pyrrolic), 8.75 ppm (pair of d, 1.9 Hz). Impurities in the 0.8–2.0 ppm region prevented assignment of the acetyl and H_X signals.

(B) 2-Hydroxybutyl. Mass spectral analysis indicated a $(M + H)^+$ at 1047 (calcd M^+ 1046). UV-vis [λ_{max}, nm]: 426, 518, 533, 604. ^1H NMR (C_6D_6): −4.17 (dd, J_{AX} = 4.3 Hz, J_{AB} = 15 Hz, 1 H, $NCH_AH_BCH_X(OH)CH_2CH_3$), −4.07 (dd, J_{BX} = 8.6 Hz, J_{AB} = 15 Hz, 1 H, H_B), −2.06 (br s, 1 H, NH), −1.6 (m, 1 H, CH_2), −1.2 (m, 1 H, CH_2), −0.9 to −1.0 (d and t, 4 H, OH and CH_3), 0.62 (br s, 1 H, H_X), 7.55 (d, 4.6 Hz, 1 H, β-pyrrolic), 7.58 (d, 4.8 Hz, 1 H, β-pyrrolic), 8.57 (d, 4.9 Hz, 1 H, β-pyrrolic), 8.61 (d, 4.8 Hz, 1 H, β-pyrrolic), 8.73–8.66 ppm (unresolved pair of doublet of doublets and singlet, 4 H, β-pyrrolic).

21-(2-Acetoxybutyl)-5,10,15,20-tetrakis(2,6-difluorophenyl)-23*H*-porphine and 21-(2-Hydroxybutyl)-5,10,15,20-tetrakis(2,6-difluorophenyl)-23*H*-porphine. The *N*-alkyl hemin was demetalated with 10% HCl/methanol at 50 °C for 1 h. Treatment of the product with acetic anhydride (5 mL) and 1 mL of concentrated HCl yielded the acetylated porphyrin after neutralization and chromatography. The isolated product was free any alkyl impurities when $PhIO_2$ was used as the oxidant.

(A) 21-(2-Acetoxybutyl). Mass spectral analysis showed $(M + H)^+$ at 873 (calcd M^+ 872.2). UV-vis [λ_{max}, nm (CH_2Cl_2)]: 424, 517, 553, 605. ^1H NMR ($CDCl_3$): −4.34 (dd, 1 H, J_{AB} = 15 Hz, J_{AX} = 3.7 Hz, $NCH_AH_BCH_X(OCOCH_3)CH_2CH_3$), −4.20 (dd, 1 H, J_{AB} = 15 Hz, J_{BX} = 3.7 Hz, H_B), −2.32 (s, 1 H, NH), −1.22 (m and t, 4 H, CH_2CH_3), −0.56 (m, 1 H, CH_2), 1.42 (s, 3 H, acetate), 1.77 (br m, 1 H, H_X), 7.22–7.47 (m, 8 H, *meso*-aryl), 7.73–7.77 (m, 4 H, *meso*-aryl), 7.87 (s, 2 H, β-pyrrolic), 8.63, 8.60, 8.53, 8.49 (4 d, 4 H total, β-pyrrolic), 8.85 ppm (s, 2 H, β-pyrrolic).

(B) 21-(2-Hydroxybutyl). UV-vis [λ_{max}, nm (CH_2Cl_2)]: 425, 516, 552, 605. ^1H NMR ($CDCl_3$): −4.27 to −4.30 (m, 2 H, $NCH_2CH(OH)CH_2CH_3$), −2.21 (s, 1 H, NH), −1.26 to −1.28 (m, 1 H, CH_2), −0.81 to −0.86 (t and m, 4 H, CH_2CH_3), −0.54 (quartet, 1 H, OH), 0.67 (m, 1 H, $CH(OH)$), 7.24–7.43 (m, 8 H, *meso*-aryl), 7.73–7.78 (m, 4 H, *meso*-aryl), 7.83 (s, 2 H, β-pyrrolic), 8.50 (m, 2 H, β-pyrrolic), 8.61 (m, 2 H, β-pyrrolic), 8.83 ppm (s, 2 H, β-pyrrolic).

Yield of 21-(2-Hydroxy-2-cyclohexylethyl)-5,10,15,20-tetrakis(2,6-dichlorophenyl)-23*H*-porphine. A solution of Fe(OCP)Cl (14 μmol) in CH_2Cl_2 containing 2 M vinylcyclohexane and dodecane as an internal standard was stirred at room temperature, and 350 equiv of PFIB was added in small portions. On consumption of the oxidant essentially all the catalyst was present as a green pigment by TLC as above. Gas chromatographic analysis of the reaction indicated 280 equiv of epoxide was formed (86% yield based on PFIB added). The solvent was removed at reduced pressure, and the porphyrin was dissolved in 3/1 acetic acid/HCl and stored at 5 °C for 24 h. After the solution was neutralized with NH_4OH at 0 °C and extracted with CH_2Cl_2, the product was chromatographed on flash silica (CH_2Cl_2 to 3% diethyl ether/CH_2Cl_2). Only one migrating band was observed; the dark material at the column origin could only be eluted with methanol/CH_2Cl_2. The yield was 70% based on starting catalyst. By ^1H NMR the isolated compound was similar to that of 3-methyl-1-butene, which we previously reported.[1b] ^1H NMR ($CDCl_3$): −4.40 (dd, 1 H), −4.15 (dd, 1 H), −2.3 to −2.4 (m, 1 H), −2.1 (br s, 1 H), −1.65 to −1.7 (br m, 2 H), −1.1 to −1.2 (br s, 1 H), −0.54 (d, 1 H), −0.15 to −0.35 (br m, 4 H), 0.4–0.0 (m, 3 H), 7.5–8.0 (m, 14 H), 8.37–8.50 (4 d, 4 H), 8.75 ppm (s, 2 H).

Stereochemistry of Heme N-Alkylation. The *N*-alkylporphyrins formed during the epoxidation of deuterated 3-methyl-1-butene by Fe(OCP)Cl/PFIB were isolated by demetalation with 3/1 acetic acid/HCl. The deuterated *N*-(2-hydroxy-3-methylbutyl) substituted porphyrins were analyzed by ^1H NMR and mass spectrometry. The ^1H NMR spectra of both *cis*- and *trans*-1-deuterio-3-methyl-1-butene adducts resembled the spectrum for the protio adduct and differed only in the −4 to −4.5 ppm region as we previously reported.[1b] Mass spectra of the deuterated adducts exhibited a molecular ion of $(M + H)^+$ at 978 compared to the protio-olefin adduct molecular ion $(M + H)^+$ of 977.

Acknowledgment. We thank the National Institutes of Health (NIH 5R37-GM17880) and the National Science Foundation (NSF CHE 88-14949) for financial assistance and the Organic Division of the American Chemical Society for a predoctoral fellowship awarded to P.D.H. (Proctor and Gamble Fellow, 1987–1988). We also acknowledge the Bio-organic, Biomedical Mass Spectrometry Resource (A. L. Burlingame, Director) supported by NIH Division of Research Resources Grant RR01614 and Chemical Analytical Services, University of California at Berkeley, Berkeley CA. We thank Dr. Robert T. Hembre and Paul S. Wagenknecht for assistance in preparing this paper.

Supplementary Material Available: Tables (1S–3S) showing partition numbers for individual experiments with three olefins (vinylcyclohexane, methylenecyclohexane, and styrene) and with the five hemin catalysts whose averages are reported in Table III (3 pages). Ordering information is given on any current masthead page.

Chemistry of Tricarbonyl Hemiketals and Application of Evans' Technology to the Total Synthesis of the Immunosuppressant (−)-FK-506

Todd K. Jones,* Robert A. Reamer,* Richard Desmond, and Sander G. Mills*

Contribution from the Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065-0900. *Received September 29, 1989. Revised Manuscript Received December 7, 1989*

Abstract: Details of model studies probing the chemistry of the tricarbonyl region of FK-506 are presented, and their use in designing a successful route to this immunosuppressant is outlined. Applications of asymmetric oxazolidinone alkylation/aldol methodology to a convergent, highly flexible synthesis of the C_{10}–C_{18} fragment and to improvements in the preparation of the C_{20}–C_{34} segment are also discussed.

FK-506, **1**, isolated from *Streptomyces tsukubaensis* (no. 9993),[1] is a unique 21-member macrolactam that possesses exceptional biological activity[2] and an array of challenging structural features, in particular an unusual α,β-diketo amide hemiketal system. The immunosuppressive potency of **1** has been shown to be superior to that of cyclosporin A in the inhibition of delayed hypersensitivity responses in a variety of allograft transplantation

(1) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033. (b) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249–1255. (c) Taga, T.; Tanaka, H.; Goto, T.; Tada, S. *Acta Crystallogr.* **1987**, *C43*, 751–753.

(2) (a) Starzl, T. E.; Fung, J.; Venkataramman, R.; Todo, S.; Demetris, A. J.; Jain, A. *Lancet* **1989**, 1000–1004. (b) Siekierka, J. J.; Hung, S. H. Y.; Poe, M.; Lin, C. S.; Sigal, N. H. *Nature* **1989**, *341*, 755–757. (c) Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L. *Nature* **1989**, *341*, 758–760. (d) Freedman, R. B. *Nature* **1989**, *341*, 692.

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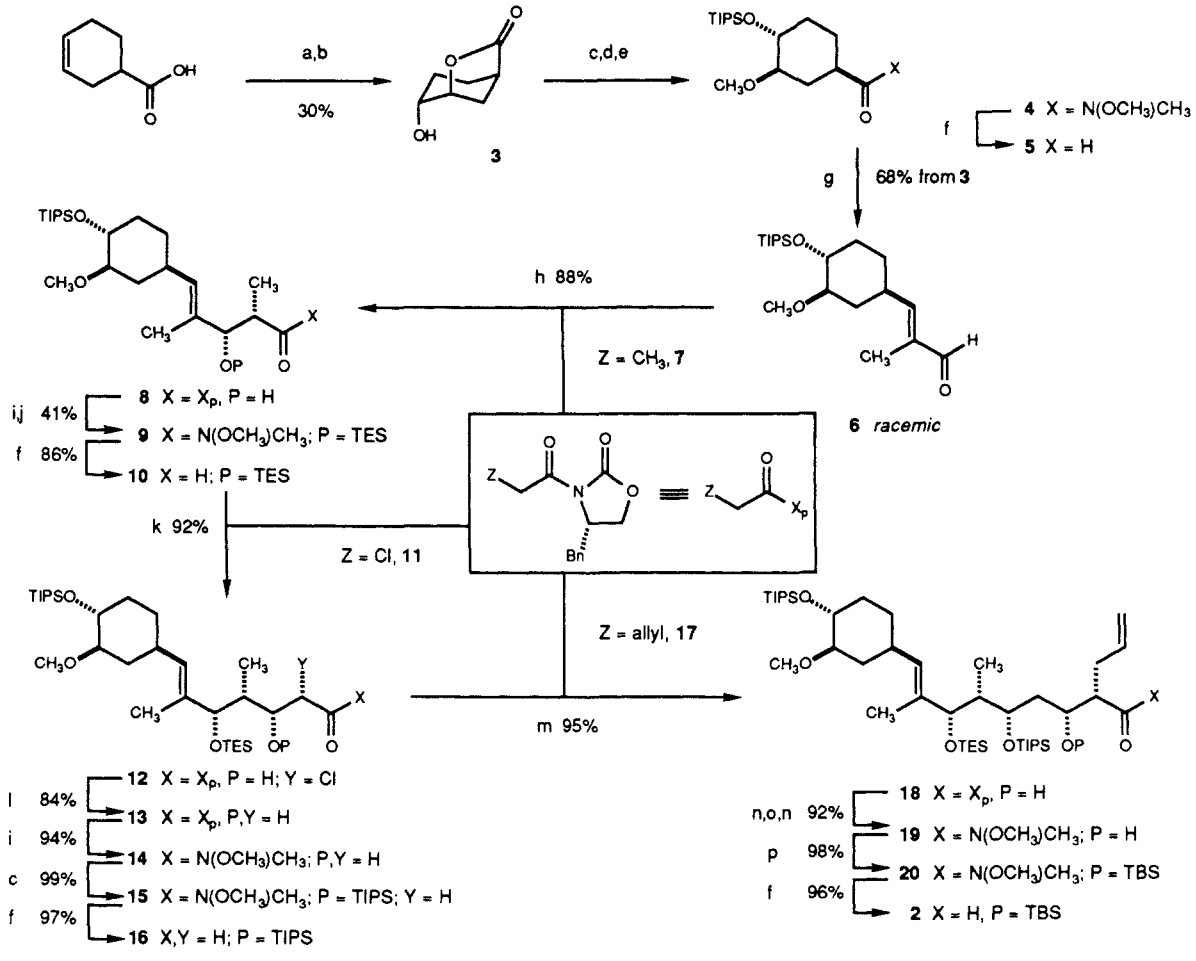
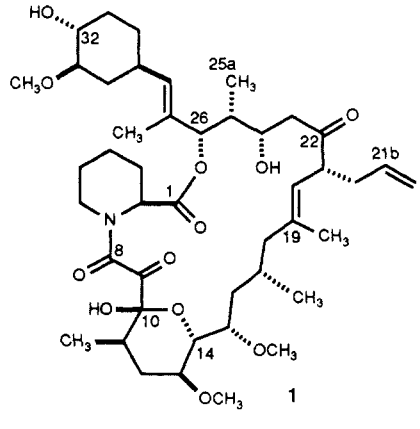
Scheme I[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) chlorobenzene, 130 °C; (c) TIPSOTf, 2.6-lutidine, CH_2Cl_2, 0 °C; (d) $Al(CH_3)_3$, $HN(OCH_3)CH_3$·HCl, toluene, 20 °C; C_4-OTIPS-**3**, 20 °C; (e) CH_3OTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 20 °C; (f) DIBAL, THF, −78 °C; (g) 2-lithio-2-(triethylsilyl)propanal, *N*-cyclohexylimine, THF, −20 °C; trifluoroacetic acid, THF, 0 °C; H_2O; 0 °C; (h) **7**, Et_3N, *n*-Bu_2BOTf, −70 °C, **6**, −50 °C; (i) $Al(CH_3)_3$, $HN(OCH_3)CH_3$·HCl, CH_2Cl_2, 0 °C; **8**, −10–20 °C; (j) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; separate; (k) **11**, Et_3N, *n*-Bu_2BOTf, −70 °C; **10**, −50 °C; (l) zinc, HOAc, THF, ultrasound irradiation, 20 °C; (m) **17**, Et_3N, *n*-Bu_2BOTf, −70 °C; **16**, −25 °C; (n) LiOH, H_2O_2, H_2O, THF, 0 °C; (o) carbonyl diimidazole, CH_2Cl_2, 20 °C; $HN(OCH_3)CH_3$, CH_2Cl_2, 20 °C; (p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

and autoimmunity models.[1b] Thus, FK-506 is an important new advance in immunosuppressant therapy.[2-6]

In preliminary communications we have reported subunit syntheses,[3a,b] related methodological studies,[3c,d] the total synthesis,[4] and chemistry of the intact FK-506 molecule.[5] Our total synthesis



1

Figure 1.

required extensive model studies on the chemistry of the tricarbonyl hemiketal of FK-506. We now detail these investigations and their application to the completion of the total synthesis. In addition, we report improvements on the synthesis of the C_{20}–C_{34} fragment and a new synthesis of the C_{10}–C_{18} segment.

Subunit Preparation and Coupling

C_{20}–C_{34} Modifications. A summary of our iterative synthesis of the C_{20}–C_{34} aldehyde **2** is shown in Scheme I. Most of this work has been described in recent publications, so we discuss here

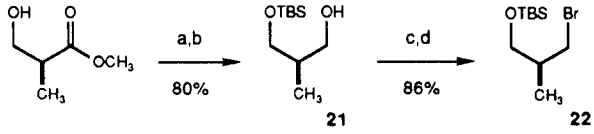
(3) (a) Mills, S. G.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281–284. (b) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277–280. (c) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 3895–3898. (d) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245–4248.

(4) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159.

(5) Askin, D.; Reamer, R. A.; Jones, T. K.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 671–674.

(6) For other synthetic chemistry surrounding FK-506, see: (a) Ragan, J. A.; Nakatsuda, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 4267–4268. (b) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785–2786. (c) Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919–922. (d) Smith, A. B., III; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037–1040. (e) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schrieber, S. L. *J. Org. Chem.* **1989**, *54*, 17–19. (f) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15–16. (g) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 12–15. (h) Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11–12. (i) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9–10. (j) Coleman, R. S.; Danishefsky, S. J. *Heterocycles* **1989**, *28*, 157–161. (k) Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A. *Tetrahedron Lett.* **1988**, *29*, 4481–4484. (l) Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643–4644. (m) Corey, E. J.; Huang, H.-C. *Tetrahedron Lett.* **1989**, *30*, 5235–5238.

Scheme II[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, 20 °C; (b) DIBAL, THF, toluene, −78–0 °C; (c) MsCl, Et_3N, CH_2Cl_2, −10 °C; (d) *n*-Bu_4NBr, acetone, reflux.

only significant changes in this work.[7]

The original synthesis of hydroxy lactone **3**, which employed tin hydride reduction of a quinic acid derivative, proved cumbersome on large scale. A more convenient protocol consisted of the *m*-CPBA epoxidation of commercially available racemic 3-cyclohexenecarboxylic acid followed by high-dilution thermolysis in chlorobenzene (Scheme I). Under these conditions the trans epoxy acid cyclized to hydroxy lactone **3**, which could be extractively separated from the acidic byproducts. The diastereomers could be separated at the C_{26}-OTES amide stage (**9**).

Since our initial preparation[3a] of aldehyde **16** we have observed that the chloroimide **11** serves as a better chiral acetate synthon.[8] Elimination to form an olefin at C_{23}–C_{24} accounted for most (12%) of the remaining material in the zinc reduction. Transamination according to Weinreb,[9] silylation, and reduction provided aldehyde **16** in 91% overall yield; completion of the synthesis of aldehyde **2** is shown in Scheme I.[4,10]

C_{10}–C_{18} Synthesis. Our previous preparation of the C_{10}–C_{18} segment suffered from three isomer separations and the intrinsic limitations of a C_2 pseudosymmetric synthesis, which necessarily limit analogue preparation. In order to eliminate these problems, a convergent approach was adopted where the fragment was divided at the C_{12}–C_{13} junction to be joined by an organometallic addition to an *N*-methoxy-*N*-methylamide.[9]

The C_{10}–C_{12} fragment was prepared from commercially available (in either enantiomeric form) methyl 3-hydroxy-2-methylpropionate as shown in Scheme II. The C_{13}–C_{18} segment was prepared as shown in Scheme III.[11] Oxidation of **23** with osmium tetraoxide/potassium periodate generated aldehyde **24** and a small amount (12%) of hydroxy ketone, which was reduced with sodium borohydride and cleaved with periodate to provide a combined 89% yield of aldehyde **24**. Aldol addition[12] proceeded rapidly at −50 °C to provide aldol adduct **25** in 84% yield.

Lithiated **22** was added to amide **26** followed by an inverse quench to provide ketone **27** in 69% yield. Six equivalents of the bromide was required for the addition because silyl migration proved to be facile under metalation conditions. However, the bromide is readily available and an appropriate change in the C_{10} protecting group should eliminate this problem.[13]

Reduction of hydroxy ketone **27** with tetramethylammonium triacetoxyborohydride[14] in 2:1 acetonitrile/acetic acid at −35 °C for 30 h provided an inseparable mixture of diastereomers in an 85:15 ratio. We found that the addition of approximately 3% (by volume) water to the reaction mixture (after cooling to −40 °C) raised the selectivity to 91/9 and decreased the reaction time to <14 h. This effect was observed with commercial as well as freshly prepared tetramethylammonium triacetoxyborohydride. The resulting diol was converted to **30** (Scheme III). The C_{13} diastereomers were easily separated once the C_{14} OPMB was removed.

The C_{10}–C_{19} subunit was completed by previously described refunctionalization (Scheme III)[4,15] to give **37**. This preparation proceeds in 20 steps, 12.8% overall yield (**7** to **37**) with 86% diastereoselectivity, compared to 24 steps, 8.6% overall yield (from divinylcarbinol to **37**) with 81% diastereoselectivity for our previous route.[16] More importantly, *nearly all isomers are readily available with this methodology.*

C_{19}–C_{20} Olefin Formation. The C_{20}–C_{34} and C_{10}–C_{19} fragments were coupled as previously reported[4,15] (Scheme IV). The resulting mixture of isomers was chromatographically separated to provide the two desired adducts (38% and 30% of higher and lower R_f components, respectively) and several species (27%) assigned as addition products arising from ortholithiation of the phosphine oxide phenyl groups. The two separated adducts were treated with potassium hexamethyldisilazide to provide (*E*)-olefin **38** and its *Z* counterpart in 82% and 84% yields, respectively. The olefin geometry was assigned by the ^{13}C chemical shift of C_{19}–CH_3 at 16.6 ppm (16.6 vs 23.6 ppm for (*E*)- and (*Z*)-olefins, respectively).[17] Since the olefin isomers are not easily separable, it is noteworthy that this technology provides homogeneous (*E*)-olefin.

Pipecolate Chemistry. The labile nature of the chiral center in (*S*)-pipecolic acid dictated that this amino acid be esterified under the mildest possible conditions. Esterification of the alcohol **40** with racemic **39** was carried out with DCC/DMAP at 25 °C to give the pipecolate ester **41** in 85% yield (Scheme V). Because of problems with rotomers in the 300-MHz ^1H NMR at 25 °C, the mixture was analyzed at 65 °C with resolution enhancement. These conditions provided sufficient separation in the C_{31} methoxy signals such that 1–2% of the minor isomer could be detected. When **40** was esterified with enantiomerically pure **39** at 25 °C, 6–7% epimer was detected by NMR. When the reaction was run at 0 °C with an excess of **39**, the isolated product showed 3–4% of the epimer. Finally, reaction at −15 °C gave the product **41** with just 1–2% scrambling at the pipecolic center, a level suitable for our needs.

(7) However, experimental procedures with full characterization are provided for selected compounds. Experimental procedures in the supplementary material are noted at the end of the paper. Abbreviations used in this paper are as follows: *m*-CPBA, *m*-chloroperoxybenzoic acid; TES, triethylsilyl; PMB, *p*-methoxybenzyl; DCC, 1,3-dicyclohexylcarbodiimide; DMAP, 4-(dimethylamino)pyridine; BOC, *tert*-butoxycarbonyl; THF, tetrahydrofuran; TMEDA, *N,N,N',N'*-tetramethylethylenediamine; TBS, *tert*-butyldimethylsilyl; TCE, 2,2,2-trichloroethyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TFA, trifluoroacetic acid; TIPS, triisopropylsilyl; NOE, nuclear Overhauser effect.

(8) (a) Evans, D. A.; Sjogren, E. B.; Conn, R. E.; Weber, A. E. *Tetrahedron Lett.* **1987**, *28*, 39–42. (b) Sjogren, E. B. Ph.D. Thesis, Harvard University, 1986. (c) The use of 2,6-lutidine was developed by: Evans, D. A.; Carreira, E. M., unpublished results and conveyed to us by private communication.

(9) (a) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, 3815–3818. (b) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (c) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.

(10) Evans, D. A.; Britton, T. C.; Ellman, J. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

(11) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

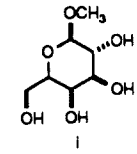
(12) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. (c) Evans, D. A.; Kaldor, S. W.; Jones, T. K. *Abstracts of Papers*, 196th National Meeting of the American Chemical Society, Los Angeles, CA; American Chemical Society: Washington, DC, 1988; ORGN 177, 178.

(13) For example, (*S*)-bromo[2-methyl-3-(phenylmethoxy)propyl]magnesium has been prepared and is stable: Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925–944. We found the organomagnesium species derived from our bromide also suffered from silyl transfer. However, *n*-butyllithium and ethylmagnesium bromide both provided addition products in >85% yield.

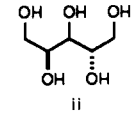
(14) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(15) For leading references on the use of phosphine oxides, see: (a) Buss, A. D.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1981**, 100–101. (b) Buss, A. D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 3931–3934.

(16) For comparative purposes, compound **41** (or the corresponding sulfone) has been reported by Danishefsky and co-workers[6g] in 23 steps, 3.1% overall yield from i and by Schreiber and co-workers[6f] in 22 steps, 2.2% overall yield from ii. The overall diastereoselectivity of these approaches was comparable to ours.



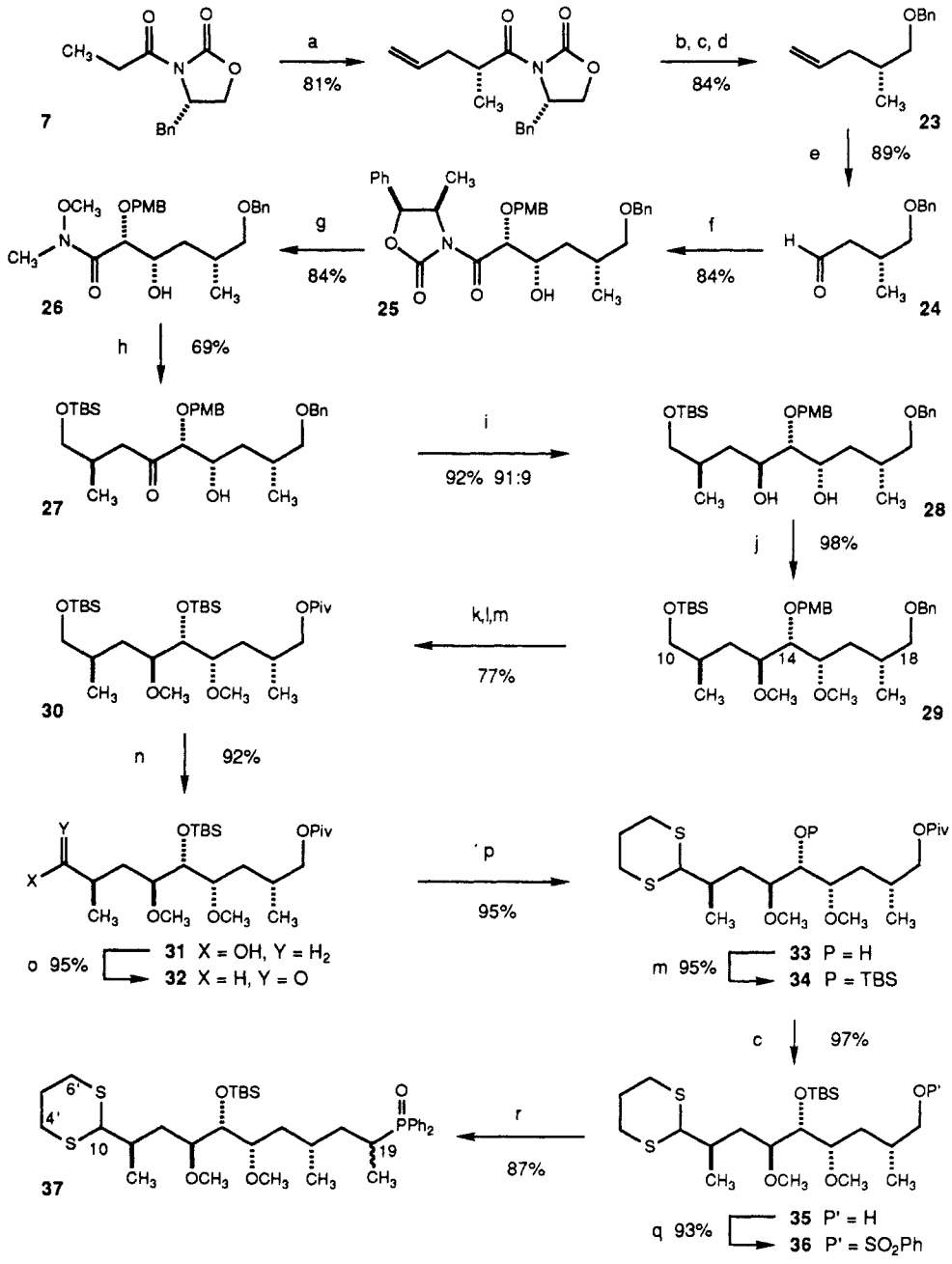
i



ii

(17) Stothers, J. B. In *Carbon-13 NMR Spectroscopy*; Blomquist, A. T., Wasserman, H., Eds.; Organic Chemistry, Vol. 24; Academic Press: New York, 1972; p 80.

