Pergamon

Tetrahedron Letters 39 (1998) 233–236

TETRAHEDRON LETTERS

SYNTHETIC STUDIES ON THE IMMUNOSUPPRESSIVE AGENT FK-506: CONSTRUCTION OF THE POLYCARBONYL REGION

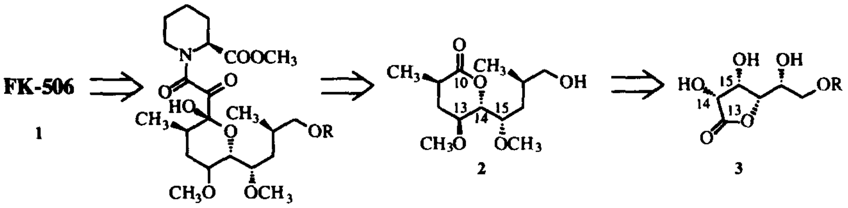
Kathleen M. Rupprecht*, Robert K. Baker, Joshua Boger, Alita A. Davis, Paul J. Hodges, and Joanne F. Kinneary

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

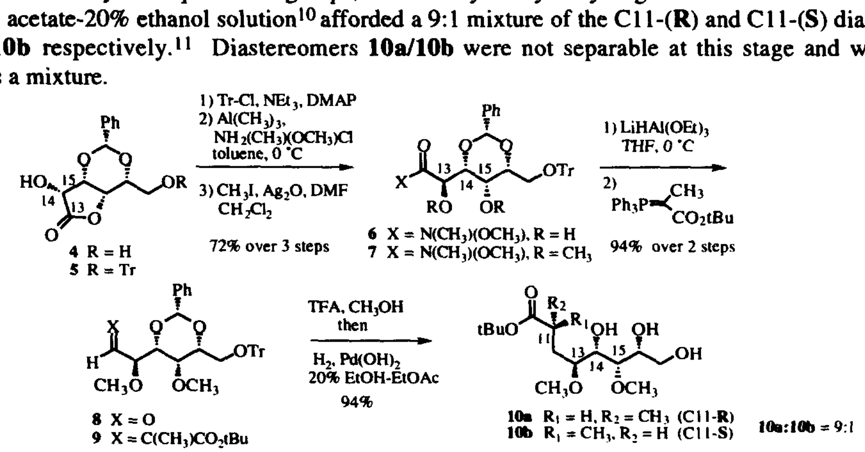
Received 22 September 1997; accepted 29 October 1997

Abstract: The C10-C17 fragment of the natural product, FK-506, has been stereoselectively synthesized from L-gulose. Methods for elaboration to the C1-C17 fragment and installation of the C9 carbonyl group are described.

Interest in the chemistry of the immunosuppressive agent FK-506 stems from its use in clinical settings and as a chemical probe of the immune response as well as from its intriguing structure, particularly the C8-C10 tricarbonyl region.[1] While several methods leading to the construction of this region have been described, additional investigation into the chemistry of this region was required in order to fully explore the biological importance of this unusual structure.[2,3] These construction studies were done with model fragment **2**, which encompasses the C10-C18 region of FK-506.

