Tetrahedron Letters, Vol.32, No.1, pp 53-56, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

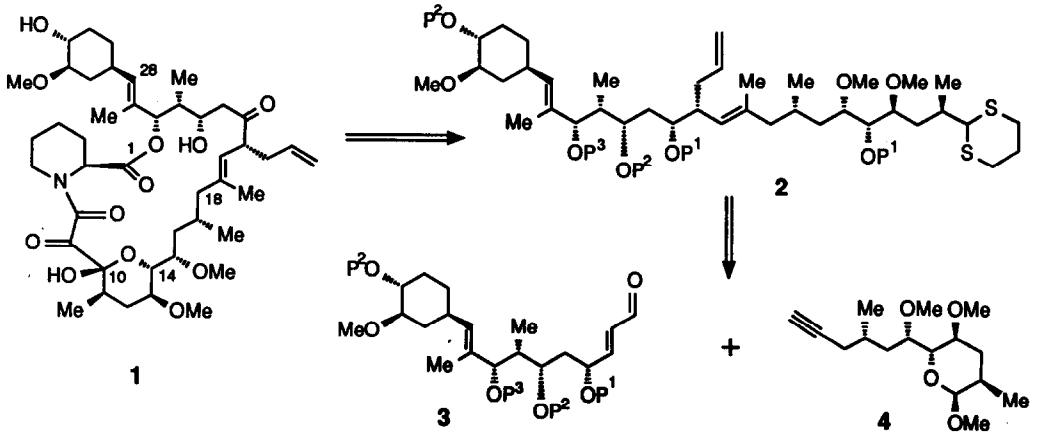
AN ENANTIOSELECTIVE SYNTHESIS OF THE C(10) TO C(20) FRAGMENT OF FK506

Martin E. Maier* and Bärbel Schöffling
Fakultät Chemie, Universität Konstanz
Postfach 5560, D-7750 Konstanz, Germany

Summary: The synthesis of the C(10) to C(20) fragment **4** of FK506 from (4S)-4-[(*tert*-butyldimethylsilyl)-oxymethyl]-4-butanolide (**9**) is described. A key reaction is the chelation controlled addition of 2-lithio-4-methyl-furan (**15b**) to aldehyde **8**.

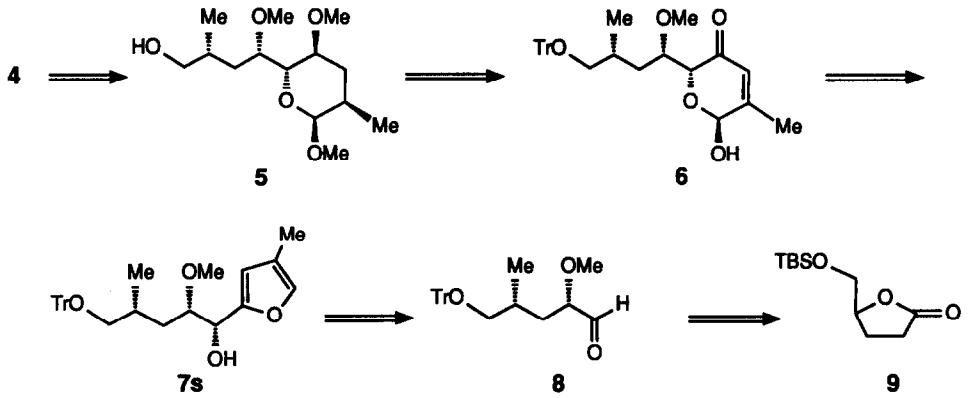
Recent biological studies regarding the mode of action of the immunosuppressive FK506 (**1**) revealed some striking similarities to the clinically used Cyclosporin A (CsA). Like the cyclic peptide CsA, the macrolide FK506 functions by inhibiting the transcription of early T cell activation genes.[1] Both compounds bind to cytosolic proteins with peptidyl-prolyl *cis-trans* isomerase activity (PPIases).[2] It was also found that FK506 binds to the corresponding binding protein in a noncovalent manner, probably with its α,β-diketoamide hemiketal portion.[3] PPIases, which are widespread in nature,[4] are involved in the control of protein folding during the process of protein biosynthesis.[4] Because FK506 and CsA bind to different proteins with high specificity, it was suggested that there might exist a whole family of PPIases, each of which controls the folding of a specific group of proteins.[2,5] Owing to this biological significance, the potential clinical use[6] and challenging structural features,[7] FK506 also became the subject of intensive synthetic studies.[8,9] Our intermediate goal in this area is the synthesis of a C(10)-C(34) fragment **2** (Scheme 1). This in turn, could be used for the incorporation of modified C(1)-C(9) substructures, thus allowing further structure activity studies. In addition to the synthesis of a C(28)-C(34) fragment,[9h] we now report an efficient synthesis of the C(10)-C(20) fragment **4**. This might be coupled with **3** using recently described methodology.[10]

