# A Highly Convergent Strategy Towards Rapamycin. Stereoselective Construction of the $C^{8}$–$C^{18}$ Fragment

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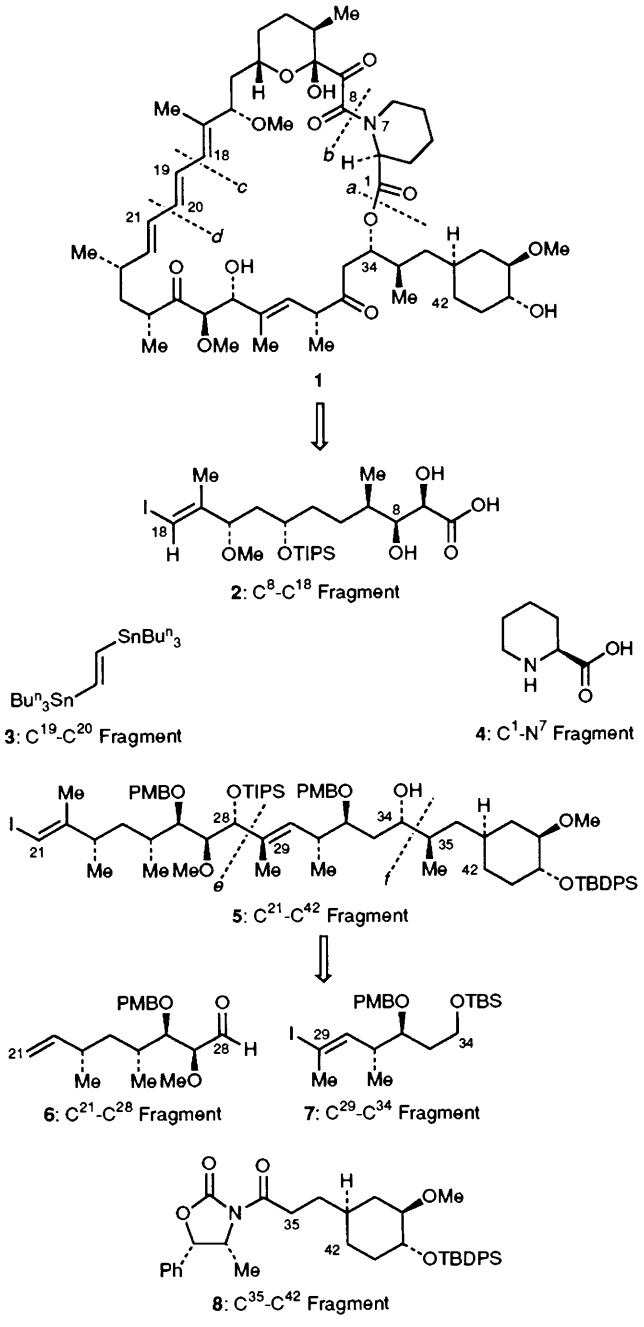
A strategy for a total synthesis of the immunosuppressant agent rapamycin **1** is outlined and the stereoselective construction of a suitably functionalized $C^{8}$–$C^{18}$ fragment **2** is described.

Rapamycin **1** (Scheme 1) is a highly functionalized, 31-membered macrocyclic natural product[1,2] with an impressive biological profile.[3] Isolated from *Streptomyces hygroscopicus*[1] and fully characterized by X-ray crystallographic and NMR analyses,[2] this compound exhibits potent immunosuppressive properties and interferes with the cell cycle, acting both as a cytotoxic and as an antibiotic agent.[3] In this communication we outline a highly convergent stragegy towards this challenging synthetic target[4] and describe a stereoselective construction of a fully functionalized $C^{8}$–$C^{18}$ fragment **2** (Scheme 2).




**Scheme 1** Strategic bond disconnections and retrosynthetic analysis of rapamycin **1**. Definition of requisite fragments for a total synthesis. PMB = *p*-methoxybenzyl; TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.

Scheme 1 depicts the strategic bond disconnections and retrosynthetic analysis of rapamycin **1**. Thus, following disconnections *a*–*d* (structure **1**) and functionalizing appropriately leads to fragments **2**–**5** (Scheme 1). Further disconnections of advanced intermediate **5** (at positions *e* and *f*) unravel fragments **6**–**8** (Scheme 1) as potential intermediates for this construction. The highly convergent nature of this strategy and its flexibility for ring construction (each of the five disconnections *a*–*e* could, in principle, be used in the macroring formation) bode well for an expedient and efficient total synthesis of **1**.

Scheme 2 presents a concise and stereocontrolled synthesis† of the $C^{8}$–$C^{18}$ fragment **2**. Thus, the Weinreb amide **10**, obtained from the readily available carboxylic acid **9**,‡ was coupled with the vinyllithium reagent derived from **11**§ to afford enone **12** in 70% yield. Reduction of this enone with $LiAlH_4$–LiI at −100 °C according to the method of Mori and Suzuki[5] gave a single alcohol (86%) which was methylated to afford compound **13** in 94% yield. Removal of the acetonide group from **13** gave the corresponding diol (93%) which was selectively mesylated and converted to epoxide **14** by standard methods (Scheme 2, 64% overall yield). The higher order cuprate[6] derived from iodide **15**¶ reacted smoothly with epoxide **14** to afford, after silylation and silicon–iodine exchange,[7] vinyl iodide **16** in 84% overall yield.