Scheme III[a]



[a] Reagents and conditions: (a) NaHMDS, allyl iodide, THF, −78 °C; (b) LiOH, H_2O_2, H_2O, THF, 0 °C; (c) LAH, Et_2O, 0–20 °C; (d) NaH, BnBr, THF, DMF, 20 °C; (e) OsO_4, $NaIO_4$, H_2O, acetone, 20 °C; (f) *p*-methoxybenzyloxyacetimide, Et_3N, *n*-Bu_2BOTf, CH_2Cl_2 −50 °C; **24**, −40 °C; (g) $Al(CH_3)_3$, $HN(OCH_3)CH_3$·HCl, THF, toluene, 0 °C; **25**, −10 °C; (h) **22**, Li, Et_2O, 0 °C; **26**, THF, −78 °C; (i) $(CH_3)_4NBH(OAc)_3$, CH_3CN, HOAc, H_2O −40 °C; (j) NaH, CH_3I, THF, 0–20 °C; (k) H_2, $Pd(OH)_2$/C, EtOAc, 20 °C; (l) PivCl, pyridine, 0 °C; (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (n) TFA, THF, H_2O, 20 °C; (o) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; **31**, −78 °C; Et_3N, −30 °C; (p) $CH_2(CH_2SH)_2$, BF_3·OEt_2, CH_2Cl_2, 0 °C; (q) $PhSO_2Cl$, pyridine, 0 °C; (r) $Ph_2P(O)Et$, *n*-BuLi, THF, −78 °C; **36**, 0 °C.

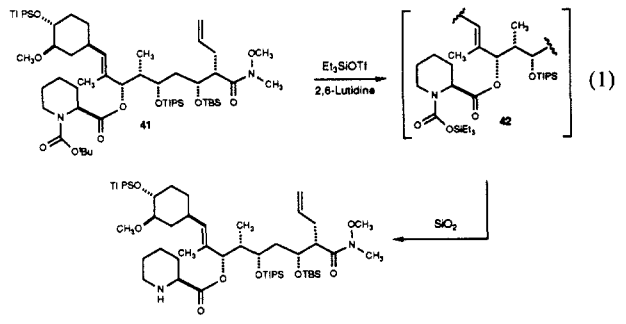
Table I. ^{13}C NMR Chemical Shift Data

compd	C_8	C_9	C_{10}
59	169.1	94.1	208.7
60	162.6	181.8	197.1
61	162.1	186.3	97.0
62	167.2	97.0	209.7

These results demonstrated that significant epimerization could occur at C_2 under macrolactonization conditions (high dilution and prolonged reaction times). Therefore, a macrolactamization strategy was adopted where the ester bond could be generated under high-concentration conditions, the sensitive tricarbonyl being revealed after macrocyclization.

Since the usual conditions for removal of the BOC group (anhydrous trifluoroacetic acid) would be incompatible with resident protecting groups, we used the method of Shioiri and Ohfune.[18] Thus, treatment of C_{20}–C_{34} amide **41** with triethylsilyl triflate in the presence of 2,6-lutidine effected complete conversion to silyl carbamate **42** (eq 1). The carbamate group survived aqueous workup and rapid passage through a flash silica gel column; the free amine could be generated cleanly either by treatment with dilute aqueous acetic acid in THF or by extended exposure to silica gel. These results demonstrated that we could accomplish the deprotection at N_7 without disrupting protecting groups in the remainder of the molecule.

(18) (a) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223–3226. (b) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543–5546.

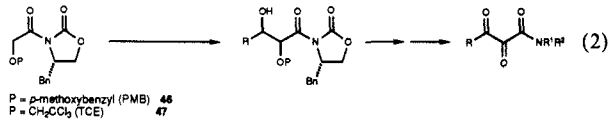


Tricarbonyl Model Studies

Dithiane Deprotonation. Our original strategy for installing the tricarbonyl region of FK-506 involved deprotonation of the dithiane followed by acylation with diethyl oxalate.[19] Limited supplies of the C_{10}–C_{34} segment led us to perform lithiation studies on model dithianes. These investigations were carried out with derivatives of the C_{10}–C_{18} segment of FK-506 because simpler compounds did not adequately simulate the intact C_{10}–C_{34} molecule.

Treatment of **43** (Scheme VI) with *n*-butyllithium revealed metalation at C_{14} followed by elimination of the C_{13} OCH_3. Attempted formation of the dianion of **44** failed in the presence of THF. However, dianion formation in neat TMEDA followed by trapping with diethyl oxalate provided a 64% yield of C-acylated product in addition to 11% recovered starting material; no C_{14} O-acylated product was observed. Since C-acylated **44** (with diethyl oxalate) was not separable from **44**, transesterification was performed with sodium methoxide to afford the separable methyl ester. Unfortunately, application of these conditions to 14,26-dihydroxy-**38** resulted primarily in metalation at C_{27} CH_3 providing **45**; only traces of the desired C_{10}-acylated material were produced. Analysis of this mixture was also complicated by the difficult separation of products and starting material.

Aldol Approach. The problems observed with the above approach arose mostly because the multifunctional backbone of the precursor did not tolerate strongly basic or acidic reaction conditions. An alternate approach to the tricarbonyl is shown in eq 2: addition of a protected α-hydroxy imide to an aldehyde followed



by bisoxidation provides the tricarbonyl. While the use of an asymmetric aldol may seem like overengineering, we have found the advantages of the boron aldol (mild reaction conditions and isolation of a single isomer in high yield) followed by hydrolysis to be superior to the corresponding methyl ester aldol (self-condensation has been reported[20] and was observed to be a serious problem). Furthermore, an important advantage of the aldol technology over the dithiane approach is the former's much greater flexibility for analogue preparation.

Selection of P on the imide (eq 2) was based on orthogonality to the other protecting groups. Preliminary experiments demonstrated that the TES, TBS, and 3,4-dimethoxybenzyl groups were not useful: they were rapidly removed under the enolization conditions. The PMB[21] imide **46** and the TCE imide **47** each reacted satisfactorily with isobutyraldehyde. Oxidative cleavage of the former and reductive removal of the latter seemed compatible with resident protecting groups, so these groups were chosen for further study. The aldehydes, **49** and **50**, employed in the aldol model studies were prepared from dithianes **35** and **48** as shown in Scheme VII.

Hydroxy–Dicarbonyl Intermediates. Sequential oxidation of C_{10} OH, C_9 OH would avoid direct preparation of a sensitive tricarbonyl intermediate. Thus, addition of the boron enolate of PMB imide **46** to the C_{10}–C_{18} aldehyde (Scheme VII) followed by Swern oxidation[22] provided the keto imide in 93% yield (Scheme VIII). Hydrolysis of the C_{14} OTES group provided a mixture of ketone and hemiketal in a 1:9 ratio, respectively. Attempts to silylate the C_{10} OH or prepare a mixed ketal with the hemiketal resulted in recovered starting material. We assumed that an ester rather than the bulky imide would provide the hemiketal exclusively. Indeed, methanolysis of β-hydroxy imide **51** followed by a Swern oxidation and desilylation provided **54** exclusively; however, removal of the PMB group proved problematic. Oxidative removal (DDQ)[21] or reductive removal [H_2/Pd(OH)$_2$] only decomposed the hemiketal—and reductive removal would be impossible with the olefins present.

Deprotection Studies. Attempted oxidative deprotection of **57** with DDQ/H_2O/CH_2Cl_2 resulted predominantly in benzoate formation at C_9 and C_{10}. When the reaction was performed with rigorous exclusion of water, benzoates were still the major products. The PMB ethers could be hydrogenolyzed with Pd(OH)$_2$/C, but these conditions are not applicable for synthesizing FK-506. The diol could be prepared by first protecting C_{10} as a TES ether followed by oxidation with DDQ (Scheme IX). The TES ether is partially cleaved under the reaction conditions and completely hydrolyzed in a separate step. The TCE group was removed from **58** with Zn/HOAc and sonication in 75% yield.

Tricarbonyl–Hemiketal Studies. The ester series had provided the most encouraging results (with respect to the hemiketal) in the sequential oxidation experiments, so concomitant oxidation in this series was explored (Scheme X). The methyl ester derived from **51** was deprotected via hydrogenolysis of the PMB (88% yield). Swern oxidation of the resulting diol[23] smoothly provided variable mixtures of the hydrate (**59**) and the free diketo ester (**60**) in 88% yield (1–3:1). Hydrolysis of the C_{14} OTES group provided variable mixtures of two hemiketals, assigned as the six- (**61**) and seven-member (**62**) rings (1–4:1, respectively) in 80% yield. The assignments were made with the aid of the ^{13}C NMR data (Table I). Equilibration experiments (acid and base catalyzed) met with failure—either no equilibration took place or the hemiketals decomposed.

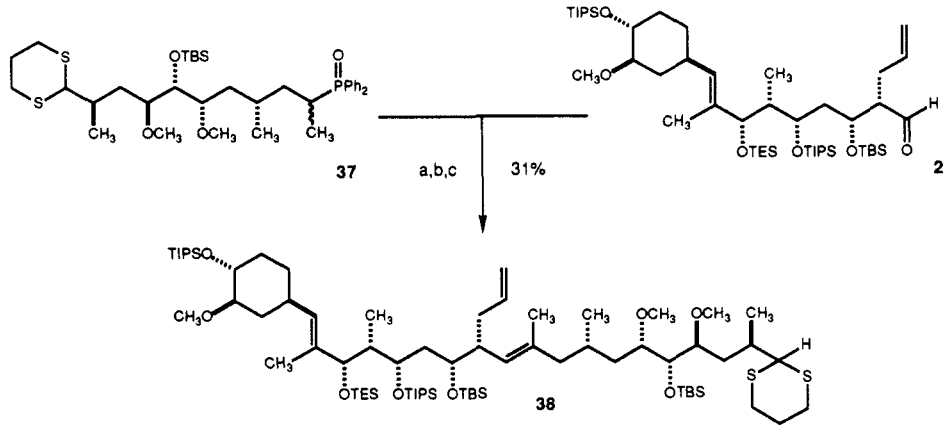
The above results indicated that the center carbonyl was effectively competing for an internal nucleophile. It seemed probable that an imide or amide at C_8 would effectively screen C_9, thus enhancing six-ring selectivity. To test this hypothesis a better synthesis of the model diols was desired. Since the yields of aldol reactions with the trichloroethoxyimide and C_{10}–C_{18} aldehyde were lower than those with a PMB imide, enolization conditions were studied by ^1H NMR. Reaction conditions of 30 min at 0 °C with 1.10 equiv of triethylamine and 1.0 equiv of *n*-Bu_2BOTf were found to completely enolize imide **47**, but the yield of the aldol adduct **52** was still only 50%. The yield could be improved by recycling recovered aldehyde.[24]

Deprotection with zinc/acetic acid produced diol **63** (Scheme XI). For model work, the diol could also be produced by hydrogenolysis [Pd(OH)$_2$] of the PMB aldol adduct. Diol **63** was oxidized to provide the yellow tricarbonyl **64** in 84% yield. No hydrate was observed (^1H and ^{13}C NMR spectra). Acidic hydrolysis of the C_{14} OTES provided imide hemiketal **65** in 66% yield. No seven-ring product or hydrate was observed by ^1H or ^{13}C NMR.

Attempts at hydrolysis of the imide **65** with LiOOH resulted in oxidative cleavage[25] to form lactone **66** (Scheme XII). Hy-

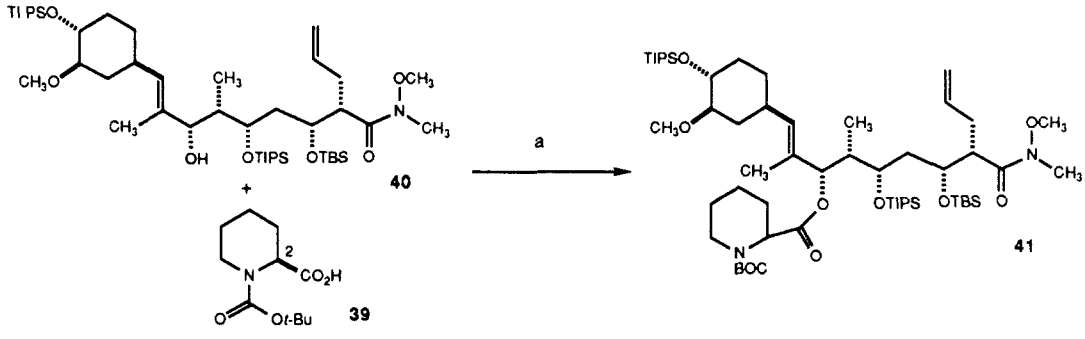
(19) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818–6820.
(20) Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, *45*, 4323–4326.
(21) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.
(22) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
(23) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198–2200. See also: Amon, C. M.; Banwell, M. G.; Gravalt, G. L. *J. Org. Chem.* **1987**, *52*, 4851–4855.
(24) After we selected PMB as the protecting group of choice, we surveyed conditions and found toluene[12c] to be a superior solvent for the aldol addition.

Scheme IV[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, **37**, 4 equiv of TMEDA, −78 °C; **2**, −78 °C; (b) chromatographic separation; (c) KHMDS, THF, 0 °C.

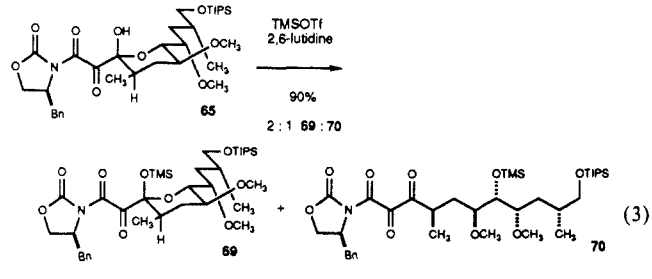
Scheme V[a]



[a] Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, −10 °C.

drolysis with LiOH gave low yields of carboxylic acid **67** along with rearrangement products. Formation of amide **68** with the resulting acid was straightforward; however, the yields for producing the carboxylate were prohibitively low.

A possible method of prohibiting undesired reactions would be silylation of C_{10} OH of **65**. Silylation with TESOTf or TMSOTf at 0 °C resulted in recovered starting material. Silylation was accomplished with TMSOTf/2,6-lutidine in dichloromethane at 20 °C over 3 h. However, the product was a 2:1 mixture of hemiketal **69** to silylated ketone **70** (eq 3). We concluded that the hemiketal should be installed at a late stage in the synthesis.



(3)

A tricarbonyl model study was therefore performed to simulate the synthesis of FK-506 with the tricarbonyl being formed after macrocyclization (Scheme XIII). Imide **46** was enolized and added to the C_{10}–C_{18} model aldehyde to produce aldol adduct **51** in 80% yield after one recycle. Conversion of **51** to **72** was straightforward,[26] but attempts to remove the PMB group from **72** resulted in a mixture of mono- and diol. The C_{10} OTES group could not be selectively removed by acidic hydrolysis. However, a cyclic phenylboronic ester could be prepared with the 9,10,14-triol **73**, as shown in Scheme XIII.[27] The C_{14} OH boronic ester **74** could then be silylated and hydrolyzed to provide the desired diol (**75**).

Table II. ^{13}C NMR Comparison Data of Vicinal Tricarbonyls

compd	C_8	C_9	C_{10}
60	162.6	181.8	197.1
64	166.7	182.0	197.3
79	165.8	185.5	198.7

However, a change in the C_{14} protecting group seemed desirable. Imide **46** was enolized in toluene[12c] and aldehyde **50** was added to form aldol adduct **76**. Conversion of **76** to amide **77** (Scheme XIV) followed by sequential treatment with DDQ and aqueous acid gave diol **78**. Swern oxidation provided the yellow tricarbonyl **79** in 85% yield. Little if any hydrate was detected by ^1H or ^{13}C NMR. The unstable tricarbonyl compound was subjected to TFA/H_2O/THF; however, only the primary TIPS ether was removed. Hydrolysis of both silyl ethers was accomplished with 48% aqueous HF/CH_3CN to give keto amide **80**. No seven-member-ring isomers were detected by ^1H or ^{13}C NMR.

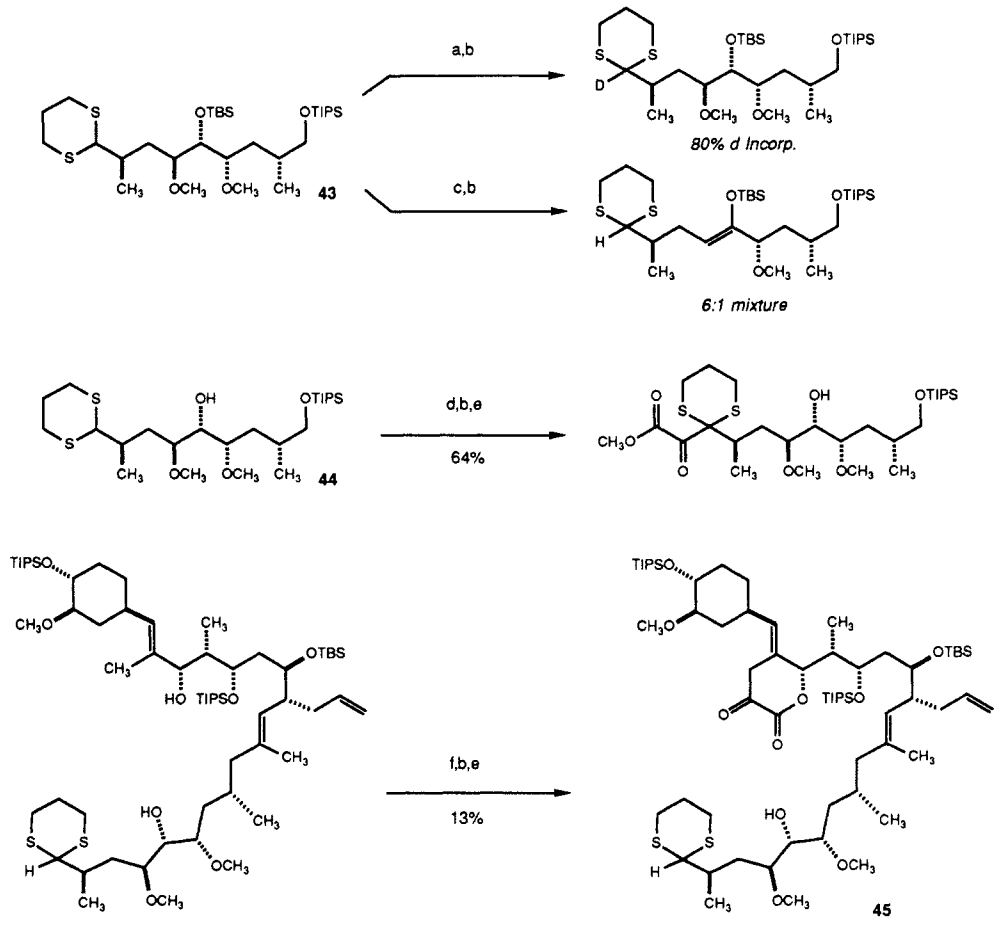
Interestingly, the differences between ester, imide, and amide do not manifest themselves in the ^{13}C chemical shifts of C_9 (Table II). The balance of six- versus seven-member-rings may well lie in steric effects.

Completion of the Synthesis

Our macrolactamization strategy mandated attachment of pipecolic acid to C_{26} before the aldol reaction (other functionality would interfere after that point). Thus, hydrolysis of (*E*)-olefin **38** produced C_{26} hydroxy compound **81** in 93% yield (Scheme XV). Installation of BOC-pipecolic acid under the previously described conditions gave the carbamate **82**. Conversion of the

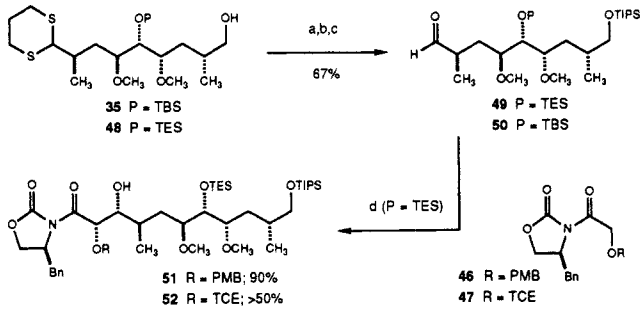
(25) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061–4066.
(26) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166.
(27) (a) Sugihara, J. M.; Bowman, C. M. *J. Am. Chem. Soc.* **1958**, *80*, 2443–2446. (b) Ferrier, R. J. *Methods Carbohydr. Chem.* **1972**, *6*, 419–426. (c) Perun, T. J.; Martin, J. R.; Egan, R. S. *J. Org. Chem.* **1974**, *39*, 1490–1493.

Scheme VI[a]



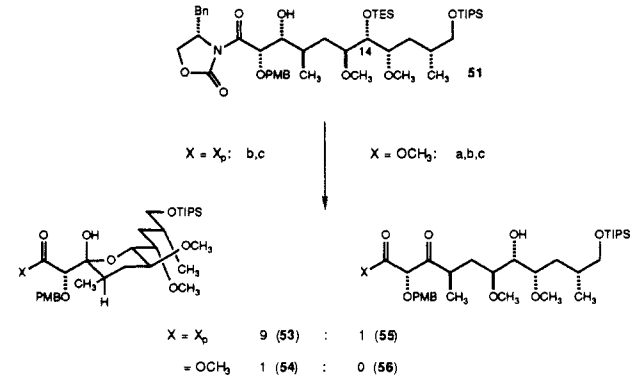
[a] Reagents and conditions: (a) 1.5 equiv of *n*-BuLi, THF-d_8, 2 equiv of HMPA, −30 °C; (b) $(CO_2Et)_2$, −30–0 °C; (c) 1.5 equiv of *n*-BuLi, DME-d_{10}, 2 equiv of HMPA, −30 °C; (d) 4.0 equiv of *n*-BuLi, neat TMEDA, −30 °C; (e) $NaOCH_3$, CH_3OH, 20 °C; (f) 6.0 equiv of *n*-BuLi, neat TMEDA, −30 °C.

Scheme VII[a]



[a] Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) $AgNO_3$, NCS, 2,6-lutidine, CH_3OH, THF, 20 °C; (c) glyoxylic acid hydrate, HOAc, CH_2Cl_2, 40 °C; (d) **46** or **47**, Et_3N, *n*-Bu_2BOTf, −50 or 0 °C, respectively; **50**, −30 °C.

Scheme VIII[a]



[a] Reagents and conditions: (a) CH_3MgBr, CH_3OH, **51**, 0 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; alcohol; Et_3N, −30 °C; (c) TFA, H_2O, THF, 20 °C.

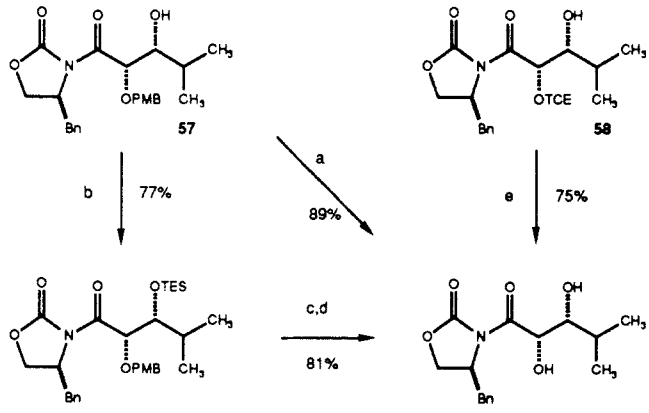
dithiane to aldehyde **83** was accomplished in two steps: modified Corey conditions[28] gave the dimethyl acetal, which was hydrolyzed to aldehyde **83** in 67% overall yield from **81**.

The key aldol addition reaction with imide **46** proved troublesome if run in dichloromethane: large amounts of unreacted aldehyde were frequently recovered, even if a considerable excess of the boron enolate was employed. Fortunately, use of toluene as solvent reproducibly provided the desired adduct **84** (Scheme XV) in 88% yield. Cleavage of the imide with lithium hydroperoxide and acidification then cleanly gave the crude acid.

Treatment of this hydroxy acid with excess TESOTf/2,6-lutidine rapidly formed the silyl ether at C_{10}, the silyl ester at C_8, and the silyl carbamate at N_7. The best mehod of converting this species to the 10-TES-amino acid **85** was to elute the compound onto a column of 230–400-mesh silica gel and allow it to age for ~1 h, followed by normal chromatographic separation. This protocol provided **85** in 80% overall yield from the imide **84**. The unstable amino acid was best treated immediately with Mukaiyama's chloropyridinium salt[26] under high-dilution conditions, which gave the macrocycle **86** in 81–85% yield. The ^1H and ^{13}C NMR spectra of **86** have several broad features (^{13}C NMR has several very broad resonances) and the macrocycle exists primarily in one rotameric conformation. Low-temperature studies on 14-OTES-**86** did not lead to sharper spectra but rather suggested that ring conformational equilibria may be responsible for the

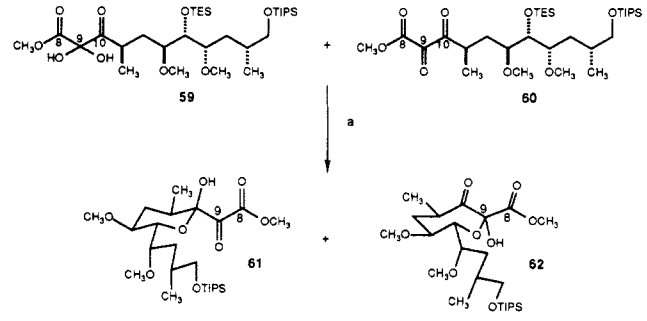
(28) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.

Scheme IX[a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$, EtOAc, 20 °C; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) DDQ, H_2O, CH_2Cl_2, 20 °C; (d) TFA, H_2O, THF, 20 °C; (e) Zn, HOAc, sonication, 30 °C.

Scheme X[a]



[a] Reagents and conditions: (a) TFA, H_2O, THF, 20 °C.

broadening observed. The fact that the C_9 OPMB affects the conformation of the macrocycle is supported by the ^1H NMR of C_9 OH,C_{10} OTES **86** where the expected amide rotamers are seen (ratio 2:1).

Exposure of **86** to excess DDQ[21] gave a mixture of the C_9 OH,C_{10} OTES macrocycle and the $C_{9,10}$ diol **87** (see Scheme XV). Aqueous acid converted the C_9 OH,C_{10} OTES macrocycle to **87**, which was obtained in an overall yield of 74%. As noted above, assignment of the cyclic structure to the product of the Mukaiyama reaction had to be done initially by analogy to the acyclic cases and by elimination of other possible structures (chromatographic behavior inconsistent with a dimerized amino acid, etc.). However, NMR investigations of the C_9 OH,C_{10} OTES macrocycle provided the first independent evidence for the formation of the lactam bond: NOE difference spectroscopy on the C_9 OH,C_{10} OTES macrocycle reveals a 5% NOE from H_9 to H_2 (major amide rotamer). Other evidence for macrocyclization was obtained by hydrolyzing **87** with HF in acetonitrile to afford (9*S*,10*R*,22*R*)-hexahydro-FK-506 in 52% yield and obtaining a high-resolution mass spectrum (EI).

Oxidation of diol **87** under Swern conditions did not proceed as smoothly as in the acyclic cases: monooxidized products were frequently observed. However, reoxidation of these materials (Scheme XVI) provided the yellow tricarbonyl **88** in 80% yield. Interestingly, treatment of the diol with the Dess–Martin periodinane[29] (see below) resulted mostly in cleavage of the C_9–C_{10} bond to give the dialdehyde. Evidently this organic hypervalent iodine species behaves similarly to the corresponding inorganic hypervalent iodine species periodic acid.

The next task was to oxidize the C_{22} hydroxyl to a ketone. Exposure of **88** to aqueous acid formed a complex mixture of partially desilylated products. We therefore removed all silyl groups with the expectation of subsequent selective reprotection. Thus, treatment of the tricarbonyl **88** with aqueous HF/acetonitrile (Scheme XVI) gave 22-dihydro-FK-506 (**89**) in 81% yield. When dihydro-FK-506 was treated with TIPSOTf/2,6-lutidine, C_{32} was rapidly silylated. Much more slowly, less polar material appeared, which was characterized by NMR as an approximately 2:1 mixture of C_{24},C_{32} and C_{22},C_{32} bis-TIPS compounds. These compounds could only be separated with difficulty, so other silylating reagents were examined. Treatment with TESCl/pyridine[30] gave a more easily separable mixture of isomers, and the desired 24,32-bis-TES-22-dihydro-FK-506 was obtained in 70% yield.

