Total Synthesis of the Immunosuppressant (-)-FK-506

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FK-506 (**1**), isolated from *Streptomyces tsukubaensis* (No. 9993),[1] is a unique 21-member macrolide that possesses exceptional biological activity and an array of challenging structural features, in particular an unusual α,β-diketo amide hemiketal system. The immunosuppressive potency of **1** has been shown to be superior to that of cyclosporin A in the inhibition of delayed hypersensitivity responses in a variety of allograft transplantation and autoimmunity models.[1b] Recently we described our efforts on the synthesis of the C_{10}–C_{18}[2a] and C_{20}–C_{34}[2b] subunits. We now describe the first total synthesis of (-)-FK-506.

Our strategy to form the macrocycle hinged on first constructing the C_{19}–C_{20} olefin. This olefination was accomplished by addition of a phosphine oxide anion to an aldehyde. The C_{10}–C_{18} fragment **2** was refunctionalized to dithiane phosphine oxide **5**[3] by using standard transformations (Scheme I). The chiral auxiliary of **6**[2b] was removed with LiOOH,[4] and the resulting acid was allowed to react with carbonyldiimidazole and then *N,O*-dimethylhydroxylamine. Treatment of the crude mixture with LiOOH (to cleave C_{22} O–carbonylimidazole) provided **7**, which was transformed to aldehyde **9**[5] (Scheme II).

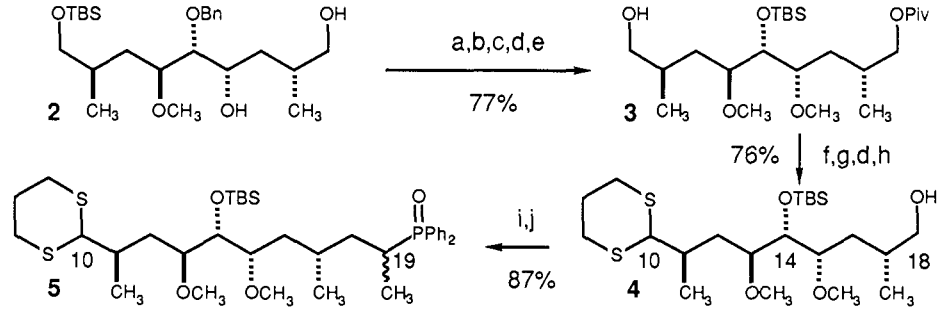
The two segments were coupled by deprotonation[6] of phosphine oxide **5** followed by addition of aldehyde **9** (Scheme III). The resulting mixture of two hydroxy phosphine oxides was chromatographically separated (38% and 39% of higher and lower R_f components, respectively). Treatment of the less polar diastereomer with potassium hexamethyldisilazide (0 °C, THF) provided (*E*)-olefin **10** in 82% yield. The olefin geometry was assigned by the ^{13}C chemical shift of C_{19}–CH_3 at 16.6 ppm (16.6 vs 23.6 ppm for *E* and *Z* olefins, respectively, in the 14-TES analogue of **10**).[7]

Model studies involving acylation at C_{26} with BOC-pipecolic acid demonstrated that significant epimerization could occur at C_2 (see Scheme IV) under macrolactonization conditions (high dilution and prolonged reaction times). We therefore adopted a macrolactamization strategy where the ester bond could be generated under high concentration conditions, the sensitive tricarbonyl being revealed after macrocyclization.[8] Our initial strategy for installation of a masked tricarbonyl system involved dithiane deprotonation followed by acylation with diethyl oxalate.[9] Deprotonation model studies (performed on C_{18}-OTIPS **4**, see Scheme I) revealed metalation at C_{14} followed by elimination of the C_{13}-OCH_3. Attempted formation of the dianion of C_{18}-OTIPS-C_{14}-hydroxy **4** failed in the presence of THF. However, dianion formation in neat TMEDA followed by trapping with diethyl oxalate provided a 64% yield of C-acylated product in addition to 11% recovered starting material; no C_{14} O-acylated product was observed. Unfortunately, application of these conditions to 14,26-dihydroxy **10** resulted primarily in metalation at C_{27}-CH_3; only traces of the desired C_{10}-acylated material were produced.

