A Total Synthesis of FK-506[1]

Robert E. Ireland,* James L. Gleason, Laura D. Gegnas, and Thomas K. Highsmith

Department of Chemistry, McCormick Road, University of Virginia, Charlottesville, Virginia 22901

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A total synthesis of FK-506 (**1**) is presented. The synthesis features a highly convergent approach utilizing a block coupling strategy. Top and bottom half sections of the molecule are coupled by addition of a vinyl cuprate with a spiroenone. The α-allyl aldol functionality is revealed by a reductive opening of the spiroenone system. The labile α,β-diketoamide hemiketal portion of the molecule is prepared by a late stage generation and oxidation of a masked enediol. Top and bottom half segments are themselves derived by coupling of smaller subunits, resulting in a very convergent route.

Introduction

In recent years, the immunosuppressants FK-506 (**1**), rapamycin, and cyclosporin A have received much attention. In addition to their medical applications in organ transplant therapy, they have been used to study the mechanisms of intracellular signal transduction. The structure of FK-506, isolated from *Streptomyces tsukubaensis*, was published in 1987.[2] This molecule was noteworthy in that its immunosuppressive activity was found to be approximately 100 times greater than that of the favored drug at that time, cyclosporin A.[3]

In addition to its interesting biological properties, FK-506 presents a significant challenge to the synthetic organic chemist. Total syntheses of FK-506 have been completed by Merck[4] in 1989 and by Schreiber[5] in 1990. In addition, Danishefsky,[6] Sih,[7] and Smith[8] have each completed formal syntheses. Numerous other groups have initiated synthetic approaches during the past several years.

Two important functionalities which must be addressed in a synthesis of FK-506 (**1**) are the α-allyl aldol (C21−C24) and the α,β-diketoamide hemiketal (C8−10).[9] In a preliminary communication we have reported the synthesis of a spiroketal analog of FK-506.[10] This accomplishment showed the utility of a spiroenone, developed in this laboratory, as a suitable precursor for the α-allyl aldol moiety of FK-506.[11] A retrosynthetic plan (Scheme 1) for FK-506 also required inclusion of methodology for construction of the α,β-diketoamide hemiketal. Our approach utilizes a silyl enediol (**2**) as the α,β-diketoamide hemiketal precursor. We envisioned that this functionality could be generated from the corresponding α-keto lactam at a late stage in the synthesis. In our spiroketal analog synthesis, a block coupling strategy was used, which required synthesis of subunits utilized early in the scheme in much larger quantities than for those used at later stages of the route. For the synthesis of FK-506, we sought a more convergent route which would would be more efficient in terms of subunit use. This retrosynthetic analysis, therefore, dissects the molecule into large "top half" (**3**) and "bottom half" (**4**) fragments which themselves arise from coupling of the smaller building blocks used in the spiroketal analog synthesis. In addition to the implementation of this general strategy, we detail a linear synthesis of the top half of the molecule which, although not ideal for production of large quantities of intermediates (*vide infra*), served as an excellent proof of stereochemistry for our final route to the top half.

Results and Discussion

The top half (**3**) was initially synthesized in a linear fashion (Scheme 2) from lactone **5**.[10] Opening of the lactone by addition of ethylmagnesium bromide in triethylamine[12] followed by methylation of the resulting hydroxy ketone afforded the methyl ether **7**. The (methylthiomethoxy)methylidene ketone **9** was obtained via condensation of the ketone with ethyl formate and MTM protection of the hydroxymethylidene ketone **8**. A two-step reduction and acid-catalyzed rearrangement[13] gave a 2.75:1 mixture of α,β-unsaturated aldehydes in 91% yield. The desired *trans*-substituted aldehyde **10** was readily separated from the undesired *cis*-isomer by chromatography (67% yield of *trans*-product).

Brown's crotyl boron chemistry[14] was then used to introduce the stereocenters at C25 and C26 resulting in isolation of olefin **11** as a 6.2:1 mixture of diastereomers.

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1996.

(1) No reprints of this paper are available.

(2) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031−5033.

(3) (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *15*, 1249−1255. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256−1265.

(4) (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157−1159. (b) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998−3017.

(5) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601.

(6) Jones, A. B.; Villalobos, A.; Linde, R. G.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786−2797.

(7) Gu, R. L.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 3287−3290.

(8) Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271−4274.

(9) FK-506 (**1**) numbering is used for all intermediates throughout this article.

(10) Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. *J. Org. Chem.* **1992**, *57*, 5071−5073.

(11) (a) Ireland, R. E.; Wipf, P.; Miltz, W.; Vanasse, B. J. *J. Org. Chem.* **1990**, *55*, 1423−1424. (b) Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284−2285.

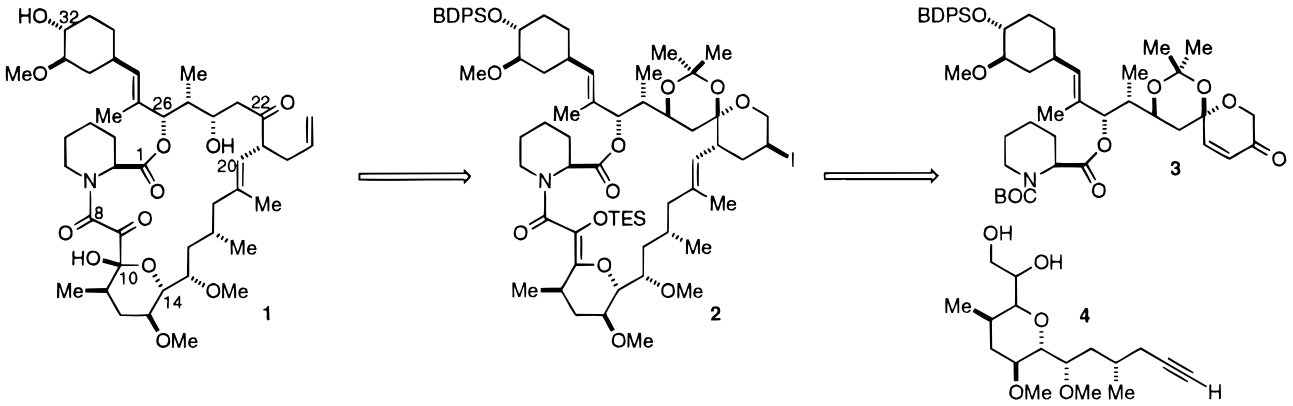
(12) The use of triethylamine as the coordinating solvent moderates the reactivity of the Grignard reagent, preventing reduction of the product ketone. For preparation of Grignard reagents in triethylamine, see Ashby, E. C.; Walker, F. W. *J. Org. Chem.* **1968**, *33*, 3821−3828.

(13) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.*, **1962**, *27*, 1620−1627.

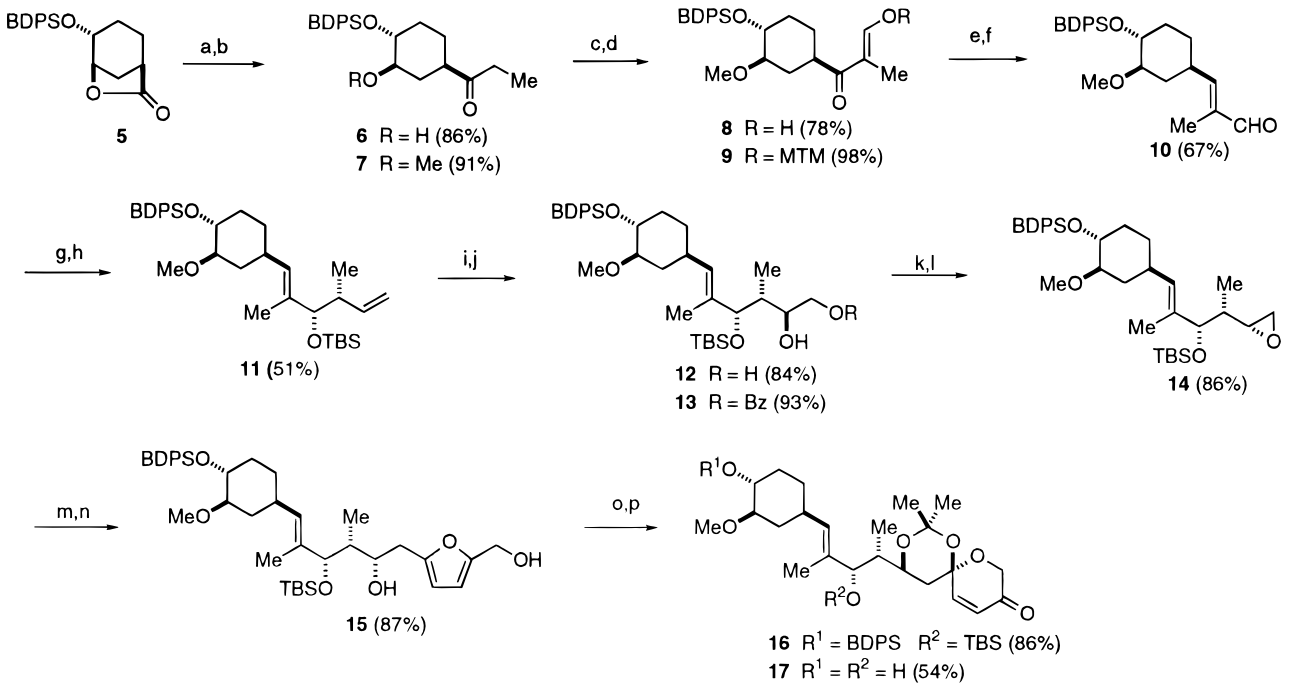
(14) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576.

S0022-3263(95)01646-X CCC: $12.00

Scheme 1. Retrosynthetic Analysis



Scheme 2. Linear Synthesis of the Top Half



Conditions: a) EtMgBr, Et_3N, 0°. b) MeOTf, pyr. c) KHMDS, HCO_2Et. d) MTMCl, K_2CO_3. e) $CeCl_3$, $NaBH_4$. f) p-TsOH. g) (*Z*)-crotyldiisopino campheylborane; H_2O_2, NaOH. h) TBSOTf, 2,6-lutidine. i) OsO_4, NMO. j) BzCl, DMAP. k) MsCl, DMAP, pyr. l) NaOMe, MeOH, 0°C. m) 5-lithiofurfuryl methoxyisopropyl ether, BF_3•OEt_2. n) CSA, THF/H_2O. o) m-CPBA, 0 °C; 2-methoxypropene, p-TsOH. p) $(HF)_n$•pyr.

Dihydroxylation of **11** led to a 9:1 mixture of diols in which the predominant isomer held the undesired configuration at C24.[15] Thus, a three-step sequence of benzoylation, mesylation, and methanolysis served to invert this center and afford the epoxide **14**. The remaining carbons required for the top half were then introduced by epoxide ring opening with 5-lithiofurfuryl methoxyisopropyl ether. Removal of the methoxy isopropyl protecting group under acidic conditions gave the furandiol **15**. Oxidation according to the procedure of DeShong[10,16] and ketalization led to the key top half precursor **16**.

At this stage, all that remained to transform **16** to the desired coupling partner **3** was the removal of the TBS group and acylation with N-BOC-(L)-pipecolic acid. Unfortunately, extreme difficulty was encountered in the attempted selective removal of the TBS protecting group from the C26 hydroxyl group. Among the large selection of deprotective conditions screened, the best results were obtained with polymeric HF−pyridine. This protocol removed the *tert*-butyldiphenylsilyl (BDPS) group as well as the TBS group, affording crystalline diol **17** in 54% yield. All other conditions that were tested either did not affect the starting material or resulted in decomposition of the spiroenone system. The identity of each stereogenic center was verified by X-ray crystallographic analysis of the diol.[17]

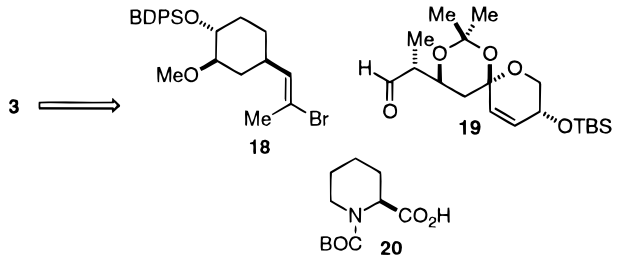
Although diol **17** could be selectively reprotected at C32 and acylated at C26, production of large quantities of material was hindered by these deprotection problems.

(15) The dihydroxylation stereochemistry was initially assigned by analogy to model studies (P. Wipf, University of Virginia) in which the stereochemistry dihydroxylation on a simplified substrate was assigned by ^1H and ^{13}C NMR analysis of a C24, C26 acetonide. Ultimate stereochemical proof arises from the X-ray structure of diol **17** and final conversion of these substrates into FK-506 (vide infra).

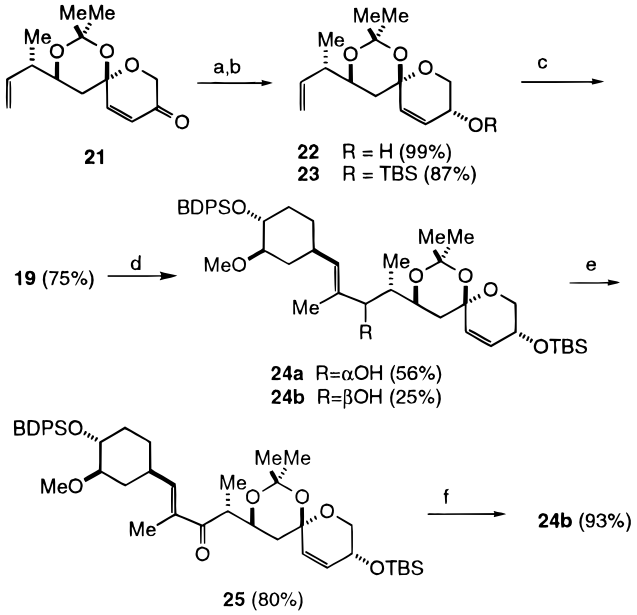
(16) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901−1910.

(17) Coordinates and unit cell parameters for diol **17** have been deposited in the Cambridge Crystallographic Data Base. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 3. Convergent Retrosynthetic Analysis of the Top Half



Scheme 4. Protection of Enone and Coupling

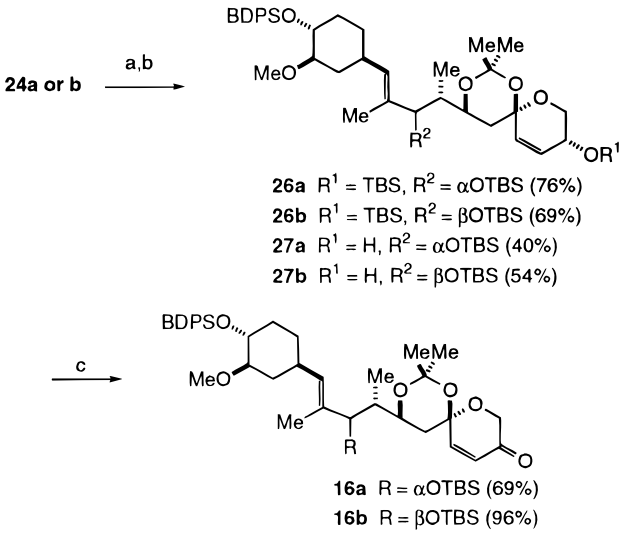


Conditions: a) $Li(s\text{-}Bu)_3BH$, -78°C. b) TBSCl, imid. c) OsO_4, NMO; $NaIO_4$. d) **18**, t-BuLi, -78°C. e) Dess-Martin periodinane. f) $NaBH_4$, $CeCl_3$, -78°C.

We therefore sought a more convergent process for this fragment which would eliminate any need for protecting groups at C26. The major disconnection in the new synthesis (Scheme 3) was the bond between C26 and C27. The top half of the molecule was then envisioned to arise from a convergent coupling of vinyl bromide **18** and aldehyde **19**, two subunits of similar size. The resulting hydroxyl group could then be directly acylated with N-BOC-(L)-pipecolic acid (**20**) after subunit coupling, eliminating any need for protection of the C26 alcohol. This disconnection has also been used both in our synthesis of an FK-506 analog[10] and in the Schreiber group total synthesis of FK-506,[5] wherein a similar cyclohexane derivative was coupled to a different aldehyde.

The syntheses of vinyl bromide **18** and spiroenone subunit **21** have been previously reported.[10] It was found that the optimal coupling procedure (Scheme 4) necessitated temporary protection of the spiroenone. Thus, 1,2-reduction of the enone with L-Selectride and protection with TBSCl gave the protected allylic alcohol **23**. Selective cleavage of the terminal double bond was then effected with OsO_4/NMO followed by periodate-mediated cleavage of the glycol to reveal the aldehyde **19**. Treatment of this aldehyde with the vinyllithium derived from cyclohexylvinyl bromide **18** afforded an 81% yield of a diastereomeric mixture of alcohols **24a** and **24b** in a 2:1 ratio.

Scheme 5. Elucidation of Stereochemistry



Conditions: a) TBSOTf, 2,6-lutidine. b) TBAF. c) Dess-Martin periodinane.

The stereochemistry of vinyllithium addition was elucidated via chemical correlation (Scheme 5) to the original "top half" spiroenone **16** prepared in the linear route above. The diastereomers resulting from vinyllithium addition were separated by flash chromatography and each was silylated at the C26 hydroxyl to give bis-TBS ethers **26a** and **26b**. Removal of the more accessible TBS group that had been used for spiroenone protection gave alcohols **27a** and **27b**. Finally, oxidation with the Dess−Martin periodinane[18] served to regenerate the spiroenones **16a** and **16b**. It was then clear that spiroenone **16a**, derived from the major diastereomer from the coupling reaction, matched the previously synthesized top half. This indicated that the alkyllithium coupling was moderately Felkin−Anh selective, favoring formation of the desired epimer at this center.

As in our inital investigation,[10] the diastereomeric mixture of alcohols **24a,b** could be oxidized with Dess−Martin periodinane to furnish a single enone **25**. Treatment of this alcohol with $CeCl_3$ at room temperature in methanol, cooling to −78 °C and subsequent addition of $NaBH_4$ provided alcohol **24b** as the sole observed diastereomer. This product was identical to the undesired minor diastereomer from the coupling reaction. Identical results were obtained on similar ketones using a variety of reducing reagents, including $Zn(BH_4)_2$ which is reported to reduce α-methyl-*β*-alkoxy ketones to give *syn*-diols.[19,20] The reason for high Felkin selectivity in these ketone reductions is unclear. However, the inability to form a chelated transition state is probably due to the steric bulk of the *gem*-dimethyl group on the ketal. No conditions could be found to reduce this ketone selectively to the desired α-oriented alcohol **24a**.

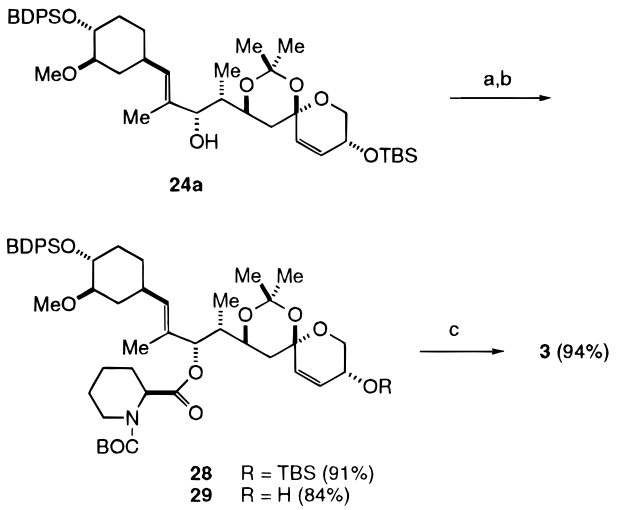
With the stereochemical outcome of the key coupling reaction assigned, the synthesis of the top half could be completed (Scheme 6). Treatment of the desired alcohol,

(18) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(19) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem Pharm. Bull.* **1984**, *32*, 1411−1415.

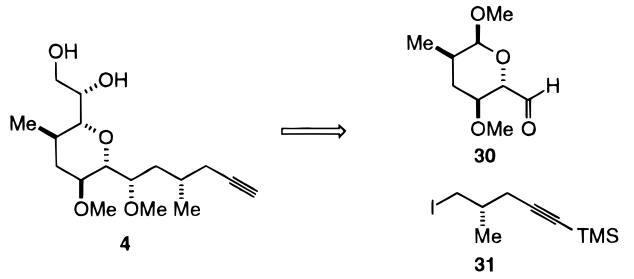
(20) This chemical correlation was not available at the time of our initial work, and thus the structural assignment for our analog synthesis[10] should be inverted at C26.