Attempts to oxidize the mixture of bis-TIPS alcohols under Swern conditions were unsuccessful. However, treatment with the Dess–Martin reagent **90** gave material that by ^1H NMR was identical with authentic 24,32-bis-TIPS-FK-506. Treatment with aqueous HF/acetonitrile then provided impure FK-506, which was identified by one- and two-dimensional NMR techniques.

A superior procedure employed 24,32-bis-TES-**89**, which could be oxidized (Scheme XVI) by the Dess–Martin reagent in 61% yield to bis-TES-FK-506 (**91**). Deprotection as above now produced pure FK-506 in 81% yield, which was identical with natural material by ^1H NMR, COSY-45 (300 MHz; $CDCl_3$ and C_6D_6),[31] ^{13}C NMR, optical rotation at six wavelengths,[32] and TLC in several solvent systems.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on EM Reagents 0.25-mm silica gel 60-F plates. Visualization was accomplished with UV light and by dipping in either an aqueous ceric ammonium molybdate solution or ethanolic phosphomolybdic acid solution followed by heating. Solvents for extraction and chromatography were reagent grade. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Other solvents for reactions were dried with 3- or 4-Å molecular sieves. Residual water content was determined by Karl Fischer titration. Solvents for boron aldol reactions were deoxygenated by bubbling nitrogen through them prior to use. Chromatography was performed by the method of Still[33] with EM Reagents silica gel 60 (230–400 mesh) with the indicated solvent system. All reactions were performed under an inert atmosphere of dry nitrogen in oven-dried (140 °C) glassware. Brine refers to a saturated aqueous solution of sodium chloride.

Optical rotations were determined on a Perkin-Elmer 241 polarimeter using the sodium D line (λ = 589 nm) at the temperature indicated and are reported as follows: $[\alpha]^{temp}_D$, concentration (c = g/100 mL), and solvent. Infrared spectra were recorded on a Perkin-Elmer 281B spectrophotometer. Peaks are reported (in cm^{-1}) with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (10–33%). The following abbreviations were also used: br (broadened), sh (shoulder). ^1H NMR spectra were recorded in deuteriochloroform on a Bruker AM-300 (300.13 MHz) spectrometer. Chemical shifts are reported in ppm from an internal standard of residual chloroform (7.27 ppm). Selected data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened, obs = obscured), coupling constants (Hz), and assignments. ^{13}C NMR spectra were recorded in deuteriochloroform on either a Bruker AM-300 (75.47 MHz) or a Bruker WM-250 (62.90 MHz) spectrometer. Chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.0 ppm). Data are reported as follows: chemical shift, assignment. Grouped shifts and assignments are provided where an ambiguity has not been resolved. All compounds are assigned by using FK-506 numbering. Proton and carbon NMR assignments were made with the aid of COSY-45 and HETCOR data. Mass spectra were obtained on a Kratos MS-50 spectrometer. Low-resolution spectra using electron impact (EI) were obtained at 70 eV. Combustion analyses were obtained in-house from our Analytical Research Department.

Starting Materials. (*S*)-Pipecolic acid, (*S*)-4-benzyl-2-oxazolidinone, and (*S*)-methyl 3-hydroxy-2-methylpropionate were purchased from Aldrich. (4*S*)-Benzyl-[1-oxo-2-(2,2,2-trichloroethoxy)ethyl]-2-oxazolidinone, (4*S*)-benzyl-[1-oxo-2-[(4-methoxyphenyl)methyl]ethyl]-2-oxa-

(29) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

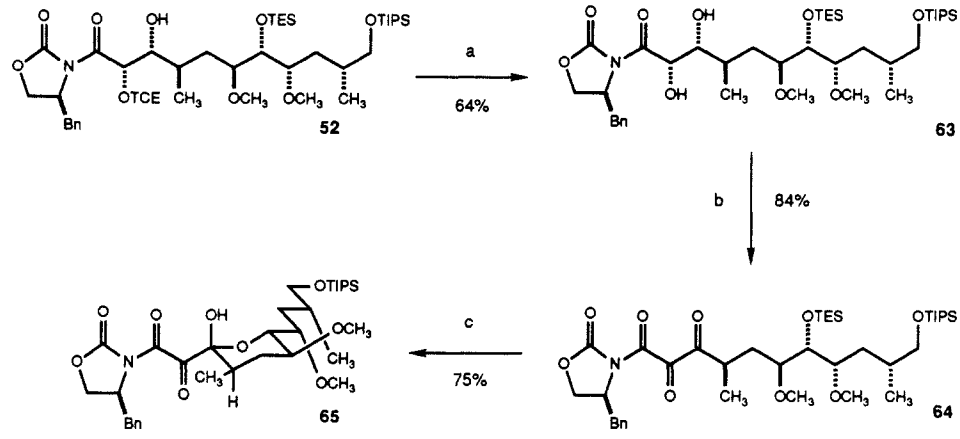
(30) Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917–5919.

(31) Significant solvent-induced shifts occur in benzene-d_6, and the 2-D spectra serve as fingerprints in each solvent.

(32) See Experimental Section.

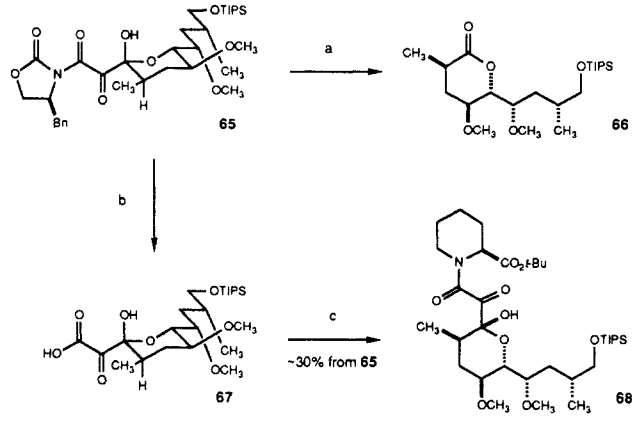
(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Scheme XI[a]



[a] Reagents and conditions: (a) Zn, HOAc, THF, sonication, 20 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (c) TFA, H_2O, THF, 20 °C.

Scheme XII[a]



[a] Reagents and conditions: (a) LiOH·H_2O, 30% H_2O_2, THF, H_2O, 0 °C; (b) LiOH, H_2O 0 °C; (c) *tert*-butyl pipecolate, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 20 °C.

zolidinone, (4*S*)-4-benzyl-3-(1-oxopropyl)-2-oxazolidinone, and (4*R*,5*S*)-4-methyl-5-phenyl-[1-oxo-2-[(4-methoxyphenyl)methyl]-ethyl]-2-oxazolidinone were prepared in analogy with literature methods.[12b,c] Di-*n*-butylboron triflate,[34] (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone,[35] (2*E*,1′*R*,3′*R*,4′*R*)-(±)-3-[4-methoxy-3-(triisopropylsiloxy)-cyclohexyl]-2-methylpropenal,[3c] and (*R*)-2-methyl-4-penten-1-ol[12b] were prepared according to literature methods.

C_{10}–C_{18} Fragment. (2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropanol (21). A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 100 mL of *N*,*N*-dimethylformamide, 6.08 g (51.5 mmol) of (*S*)-(+)-methyl-3-hydroxy-2-methylpropionate, 6.31 g (92.6 mmol) of imidazole, and 10.9 g (72.1 mmol) of *tert*-butyldimethylsilyl chloride. The reaction exothermed to +30 °C and was allowed to stir at room temperature. After 5 h, 100 mL of saturated aqueous sodium bicarbonate was added and the reaction mixture was extracted with 3 × 150 mL of hexane. The organic layers were washed with 2 × 100 mL of water, combined, dried over sodium sulfate, filtered, and concentrated to provide 14.1 g (118%) of the silylated ester. R_f = 0.33 (dichloromethane). The crude product was suitable for reduction. A 500-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 79 mL (118 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene and 80 mL of tetrahydrofuran. The reaction mixture was cooled to −70 °C and 11 g (~47 mmol) of the crude silylated ester was dissolved in 40 mL of tetrahydrofuran and added via cannula. The reaction mixture was stirred 20 min at −60 °C, rapidly warmed to 0 °C, and stirred for 2 h. The reaction was then transferred via cannula into a well-stirred mixture of 300 g of sodium potassium tartrate in 1000 mL of water and 300 mL of hexanes. The resulting slurry was stirred until two clear layers separated (approximately 2 h). The layers were separated and the aqueous layer was extracted with 3 × 200 mL of diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (6 cm × 30 cm column, dichloromethane) to provide 6.19 g (80% for two steps) of alcohol **21** as an oil: $[\alpha]^{31}_D$ +9.44° (*c* 1.97, CH_2Cl_2); R_f = 0.23 (dichloromethane); IR (film) 3590–3150 m (OH), 2960 s, 2950 s, 2890 s, 2860 s, 1470 m, 1465 m, 1405 w, 1390 m, 1360 m, 1255 s, 1090 s, 1040 s, 1005 m, 990 w, 940 m, 905 w, 840 s, 815 m, 775 s, 665 m; ^{1}H NMR δ 3.74 (dd, *J* = 9.8, 4.4, C_{10} H), 3.63 (br m, C_{12} H_2), 3.55 (dd, *J* = 9.8, 8.3, C_{10} H), 2.89 (br t, *J* = 4.4, C_{12} OH), 1.94 (m, H_{11}), 0.90 (s, $SiC(CH_3)_3$), 0.84 (d, *J* = 6.8, C_{11a} H_3), 0.08 (s, $Si(CH_3)_2$); ^{13}C NMR δ 68.7, 68.3 (C_{10}, C_{12}), 37.0 (C_{11}), 25.8 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 13.1 (C_{11a}), −5.57, −5.64 ($Si(CH_3)_2$). Anal. Calcd for $C_{10}H_{24}O_2Si$: C, 58.77; H, 11.84. Found: C, 58.49; H, 12.02.

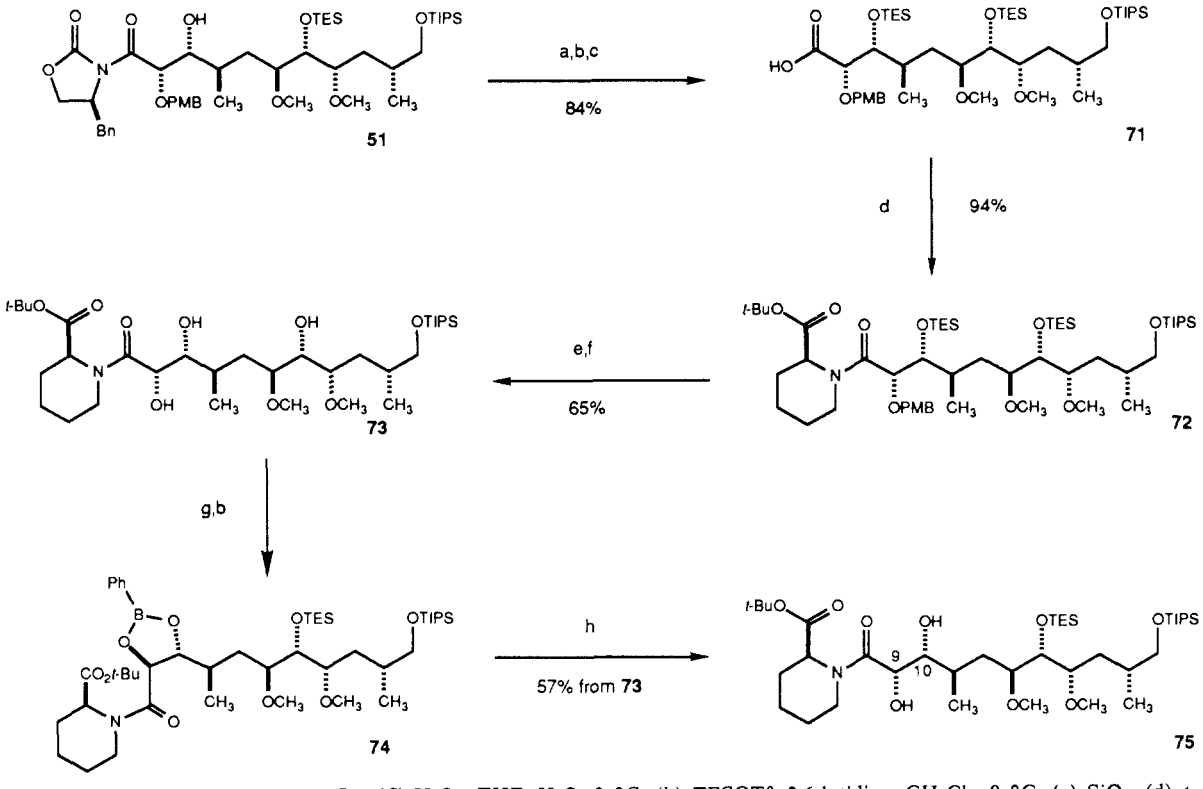
(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl Bromide (22). A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 6.19 g (30.3 mmol) of alcohol **21** and 50 mL of dichloromethane. The solution was cooled to −10 °C and 8.60 mL (6.24 g, 61.6 mmol) of triethylamine was added followed by addition of 3.45 mL (5.10 g, 44.5 mmol) of methanesulfonyl chloride over 15 min. The resulting mixture was stirred at −10 °C for 1 h and then quenched by the addition of 50 mL of 0.5 N sodium bisulfate. The reaction mixture was extracted with 4 × 50 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and rapidly chromatographed (6 cm × 25 cm column, 1:1 hexane/ethyl acetate) to provide 8.48 g (99%) of the mesylate. R_f = 0.54 (dichloromethane). The mesylate was immediately converted to the bromide. A 100-mL round-bottom flash fitted with a magnetic stirring bar, condenser, and nitrogen inlet was charged with 8.48 g (30.0 mmol) of the mesylate, 50 mL of acetone, and 29.0 g (90.0 mmol) of tetrabutylammonium bromide. The solution was heated to reflux for 6 h and cooled to room temperature. A two-phase mixture was formed by the addition of 100 mL of diethyl ether and 150 mL of water. The aqueous layer was extracted with 3 × 100 mL of diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered concentrated, chromatographed (4 cm × 25 cm column, hexane), and distilled [bp 50 °C (0.4 Torr)] to give 7.0 g (86%) of bromide **22** as a clear liquid: $[\alpha]^{27}_D$ +11.1° (*c* 1.42, CH_2Cl_2); $R_{f,Br}$ = 0.80, $R_{f,OMs}$ = 0.18 (1:1 hexane/dichloromethane); IR (film) 2960 s, 2940 s, 2910 s, 2890 s, 2865 s, 1475 m, 1465 m, 1435 w, 1410 w, 1390 m, 1365 w, 1340 w, 1260 s, 1235 m, 1195 w, 1145 m, 1105 s, 1060 w, 1025 m, 1010 m, 955 w, 945 m, 915 s, 860 m, 845 s, 820 m, 780 s, 740 s, 670 m, 665 m; ^{1}H NMR δ 3.51 (overlapping m, C_{10} H_2, C_{12} H_2), 1.98 (m, H_{11}), 0.99 (d, *J* = 6.8, C_{11a} H_3), 0.90 (s, $SiC(CH_3)_3$), 0.07 (s, $Si(CH_3)_2$); ^{13}C NMR δ 65.3 (C_{10}), 37.9 (C_{12}), 37.8 (C_{11}), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 15.4 (C_{11a}), −5.45, −5.48 ($Si(CH_3)_2$). Anal. Calcd for $C_{10}H_{23}OSiBr$: C, 44.94; H, 8.67. Found: C, 44.54; H, 8.98.

(2*R*)-Benzyl 2-Methyl-4-penten-1-yl Ether (23). A 250-mL round-bottom flask, equipped with a magnetic stirring bar and a thermometer was fitted with a septum and a nitrogen inlet. The apparatus was charged with 1.60 g (40.0 mmol) of a 60% dispersion of sodium hydride in mineral oil. The sodium hydride was washed with 3 × 20 mL of dry hexane and then suspended in 40 mL of dry *N*,*N*-dimethylformamide and cooled to 0 °C. To the stirred suspension was added 4.32 mL (6.21 g, 36.3 mmol) of benzyl bromide followed by dropwise addition of 3.47 g (34.6 mmol) of (*R*)-2-methyl-4-penten-1-ol[12b] (via cannula) dissolved in

(34) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.

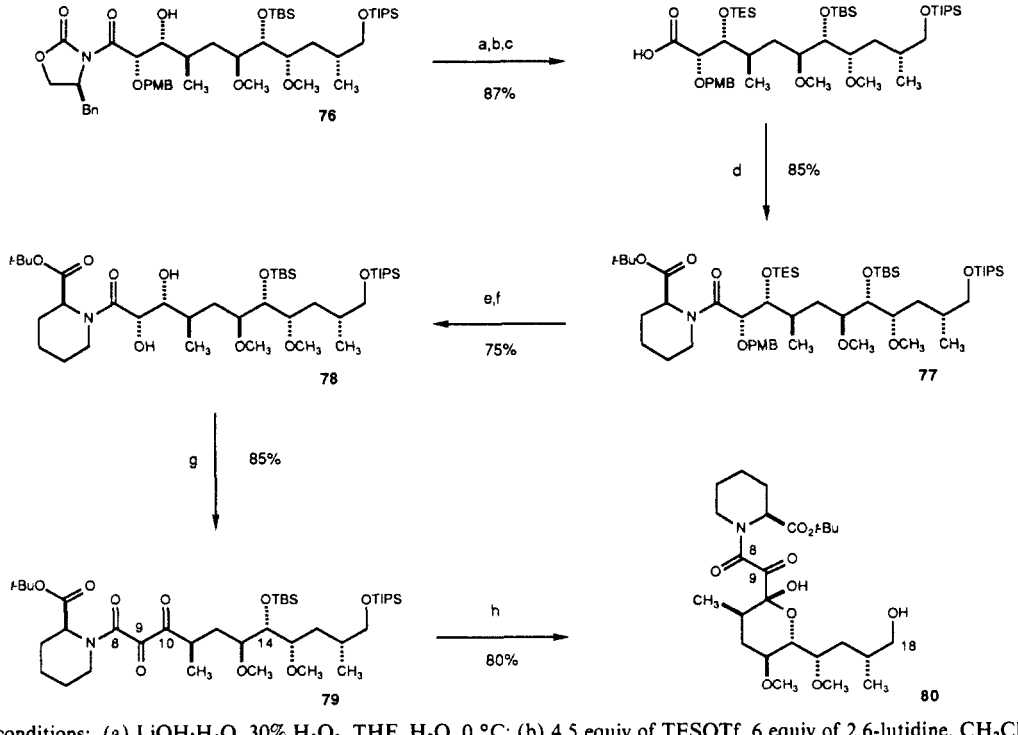
(35) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835.

Scheme XIII[a]



[a] Reagents and conditions: (a) $LiOH{\cdot}H_2O$, 30% H_2O_2, THF, H_2O, 0 °C; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) SiO_2; (d) *tert*-butyl pipecolate, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 20 °C; (e) DDQ, H_2O, CH_2Cl_2, 20 °C; (f) TFA, H_2O, THF, 20 °C; (g) $PhB(OH)_2$, C_6H_6, 20 °C; (h) H_2O, 20 °C.

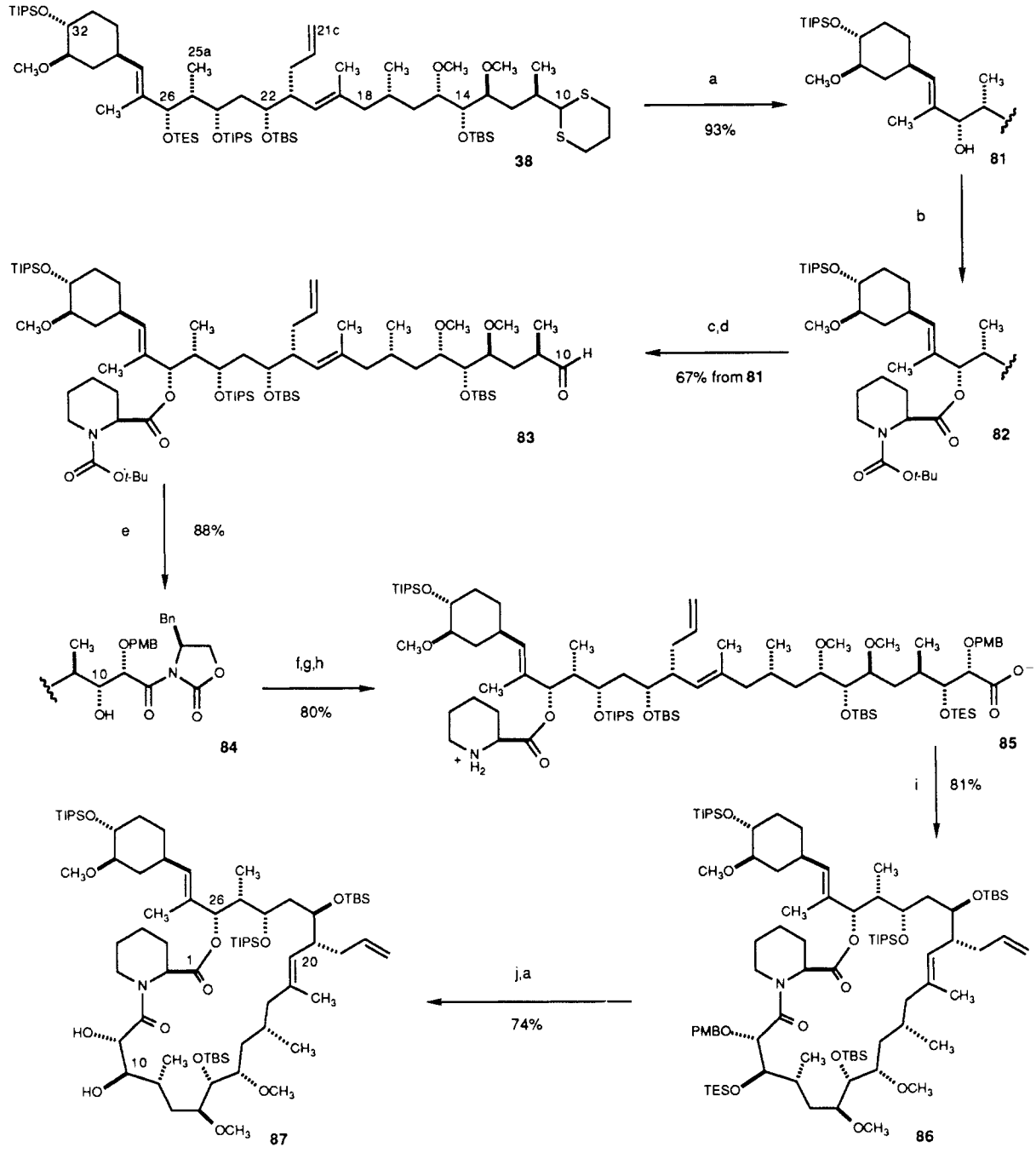
Scheme XIV[a]



[a] Reagents and conditions: (a) $LiOH{\cdot}H_2O$, 30% H_2O_2, THF, H_2O, 0 °C; (b) 4.5 equiv of TESOTf, 6 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C; (c) SiO_2; (d) *tert*-butyl pipecolate, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 20 °C; (e) DDQ, H_2O, CH_2Cl_2, 20 °C; (f) TFA, H_2O, THF, 20 °C; (g) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N; (h) 48% aqueous HF, CH_3CN, 20 °C.

10 mL of diethyl ether over 15 min, maintaining the reaction temperature at 6 °C or less. The reaction mixture was stirred for 20 min at 0 °C and then warmed to room temperature. After 12 h, 10 mL of water was cautiously added and the mixture was transferred to a 250-mL separatory funnel. The aqueous phase was extracted with 3 × 100 mL of ethyl acetate. The organic layers were individually washed with 100 mL of brine, combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (6 cm × 33 cm column, 9:1 hexane/dichloromethane) to afford 5.93 g (89%) of benzyl ether **23** as a clear, colorless liquid: $[\alpha]^{22}_{546}$ -1.6° (*c* 2.21, CH_2Cl_2); R_f = 0.20 (9:1 hexane/dichloromethane); IR (film) 3080 m, 3070 m, 3035 m, 3005 w, 2980 s, 2960 s, 2930 s, 2910 s, 2880 s, 2860 s, 2975 w, 1645 m, 1605 w, 1495 m, 1480 w, 1455 s, 1445

Scheme XV[a]

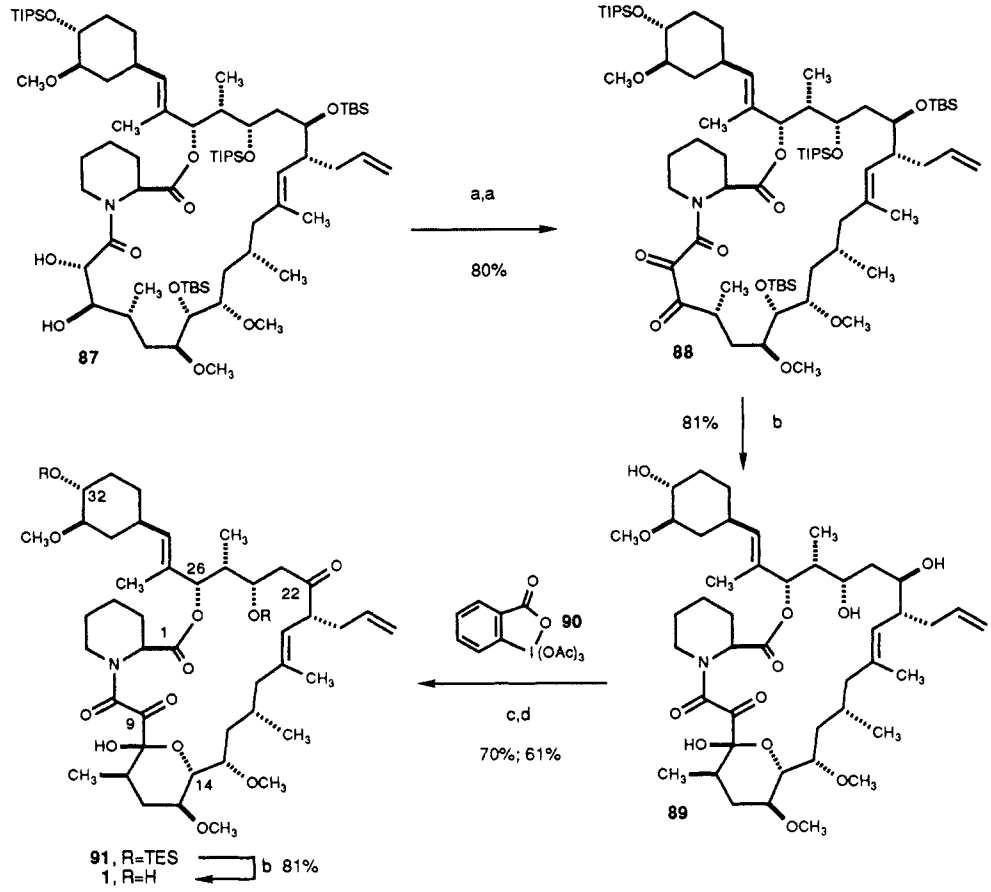


[a] Reagents and conditions: (a) TFA, H_2O, THF, 20 °C; (b) 4 equiv of BOC-pipecolic acid, DCC, DMAP, CH_2Cl_2; −15 °C; (c) $AgNO_3$, NCS, 2,6-lutidine, CH_3OH, THF, 20 °C; (d) glyoxylic acid hydrate, HOAc, CH_2Cl_2, 40 °C; (e) Et_3N, **46**, *n*-Bu_2BOTf, toluene, −50 °C; **83**, −30 °C; (f) $LiOH·H_2O$, 30% H_2O_2, THF, H_2O, 0 °C; (g) 4.5 equiv of TESOTf, 6 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C; (h) SiO_2; (i) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 20 °C; (j) DDQ, H_2O, CH_2Cl_2, 20 °C.

m, 1415 w, 1375 m, 1365 m, 1310 w, 1255 w, 1205 w, 1160 w, 1100 s, 1040 m, 995 m, 915 s, 745 s, 695 s, 605 m; ^1H NMR δ 7.30 (m, ArH), 5.79 (m, H_{15}), 5.03 (m, $C_{15a}H_2$), 4.51 (s, $ArCH_2O$), 3.31 (m, $C_{18}H_2$), 2.23 (m, H_{17}), 1.91 (m, $C_{16}H_2$), 0.93 (d, J = 6.5, $C_{17a}H_3$); ^{13}C NMR δ 138.7 ($C_{1'}$), 136.8 (C_{15}), 128.2, 127.4, 127.3 ($C_{2',6'}$, $C_{3',5'}$, $C_{4'}$), 115.8 (C_{15a}), 75.2, 72.9 (C_{18}, OCH_2Ar), 38.0 (C_{17}), 33.3 (C_{16}), 16.7 (C_{17a}). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.08; H, 9.49.

