 Hz, 2-CH_2), 1.97 (2H, m, 4-CH_2), 2.00 (3H, s, CH_3), 4.01 (2H, t, J = 6.7 Hz, 1-CH_2), 5.35 (1H, m, 5-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.9 (CH_3), 25.7 (3-CH_2), 27.9 (2-CH_2), 32.0 (4-CH_2), 64.3 (1-CH_2), 130.1 (5-CH), 171.0 (C=O);



(*E*)-1,4-Bis(diphenylphosphoryl)but-2-ene, 162.[122] To a solution of commercially available allyldiphenylphosphine oxide **143** (3.15 g, 13.0 mmol) in anhydrous dichloromethane (56 mL) was added second generation Grubbs catalyst (230 mg, 0.27 mmol, 2.1 mol%). The reaction mixture was then refluxed for 24 h, allowed to cool down, and then quenched by incorporation of diethyl ether (100 mL). The mixture was filtered and the resulting white solid was washed with more diethyl ether (100 mL). The process was repeated until no white solid was isolated out from the filtrate. The white solid (2.08 g, 70%) was proved to be the pure homodimer **162** by NMR analysis. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.02 (2H, ddd, $J_{H\text{-}P}$ = 10.7 Hz, J = 3.8, 1.7 Hz, 1-CH_2), 5.55 (1H, m, 2-CH), 7.36-7.47 (6H, m, ArH_{meta} + ArH_{para}), 7.59-7.63 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 34.9 (dd, $J_{C\text{-}P}$ = 70.7, 4.0 Hz, 1-CH_2), 124.8 (appt, $J_{C\text{-}P}$ = 15.6 Hz, 2-CH), 128.5 (appt, $J_{C\text{-}P}$ = 5.8 Hz, $ArCH_{meta}$), 130.7 (appt, $J_{C\text{-}P}$ = 4.6 Hz, $ArCH_{ortho}$), 131.7 (appbs, $ArCH_{para}$), 132.7 (d, partially hidden, ArC_{IV}); IR (thin film, Nujol) ν_{max} = 1438, 1408, 1183, 1119, 1105, 1061, 984, 842, 828, 764, 743, 718, 693, 560, 510, 428 cm^{-1}; HRMS (FAB) observed $(M+H)^+$ 457.1484, calculated for $C_{28}H_{27}O_2P_2$ 457.1486; M.p. 140 °C.

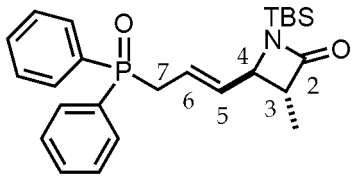


(±)-(3*R*,4*R*)-4-((*E*)-3-(Diphenylphosphoryl)prop-1-enyl)-3-methylazetidin-2-one, (±)-163.

Procedure A: Second generation Grubbs catalyst (10 mg, 12 μmol, 9.4 mol%) was added to a solution of β-lactam **(±)-119** (41.4 mg, 369 μmol) and allyldiphenyphosphine oxide **143**

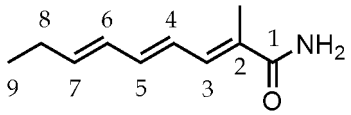
(30.2 mg, 124 µmol) in anhydrous toluene (2.0 mL). The reaction mixture was heated at 65 °C for 21 h, and was then treated with additional allyldiphenyphosphine oxide **143** (20 mg, 83 µmol), and second generation Grubbs catalyst (10 mg, 12 µmol, 9.4 mol%). After stirring the reaction for 17 h at 80 °C, the majority of the toluene was evaporated under reduced pressure, and the resulting crude solution was then purified by flash column chromatography (silica gel, 0-50% methanol in ethyl acetate). The pure heterodimer **(±)-163** was obtained as a light brownish sticky oil (46 mg, 69%).

Procedure B: Second generation Hoveyda-Grubbs catalyst (18 mg, 29 µmol, 31 mol%) was added to a solution of β-lactam **(±)-119** (33.3 mg, 297 µmol) and allyldiphenyphosphine oxide **143** (24 mg, 94 µmol) in anhydrous toluene (1.5 mL). After stirring the reaction for 13 h at 80 °C, the majority of the toluene was evaporated under reduced pressure, and the resulting crude solution was then purified by flash column chromatography (silica gel, 100% ethyl acetate) to give the pure heterodimer **(±)-163** as a light brownish sticky oil (24 mg, 78%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.22 (3H, d, J = 7.4 Hz, CH_3), 2.62 (1H, appbq, J = 7.4 Hz, C*H*CH_3, 3-CH), 3.11 (2H, m, 7-CH_2), 3.60 (1H, d, J = 7.5 Hz, 4-CH), 5.52 (1H, ddd, J = 15.1, 7.4 Hz, $J_{H\text{-}P}$ = 4.5 Hz, 5-CH), 5.73 (1H, m, 6-CH), 6.02 (1H, bs, NH), 7.47-7.55 (6H, m, ArH_{meta} + ArH_{para}), 7.68-7.73 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.5 (CH_3), 34.4 (d, $J_{C\text{-}P}$ = 68.1 Hz, 7-CH_2), 53.2 (d, $J_{C\text{-}P}$ = 2.9 Hz, 3-CH), 57.2 (d, $J_{C\text{-}P}$ = 2.3 Hz, 4-CH), 121.6 (d, $J_{C\text{-}P}$ = 9.3 Hz, 5-CH), 128.6 (d, $J_{C\text{-}P}$ = 11.8 Hz, $ArCH_{meta}$), 128.6 (d, $J_{C\text{-}P}$ = 11.8 Hz, $ArCH_{meta}$), 130.8 (d, $J_{C\text{-}P}$ = 9.2 Hz, $ArCH_{ortho}$), 130.9 (d, $J_{C\text{-}P}$ = 9.2 Hz, $ArCH_{ortho}$), 132.0 (d, $J_{C\text{-}P}$ = 3.0 Hz, $ArCH_{para}$), 132.0 (d, $J_{C\text{-}P}$ = 2.9 Hz, $ArCH_{para}$), 132.0 (d, $J_{C\text{-}P}$ = 99.6 Hz, ArC_{IV}), 132.1 (d, $J_{C\text{-}P}$ = 99.3 Hz, ArC_{IV}), 135.5 (d, $J_{C\text{-}P}$ = 11.3 Hz, 6-CH), 170.9 (2-C=O); IR (thin film) ν_{max} = 3419, 3213, 3059, 2965, 2929, 2229, 1747, 1663, 1438, 1177, 1121, 969, 721, 696 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 326.1302, calculated for $C_{19}H_{21}O_2NP$ 326.1310.



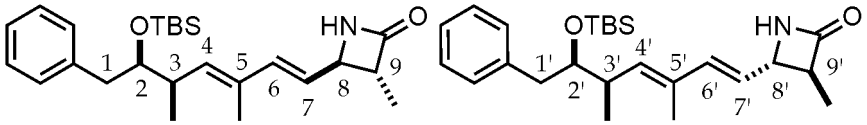
(±)-(3*R*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-((*E*)-3-(diphenylphosphoryl)prop-1-enyl)-3-methylazetidin-2-one, (±)-164. Second generation Hoveyda-Grubbs catalyst (55 mg, 88 µmol, 5.0 mol%) was added to a solution of *N*-TBS protected β-lactam **(±)-153** (399 mg, 1.77 mmol) and allyldiphenyphosphine oxide **143** (429 mg, 1.77 mmol) in anhydrous toluene

(13.5 mL). The reaction mixture was heated at 80 °C for 16 h until some additional second generation Hoveyda-Grubbs catalyst (55 mg, 88 µmol, 5.0 mol%) was added. After stirring the reaction for 17 h at 80 °C, the majority of the toluene was evaporated under reduced pressure. The crude resulting solution was then purified by flash column chromatography (silica gel, 1% TEA, 100% ethyl acetate). The pure heterodimer **(±)-164** was obtained as a light brownish sticky oil (242 mg, 31%). ^{1}H NMR (400MHz, $CDCl_3$) δ -0.02 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 1.15 (3H, d, J = 7.4 Hz, 3-CHCH_3), 2.56 (1H, qd, J = 7.4, 2.5 Hz, 3-CH), 3.04 (1H, tdd, $J_{H\text{-}P}$ = 14.0 Hz, J = 7.9, 1.0 Hz, 7-CH), 3.16 (1H, tdd, $J_{H\text{-}P}$ = 14.8 Hz, J = 6.9, 1.1 Hz, 7-CH'), 3.45 (1H, dd, J = 8.9, 2.4 Hz, 4-CH), 5.45 (1H, ddd, J = 15.3, 9.0 Hz, $J_{H\text{-}P}$ = 4.3 Hz, 5-CH), 5.72 (1H, m, 6-CH), 7.40-7.52 (6H, m, ArH_{meta} + ArH_{para}), 7.63-7.75 (4H, m, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ -5.8 ($Si(CH_3)_2$), 13.0 (3-CHCH_3), 18.2 (SiC_{IV}), 26.1 ($SiC(CH_3)_3$), 34.4 (d, $J_{C\text{-}P}$ = 68.4 Hz, 7-CH_2), 53.3 (d, $J_{C\text{-}P}$ = 2.9 Hz, 3-CH), 59.4 (d, $J_{C\text{-}P}$ = 2.2 Hz, 4-CH), 121.6 (d, $J_{C\text{-}P}$ = 9.2 Hz, 6-CH), 128.4 (d, $J_{C\text{-}P}$ = 11.8 Hz, $ArCH_{meta}$), 128.6 (d, $J_{C\text{-}P}$ = 11.7 Hz, $ArCH_{meta}$), 130.8 (d, $J_{C\text{-}P}$ = 9.2 Hz, $ArCH_{ortho}$), 130.8 (d, $J_{C\text{-}P}$ = 9.2 Hz, $ArCH_{ortho}$), 131.8 (d, $J_{C\text{-}P}$ = 2.7 Hz, $ArCH_{para}$), 131.9 (d, $J_{C\text{-}P}$ = 2.7 Hz, $ArCH_{para}$), 132.1 (d, $J_{C\text{-}P}$ = 99.7 Hz, ArC_{IV}), 132.3 (d, $J_{C\text{-}P}$ = 98.7 Hz, ArC_{IV}), 137.2 (d, $J_{C\text{-}P}$ = 11.4 Hz, 5-CH), 175.8 (2-C=O); IR (thin film) ν_{max} = 3448, 3056, 2957, 2928, 2899, 2857, 2220, 1737, 1438, 1289, 1254, 1182, 1120, 997, 840, 824, 730, 696, 549 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 440.2168, calculated for $C_{25}H_{35}O_2NSiP$ 440.2175.



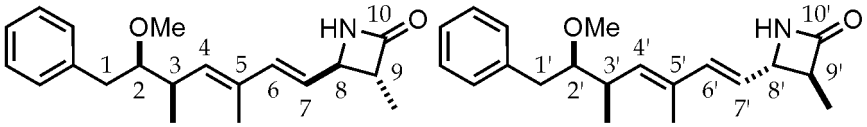
(2*E*,4*E*,6*E*)-2-Methylnona-2,4,6-trienamide, 166. A -78 °C solution of phosphine oxide **(±)-207** (30 mg, 92 µmol) in anhydrous tetrahydrofuran (2.5 mL) was treated with the slow addition of LiHMDS (93 µL, 1.06 M in THF, 99 µmol). The reaction was stirred for 20 min at -78 °C, and distilled HMPA (52 mg, 50 µL, 0.3 mmol) was then added. The reaction mixture was stirred for a further 5 min, before freshly distilled propanal (58 mg, 72 µL, 1.0 mmol) was incorporated. The reaction was allowed to warm up slowly to room temperature, and was stirred overnight under argon. The reaction was then quenched with the careful addition of water (10 mL). The phases were separated and the organic phase was washed one more time with water (10 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford the crude triene **166** as an extremely viscous yellowish oil. Purification by flash column

chromatography (silica gel, 70-100% ethyl acetate in 40-60 petroleum ether) yielded the pure triene **166** as a very viscous clear and colourless oil (10 mg, 66%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.04 (3H, t, *J* = 7.4 Hz, 9-CH_3), 1.97 (3H, d, *J* = 1.0 Hz, 2-$C_{IV}CH_3$), 2.16 (2H, appqn, *J* = 7.4 Hz, 8-CH_2), 5.58 (2H, vbs, NH_2), 5.93 (1H, dt, *J* = 15.2, 6.6 Hz, 7-CH), 6.17 (1H, ddt, *J* = 15.1, 10.3, 1.4 Hz, 6-CH), 6.36 (1H, dd, *J* = 14.8, 11.2 Hz, 4-CH), 6.48 (1H, dd, *J* = 14.8, 10.5 Hz, 5-CH), 6.99 (1H, dd, *J* = 11.1, 1.1 Hz, 3-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.0 (9-CH_3), 13.2 (2-$C_{IV}CH_3$), 25.9 (8-CH_2), 125.2 (4-CH), 127.6 (2-CH), 129.2 (6-CH), 135.4 (3-CH), 139.4 (5-CH), 140.6 (7-CH), 170.9 (1-C=O); IR (thin film) ν_{max} = 3365, 3201, 3029, 2964, 2924, 2879, 2848, 1655, 1619, 1596, 1581, 1458, 1405, 1379, 1285, 1180, 1154, 1113, 1030, 986, 797, 738 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 166.1231, calculated for $C_{10}H_{16}NO$ 166.1232.



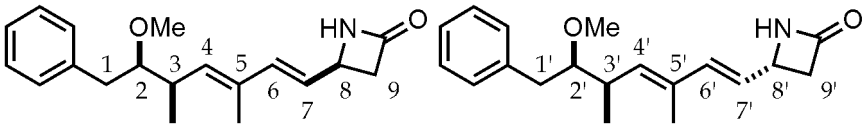
(3*R*,4*R*)-4-((1*E*,3*E*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methylazetidin-2-one, 167, (3*S*,4*S*)-4-((1*E*,3*E*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methylazetidin-2-one, 168. Second generation Hoveyda-Grubbs catalyst (35 mg, 56 µmol, 11 mol%) was incorporated into a solution of TBS-protected dienol **(*E*)-139** (173 mg, 523 µmol) and β-lactam **(±)-119** (56 mg, 500 µmol) in anhydrous toluene (4 mL). The reaction mixture was stirred at 80 °C for 2 days. The majority of the toluene was evaporated under reduced pressure, and the resulting crude solution was then purified by flash column chromatography (silica gel, 1% TEA, 0-30% ethyl acetate in 40-60 petroleum spirit). Purification enabled the recovery of the dienol **(*E*)-139** (102 mg, 59% of recovery) as well as the pure (1:1) isomeric mixture of heterodimers **167** and **168** as a light brownish sticky oil (77 mg, 37%, 87% borsm). ^{1}H NMR (400MHz, $CDCl_3$) δ -0.26 (6H, s, $SiCH_3$ + $SiCH'_3$), -0.03 (6H, s, $SiCH_3$ + $SiCH'_3$), 0.87 (18H, s, $SiC(CH_3)_3$ + $SiC(CH'_3)_3$), 0.99 (6H, d, *J* = 6.8 Hz, 3-CCH_3 + 3'-CCH_3), 1.34 (6H, 2 x d, *J* = 7.4 and 7.5 Hz, 9-CCH_3 + 9'-CCH_3), 1.56 (6H, 2 x s, 5-CCH_3 + 5'-CCH_3), 2.50 (2H, m, 3-CH + 3'-CH), 2.68 (2H, dd, *J* = 13.5, 6.6 Hz, 1-CH + 1'-CH), 2.81 (2H, dd, *J* = 13.5, 5.9 Hz, 1-CH" + 1'-CH"), 2.93 (2H, m, 9-CH + 9'-CH), 3.78 (4H, m, 2-CH + 8-CH + 2'-CH + 8'-CH), 5.45 (2H, d, *J* = 9.7 Hz, 4-CH + 4'-CH), 5.55 (2H, dd, *J* = 15.5, 8.0 Hz, 7-CH + 7'-CH), 5.92 (2H, bd, *J* = 8.9 Hz, NH + NH'), 6.23 (2H, d, *J* = 15.5 Hz, 6-CH + 6'-CH), 7.14-7.28 (10H, m, ArCH + ArCH'); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$ + $SiC'H_3$), -4.5 ($SiCH_3$ + $SiC'H_3$), 12.6 (2 peaks, 9-CCH_3 + 9'CCH_3), 12.7 (2 peaks, 5-CCH_3 +

5'-CCH_3), 15.2 (3-CCH_3 + 3'-CCH_3), 18.1 (SiC(CH_3)$_3$ + SiC'(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$ + SiC(C'H_3)$_3$), 37.2 (2 peaks, 3-CH + 3'-CH), 41.5 (1-CH_2 + 1'-CH_2), 53.8 (9-CH + 9'-CH), 58.3 (2 peaks, 8-CH + 8'-CH), 77.3 (underneath $CHCl_3$ peaks, 2-CH + 2'-CH), 125.2 (2 peaks, 7-CH + 7'-CH), 126.0 (ArCH_{para} + Ar$C'H_{para}$), 128.1 (ArCH_{ortho} + Ar$C'H_{ortho}$), 129.7 (ArCH_{meta} + Ar$C'H_{meta}$), 131.5 (5-C_{IV} + 5'-C_{IV}), 137.5 (2 peaks, 4-CH + 4'-CH) 137.9 (2 peaks, 6-CH + 6'-CH), 139.0 (2 peaks, ArC_{IV} + ArC'_{IV}), 171.4 (C=O + C'=O); IR (thin film) ν_{max} = 3390, 3029, 2957, 2929, 2856, 1752,1495, 1472, 1455, 1378, 1360, 1255, 1175, 1097, 1083, 1060, 1030, 966, 937, 874, 836, 809, 775, 738, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 414.2829, calculated for $C_{25}H_{40}O_2NSi$ 414.2828.



