UNIVERSITY OF SOUTHAMPTON

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF RAPAMYCIN

by

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A Thesis Submitted for the Degree of Doctor of Philosophy

Department of Chemistry

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ABSTRACT

FACULTY OF SCIENCE

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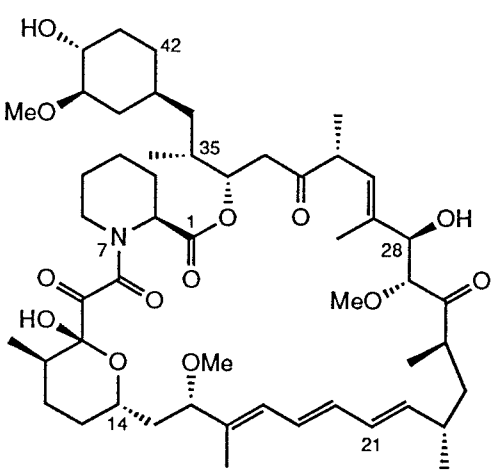
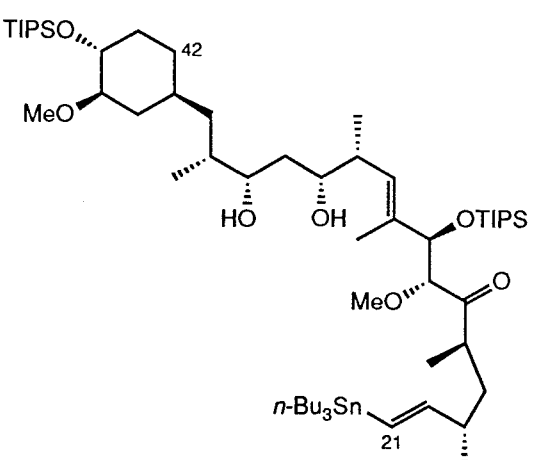
The stereocontrolled and convergent synthesis of an advanced C21-C42 fragment (**2.13.1.1**) of the potent immunosuppressant rapamycin was achieved by the coupling of C33-C42 fragment **2.13.4.1**, C26-C32 fragment **2.13.4.2** and C21-C25 fragment **2.13.4.3** using Mukaiyama and Evans aldol methodology.

The synthesis of **2.13.4.2** involved a highly diastereoselective Ireland-Claisen rearrangement and a novel use of furan photooxygenation in order to activate an all-carbon substituted allylic silane towards Fleming-Tamao oxidation under extremely mild conditions.



rapamycin



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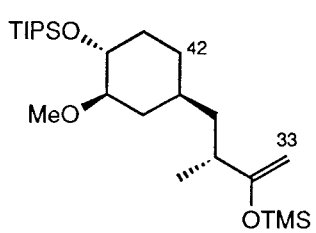

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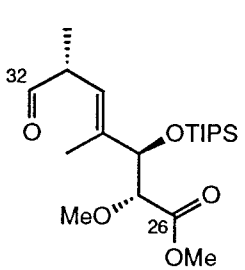

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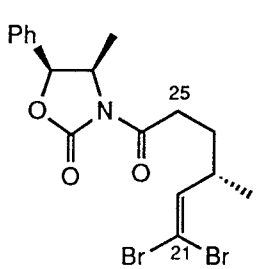

2.13.4.3

To Sonya

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobis(isobutyronitrile)
Aloc	allyloxycarbonyl
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
CI	chemical ionisation
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEIPS	diethylisopropylsilyl
DET	diethyl tartrate
DHP	dihydropyran
DIBALH	diisobutylaluminium hydride
DIC	1,3-diisopropylcarbodiimide
DIPHOS-4	1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride
e.e.	enantiomeric excess
EE	1-ethoxyethyl
EI	electron impact
Et	ethyl
FAB	fast atom bombardment
For	formyl

HCA	hexachloroacetone
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Ipc	isopinocampheyl
IR	infrared
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
NBA	*meta*-nitrobenzyl alcohol
NBD	2,5-norbornadiene
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMNO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NPSP	*N*-phenylselenylphthalimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPL	porcine pancreatic lipase
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTSA	*para*-toluenesulfonic acid
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl

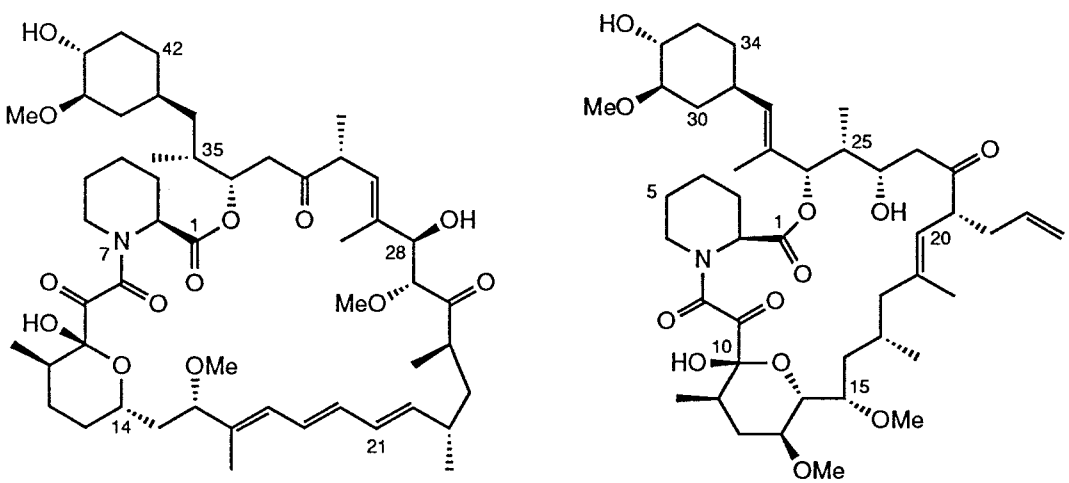
TDS	thexyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	*para*-toluenesulfonyl
UV	ultraviolet

Chapter 1

Biological Activity and Degradation of Rapamycin

1.1 Introduction

Rapamycin (Scheme **1.1.1**) is a 31-membered macrocyclic natural product first isolated[1,2] in 1975 from a strain of *Streptomyces hygroscopicus* found in an Easter Island soil sample. The structure of rapamycin was elucidated by Findlay[3,4] using a combination of chemical degradation, high field NMR spectroscopy and single-crystal X-ray analysis. In common with the structurally similar macrolide FK-506,[5] rapamycin displays potent immunosuppressive properties. Both compounds have thus attracted intense biological interest due to their potential therapeutic value in organ transplantation and in the treatment of autoimmune disorders.



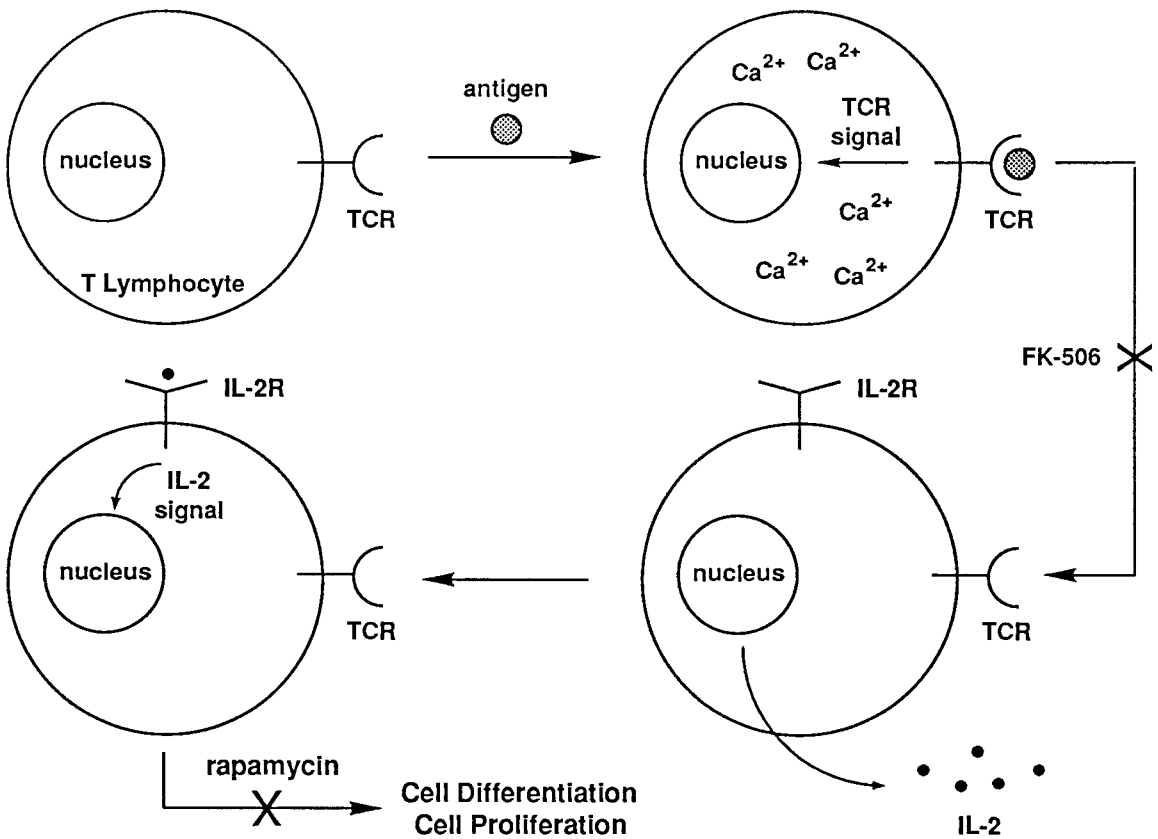
Scheme 1.1.1

Not surprisingly, the biological importance of rapamycin has led to high levels of interest at the chemical level. Notably, four total syntheses have been published, along with a number of fragment syntheses. Various degradations of rapamycin have also been reported. In this chapter a brief account of the biological activity of rapamycin will be followed by a review of the degradational studies which have been carried out. The numerous synthetic approaches to rapamycin will be reviewed separately in Chapter **2**.

1.2 Biological Activity

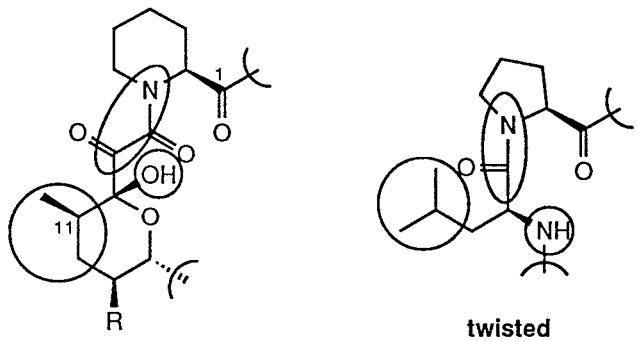
A great deal of effort has been devoted to determining the biological mode of action of rapamycin and FK-506, and the work towards this goal has been comprehensively reviewed by Schreiber.[6-10] Both rapamycin and FK-506 exert their immunosuppressive effect by inhibiting different cell signalling pathways that lead to T lymphocyte activation (Scheme **1.2.1**). T cell activation is triggered by stimulation of the T cell receptor (TCR) on the cell surface by a foreign antigen, resulting in activation of a Ca^{2+}-dependant TCR signal transmission pathway. The signal is transduced through the cytoplasm to the nucleus by an unknown mechanism and results in the extracellular secretion of the lymphokine interleukin

2 (IL-2) and also the expression of the IL-2 receptor (IL-2R) on the cell surface. When IL-2 binds to IL-2R, a Ca^{2+}-independent lymphokine receptor (LKR) signal transmission pathway is stimulated. The signal is again transduced through the cytoplasm to the nucleus, also by an unknown mechanism, leading to cell differentiation and proliferation. FK-506 blocks the initial Ca^{2+}-dependent TCR-mediated pathway, whereas rapamycin interferes with the later Ca^{2+}-independent LKR-mediated pathway.



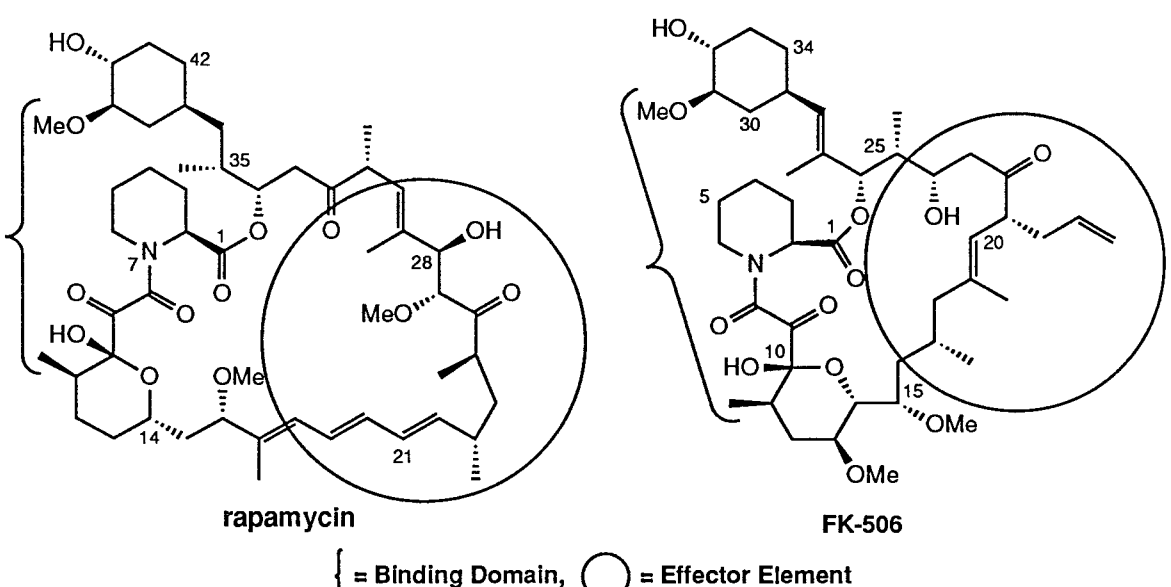
Scheme 1.2.1

Surprisingly, rapamycin and FK-506 interfere with the two pathways by first binding to the *same* cytoplasmic receptor protein, the immunophillin FKBP12 (*FK*-506 *B*inding *P*rotein). FKBP12 catalyses the interconversion of *cis*- and *trans*-rotamers of peptidyl-prolyl amide bonds and is potently inhibited by the binding of rapamycin and FK-506 through their common structural elements (C1-C11 and the cyclohexyl ring). In the solid state and when complexed with FKBP12, both rapamycin and FK-506 posess a dihedral angle of ca. 90° about the C8-C9 bond. The planar N7-C8 amide group thus places the keto carbonyl group roughly perpendicular to the plane of the pipecolinyl ring. Because the pipecolinyl ring most probably mimics the proline ring in natural peptide substrates, the keto carbonyl of rapamycin or FK-506 is in the same position as would be a twisted amide carbonyl group of a peptide undergoing rotamase catalysis. Thus, the perpendicular keto carbonyl groups of rapamycin and FK-506 allow the ligands to mimic a transition-state structure involving a twisted amide bond (Scheme **1.2.2**: structurally similar areas are circled).



Scheme 1.2.2

Because both rapamycin and FK-506 are potent inhibitors of the rotamase activity of FKBP12 yet inhibit different signalling pathways, it is evident that the biological effects of these agents are not simply due to their rotamase inhibition. Instead, it seems that the binding of rapamycin or FK-506 to FKBP12 produces an "active complex", and it is this species which is the actual effector in the inhibition of T cell activation. Rapamycin and FK-506 may therefore be viewed as prodrugs having a common *binding domain* through which they form complexes with FKBP12, but having different *effector elements* which determine the specific signalling pathway with which the immunophillin-drug complex will interfere (Scheme **1.2.3**).



Scheme 1.2.3

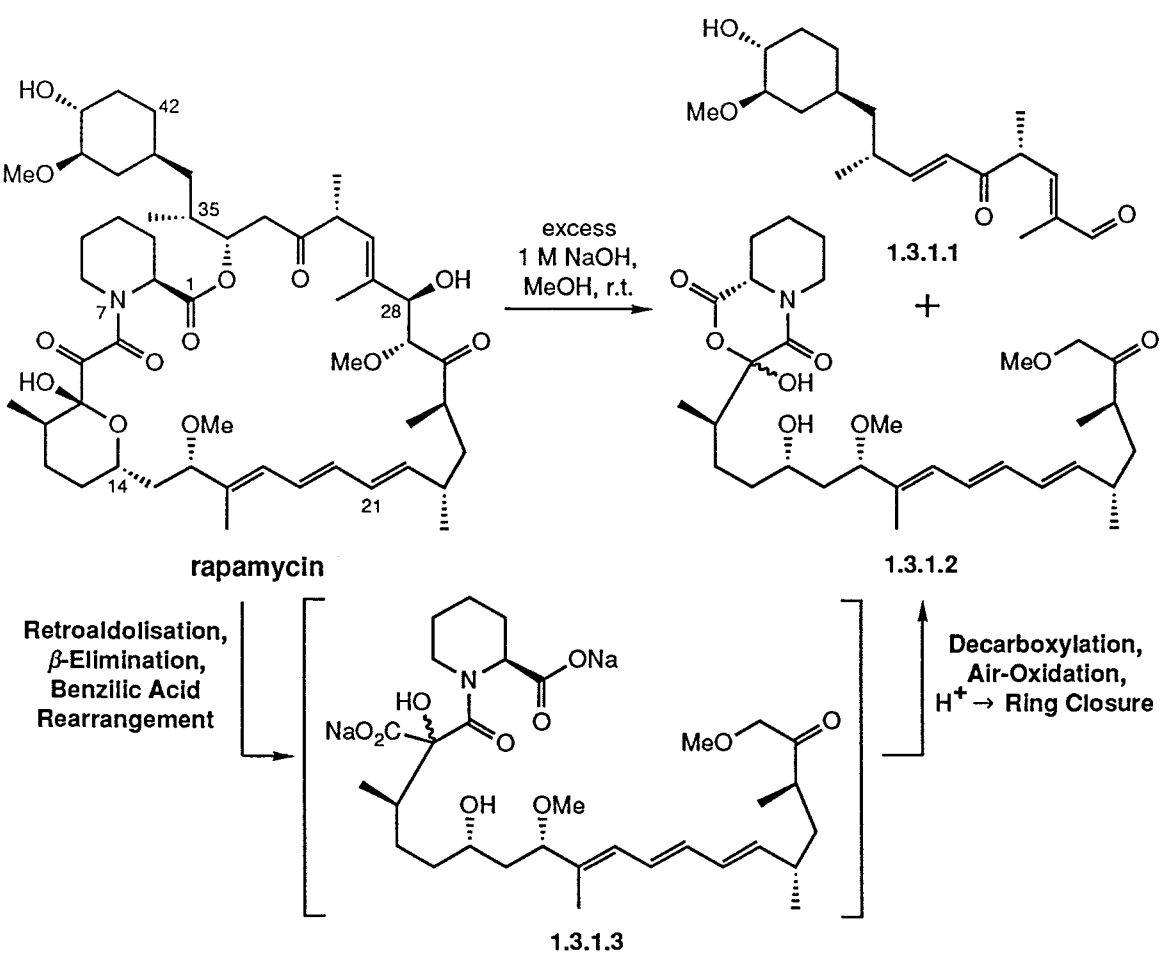
The downstream target of the FKBP12-FK-506 complex is the protein phosphatase calcineurin (CN), an enzyme which is activated by a rise in intracellular Ca^{2+} levels. Activated CN catalyses the dephosphorylation of a constitutive, cytoplasmic subunit (NF-AT_c) of the nuclear transcription factor NF-AT which regulates IL-2 transcription. Once dephosphorylated, NF-AT_c translocates into the nucleus and combines with the other constitutive subunits of NF-AT, leading to IL-2 transcription. It has been shown that the

FKBP12-FK-506 complex binds to calcineurin and potently inhibits its phosphatase activity. Thus, it is believed that the inhibition of IL-2 secretion by the FKBP12-FK-506 complex is the indirect result of inhibition of the dephosphorylation of NF-AT_c *via* binding of the complex to CN.

Rapamycin-mediated inhibition of T cell activation is thought to occur by a similar but distinct mechanism, whereby the FKBP12-rapamycin complex blocks the action of an intermediate protein involved in a Ca^{2+}-independent LKR signal transmission pathway. Indeed, such a target protein has recently been identified, although its function in signal transmission remains unclear.[11,12]

1.3 Degradation

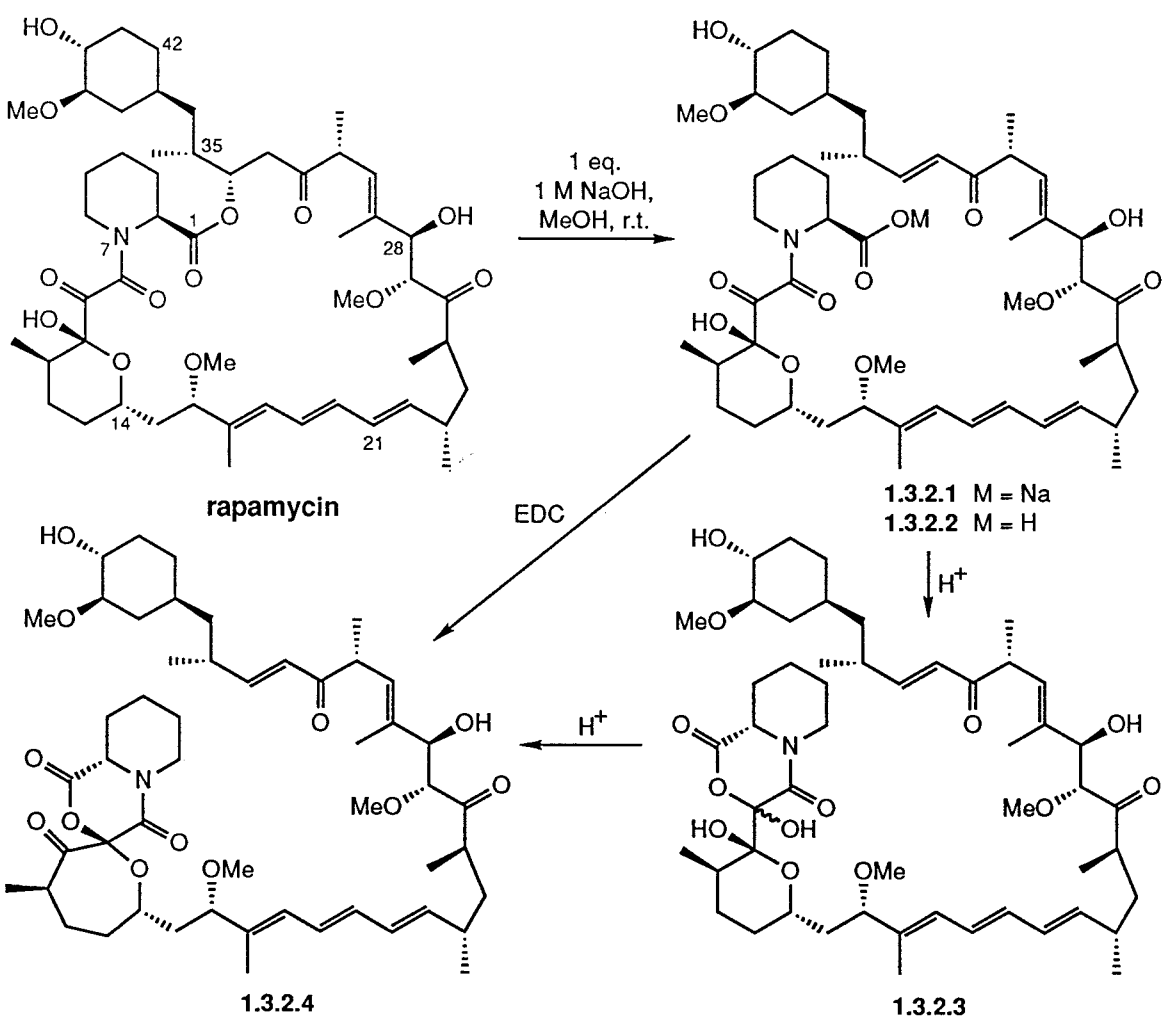
In the original structural elucidation of rapamycin, Findlay[4] showed that base-catalysed degradation (refluxing 1 M methanolic NaOH) led to a number of phenolic products derived from the C28-C42 segment. The only product isolated from the remainder of the molecule



Scheme 1.3.1

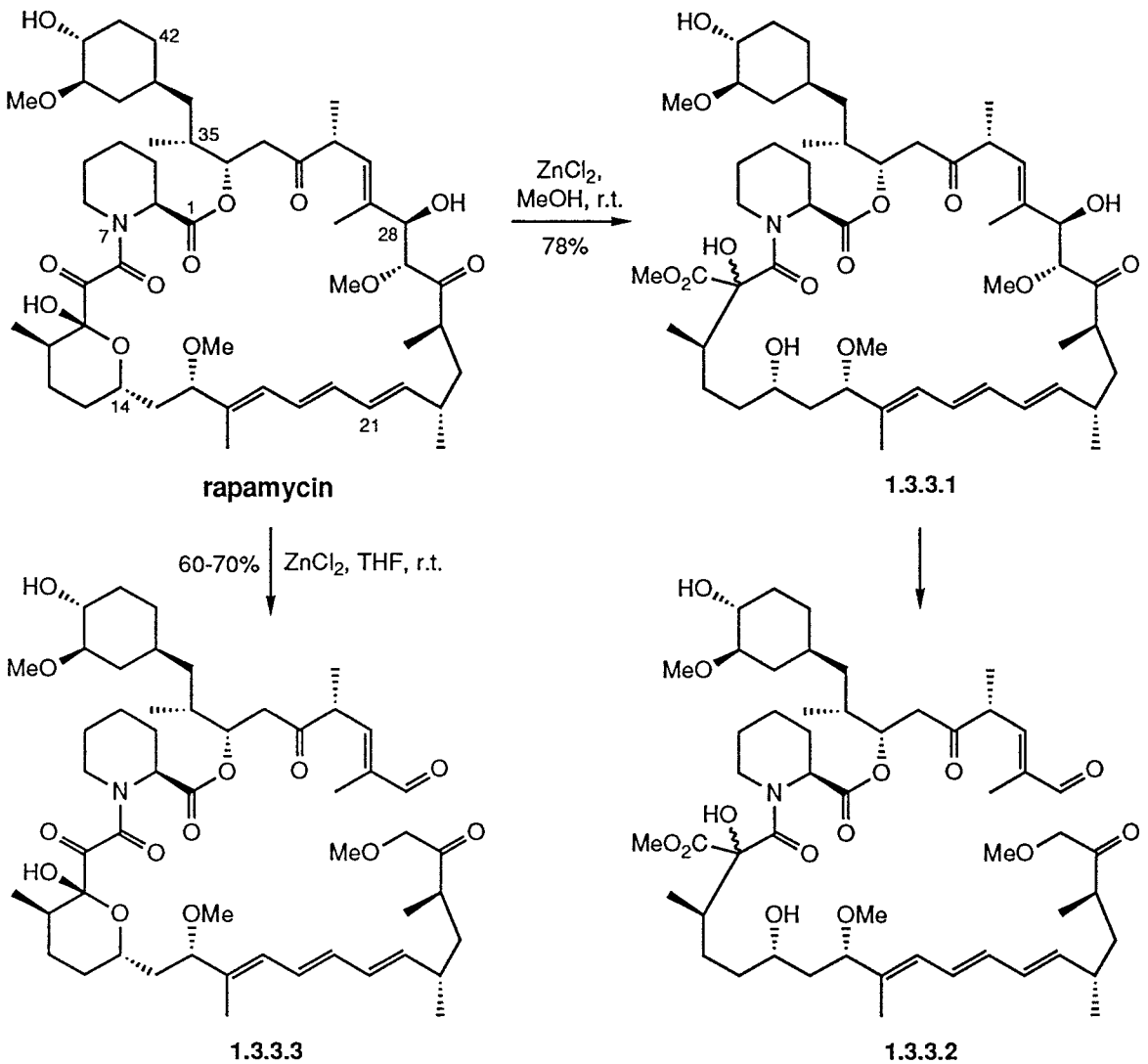
was L-pipecolinic acid. A milder base-catalysed degradation has been demonstrated by researchers at Wyeth-Ayerst,[13] whereby treatment of rapamycin with excess 1 M methanolic NaOH at room temperature (Scheme **1.3.1**) gave enone-enal **1.3.1.1** and 2-hydroxy-3,6-diketomorpholine **1.3.1.2**. The former arises from C27-C28 retroaldol cleavage and C34 carboxylate β-elimination, whereas the latter presumably arises from C8-C9 benzilic acid rearrangement of the initially formed degradation fragment to produce intermediate **1.3.1.3**, which then undergoes decarboxylation and air-oxidation to form an α-ketoamide. Upon acidification this product ring-closes to **1.3.1.2**.

By using just 1 eq. of NaOH (Scheme **1.3.2**), or by using amines as the source of base (DMAP, CH_2Cl_2, Δ *or* Et_2NH, MeOH, r.t.), benzilic acid rearrangement was suppressed and acid salt **1.3.2.1** was obtained *via* β-elimination. Interestingly, **1.3.2.1** was not epimerised at C31 when NaOH was used as the base. However, the other conditions employed (DMAP or Et_2NH) gave substantial epimerisation. Upon acidification **1.3.2.1**, although isolable as the free acid **1.3.2.2**, ring-closes to form 2-hydroxy-3,6-diketomorpholine **1.3.2.3**. Prolonged treatment with aq. HCl or treatment of **1.3.2.2** with EDC led to loss of water with the formation of spirolactone **1.3.2.4**.



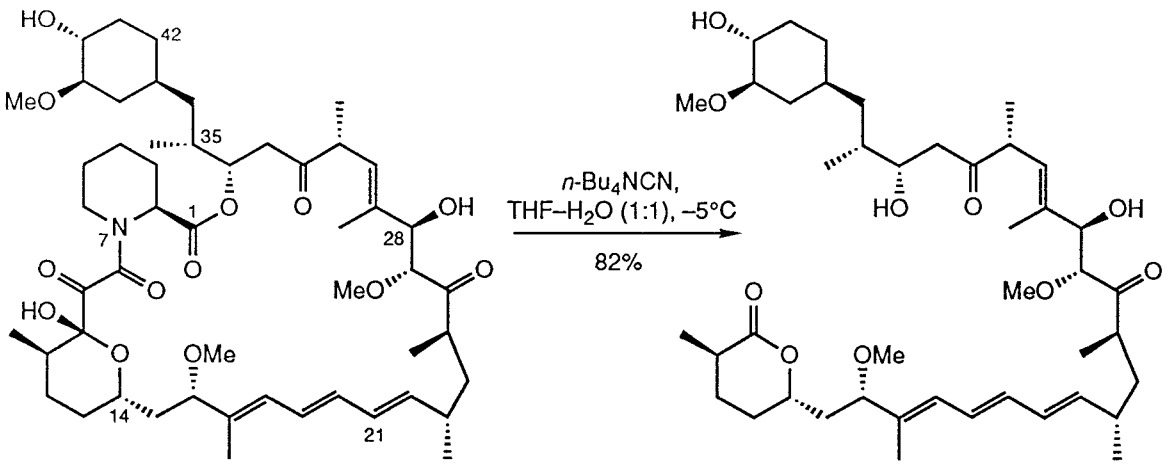
Scheme 1.3.2

Workers at SmithKline Beecham have demonstrated[14] that benzilic acid rearrangement of rapamycin also occurs under mild Lewis acid catalysis ($ZnCl_2$ in MeOH) without ring cleavage (Scheme **1.3.3**) to afford methyl ester **1.3.3.1**. Treatment of rapamycin with $ZnCl_2$/MeOH for extended periods, however, did lead to retroaldolisation, producing enal **1.3.3.2**. Interestingly, retroaldol fragmentation without accompanying benzilic acid rearrangement could be promoted by simply switching to THF as solvent, producing enal **1.3.3.3**.



Scheme 1.3.3

The SmithKline Beecham team have also reported an efficient method of removing the binding domain from rapamycin.[15] Treatment with *n*-Bu_4NCN (2 eq.) in aq. THF (Scheme **1.3.4**) provided lactone **1.3.4.1** arising from cyanide attack at the C9 carbonyl followed by retro-Claisen-like fragmentation and cyanide-catalysed ester hydrolysis.

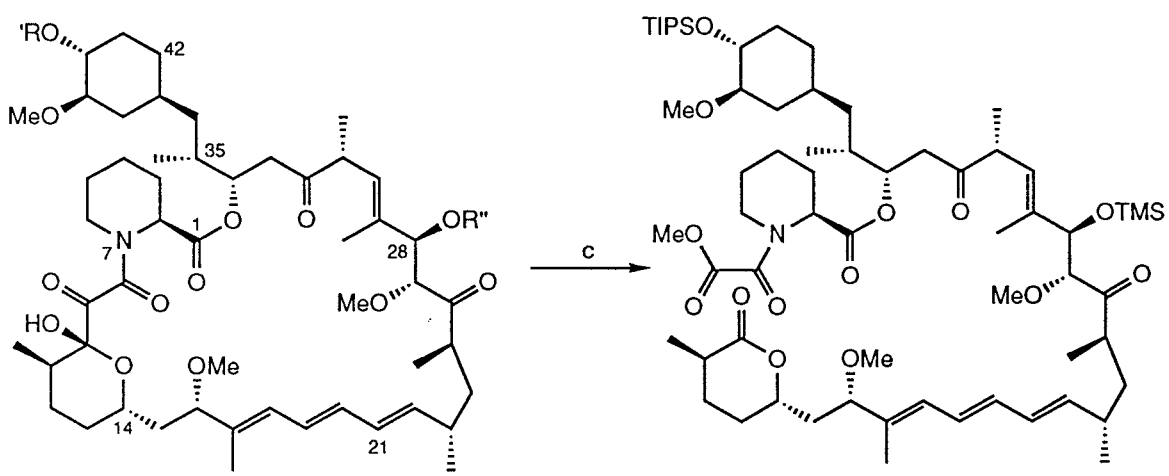


rapamycin

1.3.4.1

Scheme 1.3.4

The Danishefsky group have degraded rapamycin[16] in order to obtain key substructures for comparison with intermediates prepared in their total synthesis program (Section **2.4**). Thus, bis-silylated derivative **1.3.5.1** (Scheme **1.3.5**) was obtained from rapamycin by sequential TIPS- and TMS-protection of the C40 and C28 hydroxyls respectively. Treatment of **1.3.5.1** with $Pb(OAc)_4$ in MeOH then provided seco derivative **1.3.5.2** in excellent yield.



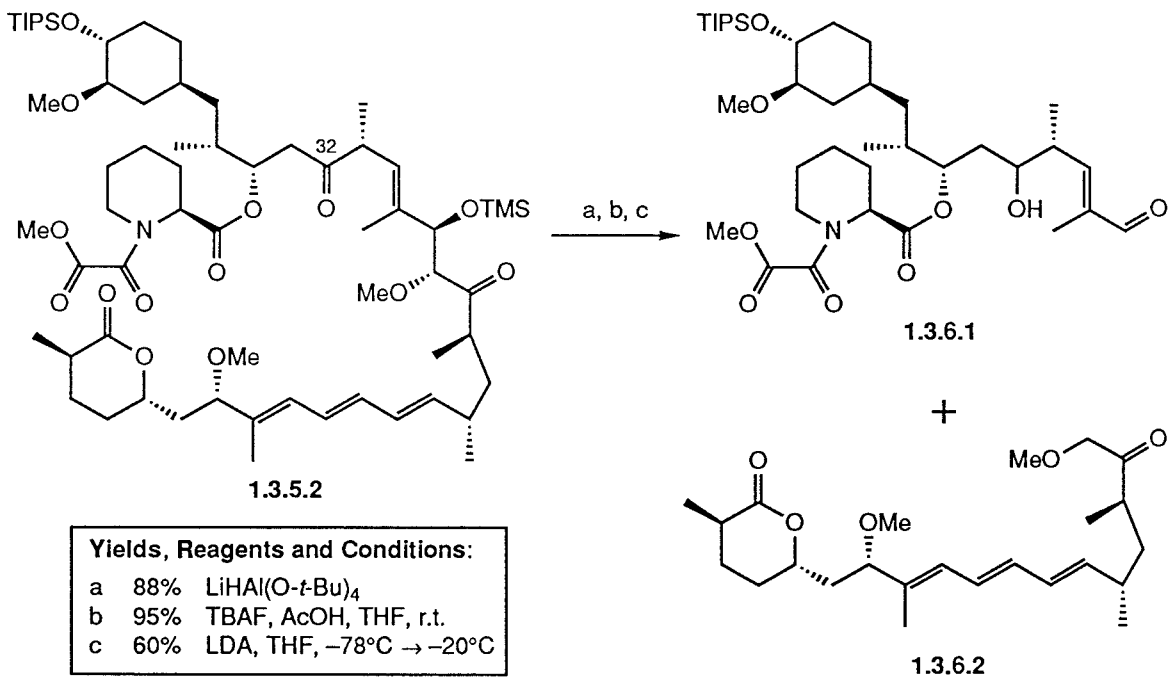
1.3.5.2

a, b → **rapamycin** R' = R" = H; 1.3.5.1 R' = TIPS, R" = TMS

Yields, Reagents and Conditions:		
a	–	TIPSOTf, 2,6-lutidine, –78°C
b	–	TMSOTf, 2,6-lutidine, –78°C
c	92%	$Pb(OAc)_4$, MeOH, 0°C

Scheme 1.3.5

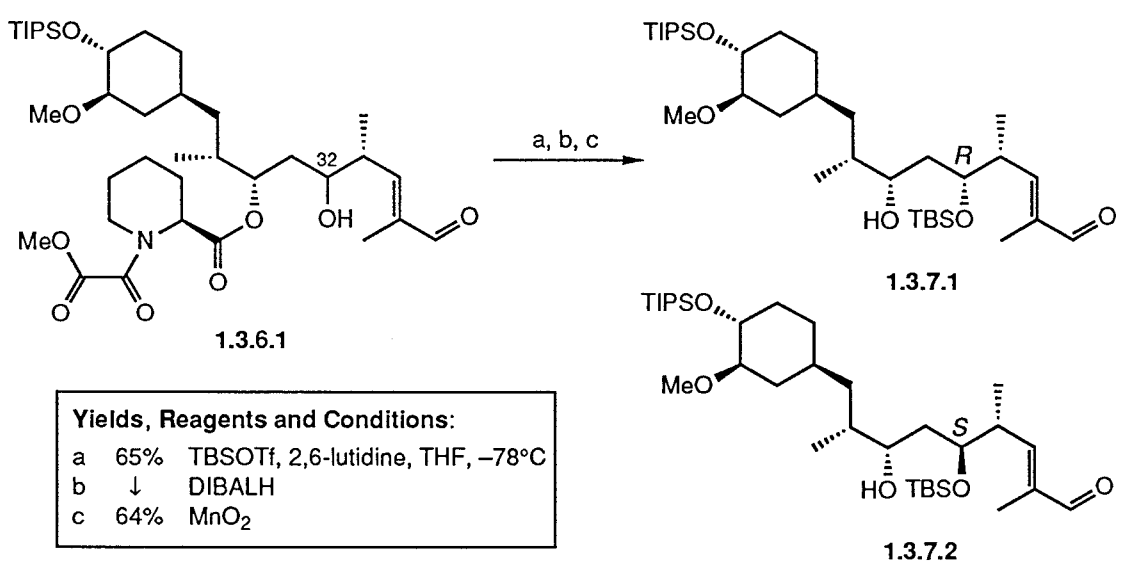
Reduction of the C32 ketone in **1.3.5.2** (Scheme **1.3.6**) with $LiHAl(O\text{-}t\text{-}Bu)_3$ afforded the corresponding alcohol as a single diastereomer (of unknown C32 stereochemistry at this stage). Removal of the TMS protecting group followed by retroaldolisation with LDA then led to enal **1.3.6.1** and lactone **1.3.6.2**.



Yields, Reagents and Conditions:		
a	88%	$LiHAl(O\text{-}t\text{-}Bu)_4$
b	95%	TBAF, AcOH, THF, r.t.
c	60%	LDA, THF, –78°C → –20°C

Scheme 1.3.6

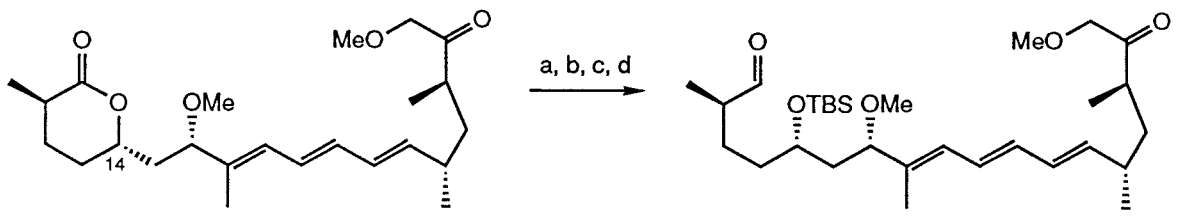
TBS protection of the C32 hydroxyl in enal **1.3.6.1** (Scheme **1.3.7**), followed by reductive deacylation of the pipecolinate moiety and reoxidation of the resulting allylic alcohol provided compound **1.3.7.1**. This product proved to be similar to, but not identical with the fully synthetic compound **1.3.7.2** possessing, unambiguously, the (*S*)-stereochemistry at C32. Correspondingly, the C32 stereocentre of **1.3.7.1** was assigned to be of the (*R*)-configuration.



Yields, Reagents and Conditions:		
a	65%	TBSOTf, 2,6-lutidine, THF, –78°C
b	↓	DIBALH
c	64%	MnO_2

Scheme 1.3.7

Lactone **1.3.6.2** (Scheme **1.3.8**) was converted to aldehyde **1.3.8.1** in four steps *via* methanolysis of the lactone and silylation of the C14 hydroxyl, followed by exhaustive reduction with DIBALH and oxidation. Compound **1.3.8.1** was found to be identical with the fully synthetic material.

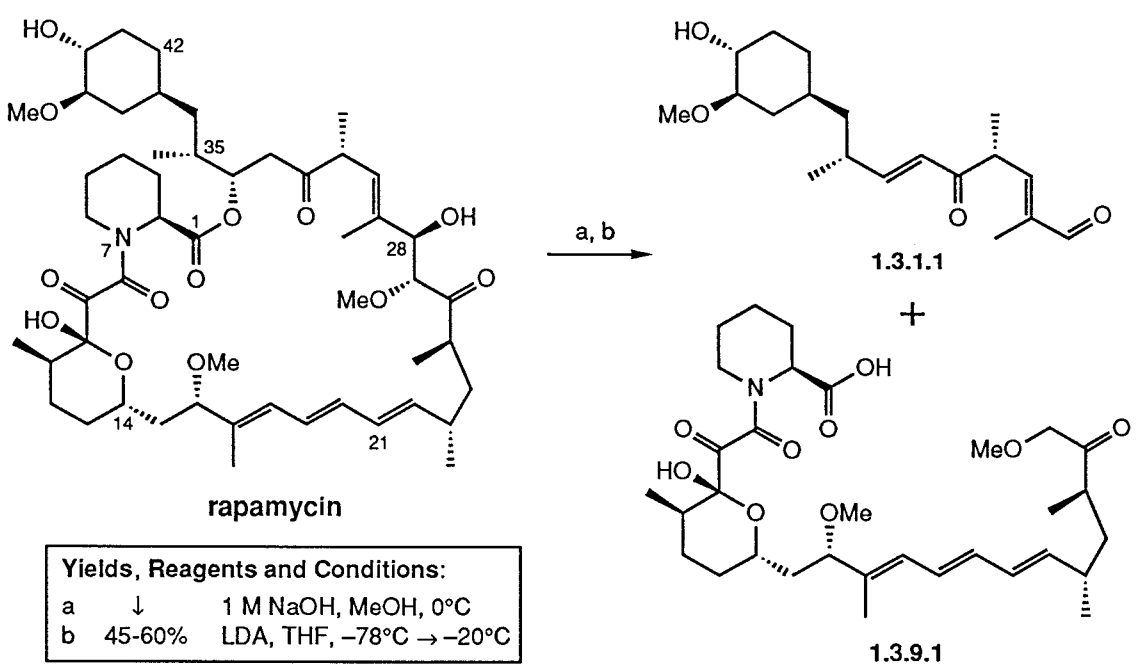


1.3.6.2 1.3.8.1

Yields, Reagents and Conditions:		
a	99%	MnO_2, MeOH
b	86%	TBSCl, imidazole
c	↓	DIBALH
d	85%	Dess-Martin Periodinane

Scheme 1.3.8

In a related study (Scheme **1.3.9**),[17] Danishefsky required C1-C27 fragment **1.3.9.1** in order to study its suitability as an acylating moiety. The requisite acid was obtained from rapamycin in two steps *via* base-catalysed deacylation at C34 followed by retroaldolisation of the resulting acid salt (**1.3.2.1**, *vide supra*) with LDA. Upon acidification **1.3.9.1** was obtained in 45-60% yield, along with previously mentioned enone-enal **1.3.1.1**.

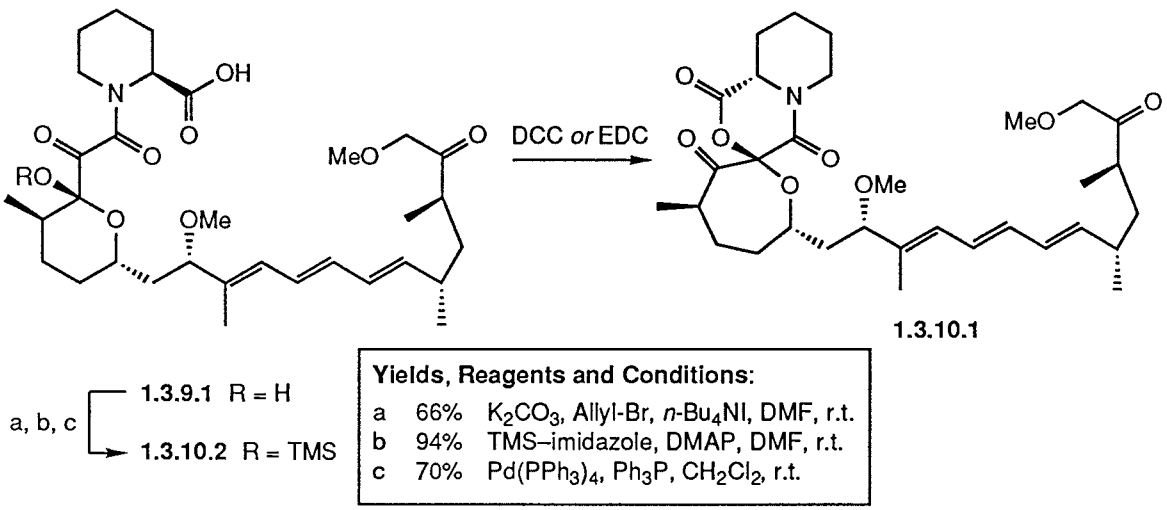


rapamycin

Yields, Reagents and Conditions:		
a	↓	1 M NaOH, MeOH, 0°C
b	45-60%	LDA, THF, −78°C → −20°C

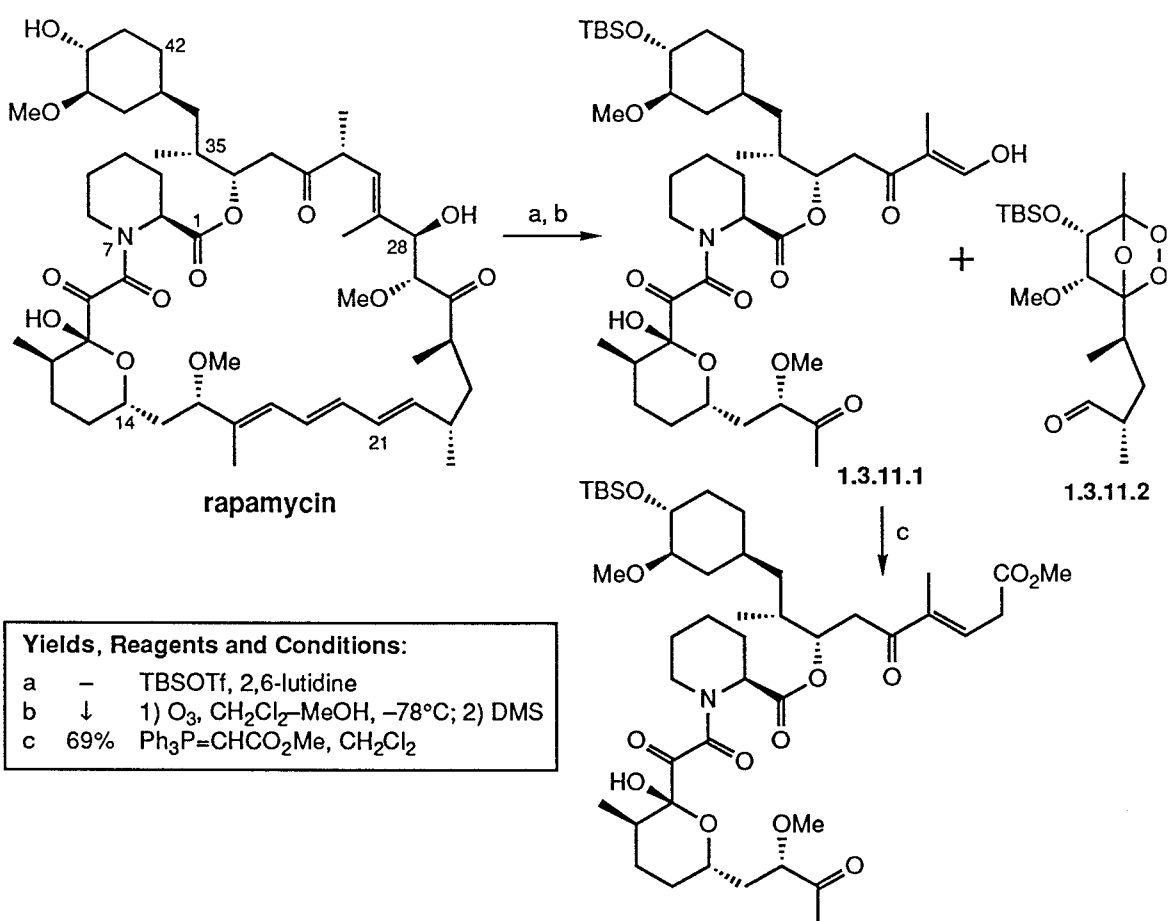
Scheme 1.3.9

Attempts to acylate several alcohols with **1.3.9.1** under carboxyl-activating conditions (DCC or EDC), however, afforded spirolactone **1.3.10.1** (cf. **1.3.2.4**) (Scheme **1.3.10**). To suppress this facile lactonisation the tertiary C10 hydroxyl was protected as its TMS ether, following initial protection of the carboxyl as the corresponding allyl ester. Deallylation with $Pd(PPh_3)_4$ then afforded mono-TMS derivative **1.3.10.2** which was successfully esterified with alcohol **1.3.7.2** (*vide supra*) in the final stages of Danishefsky's total synthesis of rapamycin.



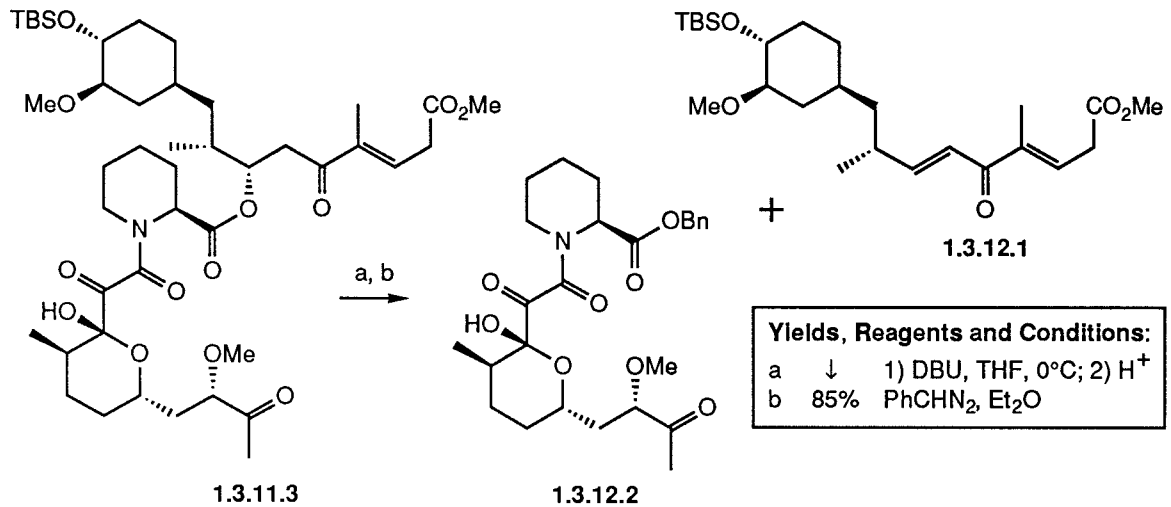
Scheme 1.3.10

Finally, researchers at Merck Sharp and Dohme have degraded rapamycin ozonolytically in order to obtain synthetically useful fragments (Scheme **1.3.11**).[18] Thus, bis-silylation of the C28 and C40 hydroxyls, followed by exhaustive ozonolysis, provided unstable enol **1.3.11.1** and bicyclic peroxide **1.3.11.2** (the latter was obtained as a single unidentified



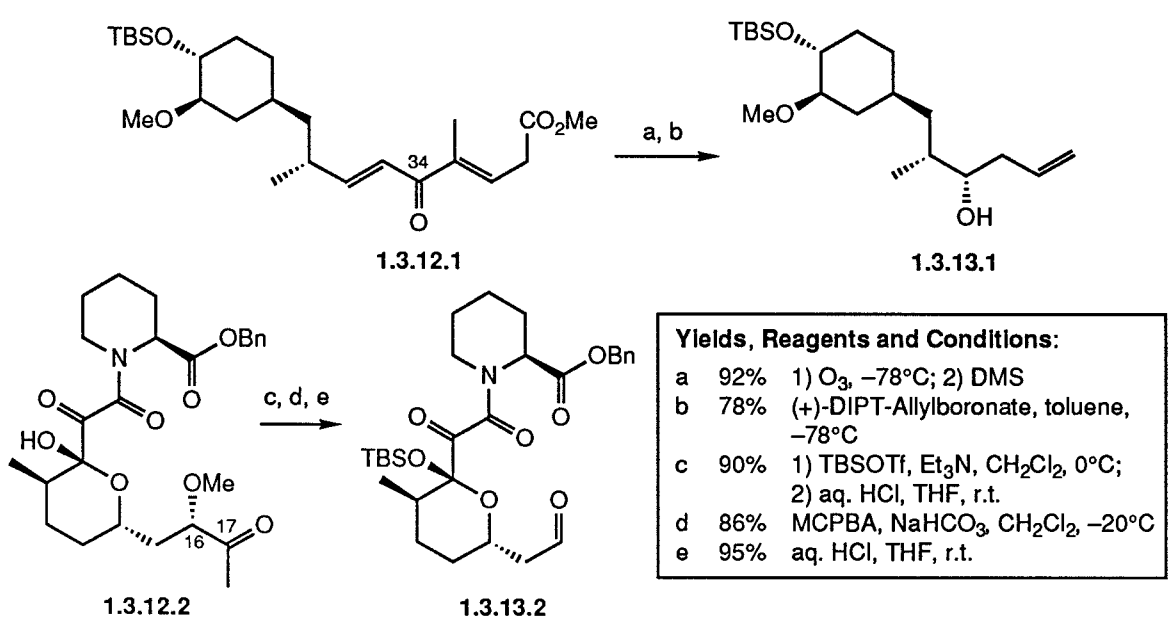
Scheme 1.3.11

diastereomer). Subsequent treatment of **1.3.11.1** with triphenylphosphoranylacetate yielded β,γ-unsaturated ester **1.3.11.3** (due to an olefin isomerisation). Elimination of the C34 acyl group by treatment of **1.3.11.3** with DBU (Scheme **1.3.12**) and exposure of the crude product to $PhCHN_2$ then yielded fragments **1.3.12.1** and **1.3.12.2**.



Scheme 1.3.12

In order to regenerate the C34 hydroxyl, dienone **1.3.12.1** was subjected to ozonolysis followed by allylboration of the intermediate aldehyde (Scheme **1.3.13**), thereby affording homoallylic alcohol **1.3.13.1**. Aldehyde **1.3.13.2** was obtained *via* Baeyer-Villiger cleavage of the C16-C17 bond in ketone **1.3.12.2** (after initial TBS protection of the tertiary hydroxyl) followed by hydrolysis of resulting mixed acetal. Fragments **1.3.13.1** and **1.3.13.2** were used in the construction of an FK-506 analogue.[19]



Scheme 1.3.13

1.4 Conclusion

In this chapter the biological mode of action of rapamycin has been outlined, and the degradative procedures which have been carried out on the natural product have been reviewed. The binding of rapamycin to FKBP12 is the first step in a complex chain of cellular reactions ultimately leading to the observed immunosuppressive effect. The latter stages of this pathway remain unclear, and the ongoing work directed towards the further elucidation of rapamycin's mode of action is an intense area of research. In this field, degradation of the natural product should play a key role, by providing intact fragments which may be reassembled to provide structural analogues with modified biological effects. Degradation has also served to identify the functional instabilities present in rapamycin (C27-C28 retroaldol cleavage, C34 carboxylate β-elimination, C8-C9 benzilic acid rearrangement, C31 epimerisation), and has provided useful fragments for comparison and relay in Danishefsky's synthetic program.

Chapter 2

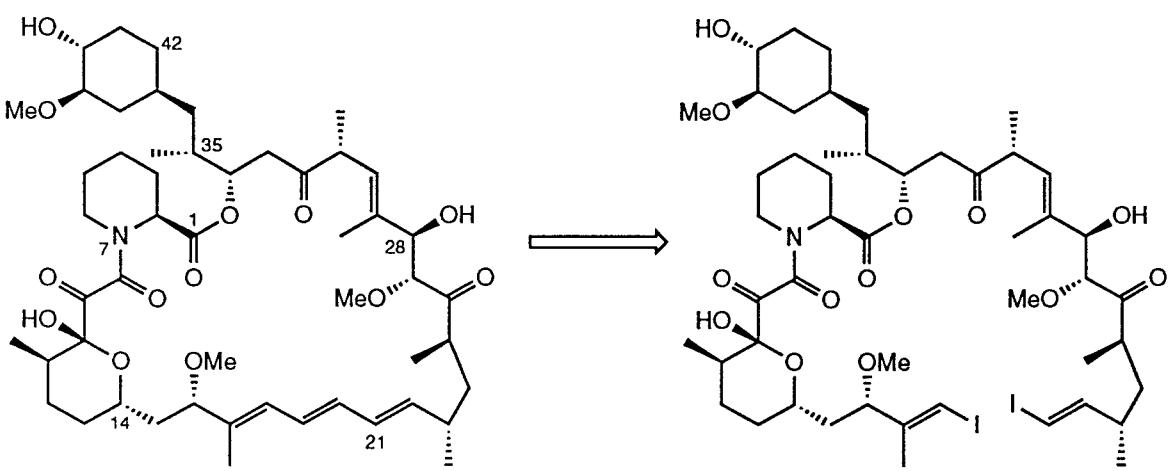
Synthetic Approaches to Rapamycin

2.1 Introduction

The first total synthesis of rapamycin was published by the Nicolaou group in 1993. This was closely followed by syntheses from Schreiber and Danishefsky, also in 1993, and later from Smith in 1995. A number of syntheses of various fragments have also been reported. In this chapter the synthetic work towards rapamycin will be reviewed, culminating in a description of the Southampton approach.

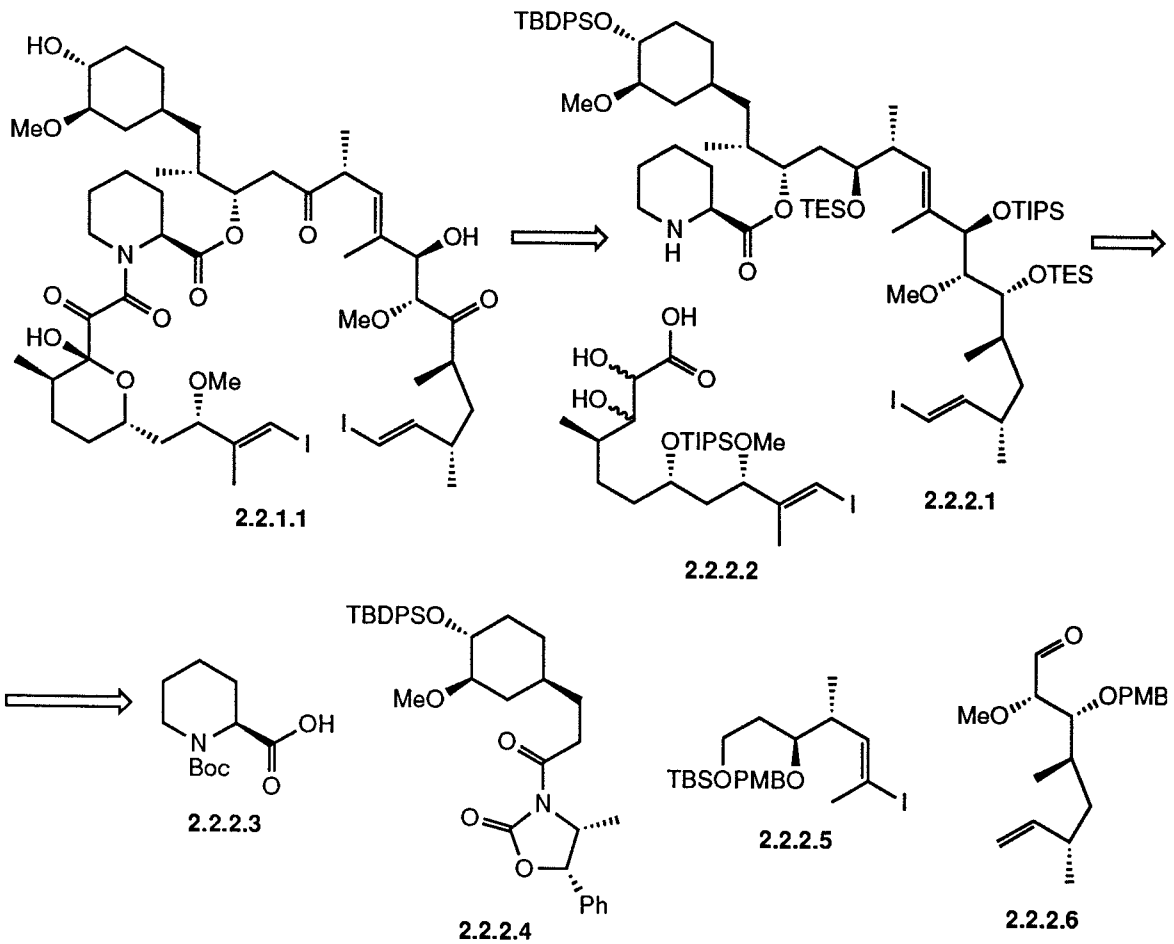
2.2 The Nicolaou Total Synthesis

Nicolaou's strategy for the synthesis of rapamycin (Scheme **2.2.1**)[20-23] identified fully functionalised acyclic precursor **2.2.1.1** and C19-C20 enedistannane **2.2.1.2** as coupling partners in a "stitching-cyclisation" process, whereby the olefinic bridging unit would bring together the two terminal vinyl iodides of **2.2.1.1** in a Stille-type reaction to form the triene and macrocycle simultaneously. Such a strategy would thus furnish the natural product in a single, final step and would avoid instability problems, deprotection steps, and late stage oxidation state adjustments.



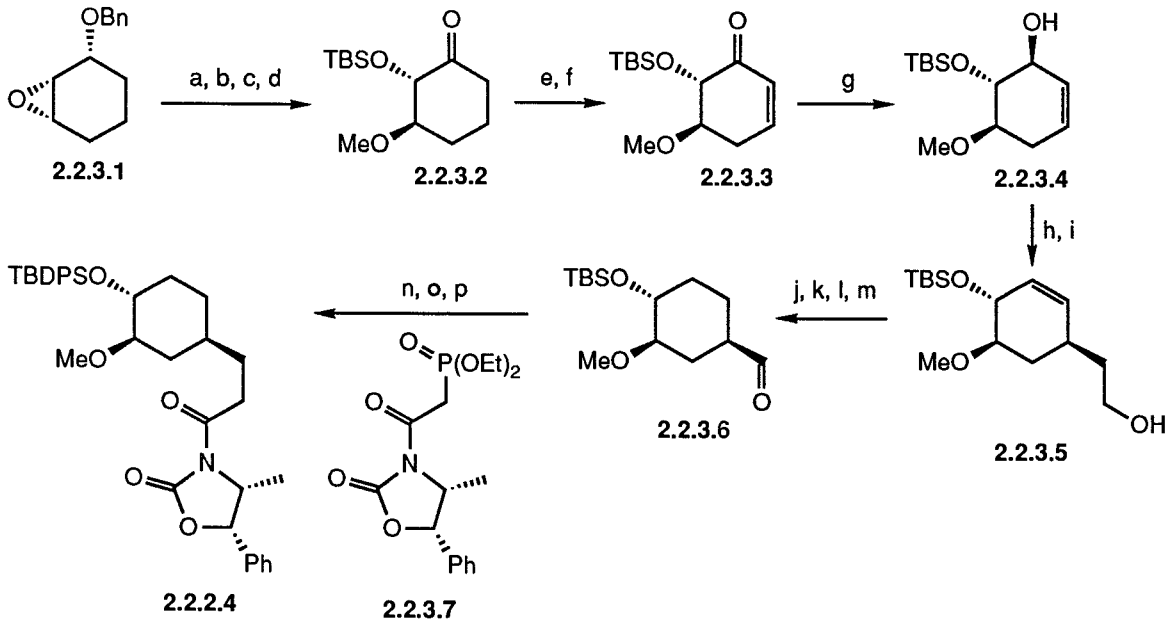
Scheme 2.2.1

Disconnection of **2.2.1.1** at the C7-C8 amide bond reveals two advanced fragments, **2.2.2.1** and **2.2.2.2** (Scheme **2.2.2**), of which the more complex **2.2.2.1** may be further dissected to identify subunits **2.2.2.3**–**2.2.2.6** as building blocks.



Scheme 2.2.2

The synthesis of cyclohexyl fragment **2.2.2.4** (Scheme **2.2.3**) began with epoxide **2.2.3.1**, prepared from 2-bromocyclohexenone by asymmetric reduction, followed by removal of the bromine with Li/*t*-BuOH, epoxidation using MCPBA, and benzylation. Regioselective opening of the epoxide with CSA in MeOH followed by standard transformations yielded ketone **2.2.3.2**. Enone **2.2.3.3** was then formed from **2.2.3.2** *via* its TMS enol ether by oxidation with $Pd(OAc)_2$. Stereoselective Luche reduction of the enone afforded allylic alcohol **2.2.3.4**, which underwent a stereospecific Eschenmoser-Claisen rearrangement upon heating with *N,N*-dimethylacetamide dimethyl acetal. The resulting amide was reduced to provide primary alcohol **2.2.3.5**, which, after hydrogenation of the double bond, was converted to aldehyde **2.2.3.6** *via* selenoxide formation/elimination and ozonolysis. Condensation of **2.2.3.6** with phosphonate **2.2.3.7** (prepared *via* an Arbuzov reaction of the corresponding bromoacetyloxazolidinone with triethyl phosphite) followed by 1,4-reduction of the resulting α,β-unsaturated *N*-acyloxazolidinone then yielded **2.2.2.4**.

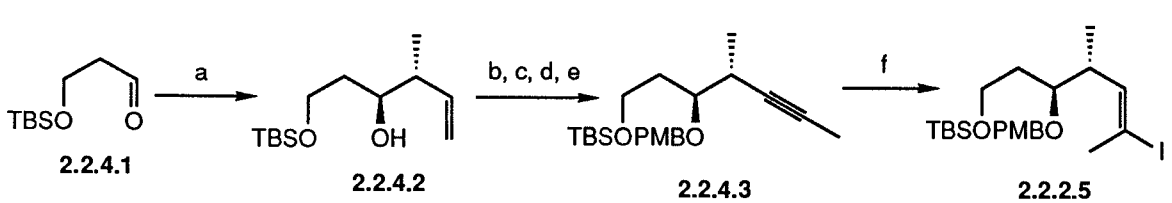


Yields, Reagents and Conditions:

a	90%	CSA, MeOH, r.t.
b	91%	TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C
c	98%	Pd/C, H_2, EtOH, r.t.
d	92%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → –10°C
e	↓	1) LDA, THF, –78°C; 2) TMSCl, –78°C → r.t.
f	83%	$Pd(OAc)_2$, MeCN, 50°C
g	95%	$LiBH_4$, $CeCl_3 \cdot 7H_2O$, THF–MeOH, –78°C
h	↓	*N,N*-dimethylacetamide dimethyl acetal, xylenes, Δ
l	97%	$LiEt_3BH$, THF, 0°C
j	↓	Pd/C, H_2, EtOH, r.t.
k	93%	*o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF, r.t.
l	86%	aq. H_2O_2, THF, r.t.
m	88%	1) O_3, CH_2Cl_2–MeOH, –78°C; 2) DMS, –78°C → r.t.
n	96%	1) **2.2.3.7**, LiCl, *i*-Pr_2NEt, MeCN, r.t.; 2) **2.2.3.6**
o	↓	1) $Rh(PPh_3)_3Cl$, Et_3SiH, 50°C; 2) aq. HF, MeCN, r.t.
p	75%	TBDPSCl, Imidazole, DMF, r.t.

Scheme 2.2.3

In the synthesis of vinyl iodide **2.2.2.5** (Scheme **2.2.4**) alcohol **2.2.4.2** was stereoselectively formed by asymmetric crotylboration of aldehyde **2.2.4.1** (prepared from but-1-en-4-ol by silylation followed by ozonolysis) using Brown's conditions. PMB-protection of the alcohol followed by ozonolysis of the terminal double bond and Corey-Fuchs homologation then provided methyl acetylene **2.2.4.3**, which was converted to **2.2.2.5** *via* hydrozirconation and quenching with iodine.

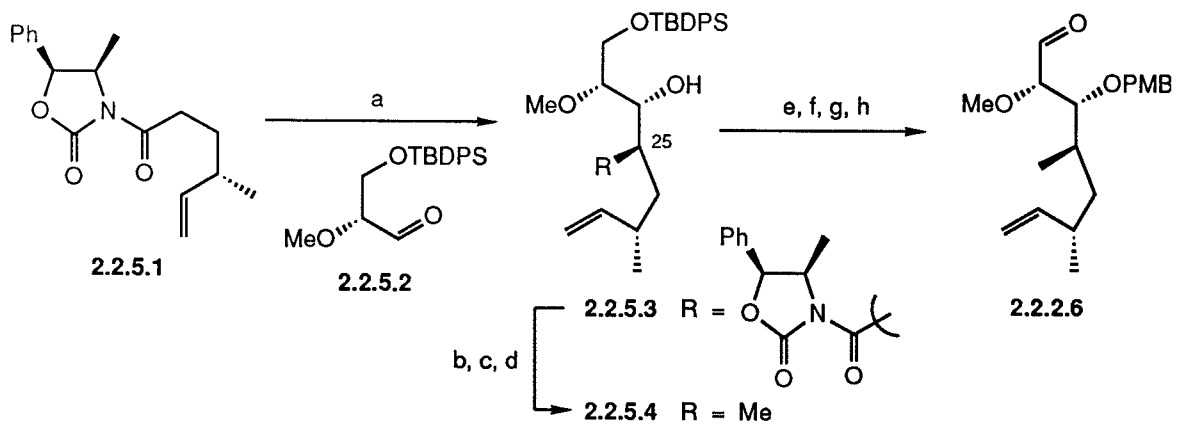


Yields, Reagents and Conditions:

a	75%	(*E*)-but-2-ene, *t*-BuOK, *n*-BuLi, (+)-Ipc_2BOMe, $BF_3 \cdot OEt_2$, THF, –78°C → r.t.
b	90%	NaHMDS, PMBBr, THF–DMF, 0°C
c	80%	1) O_3, CH_2Cl_2–MeOH–pyridine, –78°C; 2) DMS, –78°C → r.t.
d	100%	CBr_4, Ph_3P, Zn, CH_2Cl_2, r.t.
e	98%	1) *n*-BuLi, THF, –78°C → –20°C; 2) MeI, –20°C → 0°C
f	85%	1) Cp_2ZrHCl, CH_2Cl_2, r.t.; 2) I_2, 0°C

Scheme 2.2.4

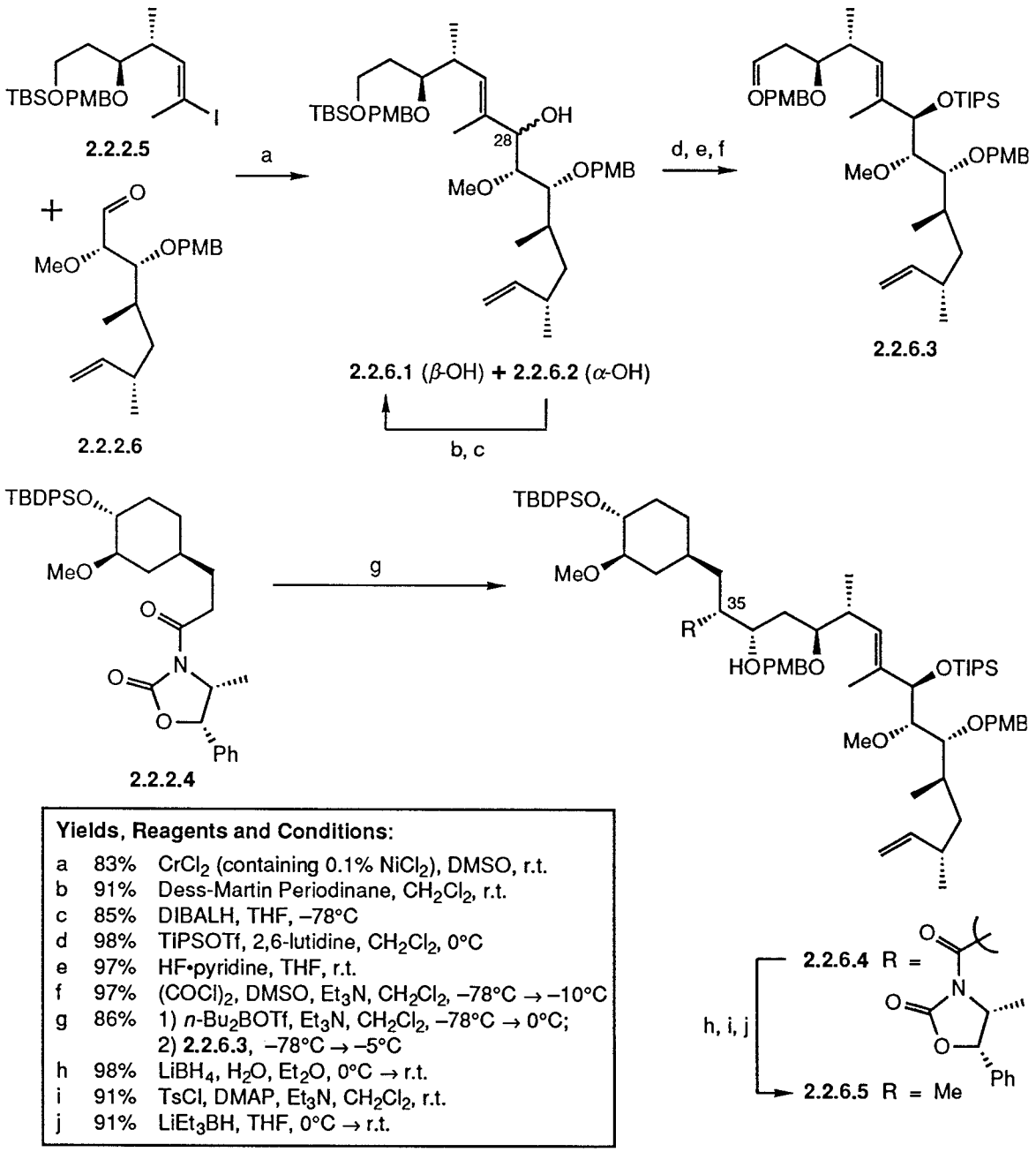
The synthesis of aldehyde **2.2.2.6** is depicted in scheme **2.2.5**. *N*-Acyloxazolidinone **2.2.5.1** was obtained from (+)-β-citronellene by selective cleavage of the trisubstituted double bond (MCPBA, $HClO_4$, $NaIO_4$, then Jones oxidation) followed by pivaloate mixed anhydride formation and condensation with the required lithio-oxazolidinone. The other requisite intermediate, aldehyde **2.2.5.2**, was prepared from bis(benzylidene)mannitol by bis-methylation, removal of the benzylidene protecting groups, selective silylation at the primary positions and cleavage of the 1,2-diol. Coupling of **2.2.5.1** and **2.2.5.2** under Evans aldol conditions yielded alcohol **2.2.5.3**. The chiral auxiliary-bearing side chain was then converted to the requisite C25 methyl group in **2.2.5.4** *via* a three-step reduction–tosylation–reduction sequence. Transformation of **2.2.5.4** to **2.2.2.6** then followed standard procedures.



