To Mum, Dad, Paul and James.

UNIVERSITY OF SOUTHAMPTON

STUDIES DIRECTED TOWARD THE SYNTHESIS OF THE SOUTHERN FRAGMENT OF RAPAMYCIN

by Richard Keith Bellingham

Doctor of Philosophy

FACULTY OF SCIENCE
DEPARTMENT OF CHEMISTRY

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ABSTRACT

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The thesis commences with a brief account of the biological action of rapamycin **(1.1.1)** followed by a comprehensive review of the chemistry and synthetic work published on rapamycin **(1.1.1)** to date. An outline of our groups approach to the total synthesis of rapamycin is followed by a detailed account of our synthesis of the C10-C18 lactone fragment **(2.2.1)** and the C21-C26 vinyl iodide fragment **(2.2.2)**. The syntheses of both fragments were achieved from a common starting material using the same key diastereoselective cyclisation reaction reported by Suzuki.

Palladium catalysed cross-coupling reactions of the vinyl iodide **(2.2.1)** with (*E*)-1,2-di(tributylstannyl)ethene gave a modest yield of the C10-C20 dienyl stannane **(5.8.1)**. However coupling reactions of vinyl iodide **(2.2.2)** with the dienyl stannane **(5.8.1)** failed to yield any desirable products. Exchange of the C26 dithio acetal protecting group for a dimethoxy acetal to yielded the vinyl iodide **(5.15.1)**. The subsequent palladium catalysed cross coupling reaction with vinyl iodide **(2.2.1)** may have yielded the desired Southern fragment of rapamycin **(5.16.1)** but with only ^{1}HNMR and UV data obtained the result is inconclusive.

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PREFACE

The research described in this thesis was carried out under the supervision of Prof. Philip Kocienski at the University of Southampton between October 1990 and October 1993. No part of this thesis has been previously submitted for a degree at this or any other University except where specific acknowledgement has been made.

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The S.E.R.C. and Galxo Group Research for financial support over the last three years.

ABBREVIATIONS

Ac	acetyl
AIBN	azo*iso*butyronitrile
Aloc	allyloxycarbonyl
Anal. Calcd.	Analysis calculated
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BuLi	refers to *n*-butyllithium
c	cyclo
CI	chemical ionisation
Cp	cyclopentadienyl
CSA	camphor sulphonic acid
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEIPS	diethyl*iso*propylsilyl
DET	diethyl tartrate
DHP	dihydropyran
DIPT	di*iso*propyl tartrate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethyl sulphide
DMSO	dimethyl sulphoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	electron impact
eq.	equivalents
Et	ethyl
EtOAc	ethyl acetate
Fu	2-furyl
HCA	hexachloroacetone

HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
i	*iso*
Ipc	*iso*pinocampheyl
IR	infrared
LAH	lithium aluminium hydride
LDA	lithium di*iso*propylamide
LRMS	low resolution mass spectrometry
m-CPBA	*meta*chloroperbenzoic acid
Me	methyl
MOM	methoxy methyl
Mpt.	melting point
Ms	methane sulphonyl
NBS	N-bromo succinimide
NCS	N-chloro succinimide
NIS	N-iodo succinimide
NMMO	N-methyl morpholine-N-oxide
NMP	N-methyl pyrrolidinone
NMR	nuclear magnetic resonance
OTf	trifluoromethane sulphonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	*para*methoxy benzyl
PPTS	pyridinium *para*toluenesulphonate
Pr	propyl
*p*TSA	*para*toluenesulphonic acid
Red-Al	sodium *bis*(2-methoxyethoxy)aluminium hydride
rt	room temperature
s	secondary
sat.	saturated
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*butyldiphenylsilyl
TBHP	*tert*butylhydroperoxide
TBS	*tert*butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
UV	ultra violet

CHAPTER 1

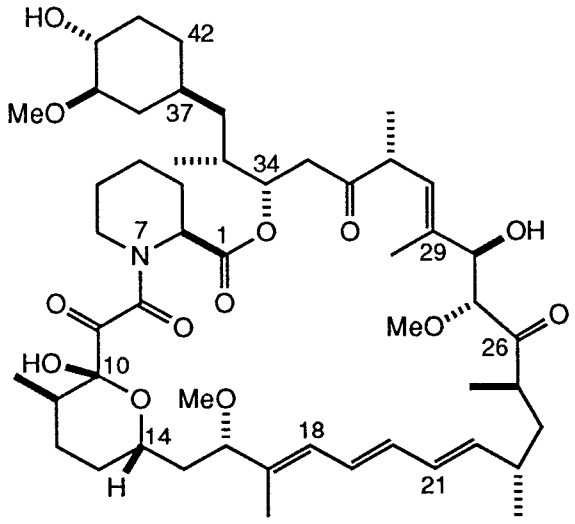
CHAPTER 1: BACKGROUND.

1.1 The biological action of rapamycin (1.1.1).

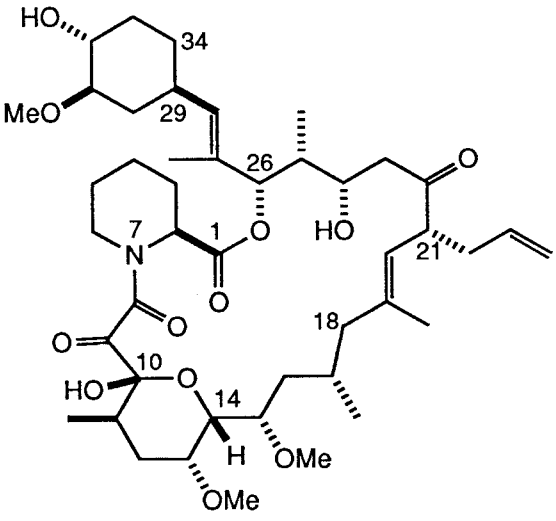
Rapamycin **(1.1.1)** is a fungal metabolite isolated from a strain of *S. Hygroscopicus* found in a soil sample from Easter island in 1975[1] . The structural determination was carried out by Findlay[2,3] using a combination of 2D NMR spectroscopy and X-ray crystallography. The numbering system used for rapamycin **(1.1.1)** in scheme 1.1 will be used throughout this thesis.

The immunosuppressant activity of rapamycin **(1.1.1)** and FK-506 **(1.1.2)**, and the implications for the treatment of organ rejection and auto immune diseases has led to considerable biological and synthetic interest.

Scheme 1.1



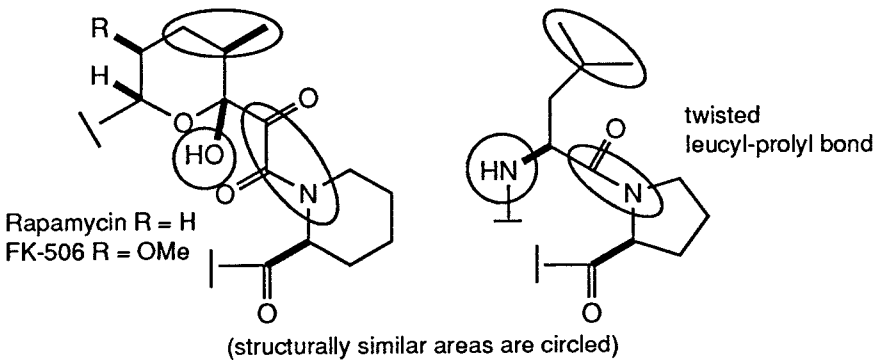
Rapamycin (1.1.1)



FK-506 (1.1.2)

Both rapamycin **(1.1.1)** and FK-506 **(1.1.2)** bind strongly to the enzyme FK binding protein (FKBP) *via* C1-C11 and the cyclohexyl portions of the molecules[4,5]. FKBP catalyses the interconversion of the *cis* and *trans* rotamers of a peptidyl prolyl amide bond. Rapamycin **(1.1.1)** and FK-506 **(1.1.2)** bind strongly to FKBP and inhibit it's rotamase activity. It is postulated that

Scheme 1.2

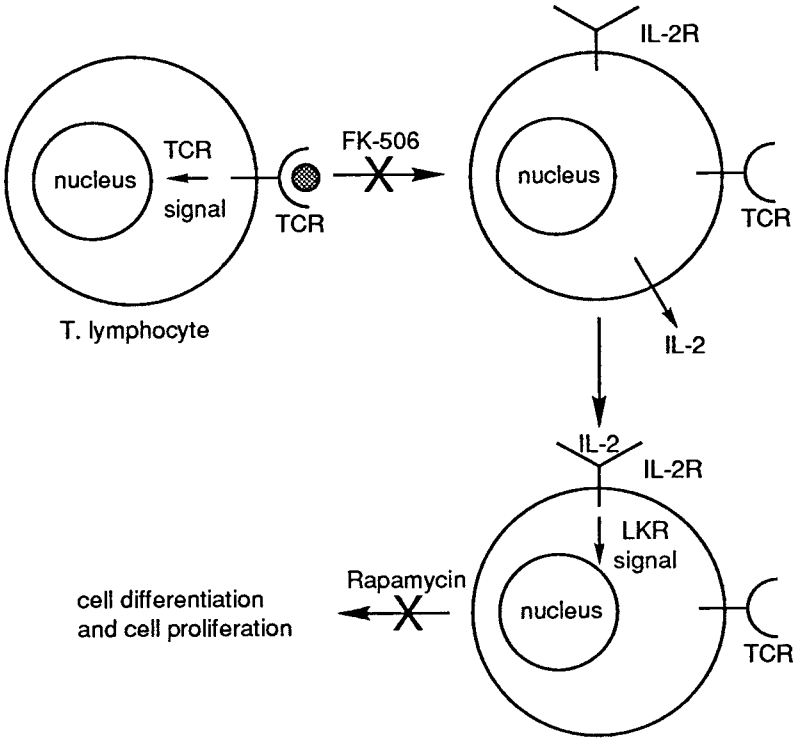


(structurally similar areas are circled)

the binding domain of rapamycin **(1.1.1)** and FK-506 **(1.1.2)** mimic the transition state structure of the twisted leucyl prolyl amide bond[6] (scheme 1.2). It is the FKBP-FK-506 or the FKBP-rapamycin complex that exerts the immunosuppressant effect by inhibiting specific signal transduction pathways that lead to T. lymphocyte activation. Interestingly the FKBP-FK-506 and the FKBP-rapamycin complexes inhibit different signal transduction pathways[7-9].

T. lymphocyte activation is triggered by stimulation of the T. cell receptor on the cell surface by a foreign antigen. The T. cell receptor (TCR) signal transmission pathway is thus activated and the signal is transduced through the cell cytoplasm to the nucleus by an unknown mechanism. The TCR signal stimulates the extracellular secretion of the lymphokine interleukin 2 (IL-2) and also the expression of IL2 receptors (IL-2R) on the cell surface. When IL-2 binds to the IL-2R, the lymphokine receptor (LKR) signal transmission pathway is stimulated. The signal is again transduced through the cytoplasm to the cell nucleus and leads to cell differentiation and proliferation (scheme 1.3).

Scheme 1.3



The first TCR pathway is calcium dependent i.e.there is an intracellular rise in the concentration of Ca^{2+} on binding of the foreign antigen to the TCR. It is thought that the FKBP-FK-506 complex inhibits the first TCR signal pathway by binding to the calmodulin dependent enzyme calcineurin (CN). CN is a heterodimeric protein composed of two subunits, calcineurin A

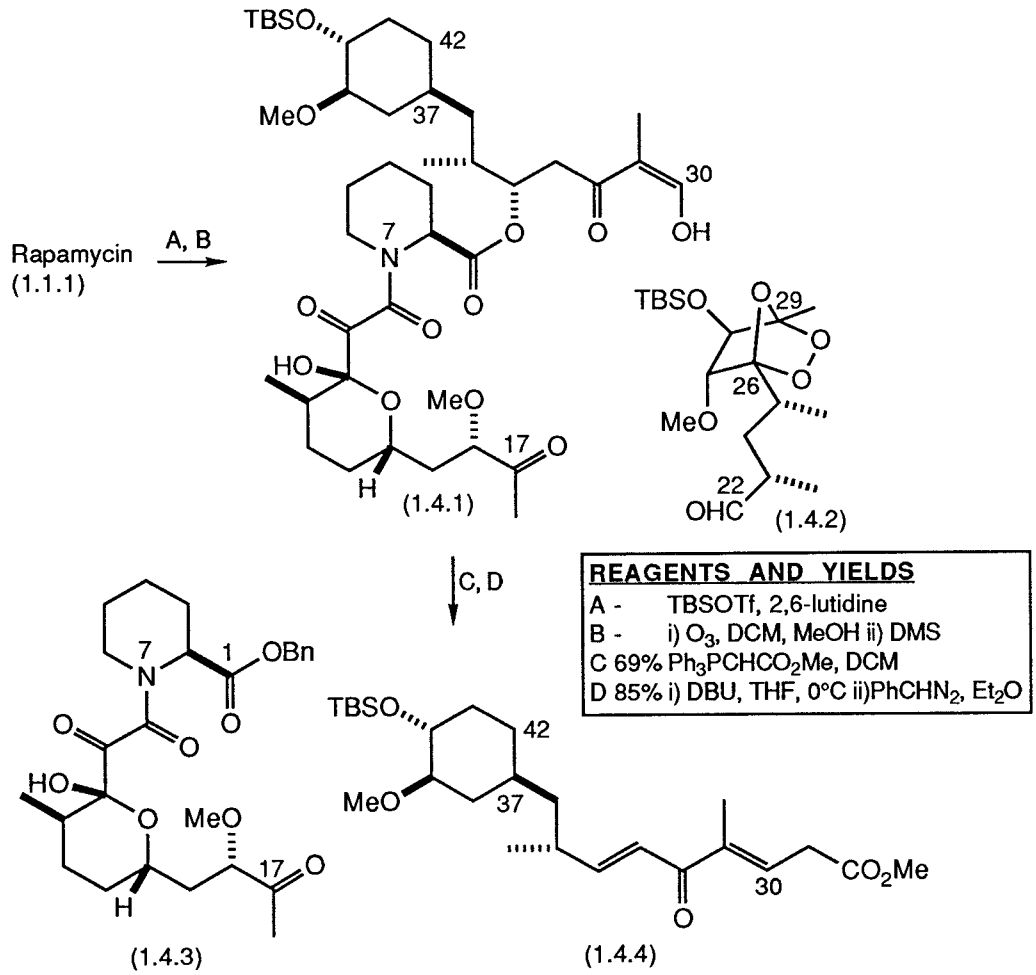
CN is a heterodimeric protein composed of two subunits, calcineurin A (CNA) a phosphatase, and calcineurin B (CNB) a Ca^{2+} binding protein. The phosphatase activity of CN is potently inhibited by binding to FKBP-FK-506 complex. The location of the 'nuclear transcription factors' in the cell is thought to be dependent on their phosphorylation state, hence the transcription of IL-2 is prevented by inhibition of the phosphatase activity of CN.

Rapamycin inhibits a second step that is Ca^{2+} independent. The mechanism of inhibition is thought to be similar to that of FK-506, in that the FKBP-rapamycin complex inhibits the action of another enzyme or protein, however the target enzyme has yet to be identified.

1.2 The chemistry of rapamycin (1.1.1).

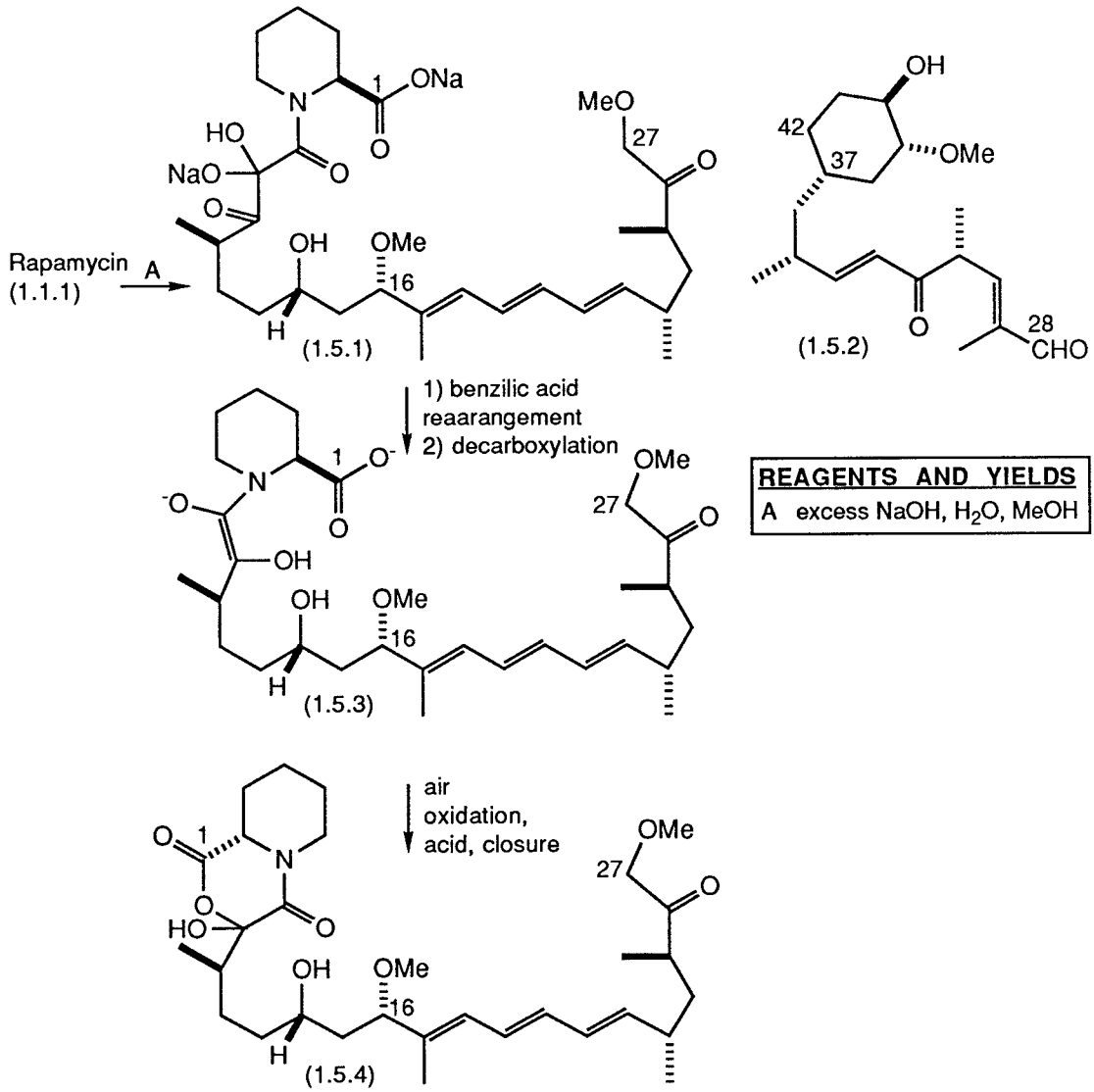
Goulet, in an attempt to obtain fragments for the synthesis of FK-506 **(1.1.2)** and rapamycin **(1.1.1)** congeners, degraded rapamycin **(1.1.1)**[10] in the manner shown in scheme 1.4. Exhaustive ozonolysis removed the triene system and yielded the keto enol **(1.4.1)** and the ozonide **(1.4.2)** as a single diastereoisomer of unknown configuration. The C30-C42 fragment was then removed by a DBU elimination reaction. Unfortunately the stereochemistry at C34 is destroyed during the course of the reaction to yield diene **(1.4.4)** and tricarbonyl region **(1.4.3)**. However Goulet also reports[10] a two step method to re-introduce the chirality at C34 of fragment **(1.4.4)**.

Scheme 1.4



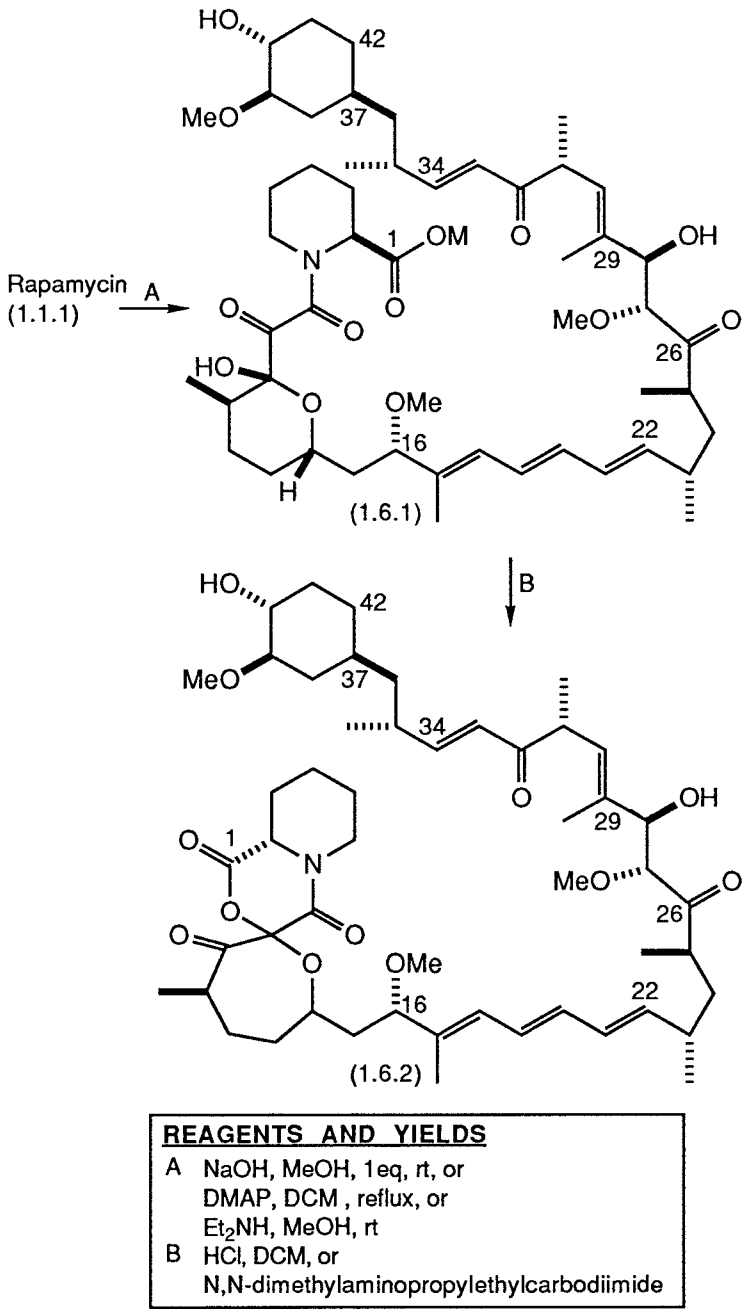
Caufield examined the base catalysed degradation of rapamycin[11]. At room temperature with an excess of aqueous methanolic sodium hydroxide, rapamycin **(1.1.1)** undergoes a β-elimination at C34 and a retro aldol reaction at C28 (scheme 1.5). The reaction may be a concerted intramolecular process.

Scheme 1.5



Under even milder conditions, using only one equivalent of sodium hydroxide or amines as the source of base, the β-elimination reaction is observed to yield the open chain acid salt **(1.6.1)** (scheme 1.6). On treatment with strong aqueous acid or dehydrating agent, **(1.6.1)** loses water and undergoes a spirolactonisation reaction to yield the seven-membered lactone **(1.6.2)**.

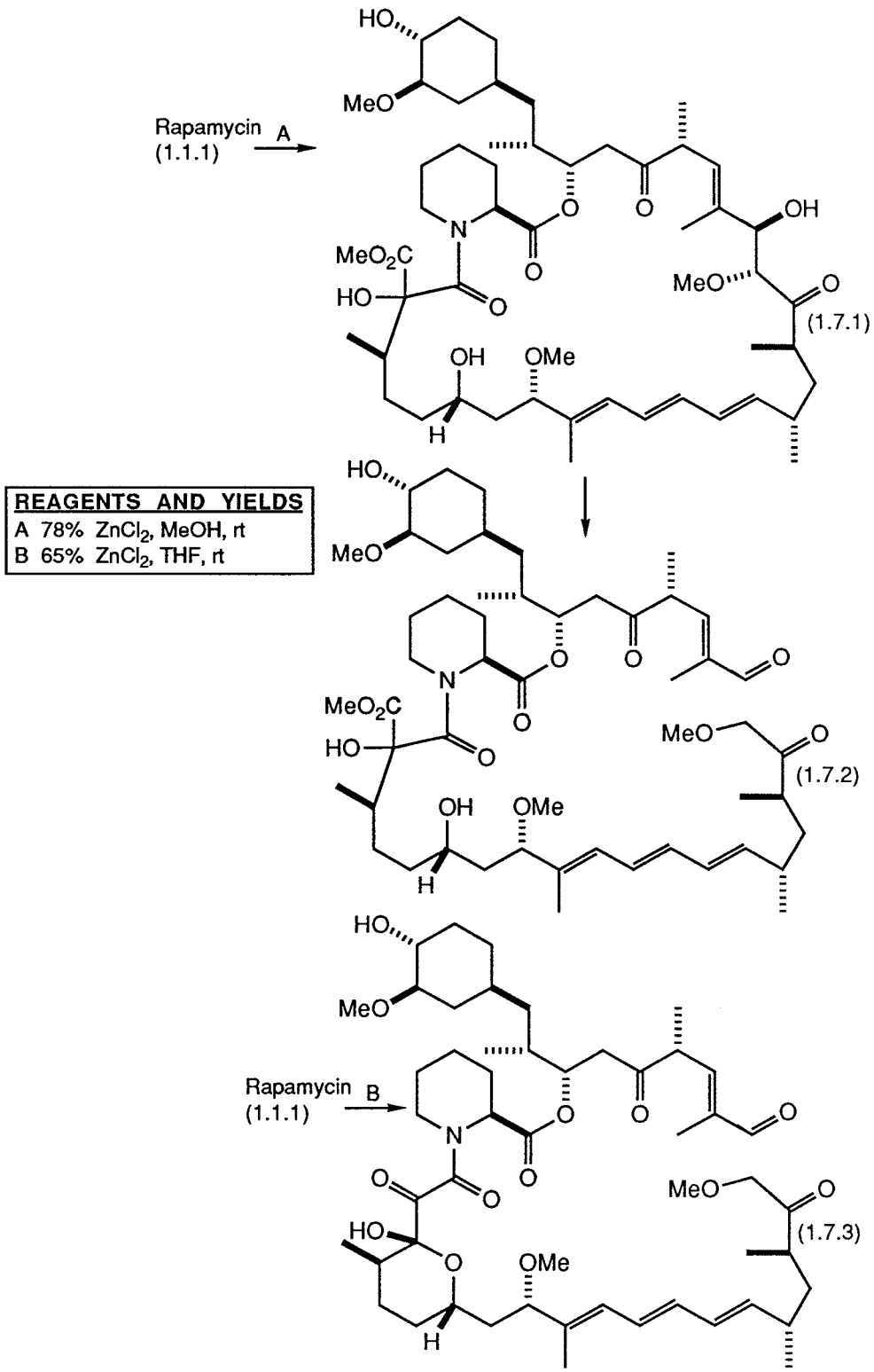
Scheme 1.6



Luengo investigated the action of Lewis acids on rapamycin **(1.1.1)**[12] (scheme 1.7) and discovered the β-elimination reaction was heavily solvent dependent. When rapamycin **(1.1.1)** was treated with zinc (II) chloride in methanol, a benzilic acid type rearrangement occurred to yield **(1.7.1)** as a mixture of diastereoisomers at C9. On prolonged exposure to the conditions above, a retro-aldol reaction between C27 and C28 occurred to yield aldehyde **(1.7.2)**. The retro-aldol reaction could also be effected without the accompanying benzilic acid rearrangement by the employment of zinc (II)

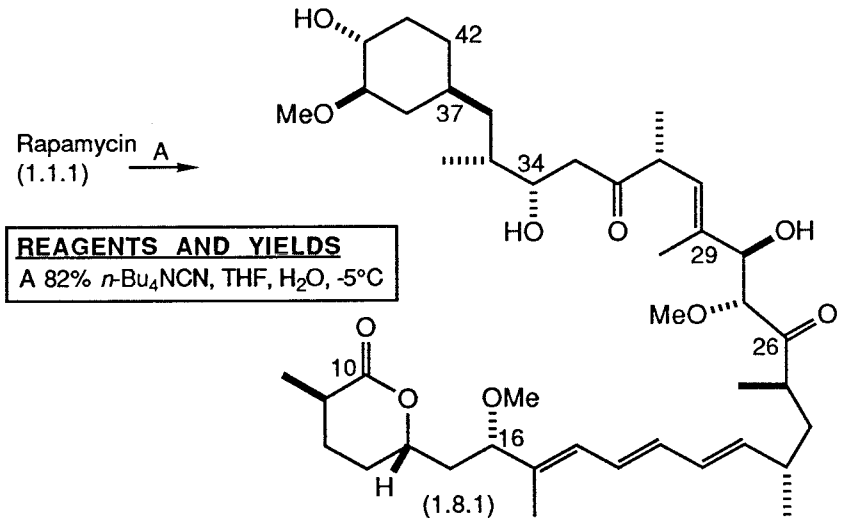
chloride in THF to yield aldehyde **(1.7.3)**. Luengo also reports[12] that treatment of aldehyde **(1.7.3)** with DBU in THF gives the β-elimination product **(1.5.2)** reported by Caufield[11].

Scheme 1.7



In a separate paper Luengo also reports[13] an efficient method (82%) of removing the pipecolinate moiety from rapamycin **(1.1.1)** using tetrabutylammonium cyanide (scheme 1.8), a method which avoids the β-elimination reaction at C34. Luengo reports that the C27-C28 retro aldol reaction can also be performed on adduct **(1.8.1)** to give access to synthetically useful fragments.

Scheme 1.8



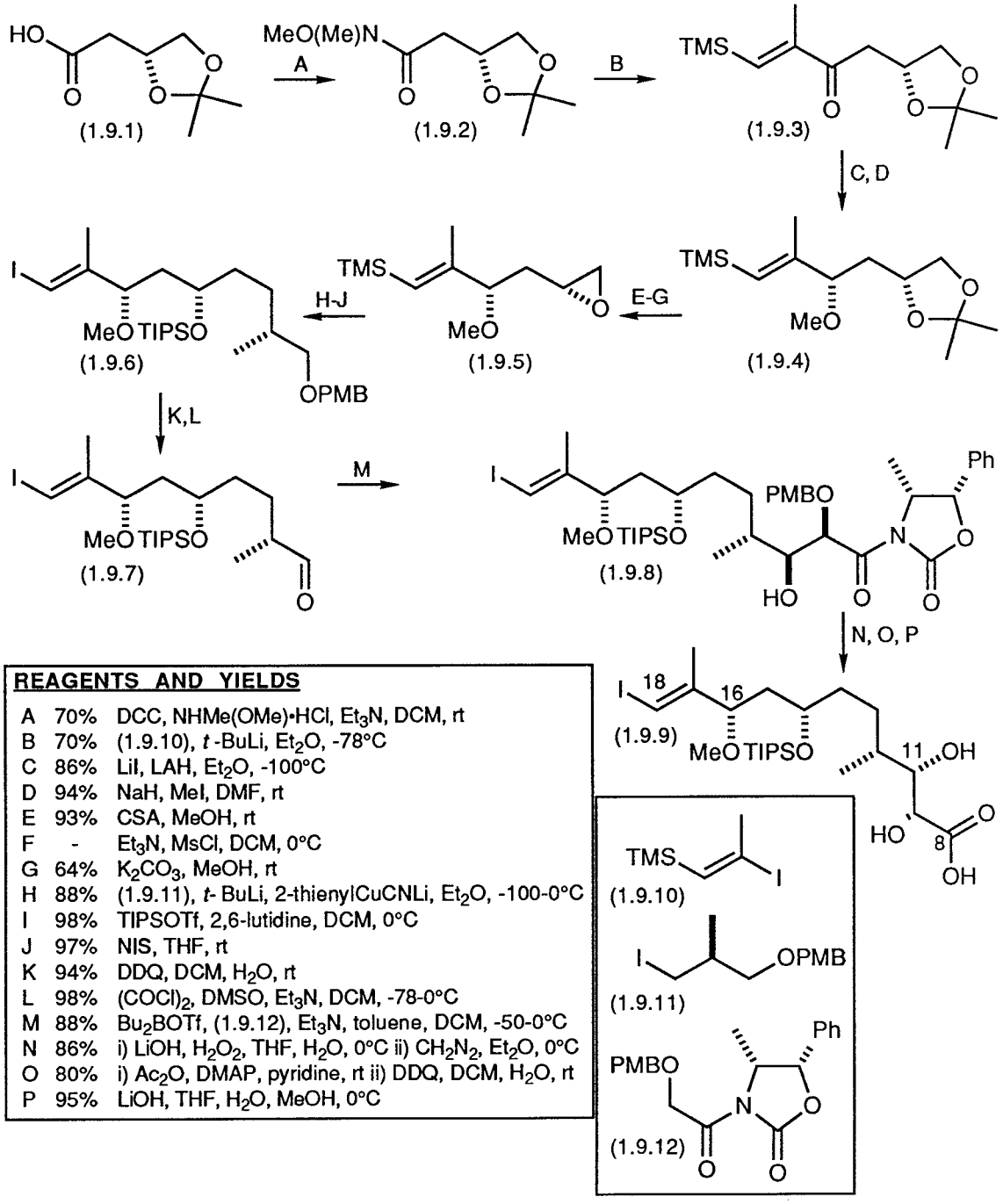
In conclusion we have seen that rapamycin **(1.1.1)** is prone to base-catalysed hydrolysis and elimination at the C34 position and retro-aldol reaction at the C27-C28 bond to generate fragments that are useful for both biological and synthetic investigations. A benzilic acid type rearrangement of the tricarbonyl region occurs under aqueous basic and aqueous Lewis acid conditions, creating *gem* hydroxy acids or esters at C9. Under ozonolysis conditions the binding domain of rapamycin **(1.1.1)** can be efficiently removed.

1.3 The total syntheses of rapamycin (1.1.1).

Nicolaou's synthesis.

Nicolaou's synthesis of rapamycin[14-16] involves the synthesis of two large fragments, the C8-C18 **(1.9.9)** and C21-C42 **(1.13.6)**. The fragments are coupled at the N7-C8 amide bond and the macrocyclisation is effected by the palladium-catalysed introduction of C19 and C20 using a Stille-type coupling of the acyclic precursor with *E*-1,2-di(tributylstannyl)ethene.

Scheme 1.9

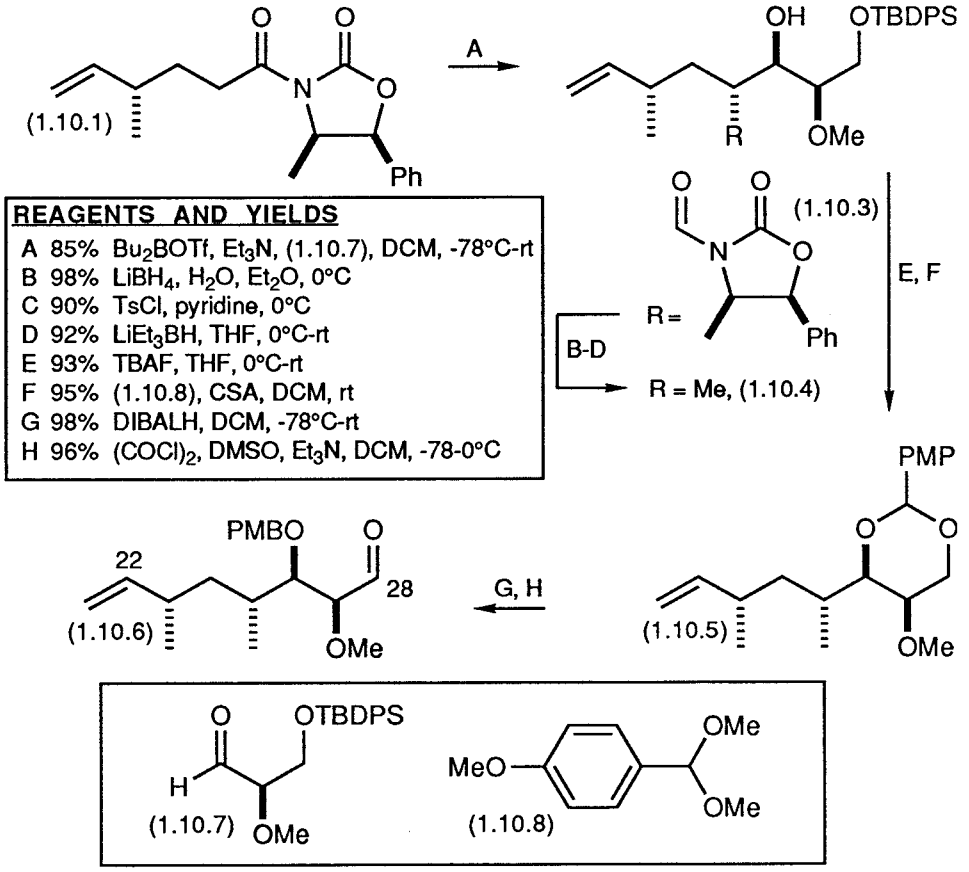


REAGENTS AND YIELDS

A	70%	DCC, NHMe(OMe)•HCl, Et_3N, DCM, rt
B	70%	(1.9.10), *t*-BuLi, Et_2O, -78°C
C	86%	LiI, LAH, Et_2O, -100°C
D	94%	NaH, MeI, DMF, rt
E	93%	CSA, MeOH, rt
F	-	Et_3N, MsCl, DCM, 0°C
G	64%	K_2CO_3, MeOH, rt
H	88%	(1.9.11), *t*-BuLi, 2-thienylCuCNLi, Et_2O, -100-0°C
I	98%	TIPSOTf, 2,6-lutidine, DCM, 0°C
J	97%	NIS, THF, rt
K	94%	DDQ, DCM, H_2O, rt
L	98%	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
M	88%	Bu_2BOTf, (1.9.12), Et_3N, toluene, DCM, -50-0°C
N	86%	i) LiOH, H_2O_2, THF, H_2O, 0°C ii) CH_2N_2, Et_2O, 0°C
O	80%	i) Ac_2O, DMAP, pyridine, rt ii) DDQ, DCM, H_2O, rt
P	95%	LiOH, THF, H_2O, MeOH, 0°C

The synthesis of the C8-C18 fragment **(1.9.9)** is outlined in scheme (1.9). Acid **(1.9.1)** was synthesised by a literature procedure from L-ascorbic acid. Conversion to the Weinreb amide **(1.9.2)**, followed by coupling to a vinyllithium species (generated *in situ* from vinyl iodide **(1.9.10)**) generated adduct **(1.9.3)**. A highly diastereoselective chelation-controlled reduction of ketone **(1.9.3)** was then achieved by the method of Mori and Suzuki thus introducing the stereochemistry of the methoxy group at C16. Elaboration of protected diol **(1.9.4)**, *via* acetal hydrolysis, mesylation, and base induced epoxidation, to epoxide **(1.9.5)** was achieved in 64% for three steps. Epoxide **(1.9.5)** was then treated with a cuprate (derived *in situ* from vinyl iodide **(1.9.11)**), yielding the PMB ether **(1.9.6)**. A sequence of protection, deprotection and oxidation steps gave aldehyde **(1.9.7)**. A diastereoselective aldol reaction using Evans chiral boron enolate was then employed to attach the C8-C9 carbons. Subsequent oxidative hydrolysis and manipulation of protecting groups yielded the desired acid **(1.9.9)**.

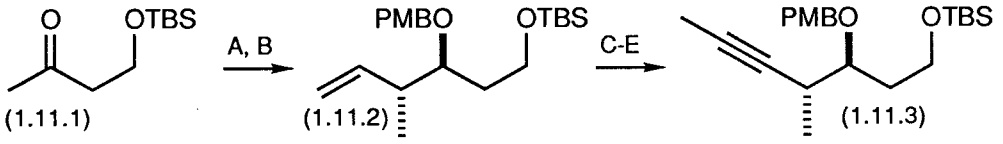
Scheme 1.10



The C21-C42 **(1.13.6)** fragment was synthesised from four components, the synthesis of the C21-C28 fragment **(1.10.6)** is shown in scheme 1.10. The oxazolidinone **(1.10.1)** was synthesised in four trivial steps from (+)-β-

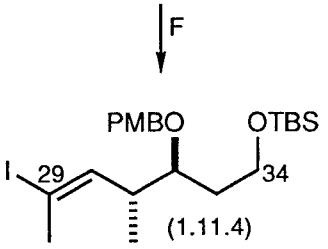
citronellene. Evans' diastereoselective aldol reaction with aldehyde **(1.10.6)** yielded adduct **(1.10.2)**. Removal of the chiral auxilliary was achieved in three steps by reduction to the alcohol, tosylation and subsequent displacement of the tosylate with hydride, giving alcohol **(1.10.3)** in 81% yield. Manipulation of the hydroxy protecting groups followed by Swern oxidation gave the desired aldehyde **(1.10.5)**.

Scheme 1.11



REAGENTS AND YIELDS

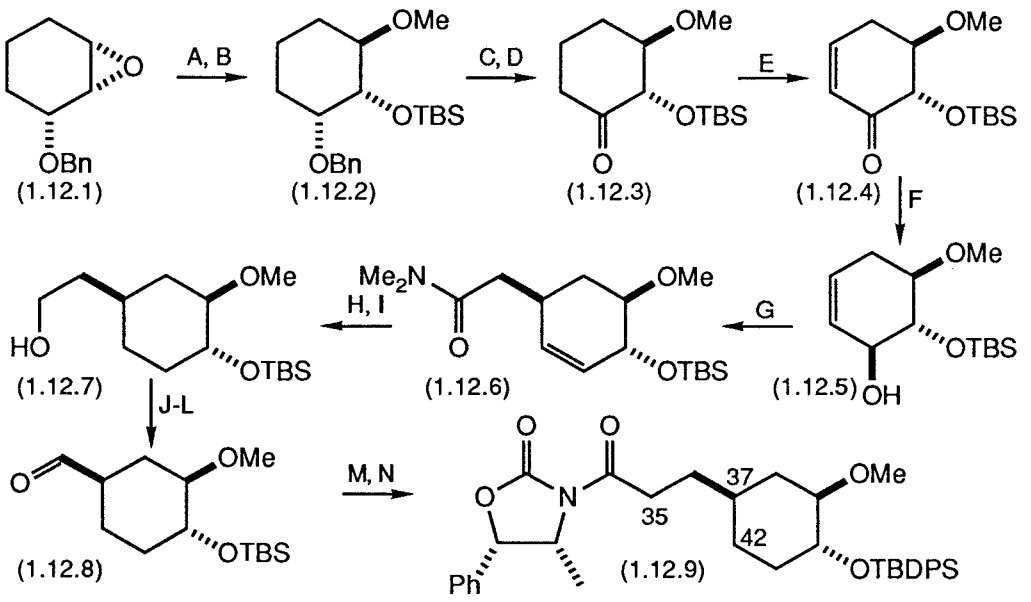
A 70% *E*-but-2-ene, KO*t*-Bu, BuLi, (+)-Ipc_2BOMe, $BF_3{\cdot}Et_2O$, THF, -78°C-rt
B 90% PMBBr, NaHMDS, THF, DMF, 0°C
C 80% i) O_3, MeOH, pyridine, DCM ii) DMS, -78-0°C
D 90% CBr_4, Zn, PPh_3, DCM, rt
E 98% i) BuLi, THF ii) MeI, -78-0°C
F 85% i) Cp_2ZrHCl, DCM ii)I_2, 0°C



The synthesis of the C29-C34 **(1.11.4)** fragment is shown in scheme 1.11. Ketone **(1.11.1)** was obtained from but-3-ene-1-ol in two steps. The chirality at C31 and C32 was introduced using Brown's asymmetric crotylboration to yield, after protection, the alkene **(1.11.2)**. Elaboration of the alkene functionality to the methyl acetylene **(1.11.3)** was achieved using standard conditions. Hydrozirconation and subsequent quench with iodine gave the *E*-vinyl iodide **(1.11.4)**.

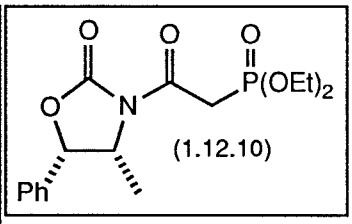
Synthesis of the C35-C42 **(1.12.9)** fragment (scheme 1.12), proceeds *via* ketone **(1.12.3)** which is generated from epoxy ether **(1.12.1)** in 4 steps. Conversion to the alcohol **(1.12.5)** was achieved by using palladium acetate oxidation of the TMS enol ether, followed by cerium-mediated borohydride reduction of the enone **(1.12.4)**. Eschenmoser-Claisen rearrangement to give amide **(1.12.6)** followed by functional group manipulation and olefination furnished fragment **(1.12.9)**.

Scheme 1.12



REAGENTS AND YIELDS

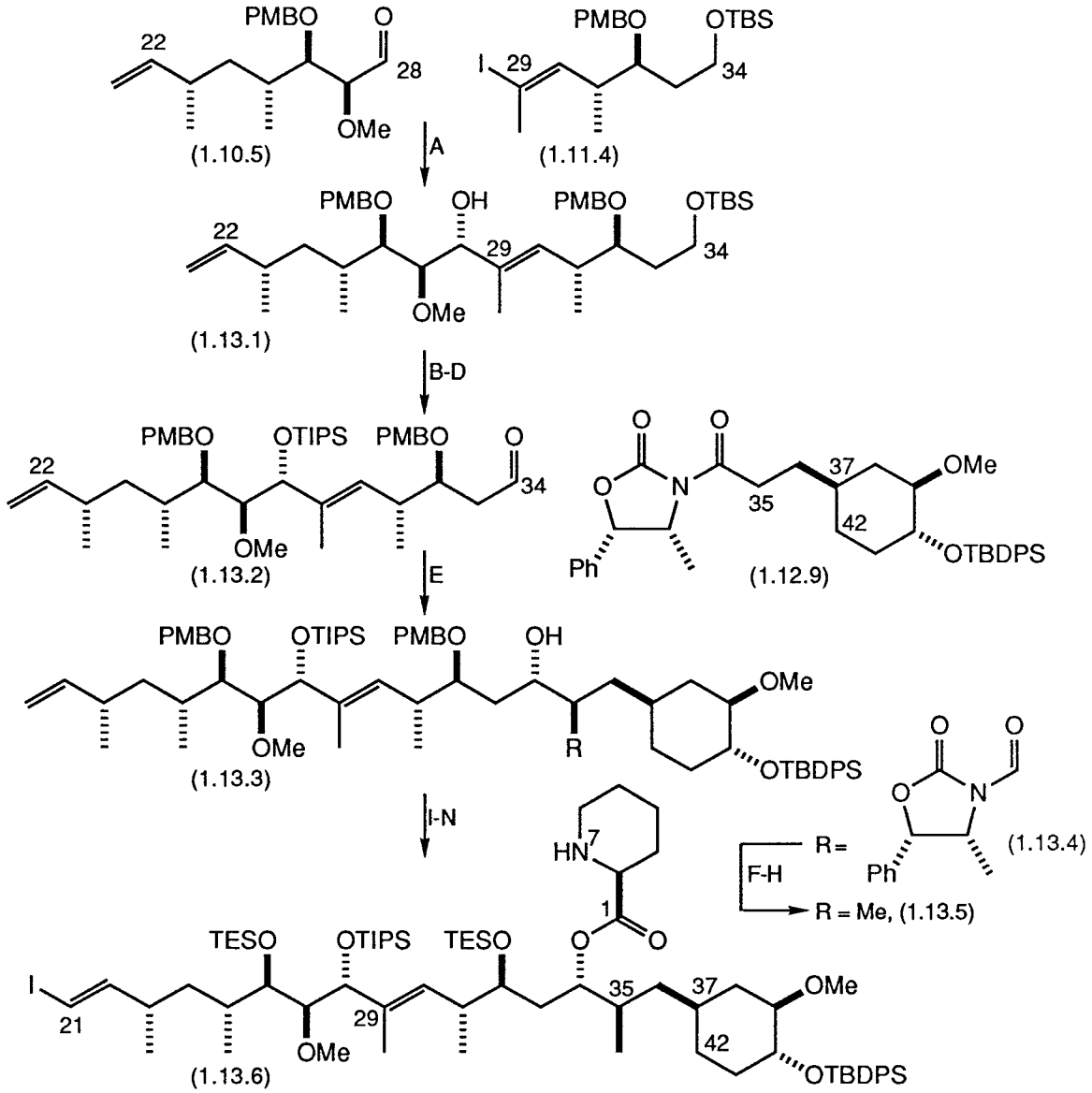
A	88%	CSA, MeOH, rt
B	98%	TBSOTf, 2,6-lutidine, DCM, 0°C
C	95%	$Pd(OH)_2/C$, H_2, EtOH, rt
D	92%	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
E	88%	i) LDA, TMSCl, THF, -78°C ii) $Pd(OAc)_2$, MeCN, 50°C
F	95%	$LiBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, THF, -78°C
G	89%	N,N-dimethylacetamide dimethyl acetal, xylene, reflux
H	92%	$LiEt_3BH$, THF, 0°C-rt
I	96%	Pd/C, H_2, EtOH, rt
J	93%	o-$NO_2C_6H_4SeCN$, Bu_3P, THF, 0-rt
K	86%	H_2O_2, H_2O, THF, 0-rt
L	92%	i) O_3, DCM, MeOH, -78°C ii) DMS, rt
M	96%	(1.12.10), LiCl, Hunig's base, MeCN, rt
N	75%	i) $Rh(PPh_3)_3Cl$, Et_3SiH, 50°C ii) HF, H_2O, MeCN, 0°C iii) TBDPSCl, imidazole, DMF, rt



(1.12.10)

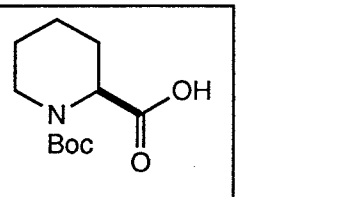
Scheme 1.13 outlines the construction of the advanced rapamycin intermediate **(1.13.6)** from the component fragments **(1.10.5)**, **(1.11.4)**, **(1.12.9)** and N-Boc-L-pipecolic acid. A chromium-mediated addition reaction effected the coupling of **(1.10.4)** and **(1.11.4)**, whilst an Evans aldol reaction was used to attach the C35-C42 fragment. Coupling of the pipecolic acid moiety was achieved using a diisopropylcarbodiimide-mediated esterification reaction. Deprotection of the amine functionality followed by functional group manipulation generated intermediate **(1.13.6)**.