Scheme 1



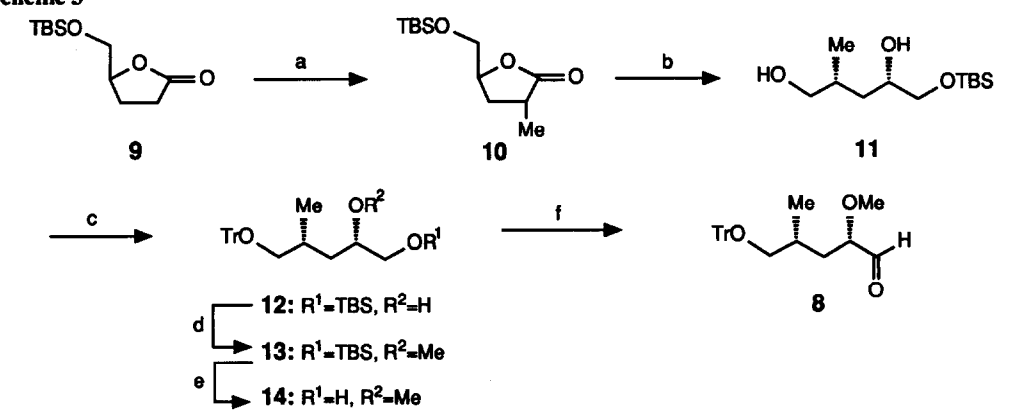
The retrosynthetic analysis of **4** is shown in Scheme 2. Compound **4** might originate from **5** which in turn could be derived from **6**. Pyranone **6** is the product of an oxidative rearrangement of furfuryl alcohol **7s**.[11] Further straightforward analysis leads via aldehyde **8** to the protected γ-lactone **9** which is available from L-glutamic acid.[12] Based on symmetry considerations, aldehyde **8** might serve also as C(10)-C(14) part. However, this would require an *anti*-selective addition of a metallated furan.[13]

Scheme 2



The preparation of aldehyde **8** is outlined in Scheme 3. Methylation[14] of lactone[12] **9** (LDA, THF, MeI) gave compound **10** ($[\alpha]^{23}_D$ +28.2° (*c* 0.5 acetone)) with high diastereoselectivity (90:10) in 75% yield. The methylated lactone **10** was reduced with borane dimethyl sulfide complex[15] to diol **11** in 69% yield. Protection of the primary hydroxyl group of **11** with trityl chloride (82%) to give **12** followed by methylation of the secondary hydroxyl group furnished **13** (87%). Desilylation of **13** led to alcohol **14** (88%, $[\alpha]^{23}_D$ -11.9° (*c* 1.0 acetone)) which was oxidized to the aldehyde **8** ($[\alpha]^{23}_D$ -30.8° (*c* 1.0 acetone)) in 83% yield.[16]

