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STEREOSELECTIVE SYNTHESIS OF THE C_{10}-C_{24} FRAGMENT OF FK-506

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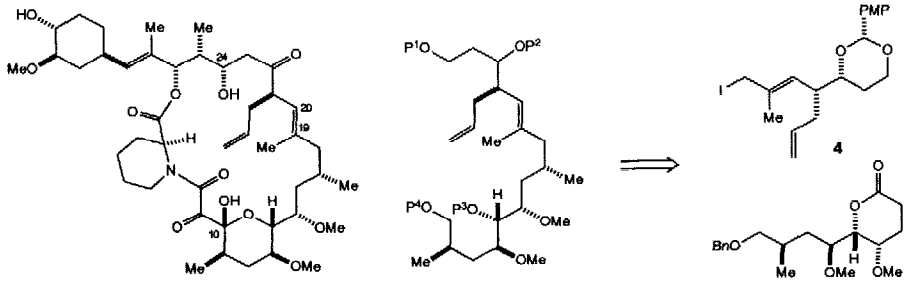
Abstract A highly stereoselective route to the C_{10}-C_{24} fragment of FK-506 is described.

Recently the potent immunosuppressant FK-506 was isolated from *Streptomyces tsukuaensis* and its structure was assigned as the novel 23-membered macrocyclic lactone **1**.[1] The activity of this unique macrolide is reported to be considerably greater than cyclosporin A itself, which is currently used in clinical organ transplants. The exceptional biological activity of FK-506 has lead to extensive studies,[2] and the first total synthesis was recently achieved by the scientists of Merck Sharp & Dohme.[3] In this communication, a synthesis of a protected C_{10}-C_{24} fragment **2** of FK-506 is reported that uses a stereoselective alkylation reaction as the key step.

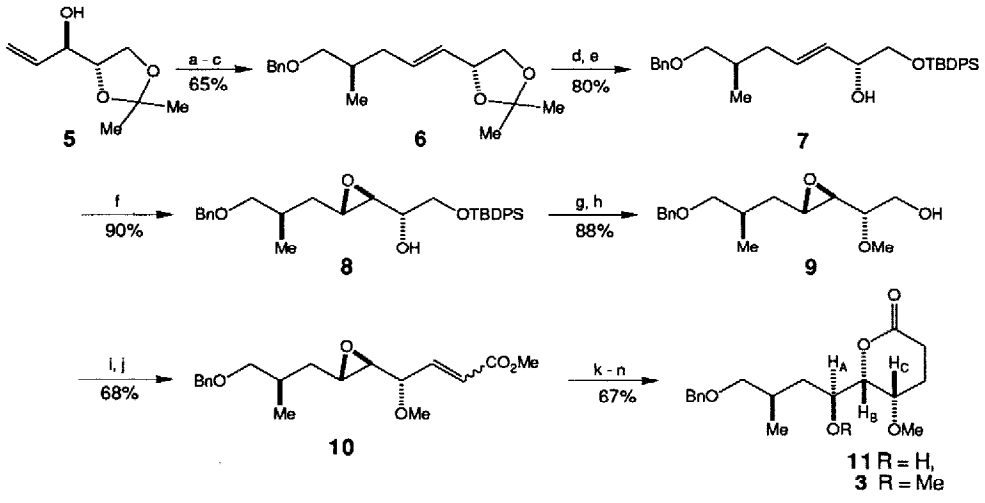


FK-506 (1) **2** **3**

In order to achieve this goal two principal fragments, lactone **3** and allylic iodide **4**, were required to construct the target molecule through a diastereoselective alkylation process. The synthesis of the lactone **3** started with the readily available allylic alcohol **5**[4] (Scheme I). The benzyl ether **6** was obtained with a diastereoselectivity of >15:1 by subjecting the propionate of **5** to the conditions for Ireland-Claisen rearrangement[5] followed by *in situ* reduction with lithium aluminum hydride and subsequent benzylation. Acidic hydrolysis of the acetonide group, followed by selective monosilylation of the resulting diol, gave **7**. Sharpless epoxidation[6] of the allylic alcohol in **7** using (+)-DIPT/Ti(*i*-PrO)$_4$ afforded the corresponding epoxide **8** with the desired stereochemistry. Methylation of **8**, followed by removal of the TBDPS group, led to **9**. Oxidation of **9** with the Dess-Martin periodinane reagent[7] gave a relatively unstable aldehyde which was immediately condensed with the Wittig reagent without purification to provide the α,β-unsaturated ester **10** as a 2:1 *E/Z* mixture. After catalytic hydrogenation, a regioselective epoxide opening was achieved by refluxing the crude methyl ester with excess sodium hydroxide in ethanol, followed by acid treatment to provide the six-membered lactone **11** as the only isolated product. This product apparently resulted from an intramolecular attack by the carboxylate group at the epoxy carbon