(3*R*)-4-(Benzyloxy)-3-methylbutanal (24). A 250-mL round-bottom flask, equipped with a magnetic stirring bar and a thermometer, was fitted with a septum and a nitrogen inlet. The apparatus was charged with benzyl 2-methyl-4-penten-1-yl ether (2.39 g, 12.5 mmol) in 75 mL of acetone and 25 mL of water followed by 0.833 mL (0.15 M aqueous solution, 0.125 mmol) of osmium tetraoxide. Three equal portions, 6.04 g (26.2 mmol) total, of potassium periodate were then added. The resulting slurry was stirred for 6 h at room temperature and decanted into a 500-mL separatory funnel. The aqueous layer was extracted with 3 × 200 mL of diethyl ether. Each washing was stirred over the solids for 5 min and washed with 150 mL of saturated aqueous sodium thiosulfate and 100 mL of saturated aqueous sodium chloride. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and chromatographed (4 × 20 cm column; 4:1 hexane/ethyl acetate) to afford 1.94 g (81%) of aldehyde **24** as a colorless oil followed by 0.33 g (12%) of the corresponding 14-hydroxy-15-ketone. A 25-mL round-bottom flask fitted with a magnetic stirring bar was charged with 0.33 g (1.39 mmol) of this ketone dissolved in 5 mL of methanol. To this clear solution was added 105 mg (2.79 mmol) of sodium borohydride in four portions. After being stirred at 20 °C for 2 h, the reaction mixture was poured into a mixture of 15 mL of ethyl acetate and 15 mL of brine. Approximately 1 mL of water was added to produce a homogeneous mixture. The layers were separated and the aqueous layer was extracted with 3 × 15 mL of ethyl acetate. The organic layers were combined, concentrated, and dissolved in 9 mL of acetone and 3 mL of water. To this solution was added 0.962 g (4.18 mmol) of potassium periodate in one portion. After being stirred at 20 °C for 5 h, the reaction mixture

Scheme XVI[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N; (b) aqueous HF, CH_3CN, 20 °C; (c) TES-Cl, pyridine, 0 °C; (d) Dess-Martin periodinane (**90**), pyridine, CH_2Cl_2, 20 °C.

was poured into a mixture of 15 mL of diethyl ether and 15 mL of brine. The layers were separated and the aqueous phase was extracted with 3 × 15 mL of diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (2 cm × 20 cm column, 4:1 hexane/ethyl acetate) to provide an additional 0.195 g (73%) of aldehyde as a clear liquid. The total yield of aldehyde was 2.135 g (89%): $R_{f,\text{hydroxyketone}} = 0.13$, $R_{f,\text{aldehyde}} = 0.37$ (4:1 hexane/ethyl acetate); IR (film) 3090 w, 3070 w, 3040 w, 2960 m, 2940 m, 2870 m, 2730 w, 1728 s (C=O), 1500 w, 1420 m, 1370 w, 1310 w, 1255 w, 1210 w, 1105 m, 930 w, 740 m; ^{1}H NMR δ 9.78 (t, J = 2.2, H_{15}); 7.33 (m, ArH), 4.51 (s, OCH_2Ar), 3.44 (dd, J = 9.3, 4.9, C_{18} H), 3.27 (dd, J = 9.3, 7.8, C_{18} H), 2.57 (ddd, J = 15.6, 6.4, 2.2, C_{16} H), 2.44 (m, H_{17}), 2.29 (ddd, J = 15.6, 6.8, 2.2, C_{16} H), 1.00 (d, J = 6.8, C_{17a} H_3); ^{13}C NMR δ 202.3 (C_{15}), 138.2 ($C_{1'}$), 128.3, 127.48 ($C_{2',6'}$, $C_{3',5'}$), 127.51 ($C_{4'}$), 74.8, 73.0 (C_{18}, CH_2Ar), 48.4 (C_{16}), 29.0 (C_{17}), 17.0 (C_{17a}). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.29. Found: C, 74.96; H, 8.29.

C_{14}-C_{15} Aldol Adduct 25. A 100-mL, three-neck, round-bottom flask was fitted with a magnetic stirring bar, nitrogen inlet, thermometer, and septum. The apparatus was flushed with nitrogen and then charged with 5.35 g (15.1 mmol) of the *p*-methoxybenzyloxyacetimide in 30 mL of degassed, sieve-dried dichloromethane and cooled to -50 °C. To this clear solution was added 2.31 mL (1.78 g, 16.6 mmol) of triethylamine followed by 3.75 mL (4.13 g, 15.1 mmol) of di-*n*-butylboron triflate over 5 min. The solution exothermed to -36 °C upon addition of di-*n*-butylboron triflate. After the resultant mixture was stirred at -50 °C for 90 min, 1.93 g (10.0 mmol) of aldehyde **24** (previously dried azeotropically with 2 × 5 mL of benzene) in 2 mL of dichloromethane (plus a 1-mL rinse) was added via cannula. The resulting pale yellow solution was stirred at -40 °C for 1 h and then warmed to 0 °C over 10 min. The reaction was quenched by addition of 15 mL of pH 7 phosphate buffer followed by 10 mL of methanol and 10 mL of tetrahydrofuran to result in a nearly homogeneous solution. After 5 min, 15 mL of 30% aqueous hydrogen peroxide in 15 mL methanol was added dropwise over 30 min (*caution*: initial reaction is highly exothermic). After being stirred for 1 h at 0 °C, the reaction mixture was concentrated by rotary evaporation. The resulting mixture was extracted with 3 × 100 mL of ethyl acetate. The individual organic extracts were washed with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of brine. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The resulting oil was chromatographed (6.5 cm × 35 cm column, 2:1 hexane/ethyl acetate) to provide 4.62 g (84%) of product as a thick oil: $[\alpha]^{28}_D$ +31.8° (*c* 2.08, CH_2Cl_2); R_f = 0.16 (2:1 hexane/ethyl acetate); IR (film) 3600-3300 w (OH), 3070 w, 3030 w, 2960 m, 2940 m, 2910 w, 2870 m, 1780 s (C=O), 1710 m (C=O), 1610 w, 1585 w, 1515 m, 1495 w, 1455 m, 1400 w, 1365 m, 1345 m, 1305 w, 1250 s, 1200 m, 1180 m, 1150 m, 1120 m, 1090 m, 1070 m, 1030 m, 1000 w, 990 w, 955 w, 910 w, 850 w, 815 w, 770 w, 735 w, 700 m; ^{1}H NMR δ 7.30 (overlapping m, ArH), 6.85 (m, PMB $H_{3,5}$), 5.61 (d, J = 6.8, $H_{5'}$), 5.15 (d, J = 2.9, H_{14}), 4.71 (m, $H_{4'}$), 4.63, 4.46 (2 d, J = 11.2, OCH_2Ar), 4.51 (s, OCH_2Ar), 4.11 (m, H_{15}), 3.79 (s, PMB OCH_3), 3.36 (m, C_{18} H_2), 2.45 (d, J = 8.8, C_{15} OH), 2.03 (m, H_{17}), 1.70 (m, C_{16} H_2), 1.02 (d, J = 6.8, C_{17a} H_3), 0.88 (d, J = 6.4, $C_{4a'}$ H_3); ^{13}C NMR δ 170.6 (C_{13}), 159.6 (PMB C_4), 153.0 ($C_{2'}$), 138.7 (Bn C_1), 133.1 ($C_{1''}$), 129.3 (PMB C_1), 130.2, 128.8, 128.7, 128.4, 127.6, 127.5, 125.6 (Ar CH), 113.9 (PMB $C_{3,5}$), 79.7, 79.6 (C_{14}, $C_{5'}$), 75.6 (C_{18}), 73.1, 72.8 (2 OCH_2Ar), 70.7 (C_{15}), 55.4, 55.3 ($C_{4'}$, OCH_3), 38.3 (C_{16}), 30.3 (C_{17}), 17.8 (C_{17a}), 14.4 ($C_{4'a}$). Anal. Calcd for $C_{32}H_{37}NO_7$: C, 70.18; H, 6.81; N, 2.56. Found: C, 70.00; H, 6.98; N, 2.70.

C_{13} Amide 26. To a suspension of 3.46 g (35.5 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 18 mL of tetrahydrofuran at 0 °C in a 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, thermometer, and nitrogen inlet was added 17.8 mL (35.5 mmol) of 2.0 M trimethylaluminum in toluene over a 5-min period (*caution*: vigorous gas evolution). After the addition was complete, the cooling bath was removed and the clear solution was stirred for 30 min at room temperature. The solution was recooled to -15 °C, and a solution of 3.89 g (7.1 mmol) of imide **25** in 18 mL of tetrahydrofuran (plus of 5-mL rinse) was added via cannula. The cloudy reaction mixture was stirred at -10 °C, at which temperature gas evolved steadily and the mixture slowly cleared. After 2 h the solution was cannulated into a mixture of 150 mL of hexane, 20 mL of dichloromethane, and 100 mL of 1.0 N aqueous tartaric acid at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 1 h. The layers were separated and the aqueous layer was extracted with 2 × 150 mL of dichloromethane. The individual organic extracts were washed with 2 × 100 mL of brine, combined, dried over sodium sulfate, filtered, and concentrated. Purification of the res-

idue by chromatography (6 cm × 30 cm column, a gradient consisting of 2 L of 5:1 dichloromethane/ethyl acetate, followed by 1 L of 4:1, 1 L of 3:2, and 1 L of 1:1) gave 2.58 g (84%) of **26**: $[\alpha]^{27}_D$ +31.5° (*c* 3.60, CH_2Cl_2); R_f = 0.19 (1:1 hexane/ethyl acetate); IR (film) 3650–3300 m (OH), 3060 w, 3030 m, 2940 s, 2940 s, 2870 s, 1750 w, 1720 w, 1665 s (C=O), 1610 m, 1585 w, 1510 s, 1455 m, 1420 m, 1390 m, 1365 m, 1305 m, 1250 s, 1210 m, 1175 m, 1090 s, 1030 s, 990 m, 910 m, 825 m, 725 s, 700 m; ^{1}H NMR δ 7.30 (overlapping m, ArH), 6.85 (m, PMB $H_{3,5}$), 4.69, 4.38 (2 d, *J* = 11.2, OCH_2Ar), 4.48 (s, OCH_2Ar), 4.21 (br d, *J* = 4.0, H_{14}), 4.02 (m, H_{15}), 3.78 (s, PMB OCH_3), 3.55 (s, $NOCH_3$), 3.32 (m, C_{18} H_2), 3.20 (s, NCH_3), 2.77 (br d, *J* = 5.9, C_{15} OH), 1.92 (m, H_{17}), 1.54 (m, C_{16} H_2), 0.98 (d, *J* = 6.8, C_{17a} H_3); ^{13}C NMR δ 171.1 (br, C_{13}), 159.2 (PMB C_4), 138.5 (Bn C_1), 129.6, 128.1, 127.3, 127.2 (aromatic CH), 129.2 (PMB C_1), 113.6 (PMB $C_{3,5}$), 77.2 (br, C_{14}), 75.1 (C_{18}), 72.8, 71.4 (2 OCH_2Ar), 69.9 (C_{15}), 61.0 ($NOCH_3$), 55.0 (PMB OCH_3), 37.1 (C_{16}), 32.2 (br, NCH_3), 30.1 (C_{17}), 17.7 (C_{17a}). Anal. Calcd for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N, 3.25. Found: C, 66.65; H, 7.82; N, 3.24.

C_{13} Ketone 27. A 50-mL pear-shaped flask was fitted with a septum, thermocouple, nitrogen inlet, and magnetic stirring bar, flushed with nitrogen, and charged with 1.09 g (39.4 mmol) of high sodium (~0.5%) 25 wt % lithium dispersion in mineral oil. The dispersion was washed with 4 × 3 mL of distilled diethyl ether (lithium floats in diethyl ether and coats the walls of the flask when solvent is removed beneath it) and then suspended in 5 mL of distilled diethyl ether. A crystal of iodine was added and the suspension was cooled to 0 °C. To the gray suspension was added via cannula 3.16 g (11.8 mmol) of bromide **22** dissolved in 8 mL (plus 2 × 2 mL rinse) of distilled diethyl ether. The suspension was stirred 1 h at 0 °C (within 15 min the suspension turned rust red). A separate 50-mL round-bottom flask was fitted with a septum, thermocouple, nitrogen inlet, and magnetic stirring bar, flushed with nitrogen, and charged with 0.850 g (1.97 mmol) of amide **26** dissolved in 5 mL of distilled tetrahydrofuran. Both reaction vessels were cooled to −78 °C and the organolithium reagent was transferred to the amide solution via cannula. An exotherm to −50 °C was observed. After being stirred at −78 °C for 30 min, the reaction mixture was warmed to −20 °C, stirred 30 min, and then transferred via cannula to a well-stirred mixture of 50 mL of saturated aqueous ammonium chloride and 20 mL of diethyl ether at 0 °C. The resulting mixture was transferred to a separatory funnel and extracted with 3 × 20 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (4.5 cm × 30 cm column, 7:1 hexane/ethyl acetate) to provide 759 mg (69%) of ketone **27** as a clear oil: $[\alpha]^{28}_D$ +29.2° (*c* 1.08, CH_2Cl_2); R_f = 0.28 (4:1 hexane/ethyl acetate); IR (film) 3600–3550 w (OH), 3080 w, 3070 w, 3030 w, 3000 sh, 2980 s, 2965 s, 2860 s, 1710 m (C=O), 1610 m, 1585 w, 1515 s, 1495 w, 1470 m, 1465 m, 1455 m, 1390 m, 1360 m, 1300 m, 1250 s, 1210 w, 1175 m, 1095 s, 1035 s, 1010 m, 835 s, 780 m, 740 m, 695 m, 665 m; ^{1}H NMR δ 7.30 (overlapping m, ArH), 6.87 (m, PMB $H_{3,5}$), 4.61, 4.38 (2 d, *J* = 11.2, OCH_2Ar), 4.48 (s, OCH_2Ar), 3.96 (m, H_{15}), 3.80 (s, PMB OCH_3), 3.68 (d, *J* = 3.4, H_{14}), 3.43 (m, C_{10} H_2), 3.31 (m, C_{18} H_2), 2.71 (d, *J* = 7.3, C_{15} OH), 2.69 (dd, *J* = 17.6, 5.4, C_{12} H), 2.38 (dd, *J* = 17.6, 7.8, C_{12} H), 2.22 (m, H_{11}), 1.96 (m, H_{17}), 1.52 (m, C_{16} H_2), 0.97 (d, *J* = 6.8, C_{17a} H_3), 0.89 (d, *J* = 6.8, C_{11a} H_3); ^{13}C NMR δ 212.1 (C_{13}), 159.5 (PMB C_4), 138.4 (Bn C_1), 129.9, 128.3, 127.5 (Ar CH), 129.2 (PMB C_1), 113.9 (PMB $C_{3,5}$), 86.7 (C_{14}), 75.3 (C_{18}), 73.1, 73.0 (2 OCH_2Ar), 70.3 (C_{15}), 67.6 (C_{10}), 55.3 (PMB OCH_3), 43.2 (C_{12}), 37.9 (C_{16}), 31.1 (C_{11}), 30.3 (C_{17}), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 17.9 (C_{17a}), 16.9 (C_{11a}), −5.38, −5.45 ($Si(CH_3)_2$). Anal. Calcd for $C_{32}H_{50}O_6Si$: C, 68.78; H, 9.02. Found: C, 68.63; H, 9.19.

C_{13},C_{15} Diol 28. A 25-mL round-bottom flask fitted with a septum, nitrogen inlet, and magnetic stirring bar was charged with 1.69 g (6.44 mmol) of tetramethylammonium triacetoxyborohydride, 5.5 mL of acetonitrile, and 2.77 mL of acetic acid. The mixture was stirred at room temperature for 10 min and then cooled to −40 °C. A solution of 0.900 g (1.61 mmol) of ketone **27** in 2 mL of acetonitrile and 0.350 mL of water was added to the reaction mixture via cannula. After the resultant mixture was stirred at −40 °C for 14 h, 1 mL of acetone was added and the reaction was warmed to 0 °C and stirred for 30 min. The ice bath was removed and 10 mL of a 1 M solution of sodium potassium tartrate was added. The resulting slurry was stirred at room temperature for 1 h. The mixture was neutralized by the *cautious* addition of 25 mL of saturated aqueous sodium bicarbonate. The resulting clear solution was extracted with 4 × 30 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (3.5 cm × 20 cm column, a gradient from 4:1 to 2:1 hexane/ethyl acetate) to afford 830 mg (92%) of inseparable diols **28** (isomer at C_{13}) as an oil that solidified on standing. HPLC analysis of the crude reaction mixture (220-nm UV detection; Zorbax RX reverse-phase column, a gradient from 70:30 acetonitrile/water to 100% acetonitrile at 15 min) showed a 91:9 (R_t 13.8 min, minor; 14.3 min, major) mixture of isomers: R_f = 0.22 (4:1 hexane/ethyl acetate); IR (film) 3600–3200 m (OH), 3090 w, 3070 w, 3030 m, 2980 s, 2930 m, 2860 s, 1610 s, 1585 m, 1515 s, 1495 m, 1470 s, 1460 s, 1455 s, 1440 m, 1390 w, 1360 m, 1305 s, 1250 s, 1210 m, 1175 s, 1160 m, 1090 s, 1040 s, 1010 s, 950 w, 940 w, 905 w, 835 s, 780 s, 740 m, 695 s, 665 m; ^{1}H NMR δ 7.32 (m, ArH), 7.23 (m, PMB $H_{2,6}$), 6.84 (m, PMB $H_{3,5}$), 4.56, 4.52 (2 d, *J* = 11.2, OCH_2Ar), 4.50 (s, OCH_2Ar), 4.00 (overlapping m, H_{13}, H_{15}), 3.90 (d, *J* = 4.4, OH), 3.79 (s, PMB OCH_3), 3.56 (dd, *J* = 9.8, 3.9, C_{10} H), 3.44 (dd, *J* = 9.8, 6.8, C_{10} H), 3.36 (d, *J* = 5.9, C_{18} H_2), 3.34 (d, *J* = 7.3, OH), 3.23 (dd, *J* = 6.4, 2.9, H_{14}), 2.04 (m, H_{17}), 1.92 (m, H_{11}), 1.01 (d, *J* = 6.8, C_{17a} H_3), 0.90 (d, *J* = 6.8, C_{11a} H_3); ^{13}C NMR δ 159.2 (PMB C_4), 138.6 ($C_{1'}$), 130.4 (PMB C_1), 129.6 (PMB $C_{2,6}$), 128.3, 127.5, 127.4 ($C_{2',6'}$, $C_{3',5'}$, $C_{4'}$), 113.7 (PMB $C_{3,5}$), 81.9 (C_{14}), 75.4 (C_{18}), 73.0 (OCH_2Ar), 72.5 (PMB CH_2), 69.3, 69.2 (C_{13}, C_{15}), 68.3 (C_{10}), 55.2 (PMB OCH_3), 38.7, 37.3 (C_{12}, C_{16}), 33.4 (C_{11}), 32.1 (C_{17}), 25.8 ($SiC(CH_3)_3$), 18.2 (C_{17a}), 17.5 (C_{11a}), −5.6 ($Si(CH_3)_2$). Anal. Calcd for $C_{32}H_{52}O_6Si$: C, 68.53; H, 9.35. Found: C, 68.82; H, 9.66.

C_{13},C_{15} Dimethyl Ether 29. A 25-mL round-bottom flask fitted with a septum, nitrogen inlet, and magnetic stirring bar was charged with 208 mg (5.19 mmol) of 60% sodium hydride dispersion. The sodium hydride was washed with 4 × 2 mL of distilled tetrahydrofuran and then suspended in 2 mL of distilled tetrahydrofuran. To the suspension were added 646 μL (1.47 g, 10.38 mmol) of methyl iodide and 970 mg (1.73 mmol) of diol **28** at 0 °C. The reaction was allowed to warm to room temperature over 30 min (an exotherm to 24 °C was observed) and then stirred at room temperature for 36 h. The reaction was cautiously quenched by the addition of 5 mL of saturated aqueous sodium thiosulfate followed by 10 mL of water. The reaction mixture was extracted with 3 × 20 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (4 cm × 18 cm column, 8:1 hexane/ethyl acetate) to provide 1.00 g (98%) of dimethyl ether **29**. Analyzed as a 9:1 mixture: R_f = 0.65 (4:1 hexane/ethyl acetate); R_f = 0.20 (8:1 hexane/ethyl acetate); IR (film) 3060 m, 3030 m, 2940 s, 2880 s, 2850 m, 1610 s, 1585 m, 1515 s, 1495 m, 1460 s, 1455 s, 1385 m, 1360 s, 1300 s, 1250 s, 1210 m, 1170 s, 1100 s, 1040 s, 1005 m, 940 m, 905 m, 835 s, 775 s, 735 s, 695 s, 665 m; ^{1}H NMR δ 7.30 (overlapping m, ArH), 6.83 (m, PMB $H_{3,5}$), 4.67, 4.55 (2 d, *J* = 10.7, OCH_2Ar), 4.49 (s, OCH_2Ar), 3.79 (s, PMB OCH_3), 3.39, 3.35 (2 s, 2 OCH_3), 0.99, 0.94 (2 d, *J* = 6.8, C_{11a} H_3); ^{13}C NMR δ 159.0 (PMB C_4), 138.7 ($C_{1'}$), 131.0 (PMB C_1), 129.6, 128.3, 127.4, 127.4 (Ar CH), 113.5 (PMB $C_{3,5}$), 80.7, 80.5, 79.7 (C_{13}, C_{14}, C_{15}), 75.7 (C_{18}), 73.7, 73.0 (2 OCH_2Ar), 68.1 (C_{10}), 58.3, 57.3 (2 OCH_3), 55.2 (PMB OCH_3), 34.9, 34.7 (C_{12}, C_{16}), 32.8, 30.4 (C_{11}, C_{17}), 26.0 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.3, 18.1 (C_{11a}, C_{17a}), −5.3 ($Si(CH_3)_2$). Anal. Calcd for $C_{34}H_{56}O_6Si$: C, 69.35; H, 9.58. Found: C, 69.35; H, 9.72.

Bis-TBS Ether 30. A 25-mL round-bottom pressure flask was charged with 927 mg (1.57 mmol) of benzyl ether **29**, 0.120 g of 20% $Pd(OH)_2$ on carbon, and 10 mL of ethyl acetate. The flask was placed under 34 psi of hydrogen and rocked for 36 h. The resulting slurry was filtered through Celite, concentrated, and chromatographed (4 cm × 25 cm column, 1:1 hexane/ethyl acetate) to provide 509 mg (85%) of the corresponding diol as an oil: $[\alpha]^{25}_D$ +3.3° (*c* 1.05, CH_2Cl_2); $R_{f,major}$ = 0.19, $R_{f,minor}$ = 0.10 (1:1 hexane/ethyl acetate); IR (film) 3550–3200 s (OH), 2960 s, 2940 s, 2900 s, 2870 s, 2830 s, 2740 w, 1475 s, 1465 s, 1390 s, 1365 s, 1260 s, 1220 m, 1190 m, 1150 sh, 1100 s, 1040 s, 1110 s, 945 m, 920 m, 840 s, 820 s, 780 s, 740 m, 670 m; ^{1}H NMR δ 3.47, 3.39 (2 s, 2 OCH_3), 2.42 (d, *J* = 5.9, C_{14} OH), 2.35 (dd, *J* = 7.3, 5.4, C_{18} OH), 0.95 (degenerate d's, *J* = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 79.8, 78.5 (C_{13}, C_{15}), 73.5 (C_{14}), 68.2, 68.0 (C_{10}, C_{18}), 57.8, 57.2 (2 OCH_3), 34.0, 33.9 (C_{12}, C_{16}), 32.32, 32.26 (C_{11}, C_{17}), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.2, 17.5 (C_{11a}, C_{17a}), −5.40, −5.45 ($Si(CH_3)_2$). Anal. Calcd for $C_{19}H_{42}O_5Si$: C, 60.27; H, 11.18. Found: C, 60.35; H, 11.45.

The diol (509 mg, 1.34 mmol) was dissolved in 5 mL of dry pyridine and cooled to 0 °C under nitrogen. Pivaloyl chloride (168 mg, 171 mL, 1.39 mmol) was added and the reaction was stirred at 0 °C for 4 h. The reaction was quenched by the addition of 10 mL of water. The resulting mixture was extracted with 4 × 20 mL of ethyl acetate. The organic extracts were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (3 cm × 20 cm column, 4:1 hexane/ethyl acetate) to provide 565 mg (91%) of the primary ester: $[\alpha]^{25}_D$ −3.0° (*c* 1.15, CH_2Cl_2); R_f = 0.80 (1:1 hexane/ethyl acetate); R_f = 0.28 (4:1 hexane/ethyl acetate); IR (film) 3520–3420 m (OH), 2950 s, 2930 s, 2860 s, 2820 m, 1730 s (C=O), 1460 m, 1400 w, 1385 w, 1360 w, 1285 m, 1255 m, 1155 s, 1095 s, 1030 w, 1005 w, 830 s, 770 m; ^{1}H NMR δ 4.02 (dd, *J* = 10.7, 5.4, C_{18} H), 3.88 (dd, *J* = 10.7, 6,4, C_{18} H), 3.43, 3.38 (2 s, 2 OCH_3), 2.31 (d, *J* = 7.3, C_{14} OH), 1.21 (s, C=O$C(CH_3)_3$), 0.98 (d, *J* = 6.8, C_{17a} H_3), 0.95 (d, *J* = 6.8, C_{11a} H_3); ^{13}C NMR δ 178.5 (C=O), 79.9 (C_{13}), 77.4 (C_{15}), 74.2 (C_{14}), 69.0 (C_{18}), 68.2 (C_{10}), 57.9, 57.3 (2 OCH_3), 38.8 (C=O$C(CH_3)_3$), 34.5 (C_{12}), 33.9 (C_{16}), 32.3 (C_{11}), 29.3

(C_{17}), 27.2 (C=OC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 18.3 (SiC(CH_3)$_3$), 18.2 (C_{11a}), 17.4 (C_{17a}), -5.4 (SiCH_3)$_2$).

A 25-mL round-bottom flask fitted with a magnetic stirring bar, nitrogen inlet, and thermocouple was charged with 520 mg (1.12 mmol) of the primary ester, 2 mL of dichloromethane, and 262 μL (240 mg, 2.25 mmol) of 2,6-lutidine. The mixture was cooled to 0 °C and 310 μL (356 mg, 1.35 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate was added. The resulting clear solution was stirred 30 min at 0 °C and quenched by the addition of 10 mL of saturated aqueous sodium bicarbonate. The mixture was extracted with 3 × 15 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (3 cm × 20 cm column, 9:1 hexane/ethyl acetate) to provide 640 mg (99%) of **30** as an oil: $[\alpha]^{25}_D$ -35.3° (*c* 1.10, CH_2Cl_2); R_f = 0.56 (4:1 hexane/ethyl acetate); IR (film) 2955 s, 2930 s, 2890 s, 2855 s, 2820 w, 1730 s (C=O), 1480 sh, 1479 m, 1460 m, 1395 w, 1385 w, 1360 w, 1280 m, 1255 m, 1155 s, 1095 s, 1035 m, 1005 w, 975 w, 940 w, 910 w, 835 s, 815 w, 775 s, 665 w; ^{1}H NMR δ 4.08 (dd, *J* = 10.7, 4.9, C_{18} H), 3.86 (dd, *J* = 5.9, 1.5, H_{14}), 3.79 (dd, *J* = 10.7, 6.8, C_{18} H), 3.45 (m, ^2J = 9.8, C_{10} H_2), 3.42, 3.31 (2 s, 2 OCH_3), 3.25 (ddd, *J* = 9.3, 2.4, 1.5, H_{13}), 3.17 (ddd, *J* = 8.3, 5.9, 2.4, H_{15}), 1.99 (m, H_{17}), 1.78 (m, H_{11}), 1.84-1.20 (overlapping m, $C_{12}H_2$, $C_{16}H_2$), 1.21 (s, C=OC(CH_3)$_3$), 0.99 (d, *J* = 6.8, C_{17a} H_3), 0.92 (d, *J* = 6.8, C_{11a} H_3), 0.90, 0.89 (2 s, 2 SiC(CH_3)$_3$), 0.08, 0.07 (2 s, Si(CH_3)$_2$), 0.03 (s, Si(CH_3)$_2$); ^{13}C NMR δ 178.5 (C=O), 81.3 (C_{15}), 80.9 (C_{13}), 73.5 (C_{14}), 68.6 (C_{18}), 68.0 (C_{10}), 58.4, 57.1 (2 OCH_3), 38.8 (C=O-C(CH_3)$_3$), 34.4 (C_{12}), 34.2 (C_{16}), 33.1 (C_{11}), 30.1 (C_{17}), 27.2 (C=O-C(CH_3)$_3$), 26.0, 25.9 (2 SiC(CH_3)$_3$), 18.3, 18.2 (2 SiC(CH_3)$_3$), 18.2 (C_{17a}), 18.1 (C_{11a}), -4.5, -4.7, -5.3, -5.4 (2 Si(CH_3)$_2$). Anal. Calcd for $C_{30}H_{64}O_6Si_2$: C, 62.45; H, 11.18. Found: C, 62.43; H, 11.46.

