Use of a Masked Aldol Unit in the Synthesis of the Right Side of FK-506

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Received February 26, 1990

Summary: A strategy for the synthesis of the C_{16}–C_{27} right side portion (**2**) of the immunosuppressant FK-506 is developed.

A synthetic strategy for the construction of the immunosuppressant FK-506[1] must consider, in addition to the assembly of the novel α,β-diketo amide hemiacetal, a means for the formation and protection of the aldol portion represented by the C_{21}–C_{24} carbon chain. Since the lability of this grouping toward dehydration and retro-aldol cleavage is well documented,[2] an initial goal of this project was the development of a subunit that would effectively resist these common aldol-type side reactions, would be useful as a synthetic intermediate for further skeletal construction, and would easily generate the desired aldol structure under very mild conditions at a late synthetic stage. Concurrent work[3] in these laboratories suggested that a masked aldol unit in the form of a spiroenone would serve this purpose. In addition to the protection of the sensitive aldol structure, such a spiroenone offered the opportunity for the assembly of the C_{16}–C_{27} portion of FK-506 (and other related macrolactones[4]) through conjugate addition reactions. A route to a suitably blocked version of the α,β-diketoamide portion of FK-506 has been reported[11] from these laboratories and an efficient synthesis of the right-side **2** of this molecule that implements this novel aldol blocking group strategy is reported here (Scheme I).

The key synthetic intermediate for the preparation of the right-side **2** is spiroenone **9**, the construction of which was elaborated from (*R*)-(benzyloxy)propanal[5] (**3**) (see Chart I). Stereoselective introduction of the vicinal asymmetric centers at C_{25} and C_{26}[6] was efficiently accomplished by the addition of Brown's (*Z*)-crotyldiisopinocampheylborane.[7]

Scheme I. Synthetic Plan for the Right Side of Immunosuppressant FK-506

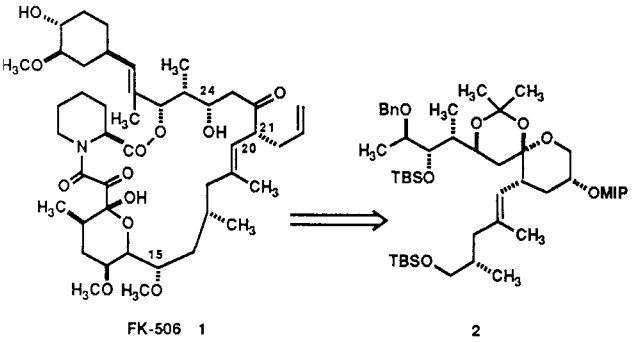
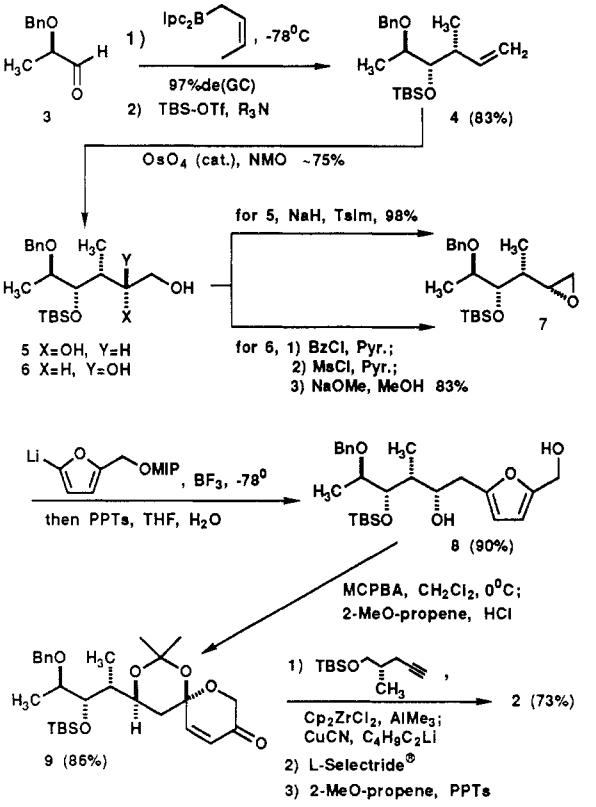


Chart I. Synthesis of Right-Side Portion of FK-506



The high diastereoselectivity of this process[8] is clearly the result of the stereochemically matched combination of substrate and reagent.[9] After silylation, the olefin **4** was cleanly obtained in excellent yield.

Stereoselective conversion of the olefin **4** to the required epoxide **7** presents a delicate stereochemical problem.[10]

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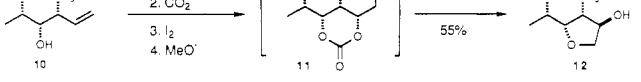
(6) FK-506 numbering.

(7) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(8) 97% de as determined by GC analysis.

(9) (*Z*)-Crotyldiisopinocampheylborane derived from (+)-α-pinene was used.