Yields, Reagents and Conditions:		
a	73%	1) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, –78°C → 0°C; 2) **2.2.5.2**, –78°C → –10°C
b	98%	$LiBH_4$, H_2O, Et_2O, 0°C → r.t.
c	78%	TsCl, Et_3N, DMAP, CH_2Cl_2, 0°C
d	92%	$LiEt_3BH$, THF, 0°C → r.t.
e	92%	TBAF, THF, r.t.
f	97%	$PMPCH(OMe)_2$, CSA, CH_2Cl_2, r.t.
g	96%	DIBALH, CH_2Cl_2, –78°C → r.t.
h	97%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → r.t.

Scheme 2.2.5

The coupling of intermediates **2.2.2.3**–**2.2.2.6** and their further elaboration to advanced fragment **2.2.2.1** was accomplished as summarised in Schemes **2.2.6** and **2.2.7**. Thus, vinyl iodide **2.2.2.5** and aldehyde **2.2.2.6** were coupled by means of a Nozaki-Kishi reaction to afford alcohol **2.2.6.1** along with its C28 epimer **2.2.6.2** in a ratio of ca. 2:1. The undesired minor isomer was converted to **2.2.6.1** *via* oxidation to the corresponding ketone followed by stereoselective reduction with DIBALH at –78°C. Three standard conversions then provided aldehyde **2.2.6.3**, which was condensed with the boron enolate of *N*-acyloxazolidinone **2.2.2.4** to stereoselectively afford aldol product **2.2.6.4**. The requisite C35 methyl group in **2.2.6.5** was then generated from the side chain bearing the chiral auxiliary *via* the three-step procedure as described earlier.

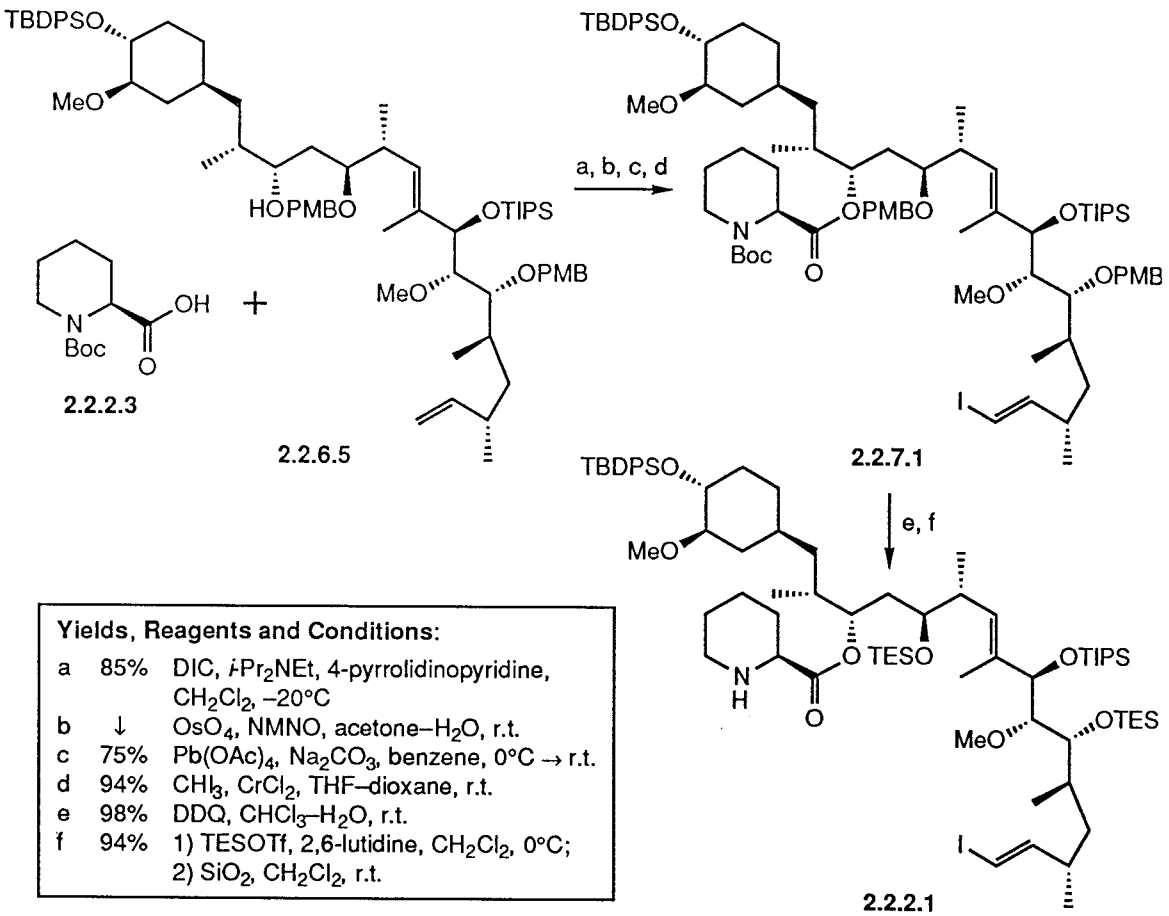


Yields, Reagents and Conditions:

a	83%	$CrCl_2$ (containing 0.1% $NiCl_2$), DMSO, r.t.
b	91%	Dess-Martin Periodinane, CH_2Cl_2, r.t.
c	85%	DIBALH, THF, –78°C
d	98%	TiPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C
e	97%	HF•pyridine, THF, r.t.
f	97%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → –10°C
g	86%	1) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, –78°C → 0°C; 2) **2.2.6.3**, –78°C → –5°C
h	98%	$LiBH_4$, H_2O, Et_2O, 0°C → r.t.
i	91%	TsCl, DMAP, Et_3N, CH_2Cl_2, r.t.
j	91%	$LiEt_3BH$, THF, 0°C → r.t.

Scheme 2.2.6

Esterification of alcohol **2.2.6.5** with *N*-Boc-L-pipecolinic acid (**2.2.2.3**) under standard carbodiimide conditions followed by cleavage of the terminal double bond and chromium-mediated iodoolefination then furnished vinyl iodide **2.2.7.1**, which was finally converted to **2.2.2.1** by exchange of the PMB for TES groups accompanied by concomitant removal of the Boc group.

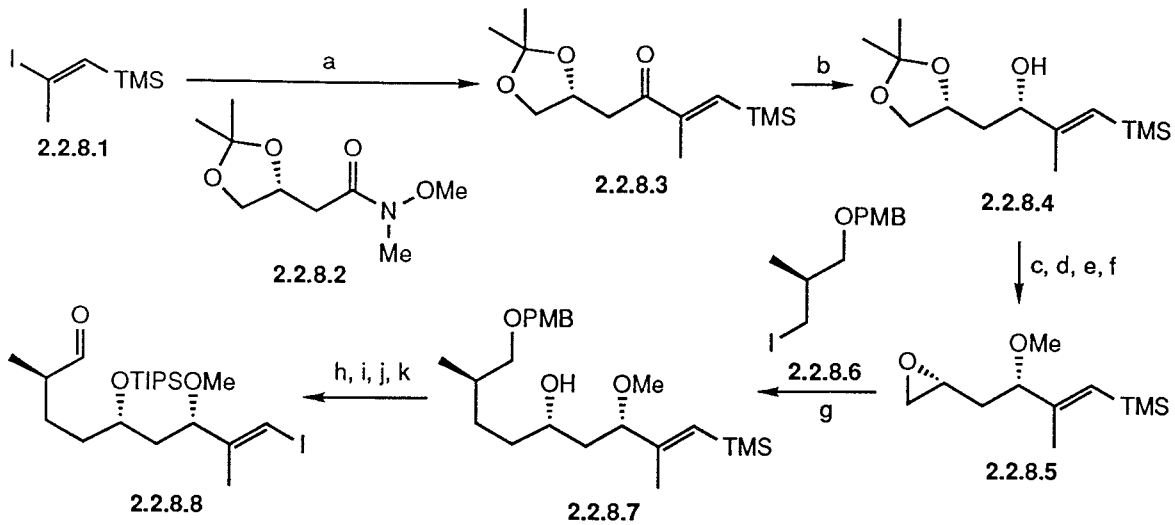


Yields, Reagents and Conditions:

a	85%	DIC, i-Pr_2NEt, 4-pyrrolidinopyridine, CH_2Cl_2, –20°C
b	↓	OsO_4, NMNO, acetone–H_2O, r.t.
c	75%	$Pb(OAc)_4$, Na_2CO_3, benzene, 0°C → r.t.
d	94%	CHI_3, $CrCl_2$, THF–dioxane, r.t.
e	98%	DDQ, $CHCl_3$–H_2O, r.t.
f	94%	1) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; 2) SiO_2, CH_2Cl_2, r.t.

Scheme 2.2.7

The synthesis of advanced fragment **2.2.2.2** is presented in Scheme **2.2.8**. Vinyl iodide **2.2.8.1**, prepared from 1-trimethylsilylpropyne by hydrostannylation followed by treatment of the resulting stannane with iodine, was converted to its lithio-derivative and coupled with Weinreb amide **2.2.8.2** (readily available from L-ascorbic acid) to afford enone **2.2.8.3**. Stereoselective reduction of **2.2.8.3** according to Suzuki's method yielded alcohol **2.2.8.4** which was converted to epoxide **2.2.8.5** using standard procedures. Regioselective opening of the epoxide with the mixed cuprate derived from the lithio-derivative of primary iodide **2.2.8.6** (prepared in four steps from methyl (*S*)-3-hydroxy-2-methylpropionate) then afforded alcohol **2.2.8.7**. TIPS-protection of the alcohol, stereospecific exchange of the TMS group for iodine, liberation of the primary alcohol and oxidation provided aldehyde **2.2.8.8**, which was finally condensed with the dianion of methyl glycolate to afford **2.2.2.2** after hydrolysis of the ester.



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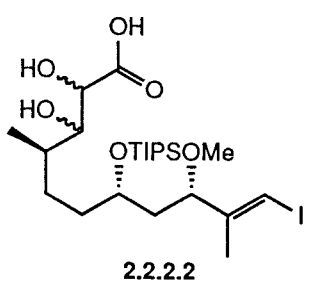


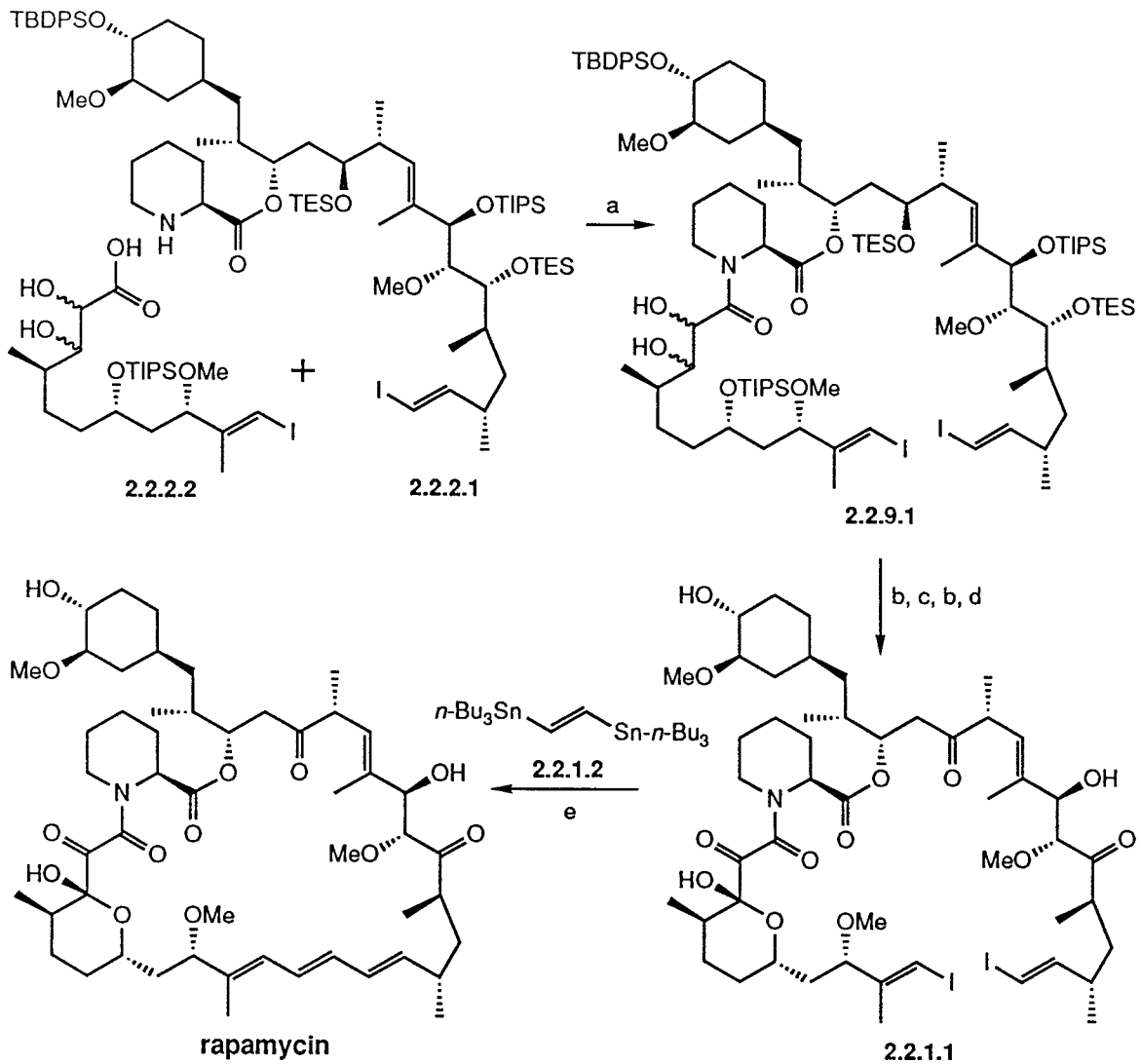
2.2.2.2

Yields, Reagents and Conditions:

a	70%	1) *t*-BuLi, Et_2O, –78°C; 2) **2.2.8.2**
b	86%	$LiAlH_4$, LiI, Et_2O, –100°C
c	94%	NaH, MeI, DMF, r.t.
d	93%	CSA, MeOH, r.t.
e	↓	MsCl, Et_3N, CH_2Cl_2, 0°C
f	64%	K_2CO_3, MeOH, r.t.
g	88%	1) **2.2.8.6**, *t*-BuLi, Et_2O, –100°C; 2) 2-thienylCu(CN)Li, –100°C → 0°C; 3) **2.2.8.5**, –30°C → 0°C
h	98%	TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C
i	97%	NIS, THF, r.t.
j	94%	DDQ, CH_2Cl_2–H_2O, r.t.
k	98%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → 0°C
l	↓	1) methyl glycolate, LDA, THF, –78°C → 0°C; 2) **2.2.8.8**, THF–HMPA, –78°C
m	95%	LiOH, THF–MeOH–H_2O, 0°C

Scheme 2.2.8

The final stages of Nicolaou's synthesis of rapamycin are shown in Scheme **2.2.9**. Thus, condensation of amine **2.2.2.1** with carboxylic acid **2.2.2.2** in the presence of HOBT and DIC resulted in the formation of amide **2.2.9.1**. A series of desilylation steps and oxidation state adjustments then led to bis(vinyl iodide) **2.2.1.1**. Finally, exposure of **2.2.1.1** to enedistannane **2.2.1.2** in the presence of $(MeCN)_2PdCl_2$ and *i*-Pr_2NEt in DMF–THF afforded rapamycin in 27% yield. A "seco-vinyl iodide", in which only one vinyl iodide (presumably the less substituted one) had reacted with **2.2.1.2**, was also isolated in small amounts; under the same Stille reaction conditions as used above, it furnished rapamycin in 70% yield.

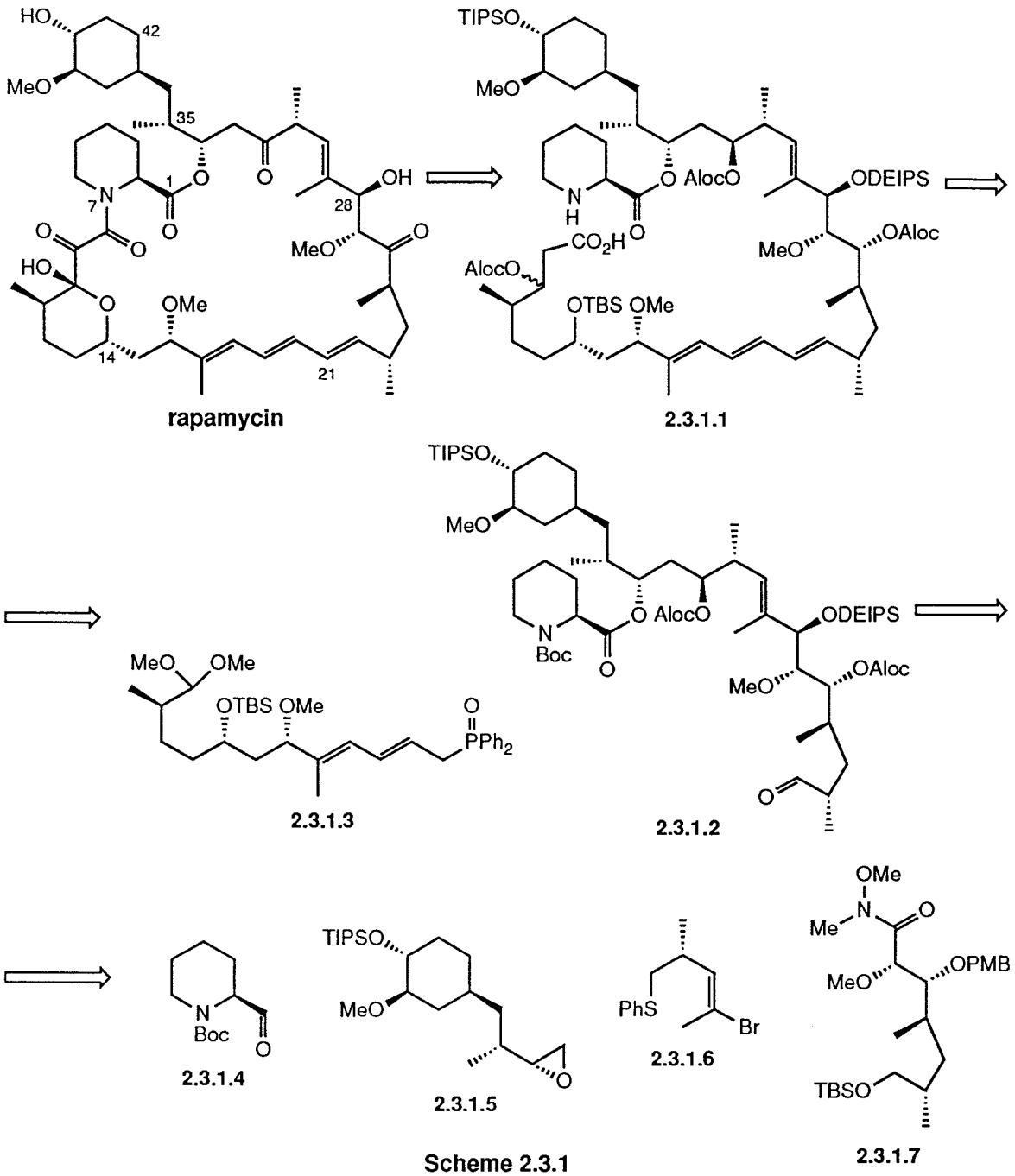


Yields, Reagents and Conditions:		
a	95%	HOBT, DIC, CH_2Cl_2, 0°C
b	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → 0°C
c	↓	HF•pyridine, THF, 0°C → r.t.
d	70%	aq. HF, MeCN, r.t.
e	27%	**2.2.1.2**, $(MeCN)_2PdCl_2$, *i*-Pr_2NEt, DMF–THF, (0.01 M), r.t.

Scheme 2.2.9

2.3 The Schreiber Total Synthesis

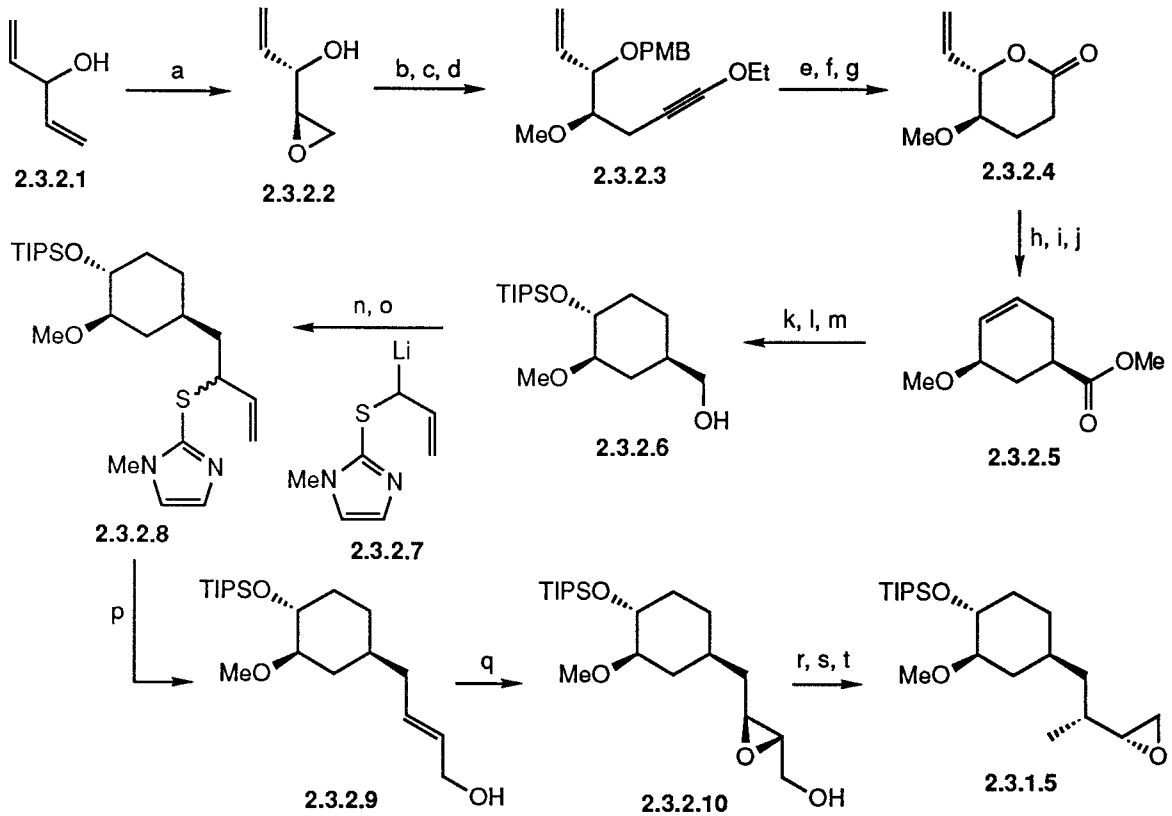
Schreiber's retrosynthetic analysis of rapamycin is shown in Scheme **2.3.1**.[24-26] Thus, disconnection of the macrocycle at the C7-C8 amide bond identifies amino acid **2.3.1.1** as a fully protected acyclic precursor to macrolactamisation. Disconnection of **2.3.1.1** at the C21-C22 olefin linkage then reveals advanced fragments **2.3.1.2** and **2.3.1.3**, of which the former may be further subdivided into building blocks **2.3.1.4**–**2.3.1.7** as initial synthetic targets.



Scheme 2.3.1

The starting material for the synthesis of epoxide **2.3.1.5** (Scheme **2.3.2**) was 1,4-pentadien-3-ol (**2.3.2.1**), which underwent Sharpless asymmetric epoxidation to afford kinetically resolved epoxy alcohol **2.3.2.2**. PMB-protection of the alcohol, regioselective opening of the epoxide with lithium ethoxyacetylide in the presence of $BF_3 \cdot OEt_2$, and methylation of the resulting alcohol then afforded alkynyl ether **2.3.2.3**. Treatment of **2.3.2.3** with ethanolic $HgCl_2$ and removal of the PMB protecting group produced a δ-hydroxy ester, which cyclised to lactone **2.3.2.4** upon treatment with PTSA. Compound **2.3.2.4** was then converted to its silyl ketene acetal, which, after prolonged heating, underwent an Ireland-Claisen rearrangement to afford methyl ester **2.3.2.5** following hydrolysis of the first-formed silyl ester and exposure of the crude acid to diazomethane. Regio- and stereoselective hydroboration of **2.3.2.5**, followed by TIPS-protection of the

resulting alcohol and reduction of the ester then provided primary alcohol **2.3.2.6**, a compound previously employed in Schreiber's total synthesis of FK-506.[27-31] Iodination then alkylation of **2.3.2.6** with lithiated allylic sulfide **2.3.2.7** regioselectively afforded α-substituted allylic thioether **2.3.2.8**. Oxidation of **2.3.2.8** to the corresponding sulfoxide then resulted in a [2,3] sigmatropic rearrangement to provide (*E*)-allylic alcohol **2.3.2.9** after *in situ* cleavage of the initially formed sulfenate ester. Sharpless asymmetric epoxidation



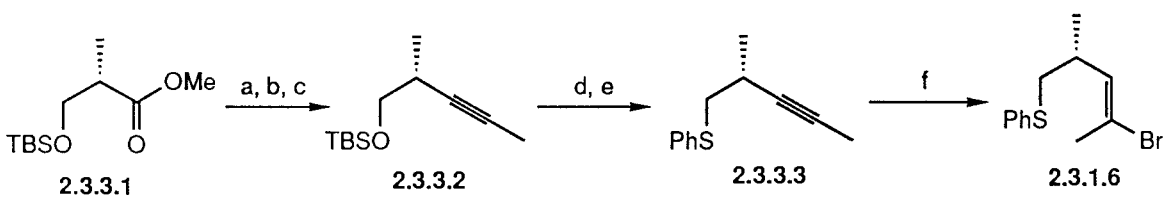
Yields, Reagents and Conditions:

a	55%	$Ti(O\text{-}iPr)_4$, (+)-DIPT, TBHP, 4Å molecular sieves, CH_2Cl_2, –20°C
b	94%	NaH, PMBBr, $n\text{-}Bu_4NI$, THF, 0°C → r.t.
c	↓	LiC≡COEt, $BF_3{\cdot}OEt_2$, THF, –78°C
d	87%	NaH, MeI, THF, 0°C → r.t.
e	↓	$HgCl_2$, EtOH, r.t.
f	78%	DDQ, H_2O, CH_2Cl_2, r.t.
g	83%	PTSA, 4Å molecular sieves, benzene, r.t.
h	↓	TBSOTf, Et_3N, CH_2Cl_2, –78°C → 0°C
i	↓	1) toluene, Δ; 2) aq. HCl, THF, r.t.
j	87%	CH_2N_2, Et_2O
k	65%	1) $BH_3{\cdot}THF$, THF, –78°C → 0°C; 2) aq. NaOH, aq. H_2O_2, 0°C → r.t.
l	↓	TIPSOTf, Et_3N, CH_2Cl_2, 0°C → r.t.
m	87%	$LiAlH_4$, THF, 0°C
n	90%	I_2, Ph_3P, imidazole
o	87%	**2.3.2.7**, THF, –78°C
p	71%	1) MCPBA, CH_2Cl_2, 0°C → r.t.; 2) Et_2NH, MeOH, r.t.
q	88%	$Ti(O\text{-}iPr)_4$, (+)-DET, TBHP, 4Å molecular sieves
r	83%	Me_3Al, hexane, 0°C
s	↓	TsCl, pyridine
t	57%	K_2CO_3, MeOH

Scheme 2.3.2

of **2.3.2.9** yielded epoxy alcohol **2.3.2.10**, which underwent regioselective epoxide opening with Me_3Al to introduce the C35 methyl group. The resulting *vic*-diol was then converted to **2.3.1.5** using standard procedures.

Four-carbon fragment **2.3.1.6** was constructed as outlined in Scheme **2.3.3**. Thus, DIBALH half-reduction of TBS-protected hydroxy ester **2.3.3.1** and Corey-Fuchs homologation of the resulting aldehyde provided methyl acetylene **2.3.3.2.** Removal of the TBS protecting group and sulfenylation of the resulting alcohol then yielded compound **2.3.3.3**, which underwent a hydrozirconation/bromination sequence to afford **2.3.1.6**.

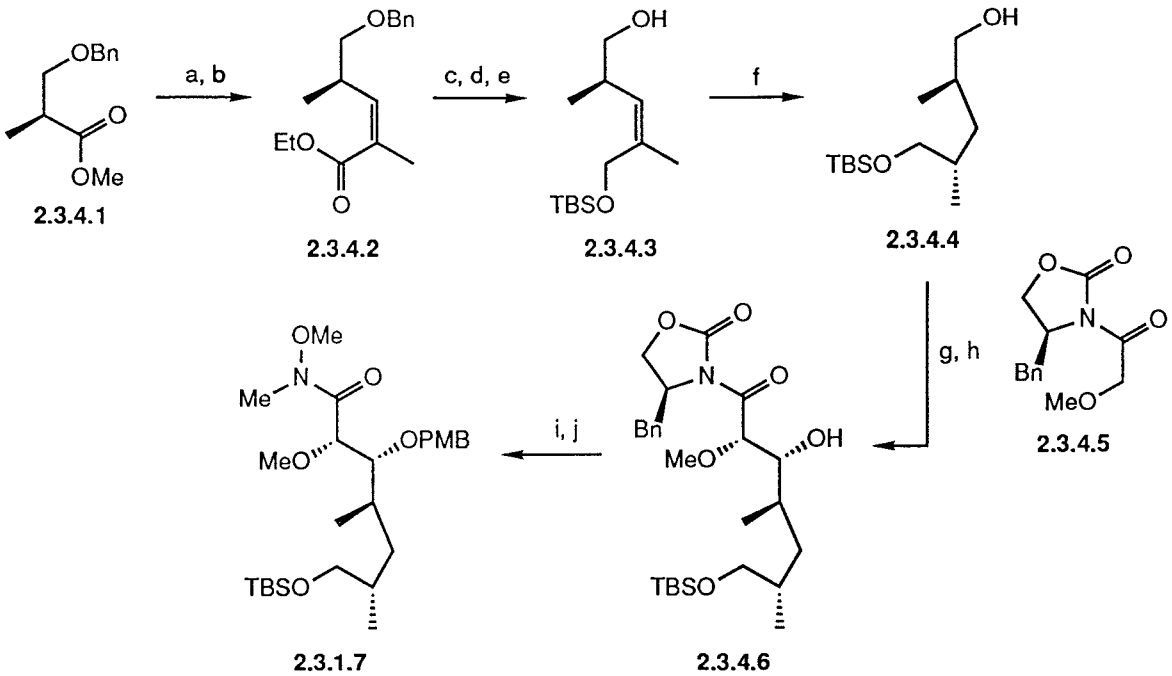


2.3.3.1 2.3.3.2 2.3.3.3 2.3.1.6

Yields, Reagents and Conditions:		
a	↓	DIBALH, CH_2Cl_2, –90°C
b	89%	CBr_4, Ph_3P, Zn, 0°C → r.t.
c	95%	1) *n*-BuLi, THF, –78°C; 2) MeI, –78°C → r.t.
d	↓	TFA, THF–H_2O
e	72%	$(PhS)_2$, *n*-Bu_3P, benzene, r.t.
f	39%	1) Cp_2ZrHCl, toluene, r.t. → 40°C; 2) Br_2, –78°C

Scheme 2.3.3

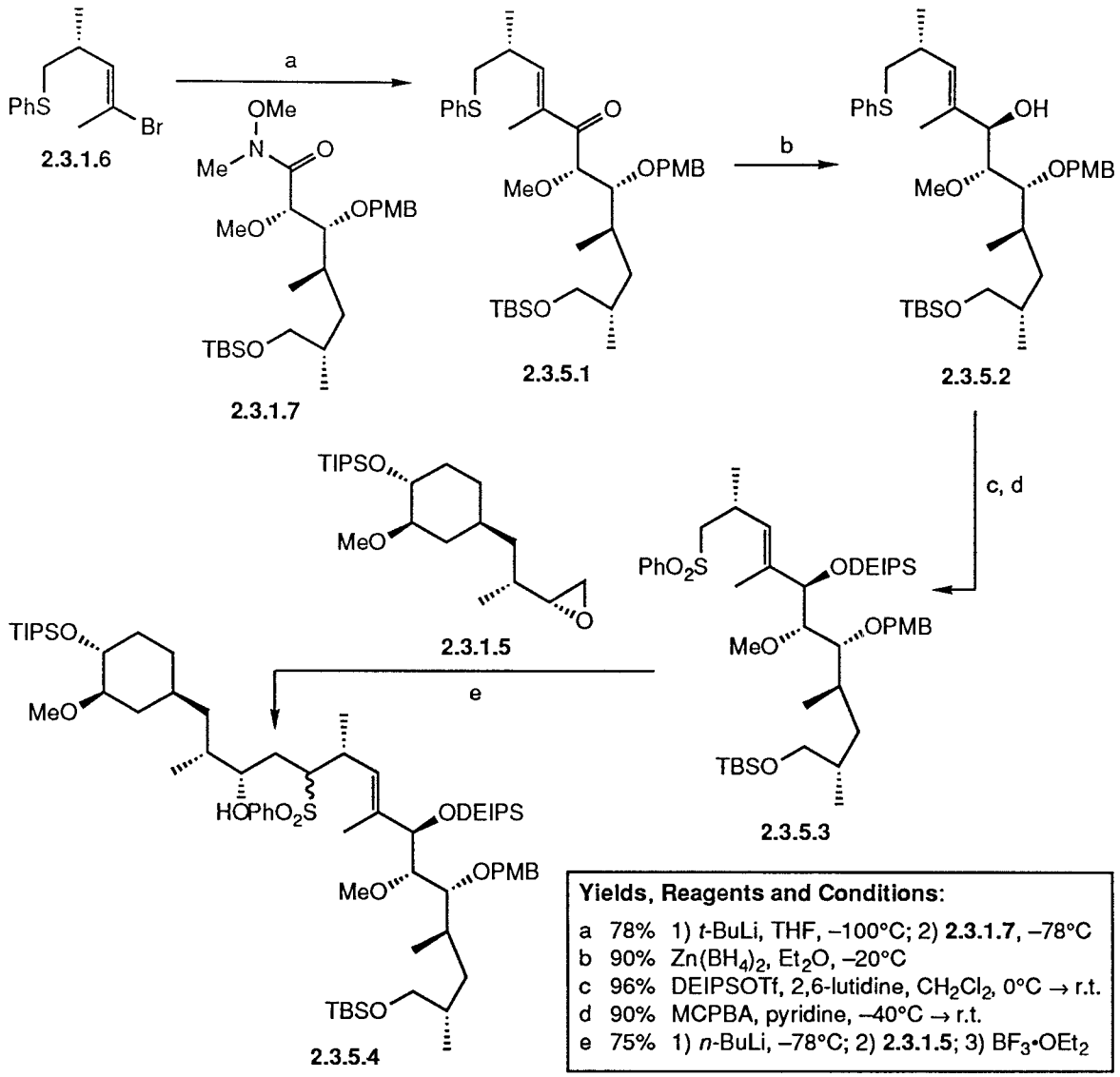
The synthesis of Weinreb amide **2.3.1.7** (Scheme **2.3.4**) began with DIBALH half-reduction of benzyl-protected hydroxy ester **2.3.4.1**. Wittig olefination of the resulting aldehyde then afforded α,β-unsaturated ester **2.3.4.2**. Reduction of the ester, TBS-protection of the resulting alcohol and debenzylation led to homoallylic alcohol **2.3.4.3**, which underwent a hydroxyl-directed Rh(I)-catalysed hydrogenation to provide *syn*-1,3-dimethyl product **2.3.4.4**. Swern oxidation of **2.3.4.4** and Evans aldol condensation of the resulting aldehyde with *N*-acyloxazolidinone **2.3.4.5** (prepared by acylation of the corresponding oxazolidinone with methoxyacetyl chloride) then yielded adduct **2.3.4.6**, which was converted to **2.3.1.7** *via* transamination and protection of the secondary alcohol as its PMB ether.



Yields, Reagents and Conditions:		
a	↓	DIBALH, CH_2Cl_2, –90°C
b	80%	$Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, r.t.
c	100%	DIBALH, CH_2Cl_2, –78°C → 0°C
d	↓	TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t.
e	94%	Na, NH_3, –78°C
f	90%	[Rh(NBD)DIPHOS-4]BF_4, H_2 (1200 psi), CH_2Cl_2, r.t.
g	↓	Swern [O]
h	50%	**2.3.4.5**, *n*-Bu_2BOTf, *i*-Pr_2NEt, toluene, –78°C → 0°C
i	63%	MeO(Me)NH•HCl, Me_3Al, CH_2Cl_2, 0°C → r.t.
j	61%	$PMBOC(N{=}H)CCl_3$, TfOH

Scheme 2.3.4

The coupling of intermediates **2.3.1.4**–**2.3.1.7** and their further elaboration to advanced fragment **2.3.1.2** is shown in Schemes **2.3.5** and **2.3.6**. Thus, Weinreb amide **2.3.1.7** reacted with the lithio-derivative of vinyl bromide **2.3.1.6** to yield enone **2.3.5.1**, which underwent a chelation-controlled $Zn(BH_4)_2$ reduction to stereoselectively afford alcohol **2.3.5.2**. DEIPS-protection of the alcohol and oxidation of the sulfide then gave sulfone **2.3.5.3**, which, upon lithiation, added to epoxide **2.3.1.5** in the presence of $BF_3{\bullet}OEt_2$ to afford γ-hydroxy sulfone **2.3.5.4**.

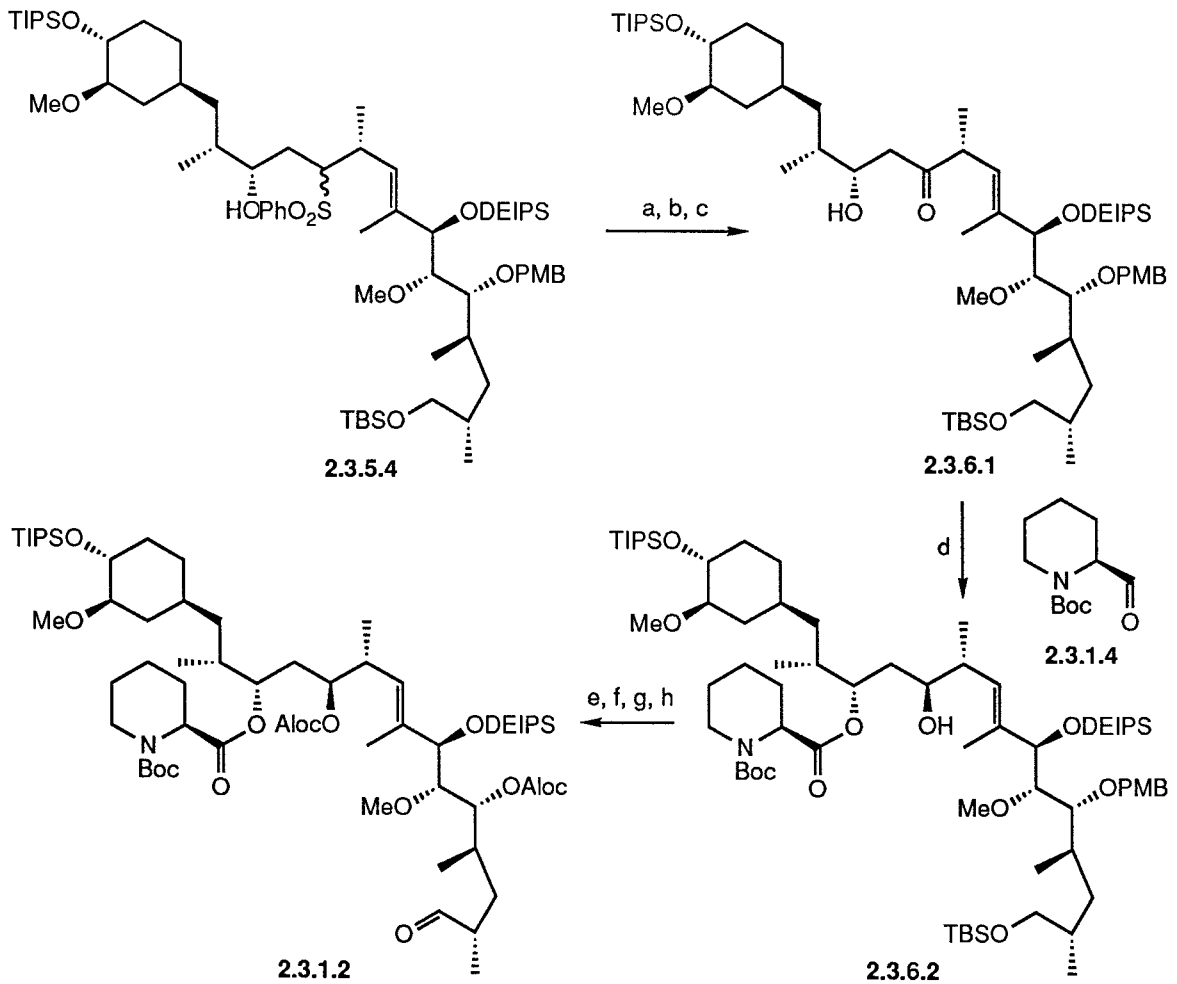


Yields, Reagents and Conditions:

a 78% 1) *t*-BuLi, THF, –100°C; 2) **2.3.1.7**, –78°C
b 90% $Zn(BH_4)_2$, Et_2O, –20°C
c 96% DEIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C → r.t.
d 90% MCPBA, pyridine, –40°C → r.t.
e 75% 1) *n*-BuLi, –78°C; 2) **2.3.1.5**; 3) $BF_3{\cdot}OEt_2$

Scheme 2.3.5

Although metallation of **2.3.5.4** could readily be achieved with *n*-BuLi, attempted oxidation of this compound with a number of electrophilic oxygen sources was generally unsuccessful; best results were obtained with $(TMSO)_2$, providing ketone **2.3.6.1** (Scheme **2.3.6**) in 16% yield. A less direct, but more efficient route to **2.3.6.1** was therefore adopted, whereby olefination of **2.3.5.4** according to the method of Julia, followed by regioselective osmylation and periodate cleavage, provided the ketone in 69% overall yield. An Evans-Tischenko reaction of **2.3.6.1** with Boc-L-pipecolinal (**2.3.1.4**) was then used to introduce the pipecolinate moiety, simultaneously reducing the C32-carbonyl to an (*S*)-carbinol, to produce coupled product **2.3.6.2** in 95% yield (the high-resolution X-ray structure of the FKBP12-rapamycin complex suggests that an (*S*)-carbinol in place of the ketone at C32 may increase the affinity of the ligand for the receptor. Schreiber has therefore undertaken a synthesis of (*S*)-C32-dihydrorapamycin, hence the introduction of the pipecolinate moiety in this manner). Four standard conversions then led to **2.3.1.2**.

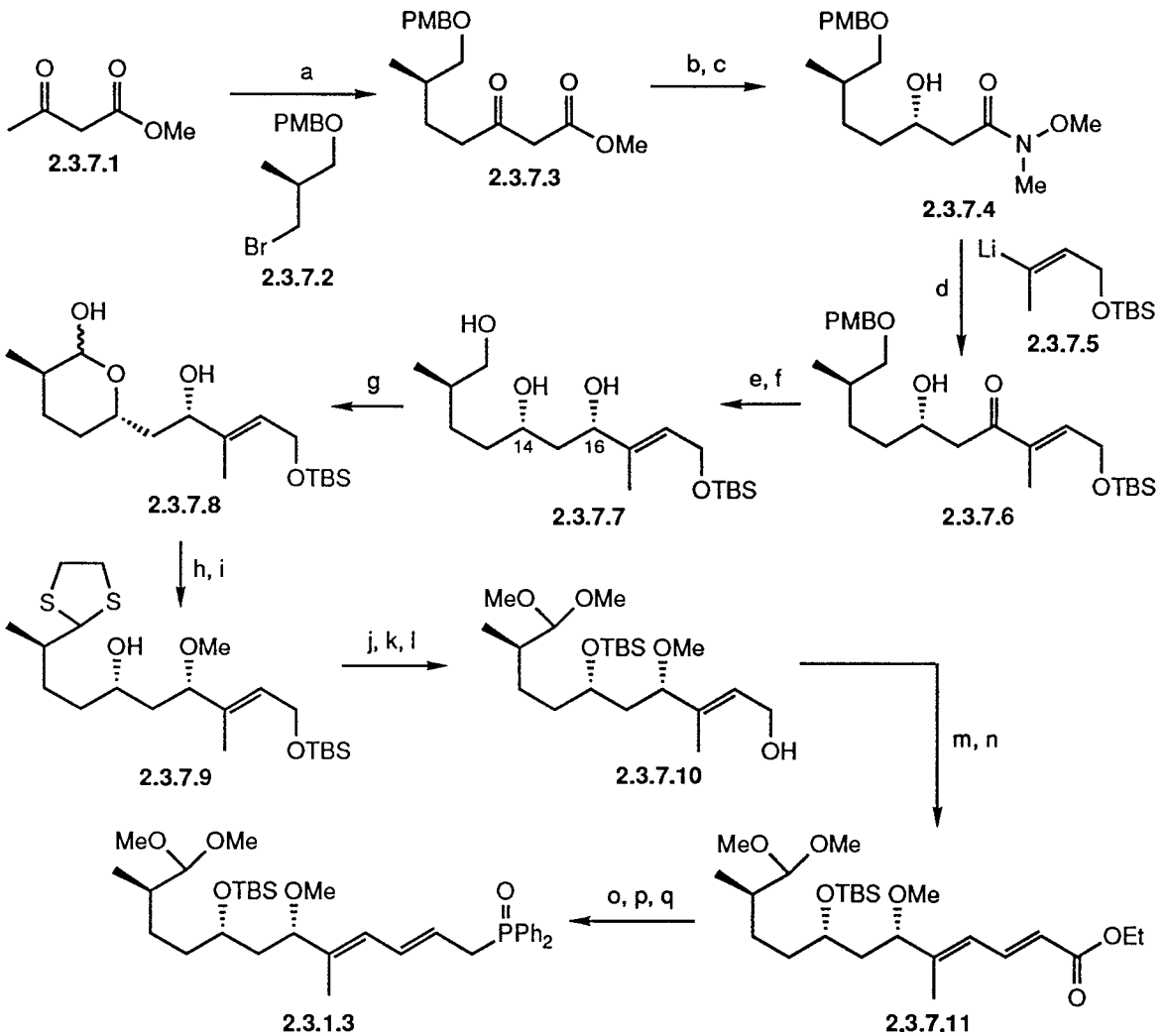


Yields, Reagents and Conditions:		
a	↓	1) *n*-BuLi, THF, –78°C; 2) CH_2I_2–*i*-PrMgCl
b	↓	1) OsO_4, pyridine; 2) $NaHSO_3$
c	69%	$NaIO_4$, SiO_2, Tris-HCl pH 7 buffer
d	95%	**2.3.1.4**, SmI_2–PhCHO (1.1:1), THF, –10°C
e	↓	DDQ, $NaHCO_3$
f	87%	AlocCl, 2,6-lutidine, pyridine, THF
g	71%	PPTS–PTSA (4:1), THF–H_2O
h	96%	Swern [O]

Scheme 2.3.6

Advanced fragment **2.3.1.3** was synthesised as depicted in Scheme **2.3.7**. Thus, alkylation of methyl acetoacetate (**2.3.7.1**) with bromide **2.3.7.2** (prepared in five steps from methyl (*R*)-3-hydroxy-2-methylpropionate) afforded β-keto ester **2.3.7.3**. Catalytic reduction of **2.3.7.3** following the conditions of Noyori provided the corresponding β-hydroxy ester, which was converted to Weinreb amide **2.3.7.4**. Vinyllithium species **2.3.7.5**, obtained (*t*-BuLi, THF, –90°C) from the corresponding vinyl bromide (prepared in three steps from (*E*)-crotyl alcohol), was then combined with the lithium alkoxide of **2.3.7.4** to yield adduct **2.3.7.6**. Removal of the PMB protecting group followed by reduction of the β-hydroxy ketone *via* the method of Prasad then yielded triol **2.3.7.7**. The C14 and C16 hydroxyls were distinguished by selective oxidation of the primary alcohol, resulting in the formation of lactol **2.3.7.8**. Bis-methylation of **2.3.7.8** followed by

treatment with 1,2-ethanedithiol/$TiCl_4$ subsequently afforded dithiolane **2.3.7.9**. Protection of the secondary alcohol in **2.3.7.9** as its TBS ether, removal of the primary TBS protecting group, and transformation of the dithiolane into a dimethyl acetal then provided primary alcohol **2.3.7.10**, which underwent allylic oxidation and Wittig elongation to yield dienallylic ester **2.3.7.11**. Reduction of the ester and conversion of the resulting alcohol to the corresponding chloride, followed by titration with $LiPPh_2$ and exposure of the product to air then yielded **2.3.1.3**.

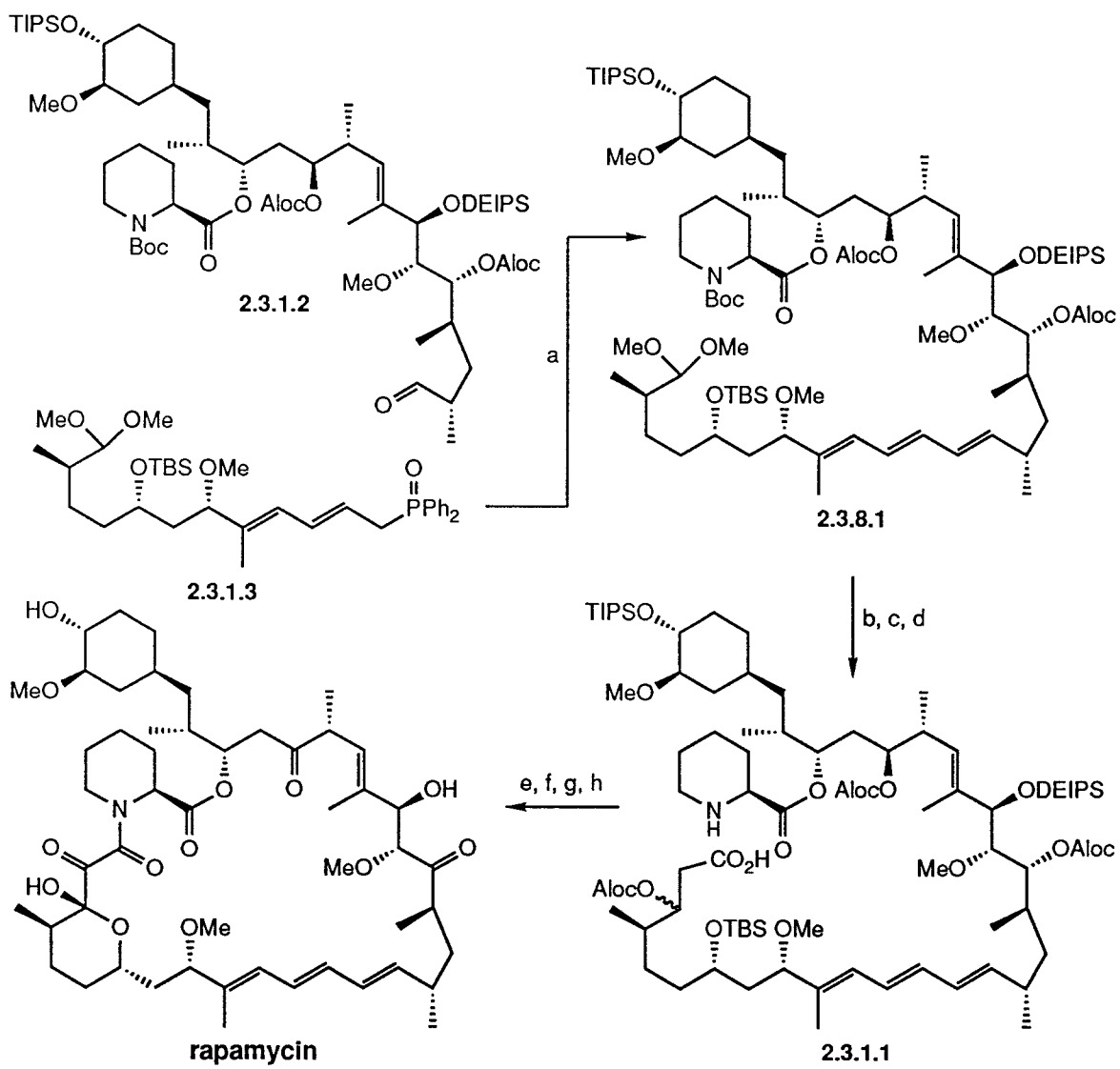


Yields, Reagents and Conditions:

a	90%	1) NaH, *n*-BuLi, HMPA, THF, 0°C; 2) **2.3.7.2**	i	60%	$HS(CH_2)_2SH$, $TlCl_4$, –78°C
b	88%	$RuCl_2$[(*S*)-BINAP]Et_3N, H_2 (1100 psi)	j	94%	TBSOTf, 2,6-lutidine
c	97%	MeO(Me)NH•HCl, Me_3Al	k	86%	HF•pyridine, pyridine, THF, r.t.
d	85%	1) *n*-BuLi, THF, –78°C; 2) **2.3.7.5**	l	73%	$(CF_3CO_2)_2IPh$, MeOH
e	93%	DDQ, CH_2Cl_2, pH 7 buffer	m	↓	$BaMnO_4$, celite, CH_2Cl_2
f	98%	Et_2BOMe, $NaBH_4$, –78°C	n	77%	$Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t.
g	↓	$RuCl_2(PPh_3)_2$, benzene, air	o	83%	DIBALH
h	78%	NaH, MeI, THF, 0°C → r.t.	p	↓	HCA, Ph_3P, 2,6-di-*tert*-butylpyridine, –40°C
			q	65%	1) $LiPPh_2$, THF, –78°C; 2) air

Scheme 2.3.7

The final stages of Schreiber's synthesis of rapamycin are shown in Scheme **2.3.8**. Thus, condensation of aldehyde **2.3.1.2** with the lithium salt of phosphine oxide **2.3.1.3** afforded triene **2.3.8.1**. Hydrolysis of the acetal was followed by an aldol reaction of the resulting aldehyde with the lithium enolate of EE acetate. Quenching of the reaction with allyl chloroformate, treatment of the crude aldol adduct with TESOTf, and exposure of the resulting silylated material to silica gel then provided amino acid **2.3.1.1**. Subjection of **2.3.1.1** to Mukaiyama's macrocyclisation conditions, removal of the three allyl carbonates, Dess-Martin oxidation of the resulting three alcohols and the C9-methylene, and final desilylation/lactolisation of the resulting tetraketone then gave rapamycin.



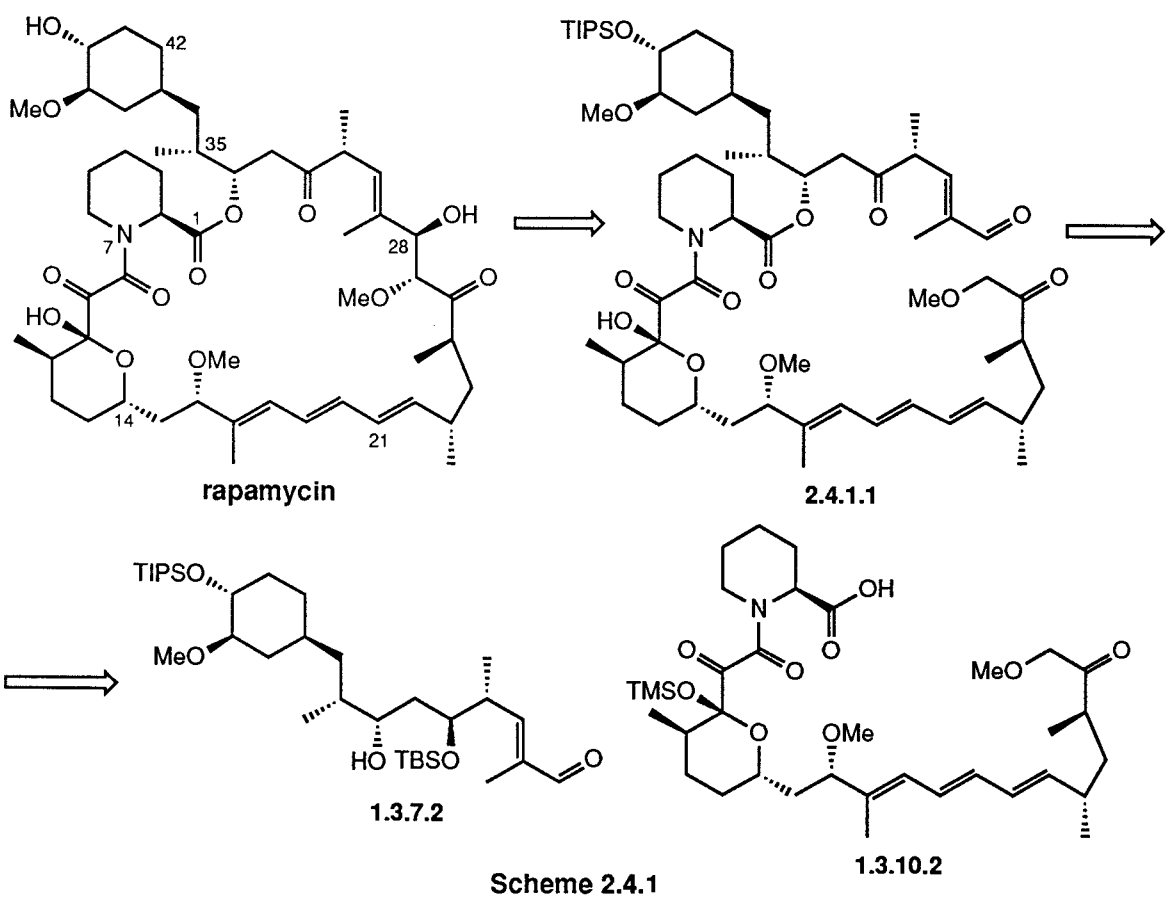
Yields, Reagents and Conditions:		
a	71%	1) *n*-BuLi, HMPA, THF, –78°C; 2) **2.3.1.2**
b	56%	PPTS, acetone, 43°C
c	↓	1) EE acetate, LDA, THF, –78°C; 2) AlocCl, 2,6-lutidine, –78°C → r.t.
d	↓	1) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; 2) SiO_2
e	40%	2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2 (0.0004 M)
f	↓	$Pd(PPh_3)_4$, $HCONH_4$, THF
g	↓	Dess-Martin Periodinane, CH_2Cl_2
h	30%	HF•pyridine, pyridine, THF

Scheme 2.3.8

2.4 The Danishefsky Total Synthesis

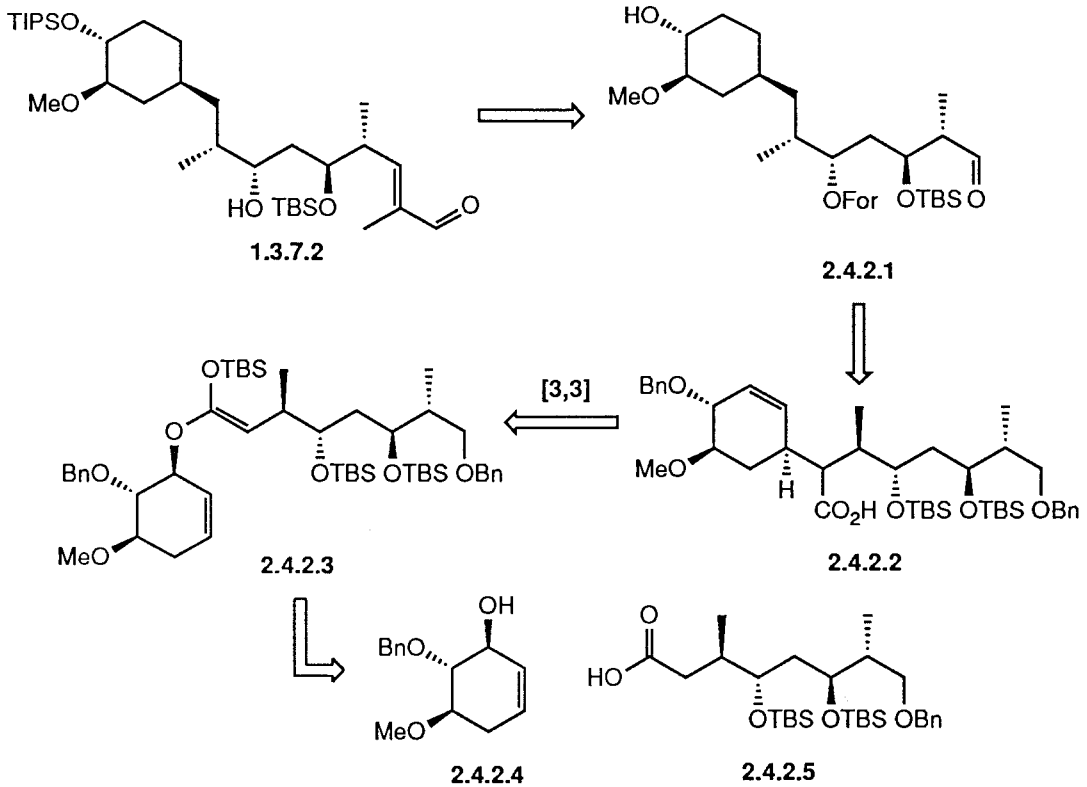
Danishefsky has published a considerable amount of material concerning synthetic[32-35] as well as degradative (Section **1.3**) studies on rapamycin. This work culminated in the total synthesis,[36] although much of the previously published chemistry was not directly used in the final construction of the natural product.

Danishefsky's initial diconnection of the macrocycle was at the C27-C28 bond, identifying acyclic keto-aldehyde **2.4.1.1** as the substrate for a novel *macroaldolisation* reaction (Scheme **2.4.1**). Cyclisation of this seco intermediate would thus yield rapamycin after deprotection of the C40 hydroxyl. Disconnection of **2.4.1.1** at the ester linkage reveals fragments **1.3.7.2** and **1.3.10.2** as advanced targets, the latter being available from rapamycin *via* degradation.



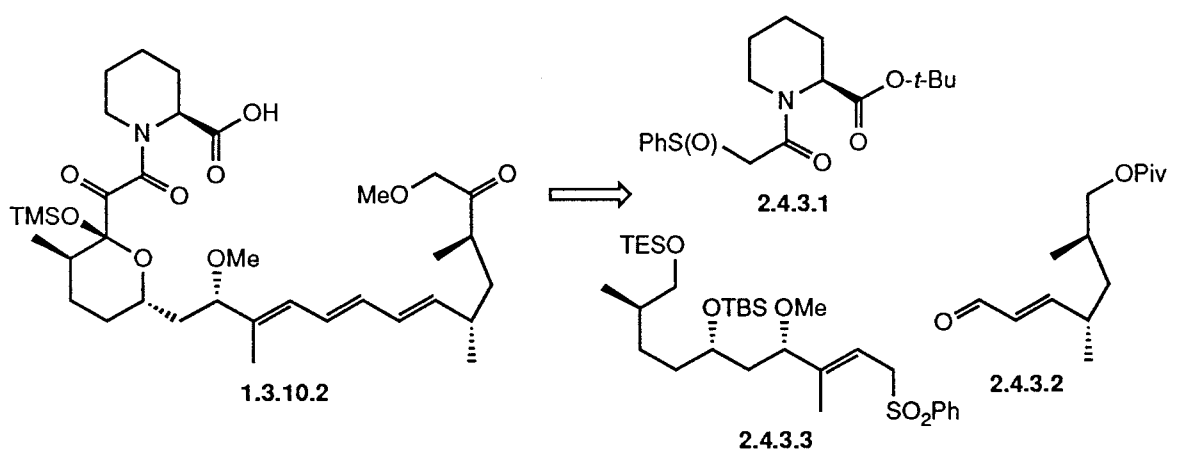
Scheme 2.4.1

The critical step in the synthesis of **1.3.7.2** would be an Ireland-Claisen rearrangement of silyl ketene acetal **2.4.2.3**, to produce carboxylic acid **2.4.2.2** (Scheme **2.4.2**). Further manipulations of **2.4.2.2** would yield **1.3.7.2** *via* a Wittig elongation of aldehyde **2.4.2.1**. Ester disconnection of rearrangement precursor **2.4.2.3** identifies cyclohexenol **2.4.2.4** and carboxylic acid **2.4.2.5** as initial targets.



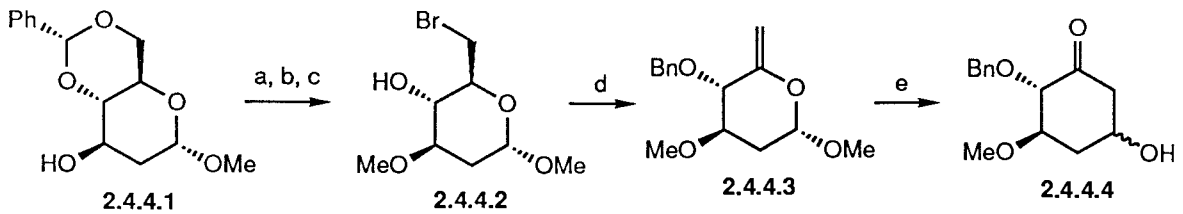
Scheme 2.4.2

Further disconnection of advanced fragment **1.3.10.2** reveals subfragments **2.4.3.1**–**2.4.3.3** as building blocks (Scheme **2.4.3**).



Scheme 2.4.3

The synthesis of cyclohexenol **2.4.2.4** (Scheme **2.4.4**) commenced with carbohydrate derivative **2.4.4.1**, whereby methylation of the free hydroxyl, cleavage of the benzylidene acetal with NBS/$BaCO_3$, and removal of the resulting benzoyl protecting group afforded alcohol **2.4.4.2**. Benzyl-protection of **2.4.4.2** with concomitant bromide elimination gave compound **2.4.4.3**, which underwent a Ferrier transformation when heated with aq. $HgCl_2$ to yield alcohol **2.4.4.4**. Conversion of **2.4.4.4** to **2.4.2.4** was achieved *via* enone **2.4.4.5** through β-elimination followed by Luche reduction.

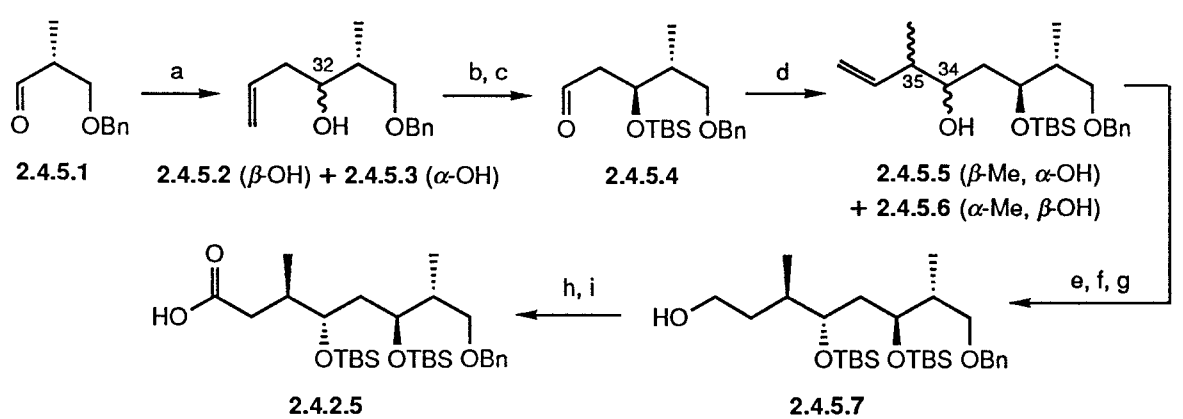


Yields, Reagents and Conditions:

a	90%	NaH, MeI, DMF, 0°C → r.t.
b	93%	NBS, $BaCO_3$, CCl_4, Δ
c	81%	NaOMe, MeOH, r.t.
d	90%	NaH, BnBr, DMF, 0°C → r.t.
e	85%	$HgCl_2$, acetone–H_2O, Δ
f	91%	MsCl, pyridine, r.t.
g	67%	$CeCl_3 \cdot 7H_2O$, $LiBH_4$, THF–MeOH, –78°C

Scheme 2.4.4

In the synthesis of carboxylic acid **2.4.2.5** (Scheme **2.4.5**), titanium-mediated allylation of benzyl-protected hydroxy aldehyde **2.4.5.1** yielded alcohol **2.4.5.2** as an inseparable mixture (7:1) with C32 epimer **2.4.5.3**. TBS-protection of the hydroxyl followed by ozonolysis of the double bond afforded aldehyde **2.4.5.4**, which underwent crotylboration to yield alcohol **2.4.5.5** along with C34,C35 epimer **2.4.5.6** (3.5:1). Desilylation and chromatography then yielded homogeneous diol, which was subjected to bis-silylation followed by hydroboration to provide primary alcohol **2.4.5.7**. Oxidation of **2.4.5.7** (Swern then $KMnO_4$) then gave **2.4.2.5**.

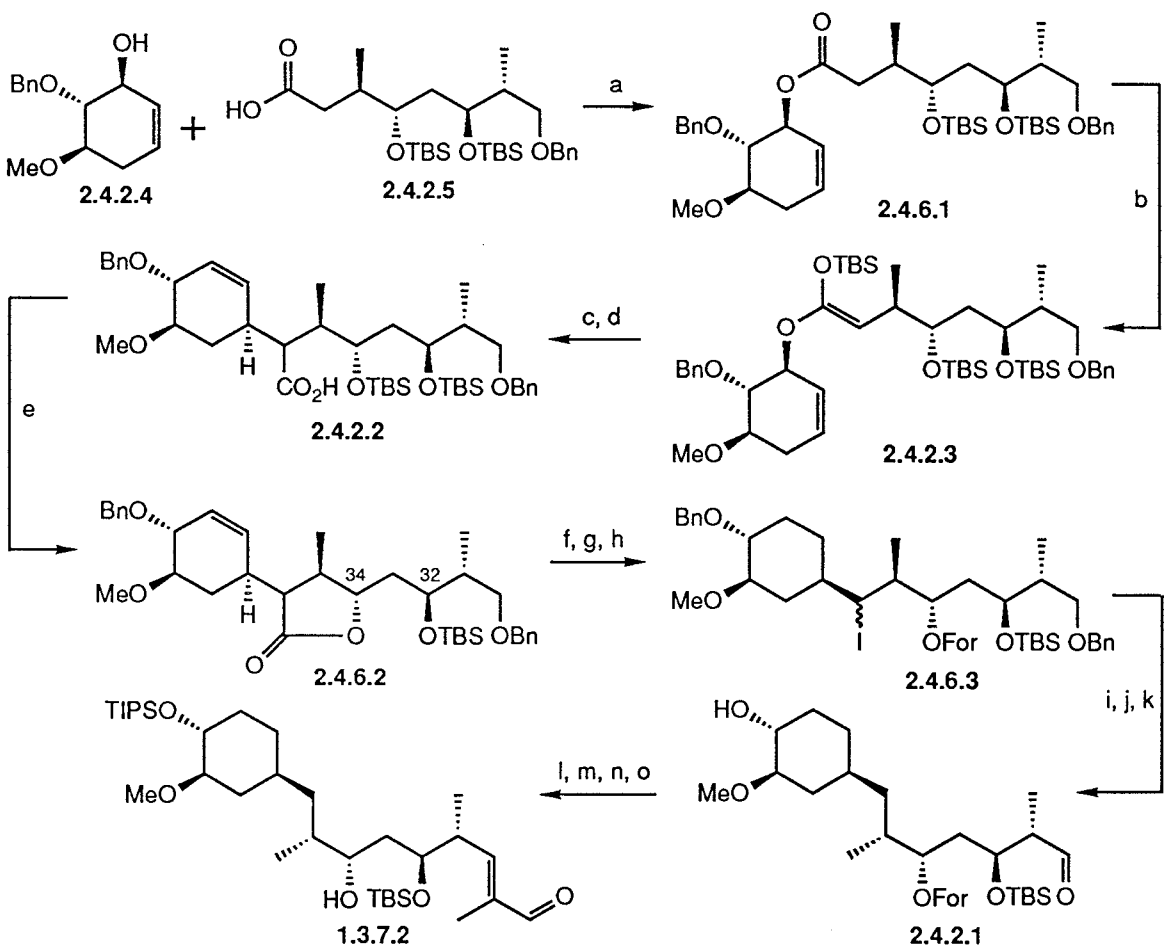


Yields, Reagents and Conditions:

a	75%	Allyl-TMS, $TiCl_4$
b	98%	TBSCl, imidazole, DMF, r.t.
c	75%	1) O_3, CH_2Cl_2–MeOH–pyridine, –78°C; 2) DMS, –78°C → r.t.
d	↓	1) (–)-DIPT-(*E*)-crotylboronate, toluene, –78°C; 2) aq. NaOH, r.t.
e	47%	TBAF, THF, r.t.; separation
f	93%	TBSCl, imidazole, DMF, r.t.
g	98%	1) 9-BBN, THF, r.t.; 2) aq. NaOH, aq. H_2O_2, 0°C
h	90%	$(COCl)_2$, DMSO, Et_3N, –78°C → r.t.
i	99%	aq. $KMnO_4$, aq. NaH_2PO_4, *t*-BuOH

Scheme 2.4.5

The coupling of intermediates **2.4.2.4** and **2.4.2.5** and their further elaboration to advanced fragment **1.3.7.2** is depicted in Scheme **2.4.6**. Thus, acylation of alcohol **2.4.2.4** with acid **2.4.2.5** was accomplished using EDC/DMAP to provide ester **2.4.6.1**, which underwent enolisation/silylation to generate the required silyl ketene acetal **2.4.2.3**. Thermolysis of **2.4.2.3** in vigorously refluxing toluene followed by hydrolysis of the resulting silyl ester then yielded carboxylic acid **2.4.2.2** as a single unidentified diastereomer. Treatment of **2.4.2.2** with $(COCl)_2$/DMAP afforded lactone **2.4.6.2**, thus distinguishing the oxygen functions at C32 and C34. Diimide reduction of the double bond

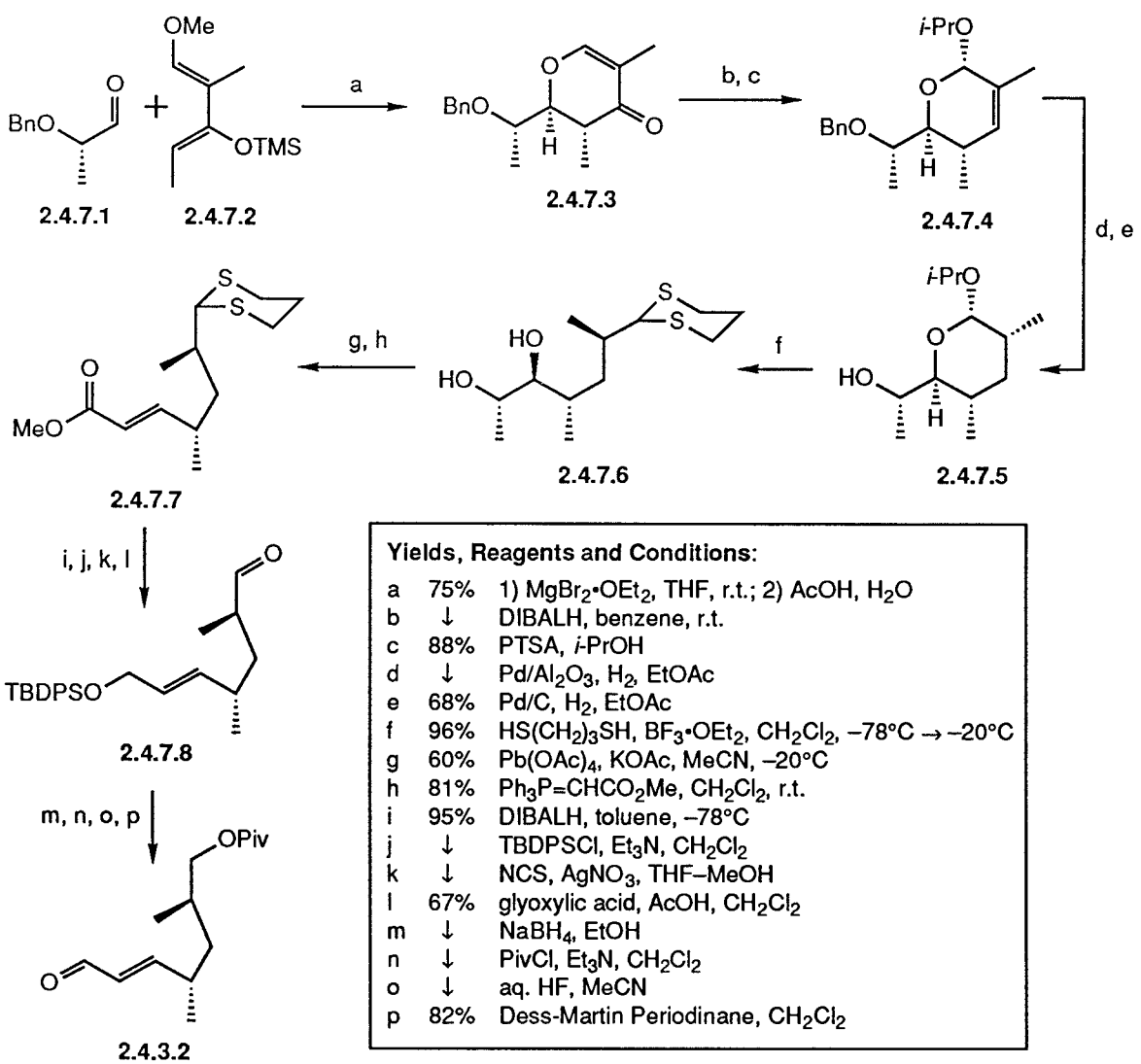


Yields, Reagents and Conditions:		
a	75%	EDC, DMAP, CH_2Cl_2, r.t.
b	–	1) LDA, THF–HMPA, –78°C; 2) TBSCl, –78°C → r.t.
c	–	toluene, Δ
d	–	aq. LiOH, THF
e	70%	$(COCl)_2$, DMAP, CH_2Cl_2
f	↓	1) $TsNHNH_2$, DME, 90°C; 2) NaOAc, H_2O
g	↓	DIBALH, toluene, –78°C
h	85%	I_2, $PhI(OAc)_2$, cyclohexane, hv
i	90%	Ph_3SnH, AIBN, toluene, Δ
j	90%	$Pd(OH)_2$, H_2, EtOAc
k	↓	4-hydroxy-TEMPO benzoate, $Ca(OCl)_2$, CH_2Cl_2–aq. $NaHCO_3$
l	73%	$Ph_3P{=}C(Me)CO_2Et$, toluene, 80°C
m	88%	TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C
n	78%	DIBALH, toluene, –78°C
o	90%	MnO_2, CH_2Cl_2

Scheme 2.4.6

was followed by reduction of the lactone with DIBALH to provide the corresponding lactol, which underwent Suárez oxidation to yield iodoformate **2.4.6.3**. Deiodnation, cleavage of the benzyl ethers and regiospecific oxidation of the primary alcohol then provided aldehyde **2.4.2.1**, which finally underwent Wittig olefination, TIPS-protection of the C40 hydroxyl, reduction of the formate and ethyl esters, and selective oxidation of the primary allylic alcohol to yield **1.3.7.2**.

