certainly be extended to any number of acyclic molecules that have derivatizable functional groups at chiral centers by empirical comparisons of unknowns to simple synthetic models. We have shown, however, that exciton-split CD spectra are governed by a few straightforward principles. Analysis and interpretation is possible whenever the mutual orientation between chromophores can be determined. The detailed interpretations that have been presented in these two papers[1] have elucidated a number of exciton interactions associated with various conformations and configurations that can serve as models in future studies of this type.

Our approach to the conformational analysis of acyclic sugar derivatives benefited from having a large number of configurationally related examples. A process of graphic analysis to determine interdependencies between coupling constants or other conformationally dependent data was introduced. By this approach, we were able to demonstrate the existence of a minor conformation having a 1,3-parallel interaction between oxygen atoms, contradicting earlier generalizations that excluded such a conformation from consideration. Recent reports have demonstrated that 1,3-parallel interactions between oxygen atoms can be stabilized by hydrogen bonds between hydroxyl groups.[35,36] Studies presented here indicate that $\pi-\pi$ stacking interactions can also offer some degree of stabilization to conformations with 1,3-parallel interactions between oxygen atoms. The dependence of exciton coupling upon interchromophoric distance makes consideration of these previously unexpected conformations particularly important for CD spectral analysis.

Experimental Section

^{1}H NMR spectra were recorded on a Brucker WM250 operated at 250 MHz. Conformational analysis by NMR was carried out in CD_3CN in order to corroborate findings with CD spectra. Vicinal coupling constants were determined by first-order analysis. Other NMR spectra were recorded in $CDCl_3$ or CD_3OD. UV measurements (acetonitrile) were performed on a Perkin-Elmer 320 UV spectrophotometer. CD spectra (acetonitrile) were recorded from 420-220 nm on a JASCO 500A spectropolarimeter driven by a JASCO DP500N data processor (1-cm quartz cell; ambient temperature; sensitivity 2 mdeg/cm; all spectra normalized to 10 μM for comparison purposes).

Prior to UV and CD measurements, all samples were purified by HPLC (EtOAc-hexane 3:7; 5 μm YMC SiO_2 gel; 2 mL/min; 311 nm UV detection). UV measurements were performed on 5-15 μM acetonitrile solutions, the concentrations of which were determined on the basis of the approximate extinction coefficient: anthroate monocinnamates $\epsilon_{311nm} = 28\,400$.

General Procedure. The sugar derivatives were treated with 1.1 equiv of 9-anthroyl chloride in dry pyridine (1-2 mL) with a small amount of DMAP (acylation catalyst).[37] After being stirred overnight under N_2, the reaction mixtures were frozen (to prevent bumping), and pyridine was removed in vacuo (1 mmHg) upon warming. Crude reaction mixtures was purified directly without workup by flash chromatography[38] ($MeOH/CH_2Cl_2$ mixtures). Subsequent treatment with excess *p*-methoxycinnamoyl chloride in a similar manner afforded the mixed anthroate cinnamate esters.

(6*S*)-(6-$^2H_1$)-1-Deoxy-D-galactitol (5). (6*S*)-(6-$^2H_1$)-D-Galactose[7a] (**4**, 100 mg) was refluxed in anhydrous hydrazine (4 mL) under argon for 48 h as previously reported for undeuterated D-galactose.[1] The reaction mixture was then frozen under argon and the hydrazine was removed under high vacuum. NMR of the crude residue indicated a mixture of desired pentitol (50%) together with 1,2-dideoxyhexitol and hex-1-enitol products. Flash chromatography ($MeOH/CH_2Cl_2$ 3:17) afforded pure **5** (32 mg, 35%). This was derivatized to **1** by general procedures as previously reported for undeuterated galactitol.[1] ^{1}H NMR (CD_3OD) (**5**): δ 4.05 (dq, 2.0, 6.6 Hz, 1 H, H-2), 3.89 (dd, 1.7, 6.2 Hz, 1 H, H-5), 3.64 (d, 6.2 Hz, 1 H, H-6R), 3.63 (dd, 1.7, 8.8 Hz, 1 H, H-4), 3.43 (dd, 2.0, 8.8 Hz, 1 H, H-3), 1.23 (d, 6.6 Hz, 3 H, Me).

(6*S*)-(6-$^2H_1$)-1-Deoxy-D-glucitol (7). (6*S*)-(6-$^2H_1$)-D-Glucose[7b] (**6**) was subjected to hydrazynolysis and hydrogenation conditions as previously described, after which a portion of the mixture was purified by flash chromatography ($MeOH/CH_2Cl_2$: gradient from 12:88 to 15:85) to give **7**. This was derivatized to **2** by general procedures as previously reported.[1] ^{1}H NMR (CD_3OD) (**7**): δ 3.86 (dq, 1 H, H-2), 3.68 (m, 1 H, H-5), 3.61 (dd, 5.2, 10.5 Hz, 1 H, H-6R), 3.57-3.53 (m, 2 H, H-3, H-4), 1.18 (d, 6.4 Hz, 3 H, Me). By comparison to the NMR of undeuterated 1-deoxyglucitol, H-6S can be assigned to the signal at 3.78 ppm (dd, 3.0, 10.5 Hz).

Note Added in Proof. Prochiral aryloxymethylene protons have also been assigned in a related CD and NMR study of glycerol dibenzoates: Uzawa, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1990**, *55*, 116-122.

Acknowledgment. These studies have been supported by NIH Grant GM 34509.

Supplementary Material Available: Preparations and figures showing complete spectral data for all intermediates and peracylated derivatives (14 pages). Ordering information is given on any current masthead page.

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Total Synthesis of FK506 and an FKBP Probe Reagent, (C_8,C_9-$^{13}C_2$)-FK506

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Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received December 12, 1989*

Abstract: Asymmetric syntheses of FK506 and (C_8,C_9-$^{13}C_2$)-FK506 are reported. The latter compound was designed to facilitate an investigation of the interactions between FK506 and its receptor, the recently discovered immunophilin, FKBP. The syntheses involved the preparation of intermediates **7-9** in nonracemic form; the key coupling reactions included a Cram-selective addition of the vinyl Grignard reagent derived from bromide **9** to aldehyde **8** and the addition of the lithioanion of phosphonamide **7** to aldehyde **51**, followed by thermal elimination. Dithiane **65** was then hydrolyzed, and glycolic ester **6** (or **6***) was added via an aldol reaction that allowed the introduction of ^{13}C labels at C_8 and C_9. Elaboration to FK506 proceeded via a Mukaiyama lactamization reaction and a selective deprotection/oxidation sequence, the efficiency of which was critically dependent upon the order of protecting group removal.

The understanding of signaling processes in the T cell that lead to transcriptional regulation of the lymphokine gene locus is a central focus of current immunological research.[1] The natural products FK506 (**1**)[2] and cyclosporin A (CsA) (**3**)[3] selectively and

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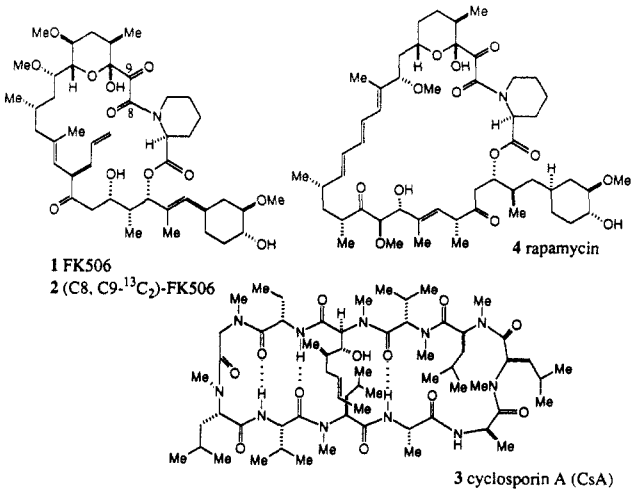
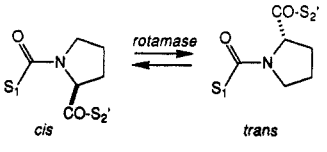
Chart I



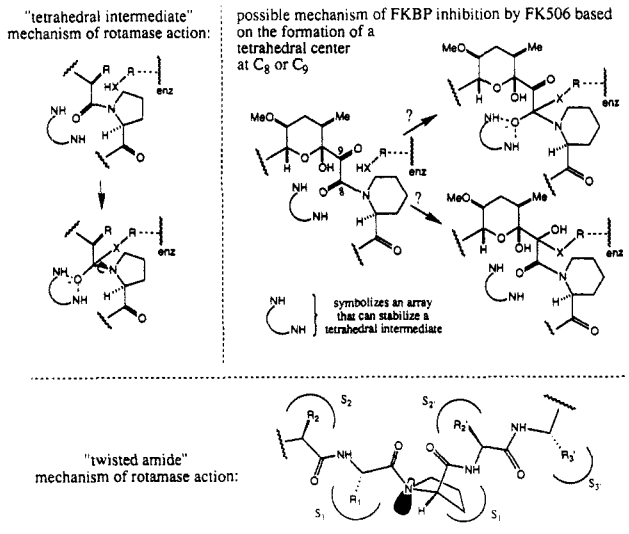
potently inhibit the expression of early T cell activation genes (interleukins-2, -3, and -4, granulocyte-macrophage colony stimulating factor, γ-interferon),[4] apparently by modulating the activity of transcriptional regulators such as nuclear factor of activated T cells (NF-AT).[5] Hence, these compounds have enormous potential as research tools for discerning the events that lead to T cell activation. A remarkable finding is that the binding proteins for CsA and FK506, cyclophilin[6] and FKBP,[7,8] respectively,



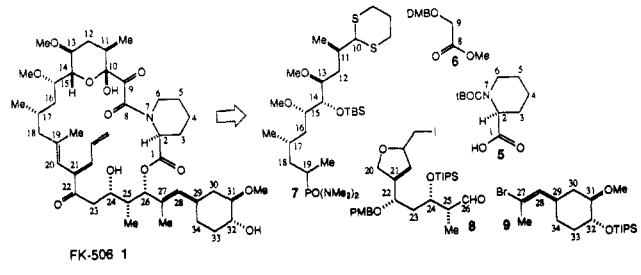
(1)

function as peptidyl-prolyl cis–trans isomerases (rotamases, eq 1), which are selectively and potently inhibited by their respective ligands. Furthermore, the rotamase inhibition is highly selective: FK506 does not inhibit the rotamase activity of cyclophilin and CsA does not inhibit FKBP (at <5 μM drug).[7,9] This information, together with recent reports of related proteins that have been implicated in signaling pathways,[10,11] led us to propose that these proteins, termed immunophilins, are involved in signaling processes leading to T cell activation.[7] A logical outgrowth of this hypothesis is the rational design of immunosuppressive agents, for use in the treatment of autoimmune disorders and the prevention of graft rejection, by targeted binding to immunophilins[12] or perhaps even

Chart II



Scheme I



by inhibition of their rotamase activity.[13] Vigorous research in this area has followed the announcement of the apparently safe and extraordinarily effective use of FK506 for the prevention of organ rejection following liver, kidney, and pancreas transplantation in humans.[14,15]

The ability to catalyze the interconversion of cis–trans proline amide rotamers implies that these enzymes recognize proline-containing epitopes and suggests that recognition involves either an enzyme-prolyl tetrahedral intermediate (Chart II, "tetrahedral intermediate" mechanism) or a twisted prolyl amide ("twisted amide" mechanism). Either species would provide an explanation for the catalytic properties of the immunophilins, as the loss of amide resonance should lower the activation barrier to rotamerization. The molecular recognition of immunophilins can be achieved by substrates that include proteins, natural products, synthetic peptides, and nonnatural small molecules.[16] For example, cyclophilin catalyzes the refolding of the protein substrate, RNase A.[17] The immunosuppressant rapamycin (**4**) (Chart I) binds to[7] and inhibits the rotamase activity of FKBP.[16] Recently, we outlined a strategy for the design of ligands to the CsA receptor, cyclophilin.[18] In order to apply this strategy to the FK506 receptor, FKBP, and to further illuminate the factors responsible for the molecular recognition of FKBP by FK506, we have undertaken the asymmetric total synthesis of several new probe reagents based on the FK506 structure. In this article, we describe a practical synthesis of FK506[19,20] and a double ^{13}C-labeled

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analogue, (C_8,C_9-$^{13}C_2$)-FK506 (**2**).

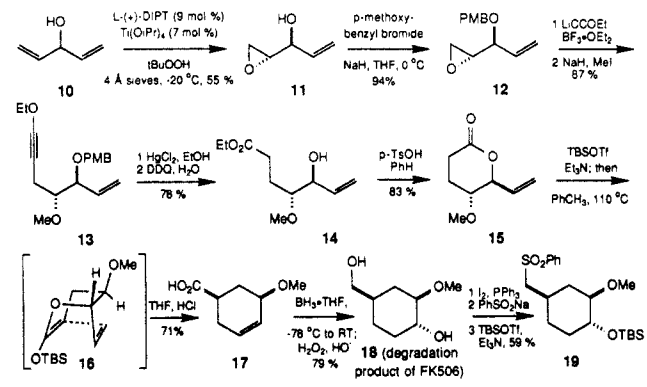
The rationale behind the choice of **2** as a target molecule for synthetic efforts is outlined in Chart II. The pipecolinyl (homoprolinyl) moiety in FK506 is flanked by an α-keto (and β-hemiketal) group that should result in increased electrophilicity of the two carbonyl carbons. Thus, one possibility is that the inhibitory properties of FK506 result from the formation of a stabilized tetrahedral intermediate in the FKBP enzyme active site. This intermediate would derive from an addition reaction of FK506 with a nucleophilic residue on the drug or enzyme or by a water molecule. We felt that the C_8 and C_9 carbonyl carbons represented potential target sites for the putative nucleophile. The amide bond of FK506 might serve as a mimic of a peptidyl-prolyl amide linkage in an endogenous substrate. Consistent with this suggestion is the isolation from *S. tsukubaensis* of FR900525, which is identical with FK506 except that the pipecolinyl amino acid is replaced by proline.[21] Reaction of an enzyme nucleophile by covalent bond formation with an electrophilic carbon that is α to a carbonyl function finds precedent in the crystallographically characterized complex of a chloromethyl ketone peptide inhibitor with the cysteine protease, papain.[22]

The ^{13}C-labeled analogue **2** was chosen as a probe reagent for use in NMR studies of the FKBP/FK506 complex in order to determine, inter alia, the tendency of the C_8 and C_9 trigonal carbons to convert to tetrahedral centers in water and in the presence of FKBP. The molecular cloning and overexpression of the human FKBP complementary DNA[7,23] by the expression cassette polymerase chain reaction (ECPCR) method[24] has provided the multimilligram quantities of human rFKBP required for these and other studies. Studies of the labeled drug/receptor complex that identify the mode of binding are described in a separate report.[25]

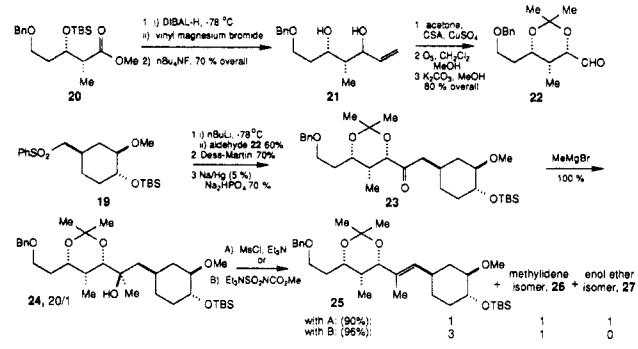
Design of the Synthetic Plan. The convergent synthesis of **1** and **2** entailed the synthesis of fragments **5–9**, followed by their sequential coupling. Elements of symmetry were considered in making the disconnections, so that the benefits of the two-directional chain synthesis strategy could be realized.[26]

Practical methods for the resolution of the C_1–N_7 pipecolinate portion **5** were available at the outset of this work.[27] The preparation of the C_8–C_9 fragment **6** was accomplished via a procedure that resulted in the preparation of FK506 with the requisite ^{13}C labels. A synthesis of the C_{10}–C_{19} fragment **7**[19j] was carried out from arabitol by the application of the class C two-directional chain synthesis strategy,[25] while the formation of the C_{20}–C_{26} chain **8**[19k] and the C_{27}–C_{34} cyclohexyl fragment **9**[19g,o] was accomplished through the use of catalytic asymmetric induction. A description of the synthesis and coupling of these fragments begins with the cyclohexyl moiety.

Scheme II



Scheme III



Catalytic Asymmetric Synthesis of the Cyclohexyl Moiety via a Group and Face Selective Addition Reaction. The group and face selective addition of a nonracemic reagent to an achiral substrate can be a powerful technique in asymmetric synthesis.[28] We have used this method in a synthesis of the cyclohexyl portion of FK506, which delivers the fragment in a form amenable to subsequent formation of the C_{27}–C_{28} olefin.[19g,o] Catalytic asymmetric epoxidation of divinylcarbinol **10** proceeded smoothly on as large as a 25-g scale. This procedure involves the coupling of a kinetic resolution to the initial asymmetric synthesis and provides the product with extremely high enantiomeric purity. A mathematical model of this process has been presented elsewhere.[27] Product isolation was simplified, and the isolated yield was improved by taking advantage of the catalytic asymmetric epoxidation procedure (Scheme II).[29]

Protection of the alcohol as the *p*-methoxybenzyl (PMB) ether could be effected in 94% yield if *p*-methoxybenzyl bromide was used as the electrophile. Care must be taken in order to prevent the formation of a product resulting from a Payne rearrangement. For example, a 1:1 mixture of **12** and the PMB ether of the rearranged compound was produced when the reaction was conducted with *p*-methoxybenzyl chloride at room temperature. Although the regioselective epoxide ring opening proceeded with only limited success with acetic acid derived anions,[30] the anion of ethoxyacetylene, in the presence of boron trifluoride etherate, reacted with **12** to afford an unstable alcohol.[31] Subjection of

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the crude reaction mixture to exhaustive methylation conditions allowed recovery of the alkynyl ether **13** in excellent overall yield. Treatment of **13** with a variety of protic acids in a number of different solvent systems resulted in the formation of a γ-lactone, indicating that demethylation had occurred. Along with this lactone, varying amounts of the desired acyclic ester were also recovered. The use of catalytic mercury(II) chloride in anhydrous ethanol furnished the most promising result. When these conditions were followed by removal of the *p*-methoxybenzyl moiety using DDQ,[32] the δ-hydroxy ester **14** was isolated in good overall yield. Acid-catalyzed lactonization of **14** afforded the lactone **15**.

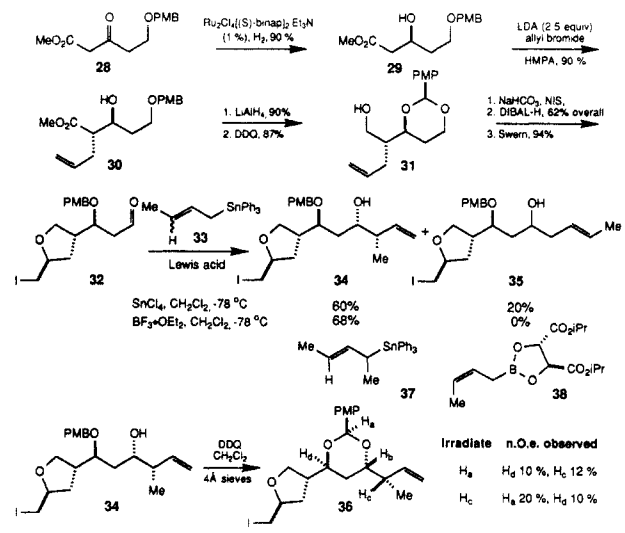
When lactone **15** was subjected to the standard conditions for the Ireland–Claisen rearrangement,[33] the only isolable product was the 1,3-diene derived from homoallylic methoxyl elimination. After some experimentation, we found that formation of the ketene acetal intermediate was best affected by using *tert*-butyldimethylsilyl triflate and triethylamine in methylene chloride. Prolonged heating of the ketene acetal formed under these conditions, followed by hydrolysis of the resultant silyl ester, resulted in the formation of the desired acid **17** (mp 57–59 °C) in 71% overall yield from lactone **15**.

Treatment of the acid **17** with a large excess of borane/THF at low temperature, followed by gradual warming of the reaction mixture to ambient temperature and oxidation, gave rise to the desired diol **18**[34] in 79% yield after chromatography. An uncharacterized minor isomer was also isolated from the product mixture in about 6% yield. Comparison of the ^{1}H NMR data reported for a degradation product of FK506 that corresponds to **18** with that of synthetic **18** confirmed that the two samples were identical.[2b] Subsequent conversion of **18** into the silyloxy sulfone **19** was accomplished without incident.

Synthesis of the C_{27}–C_{28} Trisubstituted Olefin. With a secure route to the C_{28}–C_{34} cyclohexyl portion **19** of FK506 in hand, a procedure was sought whereby the C_{27}–C_{28} trisubstituted olefin could be introduced. An initial solution to this problem was achieved in collaboration with Sam Danishefsky and co-workers at Yale University (Scheme III).[19k]

A C_{22}–C_{26} coupling partner **22** was prepared from ester **20**[35] in five steps. Sequential treatment of **20** with DIBAL-H, vinylmagnesium bromide, and Bu_4NF provided **21** in a one-pot operation.[36] The mixture of products (Cram(α)/anti-Cram(β), 3–4:1) was subjected to acetonide forming conditions. An ozonolysis reaction was followed by in situ equilibration (ancillary stereocontrol)[37] to provide the aldehyde **22** as a single diastereomer (>12:1). Coupling of **22** with the α-lithiated sulfone derived from **19** was followed by oxidation and desulfonylation to provide the ketone **23** in good yield. Addition of methylmagnesium bromide to the ketone **23** proceeded in excellent yield and with high diastereofacial selectivity to provide the tertiary alcohol **24**. The isomer depicted is that derived from a chelation-controlled addition, although this stereochemical outcome was not proven. Subjection of **24** to conditions of mesylate formation directly provided the desired olefin **25** but as a (1:1:1) mixture with two other olefin isomers (**26**, **27**). Equilibration of the isomers was attempted using SO_2, but this proved unsuccessful.[38] When the tertiary alcohol **24** was subjected to olefination conditions using the Burgess reagent, a more promising result was obtained.[39] Under these conditions only two of the previously observed isomers were obtained in a 3:1 ratio (**25**/**26**) favoring the desired trisubstituted olefin **25**.

