Synthetic approaches to rapamycin

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Reviewing the literature published up to August 1995

1 Introduction

Rapamycin (**Scheme 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.[6–10]

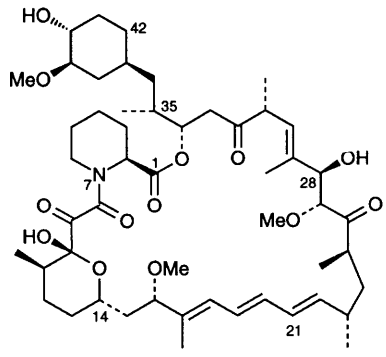
Not surprisingly, the biological importance of rapamycin has stimulated much interest in its chemistry. The first total synthesis of rapamycin was published by the Nicolaou group in 1993. This was closely followed by syntheses from Schreiber and Danishefsky, also in 1993, and later from Smith in 1995. A number of syntheses of various fragments have also been reported, as well as several degradation studies.[11–16] In this review the synthetic work towards rapamycin will be summarised.

2 The total syntheses

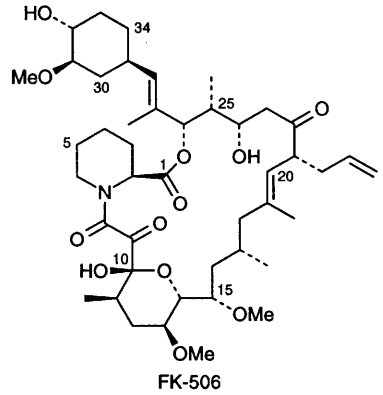
2.1 The Nicolaou total synthesis

Nicolaou's strategy for the synthesis of rapamycin (**Scheme 2**)[17–20] identified fully functionalised acyclic precursor **1** and C19–C20 enedistannane **2** as coupling partners in a 'stitching-cyclisation' process, whereby the olefinic bridging unit would bring together the two terminal vinyl iodides of **1** in a

Abbreviations
acac, acetylacetonate; AIBN, 2,2′-azo(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; Bu, butyl; Bz, benzoyl; 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; For, formyl; HCA, hexachloroacetone; HMDS, hexamethyldisilazide; HMPA, hexamethylphosphoramide; HMPT, hexamethylphosphorous triamide; HOBT, 1-hydroxybenzotriazole; Ipc, isopinocampheyl; LDA, lithium diisopropylamide; MCPBA, *m*-chloroperoxybenzoic acid; MOM, methoxymethyl; Ms, methanesulfonyl; NBD, 2,5-norbornadiene; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; NPSP, *N*-(phenylseleno)phthalimide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Piv, pivaloyl; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PPL, porcine pancreatic lipase; PPTS, pyridinium toluene-*p*-sulfonate; PTSA, toluene-*p*-sulfonic acid; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBHP, *tert*-butyl hydroperoxide; TBS, *tert*-butyldimethylsilyl; TDS, thexyldimethylsilyl; TEMPO, 2,2,6,6-tetramethylpiperidin-1-yloxyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Tr, trityl; Ts, toluene-*p*-sulfonyl.



rapamycin

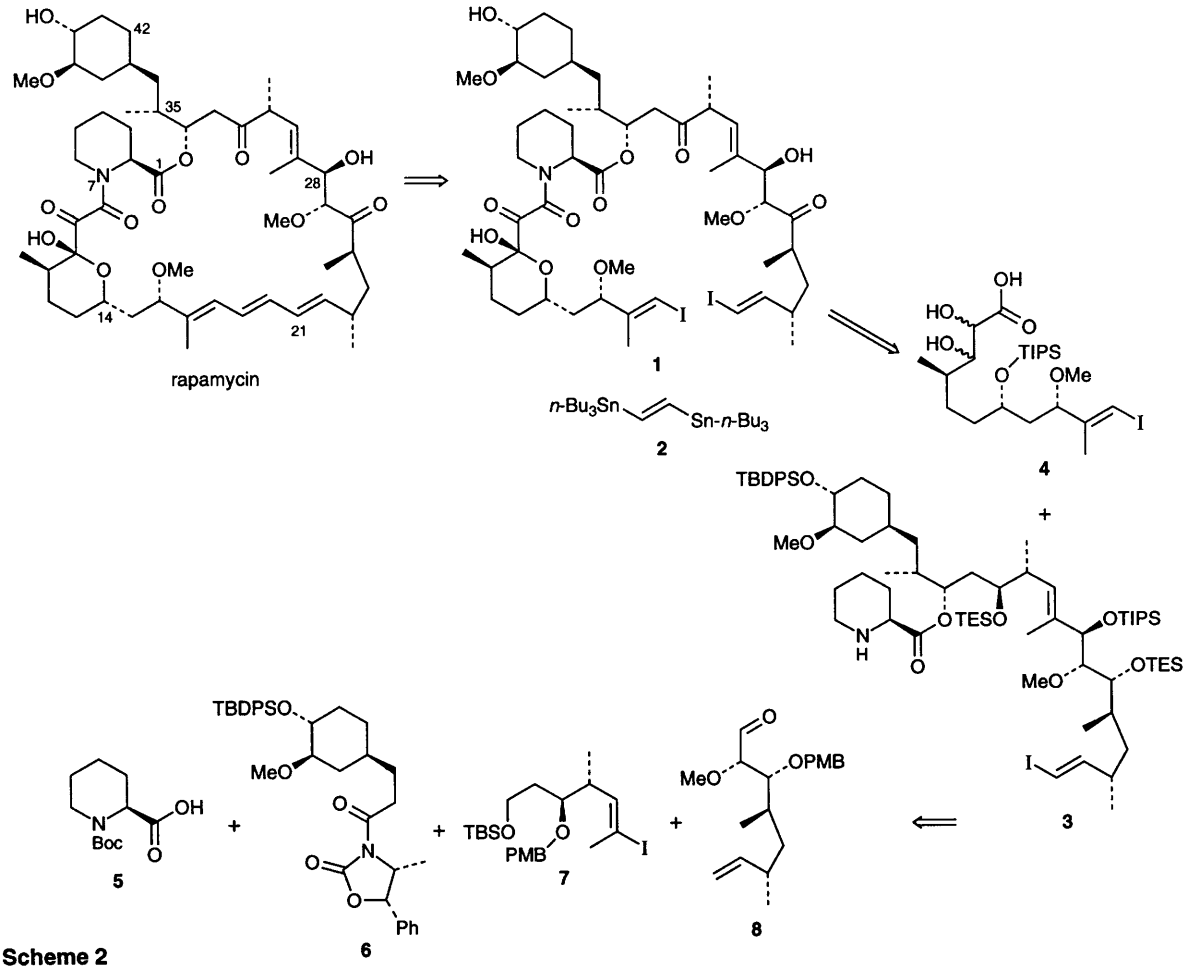


FK-506

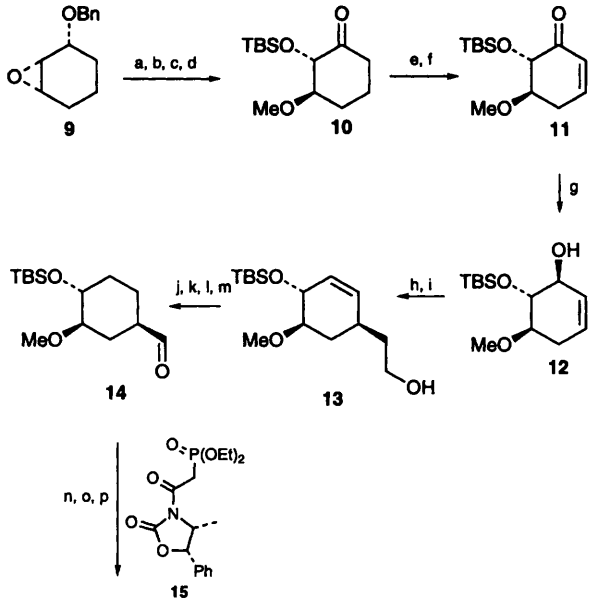
Scheme 1

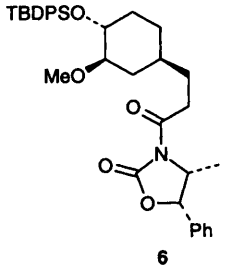
Stille-type reaction to form the triene and macrocycle simultaneously. Such a strategy would thus furnish the natural product in a single, final step and would avoid instability problems, deprotection steps, and late stage oxidation state adjustments. Disconnection of **1** at the N7–C8 amide bond reveals two advanced fragments, **3** and **4**, of which the more complex **3** may be further dissected to subunits **5**–**8** as building blocks.

The synthesis of cyclohexyl fragment **6** (**Scheme 3**) began with epoxide **9**, prepared from 2-bromocyclohexenone by asymmetric reduction, followed by removal of the bromine with Li–Bu^{t}OH, epoxidation using MCPBA, and benzylation. Regioselective opening of the epoxide with CSA in MeOH followed by standard transformations yielded ketone **10**. Enone **11** was then formed from **10** *via* its TMS enol ether by oxidation with $Pd(OAc)_2$. Stereoselective Luche reduction of the enone afforded allylic alcohol **12**, which underwent a stereospecific Eschenmoser–Claisen rearrangement upon heating with *N,N*-dimethylacetamide dimethyl acetal. The resulting amide was reduced to provide primary alcohol **13**, which, after hydrogenation of the double bond, was converted to aldehyde **14** *via* selenoxide formation–elimination and ozonolysis. Condensation of **14** with phosphonate **15** followed by 1,4-reduction of the



Scheme 2

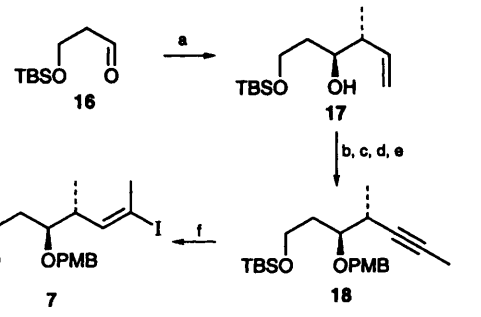




Yields, Reagents and Conditions:

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
i 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) **15**, LiCl, *i*-Pr_2NEt, MeCN, r.t.; 2) **14**
o ↓ 1) $Rh(PPh_3)_3Cl$, Et_3SiH, 50 °C; 2) aq. HF, MeCN, r.t.
p 75% TBDPSCl, imidazole, DMF, r.t.

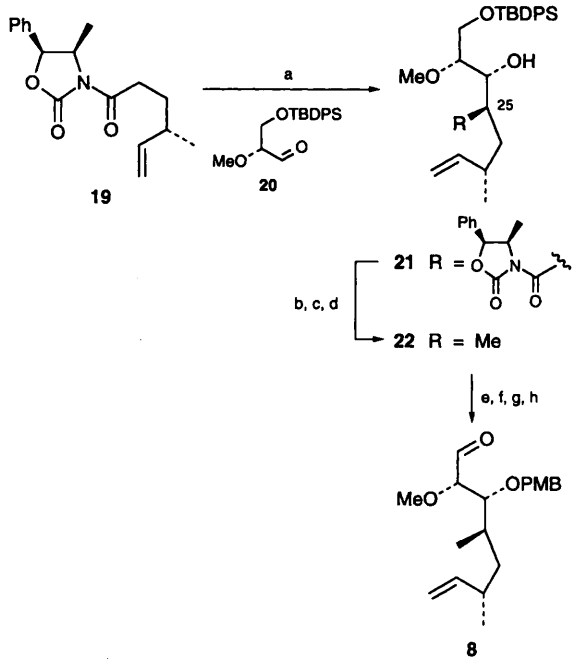
Scheme 3



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 4



Yields, Reagents and Conditions:

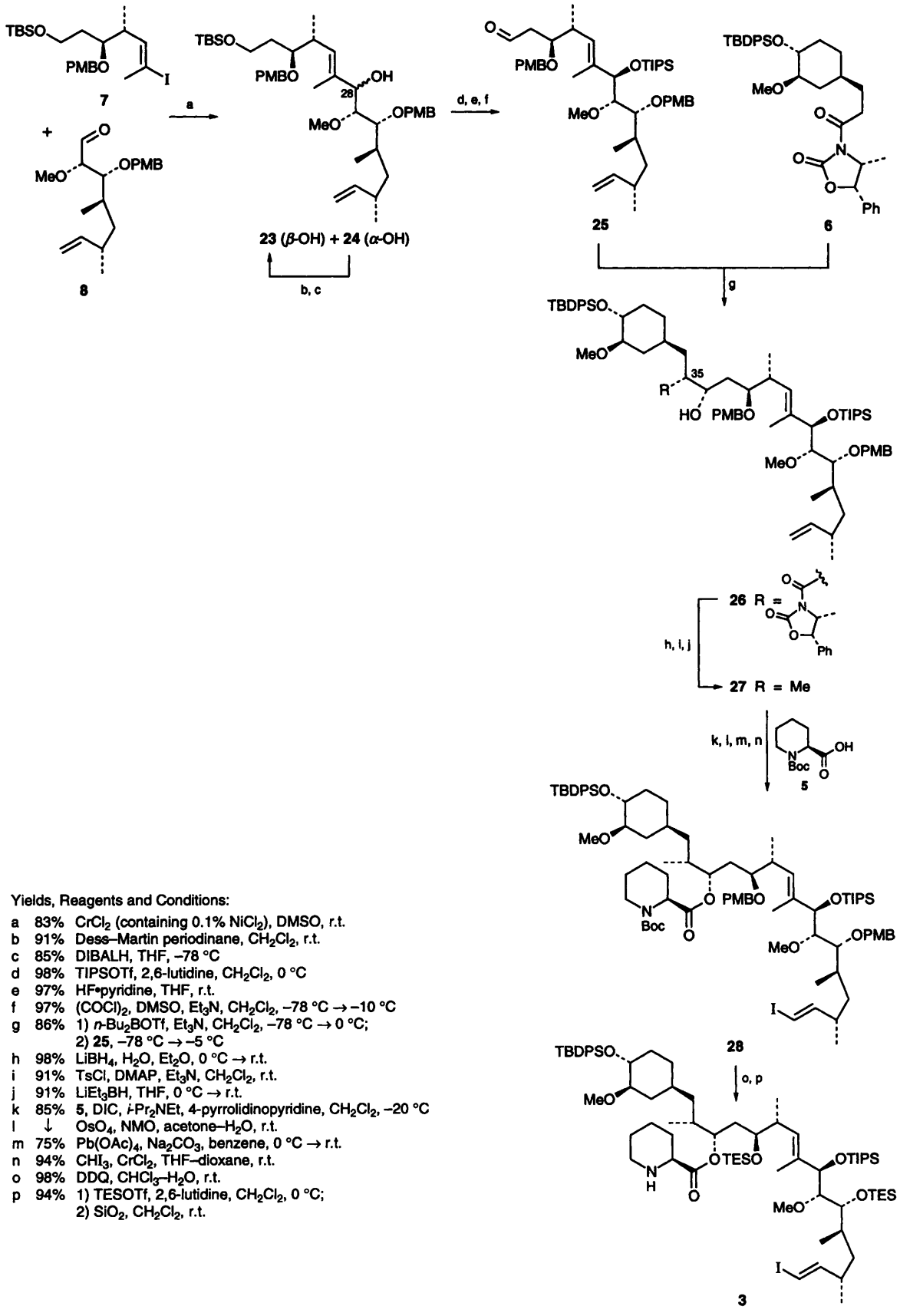
a 73% 1) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C → 0 °C; 2) **20**, −78 °C → −10 °C
b 98% $LiBH_4$, H_2O, Et_2O, 0 °C → r.t.
c 78% TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C
d 92% $LiEt_3BH$, THF, 0 °C → r.t.
e 92% TBAF, THF, r.t.
f 97% $PMPCH(OMe)_2$, CSA, CH_2Cl_2, r.t.
g 96% DIBALH, CH_2Cl_2, −78 °C → r.t.
h 97% $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → r.t.

Scheme 5

resulting α,β-unsaturated *N*-acyloxazolidinone then yielded **6**.

In the synthesis of vinyl iodide **7** (**Scheme 4**) alcohol **17** was stereoselectively formed by asymmetric crotylboration of aldehyde **16** 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 **18**, which was converted to **7** *via* hydrozirconation and quenching with iodine.