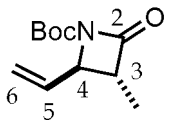
(3*R*,4*R*)-4-((1*E*,3*E*,5*R*,6*R*)-6-Methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methylazetidin-2-one, 169 and (3*S*,4*S*)-4-((1*E*,3*E*,5*R*,6*R*)-6-Methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methylazetidin-2-one, 170: To a solution of freshly purified diene **(*E*)-117** (140 mg, 608 µmol) and vinylazetidinone **(±)-119** (70.1 mg, 630 µmol) in dry toluene (8 mL) was added second generation Hoveyda-Grubbs (60 mg, 16 mol%). The mixture was then refluxed overnight, and the solvent was evaporated under reduced pressure to afford the crude product as a black viscous oil (298 mg). The black crude oil was purified by flash column chromatography (silica gel, 10-50% ethyl acetate in 40-60 petroleum ether) to afford the semi-pure desired heterodimer **169** and **170** as a colourless and very viscous oil (71 mg, 37%, 79% borsm) which was used in the next reaction without any further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 (6H, d, J = 6.7 Hz, 3-CCH_3 + 3'-CCH_3), 1.33 and 1.34 (6H, 2 x d, J = 7.5 and 7.3 Hz, 9-CCH_3 + 9'-CCH_3), 1.48 (9H, bs, 5-CCH_3 + 5'-CCH_3), 2.61 (2H, m, 3-CH + 3'-CH), 2.68 (2H, dd, J = 13.9, 7.5 Hz, 1-CH + 1'-CH), 2.80 (2H, dd, J = 13.9, 4.6 Hz, 1-CH" + 1'-CH"), 2.93 (2H, appq, J = 7.4 Hz, 9-CH + 9'-CH), 3.20 (2H, m, 2-CH + 2'-CH), 3.24 (6H, s, OCH_3 + OCH_3'), 3.78 (2H, dd, J = 7.9, 1.8 Hz, 8-CH + 8'-CH), 5.44 (2H, d, J = 9.9 Hz, 4-CH + 4'-CH), 5.59 (2H, dd, J = 15.6, 7.9 Hz, 7-CH + 7'-CH), 6.13 (2H, d, J = 4.3 Hz, NH), 6.27 (2H, d, J = 15.5, 6-CH + 6'-CH), 7.18-7.29 (10H, m, ArH + ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.6 (5-CCH_3 + 5'-CCH_3), 16.1 (2 peaks, 3-CCH_3 + 3'-CCH_3), 22.1 (9-CCH_3 + 9'-CCH_3), 36.5 (2 peaks, 3-CH + 3'-CH), 38.1 (2 peaks, 1-CH_2 + 1'-CH_2), 53.7 (9-CH + 9'-CH), 58.2 (8-CH + 8'-CH), 58.6 (2 peaks, OCH_3 + OCH_3'), 86.8 (2 peaks, 2-CH + 2'-CH), 125.6 (7-CH + 7'-CH), 125.9 (ArCH_{para}), 128.1 (2 peaks, ArCH_{ortho}),

129.3 ($ArCH_{meta}$), 132.2 (2 peaks, 5-C_{IV} + 5'-C_{IV}), 136.7 and 136.8 (4-CH + 4'-CH), 137.2 and 137.3 (6-CH + 6'-CH), 139.2 (2 peaks, ArC_{IV}), 171.4 (10-C=O); $[\alpha]^{24}_D$ +18.5, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3264, 3086, 3062, 3027, 2965, 2929, 2871, 2826, 1754, 1454, 1372, 1112, 966, 750, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 314.2121, calculated for $C_{20}H_{28}O_2N$ 314.2120.

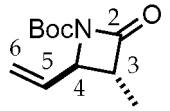


(*S*)-4-((1*E*,3*E*,5*R*,6*R*)-6-Methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)azetidin-2-one, 171 and (*R*)-4-((1*E*,3*E*,5*R*,6*R*)-6-Methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)azetidin-2-one, 172. Second generation Hoveyda-Grubbs catalyst (23 mg, 37 µmol, 10 mol%) was added to a solution of methoxydienol **(*E*)-117** (84 mg, 360 µmol) and β-lactam **(±)-151** (56 mg, 580 µmol) in anhydrous dichloromethane (3 mL). The reaction mixture was refluxed for 10 h before being cooled down to room temperature. The solvent was evaporated under reduced pressure, and the crude resulting oil (165 mg) was then purified by flash column chromatography (silica gel, 1% TEA, 0-50% ethyl acetate in 40-60 petroleum spirit) to provide the semi-pure isomeric mixture of heterodimers **171** and **172** (23 mg). A second purification by flash column chromatography (silica gel, 10% ethyl acetate in chloroform) afforded the cleaner isomeric mixture of heterodimers **171** and **172** contaminated with starting β-lactam **(±)-151** (4 mg) and as a viscous clear and colourless oil (12 mg, 11%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 and 1.04 (6H, 2 x d, *J* = 6.7 and 6.8 Hz, 3-CCH_3 + 3'CCH_3), 1.65 and 1.66 (6H, 2 x s, 5-CCH_3 + 5'-CCH_3), 2.61 (2H, m, 3-CH + 3'-CH), 2.68 (2H, dd, *J* = 13.9, 6.9 Hz, 1-CH + 1'-CH), 2.72 (4H, m, 9-CH + 9'-CH), 2.80 (2H, dd, *J* = 13.9, 4.5 Hz, 1-CH" + 1'-CH"), 3.17-3.27 (2H, m, 2-CH + 2'-CH), 3.23 and 3.24 (3H, 2 x s, OCH_3 + OCH_3'), 4.19 (2H, 2 x ddd, *J* = 7.7, 5.2, 2.6 Hz, 8-CH + 8'-CH), 5.44 (2H, bd, *J* = 9.8 Hz, 4-CH + 4'-CH), 5.59 (2H, dd, *J* = 15.4, 7.7 Hz, 7-CH + 7'-CH), 5.95 (2H, vbs, NH + NH'), 6.28 (2H, d, *J* = 15.5 Hz, 6-CH + 6'-CH), 7.15-7.29 (10H, m, ArH + ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (5-$C$$CH_3$ + 5'-$C$$CH_3$), 16.1 (2 peaks, 3-$C$$CH_3$ + 3'$C$$CH_3$), 36.6 (3-CH + 3'-CH), 38.1 (2 peaks, 1-CH_2 + 1'-CH_2), 45.6 (9-CH + 9'-CH), 49.5 (8-CH + 8'-CH), 58.6 (2 peaks, OCH_3 + OCH_3'), 86.8 (2-CH + 2'-CH), 125.9 (7-CH + 7'-CH), 126.0 ($ArCH_{para}$ + $ArC'H_{para}$), 128.2 ($ArCH_{ortho}$ + $ArC'H_{ortho}$), 129.4 ($ArCH_{meta}$ + $ArC'H_{meta}$), 132.2 (5-CH + 5'-CH), 137.0 (2 peaks, 4-CH + 4'-CH), 137.4 (2 peaks, 6-CH + 6'-CH), 139.2 (ArC_{IV}), 167.6 (2 peaks, C=O); IR (thin film) ν_{max} = 3259, 3084, 3029, 2980, 2961, 2927, 2871, 2830, 1757, 1645,

1454, 1412, 1372, 1353, 1262, 1245, 1182, 1112, 1083, 966, 749, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 300.1961, calculated for $C_{19}H_{26}O_2N$ 300.1964.

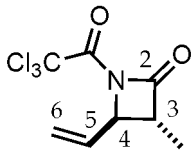


(±)-(3*R*,4*R*)-3-Methyl-2-oxo-4-vinyl-azetidine-1-carboxylic acid *tert*-butyl ester, (±)-174. A room temperature solution of lactam **(±)-119** (47 mg, 420 µmol) in anhydrous dichloromethane (10 mL) was sequentially treated with anhydrous triethylamine (56 µL, 40 µg, 0.4 µmol), DMAP (50 mg, 410 µmol) and $(Boc)_2O$ (96 mg, 440 µmol). The resulting reaction mixture was stirred overnight, and then concentrated under reduced pressure. The resulting crude yellow oil (151 mg) was purified by flash column chromatography (silica gel, 0.5% TEA, 10% ethyl acetate in 40-60 petroleum spirit) to give the pure desired *N*-Boc protected lactam **(±)-174** as a clear and colourless viscous oil (89 mg, 100%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.34 (3H, d, *J* = 7.5 Hz, 3-CCH_3), 1.48 (9H, s, $OC(CH_3)_3$), 2.91 (1H, qd, *J* = 7.5, 3.0 Hz, 3-CH), 3.96 (1H, dd, *J* = 7.7, 3.0 Hz, 4-CH), 5.27 (1H, d, *J* = 10.3 Hz, 6-CH), 5.36 (1H, d, *J* = 17.1 Hz, 6-CH'), 5.86 (1H, ddd, *J* = 17.1, 10.3, 7.7 Hz, 5-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.2 (3-CCH_3), 27.9 ($OC(CH_3)_3$), 51.1 (3-CH), 61.2 (4-CH), 83.1 ($OC(CH_3)_3$), 118.7 (6-CH_2), 134.7 (5-CH), 147.8 (O-C=O), 168.1 (2-C=O); IR (thin film) ν_{max} = 3086, 2979, 2934, 1808, 1724, 1339, 1156 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 212.1283, calculated for $C_{11}H_{18}O_3N$ 212.1287.

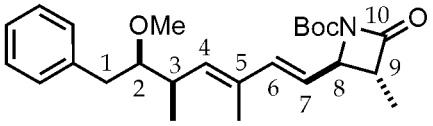


(3*R*,4*R*)-*tert*-Butyl 3-methyl-2-oxo-4-vinylazetidine-1-carboxylate, 174: To a solution of lactam **119** (27 mg, 240 µmol) in dry dichloromethane (6 mL) was added anhydrous triethylamine (34 µL, 240 µmol), DMAP (31 mg, 250 µmol) and $(Boc)_2O$ (60 mg, 280 µmol) at room temperature. The mixture was stirred overnight and then directly concentrated to afford a yellow crude oil (83 mg), which was purified by flash column chromatography (silica gel, 0.5% TEA, 10% ethyl acetate in 40-60 petroleum spirit) to give the pure desired *N*-Boc protected lactam **174** as a clear and colourless viscous oil (33 mg, 65%, *ee* = 98%). The enantiomeric excess was determined through HPLC analysis with a Chiralcel OJH column using hexane:*iso*propanol (99:1) at a flow rate of 0.75 mL/min. Data were in full

agreement with those reported for the racemic azetidinone **(±)-174**. $[\alpha]^{25}_{D}$ -39.0, (c = 1.0, $CHCl_3$).

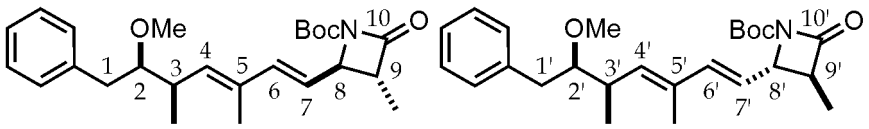


(±)-(3*S*,4*S*)-3-Methyl-1-(2,2,2-trichloroacetyl)-4-vinylazetidin-2-one, (±)-175. A solution of β-lactam **(±)-119** (244 mg, 2.20 mmol) in anhydrous dichloromethane (10 mL) was cooled down to -78 °C. The reaction mixture was then sequentially treated with anhydrous triethylamine (444 mg, 612 µL, 4.39 mmol) and trichloroacetyl chloride (803 mg, 493 µL, 4.42 mmol). Completion was reached within 10 min, as indicated by TLC analysis, and the reaction was then quenched by addition of a sat. aq. solution of sodium bicarbonate (2 mL). The phases were separated, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was diluted in dichloromethane (50 mL) and washed with water (2 x 10 mL). The organic layer was dried one more time over anhydrous sodium sulfate, and concentrated *in vacuo* to provide the crude *N*-TAC protected β-lactam **(±)-175** as an orange to brown viscous oil (961 mg). Purification by flash column chromatography (silica gel, 10% ethyl acetate in 40-60 petroleum spirit) gave the pure *N*-TAC protected β-lactam **(±)-175** as a clear and colourless viscous oil (561 mg, 100%), which turns brown when exposed to temperatures above 45°C. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 7.5 Hz, CH_3), 3.13 (1H, qd, *J* = 7.5, 3.6 Hz, 3-CH), 4.22 (1H, dd, *J* = 7.4, 3.5 Hz, 4-CH), 5.39 (1H, dd, *J* = 10.3, 0.6 Hz, 5-CH), 5.48 (1H, dd, *J* = 17.1, 0.7 Hz, 6-CH), 5.93 (1H, ddd, *J* = 17.3, 10.3, 7.4 Hz, 6-CH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.8 (CH_3), 50.9 (3-CH), 61.1 (4-CH), 91.2 (CCl_3), 120.1 (6-CH_2), 133.0 (5-CH), 157.5 (CCl_3*C*=O), 164.2 (2-C=O); IR (thin film) ν_{max} = 3089, 2975, 2935, 2875, 1811, 1713, 1281 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 255.9705, calculated for $C_8H_9NO_2Cl_3$ 255.9699.