Scheme IV



A Convergent Route to the C_{20}–C_{34} Fragment. In order to optimize the convergency of the FK506 synthesis, we focussed next on the preparation of a C_{20}–C_{25} coupling partner.[19k] These studies began with the readily available β-keto ester **28** (Scheme IV).[40] Catalytic reduction following the conditions of Noyori provided the β-hydroxy ester **29** in good yield and with excellent enantioselectivity (ee > 95% as determined by conversion of the alcohol to the corresponding Mosher ester).[41] This single stereocenter was then used to set four new stereocenters via substrate-controlled reactions.

Frater–Seebach alkylation of **29** provided the *anti*-α-allyl-β-hydroxy ester **30** in good yield.[42] Lithium aluminum hydride reduction to the diol was followed by acetal formation following the conditions of Oikawa to provide **31**.[43] The allyl group was conveniently masked as the iodo ether (4.75/1 mixture of iodomethyl diastereomers, unassigned);[44] DIBAL-H reduction then gave the primary alcohol, which could be oxidized to aldehyde **26** with the Dess–Martin periodinane (DMP) reagent.[45] Swern oxidation proved equally effective for this transformation.

Stereospecific introduction of the C_{24} and C_{25} stereocenters was attempted by using the conditions of Keck.[46] When aldehyde

(31) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. See, also: Danishefsky, S. J.; Kitahara, T.; Tsai, T.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1671.

(32) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(33) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Danishefsky, S. J.; Funk, R. L.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 6889.

(34) For a related hydroboration, see: Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.

(35) Ester **20** was prepared by an Evans aldol reaction with 3-(benzyloxy)propanal, followed by methanolysis of the chiral auxiliary (MeOMgBr) and silylation of the secondary alcohol (TBSOTf, Et_3N). See: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(36) For some related transformations, see: (a) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, T. E. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (b) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905. (c) Comins, D. L.; Herrick, J. J. *Tetrahedron Lett.* **1984**, *25*, 1321.

(37) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686.

(38) Greenlee, M. L. Ph.D. Thesis, Harvard University, June 1981.

(39) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(40) Compound **22** was readily prepared via an alkylation of the dianion of methyl acetoacetate with [(*p*-methoxybenzyl)oxy]methyl chloride, which was itself derived from the methylthiomethyl derivative of *p*-methoxybenzyl alcohol by treatment with sulfuryl chloride. See: (a) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269. (b) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.

(41) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(42) (a) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269. (b) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109. We thank Christopher S. Poss of these laboratories for his assistance with this reaction.

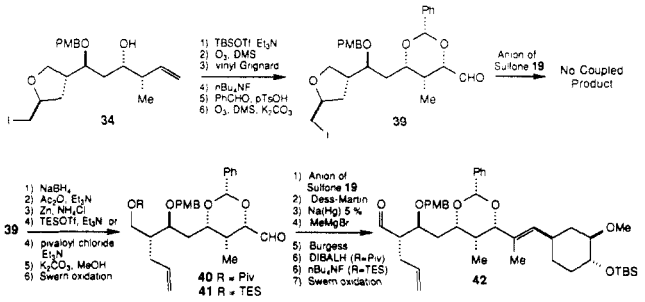
(43) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037.

(44) The major iodomethyl isomer could easily be isolated by sg chromatography and was used in initial studies to simplify spectroscopic analysis of intermediates. The isomer depicted as **32** was arbitrarily assigned as the major isomer. In later experiments, the iodo ether isomers were carried on as a mixture.

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

(46) (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265, 1879. (c) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (d) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. E. *Tetrahedron Lett.* **1984**, *25*, 3927. (e) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239 and references therein.

Scheme V



32 and stannane **33** (1:1 cis/trans, mp 49–50 °C) were combined by using a number of different Lewis acids, addition protocols, and precomplexation protocols, only one set of conditions was found, initially, to give the desired alcohol **34** as the major product. $TiCl_4$ caused deprotection of the *p*-methoxybenzyl ether, while other Lewis acids ($MgBr_2$, for example) gave low diastereofacial selectivity in reactions that proceeded slowly. When a slight excess of $SnCl_4$ was added to a mixture of aldehyde and stannane at −78 °C, there was obtained a 60% yield of the desired addition product **34**. This reaction also produced the isomeric addition product **35** in 20% yield. After sg chromatography, it was ascertained that the major product formed was indeed the desired isomer **34** via spectroscopic methods. The stereochemical assignment follows from the NOE data obtained from the derived acetal **36** as well as from analysis of spin–spin coupling constants in the ^1H NMR spectra of derivatives **39**, **40**, and **41** (Scheme V) relative to acetonide **22** (Scheme III).

Although use of the tin(IV) chloride mediated addition provided material for exploratory chemistry, the reaction was capricious and less selective when performed on a large scale.[47] To alleviate this bottleneck, an alternative solution was sought. Attempts to utilize the α-methylcrotylstannane **37** were not successful.[48,49] Addition occurred readily, but in no case was the reaction facially selective. Utilization of Roush's chiral boronate **38**[50] was also attempted, but the reaction proceeded with only 3:2 facial selectivity as determined by ^1H NMR analysis following reductive cleavage of the iodo ether.

Reetz has reported that the use of boron trifluoride etherate in allylsilane additions to β-alkoxy aldehydes provides, as the major isomer, the same product obtained in a "chelation-controlled" addition reaction.[51] While crotylsilanes are known to undergo threo-selective addition, it was hoped that using boron trifluoride etherate with the erythro-selective crotylstannane **33** might also lead to a "chelation-controlled" addition. In the event, when a precooled solution of stannane **33** was added to a precomplexed mixture of aldehyde **32** and boron trifluoride etherate at −78 °C, the desired alcohol **34** was obtained in 68% yield as a single iodomethyl diastereomer (stereochemistry was not assigned and is arbitrarily rendered). Under these conditions, the reaction produced none of the internal olefin isomer **35**.

With a route to multigram quantities of **34** firmly in hand, elaboration to the coupling partner **39** proceeded as described in Scheme V. Under the usual conditions for the Julia coupling, it was not possible to combine aldehyde **39** with the sulfone **19**, due to the presence of the iodomethyl group (Scheme V). Circumvention of this problem by a rather lengthy detour was possible: unmasking of the C_{21} allyl side chain and subsequent protection/deprotection chemistry provided the aldehydes **40** and **41**, each of which underwent smooth coupling with the sulfone **19** to provide products that were elaborated to compound **42**, containing the desired (*E*)-C_{27}–C_{28} olefin.

A route that could provide material suitable for exploration of the C_{19}–C_{20} olefin formation was now available. We soon determined, however, that the above method was not satisfactory due to several shortcomings. The lengthy sequence prevented gram quantities of intermediates to be efficiently processed. In addition, the differentiation of the C_{24} and C_{26} hydroxyl groups could not be achieved. Accordingly, an alternative method for the synthesis of the C_{20}–C_{34} fragment was sought.

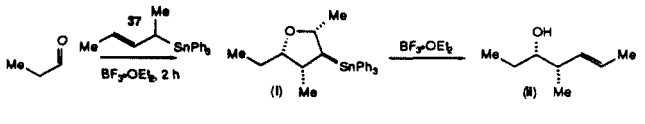
A Second Solution to the Synthesis of the C_{27}–C_{28} Trisubstituted Olefin. A more direct solution was conceived when it was realized that the requisite olefin could be formed in a more efficient and convergent manner via a vinylmetal addition to the aldehyde **8** (Scheme VI).[19o] From our earlier studies in this area, such an addition was expected to proceed with Cram selectivity. The precursor to the requisite vinylmetal species was prepared via hydrozirconation/bromination[52] of acetylene **47**, which was synthesized by a route similar to that used to prepare sulfone **19** (Scheme II). Claisen rearrangement of lactone **15** followed by treatment of the crude acid with diazomethane provided methyl ester **43** in 87% yield (Scheme VI). Hydroboration followed the same regio- and stereochemical course observed earlier to provide silyl ether **44** after treatment with triisopropylsilyl triflate. A two-step reduction/oxidation sequence provided aldehyde **45**, which was homologated to acetylene **46** in excellent yield with the diazophosphonate reagent introduced by Seyferth and applied to acetylene synthesis by Colvin and Gilbert.[53] Methylation of **46** proceeded without incident to provide **47**.

Aldehyde **8** was prepared from homoallylic alcohol **34** by a two-step sequence consisting of silylation and subsequent ozonolysis in the presence of pyridine (followed by reduction with dimethyl sulfide). This procedure provided the desired aldehyde in an overall yield of 99% for two steps. It should be noted that the use of pyridine in the ozonolysis was essential to the efficiency of this reaction; ozonolysis in methanol/dichloromethane without pyridine provided aldehyde **8** in yields of 55–68%. Apparently pyridine (which is probably slowly oxidized to pyridine *N*-oxide under the reaction conditions) serves to attenuate the reactivity of ozone toward the potentially labile *p*-methoxybenzyl ether. The beneficial effect of pyridine in the ozonolysis of dienes to α-diketones has been noted elsewhere.[54]

The coupling of **8** and **9** required considerable experimentation to discover conditions that resulted in an efficient and stereoselective outcome. First, the reaction of **9** with 2.2 equiv of *t*-BuLi resulted in smooth halogen metal exchange. The resultant vinyllithium was sequentially treated with 1.0 equiv of magnesium bromide and aldehyde **8**, which resulted in the predominant formation of the desired α-carbinol **48** together with the readily separable β-diastereomer (α/β = 4.5:1) in 77% yield. Evidence that the major isomer formed in the coupling reaction corresponded

(47) For a recent report of related difficulties, see: Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.

(48) Reactions using a stannane related to **37** are known. In a boron trifluoride mediated addition to propanal, only the erythro adduct **ii** was formed: Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1297. In repeating the Koreeda experiment with **37** in order to gain expertise in performing this reaction, we were able to isolate an intermediate tentatively assigned as **i**. Prolonged reaction or resubjection of **i** led to **ii** in accord with Koreeda's work.



(49) For the preparation and use of novel tin reagents, see: Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1299.

(50) Roush, W. R.; Ando, K.; Powers, D. B.; Hatterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579.

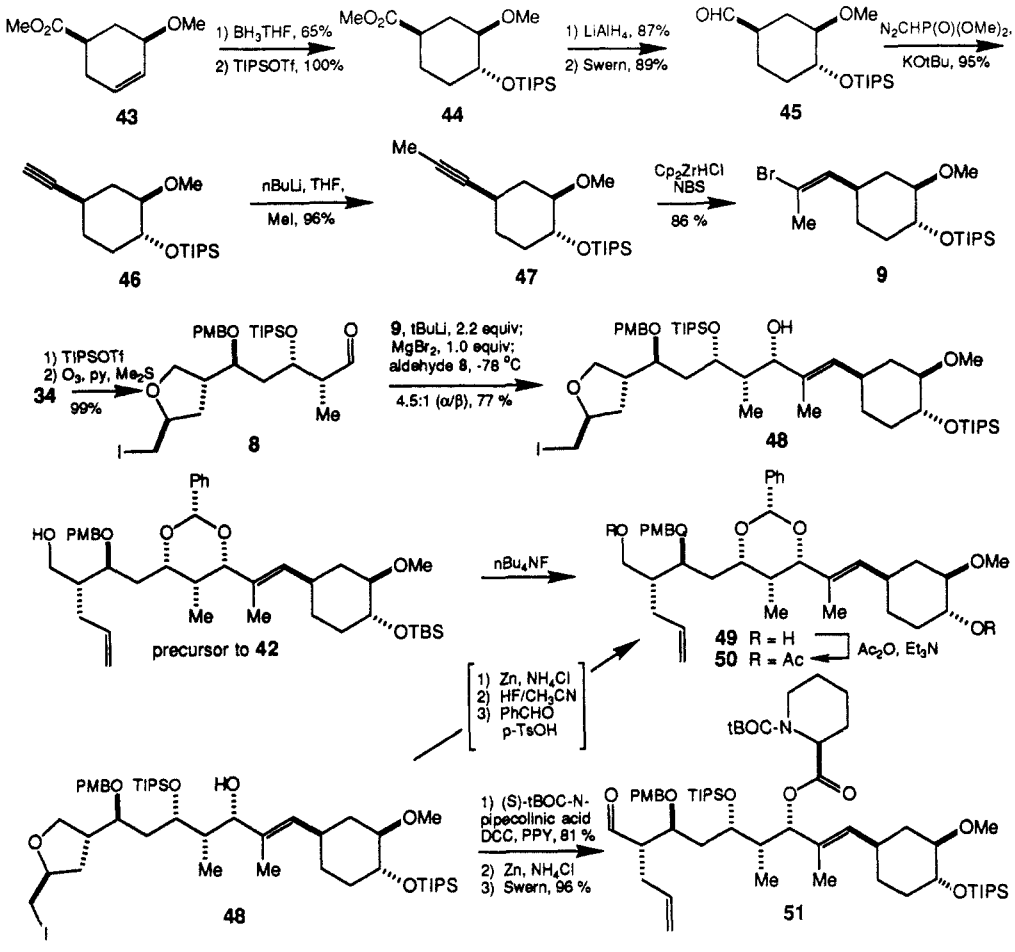
(51) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.

(52) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (c) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (d) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

(53) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151. (c) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. I* **1977**, 869. (d) Gilbert, J. C.; Weerasooriya, Y. *J. Org. Chem.* **1979**, *44*, 4997. We thank Dr. J. R. Hauske (Pfizer, Inc.) for a generous gift of $N_2CHP(O)(OMe)_2$ and helpful suggestions concerning its use.

(54) Heldeweg, R. F.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1978**, *43*, 1912.

Scheme VI



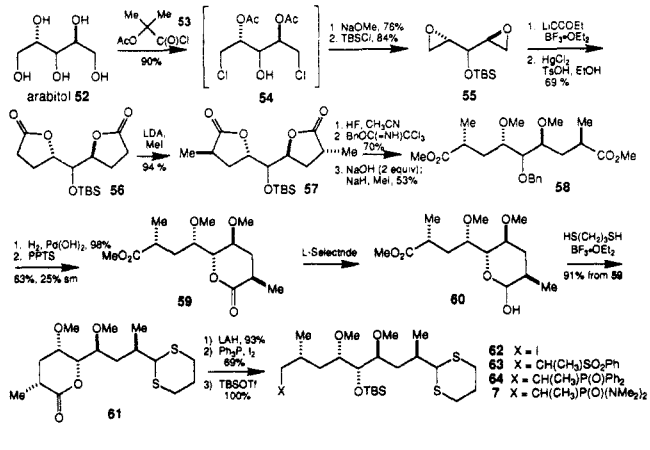
to that of a Cram-selective addition was gathered through a chemical correlation. Thus, the alcohol precursor to **42** that had been prepared via sulfone coupling chemistry was converted into the diol **49**. Examination of the 500 MHz ^{1}H NMR spectrum of this diol, and its derived bis(acetate) **50**, showed that these compounds were identical with those prepared by the second route.

This route compares quite favorably to either of the sulfone coupling procedures that were presented earlier. The requisite C_{20}–C_{34} portion of FK506 is synthesized in an efficient and highly convergent manner from achiral starting materials by using only catalytic asymmetric induction and substrate-controlled reaction processes. The C_{24} and C_{26} carbinol centers are readily distinguished; in compound **48** the C_{24} hydroxyl exists as the silyl ether, while the C_{26} carbinol is unprotected. From common precursors, this route provides an advanced intermediate in 18 fewer transformations than the sulfone based method. This development was essential to the successful outcome of the FK506 synthesis as it allowed, for the first time, efficient material processing.

We were able to take advantage of the free hydroxyl at C_{26} and fully elaborate **48** into a system containing C_1–N_7 and C_{20}–C_{34} of FK506, ready for the second trisubstituted olefination process, which introduces the C_{10}–C_{19} fragment (Scheme VIII). The direct acylation of **48** resulted in the formation of a single product when conducted at −20 °C using (*S*)-*N*-BOC-pipecolinic acid, DCC, and 4-pyrrolidinopyridine. When these same conditions were applied using racemic *N*-BOC-pipecolinic acid, the reaction gave two readily separable (sg) isomeric products, thereby confirming that epimerization at C_2 did not occur when using the nonracemic amino acid derivative. Treatment with zinc dust in the presence of ammonium chloride unmasked the C_{21} allyl side chain. Swern oxidation of the resultant primary alcohol provided the aldehyde **51** in 78% yield for the three steps.

Preparation of the C_{10}–C_{19} FK506 Fragment. Our synthesis of the C_{10}–C_{19} portion of FK506 utilized the class C two-directional chain synthesis strategy.[19j] This strategy involves the simultaneous homologation of a nascent chain in two directions and thereby benefits from double processing. Accordingly, the overall number of transformations can be decreased relative to the one-directional chain synthesis, provided that an efficient method for terminus differentiation can be achieved. Recently, we have found this strategy to be effective in the context of the first syntheses of the ansa chain of streptovaricin A,[55] the polyol sector of mycotin A,[56] and peracetyl cytosinyl hikosaminide.[57]

Scheme VII



The synthesis started with commercially available and inexpensive arabitol (**52**) (Scheme VII). A reaction with the Moffatt[58] reagent **53** on a 36-g scale was followed by acetate hydrolysis to provide a bis(epoxide) that was silylated to give **55** in 57% overall

(55) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31.
(56) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120.
(57) Ikemoto, N.; Schreiber, S. L. Unpublished results.
(58) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.

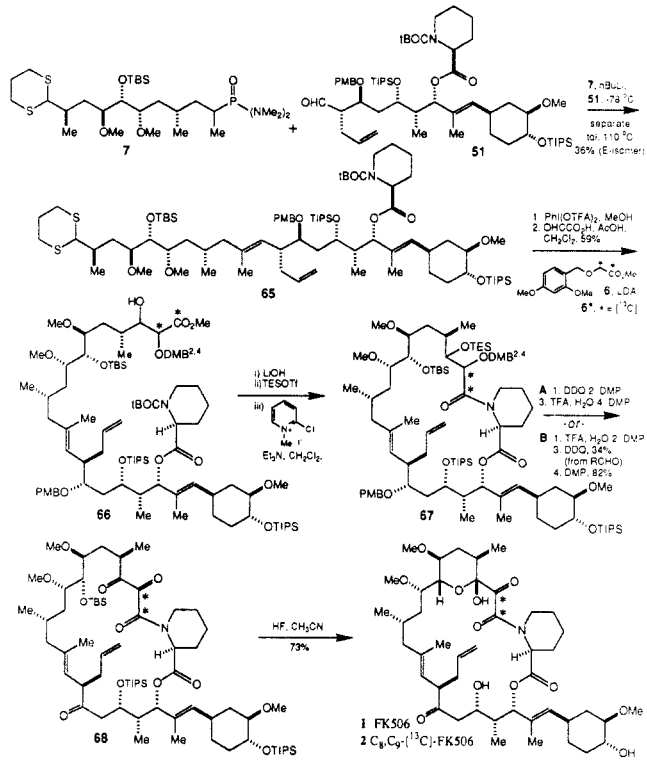
yield. Treatment of **55** with an excess of the lithium anion of ethoxyacetylene in the presence of boron trifluoride etherate furnished, after workup with weak acid, the bis(lactone) **56** (mp 102–105 °C), which could be isolated in 69% overall yield from **55**.[59] Methylation of the dianion of **56** proceeded in excellent yield and with high diastereofacial selectivity to provide **57** (mp 54–58 °C).[60] The corresponding benzyl ether was subjected to hydrolysis and exhaustive methylation to give the bis(methyl ester) **58**. Deprotection of the benzyl ether at the central carbinol center gave the corresponding alcohol, setting the stage for the crucial diastereotopic group selective terminus differentiation.

A selective lactonization was achieved via a pyridinium *p*-toluenesulfonate catalyzed cyclization of the alcohol derived from **58**, in analogy to a related system studied by Hoye.[61] This process converts the central chirotopic, nonstereogenic center into a stereogenic center. The lactonization was followed by site-specific reduction of the lactone to the lactol, which was then opened to the dithiane following treatment with propanedithiol and boron trifluoride etherate. The lactol opening proceeded with concomitant lactonization to provide the crystalline lactone **61** (mp 126–127 °C). Reduction to the diol was followed by selective functional group interchange to afford the primary iodide. The secondary alcohol was then protected as a silyl ether, giving **62** in 64% overall yield from dithiane **61**. The iodide **62** underwent displacement with a variety of organolithium reagents to provide several compounds (**63**, **64**, **7**) that proved useful in probing the chemistry of the C_{19}–C_{20} trisubstituted olefin formation. From a series of experiments with model aldehydes and intermediate **51**, phosphonamide **7** emerged as the optimal coupling partner. Accordingly, subsequent coupling reactions between the two major components of the FK506 skeleton were performed with **7** and **51**.

For the synthesis of compounds **63**, **64**, and **7**, a comparison of the two-directional and one-directional chain synthesis strategies is possible. In the present studies, compound **7** was prepared in 17 steps and 6.0% overall yield. Elsewhere, one-directional chain syntheses of **63** and **64** were achieved in 28 steps (2.3% overall yield)[19i] and 25 steps (3.1% overall yield),[19a,20] respectively. The double processing of the termini of chain substrates leading eventually to **58**, coupled with the effective terminus differentiation via a diastereotopic group selective lactonization, result in a concise two-directional solution to the problem at hand.