An alternate strategy employing α-hydroxyacetate enolate addition to **11** was therefore pursued. We chose to use α-((*p*-methoxybenzyl)oxy)acetimide **12**[10,11] rather than an achiral enolate because of the mild conditions, high yields of a single diastereomer, and facile transformations associated with the products (vide infra).[4,10] Deprotection followed by bis-oxidation[12] would provide the desired tricarbonyl compound.[8]

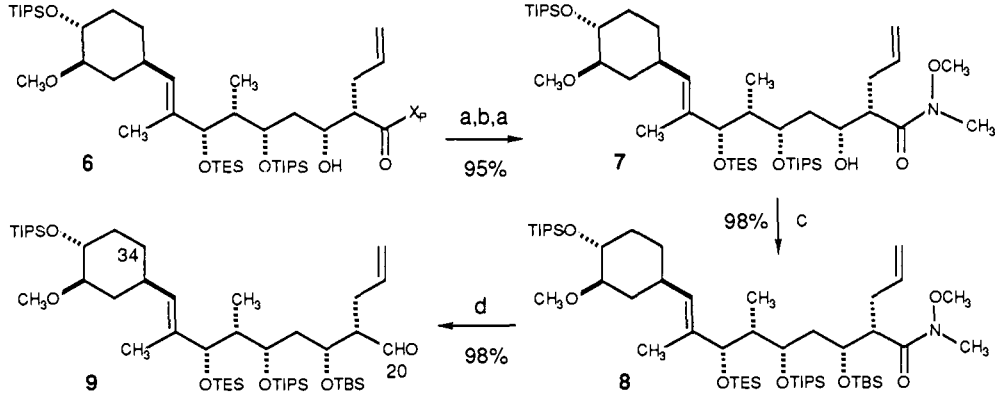
The cyclization precursor was prepared as shown in Scheme IV. After selectively removing the TES group, BOC-protected pipecolic acid was introduced under standard conditions. Aldehyde

Scheme I[a]



[a] (a) Pivaloyl chloride, pyr, 0 °C; (b) NaH, CH_3I, THF, 0 °C; (c) H_2, $Pd(OH)_2$, EtOAc; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2; (e) TFA, H_2O, THF, 20 °C; (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N; (g) $CH_2(CH_2SH)_2$, BF_3·OEt_2, CH_2Cl_2, 0 °C; (h) LAH, THF, 0 °C; (i) $PhSO_2Cl$, pyr, 0 °C; (j) $Ph_2P(O)Et$, *n*-BuLi, THF, -78 °C; benzenesulfonate of **4**, 0 °C.

Scheme II[a]



[a] (a) $LiOH·H_2O$, 30% H_2O_2, THF, H_2O, 0 °C; (b) carbonyldiimidazole, CH_2Cl_2; $HNCH_3(OCH_3)$, CH_2Cl_2, 25 °C; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBAl, THF, -30 °C.

