Asymmetric Total Synthesis of Inthomycin C and Studies Towards the Total Synthesis of Oxazolomycin B

A thesis submitted to the Board of the Mathematical, Physical and Life Sciences Division in partial fulfilment of the requirements for the degree of

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by

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and

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Declaration

This thesis and the work described herein is entirely my own, except where the help of a named person is acknowledged or where reference to a published source is given.

Sandra Balcells Garcia

University of Oxford

Trinity Term 2017

Table of Contents

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Abstract

Asymmetric Total Synthesis of Inthomycin C and Studies Towards the Total Synthesis of Oxazolomycin B

A thesis submitted for the degree of Doctor of Philosophy

Sandra Balcells Garcia **Brasenose College** **Trinity Term 2017**

This thesis describes research towards the total syntheses of two bacterial polyene natural products, inthomycin C and oxazolomycin B, as well as preliminary studies on the biological activity of inthomycin C and structural analogues against human cancer cell lines. A novel total synthesis of inthomycin C has been accomplished in 11.4% yield and 89% ee over ten linear steps from oxazole. This synthesis is the shortest and highest yielding asymmetric total synthesis of inthomycin C to date and, unlike all previous syntheses, it avoids the use of toxic organotin reagents. Main features of this synthesis include cross-metathesis as key C–C bond-forming step, methoxy group elimination to construct the triene moiety and asymmetric Mukaiyama–Kiyooka aldol addition to install the (3*R*) alcohol stereocenter on inthomycin C. Both NMR data and optical rotation data for the sample of inthomycin C synthesised in this work are in agreement with those previously reported. Viability and cytotoxicity assays of inthomycin C and analogues against various human cancer cell lines have been carried out for the first time. Despite all compounds tested having proved inactive against all cancer cell lines, an ester derivative of inthomycin C has been found to exhibit weak reversible proteasome inhibition activity against two cancer cell lines. On the other hand, and building on previous work in the Donohoe group, the synthesis of an advanced amide intermediate in the route towards oxazolomycin B has been achieved, which contains the complete carbon backbone of oxazolomycin B. Key features of this synthesis include a highly diastereoselective organocerium nucleophilic addition to an aldehyde precursor, a Nozaki–Hiyama–Kishi reaction and an amide coupling to access the final amide fragment.

Abbreviations and Acronyms

9-BBN	9-Borabicyclo[3.3.1]nonane
(*R*,*R*$_P$)-Taniaphos	(*R*$_P$)-1-[(*R*)-α-(Dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene
[α]	Specific rotation
Å	Ångström
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOPCl	bis(2-Oxo-3-oxazolidinyl)phosphinic chloride
br.	Broad
Bu	Butyl
c	Concentration
°C	Degrees Celsius
cat.	Catalytic
CBS	Corey–Bakshi–Shibata
CI	Chemical ionisation
CM	Cross-metathesis
cm^{-1}	Wavenumber
CoA	Coenzyme A
cod	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarisation transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTBMS	Di-*tert*-butylmethylsilyl
EDC·HCl	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron ionisation
eq.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
FCC	Flash column chromatography
FI	Field ionisation
Fmoc	Fluorenylmethyloxycarbonyl
FTIR	Fourier transform infrared
g	Gram(s)
G-II	Grubbs second-generation catalyst
h	Hour(s)
HATU	*O*-(7-Aza-1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HG-II	Hoveyda–Grubbs second-generation catalyst
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
i-	*iso*-
IC_{50}	Half maximal inhibitory concentration
i.e.	That is; in other words (Latin)
in situ	In position (Latin)
in vacuo	In a vacuum (Latin)
in vitro	Within the glass (Latin), i.e. outside a living system
in vivo	Within the living (Latin), i.e. within a living system
IR	Infrared
J	Coupling constant
LD_{50}	Median lethal dose
LDA	Lithium diisopropylamide
LLS	Longest linear sequence
LRMS	Low resolution mass spectrometry
L-selectride	Lithium tri-*sec*-butylborohydride

M	Molar
[M]	Generic metal
m	Multiplet (or medium)
MALDI	Matrix assisted laser desorption/ionisation
m.p.	Melting point
m/z	Mass to charge ratio
Me	Methyl
mg	Milligram(s)
MIC	Minimum inhibitory concentration
min	Minute(s)
mL	Millilitre(s)
mm	Millimetre(s)
mmol	Millimole(s)
MNBA	2-Methyl-6-nitrobenzoic anhydride
mol	Mole(s)
mol%	Molar percent
MOM	Methoxymethyl
m.p.	Melting point
Ms	Mesylate (Methanesulfonate)
MS	Molecular sieves
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
MW	Molecular weight
n-	*normal*-
N/A	Not applicable
NBS	*N*-Bromosuccinimide
NHC	N-Heterocyclic carbene
NHK	Nozaki–Hiyama–Kishi
NIS	*N*-Iodosuccinimide
nm	Nanometre(s)
NME	*N*-Methylephedrine
NMR	Nuclear magnetic resonance
NMO	*N*-Methylmorpholine-*N*-oxide
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o-	*ortho*-
p-	*para*-
PEPPSI	[1,3-bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
pH	$-\log[H_3O]^+$
Ph	Phenyl
Piv	Pivaloyl (trimethylacetyl)

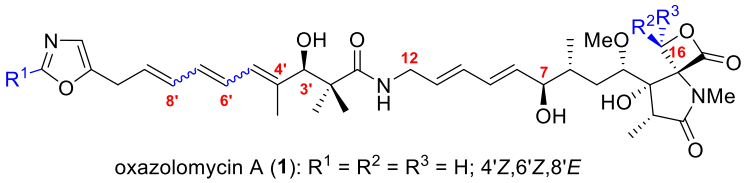
PMB	*p*-Methoxybenzyl
ppm	Parts per million
Pr	Propyl
proton sponge	*N*,*N*,*N*',*N*'-Tetramethyl-1,8-naphthalenediamine
q	Quartet
quant.	Quantitative
R	Generic alkyl group
RCM	Ring-closing metathesis
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
ROMP	Ring-opening metathesis polymerisation
RSM	Recovered starting material
r.t.	Room temperature
s	Singlet (or strong)
SAR	Structure-activity relationship
sat.	Saturated
sept	Septet
sp.	Species
T	Temperature
t	Triplet
t/tert-	*tertiary-*
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate (triflate)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSQD	*O*-Trimethylsilylquinidine
TOCSY	Total correlation spectroscopy
TosMIC	Toluenesulfonylmethyl isocyanide
Ts	*para*-Toluenesufonyl (tosyl)
UV	Ultraviolet
via	By way of (Latin)
vs/versus	Against (Latin)
VT	Variable temperature
w	Weak
w/w	By mass
X	Generic heteroatom, halide or leaving group

μL	Microlitre(s)
μm	Micrometre(s)
μW	Microwave irradiation
ν_{max}	Infrared absorption maximum
λ_{max}	Wavelength of maximum absorbance
δ	Chemical shift

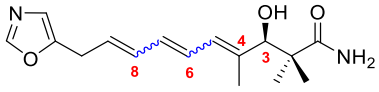
Chapter 1. Introduction

1.1. The oxazolomycin family

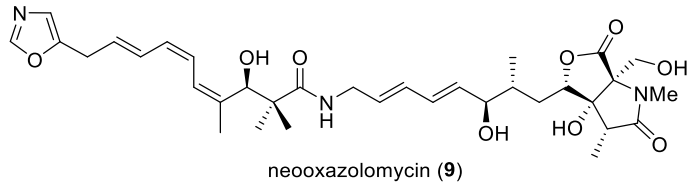
The oxazolomycins are a family of polyene natural products isolated from several *Streptomyces* sp. strains that display antibacterial,[1–9] antiviral[10] and *in vivo* antitumor[11] activity. Common structural characteristics of these compounds include a left-hand methylene-interrupted oxazolyl-triene motif, a central diene fragment and a right-hand spirofused β-lactone-γ-lactam (or fused γ-lactone-γ-lactam) core (**Figure 1**).



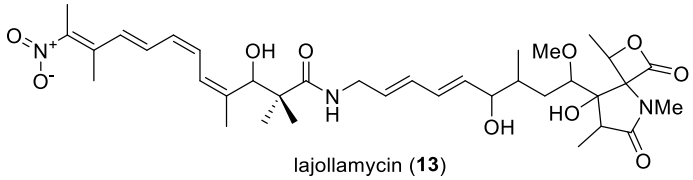
oxazolomycin A (**1**): $R^1 = R^2 = R^3 = H$; 4'*Z*,6'*Z*,8'*E*
oxazolomycin B (**2**): $R^1 = R^2 = R^3 = H$; 4'*E*,6'*E*,8'*E*
oxazolomycin C (**3**): $R^1 = R^2 = R^3 = H$; 4'*Z*,6'*E*,8'*E*
16-methyloxazolomycin (**4**): $R^1 = R^2 = H$, $R^3 = Me$; 4'*Z*,6'*Z*,8'*E*
curromycin A (**5**): $R^1 = Me$, $R^2 = CH_2OMe$, $R^3 = H$; 4'*Z*,6'*Z*,8'*E*
curromycin B (**6**): $R^1 = R^3 = Me$, $R^2 = H$; 4'*Z*,6'*Z*,8'*E*
KSM-2690 B (**7**): $R^1 = R^3 = H$, $R^2 = Me$; 4'*Z*,6'*Z*,8'*E*
KSM-2690 C (**8**): $R^1 = R^3 = H$, $R^2 = Me$; 4'*Z*,6'*E*,8'*E*



inthomycin A (**10**): 4*Z*,6*Z*,8*E*
inthomycin B (**11**): 4*Z*,6*E*,8*E*
inthomycin C (**12**): 4*E*,6*E*,8*E*



neooxazolomycin (**9**)



lajollamycin (**13**)

Figure 1. The oxazolomycins and related natural products

Due to the presence of this bicyclic motif, which resembles the pharmacophores of known 20S proteasome inhibitors such as salinosporamide A and omuralide,[12–14] and their intriguing biological properties, they have attracted much attention from synthetic chemists. After the isolation of oxazolomycin A (**1**) in 1985 by Uemura and co-workers,[15] several related compounds have also been isolated from *Streptomyces* sp., including inthomycin A (**10**) in 1990 by Omura and co-workers[8] and its geometrical isomers, inthomycin B (**11**) and

inthomycin C (**12**) in 1991 by Henkel and Zeeck.[16] The structure of the inthomycins corresponds to the left-hand primary amide fragment of the oxazolomycins. Interestingly, inthomycin A (**10**) is not an intermediate in the biosynthesis of oxazolomycin A (**1**), as demonstrated by prior feeding experiments.[17]

Previous studies on the structure of oxazolomycin suggest that a U-shaped conformation is favoured based on molecular modelling, NMR spectroscopy and X-ray analysis.[18] The gem-dimethyl group is likely to enforce a U-shaped structure due to the Thorpe–Ingold effect, which would result in a molecule with a polar head group (lactone-lactam) and a non-polar tail. These studies also showed the possibility of hydrogen bonding between the N–H residue at *C*-12 and the O–H residue at *C*-3' as stabilising force for the proposed U-shaped conformation (see **Figure 26**, **Appendix 4**).

1.2. Isolation, structural elucidation and biological activity

1.2.1. Oxazolomycin A, oxazolomycin B and oxazolomycin C

Oxazolomycin A (**1**), the parent member of the family, was first discovered together with neooxazolomycin (**9**) in 1985 by Uemura and co-workers[15] while searching for antibiotics effective against Ehrlich ascites tumor. These two natural products were isolated by extraction from the fermentation broth of a *Streptomyces* sp. strain followed by column chromatography and HPLC. In addition to inhibition against Ehrlich ascites tumor *in vivo*, oxazolomycin A (**1**) displayed activity against P-388 leukemia and gram-positive bacteria (**Table 1**). Remarkably, this antibiotic also exhibited low toxicity in mice (LD_{50} = 10.6 mg/kg) by intraperitoneal injection. The molecular formula of the named compound was determined by elemental analysis and mass spectrometry. Structural elucidation of oxazolomycin A (**1**) could be achieved through UV, IR, ^{1}H NMR and X-ray

spectroscopy analysis of the natural product and simpler fragments produced by chemical transformations of the same compound.

Oxazolomycin B (**2**) (4'*E*,6'*E*,8'*E*) and oxazolomycin C (**3**) (4'*Z*,6'*E*,8'*E*) are two geometrical isomers of oxazolomycin A (**1**) (4'*Z*,6'*Z*,8'*E*) that were first isolated in 1998 by Kanzaki and co-workers[3] from the fermentation broth of *Streptomyces albus* JA3453. Extraction from the culture filtrate, silica column chromatography and subsequent preparative reversed-phase HPLC allowed for the isolation of the three oxazolomycin isomers. Oxazolomycin B (**2**) and oxazolomycin C (**3**) were detected by HPLC analysis of the extract immediately upon fractionating the culture supernatant in the dark, which suggests that they were not originated from oxazolomycin A *via* a light-promoted isomerisation during the purification steps.

Mass spectrometry analysis confirmed the molecular weight of oxazolomycin B (**2**) and oxazolomycin C (**3**) was the same as that of oxazolomycin A (**1**). UV spectroscopy of the two newly discovered isomers showed the presence of conjugated diene and triene systems, and their ^{1}H NMR spectra mainly differed from that of oxazolomycin A (**1**) in the olefinic region, indicating that they were geometrical isomers of the parent compound. Examination of coupling constants along with ^{1}H-^{1}H COSY, nOe and NOESY analysis facilitated the assignment of all double bond absolute configurations. However, the stereochemistry of oxazolomycin B (**2**) and oxazolomycin C (**3**) remains to be established.

Oxazolomycins A, B and C (**1**–**3**) displayed similar inhibitory activity against crown gall formation. However, neither oxazolomycin B (**2**) nor oxazolomycin C (**3**) showed antibacterial activity, contrary to oxazolomycin A (**1**) which exhibited specific inhibitory activity against *Agrobacterium tumefaciens*. On the other hand, both oxazolomycin B (**2**) and oxazolomycin C (**3**) showed lower phytotoxic activity in alfalfa germination than oxazolomycin A (**1**) (**Table 1**).

In an earlier study by Kawazu and co-workers,[1] the related compound neooxazolomycin (**9**) was found not to be an inhibitor against *Agrobacterium tumefaciens* or crown gall formation, probably due to the lack of a β-lactone motif. Oxazolomycin A (**1**) selectively inhibited *Agrobacterium tumefaciens* and had no toxicity against transformed plants, which made it an inhibitor of the early step of crown gall formation. Therefore, this antibiotic could be used as a chemical probe to further understand the tumor formation process in dicotyledonous plants. Kawazu and co-workers[2] later found that several oxazolomycin A esters had inhibitory activity against crown gall formation but neither phytotoxic nor antibacterial activity, unlike oxazolomycin A (**1**) (**Table 1**). These esters could be specific inhibitors of some steps in plant transformation by *Agrobacterium tumefaciens* since their inhibitory activity appeared not to be due to any growth inhibition of the pathogen. The latter observations suggested that oxazolomycin A esters were better chemical probes for the study of the plant transformation process by the abovementioned bacterium. Furthermore, the unique activity of the oxazolomycin A esters was proved not to be due to de-esterification *in vivo*.

	ox. A (**1**)	ox. B (**2**)	ox. C (**3**)	ox. A diacetate	ox. A dipropionate	ox. A monobutyrate[a]	ox. A dibutyrate
Crown gall formation, MID (μg/disk)	0.8	0.8	0.8	1.6	1.6	1.6	1.6
Alfalfa germination, MIC (μg/mL)	12.5	25.0	50.0	>100	>100	>100	>100
Bacterial growth, MIC (μg/mL)							
Agrobacterium tumefaciens IFO13263	3.2	>100	>100	>100	>100	>100	>100
Agrobacterium tumefaciens EHA101	6.3	100	>100	-	-	-	-
Agrobacterium rhizogenes IFO13257	50	>100	>100	-	-	-	-
Cytotoxic activity							
Ehrlich ascites tumour	active	-	-	-	-	-	-
P388 leukemia	active	-	-	-	-	-	-
Antiviral activity, MIC (μg/mL)							
Influenza A	15.6	-	-	-	-	-	-
Herpes simplex type 1	15.6	-	-	-	-	-	-
Vaccinia	15.6	-	-	-	-	-	-

N.B. "ox." = oxazolomycin. "-" = data not available. All oxazolomycin A diesters had ester groups at *C*-3' and *C*-7.
[a]Oxazolomycin A monobutyrate had its ester group at *C*-7

Table 1. Summary of biological activity of oxazolomycin A, B and C (**1**–**3**) and four oxazolomycin A esters

Oxazolomycin A (**1**) also proved to be an effective antiviral agent,[10] suppressing the replication of herpes simplex type 1, influenza A and vaccinia viruses *in vitro*. Although membranotropic antibiotics generally inhibit virus uncoating as an early stage of virus replication, oxazolomycin A (**1**) seemed to inhibit later stages of influenza A replication.

Gräfe and co-workers[19] studied the mode of action of oxazolomycin A (**1**) by using an artificial lipid membrane model. This research showed that oxazolomycin A (**1**) is an effective protonophore at pH < 7.0 but conveys both protons and monovalent cations at pH > 7.5 as a passive carrier. These ionophoric properties were suggested to be correlated with its antiviral, antibacterial and cytotoxic activities. The results suggested that oxazolomycin A (**1**) acts as a general uncoupler of oxidative phosphorylation.

1.2.2. Inthomycin A, inthomycin B and inthomycin C

Inthomycin A (**10**) (also known as phthoxazolin A) was the first member of the inthomycins to be isolated in 1990 by Omura and co-workers from *Streptomyces* sp. OM-5714, during the search for inhibitors of cellulose biosynthesis with antimicrobial activity against *Phytophthora parasitica*.[8] The fermentation broth was extracted, concentrated, purified by silica column chromatography and subsequently by HPLC to afford pure phthoxazolin A (**10**). The structure of this natural product was elucidated by analysis of ^{1}H and ^{13}C NMR, ^{1}H-^{13}C COSY, ^{1}H-^{1}H COSY data.[20] Inthomycin A (**10**) displayed moderate antifungal activity against cellulose-containing *Phytophthora parasitica* and *Phytophthora capsici*,[9] whereas no inhibition was detected against 22 strains of gram-positive and gram-negative bacteria not containing cellulose, yeasts and filamentous fungi (**Table 2**). Inthomycin A (**10**) also exhibited potent herbicidal activity against radish seedlings and velvet leaf,[21] and inhibition of cellulose biosynthesis in *Acetobacter xylinum*. These initial studies revealed inthomycin A (**10**) was a specific inhibitor of cellulose synthesis in plants, fungi and bacteria, making this natural product a promising herbicide and plant growth regulator.

Legendre and co-workers[22] investigated the structure-activity relationship (SAR) of inthomycin A (**10**) to evaluate its potential herbicidal use. The natural product was chemically modified at different positions (hydroxy group at *C*-3, primary amide and oxazole nitrogen) and the phytotoxicity of the resulting products on radish seeds was evaluated. Most *O*-alkylated analogues showed a complete loss of herbicidal activity, indicating the essential role of the allylic alcohol functionality in the herbicidal activity of inthomycin A (**10**). The hydroxy derivatives that conserved some phytotoxicity were compounds that could regenerate inthomycin A (**10**) *in vivo*. Products resulting from hydrolysis or reduction of the primary amide only displayed very weak phytotoxicity. Interestingly, the oxazolidinone derivative of inthomycin A (**10**) (resulting from a Hofmann-like rearrangement between the allylic alcohol and the primary amide) showed remarkable phytotoxicity, most likely due to the geometric resemblance of the oxazolidinone ring to the terminal part of inthomycin A (**10**).

As mentioned earlier, in 1991 Henkel and Zeeck isolated inthomycin B (**11**) (4*Z*,6*E*,8*E*) and inthomycin C (**12**) (4*E*,6*E*,8*E*) and re-isolated inthomycin A (**10**) (4*Z*,6*Z*,8*E*) from *Streptomyces* sp. Gö 2.[16] Analysis of ^{1}H and ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and nOe data allowed the structural elucidation of these two novel natural products and revealed that they differed from inthomycin A (**10**) in the geometry of the triene moiety. Unlike oxazolomycin A (**1**), the inthomycins did not display antiviral or antibacterial activity.

More recent studies by Kawada and co-workers[23] found that inthomycin A (**10**) and inthomycin B (**11**) showed *in vitro* inhibitory activity against human prostate cancer growth by supressing tumor-stromal cell interactions (**Table 2**). The inhibition increased when prostate cancer DU-145 cells were cocultured with prostate stromal cells compared to when they were cultured alone.[24] Both natural products showed similar inhibitory effects but at slightly higher doses of inthomycin B (**11**) than required for inthomycin A (**10**).

In 2010, Kreiss and co-workers[25] discovered that inthomycin A (**10**) directly or indirectly affects bacterial DNA supercoiling. However, this surprising mode of action remains to be further investigated. The same study also revealed that besides gram-positive actinomycetes bacteria (*Streptomyces* sp.), gram-negative myxobacteria (*Archangium* sp.) were also able to produce the same natural product.

	inthomycin A (**10**)	inthomycin B (**11**)	inthomycin C (**12**)
Antimicrobial activity, MIC (µg/mL)			
Phytophthora parasitica IFO 4873	125	-	-
Phytophthora capsica KF-278	31.3	-	-
Herbicidal activity, MIC (µg/mL)			
Radish seedlings	100	-	-
Velvet leaf	active	-	-
Anticancer activity, MIC (µg/mL)			
Prostate cancer DU-145 cells	25	25	-

N.B. "-" = data not available

Table 2. Summary of biological activity of inthomycin A, B and C (**10–12**)

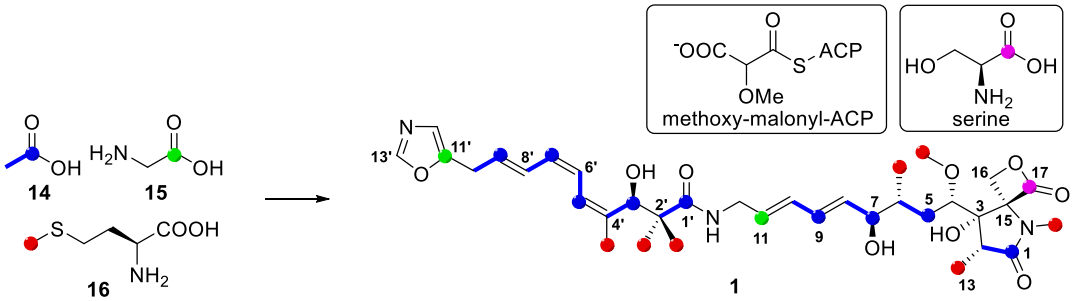
1.3. Biosynthetic studies

1.3.1. Oxazolomycin A, oxazolomycin B and oxazolomycin C

Gräfe and co-workers[17] conducted biogenetic studies on oxazolomycin A (**1**). Their investigations included feeding experiments on *Streptomyces albus* JA3453 with single doses of [^{13}C]-labelled building blocks allowed for a first plausible biosynthesis of this natural product (**Scheme 1**). The oxazole ring originates from glycine (**15**) and the oxazole polyketide starter is elongated using five malonyl-CoA units (*C*-11' to *C*-1') *via* the polyketide pathway. All methyl groups are incorporated from the C_1-pool *via* methionine (**16**). An amidase links the amino function of a second glycine (**15**) building block (or an elongated chain) to the oxazole triene carboxylic acid moiety. The right chain (*C*-11 to *C*-5) is formed *via* the polyketide pathway using three malonyl-CoA units. The *C*-1/*C*-2 unit probably originates from acetate, while *C*-17, *C*-15 and the adjacent nitrogen are derived from glycine (**15**). However, the origin of the C_3 unit linking the diene and the spiro-fused ring fragments (*C*-3, *C*-4 and *C*-16) and the origin of the *C*-13' unit could not be determined.

Feeding experiments conducted separately showed that [^{14}C]-labelled inthomycin was barely incorporated into oxazolomycin A (**1**), suggesting that the inthomycins are not intermediates in the biosynthesis of oxazolomycin A (**1**).[17]

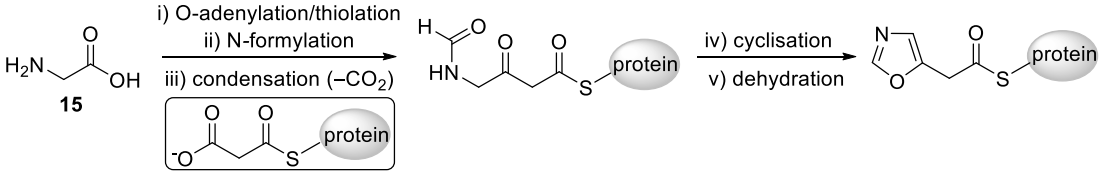
In 2010, Zhao and co-workers reported the oxazolomycin biosynthetic gene cluster from *Streptomyces albus* JA3453.[26] These studies suggested the unusual methoxy-malonyl-ACP (**Scheme 1**) as a possible building block to introduce the methoxy group at *C*-4 and serine as a building block to incorporate the *C*-16, *C*-17, *C*-15 and adjacent nitrogen unit.



Scheme 1. The biosynthesis of oxazolomycin A (**1**)

1.3.2. Inthomycin A, inthomycin B and inthomycin C

Henkel and Zeeck carried out feeding experiments to establish the biosynthetic origin of the inthomycins.[16] The results showed that the *C*-1 to *C*-10 unit of the inthomycins is biosynthetically synthesised *via* the polyketide pathway, although establishing whether the chain derived from five acetate units or from three acetate units and two propionate units was not possible. The oxazole ring (*C*-11, *C*-12 and the nitrogen atom) could be formed by incorporation of a polyketide chain into a glycine (**15**) unit followed by *N*-formylation and cyclisation/dehydration (**Scheme 2**), whereas *C*-13 could originate from the C_1-pool.



Scheme 2. The biosynthesis of the inthomycin oxazole ring

Nevertheless, further biosynthetic studies need to be pursued to fully elucidate the biosynthetic pathway of the inthomycins (feeding experiments with [1-^{13}C]propionate and [CH_3-^{13}C]methionine were not carried out in this biogenetic study).

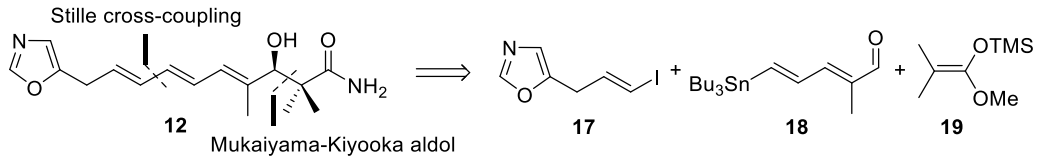
1.4. Previous syntheses of inthomycin C

To date, there have been four reported asymmetric total syntheses of inthomycin C (**12**) by Taylor,[27] Ryu,[28] Hatakeyama[29] and Hale,[30] a formal synthesis of racemic material by Maulide[31] and an asymmetric formal synthesis by Reddy.[32] Recently, Hale and Hatakeyama confirmed the absolute configuration of (−)-(3*R*)-inthomycin C (**12**) by joint collaboration.[33]

All previous syntheses rely on a Stille cross-coupling as a key C–C bond-forming step and they differ mainly in their approach towards the formation of the secondary alcohol stereocentre.

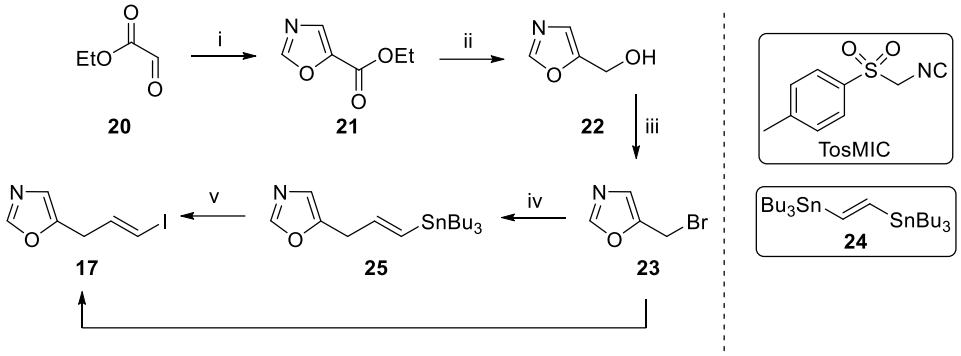
1.4.1. Taylor's asymmetric total synthesis (2008)

In 2008, Taylor and co-workers reported the first total synthesis of inthomycin C (**12**).[27] Key steps in the synthesis include a Stille cross-coupling reaction of iodide **17** and dienylstannane **18** and a Mukaiyama–Kiyooka aldol reaction with silyl ketene acetal **19** (**Scheme 3**).



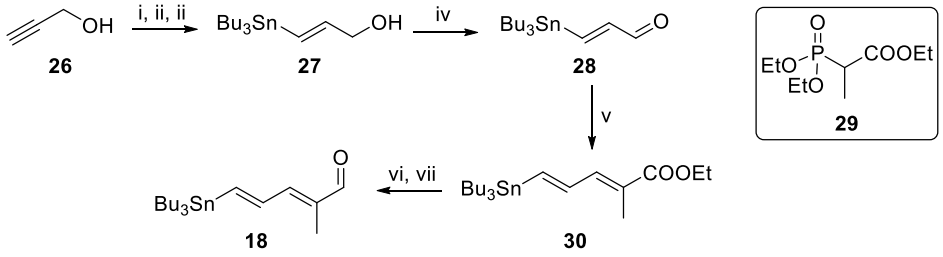
Scheme 3. Taylor's retrosynthesis of inthomycin C (**12**)

Iodide **17** was prepared from ethyl glyoxylate (**20**) in five steps. Treatment of ethyl glyoxylate (**20**) with toluenesulfonylmethyl isocyanide (TosMIC) and K_2CO_3 following van Leusen's methodology[34] afforded oxazole **21**, which was reduced to primary alcohol **22** and brominated to form bromide **23**. An sp^3-sp^2 Stille coupling between bromide **23** and stannane **24** furnished stannane **25**, which upon iodination provided iodide **17**. Alternatively, the last two steps could be performed in one pot. This way, iodide **17** was synthesised in 30% yield over five steps (or 32% yield over four steps) from ethyl glyoxylate (**20**) (**Scheme 4**).



Scheme 4. Reagents and conditions: i) TosMIC, K_2CO_3, EtOH, 80 °C, 86%; ii) $NaBH_4$, EtOH, r.t., 60 h, 85%; iii) NBS, PPh_3, CH_2Cl_2, 0 °C, 1 h, 94%; iv) Pd_2dba_3 (5 mol%), *E*-$Bu_3SnCH{=}CHSnBu_3$, THF, 80 °C, 4 h, 51%; v) I_2, CH_2Cl_2, 0 °C, 20 min, 86%; vi) Pd_2dba_3 (5 mol%), *E*-$Bu_3SnCH{=}CHSnBu_3$, THF, 80 °C, 4 h, then I_2 at 0 °C, overnight, 46%

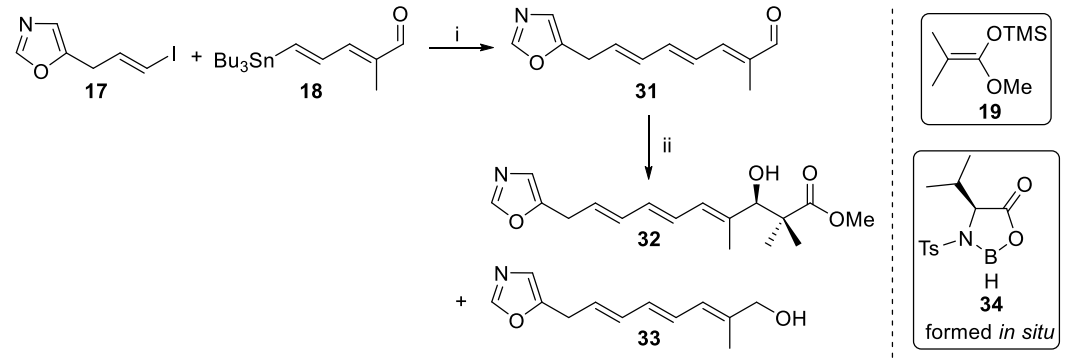
Dienylstannane **18** was synthesised in seven steps from propargyl alcohol (**26**). Wender's procedure[35] afforded allylic alcohol **27** from propargyl alcohol (**26**) *via* silylation, hydrostannylation and desilylation. Oxidation of allylic alcohol **27** furnished α,β-unsaturated aldehyde **28**. Horner–Wadsworth–Emmons reaction between aldehyde **28** and phosphonate **29** provided ester **30**. A reduction/oxidation sequence on ester **30** produced dienylstannane **18** (**Scheme 5**).



Scheme 5. Reagents and conditions: i) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 21 h; ii) poly(methyl hydrogen siloxane), bis-(tri-*n*-butyltin) oxide, AIBN, 80 °C, 2 h; iii) TBAF, THF, r.t., 2.5 h; iv) MnO_2, CH_2Cl_2, r.t., 3 days then 40 °C, 21 h, 92%; v) KHMDS, 18-crown-6, THF, −78 °C, 30 min then **29**, −78 °C to r.t., overnight, 98%; vi) DIBAL-H, CH_2Cl_2, −10 °C to r.t., 3 h, quant.; vii) MnO_2, CH_2Cl_2, r.t., 2 days, quant.

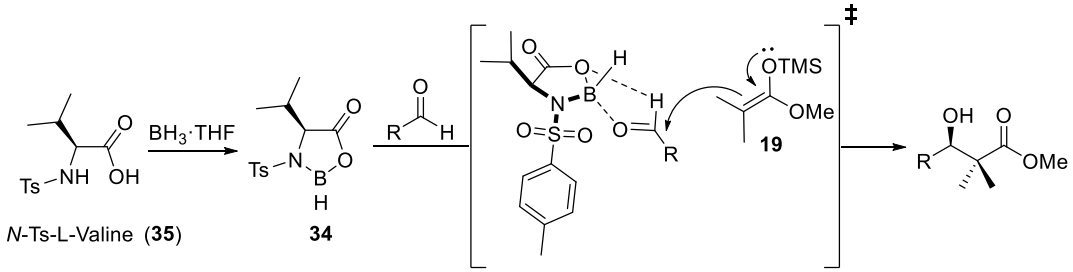
Stille coupling of vinyl iodide **17** and dienylstannane **18** afforded trienal **31** in 74% yield. Mukaiyama–Kiyooka aldol reaction of trienal **31** with silyl ketene acetal **19** furnished (*R*)-ester **32** in 50% yield and 76% ee, as determined by Mosher ester analysis. An excess of *in situ* generated oxazaborolidinone catalyst **34** was required to perform the aldol reaction,

probably due to complexation with the oxazole, and consequently competitive reduction alcohol **33** by-product was also isolated in 43% yield (**Scheme 6**).



Scheme 6. Reagents and conditions: i) 5 mol% $Pd(CH_3CN)_2Cl_2$, DMF, r.t., 2 h, 74%; ii) *N*-Ts-L-valine, BH_3·THF, CH_2Cl_2, 0 °C, 20 min then r.t., 30 min then −78 °C, 2 h, **31** and **19**, 50% **32** (76% ee) and 43% **33**

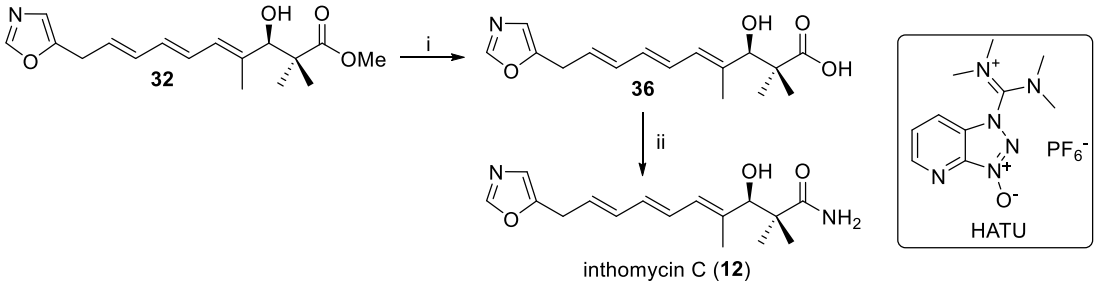
Yamamoto and co-workers reported the first amino acid-derived oxazaborolidinone catalysts and their application as chiral Lewis acids in asymmetric Diels–Alder reactions.[36] Shortly after, Kiyooka and co-workers revealed their use in enantioselective Mukaiyama aldol reactions of aldehydes with silyl ketene acetals.[37] The stereoselectivity observed in the reaction can be explained by the transition state shown below (**Scheme 7**).



Scheme 7. Mechanism of the Mukaiyama–Kiyooka aldol reaction

Oxazaborolidinone catalyst **34** is formed *in situ* by treating *N*-Ts-L-valine (**35**) with BH_3·THF before reaction with the aldehyde. The R group of the aldehyde points away from the sterically hindered top face of the catalyst and a hydrogen bond is formed between the formyl proton and the ring oxygen. Attack by silyl ketene acetal **19** occurs from the *Si*-face of the aldehyde since the *Re*-face is shielded by the bulky catalyst. Coordination of the boron atom of the catalyst with the oxygen atom of the carbonyl group together with the formyl hydrogen bond described above are proposed to fix the conformation of the aldehyde and thus contribute to achieve good enantioselectivity.[38,39]

Taylor's synthesis was completed by hydrolysis of ester **32** to afford acid **36** and HATU-mediated coupling with *in situ* generated ammonia to provide inthomycin C (**12**) in 33% yield (**Scheme 8**). However, the synthesised natural product contained 20% tetramethylurea by-product that could not be removed. The authors mentioned that further optimisation of the Mukaiyama–Kiyooka aldol reaction was required to obtain greater enantiocontrol.[27]

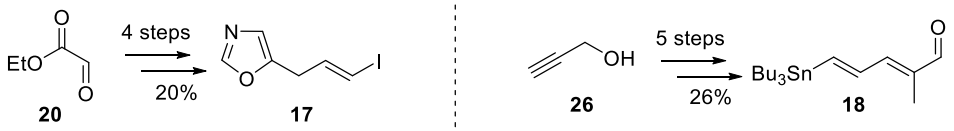


Scheme 8. Reagents and conditions: i) $LiOH \cdot H_2O$, THF-MeOH-H_2O 3:1:1, r.t., 22 h, 89%; ii) HATU, *i*-Pr_2NEt, NH_4Cl, THF, r.t., 15 h, 33%

1.4.2. Ryu's asymmetric total synthesis (2010)

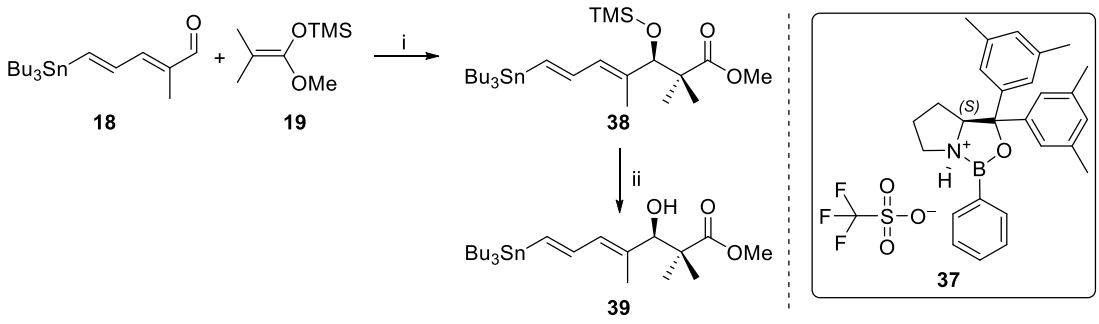
Ryu and co-workers published a total synthesis of inthomcyin C (**12**) following a similar strategy to Taylor's group but using a different catalyst for the Mukaiyama aldol reaction.[28]

The synthesis started with the preparation of dienylstannane **18** and vinyl iodide **17** according to Taylor's procedure.[27] In this way, iodide **17** was synthesised in 20% over 4 steps from ethyl glyoxylate (**20**) and stannane **18** was synthesised in 26% yield over five steps from propargyl alcohol (**26**) (**Scheme 9**).



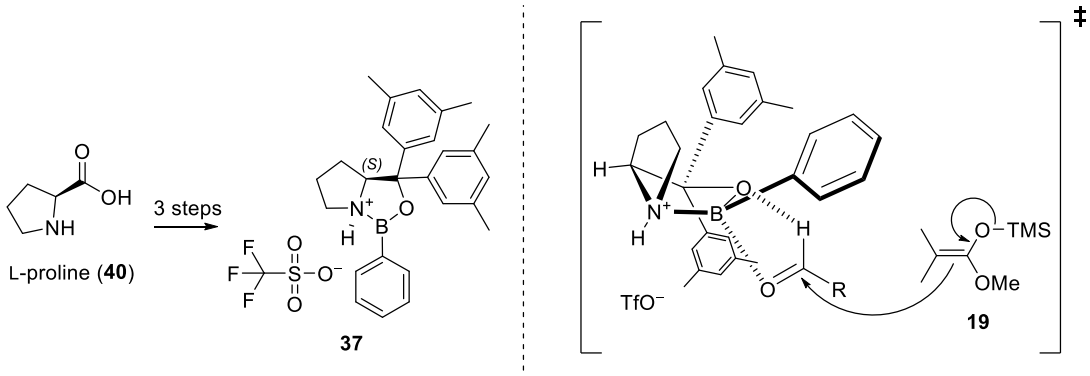
Scheme 9. Ryu's synthesis of Taylor intermediates

The next step was the Mukaiyama aldol reaction. Stannane **18** was reacted with silyl ketene acetal **19** under optimised conditions using chiral oxazaborolidinium catalyst **37** to form silylated product **38** in 86% yield and 93% ee, as determined by chiral HPLC analysis. Deprotection of aldol product **38** with TBAF afforded alcohol **39** without affecting the enantiomeric excess (**Scheme 10**).



Scheme 10. Reagents and conditions: i) **37** (20 mol%), Ph_3PO (50 mol%), PhMe, −40 °C, 36 h, 92% (93% ee); ii) TBAF, THF, −78 °C to 0 °C, 20 min, 86% (93% ee)

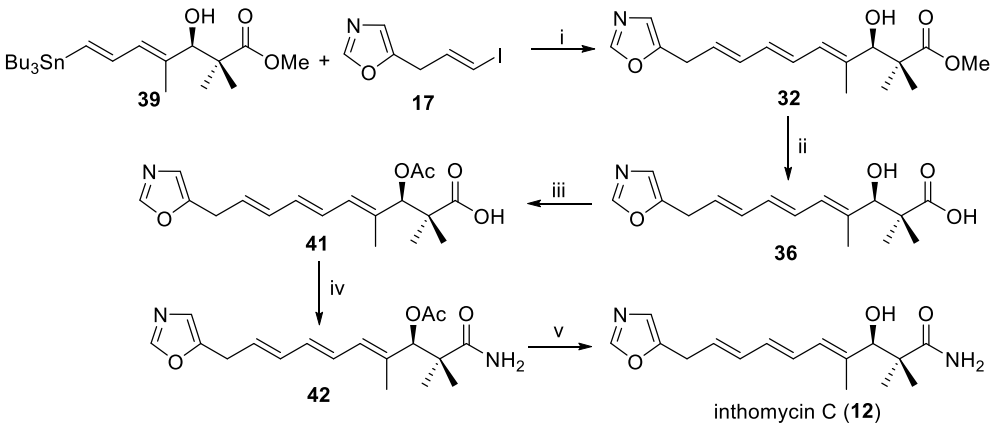
Catalyst **37** can be formed *in situ* over 3 steps from L-proline (**40**).[40] The stereoselectivity of the Mukaiyama aldol reaction can be rationalised by the transition state shown below (**Scheme 11**).



Scheme 11. Synthesis of oxazaborolidinium catalyst **37** and transition state of Mukaiyama aldol

The bulky aryl substituents on the catalyst shield the *Re* face (back) of the aldehyde from attack by the silyl ketene acetal. Therefore, nucleophilic attack of silyl ketene acetal **19** takes place from the *Si* face (front) of the aldehyde.

Stille coupling between enantioenriched alcohol **39** and vinyl iodide **17** furnished ester **32** and subsequent saponification provided acid **36**. Acetylation of **36** followed by activation with oxalyl chloride and treatment with ammonium hydroxide produced amide **42**. Finally, deprotection of the acetate group in **42** afforded inthomycin C (**12**) in 11% yield over twelve steps from propargyl alcohol (**26**) (**Scheme 12**).



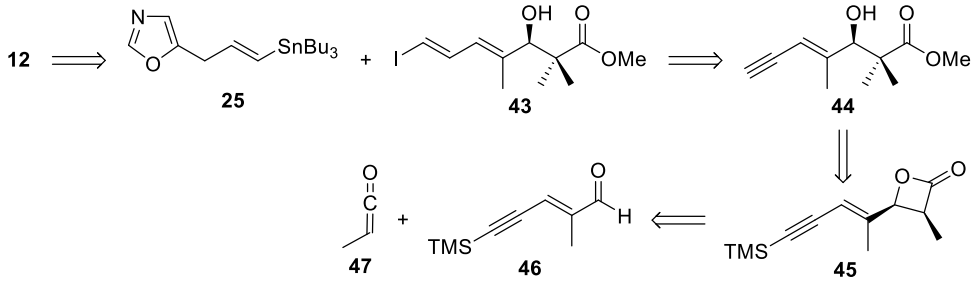
Scheme 12. Reagents and conditions: i) $Pd(PPh_3)_4$, CsF, CuI, DMF, 45 °C, 3.5 h, 85%; ii) $LiOH·H_2O$, THF-MeOH-H_2O 3:1:1, 0 °C to r.t., 22 h, 90%; iii) Ac_2O, pyridine, 0 °C to r.t., 20 h, 95%; iv) $(COCl)_2$, DMF (1 drop), CH_2Cl_2, 0 °C, 3.5 h then excess NH_4OH (28%), r.t., 12 h, 90%; v) $LiOH·H_2O$, THF-MeOH-H_2O 3:1:1, 0 °C to r.t., 2 h, 80%

Ryu's synthesis of inthomycin C (**12**) allowed the introduction of the alcohol stereocentre in higher yield and enantioselectivity than previously reported by Taylor.

1.4.3. Hatakeyama's asymmetric total synthesis (2012)

Hatakeyama and co-workers took a different synthetic strategy towards inthomycin C (**12**), where the introduction of the secondary alcohol stereocentre was accomplished *via* a *Cinchona* alkaloid-catalysed asymmetric β-lactone synthesis.[29]

The last step in the synthetic sequence was a Stille coupling between stannane **25** and iododiene **43** to complete the carbon backbone of the natural product. Iododiene **43** was obtained by a hydrometallation-iodination sequence on alkyne **44**, which originated from the ring opening of β-lactone **45**. Finally, β-lactone **45** was accessed *via* a *Cinchona* alkaloid-catalysed asymmetric [2+2] cycloaddition of aldehyde **46** and ketene **47** (**Scheme 13**).[29]

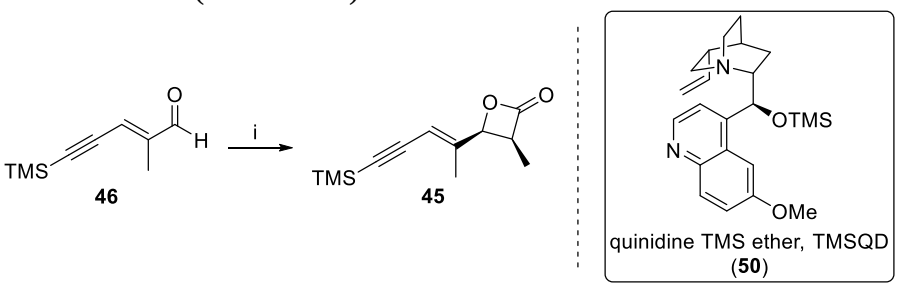


Scheme 13. Hatakeyama's retrosynthesis of inthomycin C (**12**)

Aldehyde **46** was prepared in three steps from propargyl alcohol (**26**). Negishi methylation-iodination[41] of propargyl alcohol (**26**) afforded alcohol **48**. Sonogashira coupling of alcohol **48** with ethynyltrimethylsilane gave alcohol **49**, which was subjected to MnO_2 oxidation to provide aldehyde **46** (**Scheme 14**).

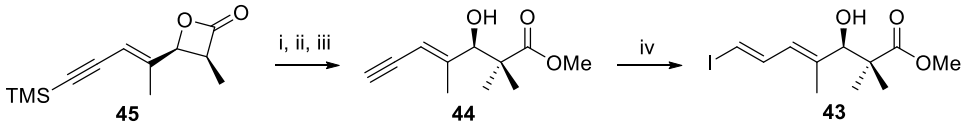
Scheme 14. Reagents and conditions: i) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2 then I_2, THF, −78 °C to r.t., 55%; ii) *i*-Pr_2NH, CuI, $PdCl_2(PPh_3)_2$, THF, ethynyltrimethylsilane, 99%; iii) MnO_2, hexane-CH_2Cl_2 1:1, 94%

Cinchona alkaloid-catalysed [2+2] cycloaddition of aldehyde **46** with propionyl chloride following Nelson's procedure[42] afforded β-lactone **45** in good yield and excellent enantio- and diastereoselectivities (**Scheme 15**).



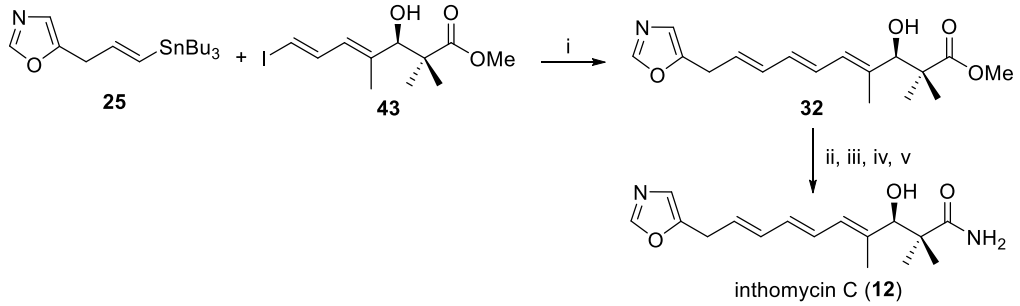
Scheme 15. Reagents and conditions: i) EtCOCl, *i*-Pr_2NEt, **50** (20 mol%), $LiClO_4$, CH_2Cl_2-Et_2O 2:1, −78 °C, 15 h, 85% (98% ee, >99% de)

Methanolysis of β-lactone **45**, followed by methylation using Seebach's protocol[43] and subsequent desilylation afforded ester **44**, which upon a stannylcupration-iodination[44] sequence provided iododiene **43** with good regioselectivity (**Scheme 16**).



Scheme 16. Reagents and conditions: i) NaOMe, MeOH; ii) LDA, CH_3I, THF, −78 °C; iii) NaOMe, MeOH, 80% over 3 steps; iv) *n*-BuLi, Bu_3SnH, CuCN, THF, −40 °C then I_2, −78 °C, 60% (7:1 regioisomeric ratio)

Stille coupling of iododiene **43** with stannane **25** produced geometrically pure triene **32**. Finally, the total synthesis was completed by hydrolysis, acetylation, amidation and acetyl group deprotection of ester **32** (**Scheme 17**).

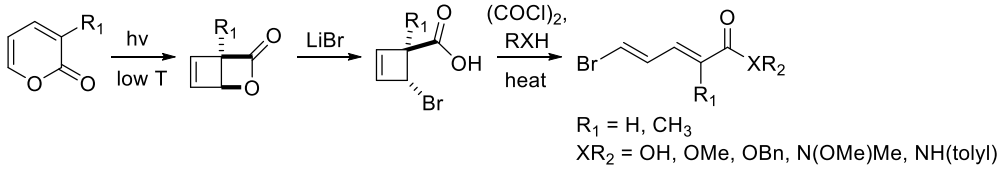


Scheme 17. Reagents and conditions: i) $Pd(PPh_3)_4$ (1 mol%), CuI (10 mol%), CsF, DMF, 79%; ii) LiOH, THF-H_2O-MeOH 3:1:1; iii) Ac_2O, pyridine then $NaHCO_3$, MeOH; iv) $SOCl_2$, DMF, CH_2Cl_2 then NH_4OH (25%); v) LiOH, THF-H_2O-MeOH 3:1:1, 22% over 4 steps

Overall, inthomycin C (**12**) was synthesised over thirteen steps in 3.6% yield. Despite the low yield, Hatakeyama's route afforded this natural product with the highest enantiomeric excess so far.

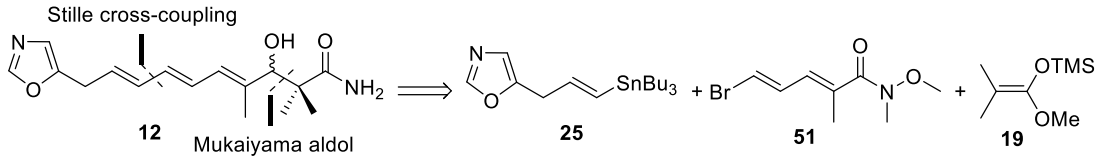
1.4.4. Maulide's formal synthesis of racemic material (2013)

In 2013, Maulide and co-workers developed a new method to access halodiene carboxylate building blocks stereoselectively from halocyclobutene precursors *via* 4π-electrocyclic conrotatory ring opening upon heating.[31] The resulting halodiene intermediates were used in Suzuki, Sonogashira and Stille cross-coupling reactions to prepare various polyenic natural product-like compounds (**Scheme 18**).



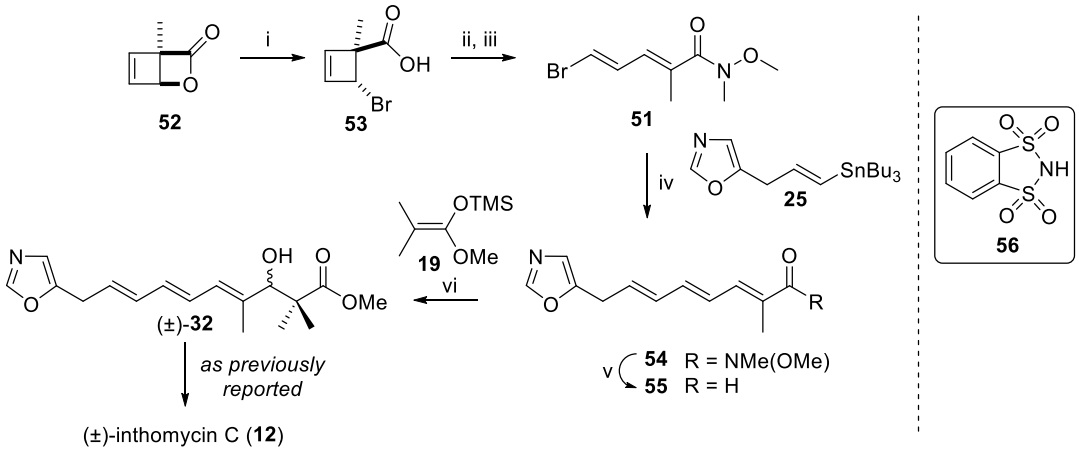
Scheme 18. Maulide's stereoselective synthesis of halodiene carboxylate building blocks

The synthetic utility of this approach was showcased by the formal synthesis of racemic inthomycin C (**12**). Maulide's retrosynthetic analysis towards inthomycin C (**12**) consists of two main disconnections: a Stille cross-coupling of bromide **51** and stannane **25** and a Mukaiyama aldol reaction with silyl ketene acetal **19** (**Scheme 19**).



Scheme 19. Maulide's retrosynthesis of (±)-inthomycin C (**12**)

Bromide **51** was prepared in three steps from β-lactone **52**. Ring opening of β-lactone **52** with lithium bromide furnished bromocyclobutene **53**, which after amide coupling and 4π-electrocyclic ring opening afforded bromide **51** as a single geometrical isomer (**Scheme 20**).



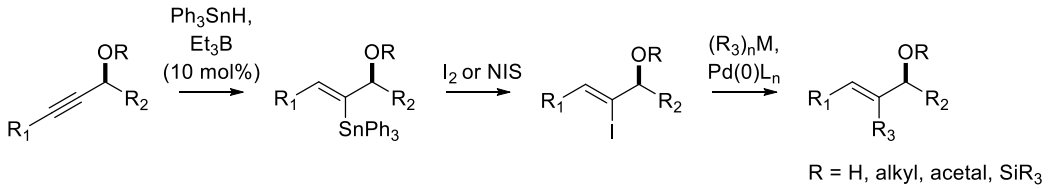
Scheme 20. Reagents and conditions: i) LiBr, THF, r.t.; ii) $(COCl)_2$, then NH(OMe)Me·HCl, CH_2Cl_2, 0 °C; iii) μW, THF, 73% over 3 steps; iv) PEPPSi (3 mol%), DMF, 50 °C, 72%; v) DIBAL-H, CH_2Cl_2, −78 °C, 63%; vi) **56** (5 mol%), CH_2Cl_2, r.t. then TBAF, THF, 0 °C, 50%

Stille cross-coupling with stannane **25** and subsequent reduction of the Weinreb amide provided aldehyde **55**. Finally, organocatalytic Mukaiyama aldol reaction of aldehyde **55** with silyl ketene acetal **19** led to racemic ester **32**, which could be converted into racemic inthomycin C (**12**) following the previously reported procedures (**Scheme 20**).[27–29]

1.4.5. Hale's asymmetric total synthesis (2014)

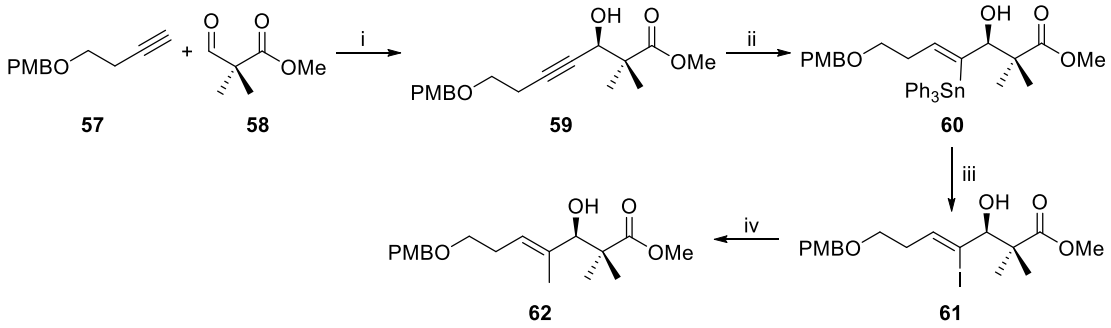
Hale and co-workers reported the total synthesis of inthomycin C (**12**) *via* an *O*-directed free radical alkyne hydrostannation reaction,[30] a methodology previously developed by the same research group to access trisubstituted alkenes.[45] Other key steps in the synthesis include a Stille cross-coupling and an asymmetric alkynylation reaction.

O-directed free radical hydrostannation of propargylically oxygenated dialkylacetylenes, followed by iodination, tin-iodine exchange and cross-coupling reactions allowed the preparation of allylic alcohols with a β-quaternary carbon centre, including inthomycin C (**12**) (**Scheme 21**).



Scheme 21. Synthesis of trisubstituted alkenes *via O*-directed free radical hydrostannation

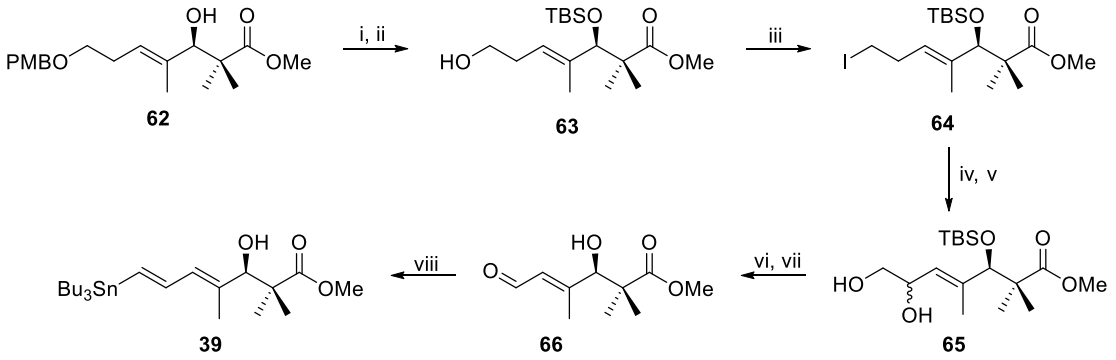
The synthesis started with the asymmetric alkynylation of aldehyde **58** with alkyne **57** to afford alcohol **59** in 83% ee and in agreement with Carreira's stereochemical model, as confirmed by Mosher ester analysis.[46] Alcohol **59** was then subjected to the *O*-directed free radical hydrostannation protocol to provide vinylstannane **60** in excellent yield and good stereoselectivity. Tin-iodine exchange and subsequent Stille cross-coupling with tetramethyltin furnished alcohol **62** (**Scheme 22**).



Scheme 22. Reagents and conditions: i) (−)-NME, $Zn(OTf)_2$, Et_3N, PhMe, 60 °C, 63 h, 82% (83% ee); ii) Ph_3SnH, Et_3B, O_2 (cat.), PhMe, r.t., 20 h, 95%; iii) NIS, CH_2Cl_2, 0 °C then r.t., 4 h, 86%; iv) Me_4Sn, CuI, CsF, $Pd(PPh_3)_4$, DMF, 45 °C, 1 h, 75%

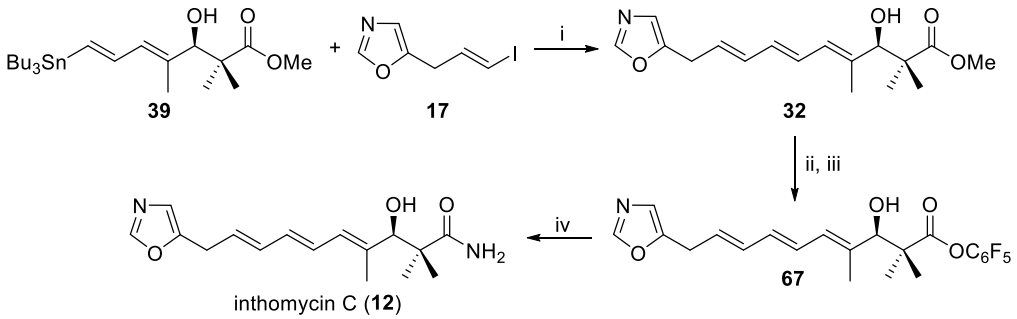
TBS-protection of alcohol **62** followed by PMB-deprotection and iodination gave iodide **64**, which after elimination and subsequent Sharpless dihydroxylation afforded diol **65**. TBS-deprotection on diol **65** and terminal diol cleavage produced enal **66**. A Hodgson

vinylstannation[47] was performed on enal **66** to afford Ryu's advanced intermediate **39** (**Scheme 23**).



Scheme 23. Reagents and conditions: i) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C then r.t., 1.5 h, 82%; ii) DDQ, CH_2Cl_2-H_2O 18:1, r.t., 18.5 h, 97%; iii) I_2, PPh_3, imidazole, PhMe, 3 h, r.t., 98%; iv) DBU, PhMe, 4 h, 45 °C, 95% (all *E*); v) AD-mix-β, *t*-BuOH-H_2O 1:1, r.t., 20.5 h, 88%; vi) 40% aq. HF, MeCN, r.t., 20 min, 84%; vii) $NaIO_4$, THF-H_2O 3:1, 80 min, r.t., 84%; viii) $CrCl_2$, (*n*-Bu)$_3$SnCHI$_2$, DMF, 0 °C to r.t., 1 h, 46%

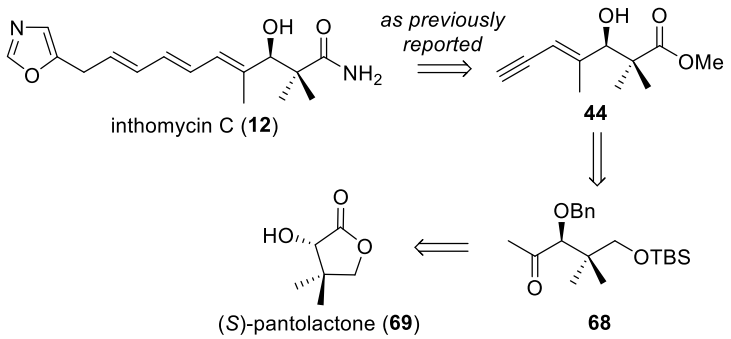
Stille cross-coupling of stannane **39** with iodide **17** provided triene **32** as a mixture of triene isomers of which the desired product predominated. Ester hydrolysis on **32**, conversion into pentafluorophenyl ester **67** and subsequent treatment with dry NH_3 completed the total synthesis of inthomycin C (**12**) (**Scheme 24**).



Scheme 24. Reagents and conditions: i) $Pd(PPh_3)_4$, CsF, CuI, DMF, 45 °C, 50 min, 71%; ii) LiOH·H_2O, THF-MeOH-H_2O 3:1:1; iii) C_6F_5OH, EDC·HCl, DMAP, CH_2Cl_2, r.t., 55 min, 58% over 2 steps; iv) NH_3 (g), THF, r.t., 30 min, 95% (5.9:1 isomeric mixture)

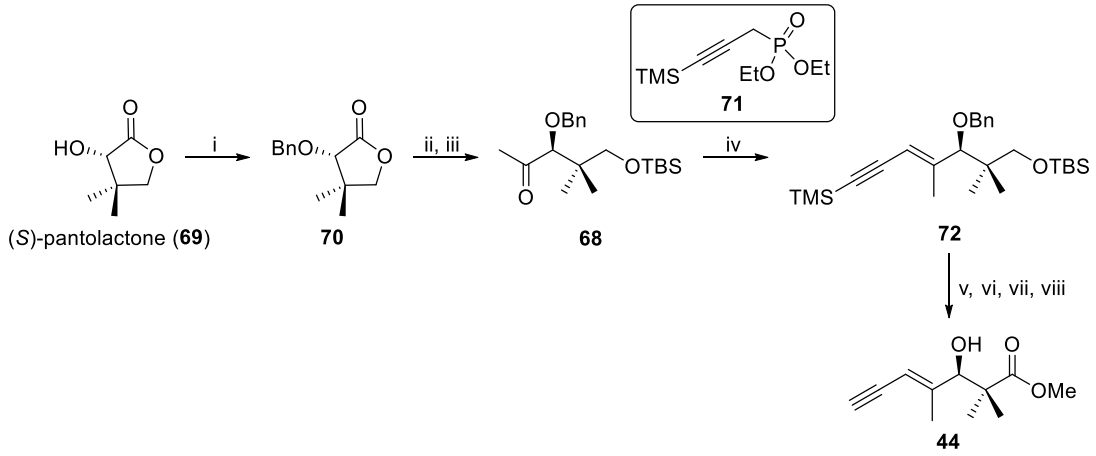
1.4.6. Reddy's asymmetric formal synthesis (2016)

Reddy and co-workers published a formal synthesis of inthomycin C (**12**)[32] starting from commercially available (*S*)-pantolactone (**69**) and intersecting enyne intermediate **44** in Hatakeyama's route.[29] Enyne **44** was prepared through a Horner–Wadsworth–Emmons reaction from Bn-protected ketoalcohol **68**, which was obtained from (*S*)-pantolactone (**69**) (**Scheme 25**).



Scheme 25. Reddy's retrosynthesis of inthomycin C (**12**)

Enyne **44** was prepared in eight steps from (*S*)-pantolactone (**69**). Benzyl protection of (*S*)-pantolactone (**69**) afforded benzyl ether **70**, which was converted into the corresponding methyl ketone *via* a Weinreb amide formation/methylation sequence and TBS-protection to furnish ketone **68**. Horner–Wadsworth–Emmons olefination of ketone **68** with phosphonate **71**[48] gave enyne **72**, which after a four-step sequence (including TBS and TMS-deprotection, Jones oxidation, esterification and Bn-deprotection) provided Hatakeyama's enyne **44** in 31% yield and 93% ee over eight steps (**Scheme 26**).



Scheme 26. Reagents and conditions: i) $BnOC(NH)CCl_3$, hexane-CH_2Cl_2 2:1, TfOH, 4 h, r.t., 87%; ii) NH(Me)OMe·HCl, MeMgBr, THF, 24 h; iii) TBSCl, imidazole, DMF, 24 h, r.t., 81% over 2 steps; iv) **71**, *n*-BuLi, THF, 2 h, 88%; v) TBAF, THF, 4 h, r.t., 92%; vi) Jones reagent (0.7 M), acetone, 0 °C; vii) $TMSCHN_2$, PhMe-MeOH 9:1, 76% over 2 steps; viii) DDQ, DCE-pH 7 buffer 9:1, 55 °C, 10 h, 71% (93% ee)

1.4.7. Inthomycin C absolute configuration determination

Henkel and Zeeck assigned the absolute configuration at *C*-3 of inthomycin C (**12**) as (*R*) by converting the natural product into the 3-*O*-(*S*)-2-phenylbutanoate ester. However, due

to the scarce availability of isolated pure material, they could not measure the $[\alpha]_D$ of inthomycin C (**12**).[16]

Taylor and co-workers completed the first total synthesis of inthomycin C (**12**) in 76% ee and with 3*R* configuration, as determined by Mosher ester analysis.[27] Taylor reported an $[\alpha]_D$ of +25.9 (c 0.27, $CHCl_3$). Nevertheless, the synthesised natural product contained 20% inseparable tetramethylurea impurity. The positive sign of the $[\alpha]_D$ value obtained by Taylor was proven to be erroneous in later studies,[33] probably due to the presence of the tetramethylurea contaminant.

All subsequent total syntheses[28–30] reported negative $[\alpha]_D$ values for inthomycin C (**12**). Hale's synthesis intersected intermediates of the two preceding syntheses: Ryu's stannane **39** and Hatakeyama's enyne **44**. Surprisingly, Hale reported positive $[\alpha]_D$ values for both intermediates, in contrast to Ryu and Hatakeyama who had previously reported negative $[\alpha]_D$ values for the same intermediates. Hale, unlike Ryu, unambiguously determined the (3*R*) configuration of stannane **39** by Mosher ester analysis of precursor **59**. The discrepancies described above led Hale to incorrectly conclude that both Ryu and Hatakeyama had actually synthesised unnatural (3*S*)-inthomcyin C (**Figure 2**).[30]

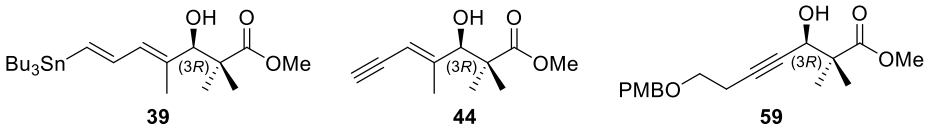


Figure 2. Intermediates towards inthomycin C (**12**)

After Hale had cast doubt on previous work, the Hatakeyama group decided to review their experimental data and they discovered an error in their published manuscript.[29] Their laboratory records revealed an $[\alpha]_D$ for enyne **44** of opposite sign to the originally published $[\alpha]_D$ value. This new finding suggested that both Hale and Hatakeyama had indeed synthesised (−)-(3*R*)-inthomycin C (**12**). To dispel any doubt, Hatakeyama converted a sample of enyne **44** the group had stored from their original 2012 total synthesis into the

(*R*)- and (*S*)-MTPA Mosher esters. The NMR spectra of both Mosher esters matched almost perfectly the NMR spectra of both Mosher esters from Hale's synthesis. Furthermore, Hatakeyama measured the $[\alpha]_D$ of their original sample of enyne **44** and found it correlated well with the value reported by Hale previously.

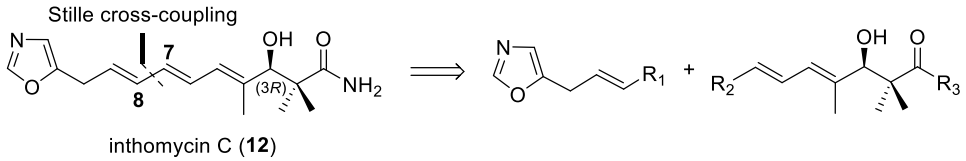
Later, collaborative work between Hatakeyama and Hale confirmed that both had synthesised (3*R*)-inthomycin C (**12**).[33] The Hale group recorded the $[\alpha]_D$ of the sample of (3*R*)-enyne **44** synthesised by the Hatakeyama team and they found it correlated nicely with the Hale group published $[\alpha]_D$ value. To put this correlation beyond any future doubt, Hale and Hatakeyama both prepared the (*R*)- and (*S*)-MTPA esters of their respective inthomycin C (**12**) samples. For the preparation of the corresponding Mosher esters, Hatakeyama had to resynthesise inthomycin C (**12**) from (3*R*)-enyne **44** since their original sample of the natural product had decomposed. Fortunately, Hale had preserved a sample of inthomycin C (**12**), which was converted into the (*R*)- and (*S*)-MTPA esters and their NMR spectra were analysed. Both Hatakeyama's and Hale's Mosher ester analyses concluded that their synthesised inthomycin C (**12**) samples had a (3*R*) configuration. Therefore, this provided further evidence that both research groups had indeed synthesised natural (3*R*)-inthomycin C (**12**). Hatakeyama also re-measured the $[\alpha]_D$ of the newly re-synthesised natural product and it was found to have a negative sign, correcting their previously reported data and suggesting that Taylor's positive $[\alpha]_D$ should be re-evaluated too. The $[\alpha]_D$ of stannane **39** measured by Ryu differed in sign from the Hale group $[\alpha]_D$ measurement, indicating that Ryu's measurement required re-examination given the unequivocally proven (3*R*)-stereochemistry of Hale's stannane **39** sample.

After careful assessment of all available evidence regarding the various total syntheses of inthomycin C (**12**), Hale and Hatakeyama concluded that the Hatakeyama, Hale, Ryu and Taylor teams had all synthesised (−)-(3*R*)-inthomycin C (**12**). They also concluded that the

incongruity in Taylor's $[\alpha]_D$ measurement was most likely due to the 20% tetramethylurea impurity that was present. This joint work between Hale and Hatakeyama allowed to then securely assign the absolute configuration of inthomycin C (**12**).[33]

1.4.8. Comparison of the syntheses

All published syntheses of inthomycin C (**12**) used a Stille cross-coupling reaction to form the *C*7–*C*8 bond. As described earlier, they differ in their approach towards the synthesis of the β-hydroxyl carbonyl moiety. A comparative table of the different syntheses of inthomycin C (**12**) that have been reported to date is given below (**Table 3**).



inthomycin C (**12**)

	R_1	R_2	R_3	Steps[a] (LLS)	Yield[b] (%)	ee (%)	$[\alpha]_D$
Asymmetric total syntheses							
Taylor (2008)	I	$SnBu_3$	OMe	11	-	76	+25.9[c] (c 0.27, $CHCl_3$)
Ryu (2010)	I	$SnBu_3$	OMe	14	10.6	93	–34.3 (c 0.1, $CHCl_3$)
Hatakeyama (2012)	$SnBu_3$	I	OMe	11	3.6	98	–7.9 (c 0.33, $CHCl_3$)
Hale (2014)	I	$SnBu_3$	OMe	16	2.5	83	–8.4[d] (c 1.0, $CHCl_3$)
Formal synthesis of racemic material							
Maulide (2013)	$SnBu_3$	Br	NMe(OMe)	10 (+2–4)[27–30]	-	N/A	N/A
Asymmetric formal synthesis							
Reddy (2016)	$SnBu_3$	I	OMe	8 (+6)[29]	30.8[e]	N/A	N/A

N.B. "LLS" = longest linear sequence. "-" = data not available. [a]Values in parentheses indicate the number of extra steps needed to complete the total synthesis. [b]Yields for initial three steps were not provided by Taylor; yields for initial five steps were not provided by Maulide. [c]Contaminated with 20% tetramethylurea. [d]5.9:1 mixture of **12** and unknown isomer. [e]Yield of formal synthesis (synthesis of enyne **44**)

Table 3. Summary of reported syntheses of inthomycin C (**12**)

Of all syntheses of inthomycin C (**12**) reported so far, Hatakeyama's synthesis[29] combines the highest enantioselectivity with the smallest number of linear steps.

1.5. Previous synthesis of oxazolomycin A

To date, only one total synthesis of oxazolomycin A (**1**) has been reported by Hatakeyama,[49] while oxazolomycin B (**2**) remains an unsolved synthetic challenge. In 2012, the Donohoe

group published the synthesis of the pyrrolidinone core **73** of the oxazolomycin family (**Figure 3**).[50]

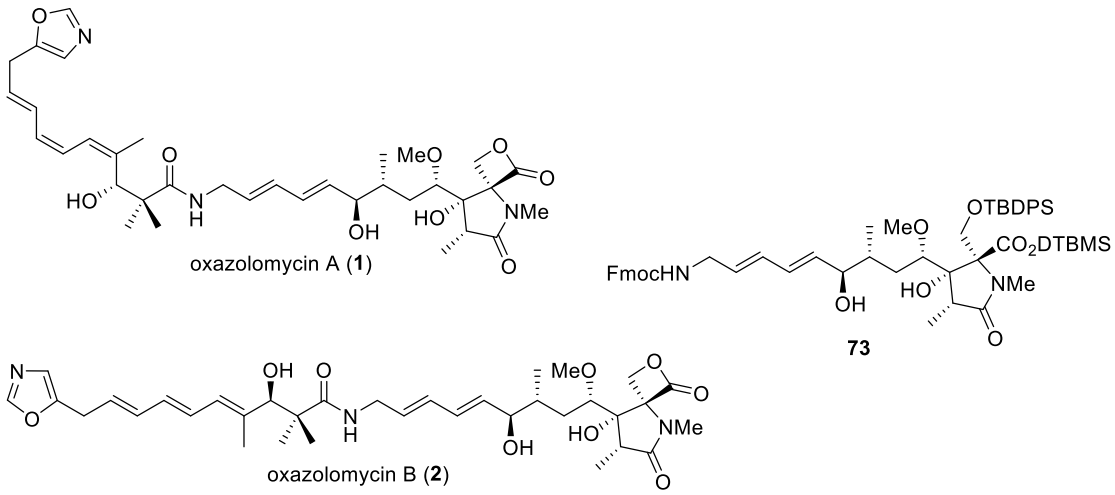


Figure 3. Oxazolomycin A (**1**), oxazolomycin B (**2**) and pyrrolidinone fragment **73**

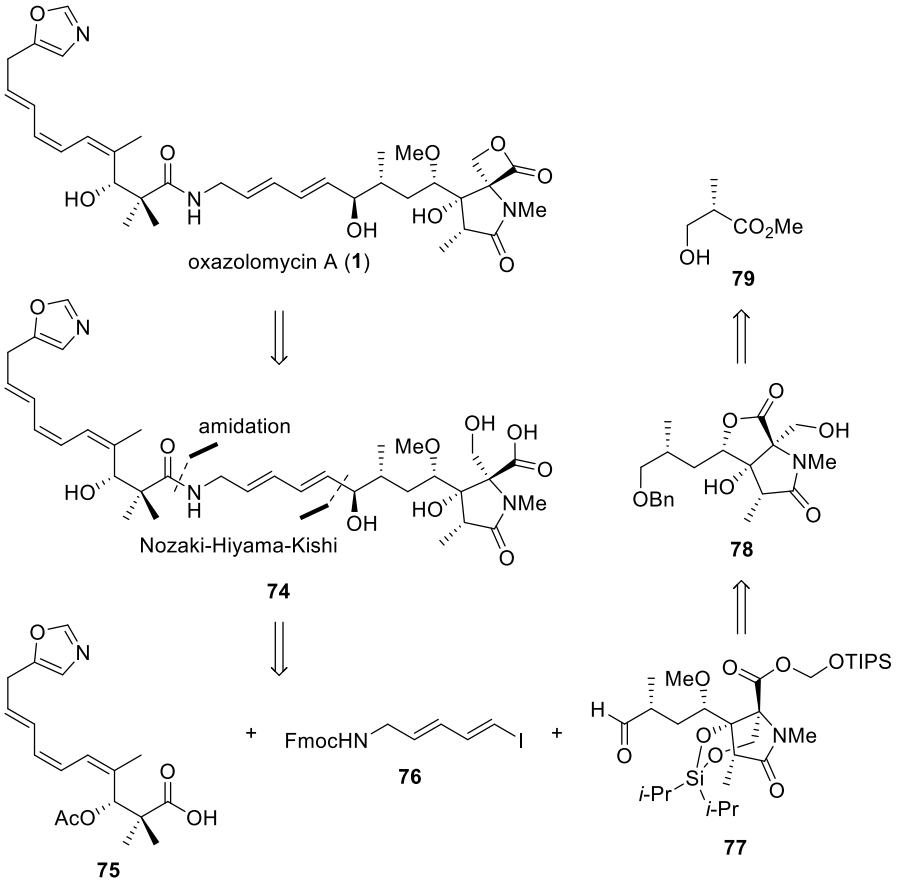
1.5.1. Hatakeyama's asymmetric total synthesis (2011)

The first and only total synthesis to date of the parent member of the oxazolomycin family, oxazolomycin A (**1**), was reported in 2011 by Hatakeyama and co-workers.[49] Although several methodologies have been developed to access the left-hand polyene fragment and the right-hand heterocyclic core, the total synthesis of other members of the oxazolomycin family, except neooxazolomycin,[51,52] has yet to be accomplished.

Key features of Hatakeyama's synthesis of oxazolomycin A (**1**) include an In(III)-catalysed Conia-ene type cyclisation[53] to construct the right-hand heterocyclic core and a *Cinchona* alkaloid-catalysed cyclocondensation of an aldehyde with an acid chloride to access the left-hand oxazolyl-triene fragment.

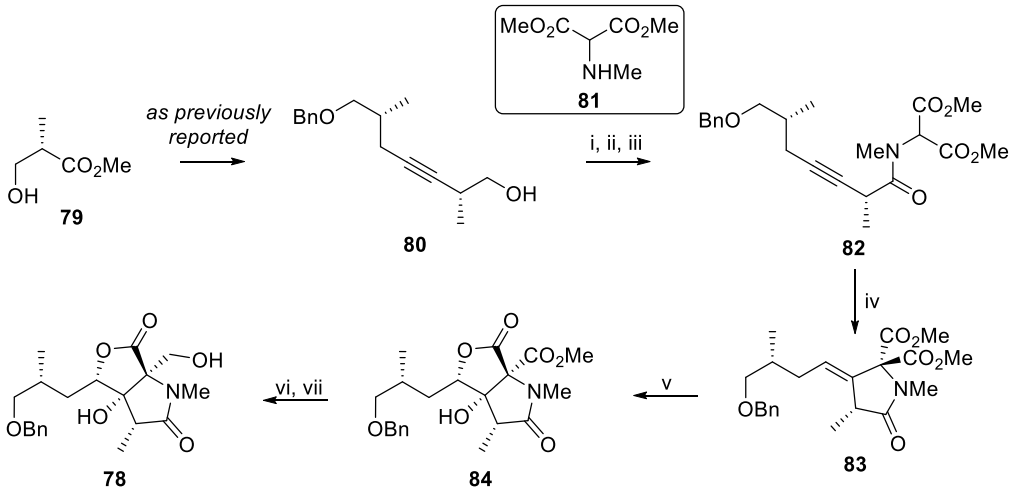
The formation the β-lactone ring from acid **74** was designed to be the last step in the synthetic sequence given its lability. Tetrahydroxy acid **74** was prepared from the left-hand acid fragment **75**, the middle diene fragment **76** and the right-hand aldehyde fragment **77** *via* a Nozaki–Hiyama–Kishi coupling[54,55] and an amidation reaction. Aldehyde **77** was obtained from γ-lactone **78** through a lactone cleavage/methylation/protection sequence. Following

an improved multistep procedure inspired by their previous synthesis of neooxazolomycin,[52] γ-lactone **78** was synthesised from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate (**79**) (**Scheme 27**).



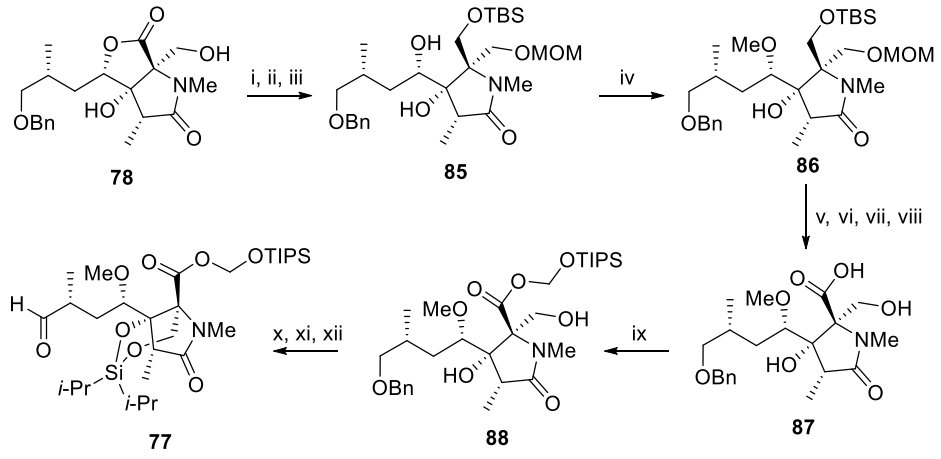
Scheme 27. Hatakeyama's retrosynthesis of oxazolomycin A (**1**)

Methyl (*S*)-3-hydroxy-2-methylpropionate (**79**) was converted into alkyne **80** employing the conditions described in their earlier neooxazolomycin synthesis publication.[52] Jones oxidation of alkyne **80** followed by conversion to the corresponding acid chloride and condensation with dimethyl 2-(methylamino)malonate (**81**) gave amide **82**. An In(III)-catalysed Conia-ene cyclisation of amide **82** afforded γ-lactam **83** with complete *E*-selectivity and without epimerisation. Dihydroxylation of γ-lactam **83** and concomitant lactonisation provided γ-lactone **84**. Chemoselective reduction of the ester group of γ-lactone **84** furnished γ-lactone **78** (**Scheme 28**).



