Stereoselective Construction of the C^{21}–C^{42} Fragment of Rapamycin

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A stereoselective construction of the C^{21}–C^{42} fragment **2** of rapamycin **1** *via* coupling and elaboration of key intermediates **3**–**6** is described.

In the preceding communication[1] we outlined a highly convergent strategy for the total synthesis of rapamycin **1**[2] and a stereoselective synthesis of an appropriately functionalized C^8–C^{18} fragment. In this communication we report enantioselective and efficient syntheses of the remaining three fragments C^{21}–C^{28} (**3**), C^{29}–C^{34} (**4**) and C^{35}–C^{42} **5** and their coupling and elaboration to the advanced C^{21}–C^{42} key intermediate **2** (Scheme 1).

Scheme 2 summarizes the construction of the C^{21}–C^{28} fragment **3**.† Thus, coupling of intermediates **7** and **8**‡ under Evans aldol conditions[3] led stereoselectively to product **9** in 85% yield. The carboximide moiety was then converted to a methyl group in 80% overall yield *via* a known three-step sequence. The resulting intermediate **10** was desilylated (93%) and converted to *p*-methoxybenzylidene derivative **11** in 95% yield. Finally, regioselective opening of the benzylidene acetal with DIBAL[5] followed by Swern oxidation afforded the targeted intermediate **3**§ in 94% overall yield.

Scheme 3 outlines the synthesis of optically active intermediate **4** starting with aldehyde **12**.¶ Asymmetric crotylboration of **12** using Brown's conditions[6] led to the corresponding *anti*-adduct in 70% yield [>20:1 diastereoselectivity and >95% enantiomeric excess (e.e.) as determined by Mosher ester formation and NMR analysis]. Protection of this compound with *p*-methoxybenzyl bromide gave **13** (90%) which was converted to acetylene **14** by (*i*) ozonolysis–Me_2S (80%); (*ii*) dibromoolefin formation[7] (90%); and (*iii*) treatment with Bu^nLi–MeI (98%). Finally hydrozirconation of **14**[8] followed by iodine quench furnished compound **4**§ in 85% yield.

Scheme 4 outlines the construction of the key intermediate **5**. Acid induced regioselective and stereospecific opening of epoxide **15**‖ with methanol followed by silylation led to intermediate **16** in 88% overall yield. Hydrogenolysis of the benzyl ether in **16** followed by Swern oxidation gave ketone **17** which was converted to enone **18** by palladium catalysed oxidation of the corresponding silyl enol ether (88%).[9] Stereoselective Luche reduction[2e,10] of **18** furnished **19** (95%) which entered a stereospecific Eschenmoser–Claisen rearrangement upon heating with *N,N*-dimethylacetamide

† All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

‡ Oxazolidinone **7** was obtained from (+)-β-citronellene by selective cleavage of the trisubstituted double bond [*m*-chloroperbenzoic acid (mCPBA), $HClO_4$, $NaIO_4$ and Jones oxidation, see: D. R. Williams, B. A. Barner, K. Nichitami and J. U. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708], followed by acid chloride formation and condensation with the lithio-oxazolidinone derived from (1*S*,2*R*)-norephedrine, see: D. A. Evans, *Aldrichim. Acta*, 1982, **15**, 23.

Aldehyde **8** was prepared from bis(benzylidene)mannitol by bis(methylation) (NaH–MeI) followed by removal of the benzylidene groups [$Pd(OH)_2$/C cat., H_2], selective silylation at the primary positions (TBDPSCl) and cleavage of the 1,2-diol system [$Pb(OAc)_4$].

