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FK-506 SYNTHETIC STUDIES. 3. AN EFFICIENT ASYMMETRIC SYNTHESIS OF THE C(24)-C(34) FRAGMENT OF FK-506, FR-900520, AND FR-900523

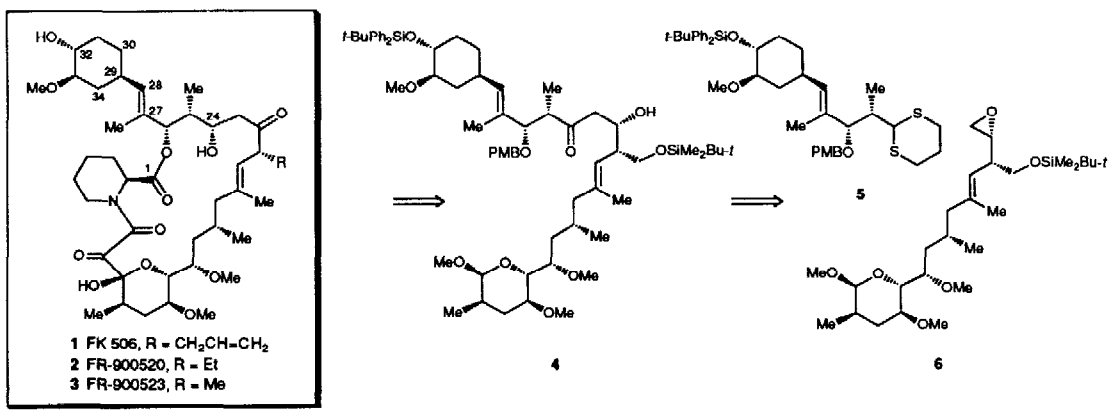
Amos B. Smith, III,* Karl J. Hale, Leif M. Laakso, Kwunmin Chen, and Antoni Riéra

Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

Summary: An efficient asymmetric synthesis of the C(24)-C(34) fragment of the FK-506 family of immunosuppressants has been achieved.

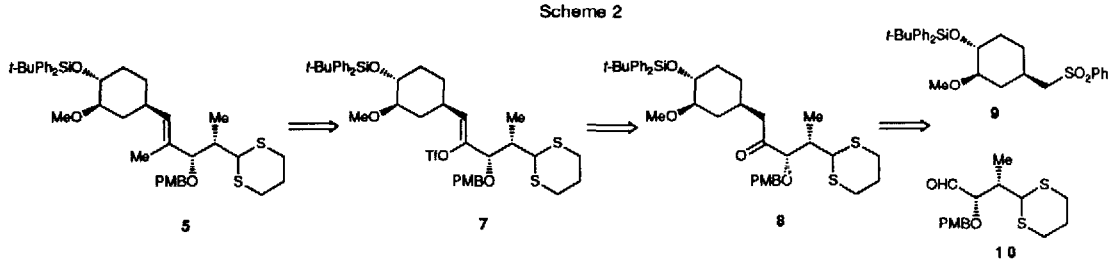
The growing medical,[1] bioorganic,[2] and synthetic[3] interest in the recently isolated immunosuppressants FK-506 (**1**),[4] FR-900520 (**2**), and FR-900523 (**3**)[5] prompts us to report our approach to an intermediate (**5**) corresponding to the C(24)-C(34) fragment of these macrolides.[6] Our strategy (Scheme 1) rests upon the proposed opening of epoxide **6** with the anion derived from **5**, or a related acyl anion equivalent; this tactic was devised to allow ready access to β-hydroxy ketone **4** after unmasking of the carbonyl group. Hydroxyl-directed reduction of **4** with tetramethylammonium triacetoxyborohydride would then effect stereocontrolled introduction of the C(24) center.[7]

Scheme 1



Inspection of the C(24)-C(34) segment reveals a number of challenging topographical features, not the least of which is the E trisubstituted olefin at C(27,28). Our plan for securing the E geometry (Scheme 2) called for displacement of the triflate moiety in **7** with retention of configuration, employing lithium dimethylcuprate according to the procedure of

