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A CHEMOENZYMATIC SYNTHESIS OF THE C_{10}-C_{19} MOIETY OF FK506

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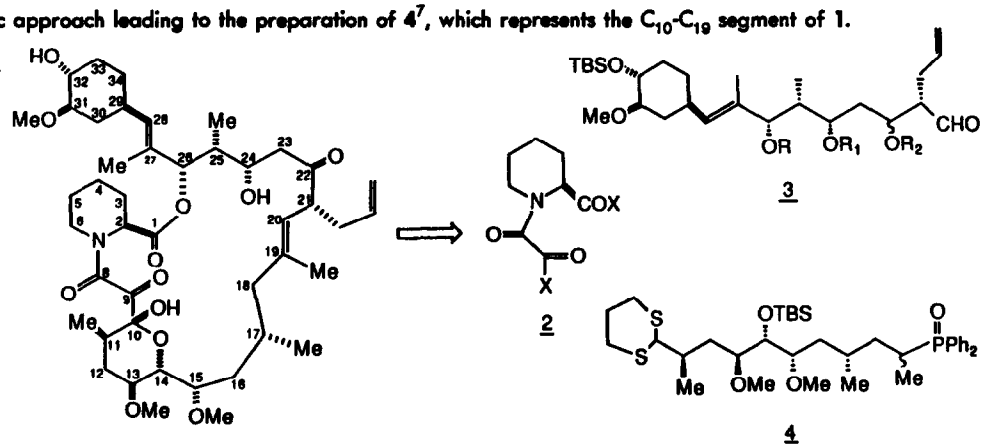
Summary: The strategy used in the synthesis of the C_{10}-C_{19} segment of FK506 is described.

The potent immunosuppressive properties of FK506, **1**, a macrolide produced by *Streptomyces tsukubaensis*[1], was first described by Ochiai et al.[2] in 1987. FK506 is structurally unrelated to cyclosporin A but shares many of its properties in the impairment of T-cell responses.[3] While the toxicity profile[4] of FK506 is not fully understood, a very recent study revealed that FK506 was remarkably effective as an immunosuppressant in human organ transplantation without serious side effects.[5] The vast therapeutic potential and structural complexity of FK506 have made it an attractive synthetic target and several imaginative syntheses of various segments[6] as well as one total synthesis[7] of FK506 have been reported. However, this problem merits continuing attention because each synthetic variant offers unique opportunities for structural alterations to probe the subtle relationship between chemical structure and biological activity. Herein, we disclose progress of our chemoenzymatic approach leading to the preparation of **4**[7], which represents the C_{10}-C_{19} segment of **1**.