Alcohol 31. A 500-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 9.49 g (16.5 mmol) of silyl ether **30** dissolved in 140 mL of tetrahydrofuran and 45 mL of water. The solution was cooled to 0 °C and 2.20 mL (3.26 g, 28.6 mmol) of trifluoroacetic acid was added dropwise. The cloudy solution was warmed to room temperature, and the resulting clear solution was stirred for 9 h. The reaction mixture was poured into a separatory funnel containing 200 mL of aqueous saturated sodium bicarbonate and 150 mL of dichloromethane. The layers were separated and the aqueous layer was extracted with 2 × 150 mL of dichloromethane. The organic layers were combined, dried over magnesium sulfate, filtered, concentrated, and chromatographed (400 g of SiO_2, 4:1 hexane/ethyl acetate) to provide 6.99 g (92%) of **31** as a clear oil: $[\alpha]^{26}_D$ -39.9° (*c* 1.09, CH_2Cl_2); R_f = 0.26 (4:1 hexane/ethyl acetate); IR (film) 3600-3250 w (OH), 2960 s, 2940 s, 2800 sh, 2860 s, 2825 m, 1730 s (C=O), 1485 m, 1475 m, 1465 m, 1400 w, 1390 w, 1365 w, 1290 m, 1255 m, 1160 br s, 1095 s, 1040 m, 990 m, 940 w, 910 w, 840 s, 815 w, 775 m; ^{1}H NMR δ 4.06 (dd, *J* = 10.7, 4.9, C_{18} H), 3.89 (dd, *J* = 5.4, 1.5, H_{14}), 3.80 (dd, *J* = 10.7, 6.8, C_{18} H), 3.42, 3.31 (2 s, 2 OCH_3), 2.64 (br m, C_{10} OH), 1.20 (s, C=OC(CH_3)$_3$), 0.98, 0.91 (2 d, *J* = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 178.6 (C=O), 81.3, 79.7 (C_{13}, C_{15}), 73.2 (C_{14}), 68.6, 67.2 (C_{10}, C_{18}), 58.6, 56.6 (2 OCH_3), 38.9 (C=OC(CH)$_3$), 34.4, 33.4 (C_{12}, C_{16}), 32.7, 30.1 (C_{11}, C_{17}), 27.3 (C(CH_3)$_3$), 26.0 (SiC(CH_3)$_3$), 18.3 (SiC(CH_3)$_3$), 18.2, 17.2 (C_{11a}, C_{17a}), -4.5, -4.6 (Si(CH_3)$_2$). Anal. Calcd for $C_{24}H_{50}O_6Si$: C, 62.29; H, 10.89. Found: C, 61.92; H, 10.87.

C_{10} Aldehyde 32. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, thermocouple probe, and nitrogen inlet was charged with 2.31 g (18.2 mmol) of oxalyl chloride in 35 mL of dichloromethane. The solution was cooled to -78 °C and 2.37 g (30.3 mmol) of dimethyl sulfoxide in 35 mL of dichloromethane was added dropwise. The solution was stirred for 1 h at -78 °C and 6.99 g (15.1 mmol) of alcohol **31** in 70 mL of dichloromethane was added via cannula over 10 min. The resulting thick white suspension was aged 1 h at -78 °C, and 7.65 g (75.7 mmol) of triethylamine was added. The mixture was stirred 15 min at -78 °C, warmed to -30 °C over 1 h, and then quenched by the addition of 100 mL of 0.5 M aqueous sodium bisulfate. The layers were separated and the aqueous layer was extracted with 2 × 50 mL of dichloromethane. The organic layers were combined, washed with 100 mL of water, dried over magnesium sulfate, filtered, concentrated, and chromatographed (230 g SiO_2, 10:1 hexane/ethyl acetate) to yield 6.65 g (95%) of aldehyde **32** as a clear oil: R_f = 0.57 (4:1 hexane/ethyl acetate); IR (film) 2960 s, 2940 s, 2910 m, 2890 m, 2860 m, 2830 m, 2720 w, 1730 s (C=O), 1485 m, 1475 m, 1465 m, 1400 w, 1390 w, 1365 w, 1335 w, 1285 m, 1255 m, 1160 s, 1095 s, 1035 w, 980 br w, 950 w, 940 w, 910 w, 840 s, 815 w, 775 m; ^{1}H NMR δ 9.60 (d, *J* = 1.0, H_{10}), 4.09 (dd, *J* = 10.7, 4.9, C_{18} H), 3.90 (dd, *J* = 5.9, 2.0, H_{14}), 3.83 (dd, *J* = 10.7, 6.8, C_{18} H), 3.43, 3.19 (2 s, 2 OCH_3), 2.54 (m, H_{11}), 1.21 (s, C=OC(CH_3)$_3$), 1.10 (d, *J* = 7.3, C_{11a} H_3), 1.01 (d, *J* = 6.8, C_{17a} H_3); ^{13}C NMR δ 203.8 (C_{10}), 178.4 (C=O), 81.1, 78.6 (C_{13}, C_{15}), 73.0 (C_{14}), 68.4 (C_{18}), 58.4, 56.7 (2 OCH_3), 43.1 (C_{11}), 38.8 (C=OC(CH_3)$_3$), 34.2, 31.5 (C_{12}, C_{16}), 30.0 (C_{17}), 27.2 (C=OC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 18.2 (SiC(CH_3)$_3$), 18.1 (C_{17a}), 12.9 (C_{11a}), -4.6, -4.8 (Si(CH_3)$_2$). Anal. Calcd for $C_{24}H_{48}O_6Si$: C, 62.56; H, 10.50. Found: C, 62.45; H, 10.62.

C_{14} Hydroxy Dithiane 33. a 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 6.65 g (14.5 mmol) of aldehyde **32** in 175 mL of dichloromethane. The solution was cooled to 0 °C and 2.34 g (21.7 mmol) of propane-1,3-dithiol was added followed by 4.10 g (28.9 mmol) of boron trifluoride etherate. The reaction was stirred at 0 °C for 1 h and poured into a separatory funnel containing 150 mL of aqueous saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with 50 mL of dichloromethane. The organic layers were combined, washed with 75 mL of aqueous saturated sodium bicarbonate, dried over magnesium sulfate, filtered, concentrated, and chromatographed (300 g of SiO_2, 4:1 hexane/ethyl acetate) to yield 6.00 g (95%) of **33** as a clear oil: $[\alpha]^{26}_D$ +4.8° (*c* 1.00, CH_2Cl_2); R_f = 0.32 (3:1 hexane/ethyl acetate); IR (film) 3600-3450 m (OH), 2970 s, 2940 s, 2919 s, 2830 m, 1730 s (C=O), 1480 m, 1460 m, 1435 m, 1400 m, 1380 m, 1370 m, 1285 s, 1250 w, 1230 w, 1165 br s, 1105 s, 1035 m, 985 w, 910 w, 880 w, 815 w, 770 w; ^{1}H NMR δ 4.22 (d, *J* = 4.0, H_{10}), 4.03 (dd, *J* = 10.7, 5.4, C_{18} H), 3.86 (dd, *J* = 10.7, 6.8, C_{18} H), 3.44, 3.38 (2 s, 2 OCH_3), 2.27 (d, *J* = 6.8, C_{14} OH), 1.13, 0.97 (2 d, *J* = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 178.4 (C=O), 79.7, 77.8 (C_{13}, C_{15}), 73.7 (C_{14}), 69.0 (C_{18}), 58.1, 57.2 (2 OCH_3), 55.1 (C_{10}), 38.8 (C=OC(CH_3)$_3$), 35.0 (C_{11}), 34.2, 34.1 (C_{12}, C_{16}), 31.1, 30.7 ($C_{4'}$, $C_{6'}$), 29.2 (C_{17}), 27.2 (C=OC(CH_3)$_3$), 26.3 ($C_{5'}$), 18.3, 17.6 (C_{11a}, C_{17a}). Anal. Calcd for $C_{21}H_{40}O_5S_2$: C, 57.76; H, 9.23. Found: C, 57.84; H, 9.21.

C_{14} Silyloxy Dithiane 34. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 2.75 g (6.30 mmol) of C_{14} hydroxy dithiane **33** dissolved in 60 mL of dichloromethane. The solution was cooled to 0 °C and 945 mg (8.82 mmol) of 2,6-lutidine was added followed by a dropwise addition of 2.00 g (7.56 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After being stirred at 0 °C for 1 h, the reaction mixture was poured into a separatory funnel containing 50 mL of aqueous saturated sodium bicarbonate and 50 mL of dichloromethane. The layers were separated and the aqueous layer was extracted with 25 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (200 g of SiO_2, 10:1 hexane/ethyl acetate) to yield 3.29 g (95%) of **34** as a colorless liquid: $[\alpha]^{26}_D$ -32.7° (*c* 1.02, CH_2Cl_2); R_f = 0.56 (4:1 hexane/ethyl acetate); IR (film) 2960 s, 2940 s, 2900 s, 2860 s, 2820 m, 1730 s (C=O), 1480 m, 1475 m, 1465 m, 1435 w, 1425 m, 1405 m, 1385 m, 1365 m, 1290 m, 1255 m, 1160 br s, 1095 s, 1030 w, 1010 w, 980 w, 960 w, 940 w, 915 w, 865 sh, 840 s, 820 w, 780 m; ^{1}H NMR δ 4.16 (d, *J* = 3.4, H_{10}), 4.08 (dd, *J* = 10.7, 4.9, C_{18} H), 3.87 (dd, *J* = 6.4, 1.5, H_{14}), 3.78 (dd, *J* = 10.7, 7.3, C_{18} H), 3.42, 3.30 (2 s, 2 OCH_3), 3.25, 3.12 (2 m, H_{13}, H_{15}), 1.19 (C=OC(C-H_3)$_3$), 1.09, 0.98 (2 d, *J* = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 178.4 (C=O), 81.3, 80.3 (C_{13}, C_{15}), 73.4 (C_{14}), 68.7 (C_{18}), 58.6, 57.2 (2 OCH_3), 54.6 (C_{10}), 38.8 (C=OC(CH_3)$_3$), 35.4 (C_{11}), 34.5 (C_{12}, C_{16}), 31.2, 30.8 ($C_{4'}$, $C_{6'}$), 30.0 (C_{17}), 27.2 (C=OC(CH_3)$_3$), 26.3 ($C_{5'}$), 25.9 (SiC(CH_3)$_3$), 18.5, 18.3 (C_{11a}, C_{17a}), 18.2 (SiC(CH_3)$_3$), -4.65, -4.72 (Si(CH_3)$_2$). Anal. Calcd for $C_{27}H_{54}O_5S_2Si$: C, 58.86; H, 9.88. Found: C, 58.94; H, 10.17.

C_{18} Hydroxy Dithiane 35. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 3.04 g (5.52 mmol) of dithiane **34** dissolved in 65 mL of tetrahydrofuran. The solution was cooled to 0 °C and 5.52 mL (5.52 mmol of a 1 M solution in diethyl ether) of lithium aluminum hydride was added dropwise. The mixture was stirred at 0 °C for 1 h and quenched by the slow addition (*caution*: vigorous gas evolution) of 100 mL of 1 M aqueous sodium potassium tartrate followed by the addition of 100 mL of hexane. The cloudy two-phase mixture was warmed to room temperature and stirred for 1 h to give two clear layers. The layers were separated and the aqueous phase was extracted with 2 × 40 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (150 g of SiO_2, a gradient from 5:1 to 2:1 hexane/ethyl acetate) to provide 2.50 g (97%) of **35** as a clear oil: $[\alpha]^{26}_D$ -23.2° (*c* 1.05, CH_2Cl_2); R_f = 0.18 (4:1 hexane/ethyl acetate). IR (film) 3600-3250 m (OH), 2970 s, 2960 s, 2940 s, 2905 s, 2860 s, 2830 m, 1470 m, 1465 m, 1435 m, 1425 m, 1390 m, 1380 m, 1365 m, 1280 m, 1255 s, 1180 m, 1130 br s, 1115 s, 1090 br s, 1050 m, 1010 m, 990 m, 975 m, 955 m, 915 m, 885 w, 865 m, 840 s, 815 m, 775 s; ^{1}H NMR δ 4.16 (d, *J* = 3.4, H_{10}), 4.00 (dd, *J* = 7.3, 1.5, H_{14}), 3.43, 3.33 (2 s, 2 OCH_3), 3.25, 3.14 (2 m, H_{13}, H_{15}), 1.11, 0.91 (2 d, *J* = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 81.6, 79.7 (C_{13}, C_{15}), 72.7 (C_{14}), 68.1 (C_{18}), 58.3, 57.1 (2 OCH_3), 54.8 (C_{10}), 35.0 (C_{11}), 34.7, 33.7 (C_{12}, C_{16}), 32.5 (C_{17}), 31.3, 31.0 ($C_{4'}$, $C_{6'}$), 26.3 ($C_{5'}$), 25.9 (SiC(CH_3)$_3$), 18.8, 18.3 (C_{11a}, C_{17a}), 18.26 (SiC(CH_3)$_3$), -4.6, -4.7 (SiCH_3)$_2$). Anal. Calcd for $C_{22}H_{46}O_4S_2Si$: C, 56.60; H, 9.93. Found: C, 56.52; H, 10.08.

Dithianephosphine Oxide 37. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 1.90 g (4.07 mmol) of C_{18} hydroxy dithiane **35** dissolved in 20 mL of pyridine. The solution was cooled to 0 °C and 1.44 g (8.14 mmol) of benzenesulfonyl chloride was added. The mixture was stirred at 0 °C for 1 h and then stored at −30 °C for 15 h. The reaction mixture was added to a separatory funnel containing 100 mL of diethyl ether and 50 mL of 1 N hydrochloric acid. The layers were separated and the aqueous layer was extracted with 100 mL of diethyl ether. The organic layers were combined and washed with 5 × 40 mL of 1 N hydrochloric acid. The acid washes were combined and extracted with 50 mL of diethyl ether. The organic layers were combined, washed with 75 mL of water followed by 50 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, concentrated, and chromatographed (125 g of SiO_2, 5:1 hexane/ethyl acetate) to yield 2.30 g (93%) of benzenesulfonate **36** as a clear unstable oil. The benzenesulfonate was unstable to storage and was used immediately in the next reaction. $R_{f\text{sulfonate}}$ = 0.41 (4:1 hexane/ethyl acetate). A 100-mL round-bottom flask fitted with a magnetic stirring bar, septum, thermocouple probe, and nitrogen inlet was charged with 1.52 g (6.59 mmol) of ethyldiphenylphosphine oxide dissolved in 35 mL of tetrahydrofuran. The solution was cooled to −78 °C (the phosphine oxide precipitated), and 4.1 mL (6.26 mmol, 1.53 M in hexane) of *n*-butyllithium was added over 10 min by syringe. The resulting bright orange solution was stirred at −78 °C for 20 min. A separate 50-mL round-bottom flask was charged with 2.10 g (3.46 mmol) of benzenesulfonate **36** and azeotropically dried with 20 mL of benzene. The benzenesulfonate was then dissolved in 10 mL of tetrahydrofuran and added to the solution of the phosphine oxide anion via cannula (plus a rinse with 2 × 5 mL of tetrahydrofuran). The reaction was allowed to warm to 0 °C after 40 min and then stirred for 30 min. The resulting clear dark red solution was quenched by the addition of 20 mL of saturated aqueous ammonium chloride. The resulting yellow mixture was added to a separatory funnel containing 75 mL of ethyl acetate and 25 mL of water. The layers were separated and the aqueous phase was extracted with 2 × 40 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (160 g of SiO_2, 1:3 hexane/ethyl acetate) to yield 2.04 g (87%) of dithianephosphine oxide **37** as a solid white 3:1 mixture of diastereomers. NMR data are reported only for the major diastereomer: $[\alpha]^{26}_D$ −46° (*c* 0.96, CH_2Cl_2); R_f = 0.50 (1:3 hexane/ethyl acetate); IR (CH_2Cl_2) 3050 s, 2980 sh, 2960 s, 2930 s, 2900 sh, 2860 m, 1460 br w, 1440 m, 1420 m, 1380 w, 1255 s, 1190 m, 1120 m, 1090 w, 955 w, 895 m, 835 m, 640 s; ^{1}H NMR δ 7.79 (m, ortho ArH), 7.46 (overlapping m, meta and para ArH), 4.12 (d, J = 3.4, H_{10}), 3.83 (dd, J = 5.9, 1.5, H_{14}), 3.37, 3.29 (2 s, 2 OCH_3), 3.21, 3.10 (2 m, H_{13}, H_{15}), 2.49 (m, H_{19}), 1.15 (dd, J = 6.8, J_{HP} = 16.6, C_{19a} H_3), 1.08, 0.88 (2 d, J = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 132.2 (d, J_{CP} = 94.1, ipso-Ar), 131.9 (d, J_{CP} = 94.5, ipso-Ar), 131.12, 131.09 (p-Ar), 130.8, 130.7 (2 d, J_{CP} = 8.7, o-Ar), 128.2 (d, J_{CP} = 10.9, m-Ar), 80.4, 79.8 (C_{13}, C_{15}), 73.3 (C_{14}), 58.8, 56.9 (2 OCH_3), 54.3 (C_{10}), 38.7 (C_{18}), 34.9 (C_{11}), 34.2 (C_{12}, C_{16}), 30.9, 30.4 ($C_{4'}$, $C_{6'}$), 29.4 (d, J_{CP} = 72.5, C_{19}), 26.2 (d, J_{CP} = 13.1, C_{17}), 26.1 ($C_{5'}$), 25.7 (SiC$(CH_3)_3$), 19.5, 18.3 (C_{11a}, C_{17a}), 17.9 (SiC$(CH_3)_3$), 11.3 (d, J_{CP} = 2.4, C_{19a}), −4.8, −4.9 (Si$(CH_3)_2$). Anal. Calcd for $C_{36}H_{59}O_4S_2SiP$: C, 63.68; H, 8.76. Found: C, 63.69; H, 8.73.

C_{19}–C_{20} Olefin Formation. Phosphine Oxide/Aldehyde Adduct. A 25-mL round-bottom flask was charged with 903 mg (1.33 mmol) of phosphine oxide **37** and azeotropically dried with 2 × 10 mL of dry benzene. The flask was then fitted with fitted with a septum, nitrogen inlet, thermocouple, and magnetic stirring bar. After the flask was flushed with nitrogen, 4.4 mL of dry, distilled tetrahydrofuran was added followed by 803 μL (618 mg, 5.32 mmol, 4 equiv) of dry *N,N,N,N*-tetramethylethylenediamine. The clear mixture was cooled to −78 °C and 1.02 mL (1.59 mmol of a 1.56 M solution in hexane) of *n*-butyllithium was added dropwise over 5 min. The resulting red solution exothermed to −71 °C and was recooled to −78 °C. After 30 min, the solution was warmed to −50 °C, held at that temperature for 5 min, and then recooled to −78 °C. In a separate 25-mL flask, aldehyde **2** was azeotropically dried with 3 × 5 mL of dry benzene. The aldehyde was then dissolved in 4 mL of dry tetrahydrofuran and added by cannula to the anion. The resulting pale yellow solution was stirred for 5 min, then warmed to 0 °C, and quenched by the addition of 10 mL of saturated aqueous ammonium chloride. The two-phase mixture was poured into a 100-mL separatory funnel containing 10 mL of saturated aqueous ammonium chloride and 50 mL of ethyl acetate. The aqueous phase was extracted with 3 × 50 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. Chromatography (6 cm × 36 cm column, 6 L of 8:1 hexane/ethyl acetate followed by 2 L of 4:1 hexane/ethyl acetate) provided four fractions that were homogeneous by TLC. [Note: $R_{f\text{ald}}$ = 0.97 (5:1 hexane/ethyl acetate)]. The first fraction (240 mg, 11%) consisted of ortho-lithiated addition products as foams: R_f = 0.32 (5:1 hexane/ethyl acetate). The second fraction was the desired (*E*)-olefin precursor (809 mg, 38%) as a foam: R_f = 0.27 (5:1 hexane/ethyl acetate). The third fraction (341 mg, 16%) consisted of ortho-lithiated addition products as a foam: R_f = 0.21 (5:1 hexane/ethyl acetate). The fourth fraction was the undesired (*Z*)-olefin precursor (639 mg, 30%) as a foam: R_f = 0.18 (5:1 hexane/ethyl acetate). Data for the desired (*E*)-olefin precursor follow: $[\alpha]^{25}_D$ −8.6° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3450–3300 w (OH), 3080 w, 3060 w, 2940 s, 2890 s, 2860 s, 1640 w, 1455 m, 1440 m, 1425 m, 1415 w, 1385 m, 1360 w, 1320 w, 1280 w, 1250 m, 1210 m, 1180 w, 1130 sh, 1105 s, 1090 sh, 1070 s, 1035 s, 1005 m, 940 w, 920 m, 880 m, 835 s, 810 m, 720 s, 665 m; ^{1}H NMR δ 8.04, 7.92 (2 m, o-ArH), 7.47 (m, ArH), 5.14 (br d, J = 8.3, H_{28}), 4.89 (overlapping m, H_{21b}, C_{21c} H_2), 4.64 (d, J = 9.3, C_{20} OH), 4.17 (d, J = 3.4, H_{10}), 4.01 (d, J = 9.8, H_{26}), 3.89 (dd, J = 5.4, 1.5, H_{14}), 3.73 (br d, J = 11.7, H_{24}), 3.54 (m, H_{32}), 3.38, 3.35, 3.32 (3 s, 3 OCH_3), 1.61 (d, J_{HP} = 17.6, C_{19a} H_3), 1.51 (d, J = 1.0, C_{27a} H_3); ^{13}C NMR δ 137.8 (C_{21b}), 135.9 (C_{27}), 132.6, 132.5 (2 d, J_{CP} = 85, Ar C_1), 132.1, 132.0 (2 s, Ar C_4), 131.2 (d, J_{CP} = 7.7, Ar $C_{2,6}$), 128.4, 128.3 (2 d, J_{CP} = 10.6, Ar $C_{3,5}$), 115.9 (C_{21c}), 84.4 (C_{31}), 80.9, 80.0 (C_{13}, C_{15}), 80.4 (C_{26}), 74.8 (C_{32}), 73.9, 70.8 (br, C_{20}, C_{22}), 72.8 (C_{14}), 69.8 (C_{24}), 58.2, 57.1, 57.0 (3 OCH_3), 54.5 (C_{10}), 45.5 (d, J_{CP} = 64.0, C_{19}), 45.4 (br, C_{21}), 39.8 (C_{25}), 35.3, 34.9 (C_{11}, C_{29}), 34.1 (C_{33}), 31.3, 31.2 ($C_{4'}$, $C_{6'}$, C_{34}), 26.3 ($C_{5'}$), 26.1, 25.9 (2 SiC$(CH_3)_3$), 25.8 (d, J_{CP} = 3.9, C_{17}), 23.6 (C_{17a}), 20.1 (C_{19a}), 18.6, 18.5, 18.00, 17.96 (2 SiC$H(CH_3)_2$), 18.2 (C_{11a}), 18.1, 17.7 (2 SiC$(CH_3)_3$), 13.2, 12.5 (2 SiC$H(CH_3)_2$), 11.6 (C_{27a}), 8.9 (C_{25a}), 6.8 (SiCH_2CH_3), 4.8 (SiCH_2CH_3), −3.6, −4.3, −4.5, −4.8 (2 Si$(CH_3)_2$). Anal. Calcd for $C_{87}H_{163}O_{10}Si_4S_2P$: C, 65.12; H, 10.24. Found: C, 64.76; H, 10.42.

(*E*)-Olefin 38. A 25-mL round-bottom flask was charged with 867 mg of (*E*)-olefin precursor (fraction 3, previous experimental procedure; 0.540 mmol) and azeotropically dried with 3 × 5 mL of benzene. The resulting foam was dissolved in 6 mL of tetrahydrofuran and cooled to −20 °C under nitrogen. To the clear solution was added 1.49 mL (0.738 mmol of a 0.48 M solution in toluene) of potassium bis(trimethylsilyl)-amide. The solution rapidly turned yellow, was warmed to 0 °C, and stirred for 1 h. The reaction was then quenched by the addition of 15 mL of saturated aqueous ammonium chloride. The reaction mixture was extracted 3 × 10 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (3 cm × 30 cm column, 24:1 hexane/ethyl acetate) to provide 614 mg (82%) of (*E*)-olefin **38** as a clear oil: $[\alpha]^{27}_D$ −17.2° (*c* 1.03, $CHCl_3$); R_f = 0.23 (24:1 hexane/ethyl acetate); IR (film) 2950 s, 2930 s, 2910 s, 2890 s, 2870 s, 1425 w, 1415 w, 1415 m, 1380 w, 1360 w, 1330 w, 1320 w, 1280 w, 1250 m, 1210 m, 1180 w, 1110 s, 1085 s, 1070 s, 1055 m, 1035 m, 1005 m, 920 m, 885 m, 835 s, 810 m, 725 s, 665 m; ^{1}H NMR δ 5.71 (m, H_{21b}), 5.18 (br d, J = 8.8, H_{28}), 4.99 (obs d, H_{20}), 4.95 (m, C_{21c} H_2), 4.19 (d, J = 3.4, H_{10}), 4.06 (d, J = 9.3, H_{26}), 3.91 (dd, J = 5.9, 1.5, H_{14}), 3.84 (br dd, J = 10.3, 3.9, H_{24}), 3.55 (m, H_{32}), 3.47 (s, OCH_3), 3.48, (obs m, H_{22}), 3.39, 3.34 (2 s, 2 OCH_3), 3.28 (br d, J = 9.8, H_{13}), 3.18 (m, H_{15}), 2.99 (m, H_{31}), 1.61 (d, J = 1.0, C_{27a} H_3), 1.55 (br s, C_{19a} H_3); ^{13}C NMR (75.47 MHz) δ 137.7 (C_{21b}), 135.8, 135.0 (C_{19}, C_{27}), 132.5 (C_{28}), 127.9 (C_{20}), 115.4 (C_{21c}), 84.6 (C_{31}), 81.2 (C_{15}), 80.4 (C_{13}), 80.3 (C_{26}), 75.0 (C_{32}), 73.6 (C_{14}), 72.9 (C_{22}), 70.0 (C_{24}), 59.0, 57.32, 57.27 (3 OCH_3), 54.7 (C_{10}), 47.1 (C_{18}), 45.1 (C_{21}), 41.2 (C_{21a}), 40.4 (C_{25}), 39.0 (C_{16}), 35.7, 35.5 (C_{23}, C_{30}), 35.47 (C_{11}), 35.1 (C_{29}), 34.7 (C_{33}), 34.3 (C_{12}), 31.4, 30.9 ($C_{4'}$, $C_{6'}$), 30.7 (C_{34}), 27.3 (C_{17}), 26.5 ($C_{5'}$), 26.0 (2 SiC$(CH_3)_3$), 20.2 (C_{17a}), 18.7, 18.6, 18.2, 18.1, (2 SiC$H(CH_3)_2$), 18.5 (C_{11a}), 18.3 (SiC$(CH_3)_3$), 16.6 (C_{19a}), 13.4, 12.7 (2 SiC$H(CH_3)_2$), 11.6 (C_{27a}), 9.0 (C_{25a}), 7.0 (SiCH_2CH_3), 5.0 (SiCH_2CH_3), −3.6, −4.3, −4.5, −4.6 (2 Si$(CH_3)_2$). Anal. Calcd for $C_{75}H_{152}O_8S_2Si_5$: C, 64.97; H, 11.05. Found: C, 64.77; H, 11.05.