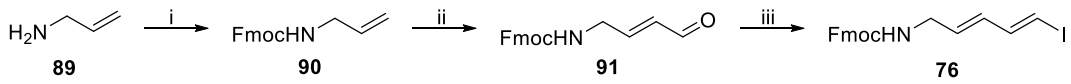
Scheme 28. Reagents and conditions: i) Jones reagent (2.7 M), acetone, 0 °C; ii) $SOCl_2$, CH_2Cl_2; iii) **81**, PhMe, 63% over 3 steps; iv) $In(OTf)_3$ (5 mol%), DBU, PhMe, reflux, 91%; v) OsO_4, NMO, THF-H_2O 3:1, 100%; vi) LiOH, THF then HCl; vii) $(COCl)_2$, DMF (cat.), CH_2Cl_2 then $NaBH_4$, THF-MeOH 9:1, −78 °C, 60% over 2 steps

Methoxymethylation of γ-lactone **78**, subsequent reduction of the lactone ring and selective silylation provided TBS ether **85**. Methylation of TBS ether **85** gave methyl ether **86**, which after a four-step sequence (including TBS-deprotection, Jones oxidation, Pinnick oxidation and MOM-deprotection) afforded acid **87**. Selective esterification of acid **87** furnished ester **88**, and protection of ester **88** as the dioxasilinane followed by debenzylation and Dess–Martin oxidation gave aldehyde **77** (**Scheme 29**).



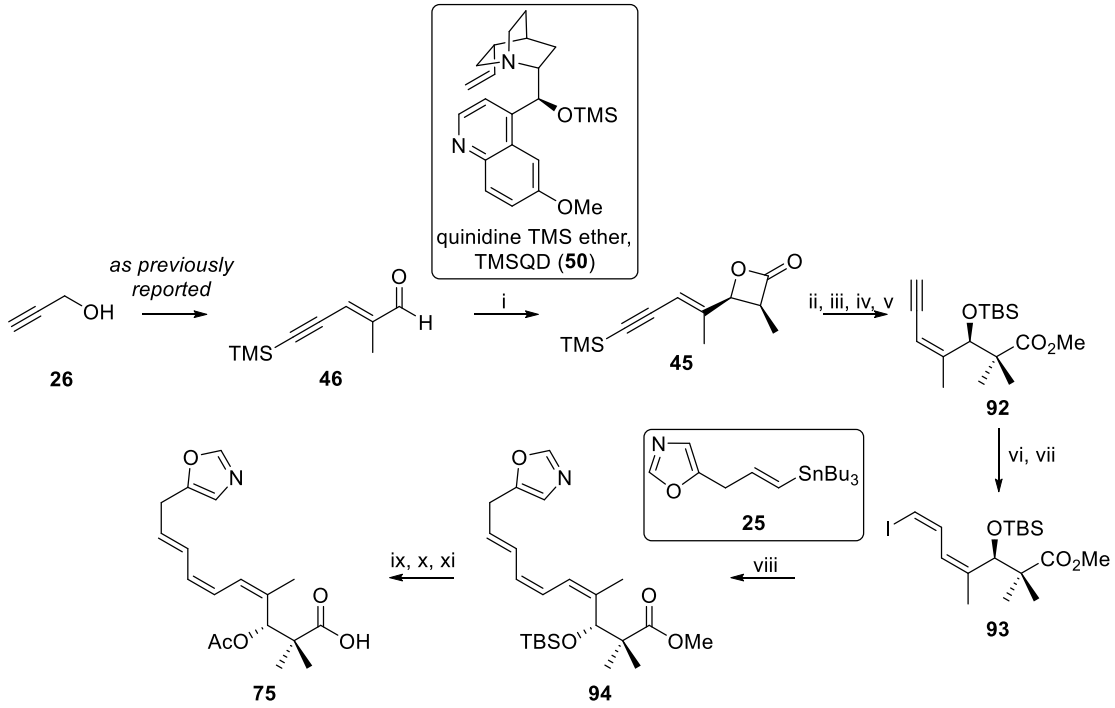
Scheme 29. Reagents and conditions: i) MOMCl, *i*-Pr_2EtN, CH_2Cl_2; ii) $NaBH_4$, THF-EtOH 1:1; iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 93% over 3 steps; iv) $Me_3O^+BF_4^-$, proton sponge, 4 Å MS, CH_2Cl_2, 95%; v) TBAF, THF; vi) Jones reagent (2.7 M), acetone, 0 °C; vii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O 5:1; viii) $ZrCl_4$, *i*-PrOH, reflux; ix) *n*-$C_{12}H_{25}SCH_2OTIPS$, $CuBr_2$, *n*-Bu_4NBr, Et_3N, 4 Å MS, CH_2Cl_2, 67% over 5 steps; x) *i*-$Pr_2Si(OTf)_2$, 2,6-lutidine, DCE, reflux, 90%; xi) H_2, $Pd(OH)_2$, EtOAc; xii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 92% over 2 steps

Middle diene fragment **76** was prepared in three steps from allylamine (**89**). Fmoc-protection, cross-metathesis with acrolein and subsequent Takai iodoalkenylation[56] afforded iodide **76** (**Scheme 30**).



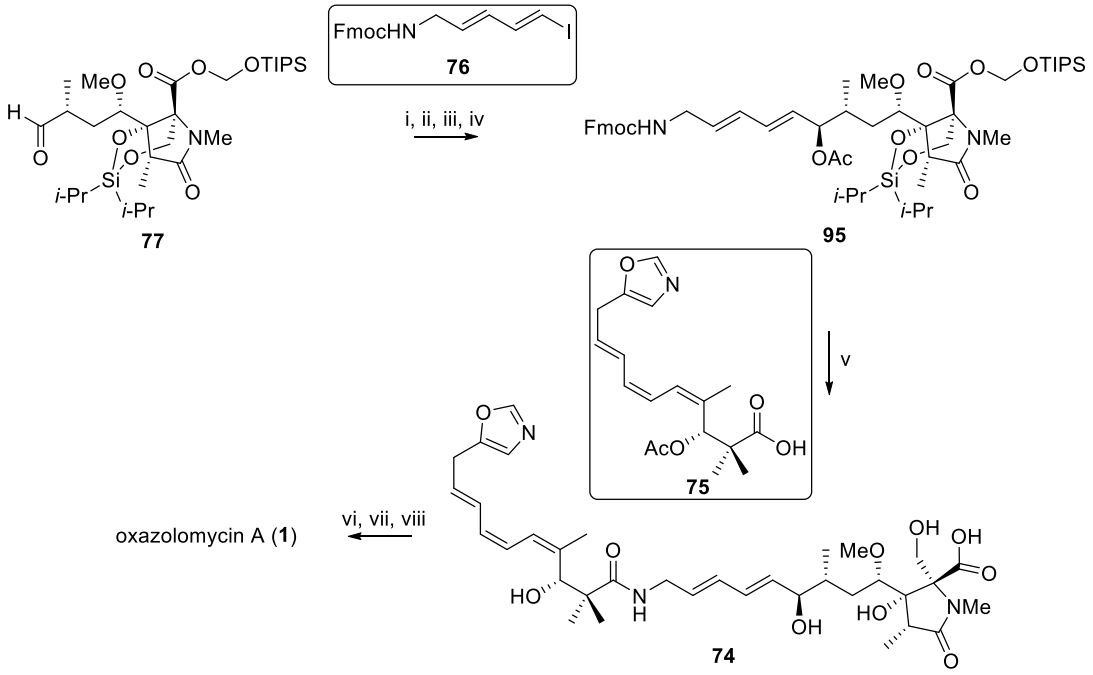
Scheme 30. Reagents and conditions: i) FmocCl, $NaHCO_3$, dioxane, 96%; ii) acrolein, HG-II (5 mol%), CH_2Cl_2, 85%; iii) $CrCl_2$, CHI_3, THF, 66% (*E*/*Z* = 8:1)

Left-hand acid fragment **75** was synthesised *via* a second-generation synthesis that was more efficient than the previously published.[52]Aldehyde **46** was obtained in three steps from propargyl alcohol (**26**) as reported earlier.[52] Subsequently, aldehyde **46** was reacted with propionyl chloride using quinidine TMS ether (**50**) as organocatalyst, following Nelson's protocol,[42] to give β-lactone **45** in excellent enantio- and diastereoselectivity. Methanolysis of β-lactone **45**, followed by a methylation/TMS-deprotection/TBS-protection sequence afforded alkyne **92**, which was then converted into iodide **93** by iodination and reduction to the alkene using *o*-nitrobenzenesulfonyl hydrazide.[57,58] Stille cross-coupling between iodide **93** and stannane **25** afforded triene **94**, which upon successive TBS-deprotection, saponification and acetylation furnished acid **75** (**Scheme 31**).



Scheme 31. Reagents and conditions: i) **50** (20 mol%), EtCOCl, $LiClO_4$, *i*-Pr_2NEt, CH_2Cl_2-Et_2O 1:1, −78 °C, 92% (98% ee, >99% de); ii) NaOMe, MeOH, 95%; iii) LDA, CH_3I, THF, −20 °C, 84%; iv) NaOMe, MeOH; v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98% over 2 steps; vi) *n*-BuLi, I_2, THF, −78 °C; vii) *o*-$(NO_2)C_6H_4SO_2NHNH_2$, Et_3N, *i*-PrOH-THF 1:1, 92% over 2 steps; viii) **25**, $Pd(PPh_3)_4$ (1 mol%), CuI (10 mol%), CsF, DMF, 83%; ix) aq. HF (47%), MeCN; x) LiOH, THF-MeOH-H_2O 3:1:1; xi) Ac_2O, pyridine then $NaHCO_3$, MeOH, 88% over 3 steps

The total synthesis of oxazolomycin A (**1**) was completed by coupling the three fragments described above together. First, the right-hand aldehyde **77** was united with iodide **76,** *via* Nozaki–Hiyama–Kishi coupling,[54,55] Dess–Martin oxidation, L-selectride reduction and subsequent acetylation, to furnish acetate **95**. Treatment of acetate **95** with DBU afforded the corresponding free amine, which was consecutively condensed with the left-hand acid **75** to provide amide **74**. Finally, desilylation of **74** followed by acetate-deprotection and β-lactonisation gave oxazolomycin A (**1**) in 34 linear steps and 1.4% overall yield (**Scheme 32**).



Scheme 32. Reagents and conditions: i) **76**, $NiCl_2$ (20 mol%), $CrCl_2$, THF-DMSO 3:1; ii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; iii) L-selectride, THF, −78 °C, 53% over 3 steps; iv) Ac_2O, pyridine, 91%; v) DBU, CH_2Cl_2 then added to the mixed anhydride prepared from **75** (BOPCl, Et_3N, CH_2Cl_2), 68%; vi) HF·pyridine, THF; vii) LiOH, THF-H_2O 4:1 then ion exchange resin (H^+ form); viii) HATU, *i*-Pr_2EtN, THF, 40% over 3 steps

1.5.2. Donohoe's asymmetric synthesis of the pyrrolidinone core (2012)

The Donohoe group published an asymmetric synthesis of the highly functionalised pyrrolidinone core of the oxazolomycin family in 2012.[50] Key steps in the synthetic route include the Birch reduction of an aromatic pyrrole nucleus, a late-stage RuO_4-catalysed pyrrolidine oxidation to introduce the lactam carbonyl group, and a diastereoselective organocerium addition to an aldehyde to install the exocyclic carbon chain.

Previous work in the Donohoe group explored the use of the partial Birch reduction of substituted aromatic pyrroles[59] to access complex natural products such as lactacystin β-lactone (**96**)[60] and the KSM-2690 B pyrrolidinone core **97** (**Figure 4**).[61] To further extend the applicability of this methodology, they tackled the synthesis of the right-hand part of the oxazolomycins, containing a β-lactone-γ-lactam core and an exocyclic carbon chain.

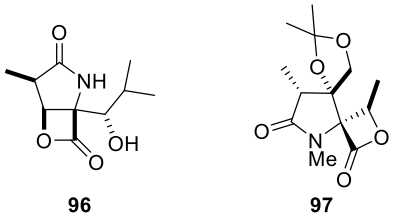
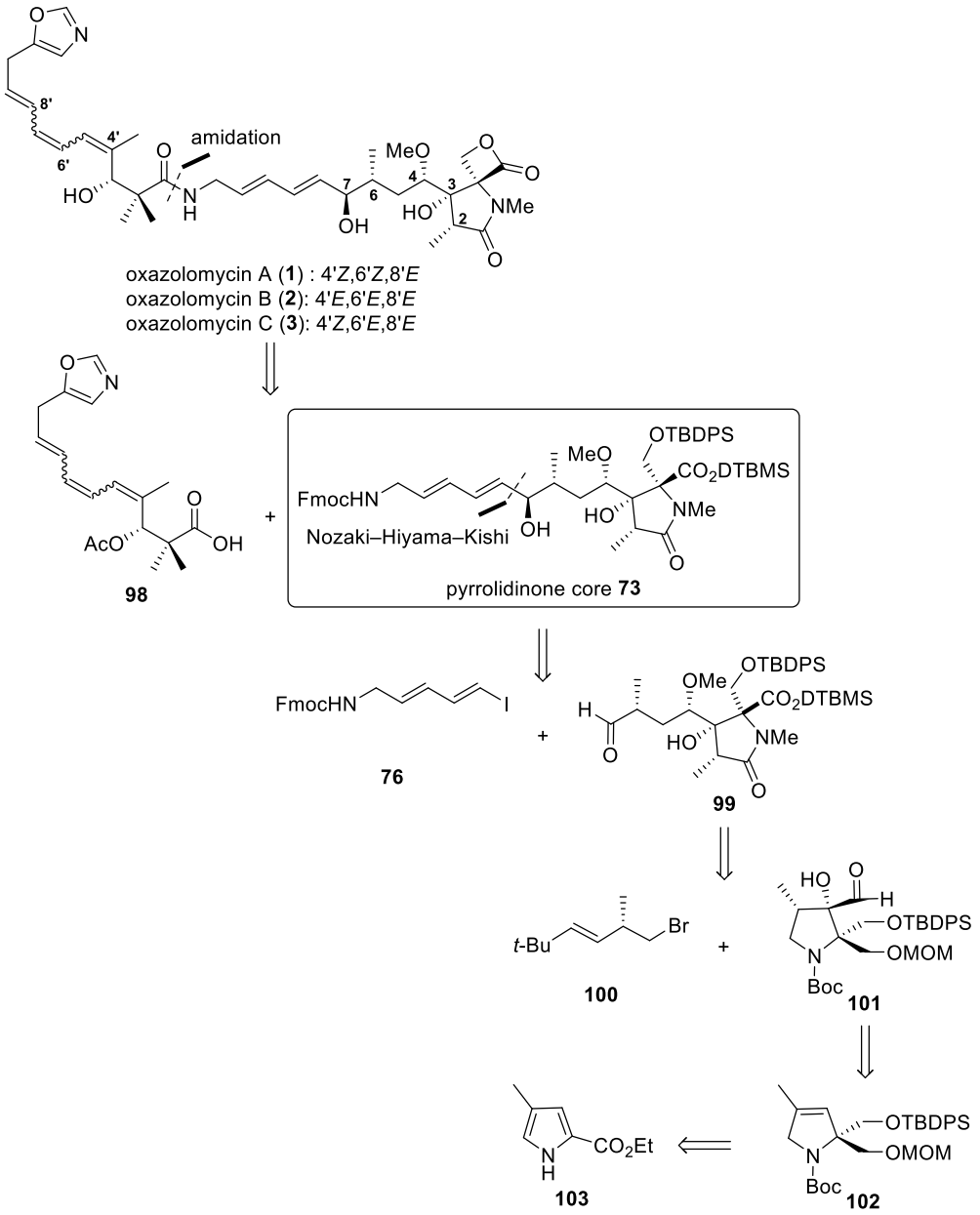


Figure 4. Lactacystin β-lactone (**96**) and KSM-2690 B pyrrolidinone core **97**

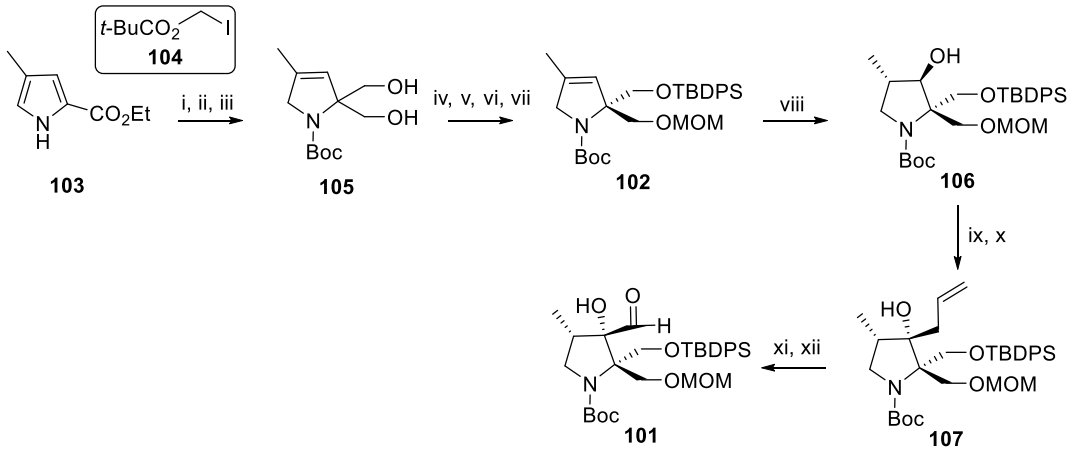
The β-lactone functionality was planned to be introduced in the last step of the synthetic route towards the oxazolomycins, given its labile nature. Nozaki–Hiyama–Kishi reaction of aldehyde **99** with vinyl iodide **76** provided target pyrrolidinone core **73**, a compound ready to be coupled with left-hand oxazolyl-triene fragment **98** in a future total synthesis. Aldehyde **99** was prepared from aldehyde **101** *via* chelation-controlled organometallic addition with bromide **100** followed by late-stage oxidation to install the lactam carbonyl group. Aldehyde **101** was synthesised from pyrroline **102** through a hydroboration/formylation sequence. Finally, pyrroline **102** was obtained from commercially available pyrrole **103** by partial Birch reduction and subsequent desymmetrisation (**Scheme 33**).



Scheme 33. Donohoe's retrosynthesis of the oxazolomycins pyrrolidinone core **73**

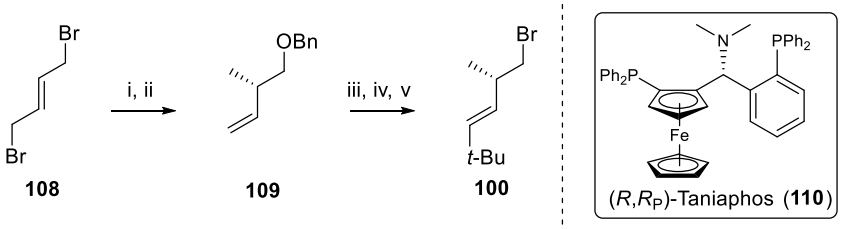
The synthesis commenced with *N*-Boc protection of pyrrole **103**, partial Birch reduction and quenching with iodomethylpivalate (**104**), followed by reduction to afford diol **105**. Enzymatic desymmetrisation of diol **105**, TBDPS-protection and exchange of the acetate group by a MOM group furnished pyrroline **102**, with protecting groups stable under subsequent hydroboration conditions. Treatment of pyrroline **102** with BH_3·THF and successive oxidative workup gave alcohol **106** with excellent regioselectivity and good diastereoselectivity, with addition occurring to the less hindered face. Dess–Martin

oxidation of alcohol **106** and addition of allylmagnesium bromide to the resulting ketone afforded homoallylic alcohol **107** with good diastereocontrol. The initial plan to add a more elaborated organometallic compound to the intermediate ketone proved unsuccessful, and hence a better electrophile for the addition was required. To this end, alcohol **107** was converted into α-hydroxyaldehyde **101** *via* isomerisation of the terminal olefin and consecutive ozonolysis (**Scheme 34**).



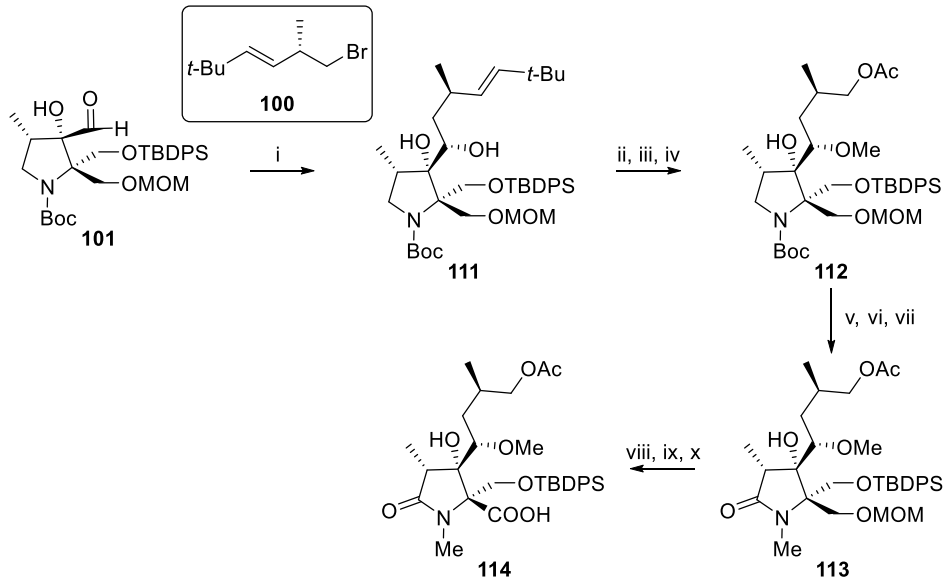
Scheme 34. Reagents and conditions: i) Boc_2O, DMAP, CH_2Cl_2, r.t.; ii) Li, NH_3, THF, −78 °C then **104**, THF, −78 °C; iii) $LiBH_4$, MeOH, Et_2O, 64% over 3 steps; iv) Lipoprotein lipase, vinyl-OAc, THF, 37 °C; v) TBDPSCl, DMAP, imidazole (cat.), CH_2Cl_2; vi) K_2CO_3, MeOH; vii) $CH_2(OCH_3)_2$, LiBr (cat.), TsOH·H_2O (cat.), 56% over 4 steps (>98% ee); viii) BH_3·THF, THF, 0 °C to r.t. then $Me_3NO·2H_2O$, PhMe, reflux, 79% (8:1 dr); ix) DMP, CH_2Cl_2; x) allyl-MgBr, Et_2O, −78 °C, 67% over 2 steps (10:1 dr); xi) G-II (5 mol%), vinyl-OTMS, PhMe, reflux; xii) O_3, CH_2Cl_2, −78 °C then Me_2S, −78 °C to r.t., 94%

For the introduction of the exocyclic carbon chain onto aldehyde **101**, bromide **100** was prepared in five steps from dibromide **108**. Benzyl-monoprotection of dibromide **108** under phase transfer conditions, followed by Feringa's asymmetric allylic alkylation[62,63] with methylmagnesium bromide and phosphine catalyst **110** gave alkene **109**. Cross-metathesis of alkene **109** with 3,3-dimethyl-1-butene, subsequent benzyl-deprotection and bromination of the resulting primary alcohol provided bromide **100** (**Scheme 35**).



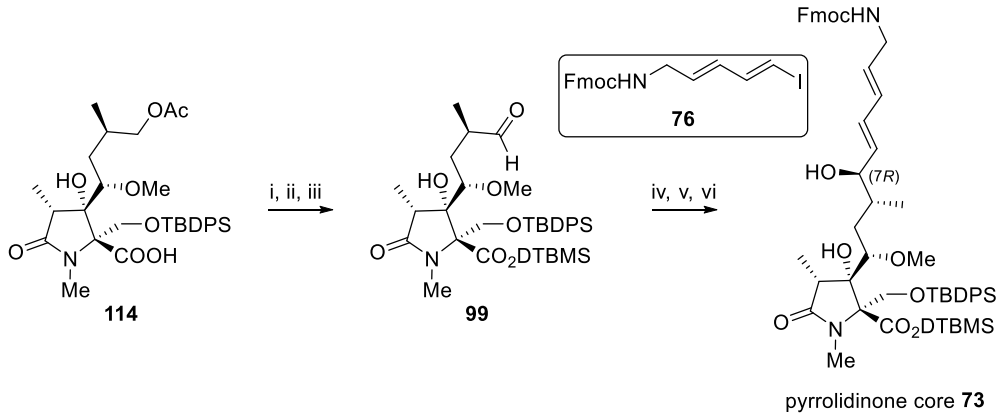
Scheme 35. Reagents and conditions: i) BnOH, aq. 2 M NaOH, Bu_4NHSO_4, CH_2Cl_2; ii) MeMgBr, CuBr·Me_2S, (*R*,R_P)-Taniaphos (**110**) (1.1 mol%), CH_2Cl_2, −78 °C, 47% over 2 steps; iii) G-II (3 mol%), CH_2=CHC$(CH_3)_3$, reflux; iv) Li, NH_3, THF, −78 °C; v) Br_2, PPh_3, CH_2Cl_2, 43% over 3 steps

With bromide **100** and aldehyde **101** in hand, the next step was the union of these two compounds through a chelation-controlled addition of an organocerium species derived from bromide **100** to afford diol **111** with excellent diastereoselectivity. Methylation of diol **111**, followed by ozonolysis/reduction sequence and acetate-protection gave acetate **112**. RuO_4-catalysed pyrrolidine oxidation of acetate **112** provided the corresponding pyrrolidinone, which was subsequently Boc-deprotected and *N*-methylated to obtain pyrrolidinone **113**. MOM-cleavage of pyrrolidinone **113** and double oxidation protocol (Dess–Martin and Pinnick oxidations) furnished carboxylic acid **114** (**Scheme 36**).



Scheme 36. Reagents and conditions: i) *t*-BuLi, then **100**, THF, −78 °C then $CeCl_3$, −35 °C then **101**, −78 °C, 76% (>20:1 dr); ii) Me_3OBF_4, proton sponge, CH_2Cl_2; iii) O_3, CH_2Cl_2-MeOH 7.5:1, −78 °C then $NaBH_4$, −78 °C; iv) Ac_2O, pyridine, 57% over 3 steps; v) RuO_2·H_2O (15 mol%), $NaIO_4$, EtOAc, H_2O; vi) TFA, Et_3SiH, CH_2Cl_2; vii) CH_3I, Cs_2CO_3, 50 °C, reflux, 58% over 3 steps; viii) TFA, MeOH, CH_2Cl_2; ix) DMP, CH_2Cl_2 x) $NaClO_2$, NaH_2PO_4, CH_3CH=C$(CH_3)_2$, *t*-BuOH-H_2O 2:1, 80% over 3 steps

Acid **114** was protected as the DTBMS ester and the acetate group cleaved before performing a Swern oxidation on the resulting primary alcohol to provide aldehyde **99**. Finally, Nozaki–Hiyama–Kishi reaction of aldehyde **99** with vinyl iodide **76**,[49] followed by a Dess–Martin oxidation/diastereoselective reduction protocol afforded the target (7*R*)-pyrrolidinone core **73** with excellent diastereoselectivity. The synthesis of the right-hand pyrrolidinone fragment **73** was achieved in 28 linear steps from pyrrole **103** and 1.3% overall yield (**Scheme 37**).



Scheme 37. Reagents and conditions: i) DTBMSOTf, Et_3N, Et_2O; ii) $LiBH_4$, THF; iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N −78 °C to r.t., 57% over 3 steps; iv) **76**, $NiCl_2$ (cat.), $CrCl_2$, DMSO; v) DMP, CH_2Cl_2; vi) $BH_3{\cdot}Me_2S$, (*S*)-(−)-2-methyl-CBS-oxazaborolidine, THF, −30 °C, 65% over 3 steps (>20:1 dr)

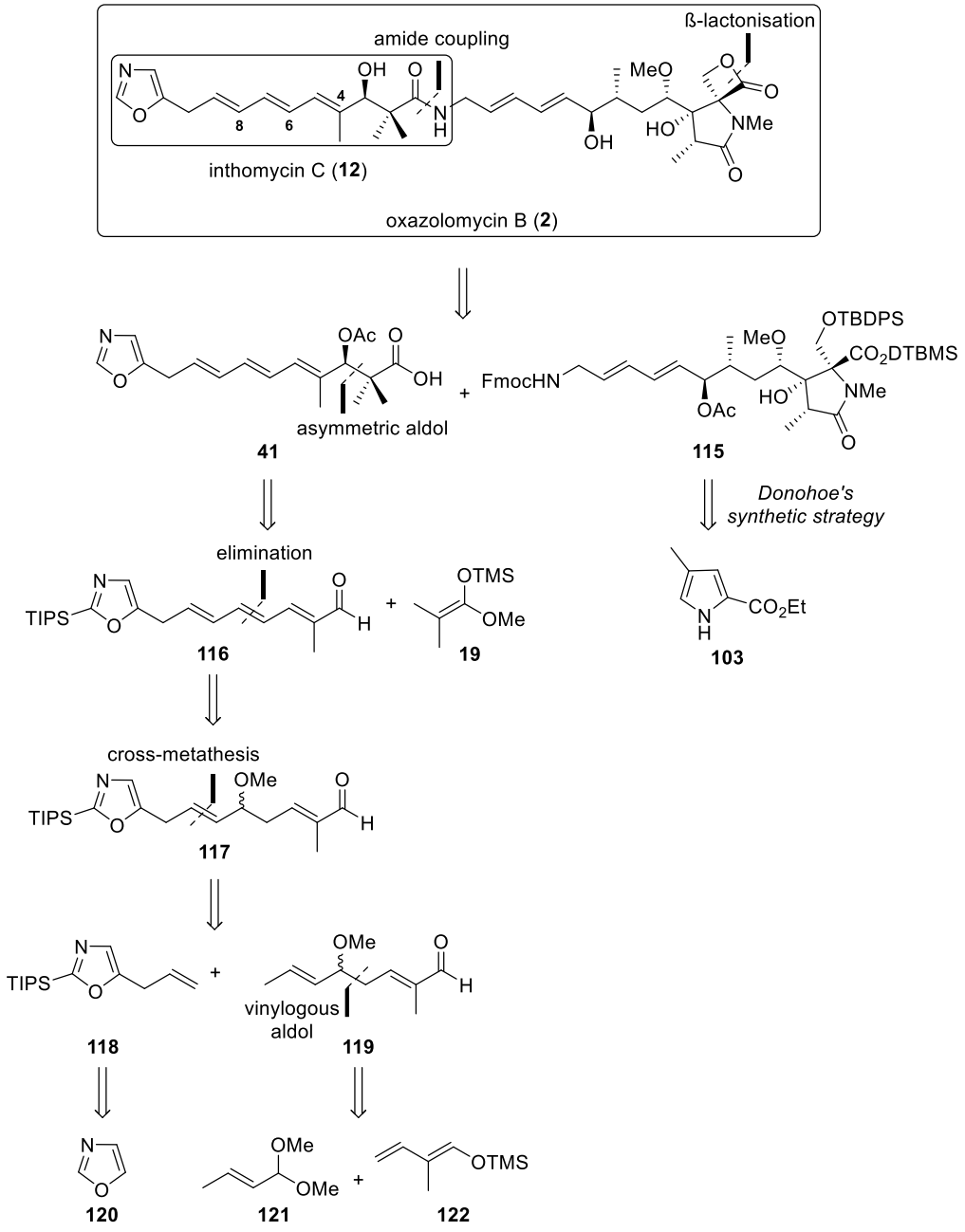
1.6. Project aims

This project aimed to develop an efficient, novel synthesis of (−)-(*3R*)-inthomycin C (**12**) that avoids the use of toxic organotin reagents on which all previous syntheses rely. Initially, it was anticipated that the main challenge of the synthesis would be to access the (*E*,*E*,*E*)-triene unit in an stereoselective manner. Building on earlier work in the Donohoe group, the preparation of the pyrrolidinone fragment[50] and its coupling to intermediate acid **41** resulting from this work would provide the first total synthesis of oxazolomycin B (**2**).

This project also aimed to investigate the biological activity of inthomycin C (**12**) and structural analogues on human cancer cell lines in collaboration with cancer biologists. Should the initially screened compounds show some activity, these investigations could

serve as a basis for future assays to further study their mechanism of action and potentially develop more active analogues.

The novel synthesis of inthomycin C (**12**) involved a cross-metathesis reaction between oxazole **118** and aldehyde **119**, an elimination of the methoxy group on aldehyde **117**, and an asymmetric aldol addition between silyl ketene acetal **19** and aldehyde **116** as key steps in the sequence. Intermediate acid **41** was incorporated into the total synthesis of oxazolomycin B (**2**) *via* amide coupling to pyrrolidinone **115**, which in turn was prepared following the Donohoe group synthetic approach.[50] The end-game strategy towards oxazolomycin B (**2**) would require the cleavage of all protecting groups followed by a β-lactonisation protocol (**Scheme 38**).



Scheme 38. Proposed retrosynthesis of inthomycin C (**12**) and incorporation into the synthesis of oxazolomycin B (**2**)

Chapter 2. Results and Discussion

2.1. Initial attempted syntheses of inthomycin C

2.1.1. First proposed synthesis

Previous synthetic studies within the Donohoe group led to a first-generation formal synthesis of racemic inthomycin C (**12**) on milligram scale.[64,65] Nevertheless, modification of the route was necessary given the poor yield of the cross-metathesis step and the formation of unwanted triene isomers during the Tsuji–Trost β-hydride elimination step (**Figure 5**).

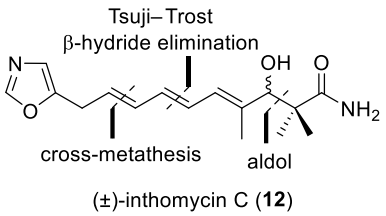
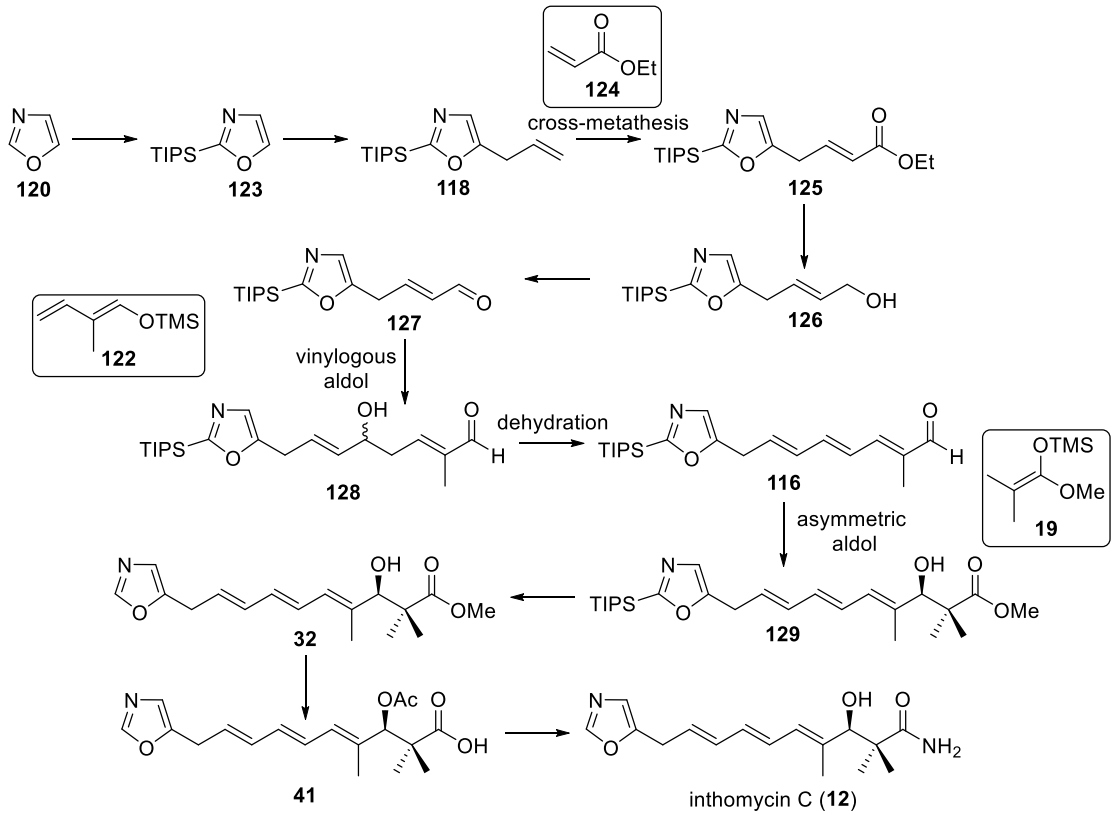


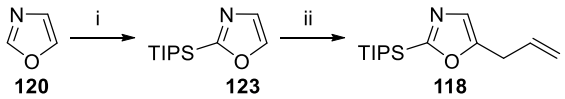
Figure 5. Main disconnections in the previously proposed synthesis of (±)-inthomycin C (**12**)[64]

Moreover, the development of an asymmetric total synthesis was also required. To this end, our investigations on a modified synthetic approach to inthomycin C (**12**) began. The initial retrosynthetic strategy towards inthomycin C (**12**) involved a cross-metathesis between oxazole **118** and ethyl acrylate (**124**), a vinylogous aldol reaction between aldehyde **127** and silyl enol ether **122**, a dehydration of alcohol **128** and an asymmetric aldol addition between silyl ketene acetal **19** and aldehyde **116** as the key disconnections. As mentioned earlier, accessing the (*E*,*E*,*E*)-triene unit stereoselectively was anticipated to be the main challenge in the synthesis of this natural product (**Scheme 39**).



Scheme 39. First proposed synthesis of inthomycin C (**12**)

Following the synthetic plan outlined above, the sequence started from commercially available oxazole (**120**), which was TIPS-protected at the more acidic *C*-2 position to afford protected oxazole **123** in 91% yield, following the procedure reported by Miller and co-workers.[66] These authors had demonstrated the suitability of the *C*-2 TIPS protecting group for oxazoles, since it proved stable to aqueous workups and column chromatography, and it could be easily removed by aqueous 1 M HCl.[66,67] Regioselective protection at the *C*-2 position was confirmed by the loss of the oxazole *C*-2 proton singlet signal at 7.92 ppm in the ^{1}H NMR spectrum. Subsequent allylation at the *C*-5 position with allyl bromide *via* lithiation and transmetallation to the cuprate[68–70] afforded oxazole **118** in 96% yield as an inseparable[67] 17:1 mixture of oxazoles **118** and **123** (**Scheme 40**).



Scheme 40. Reagents and conditions: i) *n*-BuLi (1.1 eq.), THF, −30 °C, 20 min then TIPSOTf (1.1 eq.), −30 °C, 45 min then r.t., 3.5 h, 91%; ii) *n*-BuLi (1.1 eq.), THF, −78 °C, 30 min then LiCl (0.8 eq.), CuCN (0.4 eq.), −78 °C, 2 h then allyl bromide (1.5 eq.), −78 °C to r.t., 2 h, 96% (17:1 **118**/**123** mixture)

The next synthetic target was aldehyde **127**, the substrate for the key Mukaiyama vinylogous aldol reaction. With this in mind and given that previous studies[64,65] had shown that direct cross-metathesis between oxazole **118** and either acrolein (**130**) or crotonaldehyde (**131**) resulted in either decomposition or difficulty in isolating aldehyde **127**, we sought to find an alternative cross-metathesis partner for oxazole **118** (**Figure 6**).

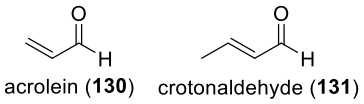
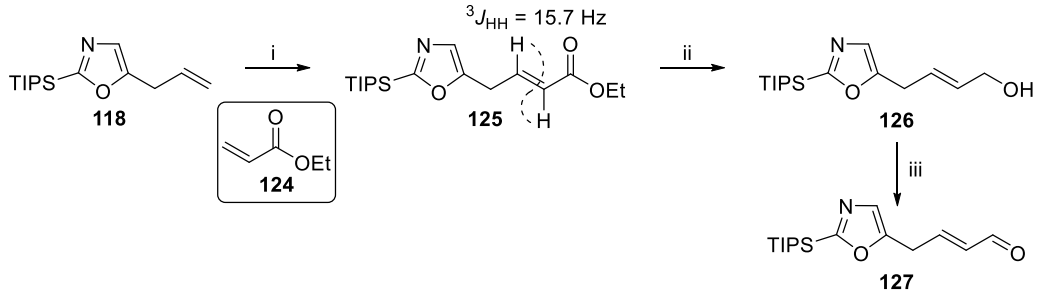


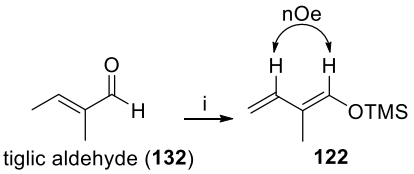
Figure 6. Acrolein (**130**) and crotonaldehyde (**131**)

To this end, a cross-metathesis between oxazole **118** and allyl alcohol followed by an oxidation protocol to aldehyde **127** was postulated as a suitable alternative. Unfortunately, the cross-metathesis between oxazole **118** and allyl alcohol only afforded alcohol **126** in 25% yield. We then hoped that cross-metathesis between oxazole **118** and ethyl acrylate (**124**) followed by a reduction-oxidation sequence would afford aldehyde **127** in higher overall yield. In this way, we were able to synthesise alcohol **126** in 60% yield over two steps from oxazole **118**, but the oxidation of alcohol **126** to aldehyde **127** proved capricious with variable yields (31–77%). We suspect that this is due to degradation during the purification of aldehyde **127**, for which we had to employ pH 7 phosphate-buffered silica column chromatography as it had proved to be unstable to silica gel (**Scheme 41**).



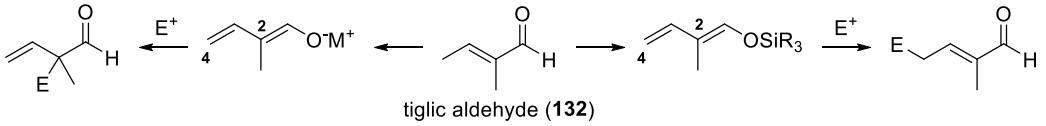
Scheme 41. Reagents and conditions: i) ethyl acrylate (**124**) (5 eq.), HG-II (5 mol%), CH_2Cl_2, 40 °C, 21 h, 75%; ii) DIBAL-H (4 eq.), CH_2Cl_2, −78 °C, 30 min then r.t., 1 h, 80%; iii) DMP (1.5 eq.), $NaHCO_3$ (5 eq.), CH_2Cl_2, 0 °C, 1 h, 77%

In order to synthesise a suitable silyl enol ether to react with aldehyde **127** in the desired vinylogous aldol addition, tiglic aldehyde (**132**) was treated with TMSOTf and Et_3N to provide TMS enol ether **122**[71] in 75% yield after distillation (**Scheme 42**).



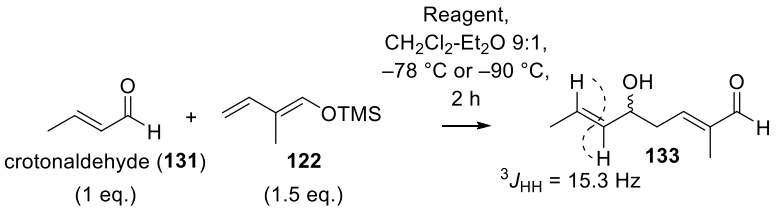
Scheme 42. Reagents and conditions: i) TMSOTf (1.1 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C, 4 h then r.t., 1 h, 75%

The principle of vinylogy was first described by Fuson in 1935, by which the influence of one functional group may be felt at a distant point in a molecule that is connected to another functional group by a conjugated double-bond linkage.[72] In polar reactions, this concept explains the extension of the nucleophilic or electrophilic character of a functional group through the π-system of a C–C double bond.[73] Vinylogy has been applied to aldol additions, by using "extended dienolates" (such as silyl enol ether **122**) derived from γ-enolisable α,β-unsaturated carbonyl compounds. Reactions of dienol ethers or ketene acetals can occur at either the α- or the γ-carbon atom of the extended conjugated system. Nevertheless, high γ-selectivity can be achieved using silyl dienolates as latent metal dienolate equivalents in Lewis acid-promoted Mukaiyama aldol reactions. The difference in regioselectivity between metallodienolates (prone to α-selectivity) and their silyl analogues (prone to γ-selectivity) can be explained by analysing their electronic structures. Computational studies by Denmark and co-workers[73] showed that silyl enol ethers have larger HOMO coefficient and electrophilic susceptibilities at *C*-4 than at *C*-2, and so γ-addition products are predicted; whereas for metallodienolates both the HOMO coefficient and the electrophilic susceptibility are greater at *C*-2 than at *C*-4, and so α-addition products are anticipated (**Scheme 43**).



Scheme 43. Different modes of vinylogous reactivity of tiglic aldehyde (**132**)

With the aim of investigating the vinylogous Mukaiyama aldol reaction between aldehyde **127** and silyl enol ether **122**, crotonaldehyde (**131**) was selected as a model aldehyde (**Table 4**).



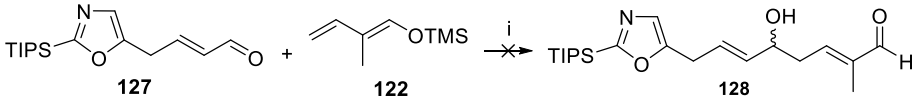
Entry	Reagent (eq.)	T (°C)	Yield **133** (%)
1	$BF_3{\cdot}OEt_2$ (2.5)	−78 °C	74
2	$Ti(O\text{-}i\text{-}Pr)_4$ (2.5)	−78 °C	decomposition
3	$Zn(OAc)_2$ (2.5)	−78 °C	decomposition
4	TMSOTf (2.5)	−78 °C	decomposition
5	$Sc(OTf)_3$ (2.5)	−78 °C	decomposition
6	$TiCl_4$ (2.5)	−78 °C	60
7	$BF_3{\cdot}OEt_2$ (1.2)	−78 °C	83
8[a]	$BF_3{\cdot}OEt_2$ (1.2)	−90 °C	54
9	TBAF (2.5)	−78 °C	decomposition

N.B. The presence of a single proton downfield alkene shift at 6.58 ppm in the ^{1}H NMR spectrum of alcohol **133** indicated the existence of an α,β-unsaturated carbonyl moiety and confirmed the γ-selectivity of the vinylogous aldol reaction. The (*E*) geometry of the trisubstituted double bond on alcohol **133** was inferred from nOe experiments performed by a co-worker[64] on an analogous α,β-unsaturated carbonyl compound prepared using the same methodology. [a]Reaction time = 4 h

Table 4. Optimisation of vinylogous aldol reaction between aldehyde **131** and silyl enol ether **122**

Initially, model aldehyde **131** was treated with 1.5 eq. of silyl enol ether **122** and 2.5 eq. of $BF_3{\cdot}OEt_2$ furnishing the corresponding aldol product **133** in 74% yield (Entry 1). Given the presence of an acid labile group (TIPS) in aldehyde **127**, several milder Lewis acids ($Ti(O\text{-}i\text{-}Pr)_4$, $Zn(OAc)_2$, TMSOTf, $Sc(OTf)_3$) were screened on model aldehyde **131** but all of them led to decomposition (Entries 2–5) except for $TiCl_4$, which provided alcohol **133** in 60% yield (Entry 6). The best yields were still observed with the initial boron Lewis acid, which suggests that a strong Lewis acid was required for this transformation. The amount of Lewis acid used could be lowered to 1.2 eq. obtaining alcohol **133** in an increased 83% yield (Entry 7). Since aldehyde **127** proved unstable when applying the latter improved conditions, the

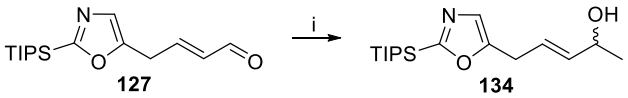
temperature of the model system reaction was then lowered to −90 °C and reaction times increased to 4 h and, in this way, alcohol **133** was afforded in an acceptable 54% yield (Entry 8). Unfortunately, the application of these re-optimised conditions on aldehyde **127** also resulted in decomposition (**Scheme 44**). Attempts to promote the vinylogous Mukaiyama aldol reaction on model aldehyde **131** *via* other methods (such as treatment with TBAF) were unsuccessful (Entry 9).



Scheme 44. Reagents and conditions: i) $BF_3{\cdot}OEt_2$ (1.2 eq.), CH_2Cl_2-Et_2O 9:1, −90 °C, 4 h

To investigate its suspected instability to Lewis acids, aldehyde **127** was treated with $BF_3{\cdot}OEt_2$ and this led to decomposition of the starting material, as observed by ^{1}H NMR analysis. It was hypothesised that aldehyde **127** may be undergoing Diels–Alder side reactions and decomposing.

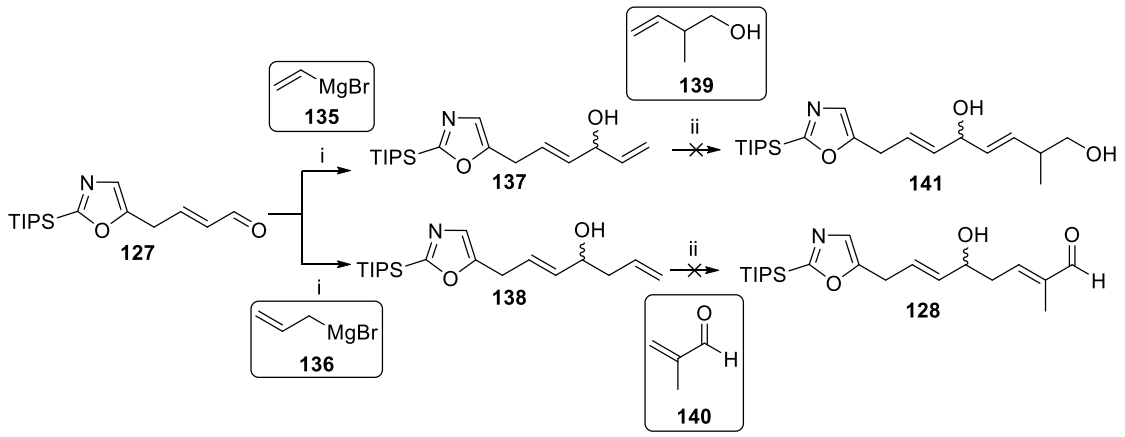
Since the vinylogous aldol reaction outlined in **Scheme 44** could not be accomplished under Lewis acid catalysis conditions, we sought to investigate other possibilities. Research focused on exploring the reactivity of aldehyde **127**, which was first treated with MeLi and the corresponding 1,2-addition product **134** was afforded in a good 72% yield (**Scheme 45**).



Scheme 45. Reagents and conditions: i) MeLi (1.1 eq.), Et_2O, −78 °C to 0 °C, 1.5 h, 72%

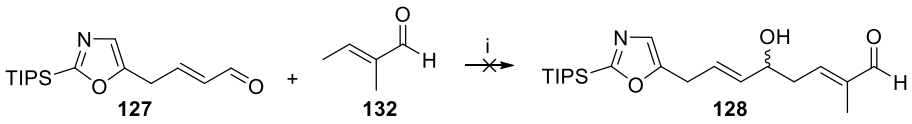
Continuing with the idea of examining the reactivity of aldehyde **127** we treated this substrate with 1.3 eq. of Grignard reagents (vinyl and allyl magnesium bromides (**135**) and (**136**)) and, pleasingly, 1,2-addition products **137** and **138** could be isolated in 46% and 69% yield respectively. Alcohols **137** and **138** were then treated with 2-methyl-3-buten-1-ol (**139**) and methacrolein (**140**) respectively in cross-metathesis reactions but, unfortunately, complex mixtures were obtained in both cases, from which the desired alcohol products **141**

and **128** could not be isolated (**Scheme 46**). From these results, we postulated that aldehyde **127** was a suitable substrate for organolithium and organomagnesium 1,2-addition reactions.



Scheme 46. Reagents and conditions: i) RMgBr (1.3 eq.), Et_2O, −78 °C, 2 h, 46% **137** or 69% **138**; ii) **139** (5 eq.) or **140** (10 eq.), HG-II (10 mol%), CH_2Cl_2, 40 °C, 24 h

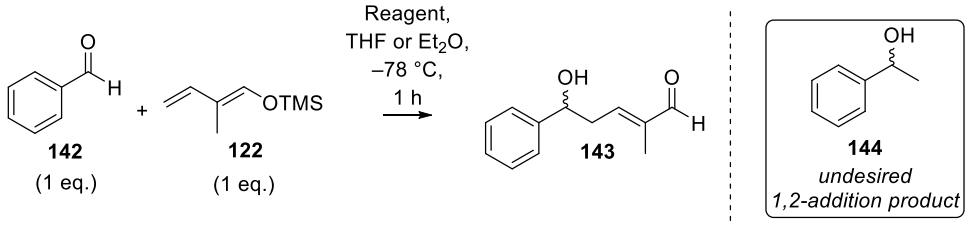
Encouraged by the latter observations we hoped that, as an alternative route to access aldehyde **128**, the treatment of tiglic aldehyde (**132**) with LDA to form its extended enolate and subsequent quenching with aldehyde **127** would provide the desired aldehyde **128** under Lewis acid-free conditions (**Scheme 47**). However, when this reaction was attempted, alcohol **128** was not observed and decomposition occurred instead, as observed by ^{1}H NMR analysis.



Scheme 47. Reagents and conditions: i) LDA (1 eq.), THF, −78 °C, 1 h

Based on the previous results, a vinylogous aldol reaction under basic conditions was still envisioned as a reasonable alternative to Lewis acid catalysis, assuming that activation of silyl enol ether **122** with a base, instead of activating aldehyde **127** with a Lewis acid, would provide the desired aldol product **128**.[74,75]

Initially, benzaldehyde (**142**) was used as a model aldehyde and *t*-BuOK and MeLi were selected as bases[76–79] to activate silyl enol ether **122** (**Table 5**).



Entry	Aldehyde	Reagent (eq.)	Solvent	Yield **143** (%)
1	**142**	*t*-BuOK (1)	THF	31
2[a]	**142**	MeLi (1)	THF	trace
3[b]	**142**	MeLi (2)	THF	trace
4[c]	**142**	CsF (1)	THF	0
5	**142**	TBAF (1)	THF	5
6	**142**	*t*-BuOLi (1)	THF	5
7[d]	**142**	LDA (1)	THF	20
8[e,f]	**142**	MeLi (1)	THF	40
9[e,g]	**142**	*t*-BuOK (1)	THF	29

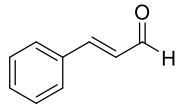
N.B. The presence of a single proton downfield alkene shift at 6.58 ppm in the ^{1}H NMR spectrum of alcohol **143** indicated the existence of an α,β-unsaturated carbonyl moiety and confirmed the γ-selectivity of the vinylogous aldol reaction. The (*E*) geometry of the trisubstituted double bond on alcohol **143** was inferred from nOe experiments performed by a co-worker[64] on an analogous α,β-unsaturated carbonyl compound prepared using the same methodology. Trace amounts of unreacted starting material **142** were recovered in all cases. [a]1,2-addition product **144** was obtained in 12% yield. [b]1,2-addition product **144** was obtained in 45% yield. [c]Tiglic aldehyde (**132**) was obtained in 11% yield. [d]Tiglic aldehyde (**132**) was used as reagent instead of silyl enol ether **122**. [e]Reaction temperature was gradually increased from −78 °C to −20 °C. [f]1,2-addition product **144** was obtained in 4% yield. [g]1,2-addition product **144** was obtained in 10% yield

Table 5. Optimisation of vinylogous aldol reaction between aldehyde **142** and silyl enol ether **122**

Satisfyingly, when using 1 eq. of *t*-BuOK regioselective formation of γ-aldol product **143** was observed, although in poor yield (31%), along with some starting material **142** (Entry 1). Doubling the amount of MeLi from 1 to 2 eq. led to an increased formation of alcohol **144**, a by-product resulting from the 1,2-addition of MeLi into aldehyde **142**, with almost no target alcohol **143** observed (Entries 2 and 3). Switching the solvent from THF to Et_2O did not have any significant impact on the yield. The utilisation of fluoride sources such as CsF or TBAF to form the enolate *in situ* resulted in either no conversion or very low yield (5%) respectively (Entries 4 and 5). Other bases were also explored (*t*-BuOLi, LDA) without success (Entries 6 and 7). Gradually increasing the temperature from −78 °C to −20 °C when using MeLi proved to be beneficial, providing the best yield for alcohol **143** at this point (Entry 8). On the other hand, the gradual increase in temperature from −78 °C to −20 °C

when using *t*-BuOK resulted in a decreased yield (Entry 9). Employing freshly prepared silyl enol ether **122** and sublimated *t*-BuOK did not improve the yield for this reaction.

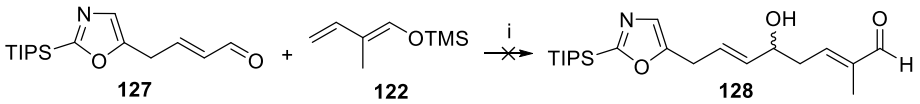
Disappointingly, when switching to *trans*-cinnamaldehyde (**145**) (**Figure 7**) or freshly distilled crotonaldehyde (**131**) (**Figure 6**) as model aldehydes, no product could be isolated upon treatment of these two aldehydes with either *t*-BuOK or MeLi. It was hypothesised that the enolate formation from silyl enol ether **122** was incomplete.



trans-cinnamaldehyde (**145**)

Figure 7. *trans*-Cinnamaldehyde (**145**)

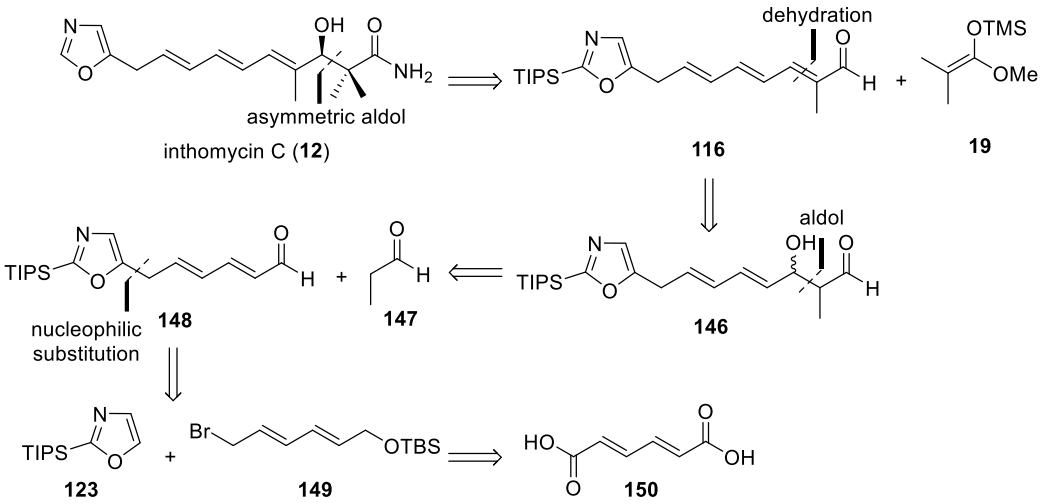
Application of the optimised conditions (Entry 8) to aldehyde **127** resulted in decomposition and no alcohol **128** could be isolated (**Scheme 48**). We postulated that the presence of acidic methylene protons on aldehyde **127** was incompatible with the basic conditions.



Scheme 48. Reagents and conditions: i) MeLi (1 eq.), THF, −78 °C to −20 °C, 1 h

2.1.2. Second proposed synthesis

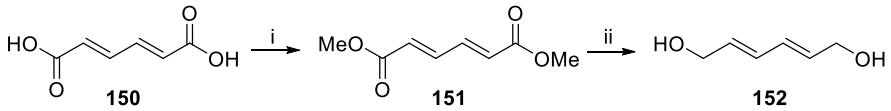
Since aldehyde **127** could not be obtained reliably due to its instability and given that the subsequent vinylogous Mukaiyama aldol reaction with silyl enol ether **122** proved to be very difficult to accomplish, we decided to investigate a new route towards inthomycin C (**12**) to overcome these problems. The key features of the new suggested synthesis include nucleophilic substitution between oxazole **123** and bromide **149** (which would be synthesised from commercially available *trans*,*trans*-muconic acid (**150**)), aldol addition with propionaldehyde (**147**), dehydration of alcohol **146**, and asymmetric Mukaiyama aldol reaction with silyl ketene acetal **19** (**Scheme 49**).



Scheme 49. Second proposed retrosynthesis of inthomycin C (**12**)

This time, the nucleophilic substitution reaction was expected to be the most challenging step in the sequence. We planned to achieve this transformation *via C*-5 lithiation of oxazole **123** followed by quenching with bromide **149**. At the same time however, we anticipated that both aldol reactions would be easier to perform than the vinylogous aldol reaction unsuccessfully attempted previously.

The first step in the sequence involved the esterification of commercially available *trans,trans*-muconic acid (**150**) to form methyl ester **151** in 99% yield using thionyl chloride and methanol.[80] Subsequently, ester **151** was reduced with DIBAL-H to the corresponding diol **152** in 77% yield (**Scheme 50**).[81] Note that the direct reduction of *trans,trans*-muconic acid (**150**) to diol **152** with $LiAlH_4$ was attempted without success.



Scheme 50. Reagents and conditions: i) $SOCl_2$ (8 eq.), MeOH-$CHCl_3$ 1:1, reflux, 4 h, 99%; ii) DIBAL-H (4 eq.), CH_2Cl_2, −78 °C to r.t., 4 h, 77%

With symmetric diol **152** in hand, our attention turned towards the exploration of a monoprotection strategy. Several conditions and protecting groups were compared and TBS-protected alcohol **153** was chosen as a substrate to be carried through the synthetic

sequence, since it could be accessed in high yield compared to its undesired disubstituted analogue (**Figure 8**).[82–92]

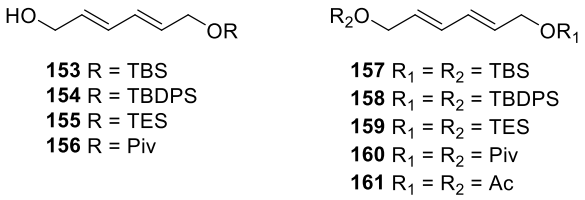
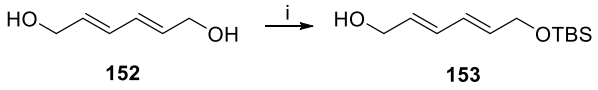


Figure 8. Synthesised monoprotected and diprotected diols. N.B. Yields: 43% **153** and 9% **157**; 46% **154** and 36% **158**; 24% **155** and 66% **159**; 37% **156** and 40% **160**; 85% **161**

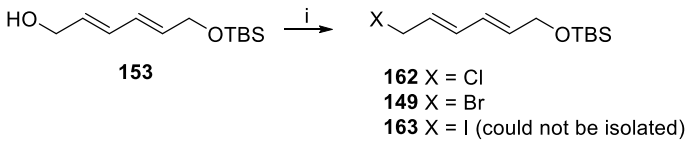
The selected TBS-protected alcohol **153** was obtained in an acceptable 43% yield,[86] given the difficulty of selective monoprotection of symmetrical diols, which usually leads to a statistical mixture (about 1:2:1 ratio) of diol/monoprotected/diprotected products (**Scheme 51**).



Scheme 51. Reagents and conditions: i) TBSCl (1.1 eq.), imidazole (1.5 eq.), DMF, r.t., 20 h, 43%

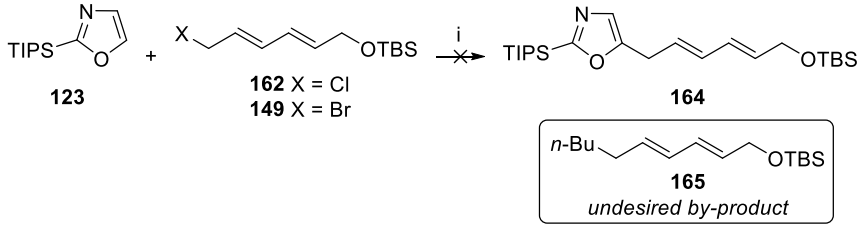
The next step involved the replacement of the free hydroxy group on alcohol **153** by a halogen to prepare the corresponding monoprotected halide **162**, **149** or **163**, which would serve as a substrate for the nucleophilic substitution reaction with oxazole **123** (**Scheme 52**). Halogenated dienes **162**, **149** and **163** proved to be unstable, possibly due to elimination of the halide, especially for iodide **163** which could not be isolated. We thus focused on bromide **149** and chloride **162**, which had to be used immediately after preparation and workup to avoid decomposition. The synthetic method found to be the most effective for the preparation of dienes **162** and **149** was to form the mesylate and then displace it with a halide source.[90–92] Full conversion of alcohol **153** into either halide **162** or **149** was observed by TLC analysis and confirmed by the change in chemical shift of the adjacent methylene protons in the ^{1}H NMR spectrum from 4.18 ppm for alcohol **153** to 4.11 ppm for either halide **162** or **149**. To remove the excess of base from crude halides **162** and **149**, purification

by flash column chromatography on silica gel was attempted; unfortunately, these conditions were not tolerated, and so workup with $CuSO_4$ was performed instead.



Scheme 52. Reagents and conditions: i) 2,4,6-collidine (4 eq.), LiX (3 eq.), DMF, r.t., 20 min then MsCl (2 eq.), 0 °C, 3 h, full conversion

Oxazole **123**, synthesised as described before (**Scheme 40**), was lithiated at the *C*-5 position with *n*-BuLi[67] and quenched with freshly prepared halides **162** and **149**. Unfortunately, these reactions did not provide any intended substitution product (diene **164**) and, in both cases, unreacted oxazole **123** was recovered. In the case of bromide **149**, trace amounts of diene **165** (an undesired alkylation by-product derived from nucleophilic attack of *n*-BuLi on bromide **149**) were also detected (**Scheme 53**).



Scheme 53. Reagents and conditions: i) *n*-BuLi (1.1 eq.), THF, −30 °C, 30 min then **162** or **149**, −30 °C to r.t., 3 h

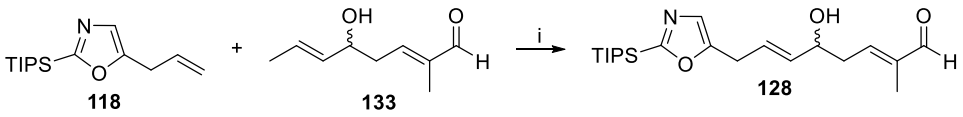
Since we had already proved that oxazole **123** could be lithiated and allylated at the *C*-5 position with allyl bromide in a S_N2/S_N2' fashion (see **Scheme 40**), we wondered whether oxazole **123** would also react with allyl chloride under the same conditions. Interestingly, the substitution reaction of oxazole **123** with allyl chloride did not provide any allylation product (oxazole **118**, see **Scheme 40**) and unreacted oxazole **123** was recovered instead, probably due to allyl chloride being too unreactive towards nucleophilic substitution. We therefore hypothesised that a more complex allylic chloride such as halide **162** was also likely to be too unreactive for such a transformation. We then decided to further evaluate the nucleophilic substitution reaction between oxazole **123** and bromide **149** (**Scheme 53**).

Unfortunately, we found that decreasing the lithiation temperature from −30 °C to −78 °C, adding chelating agents (such as DMPU), using molecular sieves (4 Å) or forming a cuprate intermediate (using analogous conditions to those depicted in **Scheme 40**) did not result in any yield improvement. We postulated that this transformation is likely to be very substrate-dependant or that bromide **149** may not be stable under the reaction conditions.

2.2. Revised synthetic approach towards inthomycin C and completion of the total synthesis

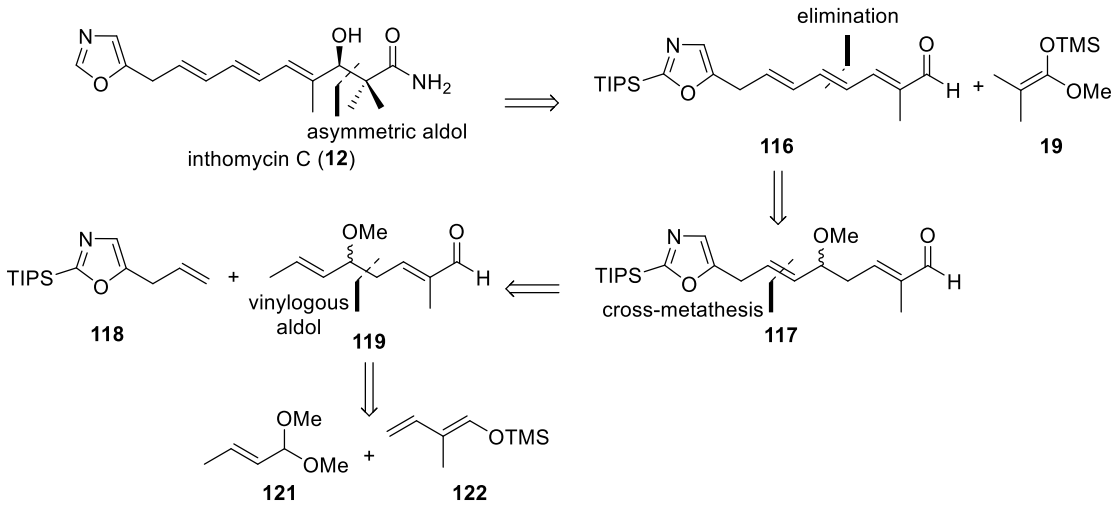
Considering the problems encountered while investigating our second route to inthomycin C (**12**), which include the low yield for the monoprotection of diol **152**, the instability of halides **162** and **149**, and the unfeasibility of the nucleophilic substitution with oxazole **123**, we decided to explore a new approach to synthesising inthomycin C (**12**).

Previous studies within the Donohoe group[64] had suggested the cross-metathesis reaction between oxazole **118** and alcohol **133** to synthesise aldehyde **128** (**Scheme 54**) as an alternative to the vinylogous aldol reaction outlined in **Scheme 44**. However, the best yield obtained for this cross-metathesis reaction was poor.[64]



Scheme 54. Reagents and conditions: i) **133** (2 eq.), HG-II (6 mol%), CH_2Cl_2, r.t., 24 h, 38%[64]

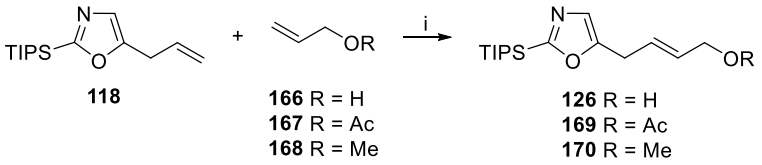
We decided to return to a synthetic approach similar to that outlined in **Scheme 39**, making the same main disconnections from a retrosynthetic point of view, but introducing several modifications to avoid the problems previously faced (**Scheme 55**).



Scheme 55. Main disconnections in the proposed revised synthesis of inthomycin C (**12**)

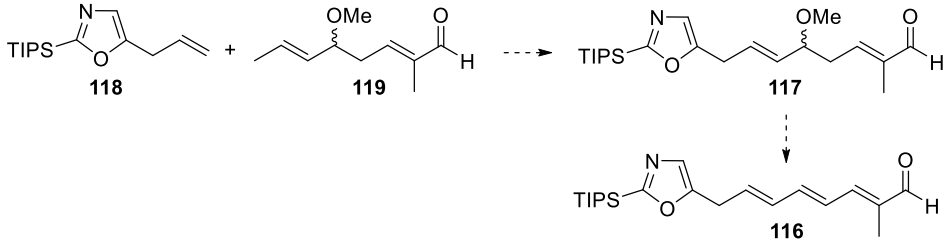
First, we prepared oxazole **118** on a multigram scale following the procedure described in **Scheme 40**. Given the difficulties in the separation of desired oxazole **118** from trace amounts of unreacted oxazole **123** by flash column chromatography on silica gel due to their similar polarity,[67] we attempted to separate them by flash column chromatography on silver nitrate-doped silica. Argentation chromatography relies on the formation of π-complexes between silver ions (π-acceptors) and alkenes (π-donors) and it has been historically used to separate geometric isomers of alkenes.[93] Although using this type of chromatography the ratio of oxazole **118** to oxazole **123** could be increased, we were unable to isolate pure oxazole **118**. We therefore decided to carry oxazole **118** forward to the next step as a mixture (containing <7% oxazole **123** for all batches), since we envisaged an easier purification at a later stage.

Following the idea of reassessing our initial synthetic approach towards inthomycin C (**12**), we evaluated the cross-metathesis between oxazole **118** and several model allylic substrates. We found that the reaction of oxazole **118** with allyl alcohol (**166**) provided a low yield (25%) compared to allyl acetate (**167**) (73%) or allyl methyl ether (**168**) (72%) (**Scheme 56**).



Scheme 56. Reagents and conditions: i) allylic reagent (10 eq.), HG-II (10 mol%), CH_2Cl_2, 50 °C, 24 h, 25% **126** or 73% **169** or 72% **170**

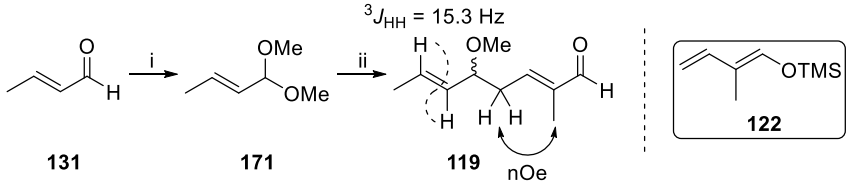
Alcohols can react unpredictably in cross-metathesis reactions; and examples of both positive and negative effects on the reaction outcome have been reported.[94] In the case of the cross-metathesis outlined in **Scheme 56**, the presence of an unprotected alcohol group on the model allylic substrate (alcohol **166**) proved detrimental for the yield of the cross-metathesis with oxazole **118**. Therefore, we predicted that the alkylation of the allylic hydroxy group on alcohol **133** (see **Scheme 54**) would increase the yield of the cross-metathesis with oxazole **118**. In this way, we expected that aldehyde **119**, resulting from the methylation of alcohol **133**, would be a better cross-metathesis partner than previously used[64] alcohol **133**. Subsequent elimination of the methoxy substituent in the corresponding cross-metathesis product (aldehyde **117**) would afford triene **116**, an intermediate which would already contain all the degrees of unsaturation of inthomycin C (**12**) (**Scheme 57**).



Scheme 57. Proposed alternative route towards triene **116**

Initial attempts to methylate alcohol **133** with trimethyloxonium tetrafluoroborate were unsuccessful. However, using a similar strategy to that for the preparation of alcohol **133** itself (see **Table 4**), aldehyde **119** could be synthesised *via* an acetal protection[95] of

crotonaldehyde (**131**) followed by a vinylogous aldol reaction of acetal **171** with TMS enol ether **122** in 53% yield over two steps (**Scheme 58**).



Scheme 58. Reagents and conditions: i) $HC(OMe)_3$ (1 eq.), MeOH (1.1 eq.), NH_4NO_3 (5 mol%), r.t., 4.5 h, 89%; ii) **122** (1.5 eq.), $BF_3{\cdot}OEt_2$ (1.2 eq.), CH_2Cl_2-Et_2O 9:1, −78 °C, 5 h, 60%. N.B. The presence of a single proton downfield alkene shift at 6.58–6.51 ppm in the ^{1}H NMR spectrum of aldehyde **119** indicated the existence of an α,β-unsaturated carbonyl moiety and confirmed the γ-selectivity of the vinylogous aldol reaction. The (*E*) geometry of the trisubstituted double bond on aldehyde **119** was confirmed by nOe experiments performed by a co-worker[96]

2.2.1. Optimisation of cross-metathesis between oxazole 118 and aldehyde 119

Research then focused on optimising the cross-metathesis reaction between oxazole **118** and aldehyde **119** to access key intermediate aldehyde **117** (see **Scheme 57**).

According to the model for selectivity in cross-metathesis reactions described by Grubbs and co-workers, olefins can be classified into four categories based on their relative reactivity (**Table 6**).[97] Type I olefins undergo rapid homodimerisation and their homodimers can participate in cross-metathesis reactions. Type II olefins slowly homodimerise and their homodimers are only slightly consumed in subsequent cross-metathesis reactions. Type III olefins form virtually no homodimers but they are still able to undergo cross-metathesis reactions with Type I and Type II olefins. Finally, Type IV olefins are unable to participate in cross-metathesis reactions but they do not deactivate the catalyst (spectator olefins). Outside these categories are olefins that deactivate the catalyst, and are therefore not suitable for cross-metathesis reactions. To render a cross-metathesis reaction selective, olefins from two different types should be used, since otherwise mixtures of homodimerisation and cross-metathesis products are normally obtained.

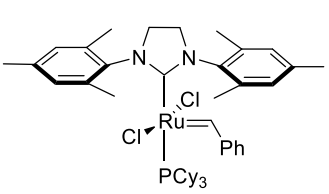
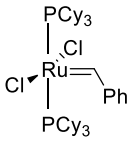
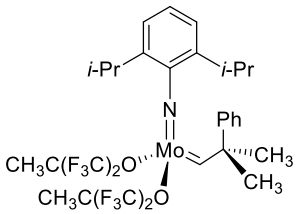
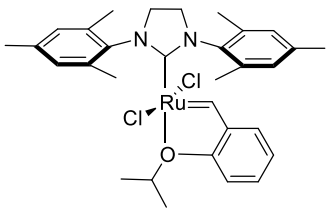
	 Grubbs second-generation catalyst (**172**)	 Grubbs first-generation catalyst (**173**)	 Schrock catalyst **174**
Olefin type	Catalyst **172**	Catalyst **173**	Catalyst **174**
Type I (fast homodimerisation)	terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large *ortho* substituents), allyl phosphonates, allyl silanes, allyl phosphine oxides, allyl sulfides, protected allyl amines	terminal olefins, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	terminal olefins, allyl silanes
Type II (slow homodimerisation)	styrenes (large *ortho* substituents), acrylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected 3º allylic alcohols, 2° allylic alcohols, perfluorinated alkane olefins	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronates	styrene, allyl stannanes
Type III (no homodimerisation)	1,1-disubstituted olefins, non-bulky trisubstituted olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substituents), protected 3° allylic alcohols	vinyl siloxanes	3° allyl amines, acrylonitrile
Type IV (spectators to cross-metathesis)	vinyl nitro olefins, protected trisubsituted allylic alcohols	1,1-disubstituted olefins, α,β-unsaturated carbonyls, 4° allylic carbon-containing olefins, perfluorinated alkane olefins, protected 3º allyl amines	1,1-disubstituted olefins

Table 6. Grubbs' olefin categories for selective cross-metathesis[97]

Although this empirical model focuses on three commonly used cross-metathesis catalysts such as Grubbs first- and second-generation catalysts[98,99] (**172** and **173**) as well as Schrock catalyst **174**,[100] it is worth noting that Hoveyda–Grubbs second-generation catalyst[101] (**175**) (**Figure 9**) is also a widely used catalyst in olefin metathesis reactions.



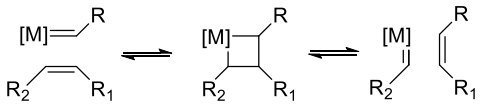
Hoveyda–Grubbs 2nd generation catalyst
(**175**)

Figure 9. Hoveyda–Grubbs second-generation catalyst (**175**)

Schrock molybdenum alkylidenes such as **174** are very powerful olefin metathesis catalysts, but due to their sensitivity to air and moisture they must be handled in a glove-box or by Schlenk techniques, and they suffer from decomposition upon storage.[98] More recently developed benzylidene ruthenium complexes such as **172** and **173** display higher air and water stability. Although initiating more slowly (possibly due to slower phosphine dissociation), second-generation catalyst **172** is more active than first-generation catalyst **173** and it has shown similar activity to earlier molybdenum carbenes such as **174**. Ruthenium catalysts have been mainly used for ring-opening metathesis polymerisation (ROMP) and ring-closing metathesis (RCM) reactions, and more recently for cross-metathesis (CM) reactions.[102] Ruthenium catalyst **175** was first introduced by Hoveyda and co-workers.[101] This recyclable complex shows similar efficiencies to the Grubbs system, but it has a slightly different substrate specificity. Catalyst **175** is a particularly suitable catalyst for metatheses involving highly electron-deficient substrates.[103] It is also an efficient catalyst for the formation of trisubstituted alkenes through catalytic RCM, and to access tetrasubstituted olefins too, although less efficiently.[101] Hoveyda–Grubbs second-generation catalyst (**175**) is more stable than Grubbs second-generation catalyst (**172**) under air and water due to the chelation of its isopropoxy ligand.[101,104] However, both catalysts are thermally stable: their half-lives at 55 °C in benzene are over a month.[105]

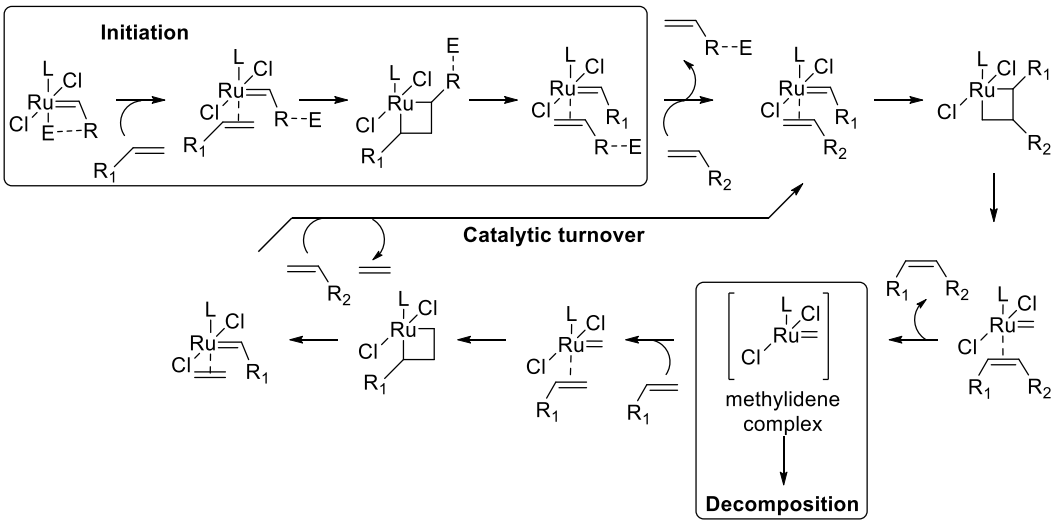
As a general trend, first-generation catalysts such as catalyst **173** are useful in the ROMP of strained cyclic olefins, as well as in the acyclic diene metathesis polymerisation (ADMET), CM and RCM of terminal olefins. Second-generation catalysts such as **172** and **175** are considerably more active than the first-generation catalysts. Besides an increased activity in RCM, they are used in CM of challenging substrates (sterically hindered or deactivated olefins). The main difference between the last two catalysts is that catalyst **175** is a faster initiator at lower temperatures.[106]

Olefin metathesis is a transalkylidenation reaction that allows the exchange of substituents between a metal carbene and an alkene *via* a [2+2] cycloaddition mechanism (**Scheme 59**).[102]



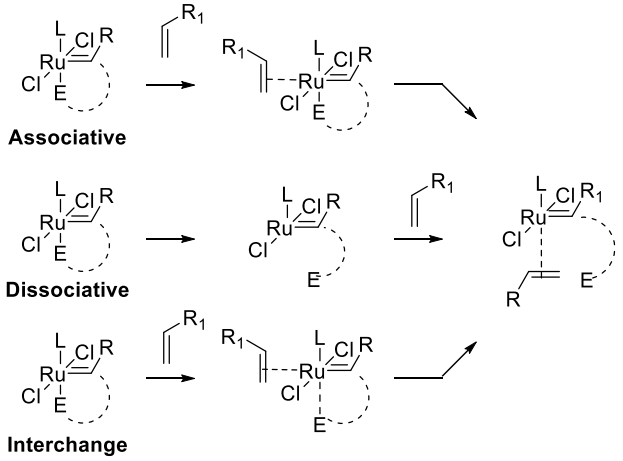
Scheme 59. Mechanism of olefin metathesis

The general mechanism for this transformation involves the dissociation/initiation of the stable pre-catalyst (typically 16-electron Ru^{II}) which is converted into an active 14-electron species, followed by propagation and termination steps. Catalyst decomposition is one of the main challenges in the study of metathesis reactions since it can compromise the efficiency of the catalytic process. Methylidene complexes, formed after catalytic turnover with terminal alkenes, are often considered the most unstable species in metathesis reactions (**Scheme 60**).[107]



Scheme 60. Key stages of alkene metathesis reactions[107]

The initiation (or activation) of the pre-catalyst dictates the rate at which active 14-electron species are formed. Most pre-catalysts are 16-electron species that must first lose a ligand by dissociation to generate a 14-electron alkylidene species (usually unobservable). There are three mechanisms for pre-catalyst activation: associative, dissociative and interchange. In the associative mechanism, the alkene binds the metal centre to afford an 18-electron intermediate before loss of the ligand. In the dissociative mechanism, a 14-electron species is formed which then binds the alkene. Finally, in the interchange mechanism the binding of the alkene and loss of the ligand occur simultaneously (**Scheme 61**).[107]



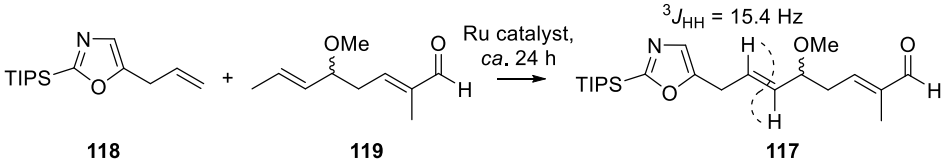
Scheme 61. Three possible mechanisms for pre-catalyst activation[107]

Grubbs-type (phosphine-containing) pre-catalysts are activated through a dissociative mechanism, so that phosphine dissociation happens first. Despite the high σ-donating ability of the N-heterocyclic carbene (NHC) *versus* the phosphine ligand, Grubbs second-generation catalyst (**172**) initiates more slowly than Grubbs first-generation catalyst (**173**). The increased activity of catalyst **172** compared to catalyst **173** has been attributed to its higher selectivity for binding π-acidic olefinic substrates in the presence of σ-donating free phosphine.[108] Computational studies on Hoveyda-type (chelating benzylidene-ether) pre-catalysts showed that these pre-catalysts are activated either *via* a dissociative or an interchange mechanism, but it has not been possible to determine which one is the favoured initiation process.[109]

For the study of the cross-metathesis reaction between oxazole **118** and aldehyde **119** (**Table 7**), we selected Grubbs second-generation and Hoveyda–Grubbs second-generation catalysts (**172** and **175**) given their higher activity and stability. Based on the model described above, we had to optimise a cross-metathesis between a Type II olefin (oxazole **118**) and a Type III olefin (the allylic methyl ether moiety on aldehyde **119**) in the presence of a Type IV olefin (the α,β-unsaturated carbonyl moiety on aldehyde **119**). We anticipated the use of an excess of less reactive Type III olefin (aldehyde **119**) to achieve good conversions to the cross-metathesis product **117**.[110] We chose dichloromethane as the solvent since it is a polar aprotic solvent that should favour ligand dissociation and posterior olefin binding.

