Tetrahedron Letters, Vol.31, No.10, pp 1443-1446, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF IMMUNOSUPPRESSIVE AGENT FK 506 : SYNTHESIS OF C-20 TO C-27 MOIETY

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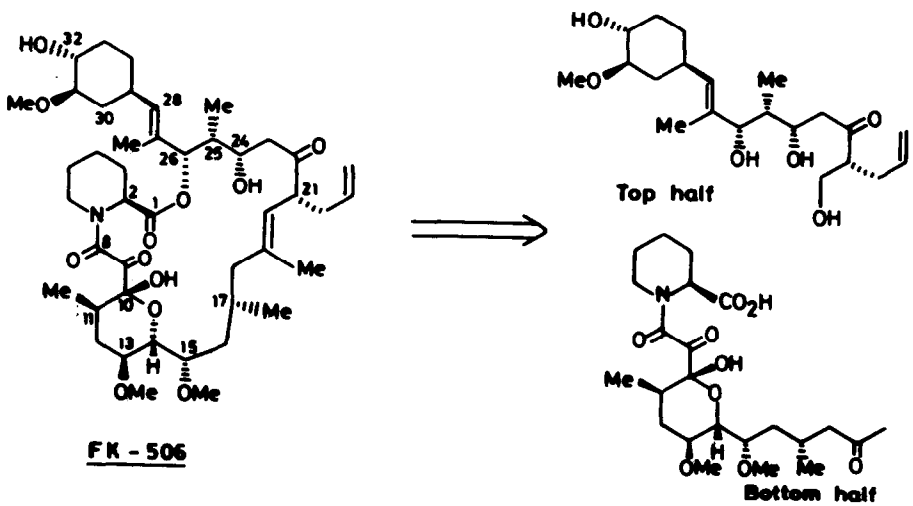
Abstract Regioselective ring opening of (2S,3R)-epoxide of 4-benzyloxy-cis-2-buten-1-ol with Me_2CuLi and diastereofacial selective aldol reaction with enolsilane are the key steps involved in the stereospecific construction of "2-methyl-1,3-diol" backbone of FK 506.

In continuation of our work on the synthesis of novel immunosuppressive agent FK-506[1] we undertook also the construction of the "top-half" of the molecule. A close inspection of the "top-half" reveals the existance of three contiguous chiral centers at C-24, C-25 and C-26 with an R-allyl group anchored at C-21 position. For the construction of this segment the attention is mainly focussed on "1,3-diol" system having the middle position occupied by a chiral methyl group. All of these three stereocenters have mutual syn-relationship. This type of structural ensemble is widely present in many natural products like erythromycin A, B, rifamycin S, tylosin etc.[2] An efficient construction of this ensemble will, thus, not only facilitate the total synthesis of FK-506, but also provide easy access to many other structurally similar complex natural products.



Though many reports have now appeared on the synthesis of this segment[3], surprisingly the single most powerful method in present day asymmetric synthesis ,namely Sharpless asymme-