The synthesis of aldehyde **2.4.3.2** (Scheme **2.4.7**) began with a chelation-controlled Diels-Alder cycloaddition of (*S*)-2-(benzyloxy)propanal (**2.4.7.1**) with diene **2.4.7.2** modulated by $MgBr_2 \cdot OEt_2$ to provide dihydropyrone **2.4.7.3**. Reduction of the carbonyl group was followed by a Ferrier rearrangement (*i*-PrOH/H^+) to yield isopropoxypseudoglycal **2.4.7.4**. Stereospecific hydrogenation of the double bond and removal of the benzyl protecting group then afforded pyranose derivative **2.4.7.5**, which was converted to dithianediol **2.4.7.6** by treatment with 1,3-propanedithiol/$BF_3 \cdot OEt_2$.



2.4.7.1 2.4.7.2 2.4.7.3 2.4.7.4 2.4.7.5 2.4.7.6 2.4.7.7 2.4.7.8 2.4.3.2

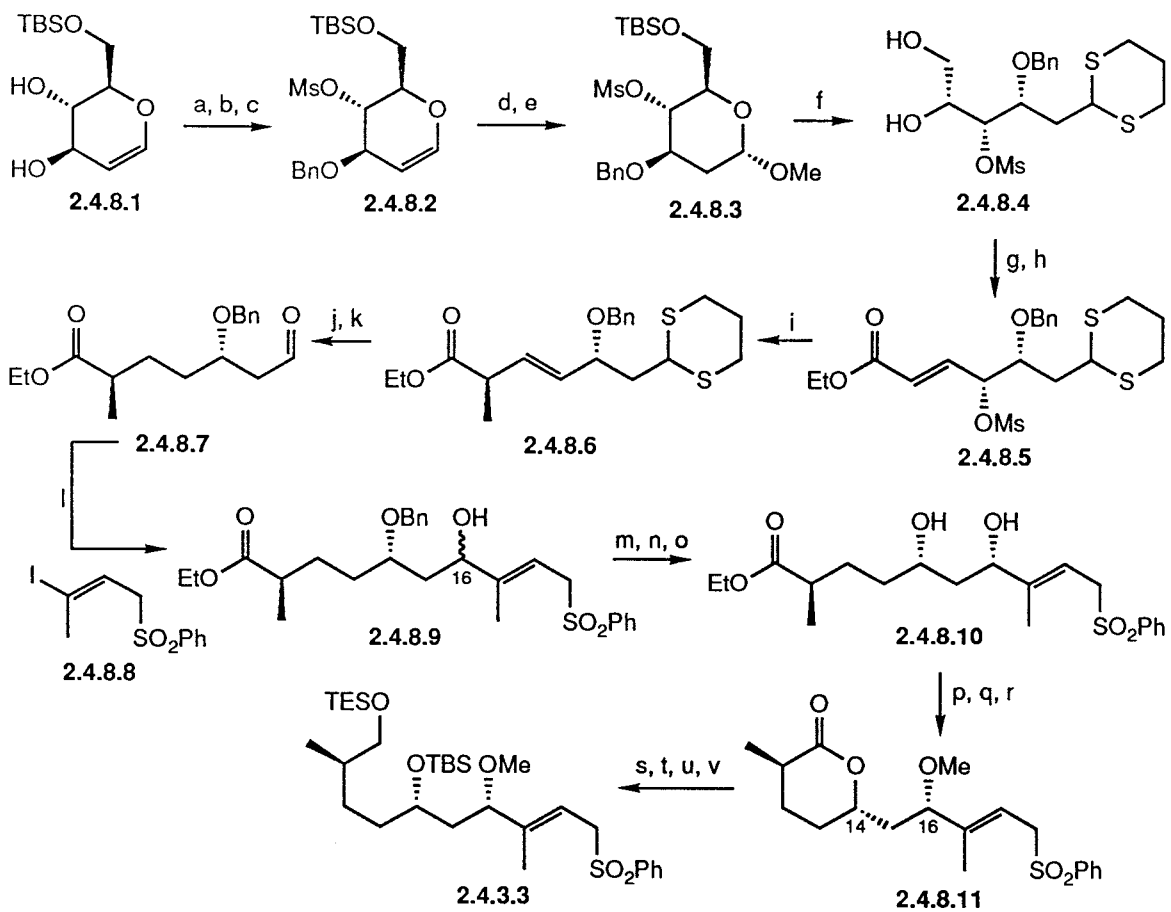
Yields, Reagents and Conditions:

a	75%	1) $MgBr_2 \cdot OEt_2$, THF, r.t.; 2) AcOH, H_2O
b	↓	DIBALH, benzene, r.t.
c	88%	PTSA, *i*-PrOH
d	↓	Pd/Al_2O_3, H_2, EtOAc
e	68%	Pd/C, H_2, EtOAc
f	96%	$HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78°C → −20°C
g	60%	$Pb(OAc)_4$, KOAc, MeCN, −20°C
h	81%	$Ph_3P{=}CHCO_2Me$, CH_2Cl_2, r.t.
i	95%	DIBALH, toluene, −78°C
j	↓	TBDPSCl, Et_3N, CH_2Cl_2
k	↓	NCS, $AgNO_3$, THF–MeOH
l	67%	glyoxylic acid, AcOH, CH_2Cl_2
m	↓	$NaBH_4$, EtOH
n	↓	PivCl, Et_3N, CH_2Cl_2
o	↓	aq. HF, MeCN
p	82%	Dess-Martin Periodinane, CH_2Cl_2

Scheme 2.4.7

Cleavage of the diol and Wittig homologation of the resulting aldehyde then yielded enoate **2.4.7.7**, which was converted to **2.4.3.2** *via* aldehyde **2.4.7.8** using standard procedures.

The starting material selected for the synthesis of sulfone **2.4.3.3** (Scheme **2.4.8**) was carbohydrate derivative **2.4.8.1**, which was converted to compound **2.4.8.2** *via* stannyl ether formation, benzylation and mesylation. Iodomethoxylation/deiodination of **2.4.8.2** then provided α-methyl-2-deoxyglucoside **2.4.8.3**, which was converted to enoate **2.4.8.5** *via* dithianediol **2.4.8.4** by the same procedure used for the conversion **2.4.7.5** → **2.4.7.7**. An Ibuka-Yamamoto (cuprate displacement) reaction was then used to prepare

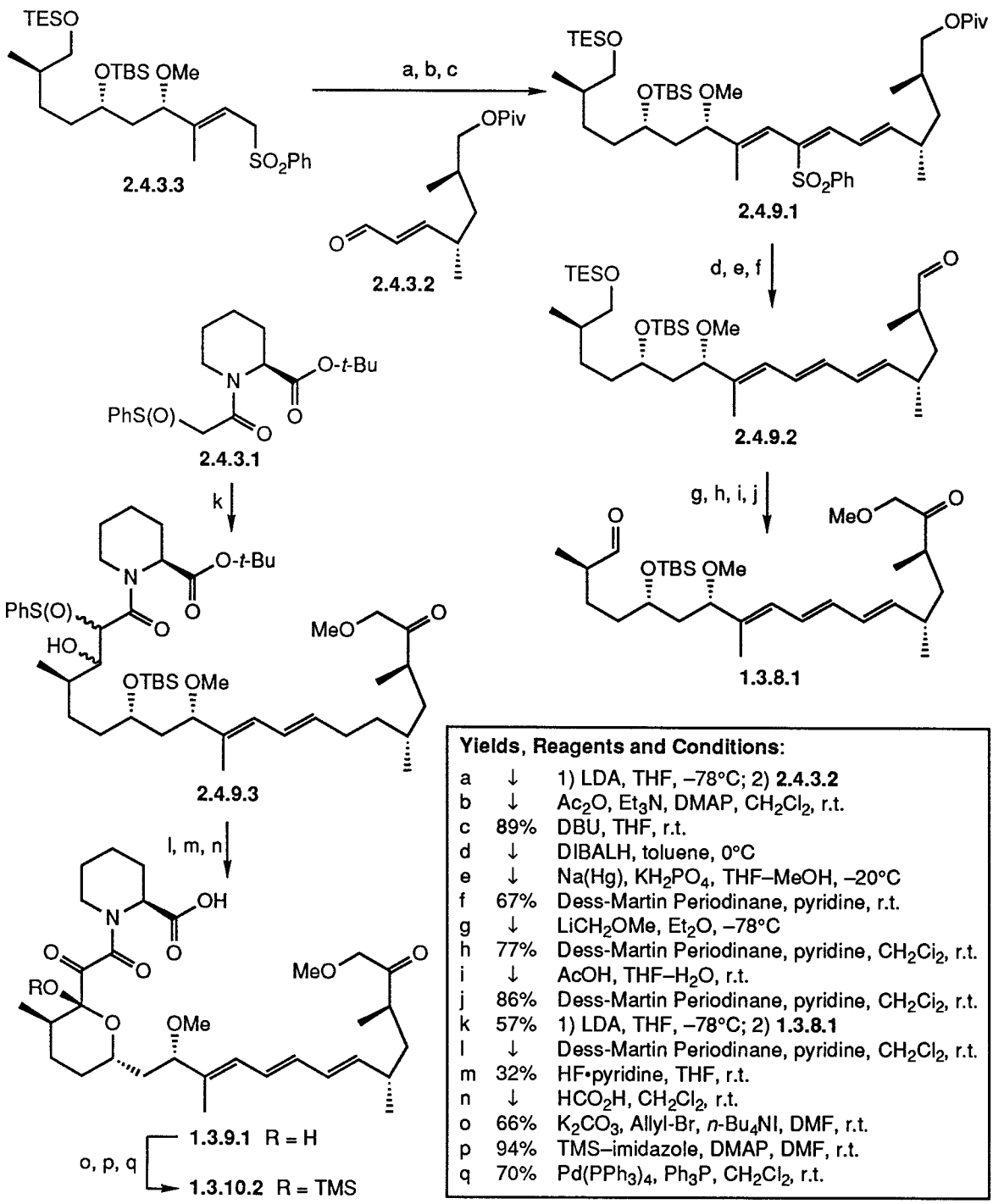


Yields, Reagents and Conditions:

a	–	*n*-Bu_2SnO	m	↓	Dess-Martin Periodinane, CH_2Cl_2, r.t.
b	–	BnBr, *n*-Bu_4NBr	n	75%	BCl_3, CH_2Cl_2, –78°C
c	99%	MsCl, pyridine, 0°C → r.t.	o	↓	Et_2BOMe, $NaBH_4$, toluene, –78°C
d	88%	NIS, MeOH, MeCN, r.t	p	↓	LiOH, THF–MeOH–H_2O, 0°C
e	71%	*n*-Bu_3SnH, AIBN, benzene, Δ	q	71%	EDC, CH_2Cl_2, r.t.
f	74%	$HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C → r.t.	r	↓	Ag_2O, MeI, r.t.
g	72%	$Pb(OAc)_4$, benzene	s	↓	K_2CO_3, MeOH, r.t.
h	62%	$Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0°C	t	86%	TBSOTf, 2,6-lutidine, 0°C
i	74%	MeCu(CN)Li·LiBr, $BF_3{\cdot}OEt_2$, THF, –78°C	u	↓	DIBALH, THF, 0°C
j	83%	$(Ph_3P)_3RhCl$, H_2, benzene, r.t	v	86%	TESCl, Et_3N, CH_2Cl_2
k	–	dithiane cleavage			
l	↓	**2.4.8.8**, $CrCl_2$ (containing 0.1% $NiCl_2$), DMSO, r.t.			

Scheme 2.4.8

α-methyl ester **2.4.8.6**. Reduction of the double bond followed by dithiane cleavage then provided aldehyde **2.4.8.7**, which was coupled with vinyl iodide **2.4.8.8** (prepared in five steps from tetrolic acid) by means of a Nozaki-Kishi reaction to provide alcohol **2.4.8.9** as a 1:1 epimeric mixture at C16. Oxidation of **2.4.8.9**, removal of the benzyl protecting group (with BCl_3), and reduction of the resulting β-hydroxy ketone *via* the method of Prasad then afforded *syn*-1,3-diol **2.4.8.10** as a single diastereomer. Hydrolysis of the ethyl ester followed by lactone formation then served to distinguish the C14 and C16 hydroxyls, the latter being subsequently methylated (Ag_2O/MeI) to yield compound **2.4.8.11**. A series of four standard transformations then provided **2.4.3.3**.



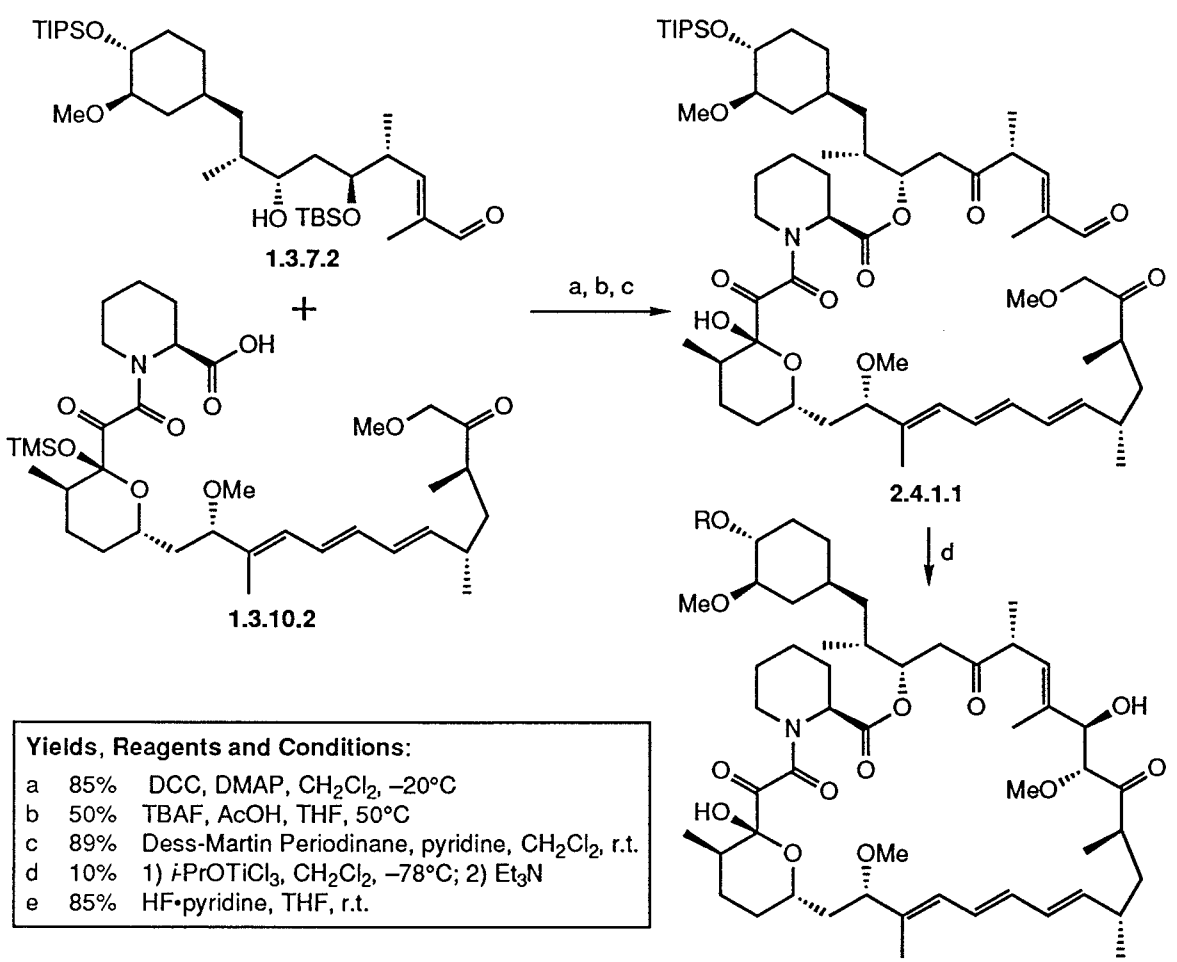
Yields, Reagents and Conditions:

a	↓	1) LDA, THF, –78°C; 2) **2.4.3.2**
b	↓	Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t.
c	89%	DBU, THF, r.t.
d	↓	DIBALH, toluene, 0°C
e	↓	Na(Hg), KH_2PO_4, THF–MeOH, –20°C
f	67%	Dess-Martin Periodinane, pyridine, r.t.
g	↓	$LiCH_2OMe$, Et_2O, –78°C
h	77%	Dess-Martin Periodinane, pyridine, CH_2Ci_2, r.t.
i	↓	AcOH, THF–H_2O, r.t.
j	86%	Dess-Martin Periodinane, pyridine, CH_2Ci_2, r.t.
k	57%	1) LDA, THF, –78°C; 2) **1.3.8.1**
l	↓	Dess-Martin Periodinane, pyridine, CH_2Cl_2, r.t.
m	32%	HF•pyridine, THF, r.t.
n	↓	HCO_2H, CH_2Cl_2, r.t.
o	66%	K_2CO_3, Allyl-Br, *n*-Bu_4NI, DMF, r.t.
p	94%	TMS–imidazole, DMAP, DMF, r.t.
q	70%	$Pd(PPh_3)_4$, Ph_3P, CH_2Cl_2, r.t.

Scheme 2.4.9

The coupling of intermediates **2.4.3.1**–**2.4.3.3** and their further elaboration to advanced fragment **1.3.10.2** is depicted in Scheme **2.4.9**. Thus, Julia coupling of aldehyde **2.4.3.2** with sulfone **2.4.3.3**, followed by acetylation and β-elimination, yielded vinyl sulfone **2.4.9.1**. Reduction of the pivaloate, reductive desulfonylation, and oxidation of the primary alcohol then afforded aldehyde **2.4.9.2**, which was converted to aldehyde **1.3.8.1** (also available by degradation) in four straightforward steps. Condensation of **1.3.8.1** with the lithio-derivative of *tert*-butyl *N*-[(phenylsulfinyl)acetyl]-L-pipecolinate (**2.4.3.1**) (prepared by EDC-induced acylation of *tert*-butyl L-pipecolinate with (phenylthio)acetic acid followed by oxidation with $NaIO_4$ in MeOH–H_2O) produced adduct **2.4.9.3**. Dess-Martin oxidation of **2.4.9.3**, followed by desilylation/lactolisation and cleavage of the *tert*-butyl ester then provided carboxylic acid **1.3.9.1**. Conversion of this product, which may also be obtained by degradation, to the requisite 10-*O*-TMS derivative **1.3.10.2** was achieved as described in Section **1.3**.

The conclusion to Danishefsky's synthesis of rapamycin is shown in Scheme **2.4.10**. Thus, initial coupling of alcohol **1.3.7.2** and acid **1.3.10.2** using DCC/DMAP at –20°C was followed by removal of the TBS and TMS protecting groups and oxidation of the C32



Yields, Reagents and Conditions:

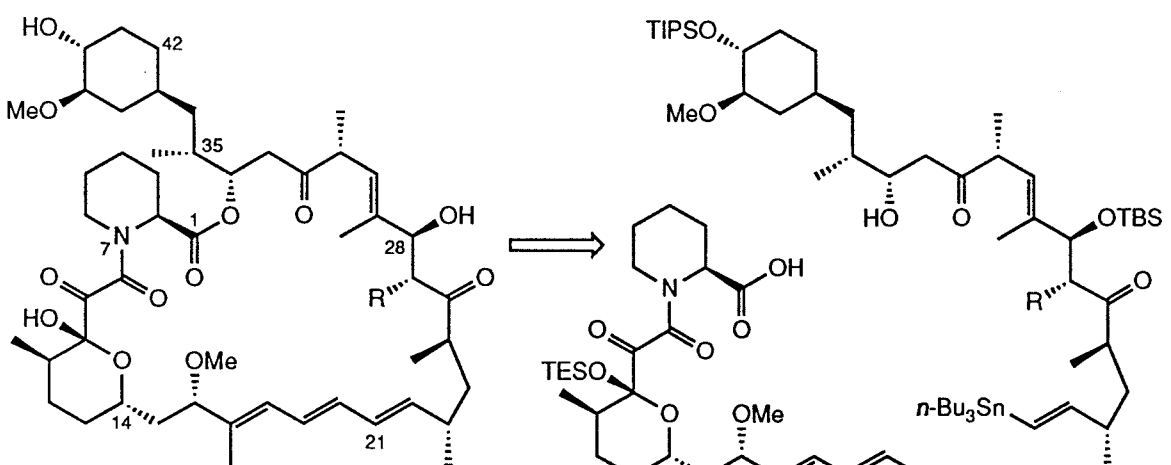
a	85%	DCC, DMAP, CH_2Cl_2, –20°C
b	50%	TBAF, AcOH, THF, 50°C
c	89%	Dess-Martin Periodinane, pyridine, CH_2Cl_2, r.t.
d	10%	1) *i*-PrOTiCl$_3$, CH_2Cl_2, –78°C; 2) Et_3N
e	85%	HF•pyridine, THF, r.t.

Scheme 2.4.10

hydroxyl to afford C40-silylated secorapamycin **2.4.1.1**, the substrate for the projected intramolecular aldolisation. The cyclisation was best carried out using *i*-$PrOTiCl_3$ as the promoter, thus affording a 33% yield of C40-silylated rapamycin **2.4.10.1** in a 1:2.3 ratio to an apparent stereoisomer. Rapamycin itself was then obtained in 85% yield by desilylation.

2.5 The Smith Total Synthesis

Smith's retrosynthetic analysis of rapamycin divided the ring into two large fragments encompassing C21–C42 (**2.5.1.1**) and C1–C20 (**2.5.1.3**) (Scheme **2.5.1**).[37-39] These fragments were designed to allow flexibility during final assembly of the macrocycle, which could be achieved *via* intermolecular acylation at C34 followed by intramolecular Pd(0)-catalysed Stille coupling between C20 and C21, or *via* initial formation of the triene seco acid followed by macrolactonisation. In the event the former strategy was used, and this protocol was also applied to the first total synthesis of 27-demethoxyrapamycin (from C21-C42 fragment **2.5.1.2**), a compound isolated from the same source as rapamycin whose structure had solely been assigned on the basis of spectral comparisons with the latter.



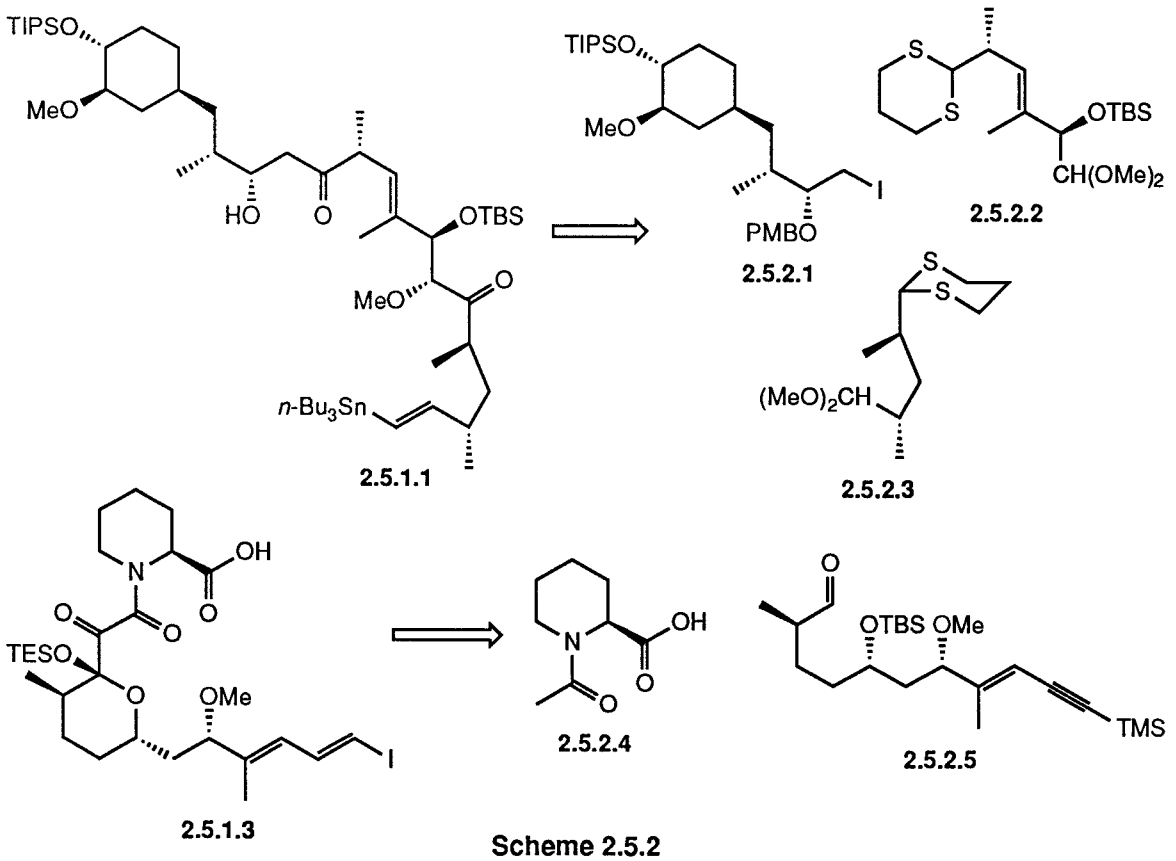
rapamycin (R = OMe)
27-demethoxyrapamycin (R = H)

2.5.1.3

2.5.1.1 (R = OMe)
2.5.1.2 (R = H)

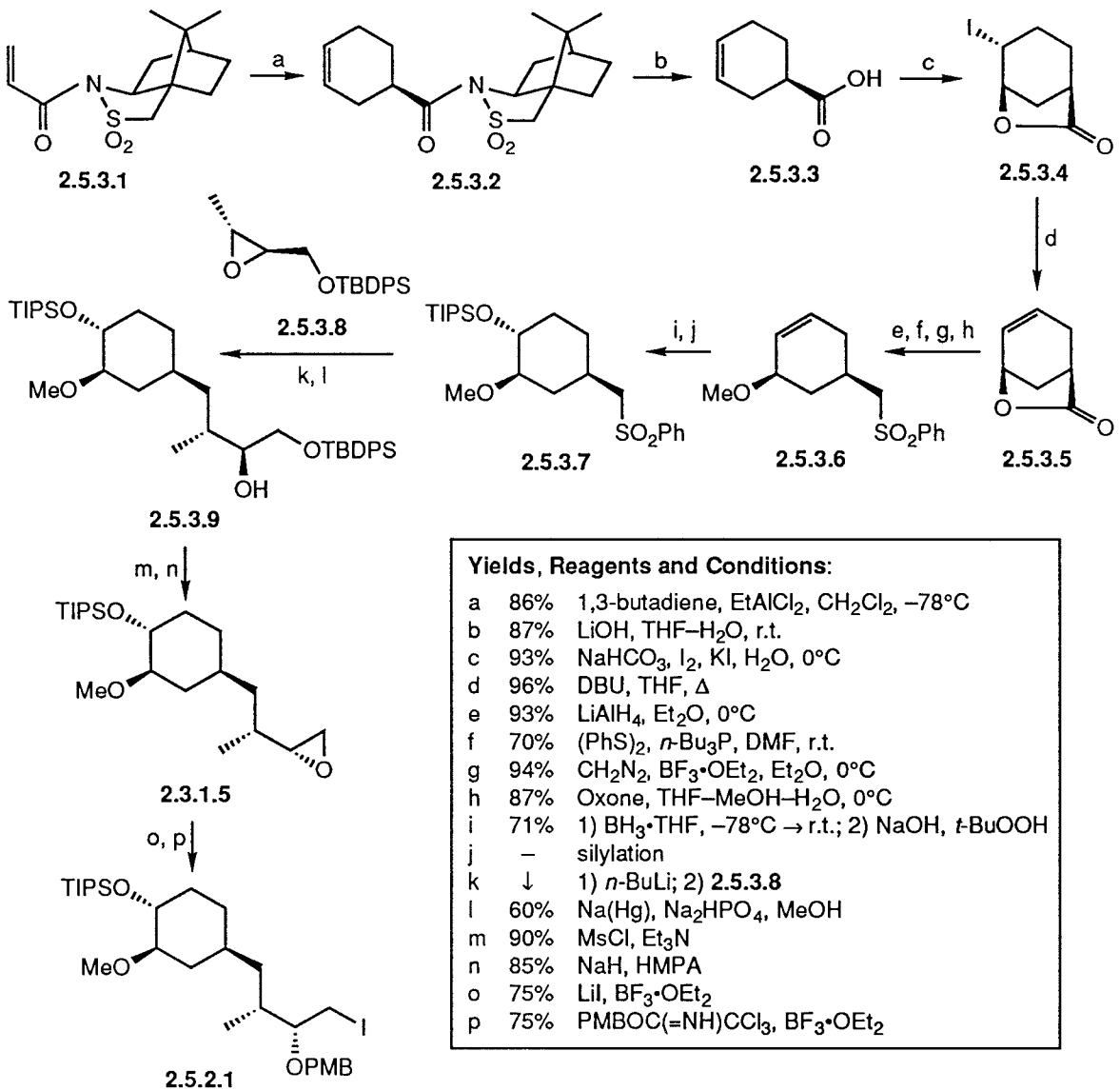
Scheme 2.5.1

Further disconnection of advanced fragments **2.5.1.1** and **2.5.1.3** identifies building blocks **2.5.2.1**–**2.5.2.5** as initial synthetic targets (Scheme **2.5.2**).



Scheme 2.5.2

The synthesis of iodide **2.5.2.1** (Scheme **2.5.3**) began with a Lewis acid-catalysed asymmetric Diels-Alder reaction of 1,3-butadiene with the *N*-acryloyl derivative **2.5.3.1** of Oppolzer's camphor sultam, to afford adduct **2.5.3.2**. Removal of the chiral auxiliary then provided (*R*)-cyclohex-3-enecarboxylic acid (**2.5.3.3**), which underwent iodolactonisation to yield compound **2.5.3.4**. DBU-induced elimination of **2.5.3.4** led to unsaturated lactone **2.5.3.5** which was reduced to the corresponding diol. Sulfenylation of the primary alcohol, methylation of the secondary alcohol, and oxidation of the sulfide then afforded 3-methoxycyclohexene derivative **2.5.3.6**. Regio- and stereoselective hydroboration of **2.5.3.6** and TIPS-protection of the resulting alcohol then yielded sulfone **2.5.3.7** (previously employed in Smith's formal synthesis of FK-506[40-42]), the lithio-derivative of which was added regioselectively to epoxide **2.5.3.8** (readily available by Sharpless asymmetric epoxidation of (*E*)-crotyl alcohol). Reductive desulfonylation then gave alcohol **2.5.3.9** which was converted to epoxide **2.3.1.5** (first used in Schreiber's total synthesis of rapamycin; Section **2.3**) through mesylation of the alcohol followed by removal of the TBDPS protecting group with NaH in HMPA. Iodohydrin formation and protection of the resulting secondary alcohol as its PMB ether then furnished **2.5.2.1**.

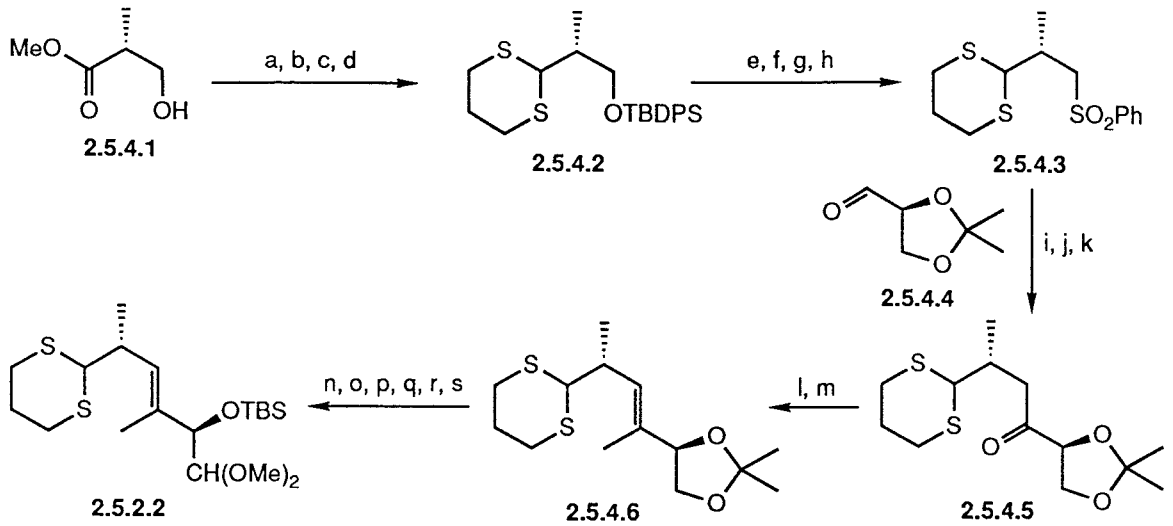


Yields, Reagents and Conditions:

a	86%	1,3-butadiene, $EtAlCl_2$, CH_2Cl_2, –78°C
b	87%	LiOH, THF–H_2O, r.t.
c	93%	$NaHCO_3$, I_2, KI, H_2O, 0°C
d	96%	DBU, THF, Δ
e	93%	$LiAlH_4$, Et_2O, 0°C
f	70%	$(PhS)_2$, *n*-Bu_3P, DMF, r.t.
g	94%	CH_2N_2, BF_3•OEt_2, Et_2O, 0°C
h	87%	Oxone, THF–MeOH–H_2O, 0°C
i	71%	1) BH_3•THF, –78°C → r.t.; 2) NaOH, *t*-BuOOH
j	–	silylation
k	↓	1) *n*-BuLi; 2) **2.5.3.8**
l	60%	Na(Hg), Na_2HPO_4, MeOH
m	90%	MsCl, Et_3N
n	85%	NaH, HMPA
o	75%	LiI, BF_3•OEt_2
p	75%	PMBOC(=NH)CCl_3, BF_3•OEt_2

Scheme 2.5.3

The synthesis of dithiane **2.5.2.2** is outlined in Scheme **2.5.4**. Sulfone **2.5.4.3** was prepared from methyl (*R*)-3-hydroxy-2-methylpropionate (**2.5.4.1**) *via* dithiane **2.5.4.2** using standard procedures. The lithio-derivative of **2.5.4.3** was then added to aldehyde **2.5.4.4**, itself prepared in three steps from L-arabinose. Swern oxidation and desulfonylation of the product afforded ketone **2.5.4.5**, which was converted to the corresponding (*Z*)-enolate and trapped with *N*-phenyltriflimide. The resulting vinyl triflate was then coupled with lithium dimethylcuprate to afford trisubstituted alkene **2.5.4.6**. A further six standard conversions provided **2.5.2.2**.

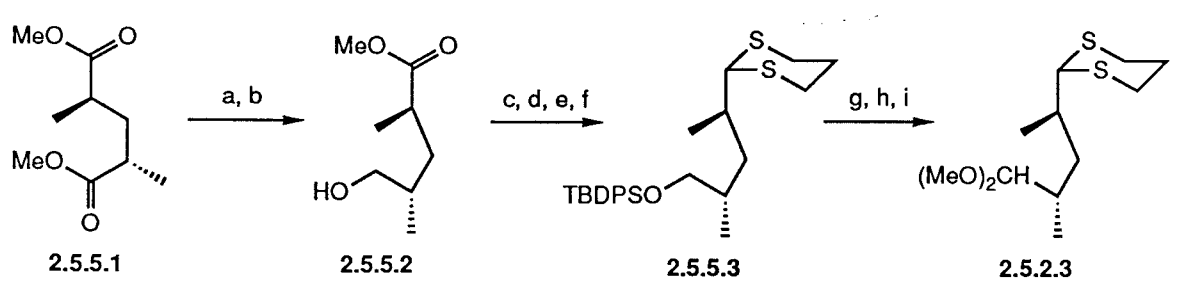


Yields, Reagents and Conditions:

a	98%	TBDPSCl, imidazole	k	46%	Al(Hg), THF
b	90%	$LiBH_4$, Et_2O	l	75%	1) LiHMDS, THF–HMPA; 2) Tf_2NPh
c	↓	Swern [O]	m	70%	Me_2CuLi, Et_2O
d	94%	$HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$	n	64%	CSA, MeOH
e	94%	TBAF, THF	o	77%	PivCl, DMAP
f	95%	TsCl, Et_3N	p	97%	TBSOTf, 2,6-lutidine
g	91%	NaI, acetone	q	99%	DIBALH
h	91%	$PhSO_2Na$, DMF	r	93%	Swern [O]
i	↓	1) *n*-BuLi; 2) **2.5.4.4**	s	–	acetalisation
j	↓	Swern [O]			

Scheme 2.5.4

The preparation of dithiane **2.5.2.3** (Scheme **2.5.5**) began with the desymmetrisation of *meso*-dimethyl 2,4-dimethylglutarate (**2.5.5.1**). Thus, enzymatic monohydrolysis and $BH_3{\cdot}DMS$ reduction of the resulting half acid afforded primary alcohol **2.5.5.2** which was converted to **2.5.2.3** *via* dithiane **2.5.5.3** in seven steps using standard procedures.



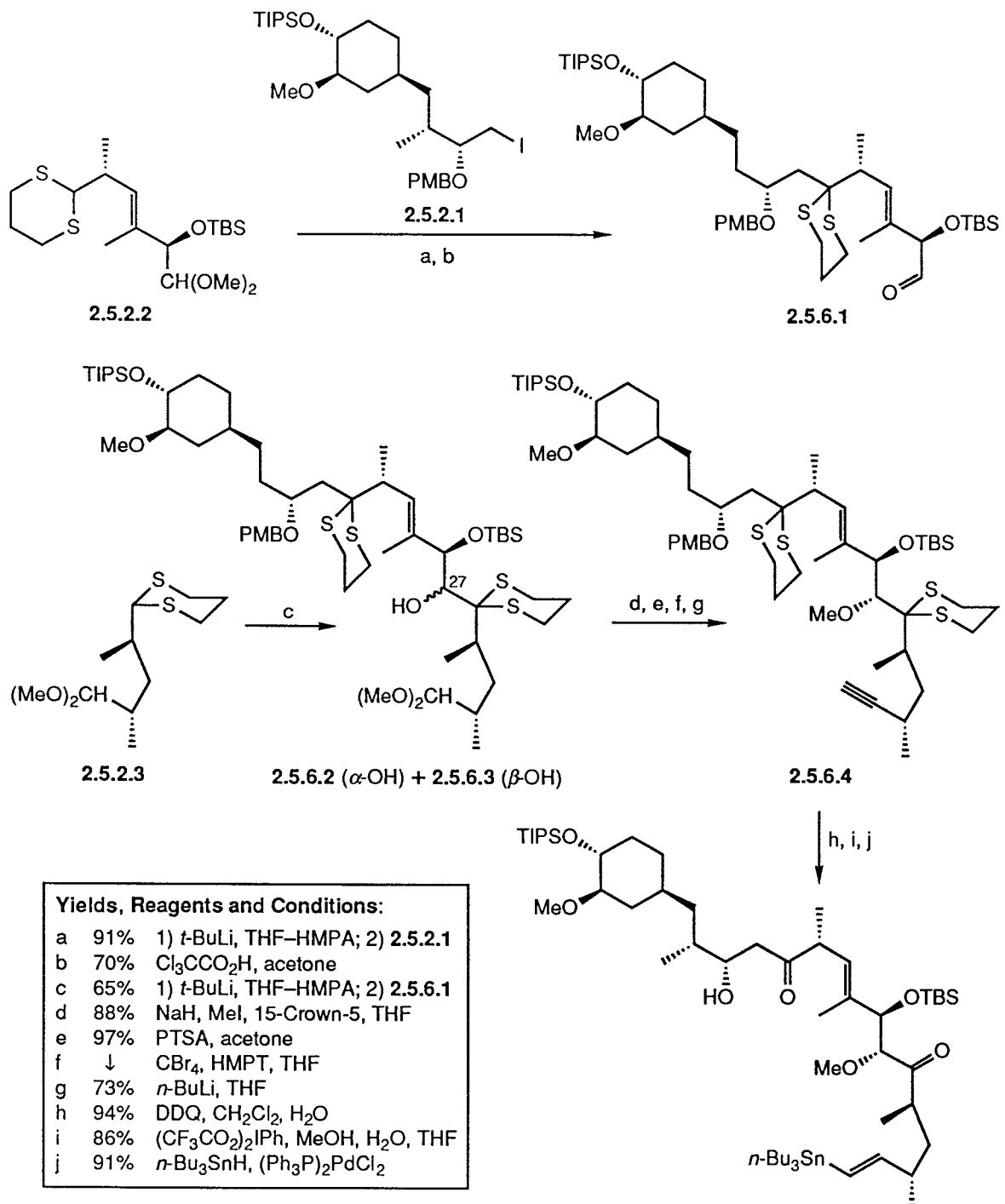
Yields, Reagents and Conditions:

a	88%	α-Chymotrypsin	f	87%	$HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$
b	100%	$BH_3{\cdot}DMS$	g	95%	TBAF
c	88%	TBDPSCl, imidazole	h	90%	Swern [O]
d	84%	DIBALH	i	–	acetalisation
e	88%	Swern [O]			

Scheme 2.5.5

The coupling of intermediates **2.5.2.1**–**2.5.2.3** and their further elaboration to advanced fragment **2.5.1.1** is depicted in Scheme **2.5.6**. Thus, lithiation of dithiane **2.5.2.2**,

alkylation with iodide **2.5.2.1**, and acetal hydrolysis furnished aldehyde **2.5.6.1**. Metallation of dithiane **2.5.2.3** and addition to **2.5.6.1** then furnished C27-epimeric alcohols **2.5.6.2** and **2.5.6.3**, with the unwanted diastereomer in slight excess (1:1.2). Methylation of the alcohol, aldehyde deprotection and Corey-Fuchs homologation then provided terminal alkyne **2.5.6.4** (the unwanted diastereomer from the coupling of **2.5.2.3** with **2.5.6.1** was separated *via* chromatography of the Corey-Fuchs vinyl dibromides). Removal of the PMB and dithiane protecting groups followed by Pd(0)-mediated hydrostannylation then completed the preparation of **2.5.1.1**.

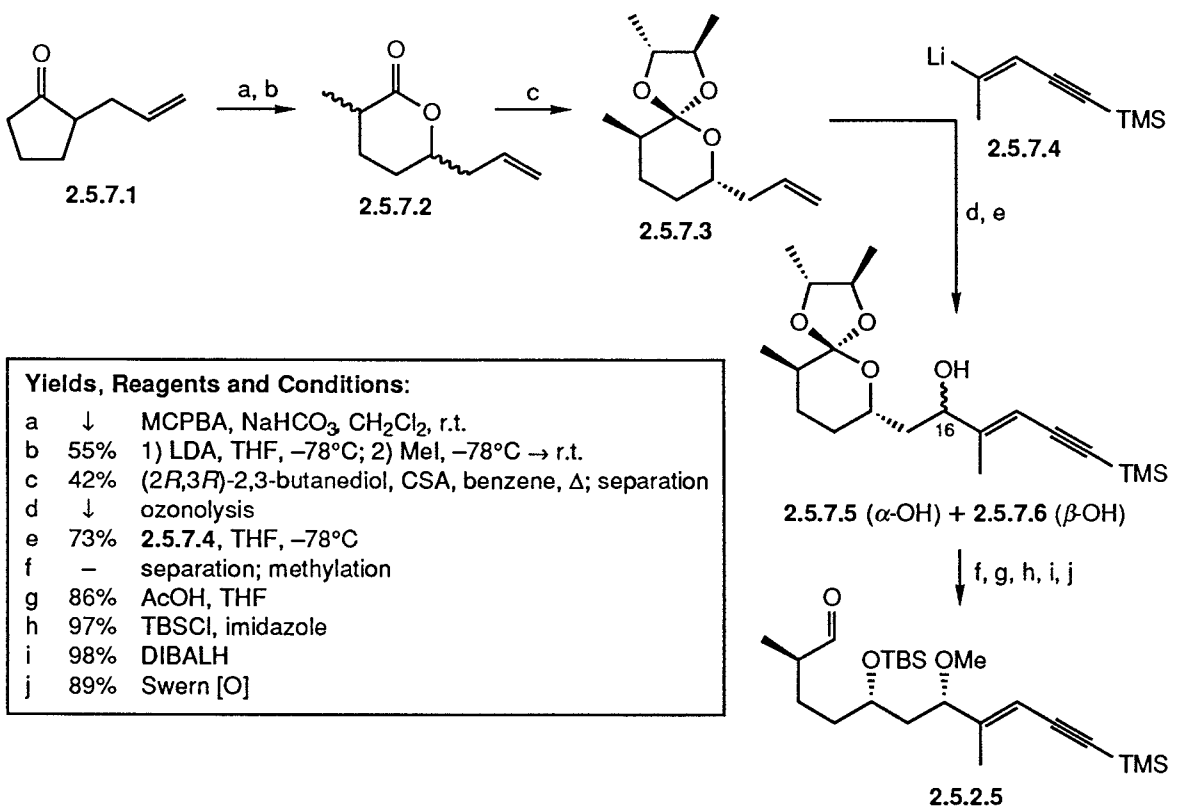


Yields, Reagents and Conditions:

a	91%	1) *t*-BuLi, THF–HMPA; 2) **2.5.2.1**
b	70%	Cl_3CCO_2H, acetone
c	65%	1) *t*-BuLi, THF–HMPA; 2) **2.5.6.1**
d	88%	NaH, MeI, 15-Crown-5, THF
e	97%	PTSA, acetone
f	↓	CBr_4, HMPT, THF
g	73%	*n*-BuLi, THF
h	94%	DDQ, CH_2Cl_2, H_2O
i	86%	$(CF_3CO_2)_2IPh$, MeOH, H_2O, THF
j	91%	*n*-Bu_3SnH, $(Ph_3P)_2PdCl_2$

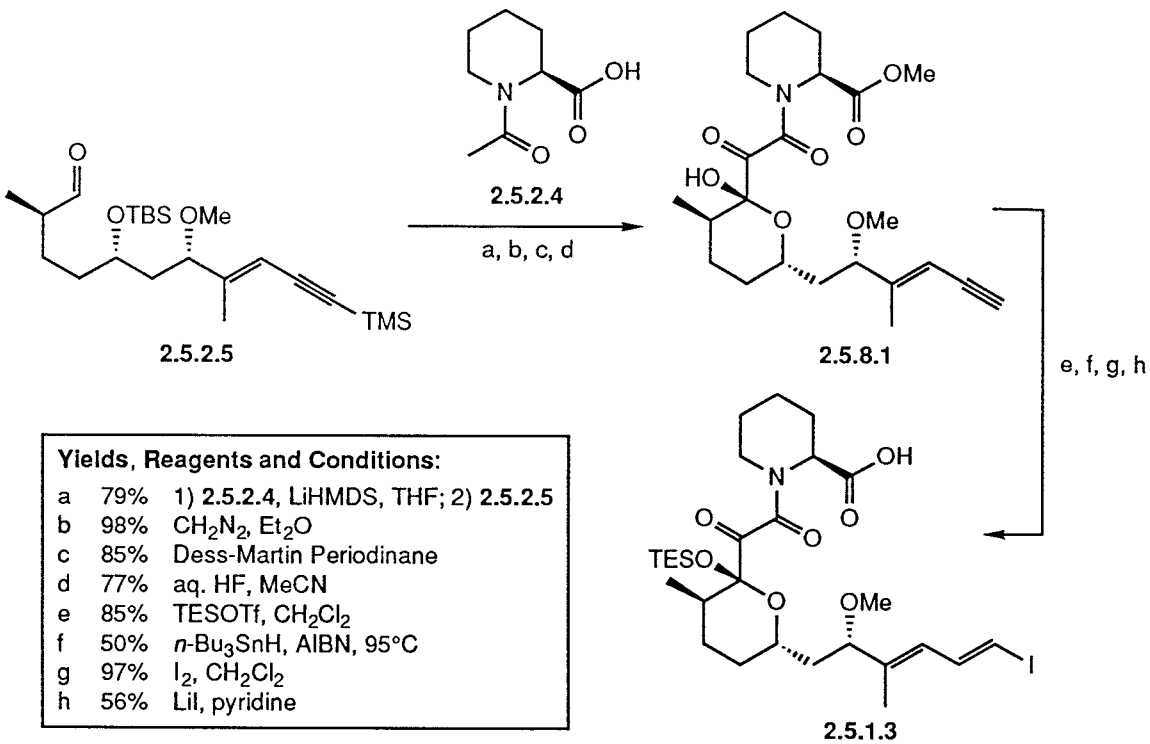
Scheme 2.5.6

The synthesis of aldehyde **2.5.2.5** (Scheme **2.5.7**) began with 2-allylcyclopentanone (**2.5.7.1**), which underwent Baeyer-Villager oxidation and alkylation to afford lactone **2.5.7.2** as a 1:1 mixture of *cis/trans* isomers. Protection of **2.5.7.2** as the corresponding orthoester with (2*R*,3*R*)-2,3-butanediol resulted in equilibration of the mixture to a 6:1 *trans/cis* ratio, from which the required diastereomer **2.5.7.3** could be separated by HPLC. Ozonolysis of **2.5.7.3** was followed by the addition of vinyllithium species **2.5.7.4**, obtained by transmetallation (*n*-BuLi) of the corresponding silylstannylenyne, itself prepared in two steps from bis(trimethylsilyl)buta-1,3-diyne (MeLi–LiBr/MeI then *n*-$Bu_3Sn(Bu)Cu(CN)Li_2$/NH_4Cl–MeOH). The resulting C16-epimeric alcohols **2.5.7.5** and **2.5.7.6** were obtained as a 1.1:1 mixture in favour of the required diastereomer. Chromatographic separation and methylation, followed by orthoester hydrolysis, silylation, ester reduction and Swern oxidation then yielded **2.5.2.5**.



Scheme 2.5.7

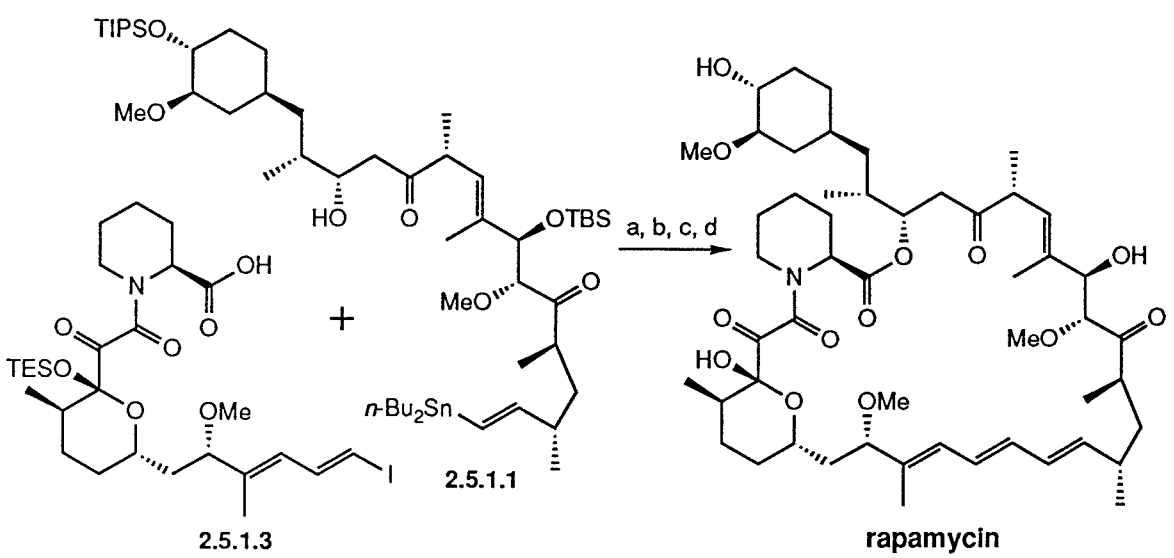
Scheme **2.5.8** outlines the elaboration of aldehyde **2.5.2.5** to advanced fragment **2.5.1.3**. Thus, condensation of **2.5.2.5** with the dianion of *N*-acetyl-L-pipecolinic acid (**2.5.2.4**), diazomethane esterification of the crude aldol mixture, and Dess-Martin oxidation gave the required tricarbonyl species. Removal of the TBS protecting group then afforded hemiketal **2.5.8.1**. Trapping of **2.5.8.1** with TESOTf followed by free-radical hydrostannylation, tin–halogen exchange and ester demethylation then completed the synthesis of **2.5.1.3**.



Yields, Reagents and Conditions:		
a	79%	1) **2.5.2.4**, LiHMDS, THF; 2) **2.5.2.5**
b	98%	CH_2N_2, Et_2O
c	85%	Dess-Martin Periodinane
d	77%	aq. HF, MeCN
e	85%	TESOTf, CH_2Cl_2
f	50%	*n*-Bu_3SnH, AIBN, 95°C
g	97%	I_2, CH_2Cl_2
h	56%	LiI, pyridine

Scheme 2.5.8

The conclusion of Smith's synthesis of rapamycin is depicted in Scheme **2.5.9**. Coupling of alcohol **2.5.1.1** and acid **2.5.1.3** was effected *via* EDC-induced acylation to afford the seco precursor, which underwent intramolecular Stille coupling with $[(2\text{-furyl})_3P]_2PdCl_2$ in DMF–THF to cleanly generate the macrolide ring. Desilylation then afforded rapamycin.

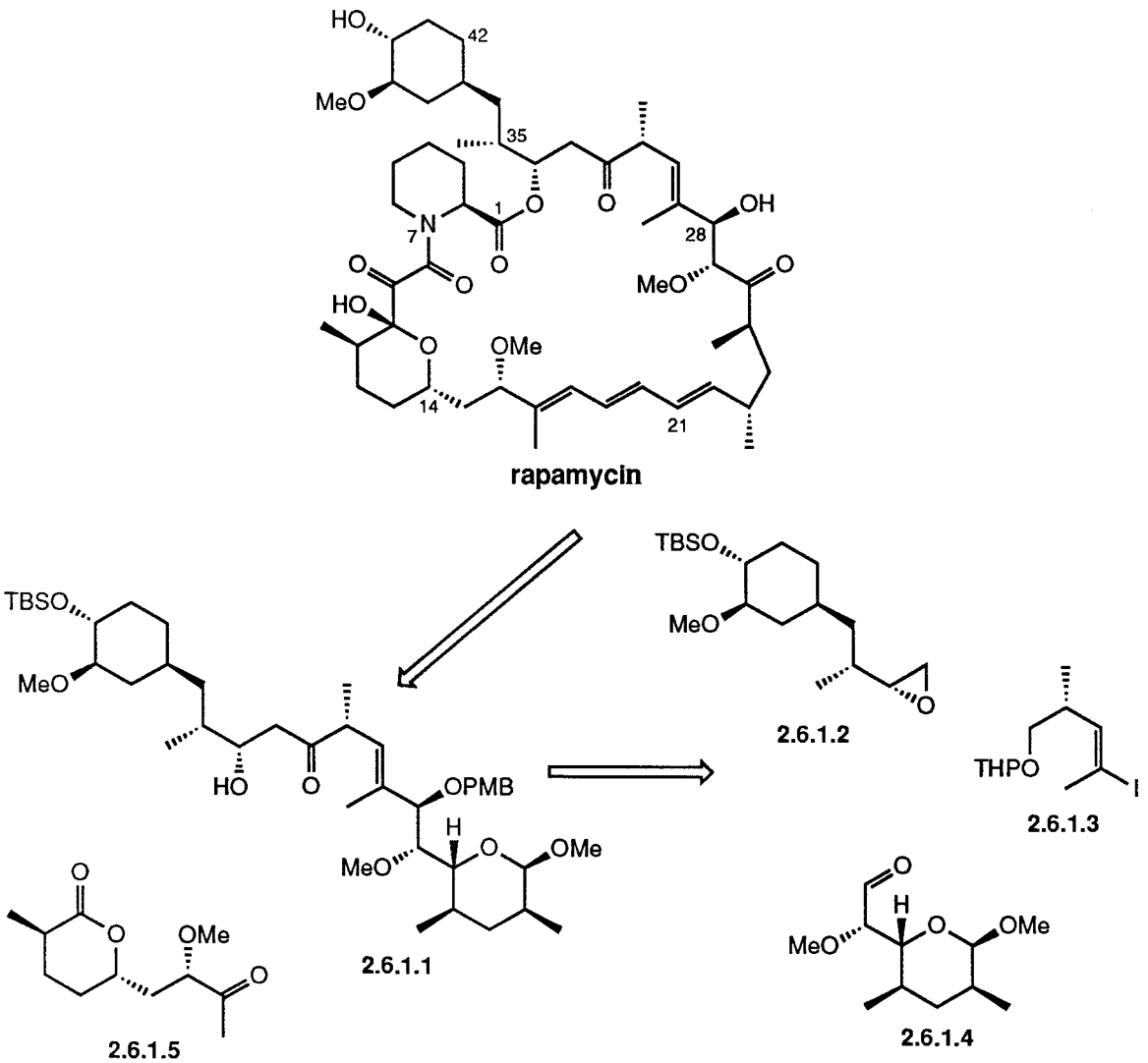


Yields, Reagents and Conditions:		
a	58%	EDC, DMAP, DMAP•HCl, CH_2Cl_2, r.t.
b	74%	$[(2\text{-furyl})_3P]_2PdCl_2$, *i*-$Pr_2NEt$, DMF–THF, r.t.
c	↓	TBAF, AcOH, 0°C
d	61%	HF•pyridine, pyridine, THF, r.t.

Scheme 2.5.9

2.6 The Ley Synthesis of the C22-C42 and C10-C17 Fragments

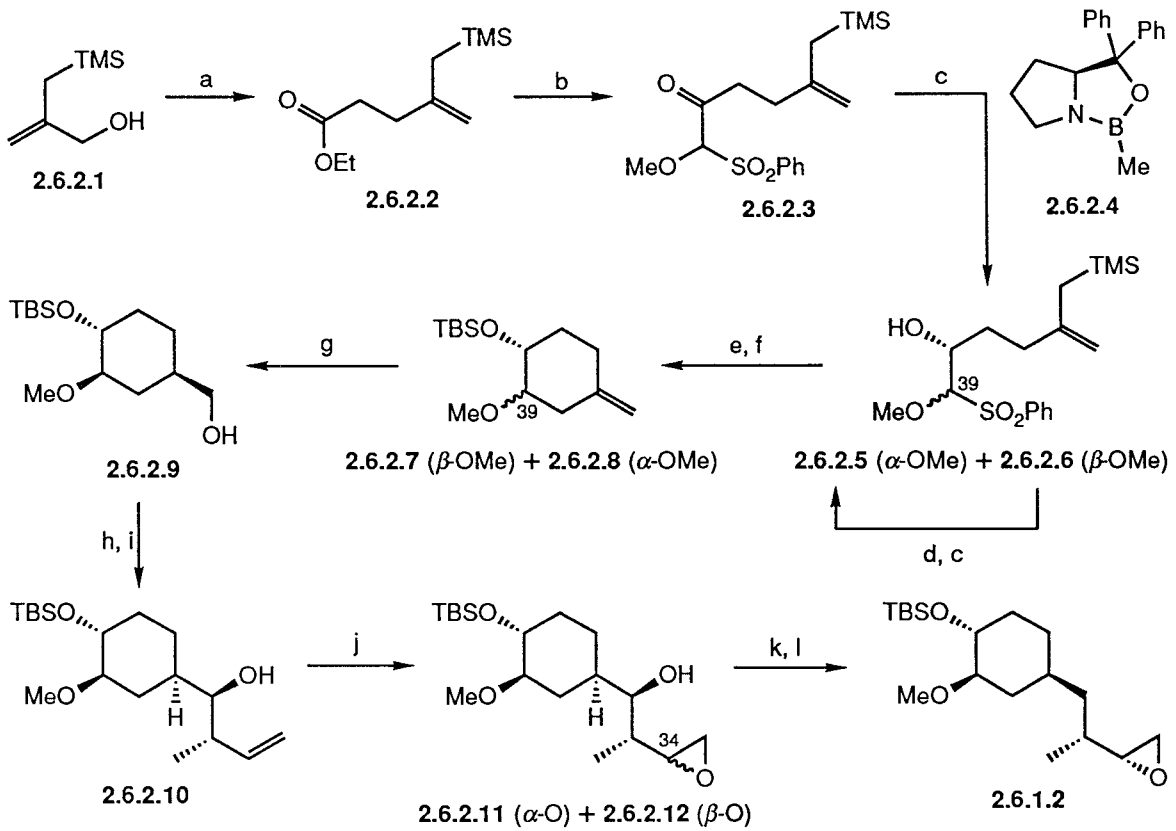
The Ley group has published syntheses of C22-C42 fragment **2.6.1.1** (derived by coupling of intermediates **2.6.1.2–2.6.1.4**) and C10-C17 lactone **2.6.1.5** (Scheme **2.6.1**).[43-45]



Scheme 2.6.1

The key step in the synthesis of epoxide **2.6.1.2** (Scheme **2.6.2**) involved an intramolecular reaction of an allylsilane with an oxonium ion, generated from an α-alkoxy sulfone, to stereoselectively form a methylene cyclohexane derivative (**2.6.2.5** → **2.6.2.7**). The synthesis began with a Claisen-Johnson rearrangement of 2-[(trimethylsilyl)methyl]-2-propen-1-ol (**2.6.2.1**) with triethyl orthoacetate to provide ester **2.6.2.2**. Condensation of **2.6.2.2** with the anion (*t*-BuLi, DME, –78°C) of methoxymethyl phenyl sulfone afforded β-keto sulfone **2.6.2.3**, which was subjected to asymmetric reduction employing BH_3•DMS and Corey's oxazaborolidine catalyst **2.6.2.4** to yield β-hydroxy sulfone **2.6.2.5** as a 1:2 mixture with C39-epimer **2.6.2.6**. The latter could be readily oxidised to **2.6.2.3** for recycling. Following silylation, **2.6.2.5** was treated with $SnCl_4$ to yield *trans*- and *cis*-methylene cyclohexane derivatives **2.6.2.7** and

2.6.2.8 as a 5:1 mixture. Hydroboration then provided alcohol **2.6.2.9**, at which stage the minor isomer from cyclisation could be separated. Swern oxidation of **2.6.2.9** and crotylboration of the intermediate aldehyde then provided alcohol **2.6.2.10**, which underwent epoxidation under standard conditions to provide epoxy alcohols **2.6.2.11** and **2.6.2.12** as a separable 4:1 mixture of diastereomers. Deoxygenation of **2.6.2.11** *via* its thionocarbonate derivative by reduction with *n*-Bu_3SnH then afforded **2.6.1.2**.

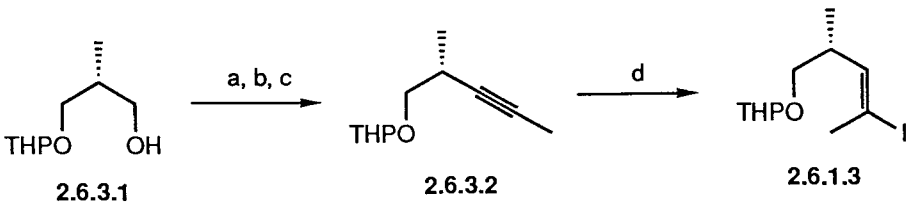


Yields, Reagents and Conditions:

a	↓	$(EtO)_3CMe$, $EtCO_2H$, 140°C	h	90%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
b	86%	MeOCH(Li)SO_2Ph, DME, –78°C → r.t.	i	70%	1) (–)-Ipc_2-(*E*)-crotylborane, THF–Et_2O, –78°C; 2) NaOH, H_2O_2
c	100%	BH_3•DMS, **2.6.2.4**, THF			
d	–	PDC, CH_2Cl_2	j	90%	TBHP, $VO(acac)_2$, CH_2Cl_2
e	↓	TBSOTf, pyridine, DMAP, CH_2Cl_2, 0°C	k	85%	*n*-BuLi, THF, –20°C; 2) ClC(=S)OPh
f	60%	$SnCl_4$, CH_2Cl_2, –78°C	l	80%	*n*-Bu_3SnH, AIBN, benzene, Δ
g	80%	1) 9-BBN, THF, 0°C → r.t.; 2) NaOH, H_2O_2			

Scheme 2.6.2

Four-carbon fragment **2.6.1.3** was prepared (Scheme **2.6.3**) in four steps from methyl (*S*)-3-hydroxy-2-methylpropionate-derived alcohol **2.6.3.1** by Swern oxidation, Corey-Fuchs homologation of the intermediate aldehyde, and hydrozirconation/iodination of the resulting methyl acetylene **2.6.3.2**.

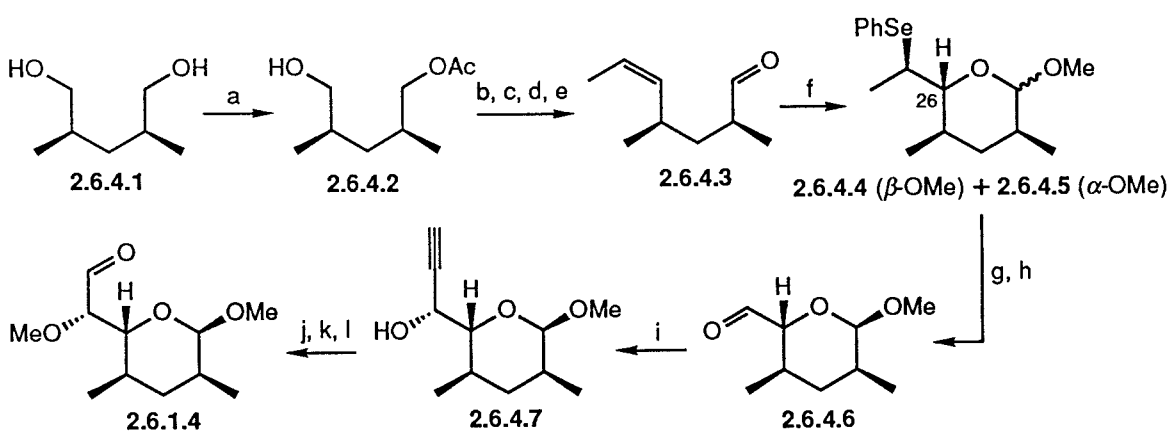


2.6.3.1 2.6.3.2 2.6.1.3

Yields, Reagents and Conditions:		
a	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → r.t.
b	77%	CBr_4, Ph_3P, CH_2Cl_2, 0°C
c	99%	1) *n*-BuLi, THF, –78°C; 2) MeI
d	85%	1) Cp_2ZrHCl, THF, r.t.; 2) I_2

Scheme 2.6.3

The key step in the synthesis of aldehyde **2.6.1.4** (Scheme **2.6.4**) involved a selenium-mediated electrophilic cyclisation of an intermediate hemiacetal derived from δ,ε-unsaturated aldehyde **2.6.4.3**, to stereoselectively afford acetals **2.6.4.4** and **2.6.4.5**. The synthesis began with the desymmetrisation of *meso*-2,4-dimethylpentane-1,5-diol (**2.6.4.1**) by enzymatic monoacyl transfer with methyl acetate. The resulting monoacetate **2.6.4.2** was elaborated to δ,ε-unsaturated aldehyde **2.6.4.3** using standard procedures. Treatment of **2.6.4.3** with NPSP and excess MeOH then afforded acetals **2.6.4.4** and **2.6.4.5** as single diastereomers at C26. Selenide oxidation/elimination followed by separation of the anomers and ozonolysis provided aldehyde **2.6.4.6**, which underwent stereoselective



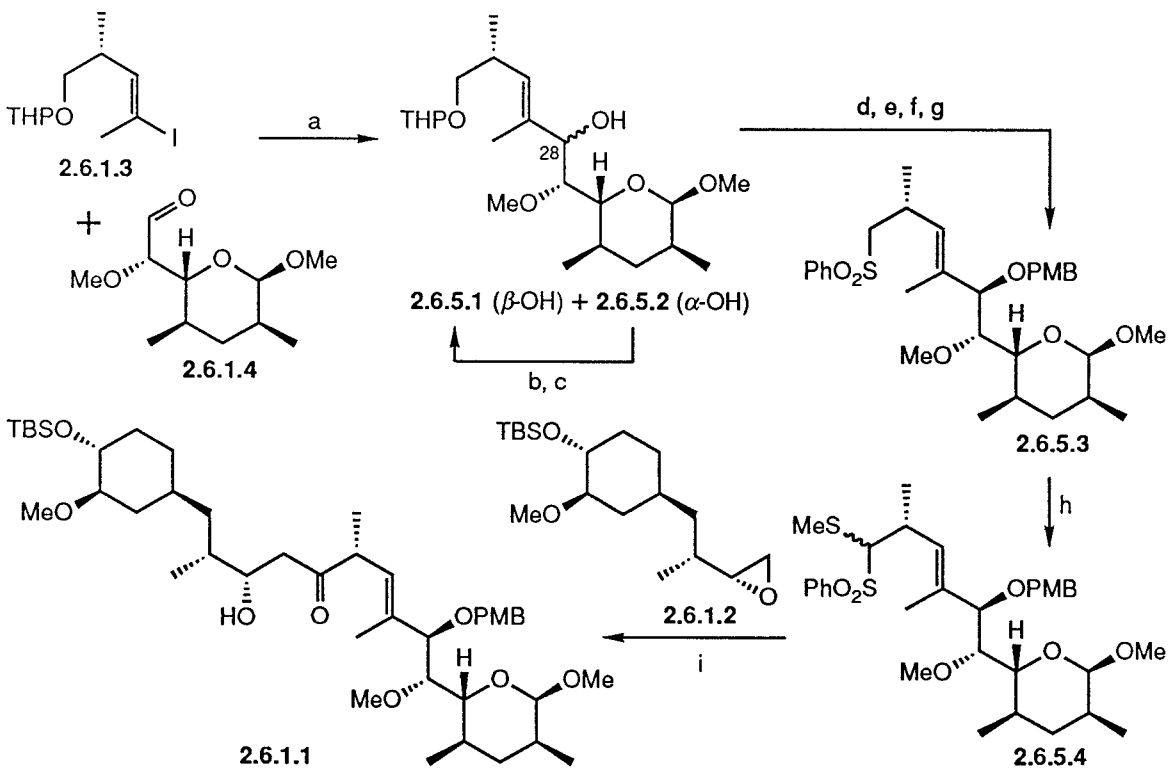
2.6.4.1 2.6.4.2 2.6.4.3 2.6.4.4 (β-OMe) + 2.6.4.5 (α-OMe) 2.6.4.6 2.6.4.7 2.6.1.4

Yields, Reagents and Conditions:		
a	55%	PPL on celite, MeOAc
b	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → r.t.
c	↓	$EtPPh_3Br$, *n*-BuLi, THF, 0°C
d	86%	aq. NaOH, *n*-Bu_4NOH, THF, Δ
e	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C → r.t.
f	66%	NPSP, MeOH, CH_2Cl_2
g	98%	H_2O_2, DHP, THF
h	83%	1) O_3, CH_2Cl_2, –78°C; 2) Ph_3P, –78°C → r.t.
i	90%	HC≡CMgBr, THF–toluene, –78°C
j	88%	Zn, MeOH–H_2O
k	99%	NaH, MeI, THF
l	–	1) O_3, CH_2Cl_2, –78°C; 2) Ph_3P, –78°C → r.t.

Scheme 2.6.4

addition of ethynylmagnesium bromide to yield propargyl alcohol **2.6.4.7**. Reduction of the triple bond to the corresponding alkene and methylation of the alcohol, followed by ozonolysis then provided **2.6.1.4**.

Coupling of vinyl iodide **2.6.1.3** with aldehyde **2.6.1.4** was achieved *via* a Nozaki-Kishi reaction (Scheme **2.6.5**) to afford alcohol **2.6.5.1** as a 3:1 mixture with C28-epimer **2.6.5.2**. The minor isomer was converted to **2.6.5.1** *via* an oxidation/chelation-controlled reduction sequence employing $Zn(BH_4)_2$. A series of four standard procedures then provided sulfone **2.6.5.3**, which was converted to its α-sulfenyl derivative **2.6.5.4**. Deprotonation of **2.6.5.4** and addition to epoxide **2.6.1.2** in the presence of $BF_3{\bullet}OEt_2$ then afforded coupled product **2.6.1.1** with the ketone function already deprotected (due to the presence of $BF_3{\bullet}OEt_2$).



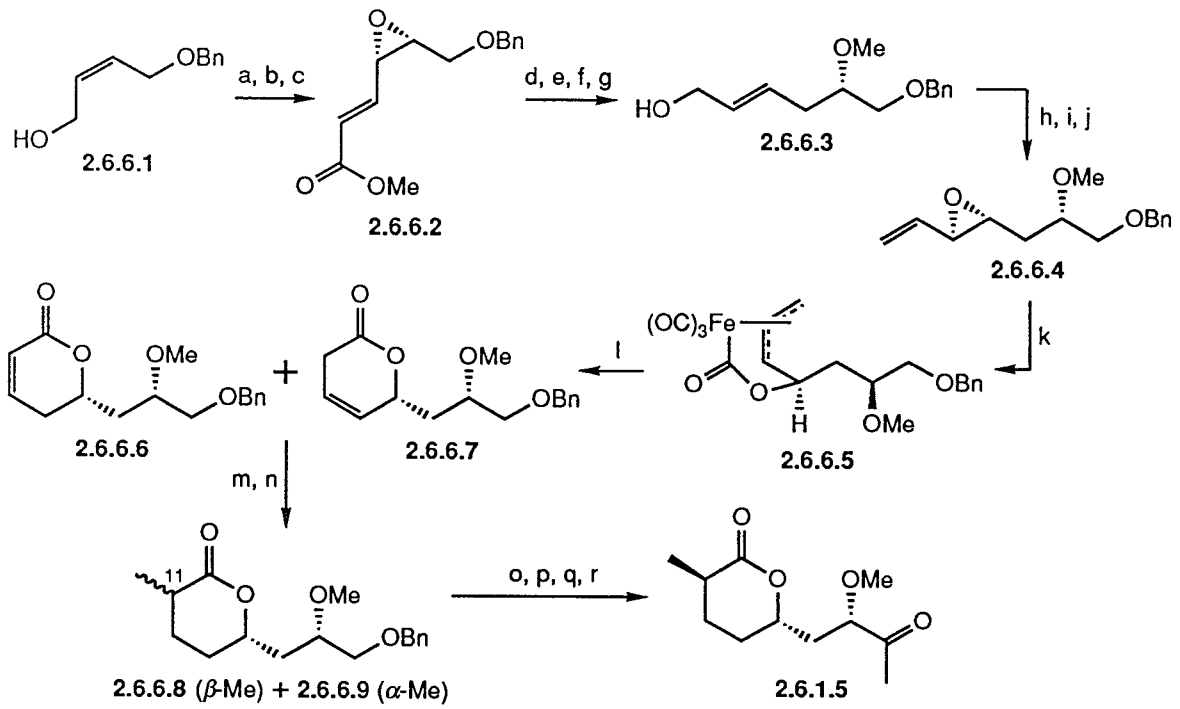
Yields, Reagents and Conditions:

a	67%	$CrCl_2$ (containing 0.5% $NiCl_2$), DMSO	f	85%	*n*-Bu_3P, *N*-phenylthiosuccinimide, benzene
b	98%	TPAP, NMNO, CH_2Cl_2	g	93%	Oxone, pH 4 buffer, THF–MeOH
c	81%	$Zn(BH_4)_2$, Et_2O, 0°C	h	81%	1) *t*-BuLi, THF, –78°C; 2) $(MeS)_2$
d	75%	NaH, PMBCl, NaI, THF, 0°C → r.t.	i	46%	1) *t*-BuLi, THF, –78°C; 2) **2.6.1.2**;
e	84%	Amberlyst-15, MeOH			3) $BF_3{\bullet}OEt_2$, –78°C → r.t.