Liberation of the primary alcohol in **16** with DDQ (94%) followed by Swern oxidation led to aldehyde **17** (98%). Evans aldol condensation of this aldehyde with the boron enolate derived from compound **18**‖ led stereoselectively to the

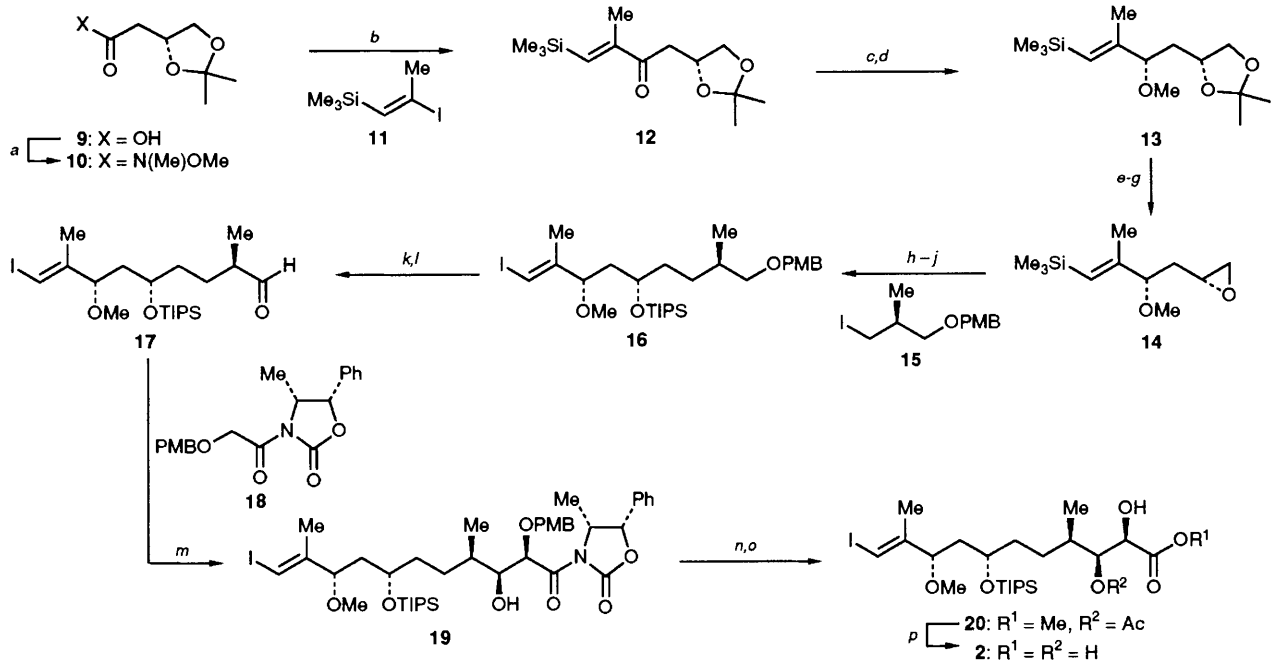
† All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

‡ Compound **9** was prepared from L-ascorbic acid according to modifications of literature methods: A. Tanaka and K. Yamashita, *Synthesis*, 1987, 570; R. Saibaba, M. S. P. Sarma and E. Abushanab, *Synth. Commun.*, 1989, **19**, 3077.

§ Vinyl iodide **11** was prepared from 1-trimethylsilylpropyne by hydrostannylation followed by treatment of the corresponding vinylstannane with iodine: H. X. Zhang, F. Guibé and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857.

¶ Primary iodide **15** was prepared form (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate by *p*-methoxybenzyl ether formation, $LiAlH_4$ reduction, tosylation, and iodide displacement.

‖ The compound **18** was utilized in order to deliver a single diastereoisomer, which allowed for convenient characterization and purification procedures. This compound was prepared from bromoacetic acid by displacement with the sodium derivative of *p*-methoxybenzyl alcohol followed by acid chloride formation and condensation with the oxazolidinone derived from (1*S*,2*R*)-(+)-norephedrine: D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy and T. J. Stout, *J. Am. Chem. Soc.*, 1990, **112**, 7001.