Scheme 3

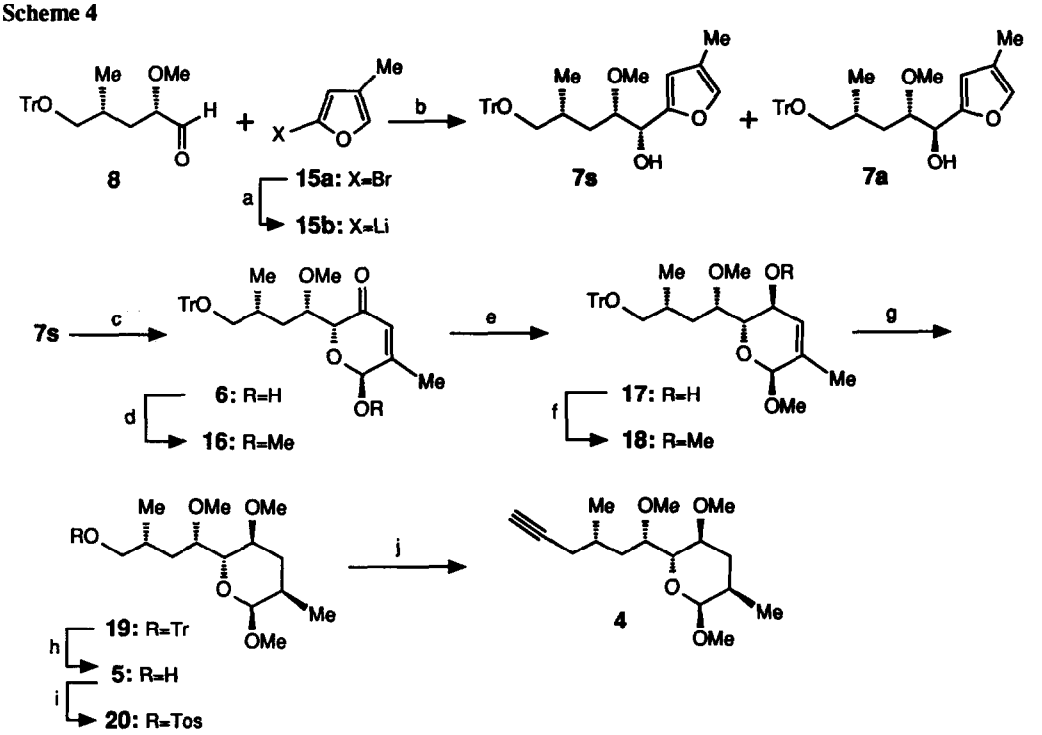


Reagents and conditions: (a) 1.1 equiv of LDA, 1.0 equiv of MeI, THF, -78 °C, 2 h, 75%; (b) 0.7 equiv of BH_3-SMe_2, THF, 23 to 65 °C, 2 h, 69%; (c) 1.2 equiv of Ph_3CCl, pyridine/CH_2Cl_2 (1:1), 23 °C, 4 d, 82%; (d) 2.0 equiv of NaH, 6.0 equiv of MeI, 10 equiv of DMEU, THF, -10 to 23 °C, 24 h, 87%; (e) 1.5 equiv of TBAF, THF, 23 °C, 2 h, 88%; (f) 4.4 equiv of DMSO, 2.2 equiv of $(COCl)_2$, 9.2 equiv of NEt_3, CH_2Cl_2, -50 °C, 1.5 h, 83%.

We found that the stereochemical course of the addition of 2-lithio-4-methyl-furan[17] (**15b**) to aldehyde **8** was highly dependent on solvents and added metal salts (Scheme 4). The lithiated furan **15b** was prepared by halogen-metal exchange of 2-bromo-4-methyl-furan[17] (**15a**) with *n*-butyllithium. In the absence of additional

metal salts, reaction of **8** with **15b** (1.0 equiv.) in THF (-78 °C, 30 min) gave a mixture of *syn* and *anti* alcohols **7s** and **7a** in a ratio[18] of 39:61 (40% yield). In the presence of 1.3 equivalents of zinc(II) bromide, (THF, 0 °C, 12 h) the *syn/anti* ratio improved to 87:13 (54% yield). Using diethyl ether as solvent and 2.0 equivalents of zinc(II) bromide, the reaction proceeded in a highly stereoselective manner (*syn/anti* > 95:5) and in high yield (10 g scale). The ^{1}H NMR spectrum showed only the presence of **7s** ($[\alpha]^{23}_D$ -2.9° (*c* 1.0 acetone)). This latter result is in accordance with a chelation controlled addition.[19]