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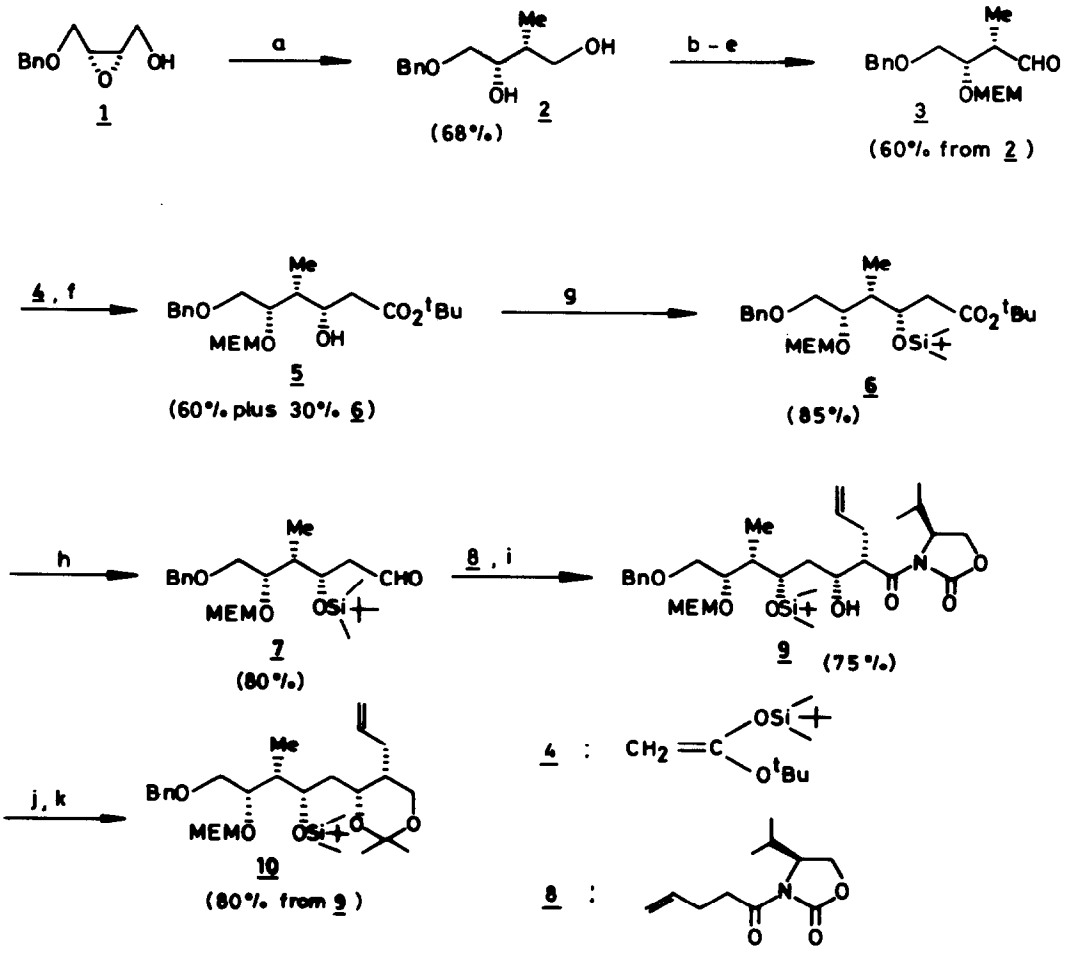
tric epoxidation[4] has so far eluded the attention. Herein, we report an efficient synthesis of C-27 to C-20 fragment of FK-506. Our synthesis began with (2S,3R)-epoxide (1)[5] of 4-benzyloxy-cis-2-buten-1-ol, a versatile synthon for many natural products[6]. Treatment of 1 with Me_2CuLi



a) i) Me_2CuLi(4 eq),Et_2O,-40°C,4 h; ii) $NaIO_4$(2.0 eq),THF:H_2O(4:1),r.t,4 h; b) Piv-Cl (1.1 eq),Py, r.t.,12 h; c) MEM-Cl,diisopropylethylamine,CH_2Cl_2,r.t.,8 h; d) MeLi,ether,0°, 30 min; e) $(COCl)_2$, DMSO,Et_3N,CH_2Cl_2,-78°, 1 h; f) 4,$BF_3.Et_2O$,CH_2Cl_2,-78°,30 min; g) TBDMS-Cl,imidazole,DMAP-(cat),DMF,r.t.,16 h; h) DIBAL-H,(1.2 eq),CH_2Cl_2,-78°,45 min; i) 8,n-Bu_2BOTf, diisopropylethyl-amine,CH_2Cl_2,-78°→ 0°,4 h ; j) $LiBH_4$(2.2 eq),THF,0°→r.t.;5 h; k) 2,2-dimethoxypropane,PTSA-(cat),r.t.,3 h.