(10) An intramolecular epoxidation of the unprotected homoallyl alcohol **10** via the corresponding iodo carbonate **11** led only to five membered ring formation:



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Expectedly, direct oxidation with MCPBA gave no stereoselection. Hydroxylation with the osmium tetroxide/NMO system[11] in the absence of chiral catalysts led to a 1:3.5 ratio of isomeric diols **5** and **6** in 77% yield. Application of the recently described Sharpless catalytic dihydroxylation procedure[12] with hydroquinidine *p*-chlorobenzoate afforded a 62% yield of a 1:1.8 ratio of the same diols. When dihydroquinine *p*-chlorobenzoate was used as an auxiliary, the diols **5** and **6** were prepared in 72% and a 1:5 ratio of stereoisomers. The configuration at C_{24} of the readily separable diols **5** and **6** was determined by NMR analysis of the derived acetonides A[13] and B,[13] which were individually prepared from each isomer by standard means.

Treated under the proper set of reaction conditions, both diols **5** and **6** are suitable precursors of the epoxide **7**. Thus, tosylation and then internal displacement of the diol **5** led in excellent yield to the desired epoxide **7**. The somewhat more elaborate procedure used to convert the diol **6** to the same epoxide **7** was hardly less efficient, and the combined process of hydroxylation and then epoxide formation proved to be a useful means for the transformation of the olefin **4** to the epoxide **7**.

With the epoxide **7** in hand, the formation of the key intermediate spiroenone **9** followed precedence[3] developed in the model studies of such spiroenones. As a result of the somewhat more complex substitution of epoxide **7**, however, the reaction conditions and reagents required some modification and rather than utilization of LiCl catalysis, the use of the 5-lithiofurfuryl alcohol ethers and $BF_3{\cdot}Et_2O$ catalysis proved more successful. After treatment with mild acid, the required diol **8** was isolated in very satisfying yield.

Oxidation of the diol **8** with MCPBA[14] proceeded in a satisfactory manner, but acetalization[3] with paraformaldehyde and sulfuric acid catalysis completely destroyed this delicate system. Utilization of the ketalization procedure[3] with 2-methoxypropene and HCl or PPTS catalysis proved to be an excellent alternative and the desired spiroenone was formed cleanly.

This masked aldol system is a particularly attractive intermediate, since functionality is present for the selective addition of a variety of cyclohexylmethylene substituents at the benzyloxy position *and* various carbon chains through conjugate addition to the enone system. For the FK-506 synthesis itself, a five-carbon olefinic chain is required. Conventional wisdom suggests the use of a vinyl cuprate reagent derived in two steps from ((*tert*-butyldimethylsilyl)oxy)-2(*S*)-methyl-4-pentyne, and while this process ultimately was successful, a more direct zirconocene dichloride catalyzed carboalumination[15]/cuprate exchange[16] sequence accomplished the same result in one step and satisfactory yield. One stereoisomer **2** resulted from either addition process, and based on previous experience[3] and NMR analysis,[17] the α(axial) orientation of the side chain and the *E* stereochemistry of the trisubstituted double bond is assigned. Since fragmentation of similar spiroketal ketals has been shown[3] to be a mild process, all that is necessary to render this addition product a viable template for the right side of FK-506 is the blocking of the saturated ketone. This was easily accomplished through L-selectride (Aldrich) reduction of spiroenone **9** followed by protection with 2-methoxypropene/PPTs and the requisite right-side intermediate **2** thus became available in 30% overall yield from **3**.

The success of this scheme demonstrates the value of the spiroenone system as a useful synthetic strategy and further transformations toward the completion of the FK-506 synthesis are being actively pursued.[18]

Acknowledgment. The authors thank the University of Virginia for support of this work and P. Wipf thanks the Swiss National Science Foundation for a fellowship.

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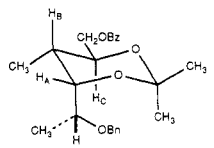
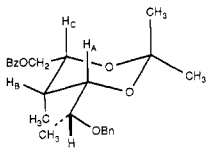
(12) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
(13) The coupling constants for the axially and equatorially oriented hydrogens on C_{24}, C_{25}, and C_{26} clearly confirm the stereochemical assignments for diols **5** and **6**. For a related system, see: Nakanishi, K.; Pawlak, J.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896.



A(5) $J_{A,B}$ = 4.9Hz, $J_{B,C}$ = 8.0Hz



B(6) $J_{A,B}$ = 2.0Hz, $J_{B,C}$ = 1.5Hz

(14) For related procedures, see: (a) DeShong, P. L.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (b) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *Tetrahedron* **1988**, *44*, 3171. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.
(15) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.
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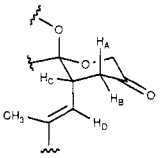
(17) The vicinal coupling constants of the spiroketal ring hydrogens correspond nicely to an axial enone addition product:



$J_{A,B}$: 15.8Hz
$J_{A,C}$: 5.5Hz
$J_{B,C}$: 4Hz
$J_{C,D}$: 10.2Hz

Additionally, the olefin geometry can be assigned based upon the characteristic ^{13}C NMR resonances of the methyl substituent in *E*- and *Z*-trisubstituted olefin systems (16 and 24 ppm, respectively; cf. refs 1b and 1o).
(18) Satisfactory ^1H and ^{13}C NMR, IR, MS, and C, H analyses data were obtained for all new compounds described in this report.