Scheme 6. Completion of the Top Half



Conditions: a) DCC, DMAP, **20**. b) TBAF. c) Dess-Martin periodinane.

Scheme 7. Retrosynthetic Analysis for the Bottom Half 4

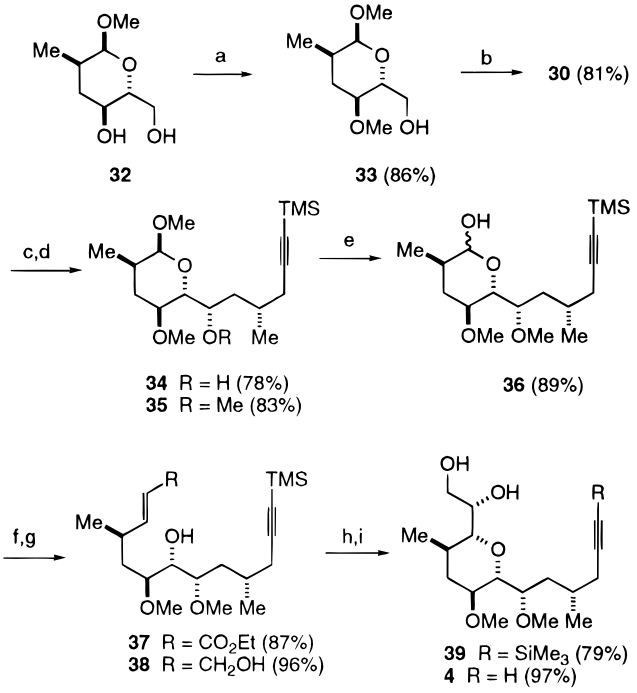


24a, with N-BOC-(L)-pipecolic acid[21] (**20**) in the presence of DCC and DMAP afforded the pipecolate ester **28**. Desilylation with TBAF and subsequent Dess−Martin oxidation of alcohol **29** regenerated the spiroenone functionality to give the complete top half **3**.

The retrosynthetic analysis of the bottom half of the molecule, outlined in Scheme 7, required coupling of the tetrahydropyran aldehyde **30** and the linker subunit **31**. The desired aldehyde **30** was obtained in four steps from the published diol **32**.[22] Treatment of the diol with trityl chloride in pyridine gave exclusively the primary trityl ether. Subjection of the crude product from this reaction to sodium hydride and methyl iodide followed by acid-mediated trityl cleavage gave the selectively methylated alcohol **33** in 86% yield. Oxidation with Dess−Martin periodinane afforded the desired aldehyde **30** for coupling (Scheme 8).

Coupling of the two subunits was achieved by metal/halogen exchange of iodide **31**[10] with *t*-BuLi, transmetalation with $MgBr_2$, and addition of the resulting Grignard reagent to aldehyde **30.** Analysis of the crude reaction product by ^1H and ^{13}C NMR spectroscopy indicated that the addition had occurred with high selectivity (>20:1). The desired alcohol **34** was isolated in 78% yield as a single diastereomer. On the basis of previous model studies,[23] it was presumed that the addition had occurred

Scheme 8. Synthesis of the Bottom Half of FK-506



Conditions: a) TrCl, pyr.; NaH, MeI; HCl, MeOH. b) Dess-Martin Periodinane. c) **31**, t-BuLi, -78°C; $MgBr_2$, 0°C. d) NaH, MeI. e) 80% aq. HOAc, 80°C. f) $Ph_3P{=}CHCO_2Et$, benzene, reflux.g) DIBAL-H. h) $Ti(Oi\text{-}Pr)_4$, (+)-DET, TBHP. i) TBAF.

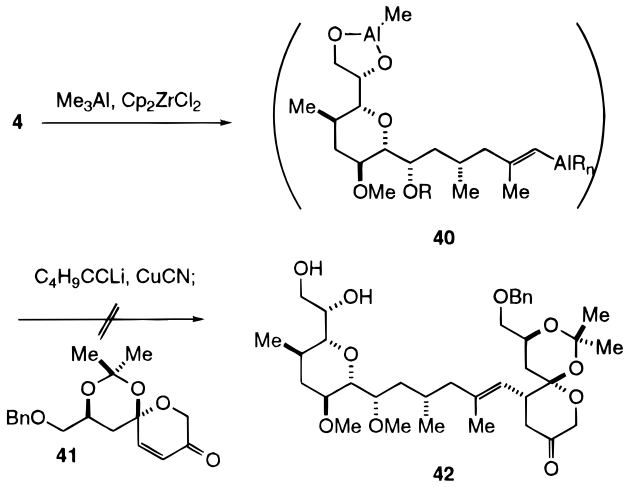
with chelation control,[24] a fact which was confirmed by a subsequent X-ray crystallographic structure (*vide infra*). Methylation of the newly generated alcohol with sodium hydride and methyl iodide gave **35** in good yield.

Addition of the requisite two carbon appendage, corresponding to C8,9, was effected by acetal hydrolysis with aqueous acetic acid followed by Wittig olefination of the hemiacetal **36**. This reaction gave an inseparable mixture of *trans*- and *cis*-olefins in a ratio of approximately 20:1, respectively. The ester was reduced with DIBAL in THF to give the diol **38** in 96% yield. It was then envisioned that the tetrahydropyran ring could be formed by epoxidation of the olefin, followed by intramolecular opening of the epoxide. In spite of the fact that the stereochemistry at both of the newly formed asymmetric centers is of no direct consequence, as both are carbonyl groups in FK-506, it was desired to form the epoxide and corresponding pyran as a single diastereoisomer to simplify subsequent spectral analysis. Sharpless epoxidation of the allylic alcohol was therefore investigated for forming the epoxide.

Use of the catalytic asymmetric epoxidation[25] gave extremely low yields and resulted in mixtures of the epoxide and pyran ring **39** formed by *in situ* closure in addition to large amounts of recovered starting material. The failure of this reaction is attributed to the sequestration of titanium catalyst by the desired product diol **39**. The stoichiometric version of the reaction[26] overcame this problem, resulting in complete consumption of the *trans*-

(21) Johnson, R. L.; Rajakumar, G.; Yu, K.; Mishra, R. K. *J. Med. Chem.* **1986**, *29*, 2104−2106.
(22) Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919−923.
(23) Gleason, J. L. Ph.D. Dissertation, University of Virginia (1994).
(24) For similar Grignard additions see: (a) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045. (b) Rao. A. V. R.; Chakraborty, T. K.; Reddy, K. L. *Tetrahedron Lett.* **1991**, *32*, 1251−1254.
(25) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(26) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.

Scheme 9. Carboalumination of the Bottom Half

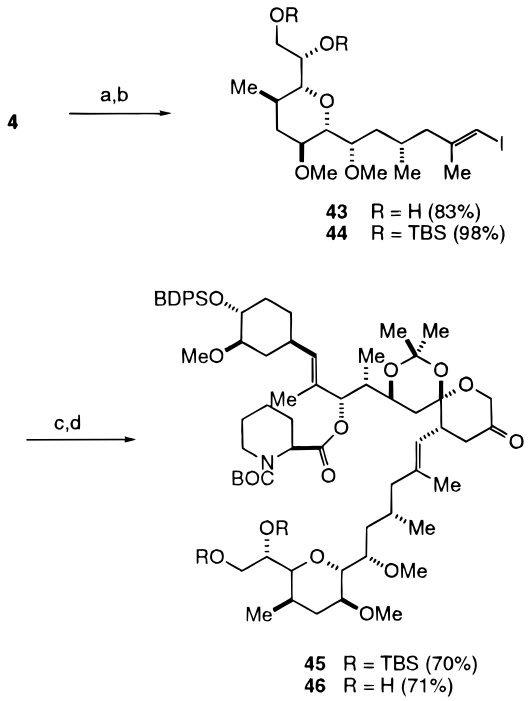


allylic alcohol **38**, leaving the minor *cis*-olefin isomer unreacted. Unlike the catalytic reaction, all of the epoxide was converted *in situ* to the desired tetrahydropyran diol **39**. With careful control of the workup conditions, the diol could be reliably produced in 75−80% yield as a crystalline solid. Recrystallization from hexanes gave needles which were of sufficient quality for X-ray analysis.[27] The crystal structure confirmed that the Grignard coupling had indeed occurred via a chelation-controlled process to produce the desired stereochemistry at C15. In addition, it confirmed that the Sharpless epoxidation and subsequent pyran formation had proceeded as expected. To complete the synthesis of the bottom half target, the trimethylsilyl group was removed from the acetylene in high yield to give **4**.

With the synthesis of the bottom half complete, attention was focused on the crucial coupling procedure. The bottom half was envisioned to be coupled to the top half by a carboalumination/transmetalation procedure[28] developed in this laboratory and previously used in the spiroketal analog synthesis.[10] Carboalumination of the terminal acetylene in **4** occurred smoothly. The reaction, however, required excess reagents and was much slower than for simple monofunctional acetylenes. Unfortunately, utilization of the aluminum−copper transmetalation conditions[28] with the intermediate vinylalane **40** failed to give any vinyl cuprate as judged by quenching with cyclohexenone and simple spiroenones such as **41** (Scheme 9).

The intermediate vinyl alane **40** could be quenched cleanly with I_2 to provide the vinyl iodide **43** in 83% yield (Scheme 10). The product was obtained as a single geometrical isomer which was confirmed by ^{1}H NMR and NOE analysis to possess the expected and desired geometry. Although the cuprate could not be formed directly from the alane, it seemed reasonable that it could be formed from the vinyl iodide **43** via a metal−halogen exchange process. In order to carry out this process it was necessary to protect the 1,2-diol. It was also realized that these alcohols would have to be differentiated at some point to allow formation of the acid for lactamization. This was originally envisioned to occur as a selective protection sequence. Unfortunately, high yields and good selectivities were elusive for the limited number of protecting groups which could be used in our synthetic plan. Fortunately, it was realized that the differentiation could occur as a selective oxidation of the primary alcohol, and thus the diol could be masked as the bis-TBS ether **44**.

Scheme 10. Conjugate Addition of Bottom Half to Top Half



Conditions: a) Me_3Al, Cp_2ZrCl_2; I_2. b) TBSCl, DMAP, imid. c) t-BuLi, -78°C; C_4H_9CCCu•2HMPT, -23°C; **3**, TMSCl; aq. HCl. d) TBAF.

The conjugate addition of the bottom half vinyl iodide **44** with the top half spiroenone **3** was now investigated. The use of both lower order and homo- and mixed-higher order cyanocuprates[29] gave very irreproducible results with the best results requiring 2.2 equiv of vinyllithium per equivalent of enone **3** and giving **45** in yields no better than 30−40%. A much more reliable protocol was the use of hexynylcopper as its bis-HMPT complex.[30] This reaction required only 1.1 equiv of vinyllithium and gave a very reproducible 70% yield of the ketone **45**. High facial selectivity was observed in this reaction; no diasteromeric conjugate addition product was observed or isolated.[11] The TBS ethers were removed to afford diol **46** in 71% yield. The success of this coupling procedure provides an ideal alternative to the problem of trisubstituted olefin synthesis encountered in previous syntheses.[4−8]

With the carbon skeleton complete, the next problem was to determine a viable sequence for macrolactamization and installation of both the α-allyl aldol and the α,β-diketoamide hemiketal. In order to transform the diol **46** into the desired intermediate **2**, our plan required that the spiroketal ketone be reduced to the corresponding alcohol, which would subsequently be converted into the

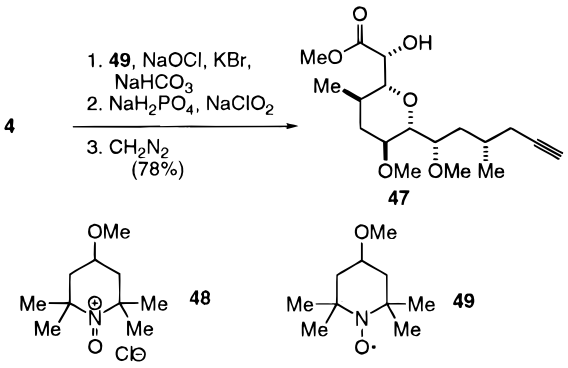
(27) Coordinates and unit cell parameters for diol **39** have been deposited in the Cambridge Crystallographic Data Base. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(28) (a) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425−1426. (b) Wipf, P.; Smitrovich, J.; Moon, C. *J. Org. Chem.* **1992** *57*, 3178−3186.

(29) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005−5038.

(30) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211.

Scheme 11. Selective Oxidation of a 1,2-Diol



necessary iodide. The silyl enol ether in **2** was expected to be generated by enolization of its corresponding ketone. Thus we were faced with a sequence in which both key functionalities required passing through ketone intermediates. Although this could likely be accomplished through a series of protecting group manipulations, a very straightforward solution was devised. The degradation studies carried out by Danishefsky[31] showed that the C22 ketone in FK-506 (**1**) could be selectively reduced in the presence of the tricarbonyl hemiketal with L-selectride. The conditions for this reduction are identical to those that would be used to reduce the spiroketal ketone, and therefore we envisioned a selective reduction of diketone **52** (*vide infra*). After conversion to the iodide, the silyl enol ether could then be formed from the remaining ketone, and this sensitive functionality would only have to survive the iodide fragmentation to the aldol.

Prior to formation of the lactam, our strategy required selective oxidation of the 1,2-diol **46**. The diol **4** was used as a model for this crucial differentiation (Scheme 11). Recent precedent[32] in the literature had indicated that the use of hindered chloro oxammonium salts should be ideal for this process. Use of the stoichiometric oxammonium salt **48** was successful but gave somewhat erratic results. Generation of the unstable salt *in situ* from 4-methoxy-TEMPO (**49**) using a catalytic process[33] proved more reliable giving 60−78% yield of the hydroxy ester **47** after oxidation of the aldehyde with $NaClO_2$ and esterification with diazomethane. With this methodology in hand, the lactamization could now be attempted.

The first approach to the key diketone **52** is outlined in Scheme 12. Selective oxidation of the diol using the conditions outlined above gave the hydroxy ester **50** in good yield. Hydrolysis of the ester was effected with LiOH and cleavage of the BOC protecting group was effected by treatment with TESOTf followed by TBAF/HOAc-mediated cleavage of the resulting silylated product. The resultant amino acid was then subjected to macrolactamization conditions (2-chloro-*N*-methylpyridinium iodide, high dilution). The desired hydroxy lactam **51** was not immediately isolated, however. Inspection of the ^1H NMR of the crude reaction mixture hinted that the lactam had formed. It also indicated that some pyridinium salt still remained. As the lactamization reagent and any intermediate acyl pyridinium salts were expected to hydrolyze rapidly upon exposure to water during workup, it was suspected that the α-hydroxyl group had reacted with the 2-chloro-*N*-methylpyridinium iodide to form a stable alkoxy pyridinium salt. Cleavage of this salt with ethylamine in ethanol[34] liberated the desired hydroxy lactam. Unfortunately, the overall yield for this process was very low. A number of cleavage conditions were analyzed and it was observed that the use of triethylamine gave a slower yet cleaner and higher yielding reaction. Regardless of this fact, the yield of **51** was still no better than 40% from the hydroxy ester **50**. Oxidation of the hydroxy lactam **51** with Dess−Martin periodinane gave the desired diketone **52** in 81% yield. Thus the overall yield of the target diketone from the hydroxy ester **50** was 32%.

Although this procedure was a viable process, the final optimized yields were still disappointing and some effort was put into improving the process. Oxidation of the hydroxy ester **50** gave a compound which, although impossible to purify, was clearly the corresponding α-keto ester by ^1H and ^{13}C NMR analysis. Submission of this compound to the lactamization sequence gave the keto lactam **52** directly. In this case no pyridinium salt was formed and the rate of lactamization was greatly accelerated. This improved protocol led to an overall yield of 53% of keto lactam **52** from the hydroxy ester **50**.

Selective reduction of the ketones in **52** was attempted under the conditions described by Danishefsky.[31] Treatment with 1.15 equiv of L-selectride gave the axially oriented alcohol **53** as the sole product in 84% yield (Scheme 13). That the reduction had occurred as desired was confirmed by examination of the ^{13}C NMR spectra. The product lacked a signal for a ketone at 209 ppm which was present in the hydroxy lactam **51**, while maintaining the ketone signal at 199 ppm which was not present in hydroxy lactam **51** but was present in the diketone **52**. The axial alcohol was converted to the equatorial iodide **54** in 83% yield with iodine and triphenylphosphine. This reaction suffered from some elimination, likely from the intermediate phosphonium salt, to form a mixture of olefins as a minor byproduct.

Formation of the silyl enol ether **2** was then effected by treatment with KHMDS and TESCl. Although **2** appeared to be formed as a single geometric isomer, definitive assignment of stereochemistry (cis or trans) could not be made. No elimination of the equatorially oriented iodide was observed, and the enol ether was obtained in 74% yield with recovery of 26% of the starting material. The choice of KHMDS as base was based on recent studies[35] which showed that this base does not enolize esters at low temperature without the use of polar solvents such as HMPA or DMPU. Thus the conditions used were not expected to result in enolization and thus epimerization of the pipecolate ester. This completed the synthesis of the key intermediate **2**, with only fragmentation to the aldol, oxidation to the tricarbonyl hemiketal and final deprotection remaining.

The fragmentation of iodide **2** was achieved using a Zn-Ag couple, which was prepared *in situ* by a reduction of $ZnCl_2$ and AgOAc with C_8K,[36] affording the aldol product **55** in 67% yield. The lower yield for this reaction, as compared to the spiroketal analog synthesis[10] was due to the competing dehydration of the aldol system. This

(31) Coleman, R. S.; Danishefsky, S. J. *Heterocycles* **1989**, *28*, 157−161.
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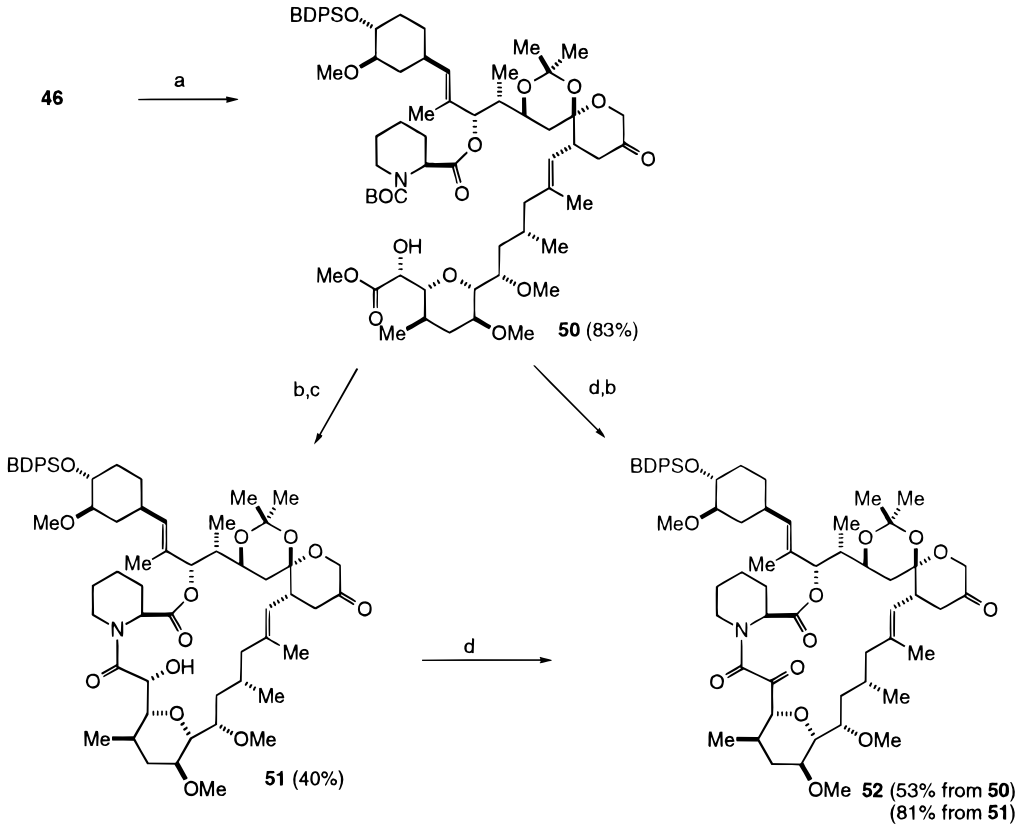
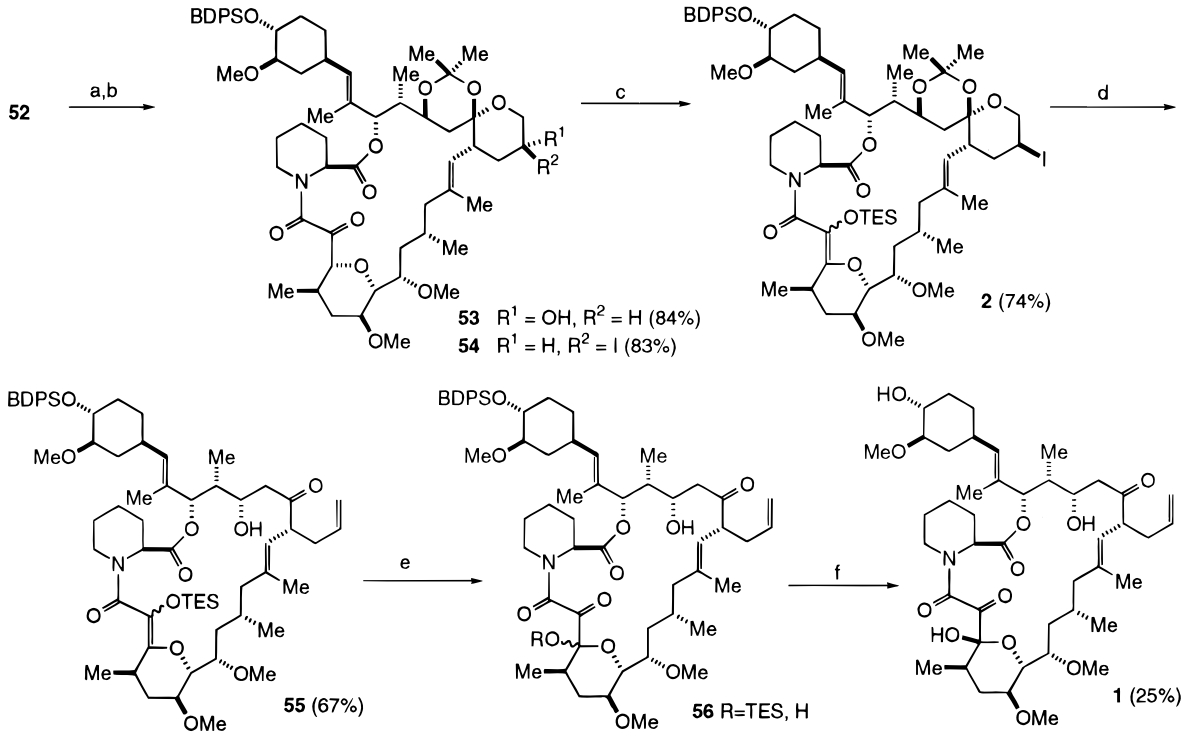
Scheme 12. Formation of the Diketo Lactam



Conditions: a) **49**, NaOCl, KBr, $NaHCO_3$; NaH_2PO_4, $NaClO_2$; CH_2N_2. b) LiOH; TESOTf, 2,6-lutidine; TBAF, HOAc; 2-chloro-1-methylpyridinium iodide, NEt_3. c) EtOH, NEt_3. d) Dess-Martin Periodinane.