Initially, we investigated the stoichiometry of the cross-metathesis reaction. Oxazole **118** was treated with an excess of aldehyde **119** and the desired cross-metathesis product **117** was obtained in 32% yield along with trace amounts of homodimer by-product **176** (**Table 7**) (Entry 1). Conversely, using an excess of oxazole **118** compared to aldehyde **119** resulted in a decreased yield of 17% and an increase in the formation of undesired homodimer **176** (Entry 2). Previous studies[65] had proven that homodimer **176** (**Figure 10**) was almost

inactive in cross-metathesis reactions, constituting a dead-end by-product. Therefore, and in line with our predictions, we decided to use an excess of aldehyde **119** in all subsequent experiments to minimise homodimerisation and potentially achieve higher yields. Running the reaction at 40 °C proved to be the most suitable option, as both higher temperatures (Entry 3) and lower temperatures (Entry 4) resulted in poorer yields. The addition of a second batch of catalyst together with an extended reaction time did not have a significant effect on the yield (Entry 5). Increasing the equivalents of aldehyde **119** improved the yield (Entries 6–8). The use of Grubbs second-generation catalyst (**172**) provided better yields than Hoveyda–Grubbs second-generation catalyst (**175**), as well as an easier product **117** purification when scaling up the reaction to 286–297 mg scale (1.08–1.12 mmol) (Entries 9 and 10).



118 **119** **117**

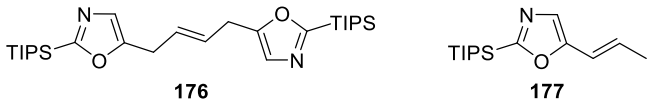
Entry	Oxazole **118** (eq.)	Aldehyde **119** (eq.)	Catalyst (mol %)	Solvent	T (°C)	Yield **117** (%)
1	1	1.5	HG-II (10)	CH_2Cl_2	40	32
2	3	1	HG-II (10)	CH_2Cl_2	40	17
3	1	2	HG-II (10)	DCE	80	26
4[a]	1	2	HG-II (10)	CH_2Cl_2	r.t.	29
5[b]	1	2	HG-II (10+5)	CH_2Cl_2	40	31
6	1	3.3	HG-II (10)	CH_2Cl_2	40	41
7[c]	1	5	HG-II (10)	CH_2Cl_2	40	48
8[a,c]	1	10	HG-II (10)	CH_2Cl_2	40	41
9[c]	1	3.4	G-II (10)	CH_2Cl_2	40	44
10[a,c]	1	4.9	G-II (10)	CH_2Cl_2	40	57
11[d]	1	5	G-II (10)	CH_2Cl_2	40	41
12[e]	1	5	G-II (10)	CH_2Cl_2	40	43

N.B. "HG-II" = Hoveyda–Grubbs second-generation catalyst. "G-II" = Grubbs second-generation catalyst. [**118**] = 0.25 M. Some homodimer **176** and trace amounts of migration by-product **177** were isolated in most cases. [a]Reaction time = *ca*. 50 h. [b]Reaction time = 70 h. [c]Syringe-pump addition of oxazole **118** over 6 h. [d]Additive: 1,4-benzoquinone (20 mol%). [e]Additive: CuI (20 mol%)

Table 7. Optimisation of cross-metathesis reaction between oxazole **118** and aldehyde **119**

In most experiments performed we could observe trace amounts of alkene migration by-product **177** (**Figure 10**). Grubbs and co-workers reported the use of 1,4-benzoquinone to

prevent olefin isomerisation on alkenes during cross-metatheses due to its quick reaction with ruthenium hydrides generated during catalyst decomposition.[111] Unfortunately, although the addition of 1,4-benzoquinone prevented the formation of migration product **177**, the yield for aldehyde **117** decreased (Entry 11). On the other hand, the addition of copper (I) iodide (a previously described catalyst stabiliser and phosphine scavenger for Grubbs second-generation-catalysed metatheses)[112] also resulted in a decreased yield for aldehyde **117** (Entry 12). It should be noted that the slow addition of oxazole **118** by syringe-pump minimised the formation of its homodimer **176** as by-product (Entries 7–10). This would also explain the higher yields of aldehyde **117** observed in these experiments.



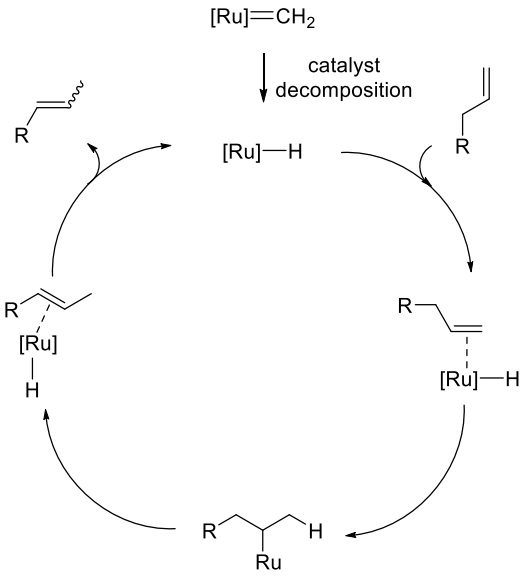
176 **177**

Figure 10. Homodimerisation by-product **176** and alkene migration by-product **177**

The best yield for the cross-metathesis reaction between oxazole **118** and aldehyde **119** was 57%, obtained when performing this reaction on a 286 mg scale (1.08 mmol). We postulated that the main reason for the moderate yield of this challenging cross-metathesis reaction could be the deactivation of the catalyst due to coordination to the nitrogen on the oxazole ring of oxazole **118**, combined with the low reactivity and partial decomposition of aldehyde **119**.

We postulated that migration by-product **177** observed in our cross-metathesis system had been formed *via* ruthenium hydride-catalysed isomerisation. The decomposition of ruthenium catalysts in cross-metatheses can lead to the formation of ruthenium hydride species,[113] which have been reported to be responsible for undesired side reactions including the isomerisation of double bonds (**Scheme 62**).[114] Upon decomposition, the ruthenium catalyst provides a ruthenium hydride species that catalyses the alkene isomerisation reaction. First, a π-complex is formed by coordination of the ruthenium hydride species to

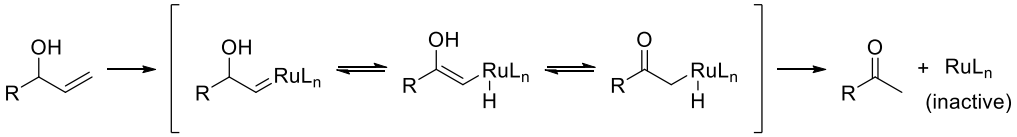
the alkene substrate. Subsequent hydrometallation furnishes a σ-alkyl complex which then undergoes β-hydride elimination followed by dissociation to give the more stable internal olefin.



Scheme 62. Mechanism for double bond isomerisation in alkenes[114]

With regard to the poor cross-metathesis yields previously[64] obtained when using allylic alcohol **133** as a substrate (38% yield, see **Scheme 54**) compared to its methyl ether analogue **119** (57% yield, see **Table 7**), we hypothesised that this could be due to the allylic alcohol being decomposed and converted into the corresponding methyl ketone by ruthenium hydride. This assumption was made based on previous studies carried out by Hoye and co-workers.[115] These authors had reported that when subjecting secondary allylic alcohols to RCM reactions they can undergo a competitive decomposition pathway that results in truncation of the unsaturated moiety and its conversion to a methyl ketone. Later, Paquette and co-workers[116] also observed this truncation while performing RCM reactions. Both these research groups proposed the following mechanism: the ruthenium carbenoid formed initially is converted to the enolyl ruthenium hydride, which undergoes tautomerisation and reductive elimination to generate the corresponding methyl ketone (**Scheme 63**). During their investigations on RCM reactions, Hoye and co-workers also found that allylic ethers

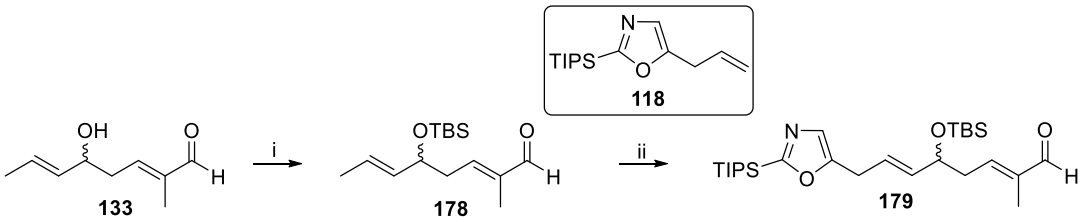
initiated more slowly than the corresponding allylic alcohols. However, in complex and highly functionalised dienes, ethers may perform better than the free alcohol, as discussed by Gennari and co-workers.[117,118]



Scheme 63. Mechanism of decomposition of secondary allylic alcohols to methyl ketones

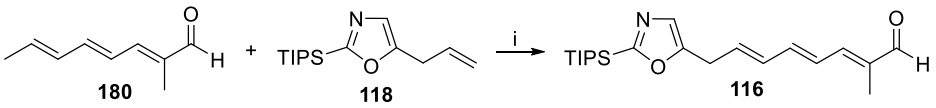
We next considered the modification of aldehyde **119** to prepare alternative substrates that could potentially provide better cross-metathesis yields and that were, in turn, suitable for the following elimination step to form triene **116** (see **Scheme 57**). With this purpose, we aimed to find an appropriate cross-metathesis partner that contained a sufficiently electron-rich and not too sterically hindered olefin able to undergo the cross-metathesis reaction, and that at the same time incorporated a good leaving group susceptible to elimination. It is worth mentioning that previous attempts to synthesise the more active terminal alkene analogue of aldehyde **119** (a compound with the same structure but missing the terminal methyl group) were unsuccessful.[64]

First, the protection of the aldehyde moiety in aldehyde **119** as an acyclic or cyclic acetal was unsuccessfully attempted. Subsequently, we explored the introduction of other substituents instead of -OMe at the allylic position, including -OTBS, -OTs, -Br, -$OCOCF_3$ and -SEt. We tried to synthesise all of these substrates from alcohol **133**. Nevertheless, either decomposition or elimination and conversion into undesired triene **180** occurred in all cases except for TBS ether **178**, which could be formed in 41% yield. The cross-metathesis of TBS ether **178** with oxazole **118** provided aldehyde **179** in 40% yield (**Scheme 64**). This result showed that a bulky TBS group was tolerated for the cross-metathesis reaction, but the yield decreased compared to that previously obtained when using methyl ether **119** as a substrate (57% yield, see **Table 7**).



Scheme 64. Reagents and conditions: i) TBSOTf (1.1 eq.), lutidine (1.5 eq.), CH_2Cl_2, 0 °C to r.t., 18 h, 41%; ii) G-II (10 mol%), CH_2Cl_2, 40 °C, 24 h, 40%

Triene **180**, the undesired by-product obtained previously, was also subjected to the optimised cross-metathesis conditions with oxazole **118** and a complex mixture of products was obtained, containing <15% of the desired triene **116** (**Scheme 65**). This result indicated that, as we expected, this triene was not a suitable substrate for the cross-metathesis reaction, and that the cross-metathesis had to be performed prior to the elimination step.



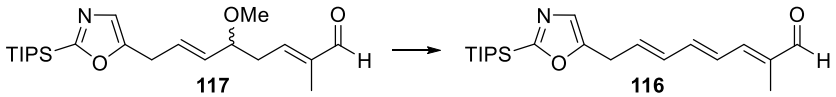
Scheme 65. Reagents and conditions: i) HG-II (10 mol%), CH_2Cl_2, 40 °C, 24 h, <15%

2.2.2. Optimisation of elimination on aldehyde 117

With aldehyde **117** in hand, we set out to explore the elimination of the methoxy substituent (**Table 8**). We hoped this elimination reaction would give triene intermediate **116**, which after TIPS-deprotection would constitute a formal synthesis of inthomycin C.

At the outset, we expected that the aldehyde functionality on aldehyde **117** would facilitate an E1cB elimination reaction by stabilising the carbanion intermediate through resonance. Initial elimination attempts using DBU[119] as base resulted in decomposition and aldehyde peak disappearance in the ^{1}H NMR spectrum (Entry 1). It was then hypothesised that elimination under basic conditions may be challenging as triene **116** methylene protons are likely to be more acidic than those in aldehyde **117**. Subsequent attempts to access triene **116** through the formation of a π-allyl complex followed by β-hydride elimination using transition metals such as Pd[120] or Ni[121] proved unsuccessful (Entries 2 and 3). At this point,

we envisaged the use of acidic conditions as an alternative strategy to achieve the desired elimination. Unfortunately, treatment of aldehyde **118** with acetic acid led to TIPS-deprotection by-product in 8% yield and recovery of trace amounts of starting material (Entry 4). Given the extensive decomposition observed for the last experiment, we opted for milder reaction conditions to activate aldehyde **118** for elimination, such as the use of Lewis acids. Hence, aldehyde **118** was reacted with TBSOTf and Et_3N to effect the required elimination. Interestingly, although desired triene **117** was not observed by initial TLC analysis of the reaction crude mixture, we were able to isolate it in 25% yield after FCC purification (Entry 5). The formation of triene **117** on silica gel column suggested that the acidity of silica was sufficient to catalyse the elimination reaction we targeted. Encouraged by the latter result, we decided to investigate other acidic sources to favour elimination. A two-step protocol involving treatment with TBSOTf/Et_3N followed by different reagents (CSA, Pyr·HBr, $BF_3{\cdot}OEt_2$-TBAF) did not provide the expected results, as TIPS-deprotection mainly occurred in all cases (Entries 6–8). Eventually, we found that working in the absence of light (to avoid potential undesired isomerisation) and employing an oxophilic Lewis acid such as $Sc(OTf)_3$ in a one-pot procedure after previous treatment with TBSOTf/Et_3N provided the desired triene in 57% yield (Entry 9). By increasing the equivalents of TBSOTf and Et_3N as well as using freshly distilled Et_3N we could achieve the desired elimination in good and reproducible yields (Entries 10 and 11). Finally, we performed two control experiments, in which we observed that $Sc(OTf)_3$ was not able to promote the elimination alone since aldehyde **118** remained unreacted (Entry 12), and that using TBSOTf without Et_3N buffer led to decomposition (Entry 13).

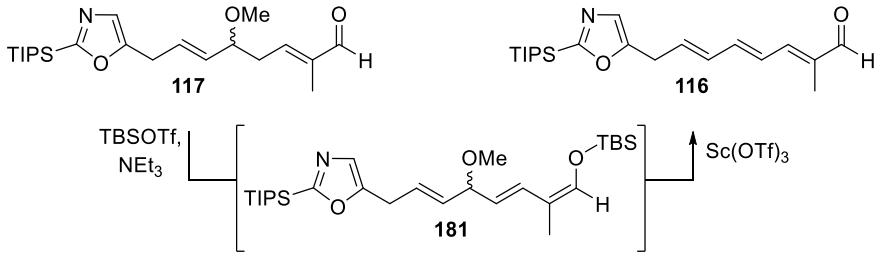


Entry	Reagents (eq.)	Solvent	T (°C)	Time (h)	Yield[a] **116** (%)
1[b]	DBU (2)	CH_2Cl_2	r.t.	6	decomposition
2	$Pd(OAc)_2$ (0.1), PPh_3 (1)	dioxane	100	27	decomposition
3[c]	$Ni(cod)_2$ (0.2), dppf (0.4)	toluene	r.t.	96	rsm
4[b,d]	AcOH (12)	neat	r.t. to 100	18	0
5[b,e]	TBSOTf (1.1), Et_3N (1.5)	CH_2Cl_2	0 to r.t.	22	25 (8.1:1)
6[b,d]	i) TBSOTf (1.5), Et_3N (2); ii) CSA (1.5)	CH_2Cl_2	0 to r.t.	20	trace
7[b,d]	i) TBSOTf (2), Et_3N (3); ii) Pyr·HBr (2)	CH_2Cl_2	0 to r.t.	55	trace
8[b,d]	i) TBSOTf (2.5), Et_3N (3); ii) $BF_3{\cdot}OEt_2$-TBAF 1:1 (1)	CH_2Cl_2	0 to r.t.	79	0
9[f]	TBSOTf (1.1), Et_3N (1.5); then $Sc(OTf)_3$ (2)	CH_2Cl_2	0 to r.t.	29	57 (15.1:1)
10[f,g]	TBSOTf (1.6), Et_3N (2.5); then $Sc(OTf)_3$ (2)	CH_2Cl_2	0 to r.t.	23	73 (12.3:1)
11[f,g]	TBSOTf (1.8), Et_3N (2.8); then $Sc(OTf)_3$ (2.2)	CH_2Cl_2	0 to r.t.	21	74 (8.3:1)
12[c]	$Sc(OTf)_3$ (2)	CH_2Cl_2	0 to r.t.	6	rsm
13	TBSOTf (2)	CH_2Cl_2	0 to r.t.	5	decomposition

N.B. "rsm" = recovered starting material. [a]Triene **116** was obtained as a mixture of geometrical isomers; isomeric ratios are indicated in parentheses. [b]Molecular sieves 4 Å were used. [c]Starting material was fully recovered. [d]TIPS deprotection occurred. [e]Product **116** was formed upon purification by FCC on silica gel. [f]One pot procedure in absence of light. [g]Freshly distilled Et_3N

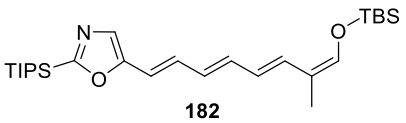
Table 8. Optimisation of elimination reaction on aldehyde **117**

We postulated that the elimination described above proceeded through a mechanism involving the formation of TBS enol ether intermediate **181** and conversion into triene **116** by subsequent treatment with Lewis acid (**Scheme 66**).



Scheme 66. Proposed mechanism for OMe elimination on aldehyde **117**

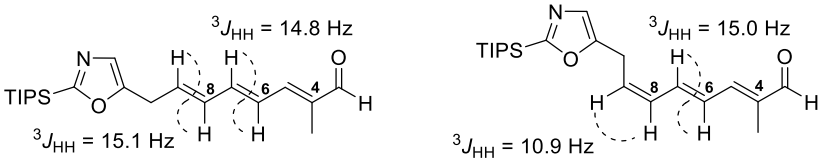
When we applied the optimised elimination conditions to aldehyde **117**, we could also isolate undesired tetraene **182** by-product, which was formed during the initial treatment with TBSOTf/Et_3N prior to the addition of $Sc(OTf)_3$, as observed by TLC analysis (**Figure 11**).



182

Figure 11. Elimination by-product **182**

It should be noted that in all cases aldehyde **116** was obtained as a mixture of geometric isomers practically inseparable by FCC, with the (4*E*,6*E*,8*E*) triene isomer being the major product (isomeric ratios ranged from 8:1 to 15:1). ^{1}H NMR analysis of the vicinal proton-proton couplings ($^{3}J_{HH}$) on the triene system for both isomers allowed the determination of their respective configurations (**Figure 12**).[96]



116 major isomer

183 minor isomer

Figure 12. Elimination product isomers with relevant *J* coupling constants determined by ^{1}H NMR (in $CDCl_3$ for **116** and in CD_2Cl_2 for **183**)[96]

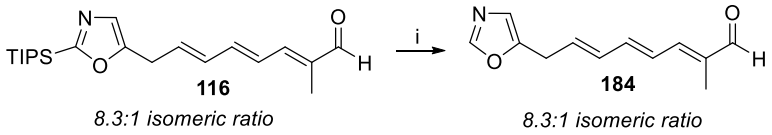
Although complete separation of the two isomers by FCC was unattainable, it was found that the undesired geometrical isomer (4*E*,6*E*,8*Z*) eluted first. Therefore, we could increase the geometrical purity of aldehyde **116** by sacrificing earlier fractions. This way, material of up to 22:1 isomeric ratio was obtained.[96]

Attempts to use catalytic iodine to promote the *cis-trans* isomerisation of the double bonds in aldehyde **116** in favour of the desired all *trans* isomer were unsuccessful.[122] The isomeric ratio obtained after treatment with iodine (8.9:1) was similar than that obtained in the elimination reaction, probably due to having achieved the thermodynamic distribution.

Similar stereocontrol issues with inthomcyin C (**12**) analogues were previously reported by the Hale group. Although the Ryu group had not commented on the geometrical purity of their prepared inthomycin C (**12**) sample,[28] the Hale group reported difficulties in obtaining pure geometrical triene sample when performing the Stille cross-coupling using the same

conditions as Ryu.[30] The Hale group synthesised inthomycin C (**12**) as a 5.9:1 mixture of triene isomers, with the (4*E*,6*E*,8*E*) isomer being the major product together with an unknown isomer. They were only able to obtain material of 17.1:1 isomeric ratio after multiple elution preparative TLC and with the sacrifice of substantial amounts of material, so they decided to carry the 5.9:1 mixture forward in their synthesis despite its lower geometrical purity for practical reasons.

On the other hand, when we subjected aldehyde **116** to aqueous 1 M HCl treatment we could isolate TIPS-deprotected aldehyde **184** in 61% yield with the isomeric ratio unchanged (**Scheme 67**). This observation suggested that the TIPS group could be easily deprotected at a later stage without significantly affecting the geometric purity of the material.



Scheme 67. Reagents and conditions: i) aq. 1 M HCl (1 eq.), CH_2Cl_2-THF 1:1, r.t., 4.5 h, 61%

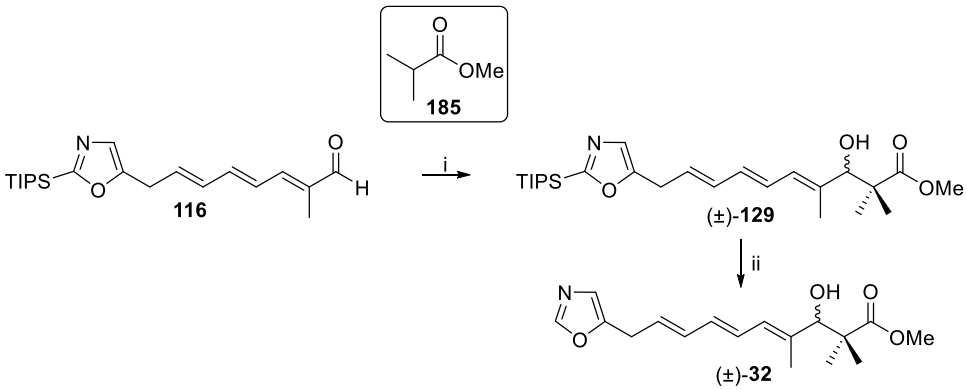
2.2.3. Optimisation of asymmetric Mukaiyama–Kiyooka aldol addition between silyl ketene acetal 19 and aldehyde 116

Having installed the triene unit on aldehyde **116**, we proceeded with the study of the subsequent Mukaiyama aldol reaction to introduce the *gem*-dimethyl carbonyl group moiety.

We planned to explore the Mukaiyama aldol reaction and the following steps (including saponification and amidation) on racemic material first and afterwards apply the optimised conditions to enantioenriched material to accomplish the asymmetric synthesis of inthomycin C (**12**).

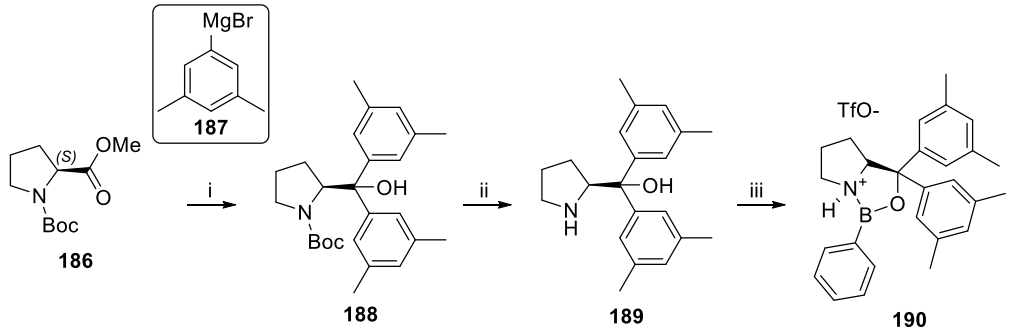
Initially, freshly prepared aldehyde **116** was treated with LDA and methyl isobutyrate (**185**) and, pleasingly, racemic ester **129** was formed in 94% yield. Subsequent TIPS-deprotection on racemic ester **129** with aqueous 1 M HCl afforded racemic ester **32** in 87% yield (**Scheme**

68). The synthesis of racemic ester **32** constituted a novel formal synthesis of (±)-inthomycin C (**12**).



Scheme 68. Reagents and conditions: i) LDA (3 eq.), **185** (3 eq.), THF, −78 °C to −10 °C, 1.5 h, 94%; ii) aq. 1 M HCl (1.1 eq.), THF, r.t., 3 h, 87%

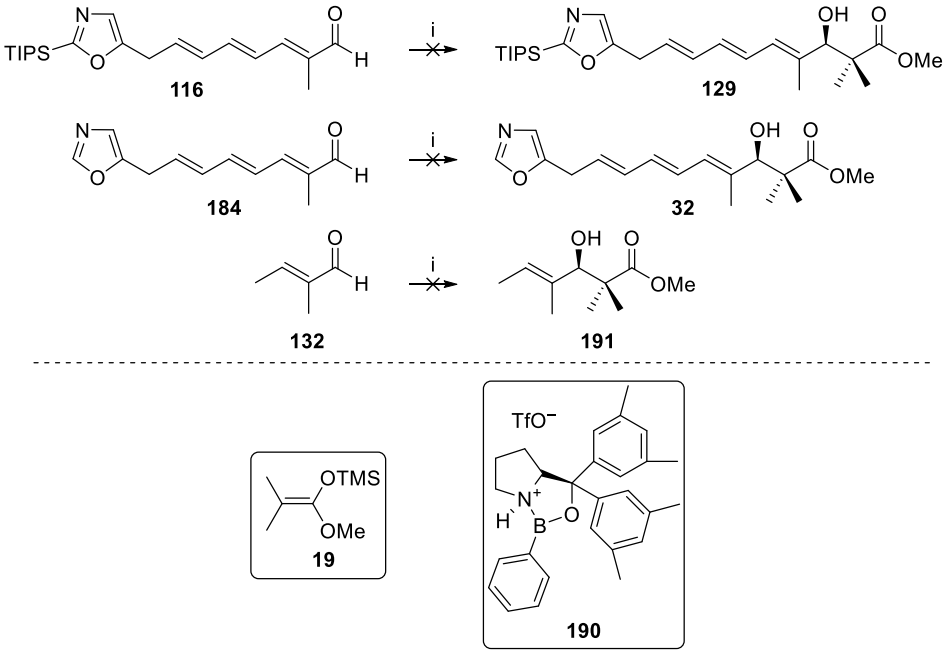
For the study of the asymmetric Mukaiyama aldol addition between aldehyde **116** and silyl ketene acetal **19**, we first intended to use Ryu's oxazaborolidinium catalyst **190**, since it had provided the highest enantioselectivity on a similar aldehyde substrate.[28] After screening several reaction conditions, we could prepare oxazaborolidinium catalyst **190** in three steps from pyrrolidine **186** *via* a double Grignard addition, followed by Boc-deprotection and treatment with triphenylboroxine to form oxazaborolidinium catalyst **190** (**Scheme 69**).



Scheme 69. Reagents and conditions: i) **187** (3.5 eq.), THF, r.t., 4.5 h, 53%; ii) KOH (10 eq.), DMSO-MeOH 4.8:1, reflux, 65 °C, 4 h, 85%; iii) triphenylboroxine (0.3 eq.), PhMe, reflux, 3 h then distilled at 60 °C and concentrated *in vacuo*, then TfOH (0.8 eq.), PhMe, −40 °C, 20 min

Unfortunately, when we used freshly prepared oxazaborolidinium catalyst **190** for the Mukaiyama aldol reaction between aldehyde **116** and silyl ketene acetal **19** we did not detect any intended aldol product (alcohol **129**) and instead starting material aldehyde **116** was recovered in 42% yield (**Scheme 70**). In parallel, we attempted the Mukaiyama aldol on

aldehyde **184** using the same conditions without success (in this case 81% of aldehyde **184** was recovered). We then decided to apply these Mukaiyama aldol reaction conditions on tiglic aldehyde (**132**), a simpler aldehyde which had already been used by the Ryu group[28] for the same transformation. Surprisingly, we were unable to isolate any aldol product (alcohol **191**) (**Scheme 70**).

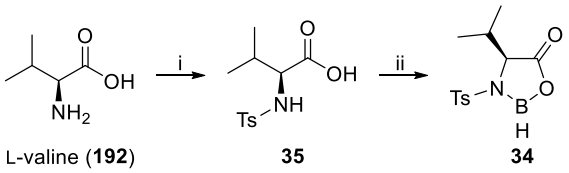


Scheme 70. Reagents and conditions: i) **19** (1.2 eq.), **190** (20 mol%), Ph_3PO (50 mol%), PhMe, −40 °C, 20 h

We hypothesised that the problems encountered in accessing alcohol **129**, **32** and **191** using the Mukaiyama aldol reaction conditions described above were due to the challenging preparation of catalyst **190** from prolinol **189** on small scale together with its reported stability only at low temperature.[123] Furthermore, in the case of aldehydes **116** and **184**, we postulated that the basic nitrogen lone pair on the oxazole ring may be coordinating to catalyst **190**.

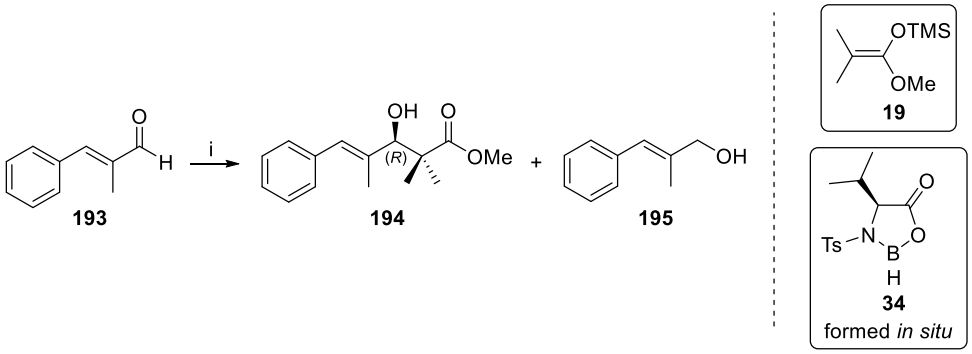
At this point, our attention turned towards the exploration of an alternative catalyst for the desired asymmetric Mukaiyama aldol reaction. Taylor and co-workers had reported the use of oxazaborolidinone **34** to catalyse the Mukaiyama–Kiyooka aldol addition in their route towards inthomycin C (**12**).[27] Although the Taylor group had only obtained their desired

aldol product in 50% yield and 76% ee, we decided to prepare oxazaborolidinone catalyst **34** and test its efficiency in our Mukaiyama aldol reaction, hoping that it would provide better results than our initial unsuccessful attempts with oxazaborolidinium catalyst **190**. We synthesised catalyst **34** in two steps from commercially available L-valine (**192**) (**Scheme 71**).[27,124]



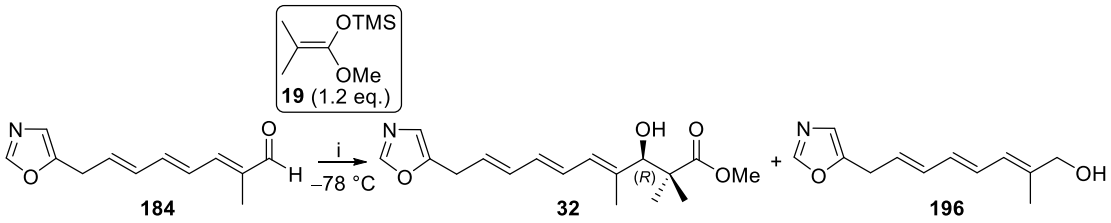
Scheme 71. Reagents and conditions: i) NaOH (2.1 eq.), TsCl (1 eq.), THF, 0 °C to r.t., 24 h, 71%; ii) BH_3·THF (0.9 eq.), CH_2Cl_2, 0 °C, 20 min then r.t., 30 min. N.B. Catalyst **34** was used *in situ* for the Mukaiyama–Kiyooka aldol reactions

Freshly prepared catalyst **34** was used *in situ* to catalyse the Mukaiyama–Kiyooka aldol addition between silyl ketene acetal **19** and α-methyl-*trans*-cinnamaldehyde (**193**) as model aldehyde (**Scheme 72**). This way, alcohol **194** was obtained in 40% yield and 83% ee, as determined by chiral HPLC analysis. Along with the desired aldol product (alcohol **194**), we could also isolate alcohol **195**, a reduction by-product, in 60% yield. Similar problems with competitive reduction reaction had already been reported by Taylor and co-workers.[27]



Scheme 72. Reagents and conditions: i) **19** (1.2 eq.), *in situ* prepared **34** (2 eq.), CH_2Cl_2, −78 °C, 2 h, 40% **194** (83% ee) and 60% **195**. N.B. The (*R*) configuration of alcohol **194** was confirmed by Mosher ester analysis performed by a co-worker[96]

Encouraged by this preliminary result, we planned to optimise the Mukaiyama–Kiyooka conditions outlined in **Scheme 72** employing aldehyde **184** as a substrate (**Table 9**).



Entry	Reagents (eq.)	Solvent	Yield **32** (%)	ee (%)	Yield **196** (%)
1[a]	*N*-Ts-L-valine (2.2), BH_3·THF (2)	CH_2Cl_2	41	81	25
2[b]	*N*-Ts-L-valine (2.2), BH_3·THF (1)	CH_2Cl_2	40	80	24
3[c]	*N*-Ts-L-valine (2.2), BH_3·THF (0.5)	CH_2Cl_2	0	N/A	0
4[d]	*N*-Ts-L-valine (2.2), BH_3·Me_2S (1)	CH_2Cl_2	0	N/A	12
5[e]	*N*-Ts-L-valine (2.2), BH_3·THF (2)	THF	0	N/A	0
6[f]	*N*-Ts-L-valine (2.2), BH_3·THF (2)	CH_2Cl_2	71	82	13
7[f]	*N*-Ts-L-valine (2.2), BH_3·THF (2)	CH_2Cl_2	68	80	12

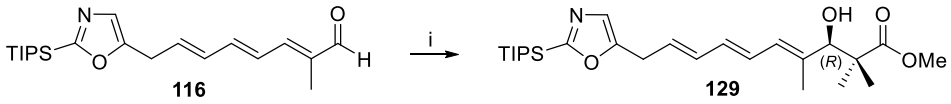
N.B. An excess of *N*-Ts-L-valine compared to BH_3·THF was used to minimise competitive reduction. ee was determined by chiral HPLC analysis. [a]Aldehyde **184** was fully consumed. [b]Trace amounts of aldehyde **184** were recovered. [c]89% recovered starting material. [d]74% recovered starting material. [e]91% recovered starting material. [f]Freshly distilled silyl ketene acetal **19.** N.B. The (*R*) configuration of alcohol **32** was confirmed by Mosher ester analysis performed by a co-worker[96]

Table 9. Optimisation of Mukaiyama–Kiyooka aldol reaction between aldehyde **184** and silyl ketene acetal **19**

When applying the initial conditions (outlined in **Scheme 72**) to aldehyde **184**, alcohol **32** was obtained in 41% yield and 81% ee, along with undesired alcohol **196** in 25% yield (Entry 1). Reducing the amount of catalyst **34** to 1 eq. provided a very similar result, although in this case trace amounts of aldehyde **184** were recovered (Entry 2). Attempts to use substoichiometric amounts of catalyst **34** resulted in no conversion (Entry 3). In line with Taylor's findings,[27] we postulated that the need for stoichiometric amounts of catalyst **34** was probably due to complexation of the oxazole nitrogen lone pair on aldehyde **184** to the catalyst and that, in turn, this excess of catalyst **34** would inevitably favour the formation of undesired reduction by-product (alcohol **196**). Changing the boron reagent to BH_3·Me_2S did not provide any alcohol **32** and instead most of aldehyde **184** was recovered (Entry 4). We hypothesised that preferred coordination of Me_2S to the catalyst over aldehyde complexation may be detrimental for the desired aldol process. At this point, we decided to use 2 eq. of catalyst **34** in all subsequent experiments to ensure complete consumption of

aldehyde **184**. Next, we changed the solvent to THF but unfortunately alcohol **32** could not be isolated (Entry 5). Using freshly distilled silyl ketene acetal **19** proved to be crucial for the reaction, providing the highest yield for ester **32** combined with the lowest yield for undesired alcohol **196** (Entry 6). Satisfyingly, the latter optimised conditions were reproducible (Entry 7).

We also applied these Mukaiyama–Kiyooka optimised conditions to TIPS-protected aldehyde **116**. In this way, aldol product **129** could be isolated in 42% yield maintaining the enantioselectivity (82% ee), with 56% recovered aldehyde **116** (**Scheme 73**). This was a preliminary result and further optimisation was required.

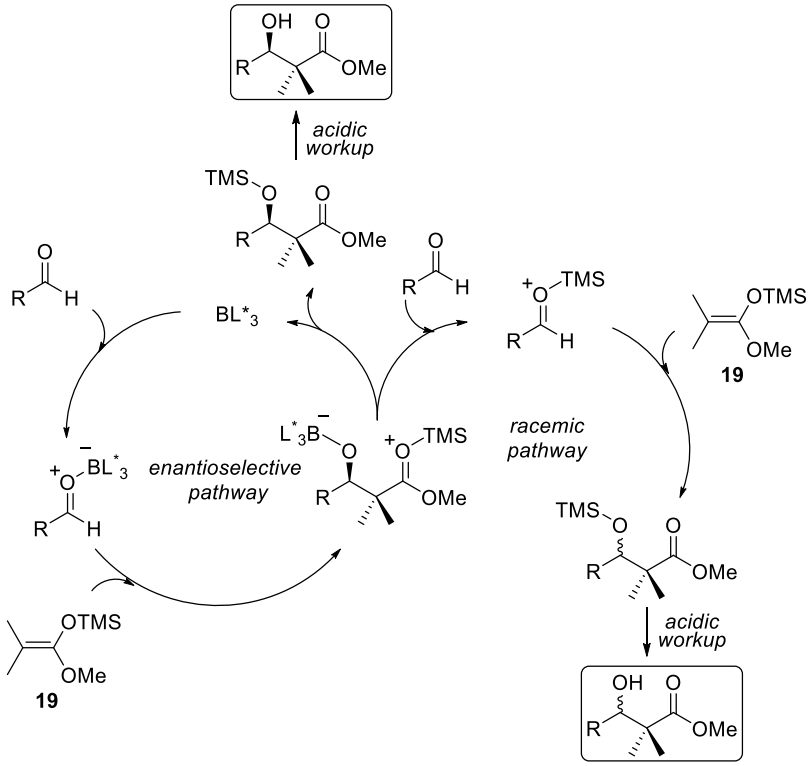


Scheme 73. Reagents and conditions: i) **19** (1.2 eq.), *in situ* prepared **34** (2 eq.), CH_2Cl_2, −78 °C, 2 h, 42% **129** (82% ee). N.B. The (*R*) configuration of alcohol **129** was inferred from Mosher ester analysis performed on analogous alcohol **32** by a co-worker[96]

In order to further investigate the key Mukaiyama–Kiyooka reaction in our route, a co-worker carried out additional optimisation experiments with catalyst **34** on model aldehyde **193** (see **Scheme 72**), which resulted in the isolation of desired alcohol **194** in 81% yield and 87% ee together with undesired alcohol **195** in 14% yield.[96] These studies showed that the slow addition of aldehyde **193** gave higher aldol product yields whilst maintaining high ee. The co-worker then subjected aldehyde **116** to the optimised conditions and observed partial TIPS-deprotection. Treatment of the crude reaction mixture with aqueous 1 M HCl before FCC purification allowed the preparation of alcohol **32** (see **Table 9**) in 63% yield and 89% ee over two steps. The latter one-pot aldol protocol was reproducible on bigger scale, and was thus used to prepare sufficient amounts of alcohol **32** for the completion of our synthesis of inthomycin C (**12**), which will be described later in this thesis. The (*R*) configurations of alcohol **194** and alcohol **32** were confirmed by Mosher ester analyses on both aldol products.[96] It should be noted that the co-worker attempted to use alternative

catalysts (by using other *N*-tosyl protected amino acid precursors or introducing alkyl/aryl substituents on boron) for the Mukaiyama aldol reaction on model aldehyde **193**, but catalyst **34** still provided the best results.[96]

We postulated that the fact that enantiomeric excesses obtained were consistently in the range of 80–89% could be due to a racemic background pathway limiting the reaction enantioselectivity (**Scheme 74**). Such racemic pathways have been previously reported, where carbonyl activation is promoted through cationic silicon species.[125] A co-worker attempted to use additives as cationic TMS species scavengers but, unfortunately, no improvement in enantioselectivity was observed.[96]



Scheme 74. Proposed mechanisms for enantioselective and racemic Mukaiyama aldol reactions

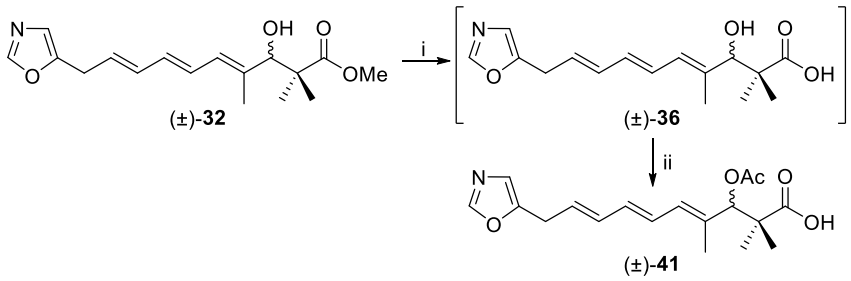
2.2.4. Completion of the synthesis of inthomycin C

With enantioenriched ester **32** in hand, our attention turned towards the final steps of the synthetic route towards inthomycin C (**12**).

Our strategy was to initially explore the hydrolysis and amidation reactions on racemic ester **32** and then apply the optimised conditions on enantioenriched ester **32** in order to achieve the asymmetric total synthesis of inthomycin C (**12**).

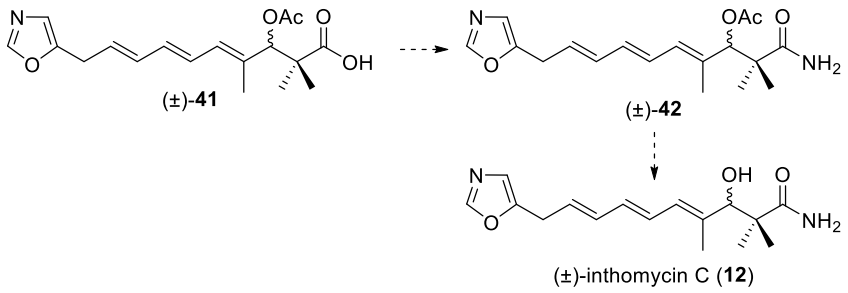
All previous asymmetric syntheses of inthomycin C (**12**) had employed either acetate-protected acid **41** or β-hydroxy acid **36** as intermediates towards the natural product.[27–30] Amongst the various reported end-game strategies towards inthomycin C (**12**), Ryu's provided the highest yield (62% yield of inthomycin C (**12**) over four steps from ester **32**).[28] Therefore, we decided to follow the Ryu group approach for the completion of our total synthesis.

In the first place, we carried out the saponification of racemic ester **32** by treatment with LiOH and the resulting crude racemic carboxylic acid **36** was acetate-protected to furnish racemic acid **41** in 84% yield over two steps (**Scheme 75**).



Scheme 75. Reagents and conditions: i) $LiOH{\cdot}H_2O$ (2.9 eq.), MeOH-THF-H_2O 1:3:1, 0 °C to r.t., 17 h then aq. 1 M HCl (until at pH 3–4); ii) pyridine (290 eq.), Ac_2O (123 eq.), 0 °C to r.t., 21 h, 84% over 2 steps

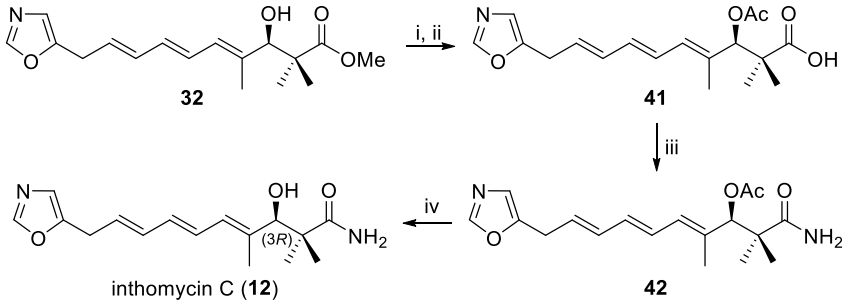
Racemic acid **41** could potentially be converted into racemic inthomycin C (**12**) *via* formation of the corresponding acid chloride and subsequent treatment with NH_4OH to give racemic amide **42**, followed by acetate-deprotection, according to Ryu's protocol (**Scheme 76**).[28]



Scheme 76. Proposed final steps towards racemic inthomycin C (**12**)

However, having optimised the reaction conditions for the synthesis of racemic acid **41**, we chose to reserve racemic acid **41** for the study of its coupling to the pyrrolidinone fragment of oxazolomycin B (**2**).[50] We would then apply the optimised conditions to enantioenriched acid **41** to progress towards the asymmetric total synthesis of oxazolomycin B (**2**), as will be discussed later.

On the other hand, the final steps of the sequence towards inthomycin C (**12**) were performed by a co-worker,[96] starting from enantioenriched ester **32**, and in this way we achieved the asymmetric total synthesis of inthomycin C (**12**) (**Scheme 77**).

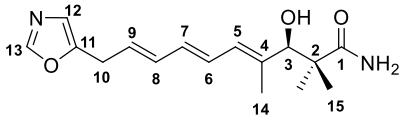


Scheme 77. Reagents and conditions:[96] i) $LiOH·H_2O$ (2.9 eq.), MeOH-THF-H_2O 1:3:1, 0 °C to r.t., 12 h then aq. 1 M HCl (until at pH 3–4); ii) pyridine (290 eq.), Ac_2O (123 eq.), 0 °C to r.t., 16 h, 87% over 2 steps; iii) $(COCl)_2$ (1.8 eq.), DMF (1 drop), CH_2Cl_2, 0 °C, 1 h then excess NH_4OH (28%) (580 eq.), r.t., 16 h, 65% **42** and 20% **12**; iv) $LiOH·H_2O$ (2.1 eq.), MeOH-THF-H_2O 1:3:1, 0 °C, 1 h then r.t., 4 h, 87% (11.1:1 isomeric mixture)

Overall, (−)-(3*R*)-inthomycin C (**12**) was synthesised in 11.4% yield and 89% ee as an 11.1:1 mixture of geometrical isomers over ten steps (80.5% average yield per step) from commercially available oxazole (**120**). This is the shortest and highest yielding asymmetric total synthesis of inthomycin C (**12**) to date.

Satisfyingly, the $[\alpha]_D$ value obtained for our sample of inthomycin C (**12**), $[\alpha]_D^{25} = -8.2$ (c 1.0, $CHCl_3$), was in agreement with optical rotation data reported in all previous asymmetric total syntheses[28–30] except for Taylor's,[27] whose erroneous positive value was probably due to an urea contaminant, as previously described (see **Table 3**).

^{13}C NMR data for our synthesised inthomycin C (**12**)[96] was in good agreement with that reported by Henkel and Zeeck in their isolation paper,[16] with chemical shift differences of ≤ 0.1 ppm for all carbons except for quaternary oxazole *C*-11 and amide carbonyl *C*-1 shifts (differences of ± 0.2 ppm in both cases) (**Table 10**).



inthomycin C (**12**)

Carbon	δ_C Isolated (ppm)	δ_C Synthetic (ppm)	$\Delta\delta_C$ (δ_C Synthetic − δ_C Isolated) (ppm)
1	180.8	180.6	−0.2
2	45.8	45.7	−0.1
3	83.7	83.8	+0.1
4	140.0	140.1	+0.1
5[a]	128.7	128.7	0
6[a]	129.1	129.1	0
7	132.7	132.7	0
8	134.2	134.2	0
9[a]	128.2	128.3	+0.1
10	Hidden[b]	29.1	N/A
11	151.6	151.8	+0.2
12	123.1	123.1	0
13	151.6	151.6	0
14	13.4	13.4	0
15_A	25.5	25.6	+0.1
15_B	22.4	22.5	+0.1

N.B. ^{13}C NMR (Acetone-d_6, 126 MHz) referenced to δ_C = 29.8 ppm for both data sets. [a]Reassignment of previous work by Henkel and Zeeck[16] i.e. *C*-5 has been reassigned as *C*-6, *C*-6 as *C*-9 and *C*-9 as *C*-5. [b]Hidden under solvent signal

Table 10. ^{13}C NMR data of isolated and synthetic inthomycin C (**12**)[96]

^1H NMR data for our synthesised inthomycin C (**12**) was also consistent with that reported previously by the groups of Taylor, Ryu, Hatakeyama and Hale.[27–30]

2.3. Biological assays of inthomycin C and structural analogues

To date, although several publications on the biological activity of inthomycin A (**10**) and inthomycin B (**11**) have been released, there has been no reported studies on the biological properties of inthomycin C (**12**).

Thanks to a collaboration with a preclinical validation facility at the Cancer Research UK Oxford Centre in the Department of Oncology, several compounds synthesised in the work described in this thesis were tested for viability/cytotoxicity against various human cancer cell lines (**Figure 13**). Besides, one of the compounds tested for cytotoxicity (ester **32**) was also tested for proteasome inhibitory activity against two cancer cell lines.

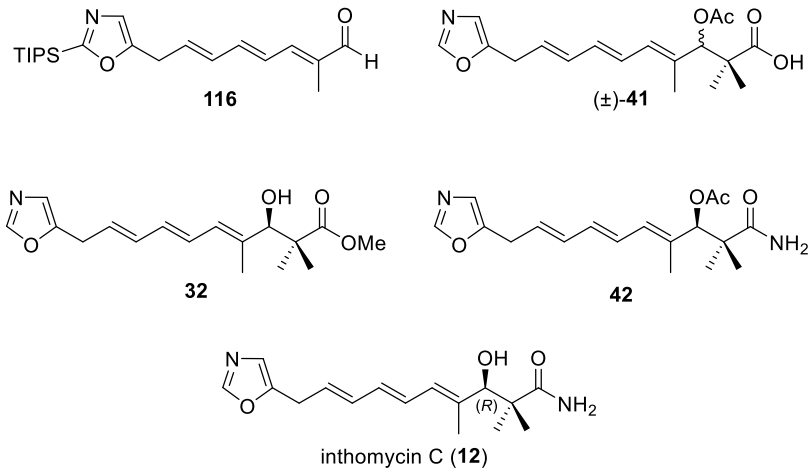


Figure 13. Compounds screened in viability assays against various human cancer cell lines

The 26S proteasome is a multiprotein complex located in the nucleus and cytosol of eukaryotic cells, responsible for the degradation of unneeded or damaged proteins, required to maintain cellular homeostasis. It contains three types of active sites (chymotrypsin-like, trypsin-like and caspase-like) with proteolytic activity. During the degradation, the hydroxy group of N-terminal threonine unit in either of the three active sites acts as a catalytic nucleophile that facilitates the cleavage of peptide bonds.[126] Proteins are marked for degradation by covalent attachment of multiple molecules of ubiquitin (a small protein). The resulting polyubiquitinated proteins are then recognised and degraded by the proteasome.[127]

Tumour cells have a high proteasome activity and are thus, much more sensitive to proteasome inhibitors than normal cells.[128] This can be explained by the need of tumour cells to eliminate damaged proteins that would be otherwise harmful to the cell.[129] Therefore, proteasome inhibition has emerged as a powerful anti-cancer therapy, inducing apoptosis in cancer cells.[130]

Initially, aldehyde **116** and racemic acid **41** were screened for viability against HeLa cervical cancer cells, H460 non-small lung cancer cells, MCF-7 breast cancer cells and PC3 prostate cancer cells; however, they were inactive on all cell lines (IC_{50} > 50 μM). Later, ester **32**, amide **42** and inthomycin C (**12**) were tested for viability against HeLa cervical cancer cells, H460 non-small lung cancer cells, MCF-7 breast cancer cells, KMS-12BM multiple myeloma cancer cells and SKOV-3 ovarian cancer cells. Unfortunately, these compounds also proved to be inactive, displaying IC_{50} > 50 μM on all cell lines (**Table 11**).

	Cytotoxicity IC_{50} (μM)				
	Aldehyde **116**	Acid **(±)-41**	Ester **32**	Amide **42**	Inthomycin C (**12**)
HeLa cells	> 50	> 50	> 50	> 50	> 50
H460 cells	> 50	> 50	> 50	> 50	> 50
MCF-7 cells	> 50	> 50	> 50	> 50	> 50
PC3 cells	> 50	> 50	-	-	-
KMS-12BM cells	-	-	> 50	> 50	> 50
SKOV-3 cells	-	-	> 50	> 50	> 50

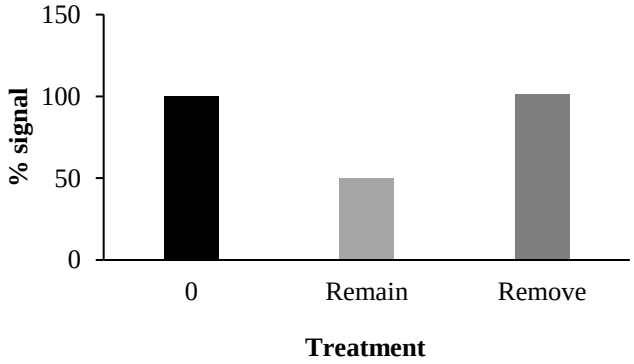
Table 11. Summary of cytotoxic activity of aldehyde **116**, acid **(±)-41**, ester **32**, amide **42** and inthomycin C (**12**)

Ester **32** was also tested for proteasome inhibition against H460 non-small lung cancer cells and KMS-12BM multiple myeloma cancer cells using the "Proteasome-Glo™ Chymotrypsin-like Cell-based" assay kit commercialised by Promega. This type of assay measures the percentage of luminescence emitted in cultured cells, which is proportional to the proteasome activity. Interestingly, this compound showed some proteasome inhibitory activity against both cell lines (IC_{50} = 10.8 μM for H460 cells and IC_{50} = 32.1 μM for KMS-12BM cells) (**Table 12**).

	Proteasome inhibition IC_{50} (μM)
	Ester **32**
H460 cells	10.8
KMS-12BM cells	32.1

Table 12. Summary of proteasome inhibition activity of ester **32**

The reversibility of proteasome inhibition for ester **32** at a 10 μM concentration on H460 cells was also evaluated. This study revealed that the proteasome inhibitory activity of ester **32** was reversible, with proteasome activity being restored upon removal of the active compound (**Figure 14**).



N.B. "% signal" = % luminescence. "0" = assay run with untreated cells (negative control experiment). "Remain" = assay run in the presence of ester **32**. "Remove" = assay run upon removal of ester **32**

Figure 14. Reversibility of proteasome inhibitory activity for ester **32** at a 10 μM concentration on H460 non-small lung cancer cells

These results suggest that, although ester **32** displays some reversible proteasome inhibitory activity at a 10 μM concentration, this inhibition is not sufficient to cause cell death at such concentration,[131] which would explain why ester **32** showed no cytotoxic activity against all the cancer cell lines screened (IC_{50} > 50 μM).

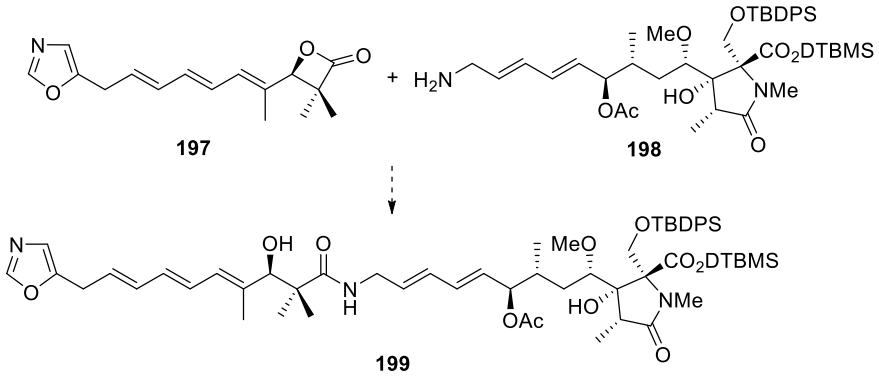
We postulated that the weak proteasome inhibition activity shown by ester **32** could be due to the ester being partially hydrolysed and converted into a β-lactone, given that several natural products reported to be proteasome inhibitors feature a β-lactone moiety which has being identified as the relevant pharmacophore.[14,132] However, further biological assays and SAR studies are necessary to better understand the biological mode of action of the inthomycins and identify their pharmacophore.

2.4. Model studies on amide coupling

After achieving the asymmetric total synthesis of inthomycin C (**12**) and with intermediate enantioenriched acid **41** in hand, we began to investigate the coupling of this acid to pyrrolidinone **115**, the right-hand fragment of oxazolomycin B (**2**),[50] with the prospect of completing a posterior total synthesis of the latter natural product (**Figure 15**).

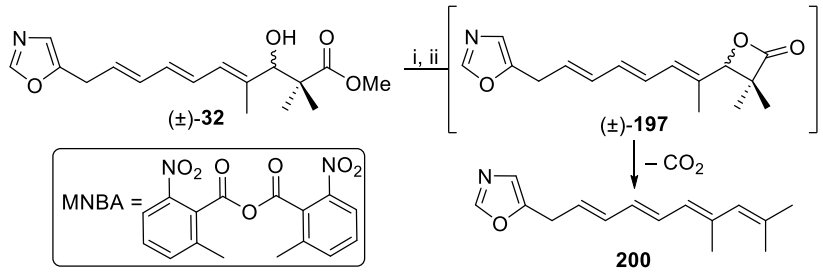
Figure 15. Compounds proposed to be coupled, acid **41** and pyrrolidinone **115**

Our primary strategy for the coupling of the two fragments outlined above was an amide coupling. As a synthetic alternative towards oxazolomycin B (**2**), we considered the opening of β-lactone **197** by the nucleophilic addition of primary amine **198**. The resulting amide **199** would contain the carbon backbone of oxazolomycin B (**2**) (**Scheme 78**).



Scheme 78. Proposed alternative strategy towards oxazolomycin B (**2**)

We planned to test the latter strategy on racemic material first. To this end, we attempted the synthesis of racemic β-lactone **197** from racemic ester **32**.[133] Unfortunately, racemic β-lactone **197** could not be isolated and tetraene **200** was obtained instead (**Scheme 79**), so this approach was discarded and our efforts were focused on the initial amide coupling strategy outlined in **Figure 15**.



Scheme 79. Reagents and conditions: i) $LiOH \cdot H_2O$ (2.9 eq.), MeOH-THF-H_2O 1:3:1, 0 °C to r.t., 17 h then aq. 1 M HCl (until at pH 3–4); ii) MNBA (1.3 eq.), DMAP (0.2 eq.), Et_3N (6 eq.), CH_2Cl_2, r.t., 9 h, 0% **197** and 41% **200**

2.4.1. Synthesis of middle diene fragment 76 and analogues

To explore the amide coupling between acid **41** and pyrrolidinone **115** (see **Figure 15**), iodide **76**, alcohol **201** and acetate **202** (**Figure 16**) were selected as model diene substrates to optimise the amide coupling conditions prior to their application to pyrrolidinone **115**, whose preparation will be discussed later.

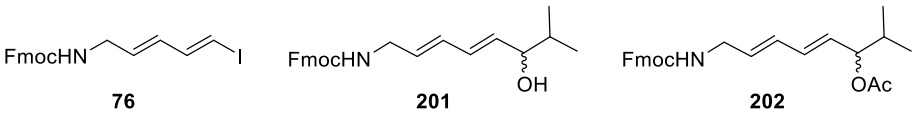
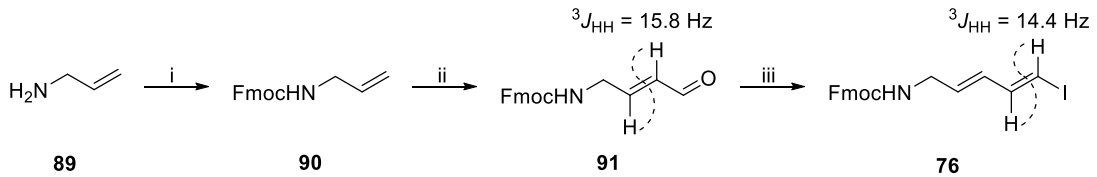


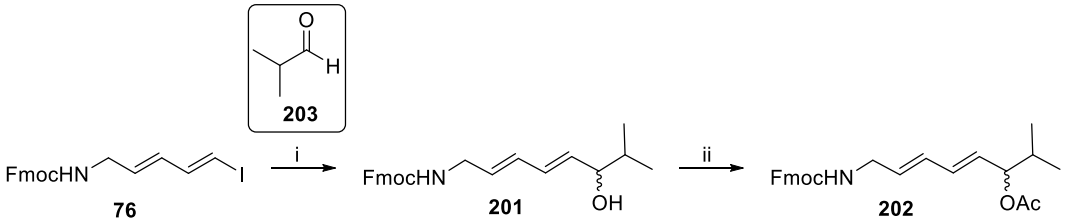
Figure 16. Model diene compounds for amide coupling studies

Iodide **76** was prepared from commercially available allylamine (**89**), following Hatakeyama's protocol.[49] Fmoc-protection of allylamine (**89**) followed by cross-metathesis with acrolein (**130**) and Takai olefination[56] furnished iodide **76** in 46% yield as a 7.1:1 *E*/*Z* mixture over three steps (**Scheme 80**). The geometric purity of iodide **76** could be improved to > 20:1 *E*/*Z* by recrystallisation with EtOAc.



Scheme 80. Reagents and conditions: i) FmocCl (0.7 eq.), $NaHCO_3$ (2 eq.), 1,4-dioxane, 0 °C to r.t., 22 h, 99%; ii) acrolein (**130**) (10 eq.), HG-II (5 mol%), CH_2Cl_2, 40 °C, 55 h, 90%; iii) $CrCl_2$ (6.5 eq.), CHI_3 (1 eq.), THF, r.t., 17 h, 51% (7.1:1 *E*/*Z* mixture; stereomerically enriched to 20:1 *E*/*Z* after recrystallisation)

Alcohol **201** was synthesised from iodide **76** *via* a Nozaki–Hiyama–Kishi[54] reaction with isobutyraldehyde (**203**) in 59% yield. Acetate-protection of alcohol **201** provided acetate **202** in 79% yield (**Scheme 81**).

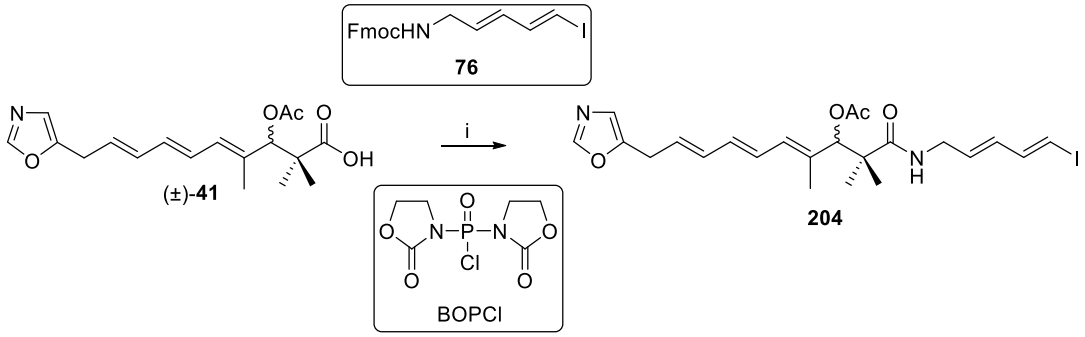


Scheme 81. Reagents and conditions: i) $CrCl_2$ (4 eq.), $NiCl_2$ (0.2 eq.), **76** (1.5 eq.), DMSO, r.t., 22 h, 59%; ii) Ac_2O (10 eq.), pyridine (125 eq.), 0 °C to r.t., 19 h, 79%

2.4.2. Optimisation of amide coupling between racemic acid 41 and diene analogues of iodide 76

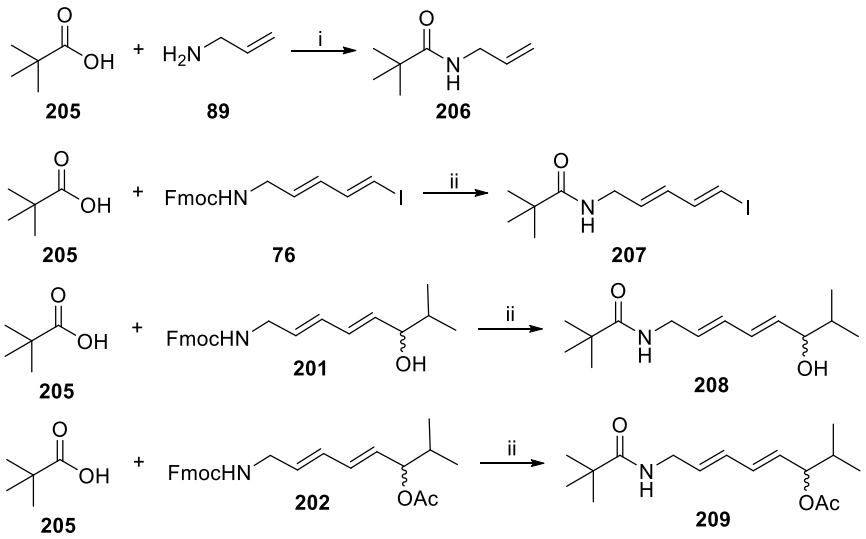
With iodide **76**, alcohol **201** and acetate **202** in hand, attention now turned to the optimisation of the amide coupling with racemic acid **41**.

First, we studied the amide coupling between racemic acid **41** and iodide **76** to form amide **204** *via* pre-activation of the acid followed by addition of the *in situ* Fmoc-deprotected amine (**Scheme 82**). After screening several coupling reagents, we found that BOPCl (the same reagent used in Hatakeyama's synthesis of oxazolomycin B (**2**))[49] was indeed the reagent that provided better results. Although we could obtain the desired amide **204** in 68% yield, this result was not very reproducible. Furthermore, racemic acid **41** and amide **204** had very similar polarity, complicating the purification of the reaction crude by FCC. Nevertheless, the structure of amide **204** was confirmed by NMR data (^{1}H, ^{13}C, ^{1}H-^{1}H COSY, HMBC) and FTIR data analysis. Comparison of FTIR spectra for acid **41** and amide **204** showed different absorption frequencies for the C=O stretches (1737 cm^{-1} and 1651 cm^{-1}, respectively) together with the corresponding absorption frequencies for their O–H (3134 cm^{-1}) and N–H (3387 cm^{-1}) stretches.



Scheme 82. Reagents and conditions: i) (±)-**41** (2 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 2 h then add a pre-stirred solution of **76** (1 eq.), DBU (1.5 eq.) and CH_2Cl_2, r.t., 5 h, 68%

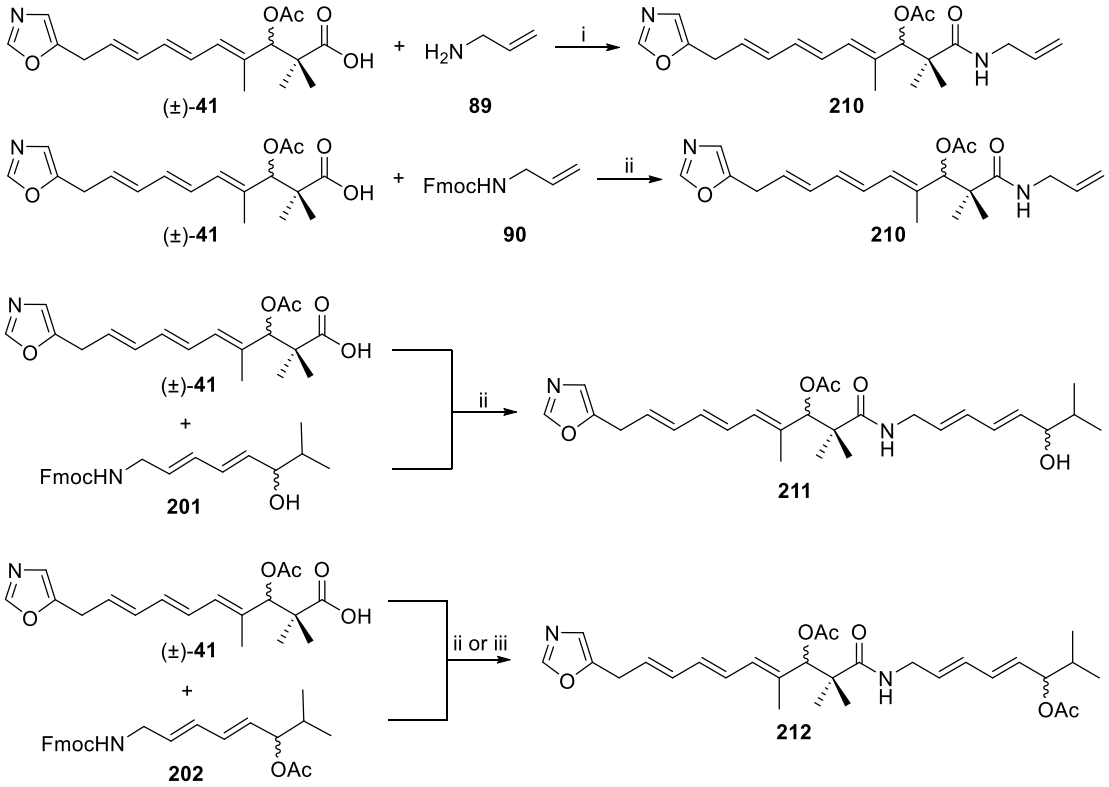
Given the difficulties in reproducibility described earlier, we decided to use simpler model substrates for the amide coupling in order to explore the reactivity of both reaction partners when employing the conditions outlined in **Scheme 82**. In this way, pivalic acid (**205**) could be coupled to allylamine (**89**) in 96% yield, while its amide coupling to amine **76** (Fmoc-deprotected *in situ*) was achieved in 74% yield. Pivalic acid (**205**) could also be coupled to alcohol **201** and acetate **202** in 59% and 80% yield, respectively (**Scheme 83**).



Scheme 83. Reagents and conditions: i) **205** (2 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 2 h then amine **89**, CH_2Cl_2, r.t., 5 h, 96% **206**; ii) **205** (2 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 2 h then add a pre-stirred solution of amine **76**, **201** or **202** (1 eq.), DBU (1.5 eq.), CH_2Cl_2, r.t., 5 h, 74% **207**, 59% **208** or 80% **209**, respectively

Encouraged by the latter results, we decided to investigate the coupling of racemic acid **41** with various amine substrates to determine whether similar results could be obtained for the compound of interest. We were able to couple racemic acid **41** with allylamine (**89**) in a

moderate 55% yield, while the amide coupling to amine **90** (Fmoc-deprotected *in situ*) was achieved in 88% yield. Additionally, the amide coupling between racemic acid **41** and alcohol **201** (Fmoc-deprotected *in situ*) afforded amide **211** in 58% yield, while the coupling between racemic acid **41** and acetate **202** (Fmoc-deprotected *in situ*) furnished the corresponding amide **212** in 71% yield. Alternatively, the latter coupling between racemic acid **41** and acetate **202** could also be achieved *via* acid chloride formation with $SOCl_2$ in 54% yield (**Scheme 84**). Pleasingly, the purification of amides **211** and **212** by FCC proved to be easier than that of amide **204** (see **Scheme 82**).

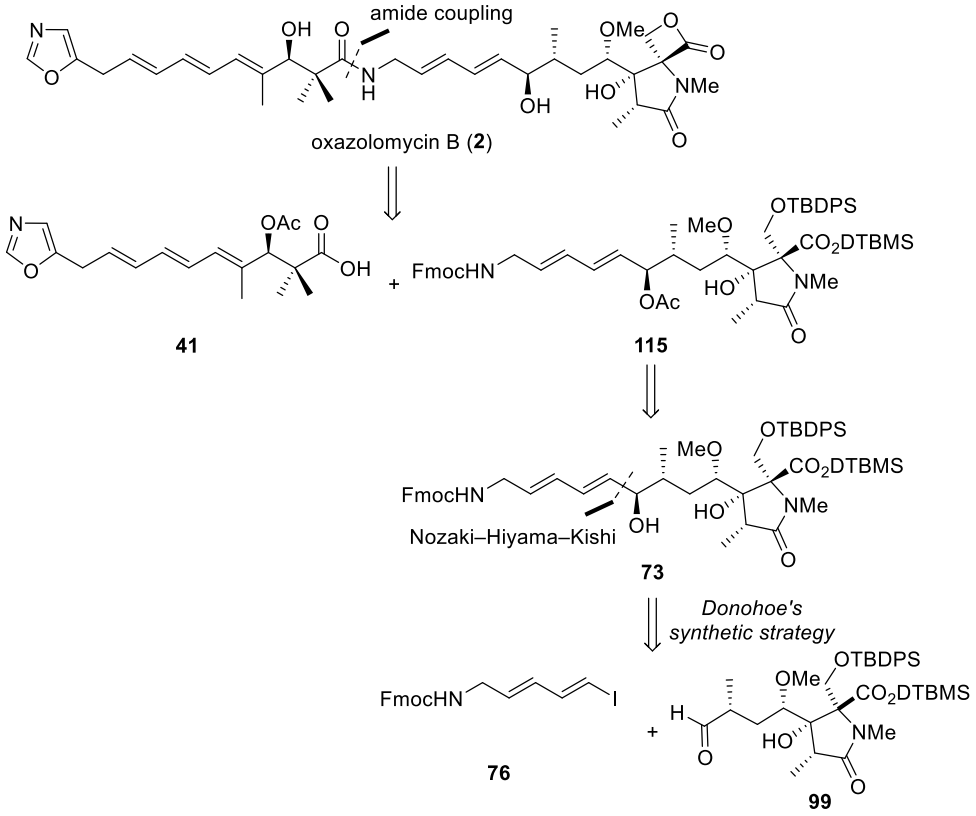


Scheme 84. Reagents and conditions: i) (±)-**41** (2 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 2 h then amine **89**, CH_2Cl_2, r.t., 6 h, 55% **210**; ii) (±)-**41** (2 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 2 h then add a pre-stirred solution of amine **90**, **201** or **202** (1 eq.), DBU (1.5 eq.), CH_2Cl_2, r.t., 5 h, 88% **210**, 58% **211** or 71% **212**, respectively; iii) (±)-**41** (1 eq.), $SOCl_2$ (1.7 eq.), DMF (1 drop), CH_2Cl_2, 0 °C to r.t., 2 h then add a pre-stirred solution of amine **202** (2 eq.), DBU (1.5 eq.), CH_2Cl_2, r.t., 5 h, 54% **212**

2.5. Synthetic progress towards oxazolomycin B

At this point, we considered that the achievement of the amide coupling between racemic acid **41** and acetate **202** in good yield set a promising precedent for the future coupling between enantioenriched acid **41** and pyrrolidinone **115**. Therefore, our attention turned

towards the preparation of pyrrolidinone **115**, the amine of interest, in view of a subsequent coupling to already synthesised enantioenriched acid **41** that would lead to an advanced intermediate in the synthesis of oxazolomycin B (**2**). Building on previous work in the Donohoe group, we planned to synthesise pyrrolidinone **115** based upon the synthetic strategy published by the group[50] towards pyrrolidinone **73** (see **Scheme 33**). Thus, pyrrolidinone **115** would ultimately be formed from iodide **76** and aldehyde **99** *via* a Nozaki–Hiyama–Kishi reaction (**Scheme 85**).

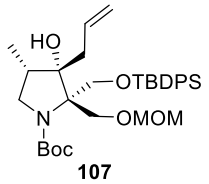


Scheme 85. Partial retrosynthetic analysis towards oxazolomycin B (**2**). N.B. For full retrosynthesis see **Scheme 33**

2.5.1. Initial steps towards the synthesis of pyrrolidinone 115

After having accomplished the total synthesis of inthomycin C (**12**) but before beginning our subsequent investigations towards the synthesis of oxazolomycin B (**2**), we had 10 g of homoallylic alcohol **107** available (**Figure 17**). This intermediate in the synthetic sequence towards oxazolomycin B (**2**) had been prepared by past members in the Donohoe group.[50] We planned to carry on the synthesis towards oxazolomycin B (**2**) from this intermediate

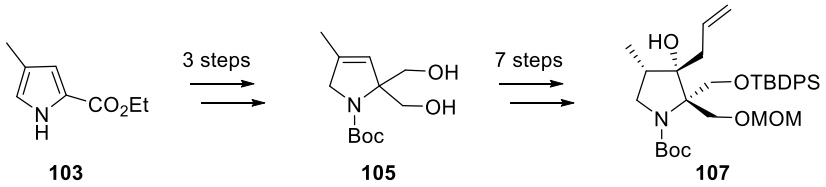
onwards, following the strategy previously developed by the Donohoe group.[50] Therefore, we would focus on the scale up of all the subsequent steps in the synthetic sequence from alcohol **107** and on the optimisation of the still unexplored end-game strategy, with the aim of completing the first synthesis of oxazolomycin B (**2**).



107

Figure 17. Available intermediate, homoallylic alcohol **107**.[50] N.B. The stereochemistry of alcohol **107** was confirmed by X-ray crystallographic analysis performed by a past member in the Donohoe group[50]

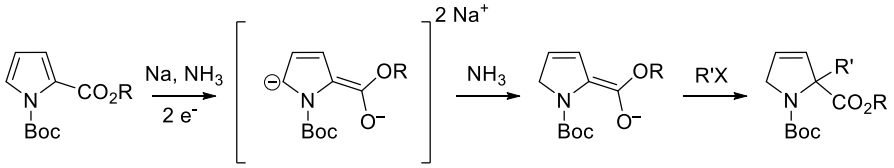
Homoallylic alcohol **107** had been synthesised in 24% yield over ten steps from commercially available pyrrole **103** (**Scheme 86**),[50] following the procedure previously outlined in **Scheme 34**.



103 **105** **107**

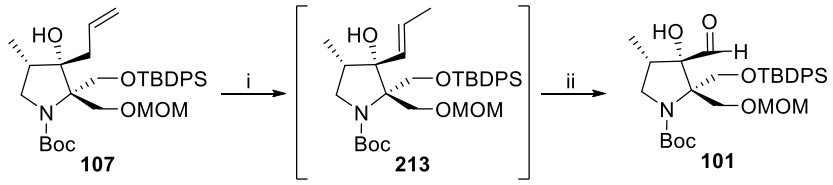
Scheme 86. Synthesis of homoallylic alcohol **107**.[50] N.B. For full synthetic procedure see **Scheme 34**

One of the main features of the synthesis of homoallylic alcohol **107** is the Birch reduction of an electron-deficient pyrrole to access intermediate diol **105**.[59,134] The mechanism of the Birch reduction of a *C*-2 ester substituted pyrrole involves the formation a dianion by transfer of two electrons to the heterocycle and subsequent protonation by ammonia at *C*-5 to provide an extended enolate, which can react with an alkyl halide to give a reductive alkylation product (**Scheme 87**).[134]



Scheme 87. Mechanism of Birch reduction of electron-deficient pyrroles[134]

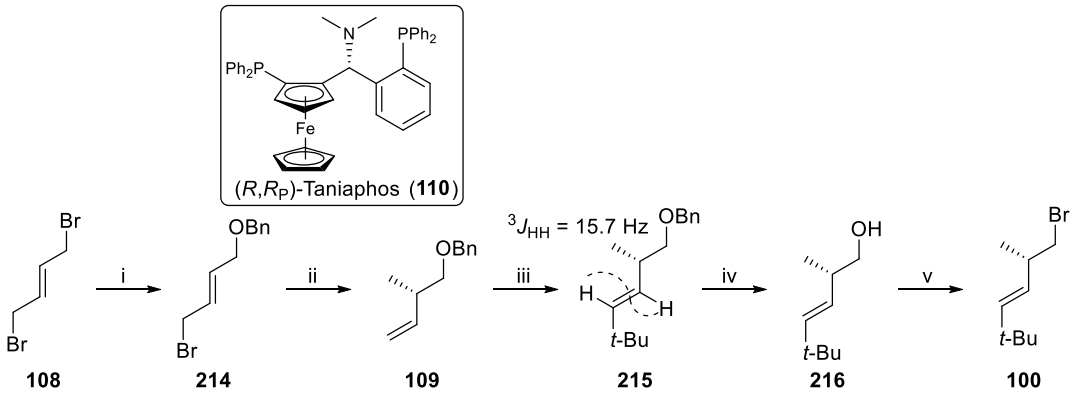
With the amount of homoallylic alcohol **107** available,[50] we started our studies towards the preparation of pyrrolidinone **115**. First, we converted homoallylic alcohol **107** into aldehyde **101** in 88% yield, on a multigram scale (4 g, 6.85 mmol), *via* isomerisation of the double bond followed by ozonolysis (**Scheme 88**).



Scheme 88. Reagents and conditions: i) G-II (5 mol%), vinyloxy-trimethylsilane (10 eq.), PhMe, reflux, 46 h; ii) O_3, CH_2Cl_2, −78 °C then Me_2S (20 eq.), −78 °C, 20 min then r.t., 20 h, 88% over 2 steps (1.5:1 mixture of Boc rotamers)

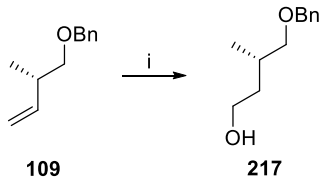
The isomerisation of the terminal olefin in alcohol **107** to the internal olefin is catalysed by a ruthenium hydride species formed *in situ* from Grubbs second-generation catalyst (**172**),[135] as described earlier (see **Scheme 62**).

The next step was the installation of the exocyclic carbon chain onto aldehyde **101**. To this end, we synthesised bromide **100**, a compound bearing the *C*-6 methyl stereocenter and an alkene unit as a masked carbonyl group. Starting from commercially available dibromide **108**, a monosubstitution under phase transfer conditions[136] with benzyl alcohol gave benzyl ether **214** in 46% yield. Subsequent asymmetric allylic methylation on benzyl ether **214** following Feringa's protocol[62,63] afforded olefin **109** in 99% yield. A cross-metathesis between olefin **109** and 3,3-dimethyl-1-butene provided olefin **215** in 55% yield. The introduction of a *tert*-butyl group at this stage was aimed at decreasing the volatility of the final compound of the sequence (bromide **100**) and, therefore, facilitate the handling of this bromide, for which a multigram scale synthesis was required to carry it forward in the total synthesis of oxazolomycin B (**2**). Finally, benzyl-deprotection on olefin **215**, followed by bromination furnished target bromide **100** in 81% yield over two steps (**Scheme 89**).



Scheme 89. Reagents and conditions: i) BnOH (1.1 eq.), aq. 2 M NaOH (1 eq.), Bu_4NHSO_4 (0.1 eq.), CH_2Cl_2, r.t., 16 h, 46%; ii) MeMgBr (1.2 eq.), CuBr·Me_2S (1 mol%), (*R*,*R*P)-Taniaphos (**110**) (1.3 mol%), CH_2Cl_2, −78 °C, 36 h, 99% (95% ee); iii) HG-II (10 mol%), CH_2=CHC$(CH_3)_3$ (89 eq.), neat, 60 °C, 16 h, 55%; iv) Li (2.2 eq.), NH_3 (11 mL·mmol^{-1}), THF, −78 °C, 1.5 h, quant.; v) Br_2 (1.2 eq.), PPh_3 (1.1 eq.), CH_2Cl_2, 0 °C, 1 h, 81%

We could determine the enantiomeric excess of olefin **109** by chiral HPLC analysis of alcohol **217**, which was formed by hydroboration of olefin **109**, following Feringa's strategy (**Scheme 90**).[62]



Scheme 90. Reagents and conditions: i) 9-BBN (1.5 eq.), THF, 0 °C to r.t., 2 h then aq. 1 M NaOH (4.4 eq.), aq. H_2O_2 30% w/w (31 eq.), 0 °C, 2 h, 74% (95% ee)

The main challenge we found in the synthesis of bromide **100** outlined in **Scheme 89** was the formation of undesired homodimer **218** in 20–40% yield during the cross-metathesis step, which explains the moderate yield observed for olefin **215**, the desired product of this reaction (**Figure 18**).

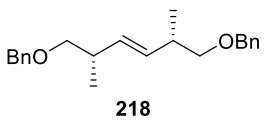
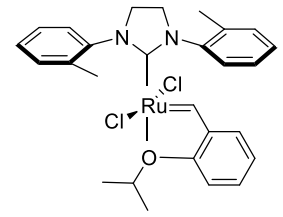


Figure 18. Homodimer **218**

We then explored the conditions for the cross-metathesis step to increase the amount of olefin **215** obtained compared to homodimer **218**. We observed higher yields of olefin **215** when performing the cross-metathesis reaction at higher temperatures (60 °C *vs* 40 °C), after

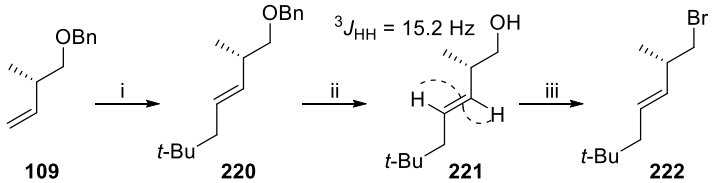
increasing the catalyst loading from 3.5 mol% to 10 mol% and when carrying out the reaction on multigram scale. Hoveyda–Grubbs second-generation catalyst (**175**) provided higher yields than Grubbs second-generation catalyst (**172**) or Stewart–Grubbs catalyst (**219**), despite the latter having been reported as an efficient catalyst for sterically hindered olefins (**Figure 19**).[137] Overall, we were able to increase the yield of olefin **215** from 30% to 55% but, although homodimer **218** was separable by FCC purification, its formation could unfortunately not be avoided.



