Synthesis of Highly Substituted Heterocycles: The Oxazolomycins

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by

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ABSTRACT

Synthesis of Highly Substituted Heterocycles: The Oxazolomycins

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This thesis is concerned with studies towards the total synthesis of a class of natural products - the oxazolomycins. Attention was focused on the left-hand side triene fragment and right-hand side lactam heterocyclic system.

This thesis describes the synthesis of a racemic terminal phenyl analogue of oxazolomycin A and C, possessing the left-hand side triene geometry as required. A novel truncated pyridine analogue is also described. The molecules represent a racemic total synthesis of analogues of phthoxazolin A and inthomycins B and C. The synthesis is based upon a crucial Stille cross-coupling reaction between stannane and diene iodide fragments. The stannane fragment was synthesised using literature precedented methods and the vinyl halide prepared using a highly stereoselective Wittig, Takai homologation or Stork reaction leading to a variety of ratios of mixtures of *Z, E* and *E, E* diene halides. These investigations led to the availability of 1:1, 3:1 and 1:3 mixtures of *Z, Z, E* : *Z, E, E* left hand side triene fragments possessing the required stereochemistries for oxazolomycin A and C.

Utilising existing methodology developed in the Moloney group, investigations were carried out towards construction of β-keto esters possessing terminal hydroxyl functions, suitable for diastereoselective aldol ring closure. Following extensive protecting group manipulation and *N*-acylation coupling optimisation, a TIPS protected β-keto acid, existing as predominantly the keto tautomer, was successfully coupled to an oxazolidine heterocycle. This *N*-acylated oxazolidine upon Dieckmann cyclisation would present an advanced intermediate of opposite configuration (L-serine is used here as a cheaper starting material for the construction of the oxazolidine instead of D-serine) to the oxazolomycin right-hand side.

ACKNOWLEDGEMENTS

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Following with tradition, no thesis from within the Moloney group would be complete without acknowledgement of some element of the Robertson Group, with whom reagents were traded with much bartering. Mike, Steve, Jon, Tom and Christoff.

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And finally Mum and Dad thanks for all your support over the past years of my education.

CONTENTS

ABBREVIATIONS

The following abbreviations are used throughout this thesis:

Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
APCI	Atmospheric Pressure Chemical Ionisation
Asp	aspartate
Ar	aromatic
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BomCl	Benzyl oxymethyl Chloride
BP	boiling point
Bz	benzoyl
c	concentration
cat.	catalytic
conc.	concentrated
CI	chemical ionisation
CDI	carbonyldiimidazole
cm	centimeter
COSY	homonuclear correlation spectroscopy
CSA	10-camphorsulfonic acid
d.e.	diastereomeric excess
δ	chemical shift
Δ	heat, reflux
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DCC	1,3-dicyclohexylcarbodiimide
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAD	dimethylazodicarboxylate

DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	*N, N'*-dimethylpropylurea
DMSO	dimethylsulfoxide
DNA	Deoxyribonucleic Acid
dppe	diphenylphosphinoethane
dppp	diphenylphosphinopropane
EDAC	ethyldimethylaminopropylcarbodiimide
e.e.	enantiomeric excess
eq	molar equivalents
Et_3N	triethylamine
FAB	fast atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
FT	Fourier Transform
GCMS	gas chromatography mass spectrometry
hrs	hours
HIV	human immunodeficiency virus
HMBC	Heteronuclear Multiple-Bond Correlation
HMDS	hexamethyldisilazide
HMQC	Heteronuclear Multiple Quantum Correlation
HOHAHA	Homonuclear Hartmann-Hahn Spectroscopy
HPLC	high performance liquid chromatography
Hz	Hertz
IBX	*o*-iodoxybenzoic acid
Im	imidazole
INEPT	Insensitive Nuclei Enhanced by Polarisation Transfer
IR	infra-red
IC_{50}	inhibitory concentration for 50% of sample
J	coupling constant
Kg	kilograms
L	litres
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LD_{50}	lethal dose for 50% of sample population

Lit	literature value
M	molar
mg	milligram
MIC	minimum inhibitory concentration
MID	minimum inhibitory dose
mins	minutes
ml	millilitres
MP	melting point
MS	mass spectrometry
mult	multiplicity
NBS	*N*-bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
PCC	pyridinium chlorochromate
PCWP	peroxotungstophosphate
PDC	pyridinium dichromate
PMB	*p*-methoxybenzyl
ppm	parts per million
py	pyridine
R_f	retention factor
RNA	Ribonucleic Acid
ROESY	Rotating Frame n.O.e Spectroscopy
RT	Room Temperature
sat.	saturated
SAR	structure activity relationship
sh	short
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	tributylsilyl
TBSOTf	tributylsilyltriflate
tert	tertiary

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N'N'*-tetramethylethylenediamine
TosMIC	tosylmethyl isocyanide
Ts	4-toluenesulfonyl
UV	Ultra Violet
μg	micrograms
μm	micrometer

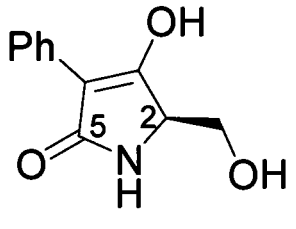
NOMENCLATURE

The nomenclature used to describe the compounds in this thesis is in accordance with the IUPAC conventions as detailed in 'Nomenclature of Organic Chemistry, Sections A, B and C'. Butterworths, London, 1979, with the following exceptions:

a) Known amino acids and derivatives thereof which do not increase the length of the main carbon chain are referred to as derivatives of the amino acid name, using standard amino acid nomenclature.

b) Trivial names are used when the S.I. name is cumbersome, or when the trivial name is more familiar than the S.I. name.

c) Some monocyclic compounds are numbered in a non-systematic way. An example of this is shown below, the amide carbonyl being labelled as atom 5 rather than 2.



STEREOCHEMISTRY

a) Absolute Stereochemsitry

Throughout this thesis the Cahn-Ingold-Prelog (*R*, *S*) convention is used for all chiral centres. For compounds containing double bonds, the (*E*, *Z*) nomenclature has been adopted.

b) Relative Stereochemistry

A broken line is used to denote the α-configuration, where the substituent lies behind the general plane of the ring system, and a solid wedged line denotes the β-configuration, where the substituent lies in front of the plane. If the stereochemistry at a centre is unknown then a solid line has been used. If a wavy line is used then it should be assumed that a mixture of isomers is present at that centre.

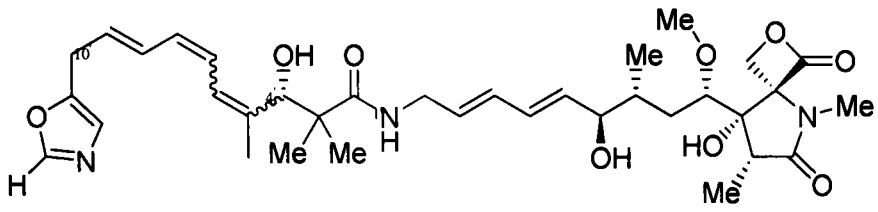
CHAPTER 1 - INTRODUCTION

1.1 Background

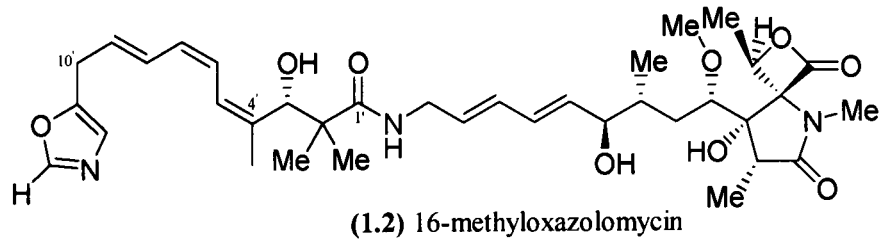
The well publicised emergence of strains of multi-drug resistant pathogenic bacteria has reduced the efficacy of many commonly used antibiotics. The emergence of viral infections amoungst immunocompromised patients has focussed unprecedented attention amongst academic institutions and the pharmaceutical industry on the identification, design, synthesis and evaluation of new drug leads that possess desirable biological activity against these new strains of bacteria.

Considering the speed with which the so called 'super-bugs' have emerged, the search for new antibiotic leads is proving to be a non-trivial problem. Although recent advances in both combinatorial chemistry and genomics are expected by many to provide an important and critical tool to assist in this endeavour, the role of total natural product synthesis nonetheless remains important. Analogues that may be constructed from such pathways, as well as the many natural products that show favourable biological activity (those already known of, and the many thousands, if not millions, that are still lying in nature, ready to be discovered) are expected to provide significant new leads.

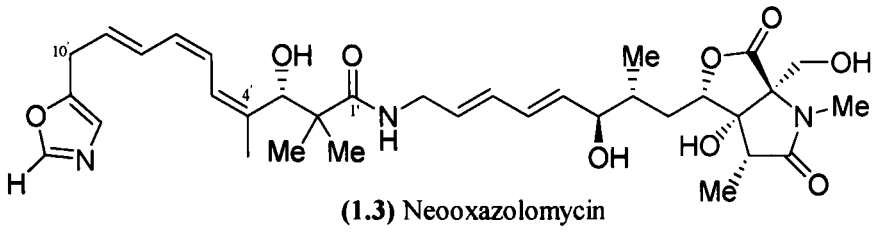
Oxazolomycin A **(1.1a)** is the parent member of a group of natural products, first isolated and characterised[1] in 1985 during a search for antibiotics with inhibitory activity against Ehrlich ascites tumor from a strain of the bacterium *Streptomyces* spp. (typically 15-20mg from a 10L culture broth). Other members of the family identified to date include oxazolomycins B **(1.1b)** and C **(1.1c)**[2], isolated from a fermentation broth of *Streptomyces albus* JA3453. Both compounds are geometrical isomers with respect to the left hand triene fragment, B possessing (4*E*, 6*E*, 8*E*) with C possessing (4 *Z*, 6*E*, 8*E*) geometry, whilst oxazolomycin A displays a (4*Z*, 6*Z*, 8*E*) system. The 16-methyl isomer **(1.2)**[3], neooxazolomycin **(1.3)**, and the curromycins[4] **(1.4)**, **(1.5)** are all produced from the strain *Streptomyces hygroscopicus*. Also from the same bacterial strain producing the oxazolomycins, two more members of the family have recently[5] been isolated, namely KSM-2690 A **(1.6a)** and B **(1.6b)**, with differing triene geometry (*Z, Z, E*) and (*E, E, E*) respectively (Scheme 1.1).



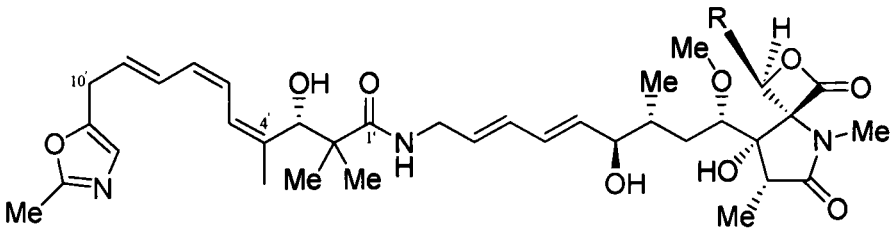
(1.1a) ZZE - Oxazolomycin A
(1.1b) EEE - Oxazolomycin B
(1.1c) ZEE - Oxazolomycin C



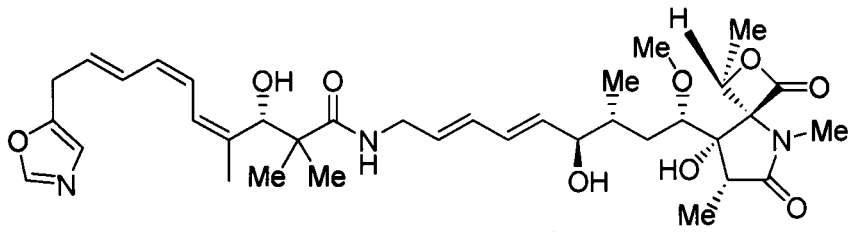
(1.2) 16-methyloxazolomycin



(1.3) Neooxazolomycin



(1.4) R=CH_2COCH_3 - Curromycin A
(1.5) R= Me - Curromycin B



(1.6a) *ZZE*, KSM-2690 B
(1.6b) *EEE*, KSM-2690 C

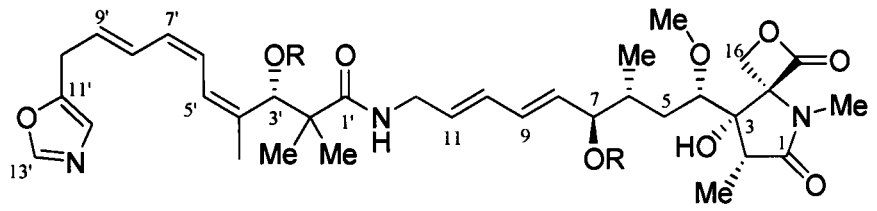
Scheme 1.1: The members of the oxazolomycin family.

Therefore, all members of this family of natural products are characterised by an unusual spiro fused β-lactone / γ-lactam linked *via* a triene and (*E, E*) diene spacer to an oxazole terminal residue, differences occur in either the triene double-bond geometry as discussed above or the β-lactone ring substitution pattern (16-methyloxazolomycin and the curromycins).

1.2 Structural Assignment

Mori *et al*[1] were first to isolate and elucidate the structure of oxazolomycin A. The molecular formula $C_{35}H_{49}N_3O_9$ was indicated by mass spectrometric methods [FAB: m/z 656 ($M+H^+$)] and elemental analysis of oxazolomycin. The UV-absorption spectrum showed peaks at 265 (ε, 28000), 275 (ε, 34000) and 285 nm (ε, 27000) indicating the triene system, and the IR spectrum revealed the presence of a β-lactone (1825 cm^{-1}). Oxazolomycin **(1.1a)** was readily acetylated with Ac_2O and pyridine to

yield the diacetate **(1.1d)**, the ^{1}H NMR spectrum of which is summarised below (Table 1.1)



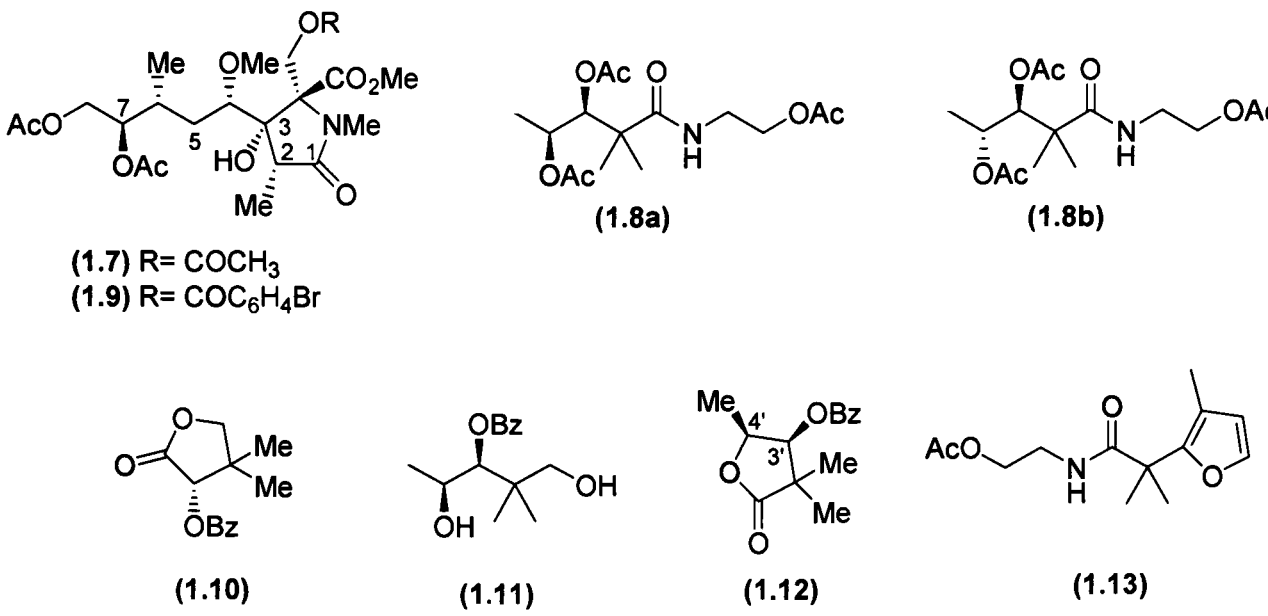
(1.1a) R=H
(1.1d) R=$COCH_3$

Assignment	δ , mult, integral	*J* (Hz)	Change on Irradiation	
6-Me	1.00, d (3)	6.8	H6	s
H5	1.18, m (1)		H4	collapsed
2'-Me	1.23, s (6)			
2-Me	1.25, d (3)	7.4	H2	s
4'-Me	1.77, br.s (3)			
H5, H6	1.94, m (2)		H7	collapsed
			H4	collapsed
-$COCH_3$	2.07, s (6)			
H2	2.40, q (1)	7.4		
N-Me	2.93, s (3)			
O-Me	3.37, s (3)			
H4	3.50, m (1)			
H10'	3.52, d (2)	7.2		
H12	3.90, br.dd (2)	5.4, 6.3	NH	collapsed
H16	4.40, d (1)	6.2[a]		
H16	4.75, d (1)	6.2[a]		
H7	5.23,[b] dd (1)	5.9, 7.7	H6	d, 7.7
			H8	d, 5.9
H8	5.56, dd (1)	7.7, 14.9	H7	d, 14.9
H11	5.71, dt (1)	6.3, 14.4	H10	t, 6.3
H9'	5.59, dt (1)	7.2, 15.3	H10'	d, 15.3
H3'	5.85,[c] s (1)			
H7'	6.00, dd (1)	11.3, 11.3	H6'	d, 11.3
			H8'	d, 11.3
N-H	6.06,[d] br.t (1)	5.4	H12	br.s
H10	6.15, dd (1)	10.0, 14.4		
H9	6.25, dd (1)	10.0, 14.9	H8	d, 10.0
H6'	6.35, dd (1)	11.3, 11.3		
H5'	6.48, br.d (1)	11.3	H6'	br.s
			4'-Me	d, 11.3
H8'	6.62, br.dd (1)	11.3, 15.3	H10'	dd, 11.3, 15.3
H12'	6.80, br.s (1)		H10'	s
H13'	7.80, s (1)			

a) AB pattern, b) δ 3.94 (1H, dd, *J* 6.2 and 6.2 Hz) in **(1.1a)**, c) δ 4.63 (1H, s) in **(1.1a)**, d) exchangeable with D_2O at 50° C.

Table 1.1: ^{1}H NMR Signals and decoupling for diacetate **(1.1d)** (360 MHz, $CDCl_3$)

Assignment of the complex spectrum was confirmed by careful chemical degradation to produce eight fragments of simpler structure.



Scheme 1.2: Oxazolomycin degradation study fragments.

Thus diacetate **(1.1d)** was cleaved by ozonolysis with exposure to a reductive work-up and the product treated with Ac_2O/pyridine, to yield **(1.7)** as well as a mixture of triacetates that were deprotected, separated by preparative TLC and individually reprotected to afford *threo* acetate **(1.8a)** and *erthyro* acetate **(1.8b)** respectively. Compound **(1.7)** was converted into the *p*-bromobenzoate **(1.9)** which was recystallised from acetone and hexane to afford orthorhombic crystals, which were unambiguously structurally characterised by X-ray crystallography.

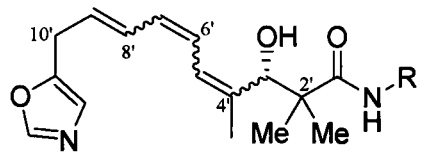
Fragment **(1.8a)** was completely characterised by chemical synthesis from L-(+)-pantolactone. Treatment of this starting material with benzyl trichloroacetimidate and BF_3 gave benzyl ester **(1.10)**, which was converted to **(1.11)** by treatment with MeMgI and then LAH *in situ*. PDC oxidation of **(1.11)** produced **(1.12)**, the stereochemistry of which was determined by observation of n.O.e between H3' and H4' in the ^1H NMR spectrum. This lactone was converted chemically to synthetic *threo* **(1.8a)** which proved identical to natural *threo* **(1.8a)** in terms of the spectroscopic data and optical rotation.

Oxazolomycin contains the conjugated triene as previously described. Furthermore, the UV-absorption at 230 nm (ε = 32000) also indicates the conjugated diene chromophore in **(1.1a)**.

The *Z* configuration of trisubstituted double bond was confirmed by observation of a 5.9% n.O.e between C4'-Me and H5'. Ozonolysis followed by reduction of oxazolomycin **(1.1a)** itself and not the diacetate gave compound **(1.13)**. Their

physico-chemical properties resemble those of a compound previously named as resistaphylin reported by Kaken *et al* in 1971[6], which seems to be identical to oxazolomycin. The optical rotation of oxazolomycin A has also been reported[2] as $[\alpha]_D^{25}$ +43.0 (*c* 0.12, MeOH).

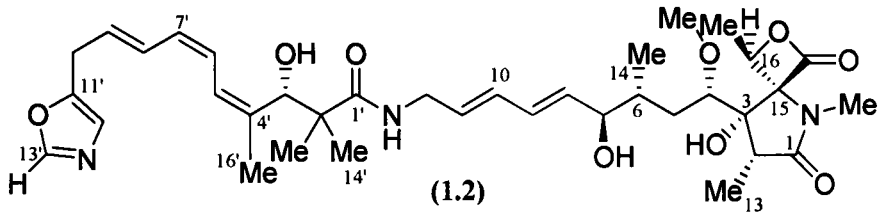
The structures of oxazolomycins B and C were determined more than 10 years later when they were first isolated by Kanzaki *et al* in 1998[2]. The two isomers were detected by HPLC analysis of the broth extract just after fractionating the culture supernatant in the dark, indicating that these compounds were not derived from oxazolomycin **(1.1a)** during the purification steps. FABMS data indicated that both compounds unsurprisingly had the same molecular mass as that of oxazolomycin A. The UV spectra showed absorption maxima at 230 and 275 nm with two shoulders at 265 and 285 nm, indicating the presence of conjugated diene and triene moieties, similar to that of oxazolomycin A. These two isomers show similar ^{1}H NMR spectra to oxazolomycin A except for differences in the olefinic region. The olefinic stereochemistry was determined entirely by NMR analysis using a range of 1 and 2D techniques including ^{1}H-^{1}H-COSY, *J* values, NOESY and n.O.e sequences. The assignment of the conjugated triene moiety is summarised in Table 1.2.



Signal	Oxazolomycin B (δ, ppm)	Oxazolomycin C(δ, ppm)
H-3	4.12	4.73
4-Me	1.78	1.79
H-5	6.08 (*J* 11.3 Hz)	6.05 (*J* 11.6 Hz)
H-6	6.48 (*J* 11.3 and 14.6 Hz)	6.59 (*J* 11.6 and 15.0 Hz)
H-7	6.26 (*J* 11.1 and 14.6 Hz)	6.20 (*J* 11.0 and 15.0 Hz)
H-8	6.32 (*J* 11.1 and 14.3 Hz)	6.31 (*J* 11.0 and 14.9 Hz)
H-9	5.82 (*J* 7.0 and 14.3 Hz)	5.80 (*J* 7.0 and 14.9 Hz)

Table 1.2: ^{1}H-NMR assignment of the conjugated triene moeity of Oxazolomycin B and C (CD_3OD)

Not surprisingly, the 16-methyloxazolomycin isomer displays a very similar ^{1}H NMR spectrum to that of oxazolomycin A **(1.1a)** (Table 1.3).[7]



(1.2)

Position	δ ^{13}C	δ ^{1}H (integral,mult.,*J* Hz)	HMBC
1	174.2		H2, NCH_3, H13
2	44.7	2.34 (H, q, 6.6)	H13
3	81.8		H2, H13, H16, 3-OH
4	83.7	3.38 (H, t, 6.9)	OCH_3, 3-OH
5	33.1	1.95 (H, m)	H7, H14
		1.15 (H, m)	
6	37.9	1.58 (H, m)	H8, H14, 7-OH
7	76.4	3.81 (H, m)	H8, H9, 7-OH
8	129.5	5.57 (H, dd, 16.8, 11.2)	H9, H10, 7-OH
9	130.0	6.14 (H, dd, 11.2, 16.8)	H7, H10, H11
10	131.5	6.09 (H, dd, 14.3, 10.8)	H8, H11, H12
11	134.0	5.59 (H, m)	H10, H12
12	42.2	3.71 (2H, m)	H10, H11, NH
13	20.8	1.03 (3H, d, 6.6)	H2
14	17.2	0.86 (3H, d, 6.2)	
15	84.7		H4, H16, 16-CH_3, NCH_3
16	78.4	4.82 (H, q, 6.3)	16-CH_3
17	170.2		H16
1'	176.2		H12, H3', H14', H15', NH 2'
	46.7		H14', H15', 3'-OH
3'	74.4	4.59 (H, s)	H5', H14', H15', H16'
4'	141.0		H3', H6', H16'
5'	124.6	6.35 (H, d, 11.3)	H3', H16'
6'	125.5	6.27 (H, dd, 10.9, 11.3)	H5', H7'
7'	128.2	5.90 (H, dd, 11.5, 10.9)	H6', H9'
8'	129.1	6.70 (H, dd, 11.5, 14.5)	H6', H7', H9', H10'
9'	129.8	5.75 (H, dt, 14.5, 4.5)	H7', H10'
10'	29.4	3.52 (2H, br.d, 7.0)	H8', H9'
11'	151.1		H9', H10', H12', H13'
12'	122.9	6.84 (H, s)	H10', H13'
13'	152.1	8.14 (H, s)	H12'
14'	22.6	0.95 (3H, s)	H3', H15'
15'	26.1	1.10 (3H, s)	H3', H14'
16'	20.9	1.70 (3H, s)	H3', H5'
16-CH_3	17.9	1.69 (3H, d, 6.3)	H3
N-CH_3	27.1	2.77 (3H, s)	
O-CH_3	57.1	3.15 (3H, s)	H4
3-OH		5.31 (H, s)	
7-OH		4.82 (H, s)	
3'-OH		5.49 (H, s)	
NH		7.63 (H, br.t, 5.9)	

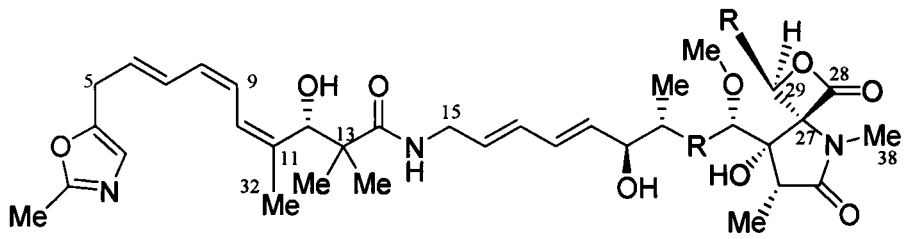
Table 1.3: ^{1}H and ^{13}C NMR data of 16-methyloxazolomycin in DMSO-d_6

The physico-chemical properties of 16-methyloxazolomycin **(1.2)** have been determined as follows: a pale yellow amorphous powder; $[\alpha]_D^{23}$ +3.6 (*c* 0.52, MeOH); UV λ_{max} (MeOH) nm (ε) 228 (23000), 266 (27200), 275 (32000) and 285 (27000), with distinctive IR stretches at 1825 cm^{-1} indicative of the β-lactone and 1690 cm^{-1} (amide) and an ESI-MS with m/z 692 $(M + Na)^+$. The ^1H NMR spectrum (Table 3) was assigned purely by using a range of 1D and 2D techniques. A later publication[3] from the same group made use of a series of chemical degradations which not only confirmed the NMR data but also established the absolute stereochemistry of the molecule as 2*R*, 3*S*, 15*S*, 16*S*, 4*S*, 6*R*, and 7*R* *via* use of the bis-(*R*) and bis-(*S*)-MTPA esters.

The structure of neooxazolomycin was determined in a similar way to that of oxazolomycin A **(1.1a)** as discussed previously. Chemical degradation formed the same two fragments **(1.9)** and **(1.8a)**. However, the IR spectrum of the natural product showed the presence of a γ-lactone (1765 cm^{-1}) rather than the β-lactone (1825 cm^{-1}) present in oxazolomycin.[8] This proposed structure was later confirmed by Kende *et al* by total synthesis.[9]

Curromycin A **(1.4)** has been reported[4] as having the following physico-chemical properties: a yellow amorphous powder; mp 103-105° C; $[\alpha]_D^{22}$ +39.0 (*c* 0.115, MeOH); FAB-MS m/z 714 $(M+H)^+$. IR absorption bands at 1825, 1690 and 1640 cm^{-1} are indicative of β-lactone and amide structural sub-units. The UV spectrum is almost identical to the other members of the oxazolomycin family; 228 nm (ε = 19800), 267 nm (ε = 16300), 275 nm (ε = 19800) and 285 nm (ε = 15100) showing that the molecule displays the conjugated triene and diene moieties characteristic of this class of antibiotics. In accordance with the molecular formula $C_{38}H_{55}N_3O_{10}$, established from the FAB-MS, the ^{13}C NMR spectrum of curromycin A revealed 38 carbons (Table 1.4), the assignment of the functional groups being made by INEPT and 2D C-H correlation spectra. This ^{13}C data accounted for 51 protons directly attached to carbons. The ^1H NMR spectrum taken at 45° C revealed the remaining four exchangeable protons at δ_H 6.75 (1H, t, *J* 5.2 Hz), 4.81 (1H, br.d, *J* 4.8 Hz), 4.23 (1H, br.s) and 2.98 (1H, br,s). 2D-COSY, *J* value calculation and n.O.e analysis provided the stereochemical assignment, which was identical to that of oxazolomycin A. Curromycin B **(1.5)** was identified by NMR analysis showing the presence of a

methyl substituent on the β-lactone ring rather than a methyl ether as in curromycin A **(1.4)**.



(1.4) R=CH_2OCH_3, Curromycin A
(1.5) R=CH_3, Curromycin B

Assignment	^{13}C and (^1H) NMR chemical shifts					
-CH_3	10.2 (1.15)	17.1 (0.94)	21.6 (1.03)	26.0 (1.29)		
-NCH_3	26.5 (2.87)					
-OCH_3	56.8 (3.30)	59.5 (3.39)				
=$CRCH_3$	13.9 (2.36)	19.6 (1.74)				
-CH_2-	32.8 (1.30, 1.98)					
-NCH_2-	41.1 (3.85)					
=$CRCH_2$-	29.1 (3.40)					
-CHRR'	37.2 (1.70)	43.3 (2.42)				
-OCHRR'	75.2 (4.58)	76.7 (3.92)	78.5 (4.75)	82.5 (3.49)		
=CH-	122.4 (6.55) 128.0 (6.60) 131.5 (6.14)	123.8 (6.14) 128.9 (5.71) 134.2 (5.63)	124.8 (6.36) 129.5 (5.63)	128.0 (5.89) 130.0 (6.14)		
RR'CR"R"'	44.9	81.6	86.2	138.5	150.2	160.7
C=O	169.0	175.1	177.9			

Table 1.4: Curromycin A ^{13}C and ^1H NMR assignments, performed in $CDCl_3$

Six years later the same structures were reported as being isolated from another strain of *Streptomyces* and named triedimycins A and B.[10] They were later confirmed by the same investigators as being 'identical' with curromycins A and B'.

More recently, the C-16 epimer KSM-2690 has been isolated[5] from a soil sample of *Streptomyces sp.* collected at Masuko-machi, Tochigi Prefecture, Japan. The UV spectrum of KSM-2690 B **(1.6b)** showed absorption maxima at 230 and 278 nm with two shoulders at 267 and 288 nm, the characteristic absorption detected in all the previous compounds indicating conjugated triene and diene moieties. Furthermore, the IR spectrum displayed bands at 1825, 1690 and 1640 cm^{-1}, suggestive of a β-lactone and amide structure. Both UV and IR data confirmed that this new compound belongs to the extended 'family' of the oxazolomycins. FAB-MS showed a peak at m/z 670 $[M+H]^+$, 14 mass units larger than that of oxazolomycin. The ^1H NMR spectrum of **(1.6b)** was also similar to oxazolomycin (Table 1.5), however, it showed three doublet methyl signals (1.71, 1.05 and 0.87 ppm) in the aliphatic region. With the molecular weight taken into consideration, **(1.6b)** was taken to be a methyl-substituted oxazolomycin. A range of 2D NMR techniques (COSY, HOHAHA, HMQC, HMBC and n.O.e) determined KSM-2690 A to have the same stereochemistry as oxazolomycin A (4*Z*, 6*Z*, 8*E*) and KSM-2690 B to have the same stereochemistry as oxazolomycin B (4*E*, 6*E*, 8*E*), hence the naming. Finally ROESY analysis (Fig. 1.1) showed n.O.e correlations around the β-lactone-γ-lactam ring's indicating a relative stereochemistry of 2*R*, 3*S*, 15*S* and 16*R* in contrast to that of 16-methyloxazolomycin (2*R*, 3*R*, 15*S* and 16*S*). Consequently, it was concluded that compound **(1.6b)** was a novel stereochemical isomer of 16-methyloxazolomycin **(1.2)**.

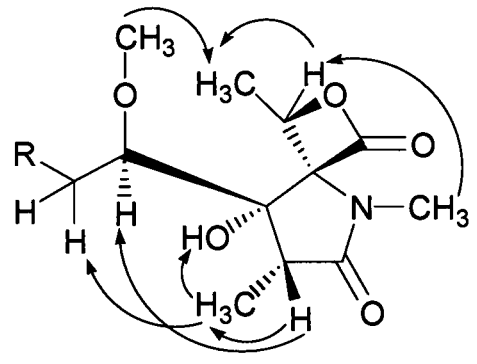
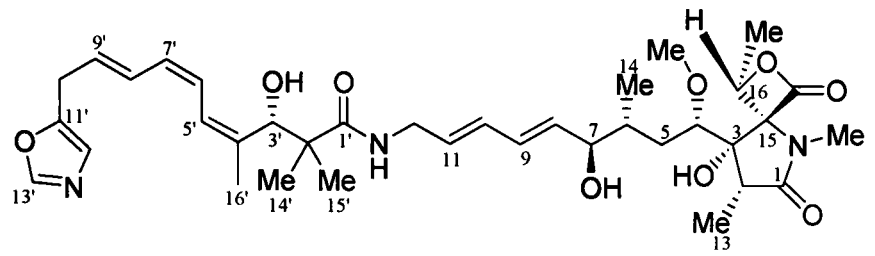


Fig. 1.1: Correlations of NOE observed in ROESY spectrum of KSM-2690 B



(1.6a) *ZZE*, KSM-2690 A
(1.6b) *EEE*, KSM-2690 B

	KSM-2690 B (1.6b)		KSM-2690 A (1.6a)	
Position	δ ^{1}H	Int, mult, J(Hz)	δ ^{1}H	Int, mult, J(Hz)
2	2.37	1H, q, 7	2.36	1H, q, 7
4	3.37	1H, t, 5	3.37	1H, t, 5
5	1.96	1H, dt, 15.0 and 5	1.96	1H, m
	1.17	1H, m	1.15	1H, m
6	1.61	1H, m	1.60	1H, m
7	3.83	1H, m	3.83	1H, m
8	5.61	2H, overlappd	5.61	2H, overlapped
9	6.13	2H, d, 15	6.12	2H, overlapped
10	6.13	2H, d, 15	6.12	2H, overlapped
11	5.61	2H, overlapped	5.61	2H, overlapped
12	3.72	2H, m	3.71	2H, m
13	1.05	3H, d, 7	1.05	3H, d, 7
14	0.87	3H, d, 7	0.87	3H, d, 7
16	5.00	1H, q, 7	5.00	2H, q, 7
3'	4.63	1H, d, 4	4.59	1H, d, 5
5'	6.40	1H, d, 12	5.93	1H, d, 11
6'	6.31	1H, t, 11	6.59	1H, dd, 15 and 11
7'	5.93	1H, t, 11	6.13	1H, overlapped
8'	6.74	1H, dd, 15 and 12	6.23	1H, overlapped
9'	5.79	1H, dt, 15 and 7	5.75	1H, dt, 15 and 7
10'	3.55	2H, m	3.51	2H, d, 7
12'	6.89	1H, s	6.89	1H, s
13'	8.22	1H, s	8.22	1H, s
14'	1.11	3H, s	1.11	3H, s
15'	0.98	3H, s	0.98	3H, s
16'	1.73	3H, s	1.68	3H, s
16-CH_3	1.71	3H, d, 6	1.71	3H, d, 6
N-CH_3	2.79	3H, s	2.79	3H, s
O-CH_3	3.17	3H, s	3.16	3H, s
3-OH	5.31	1H, s	5.31	1H, s
7-OH	4.80	1H, d, 3	4.80	1H, d, 3
3'-OH	5.45	1H, d, 5	5.44	1H, d, 5
N-H	7.64	1H, t, 5	7.64	1H, t, 5

Table 1.5: ^{1}H NMR data of KSM-2690 B and KSM-2690 C (400 MHz , DMSO-d_6), 30° C

1.3 Biological Activity[7-12]

The oxazolomycins are isolated from a variety of *Streptomyces* strains of bacteria as discussed previously (typically 15 – 20 mg from a 10 L culture broth) and exhibit wide-ranging and potent antibiotic activity (Table 1.6), including inhibitory activity against Gram positive bacteria, antiviral activity against vaccinia, herpes simplex type I and influenza A, as well as *in vivo* antitumour activity; notably, this biological activity is coupled with low toxicity (LD_{50} of 10.6 mg/Kg for intraperitoneal injection in mice). This is considered in more detail in the following sections.

NATURAL PRODUCT:	**(1.1a)**	**(1.1b)**	**(1.1c)**	**(1.2)**	**(1.3)**	**(1.4)**
Crown Gall Formation, MID (μg/disc)	0.8	0.8	0.8			3.2
Alfaalfa germination, MIC (μg/ml)	12.5	25.0	50.0			12.5
Bacterial Growth, MIC (μg/ml):	3.2	>100	>100			
Agrobacterium tumefaciens IFO 13263	5.3	100	>100			6.3
Agrobacterium tumefaciens EHA 101	50	>100	>100			6.3
Agrobacterium tumefaciens IFO 13257	>100	>100	>100			6.3
Rhizobium loti IFO 13336	>100	>100	>100			
Escherichia Coli	>100	>100	>100	5	Active	100
Chlorella vulgaris IFO 15941	-	-	-	10		
Cytotoxic Activity:						
P388 Leukemia (IC_{50}), (μg/ml)				0.23	Active	
A-549 Human lung adenocarcinoma (IC_{50}), (μg/ml)				4.6		
Mouse B16 melanoma					Active	
Friend leukemia					Active	
Viral Activity:						
Influenza A MIC (μg/ml)	15.6					
Herpes simplex MIC (μg/ml)	15.6					
Vaccinia MIC (μg/ml)	15.6					

Table 1.6: Summary of biological activity of the Oxazolomycin class of compounds

1.3.1 Antiviral Activity

Numerous antibiotics, such as vancomycin, have been investigated for their antiviral activity *in vitro*. However, only a few combine desirable properties such as high antiviral activity and low toxicity *in vivo*. Tonew[11] conducted the first studies on the antiviral activity of oxazolomycin A, the results of which are summarised in Table 6. In short, it was found that oxazolomycin A reduced significantly the plaque formation of enveloped DNA and RNA viruses by more than 90% in the range of the maximally tolerated dose (that dose at which morphological alterations of cultured cells begin to be observed). The compound prevents the replication of herpes simplex type I, vaccinia and influenza A viruses in a dose-dependant manner. However, replication of Coxsackie A9 virus was not inhibited by oxazolomycin. Electron-optical studies revealed a reduced synthesis of HSV – 1 nucleocapsids dependent on the concentration of the compound. It is notable that only oxazolomycin A (oxazolomycin B and C had not been isolated at the time of the study) displays activity in this area whilst no other 'family' members exhibit any activity at all. However, curromycins A and B have been described, in one paper by Ohno *et al*[12] in 1994, to inhibit human immunodeficiency virus (HIV) replication in both acute and chronic infection and the authors indicate that this may be due to the curromycins affecting a late step in the virus replication cycle. This statement is supported by additional studies (section 1.5).

1.3.2 Cytotoxic Activity

Few detailed studies have been conducted on the cytotoxic activities of these compounds. The oxazolomycins (A, B and C) themselves display no activity in this area, whilst interestingly, the structurally similar compound 16-methyloxazolomycin **(1.2)**, exhibits cytotoxicities against P388 leukemia cells (IC_{50}, 0.23 μg/ml) and against A-549 human lung adenocarcinoma cells(IC_{50}, 4.6 μg/ml)[7]. Curromycin A **(1.4)** shows cytotoxic activities against mouse B16 melanoma, P388 leukemia and Friend leukemia cells.[4] The more recently isolated compounds KSM-2960 B and C exhibit the same degree of potency for cytotoxicity against human bladder carcinoma T24 cell (IC_{50}, 10 μg/ml).[5] Thus, it is clear that small structural variations could lead to potent alterations in activity, and therefore detailed SAR studies are warranted.

1.3.3 Anti-Bacterial and Anti-Microbial Activity

Oxazolomycin A **(1.1a)** is an antibiotic specific to *Agrobacterium tumefaciens* and it has activity against crown gall formation (plant tumours) but neither antibacterial nor phytotoxic activity (Alfalfa germination) (Table 6) and this indicates that this compound could specifically inhibit some steps in plant transformation by *A.tumefaciens*. Therefore oxazolomycin and its analogues could be promising chemical probes for exploring the mechanism of plant transformation that is not currently completely understood. Oxazolomycins B and C exhibit[2] potent inhibitory activity against crown gall formation with the same MIC (0.8 μg/disk) as the A isomer. In contrast they displayed no antibacterial activity against *Agrobacterium tumefaciens*, whilst the A isomer has specific anti-A. *tumefaciens* activity as described above. Of the other bacteria exposed to the oxazolomycins, none proved particularly sensitive to the compound with, for example, *E.coli* requiring a large dose of greater than 100 μg/ml. The B and C isomers did, however, cause necrosis of potato tubers at doses of 6.3 and 12.5 μg/disk, respectively.

Other members of the 'family' that display activity in this area include; 16-methyloxazolomycin **(1.2)** which shows antibacterial activity against *Bacillus subtilis* 1069 and *Chlorella vulgaris* IFO 15941. Curromycin A **(1.4)** also shows activity against the *Bacillus subtilis* IAM 1026 strain. Both curromycin isomers inhibit grown gall formation on potato tubers. Diacetate and dipropionate ester analogues of both isomers exhibit potent inhibitory activity against crown gall formation (MID: 3.2 and 6.3 μg/disk) respectively.[13] KSM-2690B **(1.6a)** shows more varied activity against Gram-positive bacteria (albeit at high doses), including activity against *Bacillus subtilis* PCI 219, *Micrococcus luteus ATCC 9341* and most interestingly, *Staphylococcus aureus*, a less prevalent strain of the bacteria that is beginning to show resistance to all known antibiotics.

1.4 Biological Mode of Action

What can be concluded from these limited biological studies is that these β-lactone antibiotics may represent a new structural type of antiviral and antibacterial agent, and possibly of even more interest, is the unusual mode of action of oxazolomycin. The mode of antiviral action of membranotropic antibiotics, in general, involves inhibition of virus uncoating at an early stage of virus replication.[14,15] However, oxazolomycin apparently inhibited later stages of influenza A replication,[16] suggesting another yet unidentified ability of the compound acting during maturation and/or virus release. The lack of inhibition of the Coxsackie virus A9 poses an interesting question which will no doubt promote further studies towards the mode of antiviral action of the oxazolomycins.

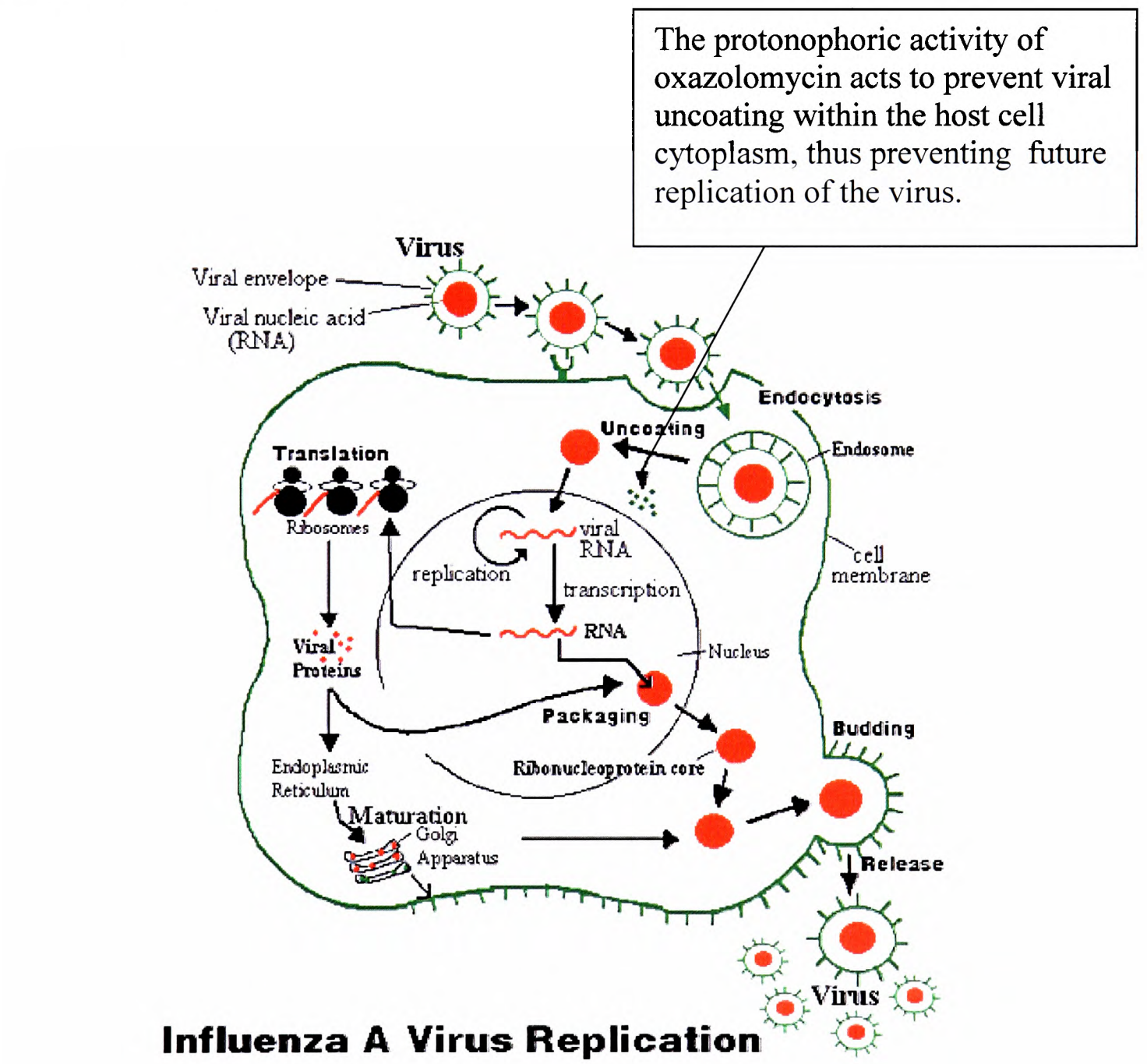


Fig. 1.2: Diagram of viral replication steps and possible site of action of oxazolomycin.
(Website of the National Museum of Health, US)

Gräfe *et al*[16] in 1992 completed the only detailed study into the biological mode of action of any of these novel antibiotics, namely that of oxazolomycin A **(1.1a)**. By use of an artificial lipid membrane model, the group showed that oxazolomycin A is an effective protonophore at pH <7.0 but it conveys both protons and monovalent cations at pH >7.5 as a passive carrier. These ionophoric properties are suggested to be correlated with its antiviral, cytotoxic and antibacterial activities. As regards the latter, oxazolomycin displays an unusual pattern, since bacterial growth is only partially inhibited.[17] Intracellular exposure to **(1.1a)** exhibits increased membrane conductivity due to its protonophoric action and activity as a monovalent ion carrier. Several independent experiments showed that **(1.1a)** acts predominantly as a protonophore at pH 4.7 to 7.0 and that its function as a potassium carrier becomes visible solely at pH >7.0.

From the results of several model system experiments, Gräfe concluded[17] that oxazolomycin **(1.1a)** acts as a general uncoupler of oxidative phosphorylation. The protonophoric activity observed below pH 7.0 could possibly be ascribed to the binding of protons to the nitrogen of the weakly basic oxazole ring and it seems reasonable that the ionophoric properties of the compound will be responsible for the reported antibacterial, antiviral and cytotoxic activities. Moreover, it seems likely that this mode of action could also be ascribed to other members of the oxazole-type antibiotics.

The significance of this mode of action is apparent from a consideration of the life-cycle of influenza A (Fig. 1.2), for which the membrane fusions essential for the ingestion of a viron by endocytosis, its release into the host cell and for the expulsion of new infectious particles have been studied in detail.[14,15] The intrinsically acidic pH of the endosome is of primary importance for the dispersal of the viral RNA replication machinery into the cytosol. Under these acidic conditions, a significant conformational change (triggered by the protonation of six Asp side-chain carboxylates in a 19 residue spacing segment, thereby reducing charge-charge repulsions) translocates a membrane-bound fusion peptide by some 100Å in such a way that it can bridge both the viral and cellular membranes, thereby facilitating fusion. Significantly, it has been shown that lipid soluble bases can inhibit viral infection by raising the pH of the normally acidic endosomes and in so doing prevent

these aforementioned protonations. This activity also forms the basis of the action of the well-known anti-influenza drugs, amantidine and rimantidine.

1.5 Biosynthetic Studies

One study on the biogenesis[17] of oxazolomycin has been reported to date and a summary of the results of various feeding experiments are shown below (Fig. 3). Feeding experiments with sodium [^{13}C]-labelled acetate, sodium [1-^{13}C]propionate, L-[*methyl*-^{13}C]methionine, L-[1-^{13}C]alanine and [1-^{13}C]glycine (Fig. 1.3) on *Streptomyces albus* (strain JA3453) produced oxazolomycin **(1.1a)**, whose ^{13}C NMR analysis provided information about the biogenetic construction of its carbon skeleton. The studies showed that the [1,2-^{13}C] labelled acetate units were incorporated intact.

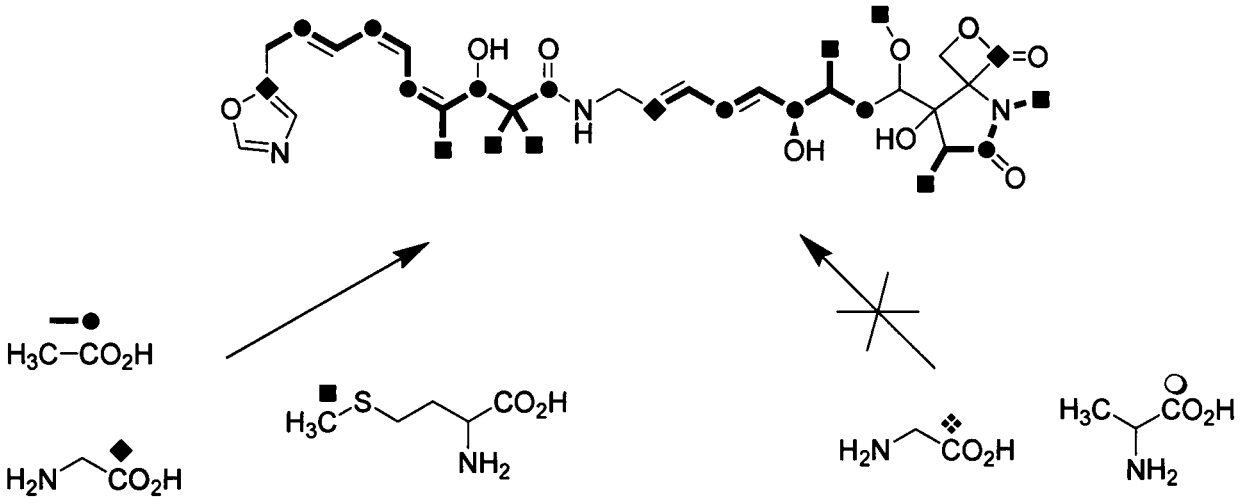
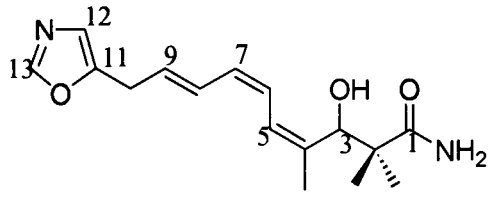


Fig. 1.3: The biosynthesis of oxazolomycin

Both the (*E, E*)-diene and the (*Z, Z, E*)-triene chains are built up from acetate via the polyketide pathway, each starting with a glycine-derived building block. The spiro-ring system is formed from acetate, glycine and a C_3 unit of unknown origin. The oxazolomycin-producing organism combines carbon, oxygen and nitrogen methylation activity *via* methionine (C_1 pool) for the biosynthesis of oxazolomycin A **(1.1a)**.

1.6 Related Compounds

From a different *Streptomyces* sp. strain, the antibiotics phthoxazolin A **(1.14)**[18] and inthomycins B and C were isolated. These compounds are closely related to the oxazolomycins, being in essence, the left hand side of the molecule. Each share the same triene stereochemistries as that of the oxazolomycins and as such they are also designated A, B and C. The only structural difference between inthomycin B and C and phthoxazolin A was later found to be the triene geometry.



(1.14)

Position	^{13}C chemical shift	^{1}H shift, mult, *J*(Hz)
1	181.2	
1-NH_2(NH)		5.70 br.s, 6.33 br.s
2	44.6	
2-Me	21.6	1.08, s
2-Me	26.1	1.35, s
3	75.3	4.64, d, 5.8
3-OH(OAc)		4.02, d, 5.8
4	138.3	
4-Me	19.4	1.84, s
5	124.8	6.41, d, 11.5
6	123.7	6.10, dd, 11.5 and 11.5
7	128.1	5.95, dd, 11.5 and 11.5
8	128.2	6.64, dd, 11.5 and 15.0
9	128.6	5.77, dt, 7.0 and 15.0
10	29.0	3.51, d, 7.0
11	150.7	
12	122.4	6.80, s
13	150.4	7.79, s

Table 1.7: ^{1}H and ^{13}C NMR data of phthoxazolin A (performed in $CDCl_3$)

Phthoxazolin A is a highly specific inhibitor of cellulose biosynthesis and it has selective antimicrobial activity against *Phytophthora* spp but it displays little of the activity[19] characteristic of the oxazolomycin 'family', suggesting that the activity of the oxazolomycins could be attributed to the β-lactone ring fragment.

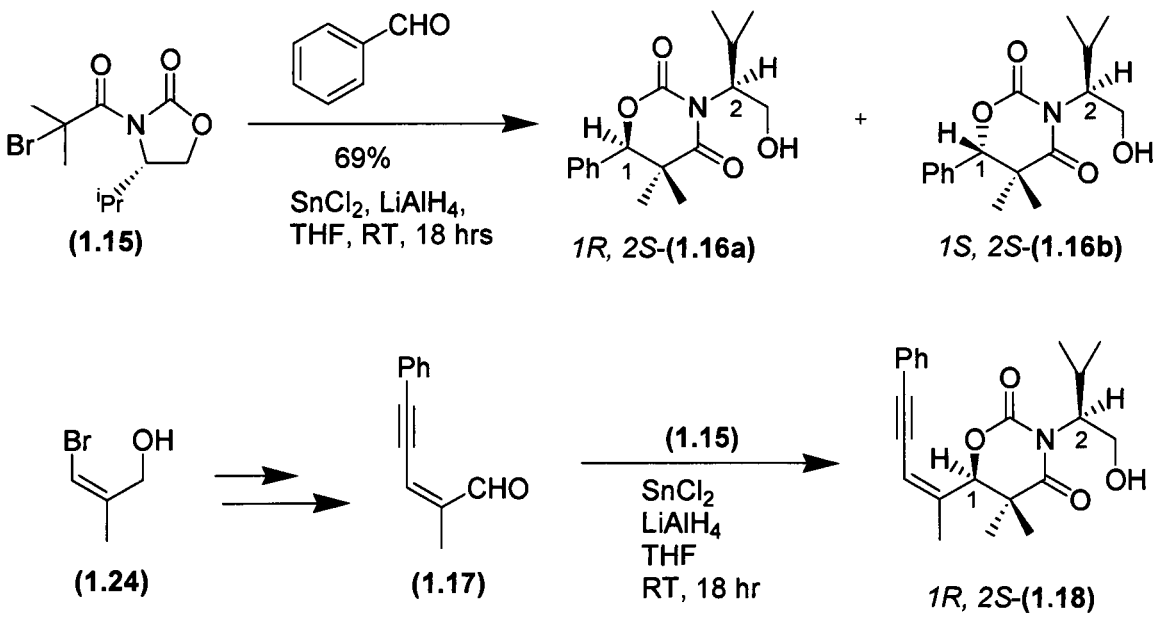
NMR studies[20] (Table 1.7) have determined the structure of both phthoxazolin A **(1.14)** and the inthomycins as being identical to the left hand side fragment of the oxazolomycins. The UV data are also very similar, displaying an absorption maxima at 275 nm (ε, 12000) with two shoulders characteristic of the triene moiety.

1.7 Total Synthesis of the Oxazolomycin Class of Natural Products

1.7.1 Total Synthesis of Neooxazolomycin

To date, only one synthesis of any of the oxazolomycin class of natural products has been reported, namely that of neooxazolomycin by Kende *et al.*[9] The same author first addressed the enantioselective synthesis of the α,α-dimethyl-β-hydroxy acid subunit present in all of the aforementioned compounds.