Scheme 13. Final Steps



Conditions: a) $Li(s\text{-}Bu)_3BH$; $NaBO_3$. b) Ph_3P, I_2, imid., PhMe, 70°C. c) KHMDS, -78°C; TESCl. d) C_8K, $ZnCl_2$, AgOAc. e) dimethyldioxirane. f) HF, MeCN.

side reaction was not observed in the spiroketal analog but was observed, however, in simpler models and may be a consequence of the relative conformational freedom of the systems.

The final functionalization reaction was the oxidation to the tricarbonyl system. Oxidation of the silyl/pyran enediol system in **55** was quite slow and required elevated reaction temperatures and the use of excess dimethyldioxirane to push the reaction to near completion. The slow oxidation of this enediol contrasts the oxidation of a cyclic acetonide enediol which was shown in model studies[23] to oxidize rapidly and cleanly at −20 °C and was used effectively in a separate synthesis of FK-506.[37,38] Fortunately, the oxidation products could be separated from the starting material allowing for recycling of this valuable material. The oxidation products **56** were isolated as a mixture which presumably consisted of silylated and unsilylated tricarbonyl hemiketal. This mixture of oxidation products was then submitted to standard desilylation conditions (HF in acetonitrile) to provide the target FK-506 (**1**) in 25% yield which showed identical spectral properties to a sample of natural FK-506. Use of milder desilylating conditions such as HF·pyridine complex resulted in a somewhat cleaner reaction. However, the reaction was complicated by formation of a byproduct of undetermined structure which contained all of the major functionality of FK-506, and thus the reaction provided no improvement over the use of straight HF.

Experimental Section

General. All NMR spectra were measured in $CDCl_3$ at 300 MHz for ^1H and at 75 MHz for ^{13}C unless otherwise noted. Chemical shifts are reported in parts per million (δ). Asterisks (*) in advanced intermediates indicate resonances for minor rotamers. Multiplicities are given as s (singlet), d (duplet), t (triplet), q (quartet), m (multiplet), and b (broad). Coupling constants are in hertz. Optical rotations were measured in chloroform in a 1.0-dm cell of 6-mL capacity. All silica gel used for column chromatography was E. Merck silica gel 60 (70−230 mesh ASTM). Elemental combustion analysis was performed by Spang Microanalytical Laboratory, Star Rt. 142, Eagle Harbor, MI 49951 and by Quantitative Technologies Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888. High resolution mass spectral analysis was provided courtesy of SmithKline Beecham Corp. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Dry solvents were distilled shortly before use from an appropriate drying agent under nitrogen. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane, *n*-hexane, toluene, benzene, diisopropylamine, triethylamine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride prior to use. All glassware, syringes, and needles were dried at 130 °C for at least 12 h prior to use and cooled under argon. Reactions were carried out under a nitrogen or argon atmosphere.

Hydroxy Ketone 6. To a solution of Et_3N (444 g, 4.4 mol) in 1 L of freshly distilled toluene was added magnesium (53.5 g, 2.2 mol) followed by ethyl bromide (229 g, 2.1 mol) slowly via dropping funnel. Once the reaction had commenced the ethyl bromide was added at such a rate as to maintain a slow reflux. After the addition was complete, the reaction was allowed to cool and stir several hours at 25 °C. (This Grignard reagent is very stable and can be kept for years under argon at 25 °C without any apparent loss of reactivity). To a solution of silyllactone **5** (50 g, 0.13 mol) in 200 mL of toluene at 0 °C was added 200 mL of the Grignard reagent while maintaining the temperature below 5 °C. As soon as all of the Grignard reagent had been added the reaction was quenched with 25 mL water and the volume doubled with Et_2O. The thick suspension was stirred with anhydrous K_2CO_3 and then filtered through Celite. The solvents were removed *in vacuo*, and the yellow oil was chromatographed on silica gel (0 → 10% EtOAc/hexanes). The product was obtained as a clear oil, 45.8 g, (86%): $[\alpha]^{23}_D$ −10.2 (*c* 0.98, $CHCl_3$); IR 3480, 2920, 2825, 1695, 1420, 1200, 810, 695 cm^{-1}; ^1H NMR δ 7.70−7.67 (m, 4H), 7.45−7.39 (m, 6H), 3.62−3.46 (m, 2H), 2.69 (bs, 1H), 7.25 (q, 2H, J = 14.5, J = 7.28), 2.12−2.09 (m, 1H), 1.75−1.68 (m, 2H), 1.39−1.13 (m, 4H), 1.07 (s, 9H), 1.00 (t, 3H, J = 7.26); ^{13}C NMR δ 212.0, 136.2, 136.1, 134.6, 134.3, 130.4, 130.2, 128.3, 128.1, 77.1, 74.9, 48.5, 34.3, 33.6, 32.0, 27.5, 26.5, 19.8, 8.2. Anal. Calcd for $C_{25}H_{34}SiO_3$: C, 73.13; H, 8.35. Found: C, 73.04; H, 8.52.

Methoxy Ketone 7. To a solution of hydroxy ketone **6** (45 g, 0.11 mol) and 2,6-di-*tert*-butyl-4-methylpyridine (45 g, 0.22 mol) in 150 mL of dry CH_2Cl_2 was added methyl triflate (24.2 mL, 0.21 mol) at 25 °C. After stirring for 48 h, the volume was doubled with Et_2O. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. Silica gel chromatography (hexanes → 10% EtOAc/hexanes) gave an oil which was dissolved in hexanes and crystallized at −20 °C to give 42.5 g (91%) of the ketone: mp 82.5−83 °C; $[\alpha]^{23}_D$ −20.6 (*c* 3.70, $CHCl_3$); IR 3020, 2905, 2820, 1698, 1445, 1200, 810, 695 cm^{-1}; ^1H NMR δ 7.75−7.70 (m, 4H), 7.43−7.34 (m, 6H), 3.61−3.55 (m, 1H), 3.30 (s, 3H), 3.13−3.09 (m, 1H), 2.40 (dq, 2H, J = 14.45, J = 7.07, J = 1.36), 2.34−2.29 (m, 1H), 2.22−2.14 (m, 1H), 1.79−1.62 (m, 2H), 1.43−1.11 (m, 3H), 1.07 (s, 9H), 1.01 (t, 3H, J = 7.27); ^{13}C NMR δ 213.1, 136.4, 136.3, 135.3, 134.6, 129.9, 128.1, 128.0, 127.9, 127.8, 84.1, 75.2, 57.6, 48.6, 34.1, 33.1, 31.8, 27.5, 26.4, 19.8, 8.2. Anal. Calcd for $C_{26}H_{36}SiO_3$: C, 73.54; H, 8.54. Found: C, 73.66; H, 8.47.

Hydroxymethylidene Ketone 8. To a suspension of KHMDS (45.5 g, 0.23 mol) in 400 mL of THF and 54 mL of HMPA (0.31 mol) at −10 °C was added ethyl ketone **7** (44 g, 0.10 mol) in 50 mL of THF. The clear yellow solution was allowed to warm to 0 °C over 1 h and was then cooled to −78 °C. Ethyl formate (16.8 mL, 0.21 mol) was added rapidly, and the cooling bath was removed. The reaction warmed slowly to 25 °C and was allowed to stir for 12 h. The reaction was then quenched with 10 mL of water and the THF was removed *in vacuo*. The oily residue was partitioned between Et_2O and water and acidified with dilute HCl. The aqueous layer was separated and extracted with two portions of Et_2O. The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The yellow oil was chromatographed on silica gel (10% EtOAc/hexanes) to yield 36.6 g (78%) of a clear oil which was crystallized from hexanes to produce an amorphous white solid: mp 106−107 °C; $[\alpha]^{23}_D$ −9.0 (*c* 1.11, $CHCl_3$); IR 3390, 2905, 1690, 1620, 1450, 1418, 1200, 812, 695 cm^{-1}; ^1H NMR δ 7.80−7.64 (m, 5H), 7.45−7.36 (m, 6H), 3.69−3.63 (m, 1H), 3.34 (s, 3H), 3.23−3.19 (m, 1H), 2.48−2.42 (m, 1H), 2.27 (bs, 1H), 2.09−2.03 (m, 1H), 1.82−1.75 (m, 1H), 1.81 (s, 3H), 1.62−1.52 (m, 1H), 1.45−1.24 (m, 3H), 1.08 (s, 9H); ^{13}C NMR δ 175.7, 136.4, 136.3, 135.4, 135.2, 134.6, 130.1, 129.9, 128.2, 127.9, 127.8, 106.8, 84.4, 75.6, 57.6, 43.0, 33.9, 31.7, 27.5, 26.8, 19.8, 13.1. Anal. Calcd for $C_{27}H_{36}SiO_4$: C, 71.64; H, 8.02. Found: C, 71.80; H, 7.96.

(Methylthiomethoxy)methylidene Ketone 9. To a solution of the hydroxymethylene ketone **7** (25.7 g, 0.057 mol) in THF (200 mL) was added anhydrous K_2CO_3 (21 g, 0.15 mol). The solid was suspended with vigorous stirring, and chloromethyl methyl sulfide (6.0 g, 0.062 mol) was added. The reaction was allowed to stir 12 h at which time it was poured into water and the aqueous phase extracted three times with Et_2O. The combined organic phases were washed with water and brine and then dried over anhydrous K_2CO_3. After removal of the solvent *in vacuo*, the yellow oil was chromatographed on silica gel (10% EtOAc/hexanes) to provide 27.9 g (98%) of a pale yellow oil: $[\alpha]^{23}_D$ −8.4 (*c* 3.1, $CHCl_3$); IR 2910, 1695, 1420, 1130, 1080, 805, 695 cm^{-1}; ^1H NMR δ 7.75−7.67 (m, 4H), 7.43−7.36 (m, 6H), 5.03 (s, 1H, major isomer), 5.02

(37) Ireland, R. E.; Liu, L.-B.; Roper, T. D.; Gleason, J. L. Manuscript in preparation.

(38) The difference in reactivity in these two systems is unclear. The enediol systems studied in model systems were all constrained to the *cis* isomers. Although no proof of the geometry of the enediol in **55** was available, it is possible that the enediol in this system is *trans*. This arrangement would lead to a reduced dipole moment and thus an inherently more stable system.

(s, 1H, minor isomer), 3.62−3.58 (m, 1H), 3.31 (s, 3H), 3.21−3.15 (m, 1H), 2.82−2.75 (m, 1H), 2.20 (s, 3H), 2.13−2.07 (m, 3H), 1.76 (s, 3H, minor isomer), 1.72 (s, 3H, major isomer), 1.63−1.21 (m, 5H), 1.10 (s, 9H, minor isomer), 1.07 (s, 3H, major isomer); ^{13}C NMR δ 201.6, 155.6, 136.5, 136.2, 135.2, 134.6, 129.8, 127.8, 118.3, 84.5, 79.2, 75.5, 67.6, 57.4, 43.2, 33.4, 33.1, 27.3, 19.7, 14.5, 9.2. Anal. Calcd for $C_{29}H_{40}SiSO_4$: C, 67.93; H, 7.86. Found: C, 67.92; H, 7.81.

Aldehyde 10. To a solution of MTM ketone **9** (23 g, 0.046 mol) in 300 mL MeOH was added $CeCl_3{\cdot}7H_2O$ (18.85 g, 0.051 mol). After stirring 1 h at 25 °C the homogeneous mixture was cooled to 0 °C, and $NaBH_4$ (1.91g, 0.056 mol) was added in small portions over 10 min. The reaction was allowed to stir for 1 h, and then the MeOH was removed *in vacuo*. The resulting oil was dissolved in 200 mL of THF and 15 mL of water, and 3 g of *p*-TsOH was added. The reaction was allowed to stir 12 h, and then the THF was removed under reduced pressure. The residue was partitioned between Et_2O and water, and the layers were separated. The organic phase was washed with water and brine and evaporated under reduced pressure. Silica gel chromatography (10% EtOAc/hexanes) gave 18 g of a mixture of aldehydes. The two isomers (*trans:cis* ratio = 2.75:1) are readily separable by subsequent chromatography (1 → 4% EtOAc/hexanes) to afford 13.2 g (67%) of the *trans*-carboxaldehyde: mp 82−83 °C; $[\alpha]^{23}_D$ −15.0 (*c* 1.2, $CHCl_3$); IR 3060, 2905, 2818, 2690, 1675, 1625, 1100, 695 cm^{-1}; ^{1}H NMR δ 9.32 (s, 1H), 7.75−7.66 (m, 4H), 7.44−7.35 (m, 6H), 6.21 (d, 1H, J = 9.3), 3.67−3.61 (m, 1H), 3.32 (s, 3H), 3.20−3.16 (m, 1H), 2.62−2.51 (m, 1H), 2.07- 2.01 (m, 1H), 1.80−1.72 (m, 1H), 1,74 (s, 3H), 1.64−1.24 (m, 4H), 1.07 (s, 9H); ^{13}C NMR δ 195.8, 157.7, 136.4, 136.3, 136.2, 135.2, 134.6, 130.1, 129.9, 129.8, 128.1, 127.9, 127.8, 83.8, 75.2, 57.8, 36.2, 34.8, 33.1, 29.5, 27.4, 19.8, 9.7. Anal. Calcd for $C_{27}H_{36}SiO_3$: C, 74.27; H, 8.31. Found: C, 74.39; H, 8.28.

Olefin 11. To a solution of 486 mg (4.33 mmol) of *t*-BuOK in 50 mL of Et_2O at −78 °C was added BuLi (1.67 mL of a 2.59 M solution in hexanes, 4.33 mmol). The mixture was warmed to 0 °C, allowed to stir at 0 °C for 30 min, and then recooled to −78 °C. *cis*-2-Butene (231 mg, 4.12 mmol) was added, and the mixture was again warmed to 0 °C, stirred for 50 min, and then recooled to −78 °C. A solution of 1.30 g (4.12 mmol) of (−)-*B*-Methoxydiisopinocampheylborane in 5 mL of ether was added. The solution was stirred for 30 min at −78 °C, and then 0.507 mL (4.12 mmol) of $BF_3{\cdot}OEt_2$ was added, followed by a solution of 900 mg (2.06 mmol) of the aldehyde **10** in 5 mL of Et_2O. The reaction mixture was stirred at −78 °C for 1.5 h, and then 5 mL of 15% NaOH and 0.420 mL of 30% H_2O_2 were added. The biphasic mixture was warmed to 25 °C and stirred vigorously for 40 min. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with H_2O and brine, dried over K_2CO_3, and concentrated. The residue containing the alcohol and isopinocampheol was dissolved in 25 mL of dry CH_2Cl_2 and cooled to 0 °C. 2,6-Lutidine (0.426 mL, 3.65 mmol) and TBSOTf (0.840 mL, 3.65 mmol) were added sequentially. The reaction was allowed to proceed at 0 °C for 12 h at which time 1 mL of H_2O was added and the solvent was removed in vacuo. The residue was partitioned between Et_2O/H_2O. The layers were separated, and the organic phase was washed with H_2O and saturated NaCl, dried over K_2CO_3, and concentrated. Silica gel chromatography (2% EtOAc/hexanes) gave 640 mg (51%) as a 6.2:1 mixture of diastereomers which were separated by preparative TLC multiple development in 1% EtOAc/hexane: $[\alpha]^{23}_D$ −16.7 (*c* 1.70, $CHCl_3$); IR 3040, 2900, 2820, 1450, 1240, 1100, 1040, 830, 690 cm^{-1}; ^{1}H NMR δ 7.78−7.69 (m, 4H), 7.40−7.30 (m, 6H), 5.60−5.47 (m, 1H), 4.96−4.78 (m, 3H), 3.60−3.51 (m, 1H), 3.55 (d, 1H, J = 7.8), 3.34 (s, 3H), 3.15−3.05 (m, 1H), 2.29−2.12 (m, 2H), 1.96−1.87(m, 1H), 1.67−1.59 (m, 1H), 1.51 (s, 3H), 1.45−1.22 (m, 4H), 1.05 (s, 9H), 0.95 (d, 3H, J = 6.6), 0.86 (s, 9H), −0.02 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 142.0, 136.4, 135.7, 134.9, 131.5, 129.7, 127.8, 127.7, 113.5, 84.7, 83.0, 76.3, 57.9, 42.8, 36.4, 35.2, 34.1, 31.0, 27.5, 26.3, 19.8, 19.6, 16.5, 12.2, −4.0, −4.6. Anal. Calcd for $C_{37}H_{58}O_3Si_2$: C, 73.21; H, 9.63. Found: C, 72.97; H, 9.58.

Diol 12. To a solution of 14.02 g (23.1 mmol) of the olefin **11** in 500 mL of THF at 0 °C was added NMO (4.00 mL of a 60% aqueous solution, 23.1 mmol) and OsO_4 (1.15 mL of a 0.2 M solution in benzene, 0.23 mmol). The mixture was allowed to stir at 0 °C → 15 °C for 10 h and then at 25 °C for 5 h. An additional aliquot of OsO_4 (0.5 mL) and NMO (2 mL) were added, and stirring was continued at 25 °C for 12 h. Sodium sulfite (50 mg) in 10 mL of H_2O was added, and the mixture was stirred vigorously for 5 min and then filtered and concentrated. The residue was partitioned between Et_2O/H_2O. The layers were separated, and the aqueous layer was extracted once with Et_2O. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over K_2CO_3, and concentrated. Chromatography (30% EtOAc/hexanes) afforded 12.44 g (84%) of the diol (major diastereomer): $[\alpha]^{23}_D$ −19.1 (*c* 1.10, $CHCl_3$); IR 3350 (b), 2910, 2840, 1450, 1420, 1380, 1240, 1100, 830, 700 cm^{-1}; ^{1}H NMR δ 7.79−7.70 (m, 4H), 7.42−7.33 (m, 6H), 5.09 (d, 1H, J = 8.7), 4.10 (d, 1H, J = 3.9), 3.69−3.53 (m, 5H), 3.49−3.42 (m, 1H), 3.34 (s, 3H), 3.17−3.08 (m, 1H), 2.28−2.15 (m, 1H), 1.99−1.89 (m, 1H), 1.85−1.77 (m, 1H), 1.70−1.63 (m, 1H), 1.63 (s, 3H), 1.43−1.24 (m, 4H), 1.06 (s, 9H), 0.87 (s, 9H), 0.68 (d, 3H, J = 6.9), 0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 136.4, 135.6, 134.8, 134.2, 132.2, 129.8, 129.7, 127.8, 127.7, 84.7, 80.0, 76.1, 74.1, 65.4, 57.9, 40.1, 36.4, 35.3, 34.0, 31.1, 27.5, 26.3, 19.8, 18.5, 14.1, 11.7, −4.1, −4.8. Anal. Calcd for $C_{37}H_{60}O_5Si_2{\cdot}{}^1/_2H_2O$: C, 68.36; H, 9.46. Found: C, 68.49; H, 9.44.

