Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4271-4274, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00812-4

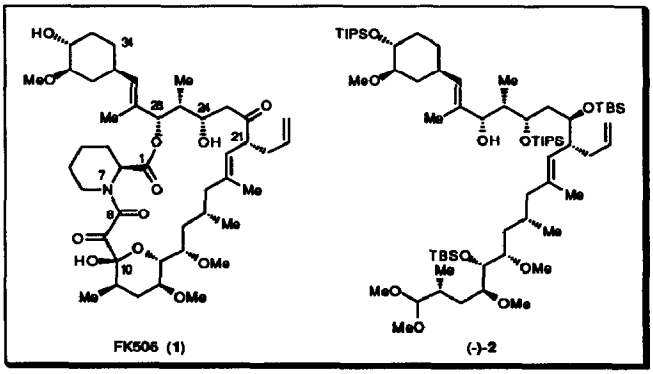
FORMAL TOTAL SYNTHESIS OF FK506. CONCISE CONSTRUCTION OF THE C(10)-C(34) SEGMENT VIA AN EFFECTIVE COUPLING TACTIC

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

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

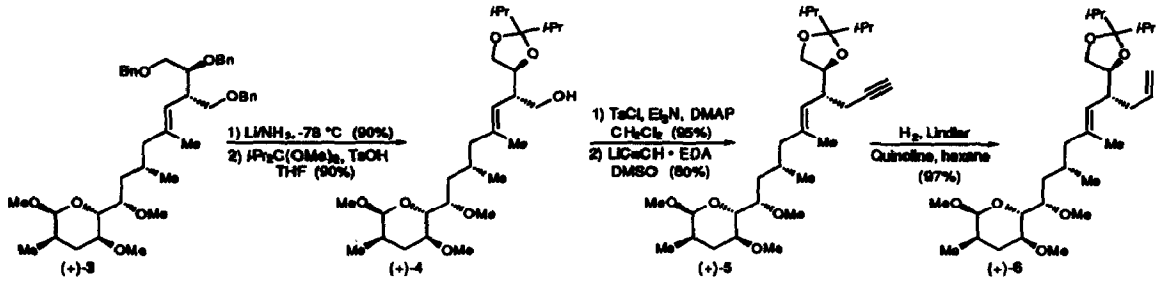
Summary: A formal total synthesis of the potent immunosuppressant FK506 (**1**) has been achieved via a concise construction of the Merck advanced intermediate (-)-**2**. Key features of the successful strategy include stereocontrolled σ-bond installation of the trisubstituted olefin moieties and an efficient coupling of the C(24)-C(34) dithiane (-)-**10** with the C(10)-C(23) α-silyloxy primary iodide (-)-**9**.

The intensive efforts currently directed toward the synthesis of FK506 (**1**) reflect the juxtaposition of its architectural complexity[1] with potent immunosuppressive activity, the latter manifest in very promising human organ-transplantation trials.[2] To date, two total syntheses,[3] two formal syntheses,[4] and numerous other approaches[5,6] to **1** have been recorded. Notwithstanding the impressive contributions emerging from these studies, effective tactics for installing the olefinic linkages and joining the major subunits have remained elusive. Herein we describe the formal synthesis of FK506 via a concise construction of the Merck advanced intermediate (-)-**2**.[3a,7] Key features of the successful strategy include stereocontrolled σ-bond generation of the trisubstituted olefin moieties[6a,b] and a reproducible, remarkably efficient coupling of the C(24)-C(34) dithiane (-)-**10** with the C(10)-C(23) α-silyloxy primary iodide (-)-**9**.



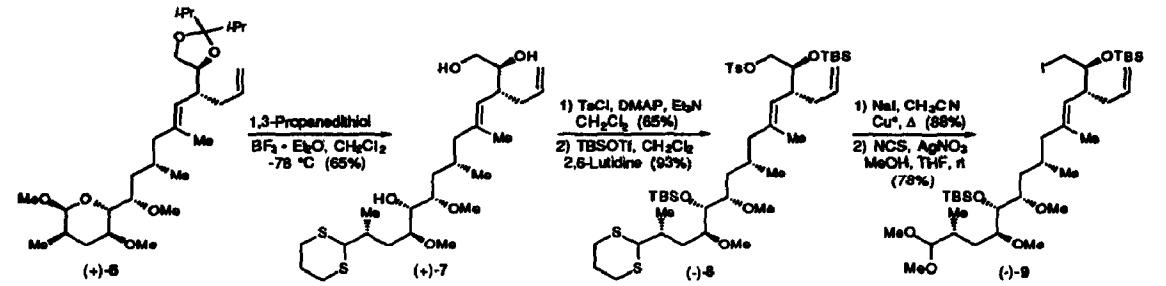
Deprotection (Li, NH_3, -78 °C) of our previously reported[6a] tribenzyl ether (+)-**3** and selective ketalization of the resultant triol (2,4-dimethyl-3-pentanone dimethyl ketal,[8] TsOH, THF, rt) afforded alcohol (+)-**4** as a single isomer in 90% yield (Scheme I). Tosylation (TsCl, Et_3N, DMAP, CH_2Cl_2, rt) followed by acetylide displacement[9] (LiC≡CH•EDA, DMSO) then generated alkyne (+)-**5**; the latter structure was secured via single-crystal X-ray analysis. Semireduction of **5** with Lindlar catalyst[10] uneventfully furnished olefin (+)-**6**.

