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STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF FK-506 PREPARATION OF A C(1) TO C(15) SEGMENT

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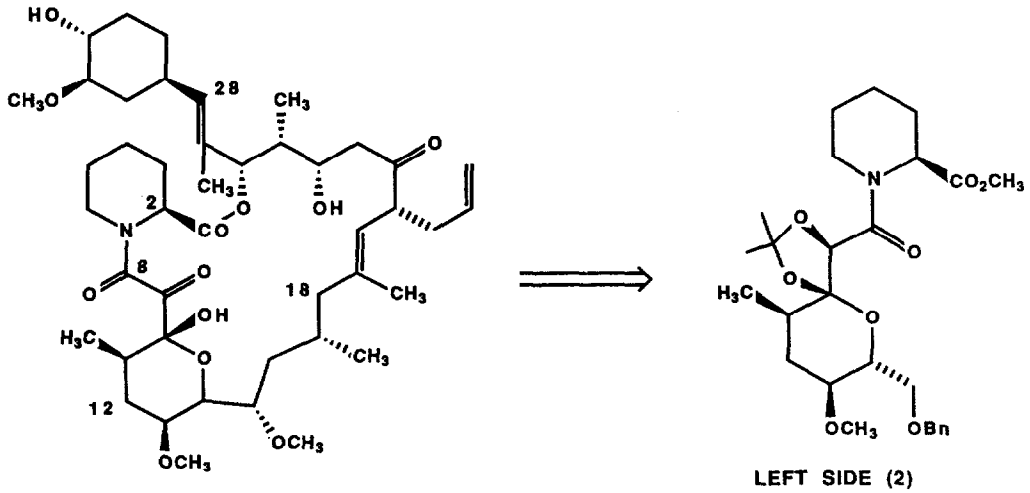
Summary: The protected C(1) to C(15) segment of FK-506 has been prepared from D-glucose, glycolic and L-pipecolic acid.

The novel, highly active immunosuppressive agent FK-506 (1) has attracted considerable attention.[1] The biological potency as well as some unique structural features render this 23-membered macrolide an ideal target for the development of new synthetic methodology on complex natural products. Moreover, a versatile synthesis for FK-506 will provide a ready access to analogues that will cast light upon the apparently similar mode of action of the neutral polyketide FK-506 and the undecapeptide cyclosporin.[2] Such studies are likely to contribute to a better understanding of the regulation mechanisms in the immune system. With these goals in mind, we have embarked on a program directed towards the total synthesis of FK-506, the structurally related rapamycin[3] and variants that will serve as probes in elucidation of the biological mode of action of these agents.

Scheme I.



FK-506 (1)

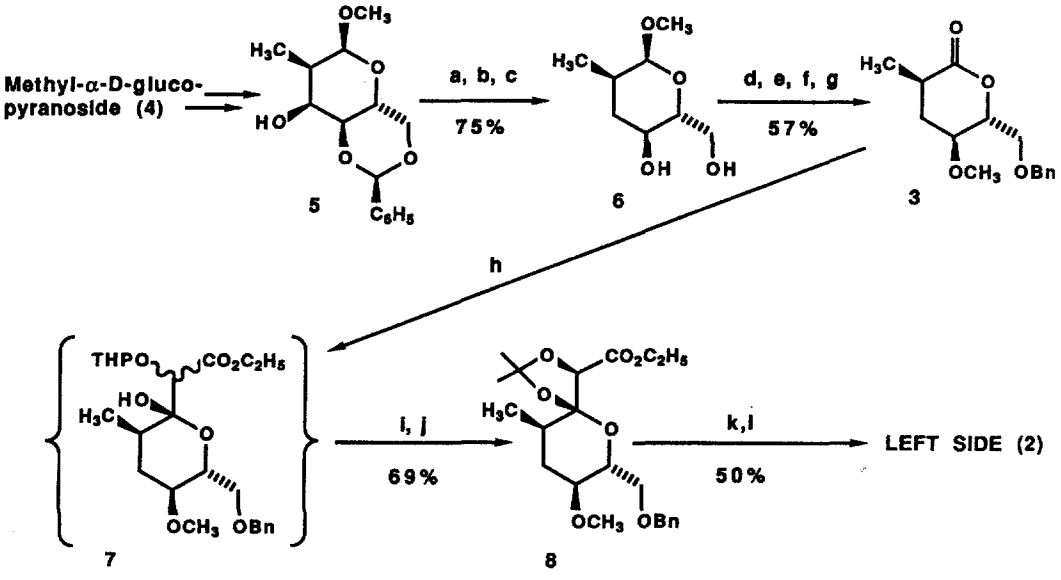
LEFT SIDE (2)

A key feature in the synthesis of FK-506 is the preparation of the α,β–diketoamide hemiketal portion of the molecule. In this report, we describe the synthesis of the left side C(1) to C(15) segment **2** in a fashion such that the reactive keto-hemiketal functionality is blocked for protection during subsequent synthetic operations and assemblage of the natural product (scheme I).