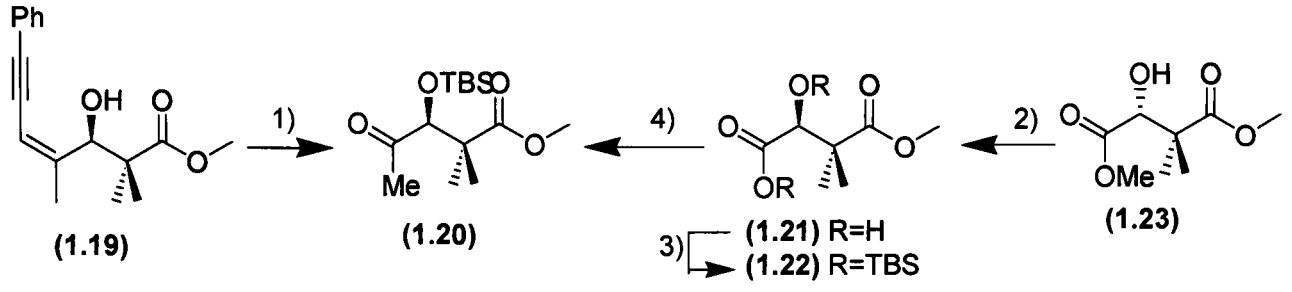
The only other enantioselective synthesis of this subunit system has been by asymmetric aldol reactions which resulted in low enantiomeric excess.[21] Kende's approach made use of the then new Evans chiral auxiliary, used in a diastereoselective 'Reformatsky type' aldol reaction resulting in both good yield and high ee.



Scheme 1.3: Model systems using the Evans Auxiliary.

Reaction of the Sn(II) enolate (Scheme 1.3), generated by the *in situ* action of $SnCl_2$-$LiAlH_4$ on oxazolidinone **(1.15)**, with benzaldehyde or unsaturated aldehyde **(1.17)** yields respectively a mixture of oxazolidinone **(1.16a)** and **(1.16b)** or oxazolidinone **(1.18)** in not less than 97:3 diastereoselectivity of the (*R,S*)-isomer. Removal of the chiral auxiliary from **(1.18)** produces an enantiopure model **(1.19)** of the natural C1'-C5' subunit of the oxazolomycins. The stereochemistry was established by

independent synthesis of the racemic *E*-ester which had a profoundly different ^{1}H NMR spectrum *via* employment of a chiral solvent.



1) TBSOTf, 2,6-lutidine; O_3/Me_2S. 2) KOH, MeOH. 3) TBSCl, imidazole. 4) $(COCl)_2$, DMF (cat.); MeMgCl, $Fe(acac)_3$.

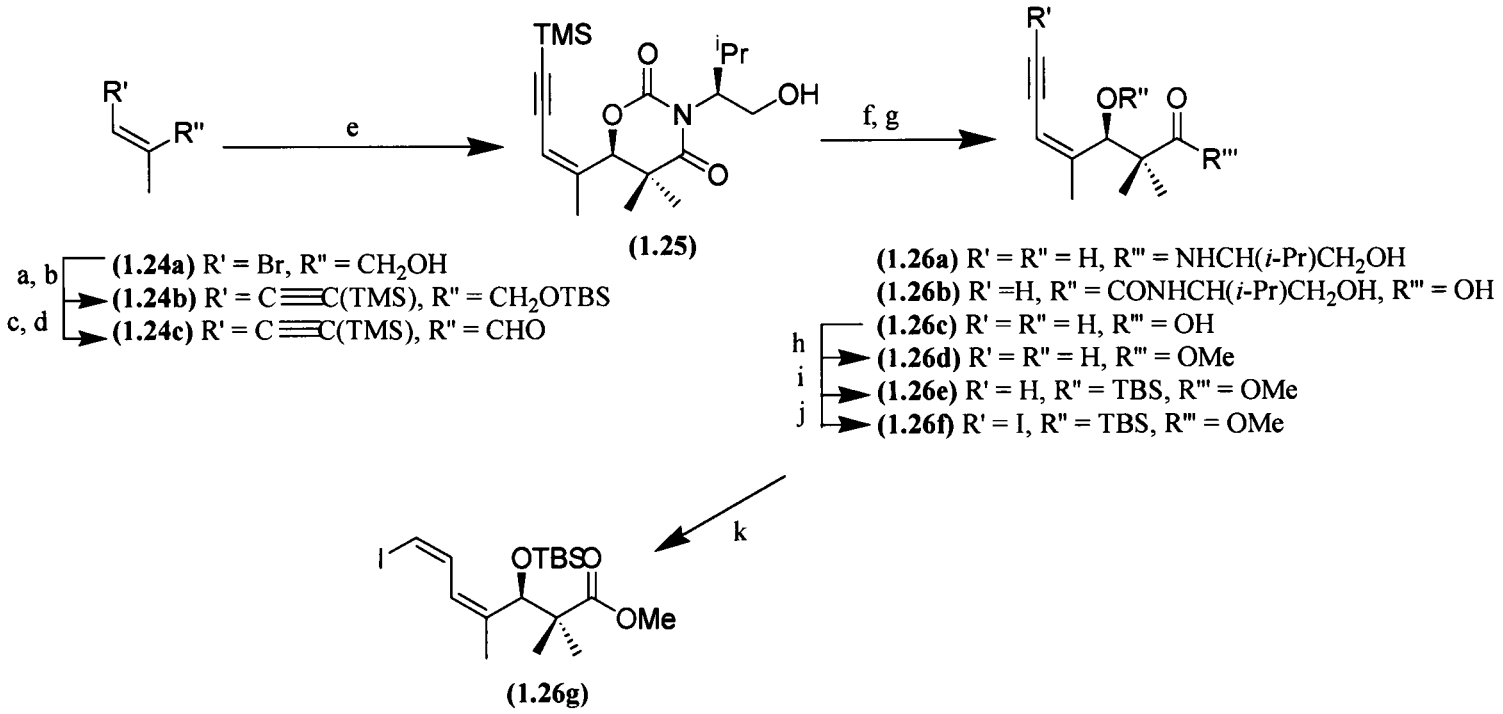
Scheme 1.4: Proof of 3R stereochemistry of the acid subunit.

Thus, the absolute configuration of **(1.19)** was shown to be 3*R* by conversion to the optically active ketoester **(1.20)**. This compound can also be prepared independently from Seebach diester **(1.23)** of known absolute stereochemistry (Scheme 1.4), to provide a 'standard' for comparative studies. The ketoester obtained from ester **(1.19)** had essentially the same specific rotation as the ketoester derived from the Seebach diester. $[\alpha]_D^{24}$ = -21.1 (c=0.8, DCM) as opposed to $[\alpha]_D^{25}$ = -23 (c=0.7, DCM) respectively.

With this methodology established for the model system, Kende's group turned their attention to the natural product neooxazolomycin **(1.3)**.[9,22] The retrosynthetic strategy involved an amide disconnection between a (*Z, Z, E*)-oxazole triene acid left half and a highly functionalised lactam-lactone aminodiene right half. The oxazole triene acid left half of neooxazolomycin was synthesised from the known[23] (*Z*)-3-bromo-2-methyl-2-propenol **(1.24a)** which was converted into the (*Z*)-aldehyde **(1.24c)** (Scheme 5) *via* a sequence involving protection as the TBS ester and palladium-catalysed coupling with (trimethylsilyl)acetylene to produce the enyne **(1.24b)**, and further manipulation by TBS selective deprotection and oxidation provided access to aldehyde **(1.24c)**, (Scheme 1.5).

Diastereoselective 'Reformatsky-type' condensation of **(1.24c)** with the tin(II) enolate derived (as previously described) from chiral acyloxazolidinone **(1.15)** (1.2 eq) by use of $SnCl_2$ (2 eq) and $LiAlH_4$ (1.0 eq) in THF proceeded in 95% yield to provide **(1.25)** having the desired 3'*R* configuration in >98% d.e. and complete retention of the alkene (*Z*) geometry (Scheme 1.5). Comparatively mild removal of the chiral auxiliary and C-silyl functionality was performed by exposure of **(1.25)** to 30% H_2O_2

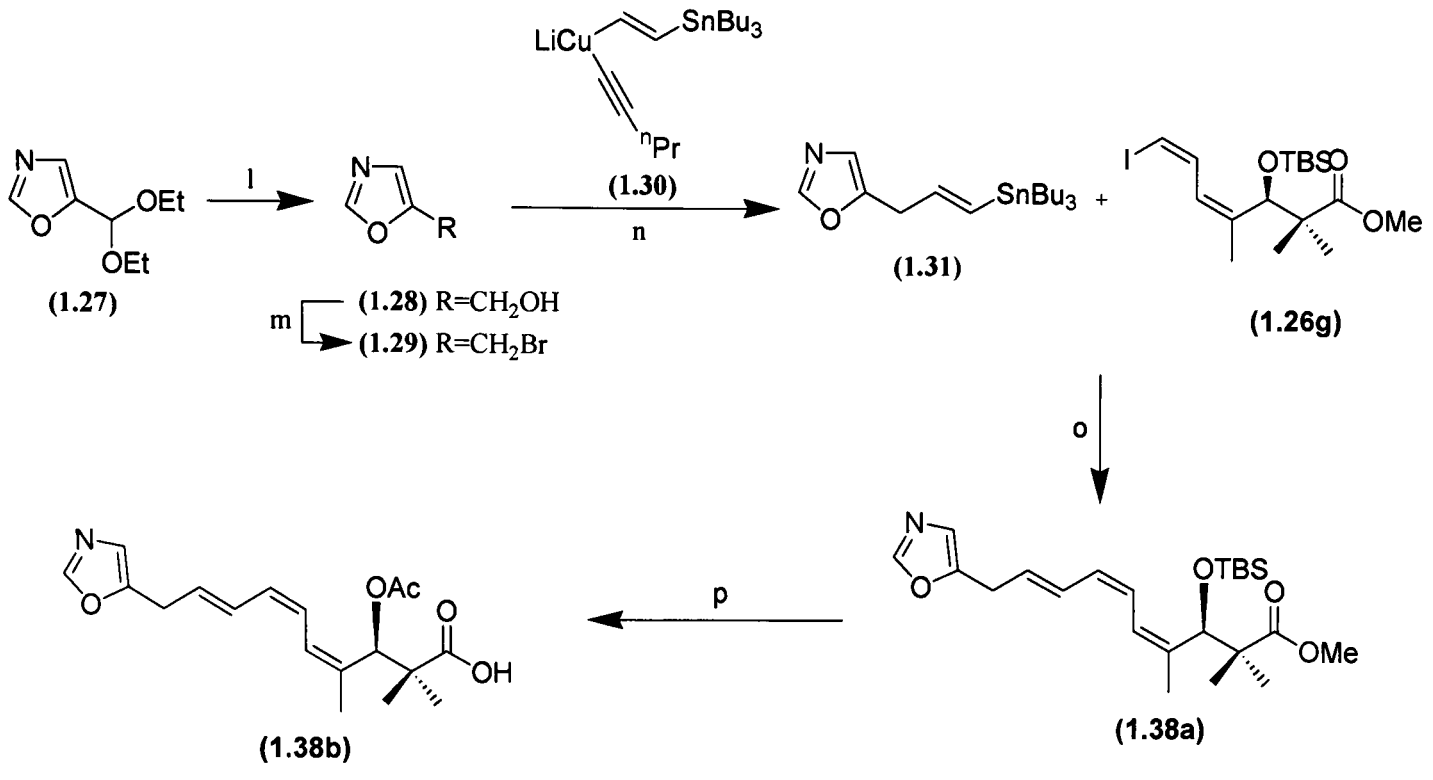
(6 eq) and LiOH (2 eq), which provided 13% of the diol amide **(1.26a)** and 87% of the desired carboxylic acids **(1.26b)** and **(1.26c)** in a 24:1 ratio. The acid was taken on as the mixture and hydrolysed with LiOH to give 85% of **(1.26c)**, along with 69% of the recovered homochiral Evans oxazolidinone. Exposure of **(1.26c)** to diazomethane gave enantiomerically pure ester **(1.26d)**, shown to be enantiomerically homogeneous (>99%) by use of $Eu(hfc)_3$ employing racemic **(1.26d)** as standard. To construct the (*Z, Z, E*) triene system, ester **(1.26d)** was protected (TBSOTf) to give silyl ether **(1.26e)** which was iodinated (BuLi then I_2) to give **(1.26f)** which was converted into **(1.26g)** by diimide reduction.



a) TBSCl, imidazole, DMF; b) (TMS)CC(H), $Pd(Ph_3P)_4$, CuI, *n*-$BuNH_2$, PhH, 18hr; c) AcOH/THF/H_2O; d) basic MnO_2, hexane/DCM; e) $SnCl_2$, $LiALH_4$, THF, then Evans oxazolidine, then **(1.24c)**; f) 30% H_2O_2, LiOH, THF/H_2O; g) LiOH (3 eq), THF/MeOH/H_2O, 24h; h) CH_2N_2, Et_2O; i) TBSOTf, 2,6-lutidine, DCM: j) *n*-BuLi, THF, -78° C, 1h, then I_2 in THF; k) NH_2NH_2 (5 eq), $CuSO_4.5H_2O$ (0.1 eq), 95% EtOH, 23° C, air (bubbled).

Scheme 1.5: Construction of the Left Hand Side of Neoxazolomycin.

The 5-substituted oxazole terminus was constructed (Scheme 1.6) by the reaction of ethyl diethoxyacetate and lithiated TosMIC using a Schöllkopf condensation to provide, 5-substituted oxazole **(1.27)**. Hydrolysis and $NaBH_4$ reduction followed by exposure to NBS/Ph_3P provided unstable bromide **(1.29)**. Immediate cuprate addition with organocuprate **(1.30)** (1.2 eq) produced (*E*)-vinylstannane **(1.31)**. Thus stannane **(1.31)** and vinyl iodide **(1.26g)** were exposed to standard Stille conditions, providing the desired triene ester **(1.38a)** in 79% yield. Protecting group manipulation and LiOH hydrolysis gave access to the acetyl-protected left hand side fragment **(1.38b)** with the desired stereochemistry and functionality intact.



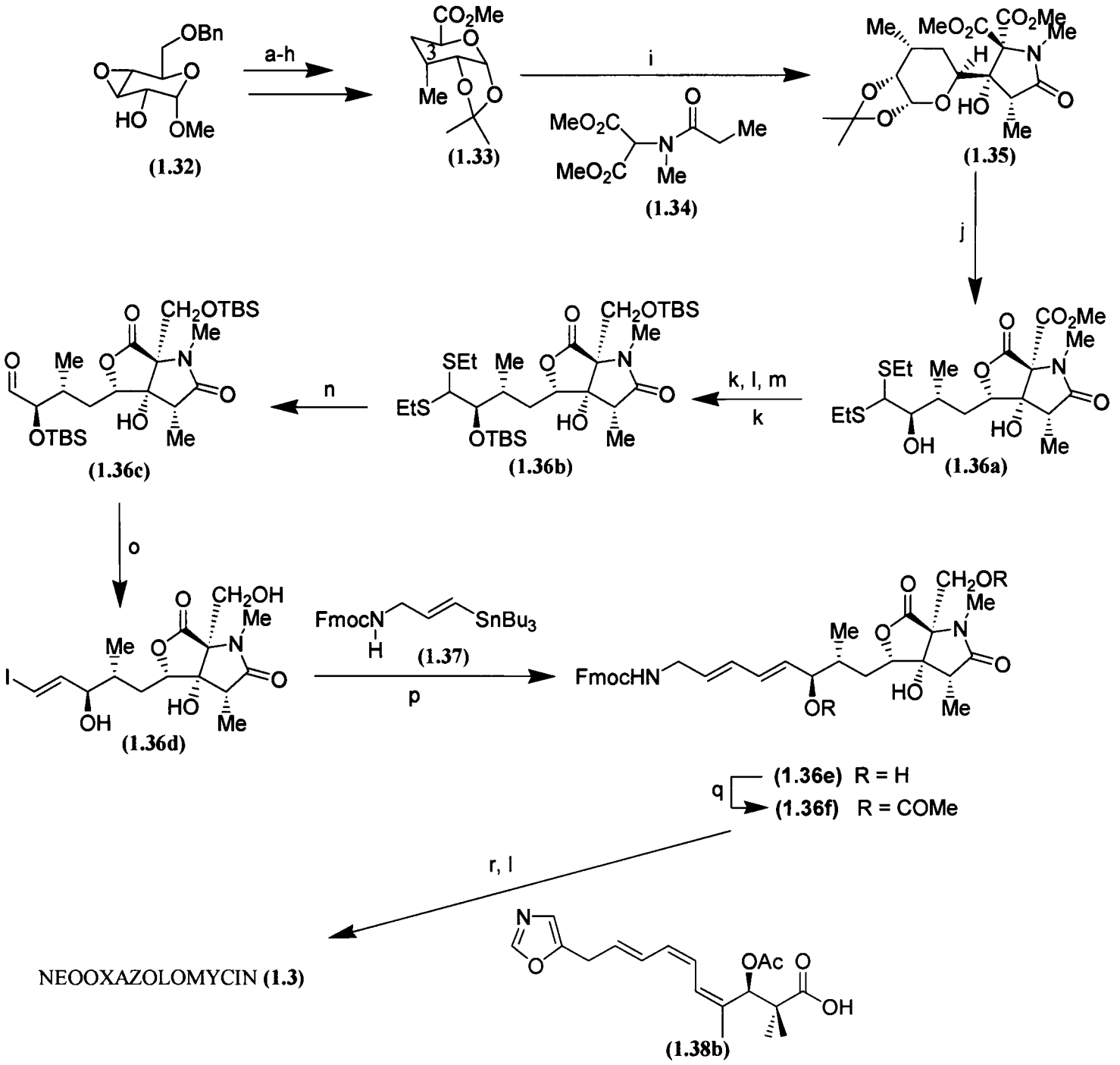
l) THF/H_2O/conc. HCl (cat.), 23 °C, 17h, then saturated $NaHCO_3$, 10 mins, $NaBH_4$; m) NBS, PPh_3, THF; n) (*E*)-$Bu_3SnCH{=}CHSnBu_3$, *n*-BuLi, THF, -78 °C - -40 °C, then addition to (Cu)CC(Pr), THF, -40 °C, 0.5h, the addition to **(1.30)**, THF, -78 °C - -10 °C; o) 3 mol % $PdCl_2(MeCN)_2$, DMF; p) i) 50% HF/MeCN, ii) Ac_2O, pyridine, then saturated $NaHCO_3$, $MeOH/H_2O$.

Scheme 1.6: Construction of oxazole terminus and final stille coupling to provide the left hand side fragment.

The Right Hand Side of Neooxazolomycin

To date, no synthesis of the spiro-fused β-lactone-γ-lactam moiety present in oxazolomycin **(1.1a)** has been reported in the literature. Kende's group however, developed an elaborate synthesis of the right hand side γ-lactone fragment of neooxazolomycin[9].

The α-substituted pyroglutamate required was formed (Scheme 1.7) by a novel condensation of the dianion derived from compound **(1.34)** onto ester **(1.33)**, readily derived from anhydrogalactaside as a chiral source. The stereogenic centre at C-3 of **(1.33)** was generated by *trans*-diaxial epoxide opening using 10 eq of Me_2Mg, thus providing direct access to lactam **(1.35)**.



a) MeLi, MeMgCl, THF/Et_2O; b) $^iPr_3SiOTf$, 2,6-lutidine, THF, -78° C - 23° C; c) $S=C(Im)_2$, $(CH_2Cl)_2$, heat, $^nBu_3SnH$, xylene, heat; d) $^nBu_4NF$, THF; e) $FeCl_3$, acetone; f) H_2, $Pd(OH)_2$, MeOH; g) $(COCl)_2$, DMSO, Et_3N, DCM, -78° C then $KMnO_4$, t-BuOH/ 5% NaH_2PO_4; h) CH_2N_2, Et_2O, 0° C; i) **(1.34)**, ^tBuLi, TMEDA, THF - 78° C then addition to **(1.33)**, THF, -78° C; j)EtSH, conc. HCl (cat); k) TBSOTf, 2,6-lutidine, DCM; l) LiOH, THF/H_2O 1 hr then 1 M HCl; m) $[Me_2N=CHCl]^+Cl^-$, MeCN/THF, 0° C, 1 hr, $NaBH_4$, DMF, -78° C - 23° C; n) $HgCl_2$ $CaCO_3$, MeCN/H_2O; o) CHI_3, $CrCl_2$, THF; p) **(1.37)**, 5 mol % $PdCl_2(MeCN)_2$, DMF; q) Ac_2O, pyridine; r) DBU, DCM, addition to the mixed anhydride [**(1.38b)**, *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride, Et_3N, DCM] the 0.5 hr, 23° C; l) LiOH, THF/H_2O.

Scheme 1.7: Kende's synthesis of the right hand side of neooxazolomycin.

Unfortunately, at this stage a major problem of this total synthesis presented itself. Contrary to model studies[22] performed on this methodology, the desired diastereoisomer was the minor product by a ratio of 1.4:1 (only the two diastereoisomers with the alkyl substituents on the lactam ring in a *trans* relationship were observed). Treatment with acidic ethanethiol then gave smooth rearrangement to the lactone-lactam **(1.36a)**.

Protecting group manipulation followed by conversion to the corresponding aldehyde **(1.36c)** ($HgCl_2$ / THF, $NaBH_4$), Wittig reaction and exposure to CHI_3 / $CrCl_2$ yielded the (*E*)-vinyl iodide **(1.36d)** and standard Stille coupling with (*E*)-vinyl stannane **(1.37)** afforded the (*E*, *E*)-dienylamide right hand side fragment of neooxazolomycin.

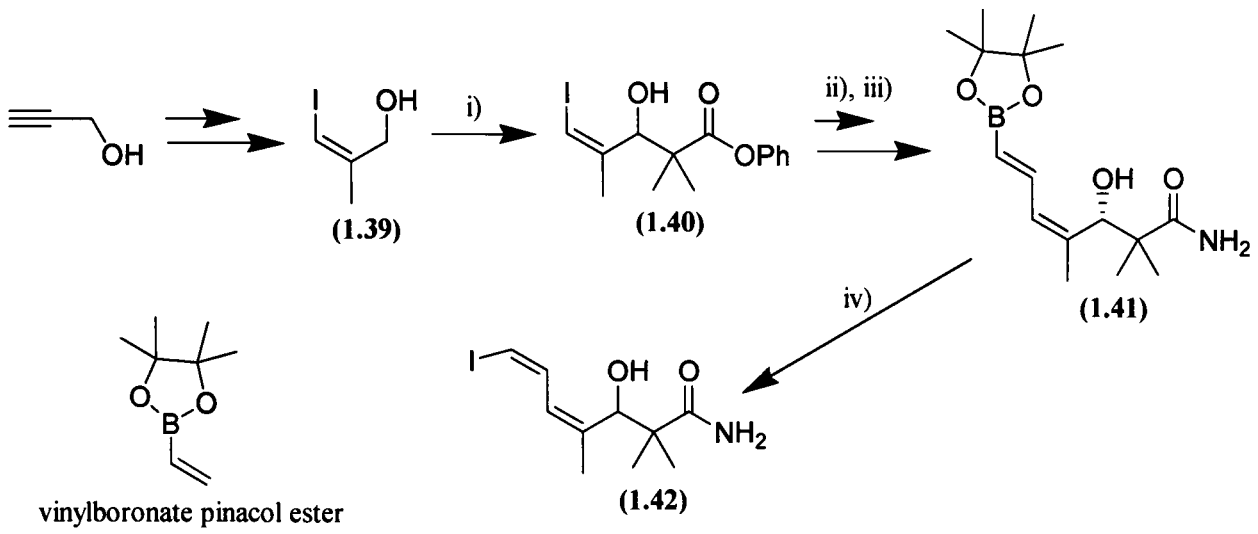
Reaction of the protected left hand side free acid **(1.38b)** with triethylamine yielded an activated anhydride to which was added a solution of the free amine right hand side fragment prepared from DBU deprotection of the Fmoc group. One hour exposure to these conditions produced neooxazolomycin triacetate in 60% yield. Finally LiOH hydrolysis yielded pure neooxazolomycin, identical to an authentic sample by 300 MHz ^{1}H NMR, HPLC and FAB MS techniques.

1.7.2 Total Synthesis of Phthoxazolin A

Whiting *et al*[24] recently published a synthesis of phthoxazolin A, essentially the left hand side of the oxazolomycin class of antibiotics, in racemic from, involving a convergent series of palladium-catalysed cross-coupling reactions to stereoselectively construct the *Z, Z, E* - trienyl moiety.

Starting with commercially available propargyl alcohol (Scheme 1.8) and applying standard methodology, alcohol **(1.39)** was obtained. Swern oxidation followed by immediate aldol condensation produced racemic phenol ester **(1.40)**. However, several attempts to form this compound enantioselectively using both chiral auxiliary and catalytic asymmetric methods proceeded without success.

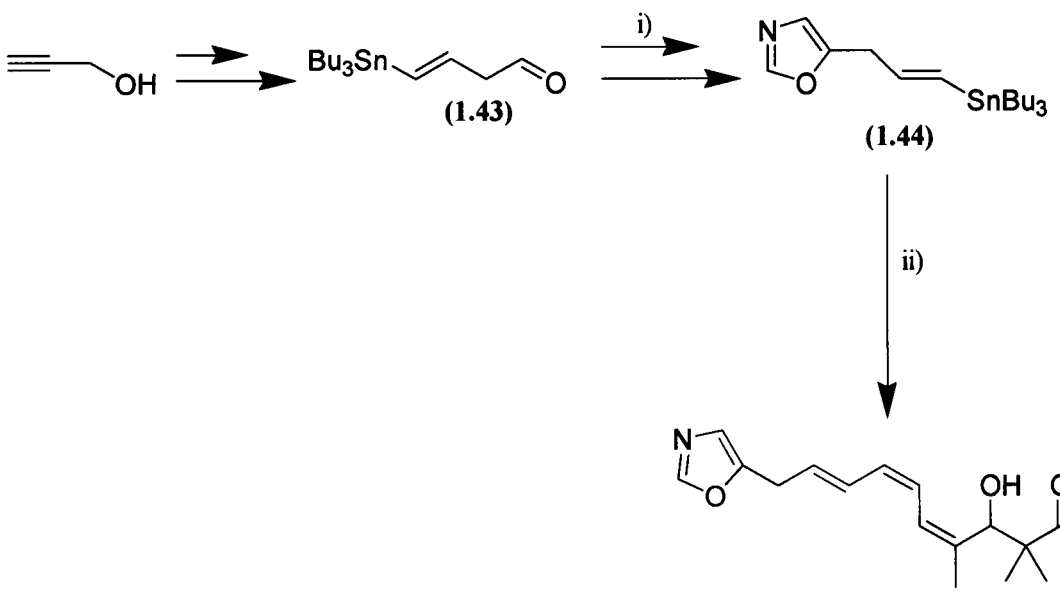
Treatment of racemic phenol ester **(1.40)** with aqueous ammonia and vinylboronate pinacol ester provided stereoselective access to dienylboronate **(1.41)** in 43% yield after a series of optimisation experiments.[25] A boronate-iodine exchange with clean inversion of the olefin stereochemistry was achieved using established methodology by the Whiting group. The resulting iodide **(1.42)** had to be used as crude owing to its instability towards silica.



i) a. Swern [O], b. $(CH_3)_2CHCOOPh$, $TiCl_4$, Et_3N; ii) $NH_3(aq)$; iii) vinylboronate pinacol ester, Et_3N, $Pd(PPh_3)_4$, 4 days; iv) ICl, MeONa, DCM, 2hr, 69%

Scheme 1.8: Whiting synthesis of one of two fragments of Phthoxazolin A.

Application of this vinylboronate chemistry in an attempt to provide the oxazole fragment was to prove unsuccessful due to the high reactivity of the resultant species in this particular system.



i) a.TosMIC; b. K_2CO_3, MeOH, Heat, 6hr, 15%, ii) DMF, $PdCl_2(MeCN)_2$, **(1.42)**

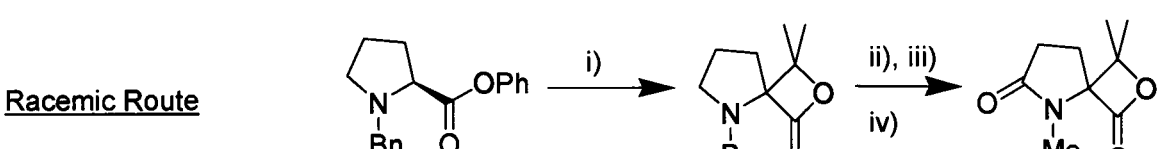
Scheme 1.9 Whiting's synthesis of the remaining fragment of Phthoxazolin A.

Access to the oxazole terminus (Scheme 1.9) was achieved by AIBN initiated hydrostannylation of propargyl alcohol followed by Swern oxidation, to yield aldehyde **(1.43)**. Direct oxazole formation with tosylmethyl isocyanide provided access to stannane **(1.44)**. Palladium-catalysed Stille cross-coupling between vinyl iodide **(1.42)** and stannane **(1.44)** yielded phthoxazolin A in 22% yield. The synthesised compound was identical to an authentic sample by NMR, HPLC and MS analysis.

1.7.3 Synthesis of the γ-lactam Right Hand Side of oxazolomycin

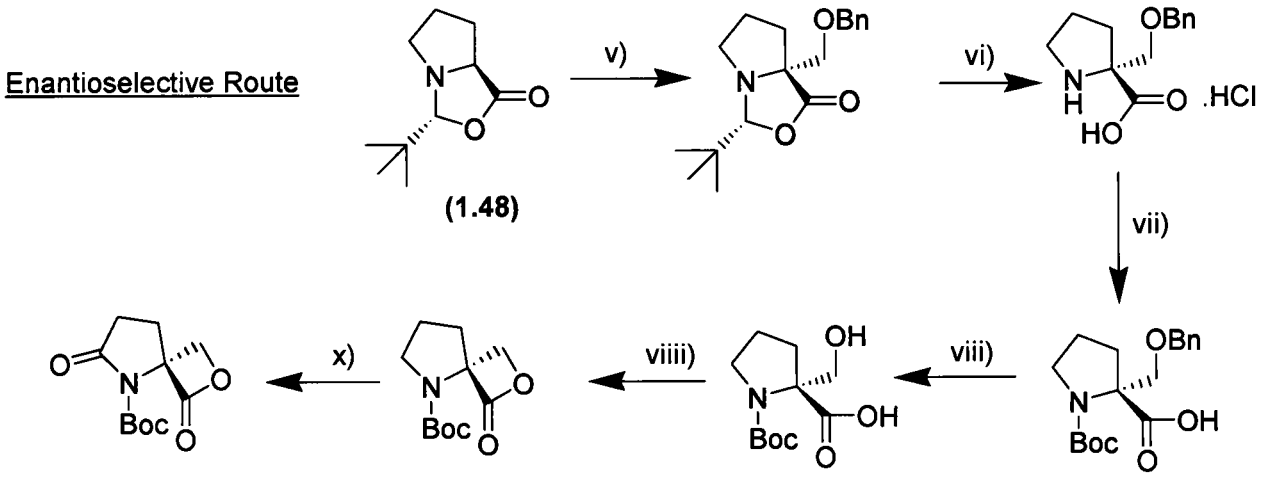
Taylor *et al*[26] described the first synthesis of the 1-oxo-2-oxa-5-azaspiro[3.4]octane ring system found in the oxazolomycins, in both racemic and enantioselective routes.

A pathway for the synthesis of the racemic compound **(1.47)** utilising a tandem aldol-condensation strategy was performed (Scheme 1.10). The enolate of *N*-benzyl proline phenyl ester **(1.45)** reacted rapidly at -78° C with acetone to afford β-lactone **(1.46)**. Palladium-catalysed hydrogenation successfully removed the *N*-benzyl protecting group, subsequent *N*-methylation resulted in clean conversion to lactone **(1.47)**. Ruthenium tetroxide was used to introduce the required γ-lactam present in the natural product *via* Sharpless methodology. It was found the nature of the *N*-protecting group greatly affected the yield of the first step and extensive optimisation was required. Alkoxycarbonyl protection provided at best mediocre yields whilst switching to alkyl *N*-protecting groups greatly increased the yield up to 100%.



(1.45) **(1.46)** **(1.47)**

i) LDA, 1.1 equiv., $C(O)Me_2$, THF, -78° C, ii) H_2, Pd/C, 10%, EtOAc, iii) MeI, K_2CO_3, DMF, iv) $RuCl_3.{}_xH_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$ 1:1:1.5, RT

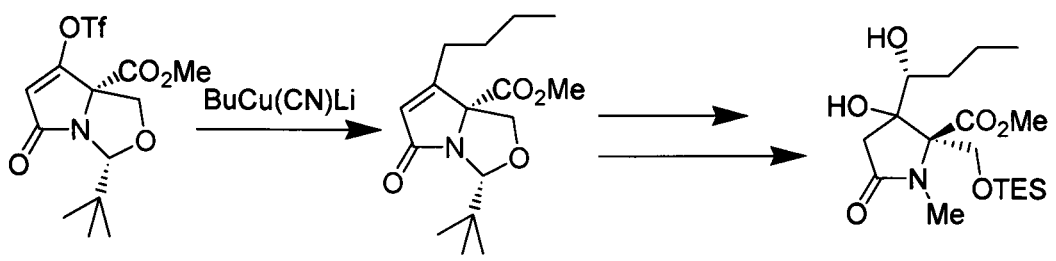


(1.48) **(1.49)** **(1.50)**

v) a: LDA, THF, -78° C, b: BomCl, -78° C to RT, vi) 3 M HCl, reflux, vii) Boc_2O, $Me_4NOH.5H_2O$, MeCN, viii) H_2, Pd/C, 10%, MeOH, viiii) DMAD, PPh_3, THF, -78° C, x) $RuCl_3.{}_xH_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$ 1:1:1.5, RT

Scheme 1.10: Taylor's synthesis of the 1-oxo-2-aza-5-azaspiro[3.4]octane ring system.

The enantioselective route relied upon the 'self-reproduction of chirality' concept introduced by Seebach *et al.* BomCl was used to alkylate **(1.48)** yielding a single diastereoisomer which underwent smooth hydrolysis to yield an α-alkylated amino acid. Protecting group manipulation and β-hydroxy acid ring closure provided *N*-Boc (4*S*) 1-oxo-2-oxa-50azaspiro[3.4]octane **(1.49)**. Sharpless methodology again introduced the desired γ-lactam functionality to afford **(1.50)**.



(1.51) **(1.52)** **(1.53)**

Scheme 1.11: Model study introducing a side chain to afford entry to the lactam core of oxazolomycin.

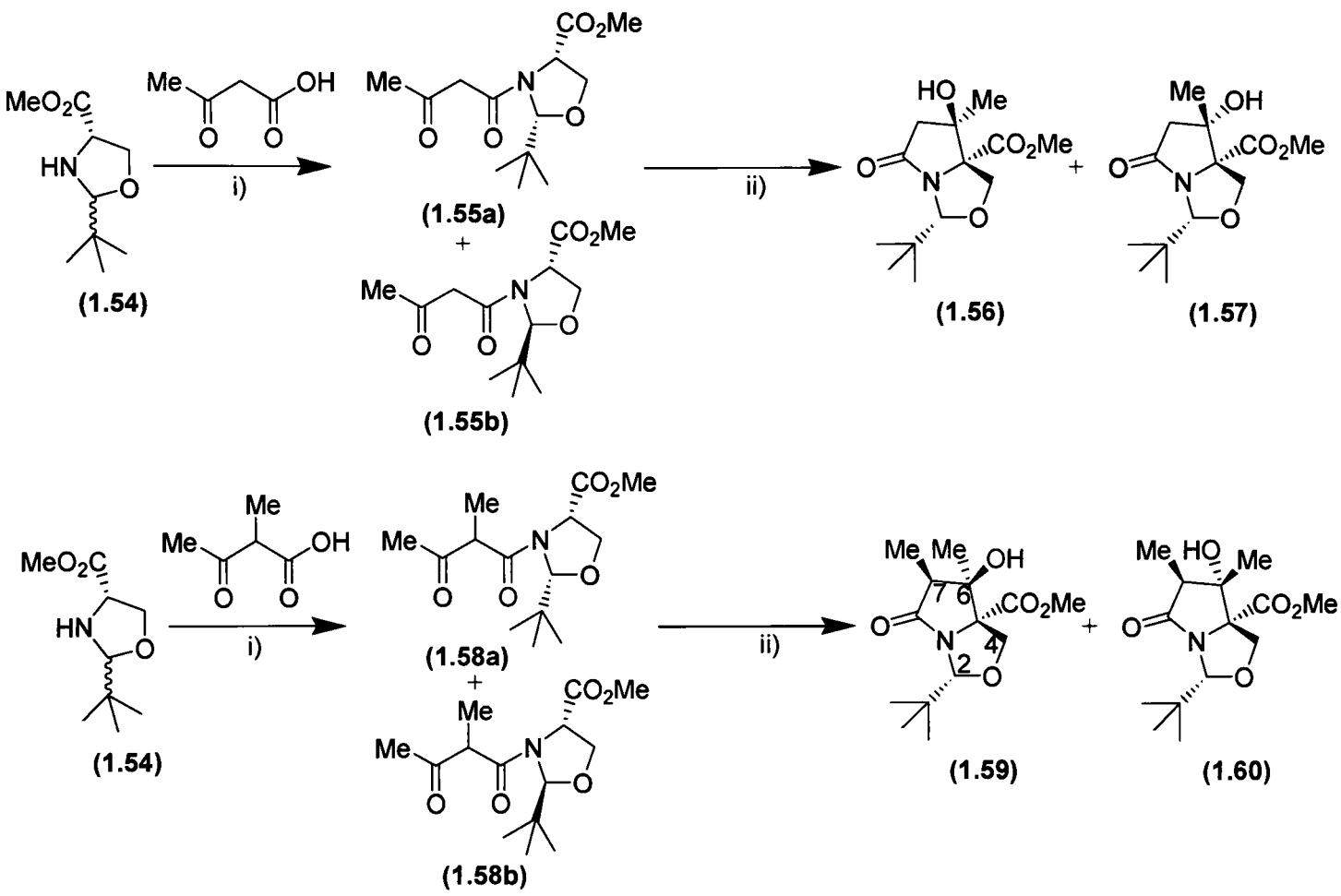
Taylor's group[26] also outlined an entry to the lactam core of oxazolomycin (Scheme 1.11). Tetramic acid enol triflate **(1.51)** could be prepared in good yield according to previous work within the Taylor group. Introduction of a model side chain using a lower order cyanocuprate proceeded efficiently to afford **(1.52)**. Deconjugation, protecting group manipulation, followed by Sharpless asymmetric dihydroxylation, afforded **(1.53)** as a single stereoisomer in 35% yield.

1.7.4 Synthesis Towards the Pyroglutamate Skeleton of Oxazolomycin

Moloney *et al*[27] described a different route to the pyroglutamate skeleton of the right hand side of oxazolomycin based upon established group methodology.[28] Oxazolidine **(1.54)**, derived from L-serine methyl ester hydrochloride, was acylated *via* use of EDAC and the appropriate acetoacetic acid (Scheme 1.12) in the presence of catalytic amounts of DMAP, to afford mixtures of *cis* and *trans*-oxazolidines as mixtures of enol and keto tautomers, **(1.55a, 1.58a)** and **(1.55b, 1.58b)**, with the *cis*-isomer being the major product.

Cis-oxazolidine **(1.55a)** underwent intramolecular aldol reaction on treatment with base to generate the epimeric alcohols **(1.56)** and **(1.57)** under thermodynamic control.

Similar cyclisation of **(1.58a)** yielded, as the major product, hydroxylated pyroglutamate **(1.59)** with an NMR-elucidated stereochemistry of (7*S*). The stereochemistry of these reaction products is presumably a result of thermodynamic control, since the reaction proceeds under equilibrating conditions.

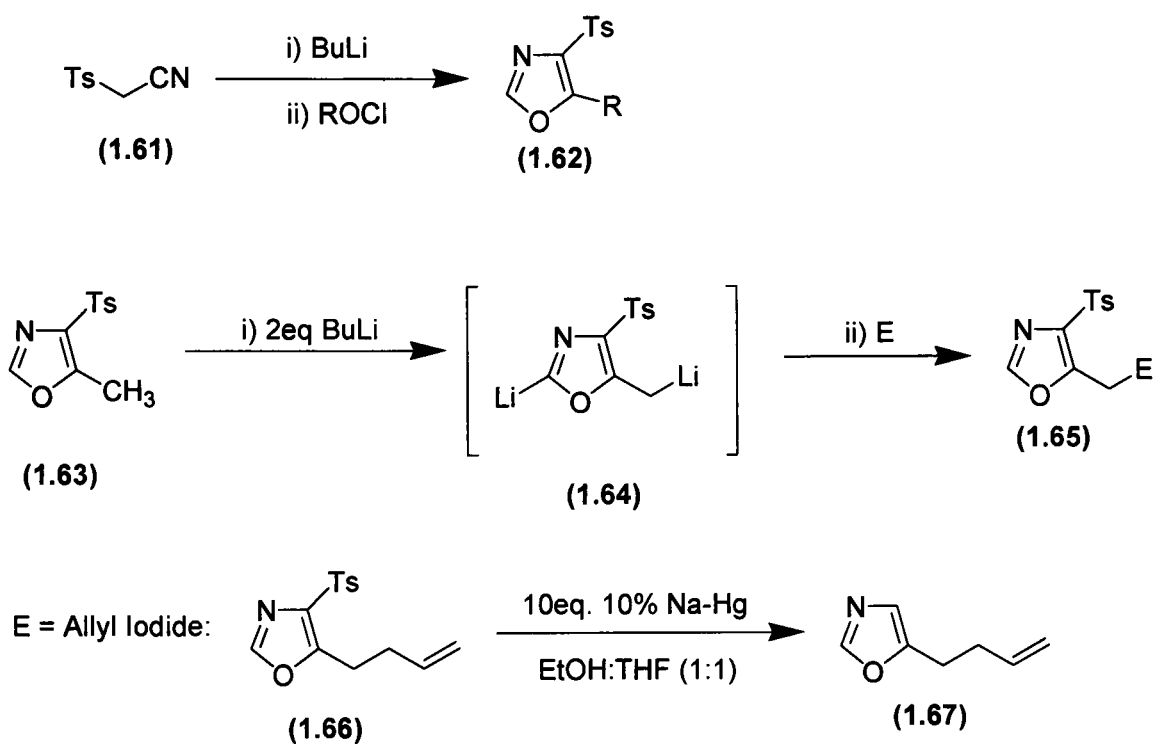


Scheme 1.12: Moloney's synthesis of the pyroglutamate skeleton of oxazolomycin.

1.7.5 Synthesis of the 5-substituted oxazole

Taylor *et al.*[29] recently reported an ultrasound-promoted desulfonylation of 5-substituted-4-tosyloxazoles. The 5-substituted oxazole moiety is common to all members of the the oxazolomycin family. The most common entry to 5-monosubstituted oxazoles is *via* the Schöllkopf condensation[30] using the highly toxic and volatile methyl isocyanide. The hazards associated with this alkyl isocyanide can be largely avoided by employing tosylmethyl isocyanide **(1.61)** (TosMIC). The

reaction of TosMIC with aldehydes under basic conditions affords 5-substituted oxazoles directly, as described by van Leusen *et al,*[31] in a process which is limited only by the availability and stability of the requisite aldehyde. The reaction of the TosMIC anion with carboxylic acid chlorides, anhydrides and esters has also been carried out by van Leusen but the resulting 5-substituted oxazoles now also possess a *p*-toluenesulfonyl substituent in the 4-position **(1.62)** (Scheme 1.13).



Scheme 1.13: Taylor's studies into 5-monosubstituted oxazoles.

Taylor anticipated that the 2-position of the oxazole ring of **(1.63)** would be the most acidic and it was hoped that a second equivalent of butyllithium would afford dianion **(1.64)** which would be susceptible to reaction with electrophiles. It was found that both benzaldehyde and allyl iodide reacted regioselectively to give 5-substituted-4-tosyloxazoles (where E = CH(OH)Ph) **(1.65)** in good yield. Unfortunately, dianion **(1.64)** did not give satisfactory results with all electrophiles. Attempts at acylation with ethyl chloroformate and benzoyl chloride failed to give the desired products.

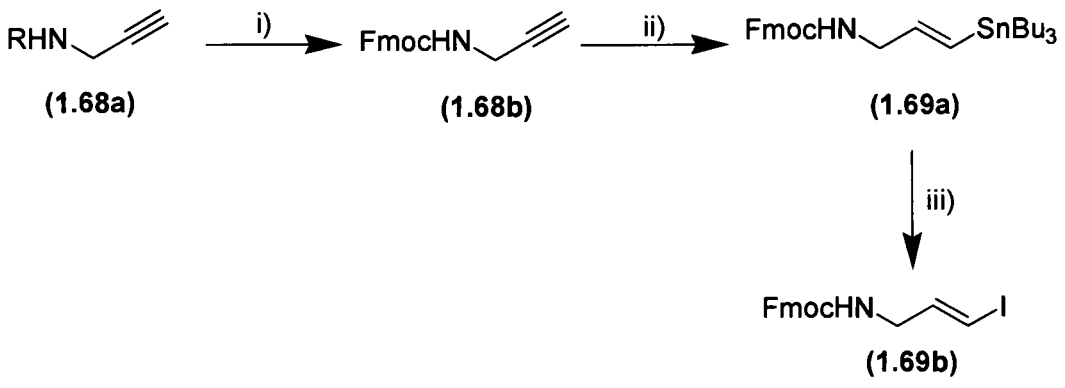
Initial attempts to effect reductive desulfonylation of **(1.66)** were unsuccessful. Many well established techniques failed to give any observable reaction including use of samarium diiodide in a range of solvents, magnesium in methanol and aluminium amalgam.

After considerable experimentation, 10% Na-Hg and an optimum solvent mixture of EtOH:THF (1:1) with ultrasound sonication effected desulfonylation in a number of

cases. Where the 5-position was substituted with an aromatic ring, yields were quantitative. Alkyl 5-substituents gave lower, but still acceptable, yields of desulfonylated products, and all products could be analysed without further purification. It was noted however, that the 5-monsubstituted oxazole products were not as stable as their 4-tosyl precursors. The desulfonylated products began to decompose after a few days under ambient conditions.

1.7.6 Synthesis of the middle fragment

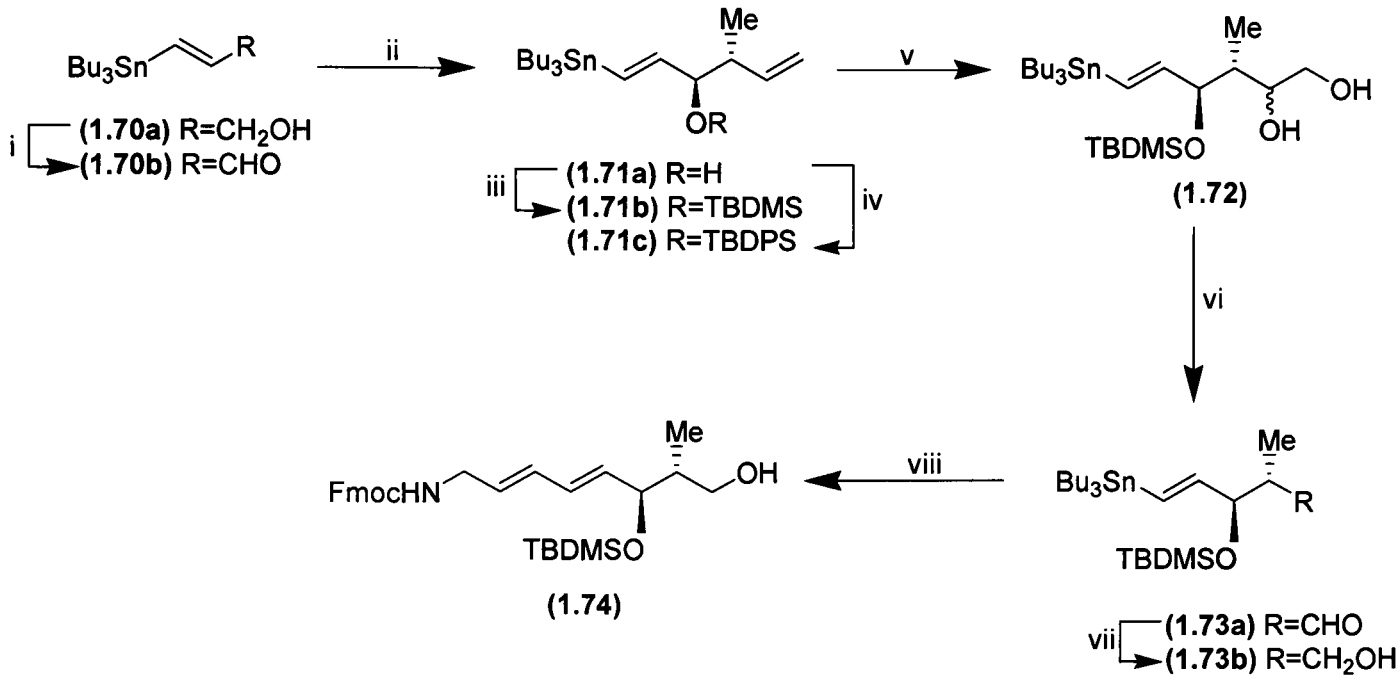
In parallel with this thesis, work has progressed within the group towards the synthesis of the central fragment of oxazolomycin. Moloney *et al*[32] recently detailed a stereoselective and direct synthesis of an (*E*, *E*)-diene suitable for application to the synthesis of both oxazolomycin and its analogues (Scheme 1.14). In a similar approach to that previously presented of Kende, a Stille coupling was planned for construction of the diene. To this end, vinylstannane **(1.69a)** was prepared from commercially available propargylamine **(1.68a)** by initial protection as its Fmoc derivative **(1.68b)** and subsequent hydrostannylation. Exposure of stannane **(1.69a)** to standard methodology (Scheme 14) provided *trans*-vinyl stannane **(1.69b)** as a Stille coupling partner.



i) FmocCl, py, DCM (83%); ii) *n*-Bu_3SnH, AIBN (73%); iii) I_2, DCM (79%).

Scheme 1.14: Moloney synthesis of the central fragement.

For the second partner, Hiyama methodology involving Cr(II)-mediated addition of an allyl bromide to an aldehyde,[33] was used for the construction of the required *anti* stereochemistry (Scheme 1.15).

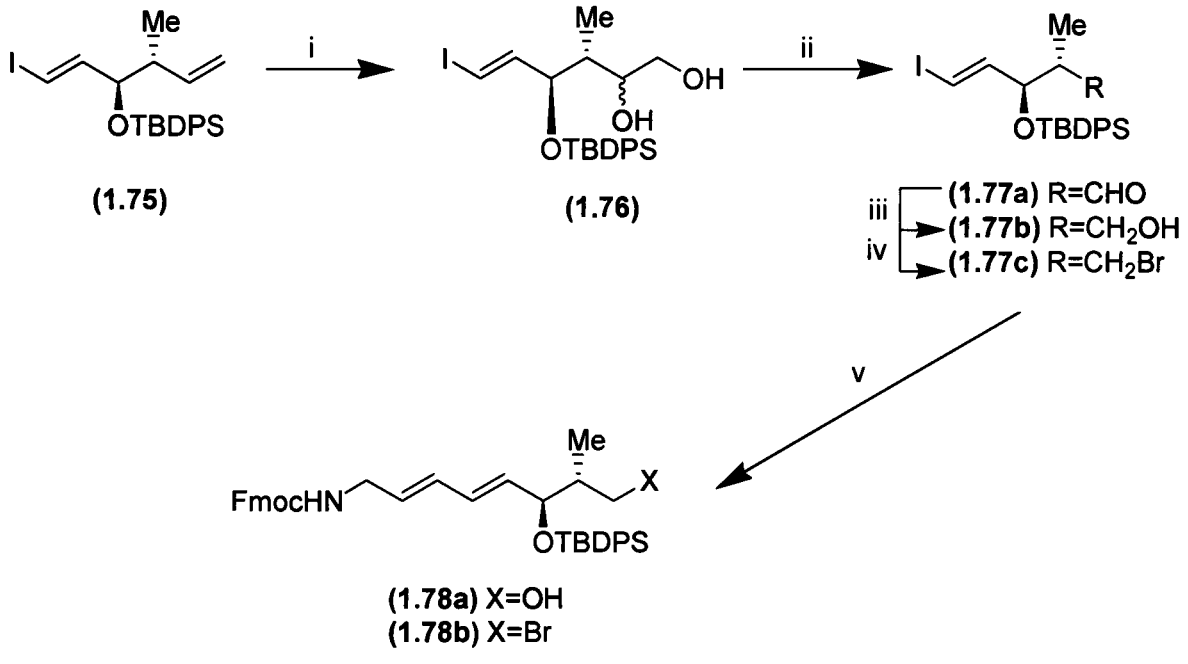


i) PCC/DCM or $(COCl)_2$/DMSO (70%); ii) crotyl bromide, $CrCl_2/LiAlH_4$ (73%); iii) TBDMSCl, imidazole, DCM (90%); iv) TBDPSCl, imidazole, DCM (90%); v) AD-mix-a, *t*-BuOH, H_2O (72%); vi) $NaIO_4$, THF, H_2O (89%); vii) $NaBH_4$, EtOH (85%); viii) **(1.69b)**, $Pd(MeCN)_2Cl_2$/THF (65%).

Scheme 1.15: Moloney's synthesis of protected central fragment **(1.74)**.

Reaction of stannane **(1.70b)** with crotyl bromide in the presence of chromium(II) chloride/lithium aluminium hydride yielded allylic alcohol **(1.71a)**, whose *anti*-stereochemistry was established using a combination of NOESY and molecular modelling analysis. Protection as the TBDMS or TBDPS ether gave **(1.71b,c)** and a point of divergence to investigate different routes. TBDMS ether **(1.71b)** was treated with AD-mix-α according to the Andrus protocol[34] to afford diol **(1.72)** as a 1:1 mixture of diastereomers, which was immediately converted to aldehyde **(1.73a)** and thence to alcohol **(1.73b)**. Coupling of this stannane with iodide **(1.69b)** under standard Stille conditions yielded diene **(1.74)**.

In order to investigate an alternative coupling strategy and to potentially provide crystalline intermediates that would provide unequivocal confirmation of stereochemistry, the silyl ether **(1.71c)** was converted to vinyl iodide **(1.75)** (Scheme 1.16) and thence to diol **(1.76)** as a 1:1 mixture of diastereoisomers by application of the Andrus protocol.[34]



i) AD-mix-a, *t*-BuOH, H_2O (65%); ii) $NaIO_4$, THF, H_2O (92%); iii) $NaBH_4$, EtOH (91%); iv)CBr_4, PPh_3, THF (85%); v) **(1.69a)**, $Pd(MeCN)_2Cl_2$/THF (65%).

Scheme 1.16: Moloney's synthesis of protected central fragment **(1.78b)**.

Compound **(1.76)** was oxidised to aldehyde **(1.77a)** *via* the use of sodium periodate and thence reduced to alcohol **(1.77b)**. These compounds however proved to be colourless oils as opposed to being crystalline, thereby precluding X-ray spectroscopic confirmation of the stereochemistry. Stille coupling of iodide **(1.77b)** with stannane **(1.69a)** yielded the diene product **(1.78a)**. Alternatively, alcohol **(1.77b)** was converted to bromide **(1.77c)** which, was in turn, coupled to vinyl stannane **(1.69a)** through standard Stille methodology to provide diene **(1.78b)**.

1.8 Conclusion

Notwithstanding the potent and selective but ill-understood biological activity of this class of compounds, the oxazolomycins present a considerable synthetic challenge and in order to both develop a greater understanding of the biological activity and the therapeutic potential of these compounds, general and flexible synthetic routes are required, which will provide access not only to the natural products themselves, but also to analogues.

To date, the only extant total synthesis of any of these compounds is that of Kende's report of neooxazolomycin which is very lengthy, and Whiting's recent disclosure of the synthesis of phthoxazolin, which is essentially the left hand side of oxazolomycin. The synthetic challenge offered by the unusual densely functionalised lactam and the sensitive diene and triene units have hitherto precluded effective syntheses of these compounds.

1.8.1 Retrosynthetic Strategy

In parallel with Kende's strategy[9], our initial investigation of the synthesis of the oxazolomycin class of compounds has used a standard amide disconnection to generated left and right hand fragments of a phenyl-substituted analogue of oxazolomycin (Scheme 1.17). The phenyl analogue was used for synthetic simplicity rather than the more sensitive 5'-substitued oxazole terminus. The right hand fragment was further disconnected into a lactam component and central diene fragment.

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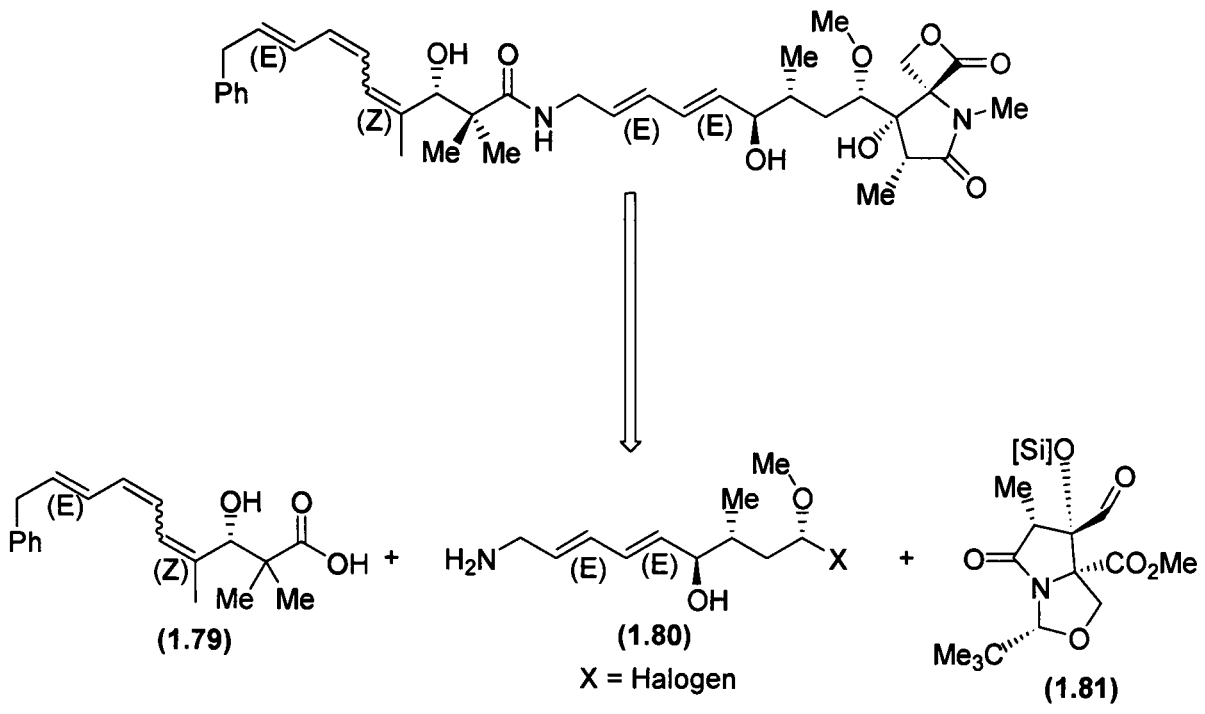
Each fragment will undergo further disconnections to provide simple target intermediates which will be discussed in detail in the individual forthcoming chapters. Moloney's route to the central diene fragment **(1.80)** has previously been discussed (Section 1.7.6).