Formation of the C_{19}–C_{20} Olefin. The reaction of the α-lithio derivative of **7** with the aldehyde **51** resulted in the formation of two readily separable pairs of diastereomeric adducts. The more rapidly eluting (R_f 0.5 (sg), 2/1 hexanes/ethyl acetate) and major pair of diastereomers underwent stereospecific elimination to provide the desired trans olefin **65** (36% overall yield) upon heating in toluene (Scheme VIII). The more polar and minor diastereomeric pair (R_f 0.3 (sg), 2/1 hexanes/ethyl acetate) produced the cis isomer of **65** under similar conditions. Evidence that the olefination conditions did not result in appreciable epimerization at C_2 (pipecolinate ring) was obtained following examination of the ester and carbamate signals in the 125 MHz ^{13}C NMR spectra of each of the olefinic isomers. This data also allowed the assignment of the C_{19}–C_{20} olefin stereochemistry. In studies of a related compound, Shinkai et al. reported characteristic ^{13}C resonances for the corresponding C_{19} methyl substituent.[20] The C_{19}-methyl carbon in (*E*)-**65** resonates at 16.0 ppm, whereas this carbon is found to resonate at 23.5 ppm in (*Z*)-**65**. These values are in close agreement with those obtained in the earlier study. The hydrolysis of the dithiane **65** to the corresponding aldehyde proved to be troublesome. Although this transformation could be achieved in one step under a variety of conditions (e.g., CH_3I, THF, CH_3CN, H_2O; PhI(OTFA)$_2$, THF, CH_3CN, H_2O; $AgNO_3$, NCS, collidine, THF, CH_3CN, H_2O) the yields ranged from 25–35%. A two-step procedure was thus employed that utilized

Scheme VIII



the Stork reagent (PhI(OTFA)$_2$, MeOH, CH_2Cl_2)[62] to provide the dimethylacetal, which in turn was hydrolyzed to the aldehyde.

Closure of the Macrocyclic Ring and Completion of the Synthesis. The next objectives were to install a two-carbon fragment corresponding to C_8 and C_9 of the target systems and to close the macrocyclic ring.

The availability of α-bromoacetic acid with 99% ^{13}C enrichment at both carbons focused our attention on this material. Several ethers of the corresponding glycolic acid were prepared from this reagent by displacement of the bromide with the sodium salt of a benzyl alcohol. Synthetic studies were performed with the *p*-methoxybenzyl, 3,4-dimethoxybenzyl, and 2,4-dimethoxybenzyl ethers of glycolic acid and the corresponding methyl ester. Eventually, we found that only methyl (*O*-2,4-dimethoxybenzyl)glycolate **6** (denoted **6*** when reference to the ($^{13}C_2$)-labeled material is intended) gave rise to a macrocyclic intermediate that could be deprotected in high yield at a late stage of the synthesis.

After considerable experimentation, we found that the next four transformations were best achieved without any purification of intermediates. An aldol reaction with the lithium enolate of **6** and the aldehyde derived from **65** resulted in the efficient coupling of these two fragments. We presume that four diastereomers of structure **66** are produced; it is apparent by TLC that two of these predominate. The mixture of adducts was sequentially treated with LiOH (which resulted in the selective saponification of the methyl ester) and triethylsilyl triflate. The resultant diastereomeric mixture of amino acids was macrolactamized with Mukaiyama's reagent[63] to provide macrolactam **67** in 53% yield from the aldehyde. In pilot experiments, separation of individual diastereomers of **67** was performed, and subsequent reactions were studied with individual isomers. As no major differences in the reactivity of subsequent intermediates were observed, the conversion of **67** into **1** (or **67*** into **2**, route A, Scheme VIII) was most conveniently performed on the diastereomeric mixture. The two benzyl ethers (C_9-2,4-DMB and C_{22}-PMB) of **67** could be deprotected with DDQ, although the yield of diol was variable (15–50%), and unidentified byproducts were invariably detected. The reticence of a PMB and 3,4-DMB ether at C_9 to undergo

(59) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(60) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1980**, 616.
(61) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. Also see ref 19i.
(62) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(63) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163. For an application to a related system, see ref 20.

oxidative deprotection under these conditions (5–25% yield) in intermediates synthesized by a similar sequence, presumably due to the electron-withdrawing property of the neighboring carbonyl function at C_8,[64] prevented their usage. This behavior was observed in each diastereomer of the macrocycle, indicating that the decreased rate of oxidation was not due to a stereochemical or conformational issue. The facility of an oxidative deprotection of a C_9-PMB ether in a structurally related macrocyclic intermediate in the earlier FK506 synthesis[20] is in striking contrast to these studies. Oxidation of the C_9,C_{22}-diol to the C_9,C_{22}-diketone with the DMP reagent, selective deprotection of the triethylsilyl ether, and oxidation (DMP) of the resultant C_{10}-alcohol provided the C_9,C_{10},C_{22}-triketone **68**. One attempt to directly convert a C_9,C_{10},C_{22}-triol to **68** with the use of a Swern reagent was unsuccessful. Final deprotection of **68** with HF in aqueous acetonitrile in a polypropylene reaction vessel provided totally synthetic FK506 (**1**) (73% yield), which was shown to be identical with the natural product (vide infra).[65]

In order to avoid the troublesome debenzylation reaction described above, we investigated the effect of a ketone substituent at C_{10}. This sequence, which involved simply the reversal of timing of the two final oxidation reactions, provided a more satisfactory outcome (route B, Scheme VIII). Selective deprotection of the triethylsilyl ether of **67** and oxidation (DMP) of the resultant C_{10}-alcohol gave rise to the C_{10}-keto derivative of **67**. Subsequent reaction with DDQ resulted in the fast deprotection of the C_{22}-PMB ether concomitant with a slow deprotection of the C_9-2,4-DMP ether, without complications of byproduct formation observed in the earlier sequence. In contrast to the often capricious deprotection reaction described earlier (route A, Scheme VIII), this reaction proved reproducible and provided the desired diol in 70–75% yield. Double oxidation proceeded without complication with the DMP reagent to afford the triketone **68**, which was converted to FK506 (**1**) as before. An identical reaction sequence resulted in the transformation of **67*** (from the aldehyde derived from **65** and **6***) into the target probe reagent **2**. Comparison of synthetic and natural samples of **1** by spectroscopic means (^{1}H NMR, ^{13}C NMR, IR), TLC mobility in several solvent systems, optical rotation ($[\alpha]^{23}_D$ −85° (*c* 0.20, $CHCl_3$); lit. $[\alpha]^{23}_D$ −84.4° (*c* 1.02, $CHCl_3$)[2b]), and inhibition of the rotamase activity of the FK506 receptor, human recombinant FKBP, confirmed the identity of these substances.

Conclusion. Total syntheses of the potent immunosuppressant FK506 and a double (^{13}C)-labeled probe reagent have been achieved. Each synthesis entails 56 total transformations. Due to the emphasis on convergency, the longest linear sequence in the present syntheses is 32 steps. These studies provide a powerful tool for gaining an understanding of the structural requirements for binding of ligands to the recently discovered FK506 receptor, FKBP. Structural investigations that utilized the probe reagent **2** have, for example, already identified the mode of binding of FK506 to its receptor, FKBP; the details are reported elsewhere.[25] In combination with ^{15}N labeled FKBP, which is available from our overexpressing strain of *E. coli*,[23] NMR based active site mapping may now proceed. The synthesis described herein allows for the ready modification of FK506 structure for the de novo construction of new probe reagents of drug/receptor interactions. These and other investigations of chemical and biological mechanisms are in progress and will be reported in due course.

Experimental Section

General Methods. Melting points are uncorrected. Combustion analyses were performed by Atlantic Microlabs, Inc. (Norcross, Ga). High-resolution mass spectra were recorded by Dr. Dan Pentek at the Yale University Chemical Instrumentation Center. Low-resolution mass spectra were obtained on a Kratos MS50 mass spectrometer by Dr. Andrew Tyler of the Harvard Chemistry Department Mass Spectrometry Facility. Tetrahydrofuran (THF) was distilled from potassium metal/benzophenone ketyl. Benzene and diethyl ether were distilled from sodium metal/benzophenone ketyl. Dichloromethane, toluene, triethylamine, acetonitrile, pyridine, and diisopropylamine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide. Dimethylsulfoxide (DMSO), hexamethylphosphoric triamide (HMPA), and dimethylformamide (DMF) were distilled from calcium hydride at reduced pressure and stored over 4Å molecular sieves. All reactions were performed in flame or oven-dried flasks under a positive pressure of nitrogen or argon unless otherwise indicated. Reactions were monitored by analytical thin-layer chromatographic methods (TLC) with use of E. Merck silica gel 60F glass plates (0.25 mm). Flash chromatography was carried out with the use of E. Merck silica gel 60 (230–400 mesh) as described by Still.[66]

(2*R*,3*S*)-1,2-Epoxy-4-penten-3-ol (11). To a flame-dried, 1-L flask equipped with a large magnetic stir bar were added 4Å molecular sieves (4.3 g, powdered) and 250 mL of dichloromethane. The flask was purged with nitrogen and cooled to −23 °C (CO_2/CCl_4), and then titanium isopropoxide (5.00 mL, 16.8 mmol) and L-(+)-diisopropyl tartrate (4.50 mL, 21.4 mmol) were added via syringe. After stirring at −23 °C for 10 min, divinylcarbinol (**10**) (20.0 g, 238 mmol) was added via cannula, followed by *tert*-butyl hydroperoxide (160 mL, 3.0 M in isooctane, 480 mmol) in several portions via syringe. The reaction vessel was then placed in a −15 °C freezer and stirred for 118 h. At freezer temperature, 17 mL of aqueous Na_2SO_4 was added, and the mixture was diluted with 250 mL of Et_2O. After stirring vigorously at ambient temperature for 2 h, the resulting slurry was filtered through a pad of Celite, washing with several portions of Et_2O. The Celite pad was transferred to an Erlenmeyer flask, heated gently with Et_2O, and then filtered through a fresh pad of Celite. The majority of the solvent was removed on a rotary evaporator with cooling to avoid undue loss of the somewhat volatile product. The resulting oil was subjected to flash chromatography (2:1 pentane/ether) followed by distillation at aspirator pressure to afford 23.6 g of product which was about 50% pure by NMR. A second flash chromatography (1:1 pentane/ether, then ether) in two batches provided the desired epoxide as a clear, colorless oil (13.1 g, 131 mmol, 55% yield): $[\alpha]^{23}_D$ +48.8° (*c* 0.73, $CHCl_3$); IR (thin film) 3400 (br), 3019, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) 5.89–5.75 (ddd, *J* = 17.2, 10.5, 6.2, 1 H), 5.34 (dt, *J* = 17.2, 1.4, 1 H), 5.22 (dt, *J* = 10.5, 1.3, 1 H), 4.26 (br s, 1 H), 3.05 (dd, *J* = 3.1, 3.3, 1 H), 2.78–2.70 (m, 2 H), 2.61 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 135.6, 117.3, 70.3, 53.9, 43.5; MS *m/e* (percent) 99 (M − H, 0.4), 57 (100).

(2*R*,3*S*)-1,2-Epoxy-3-[(4-methoxybenzyl)oxy]pent-4-ene (12). To an oven-dried, 1-L flask containing epoxide **11** (11.2 g, 111 mmol) was added 300 mL of THF, followed by 4-methoxybenzyl bromide (32 g, freshly prepared from 4-methoxybenzyl alcohol (21.2 g, 153 mmol)). Under a nitrogen atmosphere, the flask was cooled to 0 °C, and tetra-*n*-butylammonium iodide (0.756 g, 2.0 mmol) was added. With care, sodium hydride (5.00 g, 60%, 125 mmol, washed three times with hexanes) was added in several portions. Evolution of hydrogen gas accompanied each added portion of sodium hydride; when this subsided the cooling bath was removed, and the mixture was stirred at ambient temperature overnight. The mixture was then cooled to 0 °C, diluted with diethyl ether, and excess hydride was quenched by dropwise addition of water. After transferring the reaction mixture to a large separatory funnel, the organic phase was washed once with water and twice with brine. The ethereal layer was then dried over Na_2SO_4. After filtration and solvent removal, a crude chromatography was carried out (5.5–25% ether in hexanes), affording about 36 g of crude product as an oil. This material was divided into three portions, and each was subjected to flash chromatography (10% to 12.5% to 20% to 25% ether in hexanes). Upon recombination, the desired epoxide was obtained as a clear, colorless oil (23.1 g, 104 mmol, 94% yield): $[\alpha]^{22}_D$ = +33.1° (*c* 10.5, $CHCl_3$); IR (thin film) 1612, 1514, 1302, 1248, 1174, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) d 7.27 (d, *J* = 8.6, 2 H), 6.88 (d, *J* = 8.6, 2 H), 5.82 (m, 1 H), 5.38 (s, 1 H), 5.32 (m, 1 H), 4.58 (d, *J* = 11.5, 1 H), 4.40 (d, *J* = 11.5, 1 H), 3.81 (s, 3 H), 3.78 (m, 1 H), 3.07 (ddd, *J* = 4.1, 4.1, 2.7, 1 H), 2.77 (dd, *J* = 5.2, 4.1, 1 H), 2.76 (dd, *J* = 5.2, 2.7, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 159.4, 134.8, 130.4, 129.4, 119.3, 113.9, 79.1, 70.4,

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(70) On several earlier runs the two diastereomers were subjected to Dess–Martin oxidation separately and shown to provide the same product. Consequently the two isomers were combined for all subsequent oxidations.

55.2, 53.2, 44.8; MS *m/e* (percent) 220 (M^+, 3.7), 137 (24.3), 136 (21.6), 135 (11.3), 122 (10.0), 121 (100), 55 (8.0). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.00; H, 7.34.

(4*R*,5*S*)-1-Ethoxy-4-methoxy-5-[(4-methoxybenzyl)oxy]hept-1-yn-6-ene (13). To a solution of ethoxyacetylene (3.9 g, 50% by weight in hexanes, 28 mmol) in 30 mL of THF at −78 °C under argon was added *n*-BuLi (10 mL, 2.3 M in hexanes, 23 mmol), and the mixture was stirred at that temperature for 20 min. To this solution was added boron trifluoride etherate (2.8 mL, 22.8 mmol), followed by a solution of the epoxide **12** (2.017 g, 9.157 mmol) in 15 mL of THF. After 2 h, the reaction was quenched with methyl iodide (5 mL, 80.3 mmol) and stirred at −78 °C for 30 min. No methylation occurred as determined by TLC, and the reaction was then quenched with 5 mL of absolute ethanol and diluted with 100 mL of ether. After warming to ambient temperature, the reaction mixture was successively washed with saturated sodium bicarbonate (20 mL) and brine (3 × 20 mL), and then the organic layer was dried over sodium sulfate. The solution was filtered through a pad of magnesium sulfate, cooled to 0 °C, and treated with methyl iodide (15 mL, 241 mmol) and sodium hydride (1.38 g, 60%, 34.5 mmol, washed free of mineral oil with hexanes). The reaction was allowed to warm to room temperature and stirred overnight with more sodium hydride added over several hours until no further hydrogen evolution occurred. The reaction was then cooled to 0 °C and quenched carefully with ethanol and then water. After the vigorous hydrogen evolution was complete, the mixture was transferred to a separatory funnel and washed with one portion of brine. Solvent removal after drying over sodium sulfate left an oil which was purified via flash chromatography (9–20% ether in hexanes) to provide 2.414 g (87%) of product as a clear, colorless oil: $[\alpha]^{23}_D$ +29.7° (*c* 10.7, $CHCl_3$); IR (thin film) 2981, 2934, 2834, 2272, 1612, 1513, 1301, 1247, 1226, 1110, 1068, 1035, 928, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.27 (d, *J* = 8.5, 2 H), 6.87 (d, *J* = 8.5, 2 H), 5.87 (ddd, *J* = 17.6, 10.6, 7.6, 1 H), 5.37–5.28 (m, 2 H), 4.58 (d, *J* = 11.5, 1 H), 4.35 (d, *J* = 11.5, 1 H), 3.97 (q, *J* = 7.1, 2 H), 3.93 (m, 1 H), 3.79 (s, 3 H), 3.45 (s, 3 H), 3.36 (m, 1 H), 2.45 (dd, *J* = 16.6, 5.6, 1 H), 2.33 (dd, *J* = 16.6, 6.3, 1 H), 1.31 (t, *J* = 7.1, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 159.1, 135.3, 130.6, 129.2, 118.9, 113.7, 90.2, 82.5, 80.9, 73.8, 70.1, 58.3, 55.1, 33.7, 19.1, 14.1; MS *m/e* (percent) 304 (M^+, 0.5), 122 (9.5), 121 (100).

Ethyl (4*R*,5*S*)-5-Hydroxy-4-methoxyhept-6-enoate (14). A magnetically stirred solution of alkyne **13** (2.41 g, 7.93 mmol) in 50 mL of anhydrous ethanol was treated with a catalytic amount of mercury(II) chloride at ambient temperature. The solution was stirred overnight, then diluted with 200 mL of methylene chloride, and washed with two 40-mL portions of brine. The organic layer was then treated with water (6 mL) and DDQ (1.8 g, 8.1 mmol) and stirred at room temperature for 4 h. Dilution with ether was followed by washing of the organic phase with two portions of saturated aqueous sodium bicarbonate and then once with brine. After drying the organic layer over sodium sulfate, solvent was removed under reduced pressure. Crude flash chromatography (1:1 hexanes/ethyl acetate) provided 2.388 g of product contaminated with *p*-anisaldehyde. Another chromatography was performed (2:1 hexanes/ethyl acetate) to afford the desired ester as a colorless oil (1.245 g, 6.19 mmol, 78% for two steps): $[\alpha]^{23}_D$ −8.96° (*c* 5.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) 5.88 (ddd, *J* = 17.2, 10.5, 5.7, 1 H), 5.35 (dt, *J* = 17.2, 1.6, 1 H), 5.24 (dt, *J* = 10.5, 1.6, 1 H), 4.32 (m, 1 H), 4.14 (q, *J* = 7.1, 2 H), 3.43 (s, 3 H), 3.23 (ddd, *J* = 8.9, 5.0, 3.9, 1 H), 2.41 (m, 2 H), 2.18 (d, *J* = 3.8, 1 H), 1.83 (m, 2 H), 1.26 (t, *J* = 7.1, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 173.8, 136.5, 116.5, 83.0, 72.5, 60.3, 57.9, 30.2, 24.0, 14.1; IR (thin film) 3475 (br), 2980, 1735, 1731, 1252, 1171, 1108, 1030 cm^{-1}; MS *m/e* (percent) 145 (19.0), 100 (14.3), 85 (48.2), 72 (61.3), 71 (30.4), 58 (100), 45 (19.0). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.86; H, 8.77.

(4*R*,5*S*)-5-Ethenyl-4-methoxytetrahydro-2*H*-pyran-2-one (15). To a solution of ester **14** (0.693 g, 3.43 mmol) in 40 mL of benzene under nitrogen was added 4Å molecular sieves (0.554 g) and *p*-toluenesulfonic acid monohydrate (0.039 g, 0.21 mmol). The reaction was stirred at ambient temperature for 7 h, and then an additional portion of sieves (0.825 g) and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.42 mmol) were added. After stirring overnight, the mixture was diluted with ether, and 0.5 mL triethylamine was added. The solution was filtered through a pad of silica, and solvent was removed under reduced pressure. Gradient elution flash chromatography (33–50% ether in hexanes) allowed recovery of 0.0511 g (7%) of the starting material, followed by 0.412 g (77%) of the desired lactone as a clear, colorless oil: $[\alpha]^{23}_D$ −108.9° (*c* 9.52, $CHCl_3$); IR (thin film) 1737, 1242, 1163, 1100, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 5.87 (ddd, *J* = 17.2, 10.8, 4.8, 1 H), 5.43 (ddd, *J* = 17.2, 1.8, 0.9, 1 H), 5.34 (ddd, *J* = 10.8, 1.7, 0.9, 1 H), 4.96 (m, 1 H), 3.45 (m, 1 H), 3.43 (s, 3 H), 2.71 (ddd, *J* = 18.0, 10.3, 7.9, 1 H), 2.49 (ddd, *J* = 18.0, 6.1, 4.2, 1 H), 2.05 (m, 2 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) 170.2, 134.2, 117.9, 81.0, 74.9, 56.4, 25.8, 21.2; MS *m/e* (percent) 156 (M^+, 0.1), 124 (5.0), 100 (14.2), 72 (72.3), 58 (100). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.32; H, 7.77.

(1*R*,3*R*)-3-Methoxycyclohex-4-enecarboxylic Acid (17). To a flask containing lactone **15** (1.38 g, 8.84 mmol) was added 40 mL of methylene chloride via syringe. The solution was cooled to −78 °C and triethylamine (1.60 mL, 11.5 mmol) was added, followed by *tert*-butyldimethylsilyl triflate (2.20 mL, 9.56 mmol), both via syringe. The mixture was warmed to 0 °C and stirred at that temperature for 30 min. The mixture was then diluted with 100 mL of cold pentane, quickly washed with ice cold H_2O (5 mL) and ice cold brine (2 × 5 mL), and dried over K_2CO_3. The clear, colorless solution was then filtered through a K_2CO_3 plug into a 250-mL flask, and the solvent was removed under aspirator pressure with magnetic stirring (a drying tube was attached to prevent introduction of moisture to the flask). The last traces of solvent were removed under high vacuum, and then 90 mL of toluene was introduced via syringe. The flask was fitted with a reflux condenser and heated at a gentle reflux (oil bath, bath temperature 120–130 °C) for 69 h. After cooling to room temperature, 100 mL of THF was added, and the solution was treated with 20 mL of 1 N HCl. After 3 h at room temperature, the mixture was diluted with 200 mL of ether. The organic layer was separated, the aqueous layer was extracted with two portions of ether (50 mL), and then the combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the acid (0.979 g, 71%) was isolated as a white solid (mp 57–59 °C) via flash chromatography (33–50% ether in hexanes with 0.5% acetic acid): $[\alpha]^{23}_D$ −37.6° (*c* 1.86, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) 11.6 (br s, 1 H), 5.78 (m, 2 H), 3.95 (br s, 1 H), 3.39 (s, 3 H), 2.68 (m, 1 H), 2.42 (m, 1 H), 2.30 (m, 2 H), 1.65 (td, *J* = 12.3, 9.5, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 180.6, 128.3, 127.6, 75.2, 55.6, 38.0, 30.3, 27.3; IR (thin film) 3450–2400 (br), 1736, 1731, 1708, 1097, 922. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.51; H, 7.77.