Scheme 1.13



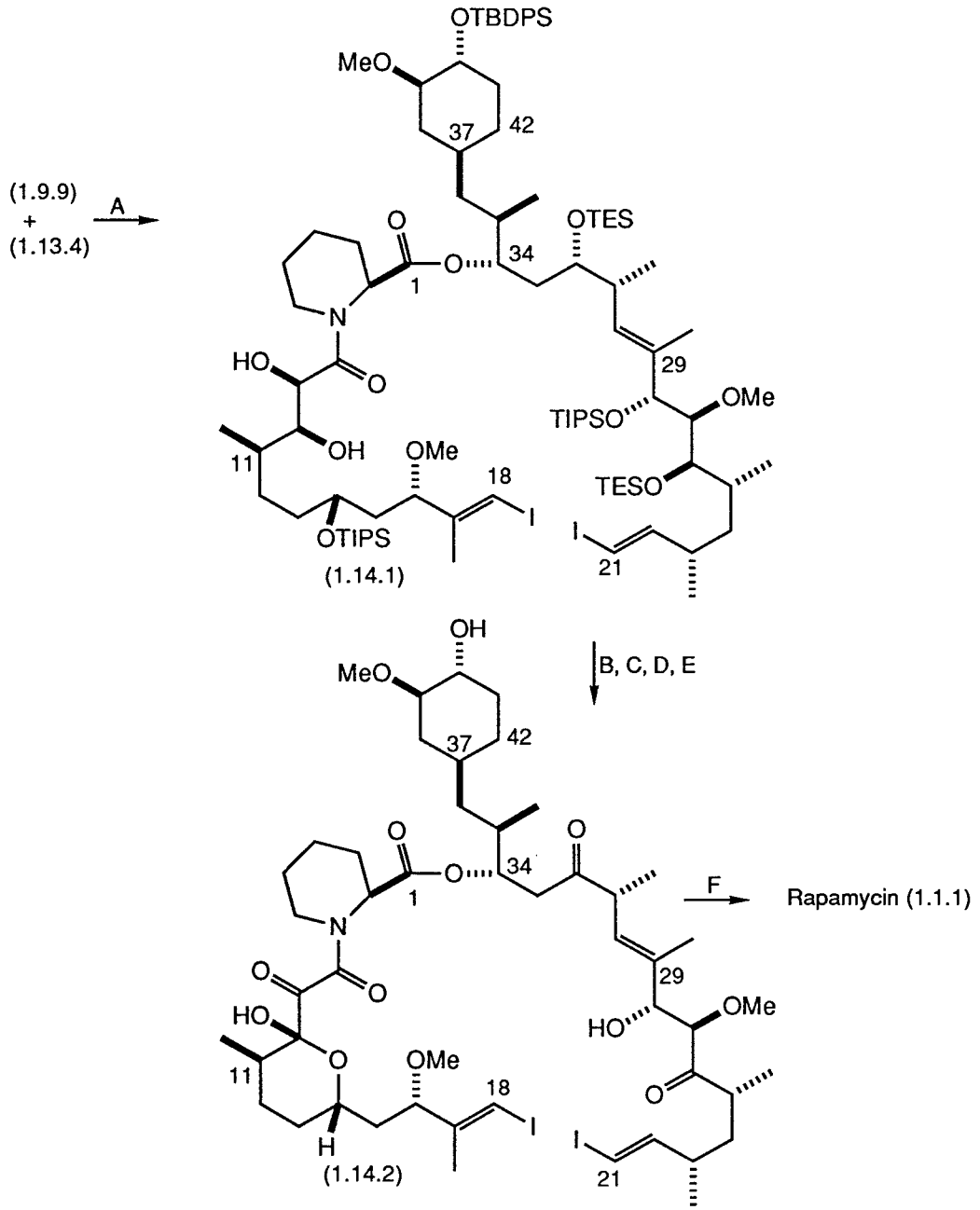
REAGENTS AND YIELDS

A	87%	$CrCl_2$, DMSO, rt
B	98%	TIPSOTf, 2,6-lutidine, DCM, 0°C
C	97%	HF•pyridine, THF, rt
D	96%	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
E	95%	Bu_2BOTf, Et_3N, DCM, -78°C-rt
F	98%	$LiBH_4$, H_2O, Et_2O, 0°C
G	90%	TsCl, Et_3N, DMAP, DCM, rt
H	91%	$LiEt_3BH$, THF, 0°C
I	85%	(1.13.7), diisopropylcarbodiimide, Hunig's base, 4-pyrrolidinopyridine, DCM, 0°C
J	-	OsO_4, NMMO, acetone, H_2O, rt
K	75%	$Pb(OAc)_4$, Na_2CO_3, C_6H_6, 0°C-rt
L	94%	CHI_3, $CrCl_2$, THF, dioxane, rt
M	98%	DDQ, $CHCl_3$, H_2O, rt
N	94%	TESOTf, 2,6-lutidine, DCM, 0°C

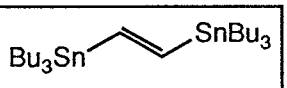


(1.13.7)

Scheme 1.14



REAGENTS AND YIELDS	
A 95%	1-hydroxy benzotriazole, DCM, diisopropylcarbodiimide, 0°C
B -	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
C -	HF / pyridine, THF, rt
D -	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
E 70%	HF, H_2O, CH_3CN, rt
F 28%	(1.14.3), Hunig's base, $Pd(CH_3CN)_2Cl_2$, DMF, rt



(1.14.3)

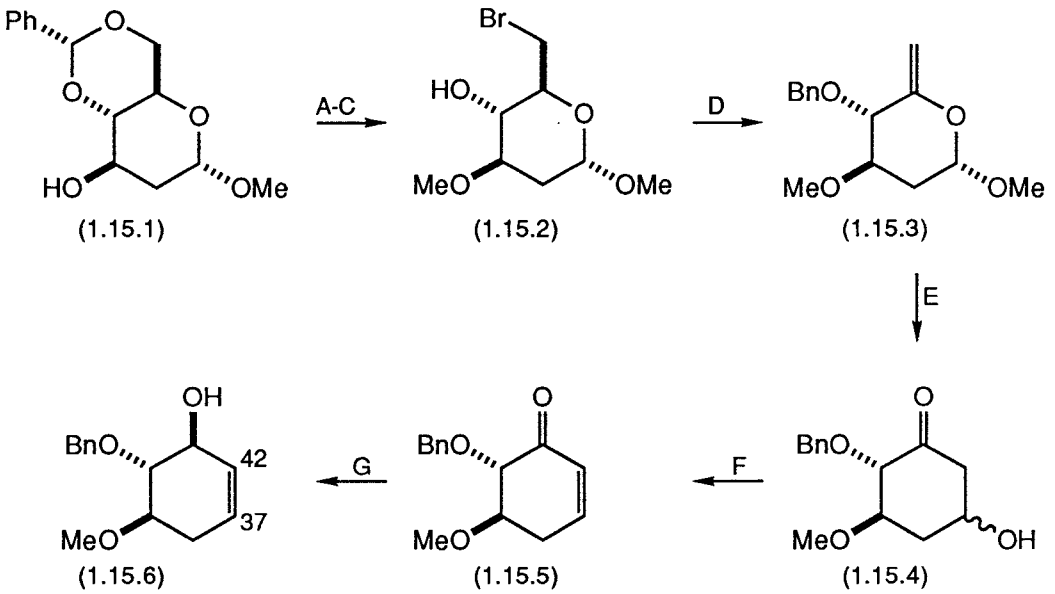
Scheme 1.14 illustrates the conclusion of Nicolaou's synthesis of rapamycin **(1.1.1)** The coupling of the two major fragments **(1.9.9)** and **(1.13.4)** was achieved by diisopropylcarbodiimide-mediated amide formation. After a

series of oxidations and selective deprotections, the macrocyclisation was effected by a palladium-catalysed cross coupling reaction to yield rapamycin **(1.1.1)**.

Danishefsky's synthesis of rapamycin (1.1.1).[17-21]

Schemes 1.15, 1.16 and 1.17 show the synthesis of the C28-C42 **(1.17.5)** fragment. The substituted cyclohexane fragment **(1.15.6)** was synthesised in seven steps from the benzylideneacetal of 2-deoxy-D-glucose (scheme 1.15), using the Ferrier transformation to rearrange the oxygen functionality.

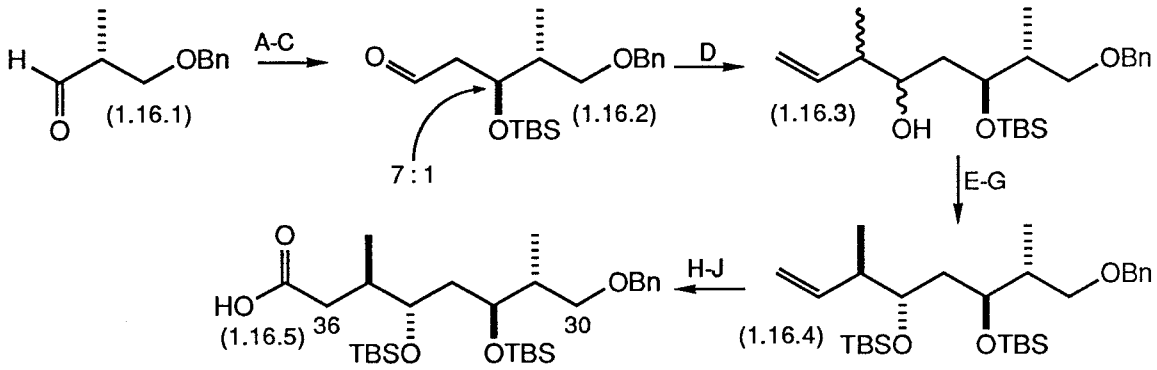
Scheme 1.15



REAGENTS AND YIELDS	
A	90% NaH, MeI, DMF, 0°C-rt
B	93% $BaCO_3$, NBS, CCl_4, reflux
C	82% NaOMe, MeOH, rt
D	90% BnBr, NaH, DMF, Bu_4NI, 0°C-rt
E	85% acetone, H_2O, $HgCl_2$, reflux
F	91% MsCl, pyridine, rt
G	67% $CeCl_3 \cdot 7H_2O$, $LiBH_4$, THF, MeOH

The C30-C36 **(1.16.5)** fragment was synthesised as shown in scheme 1.16 by a route that yielded mixtures of diastereoisomers in two steps. The desired isomer was subsequently isolated by column chromatography.

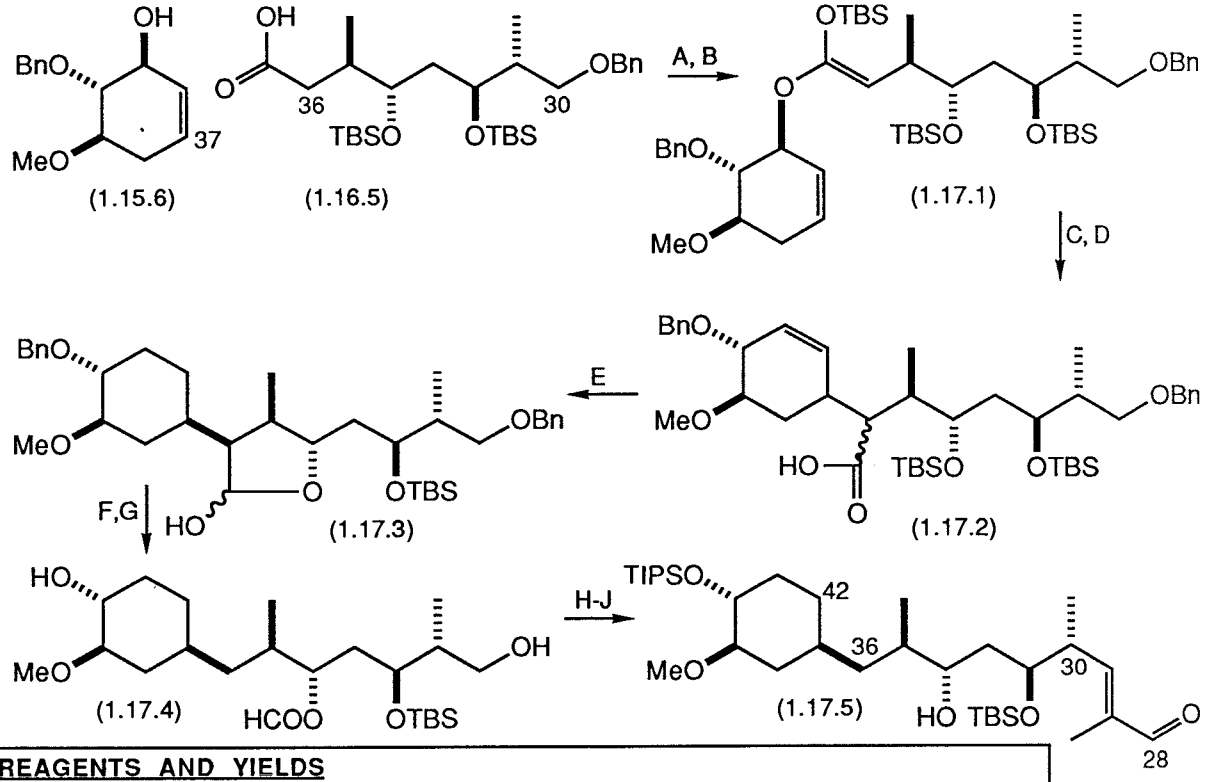
Scheme 1.16



REAGENTS AND YIELDS		
A	75%	allyl trimethyl silane, $TiCl_4$
B	98%	TBSCl, DMF, imidazole, rt
C	75%	i) O_3, MeOH, DCM, pyridine ii) DMS, -78°C
D	-	S,S-diisopropyl tartrate, E-crotylboronate, toluene, -78°C
E	-	TBAF, THF, rt
F	47%	chromatographic separation of isomers
G	93%	TBSCl, DMF, imidazole, rt
H	98%	i) 9-BBN, THF, rt ii) NaOH, H_2O
I	90%	$(COCl)_2$, DMSO, Et_3N, DCM, -78-0°C
J	99%	$KMnO_4$, *t*- BuOH, NaH_2PO_4, H_2O

The two fragments **(1.15.6)** and **(1.16.5)** were joined by means of an EDCI coupling reaction. Formation of the silyl ketene acetal, and subsequent Ireland-Claisen rearrangement yielded a silyl ester that was hydrolysed to give acid **(1.17.2)**. Lactonisation, diimide reduction of the C41-C42 double bond, DIBALH reduction, and Suarez oxidation gave lactol **(1.17.3)**. A number of trivial steps then yielded the C28-C42 fragment **(1.17.5)**.

Scheme 1.17



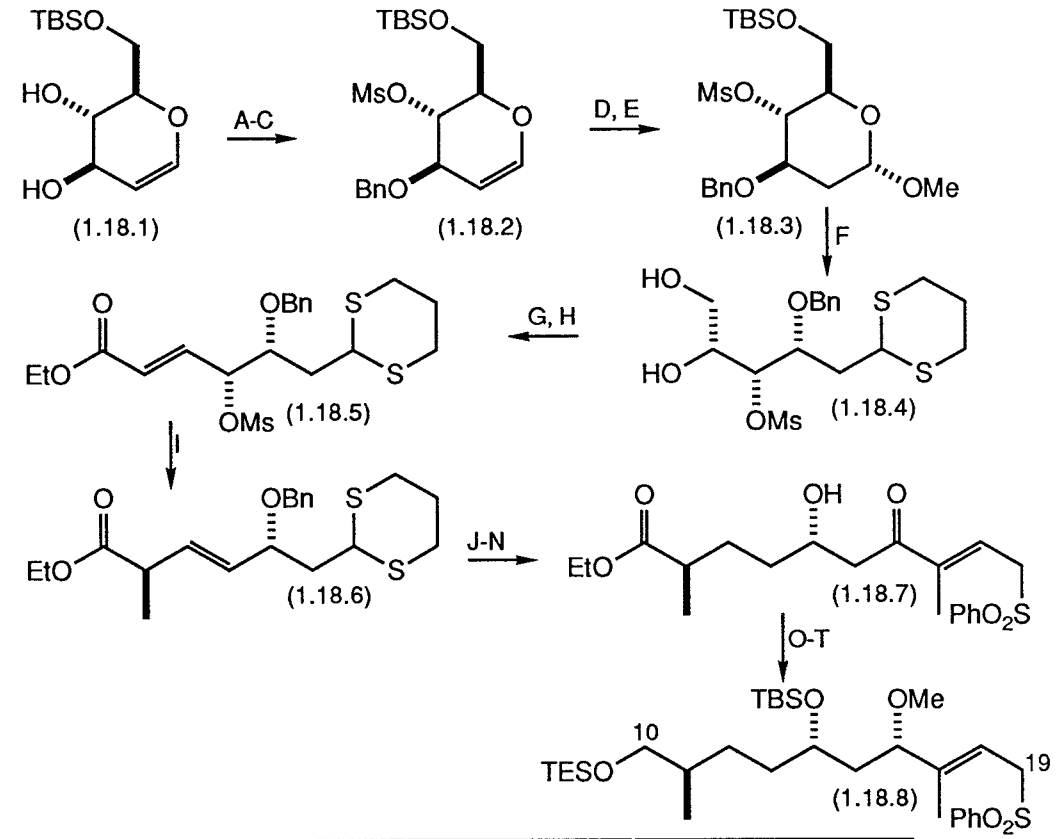
REAGENTS AND YIELDS

A	75%	EDCI, DMAP, DCM, rt
B	-	LDA, HMPA, TBSCl, THF, -78°C
C	-	toluene, reflux
D	-	LiOH, H_2O, THF, rt
E	-	i) $(COCl)_2$, DMAP, DCM ii) $TsNHNH_2$, DME, NaOAc, H_2O, 90°C iii) DIBALH, toluene, -78°C
F	85%	I_2, $PhI(OAc)_2$, cyclohexane, light
G	90%	i)Ph_3SnH, AIBN, toluene, 110°C ii) H_2, $Pd(OH)_2$,
H	-	4-hydroxy-TEMPO-benzoate, $Ca(OCl)_2$, DCM, $NaHCO_3$, H_2O
I	73%	$Ph_3PC(CH_3)CO_2Et$, toluene, 80°C
J	62%	i) TIPSOTf, 2,6-lutidine, DCM, 0°C ii) DIBALH, toluene, -78°C iii) MnO_2, DCM

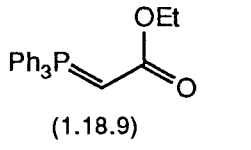
The C10-C26 triene portion of the molecule **(1.20.1)** was generated by the coupling of two small fragments **(1.18.8)** and **(1.19.9)**. The synthesis of the C10-C19 **(1.18.8)** fragment from the 6-O-TBS derivative of D-glucal is shown in scheme 1.18. The vinyl iodide fragment **(1.18.10)** was made from tetrolic acid in five steps. The addition of the vinyl chromium species to the appropriate aldehyde, gave a 1 : 1 mixture of epimers at C16. The mixture was oxidised to the corresponding ketone and diastereoselectively reduced to give alcohol

(1.18.7) as a single diastereoisomer.

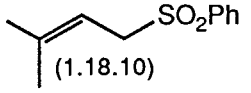
Scheme 1.18



REAGENTS AND YIELDS		
A	-	Bu_2SnO
B	-	BnBr, Bu_4NBr
C	99%	MsCl, pyridine, rt
D	88%	NIS, CH_3CN, MeOH, rt
E	71%	Bu_3SnH, AIBN, benzene
F	74%	1,3-propanedithiol, $BF_3{\cdot}Et_2O$, DCM, rt
G	72%	$Pb(OAc)_4$, benzene, rt
H	62%	(1.18.9), DCM, 0°C
I	74%	CuCN, MeLi·LiBr, $BF_3{\cdot}Et_2O$, THF, -78°C
J	83%	$(Ph_3P)_3RhCl$, H_2, benzene, rt
K	-	NBS, acetone, H_2O, -20°C
L	-	(1.18.10), $CrCl_2$, $NiCl_2$, DMSO, rt
M	-	Dess Martin periodinane
N	75%	BCl_3, DCM, -78°C
O	-	Et_2BOMe, $NaBH_4$, toluene, -78°C
P	71%	i) LiOH, THF, MeOH, H_2O, 0°C ii) EDCI, DCM, rt
Q	-	Ag_2O, MeI, rt
R	-	K_2CO_3, MeOH, rt
S	86%	TBSOTf, 2,6-lutidine, 0°C
T	86%	i) DIBALH, THF, 0°C ii) TESCl, Et_3N, DCM



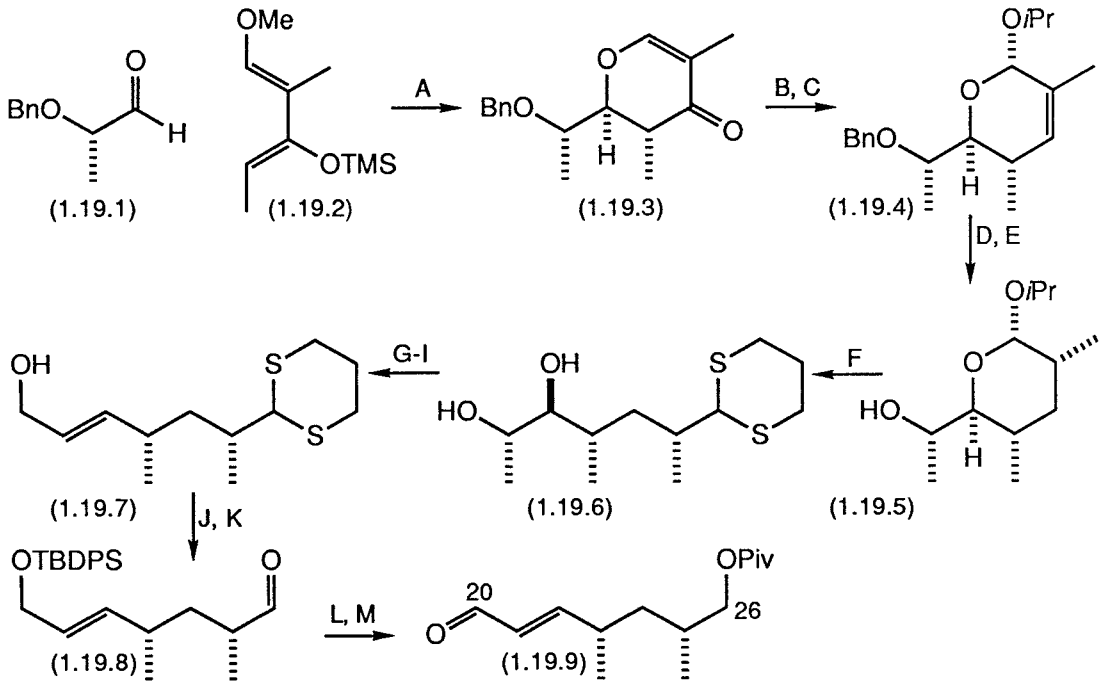
(1.18.9)



(1.18.10)

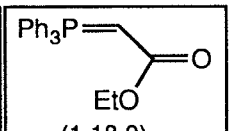
The C20-C26 fragment **(1.19.9)** was synthesised as shown in scheme 1.19. and uses identical methodology to introduce the allylic ether functionality into **(1.19.8)** as is used in the synthesis of **(1.18.6)**.

Scheme 1.19



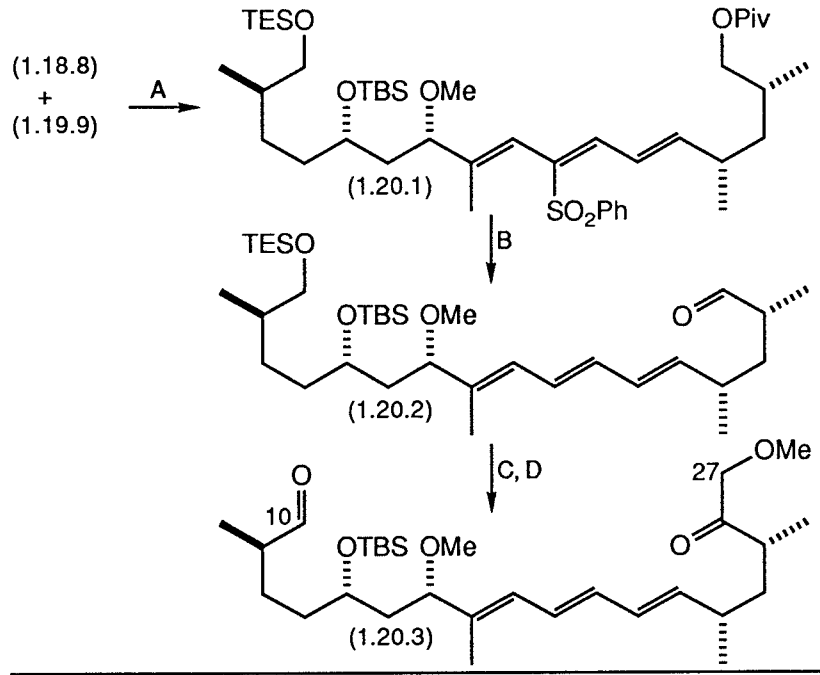
REAGENTS AND YIELDS

A	75%	$MgBr_2$, THF, rt
B	-	DIBALH, benzene, rt
C	88%	*i*-PrOH, $TsOH.H_2O$
D	-	Pd, Al_2O_3, H_2, EtOAc, rt
E	68%	Pd, C, H_2, EtOAc, rt
F	96%	1,3-propane dithiol, $BF_3{\cdot}Et_2O$, DCM, -78°C
G	60%	$Pb(OAc)_4$, CH_3CN, KOAc, -20°C
H	81%	(1.18.9), DCM, rt
I	95%	DIBALH, toluene, -78°C-rt
J	-	i) TBDPSCl, Et_3N, DCM ii) NCS, $AgNO_3$, THF, MeOH
K	67%	glyoxylic acid, AcOH, DCM
L	-	i) $NaBH_4$, EtOH ii)PivCl, Et_3N, DCM
M	82%	i) HF, CH_3CN, H_2O ii) Dess-Martin Periodinane, DCM



(1.18.9)

Scheme 1.20



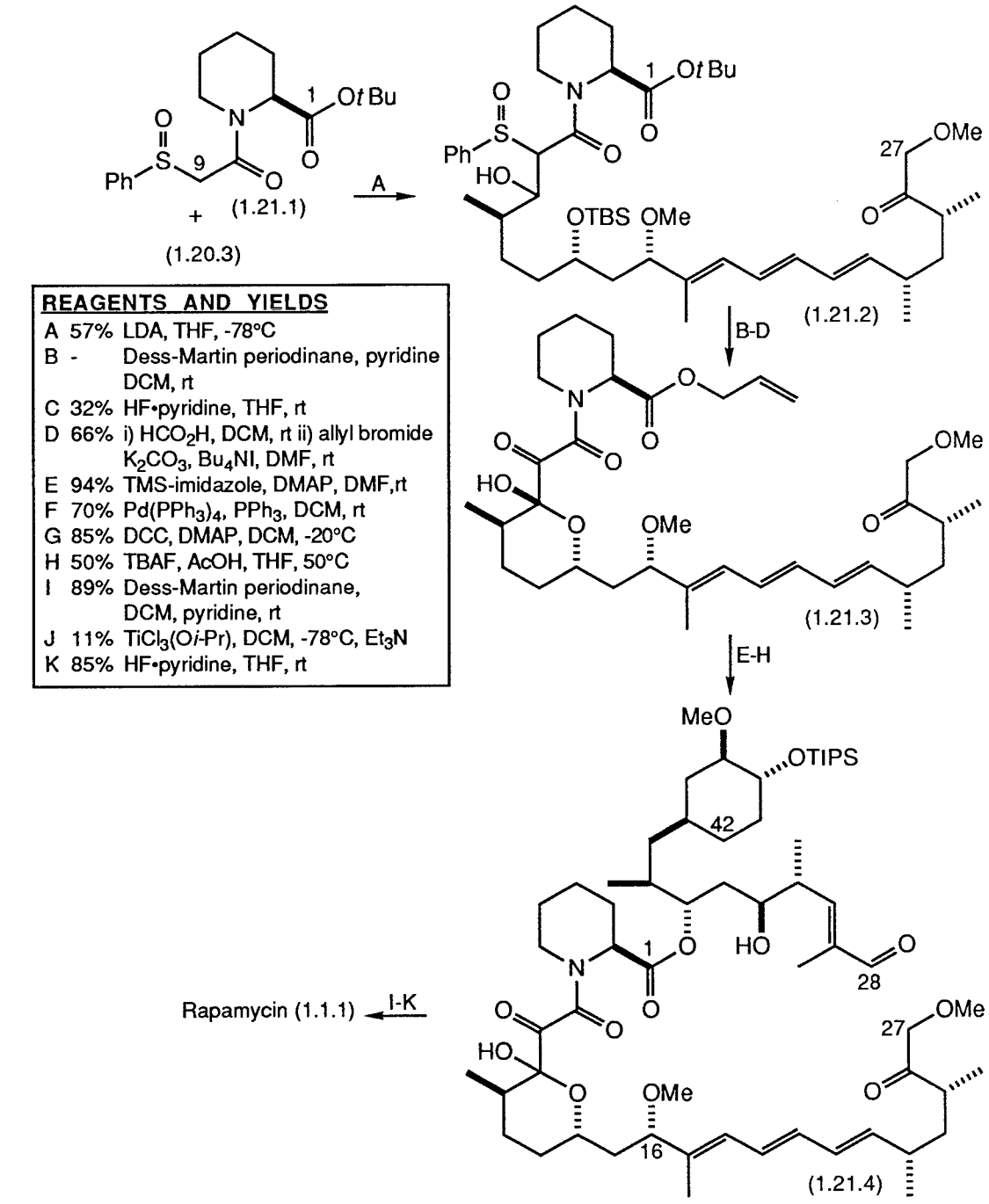
REAGENTS AND YIELDS

A 89% i) LDA, THF, -78°C ii) Ac_2O, Et_3N, DMAP, DCM iii) DBU, THF, rt
B 67% i) DIBALH, toluene, 0°C ii) Na (Hg), KH_2PO_4, THF, MeOH, -20°C, iii) Dess-Martin periodinane, pyridine
C 77% i) $LiCH_2OCH_3$, Et_2O, -78°C ii) Dess-Martin periodinane, pyridine, DCM, rt
D 86% i) AcOH, THF, H_2O, rt ii) Dess-Martin periodinane, pyridine, DCM

The fragments **(1.19.9)** and **(1.18.8)** were linked to form **(1.20.1)** by means of a sulphone anion / aldehyde coupling (scheme 1.20). The acetate and sulphone moieties were then removed using standard conditions to yield triene **(1.20.2)**. A one carbon fragment addition, and subsequent functional group interconversion yielded triene **(1.20.3)**.

The assembly of rapamycin was achieved (scheme 1.21) by the coupling of the three fragments **(1.17.5)**, **(1.20.3)** and **(1.21.1)**. (Adduct **(1.21.1)** was synthesised
from *tert*-butyl-N-[2-(phenylthio)acetyl]-L-pipecolinate with $NaIO_4$ / MeOH.) The pipecolinate moiety was attatched using a sulphoxide anion / aldehyde addition, and the C28-C42 fragment was coupled using a DCC esterification reaction. After functional group manipulation and deprotection steps the macrocyclisation was achieved *via* an aldol reaction to yield a mixture of diastereoisomers one of which was C40 TIPS rapamycin. Removal of the TIPS group with HF•pyridine complex afforded rapamycin **(1.1.1)**.

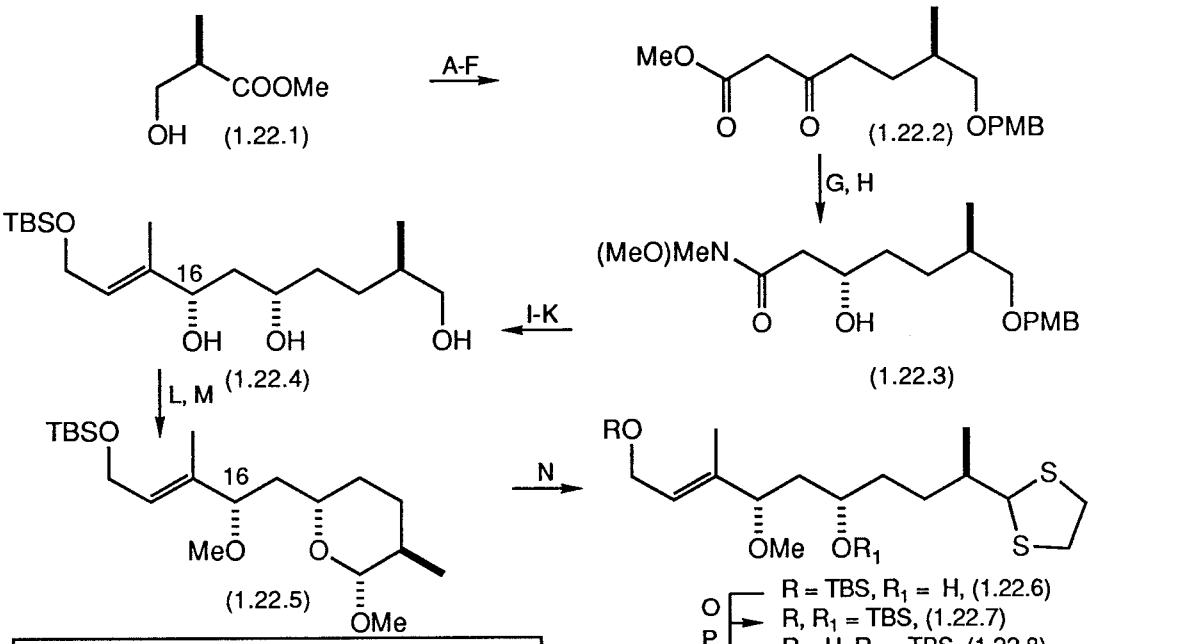
Scheme 1.21


(1.21.1)
(1.20.3)
A
(1.21.2)
B-D
(1.21.3)
E-H
(1.21.4)
I-K
Rapamycin (1.1.1)
REAGENTS AND YIELDS
A 57% LDA, THF, -78°C
B - Dess-Martin periodinane, pyridine DCM, rt
C 32% HF•pyridine, THF, rt
D 66% i) HCO2H, DCM, rt ii) allyl bromide K2CO3, Bu4NI, DMF, rt
E 94% TMS-imidazole, DMAP, DMF,rt
F 70% Pd(PPh3)4, PPh3, DCM, rt
G 85% DCC, DMAP, DCM, -20°C
H 50% TBAF, AcOH, THF, 50°C
I 89% Dess-Martin periodinane, DCM, pyridine, rt
J 11% TiCl3(Oi-Pr), DCM, -78°C, Et3N
K 85% HF•pyridine, THF, rt

Schreibers synthesis of rapamycin (1.1.1).

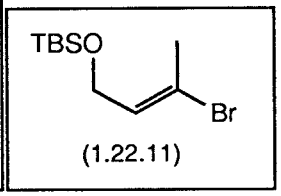
Schreibers synthesis[22-25] of the C10-C20 fragment is shown below (scheme 1.22). The synthesis starts with homochiral (*R*)-methyl-3-hydroxy-2-methylpropionate **(1.22.1)**, and uses an enantioselective reduction to secure the stereochemistry at C14 and a chelation-controlled reduction to induce the stereochemistry at C16.

Scheme 1.22



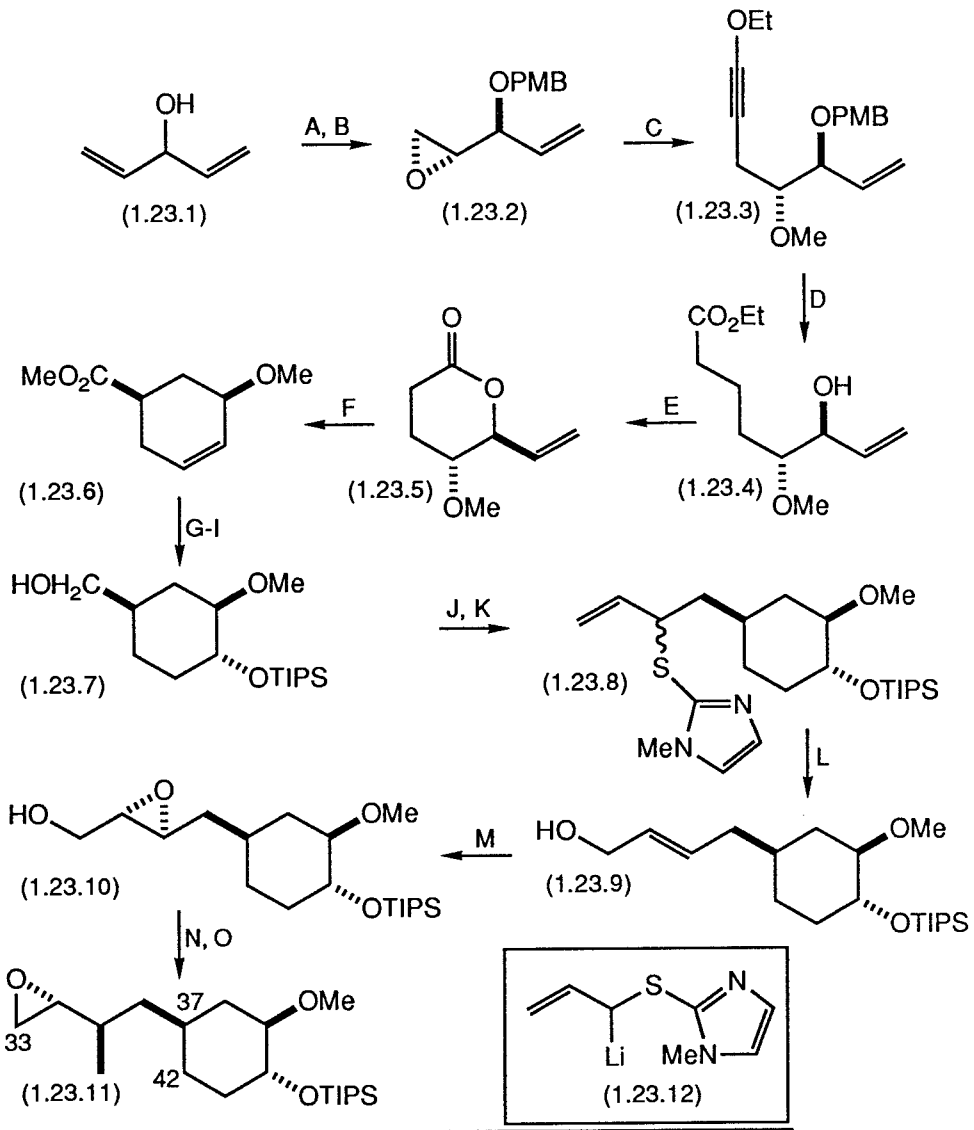
REAGENTS AND YIELDS

A	-	DHP, H^+
B	-	LAH
C	-	NaH, PMBBr
D	73%	MeOH, H^+
E	93%	PPh_3, NBS
F	90%	MeO_2CCH_2COMe, NaH, BuLi, HMPA
G	88%	$RuCl_2$[(S)-binap], Et_3N, H_2
H	97%	MeNHOMe•HCl, Me_3Al
I	85%	(i) BuLi (ii) *t*-BuLi, (1.22.11)
J	93%	DDQ
K	98%	Et_2BOMe, $NaBH_4$
L	-	$RuCl_2(PPh_3)_3$
M	78%	NaH, MeI
N	60%	$TiCl_4$, $HS(CH_2)_2SH$
O	94%	TBSOTf, 2,6-lutidine
P	86%	HF•pyr, pyr
Q	73%	$PhI(OCOCF_3)_2$, MeOH
R	-	$BaMnO_4$, Celite
S	77%	Ph_3PCHCO_2Et
T	83%	DIBALH
U	-	HCA, PPh_3, 2,6-di-*t*-butylpyridine
V	-	$LiPPh_2$
W	65%	air



(1.22.11)

Scheme 1.23



REAGENTS AND YIELDS

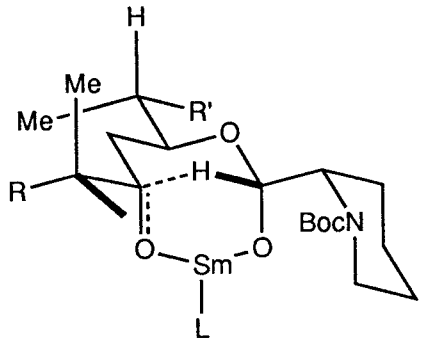
A 55% L-(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, DCM, -23°C
B 94% PMBBr, NaH, THF, 0°C
C 87% i) LiCCOEt, BF_3•Et_2O, THF, -78°C ii) NaH, MeI, Et_2O, rt
D 78% i) $HgCl_2$, EtOH, rt ii) DDQ, DCM, rt
E 83% *p*-TSA, 4Å sieves, benzene, rt
F 87% i) DCM, TBSCl, Et_3N, -78-0°C ii) toluene, 110°C iii) CH_2N_2, Et_2O
G 65% i) BH_3•THF, THF, -78-0°C ii) H_2O_2, NaOH, rt
H 100% TIPSOTf, DCM, Et_3N, 0°C-rt
I 87% LAH, THF, 0°C
J 90% I_2, Ph_3P, imidazole
K 87% (1.23.12)
L 71% *m*-CPBA, DCM, diethylamine, MeOH
M 88% L-(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*- BuOOH, DCM, -23°C
N 83% Me_3Al
O 57% i) TsCl, pyridine ii) K_2CO_3, MeOH

The synthesis of the C33-C42 fragment **(1.23.11)** is shown in scheme 1.23. The stereochemistry at C37 and C39 is ultimately derived from the kinetic resolution of allylic alcohol **(1.23.1)** under the conditions of Sharpless. Subsequent elaboration and sigmatropic rearrangement yielded cyclohexene derivative **(1.23.6)**. The chirality at C40 was introduced by the employment of a diastereoselective hydroboration followed by an oxidative aqueous work up, further elaboration of the functionality yielded the desired fragment **(1.23.11)**.

Scheme 1.25 shows the synthesis of the C22-C32 fragment **(1.25.8)** and the coupling chemistry employed to attach the C33-C42 fragment **(1.23.11)**. A diastereoselective hydogenation reaction and an Evans diastereoselective aldol reaction introduced chiral centres at C23, C26 and C27. The C33-C42 fragment **(1.23.11)** was linked by means of a sulphone anion / epoxide coupling to yield adduct **(1.25.9)**. The conversion of the sulphone moiety to the ketone functionality was achieved *via* an olefination process reported by Julia followed by oxidation to the ketone **(1.25.10)**.

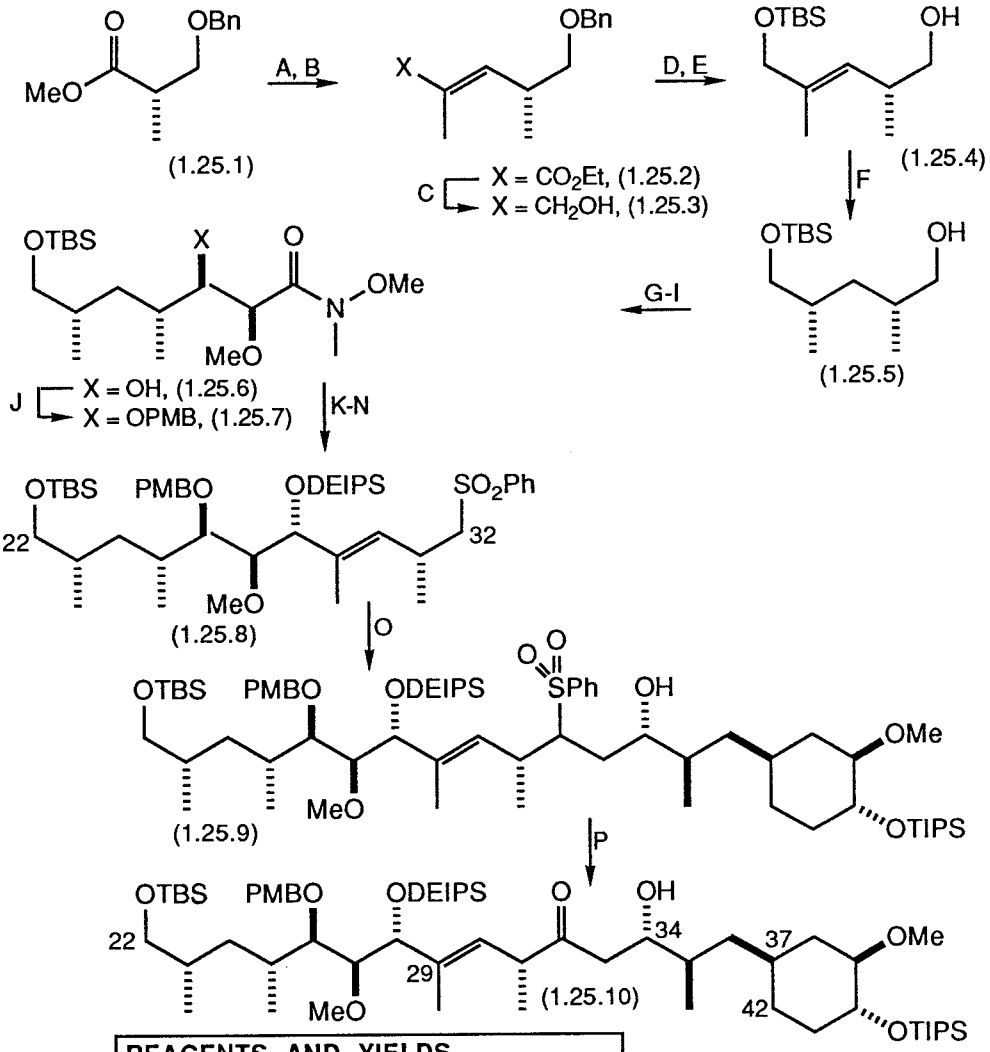
The Evans-Tischenko reaction was employed to attatch the pipecolic acid group. The reaction proceeds *via* a chelation controlled bicyclic transition state causing highly diastereoselective (>20 : 1) reduction of the ketone functionality at C34 (scheme 1.24).

Scheme 1.24



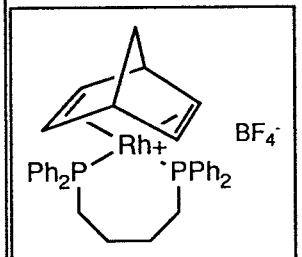
After manipulation of protecting groups and Swern oxidation, aldehyde **(1.26.2)** was condensed with phosphonate **(1.22.10)** to yield triene **(1.26.3)**.

