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SYNTHESIS OF THE C_{10}-C_{34} SEGMENT OF THE IMMUNOSUPPRESSANT FK506

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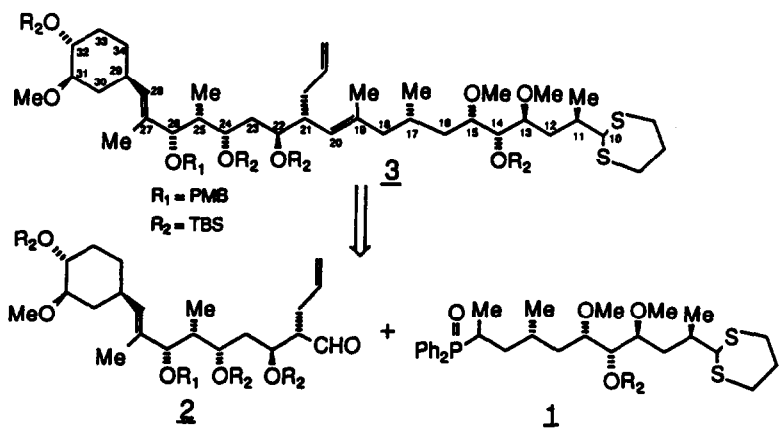
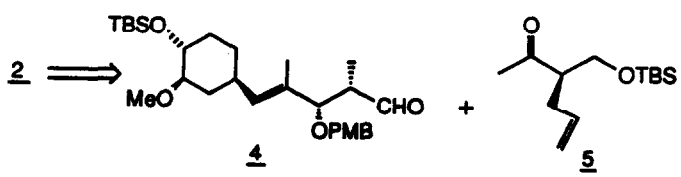
Summary: The biocatalytic strategy used in the synthesis of the C_{20}-C_{34} fragment, 2, and the methodology for its attachment to 1 to generate the C_{10}-C_{34} moiety of FK506 is disclosed.

The complex stereochemical features of the 23-membered macrolide, FK506, provides an attractive structural target for testing the power of current biocatalytic methodology and for developing new enantioselective processes in organic synthesis. We envisioned that FK506 may best be constructed in a modular fashion by dividing the molecule into several smaller fragments that can be synthesized separately and then joined together. In the previous communication[1], we disclosed the chemoenzymatic synthesis of the C_{10}-C_{19} fragment, 1, of FK506. Herein, we describe our biocatalytic strategy used for the synthesis of 2 and its attachment to 1 to generate the advanced intermediate, 3, which constitutes the C_{10}-C_{34} carbon skeleton of FK506 (Scheme 1).

Scheme 1



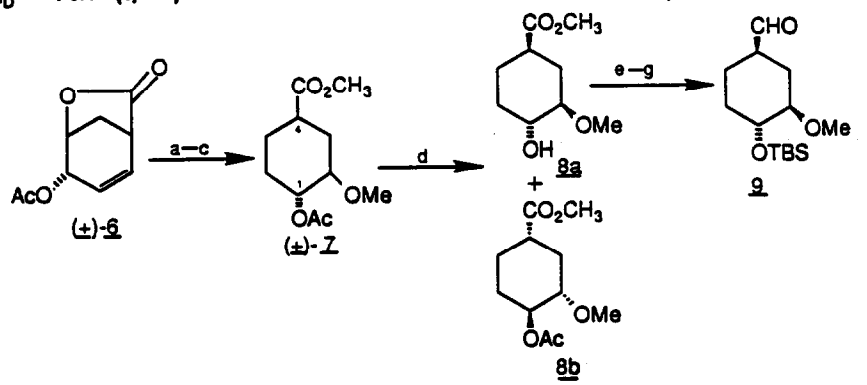
Our plan for the synthesis of the C_{20}-C_{34} segment, 2, entails the coupling of 4 and 5.



The synthesis of 4 begins with the lactone ester[2], (±)-6 (Scheme 2). As the commercial lipases[3] were unable to

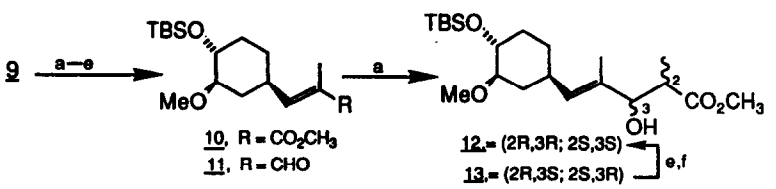
catalyze the hydrolysis of (±)-6 with high degrees of enantioselectivity, we converted (±)-6 into (±)-7 using a three-step reaction sequence as shown (93% overall). It is to be noted that if the hydrogenation step preceded the methanolysis of the lactone, epimerization of the C-4 center was observed. While several commercial lipases catalyzed the hydrolysis of (±)-7 with moderate enantioselectivity, only the lipase of *Pseudomonas sp.* (AK) was found to be uniquely chemo- and enantioselective (E = >100)[4] in cleaving only the R-acetoxy ester of 7 to yield 8a (50%), $[\alpha]_D^{23}$ = -70.1° (c, 2.0)[5]. It was then converted into 9 via the reaction sequence shown (80% overall).