Scheme 2.6.5

The synthesis of fragment **2.6.1.5** (Scheme **2.6.6**) employed π-allyltricarbonyliron chemistry in the key step to generate the lactone ring. Thus, Sharpless asymmetric epoxidation of (*Z*)-4-(benzyloxy)-2-buten-1-ol (**2.6.6.1**) followed by oxidation of the resulting epoxy alcohol and condensation of the intermediate aldehyde with diethyl

phosphonoacetate yielded enoate **2.6.6.2**. A further four steps provided allylic alcohol **2.6.6.3**, which underwent a second Sharpless epoxidation. Oxidation and Wittig methylenation then furnished alkenyl epoxide **2.6.6.4** as the precursor to the iron carbonyl chemistry. Reaction of **2.6.6.4** with $Fe_2(CO)_9$ in THF gave *endo*-complex **2.6.6.5** as the predominant product, which was subjected to exhaustive carbonylation to provide unsaturated lactones **2.6.6.6** and **2.6.6.7**. Hydrogenation and α-methylation then produced lactone **2.6.6.8** as a 1:1.5 mixture with C11-epimer **2.6.6.9** (the mixture was separable by HPLC and the unwanted major isomer could be recycled to **2.6.6.8** by deprotonation/reprotonation). A further four transformations then afforded **2.6.1.5**.

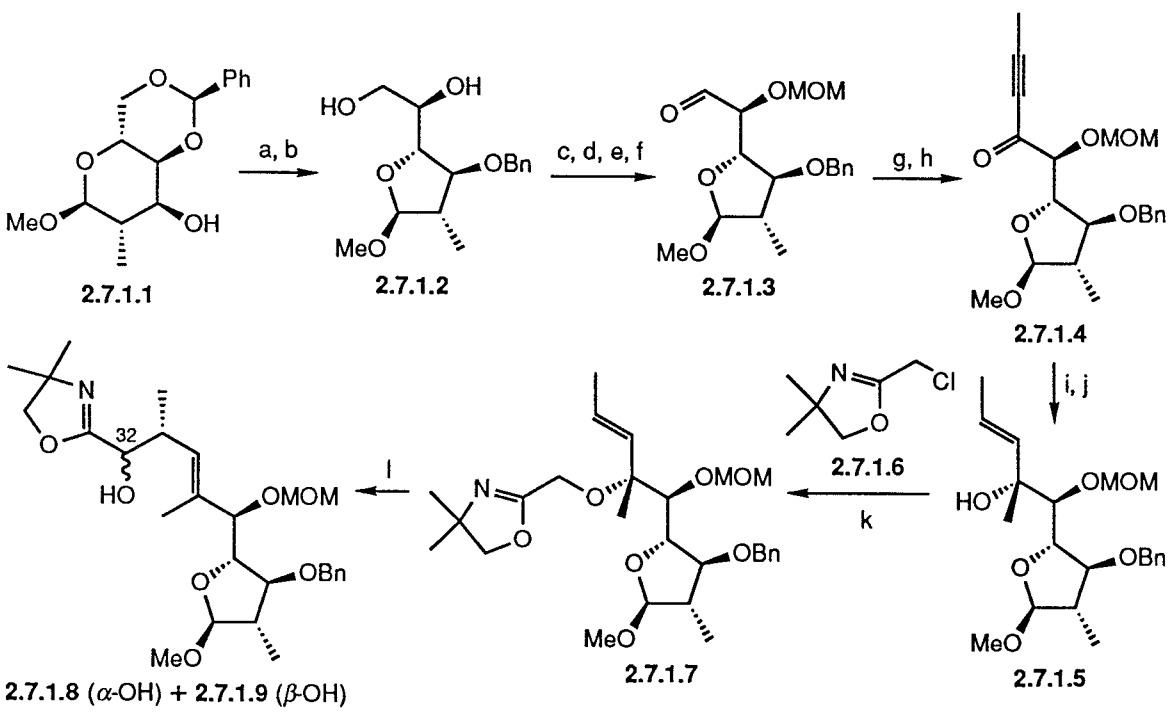


Yields, Reagents and Conditions:		
a	75%	$Ti(O\text{-}iPr)_4$, (+)-DET, TBHP, CH_2Cl_2, –25°C
b	80%	pyridine•SO_3, Et_3N, DMSO, CH_2Cl_2, 0°C → r.t.
c	68%	$(EtO)_2P(O)CH_2CO_2Me$, LiCl, DBU, MeCN, r.t.
d	↓	DIBALH, CH_2Cl_2, –78°C
e	69%	PivCl, pyridine, CH_2Cl_2, 0°C
f	94%	NaH, MeI, 0°C
g	88%	DIBALH, CH_2Cl_2, –78°C
h	80%	$Ti(O\text{-}iPr)_4$, (–)-DET, TBHP, 4Å molecular sieves, CH_2Cl_2, –23°C
i	60%	TPAP, NMNO, 4Å molecular sieves, CH_2Cl_2–MeCN
j	83%	$MePPh_3Br$, KHMDS, THF, 0°C → r.t.
k	72%	$Fe_2(CO)_9$, degassed THF
l	85%	CO (280 atm.), benzene, 70°C
m	82%	PtO_2, H_2, EtOAc, r.t.
n	80%	1) LDA, THF, –78°C; 2) MeI
o	100%	$Pd(OH)_2/C$, H_2, EtOAc, r.t.
p	↓	Dess-Martin Periodinane, *t*-BuOH, pyridine, CH_2Cl_2
q	↓	MeMgBr, Et_2O, THF, –78°C
r	70%	Dess-Martin Periodinane, *t*-BuOH, pyridine, CH_2Cl_2

Scheme 2.6.6

2.7 The Kallmerten Synthesis of the C24-C36 Fragment

Kallmerten's synthesis of C24-C36 fragment **2.7.2.4**[46] features two [2,3] Wittig rearrangements as key steps (Schemes **2.7.1** and **2.7.2**). The synthesis began with D-glucose-derived compound **2.7.1.1**, which was converted to furanose **2.7.1.2** *via* benzylation and acid-catalysed isomerisation. A further four steps then yielded aldehyde **2.7.1.3**, which, upon chelation-controlled addition of propynylmagnesium bromide and oxidation of the epimeric adducts, afforded ketone **2.7.1.4**. A second chelation-controlled Grignard addition followed by reduction of the triple bond then provided (*E*)-allylic alcohol **2.7.1.5**. Alkylation of **2.7.1.5** with chloromethyloxazoline **2.7.1.6** and treatment of the resulting ether **2.7.1.7** with *n*-BuLi resulted in rapid [2,3] rearrangement, yielding an inseparable mixture (4.5:1) of homoallylic alcohol **2.7.1.8** and its C32-epimer **2.7.1.9**.

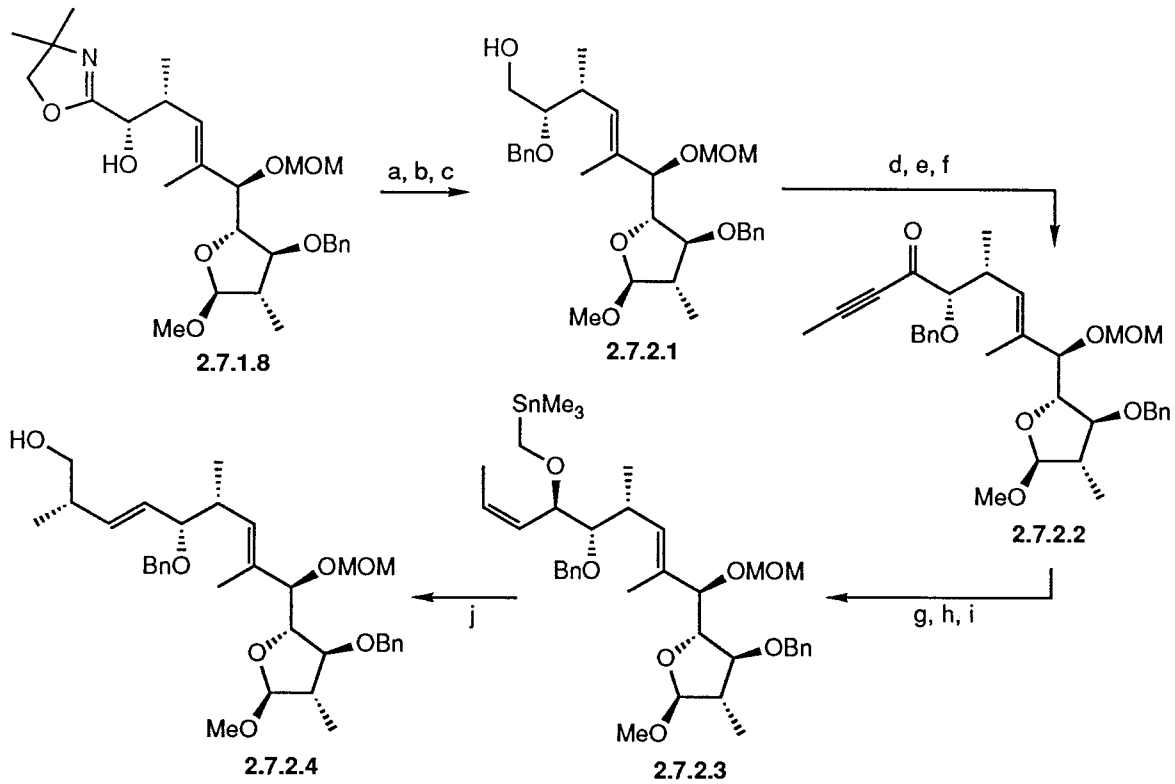


Yields, Reagents and Conditions:					
a	↓	KH, BnBr, DME	g	↓	MeC≡CMgBr, THF, –78°C
b	67%	HCl, MeOH	h	85%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
c	↓	TBSCl, imidazole, THF	i	↓	MeMgBr, THF, –78°C
d	87%	MOMCl, *i*-Pr_2NEt	j	81%	$LiAlH_4$, THF, 45°C
e	99%	TBAF, THF	k	↓	KH, **2.7.1.6**, DME
f	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2	l	70%	*n*-BuLi, THF, –78°C

Scheme 2.7.1

Benzylation and reductive cleavage of the oxazoline group then provided alcohol **2.7.2.1**, at which stage the minor isomer from rearrangement could be separated. A further three steps provided propargyl ketone **2.7.2.2**, which was converted to α-stannyl ether **2.7.2.3** by chelation-controlled reduction of the carbonyl group and Lindlar reduction of the acetylene,

followed by alkylation. Upon transmetallation, **2.7.2.3** underwent a second [2,3] rearrangement to yield **2.7.2.4**.

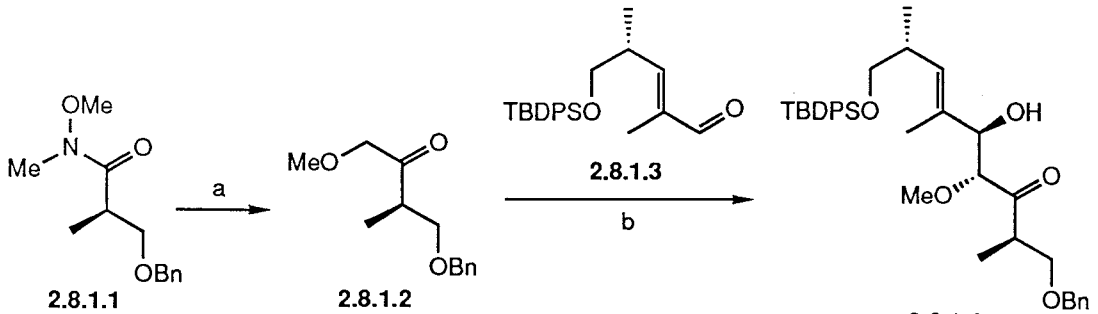


Yields, Reagents and Conditions:					
a	↓	KH, BnBr, DME	f	64%	MnO_2, CH_2Cl_2
b	↓	aq. TFA	g	↓	$NaBH_4$, $ZnCl_2$, Et_2O, 0°C
c	89%	$LiAlH_4$	h	97%	Lindlar catalyst, H_2, MeOH
d	↓	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2	i	↓	KH, Me_3SnCH_2I, DME
e	↓	MeC≡CMgBr, THF, –78°C	j	44%	MeLi, THF, –78°C

Scheme 2.7.2

2.8 The Paterson Synthesis of the C24-C32 Fragment

Paterson has reported[47] a short synthesis of C24-C32 fragment **2.8.1.4** (Scheme **2.8.1**) which features a highly π-face-selective boron-mediated *anti*-aldol reaction as the key step. Thus, Weinreb amide **2.8.1.1** was prepared in two steps from methyl (*R*)-3-hydroxy-2-methylpropionate and converted to methoxymethyl ketone **2.8.1.2**. Enal **2.8.1.3**, prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate (by TBDPS-protection of the alcohol, conversion of the ester to the corresponding aldehyde, Wittig homologation with $Ph_3P{=}C(Me)CO_2Me$, DIBALH reduction and Dess-Martin oxidation), was then condensed with the (*E*)-enol borinate of **2.8.1.2** to afford **2.8.1.4** as the sole product.



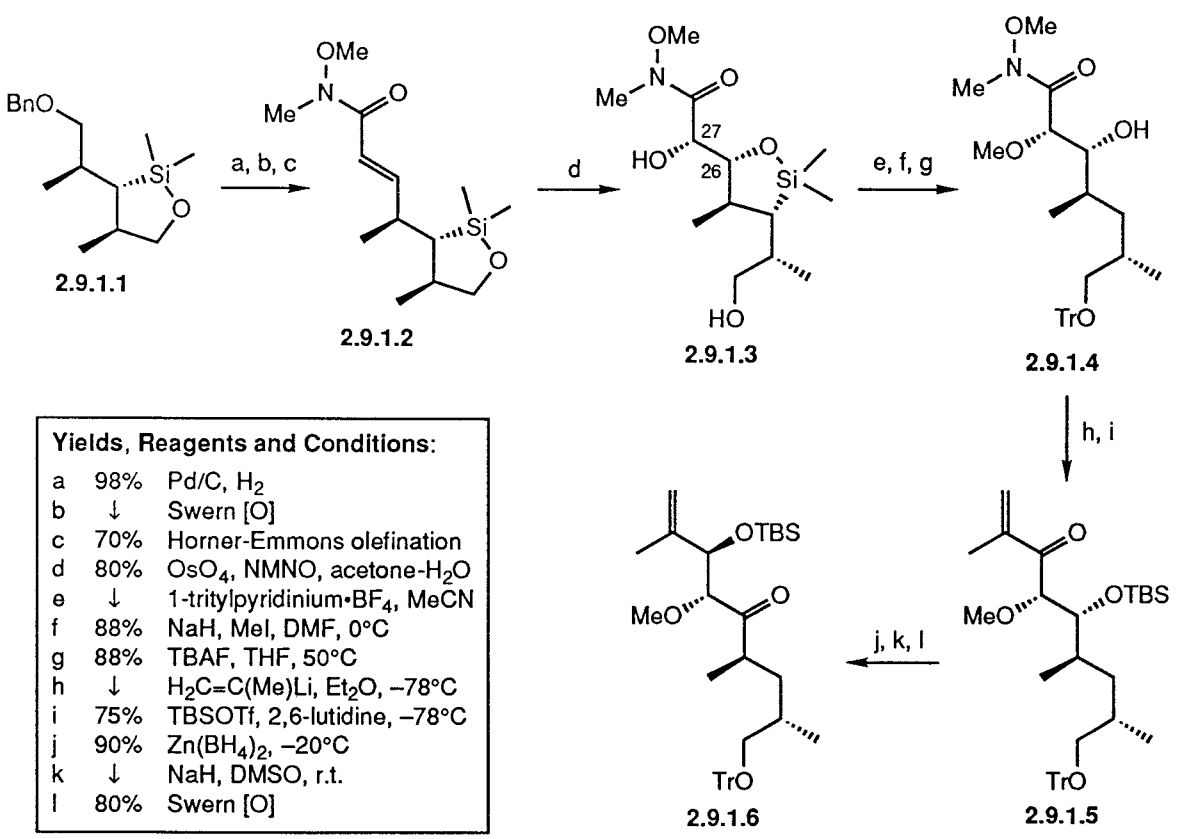
Yields, Reagents and Conditions:

a	80%	*n*-Bu_3SnCH_2OMe, *n*-BuLi, THF, –78°C → 0°C
b	94%	1) $(cyclohexyl)_2BCl$, Et_3N, Et_2O, –78°C → 0°C; 2) **2.8.1.3**, –78°C → –20°C

Scheme 2.8.1

2.9 The Hoveyda Synthesis of the C22-C29 Fragment

Hoveyda's synthesis[48] of C22-C29 fragment **2.9.1.6** (Scheme **2.9.1**) utilises the ability of a siloxane ring to relay asymmetry along an acyclic chain in order to direct a stereoselective osmylation (**2.9.1.2** → **2.9.1.3**). The synthesis began with siloxane **2.9.1.1**, prepared by intramolecular Pt-catalysed hydrosilylation of the corresponding (*E*)-allylic silyloxy hydride. Debenzylation of **2.9.1.1**, followed by Swern oxidation and Horner-Emmons olefination of the resulting aldehyde afforded unsaturated Weinreb amide



Yields, Reagents and Conditions:

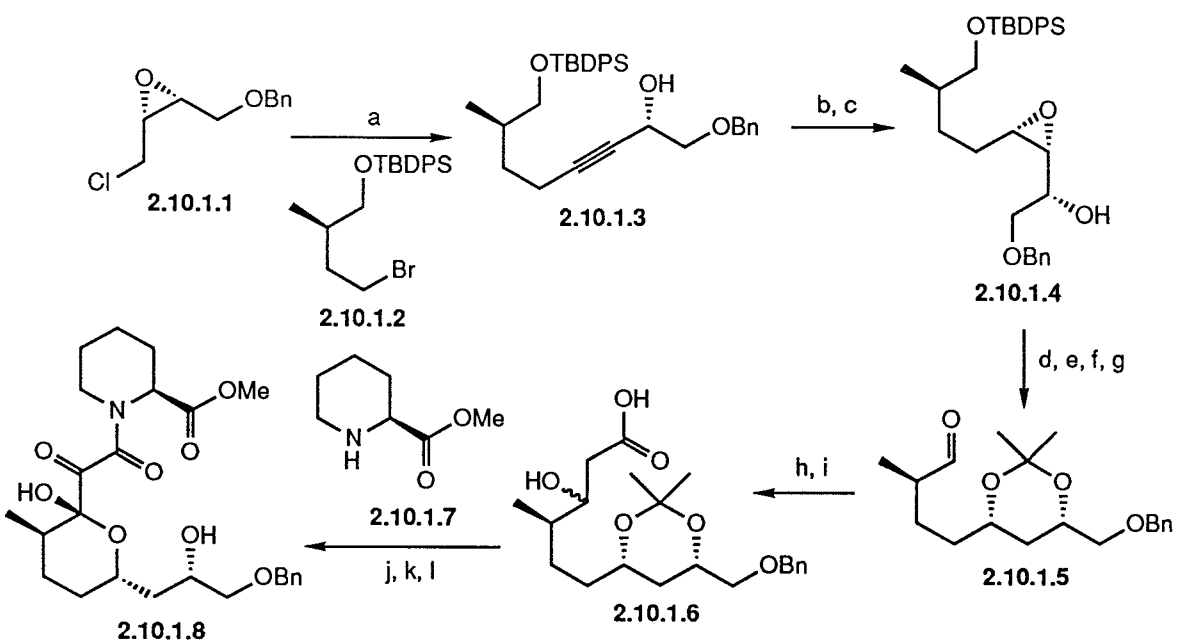
a	98%	Pd/C, H_2
b	↓	Swern [O]
c	70%	Horner-Emmons olefination
d	80%	OsO_4, NMNO, acetone-H_2O
e	↓	1-tritylpyridinium•BF_4, MeCN
f	88%	NaH, MeI, DMF, 0°C
g	88%	TBAF, THF, 50°C
h	↓	H_2C=C(Me)Li, Et_2O, –78°C
i	75%	TBSOTf, 2,6-lutidine, –78°C
j	90%	$Zn(BH_4)_2$, –20°C
k	↓	NaH, DMSO, r.t.
l	80%	Swern [O]

Scheme 2.9.1

2.9.1.2. Osmylation of **2.9.1.2** then stereoselectively afforded siloxane **2.9.1.3** (resulting from rearrangement of the initially formed 1,2-diol), thus differentiating the secondary hydroxyls at C26 and C27. Tritylation of the primary alcohol, methylation of the C27-alcohol, and removal of the siloxane afforded hydroxy amide **2.9.1.4**, which was converted to enone **2.9.1.5** *via* reaction with 2-propenyllithium followed by TBS-protection of the alcohol. Chelation-controlled reduction of the carbonyl with $Zn(BH_4)_2$ was followed by a silyl migration to the allylic carbinol induced by NaH in DMSO. The free C26-hydroxyl was then oxidised to the requisite carbonyl to afford **2.9.1.6**.

2.10 The Rama Rao Synthesis of the C1-C17 Fragment

Rama Rao has reported[49] a synthesis of C1-C17 fragment **2.10.1.8** beginning with epoxychloride **2.10.1.1** (Scheme **2.10.1**). Base-induced double elimination of **2.10.1.1** generated the corresponding propargylic alcohol which was coupled *in situ* with bromide **2.10.1.2** (prepared in six steps from methyl (*S*)-3-hydroxy-2-methylpropionate). The



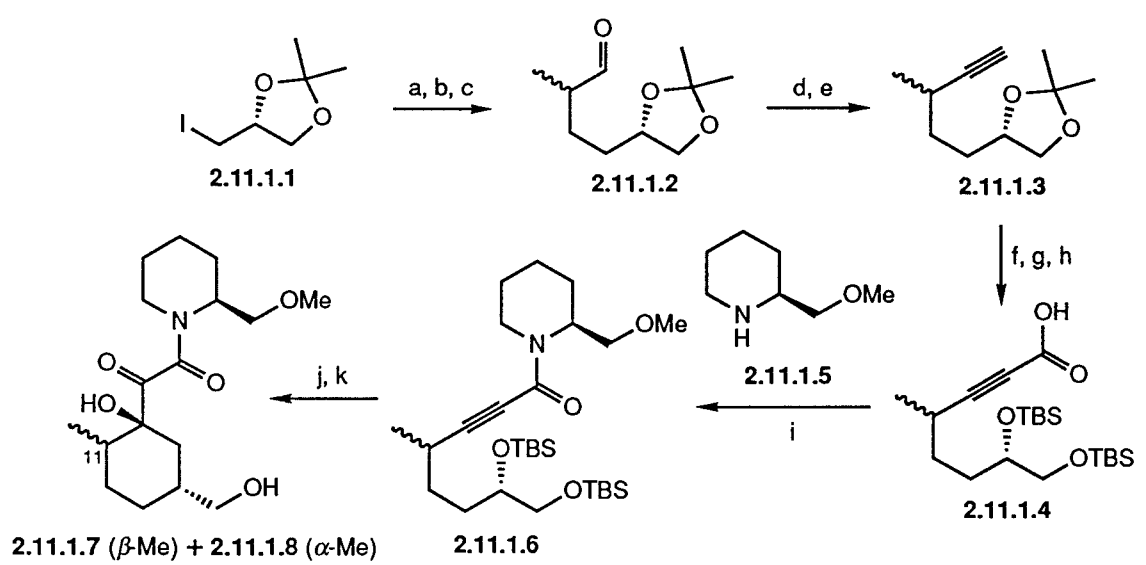
Yields, Reagents and Conditions:		
a	60%	1) $LiNH_2$–NH_3, –33°C; 2) **2.10.1.2**
b	95%	Lindlar catalyst, quinoline, MeOH
c	60%	$Ti(O\text{-}i\text{-}Pr)_4$, (–)-DIPT, TBHP, 3 Å molecular sieves, CH_2Cl_2
d	75%	Red-Al, THF, r.t.
e	↓	TBAF, THF, r.t.
f	↓	acetone, PTSA
g	80%	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C
h	70%	Zn, $BrCH_2CO_2Et$, benzene, Δ
i	70%	LiOH, DME
j	75%	**2.10.1.7**, pentafluorophenol, DCC, DMAP, CH_2Cl_2
k	60%	Dess-Martin Periodinane, pyridine, CH_2Cl_2
l	70%	0.001 M HCl, MeOH

Scheme 2.10.1

resulting product **2.10.1.3** then underwent Lindlar reduction and Sharpless asymmetric epoxidation of the resulting (*Z*)-alkene to afford epoxyalcohol **2.10.1.4**. Regioselective opening of the epoxide with Red-Al followed by a further three transformations led to aldehyde **2.10.1.5**, which was subjected to a Reformatsky reaction with Zn/ethyl bromoacetate. Hydrolysis of the resulting *β*-hydroxy ester provided acid **2.10.1.6** (as a 1:1 mixture of diastereomers) which was coupled with methyl L-pipecolinate (**2.10.1.7**). Dess-Martin oxidation to the tricarbonyl compound followed by acetonide hydrolysis then led to lactolisation, providing **2.10.1.8** in good yield.

2.11 The Pattenden Synthesis of the C1-C15 Fragment

In Pattenden's synthesis[50] of C1-C15 fragment **2.11.1.7** (Scheme **2.11.1**), a straightforward oxidation of acetylenic amide **2.11.1.6** using catalytic RuO_4 (generated *in situ* from RuO_2 and $NaIO_4$) was used to generate the tricarbonyl unit. The synthesis began with the radical-initiated addition of iodide **2.11.1.1** (derived from the corresponding carbinol) to methyl methacrylate. The resulting 1:1 mixture of diastereomeric esters was converted to aldehyde **2.11.1.2** and homologated (Corey-Fuchs) to terminal acetylene **2.11.1.3**. Removal of the acetonide and bis-silylation of the resulting diol, followed by metallation and carboxylation of the acetylene, led to acid **2.11.1.4**. Coupling of **2.11.1.4** with (*S*)-2-(methoxymethyl)piperidine (**2.11.1.5**) in the presence of BOP•PF_6 next produced **2.11.1.6**, which, upon exposure to catalytic RuO_4, afforded the required amide



Yields, Reagents and Conditions:

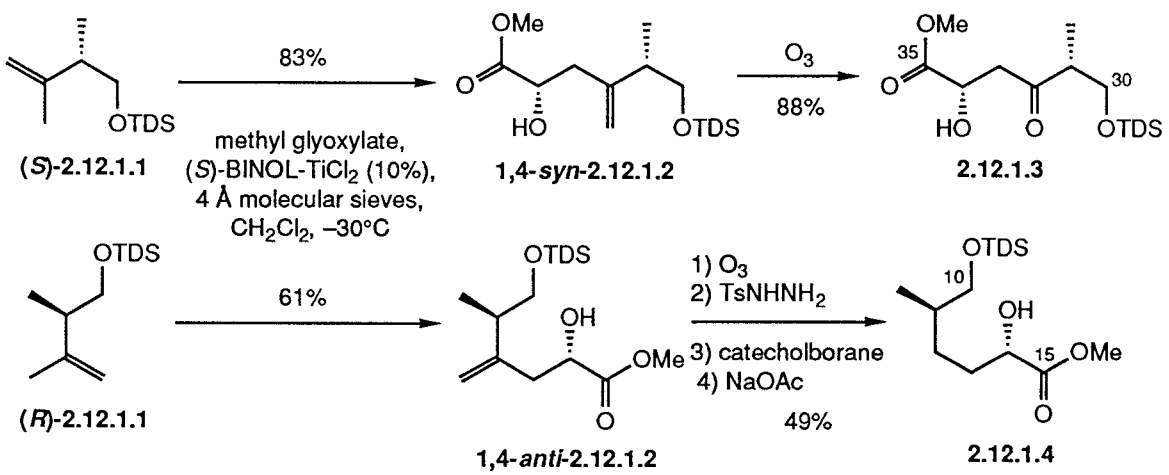
a	55%	$H_2C{=}C(Me)CO_2Me$, *n*-Bu_3SnCl–$NaBH_4$, hv, r.t.	g	↓	TBSCl, imidazole, DMF
b	↓	DIBALH, THF	h	86%	1) *n*-BuLi, HMPA, –50°C; 2) CO_2
c	↓	PCC, NaOAc	i	86%	**2.11.1.5**, BOP•PF_6
d	76%	$Ph_3P{=}CBr_2$	j	35%	RuO_2–$NaIO_4$
e	45%	*n*-BuLi, THF, –70°C	k	–	aq. HF, MeCN
f	↓	HCl, MeOH			

Scheme 2.11.1

dione. Bis-desilylation of the product then led to lactolisation, producing **2.11.1.7**, which could now be cleanly separated from the C11-epimeric material **2.11.1.8**.

2.12 The Mikami Synthesis of the C30-C35 and C10-C15 Segments

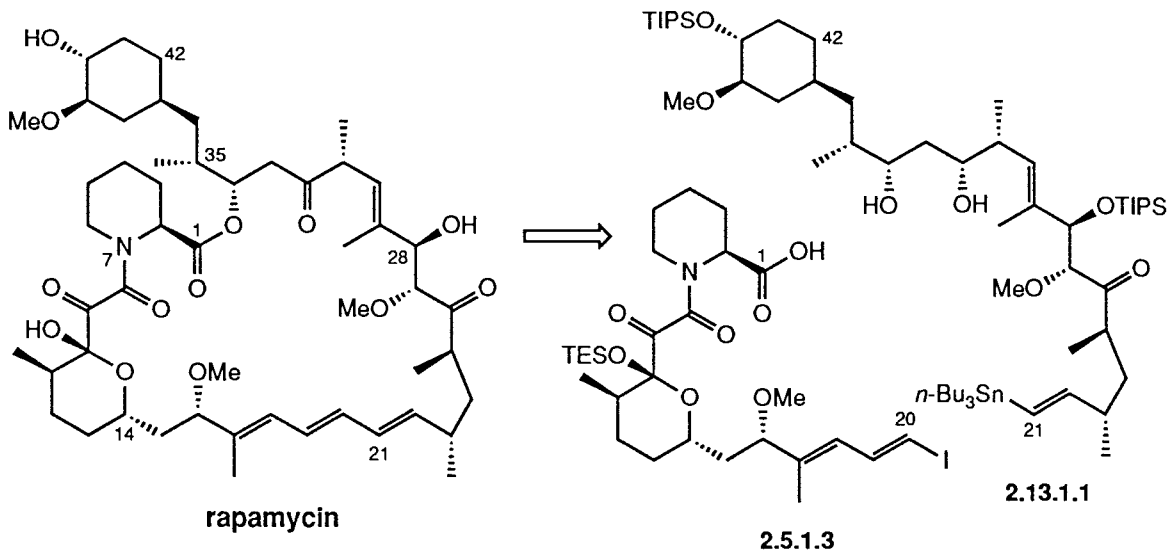
Finally, Mikami has shown[51] that the (*S*)-BINOL-$TiCl_2$-catalysed asymmetric carbonyl-ene reaction of (*S*)- and (*R*)-homoallylic silyl ethers **2.12.1.1** with methyl glyoxylate affords 1,4-*syn*- and 1,4-*anti*-products **2.12.1.2** respectively with essentially complete diastereoselectivity, independent of reactant chirality. Further transformations then led to 1,4-*syn*- and 1,4-*anti*-compounds **2.12.1.3** and **2.12.1.4**, corresponding to the C30-C35 and C10-C15 segments of rapamycin respectively.



Scheme 2.12.1

2.13 The Southampton Approach

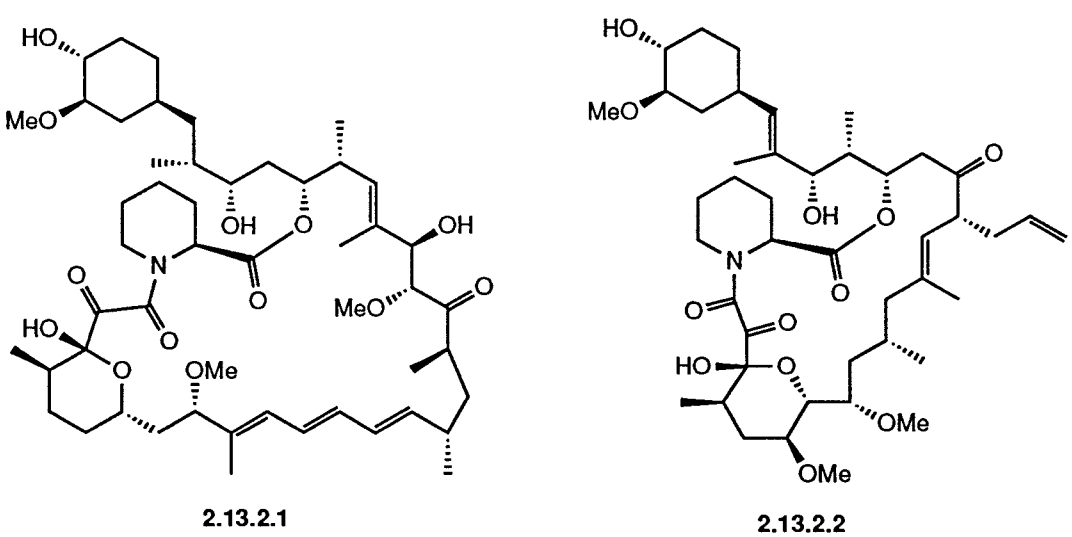
The initial disconnections in our retrosynthetic analysis of rapamycin (Scheme **2.13.1**) are the same as those used in Smith's total synthesis (Section **2.5**), whereby we divide the macrocycle into two large fragments encompassing C21-C42 (**2.13.1.1**) and C1-C20 (**2.5.1.3**) *via* disconnection of the macrolactone linkage and the C20-C21 olefin bond. Two alternative macrocyclisation strategies could then be pursued: an intermolecular esterification of **2.13.1.1** (at the C34 alcohol) with acid **2.5.1.3** followed by intramolecular Pd(0)-catalysed Stille coupling between the C20 vinyl iodide and the C21 vinyl stannane, or initial formation of the triene seco acid followed by macrolactonisation. In Smith's total synthesis the former strategy was used.



Scheme 2.13.1

C1-C20 fragment **2.5.1.3** is identical to the corresponding fragment used in Smith's total synthesis, whereas C21-C42 fragment **2.13.1.1** differs only in the nature of the C28 hydroxyl protecting group and the presence of an unprotected alcohol at C32 rather than the requisite ketone. The logic of our synthesis of **2.13.1.1** necessitated the creation of a C32,C34-diol, and a protocol for the differential protection of the two hydroxyls would have required the incorporation of a number of additional steps (with an inevitable decrease in overall yield) into our synthetic strategy. We therefore decided to avoid attempts to distinguish the hydroxyls and suffer the consequences of a potentially non-chemoselective acylation (whether inter- or intramolecular) at a late stage in the synthesis.

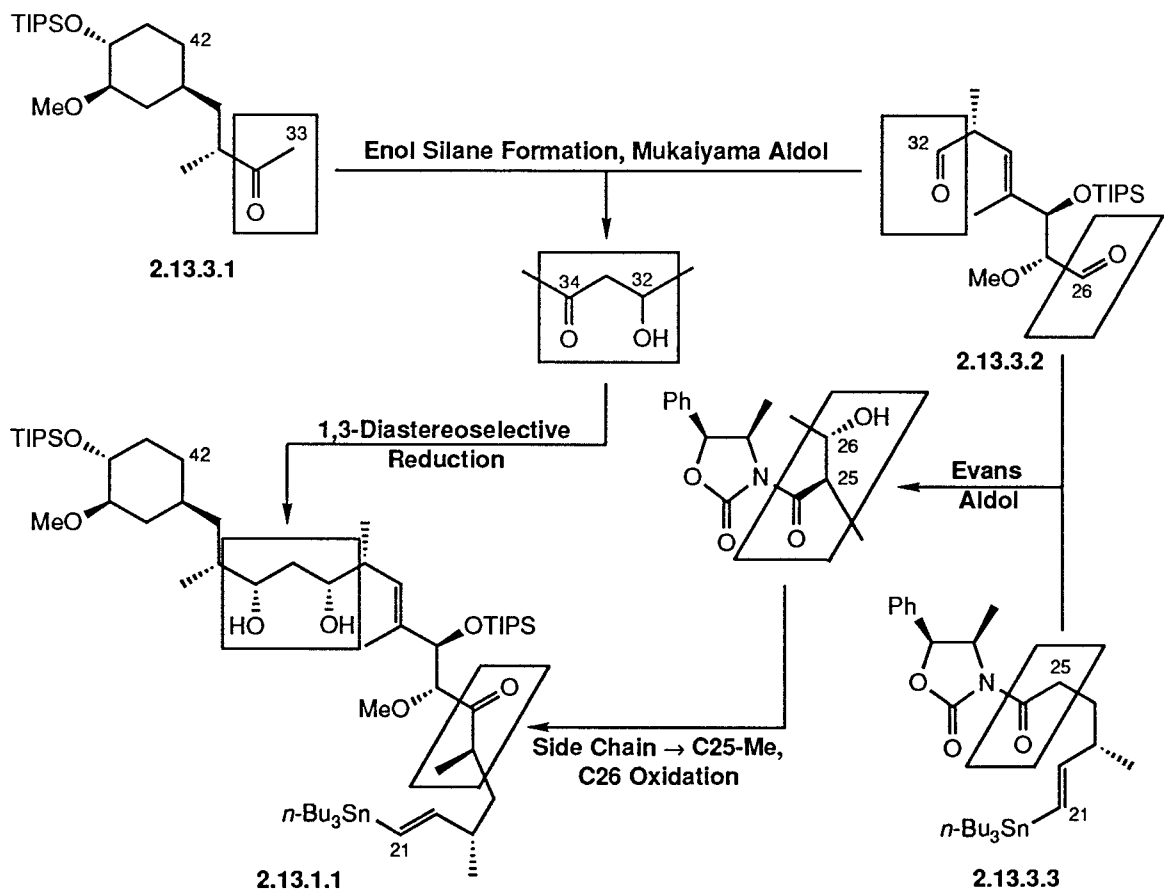
This strategy, although inherently inefficient with regard to the synthesis of rapamycin, is not as wasteful as it initially appears, since the ring-contracted analogue **2.13.2.1** (Scheme **2.13.2**) of the natural product, which would result from competitive acylation at C32,



Scheme 2.13.2

would undoubtedly be of biological interest, and has in fact been recently synthesised from rapamycin by researchers at Wyeth-Ayerst for biological evaluation.[52] In a related piece of work, researchers at Sandoz have reported the isolation of an analogous ring-contracted form of FK-506 (**2.13.2.2**) from *Streptomyces tsukubaensis*.[53]

The aim of this research was the synthesis of C21-C42 fragment **2.13.1.1**, in parallel with ongoing work directed towards the synthesis of C1-C20 fragment **2.5.1.3**. We envisaged the construction of **2.13.1.1** using aldol methodology, from fragments corresponding to C33-C42 methyl ketone **2.13.3.1**, C26-C32 bis-aldehyde **2.13.3.2** and chiral auxiliary-bearing C21-C25 fragment **2.13.3.3** (Scheme **2.13.3**).

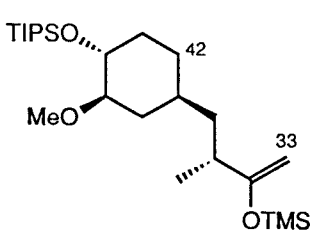


Scheme 2.13.3

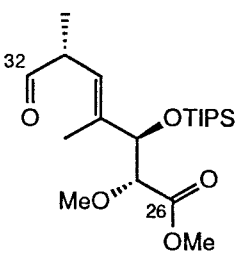
Due to the known sensitivity of the C31 stereocentre of rapamycin towards epimerisation under basic conditions (Section **1.3**), we decided to form the C32-C33 bond using a Lewis acid-mediated (Mukaiyama) aldol reaction between an enol silane derived from **2.13.3.1** and the C32 aldehyde of **2.13.3.2**. The newly generated C32 carbinol of the resulting β-hydroxy ketone would then be used to direct either a *syn*- or *anti*-1,3-diastereoselective reduction, as required, of the β-carbonyl function to stereoselectively generate the C34 carbinol.

The C25-C26 bond was to be constructed using an Evans aldol reaction of an *N*-acyloxazolidinone carrying the C21-C25 segment (provisionally formulated as **2.13.3.3**) with the C26 aldehyde of **2.13.3.2**. The same C25-C26 Evans aldol disconnection was used to construct a C21-C28 fragment in Nicolaou's total synthesis of rapamycin (Section **2.2**), wherein the C25 methyl group was generated from the side chain bearing the chiral auxiliary *via* a reduction–tosylation–reduction sequence. We intended to use this procedure in our synthesis, which, along with reoxidation of the C26 alcohol, would stereoselectively lead to the C25-C26 α-methyl ketone unit.

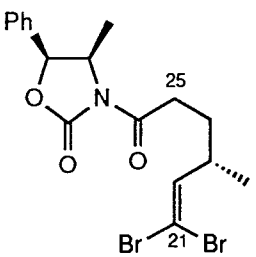
The actual fragments (**2.13.4.1–2.13.4.3**) which emerged from this strategy are shown in Scheme **2.13.4**. The syntheses of these intermediates are described in Chapters **3–5**, whereas their subsequent coupling and further elaboration to form the C21-C42 target fragment **2.13.1.1** is described in Chapter **6**.



2.13.4.1
C33-C42 Fragment



2.13.4.2
C26-C32 Fragment



2.13.4.3
C21-C25 Fragment

Scheme 2.13.4

2.14 Conclusion

The total synthesis of a natural product is not only an intellectual challenge which serves to confirm or refute the initial structural assignment, but also helps to define the scope and limitations of existing synthetic methodology. Furthermore, by minor modifications of a total synthesis, access is provided to virtually unlimited numbers of structurally-related analogues of potential biological value. A natural product of such structural complexity as rapamycin thus presents a challenging synthetic target, and the four total syntheses of this potent immunosuppressant represent major achievements in this field.

Natural product synthesis also provides a stimulus for the development of new synthetic procedures. The new methodology used in the construction of some of the rapamycin fragments described in Sections **2.6-2.12** will undoubtedly find application in other areas of synthesis.

Work at Southampton towards the synthesis of both FK-506 and rapamycin has been ongoing for a number of years. Our convergent approach to the C21-C42 fragment

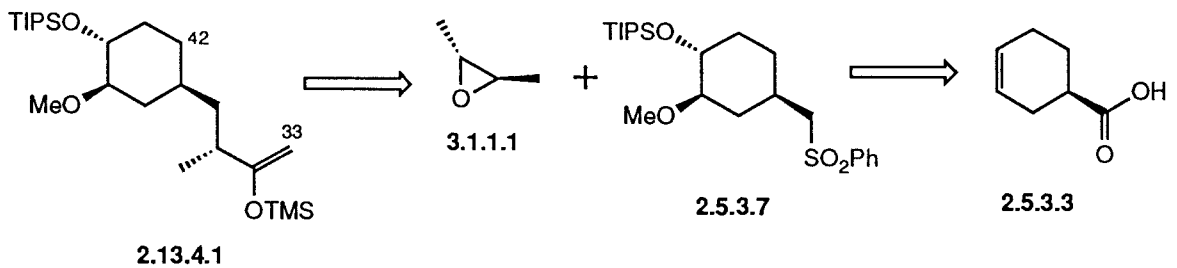
2.13.1.1 of rapamycin would involve both the efficient application of existing methodology and (in the synthesis of C26-C32 fragment **2.13.1.2**) the development of a new procedure for the Fleming-Tamao oxidation of allylic silanes to allylic alcohols, a transformation which has previously been difficult to achieve. This research will be described in detail in the ensuing chapters.

Chapter 3

Synthesis of the C33-C42 Fragment

3.1 Introduction

The cyclohexyl moiety of rapamycin is a substructure also found in FK-506, and as such has been the subject of considerable synthetic attention over the past few years.[27,31,41,54-68] A key intermediate in our route to C33-C42 fragment **2.13.4.1** was sulfone **2.5.3.7** (Scheme **3.1.1**), the lithio-derivative of which was reacted with homochiral epoxide **3.1.1.1** to form the C35-C36 bond. Sulfone **2.5.3.7** has previously been used in formal syntheses of FK-506 by both Danishefsky[58,69,70] and Smith,[40-42] and was later used in Smith's total synthesis of rapamycin (Section **2.5**). In common with Smith, our chosen starting material for the synthesis of **2.5.3.7** was (*R*)-cyclohex-3-enecarboxylic acid (**2.5.3.3**), a compound also used for the construction of the cyclohexyl fragment in various other FK-506 synthetic programs.[56,57,65,68]

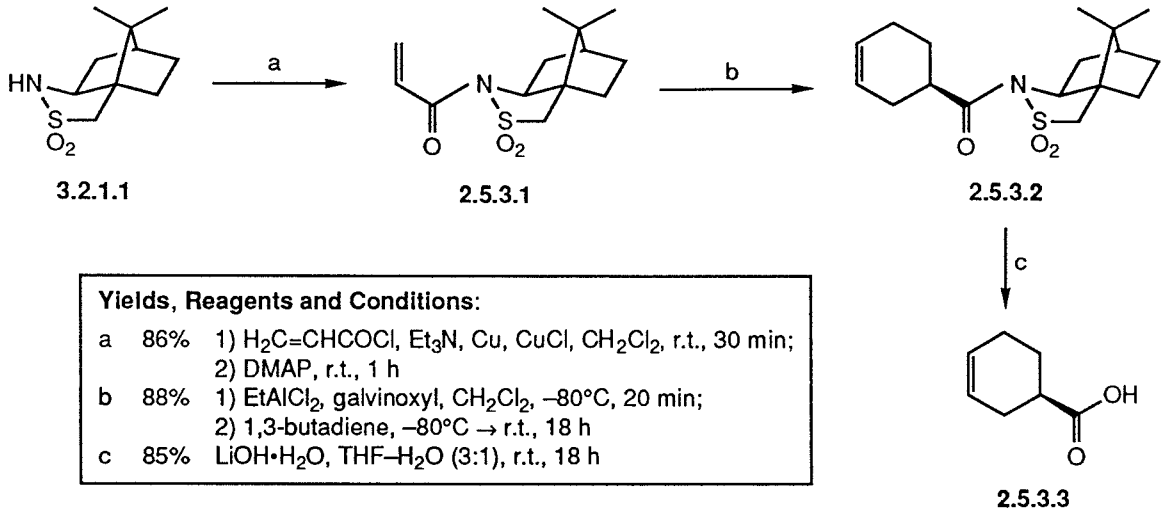


Scheme 3.1.1

3.2 Synthesis of (*R*)-Cyclohex-3-enecarboxylic Acid

As shown in Section **2.5**, (*R*)-cyclohex-3-enecarboxylic acid (**2.5.3.3**) may be prepared by the method of Oppolzer[71] *via* the Lewis acid-catalysed asymmetric Diels-Alder reaction of 1,3-butadiene with *N*-acryloyl camphor sultam **2.5.3.1**. In a previous study at Southampton[72], however, problems were encountered with the reproducibility of this reaction using Oppolzer's original conditions (1,3-butadiene, $EtAlCl_2$, CH_2Cl_2, –78°C): low yields were often observed due to $EtAlCl_2$-initiated radical copolymerisation of **2.5.3.1** with the butadiene. It was subsequently discovered that the problem could be ameliorated simply by running the reaction in the presence of a catalytic amount of the radical inhibitor galvinoxyl.

Thus, **2.5.3.1** was prepared in 86% yield by acylation of camphor sultam **3.2.1.1** with acryloyl chloride in the presence of Et_3N/DMAP and copper powder/CuCl[73] (Scheme **3.2.1**) (**2.5.3.1** may also be prepared in two steps and similarly high yield *via* acylation of the corresponding *N*-TMS derivative[74]). The cycloaddition was then carried out as described above to provide crystalline adduct **2.5.3.2** (88% yield), which was hydrolysed with $LiOH{\bullet}H_2O$ in aq. THF to provide the requisite acid **2.5.3.3** in 85% yield (87% recovery of the chiral auxillary). The e.e. of **2.5.3.3** was estimated to be >95% by comparison of its optical rotation with the literature value.[75]



3.2.1.1 2.5.3.1 2.5.3.2 2.5.3.3

Yields, Reagents and Conditions:

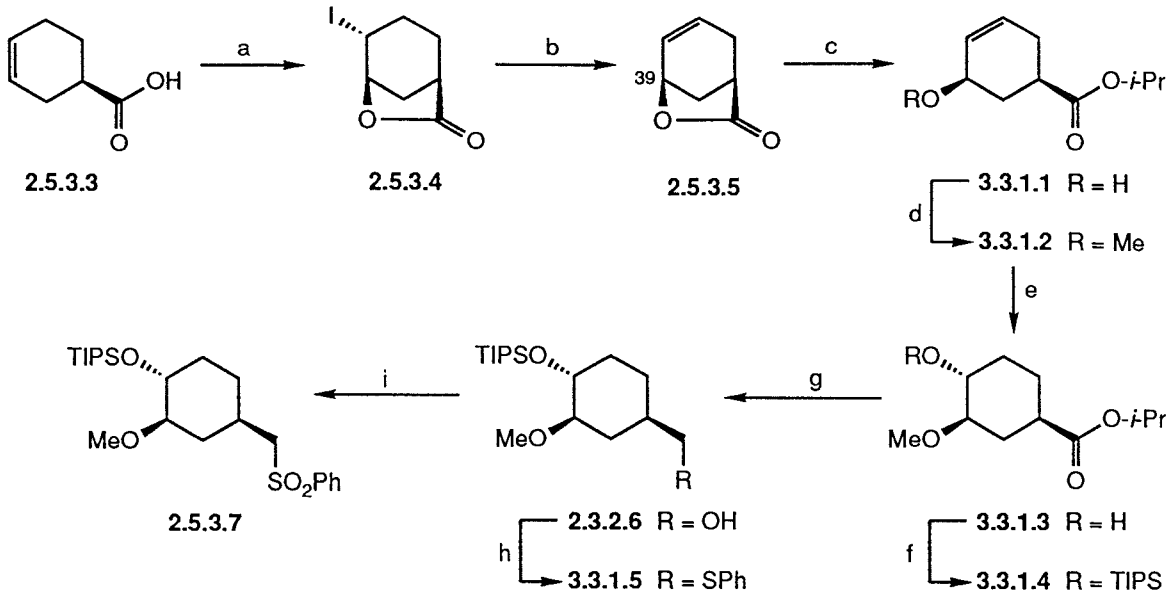
a	86%	1) H_2C=CHCOCl, Et_3N, Cu, CuCl, CH_2Cl_2, r.t., 30 min; 2) DMAP, r.t., 1 h
b	88%	1) $EtAlCl_2$, galvinoxyl, CH_2Cl_2, –80°C, 20 min; 2) 1,3-butadiene, –80°C → r.t., 18 h
c	85%	LiOH•H_2O, THF–H_2O (3:1), r.t., 18 h

Scheme 3.2.1

3.3 Synthesis of Sulfone 2.5.3.7

Sulfone **2.5.3.7** was prepared from acid **2.5.3.3** as shown in Scheme **3.3.1**. Thus, conversion of **2.5.3.3** to unsaturated bicyclic lactone **2.5.3.5**[76] was achieved *via* Bartlett's procedure[77], thereby securing the correct stereochemistry at C39: iodolactonisation of the acid afforded compound **2.5.3.4**[76] in 89% yield, which underwent dehydrohalogenation with DBU in refluxing THF to provide a 90% yield of **2.5.3.5**. Based on previous work at Southampton[78], the lactone was efficiently opened by transesterification with Ti(O-*i*-Pr)$_4$ in refluxing *i*-PrOH[79], providing allylic alcohol **3.3.1.1** in 97% yield. Methylation of **3.3.1.1** with MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine in toluene[78] then afforded allylic ether **3.3.1.2**.

Installation of the vicinal hydroxyl moiety *trans* to the methoxy group *via* hydroboration of 3-methoxycyclohexene derivatives[80] such as **3.3.1.2** is well precedented in previous syntheses of the cyclohexyl fragment of FK-506.[27,31,41,57,58,63,68] We therefore treated **3.3.1.2** with BH_3•THF (–80°C → 0°C) to provide alcohol **3.3.1.3** in 75% yield after oxidative work-up, along with ca. 15% of other isomeric products. The major isomer could be separated by careful flash chromatography and was protected as its TIPS ether **3.3.1.4** in 78% yield. Reduction of the ester in **3.3.1.4** with $LiAlH_4$ then afforded primary alcohol **2.3.2.6** (96% yield), an intermediate previously used in Schreiber's total syntheses of both FK-506[27-31] and rapamycin (Section **2.3**). Conversion of **2.3.2.6** to phenylthio ether **3.3.1.5** was achieved in 95% yield using $(PhS)_2$ and *n*-Bu_3P[81]. Oxidation of **3.3.1.5** with MCPBA then quantitatively afforded the requisite sulfone **2.5.3.7**.

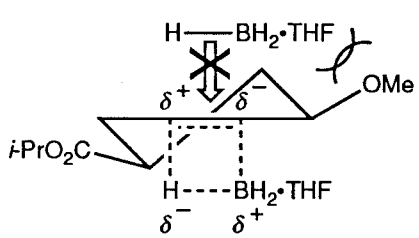


Yields, Reagents and Conditions:

a	89%	$NaHCO_3$, I_2, KI, H_2O, r.t., 18 h
b	90%	DBU, THF, Δ, 18 h
c	97%	$Ti(O\text{-}i\text{-}Pr)_4$, *i*-PrOH, Δ, 18 h
d	76%	MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, toluene, r.t., 48 h
e	75%	1) BH_3•THF, THF, –80°C, 30 min; 2) 0°C, 90 min; 3) aq. NaOH, aq. H_2O_2, 0°C → r.t., 2h
f	78%	TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C → r.t., 18 h
g	96%	$LiAlH_4$, Et_2O, 0°C, 1 h
h	95%	$(PhS)_2$, *n*-Bu_3P, THF, 0°C, 2 h
i	99%	MCPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h

Scheme 3.3.1

The regioselectivity of the hydroboration step can be explained by the inductive effect of the allylic methoxy group in **3.3.1.2**, whereas the *trans*-stereoselectivity presumably arises due to a steric interaction with the methoxy group if the addition were to occur at the opposite face of the double bond (Scheme **3.3.2**).

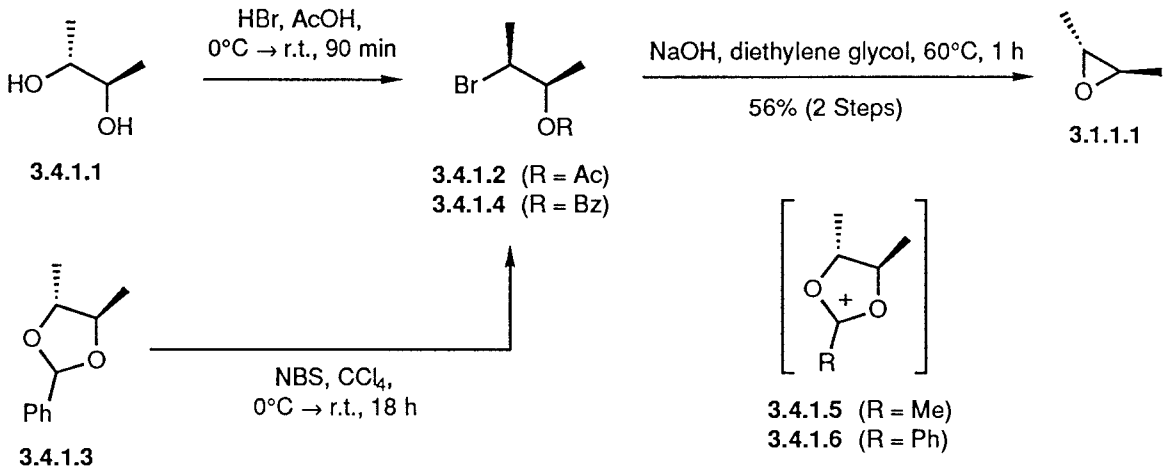


Scheme 3.3.2

3.4 Synthesis of the C33-C42 Fragment

Homochiral epoxide **3.1.1.1**[82] (Scheme **3.4.1**) was prepared in two steps (56% overall yield) from (2*R*,3*R*)-2,3-butanediol (**3.4.1.1**) *via* conversion to bromoacetate **3.4.1.2** using HBr in AcOH[83] followed by saponification with NaOH in warm diethylene glycol.[84] The volatile product was readily distilled from the reaction mixture. Alternatively, **3.1.1.1**

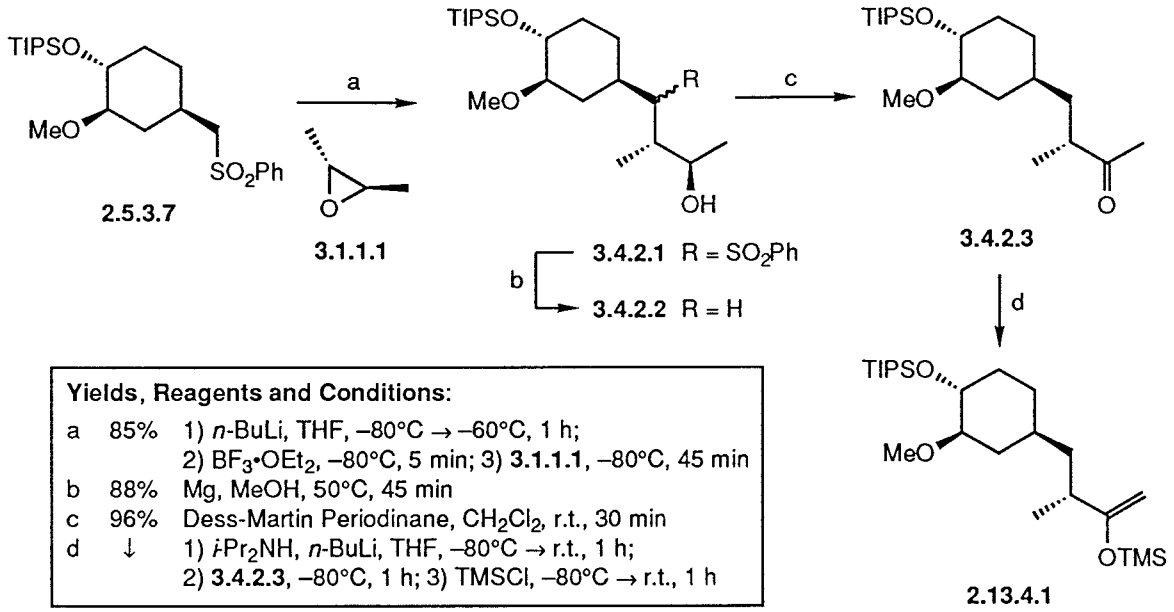
may be prepared in the same yield by treatment of the benzylidene acetal (**3.4.1.3**) of **3.4.1.1** with NBS in CCl_4[84] followed by saponification of the resulting bromobenzoate **3.4.1.4**. Both **3.4.1.1** and **3.4.1.3** may be prepared on a large scale from (–)-tartaric acid.[85]



Scheme 3.4.1

The mechanism of the reaction involves initial formation of a dioxolenyl cation (**3.4.1.5** or **3.4.1.6**) which is captured by S_N2 attack of bromide ion to form **3.4.1.2** or **3.4.1.4**. Saponification and ring closure then restores the inverted stereocentre to its original configuration, producing **3.1.1.1**.

The coupling of sulfone **2.5.3.7** with epoxide **3.1.1.1** and the further transformations leading to C33-C42 fragment **2.13.4.1** are shown in Scheme **3.4.2**. Thus, deprotonation of **2.5.3.7** with *n*-BuLi at low temperature and reaction with **3.1.1.1** in the presence of $BF_3{\cdot}OEt_2$[86] led to an 85% yield of γ-hydroxy sulfone **3.4.2.1** (72:28 mixture of diastereomers). Desulfonylation of **3.4.2.1** with Mg in MeOH at 50°C[87] then provided alcohol **3.4.2.2** (88% yield), which underwent Dess-Martin oxidation[88] to provide ketone **3.4.2.3** in 96% yield. Finally, enolisation of **3.4.2.3** with LDA at –80°C and quenching with TMSCl provided C33-C42 enol silane **2.13.4.1** as a single regioisomer. The crude enol silane was coupled with C26-C32 aldehyde **2.13.4.2** (*vide infra*) without purification.



Yields, Reagents and Conditions:		
a	85%	1) *n*-BuLi, THF, –80°C → –60°C, 1 h; 2) BF_3•OEt_2, –80°C, 5 min; 3) **3.1.1.1**, –80°C, 45 min
b	88%	Mg, MeOH, 50°C, 45 min
c	96%	Dess-Martin Periodinane, CH_2Cl_2, r.t., 30 min
d	↓	1) *i*-Pr_2NH, *n*-BuLi, THF, –80°C → r.t., 1 h; 2) **3.4.2.3**, –80°C, 1 h; 3) TMSCl, –80°C → r.t., 1 h

Scheme 3.4.2

3.5 Conclusion

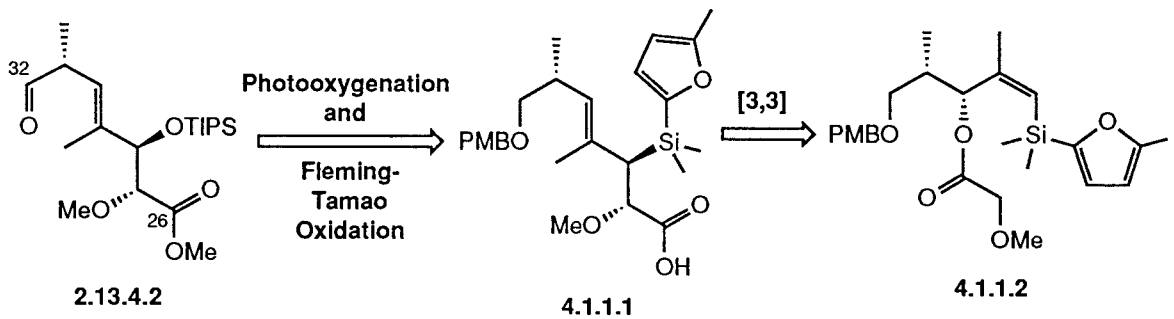
Our prime objective in the synthesis of C33-C42 fragment **2.13.4.1** was to devise a stereocontrolled and reliable route that would provide adequate supplies of material for further coupling with C26-C32 aldehyde **2.13.4.2**. This goal has been achieved in the sixteen-step sequence described herein, which has been used to prepare several grams of **2.13.4.1**. The overall yield of 14.4% (from camphor sultam **3.2.1.1**) represents an average of 89% per step.

Chapter 4

Synthesis of the C26-C32 Fragment

4.1 Introduction

Our strategy for the synthesis of C26-C32 fragment **2.13.4.2** (Scheme **4.1.1**) was based around a highly diastereoselective Ireland-Claisen rearrangement of silyl-substituted (*Z*)-allylic ester **4.1.1.2**. This afforded (*E*)-γ,δ-unsaturated acid **4.1.1.1** as a single diastereomer, thus forming the C29-C30 trisubstituted double bond as well as the C27 and C28 stereocentres (with the correct 1,2-*anti* relationship) in a single, high-yielding step.



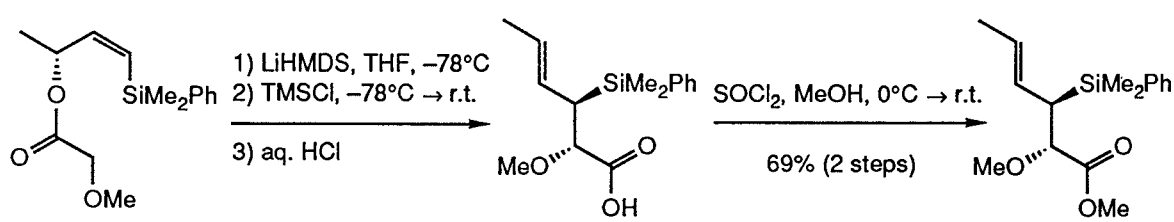
2.13.4.2 **4.1.1.1** **4.1.1.2**

Scheme 4.1.1

The purpose of the dimethyl(5-methyl-2-furyl)silyl moiety was to serve as a masked form of the C28 allylic hydroxyl group, to which it was ultimately converted *via* a two-step sequence of photooxygenation (to afford a silanol), followed by Fleming-Tamao oxidation.

4.2 Background: Ireland-Claisen Rearrangement of Silyl-Substituted (Z)-Allylic Esters

In 1992 Panek reported[89] the highly diastereoselective synthesis of various *anti*-α-alkoxy-β-(phenyldimethylsilyl)-(*E*)-hex-4-enoates *via* the Ireland-Claisen rearrangement[90,91] of silyl-substituted (*Z*)-allylic esters. In the example shown in Scheme **4.2.1**, rearrangement of (*R*)-allylic ester **4.2.1.1** provided product **4.2.1.3** in 69% yield with >40:1 selectivity for the *anti* diastereomer, following hydrolysis of the initially formed silyl ester and methylation of the resulting acid (**4.2.1.2**).

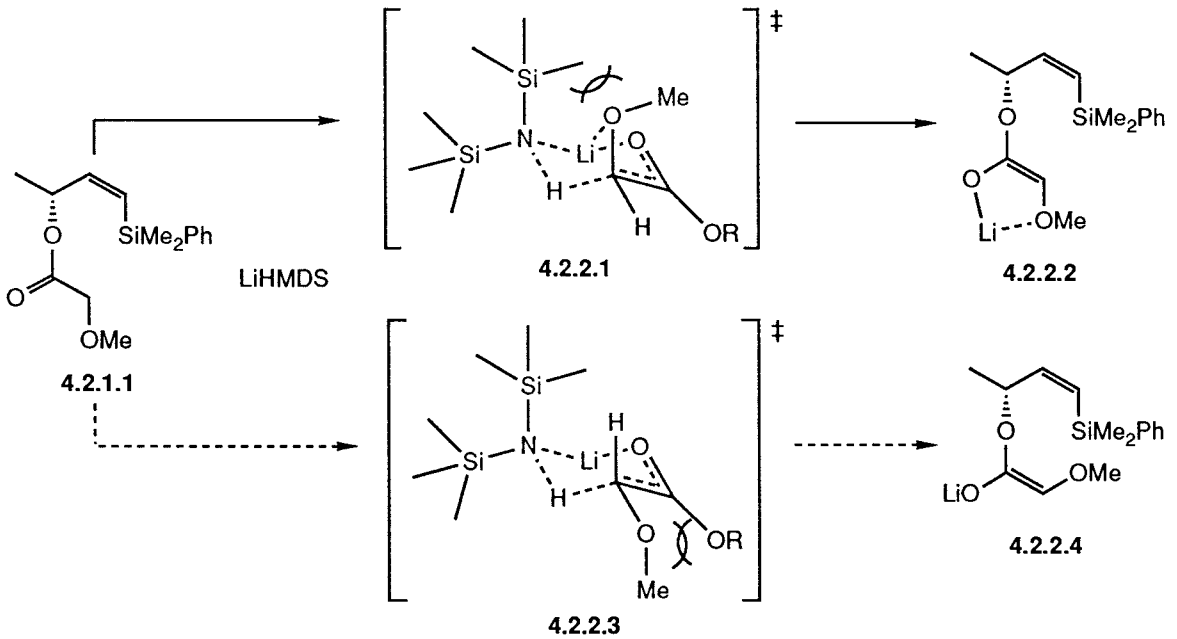


4.2.1.1 **4.2.1.2** **4.2.1.3**

Scheme 4.2.1

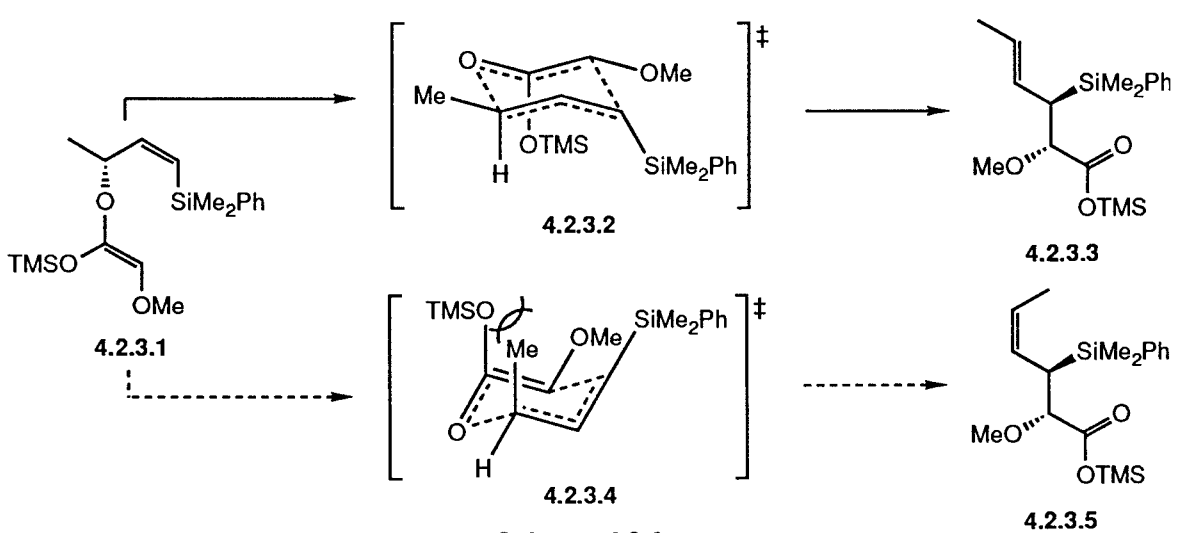
The high diastereoselectivity of the rearrangement results from selective enolisation of the ester *via* chair-like transition state **4.2.2.1** (Scheme **4.2.2**) to preferentially afford the

chelated (*E*)-enolate **4.2.2.2**. The chelating effect of the glycolate oxygen overrides the 1,3-diaxial strain present in **4.2.2.1**, even though this is a more serious interaction than the $A^{1,2}$ strain present in the alternative non-chelated transition state **4.2.2.3** (which leads to the unfavoured (*Z*)-enolate **4.2.2.4**).



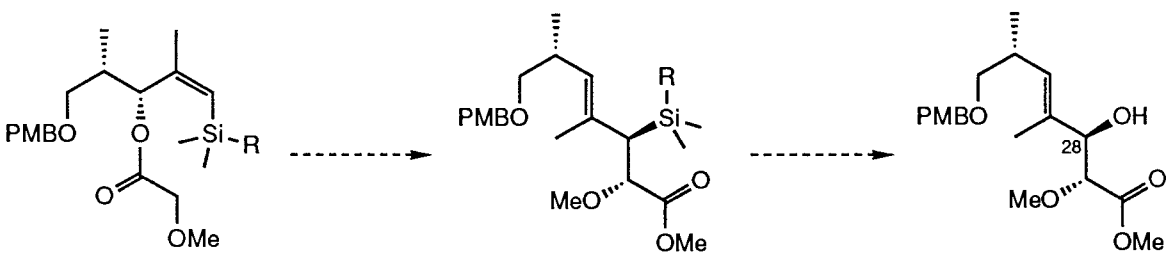
Scheme 4.2.2

Subsequent silylation of (*E*)-enolate **4.2.2.2** leads to the corresponding (*Z*)-silylketene acetal **4.2.3.1** (Scheme **4.2.3**), which rearranges *via* chair-like transition state **4.2.3.2** to afford silyl ester **4.2.3.3**, containing the requisite (*E*)-double bond. The alternative transition state **4.2.3.4**, in which there is a 1,3-diaxial interaction, would lead to the product with a (*Z*)-double bond (**4.2.3.5**): no trace of the methyl ester derived from **4.2.3.5** was observed.



Scheme 4.2.3

We envisaged the use of this reaction to construct the C26-C32 fragment of rapamycin *via* rearrangement of substrate **4.2.4.1** (Scheme **4.2.4**). The allylic silyl group of the rearranged product **4.2.4.2** would subsequently need to be converted to the requisite C28 hydroxyl in **4.2.4.3** *via* Fleming-Tamao oxidation (*vide infra*). Unfortunately, the conditions necessary for the oxidative removal of a phenyldimethylsilyl group are incompatible with the presence of a double bond elsewhere in the molecule, especially when it is allylic. The success of this strategy would therefore require the use of an alternative silyl moiety, which, although situated in an allylic position, could still be efficiently converted to the requisite oxygen function.



4.2.4.1 **4.2.4.2** **4.2.4.3**

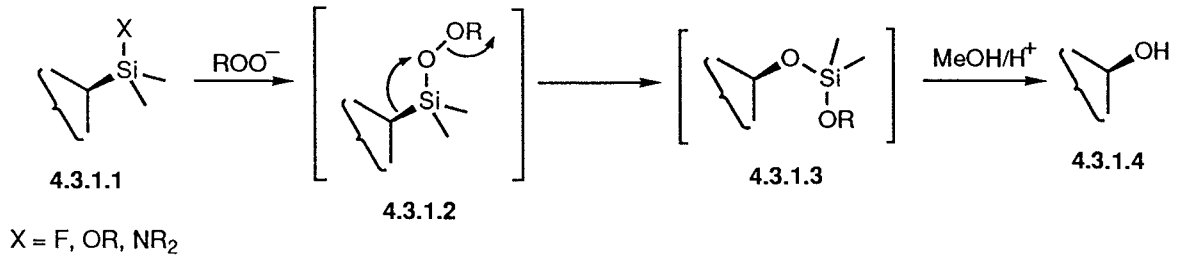
R ≠ Ph

Scheme 4.2.4

4.3 Background: Fleming-Tamao Oxidation of C-Si Bonds

The oxidation of C-Si bonds to C-OH bonds has been studied independently and concurrently by Fleming[92-94] and Tamao[95-97]. The reaction proceeds with complete retention of configuration and only occurs when a heteroatomic group (F, OR, NR_2) is attached to silicon. Fleming has used MCPBA in Et_2O as the oxidant, in the presence of Et_3N, whereas Tamao's procedure uses H_2O_2 in THF–MeOH, in the presence of KF and a bicarbonate salt (sodium or potassium).

Fleming has proposed that the MCPBA-mediated oxidations proceed *via* the mechanism shown in Scheme **4.3.1**;[94] displacement of the heteroatomic group in **4.3.1.1** by the peroxyanion produces peroxysilicon intermediate **4.3.1.2**; a rearrangement then takes place, leading to **4.3.1.3**, in which an alkyl group on silicon has migrated to the first oxygen atom with the departure of the second, possibly *via* a cyclic process where the displaced group becomes attached to the silicon. The final step leading to the free alcohol **4.3.1.4** is promoted by treatment of the crude product with methanolic HCl.



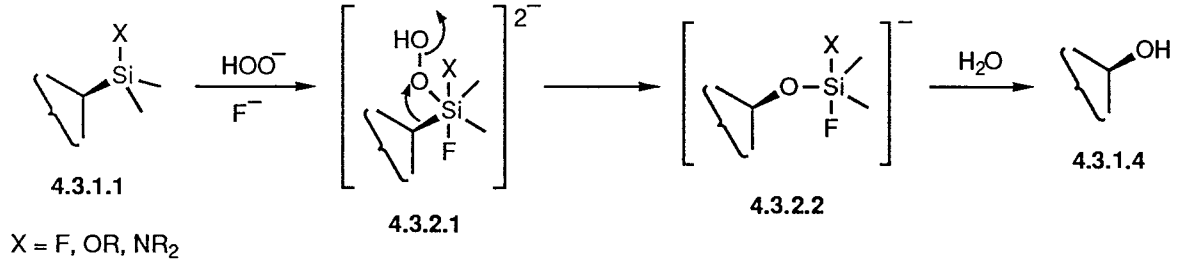
4.3.1.1 4.3.1.2 4.3.1.3 4.3.1.4

X = F, OR, NR_2

Typical Conditions : 1) MCPBA, Et_3N, Et_2O, 0°C → r.t.; 2) aq. HCl, MeOH

Scheme 4.3.1

In order to explain the role of fluoride ion (often a mandatory additive) in the H_2O_2-mediated oxidations, Tamao has proposed a similar mechanism (Scheme **4.3.2**)[97] which proceeds through hexa- and pentacoordinate hydroperoxysilicon intermediates **4.3.2.1** and **4.3.2.2** respectively. In this case the free alcohol **4.3.1.4** is obtained directly *via* cleavage of **4.3.2.2** by the hydroxylic solvent.