Scheme 1.25

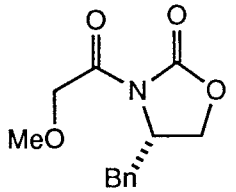


REAGENTS AND YIELDS

A	-	DIBALH
B	80%	$Ph_3PC(Me)CO_2Et$
C	100%	DIBALH
D	-	TBSCl, Et_3N
E	94%	Na / NH_3
F	90%	(1.25.11), H_2
G	-	Swern
H	50%	(1.25.12), Bu_2BOTf, Hunigs base
I	63%	MeNHOMe•HCl, Me_3Al
J	61%	$PMBOC(NH)CCl_3$, TfOH
K	78%	*t*-BuLi, (4R)-2-bromo-4-methyl-5-phenylthio-2-pentene
L	90%	$Zn(BH_4)_2$
M	96%	DEIPSOTf, 2,6-lutidine
N	90%	*m*- CPBA, pyridine
O	75%	BuLi, (1.23.11), BF_3•Et_2O
P	69%	i) BuLi, THF, CH_2I_2, *i*-PrMgCl, -78°C ii) OsO_4, pyridine, $NaHSO_3$ iii) $NaIO_4$, SiO_2, Tris HCl, pH 7 buffer

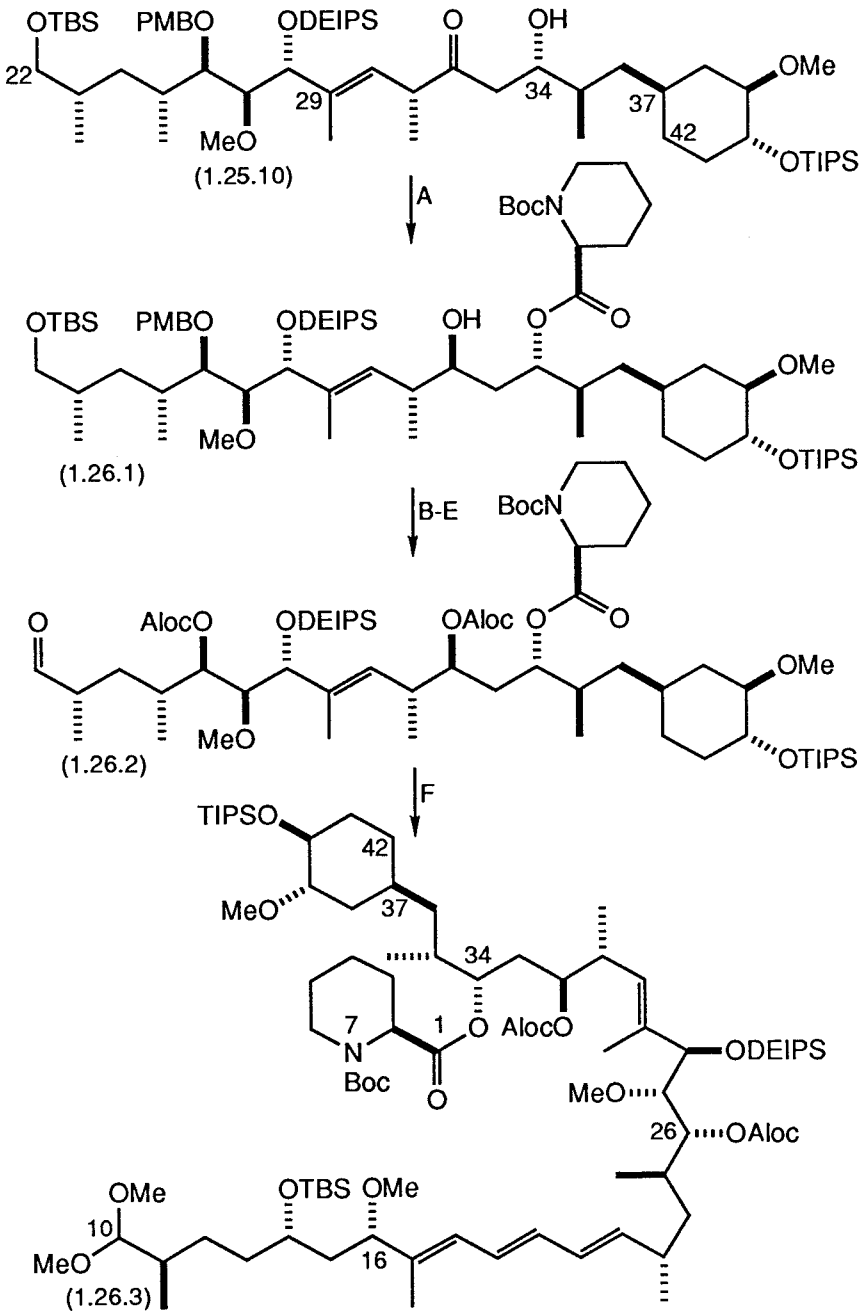


(1.25.11)



(1.25.12)

Scheme 1.26

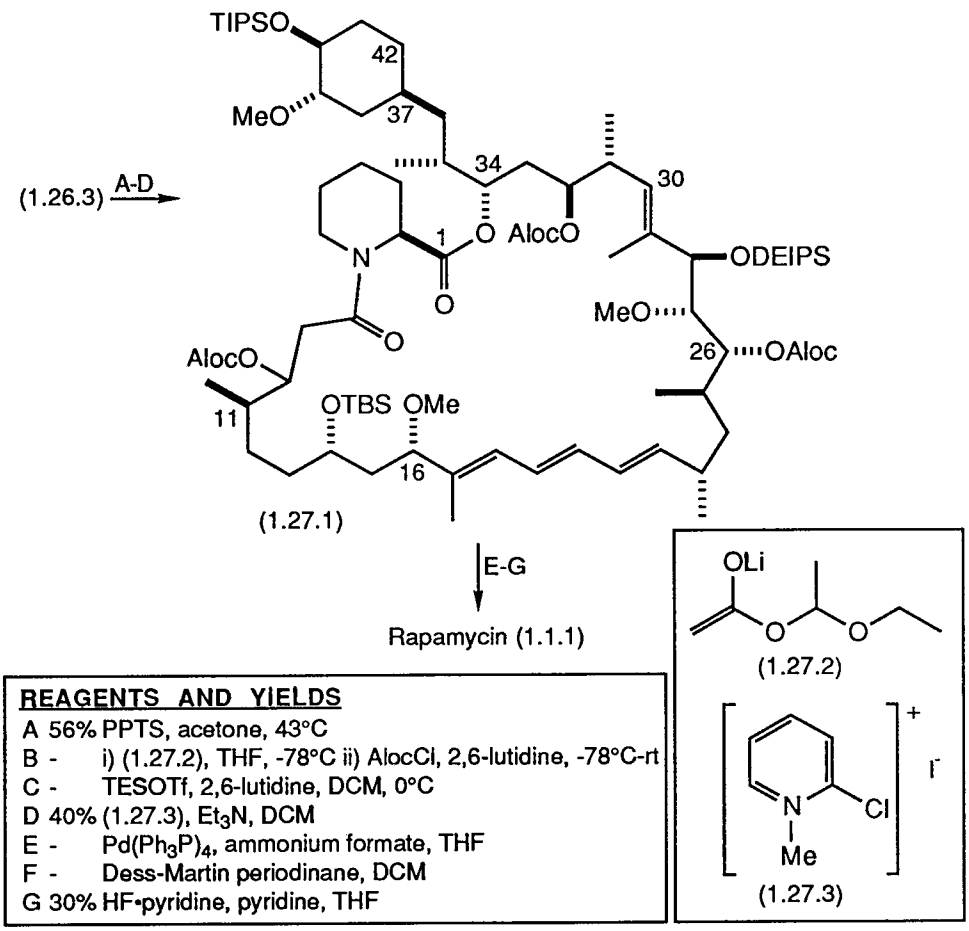


REAGENTS AND YIELDS

A 95% (S)-N-Boc pipecolinal, PhCHO, SmI_2, THF, -10°C
B - DDQ, $NaHCO_3$
C 87% AlocCl, pyridine, 2,6-lutidine, THF
D 71% PPTS, TsOH, THF, H_2O
E 96% Swern
F 71% BuLi, HMPA, (1.22.10), -78°C

Schreiber used an ingenious method to introduce the two remaining carbon atoms of the tricarbonyl unit (scheme 1.27). Treatment of the dimethoxy acetal **(1.26.3)** with PPTS in acetone gave an aldehyde which was subjected to an aldol reaction with the lithium enolate of ethoxyethylacetate **(1.27.2)**. The aldol adducts were trapped out as allyl carbonates. Treatment of the protected aldol adduct with TESOTf led to deprotection at the N7 position, and transesterification at the C8 position. After hydrolysis of the TES ester with silica, the macrocyclisation was performed using the conditions of Mukaiyama to give cyclic adduct **(1.27.1)**. Deprotection of the allyl carbonates with Pd(0) and ammonium formate followed by oxidation of the methylene group at C9 and subsequent deprotection of the remaining silyl ethers yielded rapamycin **(1.1.1)**.

Scheme 1.27



1.4 Comparison of the three total syntheses of rapamycin (1.1.1).

Nicolaou's synthesis is highly convergent, constructing the large frements **(1.13.6)** and **(1.9.8)** from several small fragments ranging in size from two to nine carbons. Extensive use of Evans' aldol chemistry secures many of the chiral centres in rapamycin **(1.1.1)**. Nicolaou's final cyclisation strategy is the most original of the three total syntheses and has the advantage of assembling the sensitive triene functionality as the last step thus avoiding the problems of functional group incompatibilty.

Danishefsky's synthesis suffers from longwinded fragment syntheses i.e. the C20-C26 fragment **(1.19.9)** (12 steps) and the C10-C18 fragment **(1.18.8)** (20 steps). However notable features of the synthesis include the elegant coupling of the cyclohexyl fragment **(1.15.6)** *via* an EDCI esterification and subsequent [2,3] sigmatropic rearrangement. The macrocyclisation was achieved using an intramolecular aldol reaction which proved to be very low yielding and proceeded with poor diastereo control.

Schreiber's synthesis is also very convergent making extensive use of small fragments **(1.25.5)**, **(1.22.11)** and (4*R*)-2-bromo-4-methyl-5-thiaphenyl-2-pentene. The notable features of the synthesis are the Evans-Tishchenko reaction used to couple the pipecolic acid moiety, the sulphone anion of **(1.25.8)** / epoxide **(1.23.11)** coupling and oxidative removal of the sulphone moiety. The final cyclisation was achieved using Mukaiyama's conditions to perform a macroamidation.

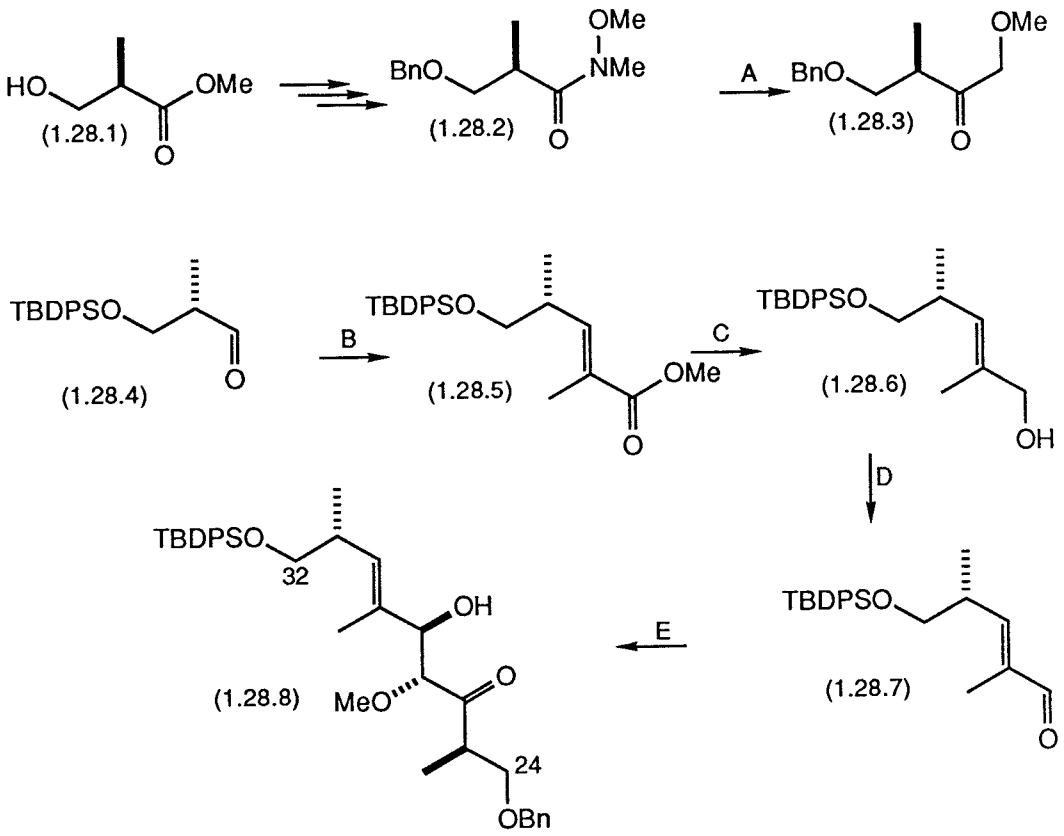
1.5 Synthesis of rapamycin (1.1.1) fragments.

Paterson's synthesis of the C24-C32 sub-unit of rapamycin

Paterson[26] has devised a convergent approach to a fragment of rapamycin using a highly anti selective aldol reaction. The two sub fragments **(1.28.3)** and **(1.28.7)** are derived, using simple chemistry, from opposite enantiomers of methyl-3-hydroxy propionate. The aldol reaction is then performed using the *E*-enol borinate of **(1.28.3)**. The reaction proceeds *via* a six centred transition state with 97% diastereoselectivity to give **(1.28.8)**.

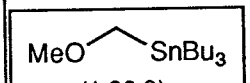
The chemistry Paterson has used is both convergent and selective but significant changes to the synthesis of sub fragment **(1.28.3)** are required if the chemistry is to be applied to a total synthesis of rapamycin **(1.1.1)**.

Scheme 1.28



REAGENTS AND YIELDS

A 80% BuLi, (1.28.9), THF, -78°C
B - $MeO_2CC(Me)PPh_3$
C - DIBALH
D - Dess-Martin periodinane
E 94% $(c\text{-}C_6H_{11})_2BCl$, Et_3N, (1.28.3)

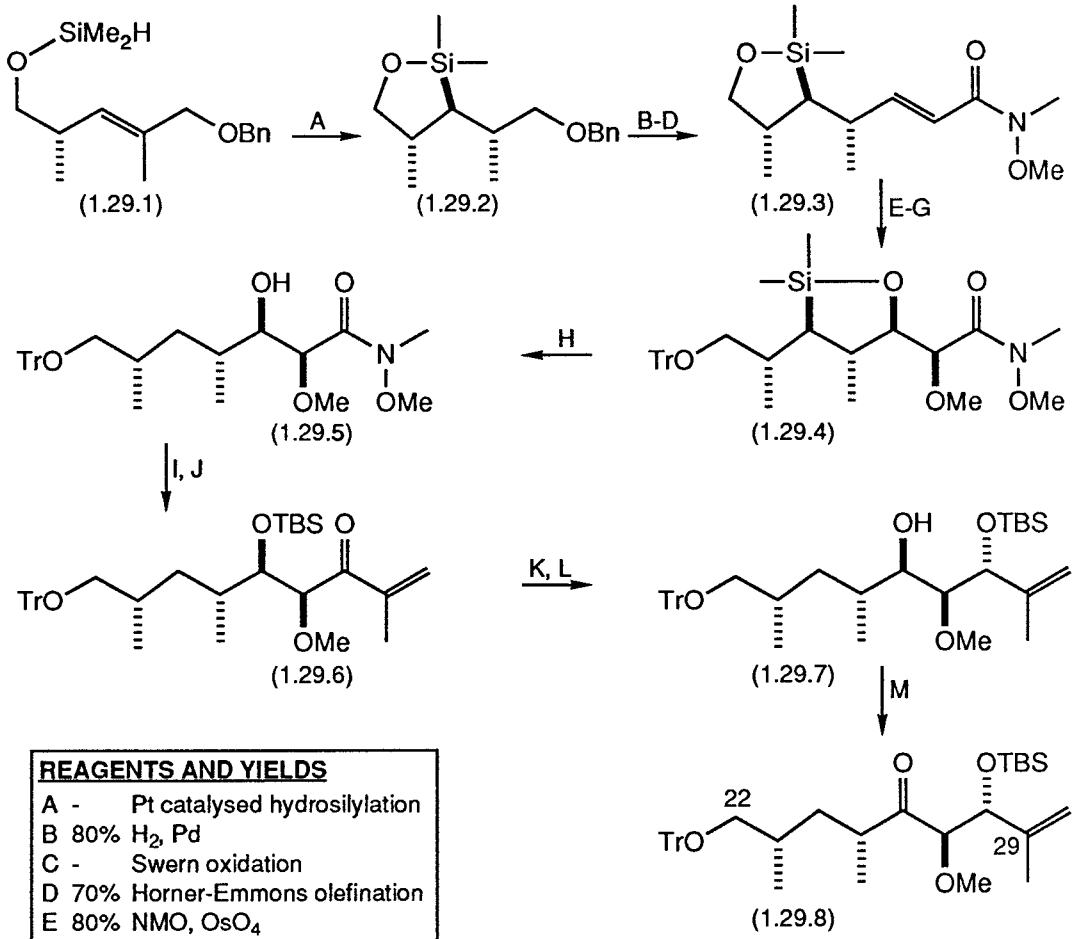


(1.28.9)

Hoveyda's synthesis of the C22-C29 fragment of rapamycin (1.1.1).

In his programme aimed at the total synthesis of rapamycin **(1.1.1)**. Hoveyda has devised a synthesis for the C22-C29 fragment[27]. The synthesis commences with a diastereoselective intramolecular platinum catalysed hydrosilylation to give siloxane **(1.29.2)**. The siloxane ring is used to relay asymmetry along the chain by employment of an osmium catalysed olefin oxidation reaction to give a 94 : 6 ratio of the desired isomer **(1.29.4)**. Subsequent diastereoselective reduction and functional group manipulation secures the final chiral centre at C28 and yields the fragment **(1.29.8)**.

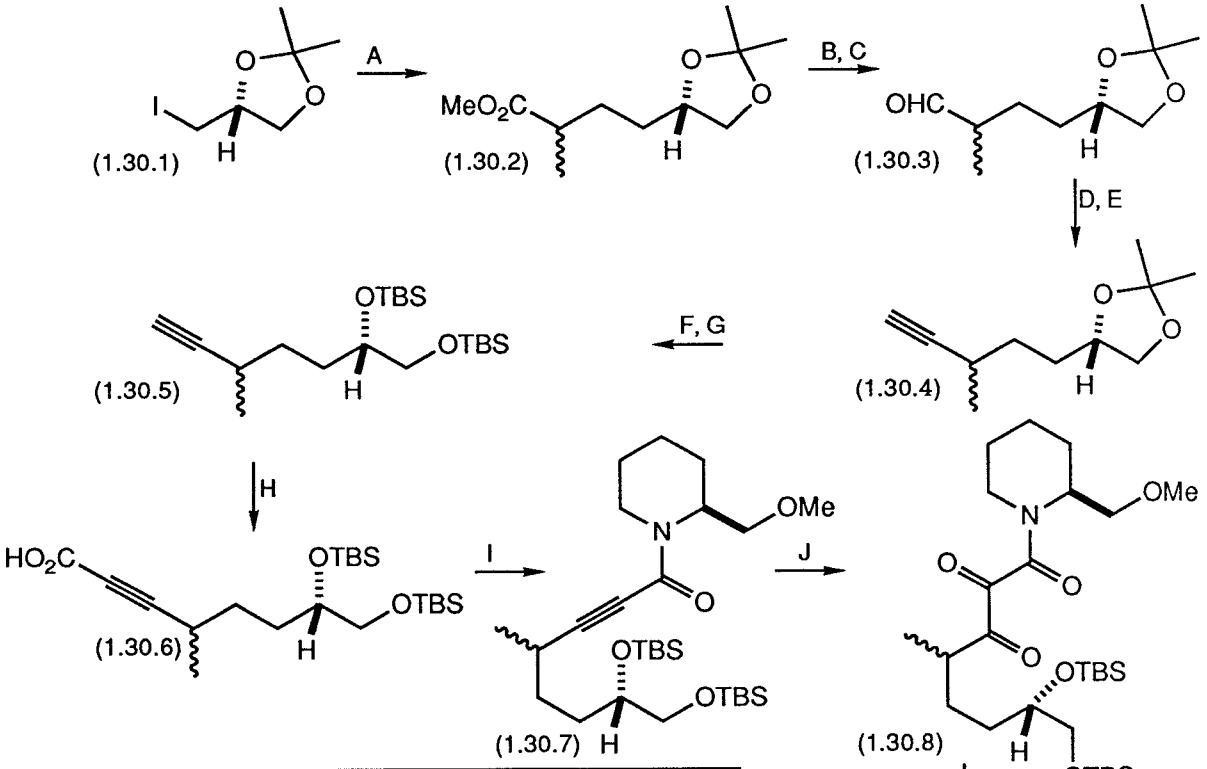
Scheme 1.29



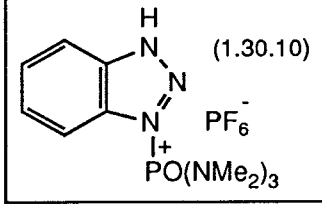
REAGENTS AND YIELDS	
A -	Pt catalysed hydrosilylation
B 80%	H_2, Pd
C -	Swern oxidation
D 70%	Horner-Emmons olefination
E 80%	NMO, OsO_4
F -	Tr•pyr•BF_4
G 88%	MeI, NaH
H 88%	TBAF
I -	2-lithio propene
J 75%	TBSOTf
K 90%	$Zn(BH_4)_2$
L -	NaH, DMSO
M 80%	Swern oxidation

Pattenden's synthesis of the C1-C15 tricarbonyl region of rapamycin (1.1.1).

Pattenden[28] uses known chemistry to yield the acetylenic amide **(1.30.7)** in nine steps (scheme 1.30). The acetylene moiety is oxidised using catalytic ruthenium (IV) oxide in the presence of $NaIO_4$ to give a 35% yield of the tricarbonyl compound **(1.30.8)**. The lactol ring is closed by acidic cleavage of the silyl ethers to give the fragment **(1.30.9)** as a 1 : 1 mixture of epimers at C11. The synthesis suffers from a lack of selectivity; a low yielding key step, and a curious choice of disconnective strategy. Scheme 1.30.

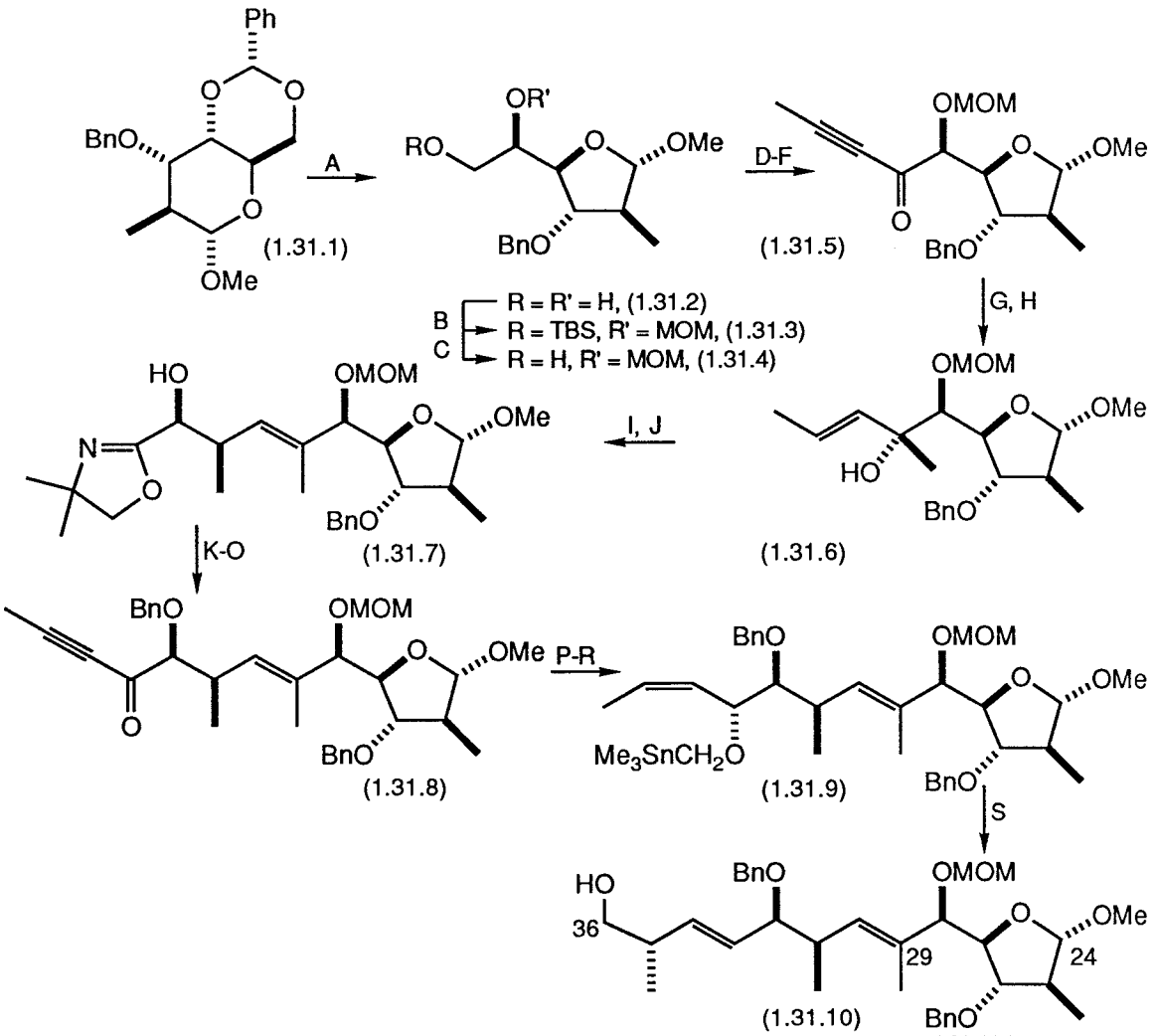


REAGENTS AND YIELDS		
A	55%	Bu_3SnCl, $NaBH_4$, light, methylmethacrylate, 20°C
B	-	DIBALH, THF
C	-	PCC, NaOAc
D	76%	dibromomethylenetriphenylphosphoranylide
E	95%	BuLi, THF, -70°C
F	-	HCl, MeOH
G	-	TBSCl, imidazole, DMF
H	86%	BuLi, HMPA, CO_2, -50°C
I	86%	(1.30.10), (2S)-2-methoxymethyl piperidine
J	35%	RuO_2, $NaIO_4$
K	-	HF, CH_3CN



Kallmerten's synthesis of the C24-C36 fragment of rapamycin (1.1.1).

Scheme 1.31

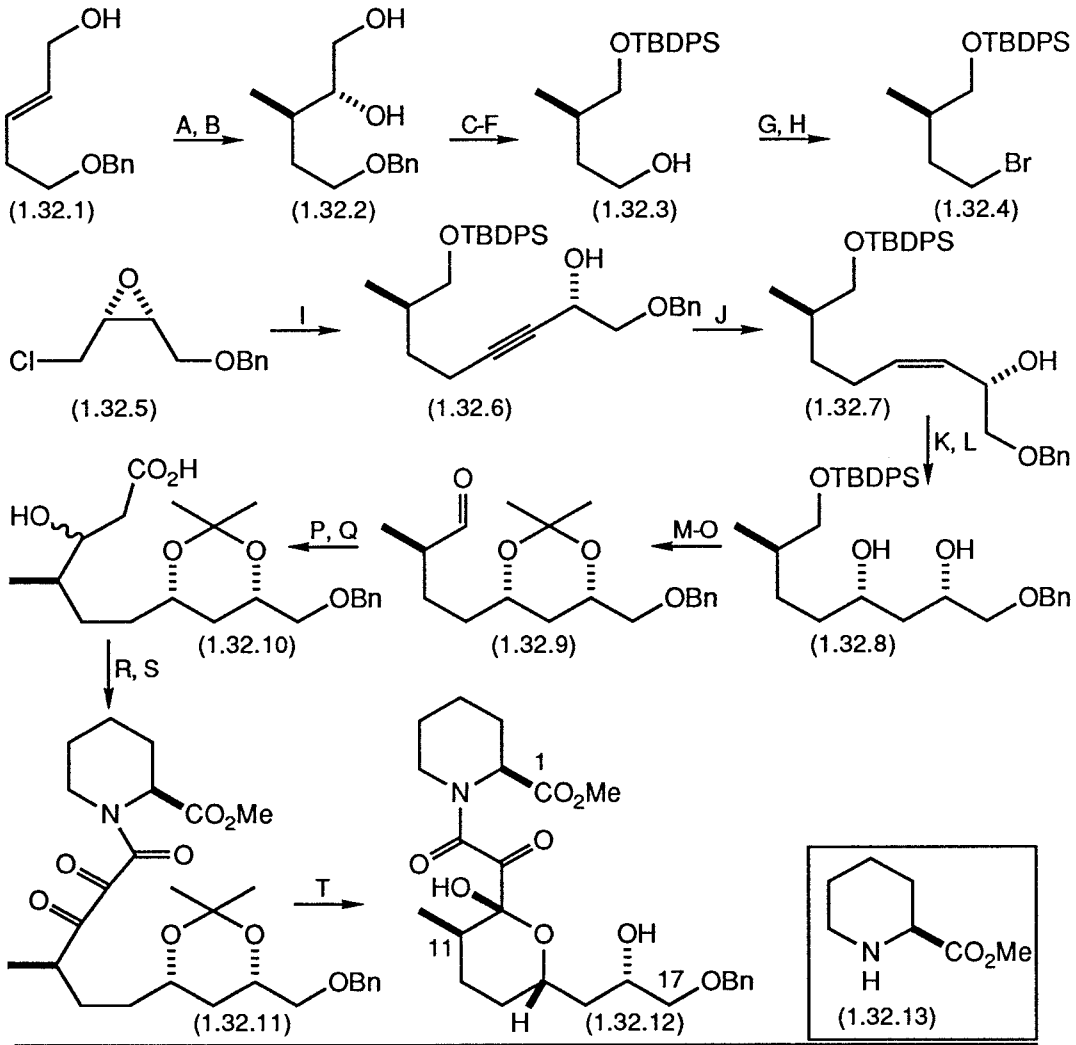


REAGENTS AND YIELDS			
A	67%	MeOH, HCl	
B	87%	i) TBSCl, imidazole, THF ii) MOMCl, Hunig's base	
C	99%	TBAF, THF	
D	-	Swern oxidation	
E	-	MeCCMgBr, THF, -78°C	
F	85%	Swern oxidation	
G	-	MeMgBr, THF, -78°C	
H	81%	LAH, THF, 45°C	
I	-	chloromethyloxazoline, KH, DME	
J	70%	BuLi, THF, -78°C	
K	-	KH, BnBr, DME	
L	89%	i) TFA, H_2O ii) LAH	
M	-	Swern oxidation	
N	-	MeCCMgBr, THF, -78°C	
O	64%	MnO_2, DCM	
P	-	$ZnCl_2$, $NaBH_4$, Et_2O, 0°C	
Q	97%	H_2, Lindlar, MeOH	
R	-	KH, Me_3SnCH_2Cl, DME	
S	44%	MeLi, THF, -78°C	

Kallmertens synthesis[29] starts with **(1.31.1)** (readily obtainable from D-glucose). The chiral centres at C31, C32 and C35 were secured by using two [2,3] Wittig rearrangements. The final fragment **(1.31.10)** suffers from two serious drawbacks:- 1) the lack of oxygen functionality at C34 means that the C33-C34 double bond must be oxidised in the presence of the C29-C30 double bond, and 2) poor disconnection strategy at C24 and C36.

Rao's synthesis of the C1-C17 fragment of rapamycin (1.1.1).

Scheme1.32



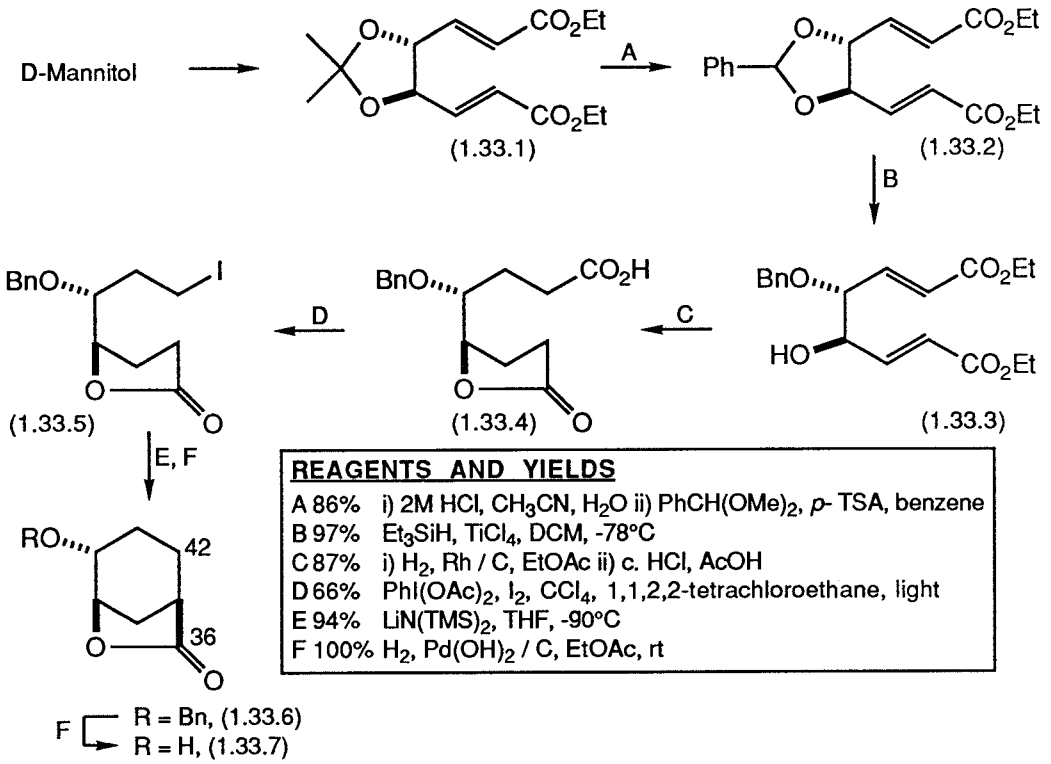
REAGENTS AND YIELDS	
A - (+)-DET, TBHP, 3Å seives, $Ti(O\textit{i}\text{-}Pr)_4$	I 60% $LiNH_2$, NH_3, (1.32.4), -33°C
B 90% Me_3Al, pentane, DCM, rt	J 95% Lindlars catalyst, H_2, quinoline, MeOH
C - $NaIO_4$, THF, H_2O, 0°C	K 60% (-)-DIPT, TBHP, 3Å seives, $Ti(O\textit{i}\text{-}Pr)_4$
D - $NaBH_4$, MeOH, 0°C	L 75% Red-Al, THF, rt
E - TBDPSCl, imidazole, DMF, 0°C	M - TBAF, THF, rt
F 80% H_2, Pd / C, MeOH, rt	N - acetone, *p*-TSA
G - MsCl, Et_3N, DCM, 0°C	O 80% Swern oxidation
H 60% LiBr, $NaHCO_3$, THF, rt	P 70% Zn, ethyl bromoacetate, benzene, 80°C
	Q 70% LiOH, DME
	R 75% F_5C_6OH, DMAP, DCC, (1.32.13)
	S 60% Dess-Martin periodinane, pyridine, DCM
	T 70% 0.001M HCl, MeOH

Rao's synthesis[30] of the C1-C17 fragment uses the Sharpless asymmetric epoxidation to introduce stereochemistry at C14 and indirectly to secure the stereochemistry of the C11 methyl group. The tricarbonyl region is introduced by means of a Reformatsky reaction of aldehyde **(1.32.9)** with ethyl bromoacetate, the central methylene is then oxidised using Dess-Martin

periodinane.

Kotsuki's synthesis of the cyclohexyl portion of rapamycin

Scheme 1.33



Kotsuki's synthesis[31] uses (D)-mannitol as it's source of chirality at C39 and C40. The final centre at C37 is introduced by means of a diastereoselective intramolecular alkylation reaction to yield the bicyclic lactone **(1.33.6)**. Removal of the benzyl protecting group was achieved using palladium catalysed hydrogenation to furnish the final product **(1.33.7)**.

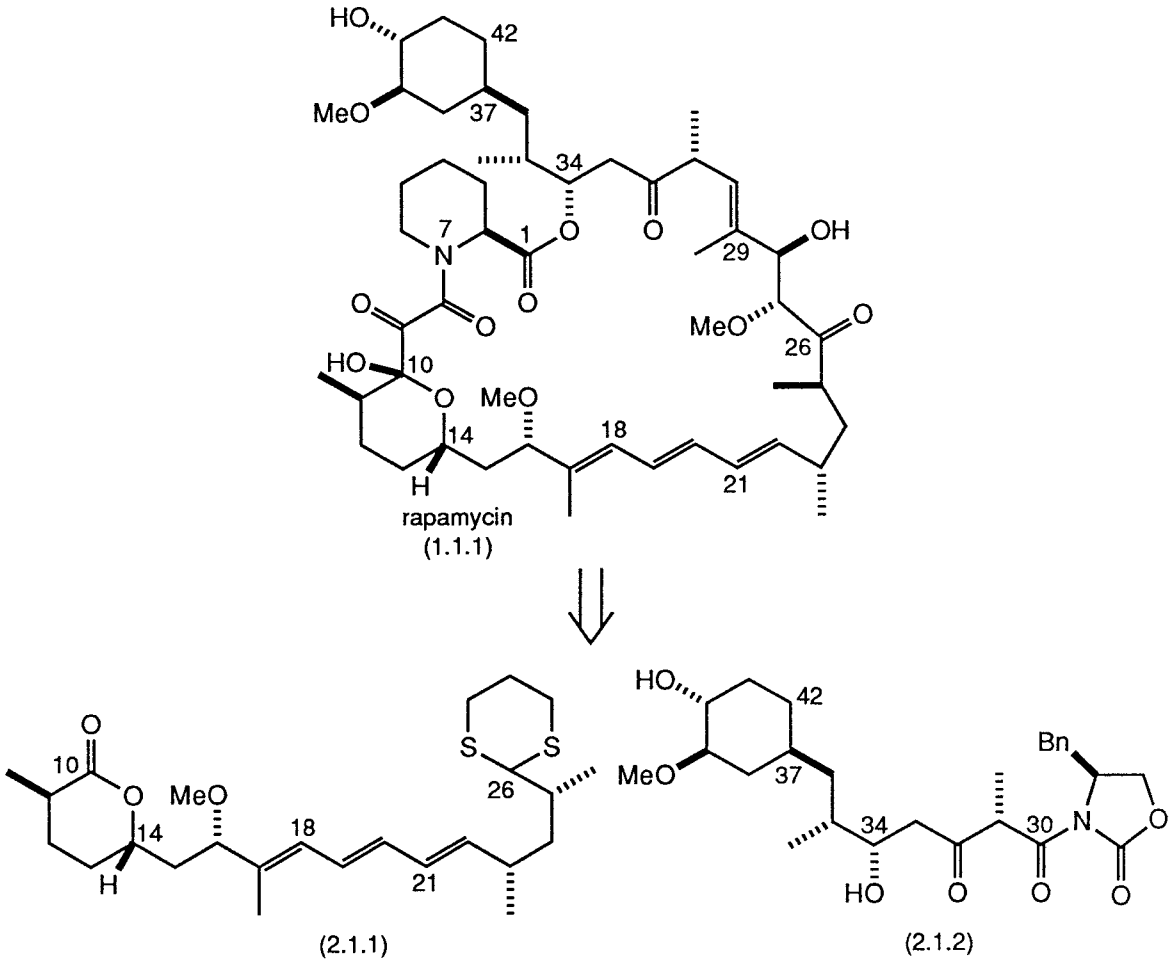
CHAPTER 2

CHAPTER 2: INTRODUCTION

2.1 The Southampton approach to rapamycin (1.1.1).

A retrosynthetic analysis of rapamycin **(1.1.1)** is shown in scheme 2.1. Rapamycin **(1.1.1)** has been disconnected at the C1 ester linkage, the C9-C10 bond, the C26-C27 bond and the C29-C30 bond, making the triene **(2.1.1)** and the dicarbonyl fragment **(2.1.2)** the major targets of our synthesis. The C30-C42 fragment **(2.1.2)** has been synthesised by Thom[32], and the technology to introduce the pipecolic acid moiety has already been devised as part of the groups approach to FK-506 **(1.1.2)**[33]. Work on model systems of the C27-C29 fragment is underway. So far no work on the coupling major fragments has been attempted.

Scheme 2.1

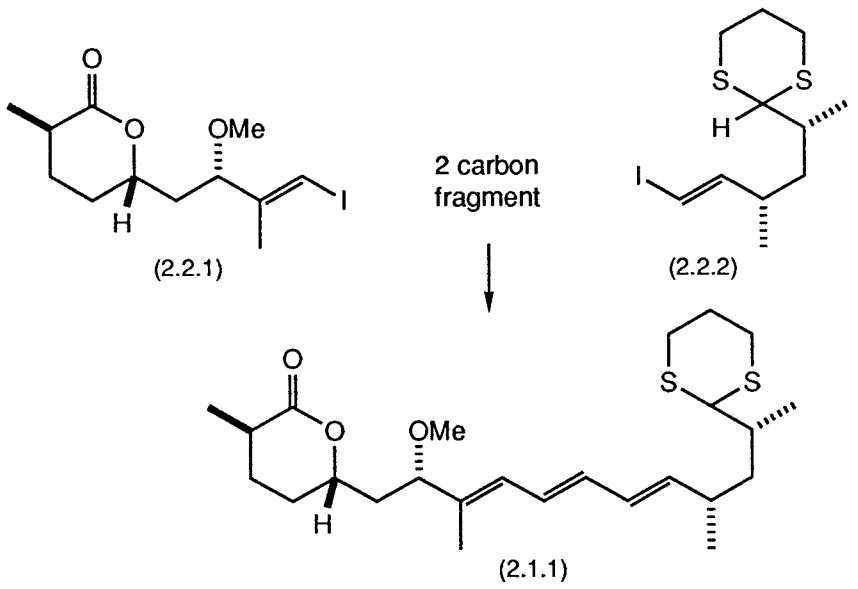


2.2 The Southampton approach to the Southern fragment (2.1.1).

The aim of the project was to develop efficient routes to vinyl iodides **(2.2.1)** and **(2.2.2)** and then use a palladium catalysed cross coupling reaction to link the fragments and generate the Southern fragment of rapamycin **(2.1.1)** (scheme 2.2). The work in chapters 3-6 describes the Southampton approach

to the triene **(2.1.1)**. Our original idea was to perform the coupling reaction with the dithioacetal in place on vinyl iodide **(2.2.2)** so that the acidity of the proton at the C2 position of the dithiane ring could be exploited in chain extension reactions. However the palladium coupling reactions of vinyl iodides with vinyl stannanes failed to yield any desirable products in the presence of the dithioacetal.

Scheme 2.2

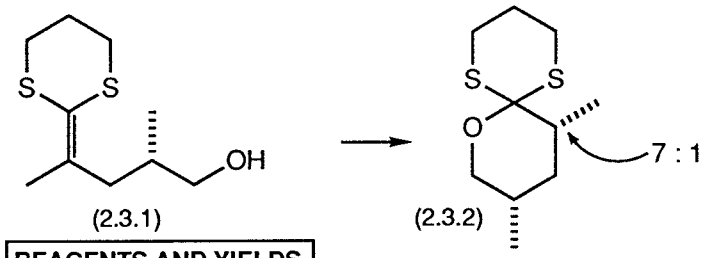


The syntheses of the two fragments **(2.2.1)** and **(2.2.2)** commence with a common starting material and involve the same key diastereoselective cyclisation of alcohols on to ketene dithioacetals[34,35], making the synthesis of the triene both convergent in its strategy and conservative in its use of methodology.

In chapter 3 the synthesis of the lactone fragment **(2.2.1)** is described. Particular reference is made to the introduction of the stereochemistry at the three stereogenic centres and also the problems we encountered due to functional group incompatibility of the oxadithiaspiro moiety with strong Lewis acids, and oxidising conditions.

Chapter 4 discusses the synthesis of vinyl iodide **(2.2.2)**, again the low yields of a number of steps were attributed to the functional group incompatibility of the dithioacetal with Lewis acids and oxidising agents. The employment of the diastereoselective cyclisation reaction in the case of ketene dithioacetal **(2.3.1)** was high yielding but less selective (7 : 1) than in other cases (scheme 2.3).

Scheme 2.3



REAGENTS AND YIELDS

A 100% HCl in DCM

Chapter 5 summarises the attempts at making dienes, ene-ynes and the triene **(2.1.1)** using palladium catalysed coupling reactions reported by Stille[36,37], Farina[38] and Kobayashi[39].

Chapter 6 describes two failed attempts to synthesis the lactone fragment **(2.2.1)**, one by using the Sharpless asymmetric epoxidation of allylic alcohols[40] to generate the chiral centre at C14, and the other by using an enantioselective enzymatic reduction[41] of a β-keto ester.

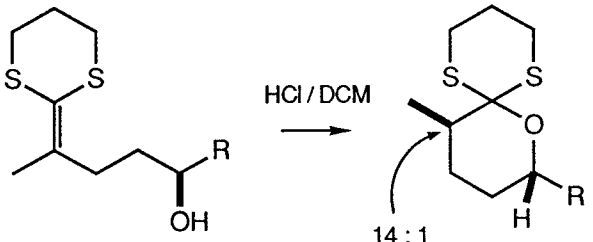
CHAPTER 3

CHAPTER 3: THE SYNTHESIS OF THE C10-C18 LACTONE (2.2.1.).

3.1 The cyclisation of ketene dithioacetals

The syntheses of fragments **(2.2.1)** and **(2.2.2)** involve as their key step the diastereoselective cyclisation of alcohols on to the ketene dithioacetal moiety (scheme 3.1). The reaction proceeds smoothly to yield predominantly diequatorally substituted ring systems. Corey[34] was the first to report the reaction as a method of lactone protection, but it was Suzuki[35] who later observed the high diastereoselectivity of the reaction when applied to 2-(1,3-dithia-2-enyl)-5-substituted pentan-5-ols (scheme 3.1).

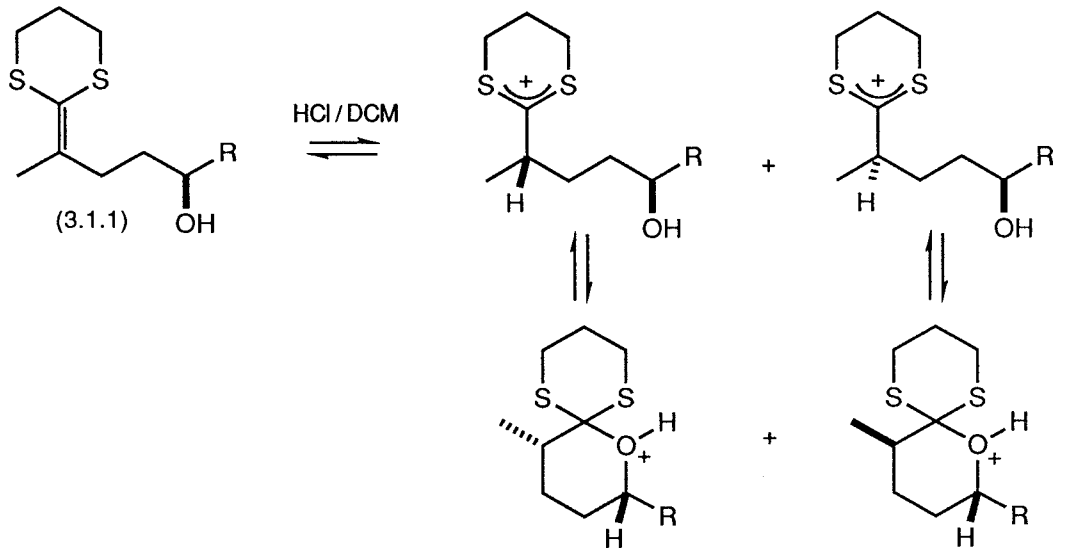
Scheme 3.1



(3.1.1) (3.1.2)

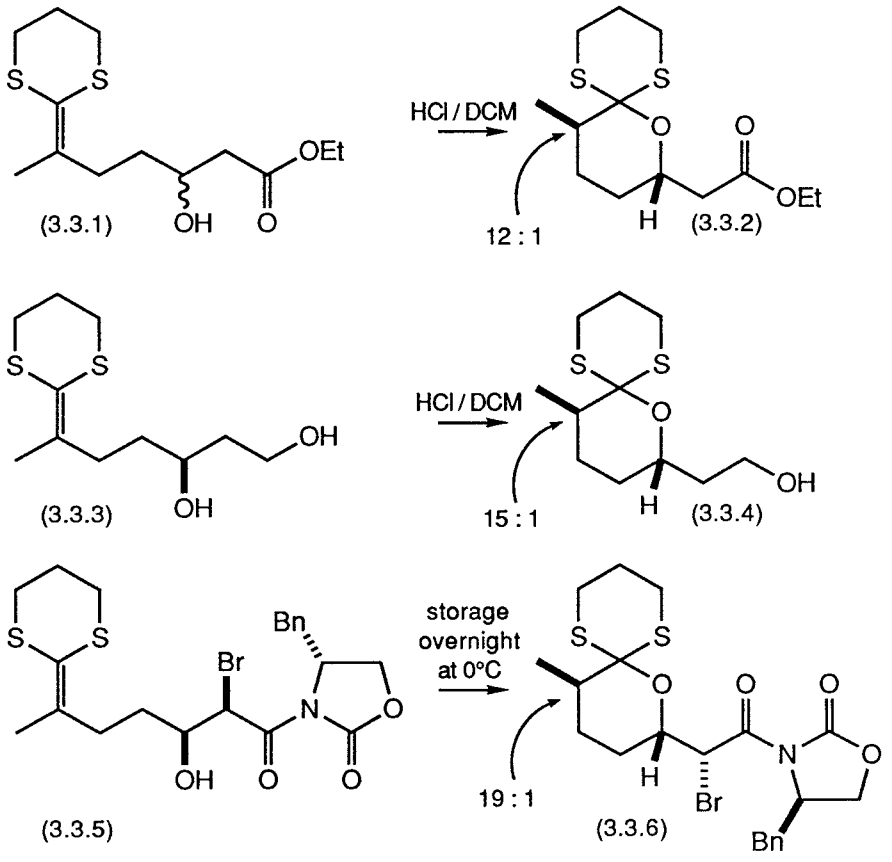
Suzuki[35] does not propose a mechanism for the reaction. Okuyama[42,43] has however published a complete analysis of the acid catalysed hydrolysis of 2-methylene-1,3-dithiolane. The first three steps of the hydrolysis are essentially the same as the cyclisation reaction. The initial step is rapid and reversible protonation of the alkene to form a sulphur stabilised carbocation (scheme 3.2). Under anhydrous conditions the carbocation is quenched with the alcohol moiety. Whether the ratio of products obtained is under kinetic or thermodynamic control is not known, but Suzuki postulates[35] that the ratio of products obtained reflects their thermodynamic stability, and the work published by Okuyama[42,43] supports Suzuki's postulate.