The synthesis of aldehyde **8** is depicted in **Scheme 5**. *N*-Acyloxazolidinone **19** was obtained from (+)-β-citronellene beginning with selective cleavage of the trisubstituted double bond (MCPBA, $HClO_4$, $NaIO_4$, then Jones oxidation) followed by conversion of the resultant carboxylic acid to a mixed anhydride with pivaloyl chloride. The mixed anhydride was then condensed with the required lithio-oxazolidinone. The other requisite intermediate, aldehyde **20**, was prepared from



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) **25**, –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.
k	85%	**5**, DIC, *i*-Pr_2NEt, 4-pyrrolidinopyridine, CH_2Cl_2, –20 °C
l	↓	OsO_4, NMO, acetone–H_2O, r.t.
m	75%	$Pb(OAc)_4$, Na_2CO_3, benzene, 0 °C → r.t.
n	94%	CHI_3, $CrCl_2$, THF–dioxane, r.t.
o	98%	DDQ, $CHCl_3$–H_2O, r.t.
p	94%	1) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 2) SiO_2, CH_2Cl_2, r.t.

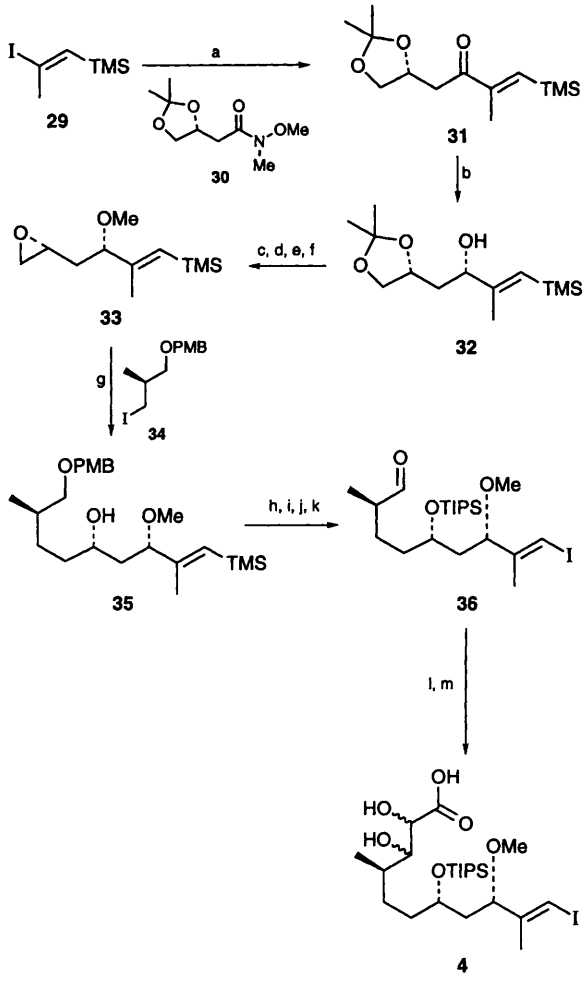
Scheme 6

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 **19** and **20** under Evans aldol conditions yielded alcohol **21**. The chiral auxiliary-bearing side chain was then converted to the requisite C25 methyl group in **22** *via* a three-step reduction–tosylation–reduction sequence. Transformation of **22** to **8** then followed standard procedures.

The coupling of intermediates **5**–**8** and their further elaboration to advanced fragment **3** was accomplished as summarised in **Scheme 6**. Thus, vinyl iodide **7** and aldehyde **8** were coupled by means of a Nozaki–Kishi reaction to afford alcohol **23** along with its C28 epimer **24** in a ratio of *ca.* 2:1. The undesired minor isomer was converted to **23** *via* oxidation to the corresponding ketone followed by stereoselective reduction with DIBALH at −78 °C. Three standard conversions then provided aldehyde **25**, which was condensed with the boron enolate of *N*-acyloxazolidinone **6** to stereoselectively afford aldol product **26**. The requisite C35 methyl group in **27** was then generated from the side chain bearing the chiral auxiliary *via* the three-step procedure as described earlier. Esterification of alcohol **27** with *N*-Boc-L-pipecolinic acid **5** under standard carbodiimide conditions followed by cleavage of the terminal double bond and chromium-mediated iodoolefination then furnished vinyl iodide **28**, which was finally converted to **3** by exchange of the PMB for TES groups accompanied by concomitant removal of the Boc group.

The synthesis of advanced fragment **4** is presented in **Scheme 7**. Vinyl iodide **29**, 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 **30** (readily available from L-ascorbic acid) to afford enone **31**. Stereoselective reduction of **31** according to Suzuki's method yielded alcohol **32** which was converted to epoxide **33** using standard procedures. Regioselective opening of the epoxide with the mixed cuprate derived from the lithio derivative of primary iodide **34** then afforded alcohol **35**. TIPS protection of the alcohol, stereoselective exchange of the TMS group for iodine, liberation of the primary alcohol and oxidation provided aldehyde **36**, which was finally condensed with the dianion of methyl glycolate to afford **4** after hydrolysis of the ester.

The final stages of Nicolaou's synthesis of rapamycin are shown in **Scheme 8**. Thus, condensation of amine **3** with carboxylic acid **4** in the presence of HOBT and DIC resulted in the formation of amide **37**. A series of desilylation steps and oxidation state adjustments then led to bis(vinyl iodide) **1**. Finally, exposure of **1** to enedistannane **2** in the presence of $(MeCN)_2PdCl_2$ and Pr^i_2NEt in DMF–THF afforded rapamycin in 27% yield. An iodostannane, in which only one vinyl iodide (presumably the less substituted one) had reacted with **2**, was also isolated in small amounts; under the same Stille reaction conditions as used above, it furnished rapamycin in 70% yield.



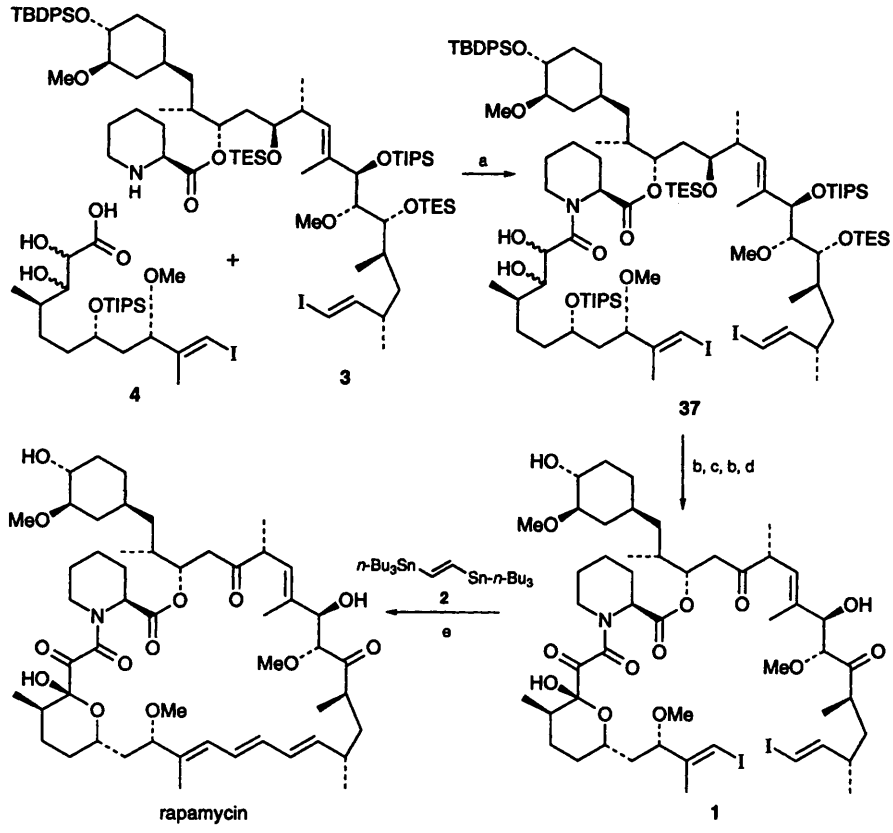
Yields, Reagents and Conditions:

a	70%	1) *t*-BuLi, Et_2O, −78 °C; 2) **30**
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) **34**, *t*-BuLi, Et_2O, −100 °C; 2) 2-thienylCu(CN)Li, −100 °C → 0 °C; 3) **33**, −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) **36**, THF–HMPA, −78 °C
m	95%	LiOH, THF–MeOH–H_2O, 0 °C

Scheme 7

2.2 The Schreiber total synthesis

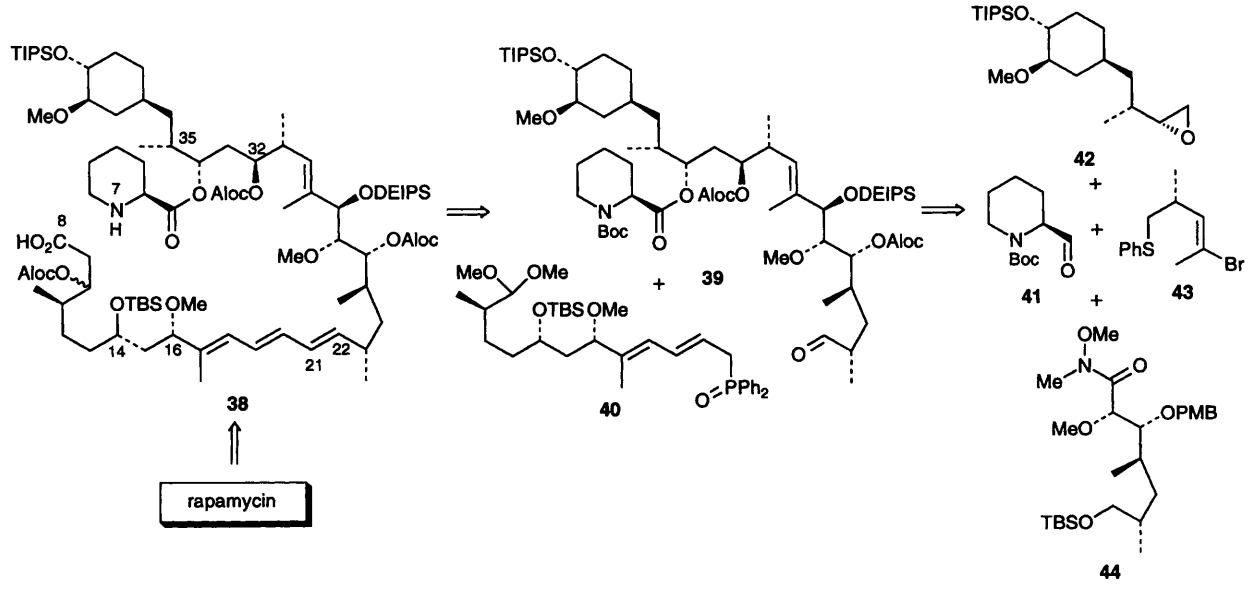
Schreiber's retrosynthetic analysis of rapamycin is shown in **Scheme 9**.[21–23] Thus, disconnection of the macrocycle at the N7–C8 amide bond identifies amino acid **38** as a fully protected acyclic precursor to macrolactamisation. Disconnection of **38** at the C21–C22 olefin linkage then reveals advanced fragments **39** and **40**, of which the former may be



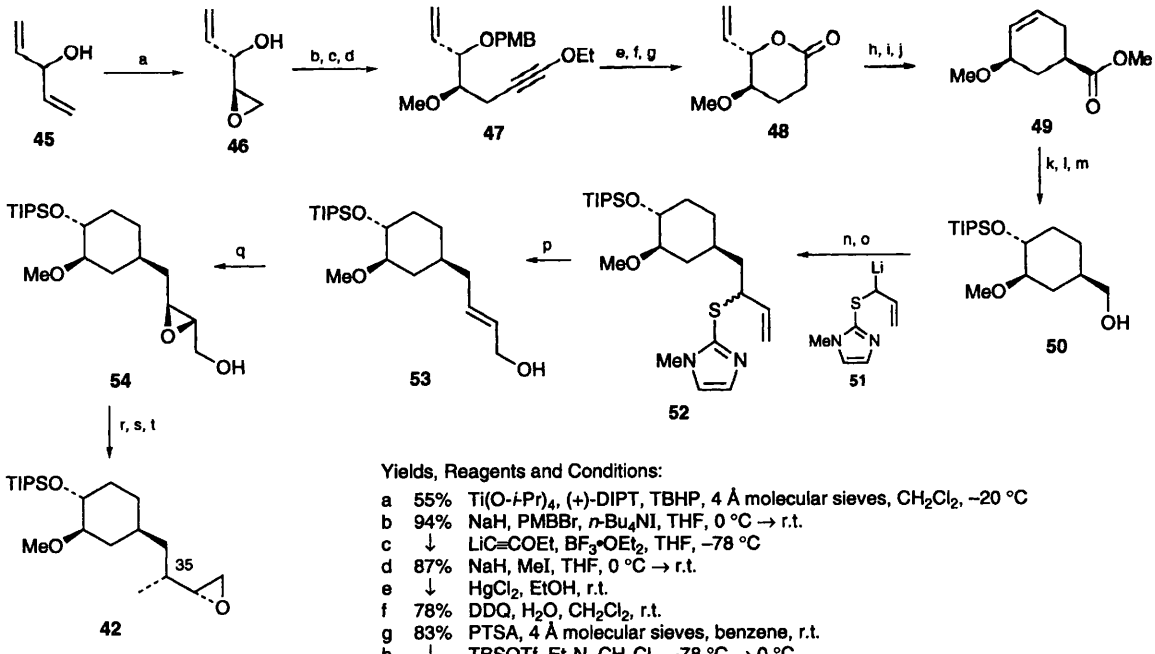
Yields, Reagents and Conditions:

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, $(MeCN)_2PdCl_2$, *i*-Pr_2NEt, DMF–THF (0.01 M), r.t.

Scheme 8



Scheme 9



Yields, Reagents and Conditions:

a 55% $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DIPT, TBHP, 4 Å 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, 4 Å 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% **51**, THF, –78 °C
p 71% 1) MCPBA, CH_2Cl_2, 0 °C → r.t.; 2) Et_2NH, MeOH, r.t.
q 88% $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DET, TBHP, 4 Å molecular sieves
r 83% Me_3Al, hexane, 0 °C
s ↓ TsCl, pyridine
t 57% K_2CO_3, MeOH

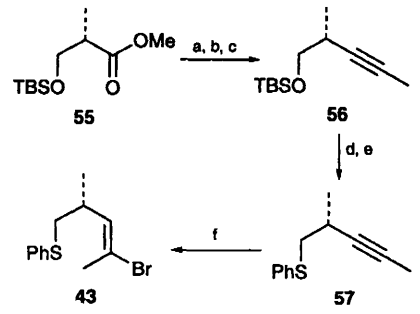
Scheme 10

further subdivided into building blocks **41**–**44** as initial synthetic targets.

The starting material for the synthesis of epoxide **42** (**Scheme 10**) was penta-1,4-dien-3-ol **45**, which underwent Sharpless asymmetric epoxidation to afford kinetically resolved epoxy alcohol **46**. 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 **47**. Treatment of **47** with ethanolic $HgCl_2$ and removal of the PMB protecting group produced a δ-hydroxy ester, which cyclised to lactone **48** upon treatment with PTSA. Compound **48** was then converted to its silyl ketene acetal, which, after prolonged heating, underwent an Ireland–Claisen rearrangement to afford methyl ester **49** following hydrolysis of the first-formed silyl ester and exposure of the crude acid to diazomethane. Regio- and stereo-selective hydroboration of **49**, followed by TIPS protection of the resulting alcohol and reduction of the ester then provided primary alcohol **50**, a compound previously employed in Schreiber's total synthesis of FK-506.[24–28] The iodide derived from alcohol **50** was alkylated with lithiated allylic sulfide **51** to regio-selectively afford substituted allylic thioether **52**. Oxidation of **52** to the corresponding sulfoxide then resulted in a [2,3]-sigmatropic rearrangement to provide (*E*)-allylic alcohol **53** after *in situ* cleavage of the initially formed sulfenate ester. Sharpless asymmetric epoxidation of **53** yielded epoxy alcohol **54**, which underwent regioselective epoxide opening with Me_3Al to introduce the C35 methyl group. The resulting vicinal diol was then converted to **42** using standard procedures.

Fragment **43** was constructed as outlined in **Scheme 11**. Thus, DIBALH reduction of TBS-protected hydroxy ester **55** and Corey–Fuchs homologation of the resulting aldehyde provided methyl acetylene **56**. Removal of the TBS protecting group and sulfenylation of the resulting alcohol then yielded compound **57**, which underwent a hydrozirconation–bromination sequence to afford bromoalkene **43**.