in ether at -40° gave 1,3-diol (**2**) as the major product (1, 3 : 1,2 = 7:3).[7,8] Oxidative cleavage of the unwanted 1,2-diol with $NaIO_4$ allowed an easy separation of the desired 1,3-diol. Our initial plan to stereospecifically fix C-24 hydroxy group by an ingenious sequence engineered to provide 1,3,5,....., (2n+1) polyol system based on Sharpless asymmetric epoxidation[9] had to be abandoned since it was found not suitable for large scale preparations. Instead, we opted for Lewis acid mediated Mukaiyama aldol reaction with enolsilane.[10] Standard functional group manipulations like selective primary hydroxyl protection of 1,3-diol (**2**) with pivaloyl chloride, secondary hydroxyl protection as MEM-ether, primary hydroxyl deprotection and finally Swern oxidation provided the chiral aldehyde (**3**).[8] For enolsilane our choice was tert-butyldimethylenol-silane (**4**) derived from t-butylacetate. Treatment of **3** with enolsilane (**4**) in presence of $BF_3.Et_2O$ at -78° in CH_2Cl_2, gave syn-isomer (**5**) as the major product (syn:anti = 95:5).[8,11]

The resulting hydroxy group was protected as t-butyldimethylsilyl ether.[12] DIBAL-H reduction of ester (**6**) directly gave aldehyde (**7**). Evan's aldol condensation finally anchored the allyl appendage on C-21 with the requisite chirality.[13] Lithium borohydride reduction removed the chiral auxiliary and the resulting diol was protected as acetonide[14], thus completing the construction of C-27 to C-20 fragment of FK-506.

In conclusion, (2S,3R)-epoxide (**1**), a versatile synthon obtained by Sharpless epoxidation of 4-benzyloxy-cis-2-buten-1-ol laid the foundation for the construction of "top-half" of FK-506. Further work is in progress.

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3. For the synthesis of "top-half" of FK-506 see (a) E.J. Corey, H.C. Huang, Tetrahedron Lett., **30**, 5235 (1989); (b) J.A. Ragan, M. Nakatsuka, D.B. Smith, D.E. Uehling and S.L. Shreiber, J. Org. Chem., **54**, 4267 (1989); (c) T.K. Jones, S.G. Mills, R.A. Reamer, D. Askin, R. Desmond, R.P. Volante and I. Shinkai, J. Am. Chem. Soc., **111**, 1157 (1989); (d) A.B. Jones, M. Yamaguchi, A. Patten, S.J. Danishefsky, J.A. Ragan, D.B. Smith, S.L. Schreiber, J. Org. Chem., **54**, 17 (1989); (e) S. Mills, R. Desmond, R.A. Reamer, R.P. Volante and I. Shinkai, Tetrahedron Lett., **29**, 281 (1988).
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5. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune and K.B. Sharpless, J. Am. Chem. Soc., **109**, 5765 (1987).
6. Some other useful applications of this synthon will be published soon.
7. Though much better ratio in favour of 1,3-diol (9:1) was obtained at -110°, the reaction was extremely slow and far from complete even after prolonged reaction time.
8. Satisfactory NMR, IR and Mass Spectra were obtained for this compound.
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11. (a) The ratio was determined by hplc separation of the corresponding acetates and ^{1}H NMR spectra of these acetates using shift reagent Eu(fod)$_3$; (b) Similar aldol reaction on **3** using lithium enolate of ethylacetate showed very poor selectivity (syn:anti = 3:2).
12. During the aldol reaction with enolsilane **4** about 30% product was isolated as t-butyldimethylsilyl ether **6**.
13. D.A. Evans, J. Bartroli and T.L. Shih, J. Am. Chem. Soc., **103**, 2127 (1981); also see ref. 3 (e).
14. ^{1}H NMR of **10** (300 MHz, $CDCl_3$): δ 7.3-7.4 (m, 5H, Ar-H), 5.76-5.08 (m, 3H, CH_2=CH), 4.88, 4.75 (two d, J = 6.9 Hz, 2H, O-CH_2O), 4.51 (s, 2H, Ph-CH_2O), 4.09-3.48 (m, 11H, CH_2-O, CH-O), 3.36 (s, 3H, -OCH_3), 2.41-1.20 (m, CH_2-, -CH-), 1.36-1.31 (two s, 6H, acetonide CH_3), 0.92 (d, J = 6.8 Hz, 3H, CH_3), 0.86 (s, 9H, -C(CH_3)$_3$), 0.02, -0.2 (two s, 6H, Si(CH_3)$_2$).

(Received in UK 4 January 1990)