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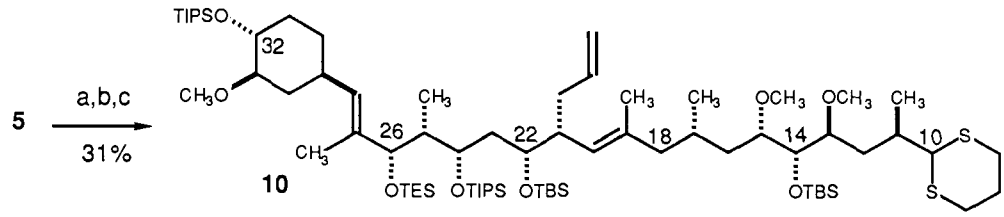
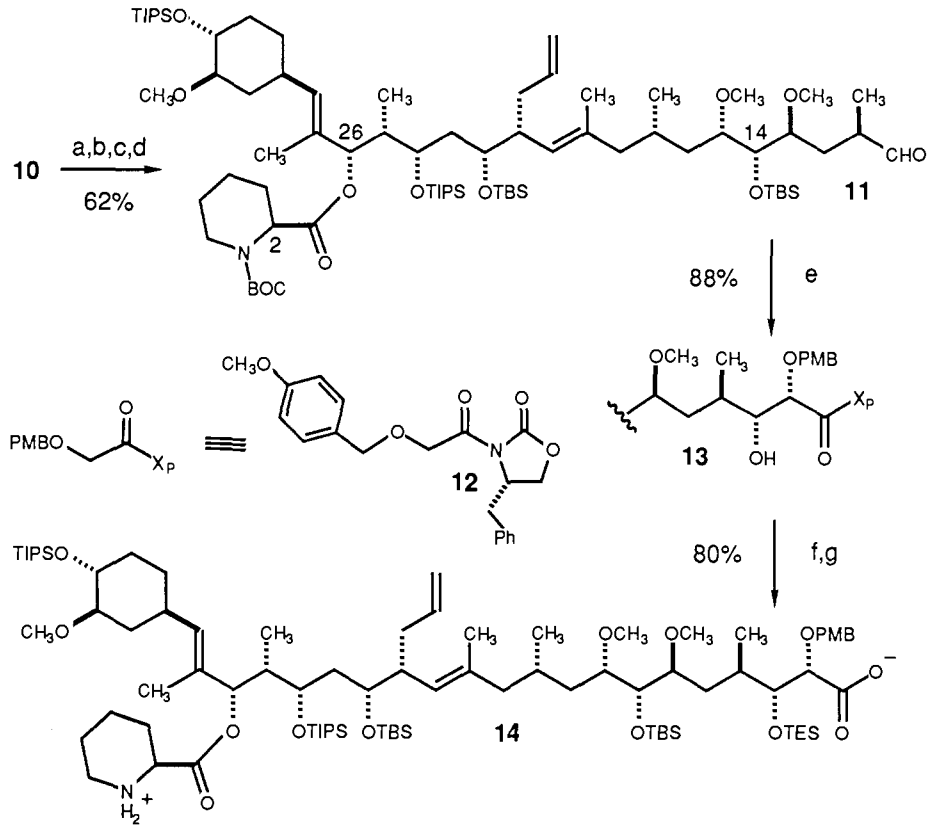
Scheme III[a]



[a](a) *n*-BuLi, THF, −78 °C; **9**; see text; (b) chromatographic separation; (c) KHMDS, THF, 0 °C; see text.

Scheme IV[a]



[a](a) TFA, H_2O, THF, 20 °C; (b) 4 equiv BOC-pipecolic acid, DCC, DMAP, CH_2Cl_2; −15 °C; (c) $AgNO_3$, NCS, 2,6-lutidine, CH_3OH, THF, 20 °C; (d) glyoxylic acid hydrate, HOAc, CH_2Cl_2, 40 °C; (e) Et_3N, **12**, *n*-Bu_2BOTf, toluene, −50 °C; **11**, −30 °C; (f) $LiOH·H_2O$, 30% H_2O_2, THF, H_2O, 0 °C; (g) 4.5 equiv TESOTf, 6 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C.

11 was prepared by methanolysis of the dithiane by using a modification of Corey's conditions[13] followed by mild acidic hydrolysis. Addition of aldehyde **11** to the boron enolate of imide **12** in toluene[11] produced adduct **13** (88% yield) which was selectively hydrolyzed with LiOOH[4] to provide the C_8 carboxylic acid. Treatment with triethylsilyl triflate simultaneously formed a silyl ether at C_{10}, a silyl ester at C_8 and transformed the BOC group to a silyl carbamate.[14] Exposure of the resulting compound to 40–63 μm silica gel for 1 h followed by routine chromatography then gave unstable amino acid **14**.

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(3) Yields represent chromatographically homogeneous material. Satisfactory spectroscopic data (including IR, ^1H, COSY-45, ^{13}C, and APT NMR), optical rotations, and microanalytical or HRMS data were obtained for stable key intermediates.