Scheme 1.17: Retrosynthetic analysis of the oxazolomycins.

1.8.2 Proposed Work

This thesis describes work undertaken towards the total synthesis of oxazolomycin. Strategies towards the phenyl-substituted left-hand triene fragment **(1.79)**, expansion of this chemistry to provide for analogue construction, and investigations to extend known group methodology towards the right-hand side lactam fragment **(1.81)** are discussed.

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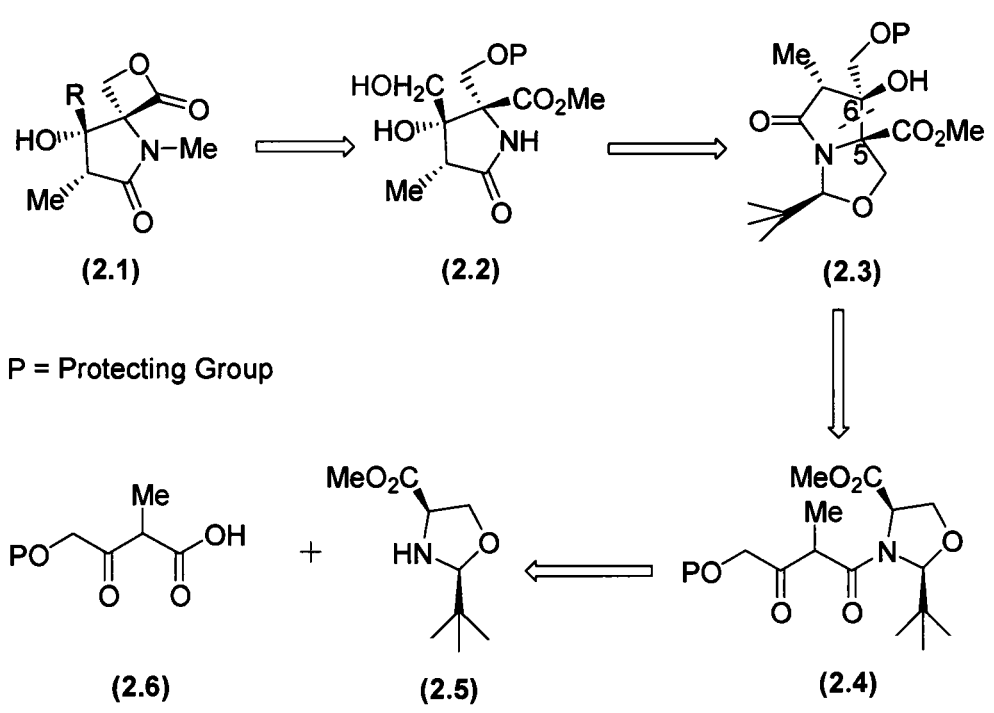
CHAPTER 2 - THE RIGHT HAND SIDE LACTAM

2.1 Retrosynthetic Analysis of the Lactam Unit of Oxazolomycin

The oxazolomycin[1] class of natural products contains the structurally complex, spiro-fused β-lactone-γ-lactam bicyclic system **(2.1)**. A retrosynthetic analysis of this structure (Scheme 2.1) by cleavage of the β-lactone ring and deprotection of the *N*-methyl group provides diol **(2.2)**, which could conceivably have been accessed by deprotection of the oxazolidine ring of bicycle **(2.3)**. Cleavage of the C(5)-C(6) bond in a retro-Aldol fashion reveals the D-serine derived *N*-acylated oxazolidine **(2.4)**. Access to similar compounds would be achieved by *N*-acylation of oxazolidine **(2.5)** by a β-keto acid of type **(2.6)**.



Scheme 2.1: Retrosynthetic analysis of the right hand side lactam

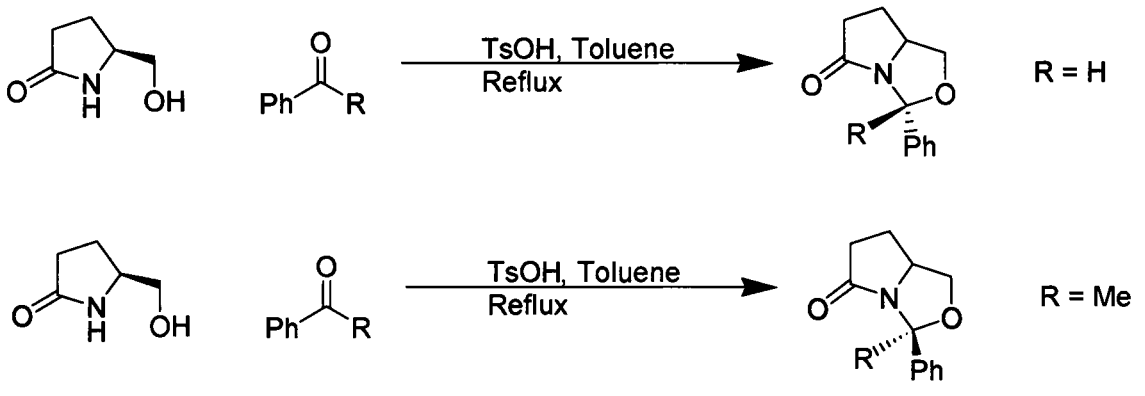
This chapter discusses investigations into the synthesis of α-substituted pyroglutamates by intramolecular aldol reactions of *N*-acyl oxazolidines of type **(2.4)**. It is hoped to eventually apply this methodology to a synthesis of the β-lactone-γ-lactam moiety present in oxazolomycin. Initial studies were carried out using L-serine, rather than its more expensive enantiomer.

2.2 Investigations of Previous Work

A wealth of experience exists within the Moloney group, concerned with the development of methodology for the construction of highly functionalised, saturated nitrogen heterocycles. Oxazolidine templates derived from amino acid precursors have provided the foundation for the group's past research and two general synthetic strategies have been developed.

In the first approach, [3.3.0] and [4.3.0]-bicyclic lactams derived from pyroglutamic acid and 6-oxopipecolic acid have been shown to be easily manipulated to highly functionalised pyrrolidinones and piperidinones by modification of the ring substituents. Sequential or tandem reactions can be used to generate diverse structural motifs based upon the heterocyclic template.

The diastereoselectivity of these reactions is dictated by inherent steric bias exhibited by the bicyclic lactam structure. Thus, alkylation of the lactam enolates has proved to be a general procedure, which proceeds with good to excellent *exo*-diastereoselectivity for a variety of sterically hindered electrophiles.[2, 3] Recent work however, suggests that contrasteric alkylation leading to reversal of the normally observed diastereoselectivity is possible. This is achieved by increasing the bulk of the hemiaminal ether substituent, which forces a more favourable stereoelectronic positioning of the lactam nitrogen lone pair, leading to a kinetically controlled *endo*-mode of attack[4] (Scheme 2.2).

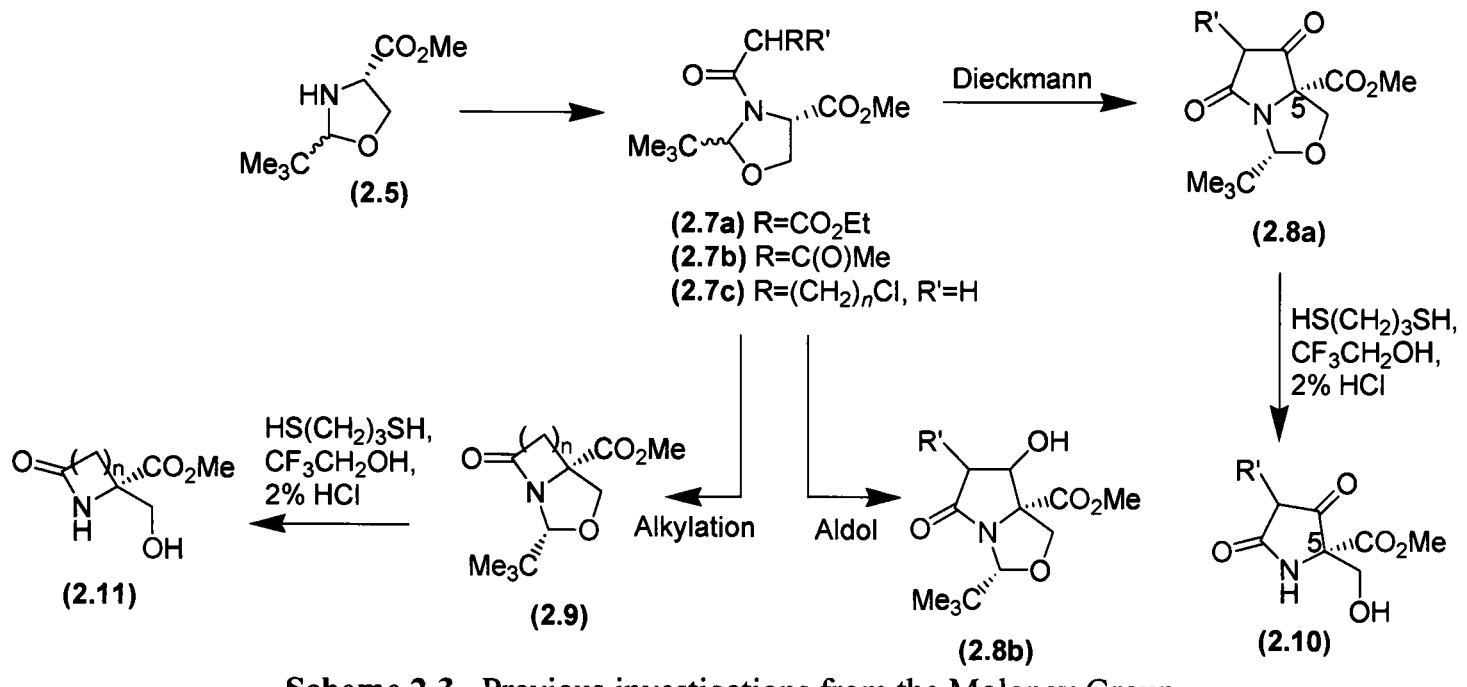


Scheme 2.2: Steric effects influence diastereoselectivity

Alternatively, an α,β-unsaturated derivative of each of the bicyclic lactams has been shown to undergo both cycloadditions[5] and conjugate additions, using carbon[6] or nitrogen[7] nucleophiles under mild conditions in excellent yield and high, if not, total diastereoselectivity. In particular, Reformatsky reagents can be used, giving rise to glutamate and homoglutamate analogues.[6] It has been shown that this efficient and versatile methodology easily provides access to diverse ring modified pyrrolidinones and piperidinones, with high diastereo- and enantiocontrol.

This approach provides the methodology for rapid synthesis of conformationally constrained nitrogen heterocycles which will be useful as peptide substructure analogues, and this methodology has been applied to the synthesis of conformationally-restricted amino acid analogues[8] and it has also shown that control of the pyrrolidinone ring conformation of kainic acid analogues by remote ring substituents, is possible.[9]

The second approach, rather than relying upon the modification of a template, constructs a ring in such a way that useful functionality, capable of further manipulations as needs be, is generated using an oxazolidine ring template to exert both regio- and stereocontrol (Scheme 2.3). The challenge in this case is to construct the heterocyclic ring such that existing chirality is maintained in the product, and that there is scope for the further introduction of substituents of defined stereochemistry[9] . Studies have shown that ring formation can be achieved from oxazolidine **(2.5)**[10] *via* amides **(2.7a-c)** using Dieckmann[11], Aldol[12] and intramolecular alkylation[13] reactions with excellent diastereo- and enantiocontrol to give the products **(2.8a)**, **(2.8b)** and **(2.9)** respectively. These can be easily deprotected under acidic conditions to provide access to the corresponding hydroxymethyl lactams **(2.10)** and **(2.11)** in excellent yield and e.e. The unusual course of these reactions has been attributed to the bulky tert-butyl substituent, which both directs the chemoselectivity of the cyclisation and ensures the retention of stereochemistry at C-5.

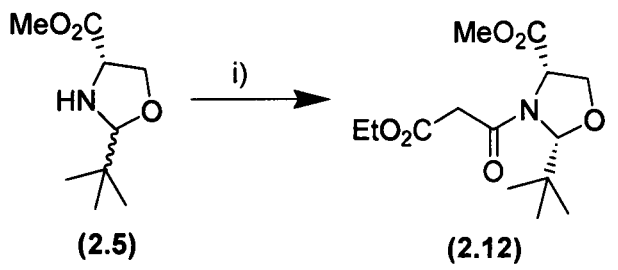


Scheme 2.3. Previous investigations from the Moloney Group

It is because of these advantages that this second approach had been chosen as the preferred route for construction of the bicyclic lactam required as a key intermediate proposed in the retrosynthetic analysis towards the right hand side of oxazolomycin. The synthesis of some of the key intermediates is described below. Initial work concentrated on verification of the earlier tetramic acid synthesis which had been developed.

2.2.1 *N*-acylation Methodology - DCC Coupling

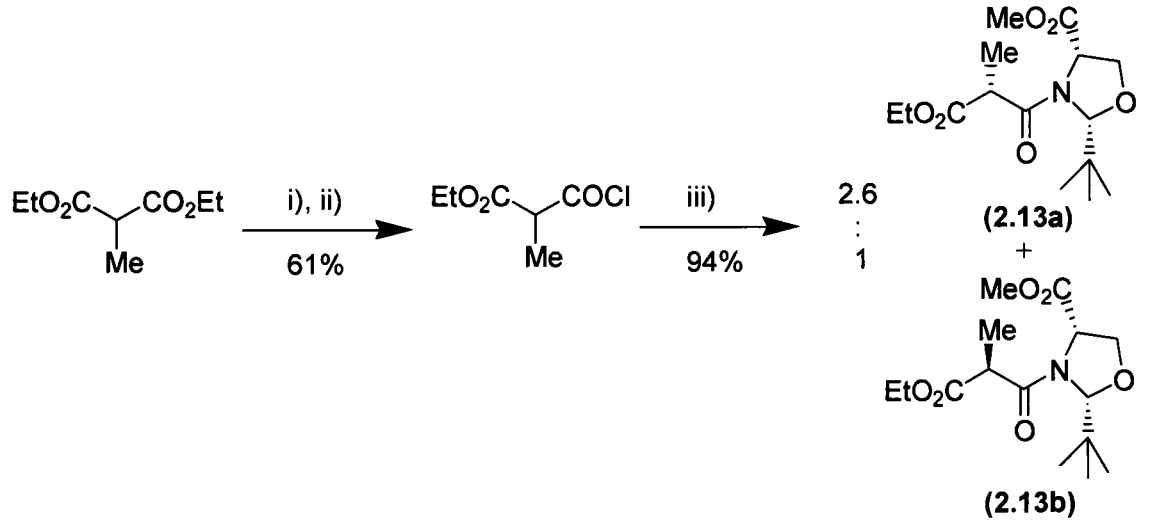
Using methods previously reported,[14] oxazolidine **(2.5)** was acylated with mono-ethyl malonate and DCC,[15,16] using DMAP as a nucleophilic catalyst, to yield diester **(2.12)** (Scheme 2.4) in 90% yield. However, it was found that the synthesis could be improved by an alternative purification methodology to column chromatography. Thus, purification was effected by loading the concentrated reaction mixture onto a short silica plug, washing with petrol to remove non-polar impurities and then washing with ethyl acetate/petrol to obtain the product, identical in all aspects to material previously prepared.



Scheme 2.4: $EtO_2CH_2CO_2H$, DCC, DMAP, DCM

2.2.2 *N*-acylation Methodology - Acid Chloride / Pyridine Coupling

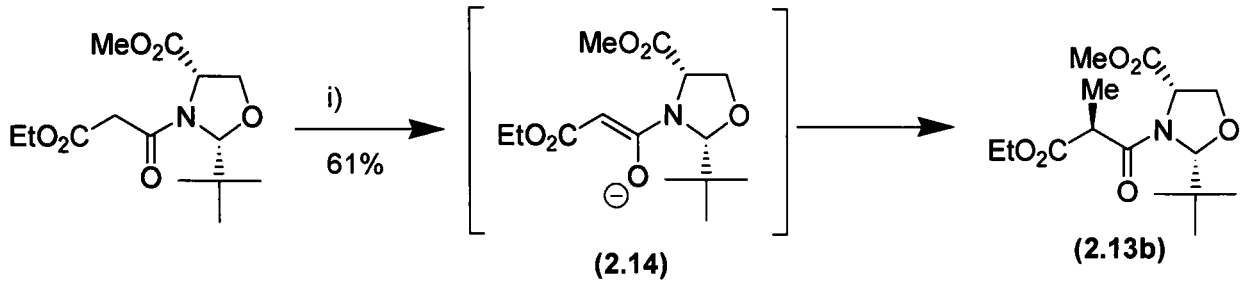
Treatment of oxazolidine **(2.5)** with pyridine and ethylα-methylmalonyl chloride[17] (Scheme 2.5) leads to a separable mixture of the two epimeric *cis*-oxazolidines **(2.13a,b)**. Acylation could also be carried out using ethylα-methylmalonic acid and DCC, giving the same two epimers but in a ratio of approximately 1:1 rather than 2.6:1 respectively. The yield in this case was also lower and problems were encountered separating the desired products from DCC-derived side products.



Scheme 2.5: i) KOH, EtOH, ii) $SOCl_2$, iii) **(2.5)**, pyridine, DCM

The side-chain stereochemistry of oxazolidine **(2.13b)** was tentatively assigned by Andrews *et al*[18] in the following manner. Adding potassium *tert*-butoxide to a solution of methyl iodide and oxazolidine **(2.12)** in THF at -65° C followed by warming to RT led to a 61% yield of oxazolidine **(2.13b)** with no sign of the side chain epimer **(2.13a)**. Assuming that a planar enolate (Scheme 2.6) was formed then it would have been most likely to adopt the conformation **(2.14)** with the carbonyl oxygen towards the bulky *tert*-butyl group. The (*Z*)-enolate shown would have been favoured over the alternative (*E*)-enolate as this places the ethyl ester away from the methyl ester attached to the oxazolidine ring. Alkylation occurring from the upper

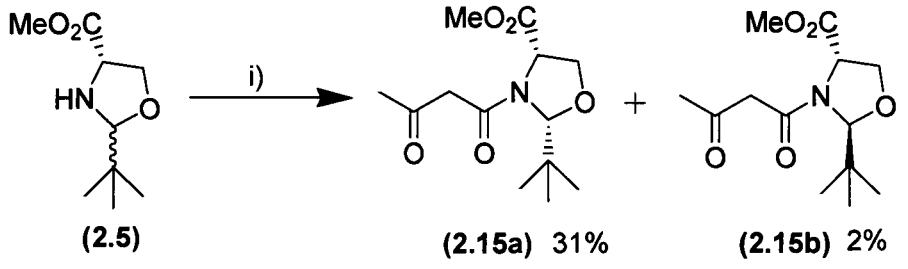
face, as drawn (*Si* face) would then have generated the oxazolidine **(2.13b)**.[18] Finally the *cis*-nature of the *tert*-butyl and methyl ester substituents were confirmed by n.O.e experimentation. Thus, this work demonstrated that acylation of the oxazolidine was possible.



Scheme 2.6: i) MeI, THF, KO^{t}Bu

2.2.3 Preparation of a Simple Model Cyclisation Precursors

In order to synthesise the required *N*-acyl oxazolidines, it was first necessary to make the β-keto acids with which to acylate oxazolidine **(2.5)**. The simplest β-keto acid is acetoacetic acid, and this was synthesised according to the procedure of Ohta *et al*[19] by the acidic hydrolysis of *tert*-butyl acetoacetate, the crude acetoacetic acid being used without further purification. Acylation of oxazolidine **(2.5)** by treatment with acetoacetic acid and DCC[18] gave the desired *cis*-oxazolidine **(2.15a)**, as a mixture of keto and enol tautomers, in 31% yield but also a 2% yield of the *trans*-oxazolidine **(2.15b)**, again as a mixture of tautomers (Scheme 2.7).

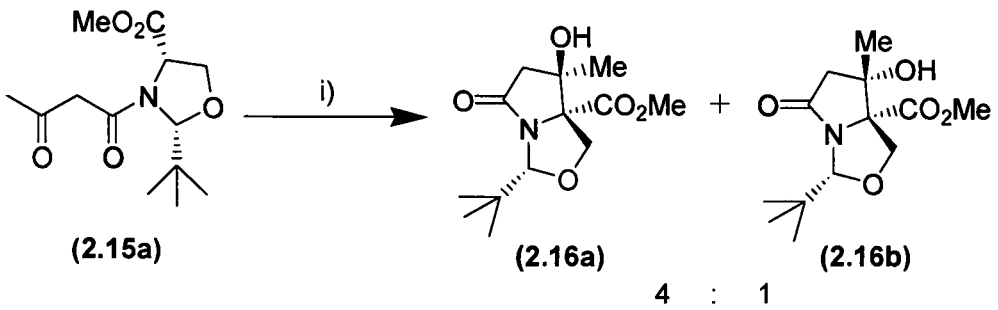


Scheme 2.7: i) $MeCOCH_2CO_2H$, DCCI, DMAP, DCM

During the course of purification by column chromatography, it was noticed that the *trans*-oxazolidine **(2.15b)** decomposed slightly on the silica column, and separation of the two isomers therefore proved difficult.

2.2.4 Cyclisation of *Cis*-oxazolidine Model Systems

Repetition of work first carried out by Andrews *et al*[18] demonstrated that stirring a solution of *cis*-oxazolidine **(2.15a)** in methanolic sodium methoxide gave a clean aldol condensation, to yield a 4:1 mixture of the two possible aldol products **(2.16a)** and **(2.16b)** respectively (Scheme 2.8). Recrystallisation from chloroform/petrol gave the major epimer **(2.16a)** in 31% yield.

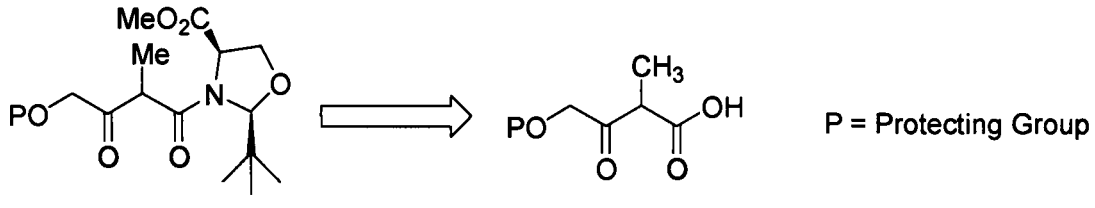


Scheme 2.8: i) NaOMe, MeOH, RT

The stereochemistry of the minor aldol product **(2.16b)** was confirmed by n.O.e. experiments. This confirmed that the major aldol product **(2.16a)** had the same relative stereochemistry as that of the oxazolomycin right hand side lactam. With these model studies demonstrating that the methodology developed 'in-group' provided access to the required stereochemistry of the right hand side lactam, attention turned to the synthesis of the β-keto acids possessing the substituents required by the target natural product.

2.3 Synthesis of the β-keto acid required for oxazolomycin

As discussed previously, methodology developed in the Moloney group gives access to model bicyclic systems such as **(2.16a)** possessing the required stereochemistry of that of the oxazolomycin target. Successful synthesis of oxazolomycin required introduction of an additional hydroxyl substituent to the *N*-acyl side chain, i.e. oxazolidine **(2.4)**. Using the same amide disconnection discussed previously, the required synthesis therefore devolved to preparation of the β-keto acid **(2.6)**. Prudent selection of the alcohol protecting group was neccessay, to allow both for easy manipulation and removal under acidic conditions later in the synthesis.

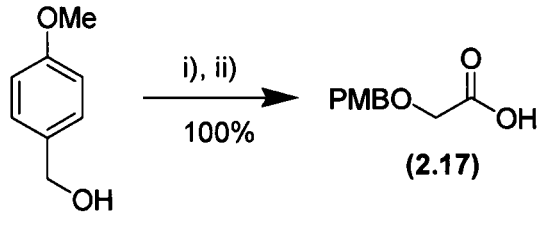


(2.4) (2.6)

2.3.1 Synthesis of PMB protected β-keto acid

With consideration of the previously discussed methodology, it was decided that a 4-methoxybenzyl (PMB)[20,21] protecting functionality would be best suited to the task in hand. It should prove easy to introduce, be resistant to all envisaged chemical transformations and would provide easy removal under mild conditions to yield the desired primary alcohol whilst leaving the installed lactam function intact. The 4-methoxybenzyl ether can be selectively cleaved with dimethylboron bromide,[22] and/or DDQ whilst leaving other protecting functionality intact.

To this end, acid **(2.17)** was synthesised in quantitative yield (Scheme 2.9) from the readily available starting materials 4-methoxybenzyl alcohol and bromoacetic acid in a modification (4 day reflux instead of 1 day, providing a quantitative yield) of the literature procedure.[23] As this was a key starting material, it was useful that this synthesis could be easily scaled up to provide in excess of 10 grams of the desired product.

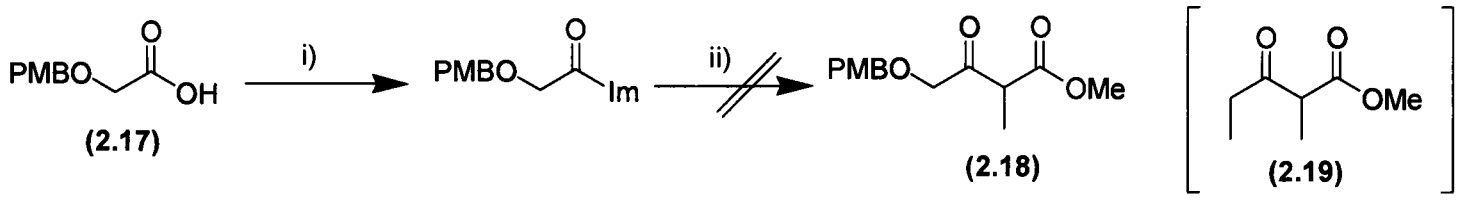


(2.17)

Scheme 2.9: i) NaOH, toluene, ii) $BrCH_2CO_2H$, Heat, 4 days

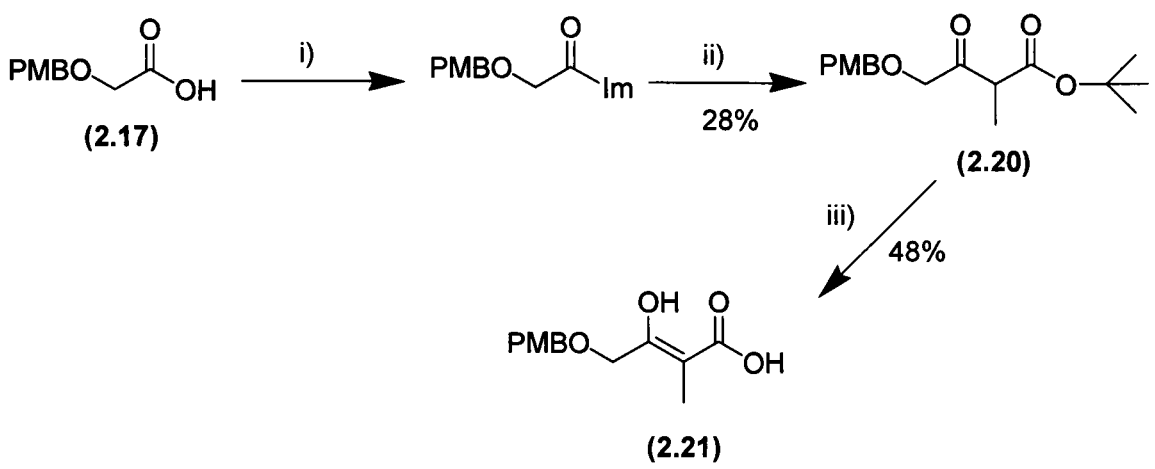
On the basis of ample literature precedent[24], it was intended that acid **(2.17)** would be activated for further manipulation to form the required β-keto acid. However, reaction with thionyl chloride or oxalyl chloride[25] both failed to yield the respective acyl chloride and although reaction with CDI (1.2 eq) with two days stirring provided the activated acyl imidazolide[26] (IR spectra showed no broad absorption for the

carboxylic acid previously present and exhibited an amide stretch at 1687 cm^{-1}), it could not be successfully coupled to the enolate of methyl propionate to form the desired β-keto acid **(2.18)** (Scheme 2.10).



Scheme 2.10: i) CDI, THF, ii) LDA, $CH_3CH_2C(O)OMe$

Instead, a competing Claisen self-condensation with methyl propionate provided almost exclusively the unexpected and unwanted β-keto methyl ester **(2.19)**. Use of the more bulky *tert*-butyl propionate prevented this side reaction and allowed formation of the desired β-keto *tert*-butyl ester as predominantly the keto tautomer (4:1 mixture of tautomers) **(2.20)**, although the relatively low yield of the desired product (28%) even after extensive optimisation (Scheme 2.11) suggested that other competing processes may still be in operation. The existence of compound **(2.20)** as the keto tautomer was evident from NMR spectroscopy: the methyl signal at δ 1.27 existed as a doublet (*J* 7.2 Hz), and the quartet at δ 3.56 (*J* 7.2 Hz), indicative of the methine proton, was present.



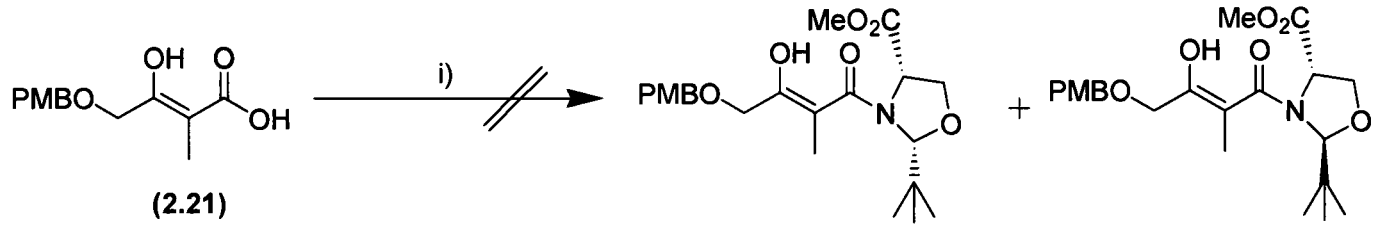
Scheme 2.11: i) CDI, THF, ii) LDA, $CH_3CH_2C(O)OMe$, iii) TsOH, anisole (0.2 eq), toluene, reflux

Deprotection of the *tert*-butyl functionality of **(2.20)** using TFA[27] proved to be unsuccessful, and the addition of a range of cation scavengers to this reaction (Et_3SiH,[28] 1,3-dimethoxybenzene[29] and anisole[30]) proved ineffective. The cation scavenger was thought necessary to prevent an intermediate carbocation from reacting with the electron rich ring system of the PMB functionality. In each case, the scavenger was isolated from column chromatography almost quantitatively and by ^1H

NMR appeared chemically unchanged (for all scavengers employed), indicative that the conditions employed were ineffective at cleaving the *tert*-butyl protecting functionality. However, it was found that the milder *para*-toluenesulphonic acid[31] combined with anisole scavenger (0.2 eq) provided the desired β-keto acid **(2.21)** in moderate yield (48%) as a 4:1 mixture of enol:keto tautomers by ^{1}H NMR, an apparent reversal of the tautomerisation state. It would seem that steric factors exert control over tautomerisation in these type of compounds.

2.3.2 *N*-Acylation of oxazolidine

With the desired β-keto acid in hand, attention was turned to *N*-acylation of oxazolidine **(2.5)** by coupling processes known to be successful from earlier work.



(2.21) **(2.22a)** **(2.22b)**

Scheme 2.12: i) oxazolidine **(2.5)**, DCCI, DMAP, DCM or Pyridine / acetyl chloride

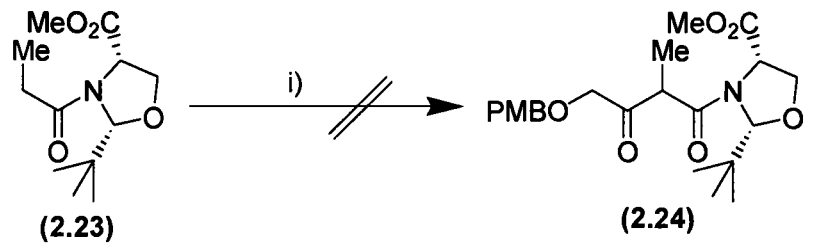
Under DCC-coupling conditions, oxazolidine **(2.5)** did not undergo *N*-acylation with the protected β-keto acid **(2.21)** (Scheme 2.12). Column chromatography of the crude reaction provided 22% recovery of the β-keto acid and almost quantitative recovery of unreacted DCC, suggesting that the activated imide intermediate was not forming and thus making *N*-acylation impossible. Longer reaction time and higher temperatures (reflux) did not improve upon this first result. Such couplings proceed by the intermediate *O*-acyl urea; the acyl group is highly reactive in this environment because the cleavage of the acyl–oxygen bond converts the carbon-nitogen double bond of the isourea to a more stable carbonyl group.[32] Variation of the coupling agent also proved unsuccessful. EDAC,[33] employed with DMAP, proceeded to provide unreacted β-keto acid in quantitative yield.

The remaining alternative approach, which had been successfully applied previously, was formation of an activated β-ketoacid chloride and treatment with oxazolidine

(2.5) and pyridine with 5 hours reflux. This also proved unfruitful in formation of oxazolidines **(2.22a)** and **(2.22b)**, providing instead an 80% recovery of the starting β-keto acid, with these results possibly indicating that the acid chloride was not formed.

In a review of the success of the previously developed *N*-acylation methodology, it seemed possible that the lack of reactivity of the PMB protected β-keto acids and their apparent inability to form the corresponding activated acyl intermediate could be attributed to the predominance of the enol tautomer in **(2.21)**. In all previous successes the β-keto acid species existed as predominantly if not exclusively the keto tautomer. Electronic withdrawing effects arising from the presence of the α-oxygen functionality could also be attributed to this overall lack of reactivity.

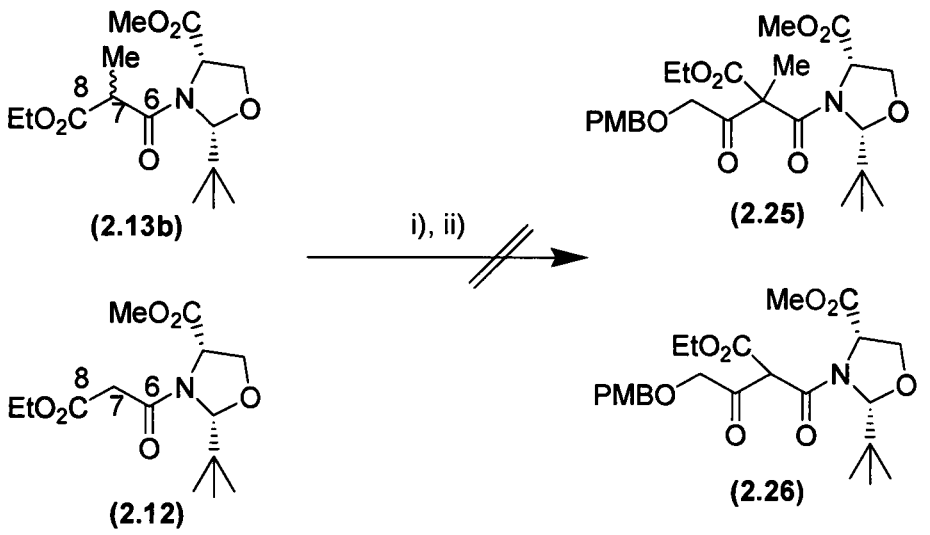
If the enolic form of β-keto acid **(2.21)** was indeed the cause of unreactivity, then a possible next step was to attempt the application of this existing synthetic route to a pre-*N*-acylated oxazolidine. Thus, instead of reaction between *tert*-butyl propionate and acid **(2.17)**, an aldol reaction between a suitably *N*-acylated oxazolidine and a suitable acid **(2.17)** should yield the desired oxazolidine **(2.24)**, complete with PMB protected side chain. Thus, oxazolidine **(2.23)** was prepared from the DCC/DMAP promoted coupling of propionic acid and oxazolidine **(2.5)** in excellent yield (93%). Oxazolidine **(2.23)** was then treated with LDA and the CDI-activated acid **(2.17)** (Scheme 2.13). Purification by column chromatography of the crude reaction mixture yielded trace amounts of oxazolidine **(2.23)** as the only fraction. A similar lack of reactivity for the reactions of enolates derived from amide (**2.23**) had previously been observed[18].



Scheme 2.13: i) a: LDA; b: $PMBOCH_2C(O)Im$

In an effort to improve the acidity of the amide function, oxazolidine **(2.13b)** (Scheme 2.14) was treated with base (LDA (-78° C) or KO^tBu) and then the appropriately protected alkoxyacetyl chloride[34] derived from **(2.17)**. It was envisioned that the

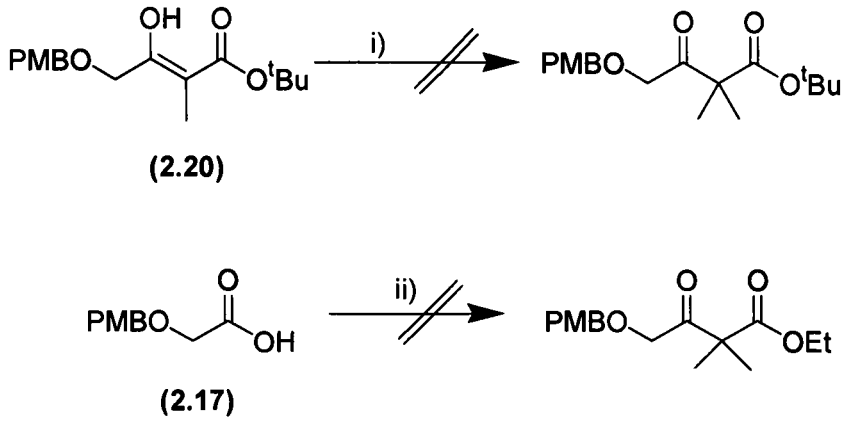
activating ethyl ester functionality could be removed at a later stage when necessary. However, reaction with both bases, LDA and KO^{t}Bu, provided only recovered acid **(2.17)**. Since this may have been due to the methyl substituent providing too hindered an acylation site in oxazolidine **(2.13b)**, the experiment was repeated with oxazolidine **(2.12)** which did not possess the additional methyl substituent. However, the result was the same and only starting acid **(2.17)** was isolated from column chromatography of the reaction mixture. Since both LDA and ^{t}BuOK are bases easily potent enough to deprotonate the activated hydrogens at C(7), it can only be assumed that the failure of this reaction is due to the unreactivity of the acid chloride derivative of acid **(2.17)**.



Scheme 2.14: i) ^{t}BuOK, $PMBOCH_2CO_2Cl$, ii) LDA, $PMBOCH_2CO_2Cl$

It was decided to concentrate on the potential problem that the enolic form of acid **(2.21)** was lowering reactivity towards *N*-acylation reactions. In all previous investigations into *N*-acylation of oxazolidine **(2.5)** by β-keto acids, all of the acids existed as predominantly, if not exclusively, the keto tautomer. It would appear that the enol tautomer does not form the desired activated intermediate with DCC, EDAC, $SOCl_2$ or $(COCl)_2$.

The only remaining alternative to rescue the PMB protected β-keto acid side chain strategy was to attempt to tip the keto/enol equilibrium in favour of the keto form. To achieve this objective, acid **(2.20)** was treated with sodium hydride, however, attempted alkylation with iodomethane (Scheme 2.15) returned unreacted starting material **(2.20)**. An alternative procedure involving reaction of the enolate of ethyl isobutyrate with acid **(2.17)** again yielded unreacted starting material.

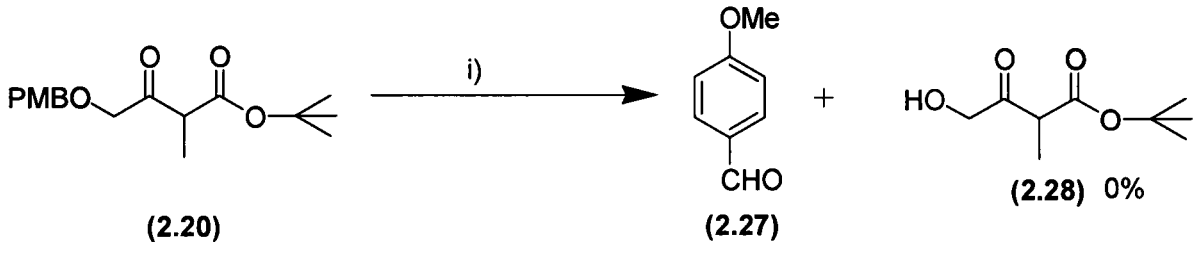


Scheme 2.15: i) NaH, MeI, reflux, ii) CDI, THF, LDA, ethyl isobutyrate

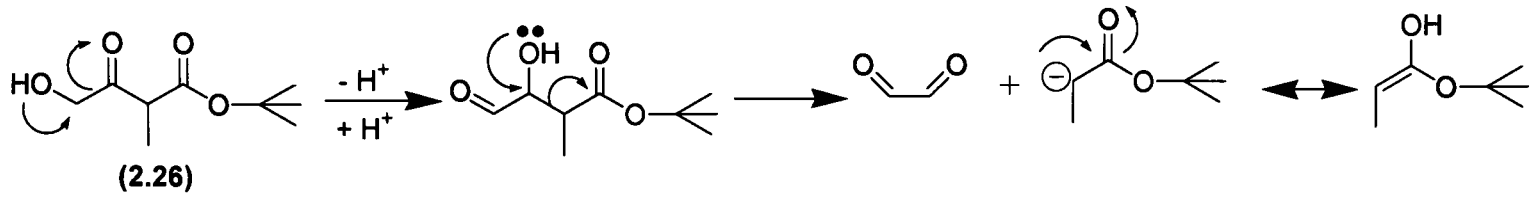
As these experiments have proved to be unsuccessful, it was decided to explore the effect of protecting groups on keto/enol equilibria in such systems.

2.4 Protecting Group Manipulation of PMB β-keto acid

To salvage the synthetic route, it was decided to manipulate the protecting group of acid **(2.20)** by a systematic deprotection / reprotection sequence. To achieve deprotection, DDQ[35,36] was employed in a 18:1 DCM:water solvent system to allow for complete dissolution of the acid; filtration to remove the $DDQH_2$ precipitate and column chromatography to yield the expected by-product *para*-methoxybenzaldehyde **(2.27)** but none of the required alcohol **(2.28)** (Scheme 2.16). This could be due to the highly polar nature of alcohol **(2.28)**, or due to instability such as that indicated (Scheme 2.17).



Scheme 2.16: i) DDQ, DCM:H_2O (18:1)



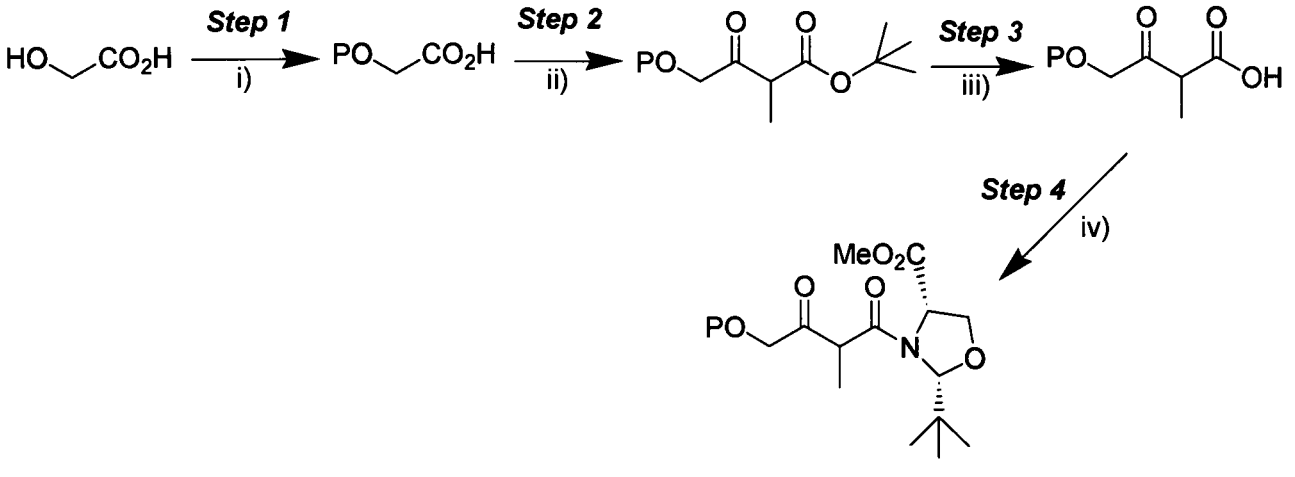
Scheme 2.17.

In an alternative approach, alcohol **(2.20)** was exposed to hydrogenation conditions (4.5 atm, EtOH, 10% Pd-C)[37] to yield a crude product of the desired alcohol by ^{1}H NMR spectroscopy, but in less than 1% yield.

Given the unsuccessful nature of these deprotection attempts, it was decided that utilisation of commercially available glycolic acid for the direct introduction of other protecting groups would be preferred.

2.5 Investigation of alternative alcohol protecting groups

The selection of an effective protecting group is limited by the requirements of easy introduction, stability to reagents and easy removal. Given that the PMB group yielded predominantly the enol tautomer in the free acid, it was of interest to consider a protecting group which may favour the keto form. All silyl groups are susceptible to cleavage by TBAF.[38] However, TBDPS is cleaved more slowly[39] than the trialkylsilyl groups, allowing if needed, selective deprotection at a later stage.



Scheme 2.18: i) PCl (P = Protecting group), imidazole, DMF, ii) a; CDI, b; LDA, $CH_3CH_2CO_2{}^tBu$, THF, iii) TsOH, toluene, iv) DCCI, DMAP, DCM, oxazolidine, **(2.5)**.

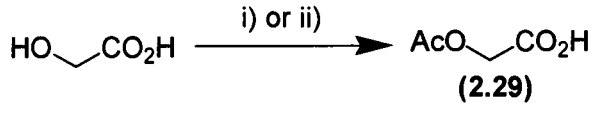
To this end acetyl, *tert*-butyl dimethylsilyl (TBDMS), *tert*-butyl diphenylsilyl (TBDPS) and triisopropylsilyl (TIPS) protecting groups were all applied to glycolic acid and using the route outlined above, aldol reaction, deprotection and *N*-acylation were attempted (Scheme 2.18 and Table 2.1).

Protecting Group	***Step 1*** Protection	***Step 2*** Claisen Condensation	***Step 3*** Deprotection	***Step 4*** *N*-Acylation
PMB	100%	28%	46%	--
Ac	--	--	--	--
TBDMS	52%	24%	--	--
TBDPS	80%	50%	--	--
TIPS	64%	29%	39%	39%

Table 2.1: Results of protecting group manipulation for construction of the protected β-ketoacid

2.5.1 Acetyl Protecting Group

The acetyl group was chosen as a cheap material to determine the feasibility of glycolic acid protection. However, neither triethylamine / DMAP / acetyl chloride nor pyridine / acetic anhydride yielded the desired protected acid[40] **(2.29)**. In both cases only glycolic acid and acetyl starting material was isolated (Scheme 2.19), and this reaction was not pursued further. Acid **(2.29)** is very polar and would be expected to be retained on the silica column during purification.

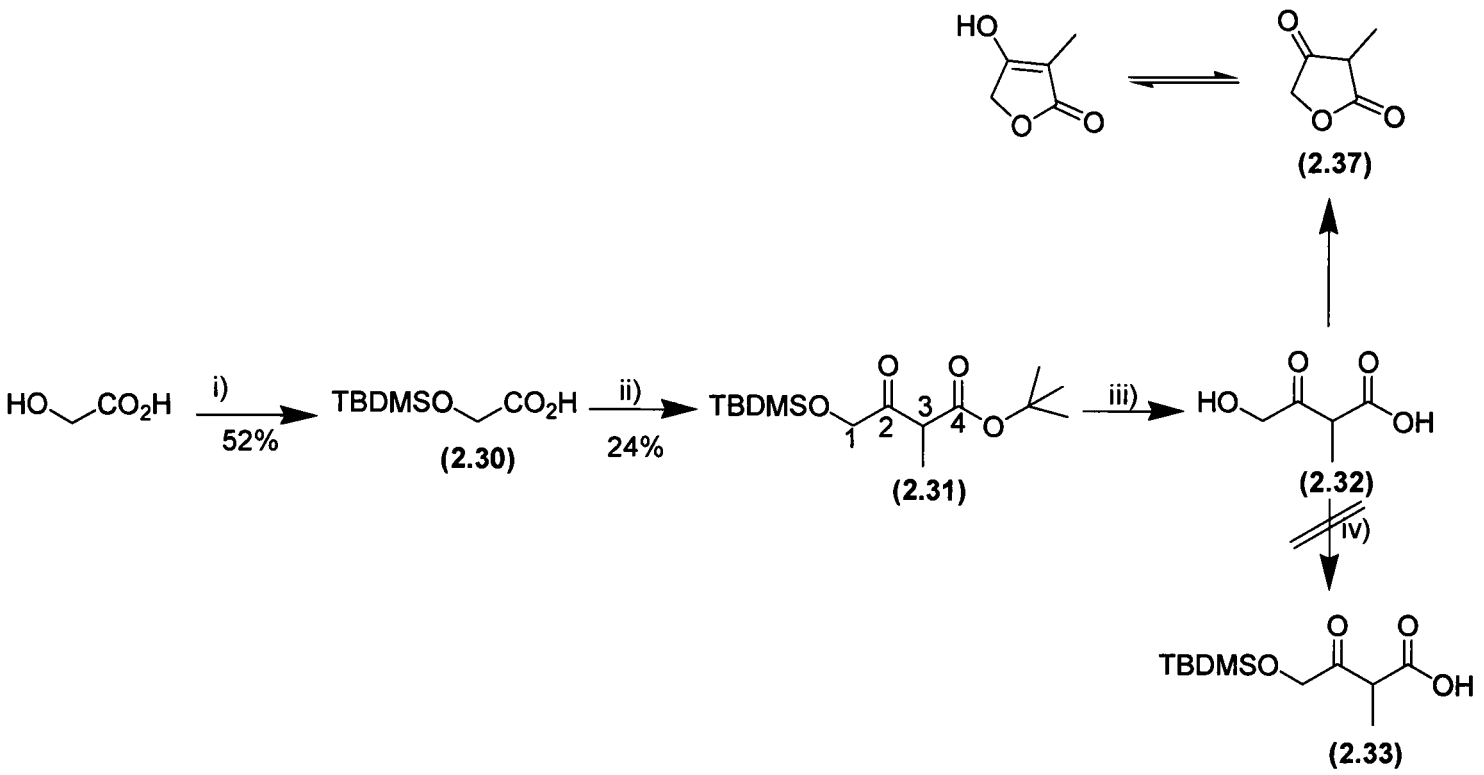


Scheme 2.19: i) NEt_3, DMAP, AcCl, ii) pyridine, acetic anhydride

2.5.2 *tert*-Butyldimethylsilyl Protecting Group

Attempts were made to protect glycolic acid with a *tert*-butyldimethylsilyl[41,42] residue (TBDMS). TBDMS-Cl, activated with imidazole in DMF, yielded the desired silyl ether **(2.30)** in a moderate but serviceable yield (52%). Silyl ether **(2.30)** underwent

aldol reaction with *tert*-butyl propionate and CDI to provide β-keto *tert*-butyl ester **(2.31)** in 24% yield (a low yield, but in keeping with the similarly low yield of ester **(2.19)** even after extensive optimisation) (Scheme 2.20). However what was noticable and encouraging was that the ester **(2.31)** was isolated as the pure keto tautomer, as clearly shown in the ^{1}H NMR spectrum, with the signal for C(3)-CH_3 a doublet (*J* 7.2 Hz) at δ 1.39, and C(3) proton existing as a quartet signal (*J* 7.2 Hz) at δ 3.69.

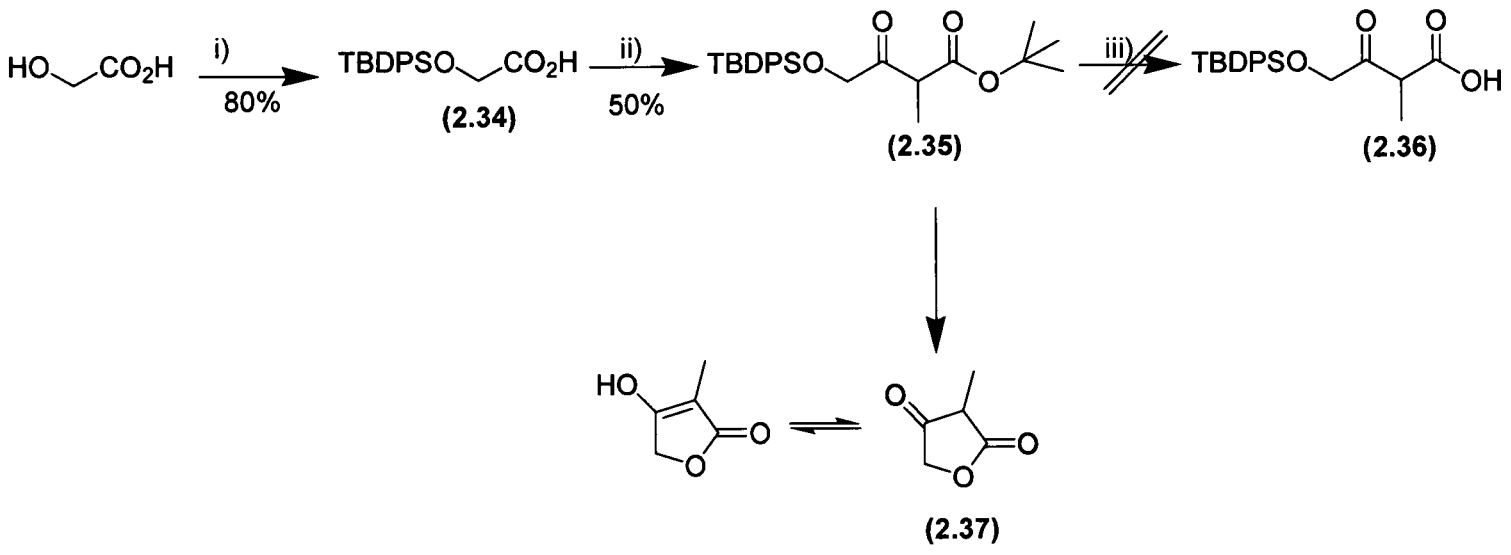


Scheme 2.20: i) TBDMSCl, DMF, imidazole, ii) CDI, LDA, $CH_3CH_2CO_2{}^tBu$, THF, iii) TsOH, toluene, iv) TBDMSCL, DMF, imidazole.

Deprotection of **(2.31)** with TsOH (0.2 eq) provided not the β-keto acid expected but instead the TBDMS deprotected alcohol, with the *tert*-butyl ester still intact. This was not unexpected given the relative activities towards deprotection of the TBDMS group compared to the *tert*-butyl group. Instead of finding alternative deprotection conditions, it was simply decided to expose β-keto ester **(2.31)** to 2.0 equivalents of TsOH, which as expected provided alcohol **(2.32)**. Given the expected polarity of this alcohol, purification was not attempted by silica-based methods. Instead, the crude alcohol was exposed to the same protecting conditions (TBDMS-Cl, imidazole, DMF) as glycolic acid in step 1 (Scheme 2.20) in an attempt to yield β-keto acid **(2.33).** The only compound isolated from the column was unreacted TBDMS-Cl. Lactonisation to form **(2.37)** under the employed acidic conditions could explain the lack of protection.

2.5.3 *tert*-Butyldiphenylsilyl Protecting Group

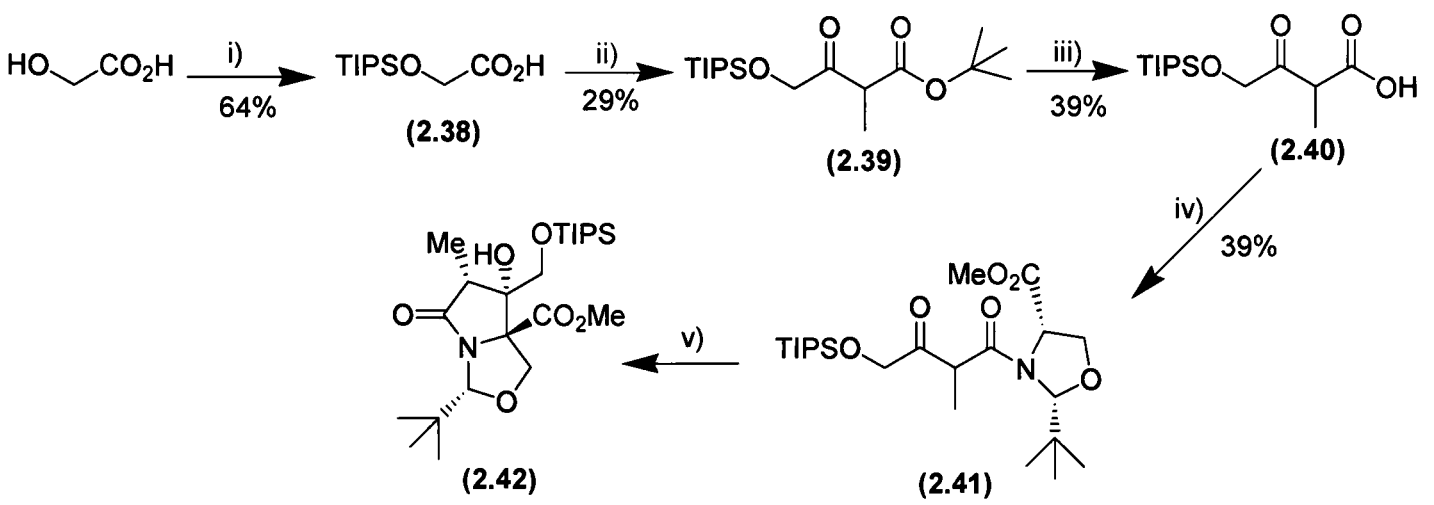
Encouraged by the existence of the keto form of compound **(2.31)**, investigations turned to the next sterically hindered available protecting group, namely *tert*-butyldiphenylsilyl (TBDPS), which was expected to be more acid stable. As with the TBDMS chemistry previously described, glycolic acid was easily protected (TBDPS-Cl, imidazole, DMF)[43,44] to provide silyl ether **(2.34)** in excellent yield (80%). Aldol reaction of **(2.34)** with *tert*-butyl propionate proceeded in a gratifying 50% yield, almost double that of the previous synthetic pathways to, provide β-dicarbonyl compound **(2.35)**. ^{1}H NMR analysis once again displayed the desired methyl doublet (*J* 7.2 Hz) at δ 1.34 and proton quartet (*J* 7.2 Hz) at δ 3.37 that indicated the keto tautomer, with no evidence of an enolic proton, indicative of the presence of the silyl protecting group on the terminal hydroxyl functionality. However, once again, exposure of **(2.35)** to TsOH conditions failed to yield the desired β-keto acid **(2.36)** (Scheme 2.21), but provided instead, after column chromatography, silyl protecting group residues, indicating that the experimental conditions were still too harsh to leave the TBDPS group intact but too mild to remove the *tert*-butyl ester. The acidic conditions employed for the removal of the silyl ether may indeed prove successful in their endevour (as evidenced by the detection of silyl residues), however in doing so promote lactonisation to compound **(2.37)**.