Stewart–Grubbs catalyst (**219**)

Figure 19. Stewart–Grubbs catalyst (**219**)

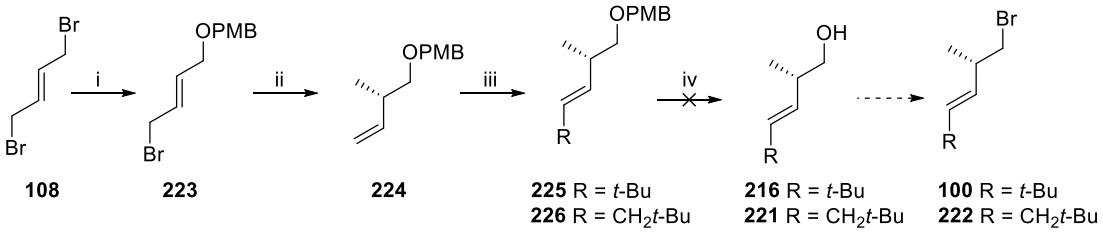
By using a less hindered olefin partner such as 4,4-dimethyl-1-pentene in the cross-metathesis with olefin **109**, we could prepare olefin **220** in 75% yield, which was converted into bromide **222** in 70% yield after benzyl-deprotection and bromination (**Scheme 91**).



Scheme 91. Reagents and conditions: i) G-II (3.5 mol%), CH_2=$CHCH_2C(CH_3)_3$ (5 eq.), neat, 50 °C, 22 h, 75%; ii) Li (2.2 eq.), NH_3 (11 mL·mmol^{-1}), THF, −78 °C, 1 h, quant.; iii) Br_2 (1.2 eq.), PPh_3 (1.1 eq.), CH_2Cl_2, 0°C, 1 h, 70%

In parallel, we decided to change the benzyl protecting group for a PMB group, as we anticipated the PMB-deprotection with DDQ to be easier to perform on multigram scale than the benzyl-deprotection with lithium wire and ammonia. In this way, bromides **222** and **100** were synthesised in five steps from dibromide **108** following the same protocol as described above but with a different protecting group strategy (**Scheme 92**). However, this synthetic

route was discarded, as the PMB-deprotection step led to the recovery of starting material and the yields for the preceding steps were lower than in the initial strategy.

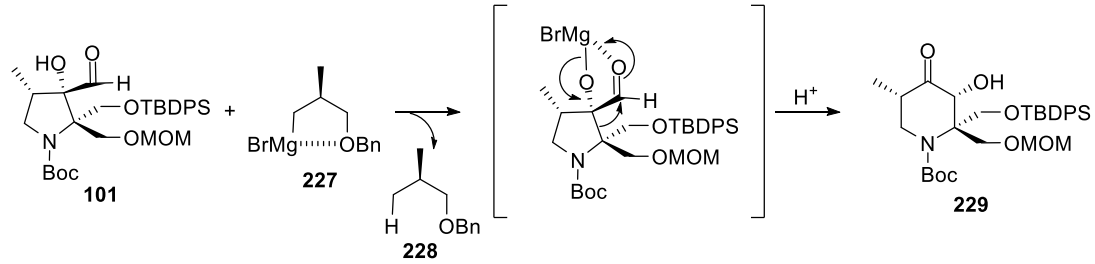


Scheme 92. Reagents and conditions: i) 4-methoxybenzyl alcohol (1.1 eq.), aq. 2 M NaOH (1 eq.), Bu_4NHSO_4 (0.1 eq.), CH_2Cl_2, r.t., 16 h, 44%; ii) MeMgBr (1.2 eq.), CuBr·Me_2S (1 mol%), (*R*,R_P)-Taniaphos (**110**) (1.3 mol%), CH_2Cl_2, −78 °C, 36 h, 79%; iii) HG-II or G-II (3.5 mol%), CH_2=$CHC(CH_3)_3$ (71 eq.) or CH_2=$CHCH_2C(CH_3)_3$ (5 eq.), neat or CH_2Cl_2, 60 °C or 55 °C, 17 h or 22 h, 29% **225** or 89% **226**; iv) DDQ (1.1 eq.), CH_2Cl_2-pH 6.8 phosphate buffer 8:1, 0 °C, 1 h, rsm

Hence, we had two alternative substrates in hand (bromide **100** and bromide **222**) for the introduction of the exocyclic carbon chain onto aldehyde **101**.

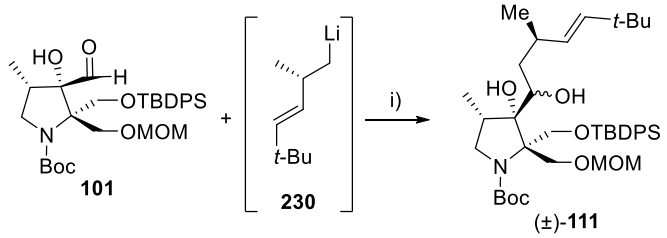
2.5.2. Optimisation of the chelation-controlled organocerium addition reaction to aldehyde 101

Previous studies within the Donohoe group[138] had shown that the addition of Grignard reagents derived from alkyl bromides containing a protected γ-hydroxy group to aldehyde **101** did not provide any desired addition product and base-promoted ring-expansion occurred instead (**Scheme 93**).[138] It was hypothesised that ring expansion occurred at a faster rate than the addition of a second equivalent of Grignard reagent, probably due to the decreased nucleophilicity of the organometallic compound as a result of a five-membered chelate ring.[138]



Scheme 93. Proposed mechanism for ring expansion of aldehyde **101** with Grignard reagents derived from protected γ-hydroxy bromides[138]

Earlier investigations had also shown that the addition of organolithium **230**, which had been prepared from bromide **100** (see **Scheme 89**) *via* bromine-lithium exchange, to aldehyde **101** provided the desired addition product **111**, although with no diastereoselectivity (a 1:1 diastereomeric mixture had been obtained) (**Scheme 94**).[139]



Scheme 94. Reagents and conditions: i) Bromide **100** (4 eq.), *t*-BuLi (8 eq.), THF, −78 °C, 30 min then aldehyde **101** (1 eq.), THF, −78 °C, 2 h, 76% (1:1 dr)[139]

Considering these previous results, the use of an organocerium reagent was deemed suitable for the installation of the exocyclic carbon chain onto aldehyde **101**, given the enhanced oxophilicity and attenuated basicity of organocerium reagents compared to their organolithium or organomagnesium counterparts.[140]

With aldehyde **101**, bromide **100** and bromide **222** in hand (**Figure 20**), we began to study the addition of the organocerium compounds derived from both bromides into aldehyde **101**.

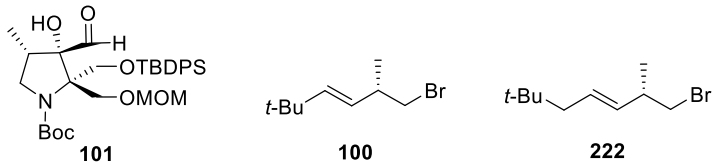
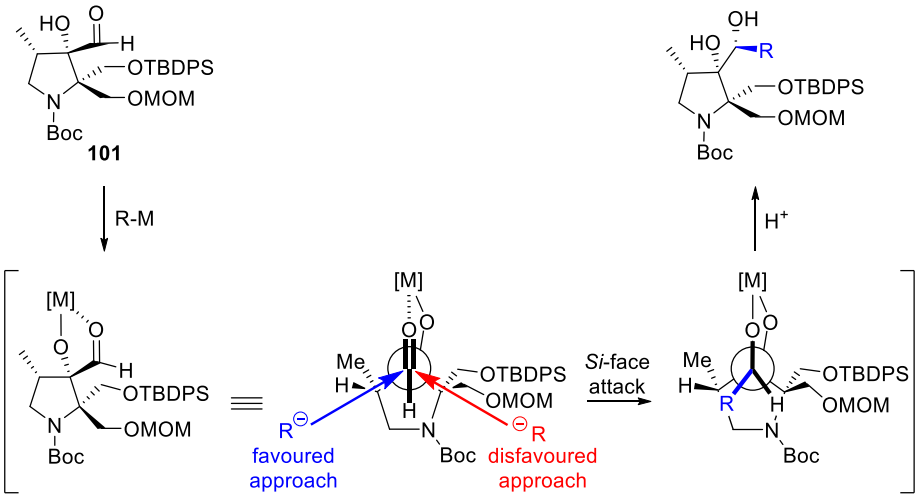


Figure 20. Aldehyde **101**, bromide **100** and bromide **222**

The stereochemical outcome of this addition can be rationalised by the chelation model previously proposed[138] (**Scheme 95**). First, hydroxy group deprotonation of aldehyde **101** with one equivalent of organometallic reagent affords the corresponding alkoxide, which forms a five-membered ring by chelation to the metal counterion. The Newman projection shows that the preferred addition of the nucleophile is to the least hindered *Si*-face of aldehyde **101** along the Bürgi–Dunitz trajectory,[141] resulting in the *syn*-diol product after workup.

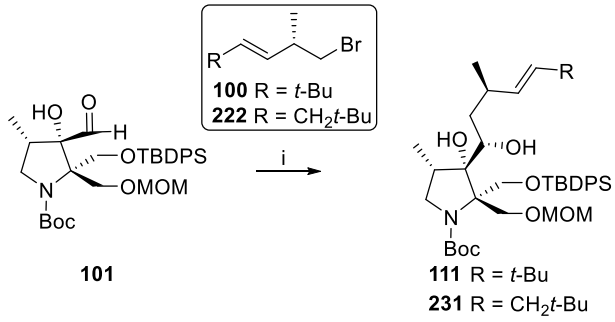


Scheme 95. Proposed chelation control model for addition to aldehyde **101**[138]

To minimise the risk of undesired ring-expansion of aldehyde **101** (see **Scheme 93**), the nucleophilic addition was carried out by reverse addition of aldehyde **101** into the organocerium solution.

Initial attempts at transferring the lithium-exchanged species derived from bromide **100** or **222** (see **Figure 20**) to a suspension of $CeCl_3$ in THF *via* cannula to form the corresponding organocerium reagent, prior to the addition of aldehyde **101**, only led to the recovery of unreacted aldehyde **101** and protonation of the corresponding lithium-exchanged species. Furthermore, when performing the organocerium reaction using $CeCl_3$ powder weighed in a glovebox, unreacted aldehyde **101** was also recovered. We postulated that the high hygroscopicity of $CeCl_3$ limited the availability of anhydrous reagent, which explained why the grinding of $CeCl_3$ beads within the reaction mixture was the only method found to allow the formation of the desired organocerium species and hence, the formation of desired alcohols **111** and **231** (**Scheme 96**). We also carried out the organocerium addition with freshly distilled Et_2O instead of THF as solvent to minimise competitive deprotonation of the solvent by *t*-BuLi,[142,143] but no improvement in yield was observed.

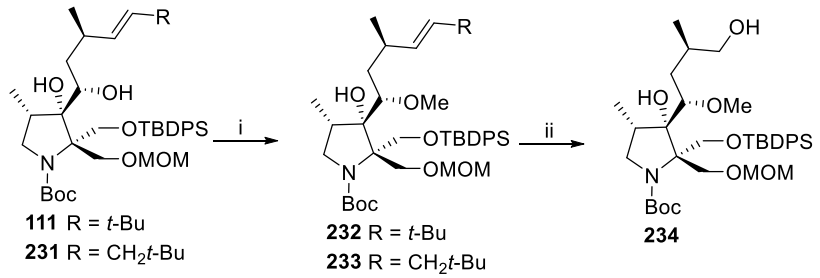
After careful optimisation of the reaction conditions for the chelation-controlled organocerium addition to aldehyde **101** using either bromide **100** or bromide **222** as starting material, we found this transformation to be very air and moisture-sensitive (**Scheme 96**). In order for the reaction to proceed, careful handling was required to ensure an inert atmosphere and anhydrous conditions. Therefore, freshly distilled THF was used for each performed organocerium addition experiment. First, in a Schlenk tube, bromide **100** or bromide **222** were treated with *t*-BuLi (2 eq.) in THF, at −78 °C, to effect bromine-lithium exchange. For the subsequent transmetalation of lithium with cerium, beads of anhydrous $CeCl_3$ were weighed in a glovebox before adding them, at −40 °C, to the solution containing the lithium-exchanged species derived from bromide **100** or **222**. A metal rod was used to grind the beads within the reaction mixture under a continuous flow of nitrogen gas to ensure an inert atmosphere throughout the reaction. Aldehyde **101** was then added to the organocerium solution at −78 °C, after having allowed enough time for the transmetalation of lithium with cerium to occur (20–24 h). When applying the optimised conditions described above, alcohol **111** could be obtained in 84% yield and 20:1 dr, whereas alcohol **231** could be formed in 64% yield and 10:1 dr (**Scheme 96**).



Scheme 96. Reagents and conditions: i) *t*-BuLi (10 eq.), **100** or **222** (5 eq.), THF, −78 °C, 30 min then $CeCl_3$ beads (15 eq.), −40 °C, 22–23 h then **101** (1 eq.), −78 °C, 5 h, 84% **111** (20:1 dr) or 64% **231** (10:1 dr). N.B. The *Si*-face organocerium addition to aldehyde **101** was confirmed by nOe experiments performed by a past member in the Donohoe group on the acetonide derivative of diol **111**[50]

Before we could consistently achieve high diastereoselectivity for the organocerium addition outlined in **Scheme 96**, our initial optimisation studies had shown similar results for the organocerium addition using either bromide **100** or bromide **222**, with the respective

alcohol products **111** and **231** being originally obtained in 60% yield and 10:1 dr in both cases. At that point, we had decided to carry both alcohol products **111** and **231** forward in the synthetic sequence towards oxazolomycin B (**2**).[50] Thus, we converted both alcohols **111** and **231** into alcohol **234** in parallel, through *O*-methylation followed by an ozonolysis/reduction protocol (**Scheme 97**). Having converged on alcohol **234** intermediate starting from either alcohol **111** or alcohol **231**, we observed that the sequence starting from alcohol **111** was more efficient, providing a higher overall yield of alcohol **234**. We therefore chose to continue our synthetic sequence from alcohol **111** rather than alcohol **231**.

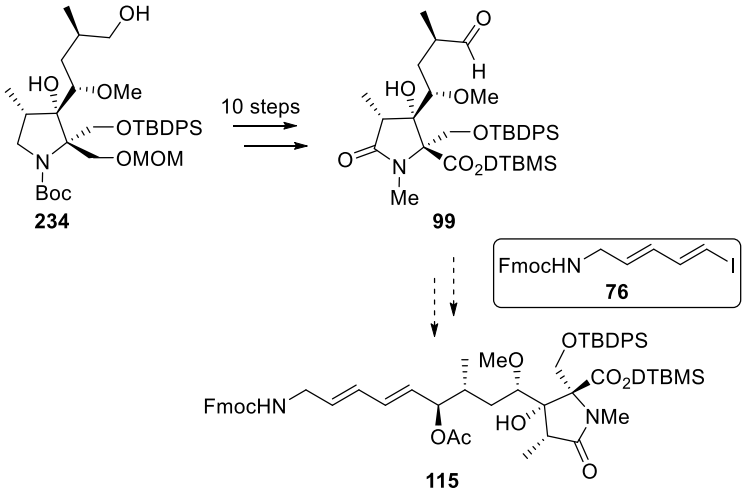


Scheme 97. Reagents and conditions: i) Me_3OBF_4 (5 eq.), proton sponge (7.5 eq.), CH_2Cl_2, r.t., 42 h, 77% **232** or 62% **233**; ii) O_3, CH_2Cl_2-MeOH 7.5:1, −78 °C, 20 min then $NaBH_4$ (5 eq.), −78 °C, 1 h then 0 °C, 4 h, 86% **234** (starting from **232**) or 76% **234** (starting from **231**)

Besides, further experiments on the organocerium addition to aldehyde **101** (see **Scheme 96**), showed that after scaling up this reaction and increasing the amount of $CeCl_3$ used from 10 eq. to 15 eq. to ensure complete transmetalation of lithium with cerium, very good diastereoselectivity could be consistently achieved when using bromide **100** compared to bromide **222** (>20:1 dr *vs* 10:1 dr, respectively). Therefore, we selected bromide **100** as the bromide partner for the organocerium addition to aldehyde **101** (see **Scheme 96**) and we scaled up this transformation to 300–400 mg scale (0.524–0.699 mmol) obtaining alcohol **231** with excellent diastereoselectivity (>20:1 dr), which in turn reinforced our previous choice of alcohol **111** as starting material for the subsequent steps in the synthetic sequence (see **Scheme 97**). On the other hand, VT NMR and 2D ROESY analysis of alcohol **111** confirmed the presence of Boc rotamers.

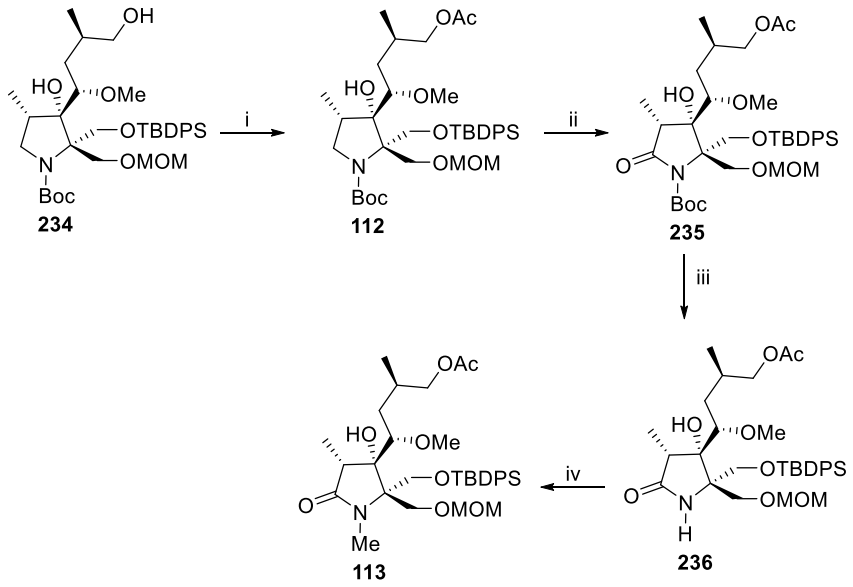
2.5.3. Synthesis of aldehyde 99

With alcohol **234** in hand, our attention turned towards the conversion of alcohol **234** into aldehyde **99**, which would be primed for Nozaki–Hiyama–Kishi reaction with already synthesised iodide **76,** a key step in the synthetic route towards pyrrolidinone **115** (**Scheme 98**).



Scheme 98. Conversion of alcohol **234** into aldehyde **99** and subsequent NHK coupling with iodide **76**, a key step towards the synthesis of pyrrolidinone **115**

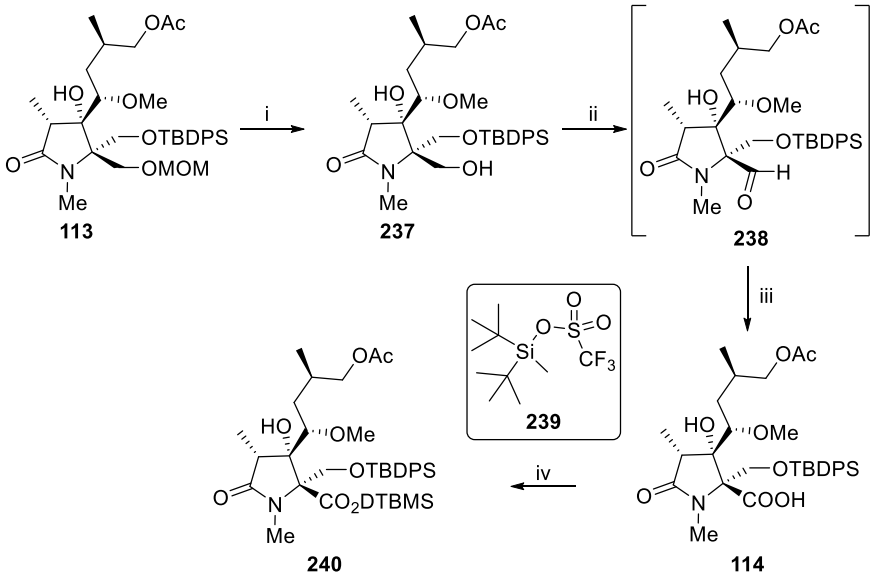
First, alcohol **234** was acetylated in 96% yield to afford acetate **112**, which was subjected to RuO_4-catalysed oxidation to form pyrrolidinone **235** in 68% yield. The *N*-Boc group on pyrrolidinone **235** was then exchanged for a *N*-Me group *via* selective Boc-deprotection using diluted TFA followed by *N*-methylation, furnishing pyrrolidinone **113** in 62% yield over two steps (**Scheme 99**). It should be noted that Boc rotamers could not be observed by NMR analysis after the oxidation of pyrrolidine **112** to pyrrolidinone **235**, simplifying NMR data analysis.



Scheme 99. Reagents and conditions: i) Ac_2O (100 eq.), pyridine (115 eq.), CH_2Cl_2, r.t., 24 h, 96%; ii) $RuO_2 \cdot H_2O$ (0.15 eq.), aq. $NaIO_4$ 10% w/w (10 eq.), EtOAc, r.t., 18 h, 68%; iii) TFA (4 eq.), Et_3SiH (2 eq.), CH_2Cl_2, r.t., 1 h, 73%; iv) Cs_2CO_3 (10 eq.), CH_3I (164 eq.), 50 °C, 85%

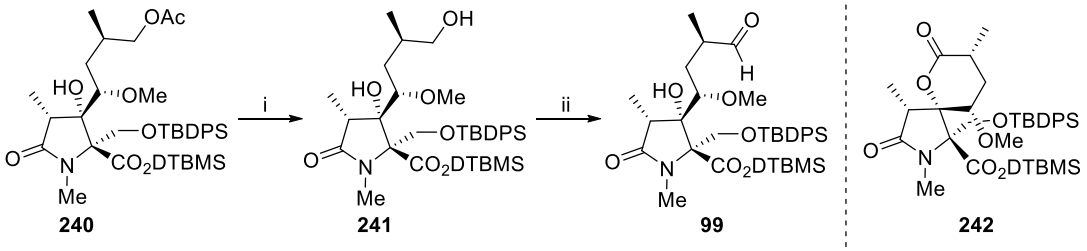
Subsequently, pyrrolidinone **113** was MOM-deprotected using a higher concentration of TFA to give alcohol **237** in 67% yield. A two-step, one-pot oxidation protocol on alcohol **237** afforded carboxylic acid **114** in 99% yield over two steps. Conversion of acid **114** into DTBMS ester **240** was achieved in 82% yield by treatment with freshly prepared DTBMSOTf **239** and Et_3N (**Scheme 100**). Previous optimisation studies carried out by a past member in the Donohoe group[139] on the protecting group strategy for acid **114** had shown that DTBMS was the most suitable protecting group, since it was stable to FCC purification while it could be readily cleaved by treatment with a fluoride source ($NH_4F \cdot HF$). Furthermore, DTBMS esters had been reported to be stable towards hydride reducing agents and acid-catalysed hydrolysis.[144] This would allow for the later selective deprotection of the acetate group on DTBMS ester **240** by reductive means, a deprotection strategy that was chosen given that preliminary attempts at using common conditions (K_2CO_3 in MeOH at 0 °C) for the acetate hydrolysis on the methyl ester analogue of DTBMS ester **240** had led to concomitant cleavage of the TBDPS group.[139] It is also worth noting that earlier studies[139] had proven that both the *O*-TBDPS and the C(=O)*O*-DTBMS groups on ester **240** could be

cleaved by treatment with $NH_4F{\cdot}HF$ in MeOH to provide the corresponding β-hydroxy acid as a precursor for β-lactonisation, which would be the last step in the planned total synthesis towards oxazolomycin B (**2**).



Scheme 100. Reagents and conditions: i) TFA (50 eq.), MeOH (2 eq.), CH_2Cl_2, r.t., 5 h, 67%; ii) DMP (1.2 eq.), CH_2Cl_2, r.t., 3 h; iii) $NaClO_2$ (10 eq.), NaH_2PO_4 (8 eq.), 2-methyl-2-butene (34 eq.), *t*-BuOH-H_2O 2.3:1, r.t., 13 h, 99% over 2 steps; iv) DTBMSOTf **239** (2 eq.), Et_3N (4 eq.), Et_2O, r.t., 30 min, 82%. N.B. The stereochemistry of acid **114** was confirmed by X-ray crystallographic analysis performed by a past member in the Donohoe group on a derivative of acid **114** lacking the *N*-methyl group[50]

The acetate group on ester **240** was cleaved by treatment with $LiBH_4$ to afford alcohol **241** in 83% yield, which was then converted into aldehyde **99** in 79% yield *via* Swern oxidation (**Scheme 101**). Earlier attempts at oxidising alcohol **241** to aldehyde **99** using base-buffered Dess–Martin periodinane had resulted in the formation of undesired lactone **242** as major product, whose reduction with DIBAL-H to recover aldehyde **99** had led to the recovery of over-reduced alcohol **241** instead.[139]

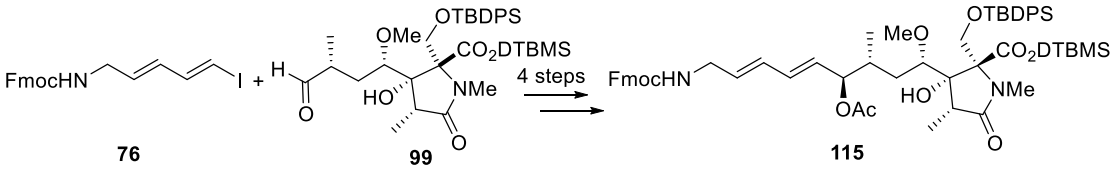


Scheme 101. Reagents and conditions: i) $LiBH_4$ (20 eq.), THF, r.t., 5 h, 83%; ii) DMSO (10 eq.), $(COCl)_2$ (5 eq.), −78 °C, 1 h, then Et_3N (20 eq.), −78 °C, 15 min then r.t., 30 min, CH_2Cl_2, 79%

All the reactions that have been described in **Section 2.5.3** were initially performed and optimised on small scale (10–50 mg) before scaling them up to a 30–500 mg scale, depending on the availability of intermediates and how advanced the intermediates were in the synthetic sequence.

2.5.4. Optimisation of the Nozaki–Hiyama–Kishi reaction between aldehyde 99 and iodide 76

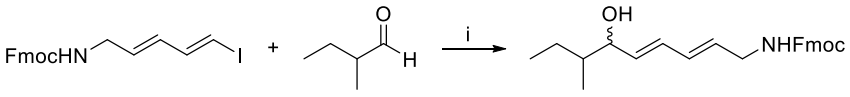
With aldehyde **99** in hand and having previously synthesised iodide **76**, our attention turned towards the exploration of the Nozaki–Hiyama–Kishi reaction between aldehyde **99** and iodide **76**. The coupling of these two compounds would lead to the synthesis of pyrrolidinone **115**, an advanced intermediate towards the synthesis of oxazolomycin B (**2**) (**Scheme 102**).



76 **99** **115**

Scheme 102. Iodide **76** and aldehyde **99**, precursors to access pyrrolidinone **115**

First, we selected 2-methylbutyraldehyde (**243**) as a model aldehyde to test the conditions for the Nozaki–Hiyama–Kishi reaction with iodide **76** (**Scheme 103**). Pleasingly, the Nozaki–Hiyama–Kishi reaction between 2-methylbutyraldehyde (**243**) and iodide **76** provided alcohol **244** in 86% yield.

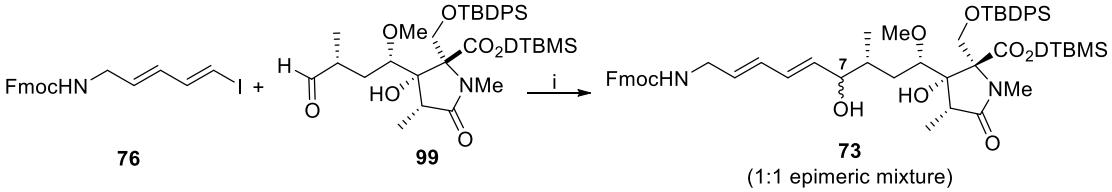


76 **243** **244**

Scheme 103. Reagents and conditions: i) $CrCl_2$ (4 eq.), $NiCl_2$ (0.2 eq.), iodide **76** (1.5 eq.), DMSO, r.t., 16 h, 86%

Having tested the Nozaki–Hiyama–Kishi conditions on model aldehyde **243**, we examined the Nozaki–Hiyama–Kishi reaction between aldehyde **99** and iodide **76** to provide pyrrolidinone **73** (**Scheme 104**). After careful manipulation of the reaction conditions, pyrrolidinone **73** could be synthesised as a 1:1 epimeric mixture in 69% yield on a 40 mg

scale (56.2 μmol) when using 8 eq. of $CrCl_2$ and 0.4 eq. of $NiCl_2$. Despite the air and moisture-sensitivity of the Nozaki–Hiyama–Kishi reaction outlined in **Scheme 104**, we were able to reproduce the reaction results to some extent on small scale (24.0–43.0 mg, 33.7–60.4 μmol), with yields for the 1:1 epimeric mixture of pyrrolidinone **73** that were within the range of 56–69% and with 10–20% unreacted aldehyde **99** recovered.



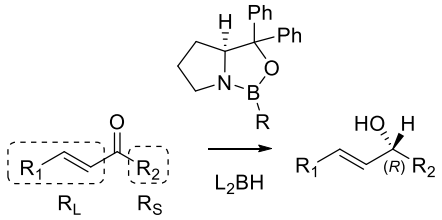
76 **99** **73** (1:1 epimeric mixture)

Scheme 104. Reagents and conditions: i) $CrCl_2$ (8 eq.), $NiCl_2$ (0.4 eq.), iodide **76** (3 eq.), DMSO, r.t., 18 h, 69% (1:1 epimeric mixture)

The Nozaki–Hiyama–Kishi reaction between aldehyde **99** and iodide **76** outlined in **Scheme 104** required careful handling to ensure an inert atmosphere and anhydrous conditions, to maximise the formation of pyrrolidinone **73**. Therefore, prior to reaction, both iodide **76** and aldehyde **99** were azeotroped with benzene, and DMSO was degassed by freeze-pump-thaw cycling technique. Furthermore, both $CrCl_2$ and $NiCl_2$ were weighed in a glovebox before being added to the Schlenk flask containing the reaction mixture, which was exposed to a continuous flow of nitrogen gas to ensure an inert atmosphere throughout the reaction. To ensure complete removal of excess DMSO from the crude reaction mixture and obtain pure pyrrolidinone **73**, dilution of the crude reaction mixture with water (10 mL H_2O per 1 mL DMSO) followed by several consecutive extractions with EtOAc was required prior to purification of the resulting crude residue by FCC.

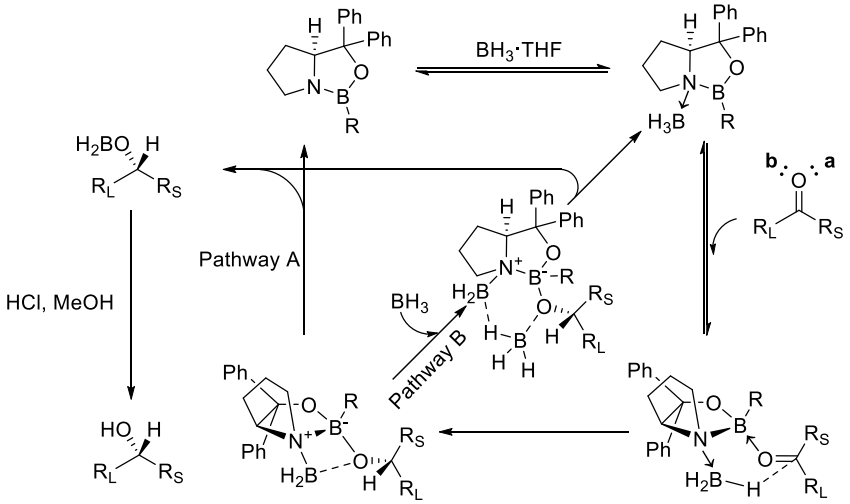
To set the *C*-7 alcohol stereocentre, we planned an oxidation of the 1:1 epimeric mixture of pyrrolidinone **73** with Dess–Martin periodinane to the corresponding ketone followed by a diastereoselective Corey–Bakshi–Shibata[145] reduction to furnish the desired (7*R*)-pyrrolidinone **73**.

The Corey–Bakshi–Shibata[145] reduction is a useful enantioselective method to access chiral secondary alcohols from the corresponding parent ketones using a chiral oxazaborolidine catalyst and a borane source. The Corey–Bakshi–Shibata reduction of acyclic α,β-enones using (*S*)-configured CBS-oxazaborolidine catalysts has been previously reported[146] to provide the corresponding (*R*)-α,β-enol products (**Scheme 105**).



Scheme 105. Enantioselective reduction of α,β-enones with (*S*)-CBS-oxazaborolidine catalysts and a borane source.[146] N.B. "R_L" = large substituent, "R_S" = small substituent

The enantioselectivity of the reaction outlined in **Scheme 105** can be rationalised by the mechanistic model proposed for the enantioselective reduction of ketones by oxazaborolidine catalysts (**Scheme 106**). In the case of acyclic α,β-enones, the olefinic portion bound to the carbonyl group of the ketone behaves as the large group substituent while the alkyl group bound to the carbonyl group behaves as the small substituent.[146]

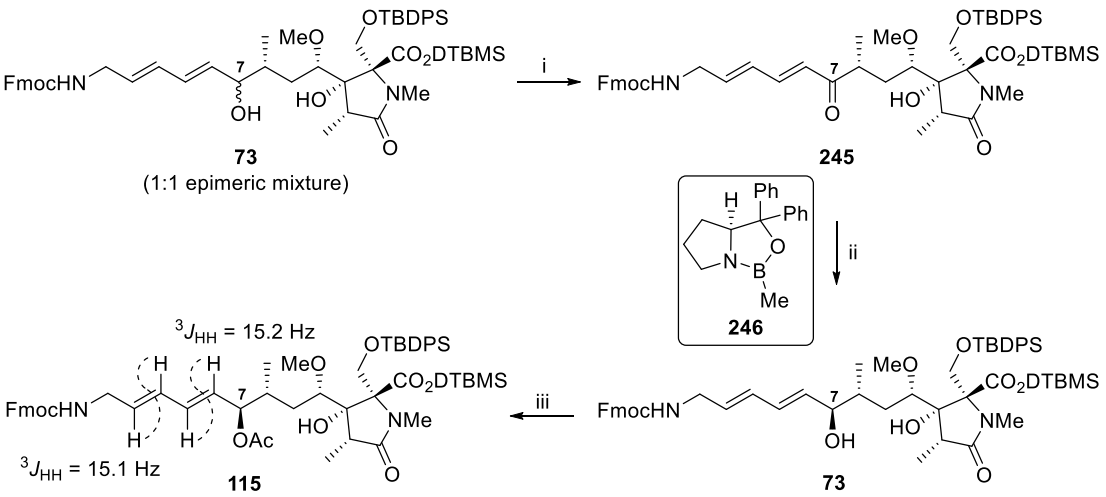


Scheme 106. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidine catalysts[146]

Initially, BH_3 coordinates to the Lewis basic nitrogen atom on the catalyst to form a *cis*-fused oxazaborolidine-BH_3 complex. This coordination activates BH_3 as a hydride donor

and, at the same time, increases the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex described above coordinates to the ketone substrate at the more accessible electron lone pair (a) to minimise unfavourable steric interactions between the oxazaborolidine substituent (R) and the ketone large substituent (R_L). Face-selective hydride transfer *via* a six-membered transition state results in the formation of an alkoxyborane complex. This complex dissociates to regenerate the oxazaborolidine catalyst and form a borinate species, which upon acidic workup provides the desired chiral alcohol product. The dissociation can occur *via* two different pathways: A) the alkoxide ligand attached to the endocyclic boron atom reacts with the adjacent boron atom, regenerating the oxazaborolidine catalyst and forming a borinate species by cycloelimination; or B) BH_3 adds to the alkoxyborane complex forming a six-membered BH_3-bridged species, which decomposes to regenerate the oxazaborolidine-BH_3 complex and the borinate species.

Following the synthetic plan described earlier, the 1:1 epimeric mixture of pyrrolidinone **73** was oxidised with Dess–Martin periodinane to afford ketone **245** in 73% yield. Subsequent diastereoselective Corey–Bakshi–Shibata[145] reduction of ketone **245** using $BH_3{\cdot}Me_2S$ and (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**246**) at −30 °C furnished (7*R*)-pyrrolidinone **73** in 99% yield and as a single diastereomer (>20:1 dr) (**Scheme 107**). The use of excess (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**246**) (4 eq.) compared to $BH_3{\cdot}Me_2S$ (2 eq.) proved crucial to achieve complete diastereoselectivity (>20:1 dr) in the reduction of ketone **245** to (7*R*)-pyrrolidinone **73**. Preliminary attempts at performing the abovementioned reduction using 2 eq. of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**246**) and 2 eq. of $BH_3{\cdot}Me_2S$ provided pyrrolidinone **73** as a 1:1 epimeric mixture. Finally, (7*R*)-pyrrolidinone **73** was acetylated in 86% yield to give target (7*R*)-pyrrolidinone **115**.

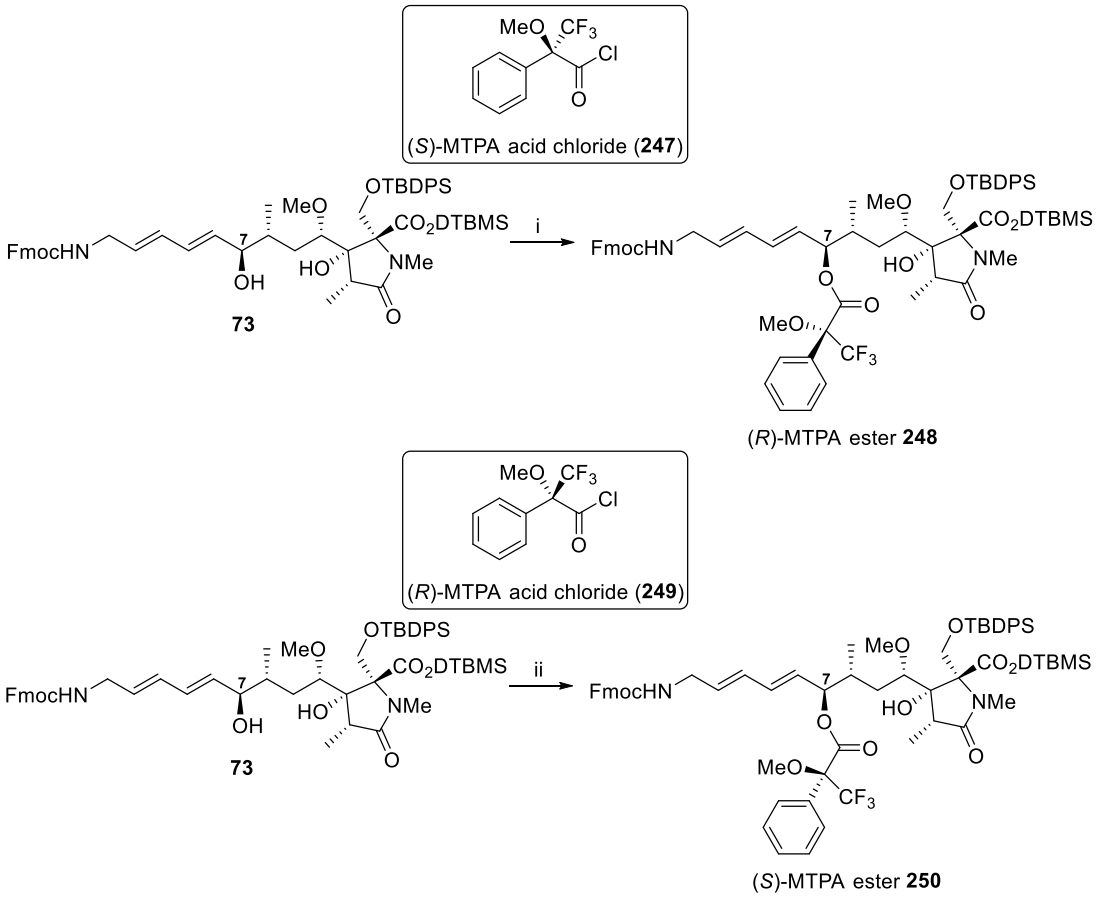


Scheme 107. Reagents and conditions: i) DMP (1.5 eq.), CH_2Cl_2, r.t., 1.5 h, 73%; ii) $BH_3{\cdot}Me_2S$ (2 eq.), (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**246**) (4 eq.), THF, −30 °C, 19 h, 99% (>20:1 dr); iii) Ac_2O (10 eq.), pyridine (126 eq.), 0 °C to r.t., 22 h, 86%

Despite the literature precedent[146] suggesting that pyrrolidinone **73** could probably have an (*R*)-configuration, an unambiguous confirmation of the absolute configuration of pyrrolidinone **73** at the *C*-7 position was required.

2.5.5. Determination of absolute stereochemistry of pyrrolidinone 73

To determine the absolute configuration of pyrrolidinone **73** at the *C*-7 stereocentre, and therefore that of the subsequent related compounds in our synthetic route (including pyrrolidinone **115**), we prepared the (*R*)- and (*S*)- Mosher esters ((*R*)- and (*S*)-MTPA esters) of pyrrolidinone **73** (esters **248** and **250**, respectively) (**Scheme 108**). Treatment of pyrrolidinone **73** with (*S*)-MTPA acid chloride (**247**) afforded (*R*)-MTPA ester **248** in 74% yield, while treatment of pyrrolidinone **73** with (*R*)-MTPA acid chloride (**249**) afforded (*S*)-MTPA ester **250** in 93% yield.



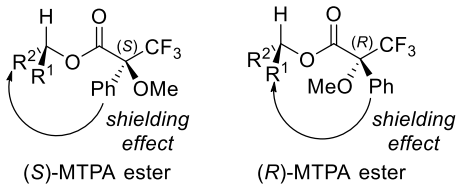
Scheme 108. Reagents and conditions: i) (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (**247**) (32 eq.), pyridine, r.t., 68 h, 74%; ii) (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (**249**) (32 eq.), pyridine, r.t., 95 h, 93%

In both cases, the workup of the reaction mixture was carried out only after observing complete consumption of pyrrolidinone **73** by TLC analysis. This was to avoid errors in the assignment of absolute configuration arising from enrichment or depletion of one stereoisomer in the MTPA ester samples by kinetic resolution.

Mosher ester analysis is an NMR-based method that has been established as a means to determine the absolute configuration of stereogenic, secondary alcohol centers.[147] Mosher ester analysis relies on the fact that the protons in diastereomeric α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters display different chemical shifts (δs) in their ^{1}H NMR spectra. By looking at the difference in chemical shifts for analogous pairs of protons ($\Delta\delta^{SR}$ values) in both diastereomeric MTPA esters, and by analysing the sign of the

$\Delta\delta^{SR}$ values obtained, the absolute configuration of the original alcohol stereocenter can be determined.[147]

The Mosher method for the assignment of stereochemistry of alcohol stereocenters can be rationalised by a conformational model in which each diastereomer adopts a *s-trans* (antiperiplanar) arrangement about its O-CO bond (180° dihedral angle), and in which both the CF_3 substituent on the MTPA moiety and the hydrogen substituent on the secondary alcohol moiety are *syn*-coplanar (0° dihedral angle) with the carbonyl group (**Scheme 109**).



Scheme 109. Conformational model for the analysis of diastereomeric Mosher esters[147]

The aryl group (Ph) imposes an anisotropic, magnetic shielding effect on protons residing above or below the plane of the phenyl ring, which results in a more upfield chemical shift for the affected protons in the NMR spectrum.[147] Therefore, protons residing within the R^2 moiety of the (*S*)-MTPA ester are relatively more shielded (and upfield in its NMR spectrum) and, conversely, protons within the R^1 moiety of the (*R*)-MTPA ester are relatively more shielded (and upfield in its NMR spectrum). From this, it can be deduced that the signs of the $\Delta\delta^{SR}$ ($\Delta\delta^{SR} = \delta_S - \delta_R$) values for protons residing in R^1 will be positive while those for protons residing in R^2 will be negative. The latter information can then be used to deduce the structures of R^1 and R^2 and, thus, determine the absolute configuration of the alcohol stereocenter of interest.[147]

We recorded ^{1}H, ^{13}C and ^{19}F NMR data for MTPA esters **248** and **250** in both C_6D_6 and in $CDCl_3$, with the aim of performing the NMR analysis of esters **248** and **250** in two different solvents. These two comparative Mosher ester analyses should lead to the same stereochemical assignment for pyrrolidinone **73**, which would, in turn, validate the conclusion reached (**Figure 21**, **Table 13** and **Table 14**).

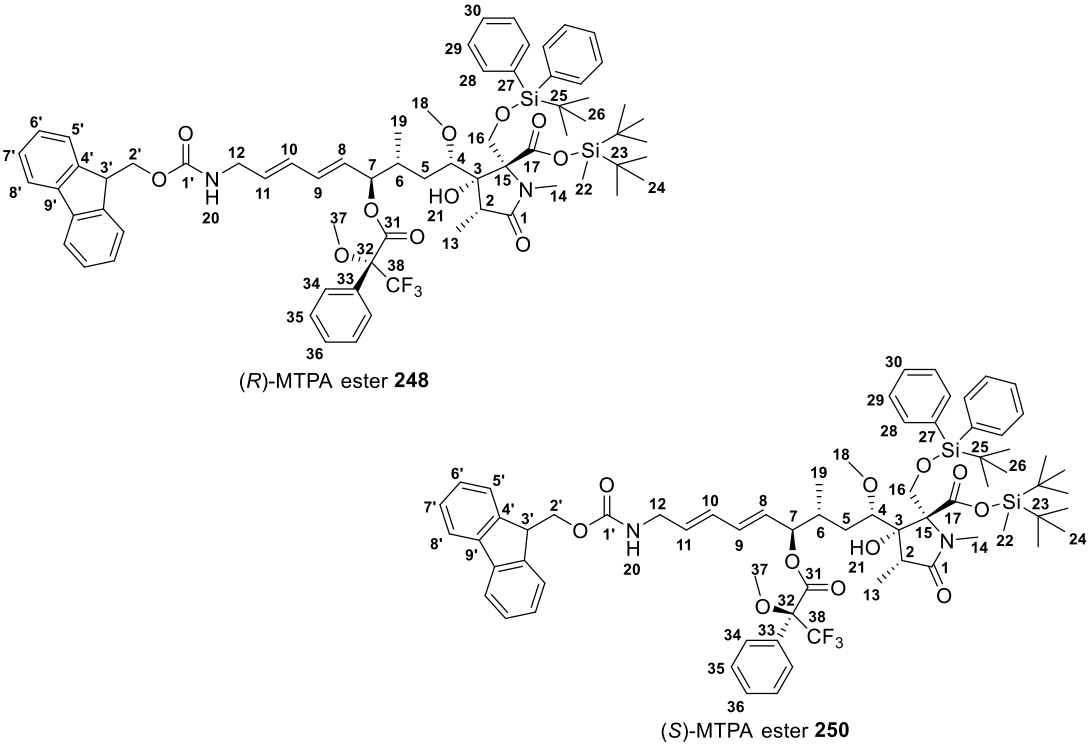


Figure 21. (*R*)- and (*S*)-MTPA esters **248** and **250**

Entry	Proton	δ (*S*)-MTPA ester **250** (ppm)	δ (*R*)-MTPA ester **248** (ppm)	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$) (ppm)	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$) Hz (500 MHz)
1	21	4.69	-	-	-
2	5a	2.19	2.08	+0.11	+55
3	16a	4.72	4.64	+0.08	+40
4	19	1.02	0.95	+0.07	+35
5	28	7.68	7.62	+0.06	+30
6	3’	3.98	3.94	+0.04	+20
7	20	4.02	3.98	+0.04	+20
8	5b	1.93	1.90	+0.03	+15
9	13	1.48	1.45	+0.03	+15
10	24a	0.94	0.91	+0.03	+15
11	37	3.50	3.47	+0.03	+15
12	12	3.46	3.43	+0.03	+15
13	7’, 29, 6’, 30, 36	7.23	7.21	+0.02	+10
14	24b	0.95	0.93	+0.02	+10
15	16b	4.23	4.22	+0.01	+5
16	34	7.72	7.71	+0.01	+5
17	2’	4.47	4.46	+0.01	+5
18	4	3.61	3.60	+0.01	+5
19	5’	7.45	7.45	0.00	0
20	7	5.82	5.82	0.00	0
21	26	1.09	1.09	0.00	0
22	22	0.25	0.25	0.00	0
23	8’	7.61	7.62	−0.01	−5
24	11	5.23	5.24	−0.01	−5
25	6	2.24	2.25	−0.01	−5
26	14	2.90	2.91	−0.01	−5
27	10	5.76	5.78	−0.02	−10
28	35	7.05	7.10	−0.05	−25
29	18	3.27	3.32	−0.05	−25
30	9	6.22	6.29	−0.07	−35
31	2	2.93	3.03	−0.10	−50
32	8	5.47	5.58	−0.11	−55

N.B. ^{1}H NMR data recorded in C_6D_6

Table 13. $\Delta\delta^{SR}$ data in C_6D_6 for the (*S*)- and (*R*)-MTPA Mosher esters **250** and **248**

Entry	Proton	δ (*S*)-MTPA ester **250** (ppm)	δ (*R*)-MTPA ester **248** (ppm)	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$)	
				(ppm)	Hz (500 MHz)
1	19	0.93	0.84	0.09	+45
2	5a	1.95	1.9	0.05	+25
3	21	4.70	4.65	0.05	+25
4	6	2.05	2.00	0.05	+25
5	16a	4.48	4.45	0.03	+15
6	7', 29, 35, 36, 30	7.40	7.38	0.02	+10
7	20	4.77	4.75	0.02	+10
8	12	3.81	3.80	0.01	+5
9	37	3.54	3.53	0.01	+5
10	13	1.22	1.21	0.01	+5
11	24b	0.90	0.89	0.01	+5
12	2'	4.42	4.41	0.01	+5
13	16b	3.92	3.91	0.01	+5
14	2	2.67	2.66	0.01	+5
15	14	2.61	2.60	0.01	+5
16	5b	1.63	1.62	0.01	+5
17	8'	7.76	7.76	0.00	0
18	28, 5'	7.61	7.61	0.00	0
19	3'	4.21	4.21	0.00	0
20	26	1.05	1.05	0.00	0
21	24a	0.92	0.92	0.00	0
22	22	0.22	0.22	0.00	0
23	34	7.50	7.51	−0.01	−5
24	6'	7.30	7.31	−0.01	−5
25	4	3.43	3.44	−0.01	−5
26	11	5.61	5.64	−0.03	−15
27	18	3.33	3.36	−0.03	−15
28	10	6.10	6.13	−0.03	−15
29	7	5.58	5.62	−0.04	−20
30	9	6.18	6.27	−0.09	−45
31	8	5.54	5.67	−0.13	−65

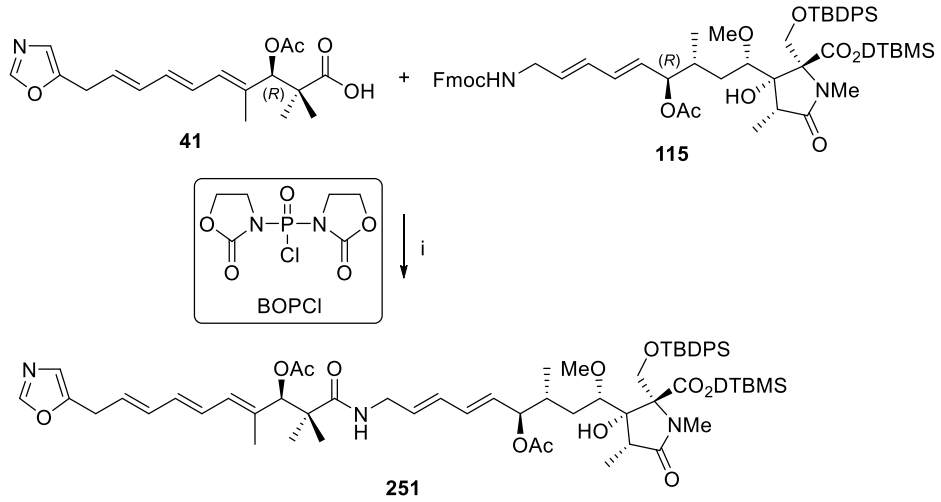
N.B. ^{1}H NMR data recorded in $CDCl_3$

Table 14. $\Delta\delta^{SR}$ data in $CDCl_3$ for the (*S*)- and (*R*)-MTPA Mosher esters **250** and **248**

The analysis of the ^{1}H NMR data in C_6D_6 and in $CDCl_3$ obtained for both MTPA esters of pyrrolidinone **73** (esters **248** and **250**) allowed the assignment of the (*R*)-configuration for the *C*-7 stereocenter of pyrrolidinone **73**, based on the model outlined in **Scheme 109**.

2.5.6. Synthesis of amide 251 and attempts to complete the total synthesis of oxazolomycin B

Having synthesised enantioenriched acid **41** and pyrrolidinone **115**, we focused our efforts on the amide coupling between these two fragments to access amide **251** (**Scheme 110**). We planned to use the reaction conditions previously optimised on a model system (the amide coupling between racemic acid **41** and acetate **202** described in **Section 2.4.2**). Although the amide coupling between racemic acid **41** and model acetate **202** had been accomplished in 71% yield, the amide coupling between enantioenriched acid **41** and pyrrolidinone **115** proved to be more challenging.



Scheme 110. Reagents and conditions: i) **41** (2.5 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 3 h; separately, **115** (1 eq.), DBU (1.5 eq.), CH_2Cl_2, r.t., 30 min; then the solution of free amine was added to the solution of activated acid, CH_2Cl_2, r.t., 14 h, 28%. N.B. All reactions were performed in the absence of light. The structure of amide **251** was confirmed by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC data analysis

Given the limited amount of pyrrolidinone **115** available at this stage in the synthetic route (43.5 mg, 41.1 µmol in total), the amide coupling between enantioenriched acid **41** and pyrrolidinone **115** was carefully optimised on milligram scale (3.0–11.5 mg, 2.8–10.9 µmol), with pyrrolidinone **115** being the limiting reagent. After meticulous handling, we could obtain the desired amide **251** in 28% yield on a 7.1 mg scale (6.7 µmol).

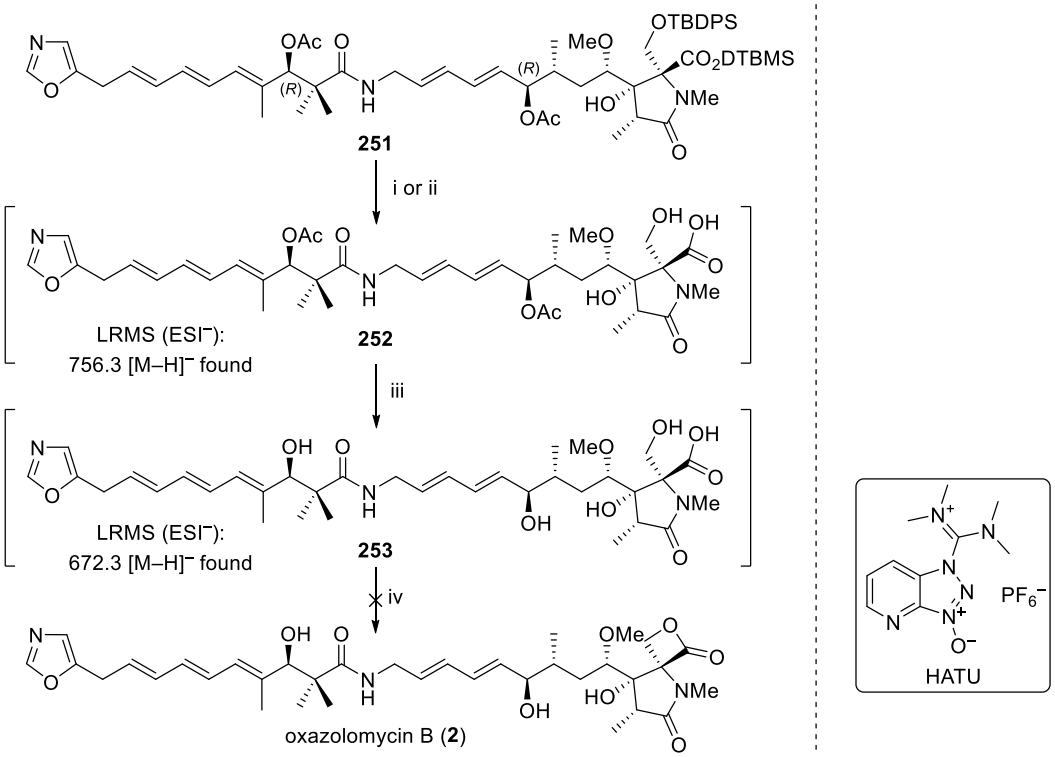
Before each amide coupling experiment, all reagents were purified. Thus, both acid **41** and pyrrolidinone **115** were azeotroped with benzene prior to reaction, while commercial BOPCl

was recrystallised from acetonitrile,[148] and Et_3N, DBU and CH_2Cl_2 were each distilled over CaH_2 and used immediately afterwards. On the other hand, purification of the crude reaction mixture was carried out by multiple elution preparative TLC, since initial attempts at purification by FCC proved difficult on such a small scale. With regard to the experimental procedure that was followed, acid **41** was first activated *via* conversion to the corresponding mixed anhydride upon treatment with BOPCl. Separately, pyrrolidinone **115** was treated with DBU to afford the corresponding primary amine. Subsequently, the solution of primary amine was added to the solution of activated acid to effect the desired amide formation reaction and afford amide **251**.

Gratifyingly, the obtained amide **251** contained the complete carbon skeleton of oxazolomycin B (**2**) and, at that point, it was the most advanced intermediate we had prepared towards the synthesis of the latter natural product. Then, with the aim of completing the total synthesis of oxazolomycin B (**2**), we attempted the final steps in our synthetic sequence.

We envisaged deprotection of all protecting groups (including *O*-TBDPS, C(=O)*O*-DTBMS and the two *O*-$COCH_3$ groups), followed by β-lactonisation as a suitable end-game strategy (**Scheme 111**). With this idea, we attempted the deprotection of the *O*-TBDPS and the C(=O)*O*-DTBMS groups on amide **251** using either HF-pyridine (following Hatakeyama's protocol)[49] or $NH_4F{\cdot}HF$ (following a protocol previously developed within the Donohoe group).[139] Given the small scale of the initial deprotection reactions (3–4 mg, 2.6–3.5 μmol), these reactions were monitored by TLC and LRMS (ESI^-) analysis. Both analyses indicated the presence of acid **252** using either HF-pyridine or $NH_4F{\cdot}HF$ (although amide **251** was only fully consumed when using $NH_4F{\cdot}HF$, while the reaction seemed to have stalled when using excess HF-pyridine, as trace amounts of amide **251** remained). In both cases the crude material obtained after workup was subjected to treatment with LiOH to hydrolyse the two

acetate groups on acid **252**. LRMS (ESI$^-$) analyses of both crude mixtures resulting from the hydrolysis step suggested the presence of tetrahydroxy acid **253** and the corresponding TLC analyses showed full conversion of what we expected to be acid **252** into potential tetrahydroxy acid **253** (although the TLC plate showed a more complex mixture in the case where HF-pyridine had been used for the initial silyl group deprotection, which could not be driven to completion). Encouraged by the possible presence of tetrahydroxy acid **253**, we took both crude mixtures resulting from the LiOH hydrolysis step and we treated each mixture with HATU and Hünig's base (*i*-Pr_2NEt) to form oxazolomycin B (**2**) *via* β-lactonisation (following Hatakeyama's protocol).[49] Unfortunately, and despite considerable efforts made towards the purification of the final crude mixtures (several consecutive multiple elution preparative TLC were attempted), no oxazolomycin B (**2**) was detected in either case (**Scheme 111**). In both instances, we obtained a complex mixture of products that we could separate by preparative TLC but, unfortunately, all the fractions (containing ≤1 mg of material each) provided complex ^{1}H NMR spectra (recorded at 700 MHz).



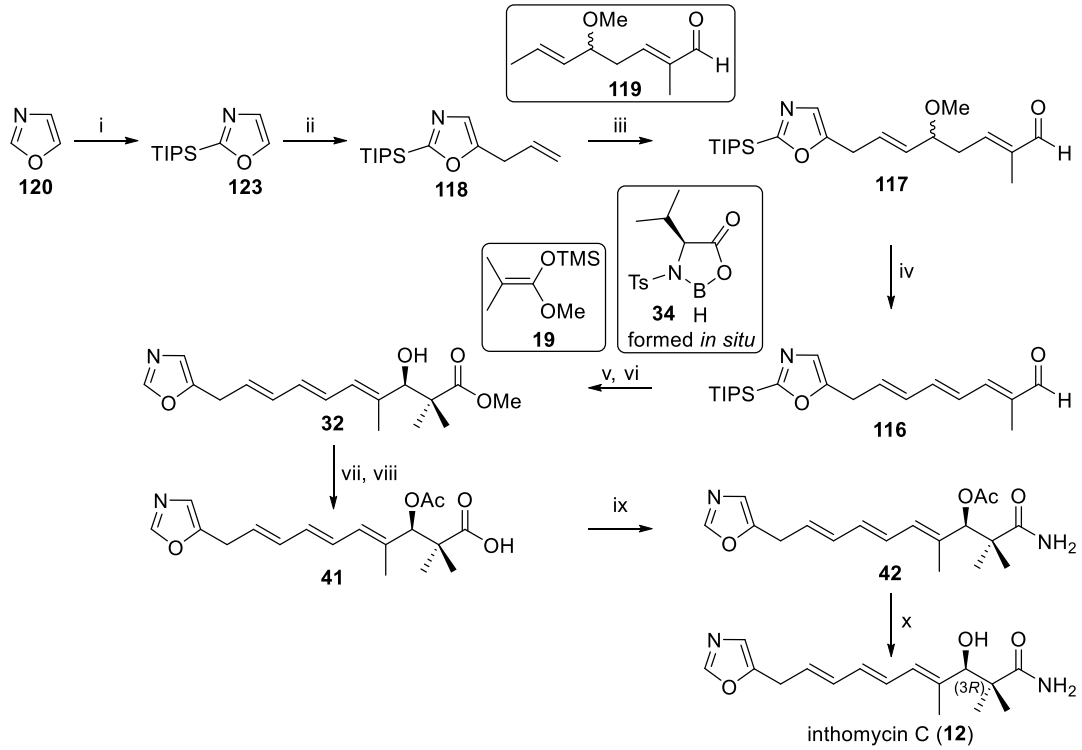
Scheme 111. Reagents and conditions: i) HF-pyridine (143 eq.), THF, 0 °C, 5 h; ii) NH_4F·HF (80 eq.), MeOH, r.t., 22 h; iii) LiOH·H_2O (10 eq.), THF-H_2O 4:1, 0 °C, 3 h; iv) HATU (2 eq.), *i*-Pr_2NEt (3.7 eq.), THF, 36–40 h. N.B. All reactions were performed in the absence of light

From the ^{1}H NMR data obtained, neither oxazolomycin B (**2**) nor any of the intermediates (amides **251**, **252** and **253** or partially deprotected analogues) could be identified. We postulated that the difficulties in synthesising oxazolomycin B (**2**) may be explained due to the practical limitations of dealing with small amounts of material (mainly to keep an inert and moisture-free atmosphere, especially throughout the β-lactonisation step) together with the light-sensitivity and instability of polyenes **251**, **252**, **253** and oxazolomycin B (**2**) itself. Considering all this, we had used freshly distilled THF and *i*-Pr_2NEt, and we had azeotroped the starting material with benzene prior to reaction as required. Furthermore, we had run all reactions outlined in **Scheme 111** in the dark and under inert atmosphere. Despite these efforts, oxazolomycin B (**2**), our target molecule, could not be isolated.

At that point, and given the lack of advanced material in our synthetic sequence and insufficient time to produce more, we concluded our investigations towards the synthesis of oxazolomycin B (**2**).

Chapter 3. Conclusions and Future Work

In conclusion, a novel synthesis of (−)-(3*R*)-inthomycin C (**12**) has been achieved in 89% ee and 11.4% overall yield over ten linear steps from commercially available oxazole (**120**) (80.5% average yield per step) (**Scheme 112**). This is the shortest and highest yielding asymmetric total synthesis of inthomycin C (**12**) to date. Key features of this novel synthetic approach include cross-metathesis between oxazole **118** and aldehyde **119** as key C–C bond-forming step, methoxy group elimination on aldehyde **117** to access the triene moiety and asymmetric Mukaiyama–Kiyooka aldol between silyl ketene acetal **19** and aldehyde **116** to install the *C*-3 (*R*) alcohol stereocenter.

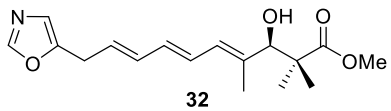


Scheme 112. Reagents and conditions: i) *n*-BuLi (1.1 eq.), THF, −30 °C, 20 min then TIPSOTf (1.1 eq.), −30 °C, 45 min then r.t., 3.5 h, 91%; ii) *n*-BuLi (1.1 eq.), THF, −78 °C, 30 min then LiCl (0.8 eq.), CuCN (0.4 eq.), −78 °C, 2 h then allyl bromide (1.5 eq.), −78 °C to r.t., 2 h, 96% (17:1 **118**/**123** mixture); iii) G-II (10 mol%), aldehyde **119** (4.9 eq.), CH_2Cl_2, 40 °C, 44 h, 57%; iv) Et_3N (2.8 eq.), TBSOTf (1.8 eq.), CH_2Cl_2, 0 ºC to r.t., 16 h then $Sc(OTf)_3$ (2.2 eq.), r.t., 5 h, 74% (8.3:1 mixture of geometrical isomers); v) *N*-Ts-L-valine (2.2 eq.), BH_3·THF (2 eq.), CH_2Cl_2, 0 ºC, 20 min then r.t., 30 min then silyl ketene acetal **19** (1.2 eq.), aldehyde **116** (1 eq.), −78 °C, 2 h; vi) aq. 1 M HCl (1.5 eq.), THF, r.t., 1 h, 63% over 2 steps (89% ee); vii) LiOH·H_2O (2.9 eq.), MeOH-THF-H_2O 1:3:1, 0 °C to r.t., 12 h then aq. 1 M HCl (until at pH 3–4); viii) pyridine (290 eq.), Ac_2O (123 eq.), 0 °C to r.t., 16 h, 87% over 2 steps; ix) $(COCl)_2$ (1.8 eq.), DMF (1 drop), CH_2Cl_2, 0 °C, 1 h then excess NH_4OH (28%) (580 eq.), r.t., 16 h, 65% **42** and 20% **12**; x) LiOH·H_2O (2.1 eq.), MeOH-THF-H_2O 1:3:1, 0 °C, 1 h then r.t., 4 h, 87% (11.1:1 isomeric mixture)

Unlike all previous syntheses of inthomycin C (**12**), which rely on Stille cross-coupling as key C–C bond-forming step, the convergent synthesis described in this work avoids the use

of toxic organotin reagents. The optical rotation data ($[\alpha]_D^{25} = -8.2$ (c 1.0, $CHCl_3$)) for the synthesised sample of inthomycin C (**12**) described herein is in agreement with that from all previous syntheses of inthomycin C (**12**),[28–30] except for Taylor's,[27] whose optical rotation data has been reported to be erroneous due to a tetramethylurea contaminant.[33] Moreover, ^{13}C NMR data for the synthesised sample of inthomycin C (**12**) prepared in this work is also consistent with ^{13}C NMR data reported for originally isolated inthomycin C (**12**).[16]

On the other hand, the work described in this thesis has been the first to explore the biological activity of (−)-(3*R*)-inthomycin C (**12**) and structural analogues on various human cancer cell lines (cervical, lung, breast, prostate, ovarian and multiple myeloma cancer cells). All compounds evaluated (aldehyde **116**, racemic acid **41**, ester **32**, amide **42** and inthomycin C (**12**); see **Figure 13**) have proven inactive (IC_{50} > 50 μM) in cytotoxicity assays against all cell lines tested. However, ester **32** (**Figure 22**) has displayed reversible proteasome inhibition activity against lung cancer cells and multiple myeloma cancer cells (IC_{50} = 10.8 μM and IC_{50} = 32.1 μM, respectively).



32

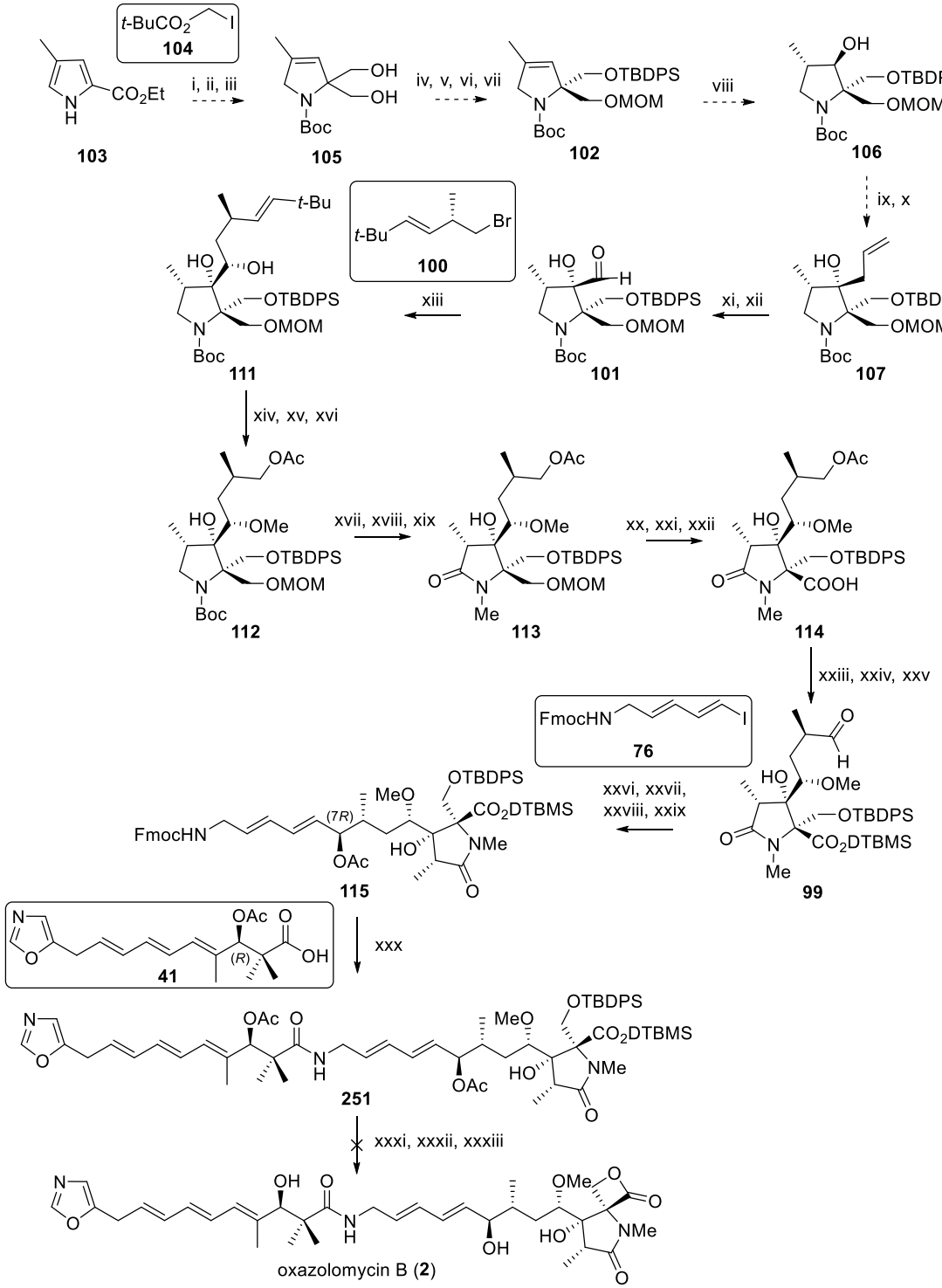
Figure 22. Ester **32**

From the results described above, it has been hypothesised that the weak proteasome activity shown by ester **32** could be due to partial conversion of ester **32** into the corresponding β-lactone, which would be the actual pharmacophore. However, further biological assays and SAR studies are required to gain a deeper understanding of the biological mode of action of the inthomycins, establish their pharmacophore and develop potentially more active analogues.

Building on previous work in the Donohoe group,[50] amide **251** has been synthesised in 0.85% yield over 20 steps from alcohol **107** (see **Figure 17**), which had been previously

prepared[50] in 19.0% yield over ten steps from commercially available pyrrole **103** (**Scheme 113**). Amide **251** is the most advanced intermediate that we have been able to prepare following the synthetic strategy towards oxazolomycin B (**2**), and it contains the complete carbon backbone of the latter natural product. The (*R*) absolute configuration at the *C*-7 stereocenter on amide **251** and preceding analogues has been determined by Mosher ester analysis of precursor intermediate pyrrolidinone **73** (see **Scheme 108**). Key features of the synthesis of amide **251** as precursor to oxazolomycin B (**2**) include previously optimised Birch reduction of an aromatic pyrrole nucleus,[50] diastereoselective organocerium nucleophilic addition on aldehyde **101** to introduce the exocyclic carbon chain fragment, Nozaki–Hiyama–Kishi reaction between aldehyde **99** and iodide **76** to install the diene moiety, and amide formation by coupling between acid **41** and pyrrolidinone **115** (**Scheme 113**).

Since cleavage of all protecting groups on amide **251** followed by β-lactonisation has proven unsuccessful, the completion of the synthesis of oxazolomycin B (**2**) remains an unsolved synthetic challenge. Future work includes the scale up of the synthetic sequence towards oxazolomycin B (**2**), with a special focus on optimisation of the end-game strategy (amide coupling between acid **41** and pyrrolidinone **115** to access amide **251** and successive deprotection/β-lactonisation protocol to form the natural product), with a view to completing the first total synthesis of oxazolomycin B (**2**). Further studies are also required to design an optimised second-generation route to oxazolomycin B (**2**).



Scheme 113. Reagents and conditions: i) Boc_2O, DMAP, CH_2Cl_2, r.t., 16 h; ii) Li, NH_3, THF, −78 °C then **104**, THF, −78 °C, 1.5 h; iii) $LiBH_4$, MeOH, Et_2O, r.t., 16 h, 64% over 3 steps; iv) Lipoprotein lipase, vinyl-OAc, THF, 37 °C, 2 days; v) TBDPSCl, DMAP, imidazole (cat.), CH_2Cl_2, r.t., 2 h; vi) K_2CO_3, MeOH, r.t., 2 h; vii) $CH_2(OCH_3)_2$, LiBr (cat.), $TsOH{\cdot}H_2O$ (cat.), r.t., 32 h, 56% over 4 steps (>98% ee); viii) $BH_3{\cdot}$THF, THF, 0 °C to r.t., 7.5 h then $Me_3NO{\cdot}2H_2O$, PhMe, reflux, 12 h, 79% (8:1 dr); ix) DMP, CH_2Cl_2, 0 °C to r.t., 1 h; x) allyl-MgBr, Et_2O, −78 °C, 2 h, 67% over 2 steps (10:1 dr); xi) G-II (5 mol%), vinyloxy-trimethylsilane (10 eq.), PhMe, reflux, 46 h; xii) O_3, CH_2Cl_2, −78 °C then Me_2S (20 eq.), −78 °C, 20 min then r.t., 20 h, 88% over 2 steps (1.5:1 mixture of Boc rotamers); xiii) *t*-BuLi (10 eq.), **100** (5 eq.), THF, −78 °C, 30 min then $CeCl_3$ beads (15 eq.), −40 °C, 22–23 h then **101** (1 eq.), −78 °C, 5 h, 84% (20:1 dr); xiv) Me_3OBF_4 (5 eq.), proton sponge (7.5 eq.), CH_2Cl_2, r.t., 42 h, 77%; xv) O_3, CH_2Cl_2-MeOH 7.5:1, −78 °C, 20 min then $NaBH_4$ (5 eq.), −78 °C, 1 h then 0 °C, 4 h, 86%; xvi) Ac_2O (100 eq.), pyridine (115 eq.), CH_2Cl_2, r.t., 24 h, 96%; xvii) $RuO_2{\cdot}H_2O$ (0.15 eq.), aq. $NaIO_4$ 10% w/w (10 eq.), EtOAc, r.t., 18 h, 68%;

xviii) TFA (4 eq.), Et_3SiH (2 eq.), CH_2Cl_2, r.t., 1 h, 73%; xix) Cs_2CO_3 (10 eq.), CH_3I (164 eq.), 50 °C, 85%; xx) TFA (50 eq.), MeOH (2 eq.), CH_2Cl_2, r.t., 5 h, 67%; xxi) DMP (1.2 eq.), CH_2Cl_2, r.t., 3 h; xxii) $NaClO_2$ (10 eq.), NaH_2PO_4 (8 eq.), 2-methyl-2-butene (34 eq.), *t*-BuOH-H_2O 2.3:1, r.t., 13 h, 99% over 2 steps; xxiii) DTBMSOTf **239** (2 eq.), Et_3N (4 eq.), Et_2O, r.t., 30 min, 82%; xxiv) $LiBH_4$ (20 eq.), THF, r.t., 5 h, 83%; xxv) DMSO (10 eq.), $(COCl)_2$ (5 eq.), −78 °C, 1 h, then Et_3N (20 eq.), −78 °C, 15 min then r.t., 30 min, CH_2Cl_2, 79%; xxvi) $CrCl_2$ (8 eq.), $NiCl_2$ (0.4 eq.), iodide **76** (3 eq.), DMSO, r.t., 18 h, 69% (1:1 epimeric mixture); xxvii) DMP (1.5 eq.), CH_2Cl_2, r.t., 1.5 h, 73%; xxviii) $BH_3{\cdot}Me_2S$ (2 eq.), (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**246**) (4 eq.), THF, −30 °C, 19 h, 99% (>20:1 dr); xxix) Ac_2O (10 eq.), pyridine (126 eq.), 0 °C to r.t., 22 h, 86%; xxx) **41** (2.5 eq.), BOPCl (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, r.t., 3 h; separately, **115** (1 eq.), DBU (1.5 eq.), CH_2Cl_2, r.t., 30 min; then the solution of free amine was added to the solution of activated acid, CH_2Cl_2, r.t., 14 h, 28%; xxxi) HF-pyridine (143 eq.), THF, 0 °C, 5 h; xxxii) $NH_4F{\cdot}HF$ (80 eq.), MeOH, r.t., 22 h; xxxiii) $LiOH{\cdot}H_2O$ (10 eq.), THF-H_2O 4:1, 0 °C, 3 h; iv) HATU (2 eq.), *i*-Pr_2NEt (3.7 eq.), THF, 36–40 h

A possible future improvement on the current route towards oxazolomycin B (**2**) includes the development of a catalytic asymmetric Nozaki-Hiyama-Kishi reaction to introduce the *C*-7 alcohol stereocentre in one step and, in turn, decrease the amount of toxic chromium (II) salts required for this transformation. Another improvement could be further optimisation of the amide coupling step between acid **41** and pyrrolidinone **115** by exploring alternative amide coupling reagents and different *N*-protecting groups on pyrrolidinone **115**.

On the other hand, and given the lack of advanced material in our synthetic sequence at the end of this work, a relay synthesis of oxazolomycin B (**2**) could be envisaged as an alternative approach to complete the total synthesis of this natural product. Provided that sufficient amounts of oxazolomycin B (**2**) isolated from *Streptomyces* sp. could be obtained, the natural product could be partially hydrolysed and converted into an advanced intermediate in our synthetic route, from which a forward synthesis to oxazolomycin B (**2**) could potentially be completed. In particular, hydrolysis of the β-lactone moiety on oxazolomycin B (**2**) would provide tetrahydroxy acid **253**, which could be selectively protected to afford amide **251** (see **Scheme 111**). Alternatively, acetylation of oxazolomycin B (**2**) followed by β-lactone hydrolysis could provide acid **252**, which could be selectively protected to furnish amide **251**. A subsequent forward synthesis from amide **251** including deprotection of all protecting groups and β-lactonisation would complete the first synthesis of oxazolomycin B (**2**).

Chapter 4. Experimental

4.1. Experimental techniques

General: All glassware was flame-dried under vacuum and reactions carried out under argon atmosphere unless otherwise noted. Compounds were named based on IUPAC guidelines using ChemDraw software and atom numbering may not be consistent with this name. This is for clarity in assignment and consistency between different classes of molecules.

Solvents and Reagents: CH_2Cl_2, THF, toluene, Et_2O, acetonitrile and MeOH were dried by filtration through an activated alumina purification column under a positive pressure of nitrogen. When required, CH_2Cl_2 was degassed by bubbling an inert gas (argon or nitrogen) through the solvent for 15–30 min. All other solvents and reagents requiring purification were purified using standard laboratory techniques.[149] Reagents obtained from commercial sources (Acros Organics, Alfa Aesar, Apollo Scientific, Fluorochem, Sigma-Aldrich, TCI) were used as supplied unless otherwise stated. Petrol refers to petroleum ether in the boiling ranges of 30–40 °C or 40–60 °C.

Chromatography: Flash column chromatography (FCC) was performed using Merck Geduran silica gel 60 (40–63 μm). The solvent systems employed are quoted in parentheses. Reactions and column chromatography were monitored by thin layer chromatography (TLC) analysis using Merck Kieselgel 60 F254 0.25 mm precoated aluminium-backed plates. Product spots were visualised under UV light (λ_{max} = 254 nm) and stained with basic potassium permanganate solution, phosphomolybdic acid solution or acidic vanillin solution as deemed appropriate for the compound.

NMR Spectroscopy: ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were recorded on Bruker spectrometers at 200 MHz, 300 MHz, 400 MHz, 500 MHz or 700 MHz (for ^{1}H NMR), at 50 MHz, 75 MHz, 101 MHz, 126 MHz or 176 MHz (for ^{13}C NMR), and at 471 MHz (for ^{19}F NMR) as specified. Chemical shifts (δ) are reported relative to residual

protic solvent peaks or tetramethylsilane (TMS) internal standard and quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR and 0.1 ppm for ^{13}C NMR and ^{19}F NMR. ^{19}F NMR spectra were not externally referenced. Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz for ^{1}H NMR. Signal splittings are recorded as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m) and/or broad (br.). Structural assignments were based on COSY, HSQC, HMBC, DEPT, TOCSY, ROESY and NOESY experiments. Some of the ^{1}H and ^{13}C NMR spectra exhibit doubling or broadening of peaks due to restricted rotation about the *N*-Boc bonds. Where possible, both rotamers have been assigned and the ratio of rotamers is given for each compound.

Mass Spectrometry: High resolution mass spectra (HRMS) under electrospray ionisation (ESI) or field ionisation (FI) were recorded on a Bruker MicroTof or a Thermo Exactive orbitrap spectrometer. HRMS under chemical ionisation (CI) or electron ionisation (EI) conditions were recorded on a Waters LCT Premier or an Agilent 7200 quadrupole time of flight (Q-ToF) spectrometer. HRMS under matrix assisted laser desorption/ionisation (MALDI) were recorded on a Waters MALDI micro MX spectrometer. Masses are reported as a ratio of mass to charge in Daltons and are given to four decimal places.

Infrared Spectroscopy: Fourier transformation infrared spectra (FTIR) were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessory as evaporated films or powders. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and labelled as strong (s), medium (m), weak (w) or broad (br.).

Polarimetry: Specific optical rotations were recorded on a Schmidt-Haensch UniPol 2000 polarimeter at the sodium D line (λ = 589.3 nm) in $CHCl_3$ or CH_2Cl_2 and are quoted in the units of 10^{-1} deg cm^2 g^{-1}. Solution concentrations are given in units of 10^{-2} g mL^{-1}.

Chiral HPLC: Enantiomeric excesses were determined by HPLC analyses and are given as a percentage. HPLC analyses were conducted using a Dionex UltiMate 3000 HPLC pump with an UltiMate 3000 variable wavelength detector and a Daicel Chiralcel® OD column.

Melting Points: Melting points (m.p.) were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

4.1.1. Phosphate-Buffered Silica Preparation

A pH 7 buffer solution was prepared by dissolving Na_2HPO_4 (3.46 g) and $NaH_2PO_4 \cdot 2H_2O$ (2.43 g) in H_2O (400 mL). The solution was mixed with Merck Geduran silica gel 60 (40–63 μm) in a ratio of 50.0 mL of buffer solution per 5.00 g of silica gel. The resulting slurry was dried overnight at 80 °C.

4.1.2. Silver Nitrate (10%) Doped Silica Preparation

$AgNO_3$ (5.50 g) was dissolved in H_2O (30.0 mL). The resulting solution was transferred to a mortar and Merck Geduran silica gel 60 (40–63 μm) (50.0 g) was added. The mixture was ground for 10 min and dried overnight at 80 °C. The doped silica gel was stored over calcium chloride in a desiccator, protected from light, and used within the same week of preparation.

4.1.3. Phosphate Buffer Solution Preparation (pH 6.865)

Following the Henderson–Hasselbalch equation:

- A 0.5 M KH_2PO_4 solution was prepared by dissolving KH_2PO_4 (34.0 g) in H_2O (500 mL).

- A 0.5 M $K_2HPO_4 \cdot 3H_2O$ solution was prepared by dissolving $K_2HPO_4 \cdot 3H_2O$ (57.0 g) in H_2O (500 mL).

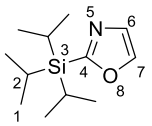
- A pH 6.865 phosphate buffer solution (500 mL) was prepared by mixing 50 mL of the 0.5 M KH_2PO_4 solution with 108 mL of the 0.5 M $K_2HPO_4 \cdot 3H_2O$ solution, and diluting the resulting mixture with H_2O to a final volume of 500 mL.

4.1.4. Titration of n-BuLi solutions

To a solution of 2,6-di-*tert*-butyl-4-methylphenol (100 mg, 0.454 mmol) and 1,10-phenanthroline (5 mg, indicator) in Et_2O (2 mL) at 0 °C was added *n*-BuLi solution (x mL) dropwise until dark red colour persisted, at which point the volume of *n*-BuLi solution added was measured. This procedure was repeated once more. The molarity of the *n*-BuLi solution was calculated from the average volume of *n*-BuLi solution added to the mixture as [*n*-BuLi solution] = (0.454 mmol 2,6-di-*tert*-butyl-4-methylphenol/ x mL *n*-BuLi solution added).