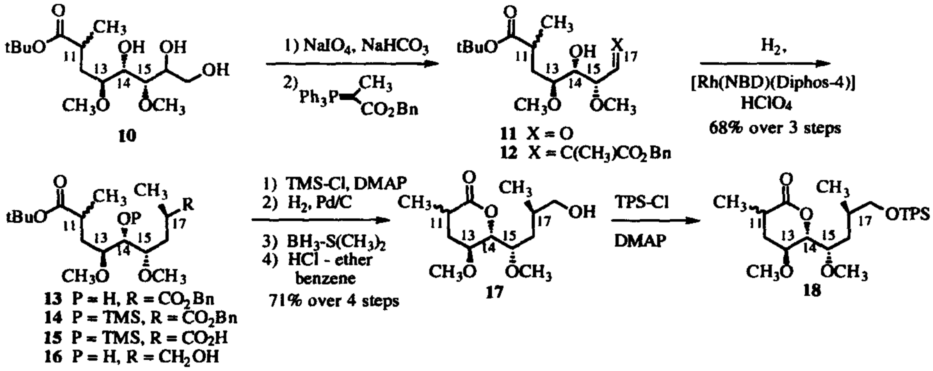


Synthesis of **2** began with the known 4,6-O-benzylidene-D-gulono-1,4-lactone **4**.[4] The primary hydroxy group of **4** was protected as the trityl ether **5** and the lactone was opened to amide **6** using a modification of the Weinreb procedure.[5,6] Amide **6** readily recyclized to **5** upon standing, and was therefore immediately permethylated under neutral conditions (CH_3I, Ag_2O, DMF)[7] to afford the crystalline hydroxamate **7**. Reduction of **7** with lithium triethoxyborohydride at 0 °C gave aldehyde **8**, which was converted to **9** by reaction with t-butyl 2-(triphenylphosphoranylidene)propanoate.[8,9] Acid catalyzed removal of the trityl and benzylidene protective groups, followed by catalytic hydrogenation of the crude mixture in an 80% ethyl acetate-20% ethanol solution[10] afforded a 9:1 mixture of the C11-(**R**) and C11-(**S**) diastereomers, **10a** and **10b** respectively.[11] Diastereomers **10a/10b** were not separable at this stage and were carried forward as a mixture.

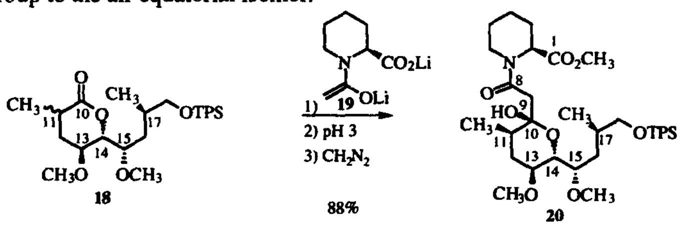


0040-4039/98/$19.00 © 1997 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(97)10533-0

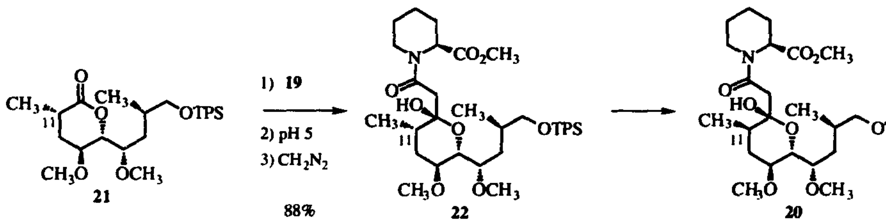
Oxidation of the diol of **10** with buffered sodium periodate afforded the unstable α-methoxy-aldehyde **11**, which was immediately condensed with benzyl 2-(triphenylphosphoranylidene)propanoate[12] to give acrylate **12**. Hydroxy-directed hydrogenation using a soluble rhodium catalyst[13] afforded **13** in 99% de by gas chromatography. The yield of **13** was 68% over the three step sequence. Attempts towards direct hydrogenation of the benzyl ester of **13** were complicated by cyclization with the C14-OH. Instead, the C14-OH was protected as the trimethylsilyl ether **14**, which was smoothly hydrogenated to afford crystalline acid **15**. The carboxy group of **15** was selectively reduced to the C18-OH **16** with borane-methylsulfide and the excess reagent was removed azeotropically with methanol. Addition of anhydrous HCl in ether-benzene to the crude reaction mixture removed the C14-trimethylsilyl ether, deprotected the C10-t-butyl ester, and effected lactonization of the C10 carboxy group with the C14-OH to afford **17** in 83% yield from **13**. Because lactone **17** was prone to head-to-tail polymerization, the C18-OH was immediately protected as the t-butyldiphenylsilyl ether **18**, whose C11 diastereomers were easily separated by silica gel flash chromatography.



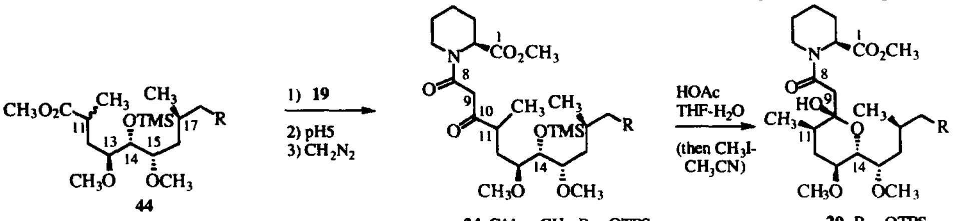
It was anticipated that the C11-(R) diastereomer (<15% of the material prepared) might be converted to its C11-(S) diastereomer by equilibration under either acidic or basic conditions but that step proved unnecessary. The dilithium salt of N-acetyl-L-pipecolic acid (**19**) added to mixture **18** to afford a single product by ^1H and ^{13}C NMR, a finding that suggested that the ketal of **20** was opening to afford equilibration of the C11 methyl group to the all-equatorial isomer.