§ *Selected physical properties of compounds.* **3**: Colourless oil; R_F 0.65 (silica, 30% ethyl acetate in light petroleum); $[\alpha]_D^{20}$ − 55.9 (*c* 5.3 in $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2929, 1731, 1612, 1513, 1460, 1248 and 1076; ^1H NMR (500 MHz, $CDCl_3$): δ 9.74 (d, *J* 1.6 Hz, CHO), 7.19 (d, *J* 8.7 Hz, 2 H, aromatic), 6.83 (d, *J* 8.7 Hz, 2 H, aromatic), 5.52 (ddd, *J* 8.6, 10.2, 17.1 Hz, 1 H, C*H*=CH_2), 4.94 (dd, *J* 1.9, 17.1 Hz, 1 H, olefinic), 4.90 (dd, *J* 1.9, 10.2 Hz, 1 H, olefinic), 4.43 (ABq, J_{AB} 11.1 Hz, $\Delta\nu_{AB}$ = 14.1 Hz, 2 H, OCH_2Ar), 3.78 (s, 3 H, ArO*Me*), 3.67 (dd, *J* 1.6, 3.6 Hz, 1 H, 27-H), 3.50 (dd, *J* 3.6, 6.4 Hz, 1 H, 26-H), 3.45 (s, 3 H, OMe), 2.2 (m, 1 H, 23-H), 1.9 (m, 1 H, 25-H), 1.44 (m, 1 H, 24-H), 1.1 (m, 1 H, 24-H'), 0.97 (d, *J* 6.7 Hz, 3 H, Me) and 0.91 (d, *J* 6.7 Hz, 3 H, Me); HRMS (FAB): Calc. for $C_{19}H_{28}O_4Cs$ (M + Cs^+): 453.1042, found *m/z* 453.1033.

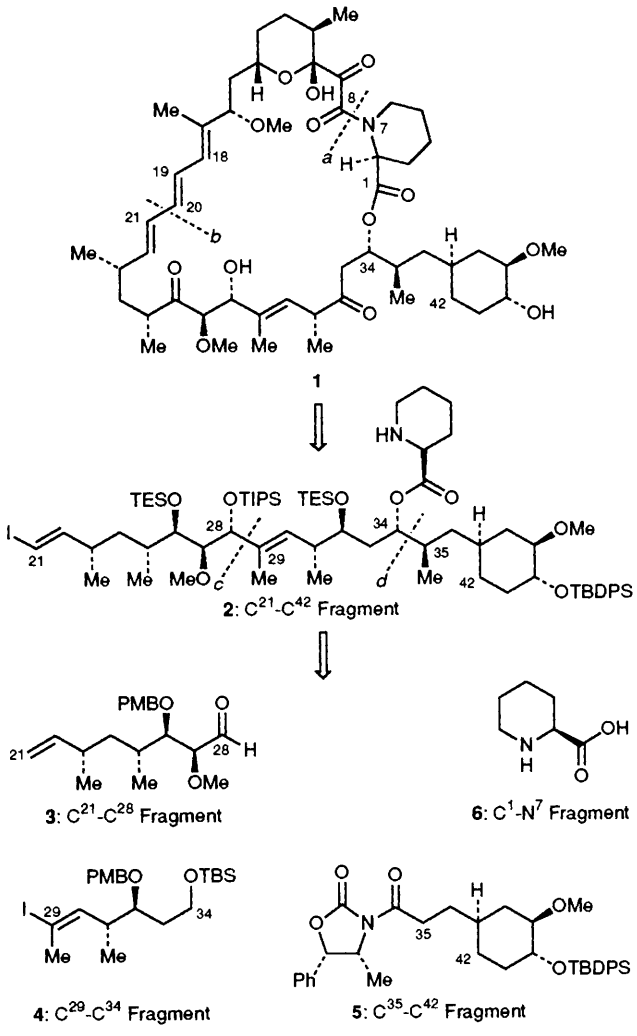
4: Colourless oil; R_F 0.45 (silica, 5% ethyl acetate in light petroleum); $[\alpha]_D^{20}$ 5.37 (*c* 1.0 in $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2952, 2858, 1612, 1512, 1463, 1378, 1300, 1249, 1174, 1093, 1042 and 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* 8.8 Hz, 2 H, aromatic), 6.86 (d, *J* 8.8 Hz, 2 H, aromatic), 6.04 (dq, *J* 1.5 and 9.8 Hz, 1 H, 30-H), 4.44 (s, 2 H, OCH_2Ar), 3.78 (s, 3 H, ArO*Me*), 3.62 (m, 1 H, 32-H), 3.43 (dd, *J* 6.5 Hz, 2 H, 34-H_2), 2.45 (m, 1 H, 31-H), 2.29 [d, *J* 1.5 Hz, 3 H, CH=C(*Me*)I], 1.64 (m, 1 H, 33-H), 1.22 (m, 1 H, 33-H'), 0.92 (d, *J* 6.8 Hz, 3 H, Me), 0.86 (s, 9 H, Bu^t), 0.026 and 0.012 (2 × s, 6 H, SiMe); HRMS (FAB): Calc. for $C_{22}H_{37}O_3SiCs$ (M + Cs^+): 637.0611, found *m/z* 637.0611.