Scheme 2.21: i) TBDPSCl, DMF, imidazole, ii) CDI, LDA, $CH_3CH_2CO_2{}^tBu$, THF, iii) TsOH, toluene

2.5.4 Triisopropylsilyl Protecting Group

The triisopropylsilane (TIPS) protecting group was next examined. Glycolic acid reacted with TIPS-Cl and imidazole in DMF, yielded[45] the desired silyl ether **(2.38)** in 64% yield. The aldol reaction with *tert*-butyl propionate once again proceeded with only a moderate yield of 29% to provide **(2.39)** as entirely the keto tautomer (with the same spectroscopic evidence as discussed for the TBDMS compound **(2.31)**). Deprotection with TsOH yielded not the deprotected alcohol but the desired β-keto acid **(2.40)** in 39% yield. The TIPS group clearly favours the keto tautomer and also has the added advantage of being resistant to the relatively harsh conditions required to cleave the *tert*-butyl ester protecting group. The ^{1}H NMR spectrum of acid **(2.40)** provided the necessary evidence that the compound had not tautomerised to the enol form during the course of the deprotection reaction. (^{1}H NMR analysis showed the presence of the methyl substituent as a doublet with a coupling constant of 7.0 Hz at δ 1.14 and a quartet at δ 3.70 with a coupling constant of 7.0 Hz). All of these results looked very promising to accommodate the methodology of the DCC coupling reaction required in the next step. Indeed, when β-keto acid **(2.40)** was exposed to the DCC/DMAP *N*-acylation coupling conditions, a gratifying and copious amount of white precipitate was observed after 24 hours of stirring at RT (a variation on the originally published report - 24 hours stirring instead of 5 hours). The precipitate was expected to be dicyclohexylurea and its formation indicated that coupling had been successful. After work-up (10% HCl, EtOAc, $NaHCO_3$) and purification by column chromatography, oxazolidine **(2.41)** was isolated in 39% yield in the keto form as confirmed by ^{1}H NMR spectroscopy. Oxazolidine **(2.41)** was exposed to standard cyclisation conditions (Scheme 2.22) to provide 8 mg (39%) of colourless powder of a compound resembling **(2.42)** by means of ^{1}H NMR spectroscopy and exhibiting the desired molecular ion by APCI-MS. However due to the low yield of this compound, comprehensive structure elucidation was not possible.

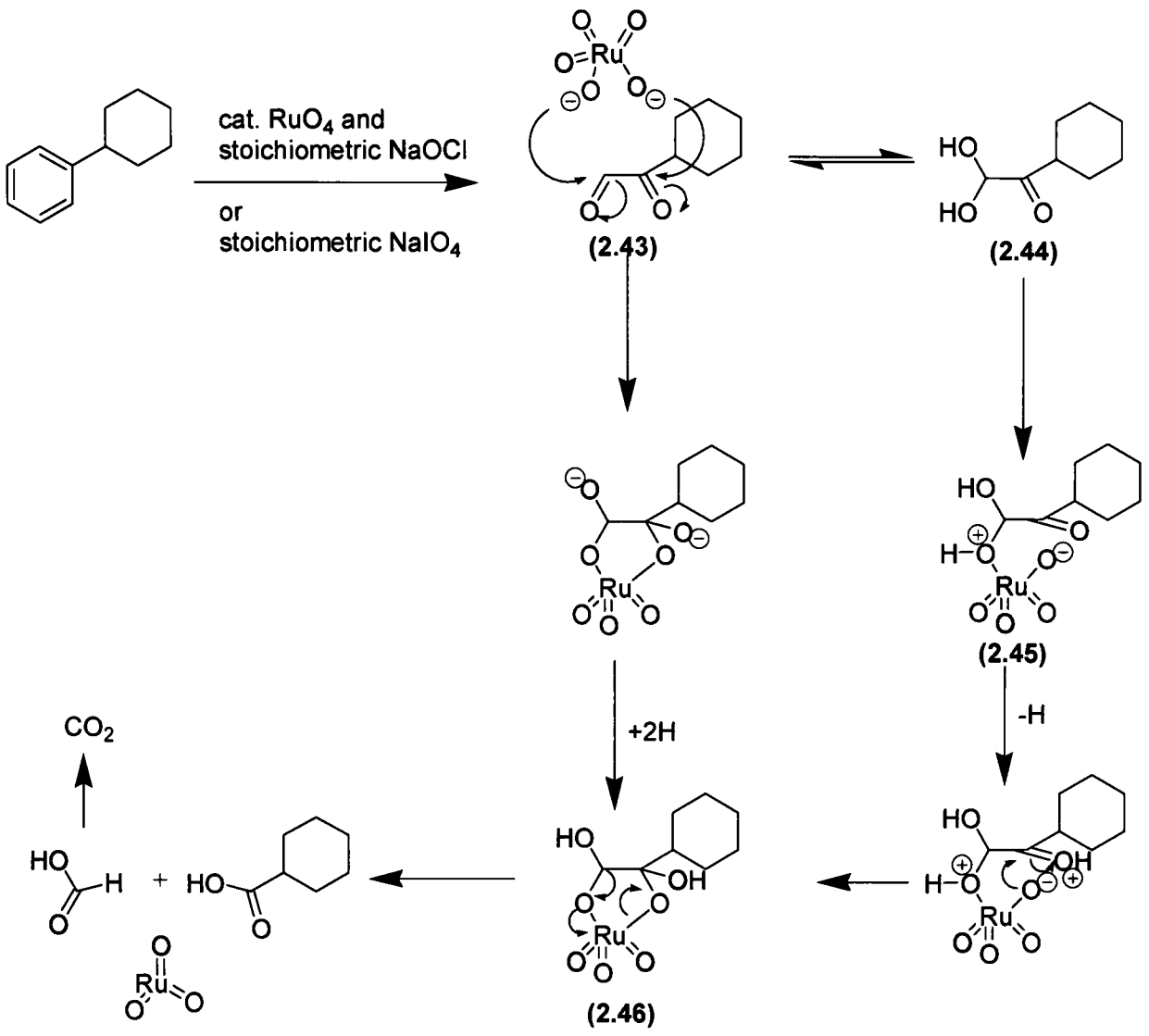


Scheme 2.22: i) TIPSCl, DMF, imidazole, ii) CDI, LDA, $CH_3CH_2CO_2{}^tBu$, THF, iii) TsOH, toluene, iv) DCCI, DMAP, DCM, oxazolidine **(2.5)**, v) ^tBuOK, ^tBuOH, reflux

The synthesis of **(2.42)** represents a success and validation of the originally devised synthetic pathway with the use of β-keto acids to *N*-acylate oxazolidine **(2.5)**. The possible success of **(2.41)** undergoing an intramolecular aldol reaction to proceed to bicycle **(2.42)** certainly warrants further investigation. With appropriate optimisation experimentation, it should prove possible to isolate compound **(2.42)** and ascertain its absolute structure. However, despite the validation of this strategy, the poor overall yield of the route, expense of triisopropylsilyl chloride and the exceptionally poor final yield of compound **(2.42)**, precluded further development of this route. It was decided that resources would be better employed directed towards a synthesis that would provide a viable amount of analogues of the desired bicycle **(2.3)**.

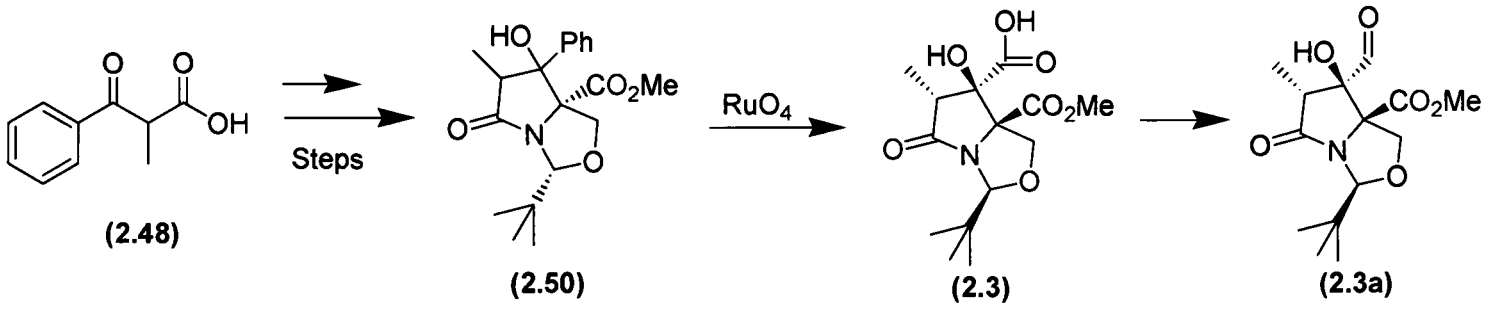
2.6 Synthesis By Application of Ruthenium Oxidants

Precedent exists[46] for the smooth transformation of a phenyl substituent into a substituted acetic acid *via* employment of ruthenium(IV) oxide (Scheme 2.23). The ruthenium(IV) oxide cleavage of a phenyl ring is exemplified by the case of an alkylated aromatic compound using the modified Lemieux-von Rudloff conditions. The reaction involves two key intermediates: the α-ketoaldehyde **(2.43)** and the ruthenium(VIII) acid diester **(2.46)**. The mechanism for the reaction of **(2.43)** to **(2.46)** is not known, but, one possibility is indicated (Scheme 2.23). Diester **(2.46)** fragments and forms the desired substituted acetic acid, RuO_3, and formic acid in the last step via a cyclic transition state. Under the reaction conditions, formic acid is oxidised further to CO_2.



Scheme 2.23.

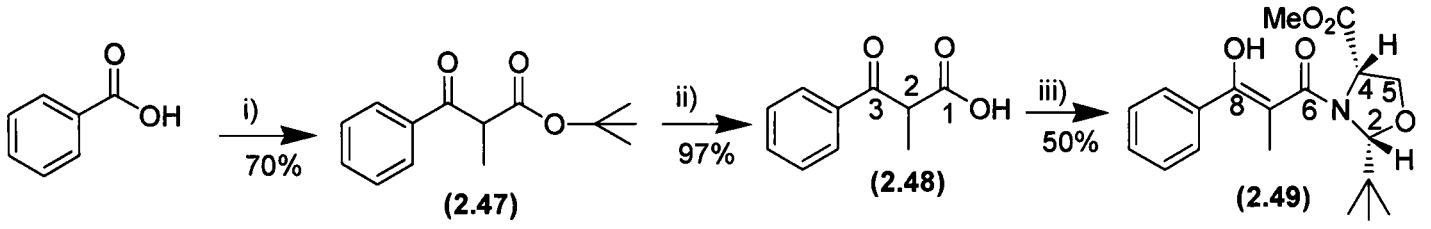
If this methodology could be utilised on a suitably constructed bicycle **(2.50),** it could provide easy access to the retrosynthetic intermediate **(2.3)**, where the carboxylic acid functionality can be considered as a masked primary hydroxyl group, which could in turn be used to access aldehyde **(2.3a)**. Such a bicycle could conceivably be constructed using the methodology previously described in this chapter *via* β-keto acid **(2.48)**, (Scheme 2.24).



Scheme 2.24: Pathway to **(2.3a)** via RuO_4 methodology

Modification of the synthetic pathway developed for the protected primary alcohol bearing β-keto acids discussed earlier in this chapter should provide convenient access to the required starting material for this new strategy, namely phenyl substituted β-ketoacid **(2.48)**.

Commercially available benzoic acid would provide a cheap entry into the existing synthetic pathway. When exposed to CDI, the activated form underwent a claisen condensation with *tert*-butyl propionate to yield *tert*-butyl ester **(2.47)** in a good 70% yield as the keto form *via* ^{1}H NMR (Scheme 2.25).

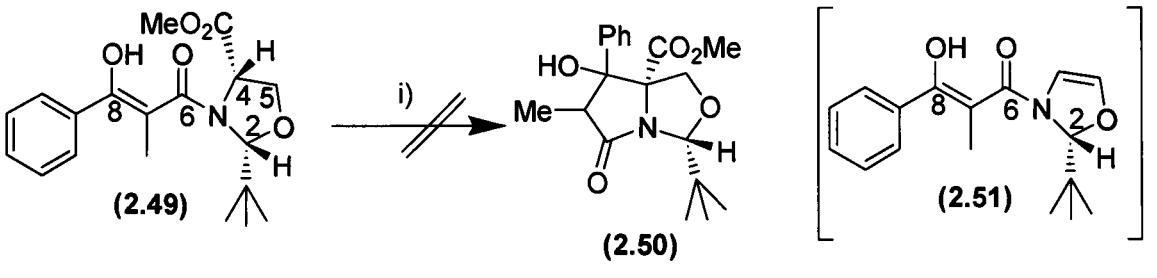


Scheme 2.25: i) CDI then LDA, $CH_3CH_2CO_2{}^tBu$, THF, ii) TsOH, toluene, iii) pyridine, $(COCl)_2$, oxazolidine **(2.5)**

Exposure of ester **(2.47)** to the standard deprotection conditions (TsOH, toluene, reflux) provided β-ketoacid **(2.48)** in almost quantitative yield (97%). ^{1}H NMR signals for the C(2) methyl at δ 1.09 exists as a doublet with a standard vicinal coupling constant of 7.0 Hz and the quartet at δ 3.18 represents the C(2) proton again with the same vicinal coupling (7.0 Hz). This information provides unequivocal evidence that acid **(2.48)** exists as the desired keto tautomer. β-Ketoacid **(2.48)** readily underwent reaction with oxazolidine **(2.5)** under pyridine catalysed *N*-acylation conditions to yield *N*-acylated oxazolidine **(2.49)** in a moderate yield of 50%. Consideration of the spectroscopic data for this compound confirmed the presence of the amide bond in the IR spectra at 1690 cm^{-1}, however, ^{1}H NMR data shows the C(8) carbonyl exists as the enol tautomer and not the desired or expected keto tautomer (providing a singlet for C(7) methyl at δ 1.54).

2.7 Cyclisation of Oxazolidine Precursors

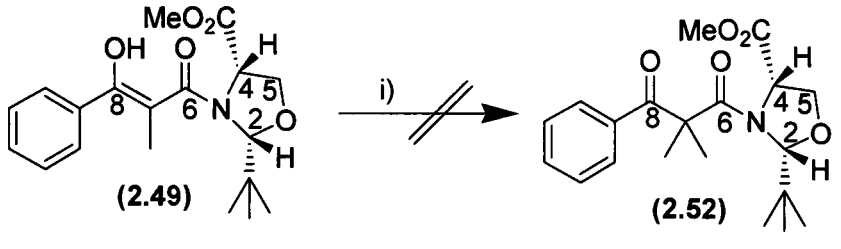
The existence of oxazolidine **(2.49)** in the enolic form did not bode well for the intramolecular aldol reaction, when considering the problems this tautomer had caused in previous investigations.



Scheme 2.26: NaOMe, MeOH, reflux or ^{t}BuOK, ^{t}BuOH, reflux

In an attempt to form bicycle **(2.50)**, oxazolidine **(2.49)** was exposed to base (NaOMe or ^{t}BuOK) in the appropriate solvent (MeOH or ^{t}BuOH respectively) at reflux. Both cases yielded unreacted oxazolidine starting material **(2.49)** and a minor product, thought to be oxazolidine **(2.51)**, the formation of which may be attributed to the possible elimination of the methyl ester functionality *via* an E_1cb mechanism. The failure of these reactions, in which the ester had been eliminated, could most obviously be attributed to the existence of the enol tautomer (Scheme 2.26).

Once again, the unfavourable keto/enol equilibrium could be corrected by introduction of a second alkyl substituent at C-7 to form **(2.52)** (Scheme 2.15). However, exposure of oxazolidine **(2.49)** to NaH and MeI under reflux conditions gave only unreacted starting material (Scheme 2.27).



i) NaH, DCM, MeI

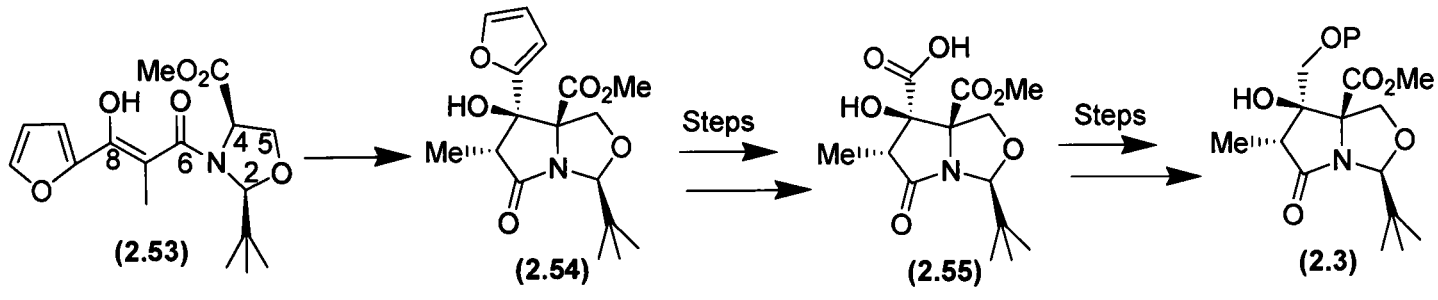
Scheme 2.27: Attempts to 'lock' keto tautomer.

Although the β-ketoacid formation in this synthetic pathway proceeds with good to excellent yields and it *N*-acylates the oxazolidine **(2.5)** with none of the previously encountered problems, the failure of oxazolidine **(2.49)** to cyclise under standard conditions represents a critical problem for this approach in being a synthetically useful route to the right hand side lactam unit of oxazolomycin.

2.8 Investigations into a C(2) Furan Substituted β-Keto Acid

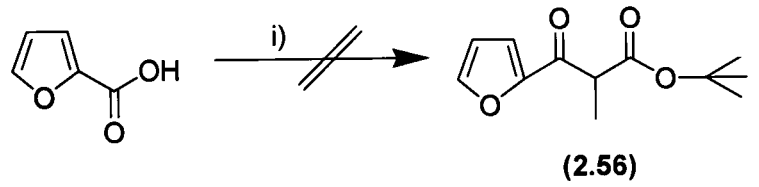
The reason for the failure of oxazolidine **(2.49)** to cyclise has already been postulated above. It was decided that introduction of a terminal furan substituent to the β-ketoacid skeleton might not only activate the C(8) position of oxazolidine **(2.53)** (drawn here with oxazolidine synthesised from D-serine to provide the correct configuration for oxazolomycin) and therefore assist in the forthcoming cyclisation reaction but also facilitate introduction of the required acid functionality (Scheme

2.28) under mild conditions. Further steps would then provide the desired primary alcohol system **(2.3)** (Scheme 2.28).



Scheme 2.28: Utilisation of C(2) Furan substituted **(2.51)** as a precursor to **(2.3)**.

To this end, the synthesis of β-keto *tert*-butyl ester **(2.56)** (Scheme 2.29) was attempted *via* exposure of commercially available 2-furoic acid to the developed claisen condensation (Section 2.5). Purification by column chromatography yielded a 50% recovery of 2-furoic acid starting material. With such a low yielding result so early in the synthetic pathway this strategy was not pursued further.



Scheme 2.29: i) CDI, LDA, $CH_3CH_2CO_2{}^tBu$, THF

2.9 Summary

This chapter has described routes to a variety of protected primary alcohols and phenyl substituted β-ketoacids, with a range of success dependent upon the tautomerisation state of the carbonyl group; this is a serious limitation of this chemistry. Control of the reaction's susceptibility to *N*-acylation appears to lie solely with the keto tautomer, the reaction proceeding to completion with good to excellent yields.

Indeed, the two β-ketoacids successfully constructed as the keto tautomer have been found to be susceptible to *N*-acylation of oxazolidine **(2.5)** *via* reported literature methodology. Thus, coupled oxazolidines **(2.41)** and **(2.49)** were prepared as key cyclisation precursors.

TIPS protected oxazolidine **(2.41)**, when exposed to intramolecular claisen conditions, appears to proceed to the desired bicycle **(2.42)**. However, due to the disappointingly low yield of this final product absolute conformation of the structure could not be ascertained. With this setback and considering the overall poor yield and relative expense of the strategy, the route was abandoned for what was hoped would be a more concise and successful route.

Whilst synthesis of **(2.49)** proceeded with excellent overall yield and low expense, the cyclisation step presented a novel problem. Surprisingly, phenyl subsituted oxazolidine **(2.49)** did not undergo Dieckman cyclisation, proceeding instead to the unsaturated oxazolidine **(2.51)**, previously unobserved in these types of system. This observation could possibly be attributed to the enol nature of the C(8) carbonyl, and the electron withdrawing nature and steric bulk of the phenyl substituent.

These studies have demonstrated that both *N*-acylation and Dieckman cyclisation methodology is highly dependent on the β-ketoacid existing as exclusively or predominantly, the keto tautomer. The success of this strategy depends on a reliable method to control equilibration. Further studies into these systems are warranted above and beyond the constraints of this project.

2.10 References

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CHAPTER 3 - LEFT HAND TRIENE FRAGMENT

3.1 Introduction: Palladium Catalysed Cross-Coupling Reactions in the Synthesis of Polyene Containing Natural Products

Palladium can catalyze carbon–carbon bond formation between aryl and vinyl halides and sulfonates and a wide variety of organometallic reagents. These are called *cross-coupling* reactions.[1] The organometallic species can be an organomagnesium, organozinc, mixed cuprate, stannane or organoboron compound. The reaction is quite general for the formation of sp^2-sp^2 and sp^2-sp bonds in biaryls, dienes, polyenes, and enynes. Conditions also exist that can couple alkyl organometallic reagents, however these reactions are less general because of the tendency of alkylpalladium intermediates to decompose by β-elimination.

The basic steps in the cross-coupling reaction include oxidative addition of the aryl or vinyl halide (or sulfonate) to Pd(0), followed by transfer of an organic ligand from the organometallic to the resulting Pd(II) intermediate (Scheme 3.1). The disubstituted Pd(II) intermediate then undergoes reductive elimination, which yields the product by carbon bond formation and regenerates the catalytically active Pd(0) oxidation state. Ligands and anions both play a crucial role in determining the rates and equilibria of the various steps by controlling the detailed co-ordination environment of the palladium centre.[2]

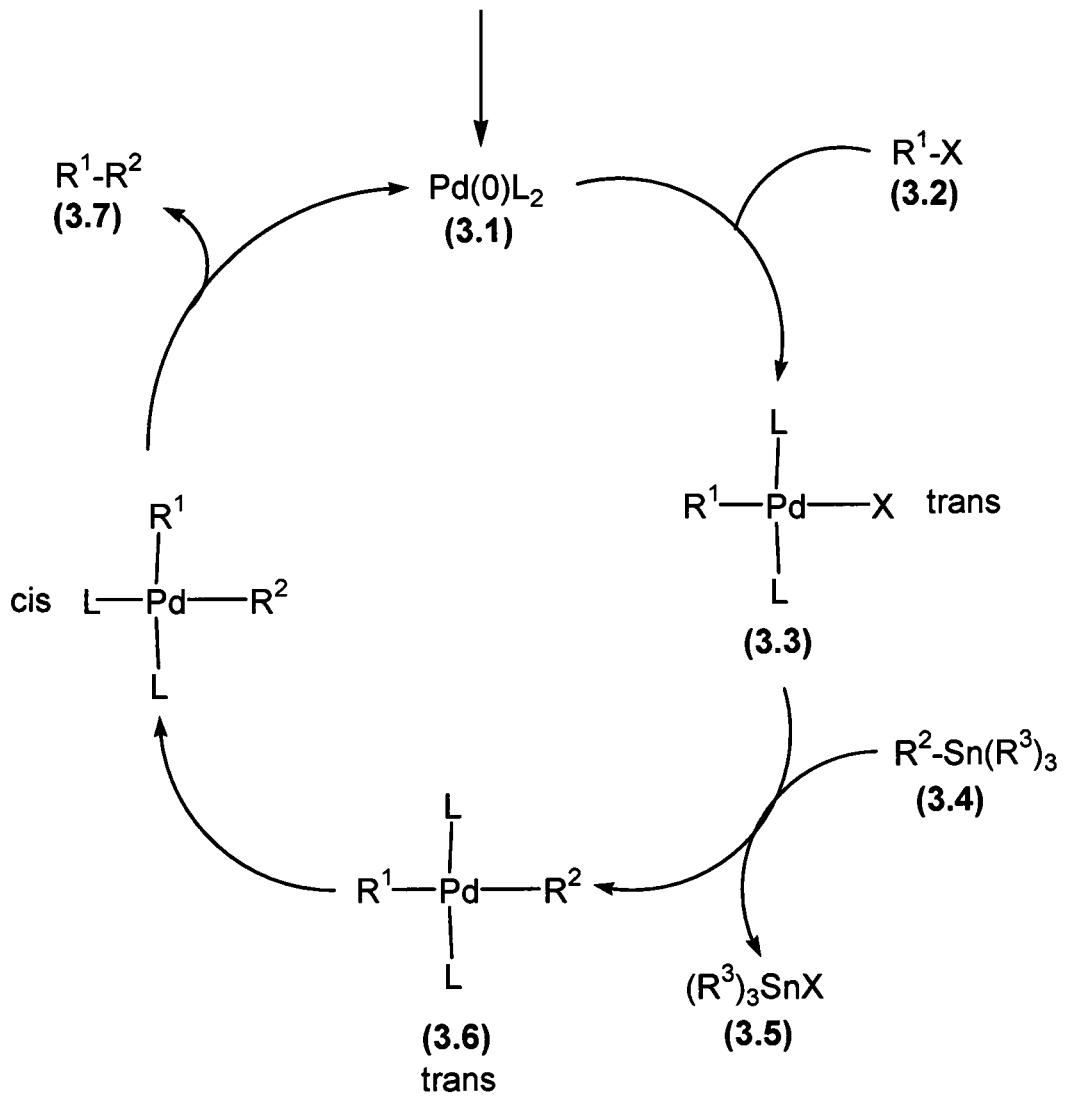
Many separate reactions have been developed along the central theme of palladium catalysed cross-coupling reactions. However, three reactions, in particular, have established themselves as invaluable tools in the construction of di- and polyene containing natural products these reactions are examined in detail herein.

The Stille Reaction

An important group of cross-coupling reactions using aryl and alkenyl stannanes as the organometallic component. This is called the *Stille reaction*[3]. The reaction has proved to be very general with respect to both the type of halide and the types of stannane that can be used. Benzylic, aryl, alkenyl and allylic halides all can be

used.[4,5] The groups that can be transferred from the stannane include alkyl, alkenyl, aryl and alkynyl. The approximate order of effectiveness of transfer of groups from tin has been established as alkynyl > alkenyl > aryl > methyl >alkyl, so that unsaturated groups are normally transferred selectively,[6] and the importance of this reaction in polyene synthesis has been substantial. Subsequent studies have identified improved ligands, including tri-2-furylphosphine[7] and triphenylarsine,[8] whilst aryl-aryl coupling rates can be increased by the presence of a Cu(I) co-catalyst.[9] This latter improvement has led to a simplified protocol in which Pd/C catalyst, along with CuI and Ph_3As gives excellent yields of biaryls.[10]

The basic mechanism of the Stille Reaction (Scheme 3.1) involves transmetallation from the tin nucleus of **(3.4)** (either directly or via an organocopper intermediate), with a Pd(II) intermediate **(3.3)** generated by oxidative addition (in which the initially formed *cis* complex rapidly isomerises to *trans*) from the aryl halide or triflate **(3.2)** to provide **(3.6)**. Isomerisation to the cis complex is then required before reductive elimination yields the alkane **(3.7)** and regenerated catalyst **(3.1)**.



Scheme 3.1: Mechanism of the Stille Reaction.

In addition to aryl-aryl coupling, the Stille reaction can be used with alkenylstannanes and alkenyl halides and triflates[11] for diene synthesis and it is this which is most applicable for the chemistry concerned within this chapter. Critically, the reactions occur with retention of configuration at both the halide and the stannane. These reactions have become very useful in stereospecific construction of dienes[12] and polyenes.[13]

The Stille reaction is an ideal construction tool for natural product total synthesis, in that the coupling reaction is very general with respect to the functionality that can be carried in both the halide and in the stannane reagent. Groups such as ester, nitrile, nitro, cyano and formyl can be tolerated. The versatility of Pd-catalysed coupling of stannanes has been further extended by the demonstration that alkenyl triflates are also active coupling partners.[14]

With the Stille products possessing extremely high geometric purity. The Stille reaction has been used extensively in the area of natural product synthesis where geometric purity is of high concern. Examples include Nicolaou's synthesis of Rapamycin[15] and Boger's synthesis of Isochrysohermidin.[16]

The main drawback to the use of the Stille reaction is usually the removal and consequent disposal of excess toxic[17] tin reagents and organotin side products from the reaction mixture. Excess tin reagents in the reaction mixture can be resistant to standard purification techniques such as column chromatography and pose considerable problems to characterisation of the reaction product. ^{1}H NMR spectroscopic signals can be hidden by the presence of tributyltin species and peaks, often critical to the structural assignment, can be barely visible. Tin, containing species also cause problems in mass spectrometric analysis.

Due to these complications in the otherwise highly useful Stille reaction, several wide-ranging methods have been developed for the removal of organotin compounds from reaction mixtures. Corey *et al*[18] recently reported a method for the removal of excess tributyltin hydride from reaction mixtures by conversion to tributyltin halides, followed by precipitation as the insoluble tributyltin fluoride by the use of a mixture of CsF:CsOH. There is also now a standard method for treating the reaction mixture with KF in MeOH.[19]

Another approach to the removal of tin residues is based on the very high solubility of organotin halides and unreacted organotin hydride in hexane and the preferential partitioning of other organic compounds into acetonitrile in the acetonitrile-hexane two phase system.[20] Crich[21] has also reported a method for the removal of organotin residues by reduction with $NaBH_3CN$. A method of treating organotin halide containing mixtures with Me_3Al to remove the tin species has also recently been reported.[22]

A recent publication[23] has shown removal of triorganotin compounds by conversion into inorganic tin compounds of low toxicity is possible. The degradation of the organotin compounds by exposure to HCl and HNO_3, followed by neutralisation of the acidic solution and addition of thioacetamide, which acts as a hydrogen sulfide equivalent, precipitates insoluble SnS_2 as a yellow solid.

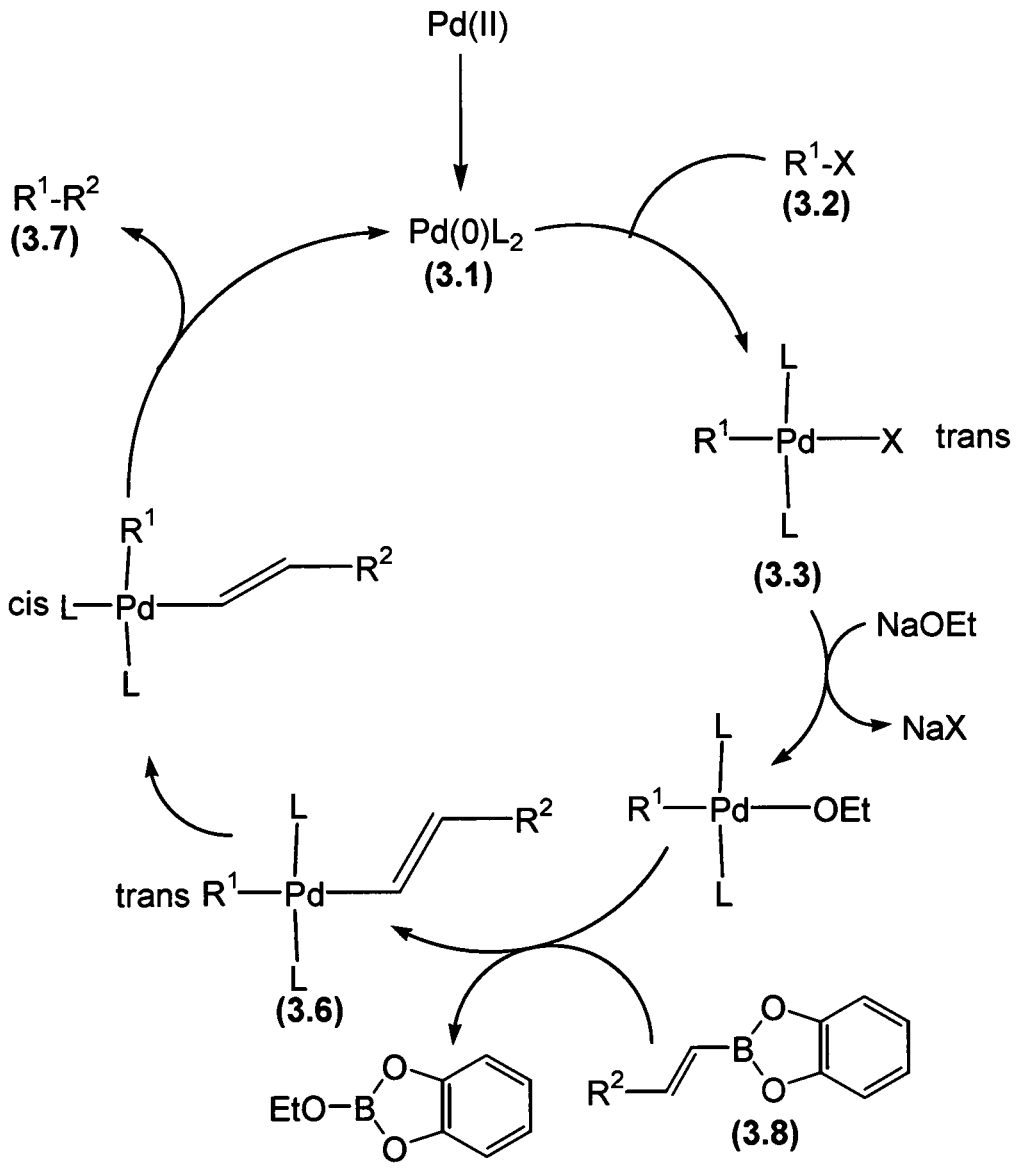
Chromatographic techniques have also been developed[24] for the removal of excess tin reagents by the use of reversed-phase flash chromatography on C-18 silica gel. To limit residual tin contamination, organotin hydrides have been anchored to solid phase scavengers so that by-products can simply be removed by filtration.[25] New allyltri–*n*-butyltin hydride reagents have been developed along this route on non-crosslinked polystyrene.[26]

The one serious disadvantage of the otherwise useful Stille reaction can be overcome by the use of any one of the methods discussed above as appropriate, making the reaction one of the most versatile and widely used tools of organic chemistry.

The Suzuki Reaction

This reaction is a cross-coupling in which the organometallic component is an aryl- or vinylboron compound.[27,28,29] The organoboron compounds that are susceptible to coupling include boronic acids,[30] boronate esters[31] and boranes.[32] Synthetically useful attributes of the Suzuki reaction include the absence of phosphine ligands[33] and the fact that they can be applied to solid phase reactions.[34]

The overall reaction (Scheme 3.2) is closely related to that of the previously discussed Stille reaction. The aryl halide or triflate **(3.2)** reacts with the Pd(0) catalyst **(3.1)** by oxidative addition to give **(3.3)** (an initially formed *cis* complex undergoes rapid isomerisation to *trans*). The organoboron compound **(3.8)** serves as the source of the second organic group by transmetalation from the boron nuclei to give **(3.6)**. The disubstituted Pd(II) **(3.6)** intermediate then rearranges to the *cis* complex before it undergoes reductive elimination to yield alkane **(3.7)**. It appears that either the oxidative addition or the transmetalation can be rate determining, depending on the reaction conditions employed.[35] With boronic acids as reactants, addition of a base is normally required and is believed to lead to the formation of the more reactive boronate anion.[36]



Scheme 3.2: Mechanism of the Suzuki reaction.

One of the potential advantages of the Suzuki reaction, especially when boronic acids are used, is that the by-product boric acid is easier to remove from the reaction mixture than the tin by-products generated in Stille-type couplings, since it is water soluble.

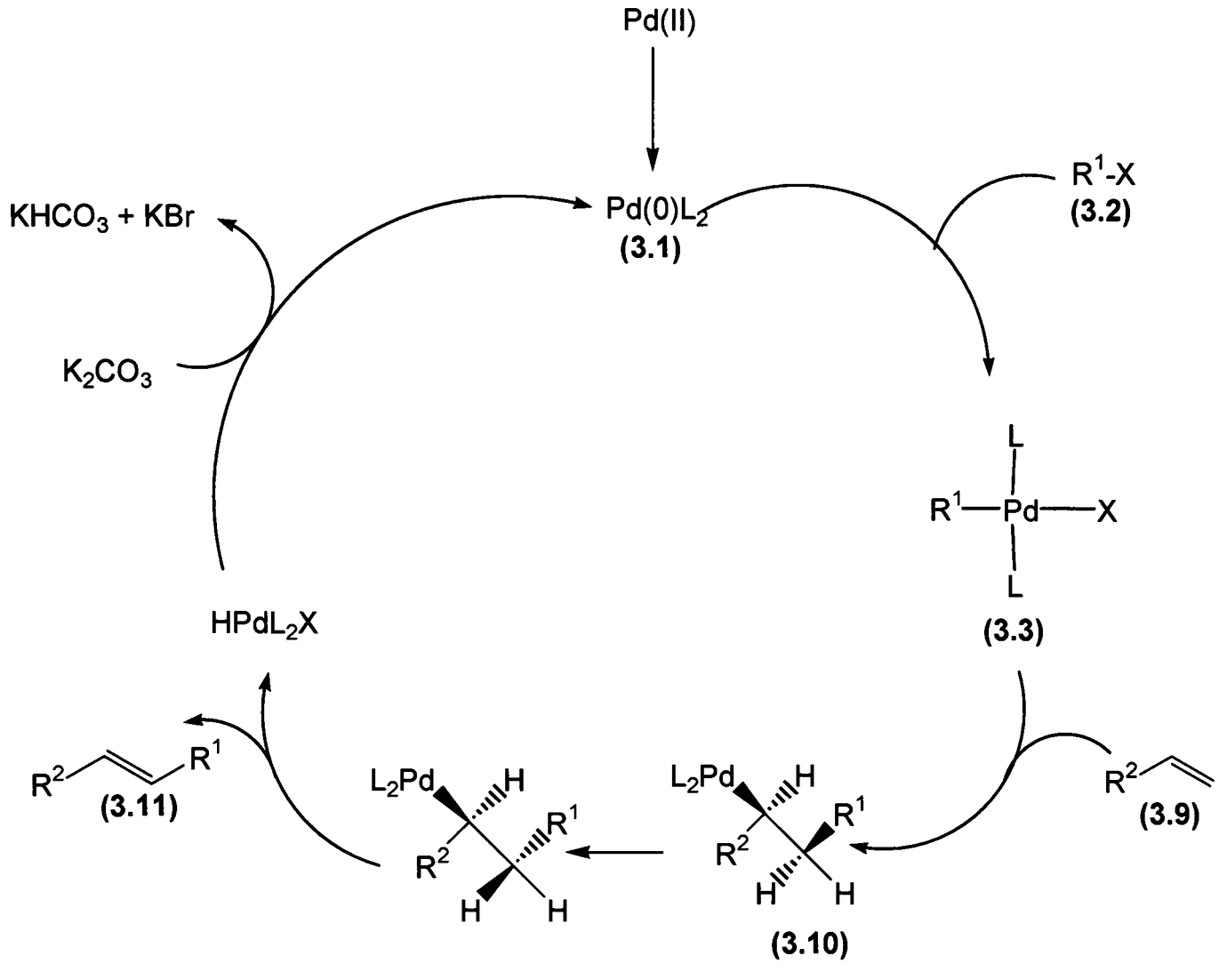
Alkenylboronic acids, alkenyl boronate esters and alkenylboranes can be coupled with alkenyl halides by palladium catalysts to provide dienes.[37,38] These reactions proceed with retention of double-bond configuration in both the boron derivative and the alkenyl halide. It has also been reported[39] that β-alkenylcatecholboranes couple stereospecifically with alkenyl bromides.

The Suzuki reaction has found application in the realm of natural product synthesis, and provides stereoselective routes to a variety of target compouds including trisporol B.[40] The Suzuki reaction can be used successfully under very mild conditions, thus making it a very useful tool for synthesis where an unstable coupling partner or product are involved, as is the case in the synthesis of the oxazolomycins.

The Heck Reaction

Aryl[41,42] and alkenyl[43,44] halides react with alkenes in the presence of catalytic amounts of palladium to give net substitution of the halide by the alkenyl group. The reaction is quite general and has been observed for simple alkenes, aryl-substituted alkenes, and electrophilic alkenes. Many procedures use $Pd(OAc)_2$ or other Pd(II) salts as catalysts, with the catalytically active Pd(0) being generated *in situ*. The reactions are usually carried out in the presence of a phosphine ligand, with tri-*o*-tolylphosphine being preferred in many cases.

The reaction (Scheme 3.3) is initiated by oxidative addition of the halide **(3.2)** to a Pd(0) species **(3.1)** generated *in situ* from the Pd(II) catalyst. The arylpalladium(II) intermediate **(3.3)** then forms a complex with the alkene **(3.9)** by syn addition, which rearranges to a σ complex **(3.10)** this complex then undergoes internal rotation. The σ complex decomposes by β-elimination with regeneration of Pd(0) **(3.1)** after exposure to a proton donor and this yields alkene **(3.11)** *via* syn elimination. At least two different Pd(0) species can be involved in both the oxidative addition and π-co-ordination steps, depending on the anions and ligands present.



Scheme 3.3: Mechanism of the Heck Reaction.

High halide concentration promotes formation of the anionic species $[PdL_2X]^-$.

Heck reactions can result in regioisomers depending on whether migration occurs to the α or β-carbon of the alkene. Alkenes possessing electron-withdrawing substituents normally result in β-arylation. However, alkenes with donor substituents give a mixture of α and β regioisomers. The regiochemistry can be controlled to some extent by specific reaction conditions. With vinyl ethers and *N*-vinylamides, it is possible to promote α-arylation by use of bidentate phosphine ligands such as dppe and dppp, using aryl triflates as reactants. These reactions are believed to occur through a more electrophilic form of Pd(II) generated by dissociation of the triflate anion.[45] Electronic factors favour migration of the aryl group to the α-carbon.

The Heck reaction has, in comparison to its cousins, found relatively little use in di- or polyene synthesis. This is mainly due to the fact that, whilst the Stille and Suzuki couplings usually proceed with retention of stereochemistry of the coupling partners,

the Heck reaction does not. The Heck and Stille reactions were recently compared in a synthesis of pateamine A[46], a diene containing macrolide. The results demonstrated the superior retention of stereochemistry provide by the Stille reaction over the Heck process.

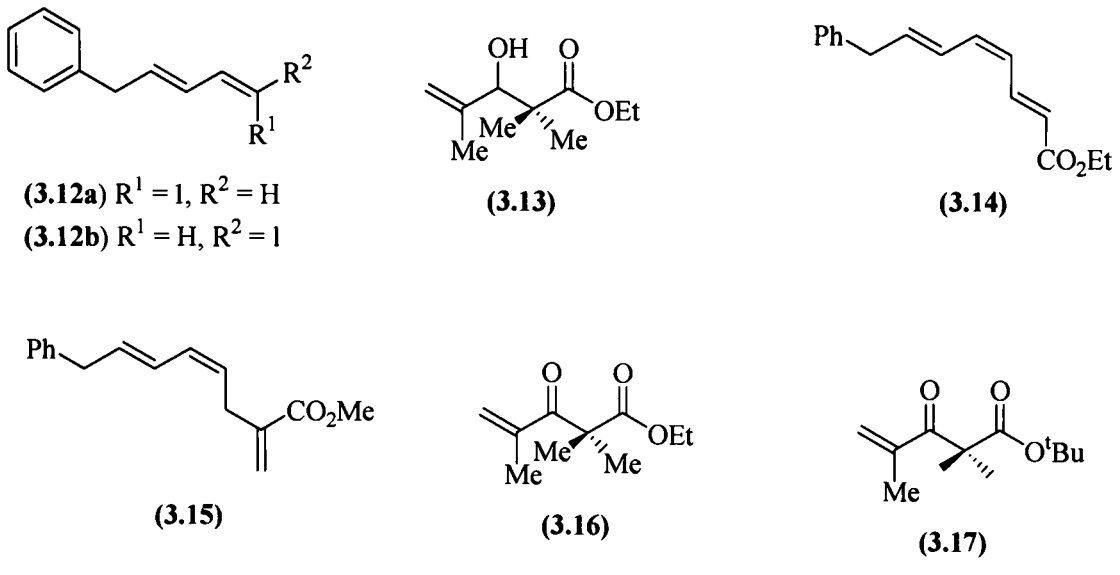
However, asymmetric Heck reactions have been demonstrated[47] and further expanded upon with the use of appropriate chiral ligands bound to palladium[48] Since 1989 reactions have been developed to form tertiary and quaternary carbon atoms[49] (e.e. >80%), although these are generally intramolecular (ring closing). Intermolecular reactions have until recently[50] been limited to reactive substrates, principally O- and N- heterocycles and to formation of tertiary centres on ring carbon atoms. The problems emanating from lack of regiocontrol in the case of unsymmetrical alkenes or the absence of a connecting tether. This version of the Heck Reaction was used in Overman's synthesis of quadrigemine C and psycholeine.[51]

Limitations of these reactions to the synthesis of the Oxazolomycins

It would appear that any of the three aforementioned reactions, with prudent design of coupling partners, would be expected to proceed stereospecifically and in high yield to the desired triene. However, consideration of previous work both from within this laboratory and elsewhere, show this may not be the case.

The Heck Reaction

Previous work from within the Moloney group[52] has applied the Heck reaction to the construction of the left hand side of the oxazolomycins *via* vinyl iodide **(3.12a)** and allylic alcohol **(3.13)** (Scheme 3.4). Application of the Jeffery procedure[53] for the Heck reaction of allylic alcohols with vinyl iodides (cat. $Pd(OAc)_2$ Ag_2CO_3, DMF, 45 °C) proved to be unsuccessful. Numerous other conditions involving variation of the catalyst, phosphine ligand, solvent, temperature, base and using various additives known to increase the rate of certain Heck reactions (such as n-Bu_4NCl,[54] TlOAc[55] and t-BuOH[56]) also all proved unsuccessful.



(3.12a) $R^1 = I$, $R^2 = H$
(3.12b) $R^1 = H$, $R^2 = I$

(3.13) **(3.14)**

(3.15) **(3.16)** **(3.17)**

Scheme 3.4: Coupling Partners used in previous investigations into Heck reactions.

Although in each case the vinyl iodide was consumed, no trace of the required product could be detected. This suggested that oxidative addition of the iodide to the Pd(0) species was taking place but insertion of the vinyl-Pd complex into the double bond of the allylic alcohol (the rate determining step[57]) was not.

To determine whether the reason for the failure was due to steric or electronic factors, either in the iodine or the alcohol, a series of further experiments were performed. Reaction of iodide **(3.12a)** with ethyl acrylate using the Jeffery conditions gave 2(*E*), 4(*Z*), 6(*E*)-triene **(3.14)** in 52% yield; reaction with methyl methacrylate also led to coupling, but surprisingly gave the exomethylene product **(3.15)** rather than the expected conjugated triene. A possible explanation for this result is that it is due to steric effects in the β-elimination step of the catalytic cycle. Noting that successful reactions were obtained with electron-deficient double bonds, coupling was attempted between ketone **(3.16)** and iodide **(3.12a)**, but this also proved unsuccessful.

To investigate the steric and electronic properties of the acceptor alkene, several analogues of ketone **(3.16)** were prepared with increasingly bulky substituents replacing one or more of the methyl functions. When subjected to the Heck reaction the only analogue to react was the *tert*-butyl ester **(3.17)** albeit only in 28% yield. This suggests that the unreactivity of allylic alcohol **(3.13)** is due not only to steric hindrance imposed by the vinylic-methyl and gem-dimethyl groups but also the electronic effects of the conjugated double bond.

Due to the failure of this key step and because the problem of the inherent unreactivity of allylic alcohol **(3.13)** could not obviously be corrected, this approach was abandoned.

The Suzuki Reaction

Whiting and Henaff recently disclosed a synthesis of racemic phthoxazolin A,[58] and the synthesis was a validation of methodology using consecutive Heck and Suzuki reactions[59] to construct conjugated polyene systems. However, as a total synthesis, the published route had several limitations.

The overall synthetic strategy has been previously discussed (Section 1.7.2). The final step in the synthesis was planned as a Suzuki coupling between a vinyl iodide diene and a vinylboronate ester. Construction of both coupling partners proved to be problematic The vinyl iodide diene **(1.42)** was obtained in a moderate 49% yield and was used in crude form in the subsequent coupling reaction due to concerns over the stability of the compound.

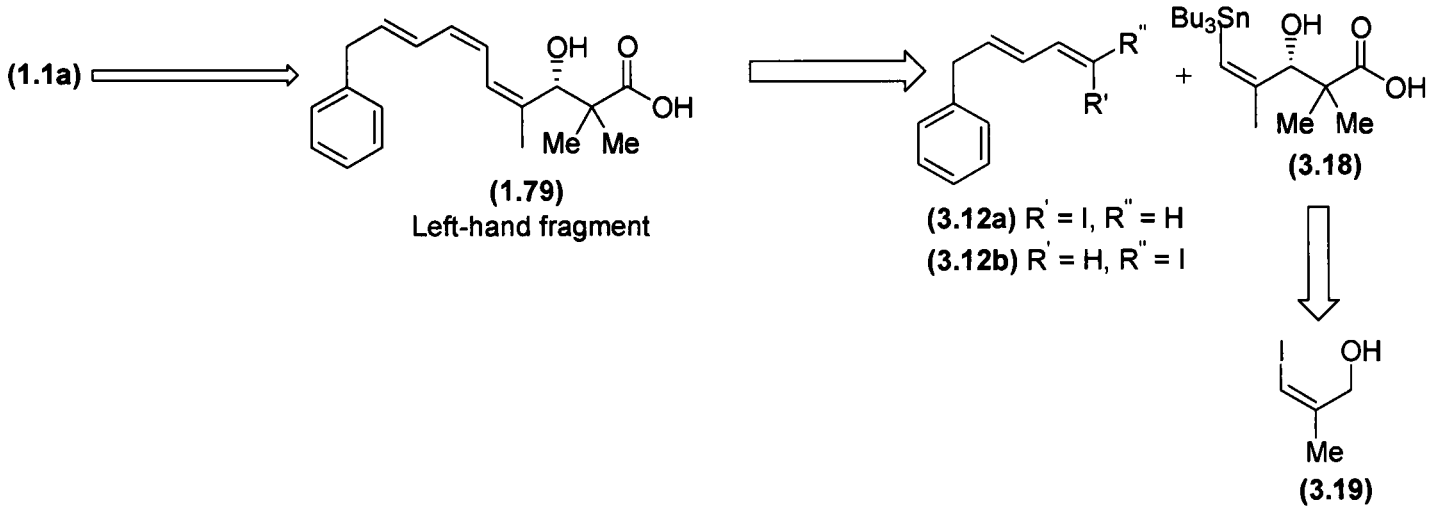
The major problem however, was encountered in the preparation of the desired final vinylboronate, despite several attempts and various methodologies a 'complete lack of success' was encountered in providing the desired boronate. In fact the Suzuki coupling strategy had to be totally abandoned in favour of a Stille reaction, which proceeded with retention of stereochemistry to yield the desired final product, albeit in low yield (22%).

Retrosynthetic Analysis of the Triene Fragment of Oxazolomycin

With careful consideration of these literature results, it was decided to proceed with a synthesis that would rely upon a key Stille coupling step between vinyl halide and stannane coupling partners to provide access to all three oxazolomycin isomers. Despite the reported low yield of the Stille reaction in Whiting's synthesis of phthoxazolin A, it was hoped that optimisation of the reaction conditions and prudent selection of coupling partners would provide a more favourable result. Attention was therefore turned to the retrosynthetic analysis of the left hand side of the oxazolomycins.

Typical to all of the oxazolomycin class of natural products is the left hand side triene system **(1.79)**, possessing an oxazole terminus. Variation in the triene geometry provides the structural differences between oxazolomycins A, B and C and indeed is responsible for the range of biological activities between the compounds.

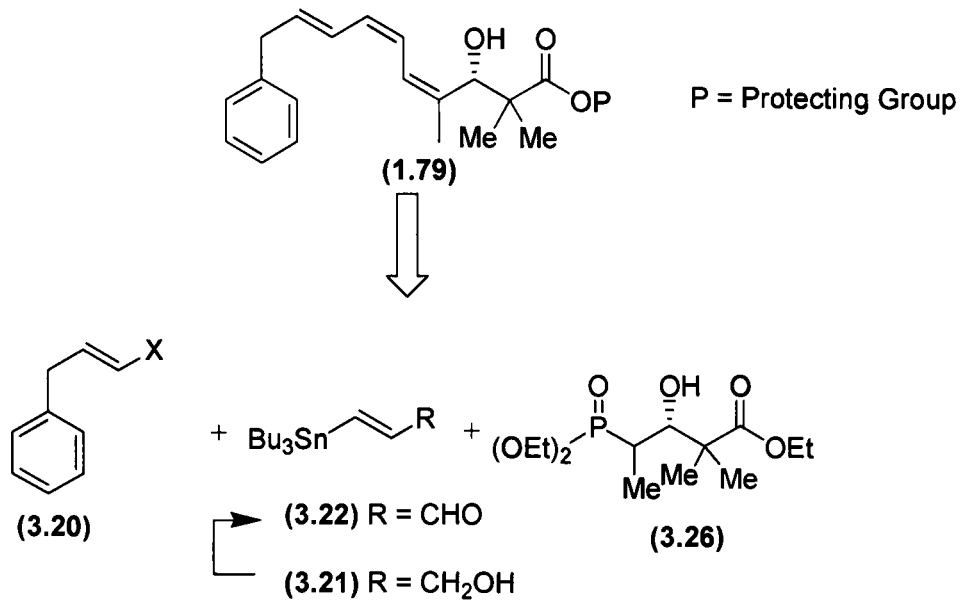
The synthetic route envisaged for this fragment uses a multi-component coupling strategy based around a pivotal Stille diene-coupling reaction. The phenyl terminus was introduced at this stage in place of the oxazole moiety for synthetic simplicity. Thus vinyl halides **(3.12)** possessing *Z, E* and *E, E* olefin stereochemistries were sought in combination with a *(Z)*-vinylstannane possessing secondary alcohol and gem dimethyl functionalities **(3.18)** (Scheme 3.5), which was expected to be accessible from known alcohol **(3.19)**.



Scheme 3.5: Retrosynthetic analysis of left hand triene system.

3.2 Investigation of Previous Work

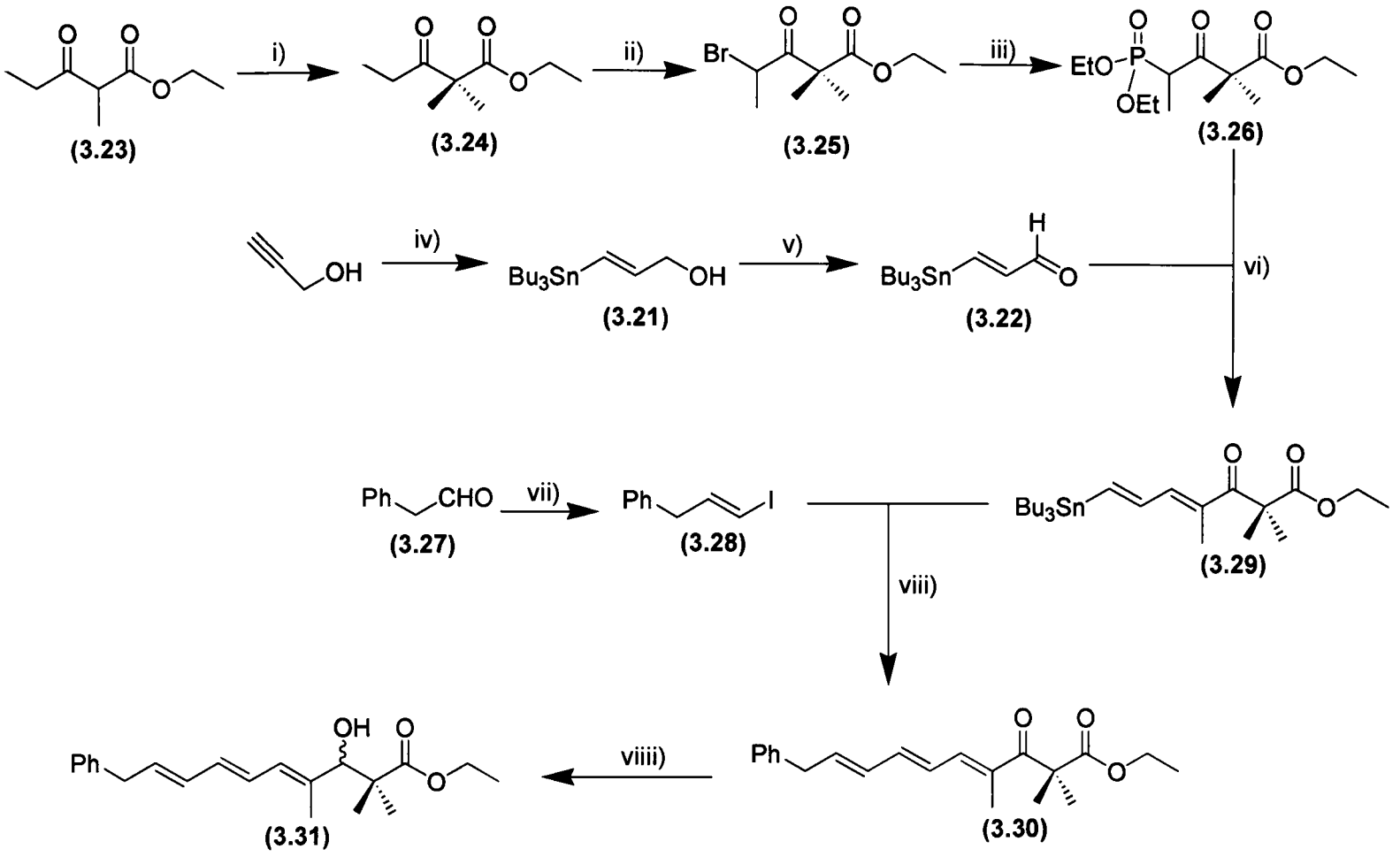
The *(E, E, E)* triene isomer has received considerable attention from within the Moloney group[52]. A successful route to the triene system of oxazolomycin B made use of regioselective Stille couplings[60,61] in a three-component coupling strategy (Scheme 3.6). Thus, *(E)*-selective Wadsworth-Emmons reaction[62,63] of aldehyde **(3.22)** using phosphonate **(3.26)**, followed by Stille reaction with vinyl halide **(3.20)** was expected to yield the triene unit in a regio- and stereoselective manner under mild, neutral conditions. Asymmetric ketone reduction followed by ester to amide conversion would then give the desired product.



