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A SYNTHESIS OF THE C16-C23 SEGMENT OF FK-506

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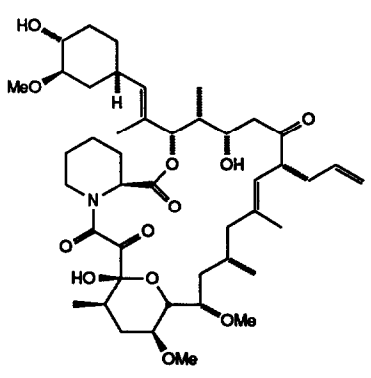
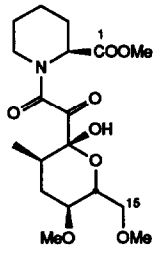
Abstract. A copper-catalysed migratory insertion reaction was used to construct the tri-substituted alkene of the C16-C23 segment 4 of the potent immunosuppressant FK-506 (Tsukubaenolide) (1).

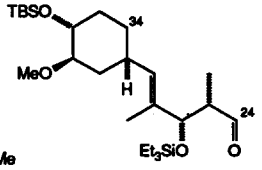
Cyclosporin has been an essential factor in the progress of transplant surgery in the past decade[1]. However, its nephrotoxicity and other limitations have stimulated a search for alternative agents. One such agent is FK-506 (tsukubaenolide) (1), a macrolide isolated from *Streptomyces tsukubaensis* by a Japanese group[2] in 1984, and shown to be immunosuppressive *in vitro* by Kino and co-workers[3] in 1987. Numerous reports soon validated the potential of FK-506 for immunosuppression *in vivo*[4]. Most dramatic of all, however, were the results communicated in *The Lancet* on October 28, 1989: FK 506 was successfully administered to human patients in desperate plight because their liver grafts were being rejected despite conventional immunosuppression[5]. Interest in FK-506 is now intense and a spate of papers has appeared recently recording a total synthesis[6] as well as syntheses of various segments[7]. Preliminary studies on the potential mode of action have also appeared[8]. We now report a synthesis of the C16-C23 segment 4 which complements the syntheses of the C1-C15 segment 2 and the C24-C34 segment 3 previously disclosed[9,10]. A salient feature of our synthesis of segment 4 is the stereoselective construction of the tri-substituted alkene using a novel copper-catalysed migratory insertion reaction.



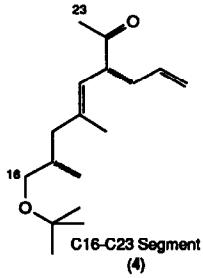
FK 506 (Tsukubaenolide)
(1)



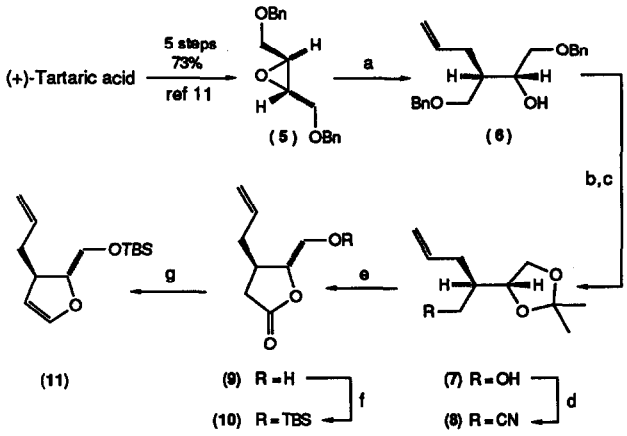
C1-C15 Segment
(2)



C24-C34 Segment
(3)



C16-C23 Segment
(4)