Tricarbonyl Model Studies. Model Dithiane 43. A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 302 mg (0.647 mmol) of alcohol **35** in 3 mL of dry dichloromethane. To this solution was added 160 μL (147 mg, 1.35 mmol) of 2,6-lutidine. The mixture was cooled to 0 °C and 0.270 mL (308 mg, 1.01 mmol) of triisopropylsilyl trifluoromethanesulfonate was added dropwise. After the resultant mixture was stirred at 0 °C for 15 min, 10 mL of saturated aqueous sodium bicarbonate was added. The resulting mixture was partitioned between 15 mL of water and 30 mL of dichloromethane. The organic layer was dried over magnesium sulfate, filtered, concentrated, and chromatographed (20 g of SiO_2, 8:1 hexane/ethyl acetate) to provide 391 mg (97%) of **43** as an oil: $[\alpha]^{26}_D$ −25.5° (*c* 1.00, CH_2Cl_2); R_f = 0.77 (4:1 hexane/ethyl acetate); IR (film) 2940 s, 2890 s, 2870 s, 2820 m, 1465 s, 1430 m, 1425 m, 1415 w, 1390 m, 1380 m, 1360 w, 1275 m, 1250 s, 1180 w, 1095 br s, 1015 m, 1005 m, 995 m, 970 w, 955 m, 935 w, 915 w, 905 m, 880 s, 835 s, 810 m, 775 s, 680 m, 655 m; ^{1}H NMR δ 4.18 (d, J = 3.4, H_{10}), 3.88 (dd, J = 5.9, 1.5, H_{14}), 3.69 (dd, J = 9.8, 4.9, C_{18} H), 3.42, 3.32 (2 s, 2 OCH_3), 3.38 (dd, J = 9.8, 7.3, C_{18} H), 3.26, 3.12 (2 m, H_{13}, H_{15}), 1.11, 0.99 (2 d, J = 6.8, C_{11a}

H_3, C_{17a} H_3); ^{13}C NMR δ 81.8, 80.2 (C_{13}, C_{15}), 73.5 (C_{14}), 68.6 (C_{18}), 58.4, 57.1 (2 OCH_3), 54.7 (C_{10}), 35.4 (C_{11}), 34.44, 34.40 (C_{12}, C_{16}), 33.4 (C_{17}), 31.3, 30.7 ($C_{4'}$, $C_{6'}$), 26.4 ($C_{5'}$), 25.9 ($SiC(CH_3)_3$), 18.4, 18.3 (C_{11a}, C_{17a}), 18.25 ($SiC(CH_3)_3$), 18.0 ($SiCH(CH_3)_2$), 12.0 ($SiCH(CH_3)_2$), -4.6, -4.7 ($Si(CH_3)_2$). Anal. Calcd for $C_{31}H_{66}O_4S_2Si_2$: C, 59.75; H, 10.68. Found: C, 59.72; H, 10.82.

Model Aldehyde 50. A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 480 mg (2.82 mol) of silver nitrate in 4 mL of sieve-dried methanol. The solution was treated with 335 mg (2.51 mmol) of *N*-chlorosuccinimide followed by 0.73 mL (672 mg, 6.27 mmol) of 2,6-lutidine. The resulting thick white slurry was protected from light and stirred at 20 °C. After 30 min, 391 mg (0.627 mmol) of dithiane **43** in 4 mL of dry tetrahydrofuran was added. The resulting mixture was stirred at 20 °C for 30 min, cooled to 0 °C, and treated with 4 mL of aqueous saturated sodium bisulfite. The resulting mixture was partitioned between 10 mL of water, 20 mL of diethyl ether, and 10 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with 3 × 30 mL of diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and chromatographed (22 g of SiO_2, 15:1 hexane/ethyl acetate) to provide 258 mg (71%) of the corresponding dimethyl acetal: $[\alpha]^{26}_D$ -26° (*c* 0.99, CH_2Cl_2); R_f = 0.57 (8:1 hexane/ethyl acetate); IR (film) 2940 s, 2890 s, 2860 s, 2830 m, 1465 m, 1385 m, 1360 w, 1255 m, 1190 m, 1000 br s, 1010 m, 1005 m, 995 m, 985 m, 950 m, 920 m, 880 m, 835 s, 820 m, 775 m, 680 m, 655 m, 645 m; ^1H NMR δ 4.07 (d, J = 5.9, H_{10}), 3.85 (dd, J = 5.9, 1.5, H_{14}), 3.67 (dd, J = 9.8, 4.9, C_{18} H), 3.40 (dd, J = 9.8, 7.3, C_{18} H), 3.41, 3.35, 3.34, 3.31 (4 s, 4 OCH_3), 0.99, 0.93 (2 d, J = 6.8, C_{11a} H_3, C_{17a} H_3); ^{13}C NMR δ 109.2 (C_{10}), 81.9, 80.9 (C_{13}, C_{15}), 73.6 (C_{14}), 68.6 (C_{18}), 58.3, 56.8 (2 OCH_3), 54.8, 53.5 ($C_{10}(OCH_3)_2$), 34.2, 33.1 (C_{12}, C_{16}), 33.4, 32.6 (C_{11}, C_{17}), 25.9 ($SiC(CH_3)_3$), 18.3, 16.1 (C_{11a}, C_{17a}), 18.0 ($SiCH(CH_3)_2$), 12.0 ($SiCH(CH_3)_2$), -4.6, -4.7 ($Si(CH_3)_2$). Anal. Calcd for $C_{30}H_{66}O_6Si_2$: C, 62.23; H, 11.49. Found: C, 62.32; H, 11.43.

A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 258 mg (0.445 mmol) of the preceding dimethyl acetal in 6 mL of dichloromethane. The solution was stirred at 20 °C and 410 mg (4.45 mmol) of glyoxylic acid monohydrate was added followed by 260 μL (273 mg, 4.45 mmol) of glacial acetic acid. The resulting mixture was heated at reflux for 1.5 h, cooled, and added in portions to a 0 °C mixture of 25 mL of dichloromethane and 25 mL of aqueous saturated sodium bicarbonate. The layers were separated and the aqueous phase was extracted with 2 × 25 mL of dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and chromatographed (20 g of SiO_2, 20:1 hexane/ethyl acetate) to yield 232 mg (98%) of aldehyde **50** as an oil. The overall yield from dithiane to aldehyde was 70%: $[\alpha]^{24}_D$ -52° (*c* 0.52, $CDCl_3$); R_f = 0.57 (8:1 hexane/ethyl acetate); IR (film) 2940 s, 2890 s, 2870 s, 2820 sh, 2710 w, 1725 m (C=O), 1460 m, 1385 m, 1360 w, 1330 w, 1250 m, 1185 w, 1100 s, 1050 sh, 1005 m, 990 w, 950 m, 940 m, 920 w, 905 w, 880 m, 835 s, 775 s, 675 s, 655 m; ^1H NMR δ 9.59 (d, J = 1.0, H_{10}), 3.89 (dd, J = 5.9, 1.5, H_{14}), 3.62 (dd, J = 9.8, 5.4, C_{18} H), 3.46 (dd, J = 9.8, 6.8, C_{18} H), 3.18, 3.14 (2 s, 2 OCH_3), 3.23-3.11 (overlapping m, H_{13}, H_{15}), 2.51 (m, H_{11}), 1.10 (d, J = 6.8, C_{11a} H_3), 0.99 (d, J = 6.8, C_{17a} H_3); ^{13}C NMR δ 204.0 (C_{10}), 81.8, 78.7 (C_{13}, C_{15}), 73.2 (C_{14}), 68.5 (C_{18}), 58.2, 56.7 (2 OCH_3), 43.2 (C_{11}), 34.3, 31.5 (C_{12}, C_{16}), 33.6 (C_{17}), 26.0 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.1 (C_{17a}), 18.1 ($SiCH(CH_3)_2$), 12.9 (C_{11a}), 12.0 ($SiCH(CH_3)_2$), -4.5, -4.8 ($Si(CH_3)_2$). Anal. Calcd for $C_{28}H_{60}O_5Si_2$: C, 63.10; H, 11.35. Found: C, 63.21; H, 11.55.

Model Aldol Adduct 76. A 15-mL, one-neck, round-bottom flask was fitted with a magnetic stirring bar, nitrogen inlet, thermometer, and septum. The apparatus was flushed with nitrogen and then charged with 200 mg (0.563 mmol, 3 equiv) of imide **46** in 2 mL of dry toluene. After being stirred for 5 min at room temperature, the solution was cooled to -50 °C. To this clear solution was added 92 μL (67 mg, 0.66 mmol) of triethylamine via syringe followed by 138 μL (152 mg, 0.554 mmol) of di-*n*-butylboron triflate. The solution exothermed to -40 °C and triethylammonium triflate formed a dense oil that occasionally crystallized. After stirring at -50 °C for 1.5 h, 100 mg (0.188 mmol) of aldehyde **50** (previously concentrated twice from 2 mL of dry toluene) in 1 mL (plus a 1-mL rinse) of toluene was added via cannula over 5 min. The resulting mixture was warmed to -30 °C over 30 min and held at -30 °C for 3 h. The reaction was quenched by warming to 0 °C and adding 1 mL of pH 7 phosphate buffer followed by 1 mL of methanol and 1 mL of tetrahydrofuran. After 5 min, 0.5 mL of 30% aqueous hydrogen peroxide was added dropwise over 5 min (*caution*: initial reaction is exothermic). After being stirred at 0 °C for 1 h, the reaction mixture was concentrated by rotary evaporation (≤20 °C) and diluted with 10 mL of saturated aqueous sodium bicarbonate. The resulting mixture was extracted with 3 × 10 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (2 cm × 20 cm column, 3:1 hexanes/ethyl acetate) to provide 150 mg (90%) of aldol adduct **76** as a clear oil: $[\alpha]^{28}_D$ -6.0° (*c* 1.13, CH_2Cl_2); $R_{f,aldol}$ = 0.20, $R_{f,ald}$ = 0.65, $R_{f,imide}$ = 0.10 (3:1 hexane/ethyl acetate); IR (film) 3580-3300 w (OH), 3070 w, 3050 w, 3010 w, 2930 br s, 2880 s, 2850 s, 2750 sh, 1780 s (C=O), 1705 s (C=O), 1605 m, 1580 w, 1510 s, 1495 m, 1460 s, 1385 s, 1355 s, 1315 m, 1295 m, 1285 m, 1245 s, 1205 s, 1195 s, 1185 s, 1180 s, 1100 br s, 1035 s, 1010 s, 990 s, 950 m, 930 m, 905 s, 875 s, 830 s, 770 s, 730 s, 695 s, 675 s, 650 m, 640 m; ^1H NMR δ 7.30 (overlapping m, ArH), 6.89 (m, PMB $H_{3,5}$), 5.23 (d, J = 2.0, H_9), 4.76, 4.39 (2 d, J = 11.2, PMB CH_2), 4.74 (m, $H_{4'}$), 4.20 (d, J = 4.4, $C_{5'}$ H_2), 3.86 (br d, J = 5.9, H_{14}), 3.80 (s, PMB OCH_3), 3.61 (obs m, H_{10}), 3.39, 3.25 (2 s, 2 OCH_3), 3.20 (d, J = 6.8, $C_{10}OH$), 2.18 (m, H_{11}), 0.96 (d, J = 6.8, C_{17a} H_3), 0.84 (d, J = 6.8, C_{11a} H_3); ^{13}C NMR δ 171.3 (C_8), 159.6 (PMB C_4), 153.3 ($C_{2'}$), 135.3 ($C_{1''}$), 130.3 (PMB $C_{2,6}$), 129.5, 129.0 ($C_{2'',6''}$, $C_{3'',5''}$), 129.4 (PMB C_1), 127.4 ($C_{4''}$), 113.8 (PMB $C_{3,5}$), 81.9 (C_{15}), 80.5 (C_{13}), 77.4 (C_9), 75.7 (C_{10}), 73.4 (C_{14}), 72.5 (PMB CH_2), 68.5 (C_{18}), 67.0 ($C_{5'}$), 58.3, 56.3 (2 OCH_3), 55.9 ($C_{4'}$), 55.3 (PMB OCH_3), 37.8 ($C_{6'}$), 34.3 (C_{16}), 33.5 (C_{17}), 33.4 (C_{11}), 33.2 (C_{12}), 26.0 ($SiC(CH_3)_3$), 18.3 (C_{17a}), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiCH(CH_3)_2$), 16.3 (C_{11a}), 12.0 ($SiCH(CH_3)_2$), -4.5, -4.8 ($Si(CH_3)_2$). Anal. Calcd for $C_{48}H_{81}NO_{10}Si_2$: C, 64.90; H, 9.19; N, 1.58. Found: C, 64.88; H, 9.44; N, 1.73.

Model Pipecolate Amide 77. A 25-mL, one-neck, round-bottom flask was fitted with a stirring bar, nitrogen inlet, thermocouple probe, and septum. The flask was charged with 323 mg (0.364 mmol) of aldol adduct **76** in 6.1 mL of tetrahydrofuran (not distilled) and 1.53 mL of water. The solution was cooled to 0 °C and was treated with 0.300 mL (2.91 mmol) of 30% hydrogen peroxide and then 31 mg (0.73 mmol) of lithium hydroxide. After 40 min at 0 °C, the mixture was carefully concentrated to about one-third volume. The resulting mixture was treated with 15 mL of hexanes and 3 mL of water and cooled to 0 °C; the pH was adjusted to 4.5 with 0.5 M aqueous sodium hydrogen sulfate. The phases were separated, the aqueous phase was extracted with 4 × 13 mL of hexanes, and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated to give 276 mg (104%) of a viscous oil. ^1H NMR analysis showed that this material was a 3:1 (mol:mol) mixture of product carboxylic acid and 4-benzyl-2-oxazolidinone, giving a 96% NMR yield of the corresponding carboxylic acid. $R_{f,acid}$ = 0.13 (3:1 hexane/ethyl acetate + 1% HOAc). A 15-mL, one-neck, pear-shaped flask was fitted with a magnetic stirring bar, a thermocouple probe, a nitrogen inlet, and a septum. The flask was charged with the crude acid in 2 mL of dry dichloromethane, the solution was cooled to 0 °C, and the mixture was treated with 0.155 mL (0.143 g, 1.33 mmol) of 2,6-lutidine and then 0.21 mL (0.25 g, 0.91 mmol) of triethylsilyl trifluoromethanesulfonate. After being stirred at 0 °C for 1 h, the solution was treated with 4 mL of hexanes and 2 mL of water. The phases were separated, the aqueous phase was extracted with 4 × 4 mL of hexanes, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated carefully to just short of dryness. The residue was placed on a 14-g silica column (dry packed, not slurry packed) with 2:1 hexanes/ethyl acetate, and the material was aged on the column about 25 min, with occasional elution of solvent to expose it to fresh silica. The product was eluted with 150 mL of 3:1 and 200 mL of 1:1 hexane/ethyl acetate followed by 200 mL of 49.75:49.75:0.5 hexane/ethyl acetate/acetic acid to give 239 mg of product and 55 mg of nonpolar materials. The latter was applied to a 6-g silica column, aged, and eluted as above, and the product fraction was combined with that above to give a total of 258 mg (87%) of the unstable TES-acid, which was carried on immediately. A 15-mL one-neck, pear-shaped flask fitted with a magnetic stirring bar, a nitrogen inlet, and a septum was charged with 258 mg (0.31 mmol) of the TES-acid and 113 mg (0.61 mmol) of (*S*)-*tert*-butyl pipecolate in 2 mL of dry dichloromethane, and this solution was treated with 0.148 mL (107 mg, 1.07 mmol) of triethylamine and then 125 mg (0.49 mmol) of 2-chloro-*N*-methylpyridinium iodide at room temperature. After 3 h, 7 mL of hexanes and 3 mL of water were added, the layers were separated, and the aqueous layer was extracted with 3 × 6 mL of hexanes. The organic layers were combined, washed with 1 mL of saturated aqueous sodium bicarbonate, dried with sodium sulfate, filtered, and concentrated. The yellow residue was chromatographed (15 g of silica, 220 mL of 12:1 hexanes/ethyl acetate and 180 mL of 2:1 hexanes/ethyl acetate) to provide 264 mg (85%) of amide **77** as a clear oil: $[\alpha]^{33}_D$ -39.4° (*c* 1.17, $CHCl_3$), R_f = 0.52 (4:1 hexane/ethyl acetate); IR ($CHCl_3$) 3005 m, 2945 s, 2865 s, 1730 m, (C=O), 1630 s (C=O), 1585 w, 1515 m, 1465 m, 1445 m, 1395 w, 1385 w, 1370 m, 1340 w, 1325 w, 1305 w, 1250 s, 1180 m, 1155 s, 1095 s, 1070 sh, 1040 s, 1010 m, 975 m, 940 w, 925 w, 885 m, 835 m, 720 m, 665 m; ^1H NMR (major rotamer; ratio 2:1) δ 7.31 (m, PMB $H_{2,6}$), 6.86 (m, PMB $H_{3,5}$), 5.36 (obs br d, J = 4.0, H_2), 4.66, 4.34 (2 d, J = 10.7, PMB CH_2), 4.49 (br d, J = 13.2, C_6 H_{eq}), 4.17 (d, J = 8.3,

H_9), 3.80 (s, PMB OCH_3), 34.1, 3.30 (2 s, 2 OCH_3), 2.26 (br d, J = 12.7, C_3 H_{eq}); ^{13}C NMR (major rotamer; ratio 2:1) δ 170.0, 169.7 (C_1, C_8), 159.1 (PMB C_4), 129.94 (PMB C_1), 129.87 (PMB $C_{2,6}$), 113.5 (PMB $C_{3,5}$), 86.1 (C_9), 83.0, 81.5 (C_{13}, C_{15}), 81.4 ($OC(CH_3)_3$), 78.0 (C_{10}), 74.4 (C_{14}), 71.8 (PMB CH_2), 68.6 (C_{18}), 58.2, 56.9 (2 OCH_3), 55.2 (PMB OCH_3), 52.7 (C_2), 42.9 (C_6), 35.0, 33.5 (C_{11}, C_{17}), 34.3, 31.0 (C_{12}, C_{16}), 28.1 ($OC(CH_3)_3$), 27.1, 25.9 (C_3, C_5), 26.0 ($SiC(CH_3)_3$), 21.2 (C_4), 20.0, 18.4 (C_{11a}, C_{17a}), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiCH(CH_3)_2$), 12.0 ($SiCH(CH_3)_2$), 7.0 ($SiCH_2CH_3$), 5.3 ($SiCH_2CH_3$), −4.5, −4.6 ($Si(CH_3)_2$). Anal. Calcd for $C_{54}H_{103}NO_{10}Si_3$: C, 64.17; H, 10.27; N, 1.39. Found: C, 64.20; H, 10.39; N, 1.34.

Model C_9,C_{10} Diol 78. A 15-mL pear-shaped flask was charged with 106 mg (0.105 mmol) of PMB amide **77** in 1 mL of dichloromethane and 50 μL of water, and the resulting suspension was treated with 120 mg (0.52 mmol) of DDQ. The flask was stoppered, the mixture was stirred at room temperature for 2 h, and the dark suspension was applied directly to a column of 13.5 g of silica with dichloromethane. The column was eluted with 100 mL of dichloromethane, 100 mL of 3:1 hexanes/ethyl acetate and 200 mL of 1:1 hexanes/ethyl acetate to give 0.056 g of a mixed fraction and 26.3 mg (32%) of diol **78** as an oil. The former material was charged into a 15-mL pear-shaped flask in 0.6 mL of tetrahydrofuran and 0.12 mL of water, and the solution was treated with 10 μL (15 mg, 0.13 mmol) of trifluoroacetic acid at room temperature. After 1.5 h, the solution was treated with 2 mL of saturated sodium bicarbonate, and the suspension was extracted with 4 × 3 mL of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, concentrated, and chromatographed (6 g of silica, 120 mL of 3:1 hexanes/ethyl acetate and 200 mL of 1:1 hexanes/ethyl acetate) to provide 34.3 mg of diol **78**, for a total yield of 60.6 mg (75%): $[\alpha]^{27}_D$ ~37.8° (c 2.50, $CDCl_3$); $R_{f,diol}$ = 0.08, $R_{f,OH,OTES}$ = 0.49 (6:1 hexane/ethyl acetate); IR ($CHCl_3$) 3550–3250 w (OH), 2940 s, 2890 s, 2870 s, 1730 m (C=O), 1640 m (C=O), 1460 m, 1390 m, 1370 m, 1340 m, 1325 m, 1250 s, 1155 s, 1095 s, 1020 m, 965 w, 955 w, 940 w, 920 w, 880 m, 835 s, 775 m, 735 m, 680 m; ^1H NMR (major rotamer; ratio 4:1) δ 5.36 (br, d, J = 5.4, H_2), 4.60 (d, J = 8.3, H_9), 3.88 (br d, J = 5.4, H_{14}), 3.80 (d, J = 8.3, C_9 OH), 3.55 (br dd, J = 9.8, 5.4, H_{10}), 3.41, 3.34 (2 s, 2 OCH_3), 3.23 (d, J = 5.4, C_{10} OH), 3.13 (m, H_{15}), 2.27 (br d, J = 13.2, C_3 H_{eq}), 2.13 (m, H_{11}); ^{13}C NMR (major rotamer; ratio 4:1) δ 172.9, 170.0 (C_1, C_8), 82.0, 81.2 (C_{13}, C_{15}), 74.4 (C_{10}), 73.6 (C_{14}), 68.6 (C_9), 68.5 (C_{18}), 58.3, 56.6 (2 OCH_3), 53.2 (C_2), 43.1 (C_6), 34.3, 33.51 (C_{12}, C_{16}), 33.47, 33.2 (C_{11}, C_{17}), 28.0 ($OC(CH_3)_3$), 26.6 (C_3), 26.0 ($SiC(CH_3)_3$), 25.4 (C_5), 20.9 (C_4), 18.2, 17.2 (C_{11a}, C_{17a}), 18.1 ($SiCH(CH_3)_2$), 12.0 ($SiCH(CH_3)_2$), −4.5, −4.8 ($Si(CH_3)_2$). Anal. Calcd for $C_{40}H_{81}NO_9Si_2$: C, 61.89; H, 10.52; N, 1.80. Found: C, 62.10; H, 10.67; N, 1.80.

Model C_9,C_{10} Dione 79. To a solution of 30 μL (44 mg, 0.338 mmol) of oxalyl chloride in 1 mL of dichloromethane at −78 °C in a 10-mL round-bottom flask fitted with a thermocouple, septum, and nitrogen inlet was added dropwise a solution of 34 μL (37 mg, 0.483 mmol) of dimethyl sulfoxide in 0.25 mL of dichloromethane. After 15 min, a solution of 75 mg (0.097 mmol) of diol **78** (previously dried azeotropically with 2 × 3 mL of benzene) in 0.5 mL (plus a 0.5-mL rinse) of dichloromethane was added via cannula at a rate to maintain the internal temperature below −60 °C. After 40 min at −78 °C, 94 μL (68 mg, 0.68 mmol) of triethylamine was added over 3 min. The reaction was allowed to warm to −30 °C over a 20-min period, and the resulting mixture was partitioned between 10 mL of 9:1 hexane/dichloromethane and 10 mL of 0.5 N aqueous sodium hydrogen sulfate. The organic layer was washed with 10 mL of saturated aqueous sodium bicarbonate and 10 mL of brine. The aqueous layers were extracted with 3 × 10 mL of 9:1 hexane/dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 20 cm column, 5:1 hexane/ethyl acetate) to afford 64 mg (85%) of the unstable dione as a yellow oil: $[\alpha]^{28}_D$ −53.4° (c 1.61, $CDCl_3$); $R_{f,dione}$ = 0.56, $R_{f,diol}$ = 0.22 (3:1 hexane/ethyl acetate); IR (film) 2940 s, 2890 m, 2860 s, 1735 m (C=O), 1715 m (C=O), 1655 s (C=O), 1460 m, 1390 w, 1370 m, 1255 m, 1220 w, 1155 s, 1100 s, 1035 w, 1020 w, 970 w, 940 w, 885 m, 840 m, 780 m, 680 m; ^1H NMR (major rotamer; ratio 5:1) δ 5.14 (br d, J = 4.9, H_2), 3.82 (dd, J = 4.9, 1.5, H_{14}), 3.63 (dd, J = 9.8, 5,4, C_{18} H), 3.43 (dd, J = 9.8, 6.8, C_{18} H), 3.39, 3.06 (2 s, 2 OCH_3), 1.15 (d, J = 6.8, C_{11a} H_3), 0.97 (d, J = 6.8, C_{17a} H_3); ^{13}C NMR (major rotamer; ratio 5:1) δ 198.7 (C_{10}), 185.5 (C_9), 169.0, 165.8 (C_1, C_8), 82.1 ($OC(CH_3)_3$), 81.8, 78.6 (C_{13}, C_{15}), 72.7 (C_{14}), 68.6 (C_{18}), 58.1, 56.3 (2 OCH_3), 52.0 (C_2), 43.7 (C_6), 36.9 (C_{11}), 34.4, 34.0 (C_{12}, C_{16}), 33.6 (C_{17}), 28.0 ($OC(CH_3)_3$), 26.4 (C_3), 25.9 ($SiC(CH_3)_3$), 25.3 (C_5), 21.0 (C_4), 18.2 ($SiC(CH_3)_3$), 18.1 (C_{17a}, $SiCH(CH_3)_2$), 14.8 (C_{11a}), 12.0 ($SiCH(CH_3)_2$), −4.6, −4.7 ($Si(CH_3)_2$).

Model Hemiketal 80. To a solution of 13.5 mL of 95:5 acetonitrile/concentrated aqueous hydrofluoric acid (47%) was added 1.5 mL of deionized water. A 2-mL aliquot of this solution was added to 35 mg (0.045 mmol) of dione **79** in a 10-mL round-bottom flask fitted with a magnetic stirring bar and stirred at room temperature. After stirring for 0.5 h, 5 mL of saturated aqueous sodium bicarbonate was cautiously added to the pale yellow reaction. The resulting mixture was partitioned between 10 mL of water and 10 mL of ethyl acetate. The aqueous phase was extracted with 3 × 10 mL of ethyl acetate and washed with 10 mL of brine. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 20 cm column, 1:1 hexane/ethyl acetate) to afford 18 mg (80%) of hemiketal **80** as a clear oil: $[\alpha]^{27}_D$ +12.1° (c 1.65, $CHCl_3$); R_f = 0.25 (1:1 hexane/ethyl acetate); IR ($CHCl_3$) 3620 w (OH), 3600–3250 w (OH), 3000 m, 2980 s, 2940 s, 2880 m, 2840 w, 1730 s (C=O), 1640 sh, 1620 s (C=O), 1455 s, 1395 m, 1380 s, 1345 w, 1330 m, 1300 w, 1285 m, 1255 m, 1210 s, 1155 s, 1145 m, 1100 s, 1080 s, 1040 s, 1025 sh, 1000 m, 990 m, 985 m, 930 w, 910 m, 890 w, 840 w, 830 w, 745 m; ^1H NMR (major rotamer; ratio 2.5:1) δ 5.27 (d, J = 1.5, C_{10} OH), 5.12 (br d, J = 4.9, H_2), 3.81 (dd, J = 9.8, 2.0, H_{14}), 3.38, 3.36 (2 s, 2 OCH_3), 1.08 (d, J = 6.4, C_{11a} H_3), 0.90 (d, J = 6.8, C_{17a} H_3); ^{13}C NMR (major rotamer; ratio 2.5:1) δ 192.5 (C_9), 168.9, 167.0 (C_1, C_8), 97.7 (C_{10}), 82.3 ($OC(CH_3)_3$), 75.7 (C_{15}), 73.6 (C_{13}), 72.1 (C_{14}), 68.7 (C_{18}), 57.5, 56.3 (2 OCH_3), 52.2 (C_2), 44.7 (C_6), 33.5 (C_{11}), 32.9 (C_{12}), 32.5 (C_{17}), 32.1 (C_{16}), 28.0 ($OC(CH_3)_3$), 26.3 (C_3), 25.1 (C_5), 20.8 (C_4), 16.6 (C_{17a}), 16.2 (C_{11a}); HRMS calcd for $C_{25}H_{44}NO_9$ (M^+ + H) 502.3020, found (FAB) 502.3030.