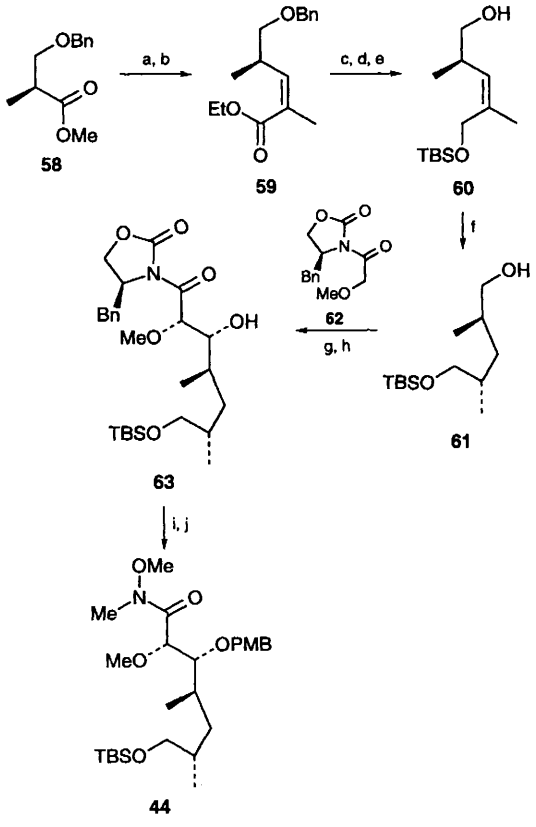
The synthesis of Weinreb amide **44** (**Scheme 12**) began with DIBALH reduction of benzyl-protected hydroxy ester **58**. Wittig olefination of the resulting aldehyde afforded α,β-unsaturated ester **59**. Reduction of the ester, TBS protection of the resulting alcohol and debenzylation led to homo-allylic alcohol **60**, which underwent a hydroxy-directed Rh^I-catalysed hydrogenation to provide



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 11



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 oxidation
h 50% **62**, *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% $PMBOC(=NH)CCl_3$, TfOH

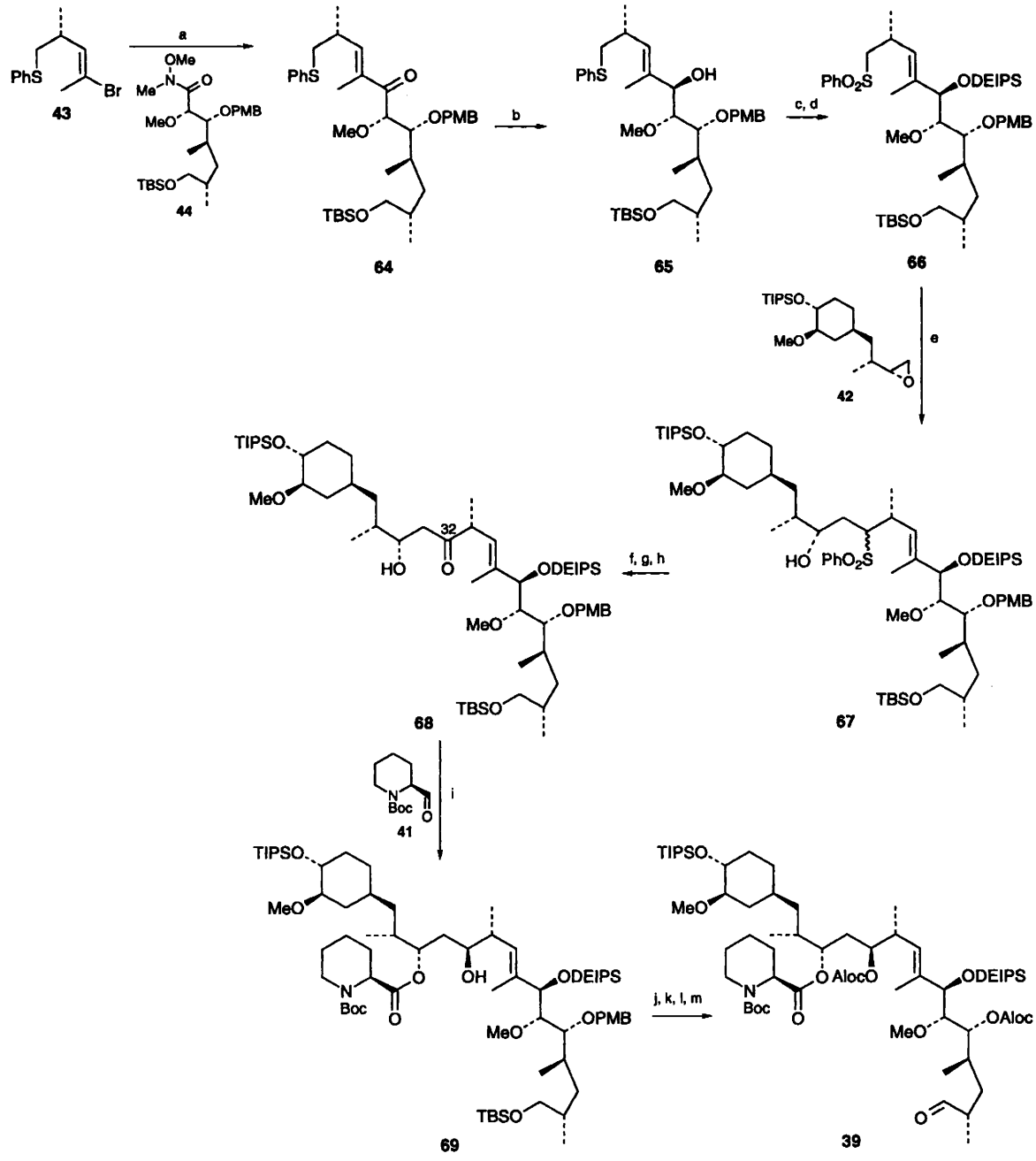
Scheme 12

syn-1,3-dimethyl product **61**. Swern oxidation of **61** and Evans aldol condensation of the resulting aldehyde with *N*-acyloxazolidinone **62** then yielded adduct **63**, which was converted to **44** *via* transamination and protection of the secondary alcohol as its PMB ether.

The coupling of intermediates **41**–**44** and their further elaboration to advanced fragment **39** is shown in **Scheme 13**. Thus, Weinreb amide **44** reacted with the lithio derivative of vinyl bromide **43** to yield enone **64**, which underwent a chelation-controlled $Zn(BH_4)_2$ reduction to stereoselectively afford alcohol **65**. DEIPS protection of the alcohol and oxidation of the sulfide then gave sulfone **66** whose lithio derivative added to epoxide **42** in the presence of $BF_3{\cdot}OEt_2$ to afford γ-hydroxy sulfone **67**. Although metallation of **67** 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 **68** in 16% yield. A less direct, but more efficient route to **68** was therefore adopted, whereby olefination of **67** according to the protocol of Julia, Lythgoe and Kocienski, followed by regioselective osmylation and periodate cleavage, provided the ketone in 69% overall yield. An Evans–Tischenko reaction of **68** with *N*-Boc-L-pipecolinal **41** was then used to introduce the pipecolinate moiety, simultaneously reducing the C32 carbonyl to an (*S*)-alcohol, to produce coupled product **69** in 95% yield. Four standard conversions then led to **39**.

Advanced fragment **40** was synthesised as depicted in **Scheme 14**. Thus, alkylation of methyl acetoacetate **70** with bromide **71** afforded β-keto ester **72**. Catalytic reduction of **72** using Noyori's conditions provided the corresponding β-hydroxy ester, which was converted to Weinreb amide **73**. Vinyllithium species **74**, obtained (Bu^{t}Li, THF, –90 °C) from the corresponding vinyl bromide, was then combined with the lithium alkoxide of **73** to yield adduct **75**. Removal of the PMB protecting group followed by reduction of the β-hydroxy ketone *via* the method of Prasad then yielded triol **76**. The C14 and C16 hydroxy groups were distinguished by selective oxidation of the primary alcohol, resulting in the formation of lactol **77**. Bismethylation of **77** followed by treatment with ethane-1,2-dithiol–$TiCl_4$ subsequently afforded dithiolane **78**. Protection of the secondary alcohol in **78** as its TBS ether, removal of the primary TBS protecting group, and transformation of the dithiolane into a dimethyl acetal then provided primary alcohol **79**, which underwent allylic oxidation and Wittig elongation to yield dienyl ester **80**. 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 **40**.

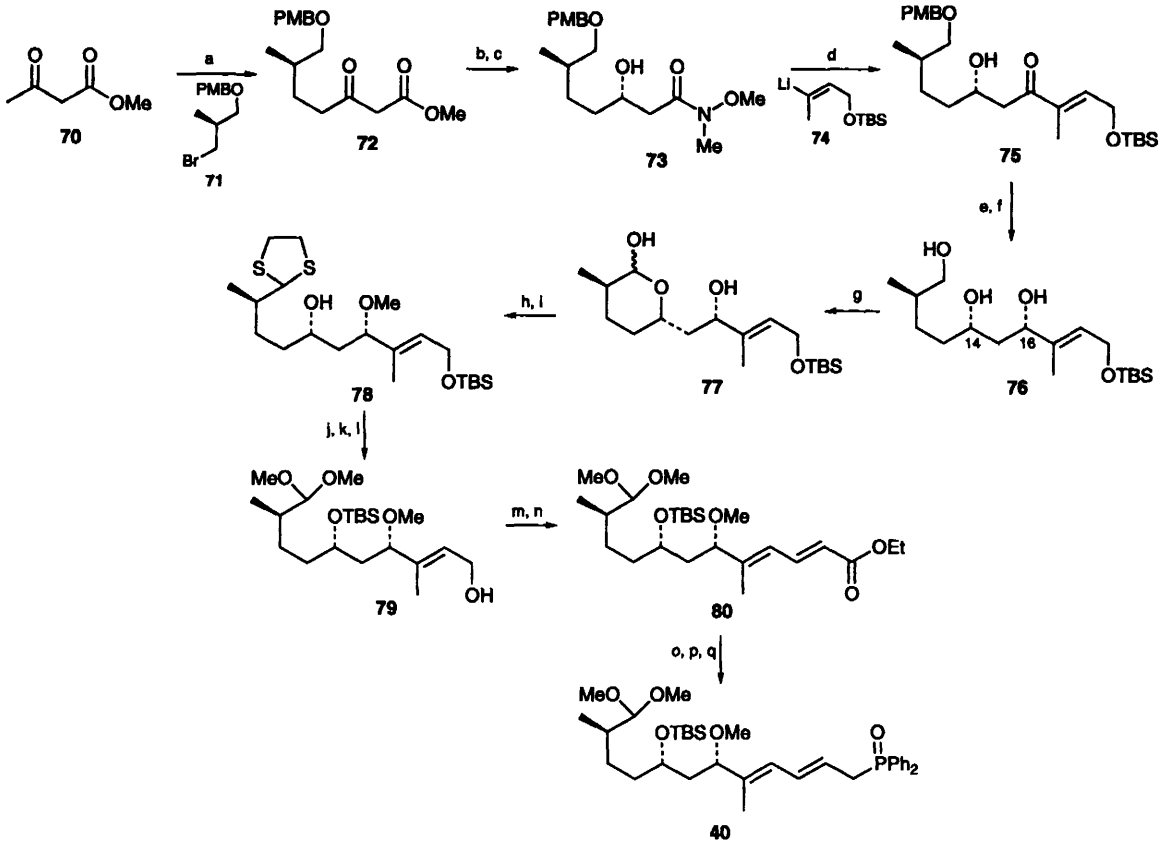
The final stages of Schreiber's synthesis of rapamycin are shown in **Scheme 15**. Thus, condensation of aldehyde **39** with the lithium salt of phosphine oxide **40** afforded triene **81**. Hydrolysis of



Yields, Reagents and Conditions:

a 78% 1) *t*-BuLi, THF, –100 °C; 2) **44**, –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) **42**; 3) $BF_3{\cdot}OEt_2$
f ↓ 1) *n*-BuLi, THF, –78 °C; 2) CH_2I_2–*i*-PrMgCl
g ↓ 1) OsO_4, pyridine; 2) $NaHSO_3$
h 69% $NaIO_4$, SiO_2, Tris-HCl pH 7 buffer
i 95% **41**, SmI_2–PhCHO (1.1:1), THF, –10 °C
j ↓ DDQ, $NaHCO_3$
k 87% AlocCl, 2,6-lutidine, pyridine, THF
l 71% PPTS–PTSA (4:1), THF–H_2O
m 96% Swern oxidation

Scheme 13



Yields, Reagents and Conditions:

a	90%	1) NaH, *n*-BuLi, HMPA, THF, 0 °C; 2) **71**	j	94%	TBSOTf, 2,6-lutidine
b	88%	$RuCl_2$[(*S*)-binap]Et_3N, H_2 (1100 psi)	k	86%	HF•pyridine, pyridine, THF, r.t.
c	97%	MeO(Me)NH•HCl, Me_3Al	l	73%	$(CF_3CO_2)_2IPh$, MeOH
d	85%	1) *n*-BuLi, THF, –78 °C; 2) **74**	m	↓	$BaMnO_4$, celite, CH_2Cl_2
e	93%	DDQ, CH_2Cl_2, pH 7 buffer	n	77%	$Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t.
f	98%	Et_2BOMe, $NaBH_4$, –78 °C	o	83%	DIBALH
g	↓	$RuCl_2(PPh_3)_2$, benzene, air	p	↓	HCA, Ph_3P, 2,6-di-*tert*-butylpyridine, –40 °C
h	78%	NaH, MeI, THF, 0 °C → r.t.	q	65%	1) $LiPPh_2$, THF, –78 °C; 2) air
i	60%	$HS(CH_2)_2SH$, $TiCl_4$, –78 °C			

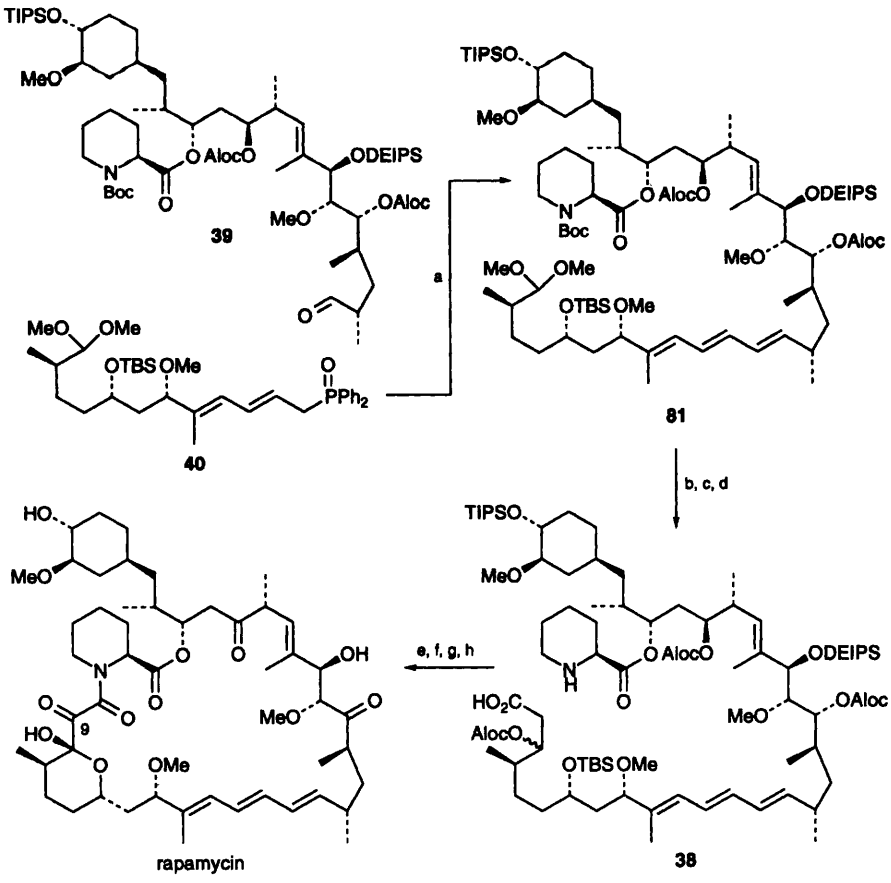
Scheme 14

the acetal was followed by an aldol reaction of the resulting aldehyde with the lithium enolate of 1-ethoxyethyl 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 **38**. Subjection of **38** 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.

