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AN ENANTIOSELECTIVE SYNTHESIS OF THE C(10) TO C(23) BACKBONE OF THE POTENT IMMUNOSUPPRESSANT FK506

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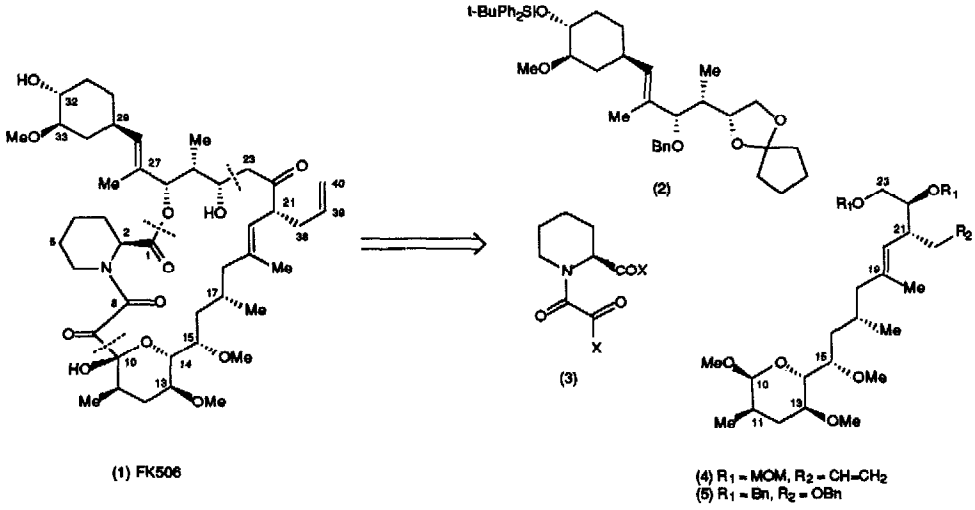
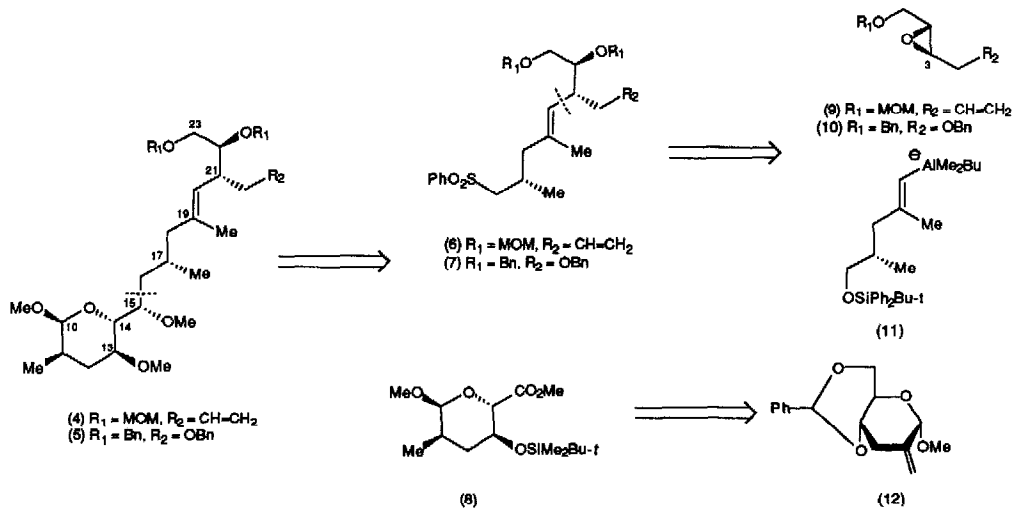
Summary: The C(10) to C(23) fragment of FK506 has been prepared in a convergent, highly stereocontrolled, fashion. The key transformations entailed opening of a symmetrical *trans*-disubstituted epoxide with a trisubstituted vinylalane ate complex, the reductive removal of a β-ketosulfonyl group with tri-*n*-butyltin hydride, and a hydroxyl-directed ketone reduction.

Although the introduction of powerful immunosuppressant drugs has led to considerable progress in the area of human organ transplantation, post-operative graft rejection remains the foremost problem faced by the transplant surgeon.[1] As a result, the discovery and development of new immunosuppressant agents is an important endeavour. One very promising candidate is the recently isolated macrolide, FK506 (**1**);[2] it inhibits interleukin 2 production, the mixed lymphocyte culture response, and cytotoxic T-cell generation at 100 times lower concentration than cyclosporin A, the most effective immunosuppressant currently available.[1c] Intrigued not only by the synthetically challenging architecture, but also by the opportunity to establish detailed structure-activity relationships, we recently embarked on a total synthesis of FK506 (**1**).[3] We record here some progress toward this goal with an enantioselective synthesis of **5**, a functional equivalent of the C(10) to C(23) fragment.



