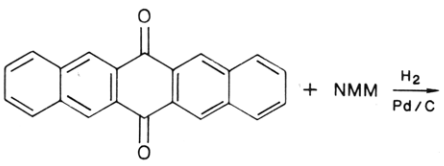
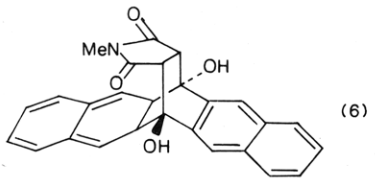
Naphthacenequinone reacts similarly to give bridgehead diol cycloadducts (exo, endo stereochemistry has not been determined). Interestingly, the procedure also extends to the pentacenequinone **10**, which affords the cycloadduct **11** when reduced in the presence of NMM.



10

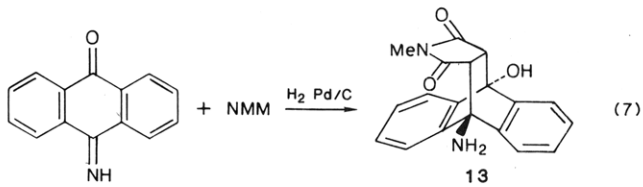


(6)

11

The monoimine[20] (**12**) of anthraquinone was prepared and subjected to in situ reduction–cycloaddition to give the novel aminoalcohol cycloadduct **13**. Preliminary results indicate that quinone–monoimines of higher benzologues can also be employed in this manner.

These reactions provide direct[21] access to bridgehead



(7)

12 **13**

alcohols and amines, in noteworthy room temperature Diels–Alder reactions. The magnitude of the observed rate enhancement encourages further efforts to design highly reactive dienes based on linear polycyclic aromatics. The free hydroxyl groups of the adducts will interfere with some functional group interconversions on the dienophile portion, and methods to convert the OH groups to protected forms are needed. This problem and the details of the cycloaddition mechanism require further study.

Acknowledgment. Support by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

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Received September 6, 1988

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Studies Relating to the Synthesis of the Immunosuppressive Agent FK-506: Synthesis of the Cyclohexyl Moiety via a Group-Selective Epoxidation

Summary: The asymmetric synthesis of the cyclohexyl moiety of FK-506 is reported. The absolute stereogenicity of the target subunit was derived from the catalytic asymmetric synthesis of an epoxide by the method of Sharpless.

Sir: The discovery of compounds capable of preventing graft rejection following bone marrow and organ transplantation is an active area of immunological research. A goal of these activities is to selectively inhibit those subsets of host T cells that recognize the offensive donor MHC (major histocompatibility) antigens in order to prevent graft rejection without rendering the patient susceptible to opportunistic infections. The discovery of cyclosporin A (CsA), an agent utilized in clinical organ transplantation, represents one of the most significant advances in this area in the past decade.[1]

Recently, several disclosures have appeared detailing the potent immunosuppressive properties of the macrolide antibiotic FK-506 (**1**)[2] (Figure 1). The suppression of in vitro immune systems, including the inhibition of lymphokine production (IL-2, IL-3, IFN) was reported to take place at concentrations 100-fold lower than that required of CsA.[3] The results of in vivo studies involving renal

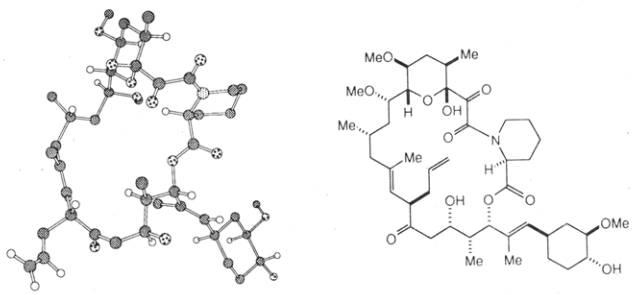

Figure 1. FK-506 (1).

allografting in the beagle dog[4] and cardiac allotransplantation in the rat[5] suggest a smaller dose requirement for FK-506 relative to CsA.

In addition to its role as a lead or candidate structure for clinical allotransplantation in humans, FK-506 serves as a new biological probe of the immune response. The recent discovery of an FK-506 binding protein[6] that is apparently related to the CsA binding protein cyclophilin[7] is illustrative. However, little is currently known con-