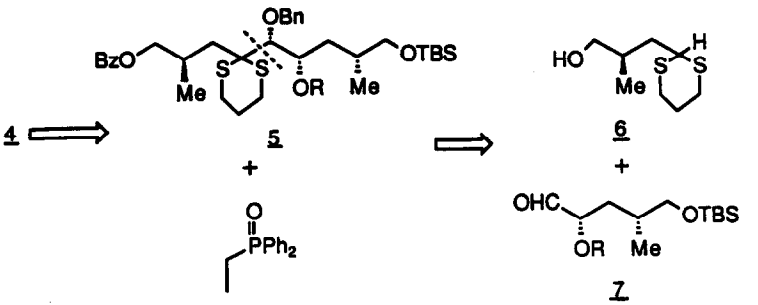
Scheme 1



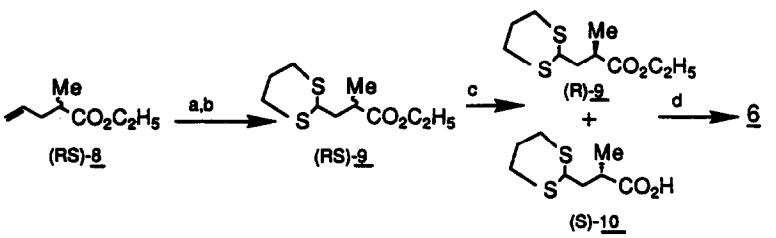
1

Retrosynthetic analysis of **1** revealed that it could be constructed from the three fragments outlined in Scheme 1. In turn, **4** could be derived from **5**, an adduct of **6** and **7** (Scheme 2). The enantiomerically-pure building blocks **6** and **7** were readily prepared by taking advantage of biocatalytic methods. The requisite substrate (RS)-**9** was prepared from (RS)-**8** in a two step procedure (77% overall yield). Exposure of (RS)-**9** to porcine pancreatic lipase (PPL) afforded (R)-**9**[8] (ee > 0.99) and (S)-**10** (ee > 0.99), indicating that the reaction was highly enantioselective (E = >100)[9]; LAH reduction of (R)-**9** furnished **6** (96%, $[\alpha]_D^{23}$ +8.5°, c = 0.8)[10] (Scheme 3).

Scheme 2



Scheme 3

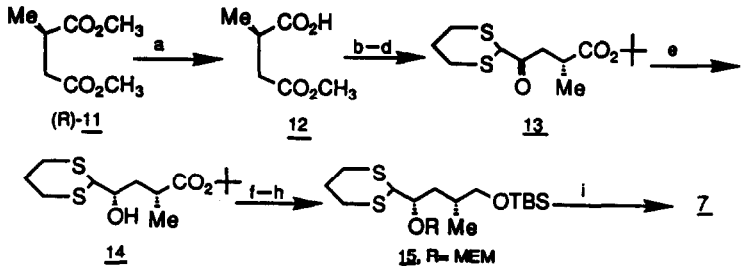


(a) O_3, CH_2Cl_2, -78°C; Ph_3P, 25°C; (b) $HS(CH_2)_3SH$, BF_3-Et_2O, CH_2Cl_2, -20°C; (c) PPL (Sigma), pH 7.6, 2 days; (d) LAH, THF, 0° to 25°C.

The lipase of *Candida cylindracea* was highly regioselective in catalyzing the hydrolysis of (R)-11[11] to yield **12** in quantitative yields. The monoacid, **12**, was converted into its sodio salt with NaH and then reacted with lithio-dithiane; esterification of the adduct with isobutylene gave **13** (77% overall). Asymmetric reduction of **13** was achieved using Bakers' yeast in tap water to give the (S)-alcohol,[12] **14** (de = >0.99) in 96% yield, which was transformed into **7** ($[\alpha]_D^{23}$ = -10.0°, c = 1.9) via the reaction sequence (74% from **14**) outlined in Scheme 4.