(2*R*,3*R*)-*tert*-Butyl 2-((1*E*,3*E*,5*R*,6*R*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methyl-4-oxoazetidine-1-carboxylate, 176. To a solution of freshly purified diene **(*E*)-117** (30 mg, 130 µmol) and *N*-Boc protected vinylazetidinone **174** (45 mg, 210 µmol, *ee* = 90%)

in dry toluene (2.0 mL) was added second generation Hoveyda-Grubbs catalyst (16 mg, 20 mol%). The mixture was then refluxed overnight (14 h), and then cooled down to room temperature. The solvent was evaporated under reduced pressure to afford a black viscous oil which was diluted with diethyl ether (10 mL), and filtered to remove the catalyst derivatives. Concentration of the filtrate under reduced pressure gave a very viscous brownish oil (76 mg). The black crude oil was purified by flash column chromatography (silica gel, 1% TEA, 0-20% ethyl acetate in 40-60 petroleum ether) to afford the pure single diasteroisomer **176** as a clear and very viscous yellowish oil (33 mg, 61%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.7 Hz, 3-CCH_3), 1.35 (3H, d, *J* = 7.4 Hz, 9-CCH_3), 1.49 (9H, s, OC$(CH_3)_3$), 1.64 (3H, d, *J* = 1.2 Hz, 5-CCH_3), 2.61 (1H, m, 3-CH), 2.69 (1H, d, *J* = 7.5 Hz, 1-CH), 2.80 (1H, d, *J* = 4.6 Hz, 1-CH'), 2.94 (1H, m, 9-CH), 3.19 (1H, m, 2-CH), 3.23 (3H, s, CH_3, OCH_3), 4.03 (1H, dd, *J* = 8.1, 3.0 Hz, 8-CH), 5.46 (1H, d, *J* = 9.8 Hz, 4-CH), 5.55 (1H, dd, *J* = 15.4, 8.1 Hz, 7-CH), 6.34 (1H, d, *J* = 15.5, 6-CH), 7.17-7.29 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 (9-CCH_3), 12.7 (5-CCH_3), 16.1 (3-CCH_3), 28.0 (OC(CH_3)$_3$), 36.6 (3-CH), 38.1 (1-CH_2), 51.6 (9-CH), 58.6 (9-CH), 61.4 (8-CH_3), 82.9 (O$C$$(CH_3)_3$), 86.9 (2-CH), 123.0 (7-CH), 126.1 (ArCH_{para}), 128.1 (ArCH_{ortho}), 129.3 129.4 (ArCH_{meta}), 132.2 (5-C_{IV}), 137.2 (4-CH), 139.2 (6-CH), 139.3 (ArC_{IV}), 147.8 (O-C=O), 168.4 (10-C=O); $[\alpha]^{24}_{D}$ +24.9, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3422, 3029, 2976, 2931, 2875, 2362, 2342, 1810, 1723, 1333, 1157, 1104 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 413.2646, calculated for $C_{25}H_{35}O_4N$ 413.2657.

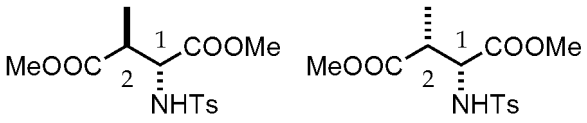


(2*R*,3*R*)-*tert*-Butyl 2-((1*E*,3*E*,5*R*,6*R*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methyl-4-oxoazetidine-1-carboxylate, 176 and (2*S*,3*S*)-*tert*-Butyl 2-((1*E*,3*E*,5*R*,6*R*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methyl-4-oxoazetidine-1-carboxylate, 177. To a solution of freshly purified diene **(*E*)-117** (30 mg, 130 µmol) and a mixture of *N*-Boc protected vinylazetidinone **(±)-174** (52 mg, 250 µmol) in dry toluene (2.0 mL) was added second generation Hoveyda-Grubbs catalyst (17 mg, 20 mol%). The mixture was refluxed overnight (14 h), and the solvent was evaporated under reduced pressure to afford a black viscous oil which was diluted with diethyl ether (10 mL), and filtered to remove the catalyst derivatives. Concentration of the filtrate under reduced pressure gave a very viscous brownish oil as crude (78 mg). The black crude oil was

purified by flash column chromatography (silica gel, 1% TEA, 0-20% ethyl acetate in 40-60 petroleum ether) to afford the pure mixture of two inseparable diastereoisomers **176** and **177** as a clear and very viscous yellowish oil (37 mg, 69%).

176. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.7 Hz, 3-CCH_3), 1.35 (3H, d, *J* = 7.4 Hz, 9-CCH_3), 1.49 (9H, s, $OC(CH_3)_3$), 1.64 (3H, d, *J* = 1.2 Hz, 5-CCH_3), 2.61 (1H, m, 3-CH), 2.69 (1H, d, *J* = 7.5 Hz, 1-CH), 2.80 (1H, d, *J* = 4.6 Hz, 1-CH'), 2.94 (1H, m, 9-CH), 3.19 (1H, m, 2-CH), 3.23 (3H, s, CH_3, OCH_3), 4.03 (1H, dd, *J* = 8.1, 3.0 Hz, 8-CH), 5.46 (1H, d, *J* = 9.8 Hz, 4-CH), 5.55 (1H, dd, *J* = 15.4, 8.1 Hz, 7-CH), 6.34 (1H, d, *J* = 15.5, 6-CH), 7.17-7.29 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 (9-CCH_3), 12.7 (5-CCH_3), 16.1 (3-CCH_3), 28.0 (OC(CH_3)$_3$), 36.6 (3-CH), 38.1 (1-CH_2), 51.6 (9-CH), 58.6 (9-CH), 61.4 (8-CH_3), 82.9 (OC(CH_3)$_3$), 86.9 (2-CH), 123.0 (7-CH), 126.1 (ArCH_{para}), 128.1 (ArCH_{ortho}), 129.3 129.4 (ArCH_{meta}), 132.2 (5-C_{IV}), 137.2 (4-CH), 139.2 (6-CH), 139.3 (ArC_{IV}), 147.8 (O-C=O), 168.4 (10-C=O);

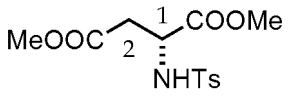
177. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.7 Hz, 3'-CCH_3), 1.36 (3H, d, *J* = 7.5 Hz, 9'-CCH_3), 1.48 (9H, s, $OC(CH_3)_3$'), 1.66 (3H, d, *J* = 1.2 Hz, 5'-CCH_3), 2.60 (1H, m, 3'-CH), 2.66 (1H, d, *J* = 7.5 Hz, 1'-CH), 2.81 (1H, d, *J* = 4.6 Hz, 1-CH"), 2.95 (1H, m, 9'-CH), 3.19 (1H, m, 2'-CH), 3.24 (3H, s, OCH_3'), 4.03 (1H, dd, *J* = 8.1, 3.0 Hz, 8'-CH), 5.45 (1H, d, *J* = 9.7 Hz, 4'-CH), 5.54 (1H, dd, *J* = 15.4, 8.1 Hz, 7'-CH), 6.33 (1H, d, *J* = 15.5 Hz, 6'-CH), 7.17-7.29 (5H, m, ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 (9'-CCH_3), 12.6 (5'-CCH_3), 16.0 (3'-CCH_3), 28.0 (OC(CH_3)$_3$'), 36.7 (3'-CH), 38.2 (1'-CH_2), 51.7 (9'-CH), 58.7 (OCH_3'), 61.3 (8'-CH_3), 82.9 (OC(CH_3)$_3$'), 86.8 (2'-CH), 123.1 (7'-CH), 126.0 (ArCH_{para}'), 128.2 (ArCH_{ortho}'), 129.4 (ArCH_{meta}'), 132.1 (5-C_{IV}'), 137.4 (4'-CH), 139.1 (6'-CH), 139.2 (ArC_{IV}'), 147.9 (O-C=O'), 168.5 (10'-C=O); $[\alpha]^{24}_D$ +9.1, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3422, 3029, 2976, 2931, 2875, 2362, 2342, 1810, 1723, 1333, 1157, 1104 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 413.2646, calculated for $C_{25}H_{35}O_4N$ 413.2657.



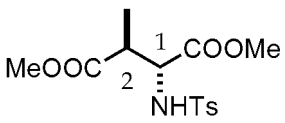
(2*S*,3*R*)-dimethyl 2-methyl-3-(4-methylphenylsulfonamido)succinate, *trans*-179 and (2*R*,3*R*)-dimethyl 2-methyl-3-(4-methylphenylsulfonamido)succinate, *syn*-179. Solid tosyl chloride (3.67 g, 19.2 mmol) was added to a solution of methylester **178** (2.53 g, 12.8 mmol) in anhydrous tetrahydrofuran (130 mL) at room temperature. The resulting mixture was then treated with the slow addition of anhydrous triethylamine (4.46 mL, 32.0

mmol), and was stirred at room temperature for 24 h under argon. Additional anhydrous triethylamine was added (1.0 mL, 7.2 mmol), and the suspension was stirred for an extra 1 h. The reaction was filtered through Celite, and flushed with ethyl acetate (300 mL total volume). The filtrate was then washed with water (3 x 40 mL), the aqueous layers were combined, and extracted with ethyl acetate (40 mL). The organic layers were combined, dried over anhydrous sodium sulphate, and concentrated *in vacuo* to yield a crude oil, which was then dissolved in diethyl ether (150 mL), and filtered. The filtrate was concentrated under vacuum, the resulting oil was then dissolved in 40-60 petroleum spirit (150 mL), and the precipitate formed was filtered out. The solid residue was washed with 40-60 petroleum spirit (3 x 100 mL), and dried to give *N*-tosyl protected dimethylaspartate as a white solid (5.176 g), which was used without any further purification.

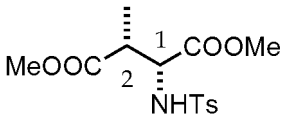
A fraction of the crude dimethylaspartate (787 mg) was dissolved in anhydrous tetrahydrofuran (8 mL). The solution was cooled down to -78 °C, and was treated by the slow addition of KHMDS (11 mL, 1.0 M in THF, 11 mmol). After stirring the mixture for 1.5 h at -78 °C, iodomethane (190 µL, 3.05 mmol) was added through a pad of basic alumina. The reaction was allowed to slowly warm up to room temperature, and was stirred for 14 h under argon. The mixture was quenched by the addition of a 1.0 M aq. solution of HCl to pH 3 and was then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and were concentrated under vacuum. Purification of the resulting crude oil (816 mg) by flash column chromatography (silica gel, 20-50% ethyl actetate in 40-60 petroleum spirit) provided the pure methylated dimethylaspartates ***trans*-179** and ***syn*-179** as a very viscous, clear and colourless oil (368 mg, 45%). The aspartates ***trans*-179** and ***syn*-179** were isolated as a 3:1 mixture of two inseparable *syn*- and *anti*-diastereoisomers.



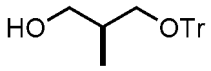
^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (3H, s, $ArCH_3$), 2.84 (1H, dd, *J* = 17.1, 4.9 Hz, 2-CH), 2.96 (1H, dd, *J* = 17.1, 4.3 Hz, 2-CH'), 3.59 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 4.14 (1H, dt, *J* = 8.1, 4.6 Hz, 1-CH), 5.65 (1H, d, *J* = 8.0 Hz, NH), 7.30 (2H, d, *J* = 8.0 Hz, ArH_{meta}), 7.74 (2H, d, *J* = 8.3 Hz, ArH_{ortho}). The data was in full agreement with the one reported in the literature.[155]



***trans*-179.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.26 (3H, d, *J* = 7.2 Hz, 2-CCH_3), 2.41 (3H, s, $ArCH_3$), 3.14 (1H, dq, *J* = 7.3, 3.1 Hz, 2-CH), 3.48 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 4.08 (1H, dd, *J* = 9.5, 4.1 Hz, 1-CH), 5.60 (1H, d, *J* = 9.5 Hz, NH), 7.29 (2H, d, *J* = 8.0 Hz, ArH_{meta}), 7.73 (2H, d, *J* = 8.3 Hz, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.5 (2-CCH_3), 21.5 ($ArCH_3$), 42.2 (2-CH), 52.1 (OCH_3), 52.6 (OCH_3), 57.7 (1-CH), 127.2 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 136.8 (ArC_{IVpara}), 143.5 (ArC_{IVipso}), 170.2 (C=O), 173.4 (C=O). The data was in full agreement with the one previously reported in the literature.[126]

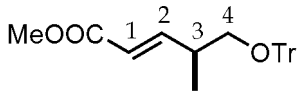


***syn*-179.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.18 (3H, d, *J* = 7.2 Hz, CH_3), 2.41 (3H, s, $ArCH_3$), 3.14 (1H, qd, *J* = 7.2, 4.9 Hz, 2-CH), 3.52 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 4.24 (1H, dd, *J* = 9.6, 4.9 Hz, 1-CH), 5.52 (1H, d, *J* = 9.6 Hz, NH), 7.29 (2H, d, *J* = 8.0 Hz, ArH_{meta}), 7.72 (2H, d, *J* = 8.0 Hz, ArH_{ortho}); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 (2-CCH_3), 21.5 ($ArCH_3$), 42.7 (2-CH), 52.1 (OCH_3), 52.7 (OCH_3), 57.4 (1-CH), 127.2 ($ArCH_{ortho}$), 129.5 ($ArCH_{meta}$), 136.5 (ArC_{IVpara}), 143.6 (ArC_{IVipso}), 170.3 (C=O), 172.5 (C=O); IR (thin film) ν_{max} = 3277, 3029, 2987, 2954, 2882, 1736, 1598, 1438, 1341, 1266, 1210, 1163, 1092, 1092, 1019, 816, 664 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 330.1006, calculated for $C_{14}H_{20}NO_6S$ 330.1011.



(*2S*)-3-Trityloxy-2-methylpropan-1-ol, 187. A solution of crude ester **120** (36.5 g, P = 69%, 70.2 mmol) in anhydrous diethyl ether (1100 mL), cooled down to -30 °C was cautiously treated with small portions of solid lithium aluminium hydride (6.09 g, 16.0 mmol). The reaction was then allowed to warm up to room temperature, and the mixture was stirred overnight. The mixture was quenched slowly and carefully by the addition of water (6 mL), followed by a solution of sodium hydroxide (15%wt, 6 mL). More water (18 mL) was then incorporated, and the mixture was stirred until a white precipitate formed. The mixture was filtered through Celite, and the solid was washed with ethyl acetate (1000 mL) until no product remained in the solid as indicated by TLC analysis. The organic filtrate was then dried over anhydrous sodium sulfate, and the solvents were evaporated under reduced pressure. Evaporation under high vacuum afforded the crude alcohol **187** as an extremely viscous yellowish oil (37.5 g) that have a tendancy to crystallise. Purification by flash column chromatography (silica gel, 1% TEA, 20% ethyl acetate, 10%

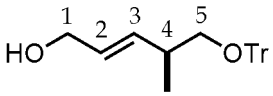
dichloromethane in 40-60 petroleum ether) provided alcohol **187** as an extremely viscous and yellowish clear oil (22.7 g, 97%), which can crystallize as a white powder after prolonged storage under high vacuum. Note: commercially available solutions of $LiAlH_4$ in diethyl ether can also be used with comparable yields (91%). The spectroscopic data was in full agreement with the one reported in the literature.[144] $[\alpha]^{26}_D$ -32.7, (c = 1.0, $CHCl_3$).



***(2E,4S)*-Methyl 5-trityloxy-4-methylpent-2-enoate, 188.** A -78 °C solution of oxalyl chloride (414 µL, 4.89 mmol) in anhydrous dichloromethane (10 mL) was treated by the slow addition of anhydrous dimethylsulfoxide (845 µL, 11.9 mmol), and the mixture was stirred for 45 min under argon. A previously prepared solution of alcohol **187** (797 mg, 2.40 mmol) in dry dichloromethane (5 mL) was then added slowly at -78 °C and the resulting mixture was stirred for 1 h at –78 °C. The reaction was treated with anhydrous triethylamine (1.50 mL, 10.88 mmol), and the solution was stirred for a further 45 min at -78 °C. The reaction was then poured into a separation funnel containing acidic water (20 mL H_2O + 7 mL 1.0 M HCl). The layers were separated, and the organic fraction was washed with water (50 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated under vacuum to afford a very sticky yellowish oil (1.06 g), which was shown to be clean by ^1H NMR, and was used immediately without any further purification.