Scheme 3.6: Retrosynthetic analysis of *(E ,E, E)* isomer

Allylic alcohol **(3.21)** was synthesised by AIBN-catalysed hydrostannylation of propargyl alcohol in a modification of the literature procedure[64] (which involved purification by column chromatography rather than distillation followed by preparative HPLC), which gave the product in 67% yield after separation from isomeric by-products. Swern oxidation afforded aldehyde **(3.22)** in excellent yield (90%).

Phosphonate **(3.26)** (Scheme 3.7), was treated with sodium hydride followed by aldehyde **(3.22)** to give (*E, E*)-diene **(3.29)** in moderate yield (50%); the (*E, E*)-geometry was consistent with a coupling constant of $J_{6,7}$ 18.5 Hz and the absence of allylic coupling for $J_{5,Me}$. To incorporate the required third olefin, vinyl iodide **(3.28)** (prepared by Takai[65] reaction of phenylacetaldehyde, and clearly the (*E*)-isomer with a coupling constant of 14.4 Hz) was reacted with stannane **(3.29)** to give (*E, E, E*)-triene **(3.30)** in 84% isolated yield (93% yield based on the recovered unreacted (*Z*)-iodide starting material **(3.28)**). Reduction with $NaBH_4$ then gave alcohol **(3.31)** in which crucially, the polyene system at no stage isomerised into conjugation with the phenyl terminus. The (*E, E, E*)-geometry, corresponding to that of oxazolomycin B, was consistent with a coupling constant of $J_{6,7}$ 14.1 and $J_{8,9}$ 14.4 Hz as well as the absence of allylic coupling for $J_{5,Me}$.



Oxazolomycin B left hand side

i) NaH/THF, MeI, 89%; ii)Br_2, AcOH, 82%; iii) $P(OEt)_3$, 89%; iv) Bu_3SnH, AIBN, 98%; v) DMSO, $(COCl)_2$, Et_3N, DCM, 90%; vi) NaH/THF, 50%, vii) $CrCl_2/CHI_3$, 79%, (E:Z 10:1), viii) $PdCl_2(MeCN)_2$, 84%, viiii) $NaBH_4$/MeOH, 92%.

Scheme 3.7: Synthesis of racemic (*E, E, E*)-isomer

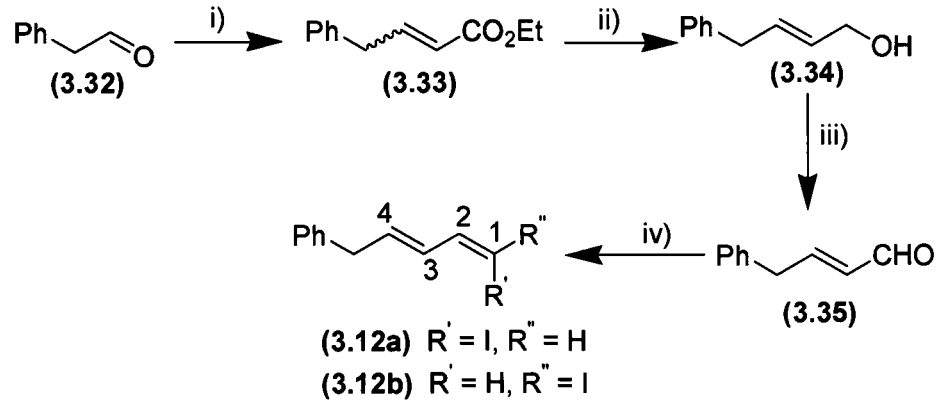
3.3 Synthesis of *(Z,Z,E)* and *(Z,E,E)* Left Hand Isomers

The chemistry detailed in this chapter describes attempts towards the left hand side fragments of oxazolomycin A - (*Z, Z, E)* and C - (*Z, E, E*). It was decided to adopt the strategy discussed previously in the retrosynthetic analysis. Thus coupling of isomeric vinyl halides **(3.12a,b)** and stannane **(rac-3.18)** would constitute the key step. This would provide a rapid, flexible route to these compounds, since by using either 1(*Z*)-**(3.12a)** or 1(*E*)-iodide **(3.12b)**, selective synthesis of the isomeric triene systems would be accomplished.

3.3.1 Synthesis of Isomeric Vinyl Iodide - 1(*Z*),3(*E*)

The (*Z*)-iodide **(3.12a)** was available *via* aldehyde **(3.35)** (Scheme 3.8), which in turn was prepared by a three step sequence involving Wittig homologation[66,67] of commercially available phenylacetaldehyde **(3.32)** with

(carboethoxymethylene)triphenylphosphorane to provide ethyl ester **(3.33)** as a 12:1 mixture of (*E*) : (*Z*) olefin geometric isomers, which proved to be separable by careful column chromatography. DIBAL-H reduction[68,69] of the ethyl ester and careful re-oxidation (PCC[70]) provided aldehyde **(3.35)** in good yield (81%) over the two steps. Alternative, more direct routes, involving direct homologation with the commercially available phosphorane Ph_3P=CHCHO, or of selective reduction of ester **(3.33)**, proved to be either unsuccessful or lower yielding.



i) Ph_3P=$CHCO_2Et$, DCM, RT, 16h, (E-isomer 87%, Z-isomer 6%); ii) DIBAL-H, THF, -78°C - -10°C, 2h, (91%); iii) PCC, DCM, RT, 2.5h, (79%); iv) Stork (69%); (iodomethyl)triphenylphosphonium iodide, NaHMDS, THF, -78° C, or Takai (68%); $CrCl_2$, CHI_3, THF, 0° C.

Scheme 3.8: Synthesis of (*Z, E*) and (*E, E*) vinyl iodides.

Aldehyde **(3.35)** was then converted into 1(*Z*),3(*E*)-iodide **(3.12a:3.12b)** *via* a (*Z*)-selective Wittig olefination, following a procedure developed by Stork and Zhao.[71] Thus (iodomethyl)triphenylphosphonium iodide was prepared in modest yield (41%), by reaction of PPh_3 with CH_2I_2;[72] deprotonation using NaHMDS, followed by careful addition of aldehyde **(3.35)** at low temperature gave the product **(3.12a:3.12b)** in good yield (69%) and as a 8:1 ratio of 1(*Z*),3(*E*) : 1(*E*),3(*E*)-isomers, which proved inseparable by column chromatography. The *cis*-stereochemistry assigned from H-1 coupling data (*J* 7.1 Hz) and n.O.e. experimentation (Fig 3.1).

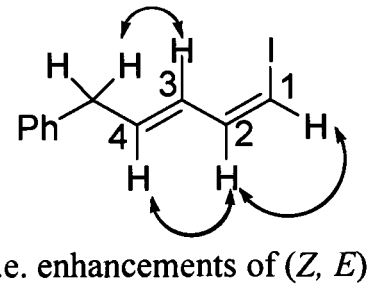


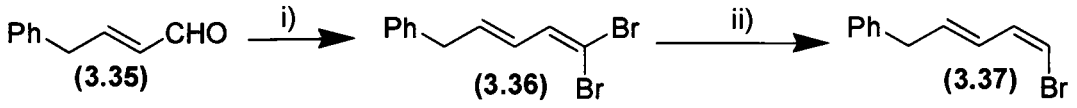
Fig 3.1: n.O.e. enhancements of (*Z, E*) iodide **(3.12a)**.

3.3.2 Synthesis of Isomeric Vinyl Iodide - 1(*E*),3(*E*)

Alternatively the 1(*E*),3(*E*)-isomer **(3.12b)** was available by Takai olefination ($CrCl_2$-CHI_3)[65] of aldehyde **(3.35)** in 68% yield as an inseparable 3.3:1 mixture of (*E*) : (*Z*)-isomers; the *trans*-stereochemistry assigned by H-1 coupling data ($J_{1,2}$ 14.4 Hz) compared to the ($J_{1,2}$ 7.2 Hz) observed in the 1(*Z*), 3(*E*) isomer **(3.12a)**). Similarly disappointing (*E*):(*Z*)-ratios in the homologation of α,β-unsaturated aldehydes had been noted by Takai. It was necessary to use commercially available $CrCl_2$, as the reagent generated *in situ* from $CrCl_3$ and $LiAlH_4$[73] proved ineffective. Thus the synthesis of iodides **(3.12a,b)** was accomplished in four steps from phenylacetaldehyde, with overall yields of 47% and 46% respectively.

3.3.3 Synthesis of Isomeric Vinyl Bromide - 1(*Z*),3(*E*)

As (*Z*)-iodide **(3.12a)** was isolated as an 8:1 mixture of 1(*Z*) : 1(*E*)-isomers *via* a (*Z*)-selective Wittig olefination (*vide supra*), it was envisaged that separation of this isomeric mixture after the crucial Stille coupling reaction would be particularly troublesome, if not impossible and so an alternative synthesis of a (*Z*)-halide which would deliver the product with greater geometric purity was desirable.



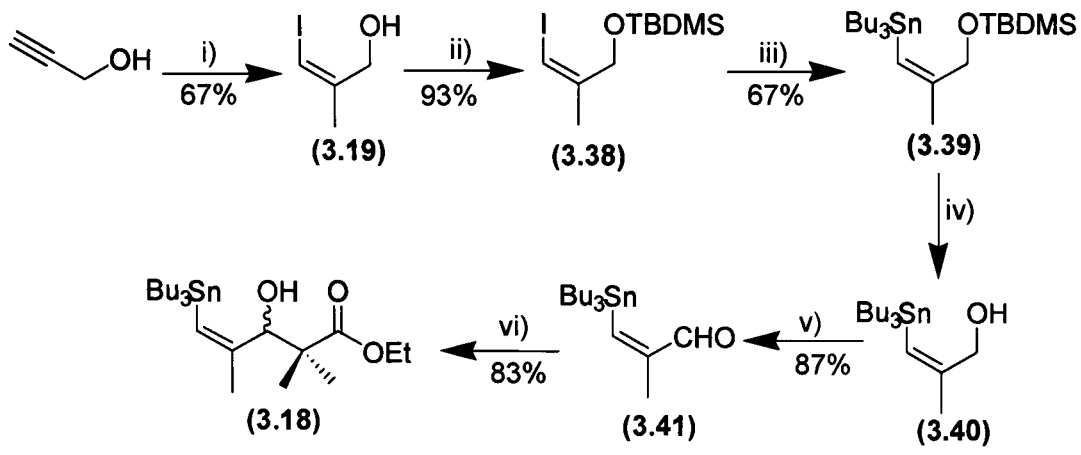
i) PPh_3, CBr_4, DCM, 0°C, 3h, (78%); ii) Bu_3SnH, cat. $Pd(PPh_3)_4$, toluene, RT, 3h, (68%);

Scheme 3.9: Synthesis of 1(*Z*), 1(*E*) vinyl bromide

To this end, conversion of aldehyde **(3.35)** into dibromide **(3.36)** (Scheme 3.9) followed by stereoselective palladium-catalysed monoreduction according to the recent literature protocol[74] yielded vinyl bromide **(3.37)** in good yield (68%) and crucially as an excellent 99:1 mixture of 1(*Z*) : 1(*E*)-isomers. Assignment of stereochemistry was provided by H-1 coupling constants (*J* 15.1 Hz for the (*E*)-geometry) and (*J* 10.2 Hz for the (*Z*)-geometry). Interestingly the monoreduction reaction only proceeded to completion when performed on the crude dibromide and not the purified compound.

3.4 Synthesis of Vinyl Stannane Coupling Partner

Known iodide **(3.19)** was prepared as a single diastereomer from propargyl alcohol following the literature procedure[75] and the free hydroxyl group was protected as its TBDMS-ether[76,77] **(3.38)** in excellent yield (93%) (Scheme 3.10).

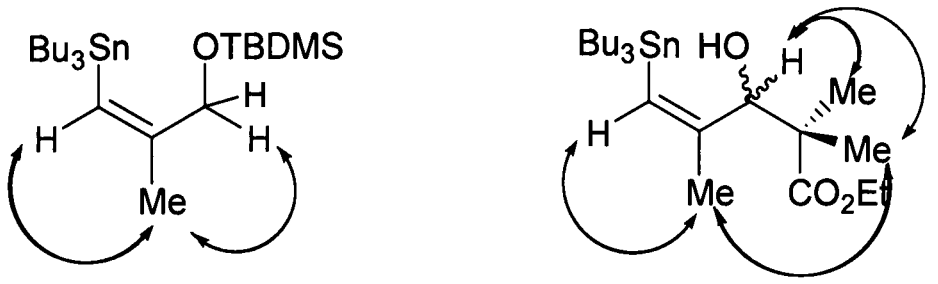


i) MeMgBr, CuI, Et_2O, -10°C - RT, 22h then I_2, 0°C, 3h, (67%); ii) TBDMSCl, ImH, DMF, RT, 22h, (93%); iii) n-BuLi, THF, -78°C, 45min then Bu_3SnCl, -78°C - 0°C, 2h, (67%); iv) TBAF, THF, RT, 2h; v) Swern (87% for 2 steps); vi) Ethyl isobutyrate, LDA, THF, -78°C (83%).

Scheme 3.10: Synthesis of vinyl stannane coupling partner.

Conversion to stannane **(3.39)** was effected by metal-halogen exchange followed by Bu_3SnCl quench but the course of this reaction was found to be very solvent dependent; only in Et_2O was the desired stannane **(3.39)** isolated in good yield (67%). Purification of this stannane compound by column chromatography proved immensely difficult and had to be performed both in large diameter columns and with 1% Et_3N in the eluent to neutralise the acidity of the silica in order to prevent protodestannylation. Removal of the silyl protecting group with TBAF[77] to provide crude alcohol **(3.40)** and immediate Swern oxidation[78] to afford aldehyde **(3.41)** proceeded over the two steps in excellent yield (87%). Aldol reaction[79] with ethyl isobutyrate then gave racemic alcohol **(rac-3.18)** in good overall yield (83%).

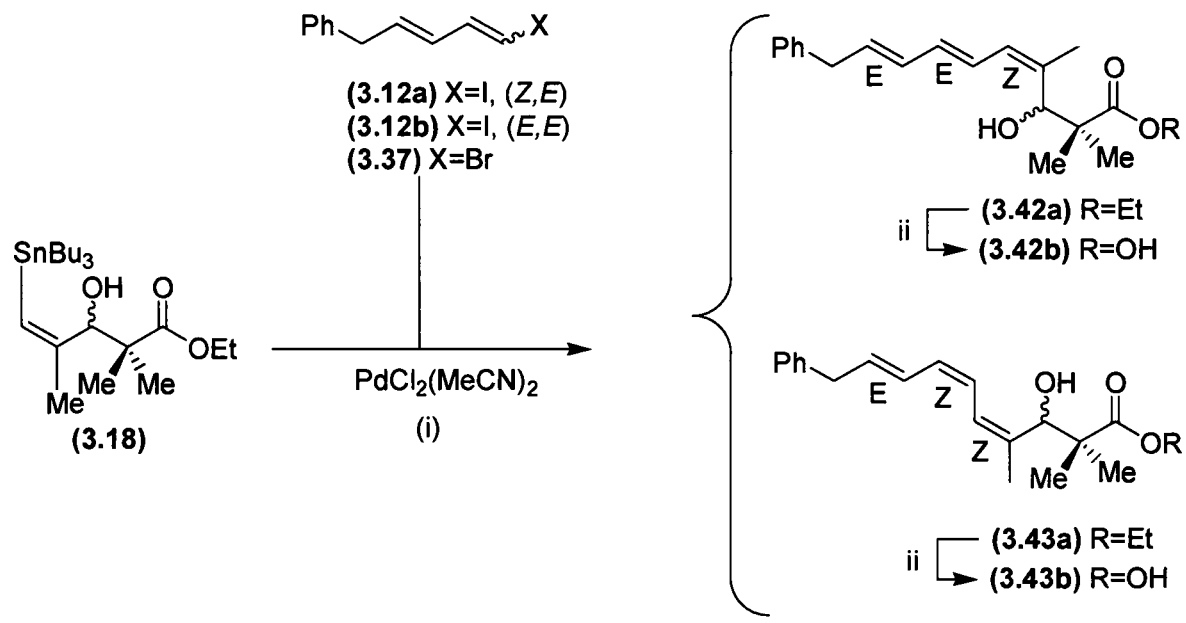
The (*Z*)-stereochemistry of stannanes **(3.39)**, **(3.41)** and **(rac-3.18)** was evident from allylic coupling (C*H*=C(Me)) values of 1.3-1.4 Hz and the presence of significant n.O.e. effects between the vinylic substituents; n.O.e. enhancements also suggested that compound **(rac-3.18)** appeared to exist in the preferred conformation indicated (Fig. 3.2). Crucially, no isomerisation of the olefin into the (*E*)-configuration was observed.



(3.39) **(3.18)**

Fig 3.2: n.O.e. data for selected stannanes.

3.5 Stille Coupling Reaction

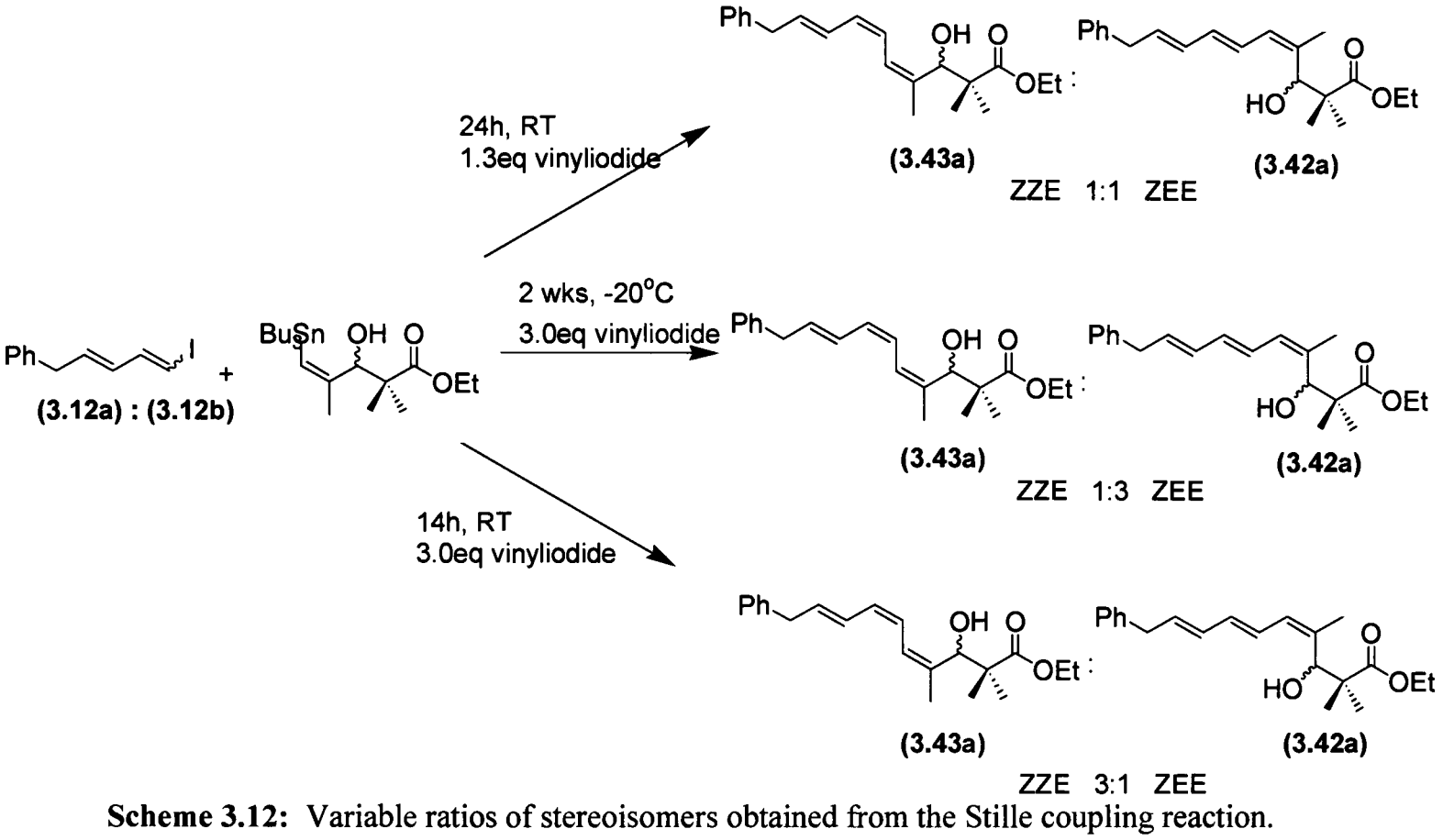


(i) $PdCl_2(MeCN)_2$, DMF, RT; (ii) LiOH, THF:H_2O:MeOH (1:1:1), rt, 24h, 52%

Scheme 3.11: Stille coupling of vinyl stannane and vinyl iodides

(*Z*)-Stannane **(rac-3.18)** was reacted under standard Stille coupling conditions ($PdCl_2(MeCN)_2$, DMF) with vinyl halides **(3.12a,b)** (Scheme 3.11). Reaction for 10 hrs with a threefold excess of (*E, E*)-**(3.12b)** (3:1 mixture of (*E, E*) : (*Z, E*) stereoisomers) gave a 72% yield of a racemic 3:1 mixture of (*Z ,Z, E*) : (*Z, E, E*) triene products **(rac-3.43a)** and **(rac-3.42a)**, in which the expected (*Z, E, E*) triene is the minor product. Selective reaction of the minor (*Z, E*)-component of the 3:1 mixture of **(3.12b) : (3.12a)** appeared to be occurring. This changed to a 1:1 ratio (*via* ^{1}H NMR spectroscopic analysis) if the reaction time was lengthened to 24 hrs and the number of equivalents of (*E, E*)-**(3.12b)** was reduced to 1.3 (Scheme 3.12). Compound **(rac-3.43a)** possesses the stereochemistry corresponding to oxazolomycin A, whilst compound **(rac-3.42a)** possesses the stereochemistry corresponding to oxazolomycin C. Purification by column chromatography was performed with 1%

Et_3N in the eluent to neutralise the acidity of the silica. These results imply that the (*Z, E*) isomer **(3.12a)** reacts faster in the Stille coupling reaction.



Scheme 3.12: Variable ratios of stereoisomers obtained from the Stille coupling reaction.

Use of (*Z, E*)-iodide **(3.12a)** in the Stille reaction (8:1 ratio of isomers, 1.3 eq) with a reaction time of 24 hrs gave a 74% yield of a 1.2:1 mixture of (*Z, Z, E*) : (*Z, E, E*) racemic triene products **(rac-3.43a)** and **(rac-3.42a)**. This surprising result suggested that triene equilibration might also be complicating the reaction, since on the basis of the earlier results, (*Z, Z, E*) **(rac-3.43a)** would have been expected to be the major product to a much greater degree.

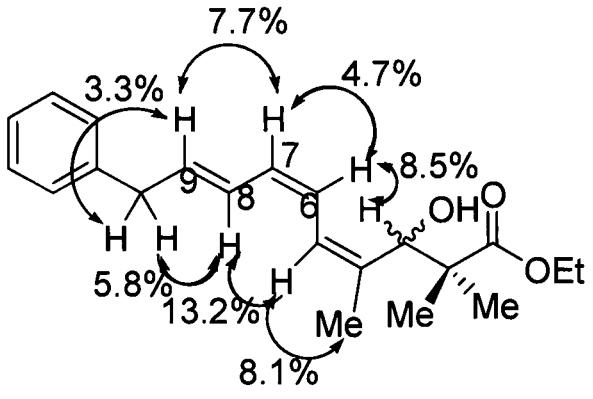
Stability Studies

^{1}H NMR spectroscopic analysis showed that a mixture of **(rac-3.43a)** and **(rac-3.42a)** (1:1), when treated with $PdCl_2(MeCN)_2$ in deuterated DMF for 24 hrs, did not lead to a change in stereoisomer ratio, indicating that these compounds were stable under the Stille conditions. However, experiments using iodides **(3.12a,b)** in deuterated DMF indicated rapid conversion of (*E, E*)-**(3.12b)** to (*Z, E*)-**(3.12a)** (but not the reverse process) over a 16 hr period at RT in the absence of Pd(0) catalyst, but that both **(3.12a)** and **(3.12b)** do not isomerise when stored at -20° C; thus, it would appear that equilibration of starting material rather than of product is responsible for the variable product ratios from the Stille reaction leading to **(rac-3.43a)** and **(rac-3.43b)**. Iodine

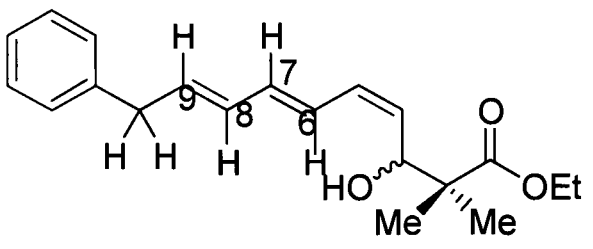
is well known to isomerise carbon-carbon double bonds and the presence of iodine could easily result from impurities from previous steps.

When the Stille coupling reaction of (*E, E*)-iodide **(3.12b)** (as a 3:1 (*E, E*) : (*Z, E*) mixture, 1.3 eq) with stannane **(rac-3.18)** at low temperature (-20° C) was investigated, the products **(rac-3.42a)** and **(rac-3.43a)** were obtained in 42% yield and a 3:1 ratio. Thus it would appear that the Stille coupling proceeds with retention of the stereochemistry inherent in the vinyl halide as would be expected, and it is the instability of the vinyl halide coupling partner that contributes to the previously observed outcome of apparent stereochemistry inversion. When the isomerisation of the vinyl halide isomers is controlled by low temperature, the resulting Stille reaction proceeds to completion with retention of stereochemistry as should be expected.

Stereoisomers **(rac-3.42a)** and **(rac-3.43a)** are not readily separable by column chromatography. The stereochemistry of the major product (*Z, Z, E*) **(rac-3.43a)** was established through careful and detailed ^{1}H NMR analysis, augmented with n.O.e. investigation. (Fig. 3.3).



(*Z, Z, E*)-isomer **(rac-3.43a)**: $J_{6,7}$ 11.7 Hz; $J_{8,9}$ 14.8 Hz



(*Z, E, E*)-isomer **(rac-3.42a)**: $J_{6,7}$ 14.2 Hz; $J_{8,9}$ 14.0 Hz

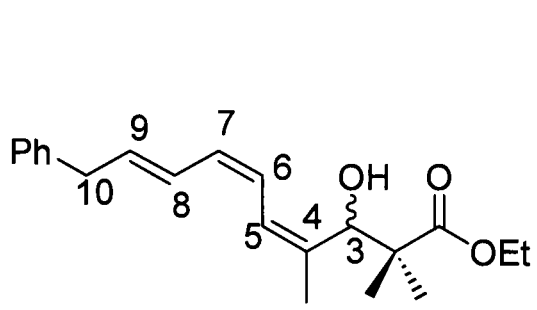
Fig. 3.3: n.O.e. enhancements and coupling constants for triene **(rac-3.43a)** and coupling constants for **(rac-3.42a)**

This spectroscopic analysis provided coupling constant values for the (*Z, Z, E*) isomer of $J_{6,7}$ 11.7 Hz, $J_{8,9}$ 14.8 Hz and was further confirmed by n.O.e. experimentation (Fig. 3.3). The stereochemistry of **(rac-3.42a)** was assigned by coupling constant values of $J_{6,7}$ 14.2 Hz and $J_{8,9}$ 14.0 Hz. It proved serendipitous that both isomers were isolated, as 11.7 Hz lies on the borderline of both *cis* and *trans* stereochemistries and without both isomers, certain geometrical assignments would not have been possible.

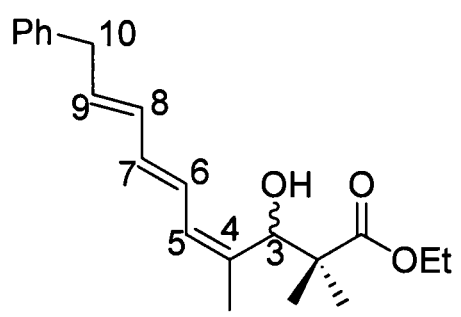
Isomerically pure (*Z, E*)-bromide **(3.37)** was subjected to the Stille coupling reaction, however the reaction was found to be unreliable, possibly due to the intrinsic lower reactivity of vinyl bromides and this was further confirmed by the lack of reactivity of stannane **(rac-3.18)** with commercially available benzyl bromide under Stille conditions, performed as a model reaction.

Hydrolysis of a 3:1 mixture of (*Z, Z, E*) : (*Z, E, E*) triene esters **(rac-3.43a)** and **(rac-3.42a)** with lithium hydroxide in a 1:1:1 solvent system of THF:water:MeOH yielded free acids **(rac-3.43b)** and **(rac-3.42b)** respectively in 70% yield (Scheme 3.8). These triene systems are analogues of the left hand side of oxazolomycin A and C respectively.

3.6 A Novel Method for the Spectroscopic Assignment of a Mixture of Polyenes



(*Z, Z, E*) - Oxazolomycin A **(rac-3.43a)**

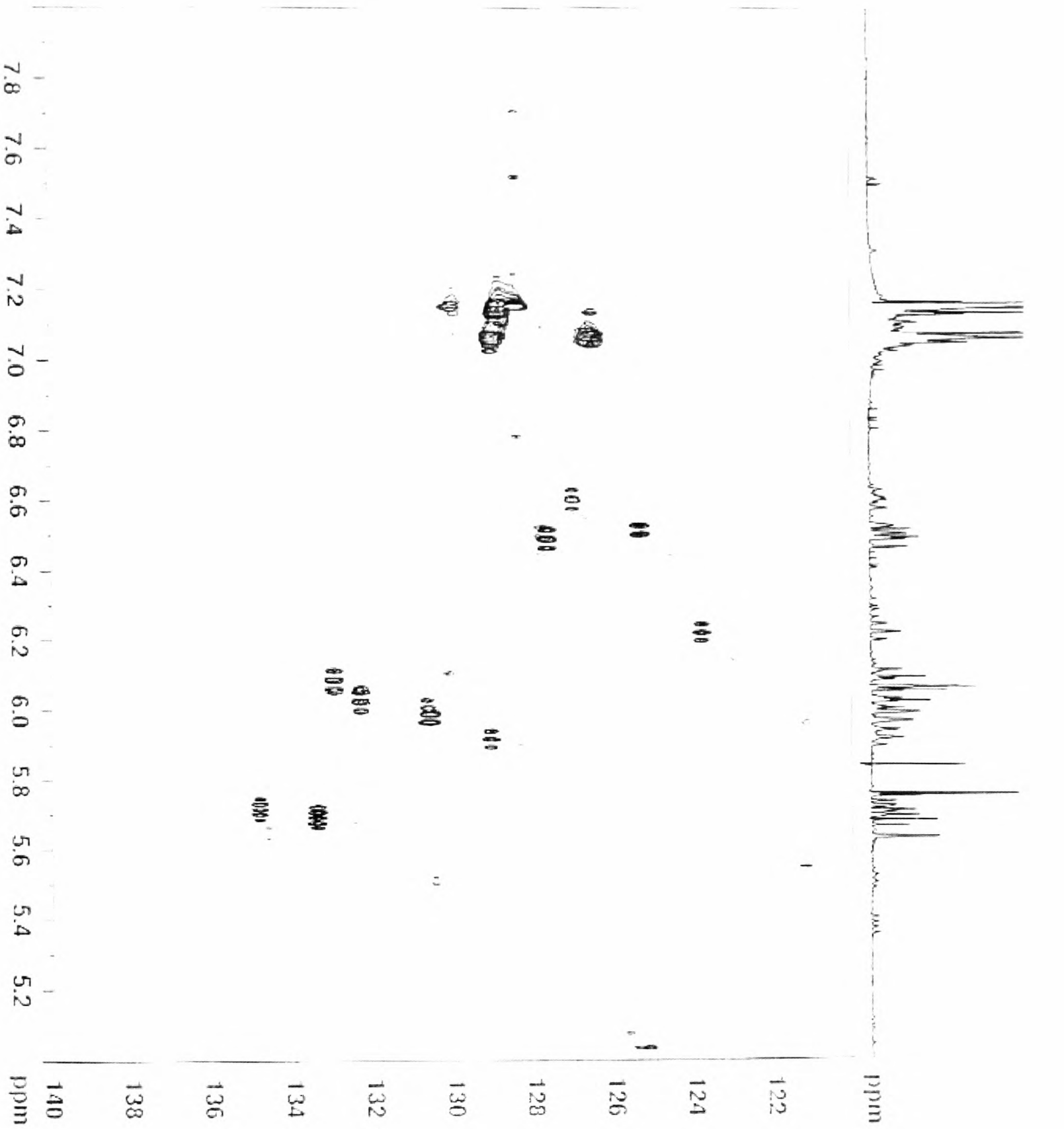


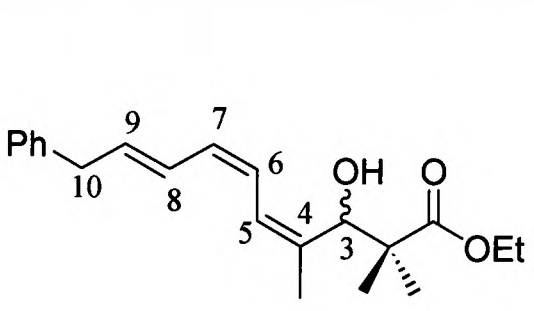
(*Z, E, E*) - Oxazolomycin C **(rac-3.42a)**

Mixtures of polyenes such as **(rac-3.42a)** and **(rac-3.43a)** result in heavily overlapped and complex spectra about the olefin region. The standard homonuclear decoupling used to determine coupling between atoms provides an even more complex pattern than the original ^{1}H spectrum, this being due to the fact that a single signal cannot be irradiated selectively, since whatever is overlapping the signal of interest is also irradiated.

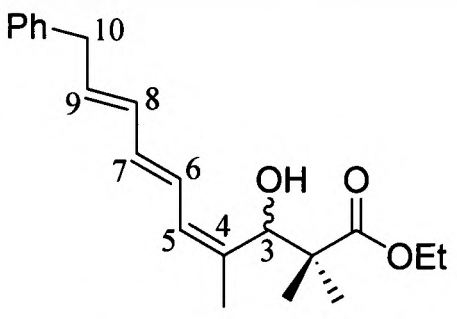
The solution, as presented here, is to tackle this problem *via* means of a different NMR based approach. Firstly, a high resolution COSY-90 was performed on the 3:1 (*Z, E, E*) : (*Z, Z, E*) mixture. Where the PhCH_2 (C-10 position) could be unequivocally assigned (or indeed any signal that could be unequivocally assigned), the remainder of the spectrum could then be assigned as far as possible.

The next step was to perform a high resolution $^{1}H/^{13}C$ coupling experiment - a HSQC (Heteronuclear Single Quantum Correlation). This is a 2D proton-detected heteronuclear shift correlation experiment which provides the same information as the closely related HMQC, that is, one-bond H-X (where X = Carbon) correlations. The principle advantage of HSQC is the slightly better resolution that can be obtained in the X-dimension, where the resonances are broadened by homonuclear proton couplings in HMQC, but not in HSQC. For most routine applications the difference is barely appreciable, but where crowding occurs in the X dimension, the HSQC provides better resolution (Fig 3.4).





(*Z, Z, E*) - Oxazolomycin A **(rac-3.43a)**



(*Z, E, E*) - Oxazolomycin C **(rac-3.42a)**

Fig 3.4: HSQC experiment performed on the olefin signature region of a 3:1 mixture of (rac-3.42a):(rac-3.43b)

The spectrum thus produced provides three valuable pieces of information (data summarised in Table 3.1).

1 The splitting patterns of each individual proton environment can be determined by the number of correlation cross-peaks they produce. For example H-7 centred on δ5.93, displays three clear spots correlating to the carbon resonance at 129 ppm whilst H-9 (δ5.72) shows five spots correlating to the carbon resonance at 134.8 ppm. Upon further experimentation, it was shown that H-7 provides a perfect double doublet (i.e. a triplet pattern) while H-9 shows a splitting pattern of five (i.e. a quintet).

2 From this HSQC spectrum, using computer editing, a slice can be taken through each position that exhibits coupling to provide a proton trace of the unique environment of each proton. Each trace is in itself a ^{1}H spectrum of just one proton, identifiable from the COSY-90 previously acquired. If this 'trace editing' is repeated for each position of interest, each proton with its splitting pattern can be seen. By lining up each of these traces and overlapping them onto the original ^{1}H spectrum *via* the use of the appropriate editing software, each proton can easily be identified within the original spectrum. When done with both the major (Fig 3.5) and minor isomers (Fig 3.6), each separate proton on both separate isomers can be observed in the original spectra. In addition to this valuable information, the coupling constants for each proton can be determined from the 'trace experiments' in the usual way.

3 A high resolution expansion of the relevant region of the original spectrum is performed and the 'trace experiments' overlapped on top of the expansion *via* the aid of computer software and the coupling constants can again be determined from the original spectrum. This would not be possible from just the expansion alone as fine coupling is observable in addition to the HSQC trace predicted splitting pattern. This is most pronounced for protons H-8, H-5 and H-9 due to the allylic coupling with the C-10 position and gem-dimethyl group.

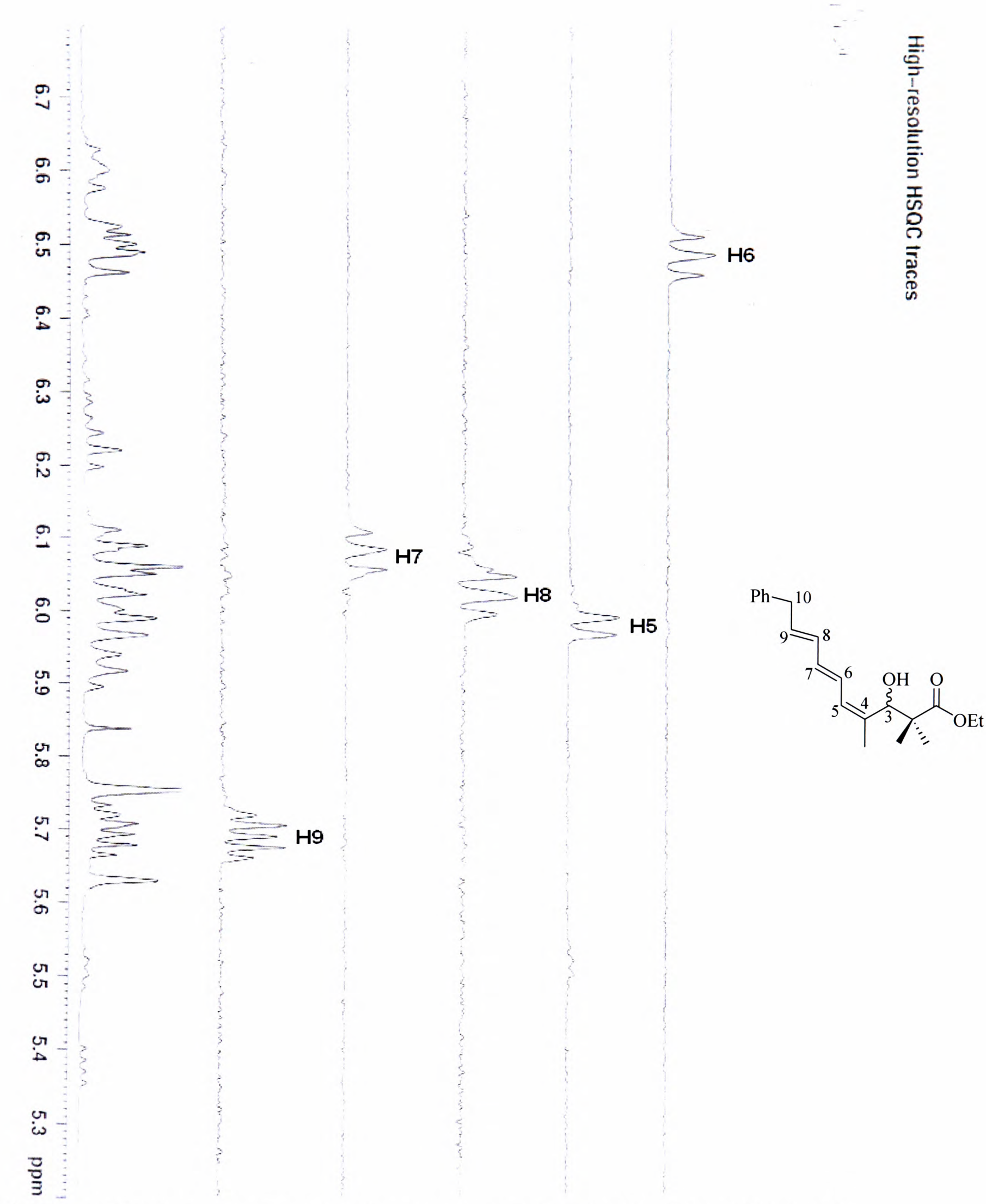


Fig 3.5: HSQC 'slice' traces of individual proton environments of the major isomer (rac-3.42a)

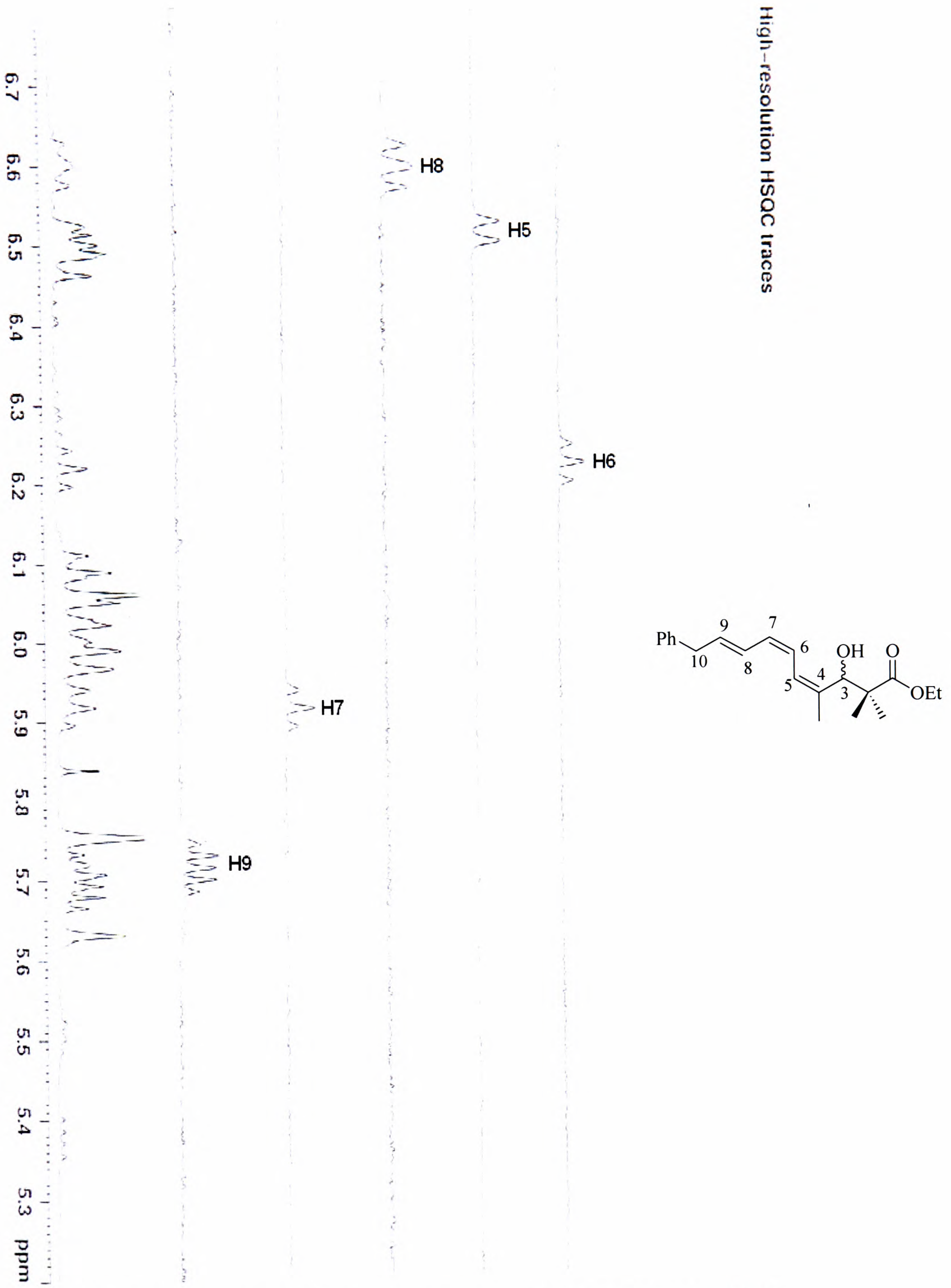


Fig 3.6: HSQC 'slice' traces for individual proton environments of the minor isomer (rac-3.43a)

In the major isomer, H-9 shows a 14.7 Hz coupling, H-8 shows a 14 Hz coupling, H-7 a 14 Hz coupling and H-6 a 14.2 Hz coupling, thus indicating an (*E, E*) system.

In the minor isomer, H-9 shows a 14.7Hz coupling and H-8 shows a 14.8 Hz coupling, characteristic of a *trans*-geometry. However, H-7 shows a 11.4 Hz coupling and H-6 shows a 11.7 Hz coupling. Both values are in the common region between *cis*- and *trans*-isomers and are therefore inconclusive. It is therefore advantageous that a mixture of the two compounds had been produced since this allowed for direct comparison of both spectra. A value of 14.1Hz of the major isomer is certainly *trans*- while the minor isomer is different from the major as shown by the COSY-90. Therefore it can be determined that for this system, a value of 11.4 Hz is indicative of a *cis*-coupling, and hence an (*E, Z*) system is identified.

In addition to the proton evidence for the stereochemistry, the HSQC spectrum shows a pronounced shift in the values of the carbon positions between the major and minor compound. Thus; C-8 and C-5 move upfield (decrease ppm) and C-7, C-9 and C-6 move downfield (increase ppm).

This effect can also be used to further support the assignment of geometry of the C=C bond. The ^{13}C shift of carbons with a single proton substituent in a *trans*- or *cis*-environment varies between typically 5 or 6 ppm. In general, the chemical shift for *trans*- stereochemistries is displaced downfield (higher ppm values) whilst *cis*-stereochemistries exhibit displacements up field (lower ppm values). This effect is due to steric crowding around the *cis*-bond (Fig 3.7).

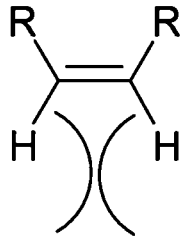


Fig 3.7: Steric Crowding around olefin centre

The vinylic protons provide a shielding effect that reduces the shift value for their attached carbons.

Finally, the geometry of the remaining C=C double bond (C(4) - C(5)) was determined by conventional n.O.e. experimentation. A long range, strong coupling between H-5 and C(4)Me is indicative of a (*Z*) stereochemistry in both the major and minor isomers. Standard techniques provide identification of the substituents and thus the overall compound structure can be assigned.

Major Isomer:

Proton	Coupling	Comment
H-9	7 Hz, 14.7 Hz	First order
H-7	11.4 Hz, 14 Hz	Second order
H-8	11.7 Hz, 14.3 Hz	Long range coupling to CH_2, 2^{nd} Order
H-5	12.1 Hz	Long range coupling to Me
H-6	11.7 Hz, 14.2 Hz	

Minor Isomer

Proton	Coupling	Comment
H-9'	7.3 Hz, 14.7 Hz	First order
H-7'	11.4 Hz, 11.4 Hz	First order
H-8'	11.2 Hz, 15 Hz, 14.8 Hz	First order, long range coupling to CH_2
H-5'	12.5 Hz	Long range coupling to Me
H-6'	11.7 Hz, 11.7 Hz	

Carbon chemical shift values (' numbers indicate minor isomer)

C-8'	127.0 ppm	
C-8	132.3 ppm	Difference = 5.3 ppm
C-7'	129.0 ppm	
C-7	133.0 ppm	Difference = 4 ppm
C-6'	123.8 ppm	
C-6	127.6 ppm	Difference = 3.8 ppm
C-5'	125.3 ppm	
C-5	130.6 ppm	Difference = 5.3 ppm
C-9'	134.8 ppm	
C-9	133.4 ppm	Difference = 1.4

Table 3.1: ^{1}H and ^{13}C NMR data for compound **(rac-3.43a)**

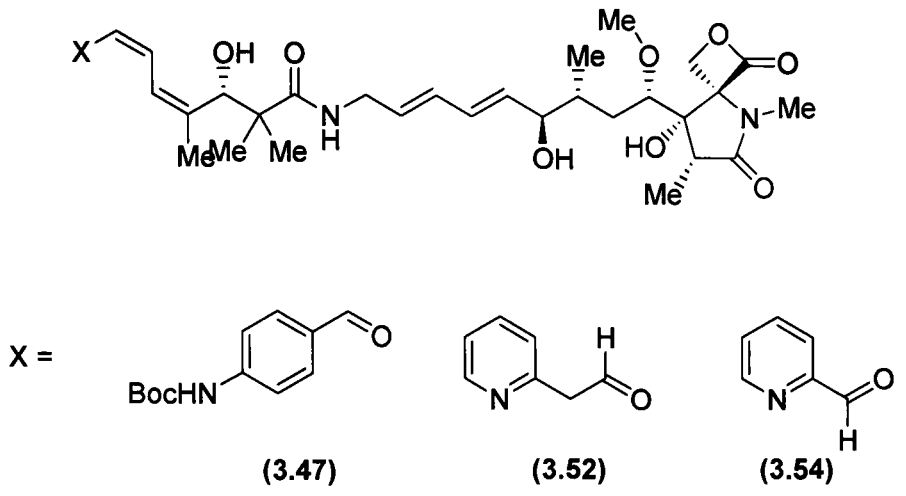
3.7 Investigations into Further Left Hand Side Triene Analogues

With a credible synthetic route in hand to provide access to both (*Z, Z, E*) and (*Z, E, E*) isomers of the phenyl analogue, attention was turned to the generation of a 'library' of compounds possessing differing aromatic termini.

The goal of this project was to gain a greater understanding of the unique biological mode of action of the oxazolomycin group of compounds. To this end, since the proposed mode of action was of protonophoric membrane bridging, it was decided to construct truncated analogues of the left hand side triene system, to investigate the effect on biological activity of shortening the molecule's length. The simplest way of achieving such truncated analogues would be by elimination of the C(10) CH_2 spacer unit. By careful selection of starting material, this 'spacer' unit could easily be manipulated, yet retain the same synthetic pathway which had been developed for construction of the triene system as described earlier in this chapter.

It was hoped that replacing the original oxazole terminus with a pyridine terminus would provide a substantial change in the biological properties of the compound, which could be used to further define the mode of biological acion of this unique class of natural product. If oxazolomycin acts as a protonophore, then introduction of a basic terminus might be expected to significantly alter its bioactivity.

It was with these considerations that the following analogue targets were investigated (Scheme 3.13).



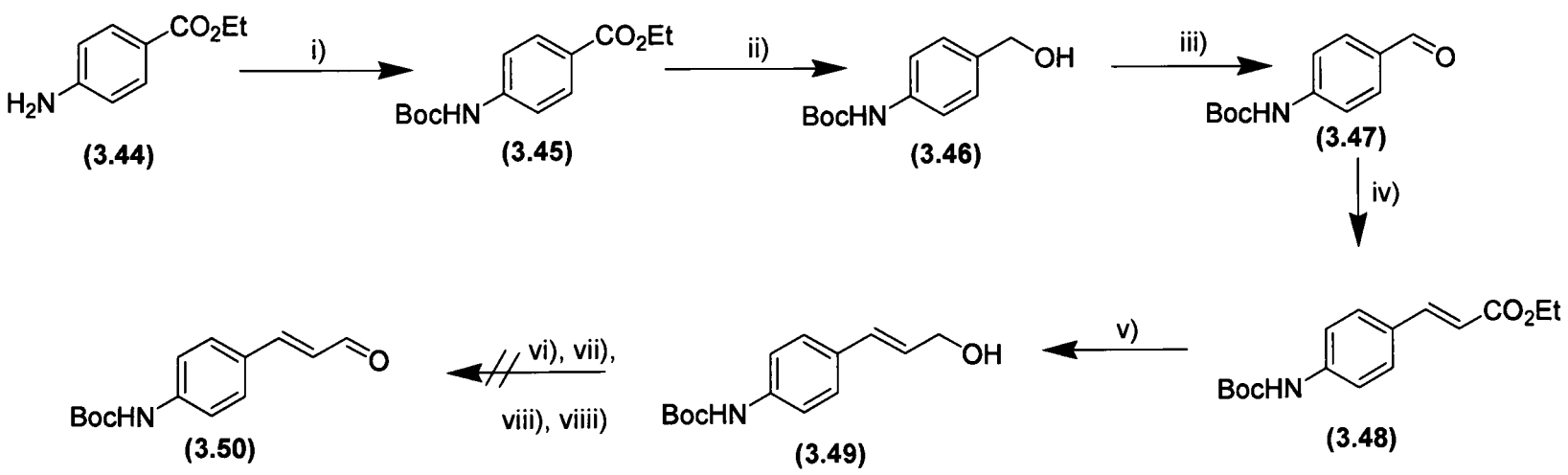
Scheme 3.13: Selection of analogue targets.

The introduction of a *para*-amino substituent onto the phenyl terminus of the triene system would be the first analogue attempted. This analogue would also be a truncated analogue due to the absence of the CH_2 (C(10)) spacer unit which is present in oxazolomycin.

Two pyridine analogues would also be investigated, utilising the appropriate commercially available alcohol as starting material, one possessing the CH_2 spacer unit and one without.

3.8 Investigation of Truncated *para*-amino Substituted Phenyl Analogue

Access to this analogue was based upon commercially available ethyl,4-aminobenzoate **(3.44)** (Scheme 3.14).



Scheme 3.14: Synthesis towards a *para*-nitro substituted phenyl analogue.

Boc protection of the amine functionality using standard literature methodology[80] proceeded in good yield (76%), to provide the protected urethane **(3.45)**.

DIBAL-H reduction of ethyl ester **(3.45)** yielded primary alcohol **(3.46)** in good yield (71%). PCC oxidation followed by Wittig olefination provided (*E*)-olefin **(3.48)** again in good yield (79%). The stereochemistry of the olefin functionality was assigned by ^{1}H NMR spectroscopy, with a vinylic coupling constant of 15.9 Hz. Whilst the crude reaction product was purified by column chromatography, it was found that the Wittig olefination in this case proceeded stereoselectively, and at no point was any of the (*Z*)-olefin isomer isolated. DIBAL-H reduction of ethyl ester **(3.48)** proceeded in a poor, unoptimised yield (11%).

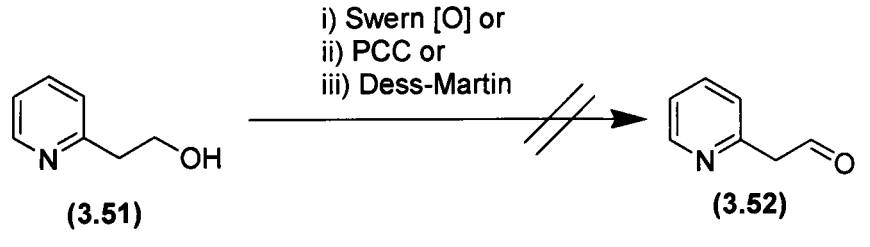
Several oxidisng reagents were employed to convert alcohol **(3.49)** to aldehyde **(3.50)**, however, neither employment of pyridinium chlorochromate, DMSO, oxalyl chloride and Et_3N, *o*-iodoxybenzoic acid[81] or manganese(IV) oxide all failed to yield any observable product and only returned unreacted starting material.

With the disappointingly low yield of the reduction to afford alcohol **(3.49)** and the apparent inability of standard oxidising methodology to provide a route to the desired aldehyde, further progress along this route to the *p*-aminophenyl analogue was deemed unlikely and so the pathway was abandoned.

3.9 Investigation of a Pyridine Analogue

A terminal pyridine aromatic residue analogue might be synthesised directly by employing the same synthetic route developed for the phenyl analogue, however starting not with phenylacetaldehyde but with the appropriate pyridylacetaldehyde.

Thus to this end, commercially available 2-pyridin-2-ylethanol **(3.51)** (Scheme 3.15) was exposed to a variety of common oxidising reagents.

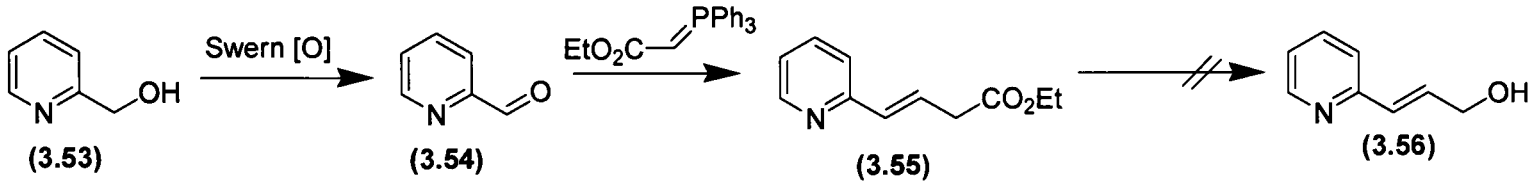


Scheme 3.15: Attempted oxidation of 2-pyridin-2-ylethanol.