2.3 The Danishefsky total synthesis

Danishefsky has extensively explored synthetic[29–32] as well as degradative[12,14] studies on rapamycin. This work culminated in the total synthesis,[33] although much of the previously published chemistry was not directly used in the final construction of the natural product. Danishefsky's initial disconnection of the macrocycle was at the C27–C28 bond, identifying acyclic keto aldehyde **82** as the substrate for a novel macroaldolisation reaction (**Scheme 16**). Cyclisation of this seco intermediate would thus yield rapamycin after deprotection of the C40 hydroxy group. Disconnection of **82** at the ester linkage reveals fragments **83** and **84** as advanced targets, the latter being available from rapamycin *via* degradation. The critical step in the synthesis of **83** was an Ireland–Claisen rearrangement of silyl ketene acetal **87**, to produce carboxylic acid **86**. Further manipulations of **86** yielded **83** *via* a Wittig elongation of aldehyde **85**. Ester disconnection of rearrangement precursor **87** identifies cyclohexenol **88** and carboxylic acid **89** as initial targets, whereas further disconnection of advanced fragment **84** reveals subfragments **90–92** as building blocks.

The synthesis of cyclohexenol **88** (**Scheme 17**) commenced with carbohydrate derivative **93**, whereby methylation of the free hydroxy group, cleavage of the benzylidene acetal with NBS–



Yields, Reagents and Conditions:

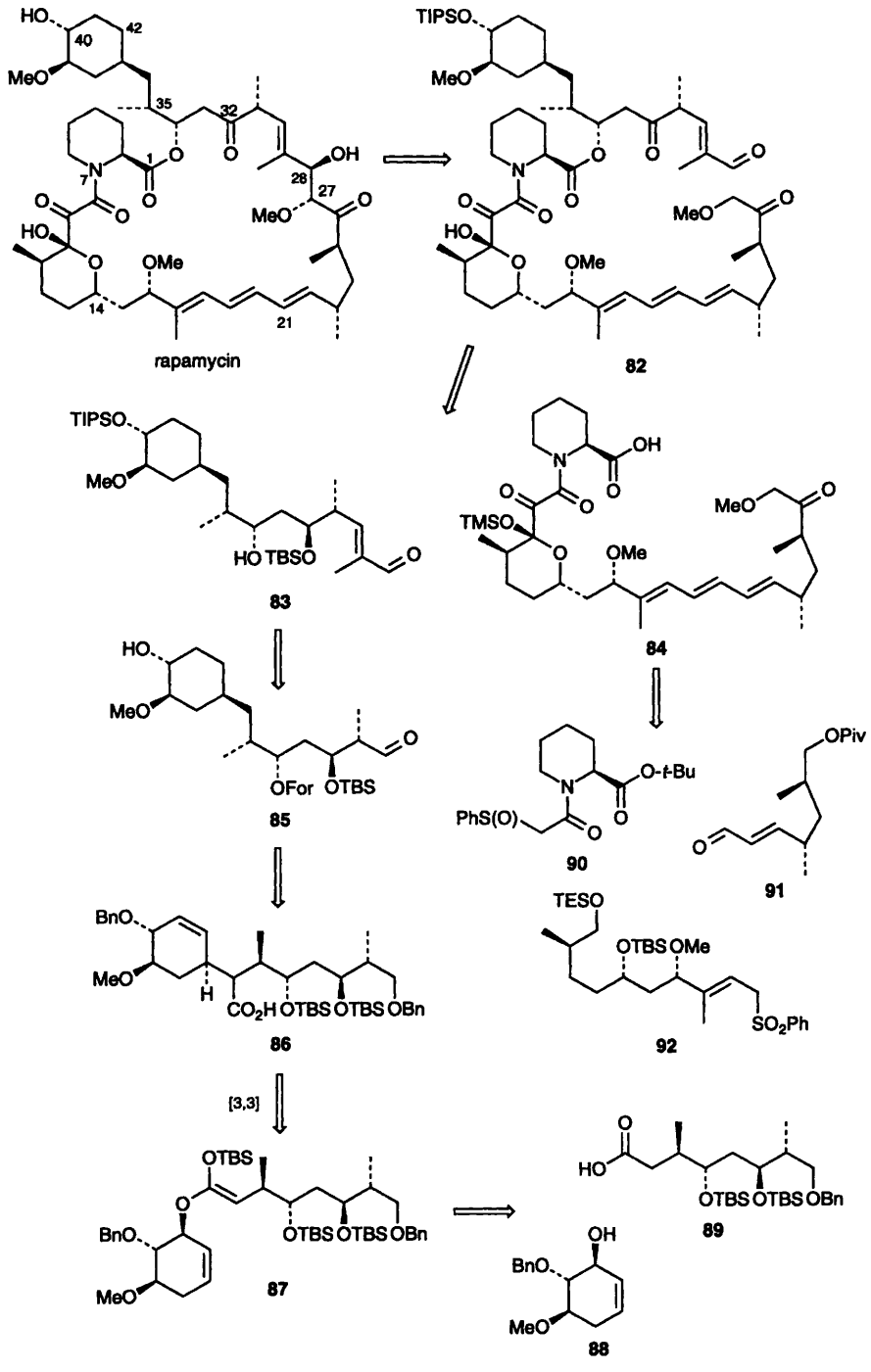
a 71% 1) *n*-BuLi, HMPA, THF, –78 °C; 2) **39**
b 56% PPTS, acetone, 43 °C
c ↓ 1) 1-ethoxyethyl acetate, LDA, THF, –78 °C; 2) AlocCl, 2,6-lutidine, –78 °C → r.t.
d ↓ 1) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 2) SiO_2
e 40% 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2 (0.0004 M)
f ↓ $Pd(PPh_3)_4$, $HCONH_4$, THF
g ↓ Dess–Martin periodinane, CH_2Cl_2
h 30% HF•pyridine, pyridine, THF

Scheme 15

$BaCO_3$, and removal of the resulting benzoyl protecting group afforded alcohol **94**. Benzyl protection of **94** with concomitant bromide elimination gave compound **95**, which underwent a Ferrier transformation when heated with aq. $HgCl_2$ to yield alcohol **96**. Conversion of **96** to **88** was achieved *via* enone **97** through *β*-elimination followed by Luche reduction.

In the synthesis of carboxylic acid **89** (**Scheme 18**), titanium-mediated allylation of benzyl-protected hydroxy aldehyde **98** yielded alcohol **99** as an inseparable mixture (7:1) with C32 epimer **100**. TBS protection of the hydroxy group followed by ozonolysis of the double bond afforded aldehyde **101**, which underwent crotylboration to yield alcohol **102** along with C34,C35 epimer **103** (3.5:1). Desilylation and chromatography then yielded homogeneous diol, which was subjected to bis-silylation followed by hydroboration to provide primary alcohol **104**. Oxidation of **104** (Swern then $KMnO_4$) then gave **89**.

The coupling of intermediates **88** and **89** and their further elaboration to advanced fragment **83** is depicted in **Scheme 19**. Thus, acylation of alcohol **88** with acid **89** was accomplished using EDC–DMAP to provide ester **105**, which underwent enolisation–silylation to generate the required silyl ketene acetal **87**. Thermolysis of **87** in vigorously refluxing toluene followed by hydrolysis of the resulting silyl ester then yielded carboxylic acid **86** as a single unidentified diastereomer. Treatment of **86** with $(COCl)_2$–DMAP afforded lactone **106**, thus distinguishing the oxygen functions at C32 and C34. Sulfonhydrazide reduction of the double bond was followed by reduction of the lactone with DIBALH to provide the corresponding lactol, which underwent Suárez oxidation to yield iodoformate **107**. Deiodination, cleavage of the benzyl ethers and regiospecific oxidation of the primary alcohol then provided aldehyde **85**, which finally underwent Wittig olefination, TIPS protection of the C40 hydroxy group, reduction of the formate and ethyl

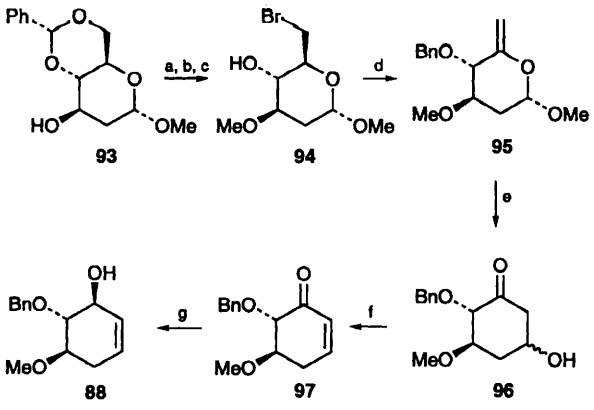


Scheme 16

esters, and selective oxidation of the primary allylic alcohol to yield **83**.

The synthesis of aldehyde **91** (**Scheme 20**) began with a chelation-controlled Diels–Alder cycloaddition of (*S*)-2-(benzyloxy)propanal **108** with diene **109** mediated by $MgBr_2 \cdot OEt_2$ to provide dihydropyrone **110**. Reduction of the carbonyl group was followed by a Ferrier rearrangement (Pr^iOH–H^+) to yield pseudoglycal **111**. Stereoselective hydrogenation of the double bond and removal of the benzyl protecting group then afforded pyranose derivative **112**, which was converted to dithianediol **113** by treatment with propane-1,3-dithiol–$BF_3 \cdot OEt_2$. Cleavage of the diol and Wittig homologation of the resulting aldehyde then yielded enoate **114**, which was converted to **91** *via* aldehyde **115** using standard procedures.

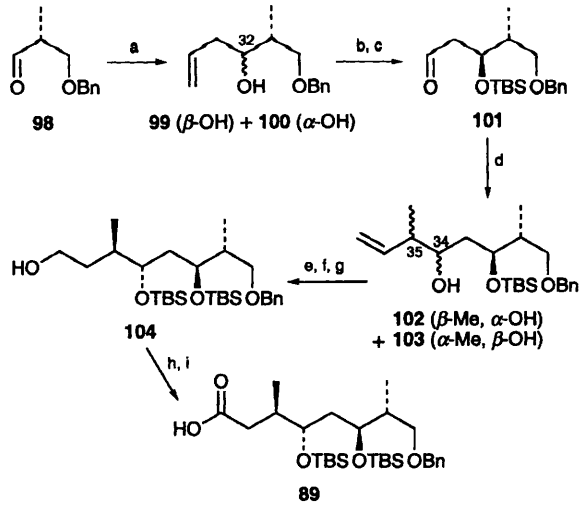
The starting material selected for the synthesis of sulfone **92** (**Scheme 21**) was carbohydrate derivative **116**, which was converted to compound **117** *via* stannyl ether formation, benzylation and mesylation. Iodomethoxylation–deiodination of **117** then provided α-methyl-2-deoxyglucoside **118**, which was converted to enoate **120** *via* dithianediol **119** by the



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

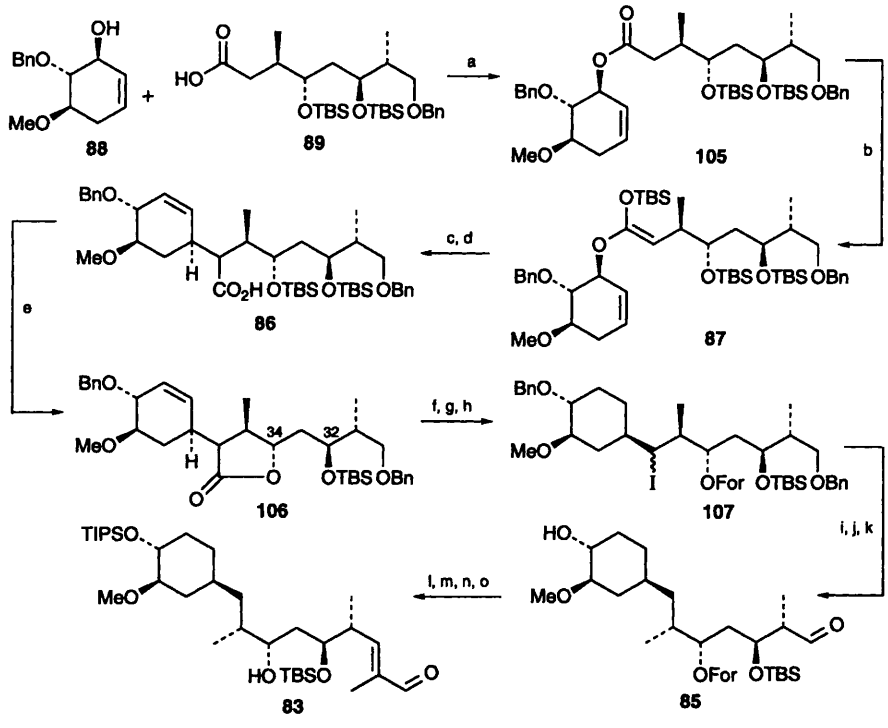
Scheme 17



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

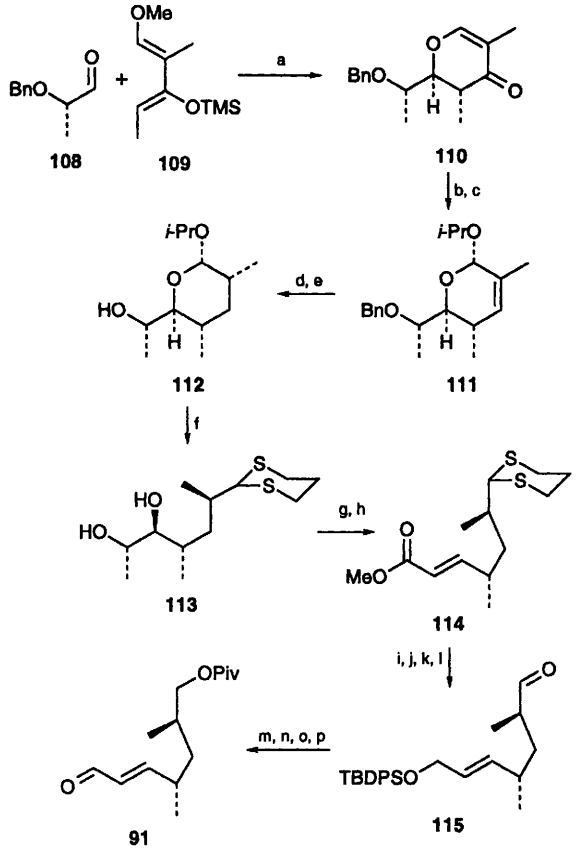
Scheme 18



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 19



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 20

same procedure used for the conversion **112**→**114**. An Ibuka–Yamamoto (cuprate displacement) reaction was then used to prepare α-methyl ester **121**. Reduction of the double bond followed by dithiane cleavage then provided aldehyde **122**, which was coupled with vinyl iodide **123** (prepared in five steps from tetrolic acid) by means of a Nozaki–Kishi reaction to provide alcohol **124** as a 1:1 epimeric mixture at C16. Oxidation of **124**, 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 **125** as a single diastereomer.

Hydrolysis of the ethyl ester followed by lactone formation then served to distinguish the C14 and C16 hydroxy groups, the latter being subsequently methylated (Ag_2O–MeI) to yield compound **126**. A series of four standard transformations then provided **92**.

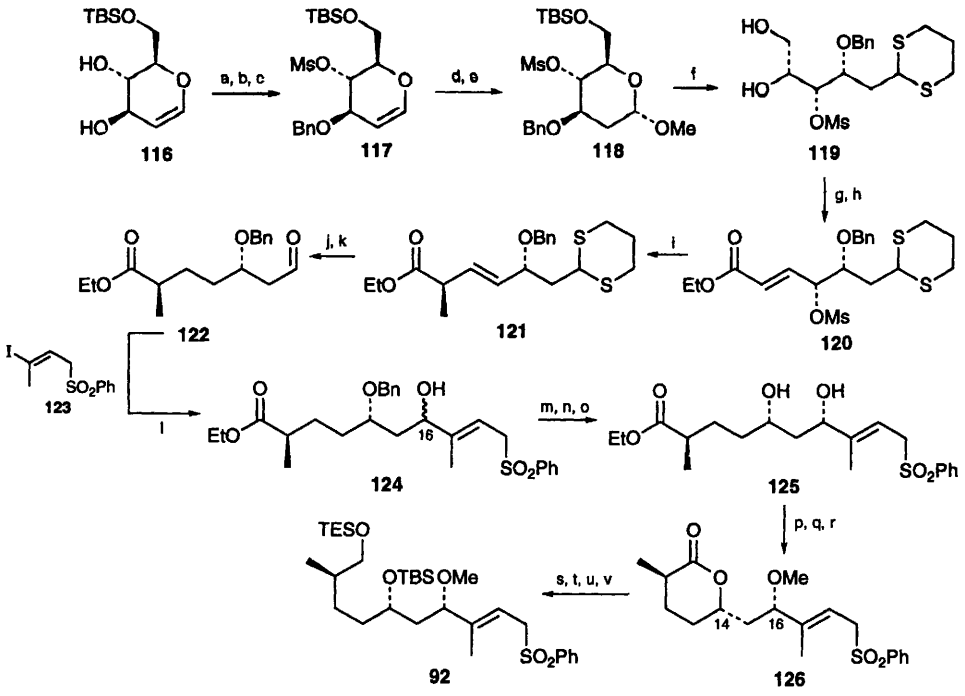
The coupling of intermediates **90**–**92** and their further elaboration to advanced fragment **84** is depicted in **Scheme 22**. Thus, Julia–Lythgoe–Kocienski coupling of aldehyde **91** with sulfone **92**, followed by acetylation and β-elimination, yielded vinyl sulfone **127**. Reduction of the pivaloate function, reductive desulfonylation, and oxidation of the primary alcohol then afforded aldehyde **128**, which was converted to aldehyde **129** in four straightforward steps. Condensation of **129** with the lithio derivative of *tert*-butyl *N*-[(phenylsulfinyl)-acetyl]-L-pipecolinate then produced adduct **130**. Dess–Martin oxidation of **130**, followed by desilylation–lactolisation and cleavage of the *tert*-butyl ester subsequently provided carboxylic acid **131**. Conversion of the carboxyl to the corresponding allyl ester and TMS protection of the tertiary C10 hydroxy group followed by deallylation with $Pd(PPh_3)_4$ then afforded **84**.