5: Colourless foam; R_F 0.35 (silica, 35% ether in light petroleum); $[\alpha]_D^{20}$ +3.58 (*c* 0.87 in $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2930, 2858, 1783, 1701, 1455, 1350, 1197 and 1110; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (m, 4 H, aromatic), 7.37 (m, 9 H, aromatic), 7.26 (m, 2 H, aromatic), 5.63 (d, *J* 7.0 Hz, 1 H, PhC*H*O), 4.71 (dq, *J* 7.0 and 7.0 Hz, 1 H, CHN), 3.53 (ddd, *J* 4.80, 8.59 and 13.29 Hz, 1 H, 40-W), 3.32 (s, 3 H, OMe), 3.05 (ddd, *J* 4.50, 8.59, and 12.91 Hz, 1 H, 39-H), 2.88 (m, 2 H, 35-H), 2.05 (m, 1 H, CH), 1.63 (m, 1 H, CH), 1.52 (m, 4 H, CH and CH_2), 1.03 (s, 9 H, Bu^t) and 0.7 (m, 1 H, CH); HRMS (FAB): Calc. for $C_{36}H_{45}NO_5SiCs$ (M + Cs^+): 732.2121, found *m/z* 732.2100.

2: Colourless foam; R_F 0.3 (silica, 70% ether in light petroleum); $[\alpha]_D^{20}$ −4.3 (*c* 0.3 in $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2926, 2863, 1733, 1459, 1377, 1236, 1187 and 1108; ^1H NMR (500 MHz, $CDCl_3$): δ 7.7 (m, 4 H, aromatic), 7.35 (m, 6 H, aromatic), 6.23 (dd, *J* 9.3 and 14.3 Hz, 1 H, 22-H), 5.91 (d, *J* 14.3 Hz, 1 H, 21-H), 5.07 (d, *J* 10.6 Hz, 1 H, 30-H), 5.07 (m, 1 H, NCHC=O), 4.08 (m, 1 H, CHO), 3.56 (dt, *J* 6.2 and 9.2 Hz, 1 H, CHO), 3.53–3.40 (m, 2 H, CHO), 3.52 (s, 3 H, 27-OMe), 3.38 (m, 1 H, CHN), 3.32 (s, 3 H, 39-OMe), 3.22 (m, 2 H, CHO), 3.03 (ddd, *J* 4.3, 8.3 and 12.5 Hz, 1 H, 39-H), 2.73 (m, 1 H, CHN), 2.6 (m, 1 H, 31-H), 2.21 (m, 1 H, 23-H) 2.05–0.6 (m, 21 H, CH and CH_2), 1.74 (s, 3 H, 29-Me), 1.07–1.03 (m, 18 H, $SiCHMe_2$), 1.02 (s, 9 H, Bu^t), 1.0 (d, *J* 6.5 Hz, 3 H, Me), 0.95 (t, *J* 7.9 Hz, 9 H, $SiCH_2Me$), 0.92 (t, *J* 7.9 Hz, 9 H, $SiCH_2Me$), 0.90 (d, *J* 7.5 Hz, 3 H, Me), 0.84 (d, *J* 6.6 Hz, 3 H, Me), 0.77 (d, *J* 6.8 Hz, 3 H, Me), 0.59 (q, *J* 7.9 Hz, 12 H, SiC*H*Me) and 0.55 (m, 3 H, $SiCHMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.69, 136.46, 135.99, 135.89, 135.21, 134.36, 130.07, 129.27, 129.22, 127.31, 127.25, 86.54, 84.51, 79.38, 78.17, 76.16, 73.41, 71.54, 61.42, 57.33, 57.27, 39.87, 38.84, 38.45, 36.57, 35.70, 33.67, 33.15, 32.87, 32.32, 30.49, 29.70, 26.98, 26.95, 21.32, 19.34, 18.42,18.29, 17.64, 14.71, 13.21, 12.39, 12.35, 7.24, 7.11, 5.61, 5.57 and 5.23; HRMS (FAB): Calc. for $C_{72}H_{128}NO_8Si_4ICs$ (M + Cs^+): 1506.6818, found *m/z* 1506.6879.