4.3.1.1 4.3.2.1 4.3.2.2 4.3.1.4

X = F, OR, NR_2

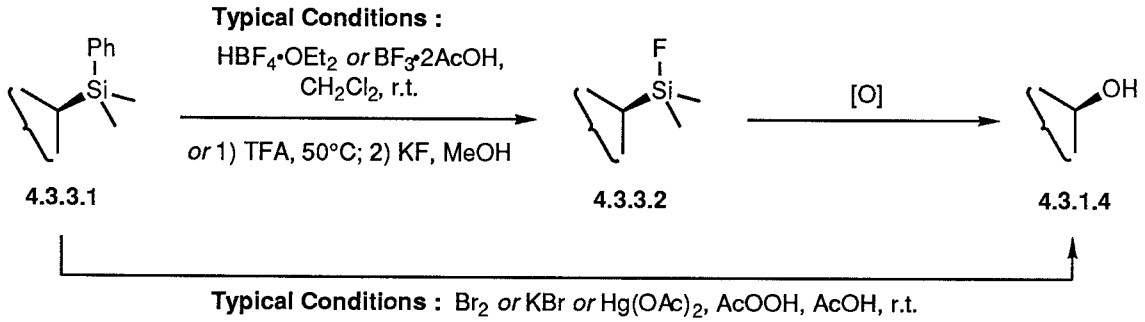
Typical Conditions : aq. H_2O_2, $NaHCO_3$ *or* $KHCO_3$, KF, THF–MeOH, r.t. *or* Δ

Scheme 4.3.2

Tamao has shown that heteroatom-substituted silyl groups may be introduced into organic structures by a variety of methods,[97-100] and they are generally oxidised immediately following their introduction. When it is necessary to carry the silyl group through a multistep sequence prior to oxidation, however, the relative hydrolytic instability of these functionalised silanes compared to their all-carbon substituted counterparts could potentially be problematic. A more stable alternative is the phenyldimethylsilyl group, which may be introduced as the corresponding cuprate reagent,[101-105] and has also been shown by both Fleming[92-94] and Tamao[96] to be a synthetic equivalent of the hydroxyl group.

The conversion of a phenyldimethylsilyl group to a hydroxyl group is a two-step procedure (Scheme **4.3.3**), the first step being functionalisation of the silane **4.3.3.1** *via* electrophilic substitution of the phenyl ring. Fleming advocates the use of HBF_4•OEt_2 or BF_3•2AcOH for this purpose[92,94], whereas Tamao has employed TFA followed by KF/MeOH.[96] The resulting fluorosilanes **4.3.3.2** may then be oxidised as above. Alternatively, Fleming has shown that a phenyldimethylsilyl group may be directly transformed to a hydroxyl in one pot

by employing electrophiles other than H^+, in combination with AcOOH in AcOH. Bromine (either directly or from KBr) and Hg^{2+} have been used in this way.[93]



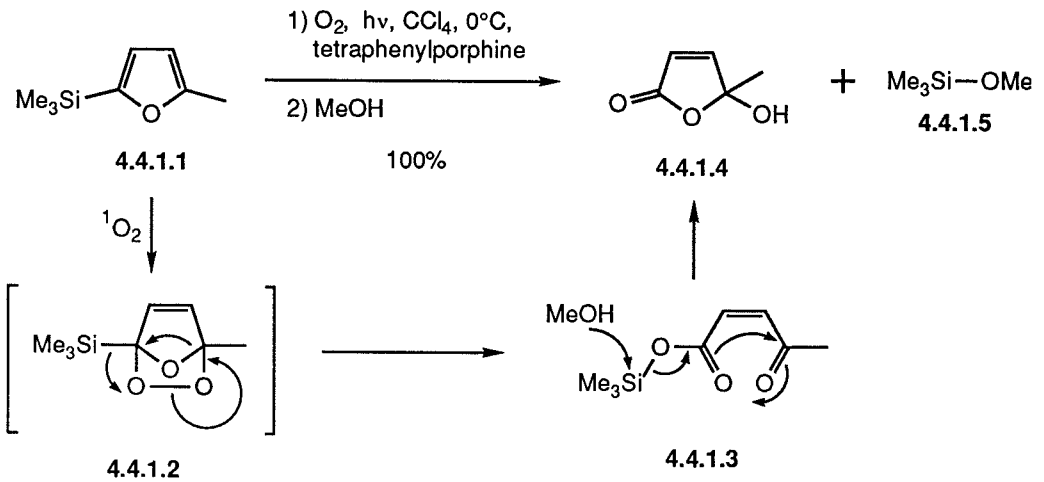
Scheme 4.3.3

These conditions for the functionalisation of phenyldimethylsilyl groups, however, are incompatible with a double bond situated elsewhere in the substrate (except in cases where it is monosubstituted[94] or conjugated to a carbonyl group[106-108]) since electrophilic desilylation of the phenyl ring cannot effectively compete with electrophilic attack at the alkene. This is especially true for double bonds which are allylic to the silicon, due to the facile desilylation of such systems *via* an S_E2' mechanism.[109] Indeed, Tamao has shown that an allyldimethylsilyl group can be used as an alternative to a phenyldimethylsilyl group, and is readily converted to a hydroxyl group *via* the two-step sequence described for phenyldimethylsilanes.[96,110]

For our purposes, therefore, an alternative silyl group was required which would survive a multistep reaction sequence and which could then be functionalised under non-electrophilic conditions. Our interest in the use of a furyldimethylsilyl group was stimulated by Stork's use of this moiety in a precursor to a Fleming-Tamao oxidation in his synthesis of reserpine.[111] The silicon was activated *via* displacement of the furan ring by fluoride ion (TBAF) prior to oxidation. An even milder method by which the silicon could be functionalised, however, was suggested to us by Adam's work on the photooxygenation of 5-methyl-2-(trimethylsilyl)furan.

4.4 Background: Photooxygenation of 5-Methyl-2-(trimethylsilyl)furan

Adam has shown that photosensitised oxygenation of 5-methyl-2-(trimethylsilyl)furan (**4.4.1.1**) yields silyl ester **4.4.1.3** *via* rearrangement of the initially formed endoperoxide **4.4.1.2** (Scheme **4.4.1**).[112] Upon methanolysis, **4.4.1.2** was quantitatively converted to γ-hydroxy-γ-lactone **4.4.1.4**, and presumably methoxytrimethylsilane (**4.4.1.5**) as by-product. Overall, therefore, a Si-C bond (in **4.4.1.1**) has been converted to a Si-O bond (in **4.4.1.5**) under extremely mild and essentially neutral conditions.

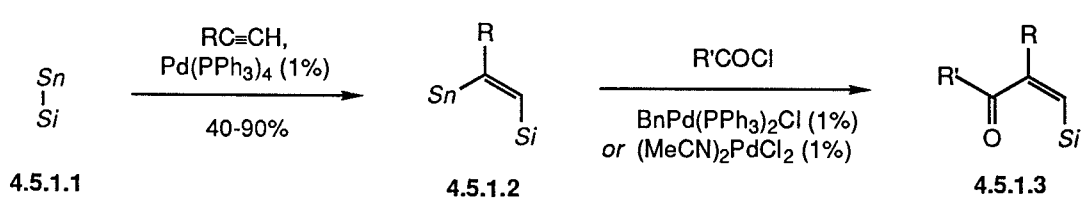


Scheme 4.4.1

We envisaged that a dimethyl(5-methyl-2-furyl)silyl group could thus be used as a masked hydroxyl in the same way as a phenyldimethylsilyl group. Unlike a phenyldimethylsilyl group, however, the initial attachment of a heteroatomic group to the silicon, *via* photooxygenation of the furan ring, should be possible even when the silyl group is allylic. We therefore set about the construction of a C26-C32 fragment (**2.13.4.2**) of rapamycin based upon this methodology.

4.5 Strategy for the Synthesis of Rearrangement-Precursor 4.1.1.2

Our strategy for the synthesis of silyl-substituted (Z)-allylic ester **4.1.1.2** was based on work carried out independently by Mitchell[113,114] and Chenard[115,116], who have demonstrated that silylstannanes **4.5.1.1** (Scheme **4.5.1**) add regio- and stereoselectively to a wide variety of terminal alkynes under Pd(0)-catalysis to yield (Z)-silylstannylalkenes **4.5.1.2**, wherein the tin is attached to the internal olefin carbon. The silylstannylalkenes obtained in this way could then be further elaborated *via* Stille coupling[117,118] with various acid chlorides to afford (Z)-β-silyl-α,β-unsaturated ketones **4.5.1.3**. Mitchell[114] used $BnPd(PPh_3)_2Cl$ as the catalyst for the coupling reactions, whereas Chenard[119] employed $(MeCN)_2PdCl_2$.

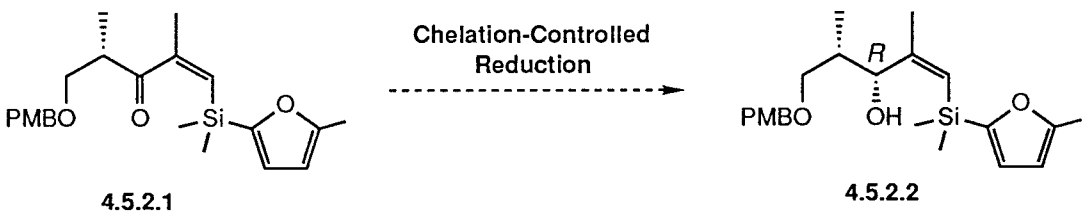


Sn = Me_3Sn, *n*-Bu_3Sn, Ph_3Sn

Si = TMS, TES, TBS, $PhMe_2Si$, *n*-$BuMe_2Si$

Scheme 4.5.1

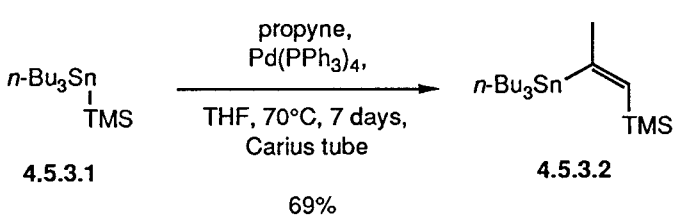
This sequence of reactions seemed ideal for our purposes, since if enone **4.5.2.1** (Scheme **4.5.2**) could be prepared in this way, then a diatereoselective, chelation-controlled reduction (*vide infra*) would provide allylic alcohol **4.5.2.2**, with the requisite (*R*)-stereochemistry at the carbinol. A simple esterification would then afford our target substrate (**4.1.1.2**) for the Ireland-Claisen rearrangement.



4.5.2.1 **4.5.2.2**

Scheme 4.5.2

To ascertain the applicability of this methodology to our system, we carried out an exploratory study starting with simple (trimethylsilyl)stannane **4.5.3.1** (Scheme **4.5.3**), readily prepared in 71% yield as described by Chenard[116] *via* deprotonation of *n*-Bu_3SnH with LDA (THF, 0°C, 1 h) and quenching with TMSCl (0°C → r.t., 1 h). Although neither Mitchell nor Chenard have reported adding silylstannanes to propyne, we found that (*Z*)-silylstannylalkene **4.5.3.2** could be obtained in 69% yield by heating the alkyne with **4.5.3.1** and 2% $Pd(PPh_3)_4$ (with a small amount of THF in order to dissolve the catalyst) at 70°C for seven days in a Carius tube. The product was readily purified by distillation. The expected (Z)-stereochemistry of **4.5.3.2** was confirmed by the ^1H NMR coupling constants of the lone vinyl proton with the tin. The values of 171 and 179 Hz are indicative of a *trans*-relationship.[120]

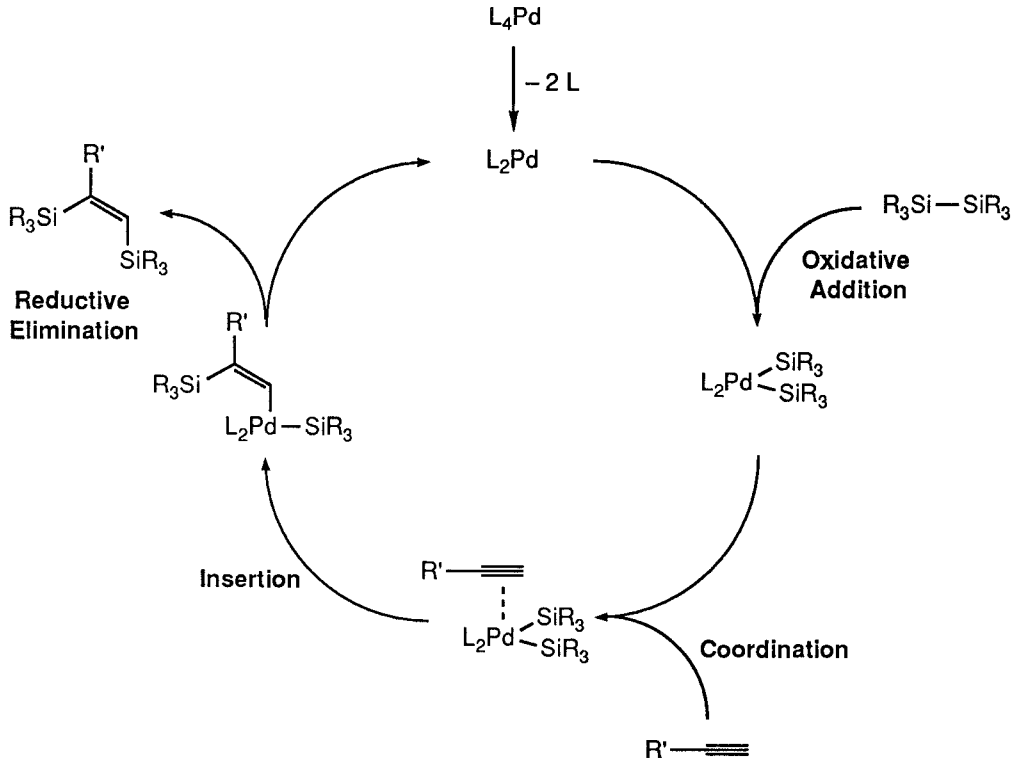


4.5.3.1 **4.5.3.2**

69%

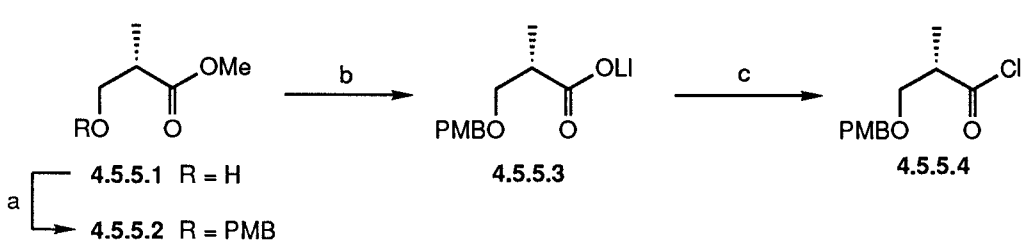
Scheme 4.5.3

The factors controlling the observed regiochemistry in this reaction are unclear. The mechanism, however, is probably similar to that proposed by Watanabe[121] for the analogous reactions of disilanes with terminal acetylenes (Scheme **4.5.4**), involving oxidative addition of the Si–Si bond to the Pd(0) catalyst, formation of an acetylene-coordinated complex, insertion of the acetylene into one of the Si–Pd bonds, and reductive elimination of the product.



Scheme 4.5.4

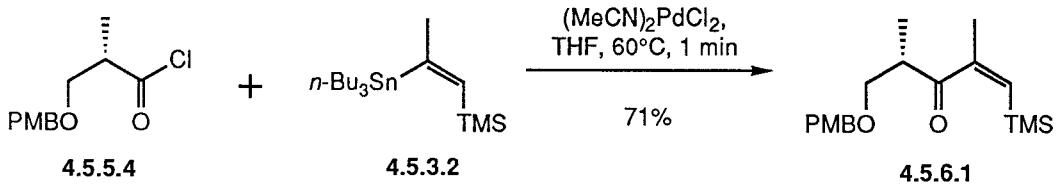
The requisite coupling partner, acid chloride **4.5.5.4** (Scheme **4.5.5**), was prepared in three steps from methyl (*S*)-3-hydroxy-2-methylpropionate (**4.5.5.1**). Thus, treatment of **4.5.5.1** with PMB 2,2,2-trichloroacetimidate in the presence of 0.3% TfOH[122] yielded PMB ether **4.5.5.2** in 67% yield. Hydrolysis of the ester with $LiOH{\cdot}H_2O$ then afforded carboxylate salt **4.5.5.3** (isolated by concentration and rigorous drying of the aq. solution), which was converted to **4.5.5.4** by treatment with $(COCl)_2$. Attempted distillation of **4.5.5.4** after filtration (to remove precipitated LiCl) and concentration led to complete decomposition, probably due to the presence of HCl in the crude product. The acid chloride was therefore used in the subsequent coupling reaction without further purification.



Yields, Reagents and Conditions:		
a	67%	PMBOC(=NH)CCl_3, TfOH, Et_2O, –80°C → r.t., 1 h
b	↓	$LiOH{\cdot}H_2O$, THF–H_2O, r.t., 12 h
c	↓	$(COCl)_2$, CH_2Cl_2, 0°C → r.t., 12 h

Scheme 4.5.5

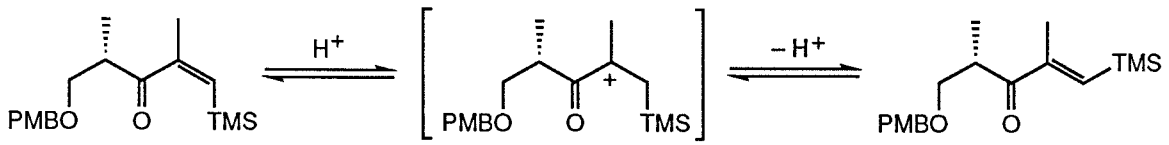
The coupling of (Z)-silylstannylalkene **4.5.3.2** with acid chloride **4.5.5.4** proceeded readily using $(MeCN)_2PdCl_2$ (5%) as the catalyst (THF, 60°C) (Scheme **4.5.6**). A 71% yield of the requisite (Z)-enone **4.5.6.1** was thus obtained after flash chromatography on Florisil.



4.5.5.4 **4.5.3.2** **4.5.6.1**

Scheme 4.5.6

A minor by-product (ca. 10%) was (*E*)-enone **4.5.7.2** (Scheme **4.5.7**), which presumably arises due to acid-catalysed isomerisation of the initially formed (Z)-enone **4.5.6.1** *via* carbocation **4.5.7.1**, in which the positive charge is stabilised by the β-silicon atom but destabilised by the adjacent carbonyl. The presence of acid (HCl) in the reaction mixture is due to the use of unpurified acid chloride in the coupling reaction.



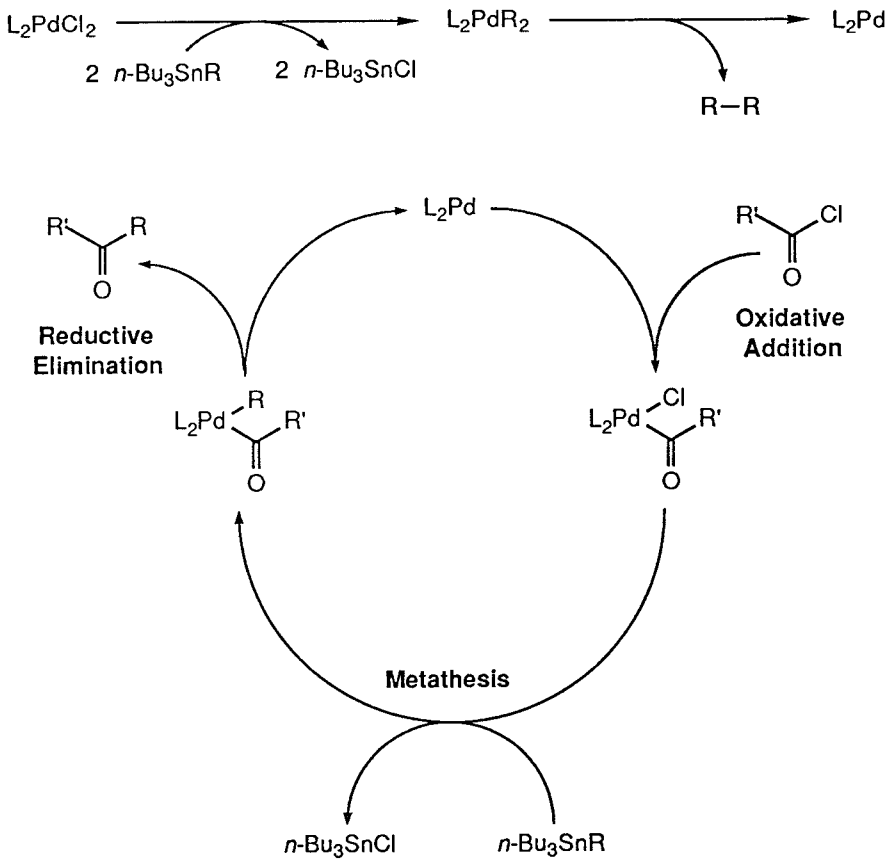
4.5.6.1 **4.5.7.1** **4.5.7.2**

Scheme 4.5.7

For reproducible results, it was necessary to use the minimum amount of THF needed to form a homogeneous solution. Under these conditions, brief heating of the reaction mixture to 60°C resulted in a rapid reaction, as indicated by an almost instantaneous change in colour of the solution from pale yellow to black (due to precipitation of Pd metal). Under more dilute conditions extended reaction times were necessary, resulting in lower yields of (Z)-enone **4.5.6.1** and increased amounts of (*E*)-enone **4.5.7.2**.

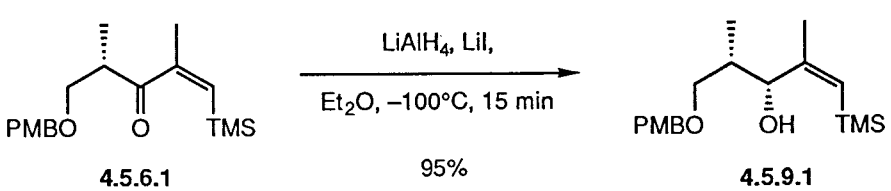
Assignment of **4.5.6.1** as the (Z)-isomer and **4.5.7.2** as the (*E*)-isomer was based upon the significantly lower ^1H NMR chemical shift (270 MHz, C_6D_6) of the vinyl proton in **4.5.6.1** (δ = 5.85) compared to **4.5.7.2** (δ = 6.68).[123]

The currently accepted mechanism[117,118] of the Stille coupling is shown in Scheme **4.5.8**. The active Pd(0) catalyst is generated from the initial Pd(II) species by a sequence of double metathesis and reductive elimination. Oxidative addition of the acid chloride then generates a Pd(II) complex, which undergoes metathesis with the tin compound and reductively eliminates the product ketone.



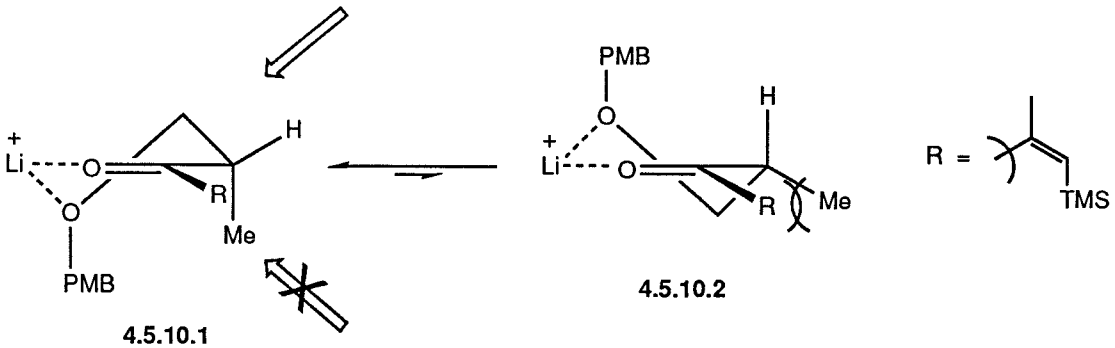
Scheme 4.5.8

The final step of this model study was the generation of the requisite (*R*)-carbinol *via* chelation-controlled, diastereoselective reduction of enone **4.5.6.1**. To our satisfaction, treatment of a mixture of **4.5.6.1** and LiI with $LiAlH_4$ (Et_2O, –100°C) according to Suzuki's method[124] resulted in rapid reduction, providing allylic alcohol **4.5.9.1** in 95% yield as a single diastereomer.



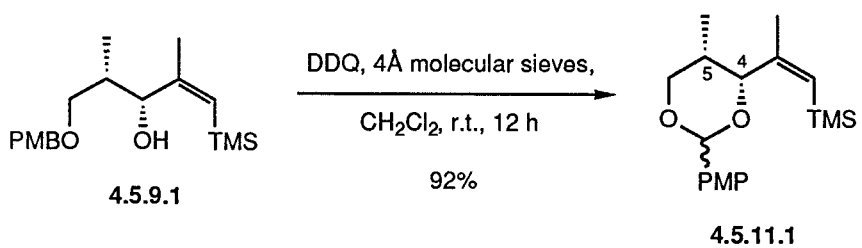
Scheme 4.5.9

The high diastereoselectivity of the reduction results from selective hydride attack at the less hindered face of six-membered chelate conformer **4.5.10.1** (Scheme **4.5.10**). Conformer **4.5.10.1** would be expected to be strongly favoured over conformer **4.5.10.2** due to the serious $A^{1,2}$ interaction in the latter between the pseudoequatorial methyl group and the sp^2-hybridised centre.



Scheme 4.5.10

The expected *syn*-relationship between the stereogenic centres was confirmed by conversion of **4.5.9.1** to benzylidene acetal **4.5.11.1** (Scheme **4.5.11**) *via* treatment with DDQ in the presence of powdered 4Å molecular sieves.[125] The 1,3-dioxane was obtained in 92% yield as an 80:20 mixture of acetal anomers, and showed a ^{1}H NMR coupling constant (360 MHz, C_6D_6) of 2.5 Hz between the C4 and C5 hydrogens, indicating a *syn*-relationship.



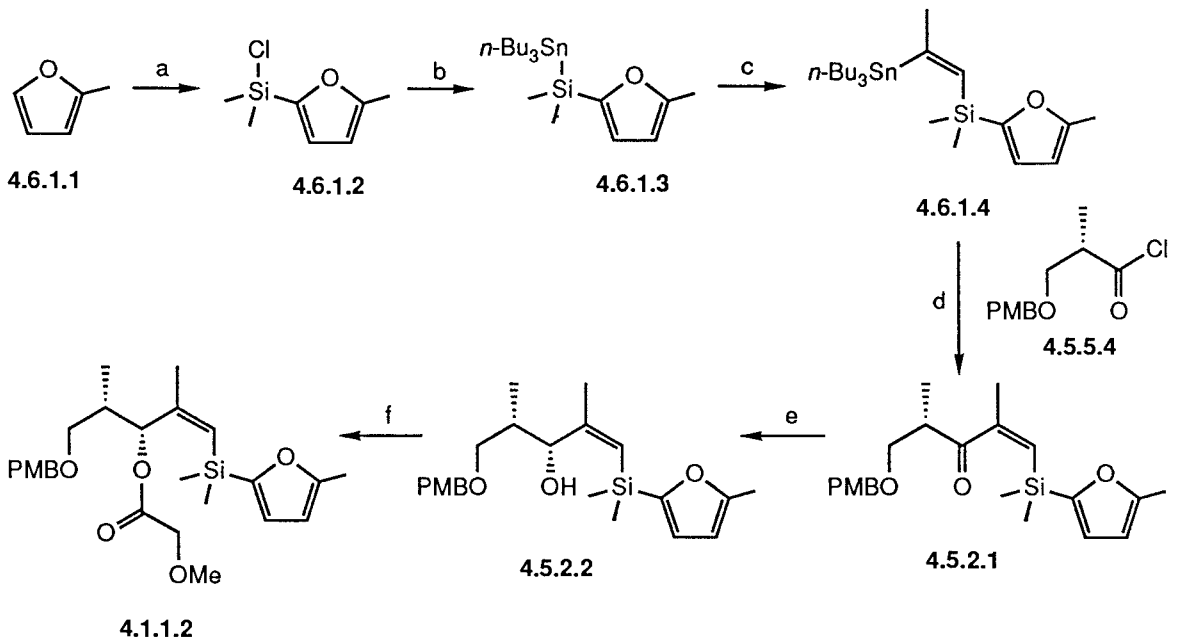
Scheme 4.5.11

4.6 Synthesis of Rearrangement Precursor 4.1.1.2

Having proven the suitability of the described strategy for the stereoselective synthesis of TMS-substituted (*Z*)-allylic alcohol **4.5.9.1**, we next embarked upon the preparation of rearrangement precursor **4.1.1.2** bearing the requisite dimethyl(5-methyl-2-furyl)silyl group. The synthesis began with 2-methylfuran (**4.6.1.1**) (Scheme **4.6.1**), which was converted to chlorosilane **4.6.1.2**[126] in 63% yield *via* deprotonation with *t*-BuLi at –80°C and quenching with a large excess (10 eq.) of Cl_2SiMe_2. Reaction of **4.6.1.2** with *n*-Bu_3SnH/LDA then gave silylstannane **4.6.1.3** in 78% yield after distillation. (*Z*)-Silylstannylalkene **4.6.1.4** was prepared in 97% yield by silylstannylation of propyne with **4.6.1.3** and $Pd(PPh_3)_4$ (2%) under identical conditions used to prepare simple (trimethylsilyl)stannylalkene **4.5.3.2**. Although not amenable to distillation, **4.6.1.4** was readily separated from minor impurities by flash chromatography.

The coupling of **4.6.1.4** with crude acid chloride **4.5.5.4** using $(MeCN)_2PdCl_2$ (5%) then provided a 48% yield of (*Z*)-enone **4.5.2.1**. As before, this reaction was best carried out in the minimum amount of THF necessary to form a homogeneous solution. Subsequent

reduction of **4.5.2.1** with $LiAlH_4$/LiI afforded allylic alcohol **4.5.2.2** in 83% yield, again as a single diastereomer. Finally, conversion of **4.5.2.2** to rearrangement precursor **4.1.1.2** was effected *via* esterification with methoxyacetic acid in the presence of DCC and 5% DMAP, producing the required product in 94% yield.

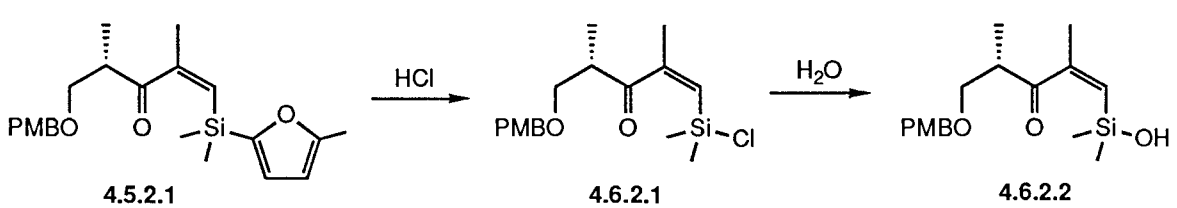


Yields, Reagents and Conditions:

a	63%	1) *t*-BuLi, THF, –80°C, 30 min; 2) 0°C, 1 h; 3) Cl_2SiMe_2, –80°C → r.t., 18 h
b	78%	1) *i*-Pr_2NH, *n*-BuLi, THF, –80°C → r.t., 1 h; 2) *n*-Bu_3SnH, 0°C, 1 h; 3) **4.6.1.2**, 0°C → r.t., 12 h
c	97%	propyne, $Pd(PPh_3)_4$, THF, 70°C, 7 days, Carius tube
d	48%	**4.5.5.4**, $(MeCN)_2PdCl_2$, THF, 60°C, 5 min
e	83%	$LiAlH_4$, LiI, Et_2O, –100°C, 1 h
f	94%	$MeOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, r.t., 12 h

Scheme 4.6.1

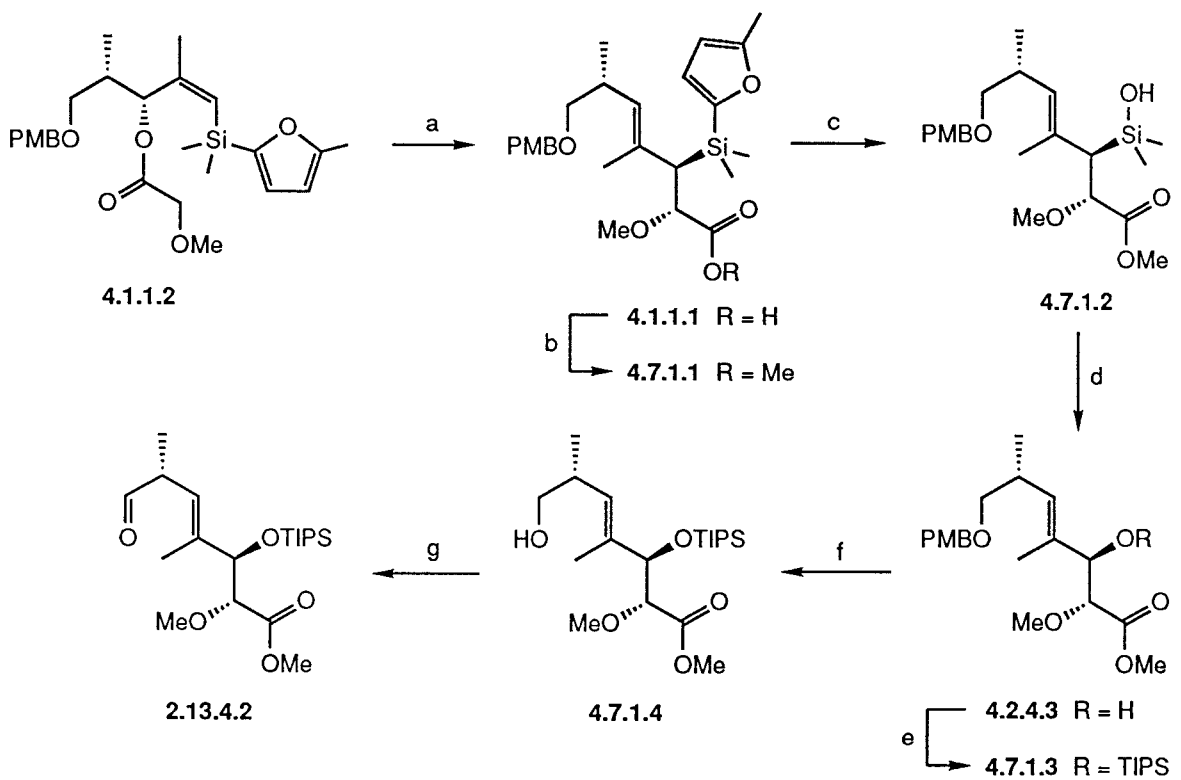
The low yield of the Stille coupling in this case was due to formation of significant amounts (up to 30%) of silanol **4.6.2.2** (Scheme **4.6.2**). This probably arises *via* protodesilylation of the furan ring in **4.5.2.1** to form chlorosilane **4.6.2.1**, which hydrolyses upon aq. work-up to produce the observed by-product. Protodesilylation of 2-(trimethylsilyl)furans is known[127] to be a facile process, and in this case is evidently faster than protonation of the double bond, since no (*E*)-enone was observed.



Scheme 4.6.2

4.7 Synthesis of the C26-C32 Fragment

With silyl-substituted (*Z*)-allylic ester **4.1.1.2** in hand, we next investigated its Ireland-Claisen rearrangement. As it turned out, this proceeded without incident, cleanly affording acid **4.1.1.1** as a single diastereomer (Scheme **4.7.1**). Thus, enolisation of **4.1.1.2** with LDA at –80°C, followed by silylation with TMSCl and gradual warming to r.t. yielded the corresponding TMS ester. This was briefly treated with 1 M HCl to effect hydrolysis to the acid, which was methylated (without chromatographic purification) under basic conditions using 1,1,3,3-tetramethylguanidine/MeI[128] to provide methyl ester **4.7.1.1** in 88% yield for the two steps.



Yields, Reagents and Conditions:		
a	↓	1) *i*-Pr_2NH, *n*-BuLi, THF, –80°C → r.t., 1 h; 2) **4.1.1.2**, –80°C, 1 h; 3) TMSCl, –80°C → r.t., 18 h; 4) aq. HCl, r.t., 5 min
b	88%	1) $(Me_2N)_2C{=}NH$, benzene, r.t., 90 min; 2) MeI, r.t., 12 h
c	98%	1) tetraphenylporphine, O_2, hv, CH_2Cl_2, 0°C, 2 h; 2) H_2O, r.t., 5 min
d	65%	aq. H_2O_2, $KHCO_3$, KF, THF–MeOH (1:1), 0°C → r.t., 24 h
e	91%	TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 2 h
f	98%	DDQ, CH_2Cl_2–H_2O (19:1), r.t., 2 h
g	↓	Dess-Martin Periodinane, CH_2Cl_2, r.t., 30 min

Scheme 4.7.1

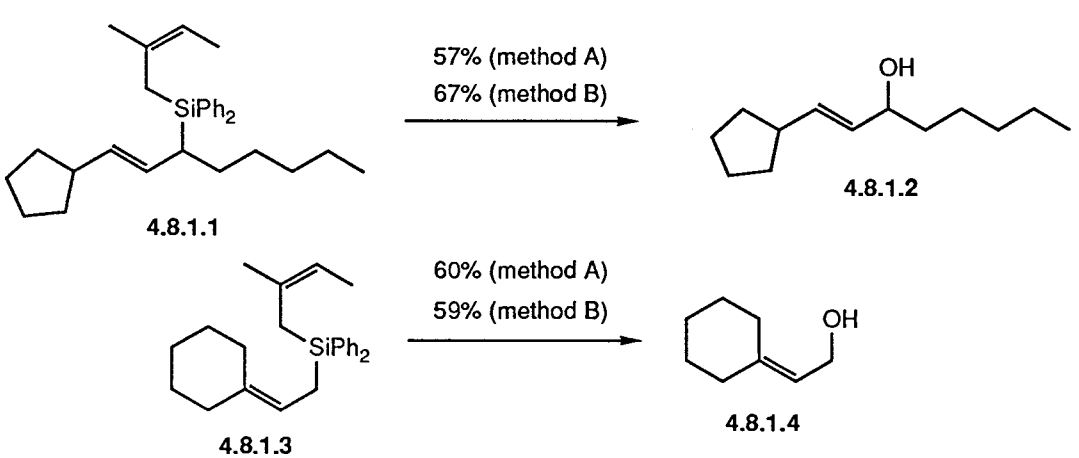
The photooxygenation step also proceeded smoothly, affording silanol **4.7.1.2** in 98% yield after aq. work-up. The reaction was carried out in CH_2Cl_2 using tetraphenylporphine as the sensitising dye. A single 150 W light bulb was sufficient for small-scale reactions. On

a larger scale, however, a number of light bulbs evenly spaced around the reaction flask were necessary to produce an acceptable rate of conversion. Oxidation of **4.7.1.2** using Tamao's standard conditions then produced a 65% yield of alcohol **4.2.4.3**. The remaining mass-balance of the reaction consisted of highly polar (possibly polymeric) material which was unidentifiable by NMR.

Protection of alcohol **4.2.4.3** using TIPSOTf/2,6-lutidine afforded silyl ether **4.7.1.3** in 91% yield. The PMB protecting group was then removed using DDQ in CH_2Cl_2–H_2O[129] to afford primary alcohol **4.7.1.4** in 98% yield. Finally, oxidation of **4.7.1.4** using Dess-Martin periodinane[88] cleanly yielded C26-C32 aldehyde **2.13.4.2**. The crude aldehyde was coupled with C33-C42 enol silane **2.13.4.1** (*vide infra*) without purification.

4.8 Recent Fleming-Tamao Oxidations of Unfunctionalised Silanes in the Presence of Double Bonds

Since the completion of a model study[130] relating to the work described in this chapter, two other reports have appeared describing the use of all-carbon substituted silyl groups which may be functionalised under *electrophilic* conditions, even in the presence of an allylic double bond. Fleming has shown that the 2-methylbut-2-enyl(diphenyl)silyl group, like the phenyldimethylsilyl group, may be introduced into organic structures by way of the corresponding cuprate reagent.[131] The highly substituted allylsilane moiety can then be removed by protodesilylation *via* treatment with BF_3•2AcOH or methanolic HCl. Oxidation of the resulting functionalised silanes using Tamao's conditions then leads to the corresponding alcohols. Allylic silanes **4.8.1.1** and **4.8.1.3** (Scheme **4.8.1**) were thus converted to the corresponding allylic alcohols **4.8.1.2** and **4.8.1.4** respectively using this method (methanolic HCl as the first step). Alternatively, the same conversion could be effected in one pot under mildly basic conditions using $KBr/H_2O_2/KF/NaHCO_3$.

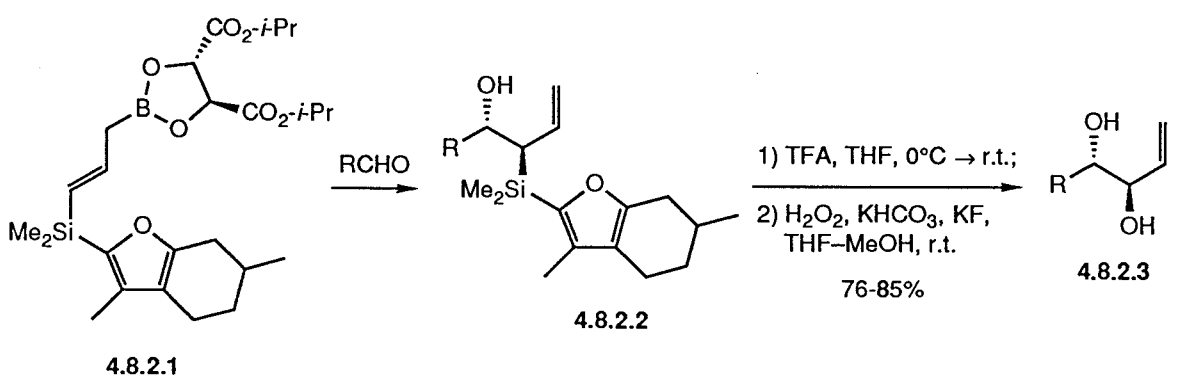


method A: 1) HCl, MeOH, r.t.; 2) H_2O_2, $NaHCO_3$, KF, THF–MeOH, Δ
method B: KBr, H_2O_2, $NaHCO_3$, KF, THF–MeOH, Δ

Scheme 4.8.1

The success of this strategy presumably resides in the fact that the retained allylic double bond in each of the substrates is only monosubstituted at the β-silyl position, and is hence less susceptible to electrophilic attack than the β-*di*substituted allylic double bond of the 2-methylbut-2-enyl(diphenyl)silyl group. The use of this hydroxyl equivalent in our system would have therefore probably met with failure, since *both* allylic double bonds present in the subtrate would be disubstituted at the β-silyl position, resulting in competitive desilylation in both directions.

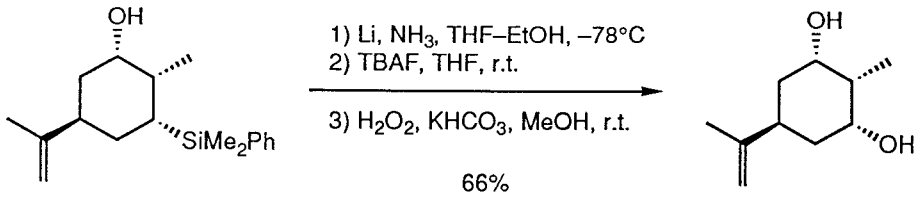
The second recently reported silyl moiety is Roush's (menthofuryl)dimethylsilyl group,[132] which may be removed under electrophilic conditions in the presence of a monosubstituted allylic double bond. The group is introduced by reaction of aldehydes with DIPT-(*E*)-γ-silyl-allylboronate reagent **4.8.2.1** (Scheme **4.8.2**), leading to a variety of 1,2-*anti*-hydroxysilanes **4.8.2.2** (a simple 5-methylfuryl substituent was not used because metallation at C3 of the furan nucleus and subsequent ring-opening occurred under the conditions used to prepare the requisite allylboronate). Protodesilylation of the menthofuryl group with TFA followed by oxidation under the standard conditions then provided diols **4.8.2.3** in good yield. Again, however, it is questionable whether this group could be removed using the reported conditions in the presence of a β-disubstituted double bond allylic to the silicon.



4.8.2.1 **4.8.2.2** **4.8.2.3**

Scheme 4.8.2

Finally, a new method of functionalising a phenyldimethylsilyl group under *non*-electrophilic conditions has been reported by Taber.[133] The two-step procedure involves Birch reduction of the phenyl ring to a 1,4-cyclohexadiene, which is displaced with fluoride ion to yield the corresponding fluorosilane. Oxidation of the fluorosilane under the standard conditions then yields the corresponding alcohol. This sequence was used to convert hydroxylsilane **4.8.3.1** (Scheme **4.8.3**), in which there is an isolated disubstituted double bond, into diol **4.8.3.2** in 66% overall yield.



4.8.3.1 4.8.3.2

Scheme 4.8.3

4.9 Conclusion

The work described in this chapter has resulted in a highly stereocontrolled synthesis of the C26-C32 fragment (**2.13.4.2**) of rapamycin, in a form suitable for coupling with C33-C42 enol silane **2.13.4.1**. The Ireland-Claisen rearrangement strategy proved to be an efficient method for simultaneously forming the C29-C30 (*E*)-trisubstituted double bond and the C27 and C28 stereogenic centres. A novel use of furan photooxygenation has led to an extremely mild and efficient method for the activation of an unfunctionalised allylic silane towards Fleming-Tamao oxidation. To the best of our knowledge, the conversion **4.7.1.1** → **4.2.4.3** (Scheme **4.7.1**) is the only reported example of the Fleming-Tamao oxidation of an all-carbon substituted allylic silane in which the allylic double bond is disubstituted at the β-silyl position.

Central to the success of this strategy were the Pd(0)-catalysed metallometallation and Stille coupling reactions used to introduce the dimethyl(5-methyl-2-furyl)silyl group. Although the lability of the furan ring towards protodesilylation led to a low yield in the Stille coupling, a simple modification of the reaction conditions (by carrying out the coupling in the presence of a tertiary amine base, for example) would be expected to alleviate the problem.

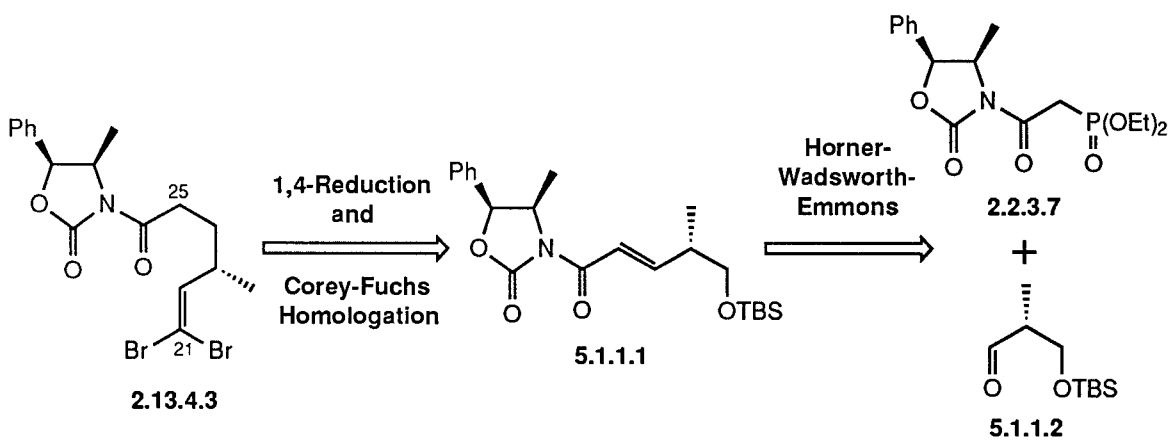
Chapter 5

Synthesis of the C21-C25 Fragment

5.1 Introduction

C21-C25 fragment **2.13.4.3** bears the requisite chiral auxiliary for the subsequent Evans aldol reaction and terminates in a 1,1-dibromoalkene, the immediate precursor to a C21-C22 alkyne required for a hydrostannylation reaction as the final step in the synthesis of C21-C42 fragment **2.13.1.1.**

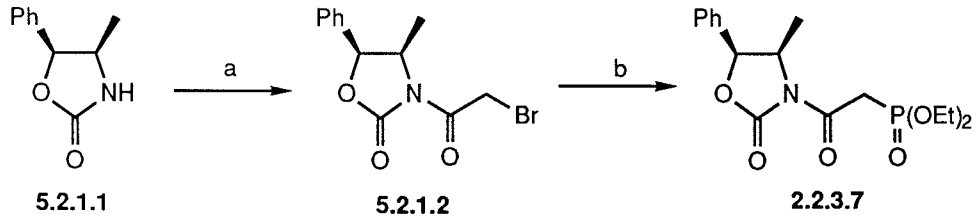
The chiral auxiliary was introduced in the form of phosphonate **2.2.3.7**, *via* a Horner-Wadsworth-Emmons olefination with chiral aldehyde **5.1.1.2**, to yield C22-C25 (*E*)-α,β-unsaturated *N*-acyloxazolidinone **5.1.1.1**. Other key transformations in the synthesis of fragment **2.13.4.3** included a regioselective 1,4-reduction of the enone system in **5.1.1.1** to provide the corresponding saturated counterpart, and the introduction of the remaining carbon (C21) of the target fragment *via* Corey-Fuchs homologation of a C22 aldehyde.



Scheme 5.1.1

5.2 Synthesis of Phosphonate 2.2.3.7 and Aldehyde 5.1.1.2

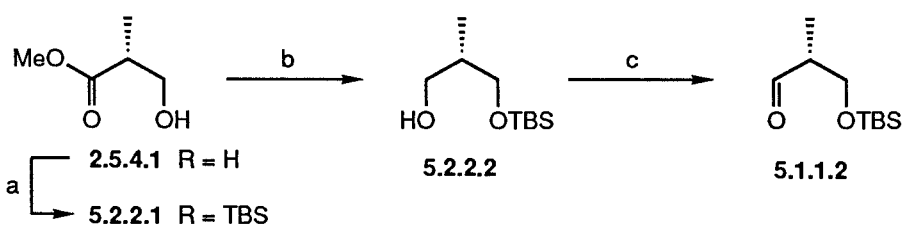
Phosphonate **2.2.3.7** has previously been employed in Nicolaou's total synthesis of rapamycin (Section **2.2**), where it was used to introduce the Evans chiral auxiliary of cyclohexyl fragment **2.2.2.4**. The preparation of **2.2.3.7**[134] began with (1*S*,2*R*)-norephedrine-derived oxazolidinone **5.2.1.1**[135] as shown in Scheme **5.2.1**. Thus, deprotonation of **5.2.1.1** with *n*-BuLi at –80°C and *N*-acylation by treatment with bromoacetyl chloride gave bromoacetyloxazolidinone **5.2.1.2**[134] in 84% yield. The requisite Horner-Wadsworth-Emmons precursor was then obtained in quantitative yield *via* an Arbuzov reaction of **5.2.1.2** with neat $(EtO)_3P$ at 50°C.



Yields, Reagents and Conditions:		
a	84%	1) *n*-BuLi, THF, –80°C → –60°C, 10 min; 2) $BrCH_2COCl$, –80°C, 1 h
b	99%	$(EtO)_3P$, 50°C, 12 h

Scheme 5.2.1

Aldehyde **5.1.1.2**[136] was prepared in three steps from methyl (*R*)-3-hydroxy-2-methylpropionate (**2.5.4.1**) (Scheme **5.2.2**) *via* protection of the alcohol as TBS ether **5.2.2.1**[136] using TBSOTf/2,6-lutidine (99% yield), reduction of the ester with DIBALH to afford primary alcohol **5.2.2.2**[136] (95% yield), and Swern oxidation.[137] The crude aldehyde was coupled with phosphonate **2.3.2.7** without purification.

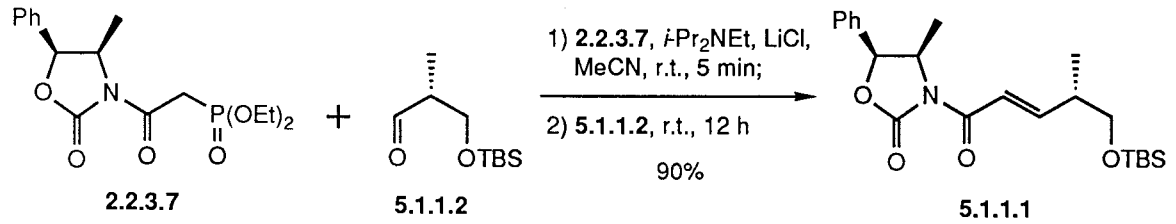


Yields, Reagents and Conditions:		
a	99%	TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h
b	95%	DIBALH, CH_2Cl_2, –25°C, 1 h
c	↓	1) $(COCl)_2$, DMSO, CH_2Cl_2, –80°C, 15 min; 2) **5.2.2.2**, –80°C → –60°C, 1 h; 3) Et_3N, –60°C → r.t., 15 min

Scheme 5.2.2

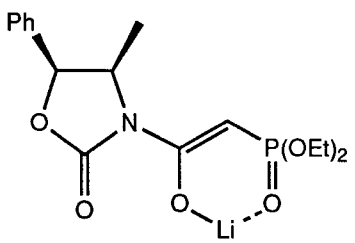
5.3 Synthesis of (*E*)-α,β-Unsaturated Acyloxazolidinone 5.1.1.1

The Horner-Wadsworth-Emmons coupling[138,139] of phosphonate **2.2.3.7** with aldehyde **5.1.1.2** was accomplished *via* Masamune and Roush's modified procedure[140], using *i*-Pr_2NEt as the base in the presence of LiCl (Scheme **5.3.1**). (*E*)-α,β-Unsaturated *N*-acyloxazolidinone **5.1.1.1** was thus obtained as a single stereoisomer in 90% yield. These conditions were used rather than one of the more standard procedures using stronger bases (*n*-BuLi, *t*-BuOK, NaH)[141] in order to avoid the potential problem of epimerisation at the chiral centre adjacent to the carbonyl group in aldehyde **5.1.1.2**.



Scheme 5.3.1

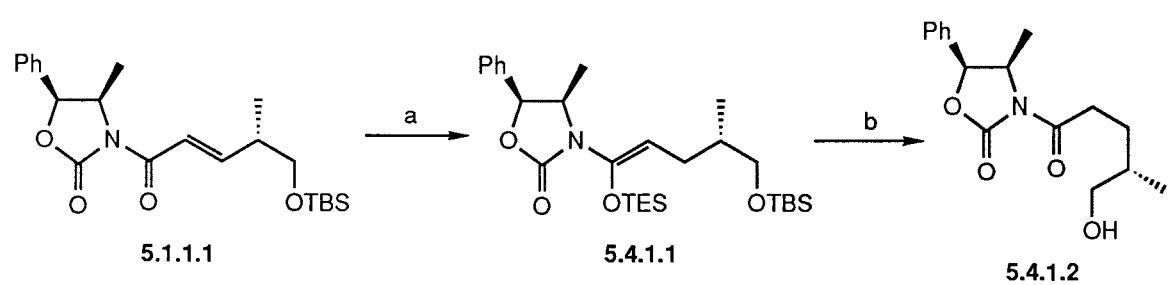
The enhanced acidity of phosphonates such as **2.2.3.7** in the presence of lithium salts is due to the ability of the corresponding enolate to form a stable chelated complex with the lithium cation (Scheme **5.3.2**). Similar results have been reported by Rathke[142] using Et_3N as the base in the presence of lithium and magnesium halides.



Scheme 5.3.2

5.4 Synthesis of the C21-C25 fragment

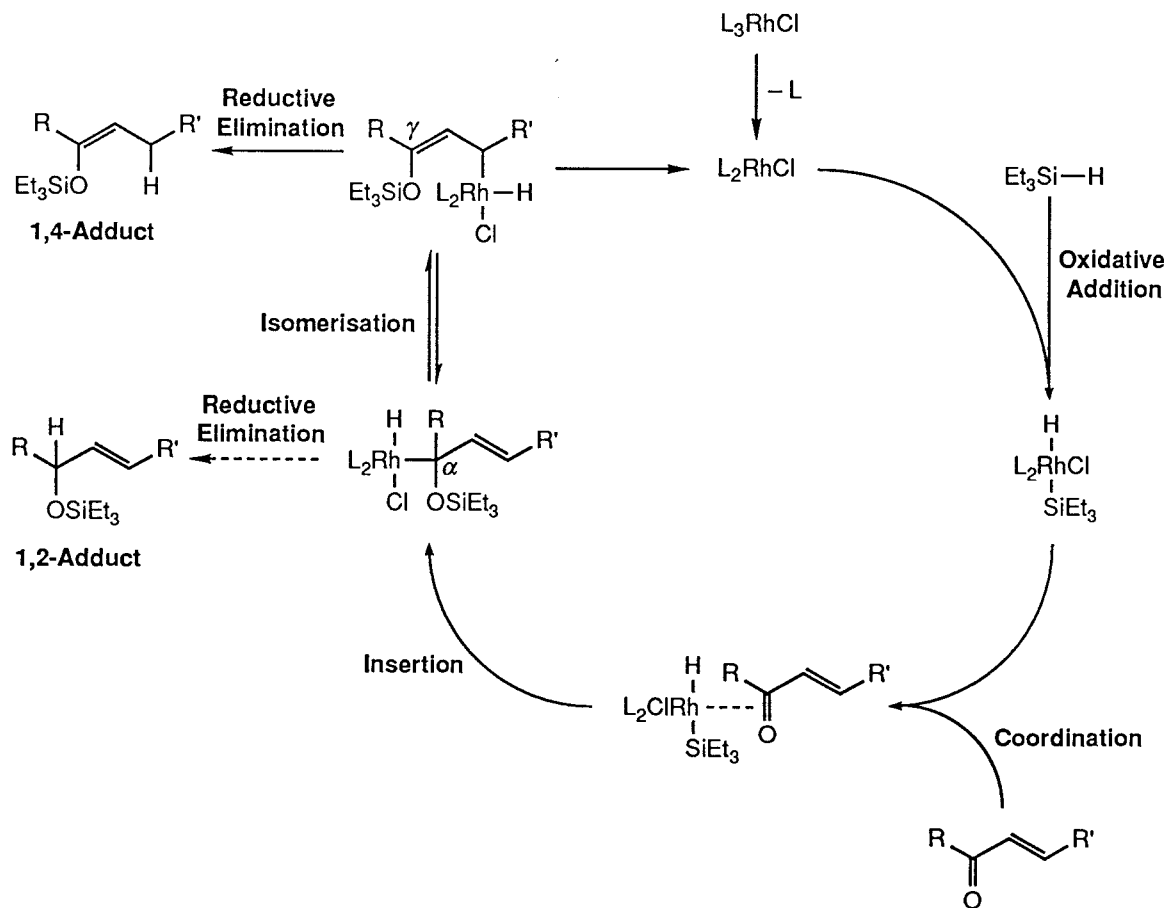
Having successfully prepared (*E*)-α,β-unsaturated *N*-acyloxazolidinone **5.1.1.1**, we next turned to the 1,4-reduction of the enone system. This was accomplished *via* hydrosilylation with Et_3SiH/Wilkinson's catalyst (5%) in refluxing benzene using Ojima's procedure[143] (Scheme **5.4.1**). The enol silane **5.4.1.1** thus obtained was not isolated, but was directly subjected to bis-desilylation using aq. HF in MeCN, thus affording saturated C22-C25 alcohol **5.4.1.2** in 85% yield.



Yields, Reagents and Conditions:		
a	↓	Et_3SiH, $(Ph_3P)_3RhCl$, benzene, Δ, 12 h
b	85%	aq. HF, MeCN, 0°C, 1 h

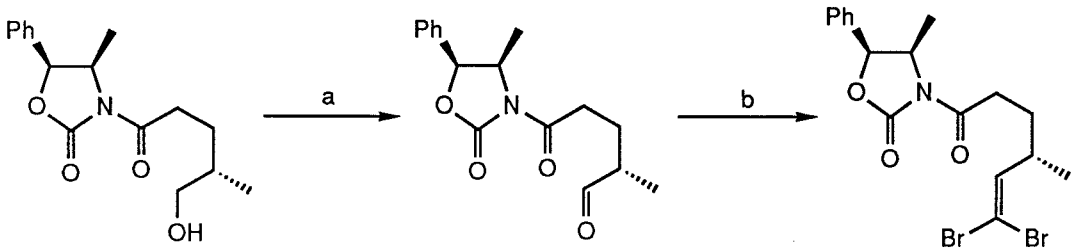
Scheme 5.4.1

The mechanism proposed to explain the observed regioselectivity of the hydrosilylation (Scheme **5.4.2**) involves initial formation of an (α-siloxyallyl)rhodium hydride species *via* oxidative addition of the Si-H bond to the Rh(I) catalyst, followed by coordination of the substrate and insertion of the carbonyl group into the Rh-Si bond. Reductive elimination from this species would lead to the 1,2-adduct. However, a rapid isomerisation to the corresponding (γ-siloxyallyl)rhodium hydride is believed to occur, due to steric repulsion between the siloxy group and the rhodium moiety in the α-siloxyallyl species. Reductive elimination from the less sterically crowded (γ-siloxyallyl)rhodium hydride then yields the observed 1,4-adduct. This mechanism is supported by the observation that exclusive 1,2-addition occurs when less sterically demanding dihydrosilanes are used in place of monohydrosilanes. In these cases, reductive elimination from the (α-siloxyallyl)rhodium hydride becomes faster than the isomerisation to the γ-siloxyallyl species.



Scheme 5.4.2

The further elaboration of C22-C25 alcohol **5.4.1.2** to C21-C25 fragment **2.13.4.3** is shown in Scheme **5.4.3**. Thus, Swern oxidation of **5.4.1.2** cleanly afforded aldehyde **5.4.3.1** which, without purification, was homologated to the requisite C21-C25 1,1-dibromoalkene **2.13.4.3** *via* the Corey-Fuchs procedure,[144] by treatment with CBr_4/Ph_3P and zinc dust (88% overall yield).



5.4.1.2 5.4.3.1 2.13.4.3

Yields, Reagents and Conditions:		
a	↓	1) $(COCl)_2$, DMSO, CH_2Cl_2, –80°C, 15 min; 2) **5.4.1.2**, –80°C → –60°C, 1 h; 3) Et_3N, –60°C → –0°C, 5 min
b	88%	1) CBr_4, Ph_3P, Zn, CH_2Cl_2, r.t., 24 h; 2) **5.4.3.1**, r.t., 2 h

Scheme 5.4.3

We did not expect to be able to carry out the second stage of the Corey-Fuchs homologation (debromination to the corresponding terminal alkyne *via* treatment with *n*-BuLi) on this substrate due to the acidity of the C25 protons and the potential for nucleophilic attack at the imide carbonyls. Indeed, treatment of **2.13.4.3** with *n*-BuLi (THF, –78°C → r.t.) resulted in a complex mixture of unidentified products. Van Hijfte's alternative procedure[145] for the conversion of 1,1-dibromoalkenes to terminal alkynes using magnesium in refluxing THF was equally unsuccessful, presumably due to the intermediacy of organometallic species in this transformation. These failures were only a minor drawback, however, since the dibromoalkene was sufficiently robust to be used in the subsequent Evans aldol reaction (*vide infra*) and remained intact during the reductive removal of the chiral auxiliary. Debromination could then be readily effected using *n*-BuLi.

5.5 Conclusion

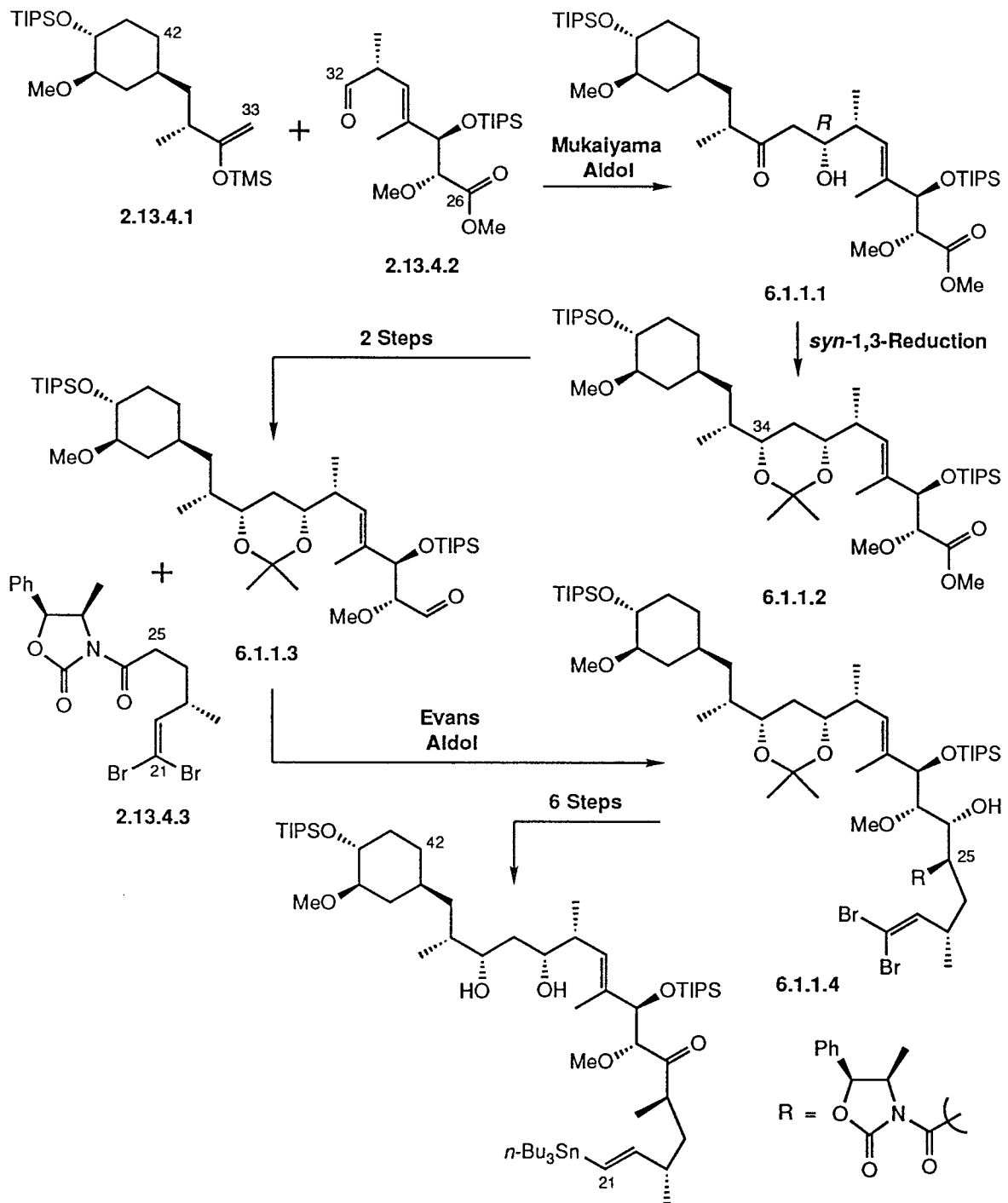
A straightforward synthesis of the C21-C25 fragment (**2.13.4.3**) of rapamycin from chiral starting materials has been achieved in 63% overall yield from methyl (*R*)-3-hydroxy-2-methylpropionate. Our failure to convert the 1,1-dibromoalkene of **2.13.4.3** into the requisite terminal acetylene did not present a problem, since this transformation could readily be achieved at a later stage in the synthesis of C21-C42 fragment **2.13.1.1**.

Chapter 6

Synthesis of the C21-C42 Fragment

6.1 Introduction

In the previous three chapters the stereocontrolled syntheses of fragments corresponding to C33-C42, C26-C32 and C21-C25 of rapamycin were described. In this chapter the coupling of these fragments to afford the C21-C42 target fragment **2.13.1.1** will be discussed. A summary of our strategy for the synthesis of **2.13.1.1** is shown in Scheme **6.1.1**.

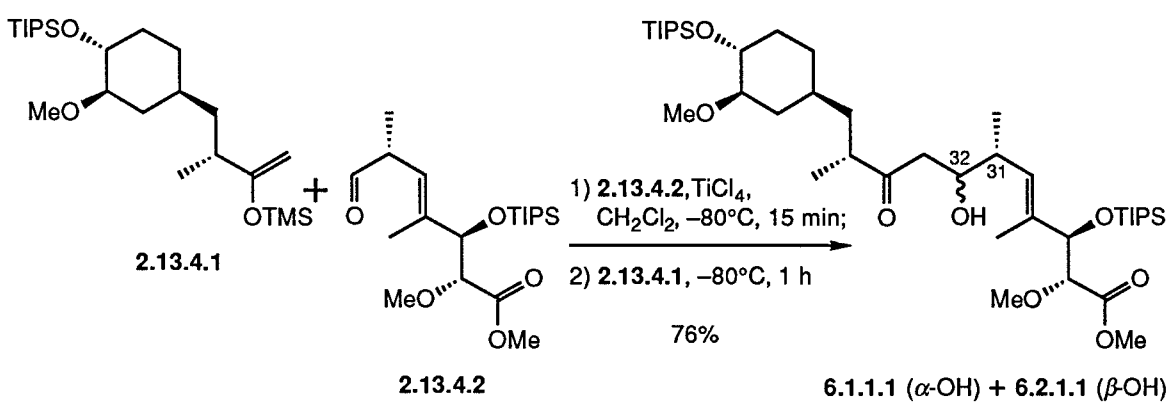


Scheme 6.1.1

The initial coupling involved a Mukaiyama aldol reaction between C33-C42 enol silane **2.13.4.1** and C26-C32 aldehyde **2.13.4.2**. This afforded β-hydroxy ketone **6.1.1.1** with good selectivity for the 32-(*R*) diastereomer. A hydroxyl-directed *syn*-1,3-diastereoselective reduction was then used to generate *syn*-acetonide **6.1.1.2** with the correct stereochemistry at C34. The second key coupling reaction entailed an Evans aldol reaction of aldehyde **6.1.1.3** with the boron enolate of C21-C25 *N*-acyloxazolidinone **2.13.4.3** to afford adduct **6.1.1.4** as a single diastereomer with the correct stereochemistry at C25.

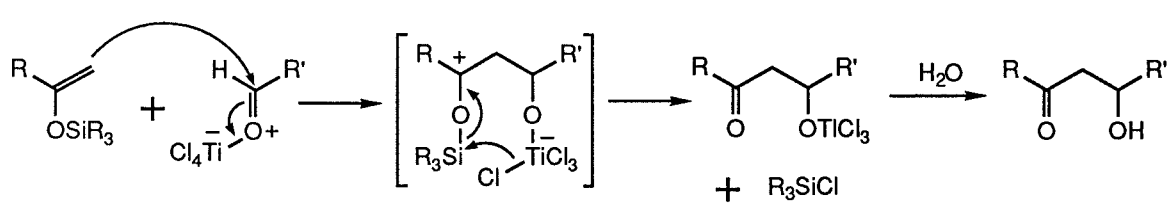
6.2 Synthesis of Mukaiyama Aldol Adduct 6.1.1.1

The Mukaiyama aldol[146] condensation of methyl ketone-derived enol silane **2.13.4.1** with α-methyl aldehyde **2.13.4.2** using $TiCl_4$ as the Lewis acid provided C31,C32-*syn* adduct **6.1.1.1** and C31,C32-*anti* adduct **6.2.1.1** in 76% total yield as a 93:7 mixture which could be separated by careful flash chromatography (Scheme **6.2.1**).



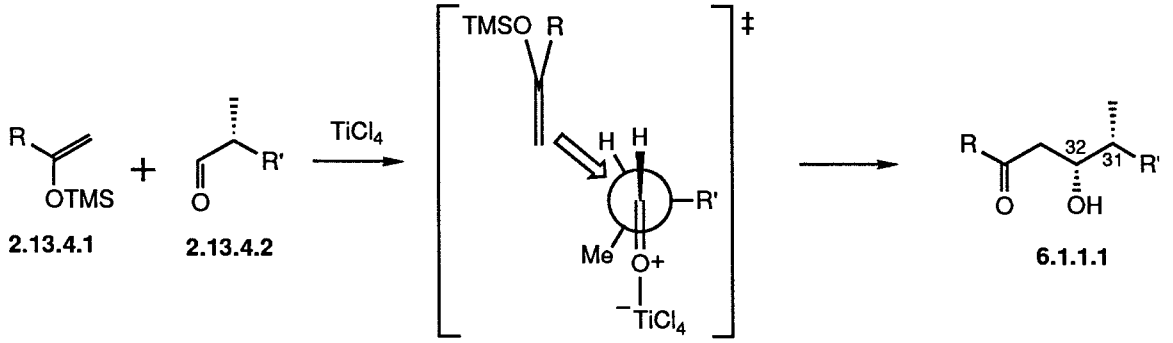
Scheme 6.2.1

Although the mechanism of the Mukaiyama aldol reaction is not yet fully understood, it is generally believed[147] that the addition proceeds through an "open" transition state, in which the Lewis acid coordinates to the carbonyl group of the aldehyde and does not intimately interact with the enol silane until after C-C bond formation has occurred (Scheme **6.2.2**).



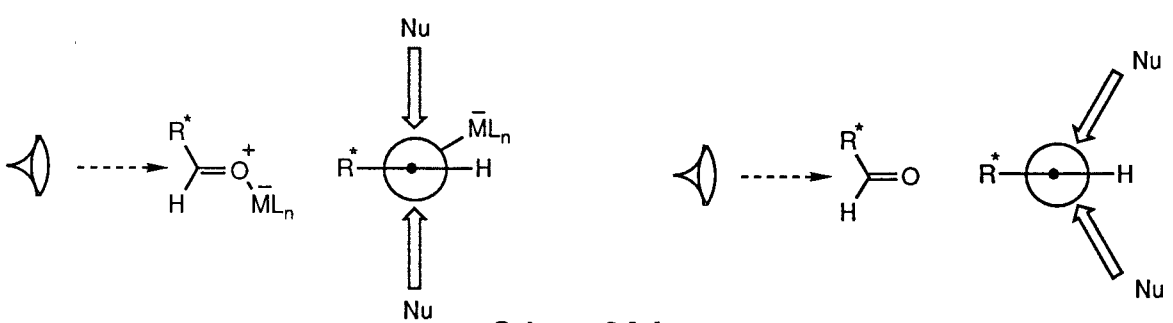
Scheme 6.2.2

The observed C31,C32-*syn* diastereofacial selectivity in the coupling of enol silane **2.13.4.1** with aldehyde **2.13.4.2** to afford *syn*-adduct **6.1.1.1** as the major product is thus readily accommodated by a Felkin-Anh[148,149] transition state model (Scheme **6.2.3**).



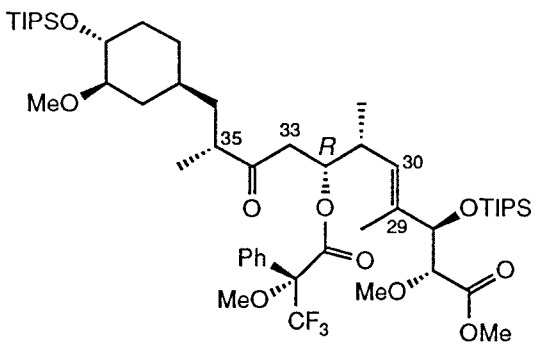
Scheme 6.2.3

An explanation for the high level of *syn* diastereoselection in the Lewis acid-mediated reaction of enol silanes derived from methyl ketones with chiral α-methyl aldehydes has been proposed by Heathcock (Scheme **6.2.4**),[150] whereby the approach trajectory of the nucleophile is thought to pass closer to the stereocentre when the carbonyl group is bound to a Lewis acid (assuming that the Lewis acid occupies a position *syn* to the aldehyde hydrogen) than in nucleophilic additions to uncomplexed aldehydes, thus increasing the interaction between the nucleophile and the stereogenic centre and hence increasing the effective asymmetric induction of the process.