**Scheme 2** Synthesis of $C^8$–$C^{18}$ fragment **2**. *Reagents and conditions*: (*a*) DCC (1 equiv.), NHMe(OMe)·HCl (1.2 equiv.), $Et_3N$ (1.2 equiv.), $CH_2Cl_2$, 25 °C, 2 h, 70%; (*b*) **11** (2 equiv.), Bu$^t$Li (4 equiv.), $Et_2O$, −78 °C, 0.5 h, then **10** (1 equiv.), −78 °C, 1 h, 70%; (*c*) LiI (5 equiv.), $LiAlH_4$ (5 equiv.), $Et_2O$, −100 °C, 10 min, 86%; (*d*) NaH (1.5 equiv.), MeI (2 equiv.), DMF, 25 °C, 1.5 h, 94%; (*e*) CSA (0.02 equiv.), MeOH, 25 °C, 5 h, 93%; (*f*) $Et_3N$ (2 equiv.), MsCl (1 equiv.), $CH_2Cl_2$, 0 °C, 5 min; (*g*) $K_2CO_3$ (1 equiv.), MeOH, 25 °C, 10 min, 64% overall from diol; (*h*) **15** (5 equiv.), Bu$^t$Li (10 equiv.), $Et_2O$, −100 °C, 15 min, then 2-thienylCuCNLi (5 equiv.), −100 to 0 °C, 15 min, then **14** (1 equiv.), −30 to 0 °C, 0.5 h, 88%; (*i*) TIPSOTf (1.2 equiv.), 2,6-lutidine (1.5 equiv.), $CH_2Cl_2$, 0 °C, 20 min, 98%; (*j*) NIS (6 equiv.), THF, 25 °C, 24 h, 97%; (*k*) DDQ (1.2 equiv.), $CH_2Cl_2$–$H_2O$ (19:1), 25 °C, 1 h, 94% (*l*) $(COCl)_2$ (1.5 equiv.), DMSO (3.2 equiv.), $Et_3N$ (6 equiv.), $CH_2Cl_2$, −78 to 0 °C, 0.5 h, 98%; (*m*) **18** (3 equiv.), Bu$^n{}_2$BOTf (2.9 equiv), $Et_3N$ (3.5 equiv.), **17** (1 equiv.), PhMe–$CH_2Cl_2$ (1:1), −50 to −30 °C, 1 h, then 0 °C, 0.5 h, 88%; (*n*) LiOH (2 equiv.), 30% $H_2O_2$ (8 equiv.), THF–$H_2O$ (4:1), 0 °C, 3 h, then $CH_2N_2$, $Et_2O$, 0 °C, 86%; (*o*) $Ac_2O$ (10 equiv.), DMAP (0.05 equiv.), pyridine, 25 °C, 4 h, then DDQ (2 equiv.), $HCH_2Cl_2$–$H_2O$ (19:1), 25 °C, 12 h, 80%; (*p*) LiOH (5 equiv.), THF–MeOH–$H_2O$ (3:1:1), 0 °C, 1 h, 95%.

DCC = dicyclohexylcarbodiimide; DMF = dimethylformamide; CSA = camphorsulfonic acid; Ms = $MeSO_2$; Tf = $CF_3SO_2$; THF = tetrahydrofuran; NIS = *N*-iodosuccinimide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMSO = dimethyl sulfoxide; DMAP = 4-dimethylaminopyridine.

*syn*-product **19** (88%). The chiral auxiliary was removed by LiOH–$H_2O_2$ treatment and the acetoxy methyl ester **20** was produced by sequential exposure to $CH_2N_2$, $Ac_2O$–DMAP, and DDQ (69% overall yield). Finally, the targeted $C^8$–$C^{18}$ fragment **2**** was prepared by alkaline hydrolysis of **20** using aqueous LiOH (95% yield).

The described chemistry points the way to a rapamycin total synthesis and to a possible entry into a variety of designed molecules of this class. The following communication[8] describes the construction of the remaining requisite fragments and their elaboration to an advanced $C^{21}$–$C^{42}$ key intermediate.

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** Selected data for **2**: $R_F$ 0.05 (silica, 10% MeOH in $CH_2Cl_2$); $[\alpha]_D^{20}$ −4.1 (*c* 1.0, $CHCl_3$); IR (neat); $\nu_{max}/cm^{-1}$ 3410, 2941, 2867, 1729, 1624, 1462, 1379, 1271, 1256, 1095, 883 and 759 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3SOCD_3$): δ 6.35 (d, *J* 1.0 Hz, 1 H, 18-H), 3.98 (d, *J* 3.0 Hz, 1 H, 9-H), 3.90–3.83 (m, 1 H, 14-H), 3.80 (dd, *J* 4.1, 8.4 Hz, 1 H, 16-H), 3.38 (dd, *J* 3.0, 7.3 Hz, 1 H, 10-H), 3.33 (s, 3 H, 16-OMe), 1.73 (ddd, *J* 4.5, 8.6, 13.6 Hz, 1 H, CH), 1.65 (d, *J* 1.0 Hz, 3 H, 17-Me), 1.60–1.10 (m, 6 H, CH, $CH_2$), 1.05–0.90 (m, 21 H, $SiCHMe_2$) and 0.88 (d, *J* 6.7 Hz, 3 H, 11-Me); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 178.71, 147.75, 82.52, 79.32, 76.50, 71.78, 70.10, 56.09, 39.77, 34.86, 32.42, 27.60, 18.76, 18.24, 15.76 and 12.62; HRMS (FAB): Calc. for $C_{23}H_{44}O_6SiICs_2$ (M − $H^+$ + $2Cs^+$): 837.0061, found *m/z* 837.0102.

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7 S. D. Burke, A. D. Piscopio and M. E. Kort, unpublished results. We thank Professor Burke for allowing us to use this technology prior to publication.

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