That the C11 diastereomers were spectroscopically different was demonstrated by generation of the C11 epimer **22** by addition of the enolate to a sample of pure **21** followed by careful neutralization of the reaction mixture to pH 5. The ^1H NMR of a fresh sample of this material indicated a new compound, **22**, which was different from that of authentic **20**, but after 24h, the spectra had become identical to that of authentic **20**.

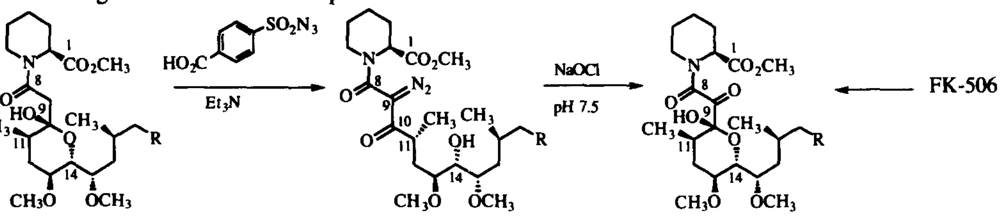


Such equilibria under acidic conditions have been described[14] and the equilibration was verified through the following sequence. The lactone **18** was opened to the methyl ester by stirring in methanol and the C14 hydroxy group was trapped as the trimethylsilyl ether **23**. The C11-epimers formed by addition of **19** were separated by flash chromatography and were easily differentiable by ^{1}H and ^{13}C NMR. Removal of the trimethylsilyl ethers of **24** and **25** under mild acidic condition afforded **20** as the only detectable product.



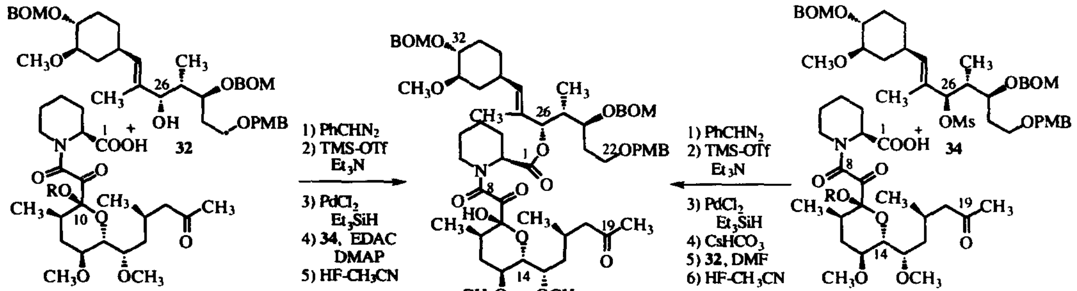
23 R = OTPS
27 R = C(S(CH$_2$)$_3$S)CH$_3$
24 C11-α-CH$_3$, R = OTPS
25 C11-β-CH$_3$, R = OTPS
20 R = OTPS
28 R = C(O)CH$_3$

The original strategy was to prepare all of the C9 oxidation levels directly from a common intermediate but oxidation of the C9-position was complicated by participation of the C14-OH substituent and by the tendency of the tricarbonyl group to rearrange under the oxidation conditions. A diazo transfer to the 9-position of **20** formed the 9-diazo analog **26**, which existed solely as the β-ketoamide. Oxidation of **26** with NaOCl (buffered to pH 7.5 with acetic acid) afforded a new product whose ^{1}H and ^{13}C NMR and mass spectra were consistent with structure **2**.[15] That this method did, in fact, produce the tricarbonyl fragment was verified by repetition using a C10-C19 fragment (**27**) that had been obtained from degradation of FK-506[1] whose C18 carbonyl group of the fragment had been protected as the dithioketal using 1,3-propanedithiol and BF_3 etherate. Enolate addition to protected lactone **27** afforded the C1-C19-skeleton **28** after deprotection of the thioketal with methyl iodide/acetonitrile. Diazotransfer occurred as before to afford the β-ketoamide **29**, which was oxidized with buffered bleach to afford a product that was identical to an authentic sample of **30** obtained via degradation of the natural product[1].