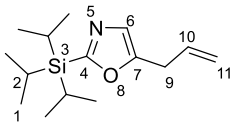
4.2. Experimental details

2-(Triisopropylsilyl)oxazole (123)[66]



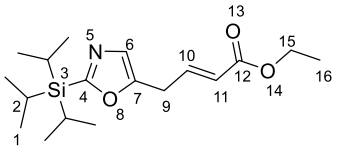
To a solution of oxazole (5.04 g, 73.0 mmol) in THF (103 mL) at –30 °C was added *n*-BuLi (34.2 mL, 2.38 M in hexanes, 79.6 mmol) dropwise over 2.5 h. The reaction mixture was stirred for 20 min before addition of TIPSOTf (21.4 mL, 79.6 mmol) over 1.5 h. The solution was stirred for 45 min at –30 °C and for 3.5 h at room temperature before being quenched with sat. aq. NH_4Cl (100 mL). The reaction mixture was extracted with EtOAc (3 × 100 mL) and the combined organic phase washed with sat. aq. NaCl (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (3% Et_2O/pentane) afforded oxazole **123** as a yellow oil (14.8 g, 91%). Data are consistent with those reported in the literature.[66] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.81 (d, J = 0.8 Hz, 1 H, H^7), 7.21 (d, J = 0.8 Hz, 1 H, H^6), 1.41 (sept, J = 7.5 Hz, 3 H, H^2), 1.13 (d, J = 7.5 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 168.8 (C4), 140.6 (C7), 126.7 (C6), 18.5 (C1), 11.1 (C2) ppm.

5-Allyl-2-(triisopropylsilyl)oxazole (118)[67]



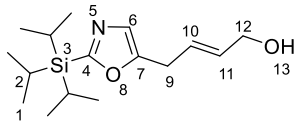
To a solution of oxazole **123** (5.09 g, 22.6 mmol) in THF (37 mL) at –78 °C was added *n*-BuLi (10.5 mL, 2.33 M in hexanes, 24.4 mmol) dropwise over 1 h. The reaction mixture was stirred for 30 min at –78 °C, then a solution of LiCl (828 mg, 19.5 mmol) and CuCN (875 mg, 9.77 mmol) in THF (74 mL) was added dropwise. [N.B. The CuCN and LiCl solution requires sonication to ensure complete dissolution prior to addition to the lithiated oxazole. LiCl was also dried prior to use by heating at 130 °C overnight under high vacuum]. After a further 2 h, freshly distilled allyl bromide (2.88 mL, 33.3 mmol) was added dropwise over 30 min and the reaction stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with sat. aq. NaCl (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O/pentane) afforded an inseparable 17:1 mixture of allyl oxazole **118** and oxazole **123** as a colourless oil (5.67 g, 96%). [N.B. Ratio determined by ^{1}H NMR; δ = 6.84 (t, J = 1.1 Hz, 1 H, H^6 major) and δ = 7.21 ppm (d, J = 0.8 Hz, 1 H, H^6 minor)]. Data are consistent with those reported in the literature.[67] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.84 (t, J = 1.1 Hz, 1 H, H^6), 5.92 (ddt, J = 17.4, 9.7, 6.4 Hz, 1 H, H^{10}), 5.19–5.08 (m, 2 H, H^{11}), 3.45 (dq, J = 6.4, 1.4 Hz, 2 H, H^9), 1.38 (sept, J = 7.5 Hz, 3 H, H^2), 1.12 (d, J = 7.4 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.9 (C4), 152.6 (C7), 133.1 (C10), 123.0 (C6), 117.5 (C11), 30.2 (C9), 18.5 (C1), 11.1 (C2) ppm.

Ethyl (*E*)-4-(2-(triisopropylsilyl)oxazol-5-yl)but-2-enoate (125)



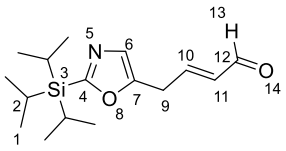
To a 10–20 mL microwave vial was added Hoveyda–Grubbs second-generation catalyst (29.5 mg, 5 mol%) which was then sealed, evacuated and backfilled with argon once. Degassed CH_2Cl_2 (3.77 mL), oxazole **118** (250 mg, 0.943 mmol) and ethyl acrylate (0.514 mL, 4.72 mmol) were sequentially added. The mixture was stirred at 40 °C for 21 h. Reaction was then allowed to cool to room temperature and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (10% EtOAc/petrol) afforded ester **125** as a yellow oil (239 mg, 75%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.01 (dt, J = 15.7, 6.5 Hz, 1 H, H^{10}), 6.90 (t, J = 1.0 Hz, 1 H, H^6), 5.87 (dt, J = 15.7, 1.7 Hz, 1 H, H^{11}), 4.19 (q, J = 7.2 Hz, 2 H, H^{15}), 3.61 (ddd, J = 6.5, 1.7, 1.0 Hz, 2 H, H^9), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.28 (t, J = 7.2 Hz, 3 H, H^{16}), 1.12 (d, J = 7.5 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 168.4 (C4), 166.0 (C12), 150.1 (C7), 142.4 (C10), 123.8 (C11), 123.6 (C6), 60.4 (C15), 28.3 (C9), 18.3 (C1), 14.2 (C16), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 2945m, 2868m, 2361w, 1723s, 1658w, 1465m, 1368w, 1270m, 1178w, 1042w, 978m, 922w, 884m, 657m cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{18}H_{32}NO_3Si^+$ $[M+H]^+$ 338.2146; found 338.2149 (Δ −0.9 ppm).

(*E*)-4-(2-(Triisopropylsilyl)oxazol-5-yl)but-2-en-1-ol (126)



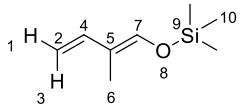
To a solution of ester **125** (420 mg, 1.24 mmol) in CH_2Cl_2 (12.4 mL) was added DIBAL-H (4.05 mL, 25% w/w in hexane solution, 4.99 mmol) dropwise at −78 °C, and the mixture stirred for 30 min at −78 °C. The solution was allowed to stir at room temperature for 1 h. The reaction was quenched by adding EtOAc (10 mL) dropwise. The mixture was then diluted with sat. aq. Rochelle's salt (potassium sodium tartrate) (20 mL) and stirred for 1 h at room temperature. Subsequently, the mixture was diluted with Et_2O (10 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and organic fractions were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30-50% EtOAc/petrol) to afford alcohol **126** as a pale yellow oil (296 mg, 80%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.83 (t, J = 1.1 Hz, 1 H, H^6), 5.82 (dt, J = 15.5, 5.5 Hz, 1 H, H^{10}), 5.76 (dt, J = 15.5, 5.0 Hz, 1 H, H^{11}), 4.14 (br. d, J = 4.9 Hz, 2 H, H^{12}), 3.46 (dd, J = 5.7, 1.1 Hz, 2 H, H^9), 1.78 (br. s., 1 H, H^{13}), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.12 (d, J = 7.5 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.8 (C4), 152.4 (C7), 132.1 (C11), 126.4 (C10), 122.7 (C6), 63.1 (C12), 28.6 (C9), 18.3 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 3350br, 2925s, 2867s, 1464m, 1074w, 970w, 884m, 825w, 677m, 657m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{16}H_{30}NO_2Si^+$ $[M+H]^+$ 296.2040; found 296.2046 (Δ −1.8 ppm).

(*E*)-4-(2-(Triisopropylsilyl)oxazol-5-yl)but-2-enal (127)



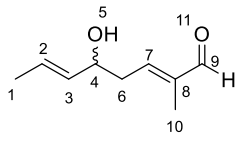
To a mixture of Dess–Martin periodinane (636 mg, 1.50 mmol) and $NaHCO_3$ (420 mg, 5.00 mmol) was added a solution of alcohol **126** (295 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) dropwise at 0°C, and the mixture was stirred at 0 °C for 1 h. The reaction was allowed to warm to room temperature, diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was quickly purified by flash column chromatography using pH 7 phosphate-buffered silica (30% EtOAc/petrol) to afford aldehyde **127** as a yellow oil (286 mg). As compound was not pure enough by NMR, a second flash column chromatography was carried out using the same type of silica (20% EtOAc/ petrol) to afford aldehyde **127** as a yellow oil (225 mg, 77%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.58 (d, J = 7.7 Hz, 1 H, H^{13}), 6.95 (t, J = 1.0 Hz, 1 H, H^6), 6.90 (dt, J = 15.7, 6.3 Hz, 1 H, H^{10}), 6.16 (ddt, J = 15.7, 7.8, 1.6 Hz, 1 H, H^{11}), 3.76 (ddd, J = 6.4, 1.6, 1.0 Hz, 2 H, H^9), 1.40 (sept, J = 7.6 Hz, 3 H, H^2), 1.13 (d, J = 7.6 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 193.3 (C12), 168.9 (C4), 151.7 (C10), 149.4 (C7), 134.6 (C11), 123.9 (C6), 28.9 (C9), 18.4 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 2945m, 2867m, 1696s, 1465w, 1123w, 1075w, 976w, 884m, 657m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{16}H_{27}NNaO_2Si^+$ $[M+Na]^+$ 316.1703; found 316.1705 (Δ −0.5 ppm).

(*E*)-Trimethyl((2-methylbuta-1,3-dien-1-yl)oxy)silane (122)[150,71]



To a solution of tiglic aldehyde (5.07 g, 60.3 mmol) in CH_2Cl_2 (75.3 mL) at 0 °C was added Et_3N (12.6 mL, 90.4 mmol). TMSOTf (12.0 mL, 66.3 mmol) was added dropwise over 20 min and the solution stirred at 0 °C for 4 h before warming to room temperature and stirring for a further 1 h. The reaction mixture was cooled to 0 °C, consecutively washed with sat. aq. $NaHCO_3$ (50 mL), with sat. aq. NH_4Cl (50 mL), and with sat. aq. $NaHCO_3$ (50 mL) again. [N.B. All aqueous solutions were cooled to 0 °C prior to use]. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* at 0 °C. Distillation of the residue (40 °C, 15 mbar) afforded silyl enol ether **122** as a colourless oil (7.02 g, 75%). Data are consistent with those reported in the literature.[150,71] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.40 (s, 1 H, H^7), 6.29 (dd, J = 17.2, 10.7 Hz, 1 H, H^4), 4.99 (dd, J = 17.2, 0.7 Hz, 1 H, H^3), 4.84 (dd, J = 10.8, 0.8 Hz, 1 H, H^1), 1.71 (d, J = 1.3 Hz, 3 H, H^6), 0.21 (s, 9 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 141.4 (C7), 137.1 (C4), 119.0 (C5), 108.4 (C2), 8.9 (C6), −0.3 (C10) ppm.

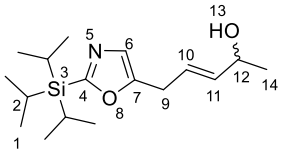
(2*E*,6*E*)-5-Hydroxy-2-methylocta-2,6-dienal (133)



To a solution of TMS enol ether **122** (100 mg, 0.641 mmol) and crotonaldehyde (29.9 mg, 0.427 mmol) in CH_2Cl_2 (5.76 mL) and Et_2O (0.641 mL) was added $BF_3{\cdot}OEt_2$ (0.132 mL, 1.07 mmol) dropwise at −78 °C. The mixture was allowed to stir at −78 °C for 2.5 h. The

reaction was quenched by adding a 5:1:0.4 mixture of THF-H_2O-HCl (6.4 mL). The solution was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (10% Et_2O/CH_2Cl_2) afforded aldehyde **133** as a yellow oil (48.8 mg, 74%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.43 (s, 1 H, H^9), 6.58 (tq, J = 7.3, 1.4 Hz, 1 H, H^7), 5.74 (dqd, J = 15.3, 6.5, 1.0 Hz, 1 H, H^2), 5.54 (ddq, J = 15.3, 7.1, 1.6 Hz, 1 H, H^3), 4.28 (q, J = 6.6 Hz, 1 H, H^4), 2.70–2.46 (m, 2 H, H^6), 1.76 (d, J = 1.0 Hz, 3 H, H^{10}), 1.72 (dd, J = 6.5, 1.6 Hz, 3 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.2 (C9), 150.0 (C7), 140.8 (C8), 133.0 (C3), 128.1 (C2), 71.7 (C4), 36.6 (C6), 17.6 (C1), 9.4 (C10) ppm. **FTIR** ν_{max} (thin film): 3417br, 2920w, 1679s, 1643m, 1406w, 1033w, 967m, 907w, 731w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_9H_{14}NaO_2^+$ $[M+Na]^+$ 177.0886; found 177.0887 (Δ −0.5 ppm).

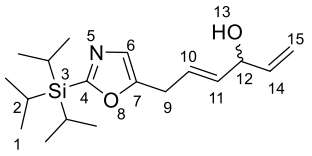
(*E*)-5-(2-(Triisopropylsilyl)oxazol-5-yl)pent-3-en-2-ol (134)



To a solution of aldehyde **127** (30.0 mg, 0.102 mmol) in Et_2O (1.02 mL) was added methyllithium (70.1 µL, 1.6 M solution in Et_2O, 0.112 mmol) dropwise at −78 °C. The mixture was allowed to stir at −78 °C for 1 h, then at 0 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl (1 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 1 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20% EtOAc/petrol) afforded alcohol **134** as a yellow oil (22.1 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.83 (s, 1 H, H^6), 5.76 (dtd, J = 15.3, 6.4, 1.0 Hz, 1 H, H^{10}), 5.64 (ddt, J = 15.3, 6.4, 1.2 Hz, 1 H, H^{11}), 4.38–4.25 (m, 1 H, H^{12}), 3.43 (d, J = 6.1 Hz, 2 H, H^9), 1.64 (br. s, 1 H, H^{13}), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.26 (d, J = 6.4 Hz, 3 H, H^{14}), 1.13 (d, J = 7.3 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.8 (C4), 152.4 (C7), 137.1 (C11), 124.7 (C10), 122.8 (C6), 68.4 (C12), 28.4 (C9), 23.3 (C14), 18.4 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 2945m, 2868m, 1465m, 1065w, 969w, 908m, 884w, 732s, 656w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{17}H_{32}NO_2Si^+$ $[M+H]^+$ 310.2197; found 310.2200 (Δ −1.2 ppm).

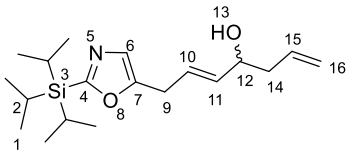
(*E*)-6-(2-(Triisopropylsilyl)oxazol-5-yl)hexa-1,4-dien-3-ol (137)



To a solution of aldehyde **127** (29.9 mg, 0.102 mmol) in Et_2O (1.02 mL) was added vinyl magnesium bromide (0.133 mL, 1 M solution in THF, 0.133 mmol) dropwise at −78 °C. The resulting mixture was stirred at −78 °C for 2.5 h, then allowed to warm to room temperature and left stirring at this temperature for 45 min. The reaction was quenched with sat. aq. NH_4Cl (1 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 1 mL). The organic fractions were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude yellow oil, which was purified by flash column chromatography (30% EtOAc/petrol) to afford alcohol **137** as a pale yellow oil (15.1 mg, 46%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.84 (t, J = 1.0 Hz, 1 H, H^6), 5.93–5.84 (m, 1 H, H^{14}), 5.84–5.77 (m, 1 H, H^{10}), 5.63 (ddt, J = 15.4, 6.4, 1.4 Hz, 1 H, H^{11}), 5.26 (dt, J = 17.2, 1.4 Hz, 1 H, H^{15a}), 5.14 (dt, J = 10.3, 1.4 Hz, 1 H, H^{15b}), 4.69–4.59 (m, 1 H, H^{12}), 3.41–3.50 (m, 2 H, H^9), 1.85 (d, J = 4.2 Hz, 1 H, H^{13}), 1.39 (sept, J = 7.4 Hz, 3 H, H^2), 1.12 (d,

J = 7.6 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.9 (C4), 152.2 (C7), 139.3 (C14), 134.0 (C11), 126.3 (C10), 122.9 (C6), 115.2 (C15), 73.3 (C12), 28.5 (C9), 18.4 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 3325br, 2945s, 2867s, 1597w, 1465s, 1386w, 1081m, 1019w, 989m, 969m, 920m, 883m, 826w, 732m, 677m, 657m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{18}H_{31}NNaO_2Si^+$ $[M+Na]^+$ 344.2016; found 344.2021 (Δ −1.4 ppm).

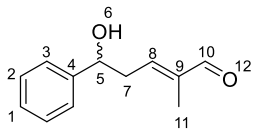
(*E*)-7-(2-(Triisopropylsilyl)oxazol-5-yl)hepta-1,5-dien-4-ol (138)



To a solution of aldehyde **127** (60.0 mg, 0.205 mmol) in Et_2O (2.05 mL) was added allyl magnesium bromide (0.266 mL, 1 M solution in Et_2O, 0.266 mmol) dropwise at −78 °C. The mixture was allowed to stir at −78 °C for 2 h, then at room temperature for 30 min. The reaction was quenched with sat. aq. NH_4Cl (3 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20% EtOAc/petrol) afforded alcohol **138** as a yellow oil (47.7 mg, 69%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.83 (t, J = 1.0 Hz, 1 H, H^6), 5.85–5.80 (m, 1 H, H^{15}), 5.80–5.74 (m, 1 H, H^{10}), 5.62 (ddt, J = 15.5, 6.4, 1.4 Hz, 1 H, H^{11}), 5.17–5.13 (m, 1 H, H^{16a}), 5.12 (t, J = 1.1 Hz, 1 H, H^{16b}), 4.23–4.12 (m, 1 H, H^{12}), 3.50–3.39 (m, 2 H, H^9), 2.38–2.22 (m, 2 H, H^{14}), 1.83 (s, 1 H, H^{13}), 1.39 (sept, J = 7.4 Hz, 3 H, H^2), 1.13 (d, J = 7.6 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.8 (C4), 152.4 (C7), 135.0 (C11), 134.0 (C15), 125.8 (C10), 122.8 (C6), 118.4 (C16), 71.2 (C12), 41.8 (C14), 28.5 (C9), 18.4 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 2945m, 2867m, 1739s, 1464m,

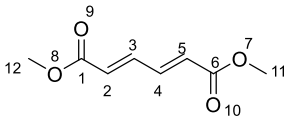
1367m, 1217m, 970m, 908w, 731s, 655w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{19}H_{33}NNaO_2Si^+$ $[M+Na]^+$ 358.2173; found 358.2178 (Δ −1.6 ppm).

(*E*)-5-Hydroxy-2-methyl-5-phenylpent-2-enal (143)



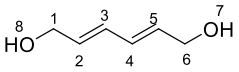
To a solution of TMS enol ether **122** (73.5 mg, 0.471 mmol) in THF (0.750 mL) was added methyllithium (0.294 mL, 1.6 M solution in Et_2O, 0.471 mmol) at −20 °C. The mixture was allowed to stir at −20 °C for 45 min, then cooled down to −78 °C. A solution of benzaldehyde (48.0 µL, 0.471 mmol) in THF (0.100 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for 15 min, then at −20 °C for 20 min. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 1 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20% EtOAc/petrol) afforded alcohol **143** as a yellow oil (36.0 mg, 40%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.38 (s, 1 H, H^{10}), 7.41–7.27 (m, 5 H, H^1, H^2, H^3), 6.58 (tq, J = 7.2, 1.4 Hz, 1 H, H^8), 4.90 (dd, J = 7.5, 5.5 Hz, 1 H, H^5), 2.92–2.71 (m, 2 H, H^7), 2.32 (br. s., 1 H, H^6), 1.69 (d, J = 1.2 Hz, 3 H, H^{11}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.1 (C10), 149.7 (C8), 143.4 (C4), 141.0 (C9), 128.7 (C2), 128.1 (C1), 125.7 (C3), 73.2 (C5), 38.4 (C7), 9.3 (C11) ppm. **FTIR** ν_{max} (thin film): 3416br, 1680m, 1454w, 1051w, 909m, 731s, 701m, 648w cm^{-1}. **HRMS** (ESI+): Calculated for $C_{12}H_{14}NaO_2^+$ $[M+Na]^+$ 213.0886; found 213.0887 (Δ −0.6 ppm).

Dimethyl (2*E*,4*E*)-hexa-2,4-dienedioate (151)[80]



To a solution of (2*E*,4*E*)-hexa-2,4-dienedioic acid (5.00 g, 35.2 mmol) in a 1:1 mixture of MeOH-$CHCl_3$ (176 mL) was added thionyl chloride (20.5 mL, 282 mmol) dropwise at 0 °C. The reaction was allowed to stir at 0 °C for 5 min, then it was heated to reflux and stirred for 4 h. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was partitioned between a 1:1 mixture of CH_2Cl_2-$CHCl_3$ (40 mL) and sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford diester **151** as a white crystalline powder (5.92 g, 99%). Data are consistent with those reported in the literature.[80] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.37–7.28 (m, 2 H, H^3, H^4), 6.26–6.16 (m, 2 H, H^2, H^5), 3.79 (s, 6 H, H^{11}, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 166.3 (C1, C6), 140.9 (C3, C4), 128.0 (C2, C5), 51.9 (C11, C12) ppm.

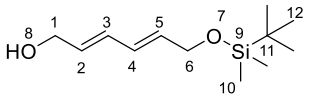
(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol (152)[81]



To a solution of diester **151** (150 mg, 0.879 mmol) in CH_2Cl_2 (4.39 mL) was added DIBAL-H (3.53 mL, 1 M solution in hexanes, 3.53 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C for 1.5 h, then at room temperature for 2.5 h. The reaction was cooled down to 0 °C and quenched with MeOH (10 mL). The obtained suspension was filtered through

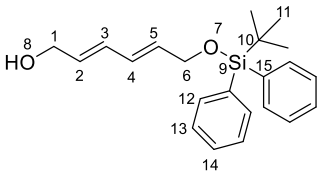
Celite, washed with MeOH and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (80% EtOAc/petrol) to afford diol **152** as a white crystalline powder (76.8 mg, 77%). Data are consistent with those reported in the literature.[81] **^{1}H NMR** (CD_3OD, 400 MHz): δ = 6.32–6.21 (m, 2 H, H^3, H^4), 5.86–5.73 (m, 2 H, H^2, H^5), 4.89 (s, 2 H, H^7, H^8), 4.09 (d, J = 5.1 Hz, 4 H, H^2, H^6) ppm. **^{13}C NMR** (CD_3OD, 101 MHz): δ = 133.6 (C3, C4), 131.5 (C2, C5), 63.4 (C1, C6) ppm.

(2*E*,4*E*)-6-((*tert*-Butyldimethylsilyl)oxy)hexa-2,4-dien-1-ol (153)[86,81]



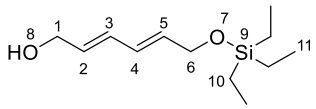
A solution of diol **152** (300 mg, 2.63 mmol) in DMF (10.1 mL) was added dropwise to a solution of imidazole (269 mg, 3.95 mmol) in DMF (10.1 mL) at room temperature. The mixture was stirred at room temperature for 1 h before adding TBSCl (436 mg, 2.89 mmol) in one portion. The mixture was allowed to stir at room temperature for 20 h. Then, the reaction was quenched with H_2O (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with sat. aq. NaCl (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (40% Et_2O/petrol) to afford alcohol **153** as a yellow oil (259 mg, 43%). Data are consistent with those reported in the literature.[86,81] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.32–6.18 (m, 2 H, H^3, H^4), 5.89–5.71 (m, 2 H, H^2, H^5), 4.22 (d, J = 4.6 Hz, 2 H, H^6), 4.18 (d, J = 5.9 Hz, 2 H, H^1) 1.58 (br. s, 1 H, H^8), 0.92 (s, 9 H, H^{12}), 0.08 (s, 6 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 133.2 (C2/C5), 131.4 (C2/C5), 130.9 (C3/C4), 128.9 (C3/C4), 63.3 (C1/C6), 63.3 (C1/C6), 25.9 (C12), 18.4 (C11), −5.2 (C10) ppm.

(2*E*,4*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexa-2,4-dien-1-ol (154)[82]



To a mixture of diol **152** (100 mg, 0.877 mmol) and imidazole (65.7 mg, 0.964 mmol) was added a solution of TBDPSCl (0.239 mL, 0.921 mmol) in DMF (17.6 mL) dropwise, and the mixture was allowed to stir at room temperature for 2.5 h. The reaction was quenched with sat. aq. NaCl (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (20% EtOAc/petrol) to afford alcohol **154** as a pale yellow oil (142 mg, 46%). Data are consistent with those reported in the literature.[82] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.69 (dd, J = 7.7, 1.6 Hz, 4 H, H^{12}), 7.47–7.36 (m, 6 H, H^{13}, H^{14}), 6.38–6.23 (m, 2 H, H^3, H^4), 5.88-5.76 (m, 2 H, H^2, H^5), 4.26 (d, J = 5.1 Hz, 2 H, H^6), 4.21 (d, J = 6.1 Hz, 2 H, H^1), 1.45 (s, 1 H, H^8), 1.08 (s, 9 H, H^{11}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 135.5 (C12), 133.6 (C15), 132.9 (C2/C5), 131.3 (C2/C5), 131.1 (C3/C4), 129.6 (C13/C14), 128.8 (C3/C4), 127.7 (C13/C14), 64.0 (C6), 63.4 (C1), 26.8 (C11), 19.2 (C10) ppm.

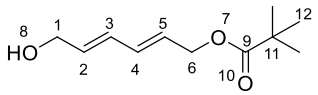
(2*E*,4*E*)-6-((Triethylsilyl)oxy)hexa-2,4-dien-1-ol (155)



To a solution of imidazole (270 mg, 3.96 mmol) and diol **152** (150 mg, 1.32 mmol) in CH_2Cl_2 (26.4 mL) was added TESCl (0.232 mL, 1.38 mmol) dropwise at room temperature.

The mixture was stirred at room temperature for 5 h. Then, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (20% EtOAc/petrol) to afford alcohol **155** as a yellow oil (72.1 mg, 24%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.32–6.19 (m, 2 H, H^3, H^4), 5.90–5.70 (m, 2 H, H^2, H^5), 4.22 (d, J = 4.6 Hz, 2 H, H^6), 4.18 (d, J = 5.6 Hz, 2 H, H^1), 1.55 (br. s, 1 H, H^8), 0.97 (t, J = 8.0 Hz, 9 H, H^{11}), 0.62 (q, J = 8.0 Hz, 6 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 133.1 (C2/C5), 131.5 (C2/C5), 130.9 (C3/C4), 129.1 (C3/C4), 63.3 (C1), 63.0 (C6), 6.7 (C11), 4.4 (C10) ppm. **FTIR** ν_{max} (thin film): 2955m, 2876m, 1458w, 1414w, 1239w, 1110w, 1082m, 988s, 803w, 730s cm^{-1}. **HRMS** (FI^+): Calculated for $C_{12}H_{24}O_2Si^+$ $[M]^+$ 228.1546; found 228.1549 (Δ +1.5 ppm).

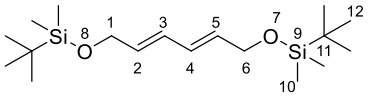
(2*E*,4*E*)-6-Hydroxyhexa-2,4-dien-1-yl pivalate (156)



To a solution of diol **152** (100 mg, 0.877 mmol) in CH_2Cl_2 (16.7 mL) were added pyridine (0.835 mL, 10.3 mmol) and pivaloyl chloride (0.113 mL, 0.921 mmol) sequentially at 0 °C. The solution was stirred at 0 °C for 30 min, then allowed to gradually warm to room temperature over 1.5 h. The reaction was quenched with a 1:1 mixture of aq. 3 M HCl-sat. aq. NaCl (4 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% EtOAc/petrol) to afford alcohol **156** as a yellow oil (65.2 mg,

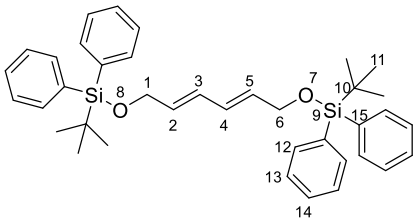
37%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.36–6.21 (m, 2 H, H^3, H^4), 5.95–5.70 (m, 2 H, H^2, H^5), 4.60 (d, J = 6.1 Hz, 2 H, H^6), 4.21 (d, J = 5.9 Hz, 2 H, H^1), 1.21 (s, 9 H, H^{11}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.3 (C9), 133.0 (C2/C5, C3/C4), 130.1 (C3/C4), 127.4 (C2/C5), 64.4 (C6), 63.1 (C1), 38.8 (C11), 27.2 (C12) ppm. **FTIR** ν_{max} (thin film): 3387br, 2975w, 1727s, 1481w, 1398w, 1282m, 1152s, 1079w, 991m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{11}H_{18}NaO_3^+$ $[M+Na]^+$ 221.1148; found 221.1153 (Δ −2.0 ppm).

(6*E*,8*E*)-2,2,3,3,12,12,13,13-Octamethyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene (157)[151,152]



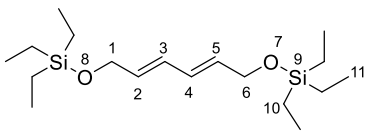
A solution of diol **152** (150 mg, 1.32 mmol) in DMF (13.2 mL) was added dropwise to a solution of imidazole (93.9 mg, 1.38 mmol) in DMF (13.2 mL) at room temperature. The mixture was stirred at room temperature for 1 h before adding TBSCl (208 mg, 1.38 mmol) in one portion. The mixture was allowed to stir at room temperature for 20 h. Then, the reaction was quenched with H_2O (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with sat. aq. NaCl (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (20% EtOAc/petrol) to afford diene **157** as a white solid (39.9 mg, 9%). Data are consistent with those reported in the literature.[151,152] **m.p.** 58–60 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.29–6.17 (m, 2 H, H^3, H^4), 5.82–5.67 (m, 2 H, H^2, H^5), 4.22 (d, J = 4.4 Hz, 4 H, H^1, H^6), 0.92 (s, 18 H, H^{12}), 0.08 (s, 12 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 132.2 (C2, C5), 129.3 (C3, C4), 63.5 (C1, C6), 25.9 (C12), 18.4 (C11), −5.2 (C10) ppm.

(6*E*,8*E*)-2,2,13,13-Tetramethyl-3,3,12,12-tetraphenyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene (158)[153]



To a mixture of diol **152** (100 mg, 0.877 mmol) and imidazole (65.7 mg, 0.964 mmol) was added a solution of TBDPSCl (0.239 mL, 0.921 mmol) in DMF (17.6 mL) dropwise, and the mixture was allowed to stir at room temperature for 2.5 h. The reaction was quenched with sat. aq. NaCl (20 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (20% EtOAc/petrol) to afford diene **158** as a yellow oil (185 mg, 36%). Data are consistent with those reported in the literature.[153] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.76–7.67 (m, 8 H, H^{12}), 7.47–7.36 (m, 12 H, H^{13}, H^{14}), 6.37–6.26 (m, 2 H, H^3, H^4), 5.82–5.70 (m, 2 H, H^2, H^5), 4.26 (d, J = 4.4 Hz, 4 H, H^1, H^6), 1.09 (s, 18 H, H^{11}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 135.5 (C12), 133.6 (C15), 132.9 (C2/C5), 131.3 (C2/C5), 131.1 (C3/C4), 129.6 (C13/C14), 128.8 (C3/C4), 127.7 (C13/C14), 64.0 (C1/C6), 63.4 (C1/C6), 26.8 (C11), 19.2 (C10) ppm.

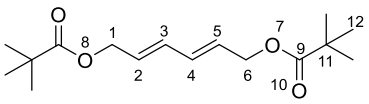
(6*E*,8*E*)-3,3,12,12-Tetraethyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene (159)



To a solution of imidazole (270 mg, 3.96 mmol) and diol **152** (150 mg, 1.32 mmol) in CH_2Cl_2 (26.4 mL) was added TESCl (0.232 mL, 1.38 mmol) dropwise at room temperature.

The mixture was stirred at room temperature for 5 h. Then, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (20% EtOAc/petrol) to afford diene **159** as a pale yellow oil (300 mg, 66%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.29–6.18 (m, 2 H, H^3, H^4), 5.82–5.68 (m, 2 H, H^2, H^5), 4.21 (d, J = 4.9 Hz, 4 H, H^1, H^6), 0.96 (t, J = 8.0 Hz, 18 H, H^{11}), 0.62 (q, J = 8.0 Hz, 12 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 132.2 (C2, C5), 129.6 (C3, C4), 63.2 (C1, C6), 6.7 (C11), 4.5 (C10) ppm. **FTIR** ν_{max} (thin film): 2955m, 2877m, 1458w, 1414w, 1378w, 1239w, 1097m, 1057w, 1007m, 988m, 800w, 728s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{18}H_{38}NaO_2Si_2^+$ $[M+Na]^+$ 365.2303; found 365.2301 (Δ −0.3 ppm).

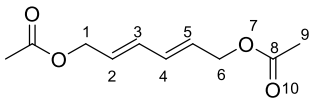
(2*E*,4*E*)-Hexa-2,4-diene-1,6-diyl bis(2,2-dimethylpropanoate) (160)



To a solution of diol **152** (100 mg, 0.877 mmol) in CH_2Cl_2 (16.7 mL) were added pyridine (0.835 mL, 10.3 mmol) and pivaloyl chloride (0.113 mL, 0.921 mmol) sequentially at 0 °C. The solution was stirred at 0 °C for 30 min, then allowed to gradually warm to room temperature over 1.5 h. The reaction was quenched with a 1:1 mixture of aq. 3 M HCl-sat. aq. NaCl (4 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% EtOAc/petrol) to afford diene **160** as a yellow oil (99.5 mg,

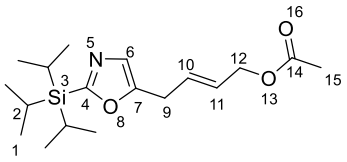
40%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.33–6.23 (m, 2 H, H^3, H^4), 5.86–5.72 (m, 2 H, H^2, H^5), 4.60 (d, J = 5.9 Hz, 4 H, H^1, H^6), 1.22 (s, 18 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.2 (C9), 132.4 (C3, C4), 128.2 (C2, C5), 64.3 (C1, C6), 38.8 (C11), 27.2 (C12) ppm. **FTIR** ν_{max} (thin film): 2973w, 1728s, 1481w, 1398w, 1280m, 1145s, 1031w, 991w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{16}H_{26}NaO_4^+$ $[M+Na]^+$ 305.1723; found 305.1731 (Δ −2.6 ppm).

(2*E*,4*E*)-Hexa-2,4-diene-1,6-diyl diacetate (161)[154]



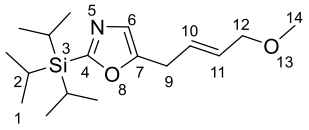
To a solution of diol **152** (36.0 mg, 0.316 mmol) in CH_2Cl_2 (3.16 mL) were added Et_3N (89.0 µL, 0.639 mmol) and DMAP (3.9 mg, 32.0 µmol) sequentially at 0 °C. Then, acetic anhydride (32.9 µL, 0.345 mmol) was added dropwise and the mixture was allowed to gradually warm to room temperature over 23 h. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (10% EtOAc/petrol) to afford diacetate **161** as a yellow oil (53.4 mg, 85%). Data are consistent with those reported in the literature.[154] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.33–6.20 (m, 2 H, H^3, H^4), 5.85–5.72 (m, 2 H, H^2, H^5), 4.58 (d, J = 5.9 Hz, 4 H, H^1, H^6), 2.06 (s, 6 H, H^9) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.6 (C8), 132.7 (C3, C4), 127.9 (C2, C5), 64.3 (C1, C6), 20.8 (C9) ppm.

(*E*)-4-(2-(Triisopropylsilyl)oxazol-5-yl)but-2-en-1-yl acetate (169)



To a 2–5 mL microwave vial was added Hoveyda–Grubbs second-generation catalyst (6.9 mg, 10 mol%). The microwave vial was sealed, evacuated and backfilled with argon once. Degassed CH_2Cl_2 (0.44 mL), oxazole **118** (30.0 mg, 0.113 mmol) and allyl acetate (0.122 mL, 1.13 mmol) were sequentially added. The mixture was stirred at 50 °C for 25 h. Then the reaction was allowed to cool to room temperature and concentrated *in vacuo* onto silica gel before purification by flash column chromatography (10% EtOAc/petrol) to afford acetate **169** as a yellow oil (27.0 mg, 73%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.85 (s, 1 H, H^6), 5.94–5.78 (m, 1 H, H^{10}), 5.77–5.66 (m, 1 H, H^{11}), 4.55 (d, J = 6.4 Hz, 2 H, H^{12}), 3.47 (d, J = 6.4 Hz, 2 H, H^9), 2.06 (s, 3 H, H^{15}), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.13 (d, J = 7.6 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.7 (C14), 167.9 (C7), 151.9 (C4), 129.8 (C10), 126.9 (C11), 123.0 (C6), 64.5 (C12), 28.5 (C9), 20.9 (C15), 18.3 (C1), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 2945m, 2867m, 1742s, 1464w, 1366w, 1227s, 1021w, 969w, 921w, 883m, 829w, 676s, 656s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{18}H_{32}NO_3Si^+$ $[M+H]^+$ 338.2146; found 338.2140 (Δ −4.3 ppm).

(*E*)-5-(4-Methoxybut-2-en-1-yl)-2-(triisopropylsilyl)oxazole (170)



To a 2–5 mL microwave vial was added Hoveyda–Grubbs second-generation catalyst (6.9 mg, 10 mol%). The microwave vial was sealed, evacuated and backfilled with argon

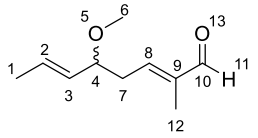
once. Degassed CH_2Cl_2 (0.452 mL), oxazole **118** (30.0 mg, 0.113 mmol) and allyl methyl ether (0.106 mL, 1.13 mmol) were sequentially added. The mixture was stirred at 50 °C for 25 h. Then reaction was allowed to cool to room temperature and concentrated *in vacuo* onto silica gel before purification by flash column chromatography (5% EtOAc/petrol) to afford ether **170** as a pale yellow oil (24.5 mg, 72%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.84 (s, 1 H, H^6), 5.87–5.77 (m, 1 H, H^{11}), 5.72–5.63 (m, 1 H, H^{10}), 3.91 (dd, J = 6.0, 0.9 Hz, 2 H, H^{12}), 3.48–3.44 (m, 2 H, H^9), 3.32 (s, 3 H, H^{14}), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.13 (d, J = 7.3 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 152.4 (C4), 129.3 (C7), 128.1 (C11), 127.5 (C10), 122.8 (C6), 72.6 (C12), 57.8 (C14), 28.7 (C9), 18.3 (C2), 10.9 (C1) ppm. **FTIR** ν_{max} (thin film): 2946m, 2868m, 1465w, 1117w, 909m, 884w, 733s, 656w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{17}H_{32}NO_2Si^+$ $[M+H]^+$ 310.2197; found 310.2200 (Δ −1.1 ppm).

(*E*)-1,1-Dimethoxybut-2-ene (171)[95]

Trimethyl orthoformate (12.0 mL, 72.3 mmol), NH_4NO_3 (289 mg, 5 mol%), and MeOH (3.22 mL, 79.5 mmol) were sequentially added to crotonaldehyde (5.07 g, 72.3 mmol). The reaction mixture was stirred for 16 h at room temperature before addition of Na_2CO_3 (0.35 g, 3.33 mmol) and filtration. Concentration of the crude mixture *in vacuo* followed by purification by flash column chromatography (10% Et_2O/pentane) through a small pad of silica afforded an inseparable 6.2:1 mixture of acetal **171** and trimethyl orthoformate as a colourless oil (7.44 g, 89%). [N.B. Ratio determined by ^{1}H NMR; δ = 4.69 (d, J = 5.5 Hz, 1 H, H^4 major) and δ = 4.96 ppm (s, 1 H, $H^{4'}$ minor)]. Data are consistent with those reported

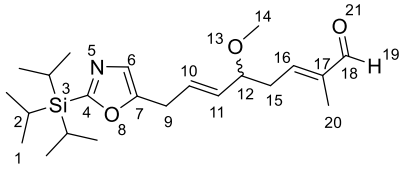
in the literature.[95] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.89–5.76 (m, 1 H, H^2), 5.53–5.42 (m, 1 H, H^3), 4.69 (d, J = 5.5 Hz, 1 H, H^4), 3.31 (s, 6 H, H^6), 1.76–1.69 (m, 3 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 130.6 (C2), 127.9 (C3), 103.6 (C4), 52.8 (C6), 17.8 (C1) ppm.

(2*E*,6*E*)-5-Methoxy-2-methylocta-2,6-dienal (119)



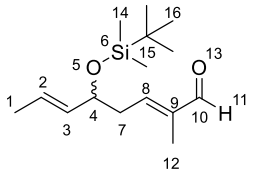
To a solution of acetal **171** (5.00 g, 43.1 mmol) in CH_2Cl_2 (388 mL) and Et_2O (43 mL) were added silyl enol ether **122** (10.1 g, 64.7 mmol) and $BF_3{\cdot}OEt_2$ (6.40 mL, 51.7 mmol) dropwise at –78 °C. The reaction was stirred for 5 h at –78 °C before addition of a 1:1 mixture of MeOH-Et_3N (200 mL). The reaction was quenched with sat. aq. $NaHCO_3$ (150 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic phases were washed with sat. aq. NaCl (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O/pentane) afforded aldehyde **119** as a yellow oil (4.99 g, 69%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.42 (s, 1 H, H^{11}), 6.54 (tq, J = 7.1, 1.4 Hz, 1 H, H^8), 5.72 (dq, J = 15.3, 6.5 Hz, 1 H, H^2), 5.33 (ddq, J = 15.3, 8.2, 1.6 Hz, 1 H, H^3), 3.67 (dt, J = 8.2, 6.4 Hz, 1 H, H^4), 3.28 (s, 3 H, H^6), 2.67–2.49 (m, 2 H, H^7), 1.77–1.71 (m, 6 H, H^1, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.2 (C10), 150.3 (C8), 140.5 (C9), 130.5 (C3), 130.0 (C2), 80.9 (C4), 56.0 (C6), 35.3 (C7), 17.7 (C1), 9.4 (C12) ppm. **FTIR** ν_{max} (thin film): 2821w, 1686s, 1645w, 1449w, 1207w, 1094m, 969m, 869w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{10}H_{16}NaO_2^+$ $[M+Na]^+$ 191.1043; found 191.1041 (Δ −0.7 ppm).

(2*E*,6*E*)-5-Methoxy-2-methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,6-dienal (117)



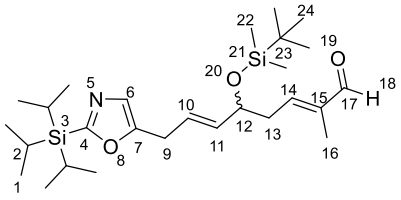
To a 10–20 mL microwave vial was added Grubbs second-generation catalyst (101 mg, 10 mol%) followed by a solution of aldehyde **119** (984 mg, 5.86 mmol) in degassed CH_2Cl_2 (2.37 mL). An 11.4:1 mixture of allyl oxazole **118** and oxazole **123** (314 mg, 1.19 mmol) in degassed CH_2Cl_2 (2.37 mL) was added dropwise to the reaction mixture over 7 h at 40 °C. The reaction was heated at 40 °C for a further 44 h. Concentration *in vacuo* followed by purification by flash column chromatography (30% Et_2O/pentane) afforded aldehyde **117** as a yellow oil (242 mg, 57%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.40 (s, 1 H, H^{19}), 6.84 (d, J = 0.9 Hz, 1 H, H^6), 6.53 (tq, J = 7.1, 1.4 Hz, 1 H, H^{16}), 5.81 (dtd, J = 15.4, 6.5, 0.8 Hz, 1 H, H^{10}), 5.46 (ddt, J = 15.4, 7.9, 1.5 Hz, 1 H, H^{11}), 3.73 (dt, J = 7.5, 6.0 Hz, 1 H, H^{12}), 3.48 (dt, J = 6.5, 1.3 Hz, 2 H, H^9), 3.27 (s, 3 H, H^{14}), 2.65–2.49 (m, 2 H, H^{15}), 1.74 (s, 3 H, H^{20}), 1.39 (sept, J = 7.5 Hz, 3 H, H^2), 1.11 (d, J = 7.5 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.2 (C18), 168.2 (C4), 152.1 (C7), 149.9 (C16), 140.8 (C17), 132.5 (C11), 129.2 (C10), 123.1 (C6), 80.6 (C12), 56.4 (C14), 35.4 (C15), 28.7 (C9), 18.5 (C1), 11.1 (C2), 9.6 (C20) ppm. **FTIR** ν_{max} (thin film): 2944m, 2867m, 1688s, 1645w, 1465m, 1101m, 973w, 920m, 884m, 733w, 676m, 657m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{22}H_{37}NNaO_3Si^+$ $[M+Na]^+$ 414.2435; found 414.2419 (Δ −3.9 ppm).

(2*E*,6*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methylocta-2,6-dienal (178)



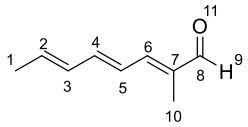
To a solution of aldehyde **133** (50.0 mg, 0.325 mmol) in CH_2Cl_2 (3.25 mL) was added imidazole (44.2 mg, 0.649 mmol), and the mixture was allowed to stir at room temperature for 15 min before adding TBSCl (58.8 mg, 0.390 mmol). The mixture was allowed to stir at room temperature for 24 h. The reaction was quenched with H_2O (3 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were combined, washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (5% Et_2O/pentane) afforded aldehyde **178** as a colourless oil (22.4 mg, 26%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.41 (s, 1 H, H^{11}), 6.56 (td, J = 7.5, 1.4 Hz, 1 H, H^8), 5.68–5.56 (m, 1 H, H^2), 5.50–5.40 (m, 1 H, H^3), 4.25 (q, J = 6.2 Hz, 1 H, H^4), 2.62–2.46 (m, 2 H, H^7), 1.75 (d, J = 1.0 Hz, 3 H, H^{12}), 1.69 (dd, J = 6.4, 0.7 Hz, 3 H, H^1), 0.88 (s, 9 H, H^{16}), 0.04 (2 s, 6 H, H^{14}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.2 (C10), 151.0 (C8), 140.4 (C9), 133.7 (C3), 126.1 (C2), 72.3 (C4), 38.0 (C7), 25.8 (C16), 18.2 (C15), 17.5 (C1), 9.4 (C12), -4.3 (C14), -4.8 (C14) ppm. **FTIR** ν_{max} (thin film): 2930m, 2857m, 1691s, 1647w, 1472w, 1361w, 1254m, 1068m, 967w, 835s, 776s, 673w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{15}H_{29}O_2Si^+$ $[M+H]^+$ 269.1931; found 269.1932 (Δ +0.3 ppm).

(2*E*,6*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,6-dienal (179)



To a 2–5 mL microwave vial was added Grubbs second-generation catalyst (12.0 mg, 10 mol%) which was then sealed, evacuated and backfilled with argon once. Degassed CH_2Cl_2 (0.590 mL), aldehyde **178** (60.0 mg, 0.224 mmol) and an 11.1:1 mixture of allyl oxazole **118** and oxazole **123** (39.0 mg, 0.147 mmol) were sequentially added, and the mixture was stirred at 40 °C for 48 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo* onto silica gel before purification by flash column chromatography (40% Et_2O/pentane) to afford aldehyde **179** as a yellow oil (30.3 mg, 45%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.40 (s, 1 H, H^{18}), 6.84–6.82 (m, 1 H, H^6), 6.58–6.50 (m, 1 H, H^{14}), 5.62–5.54 (m, 2 H, H^{10}, H^{11}), 4.35–4.27 (m, 1 H, H^{12}), 3.44 (d, *J* = 5.9 Hz, 2 H, H^9), 2.58–2.49 (m, 2 H, H^{13}), 1.74 (s, 3 H, H^{16}), 1.38 (sept, *J* = 7.3 Hz, 3 H, H^2), 1.13 (d, *J* = 7.3 Hz, 18 H, H^1) 0.87 (s, 9 H, H^{24}), 0.03 (2 s, 6 H, H^{22}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 195.1 (C17), 167.9 (C4), 152.3 (C7), 150.3 (C14), 140.6 (C15), 135.3 (C11), 125.3 (C10), 122.8 (C6), 71.6 (C12), 37.8 (C13), 28.5 (C9), 25.7 (C24), 18.4 (C1), 18.3 (C23), 10.9 (C2), 9.4 (C16), −4.3 (C22), −4.9 (C22) ppm. **FTIR** ν_{max} (thin film): 2946s, 2892w, 2867s, 1691s, 1648w, 1594w, 1464m, 1387w, 1363w, 1254m, 1074m, 970m, 884m, 836s, 777m, 677w, 658m cm^{-1}. **HRMS** (ESI$^+$): Calculated for $C_{27}H_{50}NO_3Si_2^+$ $[M+H]^+$ 492.3324; found 492.3314 (Δ −2.0 ppm).

(2*E*,4*E*,6*E*)-2-Methylocta-2,4,6-trienal (180)[155,156]



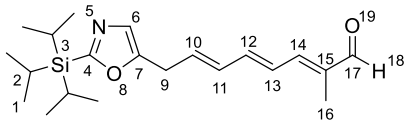
Method A:

To a 10-mL round-bottomed flask were added 4 Å activated molecular sieves (73.0 mg), aldehyde **119** (33.0 mg, 0.196 mmol) and CH_2Cl_2 (1.96 mL) sequentially. Then DBU (58.0 µL, 0.393 mmol) was added and the mixture was allowed to stir at room temperature for 6 h. The reaction was quenched by adding a 1:1 cold mixture of sat. aq. NaCl-NH_4Cl (2 mL). The layers were separated and the organic layer was washed with sat. aq. NaCl (3 × 2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (10% Et_2O/pentane) afforded triene **180** as a pale yellow oil (5.0 mg, 19%). Data are consistent with those reported in the literature.[155] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.44 (s, 1 H, H^9), 6.87 (dd, J = 11.0, 1.0 Hz, 1 H, H^6), 6.67–6.50 (m, 2 H, H^4, H^5), 6.31–6.21 (m, 1 H, H^3), 6.09–5.97 (m, 1 H, H^2), 1.88 (s, 3 H, H^1), 1.86 (d, J = 0.7 Hz, 3 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 194.7 (C8), 149.0 (C6), 141.8 (C4), 136.9 (C7), 136.2 (C2), 131.5 (C3), 125.0 (C5), 18.7 (C1), 9.5 (C10) ppm.

Method B:

To a 10–20 mL microwave vial were added $HfCl_4$·$(THF)_2$ (15.0 mg, 10 mol%) and MeCN (3.25 mL). Alcohol **133** (50.0 mg, 0.325 mmol) was added and the mixture was allowed to stir at room temperature for 1 h, then heated to reflux and allowed to stir for 17 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo* onto silica gel before purification by flash column chromatography (20% Et_2O/pentane) to afford triene **180** as a yellow oil (19.0 mg, 43%). Data are consistent with those reported in the literature.[156]

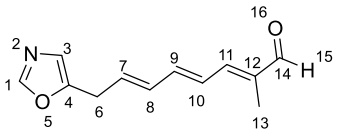
(2*E*,4*E*,6*E*)-2-Methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,4,6-trienal (116)



To a solution of aldehyde **117** (222 mg, 568 μmol) in CH_2Cl_2 (6.4 mL) at 0 °C was added Et_3N (223 μL, 1.60 mmol). After 5 min TBSOTf (234 μL, 1.02 mmol) was added dropwise and the reaction gradually warmed to room temperature over 16 h. Next, $Sc(OTf)_3$ (629 mg, 1.28 mmol) was added and the mixture was stirred for 5 h, then the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated, then the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification by flash column chromatography (30% Et_2O/pentane) afforded an 8.3:1 mixture of geometrical isomers of triene **116** as a yellow oil (152 mg, 74%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.58 (d, *J* = 6.6 Hz, 2 H, H^9 major) and δ = 3.68 ppm (d, *J* = 7.7 Hz, 2 H, H^9 minor)]. Although complete separation of the two isomers could not be achieved, it was found that the undesired (*E,E,Z*) isomer eluted first from flash column chromatography. Therefore, the purity of this compound was increased at this stage by sacrificing earlier fractions to obtain up to a maximum of 22:1 in favour of the major (*E,E,E*) isomer,[96] and this material was subsequently carried forward in the synthesis. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (major isomer) 9.45 (s, 1 H, H^{18}), 6.89–6.86 (m, 1 H, H^{14}), 6.85 (d, *J* = 1.2 Hz, 1 H, H^6), 6.66 (dd, *J* = 14.8, 10.0 Hz, 1 H, H^{12}), 6.58 (dd, *J* = 14.8, 10.5 Hz, 1 H, H^{13}), 6.29 (ddt, *J* = 15.1, 10.0, 1.5 Hz, 1 H, H^{11}), 6.06 (dt *J* = 15.1, 6.7 Hz, 1 H, H^{10}), 3.58 (d, *J* = 6.6 Hz, 2 H, H^9), 1.85 (d, *J* = 1.2 Hz, 3 H, H^{16}), 1.40 (sept, *J* = 7.4 Hz, 3 H, H^2), 1.13 (d, *J* = 7.4 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 194.8 (C17), 168.3 (C4), 151.6 (C7), 148.4 (C14), 140.6 (C12), 137.8 (C15), 133.9 (C10), 132.5 (C11), 126.9 (C13), 123.3 (C6), 29.3 (C9), 18.5

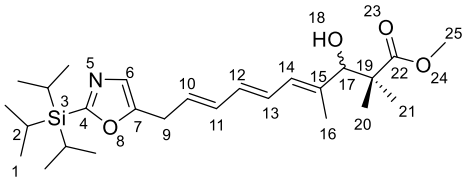
(C1), 11.1 (C2), 9.7 (C16) ppm. **FTIR** ν_{max} (thin film): 2945m, 2867m, 2360w, 1680s, 1613s, 1465w, 1197w, 999m, 884w, 836w, 678w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{21}H_{34}NO_2Si^+$ $[M+H]^+$ 360.2353; found 360.2344 (Δ −2.57 ppm).

(2*E*,4*E*,6*E*)-2-Methyl-8-(oxazol-5-yl)octa-2,4,6-trienal (184)[27,31]



To a solution of triene **116** (19.0 mg, 52.9 µmol, 8.3:1 isomeric mixture) in THF (0.529 mL) was added aq. 1 M HCl (53.0 µL, 529 µmol). The solution was allowed to stir at room temperature for 4 h. Then reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with sat. aq. NaCl (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The crude residue was concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (60% Et_2O/pentane) afforded an 8.3:1 mixture of geometrical isomers of triene **184** as a yellow oil (6.5 mg, 61%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.54 (d, *J* = 6.8 Hz, 2 H, H^6 major) and δ = 3.65 ppm (d, *J* = 7.7 Hz, 2 H, H^6 minor)]. Data are consistent with those reported in the literature.[27,31] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.43 (s, 1 H, H^{15}), 7.80 (s, 1 H, H^1), 6.87–6.81 (m, 2 H, H^{11}, H^3), 6.64–6.60 (m, 2 H, H^9, H^{10}), 6.36–6.26 (m, 1 H, H^8), 6.01 (dt, *J* = 15.1, 6.8 Hz, 1 H, H^7), 3.54 (d, *J* = 6.8 Hz, 2 H, H^6), 1.84 ppm (d, *J* = 1.2 Hz, 3 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 194.7 (C14), 150.7 (C1), 150.0 (C4), 148.2 (C11), 140.2 (C9), 138.0 (C12), 133.1 (C7), 132.8 (C8), 127.3 (C10), 123.0 (C3), 29.1 (C6), 9.6 (C13) ppm. [N.B. Isomeric ratio remained unchanged under these conditions].

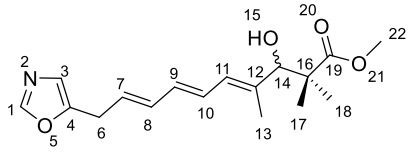
Methyl (4*E*,6*E*,8*E*)-3-hydroxy-2,2,4-trimethyl-10-(2-(triisopropylsilyl) oxazol-5-yl)deca-4,6,8-trienoate ((±)-129)



To a solution of diisopropylamine (135 µL, 0.961 mmol) in THF (1.60 mL) was added *n*-BuLi (435 µL, 2.21 M in hexanes, 0.961 mmol) dropwise at −78 °C. The solution was allowed to stir at −78 °C for 30 min, then at 0 °C for 15 min. Methyl isobutyrate (110 µL, 0.961 mmol) was added dropwise at −78 °C and the mixture was allowed to stir at −78 °C for 30 min, then at −10 °C for 30 min. A solution of triene **116** (115 mg, 0.320 mmol) in THF (1.60 mL) was added dropwise at −78 °C. The solution was allowed to stir for 45 min at −78 °C, then at −10 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and diluted with sat. aq. NaCl (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% Et_2O/pentane) to afford a 10.3:1 mixture of geometrical isomers of racemic ester **129** as a yellow oil (138 mg, 94%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.51 (d, *J* = 6.7 Hz, 2 H, H^9 major) and δ = 3.60 ppm (d, *J* = 7.6 Hz, 2 H, H^9 minor)]. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (major isomer) 6.84 (s, 1 H, H^6), 6.41–6.31 (m, 1 H, H^{13}), 6.27–6.14 (m, 2 H, H^{11}, H^{12}), 6.03 (d, *J* = 11.0 Hz, 1 H, H^{14}), 5.84–5.73 (m, 1 H, H^{10}), 4.17 (d, *J* = 5.6 Hz, 1 H, H^{17}), 3.71 (s, 3 H, H^{25}), 3.51 (d, *J* = 6.6 Hz, 2 H, H^9), 3.06 (d, *J* = 5.6 Hz, 1 H, H^{18}), 1.74 (s, 3 H, H^{16}), 1.39 (sept, *J* = 7.5 Hz, 3 H, H^2), 1.26 (s, 3 H, H^{21}), 1.21 (s, 3 H, H^{20}), 1.13 (d, *J* = 7.5 Hz, 18 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.2 (C22), 167.8 (C4), 152.4 (C7), 136.9 (C15), 133.0 (C11/C12), 132.5 (C11/C12), 128.6 (C14), 128.0 (C10), 127.7 (C13), 122.9

(C6), 82.2 (C17), 52.1 (C25), 46.9 (C19), 29.7 (C21), 29.0 (C9), 23.7 (C20), 20.7 (C1), 18.4 (C1), 13.9 (C16), 10.9 (C2) ppm. **FTIR** ν_{max} (thin film): 3425br, 3025s, 2946s, 2893m, 2868s, 1730s, 1465s, 1434w, 1385w, 1367w, 1257m, 1191w, 1130s, 1061m, 987s, 883m, 657m, 608m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{26}H_{44}NO_4Si^+$ $[M+H]^+$ 462.3034; found 462.3019 (Δ −3.31 ppm).

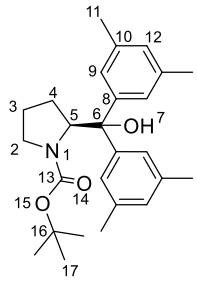
Methyl (4*E*,6*E*,8*E*)-3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate ((±)-32)[27–29]



To a stirred solution of racemic ester **129** (437 mg, 0.948 mmol) in THF (3.16 mL) was added aq. 1 M HCl (1.04 mL, 1.04 mmol) and the solution was allowed to stir at room temperature for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with sat. aq. NaCl (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (60% Et_2O/pentane) to afford a 12.0:1 mixture of geometrical isomers of racemic ester **32** as a yellow oil (250 mg, 87%). [N.B. Ratio determined by ^1H NMR; δ = 3.48 (d, *J* = 6.8 Hz, 2 H, H^6 major) and δ = 3.58 ppm (d, *J* = 7.6 Hz, 2 H, H^6 minor)]. Data are consistent with those reported in the literature.[27–29] **^1H NMR** ($CDCl_3$, 400 MHz): δ = (major isomer) 7.78 (s, 1 H, H^1), 6.79 (s, 1 H, H^3), 6.45–6.31 (m, 1 H, H^{10}), 6.29–6.15 (m, 2 H, H^8, H^9), 6.02 (d, *J* = 11.0 Hz, 1 H, H^{11}), 5.74 (dt, *J* = 14.0, 6.8 Hz, 1 H, H^7), 4.16 (d, *J* = 5.5 Hz, 1 H, H^{14}), 3.70 (s, 3 H, H^{22}), 3.48 (d, *J* = 6.9 Hz, 2 H, H^6), 3.12–3.06 (m, 1 H, H^{15}), 1.73 (d, *J* = 1.3 Hz, 3 H, H^{13}), 1.20 (s, 3 H,

H^{17}), 1.15 (s, 3 H, H^{18}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.3 (C19), 150.5 (C1), 137.4 (C4), 133.6 (C8/C9), 132.3 (C8/C9), 128.6 (C11), 128.2 (C10), 127.4 (C7), 122.7 (C3), 82.3 (C14), 52.3 (C22), 47.2 (C16), 29.0 (C6), 23.8 (C17), 20.9 (C18), 14.1 (C13) ppm.

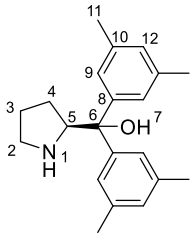
***tert*-Butyl (*S*)-2-(bis(3,5-dimethylphenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (188)**



A solution of *N*-Boc-L-proline methyl ester (2.00 g, 8.72 mmol) in THF (54.5 mL) was added to (3,5-dimethylphenyl)magnesium bromide (61.1 mL, 0.5 M in 2-MeTHF, 60.5 mmol) dropwise *via* cannula over 20 min.[157] The reaction mixture was stirred at room temperature for 4.5 h and then cooled to -78°C. Then, the mixture was quenched by slow addition of H_2O (2.2 mL) and slowly warmed to room temperature. Decantation and washing of precipitated salt with Et_2O gave a solution that was subsequently washed with sat. aq. NaCl (20 mL) and dried over anhydrous K_2CO_3, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (5 to 50% EtOAc/pentane) afforded prolinol **188** as a white crystalline solid (1.89 g, 53%). **m.p.** 45.3–47.6 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.00 (s, 4 H, H^{9}), 6.91 (br. s., 2 H, H^{12}), 4.98–4.73 (m, 1 H, H^{5}), 3.35 (br. s, 1 H, H^{2a}), 2.78 (br. s, 1 H, H^{2b}), 2.29 (s, 12 H, H^{11}), 2.16–2.03 (m, 1 H, H^{4a}), 1.99–1.87 (m, 1 H, H^{4b}), 1.44 (br. s, 10 H, H^{17}, H^{3a}), 0.85 (br. s, 1 H, H^{3b}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 146.4 (C13), 143.6 (C8), 137.0 (C10), 136.5 (C10), 128.6

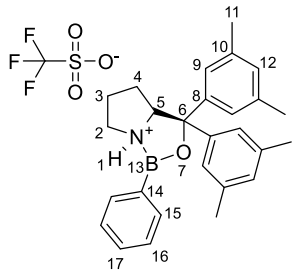
(C12), 128.5 (C12), 126.1 (C9), 125.5 (C9), 81.8 (C16), 80.4 (C6), 65.7 (C5), 47.8 (C2), 29.7 (C4), 28.3 (C17), 22.9 (C3), 21.5 (C11), 21.5 (C11) ppm. **FTIR** ν_{max} (thin film): 3344br, 2974w, 1662s, 1600w, 1392s, 1365m, 1250w, 1165s, 1128w, 1101w, 1039w, 851m, 752w, 716w, 631w, 619w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{26}H_{35}O_3NNa^+$ $[M+Na]^+$ 432.2509; found 432.2509 (Δ −0.14 ppm).

(*S*)-bis(3,5-Dimethylphenyl)(pyrrolidin-2-yl)methanol (189)[40,158]



A solution of prolinol **188** (500 mg, 1.22 mmol) and KOH (684 mg, 12.2 mmol) in MeOH (1.22 mL) and DMSO (5.80 mL) was heated at 65°C for 4 h. The reaction mixture was diluted with H_2O (7 mL) and extracted with hexane (5 × 30 mL). The layers were separated and the organic layers were combined, dried over anhydrous K_2CO_3 and concentrated *in vacuo* to afford prolinol **189** as a white solid (323 mg, 85%). Data are consistent with those reported in the literature.[40,158] **m.p.** 96.6–97.5 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.18 (s, 2 H, H^{9a}), 7.11 (s, 2 H, H^{9b}), 6.81 (s, 2 H, H^{12}), 4.52 (br. s, 1 H, H^7), 4.22 (t, *J* = 7.7 Hz, 1 H, H^5), 3.06–2.99 (m, 1 H, H^{2a}), 2.99–2.90 (m, 1 H, H^{2b}), 2.29 (2 s, 12 H, H^{11}), 1.79–1.68 (m, 2 H, H^3), 1.68–1.53 (m, 3 H, H^4, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 148.2 (C8), 145.3 (C8), 137.5 (C10), 137.2 (C10), 128.1 (C12), 128.0 (C12), 123.6 (C9), 123.2 (C9), 76.9 (C6), 64.5 (C5), 46.7 (C2), 26.2 (C4), 25.5 (C3), 21.6 (C11), 21.6 (C11) ppm.

(3*R*,7*S*)-3,3-bis(3,5-Dimethylphenyl)-1-phenylhexahydro-1*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborol-7-ium trifluoromethanesulfonate (190)[28]

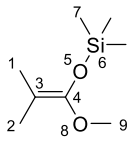


A 100-mL two-necked round-bottomed flask equipped with a stir bar, a glass stopper and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and *ca.* 10 g of 4 Å molecular sieves, functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adaptor, was charged with prolinol **189** (92.0 mg, 0.297 mmol), triphenylboroxine (31.0 mg, 0.099 mmol) and toluene (30 mL). The resulting mixture was heated to reflux (145°C). After 3 h, the reaction mixture was cooled to *ca.* 60°C and the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation to a volume of *ca.* 10 mL. This distillation protocol was repeated three times by re-charging with toluene (3 × 20 mL). The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a vacuum adaptor. Concentration *in vacuo* (*ca.* 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil. To an aliquot oxazaborolidine precursor (0.296 mmol ~20 mol%, theoretical) in toluene (1.0 mL) at −40°C was added triflic acid (0.2 M solution in toluene, freshly prepared, 1.23 mL, 0.246 mmol) dropwise under N_2. After 20 min at −40°C, a colorless homogeneous catalyst solution of oxazaborolidinium catalyst **190** was ready for use in the Mukaiyama aldol reaction.[28]

General procedure for the Mukaiyama aldol reaction:[28]

To a solution of the freshly prepared oxazaborolidinium catalyst **190** (0.296 mmol, 20 mol%) at −40°C were added a solution of triphenylphosphine oxide (171 mg, 0.616 mmol) in toluene (2 mL) and aldehyde (1.23 mmol) in toluene (0.5 mL). The mixture was allowed to stir at −40 °C for 15 min. Then silyl ketene acetal **19** (256 mg, 1.47 mmol) was added and the solution stirred at −40 °C for 20h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (2 mL), washed with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The layers were separated and the combined organic layers were washed with sat. aq. NaCl (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the corresponding aldol product.[28]

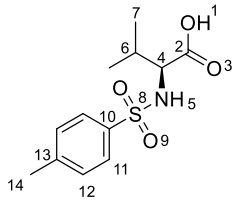
((1-Methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (19)[159,160]



To a solution of diisopropylamine (17.8 mL, 127 mmol) in THF (97.9 mL) was added *n*-BuLi (55.9 mL, 2.1 M in hexanes, 117 mmol) dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then methyl isobutyrate (10.0 g, 97.9 mmol) was added and the mixture stirred for a further 1 h. Freshly distilled TMSCl (24.9 mL, 196 mmol) was added and the mixture was stirred at 0 °C for a further 4 h. The crude reaction mixture was filtered, washed with Et_2O (15 mL) and concentrated *in vacuo*. Distillation of the residue (38 °C, 11 mbar) afforded silyl ketene acetal **19** as a colourless oil (11.7 g, 69%). Data are consistent with those reported in the literature.[159,160] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 3.49 (s, 3 H,

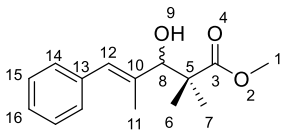
H^9), 1.57 (s, 3 H, H^2), 1.52 (s, 3 H, H^1), 0.20 (s, 9 H, H^7) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 149.5 (C4), 91.0 (C3), 56.7 (C9), 17.0 (C1), 16.3 (C2), 0.2 (C7) ppm.

Tosyl-L-valine (35)[161]



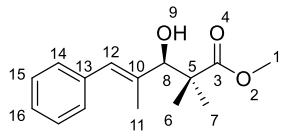
To a solution of L-valine (2.00 g, 17.1 mmol) in aq. 1 M NaOH (35.9 mL, 35.9 mmol) was added a solution of *p*-toluenesulfonyl chloride (3.25 g, 17.1 mmol) in THF (17.1 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was concentrated *in vacuo*, washed with $CHCl_3$ (6.0 mL), and the aqueous layer acidified to pH 2 with aq. 1 M HCl. The aqueous layer was extracted with EtOAc (3 × 100 mL), the layers were separated and the combined organic phases washed with sat. aq. NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford acid **35** as a colourless solid (3.27 g, 71%). Data are consistent with those reported in the literature.[161] **m.p.** 147.5–150.5 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.32 (br. s, 1 H, H^1), 7.71 (d, *J* = 8.3 Hz, 2 H, H^{11}), 7.27 (d, *J* = 8.5 Hz, 2 H, H^{12}), 5.20 (d, *J* = 9.9 Hz, 1 H, H^5), 3.78 (dd, *J* = 9.9, 4.6 Hz, 1 H, H^4), 2.40 (s, 3 H, H^{14}), 2.16–2.03 (m, 1 H, H^6), 0.95 (d, *J* = 6.8 Hz, 3 H, H^{7a}), 0.86 (d, *J* = 6.9 Hz, 3 H, H^{7b}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 176.4 (C2), 144.0 (C10), 136.7 (C13), 129.8 (C12), 127.4 (C11), 60.7 (C4), 31.5 (C6), 21.7 (C14), 19.1 (C7), 17.3 (C7) ppm.

Methyl (*E*)-3-hydroxy-2,2,4-trimethyl-5-phenylpent-4-enoate ((±)-194)[28]



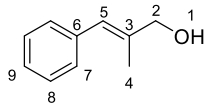
To a solution of diisopropylamine (72.0 μL, 0.513 mmol) in THF (860 μL) was added *n*-BuLi (238 μL, 2.16 M in hexanes, 0.513 mmol) dropwise at −78 °C. The solution was allowed to stir at −78 °C for 30 min, then at 0°C for 15 min. Methyl isobutyrate (59.0 μL, 0.513 mmol) was added dropwise at −78 °C and the mixture was allowed to stir at −78 °C for 30 min, then at −10 °C for 10 min. A solution of α-methyl-*trans*-cinnamaldehyde (25.0 mg, 0.171 mmol) in THF (860 μL) was added dropwise at −78 °C. The solution was allowed to stir for 45 min at −78 °C, then at −10 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl (5 mL), diluted with sat. aq. NaCl (10 mL), and the aqueous layer extracted with Et_2O (3 × 10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% Et_2O/pentane) to afford racemic ester **194** as a pale yellow oil (50.3 mg, 93%). Data are consistent with those reported in the literature.[28] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.36–7.30 (m, 2 H, H^{14}), 7.29–7.25 (m, 2 H, H^{15}), 7.25–7.20 (m, 1 H, H^{16}), 6.47 (s, 1 H, H^{12}), 4.27 (d, *J* = 5.8 Hz, 1 H, H^8), 3.73 (s, 3 H, H^1), 3.24 (d, *J* = 5.8 Hz, 1 H, H^9), 1.84 (d, *J* = 1.3 Hz, 3 H, H^{11}), 1.30 (s, 3 H, H^6), 1.24 (s, 3 H, H^7) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.4 (C3), 137.4 (C13), 137.2 (C10), 129.3 (C12), 129.2 (C15), 128.2 (C14), 126.7 (C16), 83.1 (C8), 52.3 (C1), 47.0 (C5), 24.0 (C6), 21.2 (C7), 14.9 (C11) ppm.

Methyl (*R*,*E*)-3-hydroxy-2,2,4-trimethyl-5-phenylpent-4-enoate (194)[27]



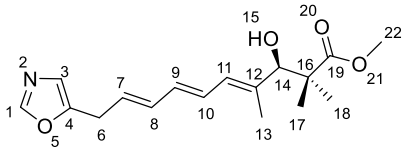
To a solution of *N*-Ts-L-valine **35** (102 mg, 376 μmol) in CH_2Cl_2 (1.42 mL) was added BH_3·THF (342 μL, 1 M in THF, 342 μmol) dropwise at 0 °C. After 20 min at 0 °C, the reaction mixture was warmed to room temperature for 30 min before cooling to –78 °C. A solution of α-methyl-*trans*-cinnamaldehyde (25.0 mg, 171 μmol) in CH_2Cl_2 (0.290 mL) was added dropwise and the mixture stirred for 5 min, then freshly distilled silyl ketene acetal **19** (35.8 mg, 205 μmol) was added. The reaction was stirred at –78 °C for a further 2 h, then the mixture was quenched with a phosphate buffer solution (pH 6.865, 2.32 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), the layers were separated and the combined organic phases washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/pentane) afforded ester **194** as a colourless oil (17.0 mg, 40%, 83% ee). Data are consistent with those reported in the literature.[27] HPLC conditions: Chiralcel OD column, 5% 2-propanol/*n*-heptane, 1.0 mL/min, 254 nm UV detector, t_1 = 10.45 min (minor) and t_2 = 12.70 min (major). **[α]$_D^{26}$** +54.7 (c 1, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.37–7.30 (m, 2 H, H^{14}), 7.29–7.25 (m, 2 H, H^{15}), 7.22 (tt, *J* = 7.2, 1.4 Hz, 1 H, H^{16}), 6.47 (s, 1 H, H^{12}), 4.26 (dd, *J* = 5.8, 0.9 Hz, 1 H, H^8), 3.73 (s, 3 H, H^1), 3.23 (d, *J* = 5.9 Hz, 1 H, H^9), 1.83 (d, *J* = 1.4 Hz, 3 H, H^{11}), 1.30 (s, 3 H, H^6), 1.24 (s, 3 H, H^7) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.4 (C3), 137.4 (C13), 137.2 (C10), 129.3 (C12), 129.2 (C15), 128.2 (C14), 126.8 (C16), 83.2 (C8), 52.3 (C1), 46.9 (C5), 24.1 (C6), 21.2 (C7), 14.9 (C11) ppm.

(*E*)-2-Methyl-3-phenylprop-2-en-1-ol (195)[162]



To a solution *N*-Ts-L-valine **35** (102 mg, 376 μmol) in CH_2Cl_2 (1.42 mL) was added BH_3·THF (342 μL, 1 M in THF, 342 μmol) dropwise at 0 °C. After 20 min at 0 °C, the reaction mixture was warmed to room temperature for 30 min before cooling to –78 °C. A solution of α-methyl-*trans*-cinnamaldehyde (25.0 mg, 171 μmol) in CH_2Cl_2 (0.290 mL) was added dropwise and the mixture stirred for 5 min, then freshly distilled silyl ketene acetal **19** (35.8 mg, 205 μmol) was added, and the reaction was stirred at –78 °C for a further 2 h. The reaction mixture was quenched with a phosphate buffer solution (pH 6.865, 2.32 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The layers were separated and the combined organic phases washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/pentane) afforded alcohol by-product **195** as a pale yellow oil (15.3 mg, 60%). Data are consistent with those reported in the literature.[162] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.38–7.31 (m, 2 H, H^7), 7.31–7.27 (m, 2 H, H^8), 7.23 (tt, *J* = 7.1, 1.4 Hz, 1 H, H^9), 6.53 (s, 1 H, H^5), 4.20 (s, 2 H, H^2), 1.91 (d, *J* = 1.3 Hz, 3 H, H^4), 1.65 (br. s, 1 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 137.8 (C3), 137.7 (C6), 129.0 (C8), 128.3 (C7), 126.6 (C9), 125.2 (C5), 69.1 (C2), 15.4 (C4) ppm.

Methyl (*R*,4*E*,6*E*,8*E*)-3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (32)[27–29,33]



Method A:

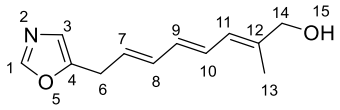
To a solution of *N*-Ts-L-valine **35** (37.9 mg, 0.140 mmol) in CH_2Cl_2 (0.529 mL) was added BH_3·THF (0.127 mL, 1 M in THF, 0.127 mmol) dropwise at 0 °C. The solution was allowed to stir at 0 °C for 20 min, then at room temperature for 30 min. A solution of triene **184** (12.9 mg, 63.5 µmol) in CH_2Cl_2 (0.106 mL) was added dropwise at −78 °C. After 5 min silyl ketene acetal **19** (13.3 mg, 76.2 µmol) was added and the resulting solution stirred at −78 °C for 2 h. The reaction was quenched with a phosphate buffer solution (pH 6.865, 1.19 mL), slowly warmed to room temperature, and extracted with CH_2Cl_2 (3 × 5 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc/pentane) to afford a 7.3:1 mixture of geometrical isomers of ester **32** as a pale yellow oil (13.7 mg, 71%, 82% ee). [N.B. Ratio determined by ^{1}H NMR; δ = 3.48 (d, *J* = 6.8 Hz, 2 H, H^6 major) and δ = 3.58 ppm (d, *J* = 7.6 Hz, 2 H, H^6 minor)]. Data are consistent with those reported in the literature.[27–29,33] HPLC conditions: Chiralcel OD column, 10% 2-propanol/*n*-heptane, 1.0 mL/min, 254 nm UV detector, t_1 = 24.39 min (minor) and t_2 = 28.83 min (major). **[α]$_D^{25}$** +1.58 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.79 (s, 1 H, H^1), 6.79 (s, 1 H, H^3), 6.45–6.32 (m, 1 H, H^{10}), 6.29–6.15 (m, 2 H, H^8, H^9), 6.01 (d, *J* = 11.0 Hz, 1 H, H^{11}), 5.74 (dt, *J* = 14.0, 7.0 Hz, 1 H, H^7), 4.17 (d, *J* = 5.1 Hz, 1 H, H^{14}), 3.70 (s, 3 H, H^{22}), 3.48 (d, *J* = 6.8 Hz, 2 H, H^6), 3.07 (br. s, 1 H, H^{15}), 1.74 (d, *J* = 1.0 Hz, 3 H, H^{13}), 1.20 (s, 3 H, H^{17}),

1.15 (s, 3 H, H^{18}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.3 (C19), 151.0 (C1), 150.6 (C4), 137.4 (C12), 133.6 (C8/C9), 132.3 (C8/C9), 128.6 (C11), 128.3 (C10), 127.4 (C7), 122.7 (C3), 82.3 (C14), 52.3 (C22), 47.1 (C16), 29.0 (C6), 23.9 (C17), 20.9 (C18), 14.1 (C13) ppm.

Method B:

To a solution of ester **129** (9.6 mg, 20.8 µmol, 82% ee) in THF (100 µL) was added aq. 1 M HCl (22.9 µL, 22.9 µmol). The solution was allowed to stir at room temperature for 3 h. Then reaction was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (3 × 2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (60% Et_2O/pentane) to afford ester **32** as a pale yellow oil (5.8 mg, 92%, 82% ee). HPLC conditions: Chiralcel OD column, 10% 2-propanol/*n*-heptane, 1.0 mL/min, 254 nm UV detector, t_1 = 24.55 min (minor) and t_2 = 29.03 min (major). [N.B. Enantiomeric excess remained unchanged under these conditions].

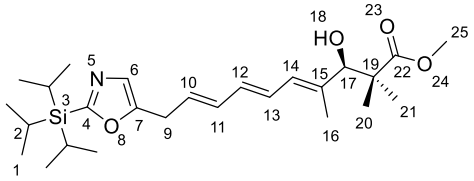
(2*E*,4*E*,6*E*)-2-Methyl-8-(oxazol-5-yl)octa-2,4,6-trien-1-ol (196)



To a solution of *N*-Ts-L-valine **35** (37.9 mg, 0.140 mmol) in CH_2Cl_2 (0.529 mL) was added BH_3·THF (0.127 mL, 1 M in THF, 0.127 mmol) dropwise at 0 °C. The solution was allowed to stir at 0 °C for 20 min, then at room temperature for 30 min. A solution of triene **184** (12.9 mg, 63.5 µmol) in CH_2Cl_2 (0.106 mL) was added dropwise at −78 °C. After 5 min

silyl ketene acetal **19** (13.3 mg, 76.2 µmol) was added and the resulting solution stirred at −78 °C for 2 h. The reaction was quenched with a phosphate buffer solution (pH 6.865, 1.19 mL), slowly warmed to room temperature and extracted with CH_2Cl_2 (3 × 5 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc/pentane) to afford a 12.9:1 mixture of geometrical isomers of alcohol by-product **196** as a pale yellow oil (1.7 mg, 13%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.49 (d, *J* = 6.7 Hz, 2 H, H^6 major) and δ = 3.59 ppm (d, *J* = 7.5 Hz, 2 H, H^6 minor)]. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.79 (s, 1 H, H^1), 6.80 (s, 1 H, H^3), 6.48–6.34 (m, 1 H, H^{10}), 6.30–6.16 (m, 2 H, H^8, H^9), 6.09 (dd, *J* = 11.0, 1.2 Hz, 1 H, H^{11}), 5.75 (dt, *J* = 13.9, 7.0 Hz, 1 H, H^7), 4.11–4.07 (m, 2 H, H^{14}), 3.71 (br. s, 1 H, H^{15}), 3.49 (d, *J* = 6.8 Hz, 2 H, H^6), 1.80 (s, 3 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 151.0 (C1), 150.6 (C4), 138.3 (C12), 133.7 (C8/C9), 131.8 (C8/C9), 128.5 (C10), 127.1 (C7), 124.7 (C11), 122.6 (C3), 68.5 (C14), 29.0 (C6), 14.4 (C13) ppm. **FTIR** ν_{max} (thin film): 3361br, 2960w, 2953m, 1723m, 1674m, 1511m, 1260w, 1096m, 992s, 965m, 913w, 801w, 732w, 648m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{12}H_{16}O_2N^+$ $[M+H]^+$ 206.1176; found 206.1177 (Δ +0.58 ppm).

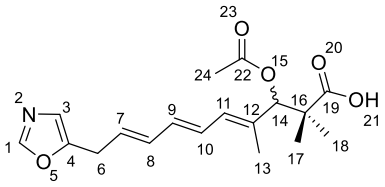
Methyl (*R*,4*E*,6*E*,8*E*)-3-hydroxy-2,2,4-trimethyl-10-(2-(triisopropylsilyl)oxazol-5-yl)deca-4,6,8-trienoate (129)



To a solution of *N*-Ts-L-valine **35** (29.9 mg, 110 µmol) in CH_2Cl_2 (0.417 mL) was added BH_3·THF (100 µL, 1 M in THF, 100 µmol) dropwise at 0 °C. After 20 min at 0 °C, the

reaction mixture was warmed to room temperature for 30 min before cooling to –78 °C. Freshly distilled silyl ketene acetal **19** (10.5 mg, 60.0 μmol) was added and the mixture stirred for 5 min, then a solution of triene **116** (18.0 mg, 50.0 μmol) in CH_2Cl_2 (83.0 μL) was added by syringe-pump over 3 h. The reaction was stirred at –78 °C for a further 2 h, then the mixture was quenched with a phosphate buffer solution (pH 6.865, 1.20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), the layers were separated and the combined organic phases washed with sat. aq. NaCl (2 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/pentane) afforded an 8.3:1 mixture of geometrical isomers of ester **129** as a yellow oil (9.6 mg, 42%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.51 (d, *J* = 6.7 Hz, 2 H, H^9 major) and δ = 3.60 ppm (d, *J* = 7.6 Hz, 2 H, H^9 minor)]. **^{1}H NMR** and **^{13}C NMR** data are in accordance with those reported for racemic ester **129**.

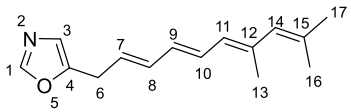
(4*E*,6*E*,8*E*)-3-Acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoic acid ((±)-41)[28,29]



$LiOH·H_2O$ (8.0 mg, 190 μmol) was added to a solution of racemic ester **32** (20.0 mg, 65.5 μmol, 12.0:1 isomeric ratio) in a 3:1:1 mixture of THF-MeOH-H_2O (1.64 mL) at 0 °C. The solution was stirred at room temperature for 17 h. The reaction was acidified to pH 3–4 with aq. 1 M HCl and extracted with EtOAc (3 × 5 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was redissolved in pyridine (1.53 mL, 18.9 mmol) and then acetic anhydride (0.760 mL, 8.02 mmol) was added to the

mixture at 0°C. The solution was allowed to warm to room temperature and then stirred for 21 h. The reaction was quenched with a solution of $NaHCO_3$ (70.0 mg) in MeOH (0.4 mL) and stirred for 2 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 40 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (5% MeOH/$CHCl_3$) to afford a 9.6:1 mixture of geometrical isomers of racemic acid **41** as a yellow oil (18.2 mg, 84%). [N.B. Ratio determined by ^{1}H NMR; δ = 3.48 (d, *J* = 6.8 Hz, 2 H, H^6 major) and δ = 3.58 ppm (d, *J* = 7.5 Hz, 2 H, H^6 minor)]. Data are consistent with those reported in the literature.[28,29] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.83 (s, 1 H, H^1), 6.81 (br. s., 1 H, H^3), 6.41–6.30 (m, 1 H, H^{10}), 6.26–6.16 (m, 2 H, H^8, H^9), 6.06 (d, *J* = 11.0 Hz, 1 H, H^{11}), 5.80–5.68 (m, 1 H, H^7), 5.43 (s, 1 H, H^{14}), 3.48 (d, *J* = 6.8 Hz, 2 H, H^6), 2.05 (s, 3 H, H^{24}), 1.79 (s, 3 H, H^{13}), 1.23 (s, 3 H, H^{17}), 1.18 (s, 3 H, H^{18}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 180.8 (C19), 169.8 (C22), 151.0 (C1), 150.7 (C4), 133.8 (C12), 133.6 (C8/C9), 132.9 (C8/C9), 129.3 (C11), 128.0 (C10), 127.6 (C7), 122.5 (C3), 81.5 (C14), 47.1 (C16), 29.0 (C6), 22.5 (C17), 21.1 (C24), 20.7 (C18), 15.4 (C13) ppm.