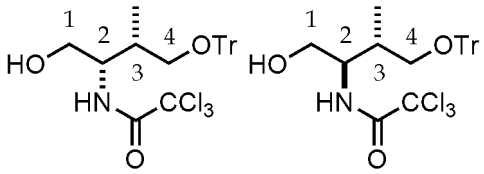
The crude was dissolved in dry dichloromethane (50 mL, regular dichloromethane was preferred when the reaction was carried out in larger scale), and Methyl(triphenylphosphoranylidene) (1.76 g, 5.26 mmol) was then added. The resulting mixture was refluxed under argon for 3 days before being cooled down to room temperature and worked up by the addition of enough 40-60 petroleum ether to force the triphenylphosphine oxide to precipitate out. The solid was discarded after filtration, and the process was repeated until no further triphenylphosphine oxide could be forced out of solution. Subsequent evaporation of the organic filtrates provided a very sticky orange oil (930 mg), which could be used without any further purification in the next step. Purification by flash column chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40-60 petroleum ether) yielded an analytically pure sample of the methyl ester **188** (835 mg,

90% over two steps) as an extremely viscous colourless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.8 Hz, 3-CCH_3), 2.58 (1H, appsept, *J* = 6.8 Hz, 3-CH), 3.02 (1H, dd, *J* = 8.6, 6.3 Hz, 4-CH), 3.04 (1H, dd, *J* = 8.8, 6.7 Hz, 4-CH'), 3.69 (3H, s, OCH_3), 5.82 (1H, appdd, *J* = 15.8, 0.8 Hz, 1-CH), 6.92 (1H, dd, *J* = 15.8, 7.3 Hz, 2-CH), 7.17-7.41 (15H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 16.2 (3-CCH_3), 37.2 (3-CH), 51.4 (OCH_3), 67.1 (4-CH_2), 86.4 ($OCPh_3$), 120.4 (1-CH), 126.9 ($ArCH_{para}$), 127.7 ($ArCH_{ortho}$), 128.6 ($ArCH_{meta}$), 144.0 (ArC_{IV}), 151.9 (2-CH), 167.1 (C=O); $[\alpha]^{25}_D$ -3.4, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3087, 3059, 3023, 2963, 2952, 2915, 2872, 1720, 1658, 1598, 1491, 1448, 1437, 1275, 1218, 1196, 1180, 1153, 1072, 1033, 983, 765, 707, 632 cm^{-1}; HRMS (EI) observed M^+ 386.1886, calculated for $C_{26}H_{26}O_3$ 386.1882.



(*4S*,*2E*)-5-Trityloxy-4-methylpent-2-en-1-ol, 189. A 0 °C solution of ester **188** (17.15 g, 44.37 mmol) in anhydrous diethyl ether (1400 mL) was treated with the slow addition of Dibal-H (1.0 M in hexanes, 121 mL, 121 mmol). The resulting mixture was then immediately allowed to warm up slowly to room temperature where it was stirred under argon until completion as indicated by TLC analysis (2 h). The reaction was then quenched by the dropwise addition of water (100 mL), followed by aq. solution of HCl (1.0 M, 10 mL). Ethyl acetate (500 mL) was added to the mixture, and the two phases were separated. The organic layer was subsequently washed with water (300 mL), acidic water (250 mL of water + 50 mL of HCl 1.0 M), and finally with water (300 mL) one last time. The aqueous layers were then combined, and extracted with ethyl acetate (300 mL). The combined organic fractions were then dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to yield a crude sticky yellowish oil residue (15.22 g). This crude oil was purified by flash column chromatography (silica gel, 1% TEA, 20% ethyl acetate, 10% dichloromethane in 40-60 petroleum ether) to give the desired allylic alcohol **189** (12.41 g, 78%, *ee* = 99%) as a clear yellowish oil. The enantiomeric excess was determined through Chiral HPLC analysis with a Chiracel AD column using hexane:*iso*propanol (99:1) at a flow rate of 0.75 mL / min (retention time (*R*) 27.62 min; (*S*) 31.86 min). The allylic alcohol **189** can also be obtained in very good yield with minimal intermediate purification from methyl ester **186** (18.51 g, 78% from **188**, 71% from (*R*)-(-)-3-hydroxy-2-methylpropionate **186**). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.07 (3H, d, *J* = 6.8 Hz, CH_3), 1.26 (1H, bs, OH), 2.50 (1H, appsept, *J* = 6.4 Hz, 4-CH), 2.95 (1H, dd, *J* = 8.7, 6.7 Hz,

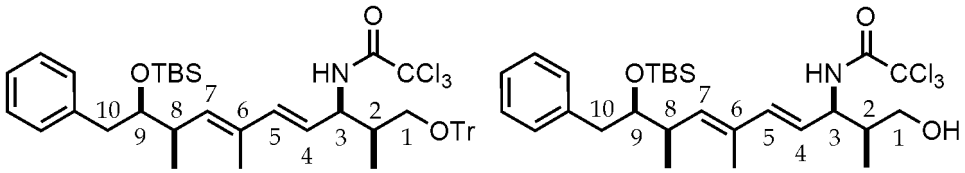
5-CH), 3.03 (1H, dd, *J* = 8.7, 6.4 Hz, 5-CH'), 4.09 (2H, bs, 1-CH_2), 5.65 (2H, m, 2-CH + 3-CH), 7.21-7.46 (15H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 17.1 (CH_3), 36.9 (3-CH), 63.7 (5-CH_2), 68.0 (1-CH_2), 86.2 ($OCPh_3$), 126.8 ($ArCH_{para}$), 127.6 ($ArCH_{ortho}$), 128.5 (2-CH), 128.7 ($ArCH_{meta}$), 135.6 (3-CH), 144.2 (ArC_{IV}); $[\alpha]^{23}_D$ +3.6, (c = 1.0, $CHCl_3$); 3580, 3375, 3087, 3059, 3022, 2961, 2952, 2913, 2870, 1597, 1491, 1448, 1218, 1071, 973, 753, 707, 633 cm^{-1}. Not detected through mass spectroscopy techniques.



2,2,2-Trichloro-*N*-((*2S,3S*)-1-hydroxy-3-methyl-4-(trityloxy)butan-2-yl)acetamide, 198 and 2,2,2-Trichloro-*N*-((*2R,3S*)-1-hydroxy-3-methyl-4-(trityloxy)butan-2-yl)acetamide 199. A stream of ozone was bubbled through a solution of (4:1) mixture of olefins **122** and **191** (161 mg, 320 µmol) in a mixture of ethanol (10 mL) and dichloromethane (2 mL) at -78 °C. After bubbling O_3 into the reaction mixture for 75 min at -78 °C, the light bluish solution was purged with argon until clean, and was then quenched with the slow and careful addition of sodium borohydride (40 mg, 1.06 mmol) at -78 °C. The reaction mixture was then allowed to warm up to room temperature overnight (20 h). The solvents were removed under reduced pressure and the white residual solid was dissolved in dichloromethane (30 mL). The resulting solution was washed with water (10 mL) and brine (10 mL), and the organic layer was dried over anhydrous sodium sulfate before being concentrated *in vacuo*. The crude mixture of alcohols **198** and **199**, obtained as a very viscous brownish oil (115 mg), was purified by flash column chromatography (silica gel, 1% TEA, 50% ethyl acetate in 40-60 petroleum ether) to afford the pure alcohols **198** and **199** in a (4:1) ratio, as an extremely viscous clear and colourless oil (50 mg, 31%).

198. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 7.2 Hz, CH_3), 2.15 (1H, m, 3-CH), 2.79 (1H, dd, *J* = 8.3, 4.4 Hz, OH), 3.13 (1H, dd, *J* = 10.1, 6.8 Hz, 4-CH), 3.17 (1H, dd, *J* = 10.1, 3.7 Hz, 4-CH'), 3.54 (1H, ddd, *J* = 11.8, 8.3, 3.5 Hz, 1-CH), 3.71 (1H, appdt, *J* = 11.8, 4.2 Hz, 1-CH'), 3.88 (1H, m, 2-CH), 7.10 (1H, bd, *J* = 8.2 Hz, NH), 7.24-7.46 (15H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.7 (CH_3), 35.1 (3-CH), 55.3 (2-CH), 61.7 (1-CH_2), 65.0 (4-CH_2), 66.5 (CPh_3), 87.7 (CCl_3), 127.3 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 128.5 ($ArCH_{meta}$), 143.2 (ArC_{IV}), 164.3 (C=O);

199. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.15 (3H, d, J = 7.1 Hz, CH_3), 2.15 (1H, m, 3-CH), 2.45 (1H, dd, J = 6.5, 7.4 Hz, OH), 3.20 (2H, m, 4-CH_2), 3.46 (1H, m, 1-CH), 3.56 (1H, mostly masked, 1-CH'), 3.94 (1H, m, 2-CH), 7.22 (1H, mostly masked d, NH), 7.24-7.46 (15H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.7 (CH_3), 34.4 (3-CH), 55.7 (2-CH), 63.7 (1-CH_2), 64.6 (4-CH_2), 66.5 (CPh_3), 87.6 (CCl_3), 127.3 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 128.5 ($ArCH_{meta}$), 143.3 (ArC_{IV}), 165.1 (C=O); IR (thin film) ν_{max} = 3396, 3303, 3088, 3060, 3017, 2969, 2927, 2882, 1677, 1525, 1491, 1448, 1218, 1067, 1034, 900, 811, 763, 747, 707, 633 cm^{-1}; Not detected by mass spectrometry.

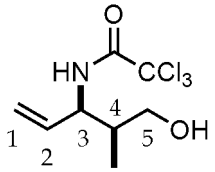


***N*-((2*S*,3*R*,4*E*,6*E*,8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-10-phenyl-1-(trityloxy)deca-4,6-dien-3-yl)-2,2,2-trichloroacetamide, 203 and *N*-((2*S*,3*R*,4*E*,6*E*,8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-2,6,8-trimethyl-10-phenyldeca-4,6-dien-3-yl)-2,2,2-trichloroacetamide, 204.** Second generation Grubbs catalyst (5 mg, 6 µmol, 12 mol%) was added to a solution of (3:1) isomeric mixture of TBS-protected dienol **(*E*)-139** and **(*Z*)-139** (16 mg, 48 µmol) and a (4:1) isomeric mixture of olefins **122** and **191** (49 mg, 97 µmol) in anhydrous dichloromethane (2 mL). The reaction mixture was refluxed for 1 h, and was then cooled down to room temperature. The solvent was evaporated under reduced pressure, and the resulting crude oil (70 mg) was then purified by flash column chromatography (silica gel, 1% TEA, 20% dichloromethane in 40-60 petroleum spirit). Purification enabled the isolation of the unclean heterodimer **203** (32 mg) as the major diastereoisomer of a complex isomeric mixture plus the unconsumed starting trichloroacetimidates **122** and **191**. A second purification by flash column chromatography (silica gel, 1% TEA, 100% chloroform) degraded the expected trichloroacetimidate **203** to the unexpected free alcohol **204**, which was obtained as a very viscous brownish oil (4 mg, 15%). As the reaction afforded a complex mixture of diastereoisomers, only the major isomers **203** and **204** are reported.

203. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.27 (3H, s, $SiCH_3$), -0.07 (3H, s, $SiCH_3$), 0.80 (3H, d, J = 7.1 Hz, 2-CCH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, J = 6.8 Hz, 8-CCH_3), 1.38 (3H, d, J = 0.9 Hz, 6-CCH_3), 2.20 (1H, m, 2-CH), 2.45 (1H, m, 8-CH), 2.67 (1H, dd, J = 13.9, 6.3 Hz, 10-CH), 2.78 (1H, dd, J = 13.6, 6.2 Hz, 10-CH'), 3.02 (1H, appt, J = 9.7 Hz, 1-CH), 3.23 (1H, dd, J =

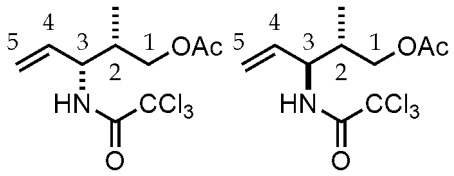
9.7, 3.9 Hz, 1-CH'), 3.74 (1H, m, 9-CH), 4.44 (1H, td, *J* = 8.0, 2.6 Hz, 3-CH), 5.11 (1H, dd, *J* = 15.6, 7.1 Hz, 4-CH), 5.36 (1H, d, *J* = 9.5 Hz, 7-CH), 6.10 (1H, d, *J* = 15.6 Hz, 5-CH), 7.24-7.44 (20H, d, *J* = 7.4 Hz, ArH), 7.78 (1H, d, *J* = 8.4 Hz, NH); LRMS (FAB) observed M+ 804. No further characterisation could be collected, as the compound **203** degraded to **204**.

204. ^{1}H NMR (400MHz, $CDCl_3$) δ -0.24 (3H, s, $SiCH_3$), -0.04 (3H, s, $SiCH_3$), 0.85 (3H, partially masked d, 2-CCH_3), 0.87 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* = 6.8 Hz, 8-CCH_3), 1.55 (3H, s, 6-CCH_3), 2.16 (1H, m, 2-CH), 2.27 (1H, m, OH), 2.48 (1H, m, 8-CH), 2.70 (1H, dd, *J* = 14.2, 6.4 Hz, 10-CH), 2.80 (1H, dd, *J* = 13.5, 6.3 Hz, 10-CH'), 3.52 (1H, m, 1-CH), 3.63 (1H, m, 1-CH'), 3.77 (1H, appdd, *J* = 10.6, 5.9 Hz, 9-CH), 4.65 (1H, m, 3-CH), 5.45 (2H, m, 4-CH + 7-CH), 6.22 (1H, d, *J* = 15.7 Hz, 5-CH), 7.10-7.32 (5H, m, ArH), 7.74 (1H, bd, *J* = 8.3 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ -4.8 ($SiCH_3$), -4.5($SiCH_3$), 12.4 (2-CCH_3), 12.6 (6-CCH_3), 14.9 (8-CCH_3), 18.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 37.0 (8-CH), 39.4 (2-CH), 41.7 (10-CH_2), 55.3 (3-CH), 65.2 (1-CH_2), 77.2 (9-CH partially masked by $CHCl_3$ peaks), (CCl_3 unresolved), 121.3 (4-CH), 126.0 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.7 ($ArCH_{meta}$), 131.4 (6-C_{IV}), 137.9 (5-CH), 138.1 (7-CH), 139.0 (ArC_{IV}), 161.6 (C=O); IR (thin film) ν_{max} = 3456, 3426, 3326, 3028, 2957, 2929, 2882, 2856, 16700, 1513, 1471, 1461, 1377, 1363, 1254, 1099, 1083, 909, 825, 735 cm^{-1}; Not detected by mass spectrometry.



2,2,2-Trichloro-*N*-((*3R,4S*)-5-hydroxy-4-methylpent-1-en-3-yl)acetamide, 205. A solution of trytil-protected alcohol **122** (545 mg, 1.08 mmol) in dichloromethane (5 mL) was treated with the slow addition of a commercially available solution of HCl in anhydrous diethyl ether (1.0 M, 2.0 mL, 2.0 mmol) at room temperature. The reaction was stirred for 1 h, and was then concentrated under vacuum without any prior work up. The crude viscous oil (550 mg) was purified by flash column chromatography (silica gel, elution gradient 5-10% ethyl acetate in 40-60 petroleum ether) to give the desired alcohol **205** (281 mg, 100%) as a very viscous, clear and colourless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 7.1 Hz, CH_3), 2.18 (1H, m, 4-CH), 2.28 (1H, dd, *J* = 5.5, 4.7 Hz, OH), 3.53 (1H, apptd, *J* = 10.6, 4.6 Hz, 5-CH), 3.65 (1H, m, 5-CH'), 4.62 (1H, m, 3-CH), 5.28 (1H, dm, *J* = 17.2 Hz, 1-CH), 5.28 (1H, dm, *J* = 10.6 Hz, 1-CH'), 5.86 (1H, ddd, *J* = 17.1, 10.7, 5.4 Hz, 2-CH), 7.80 (1H, bs, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 (CH_3), 38.6 (4-CH), 55.7 (3-CH), 65.1 (5-CH_2), 92.8 (CCl_3),

117.3 (1-CH_2), 133.4 (2-CH), 161.8 (C=O); $[\alpha]^{24}_D$ +15.6, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3468, 3427, 3321, 3085, 3017, 2966, 2934, 2882, 1698, 1644, 1516, 1241, 1036, 994, 928, 823, 757, 735, 683, 666 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 260.0007, calculated for $C_8H_{13}O_2NCl_3$ 260.0012.