Scheme 1

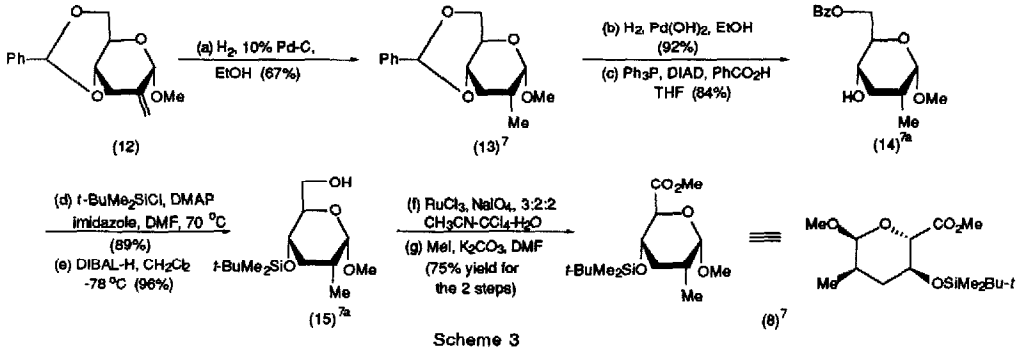
Retrosynthetic analysis of FK506 suggested that the C(10) to C(23) backbone could be readily assembled from intermediates **4** or **5**, prepared via coupling of sulfones **6** or **7** respectively with ester **8** (Scheme 2). Reductive removal of the sulfone unit, followed by a hydroxyl-directed reduction of the carbonyl group, would then establish the requisite stereochemistry at C(15). Continuing with this analysis, we anticipated that both the C(19, 20) trisubstituted olefin and the C(21) stereogenic center in **6** (FK506 numbering) could be constructed through a chelation-controlled, regiospecific addition of the vinylalane anion **11** to epoxide **9**. Precedent for such regiocontrol can be found in the work of Matthews [4]



Scheme 2

and Pfaltz.[5] These workers demonstrated that epoxy ethers are attacked almost exclusively at the distal position [i.e., C(3)] by alkyl- and alkynylalanes, presumably due to coordination of the reagent with the ether oxygen. Importantly, even if poor regioselectivity were obtained with **9**, this strategy would still prove viable if the ring opening could be achieved with epoxide **10**; this would ultimately afford **5**. Such a tactic would necessitate introduction of the C(21) allyl group at a later stage in the synthesis, but would overcome the regiochemical problem. As for ester **8**, we envisaged that it could be prepared conveniently from **12**, via hydrogenation of the exocyclic olefin on the less hindered β-face, followed by oxidation of the primary alcohol to the acid. The elements of this scenario would not only create all of the requisite stereochemistry present in this section of FK506, but would also permit considerable strategic flexibility in the later stages of the synthesis. With this overview in mind, we present here the realization of this synthetic planning.

The synthesis of **8** began with glycoside **12**[6] and is outlined in Scheme 3. The key step involved selective hydro-



