Pergamon

Tetrahedron Letters 39 (1998) 229–232

TETRAHEDRON LETTERS

SYNTHETIC STUDIES ON THE IMMUNOSUPPRESSIVE AGENT FK-506: ENANTIOSELECTIVE SYNTHESIS OF A C22-C34 FRAGMENT

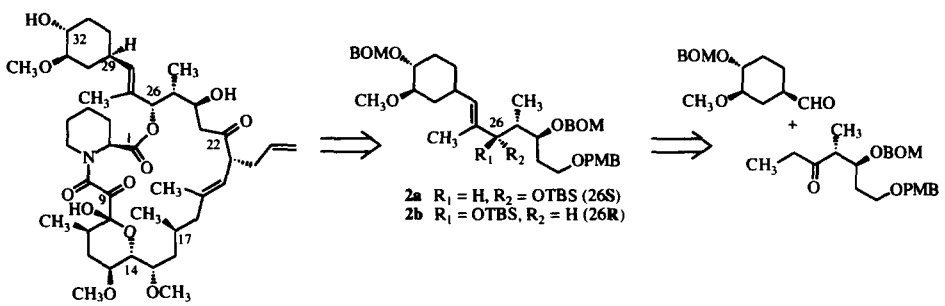
Robert K. Baker*, Kathleen M. Rupprecht*, David M. Armistead, Joshua Boger, Robert A. Frankshun, Paul J. Hodges, Karst Hoogsteen, Judith M. Pisano, and Bruce E. Witzel

Merck Research Laboratories
Department of Medicinal Chemistry
P.O. Box 2000, Rahway, New Jersey 07065-0900

Received 22 September 1997; accepted 29 October 1997

Abstract. The C28-C32 cyclohexyl group of the natural product, FK-506, was prepared enantioselectively from the iodolactone by replacement of iodide with *retention of configuration*. The C27-C28 trisubstituted olefin was introduced stereoselectively *via* a classical aldol/elimination sequence employing titanium enolate methodology. Elaboration of this chemistry has led to a synthesis of a C22-C34 fragment of the natural product.

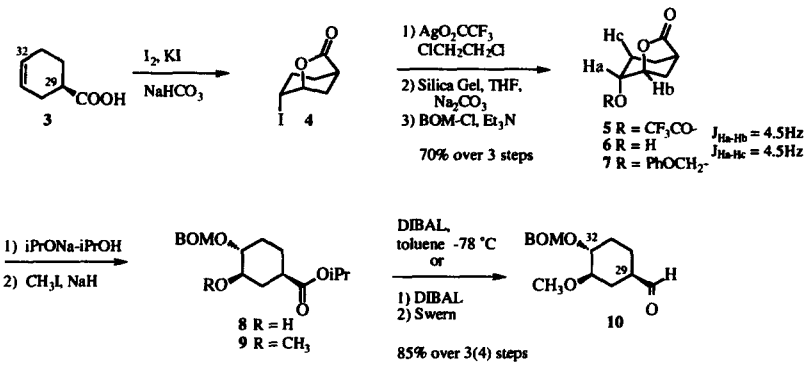
The use of FK-506 (**1**) in clinical settings, it potential as a chemical probe of the immune response, and its intriguing structure has sparked great interest in the synthetic community.[1] We first became interested in the synthesis of FK-506 to provide fragments and synthetic analogs for biological evaluation. X-ray crystallographic data from the FK-506 complex with one of its binding proteins (FKBP-12) indicates that the cyclohexyl fragment of FK-506 extends outside the protein envelope and is involved in the binding of this complex to a third component within the cell (calcineurin).[2] This report describes the stereoselective syntheses of a C22-C34 fragment (**2a**), which bears the natural (**S**) stereochemistry at C26 and a C22-C34 fragment (**2b**), which bears the unnatural (**R**) stereochemistry at C26. This allows for a macrocyclization or esterification process with retention or inversion of stereochemistry at C26, respectively, as a key step in the latter stages of a projected synthesis of FK-506.