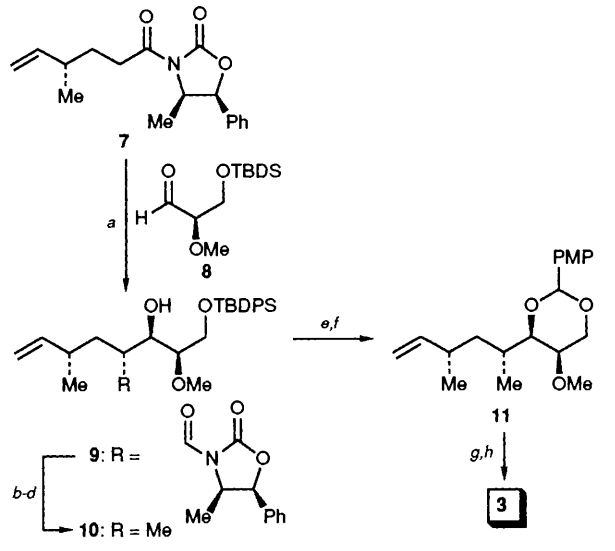
¶ Aldehyde **12** was prepared from but-3-ene-1-ol by silylation followed by ozonolysis.

‖ Epoxide **15** was prepared from 2-bromocyclohexenone by asymmetric reduction (96% e.e., see: E. J. Corey and J. O. Link, *Tetrahedron Lett.*, 1989, **30**, 6275; T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts and E. J. J. Grabowski, *J. Org. Chem.*, 1991, **56**, 763) followed by reductive removal of the bromine (Li–Bu^tOH), epoxidation (*m*CPBA, see: H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958) and benzylation (NaH–$PhCH_2Br$).



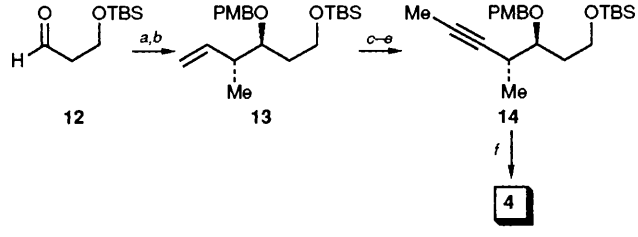
Scheme 1 Strategic bond disconnections and retrosynthetic analysis of rapamycin **1**. Definition of requisite fragments for a total synthesis.

PMB = *p*-methoxybenzyl; TES = triethylsilyl; TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.



Scheme 2 Synthesis of key intermediate **3**. *Reagents and conditions*: (*a*) **7** (1 equiv.), Bu^n_2BOTf (1.15 equiv.), Et_3N (1.3 equiv.), CH_2Cl_2 −78 to 0 °C, 1 h, then **8** (1 equiv.), −78 to 25 °C, 3 h, 85%; (*b*) $LiBH_4$ (2.2 equiv.), H_2O (2.2 equiv.), Et_2O, 0 °C, 1 h, 98%; (*c*) TsCl (1.2 equiv.), pyridine, 0 °C, 6 h, 90% (based on 20% recovered starting material); (*d*) $LiEt_3BH$ (5 equiv.), THF, 0 to 25 °C, 12 h, 92% (*e*) Bu^n_4NF (1.5 equiv.), THF, 0 to 25 °C, 1 h, 93%; (*f*) *p*-methoxybenzaldehyde dimethyl acetal (1.3 equiv.), CSA (0.2 equiv.), CH_2Cl_2, 25 °C, 4 h, 95%, (*g*) DIBAL (2 equiv.), CH_2Cl_2, −78 to 25 °C, 1 h, 98%; (*h*) $(COCl)_2$ (1.5 equiv.), DMSO (3.2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −78 to −10 °C, 1 h, 96%.

Tf = CF_3SO_2; Ts = *p*-$MeC_6H_4SO_2$; THF = tetrahydrofuran; CSA = camphorsulfonic acid; DMSO = dimethyl sulfoxide; DIBAL = diisobutylaluminium hydride.