Benzoate 13. To a solution of the diol **12** (12.0 g, 18.7 mmol) in 35 mL pyridine was added a catalytic amount of DMAP followed by slow, dropwise addition of benzoyl chloride (2.17 mL, 18.7 mmol). The reaction was allowed to stir 30 min and then was partitioned between Et_2O/H_2O. The aqueous layer was extracted with a second portion of Et_2O. The combined organic extracts were washed with H_2O and saturated aqueous $NaHCO_3$, $CuSO_4$, and NaCl. The Et_2O phase was dried over K_2CO_3 and concentrated under reduced pressure. Silica gel chromatography (hexanes → 5% EtOAc/hex → 10% EtOAc/hex) yielded 13.0 g (93%) of the benzoate: $[\alpha]^{23}_D$ −13.6 (*c* 0.90, $CHCl_3$); IR 3440, 2900, 2840, 1700, 1260, 1100, 700 cm^{-1}; ^{1}H NMR δ 8.07−7.99 (m, 2H), 7.77−7.66 (m, 4H), 7.47−7.35 (m, 9H), 5.13 (d, 1H, J = 9.0), 4.47−4.43 (m, 1H), 4.29−4.23 (m, 1H), 4.16 (d, 1H, J = 4.2), 3.86−3.78 (m, 1H), 3.62−3.52 (m, 1H), 3.34 (s, 3H), 3.18 (d, 1H, J = 3.6), 3.15−3.08 (m, 1H), 2.28−2.18 (m, 1H), 1.97−1.80 (m, 2H), 1.69−1.57 (m, 1H), 1.61 (s, 3H), 1.45−1.32 (m, 2H), 1.06 (s, 9H), 1.01−0.85 (m, 2H), 0.88 (s, 9H), 0.81 (d, 3H, J = 6.9), 0.04 (s, 3H), −0.06 (s, 3H); ^{13}C NMR δ 167.2, 136.4, 135.6, 134.8, 134.3, 133.5, 132.0, 130.5, 130.1, 129.8, 129.7, 128.8, 127.8, 127.7, 84.7, 78.8, 76.1, 72.3, 68.2, 57.9, 40.5, 36.4, 35.3, 34.0, 31.0, 27.5, 26.3, 19.8, 18.6, 13.9, 11.3, −4.0, −4.8. Anal. Calcd for $C_{44}H_{64}O_6Si_2$: C, 70.92; H, 8.66. Found: C, 70.90; H, 8.72.

Epoxide 14. To a solution of the benzoate **13** (13.0 g, 17.4 mmol) in 35 mL of pyridine at 0 °C was added MsCl (4.0 g, 34.9 mmol) and a catalytic amount of DMAP. The reaction was allowed to stir for 3 h at 0 °C then was poured into 250 mL H_2O. The layers were separated, and the aqueous layer was extracted with three portions of Et_2O. The combined organic layers were washed with 20% HCl, saturated $NaHCO_3$, saturated NaCl, dried over K_2CO_3 and concentrated. The resulting oil was dissolved in 70 mL of dry MeOH and cooled to 0 °C. Sodium methoxide (40 mL of a 25% solution in MeOH, 174 mmol) was added, and the reaction was allowed to stir for 1 h before the solvent was removed in vacuo. The residue was partitioned between Et_2O/H_2O. The layers were separated and the Et_2O layer was washed twice with H_2O. The aqueous washings were back-extracted with Et_2O. The combined organic extracts were dried over K_2CO_3 and concentrated. Chromatography (5% EtOAc/hexanes) afforded 9.37 g (86%) of the epoxide: $[\alpha]^{23}_D$ −17.4 (*c* 0.75, $CHCl_3$); IR 3040, 2920, 2840, 1450, 1250, 1100, 825, 700 cm^{-1}; ^{1}H NMR δ 7.78−7.68 (m, 4H), 7.41−7.30 (m, 6H), 5.05 (d, 1H, J = 8.1), 3.77 (d, 1H, J = 7.5), 3.60−3.51 (m, 1H), 3.35 (s, 3H), 3.17−3.07 (m, 1H), 2.62−2.58 (m, 2H), 2.45−2.41 (m, 1H), 2.25−2.15 (m, 1H), 1.97−1.89 (m, 1H), 1.70−1.60 (m, 1H), 1.53 (s, 3H), 1.40−1.25 (m, 5H), 1.06 (s, 9H), 0.97 (d, 3H, J = 6.6), 0.86 (s, 9H), 0.00 (s, 3H), −0.07 (s, 3H); ^{13}C NMR δ 136.4, 135.6, 135.2, 134.8,

131.6, 129.8, 127.8, 84.6, 80.6, 76.2, 57.9, 55.5, 47.8, 41.2, 36.3, 35.2, 34.0, 30.9, 27.5, 26.3, 19.8, 18.6, 13.4, 12.5, −4.0, −4.7. Anal. Calcd for $C_{37}H_{58}O_4Si_2$: C, 71.33; H, 9.38. Found: C, 71.20; H, 9.40.

Furandiol 15. To a solution of furfuryl methoxyisopropyl ether (0.055 g, 0.32 mmol) in 20 mL of THF at −78 °C was added *n*-BuLi (131 μL of a 2.59 M solution in hexanes, 0.34 mmol). The mixture was allowed to stir for 15 min at −78 °C and then for 15 min at −20 °C and was then recooled to −78 °C. A solution of the epoxide **14** (0.100 g, 0.16 mmol) in 10 mL of THF was added via cannula, immediately followed by 40 μL (0.32 mmol) of $BF_3{\cdot}OEt_2$. The mixture was allowed to stir for 30 min and then was placed in a −20 °C freezer for 12 h. The reaction was quenched by the addition of $NaHCO_3$. The layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over K_2CO_3 and concentrated. The residue was dissolved in THF/H_2O (3:1), and approximately 10 mg of CSA was added. After stirring for 5 min, $NaHCO_3$ was added and the THF was evaporated. The residue was extracted with CH_2Cl_2, and the organic extracts were dried over Na_2SO_4 and concentrated. Chromatography (25% EtOAc/hex) gave a mixture of the furandiol and furfurol, which was then azeotropically removed with toluene to give 0.100 g (87%) of the furandiol: $[\alpha]^{23}_D$ −20.7 (*c* 1.45, $CHCl_3$); IR 3340, 2900, 1415, 1240, 1100, 690 cm^{-1}; ^1H NMR δ 7.78−7.69 (m, 4H), 7.45−7.32 (m, 6H), 6.18 (d, 1H, *J* = 3.0), 5.98 (d, 1H, *J* = 3.0), 5.10 (d, 1H, *J* = 9.3), 4.52 (d, 2H, *J* = 6.0), 3.93−3.90 (m, 2H), 3.63−3.52 (m, 1H), 3.34 (s, 3H), 3.17−3.07 (m, 1H), 2.85−2.63 (m, 2H), 2.30−2.15 (m, 1H), 2.08−2.04 (bs, 1H), 1.99−1.90 (m, 1H), 1.70-1.22 (m, 7H), 1.48 (s, 3H), 1.06 (s, 9H), 0.89−0.86 (s, 9H; d, 3H), 0.03 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 153.8, 153.3, 136.4, 135.6, 135.2, 134.8, 131.6, 129.8, 129.7, 127.8, 109.1, 107.8, 84.7, 81.5, 76.1, 72.0, 57.9, 40.7, 36.4, 35.2, 34.8, 34.0, 31.0, 27.5, 26.3, 19.8, 18.6, 12.9, 7.8, −3.8, −4.6. Anal. Calcd for $C_{42}H_{64}O_6Si_2$: C, 69.95; H, 8.95. Found: C, 70.02; H, 8.89.

Spiroenone 16. To a solution of the furandiol **15** (3.0 g, 4.1 mmol) in 60 mL CH_2Cl_2 at 0 °C was added *m*-CPBA (0.790 g, 4.6 mmol). The reaction was allowed to stir at 0 °C for 1.5 h at which time 2-methoxypropene (2.0 mL, 21 mmol) and a catalytic amount of pTsOH·H_2O were added. After stirring for 1 h, H_2O was added. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The organic extracts were washed with H_2O and saturated NaCl, dried over K_2CO_3, and concentrated. Silica gel chromatrography (10% EtOAc/hexanes) afforded 2.77 g (86%) of the spiroenone: $[\alpha]^{23}_D$ −16.6 (*c* 2.60, $CHCl_3$); IR 2900, 2820, 1680, 1360, 1240, 1090, 690 cm^{-1}; ^1H NMR δ 7,80−7.70 (m, 4H), 7.45−7.35 (m, 6H), 6.62 (d, 1H, *J* = 10.2), 6.03 (d, 1H, *J* = 10.2), 5.03 (d, 1H, *J* = 9.0), 4.36 (d, 1H, *J* = 16.8), 4.06−4.02 (m, 1H), 4.02 (d, 1H, *J* = 16.8), 3.84 (d, 1H, *J* = 8.1), 3.61−3.53 (m, 1H), 3.35 (s, 3H), 3.17−3.09 (m, 1H), 2.31−2.20 (m, 1H), 1.99−1.91 (m, 1H), 1.83−1.59 (m, 3H), 1.54 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.54−1.23 (m, 5H), 1.06 (s, 9H), 0.92 (d, 3H, *J* = 6.6), 0.86 (s, 9H), 0.01 (s, 3H), −0.07 (s, 3H); ^{13}C NMR δ 195.7, 149.2, 136.4, 135.6, 135.2, 134.8, 132.6, 129.8, 129.7, 127.8, 127.3, 99.9, 93.8, 84.7, 79.7, 76.2, 66.6, 64.7, 57.8, 41.3, 37.1, 36.3, 35.4, 34.2, 31.1, 31.0, 27.5, 26.3, 24.0, 19.8, 18.6, 12.0, 9.7, −3.7, −4.5. Anal. Calcd for $C_{45}H_{68}O_7Si_2$: C, 69.54; H, 8.82. Found: C, 69.66; H, 8.94.

Diol 17. To a solution of the spiroenone **16** (100 mg, 0.1 mmol) in 1.5 mL anhydrous pyridine was added 0.5 mL of HF/pyridine reagent (Aldrich). The reaction was stirred at 25 °C for 12 h and was then quenched with saturated $NaHCO_3$. After stirring for several hours, the mixture was partitioned between Et_2O and water, and the organic phase washed with water, saturated $CuSO_4$, and dilute HCl. The Et_2O was dried over anhydrous K_2CO_3, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (0% to 50% EtOAc/hexanes) to provide 30 mg (54%) of the desired diol. The product could be crystallized from Et_2O: mp 161 °C; $[\alpha]^{23}_D$ +4.51 (*c* 1.33, $CHCl_3$); IR 3410, 2907, 1680, 1375, 1180, 855, 725 cm^{-1}; ^1H NMR δ 6.66 (d, 1H, *J* = 10.22), 6.07 (d, 1H, *J* = 10.19), 5.32, (d, 1H, *J* = 9.0), 4.42 (d, 1H, *J* = 16.78), 4.40−4.35 (m, 1H), 4.19−4.13 (m, 1H), 4.09 (d, 1H, *J* = 16.77), 3.43−3.35 (m, 1H), 3.40 (s, 3H), 3.04−2.96 (m, 1H), 2.70 (bs, 1H), 2.53 (bs, 1H), 2.35−2.30 (m, 1H), 2.03−1.98 (m, 2H), 1.88 (t, 1H, *J* = 12.59), 1.73−1.65 (m, 2H), 1.62 (s, 3H), 1.59 (s, 3H), 1.39 (s, 3H), 1.28−1.22 (m, 2H), 1.18−0.76 (m, 2H), 0.92 (d, 3H, *J* = 6.94); ^{13}C NMR δ 195.4, 148.8, 134.4, 130.2, 127.6, 100.1, 93.8, 84.7, 78.7, 74.0, 68.6, 66.6, 56.9, 39.4, 36.9, 35.5, 35.3, 31.8, 31.0, 30.1, 23.9, 13.8, 6.9. Anal**.** Calcd for $C_{23}H_{36}O_7$: C, 65.07; H, 8.55. Found: C, 64.91; H, 8.42.

Alcohol 22. To a solution of the enone **21** (17.0 g, 67.38 mmol) in 350 mL of THF at −78 °C was added L-Selectride (121.3 mL of a 1.0 M solution in THF, 121.3 mmol). The mixture was allowed to stir at −78 °C for 45 min. Water (350 mL) was added, followed by NaOH (29.11 g, 727.7 mmol) and H_2O_2 (82.5 mL of a 30% solution, 727.7 mmol). The mixture was allowed to warm to 25 °C and was stirred for 12 h. Saturated aqueous $Na_2S_2O_3$ was added, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over K_2CO_3 and concentrated. After evaporation with benzene to azeotropically remove the *s*-BuOH, the product was obtained in a pure state (17.26 g, 100%): $[\alpha]^{23}_D$ +70.06 (*c* 1.33, $CHCl_3$); IR (neat) 3350 (b), 3060, 2960, 2870, 1630, 1370, 1250, 1200, 1175, 1095, 1065, 1030, 950 cm-1; ^1H NMR δ 5.90 (d, 1H, *J* = 10.2), 5.77−5.66 (m, 1H), 5.59 (dd, 1H, *J* = 1.8, 10.2), 5.07−5.00 (m, 2H), 4.33−4.25 (m, 1H), 3.95−3.80 (m, 2H), 3.68−3.61 (m, 1H), 2.24−2.16 (m, 1H), 1.78 (bs, 1H), 1.58 (s, 3H), 1.64−1.41(m, 2H), 1.38 (s, 3H), 1.05 (d, 3H, *J* = 6.9); ^{13}C NMR δ 140.2, 133.2, 132.0, 115.7, 99.7, 94.1, 68.4, 63.7, 63.4, 43.5, 37.6, 31.3, 24.2, 16.2. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.88; H, 8.93.

***tert*-Butyldimethylsilyl Ether 23.** To a solution of the alcohol **22** (10.0 g, 39.3 mmol) in 130 mL of DMF was added imidazole (8.03 g, 118 mmol) and *tert*-butyldimethylsilyl chloride (8.89 g, 58.9 mmol). The reaction was allowed to stir 18 h at room temperature before an additional 2.96 g of TBSCl and 2.68 g of imidazole were added. The reaction mixture was allowed to stir an additional 7 h at which time it was partitioned between Et_2O and water. The layers were separated and the aqueous phase was extracted with Et_2O (2 × 250 mL). The combined organic extracts were washed with water (2 × 200 mL), dried over anhydrous K_2CO_3, and concentrated. Silica gel chromatography (5% EtOAc/hexane) afforded 12.67 g (87%) of the silyl ether as an oil: $[\alpha]^{23}_D$ +86.0 (c 1.2, $CHCl_3$); IR 3060, 2940, 2920, 2840, 1450, 1370, 1250, 1200, 1175, 1100, 1040, 865, 770 cm^{-1}; ^1H NMR δ 5.80 (d, 1H, *J* = 10.5), 5.75−5.66 (m, 1H), 5.50 (dd, 1H, *J* = 1.8, *J* = 10.2), 5.07−4.99 (m, 2H), 4.31 (t, 1H), 3.94−3.88 (m, 1H), 3.66 (d, 2H, *J* = 8.4), 2.24−2.16 (m, 1H), 1.57 (s, 3H), 1.59−1.50 (m, 1H), 1.49−1.39 (m, 1H), 1.37 (s, 3H), 1.05 (d, 3H, *J* = 6.9), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 140.3, 134.3, 131.1, 115.6, 99.6, 94.1, 68.3, 64.4, 63.8, 43.6, 37.9, 31.4, 26.2, 24.1, 18.5, 16.2, −4.3, −4.4. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.84. Found: C, 65.14; H, 9.93.

Aldehyde 19. To a solution of the olefin **23** (9.0 g, 24.4 mmol) in 90 mL of THF and 18 mL of H_2O was added OsO_4 (4.88 mL of a 0.2 M solution in benzene, 0.98 mmol) and NMO (5.06 mL of a 60% solution in H_2O, 29.3 mmol). The reaction was allowed to stir at room temperature for 40 min at which time 72 mL of H_2O was added followed by $NaIO_4$ (15.67 g, 73.2 mmol). After stirring for 30 min, the reaction was poured into Et_2O/H_2O. The aqueous layer was extracted with ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and concentrated. Chromatography (1% to 5% to 25% EtOAc/hexanes) on silica gel afforded 7.04 g (78%) of the aldehyde: $[\alpha]^{23}_D$ +49.6 (*c* 0.95, $CHCl_3$); IR 2960, 2920, 2840, 1720, 1450, 1370, 1250, 1100, 870, 830, 770 cm^{-1}; ^1H NMR δ 9.76 (s, 1H), 5.83 (d, 1H, *J* = 10.2), 5.50 (dd, 1H, *J* = 1.8, 10.2), 4.63−4.56 (m, 1H), 4.34−4.31 (m, 1H), 3.69 (s, 1H), 3.66 (d, 1H, *J* = 1.5), 2.46−2.44 (m, 1H), 1.59 (s, 3H), 1.61−1.54 (m, 2H), 1.35 (s, 3H), 1.11 (d, 3H, *J* = 6.9), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 204.2, 134.8, 130.6, 99.8, 93.8, 65.0, 64.3, 63.8, 50.7, 37.0, 31.1, 26.2, 24.0, 18.5, 8.6, −4.3, −4.4; Anal. Calcd for $C_{19}H_{34}O_5Si$: C, 61.58; H, 9.25. Found: C, 61.43; H, 9.34.

Alcohols 24a and 24b. The vinyl bromide **18** (4.18 g, 8.6 mmol) was dried azeotropically with toluene (3 × 10 mL). The aldehyde **19** (2.89 g, 7.8 mmol) was dried in a similar manner

in a separate flask. The vinyl bromide was dissoved in 100 mL of Et_2O and cooled to −78 °C. *t*-BuLi (9.27 mL of a 1.85 M solution in pentane, 17.2 mmol) was added dropwise via syringe. The mixture was allowed to stir 20 min at which time a solution of the aldehyde in 100 mL of Et_2O, precooled to −78 °C, was added via cannula. The reaction was allowed to stir for 1 h and was then quenched with saturated aqueous NH_4Cl. This mixture was extracted several times with Et_2O. The combined organic extracts were dried over K_2CO_3 and concentrated. Chromatography on Et_3N-treated silica gel (1% to 5% to 7% to 10% to 15% EtOAc/hex) afforded 3.38 g (56%) of the α-carbinol and 1.54 g (25%) of the *β*-carbinol.

α-carbinol 24a: $[\alpha]^{23}_D$ +17.7 (*c* 2.95, $CHCl_3$); IR 3480 (b), 2920, 2840, 1370, 1250, 1100, 860, 700 cm^{-1}; ^1H NMR *δ* 7.75−7.70 (m, 4H), 7.40−7.33 (m, 6H), 5.82 (d, 1H, *J* = 10.5), 5.50 (d, 1H, *J* = 10.2), 5.22 (d, 1H, *J* = 8.7), 4.37−4.29 (m, 2H), 4.11 (bs, 1H), 3.67−3.64 (m, 2H), 3.61−3.53 (m, 1H), 3.32 (s, 3H), 3.16−3.06 (m, 1H), 2.72 (bs, 1H), 2.27−2.21 (m, 1H), 1.96−1.88 (m, 1H), 1.82−1.25 (m, 7H), 1.55 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H), 1.00−0.93 (m, 1H), 0.88 (s, 9H), 0.83 (d, 3H, *J* = 6.9), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR *δ* 136.4, 135.6, 134.9, 134.6, 134.0, 130.8, 130.1, 129.7, 127.8, 127.7, 99.6, 94.2, 84.8, 79.1, 76.2, 68.7, 64.4, 63.9, 57.7, 39.4, 37.5, 36.7, 35.4, 34.2, 31.3, 31.1, 27.5, 26.2, 24.4, 19.8, 18.5, 13.9, 6.5, −4.2, −4.3. Anal. Calcd for $C_{45}H_{70}O_7Si_2$: C, 69.36; H, 9.05. Found: C, 69.10; H, 9.08.