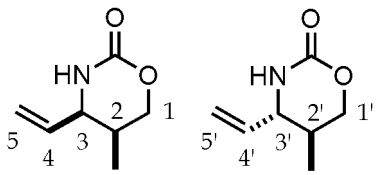


(*2S,3R*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enyl acetate, 207 and (*2S,3S*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enyl acetate, 208. A solution of a (2.5:1) isomeric mixture of trityl-protected alkenols **122** and **191** (589 mg, 1.17 mmol) in anhydrous dichloromethane (5 mL) was treated with a freshly made sat. solution of HCl in ethyl acetate (2.0 mL). After 10 min of stirring at room temperature, an additional portion of HCl was added (2.0 mL), followed by a third one (2.0 mL) 10 min later. After a further 20 min of stirring at room temperature, the solvents were evaporated under reduced pressure, and the resulting crude oil (630 mg) was purified by two consecutive flash chromatography columns (silica gel, 10% ethyl acetate in 40-60 petroleum spirit). The (2.5:1) isomeric mixture of alcohols **205** and **206** were isolated as an extremely viscous clear and colourless oil (142 mg, 47%) as well as the undesired acetates **207** and **208** as a very viscous colourless oil (29 mg, 8%).

207. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.01 (3H, d, *J* = 7.1 Hz, 2-CCH_3), 2.09 (3H, s, $OOCCH_3$), 2.23 (1H, m, 2-CH), 3.96 (1H, dd, *J* = 11.4, 8.6 Hz, 1-CH), 4.09 (1H, dd, *J* = 11.4, 4.9 Hz, 1-CH'), 4.56 (1H, m, 3-CH), 5.28 (1H, ddd, *J* = 17.0, 1.6, 0.9 Hz, 5-CH), 5.30 (1H, ddd, *J* = 10.6, 1.5, 0.9 Hz, 5-CH'), 5.80 (1H, ddd, *J* = 17.1, 10.6, 5.6 Hz, 4-CH), 7.13 (1H, vbd, *J* = 6.4 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.1 (2-*C*CH_3), 20.9 ($OOCCH_3$), 36.1 (2-CH), 55.6 (3-CH), 66.0 (1-CH_2), 92.9 (CCl_3), 117.7 (5-CH_2), 133.0 (4-CH), 161.1 (Cl_3CC=O), 170.5 (OC=O);

208. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 7.1 Hz, 2-CCH_3), 2.08 (3H, s, $OOCCH_3$), 2.23 (1H, m, 2-CH), 4.04 (1H, dd, *J* = 11.5, 4.2 Hz, 1-CH), 4.20 (1H, dd, *J* = 11.5, 5.7 Hz, 1-CH'), 4.56 (1H, m, 3-CH), 5.23 (1H, ddd, *J* = 3.7, 1.7, 0.8 Hz, 5-CH), 5.27 (1H, m, mostly masked, 5-CH'), 5.81 (1H, ddd, *J* = partially masked, 10.4, 5.2 Hz, 4-CH), (NH not observed); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.1 (2-*C*CH_3), 20.9 ($OOCCH_3$), 36.2 (2-CH), 56.0 (3-CH), 65.7 (1-CH_2), 92.9 (CCl_3), 116.7 (5-CH_2), 134.7 (4-CH), 161.6 (Cl_3CC=O), 170.8

(OC=O); IR (thin film) ν_{max} = 3415, 3338, 3085, 2970, 2935, 1714, 1517, 1240, 1038, 835, 822, 682 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 302.0110, calculated for $C_{10}H_{15}O_3NCl_3$ 302.0118.



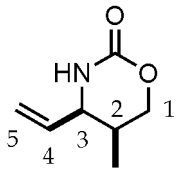
(4*R*,5*S*)-5-Methyl-4-vinyl-1,3-oxazinan-2-one, *syn*-209 and (4*S*,5*S*)-5-Methyl-4-vinyl-1,3-oxazinan-2-one, *trans*-213. A flask open to the air, containing a (3:1) mixture of trichloroacetimidate **122** and **191** (4.63 g, 9.21 mmol) in solution in *iso*-propanol (55 mL), was treated with potassium hydroxide (4.28 g, 107 mmol). The reaction was then refluxed, causing it to turn green then milky / turbid after 30 min. After being stirred for 2 h under reflux to the open air, an additional portion of potassium hydroxide (2.0 g, 50 mmol) was poured into the flask. The reaction was refluxed for an extra 2 h before being concentrated under reduced pressure. The resulting residue was then diluted in water (90 mL), and the phases were separated. The aqueous layer was then extracted with dichloromethane (200 mL), then ethyl acetate (200 mL), and the organic phases were combined, before being dried over anhydrous sodium sulphate, and concentrated *in vacuo*. The resulting crude amines ***syn*-211** and ***trans*-211** (3.05 g) were obtained as a sticky brownish oil, which was used in the next reaction step without any further purification.

A solution of a (3:1) mixture of trityl-protected aminoalcohols ***syn*-211** and ***trans*-211** (3.05 g) in ethanol (200 mL) was treated with *p*-toluenesulfonic acid monohydrate (3.61 g, 19.0 mmol) at room temperature and open to the air. The reaction was stirred overnight, and was then quenched by incorporating potassium hydroxide (1.65 g, 41.3 mmol) to the mixture. A precipitate of *p*-toluenesulfonic acid potassium salt was formed and separated out by filtration. The precipitate was washed thoroughly with ethyl acetate (200 mL), and the filtrate was concentrated under reduced pressure (< 45 °C) to give the crude volatile aminoalcohols ***syn*-210** and ***trans*-210** as a very sticky brown oil (4.53 g). The residue was subjected to a quick filtration through a short pad of silica gel, monitored by TLC analysis of the effluent. The silica gel was first flushed with 40-60 petroleum spirit to remove the trityl derivatives then with ethyl acetate and methanol to retrieve the free aminoalcohols ***syn*-210** and ***trans*-210**. This process provided, after evaporation of the solvents *in vacuo*, the crude mixture of free aminoalcohols ***syn*-210** and ***trans*-210** in a (3:1) ratio, as a yellowish oil (1.90 g), which was used without any further purification.

The (3:1) mixture of aminoalcohols ***syn*-210** and ***trans*-210** (1.90 g, 3:1) was dissolved in anhydrous dichloromethane (300 mL), and was transferred into a round-bottomed-flask containing pre-activated 4Å molecular sieves (7 g). DBU (153 mg, 150 µL, 1.00 mmol) was incorporated to the solution at room temperature, which was then treated with the slow addition of a pre-made solution of triphosgene (1.80 g, 6.07 mmol) in anhydrous dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 2 h and additional DBU (102 mg, 100 µL, 669 µmol) was added. The reaction was stirred for an extra 30 min and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethyl acetate (200 mL), and the organic solution was then washed with a basic sat. aq. solution of sodium chloride (2 x 100 mL + 1.0 g, 25 mmol KOH each). The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude carbamates ***syn*-209** and ***trans*-209** as a brown slightly viscous oil (1.78 g). Purification by flash column chromatography (silica gel, 1% TEA, 80-100% ethyl acetate in 40-60 petroleum spirit) yielded a (3:1) mixture of carbamates ***syn*-209** and ***trans*-209** as a light brown very viscous oil (274 mg, 21% over 3 steps).

***syn*-209.** ^{1}H NMR (400MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.8 Hz, CH_3), 1.80 (1H, m, 2-CH), 3.48 (1H, appt, *J* = 7.9 Hz, 3-CH), 3.85 (1H, dd, *J* = 10.9, 9.9 Hz, 1-CH), 4.15 (1H, dd, *J* = 11.0, 3.8 Hz, 1-CH'), 5.64 (1H, ddd, *J* = 17.3, 10.1, 7.4 Hz, 4-CH), 6.28 (1H, bs, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.8 (2-CCH_3), 31.2 (2-CH), 60.3 (3-CH), 70.4 (1-CH_2), 118.7 (5-CH_2), 136.5 (4-CH), 154.0 (C=O);

***trans*-209.** ^{1}H NMR (400MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 7.1 Hz, CH_3'), 2.24 (1H, m, 2'-CH), 3.93 (1H, dd, *J* = 10.9, 8.8 Hz, 1'-CH), 3.96 (1H, completely hidden m, 3'-CH), 4.06 (1H, ddd, *J* = 10.9, 3.6, 0.9 Hz, 1'-CH"), 5.74 (1H, ddd, *J* = 17.6, 9.9, 6.1 Hz, 4'-CH), 6.52 (1H, bs, NH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 11.3 (2'-CCH_3), 29.5 (2'-CH), 56.0 (3'-CH), 69.1 (1'-CH_2), 118.3 (5'-CH_2), 134.3 (4'-CH), 154.0 (C=O); IR (thin film) ν_{max} = 3378, 3257, 3122, 3092, 3062, 2973, 2933, 1705, 1478, 1438, 1270, 1180, 1144, 1119, 1069, 925, 733, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 142.0864, calculated for $C_7H_{12}O_2N$ 142.0868.



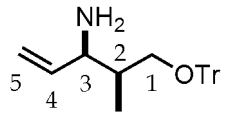
(4*R*,5*S*)-5-Methyl-4-vinyl-1,3-oxazinan-2-one, 209. A solution of trichloroacetimidate **122** (519 mg, 1.03 mmol) in *iso*-propanol (6 mL), in an open-air flask, was treated by addition of

potassium hydroxide (480 mg, 12.0 mmol). The reaction was then refluxed, initially turned orange, and became milky and turbid after 30 min. After stirring the reaction for 3 h under reflux whilst open to the air, the mixture was concentrated under reduced pressure. The resulting residue was then diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic phases were combined, dried over anhydrous sodium sulphate, and concentrated *in vacuo*. The resulting crude amine **211** (399 mg) was obtained as a sticky dark yellow oil, which was split in two, and a portion of it was used into the next reaction without any further purification.

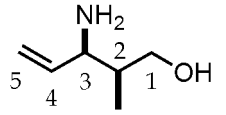
To a solution of crude trityl protected aminoalcohol **211** (136 mg) in ethanol (20 mL) was added *p*-toluenesulfonic acid monohydrate (250 mg, 1.31 mmol) at room temperature and open to the air. The reaction was stirred overnight, and was quenched by incorporating potassium hydroxide (1.0 g, 25 mmol) to the mixture. A precipitate of *p*-toluenesulfonic acid potassium salt was formed, and removed by filtration. The solution was mixed with a sat. aq. solution of sodium chloride (10 mL), and the mixture was thoroughly extracted with ethyl acetate (3 x 20 mL) and dichloromethane (20 mL). The organic extracts were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resulting volatile crude aminoalcohol **210** was obtained as a very sticky brown oil (175 mg) contaminated with *p*-toluenesulfonic acid. The residue was then subjected to a quick filtration through a short pad of silica, monitored by TLC analysis of the effluent. The silica was first flushed with 40-60 petroleum spirit, then with ethyl acetate and finally with methanol to retrieve the aminoalcohol **210**. This process provided, after evaporation of the solvents *in vacuo*, the crude aminoalcohol **210** as a yellowish oil (133 mg), which was used without any further purification.

A solution of crude aminoalcohol **210** (133 mg) in anhydrous dichloromethane (20 mL) was transferred into a round-bottomed-flask containing pre-activated 4Å molecular sieves (1 g) under argon. DBU (10 mg, 10 µL, 66 µmol) was incorporated to the solution at room temperature, and the reaction was treated with the slow addition of a pre-made solution of triphosgene (126 mg, 425 µmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at room temperature for 2 h, the solvent was then evaporated under reduced pressure and the crude residue was dissolved in ethyl acetate (20 mL). The organic solution was then washed with a basic sat. aq. solution of sodium chloride (2 x 10 mL + 0.1 g, 25.0 mmol KOH each). The phases were separated and the organic layer was dried over anhydrous sodium sulphate, and concentrated *in vacuo* to give the crude carbamate **209** as a brown slightly viscous oil (120 mg). Purification by flash column chromatography (silica

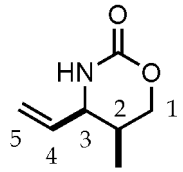
gel, 1% TEA, 80-100% ethyl acetate in 40-60 petroleum spirit) yielded the pure carbamate **209** as a light brown very viscous oil (82 mg, 18% over 3 steps).



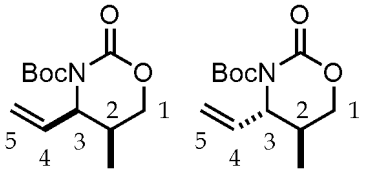
211. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.75 (3H, d, J = 6.9 Hz, CH_3), 1.28 (2H, vbs, NH_2), 1.81 (1H, m, 2-CH), 2.96 (2H, m, 1-CH_2), 3.44 (1H, m, 3-CH), 4.89 (1H, dd, J = 10.4, 0.9 Hz, 5-CH), 4.98 (1H, dd, J = 16.3, 0.9 Hz, 5-CH'), 5.64 (1H, ddd, J = 16.7, 10.4, 6.0 Hz, 4-CH), 7.12 (3H, m, ArH_{para}), 7.19 (6H, m, ArH_{ortho}), 7.36 (6H, m, ArH_{meta}); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.0 (CH_3), 38.8 (2-CH), 55.4 (3-CH), 65.7 (1-CH_2), 86.4 ($OCPh_3$), 113.7 (5-CH_2), 126.8 ($ArCH_{para}$), 127.6 ($ArCH_{ortho}$), 128.6 ($ArCH_{meta}$), 141.5 (4-CH), 144.1 (ArC_{IV}).



210. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.84 (3H, d, J = 7.1 Hz, CH_3), 1.89 (1H, m, 2-CH), 2.27 (3H, vbs, NH_2 + OH), 3.61-3.68 (3H, m, 3-CH + 1-CH_2), 5.16 (1H, bdt, J = 6.3, 1.1 Hz, 5-CH_2), 5.19 (1H, appd, J = 1.1 Hz, 5-CH'), 5.93 (1H, m, 4-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 11.7 (CH_3), 38.6 (2-CH), 58.5 (3-CH), 67.4 (1-CH_2), 115.0 (5-CH_2), 139.6 (4-CH).



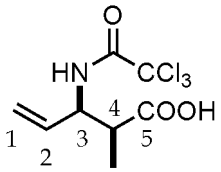
209. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.8 Hz, CH_3), 1.87 (1H, m, 2-CH), 3.53 (1H, appt, J = 8.1 Hz, 3-CH), 3.91 (1H, appt, J = 10.5 Hz, 1-CH), 4.21 (1H, dd, J = 11.0, 3.9 Hz, 1-CH'), 5.27 (1H, d, J = 3.3 Hz, 5-CH), 5.31 (1H, d, J = 10.2 Hz, 5-CH'), 5.51 (1H, bs, NH), 5.69 (1H, ddd, J = 17.3, 10.1, 7.5 Hz, 4-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.9 (CH_3), 31.4 (2-CH), 60.7 (3-CH), 70.6 (1-CH), 119.1 (5-CH_2), 136.7 (4-CH), 153.7 (C=O); $[\alpha]^{24}_{D}$ -21.2, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3378, 3257, 3122, 3092, 3062, 2973, 2933, 1705, 1478, 1438, 1270, 1180, 1144, 1119, 1069, 925, 733, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 142.0864, calculated for $C_7H_{11}NO_2$ 142.0852.