Scheme 3 Syntheses of key intermediate **4**. *Reagents and conditions*: (*a*) *trans*-but-2-ene (1.3 equiv.), KOBu^t (1 equiv.) Bu^nLi (1 equiv.), (+)-Ipc_2BOMe (1.1 equiv.), $BF_3{\cdot}Et_2O$ (1.2 equiv.), THF, −78 to 25 °C, 4 h, 70%; (*b*) PMBBr (1.1 equiv.), NaHMDS (1.1 equiv.), THF–DMF (2 : 1), 0 °C, 3 h, 90%; (*c*) O_3, CH_2Cl_2–MeOH–pyridine (5 : 5 : 1), −78 °C then Me_2S, −78 to 25 °C, 80%; (*d*) CBr_4 (2.25 equiv.), Ph_3P (2.25 equiv.), Zn (2.25 equiv.), CH_2Cl_2, 25 °C, 90%; (*e*) Bu^nLi (2.1 equiv.), MeI (5 equiv.), THF, −78 to 0 °C, 1 h, 98%; (*f*) Cp_2ZrHCl (2 equiv.), CH_2Cl_2, 25 °C, 4 h then I_2 (2 equiv.), 0 °C, 15 min., 85%.

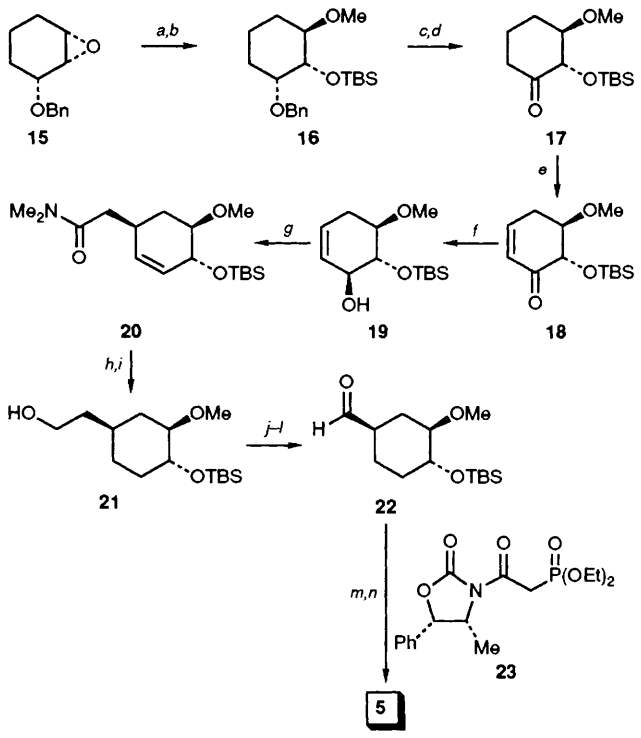
Ipc = isopinocampheyl; NaHMDS = sodium hexamethyldisilazide; Cp = cyclopentadienyl.

dimethyl acetal[2e,11] to give amide **20** in 89% yield. Reduction of **20** ($LiEt_3BH$, 92%) followed by hydrogenation of the double bond led to alcohol **21** (96%). Conversion of **21** to the corresponding terminal olefin, followed by ozonolysis gave aldehyde **22** (72% overall yield). Finally, condensation of ketophosphonate **23**** with aldehyde **22** under LiCl–Pr^i_2NEt[12] conditions, followed by reduction of the resulting α,β-unsaturated double bond [(*i*) Et_3SiH–Wilkinson's catalyst; (*ii*) $HF–H_2O$–MeCN][13] and resilylation (TBDPSCl) gave the key intermediate **5**§ in 72% overall yield.