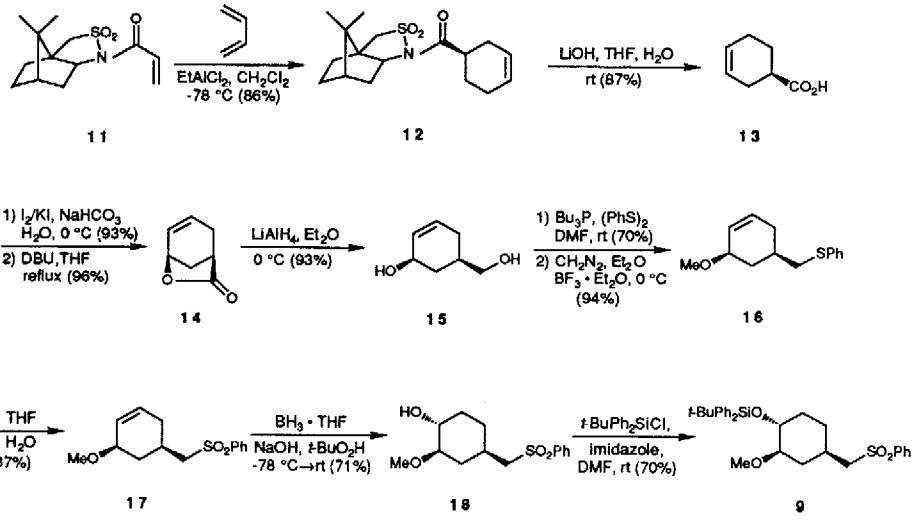
Scheme 2



McMurry.[8] Dreiding models of ketone **8** and of the two enolates expected to arise upon kinetic deprotonation[8] at C(28), as well as mechanistic considerations,[9] suggested that generation of the Z isomer leading to enol triflate **7** would be more favorable. Further disconnection of **8** pointed to sulfone **9** and aldehyde **10** as suitable progenitors.

The synthesis of sulfone **9** (Scheme 3) began with a Lewis acid-catalyzed, asymmetric Diels-Alder reaction of 1,3-butadiene with homochiral sultam **11**.[10] This afforded acid **13**[12] in good overall yield and enantiomeric purity (93% ee) after base-promoted removal of the chiral auxilliary. Iodolactonization and DBU-induced elimination[12] of the derived iodide[12] gave unsaturated lactone **14** {$[\alpha]_D^{22}$ +181.6° (*c* 1.08, $CHCl_3$); lit.[12] $[\alpha]_D^{23}$ +179.2° (*c* 9.76, $CHCl_3$)}, which in turn was reduced to diol **15**[11] with lithium aluminum hydride in ether. Treatment of **15** with tri-*n*-butylphosphine and diphenyldisulfide in

Scheme 3

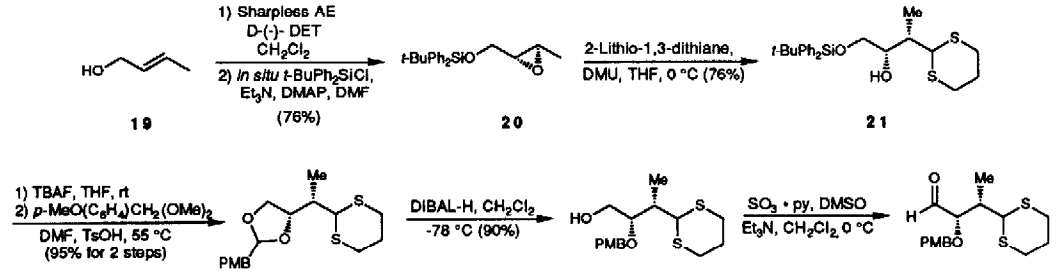


DMF[13] at room temperature selectively converted the primary alcohol to the corresponding thiophenyl ether. The remaining hydroxyl was methylated with ethereal diazomethane and BF_3,[14] and the thioether moiety oxidized with oxone to give **17**.[11a] Previous work with 3-alkoxycyclohexene derivatives revealed that hydroboration/oxidation offers a convenient protocol for trans installation of hydroxyl vicinal to the alkoxy group.[15] We therefore subjected **17** to these conditions; to our delight, **18**[11a] was obtained as the major component of a three-product mixture (17.5:1.7:1.0 by HPLC analysis). Flash chromatography furnished pure **18** in 71% yield. Silylation with *t*-butyldiphenylchlorosilane and imidazole in DMF completed the synthesis of **9** {$[\alpha]_D^{20}$ -16.4° (*c* 1.13, $CHCl_3$); mp 105.5-106.5 °C};[11] the structure was verified by single-crystal X-ray analysis.[16]