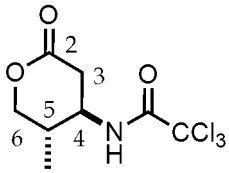
(4*R*,5*S*)-*tert*-Butyl 5-methyl-2-oxo-4-vinyl-1,3-oxazinane-3-carboxylate, *syn*-213 and (4*S*,5*S*)-*tert*-Butyl 5-methyl-2-oxo-4-vinyl-1,3-oxazinane-3-carboxylate, *trans*-213. To a solution of a (3:1) isomeric mixture of free carbamate ***syn*-209** and ***trans*-209** (54 mg, 380 µmol) in anhydrous dichloromethane (6 mL) was added sequentially anhydrous triethylamine (36 mg, 50 µL, 360 µmol), DMAP (45 mg, 370 µmol) and a pre-made solution of di-*tert*-butyl dicarbonate (87 mg, 400 µmol) in dry dichloromethane (3 mL). The mixture was left under stirring overnight, and was quenched by addition of water (5 mL). The phases were separated, and the organic layer was washed two more times with water (2 x 5 mL). The aqueous layers were combined, and extracted with diethyl ether (10 mL). All organic fractions were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting very viscous light brown oil (136 mg) was finally purified by flash column chromatography (silica gel, 1% TEA, 10-50% ethyl acetate in 40-60 petroleum ether) to afford the pure (3:1) isomeric mixture of *N*-Boc protected carbamates ***syn*-209** and ***trans*-209** as a slightly viscous and clear light yellow oil (75 mg, 81%).

***syn*-209.** ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 7.0 Hz, 2-CCH_3), 1.50 (9H, s, $OC(CH_3)_3$), 2.41 (1H, m, 2-CH), 3.98 (1H, appt, *J* = 11.3 Hz, 1-CH), 4.10 (1H, ddd, *J* = 10.8, 4.7, 1.6 Hz, 1-CH'), 4.69 (1H, bappt, *J* = 5.0 Hz, 3-CH), 5.29 (1H, d, *J* = 16.8 Hz, 5-CH), 5.38 (1H, d, *J* = 10.5 Hz, 5-CH'), 5.80 (1H, ddd, *J* = 16.9, 10.5, 6.2 Hz, 4-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.2 (CH_3), 27.8 ($OC(CH_3)_3$, 30.6 (2-CH), 59.8 (3-CH), 69.0 (1-CH_2), 83.7 (OC^tBu), 119.4 (5-CH_2), 131.7 (4-CH), 148.9 (C=O Boc), 151.5 (C=O).

***trans*-209.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.17 (3H, d, *J* = 7.0 Hz, 2-CCH_3), 1.50 (9H, s, $OC(CH_3)_3$), 2.04 (1H, m, 2-CH), 3.92 (1H, ddd, *J* = 10.7, 5.7, 0.6 Hz, 1-CH), 4.26 (1H, dd, *J* = 10.8, 3.5 Hz, 1-CH'), 4.37 (1H, bappt, *J* = 4.7 Hz, 3-CH), 5.22 (1H, d, *J* = 16.5 Hz, 5-CH), 5.38 (1H, d, *J* = 10.6 Hz, 5-CH'), 5.79 (1H, ddd, *J* = 16.8, 10.6, 6.2 Hz, 4-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.1 (CH_3), 27.8 ($OC(CH_3)_3$, 32.3 (2-CH), 62.4 (3-CH), 68.9 (1-CH_2), 83.7 (OC^tBu), 116.6 (5-CH_2), 136.6 (4-CH), 148.9 (C=O Boc), 151.9 (C=O); IR (thin film) ν_{max} = 3088, 2980, 2935, 1788, 1737, 1472, 1458, 1409, 1367, 1289, 1255, 1154, 1116, 1015, 918, 853, 775 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 242.1389, calculated for $C_{12}H_{20}O_4N$ 242.1392.

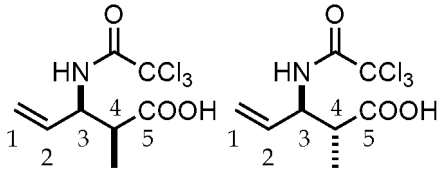


(2*S*,3*R*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enoic acid, 215. A solution of methyl ester **221** (170 mg, 590 µmol) in tetrahydrofuran (3.1 mL) was treated with an aq. solution of lithium hydroxide (1.0 M, 4.3 mL) at room temperature. After 1 h under stirring, the reaction was quenched by addition of an aq. solution of HCl (5.7 mL, 1.0 M, 5.7 mmol). Phases were separated, and the aqueous layer was extracted with ethyl acetate (10 mL). The organic fractions were combined, and dried over anhydrous magnesium sulfate. The solvents were evaporated under reduced pressure, and the crude viscous orange oil (156 mg) was purified by flash column chromatography (silica gel, 30-50% ethyl acetate in 40-60 petroleum spirit). The pure carboxylic acid **215** was obtained as a single diastereoisomer, and as an extremely viscous and clear orange oil (147 mg, 91%), that tends to form white crystals upon prolonged storage. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23 (3H, d, J = 7.3 Hz, CH_3), 2.87 (1H, qd, J = 7.2, 4.8 Hz, 4-CH), 4.54 (1H, m, 3-CH), 5.27 (1H, appdt, J = 10.3, 0.9 Hz, 1-CH), 5.30 (1H, appdt, J = 17.1, 1.0 Hz, 1-CH'), 5.80 (1H, ddd, J = 17.0, 10.4, 6.6 Hz, 2-CH), 7.72 (1H, bd, J = 8.9 Hz, NH), 9.40 (1H, vbs, OH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.3 (CH_3), 42.4 (4-CH), 55.3 (3-CH), 92.4 (CCl_3), 119.2 (1-CH_2), 131.9 (2-CH), 161.2 (Cl_3CC=O), 178.4 (5-C=O); $[\alpha]^{24}_D$ +29.2, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3411, 3344, 3201, 3088, 3021, 2986, 2927, 2855, 2651, 2552, 1709, 1510, 1265, 1216, 823, 755, 668 cm^{-1}. HRMS (CI) observed $(M+H)^+$ 273.9794, calculated for $C_8H_{11}O_3NCl_3$ 273.9805.



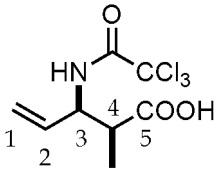
2,2,2-Trichloro-*N*-((4*R*,5*S*)-5-methyl-2-oxotetrahydro-2H-pyran-4-yl)acetamide, 216. A solution of trityl-protected alcohol **122** (1.11 g, 2.20 mmol) in acetone (40 mL) and dichloromethane (40 mL) was cooled down to 0 °C and treated by the dropwise addition of a previously made solution of Jones's reagent (1.3 mL H_2O + 2 mL $H_2SO_{4\ conc.}$ + 330 mg, 3.30 mmol CrO_3). The reaction was slowly allowed to warm up to room temperature, and was stirred overnight. Filtration through a pad of Celite, followed by concentration of the filtrate *in vacuo* provided an aqueous solution, which was extracted with dichloromethane

(2 x 100 mL). The combined organic layers were in turn washed with a sat. aq. solution of sodium bicarbonate and the resulting aqueous fraction was acidified to pH = 2 by addition of an aq. solution of 2.0 M HCl. The acidic aqueous layer was then extracted with dichloromethane (2 x 100 mL). The organic fractions were combined, and dried over anhydrous magnesium sulfate. Evaporation of the solvents under reduced pressure afforded a crude oil (864 mg), which was purified twice by flash column chromatography (silica gel, 1% methanol, 0.5% acetic acid in dichloromethane) (silica gel, 0.5% acetic acid, 40% ethyl acetate in 40-60 petroleum spirit) to isolate the lactone **216** as a very viscous, clear, and colourless oil (20 mg, 3%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.09 (3H, d, J = 6.7 Hz, CH_3), 2.16 (1H, m, 5-CH), 2.56 (1H, dd, J = 17.8, 8.2 Hz, 3-CH), 3.06 (1H, dd, J = 17.8, 7.0 Hz, 3-CH'), 3.98 (1H, dd, J = 11.4, 10.7 Hz, 6-CH), 4.06 (1H, appqn, J = 8.4 Hz, 4-CH), 4.36 (1H, dd, J = 11.7, 4.6 Hz, 6-CH'), 6.94 (1H, bd, J = 6.6 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.5 (CH_3), 34.3 (5-CH), 35.4 (3-CH_2), 50.6 (4-CH), 71.7 (6-CH_2), 92.2 (CCl_3), 161.9 (CCl_3C=O), 169.2 (2-C=O); $[\alpha]^{24}_D$ -19.2, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3415, 3330, 3020, 2973, 2935, 1708, 1523, 1216, 1048, 756 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 273.9795, calculated for $C_8H_{11}O_3NCl_3$ 273.9805.

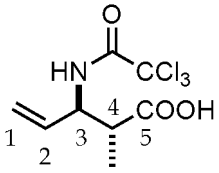


(*2R,3R*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enoic acid, 215 and (*2R,3R*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enoic acid, 220. A -78 °C solution of oxalyl chloride (113 µL, 1.34 mmol) in anhydrous dichloromethane (12 mL) was treated by the slow addition of anhydrous dimethylsulfoxide (191 µL, 2.69 mmol), and the resulting mixture was stirred at -78 °C for 45 min. A previously prepared solution of alcohol **205** (210 mg, 806 µmol) in dry dichloromethane (6 mL) was then slowly added and the reaction was stirred for a further 1 h at -78 °C. The reaction was treated with anhydrous triethylamine (521 µL, 3.74 mmol), and the reaction was allowed to warm up to room temperature and stirred for a further 1 h. The reaction was quenched by addition of water (10 mL), and the phases were separated. The organic layer was washed with water (2 x 10 mL) and the combined aqueous fractions were extracted with ethyl acetate (10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated under vacuum to afford the crude aldehyde (237 mg) as a viscous orange oil, and as a (5:3)

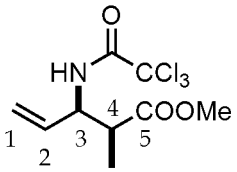
mixture of (*syn:anti*) diastereomers. The crude aldehyde was solubilised in *tert*-butanol (4.5 mL) and 2-methyl-2-butene (695 µL, 6.56 mmol) was added. This resulting solution was then treated slowly with a freshly made aq. solution of sodium chlorite (555 mg, 6.14 mmol) and sodium phosphate monobasic dehydrate (816 mg, 5.23 mmol) in water (2.2 mL total volume) at room temperature. The reaction mixture was stirred overnight at room temperature, and subsequently quenched by the dropwise addition of conc. HCl (200 µL). The acidic mixture was then extracted with ethyl acetate (3 x 15 mL) and dichloromethane (30 mL), and the combined organic extracts were dried over magnesium sulphate. The solvent was removed under reduced pressure to give the crude mixture of acids **215** and **220** (545 mg) as a viscous yellow oil. Purification by flash chromatography (silica gel, 20% ethyl acetate in 40-60 petroleum ether) afforded the carboxylic acids **215** and **220** (213 mg, 96%) as an inseparable mixture of diastereomers (*syn:anti*, 5:3) as a viscous, clear and colourless oil.



215. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.27 (3H, d, *J* = 7.3 Hz, CH_3), 2.85 (1H, m, 4-CH), 4.55 (1H, m, 3-CH), 5.33 (1H, appdt, *J* = 10.3, 0.9 Hz, 1-CH), 5.35 (1H, appdt, *J* = 17.1, 1.0 Hz, 1-CH'), 5.84 (1H, ddd, *J* = 17.0, 10.3, 6.6 Hz, 2-CH), 7.59 (1H, bd, *J* = 8.0 Hz, NH), 8.32 (1H, vbs, OH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.3 (CH_3), 42.5 (4-CH), 55.3 (3-CH), 92.6 (CCl_3), 119.4 (1-CH_2), 131.9 (2-CH), 161.2 (Cl_3CC=O), 178.8 (5-C=O); IR (thin film) ν_{max} = 3411, 3344, 3201, 3088, 3021, 2986, 2927, 2855, 2651, 2552, 1709, 1510, 1265, 1216, 823, 755, 668 cm^{-1}. HRMS (CI) observed $(M+H)^+$ 273.9794, calculated for $C_8H_{11}O_3NCl_3$ 273.9805.



220. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.35 (3H, d, *J* = 7.3 Hz, CH_3), 2.87 (1H, m, 4-CH), 4.56 (1H, m, 3-CH), 5.19 (1H, brdd, *J* = 10.5, 1.2 Hz, 1-CH), 5.24 (1H, dd, *J* = 15.9, 1.2 Hz, 1-CH'), 5.84 (1H, partially hidden m, 2-CH), 7.77 (1H, ddd, *J* = 15.9, 10.5, 5.3 Hz, NH), 8.32 (1H, vbs, OH); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.0 (CH_3), 42.6 (4-CH), 54.9 (3-CH), 91.9 (CCl_3), 117.5 (1-CH_2), 134.3 (2-CH), 161.9 (Cl_3CC=O), 180.0 (5-C=O).

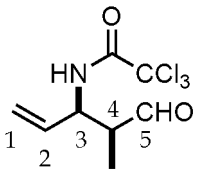


(*2S,3R*)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, 221. A -78 °C solution of oxalyl chloride (156 µL, 1.84 mmol) in anhydrous dichloromethane (3 mL) was treated with dimethylsulfoxide (317 µL, 4.46 mmol) and the mixture was stirred at -78 °C for 45 min. A previously prepared solution of alcohol **205** (235 mg, 902 µmol) in dry dichloromethane (2 mL) was then added slowly, and the resulting mixture was stirred at -78 °C for a further 1 h. The reaction was then treated slowly with anhydrous DIPEA (550 µL, 3.16 mmol), and the reaction was stirred for an extra 45 min at -78 °C. The reaction was then poured into an extraction funnel containing acidic water (8 ml H_2O + 2.6 mL 1.0 M HCl). The phases were separated, and the organic fraction was washed with water (20 mL) one more time. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the desired aldehyde intermediate as a viscous yellowish oil (311 mg).

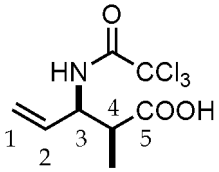
The crude aldehyde intermediate was dissolved in *tert*-butanol (5.0 mL) and 2-methyl-2-butene (773 µL, 7.30 mmol) was added to the solution. The mixture was then slowly treated with a freshly made aq. solution of sodium chlorite (621 mg, 6.87 mg) and sodium phosphate monobasic dehydrate (913 mg, 5.85 mmol) in water (2.5 mL) at room temperature. The reaction mixture was stirred until completion as indicated by TLC analysis (1 h) and was then quenched by the dropwise addition of conc. HCl (220 µL). Water (10 mL) was added to the solution, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic fractions were combined, and were dried over magnesium sulfate before being evaporated under reduced pressure to give the crude acid **215** (299 mg) as a very viscous yellow oil.

A 0°C 3.0 M aq. solution of sodium hydroxide (13 mL) topped up with diethyl ether (19 mL) was carefully treated by the addition of small portions of a suspension of *N*-methyl–*N'*-nitro-*N*-nitrosoguanidine (MNNG) (1.0 g in total, 50% in water, 3.4 mmol). After the bubbling has ceased (10 min), the yellow ethereal solution of diazomethane was transferred slowly and carefully using a polished glass pipette to a solution of the crude carboxylic acid **215** (299 mg) in diethyl ether (6 mL) at room temperature in an open air round bottom flask. The yellow solution was then stirred until completion as indicated by TLC analysis (30 min), and was subsequently quenched by the careful dropwise addition

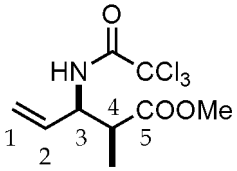
of acetic acid (150 µL, 2.62 mmol). After stirring the acidic mixture for 30 min, the solvent was evaporated under reduced pressure to give the crude methyl ester **221** (359 mg) as a viscous yellow oil. Purification by flash column chromatography (silica gel, elution gradient 0-10% ethyl acetate in 40-60 petroleum ether) provided the pure methyl ester **221** as a single diastereomer (180 mg, 69% over 3 steps), and as a colourless viscous oil.