1
FK-506

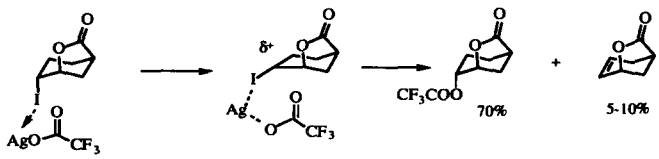
The starting material for the synthesis of the C28-C34 fragment was optically active (R)-3-cyclohexene-1-carboxylic acid, which was prepared by Diels-Alder condensation of butadiene with the acrylimide of (1R)-(+)-2,10-camphorsultam.[3,4] Following removal of the auxiliary, the 3-cyclohexene-1-carboxylic acid (**3**, 98% ee) was reacted with I_2 in the presence of KI, and $NaHCO_3$ buffer to afford the iodolactone (**4**) in 74% yield.[5] Although reaction of **4** with silver acetate in dimethylsulfoxide at 110 °C results in elimination of iodide,[6] we found that treatment of the iodolactone with 2.5 equivalents of silver trifluoroacetate in 1,2-dichloroethane at 53 °C resulted in replacement of the iodide with trifluoroacetate with retention of configuration at C32. The unstable trifluoroacetate (**5**) was not purified but was readily hydrolyzed to the hydroxy analog (**6**) in an overall yield of 70% by stirring **5** with silica gel in 1:1 tetrahydrofuran-0.01M Na_2CO_3 buffer (pH 8).

0040-4039/98/$19.00
PII: S0040-4039(97)10532-9

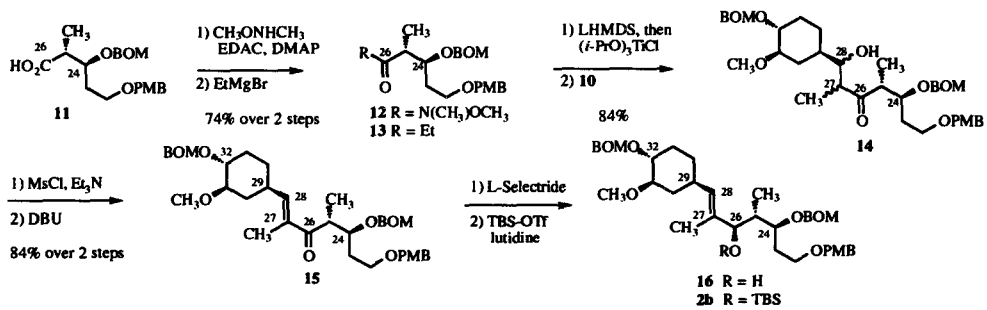


The ^{1}H NMR coupling patterns for H-3 and H-4 of **6** (and **5**) were identical to those of the iodolactone (**4**) and unlike those reported for *cis*-4-substituted lactones of that type.[5] The hydroxy group was protected as the benzyloxymethyl ether (**7**) and the lactone was opened to **8** in 93% yield using catalytic sodium isopropoxide in isopropanol.[7] Methylation of **8** with sodium hydride and methyl iodide in tetrahydrofuran afforded the appropriately substituted cyclohexane **9** in 96% yield from **7**.[8] Partial reduction of the ester of **9** with DIBAL-H afforded an 88% yield of aldehyde **10** that was identical to that obtained from exhaustive ozonolysis of 32-O-benzyloxymethyl-FK-506.

We have been intrigued by the mechanism of the iodide displacement. Because both **5** and **6** are stable to the reaction conditions, the olefin must form from the iodolactone. The reaction path (substitution *vs.* elimination) is temperature dependent, with minimal elimination (<10%) observed at 53 °C and as much as 35% elimination observed at temperatures above 65 °C. The reaction is also solvent dependent -- only elimination is observed in dimethylsulfoxide while no reaction was observed in ether solvents. In view of the close balance between the substitution and elimination pathways observed for **4** the reaction may be more S_N1 in nature and that as the Ag-I complex forms the trifluoroacetoxy group (still associated with the Ag^+ as an ion pair) attacks from the less hindered face, resulting in a net retention of configuration.[9, 10]



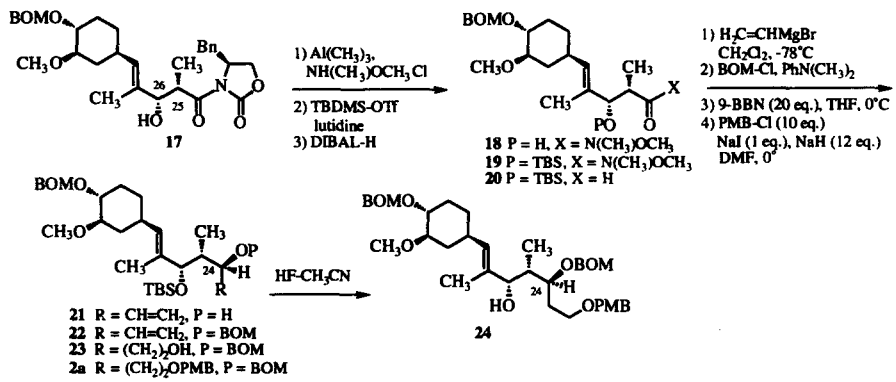
It was planned that the cyclohexyl fragment would be incorporated into the macrocycle backbone at a later stage in the synthesis using a classical aldol /elimination sequence as a method of stereoselectively introducing the C27-C28 trisubstituted olefin.