Completion of the Total Synthesis. C_{26} Hydroxy Dithiane 81. A 15-mL pear-shaped flask was fitted with a magnetic stirring bar, nitrogen inlet, thermocouple probe, and septum. The apparatus was flushed with nitrogen and then charged with 0.680 g (0.49 mmol) of C_{26}-TES (E)-olefin in 6 mL of tetrahydrofuran plus 1 mL of water. To this solution was added 0.10 mL (0.15 g, 1.3 mmol) of trifluoroacetic acid at room temperature. After being stirred for 85 min, the mixture was treated with 2 mL of saturated aqueous sodium bicarbonate. The resulting mixture was diluted with 6 mL of ethyl acetate and 4 mL of water, the layers were separated, and the aqueous layer was extracted with 3 × 15 mL of ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered, concentrated, and flash chromatographed (51 g of silica, 800 mL of 20:1 hexanes/ethyl acetate and 450 mL of 10:1 hexanes/ethyl acetate) to provide 0.578 g (93%) of **81** as a clear oil. In addition, 24 mg (3.5%) of the starting material was recovered: $[\alpha]^{27}_D$ −9.1° (c 1.02, $CHCl_3$); $R_{f,OTES}$ = 0.53, $R_{f,OH}$ = 0.32 (8:1 hexane/ethyl acetate); IR ($CHCl_3$) 3520–3400 w (OH), 3000 m, 2950 s, 2930 s, 2890 s, 2860 s, 1475 m, 1465 m, 1425 w, 1385 w, 1365 w, 1280 w, 1250 m, 1210 m, 1180 w, 1105 s, 1035 w, 1015 m, 1005 m, 1000 m, 920 w, 885 m, 860 w, 830 m, 810 m, 720 s, 665 m; ^1H NMR δ 5.71 (m, H_{21b}), 5.42 (br d, J = 9.3, H_{28}), 4.97 (m, C_{21c} H_2), 4.36 (br dd, J = 10.3, 4.9, H_{24}), 4.24 (br s, H_{26}), 4.19 (d, J = 3.4, H_{10}), 3.91 (s, C_{26} OH), 3.90 (obs dd, H_{14}), 3.46, 3.40, 3.30 (3 s, 3 OCH_3), 3.27 (br d, J = 10.3, H_{13}), 3.17 (m, H_{15}), 1.59 (br d, J = 1.0, C_{27a} H_3), 1.57 (br s, C_{19a} H_3), 1.12 (obs d, C_{11a} H_3), 0.82, 0.76 (2 d, J = 6.8, C_{17a} H_3, C_{25a} H_3); ^{13}C NMR δ 137.3 (C_{21b}), 135.6, 133.3 (C_{19}, C_{27}), 128.9 (C_{28}), 126.8 (C_{20}), 115.6 (C_{21c}), 84.7 (C_{31}), 81.1 (C_{15}), 80.3 (C_{13}), 79.2 (C_{26}), 75.2, 72.5 (C_{22}, C_{24}), 75.2 (C_{32}), 73.5 (C_{14}), 58.9, 57.5, 57.2 (3 OCH_3), 54.7 (C_{10}), 47.0 (C_{18}), 45.2 (C_{21}), 39.6, 38.9, 36.6, 36.5, 34.6 (C_{12}, C_{16}, C_{21a}, C_{23}, C_{30}), 36.4 (C_{25}), 35.4, 35.0 (C_{11}, C_{29}), 34.4 (C_{33}), 31.3, 30.8 ($C_{4'}$, $C_{6'}$), 30.9 (C_{34}), 27.3 (C_{17}), 26.4 ($C_{5'}$), 26.0, 25.9 (2 $SiC(CH_3)_3$), 20.2 (C_{17a}), 18.5 (C_{11a}), 18.2, 18.1, 18.08 (2 $SiCH(CH_3)_2$), 16.7 (C_{19a}), 14.5 (C_{27a}), 13.4, 12.6 (2 $SiCH(CH_3)_2$), 3.7 (C_{25a}), −3.5, −4.0, −4.6, −4.7 (2 $Si(CH_3)_2$). Anal. Calcd for $C_{69}H_{138}O_8S_2Si_4$: C, 65.14; H, 10.93. Found: C, 65.43; H, 10.58.

***C*$_{26}$-BOC-pipecolyl Dithiane 82.** A 15-mL pear-shaped flask, fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 578 mg (0.454 mmol) of alcohol **81** in 5 mL of dichloromethane. The solution was cooled to −78 °C and 417 mg (1.82 mmol) of BOC-L-pipecolic acid, 375 mg (1.82 mmol) of 1,3-dicyclohexylcarbodiimide, and 11 mg (0.091 mmol) of *N*,*N*-(dimethylamino)pyridine were added. The mixture gradually warmed to −10 °C and after 21 h was filtered and the solids were washed with 3 × 15 mL of hexanes. The combined organic layers were concentrated and chromatographed (24 g of SiO_2, 8:1 hexane/ethyl acetate) to yield 756 mg (112%) of **82** as a clear oil, which was used directly in the next step assuming 100% yield. A sample was rechromatographed and placed under high vacuum to provide the following data: $[\alpha]^{28}_D$ −32° (c 0.62, CH_2Cl_2); R_f = 0.20 (10:1 hexane/ethyl acetate); IR (film) 2930 s, 2890 m, 2860 m, 1740 m (C=O), 1700 s (C=O), 1465 m, 1390 m, 1365 m, 1340 w, 1325 w, 1280 w, 1250 s, 1180 m, 1160 s, 1140 s, 1110 s, 1090 s, 1045 s, 1000 m, 950 m, 915 m, 880 m, 835 s, 810 m, 775 s, 735 w, 675 s; ^1H NMR (rotamer ratio 1:1) δ 5.71 (m, H_{21b}), 5.43 (d, J = 9.3, H_{28}), 5.40 (obs d, J ~ 9, H_{26}), 5.34 (d, J = 9.3, H_{26}), 4.87, 4.68 (2 br s, H_2 (rotamers)), 4.19 (d, J = 3.4, H_{10}), 3.90 (br d, J = 5.9, H_{14}), 3.46, 3.33 (2 s, 2 OCH_3), 3.34 (br s, OCH_3), 3.27 (br d, J = 10.3, H_{13}), 3.17 (m, H_{15}), 1.63 (br s, $C_{27a}H_3$), 1.54 (s, $C_{19a}H_3$), 1.46, 1.42 (2 br s, 2 $OC(CH_3)_3$ (rotamers)), 1.12 (d, J = 6.8, $C_{11a}H_3$), 0.82 (d, J = 6.4, $C_{17a}H_3$); ^{13}C NMR (rotameric equilibrium

causes broadening and doubling of many resonances) δ 170.6, 170.5 (C_1), 155.5, 155.4 (N(C=O)O), 137.5 (C_{21b}), 136.6, 136.2 (C_{28}), 135.2, 135.0, 130.8 (C_{19}, C_{27}), 127.3 (C_{20}), 115.5 (C_{21c}), 84.4 (C_{31}), 82.3, 82.1 (C_{26}), 81.1 (C_{15}), 80.3 (C_{13}), 79.7, 79.6 ($OC(CH_3)_3$), 74.7 (C_{32}), 73.5 (C_{14}), 72.8 (C_{22}), 69.7, 69.3 (C_{24}), 58.9, 57.2, 57.1 (3 OCH_3), 54.8, 53.8 (C_2), 54.7 (C_{10}), 47.0 (C_{18}), 44.5, 44.3 (C_{21}), 42.0, 41.0 (C_6), 40.4, 38.9, 35.6, 34.6 (C_{12}, C_{16}, C_{21a}, C_{30}), 38.4, 38.1 (C_{25}), 35.8, 35.7 (C_{23}), 35.4, 35.1 (C_{11}, C_{29}), 34.1 (C_{33}), 31.3, 30.8 ($C_{4'6'}$), 30.3 (C_{34}), 27.2 (br, $OC(CH_3)_3$), 27.2 (C_{17}), 27.0, 26.7 (C_3), 26.4 ($C_{5'}$), 25.9, 25.9 (2 × $SiC(CH_3)_3$), 25.0, 24.7 (C_5), 20.8, 20.5 (C_4), 20.2 (C_{17a}), 18.6, 18.5, 18.09, 18.06 (2 × $SiCH(CH_3)_2$, C_{11}a (obs)), 18.2 ($SiC(CH_3)_3$), 16.6 (C_{19a}), 13.2, 12.6 (2 $SiCH(CH_3)_2$), 12.2 (C_{27a}), 9.3, 9.2 (C_{25a}), −3.7, −4.4, −4.6, −4.7 (2 $Si(CH_3)_2$). Anal. Calcd for $C_{80}H_{155}NO_{11}S_2Si_4$: C, 64.77; H, 10.53; N, 0.94. Found: C, 64.86; H, 10.75; N, 1.01.

C_{10} Aldehyde 83. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 242 mg (1.82 mmol) of *N*-chlorosuccinimide and 347 mg (2.04 mmol) of silver nitrate in 21.2 mL of sieve-dried methanol. The solution was treated with 529 μL (487 mg, 4.54 mmol) of 2,6-lutidine. The resulting white suspension was protected from light and stirred at ambient temperature for 25 min, and 674 mg (0.454 mmol, see preceding procedure) of dithiane **82** in 4 mL of tetrahydrofuran was added. The mixture was stirred at 20 °C for 1.5 h and cooled to 0 °C, and 20 mL of saturated aqueous sodium sulfite solution was added slowly. The mixture was stirred for 5 min and 20 mL of 10% aqueous sodium bicarbonate, 20 mL of brine, and 20 mL of water were added. The mixture was extracted with 4 × 35 mL of dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, concentrated, and chromatographed (30 g of SiO_2, gradient from 20:1 to 10:1 hexane/ethyl acetate) to provide 488 mg (75% yield over two steps) of the dimethyl acetal: R_f = 0.38 (7:1 hexane/ethyl acetate). Anal. Calcd for $C_{79}H_{155}NO_{13}Si_4$: C, 65.92; H, 10.85; N, 0.973. Found: C, 65.86; H, 10.72; H, 1.01. A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum, and nitrogen inlet was charged with 488 mg (0.339 mmol) of dimethyl acetal, 312 mg (3.39 mmol) of glyoxylic acid, and 190 μL (200 mg, 3.39 mmol) of glacial acetic acid in 8 mL of sieve-dried dichloromethane. The mixture was heated at 40 °C for 1 h, cooled, and added in portions to 50 mL of saturated aqueous sodium bicarbonate at 0 °C. The mixture was stirred for 5 min and the aqueous layer was extracted with 3 × 25 mL of dichloromethane. The organic layers were combined, washed with 20 mL of water, dried over sodium sulfate, filtered, concentrated, and chromatographed (30 g of SiO_2, 12:1 hexane/ethyl acetate) to yield 421 mg (89%) of aldehyde **83**. The overall yield from **81** to **83** was 67%: R_f = 0.38 (7:1 hexane/ethyl acetate); IR ($CHCl_3$) 2940 s, 2900 s, 2870 s, 2730 w, 1725 m (C=O), 1685 m (C=O), 1465 m, 1410 m, 1390 m, 1370 m, 1340 w, 1330 w, 1280 w, 1255 s, 1210 m, 1180 m, 1160 s, 1110 br s, 1040 m, 1000 m, 945 m, 915 m, 885 m, 835 s, 810 m, 725 m, 665 w; ^{1}H NMR (rotamer ratio 1:1) δ 9.60 (s, H_{10}), 5.70 (m, H_{21b}), 5.43 (br d, J = 9.3, H_{28}), 5.40 (obs br d, H_{26}), 5.34 (br d, J = 9.3, H_{26}), 4.88, 4.68 (2 v br, H_2 (rotamers)), 3.91 (dd, J = 5.9, 1.5, H_{14}), 3.53 (m, H_{32}), 3.43, 3.34, 3.19 (3 s, 3 OCH_3), 2.95 (m, H_{31}), 2.53 (m, H_{11}), 1.63 (br s, C_{27a} H_3), 1.54 (br s, C_{19a} H_3), 1.46, 1.42 (2 v br s, $OC(CH_3)_3$ (rotamers)), 1.10 (d, J = 6.8, C_{11a} H_3), 0.83 (d, J = 6.4, C_{17a} H_3). Anal. Calcd for $C_{77}H_{149}NO_{12}Si_4$: C, 66.38; H, 10.78; N, 1.01. Found: C, 66.32; H, 10.69; N, 1.09.

C_9–C_{10} Aldol Adduct (84). A 25-mL, one-neck, round-bottom flask was fitted with a magnetic stirring bar, nitrogen inlet, thermometer, and septum. The apparatus was flushed with nitrogen and then charged with 434 mg (1.22 mmol, 3 equiv) of imide **46** in 5 mL of dry toluene. After being stirred for 5 min at room temperature, the solution was cooled to −50 °C. To this clear solution was added 199 μL (144 mg, 1.43 mmol) of triethylamine via syringe followed by 300 μL (330 mg, 1.20 mmol) of di-*n*-butylboron triflate. The solution exothermed to −40 °C and triethylammonium triflate formed a dense oil that occasionally crystallized. After stirring at −50 °C for 1.5 h, 568 mg (0.408 mmol) of aldehyde **83** (previously concentrated twice from 2 mL of dry toluene) in 1 mL (plus a 1-mL rinse) of toluene was added via cannula over 5 min. The resulting mixture was warmed to −30 °C over 30 min and held at −30 °C for 12 h. The reaction was quenched by warming to 0 °C and adding 1.2 mL of pH 7 phosphate buffer followed by 3 mL of methanol and 5 mL of tetrahydrofuran. After 5 min, 1.2 mL of 30% aqueous hydrogen peroxide in 1.2 mL of methanol was added dropwise over 10 min (*caution*: initial reaction is exothermic). After being stirred at 0 °C for 1 h, the reaction mixture was concentrated by rotary evaporation (≤20 °C) and diluted with 40 mL of 1:1 saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The resulting mixture was extracted with 4 × 50 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (55 g of SiO_2, 3:1 hexanes/ethyl acetate) to provide 630 mg (88%) of aldol adduct **84** as a foam: $[\alpha]^{29}_D$ −23° (*c* 0.53, CH_2Cl_2); R_f = 0.25 (3:1 hexanes/ethyl acetate); IR ($CHCl_3$) 3560 w (OH), 3500–3300 w (OH), 3005 m, 2940 s, 2890 m, 2885 s, 1778 m (C=O), 1730 sh, 1715 m (C=O), 1685 m (C=O), 1615 w, 1515 w, 1460 m, 1390 s, 1370 m, 1325 w, 1280 w, 1250 s, 1205 s, 1180 m, 1160 m, 1110 s, 1085 m, 1040 m, 1015 w, 1000 m, 950 w, 915 m, 880 m, 835 m, 810 m, 720 s, 665 m. Hindered rotation of the BOC group on N_7 produced broadening (br) or doubling (dbl) of various ^{1}H and ^{13}C signals. This is noted with the assignments. ^{1}H NMR δ 7.33 (overlapping m, $H_{3'',4'',5''}$, PMB $H_{2,6}$), 7.24 (m, $H_{2'',6''}$), 6.89 (m, PMB $H_{3,5}$), 5.71 (m, H_{21b}), 5.44 (br d, J = 8.8, H_{28}), 5.40, 5.34 (dbl, br d, J = 9.0, H_{26}), 5.24 (d, J = $OC(CH_3)_3$), H_9), 4.98 (obs d, H_{20}), 4.96 (m, C_{21c} H_2), 4.88, 4.68 (dbl, br d, H_2), 4.75, 4.40 (2 d, J = 11.2, OCH_2PMB), 4.73 (obs m, $H_{4'}$), 4.20 (d, J = 4.9, $C_{5'}$ H_2), 4.03, 3.93 (dbl, br d, J = 13, C_6 H_{eq}), 3.89 (d, J = 5.4, H_{14}, obs, H_{24}), 3.79 (s, PMB OCH_3), 3.62 (ddd, J = 8.8, 6.8, 2.0, H_{10}), 3.52 (overlapping m, H_{22}, H_{32}), 3.42, 3.35, 3.27 (3 s, 3 OCH_3), 3.36 (obs, $C_{6'}$ H, H_{13}), 3.20 (d, J = 6.8, C_{10} OH), 3.13 (m, H_{15}), 2.95 (overlapping m, H_{31}, dbl C_6 H_{ax}), 2.79 (dd, J = 13.2, 9.8, $C_{6'}$ H), 1.63 (br s, C_{27a} H_3), 1.56 (br s, C_{19a} H_3), 1.46, 1.43 (dbl, br s, BOC *tert*-butyl), 0.90 (obs d, C_{25a} H_3), 0.86 (obs d, C_{11a} H_3), 0.80 (d, J = 6.4, C_{17a} H_3); ^{13}C NMR (62.90 MHz) δ 171.2 (C_8), 170.6 (C_1), 159.6 (PMB C_4), 155.4 (BOC C=O), 153.3 ($C_{2'}$), 137.5 (C_{21b}), 136.6, 136.2 (dbl, C_{28}), 135.3 ($C_{1''}$), 134.9, 131.0 (br, C_{19}, br C_{27}), 130.2 (PMB $C_{2,6}$), 129.4, 129.0 ($C_{2'',6''}$, $C_{3'',5''}$), 127.6 (br, C_{20}), 127.4 ($C_{4''}$), 115.5 (C_{21c}), 113.8 (PMB $C_{3,5}$), 84.4 (C_{31}), 82.3 (br, C_{26}), 81.4 (C_{15}), 80.9 (C_{13}), 79.6 (br, $OC(CH_3)_3$), 77.7 (C_9), 75.8 (C_{10}), 74.8 (C_{32}), 73.8 (C_{14}), 72.9 (C_{22}), 72.5 (OCH_2PMB), 69.7 (br, C_{24}), 67.0 ($C_{5'}$), 58.6, 57.1, 56.5 (3 OCH_3), 55.8 ($C_{4'}$), 55.2 (PMB OCH_3), 54.9, 53.9 (dbl, C_2), 47.2 (C_{18}), 44.5 (C_{21}), 42.1, 41.1 (dbl, C_6), 40.6 (C_{21a}), 38.7 (C_{16}), 38.6, 38.3 (dbl, C_{25}), 37.8 ($C_{6'}$), 35.8 (br, C_{23}), 35.6 (C_{30}), 35.1 (C_{29}), 34.1 (C_{33}), 33.7 (C_{11}), 33.6 (C_{12}), 30.4 (C_{34}), 28.4 ($OC(CH_3)_3$), 27.5 (C_{17}), 27.0, 24.9, 20.9 (br, C_3, C_4, C_5), 26.0 (2 $SiC(CH_3)_3$), 20.1 (C_{17a}), 18.6, 18.5, 18.1, 18.1 (2 $SiCH(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 16.7 (C_{19a}), 16.4 (C_{11a}), 13.4, 12.7 (2 $SiCH(CH_3)_2$), 12.3 (C_{27a}), 9.3 (br, C_{25a}), −3.6, −4.3, −4.5, −4.8 (2 $Si(CH_3)_2$). Anal. Calcd for $C_{97}H_{170}N_2O_{17}Si_4$: C, 66.62; H, 9.80; N, 1.60. Found: C, 66.29; H, 9.70; N, 1.43.

Macrocycle 86 via Amino Acid 85. A 25-mL round-bottom flask fitted with a magnetic stirring bar was charged with 546 mg (0.312 mmol) of aldol adduct **84** dissolved in 7 mL of tetrahydrofuran (not distilled) and 1.75 mL of deionized water. The flask was cooled to 0 °C and 255 μL (281 mg, 2.50 mmol) of 30% aqueous hydrogen peroxide was added followed by 26 mg (0.62 mmol) of lithium hydroxide hydrate in one portion. The suspension exothermed to +3 °C upon addition of the lithium hydroxide. After stirring at 0 °C for 3 h, 5 mL of saturated aqueous sodium thiosulfate was added over 5 min and the resulting slurry was stirred at 0 °C for 1 h. The reaction mixture was concentrated by rotary evaporation and then acidified to pH 3 with approximately 5 mL of 0.5 N aqueous sodium hydrogen sulfate. The suspension was extracted with 3 × 15 mL of hexane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered through Celite, and concentrated to provide 562 mg (113%) of the corresponding carboxylic acid. ^{1}H NMR analysis showed 10–25% contamination of the acid with (*S*)-4-benzyl-2-oxazolidinone. A 25-mL round-bottom flask fitted with a magnetic stirring bar was charged with the crude acid dissolved in 6 mL of anhydrous dichloromethane. The flask was cooled to 0 °C and 218 μL (200 mg, 1.87 mmol, approximately 6 equiv) of 2,6-lutidine was added, followed by 317 μL (371 mg, 1.40 mmol, approximately 4.5 equiv) of triethylsilyl triflate. After stirring at 0 °C for 35 min, 3 mL of water was added and the resulting mixture was extracted with 3 × 12 mL of hexane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated (bath temperature ≤20 °C). The crude reaction mixture was placed on a dry-packed silica column (72 g of 40–63-μm SiO_2, eluted with dichloromethane) and aged on the column for 80 min. During the aging process, dichloromethane was occasionally allowed to elute; 80 mL total was collected. The column was eluted with 600 mL of dichloromethane, 800 mL of 1% methanol in dichloromethane, 600 mL of 4% methanol in dichloromethane, and finally 900 mL of 8% methanol in dichloromethane. Amino acid **85**, 400 mg (80%), was isolated as an unstable foam and cyclized immediately. Selected data are reported for C_{14} TES-**85**: R_f = 0.32 (94:6 dichloromethane/methanol); ^{1}H NMR δ 7.28 (m, PMB $H_{2,6}$), 6.83 (m, PMB $H_{3,5}$), 5.68 (m, H_{21b}), 5.50 (br, actives), 5.45 (d, J = 9.8, H_{26}), 5.39 (br d, J = 8.8, H_{28}), 4.95 (m, C_{21c} H_2), 4.74 (br d, J = 10.3, H_{20}), 4.65, 4.24 (2 d, J = 11.2, OCH_2PMB), 3.93 (t, J = 4.0, H_{10}), 3.88 (m, H_{24}), 3.81 (d, J = 4.0, H_9), 3.78 (s, PMB OCH_3), 3.76 (br d, J = 6.8, H_{14}), 3.64 (m, H_2), 3.55 (m, H_{32}), 3.44, 3.38, 3.29 (3 s, 3 OCH_3), 3.20 (m, H_{22}), 3.17 (obs d, C_6 H_{eq}), 3.08 (br t, J = 6.5, H_{15}), 3.02 (m, H_{13}), 2.97 (m, H_{31}), 2.77 (br t, J = 11, C_6 H_{ax}), 1.65 (br s, C_{27a} H_3), 1.58 (br s, C_{19a} H_3); ^{13}C NMR (75.47 MHz) δ 175.0 (C_8), 171.2 (C_1), 159.1 (PMB C_4), 137.6 (C_{21b}), 136.4 (C_{28}), 136.0, 130.6, 130.0 (C_{19}, C_{27}, PMB C_1), 129.9 (PMB $C_{2,6}$), 128.3 (C_{20}), 115.4 (C_{21c}), 113.5 (PMB $C_{3,5}$), 84.4 (C_{31}), 82.5, 81.9, 76.5, 75.8

(C_9, C_{10}, C_{14}, C_{26}), 81.1 (C_{15}), 80.4 (C_{13}), 74.8 (C_{32}), 72.9 (C_{22}), 72.2 (OCH_2PMB), 69.5 (C_{24}), 59.7, 57.5, 56.8, 56.5 (4 OCH_3), 55.1 (C_2), 47.2 (C_{18}), 46.6 (C_{21}), 43.6, 42.1 (C_6, C_{16}), 40.4 (C_{21a}), 38.2 (C_{25}), 36.4 (C_{23}), 35.8 (C_{30}, C_{11}), 35.1 (C_{29}), 34.0 (C_{33}), 32.1 (C_{12}), 30.2 (C_{34}), 28.4, 24.9, 23.2 (C_3, C_4, C_5), 27.3 (C_{17}), 26.0 ($SiC(CH_3)_3$), 20.1 (C_{17a}), 18.54, 18.50, 18.09, 18.08 (2 $SiCH(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 17.4, 16.5 (C_{11a}, C_{19a}), 13.2, 12.6 (2 $SiCH(CH_3)_2$), 12.2 (C_{27a}), 8.6 (C_{25a}), 7.0, 6.9 (2 $SiCH_2CH_3$), 5.1, 5.0 (2 $SiCH_2CH_3$), -3.0, -4.2 ($Si(CH_3)_2$).

A 500-mL round-bottom flask was fitted with a magnetic stirring bar, nitrogen inlet, and septum. The apparatus was flushed with nitrogen and charged with 76 mg (0.30 mmol) of 2-chloro-1-methylpyridinium iodide and 65 μL (47 mg, 0.47 mmol) of triethylamine in 232 mL of dichloromethane. A 20-mL syringe was charged with 400 mg (0.249 mmol) of amino acid **85** and 109 μL (79.1 mg, 0.782 mmol) of triethylamine in 18 mL of dichloromethane and placed on a syringe pump. The amino acid was added dropwise over 65 min to the 2-chloro-1-methylpyridinium iodide suspension. The resulting yellow solution was stirred for 3 h at room temperature and then stored at −30 °C overnight. The reaction was quenched by the addition of 10 mL of water. The layers were separated and the aqueous layer was extracted with 3 × 15 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, and chromatographed (31 g of SiO_2, 30:1 hexane/ethyl acetate) to provide 324 mg (81%) of macrocycle **86** as a solid foam: mp 98–100 °C; $[\alpha]^{25}_D$ −49.7° (*c* 1.18, CH_2Cl_2); R_f = 0.39 (11:1 hexane/ethyl acetate); IR ($CHCl_3$) 3005 m, 2940 s, 2900 s, 2870 s, 1735 w (C=O), 1630 m (C=O), 1515 w, 1460 m, 1445 m, 1380 w, 1340 w, 1320 w, 1300 w, 1250 s, 1205 s, 1180 w, 1150 m, 1125 s, 1100 s, 1085 s, 1065 m, 1040 m, 1005 m, 950 m, 925 m, 885 m, 835 s, 810 s, 720 s, 665 m; ^{1}H NMR δ 7.34 (m, PMB $H_{2,6}$), 6.82 (m, PMB $H_{3,5}$), 5.69 (m, H_{21b}), 5.50 (d, *J* = 4.9, H_{26}), 5.32 (br, H_2), 5.23 (br d, *J* = 8.3, H_{28}), 4.94 (m, C_{21c} H_2), 4.74 (d, *J* = 10.7, H_{20}), 4.67, 4.35 (2 d, *J* = 10.5, OCH_2PMB), 4.45 (br d, *J* = 13.7, C_6 H_{eq}), 4.21 (d, *J* = 7.3, H_9), 4.08 (br m, H_{24}), 3.80 (s, PMB OCH_3, obs, H_{10}), 3.63 (d, *J* = 8.3, H_{14}), 3.56 (m, H_{32}), 3.52 (bs, OCH_3), 3.41, 3.20 (2 s, OCH_3), 3.39 (br, H_{22}), 3.20 (br, C_6 H_{ax}), 3.17 (br, H_{15}), 3.00 (m, H_{31}), 2.80 (m, H_{13}), 1.70 (d, *J* = 1.0, C_{27a} H_3), 1.62 (br s, C_{19a} H_3). Due to a combination of hindered rotation and interconverting ring conformations, many carbon signals were broadened and C_{26} and C_{27} were not observed. ^{13}C NMR (75.47 MHz) δ 170.2, 169.9 (br, v br, C_1, C_8), 159.0 (PMB C_4), 137.7 (C_{21b}), 136.6 (C_{19}), 132.6 (v br, C_{28}), 130.5 (PMB $C_{2,6}$), 129.9 (PMB C_1), 127.4 (br, C_{20}), 115.3 (C_{21c}), 113.3 (PMB $C_{3,5}$), 87.3 (v br, C_9), 84.4 (C_{31}), 83.3 (br, C_{13}), 78.8 (C_{15}), 77.7 (v br, C_{10}), 77.1 (C_{14}), 74.9 (C_{32}), 74.0 (br, C_{22}), 71.7 (OCH_2PMB), 69.7 (C_{24}), 60.8, 57.5, 55.7 (3 OCH_3), 55.1 (PMB OCH_3), 52.4 (C_2), 47.8 (C_{21}), 47.0 (C_{18}), 42.8 (C_6), 41.9 (C_{16}), 40.3 (C_{25}), 37.4 (C_{21a}), 36.5 (br, C_{11}), 36.3 (C_{30}), 35.0 (C_{29}), 34.0 (C_{12}), 30.7 (C_{34}), 29.4 (br, C_{33}), 26.7 (C_{17}), 26.5 (C_3), 26.3, 26.1 (2 $SiC(CH_3)_3$), 25.5 (C_5), 21.1 (br, C_4), 20.7 (C_{17a}), 18.7 (C_{11a}), 18.5, 18.45, 18.11, 18.09 (2 $SiCH(CH_3)_2$), 18.6 ($SiC(CH_3)_3$), 16.5 (C_{19a}), 13.9 (v br, C_{27a}), 12.9, 12.6 ($SiCH(CH_3)_2$), 10.1 (C_{25a}), −2.4, −4.1, −4.4, −4.7 (2 $Si(CH_3)_2$). Anal. Calcd for $C_{88}H_{165}NO_{13}Si_5$: C, 66.66; H, 10.49; N, 0.88. Found: C, 66.49; H, 10.53; N, 0.81.