center next to the methoxyl group in **10**.[8] Methylation of **11** with diazomethane was promoted with a catalytic quantity of boron trifluoride etherate in methylene chloride[9] to afford the required lactone **3** ($[\alpha]^{23}_D$ = -9.6°, c = 2, $CHCl_3$). Evidence for the indicated stereochemistry of **3** was obtained by an analysis of the ^1H NMR coupling constants (*e.g.*, J_{AB} = 9.3 Hz, J_{BC} = 1.7 Hz).

Scheme I

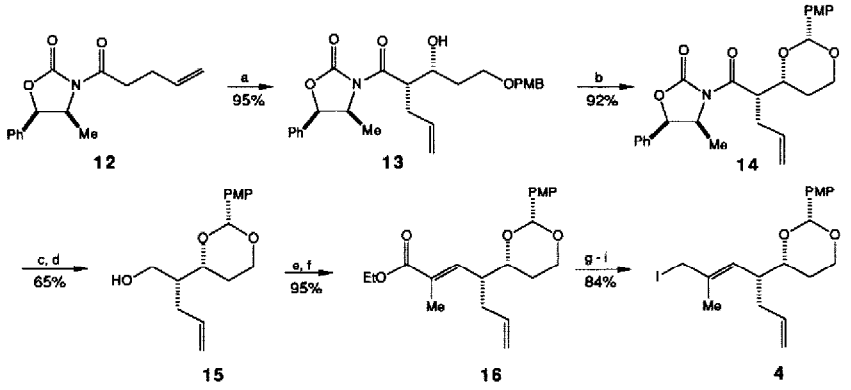


(a) $(C_2H_5CO)_2O$, Et_3N, cat. DMAP, CH_2Cl_2; (b) 2 eq. LDA, 10 eq. TMSCl, THF, -78 °C, then Et_3N and $LiAlH_4$; (c) NaH, BnBr, cat. Et_4NI, THF, reflux; (d) 3:1:1 HOAc-H_2O-THF, 50 °C; (e) TBDPSCl, imidazole, DMF; (f) $Ti(i\text{-}PrO)_4$, (+)-DIPT, t-BuOOH, CH_2Cl_2, -20 °C; (g) NaH, MeI, THF, 0 °C; (h) n-Bu_4NF, THF; (i) Dess-Martin; (j) $Ph_3P{=}CHCO_2Me$, THF; (k) H_2, Pd/C, EtOAc; (l) NaOH, EtOH, reflux; (m) cat. CSA, CH_2Cl_2. (n) CH_2N_2, $BF_3{\cdot}OEt_2$, CH_2N_2, 0 °C.

The Evans asymmetric aldol reaction[10] was employed to install the C_{21} stereocenter in the alkylating agent **4** (Scheme II). The boron enolate of **12** was condensed with 3-(*p*-methoxybenzyloxy)-propionaldehyde to provide **13** which was oxidatively cyclized to the benzylic acetal **14** with 4,5-dichloro-1,4-cyclohexadiene-1,2-dicarbonitrile (DDQ).[11] Removal of the chiral auxiliary in **14** was followed by reduction with lithium aluminum hydride to give the alcohol **15**. Subsequent Swern oxidation of **15** and treatment of the crude aldehyde with the Wittig reagent afforded the α,β-unsaturated ester **16** with a complete *E* selectivity. Ester **16** was converted to the required iodide **4** by a conventional sequence [(i) $LiAlH_4$; (ii) Ph_3P, CBr_4; (iii) NaI].