(1*R*,2*R*,4*R*)-4-(Hydroxymethyl)-2-methoxycyclohexan-1-ol (18). To a magnetically stirred solution of carboxylic acid **17** (0.255 g, 1.63 mmol) in 15 mL of THF at −78 °C was added BH_3·THF (10 mL, 1.0 M solution in THF, 10 mmol) via syringe. After the addition was complete, the solution was allowed to warm slowly to ambient temperature and stirred for 90 min at that temperature. The clear, colorless solution was then cooled to 0 °C, and the excess diborane was quenched by careful addition of water. H_2O_2 (1 mL, 30%) and 0.1 N NaOH (1 mL) were then added. After stirring this mixture for 3 h at ambient temperature, 100 mL of ethyl acetate was added, and the solution was transferred to a separatory funnel and washed with 10 mL of aqueous $Na_2S_2O_3$. The aqueous layer was separated and washed with two portions of EtOAc (50 mL, 25 mL), and then the organic layers were combined and dried over Na_2SO_4. After the solution had been filtered and the solvent was removed by rotary evaporation, the resulting oil was purified by flash chromatography (2–4% methanol in ether) to afford the desired diol as a clear, colorless oil (0.205 g, 79% yield): $[\alpha]^{23}_D$ −57.0° (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) 3.51 (m, 2 H), 3.42 (m, 1 H), 3.42 (s, 3 H), 3.01 (ddd, *J* = 11.2, 8.8, 4.3, 1 H), 2.75 (s, 1 H), 2.24 (m, 1 H), 2.05 (m, 1 H), 1.77 (m, 1 H), 1.72–1.25 (m, 3 H), 1.04 (m, 1 H), 0.86 (q, *J* = 12.0, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 84.6, 74.1, 67.6, 56.4, 39.0, 31.5, 31.1, 27.0; IR (thin film) 3500–3200 (br), 2927, 2867, 1452, 1095, 1056, 1043, 1016, 965, 914; MS *m/e* (percent) 160 (M^+, 0.1), 129 (40.7), 110 (20.3), 98 (100), 97 (19.8), 81 (17.3), 79 (25.7), 71 (18.5), 69 (29.3), 58 (33.1), 45 (27.4); HRMS calcd for $C_8H_{17}O_3$ (M + H) 161.1178, found 161.1179.

(1*R*,2*R*,4*R*)-4-(Iodomethyl)-2-methoxycyclohexan-1-ol. To a magnetically stirred solution of diol **18** (0.156 g, 0.970 mmol) in 10 mL of benzene were added triphenylphosphine (0.389 g, 1.48 mmol), pyridine (0.315 mL, 3.89 mmol), and iodine (0.364 g, 1.43 mmol), in that order. Gentle heating was applied to keep the mixture just below reflux, and after 2 h the mixture was cooled to room temperature and diluted with 30 mL of ether. After transfer to a separatory funnel and washing with 10 mL of aqueous $NaHCO_3$ and 10 mL of brine, the organic layer was dried over Na_2SO_4. The product (0.205 g, 78%) was isolated as a crystalline white solid (mp 56–58 °C) via flash chromatography (50–67% ether in hexanes). It was used immediately in the next reaction to avoid decomposition: ^1H NMR ($CDCl_3$, 250 MHz) 3.43 (s, 3 H), 3.40 (m, 1 H), 3.14 (d, *J* = 6.2, 2 H), 3.02 (ddd, *J* = 11.2, 8.8, 4.3, 1 H), 2.70 (s, 1 H), 2.31 (m, 1 H), 2.04 (m, 1 H), 1.89 (m, 1 H), 1.55 (m, 1 H), 1.37 (m, 1 H), 1.09 (dq, *J* = 13.0, 3.5, 1 H), 0.92 (q, *J* = 11.9, 1 H).

(1*R*,2*R*,4*R*)-4-[(Phenylsulfonyl)methyl]-2-methoxy-1-[(*tert*-butyldimethylsilyl)oxy]cyclohexane (19). The primary iodide (0.641 g, 2.37 mmol) was dissolved in 24 mL of DMF and treated with sodium benzenesulfinate (0.947 g, 5.60 mmol), and the resulting solution was heated to approximately 100 °C for 20 min. After cooling to room temperature, the mixture was diluted with 200 mL of ether and washed with water (2 × 20 mL) and brine (20 mL). The aqueous layers were combined and washed with either (5 × 30 mL) and ethyl acetate (2 × 30 mL), and then

the combined organic layers were dried over Na_2SO_4. After removal of solvents on the rotary evaporator, the crude oil was dissolved in 50 mL of methylene chloride and cooled to 0 °C under nitrogen. Triethylamine (3.30 mL, 23.7 mmol) was added, followed by *tert*-butyldimethylsilyl triflate (1.50 mL, 6.53 mmol). The solution was allowed to warm to ambient temperature, stirred for several hours, then diluted with 100 mL of ether, washed with aqueous $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. The product (0.712 g, 75%) was isolated as a clear, colorless oil after flash chromatography (33% ether in hexanes): $[\alpha]^{23}_D$ −23.9° (*c* 1.13, $CHCl_3$); IR (thin film) 2953, 2928, 2856, 1472, 1462, 1447, 1306, 1251, 1150, 1109, 1086, 924, 876, 836, 777, 743, 689, 668, 603, 582, 564, 528; ^1H NMR ($CDCl_3$, 250 MHz) 7.93–7.55 (m, 5 H), 3.40 (m, 1 H), 3.37 (s, 3 H), 3.03 (d, J = 6.2, 2 H), 2.92 (ddd, J = 10.9, 8.4, 4.4, 1 H), 2.18 (m, 1 H), 2.05 (m, 1 H), 1.93–1.78 (m, 2 H), 1.43–1.26 (m, 2 H), 1.16–0.92 (m, 2 H), 0.88 (s, 9 H), 0.062 (s, 3 H), 0.048 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 140.2, 133.7, 129.3, 127.8, 83.5, 74.2, 61.9, 57.9, 35.8, 32.8, 30.9, 30.3, 25.8, 18.1, −4.6, −4.8. Anal. Calcd for $C_{20}H_{34}SO_4$: C, 60.26; H, 8.60; S, 8.04. Found: C, 60.35; H, 8.63; S, 7.98.

Ketone 23. A solution of sulfone **19** (36.4 mg, 0.0913 mmol) in 0.4 mL of THF under argon at −78 °C was treated with *n*-butyllithium (0.045 mL, 0.099 mmol), and the light yellow solution was stirred at that temperature for 30 min. The aldehyde **22** (26.5 mg, 0.0906 mmol) in 0.4 mL of THF was then added via syringe, mostly discharging the yellow color of the sulfone anion. After 2 h at −78 °C, the mixture was quenched with 0.050 mL of aqueous NH_4Cl and diluted with 1.5 mL of 1:1 hexanes/ethyl acetate. The mixture was then warmed to ambient temperature and dried over sodium sulfate. Flash chromatography (20% ethyl acetate in hexanes) provided 37.0 mg (60% yield) of the β-hydroxy sulfone as a clear, colorless oil.

The oil recovered from the above reaction was taken up in 20 mL of methylene chloride, and the Dess–Martin periodinane (37 mg, 0.087 mmol) was added. After stirring for 2 h, the cloudy mixture was diluted with 4 mL of 1:1 hexanes/ethyl acetate, and 3 drops of saturated aqueous sodium thiosulfate were added. The mixture was stirred at room temperature until the organic phase became clear (about 40 min) and then dried over sodium sulfate. Flash chromatography (22% ethyl acetate in hexanes) allowed separation of 26.0 mg (70% yield) of β-keto sulfone as a clear, colorless oil.

The β-keto sulfone from the above oxidation was dissolved in methanol (2 mL), and Na_2HPO_4 (24 mg) was added. To this slurry, at 0 °C under argon, was added 6% sodium amalgam (about 0.20 g), and the mixture was stirred at that temperature for 3 h. After pouring the mixture into water and extracting twice with 1:1 hexanes/ethyl acetate, the combined organic layers were dried over sodium sulfate. Flash chromatography (14% ethyl acetate in hexanes) provided 14.5 mg (70% yield) of ketone **23**: IR (thin film) 2928, 2857, 1717, 1385, 1252, 1202, 1148, 1107, 1013, 837; ^1H NMR ($CDCl_3$, 250 MHz) 7.42–7.25 (m, 5 H), 4.54 (d, J = 12.1, 1 H), 4.47 (d, J = 12.1, 1 H), 4.27 (br s, 1 H), 4.15 (br s, 1 H), 3.57–3.43 (m, 2 H), 3.41 (s, 3 H), 3.40 (m, 1 H), 2.95 (m, 1 H), 2.50 (dd, J = 18.0, 6.3, 1 H), 2.37 (dd, J = 18.0, 6.9, 1 H), 2.07 (m, 1 H), 2.00–1.58 (m, 5 H), 1.48–1.26 (m, 2 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 1.07–0.82 (m, 2 H), 0.90 (s, 9 H), 0.78 (d, J = 6.9, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 210.4, 138.6, 128.4, 127.7, 127.7, 99.4, 84.2, 79.3, 75.4, 73.1, 69.6, 66.4, 57.8, 45.5, 36.4, 33.9, 33.7, 33.0, 30.9, 30.8, 29.8, 25.8, 19.2, 18.1, 6.0, −4.6, −4.8; HRMS calcd for $C_{31}H_{53}O_6Si$ (M + H) 549.3613, found 549.3550.

Tertiary Alcohol 24. To a solution of ketone **23** (26 mg, 0.047 mmol) in 2 mL of THF at 0 °C was added methylmagnesium bromide (0.10 mL, 2.8 M in toluene, 0.28 mmol), and the resulting mixture was stirred for 10 min. The reaction was then diluted with 6 mL of ether, quenched with 15 drops of saturated aqueous sodium bicarbonate, and then allowed to warm to ambient temperature. Solid sodium sulfate was added to remove water, and the organic layer was removed by pipette. After solvent removal, the material was purified via flash chromatography (20% ether in hexanes), giving 20.5 mg (76%) of product as a separable mixture (22:1) of addition diastereomers: ^1H NMR ($CDCl_3$, 250 MHz) 7.40–7.28 (m, 5 H), 4.53 (d, J = 11.6, 1 H), 4.48 (d, J = 11.6, 1 H), 4.05–3.98 (m, 1 H), 3.56–3.31 (m, 4 H), 3.43 (s, 3 H), 2.94 (ddd, J = 11.3, 8.5, 4.4, 1 H), 2.21 (br s, 1 H), 2.05–1.94 (m, 2 H), 1.88–1.73 (m, 2 H), 1.69–1.59 (m, 3 H), 1.54–1.48 (m, 2 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.38–1.19 (m, 2 H), 1.18 (s, 3 H), 1.02–0.85 (m, 1 H), 0.98 (d, J = 6.6, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 138.7, 128.4, 127.7, 127.6, 99.4, 84.6, 78.9, 75.6, 73.9, 73.1, 70.8, 66.8, 57.9, 42.5, 39.1, 34.1, 33.2, 33.1, 32.3, 31.7, 29.8, 25.9, 25.3, 19.6, 18.1, 6.3, −4.6, −4.8.

Trisubstituted Olefin 25. The Burgess reagent (62.0 mg, 0.260 mmol) was added to a solution of alcohol **24** (19.6 mg, 0.0336 mmol) in 1.2 mL of benzene. The heterogeneous mixture was stirred under nitrogen at ambient temperature for 12 h and then warmed briefly to 50 °C to complete the elimination. After cooling, the mixture was diluted with 5 mL of ether, and 0.5 mL of water was added. The organic layer was removed and dried by passage through a magnesium sulfate plug. Flash chromatography (25% ether in hexanes) furnished the olefinic products (18.2 mg, 96%) as an inseparable 3:1 mixture of isomers favoring the desired trisubstituted olefin: ^1H NMR ($CDCl_3$, 250 MHz) major isomer 7.40–7.30 (m, 5 H), 5.29 (d, J = 8.9, 1 H), 4.52 (br s, 2 H), 4.22 (br s, 1 H), 4.20–4.12 (m, 1 H), 3.61–3.52 (m, 2 H), 3.48–3.34 (m, 1 H), 3.42 (s, 3 H), 3.02–2.91 (m, 1 H), 2.36–0.96 (m, 10 H), 1.55 (s, 3 H), 1.53 (s, 3 H), 1.46 (s, 3 H), 0.90 (s, 9 H), 0.69 (d, J = 6.8, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H).

Methyl (3*S*)-3-Hydroxy-5-[(4-methoxybenzyl)oxy]pentanoate (29). The Noyori hydrogenation catalyst $Ru_2Cl_4[(S)\text{-BINAP}]_2Et_3N$ was prepared according to the literature procedure: $[RuCl_2(COD)]_n$ (88.7 mg, 0.315 mmol), (*S*)-(−)-BINAP (227 mg, 0.364 mmol), and Et_3N (0.50 mL, 3.6 mmol) were heated in 15 mL of toluene at a gentle reflux for 14 h. Solvent was then removed under high vacuum to leave an orange-brown residue. In a separate flask, β-keto ester **28** (8.50 g, 31.9 mmol) was dissolved in 50 mL of methanol. Under argon, the solution was frozen with liquid nitrogen and then subjected to high vacuum. Vacuum was discontinued, and the mixture was allowed to thaw. This freeze/pump/thaw cycle was repeated twice, and then the solution was transferred into the catalyst via cannula. After stirring for about 30 min with gentle warming to dissolve the catalyst, the entire solution was transferred via tygon tubing into a high-pressure hydrogenator. The apparatus was pressurized to 1450 psi, and then mechanical stirring was begun. After 70 h, the pressure had dropped to 1230 psi. The apparatus was carefully vented, and the reaction mixture was concentrated to give a dark orange oil. Flash chromatography (gradient elution, 20–50% ethyl acetate in hexanes) provided 7.69 g (90%) of the product as a clear, colorless oil: $[\alpha]^{23}_D$ +9.73° (*c* 1.12, $CHCl_3$); IR (thin film) 3500 (br), 1731, 1611, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.23 (d, J = 8.5, 2 H), 6.86 (d, J = 8.5, 2 H), 4.43 (s, 2 H), 4.21 (m, 1 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.61 (m, 2 H), 3.42 (d, J = 3.4, 1 H), 2.48 (d, J = 6.3, 2 H), 1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 172.5, 159.4, 130.3, 129.2, 114.0, 73.0, 67.7, 67.1, 55.4, 51.5, 41.6, 36.3; MS *m/e* (percent) 313 (M^+, 0.2), 268 (4.1), 176 (4.8), 138 (8.7), 137 (100), 135 (4.4), 122 (7.0), 121 (45.5), 114 (5.8). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.54; H, 7.54.

(3*S*,4*S*)-4-Carbomethoxy-3-hydroxy-1-[(4-methoxybenzyl)oxy]hept-6-ene (30). A solution of lithium diisopropylamide (67 mL, 0.565 M, 38 mmol, prepared from lithium metal, diisopropylamine, and α-methylstyrene in ether) was cooled to −78 °C, and alcohol **29** (4.15 g, 15.5 mmol) was added via cannula as a solution in 50 mL of THF. After 1 h at −78 °C, allyl bromide (3.4 mL, 39 mmol) and HMPA (5 mL) were added via syringe. The mixture was allowed to stir at −78 °C for 60 min, then warmed slowly to −20 °C, and stirred at that temperature for 60 min. TLC analysis showed a trace of starting material, so an additional portion of allyl bromide was added (1.4 mL, 16 mmol). The reaction was stirred an additional 60 min at −20 °C and then at 0 °C for 60 min before quenching with 10 mL of aqueous $NaHCO_3$. The mixture was poured into a separatory funnel containing 50 mL of Et_2O and 50 mL of 0.1 N HCl, and concentrated HCl was carefully added until the aqueous phase was pH 1–2. The layers were then separated, and the aqueous phase was extracted with three portions of Et_2O. The combined organic extracts were washed with H_2O (3×) and brine and then dried over $MgSO_4$. Filtration and concentration gave a clear, yellow oil, which was purified via flash chromatography (gradient elution from 10:1 to 1:1 hexane/ethyl acetate) to provide the desired ester as a clear, pale yellow oil (4.04 g, 13.1 mmol, 85% yield). When processing larger quantities of material, purification at this stage was omitted, and the crude product was used directly in the $LiAlH_4$ reduction. This procedure gave an overall yield for the two steps of 81% (21.5 g of diol), corresponding to an average yield per step of 90%: $[\alpha]^{23}_D$ +5.94° (*c* 1.01, $CHCl_3$); IR (thin film) 3488 (br), 1738, 1612, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.23 (d, J = 8.6, 2 H), 6.86 (d, J = 8.6, 2 H), 5.74 (ddt, J = 17.0, 10.1, 6.9, 1 H), 5.12–4.99 (m, 2 H), 4.43 (s, 2 H), 3.94 (m, 1 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.63 (m, 2 H), 3.27 (d, J = 5.6, 1 H), 2.55 (dt, J = 11.8, 5.9, 1 H), 2.37 (m, 2 H), 1.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 174.4, 159.3, 135.0, 130.3, 129.1, 116.7, 113.9, 72.9, 70.7, 67.9, 55.3, 51.3, 51.2, 34.8, 33.2; MS *m/e* (percent) 308 (M^+, 1.1), 176 (9.8), 154 (15.8), 138 (9.7), 137 (100), 136 (8.0), 135 (5.8), 122 (15.7), 121 (85.7), 94 (8.1). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.29; H, 7.88.

(3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)-1-[(4-methoxybenzyl)oxy]-hept-6-ene. To a magnetically stirred solution of ester **30** (3.292 g, 10.68 mmol) in 100 mL of tetrahydrofuran at 0 °C under argon was added lithium aluminum hydride (13.3 mL, 1.0 M in THF, 13.3 mmol). After 3 h at 0 °C, the mixture was warmed to room temperature for 1 h, then recooled to 0 °C, and carefully quenched by addition of 0.5 mL of water.

After the initial reaction subsided, the reaction was diluted with 50 mL of ethyl acetate, 0.5 mL of 15% sodium hydroxide, 1.5 mL of water, and 50 mL of ethyl acetate. Vigorous stirring was continued for 30 min, and then the reaction mixture was filtered through a pad of Celite, washing the reaction flask and Celite pad extensively with ethyl acetate. Solvents were removed, and the residue was subjected to flash chromatography (gradient elution, 33% to 50% to 66% ethyl acetate in hexanes) which afforded 2.296 g of the desired diol. Resubjection of some mixed fractions from the chromatography to the reduction conditions gave an additional 0.398 g product after chromatography, for a total of 2.694 g (90%) of product as a clear, colorless oil: $[\alpha]^{23}_D$ +10.5° (*c* 1.0, $CHCl_3$); IR (thin film) 3391 (br), 1613, 1514, 1303, 1248, 1090, 1035, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.26–6.85 (m, 4 Hh), 5.79 (m, 1 H), 5.10–5.01 (m, 2 H), 4.46 (s, 2 H), 3.93–3.60 (m, 6 H), 3.80 (s, 3 H), 3.20 (t, *J* = 5.4, 1 H), 2.24–2.02 (m, 2 H), 2.00–1.87 (m, 1 H), 1.81–1.75 (m, 1 H), 1.62–1.53 (m, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 159.3, 136.5, 129.6, 129.3, 116.4, 113.9, 75.7, 73.1, 69.4, 64.0, 55.3, 44.8, 34.6, 33.3; MS *m/e* (percent) 280 (M^+, 0.3), 231 (6.7), 150 (6.1), 138 (9.6), 137 (100), 136 (11.7), 135 (4.9), 122 (9.9), 121 (69.2). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.3; H, 8.71.

[2*R*,2(2*S*,4*S*)]-2-[2-(4-Methoxyphenyl)-1,3-dioxan-1-yl]pent-4-en-1-ol (31). To a solution of the diol (0.398 g, 1.42 mmol) in 8 mL of methylene chloride was added 3Å molecular sieves (0.1 g, powdered, activated), and the solution was stirred at ambient temperature for 10 min. DDQ (0.363 g, 1.57 mmol) was then added in one portion, and the resultant green slurry was stirred under nitrogen for 3 h. The slurry was diluted with ether, transferred to a separatory funnel, and then washed with three portions of aqueous $NaHCO_3$. The lightly colored organic layer was dried over magnesium sulfate and filtered through a pad of Celite. Solvents were removed under reduced pressure, and the products were separated by flash chromatography (1:1 hexanes/ethyl acetate). The desired acetal (0.324 g, 82%) was first to elute, followed by unreacted starting material (25 mg, 6%), and finally overoxidation product (46 mg, 11%) as a mixture of benzoates. Data for the desired acetal: $[\alpha]^{23}_D$ +26.7° (*c* 1.06, $CHCl_3$); IR (thin film) 3390 (br), 2959, 2928, 2850, 1615, 1517, 1249, 1102, 1033, 918, 829, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.38 (d, *J* = 8.7, 2 H), 6.89 (d, *J* = 8.7, 2 H), 5.81 (ddt, *J* = 16.9, 9.4, 7.5, 1 H), 5.45 (s, 1 H), 5.13–5.05 (m, 2 H), 4.28 (dd, *J* = 10.5, 4.8, 1 H), 4.00–3.70 (m, 4 H), 3.80 (s, 3 H), 2.57 (br s, 1 H), 2.28–1.76 (m, 4 H), 1.55 (dd, *J* = 13.2, 1.5, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 159.9, 136.1, 131.0, 127.1, 116.7, 113.6, 101.4, 79.8, 67.0, 63.1, 55.2, 44.8, 32.2, 29.3; MS *m/e* (percent) 278 (M^+, 3.5), 277 (7.1), 247 (4.1), 194 (5.2), 193 (46.2), 192 (13.8), 177 (7.5), 153 (20.1), 152 (27.6), 137 (58.2), 136 (56.6), 135 (100), 121 (12.8), 108 (15.8), 79 (10.3), 67 (10.7).