Scheme 3.2



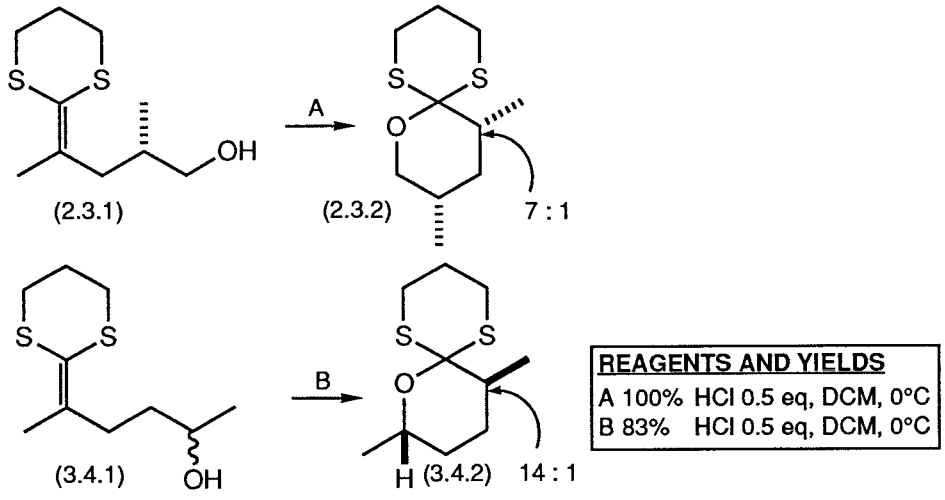
During the course of our studies a number 2-(1,3-dithia-2-enyl)-5-substituted pentan-5-ols have been synthesised and cyclised under Suzuki's conditions (scheme 3.3). The diastereoselection in each case was 12 : 1 (^{1}H NMR) or greater in favour of the desired product.

Scheme 3.3



However when the reaction was attempted using (4*S*)-2-(1,3-dithia-2-enyl)-4-methyl pentan-5-ol) a diastereoselectivity of only 7 : 1 (^{1}H NMR) was achieved (scheme 3.4). Initially we thought the small steric bulk of the methyl group was the cause of the drop in selectivity but cyclisation of alcohol **(3.4.1)** proved that this was not the case.

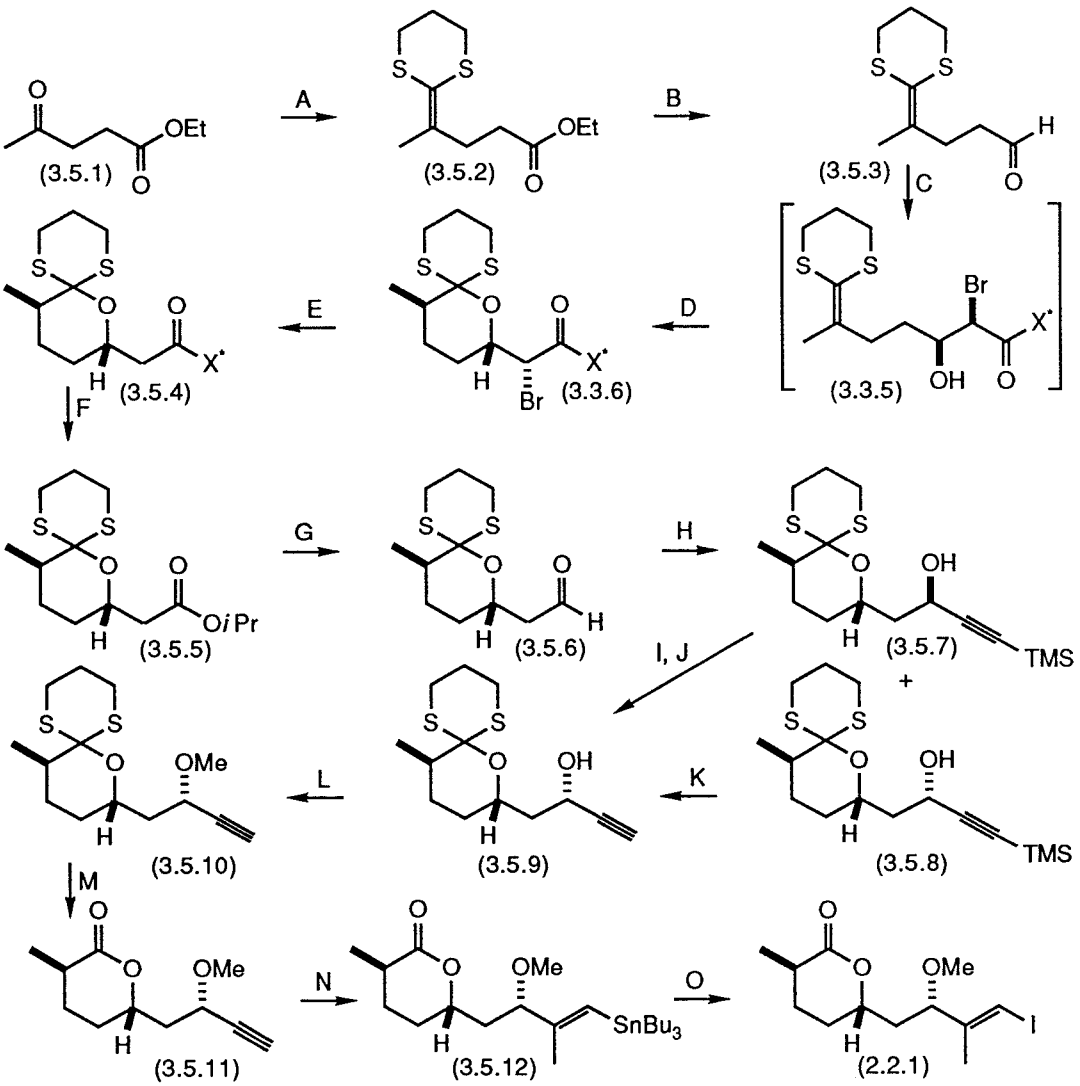
Scheme 3.4



3.2 The synthesis of the C10-C18 lactone (2.2.1)

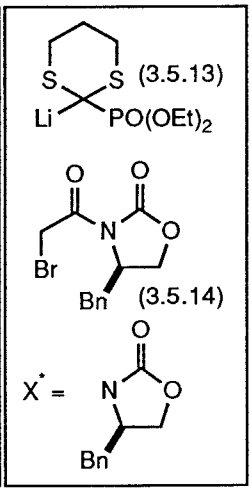
Scheme 3.5 outlines the synthesis of lactone **(2.2.1)**.

Scheme 3.5



REAGENTS AND YIELDS

A 83% (3.5.13), THF, -80°C-rt
B 80% DIBALH, DCM, -80°C
C - i) (3.5.14), Et_2O; ii) Et_3N; iii) Bu_2BOTf; iv) (3.5.3), -80-0°C
D 47% storage at 0°C for 16 h
E 82% Zn dust, MeOH, NH_4Cl, sonication, rt
F 89% *i*-PrOH, $Ti(Oi\text{-}Pr)_4$, THF, 82°C
G 88% DIBALH, DCM, -80°C
H 82% TMSCCMgBr, THF, -80°C
I 89% Ph_3P, DEAD, *p*-nitrobenzoic acid, THF, rt
J 96% NaOH, EtOH, H_2O, rt
K 88% TBAF, THF, 0°C
L 83% NaH, MeI, THF, 0°C-rt
M 95% I_2, H_2O, Et_2O, $NaHCO_3$, 37°C
N 49% i) $Bu_3Sn(Bu)Cu(CN)Li_2$, THF; ii) HMPA, MeI -80°C-rt
O 91% I_2, Et_2O, 0°C



3.3 Synthesis of aldehyde (3.5.3)

Formation of the ketene dithioacetal **(3.5.2)** from ethyl levulinate **(3.5.1)** was achieved cleanly by employing the conditions of Jacobine and Marshall[44]. Reduction of the ester functionality to aldehyde **(3.5.3)** with DIBALH was initially troublesome, with yields ranging from 50% on large scale to 80% on small scale. The problem was solved by adapting the work up procedure of Baeckstrom[45]: hence, the cold reaction mixture was transferred *via* cannula to a rapidly stirring slurry of ice, water and sodium potassium tartrate. The above procedure gave reproducible yields of 80% on 0.1 mol scale. We postulate that a high concentration of water causes rapid hydrolysis of the intermediate di-isobutyl aluminium alkoxide which itself is a reducing agent capable of further reactions.

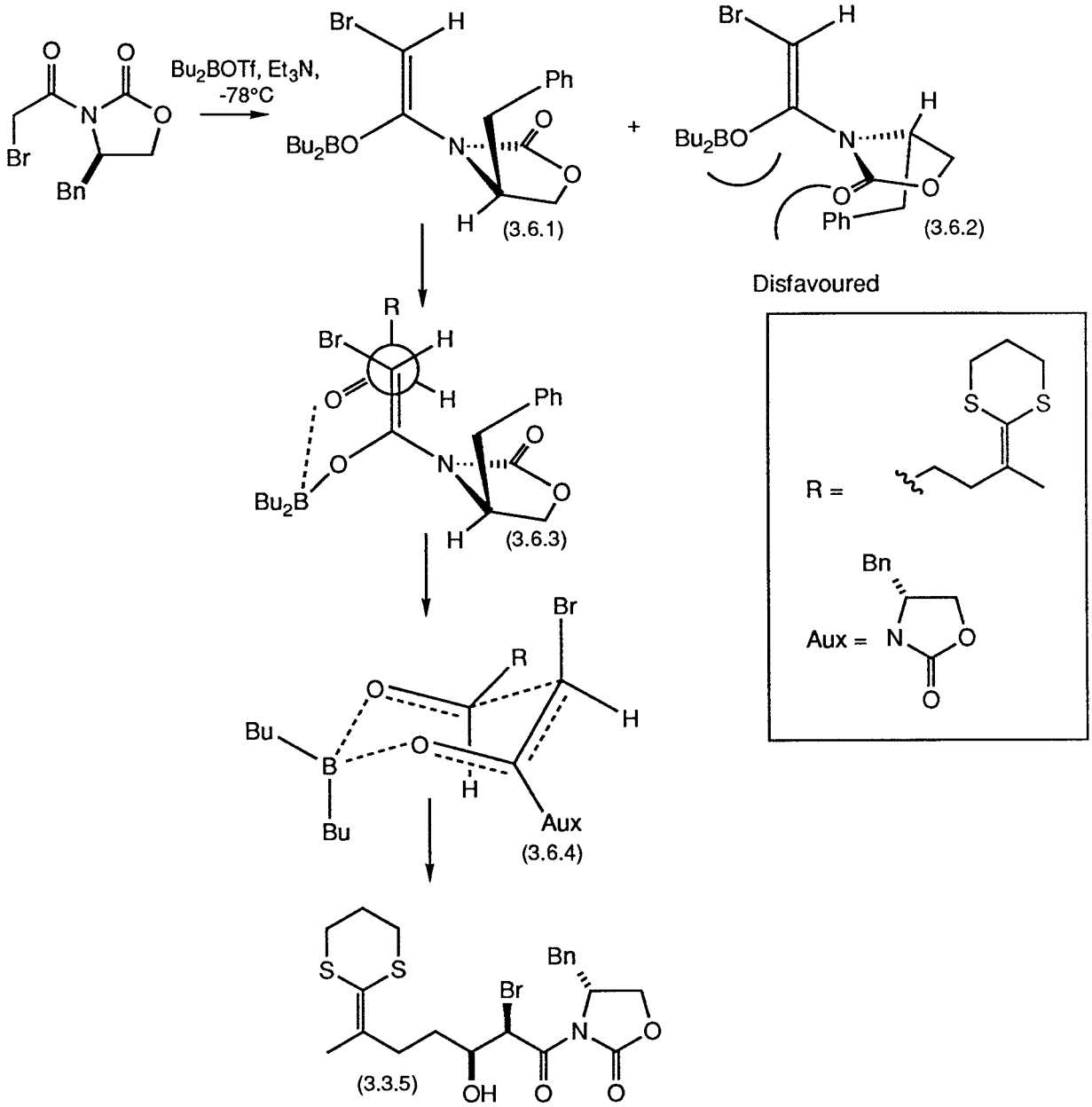
3.4 Securing the stereochemistry at C-14 and synthesis of aldehyde (3.5.6)

The stereochemistry at C14 of lactone **(2.2.1)** was introduced using Evans' diasteroselective aldol reaction[46]. Unfortunately a substituent at C15, not present in rapamycin **(1.1.1)**, is required if the reaction is to be selective. Evans has reported aldol reactions with a variety of substituents α to the carbonyl of the N-acylated oxazolidinone, including alkyl[47], alkoxy[48] and halide[46]. We opted for a bromide moiety in the hope that it could be removed under reducing conditions. 3-(bromoacetyl)-4*R*-benzyl-oxazolidinone **(3.5.14)** was prepared by a literature procedure[49].

When the N-acyl oxazolidinone **(3.5.14)** is treated with triethylamine and dibutylboron triflate at -80°C a mixture of the *Z* and *E* enolates are formed in a 75 : 25 ratio[46]. The *Z* enolate adopts a bisected conformation (either **(3.6.1)** or **(3.6.2)**) (scheme 3.6) with the plane of the oxazolidinone ring perpendicular to the plane of the enolate due to allylic strain. The conformation **(3.6.1)** is favoured over **(3.6.2)** due to the steric interactions of the butyl group and the benzyl group. The aldehyde then approaches enolate **(3.6.1)** from the opposite face to the benzyl group to form intermediate **(3.6.3)**. The configuration of intermediate **(3.6.3)** shown is favoured due to the coordination of the aldehyde oxygen to the boron atom, and the aldehyde molecule adopting a postion between the two least sterically demanding groups. The aldol reaction then ensues *via* a six centred transition state **(3.6.4)**[50] in which the sterically demanding groups adopt equatorial or pseudo equatorial positions leading to the formation of the desired product **(3.3.5)**. Evans reports that although there is a significant amount of the *E* enolate

present in the reaction mixture the difference in reaction rates is such that good selectivity (>10 : 1) can still be obtained.

Scheme 3.6



After mildy basic aqueous work up ($NaHCO_3$) and chromatography the open chain aldol adduct **(3.3.5)** cyclised on storage at 0°C overnight without an external source of acid catalysis. The source of acid may be from slight decomposition of the substrate. The modest yield (47%) of the above two steps may be due to a combination of the ketene dithioacetal binding to the dibutyl boron triflate, and the incomplete hydrolysis of the boronate intermediate. Evans recommends an oxidative aqueous work up using hydrogen peroxide[46] which is not compatible with the sulphur functionality.

Removal of the bromine atom was attempted by a number of methods, ($NaBH_3CN$, Mg/MeOH, and Bu_3SnH) and was eventually achieved by employing an adaptation of the method published by Jarowicki[51] which uses powdered zinc, ammonium chloride and methanol. Jarowicki reports that the reduction is achieved over 16 h at room temperature, in our hands no reaction occurred until sonicating conditions were employed[52]. The adduct **(3.5.4)** was then recrystallised from acetone / ether to remove the minor diastereoisomers present.

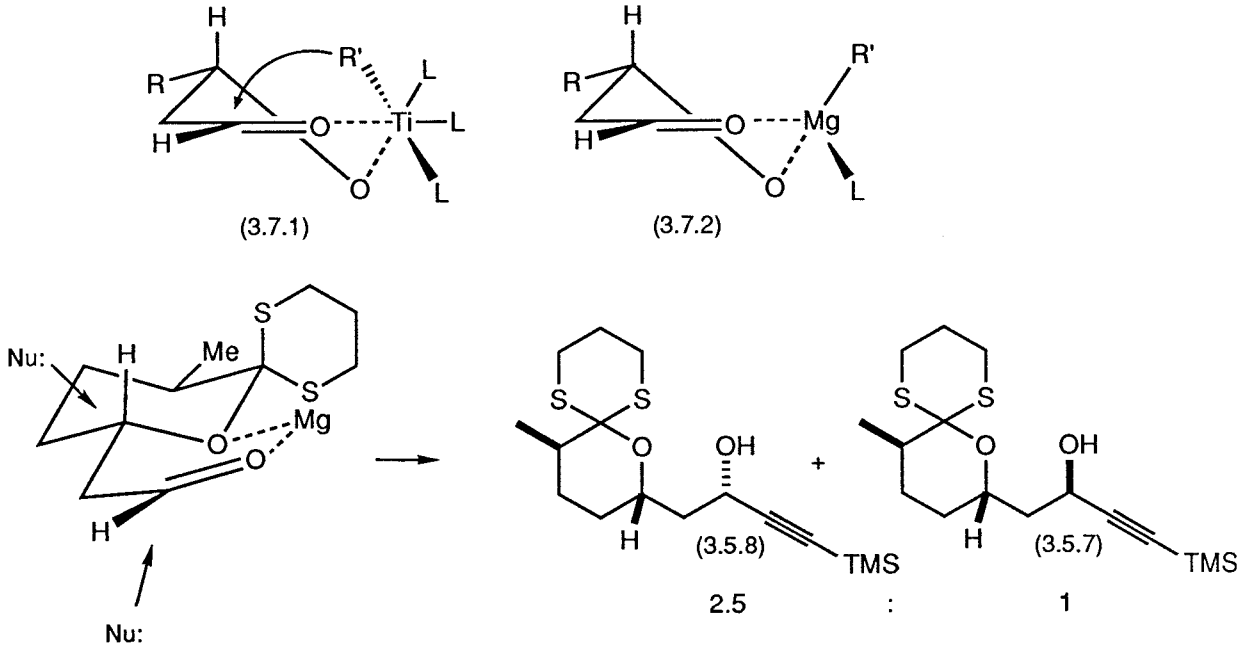
The next challenge in our synthesis was to find a high yielding method of removing the oxazolidinone auxilliary. There are many methods in the literature to affect this transformation notably LAH/THF[53], LiOBn[53], LiOOH[14], Me(MeO)NH•HCl/$AlMe_3$, and $Ti(OBn)_4$/BnOH[54]. Previous experience had taught us that performing oxidation reactions in the presence of the oxadithiaspiro moiety was at best a low yielding process (chapter four and six), hence a method that left the oxygen functionality at C16 in the carbonyl oxidation state was required. The conditions used to make the Weinreb amide (Me(MeO)NH·HCl/$AlMe_3$) or the carboxylic acid (LiOOH/H_2O) derivative were incompatible with the sulphur functionality. Transesterification using LiOBn gave the the benzyl ester but only in modest yield (50%), however treatment of adduct **(3.5.4)** with $Ti(OBn)_4$/BnOH gave the benzyl ester in good yield (90%) but on reduction with DIBALH to give aldehyde **(3.5.6)** the benzyl alcohol liberated proved to be inseparable from the product aldehyde **(3.5.6)**. The process was adapted by using $Ti(O\textit{i}\text{-Pr})_4$ in *i*-PrOH to give ester **(3.5.5)** in 89% yield. DIBALH reduction of ester **(3.5.5)** afforded the pure aldehyde **(3.5.6)** in 88% yield.

3.5 Securing the stereochemistry at C16.

Chelation controlled 1,3-chiral induction in addition reactions to chiral β-alkoxy aldehydes is a well documented reaction[55,56] and is particularly selective when titanium is the metal chelated between the two oxygen atoms (scheme 3.7). When a metal atom coordinates to the two oxygen atoms a new ring is formed which adopts a twisted chair conformation due to the Π system of the aldehyde group. Since titanium exists in an octahedral environment the alkyl group to be transferred is held over the aldehyde carbon atom and Reetz suggests[56] the addition occurs *via* an intramolecular process **(3.7.1)**. Magnesium however exists in a tetrahedral environment placing the alkyl group to be transferred pointing away from the aldehyde carbon **(3.7.2)**. We

postulate therefore that the addition of the Grignard reagent occurs *via* an intermolecular process, and the selectivity observed arises purely to the difference in steric accessability of the *si* and *re* face of the aldehyde **(3.5.6)**. Approach to the *si* face is slightly obscured by the axial C14 proton whereas approach to the *re* face is essentially unhindered.

Scheme 3.7



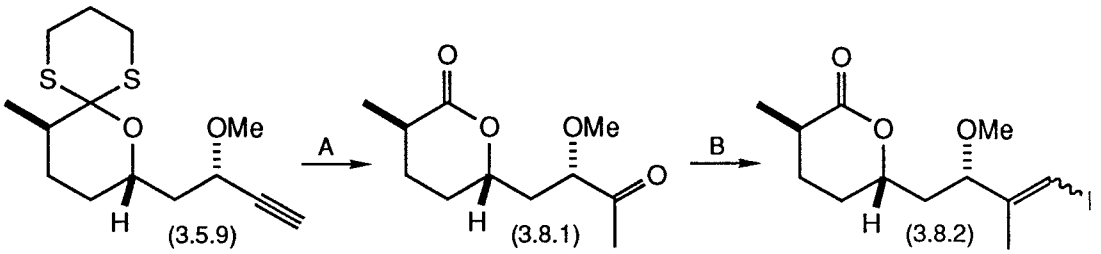
The ratio of products obtained was 2.5 : 1 in favour of the desired *S*-propargylic alcohol **(3.5.8)**. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray diffraction of *S*-propargylic ether **(3.5.10)**. The two products formed, **(3.5.7)** and **(3.5.8)**, could be separated easily by column chromatography, having a difference in R_f of 0.2. The *R*-propargylic alcohol **(3.5.7)** was efficiently recycled (90% for two steps) by using the conditions reported by Mitsunobu[57] followed by treatment with aqueous sodium hydroxide which hydrolysed the ester and the TMS group yielding propargylic alcohol **(3.5.9)**. The *S*-propargylic alcohol **(3.5.8)** was desilylated by using TBAF. Methylation was affected by sodium hydride and methyl iodide to give propargylic ether **(3.5.10)**.

3.6 Deprotection of the lactone and introduction of the trisubstituted double bond.

A mercury (II) catalysed hydrolysis[35] of protected lactone **(3.5.10)** also led to hydrolysis of the acetylene (scheme 3.8) giving a modest yield of impure methyl ketone **(3.8.1)**. Treatment of **(3.8.1)** with chromium (II) chloride and iodoform[58] afforded vinyl iodide **(3.8.2)** as a 3 : 2 (*Z* : *E*) mixture of geometric

isomers in a low yield, hence the approach was abandoned.

Scheme 3.8



REAGENTS AND YIELDS
A 41% $HgCl_2$, CH_3CN, H_2O, pH 7 buffer, rt
B 36% $CrCl_2$, CHI_3, DCM, 40°C

Oxidative hydrolysis[59] of dithiane **(3.5.10)** with iodine to yield lactone **(3.5.11)** proved to be the deprotection method of choice (scheme 3.5).

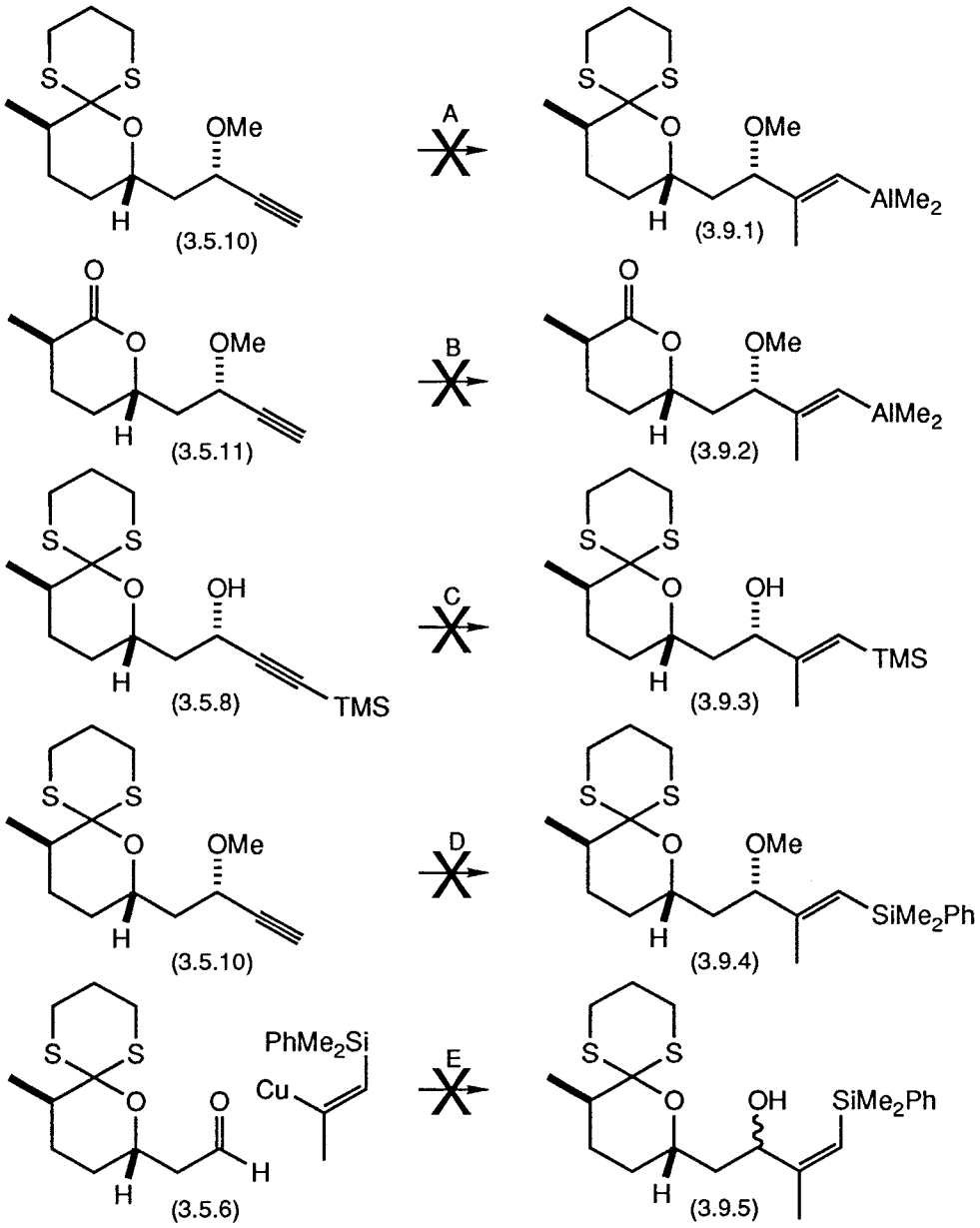
The elaboration of the acetylene functionality to yield a tri-substituted double bond was attempted *via* a number of methods (scheme 3.9). Negishi's zirconium mediated carboalumination reaction[60] failed to give any of the desired product when performed on lactone **(3.5.11)** or protected lactone **(3.5.10)**.(scheme 3.9). Other approaches to *E* or *Z* vinyl silanes, both of which can be converted to an *E* vinyl iodide[61], are listed below:-

1) copper (I) mediated addition of methyl magnesium bromide across silyl acetylene **(3.5.8)** gave only recovered starting material[62].

2) silyl cupration[63] of acetylene **(3.5.10)** gave a complex mixture of products probably due to decomposition *via* the allene.

3) silyl cupration[63] of propyne and subsequent quench of the vinyl copper species with HMPA and aldehyde **(3.5.6)** also led to a complex mixture of products.

Scheme 3.9



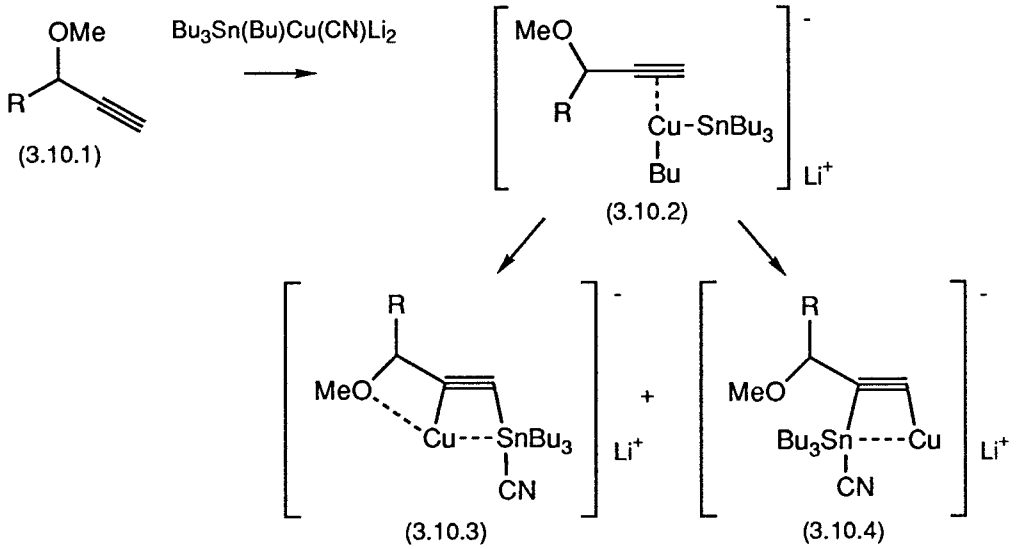
REAGENTS

A $ZrCp_2Cl_2$, $AlMe_3$, 1,2-dichloroethane, rt
B $ZrCp_2Cl_2$, $AlMe_3$, 1,2-dichloroethane, rt
C CuI, MeMgBr, THF, rt
D i) $LiSiMe_2Ph$, THF; ii) CuCN; iii) (3.5.10); iv) MeI, HMPA, rt
E THF, HMPA, rt

Lipshutz's stannyl cupration reaction[64] proved to be the method of choice for alkyne functionalisation (scheme 3.5). Although Lipshutz reports a lack of regioselectivity in his original paper[64], subsequent publications by Parsons[65] and Ricci[66] indicate that in the case of properglic ethers and amines the stannyl cuprate reacts to place the tin on the terminal carbon. Ricci has proposed that coordination of the alkyne to the stannyl cuprate leads to elimination of lithium cyanide to generate the intermediate **(3.10.2)** (scheme 3.10). The postulation that the reaction proceeds *via* **(3.10.2)** seems reasonable since HMPA has been reported to activate cuprate species in a similar manner[67]. Ricci then claims that the species **(3.10.3)** and **(3.10.4)** are formed after the metallometallation reaction and that **(3.10.3)** is stabilised over **(3.10.4)** by coordination of copper to the propargylic hetero atom. We postulate that more likely intermediates would be **(3.11.1)** and **(3.11.2)**, with **(3.11.1)** being stabilised over **(3.11.2)** by coordination of copper to the propargylic hetero atom (scheme 3.11). The vinyl copper intermediate can be methylated using methyl iodide and HMPA. Unfortunately the yield of the process is at best 50% and more ususally 35% even after rigorous purification of all the reagents. The *E* vinyl stannane **(3.5.12)** is not obtained completely pure due to incomplete methylation or regioselection. Transformation to the vinyl iodide proceeded smoothly under the conditions of Kobayashi and Sato[39].

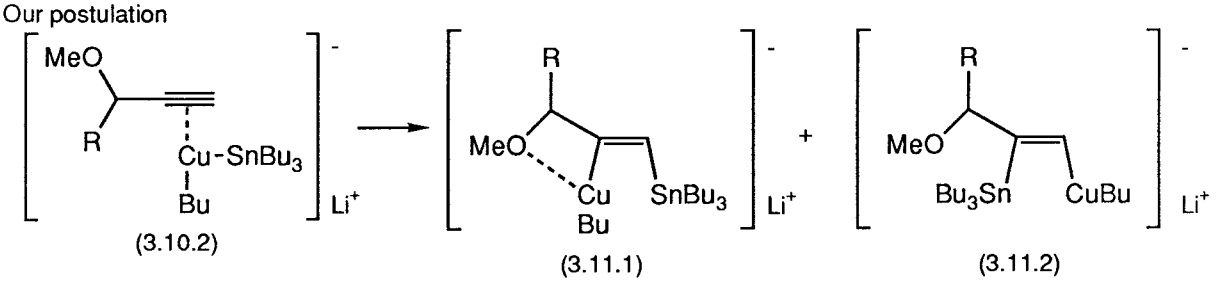
Scheme 3.10

Ricci's postulation



Scheme 3.11

Our postulation



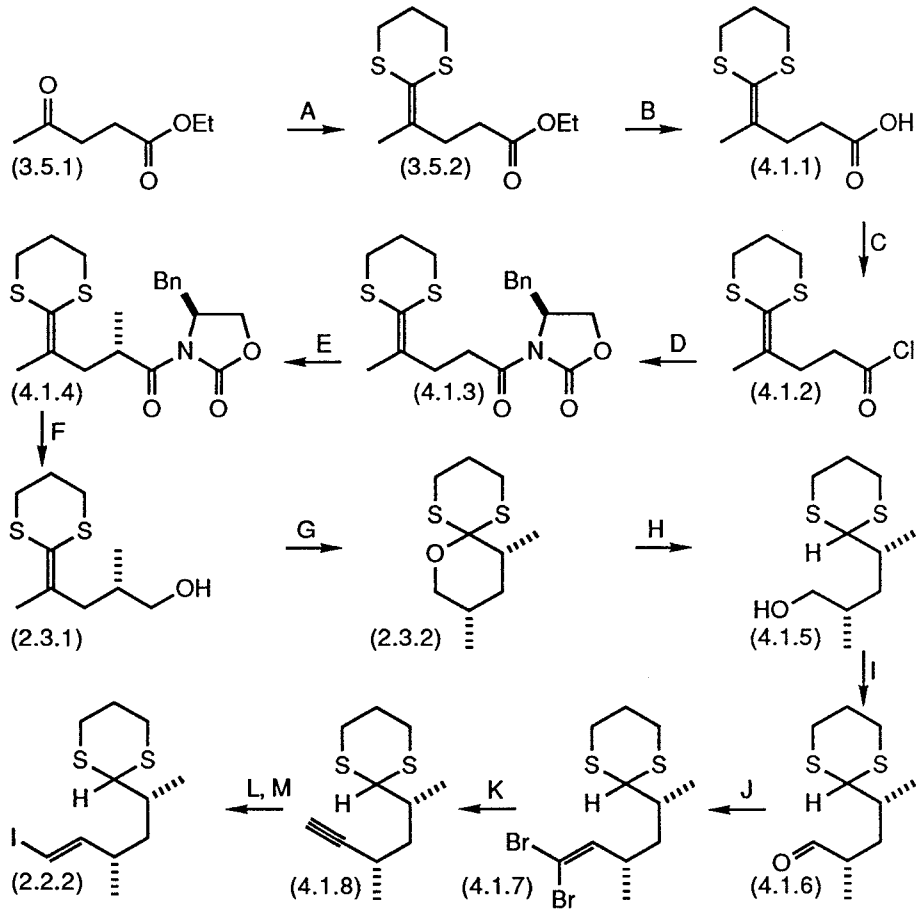
CHAPTER 4

CHAPTER 4: THE SYNTHESIS OF THE C21-C26 VINYL IODIDE FRAGMENT (2.2.2).

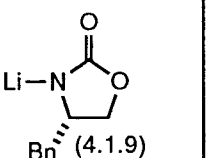
4.1 The synthesis of the C21-C26 vinyl iodide (2.2.2).

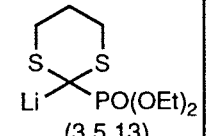
The synthesis of vinyl iodide **(2.2.2)** was achieved using Evans diastereoselective alkylation reaction[53] and Suzuki's diastereoselective cyclisation reaction[35] as key steps (scheme 4.1).

Scheme 4.1



REAGENTS AND YIELDS	
A 83%	(3.5.13), THF, -80°C-rt
B 92%	NaOH, EtOH, H_2O, rt
C -	i) NaH, THF; ii) $(COCl)_2$, toluene, rt
D 56%	(4.1.9), THF, -80°C
E 85%	i) $(TMS)_2NNa$, THF; ii) MeI, -80°C
F 77%	LAH, THF, 0°C
G 100%	HCl 0.5eq, DCM, 0°C
H 97%	DIBALH, Et_2O, rt
I 60%	3Å sieves, TPAP, NMMO, DCM, rt
J 59%	Ph_3P, CBr_4, DCM, 0°C
K 90%	Mg, THF, 65°C
L -	$HBBr_2$, DCM, DMS, 40°C
M 51%	NaOH, H_2O, Et_2O, I_2, 0°C

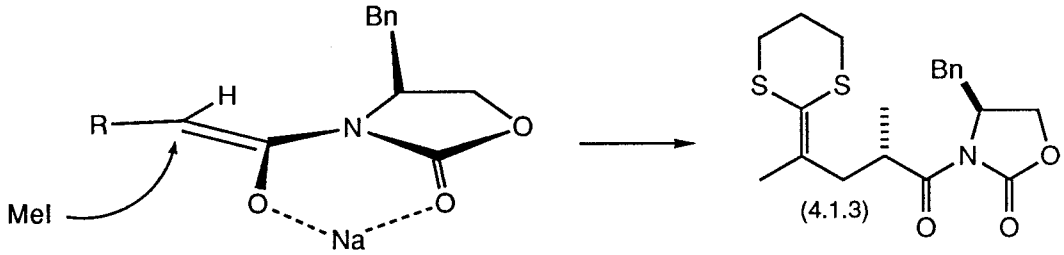




4.2 Synthesis and determination of the relative stereochemistry of ortho dithioester (2.3.2)

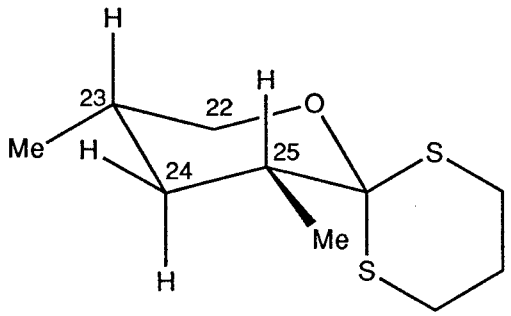
Ketene dithioacetal **(3.5.1)** was formed as in chapter three and the ester functionality hydrolysed to acid **(4.1.1)** under basic conditions. The chiral auxilliary was attached by reaction of the lithiated auxilliary **(4.1.9)** with acid chloride **(4.1.2)**[47]. Diastereoselective methylation was achieved *via* the Z sodium enolate (scheme 4.2) using a method reported by Evans[53]. Attack of the methyl iodide occurs preferentially from the opposite face to the benzyl group to give the methylated adduct **(4.1.3)**.

Scheme 4.2



Efficient removal of the chiral auxilliary was affected by LAH reduction to give alcohol **(2.3.1)**[53]. Acid catalysed cyclisation afforded protected lactone **(2.3.2)** as a 7 : 1 mixture of epimers at C25 (^{1}HNMR) that were inseparable by chromatography and were carried forward as a mixture for the remainder of the synthesis. The relative stereochemistry was determined by nmr experiments. ^{1}H^{1}H COSY allowed us to determine the chemical shift of the axial proton on C24. The signal was a quartet J = 12.0 Hz which is typical for vicinal axial-axial or geminal coupling on a six membered ring[68]. Thus proving that the protons attached to C23 and C25 are in axial positions, and the methyl groups are in equatorial positions (scheme 4.3).

Scheme 4.3

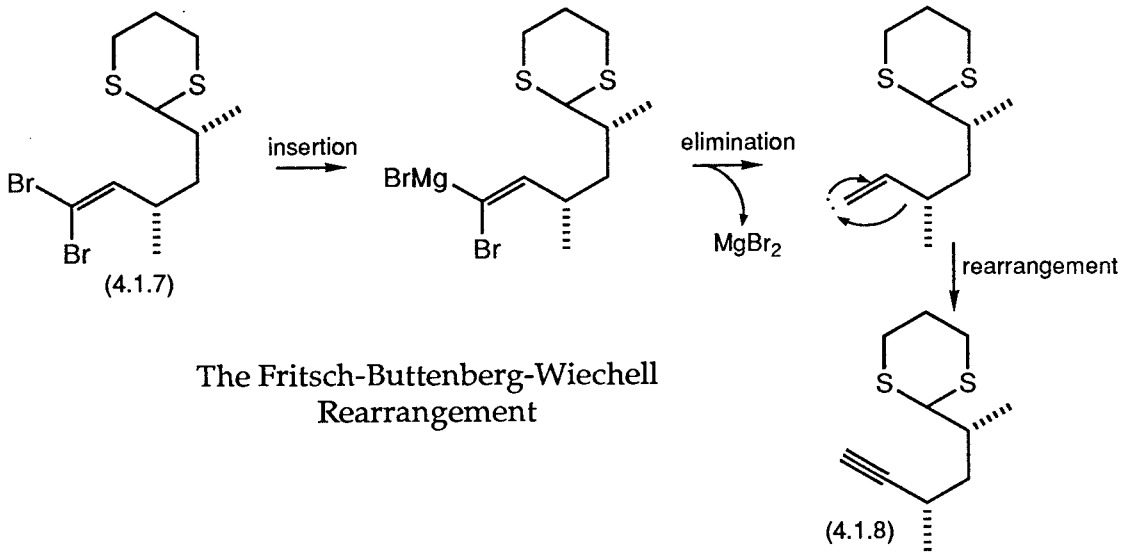


4.3 Reduction of ortho dithioester (2.3.2) and elaboration of the oxygen functionality.

Reduction of the oxadithiaspiro system to achieve chain end differentiation and yield alcohol **(4.1.5)** was attempted using a number of different sources of metal hydride (triethyl silane, LAH, BH_3, and 9BBN). DIBALH proved to be the reagent of choice. When the reduction was performed in toluene a 3 : 1 mixture of **(4.1.5)** and **(2.3.1)** was obtained, however when the reaction was performed in ether, a 97 : 3 ratio of alcohols **(4.1.5)** and **(2.3.1)** was obtained. Unsurprisingly alcohols **(2.3.1)** and **(4.1.5)** are almost co-polar by chromatography, hence separation was affected by treatment of the mixture with HCl in DCM causing cyclisation of ketene dithioacetal **(2.3.1)** and making chromatographic separation facile.

Oxidation of alcohol **(4.1.5)** to aldehyde **(4.1.6)** was particularly problematic. Swern oxidation using N-methylmorpholine as a base[69] caused complete epimerisation of the neighbouring centre. A variation of the Swern oxidation, using pyridine sulphur trioxide complex and DMSO[70], gave recovered starting material. Various chromate oxidation methods were equally unsuccessful. PCC in DCM[71] gave a low yield (25%) of partially epimerised aldehyde **(4.1.6)**, when the reaction mixture was buffered with sodium acetate only baseline material was obtained. PDC in DCM[72], and chromium trioxide pyridine complex in DCM[73] also gave baseline material. Dess-Martin periodinane[74] oxidation led to a complex mixture of products none of which were the desired aldehyde. Eventually TPAP oxidation in the presence of N-methylmorpholine N-oxide[75] proved to be the method of choice giving a good yield (72%) of the aldehyde **(4.1.6)** on small scale, and reasonable yields (52%) on gram scale, and causing no epimerisation of the adjacent chiral centre. The vinyl geminal dibromide **(4.1.7)** was formed using carbon tetrabromide and triphenylphosphine[76]. Conversion of geminal vinyl dibromide **(4.1.7)** to acetylene **(4.1.8)** was accomplished by treatment with magnesium metal in refluxing THF[77], the reaction proceeds *via* an insertion, elimination, reaarangement mechanism (scheme 4.4). The usual method of using butyllithium did not work in this case, possibly due to the acidity of the proton at the C2 position of the dithiane.

Scheme 4.4



The Fritsch-Buttenberg-Wiechell Rearrangement

The synthesis up to this point gave gram quantities of acetylene **(4.18)**.

Reduction of acetylene **(4.1.8)** was attempted using a number of metal hydride sources (DIBALH[78], zirconocene dichloride and *t*-butyl magnesium chloride[79], and catechol borane[80]). Dibromoborane dimethyl sulphide complex[81] was the only reducing reagent that worked. To obtain a good yield from the reaction ten equivalents of dimethyl sulphide was added in an attempt to inhibit the competitive coordination of borane to the dithiane functionality. Iodination of the borinic acid was achieved using aqueous sodium hydroxide and iodine giving vinyl iodide **(2.2.2)** in 51 % yield for two steps.

4.4 Choice of C26 carbonyl protecting group.

The syntheses presented in this chapter and chapter three have demonstrated the sensitivity of the dithioacetal and the ortho dithioester to oxidation reactions and Lewis acids, but with judicious choice of reagents and conditions, good yields can still be obtained. In the synthesis of lactone **(2.2.1)** the advantages of the orthodithioester (excellent stereo control of the cyclisation reaction) far outweigh the disadvantages mentioned above. However the synthesis of vinyl iodide **(2.2.2)** suffers from modest yields on a number of steps:-

1) the oxidation of alcohol **(4.1.5)**
2) olefination of aldehyde **(4.1.7)**
3) reduction of acetylene **(4.1.8)**,

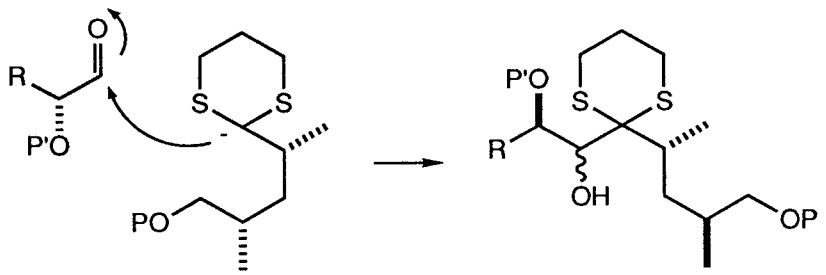
and only moderately good selectivity on cyclisation of the ketene dithioacetal

(2.3.1).

In retrospect exchange of the dithioacetal for a conventional acetal after the acid catalysed cyclisation reaction would probably have been beneficial. However the intention was to use the dithioacetal not only in one of the key stereochemical steps but also to extend the synthesis of rapamycin by one of two ways.

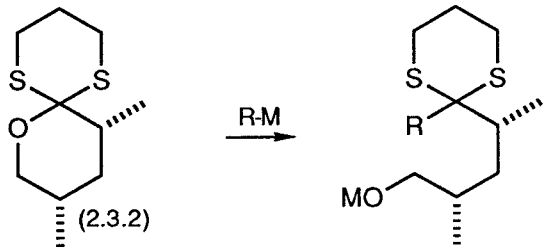
1) Conventional formation of the anion at C2 of the dithiane followed by nucleophilic attack on a carbonyl species (scheme 4.5), or

Scheme 4.5



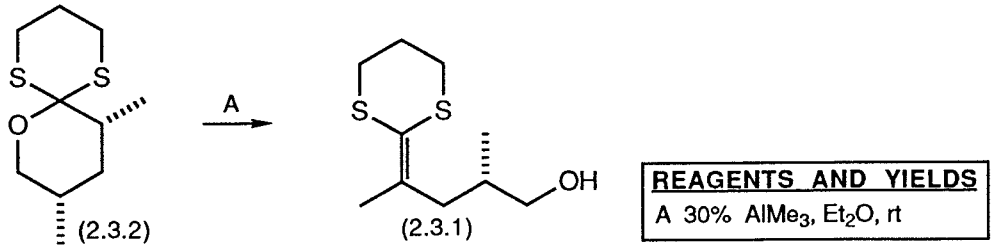
2) to extend the chemistry of the ortho dithioester and develop a method to deliver a carbon nucleophile to the quarternary centre (scheme 4.6). The chemistry in scheme 4.6 would enable us to perform nucleophilic additions on protected lactones to yield protected carbonyl species without using a protection / deprotection strategy.