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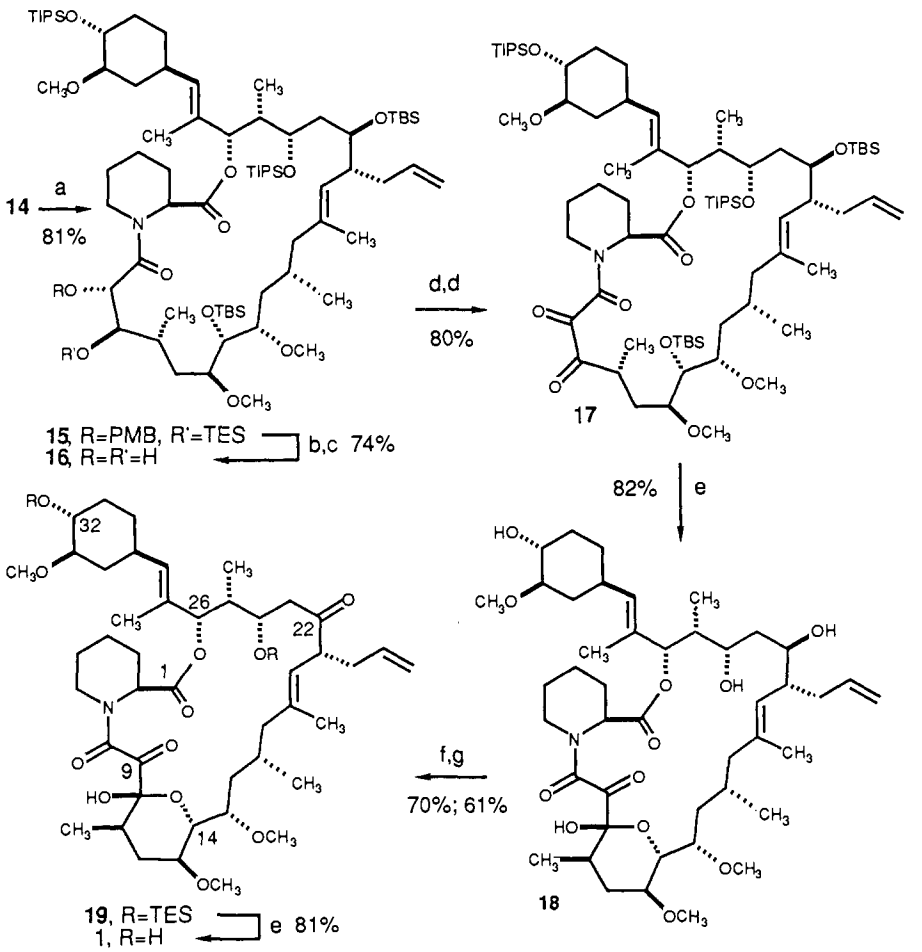
Scheme V[a]



[a] (a) 2-Chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 20 °C; (b) DDQ, H_2O, CH_2Cl_2, 20 °C; (c) TFA, H_2O, THF, 20 °C; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (e) aqueous HF, CH_3CN, 20 °C; (f) TESCl, pyridine, 0 °C; (g) Dess-Martin periodinane, pyridine, CH_2Cl_2, 20 °C.

Cyclization was accomplished with Mukaiyama's reagent[15] under high dilution conditions (1 mM, 20 °C, 3 h, CH_2Cl_2) in 81% yield (Scheme V). The 9,10-diol was obtained by treating **15** with DDQ[16] followed by aqueous acid. Two successive Swern oxidations[12,17] gave tricarbonyl **17**. Since we could not selectively remove the C_{22} TBS group, all silyl groups were removed with aqueous HF in acetonitrile to provide 22-dihydro-FK-506 (**18**). Reprotection with TESCl in pyridine[18] predominantly silylated the two least hindered hydroxyls and oxidation with Dess–Martin periodinane[19] gave 24,32-bis-TES-FK-506 (**19**). Finally treatment with aqueous HF in acetonitrile produced FK-506 (**1**), which was identical with natural material by ^1H NMR, COSY-45 (300 MHz; $CDCl_3$ and C_6D_6),[20] ^{13}C NMR, optical rotation at 6 wavelengths,[21] and TLC in several solvent systems.

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Supplementary Material Available: Procedures for the aldol, hydrolysis, and macrocyclization reactions as well as spectroscopic (including rotation data and 2-D spectra for FK-506) and mass data for key intermediates (16 pages). Ordering information is given on any current masthead page.

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(20) Significant solvent induced shifts occur in benzene-d_6, and the 2-D spectra serve as fingerprints in each solvent (see supplementary material).
(21) Natural FK-506: $[\alpha]_D^{27}$ -84.3 (*c* 0.574, $CHCl_3$). Synthetic FK-506: $[\alpha]_D^{27}$ −84.1 (*c* 0.630, $CHCl_3$). Literature value:[1a] $[\alpha]_D$ −84.4 (*c* 1.02, $CHCl_3$). See supplementary material for other wavelengths.