***β*-carbinol 24b:** $[\alpha]^{23}_D$ +23.9 (*c* 1.30, $CHCl_3$); IR 3470, 3020, 2920, 2840, 1950, 1800, 1600, 1470, 1370, 1250, 1100, 860, 670 cm^{-1}; ^1H NMR *δ* 7.77−7.71 (m, 4H), 7.42−7.33 (m, 6H), 5.82 (d, 1H, *J* = 10.2), 5.52 (dd, 1H, *J* = 10.2, *J* = 1.8), 5.15 (d, 1H, *J* = 8.7), 4.45 (d, 1H, *J* = 12.0), 4.35−4.30 (m, 1H), 3.90−3.85 (m, 1H), 3.76−3.53 (m, 3H), 3.33 (s, 3H), 3.17−3.12 (m, 1H), 2.30−2.19 (m, 1H), 1.97−1.63 (m, 6H), 1.59 (s, 3H), 1.54 (s, 3H), 1.53−1.33 (m, 4H), 1.36 (s, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.78 (d, 3H, *J* = 7.2), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR *δ* 136.5, 136.4, 135.6, 135.2, 134.9, 134.6, 132.2, 130.9, 129.8, 127.8, 127.7, 99.8, 94.2, 84.8, 80.5, 76.2, 67.6, 64.4, 63.9, 57.7, 38.7, 36.6, 35.5, 35.4, 34.2, 31.4, 31.2, 27.6, 26.3, 24.2, 19.9, 18.6, 12.8, 12.1, −4.1, −4.2. Anal. Calcd for $C_{45}H_{70}O_7Si_2$: C, 69.36; H, 9.05. Found: C, 69.40; H, 9.01.

Enone 25. To a solution of a diastereomeric mixture of alcohols **24a** and **24b** (0.200 g, 0.257 mmol) in 5 mL of CH_2Cl_2 was added Dess−Martin periodinane (0.163 g, 0.385 mmol). The mixture was allowed to stir for 1 h at 25 °C. The reaction was diluted with Et_2O and treated with saturated $NaHCO_3$ and $Na_2S_2O_3$. Stirring was continued until the organic layer was clear. The layers were separated, and the aqueous phase was extracted with Et_2O. The organic extracts were dried over K_2CO_3 and concentrated. Silica gel chromatography (1% to 5% EtOAc/hex) afforded 0.157 g (80%) of the enone: $[\alpha]^{23}_D$ +42.6 (*c* 0.80, $CHCl_3$); IR 3040, 2920, 2840, 1650, 1450, 1370, 1250, 1100, 700 cm^{-1}; ^1H NMR *δ* 7.75−7.70 (m, 4H), 7.45−7.30 (m, 6H), 6.35 (d, 1H, *J* = 8.7), 5.77 (d, 1H, *J* = 10.2), 5.42 (dd, 1H, *J* = 9.9, *J* = 1.8), 4.30−4.24 (m, 2H), 3.64−3.56 (m, 3H), 3.32 (s, 3H), 3.24−3.13 (m, 1H), 2.44−2.41 (m, 1H), 2.03−1.98 (m, 1H), 1.75 (s, 3H), 1.74−1.70 (m, 1H), 1.56 (s, 3H), 1.55−1.33 (m, 5H), 1.32 (s, 3H), 1.09 (d, 3H, *J* = 7.5), 1.07 (s, 9H), 1.08−0.95 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR *δ* 204.5, 146.4, 136.4, 136.3, 135.4, 134.6, 134.5, 130.8, 129.9, 129.8, 127.9, 127.8, 99.8, 93.8, 84.0, 75.4, 67.7, 64.3, 63.7, 57.7, 44.6, 38.0, 36.5, 35.1, 33.3, 31.3, 29.8, 27.5, 26.2, 24.1, 19.8, 18.5, 15.3, 12.0, −4.2, −4.3. Anal. Calcd for $C_{45}H_{68}O_7Si_2$: C, 69.54; H, 8.82. Found: C, 69.70; H, 9.00.

Alcohol 24b. To a solution of the enone **25** (0.290 g, 0.37 mmol) in 30 mL of MeOH was added $CeCl_3 \cdot 7H_2O$ (0.278 g, 0.75 mmol). The mixture was allowed to stir 3 min and was then cooled to −78 °C. $NaBH_4$ (0.070 g, 1.86 mmol) was added, and the reaction was allowed to stir for 1.5 h at which time it was quenched with saturated aqueous NH_4Cl and diluted with Et_2O and water. The Et_2O layer was washed with water, dried over K_2CO_3, and evaporated under reduced pressure to give 0.270 g (93%) of the alcohol.

Silyl Ether 26a. A solution of the alcohol **24a** (0.109 g, 0.14 mmol) in 2.5 mL of CH_2Cl_2 was cooled to 0 °C. 2,6-Lutidine (65 *μ*L, 0.56 mmol) and TBSOTf (80 *μ*L, 0.35 mmol) were added sequentially. After stirring for 30 min, the solvent was removed in vacuo. The residue was partitioned between Et_2O/H_2O. The organic layer was washed three times with H_2O and once with saturated NaCl, dried over Na_2SO_4, and concentrated. Chromatography (0.5% EtOAc/hexanes) afforded 0.094 g (76%) of the silyl ether: $[\alpha]^{23}_D$ +15.4 (*c* 1.56, $CHCl_3$); IR 3050, 2920, 2840, 1460, 1370, 1250, 1100, 1050 cm^{-1}; ^1H NMR *δ* 7.77−7.70 (m, 4H), 7.45−7.30 (m, 6H), 5.77 (d, 1H, *J* = 10.2), 5.48 (dd, 1H, *J* = 1.5, *J* = 10.2), 5.00 (d, 1H, *J* = 8.7), 4.30−4.25 (m, 1H), 3.98 (d, 1H, *J* = 12.3), 3.82 (d, 1H, *J* = 8.4), 3.60 (d, 1H, *J* = 8.1), 3.65−3.52 (m, 2H), 3.33 (s, 3H), 3.15−3.08 (m, 1H), 2.31−2.15 (m, 1H), 1.99−1.90 (m, 1H), 1.75−1.62 (m, 2H), 1.52 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.52−1.15 (m, 6H), 1.06 (s, 9H), 0.89 (d, 3H, *J* = 6.9), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H), −0.08 (s, 3H); ^{13}C NMR *δ* 136.5, 136.4, 135.7, 135.4, 134.8, 134.3, 132.5, 131.3, 129.7, 127.8, 127.7, 99.3, 94.1, 84.8, 80.2, 76.2, 64.4, 64.2, 63.8, 57.8, 41.3, 37.6, 36.3, 35.4, 34.2, 31.3, 31.1, 27.5, 26.4, 26.2, 24.6, 19.8, 18.6, 18.5, 11.8, 9.8, −3.7, −4.2, −4.3, −4.5. Anal. Calcd for $C_{51}H_{84}O_7Si_3$: C, 68.56; H, 9.48. Found: C, 68.65; H, 9.59.

Alcohol 27a. To a solution of the bis-TBS ether **26a** (0.080 g, 0.09 mmol) in 8 mL of THF at 0 °C was added TBAF (90 *μ*L of a 1.0 M solution in THF, 0.09 mmol). The reaction was allowed to stir for 40 min at which time H_2O and EtOAc were added. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with NaCl, dried over Na_2SO_4, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 0.048 g (69%) of the alcohol: $[\alpha]^{23}_D$ +10.0 (*c* 2.10, $CHCl_3$); IR 3400 (b), 3050, 2920, 2840, 1450, 1370, 1250, 1100 cm^{-1}; ^1H NMR *δ* 7.80−7.70 (m, 4H), 7.45−7.30 (m, 6H), 5.88 (d, 1H, *J* = 10.2), 5.57 (dd, 1H, *J* = 10.2, *J* = 1.8), 5.02 (d, 1H, *J* = 9.0), 4.30−4.21 (m, 1H), 3.99 (d, 1H, *J* = 12.0), 3.84−3.74 (m, 2H), 3.61−3.54 (m, 2H), 3.34 (s, 3H), 3.18−3.09 (m, 1H), 2.32−2.19 (m, 1H), 2.00−1.89 (m, 1H), 1.74−1.63 (m, 2H), 1.55−1.19 (m, 7H), 1.40 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.06 (s, 9H), 0.86 (s, 9H)(d, 3H), 0.00 (s, 3H), −0.07 (s, 3H); ^{13}C NMR *δ* 136.4, 135.6, 135.4, 134.8, 132.9, 132.6, 132.4, 129.7, 127.8, 127.7, 99.5, 94.1, 84.7, 79.9, 76.2, 64.4, 63.9, 57.8, 41.3, 37.4, 36.3, 35.4, 34.2, 31.3, 31.1, 27.4, 26.3, 24.5, 19.8, 18.6, 12.0, 9.8, −3.7, −4.5. Anal. Calcd for $C_{45}H_{70}O_7Si_2$: C, 69.36; H, 9.05. Found: C, 69.06; H, 9.15.

Spiroenone 16a. To a solution of the alcohol **27a** (0.078 g, 0.10 mmol) in 2 mL of CH_2Cl_2 was added Dess−Martin periodinane (0.067 g, 0.16 mmol). After stirring for 30 min, the reaction mixture was diluted with Et_2O. Saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ were added, and the biphasic mixture was vigorously stirred until the organic layer was clear. The aqueous layer was extracted twice with Et_2O, dried over K_2CO_3, and concentrated. Chromatography (5% EtOAc/hexanes) afforded 0.053 g (69%) of the enone: $[\alpha]^{23}_D$ −16.6 (*c* 2.60, $CHCl_3$); IR 2900, 2820, 1680, 1360, 1240, 1090, 690 cm^{-1}; ^1H NMR *δ* 7,80−7.70 (m, 4H), 7.45−7.35 (m, 6H), 6.62 (d, 1H, *J* = 10.2), 6.03 (d, 1H, *J* = 10.2), 5.03 (d, 1H, *J* = 9.0), 4.36 (d, 1H, *J* = 16.8), 4.06−4.02 (m, 1H), 4.02 (d, 1H, *J* = 16.8), 3.84 (d, 1H, *J* = 8.1), 3.61−3.53 (m, 1H), 3.35 (s, 3H), 3.17−3.09 (m, 1H), 2.31−2.20 (m, 1H), 1.99−1.91 (m, 1H), 1.83−1.59 (m, 3H), 1.54 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.54−1.23 (m, 5H), 1.06 (s, 9H), 0.92 (d, 3H, *J* = 6.6), 0.86 (s, 9H), 0.01 (s, 3H), −0.07 (s, 3H); ^{13}C NMR *δ* 195.7, 149.2, 136.4, 135.6, 135.2, 134.8, 132.6, 129.8, 129.7, 127.8, 127.3, 99.9, 93.8, 84.7, 79.7, 76.2, 66.6, 64.7, 57.8, 41.3, 37.1, 36.3, 35.4, 34.2, 31.1, 31.0, 27.5, 26.3, 24.0, 19.8, 18.6, 12.0, 9.7, −3.7, −4.5. Anal. Calcd for $C_{45}H_{68}O_7Si_2$: C, 69.54; H, 8.82. Found: C, 69.66; H, 8.94.

Silyl Ether 26b. A solution of the alcohol **24b** (0.342 g, 0.44 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C. 2,6-Lutidine (200 *μ*L, 1.76 mmol) and TBSOTf (250 *μ*L, 1.10 mmol) were added sequentially. After stirring for 30 min, the solvent was removed in vacuo. The residue was partitioned between Et_2O/H_2O. The organic layer was washed three times with H_2O and once with saturated NaCl, dried over Na_2SO_4, and concentrated. Chromatography (0.5% EtOAc/hexanes) afforded 0.154 g (40%) of the silyl ether: $[\alpha]^{23}_D$ +15.1 (*c* 1.13, $CHCl_3$); IR 3060, 3040, 2920, 2850, 1460, 1375, 1250, 1150, 860, 840, 770, 700 cm^{-1}; ^1H NMR *δ* 7.75−7.70 (m, 4H), 7.42−7.35 (m, 6H), 5.78 (d, 1H, *J* = 10.2), 5.50 (dd, 1H, *J* = 10.2, *J*

= 1.8), 4.99 (d, 1H, J = 8.7), 4.53 (d, 1H, J = 12.0), 4.35−4.25 (m, 1H), 3.80−3.51 (m, 4H), 3.34 (s, 3H), 3.17−3.07 (m, 1H), 2.25−2.12 (m, 1H), 1.93−1.85 (m, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H), 1.70−1.19 (m, 8H), 1.06 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.61 (d, 3H, J = 6.9), 0.07 (s, 3H), 0.06 (s, 3H), −0.02 (s, 3H), −0.11 (s, 3H); ^{13}C NMR δ 136.5, 136.4, 135.6, 134.8, 134.2, 132.6, 131.4, 130.6, 129.8, 127.8, 99.4, 94.2, 84.7, 79.9, 76.2, 64.5, 63.8, 62.8, 57.8, 41.9, 38.1, 36.5, 35.2, 34.2, 31.4, 30.6, 27.5, 26.4, 26.2, 25.0, 19.8, 18.6, 18.5, 11.1, 10.0, −3.6, −4.2, −4.3, −4.6. Anal. Calcd for $C_{51}H_{84}O_7Si_3$: C, 68.56; H, 9.48. Found: C, 68.22; H, 9.39.

Alcohol 27b. To a solution of the bis-TBS ether **26b** (0.116 g, 0.13 mmol) in 10 mL of THF at 0 °C was added TBAF (140 μL of a 1.0 M solution in THF, 0.14 mmol). The reaction was allowed to stir for 1 h at which time H_2O and EtOAc were added. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 0.055 g (54%) of the alcohol: $[\alpha]^{23}_D$ +12.4 (c 2.75, $CHCl_3$); IR 3360 (b), 3040, 2910, 2840, 1450, 1420, 1370, 1250, 1100, 700 cm^{-1}; ^{1}H NMR δ 7.80−7.70 (m, 4H), 7.45−7.32 (m, 6H), 5.84 (d, 1H, J = 10.2), 5.59 (dd, 1H, J = 10.2, J = 1.5), 5.01 (d, 1H, J = 8.7), 4.54 (d, 1H, J = 11.7), 4.33−4.20 (m, 1H), 3.84−3.73 (m, 2H), 3.66−3.53 (m, 3H), 3.36 (s, 3H), 3.17−3.09 (m, 1H), 2.30−2.15 (m, 1H), 1.95−1.87 (m, 1H), 1.75−1.27 (m, 8H), 1.56 (s, 3H), 1.50 (s, 3H), 1.33 (s, 3H), 1.07 (s, 9H), 0.86 (s, 9H), 0.63 (d, 3H, J = 6.9), 0.00 (s, 3H), −0.09 (s, 3H); ^{13}C NMR δ 136.4, 135.8, 135.6, 134.8, 132.9, 132.7, 132.6, 129.8, 127.8, 99.6, 94.2, 84.7, 79.9, 76.2, 64.0, 63.9, 62.9, 57.9, 41.9, 37.7, 36.5, 35.2, 34.1, 31.4, 30.6, 27.5, 26.4, 25.0, 19.8, 18.6, 11.1, 10.0, −3.6, −4.7. Anal. Calcd for $C_{45}H_{70}O_7Si_2$: C, 69.36; H, 9.05. Found: C, 69.13; H, 9.13.

Spiroenone 16b. To a solution of the alcohol **27b** (0.055 g, 0.07 mmol) in 2 mL of CH_2Cl_2 was added Dess−Martin periodinane (0.045 g, 0.11 mmol). After stirring for 45 min, the reaction mixture was diluted with Et_2O. Saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ were added, and the biphasic mixture was vigorously stirred until the organic layer was clear. The aqueous layer was extracted twice with Et_2O, dried over K_2CO_3, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 0.053 g (96%) of the enone: $[\alpha]^{23}_D$ −7.6 (c 2.65, $CHCl_3$); IR 3050, 2920, 2840, 1695, 1375, 1250, 1100 cm^{-1}; ^{1}H NMR δ 7.78−7.70 (m, 4H), 7.40−7.32 (m, 6H), 6.64 (d, 1H, J = 10.2), 6.04 (d, 1H, J = 10.2), 5.01 (d, 1H, J = 8.7), 4.57 (d, 1H, J = 11.7), 4.40 (d, 1H, J = 16.8), 4.05 (d, 1H, J = 16.8), 3.79 (d, 1H, J = 9.0), 3.60−3.52 (m, 1H), 3.35 (s, 3H), 3.17−3.08 (m, 1H), 2.28−2.14 (m, 1H), 1.94−1.75 (m, 2H), 1.58 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), 1.70−1.25 (m, 7H), 1.06 (s, 9H), 0.85 (s, 9H), 0.64 (d, 3H, J = 6.9), −0.02 (s, 3H), −0.10 (s, 3H); ^{13}C NMR δ 195.8, 149.3, 136.4, 135.6, 134.8, 132.8, 129.8, 129.7, 127.8, 127.3, 100.0, 93.9, 84.7, 79.9, 76.2, 66.6, 63.2, 57.9, 41.9, 37.5, 36.5, 35.2, 34.1, 31.1, 30.6, 27.5, 26.3, 24.4, 19.8, 18.6, 11.1, 10.0, −3.6, −4.7. Anal. Calcd for $C_{45}H_{68}O_7Si_2$: C, 69.54; H, 8.82. Found: C, 69.28; H, 8.90.

Pipecolate Ester 28. A flask containing the alcohol **24a** (4.0 g, 5.13 mmol) was dried under high vacuum for 1 h, and then the flask was purged with argon. N-BOC-(L)-pipecolic acid (**20**) (3.53 g, 15.4 mmol), DCC (3.50 g, 16.9 mmol), and DMAP (0.125 g, 1.03 mmol) were then added to the flask, and the contents were placed under high vacuum for 1 h. The flask was then filled with argon and cooled to −20 °C, and 350 mL of CH_2Cl_2 was added. After stirring for 10 min, the reaction flask was placed in a −20 °C freezer for 48 h. The contents were filtered and washed with hexanes, and the filtrate was concentrated. Silica gel chromatography (5% EtOAc/hexanes) gave 5.14 g (100%) of the pipecolate ester: $[\alpha]^{23}_D$ −15.6 (c 0.90, $CHCl_3$); IR 2920, 2850, 1730, 1690, 1390, 1360, 1250, 1150, 1100, 870, 780 cm^{-1}; ^{1}H NMR δ (toluene-d_8, 100 °C) 7.84−7.75 (m, 4H), 7.24−7.15 (m, 6H), 5.70 (d, 1H, J = 10.2), 5.42 (d, 1H, J = 9.9), 5.34 (d, 1H, J = 6.6), 5.25 (d, 1H, J = 8.7), 4.90−4.83 (bs, 1H), 4.25−4.18 (m, 2H), 4.05−3.90 (m, 1H), 3.78−3.55 (m, 3H), 3.12 (s, 3H), 3.12−2.97 (m, 2H), 2.20−2.02 (m, 3H), 1.97−1.86 (m, 1H), 1.80-1.65 (m, 3H), 1.56 (s, 3H), 1.49 (s, 3H), 1.47−1.12 (m, 6H), 1.40 (s, 9H), 1.40 (s, 3H), 1.16 (s, 9H), 1.04 (d, 3H, J = 6.9), 1.03−0.86 (m, 3H), 0.86 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR δ (toluene-d_8 100 °C) 170.6, 155.3, 136.4, 136.3, 135.8, 135.3, 133.9, 133.5, 131.6, 129.5, 127.5, 99.4, 94.1, 84.4, 79.9, 79.3, 75.9, 65.6, 64.8, 64.0, 56.3, 54.8, 41.9, 40.2, 37.8, 36.0, 35.4, 33.9, 31.0, 30.6, 28.5, 27.4, 27.0, 25.9, 25.2, 24.2, 21.0, 19.4, 18.2, 13.0, 9.8, −4.6. Anal. Calcd for $C_{56}H_{87}NO_{10}Si_2$: C, 67.91; H, 8.85; N, 1.41. Found: C, 68.01; H, 8.95; N, 1.46.