C_9,C_{10} Diol 87. A 10-mL round-bottom flask was fitted with a magnetic stirring bar and charged with 367 mg (0.321 mmol) of macrocycle **86** dissolved in 2.00 mL of dichloromethane and 111 μL of water. The resulting mixture was vigorously stirred for 5 min and then 263 mg (1.16 mmol) of DDQ was added in one portion. The flask was stoppered and vigorously stirred for 4.5 h. The reaction was stopped by chromatographing the crude reaction mixture (32 g of SiO_2, 2 cm × 16 cm column, gradient of 250 mL of dichloromethane followed by 600 mL of 15:1 hexane/ethyl acetate, 450 mL of 6:1 hexane/ethyl acetate, and 200 mL of 3:1 hexane/ethyl acetate). Three fractions were isolated. The first fraction consisted of 252 mg (73%) of C_9 OC,C_{10} OTES macrocycle: R_f = 0.38 (6:1 hexane/ethyl acetate). The second fraction consisted of 20 mg (5%) of C_9,C_{10} *p*-methoxybenzoates: R_f = 0.17–0.23 (6:1 hexane/ethyl acetate). The third fraction consisted of 22 mg (7%) of **87**: R_f = 0.12 (6:1 hexane/ethyl acetate). Selected data for C_{10} OTES-**87**: ^{1}H NMR (major rotamer) δ 5.67 (m, H_{21b}), 5.53 (d, *J* = 10.7, H_{26}), 5.42 (br d, *J* = 8.8, H_{28}), 5.10 (br d, *J* = 4.9, H_2), 4.93 (m, C_{21c} H_2), 4.72 (br d, *J* = 10.3, H_{20}), 4.51 (br d, *J* = 12.7, C_6 H_{eq}), 4.24 (d, *J* = 9.3, H_{10}), 4.15 (d, *J* = 9.8, H_9), 3.95 (m, H_{24}), 3.70 (d, *J* = 8.3, H_{14}), 3.54 (d, *J* = 9.8, C_9 OH), 3.51, 3.37, 3.25 (3 s, 3 OCH_3), 3.25 (obs m, C_6 H_{ax}), 1.69 (d, *J* = 1.0, C_{27a} H_3), 1.58 (br s, C_{19a} H_3). (Additional data: NOE difference spectroscopy showed a 5% NOE from H_9 to H_2, providing firm evidence for cyclization.)

A 10-mL round-bottom flask was fitted with a magnetic stirring bar and charged with 252 mg (0.172 mmol) of C_{10} OTES-**87** in 4 mL of tetrahydrofuran. The solution was stirred at room temperature and 0.8 mL of water was added followed by 158 μL (234 mg, 2.06 mmol) of trifluoroacetic acid. After stirring at room temperature for 4.5 h, 5 mL of saturated aqueous sodium bicarbonate was cautiously added. The resulting mixture was poured into a 30-mL separatory funnel containing 10 mL of ethyl acetate and 10 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with 3 × 10 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (2 cm × 20 cm column, 40 g of SiO_2, 200 mL of 6:1 hexane/ethyl acetate followed by 200 mL of 4:1 hexane/ethyl acetate) to provide 210 mg (91%) of **87** as a thick oil. The total yield of diol was 232 mg (74%) from macrocycle **86**: $[\alpha]^{27}_D$ −57.3° (*c* 1.24, $CHCl_3$); R_f = 0.12 (6:1 hexane/ethyl acetate); IR ($CHCl_3$) 3550–3350 w (OH), 3070 w, 3010 m, 2940 s, 2895 s, 2865 s, 1730 m (C=O), 1640 m (C=O), 1465 m, 1390 m, 1365 w, 1340 w, 1320 w, 1255 m, 1205 m, 1140 m, 1115 s, 1090 s, 1070 m, 1040 m, 1015 m, 950 w, 920 br w, 880 m, 835 m, 810 m, 720 br s, 665 m; ^{1}H NMR δ 5.67 (m, H_{21b}), 5.39 (br d, *J* = 7.3, H_{28}, H_2 (obs)), 5.29 (d, *J* = 8.8, H_{26}), 4.92 (m, C_{21c} H_2), 4.73 (br d, *J* = 9.8, H_{20}), 4.56 (d, *J* = 6.8, H_9), 3.94 (obs m, H_{24}), 3.90 (d, *J* = 6.8, C_9 OH), 3.73 (dd, *J* = 8.3, 1.0, H_{14}), 3.55 (m, H_{32}), 3.50, 3.39, 3.31 (3 s, 3 OCH_3), 3.38 (obs, H_{10}), 2.97 (m, H_{31}), 2.39 (d, *J* = 7.3, C_{10} OH), 1.64 (d, *J* = 1.0, C_{27a} H_3), 1.58 (br s, C_{19a} H_3), 0.78 (d, *J* = 6.4, C_{17a} H_3); ^{13}C NMR δ 172.4, 169.8 (C_1, C_8), 137.7 (C_{21b}), 136.0 (C_{19}), 135.8 (br, C_{28}), 131.0 (C_{27}), 128.7 (C_{20}), 115.3 (C_{21c}), 84.4 (C_{31}), 83.7, 80.3 (C_{13}, C_{15}), 82.7 (br, C_{26}), 76.0 (C_{14}), 75.9 (C_{10}), 74.9 (C_{32}), 73.0 (C_{22}), 70.1 (br, C_{24}), 68.1 (C_9), 60.7, 57.5, 57.3 (3 OCH_3), 52.5 (C_2), 46.9 (C_{21}), 46.7 (C_{18}), 43.1 (C_6), 41.2 (br, C_{23}), 41.1, 33.4 (C_{12}, C_{16}), 38.5 (br, C_{25}), 36.8 (C_{21a}), 35.8 (C_{30}), 35.0 (C_{29}), 34.2 (C_{11}), 34.0 (C_{33}), 30.3 (C_{34}), 26.2 (C_{17}), 26.1, 26.1 (2 $SiC(CH_3)_3$), 26.0, 25.9 (C_3, C_5), 20.4 (C_{17a}), 20.1 (C_4), 18.6, 18.1 (2 $SiCH(CH_3)_2$), 18.4, 18.3 (2 $SiC(CH_3)_3$), 16.4 (C_{19a}), 13.5, 12.8 (2 $SiCH(CH_3)_2$), 12.8 (obs, C_{27a}), 8.8 (br, C_{25a}). Anal. Calcd for $C_{74}H_{143}NO_{12}Si_4$: C, 65.78; H, 10.67; N, 1.04. Found: C, 65.54; H, 10.77; N, 1.15.

(9*S*,10*R*,22*R*)-Hexahydro-FK-506. A 10-mL round-bottom flask fitted with a magnetic stirring bar was charged with 27 mg (20 μmol) of diol **87** dissolved in 2 mL of acetonitrile followed by 3 drops (Pasteur pipet) of 48% aqueous hydrofluoric acid and stirred at 0 °C. After stirring for 12 h, 5 mL of saturated aqueous sodium bicarbonate was cautiously added to the colorless reaction. The resulting mixture was partitioned between 5 mL of water and 10 mL of ethyl acetate. The aqueous phase was extracted with 6 × 10 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 20 cm column, 20:1 dichloromethane/methanol) to afford 8.5 mg (52%) of hexahydro-FK-506 as a clear oil: R_f = 0.20 (20:1 dichloromethane/methanol); IR ($CHCl_3$) 3640–3350 w (OH), 3010 s, 2930 s, 2870 m, 2830 w, 1725 m (C=O), 1635 s (C=O), 1455 m, 1390 m, 1205 s, 1095 s, 1055 m, 1035 m, 1020 m, 910 m, 725 s, 655 m; ^{1}H NMR δ 5.78 (m, H_{21b}), 5.45 (br d, *J* = 4.4, H_2), 5.27 (br d, *J* = 9.8, H_{28}), 5.19 (d, *J* = 6.8, H_{26}), 5.01 (m, C_{21c} H_2), 4.86 (br d, *J* = 9.8, H_{20}), 4.62 (dd, *J* = 6.4, 1.0, H_9), 4.06 (d, *J* = 6.4, C_9 OH), 3.75 (dt, *J* = 10.3, 2.4, H_{24}), 3.65 (overlapping m, C_6 H_{eq}, H_{22}), 3.52 (obs m, H_{10}), 3.40, 3.36, 3.35 (3 s, 3 OCH_3), 3.21 (td, *J* = 8.3, 2.4, H_{14}), 3.13 (br t, *J* = 12.7, C_6 H_{ax}), 3.01 (d, *J* = 8.3, C_{14} OH), 2.87 (d, *J* = 7.3, C_{10} OH), 2.71 (br s, C_{32} OH), 1.59 (d, *J* = 1.0, C_{19a} H_3), 1.55 (d, *J* = 1.0, C_{27a} H_3), 1.10 (d, *J* = 6.4, C_{11a} H_3), 0.92 (d, *J* = 6.4, C_{17a} H_3), 0.91 (d, *J* = 6.8, C_{25a} H_3); ^{13}C NMR δ 171.9, 170.1 (C_1, C_8), 136.9 (C_{21b}), 136.6, 131.3 (C_{19}, C_{27}), 132.7 (C_{28}), 126.6 (C_{20}), 115.9 (C_{21c}), 84.1 (C_{31}), 82.1 (C_{26}), 81.5, 77.9 (C_{13}, C_{15}), 77.1 (C_{10}), 76.3 (C_{22}), 73.8 (C_{14}, C_{24}), 73.4 (C_{32}), 68.9 (C_9), 57.5, 57.0, 56.4 (3 OCH_3), 52.9 (C_2), 48.8 (C_{18}), 45.2 (C_{21}), 43.6 (C_6), 39.7 (C_{25}), 38.5, 37.7, 36.4, 35.04, 34.5, 31.2, 30.5 (C_{12}, C_{16}, C_{21a}, C_{23}, C_{30}, C_{33}, C_{34}), 36.0 (C_{11}), 34.96 (C_{29}), 26.7 (C_{17}), 25.8 (C_3), 25.4 (C_5), 21.3 (C_{17a}), 20.7 (C_4), 18.7 (C_{11a}), 16.6 (C_{19a}), 12.7 (C_{27a}), 8.7 (C_{25a}); HRMS calcd for $C_{44}H_{75}NO_{12}$ 809.5289, found (EI) 809.5289.

C_9,C_{10} Dione 88. To a solution of 70 μL (100 mg, 0.80 mmol) of oxalyl chloride in 1.0 mL of dichloromethane at −78 °C in a 10-mL round-bottom flask fitted with a thermocouple, septum, and nitrogen inlet was added dropwise a solution of 85 μL (94 mg, 1.20 mmol) of dimethyl sulfoxide in 0.25 mL of dichloromethane. After 10 min, a solution of 108 mg (79.9 μmol) of diol **87** (previously dried azeotropically with 2 × 3 mL of benzene) in 0.5 mL (plus a 0.5-mL rinse) of dichloromethane was added via cannula at a rate to maintain the internal temperature below −60 °C. After 2.5 h at −60 °C, 223 μL (162 mg, 1.60 mmol) of triethylamine was added over 3 min. The reaction was warmed to −30 °C, and the resulting mixture was stirred at −30 °C for 30 min and then partitioned between 10 mL of ethyl acetate and 10 mL of 0.5 N aqueous sodium hydrogen sulfate. The aqueous layer was extracted with 3 × 10 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting unstable pale yellow oil was only partially oxidized and was resubmitted to the above reaction conditions without further purification. After a second oxidation, the isolated oil was chromatographed (1 cm × 20 cm column, 12:1 hexane/ethyl acetate) to afford 86 mg (80%) of the dione as a yellow foam: $[\alpha]^{27}_D$ −54.3° (*c* 1.19, $CDCl_3$); R_f = 0.20 (6:1 hexane/ethyl

acetate); IR ($CHCl_3$) 2950 s, 2895 s, 2870 s, 1730 m (C=O), 1710 m, 1645 s (C=O), 1460 m, 1385 w, 1360 w, 1285 w, 1255 m, 1205 m, 1120 br s, 1070 m, 1045 m, 1015 m, 970 w, 950 m, 920 m, 885 m, 835 s, 810 m, 720 s, 760 m; ^1H NMR (major rotamer) δ 5.70 (m, H_{21b}), 5.44 (br d, J = 8.3, H_{28}), 5.26 (br d, J = 9.8, H_{26}), 5.21 (br d, J = 3.9, H_2), 4.94 (m, C_{21c} H_2), 4.87 (obs d, H_{20}), 3.89 (m, H_{24}), 3.74 (dd, J = 5.4, 3.4, H_{14}), 3.54 (m, H_{32}), 3.40, 3.37, 3.20 (3 s, 3 OCH_3), 3.40 (obs m, H_{11}), 3.4–3.0 (obs m, C_6 H_2), 2.95 (m, H_{31}), 1.59 (br s, C_{19a} H_3, C_{27a} H_3), 1.18 (d, J = 6.8, C_{11a} H_3), 0.86 (d, J = 6.8, C_{17a} H_3), 0.85 (d, J = 6.4, C_{25a} H_3); ^{13}C NMR (75.47 MHz, major rotamer of the tricarbonyl moiety) δ 199.2 (C_{10}), 185.9 (C_9), 165.5 (C_8).

22-Dihydro-FK-506 (89). A 25-mL round-bottom flask fitted with a magnetic stirring bar was charged with 105 mg (78.0 μmol) of tricarbonyl **88** dissolved in 0.20 mL of dichloromethane and 9 mL of acetonitrile. The yellow solution was cooled to 0 °C and 10 drops of 48% aqueous hydrofluoric acid was added. After being stirred at 0 °C for 12 h, the colorless mixture was cautiously added by pipet to a 60-mL separatory funnel containing 20 mL of saturated aqueous sodium bicarbonate, 10 mL of water, and 20 mL of ethyl acetate. The aqueous phase was extracted with 3 × 20 mL of ethyl acetate and washed with 10 mL of brine, 10 mL of saturated aqueous sodium bicarbonate, and 10 mL of brine. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 14 cm column, 9.5 g of SiO_2, 2:1 dichloromethane/acetonitrile) to afford 51 mg (81%) of 22-dihydro-FK-506 as a white solid: $[\alpha]^{25}_D$ −43.0° (*c* 1.68, $CHCl_3$); R_f = 0.15 (2:1 dichloromethane/acetonitrile); IR ($CHCl_3$) 3550–3200 br w (OH), 3010 m, 2980 sh, 2940 s, 2875 m, 2830 m, 1735 s (C=O), 1640 s (C=O), 1450 s, 1380 m, 1345 m, 1330 w, 1285 m, 1260 m, 1200 s, 1185 s, 1035 m, 1100 s, 1085 s, 1070 s, 1050 s, 910 m, 985 m, 975 m, 930 w, 910 m, 845 w, 720 m, 660 m. NMR data are reported for the major amide rotamer (amide carbonyl syn to the C_6 CH_2 as evidenced by the large nonequivalence of the geminal protons; rotamer ratio 85:15). ^1H NMR δ 5.75 (m, H_{21b}), 5.54 (br d, J = 2.4, H_{26}), 5.30 (d, J = 2.0, C_{10} OH), 5.04 (obs d, H_{28}), 4.97 (m, C_{21c} H_2), 4.92 (obs d, H_{20}), 4.42 (obs br d, C_6 H_{eq}), 4.38 (t, J = 3.9, H_2), 3.93 (m, H_{24}), 3.85 (m, H_{22}), 3.42 (s, OCH_3), 3.40 (obs m, H_{32}), 3.38, 3.30 (2 s, 2 OCH_3), 3.28 (br s, OH), 3.03 (m, H_{31}), 2.96 (td, J = 13.2, 2.9, C_6 H_{ax}), 2.87 (br s, OH), 2.68 (m, H_{21}), 2.67 (br s, OH), 2.44 (m, H_{11}), 1.66 (br s, C_{27a} H_3), 1.60 (br s, C_{19a} H_3), 1.02 (d, J = 6.8, C_{17a} H_3), 0.91 (d, J = 6.8, C_{11a} H_3), 0.82 (d, J = 7.3, C_{25a} H_3). Protons H_{13}, H_{14}, and H_{15}, were essentially degenerate in $CDCl_3$ at 3.4 ppm. Proton 1-D and 2-D NMR in C_6D_6 provides the following selected data (250.13 MHz, C_6D_6 (δ = 7.12)): δ 3.73 (d, J = 9.8, H_{14}), 3.60 (br d, J = 9.8, H_{15}), 3.44 (obs m, H_{13}); ^{13}C NMR (62.90 MHz) δ 198.6 (C_9), 169.1 (C_1), 165.7 (C_8), 136.8 (C_{21b}), 136.3 (C_{19}), 132.7 (C_{27}), 128.3 (C_{28}), 125.4 (C_{20}), 115.9 (C_{21c}), 98.6 (C_{10}), 84.3 (C_{31}), 76.1, 74.2, 73.7 (C_{13}, C_{14}, C_{15}), 75.8 (C_{26}), 74.9 (C_{22}), 74.1 (C_{24}), 73.6 (C_{32}), 57.0 (C_2), 56.6, 56.4, 56.3 (3 OCH_3), 49.1 (C_{18}), 43.3 (C_{21}), 39.2 (C_{25}), 39.0 (C_6), 37.8 (C_{23}), 35.0, 34.7 (C_{21a}, C_{30}), 34.9, 34.8 (C_{11}, C_{29}), 32.9 (C_{16}), 32.6 (C_{12}), 31.3 (C_{33}), 30.8 (C_{34}), 27.6 (C_{17}), 27.0 (C_3), 24.3 (C_5), 21.7 (C_4), 21.6 (C_{17a}), 16.0 (C_{19a}), 15.7 (C_{11a}), 14.6 (C_{27a}), 10.4 (C_{25a}); HRMS calcd for $C_{44}H_{71}NO_{12}$ 805.4976, found (EI) 805.4977.

24,32-Bis-TES-22-dihydro-FK-506. A 5-mL round-bottom flask was fitted with a magnetic stirring bar and charged with 16.0 mg (19.9 μmol) of 22-dihydro-FK-506 and 1 mL of dry pyridine. The flask was cooled to 0 °C and 16 μL (14 mg, 99 μmol) of triethylsilyl chloride was added. The reaction was stirred at 0 °C for 2 h, stored at −30 °C for 12 h, and then stopped by the pouring the mixture into 5 mL of 0.5 N sodium hydrogen sulfate and 5 mL of ethyl acetate. The pH of the aqueous phase was adjusted to 3 with approximately 1 mL of 1 N hydrochloric acid. The resulting mixture was extracted with 3 × 10 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (2 cm × 17 cm column, 30 g of SiO_2, 60:35:5 hexane/dichloromethane/acetonitrile) to afford 14.3 mg (70%) of 24,32-bis-TES-22-dihydro-FK-506 as a foam: $[\alpha]^{30}_D$ −18.8° (*c* 1.20, $CDCl_3$); R_f = 0.37 (3:1 hexane/ethyl acetate); IR ($CDCl_3$) 3670 w (OH), 3550–3250 br w (OH), 2960 s, 2940 s, 2920 s, 2880 s, 2830 w, 1745 w (C=O), 1645 m (C=O), 1460 m, 1420 w, 1380 w, 1345 w, 1285 w, 1265 w, 1240 w, 1195 w, 1175 w, 1140 w, 1100 m, 1080 m, 1040 w, 1015 m, 985 w, 890 br m, 815 s, 700 br m, 645 m; ^1H NMR δ 5.73 (m, H_{21b}), 5.57 (d, J = 2.0, C_{10} OH), 5.47 (br d, J = 3.4, H_{26}), 4.96 (overlapping m, C_{21c} H_2, H_{20}, H_{28}), 4.41 (br d, J = 13.2, C_6 H_{eq}), 4.22 (br d, J = 4.9, H_2), 3.97 (m, H_{24}), 3.76 (br d, J = 7.3, H_{22}), 3.44, 3.36, 3.29 (3 s, 3 OCH_3), 3.13 (d, J = 1.5, C_{22} OH), 2.93 (br td, J = 13.2, 3.4, C_6 H_{ax}), 2.74 (m, H_{21}), 2.59 (m, H_{11}), 1.62 (br d, J = 1.0, C_{27a} H_3), 1.61 (br s, C_{19a} H_3), 1.03 (obs d, $J \sim 6$, C_{17a} H_3), 0.87 (d, J = 6.8, C_{11a} H_3), 0.76 (obs, C_{25a} H_3); ^{13}C NMR δ 198.8 (C_9), 168.6 (C_1), 166.2 (C_8), 136.8 (C_{21b}), 136.0, 131.7 (C_{19}, C_{27}), 128.3 (C_{28}), 124.8 (C_{20}), 115.9 (C_{21c}), 99.2 (C_{10}), 84.0 (C_{31}), 76.5, 74.4, 73.7 (C_{13}, C_{14}, C_{15}), 76.2 (C_{26}), 75.3 (C_{32}), 74.5 (C_{24}), 72.9 (C_{22}), 58.2, 56.4, 56.2 (3 OCH_3), 56.9 (C_2), 49.0 (C_{18}), 42.4 (C_{21}), 38.6 (C_6), 38.3 (C_{23}), 37.7 (C_{25}), 36.9 (C_{30}), 34.8 (C_{11}, C_{29}), 34.4 (C_{21a}), 34.0 (C_{33}), 33.1 (C_{16}), 32.5 (C_{12}), 31.1 (C_{34}), 28.0 (C_{17}), 26.5 (C_3), 24.1 (C_5), 22.0 (C_{17a}), 21.8 (C_4), 16.0 (C_{19a}), 15.3 (C_{11a}), 14.6 (C_{27a}), 10.8 (C_{25a}), 7.0, 6.8 (2 $SiCH_2CH_3$), 5.00, 4.95 (2 $SiCH_2CH_3$); HRMS calcd for $C_{56}H_{99}NO_{12}Si_2$ 1033.6706, found (EI) 1033.6705.

24,32-Bis-TES-FK-506 (91). A 5-mL round-bottom flask was fitted with a magnetic stirring bar and charged with 14.0 mg (13.8 μmol) of 24,32-bis-TES-22-dihydro-FK-506 dissolved in 1 mL of dichloromethane. The flask was stirred at room temperature and 11 μL (11 mg, 138 μmol) of pyridine was added followed by 29 mg (69 μmol) of Dess–Martin periodinane. After 1.5 h at room temperature, the reaction was cooled to 0 °C and stopped by the addition of 1 mL of saturated sodium sulfite. After being stirred for 5 min at 0 °C, the reaction mixture was poured into a 30-mL separatory funnel and extracted with 3 × 10 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 20 cm column, 60:33:7 hexane/dichloromethane/acetonitrile) to provide 8.5 mg (61%) of 24,32-bis-TES-FK-506. This reaction was initially performed in an NMR tube (CD_2Cl_2) and monitored by ^1H NMR: $[\alpha]^{30}_D$ −80.3° (*c* 1.59, $CDCl_3$); $R_{f,22\text{-}OH} = R_{f,22\text{-}C=O}$ = 0.30 (60:33:7 hexane/dichloromethane/acetonitrile); IR ($CDCl_3$) 3540–3450 w (OH), 2960 s, 2940 s, 2920 s, 2880 s, 2830 w, 1740 m (C=O), 1710 m (C=O), 1650 m (C=O), 1455 m, 1420 w, 1385 w, 1350 br w, 1330 w, 1285 w, 1245 w, 1200 m, 1180 m, 1140 m, 1105 m, 1075 s, 1040 m, 1005 m, 980 w, 820 w; ^1H NMR (major rotamer; ratio ~2:1) δ 5.24 (br d, J = 8.8, H_{28}), 5.20 (d, J = 6.8, H_{26}), 4.81 (br d, J = 10.3, H_{20}), 4.42 (obs br d, C_6 H_{eq}), 4.39 (obs br d, H_2), 4.19 (d, J = 1.0, C_{10} OH), 4.08 (m, H_{24}), 3.80 (dd, J = 9.8, 1.5, H_{14}), 3.41, 3.39, 3.31 (2 s, 2 OCH_3), 1.63 (obs s, C_{19a} H_3), 1.50 (d, J = 1.0, C_{27a} H_3); ^{13}C NMR (major rotamer; ratio ~2:1) δ 209.4 (C_{22}), 196.5 (C_9), 168.9 (C_1), 164.6 (C_8), 138.4 (C_{19}), 135.6 (C_{21b}), 134.1 (br, C_{28}), 131.7 (C_{27}), 123.1 (C_{20}), 116.4 (C_{21c}), 97.5 (C_{10}), 83.9 (C_{31}), 80.8 (br, C_{26}), 75.3, 73.5, 72.8 (C_{13}, C_{14}, C_{15}), 75.1 (C_{32}), 69.6 (C_{24}), 57.9, 57.1, 56.4, 56.3 (C_2, 3 OCH_3), 53.5 (C_{21}), 49.2, 48.2 (br) (C_{18}, C_{23}), 40.7 (C_{25}), 39.0 (C_6), 36.4, 35.5, 34.6, 34.0, 32.6 (C_{12}, C_{16}, C_{21a}, C_{30}, C_{33}), 35.0, 34.7 (C_{11}, C_{29}), 30.6 (C_{34}), 27.5 (C_3), 25.4 (C_{17}), 24.2 (C_5), 20.6 (C_4), 19.5 (C_{17a}), 16.0, 15.4 (C_{11a}, C_{19a}), 12.4 (C_{27a}), 10.2 (C_{25a}), 6.81, 6.77 (2 $SiCH_2CH_3$), 6.4, 5.0 (2 $SiCH_2CH_3$); HRMS calcd for $C_{56}H_{97}NO_{12}Si_2$ 1031.6549, found (EI) 1031.6550.

FK-506 (1). A 10-mL round-bottom flask fitted with a magnetic stirring bar was charged with 10.0 mg (9.69 μmol) of 24,32-bis-TES-FK-506 (**91**) dissolved in 100 μL of dichloromethane. The solution was cooled to 0 °C and 2 mL of 85:15:5 acetonitrile/48% aqueous hydrofluoric acid/water was added. After stirring for 5 min, 2 mL of dichloromethane was added and the resulting solution was added to 10 mL of saturated aqueous sodium bicarbonate. The resulting mixture was partitioned between 5 mL of water and 10 mL of dichloromethane. The aqueous phase was extracted with 3 × 10 mL of dichloromethane. The individual organic extracts were washed with 5 mL of saturated aqueous sodium bicarbonate and 5 mL of brine. The organic layers were combined, dried over sodium sulfate, filtered, concentrated, and chromatographed (1 cm × 10 cm column, 1:1 dichloromethane/acetonitrile) to afford 6.3 mg (81%) of FK-506 as a white solid, which was identical with natural material by ^1H NMR, COSY-45 (300 MHz; $CDCl_3$ and C_6D_6), ^{13}C NMR, optical rotation at six wavelengths, and TLC in several solvent systems: R_f = 0.42 (1:1 dichloromethane/acetonitrile). All rotations for natural (n) material (*c* 0.574, $CHCl_3$) and for synthetic (s) material are (*c* 0.630, $CHCl_3$) as follows: $[\alpha]^{27}_D$ −84.3° (n), −84.1° (s); $[\alpha]^{27}_{578}$ −89.5° (n), −89.5° (s); $[\alpha]^{27}_{546}$ −106° (n), −106° (s); $[\alpha]^{27}_{436}$ −248° (n), −244° (s); $[\alpha]^{27}_{405}$ −346° (n), −344° (s); $[\alpha]^{27}_{365}$ −677° (n), −674° (s).

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Supplementary Material Available: Procedures and characterization data for **8–10**, **12–16**, **18–20**, and **2** (16 pages). Ordering information is given on any current masthead page.