Scheme I



Thioacetal generation[11] from 6 with concomitant deketalization (1,3-propanedithiol, $BF_3 \cdot Et_2O$, THF, -78 °C for 24 h, -50 °C for 72 h; Scheme II) provided triol dithiane (+)-7 in 65% yield. Selective monotosylation of 7 (TsCl, Et_3N, DMAP, CH_2Cl_2, rt) followed by bissilylation (TBS triflate, 2,6-lutidine, CH_2Cl_2, rt) then afforded primary tosylate (-)-8 (60% overall). Iodination (NaI, CH_3CN, copper bronze,[12] reflux) and dithiane methanolysis[13] (NCS, $AgNO_3$, MeOH/THF, rt) in turn gave the C(10)-C(23) iodide (-)-9 in good yield. In contrast with similar dimethyl acetals we have prepared previously, 9 could be purified by flash column chromatography without noticeable decomposition.

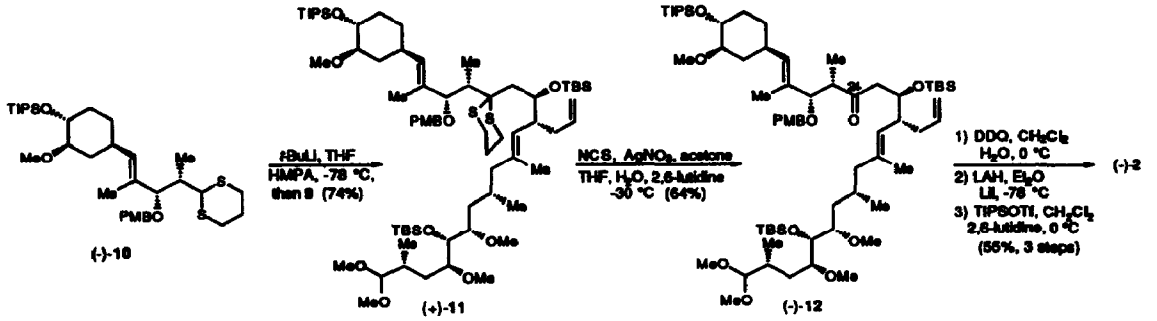
Scheme II



At this juncture we were poised to investigate the critical coupling of the C(10)-C(23) and C(24)-C(34) subunits 9 and 10. Several earlier approaches to 1 employed olefinations of C(20) aldehydes with C(19) carbanions to link the corresponding fragments, affording mixtures of isomers and modest yields.[14] In contrast, we exploited stereocontrolled σ-bond constructions of the trisubstituted olefins and elected to pursue a speculative dithiane alkylation tactic for assembly of the FK506 backbone. We were delighted to find that metalation of dithiane (-)-10[15] with *t*-BuLi (2.0 equiv each, 10% HMPA/THF, -78 °C) and treatment of the derived organolithium with the α-silyloxy primary iodide 9 (1.0 equiv, THF, -78 °C, 30 min) gave the coupling product (+)-11 in 74% yield (Scheme III). The efficacy of this protocol is particularly striking, albeit not totally unexpected in view of the activating effect expected to derive from the α-silyloxy moiety in 9.[17]

Completion of the synthesis then entailed hydrolysis of the dithiane [NCS, $AgNO_3$, 2,6-lutidine, acetone/THF/H_2O (5:5:1), -30 °C] to furnish ketone (-)-12. Oxidative removal of the *p*-methoxylbenzyl group[18] [DDQ, CH_2Cl_2/H_2O (10:1), rt] gave rise to a labile β-hydroxy ketone which was immediately subjected

Scheme III



to hydroxyl-directed anti reduction (LAH, LiI, -78 °C),[19] affording the corresponding diol as a single diastereomer. Finally, selective protection of the C(24) hydroxyl as its triisopropylsilyl ether[4a] (TIPS triflate, 2,6-lutidine, CH_2Cl_2, 0 °C) gave (-)-2, identical in all respects (^1H and ^{13}C NMR, IR, elemental analysis, optical rotation, HRMS, TLC) with an authentic sample.[20]

In summary, an efficient construction of the C(10)-C(34) segment 2 completes a formal synthesis of FK506 (1). Stereocontrolled installation of the trisubstituted olefin moieties and efficient coupling of the major fragments have been achieved. Further progress towards the synthesis of analogs of 1 will be reported in due course.