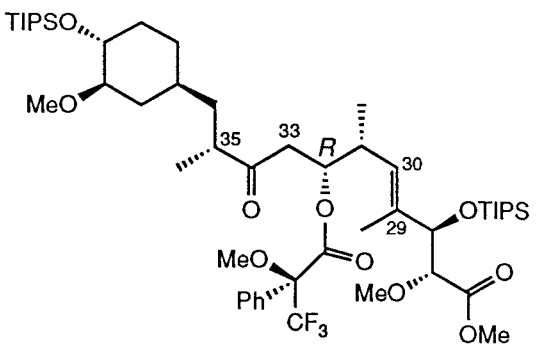


Scheme 6.2.4

The expected 32-(*R*) stereochemistry of alcohol **6.1.1.1** was confirmed by careful comparison of the 270 MHz ^{1}H NMR spectra ($CDCl_3$) of the derived diastereomeric (*R*)- and (*S*)-Mosher esters (Scheme **6.2.5**), prepared under standard conditions *via* treatment of the alcohol with (*R*)- or (*S*)-MTPA in the presence of DCC and 5% DMAP (CH_2Cl_2, r.t., 18 h; 98% yield in both cases). The observed differences in chemical shift of the signals corresponding to the C35, C33 and C30 protons and the C29 methyl group are consistent with a 32-(*R*) stereochemistry.[151]



(*R*)-Mosher Ester

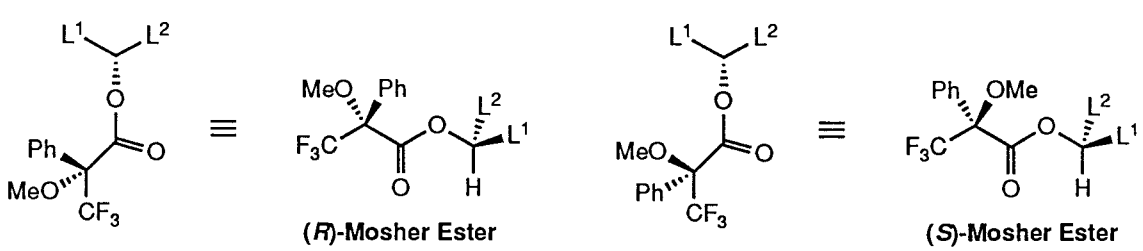


(*S*)-Mosher Ester

Signal	δ(*R*)-Ester	δ(*S*)-Ester (ppm)
C35-H	2.50	2.56
C33-H_2	2.75	2.78
C30-H	5.13	5.08
C29-Me	1.72	1.65

Scheme 6.2.5

The empirically derived model proposed by Mosher to rationalise the sense of nonequivalence in the ^{1}H NMR spectra of diastereomeric MTPA esters of chiral secondary alcohols is pictured in Scheme **6.2.6.** The esters are viewed as occupying a conformation in which the trifluoromethyl group and the carbinyl proton eclipse the carbonyl group of the ester. The ^{1}H NMR signal of the substituent which eclipses the phenyl ring in this conformation then always appears upfield from the same signal in the corresponding diastereomeric ester, presumably resulting from a time-averaged preferential shielding of this substituent by the phenyl ring.



(*R*)-Mosher Ester (*S*)-Mosher Ester

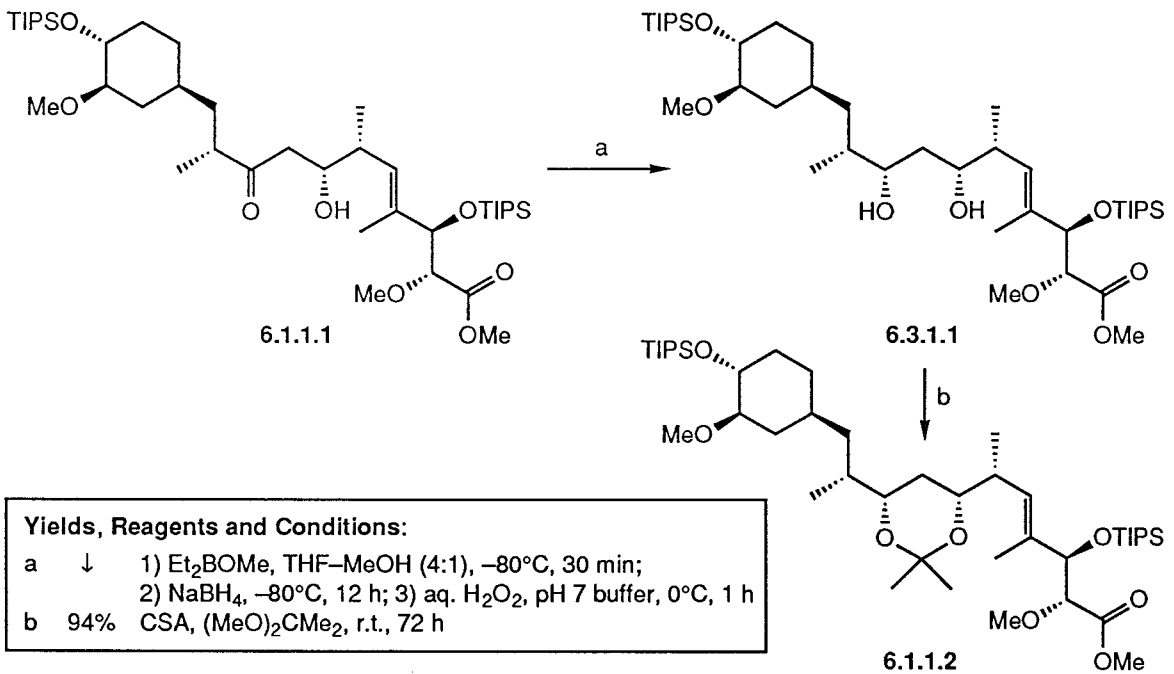
L^1 of (*R*)-Ester upfield relative to L^1 of (*S*)-Ester
L^2 of (*S*)-Ester upfield relative to L^2 of (*R*)-Ester

Scheme 6.2.6

6.3 Synthesis of *syn*-Acetonide 6.1.1.2

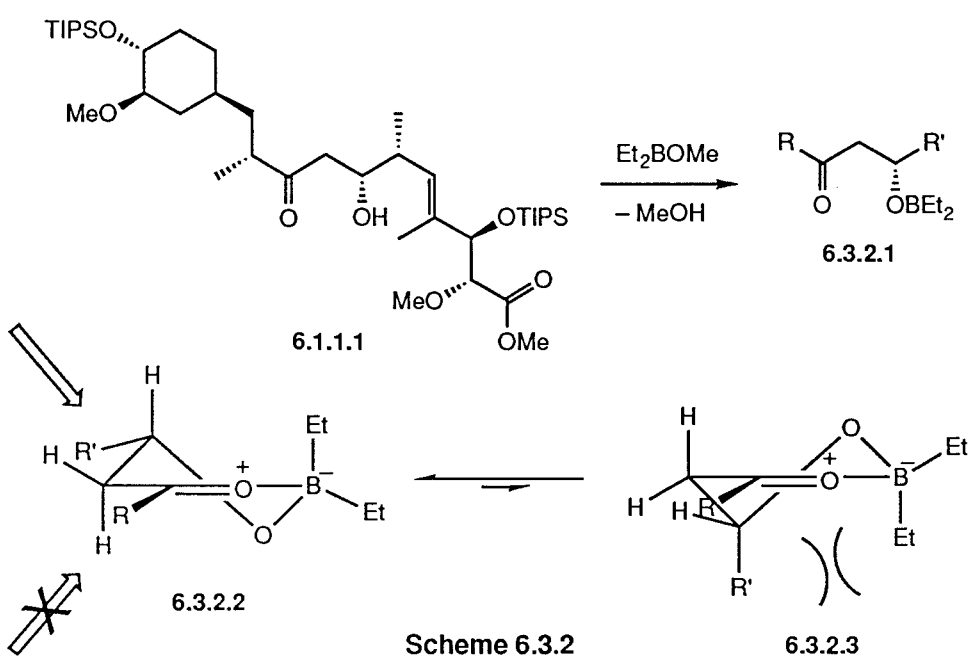
Having established the 32-(*R*) stereochemistry of alcohol **6.1.1.1** the next step was to diastereoselectively reduce the C34 ketone to the corresponding *syn*-carbinol. This was achieved by the method of Prasad,[152] *via* treatment of the β-hydroxy ketone with $NaBH_4$ at low temperature in the presence of Et_2BOMe (Scheme **6.3.1**). After oxidative work-up the resulting 1,3-diol **6.3.1.1** was subjected to acetalisation conditions (2,2-

dimethoxypropane/20% CSA) without purification to afford *syn*-acetonide **6.1.1.2** as a single diastereomer in 94% yield for the two steps. ^{13}C NMR analysis (67.5 MHz, C_6D_6) of **6.1.1.2** revealed acetal methyl chemical shifts at 31.31 and 20.64 ppm, confirming[153] the *syn* stereochemistry of the acetonide.



Scheme 6.3.1

The high diastereoselectivity of the reduction results from initial formation of diethylborinic ester **6.3.2.1** (Scheme **6.3.2**) which adopts a rigid six-membered cyclic conformation **6.3.2.2** due to coordination of the carbonyl oxygen to the boron. Hydride attack at the less hindered face of **6.3.2.2** then leads to the observed *syn*-diol. Conformer **6.3.2.2** would

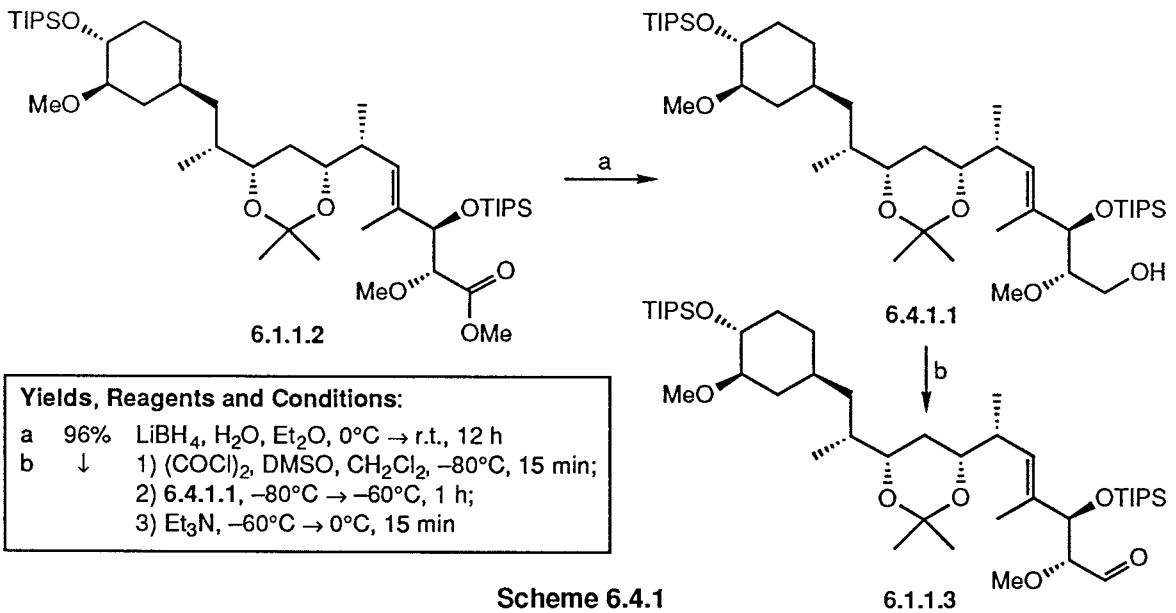


Scheme 6.3.2

be expected to be favoured over conformer **6.3.2.3** due to the 1,3-diaxial interaction present in the latter between R' and the ethyl group on boron.

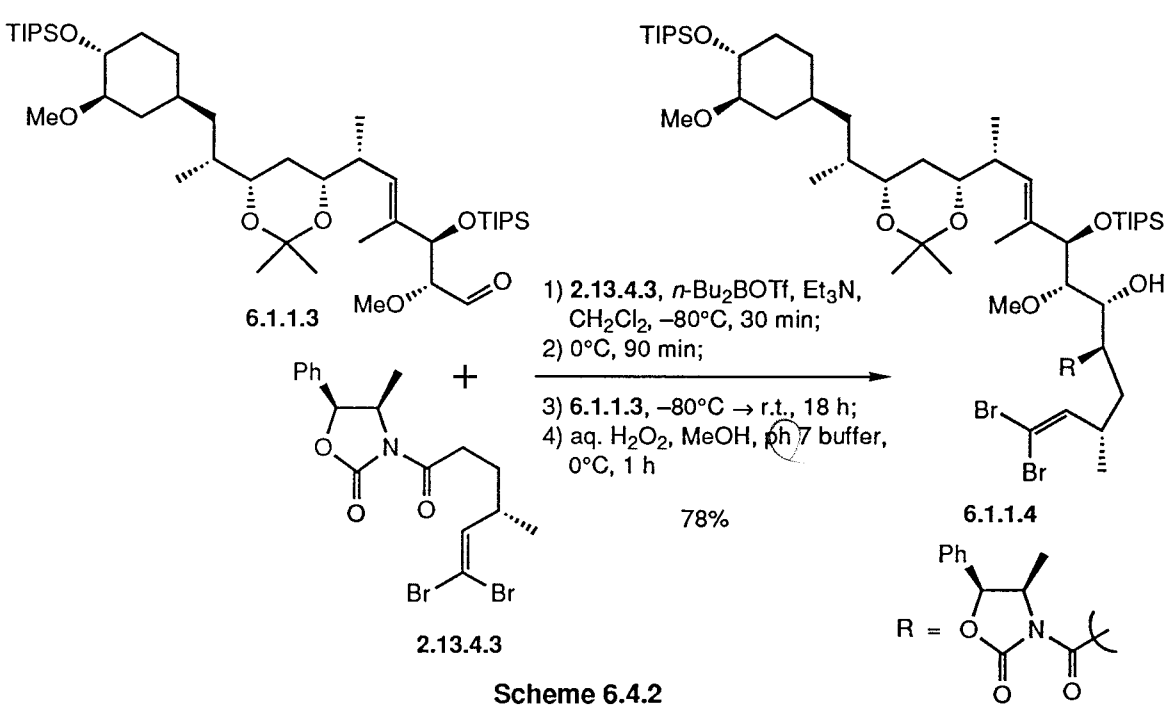
6.4 Synthesis of Evans Aldol Adduct 6.1.1.4

Aldehyde **6.1.1.3** was obtained from ester **6.1.1.2** in two steps *via* reduction with $LiBH_4$ (96% yield) to afford alcohol **6.4.1.1**, followed by Swern oxidation[137] (Scheme **6.4.1**).



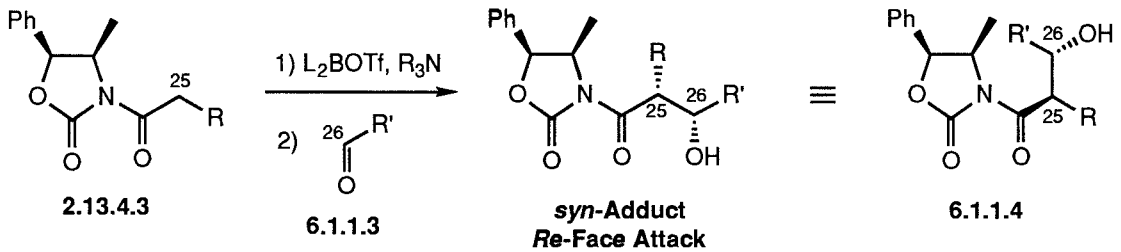
Scheme 6.4.1

The aldol condensation of unpurified **6.1.1.3** with the boron enolate of C21-C25 *N*-acyloxazolidinone **2.13.4.3** then proceeded smoothly under Evans' standard conditions[135] to afford adduct **6.1.1.4** as a single diastereomer in 78% yield (Scheme **6.4.2**).



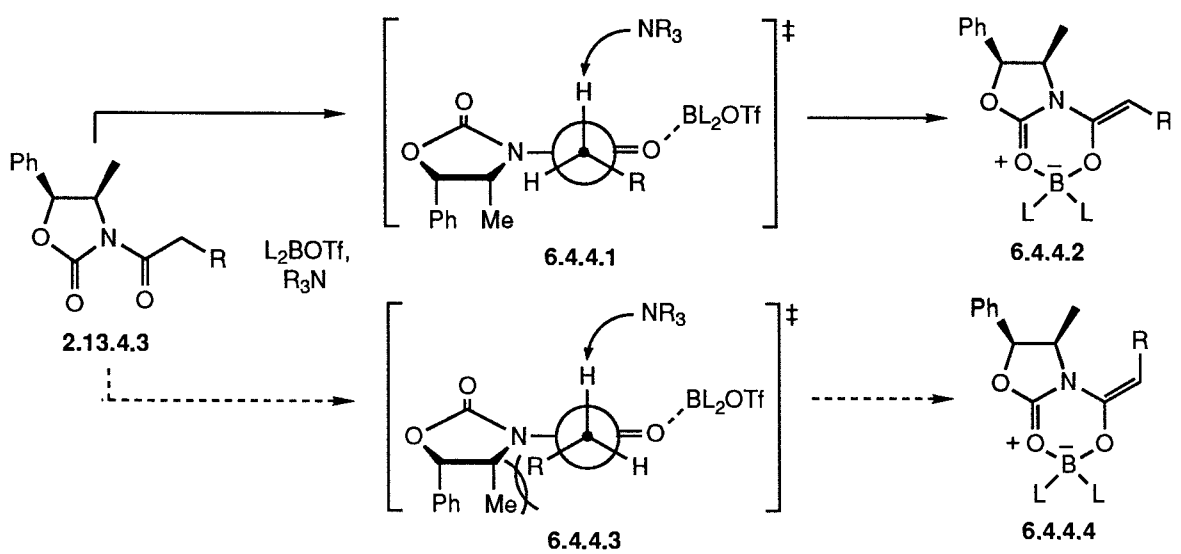
Scheme 6.4.2

No attempt was made to verify the stereochemistry of **6.1.1.4** due to the well-known and predictable *syn*-stereoselectivity and *Re*-diastereofacial selectivity in aldol condensations involving di-*n*-butylboron enolates of (1*S*,2*R*)-norephedrine-derived *N*-acyloxazolidinones such as **2.13.4.3** (Scheme **6.4.3**).[154] Furthermore, the same C25-C26 Evans aldol disconnection was used to construct a C21-C28 fragment of known stereochemistry in Nicolaou's total synthesis of rapamycin (Section **2.2**).



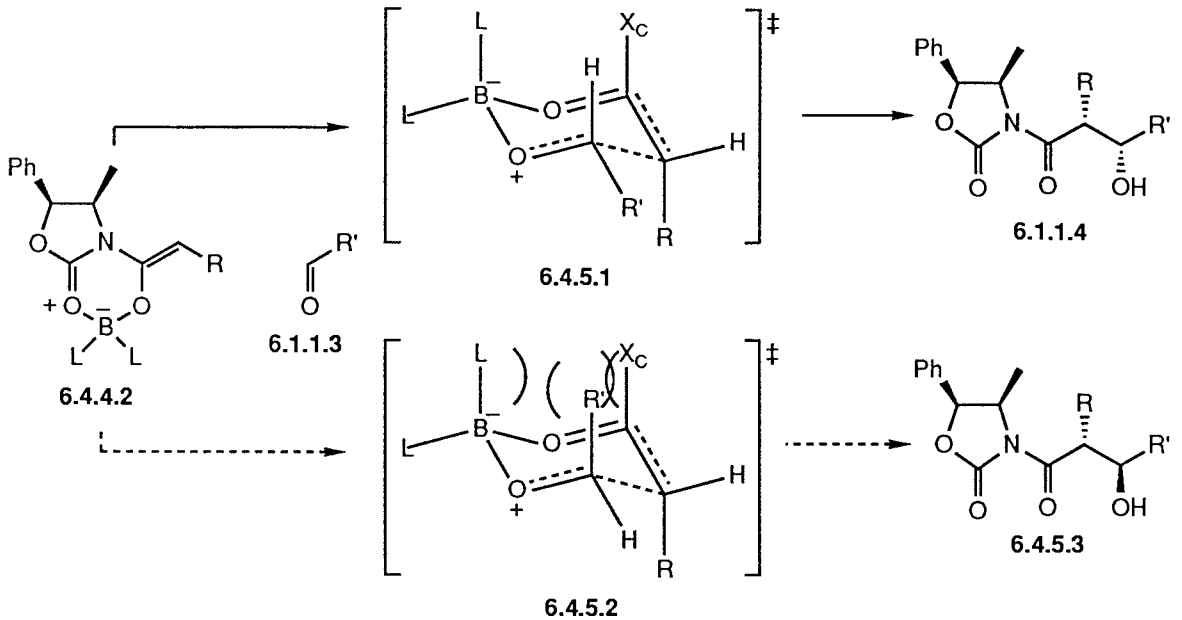
Scheme 6.4.3

The *syn*-diastereoselectivity of the reaction results from selective formation of the (*Z*)-boron enolate[154] of **2.13.4.3** which condenses with **6.1.1.3** via a Zimmerman-Traxler transition state[155] in which the steric interactions between the substituents are minimised. Thus, kinetic enolisation of **2.13.4.3** occurs *via* complex **6.4.4.1** (Scheme **6.4.4**) to form (*Z*)-enolate **6.4.4.2** rather than (*E*)-enolate **6.4.4.4**, due to the $A^{1,3}$ strain between R and the oxazolidinone in the alternative complex **6.4.4.3**.



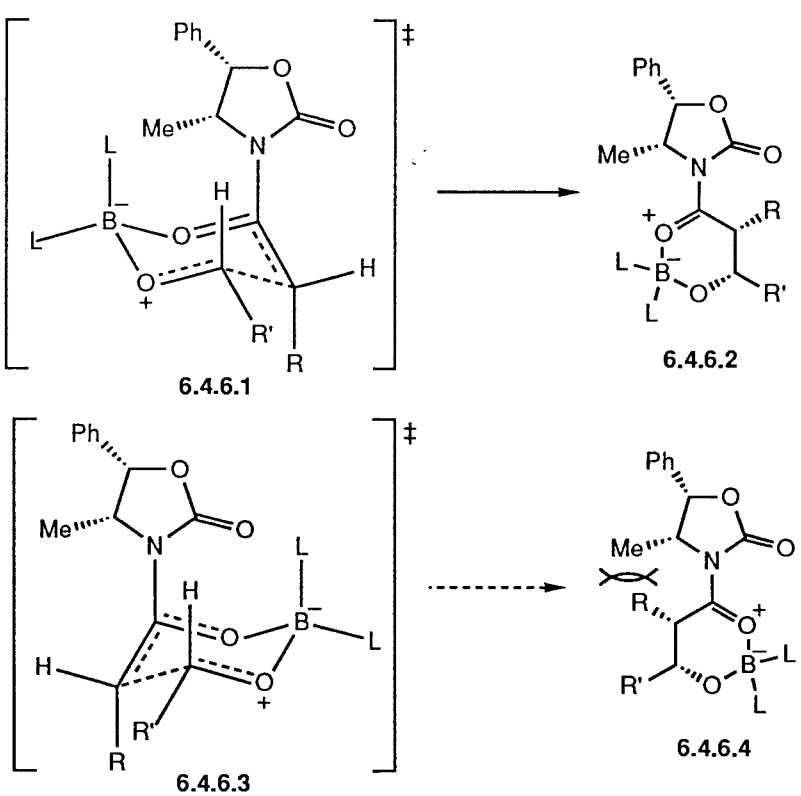
Scheme 6.4.4

Condensation of (Z)-enolate **6.4.4.2** with aldehyde **6.1.1.3** then proceeds through pericyclic transition state **6.4.5.1** (Scheme **6.4.5**) to afford the observed *syn*-adduct **6.1.1.4**. The unfavoured transition state **6.4.5.2** leading to *anti*-adduct **6.4.5.3** is destabilised relative to **6.4.5.2** due to the maximisation of 1,3-diaxial interactions.



Scheme 6.4.5

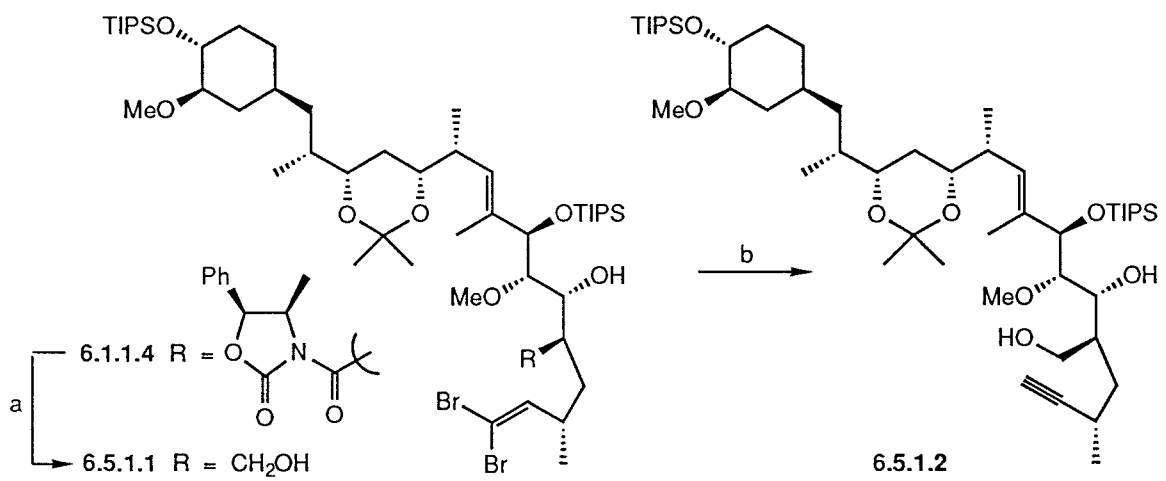
The *Re*-diastereofacial selectivity may be rationalised[156] by invoking diastereomeric transition states **6.4.6.1** and **6.4.6.3** (Scheme **6.4.6**). In both cases the chiral auxillary is oriented *exo* to the pericyclic transition state and alligned so that the developing imide resonance can be accomodated as the reaction proceeds towards the two possible chelated products **6.4.6.2** and **6.4.6.4**. The unfavourable $A^{1,3}$ strain in product **6.4.6.4** which would result if the reaction proceeded through transition state **6.4.6.3**, however, is thought to favour transition state **6.4.6.1** leading to product **6.4.6.2**, in which this strain is absent.



Scheme 6.4.6

6.5 Synthesis of the C21-C42 Fragment

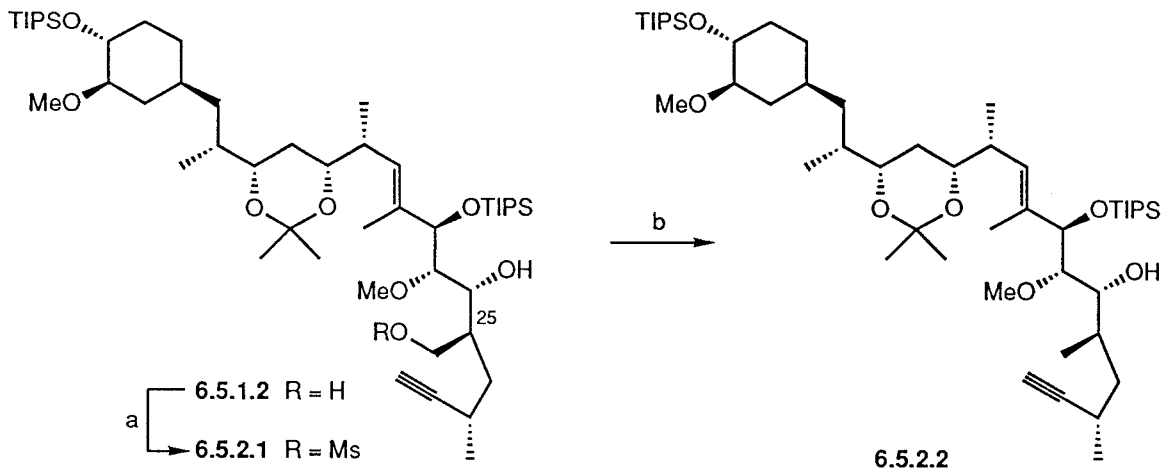
The target C21-C42 fragment **2.13.1.1** was prepared in six steps from Evans aldol adduct **6.1.1.4**. The first step in this sequence involved reductive removal of the chiral auxiliary (Scheme **6.5.1**), achieved by treatment of **6.1.1.4** with $LiBH_4$ to afford diol **6.5.1.1** in 85% yield. Having removed the chiral auxiliary, the second step of the Corey-Fuchs homologation[144] used to form the 1,1-dibromoalkene of C21-C25 fragment **2.13.4.3** could then be executed. Thus, treatment of **6.5.1.1** with excess *n*-BuLi (5 eq.) cleanly provided terminal alkyne **6.5.1.2** in 86% yield without accompanying side reactions.



Yields, Reagents and Conditions:		
a	85%	$LiBH_4$, H_2O, Et_2O, –30°C → 0°C, 2 h
b	86%	1) *n*-BuLi, THF, –80°C → –20°C, 1 h; 2) –20°C, 1 h

Scheme 6.5.1

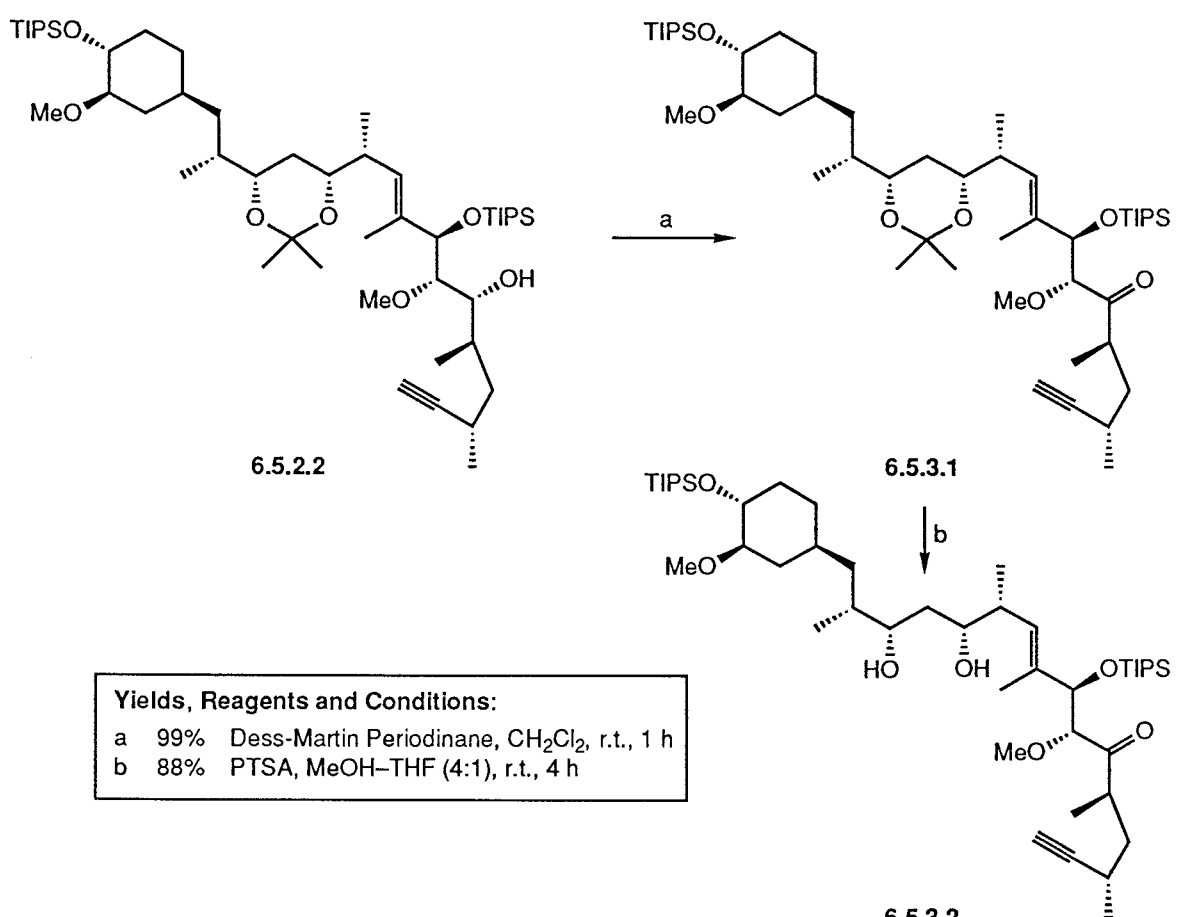
The next transformation to be attempted involved the conversion of the C25 hydroxymethyl group of diol **6.5.1.2** to the requisite methyl group *via* a two-step tosylation–reduction sequence.[157] Attempts to tosylate the primary position of **6.5.1.2** using TsCl (1 eq.) in the presence of various amine bases (Et_3N, pyridine, DMAP), however, were complicated by competitive tosylation of the secondary alcohol. Selective *mesylation* of the primary alcohol could be effected, however, using MsCl/Et_3N and by keeping the reaction temperature below –20°C (Scheme **6.5.2**). The resulting unpurified sulfonate **6.5.2.1** was then treated with excess Super-Hydride (10 eq.) to form the requisite C25-methyl compound **6.5.2.2** in 62% yield. The moderate yield of this reaction was a reflection of the significant decomposition which occurred during the oxidative work-up (necessary to destroy the triethylborane produced upon quenching). The displacement reaction itself appeared to occur cleanly as evidenced by TLC analysis of the reaction mixture before work-up.



Yields, Reagents and Conditions:		
a	↓	MsCl, Et_3N, CH_2Cl_2, –80°C → –20°C, 1 h
b	62%	1) $LiEt_3BH$, THF, 0°C → r.t., 60 h; 2) aq. NaOH, aq. H_2O_2, 0°C, 1 h

Scheme 6.5.2

Subsequent Dess-Martin oxidation[88] of alcohol **6.5.2.2** quantitatively yielded ketone **6.5.3.1** (Scheme **6.5.3**), which was treated with 20% PTSA in MeOH–THF (4:1) to afford diol **6.5.3.2** in 88% yield after one recycle of recovered acetonide. Careful monitoring of this reaction by TLC was necessary in order to avoid the formation of significant amounts of a highly polar compound, assumed to be a tetrol resulting from

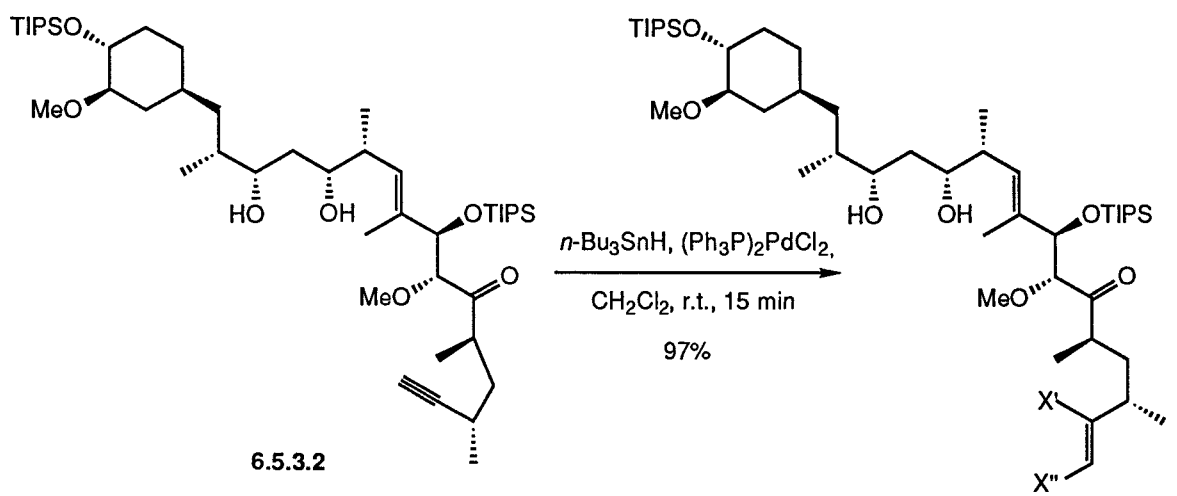


Yields, Reagents and Conditions:		
a	99%	Dess-Martin Periodinane, CH_2Cl_2, r.t., 1 h
b	88%	PTSA, MeOH–THF (4:1), r.t., 4 h

Scheme 6.5.3

concomitant methanolysis of the two TIPS ethers.

The final step in the synthesis of the C21-C42 target fragment **2.13.1.1** entailed a Pd(0)-catalysed hydrostannylation[158] of the terminal alkyne in diol **6.5.3.2**. Thus, treatment of **6.5.3.2** with *n*-Bu_3SnH in the presence of 5% $(Ph_3P)_2PdCl_2$ afforded (*E*)-vinylstannane **2.13.1.1** as a 93:7 inseparable mixture with regioisomeric stannane **6.5.4.1** (97% total yield). The mechanism of this reaction is presumably similar to that described for the Pd(0)-catalysed silylstannylation reaction used in the synthesis of the C26-C32 fragment (Chapter **4**).



Scheme 6.5.4

6.6 Conclusion

In this chapter the stereoselective coupling of C33-C42 fragment **2.13.4.1**, C26-C32 fragment **2.13.4.2** and C21-C25 fragment **2.13.4.3** has been described, providing the target C21-C42 fragment **2.13.1.1** in a form suitable for coupling with the C1-C20 fragment **2.5.1.3**.

The Mukaiyama aldol condensation of enol silane **2.13.4.1** with aldehyde **2.13.4.2** proved to be an efficient method for forming the C32-C33 bond, and the subsequent *syn*-1,3-diastereoselective reduction of the resulting β-hydroxy ketone **6.1.1.1** allowed the stereoselective generation of the requisite C34 carbinol.

The efficient formation of the C25-C26 bond and generation of the C25 stereocentre *via* Evans aldol coupling of aldehyde **6.1.1.3** with *N*-acyloxazolidinone **2.13.4.3** was marred, to some extent, by the moderate yield in the conversion of the chiral auxiliary-bearing side chain of adduct **6.1.1.4** to the requisite C25 methyl group. It seems that the inefficiency of this process was due to decomposition occurring during the oxidative work-

up. The further transformations leading to the appropriately functionalised target fragment, however, proceeded in good overall yield, providing the requisite (*E*)-vinyl stannane **2.13.1.1** as an inseparable 93:7 mixture with regioisomer **6.5.4.1**. It is hoped that the isomeric material will be separable after subsequent coupling with the C1-C20 fragment **2.5.1.3**.

Chapter 7

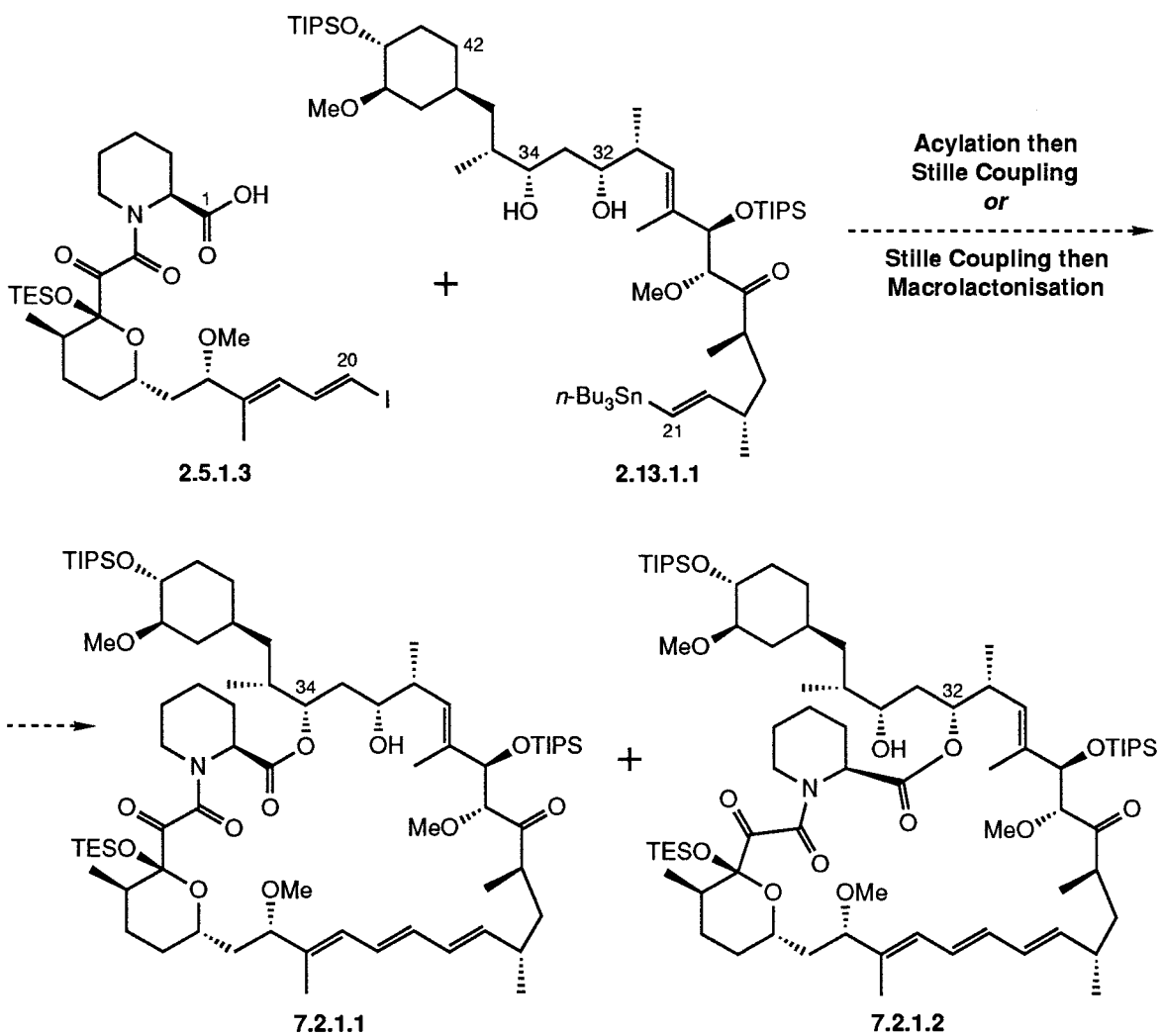
Concluding Remarks

7.1 Introduction

In the previous four Chapters the stereoselective synthesis of the C21-C42 fragment **2.13.1.1** of rapamycin was described. Work directed towards the synthesis of C1-C20 fragment **2.5.1.3** was begun at Southampton in 1990[159] and is now nearing completion. In this Chapter a description of our proposed route for the synthesis of rapamycin from advanced fragments **2.13.1.1** and **2.5.1.3** will be followed by a summary of the major contributions of the research described in this thesis.

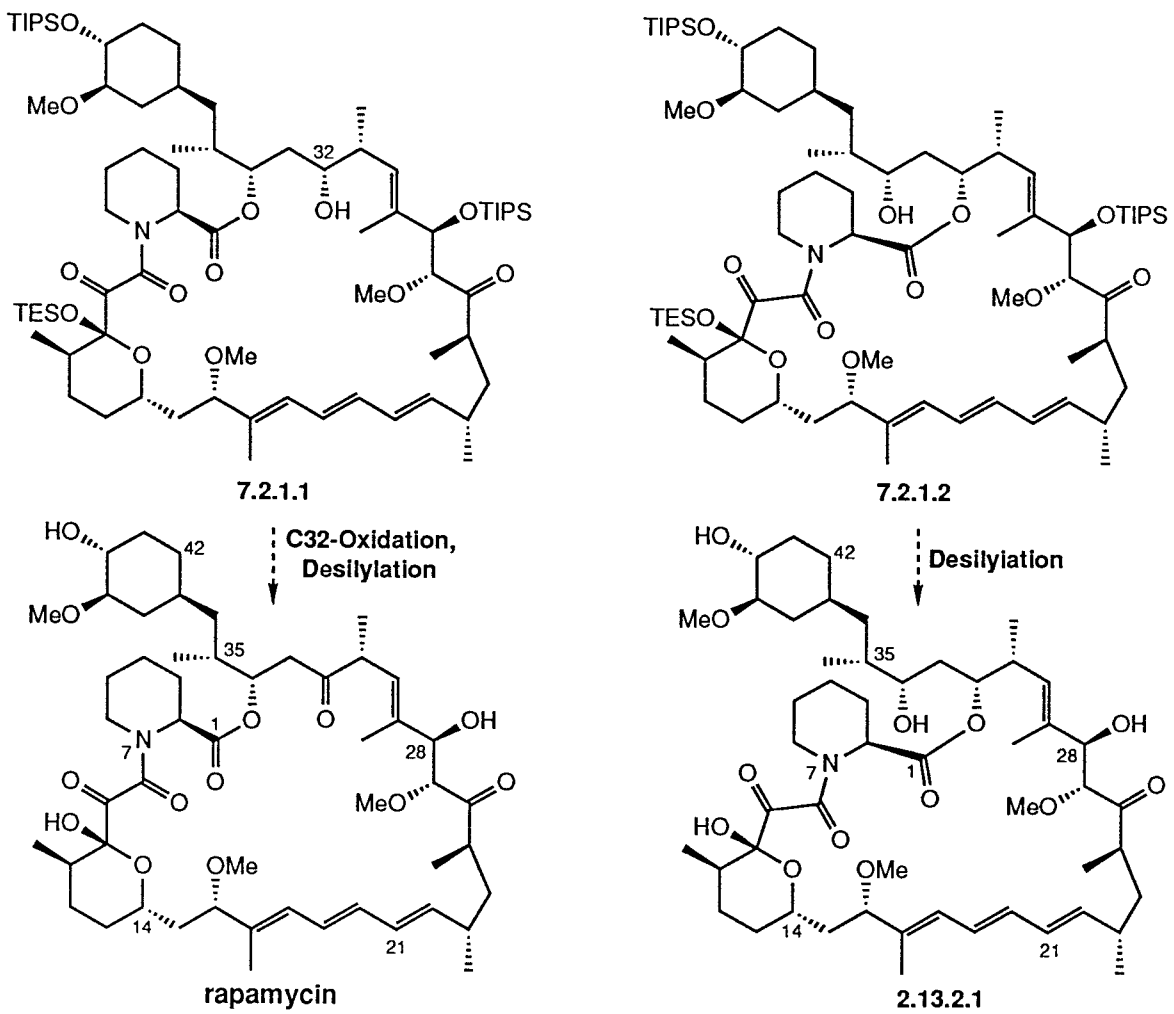
7.2 Proposed Route for the Synthesis of Rapamycin

Having established a highly convergent and stereocontrolled route to C21-C42 fragment **2.13.1.1**, and with the synthesis of C1-C20 fragment **2.5.1.3** now almost complete, the conclusion of the Southampton total synthesis of rapamycin should be a relatively straightforward matter. As mentioned in Section **2.13**, two potential macrocyclisation strategies may be pursued (Scheme **7.2.1**): an intermolecular esterification of **2.13.1.1** (at



Scheme 7.2.1

the C34 alcohol) with acid **2.5.1.3** followed by intramolecular Pd(0)-catalysed Stille coupling between the C20 vinyl iodide and the C21 vinyl stannane, or initial formation of the triene seco acid followed by macrolactonisation. Both approaches are complicated by the presence of the free hydroxyl in **2.13.1.1** at C32, however, and the formation of C32-acylated compound **7.2.1.2** along with the desired C34-acylated macrocycle **7.2.1.1** is likely using either approach. Nevertheless, oxidation of the C32 alcohol of **7.2.1.1** followed by desilylation should yield rapamycin (Scheme **7.2.2**), whereas desilylation of **7.2.1.2** without prior oxidation would be expected to afford the Wyeth-Ayerst ring-contracted analogue **2.13.2.1.**



Scheme 7.2.2

7.3 Conclusion

In summary, the major contributions of this research include:

1. The development of an extremely mild and efficient method for the activation of unfunctionalised allylic silanes towards Fleming-Tamao oxidation *via* a novel use of furan photooxygenation;

2. The highly stereocontrolled and efficient synthesis of the C26-C32 fragment of rapamycin using an Ireland-Claisen rearrangement strategy;
3. The development of practical, high-yielding and stereocontrolled syntheses of the C33-C42, and C21-C25 fragments;
4. The stereocontrolled coupling of these fragments using Mukaiyama and Evans aldol methodology to form the advanced C21-C42 fragment in a form suitable for coupling with the C1-C20 fragment.

Finally, the route outlined above should form the basis for the final construction of rapamycin from the described advanced intermediates.

Chapter 8

Experimental

8.1 General Experimental

All reactions requiring anhydrous conditions were carried out in flame-dried apparatus under an atmosphere of dry nitrogen. Dry solvents were freshly distilled prior to use: THF and diethyl ether ('ether') from sodium/benzophenone; dichloromethane, benzene and acetonitrile from calcium hydride; methanol and isopropanol from the corresponding magnesium alkoxide. Petroleum ether bp 40–60°C ('petrol') was distilled before use.

2-Methylfuran, dichlorodimethylsilane, tri-*n*-butyltin hydride, methoxyacetic acid, TMS chloride, 1,1,3,3,-tetramethylguanidine, oxalyl chloride, acryloyl chloride, DBU, mesyl chloride, tri-*n*-butylphosphine, 2,2-dimethoxypropane, bromoacetyl chloride and triethylsilane were freshly distilled prior to use. Triethyl phosphite was stored over sodium wire and freshly distilled prior to use. DMSO was distilled from calcium hydride and stored over 4Å molecular sieves. Triethylamine, diisopropylamine, diisopropylethylamine and 2,6-lutidine were distilled from calcium hydride and stored over potassium hydroxide pellets. Methyl iodide was distilled from calcium hydride and stored over copper wire/4Å molecular sieves. Magnesium turnings and zinc powder were activated by washing ten times with 1 M hydrochloric acid, then rinsed successively with five portions each of water, ethanol and ether and dried overnight at 100°C/0.2 mm Hg. Molecular sieves were freshly activated by heating with a Bunsen flame until the evolution of water ceased and then cooled under a stream of dry nitrogen. Commercial solutions of alkyllithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrazone.[160] Commercial 57–86% MCPBA was estimated by iodometric titration. All other commercial reagents were used as supplied.

PMB 2,2,2-trichloroacetimidate[122,161] and di-*n*-butylboron triflate[162] were prepared according to literature methods, stored at –20°C under an atmosphere of dry nitrogen and freshly distilled prior to use. Dess-Martin Periodinane was prepared according to the literature method[163] and stored at –20°C under an atmosphere of dry nitrogen.

All reactions were magnetically stirred and were monitored by TLC using Macherey-Nagel Düren Alugram Sil G/UV_{254} pre-coated aluminium foil plates, layer thickness 0.25 mm. Compounds were visualised by UV, then with 20 wt. % PMA in ethanol.

Organic solutions were dried, where indicated, over sodium sulfate, and concentrated using a Büchi Rotavapor R-114 at ca. 30°C/20 mm Hg.

Flash chromatography was performed on Sorbisil silica gel 60 (40–60 mesh), Merck silica gel 60 (-230 mesh) or Florisil (-200 mesh) according to the general procedure of Still.[164]

Melting points were measured on a Griffin electrothermal apparatus and are uncorrected.

Optical rotations were recorded on an Optical Activity AA-100 polarimeter at ca. 20°C.

IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm^{-1}. Broad absorptions are designated (br). Weak absorptions are not reported.

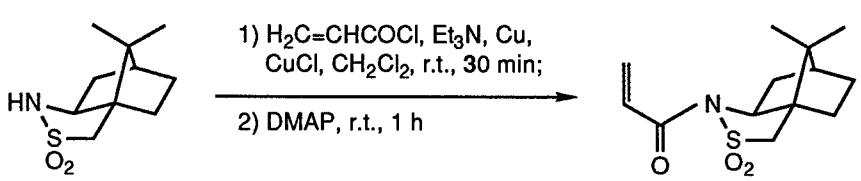
Proton NMR spectra were recorded on a Jeol JNX-GX-270 (270 MHz) or a Bruker AM 360 (360 MHz) spectrometer in either chloroform-*d* or benzene-d_6. Chemical shifts are reported as values in ppm relative to residual chloroform (δ = 7.27) or benzene (δ = 7.18). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad, (app) apparent.

Carbon-13 NMR spectra were recorded on a Jeol JNX-GX-270 (67.5 MHz) or a Bruker AM 300 (75 MHz) spectrometer in either chloroform-*d* (δ = 77.20) or benzene-d_6 (δ = 128.70). Chemical shifts are reported as values in ppm relative to the solvent. Multiplicities were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: (0) quarternary, (1) methine, (2) methylene, (3) methyl.

Mass spectra were recorded on a VG 70-250-SE spectrometer. Signals are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%).

8.2 Experimental Procedures for Chapter 3

N-Propenoyl-(2*S*)-bornane-10,2-sultam (2.5.3.1):

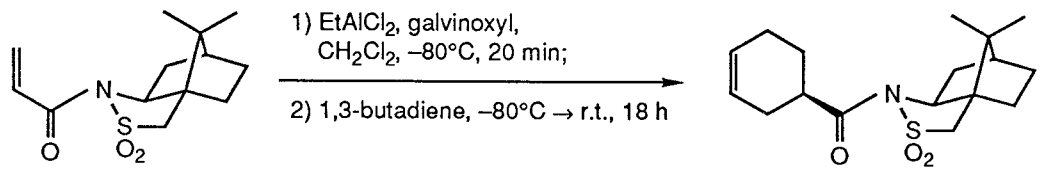


3.2.1.1 **2.5.3.1**

Acryloyl chloride (3.8 mL, 46.8 mmol, 2.0 eq.) was added dropwise to a slurry of (2*S*)-bornane-10,2-sultam (**3.2.1.1**) (5.00 g, 23.2 mmol), Et_3N (3.2 mL, 23.0 mmol, 1.0 eq.), copper powder (1.47 g, 23.1 mmol, 1.0 eq.) and CuCl (2.30 g, 23.2 mmol, 1.0 eq.) in CH_2Cl_2 (120 mL). The resulting mixture was stirred at r.t. for 30 min, then DMAP (850 mg, 6.96 mmol, 30%) was added and stirring was continued at r.t. for a further 1 h. The mixture was then diluted with CH_2Cl_2 (200 mL), washed with sat. $NaHCO_3$, filtered through celite, washed with brine, dried and concentrated. The residue was dissolved in $CHCl_3$ (100 mL), filtered through SiO_2 (eluting with $CHCl_3$), concentrated and crystallised

from $CHCl_3$ to yield **2.5.3.1** as white needles (5.40 g, 20.0 mmol, 86%): mp 192–194°C (lit.[73] 191–193°C); $[\alpha]_D$: +102° (*c* = 1.00, $CHCl_3$) [lit.[74] +102° (*c* = 1.17, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[73] values.

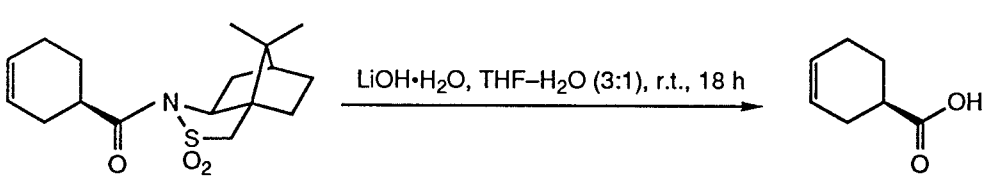
N-[(*R*)-Cyclohex-3-enecarbonyl]-(2*S*)-bornane-10,2-sultam (2.5.3.2):



2.5.3.1 **2.5.3.2**

A solution of **2.5.3.1** (5.39 g, 20.0 mmol) and galvinoxyl (253 mg, 0.600 mmol, 3%) in CH_2Cl_2 (50 mL) at –80°C was treated dropwise with a solution of $EtAlCl_2$ (3.2 mL, 30.4 mmol, 1.5 eq.) in CH_2Cl_2 (20 mL) and the resulting bright red mixture was stirred at –80°C for 20 min. 1,3-Butadiene (17 mL, 195 mmol, 10 eq.), previously condensed into a chilled (–80°C), graduated flask containing $LiAlH_4$ (ca. 1 g), was then added as a vapour *via* a cannula whose tip was submerged into the reaction mixture (the butadiene was thus added gradually over ca. 30 min by evaporation of the condensed gas as it warmed to r.t.). The mixture was stirred for 18 h as it warmed to r.t. and was then poured slowly into ice-cold H_2O (500 mL). The organic phase was separated from the resulting bright yellow mixture and was washed with brine. It was then dried, concentrated and crystallised from cyclohexane to afford **2.5.3.2** as white plates (5.66 g, 17.5 mmol, 88%): mp 142–144°C (lit.[72] 138–142°C); $[\alpha]_D$: +134° (*c* = 1.62, $CHCl_3$) [lit.[72] +136.3° (*c* = 1.68, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[72] values.

(*R*)-Cyclohex-3-enecarboxylic acid (2.5.3.3):

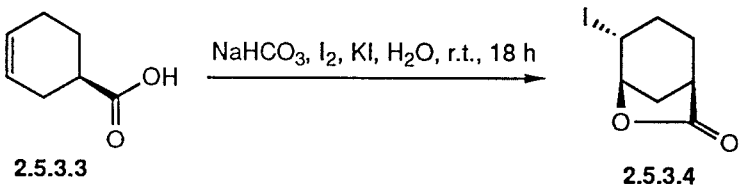


2.5.3.2 **2.5.3.3**

$LiOH{\bullet}H_2O$ (7.30 g, 174 mmol, 10 eq.) was added to a solution of **2.5.3.2** (5.64 g, 17.4 mmol) in THF–H_2O (3:1, 60 mL) and the resulting mixture was stirred at r.t. for 18 h. The suspension was then acidified (pH 1) with c. HCl, concentrated to a volume of approx. 50 mL and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (5 x 50 mL), dried, concentrated and crystallised from EtOH to afford (2*S*)-bornane-10,2-sultam (**3.2.1.1**) as white needles (3.25 g, 15.1 mmol, 87% recovery). The aq. washings were carefully acidified (pH 1) with c. HCl and extracted with CH_2Cl_2 (5 x 50 mL), then dried, concentrated and distilled to yield **2.5.3.3** as a colourless oil (1.87 g, 14.8

mmol, 85%): bp 85–87°C/0.2 mm Hg (lit.[72] 63.5–65°C/0.01 mm Hg); $[\alpha]_D$: +93.9° (*c* = 7.04, MeOH) [lit.[75] +94.5° (*c* = 7, MeOH)]. The product gave spectroscopic data in accord with lit.[72] values.

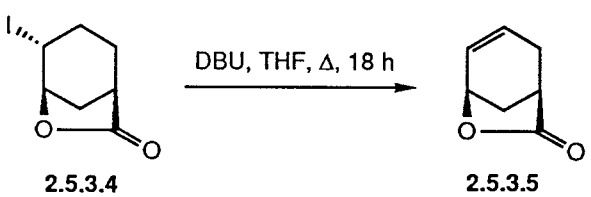
(1*R*,4*R*,5*R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (2.5.3.4):



2.5.3.3 **2.5.3.4**

A solution of I_2 (5.48 g, 21.6 mmol, 1.5 eq.) and KI (14.34 g, 86.4 mmol, 6.0 eq.) in H_2O (50 mL) was added dropwise to a solution of **2.5.3.3** (1.82 g, 14.4 mmol) and $NaHCO_3$ (3.63 g, 43.2 mmol, 3.0 eq.) in H_2O (100 mL). The resulting dark brown mixture was stirred at r.t. in the dark for 18 h, resulting in the formation of a pale yellow precipitate. The suspension was then filtered and the residue was washed with H_2O. It was subsequently dissolved in CH_2Cl_2 (200 mL), washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$ and brine, then dried, concentrated and crystallised from Et_2O–EtOH (3:1) to afford **2.5.3.4** as white needles (3.22 g, 12.8 mmol, 89%): mp 131–133°C (lit.[76] 135–136°C); $[\alpha]_D$: +40.4° (*c* = 3.04, $CHCl_3$) [lit.[76] +37.6° (*c* = 2.03, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[76] values.

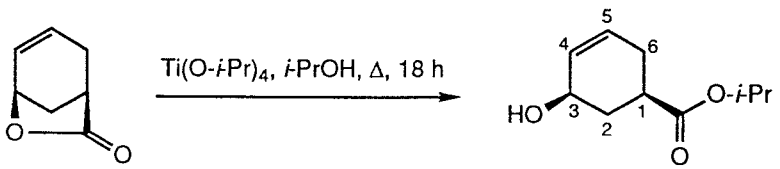
(1*R*,5*R*)-6-Oxabicyclo[3.2.1]oct-3-en-7-one (2.5.3.5):



2.5.3.4 **2.5.3.5**

A solution of **2.5.3.4** (3.21 g, 12.7 mmol) in THF (50 mL) was treated with DBU (2.3 mL, 15.4 mmol, 1.2 eq.), heated to reflux and stirred for 18 h, resulting in the formation of a white precipitate. The mixture was then cooled to 0°C, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (150 mL), washed with 2 M HCL and brine, then dried, concentrated and distilled to afford **2.5.3.5** as a low mp white solid (1.42 g, 11.4 mmol, 90%): bp 129–131°C/20 mm Hg (lit.[76] 63°C/0.1 mm Hg); $[\alpha]_D$: +191° (*c* = 2.35, $CHCl_3$) [lit.[76] +179.2° (*c* = 9.76, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[76] values.

Isopropyl (1*R*,3*R*)-3-Hydroxycyclohex-4-enecarboxylate (3.3.1.1):



2.5.3.5

3.3.1.1
$C_{10}H_{16}O_3$

To a solution of **2.5.3.5** (1.39 g, 11.2 mmol) in *i*-PrOH (50 mL) was added Ti(O-*i*-Pr)$_4$ (9.9 mL, 33.6 mmol, 3.0 eq.). The resulting mixture was heated to reflux and stirred for 18 h. It was then cooled to r.t. and poured into sat. NH_4Cl (150 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (Florisil, 30% Et_2O in petrol) to yield **3.3.1.1** as a colourless oil (2.00 g, 10.9 mmol, 97%):

$[\alpha]_D$: +5.2° (*c* = 7.87, $CHCl_3$).

IR (film): ν = 3408 (br), 3030, 2981, 2934, 2874, 1730, 1654, 1455, 1376, 1306, 1246, 1179, 1110, 1046, 986, 916, 827, 771, 698 cm^{-1}.

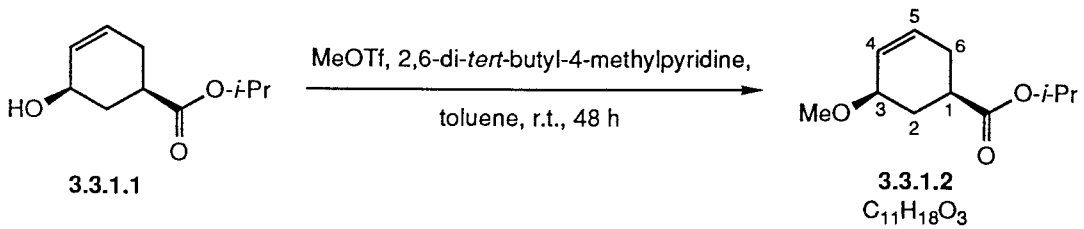
^1H NMR (270 MHz, $CDCl_3$): δ = 5.74 (2H, m, C4-H, C5-H), 5.00 (1H, septet, *J* = 6.4 Hz, isopropyl-CH), 4.28 (1H, m, C3-H), 2.65 (1H, ddt, *J* = 3.2, 10.6, 7.3 Hz, C1-H), 2.42 (1H, br d, *J* = 7.3 Hz, OH), 2.27 (3H, m, C2-H_{eq}, C6-H_2), 1.71 (1H, ddd, *J* = 7.9, 10.6, 12.9 Hz, C2-H_{ax}), 1.23 (3H, d, *J* = 6.4 Hz, isopropyl-Me), 1.22 (3H, d, *J* = 6.4 Hz, isopropyl-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.84 (0), 131.15 (1), 126.72 (1), 67.97 (1), 66.16 (1), 38.34 (1), 34.25 (2), 27.48 (2), 21.77 (3, 2C).

LRMS (CI mode, NH_3): *m/z* (%) = 202 [$(MNH_4)^+$, 10], 185 [$(MH)^+$, 14], 167 (100), 142 (5), 125 (7), 35 (5).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 202.1437. $C_{10}H_{16}O_3$ + NH_4 requires 202.1443.

Isopropyl (1*R*,3*R*)-3-Methoxycyclohex-4-enecarboxylate (3.3.1.2):



3.3.1.1 **3.3.1.2**
$C_{11}H_{18}O_3$

To a solution of **3.3.1.1** (1.85 g, 10.0 mmol) in toluene (20 mL) at r.t. was added 2,6-di-*tert*-butyl-4-methylpyridine (5.13 g, 25.0 mmol, 2.5 eq.) followed by MeOTf (2.3 mL, 20.3 mmol, 2.0 eq.). The resulting solution was stirred at r.t. for 48 h, by which time a white precipitate had developed. The suspension was concentrated and Et_2O (200 mL) was added. It was then filtered, washed with 2 M HCl, sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 10% Et_2O in petrol) to yield **3.3.1.2** as a colourless oil (1.50 g, 7.57 mmol, 76%):

$[\alpha]_D$: –20.6° (c = 1.98, $CHCl_3$).

IR (film): ν = 3033, 2980, 2934, 2821, 1732, 1653, 1454, 1375, 1305, 1270, 1249, 1177, 1146, 1107, 1062, 1007, 954, 923, 827, 773, 688 cm^{-1}.

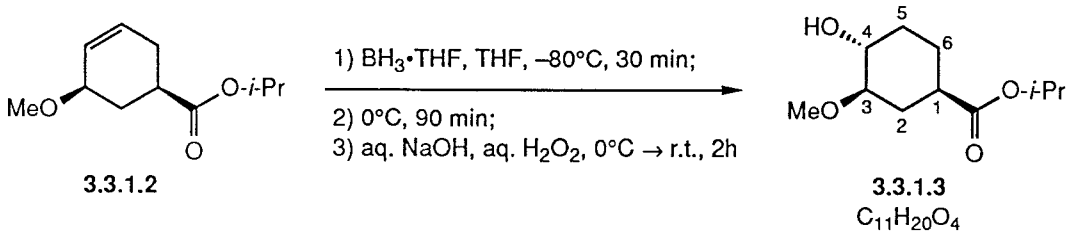
^1H NMR (270 MHz, $CDCl_3$): δ = 5.77 (2H, m, C4-H, C5-H), 5.02 (1H, septet, J = 6.4 Hz, isopropyl-CH), 3.94 (1H, m, C3-H), 3.38 (3H, s, OMe), 2.57 (1H, m, C1-H), 2.37 (1H, m), 2.25 (2H, m), 1.58 (1H, dt, J = 9.8, 12.5 Hz, C2-H_{ax}), 1.24 (6H, d, J = 6.4 Hz, isopropyl-Me_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.16 (0), 128.56 (1), 127.72 (1), 75.57 (1), 67.73 (1), 55.69 (3), 38.64 (1), 30.85 (2), 27.71 (2), 21.84 (3), 21.80 (3).

LRMS (CI mode, NH_3): m/z (%) = 216 [$(MNH_4)^+$, 4], 199 [$(MH)^+$, 98], 184 (3), 167 (100), 155 (6), 142 (2), 125 (6), 111 (14), 84 (2), 35 (15).

HRMS (CI mode, NH_3): found, $(MH)^+$, 199.1339. $C_{11}H_{18}O_3$ + H requires 199.1334.

Isopropyl (1*R*,3*R*,4*R*)-4-Hydroxy-3-methoxycyclohexanecarboxylate (3.3.1.3):



3.3.1.2 **3.3.1.3**
$C_{11}H_{20}O_4$

A solution of **3.3.1.2** (1.35 g, 6.81 mmol) in THF (20 mL) at –80°C was treated dropwise with BH_3•THF (10 mL of a 1.0 M solution in THF, 10 mmol, 1.5 eq.) and the resulting mixture was stirred at –80°C for 30 min. It was then warmed to 0°C and stirred for a further 90 min before being cautiously treated with H_2O (2 mL). 2 M NaOH (10 mL) and 30 wt. % aq. H_2O_2 (10 mL) were then added and stirring was continued for a further 2 h as the mixture warmed to r.t. It was then poured carefully into a 0°C solution of sat. $Na_2S_2O_3$ (100 mL). After stirring at 0°C for 15 min, sat. NH_4Cl (100 mL) was added and the mixture was extracted with CH_2Cl_2 (5 x 50 mL). The combined extracts were dried, concentrated and chromatographed (SiO_2, 60% Et_2O in petrol) to yield **3.3.1.3** as a colourless oil (1.10 g, 5.09 mmol, 75%):

$[\alpha]_D$: –67.5° (c = 1.36, $CHCl_3$).

IR (film): ν = 3444 (br), 2980, 2940, 2872, 2828, 1728, 1455, 1375, 1308, 1270, 1232, 1178, 1144, 1098, 1067, 1014, 963, 915, 853, 826 cm^{-1}.

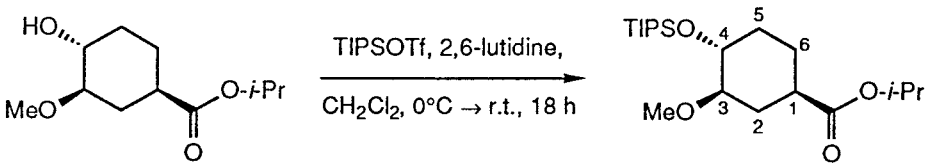
^1H NMR (270 MHz, $CDCl_3$): δ = 4.98 (1H, septet, J = 6.2 Hz, isopropyl-CH), 3.41 (1H, m, C4-H), 3.40 (3H, s, OMe), 2.98 (1H, ddd, J = 4.2, 8.7, 11.4 Hz, C3-H), 2.83 (1H, br s, OH), 2.38–2.23 (2H, m), 2.08–1.91 (2H, m), 1.54–1.26 (3H, m), 1.21 (6H, d, J = 6.2 Hz, isopropyl-Me_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.00 (0), 83.94 (1), 73.07 (1), 67.76 (1), 56.63 (3), 41.69 (1), 30.90 (2, 2C), 26.72 (2), 21.78 (3, 2C).

LRMS (CI mode, NH_3): m/z (%) = 234 [$(MNH_4)^+$, 1], 217 [$(MH)^+$, 100], 174 (2), 157 (2), 35 (39).

HRMS (CI mode, NH_3): found, $(MH)^+$, 217.1441. $C_{11}H_{20}O_4$ + H requires 217.1440.

Isopropyl (1*R*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexanecarboxylate (3.3.1.4):



3.3.1.3 **3.3.1.4**
$C_{20}H_{40}O_4Si$

To a solution of **3.3.1.3** (1.05 g, 4.85 mmol) and 2,6-lutidine (1.7 mL, 14.6 mmol, 3.0 eq.) in CH_2Cl_2 (20 mL) at 0°C was added TIPSOTf (2.8 mL, 9.67 mmol, 2.0 eq.) and the resulting solution was stirred as it warmed to r.t. over 18 h. It was then concentrated and the residue was dissolved in Et_2O (150 mL), washed with 2 M HCl, sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 10% Et_2O in petrol) to yield **3.3.1.4** as a colourless oil (1.41 g, 3.78 mmol, 78%):

$[\alpha]_D$: –37.7° (*c* = 2.53, $CHCl_3$).

IR (film): ν = 2943, 2867, 1730, 1465, 1375, 1309, 1273, 1249, 1178, 1109, 1070, 1050, 1015, 996, 966, 922, 883, 816, 765 cm^{-1}.

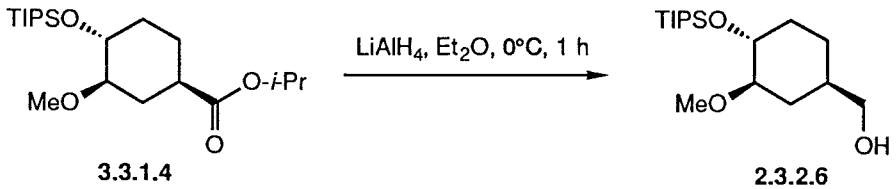
^1H NMR (270 MHz, $CDCl_3$): δ = 4.99 (1H, septet, *J* = 6.4 Hz, isopropyl-CH), 3.61 (1H, ddd, *J* = 4.3, 7.9, 9.5 Hz, C4-H), 3.38 (3H, s, OMe), 2.97 (1H, ddd, *J* = 4.0, 7.9, 10.3 Hz, C3-H), 2.27 (2H, m), 1.99 (1H, m), 1.88 (1H, m), 1.55–1.28 (3H, m), 1.22 (6H, d, *J* = 6.4 Hz, isopropyl-Me_2), 1.07 (21H, m, TIPS).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.22 (0), 83.54 (1), 73.82 (1), 67.47 (1), 57.32 (3), 41.06 (1), 32.64 (2), 31.40 (2), 26.07 (2), 21.80 (3, 2C), 18.12 (3, 6C), 12.61 (1, 3C).

LRMS (CI mode, NH_3): *m/z* (%) = 373 [$(MH)^+$, 100], 329 (11), 313 (4), 272 (4), 255 (5), 162 (5), 35 (5).

HRMS (CI mode, NH_3): found, $(MH)^+$, 373.2808. $C_{20}H_{40}O_4Si$ + H requires 373.2774.

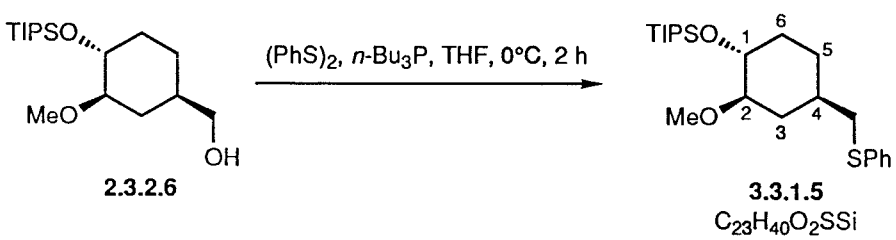
(1*R*,2*R*,4*R*)-4-(Hydroxymethyl)-2-methoxy-1-[(triisopropylsilyl)oxy]cyclohexane (2.3.2.6):



3.3.1.4 → 2.3.2.6

To a suspension of $LiAlH_4$ (129 mg, 3.40 mmol, 1.0 eq.) in Et_2O (10 mL) at 0°C was added slowly *via* cannula a solution of **3.3.1.4** (1.27 g, 3.40 mmol) in Et_2O (10 mL + 3 x 3 mL rinses). The resulting mixture was stirred at 0°C for 1 h, then quenched with H_2O (5 mL) and poured into 2 M NaOH (50 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 50% Et_2O in petrol) to yield **2.3.2.6** as a colourless oil (1.03 g, 3.25 mmol, 96%): $[\alpha]_D$: –34.9° (*c* = 0.72, $CHCl_3$) [lit.[31] –34.7° (*c* = 0.72, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[31] values.

(1*R*,2*R*,4*R*)-2-Methoxy-4-[(phenylthio)methyl]-1-[(triisopropylsilyl)oxy]cyclohexane (3.3.1.5):



2.3.2.6 → 3.3.1.5

$C_{23}H_{40}O_2SSi$

To a solution of **2.3.2.6** (3.96 g, 12.5 mmol) and $(PhS)_2$ (8.19 g, 37.5 mmol, 3.0 eq.) in THF (40 mL) at 0°C was added *n*-Bu_3P (9.3, 37.3 mmol, 3.0 eq.) and the resulting solution was stirred at 0°C for 2 h. It was then poured into H_2O (200 mL) and extracted with Et_2O (3 x 100 mL). The combined extracts were washed twice with 2 M NaOH and once with brine, then dried, concentrated and chromatographed (SiO_2, 2% Et_2O in petrol) to yield **3.3.1.5** as a colourless oil (4.85 g, 11.9 mmol, 95%):

$[\alpha]_D$: –25.3° (*c* = 2.08, $CHCl_3$).

IR (film): ν = 2938, 2864, 1585, 1480, 1464, 1439, 1383, 1244, 1197, 1115, 1069, 1036, 1025, 1014, 997, 920, 883, 812, 737, 688 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.30 (4H, m, Ph), 7.18 (1H, m, Ph), 3.58 (1H, ddd, *J* = 4.6, 8.2, 10.6 Hz, C1-H), 3.40 (3H, s, OMe), 2.94 (1H, ddd, *J* = 4.5, 8.2, 10.9 Hz, C2-

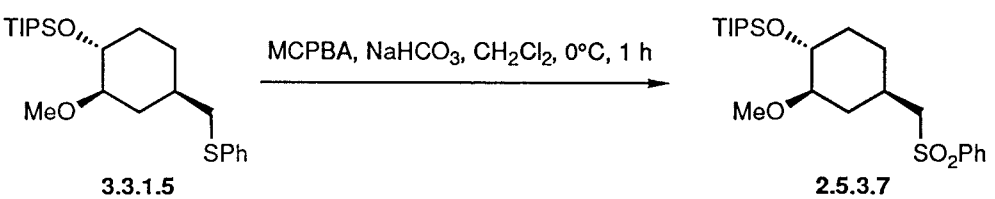
H), 2.86 (2H, d, J = 7.0 Hz, PhSCH_2), 2.27 (1H, m), 2.00–1.84 (2H, m), 1.70–1.54 (1H, m), 1.42–0.90 (3H, m), 1.08 (21H, m, TIPS).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 137.26 (0), 129.19 (1), 128.99 (1), 125.91 (1), 84.39 (1), 75.07 (1), 57.47 (3), 40.31 (2), 35.93 (1), 35.60 (2), 33.65 (2), 30.13 (2), 18.25 (3, 6C), 12.75 (1, 3C).