Coupling of intermediates **3**–**5** and elaboration to the desired C^{18}–C^{42} fragment **2** was accomplished as summarized in Scheme 5. Thus, chromium–nickel[14] mediated coupling of **3** and **4** led to the desired hydroxy compound **24** (87% based on 90% conversion).†† A silylation-selective desilylation sequence followed by Swern oxidation converted compound **24** to aldehyde **25** in 92% overall yield. Aldol condensation of the boron-enolate of **5** with aldehyde **25** under Evans conditions[3] led stereoselectively to product **26** (95%) which was converted to compound **27** by the standard reduction–tosylation–reduction procedure (80% overall yield) as detailed in Scheme 5. Esterification of **27** with *N*-Boc-L-pipecolic acid (Boc-**6**) under standard carbodiimide conditions furnished the corresponding ester (85%) which was converted to *trans*-iodoolefin **28** by OsO_4 catalysed diol formation–$Pb(OAc)_4$ cleavage (75% overall) followed by chromium mediated iodoolefination (94%).[15] Finally, exchange of the *p*-methoxybenzyl for triethylsilyl groups in **28** accompanied by

** Ketophosphonate **23** was prepared by reacting triethyl phosphite with bromoacetyloxazolidin-2-one, see: D. A. Evans, E. B. Sjogren, A. E. Weber and R. E. Conn, *Tetrahedron Lett.*, 1987, **28**, 39.

†† Two (*ca.* 4 : 1 ratio) diastereoisomers were obtained in this step (92% yield) which were separated by standard silica gel chromatography. The minor diastereoisomer was converted back to the desired one by a two step sequence, PDC oxidation followed by $Zn(BH_4)_2$ reduction (ref. 2*i*) in 70% yield, leading to the desired product **24** in 87% overall yield.



Scheme 4 Synthesis of key intermediate **5**. *Reagents and conditions*: (*a*) CSA (0.25 equiv.), MeOH, 25 °C, 2 h, 88%; (*b*) TBSOTf (1.5 equiv.), 2,6-lutidine (2 equiv.), CH_2Cl_2, 0 °C, 15 min., 98%; (*c*) 20% $Pd(OH)_2$/C, H_2, EtOH, 25 °C, 2 h, 95%; (*d*) $(COCl)_2$ (1.5 equiv.), DMSO (3.2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −78 to −10 °C, 1 h, 92% (*e*) LDA (1.1 equiv.), TMSCl (1.1 equiv.), THF, −78 °C, 0.5 h then $Pd(OAc)_2$ (1.1 equiv.), MeCN, 50 °C, 18 h, 88%; (*f*) $LiBH_4$ (4 equiv.), $CeCl_3 \cdot 7H_2O$ (2 equiv.), MeOH–THF (1 : 1], −78 °C, 0.5 h, 95%; (*g*) *N,N*-dimethylacetamide dimethyl acetal (5 equiv.), xylene, reflux, 24 h, 89%; (*h*) $LiEt_3BH$ (2.2 equiv.), THF, 0 to 25 °C, 2 h, 92%; (*i*) 10% Pd/C, H_2, EtOH, 25 °C, 2 h, 96%; (*j*) *o*-$NO_2C_6H_4SeCN$ (1.2 equiv.), Bu^n_3P (1.2 equiv.), THF, 0 to 25 °C, 2 h, 93%; (*k*) H_2O_2 (30% aq.), THF, 0 to 25 °C, 2 h, 86%; (*l*) O_3, CH_2Cl_2–MeOH (1 : 1, −78 °C, then Me_2S, −78 to 25 °C, 6 h, 92%; (*m*) **23** (1.5 equiv.), LiCl (1.7 equiv.), diisopropylethylamine (1.7 equiv.), MeCN, 25 °C, 4 h, 96% (*n*) $Rh(PPh_3)_3Cl$ (0.05 equiv.), Et_3SiH, 50 °C, 2 h then aq. HF in MeCN (10%), 0 °C, 2.5 h followed by TBDPSCl (1.5 equiv.), imidazole (3 equiv.), DMF, 25 °C, 6 h, 75% overall.

LDA = lithium diisopropylamide; TMS = trimethylsilyl; DMF = dimethylformamide; Bn = benzyl.

concomitant removal of the Boc group furnished the targeted advanced key intermediate **2**§ in 92% overall yield.

The described chemistry sets the stage for the total synthesis of rapamycin **1** and designed congeners.