Precedence in the preparation of ketal amide systems such as **2** was found in the work of Meinwald and co-workers on the pederin synthesis.[4] The left side precursor, lactone **3**, was retrosynthetically related to D-glucose as a source of the carbon skeleton and the C(10), C(13), C(14) and C(15) [5] substitution pattern (scheme II).

Scheme II. Construction of left side intermediate **2** for FK-506 synthesis*

SCHEME II: CONSTRUCTION OF LEFT SIDE (2) INTERMEDIATE FOR FK-506 SYNTHESIS*



* a, *n*BuLi, DME/TMEDA, 0°; Cl_2PONMe_2, rt, 4h; b, $HNMe_2$, rt, 4h; c, LI, THF, EtOH, $EtNH_2$, 10°, 1h; d, NaH, BnBr, THF, 0°, 36h; e, NaH, CH_3I, THF, rt, 8h; f, HOAc, H_2SO_4, H_2O, 90°, 90min; g, Ac_2O, DMSO, rt, 24h; h, LDA, THF, $THPOCH_2CO_2C_2H_5$, -78°, 3h; EtOH ; i, PPTs, THF, H_2O, 55°, 5h; j, CH_3COCH_3, P_2O_5, rt, 15h; k, LIOH, MeOH, H_2O, rt, 6h; l, $SOCl_2$, pyridine, rt, 10min; NEt_3, $C_5H_{10}NCO_2CH_3 \cdot HCl$, rt, 2h.

Methyl α-D-glucoside (**4**) was converted in 6 steps into the alcohol **5** in 56% overall yield by standard methods.[6] After formation of the C(12)-phosphorodiamidate[7] of **5**, *both* the C(12) oxygen function and the benzylidene blocking group were removed in one operation by reduction with lithium in ethylamine. Selective benzylation of the primary alcohol in **6** was achieved in 70%

yield (some dibenzylated as well as C(13)-O-monobenzylated product was removed by column chromatography). Methylation of the C(13) hydroxyl function (98%), acetal hydrolysis and Albright-Goodman oxidation[8] (83%) led in an overall yield of 57% to the desired lactone **3**.[9]

While repetition of the Meinwald protocol[4c] with δ-valerolactone reproduced the published results perfectly[10], application of this reaction sequence for the addition of a ketal ester to the lactone **3** was very unrewarding. No products that were related to the desired hemiketal ester were observed and instead a series of byproducts that included unsaturated esters and open-chain condensation products were obtained. Molecular mechanics calculations for lactone **3** do not reveal serious steric congestion due to the α-methyl group, but there is clearly a steric problem in the addition step. With methyl glycolate esters, self condensation predominated and with esters bulkier than ethyl no significant condensation was observed. The reaction is also highly sensitive to the bulk of the ether blocking group, and it was only when the tetrahydropyranyl ethyl glycolate was used that the desired condensation was observed. While the adduct **7** was labile, acetonide formation proceeded smoothly and gave the ketal ester **8**[11] in satisfactory 69% yield. Ester cleavage in ketal ester **8** was achieved with LiOH in $MeOH/H_2O$ and the highly sensitive ketal acid was used immediately. The derived acid chloride was coupled with methyl pipecolate[12] and gave the left side **2** in 50% yield. The low yield is mainly due to considerable decomposition of the intermediate acid during workup after ester cleavage and is as yet unoptimized.

The ketal amide **2**[13] exists as an approximately 3:1 mixture of two isomers in solution; a feature that amide **2** shares with the analogous portion of FK-506 and rapamycin[2] and is attributed to a restricted rotation about the amide bond. Thus, with the exception of the aromatic and the CH_3O signals, all carbon resonances appear twice in the ^{13}C spectrum (*cf.* [1f]).

In conclusion, a left side C(1) to C(15) segment of FK-506 is available by an efficient route from D-glucose as starting material. The protection of the potentially reactive C(8) to C(10) α,β-diketoamide hemiketal as a ketal amide allows a straightforward assemblage of the natural product and analogues thereof. Further studies will demonstrate the utility of this approach.