Scheme 4



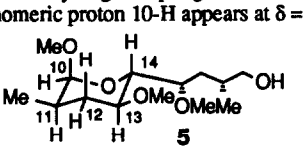
Reagents and conditions: (a) 1.0 equiv of *n*-BuLi, Et_2O, -78 to -20 °C; (b) add 2.0 equiv of $ZnBr_2$ to **15b**, then 0.8 equiv of **8**, Et_2O, -20 °C, 2h, 70% (90% based on recovered **8**); (c) 0.015 equiv of $VO(acac)_2$, 1.2 equiv of *t*-BuOOH, CH_2Cl_2, 23 °C, 2.5 h, 73%; (d) 2.0 equiv of $HC(OMe)_3$, 0.2 equiv of BF_3-Et_2O, Et_2O, 0 to 23 °C, 1.5 h, 51%; (e) 1.6 equiv of $NaBH_4$, MeOH, -20 °C, 4 h, 65%; (f) 2.0 equiv of NaH, 6.0 equiv of MeI, 10 equiv of DMEU, THF, -5 to 23 °C, 2.5 h, 86%; (g) H_2, 5% Pd on Al_2O_3, THF, 23 °C, 2.5 h, 94%; (h) excess Na, THF-NH_3, EtOH, -50 °C, 1 h, 88%; (i) 1.2 equiv of TosCl, 3.2 equiv of pyridine, CH_2Cl_2, 23 °C, 24 h, 75%; (j) 2.0 equiv of $LiCCH/H_2NCH_2CH_2NH_2$, 2.0 equiv of HMPA, THF, 0 to 23 °C, 71%.

Compound **7s** was then subjected to oxidative rearrangement with vanadylacetylacetonate/*tert*-butyl hydroperoxide[20] in dichloromethane to give the pyranone **6** as a single isomer (73%). Protection of the anomeric center (Et_2O, $HC(OMe)_3$, BF_3-Et_2O)[21] afforded **16** ($[\alpha]^{23}_D$ +4.6° (*c* 1.0 acetone)). For the introduction of the remaining stereogenic centers, we took advantage of the conformationally rigid pyran matrix. Thus, sodium borohydride reduction of **16** produced exclusively the equatorial alcohol **17** (65%) which was methylated to give **18** (86%, $[\alpha]^{23}_D$ +46.6° (*c* 1.0 acetone)). Catalytic hydrogenation of **18** (H_2, Pd/Al_2O_3, THF) gave the desired **19** as the major product (ratio 91:9, 94% yield). Further elaboration of **19** to **4** proceeded uneventfully. Detritylation[12b] (Na, THF-NH_3) gave alcohol **5**[22] ($[\alpha^{23}_D$ +116.8° (*c* 0.5 acetone)) which was converted to the tosylate **20**. Finally, treatment of **20** with lithium acetylide ethylenediamine complex in THF/HMPA[23] gave alkyne **4** ($[\alpha]^{23}_D$ +122.8° (*c* 0.5 acetone)).

Acknowledgement: Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We also thank Professor Schmidt and his group for allowing us to use their NMR- and HPLC equipment.