The conclusion to Danishefsky's synthesis of rapamycin is shown in **Scheme 23**. Thus, initial coupling of alcohol **83** and acid **84** using DCC–DMAP at −20 °C was followed by removal of the TBS and TMS protecting groups and oxidation of the C32 hydroxy group to afford C40-silylated seco-rapamycin **82**, the substrate for the projected intramolecular aldolisation. The cyclisation was best carried out using Pr^iOTiCl_3 as the promoter, thus affording a 33% yield of C40-silylated rapamycin **132** in a 1:2.3 ratio to an apparent stereoisomer. Rapamycin itself was then obtained in 85% yield by desilylation.

2.4 The Smith total synthesis

Smith's retrosynthetic analysis of rapamycin divided the ring into two large fragments encompassing C21–C42 **133** and C1–C20 **135** (**Scheme 24**).[34–36] 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 **134**), a compound isolated from the same source as rapamycin whose structure had solely been assigned on the basis of spectral comparisons with the latter. Further disconnection of advanced fragments **133** and **135** identifies building blocks **136**–**140** as initial synthetic targets.

The synthesis of iodide **136** (**Scheme 25**) began with a Lewis acid catalysed asymmetric Diels–Alder reaction of buta-1,3-diene with the *N*-acryloyl derivative **141** of Oppolzer's camphor sultam, to afford adduct **142**. Removal of the chiral auxiliary then provided (*R*)-cyclohex-3-enecarboxylic acid



Yields, Reagents and Conditions:

a	–	*n*-Bu_2SnO
b	–	BnBr, *n*-Bu_4NBr
c	99%	MsCl, pyridine, 0 °C → r.t.
d	88%	NIS, MeOH, MeCN, r.t.
e	71%	*n*-Bu_3SnH, AIBN, benzene, Δ
f	74%	$HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C → r.t.
g	72%	$Pb(OAc)_4$, benzene
h	62%	$Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C
i	74%	MeCu(CN)Li·LiBr, $BF_3{\cdot}OEt_2$, THF, –78 °C
j	83%	$(Ph_3P)_3RhCl$, H_2, benzene, r.t.
k	–	dithiane cleavage
l	↓	**123**, $CrCl_2$ (containing 0.1% $NiCl_2$), DMSO, r.t.
m	↓	Dess–Martin periodinane, CH_2Cl_2, r.t.
n	75%	BCl_3, CH_2Cl_2, –78 °C
o	↓	Et_2BOMe, $NaBH_4$, toluene, –78 °C
p	↓	LiOH, THF–MeOH–H_2O 0 °C
q	71%	EDC, CH_2Cl_2, r.t.
r	↓	Ag_2O, MeI, r.t.
s	↓	K_2CO_3, MeOH, r.t.
t	86%	TBSOTf, 2,6-lutidune, 0 °C
u	↓	DIBALH, THF, 0 °C
v	86%	TESCl, Et_3N, CH_2Cl_2

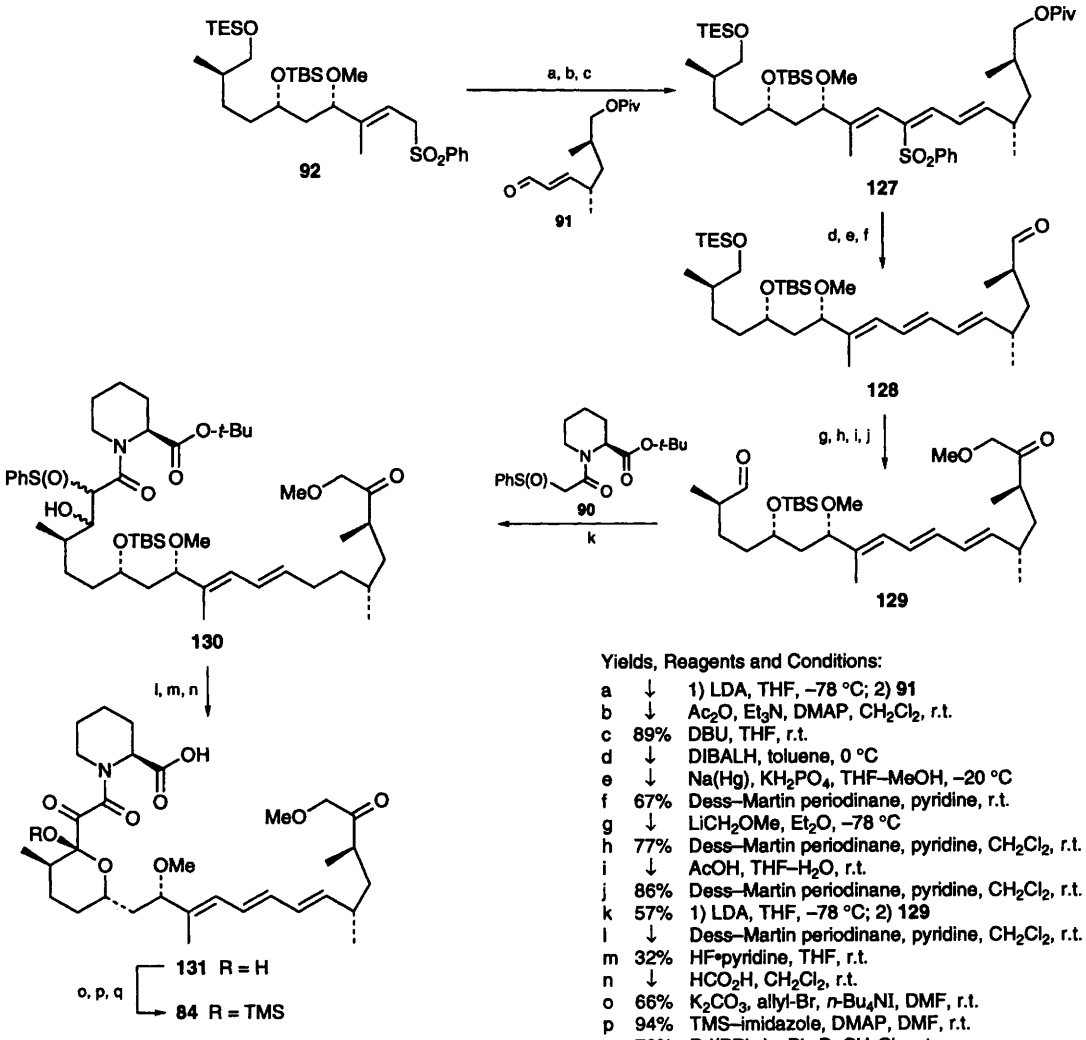
Scheme 21

143, which underwent iodolactonisation to yield compound **144**. DBU-induced elimination of **144** led to unsaturated lactone **145** which was reduced to the corresponding diol. Conversion of the primary alcohol to a phenyl sulfide, methylation of the secondary alcohol, and oxidation of the sulfide then afforded 3-methoxycyclohexene derivative **146**. Regio- and stereo-selective hydroboration of **146** and TIPS protection of the resulting alcohol then yielded sulfone **147** (previously employed in Smith's formal synthesis of FK-506[37–39]), the lithio derivative of which was added regioselectively to epoxide **148**. Reductive desulfonylation then gave alcohol **149** which was converted to epoxide **42** (first used in Schreiber's total synthesis of rapamycin; Section 2.2) 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 **136**.

The synthesis of dithiane **137** is outlined in **Scheme 26**. Sulfone **152** was prepared from methyl (*R*)-3-hydroxy-2-methylpropionate **150** *via* dithiane **151** using standard procedures. The lithio derivative of **152** was then added to aldehyde **153**, itself prepared in three steps from L-arabinose. Swern oxidation and desulfonylation of the product afforded ketone **154**, 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 **155**. A further six standard conversions provided **137**.

The preparation of dithiane **138** (**Scheme 27**) began with the desymmetrisation of *meso*-dimethyl 2,4-dimethylglutarate **156**. Thus, enzymatic hydrolysis and $BH_3{\cdot}DMS$ reduction of the resulting acid afforded primary alcohol **157** which was converted to **138** *via* dithiane **158** in seven steps using standard procedures.

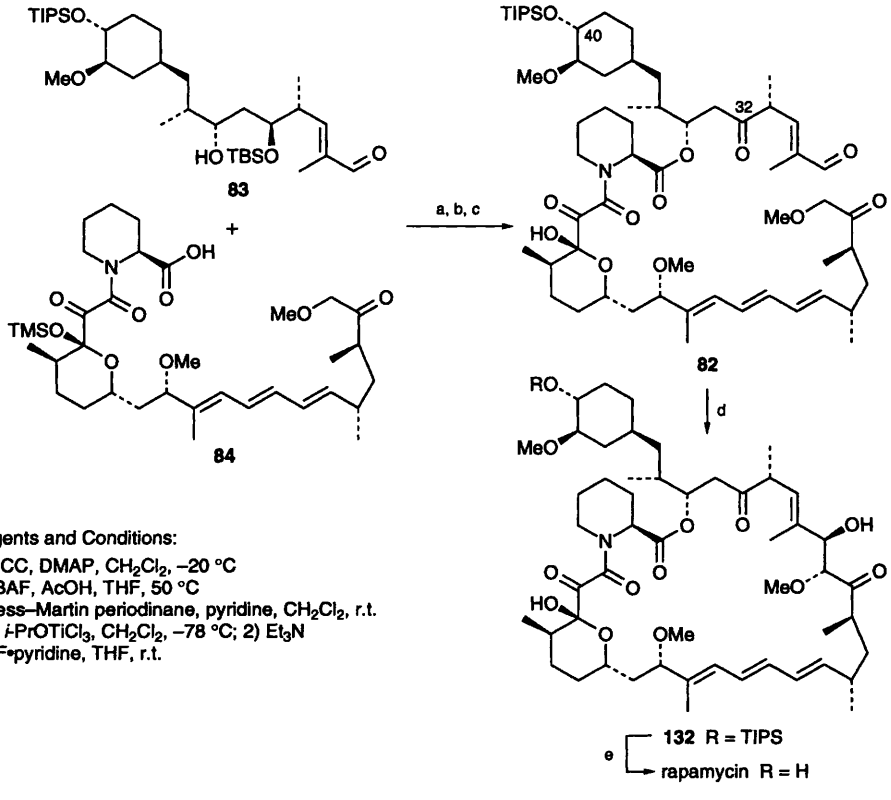
The coupling of intermediates **136–138** and their further elaboration to advanced fragment **133** is depicted in **Scheme 28**. Thus, lithiation of dithiane **137**, alkylation with iodide **136** and acetal hydrolysis furnished aldehyde **159**. Metallation of dithiane **138** and addition to **159** then furnished C27-epimeric



Yields, Reagents and Conditions:

a	↓	1) LDA, THF, –78 °C; 2) **91**
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_2Cl_2, r.t.
i	↓	AcOH, THF–H_2O, r.t.
j	86%	Dess–Martin periodinane, pyridine, CH_2Cl_2, r.t.
k	57%	1) LDA, THF, –78 °C; 2) **129**
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.

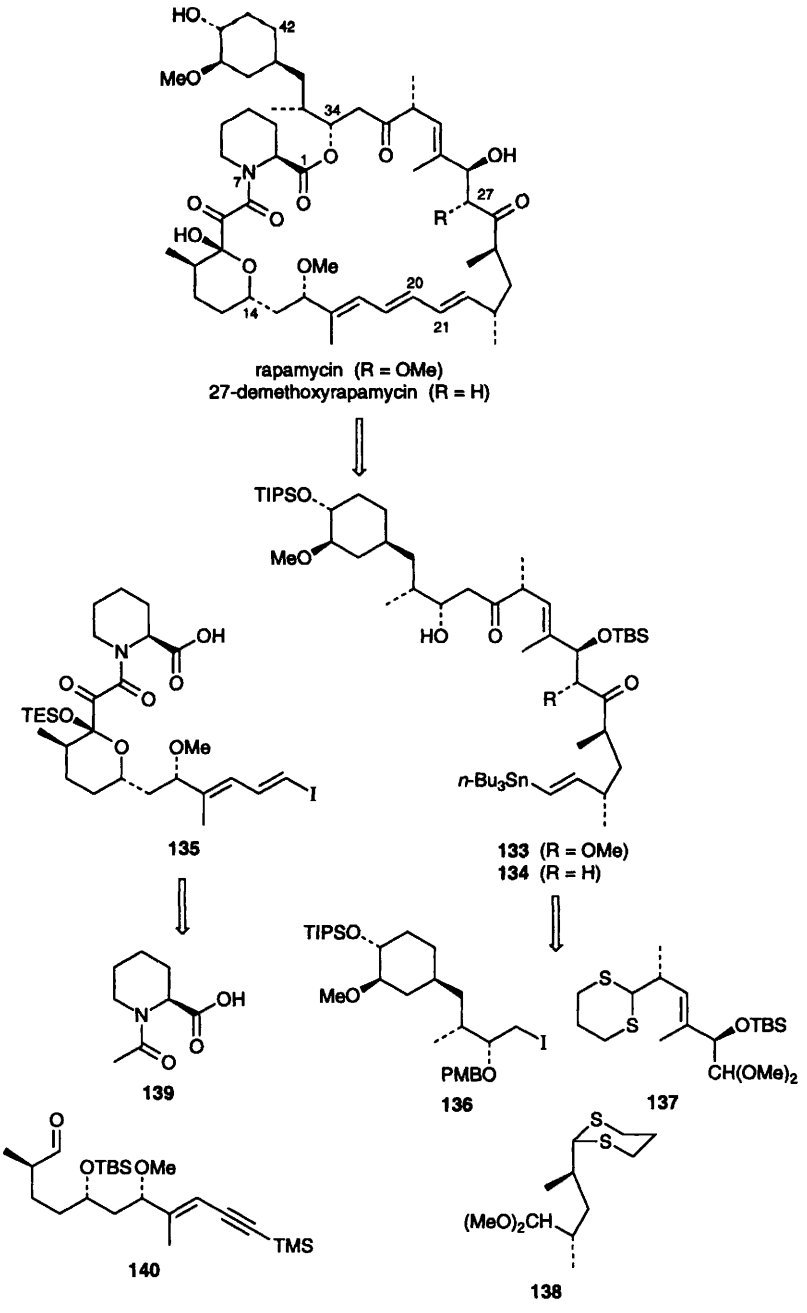
Scheme 22



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.