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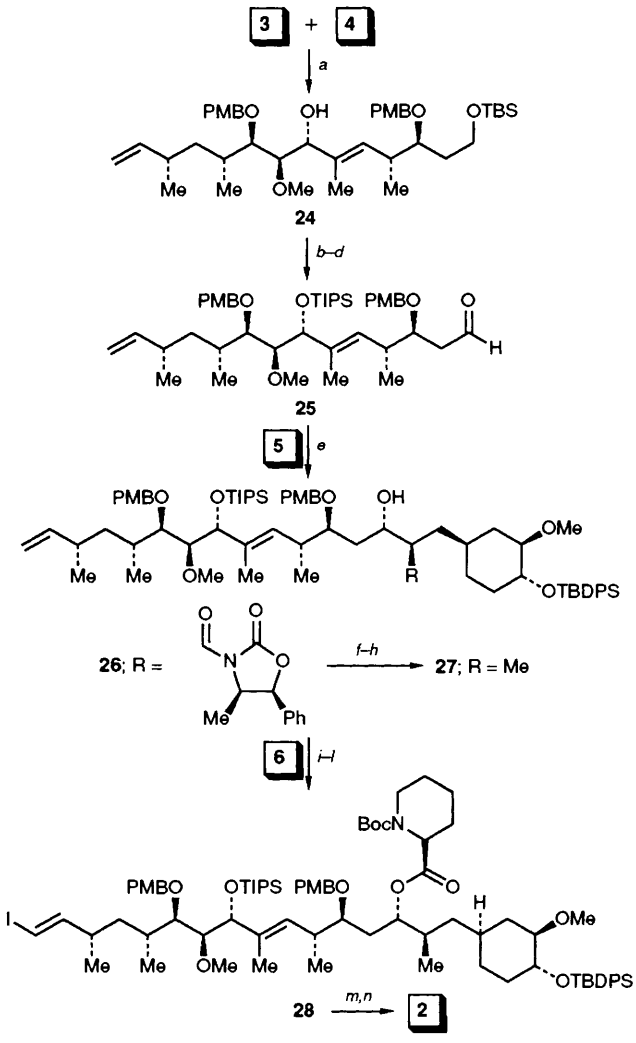

Scheme 5. Synthesis of key intermediate **2**. *Reagents and conditions*: (*a*) **3** (1.0 equiv.), **4** (2.5 equiv.), $CrCl_2$ (containing 0.1% $NiCl_2$) (10 equiv.), DMSO, 25 °C, 12 h, 87% (based on 10% recovered aldehyde); (*b*) TlPSOTf (1.5 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, 0 °C, 15 min., 98%; (*c*) HF–pyridine, THF, 25 °C, 3 h, 97%; (*d*) $(COCl)_2$ (1.5 equiv.), DMSO (3.2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −78 to −10 °C, 1 h, 96%; (*e*) **5** (2.0 equiv.), Bu^n_2BOTf (2.3 equiv.), Et_3N (2.6 equiv.), CH_2Cl_2, −78 to 0 °C, 1 h then **24** (1 equiv.),−78 to 25 °C, 3 h, 95%; (*f*) $LiBH_4$ (2.2 equiv.), H_2O (2.2 equiv.), Et_2O, 0 °C, 1 h, 98%; (*g*) TsCl (2 equiv.), Et_3N (4 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 25 °C, 24 h, 90% (based on 10% recovered diol); (*h*) $LiEt_3BH$ (10 equiv.), THF, 0 °C, 2 h, 91%; (*i*) *N*-Boc-L-pipecolic acid (Boc-**6**) (5 equiv.), diisopropylcarbodiimide (5 equiv.), diisopropylethylamine (1 equiv.), 4-pyrrolidinopyridine (0.5 equiv.), CH_2Cl_2, 0 °C, 4 h, 85%; (*j*) OsO_4 (0.2 equiv.), *N*-methylmorpholine *N*-oxide (3.5 equiv.), acetone–H_2O (2 : 1), 25 °C, 12 h; (*k*) $Pb(OAc)_4$ (2.4 equiv.), Na_2CO_3 (3 equiv.), C_6H_6, 0 to 25 °C, 15 min., 75% from olefin; (*l*) CHI_3 (4 equiv.), $CrCl_2$ (12 equiv.), THF–dioxane (4 : 1), 25 °C, 1 h, 94%; (*m*) DDQ (3 equiv.), $CHCl_3$–H_2O (19 : 1), 25 °C, 1 h, 98%; (*n*) TESOTf (15 equiv.), 2,6-lutidine (20 equiv.), CH_2Cl_2, 0 °C, 1 h then silica gel, CH_2Cl_2, 25 °C, 6 h, 94%.

DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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