Scheme 4.6



The above idea arose from the success we observed with the DIBALH reduction of orthodithioester **(2.3.2)**. The reaction was briefly investigated by reacting **(2.3.2)** with trimethyl aluminium in ether, the only product formed was ketene dithioacetal **(2.3.1)** (scheme 4.7).

Scheme 4.7



Due to time constraints no other reactions were attempted. Reactions with the less sterically hindered vinyl and acetylenic alanes may prove more fruitful.

CHAPTER 5

'Wordly wealth he cared not for, desiring only to make both ends meet'

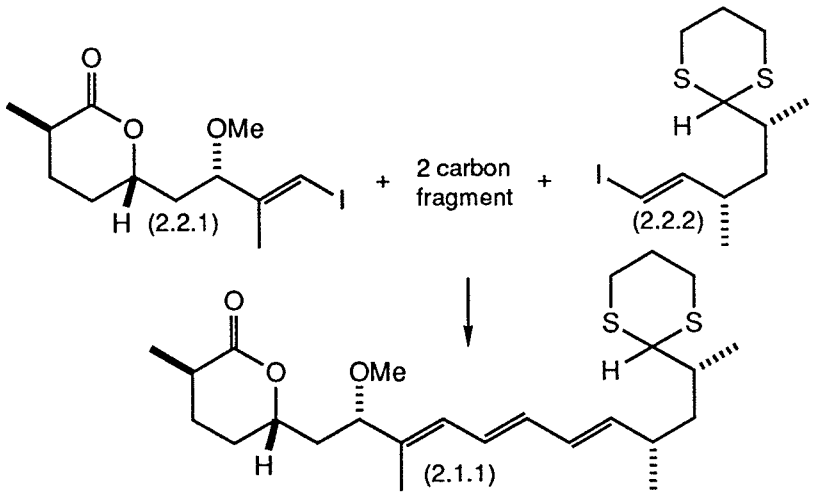
Thomas Fuller (1608-1661).

CHAPTER 5: THE COUPLING REACTIONS

5.1 Strategy for the formation of the triene (2.1.1).

In chapters three and four the syntheses of vinyl iodides **(2.2.1)** and **(2.2.2)** (scheme 5.1) have been presented. In chapter five we shall discuss the palladium catalysed coupling reactions we used to attempt the synthesis of triene **(2.1.1)**.

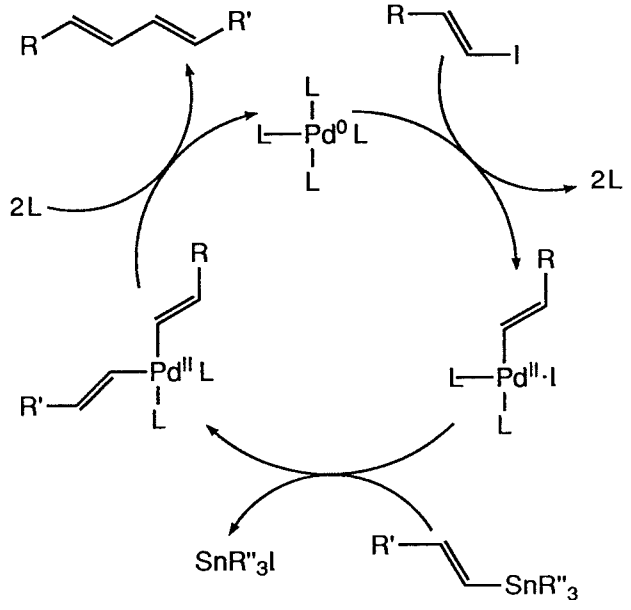
Scheme 5.1



5.2 The palladium catalysed cross-coupling reaction.

The palladium catalysed coupling of vinyl, and aryl halides with vinyl stannanes[37], boronates[82] and also terminal acetylenes[39], is a very well documented method of synthesising conjugated systems. Much of the work concerning the coupling of vinyl stannanes with vinyl iodides was reported by Stille[37]. The mechanism of catalysis (scheme 5.2) is shown below[36].

Scheme 5.2

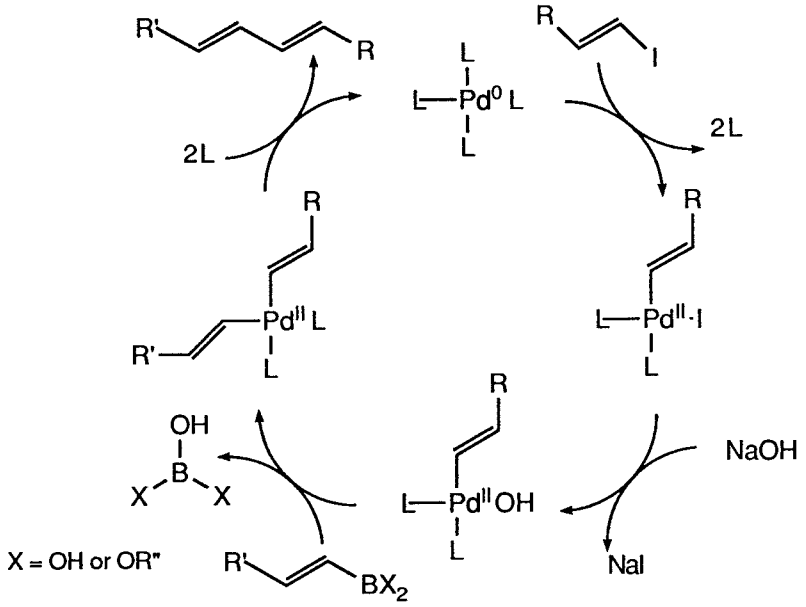


The reaction proceeds initially by the oxidative insertion of the Pd(0) catalyst into the carbon halogen bond, giving a Pd(II) species. The vinyl stannane then reacts with the Pd(II) species *via* a transmetallation process that gives trialkyltin halide as a by-product, leaving both the vinyl groups on the Pd metal centre. A reductive elimination step then occurs yielding the 1,3-diene and regenerating the catalyst. The reaction also works when a number of Pd(II) catalysts are used, the catalysts are reduced *in situ* by the vinyl stannane.

$$2R'SnBu_3 + Pd(II)X_2 \longrightarrow R'_2 + 2Bu_3SnX + Pd(0)$$

The Suzuki cross-coupling of vinyl boronic acids[82] and esters with vinyl halides needs the presence of aqueous hydroxide ion to proceed by the mechanism shown below[82] (scheme 5.3). The hydroxide ion exchanges with the iodide moiety before the transmetallation step.

Scheme 5.3

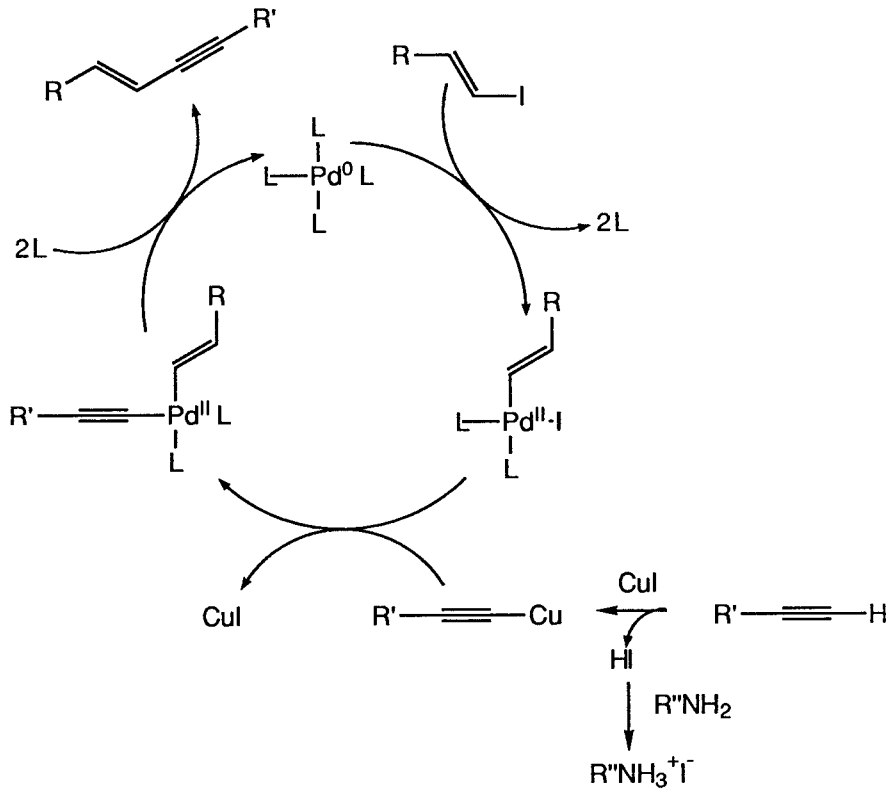


The palladium catalysed coupling of acetylenes in the presence of copper (I) iodide and stoichiometric quantities of base proceeds by the mechanism shown below (scheme 5.4)[83]. The copper salt forms a copper (I) acetylide species which undergoes a transmetallation step to regenerate the copper (I) iodide. The reductive elimination reaction then occurs as above to yield an ene-yne (scheme 5.3). Palladium (II) catalysts can also be used, the catalysts are reduced *in situ* by the acetylene [83] i.e.

$$2RCCH + 2CuI + 2R'NH_2 + L_2PdX_2 \longrightarrow RCC\text{-}CCR + L_2Pd + 2CuX + 2R'NH_3I$$

The palladium catalysed reaction has also been reported to proceed in the absence of copper (I) halides[84].

Scheme 5.4

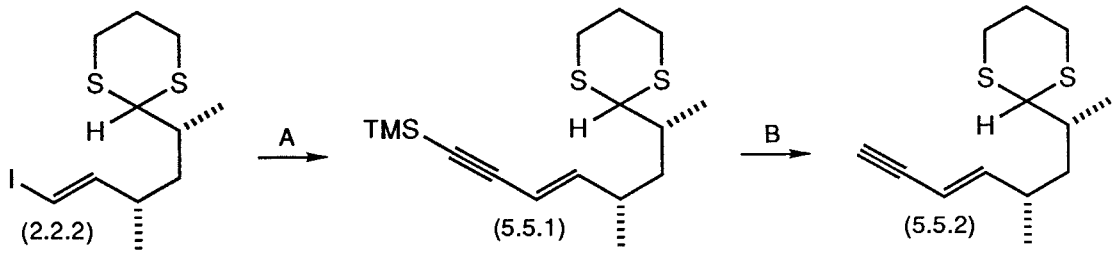


The major advantage of the acetylenic and the vinyl boronic acid coupling reactions over the original Stille coupling, is that separation of the by-products from the reaction product is facile.

5.3 Attempting to synthesise triene (2.1.1) *via* the Suzuki coupling.

Our first attempt to generate the triene involved following the work reported by Kobayashi and Sato[39] in their synthesis of Leukotriene B4. The first step was to couple vinyl iodide **(2.2.2)** with trimethylsilyl acetylene, which proceeded cleanly in high yield. The ene-yne **(5.5.2)** was furnished by treatment of trimethylsilyl acetylene **(5.5.1)** with TBAF (scheme 5.5).

Scheme 5.5



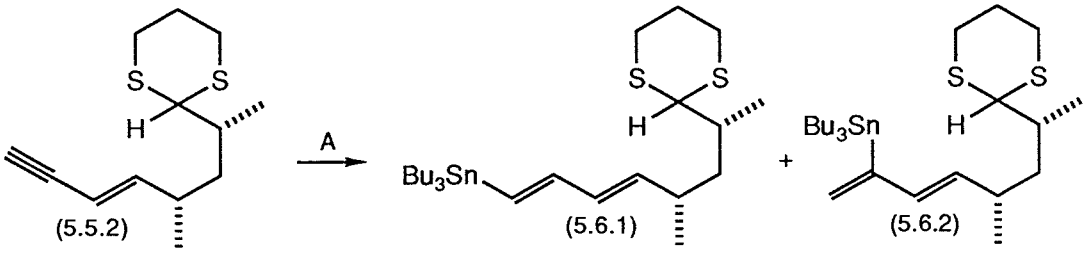
REAGENTS AND YIELDS

A 89% TMS acetylene, CuI, *n*-$PrNH_2$, $Pd(PPh_3)_4$, benzene, rt
B 100% TBAF, THF, rt

Hydroboration was then attempted using disiamyl borane. Reaction with the borane was very slow even after the addition of several equivalents and prolonged heating, and was accompanied by a significant amount of decomposition. After hydrolysis of the vinyl borane with aqueous sodium hydroxide, and addition of the lactone **(2.2.1)** and *tetrakis* triphenylphosphine palladium (0), a complex mixture of products was observed by thin layer chromatography. Subsequent treatment of lactone **(2.2.1)** with aqueous sodium hydroxide showed that extensive decomposition occurred as well as the expected hydrolysis to the δ-hydroxy acid.

The coupling of boronic esters has been reported[85] to proceed in the presence of weaker bases such as carbonates, but only when the molecule bearing the halide functionality is activated by the presence of a carbonyl group. Nicolaou also reported[86] the coupling of a boronic ester to a vinyl iodide using thallium hydroxide as the source of base in a two phase (hexane / water) system. The reaction proceeded in moderate yield (55%) in the presence of ester functionality. However in the case of lactone **(2.2.1)** there is also the problem of a chiral centre α to the carbonyl group which may well have been epimerised under the reaction conditions of Nicolaou. For these reasons and the extensive decomposition observed during hydroboration, we decided not to pursue Suzuki's method of coupling the fragments. Next we decided to attempt coupling reactions between vinyl iodides and vinyl stannanes. With the ene-yne **(5.5.2)** in hand, we performed Lipshutz's stannyl cupration reaction[64] followed by an aqueous quench. The reaction gave an inseparable mixture of the vinyl stannanes **(5.6.1)** and **(5.6.2)** in reasonable yield (64%) (^{1}H NMR) (scheme 5.6).

Scheme 5.6

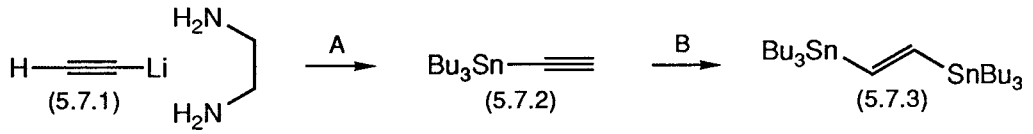


REAGENTS AND YIELDS

A 64% i) CuCN; ii) BuLi; iii) Bu_3SnH; iv) (5.5.2); v) H_2O

Due to the lack of selectivity observed in the above reaction, we decided to introduce the two central carbons of the triene from the literature compound *E*-1,2-di(tributylstannyl) ethene **(5.7.3)**. The ditin **(5.7.3)** was synthesised by the method of Stille[87] (scheme5.7).

Scheme 5.7



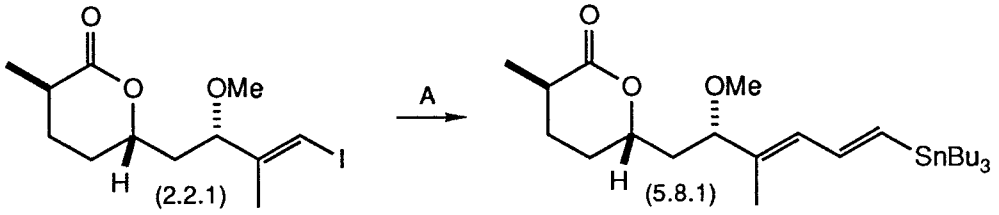
REAGENTS AND YIELDS
A 65% Bu_3SnCl, THF, rt
B 88% AIBN, Bu_3SnH

5.4 Coupling reactions of ditin (5.7.3) with lactone (2.2.1).

Coupling reactions using the ditin **(5.7.3)** were initially attempted with lactone **(2.2.1)** since we reasoned that separation of the tributyltin iodide by-product from the polar lactone fragment would be easier than separation from the dithiane containing fragment. The first catalyst we attempted to use was *bis*acetonitrile palladium dichloride in DMF / THF which Stille reports[37] to be one of the most active catalysts. A 0.5 equivalent excess of the ditin **(5.7.3)** was used to enable the reduction of the catalyst *in situ* and also to suppress the coupling of the reaction product with another molecule of lactone **(2.2.1)**. However after three days none of the desired product had been formed and only baseline material remained.

$Pd(Ph_3P)_4$ in refluxing toluene has been used to couple aryl halides and ditin **(5.7.3)**[88]. The reaction proceeds in good yield using a 1:1 mixture of reagents without the use of slow addition techniques. These results suggest that a second coupling reaction is significantly slower. However when we employed these conditions only a low yield of the desired product was obtained (scheme 5.8)

Scheme 5.8



REAGENTS AND YIELDS
A 25% $Pd(PPh_3)_4$, (5.7.3), toluene, 110°C

The reaction was also performed in refluxing THF with no improvement in yield. We also used freshly prepared $Pd(Ph_3P)_4$[89] again with no improvement in yield. The acid sensitivity of vinyl stannanes led us to try two methods of optimising the yield:-

1) purifying the product on deactivated basic alumina. Unfortunately, the dienyl stannane **(5.8.1)** completely decomposed under these conditions, probably due to hydrolysis of the lactone, and
2) adding a stoichiometric quantity of base to the reaction mixture to neutralise any hydrogen iodide that may have been formed from the hydrolysis of the tributyltin iodide by-product.
Neither of these methods caused any improvement in yield.

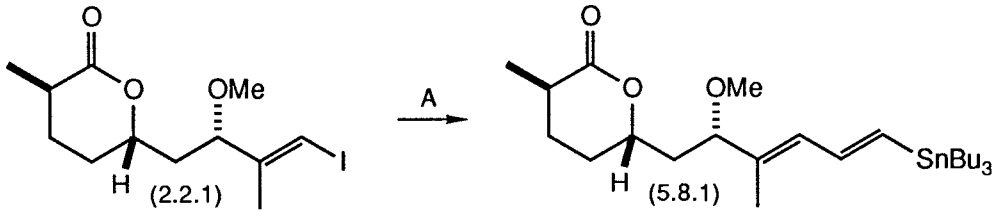
Since we had obtained low yields from using the conditions of Stille we decided to try the conditions reported by Farina[38]. Farina performed an extensive study on the effect of the ligand attached to the palladium centre on the rate of a number of cross-coupling reactions. The effects of ligands on the rate of reaction had previously been assumed to be steric in origin, but Farina showed that whilst Ph_3As and Ph_3P have essentially the same cone angles, the rate of the coupling reaction is three orders of magnitude higher when Ph_3As is the ligand. He proposed that the electronic nature of the ligand is crucial to the rate of the cross-coupling. The catalysts were formed *in situ* by treatment of $Pd_2(dba)_3$ complex with two or four eqiuvalents of the ligand.

The initial oxidative insertion into the carbon iodine bond requires strongly electron donating ligands to create an electron rich metal centre, but the transmetallation step requires an electron poor metal centre for attack of the nucleophilic stannane to be favourable. Hence ligands that are good σ-donors stabilise the first step, and ligands that dissociate readily, favour the transmetallation step, suggesting a ligand of intermediate donicity is required. Tri(2-furyl)phosphine (TFP) proved to be an exceptional ligand, providing a hundred fold rate increases over Ph_3P, and being more stable than the Ph_3As derived catalysts. Farina has shown that TFP will displace Ph_3P from $Pd(Ph_3P)_4$ at -60°C, and also dissociates more readily than Ph_3P from the Pd(II) intermediate. The reasons for the observed behaviour are unclear.

Farina also states that the solvent of choice for the cross-coupling reactions in N-methylpyrrolidinone, but does not postulate why.

Employment of TFP / $Pd_2(dba)_3$ catalyst system did increase the yield of the coupling reaction significantly to 44% (scheme 5.9)

Scheme 5.9

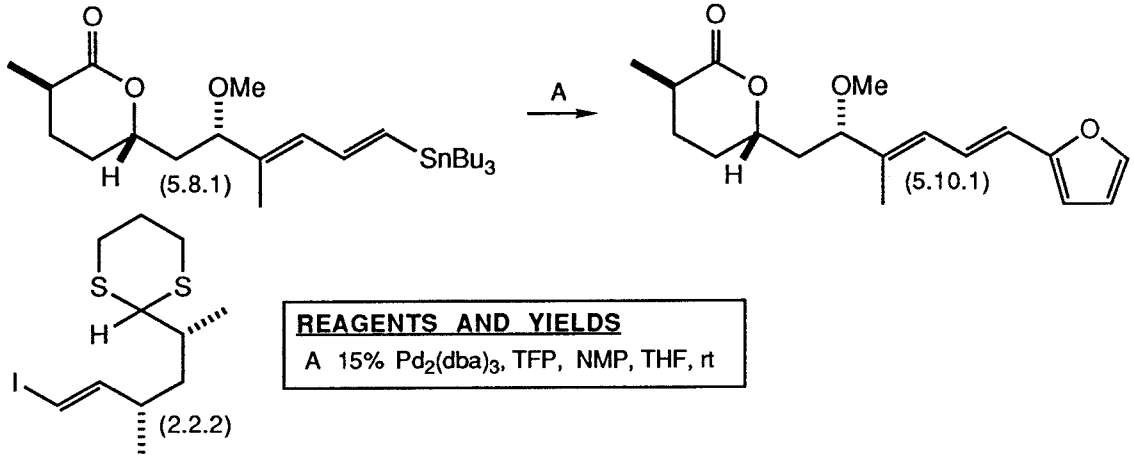


REAGENTS AND YIELDS
A 44% $Pd_2(dba)_3$, TFP, (5.7.3), NMP, THF, rt

5.5 Attempted coupling reactions between dienyl stannane (5.8.1) and vinyl iodide (2.2.2).

With small amounts of the dienyl stannane **(5.8.1)** in hand, coupling reactions with vinyl iodide **(2.2.2)** were attempted. Coupling reactions using Stille's conditions[37], $Pd(Ph_3P)_4$ in DMF / THF, N-methylpyrrolidinone / THF and benzene, all failed to react at room temperature and when warmed to 60°C decomposition occurred. The only incidence of coupling we observed, occurred when we applied the conditions reported by Farina[38]. The product we obtained we tentatively assigned (^{1}HNMR) as dienyl furan **(5.10.1)** (scheme 5.10).

Scheme 5.10

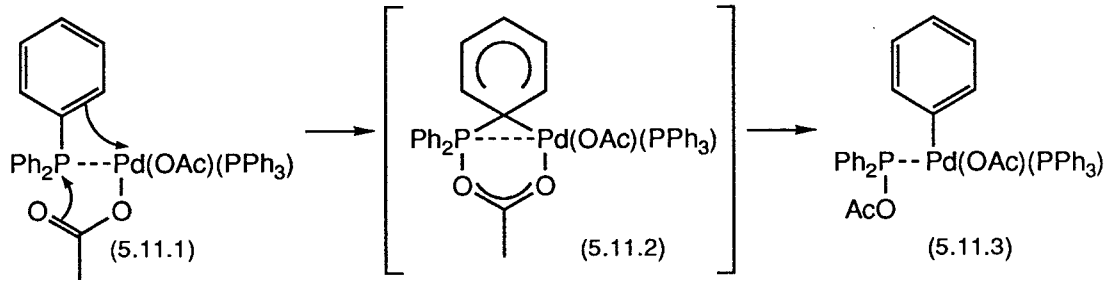


REAGENTS AND YIELDS
A 15% $Pd_2(dba)_3$, TFP, NMP, THF, rt

The above reaction presumably proceeds *via* an insertion reaction into the carbon phosphorus bond. The phosphine ligands on the palladium metal centre are usually presumed to be inert under the reaction conditions but there are occasional references in the literature[90] to the reactions of $Pd(OAc)_2(PPh_3)_2$ where the ligands participate in the reaction. On heating $Pd(OAc)_2(PPh_3)_2$ decomposes to give mixtures of *bi*-phenyl, benzene, and phenyl acetate. The above evidence suggests that the species that inserts into

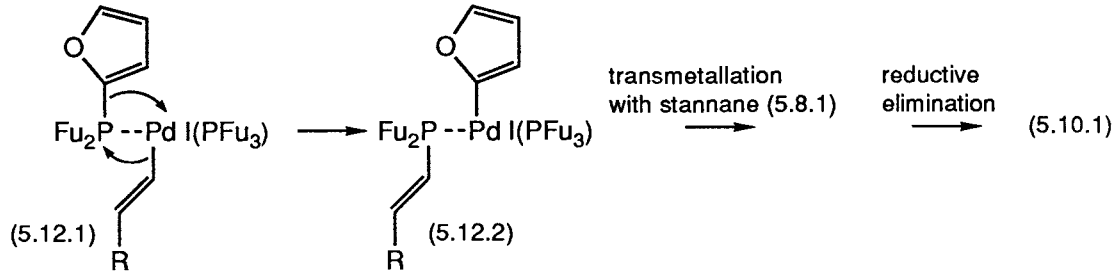
the phosphorus carbon bond is palladium (II). Goel[91] proposes the following mechanism (scheme 5.11) to explain his results.

Scheme 5.11



Obviously from intermediate **(5.11.2)** a reductive elimination reaction would yield phenyl acetate. If the **(5.11.3)** underwent the insertion reaction a second time, placing two phenyl groups on the metal centre, then a reductive elimination reaction would yield biphenyl. A similar rearrangement of the Pd(II) intermediate **(5.12.1)** may be envisaged (scheme 5.12).

Scheme 5.12



Reaction of Pd(II) intermediate **(5.12.2)** with dienyl stannane **(5.8.1)** *via* a transmetallation and reductive elimination process would yield dienyl furan **(5.10.1)**. The mechanism proposed would also result in the generation of tributyltin iodide as a by-product. Thin layer chromatography of the reaction mixture revealed a compound that streaked from R_f 0 to R_f 0.7 (50% ether in petrol), characteristic of tributyltin iodide, thus supporting the mechanism above. Interestingly the reaction using triphenyl arsine as the ligand yielded only recovered starting material.

5.6 Attempted coupling reactions between ditin (5.7.3) and vinyl iodide (2.2.2).

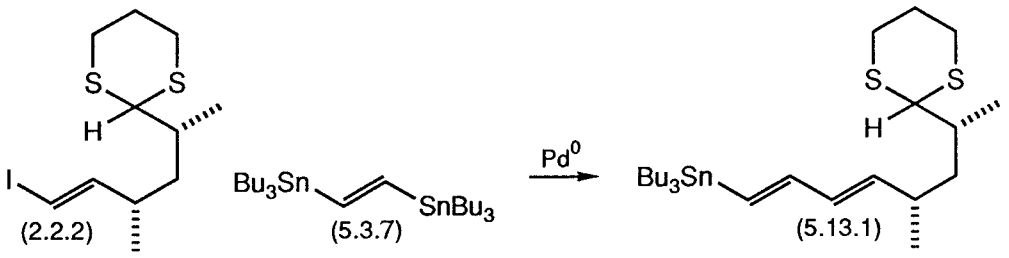
We then decided to attempt the synthesis of the triene from palladium catalysed coupling reactions between vinyl iodide **(2.2.1)** and dienyl stannane **(5.13.1)**. We decided to try this strategy for two reasons :-

1) the failure of the approach outlined above, and

2) the low yields of the steps used to form vinyl stannane **(3.5.12)** and dienyl stannane **(5.8.1)** meant that the synthesis was becoming unacceptably inefficient.

To synthesise dienyl stannane **(5.13.1)** we attempted the palladium catalysed coupling of ditin **(5.3.7)** and vinyl iodide **(2.2.2)** (scheme 5.13).

Scheme 5.13



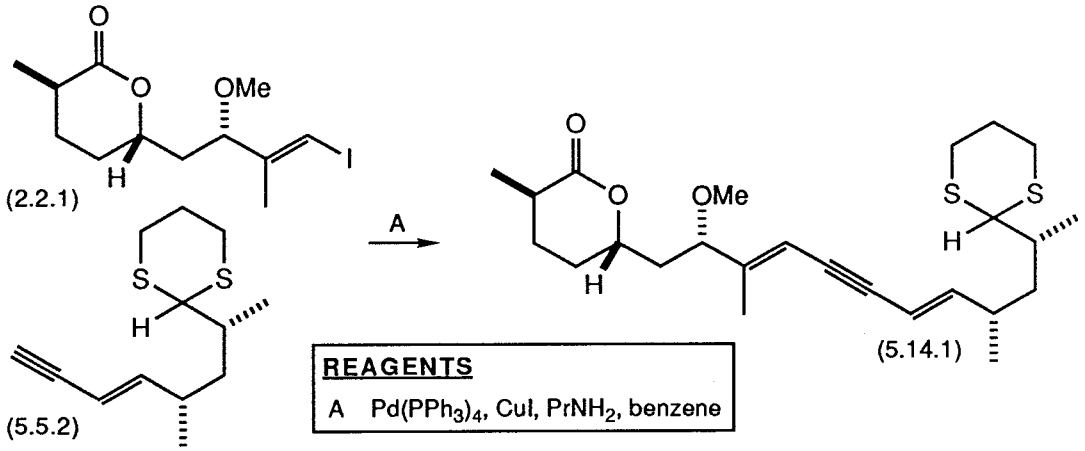
Use of the Stille conditions[37] ($Pd(PPh_3)_4$ / THF / DMF or *bis*acetonitrile palladium dichloride / THF / DMF) failed to give any product at room temperature, and on warming to 60°C decomposition to highly polar material occurred. Again we tried the conditions reported by Farina[38] but with no success.

After obtaining the results above it became apparent that the problems with the coupling reactions occur with the transmetallation step. The initial oxidative addition step with vinyl iodide **(2.2.2)** obviously occurs extremely efficiently (scheme 5.5). The transmetallation step may proceed inefficiently due to functional group incompatibilty. Functional group incompatibility may arise from the use of sulphur and tin, or sulphur and palladium. It is possible that coordination of the dithiane functionality to the tin atom prevents reaction of the vinyl stannane with the palladium (II) intermediate. But Stille type coupling reactions have been reported[92] to proceed in the presence of aromatic mono sulphur containing heterocycles, and the postulation does not account for the coupling of dienyl stannane **(5.8.1)** to the furan ligand (scheme 5.10). Another possibility is that after the oxidative addition reaction the dithiane ring coordinates to the palladium (II) metal centre. The outcome of the reaction may then be determined by how effectively the vinyl stannane or copper acetylide species competes for the metal centre. The efficiency of competition may be determined by the relative coordination energies or the relative steric demands of the two species.

5.7 Circumventing the possible functional group incompatibility.

Our first idea was to attempt an acetylene coupling between ene-yne **(5.5.2)** and vinyl iodide **(2.2.1)** (scheme 5.14). With the intention of reducing the acetylene to a double bond by zinc reduction[93], and then isomerisation to the *trans* double bond.

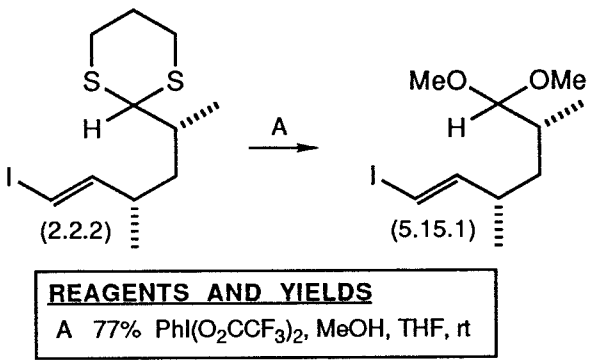
Scheme 5.14



The reaction was followed closely by thin layer chromatography and seemed to proceed cleanly although several portions of catalyst were required to enable the reaction to proceed to completion. However the reaction product decomposed on isolation before ^1H NMR studies. Unfortunately the reaction could not be repeated due the lack of material.

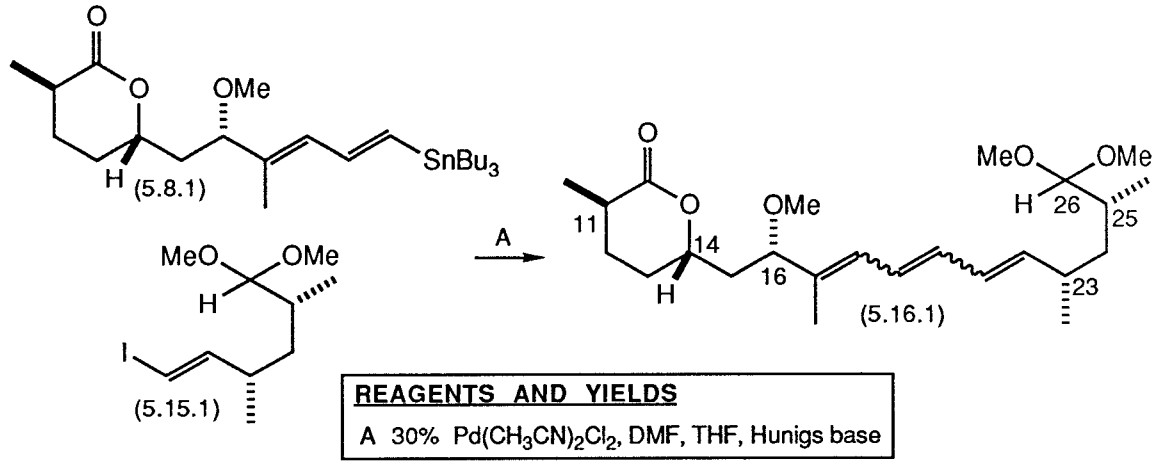
The final attempt to generate the triene involved removal of the dithioacetal *via* a transacetalisation reaction reported by Stork [94] (scheme 5.15).

Scheme 5.15



The coupling reaction with dienyl stannane **(5.8.1)** was attempted using the conditions of Nicolaou[16] (scheme 5.16).

Scheme 5.16



The reaction yielded two products in a ratio of 2 : 3 that were inseparable by flash or preparative thin layer chromatography. The mixture of compounds absorbed UV light at 266, 276 and 287nm. Analytical HPLC analysis of the mixture confirmed the presence of only two major UV active components. The ^{1}H NMR spectrum clearly showed characteristic signals from both of the component fragments **(5.8.1)** and **(5.15.1)** however most of the signals were 'doubled up' (table 5.17) and the region of the spectrum containing signals from alkene protons is very complex although the signals integrated to a total of five protons. Unfortunately the product decomposed before preparative HPLC separation or mass spectrometric analysis had been achieved. From the data below it is impossible to state categorically that the triene **(5.16.1)** was ever synthesised.

Table 5.17 characteristic signals in ^{1}HNMR of final coupling product

Chemical shift (δ scale)	Assignment
0.90, d, J = 7.0 Hz	C23 or C25 methyl group
0.93, d, J = 7.0 Hz	C23 or C25 methyl group
1.06, d, J = 6.8 Hz	C23 or C25 methyl group
1.07, d, J = 6.8 Hz	C23 or C25 methyl group
1.32, d, J = 6.9 Hz	C11 methyl group
1.33, d, J = 6.9 Hz	C11 methyl group
1.72, s	C17 methyl group
3.19, s	C16 methoxy group
3.22, s	C16 methoxy group
3.36, s	C26 methoxy acetal
3.37, s	C26 methoxy acetal

3.38, s	C26 methoxy acetal
3.86, td, J = 6.7, 1.9 Hz	C16 proton
3.92, t, J = 6.7 Hz	C16 proton
4.02, d, J = 6.1 Hz	C26 proton
4.03, d, J = 6.1 Hz	C26 proton
4.35-4.20, m	C14 proton

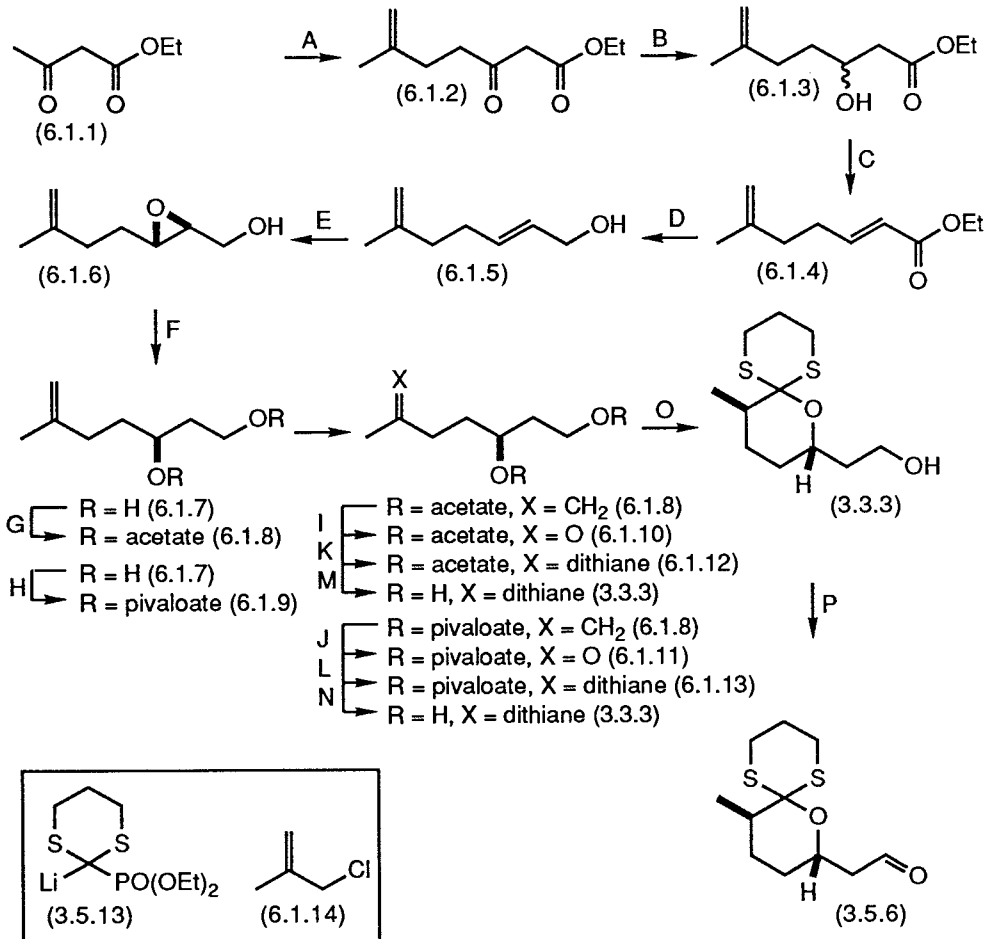
It seems probable that the triene **(5.16.1)** has been synthesised as a mixture of geometric isomers. Palladium coupling chemistry is renowned for its specificity in this regard, which suggests that isomerisation occurred on isolation or after formation in reaction mixture. Sonnet reports[95] that isomerisation of trienes to a thermodynamic mixture of *Z* and *E* isomers is a facile process. The *E, E, E* isomer is thermodynamically favoured, but in the case of triene **(5.16.1)** the presence of the C17-C18 trisubstituted double bond may cause the equlilibrated mixture to contain a substantial proportion of the *Z, E, E* isomer. Nicolaou did not report[16] any problems of isomerisation or mixtures of bond geometries but when the triene system is constrained within a ring then isomerisation may be a disfavoured process. Danishefsky[17,20] and Schreiber[23] did not note any isomerisation when they generated the triene system as a fragment.

CHAPTER 6

CHAPTER 6: THE FAILED APPROACHES TO THE C10-C18 LACTONE FRAGMENT (2.2.1).

6.1 The synthesis of aldehyde (3.5.6) using the Sharpless epoxidation.

Scheme 6.1



REAGENTS AND YIELDS

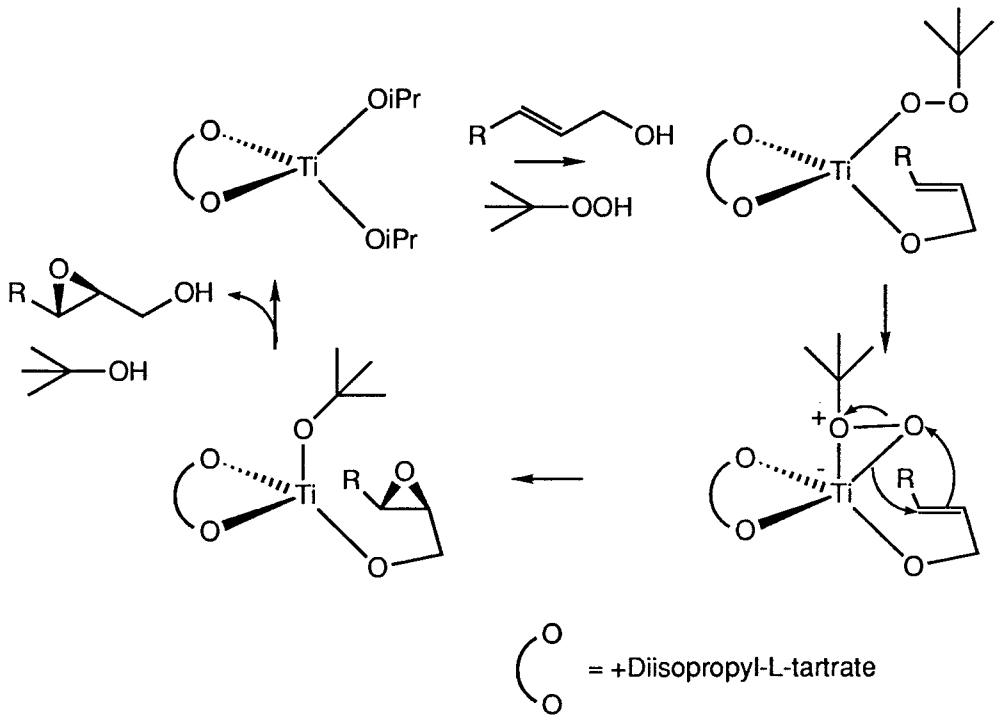
A 68% i) NaH, THF; ii) BuLi; iii) (6.1.14), 0°C
B 82% $NaBH_4$, EtOH, rt
C 86% MsCl, Et_3N, THF, -20-65°C
D 86% DIBALH, DCM, -80°C-rt
E 75% (+)-DIPT, *t*-BuOOH, $Ti(O\textit{i}\text{-}Pr)_4$, 3Å sieves, DCM, -23°C
F 97% $NaAl(OCH_2CH_2OCH_3)_2H_2$, THF, 0°C-rt
G 92% Ac_2O, pyridine, DMAP, DCM, rt
H 95% pivaloyl chloride, pyridine, DMAP, rt
I 95% i) O_3, MeOH; ii) Ph_3P, DCM, -70°C-rt
J 38% i) O_3, MeOH; ii) DMS, DCM, -70°C-rt
K - (3.5.13), THF, -80°C-rt
L 61% (3.5.13), THF, -80°C-rt
M 42% K_2CO_3, MeOH, rt
N 76% LAH, Et_2O, rt
O 70% HCl 0.5eq, DCM
P 61% DMSO, Et_3N, pyridine sulphur trioxide complex, rt

In chapters three and four syntheses of the two component fragments of the Southern portion of rapamycin **(1.1.1)** are described. Two other methods of synthesising the lactone **(2.2.1)** were devised, attempted and subsequently abandoned. The first of these used the Sharpless asymmetric epoxidation[40] of an allylic alcohol **(6.1.5)** to introduce the stereochemistry at C14 and is described in scheme 6.1.

Synthesis of **(6.1.2)** was accomplished on 0.4 mol scale by alkylation of the dianion of ethyl acetoacetate **(6.1.1)** with β-methallyl chloride **(6.1.14)**[96]. Sodium borohydride reduction in ethanol selectively reduced the ketone functionality to give β-hydroxy ester **(6.1.3)**. Elimination *via* the mesylate was achieved by refluxing in THF with 4 equivalents of triethylamine yielding α,β-unsaturated ester **(6.1.4)**. Reduction of **(6.1.4)** with DIBALH gave allylic alcohol **(6.1.5)** in virtually quantitative yield. An alternative route to alcohol **(6.1.5)** reported by Negishi[97] was also attempted without success.

Asymmetric epoxidation was then affected under the conditions reported by Sharpless[40] in 76% yield on mutligram scale. The reaction proceeds *via* the following mechanism (scheme 6.2). The face selectivity of the epoxidation is determined by the homochiral tartrate ligand.

Scheme 6.2



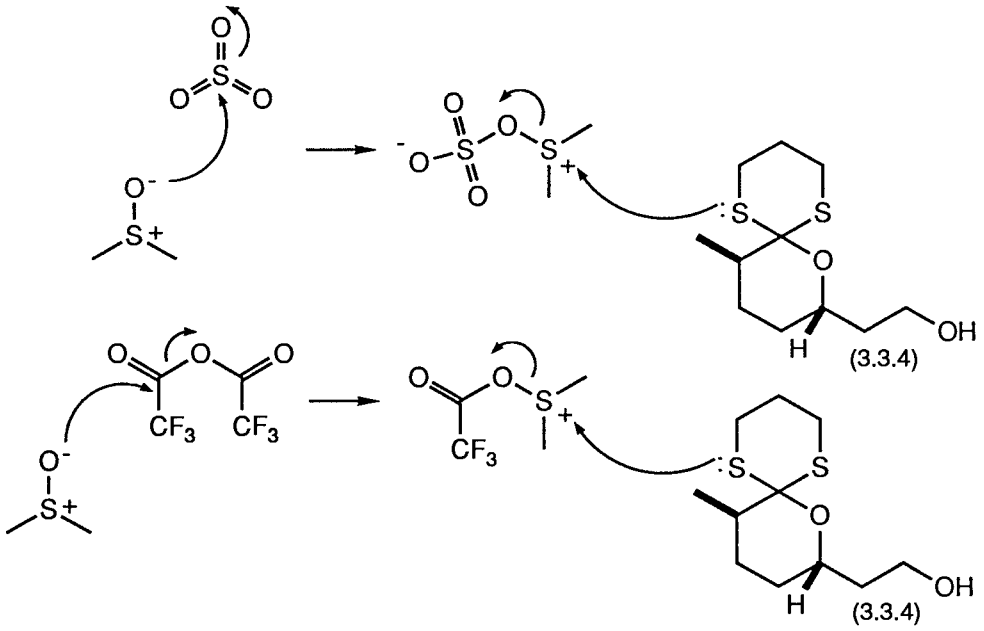
The 2,3-epoxy alcohol **(6.1.6)** was then selectively reduced to give the 1,3-diol **(6.1.7)** by employing sodium *bis*(2-methoxyethoxy)aluminium hydride[98].

6.2 Choice of protecting groups for diol (6.1.6).

Choice of protecting groups for the alcohol functionality at this point was critical. Protecting the diol as an acetal was not appropriate since removal under acidic conditions would cause either hydrolysis[42], or cyclisation of the product ketene dithioacetal **(3.3.3)**. Acetal removal with hydrogen / palladium or Lewis acid conditions would also have been incompatible with the sulphur functionality. Silyl ethers could not be used due to their sensitivity towards ozone. Hence the diol **(6.1.7)** was protected as a diester in the hope that deprotection could be accomplished using either basic hydrolysis or hydride reduction. Firstly pivaloyl esters were used but for unknown reasons the ozonolysis reaction failed to proceed to completion, thus giving only low yields of diester **(6.1.11)**. However subsequent Wadworth-Emmons olefination (61%) and hydride reduction to give diol **(3.3.3)** was efficient. Protection of diol **(6.1.6)** with acetic anhydride to yield the diacetate **(6.1.8)** followed by ozonolysis worked well, but reaction with the lithiated Wadworth-Emmons reagent **(3.5.13)** on 28 mmol scale afforded 23% of the keto diester **(6.1.10)** and 20% of partially deprotected product. Although the next step in the synthesis is the deprotection to yield diol **(3.3.3)**, it is not cost effective to use three equivalents of Wadworth-Emmons reagent **(3.5.13)** to effect this transformation. Deprotection of the diacetate **(6.1.12)** was accomplished using base catalysed methanolysis to give diol **(3.3.3)** in 96% yield. The partially deprotected material could also be converted to diol **(3.3.3)** under these conditions giving a total yield of the diol **(3.3.3)** over two steps of 42%. The diol **(3.3.3)** was then cyclised under the conditions of Suzuki[35] to give a 15 : 1 mixture of diastereo-isomers at C11 in 67% yield. At this point in the synthesis we first encountered the difficulty of performing oxidation reactions in the presence of sulphur functionality. Dess-Martin periodinane in DCM[74], gave a complex mixture of products. Oxidation with N,N-dipiperidine carbodiimide and methyl magnesium bromide[99] gave a very low (10%) yield of the desired aldehyde. TPAP oxidation in the presence of N-methylmorpholine-N-oxide[75] gave reasonable yield (62%) on small scale (0.2 mmol) but when scaled up to (1.0 mmol) the yield dropped to 35%. Two variations of the Swern oxidation were also attempted, trifluoroacetic anhydride, DMSO and triethylamine[100] gave a yield of 47%, whilst pyridine sulphur trioxide complex, DMSO and N-methyl morpholine[70] afforded 61% of the desired aldehyde on 0.4 mmol scale. It is possible that the Swern oxidation variants did not work well due to competition for the activated DMSO species by the nucleophilic sulphur atoms of the dithiane ring (scheme

6.3).