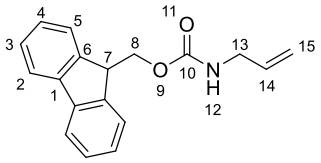
5-((2*E*,4*E*,6*E*)-7,9-Dimethyldeca-2,4,6,8-tetraen-1-yl)oxazole (200)



$LiOH·H_2O$ (9.5 mg, 228 µmol) was added to a solution of racemic ester **32** (24.0 mg, 78.0 µmol) in a 3:1:1 mixture of THF-MeOH-H_2O (1.95 mL) at 0 °C. The solution was stirred at room temperature for 21 h. The reaction was acidified to pH 3–4 with aq. 1 M HCl and extracted with EtOAc (3 × 5 mL). The layers were separated and the organic layers were

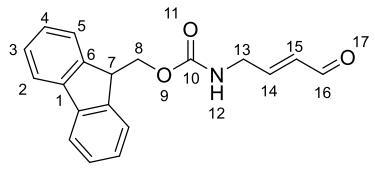
combined. washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was redissolved in CH_2Cl_2 (3.0 mL) and this solution was added to a solution of 2-Methyl-6-nitrobenzoic anhydride (34.0 mg, 98.0 µmol), DMAP (19.0 mg, 15.2 µmol) and Et_3N (64.0 µL, 456 µmol) in CH_2Cl_2 (4.6 mL) dropwise at room temperature over 7 h.[133] The mixture was allowed to stir at room temperature for additional 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) at 0 °C, and extracted with CH_2Cl_2 (3 × 10 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20% Et_2O/pentane) afforded tetraene **200** as a yellow oil (7.2 mg, 41%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.80 (s, 1 H, H^1), 6.81 (s, 1 H, H^3), 6.52–6.43 (m, 1 H, H^{10}), 6.32–6.15 (m, 2 H, H^8, H^9), 5.94 (d, *J* = 11.2 Hz, 1 H, H^{11}), 5.77–5.66 (m, 2 H, H^{14}, H^7), 3.50 (d, *J* = 6.8 Hz, 2 H, H^6), 1.90 (s, 3 H, H^{13}), 1.84 (s, 3 H, H^{17}), 1.81 (s, 3 H, H^{16}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 150.4 (C1), 136.4 (C15), 134.4 (C4), 133.9 (C8/C9), 130.4 (C8/C9), 129.5 (C10), 129.1 (C7/C14), 128.3 (C11), 126.0 (C7/C14), 122.5 (C3), 28.9 (C6), 27.4 (C17), 20.0 (C16), 17.5 (C13) ppm. **FTIR** ν_{max} (thin film): 3026w, 2962m, 2922s, 2852m, 1599w, 1510s, 1447m, 1377w, 1100s, 1062w, 986s, 965m, 896w, 823m, 647s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{15}H_{20}NO^+$ $[M+H]^+$ 230.1539; found 230.1540 (Δ −0.35 ppm).

(9*H*-Fluoren-9-yl)methyl allylcarbamate (90)[28,29,163]



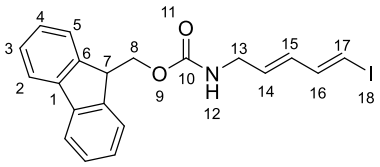
To a solution of allylamine (435 mL, 58.0 mmol) in 1,4-dioxane (387 mL) were added $NaHCO_3$ (9.74 g, 116 mmol) and 9-Fluorenylmethyl chloroformate (10.0 g, 38.7 mmol) at 0 °C. The solution was allowed to stir at room temperature for 22 h. The mixture was quenched with sat. aq. $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 300 mL). The layers were separated and the organic layers were combined, washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (25% $CHCl_3$/pentane) afforded carbamate **90** as a white solid (11.2 g, 99%). Data are consistent with those reported in the literature.[28,29,163] **m.p.** 124–126 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.78 (d, *J* = 7.6 Hz, 2 H, H^2), 7.61 (d, *J* = 7.3 Hz, 2 H, H^5), 7.42 (t, *J* = 7.5 Hz, 2 H, H^3), 7.33 (td, *J* = 7.5, 1.2 Hz, 2 H, H^4), 5.93–5.79 (m, 1 H, H^{14}), 5.24–5.11 (m, 2 H, H^{15}), 4.84 (br. s., 1 H, H^{12}), 4.44 (d, *J* = 7.1 Hz, 2 H, H^8), 4.24 (t, *J* = 6.8 Hz, 1 H, H^7), 3.84 (t, *J* = 5.3 Hz, 2 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.2 (C10), 143.9 (C6), 141.3 (C1), 134.4 (C14), 127.7 (C3), 127.0 (C4), 125.0 (C5), 120.0 (C2), 116.1 (C15), 66.7 (C8), 47.3 (C7), 43.5 (C13) ppm.

(9*H*-Fluoren-9-yl)methyl (*E*)-(4-oxobut-2-en-1-yl)carbamate (91)[28,29]



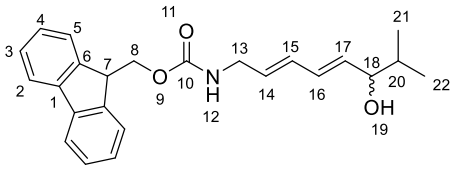
To a solution of carbamate **90** (500 mg, 1.79 mmol) in CH_2Cl_2 (59.7 mL) were added acrolein (1.20 mL, 17.9 mmol) and Hoveyda–Grubbs second-generation catalyst (34.0 mg, 3 mol%). The mixture was stirred at 40 °C for 23 h, then Hoveyda–Grubbs second-generation catalyst (11 mg, 1 mol%) was added. The mixture was refluxed for additional 9 h before adding a third batch of Hoveyda–Grubbs second-generation catalyst (11.0 mg, 1 mol%) and stirring the reaction at the same temperature for additional 23 h. The reaction was then allowed to cool to room temperature and concentrated *in vacuo* onto silica gel before purification by flash column chromatography (30% EtOAc/pentane) to afford aldehyde **91** as a pale yellow solid (498 mg, 90%). Data are consistent with those reported in the literature.[28,29] **m.p.** 103–106 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.58 (d, *J* = 7.7 Hz, 1 H, H^{16}), 7.78 (d, *J* = 7.6 Hz, 2 H, H^2), 7.60 (d, *J* = 7.3 Hz, 2 H, H^5), 7.42 (t, *J* = 7.3 Hz, 2 H, H^3), 7.33 (t, *J* = 7.3 Hz, 2 H, H^4), 6.79 (dt, *J* = 15.8, 4.5 Hz, 1 H, H^{14}), 6.18 (dd, *J* = 15.8, 7.7 Hz, 1 H, H^{15}), 5.02 (br. s., 1 H, H^{12}), 4.50 (d, *J* = 6.6 Hz, 2 H, H^8), 4.23 (t, *J* = 6.4 Hz, 1 H, H^7), 4.13–4.07 (m, 2 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 192.9 (C16), 158.0 (C10), 152.8 (C14), 143.7 (C6), 141.3 (C1), 131.9 (C15), 127.8 (C3), 127.1 (C4), 124.9 (C5), 120.0 (C2), 66.9 (C8), 47.2 (C7), 41.9 (C13) ppm.

(9*H*-Fluoren-9-yl)methyl ((2*E*,4*E*)-5-iodopenta-2,4-dien-1-yl)carbamate (76)[29]



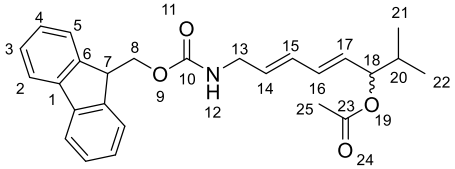
To a suspension of $CrCl_2$ (1.24 g, 10.1 mmol) in THF (15.6 mL) were added CHI_3 (0.630 g, 1.61 mmol) and aldehyde **91** (479 mg, 1.56 mmol) at 0 °C. The mixture was allowed to stir at room temperature for 17 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 30 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (40% Et_2O/pentane) afforded a 7.1:1 *E/Z*-mixture of iodide **76** as a pale yellow solid (340 mg, 51%). Data are consistent with those reported in the literature.[29] **m.p.** 133–135 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (major isomer) 7.78 (d, *J* = 7.6 Hz, 2 H, H^2), 7.60 (d, *J* = 7.3 Hz, 2 H, H^5), 7.42 (t, *J* = 7.3 Hz, 2 H, H^3), 7.32 (td, *J* = 7.5, 1.0 Hz, 2 H, H^4), 7.02 (dd, *J* = 14.4, 10.7 Hz, 1 H, H^{16}), 6.34 (d, *J* = 14.4 Hz, 1 H, H^{17}), 6.15–6.03 (m, 1 H, H^{15}), 5.77–5.66 (m, 1 H, H^{14}), 4.82 (br. s., 1 H, H^{12}), 4.45 (d, *J* = 6.6 Hz, 2 H, H^8), 4.23 (t, *J* = 6.6 Hz, 1 H, H^7), 3.82 (t, *J* = 5.3 Hz, 2 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.2 (C10), 144.2 (C16), 143.9 (C6), 141.3 (C1), 131.5 (C15), 130.4 (C14), 127.7 (C3), 127.0 (C4), 125.0 (C5), 120.0 (C2), 79.6 (C17), 66.7 (C8), 47.2 (C7), 42.7 (C13) ppm.

(9*H*-Fluoren-9-yl)methyl ((2*E*,4*E*)-6-hydroxy-7-methylocta-2,4-dien-1-yl)carbamate (201)



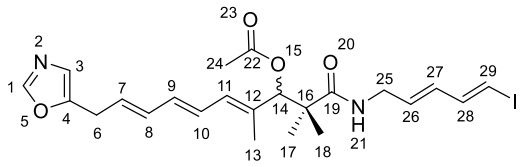
To a solution of isobutyraldehyde (28.0 µL, 310 µmol) in DMSO (3.10 mL) were added $CrCl_2$ (152 mg, 1.24 mmol), $NiCl_2$ (8.0 mg, 62.0 µmol) and iodide **76** (200 mg, 460 µmol). The resulting dark green solution was allowed to stir at room temperature for 22 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (3 × 20 mL) and with EtOAc (1 × 20 mL). The layers were separated and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% EtOAc/pentane) to afford alcohol **201** as a pale yellow solid (69.0 mg, 59%). **m.p.** 69.8–72.6 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.78 (d, *J* = 7.6 Hz, 2 H, H^2), 7.60 (d, *J* = 7.5 Hz, 2 H, H^5), 7.41 (t, *J* = 7.5 Hz, 2 H, H^3), 7.33 (t, *J* = 7.4 Hz, 2 H, H^4), 6.27–6.13 (m, 2 H, H^{16}, H^{15}), 5.76–5.64 (m, 2 H, H^{14}, H^{17}), 4.81 (br. s, 1 H, H^{12}), 4.44 (d, *J* = 6.9 Hz, 2 H, H^8), 4.24 (t, *J* = 6.9 Hz, 1 H, H^7), 3.95–3.83 (m, 3 H, H^{13}, H^{18}), 1.82–1.69 (m, 1 H, H^{20}), 0.93 (d, *J* = 6.8 Hz, 3 H, H^{21}), 0.89 (d, *J* = 6.8 Hz, 3 H, H^{22}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.2 (C10), 143.9 (C6), 141.3 (C1), 134.9 (C17), 131.3 (C15), 130.2 (C16), 129.3 (C14), 127.6 (C3), 127.0 (C4), 125.0 (C5), 119.9 (C2), 77.5 (C18), 66.7 (C8), 47.2 (C7), 42.6 (C13), 33.9 (C20), 18.2 (C21/C22), 17.9 (C21/C22) ppm. **FTIR** ν_{max} (thin film): 3321br, 2958w, 2363w, 1688s, 1534m, 1449w, 1256s, 1143w, 984s, 757m, 733s, 652w, 615w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{24}H_{27}NNaO_3^+$ $[M+Na]^+$ 400.1883; found 400.1873 (Δ −2.65 ppm).

(4*E*,6*E*)-8-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methylocta-4,6-dien-3-yl acetate (202)



To a solution of alcohol **201** (30.0 mg, 79.0 µmol) in pyridine (0.798 mL, 9.88 mmol) was added acetic anhydride (74.0 µL, 790 µmol) at 0°C. The solution was allowed to warm to room temperature and then stirred for 19 h. The reaction was treated with a solution of aq. 1 M HCl (10 mL), then with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The layers were separated and the organic layers were combined, washed with sat. aq. NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (40% Et_2O/pentane) to afford acetate **202** as a pale yellow oil (26.0 mg, 79%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.78 (d, *J* = 7.6 Hz, 2 H, H^2), 7.60 (d, *J* = 7.3 Hz, 2 H, H^5), 7.41 (t, *J* = 7.5 Hz, 2 H, H^3), 7.32 (td, *J* = 7.3, 1.0 Hz, 2 H, H^4), 6.27–6.09 (m, 2 H, H^{16}, H^{15}), 5.76–5.65 (m, 1 H, H^{14}), 5.59 (dd, *J* = 14.8, 7.5 Hz, 1 H, H^{17}), 5.07 (t, *J* = 6.8 Hz, 1 H, H^{18}), 4.86 (br. s., 1 H, H^{12}), 4.43 (d, *J* = 6.8 Hz, 2 H, H^8), 4.23 (t, *J* = 6.9 Hz, 1 H, H^7), 3.86 (t, *J* = 5.5 Hz, 2 H, H^{13}), 2.08 (s, 3 H, H^{25}), 1.82–1.94 (m, 1 H, H^{20}), 0.92 (d, *J* = 7.0 Hz, 3 H, H^{21}), 0.89 (d, *J* = 7.0 Hz, 3 H, H^{22}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.4 (C23), 156.2 (C10), 143.9 (C6), 141.3 (C1), 132.3 (C16), 131.0 (C15), 130.2 (C14), 130.0 (C17), 127.6 (C3), 127.0 (C4), 125.0 (C5), 119.9 (C2), 78.9 (C18), 66.7 (C8), 47.2 (C7), 42.6 (C13), 32.1 (C20), 21.2 (C25), 18.0 (C21, C22) ppm. **FTIR** ν_{max} (thin film): 3338br, 2963w, 1726s, 1524m, 1450w, 1370w, 1239s, 1139w, 990m, 759m, 741m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{26}H_{29}NNaO_4^+$ $[M+Na]^+$ 442.1989; found 442.1991 (Δ −0.42 ppm).

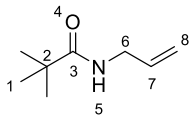
(4*E*,6*E*,8*E*)-1-(((2*E*,4*E*)-5-Iodopenta-2,4-dien-1-yl)amino)-2,2,4-trimethyl-10-(oxazol-5-yl)-1-oxodeca-4,6,8-trien-3-yl acetate (204)



To a solution of racemic acid **41** (19.5 mg, 58.5 μmol) in CH_2Cl_2 (0.910 mL) was added BOPCl (18.5 mg, 73.0 μmol) and Et_3N (20.3 μL, 0.146 mmol). The solution was allowed to stir at room temperature for 2 h. To a solution of iodide **76** (12.6 mg, 29.3 μmol) in CH_2Cl_2 (0.910 mL) was added DBU (6.50 μL, 43.8 μmol) and the resulting solution allowed to stir at room temperature for 1 h. To the solution containing the activated acid was added the mixture of free amine prepared from iodide **76**. This mixture was allowed to stir at room temperature for 5 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (50% EtOAc/pentane) to afford amide **204** as a pale yellow oil (10.4 mg, 68%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.80 (s, 1 H, H^1), 7.05–6.94 (m, 1 H, H^{28}), 6.81 (s, 1 H, H^3), 6.40–6.28 (m, 2 H, H^{10}, H^{29}), 6.27–6.16 (m, 2 H, H^8, H^9), 6.14–5.97 (m, 2 H, H^{27}, H^{11}), 5.97–5.88 (m, 1 H, H^{21}), 5.83–5.73 (m, 1 H, H^7), 5.73–5.63 (m, 1 H, H^{26}), 5.30 (s, 1 H, H^{14}), 3.92–3.81 (m, 2 H, H^{25}), 3.50 (t, *J* = 6.0 Hz, 2 H, H^6), 2.07 (s, 3 H, H^{24}), 1.79–1.73 (m, 3 H, H^{13}), 1.26 (s, 3 H, H^{17}), 1.21 (s, 3 H, H^{18}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 174.8 (C19), 169.4 (C22), 150.8 (C1), 150.4 (C4), 144.1 (C28), 133.9 (C12), 133.3 (C8/C9), 132.9 (C8/C9), 131.9 (C27), 130.2 (C26), 129.2 (C11), 127.8 (C7), 127.7 (C10), 122.5 (C3), 82.5 (C14), 79.7 (C29), 46.4 (C16), 40.9 (C25), 28.9 (C6), 22.9 (C18), 21.9 (C17), 21.0 (C24), 15.1 (C13) ppm. **FTIR** ν_{max} (thin film): 3361br, 3028w, 2921w,

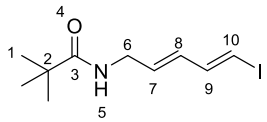
1737s, 1651m, 1511m, 1369w, 1237s, 1100w, 1025w, 984m, 802w, 647w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{23}H_{29}IN_2NaO_4^+$ $[M+Na]^+$ 547.1064; found 547.1063 (Δ −0.29 ppm).

***N*-Allylpivalamide (206)**[164]



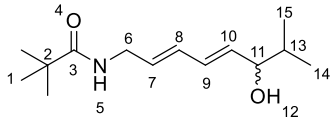
To a solution of pivalic acid (272 mg mg, 2.66 mmol) in CH_2Cl_2 (83.0 mL) was added BOPCl (846 mg, 3.32 mmol) and Et_3N (0.93 mL, 6.65 mmol). The solution was allowed to stir at room temperature for 2 h. To the solution containing the activated acid was added allylamine (100 μL, 1.33 mmol). This mixture was allowed to stir at room temperature for 5 h. The reaction was diluted with EtOAc (50 mL) and successively washed with sat. aq. NH_4Cl (100 mL), sat. aq. $NaHCO_3$ (100 mL) and sat. aq. NaCl (100 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% EtOAc/pentane) to afford amide **206** as a white solid (181 mg, 96%). Data are consistent with those reported in the literature.[164] **m.p.** 35.8–37.7°C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.93–5.77 (m, 1 H, H^7), 5.68 (br. s, 1 H, H^5), 5.23–5.09 (m, 2 H, H^8), 3.92–3.86 (m, 2 H, H^6), 1.22 (s, 9 H, H^1) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 178.7 (C3), 134.5 (C7), 116.1 (C8), 41.9 (C6), 38.7 (C2), 27.6 (C1) ppm.

***N*-((2*E*,4*E*)-5-Iodopenta-2,4-dien-1-yl)pivalamide (207)**



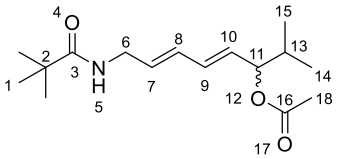
To a solution of pivalic acid (14.0 mg, 0.139 mmol) in CH_2Cl_2 (2.16 mL) were added BOPCl (44.6 mg, 0.174 mmol) and Et_3N (48.0 μL, 0.348 mmol). The solution was allowed to stir at room temperature for 3 h. To a solution of iodide **76** (30.0 mg, 0.0695 mmol) in CH_2Cl_2 (2.16 mL) was added DBU (16.0 μL, 0.104 mmol) and the resulting solution allowed to stir at room temperature for 1.5 h. To the solution containing the activated acid was added the mixture of free amine prepared from iodide **76**. The resulting mixture was allowed to stir at room temperature for 5.5 h. The reaction was diluted with EtOAc (15 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (30% EtOAc/pentane) to afford amide **207** as a pale yellow oil (15.1 mg, 74%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.01 (dd, *J* = 14.4, 10.7 Hz, 1 H, H^9), 6.33 (d, *J* = 14.4 Hz, 1 H, H^{10}), 6.08 (dd, *J* = 15.0, 10.7 Hz, 1 H, H^8), 5.76–5.66 (m, 1 H, H^7), 3.86 (t, *J* = 6.1 Hz, 2 H, H^6), 3.66–3.56 (m, 1 H, H^5), 1.21 ppm (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.2 (C3), 144.2 (C9), 131.7 (C7), 130.5 (C8), 79.4 (C10), 40.8 (C6), 38.7 (C2), 27.6 (C1) ppm. **FTIR** ν_{max} (thin film): 3339br, 2962m, 1640s, 1528s, 1481w, 1366w, 1291w, 1210w, 978m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{10}H_{16}INNaO^+$ $[M+Na]^+$ 316.0169; found 316.0168 (Δ −0.39 ppm).

***N*-((2*E*,4*E*)-6-Hydroxy-7-methylocta-2,4-dien-1-yl)pivalamide (208)**



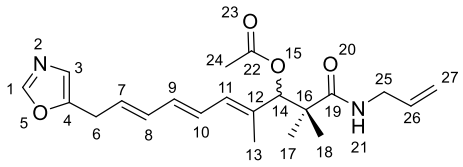
To a solution of pivalic acid (12.4 mg, 122 μmol) in CH_2Cl_2 (1.91 mL) was added BOPCl (38.8 mg, 152 μmol) and Et_3N (42.0 μL, 305 μmol). The solution was allowed to stir at room temperature for 3 h. To a solution of alcohol **201** (23.0 mg, 60.9 μmol) in CH_2Cl_2 (1.91 mL) was added DBU (13.6 μL, 91.0 μmol) and the resulting solution allowed to stir at room temperature for 3 h. To the solution containing the activated acid was added the mixture of free amine prepared from alcohol **201**. This mixture was allowed to stir at room temperature for 3 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (60% EtOAc/pentane) to afford amide **208** as a pale yellow oil (8.6 mg, 59%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.27–6.09 (m, 2 H, H^9, H^8), 5.77–5.60 (m, 3 H, H^{10}, H^7, H^5), 3.97–3.85 (m, 3 H, H^6, H^{11}), 1.80–1.64 (m, 2 H, H^{13}, H^{12}), 1.21 (s, 9 H, H^1), 0.93 (d, *J* = 6.8 Hz, 3 H, H^{15}), 0.89 (d, *J* = 6.8 Hz, 3 H, H^{14}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.2 (C3), 134.7 (C10), 131.5 (C8), 130.3 (C9), 129.4 (C7), 77.5 (C11), 41.2 (C6), 38.7 (C2), 33.9 (C13), 27.6 (C9), 18.2 (C14), 17.9 (C15) ppm. **FTIR** ν_{max} (thin film): 3346 br, 2958m, 2871w, 1641s, 1534s, 1482w, 1463w, 1424w, 1366m, 1292w, 1210m, 1027w, 988s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{14}H_{25}O_2NNa^+$ $[M+Na]^+$ 262.1778; found 262.1777 (Δ −0.06 ppm).

(4*E*,6*E*)-2-Methyl-8-pivalamidoocta-4,6-dien-3-yl acetate (209)



To a solution of pivalic acid (9.2 mg, 90.4 μmol) in CH_2Cl_2 (1.40 mL) was added BOPCl (28.8 mg, 113 μmol) and Et_3N (31.0 μL, 226 μmol). The solution was allowed to stir at room temperature for 3 h. To a solution of acetate **202** (19.0 mg, 45.2 μmol) in CH_2Cl_2 (1.40 mL) was added DBU (10.0 μL, 67.8 μmol) and the resulting solution allowed to stir at room temperature for 3 h. To the solution containing the activated acid was added the mixture of free amine prepared from acetate **202**. This mixture was allowed to stir at room temperature for 3 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (25% EtOAc/pentane) to afford amide **209** as a pale yellow oil (10.2 mg, 80%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.27–6.07 (m, 2 H, H^9, H^8), 5.68 (m, 2 H, H^7, H^5), 5.61–5.53 (m, 1 H, H^{10}), 5.05 (t, *J* = 6.8 Hz, 1 H, H^{11}), 3.90 (t, *J* = 5.9 Hz, 2 H, H^6), 2.06 (s, 3 H, H^{18}), 1.94–1.80 (m, 1 H, H^{13}), 1.21 (s, 9 H, H^1), 0.90 (d, *J* = 6.8 Hz, 3 H, H^{15}), 0.89 (d, *J* = 6.8 Hz, 3 H, H^{14}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 178.2 (C3), 170.4 (C16), 132.4 (C9), 131.2 (C8), 130.3 (C7), 129.9 (C10), 79.0 (C11), 41.2 (C6), 38.7 (C2), 32.1 (C13), 27.6 (C1), 21.2 (C18), 18.1 (C14), 18.0 (C15) ppm. **FTIR** ν_{max} (thin film): 3357br, 2962m, 1734s, 1641s, 1526s, 1369m, 1238s, 1207m, 1096w, 1018m, 989m, 802w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{16}H_{27}O_3NNa^+$ $[M+Na]^+$ 304.1883; found 304.1882 (Δ −0.47 ppm).

(4*E*,6*E*,8*E*)-1-(Allylamino)-2,2,4-trimethyl-10-(oxazol-5-yl)-1-oxodeca-4,6,8-trien-3-yl acetate (210)



Method A:

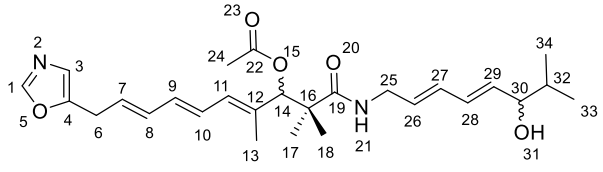
To a solution of racemic acid **41** (8.0 mg, 27.0 μmol) in CH_2Cl_2 (0.810 mL) was added BOPCl (8.3 mg, 32.5 μmol) and Et_3N (9.00 μL, 65.0 μmol). The solution was allowed to stir at room temperature for 2 h. To the solution containing the activated acid was added allylamine (1.0 μL, 13.0 μmol). This mixture was allowed to stir at room temperature for 6 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (60% EtOAc/pentane) to afford amide **210** as a pale yellow oil (5.5 mg, 55%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.80 (s, 1 H, H^1), 6.80 (s, 1 H, H^3), 6.40–6.30 (m, 1 H, H^{10}), 6.28–6.17 (m, 2 H, H^8, H^9), 6.10–6.01 (m, 1 H, H^{11}), 5.96–5.90 (m, 1 H, H^{21}), 5.90–5.79 (m, 1 H, H^{26}), 5.79–5.71 (m, 1 H, H^7), 5.30 (s, 1 H, H^{14}), 5.24–5.11 (m, 2 H, H^{27}), 3.92–3.84 (m, 2 H, H^{25}), 3.49 (d, *J* = 6.8 Hz, 2 H, H^6), 2.08 (s, 3 H, H^{24}), 1.77 (s, 3 H, H^{13}), 1.26 (s, 3 H, H^{17}), 1.21 (s, 3 H, H^{18}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 174.8 (C19), 169.4 (C22), 155.9 (C1), 149.8 (C4), 134.2 (C12), 133.9 (C26), 133.4 (C8/C9), 132.8 (C8/C9), 129.2 (C11), 127.8 (C10), 127.6 (C7), 120.9 (C3), 116.4 (C27), 82.7 (C14), 46.3 (C16), 42.0 (C25), 28.8 (C6), 23.2 (C18), 21.7 (C17), 21.0 (C24), 15.0 (C13) ppm. **FTIR** ν_{max} (thin film): 3371br, 2981w, 2917w, 1741s, 1658m, 1641w, 1511m, 1369m,

1236s, 1160w, 1028w, 986w, 965m, 922w, 647w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{21}H_{28}O_4N_2Na^+$ $[M+Na]^+$ 395.1941; found 395.1938 (Δ −0.87 ppm).

Method B:

To a solution of racemic acid **41** (12.2 mg, 42.0 μmol) in CH_2Cl_2 (0.660 mL) was added BOPCl (13.4 mg, 52.5 μmol) and Et_3N (14.6 μL, 105 μmol). The solution was allowed to stir at room temperature for 2 h. To a solution of carbamate **90** (5.8 mg, 21.0 μmol) in CH_2Cl_2 (0.660 mL) was added DBU (4.7 μL, 31.5 μmol) and the resulting solution allowed to stir at room temperature for 1 h. To the solution containing the activated acid was added the mixture of free amine prepared from carbamate **90**. This mixture was allowed to stir at room temperature for 5 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (60% EtOAc/pentane) to afford amide **210** as a pale yellow oil (6.9 mg, 88%).

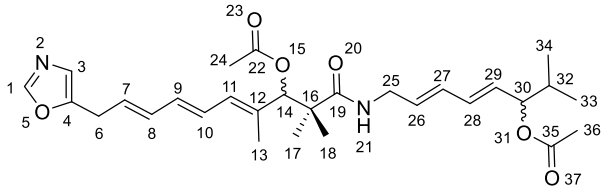
(4*E*,6*E*,8*E*)-1-(((2*E*,4*E*)-6-Hydroxy-7-methylocta-2,4-dien-1-yl)amino)-2,2,4-trimethyl-10-(oxazol-5-yl)-1-oxodeca-4,6,8-trien-3-yl acetate (211)



To a solution of racemic acid **41** (16.1 mg, 48.0 μmol) in CH_2Cl_2 (0.750 mL) was added BOPCl (15.3 mg, 60.1 μmol) and Et_3N (16.7 μL, 120 μmol). The solution was allowed to stir at room temperature for 3 h. To a solution of alcohol **201** (9.1 mg, 24.0 μmol) in CH_2Cl_2

(0.750 mL) was added DBU (5.40 μL, 36.0 μmol) and the resulting solution allowed to stir at room temperature for 1 h. To the solution containing the activated acid was added the mixture of free amine prepared from alcohol **201**. This mixture was allowed to stir at room temperature for 5 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (80% EtOAc/pentane) to afford amide **211** as a pale yellow oil (6.5 mg, 58%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.79 (s, 1 H, H^1), 6.80 (s, 1 H, H^3), 6.41–6.29 (m, 1 H, H^{10}), 6.28–6.14 (m, 4 H, H^8, H^9, H^{27}, H^{28}), 6.10–6.01 (m, 1 H, H^{11}), 5.89 (m, 1 H, H^{21}), 5.81–5.74 (m, 1 H, H^7), 5.74–5.61 (m, 2 H, H^{26}, H^{29}), 5.31 (s, 1 H, H^{14}), 3.94–3.86 (m, 3 H, H^{25}, H^{30}), 3.52–3.47 (m, 2 H, H^6), 2.07 (s, 3 H, H^{24}), 1.81–1.71 (m, 4 H, H^{13}, H^{32}), 1.27–1.25 (s, 3 H, H^{17}), 1.21 (s, 3 H, H^{18}), 0.93 (d, J = 6.8 Hz, 3 H, H^{33}), 0.90 (d, J = 6.8 Hz, 3 H, H^{34}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 174.9 (C19), 169.5 (C22), 153.2 (C1), 150.9 (C4), 135.0 (C26), 133.4 (C8/C9), 132.8 (C8/C9), 131.8 (C27/C28), 130.2 (C27/C28), 129.1 (C11), 128.5 (C29), 127.8 (C10), 127.7 (C7), 122.7 (C3), 117.1 (C12), 82.6 (C14), 77.2 (C30), 44.5 (C16), 41.3 (C25), 34.0 (C32), 28.8 (C6), 23.0 (C17), 21.8 (C18), 21.0 (C24), 18.2 (C33), 17.9 (C34), 15.0 (C13) ppm. **FTIR** ν_{max} (thin film): 3374br, 2958m, 2921m, 2851w, 1740s, 1650m, 1511w, 1466w, 1371w, 1237s, 1104w, 1026w, 989w, 647w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{27}H_{38}O_5N_2Na^+$ $[M+Na]^+$ 493.2673; found 493.2672 (Δ −0.17 ppm).

(4*E*,6*E*)-8-((4*E*,6*E*,8*E*)-3-Acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienamido)-2-methylocta-4,6-dien-3-yl acetate (212)



Method A:

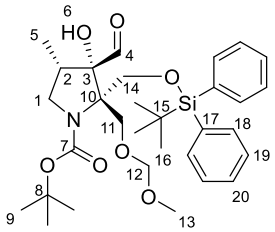
To a solution of racemic acid **41** (12.7 mg, 38.0 µmol) in CH_2Cl_2 (420 µL) was added BOPCl (8.6 mg, 33.8 µmol) and Et_3N (9.4 µL, 67.5 µmol). The solution was allowed to stir at room temperature for 3 h. To a solution of acetate **202** (5.7 mg, 13.5 µmol) in CH_2Cl_2 (420 µL) was added DBU (3.0 µL, 20.1 µmol) and the resulting solution allowed to stir at room temperature for 1 h. To the solution containing the activated acid was added the mixture of free amine prepared from acetate **202**. This mixture was allowed to stir at room temperature for 3 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (50% EtOAc/pentane) to afford amide **212** as a pale yellow oil (4.9 mg, 71%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.80 (s, 1 H, H^1), 6.81 (s, 1 H, H^3), 6.41–6.29 (m, 1 H, H^{10}), 6.29–6.08 (m, 4 H, H^8, H^9, H^{27}, H^{28}), 6.05 (d, *J* = 11.5 Hz, 1 H, H^{11}), 5.90–5.83 (m, 1 H, H^{21}), 5.82–5.73 (m, 1 H, H^7), 5.73–5.64 (m, 1 H, H^{26}), 5.62–5.53 (m, 1 H, H^{29}), 5.30 (s, 1 H, H^{14}), 5.08–5.01 (m, 1 H, H^{30}), 4.00–3.82 (m, 2 H, H^{25}), 3.52–3.46 (m, 2 H, H^6), 2.07 (2 s, 6 H, H^{24}, H^{36}), 1.92–1.82 (m, 1 H, H^{32}), 1.77 (s, 3 H, H^{13}), 1.26 (s, 3 H, H^{17}), 1.21 (s, 3 H, H^{18}), 0.90 (d, *J* = 7.1 Hz, 3 H, H^{34}), 0.89 (d, *J* = 7.1 Hz, 3 H, H^{33}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 174.8 (C19), 170.4 (C22), 169.4 (C35), 150.7 (C1), 150.4 (C4), 133.9 (C12), 133.4 (C8/C9), 132.8 (C8/C9), 132.3 (C27/C28), 131.5

(C27/C28), 130.1 (C29), 129.9 (C26), 129.2 (C11), 127.8 (C10), 127.7 (C7), 122.5 (C3), 82.6 (C14), 78.9 (C30), 46.3 (C16), 41.2 (C25), 32.1 (C32), 28.9 (C6), 23.1 (C18), 21.6 (C17), 21.2 (C24/C36), 21.0 (C24/C36), 18.1 (C33), 18.0 (C34), 15.1 (C13) ppm. **FTIR** ν_{max} (thin film): 3387br, 2963w, 1734m, 1651w, 1527w, 1511w, 1370w, 1260s, 1236m, 1096m, 1015s, 987w, 864w, 820w, 795s, 705w, 647w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{29}H_{40}O_6N_2Na^+$ $[M+Na]^+$ 535.2779; found 535.2775 (Δ −0.62 ppm).

Method B:

To a solution of racemic acid **41** (13.0 mg, 39.0 µmol) in CH_2Cl_2 (200 µL) were added $SOCl_2$ (4.8 µL, 66.3 µmol) and DMF (1 drop) at 0 °C. The solution was allowed to warm to room temperature over 2 h. To a solution of acetate **202** (3.3 mg, 7.8 µmol) in CH_2Cl_2 (200 µL) was added DBU (14.6 µL, 97.5 µmol) and the resulting solution allowed to stir at room temperature for 1 h. To the solution containing the activated acid was added the mixture of free amine prepared from acetate **202**. This mixture was allowed to stir at room temperature for 5 h. The reaction was diluted with EtOAc (5 mL) and successively washed with sat. aq. NH_4Cl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dried onto silica gel and purified by flash column chromatography (50% EtOAc/pentane) to afford amide **212** as a pale yellow oil (10.7 mg, 54%).

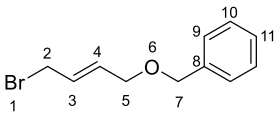
***tert*-Butyl (2*S*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-formyl-3-hydroxy-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (101)**[50]



To a solution of homoallylic alcohol **107** (4.00 g, 6.85 mmol) and Grubbs second-generation catalyst (145 mg, 2.5 mol%) in toluene (68.5 mL) was added vinyloxytrimethyl silane (10.2 mL, 68.5 mmol) and the reaction mixture was heated at reflux for 7 h. Then, another portion of Grubbs second-generation catalyst (145 mg, 2.5 mol%) was added and the mixture stirred for a further 39 h (at which point the reaction was judged to be complete by ^{1}H NMR analysis). The mixture was cooled to room temperature and concentrated *in vacuo* to yield a brown oil. The residue was dissolved in CH_2Cl_2 (137 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 20 min until the starting material was completely consumed (as observed by TLC analysis). Nitrogen gas was bubbled through the solution and Me_2S (10.1 mL, 137 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 20 h. The mixture was washed with sat. aq. NaCl (3 × 60 mL) and the layers were separated. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% Et_2O/pentane) to afford aldehyde **101** as a white solid (3.44 g, 88%). Data are consistent with those reported in the literature.[50] **m.p.** 102.6–104.7 °C. **[α]$_D^{25}$** −28.6 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (1.5:1 mixture of Boc rotamers) (major rotamer) 9.83 (s, 1 H, H^4), 7.69–7.55 (m, 4 H, H^{18}), 7.48–7.33 (m, 6 H, H^{19}, H^{20}), 4.65 (d, *J* = 6.4 Hz, 1 H, H^{12a}), 4.59 (d, *J* = 6.4 Hz, 1 H, H^{12b}), 4.30–3.89 (m, 5 H, H^{14}, H^{11}, H^6), 3.86 (dd, *J* = 10.0, 8.3 Hz, 1 H, H^{1a}), 3.34 (s, 3 H, H^{13}), 3.24–3.11 (m, 1 H, H^{1b}), 3.05–2.85 (m,

1 H, H^2), 1.13 (s, 9 H, H^9), 1.02 (s, 9 H, H^{16}), 0.85 (d, *J* = 6.4 Hz, 3 H, H^5) ppm; (minor rotamer) 9.77 (s, 1 H, H^4), 7.70–7.56 (m, 4 H, H^{18}), 7.47–7.33 (m, 6 H, H^{19}, H^{20}), 4.59 (d, *J* = 6.4 Hz, 1 H, H^{12a}), 4.54 (d, *J* = 6.4 Hz, 1 H, H^{12b}), 4.30–3.89 (m, 5 H, H^{14}, H^{11}, H^6), 3.77 (dd, *J* = 10.0, 8.3 Hz, 1 H, H^{1a}), 3.32 (s, 3 H, H^{13}), 3.24–3.11 (m, 1 H, H^{1b}), 3.05–2.86 (m, 1 H, H^2), 1.38 (s, 9 H, H^9), 1.02 (s, 9 H, H^{16}), 0.84 (d, *J* = 6.4 Hz, 3 H, H^5) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = (major rotamer) 200.7 (C4), 152.8 (C7), 135.7 (C18), 135.5 (C18), 132.4 (C17), 132.4 (C17), 129.9 (C19), 129.8 (C19), 127.8 (C20), 127.8 (C20), 96.7 (C12), 88.6 (C3), 80.2 (C8), 73.0 (C10), 67.1 (C11/C14), 65.4 (C11/C14), 55.7 (C13), 53.6 (C1), 35.0 (C2), 28.1 (C9), 26.7 (C16), 19.1 (C15), 9.2 (C5) ppm; (minor rotamer) 200.6 (C4), 152.9 (C7), 135.7 (C18), 135.5 (C18), 132.4 (C17), 132.4 (C17), 129.8 (C19), 129.8 (C19), 127.7 (C20), 127.7 (C20), 96.8 (C12), 87.8 (C3), 79.4 (C8), 73.1 (C10), 66.4 (C11/C14), 64.8 (C11/C14), 55.7 (C13), 53.5 (C1), 35.5 (C2), 28.4 (C9), 26.7 (C16), 19.1 (C15), 9.2 (C5) ppm. [N.B. alcohol **107** had been synthesised by Dr Manuel Peifer].[50,139]

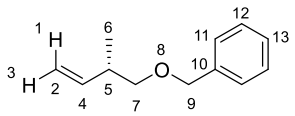
(*E*)-(((4-Bromobut-2-en-1-yl)oxy)methyl)benzene (214)[136]



To a solution of *trans*-1,4-dibromo-2-butene (25.0 g, 117 mmol) and tetrabutylammonium hydrogensulfate (3.97 g, 11.7 mmol) in CH_2Cl_2 (106 mL) was added aq. 2 M NaOH (58.5 mL, 117 mmol). Benzyl alcohol (13.3 mL, 129 mmol) was added over 20 min and the reaction mixture was allowed to stir at room temperature for 16 h. The reaction was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The layers were separated and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50%

CH_2Cl_2/pentane) to afford bromide **214** as a colourless oil (13.0 g, 46%). Data are consistent with those reported in the literature.[136] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.42–7.28 (m, 5 H, H^9, H^{10}, H^{11}), 6.06–5.86 (m, 2 H, H^3, H^4), 4.54 (s, 2 H, H^7), 4.06 (d, *J* = 5.1 Hz, 2 H, H^5), 3.99 (d, *J* = 7.1 Hz, 2 H, H^2) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 137.9 (C8), 131.6 (C4), 128.7 (C3), 128.4 (C10), 127.7 (C9), 127.7 (C11), 72.3 (C7), 69.3 (C5), 32.0 (C2) ppm.

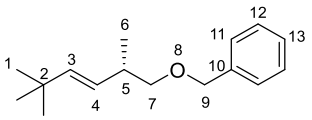
(*S*)-(((2-Methylbut-3-en-1-yl)oxy)methyl)benzene (109)[62]



To a solution of (*R*$_P$,*R*)-Taniaphos (213 mg, 311 μmol) in CH_2Cl_2 (47.8 mL) was added CuBr·Me_2S (49.0 mg, 239 μmol) and the mixture was stirred for 10 min, then cooled to −78 °C. A solution of methylmagnesium bromide (9.56 mL, 3 M solution in Et_2O, 28.7 mmol) was added dropwise over 30 min at −78 °C. A solution of bromide **214** (5.76 g, 23.9 mmol) in CH_2Cl_2 (12.0 mL) was added dropwise by syringe-pump over 2.5 h at −78 °C, and the reaction mixture was stirred for a further 36 h. The reaction mixture was quenched by the addition of MeOH (11.5 mL) and warmed to room temperature. The mixture was poured into Et_2O (50.0 mL), then washed with sat. aq. NH_4Cl (50.0 mL). The layers were separated and the organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% CH_2Cl_2/pentane) to afford alkene **109** as a colourless oil (4.20 g, 99%). Data are consistent with those reported in the literature.[62] **$[\alpha]_D^{25}$** −5.11 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.40–7.28 (m, 5 H, H^{11}, H^{12}, H^{13}), 5.84 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H, H^4), 5.11 (d, *J* = 17.4 Hz, 1 H, H^1), 5.06 (d, *J* = 10.5 Hz, 1 H, H^3), 4.56 (s, 2 H, H^9), 3.42 (dd, *J* = 8.9, 6.7 Hz, 1 H, H^{7a}), 3.34 (dd, *J* = 9.0, 6.8 Hz, 1 H, H^{7b}), 2.62–2.47 (m, 1 H,

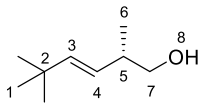
H^5), 1.08 (d, *J* = 6.8 Hz, 3 H, H^6) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 141.3 (C2), 138.6 (C8), 128.3 (C10), 127.5 (C9), 127.4 (C11), 114.0 (C1), 75.0 (C5), 72.9 (C7), 37.8 (C3), 16.6 (C4) ppm.

(*S*,*E*)-(((2,5,5-Trimethylhex-3-en-1-yl)oxy)methyl)benzene (215)[50]



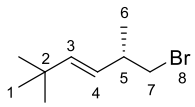
To 3,3-dimethyl-1-butene (52.0 mL, 403 mmol) was added Hoveyda–Grubbs second-generation catalyst (355 mg, 10 mol%) and the mixture was heated at reflux. A solution of alkene **109** (1.00 g, 5.67 mmol) in 3,3-dimethyl-1-butene (13.0 mL, 101 mmol) was added dropwise by syringe-pump over 7 h. The reaction mixture was stirred at 60 °C for 16 h then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% CH_2Cl_2/pentane) to afford alkene **215** as a colourless oil (729 mg, 55%). Data are consistent with those reported in the literature.[50] **[α]$_D^{25}$** −1.25 (c 1.0, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.30–7.17 (m, 5 H, H^{11}, H^{12}, H^{13}), 5.42 (dd, *J* = 15.7, 1.0 Hz, 1 H, H^3), 5.17 (dd, *J* = 15.7, 7.2 Hz, 1 H, H^4), 4.44 (s, 2 H, H^9), 3.28 (dd, *J* = 9.2, 6.2 Hz, 1 H, H^{7a}), 3.18 (dd, *J* = 9.2, 7.2 Hz, 1 H, H^{7b}), 2.46–2.28 (m, 1 H, H^5), 0.94 (d, *J* = 6.6 Hz, 3 H, H^6), 0.92 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 141.2 (C3), 138.8 (C10), 128.3 (C12), 127.5 (C11), 127.4 (C13), 127.1 (C4), 75.7 (C7), 72.8 (C9), 36.8 (C5), 32.8 (C2), 29.7 (C1), 17.5 (C6) ppm.

(*S*,*E*)-2,5,5-Trimethylhex-3-en-1-ol (216)



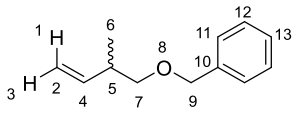
Ammonia (77.5 mL) was distilled into a 3-necked round-bottomed flask at −78 °C. Lithium wire (107 mg, 15.4 mmol) was cut into small pieces and added to the solution resulting in a colour change from colourless to blue. A solution of alkene **215** (1.62 g, 6.97 mmol) in THF (15.0 mL) was added and the mixture was stirred for 1.5 h, then quenched by the addition of MeOH (2.00 mL) resulting in the loss of the blue colour. The mixture was warmed to room temperature and the ammonia was allowed to evaporate. The residue was diluted with Et_2O (40 mL) and the mixture was washed with sat. aq. NH_4Cl (20 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to about 10 mL in volume. The crude residue was purified by flash column chromatography (20% Et_2O/pentane) to afford alcohol **216** as a colourless oil (0.991 g, quantitative). $[\alpha]_D^{25}$ −39.0 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.58 (dd, *J* = 15.7, 1.0 Hz, 1 H, H^3), 5.14 (dd, *J* = 15.7, 8.1 Hz, 1 H, H^4), 3.51–3.43 (m, 1 H, H^{7a}), 3.37–3.29 (m, 1 H, H^{7b}), 2.35–2.22 (m, 1 H, H^5), 1.37 (dd, *J* = 8.1, 4.2 Hz, 1 H, H^8), 1.01 (s, 9 H, H^1), 0.98 (d, *J* = 6.8 Hz, 3 H, H^6) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 143.8 (C3), 126.6 (C4), 67.3 (C7), 39.7 (C5), 33.0 (C2), 29.8 (C1), 16.7 (C6) ppm. **FTIR** ν_{max} (thin film): 3331br, 2957s, 2868m, 1462m, 1362m, 1033s, 972s, 951w cm^{-1}. **HRMS** (CI^+): Calculated for $C_9H_{22}NO^+$ $[M+NH_4]^+$ 160.1696; found 160.1695 (Δ +0.57 ppm).

(*S*,*E*)-1-Bromo-2,5,5-trimethylhex-3-ene (100)[50]



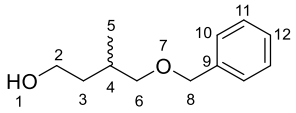
To a solution of alcohol **216** (944 mg, 6.64 mmol) in CH_2Cl_2 (6.60 mL) was added Et_3N (1.11 mL, 7.96 mmol). To a solution of triphenylphosphine (1.92 g, 7.30 mmol) in CH_2Cl_2 (13.1 mL) was added bromine (0.410 mL, 7.96 mmol) at 0 °C, and the resulting suspension was allowed to stir for 10 min. The solution of alcohol **216** and Et_3N was added dropwise to the latter suspension over 10 min, and the reaction mixture was stirred for 1 h. The mixture was concentrated *in vacuo*. The crude residue was kept at 4 °C for 1 h, filtered and the fitrate was purified by flash column chromatography (100% pentane) to afford bromide **100** as a colourless oil (1.20 g, 81%). Data are consistent with those reported in the literature.[50] **[α]$_D^{25}$** −20.2 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.53 (dd, *J* = 15.7, 1.0 Hz, 1 H, H^3), 5.20 (dd, *J* = 15.7, 7.3 Hz, 1 H, H^4), 3.35 (dd, *J* = 9.5, 5.4 Hz, 1 H, H^{7a}), 3.25 (dd, *J* = 9.5, 7.3 Hz, 1 H, H^{7b}), 2.53–2.41 (m, 1 H, H^5), 1.11 (d, *J* = 6.6 Hz, 3 H, H^6), 0.99 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 142.6 (C3), 126.7 (C4), 40.4 (C7), 38.9 (C5), 32.9 (C2), 29.6 (C1), 19.2 (C6) ppm. **FTIR** ν_{max} (thin film): 2959s, 2868w, 1475w, 1460w, 1363m, 1260w, 1226w, 971s, 949m, 653m cm^{-1}. **HRMS** (EI^+): Calculated for $C_9H_{17}{}^{79}Br^+$ $[M]^+$ 204.0514; found 204.0511 (Δ −0.20 ppm).

(((2-Methylbut-3-en-1-yl)oxy)methyl)benzene ((±)-109)[50,165]



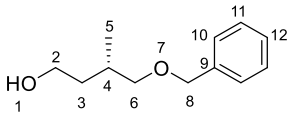
A solution of (±)-2-methyl-3-buten-1-ol (1.19 mL, 11.6 mmol) in DMF (5.00 mL) was added to a suspension of sodium hydride (696 mg, 60% dispersion in mineral oil, 17.4 mmol) in DMF (20.0 mL). The mixture was allowed to stir at room temperature for 10 min, then cooled to 0 °C. Benzyl bromide (1.66 mL, 13.9 mmol) was added dropwise over 2 min and the reaction was allowed to gradually warm to room temperature and stirred for 25 h. The reaction mixture was quenched by the addition of H_2O (5.00 mL), then diluted with Et_2O (30 mL). The layers were separated and the organic phases were washed with sat. aq. NaCl (3 × 10 mL), then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% CH_2Cl_2/pentane) to afford racemic alkene **109** as a colourless oil (1.62 g, 79%). Data are consistent with those reported in the literature.[50,165] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.43–7.26 (m, 5 H, H^{11}, H^{12}, H^{13}), 5.85 (ddd, *J* = 17.3, 10.5, 7.0 Hz, 1 H, H^4), 5.11 (d, *J* = 17.4 Hz, 1 H, H^1), 5.06 (d, *J* = 10.4 Hz, 1 H, H^3), 4.56 (s, 2 H, H^9), 3.43 (dd, *J* = 9.0, 6.6 Hz, 1 H, H^{7a}), 3.35 (dd, *J* = 9.2, 6.7 Hz, 1 H, H^{7b}), 2.64–2.43 (m, 1 H, H^5), 1.09 (d, *J* = 6.8 Hz, 3 H, H^6) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 141.3 (C2), 138.6 (C8), 128.3 (C10), 127.5 (C9), 127.4 (C11), 114.0 (C1), 75.0 (C5), 72.9 (C7), 37.8 (C3), 16.6 (C4) ppm.

4-(Benzyloxy)-3-methylbutan-1-ol ((±)-217)[50,166]



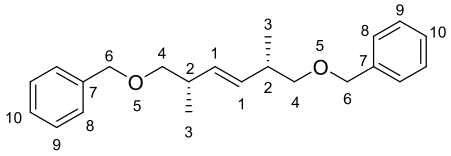
A solution of 9-borabicyclo[3.3.1]nonane (852 μL, 0.5 M solution in THF, 426 μmol) was added to a solution of racemic alkene **109** (50.0 mg, 284 μmol) in THF (1.78 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by the addition of EtOH (1.00 mL), then cooled to 0 °C. A solution of aq. 1 M NaOH (1.25 mL, 1.25 mmol) and a solution of aq. H_2O_2 (1.00 mL, 30% w/w) were added and the mixture was stirred for 2 h, then sat. aq. $Na_2S_2O_3$ (2.50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL), the layers were separated and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (60% Et_2O/pentane) to afford racemic alcohol **217** as a colourless oil (35.2 mg, 64%). Data are consistent with those reported in the literature.[50,166] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.39–7.27 (m, 5 H, H^{10}, H^{11}, H^{12}), 4.53 (s, 2 H, H^8), 3.78–3.57 (m, 2 H, H^2), 3.39 (dd, *J* = 9.0, 4.9 Hz, 1 H, H^{6a}), 3.32 (dd, *J* = 9.0, 7.3 Hz, 1 H, H^{6b}), 2.59 (br. s., 1 H, H^1), 2.02–1.89 (m, 1 H, H^4), 1.70–1.60 (m, 1 H, H^{3a}), 1.60–1.50 (m, 1 H, H^{3b}), 0.96 (d, *J* = 7.1 Hz, 3 H, H^5) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 138.0 (C9), 128.4 (C11), 127.7 (C10), 127.6 (C12), 76.0 (C6), 73.2 (C8), 61.0 (C2), 37.9 (C3), 31.3 (C4), 17.6 (C5) ppm.

(*S*)-4-(Benzyloxy)-3-methylbutan-1-ol (217)[62,167]



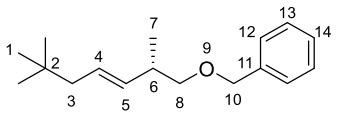
A solution of 9-borabicyclo[3.3.1]nonane (852 μL, 0.5 M solution in THF, 426 μmol) was added to a solution of alkene **109** (50.0 mg, 284 μmol) in THF (1.78 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by the addition of EtOH (1.00 mL), then cooled to 0 °C. A solution of aq. 1 M NaOH (1.25 mL, 1.25 mmol) and a solution of aq. H_2O_2 (1.00 mL, 30% w/w) were sequentially added and the mixture stirred for 2 h, then sat. aq. $Na_2S_2O_3$ (2.50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL), the layers were separated and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (60% Et_2O/pentane) to afford alcohol **217** as a colourless oil (40.6 mg, 74%, 95% ee). Data are consistent with those reported in the literature.[62,167] HPLC conditions: Chiralcel OD-H column, 2% 2-propanol/*n*-heptane, 1.0 mL/min, 205 nm UV detector, t_1 = 24.04 min (major) and t_2 = 28.02 min (minor). **$[\alpha]_D^{25}$** −6.33 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.42–7.25 (m, 5 H, H^{10}, H^{11}, H^{12}), 4.53 (s, 2 H, H^8), 3.76–3.59 (m, 2 H, H^2), 3.39 (dd, *J* = 9.0, 5.1 Hz, 1 H, H^{6a}), 3.32 (dd, *J* = 9.0, 7.3 Hz, 1 H, H^{6b}), 2.61 (br. s., 1 H, H^1), 2.04–1.88 (m, 1 H, H^4), 1.70–1.60 (m, 1 H, H^{3a}), 1.60–1.50 (m, 1 H, H^{3b}), 0.96 (d, *J* = 7.1 Hz, 3 H, H^5) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 138.0 (C9), 128.4 (C11), 127.6 (C10), 127.6 (C12), 76.0 (C6), 73.2 (C8), 61.0 (C2), 37.9 (C3), 31.3 (C4), 17.6 (C5) ppm.

(*E*)-(((2,5-Dimethylhex-3-ene-1,6-diyl)bis(oxy))bis(methylene)) dibenzene (218)[63]



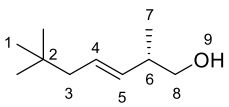
Hoveyda–Grubbs second-generation catalyst (6.2 mg, 3.5 mol%) was added to 3,3-dimethyl-1-butene (2.66 mL, 20.6 mmol) and the mixture was heated at reflux. A solution of alkene **109** (50.0 mg, 284 μmol) in 3,3-dimethyl-1-butene (0.585 mL, 4.54 mmol) was added dropwise over 6 h. The reaction mixture was stirred at 60 °C for 17 h then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% CH_2Cl_2/pentane) to afford alkene homodimer by-product **218** as a colourless oil (35.6 mg, 39%). Data are consistent with those reported in the literature.[63] **$[\alpha]_D^{25}$** −1.94 (c 1.0, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.29–7.15 (m, 10 H, H^8, H^9, H^{10}), 5.35 (dd, *J* = 3.9, 2.0 Hz, 2 H, H^1), 4.43 (s, 4 H, H^6), 3.29 (dd, *J* = 9.0, 6.4 Hz, 2 H, H^{4a}), 3.18 (dd, *J* = 9.0, 7.3 Hz, 2 H, H^{4b}), 2.45–2.33 (m, 2 H, H^2), 0.95 (d, *J* = 6.8 Hz, 6 H, H^3) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 138.7 (C7), 132.4 (C1), 128.3 (C9), 127.5 (C8), 127.4 (C10), 75.5 (C4), 72.8 (C6), 36.8 (C2), 17.2 (C3) ppm.

(*S*,*E*)-(((2,6,6-Trimethylhept-3-en-1-yl)oxy)methyl)benzene (220)



A solution of alkene **109** (3.00 g, 17.0 mmol) in CH_2Cl_2 (170 mL) was added to Grubbs second-generation catalyst (506 mg, 3.5 mol%), then 4,4-dimethyl-1-pentene (12.2 mL, 85.1 mmol) was added and the mixture was heated at 50 °C for 22 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% CH_2Cl_2/pentane) to afford alkene **220** as a colourless oil (3.15 g, 75%). **$[\alpha]_D^{25}$** +4.16 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.39–7.26 (m, 5 H, H^{12}, H^{13}, H^{14}), 5.59–5.43 (m, 1 H, H^4), 5.41–5.24 (m, 1 H, H^5), 4.53 (s, 2 H, H^{10}), 3.39 (dd, *J* = 9.0, 6.4 Hz, 1 H, H^{8a}), 3.29 (dd, *J* = 9.0, 7.1 Hz, 1 H, H^{8b}), 2.43–2.58 (m, 1 H, H^6), 1.89 (d, *J* = 7.3 Hz, 2 H, H^3), 1.05 (d, *J* = 6.8 Hz, 3 H, H^7), 0.88 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 138.7 (C11), 135.0 (C5), 128.3 (C13), 127.5 (C12), 127.4 (C14), 127.1 (C4), 75.6 (C8), 72.9 (C10), 47.1 (C3), 37.0 (C6), 30.8 (C2), 29.2 (C1), 17.5 (C7) ppm. **FTIR** ν_{max} (thin film): 2955m, 2865m, 1454m, 1363m, 1097s, 1029w, 971m, 909w, 733s, 696s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{17}H_{27}O^+$ $[M+H]^+$ 247.2056; found 247.2058 (Δ +0.56 ppm).

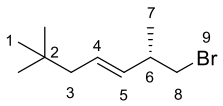
(*S*,*E*)-2,6,6-Trimethylhept-3-en-1-ol (221)



Ammonia (135 mL) was distilled into a 3-necked round-bottomed flask at −78 °C. Lithium wire (186 mg, 26.8 mmol) was cut into small pieces and added to the solution resulting in a

colour change from colourless to blue. A solution of alkene **220** (2.98 g, 12.1 mmol) in THF (27.0 mL) was added and the mixture was stirred for 1 h, then quenched by the addition of MeOH (4.00 mL) resulting in the loss of the blue colour. The mixture was warmed to room temperature and the ammonia was allowed to evaporate. The residue was diluted with Et_2O (100 mL) and the mixture was washed with sat. aq. NH_4Cl (50 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to about 15 mL in volume. The crude residue was purified by flash column chromatography (20% Et_2O/pentane) to afford alcohol **221** as a colourless oil (1.90 g, quantitative). **$[\alpha]_D^{25}$** −27.6 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.57 (dt, *J* = 15.2, 7.3 Hz, 1 H, H^4), 5.24 (dd, *J* = 15.2, 7.8 Hz, 1 H, H^5), 3.54–3.43 (m, 1 H, H^{8a}), 3.43–3.31 (m, 1 H, H^{8b}), 2.43–2.26 (m, 1 H, H^6), 1.91 (d, *J* = 7.3 Hz, 2 H, H^3), 1.47 (br. s, 1 H, H^9), 1.00 (d, *J* = 6.4 Hz, 3 H, H^7), 0.88 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 134.5 (C5), 129.3 (C4), 67.3 (C8), 47.1 (C3), 39.9 (C6), 30.7 (C2), 29.2 (C1), 16.7 (C7) ppm. **FTIR** ν_{max} (thin film): 3340br, 2954s, 2868m, 1464w, 1364m, 1241w, 1032s, 971s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{10}H_{21}O^+$ $[M+H]^+$ 157.1587; found 157.1588 (Δ +0.97 ppm).

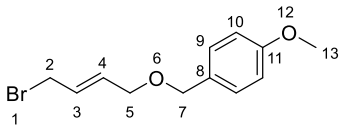
(*S*,*E*)-1-Bromo-2,6,6-trimethylhept-3-ene (222)



To a solution of alcohol **221** (355 mg, 2.27 mmol) in CH_2Cl_2 (7.49 mL) was added Et_3N (0.379 mL, 2.72 mmol). To a solution of triphenylphosphine (655 mg, 2.50 mmol) in CH_2Cl_2 (15.0 mL) was added bromine (0.139 mL, 2.72 mmol) at 0 °C, and the resulting suspension was allowed to stir for 10 min. The solution of alcohol **221** and Et_3N was added

dropwise to the latter suspension over 10 min, and the reaction mixture was stirred for 1 h. The mixture was concentrated *in vacuo.* The crude residue was kept at 4 °C for 1 h, filtered and the fitrate was purified by flash column chromatography (100% pentane) to afford bromide **222** as a colourless oil (349 mg, 70%). **[α]$_D^{25}$** −13.4 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.59–5.47 (m, 1 H, H^4), 5.34–5.25 (m, 1 H, H^5), 3.37 (dd, *J* = 9.7, 6.1 Hz, 1 H, H^{8a}), 3.30 (dd, *J* = 10.0, 6.8 Hz, 1 H, H^{8b}), 2.60–2.47 (m, 1 H, H^6), 1.89 (d, *J* = 7.5 Hz, 2 H, H^3), 1.14 (d, *J* = 6.8 Hz, 3 H, H^7), 0.88 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 134.4 (C5), 128.7 (C4), 47.0 (C3), 40.2 (C8), 39.0 (C6), 30.9 (C2), 29.2 (C1), 19.2 (C7) ppm. **FTIR** ν_{max} (thin film): 2955s, 1463w, 1432w, 1392w, 1364m, 1227w, 970s, 649m cm^{-1}. **HRMS** (CI^+): Calculated for $C_{10}H_{20}{}^{79}Br^+$ $[M+H]^+$ 219.0743; found 219.0558 (Δ −2.76 ppm).

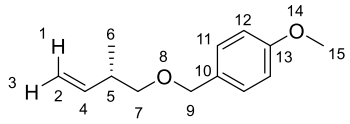
(*E*)-1-(((4-Bromobut-2-en-1-yl)oxy)methyl)-4-methoxybenzene (223)[168]



To a solution of *trans*-1,4-dibromo-2-butene (10.0 g, 46.8 mmol) and tetrabutylammonium hydrogensulfate (1.59 g, 4.68 mmol) in CH_2Cl_2 (42.5 mL) was added aq. 2 M NaOH (23.4 mL, 46.8 mmol), then 4-Methoxybenzyl alcohol (6.38 mL, 51.4 mmol) was added over 20 min and the reaction mixture allowed to stir at room temperature for 16 h. The reaction was diluted with H_2O (50.0 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The layers were separated and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50% CH_2Cl_2/pentane) to afford bromide **223** as a colourless oil (5.56 g, 44%). Data are consistent with those reported in the literature.[168] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.28 (d,

J = 8.3 Hz, 2 H, H^9), 6.90 (d, J = 8.8 Hz, 2 H, H^{10}), 6.04–5.83 (m, 2 H, H^3, H^4), 4.47 (s, 2 H, H^7), 4.03 (d, J = 5.0 Hz, 2 H, H^5), 3.98 (d, J = 7.3 Hz, 2 H, H^2), 3.82 (s, 3 H, H^{13}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.2 (C11), 131.8 (C4), 130.0 (C8), 129.4 (C9), 128.6 (C3), 113.8 (C10), 72.0 (C7), 69.1 (C5), 55.3 (C13), 32.0 (C2) ppm.

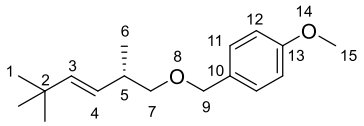
(*S*)-1-Methoxy-4-(((2-methylbut-3-en-1-yl)oxy)methyl)benzene (224)[169]



To a solution of (R_P,*R*)-Taniaphos (33.0 mg, 47.9 μmol) in CH_2Cl_2 (29.5 mL) was added $CuBr{\cdot}Me_2S$ (7.6 mg, 36.9 μmol) and the mixture was stirred for 10 min, then cooled to −78 °C. A solution of methylmagnesium bromide (1.48 mL, 3.0 M solution in Et_2O, 4.43 mmol) was added dropwise over 30 min. A solution of bromide **223** (1.00 g, 3.69 mmol) in CH_2Cl_2 (7.38 mL) was added dropwise by syringe-pump over 2.5 h, and the reaction mixture was stirred for a further 36 h. The reaction mixture was quenched by the addition of MeOH (5.00 mL) and warmed to room temperature. The mixture was poured into Et_2O (15.0 mL), then washed with sat. aq. NH_4Cl (15.0 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% CH_2Cl_2/pentane) to afford alkene **224** as a colourless oil (599 mg, 79%). Data are consistent with those reported in the literature.[169] **$[\alpha]_D^{25}$** −3.98 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.29 (d, J = 8.6 Hz, 2 H, H^{11}), 6.91 (d, J = 8.3 Hz, 2 H, H^{12}), 5.83 (ddd, J = 17.3, 10.3, 6.8 Hz, 1 H, H^4), 5.10 (d, J = 17.4 Hz, 1 H, H^1), 5.04 (d, J = 10.5 Hz, 1 H, H^3), 4.48 (s, 2 H, H^9), 3.83 (s, 3 H, H^{15}), 3.38 (dd, J = 9.3, 6.6 Hz, 1 H, H^{7a}), 3.31 (dd, J = 8.8, 6.6 Hz, 1 H, H^{7b}), 2.59–2.46 (m, 1 H, H^5), 1.06 (d, J = 6.8 Hz, 3 H, H^6) ppm.

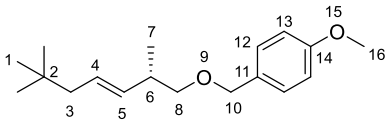
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.0 (C13), 141.3 (C4), 130.6 (C10), 129.1 (C11), 114.0 (C2), 113.7 (C12), 74.7 (C7), 72.6 (C9), 55.2 (C15), 37.8 (C5), 16.6 (C6) ppm.

(*S*,*E*)-1-Methoxy-4-(((2,5,5-trimethylhex-3-en-1-yl)oxy)methyl)benzene (225)



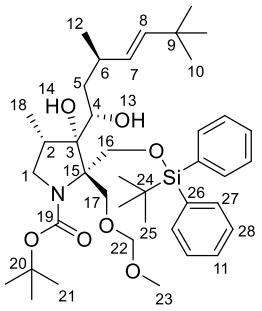
Hoveyda–Grubbs second-generation catalyst (5.3 mg, 3.5 mol%) was added to 3,3-dimethyl-1-butene (2.22 mL, 17.2 mmol) and the mixture was heated at reflux. A solution of alkene **224** (50.0 mg, 242 μmol) in 3,3-dimethyl-1-butene (0.556 mL, 4.31 mmol) was added dropwise by syringe-pump over 5 h. The reaction mixture was stirred at 60 °C for 17 h, then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% CH_2Cl_2/pentane) to afford alkene **225** as a colourless oil (18.5 mg, 29%). **$[\alpha]_D^{25}$** +2.99 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.27 (d, *J* = 8.8 Hz, 2 H, H^{11}), 6.89 (d, *J* = 8.8 Hz, 2 H, H^{12}), 5.50 (dd, *J* = 15.8, 1.1 Hz, 1 H, H^3), 5.24 (dd, *J* = 15.8, 7.1 Hz, 1 H, H^4), 4.45 (s, 2 H, H^9), 3.82 (s, 3 H, H^{15}), 3.37–3.30 (m, 1 H, H^{7a}), 3.28–3.20 (m, 1 H, H^{7b}), 2.57–2.31 (m, 1 H, H^5), 1.03 (d, *J* = 4.9 Hz, 3 H, H^6), 1.00 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.0 (C13), 141.2 (C3), 135.1 (C10), 129.1 (C11), 127.1 (C4), 113.7 (C12), 75.4 (C7), 72.4 (C9), 55.3 (C15), 36.8 (C5), 32.8 (C2), 29.8 (C1), 17.5 (C6) ppm. **FTIR** ν_{max} (thin film): 2956m, 2928m, 2856w, 1613w, 1513s, 1463m, 1362w, 1302w, 1247s, 1172w, 1092s, 1039m, 972w, 820m cm^{-1}. **HRMS** (CI^+): Calculated for $C_{17}H_{30}NO_2^+$ $[M+NH_4]^+$ 280.2271; found 280.2274 (Δ −0.66 ppm).

(*S*,*E*)-1-Methoxy-4-(((2,6,6-trimethylhept-3-en-1-yl)oxy)methyl) benzene (226)



A solution of alkene **224** (50.0 mg, 242 μmol) in CH_2Cl_2 (2.42 mL) was added to Grubbs second-generation catalyst (7.2 mg, 3.5 mol%), then 4,4-dimethyl-1-pentene (0.174 mL, 1.21 mmol) was added and the mixture was heated at 55 °C for 22 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% CH_2Cl_2/pentane) to afford alkene **226** as a colourless oil (59.8 mg, 89%). **$[\alpha]_D^{25}$** +5.57 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.27 (d, *J* = 8.7 Hz, 2 H, H^{12}), 6.89 (d, *J* = 8.7 Hz, 2 H, H^{13}), 5.57–5.41 (m, 1 H, H^4), 5.38–5.22 (m, 1 H, H^5), 4.46 (s, 2 H, H^{10}), 3.82 (s, 3 H, H^{16}), 3.35 (dd, *J* = 9.0, 6.6 Hz, 1 H, H^{8a}), 3.25 (dd, *J* = 9.2, 7.2 Hz, 1 H, H^{8b}), 2.56–2.39 (m, 1 H, H^6), 1.88 (d, *J* = 7.3 Hz, 2 H, H^3), 1.03 (d, *J* = 6.6 Hz, 3 H, H^7), 0.87 (s, 9 H, H^1) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.0 (C13), 135.1 (C5), 130.8 (C11), 129.1 (C4), 127.1 (C12), 113.7 (C13), 75.3 (C8), 72.5 (C10), 55.2 (C16), 47.1 (C3), 37.0 (C6), 30.8 (C2), 29.2 (C1), 17.5 (C7) ppm. **FTIR** ν_{max} (thin film): 2954m, 2864w, 1613w, 1513s, 1464w, 1363w, 1247s, 1172w, 1093m, 1084m, 972w, 820m cm^{-1}. **HRMS** (CI^+): Calculated for $C_{18}H_{32}NO_2^+$ $[M+NH_4]^+$ 294.2428; found 294.2432 (Δ −1.36 ppm).

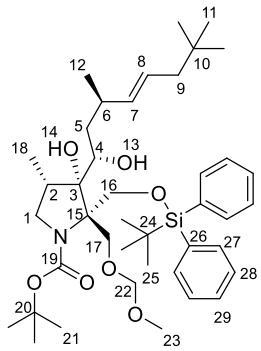
***tert*-Butyl (2*S*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*,*E*)-1-hydroxy-3,6,6-trimethylhept-4-en-1-yl)-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (111)**[50]



A solution of *t*-BuLi (3.08 mL, 5.24 mmol, 1.7 M in pentane) was added dropwise to a solution of bromide **100** (538 mg, 2.62 mmol) in THF (6.21 mL) at −78 °C over 30 min. The resulting yellow solution was treated with anhydrous beads of $CeCl_3$ (1.94 g, 7.86 mmol, weighed in a glovebox) under a constant flow of N_2 gas, and the beads were finely ground inside the solution with a metal rod. The yellow suspension was warmed to −40 °C and stirred for 22 h. The resulting grey suspension was cooled to −78 °C and treated dropwise with a solution of aldehyde **101** (300 mg, 0.524 mmol) in THF (1.28 mL) over 15 min, then stirred for 5 h at −78 °C. The grey suspension was quenched by the dropwise addition of MeOH (2.4 mL) and poured into sat. aq. NH_4Cl (36 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% to 20% EtOAc/pentane) to afford diol **111** as a colourless oil (308 mg, 84%, 20:1 dr). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** −19.2 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (major rotamer) 7.77–7.60 (m, 4 H, H^{27}), 7.49–7.33 (m, 6 H, H^{28}, H^{11}), 5.48 (d, *J* = 15.7 Hz, 1 H, H^8), 5.10–5.01 (m, 1 H, H^7), 5.06 (s, 1 H, H^{14}), 4.50 (s, 2 H, H^{22}), 4.46 (d, *J* = 10.1 Hz, 1 H, H^{16a}), 4.09 (d, *J* = 10.1 Hz, 1 H, H^{16b}), 4.02 (d, *J* = 10.4 Hz, 1 H, H^{17a}), 3.75–3.68 (m, 1 H, H^4), 3.68–

3.61 (m, 1 H, H^{1a}), 3.57 (d, J = 10.4 Hz, 1 H, H^{17b}), 3.26 (s, 3 H, H^{23}), 3.09 (t, J = 10.9 Hz, 1 H, H^{1b}), 2.84 (d, J = 8.6 Hz, 1 H, H^{13}), 2.48–2.25 (m, 2 H, H^{6}, H^{2}), 1.53–1.45 (m, 2 H, H^{5a}, H^{5b}), 1.44 (s, 9 H, H^{21}), 1.07 (s, 9 H, H^{25}), 1.13–0.92 (m, 6 H, H^{12}, H^{18}), 0.96 (s, 9 H, H^{10}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = (major rotamer) 153.2 (C19), 141.1 (C8), 135.9 (C27), 135.8 (C27), 132.0 (C26), 131.6 (C26), 130.1 (C28), 129.9 (C28), 129.5 (C7), 127.8 (C11), 127.6 (C11), 96.8 (C22), 85.3 (C20), 79.0 (C3), 71.5 (C15), 70.9 (C4), 66.1 (C17), 63.8 (C16), 55.7 (C23), 53.3 (C1), 39.3 (C5), 35.6 (C2), 33.7 (C6), 32.6 (C9), 29.8 (C10), 28.5 (C21), 26.9 (C25), 22.5 (C12), 19.1 (C24), 10.7 (C18) ppm.

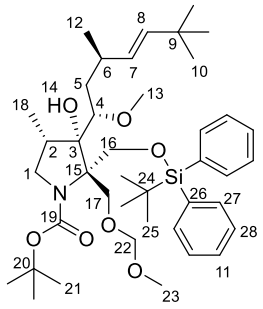
***tert*-Butyl (2*S*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*,*E*)-1-hydroxy-3,7,7-trimethyloct-4-en-1-yl)-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (231)**



A solution of *t*-BuLi (1.03 mL, 1.75 mmol, 1.7 M in pentane) was added dropwise to a solution of bromide **222** (192 mg, 0.874 mmol) in THF (2.08 mL) at −78 °C over 30 min. The resulting yellow solution was treated with anhydrous beads of $CeCl_3$ (431 mg, 1.75 mmol, weighed in a glovebox) under a constant flow of N_2 gas, and the beads were finely ground inside the solution with a metal rod. The yellow suspension was warmed to −40 °C and stirred for 23 h. The resulting grey suspension was cooled to −78 °C and treated dropwise with a solution of aldehyde **101** (100 mg, 0.175 mmol) in THF (0.425 mL) over

15 min, then stirred for 3 h at −78 °C. The grey suspension was quenched by the dropwise addition of MeOH (0.9 mL) and poured into sat. aq. NH_4Cl (12 mL). The aqueous layer was extracted with Et_2O (3 × 9 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% to 20% EtOAc/pentane) to afford diol **231** as a colourless oil (80.1 mg, 64%, 10:1 dr). **$[\alpha]_D^{25}$** −16.6 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = (major rotamer) 7.75–7.60 (m, 4 H, H^{27}), 7.48–7.35 (m, 6 H, H^{28}, H^{29}), 5.51–5.42 (m, 1 H, H^8), 5.20–5.12 (m, 1 H, H^7), 5.05 (s, 1 H, H^{14}), 4.49 (s, 2 H, H^{22}), 4.46 (d, *J* = 10.2 Hz, 1 H, H^{16a}), 4.09 (d, *J* = 10.2 Hz, 1 H, H^{16b}), 4.01 (d, *J* = 10.4 Hz, 1 H, H^{17a}), 3.76–3.68 (m, 1 H, H^4), 3.68–3.62 (m, 1 H, H^{1a}), 3.60 (d, *J* = 10.4 Hz, 1 H, H^{17b}), 3.26 (s, 3 H, H^{23}), 3.08 (t, *J* = 10.8 Hz, 1 H, H^{1b}), 2.83 (d, *J* = 8.7 Hz, 1 H, H^{13}), 2.47–2.25 (m, 2 H, H^6, H^2), 1.84 (d, *J* = 7.0 Hz, 2 H, H^9), 1.53–1.45 (m, 2 H, $H^{5a,}$ H^{5b}), 1.44 (s, 9 H, H^{21}), 1.06 (s, 9 H, H^{25}), 1.00–0.94 (m, 6 H, H^{12}, H^{18}), 0.85 (s, 9 H, H^{11}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = (major rotamer) 153.2 (C19), 137.5 (C7), 135.9 (C27), 135.8 (C27), 132.1 (C26), 131.6 (C26), 130.1 (C28), 129.9 (C28), 127.8 (C29), 127.6 (C29), 126.8 (C8), 96.9 (C22), 85.4 (C20), 79.0 (C3), 71.5 (C15), 71.1 (C4), 66.2 (C17), 63.9 (C16), 55.7 (C23), 53.3 (C1), 47.2 (C9), 39.2 (C5), 35.6 (C2), 33.9 (C6), 30.8 (C10), 29.3 (C11), 28.6 (C21), 26.9 (C25), 22.7 (C12), 19.1 (C24), 10.6 (C18) ppm. **FTIR** ν_{max} (thin film): 3442br, 2955m, 2863w, 1693s, 1474w, 1428w, 1382s, 1364s, 1159m, 1113s, 1074w, 1036s, 971w, 823w, 804w, 774w, 741w, 701s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{41}H_{66}NO_7Si^+$ $[M+H]^+$ 712.4603; found 712.4608 (Δ +0.71 ppm).

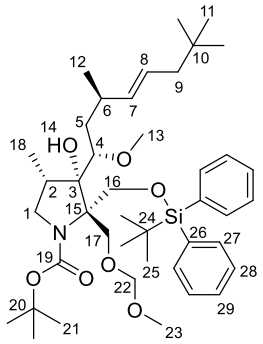
***tert*-Butyl (2*S*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*,*E*)-1-methoxy-3,6,6-trimethylhept-4-en-1-yl)-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (232)**[50]



To a solution of diol **111** (1.35 g, 1.94 mmol) and proton sponge (1.25 g, 5.82 mmol) in CH_2Cl_2 (27.0 mL) was added Me_3OBF_4 (574 mg, 3.88 mmol) and the reaction mixture was stirred at room temperature. Additional portions of proton sponge (623 mg, 2.91 mmol) and Me_3OBF_4 (287 mg, 1.94 mmol) were added after 10, 24, and 34 h and the reaction mixture was stirred for a further 8 h. The reaction mixture was quenched by the addition of MeOH (6.4 mL) and washed with aq. 1 M HCl (64 mL). The layers were separated and the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/pentane) to afford methyl ether **232** as a white foam (1.06 g, 77%). Data are consistent with those reported in the literature.[50] **m.p.** 39.8–40.2 °C. **$[\alpha]_D^{25}$** −2.3 (c 1.0, $CHCl_3$). **^{1}H NMR** (C_6D_6, 400 MHz): δ = (major rotamer) 8.01–7.85 (m, 4 H, H^{27}), 7.38–7.18 (m, 6 H, H^{28}, H^{11}), 5.55 (d, *J* = 15.4 Hz, 1 H, H^8), 5.33 (s, 1 H, H^{14}), 5.32–5.25 (m, 1 H, H^7), 5.01 (d, *J* = 10.3 Hz, 1 H, H^{16a}), 4.56 (d, *J* = 6.2 Hz, 1 H, H^{22a}), 4.53 (d, *J* = 6.2 Hz, 1 H, H^{22b}), 4.26 (d, *J* = 10.3 Hz, 1 H, H^{16b}), 4.07 (d, *J* = 9.8 Hz, 1 H, H^{17a}), 3.83–3.75 (m, 2 H, H^{17b}, H^{1a}), 3.54 (dd, *J* = 9.7, 1.8 Hz, 1 H, H^4), 3.39–3.29 (m, 1 H, H^{1b}), 3.26 (s, 3 H, H^{13}), 3.22 (s, 3 H, H^{23}), 2.59–2.46 (m, 1 H, H^2), 2.45–2.32 (m, 1 H, H^6), 1.94–1.84 (m, 1 H, H^{5a}), 1.71 (ddd, *J* = 13.6, 9.9, 3.3 Hz, 1 H, H^{5b}), 1.52 (s, 9 H, H^{21}), 1.17 (s, 9 H, H^{25}), 1.10–1.01 (m, 15 H, H^{10}, H^{18},

H^{12}) ppm. **^{13}C NMR** (C_6D_6, 101 MHz): δ = (major rotamer) 154.1 (C19), 142.1 (C8), 136.9 (C27), 136.8 (C27), 133.3 (C26), 132.9 (C26), 131.1 (C7), 130.6 (C28), 130.5 (C28), 128.5 (C11), 128.3 (C11), 97.4 (C22), 86.1 (C20), 82.0 (C4), 78.9 (C3), 71.6 (C15), 67.0 (C17), 65.3 (C16), 59.9 (C13), 55.4 (C23), 53.7 (C1), 38.8 (C5), 36.3 (C2), 35.9 (C6), 33.3 (C9), 30.4 (C10), 29.1 (C21), 27.5 (C25), 23.4 (C12), 19.7 (C24), 10.8 (C18) ppm.

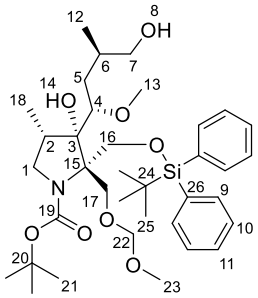
tert-Butyl (2*S*,3*S*,4*S*)-2-(((_tert_-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*,*E*)-1-methoxy-3,7,7-trimethyloct-4-en-1-yl)-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (233)



To a solution of diol **231** (84.0 mg, 0.118 mmol) and proton sponge (76.0 mg, 0.355 mmol) in CH_2Cl_2 (2.0 mL) was added Me_3OBF_4 (34.8 mg, 0.235 mmol) and the reaction mixture was stirred at room temperature. Additional portions of proton sponge (38.0 mg, 0.177 mmol) and Me_3OBF_4 (17.4 mg, 0.118 mmol) were added after 10, 24, and 34 h and the reaction mixture was stirred for a further 8 h. The reaction mixture was quenched by the addition of MeOH (0.4 mL) and washed with aq. 1 M HCl (4.0 mL). The layers were separated and the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/pentane) to afford methyl ether **233** as a colourless oil (53.5 mg, 62%). **$[\alpha]_D^{25}$** +3.9 (c 1.0, $CHCl_3$). **^{1}H NMR** (C_6D_6, 400 MHz): δ = (major rotamer) 8.01–7.85 (m, 4 H, H^{27}),

7.37–7.19 (m, 6 H, H^{28}, H^{29}), 5.64–5.50 (m, 1 H, H^{8}), 5.40 (m, 1 H, H^{7}), 5.32 (s, 1 H, H^{14}), 5.03 (d, *J* = 10.3 Hz, 1 H, H^{16a}), 4.56 (d, *J* = 6.2 Hz, 1 H, H^{22a}), 4.53 (d, *J* = 6.2 Hz, 1 H, H^{22b}), 4.28 (d, *J* = 10.3 Hz, 1 H, H^{16b}), 4.10 (d, *J* = 9.8 Hz, 1 H, H^{17a}), 3.84 (d, *J* = 9.8 Hz, 1 H, H^{17b}), 3.83–3.77 (m, 1 H, H^{1a}), 3.60 (d, *J* = 9.0 Hz, 1 H, H^{4}), 3.39–3.32 (m, 1 H, H^{1b}), 3.30 (s, 3 H, H^{13}), 3.23 (s, 3 H, H^{23}), 2.60–2.50 (m, 1 H, H^{2}), 2.49–2.38 (m, 1 H, H^{6}), 1.95 (d, *J* = 7.1 Hz, 2 H, H^{9}), 1.93–1.88 (m, 1 H, H^{5a}), 1.72 (ddd, *J* = 13.6, 9.9, 3.3 Hz, 1 H, H^{5b}), 1.52 (s, 9 H, H^{21}), 1.18 (s, 9 H, H^{25}), 1.10–1.03 (m, 6 H, H^{12}, H^{18}), 0.93 (s, 9 H, H^{11}) ppm. **^{13}C NMR** (C_6D_6, 101 MHz): δ = (major rotamer) 153.8 (C19), 138.8 (C7), 136.6 (C27), 136.5 (C27), 132.9 (C26), 132.6 (C26), 130.3 (C28), 130.2 (C28), 128.2 (C29), 127.9 (C29), 127.4 (C8), 97.1 (C22), 85.7 (C20), 81.8 (C4), 78.6 (C3), 71.2 (C15), 66.8 (C17), 64.9 (C16), 59.9 (C13), 55.1 (C23), 53.3 (C1), 47.6 (C9), 38.4 (C5), 35.9 (C2), 35.4 (C6), 31.1 (C10), 29.5 (C11), 28.8 (C21), 27.2 (C25), 23.4 (C12), 19.4 (C24), 10.5 (C18) ppm. **FTIR** ν_{max} (thin film): 3430br, 2956m, 2933m, 2893w, 2863w, 1694s, 1474w, 1428w, 1389s, 1365s, 1174w, 1157w, 1113s, 1075w, 1043s, 823w, 807w, 740w, 703m cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{42}H_{67}NNaO_7Si^+$ $[M+Na]^+$ 748.4579; found 748.4564 (Δ −1.98 ppm).