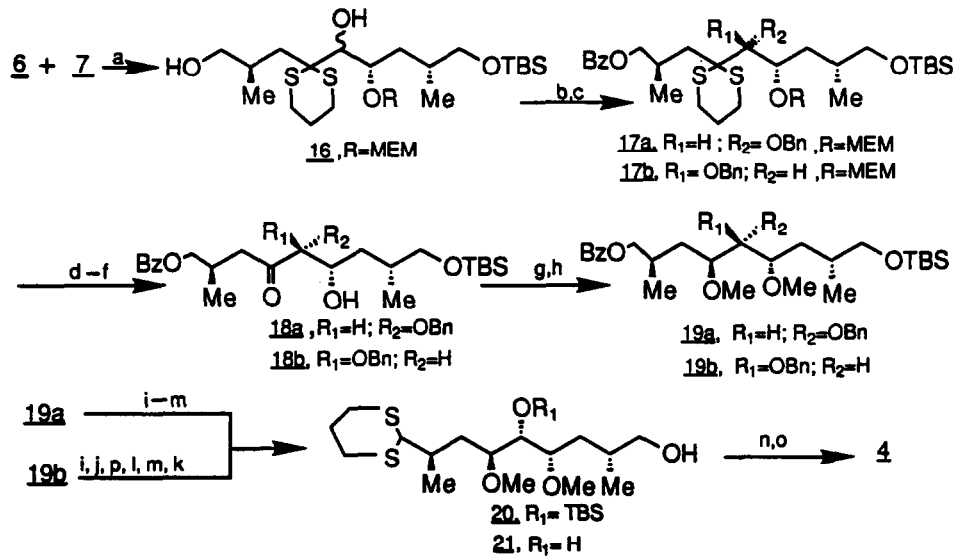
The two principal fragments **6** and **7** were coupled by deprotonation of **6** followed by addition of the aldehyde, **7**. The resulting mixture, **16** (68%), was successively reacted with benzoylchloride and benzylbromide and then separated by Sg flash chromatography to yield two pure diastereomers, **17a** and **17b** (1:1.4) (89%). The less polar diastereomer, **17a** ($[\alpha]_D^{23}$ -6.6°, c = 0.9), was converted into **18a** ($[\alpha]_D^{23}$ +31.1°, c = 0.4) by selective removal of the protecting groups (Scheme 5). Reduction of **18a** with the Evans reagent[13] gave a 93:7 (anti/syn) mixture, which was readily separated by Sg flash chromatography; methylation (CH_2N_2, HBF_4) gave **19a** (77% from **18a**). A five step reaction sequence was used to transform **19a** into **20** ($[\alpha]_D^{23}$ -16.7°, c = 3.0); **17b** was also converted into **20** via a different series of reactions (Scheme 5). The absolute configuration of **20** was established by converting it to the known diol, **21** ($[\alpha]_D^{23}$ +2.5°, c = 0.4; lit[6e] $[\alpha]_D$ +2.7°, c = 1.7). Completion of **4** was achieved by reaction of **20** with tosyl chloride followed by $Ph_2(PO)Et$ (92% from **20**).

Scheme 4



(a) *C. cylindracea* lipase (OF360 Meito-Sangyo), pH 7.5, 24 h; (b) NaH, THF, -78°C; (c) dithiane, n-BuLi, THF, -78°C to -20°C; Na salt of 12; (d) isobutylene, H_2SO_4, CH_2Cl_2, 25°C; (e) Bakers' yeast (Red Star), tap water, 3 days, 30°C; (f) MEMCl, DIEA, CH_2Cl_2, 25°C; (g) LAH, THF, 0°C to 25°C; (h) TBSCl, Py, 25°C; (i) CH_3I, $CaCO_3$, acetone/H_2O (4:1), 65°C.

Scheme 5



(a) n-BuLi, -78°C to 0°C to -78°C, add 7, to 0°C; (b) BzCl, THF, Py, 25°C; (c) NaH, THF, NaI, BnBr; (d) $TiCl_4$, CH_2Cl_2/C_5H_{12} (2:1), -5°C, 15 min; (e) $Tl(NO_3)_3 \cdot 3H_2O$, MeOH-ether (3:4), 25°C, 5 min; (f) TBSCl, CH_2Cl_2, Py; (g) $Me_4NHB(OAc)_3$, acetone-AcOH (1:1), -40°C, 20 hrs; (h) CH_2N_2, CH_2Cl_2, HBF_4, 25°C; (i) 5% $Pd(OH)_2/C$, H_2, EtOH; (j) TBSOTf, CH_2Cl_2, Et_3N, 25°C; (k) CH_3OH, K_2CO_3, 25°C; (l) periodinane, CH_2Cl_2, 25°C; (m) $HS(CH_2)_3SH$, BF_3-Et_2O, CH_2Cl_2; (n) $PhSO_2Cl$, Py, 25°C; (o) $Ph_2(PO)Et$, n-BuLi, THF, -78°C to 0°C; benzenesulfonate of 20, 25°C; (p) BF_3-Et_2O, CH_2Cl_2, -20°C, 30 min.

In the accompanying publication[14], we describe the synthesis of **3** and its coupling to **4** to form the C_{10}-C_{34} carbon skeleton of FK506.[15]

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