Scheme 6.3



The synthesis was abandoned for a number of reasons:-

1) The problems with the protecting groups; the protecting group strategy could probably be improved by experimenting with other groups, possibly benzyl ethers.

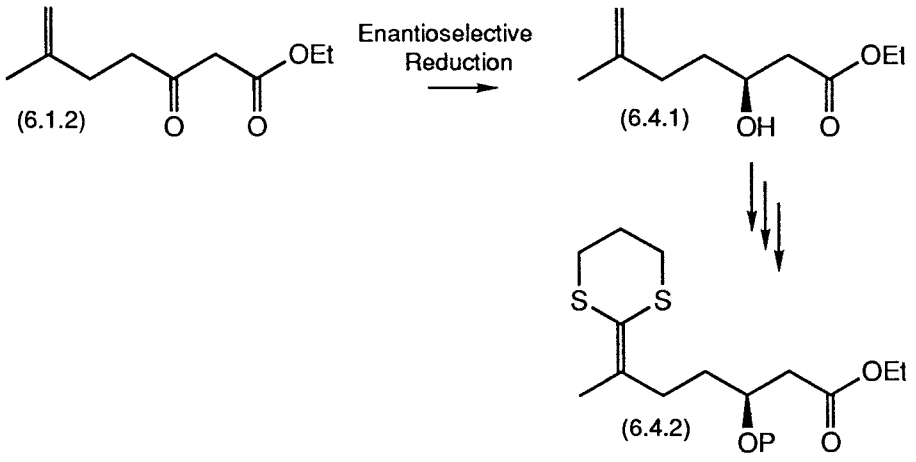
2) The moderate yield of the oxidation reaction. In our experience this will always be a low yielding step. Removal of the dithiane to improve the yield of the oxidation step may create problems later in the synthesis, since addition of a Grignard reagent to aldehyde functionality may result in epimerisation of the C11 centre.

3) The length of the synthesis. The synthesis takes twelve steps to form the eight carbon fragment **(3.5.6)**, and whilst gram quantities of alcohol **(3.3.4)** could be isolated the problems of the oxidation reaction prevented much progress beyond this point.

6.3 Enantioselective reduction of β-keto esters

To reduce the length of the synthesis presented above we reasoned that enantioselective reduction of β-keto ester **(6.1.2)** to either *R* or *S* β-hydroxy ester **(6.4.1)** followed by protecion of the alcohol functionality, ozonolysis and Wadworth-Emmons olefination to give ketene dithioacetal **(6.4.2)** (scheme 6.4).

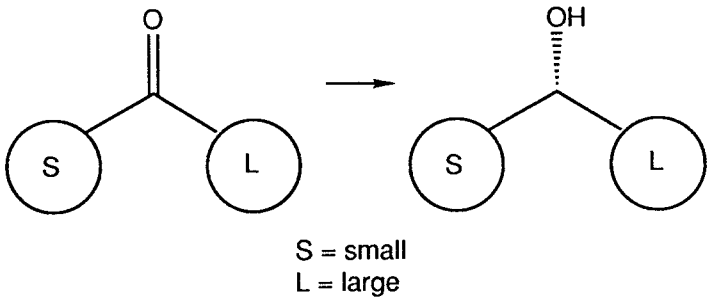
Scheme 6.4



We chose an enzymatic reduction. The enantioselective reduction of β-keto esters using bakers yeast (*Saccharomyces cerevisiae*) is well reported[41]. The reaction is performed by an alcohol dehydrogenase enzyme. These enzymes are dependent on the co-factor NADPH which acts as the reducing agent.

There are two ways to perform enzymatic reductions:- 1) use the enzyme in a whole cell, or 2) use the isolated enzyme. There are advantages and disadvantages to both methods. Using the enzyme in the whole cell has the advantage that the enzyme is in it's natural environment i.e. co-factor recycling is performed automatically by the cell; however, the enantioselectivity can often be low due to the operation of more than one alcohol dehydogenase. Using the isolated enzyme has the advantage that the enantioselectivity is more likely to be high, and the disadvantage that co-factor recycling is not performed automatically. The stereospecificity of reductions can be predicted using a convenient rule, which states that the hydride ion equivalent is delivered to the *re*-face of a pro chiral ketone (scheme 6.5).

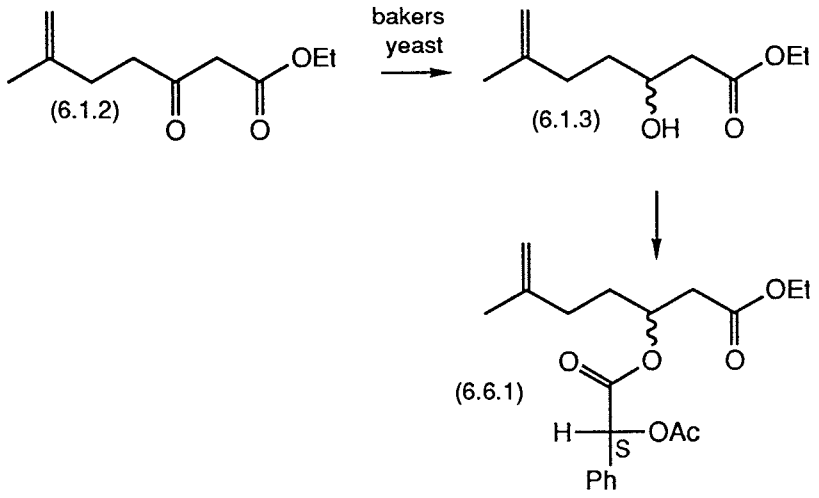
Scheme 6.5



To affect the reduction of β-keto ester **(6.1.2)** we used fresh yeast obtained from the local bakery, since dried yeast obtained from Sigma proved

to be totally inactive. The reduction proceeded tolerably well from the point of view of chemical yield (45%), but when the (*S*)-O-acetyl mandelate ester **(6.6.1)** was made proton NMR spectroscopy of the product showed that the reduction had yielded a 1 : 1 mixture of enantiomers (scheme 6.6).

Scheme 6.6



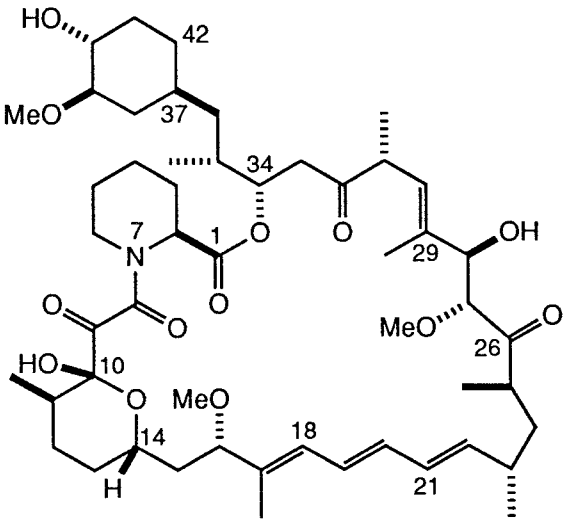
The failure of this route may well be due to the approximate equal size of the two substituents either side of the ketone or, as mentioned before, the operation of more than one alcohol dehydrogenase. Results may have improved dramatically if a long alkyl chain ester had been used instead of the ethyl group. However, due to our lack of experience with the use of biochemical systems we decided not to pursue the idea.

CHAPTER 7

CHAPTER 7: CONCLUSIONS AND FUTURE WORK

7.1 A comparison of our C10-C18 lactone fragment (2.2.1) synthesis with those in the literature.

Scheme 7.1



Rapamycin (1.1.1)

Nicolaou[14], Danishefsky[17,20] and Schreiber[23] all synthesise the lactol portion of rapamycin **(1.1.1)** in the open chain form. Nicolaou and Danishefsky synthesised the lactol fragment with the C10 oxygen in the alcohol oxidation state whilst Schreiber with the C10 oxygen in the aldehyde oxidation state. The above strategy has two major consequences:-

1) one or more oxidation reactions must be performed to close the lactol ring and attach the C11-C12 dicarbonyl fragment, and

2) the oxygen functionality at C14 must be protected throughout the synthesis.

The Southampton approach forms the C10-C14 portion of rapamycin **(1.1.1)** as a protected lactone, hence carrying the C10 oxygen functionality through the synthesis at the ester oxidation state and circumventing the need for alcohol protection at C14. When the orthodithioester is unmasked, nucleophilic addition to the lactone moiety will generate the lactol functionality present in rapamycin **(1.1.1)** directly.

Both Nicolaou and Schreiber secure the stereochemistry at C16 after the introduction of the trisubstitued double bond fragment. Danishefsky introduces the trisubstituted olefin fragment to yield a 1 : 1 mixture of epimers at C16 which are oxidised and diastereoselectively reduced to yield the desired isomer.

Our method of securing the chirality at C16 using addition of an

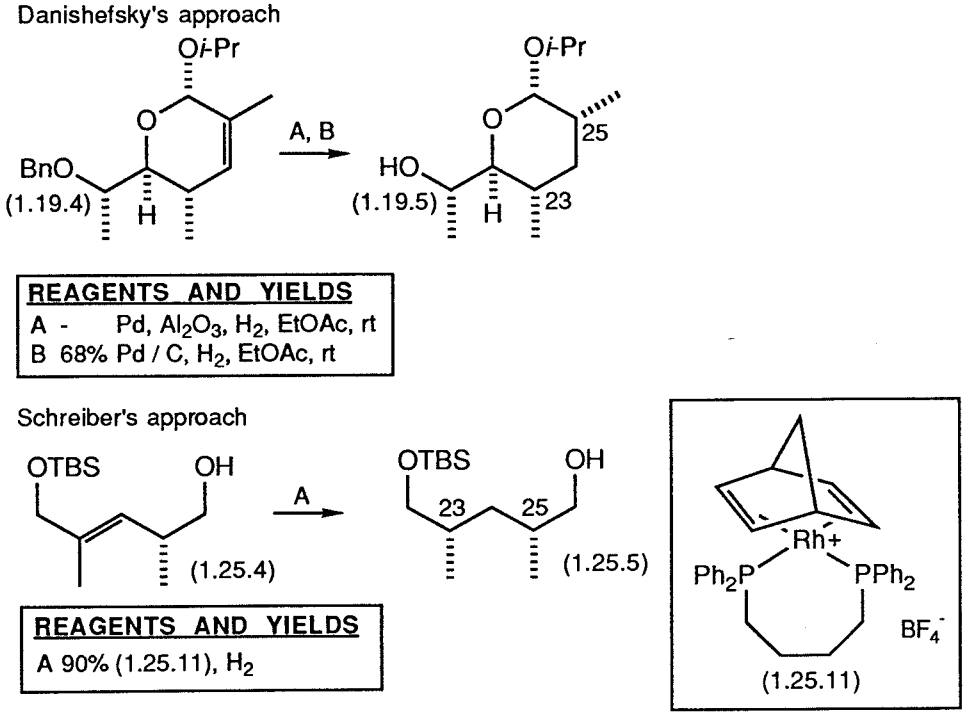
acetylenic Grignard reagent to an aldehyde gave us relatively little selectivity (2.5 : 1). However, the ease of separation of the products coupled with the efficiency of the recyling process used to convert the minor diastereoisomer in to the desired isomer, make our synthesis competitive with Danishefsky's but inferior to those of Nicolaou and Schreiber.

The point at which our synthesis may be considered inferior to those of Nicolaou, Danishefsky and Schreiber is the conversion of the acetylene functionality to the C17-C18 trisubstituted olefin using the capricious and low yielding stannyl cupration reaction. In retrospect the synthesis would have been improved by introducing the C17-C18 fragment as a preformed trisubstituted olefin.

7.2 A comparison of our C21-C26 vinyl iodide fragment (2.2.2) synthesis with those in the literature.

Both Danishefsky[17,20] and Schreiber[23] used starting materials from the chiral pool to secure the stereochemistry of the C23 and C25 methyl groups respectively, diastereoselective hydrogenation reactions of trisubstitued olefins were then employed to fix the stereochemistry of the C25 or C23 methyl groups respectively (scheme 7.2).

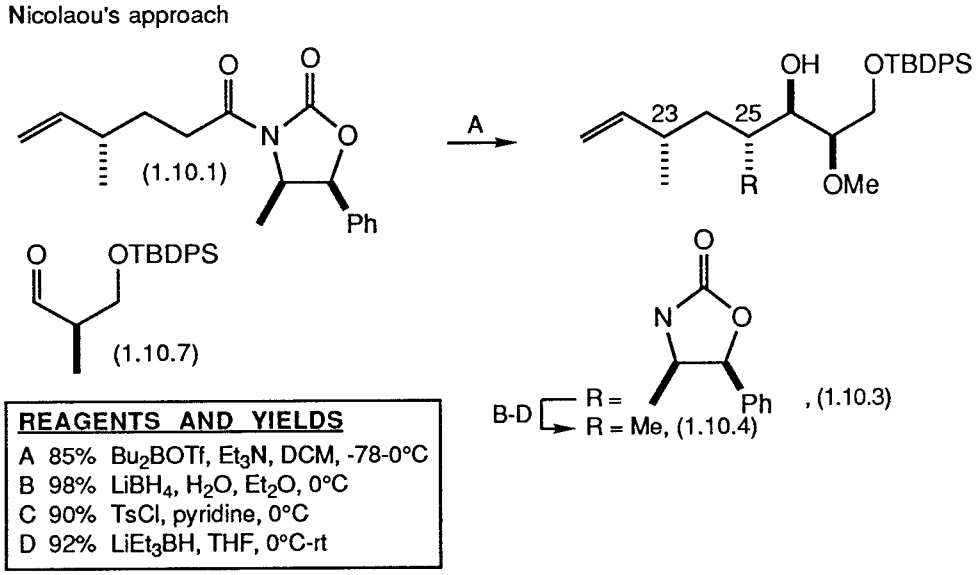
Scheme 7.2



Nicolaou[15] derived the chirality at C23 from β-citronellol and then

used Evans' aldol chemistry followed by a three step reductive removal of the auxilliary to diastereoselectively introduce the methyl group at C25 (scheme 7.3).

Scheme 7.3



Our strategy was to secure the stereochemistry of the C23 methyl group using Evans' alkylation chemistry and induce the chirality of the C25 methyl group using Suzuki's diastereoselective cyclisation. Unfortunately the cyclisation reaction gave a 7 : 1 mixture (^{1}H NMR) of epimers at C25 that were inseparable.

7.3 Future work.

Research on the synthesis of the C10-C18 fragment **(2.2.1)** should concentrate on optimisation of the stannylcupration of acetylene **(3.5.11)** or alternatively redesign the synthesis to introduce the C17-C18 fragment as a preformed trisubstituted olefin fragment.

Recently the C21-C26 fragment has been more economically prepared from chirally resolved material by the method of Robinson[101] generating a single epimer at C25.

Work on the palladium-catalysed cross coupling strategy to generate the triene is continuing with a silicon protecting group on the C26 alcohol. With access to greater quantities of material and a new protecting group strategy, the approach should soon come to fruition.

CHAPTER 8

CHAPTER 8: EXPERIMENTAL SECTION

8.1 General experimental.

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry nitrogen. Stirring was magnetic unless otherwise stated. Reactions in which ruthenium catalysts, palladium catalysts, or organocopper species, were used were conducted under a static atmosphere of dry argon using argon purged solvents. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Diethyl ether (ether), benzene, and toluene were stored over sodium wire prior to use. Methanol and *iso*-propanol were distilled from magnesium methoxide and magnesium *iso*-propoxide respectively. Dichoromethane, diethyl chlorophosphate, HMPA, and β-methallyl chloride were distilled from calcium hydride. Petroleum ether (40-60) (petrol), ethyl levulinate, titanium (IV) *iso*-propoxide and tributyltin hydride were distilled prior to use. 1,3-Dithiane and carbon tetrabromide were purified by bulb to bulb sublimation. *tert*-Butyl hydroperoxide solution was dried by refluxing under Dean and Stark conditions and then storing over 4Å molecular sieves. Ethyl acetoacetate was shaken with saturated aqueous sodium hydrogen carbonate, then water and then dried over anhydrous magnesium sulphate prior to distillation. Copper (I) cyanide was heated at 110°C at 2 mbar for at least 10 hours prior to use. Copper(I) iodide was purified by continuous extraction with refluxing THF. Molecular sieves were activated by heating in a flask with a bunsen burner until water ceased to be evolved. Methyl iodide was distilled from calcium hydride and stored over copper wire and 4Å molecular sieves. Amines were distilled from calcium hydride and stored over sodium hydroxide pellets. Dibutyl boron triflate was prepared and distilled by the method of Mukaiyama[102]. Grignard reagent concentrations were determined by iodometric titration; alkyl lithium concentrations were determined by titration against 1,3-diphenylacetone-*p*-tosylhydrazone. All other reagents and solvents were used as supplied.

Thin layer chromatography was carried out using Merck Kieselgel 60H (0.25 mm thickness mounted on glass. Quantitative chromatographic separation was performed by flash chromatography on Sorbsil C60, 40-60 mesh silica according to the method of Still[103]. The symbol Ø refers to the diameter of the column throughout the experimental.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR

machine. Absorptions are referred to as strong (s), medium (m), weak (w) and broad (br). Sample films were supported on sodium chloride plates and solutions were contained in sodium chloride cells.

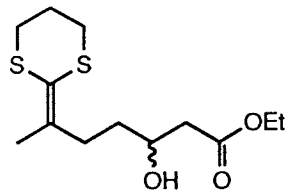
Proton NMR spectra at 270 MHz were obtained on a JEOL GX 270, at 360 MHz on a Bruker AM 360, and at 300 MHz on a Bruker 300 spectrometer. Proton spectra recorded at 250 MHz and 400 MHz were kindly provided by Glaxo Group Research. Samples were dissolved in deuterochloroform unless otherwise stated. Peak positions are quoted against the δ scale relative to the residual chloroform signal (δ 7.27) or to an internal standard of tetramethylsilane (δ 0.00), using the following abbreviations : (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet and (br) broad.

Carbon-13 NMR spectra were recorded at 67.5 MHz on the JEOL GX 270, at 90 MHz on the Bruker AM 360 and at 75 MHz on the Bruker 300. Carbon-13 spectra recorded at 62.5 MHz were kindly provided by Glaxo Group Research. The multiplicities of carbon-13 signals were elucidated using distortionless enhancement by phase transfer (DEPT) spectral editing technique with second pulses at 90° and 135°. Multiplicities are abbreviated as (0) quarternary, (1) methine, (2) methylene, (3) methyl.

Microanalytical data was obtained from University College, London and Glaxo Group Research. Mass spectra were obtained either on a Kratos MS30 spectrometer at Southampton University, or from Glaxo Group Research.

Optical rotations of compounds obtained as mixtures of diastereoisomers are not reported.

8.2 Experimental for chapters three to six.



Ethyl (RS)-6-(1,3-dithian-2-ylidene)-3-hydroxyheptanoate (3.3.1)

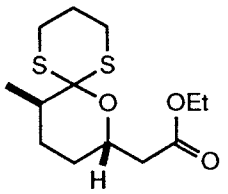
A solution of diisopropylamine (0.826 g, 8.18 mmol) in THF (7.0 mL) was cooled under nitrogen to -30°C and *n*-butyllithium (3.27 mL of 2.5M solution in hexanes, 8.18 mmol) was added, the reaction mixture was then cooled to -80°C and treated dropwise with ethyl acetate (0.720 g, 8.18 mmol), and stirred for 30 minutes. The aldehyde **(3.5.3)** (1.65 g, 8.18 mmol, in 1.5 mL THF) was then added dropwise to the reaction mixture and stirred for 40 min before the solution was allowed to warm to 0°C and stir for a further 45 min. The reaction was quenched by the addition of NH_4Cl (20 mL sat. aq. solution). The organic phase was washed with water and brine, and the aqueous phase was extracted with 3 portions of ether. The combined organic solutions were dried over ($MgSO_4$) and evaporated. The resultant oil was then chromatographed on silica (3 cm Ø x 5 cm, 40% ether in petrol) giving β-hydroxy ester **(3.3.1)** (1.27 g, 4.33 mmol, 53%) as a colourless oil:

IR (film) 3463 (bm), 2930 (s), 1732 (s), 1590 (w) cm^{-1};

^1H NMR (270 MHz) 4.14 (2H, q, J = 7.1 Hz), 4.03-3.90 (1H, dtt, J = 7.6, 7.6, 7.6 Hz), 3.12 (1H, bd, J = 7.6 Hz), 2.86-2.80 (4H, m), 2.55-2.33 (4H, m), 2.14-2.03 (2H, m), 1.88 (3H, s), 1.66-1.44 (2H, m), 1.25 (3H, t, J = 7.1 Hz);

^{13}C NMR (67.5 MHz) 172.9 (0), 139.7 (0), 119.8 (0), 67.5 (1), 60.7 (2), 41.3 (2), 34.4 (2), 31.8 (2), 30.4 (2), 30.2 (2), 25.0 (2), 20.3 (3), 14.3 (3);

LRMS (EI mode, 70 eV): m/z = 290 ($M^{+\bullet}$, 52%), 245 (9), 159 (100), 119 (83), 85 (30).



(8*SR*,11*RS*)-11-Methyl-8-(ethoxycarbonylmethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.3.2)

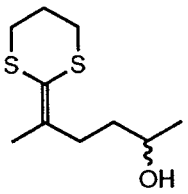
The β-hydroxy ester **(3.3.1)** (200 mg, 0.690 mmol) was cooled under nitrogen to -8°C, and a solution of HCl (0.5 mL , 0.7M solution in DCM) was added. The solution was stirred for 30 minutes before being quenched by the addition of 3 drops of triethylamine. After evaporation the resultant oil was chromatographed on silica (2 cm Ø x 4cm, 10% ether in petrol) giving the dithiaortho ester **(3.3.2)** as a colourless oil (141 mg, 0.48 mmol, 70%):

IR (film) 2961 (m), 2930 (s), 1738 (s), 1287 (s), 1178 (s), 1002 (s) cm^{-1};

^1H NMR (270 MHz) 4.44-4.33 (1H, dddd, J = 11.6, 9.5, 3.8, 2.5 Hz), 4.25-4.06 (2H, m), 3.40 (1H, ddd, J = 15.2, 7.0, 3.5 Hz), 3.18 (1H, ddd, J = 15.2, 7.0, 3.5), 2.65 (1H, dd, J = 14.0, 9.5 Hz), 2.64-2.51 (2H, m), 2.46 (1H, dd, J = 14.0, 3.8), 2.12-2.00 (1H, m), 1.98-1.78 (2H, m), 1.77-1.63 (2H, m), 1.62-1.38 (2H, m), 1.27 (3H, t, J = 7.1 Hz), 1.11 (3H, d, J = 6.6 Hz);

^{13}C NMR (67.5 MHz) 171.5 (0), 93.3 (0), 69.1 (1), 60.6 (2), 41.8 (1), 41.1 (2), 31.3(2), 27.6 (2), 26.6 (2), 25.7 (2), 24.6 (2), 18.4 (3), 14.4 (3);

LRMS (EI mode, 70 eV): m/z = 290 ($M^{+\bullet}$, 100%), 216 (52), 183 (17), 159 (19), 137 (21), 106 (65).



(2*RS*)-5-(1,3-Dithian-2-ylidene)-2-hydroxyhexane (3.4.1)

Aldehyde **(3.5.3)** (500 mg, 2.48 mmol) in THF was cooled to -80°C and treated with methylmagnesium bromide (0.9 mL of 3.0M solution in ether) over 15 sec. The reaction mixture was stirred for 0.5 h at -80°C before being allowed to warm to rt over 0.5 h. The reaction mixture was then poured into water and extracted with ether (2 x 75 mL) and the combined organic phases dried

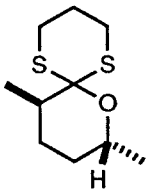
(Na_2SO_4), filtered and evaporated. The crude product was then chromatographed on silica (3cm Ø x 10 cm, 50% ether in petrol) to give alcohol **(3.4.1)** (413 mg, 1.89 mmol, 76%) as a colourless oil:

IR (film) 3372 (s), 2927 (s), 1589 (w), 1442 (s), 1276 (s), 1127 (s), 786 (m) cm^{-1};

^1H NMR (300 MHz) 3.76 (1H, tq, J = 6.1, 6.1 Hz), 2.86 (4H, t, J = 6.1 Hz), 2.53 (1H, dt, J = 13.2, 8.1 Hz), 2.33, 1H, dt, J = 13.2, 6.7 Hz), 2.17-2.06 (2H, m), 2.01 (1H, br s), 1.91 (3H, s), 1.58-1.49 (2H, m), 1.20 (3H, d, J = 6.1 Hz);

^{13}C NMR (75 MHz) 140.1 (0), 119.5 (0), 67.3 (1), 37.0 (2), 32.1 (2), 30.4 (2), 30.3 (2), 25.0 (2), 23.3 (3), 20.2 (3);

LRMS (EI mode, 70 eV): m/z = 218 ($M^{+\bullet}$, 36%), 159 (100), 119 (86), 85 (31).



(8*RS*,11*RS*)-11,8 Dimethyl-7-oxa-1,5-dithiaspiro[5.5]undecane (3.4.2)
Alcohol **(3.4.1)** (100 mg, 0.46 mmol) in DCM was cooled to 0°C before the addition of HCl in DCM (0.33 mL of 0.7M, 0.23 mmol) as a single portion. The reaction mixture was stirred for 5 min. before the addition of triethylamine (1 mL). The reaction mixture was then evaporated and chromatographed on silica (3 cm Ø x 5 cm, 10% ether in petrol) to give dithia ortho ester **(3.4.2)** (83 mg, 0.38 mmol, 83%) as a clear colourless oil:

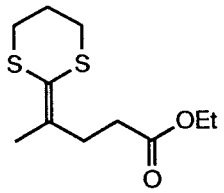
IR (film) 2928 (s), 1454 (s), 1379 (s), 1069 (s), 1002 (s), 965 (s), 801 (s) cm^{-1};

^1H NMR (300 MHz) 4.01 (1H, ddq, J = 12.7, 2.2, 6.3 Hz), 3.50 (1H, td, J = 13.2, 2.9 Hz), 2.95 (1H, td, J = 13.5, 2.6 Hz), 2.68-2.52 (2H, m), 2.14-1.30 (7H, m), 1.25 (3H, d, J = 6.3 Hz), 1.10 (3H, d, J = 6.8 Hz);

^{13}C NMR (75 MHz) 93.6 (0), 68.7 (1), 41.1 (1), 33.3 (2), 28.2 (2), 26.8 (2), 25.9 (2), 25.0 (2), 21.6 (3), 18.4 (3);

LRMS (EI mode, 70 eV): m/z = 218 ($M^{+\bullet}$, 100%), 144 (61), 106 (81), 83 (40), 55

(57), 41 (55).



Ethyl-4-(1,3-dithian-2-ylidene)pentanoate (3.5.2)

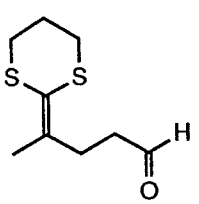
Diisopropylamine (30.4 g, 0.30 mol) in THF (360 mL) was cooled with mechanical stirring, to -80°C. *n*-butyllithium (115 mL of 2.54 M, 0.30 mol) was added over 10 min. and the solution stirred for 30 min. at -80°C. 1,3-dithiane (18.1 g, 0.150 mol) in THF (50 mL) was then added over 5 min., and the solution stirred at -80°C for 30 min. before the addition of diethyl chlorophosphate (26.1 g, 0.150 mol) in THF (50 mL) over 1 min. The internal temperature rose to -40°C and the reaction mixture stirred at this temperature for 1 h. Ethyl levulinate **(3.5.1)** (21.7 g, 0.150 mol) in THF (50 mL) was then added as a single portion. The cooling bath was then removed and the solution allowed to warm to room temperature over 1.5 h. The solution was then poured into NH_4Cl (750 mL sat. aq. solution) and the aqueous phase extracted with ether (3 x 400 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and distilled through a short path distillation apparatus (145-155°C, 0.5 mbar) to give ester **(3.5.2)** (30.69 g, 0.125 mol, 83%) as a yellow oil:

IR (film) 2979 (s), 2909 (s), 1732 (s), 1590 (w) cm^{-1};

^1H NMR (270 MHz) 4.13 (2H, q, J = 7.1Hz), 2.86 (4H, m), 2.69-2.63 (2H, m), 2.40-2.34 (2H, m), 2.15-2.06 (2H, m), 1.90 (3H, s), 1.25 (3H, t, J = 7.1 Hz);

^{13}C NMR (67.5 MHz) 173.0 (0), 137.5 (0), 121.3 (0), 60.5 (2), 32.5 (2), 31.2 (2), 30.2 (2), 30.0 (2), 24.8(2), 20.0 (3), 14.3 (3);

LRMS (EI mode, 70eV): m/z = 246 ($M^{+\bullet}$, 46%), 201 (5), 159 (100), 85 (16).



4-(1,3-Dithian-2-ylidene)-1-pentanal (3.5.3)

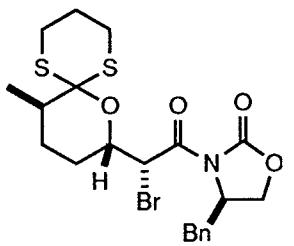
Ester **(3.5.2)** (30.69g, 0.125 mol) in DCM (500 mL) was cooled with mechanical stirring to -80°C and treated with DIBALH (102 mL of 1.5M in toluene, 0.153 mol) over 20 min. The reaction mixture was stirred at this temperature for 30 min. before being transferred *via* cannula to a rapidly stirring slurry of ice/water (500 mL) and sodium potassium tartrate (120 g). Rapid stirring was continued for 10 h. before the organic phase was separated and the aqueous phase extracted with DCM (3 x 400 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated and distilled through a short path distillation apparatus (130-134°C, 0.2 mbar) to give aldehyde **(3.5.3)** (20.20g, 0.10 mol, 80%) as a colourless oil:

IR (film) 2909 (s), 2826 (m), 2721 (m), 1721 (s), 1682 (w), 1590 (w) cm^{-1};

^1H NMR (270 MHz) 9.74 (1H, t, J = 1.7 Hz), 2.82 (4H, m), 2.66-2.54 (2H, m), 2.51-2.44 (2H, m), 2.11-2.02 (2H, m), 1.86 (3H, s);

^{13}C NMR (67.5 MHz) 201.9 (1), 137.2 (0), 121.4 (0), 42.0 (2), 30.1 (2), 30.0 (2), 28.5 (2), 24.7 (2), 20.2 (3);

LRMS (EI mode, 70 eV): m/z = 202 ($M^{+\bullet}$, 35%), 174 (10), 159 (100), 146 (54), 127 (12), 85 (23).



(8*S*,11*R*)-11-Methyl-8-((1*R*)-1-bromo-2-oxo-2-((4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl)ethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.3.6)

Oxazolidinone **(3.5.14)** (18.73 g, 0.063 mol) in ether (400 mL) was cooled to -80°C with mechanical stirring and treated with triethylamine (8.90 g, 0.088 mol) over 1 min followed by dibutyl boron triflate (18.97 g, 0.069 mol) over 1 min. The cooling bath was removed and the reaction mixture allowed to warm to rt and stir for 1.5 h. The solution was then cooled to -80°C before aldehyde **(3.5.3)** (12.70 g, 0.063 mol) in ether (30 mL) was added over 5 min. The solution was then allowed to warm to 0°C over 1.5 h and stir at 0°C for 30 min. before being poured into saturated aqueous sodium bicarbonate solution

(200 mL) and extracted with ether (3 x 400 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude oil chromatographed on silica (15 cm Ø x 20 cm, 25-30% EtOAc in petrol) to give **(3.3.5)** as a foam which cyclised on storage at -10°C. The product was then triturated with ether to give **(3.3.6)** (14.70 g, 0.029 mol, 47%) as an off-white powder:

$[\alpha]_D$ = +111.3°, (c = 0.48, $CHCl_3$); Mpt. 124-127°C;

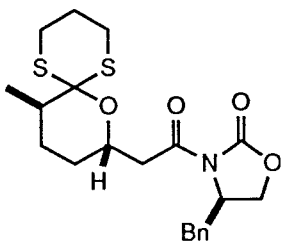
IR ($CHCl_3$) 3020 (m), 2981 (m), 2932 (m), 1785 (s), 1700 (s), 1605 (w), 1455 (m), 1384 (s), 1306 (m), 1226 (s), 1105 (m), 1066 (m), 1005 (m), 983 (m), 956 (m), 670 (w), 626 (w) cm^{-1};

^1H NMR (270 MHz) 7.40-7.23 (5H, m), 5.85 (1H, d, J = 9.1 Hz), 4.76-4.67 (1H, m), 4.50 (1H, ddd, J = 11.4, 9.1, 2.3 Hz), 4.27 (1H, dd, J = 9.6, 0.6 Hz), 4.23 (1H, dd, J = 9.6, 4.1 Hz), 3.66 (1H, td, J = 13.7, 2.5 Hz), 3.42-3.28 (2H, m overlapping signals), 2.82 (1H, dd, J = 13.5, 9.6 Hz), 2.70-2.55 (2H, m), 2.22-1.30 (7H, m), 1.17 (3H, d, J = 6.6 Hz);

^{13}C NMR (67.5 MHz) 167.4 (0), 152.4 (0), 134.8 (0), 129.5 (1), 129.1 (1), 127.5 (1), 94.0 (0), 71.8 (1), 66.3 (2), 55.4 (1), 46.2 (1), 41.7 (1), 37.0 (2), 28.4 (2), 27.2 (2), 26.5 (2), 25.7 (2), 24.8 (2), 18.2 (3);

LRMS (CI mode, NH_3): m/z = 501 ($M^{+\bullet}$, 1%), 419 (20), 314 (32), 286 (23), 230 (21), 178 (93), 137 (60), 106 (100), 91 (96), 81 (86), 41 (98);

Anal. Calcd. for $C_{21}H_{26}BrNO_4S_2$ (M = 501): C, 50.40; H, 5.24; N, 2.80; S, 12.81; Found C, 50.46; H, 5.12; N, 2.71; S, 12.68.



(8*S*,11*R*)-11-Methyl-8-(2-oxo-2-((4*R*)-4-benzyl-2-oxo-1,3-oxazolidin3-yl)ethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.4)

The α-bromo carbonyl compound **(3.3.6)** (14.60 g, 0.029 mol), zinc dust (18.69 g, 0.29 mol), ammonium chloride (6.98 g, 0.13 mol) and methanol (700 mL) were submitted to sonication in a sonic bath for 1h. The solution was then

concentrated *in vacuo* and the residue dissolved in DCM (100 mL). The resulting suspension was filtered through a pad of celite and the residue washed with DCM (3 x 100 mL). The resulting organic solution was evaporated and triturated with ether to give **(3.5.4)** (11.14 g, 0.026 mol, 91%) as a white powder which was recrystallised from acetone/ether to give the pure product **(3.5.4)** (10.10 g, 0.024 mol, 82%) as a white crystalline solid:

$[\alpha]_D$ = +56.5°, (c = 0.69, $CHCl_3$); Mpt. 148-150°C;

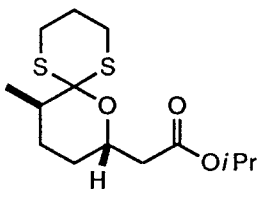
IR ($CHCl_3$) 3020 (m), 2981 (m), 2933 (m), 1783 (s), 1703 (s), 1604 (w), 1454 (m), 1388 (s), 1352 (m), 1300 (m), 1224 (s), 1100 (w), 1060 (m), 1002 (m), 986 (m), 908 (w) cm^{-1};

^1H NMR (360 MHz) 7.40-7.22 (5H, m), 4.71 (1H, m), 4.63-4.52 (1H, m), 4.23 (1H, dd, J = 9.3, 0.5 Hz), 4.17 (1H, dd, J= 16.8, 9.3 Hz), 3.47 (1H, dd, J = 17.0, 8.2 Hz), 3.31 (1H, dd, J = 13.2, 3.3 Hz), 3.53-3.35 (2H, m), 3.02 (1H, dd, J = 17.0, 4.3 Hz), 2.79 (1H, dd, J = 13.3, 9.6 Hz), 2.66-2.56 (2H, m), 2.11-1.51 (7H, m), 1.14 (3H, d, J = 6.6 Hz);

^{13}C NMR (90 MHz) 170.6 (0), 153.4 (0), 135.2 (0), 129.5 (1), 129.1 (1), 127.5 (1), 93.6 (0), 68.2 (1), 66.2 (2), 55.1(1), 41.8 (1), 41.7 (2), 38.0 (2), 31.2 (2), 27.7 (2), 26.7 (2), 25.8 (2), 24.7 (2), 18.4 (3);

LRMS (EI mode, 70 eV): m/z = 421 ($M^{+\bullet}$, 76%), 287 (93), 230 (86), 178 (48), 111 (100), 41 (65);

Anal. Calcd. for $C_{21}H_{27}NO_4S_2$ (M = 501): C, 59.53; H, 6.46; N, 3.32; S, 15.21; Found C, 59.68; H, 6.47; N, 3.28; S, 15.09.



(8*S*,11*R*)-11-Methyl-8-(*iso*propoxycarbonylmethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.5)

Oxazolidinone **(3.5.4)** (10.0 g, 0.024 mol) in THF (80 mL) at rt was treated sequentially with *iso*-propyl alcohol (72 g, 1.2 mol) and titanium (IV) *iso*-

propoxide (20.4 g, 0.072 mol) and the solution brought to reflux for 24 h. The reaction mixture was then allowed to cool and was concentrated *in vacuo*. The crude oil was then diluted with DCM (200 mL) and poured into aqueous sodium potassium tartrate solution (60 g in 400 mL) and the two phase solution stirred rapidly for 30 min. The organic phase was then separated and the aqueous phase extracted with DCM (3 x 200 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated and the crude product chromatographed on silica (7 cm Ø x 15 cm, 20% ether in petrol) to give the *iso*-propyl ester **(3.5.5)** (6.5 g, 0.021 mol, 89%) as a colourless oil:

$[\alpha]_D$ = +124.3°, (c = 0.37, $CHCl_3$)

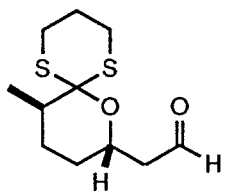
IR (film) 2976 (m), 2929 (s), 1731 (s), 1454 (w), 1383 (w), 1287 (m), 1108 (m), 1002 (m) cm^{-1}

^1H NMR (270 MHz) 5.03 (1H, septet, J = 6.3 Hz), 4.43 (1H, dddd, J = 11.4, 9.3, 3.6, 2.3 Hz), 3.42 (1H, ddd, J = 13.9, 12.8, 2.9 Hz), 3.24 (1H, ddd, J = 14.1, 12.7, 2.9 Hz), 2.62 (1H, dd, J = 15.5, 9.3 Hz), 2.66-2.52 (2H, m), 2.43 (1H, dd, J = 15.5, 3.6 Hz), 2.12-1.30 (7H, m), 1.26 (3H, d, J = 6.3 Hz), 1.25 (3H, d, J = 6.3 Hz), 1.12 (3H, d, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 171.0 (0), 93.2 (0), 69.1 (1), 67.9 (1), 41.7 (1), 41.3 (2), 31.2 (2), 27.6 (2), 26.6 (2), 25.7 (2), 24.6 (2), 22.0 (3), 21.9 (3), 18.4 (3);

LRMS (CI mode, NH_3): m/z = 304 ($(M+NH_4)^{+\bullet}$, 3%), $(M+H)^{+\bullet}$ (100), 199 (6), 106 (5), 35 (35);

HRMS (CI mode, NH_3) Found $(M+1)^{+\bullet}$, 305.1245. $C_{14}H_{24}O_3S_2$+H requires M, 305.1242.



(8*S*,11*R*)-11-Methyl-8-(2-oxoethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.6) Ester **(3.5.5)** (6.35 g, 0.021 mol) in DCM (200 mL) was cooled to -80°C and treated with DIBALH (15.3 mL of 1.5 M solution in toluene, 0.023 mol) over 10 min. The solution was strried at -80°C for 30 min before being transferred

via cannula to a rapidly mechanically stirred slurry of sodium potassium tartrate (14.5 g, 0.069 mol) in ice/water (400 mL). Rapid stirring was continued for 4h. The organic phase was then separated and the aqueous phase extracted with DCM (3 x 200 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was chromatographed on silica (7 cm Ø x 10 cm, 25% ether in petrol) to give aldehyde **(3.5.6)** (4.57 g, 0.019 mol, 88%) as a clear colourless oil:

$[\alpha]_D$= +112.1°, (c = 1.16, $CHCl_3$);

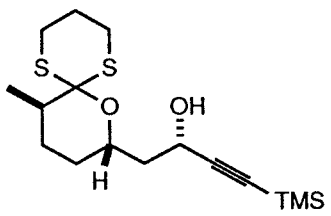
IR (film) 2929 (s), 2828 (w), 1726 (s), 1453 (m), 1433 (m), 1380 (m), 1278 (m), 1236 (w), 1189 (w), 1106 (w), 1067 (m), 1002 (m), 968 (m), 907 (m), 800 (m) cm^{-1};

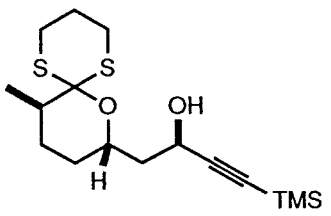
^1H NMR (270 MHz) 9.88 (1H, dd, J = 2.3, 1.5 Hz), 4.60-4.45 (1H, m), 3.37 (1H, ddd, J = 13.5, 12.7, 2.5, Hz), 3.07 (1H, ddd, J = 13.7, 13.0, 2.3 Hz), 2.83 (1H, ddd, J = 16.6, 9.1, 2.3 Hz), 2.63 (1H, dt, J = 13.7, 3.8 Hz), 2.52 (1H, ddd, J = 16.6, 3.7, 1.6 Hz), 1.98-1.44 (7H, m), 1.13 (3H, d, J = 6.4 Hz);

^{13}C NMR (67.5 MHz) 200.8 (1), 93.6 (0), 67.6 (1), 49.5 (2), 41.8 (1), 31.5 (2), 27.7 (2), 26.7 (2), 25.7 (2), 25.1 (2), 18.5 (3);

LRMS (CI mode, NH_3): m/z = 246 ($(M+H)^{+\bullet}$, 100%), 218 (4), 35 (38);

HRMS (CI mode, NH_3): Found $(M+1)^{+\bullet}$, 247.0824. $C_{11}H_{18}O_2S_2$+H requires M, 247.0827.





(8*S*,11*R*)-11-Methyl-8-((2*S*)-4-trimethylsilyl-2-hydroxy-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.8)
(8*S*,11*R*)-11-Methyl-8-((2*R*)-4-trimethylsilyl-2-hydroxy-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.7)

TMS acetylene (2.51 g, 0.026 mol) in THF (40 mL) was cooled to -80°C and subsequently treated with MeMgBr (8.0 mL of 3.0 M solution in ether, 0.024 mol) over 2 min. The cooling bath was then removed and the solution

allowed to warm to rt and was then heated to reflux for 2 h. and then allowed to cool to rt. In a separate flask aldehyde **(3.5.6)** (4.20 g, 0.0171 mol) in THF (80 mL) was cooled to -80°C under nitrogen with magnetic stirring and treated with TMS acetylene magnesium bromide (40 mL of the solution prepared above). The solution was stirred at -80°C for 30 min. and then the cooling bath removed and the solution allowed to warm to -10°C before being quenched by the addition of NH_4Cl (100 mL sat. aq. soltion). The aqueous phase was separated and extracted with ether (3 x 150 mL), and the combined organic phases dried ($MgSO_4$), filtered, evaporated and chromatographed on silica (7 cm Ø x 10 cm, 10-25% ether in petrol) to give the (*R*) alcohol **(3.5.7)** (1.38 g, 4.0 mmol, 24%):

$[\alpha]_D$= +149.4°, (c = 0.50, $CHCl_3$);

IR (film) 3455 (br m), 2957 (s), 2170 (w), 1454 (w), 1423 (w), 1379 (w), 1249 (m), 1061 (m), 842 (s) cm^{-1};

^1H NMR (300 MHz) 4.68 (1H, td, J = 7.2, 3.1 Hz), 4.42 (1H, tt, J = 10.6, 2.7 Hz), 3.35 (1H, ddd, J = 13.7, 12.5, 2.7 Hz), 3.25 (1H, ddd, J = 13.8, 12.5, 2.7 Hz), 3.00 (1H, d, J = 7.2 Hz), 2.72-2.50 (2H, m), 2.16-1.40 (9H, m), 1.13 (3H, d, 6.8 Hz), 0.14 (9H, s);

^{13}C NMR (75 MHz) 106.7 (0), 93.6 (0), 89.6 (0), 69.8 (1), 60.5 (1), 42.8 (2), 42.1 (1), 31.7 (2), 27.7 (2), 27.0 (2), 25.6 (2), 25.0 (2), 18.7 (3), 0.0 (3);

LRMS (EI mode, 70 eV): m/z = 344 ($M^{+\bullet}$, 25%), 237 (100), 221 (21), 159 (47), 106 (70), 73 (59), 55 (33), 41 (45);

and the (*S*) alcohol **(3.5.8)** (3.37 g, 9.8 mmol, 58%) as clear colourless oils:

$[\alpha]_D$= +296.7°, (c = 0.87, $CHCl_3$);

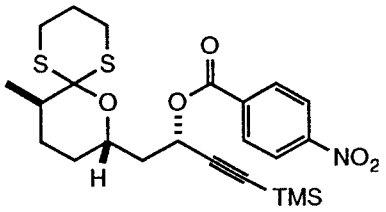
IR (film) 3604 (w), 3481 (br w), 2962 (s), 2933 (s), 2173 (w), 1455 (w), 1426 (w), 1381 (w), 1252 (s), 1050 (m), 999 (m), 908 (m), 846 (m);

^1H NMR (270 MHz) 4.79 (1H, dd, J = 7.9, 6.6 Hz), 4.21 (1H, ddt, J = 11.2, 10.3, 2.7 Hz), 3.38 (1H, ddd, J = 13.7, 12.6, 2.7 Hz), 3.12 (1H, ddd, J = 13.9, 12.7, 2.7 Hz),

2.71-2.51 (2H, m), 2.45 (1H, br s), 2.20-1.40 (9H, m), 1.13 (3H, d, J = 6.8 Hz), 0.17 (9H, s);

^{13}C NMR (67.5 MHz) 106.2 (0), 93.4 (0), 90.2 (0), 70.7 (1), 61.2 (1), 43.8 (2), 42.0 (1), 31.8 (2), 27.7 (2), 26.8 (2), 25.6 (2), 25.2 (2), 18.6 (3), 0.0 (3);

LRMS (EI mode, 70 eV): m/z = 344 ($M^{+\bullet}$, 30%), 237 (100), 221 (26), 159 (39), 106 (59), 73 (52), 41 (35).



(8*S*,11*R*)-11-Methyl-8-((2*S*)-4-trimethylsilyl-2-(4-nitrobenzoyloxy)-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.15)

A solution of triphenylphosphine (1.011 g, 3.86 mmol), 4-nitrobenzoic acid (645 mg, 3.86 mmol) and (*R*) alcohol **(3.5.7)** (1.107 g, 3.22 mmol) in THF (30 mL) was treated with DEAD (672 mg, 3.86 mmol) in THF (10 mL). The reaction mixture was allowed to stir at rt for 15h before the addition of silica (20 mL). The reaction mixture was then concentrated *in vacuo* and chromatographed on silica (7 cm Ø x 15 cm, 20% ether in petrol) to give (*S*) ester **(3.5.15)** (1.407 g, 2.85 mmol, 89%) as a yellow oil:

$[\alpha]_D$= +111.3°, (c = 0.48, $CHCl_3$);

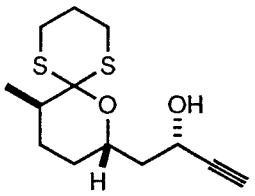
IR (film) 2961 (m), 2934 (m), 1729 (s), 1608 (w), 1531 (s), 1351 (m), 1276 (s), 1101 (m), 848 (s) cm^{-1};

^1H NMR (270 MHz) 8.33-8.20 (4H, m), 5.95 (1H, dd, J = 10.6, 4.8 Hz), 4.29 (1H, tt, J = 10.0, 2.7 Hz), 3.50 (1H, td, J = 12.9, 2.5 Hz), 3.20 (1H, td, J = 12.9, 2.5 Hz), 2.72-2.52 (2H, m), 2.30-1.40 (9H, m), 1.13 (3H, d, J = 6.6 Hz), 0.17 (9H, s);

^{13}C NMR (67.5 MHz) 163.5 (0), 150.8 (0), 135.5 (0), 131.1 (1), 123.7 (1), 101.6 (0), 93.3 (0), 92.7 (0), 69.0 (1), 63.8 (1), 42.1 (1), 41.2 (2), 31.8 (2), 27.7 (2), 26.9 (2), 25.7 (2), 25.5 (2), 18.6 (3), -0.1 (3);

LRMS (EI mode, 70 eV): m/z = 493 ($M^{+\bullet}$, 70%), 359 (38), 269 (23), 224 (33), 209

(32), 150 (100), 120 (25), 106 (92), 73 (75), 41 (31).