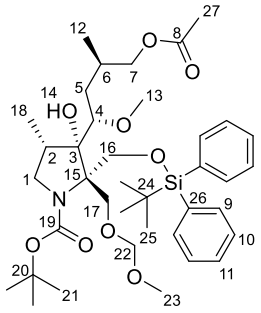
***tert*-Butyl (2*S*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*)-4-hydroxy-1-methoxy-3-methylbutyl)-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (234)**[50]



A solution of methyl ether **232** (695 mg, 976 μmol) in a 7.5:1 mixture of CH_2Cl_2-MeOH (24.4 mL) was cooled to −78 °C and ozone was bubbled through the solution for 20 min, resulting in a pale blue solution. Nitrogen gas was bubbled through the solution until the disappearance of the blue colour, then sodium borohydride (185 mg, 4.88 mmol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then warmed to 0 °C and stirred for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl (43 mL), extracted and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 17 mL), the layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (25% EtOAc/pentane) to afford alcohol **234** as a white foam (556 mg, 86%). Data are consistent with those reported in the literature.[50] **m.p.** 43.8–44.5 °C. **$[\alpha]_D^{25}$** +7.0 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = (major rotamer) 7.79–7.62 (m, 4 H, H^9), 7.48–7.33 (m, 6 H, H^{10}, H^{11}), 5.38 (s, 1 H, H^{14}), 4.64 (d, *J* = 10.3 Hz, 1 H, H^{16a}), 4.51 (d, *J* = 6.2 Hz, 1 H, H^{22a}), 4.48 (d, *J* = 6.2 Hz, 1 H, H^{22b}), 4.15 (d, *J* = 10.3 Hz, 1 H, H^{16b}), 3.86 (d, *J* = 9.8 Hz, 1 H, H^{17a}), 3.68–3.61 (m, 2 H, H^{17b}, H^{1a}), 3.60–3.54 (m, 1 H, H^4), 3.50 (dd, *J* = 10.8, 5.0 Hz, 1 H, H^{7a}), 3.43 (s, 1 H, H^8), 3.39 (dd, *J* = 10.8, 6.4 Hz, 1 H, H^{7b}), 3.32 (s, 3 H, H^{13}), 3.28 (s, 3 H, H^{23}), 3.12–3.01 (m, 1 H, H^{1b}), 2.50–2.33 (m, 1 H, H^2), 1.95–1.73

(m, 2 H, H^{6}, H^{5a}), 1.54–1.46 (m, 1 H, H^{5b}), 1.44 (s, 9 H, H^{21}), 1.06 (s, 9 H, H^{25}), 0.96 (d, J = 6.6 Hz, 3 H, H^{18}), 0.87 (d, J = 6.4 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = (major rotamer) 153.3 (C19), 135.9 (C9), 135.8 (C9), 132.3 (C26), 131.9 (C26), 130.0 (C10), 129.8 (C10), 127.8 (C11), 127.6 (C11), 97.0 (C22), 86.0 (C20), 81.3 (C4), 78.8 (C3), 70.8 (C15), 68.1 (C7), 66.3 (C17), 64.4 (C16), 58.8 (C13), 55.4 (C23), 52.8 (C1), 35.4 (C2), 34.7 (C5), 34.2 (C6), 28.5 (C21), 26.9 (C25), 19.1 (C24), 18.3 (C12), 10.1 (C18) ppm.

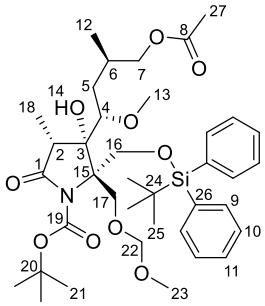
***tert*-Butyl (2*S*,3*S*,4*S*)-3-((1*S*,3*R*)-4-acetoxy-1-methoxy-3-methylbutyl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2-((methoxymethoxy)methyl)-4-methylpyrrolidine-1-carboxylate (112)**[50]



To alcohol **234** (527 mg, 799 µmol) were added pyridine (7.38 mL, 91.4 mmol) and acetic anhydride (7.37 mL, 77.9 mmol) and the reaction mixture was stirred for 24 h. The mixture was diluted with toluene and concentrated *in vacuo*. This was repeated three times. The crude product was purified by flash column chromatography (25% Et_2O/pentane) to afford acetate **112** as a colourless oil (540 mg, 96%). Data are consistent with those reported in the literature.[50] **[α]$_D^{25}$** +3.9 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = (major rotamer) 7.77–7.62 (m, 4 H, H^{9}), 7.47–7.32 (m, 6 H, H^{10}, H^{11}), 5.11 (s, 1 H, H^{14}), 4.60 (d, J = 10.2 Hz, 1 H, H^{16a}), 4.52–4.47 (m, 2 H, H^{22}), 4.10 (d, J = 10.2 Hz, 1 H, H^{16b}), 4.08 (dd, J = 10.7, 4.7 Hz, 1 H, H^{7a}), 3.89 (d, J = 10.0 Hz, 1 H, H^{17a}), 3.83 (dd, J = 10.7, 7.3 Hz, 1 H, H^{7b}), 3.64

(dd, *J* = 10.3, 8.2 Hz, 1 H, H^{1a}), 3.60 (d, *J* = 10.0 Hz, 1 H, H^{17b}), 3.47 (dd, *J* = 9.0, 2.5 Hz, 1 H, H^{4}), 3.33–3.29 (s, 3 H, H^{13}), 3.28 (s, 3 H, H^{23}), 3.12–3.02 (m, 1 H, H^{1b}), 2.45–2.32 (m, 1 H, H^{2}), 2.05 (s, 3 H, H^{27}), 2.03–1.93 (m, 1 H, H^{6}), 1.82–1.74 (m, 1 H, H^{5a}), 1.51–1.45 (m, 1 H, H^{5b}), 1.44 (s, 9 H, H^{21}), 1.05 (s, 9 H, H^{25}), 0.97 (d, *J* = 6.5 Hz, 3 H, H^{18}), 0.93 (d, *J* = 6.8 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = (major rotamer) 171.2 (C8), 153.3 (C19), 135.9 (C9), 135.9 (C9), 132.4 (C26), 132.0 (C26), 129.9 (C10), 129.8 (C10), 127.7 (C11), 127.6 (C11), 96.9 (C22), 85.7 (C20), 81.4 (C4), 78.7 (C3), 71.0 (C15), 69.0 (C7), 66.3 (C17), 64.3 (C16), 59.0 (C13), 55.4 (C23), 53.1 (C1), 35.5 (C2), 33.9 (C5), 30.4 (C6), 28.6 (C21), 26.9 (C25), 21.0 (C27), 19.1 (C24), 18.6 (C12), 10.4 (C18) ppm.

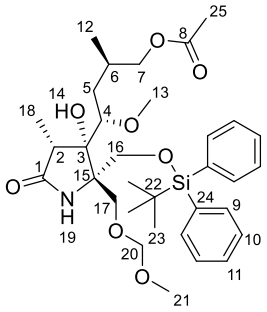
tert-Butyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*)-4-acetoxy-1-methoxy-3-methylbutyl)-2-(((_tert_-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2-((methoxymethoxy)methyl)-4-methyl-5-oxopyrrolidine-1-carboxylate (235)[50]



To aq. $NaIO_4$ (16.3 mL, 10% w/w, 7.69 mmol) was added $RuO_2 \cdot H_2O$ (17.4 mg, 115 μmol) at room temperature. A solution of acetate **112** (540 mg, 0.769 mmol) in EtOAc (16.3 mL) was added and the biphasic mixture was stirred vigorously at room temperature. Upon disappearance of the yellow colour and precipitation of a black solid, further portions of aq. $NaIO_4$ (450 μL, 10% w/w, 0.21 mmol) were added after 12, 14 and 16 h. The reaction mixture was stirred for a further 2 h, then the phases were separated and the aqueous layer

was extracted with EtOAc (3 × 45 mL). The layers were separated and isopropyl alcohol (9.0 mL) was added to the combined organic extracts. This mixture was stirred for 1 h, then dried over anhydrous $MgSO_4$, filtered through a pad of celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% Et_2O/pentane) to afford pyrrolidinone **235** as a colourless oil (373 mg, 68%). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** −14.4 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.75–7.59 (m, 4 H, H^9), 7.48–7.32 (m, 6 H, H^{10}, H^{11}), 4.73 (s, 1 H, H^{14}), 4.52 (d, *J* = 6.5 Hz, 1 H, H^{22a}), 4.47 (d, *J* = 6.5 Hz, 1 H, H^{22b}), 4.31 (s, 2 H, H^{16}), 4.08–4.02 (m, 2 H, H^{7a}, H^{17a}), 3.93 (dd, *J* = 10.9, 6.6 Hz, 1 H, H^{7b}), 3.58 (dd, *J* = 7.1, 3.8 Hz, 1 H, H^4), 3.54 (d, *J* = 10.2 Hz, 1 H, H^{17b}), 3.26 (s, 3 H, H^{13}), 3.20 (s, 3 H, H^{23}), 2.76 (q, *J* = 7.2 Hz, 1 H, H^2), 2.05 (s, 3 H, H^{27}), 2.04–1.96 (m, 1 H, H^6), 1.84 (ddd, *J* = 14.9, 8.4, 3.6 Hz, 1 H, H^{5a}), 1.48 (s, 9 H, H^{21}), 1.42–1.36 (m, 1 H, H^{5b}), 1.25 (d, *J* = 7.1 Hz, 3 H, H^{18}), 1.05 (s, 9 H, H^{25}), 0.97 (d, *J* = 6.8 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.4 (C1), 171.1 (C8), 151.2 (C19), 136.0 (C9), 135.8 (C9), 131.8 (C26), 131.7 (C26), 130.1 (C10), 130.0 (C10), 127.8 (C11), 127.7 (C11), 96.8 (C22), 83.0 (C20), 81.7 (C3), 80.6 (C4), 71.0 (C15), 68.7 (C7), 66.7 (C17), 63.0 (C16), 56.9 (C23), 55.6 (C13), 44.4 (C2), 32.9 (C5), 30.2 (C6), 28.1 (C21), 26.9 (C25), 20.9 (C27), 19.1 (C24), 18.4 (C12), 9.3 (C18) ppm.

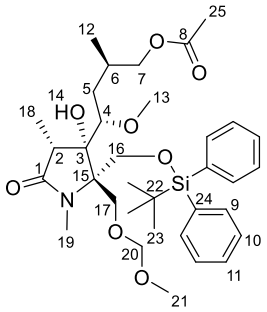
(2*R*,4*S*)-4-((2*S*,3*S*,4*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2-((methoxymethoxy)methyl)-4-methyl-5-oxopyrrolidin-3-yl)-4-methoxy-2-methylbutyl acetate (236)[50]



To a solution of pyrrolidinone **235** (387 mg, 541 μmol) in CH_2Cl_2 (5.40 mL) were added trifluoroacetic acid (166 μL, 2.16 mmol) and triethylsilane (173 μL, 1.08 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc/pentane) to afford lactam **236** as a colourless oil (244 mg, 73%). Data are consistent with those reported in the literature.[50] $[\alpha]_D^{25}$ +6.9 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.68–7.58 (m, 4 H, H^9), 7.49–7.34 (m, 6 H, H^{10}, H^{11}), 5.89 (s, 1 H, H^{19}), 4.56 (d, *J* = 6.5 Hz, 1 H, H^{20a}), 4.51 (d, *J* = 6.5 Hz, 1 H, H^{20b}), 4.04 (d, *J* = 10.3 Hz, 1 H, H^{16a}), 3.99 (dd, *J* = 11.0, 5.1 Hz, 1 H, H^{7a}), 3.88 (dd, *J* = 11.0, 5.9 Hz, 1 H, H^{7b}), 3.79 (d, *J* = 10.3 Hz, 1 H, H^{16b}), 3.74 (d, *J* = 10.8 Hz, 1 H, H^{17a}), 3.56 (t, *J* = 4.9 Hz, 1 H, H^4), 3.46 (d, *J* = 10.8 Hz, 1 H, H^{17b}), 3.30 (s, 3 H, H^{21}), 3.18 (s, 3 H, H^{13}), 2.96 (s, 1 H, H^{14}), 2.61 (q, *J* = 7.3 Hz, 1 H, H^2), 2.03 (s, 3 H, H^{25}), 1.95–1.83 (m, 2 H, H^{5a}, H^6), 1.30–1.21 (m, 1 H, H^{5b}), 1.18 (d, *J* = 7.3 Hz, 3 H, H^{18}), 1.06 (s, 9 H, H^{23}), 0.99 (d, *J* = 6.4 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 177.3 (C1), 171.0 (C8), 135.7 (C9), 135.5 (C9), 132.4 (C24), 132.3 (C24), 130.0 (C10), 130.0 (C10), 127.9 (C11), 127.8 (C11), 97.1

(C20), 82.6 (C3), 80.3 (C4), 69.7 (C17), 68.8 (C7), 67.6 (C15), 64.5 (C16), 56.7 (C13), 55.7 (C21), 43.3 (C2), 32.7 (C5), 30.3 (C6), 26.8 (C23), 20.8 (C25), 19.1 (C22), 17.7 (C12), 8.7 (C18) ppm.

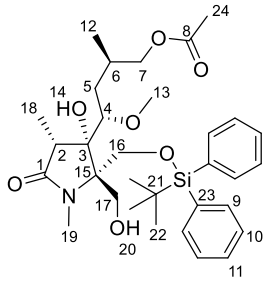
(2*R*,4*S*)-4-((2*S*,3*S*,4*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2-((methoxymethoxy)methyl)-1,4-dimethyl-5-oxopyrrolidin-3-yl)-4-methoxy-2-methylbutyl acetate (113)[50]



To a solution of lactam **236** (397 mg, 645 μmol) in CH_3I (6.60 mL, 106 mmol) in a 10–20 mL microwave vial was added Cs_2CO_3 (2.13 g, 6.53 mmol) and the reaction mixture was stirred at 50 °C for 25 h. The reaction mixture was poured into sat. aq. NH_4Cl (24 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL). The layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% to 60% EtOAc/pentane) to afford *N*-methyl pyrrolidinone **113** as a colourless oil (347 mg, 85%). Data are consistent with those reported in the literature.[50] $[\alpha]_D^{25}$ −0.4 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.69–7.59 (m, 4 H, H^9), 7.50–7.34 (m, 6 H, H^{10}, H^{11}), 4.54 (d, *J* = 6.6 Hz, 1 H, H^{20a}), 4.47 (d, *J* = 6.6 Hz, 1 H, H^{20b}), 4.14 (d, *J* = 11.2 Hz, 1 H, H^{16a}), 4.04–3.96 (m, 2 H, H^{7a}, H^{16b}), 3.90 (dd, *J* = 10.8, 5.8 Hz, 1 H, H^{7b}), 3.83 (d, *J* = 11.2 Hz, 1 H, H^{17a}), 3.61 (t, *J* = 5.0 Hz, 1 H, H^4), 3.50 (d, *J* = 11.2 Hz, 1 H, H^{17b}), 3.40 (s, 1 H, H^{14}),

3.28 (s, 3 H, H^{21}), 3.16 (s, 3 H, H^{13}), 2.91 (s, 3 H, H^{19}), 2.51 (q, *J* = 7.3 Hz, 1 H, H^{2}), 2.03 (s, 3 H, H^{25}), 1.97–1.83 (m, 2 H, H^{6}, H^{5a}), 1.34–1.27 (m, 1 H, H^{5b}), 1.19 (d, *J* = 7.3 Hz, 3 H, H^{18}), 1.07 (s, 9 H, H^{23}), 0.99 (d, *J* = 6.1 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 176.1 (C1), 171.1 (C8), 135.8 (C9), 135.6 (C9), 132.0 (C24), 130.1 (C10), 130.0 (C10), 127.9 (C11), 127.8 (C11), 96.9 (C20), 81.8 (C3), 80.5 (C4), 70.6 (C15), 68.8 (C7), 66.2 (C17), 64.7 (C16), 56.4 (C13), 55.8 (C21), 43.0 (C2), 32.7 (C5), 30.3 (C6), 26.9 (C23), 26.4 (C19), 20.9 (C25), 19.1 (C22), 17.8 (C12), 9.3 (C18) ppm.

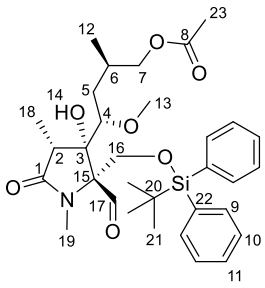
(2*R*,4*S*)-4-((2*S*,3*S*,4*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2-(hydroxymethyl)-1,4-dimethyl-5-oxopyrrolidin-3-yl)-4-methoxy-2-methylbutyl acetate (237)[50]



To a solution of *N*-methyl pyrrolidinone **113** (347 mg, 0.551 mmol) in CH_2Cl_2 (5.51 mL) were added trifluoroacetic acid (2.11 mL, 27.6 mmol) and MeOH (44.6 μL, 1.10 mmol) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (24 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% to 70% to 100% EtOAc/pentane) to afford diol **237** as a white solid (217 mg, 67%). Data are consistent with those reported in the literature.[50] **m.p.** 48.8–50.4 °C. **[α]$_D^{25}$** +7.6 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.66–7.60 (m, 4 H, H^{9}), 7.51–7.38 (m, 6 H, H^{10}, H^{11}), 4.40 (br. s, 1 H, H^{14}), 4.21 (d, *J* = 12.0 Hz, 1 H, H^{16a}),

4.04 (dd, J = 11.0, 5.0 Hz, 1 H, H^{7a}), 3.91 (dd, J = 11.0, 6.5 Hz, 1 H, H^{7b}), 3.78 (d, J = 12.0 Hz, 1 H, H^{16b}), 3.60 (dd, J = 12.0, 6.1 Hz, 1 H, H^{17a}), 3.54 (dd, J = 9.0, 2.7 Hz, 1 H, H^{4}), 3.45 (s, 3 H, H^{13}), 3.44–3.40 (m, 1 H, H^{17b}), 3.40–3.37 (m, 1 H, H^{20}), 2.75 (s, 3 H, H^{19}), 2.70 (q, J = 7.1 Hz, 1 H, H^{2}), 2.05 (s, 3 H, H^{24}), 2.03–1.87 (m, 2 H, H^{6}, H^{5a}), 1.47 (ddd, J = 13.9, 9.0, 4.4 Hz, 1 H, H^{5b}), 1.19 (d, J = 7.1 Hz, 3 H, H^{18}), 1.07 (s, 9 H, H^{22}), 0.98 (d, J = 6.6 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 175.6 (C1), 171.2 (C8), 135.9 (C9), 135.7 (C9), 131.5 (C23), 131.2 (C23), 130.4 (C10), 130.3 (C10), 128.0 (C11), 127.9 (C11), 82.2 (C3), 81.5 (C4), 70.2 (C15), 68.6 (C7), 64.4 (C16), 60.8 (C17), 60.0 (C13), 42.6 (C2), 34.6 (C5), 30.5 (C6), 26.8 (C22), 25.5 (C19), 20.9 (C24), 19.0 (C21), 18.6 (C12), 8.0 (C18) ppm.

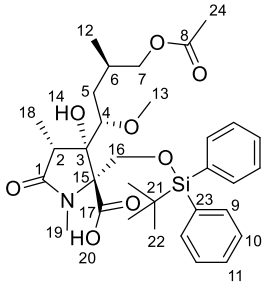
(2*R*,4*S*)-4-((2*S*,3*S*,4*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-formyl-3-hydroxy-1,4-dimethyl-5-oxopyrrolidin-3-yl)-4-methoxy-2-methylbutyl acetate (238)



To a solution of diol **237** (9.0 mg, 15.4 μmol) in CH_2Cl_2 (0.154 mL) was added Dess–Martin periodinane (7.8 mg, 18.4 μmol) and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*, diluted with Et_2O (0.9 mL), poured into a mixture of sat. aq. $Na_2S_2O_3$ (0.4 mL) and sat. aq. $NaHCO_3$ (0.4 mL), then extracted and the layers separated. The aqueous phase was extracted with Et_2O (3 × 0.4 mL) and the layers were separated. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a colourless oil. A solution of $NaClO_2$ (17.4 mg, 154 μmol, 80%) and NaH_2PO_4 (14.8 mg, 123 μmol) in H_2O (96 μL) was added to a solution

of the crude product and 2-methyl-2-butene (55.0 μL, 524 μmol) in *t*-BuOH (0.22 mL). The reaction mixture was stirred at room temperature for 13 h, then poured into sat. aq. NaCl (0.9 mL). The mixture was extracted with EtOAc (3 × 0.4 mL), the layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% EtOAc/pentane to 100% EtOAc to 1% AcOH/EtOAc) to afford aldehyde **238** as a colourless oil (1.9 mg, 21%). **$[\alpha]_D^{25}$** +5.8 (c 0.2, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 9.43 (s, 1 H, H^{17}), 7.68–7.58 (m, 4 H, H^9), 7.50–7.39 (m, 6 H, H^{10}, H^{11}), 4.31 (d, *J* = 12.0 Hz, 1 H, H^{16a}), 4.23 (d, *J* = 12.0 Hz, 1 H, H^{16b}), 3.92 (dd, *J* = 5.7, 1.1 Hz, 2 H, H^{7a}, H^{7b}), 3.47 (br. s, 1 H, H^{14}), 3.24 (s, 3 H, H^{13}), 3.24–3.20 (m, 1 H, H^4), 2.82 (s, 3 H, H^{19}), 2.53 (q, *J* = 7.3 Hz, 1 H, H^2), 2.03 (s, 3 H, H^{23}), 1.94–1.87 (m, 1 H, H^6), 1.86–1.79 (m, 1 H, H^{5a}), 1.25–1.21 (m, 1 H, H^{5b}), 1.18 (d, *J* = 7.4 Hz, 3 H, H^{18}), 1.05 (s, 9 H, H^{21}), 0.94 (d, *J* = 6.6 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 197.0 (C17), 175.5 (C1), 171.2 (C8), 135.8 (C9), 135.6 (C9), 131.6 (C22), 131.4 (C22), 130.4 (C10), 130.3 (C10), 128.1 (C11), 128.0 (C11), 83.6 (C3), 80.9 (C4), 77.5 (C15), 68.5 (C7), 63.9 (C16), 58.4 (C13), 42.3 (C2), 34.0 (C5), 30.9 (C6), 27.5 (C19), 26.8 (C21), 20.9 (C23), 19.0 (C20), 18.2 (C12), 8.6 (C18) ppm. **FTIR** ν_{max} (thin film): 2970s, 2919s, 2850s, 1736s, 1679s, 1436w, 1428w, 1392m, 1261m, 1106s, 1077s, 798m, 703m, 630w cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{32}H_{45}NNaO_7Si^+$ $[M+Na]^+$ 606.286; found 606.285 (Δ −0.78 ppm).

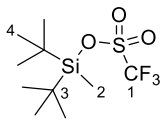
(2*S*,3*S*,4*R*)-3-((1*S*,3*R*)-4-Acetoxy-1-methoxy-3-methylbutyl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylic acid (114)[50]



To a solution of diol **237** (60.0 mg, 102 μmol) in CH_2Cl_2 (1.02 mL) was added Dess–Martin periodinane (52.2 mg, 123 μmol) and the reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated *in vacuo*, diluted with Et_2O (6.0 mL), poured into a mixture of sat. aq. $Na_2S_2O_3$ (6.0 mL) and sat. aq. $NaHCO_3$ (6.0 mL), then extracted and the layers separated. The aqueous phase was extracted with Et_2O (3 × 6.0 mL) and the layers were separated. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a colourless oil. A solution of $NaClO_2$ (92.0 mg, 1.02 mmol, 80%) and NaH_2PO_4 (98.0 mg, 0.816 mmol) in H_2O (0.64 mL) was added to a solution of the crude product and 2-methyl-2-butene (0.367 mL, 3.46 mmol) in *t*-BuOH (1.55 mL). The reaction mixture was stirred at room temperature for 13 h, then poured into sat. aq. NaCl (6.0 mL). The mixture was extracted with EtOAc (3 × 3.0 mL), the layers were separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% EtOAc/pentane to 100% EtOAc to 1% AcOH/EtOAc) to afford acid **114** as a white solid (61.1 mg, 99%). Data are consistent with those reported in the literature.[50] **m.p.** 52.8–54.6 °C. **$[\alpha]_D^{25}$** +11.9 (c 1.0, $CHCl_3$). **^{1}H NMR** (DMSO-d_6, 500 MHz): δ = 13.01 (br. s, 1 H, H^{20}), 7.75–7.62 (m, 4 H, H^9), 7.51–7.39 (m, 6 H, H^{10}, H^{11}), 5.15 (br. s, 1 H, H^{14}), 4.42 (d, *J* = 11.1 Hz, 1 H, H^{16a}), 3.94–3.88 (m, 2 H, H^{16b}, H^{7a}), 3.66 (dd, *J* = 10.8, 7.5 Hz, 1 H, H^{7b}),

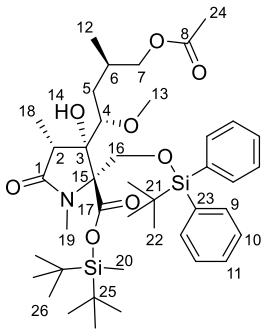
3.26 (s, 3 H, H^{13}), 3.21–3.15 (m, 1 H, H^{4}), 2.91 (s, 3 H, H^{19}), *ca*. 2.56–2.51 (m, 1 H, H^{2}, hidden under solvent signal), 1.96 (s, 3 H, H^{24}), 1.88–1.77 (m, 1 H, H^{6}), 1.68–1.57 (m, 1 H, H^{5a}), 1.51–1.43 (m, 1 H, H^{5b}), 0.97 (s, 9 H, H^{22}), 0.96 (d, J = 7.4 Hz, 3 H, H^{18}), 0.86 (d, J = 6.8 Hz, 3 H, H^{12}) ppm. **^{13}C NMR** (DMSO-d_6, 126 MHz): δ = 175.1 (C17), 170.4 (C1), 170.3 (C8), 135.6 (C9), 135.1 (C9), 132.8 (C23), 131.8 (C23), 129.9 (C10), 128.0 (C10), 127.7 (C11), 81.8 (C3), 80.7 (C4), 75.2 (C15), 68.3 (C7), 66.0 (C16), 59.7 (C13), 41.2 (C2), 33.3 (C5), 29.7 (C6), 28.2 (C19), 26.6 (C22), 20.7 (C24), 18.7 (C21), 18.5 (C12), 7.7 (C18) ppm.

Di-*tert*-butyl(methyl)silyl trifluoromethanesulfonate (239)[144]



To di-*tert*-butylmethylsilane (1.50 g, 9.47 mmol) was added trifluoromethanesulfonic acid (0.923 mL, 10.4 mmol) dropwise at 4 ºC. The reaction mixture was warmed to room temperature and stirred for 16 h, during which time hydrogen evolution occurred. The resulting clear yellow solution was distilled (96-98 ºC, 20 mbar) to afford triflate **239** as a colourless oil (2.24 g, 77%). Data are consistent with those reported in the literature.[144] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 1.09 (s, 18 H, H^{4}), 0.47 (s, 3 H, H^{2}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 118.6 (q, J = 317.2 Hz, C1), 26.8 (C4), 20.6 (C3), −7.5 (C2) ppm. **^{19}F NMR** ($CDCl_3$, 377 MHz): δ = −76.4 (C1F_3) ppm.

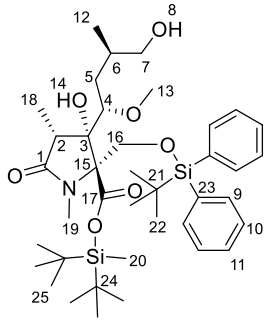
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*)-4-acetoxy-1-methoxy-3-methylbutyl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (240)[50]



To a solution of acid **114** (213 mg, 355 μmol) and Et_3N (198 μL, 1.42 mmol) in Et_2O (14.2 mL) as added di-*tert*-butyl(methyl)silyl triflate (218 mg, 710 μmol) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured into sat. aq. NH_4Cl (20 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography (25% to 50% EtOAc/pentane) to afford acetate **240** as a white solid (221 mg, 82%). Data are consistent with those reported in the literature.[50] **m.p.** 45.9–47.1 °C. **$[\alpha]_D^{25}$** +15.7 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.69–7.61 (m, 4 H, H^9), 7.49–7.36 (m, 6 H, H^{10}, H^{11}), 4.60 (br. s, 1 H, H^{14}), 4.47 (d, *J* = 12.0 Hz, 1 H, H^{16a}), 4.06 (dd, *J* = 10.9, 5.0 Hz, 1 H, H^{7a}), 3.97 (d, *J* = 12.0 Hz, 1 H, H^{16b}), 3.88 (dd, *J* = 10.9, 6.8 Hz, 1 H, H^{7b}), 3.40 (dd, *J* = 8.8, 2.9 Hz, 1 H, H^4), 3.32 (s, 3 H, H^{13}), 2.70 (q, *J* = 7.2 Hz, 1 H, H^2), 2.68 (s, 3 H, H^{19}), 2.05 (s, 3 H, H^{24}), 2.00–1.91 (m, 1 H, H^6), 1.87 (ddd, *J* = 14.1, 8.6, 2.9 Hz, 1 H, H^{5a}), 1.64 (ddd, *J* = 14.1, 8.8, 5.0 Hz, 1 H, H^{5b}), 1.21 (d, *J* = 7.3 Hz, 3 H, H^{18}), 1.06 (s, 9 H, H^{22}), 0.97 (d, *J* = 6.6 Hz, 3 H, H^{12}), 0.93 (s, 9 H, H^{26}), 0.91 (s, 9 H, H^{26}), 0.23 (s, 3 H, H^{20}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.6 (C1), 171.1 (C8), 169.0 (C17), 135.9 (C9), 135.7 (C9), 131.5 (C23), 131.1 (C23), 130.4 (C10), 130.3 (C10), 128.0

(C11), 127.9 (C11), 83.7 (C3), 80.5 (C4), 74.1 (C15), 68.8 (C7), 63.5 (C16), 59.1 (C13), 42.7 (C2), 33.6 (C5), 30.4 (C6), 27.7 (C26), 27.5 (C26), 26.9 (C22), 26.8 (C19), 21.0 (C24), 20.4 (C25), 20.1 (C25), 19.0 (C21), 18.4 (C12), 8.1 (C18), −7.6 (C20) ppm.

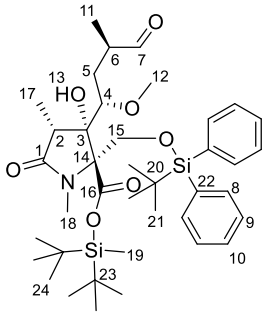
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*)-4-hydroxy-1-methoxy-3-methylbutyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (241)[50]



To a solution of acetate **240** (221 mg, 292 μmol) in THF (5.84 mL) was added $LiBH_4$ (127 mg, 2.92 mmol) and the reaction mixture was stirred at room temperature for 2 h. An additional portion of $LiBH_4$ (127 mg, 2.92 mmol) was added and the reaction mixture was stirred at room temperature for a further 3 h. The reaction mixture was poured into sat. aq. NH_4Cl (15 mL) and the aqueous layer was extracted with EtOAc (3 × 15 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography (30% to 50% EtOAc/pentane to 100% EtOAc) to afford diol **241** as a white solid (172 mg, 83%). Data are consistent with those reported in the literature.[50] **m.p.** 56.5–58.0 °C. **$[\alpha]_D^{25}$** +12.2 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.74–7.57 (m, 4 H, H^9), 7.50–7.34 (m, 6 H, H^{10}, H^{11}), 4.82 (br. s, 1 H, H^{14}), 4.49 (d, *J* = 12.2 Hz, 1 H, H^{16a}), 3.98 (d, *J* = 12.2 Hz, 1 H, H^{16b}), 3.56 (dd, *J* = 11.0, 4.7 Hz, 1 H, H^{7a}), 3.52–3.45 (m, 2 H,

H^{7b}, H^{4}), 3.30 (s, 3 H, H^{13}), 2.73 (q, *J* = 7.3 Hz, 1 H, H^{2}), 2.70 (s, 3 H, H^{19}), 2.31 (br. s, 1 H, H^{8}), 1.91–1.78 (m, 2 H, H^{5a}, H^{6}), 1.66–1.55 (m, 1 H, H^{5b}), 1.18 (d, *J* = 7.3 Hz, 3 H, H^{18}), 1.06 (s, 9 H, H^{22}), 0.94 (d, *J* = 3.4 Hz, 3 H, H^{12}), 0.93 (s, 9 H, H^{25}), 0.91 (s, 9 H, H^{25}), 0.25 (s, 3 H, H^{20}) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 176.5 (C1), 169.1 (C17), 135.9 (C9), 135.7 (C9), 131.4 (C23), 131.1 (C23), 130.3 (C10), 130.3 (C10), 128.0 (C11), 127.9 (C11), 83.8 (C3), 80.4 (C4), 74.0 (C15), 67.5 (C7), 63.8 (C16), 58.9 (C13), 42.6 (C2), 34.0 (C5), 33.9 (C6), 27.8 (C25), 27.4 (C25), 26.9 (C19), 26.8 (C22), 20.4 (C24), 20.0 (C21), 18.2 (C12), 14.2 (C18), −7.6 (C20) ppm.

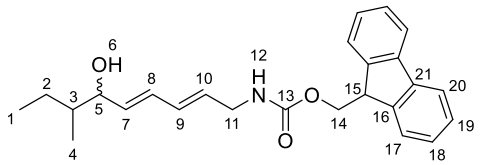
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-((1*S*,3*R*)-1-methoxy-3-methyl-4-oxobutyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (99)[50]



To a solution of oxalyl chloride (18.3 μL, 216 μmol) in CH_2Cl_2 (0.864 mL) was added DMSO (30.8 μL, 433 μmol) at –78 °C and the reaction mixture was stirred for 15 min. A solution of diol **241** (31.0 mg, 43.3 μmol) in CH_2Cl_2 (0.864 mL) was added at –78 °C and the reaction mixture was stirred for 1 h, then Et_3N (121 μL, 868 μmol) was added. The mixture was stirred at –78 °C for 15 min, then warmed to room temperature and stirred for a further 30 min. The reaction mixture was diluted with EtOAc, then poured into aq. 1 M HCl (13 mL) and the aqueous layer was extracted with Et_2O (3 × 6.0 mL). The layers were

separated and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (25% to 33% EtOAc/pentane) to afford aldehyde **99** as a colourless oil (24.3 mg, 79%). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** +9.1 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 9.56 (d, *J* = 2.1 Hz, 1 H, H^7), 7.70–7.62 (m, 4 H, H^8), 7.51–7.36 (m, 6 H, H^9, H^{10}), 4.61 (br. s, 1 H, H^{13}), 4.48 (d, *J* = 12.1 Hz, 1 H, H^{15a}), 3.99 (d, *J* = 12.1 Hz, 1 H, H^{15b}), 3.26 (dd, *J* = 9.4, 2.9 Hz, 1 H, H^4), 3.21 (s, 3 H, H^{12}), 2.75 (s, 3 H, H^{18}), 2.70 (q, *J* = 7.3 Hz, 1 H, H^2), 2.60–2.51 (m, 1 H, H^6), 2.06 (ddd, *J* = 14.2, 8.8, 2.9 Hz, 1 H, H^{5a}), 1.98 (ddd, *J* = 14.0, 9.4, 4.0 Hz, 1 H, H^{5b}), 1.20 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.09–1.04 (m, 3 H, H^{11}), 1.07 (s, 9 H, H^{21}), 0.94 (s, 9 H, H^{24}), 0.93 (s, 9 H, H^{24}), 0.22 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 204.6 (C7), 176.4 (C1), 169.4 (C16), 136.1 (C8), 135.9 (C8), 131.6 (C22), 131.2 (C22), 130.5 (C9), 130.5 (C9), 128.1 (C10), 128.1 (C10), 83.9 (C3), 80.2 (C4), 74.0 (C14), 63.8 (C15), 59.6 (C12), 43.8 (C6), 42.9 (C2), 31.3 (C5), 28.0 (C24), 27.6 (C24), 27.1 (C18), 27.0 (C21), 20.6 (C23), 20.2 (C23), 19.1 (C20), 14.0 (C11), 8.2 (C17), −7.5 (C19) ppm.

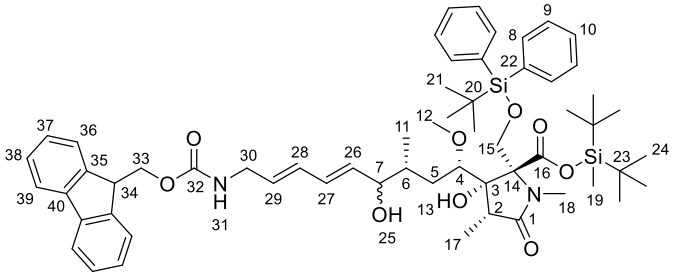
(9*H*-Fluoren-9-yl)methyl ((2*E*,4*E*)-6-hydroxy-7-methylnona-2,4-dien-1-yl)carbamate (244)



To a solution of 2-methylbutyraldehyde (578 μL, 54.1 μmol) in DMSO (1.08 mL) were added $CrCl_2$ (26.5 mg, 216 μmol), $NiCl_2$ (1.4 mg, 10.8 μmol) and iodide **76** (35.0 mg, 81.2 μmol), and the resulting dark green solution was stirred at room temperature for 16 h. The reaction mixture was poured into sat. aq. NH_4Cl (6.0 mL) and the aqueous layer was

extracted with EtOAc (5 × 4.0 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography (25% to 50% EtOAc/pentane) to afford alcohol **244** as a colourless oil (18.2 mg, 86%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.77 (d, *J* = 7.5 Hz, 2 H, H^{20}), 7.59 (d, *J* = 7.5 Hz, 2 H, H^{17}), 7.40 (t, *J* = 7.5 Hz, 2 H, H^{19}), 7.31 (td, *J* = 7.5, 1.2 Hz, 2 H, H^{18}), 6.27–6.09 (m, 2 H, H^8, H^9), 5.77–5.57 (m, 2 H, H^7, H^{10}), 4.85 (br. s, 1 H, H^{12}), 4.42 (d, *J* = 6.9 Hz, 2 H, H^{14}), 4.22 (t, *J* = 6.9 Hz, 1 H, H^{15}), 4.01 (dt, *J* = 13.0, 6.0 Hz, 1 H, H^5), 3.86 (t, *J* = 6.1 Hz, 2 H, H^{11}), 1.59–1.42 (m, 2 H, H^{2a}, H^3), 1.19–1.03 (m, 1 H, H^{2b}), 0.94–0.89 (m, 3 H, H^1), 0.86 (d, *J* = 6.7 Hz, 3 H, H^4) ppm. **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.4 (C13), 144.1 (C16), 141.5 (C21), 135.5 (C7), 134.8 (C7), 131.5 (C9), 131.5 (C9), 130.5 (C8), 130.0 (C8), 129.4 (C10), 129.3 (C10), 127.8 (C19), 127.2 (C18), 125.2 (C17), 120.1 (C20), 76.5 (C5), 76.1 (C5), 66.8 (C14), 47.4 (C15), 42.8 (C11), 40.8 (C3), 40.8 (C3), 25.5 (C2), 25.2 (C2), 14.6 (C4), 14.3 (C4), 11.9 (C1), 11.7 (C1) ppm. **FTIR** ν_{max} (thin film): 3412br, 3337br, 2961m, 2929w, 2874w, 1702s, 1523m, 1450m, 1250s, 1138w, 991s, 759m, 741s cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{25}H_{29}NNaO_3^+$ $[M+Na]^+$ 414.2040; found 414.2044 (Δ +0.99 ppm).

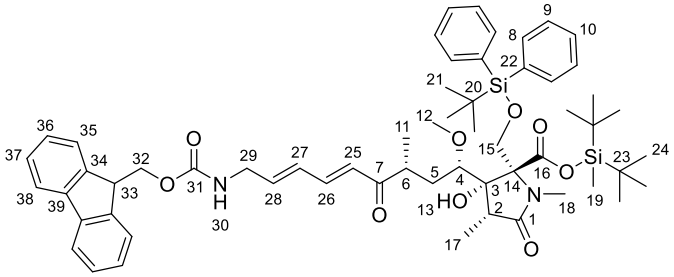
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-hydroxy-1-methoxy-3-methylnona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (73)[50] (1:1 epimeric mixture)



To a freeze-pump-thaw degassed solution of aldehyde **99** (40.0 mg, 56.2 μmol) in DMSO (1.12 mL) were added $CrCl_2$ (55.2 mg, 449 μmol), $NiCl_2$ (2.9 mg, 22.5 μmol) and iodide **76** (72.7 mg, 169 μmol), and the resulting dark green solution was stirred at room temperature for 18 h. The reaction mixture was poured into sat. aq. NH_4Cl (0.5 mL), sat. aq. Rochelle's salt (potassium sodium tartrate) (1.25 mL) and further diluted with H_2O (11.2 mL), and the aqueous layer was extracted with EtOAc (5 × 1.0 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% to 50% EtOAc/pentane) to afford a 1:1 mixture of diastereomers of alcohol **73** as a colourless oil (39.7 mg, 69%). Data are consistent with those reported in the literature.[50] $[\alpha]_D^{25}$ +13.3 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.80–7.56 (m, 8 H, H^{36}, H^8, H^{39},), 7.49–7.28 (m, 10 H, H^9, H^{10}, H^{38}, H^{37}), 6.29–6.09 (m, 2 H, H^{27}, H^{28}), 5.76–5.59 (m, 2 H, H^{26}, H^{29}), 4.95 (br. t, *J* = 5.7 Hz, 0.5 H, H^{31}), 4.91 (br. t, *J* = 5.9 Hz, 0.5 H, H^{31}), 4.80 (s, 0.5 H, H^{25}), 4.65 (s, 0.5 H, H^{25}), 4.51 (dd, *J* = 12.0, 0.3 Hz, 0.5 H, H^{15a}), 4.48 (d, *J* = 11.8 Hz, 0.5 H, H^{15a}), 4.41 (d, *J* = 6.6 Hz, 2 H, H^{33}), 4.30–4.25 (m, 0.5 H, H^7), 4.21 (br. t, *J* = 6.6 Hz, 1 H, H^{34}), 4.00 (d, *J* = 11.9 Hz, 0.5 H, H^{15b}), 3.98 (d, *J* = 12.0 Hz, 0.5 H, H^{15b}), 3.97–3.92 (m, 0.5 H, H^7), 3.90–3.75 (m, 2 H, H^{30}), 3.55 (dd, *J* = 7.9, 2.6 Hz, 0.5 H, H^4), 3.50 (dd, *J* = 8.3,

2.4 Hz, 0.5 H, H^4), 3.32 (s, 1.5 H, H^{12}), 3.31 (s, 1.5 H, H^{12}), 2.73 (q, *J* = 7.3 Hz, 0.5 H, H^2), 2.71–2.65 (m, 0.5 H, H^2), 2.69 (s, 1.5 H, H^{18}), 2.68 (s, 1.5 H, H^{18}), 2.04–1.96 (m, 0.5 H, H^{5a}), 1.86–1.74 (m, 1 H, H^6), 1.72–1.64 (m, 0.5 H, H^{5a}), 1.64–1.56 (m, 1 H, H^{5b}), 1.21 (d, *J* = 7.1 Hz, 1.5 H, H^{17}), 1.20 (d, *J* = 7.2 Hz, 1.5 H, H^{17}), 1.07 (s, 9 H, H^{21}), 0.94 (d, *J* = 10.2 Hz, 9 H, H^{24}), 0.91 (s, 9 H, H^{24}), *ca*. 0.90 (d, 3 H, H^{11}, hidden under H^{24} signal), 0.26 (s, 1.5 H, H^{19}), 0.24 (s, 1.5 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.7 (C1), 176.7 (C1), 169.4 (C16), 169.2 (C16), 156.4 (C32), 156.4 (C32), 144.1 (C35), 141.4 (C40), 136.1 (C22), 135.8 (C8), 135.8 (C8), 135.0 (C26), 134.3 (C26), 131.7 (C28/C27), 131.6 (C28/C27), 131.5 (C28/C27), 131.4 (C27/C28), 131.2 (C27/C28), 130.9 (C27/C28), 130.5 (C9/C10), 130.4 (C9/C10), 130.4 (C9/C10), 130.3 (C9/C10), 129.8 (C29), 129.7 (C29), 129.3 (C29), 128.1, (C38), 127.8 (C38), 127.2 (C37), 125.2 (C39), 120.1 (C36), 84.2 (C3), 84.0 (C3), 81.1 (C4), 80.4 (C4), 77.4 (C7), 74.7 (C14), 74.3 (C14), 73.6 (C7), 66.8 (C33), 63.9 (C15), 63.9 (C15), 58.7 (C12), 58.6 (C12), 47.4 (C34), 42.8 (C30), 42.8 (C2), 37.9 (C6), 36.8 (C6), 33.7 (C5), 32.8 (C5), 27.9 (C24), 27.9 (C24), 27.6 (C21), 27.6 (C21), 27.1 (C18), 27.0 (C18), 20.5 (C23), 20.5 (C23), 20.2 (C23), 20.1 (C20), 16.9 (C11), 8.5 (C17), 8.2 (C17), −7.4 (C19), −7.5 (C19) ppm.

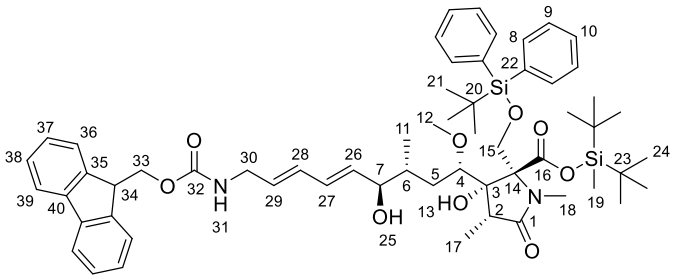
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-oxonona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (245)[50]



To a solution of a 1:1 epimeric mixture of alcohol **73** (19.2 mg, 18.9 μmol) in CH_2Cl_2 (188 μL) was added Dess–Martin periodinane (12.0 mg, 28.3 μmol) and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed by a stream of nitrogen gas and the residue diluted with sat. aq. $Na_2S_2O_3$ (3.6 mL) and sat. aq. $NaHCO_3$ (3.6 mL). The aqueous layer was extracted with Et_2O (5 × 2.4 mL), the layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% to 50% EtOAc/pentane) to afford ketone **245** as a colourless oil (14.0 mg, 73%). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** +8.9 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.81–7.53 (m, 8 H, H^{35}, H^8, H^{38}), 7.49–7.28 (m, 10 H, H^9, H^{10}, H^{36}, H^{37}), 7.18 (dd, *J* = 15.4, 10.8 Hz, 1 H, H^{26}), 6.28–6.17 (m, 2 H, H^{25}, H^{27}), 6.13–6.02 (m, 1 H, H^{28}), 4.84 (br. t, *J* = 6.3 Hz, 1 H, H^{30}), 4.53–4.39 (m, 4 H, H^{15a}, H^{13}, H^{32}), 4.21 (t, *J* = 6.7 Hz, 1 H, H^{33}), 4.03 (d, *J* = 11.8 Hz, 1 H, H^{15b}), 3.93–3.83 (m, 2 H, H^{29}), 3.21 (dd, *J* = 8.4, 3.0 Hz, 1 H, H^4), 3.18 (s, 3 H, H^{12}), 3.10–3.00 (m, 1 H, H^6), 2.73 (s, 3 H, H^{18}), 2.64 (q, *J* = 7.1 Hz, 1 H, H^2), 2.36–2.24 (m, 1 H, H^{5a}), 1.82–1.72 (m, 1 H, H^{5b}), 1.23 (d, *J* = 7.2 Hz, 3 H, H^{17}), 1.09 (d, *J* = 7.0 Hz, 3 H, H^{11}), 1.06 (s, 9 H, H^{21}), 0.95 (s, 9 H, H^{24}), 0.93 (s, 9 H, H^{24}), 0.23 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 203.2 (C7), 176.6 (C1), 169.5 (C16),

156.3 (C31), 143.9 (C34), 141.5 (C39), 141.3 (C26), 139.2 (C28), 136.1 (C8), 135.8 (C8), 131.8 (C22), 131.4 (C22), 130.4 (C9/C10), 130.2 (C9/C10), 129.8 (C27), 128.8 (C25), 128.1 (C36), 128.1 (C36), 127.9 (C37), 127.2 (C37), 125.1 (C38), 120.1 (C35), 84.0 (C3), 80.7 (C4), 74.9 (C14), 66.9 (C32), 63.9 (C15), 58.9 (C12), 47.4 (C33), 43.1 (C2), 42.7 (C29), 41.3 (C6), 32.8 (C5), 27.9 (C24), 27.7 (C24), 27.3 (C18), 27.0 (C21), 20.5 (C23), 20.2 (C23), 19.1 (C20), 18.6 (C11), 8.6 (C17), −7.5 (C19) ppm.

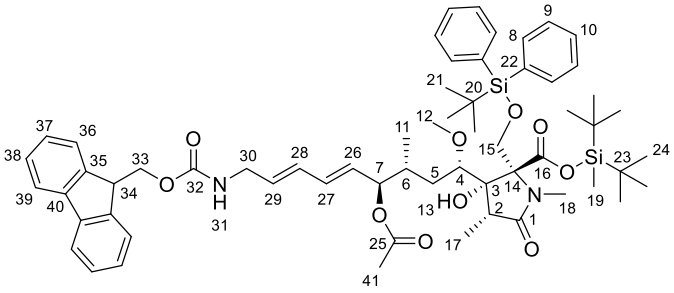
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-hydroxy-1-methoxy-3-methylnona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (73)[50]



To a solution of ketone **245** (10.1 mg, 9.95 μmol) and (*S*)-(−)-2-methyl-CBS-oxazaborolidine (11.0 mg, 39.9 μmol) in THF (0.331 mL) was added $BH_3{\cdot}Me_2S$ (9.95 μL, 2 M in toluene, 19.9 μmol) at −30 °C, and the reaction mixture was stirred for 19 h. The reaction mixture was cooled to −78 °C, quenched by dropwise addition of sat. aq. NH_4Cl (5.0 mL) and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (5 × 3.0 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% to 50% EtOAc/pentane) to afford alcohol **73** as a colourless oil (10.1 mg, 99%). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** +8.3 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.79–7.57 (m, 8 H, H^{36}, H^{8}, H^{39}), 7.49–7.28 (m, 10 H, H^{9}, H^{10}, H^{37}, H^{38}), 6.27–6.10 (m, 2 H, H^{27}, H^{28}), 5.73–5.60 (m, 2 H, H^{26}, H^{29}), 4.85 (t, *J* = 6.0 Hz, 1 H, H^{31}), 4.83 (br. s, 1 H, H^{25}), 4.51 (d, *J* = 12.0 Hz, 1 H, H^{15a}), 4.42 (d, *J* = 6.7 Hz, 2 H, H^{33}), 4.22 (t, *J* = 6.8 Hz, 1 H, H^{34}), 3.98 (d, *J* = 12.0 Hz, 1 H, H^{15b}), 3.97–3.92 (m, 1 H, H^{7}), 3.89–3.80 (m, 2 H, H^{30}), 3.55 (dd, *J* = 7.9, 2.7 Hz, 1 H, H^{4}), 3.32 (s, 3 H, H^{12}), 2.74 (q, *J* = 7.2 Hz, 1 H, H^{2}), 2.67 (s, 3 H, H^{18}), 2.29 (br. s, 1 H, H^{13}), 2.07–1.94 (m, 1 H, H^{5a}), 1.82–1.73 (m, 1 H, H^{6}), 1.73-1.60 (m, 1 H, H^{5b}), 1.20 (d, *J* = 7.2 Hz, 3 H, H^{17}), 1.07 (s, 9 H, H^{21}), 0.94 (s, 9 H, H^{24}), 0.92 (s, 9 H, H^{24}), *ca*.

0.90 (d, 3 H, H^{11}, hidden under H^{24} signal), 0.24 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.7 (C1), 169.3 (C16), 156.3 (C32), 144.1 (C35), 141.5 (C40), 136.1 (C8), 135.8 (C8), 134.4 (C26), 131.7 (C22), 131.5 (C28), 131.2 (C22), 130.9 (C27), 130.5 (C9/C10), 130.4 (C9/C10), 129.7 (C29), 128.1 (C37), 127.8 (C38), 127.2 (C38), 125.2 (C39), 120.1 (C36), 84.3 (C3), 81.1 (C4), 77.4 (C7), 74.2 (C14), 66.9 (C33), 63.9 (C15), 58.7 (C12), 47.4 (C34), 42.9 (C30), 42.8 (C2), 37.9 (C6), 33.8 (C5), 28.0 (C24), 27.6 (C24), 27.0 (C21), 27.0 (C18), 20.6 (C23), 20.2 (C20), 17.0 (C11), 8.2 (C17), −7.4 (C19) ppm. **^{1}H NMR** (C_6D_6, 500 MHz): δ = 7.81–7.42 (m, 8 H, H^8, H^{36}, H^{39}), 7.28–7.18 (m, 10 H, H^{37}, H^9, H^{10}, H^{38}), 6.11 (dd, *J* = 15.3, 10.5 Hz, 1 H, H^{27}), 5.90 (dd, *J* = 15.3, 10.5 Hz, 1 H, H^{28}), 5.58 (dd, *J* = 15.3, 6.8 Hz, 1 H, H^{26}), 5.33 (dt, *J* = 14.5, 6.1 Hz, 1 H, H^{29}), 4.72 (d, *J* = 11.7 Hz, 1 H, H^{15a}), 4.62 (br. s, 1 H, H^{25}), 4.47 (d, *J* = 6.3 Hz, 2 H, H^{33}), 4.39 (d, *J* = 11.7 Hz, 1 H, H^{15b}), 4.16 (br. t, *J* = 5.4 Hz, 1 H, H^{31}), 4.01 (t, *J* = 6.3 Hz, 1 H, H^{34}), 3.85 (t, *J* = 6.4 Hz, 1 H, H^7), 3.71–3.64 (m, 1 H, H^4), 3.54 (t, *J* = 6.1 Hz, 2 H, H^{30}), 3.20 (s, 3 H, H^{12}), 3.01 (s, 3 H, H^{18}), 2.99 (q, *J* = 7.4 Hz, 1 H, H^2), 2.29–2.20 (m, 1 H, H^{5a}), 1.91–1.79 (m, 2 H, H^6, H^{5b}), 1.51 (d, *J* = 7.2 Hz, 3 H, H^{17}), 1.12 (s, 9 H, H^{21}), 1.00 (s, 9 H, H^{24}), *ca*. 0.98 (d, 3 H, H^{11}, hidden under H^{24} signal), 0.97 (s, 9 H, H^{24}), 0.30 (s, 3 H, H^{19}) ppm. **^{13}C NMR** (C_6D_6, 126 MHz): δ = 176.2 (C1), 169.8 (C16), 156.1 (C32), 144.7 (C35), 141.9 (C40), 136.4 (C8), 136.1 (C8), 134.5 (C26), 132.5 (C22), 132.0 (C22), 131.2 (C28), 131.0 (C27), 130.5 (C9/C10), 130.2 (C29), 128.6 (C38), 128.4 (C9/C10), 127.4 (C37), 125.4 (C39), 120.3 (C36), 84.4 (C3), 81.8 (C4), 76.9 (C7), 75.6 (C14), 66.3 (C33), 65.0 (C15), 58.3 (C12), 47.9 (C34), 43.2 (C2), 42.8 (C30), 37.8 (C6), 34.0 (C5), 28.1 (C24), 27.8 (C24), 27.6 (C18), 27.1 (C21), 20.6 (C23), 20.3 (C23), 19.3 (C20), 17.2 (C11), 8.9 (C17), −7.3 (C19) ppm.

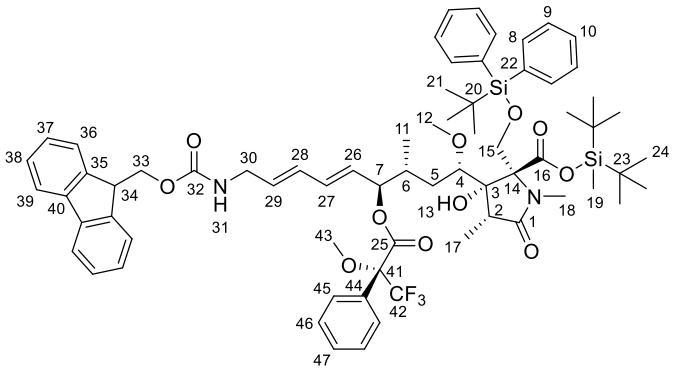
Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-acetoxy-1-methoxy-3-methylnona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (115)[50]



To a solution of alcohol **73** (11.0 mg, 10.8 μmol) in pyridine (110 μL, 1.36 mmol) was added acetic anhydride (10.2 μL, 108 μmol) at 0 °C, and the reaction mixture was allowed to gradually warm to room temperature over 22 h. The reaction mixture was diluted with EtOAc (3.3 mL) and sequentially washed with aq. 1 M HCl (3.3 mL), sat. aq. $NaHCO_3$ (3.3 mL) and sat. aq. NaCl (3.3 mL). The layers were separated and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% to 50% EtOAc/pentane) to afford acetate **115** as a colourless oil (9.8 mg, 86%). Data are consistent with those reported in the literature.[50] **$[\alpha]_D^{25}$** +16.1 (c 1.0, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.76 (d, *J* = 7.5 Hz, 2 H, H^{39}), 7.65–7.56 (m, 6 H, H^8, H^{36}), 7.48–7.43 (m, 2 H, H^{10}), 7.43–7.36 (m, 6 H, H^9, H^{38}), 7.30 (td, *J* = 7.5, 1.2 Hz, 2 H, H^{37}), 6.26 (dd, *J* = 15.2, 10.5 Hz, 1 H, H^{27}), 6.15 (dd, *J* = 15.1, 10.5 Hz, 1 H, H^{28}), 5.68 (dt, *J* = 15.1, 6.1 Hz, 1 H, H^{29}), 5.61 (dd, *J* = 15.2, 7.5 Hz, 1 H, H^{26}), 5.27 (dd, *J* = 7.5, 4.9 Hz, 1 H, H^7), 4.78 (br. t, *J* = 5.0 Hz, 1 H, H^{31}), 4.70 (s, 1 H, H^{13}), 4.48 (d, *J* = 12.0 Hz, 1 H, H^{15a}), 4.41 (d, *J* = 7.1 Hz, 2 H, H^{33}), 4.21 (t, *J* = 6.9 Hz, 1 H, H^{34}), 3.91 (d, *J* = 12.1 Hz, 1 H, H^{15b}), 3.82 (t, *J* = 6.1 Hz, 2 H, H^{30}), 3.48 (dd, *J* = 8.9, 2.2 Hz, 1 H, H^4), 3.35 (s, 3 H, H^{12}), 2.71 (q, *J* = 7.1 Hz, 1 H, H^2), 2.61 (s, 3 H, H^{18}), 2.06 (s, 3 H, H^{41}), 2.00–1.93 (m, 2 H, H^{5a}, H^6), 1.65–1.59 (m, 1 H, H^{5b}), 1.23 (d,

J = 7.3 Hz, 3 H, H^{17}), 1.06 (s, 9 H, H^{21}), 0.93 (d, *J* = 3.5 Hz, 3 H, H^{11}), 0.92 (s, 9 H, H^{24}), 0.90 (s, 9 H, H^{24}), 0.22 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.9 (C1), 170.3 (C25), 169.1 (C16), 156.3 (C32), 144.1 (C35), 141.5 (C40), 136.1 (C8), 135.8 (C8), 133.2 (C27), 131.7 (C22), 131.2 (C28), 130.7 (C29), 130.6 (C10), 130.4 (C10), 128.7 (C26), 128.1 (C9), 128.1 (C9), 127.8 (C38), 127.2 (C37), 125.2 (C36), 120.1 (C39), 84.0 (C3), 80.8 (C4), 77.4 (C7), 74.1 (C14), 66.9 (C33), 63.5 (C15), 59.2 (C12), 47.4 (C34), 42.9 (C2), 42.8 (C30), 34.8 (C6), 33.1 (C5), 27.9 (C24), 27.7 (C24), 27.0 (C21), 26.8 (C18), 21.5 (C41), 20.5 (C23), 20.3 (C23), 19.1 (C20), 16.4 (C11), 8.3 (C17), −7.4 (C19) ppm. **^{1}H NMR** (C_6D_6, 500 MHz): δ = 7.73–7.68 (m, 4 H, H^{8}), 7.61 (d, *J* = 7.5 Hz, 2 H, H^{36}), 7.46 (d, *J* = 7.5 Hz, 2 H, H^{39}), 7.29–7.13 (m, 10 H, H^{37}, H^{10}, H^{38}, H^{9}), 6.39–6.27 (m, 1 H, H^{27}), 5.87 (dd, *J* = 15.3, 10.5 Hz, 1 H, H^{28}), 5.65–5.56 (m, 2 H, H^{26}, H^{7}), 5.30 (dt, *J* = 15.3, 6.0 Hz, 1 H, H^{29}), 4.79 (s, 1 H, H^{13}), 4.74 (d, *J* = 11.9 Hz, 1 H, H^{15a}), 4.46 (d, *J* = 6.2 Hz, 2 H, H^{33}), 4.24 (d, *J* = 11.9 Hz, 1 H, H^{15b}), 4.05 (br. t, *J* = 6.2 Hz, 1 H, H^{31}), 3.99 (t, *J* = 6.2 Hz, 1 H, H^{34}), 3.69 (dd, *J* = 9.1, 2.6 Hz, 1 H, H^{4}), 3.52–3.44 (m, 2 H, H^{30}), 3.31 (s, 3 H, H^{12}), 3.00 (q, *J* = 7.2 Hz, 1 H, H^{2}), 2.91 (s, 3 H, H^{18}), 2.28–2.12 (m, 2 H, H^{5a}, H^{6}), 1.92 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 1 H, H^{5b}), 1.77 (s, 3 H, H^{41}), 1.51 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.11 (s, 9 H, H^{21}), 1.04 (d, *J* = 6.6 Hz, 3 H, H^{11}), 0.97 (s, 9 H, H^{24}), 0.95 (s, 9 H, H^{24}), 0.27 (s, 3 H, H^{19}) ppm. **^{13}C NMR** (C_6D_6, 126 MHz): δ = 176.2 (C1), 169.6 (C16), 169.5 (C25), 156.0 (C32), 144.7 (C35), 141.9 (C40), 136.3 (C8), 136.1 (C8), 134.0 (C27), 132.2 (C22), 131.7 (C22), 131.5 (C29), 130.7 (C28), 130.6 (C9/C10), 128.6 (C26), 128.4 (C38), 127.5 (C37), 127.4 (C9/C10), 125.3 (C39), 120.3 (C36), 84.4 (C3), 81.5 (C4), 77.5 (C7), 74.4 (C14), 66.2 (C33), 64.4 (C15), 59.2 (C12), 47.9 (C34), 43.2 (C2), 42.7 (C30), 35.1 (C6), 33.7 (C5), 28.1 (C24), 27.8 (C24), 27.1 (C21), 27.0 (C18), 20.9 (C41), 20.6 (C23), 20.3 (C23), 19.2 (C20), 16.7 (C11), 8.6 (C17), −7.3 (C19) ppm.

Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (248)

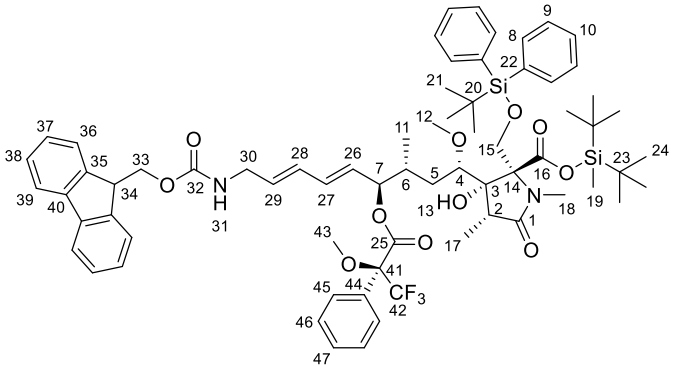


To a solution of alcohol **73** (3.0 mg, 2.94 µmol) in pyridine (18.6 µL, 230 µmol) were added $CDCl_3$ (60 µL, previously filtered through a small pad of silica) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (17.6 µL, 94.1 µmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 68 h. The solvent was removed by a stream of nitrogen gas and the crude product was purified twice by flash column chromatography (30% to 80% EtOAc/pentane) to afford (*R*)-MTPA ester **248** as a colourless oil (2.7 mg, 74%). $[\alpha]_D^{25}$ +14.7 (c 0.3, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.76 (d, *J* = 7.5 Hz, 2 H, H^{39}), 7.68–7.54 (m, 6 H, H^8, H^{36}), 7.53–7.48 (m, 2 H, H^{45}), 7.47–7.33 (m, 11 H, H^{38}, H^9, H^{46}, H^{47}, H^{10}), 7.33–7.28 (m, 2 H, H^{37}), 6.32–6.23 (m, 1 H, H^{27}), 6.19–6.08 (m, 1 H, H^{28}), 5.69–5.65 (m, 1 H, H^{26}), 5.65–5.64 (m, 1 H, H^{29}), 5.63–5.61 (m, 1 H, H^7), 4.79–4.72 (m, 1 H, H^{31}), 4.65 (s, 1 H, H^{13}), 4.45 (d, *J* = 12.0 Hz, 1 H, H^{15a}), 4.43–4.38 (m, 2 H, H^{33}), 4.24–4.17 (m, 1 H, H^{34}), 3.91 (d, *J* = 12.0 Hz, 1 H, H^{15b}), 3.84–3.76 (m, 2 H, H^{30}), 3.53 (s, 3 H, H^{43}), 3.45–3.41 (m, 1 H, H^4), 3.36 (s, 3 H, H^{12}), 2.71–2.63 (m, 1 H, H^2), 2.60 (s, 3 H, H^{18}), 2.03–1.97 (m, 1 H, H^6), 1.95–1.87 (m, 1 H, H^{5a}), 1.62–1.55 (m, 1 H, H^{5b}), 1.21 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.05 (s, 9 H, H^{21}), 0.92 (s, 9 H, H^{24}), 0.89 (s, 9 H, H^{24}), 0.84 (d, *J* = 6.6 Hz, 3 H, H^{11}), 0.22 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.8 (C1),

169.1 (C16), 165.8 (C25), 156.3 (C32), 144.0 (C35), 141.5 (C40), 136.1 (C8), 135.8 (C8), 134.5 (C27), 132.5 (C22), 131.7 (C22), 131.6 (C29), 131.1 (C44), 130.6 (C28), 130.4 (C38), 128.6 (C9/C46/C47/C10), 128.2 (C9/C46/C47/C10), 128.1 (C9/C46/C47/C10), 127.9 (C9/C46/C47/C10), 127.5 (C45), 127.2 (C37), 126.0 (C26), 125.2 (C36), 120.1 (C39), 84.7 (C41), 83.9 (C3), 80.4 (C4), 79.2 (C7), 74.2 (C14), 66.8 (C33), 63.5 (C15), 59.3 (C12), 55.5 (C43), 47.4 (C34), 42.9 (C2), 42.7 (C30), 34.5 (C6), 32.1 (C5), 27.9 (C24), 27.7 (C24), 27.0 (C21), 26.8 (C18), 20.5 (C23), 20.3 (C23), 19.1 (C20), 15.4 (C11), 8.3 (C17), −7.4 (C19) ppm. [N.B. Correlation between H^{43} and C41 can be observed in the HMBC spectrum, which allows to assign the ^{13}C-chemical shift of C41, although the corresponding quartet splitting pattern cannot be observed due to the low intensity of the signal. The expected ^{13}C quartet signal at *ca.* 123.6 ppm for C42 cannot be observed given its low intensity]. **^{19}F NMR** ($CDCl_3$, 471 MHz): δ = −71.3 (C42F_3) ppm. **^{1}H NMR** (C_6D_6, 500 MHz): δ = 7.72–7.69 (m, 2 H, H^{45}), 7.69–7.58 (m, 6 H, H^{8}, H^{39}), 7.48–7.41 (m, 2 H, H^{36}), 7.28–7.19 (m, 10 H, H^{9}, H^{38}, H^{37}, H^{10}), 7.13–7.09 (m, 3 H, H^{47}, H^{46}), 6.29 (dd, *J* = 15.6, 10.5 Hz, 1 H, H^{27}), 5.85–5.80 (m, 1 H, H^{7}), 5.81–5.75 (m, 1 H, H^{28}), 5.58 (dd, *J* = 15.6, 8.0 Hz, 1 H, H^{26}), 5.28–5.19 (m, 1 H, H^{29}), 4.64 (d, *J* = 11.8 Hz, 1 H, H^{15a}), 4.50–4.44 (m, 2 H, H^{33}), 4.22 (d, *J* = 11.8 Hz, 1 H, H^{15b}), 3.98 (d, *J* = 5.4 Hz, 1 H, H^{31}), 3.94 (t, *J* = 5.5 Hz, 1 H, H^{34}), 3.60 (d, *J* = 7.2 Hz, 1 H, H^{4}), 3.47 (s, 3 H, H^{43}), 3.45–3.40 (m, 2 H, H^{30}), 3.32 (s, 3 H, H^{12}), 3.06–3.01 (m, 1 H, H^{2}), 2.91 (s, 3 H, H^{18}), 2.31–2.22 (m, 1 H, H^{6}), 2.10–2.04 (m, 1 H, H^{5a}), 1.93–1.84 (m, 1 H, H^{5b}), 1.45 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.09 (s, 9 H, H^{21}), 0.95 (s, 9 H, H^{24}), 0.93 (s, 9 H, H^{24}), 0.91–0.90 (m, 3 H, H^{11}), 0.25 (s, 3 H, H^{19}) ppm. **^{13}C NMR** (C_6D_6, 126 MHz): δ = 177.8 (C1), 170.1 (C25), 169.0 (C16), 166.0 (C32), 144.5 (C35), 141.9 (C40), 136.3 (C8), 136.0 (C8), 135.3 (C27), 132.4 (C29), 132.1 (C22), 131.5 (C44), 130.7 (C9/C38/C37/C10), 130.4 (C9/C38/C37/C10), 130.2 (C28), 129.8 (C9/C38/C37/C10), 129.3 (C46), 128.4 (C47), *ca*. 128.1 (C9/C38/C37/C10, hidden under solvent signal), 127.9

(C45), 125.8 (C26), 125.3 (C36), 120.3 (C39), 85.0 (C41), 84.4 (C3), 80.8 (C4), 79.6 (C7), 75.2 (C14), 66.3 (C33), 64.3 (C15), 59.3 (C12), 55.4 (C43), 47.8 (C34), 43.4 (C2), 42.6 (C30), 34.7 (C6), 32.9 (C5), 28.0 (C24), 27.7 (C24), 27.6 (C18), 27.0 (C21), 20.6 (C23), 20.2 (C23), 19.2 (C20), 15.6 (C11), 8.4 (C17), −7.4 (C19) ppm. [N.B. Correlation between H^{43} and C41 can be observed in the HMBC spectrum, which allows to assign the ^{13}C-chemical shift of C41, although the corresponding quartet splitting pattern cannot be observed due to the low intensity of the signal. The expected ^{13}C quartet signal at *ca.* 123.6 ppm for C42 cannot be observed given its low intensity]. **^{19}F NMR** (C_6D_6, 471 MHz): δ = −71.4 (C42F_3) ppm. **FTIR** ν_{max} (thin film): 3359br, 3195w, 2955w, 2924m, 2854m, 1726s, 1684m, 1466m, 1429w, 1392w, 1388w, 1260s, 1242m, 1185m, 1170m, 1110m, 1082m, 1020m, 994w, 826m, 803m, 741s, 720w, 702m cm^{-1}. **HRMS** (MALDI-TOF): Calculated for $C_{69}H_{87}F_3N_2NaO_{11}Si_2^+$ $[M+Na]^+$ 1255.5693; found 1255.6151 (Δ +36.5 ppm).

Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (250)

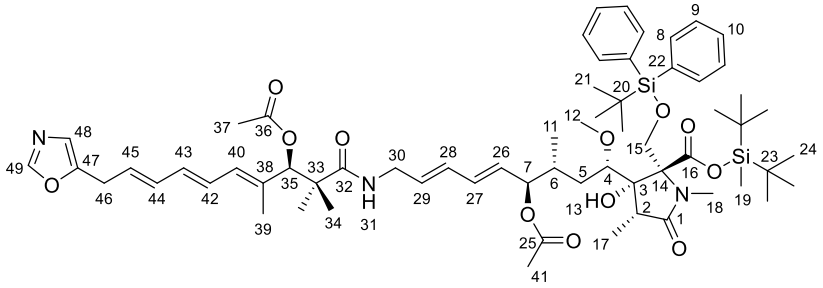


To a solution of alcohol **73** (3.0 mg, 2.94 µmol) in pyridine (9.30 µL, 115 µmol) were added $CDCl_3$ (920 µL, previously filtered through a small pad of silica) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.83 µL, 47.2 µmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 23 h, then additional portions of pyridine (9.30 µL, 115 µmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.83 µL, 47.2 µmol) were added and the reaction was stirred for a further 72 h at room temperature. The solvent was removed by a stream of nitrogen gas and the crude product was purified twice by flash column chromatography (30% to 80% EtOAc/pentane) to afford (*S*)-MTPA ester **250** as a colourless oil (3.4 mg, 93%). $[\alpha]_D^{25}$ −2.1 (c 0.3, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.80–7.73 (m, 2 H, H^{39}), 7.67–7.55 (m, 6 H, H^8, H^{36}), 7.53–7.48 (m, 2 H, H^{45}), 7.48–7.37 (m, 11 H, H^{38}, H^9, H^{46}, H^{47}, H^{10}), 7.33–7.28 (m, 2 H, H^{37}), 6.22–6.14 (m, 1 H, H^{27}), 6.14–6.05 (m, 1 H, H^{28}), 5.65–5.59 (m, 1 H, H^{29}), 5.58 (s, 1 H, H^7), 5.56–5.52 (m, 1 H, H^{26}), 4.80–4.74 (m, 1 H, H^{31}), 4.70 (s, 1 H, H^{13}), 4.48 (d, *J* = 12.0 Hz, 1 H, H^{15a}), 4.44–4.37 (m, 2 H, H^{33}), 4.21 (t, *J* = 6.7 Hz, 1 H, H^{34}), 3.92 (d, *J* = 12.0 Hz, 1 H, H^{15b}), 3.85–3.76 (m, 2 H, H^{30}), 3.54 (s, 3 H, H^{43}), 3.46–3.41 (m, 1 H, H^4), 3.33 (s, 3 H, H^{12}), 2.70–2.64 (m, 1 H, H^2), 2.61 (s, 3 H, H^{18}), 2.08–2.04 (m, 1 H, H^6), 1.99–

1.91 (m, 1 H, H^{5a}), 1.66–1.61 (m, 1 H, H^{5b}), 1.22 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.05 (s, 9 H, H^{21}), 0.94–0.92 (m, 3 H, H^{11}), 0.92 (s, 9 H, H^{24}), 0.90 (s, 9 H, H^{24}), 0.22 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 176.7 (C1), 169.2 (C16), 165.8 (C25), 156.3 (C32), 144.1 (C35), 141.5 (C40), 136.1 (C8), 135.8 (C8), 134.1 (C27), 132.4 (C22), 131.7 (C22), 131.4 (C29), 131.1 (C44), 130.6 (C28), 130.4 (C38), 128.5 (C9/C10), 128.5 (C10/C9), 128.2 (C46/C47), 128.1 (C47/C46), 127.6 (C45), 127.2 (C37), 126.2 (C26), 125.2 (C36), 120.1 (C39), 84.7 (C41), 84.0 (C3), 80.7 (C4), 79.3 (C7), 74.2 (C14), 66.8 (C33), 63.5 (C15), 59.2 (C12), 55.6 (C43), 47.4 (C34), 42.9 (C2), 42.8 (C30), 34.8 (C6), 32.1 (C5), 27.9 (C24), 27.7 (C24), 27.0 (C21), 26.8 (C18), 20.5 (C23), 20.2 (C23), 19.1 (C20), 15.8 (C11), 8.3 (C17), −7.4 (C19) ppm. [N.B. Correlation between H^{43} and C41 can be observed in the HMBC spectrum, which allows to assign the ^{13}C-chemical shift of C41, although the corresponding quartet splitting pattern cannot be observed due to the low intensity of the signal. The expected ^{13}C quartet signal at *ca.* 123.6 ppm for C42 cannot be observed given its low intensity]. **^{19}F NMR** ($CDCl_3$, 471 MHz): δ = −71.3 (C42F_3) ppm. **^{1}H NMR** (C_6D_6, 500 MHz): δ = 7.72 (d, *J* = 7.8 Hz, 2 H, H^{45}), 7.68 (dt, *J* = 7.1, 1.9 Hz, 4 H, H^{8}), 7.61 (d, *J* = 7.5 Hz, 2 H, H^{39}), 7.48–7.43 (m, 2 H, H^{36}), 7.28–7.19 (m, 11 H, H^{38}, H^{9}, H^{37}, H^{10}, H^{47}), 7.09–6.98 (m, 2 H, H^{46}), 6.22 (dd, *J* = 15.4, 10.5 Hz, 1 H, H^{27}), 5.85–5.80 (m, 1 H, H^{7}), 5.80–5.71 (m, 1 H, H^{28}), 5.49–5.44 (m, 1 H, H^{26}), 5.28–5.18 (m, 1 H, H^{29}), 4.72 (d, *J* = 11.9 Hz, 1 H, H^{15a}), 4.69 (s, 1 H, H^{13}), 4.47 (dd, *J* = 6.2, 2.6 Hz, 2 H, H^{33}), 4.23 (d, *J* = 11.9 Hz, 1 H, H^{15b}), 4.02 (br. t, *J* = 5.9 Hz, 1 H, H^{31}), 3.98 (t, *J* = 6.2 Hz, 1 H, H^{34}), 3.61 (d, *J* = 7.6 Hz, 1 H, H^{4}), 3.50 (s, 3 H, H^{43}), 3.49–3.43 (m, 2 H, H^{30}), 3.27 (s, 3 H, H^{12}), 2.93 (d, *J* = 7.2 Hz, 1 H, H^{2}), 2.90 (s, 3 H, H^{18}), 2.28–2.22 (m, 1 H, H^{6}), 2.22–2.16 (m, 1 H, H^{5a}), 1.97–1.88 (m, 1 H, H^{5b}), 1.48 (d, *J* = 7.2 Hz, 3 H, H^{17}), 1.09 (s, 9 H, H^{21}), 1.02 (d, *J* = 6.9 Hz, 3 H, H^{11}), 0.95 (s, 9 H, H^{24}), 0.94 (s, 9 H, H^{24}), 0.25 (s, 3 H, H^{19}) ppm. **^{13}C NMR** (C_6D_6, 126 MHz): δ = 175.9 (C1), 173.5 (C25), 169.8 (C16), 166.0 (C32), 144.7 (C35), 141.9

(C40), 136.3 (C8), 136.1 (C8), 134.9 (C27), 132.3 (C29), 132.2 (C22), 131.6 (C44), 130.7 (C9/C38/C37/C10), 130.3 (C37/C10/C38/C9), 130.2 (C28), 129.8 (C37/C10/C38/C9), 129.3 (C46), 128.4 (C47), *ca.* 128.1 (C38/C9/C37/C10, hidden under solvent signal), 127.8 (C45), 126.0 (C26), 125.3 (C36), 120.3 (C39), 85.4 (C41), 84.4 (C3), 81.3 (C4), 79.7 (C7), 74.5 (C14), 66.2 (C33), 64.4 (C15), 59.1 (C12), 55.6 (C43), 47.9 (C34), 43.2 (C2), 42.7 (C30), 35.1 (C6), 32.4 (C5), 28.1 (C24), 27.8 (C24), 27.7 (C18), 27.0, (C21), 20.6 (C23), 20.2 (C23), 19.2 (C20), 16.1 (C11), 8.7 (C17), −7.4 (C19) ppm. [N.B. Correlation between H^{43} and C41 can be observed in the HMBC spectrum, which allows to assign the ^{13}C-chemical shift of C41, although the corresponding quartet splitting pattern cannot be observed due to the low intensity of the signal. The expected ^{13}C quartet signal at *ca.* 123.6 ppm for C42 cannot be observed given its low intensity]. **^{19}F NMR** (C_6D_6, 471 MHz): δ = −71.3 (C42F_3) ppm. **FTIR** ν_{max} (thin film): 3359br, 3192w, 2955w, 2924s, 2853m, 1726m, 1684w, 1660s, 1632s, 1468m, 1428w, 1411w, 1379w, 1258s, 1240m, 1184w, 1168w, 1113m, 1080m, 1020m, 993w, 826w, 802w, 740m, 721w, 703m cm^{-1}. **HRMS** (MALDI-TOF): Calculated for $C_{69}H_{87}F_3N_2NaO_{11}Si_2^+$ $[M+Na]^+$ 1255.5693; found 1255.9026 (Δ +265 ppm).

Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-4-acetoxy-9-((*R*,4*E*,6*E*,8*E*)-3-acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienamido)-1-methoxy-3-methylnona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate (251)



To a solution of acid **41** (5.6 mg, 16.8 µmol) in CH_2Cl_2 (209 µL) were added freshly recrystallised[148] BOPCl (4.3 mg, 16.7 µmol) and freshly distilled Et_3N (4.70 µL, 33.5 µmol) at room temperature. This mixture was stirred at room temperature for 3 h in the dark to afford the mixed anhydride. To a solution of acetate **115** (7.1 mg, 6.70 µmol) in CH_2Cl_2 (209 µL) was added freshly distilled DBU (1.50 µL, 10.0 µmol) at room temperature. This mixture was stirred at room temperature for 30 min in the dark to afford the free amine. The solution of free amine was added to the solution of activated acid at room temperature, and the resulting mixture was stirred at room temperature for 14 h in the dark. The reaction mixture was diluted with EtOAc (4.7 mL) and sequentially washed with aq. 1 M HCl (4.7 mL), sat. aq. $NaHCO_3$ (4.7 mL) and sat. aq. NaCl (4.7 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by multiple elution preparative TLC (70% EtOAc/cyclohexane) to afford amide **251** as a colourless oil (2.2 mg, 28%). **^{1}H NMR** ($CDCl_3$, 700 MHz): δ = 7.82 (s, 1 H, H^{49}), 7.62 (ddd, *J* = 18.0, 8.0, 1.2 Hz, 4 H, H^8), 7.48–7.37 (m, 6 H, H^{10}, H^9), 6.82 (s, 1 H, H^{48}), 6.39–6.31 (m, 1 H, H^{42}), 6.29–6.18 (m, 3 H, H^{27}, H^{44}, H^{43}), 6.15 (dd, *J* = 15.1, 10.6 Hz, 1 H, H^{28}), 6.03 (d, *J* = 11.1 Hz, 1 H, H^{40}), 5.86 (t, *J* = 5.5 Hz, 1 H, H^{31}), 5.75 (dt, *J* = 13.5, 7.0 Hz, 1 H, H^{45}), 5.66 (dt, *J* = 15.1, 6.5 Hz, 1 H, H^{29}), 5.59 (dd, *J* = 15.3, 7.5 Hz, 1 H, H^{26}), 5.30 (s, 1 H, H^{35}),

5.26–5.22 (m, 1 H, H^{7}), 4.47 (d, *J* = 12.1 Hz, 1 H, H^{15a}), 3.91 (d, *J* = 12.1 Hz, 1 H, H^{15b}), 3.93–3.80 (m, 2 H, H^{30}), 3.49 (d, *J* = 6.8 Hz, 2 H, H^{46}), 3.46 (dd, *J* = 8.7, 2.6 Hz, 1 H, H^{4}), 3.34 (s, 3 H, H^{12}), 2.69 (q, *J* = 7.3 Hz, 1 H, H^{2}), 2.60 (s, 3 H, H^{18}), 2.05 (s, 3 H, H^{37}), 2.05 (s, 3 H, H^{41}), 1.99–1.95 (m, 1 H, H^{5a}), 1.95–1.91 (m, 1 H, H^{6}), 1.75 (s, 3 H, H^{39}), 1.57–1.54 (m, 1 H, H^{5b}), 1.22 (d, *J* = 7.3 Hz, 3 H, H^{17}), 1.18 (s, 3 H, H^{34}), 1.15 (s, 3 H, H^{34}), 1.06 (s, 9 H, H^{21}), 0.92 (d, *J* = 3.5 Hz, 3 H, H^{11}), 0.91 (s, 9 H, H^{24}), 0.89 (s, 9 H, H^{24}), 0.22 (s, 3 H, H^{19}) ppm. **^{13}C NMR** ($CDCl_3$, 176 MHz): δ = 176.8 (C1), 175.0 (C32), 170.3 (C25), 169.5 (C36), 169.1 (C16), 161.9 (C49), 150.9 (C47), 136.1 (C8), 135.8 (C8), 134.1 (C38), 133.5 (C44), 133.2 (C27), 132.9 (C43), 131.6 (C28), 131.1 (C22), 130.6 (C10), 130.4 (C29), 129.3 (C40), 128.9 (C26), 128.2 (C9), 128.1 (C9), 128.0 (C42), 127.8 (C45), 122.9 (C48), 84.0 (C3), 82.7 (C35), 80.8 (C4), *ca*. 77.5 (C7, hidden under solvent signal), 74.2 (C14), 63.5 (C15), 59.1 (C12), 46.4 (C33), 42.8 (C2), 41.5 (C30), 34.8 (C6), 33.0 (C5), 29.1 (C46), 27.9 (C24), 27.7 (C24), 27.0 (C21), 26.8 (C18), 23.2 (C34), 21.7 (C34), 21.5 (C37), 21.2 (C41), 20.5 (C23), 20.2 (C23), 19.1 (C20), 16.5 (C11), 15.2 (C39), 8.4 (C17), −7.4 (C19) ppm. **HRMS** (MALDI-TOF): Calculated for $C_{64}H_{94}N_3O_{12}Si_2^+$ $[M+H]^+$ 1152.6371; found 1152.8665 (Δ +199 ppm). Calculated for $C_{64}H_{93}N_3NaO_{12}Si_2^+$ $[M+Na]^+$ 1174.6190; found 1174.8641 (Δ +209 ppm). [N.B. Optical rotation and **FTIR** data for this compound have not been recorded due to limited amount of available material. Priority has been given to its use as starting material for the final steps of the total synthesis].