[3*S*,3(2*S*,4*R*)]-3-(4-Methoxybenzyl)-3-[2-(iodomethyl)tetrahydrofuran-4-yl]propan-1-ol. To a magnetically stirred 0 °C solution of the acetal **31** (0.320 g, 1.15 mmol) in 15 mL of acetonitrile under nitrogen atmosphere was added solid $NaHCO_3$ (0.293 g, 3.48 mmol), followed by *N*-iodosuccinimide (0.600 g, 2.67 mmol). After 1 h the ice bath was removed, and the solution was stirred for an additional hour at ambient temperature. The mixture was then diluted with excess hexane/ethyl acetate (1:1) and washed in a separatory funnel with two portions of saturated aqueous sodium thiosulfate. The organic phase was then passed through a pad of silica and concentrated to give a clear, yellow oil, which was taken up in 20 mL of methylene chloride and cooled to −78 °C. Diisobutylaluminum hydride (2.0 mL, 1.0 M in methylene chloride, 2.0 mmol) was then added, and the reaction was allowed to warm slowly to room temperature. After 2 h, the mixture was cooled to −78 °C and quenched with 2 mL of methanol, then 10 mL of saturated aqueous ammonium chloride was added, and the dry ice bath was removed. Dilution with 100 mL of hexanes/ethyl acetate (1:1) was followed by addition of 10 mL of a saturated aqueous solution of sodium potassium tartrate. The mixture was stirred vigorously until the organic phase was clear, and then the organic layer was separated and dried over sodium sulfate. The product (0.288 g, 62% for two steps, about a 4.8/1 mixture of iodomethyl diastereomers) was isolated via flash chromatography (1:1 hexanes/ethyl acetate): IR (thin film) 3440 (br), 2935, 2866, 1612, 1514, 1302, 1248, 1174, 1068, 1034, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) major isomer 7.23 (d, *J* = 8.6, 2 H), 6.87 (d, *J* = 8.6, 2 H), 5.29 (s, 1 H), 4.52 (d, *J* = 10.9, 1 H), 4.42 (d, *J* = 10.9, 1 H), 4.08–3.95 (m, 2 H), 3.83–3.72 (m, 2 H), 3.80 (s, 3 H), 3.59 (m, 1 H), 3.30–3.17 (m, 2 H), 2.72–2.61 (m, 1 H), 2.30 (br s, 1 H), 2.22–2.11 (m, 1 H), 2.02–1.63 (m, 2 H), 1.33 (dt, *J* = 12.1, 9.6, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) major isomer 159.2, 129.9, 129.4, 113.8, 79.3, 78.7, 71.7, 71.6, 59.5, 55.2, 44.4, 35.7, 34.2, 9.8; MS *m/e* (percent) 406 (M^+, 0.4), 150 (10.0) 138 (9.7) 137 (100), 122 (6.9), 121 (100).

(*E* and *Z*)-1-(Triphenylstannyl)-2-butene (33). A solution of LDA was prepared at 0 °C under argon atmosphere by treating diisopropylamine (3.0 mL, 21 mmol) in 75 mL of THF with nBuLi (12.5 mL, 1.45 M, 18.1 mmol). To this solution was added via cannula a solution of triphenyltin hydride (5.00 g, 14.2 mmol) in 25 mL of THF, and the resultant light yellow solution was stirred at 0 °C for 15 min. After cooling to −78 °C, crotyl chloride (5.0 mL, about 7:1 trans/cis, 51 mmol) was added all at once via syringe. The mixture was then allowed to warm slowly to ambient temperature. After the mixture had reached room temperature, it was poured into 100 mL of 7:1 hexanes/ethyl acetate and washed sequentially with 50 mL each of saturated aqueous sodium bicarbonate, water, brine, 10% HCl, and brine. The solution was then dried over sodium sulfate and filtered through a pad of silica. Solvent was removed under reduced pressure, and the residual oil was subjected to flash chromatography (50:1 hexanes/ethyl acetate) to give 6.24 g of a crude oil. This oil was taken up in about 60 mL of hot methanol and filtered, and the resultant solution was allowed to cool slowly to room temperature. The white crystals which separated (3.7 g, 64%, 4:1 trans/cis) were collected by suction filtration. A second crop (1.1 g, 19%, 2.5:1 trans/cis) was collected. Data reported below were collected on a 1:1 cis/trans mixture, mp = 49–50 °C: ^1H NMR ($CDCl_3$, 500 MHz) trans isomer 7.61–7.31 (m, 15 H), 5.71–5.66 (m, 1 H), 5.44–5.37 (m, 1 H), 2.39 (d, *J* = 8.3, 2 H), 1.61 (d, *J* = 6.4, 3 H); cis isomer 7.61–7.31 (m, 15 H), 5.78–5.72 (m, 1 H), 5.32–5.26 (m, 1 H), 2.42 (d, *J* = 8.9, 2 H), 1.49 (dd, *J* = 6.7, 0.9, 3 H). Anal. Calcd for $C_{22}H_{22}Sn$: C, 65.23; H, 5.47. Found: C, 65.31; H, 5.48.

[3*S*,3(2*S*,4*R*)]-3-(4-Methoxybenzyl)-3-[2-(iodomethyl)tetrahydrofuran-4-yl]propanal (32). An oven-dried flask fitted with a magnetic stir bar and argon line was charged with 50 mL of methylene chloride and cooled to −78 °C. Oxalyl chloride (0.90 mL, 10 mmol) was added, followed by dimethyl sulfoxide (0.90 mL, 13 mmol). After 5 min, the alcohol (2.674 g, 6.581 mmol) in 20 mL of methylene chloride was added via cannula, and the mixture was stirred at −78 °C for 30 min. Triethylamine (2.75 mL, 19.7 mmol) was added via syringe, and the solution was allowed to warm to ambient temperature. The mixture was diluted with methylene chloride and washed once with brine, and then the organic layer was dried over magnesium sulfate. After solvent removal, flash chromatography (1:1 methylene chloride/benzene with 9% ether) provided the desired product as a clear, colorless oil (2.5 g, about a 5:1 mixture of iodomethyl diastereomers, 94%): IR (thin film) 1721, 1612, 1514, 1247, 1174, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 9.84 (t, *J* = 1.9, 1 H), 7.22 (d, *J* = 8.5, 2 H), 6.88 (d, *J* = 8.5, 2 H), 4.53 (d, *J* = 11.0, 1 H), 4.42 (d, *J* = 11.0, 1 H), 4.06–3.88 (m, 3 H), 3.81 (s, 3 H), 3.27–3.24 (m, 3 H), 2.68 (dd, *J* = 5.2, 1.9, 2 H), 2.63 (m, 1 H), 2.15 (m, 1 H), 1.35 (dt, *J* = 12.2, 9.4, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 200.5, 159.3, 129.7, 129.4, 113.9, 78.8, 75.8, 71.8, 71.2, 55.3, 47.2, 45.1, 35.5, 9.5; MS *m/e* (percent) 386 (M − 18, 0.5), 259 (8.6), 150 (11.6), 138 (11.3)8 137 (100), 122 (8.3), 121 (80.5), 109 (8.2); HRMS calcd for $C_{16}H_{22}IO_4$ (M + H) 405.0564, found 405.0551.

[3*S*,4*S*,6*S*,6(2*S*,4*R*)]-4-Hydroxy-6-[(4-methoxybenzyl)oxy]-3-methyl-6-[2-(iodomethyl)tetrahydrofuran-4-yl]hex-1-ene (34). A solution of aldehyde **32** (0.790 g, 1.95 mmol, approximately 5:1 iodo ether diastereomeric mixture) in 20 mL of methylene chloride was cooled to −78 °C with stirring under argon, and then boron trifluoride etherate (0.260 mL, 2.11 mmol) was added via syringe. After allowing 10 min for complexation, a solution of triphenylcrotylstannane (1.48 g, 3.65 mmol, approximately 4:1 trans/cis) in 10 mL of methylene chloride (precooled to −78 °C) was added via cannula. After about 30 s, during the stannane addition, the clear, colorless solution began to slowly turn a cloudy white color. The mixture was stirred at −78 °C under argon for 100 min and then quenched with 10 mL of saturated aqueous sodium bicarbonate. After warming to ambient temperature, the mixture was diluted with methylene chloride and poured into a large separatory funnel. The organic layer was removed, and the aqueous slurry was washed twice with 50 mL of methylene chloride. The combined organic layers were dried over sodium sulfate. Solvent was removed via rotary evaporation, and the oily residue was subjected to flash chromatography (1:1 benzene/methylene chloride with 3% ether and then with 6% ether) to provide the desired product as a clear, colorless oil (0.484 g, 54%). ^1H NMR analysis indicated that the product was >97% diastereomerically pure. Further product could be obtained by performing another chromatography of the mixed fractions, although this was usually done with the combined mixed fractions from several reactions: $[\alpha]^{23}_D$ +14.8° (*c* 0.62, $CHCl_3$); IR (thin film) 3476 (br), 2959, 2869, 1613, 1514, 1248, 1067, 1034, 916, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.25–6.88 (m, 4 H), 5.80–5.73 (m, 1 H), 5.09 (d, *J* = 16.4, 1 H), 5.08 (d, *J* = 11.3, 1 H), 4.58 (d, *J* = 11.0, 1 H), 4.43 (d, *J* = 11.0, 1 H), 4.06 (t, *J* = 8.1, 1 H), 4.00–3.95 (m, 1 H), 3.81 (s, 3 H), 3.77–3.74 (m, 2 H), 3.65 (ddd, *J* = 9.0, 6.3, 3.1, 1 H), 3.27 (dd, *J* = 10.0, 5.1, 1 H), 3.24 (dd, *J* = 10.0, 6.3, 1 H), 2.75 (d, *J* = 3.3, 1 H), 2.69 (m, 1 H), 2.26 (m, 1 H), 2.13 (m, 1 H), 1.73 (ddd, *J* = 14.8, 10.5, 3.1, 1 H), 1.62 (ddd, *J* = 14.8, 6.2, 1.8, 1 H), 1.28 (dt, *J* = 12.2, 9.7, 1 H), 1.06 (d, *J* = 6.8, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 159.4, 140.6, 129.8, 129.6, 115.3, 113.9, 79.4, 78.7, 72.0, 71.9, 71.3, 55.2,

44.2, 44.1, 35.8, 35.1, 15.1, 9.9. Anal. Calcd for $C_{20}H_{29}IO_4$: C, 52.18; H, 6.35; I, 27.57. Found: C, 52.10; H, 6.32; I, 27.64.

Coupling of Aldehyde 41 and Sulfone 19. A solution of sulfone **19** (50.0 mg, 0.125 mmol) in 0.45 mL of THF under argon at −78 °C was treated with *n*-butyllithium (0.080 mL, 0.12 mmol), and the light yellow solution was stirred at that temperature for 15 min. The aldehyde **41** (51.0 mg, 0.0898 mmol) in 0.7 mL of THF was then added via syringe, mostly discharging the yellow color of the sulfone anion. After 1.5 h at −78 °C, the mixture was briefly warmed to 0 °C and then recooled to −78 °C. After quenching with 0.050 mL of aqueous NH_4Cl and diluting with 2 mL of 1:1 hexanes/ethyl acetate, the mixture was warmed to ambient temperature and dried over sodium sulfate. Solvents were removed under reduced pressure, and the product was used directly in the next reaction.

The oil recovered from the above reaction was taken up in 1 mL of methylene chloride, and the Dess–Martin periodinane (84.2 mg, 0.199 mmol) was added. After stirring for 2 h under argon, the cloudy mixture was diluted with 6 mL of 1:1 hexanes/ethyl acetate, and 8 drops of saturated aqueous sodium thiosulfate were added. The mixture was stirred at room temperature until the organic phase became clear and then dried over sodium sulfate. Flash chromatography (9% to 14% to 20% ethyl acetate in hexanes) allowed separation of 59.6 mg of β-keto sulfone as a clear, colorless oil, which was used immediately in the next reaction.

The β-keto sulfone from the above oxidation was dissolved in THF (3.3 mL) and methanol (1.7 mL), and then NaH_2PO_4 (60 mg, 0.50 mmol) was added. To this slurry, at −30 to −20 °C under argon, was added 6% sodium amalgam (about 0.15 g), and the mixture was stirred at that temperature for 3 h. After pouring the mixture into water and extracting twice with 1:1 hexanes/ethyl acetate, the combined organic layers were dried over sodium sulfate. Flash chromatography (12% ethyl acetate in hexanes) provided 25.4 mg of the desired ketone (34% for three steps): $[\alpha]^{23}_D$ −65.0° (*c* 0.20, $CHCl_3$); IR (thin film) 2937, 1719, 1615, 1514, 1460, 1297, 1110, 836; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.45–7.33 (m, 5 H), 7.25 (d, *J* = 8.5, 2 H), 6.82 (d, *J* = 8.5, 2 H), 5.81 (m, 1 H), 5.22 (s, 1 H), 5.06–4.98 (m, 2 H), 4.57 (d, *J* = 11.5, 1 H), 4.35 (d, *J* = 11.5, 1 H), 4.18 (d, *J* = 2.5, 1 H), 3.98–3.90 (m, 1 H), 3.71 (s, 3 H), 3.64 (dd, *J* = 10.1, 4.4, 1 H), 3.51 (dd, *J* = 10.1, 7.2, 1 H), 3.42–3.35 (m, 2 H), 3.40 (s, 3 H), 2.94 (m, 1 H), 2.58 (dd, *J* = 18.3, 6.1, 1 H), 2.44 (dd, *J* = 18.3, 7.1, 1 H), 2.30–2.27 (m, 1 H), 2.07–1.84 (m, 4 H), 1.83–1.76 (m, 2 H), 1.66–1.60 (m, 1 H), 1.42–1.31 (m, 2 H), 1.23–1.19 (m, 1 H), 1.10–0.82 (m, 14 H), 0.89 (s, 9 H), 0.56 (q, *J* = 8.0, 6 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 209.8, 159.1, 138.4, 137.7, 131.0, 129.8, 128.7, 128.0, 126.1, 115.8, 113.7, 100.8, 85.8, 84.1, 75.4, 75.3, 74.3, 71.1, 62.1, 58.0, 55.2, 45.9, 43.2, 36.4, 34.6, 34.1, 33.7, 30.8, 30.7, 30.6, 25.9, 18.2, 7.2, 6.8, 4.3, −4.5, −4.8. HRMS calcd for $C_{47}H_{77}O_8Si_2$ (M + H) 825.5159, found 825.5143.

Methyl (1*R*,3*R*)-3-Methoxycyclohex-4-enecarboxylate (43). To a −78 °C solution of lactone **15** (1.619 g, 10.37 mmol) in 50 mL of CH_2Cl_2 were added Et_3N (1.90 mL, 13.6 mmol) and *tert*-butyldimethylsilyl triflate (2.90 mL, 12.6 mmol). The resulting solution was stirred at −78 °C for 90 min and then at 0 °C for 60 min. The reaction mixture was poured into a separatory funnel containing 50 mL of pentane and 50 mL of ice cold brine, rinsing with an additional 75 mL of pentane. The organic layer was separated, dried over K_2CO_3, and filtered into a 1-L, oven-dried flask. The solvent was removed in vacuo to give a clear, pale yellow oil, which was dissolved in 100 mL of toluene and heated to reflux for 76 h. After cooling to room temperature, the reaction mixture was treated with a solution consisting of K_2CO_3 (1.52 g, 11.0 mmol) in H_2O (25 mL), THF (50 mL), and MeOH (50 mL). After 1 h, a solution consisting of LiOH (0.21 g, 5.0 mmol) in H_2O (25 mL), THF (25 mL), and MeOH (25 mL) was added. After 5 h, the mixture was poured into 100 mL of aqueous $NaHCO_3$ and 100 mL of Et_2O, and the organic layer was extracted with aqueous $NaHCO_3$ (3 × 50 mL). The combined aqueous extracts were acidified to pH 1 with 1 N HCl and then washed with four portions of Et_2O and two portions of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated to ca. 500 mL, and then treated with an ethereal solution of diazomethane. Concentration of this solution followed by flash chromatography (10:1 to 5:1 to 3:1 to 2:1 to 1:1 hexane/ethyl acetate) provided the desired methyl ester as a colorless oil (1.529 g, 87% from lactone **15**): $[\alpha]^{23}_D$ −28.3° (*c* 0.46, $CHCl_3$); IR (thin film) 2953, 1736, 1437, 1250, 1173, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 5.79–5.76 (m, 1 H), 5.74–5.71 (m, 1 H), 3.92–3.90 (m, 1 H), 3.69 (s, 3 H), 3.36 (s, 3 H), 2.64–2.61 (m, 1 H), 2.38–2.34 (m, 1 H), 2.27–2.24 (m, 2 H), 1.61 (dt, *J* = 9.5, 12.4, 1 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 174.8, 128.4, 127.5, 75.3, 55.6, 51.7, 38.2, 30.8, 27.7.

(1*R*,2*R*,4*R*)-4-Carbomethoxy-2-methoxycyclohexan-1-ol. To a −78 °C solution of ester **43** (1.529 g, 8.984 mmol) in 90 mL of THF was added a 1.0 M solution of BH_3·THF complex (13.5 mL, 13.5 mmol), and the resulting mixture was stirred at −78 °C for 30 min and then at 0 °C for 90 min. The reaction was quenched with 3 N NaOH (5.0 mL, 15 mmol) and 30% H_2O_2 (1.7 g, 15 mmol) and then stirred at room temperature for 3 h. Following treatment with 10 mL of aqueous $Na_2S_2O_3$ (5% w/v) for 10 min, the mixture was poured into 25 mL of aqueous NH_4Cl, rinsing with 150 mL of Et_2O. The aqueous layer was extracted with four portions of Et_2O and six portions of EtOAc, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a colorless oil. Flash chromatography (2:1 to 1:1 to 1:2 hexane/ethyl acetate) provided the desired alcohol as a clear, colorless oil (1.099 g, 5.839 mmol, 65%) along with a second, unidentified isomer (0.110 g, 0.584 mmol, 6.5%). Data are as follows for the major isomer: $[\alpha]^{23}_D$−72.4° (*c* 1.25, $CHCl_3$); IR (thin film) 3457 (br), 2948, 2872, 1734, 1098, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 3.68 (s, 3 H), 3.46–3.40 (m, 1 H), 3.41 (s, 3 H), 3.01–2.97 (m, 1 H), 2.76 (br s, 1 H), 2.41–2.33 (m, 2 H), 2.07 (ddd, *J* = 12.7, 4.5, 3.6, 1 H), 2.00–1.96 (m, 1 H), 1.48 (dq, *J* = 3.4, 13.1, 1 H), 1.38–1.27 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 174.8, 83.8, 73.0, 56.5, 51.8, 41.3, 30.8, 30.6, 26.6. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.55; H, 8.43.

(1*R*,2*R*,4*R*)-4-Carbomethoxy-2-methoxy-1-[(triisopropylsilyl)oxy]-cyclohexane (44). To a 0 °C solution of the hydroxy ester (1.099 g, 5.839 mmol) in 60 mL of CH_2Cl_2 were added Et_3N (1.48 mL, 10.6 mmol) and triisopropylsilyl triflate (2.58 mL, 9.60 mmol). The resulting solution was stirred for 60 min at 0 °C to room temperature and then poured into aqueous $NaHCO_3$. The aqueous layer was extracted with two additional portions of CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. Filtration and concentration provided a colorless oil, which was purified via flash chromatography (10:1 to 7:1 to 5:1 hexane/ethyl acetate) to give the desired silyl ether (2.286 g). This material was contaminated with triisopropylsilyl alcohol by ^{13}C NMR and IR but could be used directly in the next reaction. Further chromatography provided analytically pure material: $[\alpha]^{23}_D$ −43.0° (*c* 1.62, $CHCl_3$); IR (thin film) 2946, 2867, 1740, 1462, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 3.67 (s, 3 H), 3.63 (ddd, *J* = 9.7, 7.9, 4.5, 1 H), 3.37 (s, 3 H) 3.00 (ddd, *J* = 10.1, 7.7, 4.1, 1 H), 2.34 (tt, *J* = 10.8, 3.8, 1 H), 2.29–2.26 (m, 1 H), 2.02–1.98 (m, 1 H), 1.92–1.86 (m, 1 H), 1.53–1.45 (m, 2 H), 1.41–1.35 (m, 1 H), 1.09–1.06 (m, 21 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 175.2, 83.2, 73.4, 57.2, 51.6, 40.5, 32.3, 31.0, 25.7, 18.0, 12.5; MS *m/e* (percent) 345 (23.5), 313 (24.0), 301 (14.3), 175 (4.3); HRMS calcd for $C_{18}H_{36}O_4Si$ (M + H) 345.2462, found 345.2463. Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.61; H, 10.65.

(1*R*,2*R*,4*R*)-4-(Hydroxymethyl)-2-methoxy-1-[(triisopropylsilyl)-oxy]cyclohexane. To a solution of silyl ether **44** (≤5.839 mmol, from above reaction) in 60 mL of THF at 0 °C was added lithium aluminum hydride (6.0 mL of a 1.0 M solution in THF). After 30 min the reaction was carefully quenched with 228 μL of H_2O, followed by 228 μL of 15% NaOH, and then 683 μL of H_2O. The resulting solution was stirred vigorously for 10 min, treated with solid Na_2SO_4 for another 20 min, then filtered, and concentrated to give a clear, colorless oil. Flash chromatography (3:1 to 2:1 to 1:1 hexane/ethyl acetate) provided the desired alcohol as a colorless oil (1.621 g, 5.121 mmol, 87% from the hydroxy ester): $[\alpha]^{23}_D$ −34.7° (*c* 0.72, $CHCl_3$); IR (thin film) 3400 (br), 2942, 2867, 1464, 1383, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 3.56 (ddd, *J* = 10.6, 8.2, 4.7, 1 H), 3.47 (br t, *J* = 5.3, 2 H), 3.38 (s, 3 H), 2.96 (ddd, *J* = 10.8, 8.1, 4.5, 1 H), 2.13 (m, 1 H), 1.95 (m, 1 H), 1.74–1.69 (m, 1 H), 1.57–1.53 (m, 1 H), 1.49 (br s, 1 H), 1.38–1.32 (m, 1 H), 1.07–1.04 (m, 21 H), 1.05–0.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 84.2, 74.9, 67.6, 57.4, 38.4, 33.3, 32.4, 26.8, 18.1, 12.6; HRMS calcd for $C_{17}H_{36}O_3Si$ (M + H) 317.2510, and 317.2515. Anal. Calcd for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46. Found: C, 63.92; H, 11.47.