Alcohol 29. To a solution of the silyl ether **28** (0.430 g, 0.43 mmol) in 50 mL of THF at 0 °C was added TBAF (0.480 mL of a 1.0 M solution in THF, 0.48 mmol). The reaction was allowed to stir for 25 min and then was partitioned between EtOAc/H_2O. The organic layer was washed with H_2O, dried over K_2CO_3, and concentrated. Chromatography (5% to 25% to 50% EtOAc/hexanes) afforded 0.327 g (84%) of the alcohol: $[\alpha]^{23}_D$ −21.5 (c 0.70, $CHCl_3$); IR 3420, 2940, 2860, 1730, 1690, 1370, 1250, 1150, 1100, 790 cm^{-1}; ^{1}H NMR δ (toluene-d_8, 100 °C) 7.83−7.75 (m, 4H), 7.25−7.14 (m, 6H), 5.58 (d, 1H, J = 9.9), 5.40 (d, 1H, J = 10.2), 5.35 (d, 1H, J = 6.9), 5.26 (d, 1H, J = 8.7), 4.95−4.85 (m, 1H), 4.23−4.14 (m, 1H), 4.10−3.85 (m, 3H), 3.75−3.62 (m, 1H), 3.51 (d, 2H, J = 8.1), 3.14 (s, 3H), 3.12−2.99 (m, 2H), 2.17−2.04 (m, 3H), 1.98−1.87 (m, 1H), 1.80−1.70 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H), 1.41 (s, 9H), 1.18 (s, 9H), 1.60−1.25 (m, 7H), 1.05 (d, 3H, J = 6.6), 1.00−0.78 (m, 3H); ^{13}C NMR (toluene-d_8, 100 °C) δ 170.7, 155.4, 136.4, 136.3, 135.8, 135.3, 133.7, 133.0, 132.0, 131.4, 129.5, 127.6, 127.5, 99.4, 94.1, 84.4, 80.0, 79.4, 75.9, 65.6, 64.1, 63.4, 56.3, 54.9, 42.0, 40.1, 37.6, 36.0, 35.4, 33.9, 31.0, 30.6, 28.5, 27.4, 27.0, 25.2, 24.2, 20.9, 19.4, 13.0, 9.8. Anal. Calcd for $C_{50}H_{73}NO_{10}Si$: C, 68.54; H, 8.40; N, 1.60. Found: C, 68.36; H, 8.43; N, 1.53.

Spiroenone 3. To a solution of the alcohol **29** (0.321 g, 0.37 mmol) in 10 mL of CH_2Cl_2 was added Dess−Martin periodinane (0.233 g, 0.55 mmol). After stirring for 45 min, the reaction mixture was diluted with Et_2O. Saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ were added, and the biphasic mixture was vigorously stirred until the organic layer was clear. The aqueous layer was extracted twice with Et_2O, dried over K_2CO_3, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 0.302 g (94%) of the enone: $[\alpha]^{23}_D$ −38.9 (c 1.70, $CHCl_3$); IR 3050, 2930, 2840, 1730, 1700, 1690, 1380, 1250, 1150, 1100, 780, 700 cm^{-1}; ^{1}H NMR (toluene-d_8, 100 °C) δ 7.83−7.78 (m, 4H), 7.21−7.19 (m, 6H), 6.20 (d, 1H, J = 9.9), 5.74 (d, 1H, J = 10.2), 5.34 (d, 1H, J = 6.3), 5.24 (d, 1H, J = 9.0), 4.90−4.84 (bs, 1H), 4.18 (d, 1H, J = 16.5), 4.20−4.09 (m, 1H), 4.05−3.93 (m, 1H), 3.81 (d, 1H, J = 16.5), 3.71−3.61 (m, 1H), 3.15 (s, 3H), 3.13−2.97 (m, 2H), 2.23−2.03 (m, 3H), 1.97−1.88 (m, 1H), 1.80−1.71 (m, 2H), 1.56 (s, 3H), 1.56−1.45 (m, 1H), 1.39 (s, 9H), 1.39 (s, 3H), 1.31 (s, 3H), 1.17 (s, 9H), 1.40−1.09 (m, 7H), 1.01 (d, 3H, J = 6.9), 0.89−0.75 (m, 2H); ^{13}C NMR (toluene-d_8, 100 °C) δ 193.0, 170.7, 155.5, 148.0, 136.4, 136.3, 135.7, 135.3, 133.6, 131.4, 129.6, 127.6, 127.5, 126.9, 99.8, 93.7, 84.3, 79.4, 79.2, 75.9, 66.5, 65.9, 56.4, 54.8, 42.0, 40.0, 36.8, 36.0, 35.3, 33.8, 30.7, 30.6, 28.5, 27.4, 27.0, 25.2, 23.6, 20.9, 19.4, 13.1, 9.6. Anal. Calcd for $C_{50}H_{71}NO_{10}Si$: C, 68.70; H, 8.19; N, 1.60. Found: C, 68.42; H, 8.14; N, 1.54.

[2*S*,3*R*,5*S*,6*R*]-2,5-Dimethoxy-6-(hydroxymethyl)-3-methyltetrahydropyran (33). To a solution of 7.58 g (43.0 mmol) of diol **32** in 75 mL of pyridine was added 18.0 g (64.6 mmol) of TrCl, and the solution was allowed to stir for 12 h at room temperature. The reaction was diluted with ether and washed with water, saturated $CuSO_4$, and brine. The aqueous washings were back extracted with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude trityl ether thus obtained was dissolved in 150 mL of THF, and 3.9 g (130 mmol) of an 80% dispersion of NaH was added in portions, followed by 8.0 mL (129 mmol) of iodomethane. The reaction was stirred for 24 h and was then quenched by slow addition of water. The reaction was filtered through Celite, and the THF was removed in vacuo. The residue was diluted with ether and washed with water and brine. The aqueous extracts were back extracted with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude methyl ether was then diluted with 200 mL of MeOH, and concd HCl was added until pH = 2. The reaction was stirred for 5 h, solid $NaHCO_3$ was added, and the reaction was filtered. The

solvent was removed in vacuo, and the residue was diluted with EtOAc and was washed with water and brine. The aqueous washings were back extracted with EtOAc (4×) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 30%) as eluent to give 7.07 g (86%) of alcohol **33**: $[\alpha]^{23}_D$ +209.5 (c = 1); IR (neat) 3470, 2925, 2890, 2820, 1450, 1380, 1185, 1100, 1060, 1030, 955, 925 cm^{-1}; ^1H NMR 4.43 (d, 1H, J = 3.3), 3.68−3.84 (m, 2H), 3.52 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.21 (m, 1H), 2.06 (dd, 1H, J = 5.6, 7.4), 1.96 (m, 1H), 1.79 (m, 1H), 1.43 (m, 1H), 0.94 (d, 3H, J = 6.9); ^{13}C NMR 101.20, 76.25, 71.07, 63.60, 56.51, 55.20, 34.44, 31.42, 16.71. Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.99; H, 9.63.

[2*S*,3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2,5-Dimethoxy-6-[1-hydroxy-3-methyl-6-(trimethylsilyl)hex-5-ynl]-3-methyltetrahydropyran (34). To a solution of 1.50 g (7.9 mmol) of alcohol **33** in 10 mL of CH_2Cl_2 was added 4.18 g (9.85 mmol) of Dess−Martin periodinane. The reaction was stirred for 1 h. The reaction was diluted with 25 mL of ether and 25 mL of hexane. The mixture was filtered through Celite. The filtrate was stirred over freshly ground K_2CO_3 for 30 min and then filtered again through Celite. The filtrate was concentrated and the residue was distilled (205 °C) under argon in a kugelrohr oven to give 1.20 g (81%) of aldehyde **30** which was used immediately: ^1H NMR 9.80 (s, 1H), 4.53 (d, 1H, J = 3.3), 4.03 (d, 1H, J = 10.2), 3.36 (2s, 6H), 3.30−3.40 (m, 1H), 2.03 (dt, 1H, J = 12.0, 4.2), 1.80 (m, 1H), 1.55 (m, 1H), 0.95 (d, 3H, J = 6.9); ^{13}C NMR 199.85, 101.35, 75.76, 75.19, 56.63, 55.73, 33.68, 31.79, 16.59.

A slurry of $MgBr_2$ was prepared by adding 6.93 mL (80.4 mmol) of 1,2-dibromomethane to a stirred mixture of 2.44 g (100.4 mmol) of Mg in 100 mL of ether at a rate such that a slow reflux was maintained (approximately 45 min). After the addition was complete, the reaction was stirred for an additional 2 h to ensure complete consumption of the dibromide.

To a solution of 11.27 g (40.2 mmol) of iodide **31** in 150 mL of ether at −78 °C was added 45.6 mL (84.4 mmol) of a 1.85 M solution of *t*-BuLi in pentane. The reaction was stirred for 15 min, and then the above $MgBr_2$ slurry was added via cannula. The reaction was warmed to 0 °C for 30 min, and then a solution of 5.045 g (26.8 mmol) of aldehyde **30** in 20 mL of ether was slowly added. The reaction was stirred for 1 h at 0 °C, and then the reaction was quenched by addition of saturated NH_4Cl. The mixture was warmed to room temperature, and 1 M HCl was added until all solids had dissolved (ca. 100 mL). The resulting two phase mixture was partitioned and the aqueous layer back extracted with ether. The organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 15%) as eluent to give 7.14 g (78%) of alcohol **34** as a single diastereomer: $[\alpha]^{23}_D$ +91.7 (c = 1.1); IR (neat) 3480, 2960, 2170, 1410, 1380, 1250, 1100, 1045, 1025, 955, 845, 760 cm^{-1}; ^1H NMR 4.41 (d, 1H, J = 3.0), 3.93 (m, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 3.30−3.35 (m, 2H), 2.25 (dd, 1H, J = 16.8, 5.7), 2.15 (dd, 1H, J = 16.8, 5.7), 1.80−2.00 (m, 3H), 1.74 (m, 1H), 1.54 (m, 2H), 1.38 (m, 1H), 1.02 (d, 3H, J = 6.6), 0.90 (d, 3H, J = 6.9), 0.11 (s, 9H); ^{13}C NMR 106.58, 101.36, 86.05, 74.83, 72.72, 67.69, 56.60, 55.23, 40.58, 34.30, 31.55, 29.82, 27.14, 20.77, 16.70, 0.57. Anal. Calcd for $C_{18}H_{34}O_4Si$ C, 63.11; H, 10.00. Found: C, 62.97; H, 10.04.

[2*S*,3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2,5-Dimethoxy-6-[1-methoxy-3-methyl-6-(trimethylsilyl)hex-5-ynl]-3-methyltetrahydropyran (35). To a solution of 13.62 g (39.8 mmol) of alcohol **34** in 100 mL of THF at 0 °C was added 3.01 g (119 mmol) of 95% NaH followed by 15 mL (240 mmol) of iodomethane. The reaction was allowed to warm to room temperature. After 6 h, the reaction was cooled to 0 °C, and 1 M HCl was added slowly until the mixture was acidic. The reaction was diluted with EtOAc, and the layers were partitioned. The organic layer was washed with saturated $NaHCO_3$ and brine. The aqueous washings were back extracted, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (8% to 12%) as eluent to give 11.70 g (83%) of methyl ether **35** and 2.41 g of product which had been desilylated. This latter material was dissolved in 25 mL of THF and treated at 0 °C with 10 mL (10 mmol) of a 1 M solution of LiHMDS. After 5 min, 1.61 mL (12.7 mmol) of TMSCl was added. After 5 min, the reaction was quenched with saturated $NaHCO_3$, extracted twice with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography as above gave an additional 2.13 g of alcohol (total 13.83 g, 98%): $[\alpha]^{23}_D$ +110.9 (c = 0.1); IR (neat) 2960, 2930, 2820, 2170, 1455, 1375, 1245, 1095, 1140, 955, 840, 760 cm^{-1}; ^1H NMR 4.42 (d, 1H, J = 3.0), 3.59 (t, 1H, J = 6.9), 3.30−3.42 (m, 2H), 3.38 (s, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 2.17 (m, 2H), 1.95 (dt, 1H, J = 12.0, 3.6), 1.65−1.85 (m, 3H), 1.55 (m, 1H), 1.32 (m, 1H), 0.98 (d, 3H, J = 6.3), 0.87 (d, 3H, J = 6.9), 0.09 (s, 9H); ^1C NMR 106.25, 101.56, 86.13, 76.40, 74.57, 71.77, 58.93, 56.09, 55.49, 36.17, 34.11, 31.60, 29.71, 28.29, 20.20, 16.74, 0.55. Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 63.80; H, 10.29.

[2*RS*,3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2-Hydroxy-5-methoxy-3-methyl-6-[1-methoxy-3-methyl-6-(trimethylsilyl)hex-5-ynyl]-tetrahydropyran (36). A solution of 1.002 g (2.81 mmol) of methyl acetal **35** in 30 mL of acetic acid and 7.5 mL of water was heated to 80 °C for 7 h. The reaction was cooled and diluted with water, and the product was extracted with ether. The organic layer was washed with saturated $NaHCO_3$, and the aqueous layers were back extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 30%) as eluent to give 852 mg (89%) of hemiacetal **36:** $[\alpha]^{23}_D$ +58.8 (c = 1); IR (neat) 3400, 2920, 2170, 1455, 1370, 1245, 840, 760 cm^{-1}; ^1H NMR 5.03 (s(br), 0.5H), 4.27 (d(br), 0.5H, J = 6.6), 3.53−3.64 (m, 2H), 3.41, 3.40 (2s, 3H), 3.36 (s, 3H), 3.34−3.40 (m, 0.5H), 3.16 (d, 0.5H, J = 9.0), 2.61 (s(br), 0.5H) 2.09−2.31 (m, 2.5H), 1.99 (dt, 1H, J = 11.7, 4.2), 1.83 (m, 1H), 1.36−1.75 (m, 4H), 0.93−1.03 (4d, 6H), 0.14 (s, 9H); ^{13}C NMR 106.78, 106.39, 107.81, 94.57, 86.18, 79.94, 76.43, 74.72, 74.25, 71.59, 58.82, 58.77, 56.67, 56.20, 37.40, 36.27, 35.99, 34.24, 31.09, 29.70, 28.26, 28.06, 20.26, 20.16, 17.05, 0.58. Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 62.95; H, 10.16.

[2*E*,4*R*,6*S*,7*R*,8*S*,10*S*]-6,8-Dimethoxy-4,10-dimethyl-7-hydroxy-13-(trimethylsilyl)tridec-2-en-12-ynoic Acid Ethyl Ester (37). To a solution of 4.99 g (14.6 mmol) of hemiacetal **36** in 75 mL of benzene was added 12.67 g (36.4 mmol) of (carbethoxymethylene)triphenylphosphorane and 400 μL (2.87 mmol) of triethylamine. The reaction was heated at reflux for 36 h. The reaction was cooled and the solvent removed in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 15%) as eluent to give 5.24 mg (87%) of enoate **37**: $[\alpha]^{23}_D$ −16.4 (c = 0.5); IR (neat) 3450, 2950, 2820, 2170, 1715, 1645, 1450, 1365, 1250, 1170, 1090, 1035, 845, 760 cm^{-1}; ^1H NMR 6.86 (dd, 1H, J = 15.6, 8.7), 5.82 (d, 1H, J = 15.6), 4.19 (q, 2H, J = 7.2), 3.41 (s, 3H), 3.36 (s, 3H), 3.35−3.45 (m, 2H), 3.12 (m, 1H), 2.62 (m, 1H), 2.27 (dd, 1H, J = 16.8, 5.7), 2.17 (m, 2H), 1.76 (m, 1H), 1.58−1.68 (m, 2H), 1.47 (m, 1H), 1.29 (t, 3H, J = 7.2), 1.10 (d, 3H, J = 6.9), 1.01 (d, 3H, J = 6.6), 0.14 (s, 9H); ^{13}C NMR 167.13, 154.56, 120.80, 106.09, 86.41, 79.87, 78.25, 74.18, 60.61, 58.19, 37.97, 36.59, 33.68, 29.40, 27.92, 21.24, 20.30, 14.69, 0.56. Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 63.81; H, 9.97.

[2*E*,4*R*,6*S*,7*R*,8*S*,10*S*]-1,7-Dihydroxy-6,8-dimethoxy-4,10-dimethyl-13-(trimethylsilyl)tridec-2-en-12-yne (38). To a solution of 5.24 g (12.7 mmol) enoate **37** in 50 mL of THF at −78 °C was added 34 mL (51 mmol) of a 1.5 M solution of DIBAL in toluene. The reaction was warmed to 0 °C and allowed to stir for 30 min. The reaction was quenched by careful addition of 200 mL of a 0.5 M solution of sodium potassium tartrate. Ether (50 mL) was added, and the mixture was stirred vigorously for 2 h. The layers were separated, and the aqueous layer was back extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 50%) as eluent to give 4.50 g (96%) of diol **38**: $[\alpha]^{23}_D$ −11.1 (c = 1); IR (neat) 3420, 2960, 2930, 2170, 1665(w), 1450, 1375, 1245, 1185, 975, 845, 760,

650 cm^{-1}; ^1H NMR 5.63 (m, 1H), 5.51 (dd, 1H, J = 15.6, 7.8), 4.08 (s(br), 2H), 3.40 (s, 3H), 3.36 (s, 3H), 3.30−3.40 (m, 2H), 3.14 (m, 1H), 2.43 (m, 1H), 2.32 (d, 1H, J = 6.9), 2.25 (dd, 1H, J = 16.8, 5.4), 2.14 (dd, 1H, J = 16.8, 6.6), 1.75 (m, 2H), 1.38−1.65 (m, 4H), 1.02 (d, 3H, J = 6.6), 1.00 (d, 3H, J = 6.3), 0.12 (s, 9H); ^{13}C NMR 138.67, 128.91, 106.16, 86.45, 79.91, 78.40, 74.45, 64.01, 58.12, 38.70, 36.79, 33.79, 29.42, 27.92, 22.24, 20.33, 0.57. Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.34. Found: C, 64.61; H, 10.32.

[2*R*,2(1*S*),3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2-(1,2-Dihydroxyethyl)-5-methoxy-3-methyl-6-[1-methoxy-3-methyl-6-(trimethylsilyl)hex-5-ynl]tetrahydropyran (39). To a slurry of 1.4 g of 4 Å powdered molecular sieves in 30 mL of CH_2Cl_2 at −25 °C was added 7.04 mL (23.9 mmol) of titanium tetraisopropoxide followed by addition of 4.30 mL (25.1 mmol) of L-(+)-diethyl tartrate over 2 min. The mixture was stirred for 10 min, and 11.95 mL (35.85 mmol) of a 3 M solution of *tert*-butyl hydroperoxide in isooctane was added. After 15 min, a solution of 4.43 g (11.95 mmol) of diol **38** in 30 mL of CH_2Cl_2 was added. The reaction was stirred vigorously for 30 min and was then placed in a freezer (−26 °C) for 18 h. The cold reaction mixture was poured into a solution of 50 g of tartaric acid and 35 g of ferric sulfate heptahydrate in 500 mL of water. CH_2Cl_2 (200 mL) was added, and the mixture was stirred vigorously for 2 h. The resulting two phase mixture was separated, and the aqueous layer was reextracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in 150 mL of THF and 100 mL of water, and 25 mL of a 15% solution of NaOH was added. The reaction was stirred for 1 h and was then quenched by addition of saturated NH_4Cl. The solvents were removed in vacuo, and the product was extracted with 3 portions of EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (30% to 80%) as eluent to give 3.64 g (79%) of diol **39** which crystallized on standing. The product could be recrystallized from hexanes to give rods (mp 84−85 °C) which were suitable for X-ray analysis: $[\alpha]^{23}_D$ +32.5 (c = 1); IR (neat) 3430, 2950, 2920, 2820, 2170, 1455, 1375, 1245, 1190, 1100, 840, 760, 695, 645 cm^{-1}; ^1H NMR 3.86 (dd, 1H, J = 11.1, 3.3), 3.63−3.71 (m, 2H), 3.57 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.36 (m, 1H), 3.26 (dd, 1H, J = 10.5, 2.7), 2.98 (dd, 1H, J = 9.3, 1.5), 2.87 (d, OH, J = 10.5), 2.64 (s(br), OH), 2.28 (dt, 1H, J = 12.3, 4.2), 2.21 (m, 2H), 1.50−1.76 (m, 4H), 1.07 (m, 1H), 0.99 (d, 3H, J = 6.6), 0.92 (d, 3H, J = 6.6), 0.15 (s, 9H); ^{13}C NMR 106.13, 87.08, 86.45, 81.37, 76.44, 74.44, 70.87, 63.09, 58.63, 56.59, 37.94, 36.23, 32.24, 29.59, 28.28. 20.25, 17.40, 0.57. Anal. Calcd for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91. Found: C, 62.17; H, 10.17.

