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Synthetic Studies Towards the Immunosuppressant FK-506 Synthesis of the C_{10}-C_{34} Fragment

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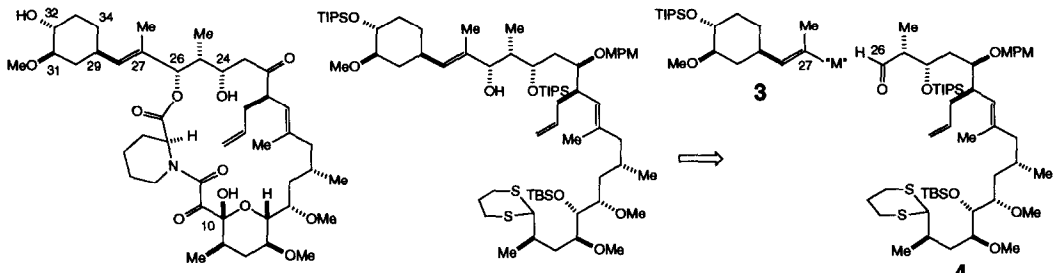
Abstract: *The synthesis of the cyclohexyl moiety of FK-506 and its coupling reaction with the C_{10}-C_{26} fragment to provide an advanced synthetic intermediate(C_{10}-C_{34}) are described.*

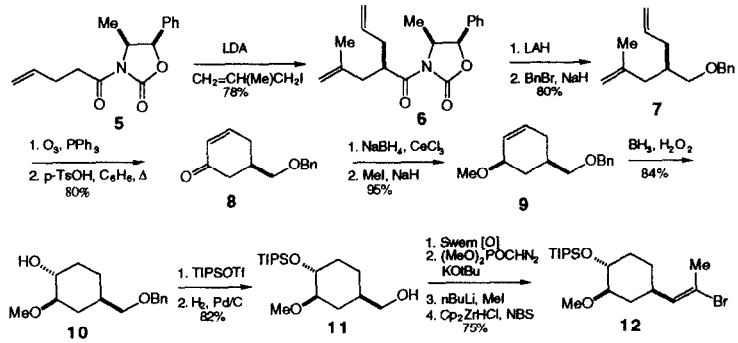
Since the discovery of the potent immunosuppressant FK-506 (Figure 1) by the Fujisawa scientists in 1987[1], its potential application in organ transplants and in a variety of autoimmune diseases has been fascinating the scientific community and has resulted in numerous synthetic studies.[2,3,4] Previously from this laboratory[5] was disclosed a highly stereoselective synthesis of the C_{10}-C_{24} fragment of FK-506. Herein we report[6] an efficient synthesis of the cyclohexyl portion (C_{28}-C_{34}) and its coupling with the previously synthesized fragment through the formation of the C_{26}-C_{27} bond by employing a vinyl anion coupling process[2b,3o] to form the advanced intermediate **2** (C_{10}-C_{34} fragment).

Figure 1



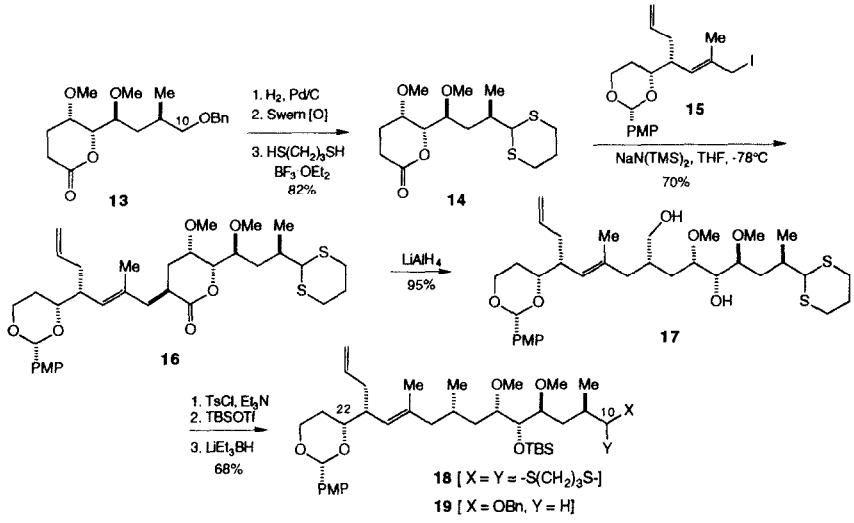
The synthesis of the cyclohexyl portion began with a diastereoselective alkylation reaction of a chiral enolate (Scheme 1). The Evans type chiral N-acyloxazolidone **5**, which was previously used in the synthesis of C_{10}-C_{24} segment,[5] was alkylated with methallyl iodide to provide **6** in 78% yield with >97% diastereoselectivity.[7] The chiral auxiliary in **6** was reductively removed with lithium aluminum hydride, followed by benzylation, to afford benzyl ether **7** in 80% yield over two steps. Ozonolysis of **7** gave a keto-