Swern, PCC and the Dess Martin[81] methodologies all failed to deliver the necessary aldehyde **(3.52)**. In all cases, purification by column chromatography yielded the starting alcohol as the sole product.

3.10 Investigation of a Truncated Pyridine Analogue

Commercially available 2-pyridinemethanol **(3.53)** readily undergoes oxidation under standard Swern conditions to provide aldehyde **(3.54)** in excellent yield (76%). PCC oxidation however, performed on the same alcohol, yielded no trace of the desired aldehyde. Wittig olefination using (carboethoxymethylene)triphenylphosphorane proceeded in a completely stereoselective manner to yield exclusively (*E*)-olefin **(3.55)** in again, excellent yield (79%) (Scheme 3.16).



(3.53) (3.54) (3.55) (3.56)

(3.57)

Scheme 3.16: Studies towards the synthesis of a truncated pyridine analogue.

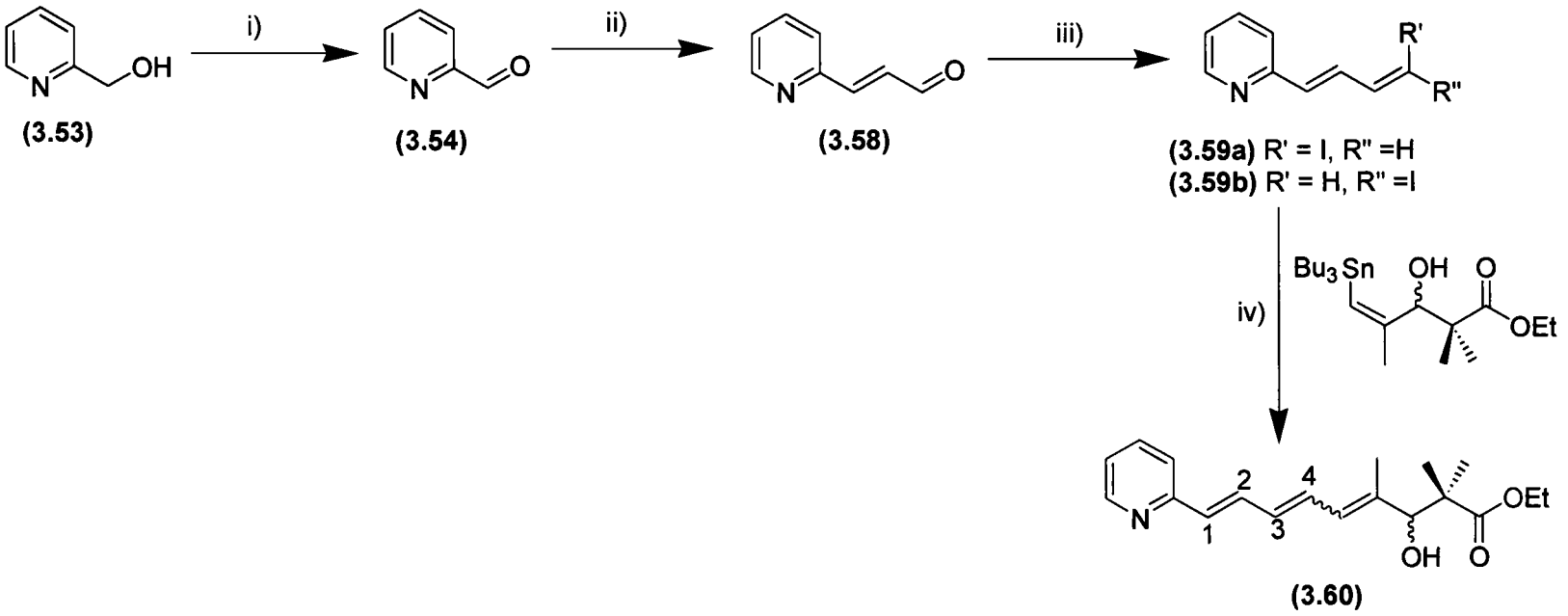
Reduction of ethyl ester **(3.55)** with DIBAL-H provided not the desired primary alchohol **(3.56)** but instead completely reduced alcohol **(3.57)** in trace amounts. The structure was confirmed by the presence of multiple CH_2 peaks in the ^1H NMR spectra and the absence of aromatic signals. Such an observation is contrary to the general reduction rates of DIBAL-H, which has been shown[82] to reduce pyridine substantially more slowly (24 hrs) than ethyl esters (0.5 hrs) in the formation of aldehydes.

Partial reduction from ester to aldehyde results from the relative stability of the hemiacetal intermediate that is formed. The aldehyde is not liberated until the hydrolytic work up, and is therefore not subject to over-reduction. At higher temperature, where the intermediate undergoes elimination, DIBAL-H reduces esters

to primary alcohols. However, even if temperature control was not totally accurate in the reaction, this would not explain the reduction of the pyridine system.

With this route proving problematic, it was decided to examine a Wittig homologation using commercially available (formylmethylene)triphenylphosphorane. It was found that this underwent stereoselective Wittig olefination with pyridine aldehyde **(3.54)** to afford (*E*)-olefin aldehyde **(3.58)** in excellent yield (71%) and complete stereochemical control (100% (*E*)-isomer) (Scheme 3.17).

Thus aldehyde **(3.58)** became available in gram quantities from a two step synthesis. Application of the Takai homologation to aldehyde **(3.58)** yielded an inseparable 1:1 mixture of (*Z, E*) : (*E, E*) olefin isomers of vinyl iodides **(3.59a,b)** in low yield (26%) compared to that of the phenyl analogue. The stereochemistry was assigned by ^{1}H NMR analysis; thus (*Z, E*)-iodide **(3.59a)** exhibited coupling constants of $J_{1,2}$ 7.6 Hz and $J_{3,4}$ 15.5 Hz, whilst (*E, E*)-iodide **(3.59b)** exhibited coupling constants of $J_{1,2}$ 10.9 Hz and $J_{3,4}$ 15.5 Hz.

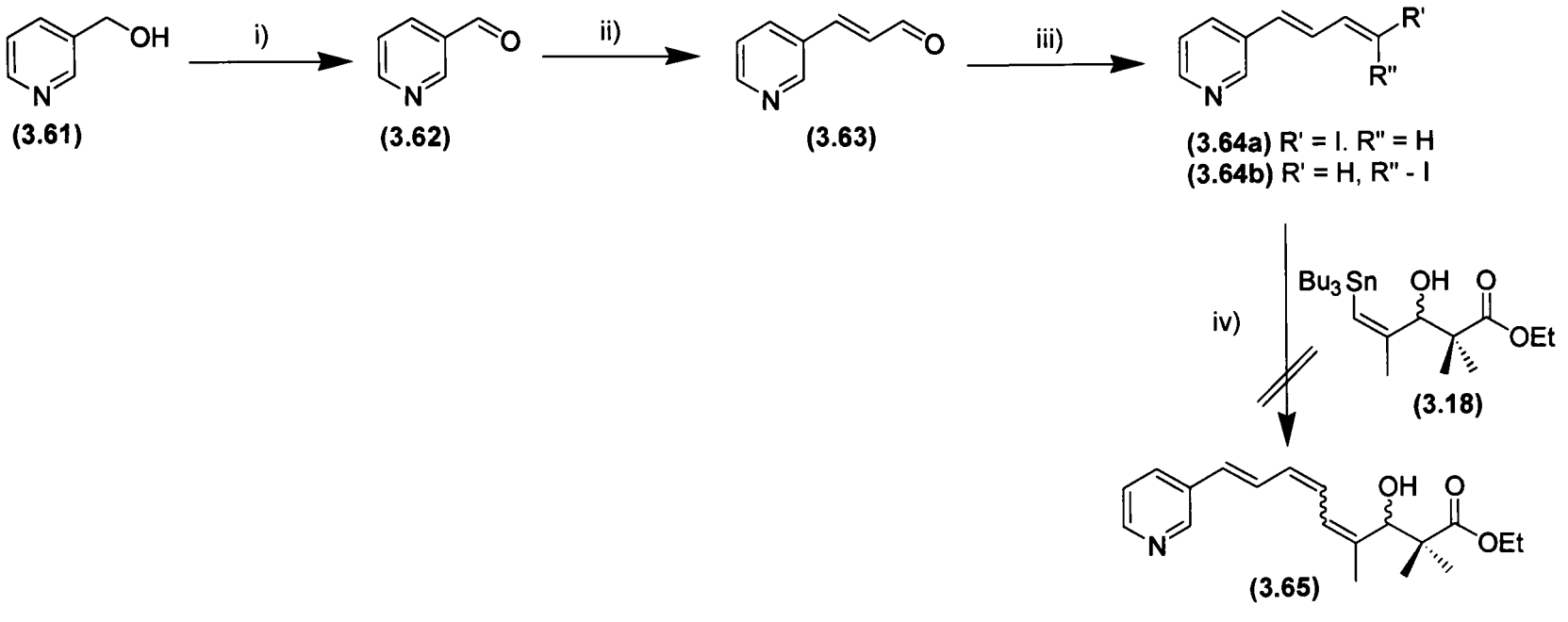


i) $(COCl)_2$, DMSO, NEt_3, DCM, 76%; ii) Ph_3P=CHCHO, DCM, 71% (100% *E*); iii) $CrCl_2$, CHI_3, THF, 26%; iv) $PdCl_2(MeCN)_2$, THF, **(rac-3.18)**, 49%

Scheme 3.17: Synthesis of a truncated pyridine triene analogue.

Stille coupling under standard conditions ($PdCl_2(MeCN)_2$, DMF, 14 hrs, RT) employed upon stannane **(rac-3.18)** and vinyl iodide mixture **(3.59a,b)** yielded, in moderate yield (49%, based on recovered starting material), a racemic 3:1 mixture of (*Z, Z, E*) : (*Z, E, E*) trienes **(rac-3.60)** along with four other unidentified impurities. Application of NMR techniques previously described in Section 3.6 provided unequivocal assignment of the stereochemistry, namely (*Z, Z, E*)-isomer $J_{1,2}$ 15.5 Hz and $J_{3,4}$ 7.6 Hz and (*Z, E, E*)-isomer $J_{1,2}$ 15.4 Hz and $J_{3,4}$ 11.8 Hz.

With the 2 substituted pyridine triene analogue in hand, attention was turned to a 3-substituted pyridine terminal moiety, and to this end, commercially available pyridyl-3-carbinol **(3.61)** was subjected to Swern oxidation in good yield (71%) (Scheme 3.18).



i) $(COCl)_2$, DMSO, NEt_3, DCM, 71%; ii) Ph_3P=CHCHO, DCM, 74% (100% *E*); iii) $CrCl_2$, CHI_3, THF, 34%; iv) $PdCl_2(MeCN)_2$, THF, **(rac-3.18)**

Scheme 3.18: Synthesis of a 3-substituted pyridine triene analogue.

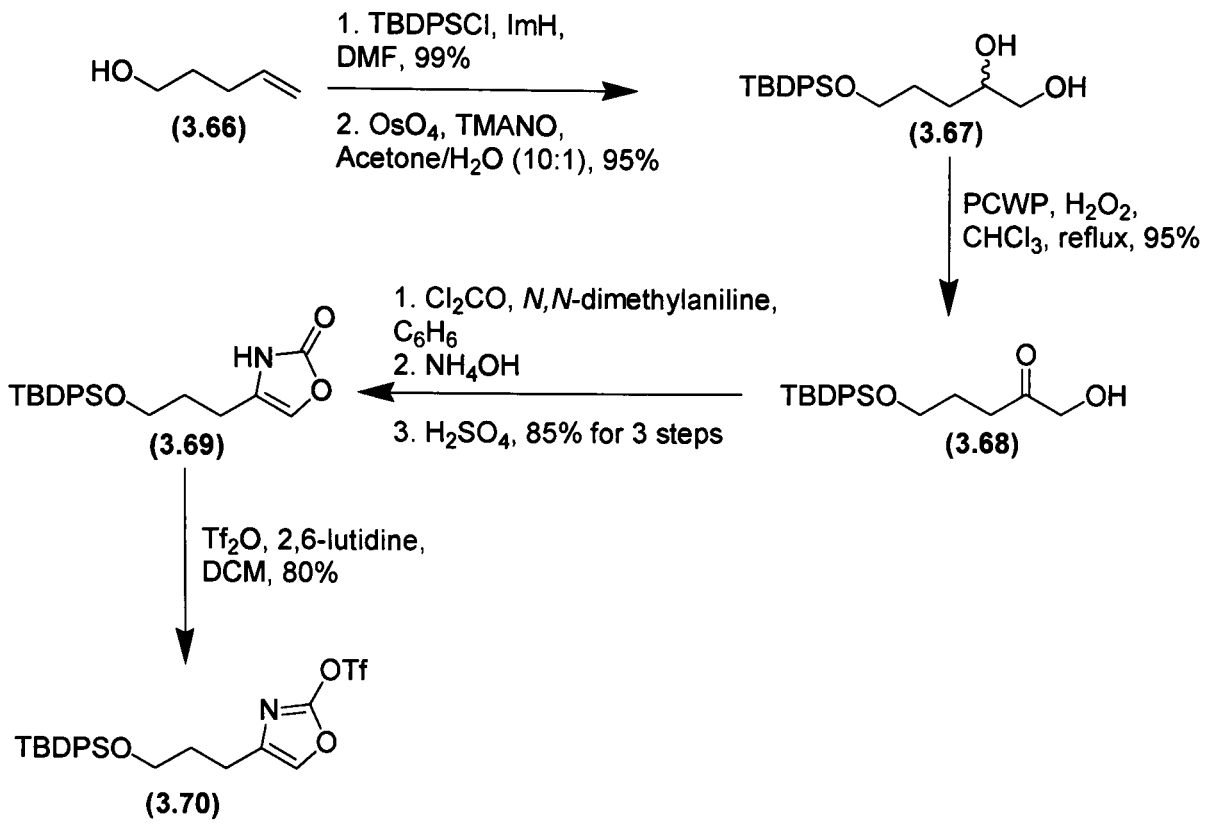
Stereoselective Wittig olefination with commercially available (formylmethelene)triphenylphosphorane proceeded in 74% yield and excellent 100% stereoselectivity to yield (*E*)-olefin **(3.62)**. This compound was readily purified by acidic wash, making use of the basic character of the pyridine residue; this allowed easy removal of the residual triphenylphosphine oxide. Takai homologation using standard reagents and conditions provided in somewhat poor yield (34%) a 1:1 mixture of (*E, E*) : (*Z, E*) vinyl halides **(3.64a,b)**. Application of standard Stille coupling conditions to stannane **(rac-3.18)** and vinyl iodide mixture **(3.64a,b)** failed to provide the expected triene product **(rac-3.65)** and instead yielded only unreacted stannane **(rac-3.18)**.

Whilst the failure to synthesise a truncated 3-substituted pyridine analogue of the left hand side triene system was disappointing, it should be borne in mind that only one attempt at the pivotal Stille coupling reaction was attempted and this was performed on a small scale. Given sufficient resources to continue investigation of this chemistry, a truncated 3-substituted pyridine analogue should be obtainable by optimisation of the coupling step.

3.11 Investigations towards the Synthesis of an Oxazole Terminus

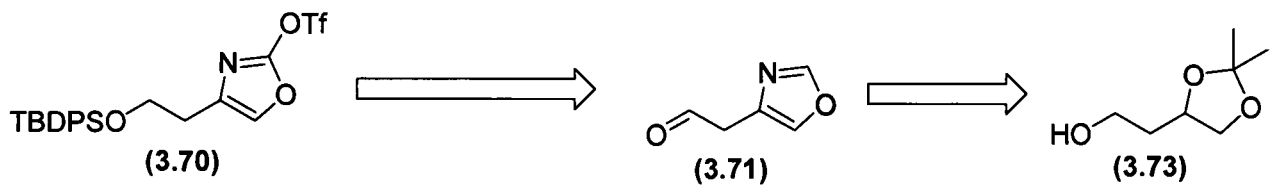
Panek *et al.*[83] recently published a synthesis of the C1'-C11' oxazole-containing side chain of leucascandrolide A. The synthesis relied upon a cross-coupling reaction of two fragments, one of which could conceivably, with slight modification, be utilised in a synthetic scheme to furnish the naturally occuring oxazole containing left hand side of oxazolomycin.

Panek's synthesis (Scheme 3.19) of this fragment **(3.70)** began with the protection of commercially available 4-penten-1-ol **(3.66)** as its TBDPS ether and subsequent dihydroxylation of the resulting silyl ether with osmium tetroxide to afford diol **(3.67)** in 95% yield. Selective oxidation of the secondary alcohol using the conditions described by Ishii,[84] (1.6 ml % of peroxotungstophosphate (PCWP) and hydrogen peroxide), gave hydroxyketone **(3.68)** in excellent yield. Cyclisation was accomplished using a three-step one-pot protocol. Treatment of **(3.68)** with a solution of phosgene in toluene, followed by exposure to aqueous NH_4OH, and then brief acidification (pH <3.5) with concentrated H_2SO_4 afforded oxazolone **(3.69)**. Treatment of this oxazolone with 2,6-lutidine in the presence of trifluoromethanesulfonic anhydride (Tf_2O) gave the desired trifloyloxazole **(3.70)**, which, due to its chemical instability, had to be used immediately.



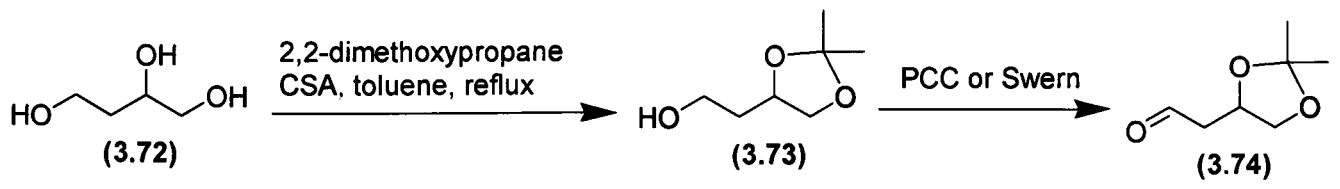
Scheme 3.19: Panek's synthesis of oxazole fragment **(3.70)**.

Compound **(3.70)** resembles very closely the compound which would be required to undergo the synthetic pathway developed herein to provide the naturally occurring left hand side triene fragment of the oxazolomycins (Scheme 3.20).



Scheme 3.20: Retrosynthesis of the required oxazole fragment for oxazolomycin.

As can be seen, compound **(3.70)** resembles the required oxazole compound necessary for construction of the naturally occurring left hand side triene fragment. The undesired OTf functionality could conceivably be removed *via* a palladium catalysed reduction. Thus aldehyde **(3.71)** would become the desired target. Since Panek had noted the chemical instability of the oxazole terminus, it was decided that formation of this functionality should be at the last possible opportunity and therefore protected triol **(3.73)** (Scheme 3.21) was considered as the starting material for this route.

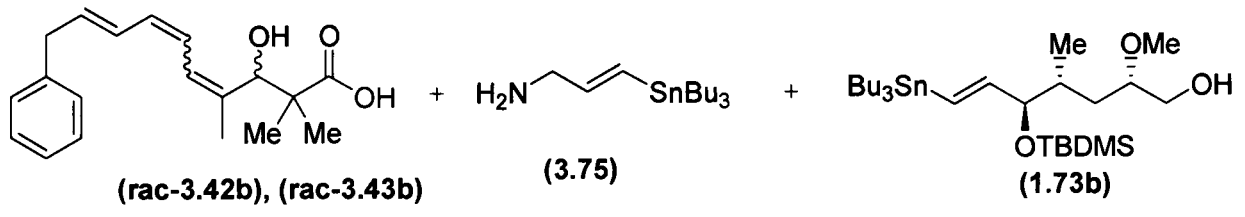


Scheme 3.21: Studies towards an oxazole triene fragement.

Commercially available 1,2,4-butanetriol **(3.72)** was protected as the acetonide *via* exposure to 2,2-dimethoxypropane and catalytic CSA, the reaction forced to completion by continuous removal of MeOH. Acetonide **(3.73)** was produced in moderate yield (44%), due, in part, to the formation of the less favoured 6-membered acetonide, as observed by NMR spectroscopy. Oxidation of alcohol **(3.73)** with PCC provided only a very poor (2%) yield of aldehyde **(3.74)**. Swern conditions were only marginally better (18%) yield. Protecting group manipulation of **(3.72)** and appropriate chemistry would be expected to provide the desired aldehyde **(3.74)**, this method should be considered as an alternative route to the oxazole terminus and is worthy of further study.

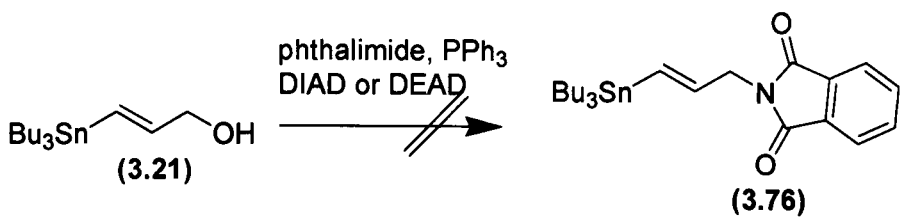
3.12 Investigation for Coupling Triene Fragments to the Central Fragment

Previous work from within the Moloney group has provided an efficient synthesis of the central fragment of oxazolomycin.[85] It was therefore decided to investigate methods for the coupling of the left hand side racemic phenyl trienes **(rac-3.42b)** and **(rac-3.43b)** to central fragment **(1.73b)** (Section 1.7.6). The method decided upon was construction of an (*E*)-olefin linker possessing amine and stannane functionalities to allow for amide bond formation to the left hand side triene fragment and a Stille coupling reaction to central fragment **(1.73b)** (Scheme 3.22). Either the stannane present in the allylic amine 'linker' unit or in fragment **(1.73b)** could easily be converted into a vinyl iodide functionality by reaction with I_2 in DCM.



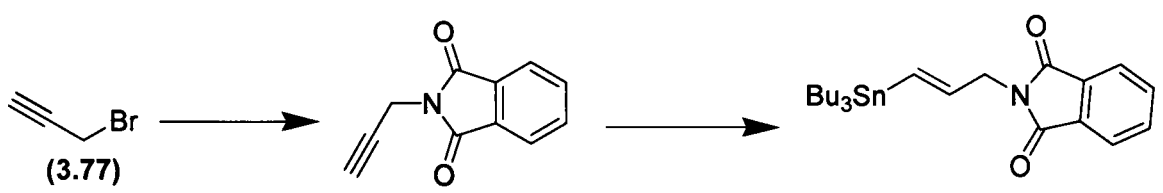
Scheme 3.22: Coupling of left hand side fragment to central fragment.

To this end, known stannane **(3.21)**, previously discussed as a route to the (*E, E, E*) triene system, was again synthesised in moderate yield (50%), according to a modified literature proceedure.[64] To introduce the required amine functionality, phthalimide was chosen as the reagent of choice. However, reaction of this alcohol with phthalimide and triphenylphosphine in dry THF either with DIAD or DEAD coupling agents failed to yield the expected stannane **(3.76)** (Scheme 3.23).



Scheme 3.23: Attempted synthesis of stannane **(3.76)**.

Given the failure of this route, an alternative strategy was sought (Scheme 3.24). Commercially available propargyl bromide **(3.77)** was reacted with potassium phthalimide at room temperature, recrystallisation yielded the desired alkyne **(3.78)** in good yield (71%). AIBN initiated free radical chemistry performed upon **(3.78)** with tributyltin hydride provided the expected (*E*)-stannane **(3.76),** albeit in poor yield (4%). The olefin geometry was assigned on the basis of a coupling constant of 18.6 Hz from ^{1}H NMR analysis. An alternative approach[86] making use of $Bu_3Sn(Bu)Cu(CN)Li_2$ generated *in situ*, provided the desired (*E*)-alkene (*J* 18.6 Hz) in even worse yield (<1%).

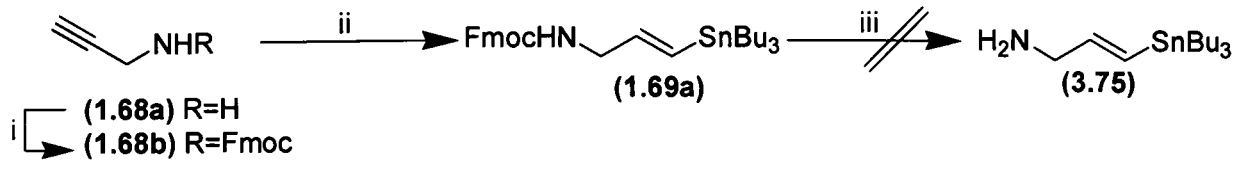


i) Potassium phthalimide, DMF, 71%; ii) AIBN, Bu_3SnH, toluene, 4% or $Bu_3Sn(Bu)Cu(CN)Li_2$, THF, 1%

Scheme 3.24: Synthesis of stannane **(3.76)**.

The disappointingly low yields of stannane **(3.76)**, perhaps due to protodestannylation during the purification step or the tin exerting a deleterious electronic effect on the system, would preclude further investigations along this synthetic route and therefore a different approach towards the linker unit was required.

As previously discussed (Section 1.7.6), Fmoc protected stannane **(1.69a)** had been successfully synthesised by Moloney[85] *en route* to the middle fragment of oxazolomycin (Scheme 3.25) and this chemistry was repeated to provide Fmoc protected stannane **(1.69a)** in a 32% overall yield.



i)Fmoc-Cl, py, DCM (30%); ii) Bu_3SnH, AIBN (35%), iii) TBAF, DMF

Scheme 3.25: Attempted synthesis of 'linker' unit **(3.75)**.

Attempts to deprotect the Fmoc group ($NaBH_4$ in $EtOH_{(aq)}$[87] or TBAF in DMF[88]) failed to provide (*E*)-amine, a 30% recovery of the protected amine was the only product isolated from column chromatography purification.

3.13 Conclusion

This chapter has described the successful synthesis of two analogues of the left hand side triene fragment - a racemic phenyl analogue and a racemic truncated 2-substituted pyridine analogue, possessing triene geometries corresponding to that of oxazolomycin A **(rac-3.43b)** and C **(rac-3.42b)** and a 1:1 mixture **(rac-3.50)**. Judicous choice of reaction conditions provided 3:1 mixtures of the phenyl analogue with either oxazolomycin A or oxazolomycin C stereochemistries in abundance over the other. A 1:1 mixture of oxazolomycin A and C stereochemistries was achieved for the truncated 2-substituted pyridine analogue. In all cases, these mixtures proved highly unstable, difficult to handle and inseparable by column chromatography. Despite this difficulty, total synthesis of two terminal residue analogues of racemic phthoxazolin A and racemic inthomycin B and C are presented.

Access to these compounds provides validation of the planned synthetic route. The synthesis presented in this chapter has several distinct advantages over the total synthesis of phthoxazolin A presented by Whiting. In their work, only relatively low quantities of both coupling partners and final product were accessible. Their final Stille coupling proved to be unreliable and low yielding.

In contrast, the synthesis presented herein provided access to relatively large quantities of trienes in moderate to good yields (72% and 42%). Indeed **(rac-3.43b)** and **(rac-3.42b)** were provided in 52% yield and in quantities above 100 mg. This was due in part to high yielding routes to the required coupling partners, the stannane (71%, 639 mg) and vinyl halides (69%, 340 mg), although unfortunately these were not diastereoisomerically pure.

Instability of the vinyl iodides at room temperature was overcome by performing the Stille reaction at low temperature, which resulted in retention of the desired geometry. Thus routes to both and oxazolomycin A (*Z, Z, E*) (*via* room temperature coupling) and oxazolomycin C (*Z, E, E*) (*via* low temperature coupling) have been developed. Both isomers have been completely characterised and match those reported of the natural products by ^{1}H and ^{13}C NMR, IR and UV methods. Although no problems were encountered with the stability of the final trienes, both compounds were difficult to purify by column chromatography due to the presence of organotin residues. The

resulting enhanced stability of the triene system is most likely attributable to the replacement of the oxazolyl residue with a phenyl group.

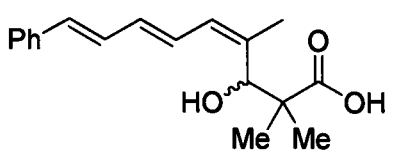
Throughout the developed pathways, the chemistry involved was not simple. The combined use of allyl-tin reagents, unstable iodine dienes, and sensitive palladium catalysts proved difficult to work with and extremely difficult to purify. Most column chromatography purification had to be performed in large diameter columns with equally large amounts of silica utilised.

In the course of characterising these complex mixtures of triene geometries a practical ^{1}H NMR spectroscopic technique has been identified to assign unequivocally each constituent isomer of the mixture.

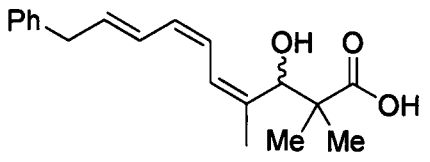
Three valuable synthetic intermediates have been synthesised *en route* to two new analogues of the left hand side triene system. Truncated 3-substituted pyridine vinyl iodide mixture **(3.64a,b)**, whilst failing to undergo Stille coupling after one attempt is certainly worthy of further investigation.

Boc-protected aldehyde **(3.47)** is an advanced intermediate towards the synthesis of a truncated nitro-substituted phenyl left hand fragment. It is postulated that aldehyde **(3.47)** could be exposed to the (formylmethylene)triphenylphosphorane Wittig reagent as employed in the synthesis of the pyridine analogue. This should allow direct access to aldehyde **(3.50)** in one step, thereby avoiding the difficulties encountered with reduction of the respective ester Wittig reagent. Further manipulation may be expected to provide access to the desired truncated *para*-amine substituted phenyl triene analogue.

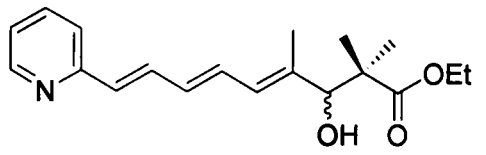
Aldehyde **(3.74)**, produced in 20% yield, would be expected to undergo further manipulation as described by Panek and thus provide a route to access the oxazole terminus present in oxazolomycin as an alternative route to the chemistry previously described in Chapter 1. Optimisation of conditions and possible protecting group manipulation would provide the aldehyde in sufficient quantities for further investigation.



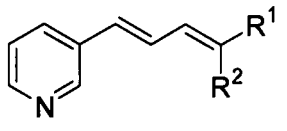
(rac-3.42b)



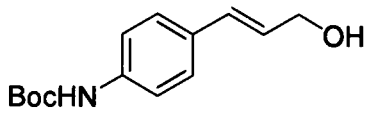
(rac-3.43b)



(3.50)



(3.64a) R^1 = I, R^2 = H
(3.64b) R^1 = H, R^2 = I



(3.49)

Fig. 3.5 Advanced intermediates synthesised in Chapter 3.

3.14 References

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CHAPTER 4 - EXPERIMENTAL

General Experimental Techniques

^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AM200 (200 MHz), Bruker DPX400 (400 MHz) or Bruker AM500 and AMX500 (500 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual protonated solvent peak. Abbreviations used in the description of multiplicities are s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz. Two dimensional COSY (correlation spectroscopy) spectra were measured at 500 MHz on a Bruker AM500 or a DPX400 spectrometer. Nuclear Overhauser experiments (n.O.e) and NOESY spectra were acquired on a Bruker AMX500 spectrometer and signal intensities recorded as the percentage enhancement.

^{13}C NMR spectra were recorded on Varian Gemini 200 (50.3 MHz) or Bruker AM200 (50.3 MHz), Bruker DPX400 (100 MHz) or Bruker AM500 and AMX500 (125.8 MHz) spectrometers. Chemical shifts are quoted in ppm and referenced to the residual protonated solvent peak with proton decoupling, using DEPT, HMQC, and HMSC editing to aid assignment.

Infrared (IR) spectra were recorded using spectroscopic grade $CHCl_3$ solutions or thin films using a Perkin-Elmer 1750 FT-IR or a Perkin-Elmer Paragon 1000 FTIR spectrometer. Only selected peaks are reported, absorption maxima being recorded in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w) or broad (br).

Low resolution mass spectra (*m/z*) were recorded on a Micromass Platform 1 spectrometer using atmospheric pressure chemical ionisation (APCI) in the positive or negative mode, or a VG Masslab 20-250 spectrometer using the chemical ionisation (CI) or positive argon fast atom bombardment (FAB). Gas chromatography mass spectra (GCMS) were recorded on a VG-Trio-1 spectrometer using chemical ionisation (CI) or (EI), all with ammonia as the ionising source. *m/z* values of major

peaks are reported in Daltons, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on VG ZAB-E spectrometer by manual peak matching and were conducted either within the Dyson Perrins Laboratory or at the National Mass Spectometry Service Centre, University College, Swansea.
Thin layer chromatography (TLC) was performed on Merck aluminium foil backed sheets precoated with 0.2mm Kieselgel 60 F_{254}. Product spots were visualised by the quenching of UV fluorescence (λ_{max} 254 nm), or by staining with a solution of 5% (w/v) dodec*a*molybdophosphoric acid in ethanol or a 0.1 M aqueous solution of $KMnO_4$ followed by heating. Retention factors (R_f) are quoted to the nearest 0.1 cm.

Flash column chromatography was performed upon silica gel (Sorbisil^{TM} C_{60} 40-60 μm).

Small scale reduced pressure distillations were performed using a horizontal Kugelröhr apparatus (Buchi GKR-51).

Dry DCM, dry toluene, dry benzene and dry Et_3N were obtained by distillation from calcium hydride (5% w/v) in a continuous still and stored over 4Å molecular sieves under argon. Dry $^{i}PrNH_2$ was obtained by atmospheric pressure distillation and stored over 4Å molecular sieves under nitrogen. Dry DMSO was obtained by reduced pressure distillation from calcium hydride (5% w/v), further dried over two batches of 4Å molecular sieves over a period of 48 hours and stored over new 4Å molecular sieves under argon. Dry DMF was stirred from calcium hydride (5% w/v) overnight, filtered, distilled under reduced pressure and stored over new 4Å molecular sieves under argon.

THF was distilled from sodium/benzophenone under nitrogen prior to use. 30-40 and 40-60 petroleum ether (Petrol) refers to those fractions which distil at 30-40° C and 40-60° C respectively, these were distilled prior to use. Reagent grade chloroform was used as supplied. Diethyl ether was used as supplied, or if required dry, ether was distilled from sodium/benzophenone. All other solvents were used as supplied.

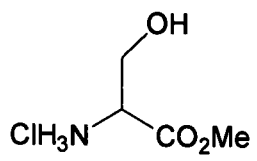
All reagents were obtained either from Aldrich Chemicals Ltd or Lancaster Chemicals Ltd and used as supplied, without further purification unless specified. Sodium

hydride was obtained as a 60% dispersion in mineral oil and was washed with petroleum ether (40/60) followed by drying under high vacuum prior to use. *n*-BuLi, *sec*-BuLi and LiHMDS were used as solutions in hexane and were standardised with diphenylacetic acid prior to use.

All reactions were performed under atmospheres of nitrogen or argon unless otherwise stated. Reaction times were recorded in hours (hrs) and minutes (mins). Solvents were removed at 40° C, unless otherwise stated, using a Büchi RE111 Rotary Evaporator attached to a Vacubrand CVC2 pump and pressure control system. Temperatures below 25° C were obtained using the following cold baths: 0° C (ice/water), -15° C (ethylene glycol/CO_2(s)), -50° C (acetonitrile/CO_2(s)), -78° C (acetone/CO_2(s)).

Experimental Details for Chapter 2 - The Right Hand Side Fragment

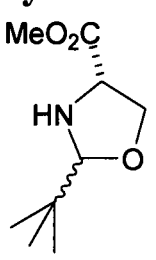
L-serine methyl ester hydrochloride[1,2]



Using the literature protocol, through a suspension of L-serine (4.23 g, 40 mmol) in MeOH (150 ml) was bubbled HCl gas (undried) until a saturated solution was obtained (4 hr). The mixture was stored at 0° C for 16 hrs and evaporated *in vacuo* to yield a white crystalline solid (5.88 g, 95%): m.p. 156-159° C; δ_H(200 MHz; D_2O) 3.72 (3H, s, CO_2CH_3), 3.85 (2H, t, *J* 6 Hz, CH_2OH), 4.12 (1H, m, $CHCH_2OH$).

Lit[3] m.p. 157-159° C; NMR: δ_H(200 MHz; D_2O) 3.65 (3H, s, CO_2CH_3), 3.85 (2H, m, CH_2OH), 4.08 (1H, m, $CHCH_2OH$).

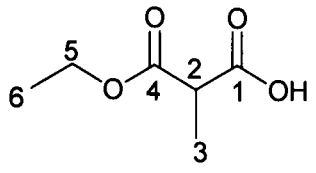
(4*S*)-2-*tert*-Butyl-4-methoxycarbonyl-1,3-oxazolidine (2.5)[1,4]



Using the literature protocol, to a suspension of finely powdered L-serine methyl ester hydrochloride (1.5 g, 9.6 mmol) in petroleum ether (bp 40° C – 60° C, 15 ml) was added NEt_3 (1.16 g, 11.5 mmol) and trimethylacetaldehyde (1.24 g, 14.4 mmol). The mixture was heated at reflux, with continuous removal of water for 24 hr, filtered and the residue washed with Et_2O (3 x 50 ml). The combined filtrates were evaporated *in vacuo* to yield a crude 1:1 mixture of *cis* and *trans* isomers as a pale yellow oil (1.14 g, 64%): δ_H(200 MHz; $CDCl_3$) 0.91 and 0.98 (9H, s, $C(CH_3)_3$), 2.65 (1H, br, N*H*), 3.6-4.4 (6H, m, CO_2CH_3, C(4)*H* and C(5)*HH'*) and 4.28 (1H, s, C(2)*H*); *m/z* (GCMS) 188 $[MH]^+$ (8%), 130 $[MH^+ - {}^tBu]$ (100%), 102 (20%).

Lit[1] NMR: δ_H(200 MHz; $CDCl_3$) 0.91 and 0.98 (9H, s, $C(CH_3)_3$), 2.45 (1H, br, N*H*), 3.6-4.1 (6H, m, CO_2CH_3, C(4)*H* and C(5)*HH'*) and 4.26 (1H, s, C(2)*H*).

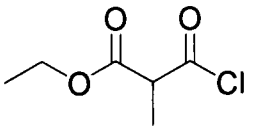
Ethylα-methylmalonic acid[1]



Using the literature protocol; to a solution of potassium hydroxide (8.05 g, 143.5 mmol) in EtOH (150 ml) at 0° C was added a solution of diethylα-methylmalonate (25g, 143.5 mmol) in EtOH (150 ml). The reaction mixture was stirred at RT for 2 hrs and at reflux for 30 mins. The solution was cooled, filtered and concentrated *in vacuo*. The residue was dissolved in H_2O (75 ml) and washed with petrol (2 x 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield unreacted starting material (2.57 g, 14.7 mmol, 10.2%). The aqueous layer was cooled to 0 °C, acidified (conc HCl) and extracted with Et_2O (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (6.37 g, 30%) as predominantly the **keto tautomer:** δ_H(200 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.45 (3H, d, *J* 7.4 Hz, $CHCH_3$), 3.47 (1H, q, *J* 7.4 Hz, $CHCH_3$), 4.22 (2H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$);

Lit[1] NMR: δ_H(200 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.47 (3H, d, *J* 7.5 Hz, $CHCH_3$), 3.50 (1H, q, *J* 7.5 Hz, $CHCH_3$), 4.24 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$).

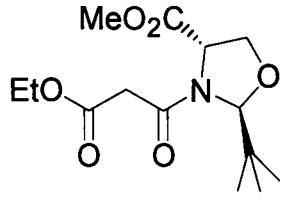
Ethyl-α-methylmalonyl chloride[1]



Using the literature protocol; to ethylα-methylmalonic acid (2 g, 13.6 mmol) was added neat thionyl chloride (10 ml, 6.8 mmol) and the solution heated at 40° C for 2 hrs. The excess thionyl chloride was evaporated *in vacuo*. Purification by Kugelröhr distillation (175° C / 4 mbar) yielded the title compound as a pale yellow oil (1.87 g, 84%): δ_H(200 MHz; $CDCl_3$) 1.31 (3H, t *J* 6.9 Hz, $CO_2CH_2CH_3$), 1.53 (3H, d, *J* 6.9 Hz, $CHCH_3$), 3.87 (1H, q, *J* 6.9 Hz, $CHCH_3$), 4.25 (2H, q, *J* 6.8 Hz, $CO_2CH_2CH_3$).

Lit[1] NMR: δ_H(200 MHz; $CDCl_3$) 1.32 (3H, t *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.54 (3H, d, *J* 7.0 Hz, $CHCH_3$), 3.86 (1H, q, *J* 7.0 Hz, $CHCH_3$), 4.27 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$).

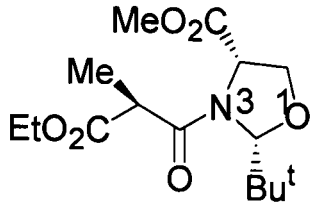
2-*tert*-Butyl-3-ethoxycarbonylacetyl-oxazolidine-4-carboxylic acid methyl ester (2.12)[5]



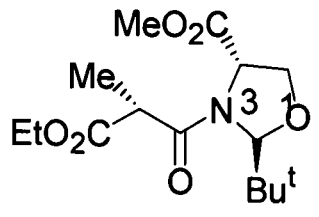
Using the literature protocol; to a stirred solution of oxazolidine **(2.5)** (1 g, 5.35 mmol, 1.0 eq), DMAP (60 mg, 0.495 mmol, 0.11 eq) and DCCI (1.74g, 8.68 mmol, 1.6 eq) in DCM (15 ml) at 0° C was added a solution of ethyl hydrogen malonate (1.11 g, 5.35 mmol, 1.0 eq) in DCM (5 ml). The reaction mixture was stirred at 0° C for 15 mins and then at RT for 5 hrs. The solution was filtered to remove dicyclohexylurea, washed with KH_2PO_4 (3 x 50 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude compound was dissolved in EtOAc:petrol (3:7 v/v) (10 ml), loaded onto a silica plug (100 ml) and washed through with EtOAc:petrol (1:19 v/v) (200 ml) and then EtOAc:petrol (1:1 v/v) (300 ml). The combined organic washings were concentrated *in vacuo* to yield the title compound as a yellow oil (1.51g, 94%); δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, $C(CH_3)_3$), 1.27 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 3.51 (1H, d, *J* 15.4 Hz, COCHH'CO), 3.69 (1H, d, *J* 15.4 Hz, COCHH'CO), 3.79 (3H, s, CO_2CH_3), 3.99 (1H, m, C(5)HH'), 4.23 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 4.56 (1H, m, C(5)HH'), 4.72 (1H, m, C(4)H), 5.34 (1H, s, C(2)H).

Lit[1] NMR: δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, $C(CH_3)_3$), 1.30 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 3.51 (1H, d, *J* 15.4 Hz, COCHH'CO), 3.69 (1H, d, *J* 15.4 Hz, COCHH'CO), 3.80 (3H, s, CO_2CH_3), 4.01 (1H, m, C(5)HH'), 4.22 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.56 (1H, m, C(5)HH'), 4.72 (1H, m, C(4)H), 5.33 (1H, s, C(2)H).

(2*R*, 4*S*)-2-(*tert*-Butyl)-4-methoxycarbonyl-3-(2'ethoxycarbonylpropanoyl)-oxazolidine (2.13b)[1]



(2.13a)



(2.13b)

Using the literature protocol; to a stirred mixture of oxazolidine **(2.5)** (1.06 g, 5.7 mmol) and pyridine (1.2 ml, 15 mmol) in DCM (25 ml) at 0° C was added ethylα-methylmalonoyl chloride (1.87 g, 11.4 mmol) dropwise. The reaction mixture was stirred at 0° C for a further 15 mins and for 5 hrs at RT. The solution was made up to 50 ml with DCM and washed with $NH_4Cl_{(aq)}$ (40 ml), 10% $NaHCO_3$ (40 ml), brine (40 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc increasing polarity to 3:2 v/v) yielded **(2.13a)** as a viscous colourless oil (530 mg, 30%), a 2:1 mixture of **(2.13a):(2.13b)** as a colourless viscous oil (830 mg, 46%) and **(2.13b)** (5 mg, 0.3%) as a colourless crystalline solid.

(2.13a): R_f 0.62 (4:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 0.88 (9H, s, C(CH_3)$_3$), 1.23 (3H, t, *J* 6.9 Hz, $CO_2CH_2CH_3$), 1.45 (3H, d, *J* 6.5 Hz, CH_3), 3.75 (1H, q, *J* 6.5 Hz, $CHCH_3$), 3.82 (3H, s, CO_2CH_3), 3.93 (1H, m, C-(5)H), 4.13 (2H, q, *J* 6.9 Hz, $CO_2CH_2CH_3$), 4.55 (1H, dd, *J* 2.0 Hz and 8.5 Hz, C(5)H*H'*), 4.91 (1H, dd, *J* 2.0 Hz and 6.9 Hz, C(4)*H*), 5.32 (1H, s, C(2)H).

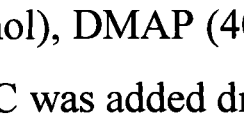
(2.13b): R_f 0.13 (4:1 petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.24 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.40 (3H, d, *J* 7.0 Hz, CH_3), 3.67 (1H, q, *J* 7.0 Hz, $CHCH_3$), 3.75 (3H, s, CO_2CH_3), 3.90-4.10 (3H, m, C(4)*H*C(5)H_2), 4.17 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 5.34 (1H, s, C(2)H).

Lit[1] NMR: **(2.13a):** δ_H(200 MHz; $CDCl_3$) 0.87 (9H, s, C(CH_3)$_3$), 1.24 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.46 (3H, d, *J* 6.5 Hz, CH_3), 3.76 (1H, q, *J* 6.5 Hz, $CHCH_3$), 3.79 (3H, s, CO_2CH_3), 3.95 (1H, m, C-(5)H), 4.16 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 4.56 (1H, dd, *J* 2.0 Hz and 8.5 Hz, C(5)H*H'*), 4.91 (1H, dd, *J* 2.0 Hz and 7.0 Hz, C(4)*H*), 5.33 (1H, s, C(2)H).

(2.13b): δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.25 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.40 (3H, d, *J* 7.0 Hz, CH_3), 3.68 (1H, q, *J* 7.0 Hz, $CHCH_3$), 3.76 (3H,

s, CO_2CH_3), 3.90-4.07 (1H, m, C(5)*H*), 4.18 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 4.42-4.60 (2H, m, C(4)*H*C(5)*H'*), 5.33 (1H, s, C(2)H).

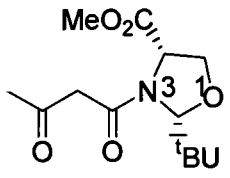
Acetoacetic acid[6]



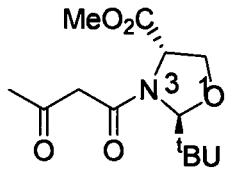
A solution of *tert*-butyl acetoacetate (2.00 g, 13.0 mmol) in TFA (5 ml) was stirred at RT for 16hr. The TFA was removed by co-evaporation with toluene to yield the title compound as a viscous colourless oil which was a 4:1 mixture of keto:enol tautomers (0.75 g, 57%): δ_H(200 MHz; $CDCl_3$) 2.15 (3H, s, C*H*$_3$, enol), 2.30 (3H, s, C*H*$_3$, keto), 3.50 (2H, s, C*H*$_2$, keto), 5.01 (1H, C*H*, enol) and 8.70 (1H, br, s, CO_2H).

Lit[3] NMR: δ_H(200 MHz; $CDCl_3$) 2.01 (3H, s, C*H*$_3$, enol), 2.33 (3H, s, C*H*$_3$, keto), 3.55 (2H, s, C*H*$_2$, keto), 5.05 (1H, C*H*, enol) and 7.95 (1H, br, s, CO_2H).

(2R, 4S)-3-Acetoacetyl-2-(*tert*-butyl)-4-methoxycarbonyl-oxazolidine (2.15a) and (2S, 4S)-3-acetoacetyl-2-(*tert*-butyl)-4-methoxycarbonyl-oxazolidine (2.15b)[6]



(2.15a)



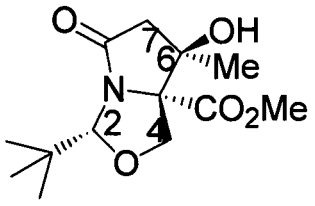
(2.15b)

Using the literature protocol; to a stirred solution of 2-*tert*-butyl-4-methoxycarbonyl-1,3-oxazolidine (800 mg, 4.27 mmol), DMAP (40 mg, 0.33 mmol) and DCCI (1.03 g, 4.99 mmol) in DCM (14 ml) at 0° C was added dropwise a solution of acetoacetic acid (0.51 g, 5.0 mmol) in DCM (6 ml). The mixture was stirred at 0° C for 15 mins then at RT for 4 hr. The reaction mixture was filtered to remove dicyclohexyl urea, the residue being washed with DCM (3 x 15 ml) and the combined filtrates were evaporated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded *cis*-oxazolidine (349 mg, 30%) as a yellow oil, a mixture of *cis*:*trans*-oxazolidine (165 mg, 14%) and *trans*-oxazolidine (16 mg, 1%) as a slightly silica unstable yellow oil. **Cis-oxazolidine:** δ_H(400 MHz; $CDCl_3$); **Keto-tautomer:** 0.89

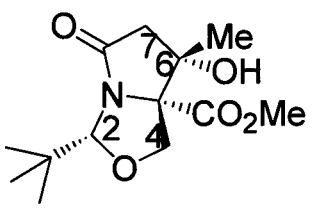
(9H, m, C(CH_3)$_3$), 2.30 (3H, s, CH_3C(O)), 3.65 (2H, s, CH_2), 3.75 (3H, s, CO_2CH_3), 4.23-4.33 (3H, m, C(4)*H* and C(5)H_2) and 5.30 (1H, s, C(2)*H*); **Enol-tautomer:** 0.95 (9H, m, C(CH_3)$_3$), 1.95 (3H, s, CH_3C(OH)), 3.75 (3H, s, CO_2CH_3), 4.23-4.33 (3H, m, C(4)*H* and C(5)H_2), 5.12 (1H, s, C(OH)=C*H*C(O)) and 5.30 (1H, s, C(2)*H*).

Lit[3] NMR: **Cis-oxazolidine:** δ_H(400 MHz; $CDCl_3$); **Keto-tautomer:** 0.89 (9H, s, C(CH_3)$_3$), 2.30 (3H, s, CH_3C(O)), 3.69 (2H, s, CH_2), 3.79 (3H, s, CO_2CH_3), 4.02 (1H, m) and 4.43-4.63 (2H, m, C(4)*H* and C(5)H_2) and 5.30 (1H, s, C(2)*H*); **Enol-tautomer:** 0.92 (9H, s, C(CH_3)$_3$), 1.97 (3H, s, CH_3C(OH)), 3.79 (3H, s, CO_2CH_3), 4.02 (1H, m) and 4.43-4.63 (2H, m, C(4)*H* and C(5)H_2), 5.10 (1H, s, C(OH)=C*H*C(O)) and 5.30 (1H, s, C(2)*H*).

(2*R*, 5*R*, 6*R*)-2-(*tert*-Butyl)-6-hydroxy-5-methoxycarbonyl-6-methyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane (2.16a) and (2*R*, 5*R*, 6*S*)-2-(*tert*-butyl)-6-hydroxy-5-methoxycarbonyl-6-methyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane (2.16b)[6]



(2.16a)

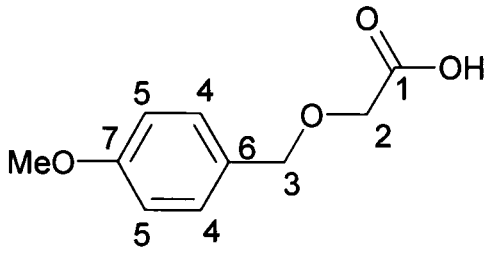


(2.16b)

Using the literature protocol; to a solution of (2R, 4S)-3-acetoacetyl-2-(*tert*-butyl)-4-methoxycarbonyl-oxazolidine **(2.15a)** (100 mg, 0.37 mmol, 1.1 eq) in methanol (10 ml) was added sodium methoxide (21 mg, 0.39 mmol, 1.1 eq). The mixture was stirred at RT for 20 hr, partitioned between Et_2O (30 ml) and ammonium chloride$_{(aq)}$ (30 ml) and the organic layer separated, washed with brine (25 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield the title compound as a crude 4:1 mixture of (2*R*, 5*R*, 6*S*):(2*R*, 5*R*, 6*R*) isomers. Recrystallisation from $CHCl_3$:petrol 1:1 v/v yielded colourless needles of the major epimer **(2.16a)** (60 mg, 30%): δ_H(200 MHz; $CDCl_3$); 0.89 (9H, s, C(CH_3)$_3$), 1.32 (3H, s, C(OH)CH_3), 2.45 (1H, d, *J* 15.8 Hz, C-7*H*H'), 2.69 (1H, s, O*H*), 3.21 (1H, d, *J* 15.8 Hz, C-7H*H'*), 3.80 (3H, s, CO_2CH_3), 4.32 (1H, d, *J* 9.0 Hz, C-4*H*H'), 4.56 (1H, d, *J* 9.0 Hz, C-4H*H'*) and 4.98 (1H, s, ^{t}BuC*H*).

Lit[3] NMR: δ_H(200 MHz; $CDCl_3$); 0.88 (9H, s, C(CH_3)$_3$), 1.33 (3H, s, C(OH)CH_3), 2.45 (1H, d, *J* 16.0 Hz, C-7*H*H'), 2.70 (1H, s, O*H*), 3.24 (1H, d, *J* 16.0 Hz, C-7H*H'*), 3.81 (3H, s, CO_2CH_3), 4.32 (1H, d, *J* 9.0 Hz, C-4*H*H'), 4.56 (1H, d, *J* 9.0 Hz, C-4H*H'*) and 4.98 (1H, s, ^{t}BuC*H*).

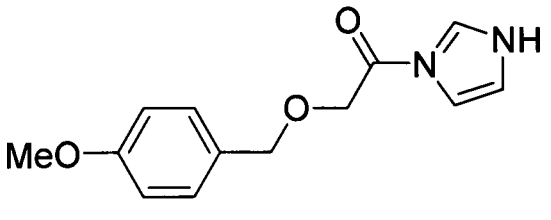
(4-Methoxy-benzyloxy)-acetic acid (2.17)[7]



To a cooled solution of 4-methoxybenzyl alcohol (6.9 g, 50 mmol) in toluene (150 ml) was added dropwise a suspension of sodium hydride (3.6 g, 6 mmol) in toluene (20 ml). The solution was allowed to warm to RT and stirred for 1 hr, and then bromoacetic acid (6.97 g, 50 mmol) was added dropwise and the reaction mixture was heated under reflux for 4 days. The solution was quenched with 10% HCl (100 ml), the layers separated and the aqueous layer extracted with EtOAc (3 x 80 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to yield the title compound (9.84 g, 100%) as a yellow oil: δ_H(400 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 4.14 (2H, s, CH_2-2), 4.59 (2H, s, CH_2-3), 6.91 (2H, d, *J* 7.6 Hz, ArH), 7.31 (2H, d, *J* 7.6 Hz, ArH).

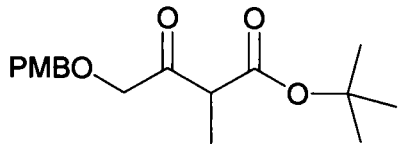
Lit[8] NMR: δ_H(200 MHz; $CDCl_3$) 3.81 (3H, s, CH_3), 4.11 (2H, s, CH_2-2), 4.58 (2H, s, CH_2-3), 6.89 (2H, d, *J* 8.8 Hz, H ortho to OMe), 7.29 (2H, d, *J* 8.8 Hz, H meta to OMe), 9.78 (1H, br, s, O*H*).

(4-Methoxy-benzyloxy)-acetic acid imidazolide



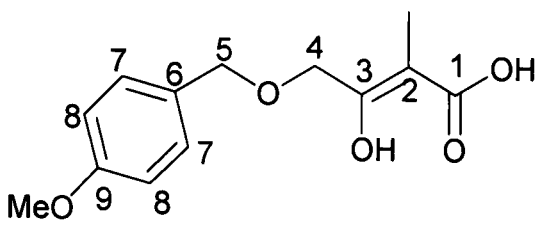
To a solution of (4-methoxybenzyloxy)-acetic acid **(2.17)** (1 g, 5.1 mmol, 1.0 eq) in dry THF (20 ml) was added CDI (0.97 g, 6.0 mmol, 1.2 eq) and the mixture stirred at RT for 24 hrs. The mixture was used immediately without further purification.

tert-Butyl-4-(4-methoxy-benzyloxy)-2-methyl-3-oxo-butyrate (2.20)



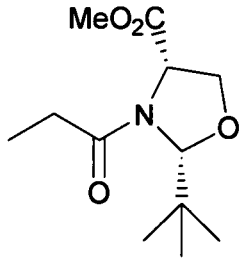
To a stirred solution of LDA [from a solution of diisopropylamine (1.16 ml, 10.2 mmol, 2.0 eq) in dry THF (12 ml) and ^{n}BuLi (6.38 ml of a 1.6 M solution in hexanes, 10.2 mmol, 2.0 eq) stirred at –78° C for 1 hr] was added dropwise a solution of *tert*-butyl propionate (0.45 g, 5.1 mmol, 1.0 eq) in THF (5 ml) and the mixture stirred for 1 hr at –78° C. To this colourless solution was added the imidazolide of acid **(2.17)** cooled to -78° C, *via* cannula. The pale yellow solution was stirred at –78° C for 0.5 hr and allowed to warm to RT over a further 0.5 hr. The reaction was quenched with 10% HCl (20 ml) and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml), the organic layers combined, dried ($MgSO_4$), filtered and evapourated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the previously unreported desired compound as a colourless oil (440 mg, 28%): R_f 0.27 and 0.21 (4:1 petrol:EtOAc); **Keto tautomer:** ν_{max}(film)/cm^{-1} 1780 (s), 1540, 1260, 1180 (all m), 1020, 825 (all w); δ_H(200 MHz; $CDCl_3$) 1.27 (3H, d, *J* 7.2 Hz, C*H*$_3$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 3.56 (1H, q, *J* 7.2 Hz, C*H*CH$_3$), 3.81 (3H, s, OC*H*$_3$), 4.15 (2H, s, PMBOC*H*$_2$C(O)), 4.52 (2H, s, MeOC$_6$H$_4$C*H*$_2$), 6.89 (2H, d, *J* 8.8 Hz, Ar*H*), 7.29 (2H, d, *J* 8.8 Hz, Ar*H*); δ_C(50.3 MHz; $CDCl_3$); 12 (*C*H(CH$_3$)), 27.5 (C(*C*H$_3$)$_3$), 49 (O*C*H$_3$), 55 (*C*H(CH$_3$)), 73-74 (MeOC$_6$H$_4$*C*H$_2$) and (PMBO*C*H$_2$), 82 (*C*(CH$_3$)$_3$), 124 (Ar*H*), 129 (Ar*H*), 159 (*ortho-C*), 168 (^{t}BuO*C*(O)), 204 (PMBOCH$_2$*C*(O)); *m/z* (APCI) 307 [M-H$^-$] (100%), 233(20), 113(90); HRMS: Found 326.1971 [M+NH$_4^+$], $C_{17}H_{28}NO_5$ requires 326.1967.