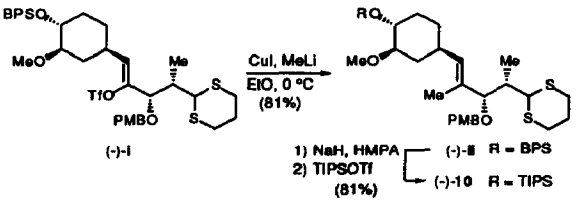
Acknowledgments. This work was supported by the National Institutes of Health (Institute of General Medical Sciences) through grant no. GM29028. We thank Drs. G. Furst and P. Carroll and Mr. J. Dykins, directors of the University of Pennsylvania Spectroscopy Center, for assistance in obtaining NMR, X-ray, and mass spectral data, respectively.

REFERENCES AND NOTES

1. Isolation and structure elucidation: Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031.
2. Thomson, A. W. *Immunol. Today* **1989**, *10*, 6.
3. Total syntheses: (a) 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.; Joe, D.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1990**, *55*, 5451. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
4. Formal total syntheses: (a) Jones, A. B.; Villalobos, A.; Linde, R. G. II; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786. (b) Gu, R.; Sih, C. *Tetrahedron Lett.* **1990**, *31*, 3287.
5. (a) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277. (b) Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Ibid.* **1988**, *29*, 281. (c) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Ibid.* **1988**, *29*, 3895. (d) Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643. (e) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 2425. (f) Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A. *Ibid.* **1988**, *29*, 4481. (g) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 11. (h) Egbertson, M.; Danishefsky, S. *J. Ibid.* **1989**, *54*, 11. (i) Villalobos, A.; Danishefsky, S. J. *Ibid.* **1989**, *54*, 12. (j) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *Ibid.* **1989**, *54*, 17. (k) Jones, A. B.; Yamaguchi, M.; Pattern, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *Ibid.* **1989**, *54*, 17. (l)

Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919. (m) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785. (n) Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *Ibid.* **1989**, *54*, 4267. (o) Corey, E. J.; Huang, H. C. *Tetrahedron Lett.* **1989**, *30*, 5235. (p) Wang, Z. *Ibid.* **1989**, *30*, 6611. (q) Linde, R. G. II; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2771. (r) Villalobos, A.; Danishefsky, S. J. *Ibid.* **1990**, *55*, 2776. (s) Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L. *Tetrahedron Lett.* **1990**, *31*, 1439. (t) Rao, A. V. R.; Chakraborty, T. K.; Purandare, A. V. *Ibid.* **1990**, *31*, 1443. (u) Stocks, M.; Kocienski, P. *Ibid.* **1990**, *31*, 1637. (v) Gu, R.; Sih, C. *Ibid.* **1990**, *31*, 3283. (w) Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284. (x) Maier, M. E.; Schoeffling, B. *Tetrahedron Lett.* **1991**, *32*, 53. (y) Maruoka, K.; Saito, S.; Ooi, T.; Yamamoto, H. *Synlett*, **1991**, 579. (z) Morimoto, Y.; Mikami, A.; Kuwabe, S.; Shirahama, H. *Ibid.* **1991**, *32*, 2909. (aa) Wang, Z. *Tetrahedron Lett.* **1991**, *32*, 4631. (bb) Chini, M.; Crotti, P.; Macchia, F.; Pineschi, M.; Flippin, L. A. *Tetrahedron* **1992**, *48*, 539. (cc) Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. *J. Org. Chem.* **1992**, *57*, 5071.

6. (a) Smith, A. B. III; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037. (b) Smith, A. B. III; Hale, K. J.; Laakso, L. M.; Chen, K.; Riera, A. *Ibid.* **1989**, *30*, 6963.
7. This work was first presented at the Cope Scholar Symposium at the Fourth Chemical Congress of North America, New York, NY, August 25-30, 1991.
8. Napolitano, E.; Fiaschi, R.; Mastrotilli, E. *Synthesis* **1986**, 122.
9. Interestingly, a higher-order vinyl cuprate (CuCN, vinyllithium, Et_2O, 0 °C) gave **6** in only 37% yield, together with 44% of **4**.
10. Marvell, E. N.; Li, T. *Synthesis* **1973**, *8*, 457.
11. Nakata, T.; Nagao, S.; Mori, N.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461, 6465.
12. The inclusion of copper-bronze powder to prevent autocatalytic decomposition has been recommended previously: Taber, D. F.; Petty, E. M.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
13. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
14. See refs. 3a,b and 4a,b. For related results, see also: Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.*, **1992**, *57*, 5060.
15. Dithiane (-)-**10** was prepared from the known[6b] BPS-protected enol triflate (-)-**I** via methylation with lithium dimethyl cuprate in ether (rather than THF[16]) followed by a two-step protecting group interchange.



16. Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.
17. For a detailed study of the rate acceleration induced by electron-withdrawing substituents at the β-carbon atom in S_N2 reactions, see: Holtz, H. D.; Stock, L. M. *J. Am. Chem. Soc.* **1965**, *87*, 2404.
18. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
19. Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631.
20. We thank Dr. Ichiro Shinkai (Merck Research Laboratories) for kindly providing an authentic sample of (-)-**2**.

(*Received in USA 5 April* 1994; *accepted* 20 *April* 1994)