Scheme 2



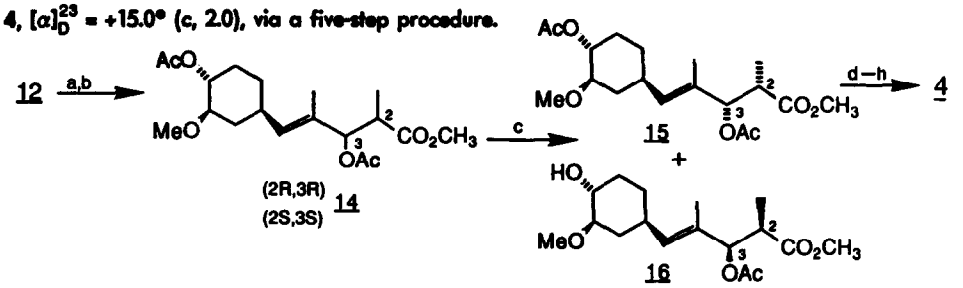
(a) K_2CO_3, MeOH, 0°C, 10 min; (b) 5% Pd-C/H_2, AcOEt, 10 hrs; (c) CH_2N_2, HBF_4, CH_2Cl_2, 25°C; (d) Lipase AK (Amano), pH 7.6, 25°C, 3 days; (e) TBSOTf, Et_3N, CH_2Cl_2, 0°C, 30 min; (f) LAH, THF, 0°C to 25°C, 30 min; (g) Periodinane, CH_2Cl_2, 25°C, 30 min.

Two successive Reformatsky reactions were used to transform 9 into 4. Thus, reaction of 9 with (±)-methyl-2-bromopropionate afforded a mixture of alcohols, which was mesylated and dehydrated to yield only the E-olefin, 10 (75% overall). In turn, it was converted to the aldehyde, 11 (74%) $[\alpha]_D^{23}$ = -25° (c, 1.4); lit.[6] $[\alpha]_D^{23}$ = -23.5° ($CHCl_3$). A second reaction of 11 with (±)-methyl-2-bromopropionate yielded a mixture of erythro and threo isomers (3:7) (92% yield). The threo isomers(13) (1:1) were readily separated from each other and the erythro isomers by Sg chromatography [EtOAc-hexane (1:10)]. The less polar 2S,3R-threo isomer was converted to the 2S,3S-erythro isomer without epimerization of the C-2 center via oxidation followed by reduction with $Zn(BH_4)_2$.[7]



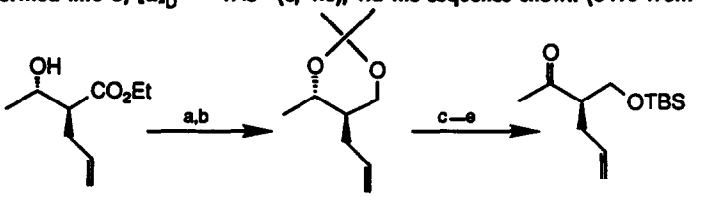
(a) (±)-$CH_3BrCHCO_2CH_3$, Zn, benzene, reflux, 30 min; (b) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min; (c) DBU, benzene, 25°C, 1 hr; (d) LAH, THF, 0°C to 25°C, 30 min; (e) Periodinane, CH_2Cl_2, 25°C, 30 min; (f) $Zn(BH_4)_2$, Et_2O, 0°C, 1 hr.

However, the erythro isomers, 12, resisted conventional chemical separation. Therefore, they were converted into the diacetates, 14, and exposed to the *Pseudomonas sp.* (K-10) lipase. This enzyme catalyzed a highly chemo- and diastereoselective hydrolysis of the 2R,3R-isomer of 14 to yield the monoacetate, 16, which was readily separated from 15 (de_s = 0.93, $[\alpha]_D^{23}$ = -17.5°, c = 0.2). The desired 2S,3S-isomer, 15, was transformed into 4, $[\alpha]_D^{23}$ = +15.0° (c, 2.0), via a five-step procedure.