LRMS (CI mode, NH_3): m/z (%) = 409 [$(MH)^+$, 100], 377 (29), 365 (87), 235 (31), 203 (77), 162 (9), 145 (15), 123 (49), 93 (24).

HRMS (EI mode, 70 eV): found, $M^{+\bullet}$, 408.2539. $C_{23}H_{40}O_2SSi$ requires 408.2518.

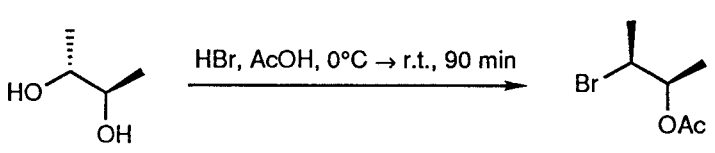
(1*R*,2*R*,4*R*)-2-Methoxy-4-[(phenylsulfonyl)methyl]-1-[(triisopropylsilyl)oxy]cyclohexane (2.5.3.7):



3.3.1.5 2.5.3.7

A suspension of **3.3.1.5** (4.85 g, 11.9 mmol) and $NaHCO_3$ (4.00 g, 47.6 mmol, 4.0 eq.) in CH_2Cl_2 (125 mL) at 0°C was treated with 71% MCPBA (7.23 g, 29.7 mmol, 2.5 eq.) and the resulting mixture was stirred at 0°C for 1 h. It was then poured into sat. $Na_2S_2O_3$ (200 mL), the organic phase was separated, and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase and extracts were then washed with sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 40% Et_2O in petrol) to yield **2.5.3.7** as a colourless oil (5.19 g, 11.8 mmol, 99%): $[\alpha]_D$: –25.9° (c = 2.24, $CHCl_3$) [lit.[58] –12.4° (c = 0.37, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[58] values.

(2*R*,3*S*)-2-Acetoxy-3-bromobutane (3.4.1.2):

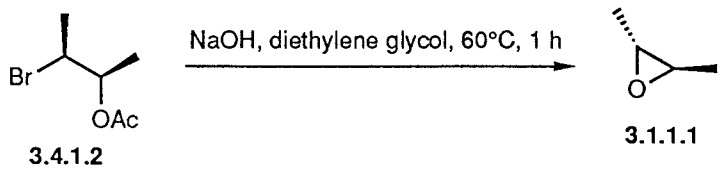


3.4.1.1 3.4.1.2

HBr (99 mL of a 30 wt. % solution in AcOH, 497 mmol, 3.0 eq.) was added over 30 min to neat (2*R*,3*R*)-2,3-butanediol (**3.4.1.1**) (14.93 g, 166 mmol) at 0°C. The resulting orange mixture was stirred at r.t. for 1 h, then treated with H_2O (300 mL) and neutralised carefully with solid Na_2CO_3. The resulting solution was extracted with Et_2O (5 x 100 mL), then the

extracts were dried and concentrated to yield crude **3.4.1.2** as a pale yellow oil which was used without further purification.

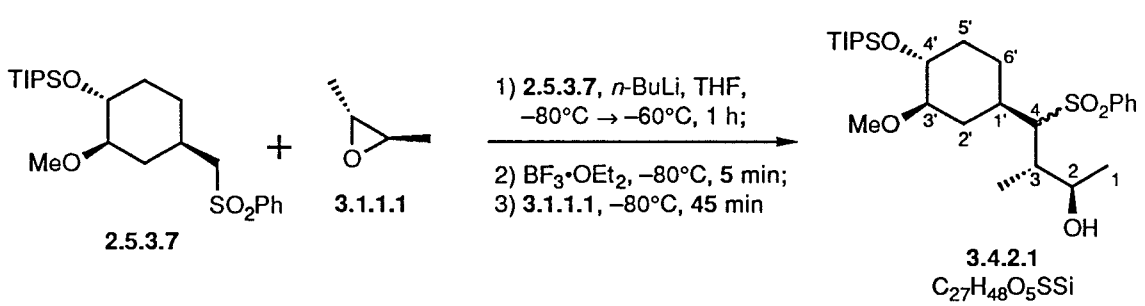
(2*R*,3*R*)-2,3-Epoxybutane (3.1.1.1):



3.4.1.2 3.1.1.1

To a stirred solution of crude **3.4.1.2** (166 mmol) in diethylene glycol (200 mL) was added ground NaOH (13.28 g, 332 mmol, 2.0 eq.). The reaction flask was immediately evacuated to 20 mm Hg, heated to 60°C, and the distillate collected in a cold (–80°C) trap connected to the reaction flask by plastic tubing. Stirring was continued at 60°C for 1 h, then the vacuum was released and the cold distillate was treated with CaH_2 (ca. 5 g) and allowed to warm slowly until effervescence commenced. The trap was then recooled to –80°C and the cycle of warming–effervescence–recooling repeated until all gas evolution had ceased. The suspension was then distilled to yield **3.1.1.1** as a volatile colourless oil (6.67 g, 92.5 mmol, 56%): bp 55°C (lit.[82] 52-55°C); $[\alpha]_D$: +60.7° (*c* = 1.87, Et_2O) [lit.[82] +55.4° (*c* = 1.9, Et_2O)]. The product gave spectroscopic data in accord with lit.[82] values.

(2*R*,3*S*,4*RS*)-4-[(1*R*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3-methyl-4-(phenylsulfonyl)butan-2-ol (3.4.2.1):



2.5.3.7 3.1.1.1 3.4.2.1
$C_{27}H_{48}O_5SSi$

A solution of **2.5.3.7** (5.18 g, 11.8 mmol) in THF (50 mL) at –80°C was treated dropwise with *n*-BuLi (11.6 mL of a 1.53 M solution in hexanes, 17.7 mmol, 1.5 eq.) and stirred for 1 h as it warmed to –60°C. The bright yellow solution was then recooled to –80°C and treated with BF_3•OEt_2 (1.6 mL, 13.0 mmol, 1.1 eq.). After stirring at –80°C for 5 min, **3.1.1.1** (1.2 mL, 13.4 mmol, 1.1 eq.) was added and stirring was continued at –80°C for a further 45 min. The mixture was then quenched with sat. $NaHCO_3$ (10 mL) and allowed to warm to r.t. It was then poured into sat. $NaHCO_3$ (100 mL) and extracted with Et_2O (3 x 100 mL). The combined extracts were dried, concentrated and chromatographed (SiO_2, 70%

Et_2O in petrol) to yield **3.4.2.1** as a white foam (5.14 g, 10.0 mmol, 85%, 72:28 mixture of diastereomers):

$[\alpha]_D$: –18.9° (c = 2.75, $CHCl_3$).

IR (film): ν = 3493 (br), 2942, 2865, 1463, 1447, 1383, 1303, 1244, 1190, 1144, 1083, 998, 917, 883, 815, 730, 688, 620 cm^{-1}.

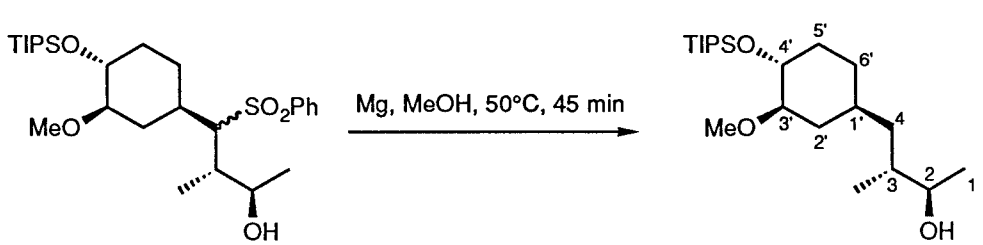
^1H NMR (270 MHz, $CDCl_3$): δ = 7.89 (2H, m, Ph), 7.68–7.54 (3H, m, Ph), 3.93 (1H, m, C2-H), 3.57–3.39 (1H, m, C4'-H), 3.43/3.33 (3H, s, *minor/major* OMe), 3.15/3.08 (1H, br s, *major/minor* C4-H), 2.88–2.63 (1H, m, C3'-H), 2.18–1.50 (6H, m), 1.40/1.20 (3H, d, J = 7.3 Hz, *minor/major* C1-H_3), 1.32–0.81 (3H, m), 1.25/1.03 (3H, d, J = 6.4 Hz, *minor/major* C3-Me), 1.05 (21H, m, TIPS).

^{13}C NMR (67.5 MHz, $CDCl_3$): *major* diastereomer; δ = 139.83 (0), 133.58 (1), 129.22 (1, 2C), 128.43 (1, 2C), 85.05 (1), 74.67 (1), 72.06 (1), 69.31 (1), 57.23 (3), 39.35 (1), 35.75 (1), 34.67 (2), 33.52 (2), 30.10 (2), 20.82 (3), 18.15 (3, 6C), 12.64 (1, 3C), 11.49 (3): *minor* diastereomer; δ = 139.70 (0), 133.83 (1), 129.44 (1, 2C), 128.30 (1, 2C), 84.66 (1), 74.59 (1), 72.06 (1), 69.77 (1), 57.58 (3), 39.02 (1), 36.24 (1), 33.82 (2), 30.61 (2), 29.77 (2), 21.61 (3), 18.15 (3, 6C), 12.64 (1, 3C), 10.69 (3).

LRMS (CI mode, NH_3): m/z (%) = 530 [$(MNH_4)^+$, 3], 513 [$(MH)^+$, 92], 481 (39), 469 (44), 307 (28), 283 (17), 255 (34), 165 (100), 147 (52), 121 (89), 93 (14).

HRMS (CI mode, NH_3): found, $(MH)^+$, 513.3019. $C_{27}H_{48}O_5SSi$ + H requires 513.3070.

(2*R*,3*R*)-4-[(1*S*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3-methylbutan-2-ol (3.4.2.2):



3.4.2.1 **3.4.2.2**
$C_{21}H_{44}O_3Si$

A mixture of magnesium turnings (3.65 g, 150 mmol, 15 eq.) and MeOH (50 mL) was heated to 50°C, at which point hydrogen evolution commenced. A solution of **3.4.2.1** (5.14 g, 10.0 mmol) in MeOH (30 mL + 3 x 5 mL rinses) was then added *via* cannula and stirring was continued without external heating for 45 min. The cloudy mixture was then

decanted into 2 M HCl (200 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The combined extracts were washed with sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 30% Et_2O in petrol) to yield **3.4.2.2** as a colourless oil (3.28 g, 8.80 mmol, 88%):

$[\alpha]_D$: –18.6° (c = 1.23, $CHCl_3$).

IR (film): ν = 3383 (br), 2925, 2861, 1463, 1382, 1328, 1285, 1256, 1190, 1115, 1069, 1014, 998, 921, 883, 813, 679 cm^{-1}.

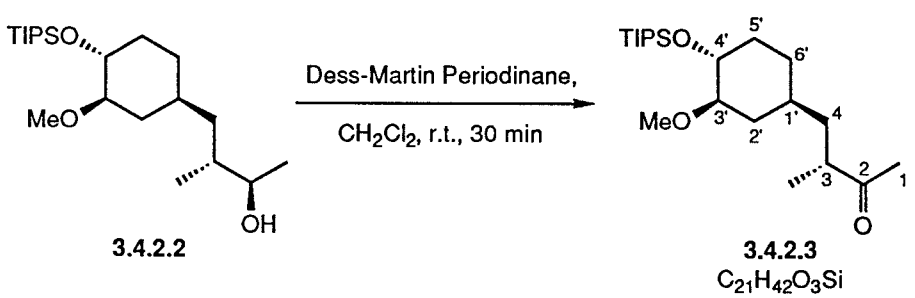
^1H NMR (270 MHz, $CDCl_3$): δ = 3.67 (1H, dq, J = 4.3, 6.4 Hz, C2-H), 3.54 (1H, ddd, J = 4.8, 8.4, 10.8 Hz, C4'-H), 3.40 (3H, s, OMe), 2.91 (1H, ddd, J = 4.5, 8.4, 11.2 Hz, C3'-H), 2.09 (1H, m), 1.92 (1H, m), 1.66–1.47 (3H, m), 1.46–0.67 (6H, m), 1.14 (3H, d, J = 6.4 Hz, C1-H_3), 1.07 (21H, m, TIPS), 0.87 (3H, d, J = 6.8 Hz, C3-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 85.02 (1), 75.70 (1), 71.50 (1), 57.71 (3), 39.79 (2), 37.01 (1), 36.12 (2), 34.42 (2), 33.43 (1), 32.00 (2), 20.57 (3), 18.28 (3, 6C), 14.38 (3), 12.83 (1, 3C).

LRMS (CI mode, NH_3): m/z (%) = 390 [$(MNH_4)^+$, 2], 373 [$(MH)^+$, 100], 341 (12), 329 (8), 167 (7), 149 (9), 35 (20).

HRMS (CI mode, NH_3): found, $(MH)^+$, 373.3157. $C_{21}H_{44}O_3Si$ + H requires 373.3138.

(*R*)-4-[(1*S*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3-methylbutan-2-one (3.4.2.3):



3.4.2.2 **3.4.2.3**
$C_{21}H_{42}O_3Si$

To a solution of **3.4.2.2** (3.21 g, 8.61 mmol) in CH_2Cl_2 (60 mL) was added Dess-Martin Periodinane (5.48 g, 12.9 mmol, 1.5 eq.) and the resulting cloudy white solution was stirred at r.t. for 30 min. It was then diluted with Et_2O (100 mL) and shaken with a 1:1 solution of sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ (100 mL). The organic phase was then separated, washed with sat. $NaHCO_3$ and brine, then dried, concentrated and

chromatographed (SiO_2, 15% Et_2O in petrol) to yield **3.4.2.3** as a colourless oil (3.06 g, 8.26 mmol, 96%):

$[\alpha]_D$: –44.4° (c = 1.40, $CHCl_3$).

IR (film): ν = 2936, 2866, 1716, 1462, 1382, 1357, 1244, 1190, 1145, 1114, 1070, 1014, 997, 920, 883, 812, 679 cm^{-1}.

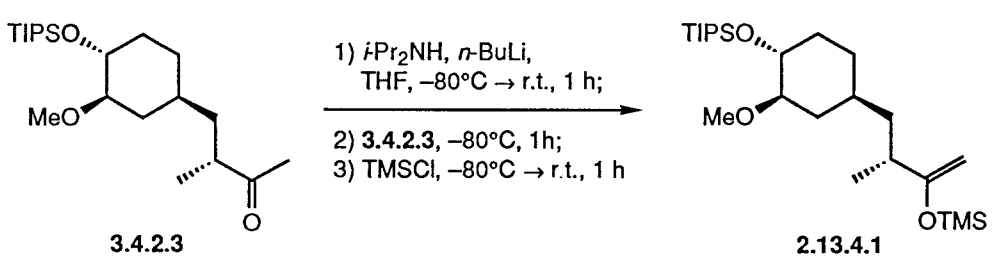
^1H NMR (270 MHz, $CDCl_3$): δ = 3.52 (1H, ddd, J = 4.8, 8.3, 11.0 Hz, C4'-H), 3.39 (3H, s, OMe), 2.90 (1H, ddd, J = 4.6, 8.3, 11.2 Hz, C3'-H), 2.60 (1H, sextet, J = 7.1 Hz, C3-H), 2.13 (3H, s, C1-H_3), 2.03 (1H, m), 1.91 (1H, m), 1.70–1.54 (2H, m), 1.38–0.73 (5H, m), 1.07 (3H, d, J = 7.1 Hz, C3-Me), 1.06 (21H, m, TIPS).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 212.36 (0), 84.60 (1), 75.37 (1), 57.50 (3), 44.69 (1), 39.59 (2), 36.37 (2), 34.06 (2), 33.65 (1), 30.92 (2), 27.93 (3), 18.15 (3, 6C), 16.79 (3), 12.67 (1, 3C).

LRMS (CI mode, NH_3): m/z (%) = 388 [$(MNH_4)^+$, 10], 371 [$(MH)^+$, 100], 339 (8), 327 (6), 165 (11), 35 (46).

HRMS (CI mode, NH_3): found, $(MH)^+$, 371.3002. $C_{21}H_{42}O_3Si$ + H requires 371.2981.

(*R*)-4-[(1*S*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3-methyl-2-[(trimethylsilyl)oxy]but-1-ene (2.13.4.1):

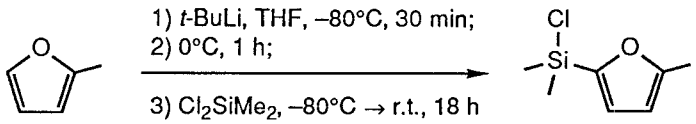


3.4.2.3 **2.13.4.1**

A solution of i-Pr_2NH (1.8 mL, 12.8 mmol, 2.0 eq.) in THF (30 mL) at –80°C was treated with n-BuLi (6.3 mL of a 1.53 M solution in hexanes, 9.64 mmol, 1.5 eq.) and the resulting mixture was stirred as it warmed to r.t. over 1 h. It was then recooled to –80°C and **3.4.2.3** (2.37 g, 6.39 mmol) in THF (10 mL + 3 x 3 mL rinses) was added dropwise *via* cannula. The solution was stirred at –80°C for 1 h, then TMSCl (2.4 mL, 18.9 mmol, 3.0 eq.) was added and stirring was continued for a further 1 h as the mixture warmed to r.t. The solution was then poured into sat. $NaHCO_3$ (100 mL) and diluted with Et_2O (200 mL). The organic phase was separated, washed with sat. $NaHCO_3$ and brine, then dried and concentrated to yield crude **2.13.4.1** as a pale yellow oil which was used without further purification.

8.3 Experimental Procedures for Chapter 4

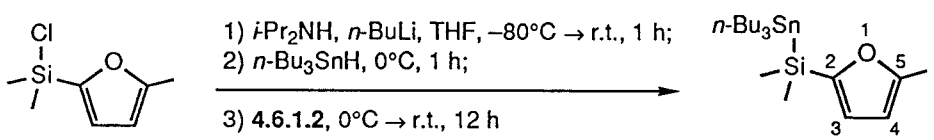
Chlorodimethyl(5-methyl-2-furyl)silane (4.6.1.2):



4.6.1.1 4.6.1.2

A solution of 2-methylfuran (**4.6.1.1**) (30 mL, 333 mmol) in THF (100 mL) at –80°C was treated with *t*-BuLi (200 mL of a 1.67 M solution in pentane, 334 mmol, 1.0 eq.) dropwise and the resulting bright yellow suspension was stirred at –80°C for 30 min. It was then warmed to 0°C and stirred for a further 1 h, then added dropwise *via* cannula to a mixture of Cl_2SiMe_2 (400 mL, 3.30 mol, 10 eq.) and THF (50 mL) at –80°C. The resulting white suspension was stirred for 18 h as it warmed slowly to r.t. It was then concentrated and petrol (300 mL) was added. The slurry was filtered through celite, concentrated and distilled to yield **4.6.1.2** as a colourless oil (36.65 g, 210 mmol, 63%): bp 74–77°C/20 mm Hg (lit.[126] 80–84°C/21 mm Hg). The product gave spectroscopic data in accord with lit.[126] values.

[Dimethyl(5-methyl-2-furyl)silyl]tri-*n*-butylstannane (4.6.1.3):



4.6.1.2

4.6.1.3
$C_{19}H_{38}OSiSn$

A solution of *i*-Pr_2NH (25 mL, 178 mmol, 1.2 eq.) in THF (200 mL) at –80°C was treated with *n*-BuLi (109 mL of a 1.50 M solution in hexanes, 164 mmol, 1.1 eq.) and the resulting solution was stirred as it warmed to r.t. over 1 h. It was then cooled to 0°C and *n*-Bu_3SnH (40 mL, 149 mmol) was added dropwise. The solution was stirred at 0°C for 1 h, then **4.6.1.2** (31.24 g, 179 mmol, 1.2 eq.) in THF (30 mL + 3 x 5 mL rinses) was added, and stirring was continued for a further 12 h as the mixture warmed slowly to r.t. The resulting white suspension was then concentrated, Et_2O (300 mL) was added, and the slurry was filtered through celite, concentrated and distilled to yield **4.6.1.3** as a colourless oil (49.80 g, 116 mmol, 78%): bp 113°C/0.2 mm Hg;

IR (film): ν = 2956, 2924, 2872, 2854, 1593, 1491, 1484, 1376, 1244, 1216, 1186, 1070, 1017, 957, 922, 835, 804, 782, 652 cm^{-1}.

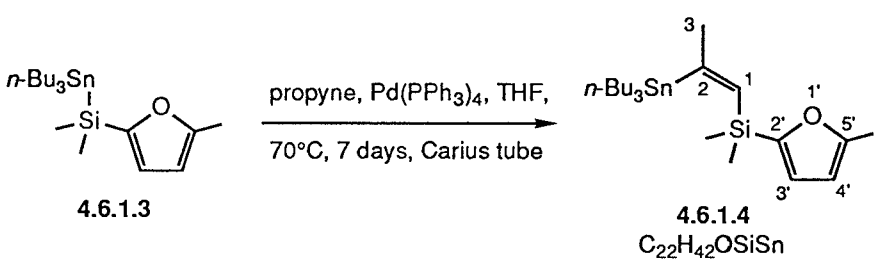
^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.47 (1H, dm, J = 3.1 Hz, C4-H), 5.97 (1H, dq, J = 3.1, 1.0 Hz, C3-H), 2.32 (3H, m, C5-Me), 1.45 [6H, m, $Sn(CH_2CH_2CH_2Me)_3$], 1.28 [6H, sextet, J = 7.0 Hz, $Sn(CH_2CH_2CH_2Me)_3$], 0.89 [15H, m, $Sn(CH_2CH_2CH_2Me)_3$], 0.46 (6H, s, $J_{Sn,H}$ = 24.5, 23.4 Hz, $SiMe_2$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 158.49 (0), 156.79 (0), 121.03 (1), 106.08 (1), 30.29 (2, 3C, $J_{Sn,C}$ = 17.6 Hz), 27.71 (2, 3C, $J_{Sn,C}$ = 49.9 Hz), 13.91 (3, 3C), 13.86 (3), 8.45 (2, 3C, $J_{Sn,C}$ = 263, 251 Hz), –0.58 (3, 2C, $J_{Sn,C}$ = 46.0 Hz).

LRMS (CI mode, NH_3): *m/z* (%) = 431* [$(MH)^+$, 37), 390* (46), 366* (95), 349* (35), 334* (15), 308* (27), 261* (11), 199 (15), 156 (100), 132 (38), 91 (20), 76 (41), 35 (30); Sn isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing ^{120}Sn).

HRMS (CI mode, NH_3): found, $(MH)^+$, 431.1796. $C_{19}H_{38}OSiSn$ + H requires 431.1792.

(Z)-1-[Dimethyl(5-methyl-2-furyl)silyl]-2-(tri-*n*-butylstannyl)prop-1-ene (4.6.1.4):



4.6.1.3 **4.6.1.4**
$C_{22}H_{42}OSiSn$

A Carius tube fitted with a Young tap was charged with **4.6.1.3** (49.80 g, 116 mmol), $Pd(PPh_3)_4$ (2.68 g, 2.32 mmol, 2%) and THF (25 mL), then cooled to –80°C. Propyne (33 mL, 581 mmol, 5.0 eq.), previously condensed into a chilled (–80°C), graduated flask containing THF (17 mL), was added to this mixture *via* cannula. The tap was then closed and the tube was warmed to 70°C. The resulting yellow solution was shielded from light and stirred for 7 days. It was then allowed to cool to r.t. and concentrated. Petrol (300 mL) was added and the resulting orange slurry was filtered through celite, concentrated and chromatographed (SiO_2, petrol) to yield **4.6.1.4** as a bright yellow oil (52.54 g, 112 mmol, 97%):

IR (film): ν = 2956, 2924, 2855, 1594, 1565, 1496, 1464, 1376, 1248, 1217, 1186, 1069, 1017, 984, 958, 923, 828, 782, 670 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.54 (1H, app d, J = 3.1 Hz, C4'-H), 6.53 (1H, q, J = 1.7 Hz, $J_{Sn,H}$ = 173, 165 Hz, C1-H), 5.97 (1H, dq, J = 3.1, 1.0 Hz, C3'-H), 2.34 (3H,

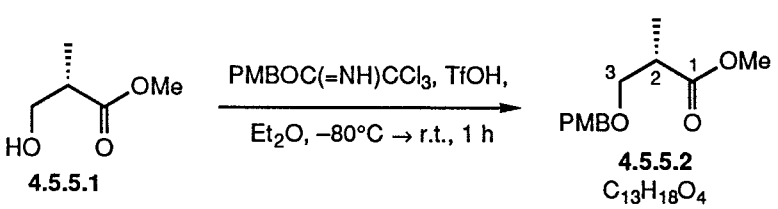
m, C5'-Me), 2.15 (3H, d, J = 1.7 Hz, $J_{Sn,H}$ = 39.4, 37.6 Hz, C3-H_3), 1.44 [6H, m, $Sn(CH_2CH_2CH_2Me)_3$], 1.30 [6H, sextet, J = 7.0 Hz, $Sn(CH_2CH_2CH_2Me)_3$], 0.88 [15H, m, $Sn(CH_2CH_2CH_2Me)_3$], 0.33 (6H, s, $SiMe_2$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 164.4 (0, $J_{Sn,C}$ = 386, 370 Hz), 157.50 (0), 156.71 (0), 140.81 (1, $J_{Sn,C}$ = 59.7 Hz), 122.15 (1), 106.10 (1), 35.00 (3, $J_{Sn,C}$ = 56.7 Hz), 29.41 (2, 3C, $J_{Sn,C}$ = 18.6 Hz), 27.67 (2, 3C, $J_{Sn,C}$ = 59.7 Hz), 13.85 (3, 4C), 10.87 (2, 3C, $J_{Sn,C}$ = 325, 310 Hz), –0.91 (3, 2C).

LRMS (CI mode, NH_3): m/z (%) = 471* [$(MH)^+$, 2], 413* (58), 389* (45), 308* (100), 291* (24), 181 (45), 156 (22), 116 (66), 35 (32); Sn isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing ^{120}Sn).

HRMS (CI mode, NH_3): found, $(MH)^+$, 471.2085. $C_{22}H_{42}OSiSn$ + H requires 471.2105.

Methyl (*S*)-3-[(4-Methoxybenzyl)oxy]-2-methylpropionate (4.5.5.2):



4.5.5.1 **4.5.5.2**
$C_{13}H_{18}O_4$

A solution of methyl (*S*)-3-hydroxy-2-methylpropionate (**4.5.5.1**) (14.36 g, 130 mmol) and PMB 2,2,2-trichloroacetimidate (36.73 g, 130 mmol, 1.0 eq.) in Et_2O (200 mL) at –80°C was treated with TfOH (0.04 mL, 0.452 mmol, 0.3%) and the resulting solution was stirred as it warmed to r.t. over 1 h. It was then poured carefully into sat. $NaHCO_3$ (200 mL) and the organic phase was separated. The aq. phase was extracted with CH_2Cl_2 (3 x 200 mL), then the combined organic phase and extracts were concentrated. Petrol (200 mL) was added to the resulting white slurry, which was filtered, dried, concentrated, chromatographed (SiO_2, 15% Et_2O in petrol) and distilled to yield **4.5.5.2** as a colourless oil (20.65 g, 86.7 mmol, 67%): bp 116–118°C/0.2 mm Hg;

$[\alpha]_D$: +7.8° (c = 1.60, $CHCl_3$).

IR (film): ν = 2951, 2906, 2860, 1739, 1612, 1586, 1513, 1459, 1363, 1302, 1248, 1201, 1090, 1035, 820 cm^{-1}.

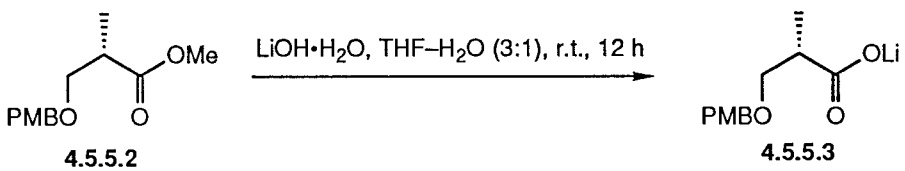
^1H NMR (270 MHz, $CDCl_3$): δ = 7.24 (2H, dm, J = 8.7 Hz, Ar), 6.88 (2H, dm, J = 8.7 Hz, Ar), 4.46 (2H, s, $ArCH_2$), 3.81 (3H, s, $ArOMe$), 3.70 (3H, s, CO_2Me), 3.63 and 3.46

(2H, A and B of ABX, J_{AB} = 9.1 Hz, J_{AX} = 7.2 Hz, J_{BX} = 5.9 Hz, C3-H_2), 2.78 (1H, d quintet, J = 5.9, 7.2 Hz, C2-H), 1.17 (3H, d, J = 7.2 Hz, C2-Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.52 (0), 159.35 (0), 130.40 (0), 129.36 (1, 2C), 113.91 (1, 2C), 72.92 (2), 71.81 (2), 55.42 (3), 51.87 (3), 40.33 (1), 14.16 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 256 [$(MNH_4)^+$, 21], 154 (14), 138 (36), 121 (100), 35 (39).

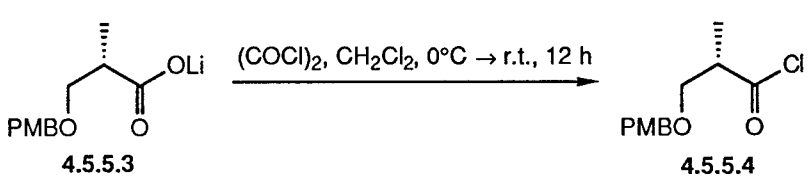
Lithium (*S*)-3-[(4-Methoxybenzyl)oxy]-2-methylpropionate (4.5.5.3):



4.5.5.2 4.5.5.3

To a solution of **4.5.5.2** (3.07 g, 12.9 mmol) in THF–H_2O (3:1, 40 mL) was added LiOH•H_2O (491 mg, 11.7 mmol, 0.9 eq.) and the resulting solution was stirred at r.t. for 12 h. It was then concentrated to a volume of ca. 10 mL and Et_2O (100 mL) was added. The aq. phase was separated and the organic phase was extracted with H_2O (3 x 50 mL). The combined aq. phase and extracts were then concentrated at 70°C/20 mm Hg and the residue was transferred to a drying pistol containing P_2O_5. After drying at 50°C/0.2 mm Hg for 18 h, crude **4.5.5.3** was obtained as a white solid which was used without further purification.

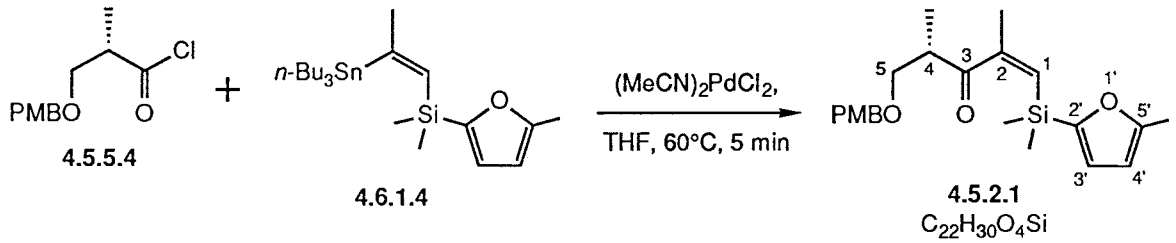
(*S*)-3-[(4-Methoxybenzyl)oxy]-2-methylpropionyl Chloride (4.5.5.4):



4.5.5.3 4.5.5.4

A solution of crude **4.5.5.3** (11.7 mmol) in CH_2Cl_2 (250 mL) at 0°C was treated dropwise with $(COCl)_2$ (1.3 mL, 14.9 mmol, 1.3 eq.) and stirred for 12 h as it warmed slowly to r.t. The resulting white suspension was then concentrated, petrol (100 mL) was added, and the slurry was filtered through celite and concentrated to afford crude **4.5.5.4** as a pale yellow oil which was used without further purification.

(*S*)-(*Z*)-1-[Dimethyl(5-methyl-2-furyl)silyl]-5-[(4-methoxybenzyl)oxy]-2,4-dimethylpent-1-en-3-one (4.5.2.1):



To a mixture of crude **4.5.5.4** (11.7 mmol), **4.6.1.4** (5.49 g, 11.7 mmol) and THF (5 mL) at r.t. was added $(MeCN)_2PdCl_2$ (152 mg, 0.586 mmol, 5%). The resulting yellow solution was warmed to 60°C and stirred for 5 min, by which time a thick black precipitate had developed. The mixture was then allowed to cool to r.t., diluted with Et_2O (200 mL), filtered through celite and shaken vigorously with half-sat. aq. KF (200 mL), resulting in the formation of a white precipitate. The organic phase was then separated, filtered through celite, washed with H_2O and brine, then dried, concentrated and chromatographed (Florisil, 5% Et_2O in petrol) to yield **4.5.2.1** as pale yellow oil (2.18 g, 5.64 mmol, 48%):

$[\alpha]_D$: +29.0° (c = 1.33, $CHCl_3$).

IR (film): ν = 2956, 2858, 1685, 1613, 1587, 1514, 1453, 1363, 1303, 1248, 1173, 1100, 1037, 1018, 956, 921, 846, 821, 784 cm^{-1}.

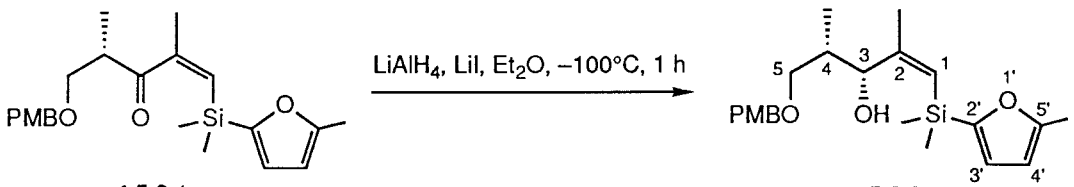
^1H NMR (270 MHz, C_6D_6): δ = 7.18 (2H, dm, J = 8.7 Hz, Ar), 6.80 (2H, dm, J = 8.7 Hz, Ar), 6.72 (1H, app d, J = 3.1 Hz, C4'-H), 6.27 (1H, q, J = 1.5 Hz, C1-H), 5.95 (1H, dq, J = 3.1, 1.0 Hz, C3'-H), 4.29 and 4.24 (2H, AB q, J_{AB} = 11.7 Hz, ArCH_2), 3.63 and 3.26 (2H, A and B of ABX, J_{AB} = 8.7 Hz, J_{AX} = 7.7 Hz, J_{BX} = 5.8 Hz, C5-H_2), 3.30 (3H, s, OMe), 3.08 (1H, m, C4-H), 2.15 (3H, m, C5'-Me), 1.84 (3H, d, J = 1.5 Hz, C2-Me), 0.90 (3H, d, J = 7.0 Hz, C4-Me), 0.70 (3H, s, SiMe), 0.67 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 205.49 (0), 160.68 (0), 160.41 (0), 156.83 (0), 151.62 (0), 142.13 (1), 131.48 (0), 130.07 (1, 2C), 122.01 (1), 114.73 (1, 2C), 106.99 (1), 73.83 (2), 73.21 (2), 55.44 (3), 42.84 (1), 23.41 (3), 14.45 (3), 14.36 (3), –1.29 (3), –1.55 (3).

LRMS (CI mode, NH_3): m/z (%) = 404 [$(MNH_4)^+$, 4], 387 [$(MH)^+$, 21], 305 (100), 202 (26), 185 (72), 169 (16), 154 (10), 137 (14), 121 (79), 35 (66).

HRMS (CI mode, NH_3): found, $(MH)^+$, 387.2030. $C_{22}H_{30}O_4Si$ + H requires 387.1992.

(3*R*,4*S*)-(*Z*)-1-[Dimethyl(5-methyl-2-furyl)silyl]-5-[(4-methoxybenzyl)oxy]-2,4-dimethylpent-1-en-3-ol (4.5.2.2):



4.5.2.1

4.5.2.2
$C_{22}H_{32}O_4Si$

A solution of **4.5.2.1** (11.21 g, 29.0 mmol) and LiI (19.41 g, 145 mmol, 5.0 eq.) in Et_2O (500 mL) at –100°C was treated with $LiAlH_4$ (73 mL of a 2.0 M solution in Et_2O, 146 mmol, 5.0 eq.) dropwise. The resulting mixture was stirred at –100°C for 1 h, then carefully treated with 2 M NaOH (50 mL) and allowed to warm to r.t. The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 20% Et_2O in petrol) to yield **4.5.2.2** as a colourless oil (9.36 g, 24.1 mmol, 83%):

$[\alpha]_D$: +5.2° (c = 1.45, $CHCl_3$).

IR (film): ν = 3463 (br), 2958, 2922, 2860, 1614, 1514, 1443, 1363, 1302, 1249, 1215, 1174, 1097, 1036, 1018, 956, 921, 845, 786 cm^{-1}.

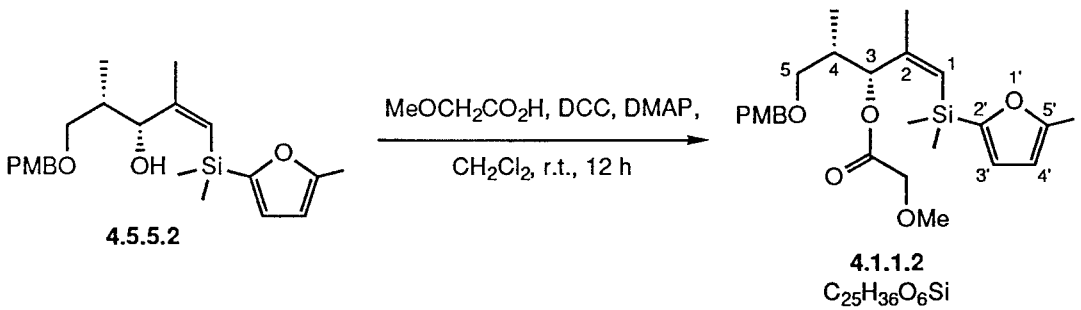
^1H NMR (270 MHz, C_6D_6): δ = 7.18 (2H, dm, J = 8.7 Hz, Ar), 6.81 (2H, dm, J = 8.7 Hz, Ar), 6.64 (1H, app d, J = 3.1 Hz, C4'-H), 5.90 (1H, dq, J = 3.1, 1.0 Hz, C3'-H), 5.70 (1H, quintet, J = 1.2 Hz, C1-H), 4.38 (1H, br t, J = 3.1 Hz, C3-H), 4.25 (2H, s, ArCH_2), 3.31 (3H, s, OMe), 3.29 and 3.22 (2H, A and B of ABX, J_{AB} = 9.0 Hz, J_{AX} = 5.4 Hz, J_{BX} = 5.3 Hz, C5-H_2), 2.49 (1H, br d, J = 3.1 Hz, OH), 2.10 (3H, m, C5'-Me), 1.95 (1H, m, C4-H), 1.75 (3H, d, J = 1.2 Hz, C2-Me), 1.04 (3H, d, J = 7.0 Hz, C4-Me), 0.58 (3H, s, SiMe), 0.57 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 160.54 (0), 160.42 (0), 158.26 (0), 156.96 (0), 131.51 (0), 130.04 (1, 2C), 124.91 (1), 121.99 (1), 114.78 (1, 2C), 107.05 (1), 77.80 (1), 74.36 (2), 73.73 (2), 55.44 (3), 37.77 (1), 23.42 (3), 14.28 (3), 12.59 (3), 1.12 (3), 0.96 (3).

LRMS (CI mode, NH_3): m/z (%) = 307 [(MH – 2-methylfuran)$^+$, 11], 187 (16), 138 (11), 121 (100), 83 (11), 35 (12).

HRMS (Ar FAB mode, NBA matrix + NaI): found, $(MNa)^+$, 411.1936. $C_{22}H_{32}O_4Si$ + Na requires 411.1968.

(3*R*,4*S*)-(*Z*)-1-[Dimethyl(5-methyl-2-furyl)silyl]-3-(methoxyacetoxy)-5-[(4-methoxybenzyl)oxy)]-2,4-dimethylpent-1-ene (4.1.1.2):



4.5.5.2

4.1.1.2
$C_{25}H_{36}O_6Si$

To a solution of **4.5.2.2** (9.34 g, 24.0 mmol) in CH_2Cl_2 (500 mL) were added methoxyacetic acid (3.7 mL, 48.2 mmol, 2.0 eq.), DCC (12.38 g, 60.0 mmol, 2.5 eq.) and DMAP (147 mg, 1.20 mmol, 5%). A white precipitate appeared immediately and the suspension was stirred at r.t. for 12 h. It was then concentrated and petrol (300 mL) was added. The resulting slurry was filtered, concentrated and chromatographed (SiO_2, 20% Et_2O in petrol) to yield **4.1.1.2** as a colourless oil (10.36 g, 22.5 mmol, 94%):

$[\alpha]_D$: –48.6° (*c* = 1.40, $CHCl_3$).

IR (film): ν = 2956, 2923, 1755, 1614, 1514, 1451, 1376, 1302, 1249, 1190, 1129, 1036, 1019, 958, 923, 834, 787 cm^{-1}.

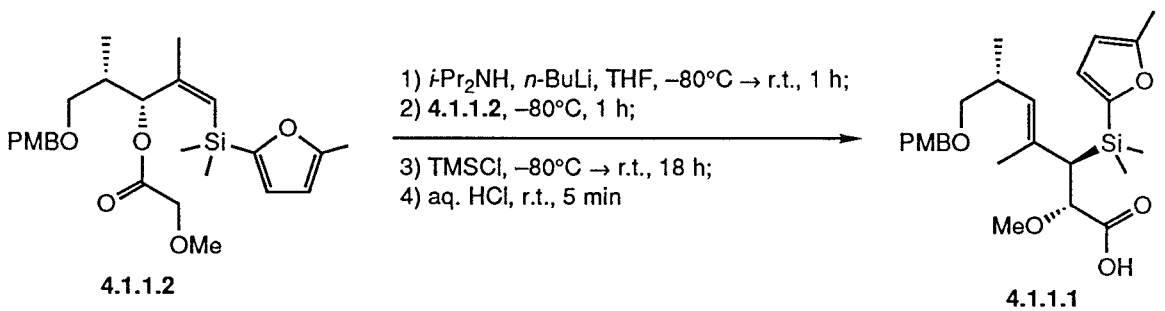
^1H NMR (270 MHz, C_6D_6): δ = 7.22 (2H, dm, *J* = 8.7 Hz, Ar), 6.82 (2H, dm, *J* = 8.7 Hz, Ar), 6.73 (1H, app d, *J* = 3.1 Hz, C4'-H), 5.91 (1H, dq, *J* = 3.1, 1.0 Hz, C3'-H), 5.87 (1H, d, *J* = 8.3 Hz, C3-H), 5.73 (1H, q, *J* = 1.4 Hz, C1-H), 4.32 and 4.25 (2H, AB q, J_{AB} = 11.4 Hz, Ar*CH*$_2$), 3.73 and 3.69 (2H, AB q, J_{AB} = 16.3 Hz, MeOC*H*$_2$), 3.34 (3H, s, ArO*Me*), 3.25 and 3.05 (2H, A and B of ABX, J_{AB} = 9.1 Hz, J_{AX} = 5.5 Hz, J_{BX} = 6.8 Hz, C5-H_2), 3.15 (3H, s, CH_2O*Me*), 2.19 (1H, m, C4-H), 2.13 (3H, m, C5'-Me), 1.82 (3H, d, *J* = 1.4 Hz, C2-Me), 1.06 (3H, d, *J* = 6.6 Hz, C4-Me), 0.70 (3H, s, SiMe), 0.56 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, C_6D_6) δ = 169.97 (0), 160.38 (0), 158.26 (0), 157.47 (0), 152.82 (0), 131.70 (0), 130.10 (1, 2C), 128.74 (1), 123.09 (1), 114.71 (1, 2C), 107.20 (1), 78.75 (1), 73.66 (2), 72.42 (2), 70.43 (2), 59.55 (3), 55.43 (3), 38.26 (1), 23.09 (3), 14.72 (3), 14.33 (3), –0.32 (3), –0.40 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 478 [$(MNH_4)^+$, 8], 461 [$(MH)^+$, 1], 379 (26), 164 (22), 147 (26), 121 (100), 35 (56).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 478.2654. $C_{25}H_{36}O_6Si$ + NH_4 requires 478.2625.

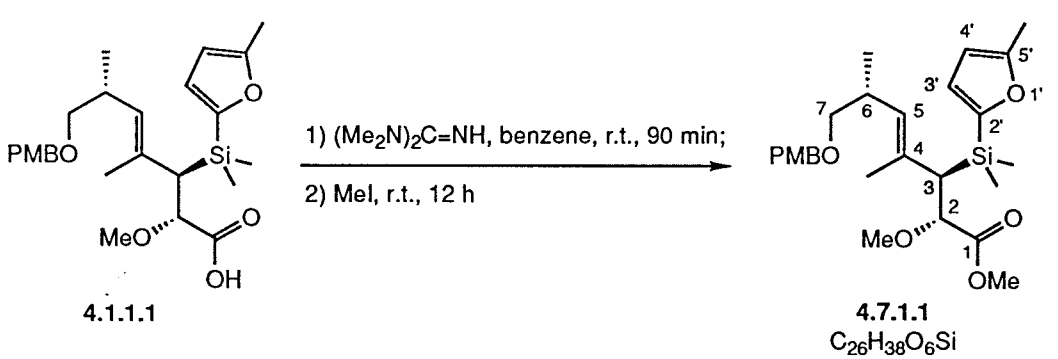
(2*S*,3*R*,6*R*)-(*E*)-3-[Dimethyl(5-methyl-2-furyl)silyl]-2-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethylhept-4-enoic Acid (4.1.1.1):



4.1.1.2 4.1.1.1

A solution of *i*-Pr_2NH (5.7 mL, 40.7 mmol, 1.8 eq.) in THF (100 mL) at –80°C was treated with *n*-BuLi (25 mL of a 1.46 M solution in hexanes, 36.5 mmol, 1.6 eq.) and the resulting solution was stirred as it warmed to r.t. over 1 h. It was then recooled to –80°C and **4.1.1.2** (10.36 g, 22.5 mmol) in THF (20 mL + 3 x 5 mL rinses) was added dropwise *via* cannula. The solution was stirred at –80°C for 1 h, then TMSCl (17 mL, 134 mmol, 6.0 eq.) was added and stirring was continued for a further 18 h as the mixture warmed slowly to r.t. The resulting cloudy solution was treated with 1 M HCl (100 mL) and stirred at r.t. for a further 5 min. The organic phase was then separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase and extracts were dried and concentrated to yield crude **4.1.1.1** as a pale yellow oil which was used without further purification.

Methyl (2*S*,3*R*,6*R*)-(*E*)-3-[Dimethyl(5-methyl-2-furyl)silyl]-2-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethylhept-4-enoate (4.7.1.1):



4.1.1.1 **4.7.1.1** $C_{26}H_{38}O_6Si$

A solution of crude **4.1.1.1** (22.5 mmol) in benzene (100 mL) was treated with 1,1,3,3-tetramethylguanidine (7.1 mL, 56.6 mmol, 2.5 eq.) and the resulting solution was stirred at r.t. for 90 min. MeI (4.9 mL, 78.7 mmol, 3.5 eq.) was then added and stirring was continued for a further 12 h, by which time a brown precipitate had appeared. The

suspension was filtered through celite, concentrated and chromatographed (SiO_2, 20% Et_2O in petrol) to yield **4.7.1.1** as a colourless oil (9.40 g, 19.8 mmol, 88%):

$[\alpha]_D$: –50.4° (c = 1.27, $CHCl_3$).

IR (film): ν = 2955, 2925, 2856, 1752, 1613, 1588, 1514, 1454, 1354, 1302, 1248, 1196, 1116, 1037, 1018, 957, 923, 824, 808, 784 cm^{-1}.

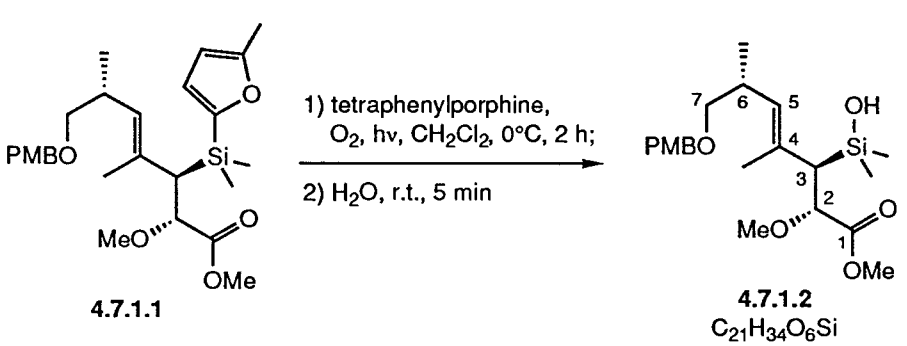
^1H NMR (270 MHz, C_6D_6): δ = 7.27 (2H, dm, J = 8.7 Hz, Ar), 6.83 (2H, dm, J = 8.7 Hz, Ar), 6.59 (1H, d, J = 3.1 Hz, C4'-H), 5.90 (1H, dq, J = 3.1, 0.8 Hz, C3'-H), 5.28 (1H, br d, J = 9.2 Hz, C5-H), 4.36 and 4.32 (2H, AB q, J_{AB} = 11.6 Hz, ArCH_2), 4.00 (1H, d, J = 5.4 Hz, C2-H), 3.38 (3H, s, CO_2Me), 3.34 (3H, s, ArO*Me*), 3.31 and 3.21 (2H, A and B of ABX, J_{AB} = 8.8 Hz, J_{AX} = 6.4 Hz, J_{BX} = 7.2 Hz, C7-H_2), 3.20 (3H, s, C2-OMe), 2.78 (1H, app d sextet, J = 9.2, 6.8 Hz, C6-H), 2.51 (1H, d, J = 5.4 Hz, C3-H), 2.11 (3H, app s, C5'-Me), 1.76 (3H, d, J = 1.0 Hz, C4-Me), 1.04 (3H, d, J = 6.8 Hz, C6-Me), 0.47 (3H, s, SiMe), 0.40 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 172.51 (0), 160.26 (0), 157.74 (0), 157.31 (0), 133.75 (0), 132.20 (0), 131.81 (1), 129.98 (1, 2C), 123.13 (1), 114.66 (1, 2C), 107.00 (1), 83.36 (1), 76.33 (2), 73.45 (2), 59.01 (3), 55.44 (3), 51.51 (3), 44.21 (1), 34.39 (1), 18.90 (3), 18.33 (3), 14.28 (3), –2.02 (3), –2.33 (3).

LRMS (CI mode, NH_3): m/z (%) = 492 [$(MNH_4)^+$, 100], 475 [$(MH)^+$, 2], 393 (35), 273 (18), 170 (13), 137 (12), 121 (64), 106 (16), 35 (39).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 492.2792. $C_{26}H_{38}O_6Si$ + NH_4 requires 492.2781.

Methyl (2*R*,3*R*,6*R*)-(*E*)-3-(Dimethylhydroxysilyl)-2-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethylhept-4-enoate (4.7.1.2):



4.7.1.1 **4.7.1.2**
$C_{21}H_{34}O_6Si$

A rapidly stirred solution of **4.7.1.1** (9.40 g, 19.8 mmol) and tetraphenylporphine (243 mg, 0.395 mmol, 2%) in CH_2Cl_2 (300 mL) at 0°C under O_2 was irradiated with three evenly spaced 150 W light bulbs for 2 h. The purple solution was then treated with H_2O (100 mL) and stirred for a further 5 min, then the organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase and extracts were dried, concentrated and chromatographed (SiO_2, 50% Et_2O in petrol) to yield **4.7.1.2** as a colourless oil (7.97 g, 19.4 mmol, 98%):

$[\alpha]_D$: –10.3° (c = 1.38, $CHCl_3$).

IR (film): ν = 3448 (br), 2955, 2869, 1751, 1613, 1514, 1457, 1356, 1302, 1249, 1197, 1180, 1101, 1036, 1007, 929, 835, 780 cm^{-1}.

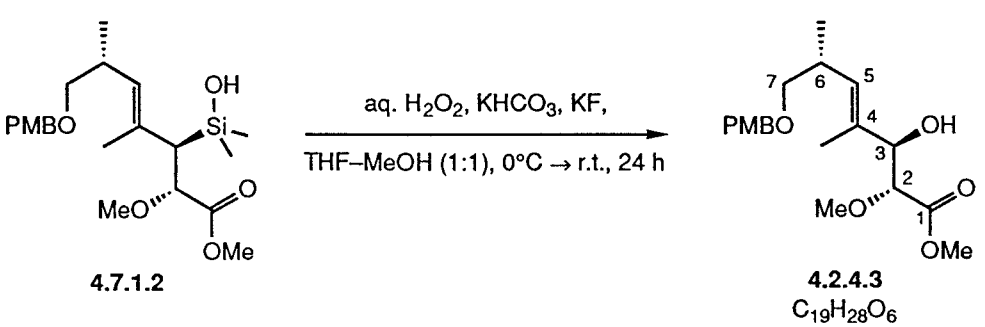
^1H NMR (270 MHz, C_6D_6): δ = 7.27 (2H, dm, J = 8.7 Hz, Ar), 6.84 (2H, dm, J = 8.7 Hz, Ar), 5.22 (1H, dq, J = 9.3, 1.0 Hz, C5-H), 4.36 and 4.33 (2H, AB q, J_{AB} = 11.7 Hz, ArCH_2), 4.05 (1H, d, J = 6.1 Hz, C2-H), 3.41 (3H, s, CO_2Me), 3.33 (3H, s, ArO*Me*), 3.28 and 3.21 (2H, A and B of ABX, J_{AB} = 8.9 Hz, J_{AX} = 7.0 Hz, J_{BX} = 6.8 Hz, C7-H_2), 3.15 (3H, s, C2-OMe), 2.80 (1H, app d sextet, J = 9.3, 6.8 Hz, C6-H), 2.58 (1H, v br s, OH), 2.12 (1H, d, J = 6.1 Hz, C3-H), 1.86 (3H, d, J = 1.0 Hz, C4-Me), 1.03 (3H, d, J = 6.8 Hz, C6-Me), 0.25 (3H, s, SiMe), 0.23 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 172.75 (0), 160.32 (0), 134.04 (0), 132.00 (0), 131.38 (1), 130.08 (1, 2C), 114.71 (1, 2C), 83.32 (1), 76.23 (2), 73.48 (2), 58.87 (3), 55.43 (3), 51.67 (3), 45.95 (1), 34.28 (1), 19.04 (3), 18.67 (3), 0.70 (3), 0.25 (3).

LRMS (CI mode, NH_3): m/z (%) = 428 [$(MNH_4)^+$, 12], 410 [$(MNH_4 - H_2O)^+$, 5], 393 (100), 347 (7), 273 (8), 154 (12), 137 (18), 121 (96), 35 (93).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 428.2494. $C_{21}H_{34}O_6Si$ + NH_4 requires 428.2468.

Methyl (2*R*,3*R*,6*R*)-(*E*)-3-Hydroxy-2-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethylhept-4-enoate (4.2.4.3):



4.7.1.2 → **4.2.4.3**

$C_{19}H_{28}O_6$

A solution of **4.7.1.2** (7.97 g, 19.4 mmol), $KHCO_3$ (19.42 g, 194 mmol, 10 eq.) and KF (5.64 g, 97.1 mmol, 5.0 eq.) in THF–MeOH (1:1, 400 mL) at 0°C was treated with 30 wt. % aq. H_2O_2 (40 mL, 392 mmol, 20 eq.). The resulting mixture was allowed to warm to r.t. and stirred for 24 h, by which time a white precipitate had appeared. It was then poured carefully into a 0°C solution of sat. $Na_2S_2O_3$ (300 mL). After stirring at 0°C for 15 min the mixture was extracted with CH_2Cl_2 (5 x 100 mL). The combined extracts were washed with brine, dried, concentrated and chromatographed (SiO_2, 50% Et_2O in petrol) to yield **4.2.4.3** as a colourless oil (4.45 g, 12.6 mmol, 65%):

$[\alpha]_D$: –2.7° (*c* = 1.53, $CHCl_3$).

IR (film): ν = 3476 (br), 2956, 2870, 1746, 1613, 1514, 1458, 1363, 1302, 1248, 1202, 1177, 1121, 1095, 1035, 822 cm^{-1}.

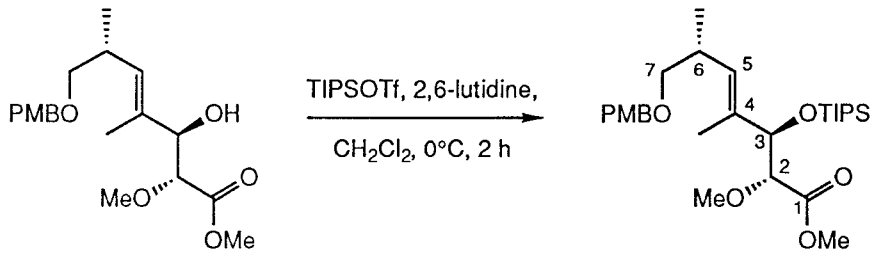
^1H NMR (270 MHz, C_6D_6): δ = 7.25 (2H, dm, *J* = 8.7 Hz, Ar), 6.83 (2H, dm, *J* = 8.7 Hz, Ar), 5.44 (1H, br d, *J* = 9.3, 1.2 Hz, C5-H), 4.41 (1H, br d, *J* = 5.8 Hz, C3-H), 4.34 (2H, s, ArCH_2), 3.87 (1H, d, *J* = 5.8 Hz, C2-H), 3.39 (3H, s, CO_2Me), 3.34 (3H, s, ArOMe), 3.28 and 3.18 (2H, A and B of ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.1 Hz, C7-H_2), 3.13 (3H, s, C2-OMe), 2.82 (1H, br s, OH), 2.79 (1H, app d sextet, *J* = 9.3, 6.8 Hz, C6-H), 1.71 (3H, d, *J* = 1.2 Hz, C4-Me), 1.03 (3H, d, *J* = 6.8 Hz, C6-Me).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 171.43 (0), 160.29 (0), 134.85 (0), 132.02 (0), 132.00 (1), 129.98 (1, 2C), 114.71 (1, 2C), 84.15 (1), 77.70 (1), 75.69 (2), 73.44 (2), 58.88 (3), 55.46 (3), 51.83 (3), 33.83 (1), 18.44 (3), 13.47 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 370 [$(MNH_4)^+$, 18], 353 [$(MH)^+$, 2], 266 (30), 249 (16), 137 (22), 121 (100), 35 (50).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 370.2219. $C_{19}H_{28}O_6$ + NH_4 requires 370.2230.

Methyl (2*R*,3*R*,6*R*)-(*E*)-2-Methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethyl-3-[(triisopropylsilyl)oxy]hept-4-enoate (4.7.1.3):



4.2.4.3

4.7.1.3
$C_{28}H_{48}O_6Si$

To a solution of **4.2.4.3** (4.45 g, 12.6 mmol) and 2,6-lutidine (4.4 mL, 37.8 mmol, 3.0 eq.) in CH_2Cl_2 (100 mL) at 0°C was added TIPSOTf (5.1 mL, 19.0 mmol, 1.5 eq.) and the resulting solution was stirred at 0°C for 2 h. It was then concentrated and the residue was dissolved in Et_2O (200 mL), washed with 2 M HCl, sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 10% Et_2O in petrol) to yield **4.7.1.3** as a colourless oil (5.85 g, 11.5 mmol, 91%):

$[\alpha]_D$: –8.5° (*c* = 1.27, $CHCl_3$).

IR (film): ν = 2946, 2866, 1748, 1613, 1587, 1514, 1464, 1359, 1302, 1248, 1197, 1174, 1094, 1038, 1000, 920, 883, 823, 758, 681 cm^{-1}.

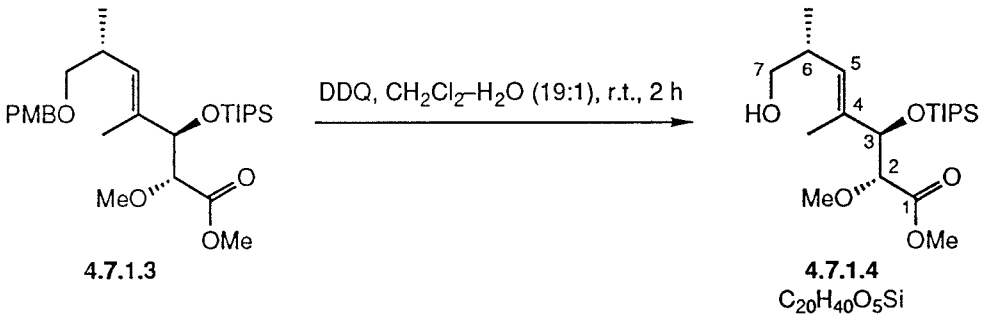
^1H NMR (270 MHz, C_6D_6): δ = 7.25 (2H, dm, *J* = 8.5 Hz, Ar), 6.82 (2H, dm, *J* = 8.5 Hz, Ar), 5.36 (1H, br d, *J* = 9.3 Hz, C5-H), 4.64 (1H, d, *J* = 6.2 Hz, C3-H), 4.35 and 4.33 (2H, AB q, J_{AB} = 12.5 Hz, ArCH_2), 3.91 (1H, d, *J* = 6.2 Hz, C2-H), 3.46 (3H, s, CO_2Me), 3.34 (3H, s, ArO*Me*), 3.29 and 3.20 (2H, A and B of ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.0 Hz, C7-H_2), 3.18 (3H, s, C2-OMe), 2.79 (1H, app d sextet, *J* = 9.3, 6.6 Hz, C6-H), 1.79 (3H, d, *J* = 1.2 Hz, C4-Me), 1.14 (21H, m, TIPS), 1.05 (3H, d, *J* = 6.6 Hz, C6-Me).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 171.72 (0), 160.30 (0), 135.80 (0), 133.05 (1), 132.08 (1), 129.92 (1, 2C), 114.69 (1, 2C), 85.49 (1), 80.31 (1), 75.70 (2), 73.48 (2), 59.01 (3), 55.46 (3), 51.73 (3), 34.00 (1), 18.98 (3, 6C), 18.16 (3), 13.54 (1, 3C), 13.10 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 526 [$(MNH_4)^+$, 87], 509 [$(MH)^+$, 2], 465 (13), 405 (9), 335 (27), 137 (16), 121 (100), 35 (56).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 526.3533. $C_{28}H_{48}O_6Si$ + NH_4 requires 526.3564.

Methyl (2*R*,3*R*,6*R*)-(*E*)-7-Hydroxy-2-methoxy-4,6-dimethyl-3-[(triisopropylsilyl)oxy]hept-4-enoate (4.7.1.4):



4.7.1.3

4.7.1.4
$C_{20}H_{40}O_5Si$

To a solution of **4.7.1.3** (1.68 g, 3.30 mmol) in CH_2Cl_2–H_2O (19:1, 40 mL) was added DDQ (824 mg, 3.63 mmol, 1.1 eq.) and the resulting dark green suspension was stirred at r.t. for 2 h. It was then diluted with Et_2O (250 mL), washed 3 times with sat. $NaHCO_3$ and once with brine, then dried, concentrated and chromatographed (SiO_2, 50% Et_2O in petrol) to yield **4.7.1.4** as a colourless oil (1.26 g, 3.24 mmol, 98%):

$[\alpha]_D$: +48.9° (c = 1.33, $CHCl_3$).

IR (film): ν = 3460 (br), 2948, 2868, 1748, 1463, 1436, 1384, 1368, 1312, 1264, 1197, 1094, 1067, 1040, 1014, 999, 920, 883, 833, 798, 682 cm^{-1}.

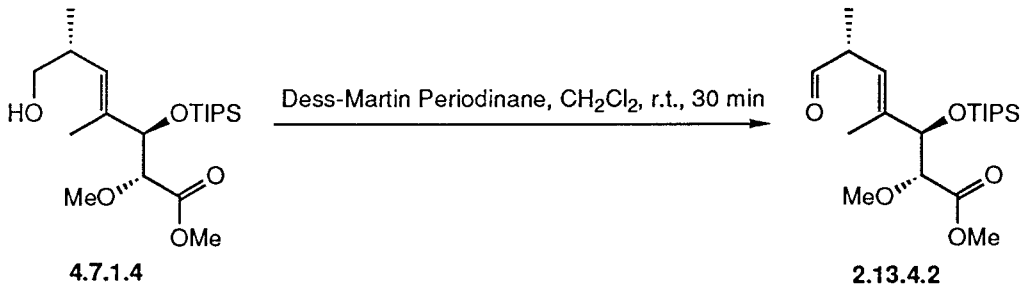
^1H NMR (270 MHz, C_6D_6): δ = 5.05 (1H, br d, J = 9.9 Hz, C5-H), 4.60 (1H, d, J = 6.6 Hz, C3-H), 3.86 (1H, d, J = 6.6 Hz, C2-H), 3.47 and 3.20 (2H, A and B of ABX, J_{AB} = 10.4 Hz, J_{AX} = 5.0 Hz, J_{BX} = 8.6 Hz, C7-H_2), 3.44 (3H, s, CO_2Me), 3.12 (3H, s, C2-OMe), 2.63 (1H, m, C6-H), 2.29 (1H, br s, OH), 1.80 (3H, d, J = 1.4 Hz, C4-Me), 1.11 (21H, m, TIPS), 0.82 (3H, d, J = 6.8 Hz, C6-Me).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 172.24 (0), 137.79 (0), 133.11 (1), 84.99 (1), 80.51 (1), 68.13 (2), 58.88 (3), 51.93 (3), 36.35 (1), 18.88 (3, 6C), 16.95 (3), 13.44 (1, 3C), 12.91 (3).

LRMS (CI mode, NH_3): m/z (%) = 406 [$(MNH_4)^+$, 100], 389 [$(MH)^+$, 4], 345 (9), 285 (8), 232 (10), 215 (26), 202 (24), 170 (14), 153 (15), 35 (61).

HRMS (CI mode, NH_3): found, $(MNH_4)^+$, 406.2981. $C_{20}H_{40}O_5Si$ + NH_4 requires 406.2989.

Methyl (2*R*,3*R*,6*R*)-(*E*)-2-Methoxy-4,6-dimethyl-7-oxo-3-[(triisopropylsilyl)oxy]hept-4-enoate (2.13.4.2):

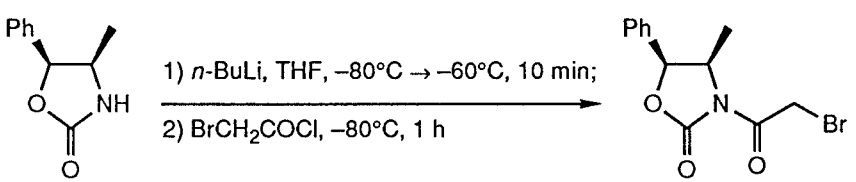


4.7.1.4 2.13.4.2

To a solution of **4.7.1.4** (1.26 g, 3.24 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin Periodinane (2.05 g, 4.83 mmol, 1.5 eq.) and the resulting cloudy solution was stirred at r.t. for 30 min. It was then diluted with Et_2O (150 mL) and shaken with a 1:1 solution of sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ (100 mL). The organic phase was then separated, washed with sat. $NaHCO_3$ and brine, then dried and concentrated to yield crude **2.13.4.2** as a pale yellow oil which was used without further purification.

8.4 Experimental Procedures for Chapter 5

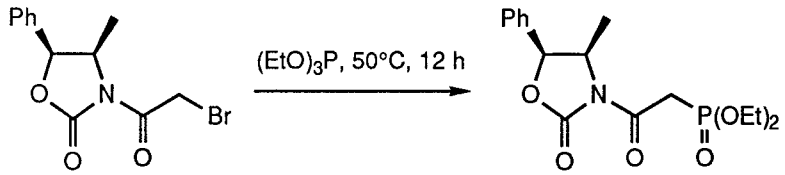
(4*R*,5*S*)-4-Methyl-3-(1-oxo-2-bromoethyl)-5-phenyloxazolidin-2-one (5.2.1.2):



5.2.1.1 5.2.1.2

A solution of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one (**5.2.1.1**) (5.00 g, 28.2 mmol) in THF (130 mL) at–80°C was treated with *n*-BuLi (20 mL of a 1.55 M solution in hexanes, 31.0 mmol, 1.1 eq.), warmed to –60°C, and stirred for 10 min. The orange solution was then recooled to –80°C and bromoacetyl chloride (2.6 mL, 31.2 mmol, 1.1 eq.) was added dropwise. The resulting bright yellow solution was stirred at –80°C for 1 h, then quenched with sat. NH_4Cl (5 mL) and sat. $NaHCO_3$ (10 mL). After warming to r.t., the mixture was poured into sat. $NaHCO_3$ (100 mL) and the organic phase was separated. The aq. phase was extracted with Et_2O (3 x 100 mL), then the combined organic phase and extracts were washed with H_2O and brine, then dried, concentrated and chromatographed (SiO_2, 35% Et_2O in petrol) to yield **5.2.1.2** as a colourless oil (7.09 g, 23.8 mmol, 84%): $[\alpha]_D$: +18.8° (*c* = 1.47, $CHCl_3$) [lit. [134]+17.2° (*c* = 1.46, $CHCl_3$)]. The product gave spectroscopic data in accord with lit.[134] values.

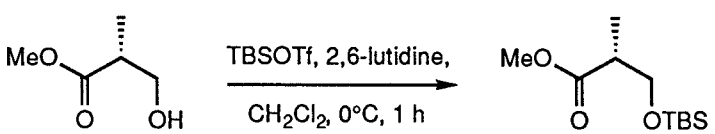
Diethyl 2-[(4*R*,5*S*)-4-Methyl-2-oxo-5-phenyloxazolidin-3-yl]-2-oxoethanephosphonate (2.2.3.7):



5.2.1.2 2.2.3.7

A mixture of **5.2.1.2** (7.04 g, 23.6 mmol) and $(EtO)_3P$ (4.5 mL, 26.2 mmol, 1.1 eq.) was heated at 50°C under an air-cooled reflux condenser for 12 h. The mixture was then concentrated at 50°C/0.2 mm Hg for 24 h to yield **2.2.3.7** as a pale yellow oil (8.33 g, 23.4 mmol, 99%) which required no further purification: $[\alpha]_D$: +19.4° (*c* = 1.71, $CHCl_3$). The product gave spectroscopic data in accord with lit.[134] values.

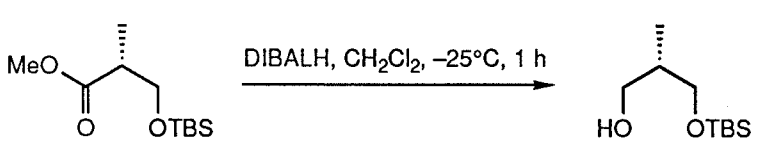
Methyl (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropionate (5.2.2.1):



2.5.4.1 5.2.2.1

A solution of (*R*)-3-hydroxy-2-methylpropionate (**2.5.4.1**) (3.0 mL, 27.2 mmol) in CH_2Cl_2 (100 mL) at 0°C was treated with 2,6-lutidine (9.5 mL, 81.6 mmol, 3.0 eq.) then TBSOTf (9.4 mL, 40.9 mmol, 1.5 eq.). The resulting mixture was stirred at 0°C for 1 h. It was then concentrated, dissolved in Et_2O (100 mL), washed with 2 M HCl, sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 5% Et_2O in petrol) to yield **5.2.2.1** as a colourless oil (6.26 g, 26.9 mmol, 99%): $[\alpha]_D$: –21.2° (*c* = 3.27, CH_2Cl_2) [lit.[136] –20.5° (*c* = 3.21, CH_2Cl_2)]. The product gave spectroscopic data in accord with lit.[136] values.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropan-1-ol (5.2.2.2):

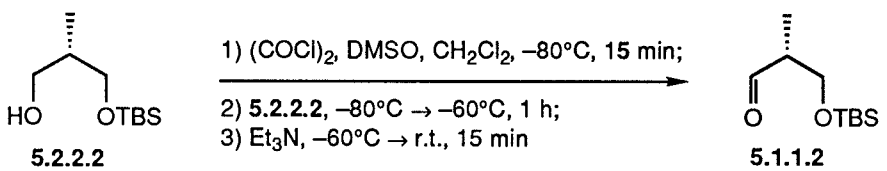


5.2.2.1 5.2.2.2

A solution of **5.2.2.1** (3.23 g, 13.9 mmol) in CH_2Cl_2 (35 mL) at –25°C was treated with DIBALH (20 mL of a 1.5 M solution in toluene, 30.0 mmol, 2.2 eq.) dropwise. The resulting solution was stirred at –25°C for 1 h, then quenched with 2 M NaOH (40 mL) and allowed to warm to r.t. The suspension was diluted with Et_2O (50 mL) and stirred

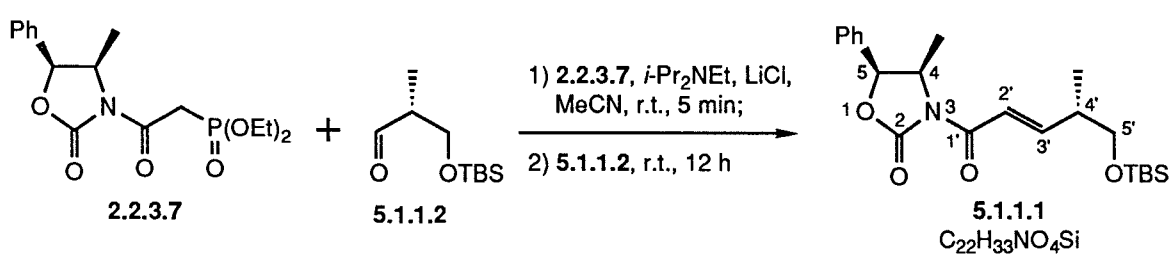
vigorously for 15 min, then the organic phase was separated. The aq. phase was extracted with Et_2O (3 x 30 mL), then the combined organic phase and extracts were washed with brine, dried and concentrated to yield **5.2.2.2** as a colourless oil (2.70 g, 13.2 mmol, 95%) which required no further purification: $[\alpha]_D$: –10.9° (*c* = 2.13, CH_2Cl_2) [lit.[136] –10.0° (*c* = 2.06, CH_2Cl_2)]. The product gave spectroscopic data in accord with lit.[136] values.

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropanal (5.1.1.2):



A solution of $(COCl)_2$ (1.0 mL, 11.5 mmol, 1.2 eq.) in CH_2Cl_2 (40 mL) at –80°C was treated with DMSO (1.7 mL, 24.0 mmol, 2.4 eq.) and the resulting mixture was stirred at –80°C for 15 min. A solution of **5.2.2.2** (2.02 g, 9.88 mmol) in CH_2Cl_2 (6 mL + 3 x 2 mL rinses) was then added *via* cannula, resulting in the formation of a white precipitate. Stirring was continued for a further 1 h as the mixture warmed gradually to –60°C, then Et_3N (6.9 mL, 49.5 mmol, 5.0 eq.) was added and the mixture was stirred for a further 15 min as it warmed to r.t. It was then treated with H_2O (50 mL) and diluted with Et_2O (100 mL). The organic phase was separated, washed with H_2O and brine, then dried and concentrated to yield crude **5.1.1.2** as a pale yellow oil which was used without further purification.

(4*R*,5*S*)-3-[(*S*)-(*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-1-oxopent-2-enyl]-4-methyl-5-phenyloxazolidin-2-one (5.1.1.1):



To a solution of **2.2.3.7** (4.21 g, 11.8 mmol, 1.2 eq.) in MeCN (100 mL) was added LiCl (586 mg, 13.8 mmol, 1.4 eq.) followed by *i*-Pr_2NEt (2.4 mL, 13.8 mmol, 1.4 eq.). The resulting mixture was stirred at r.t. for 5 min, then crude **5.1.1.2** (9.88 mmol) in MeCN (4 mL + 3 x 2 mL rinses) was added *via* cannula. The resulting solution was stirred at r.t. for 12 h. It was then diluted with Et_2O (300 mL) and poured into H_2O (100 mL). The organic phase was separated and washed with H_2O (2 x 100 mL), then the combined aq. phase and washings were extracted with Et_2O (2 x 50 mL). The combined organic phase and extracts were washed with 2 M HCl and sat. $NaHCO_3$ (back-extracting each time with 2 x 50 mL of

Et_2O), then dried, concentrated and chromatographed (SiO_2, 30% Et_2O in petrol) to yield **5.1.1.1** as a colourless oil (3.60 g, 8.92 mmol, 90%):

$[\alpha]_D$: –5.4° (c = 1.85, CH_2Cl_2).