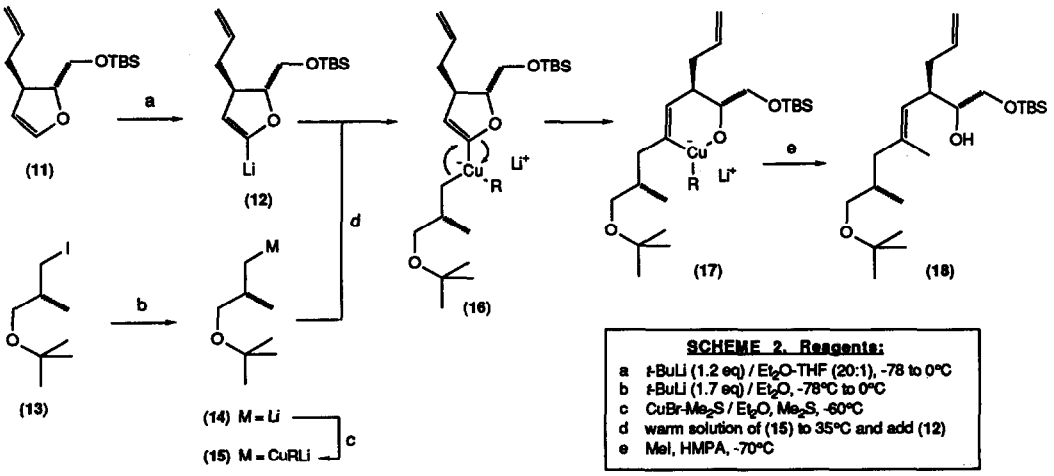


SCHEME 1. Yields and Reagents:

a	93%	AllylMgBr / THF, -20°C
b	-	Na / THF-NH_3
c	63%	Acetone/ptsa
d	75%	(i) TsCl / pyridine; (ii) NaCN / DMSO
e	74%	10% HCl in MeOH
f	98%	TBSCl / imidazole / CH_2Cl_2
g	86%	(i) DIBAlH,-78°C ; (ii) MsCl, Et_3N / THF, -30°C to 50°C

Our synthesis began (Scheme 1) with (+)-tartaric acid which was converted to the oxiran **5** in 73% overall yield according to known procedures[11]. Nucleophilic scission of the oxiran ring with allylmagnesium bromide gave the alcohol **6** from which the benzyl protecting groups were removed using dissolving metal reduction. The resultant triol was not purified owing to high water solubility; consequently, the crude triol was converted to the acetonide **7** in 63% overall yield in the usual way. The alcohol function in **7** was converted to the corresponding *p*-toluenesulphonate ester which underwent nucleophilic displacement with cyanide to give the nitrile **8** in 75% overall yield from **7**. Hydrolysis of the acetonide and cyano functions and lactonisation were all accomplished in a single operation on treatment of nitrile **8** with HCl in MeOH. After protection of the primary hydroxyl function as the *t*-butyldimethylsilyl ether, the lactone carbonyl in **10** was reduced with diisobutylaluminium hydride. The resultant mixture of diastereoisomeric lactols was then dehydrated *via* the methanesulphonate ester. Attempts to eliminate the methanesulphonate in dichloromethane under a variety of conditions proceeded in poor yield. However, by using tetrahydrofuran as solvent the elimination reaction was clean and efficient affording the desired homochiral dihydrofuran **11** in 86% overall yield from lactone **10**.

The key step in our synthetic plan (Scheme 2) was a migratory insertion of the higher order cuprate[12,13] intermediate **16** prepared by reaction of the lithiated dihydrofuran **12** with the homocuprate **15**. As expected from earlier studies, the migratory insertion of **16** took place with clean inversion of stereochemistry to give the putative higher order oxycuprate **17**. Intermediate **17** underwent alkylation with retention of configuration at low temperature to give the tri-



SCHEME 2. Reagents:

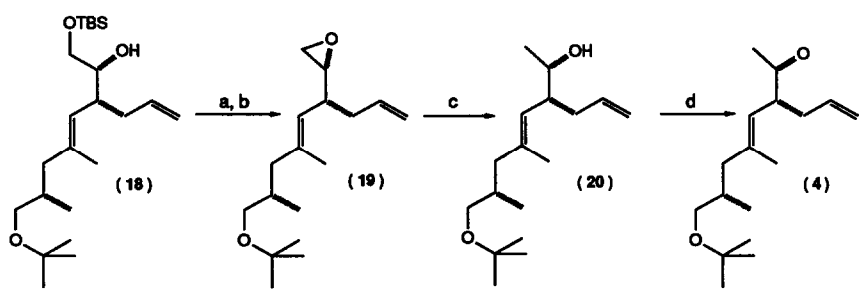
a	t-BuLi (1.2 eq) / Et_2O-THF (20:1), -78 to 0°C
b	t-BuLi (1.7 eq) / Et_2O, -78°C to 0°C
c	CuBr-Me_2S / Et_2O, Me_2S, -60°C
d	warm solution of (15) to 35°C and add (12)
e	MeI, HMPA, -70°C

substituted alkene **18** in 57% overall yield from **11**. Considerable effort was expended to ascertain the optimum conditions for achieving the requisite rearrangement. The principal problems were the thermal instability of the cuprate **15** *versus* the relatively high temperature (35°C)[14] required for the migratory insertion. These were eventually reconciled by adding dimethyl sulphide to the reaction mixture to stabilise the cuprate **15**. The critical experimental procedure is detailed below:

To a magnetically stirred solution of (2R)-2-methyl-3-*t*-butoxy-1-iodopropane **13** (396 mg, 1.55 mmol) in Et_2O (3 ml) at -78°C was added *t*-BuLi in pentane (1.7 M, 1.55 ml, 2.64 mmol). The mixture was warmed to 0°C and stirred for 10 min whereupon THF (0.5 ml) was added dropwise to destroy excess *t*-BuLi. After 20 min at 0°C, the mixture was cooled to -78°C and a solution of $CuBr{\cdot}SMe_2$ (160 mg, 0.775 mmol) in SMe_2 (2 ml) was added dropwise. The mixture was allowed to slowly warm to room temperature during which time the mixture became a homogeneous yellow solution (at *ca.* -20°C). The mixture was then heated to reflux whilst a solution of the lithiated dihydrofuran **12** [prepared in Et_2O from 100 mg (0.388 mmol) of **11** and 1.1 eq of *t*-BuLi] was added dropwise. After addition was complete the mixture was heated under reflux for 30 min and then cooled to -78°C whereupon HMPA (95 µl, 0.775 mmol) was added followed by MeI (177 mg, 1.16 mmol). The mixture was then stirred at -40°C for 1 h and allowed to attain room temperature over 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl and the product extracted into Et_2O. The extract was dried over $MgSO_4$, concentrated *in vacuo*, and the residue purified by column chromatography on silica gel 60 eluting with 5% Et_2O in hexane to give **18** (89 mg, 57%) as a colourless oil: $[\alpha]_D$ -5.8° (*c.* 2 in $CHCl_3$); IR (film) 3473 br, 2956 s, 2858 s, 1640 w, 1472 m, 1362 m, 1254 m, 1198 m, 1081 s, 836 s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 5.76 (1H, dddd, J = 17, 10, 7, 7 Hz), 5.1(1H, d, J = 10 Hz), 5.03 (1H, d, J = 17 Hz), 4.96 (1H, d, J = 10 Hz), 3.4-3.7 (3H, m), 3.17 (1H, dd, J = 8.5, 3 Hz), 3.08 (1H, dd, J = 7.5, 7.0 Hz), 2.56-2.43 (1H, m), 2.4-2.0 (4H, m), 1.9-1.6 (2H, m), 1.58 (3H, s), 1.17 (9H, s), 0.90 (9H, s), 0.82 (3H, d, J = 6.4 Hz), 0.04 (6H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) 137.3 (d), 136.3 (s), 125.6 (d), 115.9 (t), 74.3 (d), 72.5 (s), 67.5 (t), 65.9 (t), 44.7 (t), 40.4 (d), 36.8 (t), 32.1 (d), 27.8 (q), 26.5 (q), 26.0 (q), 18.1 (s), 17.0 (q), 16.7 (q), 4.24 (q); LRMS (CI mode, NH_3): m/z 399 $(M+1)^+$, 343 (100), 211 (44), 193 (63), 99 (67).

To complete the synthesis (Scheme 3), the protecting group was removed from **18** and the resultant diol selectively converted to the terminal methanesulphonate ester. On treatment with potassium carbonate in MeOH, this was converted in high yield to the oxiran **19**. Reductive opening of the oxiran ring in **19** occurred regioselectively to afford the alcohol **20** which underwent smooth oxidation to the desired ketone **4** using the Dess-Martin reagent[15]. Under these conditions the product **4** was obtained efficiently without racemisation[16].

In conclusion, we have demonstrated the value of copper-catalysed migratory insertion chemistry for the elaboration of polyketide chains incorporating tri-substituted alkenes flanked by stereogenic centres. Efforts are now underway to link segments **2**, **3**, and **4** or derivatives thereof and thus accomplish a total synthesis of FK-506.



SCHEME 3. Yields and Reagents:
a 97% TBAF / THF
b 91% (i) MsCl / Et_3N-THF, -70 to 20°C; (ii) K_2CO_3 / MeOH
c 96% $LiAlH_4$ / THF
d 92% Dess-Martin oxidation

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