Synthesis of 4-(4-methoxy-benzyloxy)-2-methyl-3-oxo-butyric acid (2.21)



To a stirred solution of 4-(4-methoxybenzyloxy)-2-methyl-3-oxo-butyrate **(2.20)** (500 mg, 1.63 mmol, 1.0 eq) in toluene (2 ml) was added anisole (35 mg, 0.33 mmol, 0.2 eq) and a solution of *p*-toluenesulphonic acid (31 mg, 0.16 mmol, 0.1 eq) in toluene (2 ml). The mixture was heated at reflux for 0.5 hr, concentrated *in vacuo* and the residue purified by column chromatography (4:1 v/v petrol:EtOAc) to yield the title previously unreported compound as an orange oil, as a 4:1 mixture of enol:keto tautomers (189 mg, 46%): R_f 0.29 (4:1 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 3400 (s, br), 2900 (s), 1756 (s), 1625 (m), 1520 (m), 1450 (m), 1310 (m), 1060 (m); δ_H(200 MHz; $CDCl_3$) **Keto tautomer:** 1.41 (3H, d, *J* 6.4 Hz, CH(C*H*$_3$)), 3.04 (2H, q, *J* 6.4 Hz, C*H*(CH$_3$)), 3.65 (1H, s, PMBOC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 4.37 (1H, d, MeOC$_6$H$_4$C*H*$_2$O), 6.78 (2H, d, *J* 6.6 Hz, Ar*H*), 7.04 (2H, d, *J* 6.6 Hz, Ar*H*). **Enol tautomer:** 1.41 (3H, s, C*H*$_3$), 3.65 (2H, s, PMBOC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 4.37 (1H, s, MeOC$_6$H$_4$C*H*$_2$O), 6.78 (2H, d, *J* 6.6 Hz, Ar*H*), 7.04 (2H, d, *J* 6.7 Hz, Ar*H*); δ_C(50.3 MHz; $CDCl_3$) **Keto tautomer:** 51.08 (C(2)), 55.16 (OC*H*$_3$), 72.68 (C(5)), 114.16 (C(8)), 126.12 (C(7)), 130.50 (C(6)), 159.05 (C(9)), 177.06 (C(1)), 210.97 (C(3)); *m/z* (GCMS-CI) 253 $[MH]^+$ (10%), 252 (72), 210 (70), 193 (22), 122 (48) 121 (100); HRMS: Found 252.1238, $C_{13}H_{18}NO_4$ requires 252.1235.

2-*tert*-Butyl-3-propionyl-oxazolidine-4-carboxylic acid methyl ester (2.23)[3]

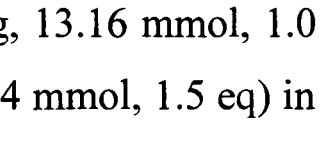


Using the literature protocol, to a stirred solution of oxazolidine **(2.5)** (50 mg, 0.27 mmol, 1.0 eq), DCCI (56 mg, 0.27 mmol, 1.0 eq) and DMAP (4 mg, 0.027 mmol, 0.1 eq) in DCM (10 ml) at 0° C was added propionic acid (21 mg, 0.27 mmol, 1.0 eq) in DCM (5 ml) dropwise. The mixture was stirred for 15 mins at 0° C, warmed to RT and stirred for a further 5 hrs. The solution was filtered, the solid residue washed with

DCM (3 x 15 ml) and the combined organic layers concentrated *in vacuo*. Purification by column chromatography (1:1 v/v petrol:EtOAc) yielded the title compound as white crystals (60 mg, 93%). R_f 0.20 (1:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.15 (3H, t, *J* 7.5 Hz, CH_3), 2.35-2.42 (2H, m, CH_2CH$_3$), 3.82 (3H, s, CO_2CH_3), 4.08-4.15 (1H, m, C-(5)H), 4.44-4.55 (2H, m, C(4)HC(5)H'), 5.32 (1H, s, C(2)H).

Lit[3] NMR: δ_H(200 MHz; $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.13 (3H, t, *J* 7.1 Hz, CH_3), 2.33-2.40 (2H, m, CH_2CH$_3$), 3.80 (3H, s, CO_2CH_3), 4.11 (1H, m, C-(5)H), 4.44-4.55 (2H, m, C(4)HC(5)H'), 5.36 (1H, s, C(2)H).

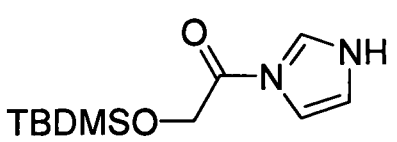
(*tert*-Butyldimethylsilyloxy)acetic acid (2.30)



To a solution of glycolic acid (1 g, 13.16 mmol, 1.0 eq) in dry DMF (50 ml) at 0° C was added imidazole (1.34 g, 19.74 mmol, 1.5 eq) in portions over five minutes and a solution of TBDMSCl (2.77 g, 18.4 mmol, 1.4 eq) in dry DMF (10 ml) dropwise. The mixture was stirred at 0° C for 1 hr and then at RT for 22 hrs. The solution was partitioned between Et_2O (150 ml) and 10% HCl (50 ml). The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 ml). The organic washing's were combined and washed with sat. aq. $NaHCO_3$ (80 ml) and brine (80 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was obtained, without further purification as a white powder (1.31 g, 52%): δ_H(400 MHz; $CDCl_3$) 0.19 (3H, s, Si-CH_3), 0.29 (3H, s, Si-CH_3), 0.92 (9H, s, Si(C(CH_3)$_3$)), 4.21 (2H, s, CH_2).

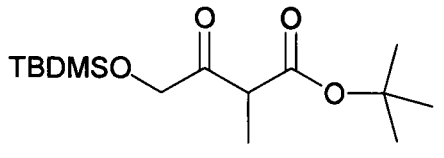
Lit[9] NMR: δ_H(300 MHz; $CDCl_3$) 0.15 (6H, s), 0.95 (9H, s), 4.3 (2H, s).

(*tert*-Butyldimethylsilyloxy)acetic acid imidazolide



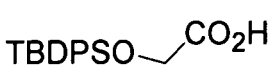
To a solution of (*tert*-butyldimethylsilyloxy) acetic acid **(2.30)** (500mg, 2.63 mmol, 1.0 eq) in dry THF (20 ml) was added CDI (0.5g, 3.09 mmol, 1.2 eq) and the mixture stirred at RT for 24 hrs. The mixture was used immediately without further purification.

4-(*tert*-Butyldimethylsilyloxy)-2-methyl-3oxobutyric acid *tert*-butyl ester (2.31)



To a stirred solution of LDA [from a solution of diisopropylamine (0.6 ml, 5.26 mmol, 2.0 eq) in dry THF (12 ml) and ^{n}BuLi (3.3 ml of a 1.6 M solution in hexanes, 5.26 mmol, 2.0 eq) stirred at –78° C for 1 hr] was added a solution of *tert*-butyl propionate (0.23 g, 2.63 mmol, 1.0 eq) in THF (5 ml) dropwise and the mixture stirred for 1 hr at –78° C. To the colourless solution was added the imidazolide prepared from acid **(2.30)**, cooled to –78° C, *via* cannula. The red solution was stirred at –78° C for 0.5 hr and allowed to warm to RT over a further 0.5 hr. The reaction was quenched with 10% HCl (20 ml) and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml), the organic layers combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded a white solid of the desired previously unreported compound (190 mg, 24%): R_f 0.52 (4:1 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 2932(br, s), 1723(br, s), 1462(m), 1369(m), 1259(s), 1153(s), 840(s); δ_H(400 MHz; $CDCl_3$) 0.11 (6H, s, Si-(C*H*$_3$)$_2$), 0.89 (9H, s, Si(C(C*H*$_3$)$_3$)), 1.39 (3H, d, *J* 7.2 Hz, C*H*$_3$), 1.47 (9H, s, ^{t}Bu), 3.69 (1H, q, *J* 7.2 Hz, C*H*(CH$_3$)), 4.29 (2H, s, C*H*$_2$); δ_C(50.3 MHz; $CDCl_3$) -5.59 (Si-*C*H$_3$), 0.98 (Si-*C*H$_3$), 12.32 (*C*H$_2$), 25.61 (SiC(*C*H$_3$)$_3$), 25.74 (SiC(*C*H$_3$)$_3$), 25.90 (SiC(*C*H$_3$)$_3$), 27.89 (OC(*C*H$_3$)$_3$), 28.04 (OC(*C*H$_3$)$_3$), 28.09 (OC(*C*H$_3$)$_3$), 49.11 (*C*H(CH$_3$)), 68.53 (*C*H$_2$); *m/z* (APCI) 301 [M-H$^-$] (100%), 254 (2), 241(2), 168(10).

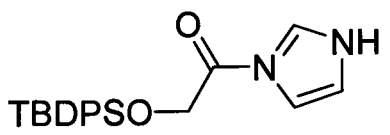
(*tert*-Butyldiphenylsilyloxy)acetic acid (2.34)



To a stirred solution of glycolic acid (500 mg, 6.58 mmol) in dry DMF (50 ml) at 0° C was added imidazole (1.34 g, 19.74 mmol) portionwise followed by a solution of TBDMSCl (2.54 g, 9.2 mmol) in dry DMF (5 ml) dropwise. The reaction mixture was stirred at 0° C for 1 hr and at RT for 48 hrs. The solution was partitioned between Et_2O (150 ml) and 10% HCl (50 ml), the aqueous layer separated and extracted with Et_2O (2 x 30 ml). The combined organic layers were washed with sat. aq. $NaHCO_3$ (80 ml), brine (80 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the title compound as a yellow oil (1.66 g, 80%); δ_H(200 MHz; $CDCl_3$) 1.07 (9H, s, ^tBu), 4.38 (2H, s, C*H*$_2$), 7.34-7.75 (10H, m, Ar*H*).

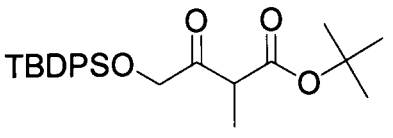
Lit[10] NMR: δ_H(500 MHz; $CDCl_3$) 1.19 (9H, s), 4.29 (2H, s), 7.49 (4H, t, *J* 7.3 Hz), 7.53 (2H, dd, *J* 7.8 and 1.5 Hz), 7.72 (4H, dd, *J* 7.8 and 1.5 Hz).

(*tert*-Butyldiphenylsilyloxy)acetic acid imidazolide



To a solution of acid **(2.34)** (1.66 g, 5.28 mmol, 1.0 eq) in dry THF (50 ml) was added carbonyldiimidazole (1.8 g, 7.4 mmol, 1.5 eq) and the mixture stirred at RT for 48 hrs. The mixture was used immediately without further purification.

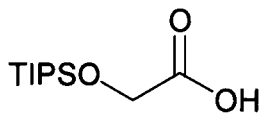
4-(*tert*-Butyldiphenylsilyloxy)-2-methyl-3oxobutyric acid *tert*-butyl ester (2.35)



To a stirred solution of LDA [from a solution of diisopropylamine (1.18 ml, 10.17 mmol, 2.0 eq) in dry THF (10 ml) and ^nBuLi (6.51 ml of a 1.6 M solution in hexanes, 10.17 mmol, 2.0 eq) stirred at –78° C for 1 hr] was added a solution of *tert*-butyl propionate (525 mg, 5.28 mmol, 1.0 eq) in THF (5 ml) dropwise and the mixture

stirred for 1 hr at –78° C. To the colourless solution was added the imidazolide of acid **(2.34)**, cooled to –78° C, *via* cannula. The solution was stirred at –78° C for 0.5 hr and allowed to warm to RT over a further 0.5 hr. The reaction was quenched with 10% HCl (20 ml) and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml), the organic layers combined, dried ($MgSO_4$), filtered and evapourated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAC) yielded a viscous yellow oil of the previously unreported title compound (1.13 g, 50%), as the **keto tautomer:** R_f 0.59 (4:1 v/v petrol:EtOAc): δ_H(200 MHz; $CDCl_3$) 1.09 (9H, s, ^tBu), 1.34 (3H, d, *J* 7.2 Hz, C(H)CH_3), 1.41 (9H, s, ^tBu-Si), 3.37 (1H, q, *J* 7.2 Hz, C(*H*)CH_3), 4.38 (2H, s, CH_2), 7.34-7.75 (10H, m, Ar*H*); δ_C(50.3 MHz; $CDCl_3$) 8.49 (C(H)*C*H_3), 13.34 (Si-*C*$(CH_3)_3$), 23.87 (Si-C(*C*$H_3)_3$), 28.79 (O-C(*C*$H_3)_3$), 57.34 (*C*(H)CH_3), 62.90 (*C*H_2), 73.2 (O-*C*$(CH_3)_3$), 128.1, 129.8, 135.8 (Ar-*C*H), 133.02 (*ipso-C*), 172.31 (*C*(O)O^{t}Bu), 207.18 (TBDPSOCH_2-*C*(O)); *m/z* (APCI) 427 $[MH]^+$ (100%), 172 $[M\text{-}OTBDMS]^+$ (80).

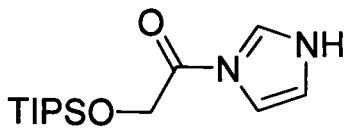
(Triisopropylsilyloxy)-acetic acid (2.38)[11]



To a solution of glycolic acid (500 mg, 6.58 mmol) in DMF (60 ml) at 0° C was added imidazole (670 mg, 9.87 mmol) portionwise and a solution of triisopropylchlorosilane (3.175 g, 16.45 mmol) in DMF (5 ml) dropwise. The mixture was stirred at 0° C for 1hr and then at RT for a further 24hr. The reaction solution was partitioned between Et_2O (100 ml) and 10% HCl (50 ml), the organic layer separated and the aqueous layer extracted with Et_2O (2 x 40 ml). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 ml) and brine (50 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by Kugelröhr distillation (225 °C / 4 mbar) yielded the title compound as a viscous yellow oil (857mg, 64%): δ_H(400 MHz; $CDCl_3$) 1.09 (18H, d, *J* 6.3 Hz Si(CH(C$H_3)_2)_3$), 1.32 (3H, q, *J* 6.3 Hz, Si(C*H*$(CH_3)_2)_3$) and 4.30 (2H, s, CH_2).

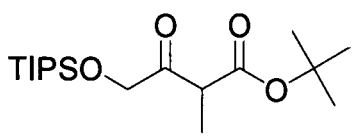
Lit[12] NMR: δ_H(300 MHz; $CDCl_3$) 1.00-1.19 (21H, m), 4.28 (2H, s), 9.3 (1H, br,s).

(Triisopropylsilyloxy)-acetic acid imidazolide



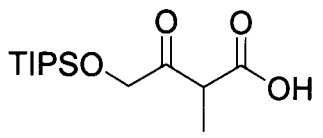
To a solution of acid **(2.38)** (500 mg, 2.47 mmol, 1.0 eq) in dry THF (50 ml) was added carbonyldiimidazole (860 mg, 3.51 mmol, 1.2 eq) and the mixture stirred at RT for 48 hrs. The mixture was used immediately without further purification.

4-(Triisopropylsilyloxy)-2-methyl-3oxobutyric acid *tert*-butyl ester (2.39)



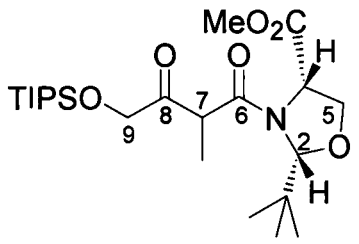
To a stirred solution of LDA [from a solution of diisopropylamine (0.56 ml, 4.91 mmol, 2.0 eq) in dry THF (10 ml) and ^{n}BuLi (3.2 ml of a 1.6 M solution in hexanes, 4.91 mmol, 2.0 eq) stirred at –78° C for 1 hr] was added a solution of *tert*-butyl propionate (220 mg, 2.51 mmol, 1.0 eq) in THF (5 ml) dropwise and the mixture stirred for 1 hr at –78° C. To the colourless solution was added the imidazolide derived of acid **(2.38)** cooled to –78° C, *via* cannula. The solution was stirred at –78° C for 0.5 hr and allowed to warm to RT over a further 0.5 hr. The reaction was quenched with 10% HCl (20 ml) and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml), the organic layers combined, dried ($MgSO_4$), filtered and evapourated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded a viscous yellow oil of the previously unreported title compound (250mg, 29%), as the **keto tautomer:** R_f 0.50 (4:1 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 2945(s), 1732 (br, s), 1152(s), 883(m); δ_H(400 MHz; $CDCl_3$) 1.01-1.09 (21H, m, TIPS), 1.34 (3H, d, *J* 7.3 Hz, C(H)CH_3), 1.42 (9H, s, ^{t}Bu), 3.36 (1H, q, *J* 7.3 Hz, C(*H*)CH_3), 4.30 (2H, s, CH_2); δ_C(100 MHz; $CDCl_3$) 11.70 (C(H)CH_3), 17.23, 17.43, 17.55, 17.60, 17.70 (TIPS CH_3), 27.78, 28.38 (C(CH_3)$_3$), 46.81 (*C*(H)CH_3), 61.63 (*C*(CH_3)$_3$), 169.31 (*C*(O)O^{t}Bu), 175.49 (*C*(O)CH_2OTIPS); m/z (GCMS) 345 [MH]$^+$ (5%), 250 (100), 233 (90), 189 (25), 148 (65); HRMS (GCMS): Found 345.2446, $C_{18}H_{37}SiO_4$ requires 345.2441.

4-(Triisopropylsilyloxy)-2-methyl-3oxobutyric acid (2.40)



To a stirred solution of ester **(2.39)** (130 mg, 0.45 mmol) in toluene (2 ml) was added TsOH (9.2 mg, 0.05 mmol) and anisole (20 mg, 0.05 mmol). The reaction mixture was heated at reflux for 2 hrs, allowed to cool and concentrated *in vacuo*. Purification by column chromatography (4:1 v/v petrol: EtOAc) yielded the desired previously unreported acid as a white powder (50 mg, 39%): R_f 0.24 (4:1 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 3389 (br, s), 2940 (s), 1784 (s), 1652 (m), 1534 (m), 1450 (m); δ_H(400 MHz; $CDCl_3$) 1.02-1.10 (21H, m, TIPS), 1.14 (3H, d, *J* 7.0 Hz, C(H)CH_3), 3.70 (1H, q, *J* 7.0 Hz, C(*H*)CH_3), 4.30 (2H, s, OCH_2); δ_C(100 MHz; $CDCl_3$) 11.78 (C(H)CH_3), 17.21, 17.42, 17.54, 17.57, 17.70 (TIPS CH_3), 46.80 (*C*(H)CH_3), 169.33 (*C*(O)OH), 175.49 (*C*(O)CH_2OTIPS); *m/z* (ESI) 231 (100%), 205 (20%), 173 (5%).

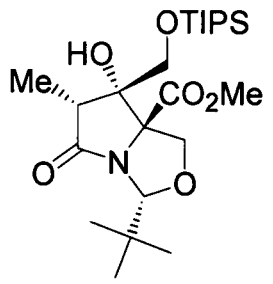
(2*R*, 4S)-2-*tert*-Butyl-3-[2'-methyl-3'-oxo-4'-(triisopropylsilyloxy)butyryl] oxazolidine-4-carboxylic acid methyl ester (2.41)



To a solution of oxazolidine **(2.5)** (25 mg, 0.13 mmol) in DCM (5 ml) at 0° C was added DCCI (29 mg, 0.14 mmol), DMAP (1 mg, 0.01 mmol) and a solution of TIPS acid **(2.40)** (40 mg, 0.14 mmol) in DCM (2 ml). The reaction mixture was stirred at 0° C for 15 mins and then at RT for 24 hrs. The solution was filtered to remove precipitated dicyclohexylurea, the residue washed with DCM (10 ml), the organic layers combined and concentrated *in vacuo*. Purification by column chromatography (3:2 v/v petrol:EtOAc) yielded the previously unreported title compound as colourless crystals (25 mg, 0.05 mmol, 39%); R_f 0.55 (3:2 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 3314 (br, w), 2930 (s), 2852 (m), 1733, 1699, 1652, 1635, 1550 (all s), 1539 (m), 1506 (m), 1258 (w), 665 (m); δ_H(200 MHz; $CDCl_3$); 0.98 (9H, s, C(CH_3)$_3$), 1.11-1.39 (21H, m, TIPS-CH_3 and C(H)CH_3), 1.64-1.75 (3H, m TIPS-C*H*), 3.48 (1H, q, *J* 7.0 Hz, C(*H*)CH_3), 3.72 (2H, s, CH_2), 3.74 (3H, s, CO_2CH_3), 3.92 (1H, m, C(5)*H*), 4.09 (1H, m, C(5)*H'*), 4.35 (1H, m, C(4)*H*), 4.77 (1H, s, C(2)*H*); δ_C(100 MHz; $CDCl_3$) 0.96

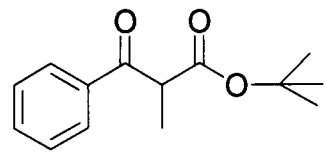
(TIPS-*C*H), 25.18 (TIPS-*C*H_3), 29.63 (*C*(CH_3)$_3$), 34.87 (C(*C*H_3)), 52.46 (*C*(H)CH_3), 55.70 (CO_2*C*H_3), 59.56 (C-4), 68.91 (C-5), 72.24 (C-9), 99.17 (C-2), 109.03 (*C*O_2CH_3), 139.75 (C-6); m/z (ESI) 480 $[M+Na]^+$ (30%); (TOFMS CI) 225 $[M-OTIPS]^+$ (100), 184 $[M-TIPSOCH_2C(O)]^+$ (90).

2-(*tert*-Butyl)-6-hydroxy-5-methoxycarbonyl-6-triisopropylsiloxy-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane (2.42)



A solution of oxazolidine **(2.41)** (25 mg, 0.05 mmol) and ^{t}BuOK (8 mg, 0.07 mmol) in freshly distilled ^{t}BuOH (5 ml) was heated at reflux for 3 hrs under inert atmosphere then cooled to room temperature and water (10 ml) added. The aqueous layer was separated and washed with ether (2 x 15 ml). The aqueous layer was acidified (pH <7) with 10% HCL and then washed with ether (2 x 10 ml), dried ($MgSO_4$) filtered and concentrate *in vacuo* to yield a colourless powder (8 mg, 0.02 mmol) of what appeared to be the title compound by ^{1}H NMR (data not presented as poor quality spectra produced from small amount of material). *m/z* (APCI) (25%) 358.16 $[MH^+]$, 299.18 $[MH^+ - CO_2Me]$ (16%).

2-Methyl-3-oxo-3-phenyl-propionic acid *tert*-butyl ester (2.47)

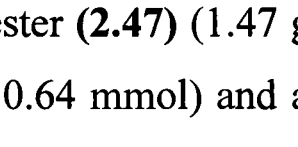


To a stirred solution of LDA [from a solution of diisopropylamine (3.7 ml, 32.8 mmol, 2.0 eq) in dry THF (20 ml) and ^{n}BuLi (20.4 ml of a 1.6 M solution in hexanes, 32.8 mmol, 2.0 eq) stirred at –78° C for 1 hr] was added a solution of *tert*-butyl propionate (1.44 g, 16.39 mmol, 1.0 eq) in THF (5 ml) dropwise and the mixture was stirred for 1 hr at –78° C. To the colourless solution was added the imidazolide of benzoic acid cooled to –78° C, *via* cannula. The solution was stirred at –78° C for 0.5

hr and allowed to warm to RT over a further 0.5 hr. The reaction was quenched with 10% HCl (20 ml) and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml), the organic layers combined, dried ($MgSO_4$), filtered and evapourated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAC) yielded a viscous yellow oil of the title compound (2.69 g, 70%), as the keto tautomer: R_f 0.55 (4:1 v/v petrol:EtOAc): δ_H(400 MHz; $CDCl_3$) 1.06 (3H, d, *J* 7.2 Hz, C(H)C*H*$_3$), 1.32 (9H, s, ^{t}Bu), 3.01 (1H, q, *J* 7.2 Hz, C(*H*)CH$_3$), 7.44-7.61 (3H, m, *meta* and *para* ArC*H*), 8.12 (2H, d, *J* 7.2 Hz, *ortho*-ArC*H*).

Lit[13] NMR: δ_H(neat) 0.9 (9H, s), 1.03 (3H, d), 4.0 (1H, q), 7.04 (3H, m), 7.5 (2H, m).

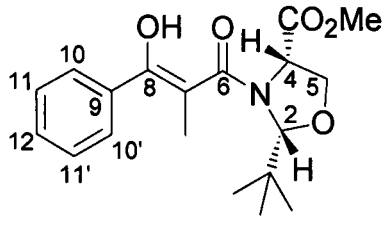
2-Methyl-3-oxo-3-phenyl-propionic acid (2.48)



To a stirred solution of *t*-butyl ester **(2.47)** (1.47 g, 6.28 mmol, 1.0 eq) in toluene (20 ml) was added TsOH (132 mg, 0.64 mmol) and anisole (2 drops). The reaction was heated at reflux for 3 hrs and concentrated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the title compound as a colourless powder (1.08 g, 97%); R_f 0.55 (4:1 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 1.09 (3H, d, *J* 7.0 Hz, C(H)C*H*$_3$), 3.18 (1H, q, *J* 7.0 Hz, C(*H*)CH$_3$), 7.49 (2H, m, *meta*-ArC*H*), 7.62 (1H, m, *para-Ar*C*H*), 8.12 (2H, d, *J* 7.1 Hz, *ortho*-ArC*H*).

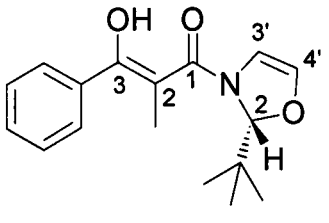
Lit[14] NMR: δ_H(200 MHz; $CDCl_3$) 1.5 (3H, d), 4.2 (1H, q), 7.3-7.55 (3H, m), 7.8-8.05 (2H, m), 10.1 (1H, s).

2-*tert*-Butyl-3-(2-methyl-3-oxo-3-phenylpropionyl)-oxazolidine-4-carboxylic acid methyl ester (2.49)



To a stirred solution of oxazolidine **(2.5)** (269 mg, 1.45 mmol) in DCM (40 ml) at 0° C was added pyridine (0.23 ml, 2.89 mmol) dropwise and acid chloride derived from acid **(2.48)**, (500 mg, 2.89 mmol) [prepared from: to a solution of acid **(2.48)** (500 mg, 2.89 mmol) in DCM (50 ml) was added $(COCl)_2$ (450 mg, 3.54 mmol, 1.2 eq) dropwise and DMF (2 drops, cat.) and the reaction mixture stirred at 0° C for 1 hr, the solution was concentrated *in vacuo* and used immediately.] dropwise. The reaction mixture was stirred at 0° C for 15 mins and at RT for 5 hrs. The solution was made up to 50 ml with DCM, washed with NH_4Cl (40 ml), 10% $NaHCO_3$ (40 ml) and brine (40 ml), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the previously unreported title compound as a white solid (250 mg, 50%); R_f 0.28 (4:1 v/v petrol:EtOAc); $\nu_{max}(CHCl_3)/cm^{-1}$ 3155, 2959, 1794, 1657, 1468, 1380, 1095 all (s); δ_H(400 MHz; $CDCl_3$) 0.98 (9H, s, $C(CH_3)_3$), 1.54 (3H, s, $C(CH_3)$), 3.78 (4H, m, CO_2CH_3 and C(4)*H*), 4.39 (1H, d, *J* 6.1Hz, C(5)*H'*), 4.48 (1H, dd, *J* 6.1 Hz and 1.2 Hz, C(5)*H*), 5.53 (1H, s, C(2)*H*), 7.3-7.5, 5H, m, Ar*H*); δ_C(100 MHz; $CDCl_3$); 25.77 ($C(CH_3)$), 36.51 ($C(CH_3)$), 52.55 (CO_2CH_3), 62.18 (C(4)), 68.72 (C(5)), 97.12 (C(2)), 95.67 (C(7)), 127.66 (Ar-C), 128.47 (C(11+11'), 131.02 (C(12)), 136.41 (C(9)), 184.63 (C(6); m/z (CI TOF) 292 (92%), 234 (60), 206 (100), 105 (70).

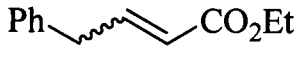
(*R*,*Z*)-1-(2-*tert*-Butyloxazol-3(2*H*)-yl)-3-hydroxy-2-methyl-3-phenylprop-2-en-1-one (2.51)



A solution of oxazolidine **(2.49)** (100 mg, 0.29 mmol) and ^{t}BuOK (43 mg, 0.38 mmol) in freshly distilled ^{t}BuOH (10 ml) was heated at reflux for 3 hrs under inert atmosphere then cooled to room temperature and water (10 ml) added. The aqueous layer was separated and washed with ether (2 x 15 ml). The aqueous layer was acidified (pH <7) with 10% HCL and then washed with ether (2 x 10 ml), dried ($MgSO_4$) filtered and concentrate *in vacuo* to yield a yellow oil (10 mg, 0.035 mmol): δ_H(400 MHz; $CDCl_3$) 0.98 (9H, s, C(C*H*$_3$)$_3$), 1.54 (3H, s, C(C*H*$_3$)), 4.10 (1H, d, *J* 6.2 Hz, C(3')*H*), 4.39 (1H, d, *J* 6.2Hz, C(4')*H*, 5.53 (1H, s, C(2)*H*), 7.3-7.5, 5H, m, Ar*H*).

EXPERIMENTAL FOR CHAPTER 3: THE LEFT-HAND SIDE

Ethyl 4-phenylbut-2-enoate (3.33)[15]



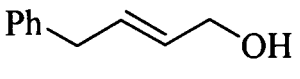
To a stirred solution of phenylacetaldehyde (6.00 g, 50 mmol) in dry DCM (100 ml) at RT was added (carboethoxymethylene)triphenylphosphorane (21 g, 60 mmol). The mixture was stirred for 24 hrs, concentrated *in vacuo*, redissolved in 10:1 petrol:Et_2O, filtered and concentrated. This was repeated twice to precipitate Ph_3PO. Purification by column chromatography (24:1 v/v Petrol:EtOAc) yielded the (*Z*)-isomer (60 mg, 1%), the (*E*)-isomer (8.08 g, 85%) and a 1:1 (*Z:E*) mixture (1.20 g, 12%), all as colourless oils.

(*Z*)-isomer (R_f 0.36, 24:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.07 (2H, dd, *J* 7.5 and 1.6 Hz, $PhCH_2$), 4.25 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.90 (1H, dt, *J* 11.4 and 1.6 Hz, CHCO), 6.40 (1H, dt, *J* 11.4 and 7.5 Hz, CH_2CH), 7.20-7.45 (5H, m, ArH).

(*E*)-isomer (R_f 0.30, 24: v/v Petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.55 (2H, dd, *J* 6.8 and 1.5 Hz, $PhCH_2$), 4.22 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.85 (1H, dt, *J* 15.5 and 1.5 Hz, CHCO), 7.15 (1H, dt, *J* 15.5 and 6.8 Hz, CH_2CH), 7.22-7.43 (5H, m, ArH).

Lit[16] NMR: **(*E*)-isomer** δ_H(400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.52 (2H, dd, *J* 7.1 and 1.6 Hz, $PhCH_2$), 4.17 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.81 (1H, dt, *J* 15.8 and 1.6 Hz, CHCO), 7.10 (1H, dt, *J* 15.8 and 7.1 Hz, CH_2CH), 7.15-7.36 (5H, m, ArH).

4-Phenylbut-2-en-1-ol (3.34) [17]

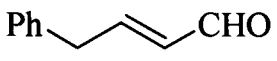


To a stirred solution of (*E*)-ester **(3.33)** (2.00 g, 10.51 mmol) in dry THF (50 ml) at -78° C was added DIBAL-H (18.2 ml of a 1.5 M solution in toluene, 27.33 mmol) over

20 minutes. The mixture was stirred for 1 h at -78° C and then for 1 h at -10° C. 1 M HCl (40 ml) was added, and the solution stirred for 5 minutes at RT. The solution was extracted with EtOAc (2 x 100 ml) and dried ($MgSO_4$). Purification by column chromatography (7:3 v/v Petrol:EtOAc) yielded the title compound (1.47 g, 95%) as a colourless oil: R_f 0.32 (7:3 v/v Petrol: EtOAc); δ_H(200 MHz; $CDCl_3$) 1.95 (1H, br, s, O*H*), 3.50 (2H, d, *J* 6.6 Hz, PhCH_2), 4.18 (2H, dd, *J* 5.6 and 1.1 Hz, CH_2OH), 5.70-6.03 (2H, m, *H*-2, *H*-3), 7.20-7.35 (5H, m, ArH).

Lit[17] NMR: δ_H(60 MHz; $CDCl_3$) 3.30 (2H, d, *J* 4 Hz, PhCH_2), 3.64 (1H, s, O*H*), 4.02 (2H, d, *J* 4 Hz, CH_2OH), 5.68 (2H, m, *H*-2, *H*-3), 7.18 (5H, s, ArH).

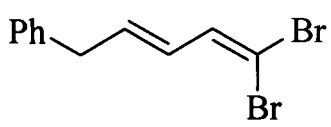
4-Phenylbut-2(*E*)-enal (3.35) [18]



To a stirred suspension of PCC (655 mg, 3.04 mmol) in dry DCM (10 ml) was added a solution of alcohol **(3.34)** (300 mg, 2.02 mmol) in dry DCM (10 ml). The mixture was stirred for 2.5 h at RT and then Et_2O (30 ml) added. The mixture was filtered through Celite®, washed with Et_2O (300 ml) and concentrated. Purification by column chromatography (17:3 v/v Petrol:EtOAc) yielded the title compound (280 mg, 96%) as a yellow oil: R_f 0.36 (17:3 v/v Petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 3.67 (2H, dd, *J* 6.7 and 1.6 Hz, C-4), 6.18 (1H, ddt, *J* 15.6, 7.9 and 1.6 Hz, C-2), 6.98 (1H, dt, *J* 15.6 and 6.7 Hz, C-3), 7.22-7.53 (5H, m, Ar*H*) and 9.54 (1H, d, *J* 7.9 Hz, C-1).

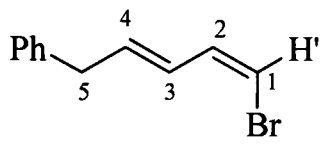
Lit[18] NMR: δ_H(270 MHz) 3.65 (2H, dd, *J* 6.4 and 1.7 Hz, C-4), 6.11 (1H, ddt, *J* 15.8, 7.7 and 1.7 Hz, C-2), 6.97 (1H, dt, *J* 15.8 and 6.4 Hz, C-3), 9.53 (1H, d, *J* 7.7 Hz, C-1).

1,1-Dibromo-5-phenylpenta-1,3(*E*)-diene (3.36)[19]

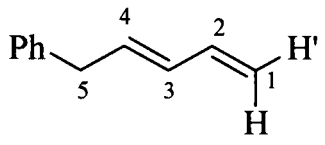


To a stirred solution of CBr_4 (0.35 g, 1.056 mmol) in dry DCM (10 ml) at 0° C was added portionwise PPh_3 (0.55 g, 2.112 mmol). After 5 minutes a solution of aldehyde **(3.35)** (140 mg, 0.96 mmol) in dry DCM (5 ml) was added dropwise to the orange reaction mixture. The solution was stirred at 0° C for 3 h, washed with water (1x 10 ml), sat. aq. $Na_2S_2O_4$ (1 x 10 ml), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (petrol) yielded the previously unreported title compound (200 mg, 70%) as an orange oil: R_f 0.42 (petrol); ν_{max}(film)/cm^{-1} 3027(m), 1765(m), 1602(w), 1495(m), 1453(m), 1235(w), 967(s), 803(s), 748(s), 698(s); δ_H(400 MHz; $CDCl_3$) 3.45 (2H, d, *J* 6.5 Hz, H-5), 6.04 (1H, dt, *J* 15.1 and 6.5 Hz, H-4), 6.18 (1H, dd, *J* 15.1 and 9.5 Hz, H-3), 6.94 (1H, d, *J* 9.5 Hz, H-2), 7.16-7.37 (5H, m, Ar*H*); δ_C(50.3 MHz; $CDCl_3$) 39.3 (C-5), 89.6 (C-1), 126.4 (C-3), 128.2 (*meta*-*C*H), 128.6 (*para*-*C*H), 131.4 (*ortho*-*C*H), 136.7 (C-4), 137.3 (C-2), 139 (*ipso*-*C)*; *m/z* (EI) 304, 302 and 300 (3, 6 and 3%, M^+), 223 and 221 (23, $[M - Br]^+$), 142 (100, $[M - Br_2]^+$), 128 (19), 115 (29), 90 (43), 65 (14).

1-Bromo-5-phenylpenta-1(*Z*), 3(*E*)-diene (3.37)



(3.37)



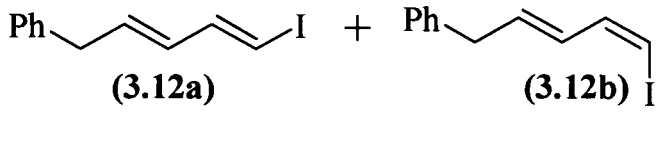
(3.37a)

To a stirred solution (in a light excluded flask) of crude dibromide **(3.36)** (230 mg, 0.76 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.05 mmol) in dry benzene (10 ml) was added dropwise Bu_3SnH (242 mg, 0.23 ml, 0.83 mmol). The mixture was stirred for 3 h at RT. Water (5 ml) was added and the mixture extracted with petrol (3 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (Petrol) yielded the title compound as a mixture of previously unreported bromide **(3.37)**: alkene **(3.37a)** (1:0.7), separable only by gas chromatography; (110 mg, 67%) as a colourless oil: R_f 0.44 (Petrol); **Bromide (3.37)**; ν_{max}(film)/cm^{-1} 3027(s), 1644(w), 1603(w), 1582(w), 1494(s), 1452(s), 1334(m), 973(s), 697(s); δ_H(400 MHz; $CDCl_3$) 3.48 (2H, d, *J* 7.2 Hz, H-5), 6.05 (1H, dt, *J* 15.1 and 7.2 Hz, H-4), 6.09 (1H, d, *J* 7.0 Hz, H-1), 6.48 (1H, dd, *J* 15.1 and 10.2 Hz, H-3), 6.63 (1H, dd, *J* 10.2 and 7.0 Hz, H-2), 7.20-7.34 (5H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 39.4 (C-5), 106.6 (C-1), 126.3

(*para*-*C*H), 127.1 (C-3), 128.5 (*meta*-*C*H), 128.7 (*ortho*-*C*H), 132.4 (C-2), 137.4 (C-4), 139.4 (*ipso*-C); *m/z* (GCMS, EI) 224 and 222 (8%, MH^+), 143 (100, $[M-Br]^+$), 128 (89), 115 (43), 90 (25), 77 (9); HRMS: Found: 222.0015 (M^+), $C_{11}H_{11}{}^{79}Br$ requires 222.0044.

Alkene (3.37a); δ_H(400 MHz; $CDCl_3$) 3.43 (2H, d, *J* 7.0 Hz, H-5), 5.01 (1H, dt, *J* 0.54 and 10.1 Hz, H-1'), 5.12 (1H, dt, *J* 17.0 and 0.50 Hz, H-1), 5.86 (1H, dt, *J* 15.1 and 7.2 Hz, H-4), 6.09 (1H, d, *J* 15.1 and 10.2 Hz, H-3), 6.28 (1H, dd, *J* 10.2 and 7.0 Hz, H-2), 7.12-7.37 (5H, m, Ar*H*); δ_C(100 MHz; $CDCl_3$) 38.90 (C-5), 115.71 (C-1), 126.11 (*para*-*C*H), 126.30 (C-3), 128.44 (*meta*-*C*H), 136.90 (C-4); *m/z* (GCMS, EI) 144 (10, MH^+), 128 (100), 115 (70), 91 (32), 77 (9).

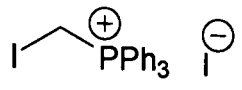
1-Iodo-5-phenylpenta-1,3(*Z*)-diene (3.12a) : 1-Iodo-5-phenylpenta-1,3(*E*)-diene (3.12b)



(3.12a) **(3.12b)**

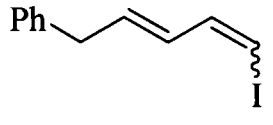
To a stirred suspension of $CrCl_2$ (1.637 g, 13.32 mmol, 6.0 eq) in dry THF (20 ml) was added dropwise a solution of aldehyde **(3.35)** (324 mg, 2.22 mmol, 1.0 eq) and CHI_3 (1.748 g, 4.46 mmol, 2.0 eq) in dry THF (8 ml) at 0° C. The mixture was stirred at 0° C for 1 h then for 30 minutes at RT. Water (50 ml) was added, the layers separated and the aqueous layer extracted with Et_2O (4 x 25 ml). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (50 ml), brine (50 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (99:1 v/v Petrol:Et_2O) yielded the previously unreported title compound (340 mg, 77%) as a mixture of 1(*E*):1(*Z*) of ratio 3:1 as an orange oil: R_f 0.37 (Petrol); ν_{max}(film)/cm^{-1} 3024(s), 2359(m), 1494(s), 1451(m), 979(s), 749(m), 697(s). **Data for major 1(*E*)-isomer**: δ_H(400 MHz; $CDCl_3$) 3.39 (2H, d, *J* 6.8 Hz, H-5), 5.89 (1H, dt, *J* 6.8 and 15.1 Hz, H-4), 6.07 (1H, dd, *J* 10.4 and 15.1 Hz, H-3), 6.28 (1H, d, *J* 14.4 Hz, H-1), 7.07 (1H, dd, *J* 10.4 and 14.4 Hz, H-2), 7.15-7.35 (5H, m, Ar*H*); δ_C(100 MHz; $CDCl_3$), 38.6 (C-5), 77.3 (C-1), 126.2 (*ortho*-*C*H), 128.3 (*para*-*C*H), 131.2 (C-3), 134.1 (C-4), 139.2 (*ipso*-*C*), 145.0 (C-2); *m/z* (GCMS-EI) 270 (15, MH^+), 143 (60), 128 (85), 91 (100), 51 (65); HRMS: Found 269.9911, $C_{11}H_{11}I$ requires 269.9906.

(Iodomethyl)triphenylphosphonium iodide[20]



A solution of triphenylphosphine (3.00 g, 11.40 mmol) and diiodomethane (3.98 g, 14.90 mmol) in dry toluene (10 ml) in a flask protected from the light was stirred at 50° C for 24 hrs. The mixture was cooled to RT, filtered and washed thoroughly with toluene. The residue was dried *in vacuo* at RT to yield the title compound as a white powder (3.00 g, 50%); mp 227-229° C (Lit[20] 228-230° C).

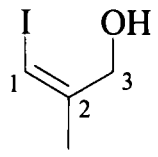
1-Iodo-5-phenylpenta-1,3(*Z*)-diene (3.12a) : 1-Iodo-5-phenylpenta-1,3(*E*)-diene (3.12b)



NaHMDS (2.5 ml of a 1 M solution in THF, 2.5 mmol) was added dropwise to a stirred suspension of (iodomethyl)triphenylphosphonium iodide (1.36 g, 2.5 mmol) at RT. After 5 minutes, the red solution was cooled to -78° C, before a solution of 4-phenyl-but-2-(*E*)-enal **(3.35)** (250 mg, 1.71 mmol) in dry THF (5 ml) was added at such a rate so as to keep the internal temperature below -70° C. The mixture was stirred at -78° C for 15 mins, allowed to warm to RT and stirred for 2 h. Sat. aq. NH_4Cl (10 ml) was added, the layers separated and the aqueous layer extracted with Et_2O (3 x 25 ml), the combined organic layers were dried ($MgSO_4$) and concentrated to yield the crude product. Purification by column chromatography (Petrol) yielded the previously unreported title compound (320 mg, 69%) as a yellow/orange oil as a 8:1 mixture of 1(*Z*):1(*E*) isomers: R_f 0.53 (24:1 v/v petrol:EtOAc); $\nu_{max}(CHCl_3)/cm^{-1}$ 3062(m), 3025(m), 1640(m), 1602(m), 1494(m), 1452(m), 972(s), 748(s), 698(s), 576(s). **Data for major 1(*Z*)-isomer**: δ_H(400 MHz; $CDCl_3$) 3.51 (2H, d, *J* 7.1 Hz, H-5), 6.14 (1H, dt, *J* 15.1 and 7.2 Hz, H-4), 6.18 (1H, d, *J* 7.2 Hz, H-1),6.32 (1H, dd, *J* 15.1 and 9.8 Hz, H-3), 6.73 (1H, dd, *J* 9.8 and 7.7 Hz, H-2), 7.30-7.49 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$) 39.4 (C-5), 80.6 (C-4), 126.3 (*para*-*C*H), 128.5 (*ortho*-*C*H), 128.6 (*meta*-*C*H), 131.5 (C-2), 138.1 (C-3), 138.2 (C-1), 139.3 (*ipso*-C); *m/z* (GCMS,

EI) 270 (18, MH^+), 254(51), 143(98), 128(100), 115(72), 91(52), 65(42); HRMS (TOF MS FI^+) Found 269.9904, $C_{11}H_{11}I$ requires 269.9906.

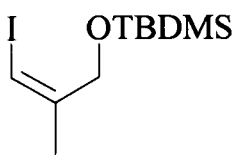
2-Methyl-3-iodoprop-2(*Z*)-en-1-ol (3.19)[21]



To a stirred solution of propargyl alcohol (1.26 g, 22.40 mmol) and copper(I) iodide (0.43 g, 2.24 mmol) in dry Et_2O (70 ml) at -10° C was added MeMgBr (18.60 ml of a 3 M solution in Et_2O, 56.00 mmol) dropwise. The mixture was stirred at –10° C for 2 hrs, at RT for 20 h, then recooled to 0° C before finely ground I_2 (15.35 g, 60.48 mmol) was added in portions. The mixture was stirred at 0° C for 90 mins. Sat. aq. NH_4Cl (70 ml) was cautiously added. The layers were separated, and the aqueous layer extracted with Et_2O (3 x 45 ml). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (80 ml), brine (80 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (21:4 v/v Petrol:EtOAc) yielded the title compound (2.16 g, 47%) as a dark orange oil: R_f 0.26 (21:4 v/v Petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 1.97 (3H, s, C*H*$_3$), 4.26 (2H, s, C*H*$_2$OH), 5.98 (1H, s, C*H*I).

Lit[22] NMR: δ_H(200 MHz; $CDCl_3$) 1.71 (1H, s, O*H*, disappears upon addition of D_2O), 1.92 (3H, d, *J* 1.5 Hz, C*H*$_3$), 4.20 (2H, s, C*H*$_2$OH), 5.95 (1H, d, *J* 1.5 Hz, C*H*I).

1-(*tert*-Butyldimethylsilyloxy)-3-iodo-2-methylprop-2(*Z*)-ene (3.38)

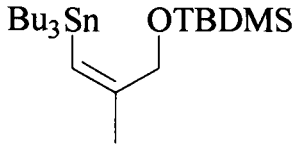


To a stirred solution of alcohol **(3.19)** (2.28 g, 11.46 mmol) in dry DMF (15 ml) at 0° C was added imidazole (1.18 g, 17.30 mmol) in portions, followed by a solution of TBDMSCl (2.43 g, 16.15 mmol) in dry DMF (5 ml) dropwise. The mixture was stirred for 1 h at 0° C, then for 22 hrs at RT. The mixture was partitioned between

Et_2O (150 ml) and 10% HCl (50 ml). The aqueous layer was separated and extracted with Et_2O (2 x 20 ml). The combined organic layers were washed with sat. aq. $NaHCO_3$ (80 ml), brine (80 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (23:2 v/v Petrol:Et_2O) yielded the title compound (3.0 g, 84%) as a red oil: R_f 0.34 (Petrol): ν_{max}(film)/cm^{-1} 2955(s), 2929(s), 1471(m), 1463(m), 1252(s), 1100(s), 839(s), 777(s), 666(m); δ_H(400 MHz; $CDCl_3$) 0.12 (6H, s, Si(CH_3)$_2$), 0.92 (9H, s, SiC(CH_3)$_3$), 1.91 (3H, d, *J* 1.4 Hz, CH=C(CH_3)), 4.27 (2H, s, H-1), 5.87 (1H, q, *J* 1.4 Hz, H-3); δ_C(100.6 MHz; $CDCl_3$) -3.6 (Si(CH_3)$_2$), 18.2 (SiC(CH_3)$_3$), 21.4 (C(CH_3)), 25.8 (SiC(CH_3)$_3$), 68.6 (C-1), 72.4 (C-3), 146.7 (C-2); *m/z* (GCMS CI) 330 (15%, MNH_4^+), 313 (75, MH^+), 255 (32, $[M - tBu]^+$), 185 (25, $[M - I]^+$), 75 (52), 73 (46), 53 (34), 43 (95); Found 330.0752 $[MNH_4]^+$, $C_6H_{16}INOSi$ requires 330.0750.

Previously reported[23], however no data presented.

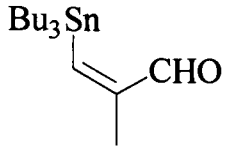
1-(*tert*-Butyldimethylsilyoxy)-2-methyl-3-(tributylstannyl)prop-2(*Z*)-ene (3.39)



To a stirred solution of iodide **(3.38)** (2.16 g, 6.912 mmol) in dry Et_2O (15 ml) was added n-BuLi (7.00 ml of a 1.6 M solution in hexanes, 17.75 mmol) dropwise over 20 minutes at -78° C. After 90 mins a solution of Bu_3SnCl (3.59 g, 11 mmol) in dry Et_2O (5 ml) was added dropwise. The mixture was stirred at -78° C for 3 hrs, then for 2 hrs at 0° C, before being quenched with sat. aq. NH_4Cl (10 ml). The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 ml), the layers were combined and dried (Na_2SO_4). Purification by column chromatography (Petrol + 1% Et_3N) yielded the previously unreported title compound (2.94 g, 93%) as a colourless oil: R_f 0.35 (Petrol); ν_{max}(film)/cm^{-1} 2957(s), 2928(s), 2856(s), 1610(w), 1463(s), 1254(s), 1251(s), 1084(s), 856(s), 836(s), 776(s), 666(m); δ_H(400 MHz; $CDCl_3$) 0.08 (6H, s, Si(CH_3)$_2$), 0.85-0.94 (15H, m, alkyl), 0.89 (9H, s, SiC(CH_3)$_3$), 1.25-1.58 (12H, m, ($CH_3CH_2CH_2CH_2$)$_3$Sn and ($CH_3CH_2CH_2CH_2$)$_3$Sn), 1.92 (3H, d, *J* 1.3 Hz, C(CH_3)CH_2O), 4.03 (2H, s, H-1), 5.60 (1H, q, *J* 1.3 Hz, SnC*H*=C, ^{117,119}Sn satellites give $^2J_{H,Sn}$ 66 Hz); δ_C(100.6MHz; $CDCl_3$) –5.4 (Si(CH_3)$_2$), 10.3

(($CH_3CH_2CH_2CH_2)_3Sn$), 13.6 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 22.6 (($CH_3CH_2CH_2CH_2)_3Sn$), 23.6 ($C(CH_3)OTBDMS$), 25.9 ($SiC(CH_3)_3$, 27.3 (($CH_3CH_2CH_2CH_2)_3Sn$), 29.1 (($CH_3CH_2CH_2CH_2)_3Sn$), 69.4 (CH_2O), 124.3 (SnCH=C), 154.1 ($C(CH)_3CH_2O$); *m/z* (EI) 419 (100, $[M - {}^tBu]^+$), 291 (23), 267 (14) 235 (34), 177 (48), 121 (21), 73 (35), 58(32).

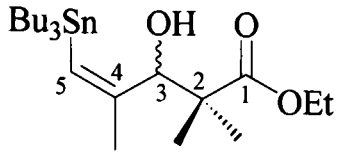
2-Methyl-3-(tributylstannyl)prop-2(*Z*)-enal (3.41)



To a stirred solution of silyl ether **(3.39)** (1.00 g, 2.3 mmol) in dry THF (7 ml) at RT was added TBAF (7 ml of a 1 M solution in THF, 7 mmol) dropwise. The mixture was stirred for 2 hrs, then quenched with sat. aq. NH_4Cl (3 ml). The THF was removed *in vacuo*, and the residue partitioned between Et_2O (20 ml) and brine (15 ml). The layers were separated and the aqueous layer extracted with Et_2O (3 x 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the crude alcohol. To a stirred solution of $(COCl)_2$ (0.61 g, 5 mmol) in dry DCM (8 ml) at -78° C was added dry DMSO (0.7 ml, 10 mmol) dropwise. After 10 minutes a solution of the crude alcohol in dry DCM (2 ml) was added dropwise. After 15 mins dry Et_3N (3.5 ml, 50 mmol) was added dropwise. The mixture was stirred at -78° C for 5 mins, warmed to RT over 10 mins and then stirred for another 10 mins. Sat. aq. $NaHCO_3$ (10 ml) was added. The layers were separated and the aqueous layer extracted with DCM (3 x 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (24:1 v/v Petrol:EtOAc + 1% Et_3N) yielded the title compound (0.77 g, 77%) as a yellow oil: R_f 0.46 (24:1 v/v Petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 0.86-1.54 (27H, m, Bu_3Sn), 1.97 (3H, d, *J* 1.4 Hz, $C(CH_3)CHO$), 7.42 (1H, d, *J* 1.4 Hz, H-3, $^{117, 119}Sn$ satellites give $^2J_{H,Sn}$ 48 Hz), 9.49 (1H, s, H-1, $^{117, 119}Sn$ satellites give $^4J_{H,Sn}$ 2 Hz).

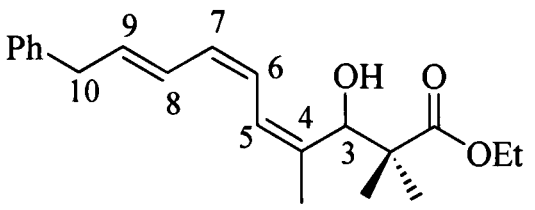
Lit[24] NMR: δ_H(500 MHz; $CDCl_3$) 0.82-0.97 (15H, m), 1.24-1.39 (6H, m), 1.44-1.56 (6H, m), 1.74 (3H, s), 3.30 (6H, s), 4.53 (1H, s), 5.96 (1H, s).

Racemic Ethyl 3-Hydroxy-5-(tributylstannyl)-2,2,4-trimethylpent-4(*Z*)-enoate (rac-3.18)

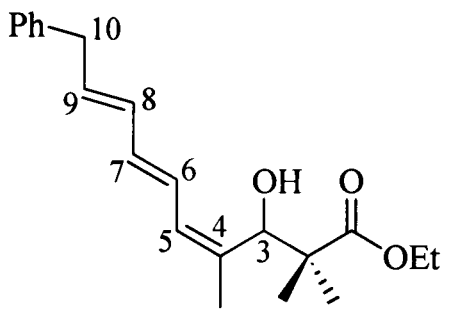


To a stirred solution of dry $^{i}Pr_2NH$ (0.9 ml, 6.31 mmol) in dry THF (10 ml) at -78° C was added n-BuLi (4 ml of a 1.6 M solution in THF, 6.31 mmol) dropwise. After 1 hr, a solution of ethyl isobutyrate (0.78 g, 6.11 mmol) in dry THF (5 ml) was added dropwise. After a further 1 hr a solution of aldehyde **(3.41)** (0.837 g, 1.91 mmol) in dry THF (5 ml) was added dropwise. The mixture was stirred at -78° C for 30 mins, sat. aq. NH_4Cl (5 ml) was added and the cold slurry immediately partitioned between Et_2O (20 ml) and water (10 ml). The layers were separated and the aqueous layer extracted with EtOAc (4 x 10 ml). The combined organic layers were washed with brine (25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (23:2 v/v Petrol:EtOAc + 1% Et_3N) yielded the previously unreported title compound (0.639 g, 71%) as a pale yellow oil: R_f 0.42 (23:2 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 3487 (br, s), 2957(s), 1704(s), 1604(w), 1466(s), 1253(s), 1140(s), 667(s); δ_H(200 MHz; $CDCl_3$) 0.84-0.93 (15H, m, ($CH_3CH_2CH_2CH_2$)$_3$Sn and ($CH_3CH_2CH_2CH_2$)$_3$Sn), 1.18 (3H, s, C(CH_3)(CH_3)), 1.29 (3H, s, CH_3), 1.31 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.36 (6H, m, alkyl C-*H*), 1.50 (6H, m, alkyl, C-*H*), 1.79 (3H, d, *J* 1.3 Hz, SnCH=C(CH_3)), 3.72 (1H, d, *J* 7.2 Hz, exch. D_2O, O*H*), 3.93 (1H, d, *J* 7.2 Hz, H-3), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.72 (1H, d, *J* 1.3 Hz, H-5, ^{117,119}Sn satellites $^{2}J_{H,Sn}$ 62 Hz); δ_C(50.3 MHz; $CDCl_3$) 10.5 (($CH_3CH_2CH_2CH_2$)$_3$Sn), 13.5 (($CH_3CH_2CH_2CH_2$)$_3$Sn), 13.9 (OCH_2CH_3), 14.00 (SnCH=C(CH_3)), 21.3 (C(CH_3)(CH_3)), 21.5 (C(CH_3)(CH_3)), 25.4 ($CH_3CH_2CH_2CH_2$)$_3$Sn), 27.3 ($CH_3CH_2CH_2CH_2$)$_3$Sn), 44.8 (*C*(CH_3)$_2$), 61.0 (OCH_2CH_3), 83.9 (*C*H(OH)), 131.0 (C-5), 152.8 (C-4), 178.6 (C-1); *m/z* (EI) 419 (11%, [M – Bu]$^+$), 349 (22), 303 (100), 279 (21), 269 (23), 247 (49), 191 (39), 177 (39), 121 (25), 81 (28), 69 (47).