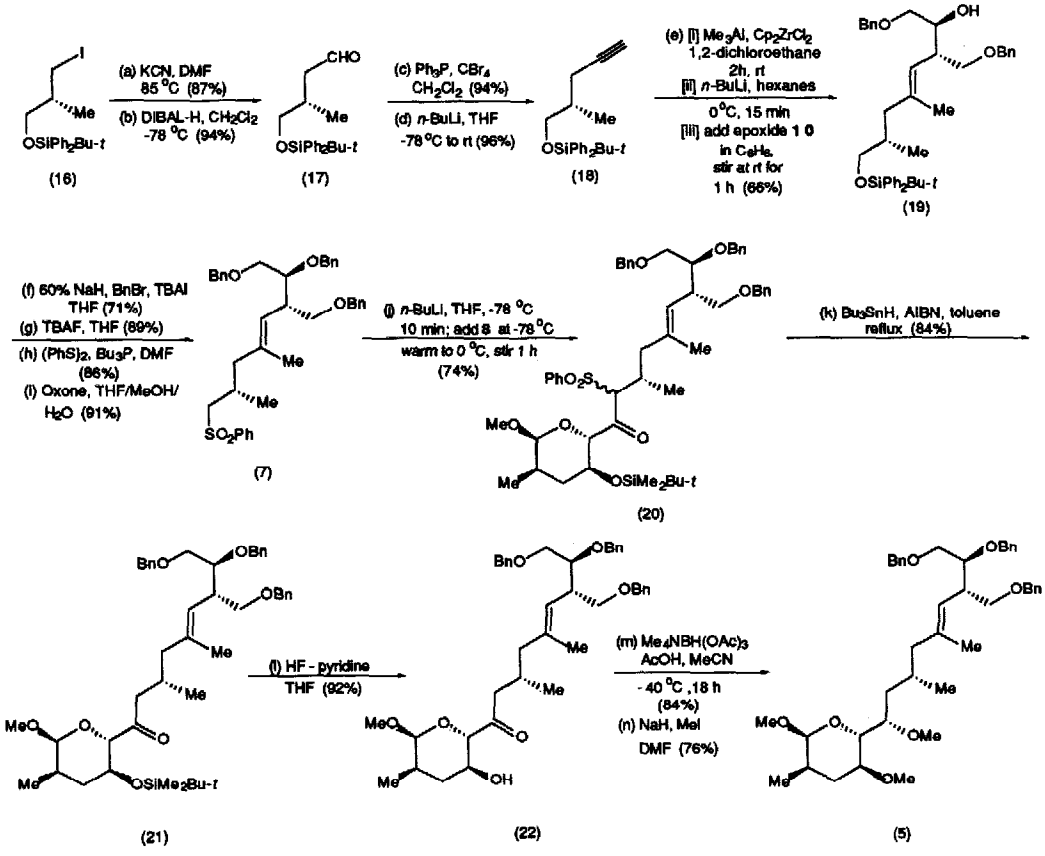
Scheme 3

genation of the exocyclic olefin in **12** to produce a 3.5: 1 mixture of **13** and its axial epimer; **13**[7] could be isolated readily in 67% yield by fractional crystallization.[8]

Our approach to sulfones **6** and **7** began with reaction of homochiral iodide **16**[9] with potassium cyanide in hot DMF (Scheme 4). Reduction of the cyano group with DIBAL-H followed by an aqueous work up produced aldehyde **17**.[7a]

was converted to the corresponding dibromoolefin by reaction with triphenylphosphine and carbon tetrabromide. Reaction of the dibromoolefin with two equivalents of *n*-butyllithium[10] then afforded alkyne **18**,[7] substrate for the proposed carboalumination-alkylation coupling process.

Carboalumination was achieved by treating **18** with two equivalents of trimethylaluminum in the presence of a catalytic amount of zirconocene dichloride (0.1 equiv., $ClCH_2CH_2Cl$, 2 h).[11] After removal of the excess trimethylaluminum by distillation, the vinylalane was converted to ate complex **11** by treatment with *n*-butyllithium in hexane at 0 °C. Initially, we investigated the coupling of **11** with epoxide **9**. Even under high dilution conditions this led to a 1:1 mixture of ring opened products. We therefore explored the alternative coupling strategy with the symmetrical *trans*-disubstituted epoxide **10**.[12] As expected, reaction of **11** with homochiral **10** proved facile, furnishing **19**[7] in 66% yield, even on large scale (16 g of **18**). Olefin **19** was subsequently benzylated, desilylated, converted to the thiophenyl ether,[13] and then oxidized to sulfone **7**;[7,14] the overall yield for the four-step sequence was 50%.



Scheme 4

Turning next to the union of **7** with **8**, two equivalents of the anion derived from **7** were treated with **8**, for 5 min at -78 °C and then at 0 °C for 1 h;[15] the result was a 74% yield of **20**.[7a,16] With ample quantities of **20** in hand, we attempted the reductive removal of the sulfone group with freshly prepared aluminum amalgam in aqueous THF.[17] Surprisingly, this reaction never went to completion. After considerable experimentation, we discovered that tri-*n*-butyltin hydride in toluene

at reflux cleanly effected removal of the sulfone molety to afford **21**[7a] in 84% yield. Desilylation with the HF-pyridine complex in THF also proceeded smoothly, to deliver β-hydroxy ketone **22**[7] in 92% yield.[18] The final stereogenic center of **5** was introduced via a hydroxyl-directed reduction of the C(15) carbonyl group with tetramethylammonium triacetoxyborohydride.[19] This process (on ca. 1.5 g scale) resulted in a 20:1 mixture of the *anti* and *syn* 1,3-diols[7] (84%), which proved easily separable by flash chromatography.[20] Completion of **5**[7a] was then accomplished by methylation of the major *anti*-diol with sodium hydride and methyl iodide in DMF.

In summary, we have completed a highly convergent, stereocontrolled synthesis of the C(10) to C(23) backbone of FK506. Our approach is noteworthy for a number of reasons. First, we have demonstrated for the first time that the opening of *trans*-disubstituted acyclic epoxides with vinylalane ate complexes is an effective means of constructing *E*-trisubstituted olefins with the stereocontrolled incorporation of an allylic stereogenic center. Second, we have discovered the utility of tri-*n*-butyltin hydride for the efficient desulfonylation of β-ketosulfones. Further work in each of these areas, as well as progress towards the total synthesis of FK506, will be reported in due course.

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6. Glycoside **12** was prepared in six steps from methyl α-D-glucopyranoside; see: Inch T.D; Lewis, G.J. *Carbohydrate Res.* **1972**, *22*, 91.
7. (a) The structure assigned to each new compound is in accord with its infrared and high field (500 MHz) ^{1}H NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or liquid chromatography, gave satisfactory combustion analysis within 0.4 %.
8. This isomer ratio could be improved to 6.5:1 by carrying out the reduction on much smaller scale in a 1:1 mixture of *N*-methylformamide and dimethylformamide.
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