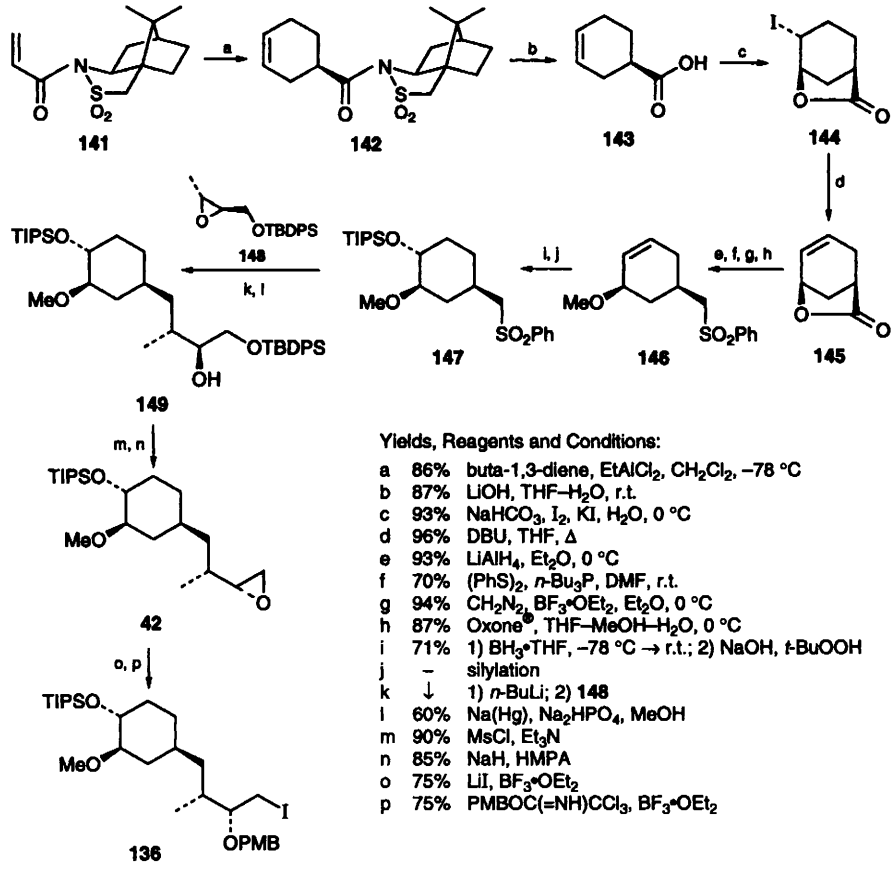
Scheme 23



Scheme 24

alcohols **160** and **161**, with the unwanted diastereomer in slight excess (1:1.2). Methylation of the alcohol, aldehyde deprotection and Corey–Fuchs homologation then provided terminal alkyne **162** (the unwanted diastereomer from the coupling of **138** with **159** was separated *via* chromatography of the Corey–Fuchs dibromoalkenes). Removal of the PMB and dithiane protecting groups followed by Pd^0-mediated hydrostannylation then completed the preparation of **133**.

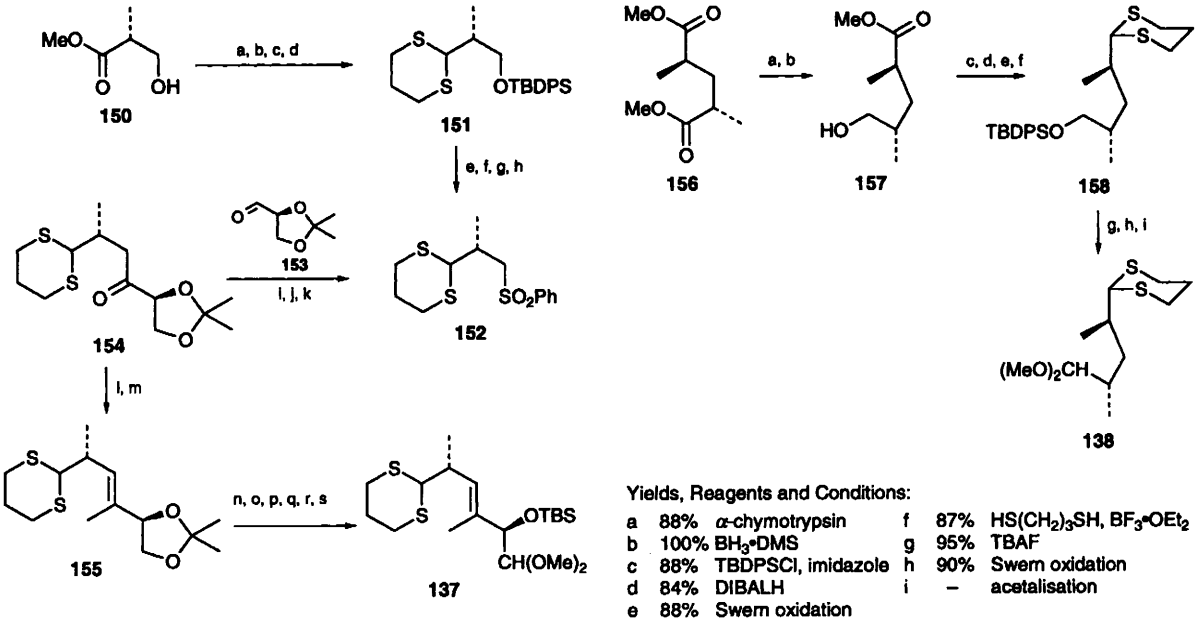
The synthesis of aldehyde **140** (**Scheme 29**) began with 2-allylcyclopentanone **163**, which underwent Baeyer–Villiger oxidation and alkylation to afford lactone **164** as a 1:1 mixture of *cis/trans* isomers. Protection of **164** as the corresponding orthoester with (2*R*,3*R*)-butane-2,3-diol resulted in equilibration of the mixture to a 6:1 *trans/cis* ratio, from which the required diastereomer **165** could be separated by HPLC. Ozonolysis of **165** was followed by the addition of vinyllithium species **166**, 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 **167** and **168** 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 **140**.



Yields, Reagents and Conditions:

a	86%	buta-1,3-diene, $EtAlCl_2$, 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) **148**
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 25



Yields, Reagents and Conditions:

a	98%	TBDPSCl, imidazole
b	90%	$LiBH_4$, Et_2O
c	↓	Swern oxidation
d	94%	$HS(CH_2)_3SH$, BF_3•OEt_2
e	94%	TBAF, THF
f	95%	TsCl, Et_3N
g	91%	NaI, acetone
h	91%	$PhSO_2Na$, DMF
i	↓	1) n-BuLi; 2) **153**
j	↓	Swern oxidation
k	46%	Al(Hg), THF
l	75%	1) LiHMDS, THF–HMPA; 2) Tf_2NPh
m	70%	Me_2CuLi, Et_2O
n	64%	CSA, MeOH
o	77%	PivCl, DMAP
p	97%	TBSOTf, 2,6-lutidine
q	99%	DIBALH
r	93%	Swern oxidation
s	–	acetalisation

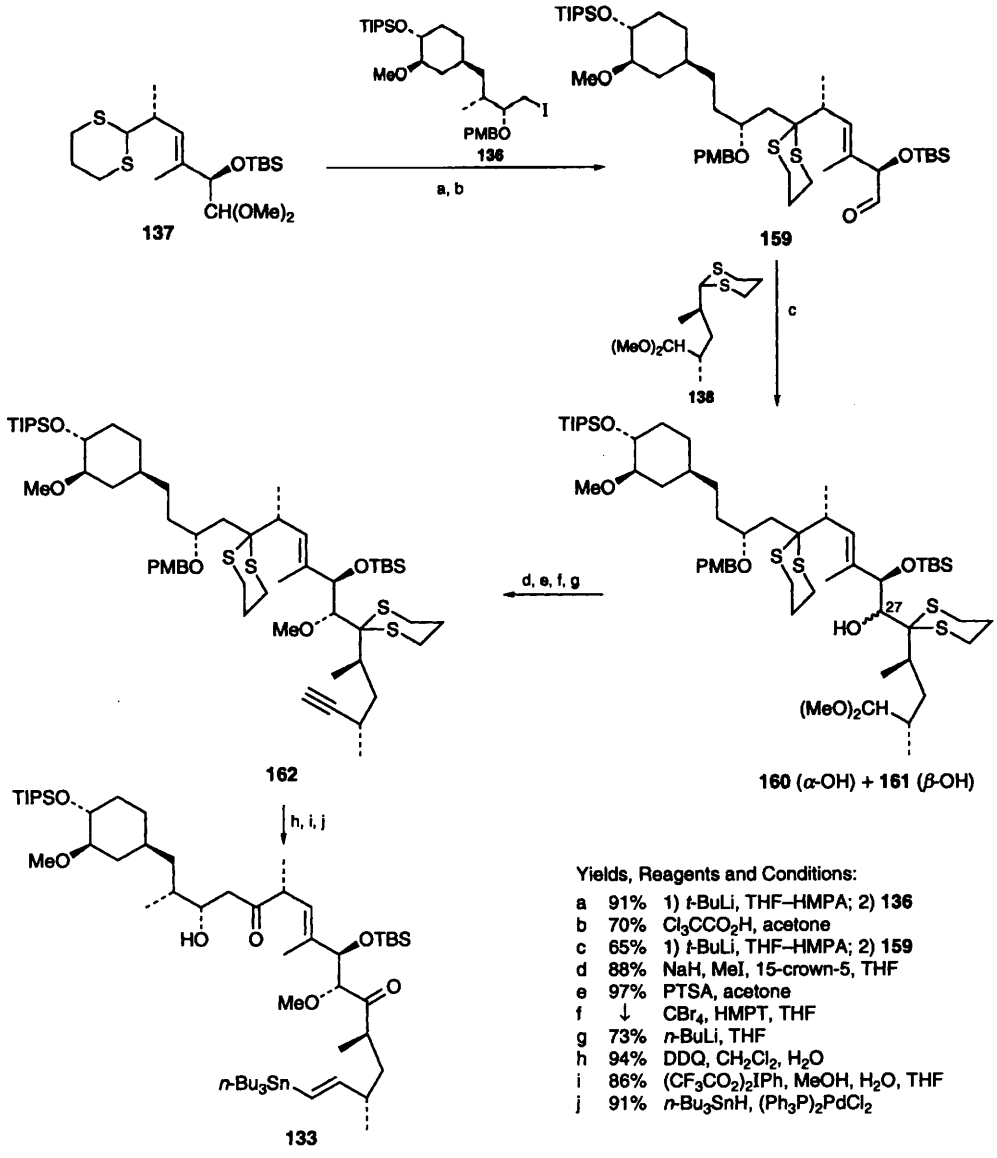
Scheme 26

Yields, Reagents and Conditions:

a	88%	α-chymotrypsin	f	87%	$HS(CH_2)_3SH$, BF_3•OEt_2
b	100%	BH_3•DMS	g	95%	TBAF
c	88%	TBDPSCl, imidazole	h	90%	Swern oxidation
d	84%	DIBALH	i	–	acetalisation
e	88%	Swern oxidation			

Scheme 27

Scheme 30 outlines the elaboration of aldehyde **140** to advanced fragment **135**. Thus, condensation of **140** with the dianion of *N*-acetyl-L-pipecolinic acid **139**, 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 **169**.



Scheme 28

Trapping of **169** with TESOTf followed by free radical hydrostannylation, tin–halogen exchange and ester demethylation then completed the synthesis of **135**.

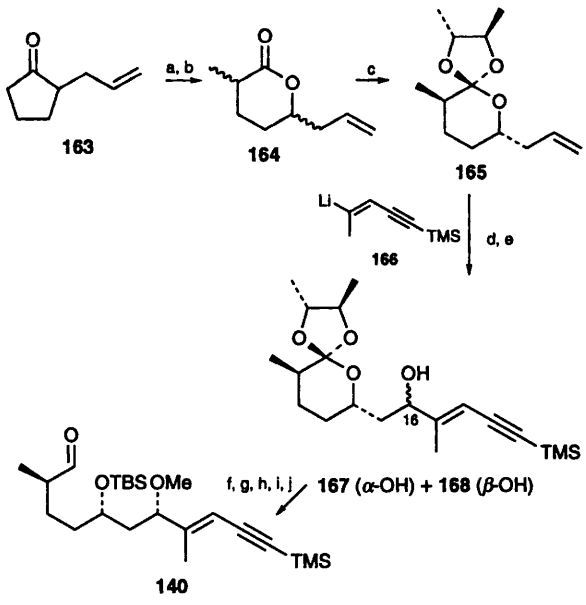
The conclusion of Smith's synthesis of rapamycin is depicted in **Scheme 31**. Coupling of alcohol **133** and acid **135** was effected *via* EDC-induced acylation to afford the seco precursor, which underwent intramolecular Stille coupling with $[(2\text{-furyl})_3P]_2PdCl_2$ in DMF–THF to cleanly generate the macrolide ring. Desilylation then afforded rapamycin.

3 The fragment syntheses

3.1 The Ley synthesis of the C22–C42 and C10–C17 fragments

The Ley group has published syntheses of C22–C42 fragment **170** (derived by coupling of intermediates **171**–**173**) and C10–C17 lactone **174** (**Scheme 32**).[40–42]

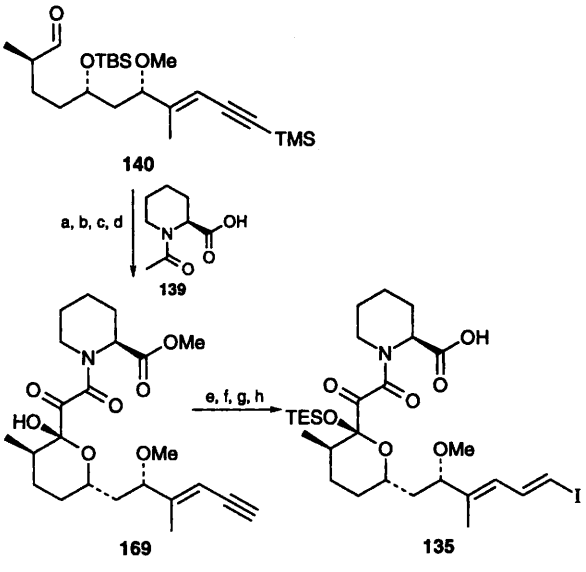
The key step in the synthesis of epoxide **171** (**Scheme 33**) involved an intramolecular reaction of an allylsilane with an oxonium ion, generated from an α-alkoxy sulfone, to stereoselectively form a methylene cyclohexane derivative (**179**→**181**). The synthesis began with a Claisen–Johnson rearrangement of 2-[(trimethylsilyl)methyl]prop-2-en-1-ol **175** with triethyl orthoacetate to provide ester **176**. Condensation of **176** with the anion of methoxymethyl phenyl sulfone (Bu^tLi, DME, −78 °C) afforded β-keto sulfone **177**, which was subjected to asymmetric reduction employing BH_3·DMS and Corey's oxazaborolidine catalyst **178** to yield β-hydroxy sulfone **179** as a 1:2 mixture with C39 epimer **180**. The latter could be readily oxidised to **177** for recycling. Following silylation, **179** was treated with $SnCl_4$ to yield *trans*- and *cis*-methylene cyclohexane derivatives **181** and **182** as a 5:1



Yields, Reagents and Conditions:

a ↓ MCPBA, $NaHCO_3$, CH_2Cl_2, r.t.
b 55% 1) LDA, THF, –78 °C; 2) MeI, –78 °C → r.t.
c 42% (2*R*,3*R*)-butane-2,3-diol, CSA, benzene, Δ; separation
d ↓ ozonolysis
e 73% **166**, THF, –78 °C
f – separation; methylation
g 86% AcOH, THF
h 97% TBSCl, imidazole
i 98% DIBALH
j 89% Swern oxidation

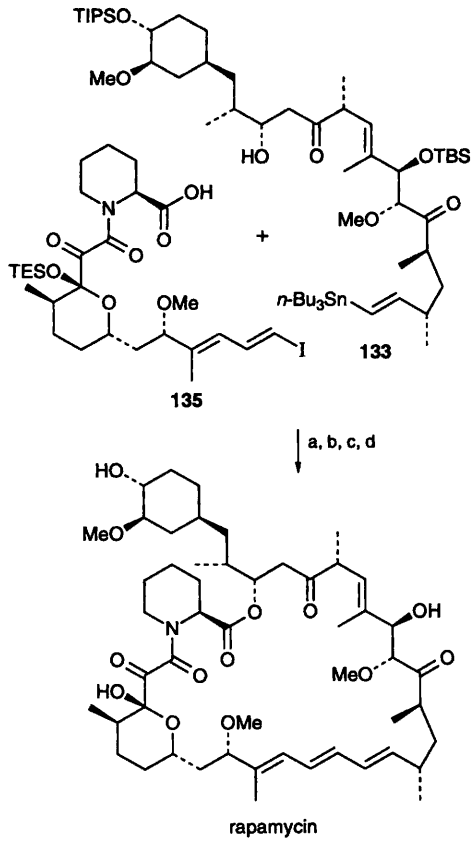
Scheme 29



Yields, Reagents and Conditions:

a 79% 1) **139**, LiHMDS, THF; 2) **140**
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 30



Yields, Reagents and Conditions:

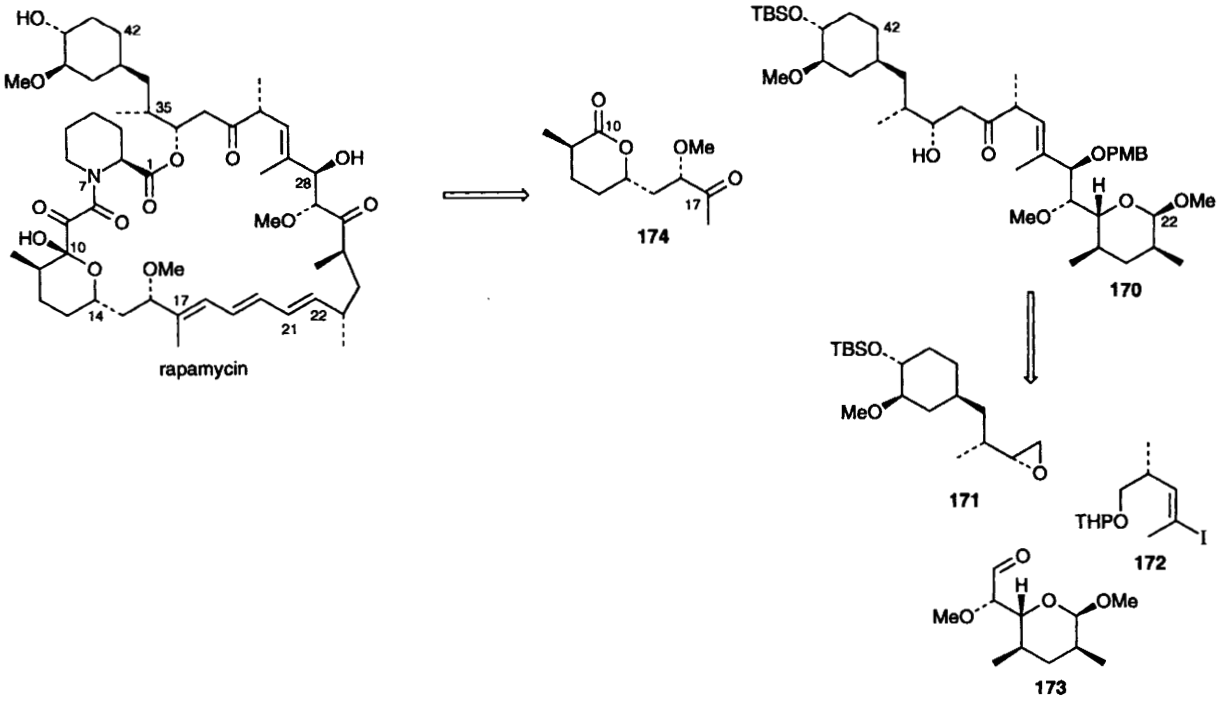
a 58% EDC, DMAP, DMAP•HCl, CH_2Cl_2, r.t.
b 74% $[(2\text{-furyl})_3P]_2PdCl_2$, *i*-$Pr_2NEt$, DMF–THF, r.t.
c ↓ TBAF, AcOH, 0 °C
d 61% HF•pyridine, pyridine, THF, r.t.

Scheme 31

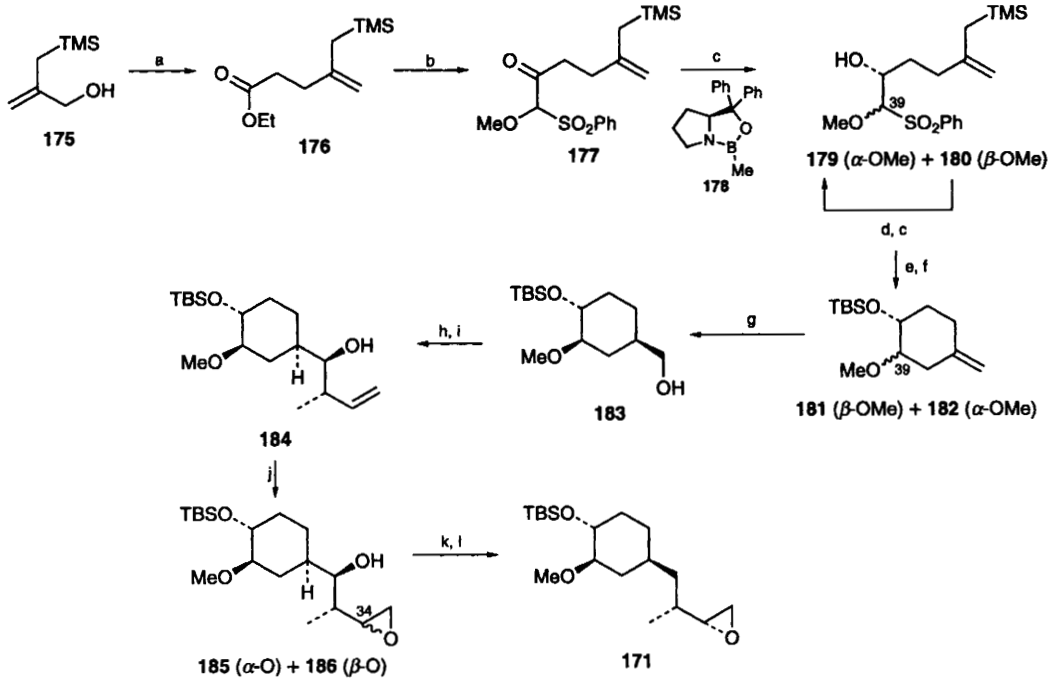
mixture. Hydroboration then provided alcohol **183**, at which stage the minor isomer from cyclisation could be separated. Swern oxidation of **183** and crotylboration of the intermediate aldehyde then provided alcohol **184**, which underwent epoxidation under standard conditions to provide epoxy alcohols **185** and **186** as a separable 4:1 mixture of diastereomers. Deoxygenation of **185** *via* its thionocarbonate derivative by reduction with *n*-Bu_3SnH then afforded **171**.

Fragment **172** was prepared (**Scheme 34**) in four steps from methyl (S)-3-hydroxy-2-methyl-propionate-derived alcohol **187** by Swern oxidation, Corey–Fuchs homologation of the intermediate aldehyde, and hydrozirconation–iodination of the resulting methyl acetylene **188**.

The key step in the synthesis of aldehyde **173** (**Scheme 35**) involved a selenium-mediated electrophilic cyclisation of an intermediate hemiacetal derived from unsaturated aldehyde **191**, to stereoselectively afford acetals **192** and **193**. The synthesis began with the desymmetrisation of *meso*-2,4-dimethylpentane-1,5-diol **189** by enzymatic monoacyl transfer with methyl acetate. The resulting monoacetate **190** was elaborated to unsaturated



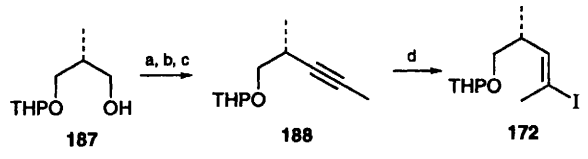
Scheme 32



Yields, Reagents and Conditions:

a ↓ $(EtO)_3CMe$, $EtCO_2H$, 140 °C
b 86% $MeOCH(Li)SO_2Ph$, DME, –78 °C → r.t.
c 100% BH_3•DMS, **178**, THF
d – PDC, CH_2Cl_2
e ↓ TBSOTf, pyridine, DMAP, CH_2Cl_2, 0 °C
f 60% $SnCl_4$, CH_2Cl_2, –78 °C
g 80% 1) 9-BBN, THF, 0 °C → r.t.; 2) NaOH, H_2O_2
h 90% $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
i 70% 1) (–)-Ipc_2-(*E*)-crotylborane, THF–Et_2O, –78 °C; 2) NaOH, H_2O_2
j 90% TBHP, $VO(acac)_2$, CH_2Cl_2
k 85% *n*-BuLi, THF, –20 °C; 2) ClC(=S)OPh
l 80% *n*-Bu_3SnH, AIBN, benzene, Δ

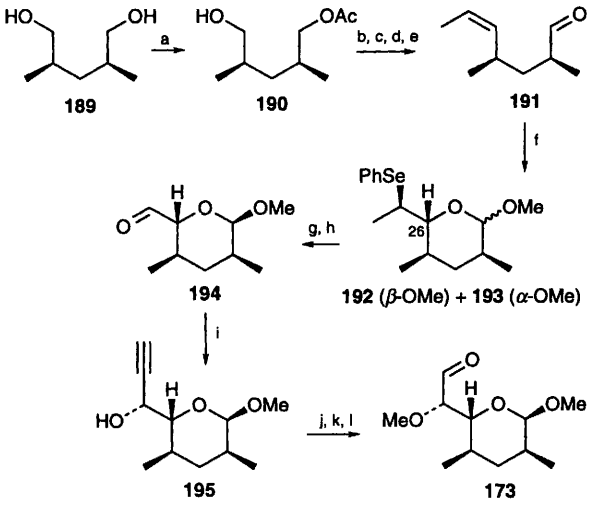
Scheme 33



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

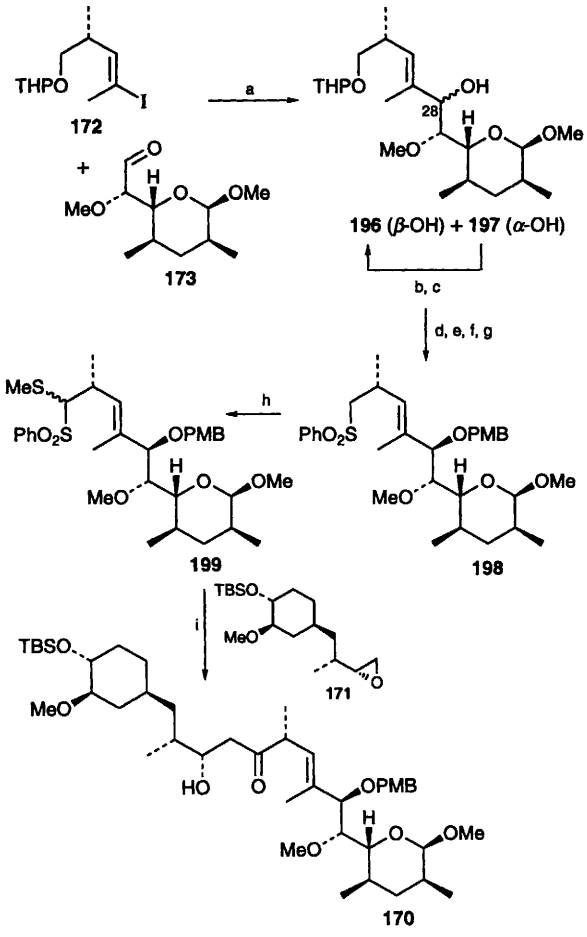
Scheme 34



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 35



Yields, Reagents and Conditions:

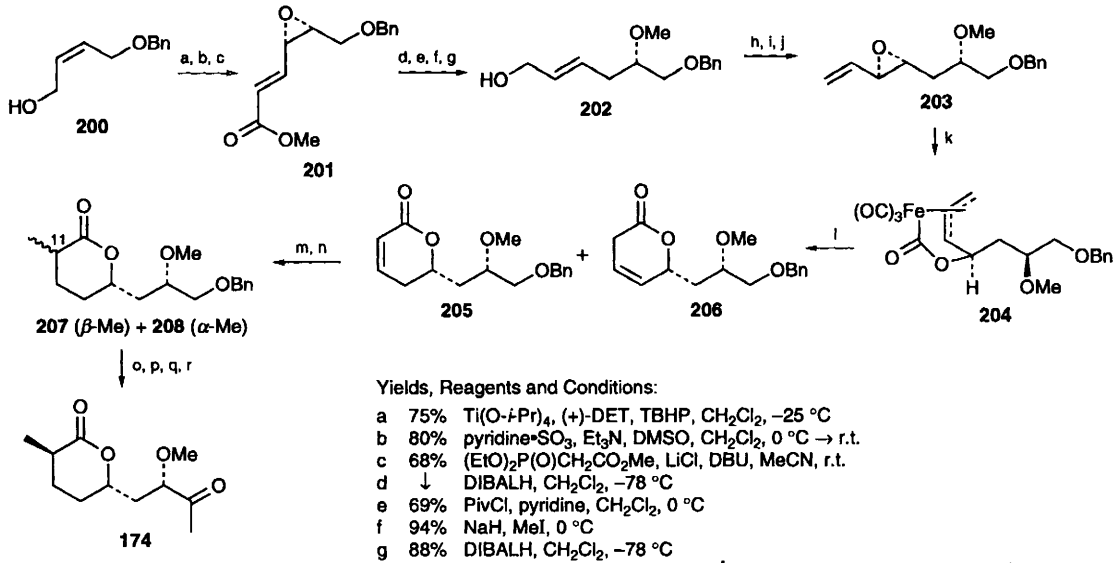
a 67% $CrCl_2$ (containing 0.5% $NiCl_2$), DMSO
b 98% TPAP, NMO, CH_2Cl_2
c 81% $Zn(BH_4)_2$, Et_2O, 0 °C
d 75% NaH, PMBCl, NaI, THF, 0 °C → r.t.
e 84% Amberlyst-15, MeOH
f 85% *n*-Bu_3P, *N*-phenylthiosuccinimide, benzene
g 93% Oxone®, pH 4 buffer, THF–MeOH
h 81% 1) *t*-BuLi, THF, –78 °C; 2) $(MeS)_2$
i 46% 1) *t*-BuLi, THF, –78 °C; 2) **171**;
3) BF_3•OEt_2, –78 °C → r.t.

Scheme 36

aldehyde **191** using standard procedures. Treatment of **191** with NPSP and excess MeOH then afforded acetals **192** and **193** as single diastereomers at C26. Selenide oxidation–elimination followed by separation of the anomers and ozonolysis provided aldehyde **194**, which underwent stereoselective addition of ethynylmagnesium bromide to yield prop-2-ynyl alcohol **195**. Reduction of the triple bond to the corresponding alkene and methylation of the alcohol, followed by ozonolysis then provided **173**.

Coupling of vinyl iodide **172** with aldehyde **173** was achieved *via* a Nozaki–Kishi reaction (**Scheme 36**) to afford alcohol **196** as a 3:1 mixture with C28 epimer **197**. The minor isomer was converted to **196** *via* an oxidation–chelation-controlled reduction sequence employing $Zn(BH_4)_2$. A series of four standard procedures then provided sulfone **198**, which was converted to its α-methylsulfanyl derivative **199**. Deprotonation of **199** and addition to epoxide **171** in the presence of $BF_3 \cdot OEt_2$ then afforded coupled product **170** with the ketone function already deprotected (due to the presence of $BF_3 \cdot OEt_2$).