[2*R*,2(1*S*),3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2-(1,2-Dihydroxyethyl)-5-methoxy-3-methyl-6-(1-methoxy-3-methylhex-5-ynyl)-tetrahydropyran (4). To a solution of 3.37 g (8.72 mmol) of silyl acetylene **39** in 50 mL of THF at 0 °C was added 13 mL (13 mmol) of a 1 M solution of TBAF in THF. The reaction was stirred for 20 min and quenched by addition of saturated NH_4Cl. The THF was removed in vacuo, and the product was extracted with EtOAc (2×). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (60% to 90%) as eluent to give 2.67 g (97%) of diol acetylene **4**. An anyltical sample was prepared by kugelrohr distillation (155 °C, 0.5mm) to give the hemihydrate: $[\alpha]^{23}_D$ +44.4 (c = 1.2); IR (neat) 3410, 3280, 2920, 2810, 2110, 1450, 1375, 1190, 1135, 1095, 960, 910, 875 cm^{-1}; ^1H NMR 3.78 (dd, 1H, J = 11.1, 4.2), 3.63 (m, 2H), 3.52 (m, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 3.18 (dd, 1H, J = 10.5, 3.0), 3.08 (d, OH, J = 9), 2.96 (dd, 1H, J = 9.3, 1.5), 2.24 (dt, 1H, J = 12.3, 4.2), 2.12 (m, 2H), 2.00 (t, 1H, J = 2.4), 1.78 (m, 1H), 1.66 (m, 1H), 1.57 (m, 1H), 1.46 (m, 1H), 1.03 (m, 1H), 0.96 (d, 1H, J = 6.6), 0.88 (d, 3H, J = 6.6); ^1C NMR 87.01, 83.51, 81.06, 76.47, 74.39, 71.13, 70.17, 63.06, 58.46, 56.60, 38.02, 35.69, 32.25, 29.59, 26.88, 20.23, 17.39. Anal. Calcd for $C_{17}H_{30}O_5 \cdot {}^1/_2H_2O$: C, 63.13; H, 9.66. Found: C, 61.10; H, 9.83.

[2*R*,2(1*S*),3*R*,5*S*,6*R*,6(1*S*,3*S*,5*E*)]-2-(1,2-Dihydroxyethyl)-5-methoxy-3-methyl-6-(6-iodo-3,5-dimethyl-1-methoxyhex-5-enyl)tetrahydropyran (43). To a solution of 4.19 mg (14.3 mmol) of Cp_2ZrCl_2 in 40 mL of CH_2Cl_2 was added 11.0 mL (115 mmol) of neat Me_3Al. The reaction was stirred for 15 min, and then a solution of 1.805 g (5.74 mmol) of diol **4** in 10 mL of CH_2Cl_2 was added via syringe pump over 1 h. The reaction was stirred for 4 days at room temperature. The reaction was cooled to −20 °C, and a solution of 5.25 g (20.7 mmol) of iodine in 20 mL of THF, to which had been added 50 μL of Me_3Al (to ensure dryness), was added via cannula. The reaction was stirred for 10 min and was then quenched at room temperature by slow addition of saturated K_2CO_3. When methane evolution had ceased, the reaction was diluted with water and saturated K_2CO_3 and ether was added, and the reaction was stirred vigorously for 5 h. The product was extracted with three portions of ethyl acetate, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate/hexanes (50% to 90%) as eluent to give 2.184 g of iodide **43** (83%): $[\alpha]^{23}_D$ +33.7 (c = 1.6); IR (neat) 3450, 2920, 1460, 1385, 1100 cm^{-1}; ^1H NMR 5.80 (s, 1H), 3.47−3.75 (m, 4H), 3.30 (s, 3H), 3.29 (s, 3H), 3.23−3.34 (m, 1H), 3.12 (dd, 1H, J = 10.5, 2.7), 3.02 (m, 2H), 2.90 (d, 1H, J = 9.3), 2.14−2.24 (m, 2H), 1.97 (dd, 1H, J = 13.5, 8.1), 1.74 (s, 3H), 1.35−1.62 (m, 4H), 0.99 (m, 1H), 0.86 (d, 3H, J = 6.6), 0.79 (d, 3H, J = 6.3); ^{13}C NMR 147.00, 86.79, 81.14, 76.46, 76.23, 74.41, 71.32, 63.13, 58.61, 56.54, 48.36, 37.99, 36.82, 32.34, 28.00, 24.15, 20.02, 17.53.

[2*R*,2(1*S*),3*R*,5*S*,6*R*,6(1*S*,3*S*,5*E*)]-2-[1,2-bis(*tert*-butyldimethylsilyloxy)ethyl]-5-methoxy-3-methyl-6-(6-iodo-3,5-dimethyl-1-methoxyhex-5-enyl)tetrahydropyran (44). To a solution of 413 mg (0.905 mmol) of diol **43** in 5 mL of DMF were added 370 mg (5.43 mmol) of imidazole, 409 mg (2.71 mmol) of TBSCl, and a catalytic amount of DMAP. The reaction was stirred for 4 h and was then diluted with water. The product was extracted into ether (2×), and the organic layers were washed with water. The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate/hexanes (10%) as eluent to give 605 mg of silyl ether **44** (98%): $[\alpha]^{23}_D$ +13.4 (c = 0.9); IR (neat) 2920, 1465, 1260, 1100, 840, 785 cm^{-1}; ^1H NMR 5.85 (s, 1H), 3.86 (dt, 1H, J = 1.5, 6.3), 3.67 (dd, 1H, J = 9.9, 5.7), 3.51-3.61 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.26−3.39 (m, 1H), 2.96 (m, 2H), 2.21-2.32 (m, 2H), 1.98 (dd, 1H, J = 13.8, 9.0), 1.81 (d, 3H, J = 0.9), 1.75 (m, 1H), 1.44−1.61 (m, 2H), 1.02 (m, 1H), 0.93 (d, 3H, J = 6.6), 0.89 (s, 9H), 0.88 (s, 9H), 0.85 (d, 3H, J = 6.6), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR 147.42, 86.04, 82.19, 76.77, 75.85, 75.41, 74.79, 65.29, 58.07, 56.39, 48.02, 38.81, 37.04, 31.56, 27.98, 26.35, 24.26, 20.33, 18.74, 18.54, 18.13, −4.04, −4.18, −4.82, −4.94; FABHRMS calcd for $C_{30}H_{61}IO_5Si_2$ + Na 707.3001; found 707.3002.

Ketone 45. To a solution of 150 mg (0.22 mmol) of vinyl iodide **44** in 4 mL of ether at −78 °C was added 232 μL (0.46 mmol) of a 1.98 M solution of t-BuLi in pentane. After 15 min, a mixture of 35 mg (0.24 mmol) of hexynylcopper,[39] and 88 μL (0.48 mmol) of HMPT in 1.5 mL of ether was added via cannula. The cuprate was stirred for 10 min and then warmed to −23 °C. A solution of 160 mg (0.18 mmol) of enone **3** in 3 mL of ether was added, followed immediately by 83 μL (0.65 mmol) of TMSCl. After 20 min, the enone had been completely consumed. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic extracts were washed with $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (5% to 10%) as eluent to give 97 mg (37%) of ketone **45** and 106 mg (38%) of the corresponding trimethylsilyl enol ether. The silyl enol ether was dissolved in 3 mL of THF and 1 mL of water, and 1 drop of 1 M HCl was added. After stirring for 45 min, the reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography as before gave 86 mg (33%) of enone (total 183 mg, 70%): $[\alpha]^{23}_D$ −5.0 (c = 0.5); IR (neat) 2920, 2850, 1735, 1720, 1690, 1450, 1365, 1245, 1150, 1095, 1000, 830, 775,

(39) Castro, C. E.; Gaughahn, E. G.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071−4078.

700 cm^{-1}; ^1H NMR 7.72 (t(obs), 4H, J = 7.2), 7.36 (m, 6H), 5.20 (d, 1H, J = 9.0), 5.15 (m, 1H), 5.04 (d, 1H, J = 9.6), 4.85 (s(br), 0.5H), 4.67 (s(br), 0.5H), 4.09 (d, 1H, J = 16.8), 3.97 (d(br), 1H, J = 11.4), 3.84 (m, 2H), 3.68 (dd, 1H, J = 10.5, 5.4), 3.55 (m, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 3.35 (m, 1H), 3.30 (s, 3H), 3.10 (m, 1H), 2.94 (m, 4H), 2.21 (m, 6H), 1.89 (m, 1H), 1.59, 1.43, 1.41, 1.33, 1.25, 1.05 (6s, 30H), 0.92 (d, 3H, J = 7.2), 0.88, 0.87 (2s, 18H), 0.77 (d, 3H, J = 5.4), 0.05, 0.03 (2s, 12H); ^{13}C NMR 208.38, 208.24, 171.33, 171.28, 156.03, 155.60, 138.40, 136.42, 136.33, 135.52, 134.77, 134.57, 130.74, 130.63, 129.76, 127.76, 127.71, 123.87, 99.68, 97.52, 86.18, 84.52, 82.57, 81.75, 80.97, 80.10, 76.64, 75.94, 75.40, 74.83, 68.75, 65.52, 65.30, 64.86, 58.12, 57.53, 56.33, 55.24, 54.22, 47.90, 45.10, 42.44, 41.37, 41.20, 38.97, 38.83, 37.93, 36.23, 35.40, 35.28, 34.05, 31.67, 31.13, 30.85, 28.79, 27.63, 27.44, 27.19, 26.43, 26.36, 25.38, 25.16, 24.09, 21.12, 21.01, 20.00, 19.77, 18.73, 18.52, 18.16, 16.87, 12.78, 12.58, 9.86, 9.78, −4.04, −4.16, −4.81, −4.93. Anal. Calcd for $C_{80}H_{135}NO_{15}Si$: C, 67.04; H, 9.35; N, 0.98. Found: C, 67.04; H, 9.28; N, 0.96.

Keto Diol 46. To a solution of 879 mg (0.61 mmol) of bis-TBS ether **45** in 15 mL of THF was added 1.84 mL (1.84 mmol) of a 1 M solution of TBAF in THF. After 2 h, the reaction was quenched with NH_4Cl, and the THF was removed in vacuo. The product was extracted into EtOAc, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (20% to 50%) as eluent to give 525 mg (71%) of diol **46**: $[\alpha]^{23}_D$ +1.5 (c = 1.3); IR (neat) 3450, 2920, 1740, 1675, 1365, 1245, 1195, 1150, 1095, 995, 950, 865, 820, 750, 700 cm^{-1}; ^1H NMR 7.70 (t(obs), 4H, J = 7.5), 7.35 (q(obs), 6H, J = 7.2), 5.20 (d, 1H, J = 9.0), 5.14 (m, 1H), 5.04 (d, 1H, J = 9.6), 4.854 (s(br), 0.5H), 4.68 (s(br), 0.5H), 4.08 (d, 1H, J = 16.8), 3.95 (m 1H), 3.84 (m, 2H), 3.66 (m,2H), 3.55 (m, 2H), 3.35 (s, 6H), 3.29 (s, 3H), 3.23 (dd, 1H, J = 10.2, 2.4), 3.09 (m, 1H), 2.60−3.00 (m, 6H), 2.05−2.30 (m, 4H), 1.88 (d, 1H, J = 12.3), 1.58 (s(br), 6H), 1.40 (s(br), 12H), 1.32 (s, 3H), 1.04 (s, 9H), 0.91 (d, 3H, J = 6.9), 0.89 (d, 3H, J = 7.5), 0.77 (d, 3H, J = 5.4); ^{13}C NMR 208.56, 208.42, 171.31, 156.04, 155.63, 137.93, 136.42, 136.33, 135.54, 134.78, 134.34, 130.79, 130.64, 129.75, 129.72, 127.76, 127.71, 124.30, 99.72, 97.44, 87.05, 84.51, 81.45, 80.78, 80.23, 80.14, 76.42, 75.94, 74.46, 70.86, 68.78, 65.57, 64.98, 63.11, 58.67, 57.56, 56.59, 55.24, 54.23, 48.52, 45.09, 42.46, 41.37, 41.22, 38.97, 37.94, 37.86, 36.24, 35.40, 35.22, 34.06, 32.31, 31.12, 30.85, 28.79, 27.78, 27.43, 27.19, 25.37, 25.15, 24.07, 21.09, 21.01, 19.78, 19.58, 17.42, 16.86, 12.83, 12.64, 9.89, 9.81. Anal. Calcd for $C_{68}H_{105}NO_{15}Si$: C, 67.80; H, 8.79; N, 1.16. Found: C, 67.68; H, 8.92; N, 1.11.

[2*R*,2(1*R*),3*R*,5*S*,6*R*,6(1*S*,3*S*)]-2-(Carbethoxyhydroxymethyl)-5-methoxy-3-methyl-6-(1-methoxy-3-methylhex-5-ynl)tetrahydropyran (47). To a solution of 75 mg (0.239 mmol) of diol **4** in 3 mL of CH_2Cl_2 were added 1.5 mL of saturated $NaHCO_3$ and a catalytic amount of KBr. The mixture was cooled to 0 °C, and a catalytic amount of 4-methoxy-2,2,6,6-tetramethylpiperidinyloxy free radical[40] was added. The mixture was stirred vigorously, and 340 μL (0.261 mmol) of a 0.77 M solution of NaOCl was added. After 30 min the reaction was quenched by addition of 1 mL of saturated $Na_2S_2O_3$ and excess saturated $NaHCO_3$, and the product was extracted with two portions of EtOAc. The aqueous layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

The crude hydroxy aldehyde was then dissolved in 5 mL of t-BuOH and 2 mL of 2-methylbutene. To this solution was added a freshly prepared mixture of 86 mg (0.95 mmol) of $NaClO_2$ and 57 mg (0.48 mmol) of NaH_2PO_4 in 2 mL of water. The reaction was stirred for 2 h. The reaction was diluted with EtOAc, the layers were separated, and the aqueous layer back extracted. The combined organic was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude acid was dissolved in ether and titrated with a solution of diazomethane in ether until nitrogen evolution ceased and the solution turned pale yellow. The solution was concentrated, and the residue was chromatographed on silica gel with EtOAc/hexanes (40% to 60%) as eluent to give 64 g (78%) of hydroxy ester **46**: ^1H NMR 4.32 (s(br), 1H), 3.75 (s, 3H), 3.58 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.30−3.40 (m, 1H), 3.23 (dd, 1H, J = 10.2, 2.4), 3.02 (dd, 1H, J = 9.3, 2.1), 2.25 (dt, 1H, J = 12.6, 3.9), 2.15 (dd, 2H, J = 5.7, 2.4), 2.01 (t, 1H, J = 2.4), 1.65−1.90 (m, 3H), 1.52 (m, 1H), 1.00 (d, 3H, J = 6.6), 0.92 (d, 3H, J = 6.6); ^{13}C NMR 172.57, 86.27, 83.62, 81.83, 76.29, 74.39, 72.22, 70.02, 57.78, 56.66, 52.65, 38.07, 35.30, 31.11, 29.49, 26.70, 20.34, 17.30. Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 63.18; H, 8.64.

Hydroxy Ester 50. To a solution of 585 mg (0.485 mmol) of diol **46** in 20 mL of CH_2Cl_2 was added 10 mL of saturated $NaHCO_3$ and a catalytic amount (ca. 5 mg) of KBr. The mixture was cooled to 0 °C, and a catalytic amount of 4-methoxy-2,2,6,6-tetramethylpiperidinyloxy free radical was added. The mixture was stirred vigorously, and 776 μL (0.56 mmol) of a 0.72 M solution of NaOCl was added over a period of 10 min. After 1 h, an additional aliquot (100 μL) of NaOCl was added to push the reaction to completion. After 20 min, the reaction was quenched by addition of 1 mL of saturated $Na_2S_2O_3$ and excess saturated $NaHCO_3$, and the product was extracted with two portions of ether. The aqueous layers were dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude hydroxy aldehyde was then dissolved in 10 mL of t-BuOH and 4 mL of 2-methylbutene. To this solution was added a freshly prepared mixture of 132 mg (1.46 mmol) of $NaClO_2$ and 87 mg (0.73 mmol) of NaH_2PO_4 in 4 mL of water. The reaction was stirred for 2 h. The reaction was diluted with ether and 1 M NaH_2PO_4 solution. The layers were separated, and the aqueous layer was back extracted with ether. The combined orgainc was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude acid was dissolved in ether and titrated with a solution of diazomethane in ether until nitrogen evolution ceased and the solution turned pale yellow. The solution was concentrated, and the residue was chromatographed on silica gel with EtOAc/hexanes (30% to 35%) as eluent to give 495 g (83%) of hydroxy ester **50**: $[\alpha]^{23}_D$ +0.7 (c = 0.5); IR (neat) 3420, 2930, 1735, 1695, 1320, 1250, 1100, 755 cm^{-1}; ^1H NMR 7.70 (m, 4H), 7.35 (m, 6H), 5.20 (d, 1H, J = 9.0), 5.15 (d, 1H, J = 6.0), 5.04 (d, 1H, J = 9.6), 4.84 (s(br), 0.5H), 4.67 (s(br), 0.5H), 4.31 (m, 1H), 4.08 (d, 1H, J = 16.8), 3.96 (d, 1H, J = 10.8), 3.84 (d, 1H, J = 16.5), 3.75 (s, 3H), 3.44−3.61 (m, 2H), 3.34 (s, 3H), 3.32 (s, 3H), 3.29 (s, 3H), 2.8−3.3 (m, 7H), 2.1−2.3 (m, 4H), 1.86 (m, 1H); ^{13}C NMR 208.57, 208.43, 172.79, 171.31, 156.03, 155.66, 138.13, 136.42, 136.33, 135.54, 135.37, 134.78, 134.51, 130.76, 130.64, 129.75, 127.76, 124.13, 99.70, 97.53, 86.11, 84.52, 82.23, 81.73, 80.93, 80.17, 80.14, 76.25, 75.94, 74.44, 72.33, 68.76, 65.56, 64.89, 57.88, 57.57, 56.59, 55.23, 54.22, 52.70, 48.35, 45.11, 42.44, 41.37, 41.22, 38.93, 38.08, 37.40, 36.23, 35.40, 35.23, 34.06, 31.29, 31.12, 30.84, 28.81, 27.67, 27.43, 25.38, 25.16, 21.11, 21.04, 19.77, 17.32, 16.78, 12.79, 12.60, 9.89, 9.79. Anal. Calcd for $C_{69}H_{105}NO_{16}Si$: C, 67.23; H, 8.59; N, 1.14. Found: C, 67.07; H, 8.56; N, 1.09.

Hydroxy Lactam 51. To a solution of 160 mg (0.130 mmol) of ester **50** in 4 mL of THF and 1 mL of water was added 14 mg (0.33 mmol) of $LiOH·H_2O$. The reaction was stirred for 5 h at room temperature and then quenched by addition of 1 M NaH_2PO_4. The product was extracted with ether (2×), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude acid was then dissolved in 5 mL of CH_2Cl_2 and at 0 °C were added 151 μL (1.30 mmol) of 2,6-lutidine and 205 μL (0.91 mmol) of TESOTf. After 1 h, the reaction was quenched with H_2O, diluted with a 0.2 M phosphate buffer (pH = 7.2), and extracted into ether. The organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in 5 mL of THF, cooled to 0 °C, and treated with 8 drops HOAc and 1.04 mL (1.04 mmol) of a 1 M solution of TBAF in THF. The reaction was stirred for 1 h and then quenched by addition of 0.2 M phosphate buffer (pH = 7.2). The amino acid was extracted with ether and washed twice with water and then with brine. The aqueous washings were sequentially back extracted with two further portions of ether, and the combined organic extracts were dried over freshly powdered Na_2SO_4, filtered, and concentrated in vacuo. The residual triethylsilanol was then

(40) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985** *50*, 1332−1334.

removed by azeotroping with methanol (5 × 50 mL), followed by toluene (2 × 50 mL).