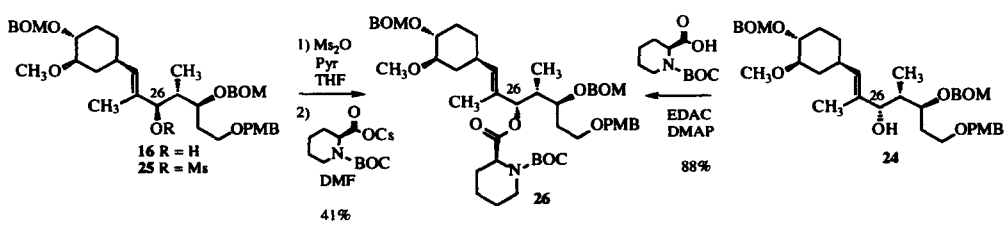
A C22-C27 fragment was constructed by the following sequence: Carboxylic acid **11**[11] was activated as the Weinreb amide **12** and then treated with ethylmagnesium bromide to give the ethyl ketone **13**.[12] Kinetic

deprotonation of this ketone followed by sequential addition of chlorotitanium triisopropoxide[13] and then aldehyde **10** gave the aldol adducts **14** as a 1:1 mixture of two of the four possible diastereomers. These are most likely the two *erythro* isomers that resulted from an unbiased facial attack on the aldehyde by the preferred[14] *E*-enolate derived from ketone **13**. Evidence for this was obtained when the separated diastereomers were mesylated and then treated with DBU. In both cases the *anti*-elimination protocol provided enone **15** as a single product. No epimerization or elimination at C25 was observed during this reaction sequence. Reduction of the enone **15** with L-Selectride® in THF at -78 °C gave a single product[15] which was assigned as **16** on the basis of the Felkin-Ahn model[16] and by comparison with a fragment of known relative stereochemistry at C26.

The C26-(S) isomer was prepared by the following sequence. The Evans aldol adduct **17**[17,18] was converted to the Weinreb amide **18** whose stereochemistry at C26 was confirmed by X-ray crystallography. Sequential protection of **18** and reduction gave aldehyde **20** which afforded a 2.5:1 mixture of C24 diastereomers (e.g. **22**) upon reaction with vinylmagnesium bromide. After protection of the C24 hydroxy group and hydroboration, alcohol **24** was separated from the minor C24 diastereomer by flash chromatography. Finally, protection of the primary hydroxy group (**2**) and removal of the TBS group gave **24**. Examination of the ^{13}C spectra of **16** and **24** reaffirmed the assignment of the stereochemical outcome of the enone reduction step.[19, 20]



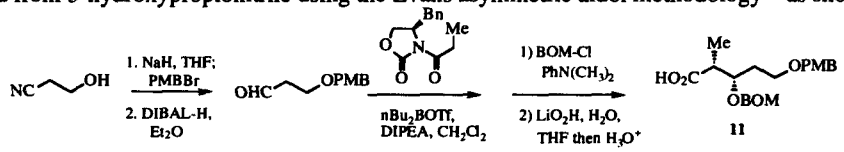
While esterification of the C26 hydroxy group with pipecolic acid occurs without complication, esterifications with larger fragments have been problematic.[21,22] Forming the ester bond through an inversion/esterification of the C26 hydroxy group of **16** should circumvent some of these issues. The C26 hydroxy group of **16** was activated with methanesulfonic anhydride and then the resulting mesylate **25** was reacted with the cesium salt of N-BOC-L-pipecolic acid[23] in DMF at 40 °C to afford a new product **26** whose mass spectrum incorporated both reacting fragments and whose NMR spectra were consistent with the C26-(S) ester. That the new ester **26** was identical to the product obtained by EDAC-mediated esterification of **24** with N-BOC-L-pipecolic acid confirmed the structural assignment.



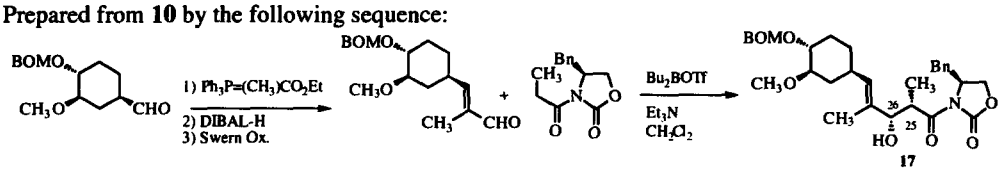
Acknowledgements: We would like to thank Drs. R. P. Volante and I. Shinkai for preprints of the supplementary material that accompanies their total synthesis publication, Dr. L. Colwell for mass spectral analyses and Mrs. J. E. Perkins and Mrs. J. T. Wu for microanalyses.