Our approach to aldehyde **10** (Scheme 4) began with a Sharpless asymmetric epoxidation of crotyl alcohol **19** to provide **20**[11] in 76% yield after *in situ* silylation.[17] Treatment of the latter with excess 2-lithio-1,3-dithiane in tetrahydrofuran, employing DMPU as a cosolvent,[18] led exclusively to the C(3)-alkylated product (**21**)[11] in 76% yield. The direct protection of **21** as its *p*-methoxybenzyl ether proved problematic under a variety of conditions. Accordingly, we opted for a three-step sequence involving desilylation with TBAF, conversion of the resulting diol to the *p*-methoxybenzylidene acetal (**22**),[11] and reduction with DiBAL-H;[19] the result was a 5:1 mixture of regioisomers in which the desired product (**23**)[11] predominated.

Although, oxidation of **23** to **10** initially was complicated by facile epimerization at the α-center, success was eventually achieved by employing an excess of the SO_3-pyridine-DMSO complex and triethylamine.[20]

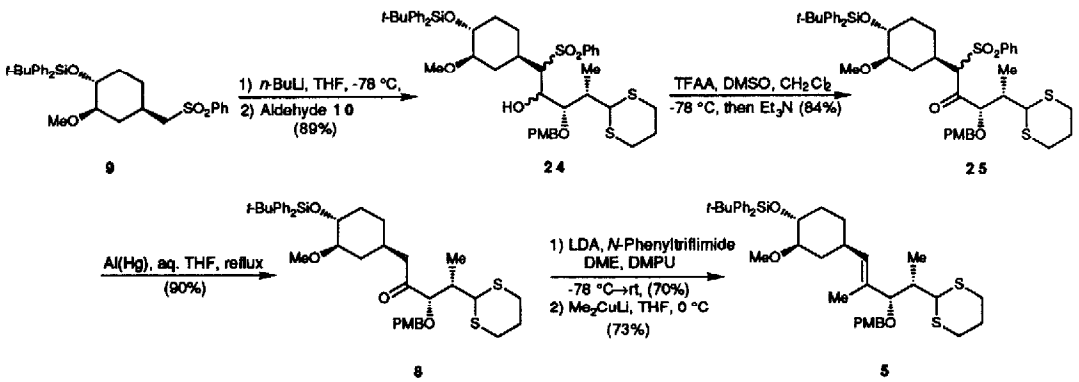
Scheme 4



19 **20** **21** **22** **23** **10**

The resulting aldehyde **10** coupled smoothly with the anion derived from sulfone **9** in THF at -78 °C (Scheme 5), affording a mixture of diastereomeric hydroxy sulfones **24** in 89% yield. Oxidation of this mixture with excess trifluoroacetic anhydride and DMSO[21] provided β-keto sulfone **25** (84%). We first attempted reductive removal of the phenylsulfonyl group in **25** via our recently developed tri-*n*-butyltin hydride method;[6b] not surprisingly, dithiane reduction intervened as a significant competing reaction. However, this difficulty was readily surmounted using Al(Hg) amalgam as the reducing agent.[22] Kinetic deprotonation of the resulting ketone (**8**)[11] was then best accomplished with lithium diisopropylamide (2.5 equiv) in dry DME at -78 °C for 30 min. After the addition of DMPU (3 equiv) and stirring for 15 min, a solution of *N*-phenyltrifluoromethane sulfonimide[23] (5 equiv) in DME was introduced and the mixture warmed to room temperature. This protocol afforded exclusively (>99:1) the requisite Z enol triflate (**7**), whereas the use of THF without DMPU as cosolvent