(a) 5% HF, CH_3CN, 25°C, 30 min; (b) Ac_2O, Py, DMAP, 25°C, 30 min; (c) Lipase K-10 (Amano), pH 7.6, 8 hr, 25°C; (d) LAH, THF, 0°C to 25°C, 30 min; (e) *p*-$CH_3OC_6H_4CH(OCH_3)_2$, *p*-TsOH, DMF, 55°C, 30 min; (f) TBSOTf, Et_3N, CH_2Cl_2, 25°C; (g) DIBAL, CH_2Cl_2, 10 min, 25°C; (h) Periodinane, CH_2Cl_2, 25°C.

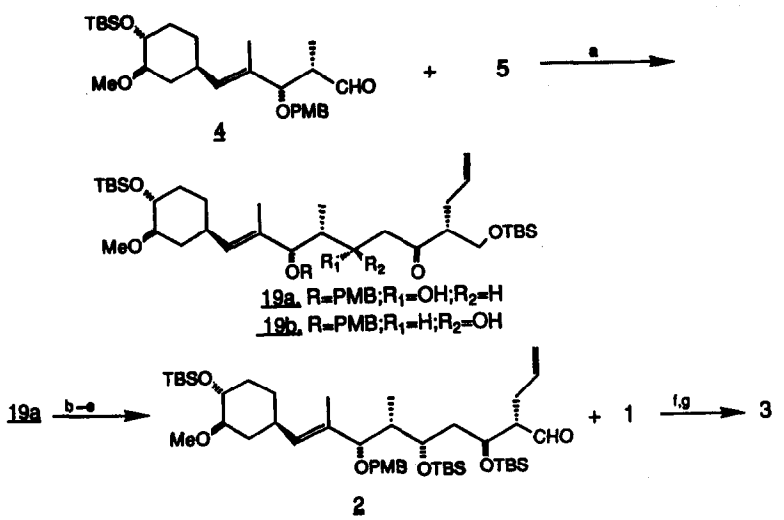
The known ester obtained as a diastereomeric mixture (2RS,3S, 7:3), 17, was prepared via Bakers' yeast reduction.[8] It was reduced with LAH and then treated with 2,2-dimethoxypropane. The resulting diastereomeric mixture was conveniently separated by Sg chromatography [AcOEt-CH_2Cl_2-hexane (1:16:83)] to yield 18 (70% overall); it was transformed into 5, $[\alpha]_D^{23}$ = -19.5° (c, 1.8), via the sequence shown (64% from 18).



(a) LAH, THF, 0°C to 25°C, 30 min; (b) 2,2-dimethoxypropane, *p*-TsOH, acetone, 0°C, 30 min; (c) *p*-TsOH, MeOH, 24 hrs; (d) TBSCl, Py, 1.5 hrs; (e) Periodinane, CH_2Cl_2, 25°C.

Having the required chiral synthons in hand, we then focused our attention on the problem of assembly using standard methodology (Scheme 3). Condensation of 4 with 5 furnished 19a and 19b in a ratio of 4:6 (81% yield). The desired isomer, 19a {$[\alpha]_D^{23}$ = +7.0° (c, 1.3)}, was converted into 2 using a four-step procedure (64% overall). The synthesis of the target molecule, 3, was completed by the coupling of the phosphonate, 1, to 2 at -78°C to furnish a pair of readily separable diastereomeric adducts (1:1). The less polar pair were treated with potassium hexamethyldisilazide to yield the highly functionalized intermediate 3, $[\alpha]_D^{23}$ = -2.2° (c, 0.5), which could be transformed into FK506[9].

Scheme 3



(a) LDA, Et_2O, -10°C, 5, 20 min, $ZnCl_2$, -10°C; 4, 10 min; (b) $Me_4NHB(OAc)_3$, AcOH/CH_3CN (1:1), -40°C, 16 hrs; (c) TBSOTf, Et_3N, CH_2Cl_2, 25°C; (d) TFA, THF-H_2O (10:1); (e) Periodinane, CH_2Cl_2, 25°C; (f) n-BuLi, THF, -78°C to 0°C; (g) KHMDS, THF, 0°C.

In conclusion, the simplicity and efficiency of the biocatalytic methodology serve to underscore the viability of this strategy for FK506 synthesis. We are now devoting our attention to modification of the route to allow for the synthesis of structural analogs. The results of this endeavor will be reported in due course.[10]

References and Notes

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3. See Table 3 in C. S. Chen and C. J. Sih, *Angew. Chem. Int. Ed. Engl.* **28** (1989) 695.
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10. This investigation was supported in part by grant GM33149 from the National Institutes of Health. We thank Dr. Anthony Levorse for the preparation of **17**.

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