Scheme 1



aldehyde which, without purification, was cyclized to **8** ($[\alpha]^{23}_D$ = -61.7°, c = 4, $CHCl_3$, lit.[8] $[\alpha]^{23}_D$ = -59.8°, c = 1.5, $CHCl_3$)) in 80% yield upon treatment with a catalytic amount of p-toluenesulfonic acid in refluxing benzene. Reduction of **8** under Luche conditions[9] provided an equatorial alcohol as the predominant product (>20:1 judged by 250 MHz ^{1}H NMR) in quantitative yield which was methylated under standard conditions to produce **9** in 95% yield. The installation of a hydroxyl moiety vicinal and trans to the methoxy group was realized by subjection of **9** to hydroboration/oxidation, which have previously been employed by others in related studies,[3f, 3q, 10] to provide **10** in 84% yield along with 5% of other isomers.[11] Silylation followed by debenzylation afforded the cyclohexyl moiety **11** ($[\alpha]^{23}_D$ = -28.1°, c = 2, $CHCl_3$) in an overall yield of 33% from the N-acyloxazolidone **6**. The conversion of **11** to the vinyl bromide **12** was completed in four steps according to Schreiber's procedure.[3o]

Scheme 2

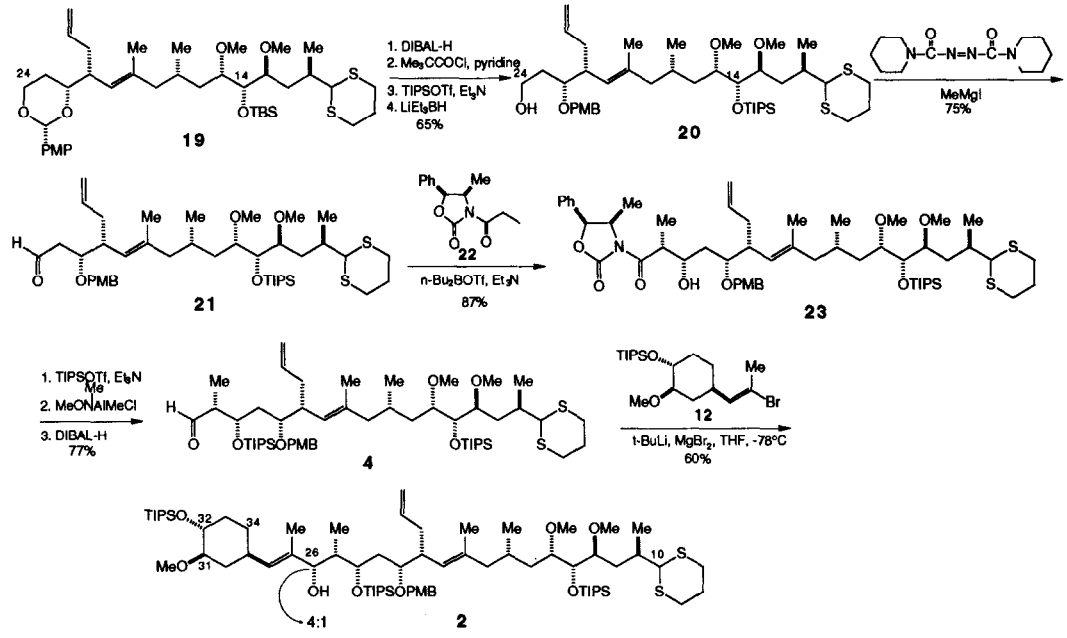


In our earlier synthesis of the C_{10}-C_{24} fragment **19**[5], we anticipated difficulties in removing the benzyl ether group at C_{10} in the presence of the p-methoxybenzyl ether group at C_{22}. Thus, a dithioacetal was

introduced at the stage of lactone **13** (Scheme 2). Debenzylation of **13** followed by Swern oxidation and ketalization with 1,3-propanedithiol gave rise to **14** in 82% yield. The alkylation of **14** with allylic iodide **15** and the introduction of the methyl substitutent at C_{17} proceeded in the same fashion as reported earlier to provide the modified C_{10}-C_{24} fragment **18**.

Reductive cleavage of the p-methoxybenzylidene acetal in **18** with DIBAL-H generated a primary hydroxyl group at C_{24} and also resulted in extensive desilylation at C_{14} (Scheme 3). A triisopropylsilyl ether was introduced at C_{14} to give **20** through protective group manipulations. Oxidation of **20** to aldehyde **21** proved troublesome due to the sensitivity of the dithioacetal group towards many oxidizing agents. After several unsuccessful attempts, aldehyde **21** was obtained in 75% yield by oxidation of the corresponding magnesium alkoxide with 1,1-(azodicarbonyl)dipiperidine[12] without interference from the dithioacetal group. Condensation of **21** with the Evans boron enolate[13] of **22** provided a single aldol product **23**, which was subjected to several standard transformations to afford aldehyde **4**. Finally, the addition of the vinyl anion derived from **12** to aldehyde **4** produced a 4:1 mixture of diastereomers with **2** as the predominant product corresponding to the highly functionalized C_{10}-C_{34} fragment of FK-506. The Cram-selective addition observed here is in agreement with the results reported in the earlier studies by the Schreiber group.[2b,3o]

Scheme 3



In summary, an advanced intermediate corresponding to the C_{10}-C_{34} fragment has been synthesized in a highly convergent manner. The free hydroxyl at C_{26} and the dithioacetal at C_{10} allow for the direct attachment of the C_{26}-pipecolinate and the tricarbonyl moieties.

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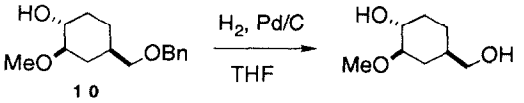

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