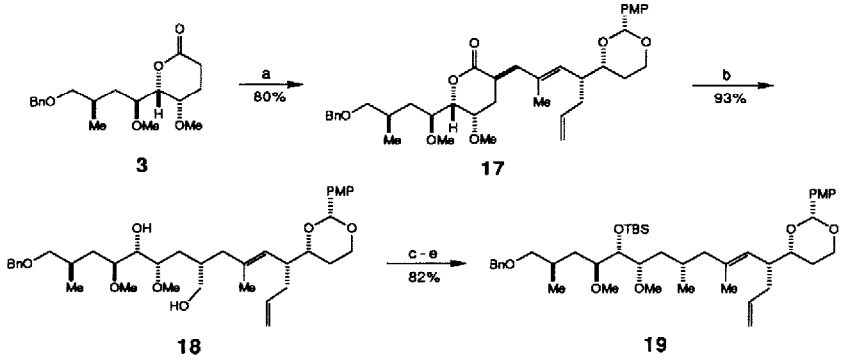
With these subunits in hand, the alkylation of lactone **3** with iodide **4** was explored (Scheme III)[12]. The best result was obtained by enolization of **3** with sodium hexamethyldisilazide and subsequent reaction with **4** to yield the desired product **17** along with its epimer in a ratio of 8:1, which were easily separated by HPLC. The major product was then reduced with lithium aluminum hydride to provide the diol **18**, which upon monotosylation of the primary hydroxyl group, silylation of the secondary hydroxyl group, and finally reduction with super-hydride ($LiEt_3BH$) completed the properly protected C_{10}-C_{24} backbone **19** ($[\alpha]^{23}_D$ = -18.4°, c = 1, $CHCl_3$) of FK-506.[13]

Scheme II



(a) $(c\text{-}C_5H_9)_2OTf$, $i\text{-}Pr_2NEt$, then $PMBOCH_2CH_2CHO$, CH_2Cl_2, -78 °C; (b) DDQ, CH_2Cl_2; (c) LiOH, H_2O_2, $THF\text{-}H_2O$; (d) $LiAlH_4$, THF, 0°C; (e) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (f) $Ph_3P{=}C(Me)CO_2Et$, THF; (g) $LiAlH_4$, Et_2O, -20°C; (h) Ph_3P, CBr_4, CH_2Cl_2; (i) NaI, acetone.

Scheme III



(a) $LiN(TMS)_2$, THF, -78 °C, then **4**; (b) $LiAlH_4$, THF, -20 °C; (c) p-TsCl, Et_3N, cat. DMAP, CH_2Cl_2; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2; (e) $LiEt_3BH$, THF.

In conclusion, a highly stereocontrolled synthesis of the C_{10}-C_{24} fragment of FK-506 has been accomplished. It is noteworthy that the strategy developed here, consisting of an *E* selective Wittig reaction and a diastereoselective alkylation, offers an alternative solution for the introduction of the C_{19}-C_{20} *E* trisubstituted olefin and the C_{17} stereocenter of FK-506. Further synthetic work towards FK-506 will be reported in due course.

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References and Footnotes

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4. The addition of vinyl Grinard to *S*-glyceraldehyde acetonide gave a mixture of **5** and its diastereomeric isomer in a ratio of 1.5:1, see: Walton, D. *J. Can. J. Chem.* **1967**, *45*, 2921. Due to the difficulties involved in the separation task, **5** used in this study was prepared in large quantity from *L*-arabinose through the following sequence: (a) EtSH, HCl; (b) acetone, cat. CSA; (c) $HgCl_2$, HgO; (d) $NaBH_4$; (e) TsCl, Et_3N; (f) NaI; (g) Zn dust. The overall yield of this process is 60% from *L*-arabinose and chromatography is not required for any intermediates.
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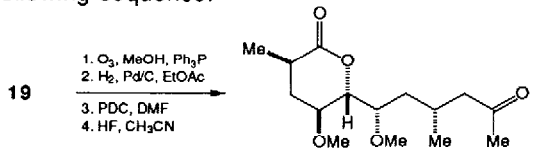
13. The structure of **19** was proved by converting it to the known degradation product **20** of FK-506 through the following sequence:



20 $[\alpha]^{23}_D$ = +82.0°, c = 0.3, $CHCl_3$

The richly detailed 250 MHz ^1H NMR and optical rotation of **20** are in complete agreement with those of the authentic sample ($[\alpha]^{23}_D$ = + 78.9°, c = 0.4, $CHCl_3$) provided by Dr. M. T. Goulet.

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