(1*R*,3*R*,4*R*)-3-Methoxy-4-[(triisopropylsilyl)oxy]cyclohexanecarboxaldehyde (45). To a −78 °C solution of oxalyl chloride (580 μL, 6.65 mmol) in 30 mL of CH_2Cl_2 was added dimethyl sulfoxide (980 μL, 13.8 mmol). The resulting solution was stirred for 10 min, and then the alcohol (1.621 g, 5.121 mmol) was added via cannula in 10 mL of CH_2Cl_2, with two 5-mL rinses. After 10 min, Et_3N was added (3.90 mL, 28.0 mmol), and the solution was allowed to warm to ambient temperature over a period of 15 min. The reaction was quenched with aqueous NH_4Cl, and the aqueous layer was extracted with three portions of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, then filtered and concentrated to provide the crude product as a yellow oil. Flash chromatography (20:1 to 10:1 to 5:1 hexane/ethyl acetate) gave the desired aldehyde as a clear, colorless oil (1.426 g, 4.534 mmol, 89% yield): $[\alpha]^{23}_D$ −49.7° (*c* 1.25, $CHCl_3$); IR (thin film) 2944, 2867, 1730, 1464, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) 9.68 (s, 1 H), 3.77 (dt, *J* = 6.6, 3.0, 1 H), 3.35 (s, 3 H), 3.19–3.12 (m, 1 H), 2.29–2.21 (m, 2 H), 1.95–1.88 (m, 2 H), 1.72–1.58 (m, 2 H), 1.50–1.42 (m, 1 H), 1.08–1.06 (m, 21 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 203.4, 81.4, 71.0, 57.0, 46.3, 29.2, 27.2, 21.0, 18.2, 12.6; MS *m/e* (percent) 315 (M + H, 4.9), 299 (4.4), 287 (6.9), 283 (11.7), 271 (21.8), 145 (9.5), 117 (4.8),

75 (4.7); HRMS calcd for $C_{17}H_{34}O_3Si$ (M + H) 315.2356 found 315.2371.

(1*R*,2*R*,4*R*)-4-Ethynyl-2-methoxy-1-[(triisopropylsilyl)oxy]cyclohexane (46). A slurry of potassium *tert*-butoxide (0.543 g, 4.84 mmol) in 15 mL of THF was cooled to −78 °C under argon. To this was added via cannula a solution of the Seyferth diazophosphonate reagent[50] (0.727 g, 4.84 mmol) in 15 mL of THF (plus a 15 mL rinse), followed after 10 min by a solution of aldehyde **45** (1.384 g, 4.400 mmol) in 15 mL of THF precooled to −78 °C (followed by two 15-mL rinses). The resulting solution was stirred at −78 °C for 10 h and then maintained at −20 °C for another 10 h. The reaction was quenched with aqueous $NaHCO_3$ and then poured into a mixture of Et_2O and aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with four portions of Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a pale yellow oil. Flash chromatography (20:1 to 10:1 hexane/ethyl acetate) provided the desired acetylene as a clear, colorless oil (1.303 g, 4.196 mmol, 95% yield): $[\alpha]^{23}_D$ −48.8° (*c* 1.22, $CHCl_3$); IR (thin film) 3312, 2944, 2867, 2118, 1464, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 3.63–3.54 (m, 1 H), 3.39 (s, 3 H), 2.92 (ddd, *J* = 10.7, 8.1, 4.2, 1 H), 2.36–2.25 (m, 2 H), 2.04 (d, *J* = 2.2, 1 H), 2.00–1.90 (m, 2 H), 1.45–1.25 (m, 2 H), 1.08–1.06 (m, 21 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 87.2, 83.5, 74.0, 67.9, 57.2, 35.3, 33.3, 30.6, 27.4, 18.2, 12.7; MS *m/e* (percent) 311 (M + H, 14.9), 279 (23.5), 268 (12.1), 267 (46.5), 145 (17.9), 117 (5.9), 89 (3.3); HRMS calcd for $C_{18}H_{34}O_2Si$ (M + H) 311.2407, found 311.2400. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.6; H, 11.0. Found: C, 69.3; H, 11.1.

(1*R*,2*R*,4*R*)-4-(1-Propyn-1-yl)-2-methoxy-1-[(triisopropylsilyl)oxy]-cyclohexane (47). To a −78 °C solution of acetylene **46** (1.292 g, 4.161 mmol) in 40 mL of THF was added nBuLi (2.20 mL of a 2.30 M solution, 5.06 mmol). The resulting solution was stirred at −78 to −35 °C over 2 h, then cooled to −78 °C, and treated with excess MeI (5.20 mL, 83.5 mmol). After stirring for 14 h at −78 °C to ambient temperature, the reaction was quenched by the addition of aqueous $NaHCO_3$ and poured into a mixture of Et_2O and aqueous $NaHCO_3$. The aqueous layer was extracted with three portions of Et_2O, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to provide a pale yellow oil. Flash chromatography (40:1 to 20:1 hexane/ethyl acetate) gave the desired product as a clear, light yellow oil (1.302 g, 4.012 mmol, 96% yield): $[\alpha]^{23}_D$ −46.3° (*c* 1.00, $CHCl_3$); IR (thin film) 2944, 2867, 1464, 1383, 1144, 1113, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.58–3.51 (m, 1 H), 3.37 (s, 3 H), 2.93–2.85 (m, 1 H), 2.29–2.19 (m, 2 H), 1.95–1.82 (m, 2 H), 1.77 (d, *J* = 2.1, 3 H), 1.34–1.16 (m, 2 H), 1.07–1.06 (m, 21 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 83.9, 76.6, 75.3, 74.3, 57.0, 35.9, 33.4, 31.0, 27.6, 17.7, 12.3, 3.0; MS *m/e* (percent) 325 (M + H, 11.2), 293 (15.7), 281 (37.9), 151 (8.3), 119 (12.4); HRMS calcd for $C_{19}H_{36}O_2Si$ (M + H) 325.2564, found 325.2560. Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.3; H, 11.2. Found: C, 70.3; H, 11.2.

(1*R*,2*R*,4*R*)-4-[(*E*)-2-Bromo-1-propen-1-yl]-2-methoxy-1-[(triisopropylsilyl)oxy]cyclohexane (9). To a solution of acetylene **47** (275 mg, 0.848 mmol) in 9 mL of benzene was added Cp_2ZrHCl[67] (656 mg, 2.54 mmol) in one portion. The resulting solution was heated to 35–40 °C for 70 min and cooled to room temperature, and *N*-bromosuccinimide (498 mg, 2.80 mmol) was added. After stirring for 25 min, the reaction was quenched with 5 mL of 5% (w/v) aqueous $Na_2S_2O_3$, stirred vigorously for 5 min and then filtered through a pad of Celite, rinsing with Et_2O. The layers were separated, and the aqueous layer was extracted with three portions of Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a yellow oil plus a granular white solid. Flash chromatography of this material (3:1 to 2:1 hexane/CH_2Cl_2) provided the desired vinyl bromide as a clear, colorless oil (295 mg, 0.728 mmol, 86% yield): $[\alpha]^{23}_D$ −35.0° (*c* 0.90, $CHCl_3$); IR (thin film) 2942, 2867, 1468, 1146, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 5.69 (br d, *J* = 9.7, 1 H), 3.59–3.52 (m, 1 H), 3.38 (s, 3 H), 3.00–2.92 (7, 1 H), 2.24 (d, *J* = 1.3, 3 H), 2.26–2.18 (m, 1 H), 2.05–1.92 (m, 2 H), 1.66–1.59 (m, 2 H), 1.42–1.31 (m, 1 H), 1.19–0.98 (m, 1 H), 1.08–1.06 (m, 21 H); ^{13}C NMR ($CDCl_3$, 300 MHz) 136.2, 118.9, 84.0, 74.4, 57.2, 37.1, 35.5, 33.5, 30.2, 23.3, 18.1, 12.7; MS *m/e* (percent) 407 (M + H, 9.5), 405 (9.5), 375 (8.2), 373 (8.0), 363 (10.0), 361 (9.4), 293 (3.4), 233 (4.9), 231 (5.0), 201 (7.5), 199 (7.5), 151 (3.1), 145 (5.3), 121 (2.8), 119 (4.1), 117 (2.1), 91 (1.2), 89 (0.9), 69 (1.3), 67 (1.2); HRMS calcd for $C_{19}H_{37}BrO_2Si$ (M + H) 407.1805, found 407.1808. Anal. Calcd for $C_{19}H_{37}BrO_2Si$: C, 56.3; H, 9.2; Br, 19.7. Found: C, 56.3; H, 9.3; Br, 19.8.

[3*S*,4*S*,6*S*,6(2*S*,4*R*)]-6-[2-(Iodomethyl)tetrahydrofuran-4-yl]-6-[(4-methoxybenzyl)oxy]-3-methyl-4-[(triisopropylsilyl)oxy]-1-hexene. To a solution of alcohol **34** (0.691 g, 1.50 mmol) in 20 mL of dichloromethane were added triethylamine (335 μL, 2.40 mmol) and triisopropylsilyl triflate (0.56 mL, 1.4 mmol). The resulting solution was stirred at room temperature for 3 h and then poured into aqueous $NaHCO_3$, rinsing with dichloromethane. The layers were separated, and the aqueous was extracted with three portions of dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a yellow-orange oil, which was purified via flash chromatography (20:1 to 10:1 hexane/ethyl acetate) to provide the desired silyl ether as a clear, pale yellow oil (1.013 g, >100% of theoretical due to the presence of triisopropylsilanol). This material was generally used in the next reaction without further purification. A second chromatography provided analytically pure material, data for which are reported below: $[\alpha]^{23}_D$ −12.6° (*c* 0.78, $CHCl_3$); IR (thin film) 2944, 2867, 1613, 1514, 1464, 1248, 1092, 1065, 1038, 884, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.23 (d, *J* = 8.6, 2 H), 6.88 (d, *J* = 8.6, 2 H), 6.06 (ddd, *J* = 17.4, 10.6, 5.7, 1 H), 5.07 (d, *J* = 10.6, 1 H), 5.02 (d, *J* = 17.4, 1 H), 4.44 (s, 2 H), 4.03–3.98 (m, 3 H), 3.85 (t, *J* = 8.3, 1 H), 3.81 (s, 3 H), 3.64–3.61 (m, 1 H), 3.29–3.23 (m, 2 H), 2.69 (m, 1 H), 2.47 (br s, 1 H), 2.17–2.12 (m, 1 H), 1.69 (ddd, *J* = 14.5, 8.8, 3.5, 1 H), 1.44 (m, 1 H), 1.08 (br s, 21 H), 0.99 (d, *J* = 7.0, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 159.1, 140.1, 130.7, 128.9, 114.2, 113.8, 78.8, 77.5, 73.8, 70.8, 70.2, 55.2, 44.5, 42.8, 36.9, 35.5, 18.3, 18.3, 14.1, 13.0, 9.7; MS *m/e* (percent) 639 (12, M + Na), 241 (31), 121 (100). Anal. Calcd for $C_{29}H_{49}IO_4Si$: C, 56.48; H, 8.01; I, 20.58. Found: C, 56.44; H, 8.06; I, 20.68.

[2*R*,3*S*,5*S*,5(2*S*,4*R*)]-5-[2-(Iodomethyl)tetrahydrofuran-4-yl]-5-[(4-methoxybenzyl)oxy]-2-methyl-3-[(triisopropylsilyl)oxy]pentanal (8). A solution of the olefin (1.50 mmol, from the above reaction) in 25 mL of 1:1 methanol/dichloromethane with 1.5 mL of pyridine and two drops of Sudan III indicator was cooled to −78 °C and treated with ozone until the solution's pink color had been replaced with a steel blue color. The solution was purged with nitrogen, allowed to warm to ambient temperature, and then treated with 5 mL of dimethyl sulfide. After 13 h the solution was concentrated to a volume of ca. 3 mL and diluted with 50 mL of ether. This solution was extracted with five portions of saturated aqueous $CuSO_4$, at which point TLC analysis indicated complete removal of the pyridine from the organic phase. The solution was then washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a clear, pale yellow oil. Flash chromatography (60 to 40:1 dichloromethane/ether) provided the desired aldehyde as a colorless oil (0.917 g, 1.48 mmol, 98.7% yield for the two step sequence): $[\alpha]^{23}_D$ −15.9° (*c* 1.13, $CHCl_3$); IR (thin film) 2944, 2867, 1725, 1514, 1464, 1250, 1100, 1065, 1038, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 9.85 (s, 1 H), 7.21 (d, 8.6, 2 H), 6.88 (d, *J* = 8.6, 2 H), 4.46 (d, *J* = 11.0, 1 H), 4.40 (d, *J* = 11.0, 1 H), 4.43–4.39 (m, 1 H), 4.02–3.96 (m, 2 H), 3.88–3.83 (m, 1 H), 3.81 (s, 3 H), 3.57 (ddd, *J* = 8.6, 6.6, 3.7, 1 H), 3.30–3.24 (m, 2 H), 2.72–2.66 (m, 1 H), 2.59–2.55 (m, 1 H), 2.17–2.12 (m, 1 H), 1.90–1.84 (m, 1 H), 1.63–1.58 (m, 1 H), 1.49–1.42 (m, 1 H), 1.08 (d, *J* = 7.9, 3 H), 1.08–1.05 (m, 21 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 204.9, 159.2, 129.0, 113.9, 113.8,, 78.8, 77.5, 71.1, 70.6, 70.0, 55.3, 52.1, 44.3, 37.8, 35.4, 18.3, 13.0, 9.6; 8.0; MS *m/e* (percent) 641 (3, M + Na), 241 (1), 121 (100). Anal. Calcd for $C_{28}H_{47}IO_5Si$: C, 54.36; H, 7.66; I, 20.51. Found: C, 54.19; H, 7.47; I, 20.62.

[1(1*R*,3*R*,4*R*),1*E*,3*S*,4*S*,5*S*,7*S*,7(2*S*,4*R*)]-2,4-Dimethyl-3-hydroxy-7-[2-(iodomethyl)tetrahydrofuran-4-yl]-7-[(4-methoxybenzyl)-oxy]-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl]-5-[(triisopropylsilyl)oxy]-1-heptene (48). Vinyl bromide **9** (275 mg, 0.678 mmol) was dried azeotropically with three 2-mL portions of xylene in a 100-mL flask under high vacuum and then purged with argon. THF (6 mL) was added, the solution was cooled to −78 °C, and tBuLi (763 μL of a 1.95 M solution in pentane, 1.49 mmol) was added dropwise. The solution was stirred for 40 min at −78 °C and then treated with the magnesium bromide solution prepared below (700 μL of a 1.0 M solution, 0.70 mmol). The resulting heterogeneous solution was stirred for an additional 20 min at −78 °C then treated with aldehyde **8** (332 mg, 0.537 mmol, dried azeotropically with three 2-mL portions of xylene), which was added via cannula in 2 × 3 mL dichloromethane and precooled to −78 °C. The reaction was allowed to proceed 65 min at −78 °C and 30 min at room temperature before quenching with 5 mL of aqueous ammonium chloride. After diluting with an additional 15 mL of dichloromethane, the layers were separated, and the aqueous phase was extracted with three 15-mL portions of dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a colorless oil, which was purified via flash chromatography (30:10:1 to 23:7:1 to 15:5:1 to 20:0:1 to 10:0:1 dichloromethane/hexane/ether) to provide the β-carbinol (70.6 mg, 0.0747 mmol, 14%) plus the desired α-carbinol (318 mg, 0.336 mmol, 63%); $[\alpha]^{23}_D$ +7.5° (*c* 1.08, $CHCl_3$); IR (thin film) 3480 (br), 2942, 2867, 1613, 1514, 1464, 1248, 1109, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.22 (d, *J* = 6.7, 2 H), 6.88 (d, *J* = 6.7, 2 H), 5.35 (br d, *J* = 9.0, 1 H), 4.45 (d, *J* = 11.3, 1 H), 4.41 (d, *J* = 11.3, 1 H), 4.18 (d, *J* = 2.1, 1 H), 4.13 (m, 1 H), 4.03–3.96 (m, 2 H), 3.86–3.80 (m, 1 H), 3.81 (s, 3 H), 3.56–3.54 (m, 1 H), 3.43–3.36 (m, 1 H), 3.41 (s, 3 H), 3.29–3.22 (m, 2 H), 3.00–2.97 (m, 1 H), 2.84 (br s, 1 H), 2.64–2.59 (m, 1 H), 2.27–2.23 (m, 1 H), 2.14–2.11 (m, 1 H), 2.08–2.03 (m, 1 H), 2.00–1.92 (m, 2 H), 1.77–1.73 (m, 1 H), 1.67–1.61

(m, 2 H), 1.55–1.50 (m, 1 H), 1.53 (d, J = 1.1, 3 H), 1.42–1.36 (m, 1 H), 1.10–1.08 (m, 42 H), 1.03–0.96 (m, 1 H), 0.93–0.90 (m, 1 H), 0.86 (d, J = 7.0, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.1, 134.1, 130.0, 129.8, 128.8, 113.7, 84.4, 78.7, 78.3, 76.3, 75.3, 74.9, 70.6, 69.8, 57.2, 55.0, 44.0, 39.2, 38.0, 36.2, 35.1, 34.8, 34.1, 30.6, 26.6, 18.0, 17.9, 13.2, 12.5, 9.2, 5.7; MS m/e (percent) 967 (M + Na, 23.2), 561 (12.0), 423 (46.2), 397 (11.1), 279 (14.3), 267 (13.8), 255 (10.6), 251 (27.3), 241 (16.4), 239 (10.1), 215 (22.7), 213 (18.0), 201 (14.5); HRMS calcd for $C_{47}H_{85}IO_7Si_2$ (M + Na) 967.4774, found 967.47389. Anal. Calcd for $C_{47}H_{85}IO_7Si_2$: C, 59.7; H, 9.1. Found: C, 59.1; H, 9.0.

Preparation of Magnesium Bromide Solution. To a slurry of powdered magnesium (0.520 g, 21.4 mmol) in 15 mL of ether was added 1,2-dibromoethane (1.72 mL, 20.0 mmol) in 5 mL of benzene dropwise over 45 min (the rate of addition was adjusted so as to maintain a gentle reflux). The resulting solution was stirred for another 30 min and then allowed to stand for 1–2 h before being used in the vinyl bromide coupling. The concentration of magnesium bromide was assumed to be 1.0 M.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic acid (5). A mixture of DL-pipecolinic acid (8.33 g, 64.5 mmol) and D-tartaric acid (10.5 g, 70.0 mmol) was dissolved in 300 mL of hot ethanol and filtered by gravity through a piece of fluted filter paper. The resultant clear solution was reduced in volume to 100 mL by boiling and then allowed to cool slowly to ambient temperature. After 2 days, the mixture was cooled to about 5 °C for 3 h, and then the crystals (7 g) were collected by suction filtration. The product thus obtained was recrystallized two more times from ethanol to yield 3.28 g (36% yield) of clean, white crystals, mp 181–182 °C dec: $[\alpha]^{23}_D$ −20.1° (c 10.0, H_2O) [lit. mp 182 °C, $[\alpha]^{23}_D$ −20.2° (c 10.0, H_2O)].[26]

A solution of the salt (2.0 g, 7.2 mmol) prepared above in 10 mL of 4:1 THF/H_2O was treated with triethylamine (4.0 mL, 29 mmol) and BOC-ON (2.288 g, 9.198 mmol) and stirred at room temperature for 40 h. After the solution was made basic with excess aqueous sodium bicarbonate, the mixture was reduced in volume under reduced pressure. The aqueous residue was washed with three portions of ether, and the ether layers were discarded. The aqueous phase was then adjusted to pH 3, initially with 10% aqueous HCl and then with about 1% aqueous HCl. The organics were extracted from the now cloudy solution with two portions of ethyl acetate, and then the combined organic layers were dried over sodium sulfate. Solvent removal was followed by flash chromatography (50% ethyl acetate in hexanes) to give 1.4 g of crude solid. Pure product was obtained upon recrystallization from 1:1 hexanes/ethyl acetate. The colorless, crystalline product (mp 120–121 °C, 1.114 g, 68%) gave ^{1}H and ^{13}C NMR spectra which indicated a mixture of rotamers: $[\alpha]^{23}_D$ − 45.8° (c 0.6, MeOH) [lit. mp 121–122 °C, $[\alpha]^{23}_D$ −45.1° (c 1.08 MeOH);[68] ^{1}H NMR ($CDCl_3$, 250 MHz) 9.45 (br s, 1 H), 4.93 and 4.80 (rotamers, br s, 1 H), 3.96 (m, 1 H), 2.97 (m, 1 H), 2.24 (m, 1 H), 1.80–1.59 (m, 3 H), 1.58–1.25 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 177.8, 156.1, 155.5, 80.3, 54.7, 53.5, 42.1, 41.0, 28.3, 26.6, 24.7, 24.5, 20.8, 20.7; IR (thin film) 3500–2400 (br), 2977, 2940, 2863, 1748, 1701, 1659, 1478, 1412, 1395, 1368, 1161 cm^{-1}; Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.73; H, 8.39; N, 6.07.