Racemic 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*Z*),8(*E*)-trienoate (rac-3.43a) : 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*E*),8(*E*)-trienoate 3:1 (rac-3.42a)



(rac-3.43a)



(rac-3.42a)

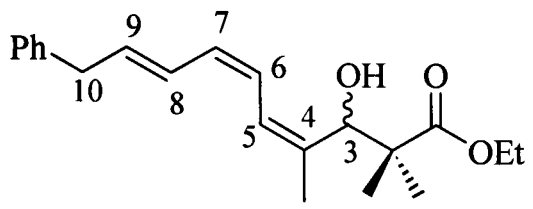
To a stirred solution of $PdCl_2(MeCN)_2$ (3.4 mg, 0.012 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **(3.12a,b)** (200 mg, 0.74 mmol) in dry DMF (2 ml) followed by a solution of racemic stannane **(rac-3.18)** (118 mg, 0.25 mmol) in dry DMF (1 ml). The mixture was stirred for 7 -13 hrs, diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 x 20 ml). The combined aqueous washings were extracted with EtOAc (3 x 15 ml), the combined organic layers were washed with brine (2 x 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (22:3 v/v petrol:EtOAc + 1% Et_3N) yielded the previously unreported title compound as a 3:1 mixture of 4(*Z*),6(*Z*),8(*E*) : 4(*Z*),6(*E*),8(*E*) (60mg, 72%) as a viscous oil: R_f 0.16 (22:3 v/v petrol:EtOAc); λ_{max} (MeOH)/nm 269sh (ε/dm^3 mol^{-1} cm^{-1} 26970), 279 (33600), 290(26970, sh); ν_{max}(film)/cm^{-1} 3470 (br, s), 2980(s), 1720(s), 1450(m), 1255(s), 1140(s); *m/z* (APCI$^+$) 311 (18%,[M-OH]$^+$), 237 (28), 195 (48), 167 (25), 149 (50), 118 (100), 113 (30); HRMS (CI$^+$): Found 311.2009, $C_{21}H_{27}O_2$ requires 311.2011, (M-OH$^+$).

4(*Z*),6(*Z*),8(*E*)-isomer: δ_H(500 MHz; $CDCl_3$) 0.89 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 1.23 (6H, s, $(CH_3)_2$), 1.85 (3H, s, C(4)-CH_3), 3.50 (1H, d, J 7.6, O*H*), 3.52 (2H, d, *J* 7.0 Hz, H-10), 4.20 (2H, q, *J* 7.4 Hz, OCH_2), 4.81 (1H, s, H-3), 5.93 (1H, dt, *J* 14.8 and 7.1 Hz, H-9), 6.03 (1H, m, H-7), 6.20 (1H, dd, *J* 11.1 and 11.9 Hz, H-6), 6.52 (1H, d, *J* 11.9 Hz, H-5), 6.66 (1H, dd, *J* 14.8 and 11.2 Hz, H-8), 7.15-7.35 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$); 14.1 (OCH_2CH_3), 19.6 ($C(CH_3)(CH_3)$), 20.9 ($C(CH_3)(CH_3)$), 24.5 (CH_3), 39.3 ($C_6H_5CH_2$), 61.0 (OCH_2CH_3), 75.0 (*C*-OH), 125.1 (C(5)), 126.1 (C(9)), 126.6 (Ar*C*), 128.5 (Ar*C*), 128.7 (ArC), 131.6 (C(6)), 132.5 (C(7)), 133.1 (C(8)), 134.4 (ArC);

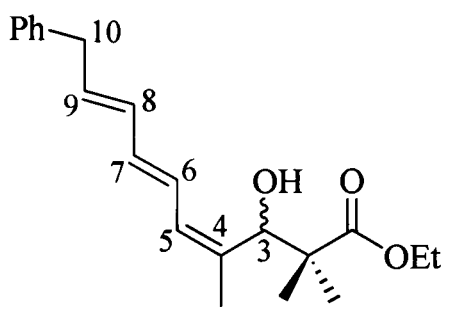
4(*Z*),6(*E*),8(*E*)-isomer: δ_H(500 MHz; $CDCl_3$) all signals overlapping with major isomer, except 3.41 (1H, d, *J* 7.6 Hz, O*H*); δ_C(400 MHz; $CDCl_3$); 13.9 (OCH_2CH_3),

19.4 ($C(CH_3)(CH_3)$), 20.9 ($C(CH_3)(CH_3)$), 23.7 (CH_3), 39.1 ($C_6H_5CH_2$), 60.8 (OCH_2CH_3), 74.6 (*C*-OH), 126.4 (Ar*C*), 127.6 (C(6)), 128.4 (Ar*C*), 128.5 (ArC). 130.6 (C(5)), 132.8 (C(C8)), 133.0 (C(C7)), 133.4 (C(9)).
(Assignment performed *via* use of ^1H, ^{13}C, COSY, DEPT and n.O.e experiments).

Racemic 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*Z*),8(*E*)-trienoate (rac-3.43a) : 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*E*),8(*E*)-trienoate 1:1 (rac-3.42a)



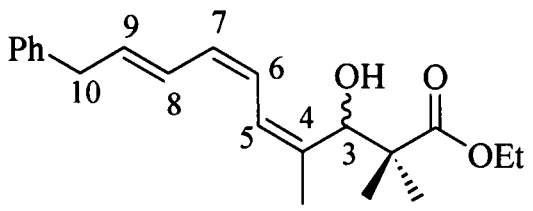
(rac-3.43a)



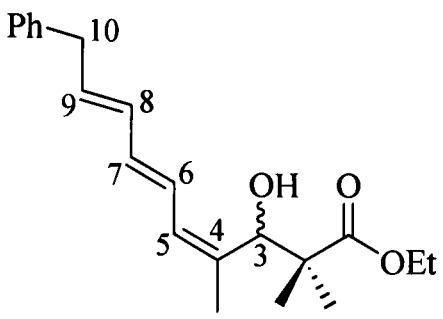
(rac-3.42a)

To a stirred solution of $PdCl_2(MeCN)_2$ (4 mg, 0.015 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **(3.12a,b)** (105 mg, 0.31 mmol) in dry DMF (2 ml) followed by a solution of racemic stannane **(rac-3.18)** (143 mg, 0.30 mmol) in dry DMF (1 ml). The mixture was stirred for 24 hrs, diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 x 20 ml). The combined aqueous washings were extracted with EtOAc (3 x 15 ml), the combined organic layers were washed with brine (2 x 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (22:3 v/v petrol:EtOAc + 1% Et_3N) yielded the previously unreported title compound as a 1:1 mixture of 4(*Z*),6(*Z*),8(*E*) : 4(*Z*),6(*E*),8(*E*) (76mg, 77%) as a viscous oil: R_f 0.16 (22:3 v/v petrol:EtOAc). Spectroscopic data identical to the above.
(Assignment was aided by NMR technique described in section 3.6).

Racemic 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*Z*),8(*E*)-trienoate (rac-3.43a) : 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*E*),8(*E*)-trienoate 1:3 (rac-3.42a) *via* low temperature Stille coupling



(rac-3.43a)



(rac-3.42a)

To a stirred solution of $PdCl_2(MeCN)_2$ (20 mg, 0.6 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **(3.12a,b)** (391 mg, 1.45 mmol) in dry DMF (2 ml) followed by a solution of racemic stannane **(rac-3.18)** (300 mg, 1.15 mmol) in dry DMF (1 ml). The reaction solution was kept at -20° C for 14 days. The mixture was diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 x 20 ml). The combined aqueous washings were extracted with EtOAc (3 x 15 ml), the combined organic layers were washed with brine (2 x 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (43:7 v/v petrol:EtOAc + 1% Et_3N) yielded the previously unreported title compound as a 3:1 mixture of 4(*Z*),6(*E*),8(*E*) : 4(*Z*),6(*Z*),8(*E*) (160 mg, 42%) as a viscous oil: R_f 0.58 (43:7 v/v petrol:EtOAc); λ_{max} (MeOH)/nm 269sh (ε/dm^3 mol^{-1} cm^{-1} 26970), 279 (33560), 290sh (26970); ν_{max}($CHCl_3$)/cm^{-1} 2980(s), 1723(s), 1453(m), 1254(s), 1136(s); *m/z* (APCI) 311 (5, M-OH$^+$), 295 (100), 195 (30), 167 (50), 148 (45), 118 (20); HRMS (CI): Found 311.2003, $C_{21}H_{27}O_2$ requires 311.2011, (M-OH$^+$);

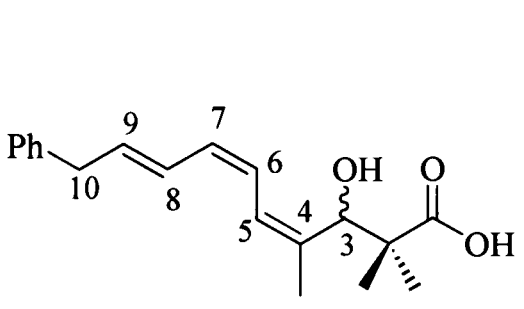
4(*Z*),6(*Z*),8(*E*)-isomer (minor): δ_H(500 MHz; C_6D_6) 0.91 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 1.25 (6H, s, $(CH_3)_2$), 1.84 (1H, d, *J* 7.6 Hz, O*H*), 1.85 (3H, m, C(4)-CH_3), 3.25 (2H, d, *J* 7.3 Hz, H-10), 3.82 (2H, q, *J* 7.4 Hz, OCH_2), 4.83 (1H, s, H-3), 5.72 (1H, dd, *J* 14.7 and 7.3 Hz, H-9), 5.93 (1H, m, H-7), 6.23 (1H, t, *J* 11.7 and 11.7 Hz, H-6), 6.50 (1H, d, *J* 12.5 Hz, H-5), 6.57 (1H, dd, *J* 14.8 and 11.2 Hz, H-8), 7.15-7.3 (5H, m, Ar*H*);

δ_C(400 MHz; $CDCl_3$); 14.2 (OCH_2CH_3), 21.1 (C(5)-CH_3), 23.3 ($C(CH_3)(CH_3)$), 24.3 ($C(CH_3)(CH_3)$), 39.6 (C-10), 61.0 (OCH_2CH_3), 80.7 (C-3), 123.8 (C-6), 125.3 (C-5), 127.0 (C-8), 127.94 (*m*-Ar*C*), 128.42 (*m*-Ar*C*), 128.53 (*o*-Ar*C*), 128.91 (*o*-Ar*C*), 129.0 (C-7), 134.8 (C-9), 137.23 (*ipso*-Ar*C*).

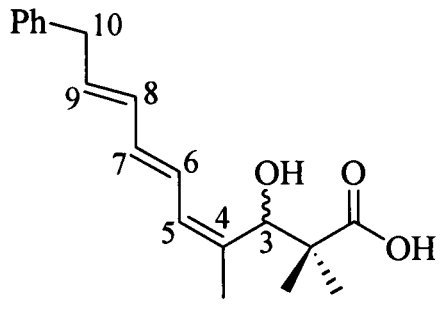
4(*Z*),6(*E*),8(*E*)-isomer (major): δ_H(500 MHz; C_6D_6) 0.91 (3H, t, *J* 7.3 Hz, OCH_2CH_3), 1.27 (6H, s, $(CH_3)_2$), 1.71 (1H, d, *J* 7.6 Hz, O*H*), 1.81 (3H, m, C(4)-CH_3), 3.22 (2H, d, *J* 7.3 Hz, H-10), 3.91 (2H, q, *J* 7.3 Hz, OCH_2), 4.90 (1H, s, H-3), 5.70 (1H, dd, *J* 14.7 and 7.0 Hz, H-9), 6.02 (1H, d, *J* 12.1 Hz, H-5), 6.03 (1H, dd, *J* 14.0

and 11.7 Hz, H-8), 6.09 (1H, dd, *J* 11.4 and 14.2 Hz, H-7), 6.45 (1H, dd, *J* 11.7 and 14.2 Hz, H-6), 7.15-7.3 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$); 14.2 (OCH_2CH_3), 21.5 (C(5)-CH_3), 24.8 ($C(CH_3)(CH_3)$), 24.9 ($C(CH_3)(CH_3)$), 39.6 (C-10), 61.1 (OCH_2CH_3), 80.8 (C-3), 126.6 (*p*-Ar*C*), 127.6 (C-6), 128.2 (*m*-Ar*C*), 128.5 (*m*-Ar*C*), 129.1 (*o*-Ar*C*), 130.6 (C-5), 132.3 (C-8), 133.0 (C-7), 133.4 (C-9), 137.2 (*ipso*-Ar*C*).
(Assignment was aided by application of the NMR technique discussed in section 3.6. Unequivocal assignment of H-10 at δ3.25 was available *via* ^1H and COSY techniques. COSY experimentation displayed a strong correlation of the H-10 signal to the H-9 signal at δ5.93 thus unequivocal assignment *via* extended correlation was possible for the olefin region. The number of cross peaks observed displayed the splitting pattern of the ^1H signal (H-9 provides a 5 cross peak distribution, the ^1H signal exists as a double triplet, i.e. a quintet). HSQC experimentation with computer editing provided high resolution 'slices' of each proton environment allowing coupling constants to be calculated, thus H-9 was calculated as *J* 14.7 and 7.0 Hz (which would not have been possibly through 'standard' ^1H NMR techniques due to a highly overlapped spectra). Whilst used mainly for the higher resolution properties, the HSQC also allowed complete assignment of the ^{13}C spectrum for the olefinic protons (Table 3.1)).

Racemic 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*Z*),8(*E*)-trienoate (rac-3.43b) : 3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*E*),8(*E*)-trienoate 1:1 (rac-3.42b)



(rac-3.43b)



(rac-3.42b)

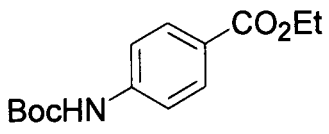
A racemic mixture of 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*Z*),8(*E*)-trienoate **(rac-3.43a)** : 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-4(*Z*),6(*E*),8(*E*)-trienoate 1:1 **(rac-3.42a)** (220 mg, 0.67 mmol) in dry THF (5 ml) was added dropwise to a suspension of lithium hydroxide (0.09 g, 2.1 mmol) in a solvent mixture of THF:MeOH:H_2O (1:1:1) (30 ml). The solution was stirred at RT for 24 hrs. 10%

HCl (5 ml) in H_2O (3 ml) was added and the solution immediately extracted with EtOAc (3 x 30 ml), the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (43:7 v/v petrol:EtOAc and 1% Et_3N) yielded the previously unreported title compound as a viscous yellow oil (105 mg, 52%): R_f 0.30 (24:1 v/v petrol:EtOAc); ν_{max}(film)/cm^{-1} 2850(br, s), 1727(s), 1453(m), 1254(w), 1137(w); *m/z* (APCI) 283 [MH-OH$^+$] (30%), 237 (60), 195 (100), 180 (40), 155 (50), 149 (40), 127 (35), 117 (50), 102 (70); HRMS (CI) Found 283.1696, $C_{19}H_{23}O_3$ requires 283.1698 (M-OH$^+$).

4(*Z*),6(*Z*),8(*E*)-isomer (major): δ_H(400 MHz; $CDCl_3$) 0.89 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 1.23 (6H, s, $(CH_3)_2$), 1.45 (3H, m, C(4)-CH_3), 3.45 (1H, d, *J* 7.6 Hz, O*H*), 3.46 (2H, d, *J* 7.0 Hz, H-10), 5.71 (1H, s, H-3), 5.83 (1H, dt, *J* 14.8 and 7.1 Hz, H-9), 5.91 (1H, m, H-7), 6.20 (1H, dd, *J* 11.1 and 11.9 Hz, H-6), 6.52 (1H, d, *J* 11.9 Hz, H-5), 6.59 (1H, dd, *J* 14.8 and 11.1 Hz, H-8), 7.15-7.35 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$) 16.2 (C(2)(CH_3)$_2$), 17.3 (C(4)CH_3), 38.9 (*C*-10), 48.7 (*C*-2), 80.1 (*C*-3), 120.7 (*C*-5), 125.7 (*C*-9), 125.5, 128.4, 129.2 (Ar-*C*H), 129.5 (*C*-8), 129.9 (*C*-7 and *C*-6), 137.7 (*ipso*-*C*), 140.4 (*C*-4), 179.0 (*C*-3).

(Assignment was aided by NMR technique previously described in Section 3.6).

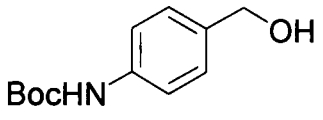
4-*tert*-Butoxycarbonylaminobenzoic acid ethyl ester (3.45)[25]



Using the literature protocol, to a stirred solution of ethyl-4-aminobenzoate (4.0 g, 24.2 mmol) in DCM (100 ml) at 0° C was added NEt_3 (5 ml, 36.4 mmol), $(Boc)_2O$ (7.5 g, 36.4 mmol) and DMAP (300mg, cat) and the reaction mixture stirred at RT for 2 hrs. The solution was concentrated *in vacuo* and water (50 ml) added to the residue. The aqeuous phase was extracted with EtOAc (3 x 30 ml) and the combined organic layers washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (5:2 v/v petrol:EtOAc) yielded the title compound as a white powder (4.86 g, 76%); R_f 0.52 (5:2 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$); 1.31 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.39 (9H, s, ^{t}Bu), 4.29 (2H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 6.49 (1H, br, N*H*), 7.74 (2H, d, *J* 8.7 Hz, Ar*H*), 7.96 (2H, d, *J* 8.7 Hz Ar*H*).

Lit[26] NMR: δ_H(200 MHz; $CDCl_3$); 1.27 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.39 (9H, s, ^tBu), 4.31 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 6.52 (1H, br, N*H*), 7.70 (2H, d, *J* 8.7 Hz, Ar*H*), 7.94 (2H, d, *J* 8.7 Hz Ar*H*).

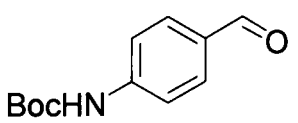
4-*tert*-Butoxycarbonylaminobenzyl alcohol (3.46)



To a stirred solution of ester **(3.45)** (2.5 g, 9.43 mmol) in dry THF (30 ml) at -78° C was added DIBAL-H (23 ml of a 1.5 M solution in toluene, 49.0 mmol) dropwise, the solution stirred for 1 hr, warmed to -15° C and stirred for a further 1 hr. The reaction mixture was quenched with 10% HCl (30 ml) CARE! at -15° C and stirred until two clear phases had formed. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 25 ml), the combined organic washings were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (3:2 v/v petrol:EtOAc) yielded the title compound as a colourless viscous oil (1.74g, 83%); R_f 0.31 (3:2 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 1.49 (9H, s, ^tBu), 4.61 (2H, s, C*H*$_2$), 6.45 (1H, br, N*H*), 7.20 (2H, d, *J* 8.7 Hz, Ar*H*), 7.36 (2H, d, *J* 8.7 Hz, Ar*H*).

Lit[27] NMR: δ_H(200 MHz; $CDCl_3$) 1.51 (9H, s), 2.35 (1H, s), 4.57 (2H, s), 6.72 (1H, br, s), 7.23 (2H, d, *J* 8.3 Hz), 7.31 (2H, d, *J* 8.3 Hz).

4-*tert*-Butoxycarbonylaminobenzaldehyde (3.47)

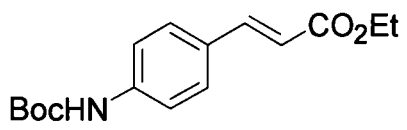


To a stirred suspension of PCC (4.7 g, 21.7 mmol) in dry DCM (100 ml) was added alcohol **(3.46)** (3.2 g, 14.5 mmol) in dry DCM (5 ml) and the reaction mixture stirred for 2.5 hrs. Et_2O (30 ml) was added and the solution filtered through Celite® washing thoroughly with Et_2O. The combined organic washing were concentrated *in vacuo*. Purification by column chromatography (17:3 v/v petrol:EtOAc) yielded the title compound as a white powder (2 g, 63%); R_f 0.17 (17:3 v/v petrol:EtOAC);

δ_H(200 MHz; $CDCl_3$) 1.54 (9H, s, ^tBu), 6.73 (1H, br, N*H*), 7.47 (2H, d, *J* 8.7 Hz, Ar*H*), 7.59 (2H, d, *J* 8.7 Hz, Ar*H*), 9.82 (1H, s, C*H*O).

Lit[28] NMR: δ_H(400 MHz; $CDCl_3$) 1.45 (9H, s), 6.9 (1H, s), 7.5 (2H, d), 7.8 (2H, d), 9.9 (1H, s).

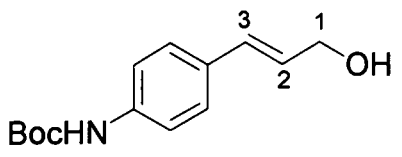
3-(4-*tert*-Butoxycarbonylamino-phenyl)-(*E*)acrylic acid ethyl ester (3.48)



To a stirred solution of aldehyde **(3.47)** (2 g, 9.05 mmol) in DCM (100 ml) was added (carbethoxymethylene)triphenylphosphorane (3.8 g, 10.86 mmol) and the reaction mixture stirred at RT for 24 hrs. The solution was concentrated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the title compound as a white powder (2.08 g, 79%); R_f 0.42 (4:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.54 (9H, s, ^tBu), 4.23 (2H, q, *J* 7.1 Hz, CH_2CH_3), 6.33 (1H, d, *J* 16 Hz, ArC*H*=CH), 6.58 (1H, br, N*H*), 7.37 (2H, d, *J* 8.6 Hz, *ArH*), 7.49 (2H, d, *J* 8.6 Hz, Ar*H*), 7.62 (1H, d, *J* 16 Hz, CH=C*H*CO_2Et).

Lit[29] NMR: δ_H(200 MHz; $CDCl_3$) 1.33 (3H, t, *J* 7.13 Hz, CH_2CH_3), 1.52 (9H, s, ^tBu), 4.25 (2H, q, *J* 7.19 Hz, CH_2CH_3), 6.34 (1H, d, *J* 15.72 Hz, ArC*H*=CH), 6.79 (1H, br, N*H*), 7.39 (2H, d, *J* 9.14 Hz, *ArH*), 7.45 (2H, d, *J* 9.12 Hz, Ar*H*), 7.63 (1H, d, *J* 15.72 Hz, CH=C*H*CO_2Et).

3-(4-*tert*-Butoxycarbonylaminophenyl)-2-prop(*E*)enol (3.49)



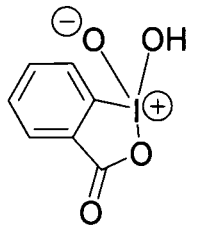
To a stirred solution of ethyl ester **(3.48)** (1 g, 3.57 mmol) in dry THF (30 ml) at -78° C was added DIBAL-H (8.7 ml of a 1.5 M solution in toluene, 18.56 mmol) dropwise. The reaction mixture was stirred at -78° C for 1 hr and at -15° C for 1 hr. The

reaction was quenched with 10% HCl (30 ml) and stirred for 10 mins until two clear phases had formed. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 25 ml), the combined organic washings were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (3:2 v/v petrol:EtOAc increasing polarity to 1:1 v/v petrol:EtOAc) yielded the previously unreported title compound as a yellow powder (470 mg, 53%); R_f 0.64 (1:1 v/v petrol:EtOAc); $\nu_{max}(CHCl_3)/cm^{-1}$ 3325(br, w), 2977(w), 1707(s), 1526(s), 1238(w), 1162(s), 1054(m), 733(w); δ_H(200 MHz; $CDCl_3$) 1.52 (9H, s, ^tBu), 4.18 (2H, d, *J* 6.7 Hz, CH_2), 6.20 (1H, d, *J* 16.2 Hz, PhC*H*=CH), 6.52 (1H, q, *J* 16.2 Hz, CH=C*H*CH_2OH), 6.61 (1H, br, N*H*), 7.20 (2H, d, *J* 8.6 Hz, *ArH*), 7.39 (2H, d, *J* 8.6 Hz, Ar*H*); δ_C(50.3 MHz; $CDCl_3$) 28.73 (C(CH_3)$_3$), 65.62 (CH_2), 70.61 ($C(CH_3)_3$), 120.31 (Ar-*C*H), 126.34 (Ar-*C*H), 125.56 (C-2), 127.65 (C-3), 130.45 (*ipso-C*-CH=$CHCH_2OH$), 137.43 (*ipso-C*-NHBoc); m/z 250 $[MH]^+$ (40%), 174 (22), 158 (100), 148 (31), 134 (24).

Preparation of Manganese (IV) Oxide[30]

To a solution of $KMnO_4$ (5 g, 31.65 mmol, 8.7 eq) in water (250 ml) at 70° C was added a solution of $MnSO_4.4H_2O$ (738 mg, 3.6 mmol, 1.0 eq) in water (50 ml) and a solution of 40% NaOH (2 g in 50 ml) dropwise simultaneously. The reaction mixture was stirred for 1 hr at 70° C, allowed to cool to RT, filtered and washed with water until the residue became colourless. The colourless powder was oven dried (200° C) and ground to a fine powder (5 g).

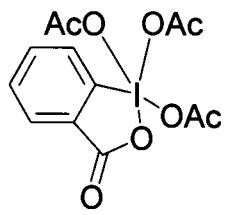
Preparation of IBX[31] – CARE!



To a stirred suspension of 2-iodobenzoic acid (5 g, 30.16 mmol, 1.0 eq) in 0.73 M H_2SO_4 (150 ml) was added $KBrO_3$ (4.4 g, 26.21 mmol, 1.3 eq) portionwise over a 30 minute period so as to keep the internal temperature below 55° C. The reaction

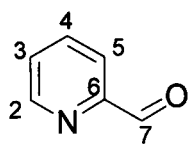
mixture was heated at 65° C for 36 hrs. The solution was cooled to 0° C, filtered, washed with water (200 ml), EtOH (2 x 25 ml) and suction dried to yield the title compound as an off-white solid (4.17 g, 74%) which was immediately carried forward.

Preparation of the Dess Martin Periodinane[31] – CARE!



To a stirred slurry of IBX (4.17 g, 14.89 mmol, 1.0 eq) in acetic acid (50 ml) was added acetic anhydride (13.44 g, 7.45 mmol, 0.5 eq) and the reaction mixture heated at 100° C for 40 mins until the solid had dissolved. The solution was concentrated *in vacuo* at 25° C and filtered under an inert atmosphere, washing with Et_2O (100 ml) to yield an off white solid (3.1 g, 48%) of the title compound. Mp 121-123 °C (Lit.[31] 124-126 °C); δ_H(200 MHz; $CDCl_3$) 2.01 (6H, s, C*H*$_3$), 2.29 (3H, s, C*H*$_3$), 7.87 (Ar-C*H*), 8.71 (Ar-C*H*), 8.34 (Ar-C*H*).

Pyridine-2-carbaldehyde (3.54)

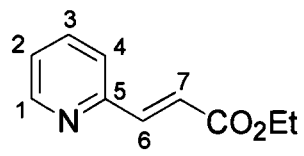


To a stirred solution of $(COCl)_2$ (4.88 g, 40.32 mmol) in dry DCM (10 ml) at -78° C was added dry DMSO (5.6 ml, 78.76 mmol) dropwise and the solution stirred for 10 mins. A solution of pyridyl-2-carbinol (2 g, 18.32 mmol) in dry DCM (5 ml) was added dropwise and stirring continued for 5 mins. Dry NEt_3 (30.4 ml, 216 mmol) was added dropwise and the reaction mixture stirred for 5 mins, allowed to warm to RT and stirred for a further 10 mins. Sat. aq. $NaHCO_3$ (20 ml) was added and the layers separated. The aqueous layer was extracted with DCM (3 x 20 ml), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (17:3 v/v petrol:EtOAc) yielded the title compound as a

yellow oil (1.5 g, 76%): R_f 0.15 (17:3 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 7.51 (1H, m, H-3), 7.89 (1H, m, H-5), 8.00 (1H, t, *J* 5.6 Hz, H-4), 8.79 (1H, d, *J* 4.1 Hz, H-2), 10.70 (1H, s, H-7).

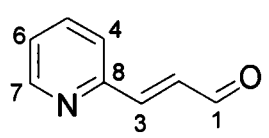
Lit[32] NMR: δ_H(300 MHz; $CDCl_3$) 7.5-7.6 (1H, m), 7.9-8.0 (2H, m), 8.8-8.9 (1H, m), 10.1 (1H, s).

(*E*)-Ethyl 3-(pyridin-2-yl)prop-2-enoate (3.55)



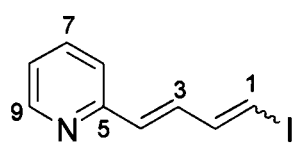
To a stirred solution of aldehyde **(3.54)** (1.88 g, 17.57 mmol) in DCM (100 ml) was added (carbethoxymethylene)triphenylphosphorane (7.40 g, 20.97 mmol) and the reaction mixture stirred at RT for 24 hrs. The solution was concentrated and redissolved in a 10:1 (v/v petrol:EtOAc) solution (50 ml), filtered and concentrated *in vacuo*, and was repeated twice more. Purification by column chromatography (23:2 v/v petrol:EtOAc, increasing polarity to EtOAc) yielded the previously unreported title compound (in exclusive *E* isomer) as a colourless oil (2.66 g, 79%): R_f 0.11 (23:2 v/v petrol:EtOAc), ν_{max}(film)/cm^{-1} 2981 (s, br), 1714(s), 1645(s), 1582(s), 1433(s), 1298(s), 1204(s), 1035(m), 982(m), 786(m); δ_H(400 MHz; $CDCl_3$); 1.42 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.28 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 6.91 (1H, d, *J* 15.7 Hz, H-7), 7.25 (1H, m, H-2), 7.38 (1H, d, *J* 7.8 Hz H-4), 7.67 (1H, d, *J* 15.7 Hz, H-6), 7.70 (1H, t, *J* 4.3 Hz, H-3), 8.66 (1H, d, *J* 4.5 Hz, H-1); δ_C(50.3 MHz; $CDCl_3$) 14.23 (OCH_2CH_3), 60.63 (OCH_2CH_3), 122.56 (C-7), 124.05 (C-2), 124.17 (C-4), 136.81 (C-3), 143.12 (C-6), 150.00 (C-1), 152.91 (C-5), 166.69 (C=O); m/z 178 $[MH]^+$ (100%), 200 $[M+Na]^+$ (75); HRMS (GCMS): Found 178.0873, $C_{10}H_{12}NO_2$ requires 178.0868.

(*E*)-3-(Pyridin-2-yl)arcrylaldehyde (3.58)



To a stirred solution of aldehyde **(3.54)** (500 mg, 4.67 mmol) in dry DCM (50 ml) was added (formylmethelene)triphenylphosphorane (1.8 g, 5.6 mmol) and the reaction mixture stirred at RT for24 hrs. The solution was concentrated *in vacuo*. Purification by column chromatography (4:1 v/v petrol:EtOAc) yielded the title compound as a dark brown oil which solidified upon standing, as exclusively the *E* alkene (440 mg, 71%); R_f 0.11 (4:1 v/v petrol:EtOAc); MP 36-37° C (Lit[33] MP 39-40° C).

1-iodo-5-(pyridin-2-yl)buta-1,3-(*Z,E*)-diene (3.59b) : 1-iodo-5-(pyridin-2-yl)buta-1,3-(*E,E*)-diene (3.59a)



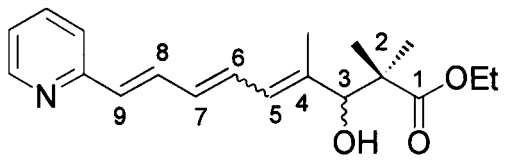
To a stirred suspension of $CrCl_2$ (2.44 g, 19.85 mmol) in dry THF (20 ml) and CHI_3 (2.6 g, 6.62 mmol) was added a solution of aldehyde **(3.58)** (440 mg, 3.31 mmol) in dry THF (8 ml) at 0° C. The reaction mixture was stirred at 0° C for 1 hr and at RT for 30 mins. Water (50 ml) was added, the organic layer separated and the aqueous layer extracted with Et_2O (3 x 25 ml). The combined organic layers were washed with $Na_2S_2O_3$ (25ml), brine (25 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (99:1 v/v petrol:Et_2O increasing polarity to Et_2O) yielded the previously unreported title compound as an orange oil (220 mg, 26%), as a 1:1 mixture of *E:Z* isomers: R_f 0.11 (99:1 v/v petrol:Et_2O); $\nu_{max}(CHCl_3)/cm^{-1}$ 2360, 1568, 1472, 1440, 1324 (all s); m/z (CI-TOF) 258 $[MH]^+$ (100%), 130 (80), 95 (8).

***Z, E* -isomer:** δ_H(400 MHz; $CDCl_3$) 6.56 (1H, d, *J* 7.6 Hz, H-1), 6.68 (1H, dd, *J* 13.5 and 6.5 Hz, H-6), 6.93 (1H, d, *J* 15.5 Hz, H-4), 7.01 (1H, dd, *J* 7.6 and 2.1 Hz, H-2), 7.18-7.33 (1H, m, H-7), 7.40 (1H, dd, *J* 15.5 and 1.1 Hz, H-3), 7.70 (1H, dd, *J* 7.7 and 1.8 Hz, H-8), 8.61 (1H, d, *J* 8.3 Hz, H-9); δ_C(100 MHz; $CDCl_3$) 82.66 (C-1), 122.07 (C-6), 122.56 (C-8), 131.88 (C-3), 132.32 (C-4), 136.46 (C-7), 138.14 (C-2), 149.78 (C-9), 154.76 (C-5).

***E, E* -isomer:** δ_H(400 MHz; $CDCl_3$) 6.56 (1H, d, *J* 10.9 Hz, H-1), 6.65 (1H, dd, *J* 12.0 and 6.4 Hz, H-6), 6.93 (1H, d, *J* 15.5 Hz, H-4), 7.02 (1H, d, *J* 10.9 and 4.2 Hz, H-2), 7.18-7.33 (1H, m, H-7), 7.41 (1H, dd, *J* 15.5 and 1.1 Hz, H-3), 7.65 (1H, dd, *J* 7.8 and 1.9 Hz, H-8), 8.65 (1H, d, *J* 8.4 Hz, H-9); δ_C(100 MHz; $CDCl_3$) 85.59 (C-1),

122.44 (C-6), 122.58 (C-8), 132.16 (C-3), 136.17 (C-4), 136.57 (C-7), 144.82 (C-2), 149.87 (C-9), 155.08 (C-5).

Racemic 3-Hydroxy-2,2,4-trimethyl-9-(pyridin-2-yl)nona-4(*E*),6(*Z*),8(*Z*)-trienoic acid ethyl ester : 3-hydroxy-2,2,4-trimethyl-9-(pyridin-2-yl)nona-4(*E*),6(*E*),8(*Z*)-trienoic acid ethyl ester (rac-3.60a) : (rac-3.60b)



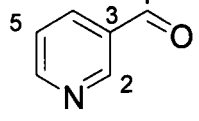
To a stirred suspension of $PdCl_2(MeCN)_2$ (3.9 mg, 0.014 mmol) in dry DMF (5 ml) was added a solution of 2-pyridyl vinyl iodide **(3.59a,b)** (220 mg, 0.86 mmol) in dry DMF (2 ml) and racemic stannane **(rac-3.18)** (137 mg, 0.29 mmol) in dry DMF (2 ml) dropwise. The reaction mixture was stirred for 24 hrs and diluted with Et_2O (50 ml). The Et_2O layer was separated and the DMF layer extracted with EtOAc (3 x 25ml), the combined washings were washed with aq. KF (80 ml), brine (80 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (22:3 v/v petrol:EtOAc + 1% Et_3N) yielded the previously unreported title compound as an orange oil (80 mg, 88%) as an inseparable 1:1 mixture of *E:Z* isomers; R_f: 0.16 and 0.23 (22:3 v/v petrol:EtOAc): $\nu_{max}(CHCl_3)/cm^{-1}$ 3249(Br), 2953(s), 2925(s), 2360(m), 1723(m), 1586(s), 1468(s), 1429(s), 980(s), 735(s); *m/z* (ESI) 338 [$M+Na^+$] (100%), 316 [MH^+] (84%), 298 [M-OH] (54%); (GCMS-TOFES) 316 [MH^+] (100%), 298 [M-OH] (42%); HRMS $C_{19}H_{26}NO_3$ requires 316.1926, Found 316.1912.

***Z,Z,E* -isomer:** δ_H(400 MHz; $CDCl_3$) 1.21 (6H, s, $C(CH_3)_2$), 1.27 (3H, t, *J* 7.7 Hz, OCH_2CH_3), 1.71 (3H, s, CH_3), 4.16 (2H, q, *J* 7.7 Hz, OCH_2CH_3), 4.94 (1H, d, *J* 2.2 Hz, H-12), 6.51 (1H, d, *J* 10.4 Hz, H-10), 6.60 (1H, m, H-4), 6.87 (1H, dd, *J* 15.5 and 6.7 Hz, H-7), 6.97 (1H, t, *J* 8.3 Hz, H-9), 7.16 (1H, m, H-4), 7.25 (1H, t, *J* 7.8 Hz, H-2), 7.35 (1H, t, *J* 8.3 Hz, H-8), 7.41 (1H, d, *J* 15.5 Hz, H-6), 7.67 (1H, m, H-3), 8.59 (1H, d, *J* 8.3 Hz, H-1); δ_C(100 MHz; $CDCl_3$) 13.6 (OCH_2CH_3), 16.5 (C-13(CH_3)$_2$), 46.4 (C-13), 62.1 (OCH_2CH_3), 85.5 (C-12), 120.7 (C-10), 122.4 (C-4), 122.6 (C-2), 129.8 (C-9), 129.7 (C-8), 131.9 (C-7), 132.3 (C-6), 136.6 (C-3), 144.8 (C-11), 149.8 (C-1).

***Z,E,E* -isomer:** δ_H(400 MHz; $CDCl_3$) 1.21 (6H, s, C(CH_3)$_2$), 1.27 (3H, t, *J* 7.8 Hz OCH_2CH_3), 1.71 (3H, s, C(11)CH_3), 4.16 (2H, q, *J* 7.8 Hz, OCH_2CH_3), 4.98 (1H, d, *J* 3.9 Hz, H-12), 6.53 (1H, d, *J* 15.4 Hz, H-6), 6.57 (1H, d, *J* 10.4 Hz, H-10), 6.88 (1H, t, *J* 15.4 Hz, H-7), 6.97 (1H, t, *J* 11.8 Hz, H-9), 7.18 (1H, m, H-4), 7.27 (1H, t, *J* 7.8 Hz, H-2), 7.38 (1H, t, *J* 11.8 Hz, H-8), 7.42 (1H, d, *J* 15.4 Hz, H-6), 7.69 (1H, m, H-3), 8.65 (1H, d, *J* 8.1 Hz H-1); δ_C(100 MHz; $CDCl_3$) 13.4 (OCH_2CH_3), 16.4 (C-13(CH_3)$_2$), 46.1 (C-13), 62.0 (OCH_2CH_3), 85.3 (C-12), 132.2 (C-6), 136.5 (C-3), 138.1 (C-11).

(Assignment was aided by application of the NMR technique described in Section 3.6. In particular it was used to assign coupling constants for the olefin region and ^{13}C signals. However, due to the truncated nature of this compound no unequivocal assignment of a proton environment with correlation to the olefin region was possible. Therefore the ^1H signals were identified from 1 and 2D standard techniques).

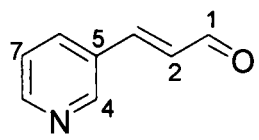
Pyridine-3-carbaldehyde (3.62)



To a stirred solution of $(COCl)_2$ (2.44 g, 20.16 mmol) in dry DCM (20 ml) at -78° C was added dry DMSO (2.8 ml, 39.48 mmol) dropwise and the solution stirred for 10 mins. A solution of 3-pyridylcarbinol (1 g, 9.16 mmol) in dry DCM (5 ml) was added dropwise and the solution stirred for 15 mins. Dry NEt_3 (15.2 ml, 108 mmol) was added dropwise, the solution stirred for 5 mins at -78° C, allowed to warm to RT and stirred for a further 10 mins. Sat. aq. $NaHCO_3$ (40 ml) was added and the organic separated, the aqueous layer was extracted with DCM (3 x 25 ml), the combined organic washing were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (17:3 v/v petrol:EtOAc) yielded the title compound as a yellow oil (700 mg, 71%): R_f 0.06 (17:3 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 7.45 (1H, dd, *J* 7.9 and 4.9 Hz, H-5), 8.13 (1H, ddd, *J* 7.9, 3.9 and 2.0 Hz, H-4), 8.78 (1H, d, *J* 3.1 Hz, H-6), 9.07 (1H, s, H-2), 10.09 (1H, s, H-1).

Commercial sample obtained from Aldrich: δ_H(400 MHz; $CDCl_3$) 7.43 (1H, dd, *J* 7.7 and 4.9 Hz, H-5), 8.15 (1H, ddd, *J* 7.7, 4.9 and 1.9 Hz, H-4), 8.76 (1H, d, *J* 3.1 Hz, H-6), 9.07 (1H, s, H-2), 10.11 (1H, s, H-1).

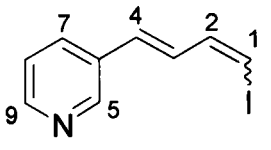
3-(Pyridin-3-yl)-prop-2(*E*)-aldehyde (3.63)



To a stirred solution of aldehyde **(3.62)** (600 mg, 5.6 mmol) in dry DCM (50 ml) was added (formylmethylene)triphenylphosphorane (2.16 g, 6.72mmol) portionwise and the reaction mixture stirred for 48 hrs at RT. 10% HCl was added to attain pH <6. The water layer was separated and neutralised with 3 M NaOH, extracted with EtOAc (3 x 25 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc) yielded the title compound as a yellow powder of the (*E*)-isomer (360 mg, 48%, 74% based on recovered starting aldehyde): R_f 0.00 (4:1 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 6.77 (1H, dd, *J* 16.1 and 7.6 Hz, H-2), 7.41 (1H, m, H-7), 7.56 (1H, d, *J* 16.0 Hz, H-3), 7.89 (1H, d, *J* 8.0 Hz, H-6), 8.67 (1H, d, *J* 6.1 Hz H-8), 8.80 (1H, s, H-4), 9.75 (1H, d, *J* 7.5 Hz, H-1).

Lit[34] NMR: δ_H(400 MHz; $CDCl_3$) 6.75 (1H, q, H-2), 7.35 (1H, q), 7.52 (1H, d, H-3), 7.9 (1H, m), 8.6 (1H, q), 8.76 (1H, d), 9.7 (1H, d, H-1).

1-iodo-5-(pyridin-3-yl)buta-1,3-(*Z,E*)-diene (3.64b) : 1-iodo-5-(pyridin-3-yl)buta-1,3-(*E,E*)-diene (3.64a)



To a stirred suspension of $CrCl_2$ (1.22 g, 9.90 mmol) in dry THF (20 ml) and CHI_3 (1.3 g, 3.31 mmol) was added a solution of aldehyde **(3.63)** (220 mg, 1.65 mmol) in dry THF (8 ml) at 0° C. The reaction mixture was stirred at 0° C for 1 hr and at RT for 30 mins. Water (50 ml) was added, the organic layer separated and the aqueous

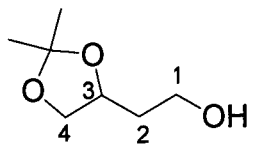
layer extracted with Et_2O (3 x 25 ml). The combined organic layers were washed with $Na_2S_2O_3$ (25 ml), brine (25 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (99:1 v/v petrol:Et_2O increasing polarity to Et_2O) yielded the title compound as an orange oil (130 mg, 34%), as a 1:1 mixture of *E:Z* isomers: R_f 0.11 (99:1 v/v petrol:Et_2O); $\nu_{max}(CHCl_3)/cm^{-1}$ 2360, 1568, 1472, 1440, 1324 (all s); m/z (CI-TOF) 258 $[MH]^+$ (100%), 130 (80), 95 (8).

***Z, E* -isomer:** δ_H(400 MHz; $CDCl_3$) 6.47 (1H, d, *J* 10.4 Hz, H-1), 6.72 (1H, d, *J* 15.9 Hz, H-4), 6.91 (1H, dd, *J* 15.9 and 4.9 Hz, H-3), 7.21-7.31 (1H, m, H-8), 7.45 (1H, t, *J* 10.4 Hz, H-2), 7.73 (1H, m, H-7), 8.48 (1H, d, *J* 6.0 Hz, H-9), 8.63 (1H, s, H-5); δ_C(100 MHz; $CDCl_3$) 84.78 (C-1), 123.71 (C-8), 128.35 (C-4), 130.55 (C-6), 131.89 (C-3), 132.13 (C-7), 133.13 (C-2), 144.76 (C-5).

***E, E* -isomer:** δ_H(400 MHz; $CDCl_3$) 6.56 (1H, d, *J* 15.3 Hz, H-1), 6.79 (1H, d, *J* 15.9 Hz, H-4), 6.98 (1H, dd, *J* 15.9 and 4.7 Hz, H-3), 7.21-7.31 (1H, m, H-8), 7.54 (1H, t, *J* 15.3 Hz, H-2), 7.87 (1H, s, H-7), 8.53 (1H, d, *J* 6.0 Hz, H-9), 8.66 (1H, s, H-5); δ_C(100 MHz; $CDCl_3$) 95.67 (C-1), 128.41 (C-8), 128.90 (C-4), 130.91 (C-6), 132.03 (C-3), 132.54 (C-7), 137.92 (C-2), 148.86 (C-5).

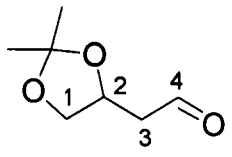
Previously reported[35], however, no data obtained as used as crude.

2-(4,4-Dimethyl-[1,3]dioxalan-2-yl) ethanol (3.73)



To a stirred solution of 1,2,4-butanetriol (2 g, 18.86 mmol) in toluene (100 ml) was added 2,2-dimethoxypropane (1.96 g, 18.86 mmol) and CSA (20 mg, cat.). The reaction mixture was heated at reflux with continuous removal of water for 24 hrs. The solution was concentrated *in vacuo*. Purification by Kugelröhr distillation (200° C/10 mmHg) yielded the title compound as a colourless oil which crystalised upon standing (1.22 g, 44%); BP 52-56° C (0.05 mm), Lit[36] BP 55-61° C (0.05 mm).

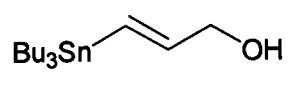
(2,2-Dimethyl-[1,3]dioxolan-4-yl)-acetaldehyde (3.74)



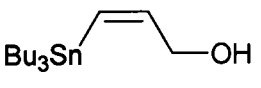
To a stirred solution of $(COCl)_2$ (910 mg, 7.52 mmol) in dry DCM (20 ml) at -78° C was added dry DMSO (1.04 ml, 14.7 mmol) dropwise and the solution stirred for 10 mins. A solution of alcohol **(3.73)** (500 mg, 3.42 mmol) in dry DCM (5 ml) was added dropwise and the solution stirred for 15 mins. Dry NEt_3 (5.67 ml, 40.3 mmol) was added dropwise, the solution stirred for 5 mins at -78° C, allowed to warm to RT and stirred for a further 10 mins. Sat. aq. $NaHCO_3$ (40 ml) was added and the organic separated, the aqueous layer was extracted with DCM (3 x 25 ml), the combined organic washing were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (17:3 v/v petrol:EtOAc) yielded the title compound as a colourless oil (90 mg, 18%): R_f 0.10 (17:3 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 1.34 (6H, s, C*H*$_3$), 2.54 (2H, t, *J* 7.6 Hz, *H*-3), 3.91 (2H, t, *J* 7.9 Hz, *H*-1), 4.08 (1H, m, *H*-2), 9.78 (1H, t, *J* 7.6 Hz, C*H*O).

Lit[36] NMR: δ_H(400 MHz; $CDCl_3$) 1.37 (3H, s), 1.41 (3H, s), 2.74 (2H, m), 9.80 (1H, t, *J* 8.6 Hz).

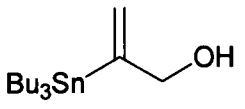
3-(Tributylstannyl)-prop-2(E)-en-1-ol (3.21), 3-(Tributylstannyl)-prop-2(Z)-en-1-ol (3.21b) & 2-(tributylstannyl)-prop-2-ene-1-ol (3.21c)[37]



(3.21)



(3.21b)



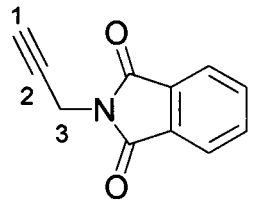
(3.21c)

To a mixture of neat tributyltin hydride (3.00 g, 10.31 mmol) and propargyl alcohol (0.45 g, 7.93 mmol) was added AIBN (50 mg, 0.32 mmol),a reflux condenser attached to the reaction flask and the mixture heated at 80° C for 3 hr. The mixture was cooled to RT and hexane (2 ml) added. Purification by column chromatography

(24:1 v/v petrol:EtOAc until the **(3.21b)** (R_f 0.26 (24:1 v/v petrol:EtOAc), (750 mg, 27%) and **(3.21c)** (R_f 0.19 (24:1 v/v petrol:EtOAc), 790 mg, 29%) isomers have eluted and then 22:3 petrol:EtOAc) yielded the title *E*-isomer as a colourless oil (1.5 g, 52%): (R_f 0.12, 24:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$); 0.74-1.09 (27H, m, Bu_3Sn), 4.18 (2H, m, CH_2OH), 6.18 (1H, d, *J* 17.2 Hz, SnC*H*=C*H*), 5.92 (1H, t, *J* 17.2 Hz, SnCH=C*H*).

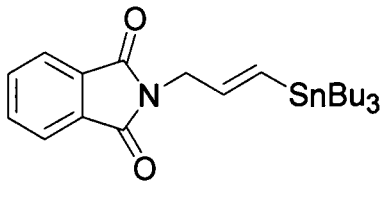
Lit[37] NMR: **(3.21)**: δ_H(200 MHz; $CDCl_3$) 4.17 (2H, CH_2OH), 6.19 (2H, *J* 19.2 Hz, SnC*H*=CH and SnCH=C*H*); **(3.21b)**: δ_H(200 MHz; $CDCl_3$) 4.11 (2H, CH_2OH), 6.07 (1H, *J* 12.8 Hz, SnC*H*=CH), 6.69 (1H, *J* 12.8 Hz, SnCH=C*H*).

2-Prop-2-ynylisoindole-1,3-dione (3.78)[38]



To a stirred suspension of potassium phthalimide (2 g, 10.8 mmol) in DMF (50 ml) was added propargyl bromide (1 g, 8.4 mmol) dropwise. The solution was stirred for 16 hrs at RT, diluted with water (40 ml) and extracted with $CHCl_3$ (3 x 100 ml). The combined organic layers were washed with 3 M NaOH (50 ml) and water (50 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was recrystallised from 1:1 petrol:acetone to provide a brown supernatant which yielded the title compound as colourless crystals (1.1 g, 71%); MP 149-152° C, Lit[39] MP 149-150° C.

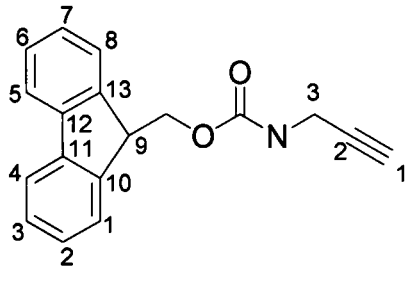
2-[3-(Tributylstannyl)allyl]isoindole-1,3-dione (3.76)[40]



To a solution of phthalimide derivative **(3.78)** (250 mg, 1.45 mmol) in toluene (30 ml) was added tributyltin hydride (625 mg, 3.53 mmol) and AIBN (25 mg, 0.16 mmol,

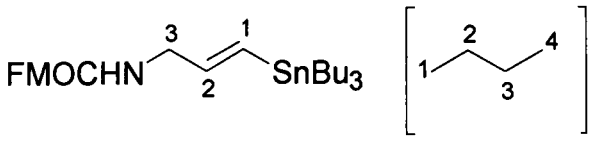
cat.). The mixture was refluxed for 4 hrs, cooled to RT and concentrated *in vacuo*. Purification by column chromatography (24:1 v/v petrol:EtOAc +1% Et_3N) yielded an off-white powder of the *trans* title compound (30 mg, 4%): R_f 0.17 (24:1 v/v petrol:EtOAc); δ_H(400 MHz; $CDCl_3$) 0.81-0.95 (15H, m, $(CH_3CH_2CH_2CH_2)_3Sn$ and $(CH_3CH_2CH_2CH_2)_3Sn$), 1.20-1.58 (12H, m, $(CH_3CH_2CH_2CH_2)_3Sn$ and $(CH_3CH_2CH_2CH_2)_3Sn$), 4.24 (2H, d, *J* 5.2 Hz, CH_2), 5.98 (1H, dt, *J* 18.9 and 5.0 Hz, CH_2CH=CH), 6.15 (1H, dd, *J* 18.6 and 5.0 Hz, CH_2CH=CH), 7.64-7.91 (4H, Ar*H*). Lit[41] NMR: δ_H(400 MHz; $CDCl_3$) 0.80-0.95 (15H, m), 1.10-1.60 (12H, m), 4.30 (2H, m), 5.94 (1H, dt, *J* 19 and 5 Hz), 6.13 (1H, d, *J* 19 Hz), 7.70 (2H, m), 7.85 (2H, m).

3-[(Fluoren-9-ylmethoxycarbonyl)amino]propyne (1.68b)[42]



To a stirred solution of 9-fluorenyl chloroformate (FmocCl) (5.2 g, 18.18 mmol) in DCM (100 ml) was added propargyl amine (1 g, 18.18 mmol) and pyridine (1.68 g, 18.18 mmol) and the reaction mixture stirred at RT for 1.5 hrs. The mixture was diluted with EtOAc (20 ml) and washed with water (25 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from EtOAc yielded the title compound as brown crystals (1.51 g, 30%); MP 123-125° C, Lit[42] MP 126-127° C.

N-Fmoc-3-amino-1-(tributylstannyl)prop-1(*E*)-ene (1.69a)[42]

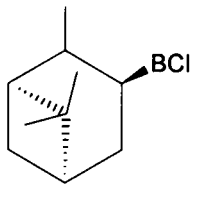


To a stirred solution of protected amine **(1.68b)** (1 g, 3.61 mmol) in benzene (10 ml) was added tributyl tin hydride (1.26 g, 4.33 mmol) and AIBN (0.03 eq, cat.). The reaction mixture was heated at reflux for 6 hrs, allowed to cool to RT and concentrated *in vacuo*. Purification by column chromatography (15:1 v/v petrol:EtOAc increasing polarity to 10:1 v/v petrol:EtOAC) yielded the title

compound as a colourless viscous oil (670 mg, 35%); R_f 0.59 (10:1 v/v petrol:EtOAc); δ_H(200 MHz; $CDCl_3$) 0.93 (15H, t, *J* 7.3 Hz, Bu H-1 and H-4), 1.25-1.67 (12H, m, Bu H-2 and H-3), 3.95 (2H, t, *J* 7.3 Hz, H-3), 4.27 (1H, t , *J* 6.8 Hz, Fmoc H-9), 4.44 (2H, d, *J* 6.8 Hz, Fmoc CH_2), 5.01 (1H, br, Fmoc-NH), 6.00 (1H, dt, *J* 19.1 and 4.8 Hz, H-2), 6.21 (1H, d, *J* 19.1 Hz, H-1) 7.31-7.80 (8H, m, Fmoc Ar-H).

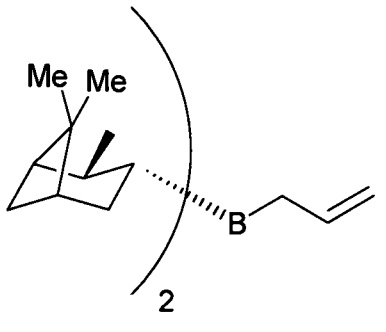
Lit[42] NMR: δ_H(200 MHz; $CDCl_3$) 0.92 (15H, t, *J* 7.1 Hz, Bu H-1 and H-4), 1.36-1.61 (12H, m, Bu H-2 and H-3), 3.92 (2H, t, *J* 7.1 Hz, H-3), 4.25 (1H, t , *J* 6.5 Hz, Fmoc H-9), 4.45 (2H, d, *J* 6.5 Hz, Fmoc CH_2), 5.00 (1H, br, Fmoc-NH), 6.00 (1H, dt, *J* 18.7 and 4.8 Hz, H-2), 6.17 (1H, d, *J* 18.7 Hz, H-1) 7.55-7.80 (8H, m, Fmoc Ar-H).

Preparation of (-)-B-chlorodiisopinocamphenylborane[43,44]



To a solution of boron trichloride (3 g, 25.6 mmol) in dry Et_2O (16 ml) in an argon flushed reaction vessel at 0° C was added a solution of $LiBH_4$ (550 mg, 25 mmol) in dry Et_2O (18 ml) dropwise over 20 mins. The mixture was stirred at 0° C for 15 mins. (+)-α-pinene (13.6 g, 100 mmol) was added to the solution and stirring continued for 1 hr. The mixture was used immediately without further purification.

Preparation of (-)-B-allyldiisopinocamphenylborane[43,44]



To a solution of magnesium turnings (85 mg, 3.5 mmol) in dry ether (5 ml) and a single crystal of iodine in a dry reaction vessel fitted with calcium chloride guard tubes was added a solution of allylbromide (380 mg, 3.1 mmol) in dry ether (5 ml)

with continuous stirring at such a rate to as maintain reflux. After complete addition the solution was refluxed for 10 mins. The reaction mixture was cooled to -78° C and a solution of (-)-B-chlorodiisopinocamphenylborane (1 g, 3.1 mmol) in dry ether (5 ml) was added dropwise over 5 mins. The reaction mixture was sirred for 30 mins at –78° C and allowed to warm over 1 hr to RT. Precipitation of magnesium salts indicated formation of the product, which was used as crude *in situ*.

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