The crude amino acid was then dissolved in 2 mL of CH_2Cl_2 and 180 μL (1.29 mmol) of NEt_3 was added. This solution was then added via syringe pump over a period of 5 h to a solution of 133 mg (0.52 mmol) of 2-chloro-1-methylpyridinium iodide and 10 μL (72 μmol) NEt_3 in 75 mL of CH_2Cl_2 at reflux. The reaction was then maintained at reflux for 12 h and then was cooled, and most of the CH_2Cl_2 was removed in vacuo. The product was partitioned with EtOAc and 1 M NaH_2PO_4 and washed with $NaHCO_3$. The aqueous layers were back extracted and the combined organic dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude pyridinium salt thus obtained was dissolved in 5 mL of EtOH and treated with 500 μL of NEt_3. After 5 h, the reaction was quenched with 1 M NaH_2PO_4 and extracted twice with EtOAc. The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (30% to 35%) as eluent to give 56.5 mg (40%) of hydroxy lactam **51**: $[\alpha]^{23}_D$ −7.3 (c = 0.5); IR (neat) 3430, 2930, 1720, 1640, 1450, 1375, 1255, 1195, 1140, 1100, 1010, 975, 870, 825, 745, 710 cm^{-1}; ^{1}H NMR 7.72 (m, 4H), 7.37 (m, 6H), 5.27 (d, 1H, J = 7.2), 5.14 (s, 1H), 4.86 (d, 1H, J = 8.7), 4.62 (m, 1H), 4.43 (m, 1H), 4.14 (m, 1H), 4.10 (d, 1H, J = 17.1), 3.96 (m, 1H), 3.91 (d, 1H, J = 17.1), 3.53 (m, 2H), 3.35 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 3.03−3.41 (m, 4H), 2.90 (d, 1H, J = 9.0), 2.81 (dd, 1H, J = 9.9, 3.9), 2.1−2.3 (m, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.05 (s, 9H), 0.90 (m, 9H); ^{13}C NMR 209.40, 172.75, 170.22, 139.13, 136.45, 135.57, 134.86, 134.34, 129.74, 129.67, 128.66, 127.76, 127.69, 123.70, 99.92, 97.85, 88.27, 84.64, 79.85, 76.51, 76.06, 75.25, 74.14, 70.52, 68.30, 68.17, 57.79, 56.91, 56.82, 54.60, 48.43, 43.87, 43.01, 41.47, 39.31, 38.41, 36.73, 35.12, 33.92, 31.22, 31.08, 27.44, 26.67, 25.17, 24.19, 23.29, 21.35, 21.20, 20.68, 19.77, 17.25, 15.99, 15.06, 9.66. Anal. Calcd for $C_{63}H_{93}NO_{13}Si$: C, 68.76; H, 8.52; N, 1.27. Found: C, 68.71; H, 8.64; N, 1.46.

Keto Lactam 52. To a solution of 80 mg (72.7 μmol) of hydroxy lactam **51** in 3 mL of CH_2Cl_2 was added 62 mg (0.15 mmol) of Dess−Martin periodinane. The reaction was stirred at room temperature for 3 h and diluted with ether, and saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ were added. The two-phase mixture was stirred vigorously until the organic layer was clear. The layers were separated, and the aqueous layer was back extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo, and the residue was chromatographed on silica gel with EtOAc/hexanes (20% to 25%) as eluent to give 65 mg (81%) of keto lactam **58**: $[\alpha]^{23}_D$ +9.3 (c = 0.9); IR (neat) 2920, 1740, 1720, 1640, 1440, 1370, 1100, 1000, 700 cm^{-1}; ^{1}H NMR 7.72 (m, 4H), 7.37 (m, 6H), 5.17 (s(br), 2H), 5.01* (d, 1H, J = 9.0), 4.93 (d, 1H, J = 9.0), 4.87 (d, 1H, J = 5.4), 4.34* (d, 1H, J = 13.0), 4.10 (d+m, 2H, J = 17.1), 3.94 (d, 1H, J = 17.1), 3.89* (d, 1H, J = 10.2), 3.70 (d, 1H, J = 10.2), 3.35−3.60 (m, 2H), 3.35, 3.31, 3.30, 3.27 (4s, 9H), 2.98−3.18 (m, 4H), 2.80 (t(br), 1H, J = 7.0), 2.58* (m, 1H), 2.33 (m, 1H), 2.10−2.23 (m, 3H), 1.80−1.97 (m, 6H), 1.65, 1.62, 1.57, 1.55, 1.48, 1.39, 1.36 (7s, 12H), 1.04 (s, 9H), 0.86−0.97 (m, 9H); ^{13}C NMR 209.35, 208.30*, 199.34, 197.83*, 169.25, 169.13*, 166.57, 165.68*, 138.63, 138.16*, 136.44, 136.36, 135.53*, 134.81, 133.17, 1311.60, 129.96, 129.76, 127.77, 127.70, 124.36*, 123.48*, 99.98*, 99.83*, 97.65, 97.00*, 88.52*, 85.15, 84.56, 84.48*, 81.26, 80.74*, 78.11*, 76.42, 75.99, 74.02, 73.87*, 69.13*, 69.02, 67.91, 67.71*, 57.79, 57.71*, 57.46, 57.01*, 56.85*, 56.65, 52.21, 48.68*, 47.72, 47.70*, 44.42, 43.70, 41.31, 40.27*, 39.71, 39.57*, 38.34, 37.68*, 36.68*, 26.61, 35.15, 34.91*, 34.65*, 33.88, 31.95, 31.23, 31.07, 30.11*, 27.44, 27.13, 26.82, 24.89*, 24.74, 24.07, 21.89, 21.39*, 21.23*, 20.81, 19.77, 17.38, 16.93, 15.50*, 15.29*, 15.13, 10.54. Anal. Calcd for $C_{63}H_{91}NO_{13}Si$: C, 68.88; H, 8.35; N, 1.28. Found: C, 68.60; H, 8.31; N, 1.18.

Alternative Route to Keto Lactam 52. To a solution of 101 mg (81.9 μmol) hydroxy ester **50** in 4 mL of CH_2Cl_2 was added 70 mg (0.17 mmol) of Dess−Martin periodinane. After 1 h, the reaction was diluted with ether, and saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ were added. The two-phase mixture was stirred vigorously until the organic layer was clear. The layers were separated, and the aqueous layer was back extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the keto ester which was used without further purification.

The keto ester was dissolved in 3 mL of THF and 1 mL of water, and 7 mg (0.17 mmol) of $LiOH\cdot H_2O$ was added. The reaction was stirred for 30 min and was then quenched with 1 M NaH_2PO_4. The acid was extracted into ether (2×), and the organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude keto acid was dissolved in 4 mL of CH_2Cl_2 and at 0 °C were added 95 μL (0.82 mmol) of 2,6-lutidine and 130 μL (0.57 mmol) of TESOTf. After 1 h, the reaction was quenched with H_2O, diluted with a 0.1 M phosphate buffer (pH = 7.2), and extracted into ether. The organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in 5 mL of THF, cooled to 0 °C, and treated with 8 drops HOAc and 655 μL (0.655 mmol) of a 1 M solution of TBAF in THF. The reaction was stirred for 1 h and then quenched by addition of 0.2 M phosphate buffer (pH = 7.2). The amino acid was extracted with ether and washed twice with water and then with brine. The aqueous washings were sequentially back extracted with ether, and the combined organic extracts were dried over freshly powdered Na_2SO_4, filtered, and concentrated in vacuo. The residual triethylsilanol was then removed by azeotroping with methanol (5 × 50 mL), followed by toluene (2 × 50 mL).

The crude amino acid was then dissolved in 2 mL of CH_2Cl_2, and 114 μL (0.82 mmol) of NEt_3 was added. This solution was then added via syringe pump over a period of 5 h to a solution of 84 mg (0.33 mmol) of 2-chloro-1-methylpyridinium iodide and 25 μL (0.18 mmol) of NEt_3 in 60 mL of CH_2Cl_2 at reflux. The reaction was then stirred for 1 h at reflux and was cooled, and then saturated $NaHCO_3$ was added. The layers were separated, and the organic layer was washed with brine. The aqueous layers were back extracted with EtOAc and the combined organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (20%) as eluent to give 47.3 mg (53%) of keto lactam **52**.

Keto Alcohol 53. To a solution of 269 mg (0.245 mmol) of diketone **52** in 10 mL of THF at −78 °C was added slowly 469 μL (0.281 mmol) of a 0.6 M solution of L-Selectride. The reaction was stirred for 30 min and was then quenched by addition of water and 435 mg (2.82 mmol) of $NaBO_3\cdot 4H_2O$. The mixture was stirred for 3 h, and the product was then extracted into ether (2×) and washed with brine. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (30% to 35%) as eluent to give 226 mg (84%) of alcohol **53**: $[\alpha]^{23}_D$ +4.8 (c = 1.2); IR (neat) 3510, 2940, 1750, 1645, 1465, 1380, 1200, 1100, 970, 750, 710 cm^{-1}; ^{1}H NMR 7.72 (m, 4H), 7.37 (m, 6H), 5.47* (d, 1H, J = 8.5), 5.37 (d, 1H, J = 9.3), 5.19* (s, 1H), 5.09 (d, 1H, J = 5.1), 5.04 (s, 1H), 4.99* (d, 1H, J = 9.6), 4.88 (d, 1H, J = 8.7), 4.34* (d, 1H, J = 13.5), 3.90−4.08 (m, 1H), 3.50−3.75 (m, 4H), 3.36*, 3.34, 3.33, 3.32, 3.31*, 3.28* (6s, 9H), 3.30−3.45 (m, 4H), 2.96−3.15 (m, 3H), 2.55 (m, 1H), 2.33 (m, 2H), 2.19 (m, 3H), 1.64*, 1.59, 1.57, 1.55, 1.53*, 1.35 (6s, 12H), 1.05 (s, 9H), 0.83−1.01 (m, 9H); ^{13}C NMR 199.38, 169.23, 166.54, 136.44, 136.36, 135.54, 134.82, 134.52, 131.24, 129.76, 129.69, 129.01, 127.77, 126.70, 124.78, 99.87, 99.42*, 98.24, 97.47*, 88.79*, 87.24, 84.62, 84.53*, 81.75, 80.92*, 79.97, 76.87, 76.32*, 76.04, 74.21, 73.89*, 68.27, 67.13*, 66.46*, 66.26, 65.78*, 65.47, 57.89, 57.67, 56.97*, 56.86*, 56.25, 52.55, 48.86*, 47.58, 43.93, 41.36, 41.19*, 39.58*, 38.91, 38.29, 37.74*, 36.65, 36.05, 35.18, 35.09, 33.96, 33.88, 32.00, 31.47, 31.25, 31.16, 31.10, 27.44, 26.08, 24.95, 24.81*, 24.14, 22.00, 21.88*, 21.45*, 21.06, 19.77, 18.01, 17.12, 16.76*, 15.65, 15.28*, 14.75, 10.80. Anal. Calcd for $C_{63}H_{93}O_{13}NSi$: C, 68.76; H, 8.52; N, 1.27. Found: C, 68.75; H, 8.31; N, 1.14.

Keto Iodide 54. To a solution of 62 mg (0.24 mmol) of iodine in 10 mL of toluene was added 77 mg (0.29 mmol) of triphenylphosphine. The mixture was stirred for 5 min and then 40 mg (0.59 mmol) of imidazole was added. After 5 min, a solution of 108 mg (98.1 μmol) of alcohol **53** in 4 mL of toluene was added. The reaction was then heated to 75 °C over a

period of 30 min, at which time the reaction appeared to be complete by TLC analysis. The reaction was cooled, and saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ were added. The product was extracted with hexanes, and the aqueous layer was back extracted with hexanes. The organic extracts were dried over $MgSO_4$, filtered, and concetrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 20%) as eluent to give 97 mg (83%) of iodide **54**: $[\alpha]^{23}_D$ +9.5 (c = 0.9); IR (neat) 2910, 1735, 1635, 1435, 1365, 1095, 1000, 965, 730, 700 cm^{-1}; ^1H NMR 7.72 (m, 4H), 7.37 (m, 6H), 5.33 (d, 1H, J = 8.1), 5.15 (s, 1H), 4.93 (m, 2H), 4.31 (m, 1.5H), 4.10 (d, 0.5H, J = 3.3), 3.95 (m, 2H), 3.83 (dd, 0.5H), J = 10.2, 3.6), 3.73 (m, 0.5H), 3.68 (d, 1H, J = 10.5), 3.18−3.55 (m, 4.5H), 3.36, 3.33, 3.32, 3.31, 3.28 (5s, 9H), 3.11 (m, 1H), 3.01 (d, 0.5H, J = 9.0), 2.68 (dt, 1H, J = 12.6, 3.0), 2.57 (m, 1H), 2.35 (m, 1.5H), 1.78−2.24 (m, 11H), 1.64, 1.60, 1.56, 1.53, 1.39, 1.36 (6s, 12H), 1.05 (s, 9H), 0.83−0.96 (m, 9H); ^{13}C NMR 199.26, 197.95, 169.28, 169.09, 166.50, 165.71, 136.89, 136.46, 136.37, 135.55, 135.49, 134.83, 131.46, 129.91, 129.77, 129.70, 127.78, 127.71, 124.38, 123.33, 99/90, 99.67, 97.25, 96.95, 88.63, 85.68, 84.59, 84.51, 81.48, 80.89, 78.87, 76.58, 76.33, 76.01, 74.29, 73.92, 67.97, 67.66, 67.16, 57.81, 57.71, 57.63, 57.33, 57.03, 56.86, 56.65, 52.20, 48.97, 47.63, 47.17, 47.07, 43.75, 39.59, 38.92, 38.83, 38.33, 37.73, 36.70, 36.61, 35.81, 35.16, 35.00, 33.91, 33.19, 31.36, 31.19, 31.08, 27.45, 27.31, 27.23, 27.05, 24.84, 24.57, 24.11, 23.51, 21.81, 21.56, 21.44, 21.11, 19.78, 17.31, 17.09, 16.80, 15.70, 15.19, 15.02, 10.68. Anal. Calcd for $C_{63}H_{92}O_{12}NSiI$: C, 62.52; H, 7.66; N, 1.16; I, 10.48. Found: C, 62.78; H, 7.95; N, 1.08; I, 10.25.

Iodo Enol Ether 2. To a solution of 191 mg (0.158 mmol) of iodide **54** in 10 mL of THF at −78 °C was added 1.26 mL (0.63 mmol) of a 0.5 M solution of KHMDS in toluene. The reaction was stirred for 30 min, and then 185 μL (1.11 mmol) of TESCl was added to the reddish solution. The color instantly dissipated, and after 30 min the reaction was quenched by addition of saturated $NaHCO_3$. The product was extracted with two portions of ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (10% to 20%) as eluent to give 155 mg (74%) of silylated enediol **2** and 50 mg (26%) of the starting ketone **54**; $[\alpha]^{23}_D$ −30.4 (c = 1.2); IR (neat) 1920, 1740, 1620, 1420, 1370, 1185, 1150, 1100, 1005, 870, 740, 700 cm^{-1}; ^1H NMR 7.73 (m, 4H), 7.38 (m, 6H), 5.42 (m, 2H), 4.92 (m, 2H), 4.41 (m, 1H), 3.75-4.00 (m, 6H) 3.55 (m, 2H), 3.36 (s, 3H), 3.33 (s, 6H), 3.12 (m, 2H), 2.88 (s(br), 1H), 2.68 (m, 1H), 2.13−2.29 (m, 3H), 2.02 (d, 1H, J = 9.9), 1.92 (d, 1H, J = 12.3), 1.62, 1.58, 1.56, 1.38 (4s, 12H), 1.32 (d, 3H, J = 7.2) 1.06 (s, 9H), 0.96 (t, 9H, J = 7.8), 0.89 (m, 6H), 0.70 (q, 6H, J = 8.1); ^{13}C NMR 169.62, 167.16, 145.43, 137.75, 136.44, 136.36, 135.56, 134.77, 131,86, 129.76, 129.72, 129.35, 129.31, 127.76, 127.72, 123.67, 99.69, 96.69, 84.60, 80.41, 78.19, 76.04, 75.40, 68.46, 67.78, 57.78, 57.13, 56.60, 51.37, 47.35, 46.73, 44.45, 40.38, 39.32, 38.52, 36.66, 35.86, 35.26, 34.02, 32.37, 31.42, 31.14, 30.13, 29.80, 27.76, 27.44, 26.92, 26.22, 23.89, 23.13, 22.05, 19.77, 19.54, 18.53, 15.07, 14.56, 10.99, 7.29, 5.72. Anal. Calcd for $C_{69}H_{106}O_{12}NSi_2I$: C, 62.56; H, 8.07; N, 1.06; I, 9.58. Found: C, 62.81; H, 8.21; N, 0.96; I, 9.41.

Aldol 55. In a round bottom flask outfitted with a condenser was placed 204 mg (2.12 mmol) of graphite. The graphite was heated under argon to 150 °C for 15 min, at which point an 80 mg (2.0 mmol) chip of freshly cut potassium was added, and the mixture was stirred at 150 °C for 15 min. To the cooled mixture was added via cannula a slurry of 204 mg (1.5 mmol) of freshly fused $ZnCl_2$ and 25 mg of AgOAc in 6 mL of THF. The reaction was heated to reflux for 30 min and then cooled to room temperature. To the reducing media was added via cannula a solution of 114.2 mg (28 μmol) of iodide **2** in 4 mL of THF. The reaction was allowed to stir for 1.5 h and was then filtered through a pad of Celite. The solids were washed with 100 mL of THF. Saturated NH_4Cl was added, and the THF removed *in vacuo*. The product was extracted into EtOAc, and the organic layer was dried over $MgSO_4$. The residue was chromatographed on silica gel with ethyl acetate/hexanes (15% to 25%) as eluent to give 66.3 mg (67%) of aldol **55**: $[\alpha]^{23}_D$ −30.4 (c = 0.21); IR (neat) 3450, 2930, 1745, 1700, 1625, 1430, 1105, 820, 745, 705 cm^{-1}; ^1H NMR 7.72 (m, 4H), 7.38 (m, 6H), 5.69 (m, 1H), 5.30 (s(br), 1H), 4.48−5.04 (m, 6H), 4.01 (m, 1H), 3.83 (d, 1H, J = 8.1), 3.20−3.70 (m, 4H), 3.42 (s, 3H), 3.34 (s, 3H), 3.32 (s, 3H), 3.11 (m, 1H), 2.89 (d, 1H, J = 17.1), 2.76 (m, 1H), 2.46 (m, 1H), 2.22 (m, 6H), 1.93 (d, 1H, J = 12.6), 1.71, 1.61 (2s, 6H), 1.28 (d(br), 3H, J = 7.2), 1.05 (s, 9H, J = 7.8), 0.95 (t, 9H, J = 7.8), 0.78 (d, 3H, J = 6.6), 0.68 (q, 6H, J = 7.8); ^{13}C NMR 212.30, 169.81, 167.02, 144.13, 141.16, 136.36, 135.53, 134.79, 132.08, 129.77, 127.77, 127.71, 123.46, 116.63, 84.52, 80.14, 75.93, 74.72, 70.34, 58.26, 57.79, 56.64, 53.67, 51.90, 45.98, 44.50, 43.67, 40.94, 37.91, 36.55, 35.18, 34.48, 33.88, 32.36, 31.06, 30.13, 28.16, 27.81, 27.44, 26.28, 23.12, 22.05, 20.47, 19.77, 19.54, 17.15, 15.00, 14.99, 9.99, 7.26, 5.62; FABHRMS calcd for $C_{66}H_{101}NO_{11}Si_2$ + Na 1162.6810; found 1162.6765.

FK-506 (1). To a solution of 23.5 mg (20.6 μmol) of enol ether **55** in 2 mL of CH_2Cl_2 at −45 °C was added 482 μL (22.7 μmol) of a 0.047 M solution of dimethyldioxirane in acetone. The reaction was warmed to −25 °C for 1 h and then to 0 °C for 1 h. The solvents were removed *in vacuo*, and the residue was chromatographed on silica gel with ethyl acetate/hexanes (10% to 40%) as eluent to give 13.5 mg (57%) of oxidized products **56** and 10.0 mg (43%) of starting enol ether **55**. Recycling of the starting material provided a total of 23.5 mg of oxidation product after two recycles.

The crude oxidation product was dissolved in 2.5 mL of MeCN in a Nalgene flask, and 0.72 mL of 40% HF was added (final 9% HF/MeCN). The reaction was stirred for 6 h. The reaction was carefully quenched into excess saturated $NaHCO_3$ and extracted with several portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate/hexanes (50%) followed by MeOH/CH_2Cl_2 (2%) as eluents to give 4.1 mg (25%) of FK-506 (**1**) as a white solid which showed identical spectral properties to a natural sample of FK-506: $[\alpha]^{23}_D$ −81.5 (c = 0.27), TLC R_f = 0.6 (80% EtOAc/20% hexanes); ^{13}C NMR 212.74, 212.61, 195.97, 168.96, 168.69, 164.62, 139.84, 138.96, 135.53, 135.32, 132.41, 131.75, 129.64, 122.65, 122.41, 116.69, 97.02, 84.14, 77.84, 75.15, 73.62, 73.55, 72.79, 72.19, 70.01, 68.91, 56.98, 56.60, 56.31, 52.90, 52.73, 48.55, 48.39, 43.85, 43.16, 40.41, 39.83, 39.25, 35.58, 35.44, 35.12, 34.87, 34.73, 34.57, 33.62, 32.90, 32.70, 32.56, 31.17, 30.62, 29.70, 32.56, 31.17, 30.62, 29.70, 27.68, 26.22, 26.01, 24.57, 24.53, 21.14, 20.85, 20.44, 19.41, 16.26, 16.01, 15.77, 14.26, 14.15, 9.82, 9.49.

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