[1(1*R*,3*R*,4*R*),1*E*,3(2*S*),3*S*,4*S*,5*S*,7*S*,7(2*S*,4*R*)]-3-[*N*-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy]-2,4-dimethyl-7-[2-(iodomethyl)-tetrahydrofuran-4-yl]-7-[(4-methoxybenzyl)oxy]-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl]-5-[(triisopropylsilyl)oxy]-1-heptene. Alcohol **48** (240 mg, 0.254 mmol) was combined with t-BOC-(L)-pipecolinic acid (233 mg, 1.02 mmol), dicyclohexylcarbodiimide (236 mg, 1.14 mmol), and 4-pyrrolidinopyridine (56 mg, 0.38 mmol) and evacuated under high vacuum for 60 min. The mixture was then purged with argon, cooled to −20 °C, and dissolved in 9 mL of dichloromethane. The resulting cloudy white solution was stirred at −20 °C for 9 h and then stored in a freezer overnight. After 19 h of total reaction time, the mixture was filtered through a pad of Celite and concentrated to give an oily white solid, which was purified via flash chromatography (23:7:1 to 15:5:1 to 20:0:1 dichloromethane/hexane/ether) to provide the desired pipecolinic ester as a white foam (238 mg, 0.205 mmol, 81% yield): $[\alpha]^{23}_D$ −21.5° (c 1.09, $CHCl_3$); IR (thin film) 2947, 2867, 1742, 1698, 1514, 1464, 1366, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.22 (d, J = 8.2, 2 H), 6.88 (d, J = 8.2, 2 H), 5.40–5.29 (m, 1 H), 5.35 (d, J = 5.9, 1 H) 4.86 and 4.68 (rotamers, br s, 1 H), 4.42 (br s, 2 H), 4.03–3.98 (m, 2 H), 3.95–3.91 (m, 1 H), 3.86–3.81 (m, 1 H), 3.82 (s, 3 H), 3.56–3.52 (m, 1 H), 3.37 and 3.36 (rotamers, s, 3 H), 3.27–3.23 (m, 2 H), 3.05–2.90 (m, 2 H), 2.62–2.53 (m, 1 H), 2.25–2.15 (m, 2 H), 2.13–2.06 (m, 1 H), 1.96–1.88 (m, 4 H), 1.68–1.60 (m, 3 H), 1.57–1.55 (m, 3 H), 1.54–1.48 (m, 2 H), 1.43 and 1.41 (rotamers, s, 9 H), 1.41–1.31 (m, 2 H), 1.26–1.23 (m, 1 H), 1.21–1.13 (m, 2 H), 1.07–1.04 (m, 42 H), 1.10–1.01 (m, 2 H), 0.97–0.94 (m, 1 H), 0.91 (d, J = 6.7, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.6, 159.2, 155.6, 155.3, 136.0, 134.0, 131.7, 131.1, 130.4, 130.1, 129.0, 128.9, 113.8, 84.3, 81.5, 79.6, 79.2, 78.8, 77.4, 77.2, 74.8, 71.2, 70.4, 70.3, 69.9, 57.2, 55.2, 54.9, 53.8, 44.5, 43.9, 42.0, 41.0, 39.9, 38.8, 37.9, 37.4, 36.0, 35.8, 35.6, 35.3, 35.0, 34.1, 30.5, 28.3, 26.9, 24.9, 24.7, 20.8, 20.6, 18.4, 18.1, 13.3, 12.9, 12.6, 12.3, 12.2, 9.9, 9.6, 9.4, 9.3; HRMS calcd for $C_{58}H_{102}INO_{10}Si_2$(M + Na) 1178.5981, found 1178.6061.

[1(1*R*,3*R*,4*R*),1*E*,3(2*S*),3*S*,4*S*,5*S*,7*S*,8*R*]-3-[*N*-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy]-2,4-dimethyl-8-(hydroxymethyl)-7-[(4-methoxybenzyl)oxy]-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl]-5-[(triisopropylsilyl)oxy]-1,10-undecadiene. The pipecolinate ester (238 mg, 0.205 mmol) was dissolved in 6 mL of 95% ethanol and treated with zinc dust (134 mg, 2.05 mmol) and ammonium chloride (55 mg, 1.0 mmol) with gentle heating to 35–40 °C for 60 min. After cooling to room temperature, the solution was filtered through a pad of Celite and concentrated to give an oily white solid, which was purified via flash chromatography (15:5:1 to 20:0:1 dichloromethane/hexane/ether) to provide the desired alcohol as a clear, pale yellow oil (210 mg, 0.204 mmol, 99% yield): $[\alpha]^{23}_D$ −33.7° (c 0.83, $CHCl_3$); IR (thin film) 3580 (br), 2942, 2867, 1742, 1698, 1514, 1464, 1248, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.23 (d, J = 8.2, 2 H), 6.88 (d, J = 8.2, 2 H), 5.82–5.70 (m, 1 H), 5.37 (d, J = 5.7, 1 H), 5.31 and 5.27 (rotamers, d, J = 8.3 and 10.0, 1 H), 5.10–5.02 (m, 2 H), 4.85 and 4.69 (rotamers, br s, 1 H), 4.51–4.38 (m, 2 H), 4.04 and 3.65 (rotamers, br m, 1 H), 3.47 and 3.05 (rotamers, br m, 1 H), 3.96–3.87 (m, 2 H), 3.81 (s, 3 H), 3.59–3.50 (m, 2 H), 3.37 and 3.35 (rotamers, s, 3 H), 2.98–2.85 (m, 2 H), 2.59 and 2.34 (rotamers, m, 1 H), 2.32 (br s, 1 H), 2.28–2.19 (m, 3 H), 2.08–2.00 (m, 1 H), 1.96–1.91 (m, 2 H), 1.85–1.78 (m, 2 H), 1.67–1.63 (m, 3 H), 1.57 and 1.54 (rotamers, br s, 3 H), 1.45 and 1.43 (rotamers, s, 9 H), 1.41–1.33 (m, 2 H), 1.27–1.24 (m, 1 H), 1.20–1.13 (m, 2 H), 1.09–1.03 (m, 42 H), 1.01–0.94 (m, 2 H), 0.92 (d, J = 6.6, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.6, 159.2, 155.9, 137.4, 136.7, 136.2, 133.7, 131.7, 130.5, 129.3, 129.0, 126.0, 116.9, 116.5, 113.8, 84.3, 81.7, 79.8, 79.0, 78.7, 74.8, 74.5, 71.5, 71.0, 69.4, 62.2, 61.9, 57.3, 57.2, 55.3, 55.2, 54.9, 53.8, 43.4, 42.3, 42.0, 41.0, 39.4, 38.1, 36.6, 36.0, 35.8, 35.0, 34.1, 33.2, 30.6, 30.5, 28.4, 26.9, 24.9, 24.7, 20.8, 20.6, 18.5, 18.4, 18.1, 18.0, 13.4, 13.3, 13.0, 12.6, 12.2, 12.1, 9.4, 8.9; HRMS calcd for $C_{58}H_{103}NO_{10}Si_2$ (M + Na) 1052.7013, found 1052.7005.

[1(1*R*,3*R*,4*R*),1*E*,3(2*S*),3*S*,4*S*,5*S*,7*S*,8*S*]-3-[*N*-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy]-7-[(4-methoxybenzyl)oxy]-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl]-2,4-dimethyl-8-(2-propen-1-yl)-5-[(triisopropylsilyl)oxy]-1-nonen-9-al (51). To a −78 °C solution of oxalyl chloride (105 μL of a 2.0 M solution, 0.210 mmol) in 1.5 mL of dichloromethane was added dimethyl sulfoxide (32 μL, 0.45 mmol). After 15 min, the primary alcohol (144 mg, 0.140 mmol) was added in 1 mL of dichloromethane via cannula, with two 0.75-mL rinses. The resulting solution was stirred for 15 min, and then treated with triethylamine (117 μL, 0.839 mmol). The dry ice/acetone bath was removed, and the solution was allowed to warm gradually to room temperature over 60 min. The reaction was quenched by the addition of 2 mL of aqueous ammonium chloride. The layers were separated, and the aqueous layer was extracted with three 5-mL portions of dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a pale yellow oil, which was purified via flash chromatography (11:9:1 hexane/dichloromethane/ether) to provide the desired aldehyde as a clear, colorless oil (139 mg, 0.136 mmol, 97% yield): $[\alpha]^{23}_D$ −23.7° (c 0.66, $CHCl_3$); IR (thin film) 2942, 2867, 1742, 1727, 1698, 1514, 1464, 1391, 1366, 1250, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 9.75 and 9.73 (rotamers, br s, 1 H), 7.22 (d, J = 8.5, 2 H), 6.89 (d, J = 8.5, 2 H), 5.79–5.68 (m, 1 H), 5.38 (br d, J = 8.7, 1 H), 5.35–5.32 (m, 1 H), 5.07–5.03 (m, 2 H), 4.86 and 4.69 (rotamers, br s, 1 H), 4.46–4.43 (m, 2 H), 4.04 and 3.71 (rotamers, m, 1 H), 3.64 and 3.03 (rotamers, m, 1 H), 3.93–3.88 (m, 2 H), 3.82 (s, 3 H), 3.56–3.51 (m, 1 H), 3.37 and 3.36 (rotamers, s, 3 H), 2.98–2.93 (m, 1 H), 2.60–2.53 (m, 2 H), 2.50–2.47 (m, 1 H), 2.38–2.33 (m, 1 H), 2.26–2.14 (m, 2 H), 2.05–2.00 (m, 1 H), 1.98–1.92 (m, 2 H), 1.90–1.86 (m, 1 H), 1.69–1.62 (m, 4 H), 1.56 and 1.54 (rotamers, br s, 3 H), 1.46–1.44 (br s, 9 H), 1.43–1.36 (m, 2 H), 1.22–1.14 (m, 2 H), 1.10–1.04 (m, 42 H), 1.01–0.96 (m, 1 H), 0.91 (d, J = 6.6, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 203.8, 203.2, 170.7, 159.3, 170.7 155.7, 155.4, 136.2, 135.5, 135.2, 134.4, 131.4, 130.9, 130.1, 129.8, 129.1, 129.0, 117.4, 117.1, 113.8, 84.3, 81.5, 79.7, 79.6, 75.9, 75.7, 74.8, 70.9, 70.7, 69.8, 57.2, 55.3, 54.9, 54.1, 53.9, 53.8, 42.0, 41.0, 39.4, 38.6, 37.4, 37.0, 35.9, 35.8, 35.0, 34.1, 30.5, 29.7, 29.6, 28.3, 26.9, 24.9, 24.7, 20.8, 20.6, 18.5, 18.4, 18.1, 18.0, 13.3, 13.2, 12.8, 12.7, 12.6, 12.4, 12.2, 9.4, 9.1; HRMS calcd for $C_{58}H_{101}NO_{10}Si_2$ (M + Na) 1050.6856, found 1050.6881.

(2*R*,4*R*)-2,4-Diacetoxy-1,5-dichloro-3-pentanol (54). To a 0 °C slurry of L-arabitol (28.9 g, 0.190 mol) in CH_3CN (dried over 4 Å molecular sieves prior to use) was added via syringe α-acetoxyisobutyric acid chloride (71.7 g, 0.436 mol).[54] The slurry was stirred at 0 °C for 1.5 h, then warmed to ambient temperature, and stirred for 15 h. The

resulting solution was diluted with 2:1 hexanes/ethyl acetate (150 mL) and washed with 0.1 N NaOH (4 × 150 mL), followed by water (150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual solvent was removed under high vacuum to afford 46.8 g (90% yield) of a pale yellow oil judged to be an ca. 7:3 mixture of the title compound with chloride/acetoxy regioisomers, which was normally used without further purification in subsequent reactions. An analytical sample of the primary bis-chloride was prepared by recrystallization (ether/hexanes) to provide prisms, mp 84–88 °C: $[\alpha]_D^{23}$ +4.5° (*c* = 1.1, $CHCl_3$); IR ($CHCl_3$) 3381 (br), 3025, 1748, 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 5.17 (t, *J* = 6.6, 1 H), 1.02 (dt, *J* = 9.3, 3.4, 1 H), 4.27 (m, 1 H), 4.27 (m, 1 H), 3.89 (d, *J* = 3.3, 1 H), 3.80–3.60 (m, 2 H), 2.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.0, 169.9, 71.0, 70.4, 68.0, 44.1, 41.0, 20.7, 20.6; MS *m/e* (percent) 273 (M^+, 18), 257 (60), 255 (88), 215 (42), 213 (66), 154 (67), 138 (92), 136 (100), 107 (39), 89 (55), 77 (63), 65 (28), 63 (30), 57 (30), 55 (32), 51 (37). Anal. Calcd for $C_9H_{14}O_5Cl_2$: C, 39.58; H, 5.17. Found: C, 39.68; H, 5.18.

(2*S*,4*S*)-1,2:4,5-Diepoxy-3-pentanol. To a 0 °C solution of bis-chloride **54** (6.00 g, 22.0 mmol) in 100 mL of THF was added sodium methoxide (7.13 g, 132 mmol) in one portion. The slurry was allowed to warm to ambient temperature and stirred vigorously for 30 min. The mixture was poured into ether (200 mL), and the cloudy solution was filtered through a fritted glass funnel. The solution was concentrated to leave a yellow oil, which was purified by flash chromatography (3:2 to 3:1 ether/pentane) to afford 1.92 g (76% yield) of the diepoxide judged sufficiently pure by ^1H NMR analysis to be used in the subsequent reaction: ^1H NMR ($CDCl_3$, 250 MHz) 3.56 (q, *J* = 4.9, 1 H), 3.20–3.05 (m, 2 H), 2.89–2.78 (m, 4 H), 2.12 (d, 1 H, *J* = 5.4).

(2*S*,4*S*)-1,2:4,5-Di(epoxy)-3-[(*tert*-butyldimethylsilyl)oxy]pentane (55). A 100-mL flask was charged with a solution of the crude hydroxy diepoxide (2.87 g, 24.9 mmol) in THF (24 mL). The mixture was cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (4.13 g, 27.4 mmol) and NaH (1.75 g, 60%, washed 3 times with hexanes, 43.5 mmol) were added via powder funnel, the latter being added portionwise to avoid excessive hydrogen evolution. After 5 min the stirred slurry was allowed to warm to ambient temperature and stirred for an additional 30 min. The mixture was quenched by the slow addition of saturated aqueous $NaHCO_3$ (30 mL) and extracted with 1:1 hexanes/ethyl acetate (2 × 90 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil. Flash chromatography (8:1 hexanes/ethyl acetate) provided the desired silyl ether as a clear, colorless oil (4.79 g, 84% yield): IR (thin film) 2957, 2859, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 3.31 (t, *J* = 5.3, 1 H), 3.15–2.95 (m, 2 H), 2.83 (t, *J* = 4.7, 1 H), 2.77 (t, *J* = 4.8, 1 H), 2.71–2.68 (m, 2 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 73.4, 53.7, 52.0, 44.4, 44.0, 25.7, 18.1, −4.9, −5.0; MS *m/e* (percent) 253 (M + Na, 6), 117 (9), 75 (30), 73 (100), 59 (18), 55 (14). Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.47; H, 9.57.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3,7,8-tetradeoxy-L-glycero-L-manno-nonaric Acid, Di-γ-lactone (56). A 1-L, round-bottomed flask was charged with THF (200 mL) and ethoxyacetylene (36 mL of a freshly distilled 50% w/w solution in hexanes, ca. 180 mmol). The solution was cooled to −78 °C and treated with *n*-BuLi (75 mL of a 2.39 M solution in hexanes, 180 mmol). The cloudy white mixture was stirred at −78 °C for 30 min and treated with a solution of silyl diepoxide **55** (7.66 g, 33.3 mmol) in THF (40 mL, plus a 30-mL rinse, added via cannula), followed by boron trifluoride etherate (21.5 mL, 175 mmol). The brownish mixture was stirred for 1 h at −78 °C and then quenched with aqueous $NaHCO_3$ (250 mL). The mixture was extracted with 1:1 hexanes/ethyl acetate (2 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 1.40 g of crude bis-acetylenic alcohol as a dark brown oil.

To this material was added $HgCl_2$ (176 mg) and *p*-toluenesulfonic acid hydrate (0.50 g), and the mixture was taken up in ethanol (200 mL) and stirred for 12 h. The volatiles were removed with a rotary evaporator, and additional $TsOH{\cdot}H_2O$ (200 mg) was added. The mixture was taken up in ethanol (200 mL) and heated at reflux for 12 h. The solvent was removed, and the residue was subected to flash chromatography (1:1 hexanes/ethyl acetate) to afford a high mobility fraction (presumably consisting of nonlactonized material), followed by the dilactone (5.2 g) as a yellow solid. The first fraction was dissolved in benzene (200 mL), and $TsOH{\cdot}H_2O$ (0.42 g) was added. The mixture was heated at reflux for 18 h and cooled to room temperature, and the solvent was removed with a rotary evaporator to leave a brown residue. Flash chromatography as above afforded an additional 2.0 g of dilactone (total of 7.2 g, 69% yield), judged to be pure by ^1H NMR spectroscopy. An anlytical sample was prepared by recrystallization (ether/hexanes) to afford needles, mp 102–105 °C: $[\alpha]_D^{23}$ +20.0° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 2932, 2859, 1775, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 4.62–4.48 (m, 2 H), 4.05 (t, *J* = 2.9, 1 H), 2.70–2.20 (m, 8 H), 0.90 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 176.5, 176.3, 80.9, 80.3, 73.9, 28.5, 28.1, 25.8, 23.9, 22.0, 18.1, −4.2, −4.6; MS *m/e* (percent) 315 (M + H, 17), 257 (11), 85 (41), 75 (37), 73 (100), 55 (22). Anal. Calcd for $C_{15}H_{26}OSi$: C, 57.29; H, 8.33. Found: C, 57.07; H, 8.38.

(2*R*,8*R*)-5-*O*-(*tert*-Butylidimethylsilyl)-2,8-dimethyl-2,3,7,8-tetradeoxy-L-glycerol-L-*manno*-nonaric Acid, Di-γ-lactone (57). To a −78 °C solution of diisopropylamine (7.0 mL, 50.0 mmol) in THF (200 mL) was added *n*-BuLi (20.3 mL of a 2.39 M solution in hexanes, 48.6 mmol). The mixture was stirred for 15 min at −78 °C, and then treated with a solution of dilactone **56** (7.10 g, 22.6 mmol) in THF (30 mL, 20 mL rinse) which was added via cannula. The mixture was stirred at −78 °C for 20 min, treated with methyl iodide (11.3 mL, 182 mmol), then warmed gradually to −10 °C over 2 h. The yellow solution was allowed to warm to ambient temperature, quenched with aqueous $NaHCO_3$, (100 mL) and extracted with 1:1 hexanes/ethyl acetate (2 × 150 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentration to provide the crude product as a cloudy, orange oil. Purification by flash chromatography (2:1 to 1:1 hexanes/ethyl acetate) provided 7.2 g (94% yield) of the desired lactone **57** as an oil that solidified upon standing. The product was judged by ^1H NMR to be a 10:1 mixture of the desired isomer plus an uncharacterized minor isomer and was used in subsequent steps without further purification. An analytical sample was prepared by recrystallization (ether/hexanes) to give a white solid, mp 84–88 °C: $[\alpha]_D^{23}$ +26.7° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3023, 2934, 1773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 4.57 (ddd, *J* = 7.6, 6.5, 2.8, 1 H), 4.49 (ddd, *J* = 8.2, 4.9, 4.1, 1 H), 3.98 (dd, *J* = 3.7, 3.1, 1 H), 2.74–2.56 (m, 3 H), 2.31 (ddd, *J* = 13.1, 9.4, 4.9, 1 H), 1.96–1.87 (m, 2 H), 1.264 (d, *J* = 7.4, 3 H), 1.257 (d, *J* = 7.3, 3 H), 0.87 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 179.6, 179.3, 78.7, 78.2, 74.3, 34.5, 34.0, 32.2, 29.9, 25.8, 16.6, 16.3, −4.2, −4.5; MS *m/e* (percent) 343 (M + H, 1), 99 (22), 73 (100), 59 (18). Anal. Calcd for $C_{17}H_{30}O_5Si$: C, 59.61; H, 8.83. Found: C, 59.58; H, 8.84.

(2*R*,8*R*)-2,8-Dimethyl-2,3,7,8-tetradeoxy-L-*glycero*-L-*manno*-nonaric Acid, Di-γ-lactone. Lactone **57** (7.30 g, 21.3 mmol) was dissolved in 80 mL of 1.5 M HF/CH_3CN and stirred at ambient temperature for 40 h. Additional HF/CH_3CN (25 mL of a 3 M solution) was added, and the mixture was stirred another 20 h. The mixture was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the desired alcohol as a white solid (mp 143–145 °C): $[\alpha]_D^{23}$ +46.3° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3027, 1773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 4.69 (ddd, *J* = 6.6, 4.2, 2.4, 1 H), 4.61 (ddd, *J* = 8.0, 6.3, 4.3, 1 H), 3.69 (dd, *J* = 6.3, 2.4, 1 H), 2.88 (dq, *J* = 9.3, 7.4, 1 H), 2.75 (dq, *J* = 9.3, 7.2, 1 H), 3.38 (ddd, *J* = 13.3, 9.3, 4.3, 1 H), 2.49 (ddd, *J* = 13.1, 6.6, 1 H), 2.04–1.98 (m, 2 H), 1.28 (d, *J* = 7.2, 3 H), 1.27 (d, *J* = 7.4, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 180.8, 180.4, 77.8, 77.4, 73.9, 34.1, 33.8, 32.4, 31.4, 16.2, 16.0; MS *m/e* (percent) 229 (M + H, 67), 205 (18), 154 (62), 137 (65), 136 (73), 121 (37), 107 (46), 99 (95), 89 (57), 85 (41), 73 (60), 69 (63), 57 (89), 55 (100). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.72; H, 7.06.