20 R = OTPS
28 R = C(O)CH$_3$
26 R = OTPS
29 R = C(O)CH$_3$
2 R = OTPS
30 R = C(O)CH$_3$

While esterification of the C26 hydroxy group with pipecolic acid occurs without problem, esterifications with larger fragments have been problematic.[16,17]



30 R = H
31 R = TMS
28%
33
34%
30 R = H
31 R = TMS

To suppress undesired reactions with the tricarbonyl region, the C10 hydroxy group was first protected as the trimethylsilyl ether in a 3-step sequence: Carboxy group of acid **30**[1] was esterified with phenyldiazomethane;

the C10 hydroxy group was silylated with trimethylsilyl triflate/triethylamine; and the carboxy group was regenerated with $PdCl_2$/triethylsilane. EDAC-mediated esterification with alcohol **32**[3] afforded **33**, whose C10 silyl group was removed by treatment with HF in acetonitrile in 28% overall yield from **30**. Alternatively, careful neutralization of acid **31** with $CsHCO_3$ afforded the corresponding cesium salt, which reacted in DMF[18] with mesylate **34**[3] to give the same product **33** in 34% overall yield after removal of the C10 silyl group.

Additional synthetic and degradative studies of FK-506 will be described in future reports.

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. K. Wilson for FT-IR spectra, Dr. L. Colwell for mass spectral analyses and Mrs. J. E. Perkins and Mrs. J. T. Wu for microanalyses.

References and Notes:

1. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031; Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, 1256; Ochiai, T.; Nagata, M.; Nakajima, K.; Suzuki, T.; Sakamoto, K.; Enomoto, K.; Gunji, Y.; Uematsu, T.; Goto, T.; Hori, S.; Kenmochi, T.; Nakagouri, T.; Asano, T.; Isono, K.; Hamaguchi, K.; Tsuchida, H.; Nakahara, K.; Inamura, N.; Goto, T. *Transplantation*, **1987**, *44*, 729; Inamura, N.; Nakahara, K.; Kino, T.; Goto, T.; Aoki, H.; Yamaguchi, I.; Kohsaka, M.; Ochiai, T. *Transplantation*, **1988**, *45*, 206.
2. 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.
3. Baker, R.K.; Rupprecht, K.M.; Armistead, D.A.; Boger, J.; Frankshun, R.A.; Hodges, P.J.; Hoogsteen, K.; Pisano, J.M.; Witzel, B.E. *accompanying communication*, **1997.**
4. Crawford, T.C. US Patent 4,111,958, **1978.**
5. All compounds were characterized by ^{1}H NMR,^{13}C NMR and mass spectral analysis.
6. Levin, J.I.; Turos, E.; Weinreb, S.M. *Syn. Commun.* **1982**, *12*, 989; Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815; Basha, A.; Lipton, M; Weinreb, S.M. *Tetrahedron Lett.* **1977**, 4171.
7. Kuhn, R.; Baer, H. *Chem. Ber.* **1956**, *89*, 504.
8. Stotter, P.L.; Hill, K.A. *Tetrahedron Lett.* **1975**, 1679.
9. All purifications were effected by crystallization (for **4**, **5**, **6**, and **7**) or by a crude filtration through silica gel (to separate methoxytriphenylmethane from acrylate **9**).
10. We believe the stereoselection in this reduction results from coordination of the catalyst with the 14-hydroxy group of **9**. Hydrogenation with methanol as solvent results in a 1:1 mixture of **10a** and **10b**.
11. Hydrogenation of the partially protected acrylate required more forcing conditions, and the C10-C11 olefin was reduced prior to hydrogenolysis of the benzylidene substituent. When the benzylidene group is present, the acrylate shows a facial selectivity opposite to that of **9**, and hydrogenation resulted in a 1: 4 diastereomeric mixture of **10a** and **10b**, even when methanol was used as the solvent.
12. Montgomery, J.A.;Thomas, H.J. *J. Org. Chem.* **1981**, *46*, 594.
13. Melillo, D. G.; Larsen, R. D.; Mathre, D. J.;Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5243-5250.
14. Schreiber, S. L.; Hulin, B. *Tetrahedron Lett.* **1986**, *27*, 4561-4564.
15. For oxidation of diazo compounds see: Curci, R.; DiFuria, F.; Ciabattoni, J.; Concannon, P.; *J. Org. Chem.* **1974**, *39*, 3295-3297; Baganz, H.; May, H. J. *Chem. Ber.* **1966**, *99*, 3766-3370.
16. Jones, A.B.; Villalobos, A.; Linde, R.G. II; Danishefsky, S.J. *J. Org. Chem.* **1990**, *55*, 2786-2797.
17. Goulet, M.T.; Boger, J. *Tetrahedron Lett.* **1990**, *31*, 4845-4848; Goulet, M.T.; Hodkey, D.W. *Tetrahedron Lett.* **1991**, *32*, 4627-4630.
18. 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.