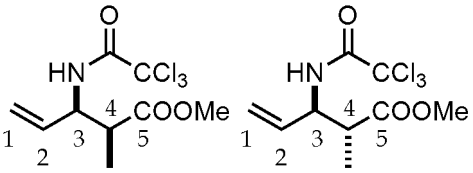
^{1}H NMR (400MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 7.5 Hz, CH_3), 2.78 (1H, qd, *J* = 7.4, 4.2 Hz, 4-CH), 4.65 (1H, m, 3-CH), 5.28 (2H, m, 1-CH_2), 5.82 (1H, ddd, *J* = 17.10, 10.3, 6.7 Hz, 2-CH), 7.41 (1H, bd, *J* = 8.9 Hz, NH), 9.66 (1H, s, CHO); ^{13}C NMR (100MHz, $CDCl_3$) δ 10.4 (CH_3), 48.9 (4-CH), 54.4 (3-CH), 92.4 (CCl_3), 119.1 (1-CH_2), 132.6 (2-CH), 161.1 (Cl_3CC=O), 203.4 (5-C=O).



215. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23 (3H, d, *J* = 7.3 Hz, CH_3), 2.87 (1H, qd, *J* = 7.2, 4.8 Hz, 4-CH), 4.54 (1H, m, 3-CH), 5.27 (1H, appdt, *J* = 10.3, 0.9 Hz, 1-CH), 5.30 (1H, appdt, *J* = 17.1, 1.0 Hz, 1-CH'), 5.80 (1H, ddd, *J* = 17.0, 10.4, 6.6 Hz, 2-CH), 7.72 (1H, bd, *J* = 8.9 Hz, NH), 9.40 (1H, vbs, OH).

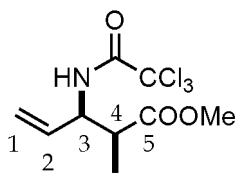


221. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 7.3 Hz, CH_3), 2.84 (1H, qd, *J* = 7.3, 4.7 Hz, 4-CH), 3.70 (3H, s, OCH_3), 4.51 (1H, m, 3-CH), 5.26 (1H, appdt, *J* = 10.3, 1.0 Hz, 1-CH), 5.28 (1H, appdt, *J* = 17.1, 1.0 Hz, 1-CH'), 5.77 (1H, ddd, *J* = 17.0, 10.3, 6.6 Hz, 2-CH), 7.71 (1H, bd, *J* = 7.2 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.4 (CH_3), 42.5 (4-CH), 52.1 (OCH_3), 55.5 (3-CH), 92.6 (CCl_3), 118.9 (1-CH_2), 132.2 (2-CH), 160.9 (Cl_3CC=O), 173.8 (5-C=O); $[\alpha]^{24}_{D}$ +65.6, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (ESI) observed $(M+H)^{+}$ 287.9956, calculated for $C_9H_{13}O_3NCl_3$ 287.9955.

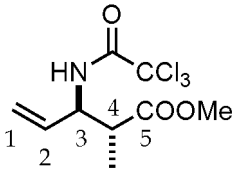


(*2S,3R*)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, 221 and (*2R,3R*)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, 222. A solution of a (5:3) diastereoisomeric mixture of acids **215** and **220** (210 mg, 770 µmol) in anhydrous diethyl ether (4.5 mL) was treated with the dropwise addition of a commercial solution of TMS-diazomethane in hexanes (0.8 mL, 2.0 M, 1.6 mmol). The resulting yellow solution was stirred overnight, and was subsequently quenched by the sequential and careful addition of glacial acetic acid (180 µL, 2.62 mmol) and potassium fluoride (50 mg, 860 µmol). After the mixture was stirred for 10 min, the solution was treated with an aq. solution of HCl (1.0 M, 2 x 10 mL), and the layers were subsequently separated. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to afford the crude esters **221** and **222** (359 mg) as a yellow oil. Purification by flash column chromatography (silica gel, elution gradient 0-10% ethyl acetate in 40-60 petroleum ether) provided the desired methyl esters **221** and **222** as a viscous, clear oil and as an inseparable (5:3) mixture of *syn*- and *anti*-diastereomers (60 mg, 27%). The TMS-methyl esters **223** and **224** (115 mg, 42%, d.r. 5:3) were also isolated as an inseparable mixture of diastereomers.

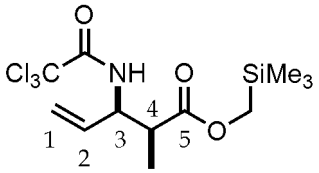
The diastereomeric mixture was then loaded onto a semi-preparative HPLC under reverse phase conditions as a MeCN / H_2O (50:50) stock solution (C18 column). The separation was achieved using the following elution profile: initial elution gradient increased the acetonitrile concentration from 25% to 45% over 20 min. The concentration was kept at 45% for 55 min and was then increased from 45% to 95% over 5 min. Finally, the concentration was kept at 95% for an additional 10 min at which point the run was terminated. Methyl ester **221** was isolated after 52.85 min. Methyl ester **222** was isolated after 55.90 min. Finally, the enriched fraction containing TMS methylene ester **223** was isolated after 68.48 min (*syn:anti* 7.5:1.0). In all cases, the optimized detection wavelength was 214 nm.



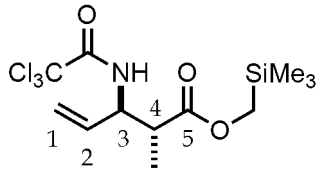
221. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 7.3 Hz, 4-CH_3), 2.84 (1H, qd, *J* = 7.3, 4.7 Hz, 4-CH), 3.70 (3H, s, OCH_3), 4.51 (1H, m, 3-CH), 5.26 (1H, appdt, *J* = 10.3, 1.0 Hz, 1-CH), 5.28 (1H, appdt, *J* = 17.1, 1.0 Hz, 1-CH'), 5.77 (1H, ddd, *J* = 17.0, 10.3, 6.6 Hz, 2-CH), 7.71 (1H, bd, *J* = 7.2 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.4 (CH_3), 42.5 (4-CH), 52.1 (OCH_3), 55.5 (3-CH), 92.6 (CCl_3), 118.9 (1-CH_2), 132.2 (2-CH), 160.9 (Cl_3CC=O), 173.8 (5-C=O); $[\alpha]^{24}_D$ +65.6, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (ESI) observed $(M+H)^+$ 287.9956, calculated for $C_9H_{13}O_3NCl_3$ 287.9955.



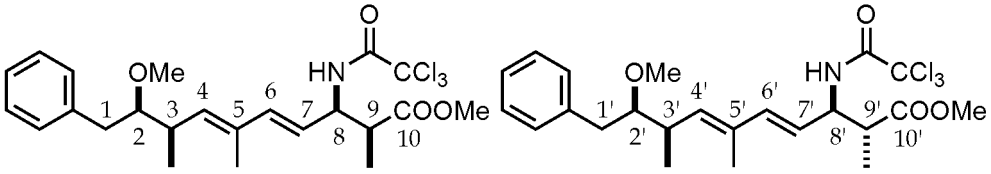
222. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.30 (3H, d, *J* = 7.2 Hz, 4-CH_3), 2.84 (1H, qd, *J* = 7.2, 3.8 Hz, 4-CH), 3.71 (3H, s, OCH_3), 4.55 (1H, m, 3-CH), 5.20 (1H, ddd, *J* = 10.5, 1.5, 0.5 Hz, 1-CH), 5.27 (1H, ddd, *J* = 17.2, 1.6, 0.5 Hz, 1-CH'), 5.80 (1H, ddd, *J* = 17.2, 10.5, 5.2 Hz, 2-CH), 8.02 (1H, bd, *J* = 5.6 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.3 (CH_3), 42.4 (4-CH), 52.1 (OCH_3), 55.2 (3-CH), 92.8 (CCl_3), 116.9 (1-CH_2), 134.7 (2-CH), 161.9 (Cl_3CC=O), 175.7 (5-C=O); $[\alpha]^{24}_D$ +26.8, (c = 1.0, $CHCl_3$).



(*2S,3R*)-(Trimethylsilyl)methyl-2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, 223. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.07 (9H, s, $Si(CH_3)_3$), 1.23 (3H, d, *J* = 7.3 Hz, 4-CCH_3), 2.84 (1H, qd, *J* = 7.3, 4.6 Hz, 4-CH), 3.77 (1H, d, *J* = 14.1 Hz, OCH_3), 3.88 (1H, d, *J* = 14.1 Hz, $OCHSiMe_3$), 4.51 (1H, m, $OCH'SiMe_3$), 5.28 (1H, appdt, *J* = 10.4, 1.0 Hz, 1-CH), 5.31 (1H, appdt, *J* = 17.2, 1.0 Hz, 1-CH'), 5.79 (1H, ddd, *J* = 17.1, 10.4, 6.7 Hz, 2-CH), 7.85 (1H, bd, *J* = 7.4 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ -3.1 ($Si(CH_3)_3$), 13.8 (4-CCH_3), 42.7 (4-CH), 55.8 (OCH_2), 58.6 (3-CH), 92.7 (CCl_3), 119.1 (1-CH_2), 132.2 (2-CH), 161.0 (Cl_3CC=O), 174.3 (5-C=O). $[\alpha]^{24}_D$ +41.9, (c = 1.0, $CHCl_3$) enriched fraction (*syn:anti* 7.5:1.0).



(*2R,3R*)-(Trimethylsilyl)methyl-2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, 224. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.06 (9H, s, $Si(CH_3)_3$), 1.29 (3H, d, J = 7.2 Hz, 4-CCH_3), 2.84 (1H, qd, J = 7.2, 3.8 Hz, 4-CH), 3.81 (1H, s, OCH_3), 3.82 (1H, s, $OCHSiMe_3$), 4.51 (1H, m, $OCH'SiMe_3$), 5.20 (1H, ddd, J = 10.4, 1.5, 0.6 Hz, 1-CH), 5.26 (1H, ddd, J = 17.1, 1.5, 0.6 Hz, 1-CH'), 5.79 (1H, ddd, J = 17.1, 10.4 Hz, 1 unresolved coupling, 2-CH), 8.14 (1H, bd, J = 8.2 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ -3.1 ($Si(CH_3)_3$), 15.5 (4-C*C*H_3), 42.5 (4-CH), 55.2 (OCH_2), 58.6 (3-CH), 92.8 (CCl_3), 116.8 (1-CH_2), 134.9 (2-CH), 162.0 (Cl_3CC=O), 175.6 (5-C=O). IR (thin film) ν_{max} = 3340, 2958, 1718, 1509, 1298, 1252, 1180, 1154, 843, 822, 681 cm^{-1}; HRMS (FAB+) observed $(M+H)^+$ 360.0355, calculated for $C_{12}H_{21}O_3NCl_3Si$ 360.0356.



(*2S,3R,4E,6E,8R,9R*)-Methyl 9-methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoate (*enantio-N*-TAC-*iso*-ADDA methyl ester), 235; and (*2R,3R,4E,6E,8R,9R*)-Methyl 9-methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoate (*enantio-N*-TAC-ADDA methyl ester), 236.

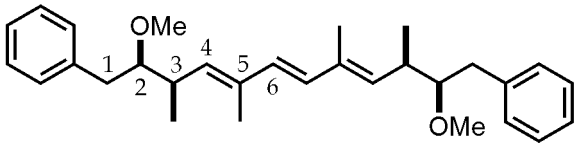
General procedure: Neat methoxy diene **(*E*)-117** (140 mg, 608 µmol) and the (5:3) diastereomeric mixture of methyl esters **221** and **222** (263 mg, 911 µmol) were placed in a round bottom flask equipped with a reflux condenser, and wrapped up in aluminium foil. Second generation Hoveyda-Grubbs catalyst (40 mg, 64 µmol, 7.0 mol%) was then quickly introduced to the reaction followed by the fast addition of anhydrous tetrahydrofuran (20 mL). The mixture was then immediately placed in an oil bath pre-heated at 110 °C, and the reaction mixture was refluxed under argon until completion as indicated by TLC analysis (24 h). The reaction was cooled down to room temperature, and was then diluted with hexanes (30 mL), which caused the catalyst derivatives to crash out of solution. Filtration of the solid residue, followed by concentration of the remaining organic solvent under reduced pressure afforded a crude light brown oil. [**Note:** When dealing with microscale amounts, a better work-up procedure involves the simple evaporation of the solvent under vacuum followed by purification of the crude residue]. The crude oil was purified

by flash column chromatography (silica gel, elution gradient 0-10% ethyl acetate in 40-60 petroleum ether) to afford the heterodimers **235** and **236** as a light brown and very sticky clear oil. A second purification by flash column chromatography (silica gel, 100% toluene) was necessary to give the analytically pure heterodimers **235** and **236** (269 mg, 90%) as an inseparable (5:3) mixture of diastereomers.

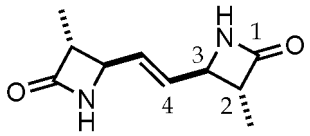
The same procedure was repeated for the successful cross coupling of each individual diastereomerically pure ester **235** and **236**.

***Enantio-N*-TAC-*iso*-ADDA methyl ester, 235.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.8 Hz, 3-CCH_3), 1.23 (3H, d, *J* = 7.3 Hz, 9-CCH_3), 1.62 (3H, d, *J* = 1.2 Hz, 5-CCH_3), 2.61 (1H, m, 3-CH), 2.68 (1H, dd, *J* = 13.9, 7.4 Hz, 1-CH), 2.79 (1H, dd, *J* = 13.9, 4.6 Hz, 1-CH'), 2.88 (1H, qd, *J* = 7.2, 4.5 Hz, 9-CH), 3.20 (1H, m, 2-CH), 3.24 (3H, s, 2-$COCH_3$), 3.73 (3H, s, 10-$COOCH_3$), 4.57 (1H, apptm, *J* = 7.9 Hz, 8-CH), 5.42 (1H, dd, *J* = 15.3, 7.5 Hz, 7-CH), 5.43 (1H, d, *J* = 10.6 Hz, 4-CH), 6.28 (1H, d, *J* = 15.6 Hz, 6-CH), 7.17-7.29 (5H, m, ArH), 7.72 (1H, d, *J* = 8.8 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (5-CCH_3), 13.7 (9-CCH_3), 16.1 (3-CCH_3), 37.7 (3-CH), 38.2 (1-CH_2), 43.0 (9-CH), 52.1 ($COOCH_3$), 55.7 (8-CH), 58.6 (2-$COCH_3$), 86.8 (2-CH), 92.8 (CCl_3), 120.3 (4-CH), 126.0 ($ArCH_{para}$), 128.2 ($ArCH_{ortho}$), 129.4 ($ArCH_{meta}$), 132.2 (ArC_{IV}), 137.4 (7-CH), 139.3 (5-C_{IV}), 139.7 (6-CH), 160.8 (Cl_3CC=O), 174.2 (10-C=O); $[\alpha]^{24}_D$ +12.4, (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3408, 3356, 3029, 2980, 2953, 2935, 2879, 1718, 1509, 1456, 1266, 1200, 822, 739, 702 cm^{-1}; HRMS (ESI) observed $(M+H)^+$ 490.1313, calculated for $C_{23}H_{31}O_4NCl_3$ 490.1313.