References and Notes:

1. For a review of syntheses of FK-506, see: Goulet, M.T.; Mills, S.G.; Parsons, W.H.; Rupprecht, K.M.; Wyvratt, M.J. "Chemistry of FK-506" Recent Progress in Chemical the Chemical Synthesis of Antibiotics and Related Microbial Products, Ed. J. Lukacs, Springer Verlag,**1993**, Volume 2, 141-212.
2. VanDuyne, G.D.; Standaert, R.F.; Karplus, P.A.; Schreiber, S.L. *Science* **1991**, *252*, 839-842; Milan, D.; Griffith, J.; Su, M.; Price, E. R.; McKeon, F. *Cell* **1994**, *79*, 437-447; Griffith, J.P.; Kim, J.L.; Kim, E.E.; Sintchak, M.D.; Thomson, J.A.; Fitzgibbon, M.J.; Fleming, M.A.; Caron, P.R.; Hsinao, K.; Navia, M.A. *Cell* **1995**, *82*, 507-522.
3. Oppolzer, W.; Chapuis, C.; Kelly, M.J. *Helv. Chim. Acta* **1983**, *66*, 2358-2361; Oppolzer, W.; Chapuis, C.; Bernardineli, G. *Helv. Chim. Acta* **1984**, 1397-1401.
4. All compounds were characterized by ^1H NMR, ^{13}C NMR and mass spectral analysis.
5. Grewe, R.; Heinke, A.; Sommer, C. *Chem. Ber.* **1956**, *89*, 1978-1988.
6. Kato, M.; Kageyama, M.; Reiko, T.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932-41.
7. Kamiyama, K.; Kobayashi, S.; Ohno, M. *Chem. Lett.* **1987**, 29-32.
8. Under the same conditions, the methyl ester of **8** gave 30% yield of alkylated product and 60% of the **7**.
9. For discussions about a similar displacement with iodohydroperoxides, see Bloodworth, A.J.; Bowyer, K. J.; Mitchell, J. C. *J. Org. Chem.* **1987**, *52*, 1124-1128. For these cases, the authors suggested a cyclic S_N2 mechanism with front-side attack to explain the stereospecificity of the displacements.
10. One would expect that delocalization of the unshared electrons of the adjacent oxygen substituent into the ester carbonyl would preclude participation in oxonium ion formation. (See Koçovsky, P. *J. Org. Chem.* **1988**, *53*, 5816-5819.)
11. Prepared from 3-hydroxypropionitrile using the Evans asymmetric aldol methodology[17] as shown below:



12. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
13. Aldol condensations in the absence of $ClTi(OiPr)_3$ gave lower conversions due to the reversible nature of the reaction. For example, see: Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.
14. For a review, see: Heathcock, C. H. "Asymmetric Synthesis." Ed. J. D. Morrison, Academic Press, **1984**; Volume 3, 111-212.
15. Reduction of **15** with DIBAL-H in THF at -78° C gave analogous results.
16. For a discussion of the Felkin model, see: Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry." Pergamon Press, New York, **1983**, 210.
17. Prepared from **10** by the following sequence:



18. For a review, see: Evans, D. A. *Aldrichimica Acta.* **1982**, *15*, 23.
19. Also, it should be noted that Swern oxidation of **2a** gave, as expected, enone **15**, thus confirming our assignment of stereochemistry at C24 in the Grignard addition.
20. An important observation was that direct access to **24** from enone **15**, using a "chelation controlled reduction": $Zn(BH_4)_2$, Et_2O, -40° C (Oishi, T.; Nakata, T. *Acc. Chem. Rec.* **1984**, *17*, 338), was denied to us. Instead, **16** was obtained in 82% yield.
21. Jones, A.B.; Villalobos, A.; Linde, R.G. II; Danishefsky, S.J. *J. Org. Chem.* **1990**, *55*, 2786-2797.
22. Goulet, M.T.; Hodkey, D.W. *Tetrahedron Lett.* **1991**, *32*, 4627-4630.
23. Wang, S.S.; Gisin, B.F.; Winter, D.P.; Makofske, R.; Kulesha, I.D.; Tzourgraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286-1287.