References and Notes

1. M.J. Tocci, D.A. Matkovich, K. A. Collier, P. Kwok, F. Dumont, S. Lin, S. Degudicibus, J.J. Siekierka, J. Chin, N.I. Hutchinson, *J. Immunology*, **143** (1989) 718.
2. (a) J.J. Siekierka, S.H.Y. Hung, M. Poe, C.S. Lin, N.H. Sigal, *Nature* **341** (1989) 755. (b) M. W. Harding, A. Golat, D.E. Uehling, S.L. Schreiber, *Nature* **341** (1989) 758.
3. M.K. Rosen, R.F. Standaert, A. Galat, M. Nakatsuka, S.L. Schreiber, *Science* **248** (1990) 863.
4. (a) G. Fischer, F.X. Schmid, *Biochemistry* **29** (1990) 2205. (b) M. Tropschug, E. Wachter, S. Mayer, E.R. Schönbrunner, F.X. Schmid, *Nature* **346** (1990) 674 and references therein.
5. A. Maelicke, *Nachr. Chem. Tech. Lab.* **37** (1989) 1299 and references therein.
6. A.W. Thomson, *Immunology Today* **11** (1990) 35.
7. (a) T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiotics* **40** (1987) 1249. (b) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, T. Taga, *J. Am. Chem. Soc.* **109** (1987) 5031.
8. For total syntheses and formal total syntheses of FK506, see: (a) T.K. Jones, R.A. Reamer, R. Desmond, S.G. Mills, *J. Am. Chem. Soc.* **112** (1990) 2998. (b) A.B. Jones, A. Villalobos, R.G. Linde II, S.J. Danishefsky, *J. Org. Chem.* **55** (1990) 2786. (c) M. Nakatsuka, J. Ragan, T. Sammakia, D.B. Smith, D.E. Uehling, S.L. Schreiber, *J. Am. Chem. Soc.* **112** (1990) 5583. (d) R.L. Gu, C.J. Sih, *Tetrahedron Lett.* **31** (1990) 3287.
9. For a compilation of early synthetic studies, see ref. 8c.
   Recent syntheses of fragments: (a) P. Kocienski, M. Stocks, D. Donald, M. Perry, *Synlett* **1990**, 38. (b) A.V. Rama Rao, T.K. Chakraborty, K. Laxma Reddy, *Tetrahedron Lett.* **31** (1990) 1439. (c) A.V. Rama Rao, T.K. Chakraborty, A.V. Purandare, *Tetrahedron Lett.* **31** (1990) 1443. (d) M. Stocks, P. Kocienski, D. Donald, *Tetrahedron Lett.* **31** (1990) 1637. (e) R.G. Linde II, M. Egbertson, R.S. Coleman, A.B. Jones, S.J. Danishefsky, *J. Org. Chem.* **55** (1990) 2771. (f) A. Villalobos, S.J. Danishefsky, *J. Org. Chem.* **55** (1990) 2776. (g) R.E. Ireland, P. Wipf, T.D. Roper, *J. Org. Chem.* **55** (1990) 2284. (h) M.E. Maier, B. Schöffling, *Tetrahedron Lett.* **31** (1990) 3007. (i) R.L. Gu, C.J. Sih, *Tetrahedron Lett.* **31** (1990) 3283.
10. R.E. Ireland, P. Wipf, *J. Org. Chem.* **55** (1990) 1425.
11. For a summary of this strategy, see: S.F. Martin, C. Gluchowski, C.L. Campbell, R.C. Chapman, *Tetrahedron* **44** (1988) 3171 and references therein.
12. (a) M. Okabe, R.C. Sun, S.Y. K. Tam, L. J. Todaro, D.L. Coffen, *J. Org. Chem.* **53** (1988) 4780. (b) For the use of L-glutamic acid as chiral template in natural product synthesis, see: S. Hanessian, N.G. Cooke, B. DeHoff, Y. Sakito, *J. Am. Chem. Soc.* **112** (1990) 5276 and references therein.
13. For some recent examples of the addition of metallated furans to α-alkoxy-aldehydes, see: (a) K. Suzuki, Y. Yuki, T. Mukaiyama, *Chem. Lett.* **1981**, 1529. (b) S. Pikul, J. Raczko, K. Ankner, J. Jurczak, *J. Am. Chem. Soc.* **109** (1987) 3981. (c) K. Mori, H. Kikuchi, *Liebigs Ann. Chem.* **1989**, 963.
14. K. Tomioka, Y.S. Cho, F. Sato, K. Koga, *J. Org. Chem.* **53** (1988) 4094.
15. H.C. Brown, Y.M. Choi, S. Narasimhan, *J. Org. Chem.* **47** (1982) 3153.
16. A similiar aldehyde has recently be prepared using a chemoenzymatic approach: see ref. 9i.
17. D.W. Knight, D.C. Rustigde, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 679.
18. Ratios were determined by ^{1}H NMR integration of the 14-H (FK506 numbering) protons (**7s**: $\delta = 4.42$, $J = 5.9$ Hz; **7a**: $\delta = 4.80$, $J = 4.3$ Hz).
19. M.T. Reetz, *Angew. Chem.* **96** (1984) 542; *Angew. Chem. Int. Ed. Engl.* **23** (1984) 556 and references therein.
20. D.Y. Jackson, *Synth. Commun.* **18** (1988) 337.
21. O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron* **27** (1971) 1973.
22. The stereochemistry in the pyran ring was determined by analysis of the ^{1}H NMR spectrum (benzene-d_6) of **5**. The trans-diaxial orientation of 13-H ($\delta = 3.41$) and 14-H ($\delta = 3.58$) is evident from the coupling constant $J_{13,14} = 9.3$ Hz. In addition, 12-H_{ax} ($\delta = 1.50$) shows only large coupling constants $J_{11,12ax} = J_{12ax,13} = 11.2$ Hz, thus proving the configuration at C-11. The anomeric proton 10-H appears at $\delta = 4.42$ ($J_{10,11} = 2.9$ Hz).



5

23. A. Takle, P. Kocienski, *Tetrahedron* **46** (1990) 4503.

(Received in Germany 21 September 1990)