Scheme 5



9 **24** **25** **8** **5**

led to a 9:1 mixture of Z and E enol isomers.[24] Treatment of **7** with lithium dimethylcuprate gave rise to two major products (7:1) according to HPLC analysis. The desired E isomer (**5**) {$[\alpha]_D^{22}$ -38° (*c* 1.96, $CHCl_3$)}[11] could be isolated in 73% yield by column chromatography. The minor component actually comprised a 2:1 mixture of as yet unidentified products, neither of which proved to be the Z isomer. The E olefin geometry in **5** was assigned via a combination of ^1H NOE difference[25] and ^{13}C NMR spectroscopy.[26] Thus, irradiation of the singlet at δ 1.54, corresponding to the methyl group of the trisubstituted olefin, led to significant enhancement of the H(29) and H(26) resonances at δ 2.35 and 3.63, respectively, but caused no

enhancement of the H(28) vinyl resonance at δ 5.24. Similarly, irradiation of this vinylic proton markedly enhanced the H(26) resonance, but did not lead to enhancement of the singlet at δ 1.54. Molecular models suggest that only the E formulation is compatible with these observations. Further support for this assignment came from the ^{13}C NMR spectrum of **5**, wherein the C(27) methyl signal appeared to be strongly shielded (δ 11.0) by the cis-cyclohexyl moiety. The Merck group[3] reported similar chemical shifts (δ 12-13) for the C(27) methyl group in several FK-506 intermediates; likewise, the C(27) methyl group of FK-506 resonates at δ 13.7.[4]

In conclusion, we have completed an efficient, stereocontrolled synthesis of an advanced intermediate (**5**) corresponding to the C(24)-C(34) fragment of the FK-506 family of immunosuppressants. Further progress toward the total synthesis of these natural products will be reported in due course.

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References

1. 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*, 734.
2. Warty, V.; Diven, W.; Cadoff, E.; Todo, S.; Starzl, T.; Sanghvi, A. *Transplantation* **1988**, *46*, 453.
3. For the Merck total synthesis of FK506, see: Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante,R. P.; Shinkai, I. *J.Am. Chem. Soc.* **1989**, *111*, 1157. Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277. Mills, S.; Desmond, R.; Reamer; R.A.; Volante, R.P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281. For synthetic studies directed toward FK-506, see: Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643; Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A *Tetrahedron Lett.* **1988**, *29*, 4481. Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9. Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11. Villabolos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 12. Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15. Jones, A. B.; Yamaguchi, M.; Patten, P.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Shreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17. Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919. Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785.
4. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031.
5. Kino, T.; Miyata, S.; Inamra, N.; Kuroda, A.; Goto, T.; Tanaka, H.; Okuhara, M. *J. Antibiotics* **1988**, *41*, 1592.
6. For parts 1 and 2 of this series, see: (a) Smith, III, A. B.; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037. (b) Smith, III, A. B.; Hale, K. J.; McCauley, J. P. *Tetrahedron Lett.* , in press.
7. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3561.
8. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.
9. For a review on enolates, see: d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.
10. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.
11. (a) The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H, and 125- or 62.5-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis.
12. Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209.
13. Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc. Perkin. Trans. 1*, **1983**, 1315.
14. Neeman, M.; Hashimoto, Y. *J. Am. Chem. Soc.* **1962**, *84*, 2972.
15. Pasto, D. J.; Hickman, J. *J. Am. Chem. Soc.* **1968**, *90*, 4445.Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9.
16. For a similar approach to sulfone **18**, see: Egbertson, M. Ph. D. Dissertation, Yale University, New Haven, CT, 1988.
17. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
18. Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
19. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem Lett.* **1983**, 1593.
20. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
21. Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
22. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
23. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
24. For examples of regiospecific alkylations of enolates in presence of HMPA, see: Fataftah, Z. A.; Kopka. I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959, and references cited therein.
25. Neuhaus, D.; Williamson M. The Nuclear Overhauser Effect in Structural and Conformational Analysis; VCH:London, 1989.
26. Breitmaier, E; Bauer, E. ^{13}C NMR Spectroscopy: A Working Manual with Exercises", Harwood Academic: New York, 1984, p 58.

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