(8*S*,11*R*)-11-Methyl-8-((2*S*)-2-hydroxy-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.9)

(*S*) ester **(3.5.15)** (1.307 g, 2.65 mmol) in ethanol (20 mL) at rt,was treated with sodium hydroxide (233 mg, 5.83 mmol) in water (10 mL) over 5 min and the recation mixture stirred for 1h. The reaction mixture was then evaporated and partitioned between DCM (50 mL) and water (100 mL). The aqueous phase was then extracted with DCM (4 x 40 mL) and the combined organic phases dried ($MgSO_4$), filtered, evaporated and the crude product chromatographed (3 cm Ø x 5 cm, 50% ether in petrol) to give (*S*) alcohol **(3.5.9)** (692 mg, 2.54 mmol, 96%) as a clear colourless oil:

$[\alpha]_D$= +168.8°, (c = 0.75, $CHCl_3$);

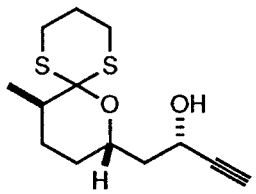
IR (film) 3287 (s), 2918 (s), 2112 (w), 1454 (m), 1379 (m), 1277 (m), 1100 (m), 999 (m), 907 (m), 800 (m) cm^{-1};

^1H NMR (300 MHz) 4.69 (1H, ddd, J = 8.4, 6.5, 2.1 Hz), 4.17 (1H, tt, J = 10.5, 2.7 Hz), 3.35 (1H, td, J = 13.4, 2.5 Hz), 3.05 (1H, ddd, J = 13.8, 12.7, 2.8 Hz), 2.90 (1H, br s), 2.68-2.51 (2H, m), 2.49 (1H, d, J = 2.1 Hz), 2.17-1.35 (9H, m), 1.09 (3H, d, J = 6.7 Hz);

^{13}C NMR (75 MHz) 93.5 (0), 84.5 (0), 73.6 (1), 70.6 (1), 60.6 (1), 43.7 (2), 42.0 (1), 31.7 (2), 27.6 (2), 26.8 (2), 25.5 (2), 25.0 (2), 18.6 (3);

LRMS (EI mode, 70 eV): m/z = 272 ($M^{+\bullet}$, 22%), 199 (25), 165 (36), 106 (100), 55 (55), 41 (73);

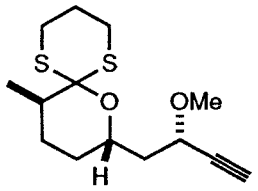
HRMS (EI mode, 70 eV): Found $(M)^{+\bullet}$ 272.0905. $C_{13}H_{20}O_2S_2$ requires M, 272.0890.



(8*S*,11*R*)-11-Methyl-8-((2*S*)-2-hydroxy-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.9)

Silyl acetylene **(3.5.8)** (3.162 g, 9.19 mmol) in THF (30 mL) was cooled to 0°C and treated with TBAF (8.8 mL of 1.1 M solution in THF) over 5 min and the solution stirred for 10 min. Silica (20 mL) was then added and the reaction mixture concentrated *in vacuo* and chromatographed on silica (3cm Ø x 15 cm, 60% ether in petrol) to give (*S*) alcohol **(3.5.9)** (2.19 g, 8.06 mmol, 88%) as a clear colourless oil:

DATA AS REPORTED ABOVE



(8*S*,11*R*)-11-Methyl-8-((2*S*)-2-methoxy-3-butynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.10)

(*S*) alcohol **(3.5.9)** (2.800 g, 10.3 mmol) in THF (40 mL) was treated with sodium hydride (617 mg of 60% dispersion in mineral oil = 370 mg of NaH, 15.4 mmol) as a single portion. The reaction mixture was then gently warmed until effervesence occurred, the solution was then cooled to 0°C and treated with methyl iodide (1.61 g, 11.3 mmol) and the solution allowed to warm to rt and stir for 1.5 h. The reaction mixture was quenched by the dropwise addition of methanol (5 mL) followed by silica (20 mL). The solution was then concentrated *in vacuo* and chromatographed on silica (5 cm Ø x 12 cm, 0-10% ether in petrol) to give a white solid that was crystallised from EtOAc/petrol to give propargylic ether **(3.5.10)** (2.436 g, 8.51 mmol, 83%) as white crystals:

$[\alpha]_D$= +172.5°, (c = 0.48, $CHCl_3$); Mpt. 91-92°C;

IR ($CHCl_3$) 3305 (w), 2932 (m), 2253 (s), 1793 (w), 1709 (w), 1643 (w), 1455 (m), 1381 (m), 1096 (m), 1000 (m), 800 (w) cm^{-1};

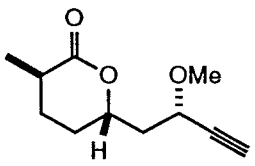
^1H NMR (270 MHz) 4.25 (1H, ddd, J = 9.9, 5.2, 2.1 Hz), 4.25-4.14 (1H, m), 3.42

(3H, s), 3.50-3.37 (1H, m), 3.12 (1H, ddd, J = 13.8, 12.8, 2.8 Hz), 2.70-2.52 (2H, m), 2.49 (1H, d, 2.1 Hz), 2.20-1.40 (9H, m), 1.12 (3H, d, J = 6.6 Hz);

^{13}C NMR (67.5 MHz) 93.4 (0), 82.5 (0), 74.9 (1), 69.3 (1), 68.8 (1), 56.7 (3), 42.2 (1), 41.8 (2), 31.8 (2), 27.8 (2), 26.9 (2), 25.8 (2), 25.2 (2), 18.6 (3);

LRMS (CI mode, NH_3): m/z = 286 ($(M+H)^{+\bullet}$,100%), 35 (47);

HRMS (CI mode, NH_3): Found $(M+1)^{+\bullet}$ 287.1139. $C_{14}H_{22}O_2S_2$+H requires M, 287.1133.



(3*R*,6*S*)-6-((2*S*)-2-Methoxy-3-butynyl)-3-methyloxan-2-one (3.5.11)
Propargylic ether **(3.5.10)** (2.322 g, 8.12 mmol) in ether (70 mL) was treated with sodium hydrogen carbonate (1.64 g, 19.49 mmol) in water (35 mL). The two phase reaction mixture was then rapidly stirred and treated with iodine (2.06 g, 8.12 mmol) in ether (35 mL) over 10 min. The solution was then gently warmed until the ether phase refluxed. Refluxing was continued for 30 min until the iodine colour faded. The reaction mixture was then cooled to rt and saturated aqueous sodium thiosulphate solution (50 mL) added and stirring continued until the residual iodine colour disappeared. The aqueous phase was then extracted with ether (5 x 200 mL) and the combined organic phases dried (Na_2SO_4), filtered, concentrated *in vacuo* and the crude product chromatographed on silica (5 cm Ø x 10 cm, 10-40% ether in petrol) to give lactone **(3.5.11)** (1.505 g, 7.68 mmol, 95%) as an off-white foam that crystallised from ether to give white crystals:

$[\alpha]_D$= +29.7°, (c = 0.33, $CHCl_3$); Mpt. 74-75°C;

IR ($CHCl_3$) 3305 (w), 3018 (m), 2935 (w), 1723 (s), 1460 (w), 1380 (w), 1330 (w), 1242 (w), 1175 (m), 1087 (s), 1017 (w), 934 (w) cm^{-1};

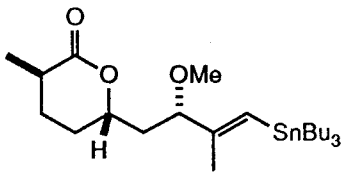
^1H NMR (270 MHz) 4.58-4.46 (1H, m), 4.23 (1H, ddd, J = 8.9, 5.6, 2.1 Hz), 3.38 (3H, s), 2.47 (1H, d, J = 2.1 Hz), 2.47-2.35 (1H, m), 2.12 (1H, ddd, J = 14.0, 8.7, 5.6 Hz), 2.05-1.91 (2H, m), 1.87 (1H, ddd, J = 14.0, 8.9, 4.2 Hz), 1.72-1.57 (2H, m), 1.27

(3H, d, J = 7.2 Hz);

^{13}C NMR (67.5 MHz) 174.1 (0), 81.7 (0), 78.7 (1), 75.1 (1), 67.9 (1), 56.7 (3), 42.0 (2), 36.2 (1), 29.5 (2), 28.5 (2), 17.5 (3);

LRMS (CI mode): m/z = 196 ($(M+NH_4)^{+\bullet}$, 100%), $(M+H)^{+\bullet}$ (40), 167 (12), 69 (7), 35 (14);

Anal. Calcd. for $C_{11}H_{16}O_3$ (M = 196): C, 67.32; H, 8.21; Found C, 67.39; H 8.43.



(3*R*,6*S*)-6-[(2*S*,3*E*)-4-(Tri-*n*-butylstannyl)-3-methyl-2-methoxy-3-butenyl]-3-methyloxan-2-one (3.5.12)

Copper (I) cyanide (91 mg, 1.02 mmol) in THF (5 mL) was cooled to -80°C and treated with *n*-butllithium (1.4 mL of 1.45 M solution in hexanes, 2.04 mmol) over 10 s. The reaction mixture was then warmed slightly to enable dissolution and recooled to -80°C. Tributyltin hydride (549 mg, 2.04 mmol) was then added over 15 s and stirred at -80°C for 15 min before lactone **(3.5.11)** (100 mg, 0.51 mmol) in THF (2 mL) was added to the bright yellow solution. The reaction mixture was stirred at -80°C for 30 min before HMPA (366 mg, 2.04 mmol) was added over 10 s. The solution was stirred for a further 30 min. at -80°C before the addition of methyl iodide (724 mg, 5.1 mmol) as a single portion. The brown solution was then allowed to warm to rt over 16 h. before being poured into NH_4Cl (10 mL sat. aq. solution) and stirred for 15 min. The aqueous phase was then separated and extracted with ether (4 x 20 mL), and the combined organic phases dried (Na_2SO_4), filtered, evaporated and the crude product chromatographed on silica (3 cm Ø x 5 cm, 20% ether in petrol) to give vinyl stannane **(3.5.12)** (124 mg, 0.25 mmol, 49%) as a clear colourless oil:

$[\alpha]_D$= +16.0°, (c = 0.55, $CHCl_3$);

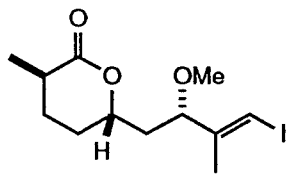
IR (film) 2926 (s), 1735 (s), 1608 (w), 1459 (m), 1241 (m), 1174 (m), 1088 (s), 1017 (m) cm^{-1};

^{1}H NMR (270 MHz) 5.83 (1H, s, J_{SnH} = 58.4 Hz), 4.36-4.24 (1H, m), 3.82 (1H, t, J = 7.0 Hz), 3.17 (3H, s), 2.45 (1H, ddq, J = 11.2, 6.7, 6.7 Hz), 2.04 (1H, ddd, J = 14.1, 14.1, 7.0 Hz), 2.06-1.85 (2H, m), 1.66 (3H, s), 1.29 (3H, d, J = 6.7 Hz), 1.75-1.20 (15H, m), 0.96-0.84 (15H, m);

^{13}C NMR (75 MHz) 174.4 (0), 151.9 (0), 128.5 (1), 85.0 (1), 79.2 (1), 55.9 (3), 40.3 (2), 36.2 (1), 29.4 (2), 29.3 (2), 28.6 (2), 27.4 (2), 18.2 (3), 17.6 (3), 13.8 (3), 10.2 (2);

LRMS (CI mode, NH_3): m/z = 502 ($(M+H)^{+\bullet}$, 100%), 489 (10), 445 (14), 308 (28), 230 (77), 213 (40), 85 (16), 72 (14).

HRMS (CI mode, NH_3): Found $(M+1)^{+\bullet}$, 503.2599. $C_{24}H_{46}O_3Sn$+H requires M, 503.2547.



(3*R*,6*S*)-6-[(2*S*,3*E*)-4-Iodo-3-methyl-2-methoxy-3-butenyl]-3-methyloxan-2-one (2.2.1)

Vinyl stannane **(3.5.12)** (124 mg, 0.25 mmol) in ether (3 mL) was cooled to 0°C. Iodine (63.5 mg, 0.25 mmol) in ether (1 mL) was then added over 1 min. The reaction mixture was then stirred for 2 min before the addition of saturated aqueous sodium thiosulphate solution (5 mL), the two phase solution was then stirred for 5 min before the aqueous phase was separated and extracted with ether (3 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed on silica (2 cm Ø x 5 cm, 10-40% ether in petrol) to give vinyl iodide **(2.2.1)** (77.0 mg, 0.23 mmol, 91%) as a pale yellow oil:

$[\alpha]_D$= +45.9°, (c = 0.95, $CHCl_3$);

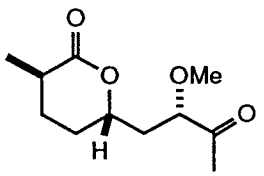
IR (film) 2929 (s), 1732 (s), 1615 (w), 1460 (m), 1377 (m), 1241 (m), 1173 (m), 1088 (s), 1011 (m) cm^{-1};

^{1}H NMR (270 MHz), 6.33 (1H, s), 4.20 (1H, ddt, J = 10.0, 6.6, 3.1 Hz), 3.98 (1H, dd, J = 7.2, 6.0 Hz), 3.18 (3H, s), 2.44 (1H, ddq, J = 11.5, 6.8, 6.8 Hz), 1.74 (3H, s), 2.07-1.46 (6H, m), 1.29 (3H, d, J = 6.8 Hz);

^{13}C NMR (75 MHz) 174.0 (0), 146.6 (0), 81.8 (1), 80.7 (1), 78.3 (1), 56.2 (3), 41.1 (2), 36.1 (1), 29.2 (2), 28.3 (2), 18.3 (3), 17.4 (3);

LRMS (CI mode, NH_3): m/z = 338 ($(M+NH_4)^{+\bullet}$, 95%), $(M)^{+\bullet}$ (7), 324 (12), 307 (12), 230 (100), 211 (82), 200 (32), 181 (61), 144 (31), 58 (31), 52 (28), 44 (81);

HRMS (CI mode, NH_3): Found $(M+NH_4)^{+\bullet}$, 356.0709. $C_{12}H_{19}O_3+NH_4$ requires M, 356.0723.



(3*R*,6*S*)-6-[(2*S*)-3-Oxo-2-methoxybutanyl]-3-methyloxan-2-one (3.8.1)
A solution of dithia ortho ester **(3.5.10)** (100 mg, 0.35 mmol) in acetonitrile (6.7 mL), THF (1.3 mL) and pH 7 buffer (0.67 mL), was treated with mercury (II) chloride (239 mg, 0.88 mmol) as a single portion and stirred at rt for 15 min. The reaction mixture was then filtered through Celite. The resulting solution was then poured into pH 7 buffer and extracted with ether (5 x 15 mL), dried ($MgSO_4$), filtered, evaporated and the residue chromatographed on silica (2 cm Ø x 2.5 cm, 25% EtOAc in petrol) to give lactone **(3.8.1)** (28.1 mg, 0.14 mmol, 41%) as a yellow oil:

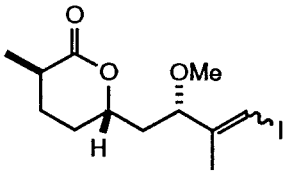
IR ($CHCl_3$) 3019 (s), 2937 (w), 1723 (s), 1459 (w), 1355 (w), 1224 (m), 1091 (m), 788 (m) cm^{-1};

^1H NMR (270 MHz) 4.51-4.40 (1H, m), 3.78 (1H, t, J = 6.6 Hz), 3.37 (3H, s), 2.42 (1H, ddq, J = 11.5, 7.1, 7.1 Hz), 2.23 (3H, s), 2.14-1.87 (4H, m), 1.74-1.45 (2H, m), 1.28 (3H, d, J = 7.1 Hz);

^{13}C NMR (67.5 MHz) 210.6 (0), 173.9 (0), 83.2 (1), 78.0 (1), 58.2 (3), 37.7 (2), 36.2 (1), 29.5 (2), 29.1 (2), 25.8 (3), 17.5 (3);

LRMS (CI mode, NH_3): m/z = 214 ($(M+NH_4)^{+\bullet}$, 50%), $(M+H)^{+\bullet}$ (67), 35 (100);

HRMS (CI mode, NH_3): Found $M^{+\bullet}$, 215.1278. $C_{11}H_{18}O_4$ requires M, 215.1283.



(3*R*,6*S*)-6-[(2*S*,3*EZ*)-4-Iodo-3-methyl-2-methoxy-3-butenyl]-3-methyloxan-2-one (3.8.2)

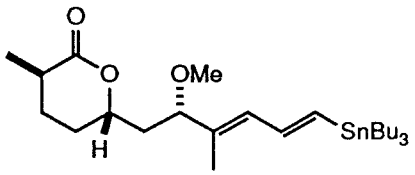
To a stirred suspension of chromium (II) chloride (55 mg, 0.45 mmol) in THF (1 mL) was treated at rt with a solution of iodoform (59 mg, 0.15 mmol) and ketone **(3.8.1)** (16 mg, 0.075 mmol) in THF (1.5 mL) as a single portion. The reaction mixture was stirred for 4 h and then brought to reflux for 16 h. The solution was then allowed to cool before being poured into water and extracted with ether (3 x 20 mL), dried (Na_2SO_4), filtered, evaporated and the residue chromatographed on silica (2 cm Ø x 2.5 cm, 25% EtOAc in petrol) to give vinyl iodide **(3.8.2)** (9.2 mg, 0.027 mmol, 36%) as an inseparable 3 : 2 (*Z* : *E*) mixture of geometric isomers:

DATA AS REPORTED ABOVE FOR *E* ISOMER

Z isomer

^{1}H NMR (270 MHz) 6.17 (1H, m), 4.49-4.38 (1H, m), 4.31 (1H, dd, J = 8.7, 5.0 Hz), 3.22 (3H, s), 2.52-2.37 (1H, m), 2.20-1.55 (6H, m), 1.80 (3H, d, J = 1.3 Hz), 1.33 (3H, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 174.0 (0), 145.5 (0), 81.1 (1), 78.8 (1), 77.7 (1), 56.5 (3), 39.9 (2), 36.3 (1), 28.9 (2), 28.3 (2), 18.3 (3), 17.6 (3).



(3*R*,6*S*)-6-[(2*S*,3*E*,5*E*)-6-(Tri-*n*-butylstannyl)-3-methyl-2-methoxy-3,5-hexadienyl]-3-methyloxan-2-one (5.8.1)

A solution of vinyl iodide **(2.2.1)** (34 mg, 0.10 mmol) and tri-(2-furyl) phosphine (4.7 mg, 0.02 mmol) in THF (1 mL) magnetically stirring over 4Å molecular sieves (245 mg) at rt was degassed with a slow stream of argon for 10 min. *Tris*-dibenzylideneacetone palladium (0) (5.2 mg, 0.005 mmol) was then added under a purge of argon and the purple solution turned yellow over 10 min. *E*-1,2-di(tributyltin)ethene (121 mg, 0.20 mmol) in N-methylpyrolidinone (1 mL) and THF (0.5 mL) was added as a single portion

and the reaction mixture protected from light with aluminium foil. Stirring at rt was continued for 5 h before the THF was removed *in vacuo* and the residual reaction mixture chromatographed on silica (2 cm Ø x 10 cm, 10-25% ether in petrol) to give recovered vinyl iodide **(2.2.1)** (3.6 mg, 0.011 mmol) dienyl stannane **(5.8.1)** (21 mg, 0.040 mmol, 40%), (44% based on recovered starting material) as a clear colourless oil:

$[\alpha]_D$= +42.7°, (c = 1.05, $CHCl_3$);

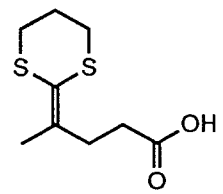
IR ($CHCl_3$) 3011 (m), 2957 (s), 2929 (s), 2872 (m), 1720 (s), 1462 (m), 1379 (m), 1178 (m), 1081 (s), 990 (w) cm^{-1};

^1H NMR (270 MHz), 6.78 (1H, dd, J = 18.5, 10.2, J_{SnH} = 57.0 Hz), 6.30 (1H, d, J = 18.5, J_{SnH} = 69.8 Hz), 6.07 (1H, dbr, J = 10.2, J_{SnH} = 68.8 Hz), 4.34-4.22 (1H, m), 3.78 (1H, t, J = 7.2 Hz), 3.18 (3H, s), 2.44 (1H, ddq, J = 11.3, 6.5, 6.5 Hz), 2.12-1.88 (3H, m), 1.72 (3H, d, J = 1.2 Hz), 1.30 (3H, d, J = 6.5 Hz), 1.79-1.24 (15H, m), 1.06-0.80 (15H, m);

^{13}C NMR (67.5 MHz) 174.4 (0), 142.2 (1), 135.6 (1), 134.5 (0), 132.4 (1), 83.0 (1), 79.0 (1), 56.1 (3), 40.2 (2), 36.3 (1), 29.4 (2), 29.3 (2), 28.5 (2), 27.5 (20), 17.6 (1), 13.9 (3), 11.1 (3), 9.7 (2);

LRMS (CI mode, NH_3): m/z = 528 $(M+H)^{+\bullet}$, 62%), 308 (51), 256 (46), 224 (100), 207 (26);

HRMS (CI mode, NH_3): Found $(M+1)^{+\bullet}$, 529.2707. $C_{26}H_{48}O_3Sn$+H requires M, 529.2704.



4-(1,3-Dithi-2-ylidene)pentanoic acid (4.1.1)

Ester **(3.5.2)** (1.00 g, 4.1 mmol) in ethanol (7 mL) at rt was treated dropwise over 5 min. with a solution of sodium hydroxide (365 mg, 9.1 mmol) in water (3 mL). The solution was stirred at rt for 16 h before being concentrated under reduced pressure and then poured into hydrochloric acid (50 mL of 1M aqueous solution). The aqueous phase was then extracted with ethyl acetate (3

x 70 mL). The combined organic phases were then dried ($MgSO_4$), filtered and evaporated to yield **(4.1.1)** as a yellow oil (0.82 g, 3.8 mmol, 92%) that was pure by ^{1}HNMR. When the above procedure was repeated on larger scale (67 mmol) the product was isolated as a solid and subsequently recrystallised from ether / petrol to yield **(4.1.1)** as a white solid:

Mpt. 75-76°C:

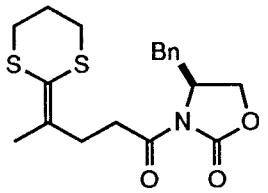
IR ($CHBr_3$) 3092 (m), 2985 (m), 2909 (m), 1705 (s), 1423 (m), 1300 (w), 1276 (w), 912 (w) cm^{-1};

^{1}H NMR (250 MHz) 2.88 (4H, m), 2.73-2.64 (2H, m), 2.48-2.38 (2H, m), 2.18-2.06 (2H, m), 1.91 (3H, s);

^{13}C NMR (75 MHz) 179.5 (0), 136.9 (0), 121.7 (0), 32.3 (2), 30.8 (2), 30.1 (2), 29.9 (2), 24.7 (2), 20.0 (3);

LRMS (EI mode, 70 eV): m/z = 218 ($M^{+\bullet}$, 47%), 159 (100), 85 (23);

Anal. Calcd. for $C_9H_{14}OS_2$: C, 49.50; H, 6.40; Found C, 49.27; H, 6.66.



(4*S*)-*N*-[4-(1,3-Dithian-2-ylidene)-pentanoyl]-4-benzyl-1,3-oxazolidin-2-one (4.1.3)

Sodium hydride (1.80g of 60% dispersion in mineral oil = 1.08g of sodium hydride, 0.045 mol) suspended in THF (20 mL) at rt was treated with the acid **(4.1.1)** (8.91 g, 41 mmol) in THF (20 mL) over 10 min. The solution was then stirred at rt for 15 min before being concentrated under reduced pressure and subsequently stored under vacuum (*ca.* 0.4 mbar) for 1 h to yield an off-white solid. The solid was then suspended in toluene (30 mL) at rt and treated with oxalyl chloride (5.7 g, 3.9 mL, 45 mmol) over 15 min. The solution was then stirred at rt for 2 h before being concentrated under reduced pressure and stored under vacuum (0.4 mbar) for 1h to yield the crude acid chloride **(4.1.2)**.

(4*S*)-4-benzyl oxazolidinone (7.26 g, 41 mmol) in THF (90 mL) was

cooled to -78°C and the solution treated with *n*-butyllithium (17.2 mL of 2.5M solution in hexanes, 43 mmol) at such a rate that the internal temperature did not rise above -65°C. The acid chloride in THF (40 mL) was then added dropwise at such a rate that the internal temperature did not rise above -70°C. The solution was then stirred at -70°C for 20 min. before the cooling bath was removed and the solution allowed to warm to rt and stir for a further 10 min. The solution was then poured into NH_4Cl (150 mL sat. aq. solution) and extracted with ether (3 x 100 mL). The combined organic phases were then dried ($MgSO_4$), filtered, evaporated and the brown oil chromatographed on silica (7 cm Ø x 13 cm, 20% EtOAc in petrol) to yield **(4.1.3)** as an off-white solid (8.71 g, 23 mmol, 56%) that was recrystallised from EtOAc / petrol to yield a white crystalline solid:

$[\alpha]_D$= +33.3°, (c = 0.27, $CHCl_3$); Mpt. 88-91°C:

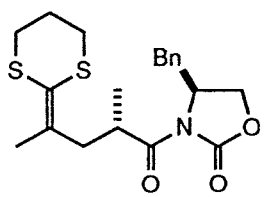
IR ($CHBr_3$) 2912 (w), 1778 (s), 1697 (s), 1453 (w), 1383 (s), 1350 (m), 1275 (w), 1210 (m), 1049 (w), 746 (w) cm^{-1};

^1H NMR (250 MHz) 7.40-7.18 (5H, m), 4.65 (1H, ddt, J= 6.4, 9.6, 3.3 Hz), 4.22 (1H, t, J= 9.0 Hz), 4.12 (1H, dd, J= 9.0, 3.3 Hz), 3.31 (1H, dd, J= 13.5, 3.3 Hz), 3.10-2.95 (2H, m), 2.92-2.80 (4H, m), 2.80-2.65 (3H, m), 2.20-2.04 (2H, m), 1.95 (3H, s);

^{13}C NMR (62.5 MHz) 172.4 (0), 153.4 (0), 137.2 (0), 135.3 (0), 129.4 (1), 128.9 (1), 127.3 (1), 121.6 (1), 66.2 (2), 55.2 (1), 37.8 (2), 33.7 (2), 30.5 (2), 30.1 (2), 29.9 (2), 24.7 (2), 20.1 (3);

LRMS (CI mode, NH_3): m/z = 377 $(M+NH_4)^{+\bullet}$ (10%), $(M+H)^{+\bullet}$, (100);

Anal. Calcd. for $C_{19}H_{23}NO_3S_2$: C, 60.40; H, 6.10; N, 3.70; Found C, 60.53; H 6.18; N, 3.70.



(4*S*)-*N*-[(2*S*)-4-(1,3-Dithian-2-ylidene)-2-methyl-pentanoyl]-4-benzyl-1,3-oxazolidin-2-one (4.1.4)

Substrate **(4.1.3)** (8.71g, 23 mmol) in THF (80 mL) was cooled to -72°C before

the addition of sodium *bis*(trimethylsilyl)amide (35 mL of 1.0 M solution in THF, 35 mmol) over 15 min. The solution was then stirred for 1 h at -72°C before methyl iodide (16.3 g, 7.2 mL, 115 mmol) over 5 min. and the solution stirred at -74°C for 4 h. The reaction mixture was then poured into NH_4Cl (200 mL sat. aq. solution) and extracted with ether (3 x 150 mL). The combined organic phases were then dried ($MgSO_4$), filtered and evaporated. The crude oil was then chromatographed on flash silica (7 cm Ø x 10 cm, 20% EtOAc in petrol) to give **(4.1.4)** as a viscous yellow oil (7.60 g, 19 mmol, 85%):

$[\alpha]_D$= +64.9°, (c = 1.10, $CHCl_3$);

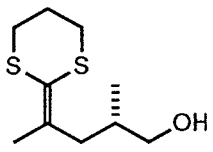
IR ($CHBr_3$) 2911 (m), 1775 (s), 1694 (s), 1453 (m), 1382 (s), 1348 (m), 1239 (m), 1210 (m), 1013 (w), 968 (w), 746 (w) cm^{-1};

^1H NMR (250 MHz) 7.40-7.18 (5H, m), 4.67 (1H, ddt, J= 10.5, 8.6, 3.0 Hz), 4.25 (1H, t, J= 8.8 Hz), 4.15 (1H, dd, J= 8.8, 2.5 Hz), 4.00 (1H, qdd, J= 7.0, 7.0, 7.0 Hz), 3.28 (1H, dd, J= 13.5, 3.0 Hz), 3.00-2.80 (4H, m), 2.80-2.60 (3H, m), 2.20-2.00 (2H, m), 1.90 (3H, s), 1.20 (3H, s);

^{13}C NMR (62.5 MHz) 176.6 (0), 153.0 (0), 136.6 (0), 135.4 (0), 129.5 (1), 128.9 (1), 127.3 (1), 122.9 (0), 66.1 (2), 55.7 (1), 39.5 (2), 37.8 (2), 36.3 (1), 30.2 (2), 29.9 (2), 24.7 (2), 20.3 (3), 16.7 (3);

LRMS (CI mode, NH_3): m/z = 392 ($(M+NH_4)^{+\bullet}$, 22%), $(M+H)^{+\bullet}$ (100);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 391.1275. $C_{20}H_{25}NO_3S_2$ requires M, 391.1276.



(2*S*)-4-(1,3-Dithian-2-ylidene)-2-methyl-1-pentanol (2.3.1)

LAH (2.17 g, 57 mmol) was suspended in THF (40 mL) and cooled to 0°C before the dropwise addition of substrate **(4.1.4)** (7.29 g, 19 mmol) in THF (40 mL) over 45 min. The reaction mixture was stirred at 0°C for 15 min before the cautious dropwise addition of 2M aqueous sodium hydroxide. The addition of sodium hydroxide was ended when a white precipitate had

formed and no grey colour remained. The excess water was removed with anhydrous $MgSO_4$ before the solution was filtered and evaporated and the crude oil chromatograhed on silica (7 cm Ø, x 10 cm, 20% EtOAc in petrol) to give **(2.3.1)** (3.21g, 15 mmol, 77%) as a clear colourless oil:

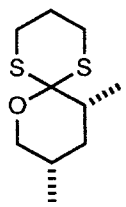
$[\alpha]_D$= +18.5°, (c = 0.67, $CHCl_3$);

IR ($CHBr_3$) 3610 (m), 3450 (m), 2991 (m), 2954 (s), 2909 (s), 2869 (m), 1453 (m), 1423 (m), 1372 (m), 1276 (m), 1240 (m), 1168 (w), 1027 (s), 911 (m) cm^{-1};

^1H NMR (250 MHz) 3.48 (2H, d, J= 4.5 Hz), 3.00-2.78 (4H, m), 2.48 (1H, dd, J= 13.5, 8.0 Hz), 2.18 (1H, dd, J= 13.5, 7.0 Hz), 2.12 (2H, m), 1.93 (3H, s), 1.86-1.80 (1H, m), 0.96 (3H, d, J= 6.5 Hz);

^{13}C NMR (62.5 MHz) 138.9 (0), 120.4 (0), 67.2 (2), 39.3 (2), 34.7 (1), 30.3 (2), 30.1 (2), 24.8 (2), 20.5 (3), 16.9 (3);

LRMS (CI mode, NH_3): m/z = 218 ($(M+H)^{+\bullet}$, 100%);



(9*S*,11*R*)-9,11-Dimethyl-7-oxa-1,5-dithiaspiro[5.5]undecane (2.3.2)
Alcohol **(2.3.1)** (7.88 g, 36 mmol) in DCM (650 mL) was cooled to 0°C. The solution was then treated with a staurated solution of HCl in DCM (30 mL of 0.7 M, 21 mmol) and stirred for 5 min before the addition of triethylamine (30 mL). The solution was then evaporated and the residual oil chromatographed on silica (7 cm Ø x 7 cm, 2.5% EtOAc in petrol) to give **(2.3.2)** (7.70 g, 35 mmol, 98%) as a clear, colourless oil:

IR ($CHBr_3$) 2958 (m), 2915 (m), 2817 (w), 1454 (m), 1422 (w), 1378 (w), 1276 (w), 1070 (m), 1033 (s), 990 (w), 957 (w), 892 (w), 871 (w), 800 (m) cm^{-1};

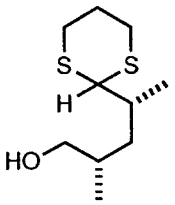
^1H NMR (400 MHz) 3.68 (1H, ddd, J = 2.3, 4.8, 10.9 Hz), 3.53 (1H, t, J = 10.9 Hz), 3.46 (1H, ddd, J = 2.5, 12.8, 13.4 Hz), 2.97 (1H, ddd, J = 2.5, 12.8 13.0 Hz), 2.67-2.60 (1H, m), 2.58-2.52 (1H, m), 2.12-2.03 (1H, m), 1.98-1.76 (2H, m), 1.53 (1H, ddd, J = 2.3, 3.9, 13.0 Hz), 1.30 (1H, q, J = 12.0 Hz), 1.11 (3H, d, J = 6.9 Hz), 0.83 (3H, d, J =

6.8 Hz);

^{13}C NMR (62.5 MHz) 92.9 (0), 68.6 (2), 42.0 (1), 36.0 (2), 30.7 (1), 26.5 (2), 25.5 (2), 24.6 (2), 18.3 (3), 16.7 (3);

LRMS (CI mode, NH_3): m/z = 218 ($(M+H)^{+\bullet}$, 100%), 187 (5);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 218.0805. $C_{10}H_{18}OS_2$ requires M, 218.0799.



2-((1*R*,3*S*)-4-Hydroxy-1,3-dimethylbutyl)-1,3-dithiane (4.1.5)
Dithiaortho ester **(2.3.2)** (5.90 g, 27.0 mmol) in ether (250 mL) at rt was treated with DIBALH (54 mL of 1.5 M solution in toluene, 81 mmol) over 5 min. The solution was then stirred at rt for 2 h. An aqueous solution of sodium potassium tartrate (66 g, 0.23 mol in water 150 mL) was cautiously added dropwise. The two phase solution was then stirred vigorously for 15 h. The organic phase was then separated and the aqueous phase extracted with ether (3 x 150 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated to give a mixture (6.2 g) of the desired product **(4.1.5)** and **(2.3.1)**.

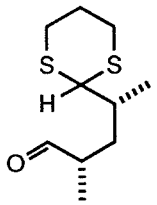
Separation of 2-((1*R*,3*S*)-4-hydroxy-1,3-dimethylbutyl)-1,3-dithiane (4.1.5) from (2*S*)-4-(1,3-dithian-2-ylidene)-2-methyl-1-pentanol (2.3.1)
The crude mixture of **(4.1.5)** and **(2.3.1)** (6.2 g) in DCM (140 mL) was cooled to 0°C. A saturated solution of HCl in DCM (5 mL) was then added as a single portion. The solution was stirred for 5 min. before the addition of triethylamine (5 mL). The solution was then evaporated and chromatographed on silica (7 cm Ø x 7 cm, 10-30% EtOAc in petrol). Chromatographic separation of **(4.1.5)** from **(2.3.2)** was facile, and yielded **(2.3.2)** (232 mg, 1.06 mmol, 3%) (DATA AS ABOVE), and **(4.1.5)** (5.76 g, 26 mmol, 97%) as a clear colourless oil:

IR ($CHBr_3$) 3612 (m), 2960 (s), 2900 (s), 2871 (m), 1454 (m), 1422 (m), 1380 (w), 1275 (m), 1183 (w), 1029 (s), 907 (m), 764 (m) cm^{-1};

^{1}H NMR (250 MHz) 4.17 (1H, d, J = 3.8 Hz), 3.55 (1H, dd, J = 10.8, 4.8 Hz), 3.43 (1H, dd, J = 10.8, 5.8 Hz), 3.00-2.79 (4H, m), 2.12 (1H, apparent ddt, J = 13.8, 6.8, 3.0 Hz), 3.00-2.79 (4H, m), 2.06-1.65 (4H, m), 1.42 (1H, br m), 1.20-1.03 (1H, m), 1.10 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 67.5 (2), 55.0 (1), 37.7 (2), 35.8 (1), 33.1 (1), 31.1 (2), 30.6 (2), 26.3 (2), 17.6 (3), 17.3 (3);

LRMS (EI mode, 70 eV): m/z = 220 ($M^{+\bullet}$, 24%), 119 (100), 41 (20).



2-((1*R*,3*S*)-4-oxo-1,3-Dimethylbutyl)-1,3-dithiane (4.1.6)
A solution of **(4.1.5)** (254 mg, 1.15 mmol) in DCM (5 mL) over 3Å molecular sieves at rt was treated with N-methylmorpholine-N-oxide (202 mg, 1.73 mmol) under a purge of argon. The solution was stirred for 5 min before the addition of TPAP catalyst (32 mg, 0.095 mmol) under a purge of argon. The reaction mixture was stirred for 20 min before being filtered through silica (4 cm Ø x 2 cm, DCM) to yield **(4.1.6)** (150.3 mg, 0.69 mmol, 60%) as a pale yellow oil:

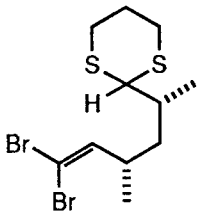
IR (film) 2963 (s), 2900 (s), 2825 (m), 2711 (m), 1723 (s), 1456 (m), 1422 (m), 1380 (m), 1277 (m), 1186 (m), 969 (w), 909 (m) cm^{-1};

^{1}H NMR (270 MHz) 9.59 (1H, d, J = 2.5 Hz), 4.13 (1H, d, J = 3.7 Hz), 3.00-2.80 (4H, m), 2.55-2.38 (1H, m), 2.20-1.75 (4H, m), 1.35 (1H, ddd, J = 5.6, 7.8, 15.9 Hz), 1.13 (3H, d, J = 6.9 Hz), 1.11 (3H, d, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 204.8 (1), 55.0(1), 44.3 (1), 36.2 (1), 35.2 (2), 31.2 (2), 30.8 (2), 26.4 (2), 17.4 (3), 14.4 (3);

LRMS (EI mode, 70 eV): m/z = 218 ($M^{+\bullet}$, 38%), 119 (100), 41 (30);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 218.0796. $C_{10}H_{18}OS_2$ requires M, 218.0799.



2-((1*R*,3*S*)-5,5-Dibromo-1,3-dimethyl-4-pentenyl)-1,3-dithane (4.1.7)

A solution of triphenylphosphine (524 mg, 2.0 mmol) and carbon tetrabromide (332 mg, 1.0 mmol) in DCM (3 mL) was treated with aldehyde **(4.1.6)** (110 mg, 0.50 mmol) as a single portion. The reaction mixture was stirred at 0°C for 30 min before being evaporated and chromatographed on silica (2 cm Ø x 4 cm, 2% ether in petrol) to give **(4.1.7)** (110 mg, 0.29 mmol, 59%) as a clear pale yellow oil:

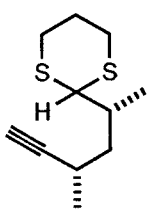
IR (film) 2960 (s), 2926 (s), 1614 (w), 1455 (m), 1422 (m), 1380 (m), 1276 (m), 1184 (w), 1147 (w), 910 (w), 786 (s) cm^{-1};

^1H NMR (270 MHz) 6.15 (1H, d, J = 9.5 Hz), 4.10 (1H, d, J = 4.2 Hz), 3.00-2.80 (4H, m), 2.65-2.48 (1H, m), 2.12 (1H, m), 2.00-1.74 (2H, m), 1.66 (1H, ddd, J = 13.2, 10.7, 3.8 Hz), 1.39 (1H, ddd, J = 13.7, 9.9, 4.1 Hz), 1.12 (3H, d, J = 6.8 Hz), 1.04 (3H, d, J = 6.8 Hz);

^{13}CNMR (67.5 MHz) 143.1 (1), 88.3 (0), 56.7 (1), 41.2 (2), 38.5 (1), 37.4 (1), 32.2 (2), 31.1 (2) 27.2 (2), 21.8 (3), 18.2 (3);

LRMS (EI mode, 70 eV): (^{79}Br) m/z = 372 ($M^{+\bullet}$, 15%), $M^{+\bullet}$ (26), $M^{+\bullet}$ (14), 159 (90), 148 (23), 119 (100), 106 (26), 41 (25);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 371.9214. $C_{11}H_{18}Br_2S_2$ requires M, 371.9217.



2-((1*R*,3*S*)-1,3-Dimethyl-4-pentynyl)-1,3-dithane (4.1.8)

Magnesium turnings (98 mg, 4.1 mmol) in THF (2 mL) was heated until reflux commenced. The refluxing solution was treated with a mixture of

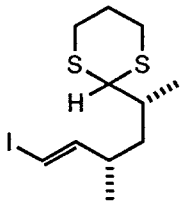
dibromoethane (65 mg, 0.34 mmol), dibromo olefin **(4.1.7)** (128 mg, 0.34 mmol) and THF (4 mL) over 30 min. Refluxing was continued for 5 h before the reaction mixture was poured into NH_4Cl (10 mL sat. aq. solution) and the aqueous phase extracted with ether (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated and the crude product chromatographed on silica (2 cm Ø x 4 cm, 2% ether in petrol) to give alkyne **(4.1.8)** (66 mg, 0.3 mmol, 90%) as a clear colourless oil:

IR (film) 3293 (m), 2967 (s), 2898 (s), 2109 (w), 1454 (m), 1422 (m), 1380 (m), 1276 (m), 1186 (m), 909 (m), 767 (m), 630 (s) cm-1;

^{1}H NMR (270 MHz) 4.12 (1H, d, J = 4.0 Hz), 2.95-2.72 (4H, m), 2.60-2.40 (1H, m), 2.25 (1H, apparent tdd, J = 13.9, 6.6, 3.3 Hz) 2.15-2.00 (1H, m), 2.05 (1H, d, J = 2.3 Hz), 1.90-1.65 (2H, m), 1.40 (1H, ddd, J = 13.2, 10.3, 4.6 Hz), 1.19 (3H, d, J = 6.8 Hz), 1.08 (3H, d, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 88.0 (0), 69.1 (1), 56.0 (1), 41.1 (2), 36.6 (1), 31.1 (2), 30.9 (2), 26.4 (2), 23.8 (1), 21.7 (3), 16.5 (3);

LRMS (EI mode, 70 eV): m/z = 214 ($M^{+\bullet}$, 17%), 148 (27), 119 (100), 41 (23).



2-((1*R*,3*S*,4*E*)-5-Iodo-1,3-dimethyl-4-pentenyl)-1,3-dithane (2.2.2)

A solution of acetylene **(4.1.8)** (46.6 mg, 0.22 mmol) in DCM (2 mL) was purged with nirogen for 2 min. before the addition of dimethyl sulphide (141 mg, 2.3 mmol). The reaction mixture was then brought to reflux before the addition of dibromoborane dimethyl sulphide complex (0.75 mL of 1.0 M solution in DCM, 0.75 mmol) over 10 s. The solution was then refluxed for 24 h before being cooled to rt and poured into ice/water (10 mL) and ether (20 mL). The two phase solution was stirred rapidly until effervesence ceased. The organic phase was then separated and washed with cold water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was filtered through a plug of silica (2 cm Ø x 2cm, 100% ether) to remove non-polar impurities giving the borinic acid (42 mg, 0.16 mmol, 73%) as a colourless oil.

The borinic acid (42 mg, 0.16 mmol) in ether (2 mL) was cooled to 0°C and treated with sodium hydroxide (20 mg, 0.48 mmol in water 2 mL) as a single portion. Iodine (49 mg, 0.19 mmol) in ether (1 mL) was then added dropwise over 30 sec. The pale orange solution was then stirred for 15 min. before the addition of saturated aqueous sodium thiosulphate solution (5 mL). The reaction mixture was stirred until the orange colour disappeared. The aqueous phase was then separated and extracted with ether (2 x 10 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated. The crude product was then chromatographed on silica (2 cm Ø x 4 cm, 2% ether in petrol) to yield vinyl iodide **(2.2.2)** (37 mg, 0.11 mmol, 67%. 51% for two steps) as a yellow oil:

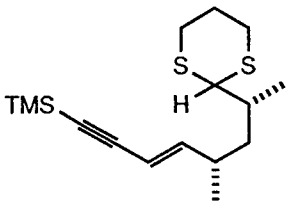
IR (film) 2957 (s), 2897 (s), 1601 (w), 1454 (m), 1420 (m), 1379 (m), 1275 (m), 1183 (m), 950 (m) cm^{-1};

^1H NMR (270 MHz) 6.34 (1H, dd, J = 14.3, 8.7 Hz), 6.01 (1H, dd, J = 14.3, 0.6 Hz), 4.10 (1H, d, J = 4.0 Hz), 2.98-2.78 (4H, m), 2.38-2.20 (1H, m), 2.11 (1H, apparent dddd, J = 14.1, 6.4, 3.2, 3.2 Hz), 1.98-1.75 (2H, m), 1.62 (1H, ddd, J = 13.8, 10.0, 4.2 Hz), 1.30 (1H, ddd, J = 13.8, 10.0, 4.8 Hz), 1.06 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz);

^{13}C NMR (75 MHz) 151.3 (1), 74.0 (1), 55.8 (1), 40.5 (2), 38.8 (1), 36.2 (1), 31.1 (2), 30.9 (2), 26.4 (2), 20.8 (3), 16.9 (3);

LRMS (EI mode, 70 eV): m/z = 342 ($M^{+\bullet}$, 1%), $(M-I)^{+\bullet}$ (15), 159 (35), 148 (19), 119 (100), 109 (36), 41 (24);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 341.9957. $C_{11}H_{19}IS_2$ requires M, 341.9972.



2-((1*R*,3*S*,4*E*)-7-(Trimethylsilyl)-1,3-dimethyl-4-hepen-6-ynyl)-1,3-dithane (5.5.1)

Vinyl iodide **(2.2.2)** (53 mg, 0.155 mmol) in benzene (2.5 mL) was purged with argon for 10 min. Trimethylsilyl acetylene (33 mg, 0.33 mmol), *n*-propylamine (30 mg, 0.50 mmol), copper (I) iodide (2.2 mg, 0.012 mmol) and

tetrakis(triphenylphosphine) palladium (0) (5.8 mg, 0.005 mmol) were then added under a purge of argon and the solution was stirred for 9 h. Silica (*ca.*2 mL) was added and the solution evaporated and the crude product chromatographed on silica (2 cm Ø x 5 cm, 3% ether in petrol) to give the silyl acetylene **(5.5.1)** (43 mg, 0.14 mmol, 89%) as a colourless oil:

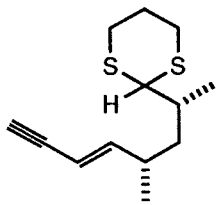
IR (film) 2958 (m), 2898 (m), 2163 (w), 1455 (w), 1421 (w), 1379 (w), 1248 (s), 1074 (w), 958 (w), 843 (s) cm^{-1};

^1H NMR (270 MHz) 6.03 (1H, dd, J = 15.8, 8.7 Hz), 5.50 (1H, dd, J = 15.8, 1.0 Hz), 4.09 (1H, d, J = 4.1 Hz), 2.97-2.80 (4H, m), 2.35-2.18 (1H, m), 2.17-2.04 (1H, m), 1.97-1.73 (2H, m), 1.58 (1H, ddd, J = 14.1, 10.0, 4.3 Hz), 1.34 (1H, ddd, J = 14.1, 10.2, 4.8 Hz), 1.05 (3H, d, J = 7.0 Hz), 1.01 (3H, d, J = 6.8 Hz), 0.18 (9H, s);

^{13}C NMR (67.5 MHz) 150.7 (0), 109.1 (1), 104.1 (0), 93.1 (0), 56.2 (1), 41.0 (2), 36.3 (1), 35.5 (1), 31.3 (2), 31.0 (2), 26.5 (2), 21.3 (3), 16.7 (3), 0.1 (3);

LRMS (EI mode, 70 eV): m/z = 312 ($M^{+\bullet}$, 17%), $(M\text{-}Me)^{+\bullet}$ (42), 159 (98), 148 (85), 119 (100), 106 (26), 73 (57), 59 (21);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 312.1387. $C_{16}H_{28}S_2Si$ requires M, 312.1402.