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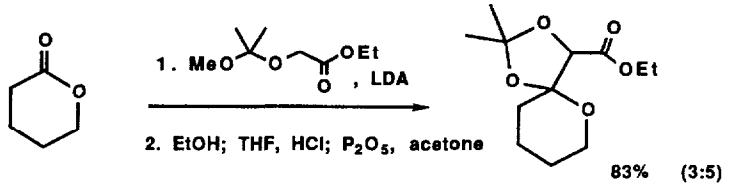
9. For partial characterization of **3**: ^{1}HNMR(300 MHz, $CDCl_3$) δ 7.31(s, 5 arom. H);4.59,4.51 (AB, J=12.0Hz,$PhCH_2O$);4.23 (dt,J=7.7Hz and J=3.8Hz, HC(14));3.6-3.8(m,3H,H_2C(15) and HC(13)); 3.34(s,CH_3O); 2.4-2.6(m,1H, HC(11)); 2.2-2.3, 1.4-1.6(2m,2H,H_2C(12)); 1.28(d,J=7.0Hz,CH_3-C(11)). ^{13}CNMR(75 MHz,$CDCl_3$) δ 173.8(s,C(10)): 138.2, 128.7, 128.1, 128.0(6 arom. C); 82.5 (d,C(14)); 73.9, 69.6(2t,$PhCH_2OCH_2$); 73.3(d,C(13)); 57.3(q,CH_3O); 33.8 (d, C(11)); 32.6(t, C(12)): 17.6(q,CH_3-C(11)). MS(EI): found: M^+ 264.1345; $C_{15}H_2O_4$ requires M^+ 264.1356.
10. Scheme III.



11. For partial characterization of **8**: ^{1}HNMR(300MHz,$CDCl_3$) δ 7.30 (s,5 arom H): 4.54 (s,HC(9)); 4.54, 4.48 (AB, J=12.2Hz, $PhCH_2O$); 4.16(q,J=7.0Hz,$CH_3C\underline{H_2}O$); 3.5-3.8, 3.2-3.4(2m,4H, HC(13),HC(14) and H_2C(15)); 3.34(s,CH_3O); 2.0-2.2, 1.4-1.6(2m,3H,HC(11) and H_2C(12)); 1.61, 1.42 (2s, $(H_3C)_2C$); 1.18(t,J=7.0Hz,$C\underline{H_3}CH_2O$); 1.01(d,J=6.4Hz,H_3C-C(11)). ^{13}CNMR (75MHz,$CDCl_3$) δ 168.4(s,C(8); 139.3, 128.6, 127.8, 127.7(6 arom. C); 113.0, 106.9(2s, $(CH_3)_2\underline{C}$ and C(10)); 80.1(d,C(9)); 74.6, 74.5(2d, C(13) and C(14)); 73.7, 69.8(2t, C(15) and CH_2Ph); 61.4(t, $\underline{C}H_2CH_3$); 57.0 (q,CH_3O); 33.9(d,t,C(11) and C(12)); 27.5, 28.1(2q, $(\underline{C}H_3)_2C$); 16.5(q,$H_3\underline{C}$-C(11)); 14.6(q,$CH_2\underline{C}H_3$). MS(EI): found: M^+ 408.2159; $C_{22}H_{32}O_7$ requires M^+ 408.2139). The configuration at C(9) was determined by NOE experiments.
12. Prepared by $SOCl_2$/MeOH esterification of L-(-)-pipecolic acid (Aldrich).
13. For partial characterization of **2**: IR($CHCl_3$) cm^{-1} 2990(m), 2930(s), 2855(w), 1732(s), 1618(s), 1449(m), 1373(w), 1245(m), 1171(m), 1090(s), 990(m). ^{13}CNMR(75MHz,$CDCl_3$) δ 173.5, 172.0 (s,C(1)); 167.5, 166.3(s,C(8)); 139.1, 138.8, 128.6, 127.7, 127.6(6 arom. C); 112.1, 111.4, 106.8, 106.6(2s,$(CH_3)_2\underline{C}$ and C(10));82.7, 82.1(d,C(9)); 75.3, 74.8, 73.7, 73.3(2d,C(13) and C(14)); 73.5,73.3, 71.0, 70.6 (2t,$PhCH_2O$ and C(15)); 56.8(q,CH_3O);55.8, 53.6 (d, C(2)); 52.3(q,$\underline{C}H_3O$-C(1)); 43.9, 40.9(t,C(6)); 34.0, 33.9(t,C(12)); 33.6,32.8(d,C(11)); 27.6, 27.2, 25.5, 25.1, 21.7, 21.6 (3t,C(3),C(4) and C(5)); 27.8, 26.8(q,$(\underline{C}H_3)_2C$); 16.9, 16.7(q,$\underline{C}H_3$-C(11)). MS(EI): found: M^+ 505.2666; $C_{27}H_{39}NO_8$ requires M^+ 505.2665.

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