References

1. Kawai, S.; Kawabata, G.; Kobayashi, A.; Kawazu, K. *Agric. Biol. Chem.* **1989**, *53*, 1127.
2. Kawazu, K.; Kanzaki, H.; Kawabata, G.; Kawai, S.; Kobayashi, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1382.
3. Kanzaki, H.; Wada, K.; Nitoda, T.; Kawazu, K. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 438.
4. Ryu, G.; Hwang, S.; Kim, S. K. *J. Antibiot. (Tokyo).* **1997**, *50*, 1064.
5. Ogura, M.; Nakayama, H.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot. (Tokyo).* **1985**, *38*, 669.
6. Otani, T.; Yoshida, K. I.; Kubota, H.; Kawai, S.; Ito, S.; Hori, H.; Ishiyama, T.; Oki, T. *J. Antibiot. (Tokyo).* **2000**, *53*, 1397.
7. Manam, R. R.; Teisan, S.; White, D. J.; Nicholson, B.; Grodberg, J.; Neuteboom, S. T. C.; Lam, K. S.; Mosca, D. A.; Lloyd, G. K.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 240.
8. Omura, S.; Tanaka, Y.; Kanaya, I.; Shinose, M.; Takahashi, Y. *J. Antibiot. (Tokyo).* **1990**, *43*, 1034.
9. Tanaka, Y.; Kanaya, I.; Takahashi, Y.; Shinose, M.; Tanaka, H.; Omura, S. *J. Antibiot. (Tokyo).* **1993**, *46*, 1208.
10. Tonew, E.; Tonew, M.; Gräfe, U.; Zöpel, P. *Acta Virol.* **1992**, *36*, 166.
11. Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discov. Technol.* **2004**, *1*, 181.
12. Groll, M.; Huber, R.; Potts, B. C. M. *J. Am. Chem. Soc.* **2006**, *128*, 5136.
13. Hogan, P. C.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 15386.
14. Groll, M.; Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 14981.

15. Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073.

16. Henkel, T.; Zeeck, A. *Liebigs Ann. Chem.* **1991**, 367.

17. Gräfe, U.; Kluge, H.; Thiericke, R. *Liebigs Ann. Chem.* **1992**, 429.

18. Bagwell, C. L.; Moloney, M. G.; Thompson, A. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4081.

19. Grigorjev, P. A.; Schlegel, R.; Gräfe, U. *Pharmazie* **1992**, *47*, 707.

20. Tanaka, Y.; Kanaya, I.; Shiomi, K.; Tanaka, H.; Omura, S. *J. Antibiot. (Tokyo).* **1993**, *46*, 1214.

21. Omura, S. *Gene* **1992**, *115*, 141.

22. Legendre, F.; Maturano, M. D.; Etienne, G.; Klaebe, A.; Tiraby, G. *J. Antibiot. (Tokyo).* **1995**, *48*, 341.

23. Kawada, M.; Inoue, H.; Usami, I.; Ikeda, D. *Cancer Sci.* **2009**, *100*, 150.

24. Kawada, M.; Yoshimoto, Y.; Minamiguchi, K.; Kumagai, H.; Someno, T.; Masuda, T.; Ishizuka, M.; Ikeda, D. *Anticancer Res.* **2004**, *24*, 1561.

25. Kreiss, W.; Fröde, R.; Möhrle, V.; Eberz, G. *Anal. Bioanal. Chem.* **2010**, *398*, 2081.

26. Zhao, C.; Coughlin, J. M.; Ju, J.; Zhu, D.; Wendt-Pienkowski, E.; Zhou, X.; Wang, Z.; Shen, B.; Deng, Z. *J. Biol. Chem.* **2010**, *285*, 20097.

27. Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778.

28. Senapati, B. K.; Gao, L.; Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 5088.

29. Yoshino, M.; Eto, K.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Biomol. Chem.* **2012**, *10*, 8164.

30. Hale, K. J.; Grabski, M.; Manaviazar, S.; Maczka, M. *Org. Lett.* **2014**, *16*, 1164.

31. Souris, C.; Frébault, F.; Patel, A.; Audisio, D.; Houk, K. N.; Maulide, N. *Org. Lett.* **2013**, *15*, 3242.

32. Athawale, P. R.; Kashinath, K.; Reddy, D. S. *ChemistrySelect* **2016**, *1*, 495.

33. Hale, K. J.; Hatakeyama, S.; Urabe, F.; Ishihara, J.; Manaviazar, S.; Grabski, M.; Maczka, M. *Org. Lett.* **2014**, *16*, 3536.

34. van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *13*, 2369.

35. Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

36. Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194.

37. Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276.

38. Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321.

39. Fujiyama, R.; Goh, K.; Kiyooka, S. *Tetrahedron Lett.* **2005**, *46*, 1211.

40. Ó Dálaigh, C.; Connon, S. J. *J. Org. Chem.* **2007**, *72*, 7066.

41. Tan, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 2783.

42. Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.

43. Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1985**, *63*, 109.

44. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

45. Dimopoulos, P.; Athlan, A.; Manaviazar, S.; George, J.; Walters, M.; Lazarides, L.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2005**, *7*, 5369.

46. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

47. Hodgson, D. M.; Foley, A. M.; Boulton, L. T.; Lovell, P. J.; Maw, G. N. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2911.

48. Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis* **1991**, 414.

49. Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*, 5398.

50. Donohoe, T. J.; O'Riordan, T. J. C.; Peifer, M.; Jones, C. R.; Miles, T. J. *Org. Lett.* **2012**, *14*, 5460.

51. Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070.

52. Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6703.

53. Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6244.

54. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

55. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

56. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

57. Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

58. Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem. Int. Ed.* **1965**, *4*, 271.

59. Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc. Perkin Trans. 1* **1998**, 667.

60. Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 2293.

61. Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421.

62. van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558.

63. van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994.

64. Walker, J. C. L., Part II thesis, University of Oxford, **2013**.

65. Baker, D. B., DPhil thesis, University of Oxford, **2014**.

66. Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935.

67. Miller, R. A.; Smith, R. M.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074.

68. Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

69. Piazza, C.; Knochel, P. *Angew. Chem.* **2002**, *114*, 3397.

70. Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489.

71. Gieseler, M. T.; Kalesse, M. *Org. Lett.* **2011**, *13*, 2430.

72. Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.

73. Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.

74. Bluet, G.; Campagne, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5507.

75. Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293.

76. Duhamel, P.; Cahard, D.; Poirier, J.-M. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2509.

77. Duhamel, L.; Guillemont, J.; Poirier, J.-M.; Chabardes, P. *Tetrahedron Lett.* **1991**, *32*, 4495.

78. Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232.

79. Cahard, D.; Poirier, J.-M.; Duhamel, P. *Tetrahedron Lett.* **1998**, *39*, 7093.

80. Boisvert, L.; Beaumier, F.; Spino, C. *Org. Lett.* **2007**, *9*, 5361.

81. Huang, Y.; Fañanás-Mastral, M.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2013**, *49*, 3309.

82. Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. *Tetrahedron* **1996**, *52*, 15325.

83. Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc. Chem. Commun.* **1995**, 355.

84. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

85. Chan, C.; Zheng, S.; Zhou, B.; Guo, J.; Heid, R. M.; Wright, B. J. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 1749.

86. Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559.

87. Han, C.-Q.; DiTullio, D.; Wang, Y.-F.; Sih, C. J. *J. Org. Chem.* **1986**, *51*, 1253.

88. Hayashida, J.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4373.

89. Ohtsuki, K.; Matsuo, K.; Yoshikawa, T.; Moriya, C.; Tomita-Yokotani, K.; Shishido, K.; Shindo, M. *Org. Lett.* **2008**, *10*, 1247.

90. Lee, K.; Kim, H.; Hong, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5735.

91. Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

92. Bérubé, G.; Deslongchamps, P. *Can. J. Chem.* **1990**, *68*, 404.

93. Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.

94. Lautens, M.; Maddess, M. L. *Org. Lett.* **2004**, *6*, 1883.

95. Childs, R. F.; Hagar, M. E. *Can. J. Chem.* **1980**, *58*, 1788.

96. Haughey, M. B., Part II thesis, University of Oxford, **2016**.

97. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

98. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

99. Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

100. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

101. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

102. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

103. Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.

104. Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508.

105. Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961.

106. Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45.

107. Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Chem. Commun.* **2014**, *50*, 10355.

108. Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

109. Nuñez-Zarur, F.; Solans-Monfort, X.; Rodríguez-Santiago, L.; Sodupe, M. *Organometallics* **2012**, *31*, 4203.

110. Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

111. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

112. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697.

113. van Rensburg, W. J.; Steynberg, P. J.; Kirk, M. M.; Meyer, W. H.; Forman, G. S. *J. Organomet. Chem.* **2006**, *691*, 5312.

114. Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865.

115. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.

116. Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492.

117. Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913.

118. Clark, D. A.; Clark, J. R.; Diver, S. T. *Org. Lett.* **2008**, *10*, 2055.

119. Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161.

120. Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075.

121. Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389.

122. Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.

123. Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

124. Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2011.

125. Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. *Org. Lett.* **2001**, *3*, 2101.

126. Kisselev, A. F.; van der Linden, W. A.; Overkleeft, H. S. *Chem. Biol.* **2012**, *19*, 99.

127. Kisselev, A. F.; Goldberg, A. L. *Chem. Biol.* **2001**, *8*, 739.

128. Adams, J. *Cancer Cell* **2004**, *5*, 417.

129. Arlt, A.; Bauer, I.; Schafmayer, C.; Tepel, J.; Müerköster, S. S.; Brosch, M.; Röder, C.; Kalthoff, H.; Hampe, J.; Moyer, M. P.; Fölsch, U. R.; Schäfer, H. *Oncogene* **2009**, *28*, 3983.

130. Manasanch, E. E.; Orlowski, R. Z. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 417.

131. Suraweera, A.; Münch, C.; Hanssum, A.; Bertolotti, A. *Mol. Cell* **2012**, *48*, 242.

132. Gulder, T. A. M.; Moore, B. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 9346.

133. Shiina, I.; Umezaki, Y.; Kuroda, N.; Iizumi, T.; Nagai, S.; Katoh, T. *J. Org. Chem.* **2012**, *77*, 4885.

134. Donohoe, T. J.; Thomas, R. E. *Nat. Protoc.* **2007**, *2*, 1888.

135. Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.

136. Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *J. Med. Chem.* **2002**, *45*, 2289.

137. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.

138. O'Riordan, T. J. C., DPhil thesis, University of Oxford, **2009**.

139. Peifer, M., Postdoctoral report, University of Oxford, **2010**.

140. Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803.

141. Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065.

142. Clayden, J.; Yasin, S. A. *New J. Chem.* **2002**, *26*, 191.

143. Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

144. Bhide, R. S.; Levison, B. S.; Sharma, R. B.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1986**, *27*, 671.

145. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

146. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

147. Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.

148. van der Auwera, C.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1986**, *95*, 203.

149. Chai, C.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, *5th Edition*, Butterworth-Heinemann, **2003**.

150. Liu, G.-S.; Dong, Q.-L.; Yao, Y.-S.; Yao, Z.-J. *Org. Lett.* **2008**, *10*, 5393.

151. Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.

152. Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708.

153. Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 574.

154. Matsuda, T.; Yamada, Z. *Nippon Kagaku Kaishi* **1973**, 99.

155. Burr, D. A.; Chen, X. B.; Vederas, J. C. *Org. Lett.* **2007**, *9*, 161.

156. Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* **2001**, 1690.

157. Price, M. D.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2002**, *67*, 7769.

158. Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

159. Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.

160. Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125.

161. Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, *68*, 974.

162. Bausch, C. C.; Patman, R. L.; Breit, B.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5687.

163. Volkmer-Engert, R.; Hoffmann, B.; Schneider-Mergener, J. *Tetrahedron Lett.* **1997**, *38*, 1029.

164. Moon, N. G.; Harned, A. M. *Tetrahedron Lett.* **2013**, *54*, 2960.

165. Grandguillot, J.-C.; Rouessac, F. *Tetrahedron* **1991**, *47*, 5133.

166. Grisenti, P.; Ferraboschi, P.; Casati, S.; Santaniello, E. *Tetrahedron: Asymmetry* **1993**, *4*, 997.

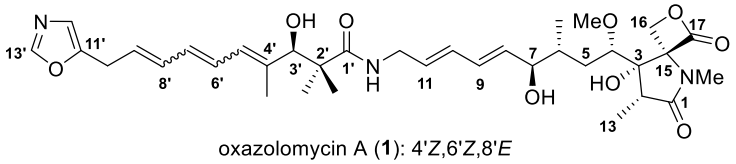
167. Kanada, R. M.; Itoh, D.; Nagai, M.; Nijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350.

168. Boeckman, R. K.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572.

169. Wünsch, S.; Breit, B. *Chem. Eur. J.* **2015**, *21*, 2358.

Appendices

Appendix 1. ^{1}H NMR data of isolated oxazolomycins A, B and C



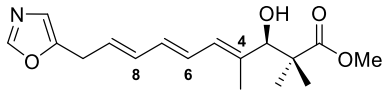
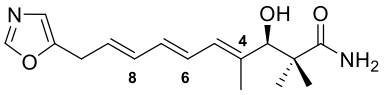
oxazolomycin A (**1**): 4'*Z*,6'*Z*,8'*E*
oxazolomycin B (**2**): 4'*E*,6'*E*,8'*E*
oxazolomycin C (**3**): 4'*Z*,6'*E*,8'*E*

Proton	Oxazolomycin A (**1**)		Oxazolomycin B (**2**)		Oxazolomycin C (**3**)	
	δ (ppm)	multiplicity, *J* (Hz)	δ (ppm)	multiplicity, *J* (Hz)	δ (ppm)	multiplicity, *J* (Hz)
6-CH_3	1.04	d, *J* = 6.8 Hz	1.04	d, *J* = 6.7 Hz	1.04	d, *J* = 6.7 Hz
2'-CH_3	1.11	s	1.13	s	1.12	s
2-CH_3	1.22	d, *J* = 7.3 Hz	1.22	d, *J* = 7.3 Hz	1.22	d, *J* = 7.3 Hz
2'-CH_3	1.30	s	1.24	s	1.30	s
5-H	1.36	ddd, *J* = 4.9, 8.0, 15.0 Hz	1.38	m	1.36	ddd, *J* = 4.9, 7.6, 15.3Hz
6-H	1.79	m	1.80	m	1.80	m
4'-CH_3	1.84	br.s	1.78	s	1.79	s
5-H	2.10	ddd, *J* = 5.3, 5.3, 15.1 Hz	2.10	ddd, *J* = 5.2, 5.2, 15.5 Hz	2.10	ddd, *J* = 5.5, 5.5, 15.3 Hz
2-H	2.54	q, *J* = 7.3 Hz)	2.54	q, *J* = 7.3 Hz	2.54	q, *J* = 7.3 Hz
N-CH_3	2.94	s	2.94	s	2.94	s
O-CH_3	3.36	s	3.37	s	3.37	s
4-H	3.56	dd, *J* = 4.9, 5.3 Hz	3.56	dd, *J* = 5.2, 5.2 Hz	3.57	dd, *J* = 4.9, 5.5 Hz
10'-H	3.61	d, *J* = 6.8 Hz	3.56	d, *J* = 7.0 Hz	3.56	d, *J* = 7.0 Hz
12-H	3.87	d, *J* = 5.8 Hz	3.87	d, *J* = 5.8 Hz	3.87	d, *J* = 5.8 Hz
7-H	4.02	dd, *J* = 5.0, 6.5 Hz	4.02	dd, *J* = 5.4, 6.7 Hz	4.03	dd, *J* = 5.5, 6.7 Hz
16-H	4.55	d, *J* = 6.2 Hz	4.54	d, *J* = 6.4 Hz	4.54	d, *J* = 6.4 Hz
3'-H	4.75	s	4.12	s	4.73	s
16-H	4.89	d, *J* = 6.2 Hz	4.89	d, *J* = 6.4 Hz	4.89	d, *J* = 6.4 Hz
8-H	5.73	dd, *J* = 6.5, 14.2 Hz	5.73	dd, *J* = 6.7, 14.3 Hz	5.73	dd, *J* = 6.7, 14.6 Hz
11-H	5.73	dt, *J* = 5.8, 14.2 Hz	5.73	dt, *J* = 5.8, 14.3 Hz	5.73	dt, *J* = 5.8, 14.6 Hz
9'-H	5.84	dt, *J* = 6.8, 15.0 Hz	5.82	dt, *J* = 7.0, 14.3 Hz	5.80	dt, *J* = 7.0, 14.9 Hz
7'-H	6.01	dd, *J* = 10.7, 12.3 Hz	6.26	dd, *J* = 11.1, 14.6 Hz	6.20	dd, *J* = 11.0, 15.0 Hz
9-H	6.28	d, *J* = 14.2 Hz	6.27	d, *J* = 14.3 Hz	6.27	d, *J* = 14.6 Hz
10-H	6.28	d, *J* = 14.2 Hz	6.26	d, *J* = 14.3 Hz	6.27	d, *J* = 14.6 Hz
6'-H	6.33	dd, *J* = 10.7, 11.7 Hz	6.48	dd, *J* = 11.3, 14.6 Hz	6.59	dd, *J* = 11.6, 15.0 Hz
5'-H	6.50	d, *J* = 11.7 Hz	6.08	d, *J* = 11.3 Hz	6.05	d, *J* = 11.6 Hz
8'-H	6.77	dd, *J* = 12.3, 15.0 Hz	6.32	dd, *J* = 11.1, 14.3 Hz	6.31	dd, *J* = 11.0, 14.9 Hz
12'-H	6.90	s	6.89	s	6.89	s
13'-H	8.15	s	8.12	s	8.12	s

N.B. ^{1}H NMR data recorded in CD_3OD. 5'-H and 8'-H signals are shifted downfield in oxazolomycin A. 3'-H signal is shifted upfield in oxazolomycin B.

Table 15. ^{1}H NMR data[1,3] of isolated oxazolomycins A (**1**), B (**2**) and C (**3**)

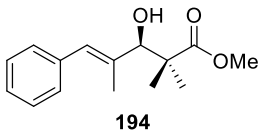
Appendix 2. Optical rotation data of ester 32 and inthomycin C

Author	 **32** $[\alpha]_D$	enantiomeric excess	 (-)-(3*R*)-inthomycin C (**12**) $[\alpha]_D$	enantiomeric excess
This work[96]	+1.2 (c 1.0, $CHCl_3$)	89% ee 13.3:1 mixture of **32** and (4*E*,6*E*,8*Z*) isomer	–8.2 (c 1.0, $CHCl_3$)	89% ee 11.1:1 mixture of **12** and (4*E*,6*E*,8*Z*) isomer
Hale[30]	–0.43 (c 0.7, $CHCl_3$)	83% ee 17:1 mixture of **32** and unknown isomer	–8.4 (c 1.0, $CHCl_3$)	83% ee 5.9:1 mixture of **12** and unknown isomer
Hatakeyama (Corrected data)[29,33]	+0.78 (c 1.39, $CHCl_3$)	98% ee	–7.9 (c 0.33, $CHCl_3$)	98% ee
Ryu[28]	+8.48 (c 0.9, $CHCl_3$)	93% ee	–34.33 (c 0.1, $CHCl_3$)	93% ee
Taylor[27]	+5.2 (c 1.55, $CHCl_3$)	76% ee	+25.9 (c 0.27, $CHCl_3$)	76% ee contaminated with 20% tetramethyl urea

N.B. "$[\alpha]_D$" = specific rotation at the sodium D line (λ = 589 nm). "c" = concentration (g/100 mL)

Table 16. Summary of reported optical rotation data of ester **32** and inthomycin C (**12**)

Appendix 3. HPLC data



194
(83% ee)

HPLC conditions: Chiralcel OD column, 5% 2-propanol/*n*-heptane, 1.0 mL/min, 254 nm UV detector, t_1 = 10.45 min (minor) and t_2 = 12.70 min (major).

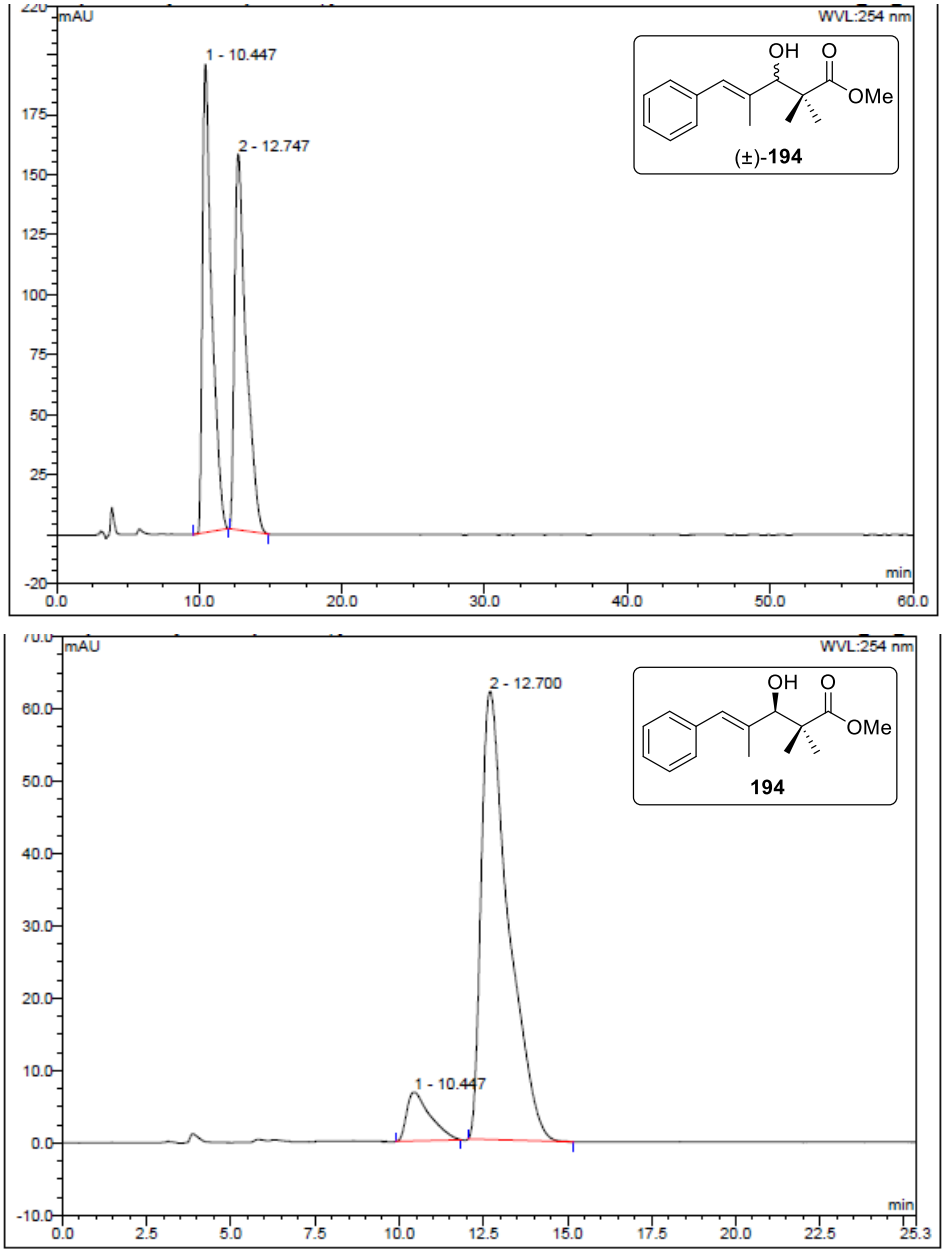
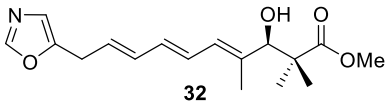


Figure 23. HPLC chromatograms of racemic alcohol **194** and enantioenriched alcohol **194**



32

(82% ee)

HPLC conditions: Chiralcel OD column, 10% 2-propanol/*n*-heptane, 1.0 mL/min, 254 nm UV detector, t_1 = 24.39 min (minor) and t_2 = 28.83 min (major).

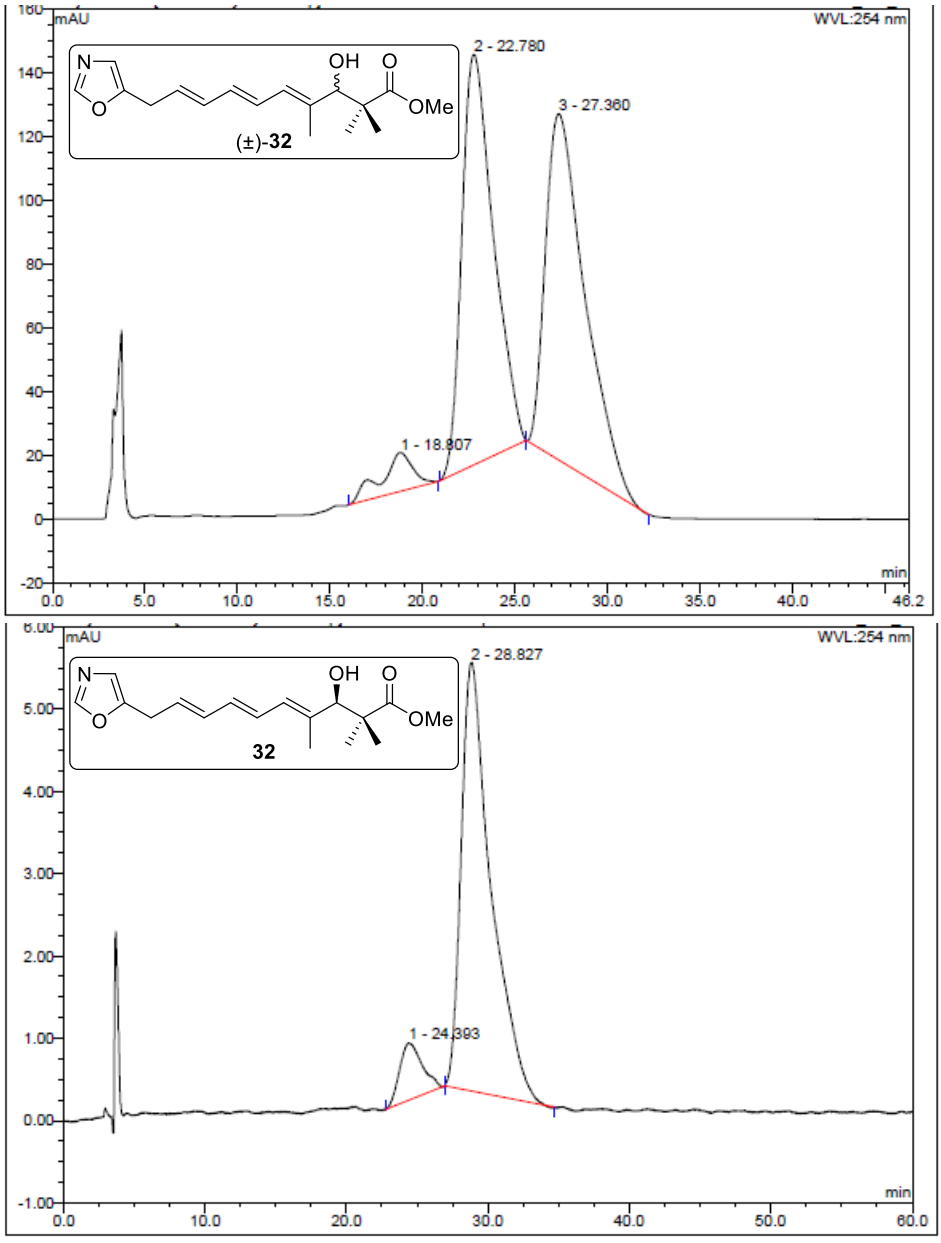
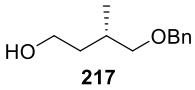


Figure 24. HPLC chromatograms of racemic alcohol **32** and enantioenriched alcohol **32**. N.B. Enantioenriched alcohol **32** was later obtained in an improved 89% ee by a co-worker, after optimisation of the Mukaiyama–Kiyooka aldol conditions[96]



217

(95% ee)

HPLC conditions: Chiralcel OD-H column, 2% 2-propanol/*n*-heptane, 1.0 mL/min, 205 nm UV detector, t_1 = 24.04 min (major) and t_2 = 28.02 min (minor).

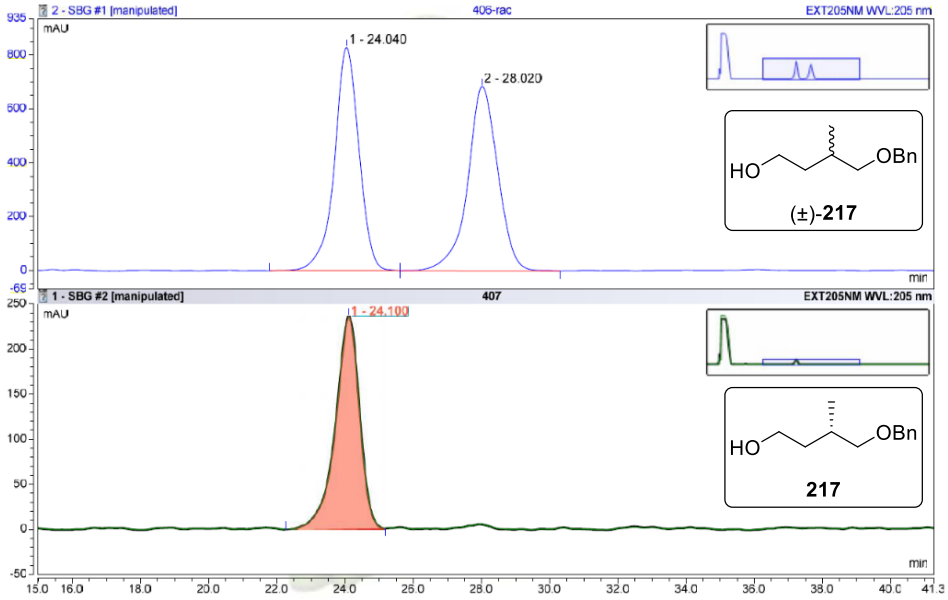


Figure 25. HPLC chromatograms of racemic alcohol **217** and enantioenriched alcohol **217**

Appendix 4. Molecular modelling of oxazolomycin B

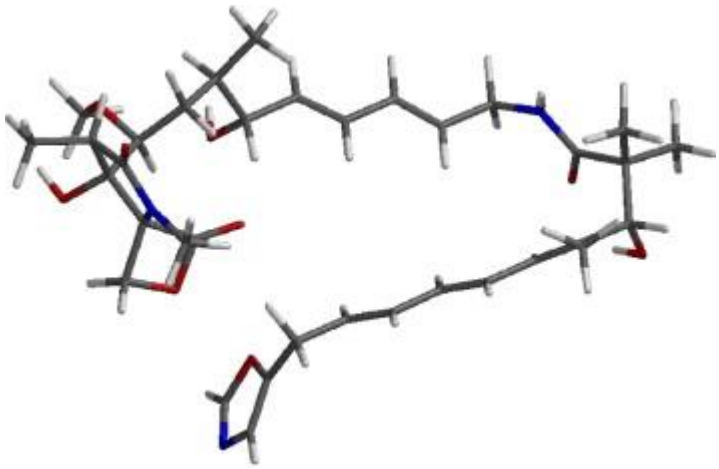
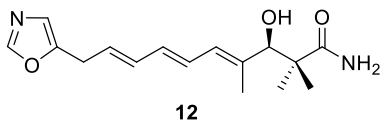


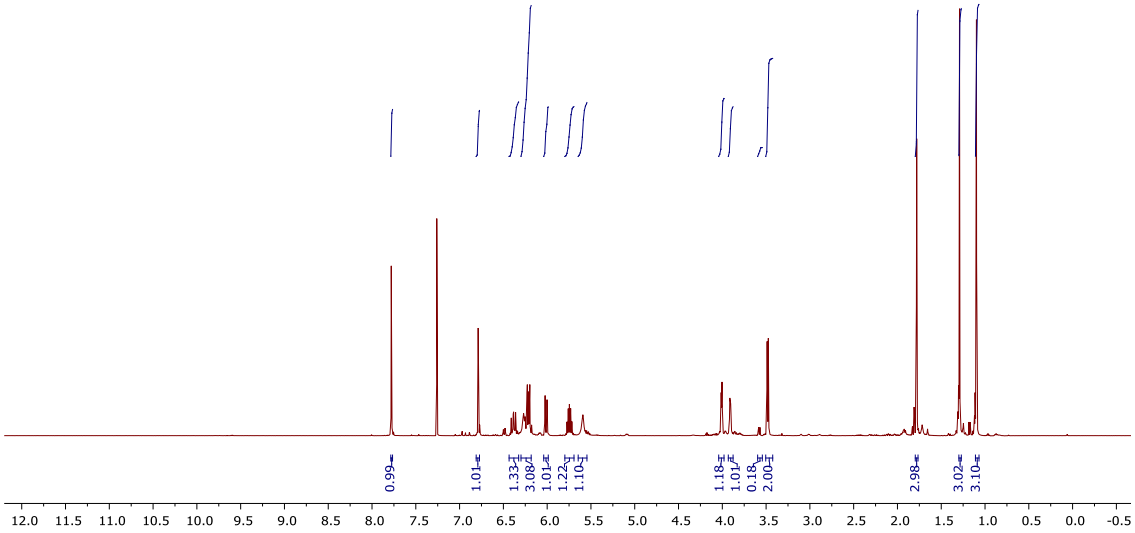
Figure 26. Minimum energy conformation for oxazolomycin B (energy = −252.4 kcal/mol, NH. . .O distance 4.07 Å)[18]

Appendix 5. ^{1}H and ^{13}C NMR data of compounds 12, 116, 248, 250 and 251

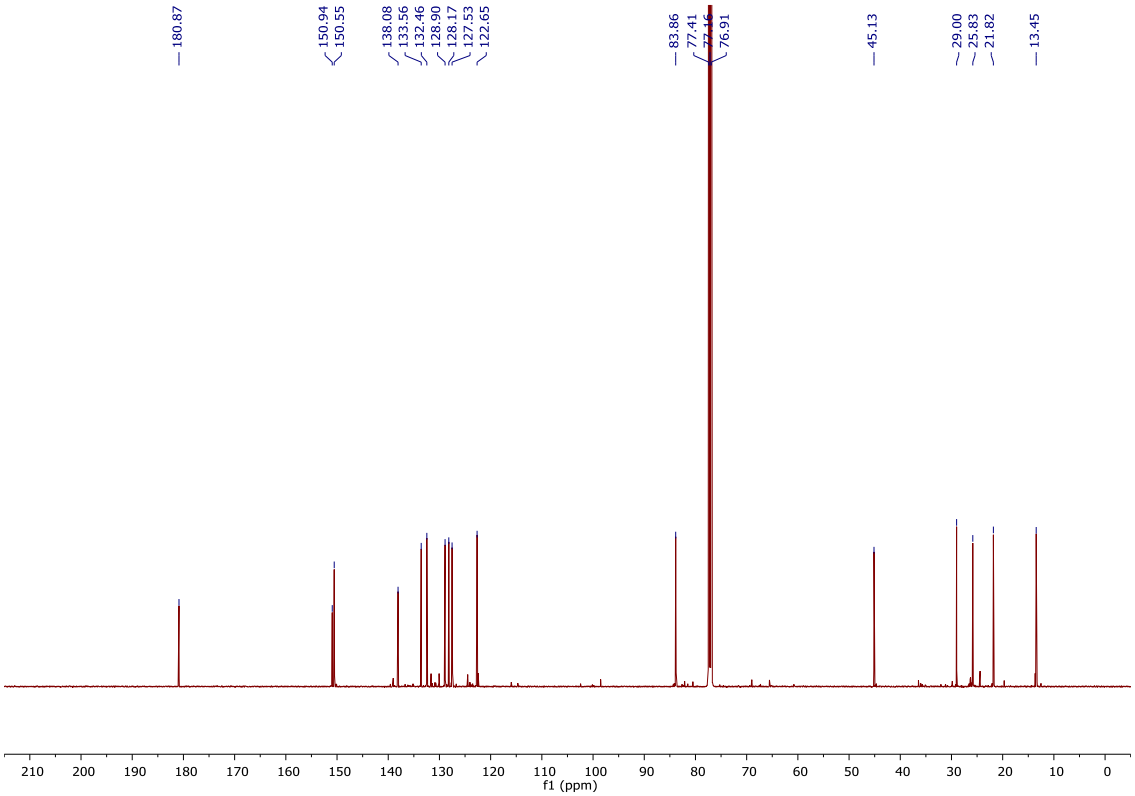
^{1}H NMR (500 MHz, $CDCl_3$): (–)-(3*R*)-Inthomycin C



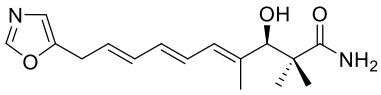
12



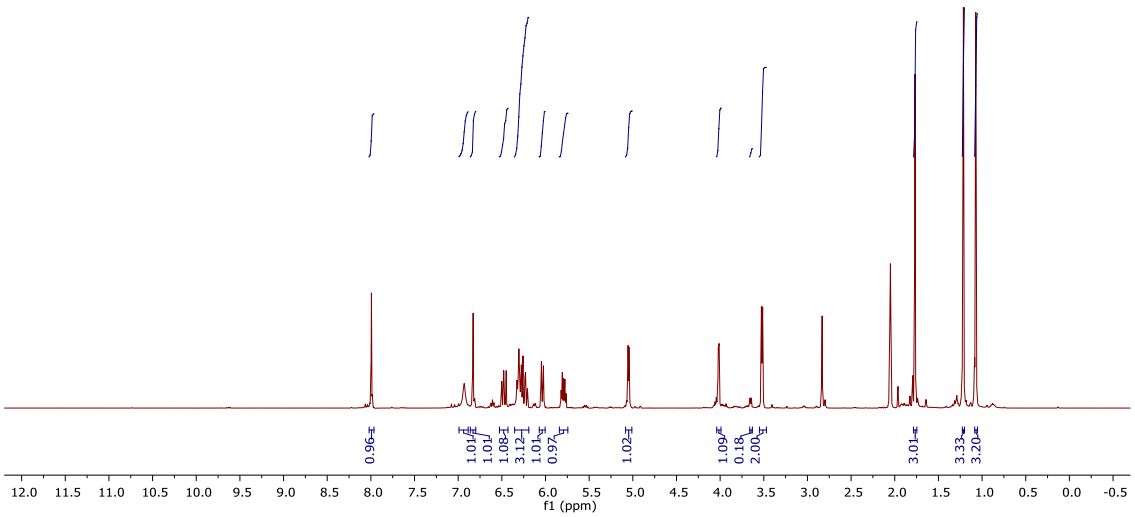
^{13}C NMR (126 MHz, $CDCl_3$):



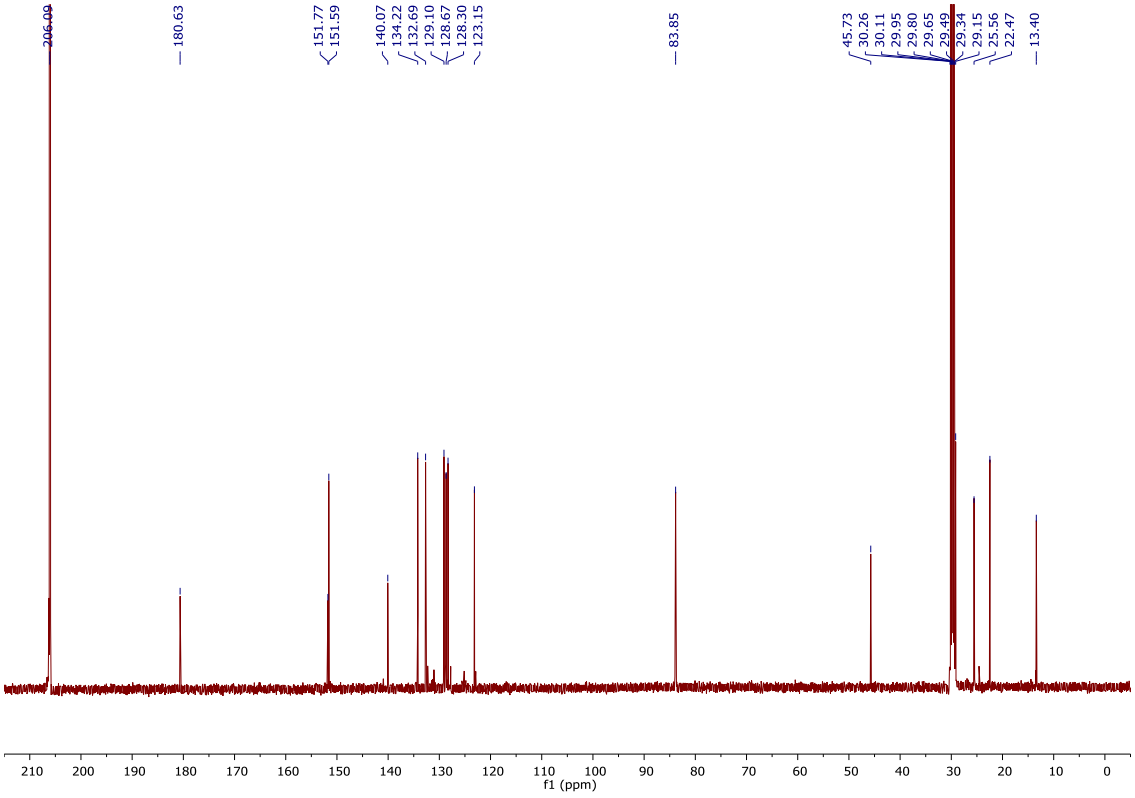
^{1}H NMR (500 MHz, Acetone-d_6): (–)-(3*R*)-Inthomycin C



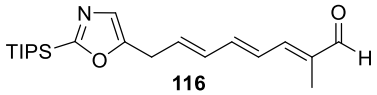
12



^{13}C NMR (126 MHz, Acetone-d_6):



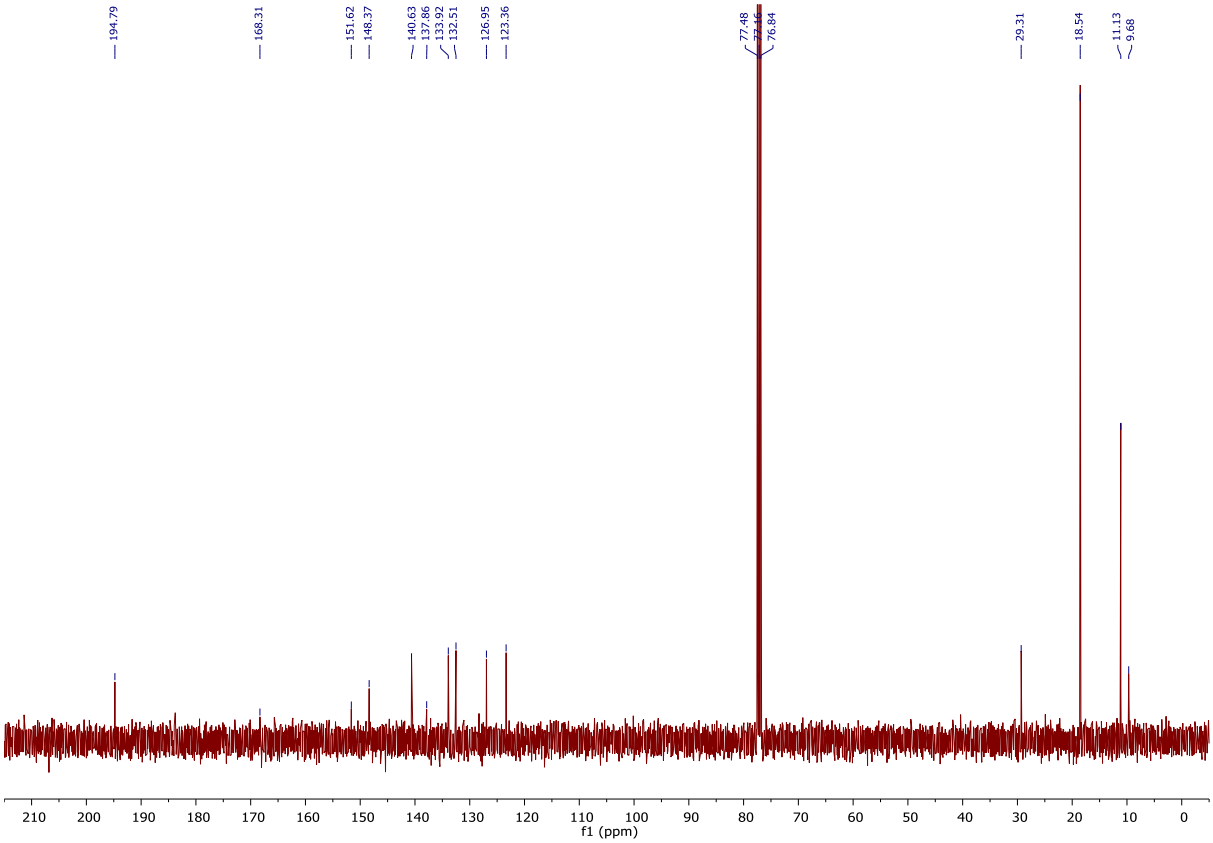
^{1}H NMR (400 MHz, $CDCl_3$): (2*E*,4*E*,6*E*)-2-Methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,4,6-trienal



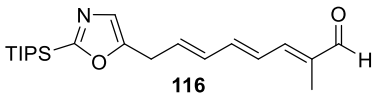
116

8:1 mixture

^{13}C NMR (101 MHz, $CDCl_3$):



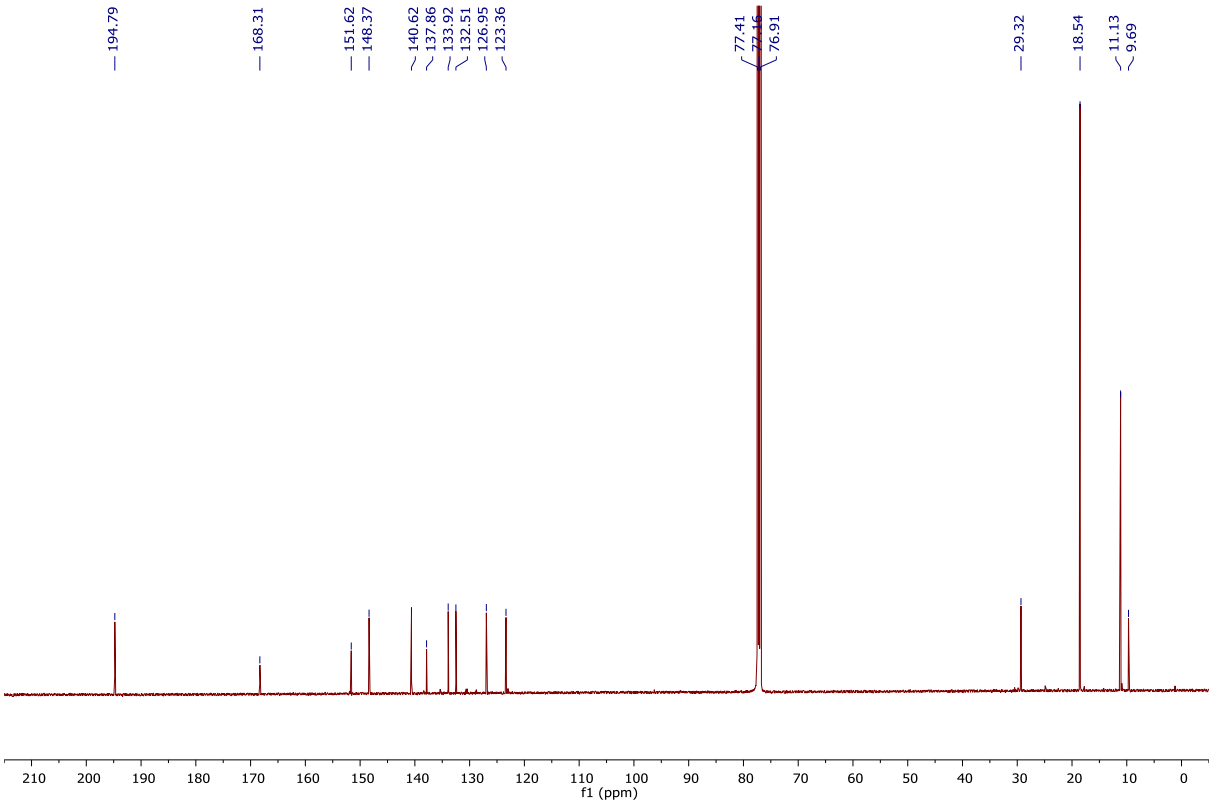
^{1}H NMR (500 MHz, $CDCl_3$): (2*E*,4*E*,6*E*)-2-Methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,4,6-trienal



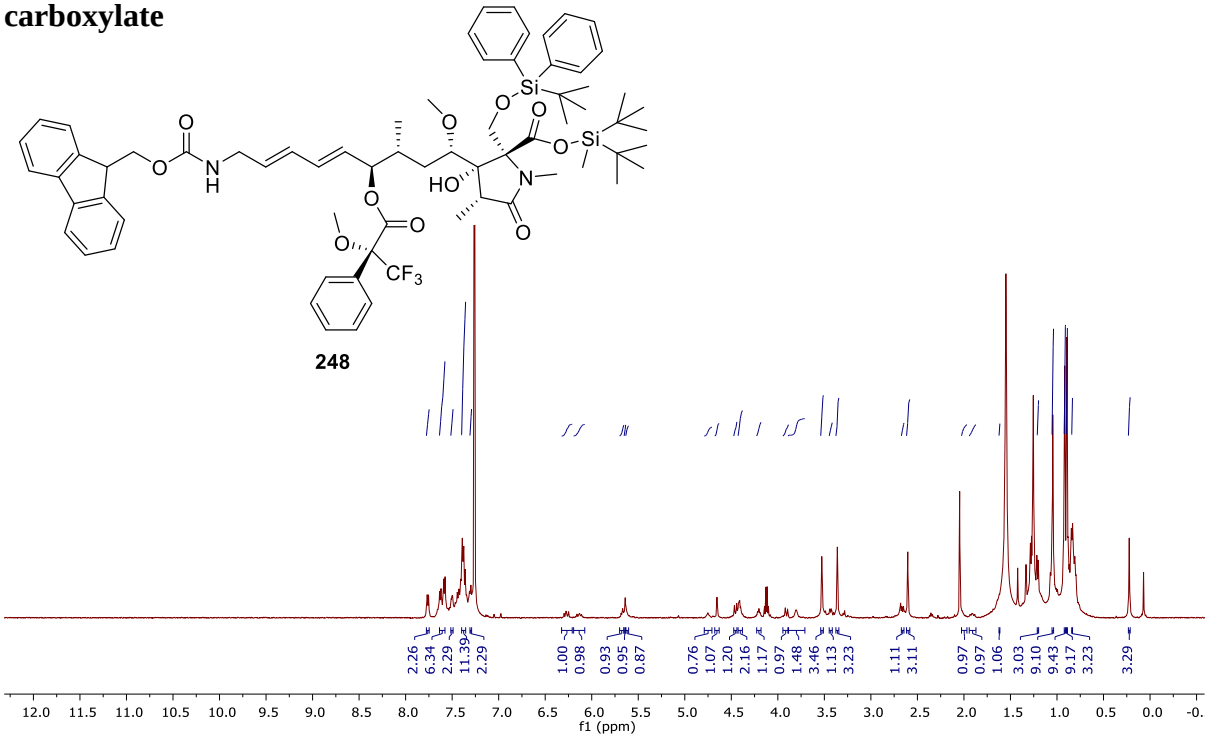
116

22:1 mixture

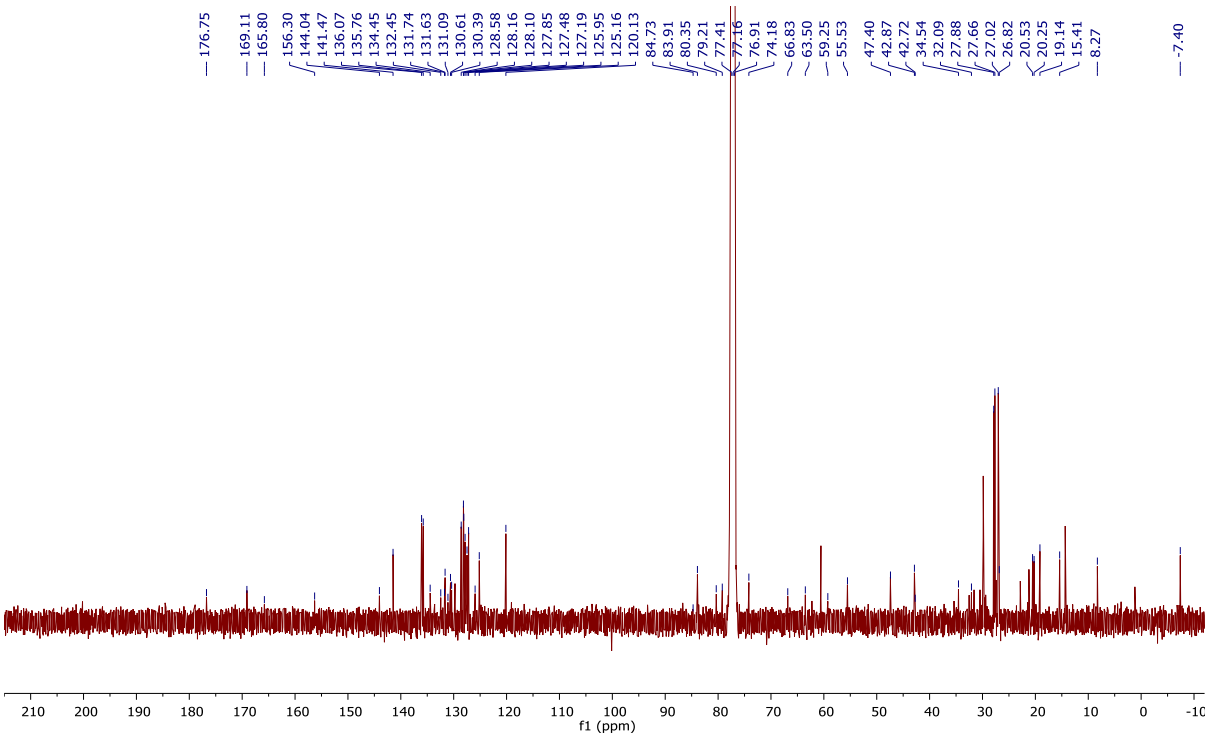
^{13}C NMR (126 MHz, $CDCl_3$):



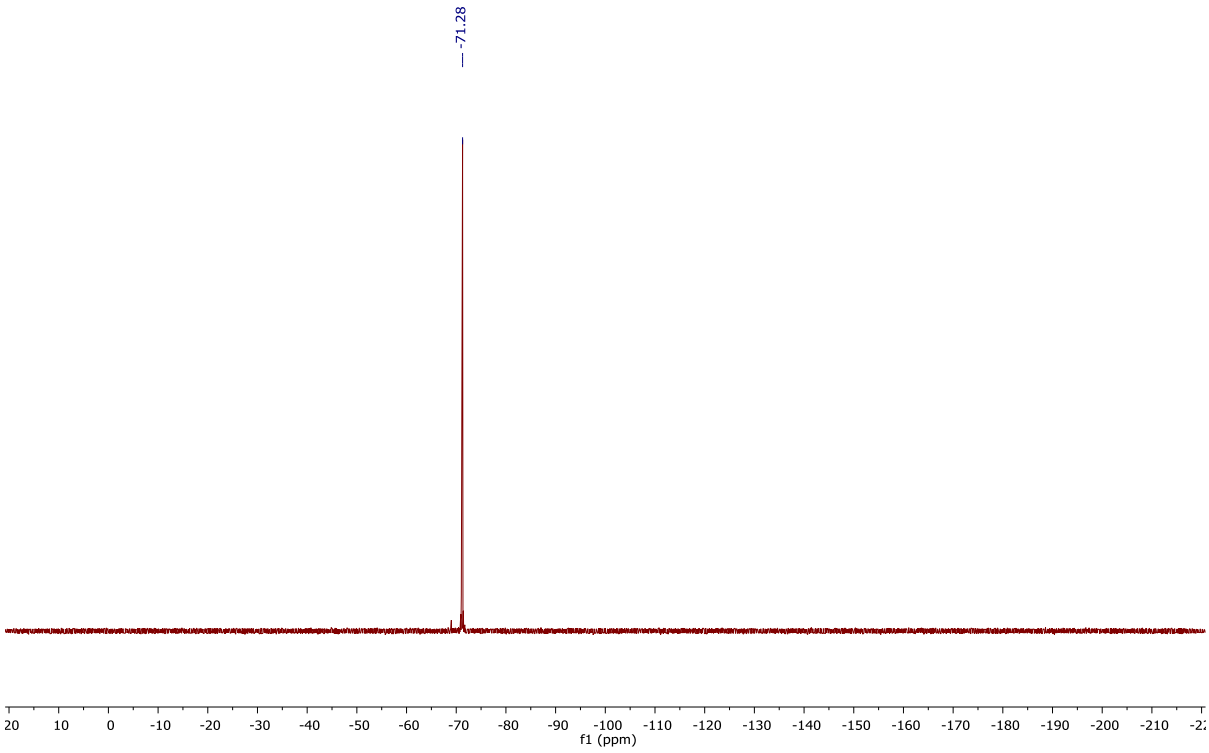
^{1}H NMR ($CDCl_3$, 500 MHz): Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate



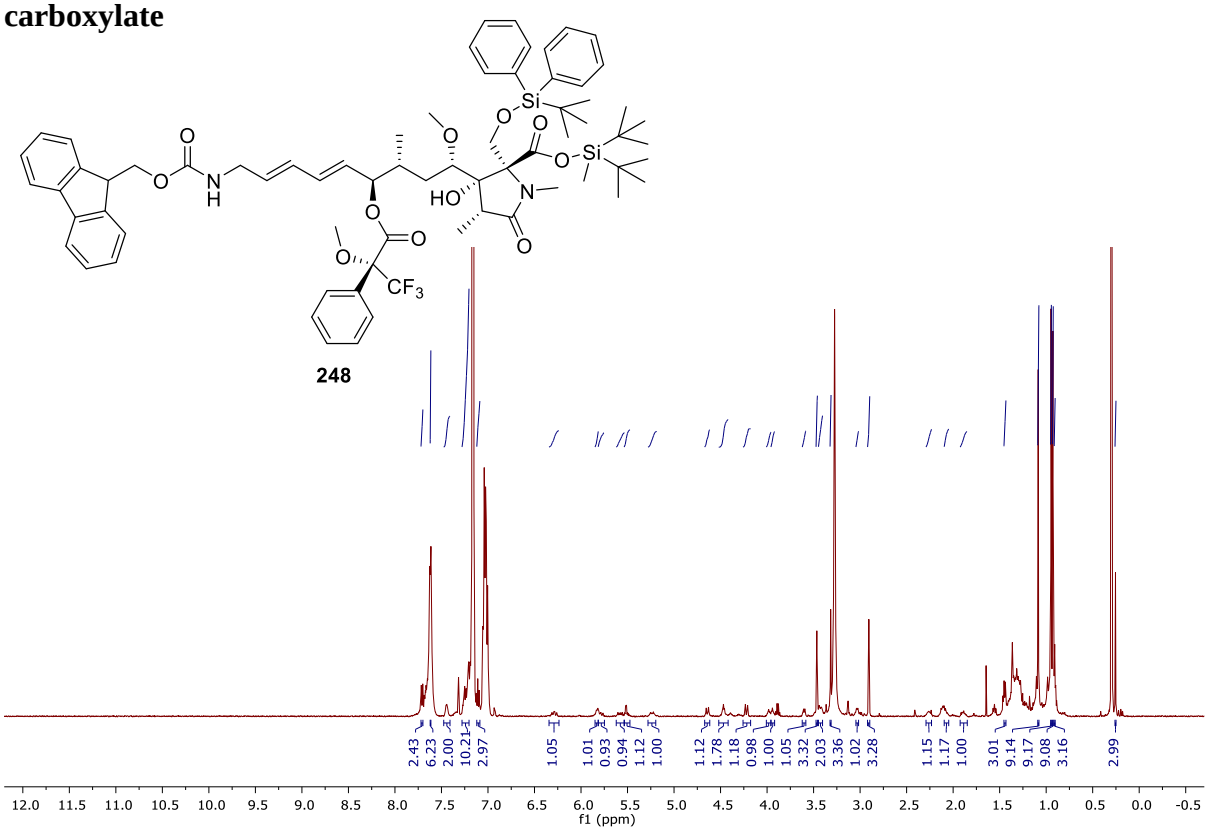
^{13}C NMR ($CDCl_3$, 126 MHz):



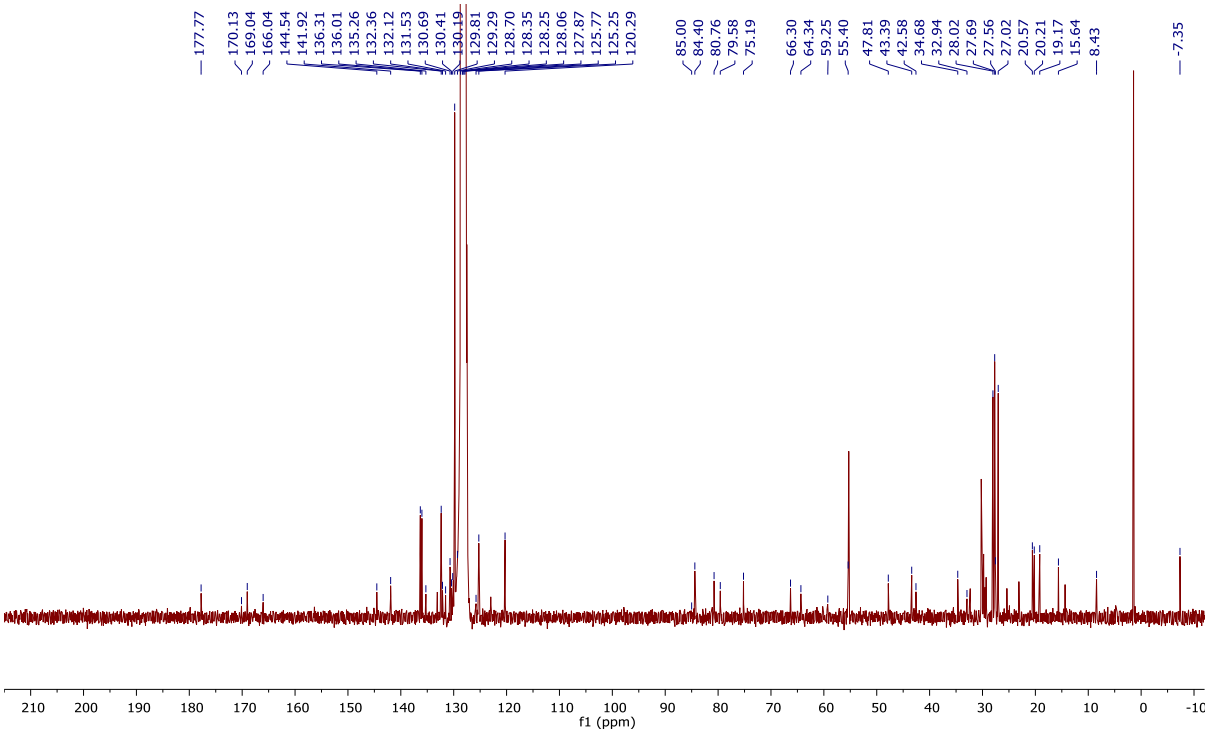
^{19}F NMR ($CDCl_3$, 471 MHz):



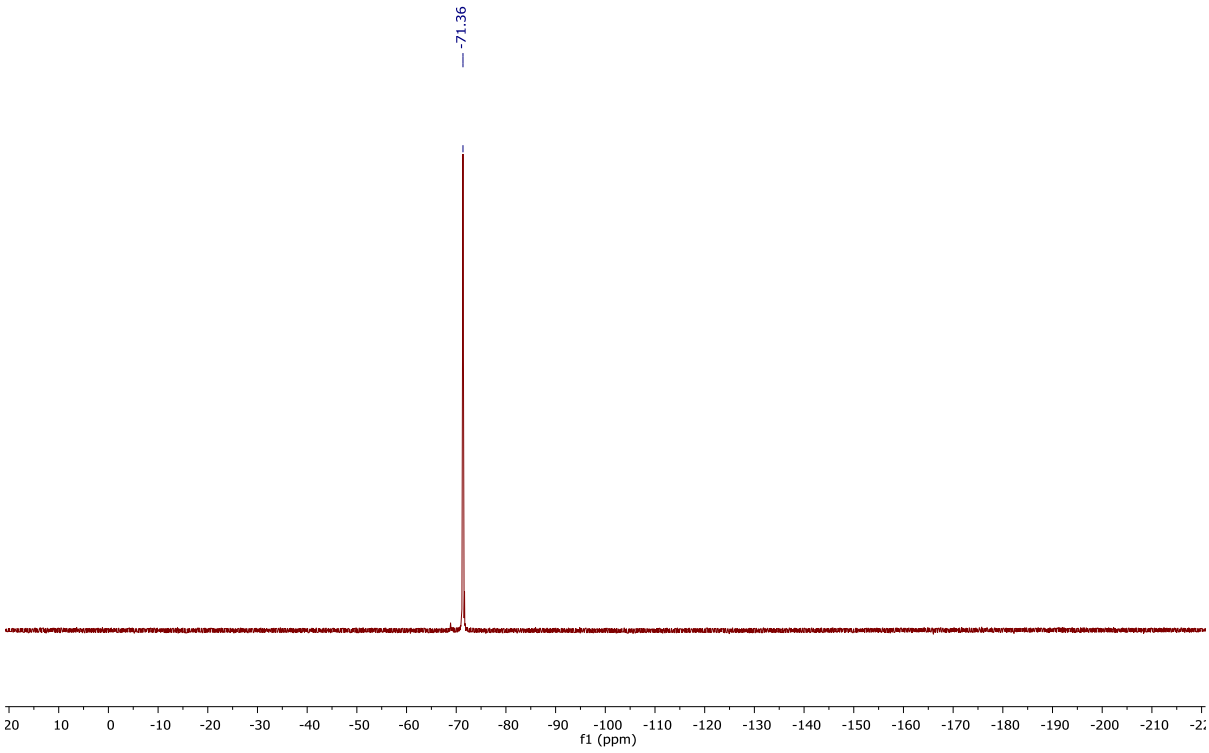
^{1}H NMR (C_6D_6, 500 MHz): Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate



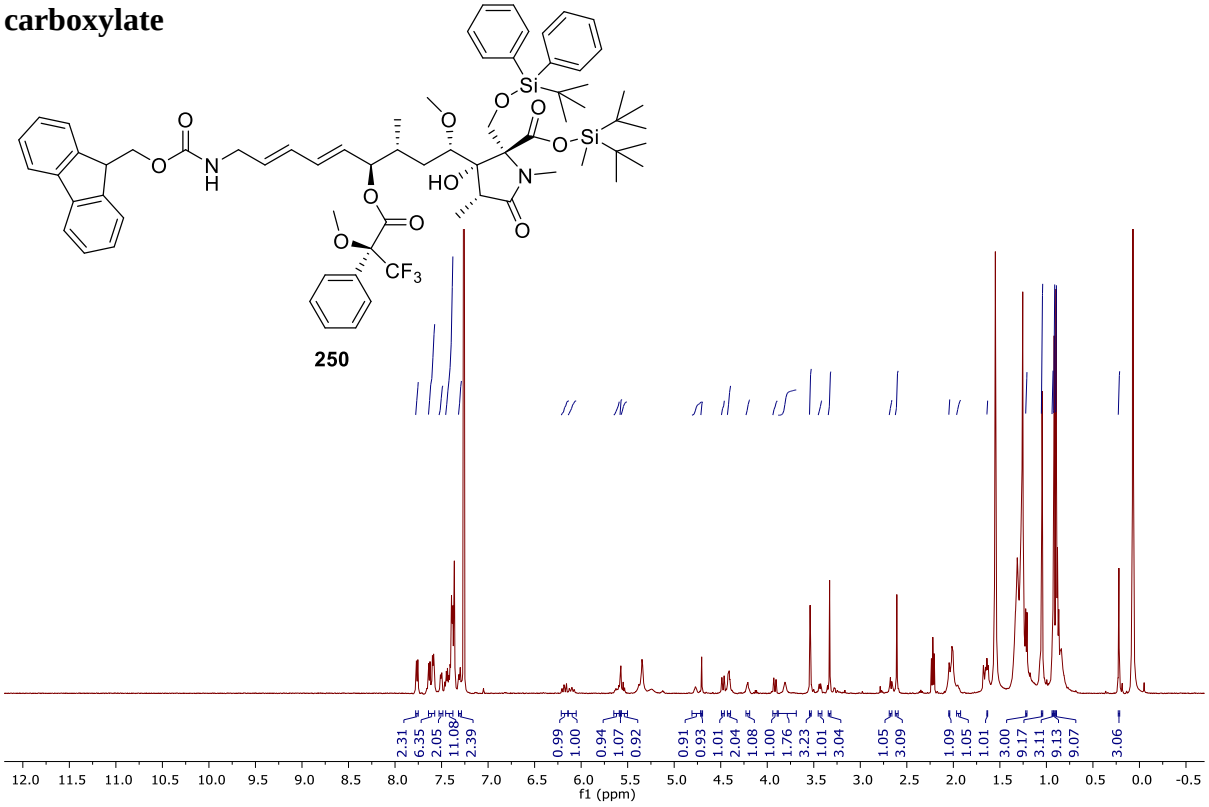
^{13}C NMR (C_6D_6, 126 MHz):



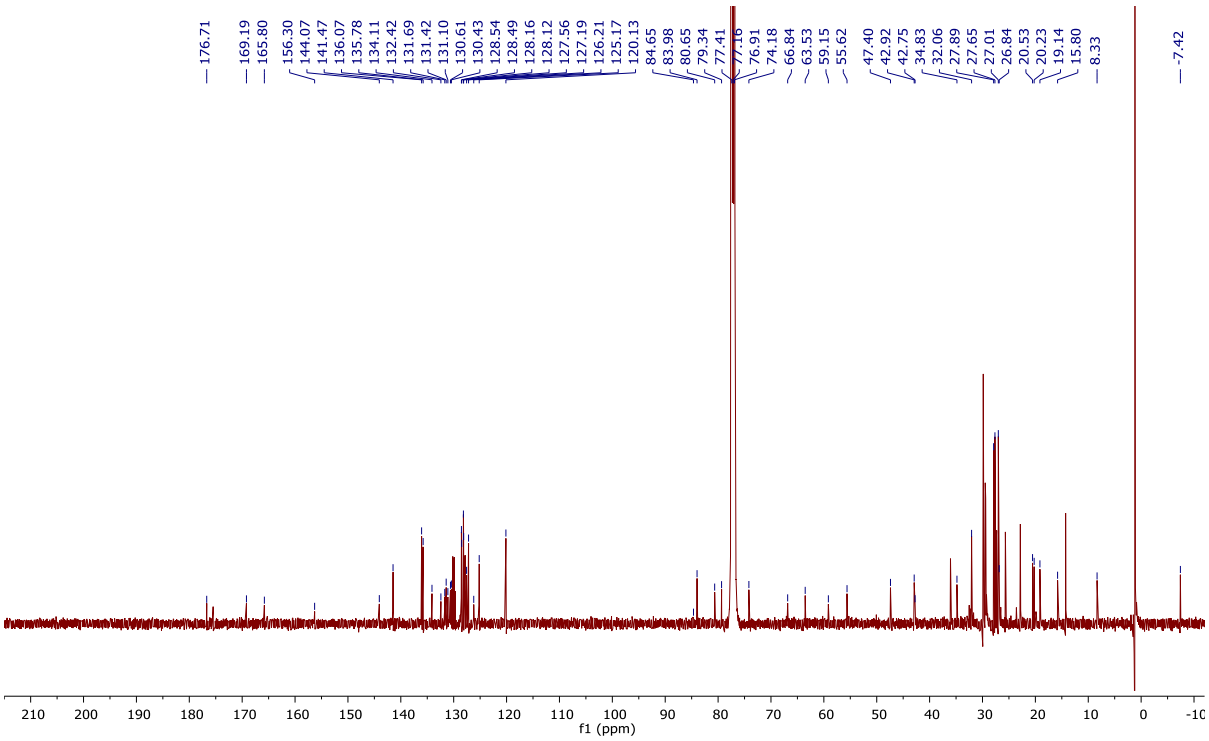
^{19}F NMR (C_6D_6, 471 MHz):



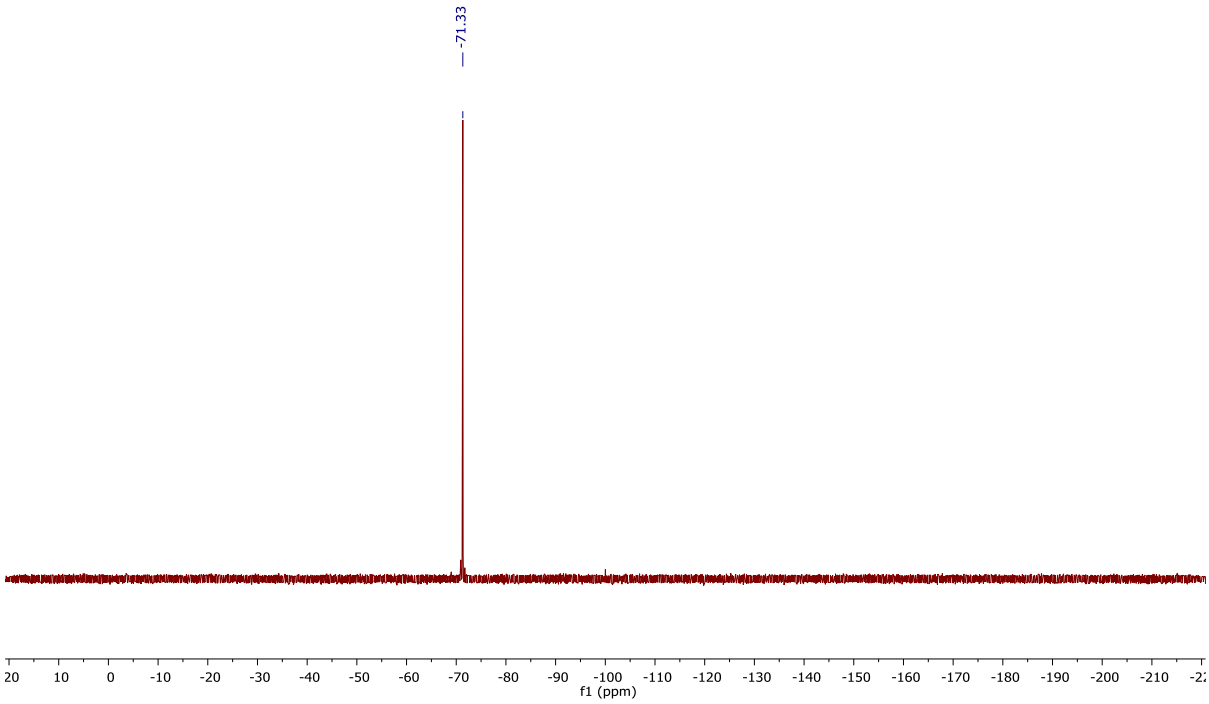
^{1}H NMR (CDCl$_3$, 500 MHz): Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate



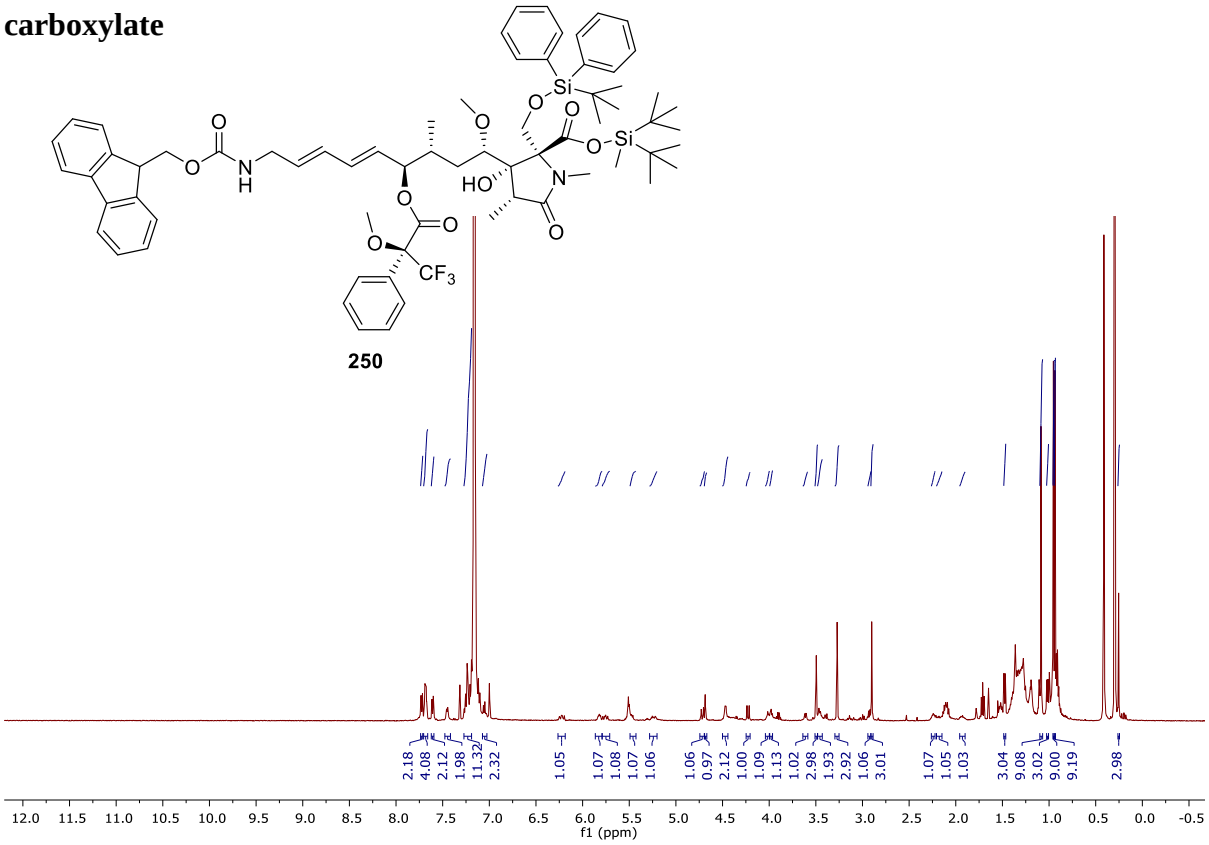
^{13}C NMR (CDCl$_3$, 126 MHz):



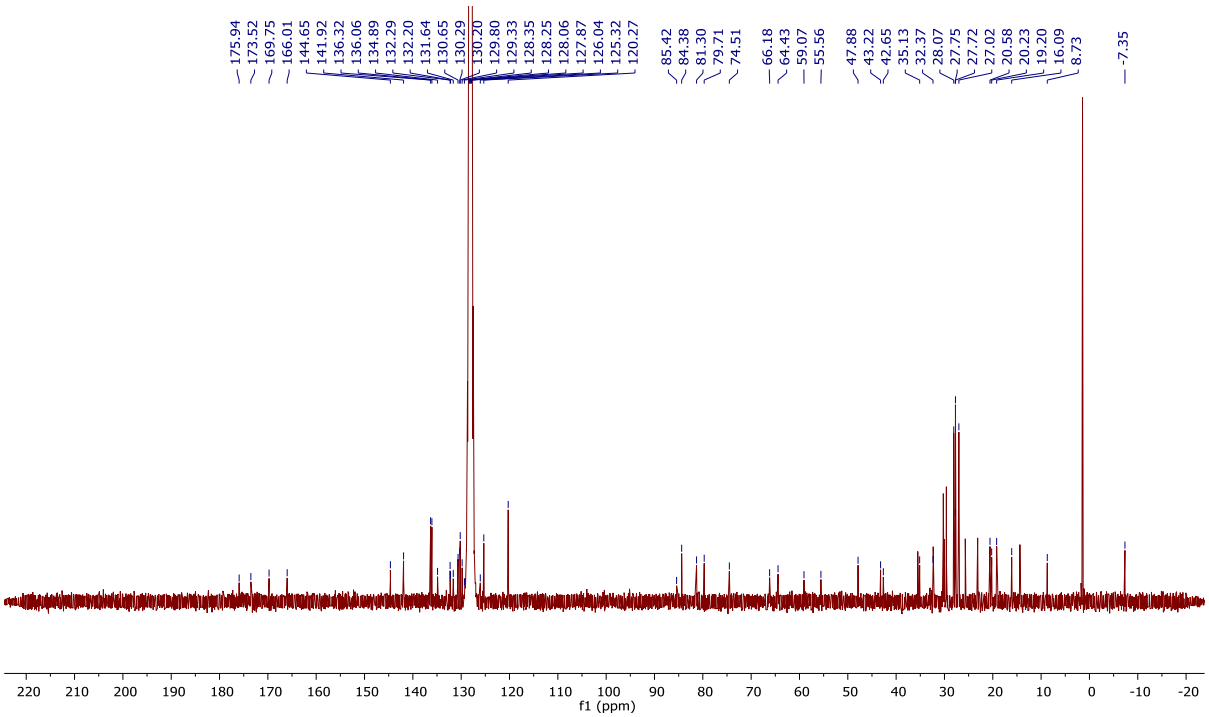
^{19}F NMR ($CDCl_3$, 471 MHz):



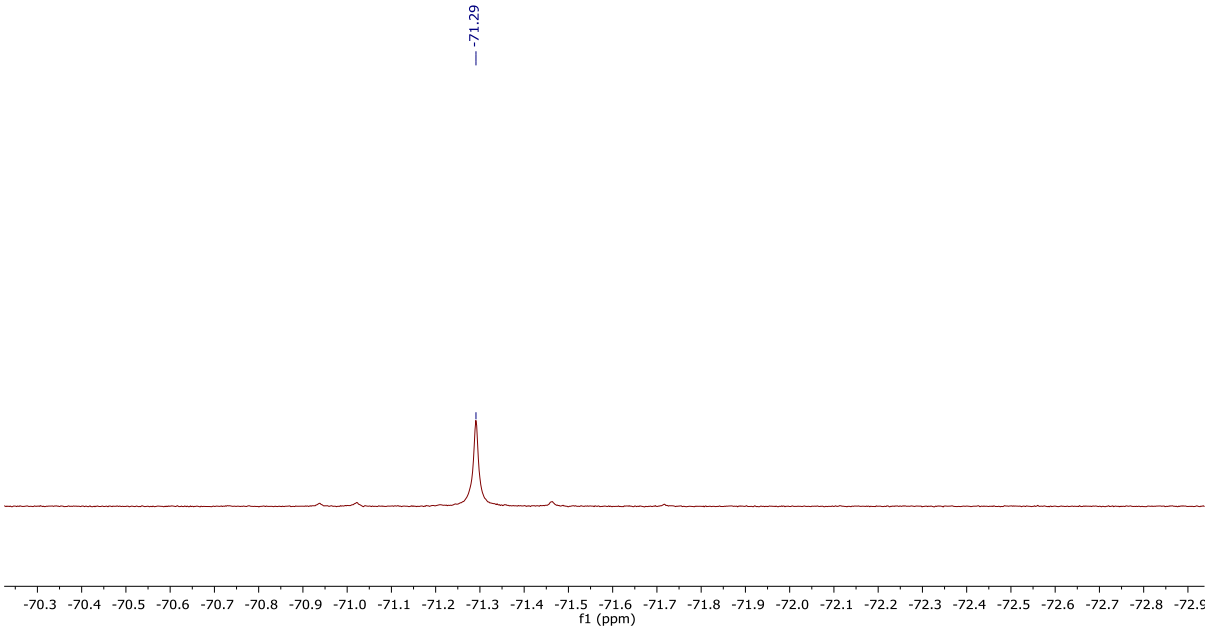
^{1}H NMR (C_6D_6, 500 MHz): Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-9-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-methoxy-3-methyl-4-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate



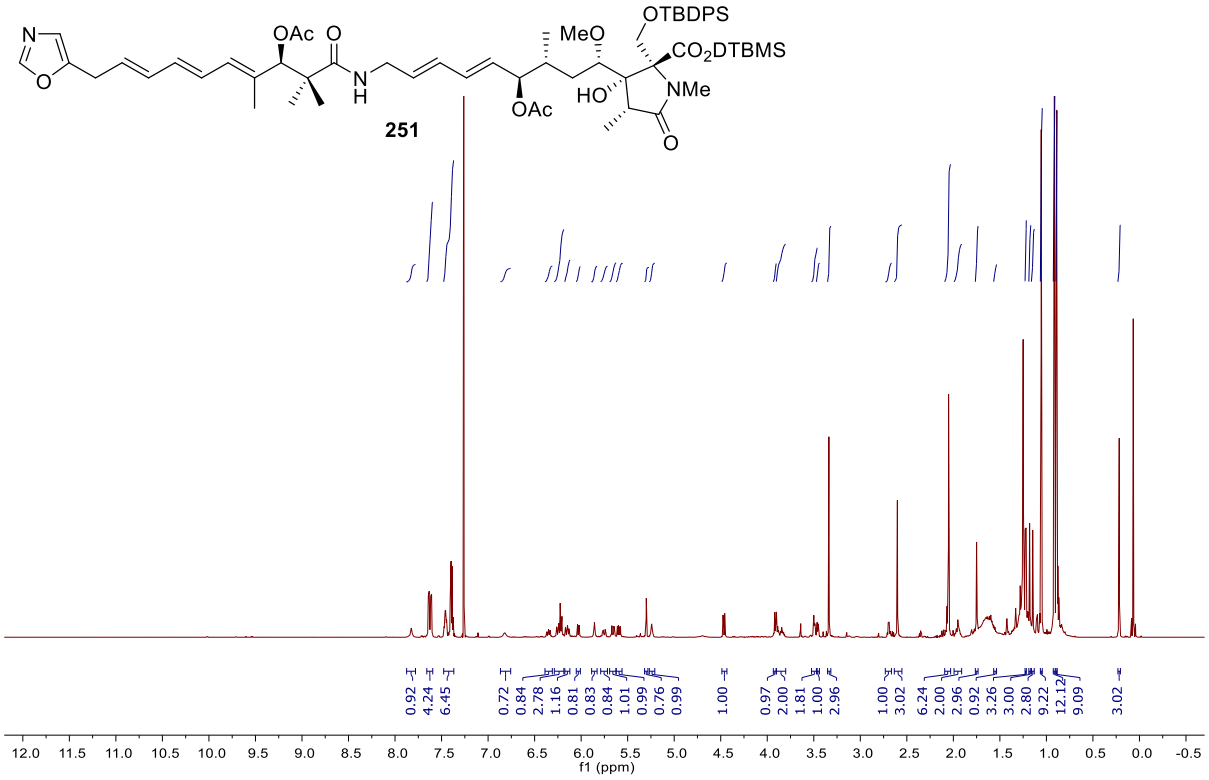
^{13}C NMR (C_6D_6, 126 MHz):



^{19}F NMR (C_6D_6, 471 MHz):



^{1}H NMR ($CDCl_3$, 700 MHz): Di-*tert*-butyl(methyl)silyl (2*S*,3*S*,4*R*)-3-((1*S*,3*R*,4*R*,5*E*,7*E*)-4-acetoxy-9-((*R*,4*E*,6*E*,8*E*)-3-acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienamido)-1-methoxy-3-methylnona-5,7-dien-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate



^{13}C NMR ($CDCl_3$, 176 MHz):