2-((1*R*,3*S*,4*E*)-1,3-Dimethyl-4-hepen-6-ynyl)-1,3-dithane (5.5.2)
The silyl enyne **(5.5.1)** (43 mg, 0.14 mmol) in THF (3 mL) was cooled to 0°C before TBAF (0.13 mL of 1.1 M solution in THE, 0.14 mmol) was added dropwise. The solution was then stirred for 7 min before being evaporated. The residue was dissolved in DCM (1 mL) and chromatographed on silica (2 cm Ø x 3 cm, 3% ether in petrol) to give enyne **(5.5.2)** (33 mg, 0.14 mmol, 100%) as a colourless oil:

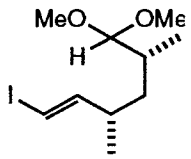
IR (film) 3305 (s), 2965 (s), 2904 (s), 2101 (w), 1627 (w), 1456 (m), 1424 (m), 1381 (m), 1277 (m), 1228 (m), 961 (s), 645 (s), 611 (s) cm^{-1};

^{1}H NMR (270 MHz) 6.06 (1H, dd, J = 16.0, 8.7 Hz), 5.45 (1H, dd, J = 16.0, 2.1 Hz with fine splitting), 4.09 (1H, d, J = 3.9 Hz), 2.97-2.82 (4H, m), 2.79 (1H, d, J = 2.1 Hz), 2.38-2.20 (1H, m), 2.18-2.04 (1H, m), 1.98-1.73 (2H, m), 1.62 (1H, ddd, J = 13.8, 10.0, 4.3 Hz), 1.35 (1H, ddd, J = 13.8, 10.0, 4.5 Hz), 1.05 (3H, d, J = 7.5 Hz), 1.02 (3H, d, J = 7.3 Hz);

^{13}C NMR (67.5 MHz) 151.5 (1), 107.9 (1), 82.5 (0), 76.2 (1), 56.1 (1), 40.9 (2), 36.3 (1), 35.5 (1), 31.3 (2), 31.0 (2), 26.5 (2), 21.2 (3), 16.9 (3);

LRMS (EI mode, 70 eV): m/z = 240 ($M^{+\bullet}$, 12%), 193 (14), 159 (54), 148 (55), 119 (100), 106 (31), 77 (21), 41 (25);

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 240.1014. $C_{13}H_{20}S_2$ requires M, 240.1006.



(3*S*,5*R*,1*E*)-6,6-Dimethoxy-3,5-dimethyl-1-iodo-1-hexene (5.15.1)

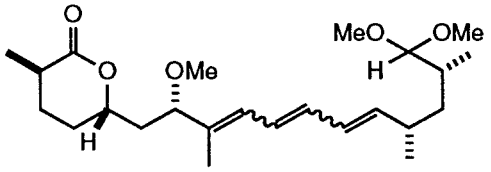
Vinyl iodide **(2.2.2)** (28 mg, 0.082 mmol) in methanol (2 mL) and THF (0.5 mL) was stirred over 4Å molecular sieves (250 mg) under argon for 30 min before the addition of *bis*-(trifluoroacetoxy)phenyliodide (53 mg, 0.12 mmol) under a purge of argon. The reaction mixture was stirred for 5 min at rt before being poured into saturated aqueous sodium hydrogen carbonate solution (10 mL) and extracted with ether (4 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The crude product was then chromatographed on silica (2 cm Ø x 4 cm, 3% ether in petrol) to give dimethoxy acetal **(5.15.1)** (18 mg, 0.062 mmol, 74%) as a colourless oil:

IR (film) 2956 (s), 2927 (s), 2826 (m), 1602 (w), 1456 (m), 1378 (w), 1187 (m), 1104 (s), 1064 (s), 949 (s) cm^{-1};

^{1}H NMR (300 MHz, C_6D_6) 6.46 (1H, dd, J = 14.6, 8.8 Hz), 5.96 (1H, d, J = 14.6 Hz), 4.08 (1H, d, J = 5.9 Hz), 3.36 (3H, s), 3.35 (3H, s), 2.30-2.14 (1H, m), 2.03-1.89 (1H, m), 1.73 (1H, ddd, J = 13.8, 10.7, 3.4 Hz), 1.16 (1H, ddd, 13.8, 10.0, 4.1 Hz), 1.09 (3H, d, J = 6.7 Hz), 0.98 (3H, d, J = 6.6 Hz);

^{13}C NMR (75 MHz, C_6D_6) 152.0 (1), 109.0 (1), 74.0 (1), 53.9 (3), 53.7 (3), 38.8 (1), 38.4 (2), 33.7 (1), 21.1 (3), 14.7 (3);

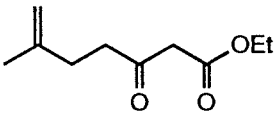
LRMS (CI mode, NH_3): m/z = 298 ((M-OMe)$^{+\bullet}$, 100%), 252 (62), 235 (24), 215 (23), 183 (18), 139 (66), 85 (36), 75 (35).



(3*R*,6*S*)-6-[(2*S*,3*EZ*,5*EZ*,7*EZ*,11*R*,9*S*)-12,12-Dimethoxy-11,9-dimethyl-3-methyl-2-methoxy-3,5,7-dodecatrienyl]-3-methyloxan-2-one (5.16.1).
A solution of dienylstannane **(5.8.1)** (13 mg, 0.025 mmol) and vinyl iodide **(5.15.1)** (8.1 mg, 0.027 mmol) in DMF (2 ml) and THF (1 ml) was purged with argon for 10 min before the addition of diisopropylethylamine (4.8 mg, 6.5 µl, 0.038 mmol) and *bis*acetonitrile palladium dichloride (1.3 mg, 0.005 mmol). The solution was then stirred at rt for 24 h before the solvent was removed under vacuum (*ca.* 0.1 mbar). The residual oil was purified by column chromatography (1 cm Ø x 4 cm, 40% ether in petrol), and then preparative thin layer chromatography (40% ether in petrol) to give **(5.16.1)** (3 mg, 0.008mmol, 30%), as a mixture of two major components:

^1H NMR (300 MHz) 0.90 (3H, d, J = 7.0 Hz), 0.93 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 6.8 Hz), 1.07 (3H, d, J = 6.8 Hz), 1.32 (3H, d, J = 6.9 Hz), 1.33 (3H, d, J = 6.9 Hz), 1.72 (3H, s), 2.12-1.88 (8H, m), 3.19 (3H, s), 3.22 (3H, s), 3.36 (3H, s), 3.37 (3H, s), 3.38 (3H, s), 3.86 (1H, td, J = 6.7, 1.9 Hz), 3.92 (1H, t, J = 6.7 Hz), 4.02 (d, J = 6.1 Hz), 4.03 (1H, d, J = 6.1 Hz), 4.35-4.20 (1H, m), 5.50-6.65 (5H, m) many proton signals in the methylene region of the spectrum are obscured by a large water signal at δ 1.62 and one other impurity at δ 1.30.

UV λ_{max} 287 nm absorbance = 0.634, 276 nm absorbance = 0.827, 266 nm absorbance = 0.693. The absorbances above were observed at a concentration of 0.03 $mgmL^{-1}$. Molar extinction coefficients cannot be calculated since the concentration of each component is unknown.



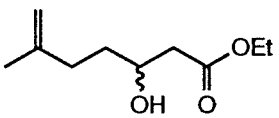
Ethyl 6-methyl-3-oxo-6-heptenoate (6.1.2)

Sodium hydride (10.0 g of 60% dispersion in mineral oil = 0.25 mol of NaH) was washed with petrol. THF (300 mL) was then added and the solution cooled to 0°C. Ethyl acetoacetate **(6.1.1)** (30.0 g, 29.4 mL, 0.23 mol) was added over 15 min keeping the temperature below 5°C. The solution was stirred for 10 min before the addition of *n*-butyllithium (100 mL of 2.5 M in hexanes, 0.25 mol) over 30 min keeping the temperature below 5°C. The solution was then stirred for 15 min before the dropwise addition of β-methallyl chloride **(6.1.15)** (19.9 g, 21.5 mL, 0.22 mol) over 30 min maintaining the temperature below 3°C. The solution was stirred between -5-0°C for 1 h before being quenched by pouring into 1 M HCl (300 mL aq.). The organic phase was separated and the aqueous phase extracted with two portions of ether (300 mL). After drying ($MgSO_4$) and evaporation, the residual brown oil was distilled through a short path distillation apparatus (major fraction 120-128°C, 17 mm Hg), giving keto ester **(6.1.2)** (27.7 g, 0.15 mol, 68%) as a colourless oil: compound previously prepared by Huckin[96].

IR (film) 2981 (s), 1745 (s), 1716 (s), 1649 (m), 1318 (s), 1240 (s), 1030 (m), 891 (m) cm^{-1};

^1H NMR (270 MHz) 4.72 (1H, br s), 4.63 (1H, br s), 4.17 (2H, q, J = 7.1 Hz), 3.42 (2H, s), 2.66 (2H, t, J = 7.3 Hz), 2.26 (2H, t, J = 7.3 Hz), 1.69 (3H, s), 1.26 (3H, t, J = 7.1 Hz);

^{13}C NMR (67.5 MHz) 203.5 (0), 167.2 (0), 143.9 (0), 110.4 (2), 61.3 (2), 49.3 (2), 41.1 (2), 31.1 (2), 22.6 (3), 14.1 (3).



(2*RS*)Ethyl-6-methyl-2-hydroxy-6-heptenoate (6.1.3)

To a mechanically stirred solution of β-ketoester **(6.1.2)** (25.0 g, 0.14 mol) in ethanol (250 mL) at 0°C, was added a solution of sodium borohydride (1.58 g, 0.041 mol in ethanol 150 mL) over 15 min. The solution was allowed to warm to rt and stir for 2 h. The reactio mixture was then evaporated and

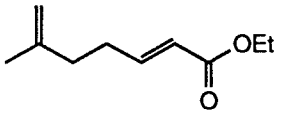
quenched by pouring into 1:1 ; ethyl acetate : water (v:v 600 mL total). The organic layer was separated and the aqueous layer extracted with ethyl acetate (750 mL). The combined organic phases washed with saturated brine (300 mL), dried ($MgSO_4$) and distilled through a short path distillation apparatus (70-80°C, 0.05 mbar) giving β-hydroxy ester **(6.1.3)** (20.7 g, 0.11 mol, 82%) as a pale yellow oil:

IR (film) 3458 (m), 3075 (w), 2981 (m), 1732 (s), 1650 (m), 1446 (m), 1375 (m), 1246 (m), 1186 (m), 1094 (m), 1031 (m), 881 (m), 738 (m) cm^{-1};

^1H NMR (270 MHz) 4.74-4.66 (2H, m), 4.15 (2H, q, J = 7.2 Hz), 4.06-3.92 (1H, apparent ddt, J = 4.0, 4.0, 4.0 Hz), 3.12 (1H, d, J = 4.0 Hz), 2.55-2.35 (2H, m), 2.24-2.00 (2H, m), 1.71 (3H, br s), 1.70-1.50 (2H, m), 1.25 (3H, t, J = 7.2 Hz);

^{13}C NMR (67.5 MHz) 173.0 (0), 145.4 (0), 110.3 (2), 67.8 (1), 60.8 (2), 41.4 (2), 34.5 (2), 33.8 (2), 22.6 (3), 14.3 (3).

LRMS (CI mode, NH_3): m/z = 186 $(M+NH_4)^{+\bullet}$, 50%), $(M+H)^{+\bullet}$ (100), 35 (34).



(2*E*)-Ethyl-6-methyl-2,6-heptadienoate (6.1.4)

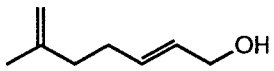
The β-hydroxy ester **(6.1.3)** (19.2 g, 0.10 mol) was taken up in THF (200 mL) and cooled with mechanical stirring to -8°C. Triethylamine (52.0 g, 0.52 mol, 68 mL) was added over 15 min and the solution allowed to stir for 10 min. Mesyl chloride (13.0 g, 0.11 mol, 8.8 mL in THF 20 mL) was added over 15 min allowing the temperature to rise to 4°C, a pale yellow precipitate formed. The solution was then allowed to warm to rt over 1 h and was brought to reflux for 10 h. The solution was quenched by pouring into 2 M HCl (250 mL aq). The organic layer was separated and washed with 10% NaOH solution (250 mL aq). The combined aqueous phases were then extracted with ether (750 mL) and the combined organic phases dried ($MgSO_4$) and evaporated. The crude product was distilled through a short path distillation appartus (52-54°C, 0.05 mbar), giving α,β-unsaturated ester **(6.1.4)** (14.9 g, 0.089 mol, 86%) as a colourless oil: compound previously prepared by Gricco[104].

IR (film) 3076 (w), 2981 (m), 2937 (m), 1723 (s), 1655 (m), 1447 (w), 1368 (m),

1316 (m), 1267 (m), 1199 (m), 1153 (m), 1093 (w), 1044 (m), 972 (w), 890 (m) cm^{-1};

^1H NMR (270 MHz) 6.93 (1H, dt, J =15.6, 6.8 Hz), 5.81 (1H, dt, J = 15.6, 1.50 Hz), 4.74-4.71 (1H, m), 4.69-4.66 (1H, m), 4.15 (2H, q, J = 7.2 Hz), 2.36-2.27 (2H, m), 2.17-2.09 (2H, t, J = 8.3 Hz), 1.70 (3H, dd, J = 1.4, 1.0 Hz), 1.25 (3H, t, J = 7.2 Hz);

^{13}C NMR (67.5 MHz) 166.7 (0), 148.6 (1), 144.3 (0), 121.6 (1), 110.8 (2), 60.2 (2), 36.0 (2), 30.3 (2), 22.5 (3), 14.4 (3).



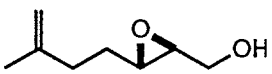
(2*E*)-6-Methyl-2,6-heptadiene-1-ol (6.1.5)

The α,β-unsaturated ester **(6.1.4)** (11.37 g, 0.068 mol) in DCM (100 mL) was cooled with mechanical stirring to -80°C. DIBALH (99 mL of 1.5 M solution in toluene, 0.15 mol) was added over 30 min and the solution stirred for a further 30 min at -80°C. The solution was then allowed to warm to rt over 1 h and stir for 30 min. The reaction mixture was subsequently cooled to -10°C before being quenched by the cautious addition of 2 M HCl (100 mL aq.). The organic phase was separated and the aqueous phase extracted with DCM (500 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residual oil was distilled through a short path distillation apparatus (42-44°C, 0.05 mbar), giving allyl alcohol **(6.1.5)** (7.41 g, 0.058 mol, 86%) as a colourless oil: compound previously prepared by Negishi[97].

IR (film) 3351 (s), 3075 (w), 2968 (s), 2894 (s), 1650 (m), 1447 (m), 1375 (m), 1269 (m), 1136 (w), 1105 (s), 1045 (m), 1010 (m), 970 (m), 888 (s) cm^{-1};

^1H NMR (270 MHz) 5.66 (1H, dd, J = 15.3, 4.8 Hz with fine splitting), 5.61 (1H, dd, J = 15.3, 4.8 Hz with fine splitting), 4.71-4.67 (1H, m), 4.67-4.63 (1H, m), 4.02 (2H, d, J = 3.2 Hz), 2.46 (1H, br s), 2.22-2.12 (2H, m), 2.12-2.02 (2H, m), 1.69 (3H, s with fine splitting);

^{13}C NMR (67.5 MHz) 145.3 (0), 132.4 (1), 129.3 (1), 110.2 (2), 63.5 (2), 37.3 (2), 30.3 (2), 22.5 (3).



(2*S*,3*S*)-6-Methyl-2,3-epoxy-6-hepten-1-ol (6.1.6)

DCM (100 mL) was cooled to -35°C. Titanium isopropoxide (1.27 g, 4.45 mmol, 1.33 mL), (+)-diisopropyl-(L)-tartrate (1.25 g, 5.34 mmol), and *tert*-butyl hydroperoxide (35 mL of a 3.8 M solution in toluene) were added in the above order allowing the temperature to rise to -30°C. The solution was then allowed to stir at -30°C for 1 h. Allyl alcohol **(6.1.5)** (11.18 g, 0.089 mol) was added dropwise over 25 min and the solution stirred at between -30 and -20°C for 4 h. The reaction was subsequently quenched by the addition of 10% NaOH solution (aq.) saturated with NaCl (20 mL). The organic phase was separated, and the aqueous phase extracted with DCM (700 mL). The combined organic phases were dried ($MgSO_4$), evaporated and chromatographed on silica (10 cm Ø x 15 cm, 17-80% EtOAc in petrol). The residual oil was distilled through a short path distillation apparatus (75-80°C, 0.05 mbar), giving epoxy alcohol **(6.1.6)** (9.43 g, 0.066 mol, 75%) as a colourless oil:

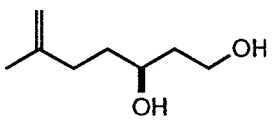
$[\alpha]_D$= -30.0°, (c = 0.53, $CHCl_3$);

IR (film) 3419 (s), 3075 (w), 2972 (s), 1650 (m), 1450 (s), 1376 (m), 1226 (w), 1092 (m), 1028 (m), 886 (s);

^{1}H NMR (270 MHz) 4.75-4.72 (1H, br s), 4.71-4.68 (1H, br s), 3.88 (1H, ddd, J = 12.6, 5.6, 2.3 Hz), 3.58 (1H, ddd, J = 12.6, 6.6, 4.5 Hz), 2.99-2.91 (2H, m), 2.41 (1H, t, J = 6.3 Hz), 2.15 (1H, apparent td, J = 8.5, 2.5 Hz), 2.15 (1H, br s), 1.72 (3H, br s), 1.75-1.66 (2H, m);

^{13}C NMR (67.5 MHz) 144.7 (0), 110.7 (2), 61.9 (2), 58.8 (1), 55.8 (1), 34.0 (2), 29.7 (2), 22.5 (3);

LRMS (CI mode, NH_3): m/z = 142 ($(M+NH_4)^{+\bullet}$,100%), 125 (27), 35 (75).



(3*S*)-6-Methyl-6-heptene-1,3-diol (6.1.7)

Epoxy alcohol **(6.1.6)** (12.3 g, 0.087 mol), in THF (150 mL) was cooled to -5°C. The solution was then treated with sodium *bis* (2-methoxyethoxy) aluminium hydride (44 mL of 3.4 M solution in toluene diluted with THF 100 mL), keeping the temperature below 0°C. The solution was stirred for 2 h at

0°C and then allowed to warm to rt and stir overnight. The solution was quenched by the cautious dropwise addition of 1 M sodium hydroxide (100 mL). The organic phase was separated and the aqueous phase extracted with ether (900 mL). The combined organic phases were dried ($MgSO_4$) and then evaporated. The crude product was distilled through a short path distillation apparatus (82-90°C, 0.05 mbar) yielding **(6.1.7)** (12.1g, 0.084 mol, 97%) as a clear colourless oil:

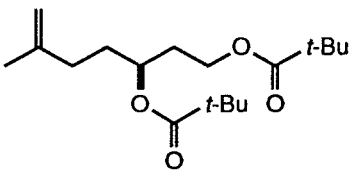
$[\alpha]_D$= -14.7°, (c = 0.57, $CHCl_3$);

IR (film) 3346 (s), 3075 (s), 2938 (s), 1650 (m), 1446 (m), 1375 (m), 1058 (s), 978 (w), 925 (w), 886 (m);

^1H NMR (270 MHz) 4.76-4.70 (2H, m), 3.95-3.76 (3H, m), 2.96 (2H, br s), 2.24-2.00 (2H, m), 1.74 (3H, br s), 1.78-1.58 (4H, m);

^{13}C NMR (67.5 MHz) 145.5 (0), 110.0 (2), 70.6 (1), 60.6 (2), 38.5 (2), 35.4 (2), 33.8 (2), 22.4 (3);

LRMS (CI mode, NH_3): m/z = 144 ($(M+H)^{+\bullet}$, 100%), 127 (32), 99 (35).



(3*S*)-1,3-(Di-trimethylacetoxy)-6-methyl-6-heptene (6.1.9)

The diol **(6.1.7)** (1.00g, 6.94 mmol) was taken up in DCM (10 mL) and pyridine (1.4g, 1.4 mL, 17.4 mmol) was added as a single portion, and the solution stirred at rt 10 min. Trimethylacetyl chloride (2.1g, 2.1mL, 17.4 mmol) was added as a single portion and the solution stirred for 1h at rt. At this point the reaction had not gone to completion hence pyridine (0.7g, 0.7 mL, 8.7mmol) and trimethylacetyl chloride (1.1g, 1.1 mL, 8.7mmol) were added as single portions and the solution left to stir at rt for 16h. The solution was then poured into HCl (50 mL of 1M aq. solution). The was organic phase separated and washed with $NaHCO_3$ (50 mL of sat. aq. solution), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica (3 cm Ø x 10 cm, 20% ether in petrol) and Kugelrohr distilled (200°C (bath), 0.3 mbar),

giving diester **(6.1.9)** (2.06g, 6.6mmol, 95%) as a clear colourless oil:

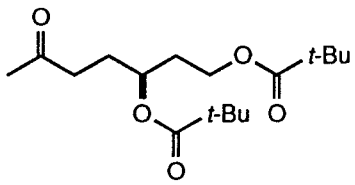
$[\alpha]_D$= +12.6°, (c = 1.06, $CHCl_3$);

IR (film) 2970 (s), 2872 (m), 1728 (s), 1649 (w), 1480 (m), 1460 (m), 1396 (m), 1366 (m), 1284 (m), 1229 (w), 1151 (s), 1081 (m), 1034 (m), 888 (m), 770 (w) cm^{-1};

^1H NMR (270 MHz) 4.97 (1H, tt, J = 5.4, 5.4 Hz), 4.75-4.70 (1H, m), 4.76-4.65 (1H, m), 4.16-3.99 (2H, 2 overlapping ddd, J = 11.0, 7.4, 6.5 Hz, J = 11.0, 6.5, 4.9 Hz), 2.03 (2H, t, J = 7.8 Hz), 1.95-1.86 (2H, m), 1.72 (3H, br s), 1.21 (9H, s), 1.19 (9H, s);

^{13}C NMR (67.5 MHz) 178.5 (0), 177.9 (0), 144.7 (0), 110.5 (0), 70.2 (1), 60.6 (2), 39.0 (0), 38.8 (0), 33.4 (2), 33.1 (2), 32.3 (2), 27.3 (3), 27.3 (3), 22.5 (3);

LRMS (CI mode, NH_3): m/z = 312 ($(M+NH_4)^{+\bullet}$, 87%), $(M+H)^{+\bullet}$ (22), 211 (100), 108 (35), 93 (10), 80 (6), 57 (7).



(3*S*)-1,3-(Di-trimethylacetoxy)-6-oxoheptane (6.1.11)

The alkene **(6.1.9)** (1.89g, 6.1mmol) in DCM under a stream of oxygen, was cooled to -80°C and a stream of ozone was passed through the solution until it turned pale blue. The solution was then purged with nitrogen until the blue colour disappeared. Dimethyl sulphide (5.6 g, 90 mmol, 6.6 mL) was added as a single portion and the solution allowed to warm to rt by removing the cooling bath. The reaction mixture was stirred overnight before evaporation. The crude oil was chromatographed on silica (3cm Ø x 5 cm, 10% ether in petrol) yielding the product **(6.1.11)** (0.727g, 2.32 mmol, 38%) as a pale yellow oil:

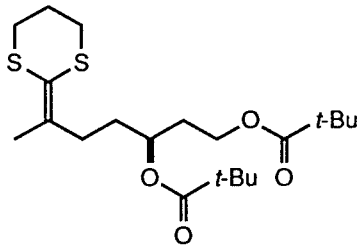
$[\alpha]_D$= +8.8°, (c = 1.16, $CHCl_3$);

IR (film) 2972 (m), 2931 (m), 2872 (m), 1726 (s), 1481 (m), 1461 (m), 1397 (m), 1366 (m), 1284 (m), 1154 (s), 1088 (w), 1034 (w), 939 (w), 861 (w), 770 (w), 737 (w) cm^{-1};

^{1}H NMR (270 MHz) 5.03-4.92 (1H, m), 4.15-3.98 (2H, m), 2.46 (2H, t, J = 7.9 Hz), 2.14 (3H, s), 2.01-1.74 (4H, m), 1.20 (9H, s), 1.19 (9H, s);

^{13}C NMR (67.5 MHz) 207.2 (0), 178.2 (0), 177.8 (0), 69.5 (1), 60.2 (2), 39.1 (2), 38.8 (0), 38.6 (0), 33.2 (2), 29.8 (3), 28.0 (2), 27.1 (3);

LRMS (CI mode, NH_3): m/z = 314 ($(M+NH_4)^{+\bullet}$, 100%), 213 (46).



(3*S*)-1,3-(Di-trimethylacetoxy)-6-(1,3-dithian-2-ylidene) heptane (6.1.13)
Diisopropylamine (0.94 g, 9.3 mmol, 1.30 mL) in THF (10 mL) was cooled to -30°C and*n*-butyllithium (5.8 mL of 1.6 M solution in hexanes, 9.3 mmol) was then added at such a rate that the temperature did not rise above -25°C. The reaction mixture was cooled to -80°C before being treated with 1,3-dithiane (0.556 g, 4.6 mmol, in THF (5 mL)) at such a rate that the temperature did not rise above -75°C. The solution was then stirred at -80°C for 0.5h. Diethyl chlorophosphate (0.85 g, 4.6 mmol, 0.71 mL) was added at such a rate that the temperature did not rise above -40°C stirring continued at -40°C for 1h. The ketone **(6.1.11)** (0.727 g, 2.3 mmol) was then added and the reaction mixture stirred at -40°C for 1h before the cooling bath was removed and the solution allowed to warm to rt. The reaction mixture was poured into NH_4Cl (50 mL sat. aq. solution) and extracted with ether (2 x 100 mL). The combined organic phases were evaporated and the crude oil chromatographed on silica (3cm Ø x 5cm, 0-5% ether in petrol) and Kugelrohr distilled (250°C (bath), 0.01 mbar) giving dithianylidene **(6.1.13)** (0.583g, 1.40mmol, 61%) as a clear colourless oil:

$[\alpha]_D$= +18.6°, (c = 1.18, $CHCl_3$);

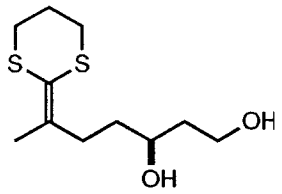
IR (film) 2970 (m), 2872 (m), 1728 (s), 1480 (m), 1462 (m), 1397 (w), 1367 (w), 1284 (m), 1151 (s), 1082 (w), 1034 (w), 939 (w), 913 (w), 770 (w) cm^{-1};

^{1}H NMR (270 MHz) 4.95 (1H, apparent quintet, J = 5.8 Hz), 4.11 (1H, dt, J = 11.2, 6.4 Hz), 4.05 (1H, dt, J = 11.2, 7.1 Hz), 2.90-2.81 (4H, m), 2.40-2.32 (2H, m), 2.16-

2.06 (2H, m), 1.96-1.86 (2H, m), 1.89 (3H, s), 1.72-1.61 (2H, m), 1.21 (9H, s) 1.20 (9H, s);

^{13}C NMR (67.5 MHz) 178.2 (0), 177.7 (0), 138.5 (0), 120.2 (0), 70.0 (1), 60.5 (2), 38.8 (0), 38.6 (0), 32.0 (2), 31.4 (2), 30.0 (2), 29.9 (2), 27.1 (3), 24.8 (2), 20.0 (3);

LRMS (CI mode, NH_3): m/z = 476 ($(M+H)^{+\bullet}$ 100%), 345 (7), 35 (84).



(3*S*)-6-(1,3-Dithian-2-ylidene) heptan-1,3-diol (3.3.3)

A stirred suspension of LAH (245 mg, 5.92 mmol), in ether (3 mL) at rt, was treated with the diester **(6.1.13)** (573 mg) in ether (8 mL) over 5 min. The solution was allowed to stir at rt for 20 min before being quenched by the cautious dropwise addition of NaOH (10% aq. solution). Addition of aqueous sodium hydroxide was ceased when the grey colour had disappeared. The solution was then filtered and the white powder washed with DCM (120 mL). The solution was subsquently evaporated and the crude oil chromatographed on silica (3cm Ø x 7cm, 50% EtOAc in petrol), yielding the diol **(3.3.3)** (279 mg, 1.13 mmol, 76%) as a colourless oil:

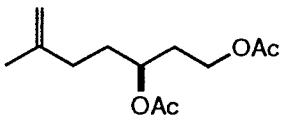
$[\alpha]_D$= -6.5°, (c = 0.43, $CHCl_3$);

IR ($CHCl_3$) 3617 (m), 3476 (m), 3018 (s), 2937 (s), 1513 (w), 1434 (m), 1373 (w), 1302 (w), 1277 (w), 1223 (s), 1065 (m), 1024 (m), 912 (m), 846 (w) cm^{-1};

^1H NMR (360 MHz) 3.91-3.77 (3H, m), 3.10-2.65 (2H, br s), 2.88 (2H, apparent d, J = 5.8 Hz), 2.86 (2H, apparent dd, J = 4.6, 1.0 Hz), 2.55 (1H, dt, J = 13.3, 8.0 Hz), 2.34 (1H, ddd, J = 13.3, 7.7, 6.1 Hz), 2.15-2.07 (2H, m), 1.92 (3H, s), 1.72 (2H, t, J = 5.3 Hz), 1.62-1.55 (2H, m);

^{13}C NMR (90 MHz) 139.7 (0), 119.7 (0), 71.5 (1), 61.9 (2), 38.3 (2), 35.5 (2), 31.8 (2), 30.4 (2), 30.2 (2), 25.0 (2), 20.2 (3);

LRMS (CI mode, NH_3): m/z = 248 CI, NH_3, ($(M+NH_4)^{+\bullet}$, 5%), $(M+H)^{+\bullet}$, 100), 231 (3), 159 (5), 143 (4), 119 (7), 35 (32).



(3*S*)-6-Methyl-1,3-diacetoxy-6-heptene (6.1.8)

The diol **(6.1.7)** (0.500 g, 3.47 mmol), in DCM (15 mL) at rt was treated with pyridine (1.10 g, 0.014 mol, 1.13 mL) and DMAP (17 mg) as single portions and the solution stirred for 5min. Acetic anhydride (1.43 g, 0.014 mol, 1.33 mL) was then added as a single portion and the solution left to stir at rt for 5h. The reaction was quenched by the addition of methanol (2 mL) and the solution stirred for 5 min before being poured into HCl (30 mL of 2M aq. solution). The aqueous phase was then separated and extracted with DCM (3 x 40 mL). The combined organic phases were washed with $NaHCO_3$ (100 mL of sat. aq. solution) and dried ($MgSO_4$). The solution was evaporated and the product Kugelrohr distilled (150°C (bath), 0.1 mbar) yielding diester **(6.1.8)** (728 mg, 3.19 mmol, 92%) as a clear colourless oil:

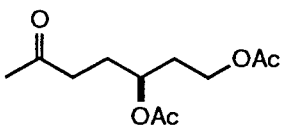
$[\alpha]_D$= +18.1°, (c = 1.12, $CHCl_3$);

IR (film) 3076 (w), 2976 (m), 2848(w), 1739 (s), 1651 (w), 1446 (m), 1373 (m), 1236 (s), 1049 (m), 962 (w), 890 (m), 734 (w) cm^{-1};

^1H NMR (270 MHz) 4.99 (1H, tt, J = 7.3, 5.2 Hz), 4.74-4.70 (1H, s with fine splitting), 4.68-4.65 (1H, s with fine splitting), 4.10 (2H, dd, J = 7.0, 6.2 Hz), 2.05 (3H, s), 2.04 (3H, s), 1.98-1.58 (6H, m), 1.72 (3H, t, J = 1.0 Hz);

^{13}C NMR (67.5 MHz) 171.0 (0), 171.0 (0), 144.7 (0), 110.4 (2), 70.9 (1), 60.8 (2), 33.4 (2), 33.0 (2), 32.2 (2), 22.5 (3), 21.2 (3), 21.0 (3);

LRMS (CI mode, NH_3): m/z = 228 ($(M+NH_4)^{+\bullet}$, 83%), 169 (25), 35 (100).



(3*S*)-1,3-Diacetoxy-6-oxoheptane (6.1.10)

The alkene **(6.1.8)** (2.00 g, 8.78 mmol) in methanol (100 mL), was cooled under a stream of oxygen to -80°C. Ozone was bubbled through the solution (~15 min.) until it turned pale blue. The solution was then purged with nitrogen

(~20 min) until the blue colour disappeared. After warming to -70°C the reaction mixture was treated with triphenylphosphine (4.6 g, 0.018 mol) in DCM (25 ml) as a single portion. The cooling bath was removed and the solution warmed to rt and stirred for 2h. The reaction mixture was evaporated and the crude product taken up in DCM and preabsorbed on silica. The crude product was chromatographed on silica (6 cm Ø x 7 cm, 0-30% EtOAc in petrol) and Kugelrohr distilled (200°C (bath), 0.05 mbar) yielding ketone **(6.1.10)** (1.91 g, 8.33 mmol, 95%) as a clear, colourless oil:

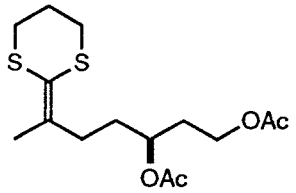
$[\alpha]_D$= +19.6°, (c = 1.60, $CHCl_3$);

IR (film) 2961 (s), 1736 (s), 1734 (s), 1711 (s), 1427 (m), 1366 (s), 1242 (s), 1164 (m), 1045 (s), 1020 (s), 963 (m), 844 (w), 777 (w), 736(w) cm^{-1};

^1H NMR (270 MHz) 4.95 (1H, dddd, J = 8.1, 6.3, 6.0, 4.4 Hz), 4.05 (2H, t, J = 6.4 Hz), 2.45 (2H, t, J = 7.3 Hz), 2.12 (3H, s), 2.01 (6H, s), 2.25-1.68 (4H, m);

^{13}C NMR (67.5 MHz) 207.5 (0), 171.0 (0), 170.7 (0), 70.3 (1), 60.6 (2), 39.2 (2), 33.2 (2), 29.9 (3), 28.1 (2), 21.0 (3), 20.9 (3);

LRMS (CI mode, NH_3): m/z = 230 ($(M+NH_4)^{+\bullet}$, 100%), 171 (35), 35 (62).



(3*S*)-6-(1,3-Dithian-2-ylidene)-1,3-diacetoxyheptane (6.1.12)

Diisopropylamine (17.0 g, 168 mmol, 23.5 mL) in THF (60 mL) was cooled with stirring to -80°C. *n*-Butyllithium (68.5 mL of 2.45 M solution in hexanes, 168 mmol) was added over 10 min and the solution stirred for 20 min before being re cooled to -80°C. 1,3-Dithiane (9.98 g, 83 mmol) in THF (30 mL) was then added over 10 min and the solution stirred at -80°C for 30min. The reaction mixture was subsequently treated with diethyl chlorophosphate (14.3 g, 83 mmol, 12 mL) in THF (10 mL) over 5 min and stirred at -40°C for 1h. The ketone **(6.1.10)** (6.38 g, 28 mmol) in THF (10 mL) was then added over 15 min and left to stir at -40°C for 30min. The reaction mixture was quenched by pouring into NH_4Cl (250 mL sat. aq. solution), the aqueous phase was separated and extracted with ether (3 x 250 mL). The combined organic phases

were dried ($MgSO_4$), evaporated and the crude oil chromatographed on silica (6cm Ø x 10 cm, 5-20% EtOAc in petrol) yielding some partially deprotected material (1.62 g, 5.6 mmol, 20%) and the desired dithianylidene adduct **(6.1.12)** (2.12 g, 6.4 mmol, 23%) as a pale yellow oil:

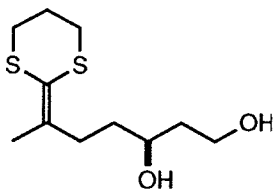
$[\alpha]_D$= +18.6°, (c = 0.71, $CHCl_3$);

IR (film) 2930 (s), 2858 (m), 1732 (s), 1427 (m), 1371 (s), 1236 (s), 1180 (w), 1118 (w), 1097 (w), 1045 (m), 1025 (m), 963 (w), 911 (w), 813 (w), 745 (w);

^1H NMR (270 MHz) 4.95 (1H, m), 4.10 (2H, dd, J = 6.9, 6.2 Hz), 2.85 (4H, m), 2.37 (2H, t, J = 8.1 Hz with fine splitting), 2.14-2.07 (2H, m), 2.06 (3H, s), 2.05 (3H, s), 2.00-1.86 (2H, m), 1.89 (3H, s), 1.72-1.60 (2H, m);

^{13}C NMR (67.5 MHz) 171.0 (0), 170.6 (0), 138.6 (0), 120.3 (0), 70.8 (1), 60.9 (2), 32.8 (2), 32.0 (2), 31.4 (2), 30.2 (2), 30.1 (2), 24.9 (2), 21.2 (3), 21.0 (3), 20.1 (3);

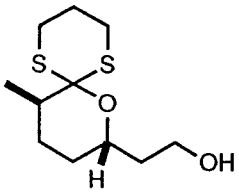
LRMS (CI mode, NH_3): m/z = 332 ($(M+NH_4)^{+\bullet}$, 83%), $(M+H)^{+\bullet}$ (100), 159 (12), 35 (17).



(3*S*)-6-(1,3-Dithian-2-ylidene)heptan-1,3-diol (3.3.3)

Diester **(6.1.12)** (100 mg, 0.3 mmol) in methanol (5 mL) was treated with potassium carbonate (41 mg, 0.3 mmol) and the solution stirred at rt for 16 h. The solution was then evaporated and the crude residue chromatographed on silica (3cm Ø x 5 cm, 50% EtOAc in petrol) to give the diol **(3.3.3)** (72 mg, 0.29 mmol, 96%) as a colourless oil:

DATA AS REPORTED ABOVE.



(8*S*,11*R*)-11-Methyl-8-(2-hydroxyethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.3.4)

The diol **(3.3.3)** (394 mg, 1.67 mmol) in DCM (5 mL) and cooled to -10°C. A saturated solution of HCl in DCM (1 mL of 0.7 M solution) was then added and the solution stirred for 30 min. The solution was then evaporated and the crude oil was chromatographed on silica (2 cm Ø x 5 cm, 25% EtOAc in petrol) giving **(3.3.4)** (276 mg, 1.2 mmol, 70%) as a colourless oil:

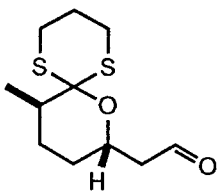
$[\alpha]_D$= +120.6°, (c = 0.65, $CHCl_3$);

IR (film) 3419 (s), 2928 (s), 1654 (vw), 1454 (m), 1423 (m), 1380 (m), 1277 (w), 1062 (s), 1002 (s), 967 (m), 906 (w), 799 (m) cm^{-1};

^1H NMR (270 MHz) 4.15 (1H, dddd, J = 11.2, 8.7, 3.7, 2.3 Hz), 3.91-3.77 (2H, m), 3.39 (1H, ddd, J = 15.7, 12.8, 2.9 Hz), 2.98 (1H, ddd, J = 13.9, 12.7, 2.7 Hz), 2.72-2.57 (2H, m), 2.40-1.34 (9H, m), 1.11 (3H, d, J = 6.8 Hz);

^{13}C NMR (67.5 MHz) 93.6 (0), 71.4 (1), 60.7 (2), 42.1 (1), 38.2 (2), 31.7 (2), 27.8 (2), 27.0 (2), 25.7 (2), 24.9 (2), 18.6 (2);

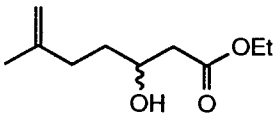
LRMS (CI mode, NH_3): m/z = 248 ($(M+H)^{+\bullet}$, 100%), 106 (6).



(8*S*,11*R*)-11-Methyl-8-(2-oxoethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (3.5.6)

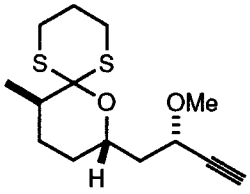
The alcohol **(3.3.3)** (93.4 mg, 0.38 mmol) in DMSO (2.5 mL) was stirred at rt over 3Å molecular sieves (360 mg) for 90min. Triethylamine (262 mg, 2.6 mmol, 0.36 mL) and pyridine sulphur trioxide complex (186 mg, 1.2 mmol) were then added and the solution stirred at rt for 8h. The solution subsequently poured into $KHSO_4$ (50 mL of 5% aq. solution) and the aqueous phase extracted with DCM (200 mL). The organic phase was dried (Na_2SO_4)

and then evaporated. The crude product was chromatographed on silica (3 cm Ø x 6 cm, 7.5% ether in petrol) yielding aldehyde **(3.5.6)** (57.7 mg, 0.23 mmol, 61%) as an oil:
DATA AS REPORTED ABOVE.



(2*RS*)Ethyl-6-methyl-2-hydroxy-6-heptenoate (6.1.3)
Water (250 ml), sucrose (25.0 g), and fresh bakers yeast (25.0 g) were warmed to 30°C and stirred for 15 min. β-keto ester **(6.1.2)** (1.29 g, 7.0 mmol) was then added and the mixture stirred for 24 h before the addition of Celite (7.3 g). The resulting suspension was filtered and the aqueous phase extracted with ether (3 x 250 ml). The combined organic phases were dried (Na_2SO_4), and evaporated and the crude product chromatographed on silica (6 cm Ø x 6 cm, 10-15% ether in petrol) to give b-hydroxy ester **(6.1.3)** (621 mg, 3.34 mmol, 48%) as a pale yellow oil, and recovered starting material **(6.1.2)** (363 mg, 1.97 mmol, 28%): DATA AS REPORTED ABOVE.

APPENDIX



(3.5.10)

Propargylic ether **(3.5.10)** crystallised in the P2 (1) space group with unit cell dimensions a = 7.195 Å, b = 13.973 Å and c = 8.660 Å and unit cell angles α = 90.000°, β = 113.290° and γ = 90.000°. The following X-ray coordinates were recorded.

41 S3 -0.04163 -0.10463 -0.50119 13 20 0 0 0 0 0 0 0.00
0 1
42 S5 0.26601 0.01024 -0.57994 13 17 0 0 0 0 0 0 0.00
0 1
43 O7 0.24042 0.01619 -0.29271 5 13 0 0 0 0 0 0 0.00
0 1
44 O15 0.16868 0.22026 0.03179 11 31 0 0 0 0 0 0 0.00
0 1
45 C8 0.22495 -0.01979 -0.13858 3 6 7 23 0 0 0 0 0.00
0 1
46 H8 0.09487 -0.05274 -0.16721 5 0 0 0 0 0 0 0 0.00
0 1
47 C13 0.25776 0.06616 -0.02352 5 8 9 11 0 0 0 0 0.00
0 1
48 H13A 0.25500 0.04721 0.08211 7 0 0 0 0 0 0 0 0.00
0 1
49 H13B 0.39050 0.09048 -0.00201 7 0 0 0 0 0 0 0 0.00
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0 1
51 C14 0.11055 0.14809 -0.09644 4 7 10 12 0 0 0 0 0.00
0 1
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0 1
53 C4 0.21536 -0.05399 -0.41761 1 2 3 35 0 0 0 0 0.00
0 1
54 C1 -0.14084 0.05736 -0.70746 15 16 17 20 0 0 0 0 0.00

0 1
55 H1A -0.23768 0.10781 -0.75350 14 0 0 0 0 0 0 0 0.00
0 1
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60 C2 -0.18835 0.00340 -0.57695 1 14 21 22 0 0 0 0 0.00
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0 1
63 C9 0.38255 -0.09728 -0.06168 5 24 25 26 0 0 0 0 0.00
0 1
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0 1
65 H9B 0.37171 -0.12247 0.03756 23 0 0 0 0 0 0 0 0.00
0 1
66 C10 0.35986 -0.17594 -0.18907 23 27 28 35 0 0 0 0 0.00
0 1
67 H10A 0.45844 -0.22554 -0.14171 26 0 0 0 0 0 0 0 0.00
0 1
68 H10B 0.22764 -0.20333 -0.22008 26 0 0 0 0 0 0 0 0.00
0 1
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0 1
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0 1
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0 1
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0 1
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0 1
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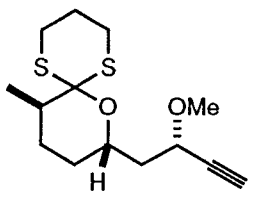
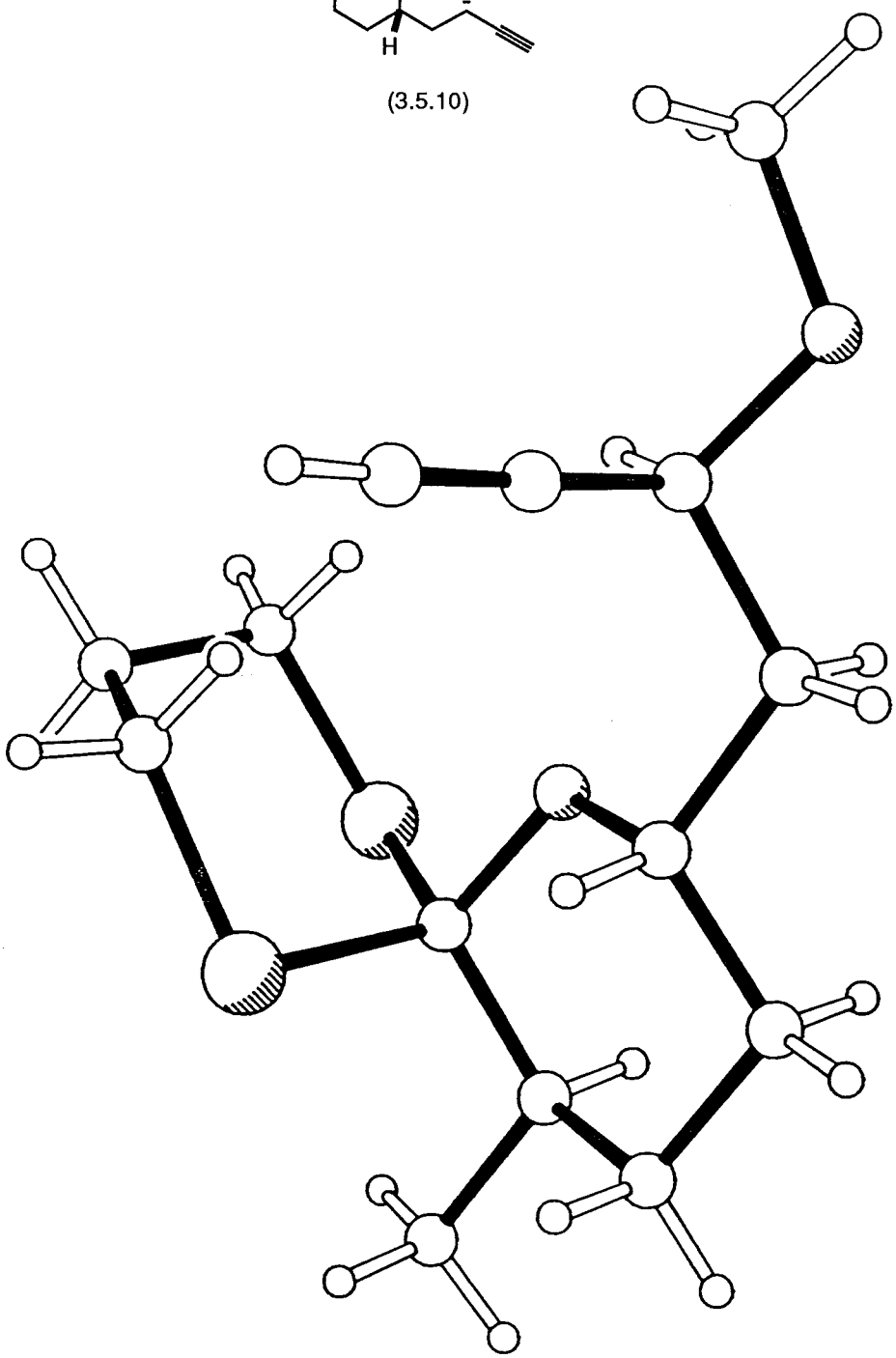


(3.5.10)



AH/SOTON in P2(1)

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