The synthesis of fragment **174** (**Scheme 37**) employed π-allyltricarbonyliron chemistry in the key step to generate the lactone ring. Thus, Sharpless asymmetric epoxidation of (*Z*)-4-(benzyloxy)but-2-en-1-ol **200** followed by oxidation of the resulting epoxy alcohol and condensation of the intermediate aldehyde with diethyl phosphonoacetate yielded



Yields, Reagents and Conditions:

a 75% $Ti(O\text{-}i\text{-}Pr)_4$, (+)-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% $Ti(O\text{-}i\text{-}Pr)_4$, (–)-DET, TBHP, 4 Å molecular sieves, CH_2Cl_2, –23 °C
i 60% TPAP, NMO, 4 Å 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 37

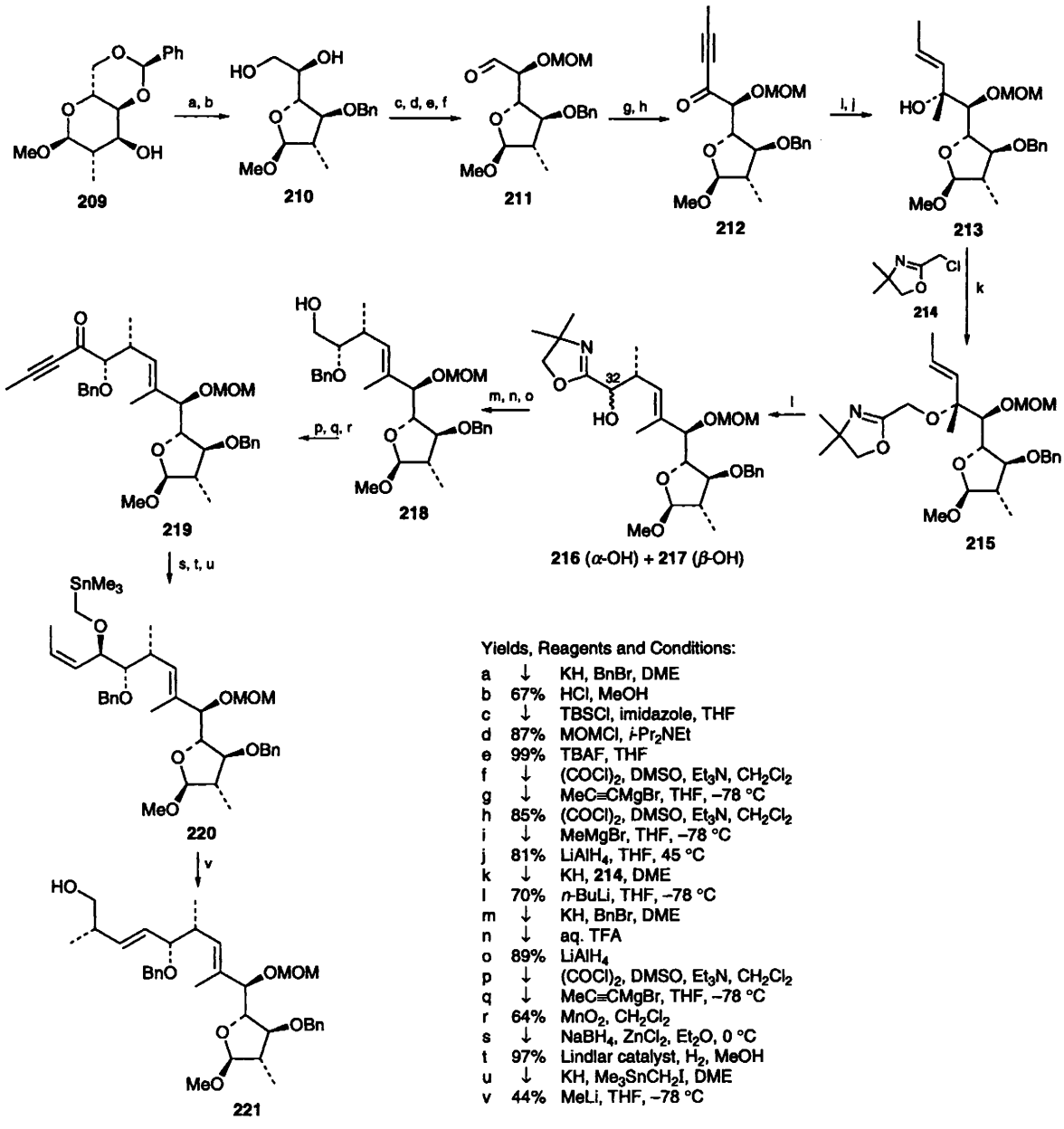
enoate **201**. A further four steps provided allylic alcohol **202**, which underwent a second Sharpless epoxidation. Oxidation and Wittig methylenation then furnished alkenyl epoxide **203** as the precursor to the iron carbonyl chemistry. Reaction of **203** with $Fe_2(CO)_9$ in THF gave *endo*-complex **204** as the predominant product, which was subjected to exhaustive carbonylation to provide unsaturated lactones **205** and **206**. Hydrogenation and methylation then produced lactone **207** as a 1:1.5 mixture with C11 epimer **208** (the mixture was separable by HPLC and the unwanted major isomer could be recycled to **207** by deprotonation–reprotonation). A further four transformations then afforded **174**.

3.2 The Kallmerten synthesis of the C24–C36 fragment

Kallmerten's synthesis of C24–C36 fragment **221**[43] features two [2,3]-Wittig rearrangements as key steps (**Scheme 38**). The synthesis began with D-glucose-derived compound **209**, which was converted to furanose **210** *via* benzylation and acid-catalysed isomerisation. A further four steps then yielded aldehyde **211**, which, upon chelation-controlled addition of propynylmagnesium bromide and oxidation of the epimeric adducts, afforded ketone **212**. A second chelation-controlled Grignard addition followed by reduction of the triple bond then provided (*E*)-allylic alcohol **213**. Alkylation of **213** with chloromethyloxazoline **214** and treatment of the resulting ether **215** with *n*-BuLi resulted in rapid [2,3]-sigmatropic rearrangement, yielding an inseparable mixture (4.5:1) of homoallylic alcohol **216** and its C32 epimer **217**. Benzylation and reductive cleavage of the oxazoline group then provided alcohol **218**, at which stage the minor isomer from rearrangement could be separated. A further three steps provided prop-2-ynyl ketone **219**, which was converted to α-stannyl ether **220** by chelation-controlled reduction of the carbonyl group and Lindlar reduction of the acetylene, followed by alkylation. Upon transmetallation, **220** underwent a second [2,3]-sigmatropic rearrangement to yield **221**.

3.3 The Paterson synthesis of the C24–C32 fragment

Paterson has reported[44] a short synthesis of C24–C32 fragment **225** (**Scheme 39**) which features a highly π-face-selective boron-mediated *anti*-aldol reaction as the key step. Thus, Weinreb amide **222** was prepared in two steps from methyl (*R*)-3-hydroxy-2-methylpropionate and converted to methoxymethyl ketone **223**. Enal **224**, 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 **223** to afford **225** as the sole product.



Scheme 38

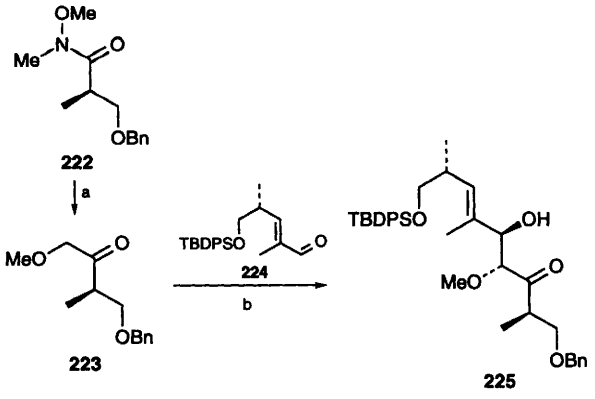
3.4 The Hoveyda synthesis of the C22–C29 fragment

Hoveyda's synthesis[45] of C22–C29 fragment **231** (**Scheme 40**) utilises the ability of a siloxane ring to relay asymmetry along an acyclic chain in order to direct a stereoselective osmylation (**227**→**228**). The synthesis began with siloxane **226**, prepared by intramolecular Pt-catalysed hydrosilylation of the corresponding (*E*)-allylic silyloxy hydride. Debenzylation of **226**, followed by Swern oxidation and Horner–Emmons olefination of the resulting aldehyde afforded unsaturated Weinreb amide **227**. Osmylation of **227** then stereoselectively afforded siloxane **228** (resulting from rearrangement of the initially formed 1,2-diol), thus differentiating the secondary hydroxy groups at C26 and C27.

Tritylation of the primary alcohol, methylation of the C27 alcohol and removal of the siloxane afforded hydroxy amide **229**, which was converted to enone **230** *via* reaction with prop-2-enyllithium 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 hydroxy group was then oxidised to the requisite carbonyl to afford **231**.

3.5 The Rama Rao synthesis of the C1–C17 fragment

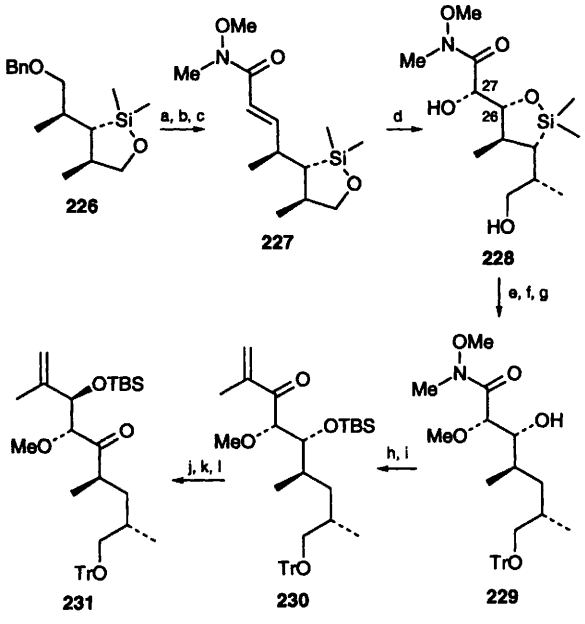
Rama Rao has reported[46] a synthesis of C1–C17 fragment **239** beginning with epoxychloride **232** (**Scheme 41**). Base-induced double elimination of



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) **224**, –78 °C → –20 °C

Scheme 39

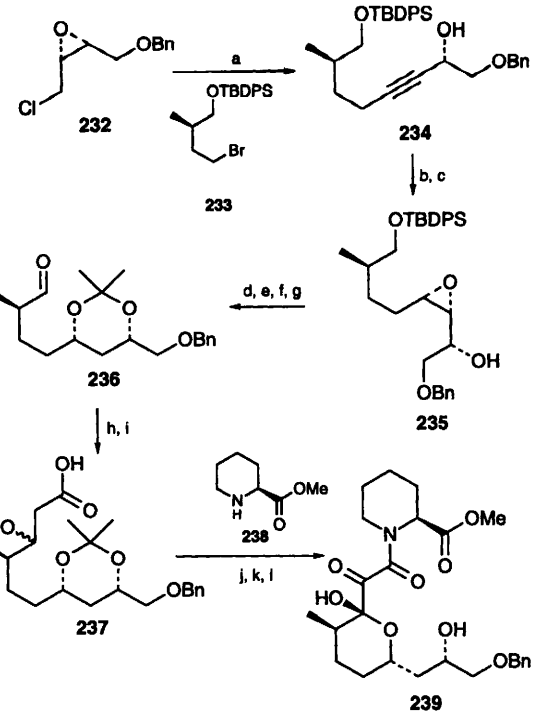


Yields, Reagents and Conditions:

a 98% Pd/C, H_2
b ↓ Swern oxidation
c 70% Horner–Emmons olefination
d 80% OsO_4, NMO, 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 oxidation

Scheme 40

232 generated the corresponding prop-2-ynylic alcohol which was coupled *in situ* with bromide **233** (prepared in six steps from methyl (*S*)-3-hydroxy-2-methylpropionate). The resulting product **234** then underwent Lindlar reduction and Sharpless



Yields, Reagents and Conditions:

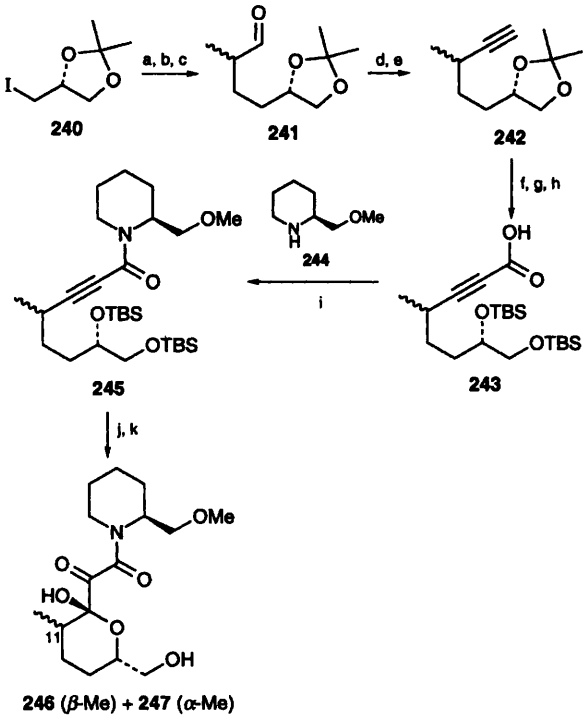
a 60% 1) $LiNH_2$–NH_3, –33 °C; 2) **233**
b 95% Lindlar catalyst, quinoline, MeOH
c 60% $Ti(O\text{-}i\text{-}Pr)_4$, (–)-DIPT, TBHP, 3 Å molecular sieves, CH_2Cl_2
d 75% Red-Al, THF, r.t.
e ↓ TBAF, THF, r.t.
f ↓ acetone, PTSA
g 80% $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C
h 70% Zn, $BrCH_2CO_2Et$, benzene, Δ
i 70% LiOH, DME
j 75% **238**, pentafluorophenol, DCC, DMAP, CH_2Cl_2
k 60% Dess–Martin periodinane, pyridine, CH_2Cl_2
l 70% 0.001 M HCl, MeOH

Scheme 41

asymmetric epoxidation of the resulting (*Z*)-alkene to afford epoxyalcohol **235**. Regioselective opening of the epoxide with Red-Al followed by a further three transformations led to aldehyde **236**, which was subjected to a Reformatsky reaction with Zn–ethyl bromoacetate. Hydrolysis of the resulting β-hydroxy ester provided acid **237** (as a 1:1 mixture of diastereomers) which was coupled with methyl L-pipecolinate **238**. Dess–Martin oxidation to the tricarbonyl compound followed by acetonide hydrolysis then led to lactolisation, providing **239** in good yield.

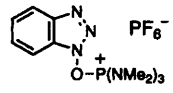
3.6 The Pattenden synthesis of the C1–C15 fragment

In Pattenden's synthesis[47] of C1–C15 fragment **246** (**Scheme 42**), a straightforward oxidation of acetylenic amide **245** 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 **240**



Yields, Reagents and Conditions:

a 55% $H_2C{=}C(Me)CO_2Me$, n-Bu_3SnCl–$NaBH_4$, hv, r.t.
b ↓ DIBALH, THF
c ↓ PCC, NaOAc
d 76% $Ph_3P{=}CBr_2$
e 45% n-BuLi, THF, –70 °C
f ↓ HCl, MeOH
g ↓ TBSCl, imidazole, DMF
h 86% 1) n-BuLi, HMPA, –50 °C; 2) CO_2
i 86% **244**, BOP•PF_6
j 35% RuO_2–$NaIO_4$
k – aq. HF, MeCN

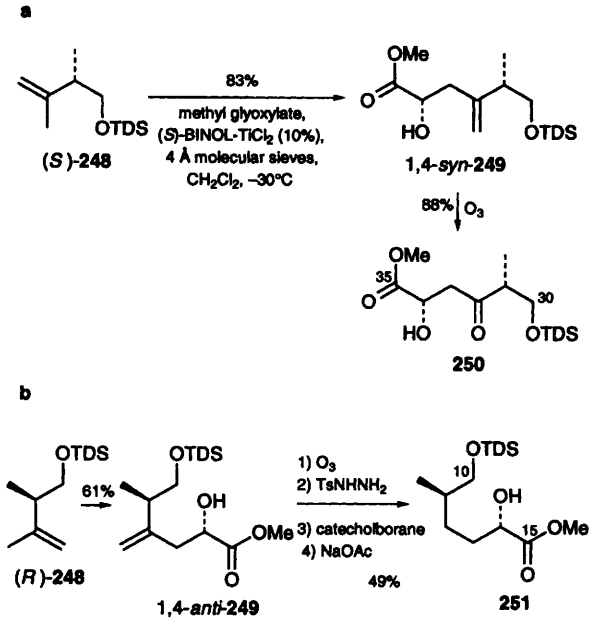
BOP•PF_6 = 

Scheme 42

(derived from the corresponding carbinol) to methyl methacrylate. The resulting 1:1 mixture of diastereomeric esters was converted to aldehyde **241** and homologated (Corey–Fuchs) to terminal acetylene **242**. Removal of the acetonide and bis-silylation of the resulting diol, followed by metallation and carboxylation of the acetylene, led to acid **243**. Coupling of **243** with (*S*)-2-(methoxymethyl)piperidine **244** in the presence of BOP·PF_6 next produced **245**, which, upon exposure to catalytic RuO_4, afforded the required amide dione. Bis-desilylation of the product then led to lactolisation, producing **246**, which could be cleanly separated from the C11-epimeric material **247**.

3.7 The Mikami synthesis of the C30–C35 and C10–C15 fragments

Finally, Mikami has shown[48] that the (*S*)-BINOL-$TiCl_2$-catalysed asymmetric carbonyl-ene reaction of (*S*)- and (*R*)-homoallylic silyl ethers **248** with methyl



Scheme 43

glyoxylate affords 1,4-*syn*- and 1,4-*anti*-products **249** respectively with essentially complete diastereoselectivity, independent of reactant chirality (**Scheme 43**). Further transformations led to 1,4-*syn*- and 1,4-*anti*-compounds **250** and **251** respectively, corresponding to the C30–C35 and C10–C15 segments of rapamycin.

4 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 rapamycin and its fragments will undoubtedly find application in other areas of synthesis.

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