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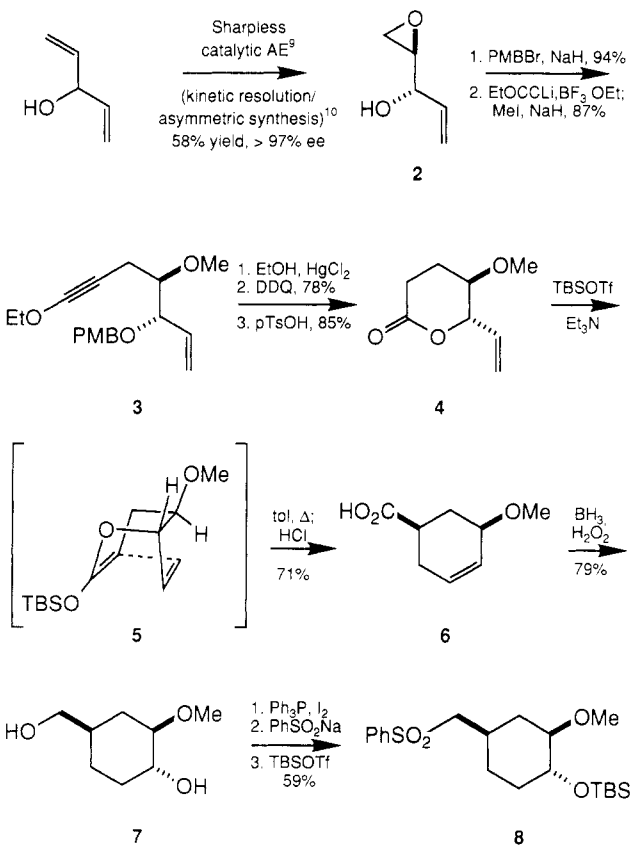
Scheme I



cerning the structural requirements for "fujiphilin" binding or immune suppression. With these considerations in mind, we have initiated a synthetic effort aimed at the modular synthesis of this macrolide that would provide access to materials to probe these phenomena. In this paper, we report an efficient and enantioselective synthesis of the cyclohexyl moiety found within the natural product[8] (Scheme I).

The group- and face-selective epoxidation of divinylcarbinol was achieved with use of the catalytic procedure of Sharpless.[9] As discussed in an earlier report, this reaction couples a kinetic resolution to the initial asymmetric synthesis and consequently results in product **2** ($[\alpha]^{24}_D$ = +48.0°, c = 2.76, $CHCl_3$) with a high level of enantiomeric purity.[10] The epoxy alcohol **2** was protected as the corresponding *p*-methoxybenzyl ether (PMBO) in 94% yield without complications of a Payne rearrangement[11] when performed in THF at 0 °C. The regiospecific epoxide opening was achieved by the method of Yamaguchi:[12] the *p*-methoxybenzyl ether of **2** (in THF) was added to the lithium anion of ethoxyacetylene and boron trifluoride etherate (1:1 ratio in THF, −78 °C). After a low-temperature (−78 °C) quench, aqueous workup, and drying of the organic layer, the solution was filtered and directly subjected to conditions of methylation (NaH, MeI, 0 °C) to provide the methyl ether **3** ($[\alpha]^{22}_D$ = +29.7°, c = 10.7, $CHCl_3$) in 87% yield after silica gel (sg) chromatography. Ethanolysis of **3** (EtOH, catalytic $HgCl_2$) was followed by the deprotection of the *p*-methoxybenzyl ether (CH_2Cl_2, H_2O, DDQ) to afford a 78% yield of the δ-hydroxy ester, which was cyclized to lactone **4** ($[\alpha]^{22}_D$ = −108.9°, c = 9.52, $CHCl_3$) in 85% yield (pTsOH, PhH, 4-Å molecular sieves). The Ireland–Claisen rearrangement[13] of silyl ketene acetal **5** (TBSOTf, Et_3N, CH_2Cl_2, −78 °C → 0 °C) proceeded smoothly upon heating in toluene (110 °C) to provide, after hydrolysis of the silyl ester (THF, 1 N HCl), the carboxylic acid **6** ($[\alpha]^{22}_D$ = −37.6°, c = 1.86, $CHCl_3$, mp = 57–59 °C) in 71% overall yield. The strict translation of stereogenicity in this permutation of the Claisen rearrangement was noted by Danishefsky in his earlier studies in this area.[14]

The reaction of **6** with excess BH_3·THF (THF, −78 °C to ambient; NaOH, H_2O_2) provided diol **7** ($[\alpha]^{23}_D$ = −57.0°, c = 0.30, $CHCl_3$) in 79% yield after sg chromatography. The ^1H NMR spectrum of **7** was consistent with the reported spectrum of this compound prepared previously by the Fujisawa group by degradation of FK-506.[2] The diol was selectively monoiodinated (Ph_3P, pyridine, I_2, PhH, 80 °C) to provide the primary iodide as a white solid (mp = 56–58 °C), which was converted to the target sulfone **8** ($[\alpha]^{23}_D$ = −23.9°, c = 1.13, $CHCl_3$) ($NaSO_2Ph$, DMF, 100 °C; TBSOTf, Et_3N, CH_2Cl_2) in 59% yield for the three steps.

In summary, the cyclohexyl moiety of FK-506 has been prepared from divinylcarbinol in a form that is amenable to subsequent coupling with concomitant olefin formation.[15] The absolute stereogenicity of the heterocycle **4** was controlled through the Sharpless catalytic asymmetric epoxidation and was translated into carbocyclic stereogenicity by a stereospecific Ireland–Claisen rearrangement.

Acknowledgment. Financial support of this project by the NIGMS, the NSF, Pfizer, and Hoffmann-La Roche Inc. is gratefully acknowledged. We thank Professors Samuel Danishefsky and Robert Handschumacher for stimulating discussions and exchange of information.

Supplementary Material Available: ^1H NMR spectra for **3**, **4**, and **6–8** (8 pages). Ordering information is given on any current masthead page.

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