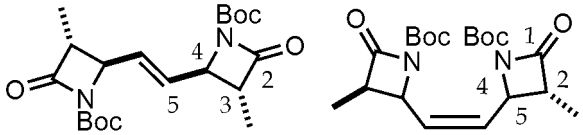
***Enantio-N*-TAC-ADDA methyl ester, 236.** ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.8 Hz, 3'-CCH_3), 1.30 (3H, d, *J* = 7.2 Hz, 9'-CCH_3), 1.60 (3H, d, *J* = 0.9 Hz, 5'-CCH_3), 2.60 (1H, m, 3'-CH), 2.67 (1H, dd, *J* = 13.9, 7.5 Hz, 1'-CH), 2.79 (1H, dd, *J* = 13.9, 4.6 Hz, 1'-CH"), 2.86 (1H, qd, *J* = 7.2, 4.0 Hz, 9'-CH), 3.18 (1H, m, 2'-CH), 3.23 (3H, s, 2'-$COCH_3$), 3.72 (3H, s, 10'-$COOCH_3$), 4.59 (1H, m, 8'-CH), 5.41 (1H, d, *J* = 9.5 Hz, 7'-CH), 5.44 (1H, dd, *J* = 15.8, 6.5 Hz, 4'-CH), 6.24 (1H, d, *J* = 15.6 Hz, 6'-CH), 7.17-7.29 (5H, m, ArH'), 8.01 (1H, d, *J* = 9.0 Hz, NH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (5'-CCH_3), 15.3 (9'-CCH_3), 16.1 (3'-CCH_3), 36.7 (3'-CH), 38.2 (1'-CH_2), 43.3 (9'-CH), 52.1 ($COOCH_3$'), 55.3 (8'-CH), 58.7 (2'-$COCH_3$), 86.9 (2'-CH), 92.9 (CCl_3'), 122.9 (4'-CH), 126.0 ($ArCH_{para}$'), 128.2 ($ArCH_{ortho}$'), 129.4 ($ArCH_{meta}$'), 132.1 (ArC_{IV}'), 137.2 (7'-CH), 137.6 (6'-CH), 139.3 (5'-C_{IV}), 161.7 (Cl_3CC=O'), 175.9 (10'-C=O); $[\alpha]^{24}_D$ +11.2, (c = 1.0, $CHCl_3$).



((2*R*,3*R*,4*E*,6*E*,8*E*,10*R*,11*R*)-2,11-Dimethoxy-3,5,8,10-tetramethyldodeca-4,6,8-triene-1,12-diyl)dibenzene, 238. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 6.7 Hz, 3-CCH_3), 1.70 (3H, d, *J* = 1.1 Hz, 5-CCH_3), 2.62 (1H, appdt, *J* = 9.7, 6.7 Hz, 3-CH), 2.70 (1H, dd, *J* = 13.9, 7.5 Hz, 1-CH), 2.84 (1H, dd, *J* = 13.9, 4.5 Hz, 1-CH'), 3.20 (1H, m, 2-CH), 3.25 (3H, s, OCH_3), 5.43 (1H, dd, *J* = 9.8, 1.1 Hz, 4-CH), 6.20 (1H, bs, 6-CH), 7.17-7.29 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.7 (5-CCH_3), 16.4 (3-CCH_3), 36.8 (3-CH), 38.3 (1-CH_2), 58.6 (OCH_3), 87.1 (2-CH), 125.9 ($ArCH_{para}$), 128.1 ($ArCH_{ortho}$), 129.5 ($ArCH_{meta}$), 131.6 (6-CH), 133.6 (5-C_{IV}), 135.1 (4-CH), 139.4 (ArC_{IV}); $[\alpha]^{23}_{D}$ = + 15.0 ° (C = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3086, 3063, 3027, 3007, 2962, 2928, 2871, 2857, 2827, 2245, 1721, 1496, 1455, 1375, 1265, 1217, 1106, 1082, 909, 759, 732, 701 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 433.3105, calculated for $C_{30}H_{41}O_2$ 433.3107.

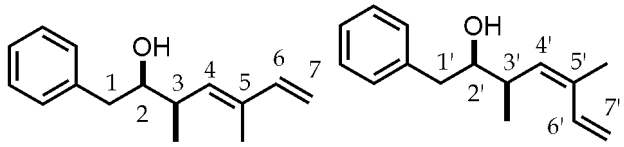


(3*R*,3'*R*,4*R*,4'*R*)-4,4'-((*E*)-Ethene-1,2-diyl)bis(3-methylazetidin-2-one), (±)-239. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.32 (3H, d, *J* = 7.4 Hz, CH_3), 2.89 (1H, qm, *J* = 7.4 Hz, 2-CH), 3.74 (1H, appsex, *J* = 2.0 Hz, 3-CH), 5.81 (1H, m, 4-CH), 6.55 (1H, bd, *J* = 8.8 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.6 (CH_3), 53.4 (2-CH), 56.9 (3-CH), 131.6 (4-CH), 171.4 (1-C=O); IR (thin film) ν_{max} = 3260, 2968, 2927, 2875, 1735, 1721, 1458, 1383, 1363, 1174, 971, 831, 740, 704 cm^{-1}.



(±)-*(3R,3'R,4R,4'R)-tert*-Butyl 4,4'-((*E*)-ethene-1,2-diyl)bis(3-methyl-2-oxoazetidine-1-carboxylate), (±)-240*E* and (±)-*(3R,3'R,4R,4'R)-tert*-Butyl 4,4'-((*Z*)-ethene-1,2-diyl)bis(3-methyl-2-oxoazetidine-1-carboxylate), (±)-240*Z*. (*E*/*Z* = 1:1) ^{1}H NMR (400MHz, $CDCl_3$) δ 1.36 and 1.37 (6H, d, *J* = 7.5 Hz, CH_3), 1.49 and 1.50 (18H, s, $OC(CH_3)_3$), 2.94 (2H, m, 3-CH), 4.02 (2H, m, 4-CH), 5.85 and 5.86 (2H, d, *J* = 2.2 Hz, 5-CH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.3 and 12.4 (2 x CH_3), 27.9 (2 x $OC(CH_3)_3$), 51.4 (2 x 3-CH), 59.5 and 59.8 (2 x 4-CH), 83.4

(2 x $OCMe_3$), 130.8 and 131.1 (2 x 5-CH), 147.7 and 147.8 (2 x COO^tBu), 167.7 (2 x 2-C=O); IR (thin film) ν_{max} = 2974, 2932, 2874, 1806, 1723, 1477, 1456, 1369, 1337, 1315, 1259, 1158, 1102, 1069, 952, 913, 846, 797, 772, 733 cm^{-1}; Not detected by mass spectroscopy.

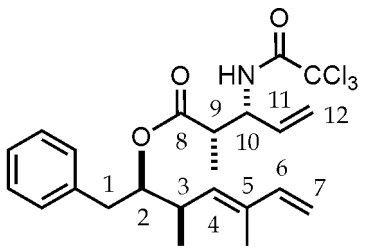


(2*R*,3*R*,*E*)-3,5-Dimethyl-1-phenylhepta-4,6-dien-2-ol, (*E*)-241, and (2*R*,3*R*,*Z*)-3,5-Dimethyl-1-phenylhepta-4,6-dien-2-ol, (*Z*)-241. A (2.5:1) isomeric mixture of *O*-TBS protected dienes **(*E*)-139** and **(*Z*)-139** (450 mg, 1.36 mmol) was dissolved in anhydrous THF (25 mL), and was transferred into a round bottom flask containing flame-activated powdered 4Å molecular sieves (2 g). The suspension was treated with tetrabutylammonium fluoride (1.0 M in THF, 4.0 mL, 4.0 mmol), and the resulting reaction mixture was stirred at room temperature until completion (15 min). The mixture was then quenched with water (40 mL), and the reaction extracted with ethyl acetate (2 x 20 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and the solvents were removed under vacuum. The resulting brown oil (368 mg) was then purified by flash column chromatography (silica gel, 10% ethyl acetate in 40-60 petroleum ether) to afford a (2.5:1) isomeric mixture of dienols **(*E*)-241** and **(*Z*)-241** as a colourless and clear viscous oil (280 mg, 95%).

(*E*)-241. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6.7 Hz, 3-CCH_3), 1.59 (1H, d, *J* = 4.3 Hz, OH), 1.78 (3H, d, *J* = 1.1 Hz, 5-CCH_3), 2.56 (1H, dd, *J* = 13.8, 9.4 Hz, 3-CH), 2.61-2.67 (1H, m, 1-CH), 2.91 (1H, dd, *J* = 13.8, 3.1 Hz, 1-CH'), 3.64 (1H, m, 2-CH), 5.00 (1H, d, *J* = 10.7 Hz, 7-CH), 5.15 (2H, d, *J* = 17.4, 7-CH'), 5.44 (1H, d, *J* = 9.8 Hz, 4-CH), 6.41 (1H, dd, *J* = 17.4, 10.6 Hz, 6-CH), 7.20-7.33 (5H, m, ArH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.2 (5-CCH_3), 16.4 (3-CCH_3), 38.6 (3-CH), 41.6 (1-CH_2), 76.7 (2-CH), 111.4 (7-CH_2), 126.4 ($ArCH_{para}$), 128.5 ($ArCH_{ortho}$), 129.3 ($ArCH_{meta}$), 134.2 (5-C_{IV}), 135.2 (4-CH), 138.8 (ArC_{IV}), 141.5 (6-CH).

(*Z*)-241. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.09 (3H, d, *J* = 6.8 Hz, 3'-CCH_3), 1.62 (1H, d, *J* = 2.9 Hz, OH'), 1.77 (3H, d, *J* = 1.1 Hz, 5'-CCH_3), 2.56-2.67 (2H, masked, 3'-CH and 1'-CH), 2.85 (1H, dd, *J* = 13.7, 3.8 Hz, 1'-CH"), 3.72 (1H, m, 2'-CH), 5.00 (1H, masked, 7'-CH), 5.15 (2H, masked, 7'-CH"), 5.52 (1H, d, *J* = 9.8 Hz, 4'-CH), 6.44 (1H, dd, *J* = 17.4, 10.4 Hz, 6'-CH), 7.20-7.33 (5H, m, ArH'); ^{13}C NMR (100MHz, $CDCl_3$) δ 17.2 (5'-CCH_3), 25.6 (3'-CCH_3), 38.1 (3'-CH), 41.1 (1'-CH_2), 76.4 (2'-CH), 111.4 (7'-CH_2), 126.3 ($ArCH_{para}$'), 128.4 ($ArCH_{ortho}$'),

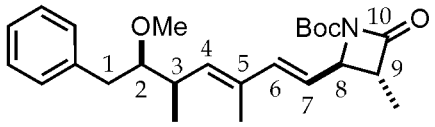
129.3 ($ArCH_{meta}$'), 134.0 (5'-C_{IV}), 135.2 (4'-CH), 138.8 (ArC_{IV}'), 141.5 (6'-CH); HRMS (CI) observed $(M+H)^+$ 217.1587, calculated for $C_{15}H_{21}O$ 217.1592.



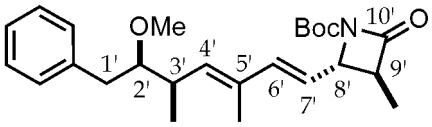
(2*S*,3*R*)-((2*R*,3*R*,*E*)-3,5-Dimethyl-1-phenylhepta-4,6-dien-2-yl) 2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, (*E*)-247. To a solution of carboxylic acid **215** (130 mg, 474 µmol) in anhydrous tetrahydrofuran (8 mL) was added DIPEA (122 µL, 700 µmol) and 2,4,6-trichlorobenzoyl chloride (141 mg, 90.2 µL, 576 µmol). The reaction was stirred 40 min at room temperature before being treated with additional anhydrous triethylamine (36.3 mg, 50.3 µL, 359 µmol). After stirring for 80 min, the suspension was diluted with hexane (20 mL), and filtered through a short pad of Celite. The Celite was flushed with hexane (80 mL in total), and the solvent was evaporated under reduced pressure. The resulting crude residue was placed into a round-bottomed-flask and carefully dried under high vaccum. Anhydrous toluene (8 mL) was added to the dry residue under argon, and this solution was treated with a solution of a (2.5:1) isomeric mixture of dienols **(*E*)-241** and **(*Z*)-241** (150 mg, 693 µmol) and DMAP (80 mg, 660 µmol) in dry toluene (3 mL). The reaction turned quickly into a cloudy suspension, which was stirred at room temperature for 2 h, before being filtered through a short pad of Celite. After flushing the Celite with hexane (80 mL), the solvents were evaporated and the crude oil (469 mg) was purified by flash column chromatography (silica gel, 100% chloroform). The pure ester **(*E*)-247** was isolated as the major isomer of a complex mixture of inseparable minor isomers, and as an extremely viscous clear and colourless oil (175 mg, 78%). It is worth noticing that the excess of dienol was easily recovered during the chromatographic separation. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.02 (3H, d, J = 6.7 Hz, 3-CCH_3), 1.18 (3H, d, J = 7.3 Hz, 9-CCH_3), 1.71 (3H, d, J = 0.8 Hz, 5-CCH_3), 2.63-2.82 (3H, m, 1-CH + 9-CH + 3-CH), 2.97 (1H, dd, J = 14.3, 4.2 Hz, 1-CH'), 4.39 (1H, m, 10-CH), 5.02 (1H, d, J = 10.7 Hz, 7-CH), 5.12-5.24 (4H, m, 7-CH' + 2-CH + 12-CH_2), 5.30-5.47 (2H, m, 4-CH + 11-CH), 6.37 (1H, m, 6-CH), 7.14-7.27 (5H, m, ArH), 7.68 (1H, bd, J = 8.6 Hz, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ 12.2 (5-CCH_3), 13.9 (9-CCH_3), 16.6 (3-CCH_3), 36.2 (3-CH), 38.2 (1-CH_2), 42.6 (9-CH), 55.7 (10-CH), 78.8 (2-CH), 92.7 (CCl_3), 112.1 (7-CH_2), 119.4 (12-CH_2), 126.6 (ArCHpara), 128.4 ($ArCH_{ortho}$), 129.1

($ArCH_{meta}$), 131.9 (11-CH), 133.2 (4-CH), 134.9 (5-C_{IV}), 137.2 (ArC_{IV}), 141.1 (6-CH), 160.9 (Cl_3CC=O), 173.0 (O-C=O); IR (thin film) ν_{max} = 3407, 3352, 3088, 3066, 3025, 2972, 2924, 2875, 1718, 1499, 1456, 1217, 1157, 756 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 472.1215, calculated for $C_{23}H_{29}NO_3Cl_3$ 472.1213.

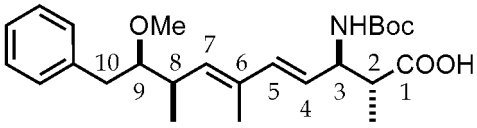
3 - COSY CORRELATIONS



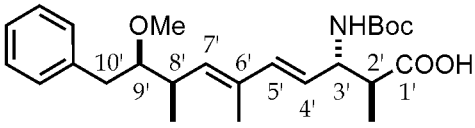
H_A	H_B	J_{AB} values
1	2	7.5 Hz
1’	2	4.6 Hz
2	3	undefined
3	4	9.8 Hz
3	3-CCH_3	6.7 Hz
4	5-CCH_3	1.2 Hz
6	7	15.4 Hz
7	8	8.1 Hz
8	9	3.0 Hz
9	9-CCH_3	7.4 Hz



H_A	H_B	J_{AB} values
1’	2’	7.5 Hz
1”	2’	4.6 Hz
2’	3’	undefined
3’	4’	9.7 Hz
3’	3’-CCH_3	6.7 Hz
4’	5’-CCH_3	1.2 Hz
6’	7’	15.4 Hz
7’	8’	8.1 Hz
8’	9’	3.0 Hz
9’	9’-CCH_3	7.4 Hz



H_A	H_B	J_{AB} values
2	2-CCH_3	7.4 Hz
2	3	unseen
3	4	6.1 Hz
3	NH	undefined
4	5	15.6 Hz
7	6-CCH_3	undefined
7	8	9.8 Hz
8	8-CCH_3	6.7 Hz
8	9	undefined
9	10	7.5 Hz
9	10’	4.5 Hz



H_A	H_B	J_{AB} values
2	2-CCH_3	7.4 Hz
2	3	unseen
3	4	6.1 Hz
3	NH	undefined
4	5	15.6 Hz
7	6-CCH_3	undefined
7	8	9.8 Hz
8	8-CCH_3	6.7 Hz
8	9	undefined
9	10	7.5 Hz
9	10’	3.8 Hz

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