IR (film): ν = 2955, 2929, 2895, 2857, 1783, 1683, 1636, 1457, 1348, 1302, 1256, 1218, 1196, 1119, 1091, 1040, 1008, 977, 837, 777, 701 cm^{-1}.

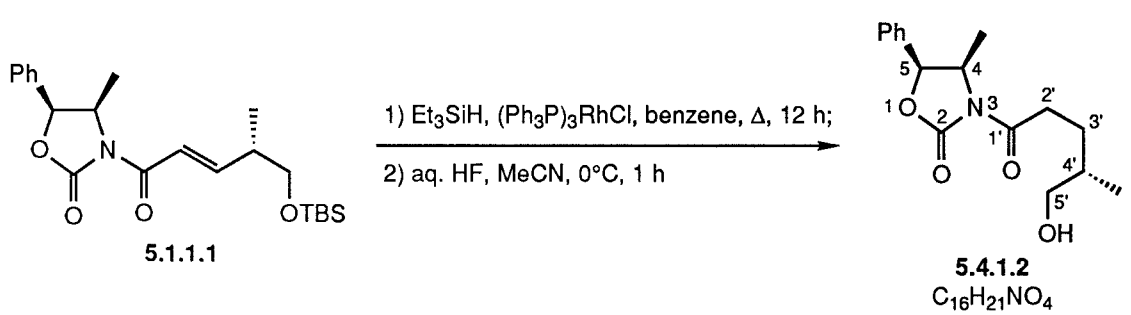
^1H NMR (270 MHz, C_6D_6): δ = 7.82 and 7.49 (2H, A and B of ABX, J_{AB} = 15.5 Hz, J_{AX} = 1.3 Hz, J_{BX} = 7.2 Hz, C2'-H and C3'-H), 7.02 (3H, m, Ph), 6.86 (2H, m, Ph), 4.70 (1H, d, J = 5.3 Hz, C5-H), 4.35 (1H, app quintet, J = 6.8 Hz, C4-H), 3.45 and 3.42 (2H, A and B of ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.4 Hz, J_{BX} = 5.9 Hz, C5'-H_2), 2.48 (1H, m, C4'-H), 1.00 (3H, d, J = 7.0 Hz, C4'-Me), 0.99 (9H, s, t-Bu), 0.65 (3H, d, J = 6.6 Hz, C4-Me), 0.06 (6H, s, $SiMe_2$).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 165.26 (0), 153.80 (1), 153.58 (0), 134.92 (0), 129.32 (1, 2C), 129.20 (1), 126.60 (1, 2C), 121.60 (1), 79.27 (1), 67.88 (2), 55.41 (1), 40.50 (1), 26.77 (3, 3C), 19.16 (0), 16.42 (3), 15.08 (3), –4.60 (3, 2C).

LRMS (CI mode, NH_3): m/z (%) = 404 [$(MH)^+$, 100], 373 (23), 346 (68), 302 (42), 169 (36).

HRMS (CI mode, NH_3): found, $(MH)^+$, 404.2245. $C_{22}H_{33}NO_4Si$ + H requires 404.2257.

(4*R*,5*S*)-3-[(*S*)-5-Hydroxy-4-methyl-1-oxopentyl]-4-methyl-5-phenyloxazolidin-2-one (5.4.1.2):



5.1.1.1

5.4.1.2
$C_{16}H_{21}NO_4$

A solution of **5.1.1.1** (3.60 g, 8.92 mmol) and $(Ph_3P)RhCl$ (413 mg, 0.466 mmol, 5%) in benzene (90 mL) was treated with Et_3SiH (2.1 mL, 13.1 mmol, 1.5 eq.), heated to reflux and stirred for 12 h. The resulting brown solution was then allowed to cool to r.t. and concentrated. The residue was dissolved in MeCN (50 mL), transferred to a polypropylene bottle, cooled to 0°C and treated with 48 wt. % aq. HF (8.6 mL, 268 mmol, 30 eq.). After stirring at 0°C for 1 h the mixture was diluted with Et_2O (200 mL) and poured carefully into

sat. $NaHCO_3$ (200 mL). The organic phase was separated and the aq. phase was extracted with Et_2O (3 x 100 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 90% Et_2O in petrol) to yield **5.4.1.2** as a colourless oil (2.21 g, 7.59 mmol, 85%):

$[\alpha]_D$: +21.2° (c = 2.40, CH_2Cl_2).

IR (film): ν = 3450 (br), 2930, 2874, 1782, 1701, 1456, 1351, 1219, 1199, 1152, 1122, 1090, 1068, 1037, 990, 962, 768, 730, 701 cm^{-1}.

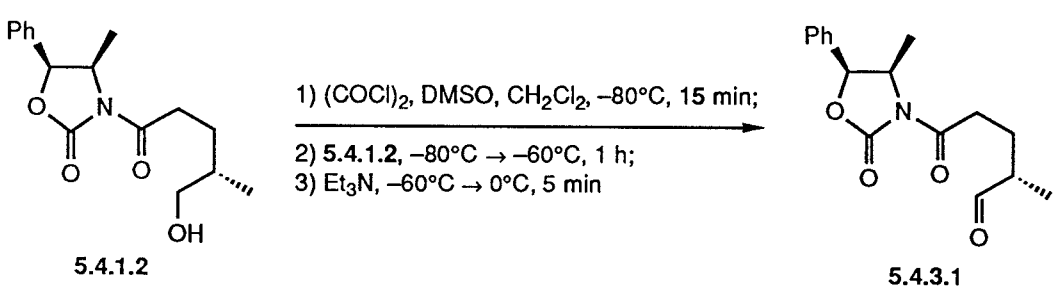
^1H NMR (270 MHz, C_6D_6): δ = 7.03 (3H, m, Ph), 6.88 (2H, m, Ph), 4.77 (1H, d, J = 7.3 Hz, C5-H), 4.26 (1H, app quintet, J = 6.8 Hz, C4-H), 3.37 and 3.33 (2H, A and B of ABX, J_{AB} = 10.8 Hz, J_{AX} = 5.5 Hz, J_{BX} = 5.7 Hz, C5'-H_2), 3.11 and 2.99 (2H, A and B of ABXY, J_{AB} = 16.5 Hz, J_{AX} = 5.8 Hz, J_{AY} = 9.2 Hz, J_{BX} = 8.8 Hz, J_{BY} = 6.4 Hz, C2'-H_2), 1.92 (1H, m, C4'-H), 1.62 (3H, m, C3'-H_2, OH), 0.90 (3H, d, J = 6.6 Hz, C4'-Me), 0.62 (3H, d, J = 6.6 Hz, C4-Me).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 173.91 (0), 153.78 (0), 134.85 (0), 129.38 (1, 2C), 129.28 (1), 126.63 (1, 2C), 79.41 (1), 68.05 (2), 55.31 (1), 36.42 (1), 34.35 (2), 28.82 (2), 17.50 (3), 15.07 (3).

LRMS (EI mode, 70 eV): m/z (%) = 291 ($M^{+\bullet}$, 1), 273 (8), 232 (8), 219 (13), 177 (22), 134 (12), 115 (20), 107 (100), 91 (11), 79 (31), 55 (13), 42 (17).

HRMS (EI mode, 70 eV): found, $M^{+\bullet}$, 291.1478. $C_{16}H_{21}NO_4$ requires 291.1471.

(4*R*,5*S*)-3-[(*S*)-4-Methyl-1,5-dioxopentyl]-4-methyl-5-phenyloxazolidin-2-one (5.4.3.1):

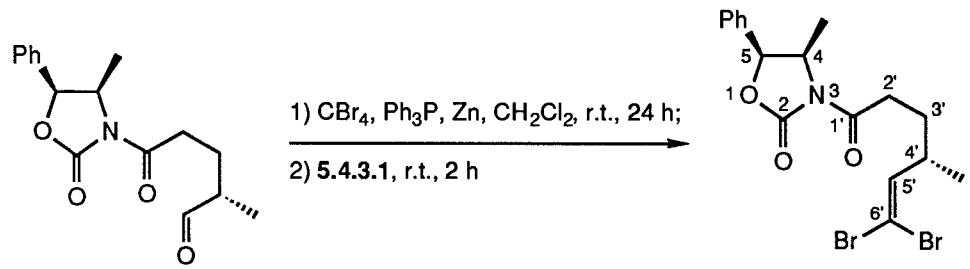


5.4.1.2 **5.4.3.1**

A solution of $(COCl)_2$ (1.3 mL, 14.9 mmol, 2.0 eq.) in CH_2Cl_2 (30 mL) at –80°C was treated with DMSO (1.6 mL, 22.5 mmol, 3.0 eq.) and the resulting mixture was stirred at –80°C for 15 min. A solution of **5.4.1.2** (2.21 g, 7.59 mmol) in CH_2Cl_2 (10 mL + 3 x 3 mL rinses) was then added *via* cannula, resulting in the formation of a white precipitate. Stirring was continued for a further 1 h as the mixture warmed gradually to –60°C, then

Et_3N (6.3 mL, 45.2 mmol, 6.0 eq.) was added and the mixture was warmed to 0°C and stirred for a further 5 min. It was then treated with H_2O (100 mL) and diluted with Et_2O (200 mL). The organic phase was separated and the aq. phase was extracted with Et_2O (3 x 100 mL). The combined organic phase and extracts were then dried and concentrated to yield crude **5.4.3.1** as a pale yellow oil which was used without further purification

(4*R*,5*S*)-3-[(*S*)-6,6-Dibromo-4-methyl-1-oxohex-5-enyl]-4-methyl-5-phenyloxazolidin-2-one (2.13.4.3):



5.4.3.1

2.13.4.3
$C_{17}H_{19}Br_2NO_3$

An orange solution of CBr_4 (10.07 g, 30.4 mmol, 4.0 eq.) and Ph_3P (7.96 g, 30.3 mmol, 4.0 eq.) in CH_2Cl_2 (100 mL) was treated with zinc dust (1.98 g, 30.3 mmol, 4.0 eq.) and the resulting yellow-green slurry was stirred for 24 h at r.t. To this mixture, now a thick grey-pink sludge, was added *via* cannula a solution of crude **5.4.3.1** (7.59 mmol) in CH_2Cl_2 (20 mL + 3 x 3 mL rinses). The resulting slurry was stirred for 2 h at r.t. It was then concentrated to a volume of approx. 10 mL, filtered through SiO_2 (eluting with CH_2Cl_2), concentrated and chromatographed (SiO_2, 20% Et_2O in petrol) to yield **2.13.4.3** as a colourless oil (2.97 g, 6.67 mmol, 88%):

$[\alpha]_D$: +33.2° (c = 2.47, CH_2Cl_2).

IR (film): ν = 2964, 2930, 2871, 1783, 1699, 1620, 1496, 1455, 1348, 1279, 1249, 1198, 1150, 1122, 1090, 1067, 1039, 990, 963, 850, 798, 768, 731, 700 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 7.04 (3H, m, Ph), 6.88 (2H, m, Ph), 5.99 (1H, d, J = 9.7 Hz, C5'-H), 4.87 (1H, d, J = 7.5 Hz, C5-H), 4.30 (1H, app quintet, J = 6.8 Hz, C4-H), 3.02 and 2.87 (2H, A and B of ABXY, J_{AB} = 17.1 Hz, J_{AX} = 7.1 Hz, J_{AY} = 8.0 Hz, J_{BX} = 6.3 Hz, J_{BY} = 7.8 Hz, C2'-H_2), 2.53 (1H, m, C4'-H), 1.60 (2H, m, C3'-H_2,), 0.75 (3H, d, J = 6.8 Hz, C4'-Me), 0.65 (3H, d, J = 6.6 Hz, C4-Me).

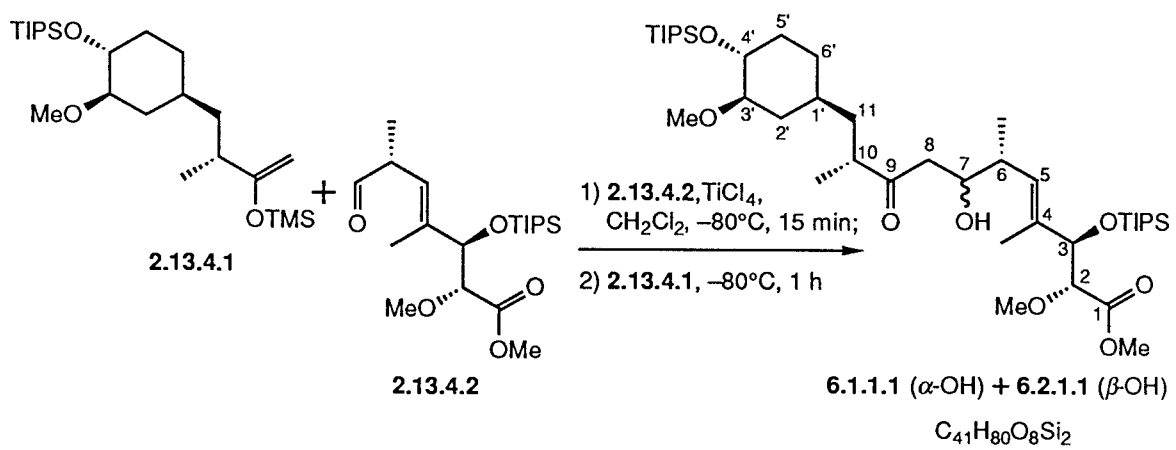
^{13}C NMR (67.5 MHz, C_6D_6): δ = 172.77 (0), 153.45 (0), 144.54 (1), 134.81 (0), 129.38 (1, 2C), 129.28 (1), 126.57 (1, 2C), 89.36 (0), 79.30 (1), 55.24 (1), 38.88 (1), 34.22 (2), 31.15 (2), 19.69 (3), 15.13 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 461* [$(MNH_4)^+$, 15], 444* [$(MH)^+$, 18], 383 (28), 366 (44), 303 (37), 286 (100), 242 (16), 195 (23), 178 (29), 134 (33), 118 (19), 35 (28); Br isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing $^{79}Br/^{79}Br$).

HRMS (EI mode, 70 eV): found, $M^{+\bullet}$, 442.9706. $C_{17}H_{19}Br_2NO_3$ requires 442.9732.

8.5 Experimental Procedures for Chapter 6

Methyl (2*R*,3*R*,6*R*,7*R*,10*R*)-(*E*)-7-Hydroxy-2-methoxy-11-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-4,6,10-trimethyl-9-oxo-3-[(triisopropylsilyl)oxy]undec-4-enoate (6.1.1.1):



A solution of crude **2.13.4.2** (3.24 mmol) in CH_2Cl_2 (10 mL) at –80°C was treated dropwise with $TiCl_4$ (9.7 mL of a 1.0 M solution in CH_2Cl_2, 9.7 mmol, 3.0 eq.) and the resulting orange solution was stirred at –80°C for 15 min. A solution of crude **2.13.4.1** (6.39 mmol, 2.0 eq.) in CH_2Cl_2 (10 mL + 3 x 2 mL rinses) was then added dropwise *via* cannula. The resulting deep red solution was stirred at –80°C for 1 h. It was then transferred *via* cannula into a rapidly stirred solution of ice-cold sat. $NaHCO_3$ (100 mL). The resulting white mixture was extracted with CH_2Cl_2 (3 x 100 mL), then the combined extracts were dried, concentrated and chromatographed (SiO_2, 10 → 25% Et_2O in petrol) to yield ketone **3.4.2.3** (1.45 g, 3.91 mmol, 124% theoretical recovery), then **6.1.1.1** (1.74 g, 2.30 mmol, 71%), then **6.2.1.1** (131 mg, 0.173 mmol, 5%) as colourless oils (total yield: 76%, 93:7 mixture of diastereomers).

Characterisation data for **6.1.1.1**:

$[\alpha]_D$: +2.4° (*c* = 2.81, $CHCl_3$).

IR (film): ν = 3518 (br), 2943, 2867, 1752, 1705, 1463, 1383, 1263, 1195, 1114, 1067, 1014, 998, 883, 813, 680 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 5.11 (1H, br d, J = 10.2 Hz, C5-H), 4.61 (1H, d, J = 5.9 Hz, C3-H), 3.91 (1H, d, J = 5.9 Hz, C2-H), 3.86 (1H, br t, J = 9.4 Hz, C7-H), 3.62 (1H, ddd, J = 4.8, 8.2, 10.9 Hz, C4'-H), 3.43 (3H, s, CO_2Me), 3.28 (4H, s, OH, CHO*Me*), 3.20 (3H, s, CHO*Me*), 2.86 (1H, ddd, J = 4.3, 8.2, 10.7 Hz, C3'-H), 2.80 and 2.44 (2H, A and B of ABX, J_{AB} = 17.5 Hz, J_{AX} = 2.1 Hz, J_{BX} = 9.4 Hz, C8-H_2), 2.56 (1H, m, C6-H), 2.53 (1H, sextet, J = 7.0 Hz, C10-H), 2.03 (1H, m), 1.93 (1H, m), 1.80 (3H, d, J = 1.2 Hz, C4-Me), 1.68 (1H, dt, J = 14.0, 7.0 Hz, C11-H), 1.53 (1H, m), 1.47–0.64 (5H, m), 1.22 (21H, m, TIPS), 1.17 (3H, d, J = 7.0 Hz, CH*Me*), 1.13 (21H, m, TIPS), 1.02 (3H, d, J = 7.0 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 215.94 (0), 171.79 (0), 136.56 (0), 132.69 (1), 85.64 (1), 85.39 (1), 80.38 (1), 76.38 (1), 72.83 (1), 59.10 (3), 57.60 (3), 51.86 (3), 46.83 (2), 45.35 (1), 40.44 (2), 39.37 (1), 37.07 (2), 35.13 (2), 34.51 (1), 31.80 (2), 19.16 (3, 6C), 18.93 (3, 6C), 17.50 (3), 17.33 (3), 13.74 (1, 3C), 13.46 (1, 3C), 13.17 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 774 [$(MNH_4)^+$, 14], 757 [$(MH)^+$, 10), 565 (4), 404 (100), 371 (95), 339 (8), 283 (5), 213 (4), 165 (8), 122 (5), 58 (4).

Characterisation data for **6.2.1.1**:

$[\alpha]_D$: –16.9° (c = 2.83, $CHCl_3$).

IR (film): ν = 3504 (br), 2938, 2866, 1751, 1708, 1463, 1383, 1313, 1258, 1195, 1112, 1067, 997, 920, 883, 836, 813, 680 cm^{-1}.

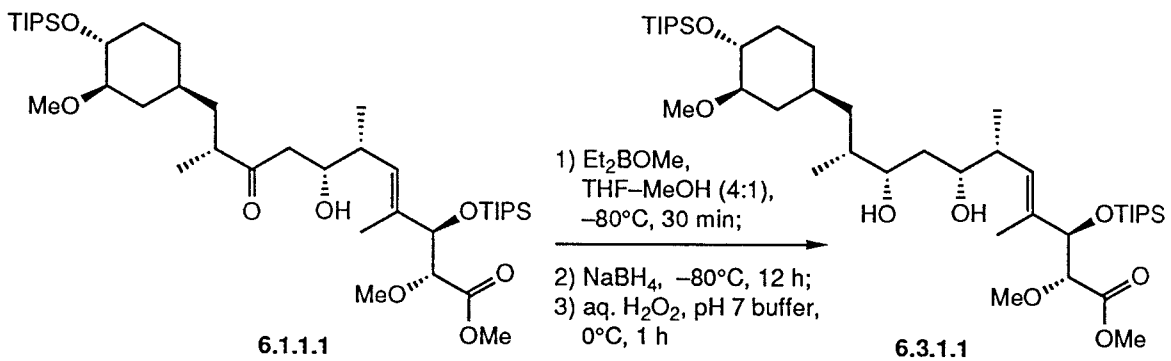
^1H NMR (270 MHz, C_6D_6): δ = 5.34 (1H, br d, J = 10.2 Hz, C5-H), 4.68 (1H, d, J = 5.6 Hz, C3-H), 3.97 (1H, ddd, J = 2.8, 4.8, 9.4 Hz, C7-H), 3.94 (1H, d, J = 5.6 Hz, C2-H), 3.64 (1H, ddd, J = 4.5, 8.1, 10.9 Hz, C4'-H), 3.47 (3H, s, CO_2Me), 3.27 (3H, s, CHO*Me*), 3.20 (3H, s, CHO*Me*), 3.04 (1H, br s, OH), 2.87 (1H, ddd, J = 4.5, 8.1, 10.9 Hz, C3'-H), 2.70 and 2.35 (2H, A and B of ABX, J_{AB} = 16.6 Hz, J_{AX} = 9.4 Hz, J_{BX} = 2.8 Hz, C8-H_2), 2.60 (1H, sextet, J = 7.0 Hz, C10-H), 2.41 (1H, m, C6-H), 2.07 (1H, m), 1.95 (1H, m), 1.84 (3H, d, J = 1.2 Hz, C4-Me), 1.74 (1H, dt, J = 13.8, 7.0 Hz, C11-H), 1.56 (1H, m), 1.49–0.66 (5H, m), 1.23 (21H, m, TIPS), 1.13 (21H, m, TIPS), 1.07 (3H, d, J = 7.0 Hz, CH*Me*), 1.04 (3H, d, J = 7.0 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 214.85 (0), 171.84 (0), 137.40 (0), 131.36 (1), 85.79 (1), 85.45 (1), 80.54 (1), 76.41 (1), 72.62 (1), 59.21 (3), 57.60 (3), 52.01 (3), 46.44 (2),

45.39 (1), 40.31 (2), 38.97 (1), 37.16 (2), 35.18 (2), 34.51 (1), 31.79 (2), 19.16 (3, 6C), 18.93 (3, 6C), 17.85 (3), 17.62 (3), 13.74 (1, 3C), 13.41 (1, 3C), 13.18 (3).

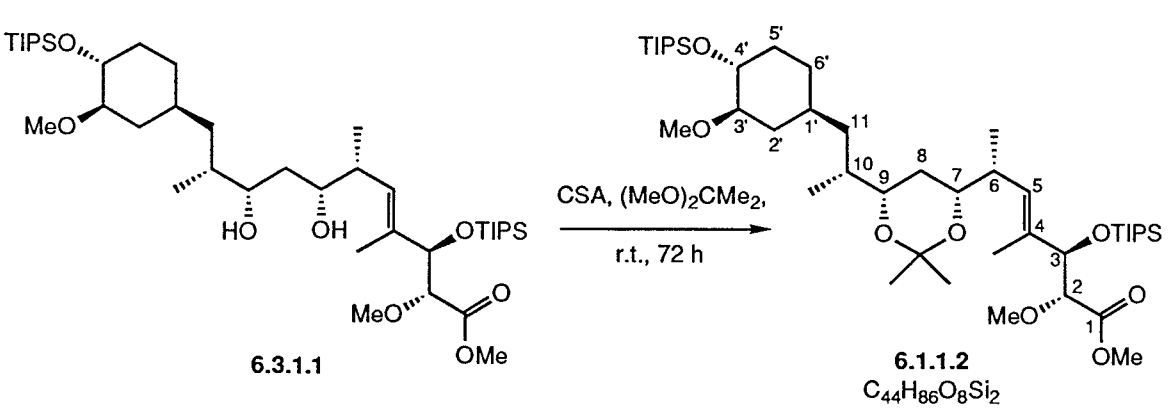
LRMS (CI mode, NH_3): *m/z* (%) = 774 [$(MNH_4)^+$, 13], 757 [$(MH)^+$, 9], 565 (4), 404 (100), 371 (94), 327 (8), 283 (5), 213 (12), 165 (8), 122 (7), 58 (6).

Methyl (2*R*,3*R*,6*R*,7*R*,9*S*,10*R*)-(*E*)-7,9-Dihydroxy-2-methoxy-11-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-4,6,10-trimethyl-3-[(triisopropylsilyl)oxy]undec-4-enoate (6.3.1.1):



A solution of **6.1.1.1** (1.98 g, 2.61 mmol) in THF–MeOH (4:1, 50 mL) at –80°C was treated with Et_2BOMe (3.9 mL of a 1.0 M solution in THF, 3.90 mmol, 1.5 eq.). The resulting solution was stirred at –80°C for 30 min, then $NaBH_4$ (247 mg, 6.53 mmol, 2.5 eq.) was added and stirring was continued at –80°C for a further 12 h. pH 7 Buffer solution (50 mL) was then added carefully. The mixture was subsequently warmed to 0°C, treated with 30 wt. % aq. H_2O_2 (50 mL) and stirred for 1 h. It was then poured into brine (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried and concentrated to yield crude **6.3.1.1** as a white foam which was used without further purification.

Methyl (2*R*,3*R*,6*R*,7*R*,9*S*,10*R*)-(*E*)-7,9-*O*-Isopropylidene-7,9-dihydroxy-2-methoxy-11-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-4,6,10-trimethyl-3-[(triisopropylsilyl)oxy]undec-4-enoate (6.1.1.2):



A solution of crude **6.3.1.1** (2.61 mmol) in $(MeO)_2CMe_2$ (40 mL) was treated with CSA (121 mg, 0.521 mmol, 20%) and stirred at r.t. for 72 h. The solution was then diluted with Et_2O (200 mL) and poured into sat. $NaHCO_3$ (100 mL). The organic phase was separated and the aq. phase was extracted with Et_2O (3 x 50 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 10% Et_2O in petrol) to yield **6.1.1.2** as a colourless oil (1.97 g, 2.46 mmol, 94%):

$[\alpha]_D$: –5.1° (c = 2.53, CH_2Cl_2).

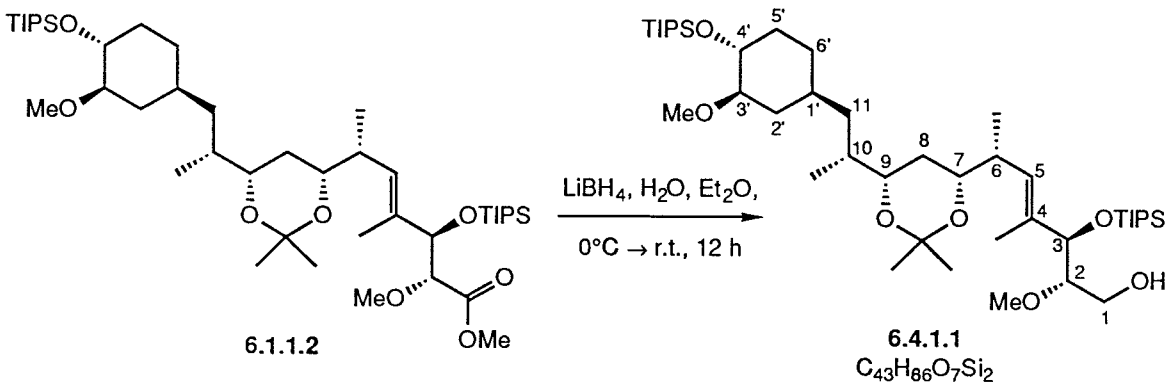
IR (film): ν = 2942, 2866, 1749, 1463, 1379, 1256, 1199, 1174, 1114, 1067, 998, 920, 883, 809, 680 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 5.24 (1H, br d, J = 10.1 Hz, C5-H), 4.64 (1H, d, J = 6.9 Hz, C3-H), 3.86 (1H, d, J = 6.9 Hz, C2-H), 3.64 (1H, ddd, J = 4.8, 8.5, 11.0 Hz, C4'-H), 3.56–3.39 (2H, m, C7-H, C9-H), 3.48 (3H, s, CO_2Me), 3.26 (3H, s, CHO*Me*), 3.20 (3H, s, CHO*Me*), 2.90 (1H, ddd, J = 4.4, 8.5, 11.2 Hz, C3'-H), 2.56 (1H, m, C6-H), 2.17 (1H, m), 1.96 (1H, m), 1.80–0.70 (10H, m), 1.71 (3H, d, J = 1.4 Hz, C4-Me), 1.57 (3H, s, isopropylidene-Me), 1.40 (3H, s, isopropylidene-Me), 1.22 (21H, m, TIPS), 1.18 (3H, d, J = 6.6 Hz, CH*Me*), 1.14 (21H, m, TIPS), 0.92 (3H, d, J = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 171.95 (0), 135.96 (0), 132.79 (1), 99.20 (0), 85.75 (1), 84.74 (1), 80.54 (1), 76.58 (1), 74.56 (1), 74.17 (1), 58.91 (3), 57.53 (3), 51.77 (3), 40.51 (2), 39.73 (1), 36.62 (1), 36.55 (2), 35.49 (2), 34.45 (1), 33.08 (2), 32.98 (2), 31.31 (3), 20.64 (3), 19.16 (3, 6C), 18.98 (3, 6C), 17.23 (3), 16.12 (3), 13.76 (1, 3C), 13.59 (1, 3C), 12.92 (3).

LRMS (Ar FAB mode, NBA matrix + NaI): m/z (%) = 821 [$(MNa)^+$, 9], 351 (23), 217 (40), 202 (32), 117 (35), 157 (56), 145 (82), 133 (29), 115 (100), 103 (43), 89 (78), 75 (96), 59 (96).

(2*S*,3*R*,6*R*,7*R*,9*S*,10*R*)-(*E*)-7,9-*O*-Isopropylidene-2-methoxy-11-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-4,6,10-trimethyl-3-[(triisopropylsilyl)oxy]undec-4-ene-1,7,9-triol (6.4.1.1):



6.1.1.2

6.4.1.1
$C_{43}H_{86}O_7Si_2$

A solution of **6.1.1.2** (1.73 g, 2.16 mmol) in Et_2O (25 mL) containing H_2O (0.39 mL, 21.64 mmol, 10 eq.) at 0°C was treated with $LiBH_4$ (11 mL of a 2.0 M solution in THF, 22.0 mmol, 10 eq.) dropwise and the resulting cloudy white mixture was stirred as it warmed slowly to r.t. over 12 h. It was then recooled to 0°C and quenched with sat. NH_4Cl (10 mL). After stirring at 0°C for 10 min, the mixture was diluted with CH_2Cl_2 (100 mL) and poured into sat. NH_4Cl (100 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 30% Et_2O in petrol) to yield **6.4.1.1** as a colourless oil (1.60 g, 2.07 mmol, 96%):

$[\alpha]_D$: –23.2° (*c* = 1.86, CH_2Cl_2).

IR (film): ν = 3460 (br), 2940, 2866, 1464, 1379, 1256, 1200, 1113, 1013, 997, 920, 883, 810, 679 cm^{-1}.

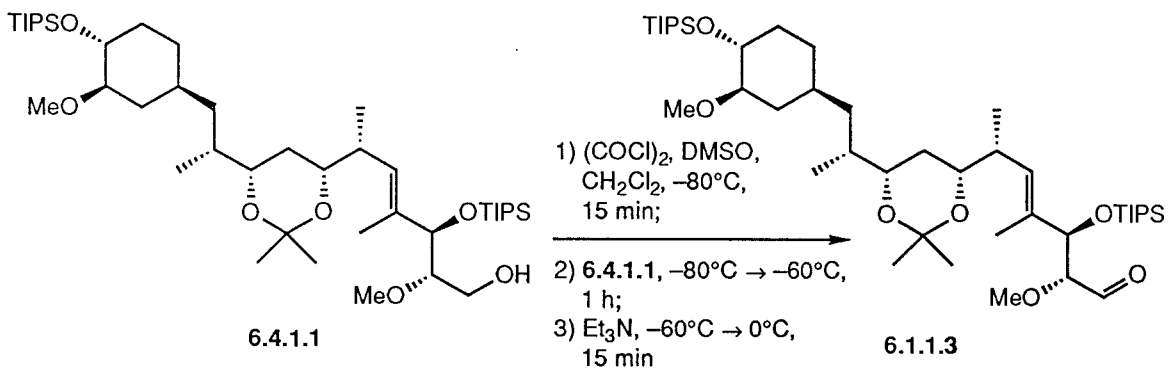
^1H NMR (270 MHz, C_6D_6): δ = 5.32 (1H, br d, *J* = 10.2 Hz, C5-H), 4.34 (1H, d, *J* = 5.6 Hz, C3-H), 3.80 and 3.76 (2H, A and B of ABX, J_{AB} = 11.7 Hz, J_{AX} = 4.7 Hz, J_{BX} = 4.0 Hz, C1-H_2), 3.67 (1H, ddd, *J* = 5.0, 8.5, 11.1 Hz, C4'-H), 3.52 (2H, m, C7-H, C9-H), 3.30 (3H, s, OMe), 3.25 (3H, s, OMe), 3.17 (1H, app q, *J* = 4.8 Hz, C2-H), 2.93 (1H, ddd, *J* = 4.4, 8.5, 11.2 Hz, C3'-H), 2.59 (1H, m, C6-H), 2.19 (1H, m), 1.99 (1H, m), 1.75–0.74 (11H, m), 1.69 (3H, d, *J* = 1.1 Hz, C4-Me), 1.57 (3H, s, isopropylidene-Me), 1.39 (3H, s, isopropylidene-Me), 1.24 (21H, m, TIPS), 1.17 (24H, m, CH*Me*, TIPS), 0.94 (3H, d, *J* = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 136.69 (0), 131.41 (1), 99.21 (0), 85.78 (1), 84.76 (1), 79.54 (1), 76.61 (1), 74.51 (1), 74.25 (1), 61.60 (2), 59.07 (3), 57.63 (3), 40.51 (2), 39.52 (1), 36.61 (2), 36.58 (1), 35.47 (2), 34.49 (1), 33.10 (2), 32.78 (2), 31.28 (3),

20.61 (3), 19.17 (3, 6C), 19.11 (3, 6C), 17.23 (3), 16.19 (3), 13.77 (1, 3C), 13.72 (3), 13.64 (1, 3C).

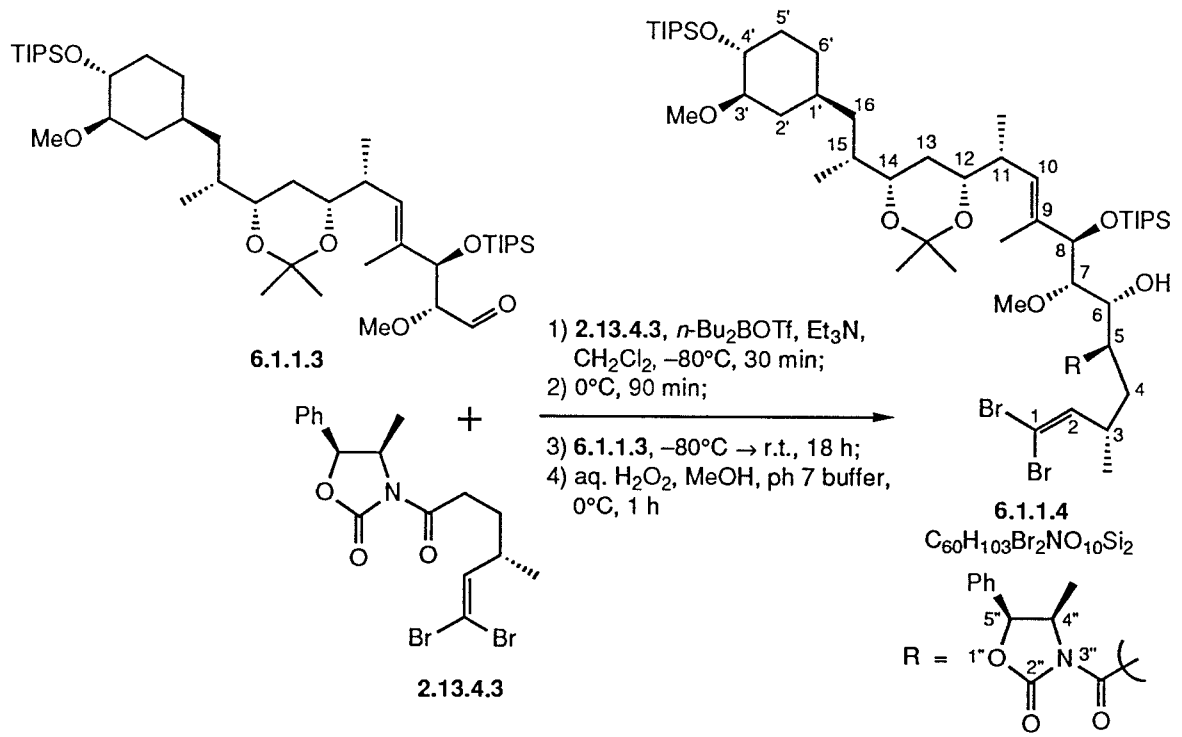
LRMS (EI mode, 70 eV): *m/z* (%) = 771 ($M^{+\bullet}$, 1), 695 (33), 463 (22), 383 (36), 351 (58), 339 (40), 177 (44), 145 (100), 117 (65), 103 (59), 89 (59), 75 (83).

(2*R*,3*R*,6*R*,7*R*,9*S*,10*R*)-(*E*)-7,9-*O*-Isopropylidene-7,9-dihydroxy-2-methoxy-11-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-4,6,10-trimethyl-3-[(triisopropylsilyl)oxy]undec-4-enal (6.1.1.3):



A solution of $(COCl)_2$ (0.36 mL, 4.13 mmol, 2.0 eq.) in CH_2Cl_2 (20 mL) at –80°C was treated with DMSO (0.44 mL, 6.20 mmol, 3.0 eq.) and the resulting mixture was stirred at –80°C for 15 min. A solution of **6.4.1.1** (1.60 g, 2.07 mmol) in CH_2Cl_2 (10 mL + 3 x 3 mL rinses) was then added *via* cannula, resulting in the formation of a white precipitate. Stirring was continued for a further 1 h as the mixture warmed gradually to –60°C, then Et_3N (1.7 mL, 12.2 mmol, 6.0 eq.) was added and the mixture was warmed to 0°C and stirred for a further 15 min. It was then diluted with Et_2O (100 mL), washed with H_2O and brine, then dried and concentrated to yield crude **6.1.1.3** as a pale yellow oil which was used without further purification.

(3*S*,5*R*,6*R*,7*S*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-1,1-dibromo-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,9,11,15-tetramethyl-5-[[(4*R*,5*S*)-4-methyl-2-oxo-5-phenyl-oxazolidin-3-yl]oxomethyl]-8-[(triisopropylsilyl)oxy]hexadeca-1,9-diene-6,12,14-triol (6.1.1.4):



A solution of **2.13.4.3** (1.84 g, 4.13 mmol, 2.0 eq.) in CH_2Cl_2 (10 mL) at –80°C was treated with *n*-Bu2BOTf (1.3 mL, 5.22 mmol, 2.5 eq.) and stirred at –80°C for 5 min. Et_3N (0.87 mL, 6.24 mmol, 3.0 eq.) was then added dropwise and the resulting bright yellow solution was stirred at –80°C for 30 min. It was then warmed to 0°C and stirred for a further 90 min before being recooled to –80°C. A solution of crude **6.1.1.3** (2.07 mmol) in CH_2Cl_2 (6 mL + 3 x 3 mL rinses) was then added dropwise *via* cannula and stirring was continued for a further 18 h as the mixture warmed gradually to r.t. It was then cooled to 0°C and treated successively with pH 7 buffer solution (30 mL), MeOH (50 mL) and 30 wt. % aq. H_2O_2 (20 mL). Stirring was continued at 0°C for a further 1 h, then the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2, 15% Et_2O in petrol) to yield **6.1.1.4** as a white foam (1.96 g, 1.61 mmol, 78%), then **2.13.4.3** as a colourless oil (882 mg, 1.98 mmol, 96% theoretical recovery):

$[\alpha]_D$: –15.0° (*c* = 1.91, CH_2Cl_2).

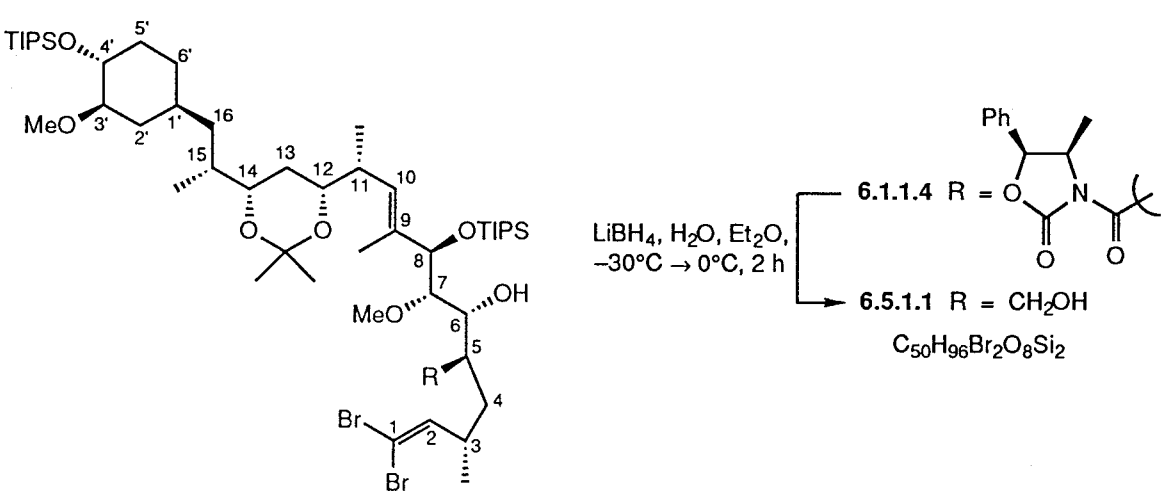
IR (film): ν = 3472 (br), 2941, 2866, 1785, 1694, 1456, 1379, 1340, 1255, 1191, 1118, 1068, 987, 883, 680 cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 7.04 (3H, m, Ph), 6.94 (2H, m, Ph), 6.20 (1H, d, J = 9.5 Hz, C2-H), 5.62 (1H, br d, J = 9.7 Hz, C10-H), 5.17 (1H, d, J = 7.2 Hz, C5"-H), 4.58 (1H, d, J = 4.9 Hz, C8-H), 4.51 (1H, app quintet, J = 6.9 Hz, C4"-H), 4.41 (2H, m, C5-H, C6-H), 3.71–3.27 (5H, m, C7-H, C12-H, C14-H, C4'-H, OH), 3.45 (3H, s, OMe), 3.30 (3H, s, OMe), 2.93 (1H, ddd, J = 4.4, 8.5, 10.8 Hz, C3'-H), 2.76–2.56 (2H, m, C3-H, C11-H), 2.34 (1H, m), 2.20 (1H, m), 2.02 (2H, m), 1.78 (3H, d, J = 0.8 Hz, C9-Me), 1.78–0.74 (10H, m), 1.55 (3H, s, isopropylidene-Me), 1.36 (3H, s, isopropylidene-Me), 1.23 (45H, m, CH*Me*, 2 x TIPS), 0.94 (3H, d, J = 6.0 Hz, CH*Me*), 0.92 (3H, d, J = 6.8 Hz, CH*Me*), 0.82 (3H, d, J = 6.6 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 174.63 (0), 153.35 (0), 144.80 (1), 136.07 (0), 134.58 (0), 131.88 (1), 129.46 (1, 2C), 129.35 (1), 126.48 (1, 2C), 99.21 (0), 89.64 (0), 85.74 (1), 84.38 (1), 80.39 (1), 79.33 (1), 76.58 (1), 74.55 (1), 73.99 (1), 72.58 (1), 60.39 (3), 57.63 (3), 56.02 (1), 46.90 (1), 40.55 (2), 39.55 (1), 37.72 (1), 36.71 (1), 36.62 (2), 35.90 (2), 35.47 (2), 34.49 (1), 33.14 (2), 32.81 (2), 31.25 (3), 20.68 (3), 20.55 (3), 19.16 (3, 6C), 19.11 (3, 6C), 17.03 (3), 16.26 (3), 15.41 (3), 14.46 (3), 13.74 (1, 3C), 13.69 (1, 3C).

LRMS (Ar FAB mode, NBA matrix + NaI): *m/z* (%) = 1235* [(MNa)$^+$, 100], 518* (42), 474* (62), 427* (44), 383 (61); Br isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing ^{79}Br/^{79}Br).

(3*S*,5*S*,6*R*,7*S*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-1,1-dibromo-6-hydroxy-5-(hydroxymethyl)-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,9,11,15-tetramethyl-8-[(triisopropylsilyl)oxy]hexadeca-1,9-diene-6,12,14-triol (6.5.1.1):



A solution of **6.1.1.4** (1.00g, 0.823 mmol) in Et_2O (15 mL) containing H_2O (33 mg, 1.83 mmol, 2.2 eq.) at –30°C was treated with $LiBH_4$ (0.91 mL of a 2.0 M solution in THF, 1.82

mmol, 2.2 eq.) and the resulting solution was stirred for 2 h as it warmed slowly to 0°C. The cloudy white mixture was then treated with sat. NH_4Cl (5 mL), diluted with CH_2Cl_2 (100 mL) and poured into sat. NH_4Cl (100 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 20% Et_2O in petrol) to yield **6.5.1.1** as a white foam (731 mg, 0.702 mmol, 85%):

$[\alpha]_D$: –16.5° (c = 2.78, CH_2Cl_2).

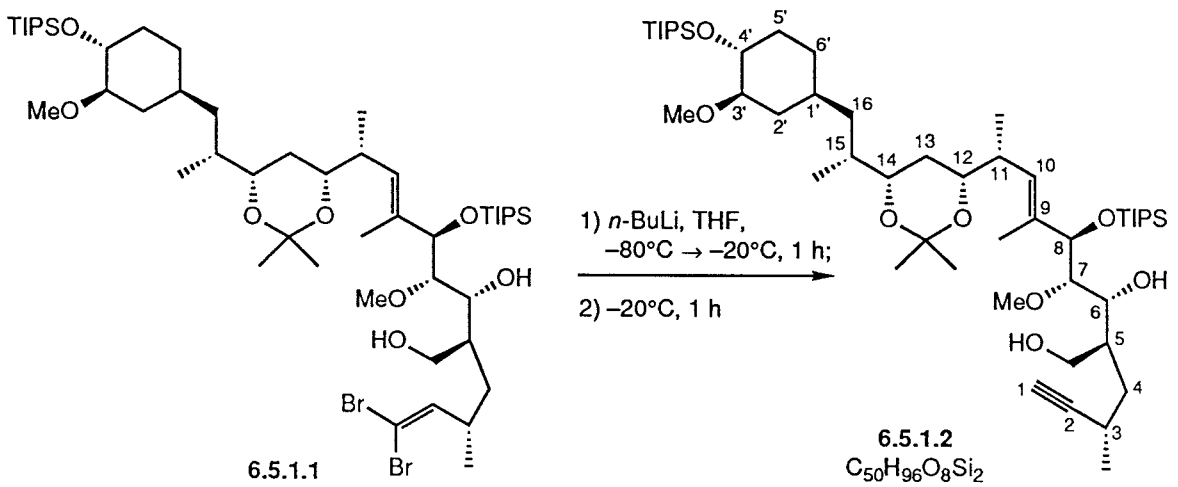
IR (film): ν = 3446 (br), 2941, 2866, 1463, 1379, 1256, 1200, 1113, 1064, 1017, 995, 883, 808, 784, 679 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 6.14 (1H, d, J = 9.7 Hz, C2-H), 5.36 (1H, br d, J = 9.3 Hz, C10-H), 4.35 (1H, d, J = 3.8 Hz, C8-H), 3.97–3.85 (3H, m, C6-H, HOC*H*$_2$), 3.72–3.56 (3H, m, C12-H, C14-H, C4'-H), 3.42 (3H, s, OMe), 3.35 (1H, dd, J = 3.8, 5.0 Hz, C7-H), 3.34 (3H, s, OMe), 2.98 (1H, d, J = 3.6 Hz, C6-OH), 2.95 (1H, ddd, J = 4.5, 8.5, 11.0 Hz, C3'-H), 2.77–2.61 (2H, m, C3-H, C11-H), 2.42 (1H, br s, CH_2O*H*), 2.24 (1H, m), 1.99 (1H, m), 1.83 (3H, d, J = 1.0 Hz, C9-Me), 1.83–0.73 (13H, m), 1.60 (3H, s, isopropylidene-Me), 1.42 (3H, s, isopropylidene-Me), 1.24 (21H, m, TIPS), 1.17 (24H, m, CH*Me*, TIPS), 0.98 (3H, d, J = 6.8 Hz, CH*Me*), 0.87 (3H, d, J = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 145.37 (1), 136.66 (0), 132.07 (1), 99.24 (0), 88.98 (0), 85.76 (1), 85.36 (1), 80.15 (1), 76.59 (1), 74.53 (1), 74.17 (1), 74.03 (1), 64.86 (2), 61.16 (3), 57.67 (3), 40.81 (1), 40.45 (2), 39.30 (1), 37.13 (1), 36.65 (1), 36.57 (2), 35.47 (2), 34.49 (1), 33.14 (2), 32.84 (2), 32.62 (2), 31.25 (3), 20.94 (3), 20.64 (3), 19.19 (3, 6C), 19.14 (3, 6C), 17.04 (3), 16.32 (3), 14.44 (3), 13.74 (3, 3C), 13.54 (3, 3C).

LRMS (Ar FAB mode, NBA matrix + NaI): m/z (%) = 1062* [$(MNa)^+$, 8], 351 (23), 177 (25), 145 (63), 115 (89), 89 (71), 75 (91), 59 (100); Br isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing $^{79}Br/^{79}Br$).

(3*S*,5*S*,6*R*,7*S*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-5-(hydroxymethyl)-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,9,11,15-tetramethyl-8-[(triisopropylsilyl)oxy]hexadec-9-en-1-yne-6,12,14-triol (6.5.1.2):



A solution of **6.5.1.1** (654 mg, 0.628 mmol) in THF (10 mL) at –80°C was treated dropwise with *n*-BuLi (2.1 mL of a 1.51 M solution in hexanes, 3.17 mmol, 5.0 eq.) and the resulting solution was stirred for 1 h as it warmed slowly to –20°C. After stirring for a further 1 h at –20°C, sat. NH_4Cl (5 mL) was added and the mixture was allowed to warm to r.t. It was then diluted with CH_2Cl_2 (100 mL) and poured into sat. NH_4Cl (100 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (SiO_2, 25% Et_2O in petrol) to yield **6.5.1.2** as a white foam (477 mg, 0.541 mmol, 86%):

$[\alpha]_D$: –15.1° (c = 2.82, CH_2Cl_2).

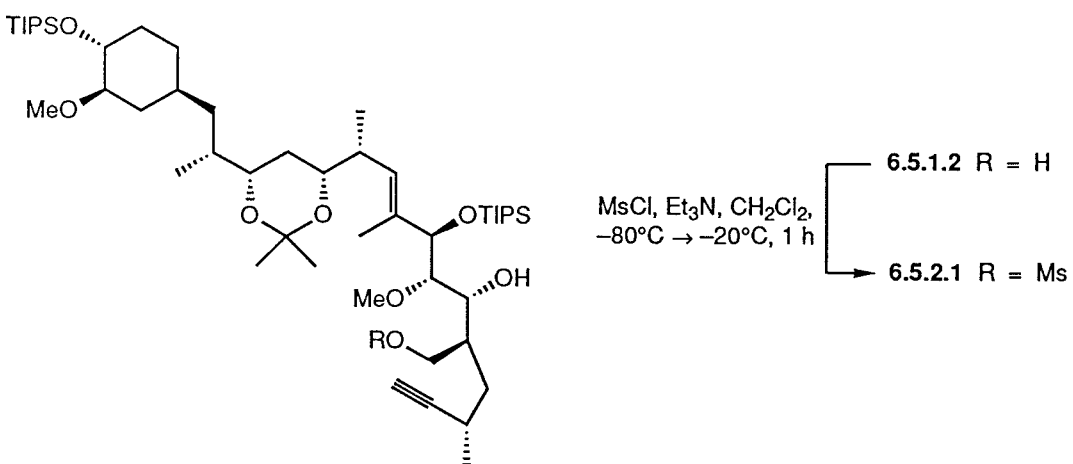
IR (film): ν = 3453 (br), 3310, 2940, 2867, 1463, 1379, 1256, 1201, 1114, 1063, 1014, 883, 809, 680, 634 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 5.37 (1H, br d, J = 9.7 Hz, C10-H), 4.45 (1H, d, J = 3.4 Hz, C8-H), 3.96 (3H, m, C6-H, HOC*H*$_2$), 3.67 (1H, ddd, J = 4.7, 8.5, 10.9 Hz, C4'-H), 3.56 (2H, m, C12-H, C14-H), 3.47 (3H, s, OMe), 3.43 (1H, dd, J = 3.4, 6.5 Hz, C7-H), 3.33 (3H, s, OMe), 2.98 (1H, br s, C6-OH), 2.94 (1H, ddd, J = 4.4, 8.5, 11.2 Hz, C3'-H), 2.73–2.60 (3H, m, C3-H, C11-H, CH$_2$O*H*), 2.21 (2H, m), 1.99 (2H, m), 1.94–0.76 (11H, m), 1.90 (1H, d, J = 2.3 Hz, C1-H), 1.87 (3H, br s, C9-Me), 1.58 (3H, s, isopropylidene-Me), 1.40 (3H, s, isopropylidene-Me), 1.24 (21H, m, TIPS), 1.18 (27H, m, 2 x CH*Me*, TIPS), 0.96 (3H, d, J = 6.6 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 136.89 (0), 131.94 (1), 99.31 (0), 89.38 (1), 86.23 (1), 85.78 (1), 79.98 (1), 76.64 (1), 74.69 (1), 74.52 (1), 73.97 (1), 70.14 (0), 64.92 (2), 61.37 (3), 57.63 (3), 41.52 (1), 40.48 (2), 39.26 (1), 36.62 (1), 36.55 (2), 35.49 (2), 34.51 (1), 33.10 (2), 32.75 (2), 32.63 (2), 31.25 (3), 24.49 (1), 22.76 (3), 20.61 (3), 19.17 (3, 6C), 19.10 (3, 6C), 16.90 (3), 16.25 (3), 14.41 (3), 13.76 (1, 3C), 13.44 (1, 3C).

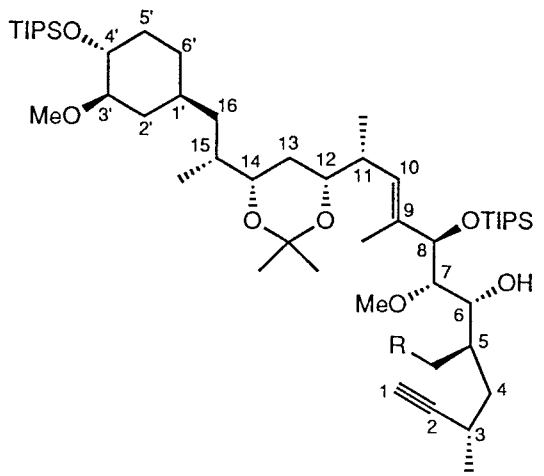
LRMS (Ar FAB mode, NBA matrix + NaI): *m/z* (%) = 904 [$(MNa)^+$, 26], 351 (28), 253 (21), 177 (32), 157 (50), 145 (63), 115 (91), 103 (44), 89 (70), 75 (96), 59 (100).

(3*S*,5*S*,6*R*,7*S*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-[[(methanesulfonyl)oxy]methyl]-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,9,11,15-tetramethyl-8-[(triisopropylsilyl)oxy]hexadec-9-en-1-yne-6,12,14-triol (6.5.2.1):



A solution of **6.5.1.2** (401 mg, 0.455 mmol) and Et_3N (0.19 mL, 1.36 mmol, 3.0 eq.) in CH_2Cl_2 (8 mL) at –80°C was treated dropwise with MsCl (0.07 mL, 0.904 mmol, 2.0 eq.). The resulting solution was stirred for 1 h as it warmed gradually to –20°C. It was then treated with H_2O (1 mL) and allowed to warm to r.t. The mixture was diluted with Et_2O (50 mL), washed with H_2O and brine, then dried and concentrated to yield crude **6.5.2.1** as a white foam which was used without further purification.

(3*S*,5*R*,6*R*,7*S*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,5,9,11,15-pentamethyl-8-[(triisopropylsilyl)oxy]hexadec-9-en-1-yne-6,12,14-triol (6.5.2.2):



1) $LiEt_3BH$, THF, 0°C → r.t., 60 h;
2) aq. NaOH, aq. H_2O_2, 0°C, 1 h

6.5.2.1 R = OMs

6.5.2.2 R = H

$C_{50}H_{96}O_7Si_2$

A solution of crude **6.5.2.1** (0.455 mmol) in THF (5 mL) at 0°C was treated dropwise with $LiEt_3BH$ (4.6 mL of a 1.0 M solution in THF, 4.6 mmol, 10 eq.). The resulting solution was warmed to r.t. and stirred for 60 h. It was then recooled to 0°C and carefully quenched with a few drops of MeOH (until effervescence ceased). 1 M NaOH (15 mL) was then added, followed (very slowly at first) by 30 wt. % aq. H_2O_2 (15 mL). After stirring at 0°C for 1 h, the mixture was poured into sat. $NaHCO_3$ (30 mL) and extracted with Et_2O (3 x 30 mL). The combined extracts were washed with brine, then dried, concentrated and chromatographed (SiO_2, 8% Et_2O in petrol) to yield **6.5.2.2** as a colourless oil (244 mg, 0.282 mmol, 62%):

$[\alpha]_D$: –14.1° (*c* = 2.20, CH_2Cl_2).

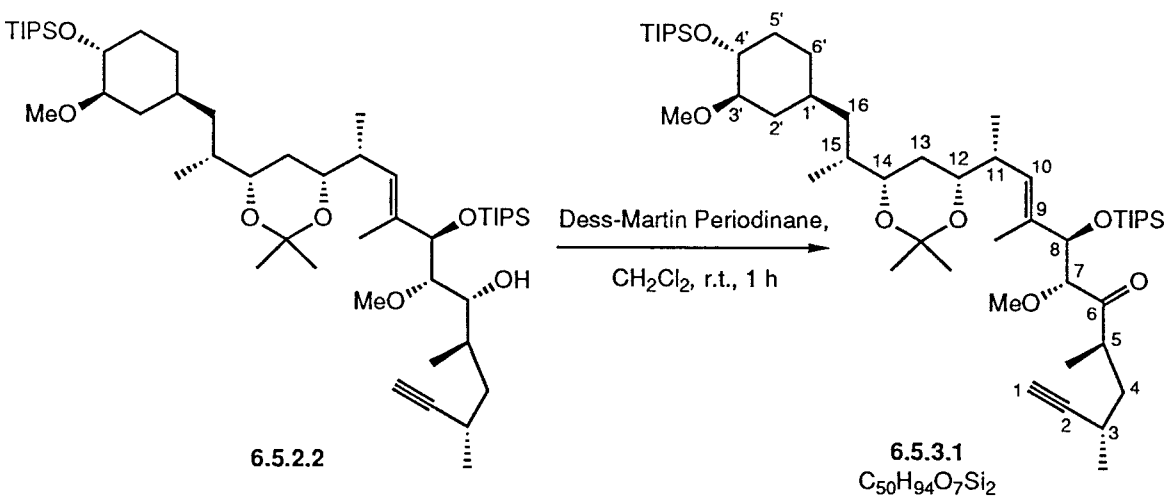
IR (film): ν = 3477 (br), 3310, 2940, 2865, 1462, 1378, 1255, 1200, 1111, 1065, 984, 882, 810, 679, 629 cm^{-1}.

^1H NMR: δ = 5.37 (1H, br d, *J* = 9.7 Hz, C10-H), 4.46 (1H, d, *J* = 5.2 Hz, C8-H), 3.71–3.53 (4H, m, C6-H, C12-H, C14-H, C4'-H), 3.42 (3H, s, OMe), 3.37 (1H, dd, *J* = 3.6, 5.2 Hz, C7-H), 3.31 (3H, s, OMe), 2.93 (1H, ddd, *J* = 4.3, 8.6, 11.3 Hz, C3'-H), 2.70–2.45 (3H, m, C3-H, C11-H, C6-OH), 2.20 (2H, m), 1.99 (2H, m), 1.92 (1H, d, *J* = 2.3 Hz, C1-H), 1.82 (3H, d, *J* = 1.0 Hz, C9-Me), 1.82–0.74 (11H, m), 1.57 (3H, s, isopropylidene-Me), 1.40 (3H, s, isopropylidene-Me), 1.24–1.15 (48H, m, 2 x CH*Me*, 2 x TIPS), 1.10 (3H, d, *J* = 6.8 Hz, CH*Me*), 0.95 (3H, d, *J* = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 136.94 (0), 131.90 (1), 99.27 (0), 89.29 (1), 85.76 (1), 84.71 (1), 79.90 (1), 76.61 (1), 75.21 (1), 74.53 (1), 74.20 (1), 69.94 (0), 61.32 (3), 57.60 (3), 40.50 (2), 39.88 (2), 39.53 (1), 36.62 (1), 36.58 (2), 35.59 (1), 35.49 (2), 34.49 (1), 33.10 (2), 32.79 (2), 31.28 (3), 24.69 (1), 22.89 (3), 20.63 (3), 19.19 (3, 6C), 19.14 (3, 6C), 17.43 (3), 17.16 (3), 16.25 (3), 14.12 (3), 13.77 (1, 3C), 13.63 (1, 3C).

LRMS (EI mode, 70 eV): *m/z* (%) = 864 ($M^{+\bullet}$, 2), 695 (63), 383 (43), 351 (100), 255 (52), 177 (81), 145 (96), 117 (62), 103 (43), 89 (47), 75 (80).

(3*S*,5*R*,7*R*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-12,14-*O*-Isopropylidene-7-methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,5,9,11,15-pentamethyl-6-oxo-8-[(triisopropylsilyl)oxy]hexadec-9-en-1-yne-12,14-diol (6.5.3.1):



6.5.2.2

6.5.3.1
$C_{50}H_{94}O_7Si_2$

To a solution of **6.5.2.2** (241 mg, 0.278 mmol) in CH_2Cl_2 (6 mL) was added Dess-Martin Periodinane (177 mg, 0.417 mmol, 1.5 eq.) and the resulting cloudy white solution was stirred at r.t. for 1 h. It was then diluted with Et_2O (50 mL) and shaken with a 1:1 solution of sat. Na_2S2O_3 and sat. $NaHCO_3$ (50 mL). The organic phase was then separated, washed with sat. $NaHCO_3$ and brine, then dried, concentrated and chromatographed (SiO_2. 7% Et2O in petrol) to yield **6.5.3.1** as a colourless oil (238 mg, 0.276 mmol, 99%):

$[\alpha]_D$: –36.7° (*c* = 2.00, CH_2Cl_2).

IR (film): ν = 3312, 2939, 2866, 1726, 1461, 1378, 1255, 1199, 1114, 1066, 996, 883, 810, 680, 632 cm^{-1}.

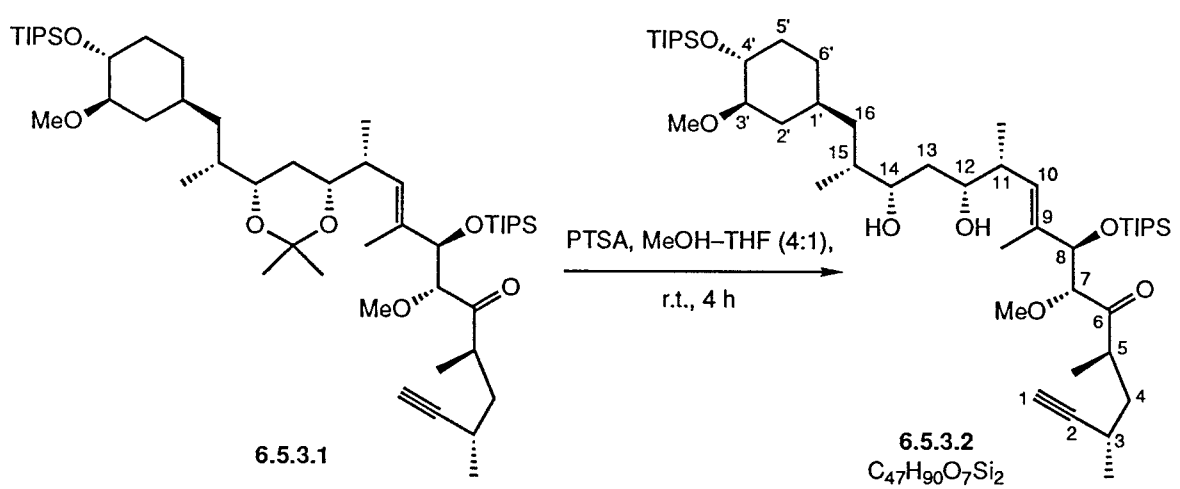
^1H NMR: δ = 5.45 (1H, br d, *J* = 9.9 Hz, C10-H), 4.76 (1H, d, *J* = 4.8 Hz, C8-H), 4.06 (1H, d, *J* = 4.8 Hz, C7-H), 3.66 (1H, ddd, *J* = 4.9, 8.4, 11.1 Hz, C4'-H), 3.58 (2H, m, C12-H, C14-H), 3.29 (1H, m, C5-H) and (6H, s, 2 x OMe), 2.92 (1H, ddd, *J* = 4.4, 8.4,

11.0 Hz, C3'-H), 2.60 (1H, m, C11-H), 2.37 (1H, m, C3-H), 2.21 (1H, m), 1.98 (1H, m), 1.90 (1H, d, J = 2.3 Hz, C1-H), 1.87–0.73 (12H, m), 1.80 (3H, d, J = 1.0 Hz, C9-Me), 1.59 (3H, s, isopropylidene-Me), 1.42 (3H, s, isopropylidene-Me), 1.27–1.17 (45H, m, CH*Me*, 2 x TIPS), 1.14 (3H, d, J = 6.8 Hz, CH*Me*), 1.07 (3H, J = 6.8 Hz, CH*Me*), 0.97 (3H, d, J = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 211.71 (0), 135.87 (0), 131.80 (1), 99.27 (0), 88.37 (1), 88.32 (1), 85.76 (1), 80.61 (1), 76.61 (1), 74.56 (1), 74.13 (1), 70.42 (0), 59.34 (3), 57.56 (3), 43.04 (1), 40.52 (2), 39.88 (2), 39.52 (1), 36.62 (1), 36.57 (2), 35.50 (2), 34.46 (1), 33.08 (2), 32.85 (2), 31.30 (3), 24.56 (1), 22.31 (3), 20.66 (3), 19.17 (3, 12C), 17.01 (3), 16.19 (3), 15.27 (3), 14.05 (3), 13.77 (1, 3C), 13.72 (1, 3C).

LRMS (Ar FAB mode, NBA matrix + NaI): *m/z* (%) = 886 [(MNa)$^+$, 21], 351 (31), 281 (83), 177 (41), 157 (54), 145 (64), 115 (100), 89 (63), 75 (87), 59 (87).

(3*S*,5*R*,7*R*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*)-7-Methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,5,9,11,15-pentamethyl-6-oxo-8-[(triisopropylsilyl)oxy]hexadec-9-en-1-yne-12,14-diol (6.5.3.2):



6.5.3.1

6.5.3.2
$C_{47}H_{90}O_7Si_2$

A solution of **6.5.3.1** (188 mg, 0.218 mmol) in MeOH–THF (4:1, 5 mL) was treated with PTSA (8 mg, 0.042 mmol, 20%) and the resulting mixture was stirred at r.t. for 4 h. The solution was then diluted with Et_2O (50 mL) and poured into sat. $NaHCO_3$ (30 mL). The organic phase was separated and the aq. phase was extracted with Et_2O (3 x 30 mL). The combined organic phase and extracts were then dried, concentrated and chromatographed (10 → 40% Et_2O in petrol) to yield **6.5.3.1** as a colourless oil (56 mg, 0.065 mmol, 30% recovery), then **6.5.3.2** as a white foam (120 mg, 0.146 mmol, 67%). The recovered acetonide was resubjected to the reaction conditions to provide a further 37 mg of **6.5.3.2** (total yield: 157 mg, 0.191 mmol, 88%):

$[\alpha]_D$: –33.2° (c = 2.13, CH_2Cl_2).

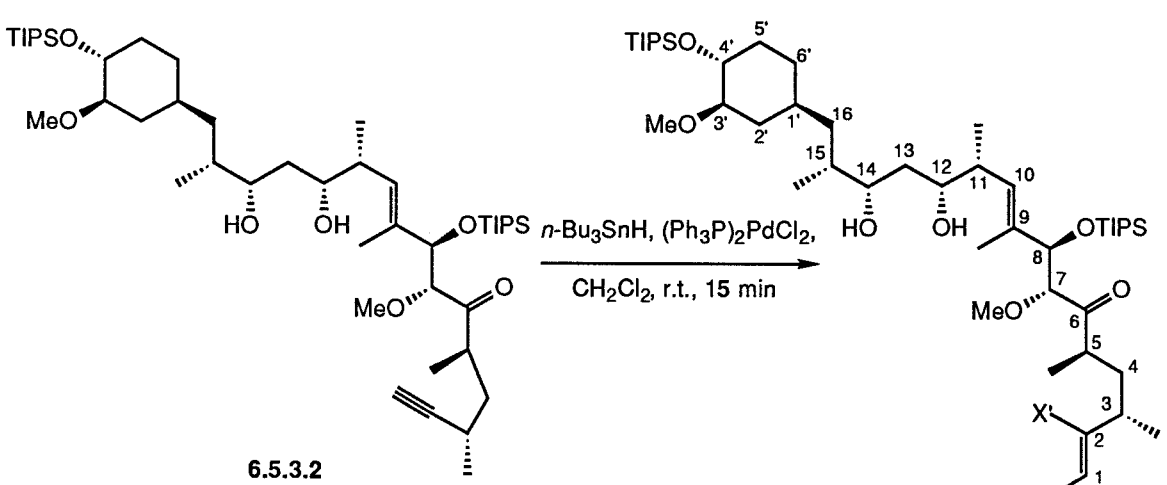
IR (film): ν = 3411 (br), 3312, 2940, 2866, 1724, 1462, 1382, 1328, 1248, 1192, 1115, 1014, 919, 883, 808 cm^{-1}.

^1H NMR (270 MHz, C_6D_6): δ = 5.42 (1H, br, d, J = 9.9 Hz, C10-H), 4.70 (1H, d, J = 4.8 Hz, C8-H), 4.06 (1H, d, J = 4.8 Hz, C7-H), 3.83–3.63 (5H, m, C12-H, C14-H, C4'-H, 2 x OH), 3.33 (3H, s, OMe), 3.27 (1H, m, C5-H) and (3H, s, OMe), 2.92 (1H, ddd, J = 4.5, 8.4, 11.1 Hz, C3'-H), 2.56 (1H, m, C11-H), 2.36 (1H, m, C3-H), 2.20 (1H, m), 1.99 (1H, m), 1.95 (1H, d, J = 2.3 Hz, C1-H), 1.84 (3H, d, J = 0.9 Hz, C9-Me), 1.78–0.74 (12H, m), 1.26–1.15 (45H, m, CH*Me*, 2 x TIPS), 1.11 (3H, d, J = 6.0 Hz, CH*Me*), 1.09 (3H, d, J = 6.6 Hz, CH*Me*), 1.02 (3H, d, J = 6.8 Hz, CH*Me*).

^{13}C NMR (67.5 MHz, C_6D_6): δ = 212.61 (0), 136.13 (0), 132.34 (1), 88.83 (1), 88.31 (1), 85.76 (1), 80.70 (1), 78.34 (1), 78.00 (1), 76.59 (1), 70.50 (0), 59.46 (3), 57.70 (3), 43.03 (1), 40.28 (1), 39.76 (2), 39.72 (2), 37.79 (1), 37.30 (2), 36.57 (2), 35.41 (2), 34.41 (1), 33.08 (2), 24.53 (1), 22.31 (3), 19.16 (3, 6C), 19.11 (3, 6C), 16.52 (3), 16.48 (3), 15.18 (3), 13.89 (3), 13.76 (1, 3C), 13.64 (1, 3C).

LRMS (Ar FAB mode, NBA matrix + NaI): m/z (%) = 846 [$(MNa)^+$, 33], 449 (12), 281 (55), 255 (45), 157 (66), 145 (58), 115 (94), 103 (42), 89 (67), 75 (89), 59 (100).

(3*S*,5*R*,7*R*,8*R*,11*R*,12*R*,14*S*,15*R*)-(*E*,*E*)-7-Methoxy-16-[(1*S*,3*R*,4*R*)-3-methoxy-4-[(triisopropylsilyl)oxy]cyclohexyl]-3,5,9,11,15-pentamethyl-6-oxo-1-(tri-*n*-butylstannyl)-8-[(triisopropylsilyl)oxy]hexadeca-1,9-diene-12,14-diol (2.13.1.1):



6.5.3.2

2.13.1.1 (X' = H, X" = *n*-Bu_3Sn)
+ 6.5.4.1 (X' = *n*-Bu_3Sn, X" = H)
$C_{59}H_{118}O_7Si_2Sn$

n-Bu_3SnH (0.26 mL of a 0.5 M solution in CH_2Cl_2, 0.130 mmol, 1.2 eq.) was added over 15 min to a stirred solution of **6.5.3.2** (90 mg, 0.109 mmol) and $(Ph_3P)_2PdCl_2$ (4 mg, 0.006 mmol, 5%) in CH_2Cl_2 (3 mL) at r.t. The resulting brown mixture was then concentrated and chromatographed (SiO_2, 35% Et_2O in petrol) to yield **2.13.1.1** as a colourless oil, contaminated with a small amount of **6.5.4.1** (total yield: 118 mg, 0.106 mmol, 97%, 93:7 mixture of regioisomers):

$[\alpha]_D$: –24.8° (*c* = 1.07, CH_2Cl_2).

IR (film): ν = 3386 (br), 2926, 2867, 1712, 1597, 1463, 1378, 1327, 1274, 1192, 1115, 1065, 1014, 992, 883, 807 cm^{-1}.

^1H NMR of **2.13.1.1** (270 MHz, C_6D_6): δ = 6.08 and 5.94 (2H, A and B of ABX, J_{AB} = 18.9 Hz, J_{AX} = 0 Hz, J_{BX} = 7.1 Hz, $J_{Sn,A}$ = 78.0, 74.6 Hz, $J_{Sn,B}$ = 67.3, 63.3 Hz, C1-H and C2-H), 5.43 (1H, br d, *J* = 9.7 Hz, C10-H), 4.78 (1H, d, *J* = 5.1 Hz, C8-H), 4.03 (1H, d, *J* = 5.1 Hz, C7-H), 3.80–3.63 (5H, m, C12-H, C14-H, C4'-H, 2 x OH), 3.36 (3H, s, OMe), 3.33 (3H, s, OMe), 3.02 (1H, m, C5-H), 2.92 (1H, ddd, *J* = 4.4, 8.3, 10.8 Hz, C3'-H), 2.56 (1H, m), 2.34 (1H, m), 2.21 (1H, m), 1.98 (1H, m), 1.86 (3H, d, *J* = 0.8 Hz, C9-Me), 1.85–0.73 (12 H, m), 1.65 [6H, m, $Sn(CH_2CH_2CH_2Me)_3$], 1.43 [6H, sextet, *J* = 7.6 Hz, $Sn(CH_2CH_2CH_2Me)_3$], 1.27–1.14 (45H, m, CH*Me*, 2 x TIPS), 1.10–0.96 [24H, m, 3 x CH*Me*, $Sn(CH_2CH_2CH_2Me)_3$].

^{13}C NMR of **2.13.1.1** (67.5 MHz, C_6D_6): δ = 213.02 (0), 155.11 (1), 136.09 (0), 132.57 (1), 127.55 (1, $J_{Sn,C}$ = 391, 375 Hz), 88.87 (1), 85.75 (1), 80.58 (1), 78.41 (1), 78.08 (1), 76.58 (1), 59.72 (3), 57.67 (3), 42.71 (1), 40.55 (1), 40.32 (1), 39.76 (2), 39.50 (2), 37.80 (1), 37.33 (2), 36.52 (2), 35.40 (2), 34.41 (1), 33.08 (2), 30.27 (2, 3C, $J_{Sn,C}$ = 20.5 Hz), 28.36 (2, 3C, $J_{Sn,C}$ = 52.4 Hz), 22.41 (3), 19.17 (3, 6C), 19.11 (3, 6C), 16.51 (3), 16.47 (3), 15.67 (3), 14.65 (3, 3C), 13.87 (3), 13.77 (1, 3C), 13.60 (1, 3C), 10.52 (2, 3C, $J_{Sn,C}$ = 341, 325 Hz).

LRMS (Ar FAB mode, NBA matrix + NaI): *m/z* (%) = 1138* [$(MNa)^+$, 18], 291 (22), 255 (23), 235 (42), 177 (82), 157 (78), 115 (100), 87 (62), 73 (74), 59 (96); Sn isotope pattern observed for peaks marked with an asterisk (peaks reported are those corresponding to fragments containing ^{120}Sn).

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