(2*R*,8*R*)-5-*O*-Benzyl-2,8-dimethyl-2,3,7,8-tetradeoxy-L-*glycero*-L-*manno*-nonaric Acid, Di-γ-lactone. To a solution of the above alcohol (3.70 g, 16.2 mmol) in 200 mL of 1:1 CH_2Cl_2/cyclohexane under a nitrogen atmosphere was added benzyl trichloroacetimidate (6.20 mL, 33.4 mmol), followed by trifluoromethanesulfonic acid (250 μL, 2.80 mmol). The pale yellow slurry was stirred for 3 h, then quenched with aqueous $NaHCO_3$ (100 mL), and extracted with 1:1 hexanes/ethyl acetate (2 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a pale yellow oil, which was purified via flash chromatography (2:1 to 1:1 hexanes/ethyl acetate) to provide the desired benzyl ether (3.65 g, 70% yield from **57**): IR (thin film) 2935, 1771, 1761, 1456, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.40–7.30 (m, 5 H), 4.75 (d, *J* = 11.3, 1 H), 4.65 (d, *J* = 11.3, 1 H), 2.20–1.90 (m, 3 H), 1.26 (d, *J* = 7.3, 3 H), 1.23 (d, *J* = 7.4, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 179.7, 136.9, 128.5, 128.3, 128.2, 128.1, 80.9, 78.7, 77.4, 75.8, 34.2, 33.7, 31.0, 16.3, 16.1. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.99; H, 7.00.

(2*R*,8*R*)-2,8-Dimethyl 5-*O*-Benzyl-4,6-di-*O*-methyl-2,3,7,8-tetradeoxy-L-*glycero*-L-*manno*-nonarate (58). To a solution of the above benzyl ether (1.36 g, 4.27 mmol) in 32 mL of THF was added 1.0 N aqueous NaOH (9.0 mL) and methanol (10 mL). The solution was stirred for 10 min and then diluted with 1:1 benzene/absolute ethanol (25 mL). The mixture was concentrated with a rotary evaporator and diluted with 1:1 benzene/ethanol (25 mL). The procedure of concentrating and taking up in 1:1 benzene/ethanol was repeated several times to leave a gummy solid which, after pumping under high vacuum, became a yellow powder. Sodium hydride (590 mg, 60%, washed three times with hexanes) and dry *N*,*N*-dimethylformamide (4.5 mL) were added,

and the resulting slurry was cooled to 0 °C. Methyl iodide (4.5 mL) was added, and the contents were allowed to warm gradually to room temperature. After ca. 30 min, the reaction became exothermic, and a gelatin-like polymeric material formed. The mixture was carefully quenched after 10 min with saturated aqueous $NaHCO_3$ (30 mL) and extracted several times with 1:1 hexanes/ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to leave a yellow oil. Flash chromatography (3:1 to 2:1 hexanes/ethyl acetate) provided the desired dimethyl ester as a pale yellow oil, judged by ^1H NMR spectroscopy to consist of >90% one diastereomer (936 mg, 53% yield): IR (thin film) 2940, 1742, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 7.36 (m, 5 H), 4.75 (d, J = 11.5, 1 H), 4.66 (d, J = 11.5, 1 H), 3.69 (s, 6 H), 3.67 (m, 1 H), 3.40 (s, 3 H), 3.30 (s, 3 H), 3.23 (m, 2 H) 2.75 (m, 2 H), 1.95–1.50 (m, 4 H), 1.19 (d, J = 7.2, 6 H). Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.37; H, 8.35. Found: C, 64.45; H, 8.36.

(2*R*,8*R*)-2,8-Dimethyl 4,6-Di-*O*-methyl-2,3,7,8-tetradeoxy-L-*glycero*-L-*manno*-nonarate. To a solution of benzyl ether **58** (897 mg, 2.19 mmol) in 7 mL of ethyl acetate was added 5% $Pd(OH)_2$ on carbon (45 mg). The mixture was stirred vigorously under 1 atm of H_2, and an additional portion of catalyst (56 mg) was added. The slurry was stirred under H_2 for 12 h, then filtered, and subjected to flash chromatography (2:1 to 1:1 hexanes/ethyl acetate) to afford the desired hydroxy alcohol as a clear, colorless oil (688 mg, 98% yield): $[\alpha]^{23}_D$ −24.2° (c 1.8, $CHCl_3$); IR (thin film) 3479 (br), 2938, 1775, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 3.70 (s, 3 H), 3.69 (s, 3 H), 3.50 (m, 1 H), 3.43 (s, 3 H), 3.33 (s, 3 H), 3.45–3.15 (m, 2 H), 2.70 (m, 2 H), 2.33 (d, J = 6.2, 1 H), 1.99 (m, 2 H), 1.60 (m, 2 H), 1.20 (d, 6 H, J = 7.0); ^{13}C NMR ($CDCl_3$, 125 MHz) 177.2, 176.9, 73.2, 35.6, 35.3, 35.0, 33.4, 18.4, 18.0; MS m/e (percent) 321 (M + H, 8), 257 (20), 145 (67), 85 (100), 55 (28). Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 56.02; H, 8.88.

[3*R*,5*S*,6*R*,6(1*S*,3*R*)]-6-(3-Carbomethoxy-1-methoxybutan-1-yl)-5-methoxy-3-methyltetrahydro-2*H*-pyran-2-one (59). The hydroxy ester (720 mg, 2.25 mmol, prepared above) and pyridinium p-toluenesulfonate (580 mg, 2.30 mmol) were dissolved in reagent grade CH_2Cl_2 (5.0 mL) and stirred under nitrogen for 14 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with 1:1 hexanes/ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to leave a yellow oil consisting of a mixture of lactone and starting ester. Flash chromatography (30% ethyl acetate in benzene) provided 293 mg of the desired lactone along with 317 mg of recovered starting material. The starting ester was resubjected to the same reaction conditions to afford 181 mg of starting material (0.566 mmol, 25%) plus an additional 115 mg of lactone (408 mg total, 63% yield): IR (thin film) 2938, 1736, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 4.03 (dd, J = 8.1, 2.1, 1 H), 3.69 (s, 3 H), 3.69–3.50 (m, 1 H), 3.50–3.45 (m, 1 H), 3.43 (s, 3 H), 3.40 (s, 3 H), 2.68 (q, J = 7.2, 1 H), 2.55–2.25 (m, 2 H), 1.90 (d, J = 5.8, 1 H), 1.87 (d, J = 6.8, 1 H), 1.56 (m, 1 H), 1.31 (d, J = 7.0, 3 H), 1.21 (d, J = 7.1, 3 H), 1.20 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 176.7, 173.1, 84.2, 77.4, 73.2, 59.5, 56.3, 51.6, 36.0, 34.5, 33.4, 32.0, 17.9, 17.1; MS m/e (percent) 289 (M + H, 28), 257 (64), 165 (14), 145 (55), 99 (40), 85 (100), 71 (26), 55 (43). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.35; H, 8.41.

[3*R*,5*S*,6*R*,6(1*S*,3*R*)]-6-[3-(1,3-Dithian-2-yl)-1-methoxybutan-1-yl]-5-methoxy-3-methyltetrahydro-2*H*-pyran-2-one (61). To a −78 °C solution of lactone methyl ester **59** (378 mg, 1.31 mmol) in 12 mL of THF was added L-Selectride (1.44 mL of a 1.0 M solution in THF, 1.44 mmol). The mixture was stirred at −78 °C for 1.5 h and then quenched by the addition of aqueous $NaHCO_3$ (20 mL). The mixture was extracted with 1:1 hexanes/ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 0.70 g of a colorless oil. Most of the reagent-derived byproducts were removed by passage of the material through a short silica gel column (1:1 hexanes/ethyl acetate) to afford 414 mg of crude lactol reduction product. This material was dissolved in 10.0 mL of CH_2Cl_2 and cooled to −78 °C under N_2. The mixture was treated successively with 1,3-propanedithiol (215 μL, 2.14 mmol) and boron trifluoride etherate (192 μL, 1.56 mmol). After 10 min, the mixture was allowed to warm to 0 °C and stirred for 1 h. The mixture was then warmed to ambient temperature and stirred for 13 h. Following the addition of aqueous $NaHCO_3$ (30 mL), the mixture was extracted with 1:1 hexanes/ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 609 mg of a yellow oil that solidified upon standing. Purification by flash chromatography (1:1 hexanes/ethyl acetate) afforded lactone **61** as a white, crystalline solid (418 mg, 91% yield from **59**). An analytical sample was prepared by recrystallization from ether/hexanes to give prisms, mp 126–127 °C: $[\alpha]^{23}_D$ −21.7° (c 0.5, $CHCl_3$); IR ($CHCl_3$) 2930, 2899, 1746, 1107; ^1H NMR ($CDCl_3$, 250 MHz) 4.27 (d, J = 3.1, 1 H), 3.97 (dd, J = 8.8, 1.7, 1 H), 3.85 (dt, J = 6.9, 2.3, 1 H), 3.65 (m, 1 H), 3.44 (s, 3), 3.33 (s, 3), 3.00–2.70 (m, 6 H), 2.55 (m, 1 H), 2.45–2.10 (m, 5 H), 1.95–1.45 (m, 5 H), 1.25 (d, J = 6.6, 3 H), 1.15 (d, J = 6.7, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 174.5, 80.8, 76.6, 72.0, 58.4, 55.9, 55.2, 32.2, 31.1, 30.5, 26.3, 18.1, 16.5; MS m/e (percent) 349 (M + H, 22), 348 (M^+, 18), 317 (6), 159 (15), 146 (36), 119 (100), 107 (34), 99 (90), 85 (78), 55 (43). Anal. Calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10. Found: C, 55.27; H, 8.14.

(2*R*,4*S*,5*R*,6*S*,8*R*)-4,6-Dimethoxy-8-(1,3-dithian-2-yl)-2-methylnonane-1,5-diol. To a 0 °C slurry of $LiAlH_4$ (30.0 mg, 0.79 mmol) in THF (4.0 mL) was added via cannula a solution of lactone dithiane **61** (263 mg, 0.75 mmol) in THF (6.0 mL, 2 × 1.0 mL rinse). The resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by the successive addition of H_2O (30 μL), 15% aqueous NaOH (30 μL), and H_2O (90 μL). The mixture was filtered through a glass frit, rinsing three times with 1:1 hexanes/ethyl acetate. The filtrate was concentrated to give a colorless oil, which was purified by flash chromatography (2:1 ethyl acetate/hexanes) to provide the desired dithiane as a colorless oil (246 mg, 93% yield): $[\alpha]_D^{23}$ +2.7° (c 1.7, $CHCl_3$); IR (thin film) 3440 (br), 2928, 1089; ^1H NMR ($CDCl_3$, 250 MHz) 4.22 (d, J = 3.4, 1 H), 3.72 (q, J = 5.0, 1 H), 3.48 (s, 3 H), 3.45 (m, 1 H), 3.40 (s, 3 H), 3.35 (m, 1 H), 3.00–2.80 (m, 5 H), 2.62 (m, 1 H), 2.42 (d, J = 5.0, 1 H), 2.25–2.05 (m, 2 H), 1.95–1.50 (m, 7 H), 1.14 (d, J = 6.9, 3 H), 0.95 (d, J = 7.6, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 128.2, 79.0, 72.9, 68.0, 57.1, 55.0, 34.9, 34.1, 33.6, 32.2, 31.1, 30.8, 26.3, 18.4, 17.7; MS m/e (percent) 352 (M^+, 4), 245 (20), 205 (33), 146 (42), 119 (74), 107 (39), 99 (93), 85 (100), 73 (28), 55 (39). Anal. Calcd for $C_{16}H_{32}O_4S_2$: C, 54.51; H, 9.15. Found: C, 54.48; H, 9.23.

(2*R*,4*S*,5*S*,6*S*,8*R*)-4,6-Dimethoxy-8-(1,3-dithian-2-yl)-5-hydroxy-1-iodo-2-methylnonane. A solution of the above diol (325 mg, 0.922 mmol, dried azeotropically with toluene) and triphenylphosphine (370 mg, 1.41 mmol) in 13 mL of benzene was cooled to 0 °C and treated with pyridine (220 μL, 2.90 mmol) and iodine (353 mg, 1.39 mmol). The resulting brownish slurry was stirred rapidly at 0 °C for 1 h, then warmed to room temperature, and stirred for 6 h. The reaction mixture was quenched by the addition of aqueous Na_2SO_3 (20 mL) and partitioned between saturated aqueous $NaHCO_3$ (30 mL) and 1:1 hexanes/ethyl acetate (40 mL). The aqueous layer was extracted with 1:1 hexanes/ethyl acetate (2 × 20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give 0.85 g of a semisolid yellowish material. Purification by flash chromatography (4:1 hexanes/ethyl acetate) provided the desired hydroxy iodide as a clear, colorless oil (296 mg, 69% yield). This material was used immediately in the next reaction to avoid decomposition: IR (thin film) 3500 (br), 2950, 1120 cm^{-1}.

(2*R*,4*S*,5*S*,6*S*,8*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4,6-dimethoxy-8-(1,3-dithian-2-yl)-1-iodo-2-methylnonane (62). To a 0 °C solution of the hydroxy iodide (296 mg, 0.641 mmol) in 6.0 mL of CH_2Cl_2 was added triethylamine (200 μL, 1.43 mmol) followed by *tert*-butyldimethylsilyl triflate (234 μL, 1.02 mmol). The solution was stirred at 0 °C for 45 min, quenched by the addition of aqueous $NaHCO_3$ (30 mL), and extracted with 1:1 hexanes/ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 460 mg of a cloudy oil. Purification by flash chromatography (8:1 hexanes/ethyl acetate) gave the desired silyloxy iodide **62** as a clear, colorless oil (372 mg, 100% yield). This material was used immediately in the next step to avoid decomposition: IR (thin film) 2955, 2928, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 4.23 (d, J = 3.1, 1 H), 3.89 (d, J = 6.3, 1 H), 3.44 (s, 3 H), 3.36 (m, 1 H), 3.35 (s, 3 H), 3.33–3.20 (m, 2 H), 3.10 (m, 1 H), 2.92–2.80 (m, 4 H), 2.25–2.10 (m, 1 H), 2.00–1.20 (m, 5 H), 1.14 (d, J = 6.9, 3 H), 1.04 (d, J = 6.3, 3 H), 0.92 (s, 9 H), 0.10 (s, 6 H); MS m/e (percent) 519 (M − C_4H_9, 1.0), 391 (1.5), 377 (1.0), 205 (20), 119 (20), 99 (57), 73 (100), 59 (22).

(2*RS*,4*R*,6*S*,7*R*,8*S*,10*R*)-2-[Bis(dimethylamino)phosphono]-7-[(*tert*-butyldimethylsilyl)oxy]-6,8-dimethoxy-10-(1,3-dithian-2-yl)-4-methylundecane (7). In a Kontes tube under nitrogen a solution of ethyl bis(dimethylamino)phophonamide[69] (203 mg, 1.24 mmol) in 5.0 mL of THF was cooled to −78 °C and treated with *n*-BuLi (490 μL of a 2.50 M solution in hexanes, 1.22 mmol). The bright yellow solution was allowed to warm to 0 °C and stirred for 40 min, during which time a clear, orange-brown color developed. The mixture was cooled to −78 °C and treated with a solution of silyloxy iodide **62** (372 mg) in THF (1.5 mL, 2 × 0.75-mL rinse). The resulting solution was stirred at −78 °C for 25 min, allowed to warm to 0 °C, and stirred for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with 1:1 hexanes/ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 460 mg of a yellow oil. Purification by flash chromatography (1:1 hexanes/ethyl acetate to 16:4:1 ether/$CHCl_3$/methanol) provided the desired dimethylamino phosphonamide as a yellow oil, which ^1H NMR analysis showed to be a ca. 1.5:1 mixture of diastereomers (341 mg, 89% yield): IR (thin film) 2928, 2894, 1090, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz)

(minor diastereomer in parentheses) (4.19) 4.18 (d, J = 3.2, 1 H), (3.92) 3.89 (dd, J = 5.9, 1.1, 1 H), 3.44 (s, 3 H), (3.43), (3.33), 3.32 (s, 3 H), 3.31 (m, 1 H), 3.16 (m, 1 H), (3.12), 2.93 (dt, J = 14.3, 3.1, 1 H), 2.85 (m, 3 H), (2.66), 2.64 (d, J = 9.1, 12 H), 2.15 (m, 2 H), 1.93–1.20 (m, 7 H), 1.15 (d, J = 7.1, 3 H), 1.11 (m, 3 H), (1.11), 0.90 (d, J = 8.1, 3 H), 0.90 (s, 9 H), 0.85 (s, 3 H), 0.08 (s, 3 H), (0.07); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of diastereomers) 82.7, 81.0, 80.3, 80.1, 73.6, 72.9, 58.9, 57.9, 57.3, 57.2, 54.7, 54.6, 39.0, 38.0, 37.9, 36.7, 36.6, 36.1, 35.6, 35.5, 35.4, 35.0, 34.6, 31.3, 30.8, 30.8, 29.6, 29.5, 21.9, 19.7, 18.5, 18.4, 18.2, 18.2, 15.2, 13.8, 13.8, 12.9, 12.9, –4.5, –4.7, –4.7; MS m/e (percent) 613 (M + H, 50), 555 (10), 135 (19), 119 (21), 99 (30), 85 (38), 69 (83), 55 (100).

[1(1*R*,3*R*,4*R*),1*E*,3(2*S*),3*S*,4*S*,5*S*,7*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*]-3-[*N*-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy]-15-[(*tert*-butyldimethylsilyl)oxy]-14,16-dimethoxy-18-(1,3-dithian-2-yl)-7-[(4-methoxybenzyl)oxy)-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl]-2,4,10,12-tetramethyl-8-(2-propen-1-yl)-5-[(triisopropylsilyl)oxy]-1,9-nonadecadiene (65). In a flame-dried Kontes tube bis(dimethylamino)phosphonamide **7** (166 mg, 0.271 mmol) was dried azeotropically with 2 mL of toluene under high vacuum. After purging with nitrogen the flask was charged with 1.5 mL of THF and cooled to –78 °C. This solution was treated with *n*-BuLi (115 μL of a 2.50 M solution, 0.288 mmol), and the resulting deep orange solution was stirred for 5 min at –78 °C and 25 min at 0 °C. After cooling to –78 °C, the solution was treated with HMPA (45 μL, 0.26 mmol), and then aldehyde **51** (271 mg, 0.263 mmol, dried azeotropically with two 1-mL portions of toluene) in 2.0 mL of THF was added via syringe over 5 min, rinsing with two 0.5-mL portions of THF. The resulting solution was stirred at –78 °C for 35 min, then warmed to 0 °C, and stirred an additional 10 min before quenching with aqueous $NaHCO_3$. This solution was extracted with three portions of 1:1 hexane/ethyl acetate, and the combined organic extracts were dried over Na_2SO_4. Filtration and concentration provided 459 mg of a pale yellow oil which was purified via flash chromatography (5:1 to 1:1 hexane/ethyl acetate, followed by 16:4:1 chloroform/ether/methanol to recover any unreacted phosphonamide) to provide 173 mg of the desired pair of hydroxy phosphonamide diastereomers plus 116 mg of the undesired pair of diastereomers. The desired pair of diastereomers was heated to a gentle reflux in 3.0 mL of toluene for 5 hr and then stirred overnight at 75–80 °C. After cooling to ambient temperature, the reaction mixture was concentrated, and the resulting pale yellow oil was chromatographed (5:1 hexane/ethyl acetate) to provide the desired trisubstituted olefin as a clear, colorless oil (139 mg, 0.0934 mmol, 36% yield from aldehyde **51**): $[\alpha]^{23}_D$ –36.0° (c 1.04, $CHCl_3$); IR (thin film) 2943, 2867, 1742, 1699, 1514, 1464, 1248, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.26 (d, J = 8.5, 2 H), 6.89 (d, J = 8.5, 2 H), 5.76–5.66 (m, 1 H), 5.42–5.36 (m, 1 H), 5.35–5.29 (m, 1 H), 5.13 (br d, J = 9.0, 1 H), 4.99 (d, J = 17.2, 2 H), 4.88 and 4.68 (rotamers, br s, 1 H), 4.50 (d, J = 11.2, 1 H), 4.42 (d, J = 11.2, 1 H), 4.19, (d, J = 3.3, 1 H), 4.03 and 3.79 (rotamers, br s, 1 H), 3.77 and 3.00 (rotamers, br s, 1 H), 3.92 (d, J = 6.1, 1 H), 3.82 (s, 3 H), 3.56–3.51 (m, 1 H), 3.45 (s, 3 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.30–3.27 (m, 1 H), 3.19–3.15 (m, 1 H), 2.97–2.91 (m, 2 H), 2.87–2.80 (m, 2 H), 2.58–2.46 (m, 1 H), 2.33–2.25 (m, 4 H), 2.21–2.15 (m, 4 H), 2.11–2.04 (m, 2 H), 1.95–1.90 (m, 4 H), 1.87–1.81 (m, 4 H), 1.76–1.72 (m, 2 H), 1.68–1.62 (m, 4 H), 1.58 (br s, 3 H), 1.54 (br s, 3 H), 1.56–1.51 (m, 2 H), 1.46 and 1.43 (rotamers, s, 9 H), 1.40–1.31 (m, 2 H), 1.19–1.16 (m, 1 H), 1.13 (d, J = 7.0, 3 H), 1.09–1.03 (m, 45 H), 0.92 (s, 9 H), 0.87–0.83 (m, 2 H), 0.81 (d, J = 6.6, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.7, 159.1, 155.4, 137.8, 137.6, 137.4, 136.4, 136.1, 136.0, 135.5, 131.3, 131.0, 130.8, 129.0, 127.0, 126.1, 126.0, 125.2, 115.7, 115.6, 113.7, 84.3, 82.1, 81.5, 81.4, 81.1, 80.4, 80.3, 80.1, 79.7, 79.6, 78.4, 74.6, 73.5, 73.4, 70.7, 70.6, 70.5, 70.1, 60.3, 58.8, 58.7, 57.3, 57.2, 57.1, 55.2, 54.8, 54.7, 54.6, 53.8, 46.7, 42.0, 41.0, 40.6, 39.8, 39.3, 38.8, 38.5, 38.4, 36.6, 36.2, 35.7, 35.5, 35.4, 35.0, 34.6, 34.1, 31.3, 31.2, 31.1, 30.8, 30.7, 30.4, 28.3, 26.9, 26.4, 26.3, 25.9, 25.7, 25.0, 24.7, 23.4, 21.4, 21.0, 20.9, 20.8, 20.5, 20.0, 18.5, 18.4, 18.2, 18.1, 18.0, 16.0, 14.1, 13.5, 13.2, 13.0, 12.8, 12.6, 12.3, 12.2, 12.0, 9.0, 8.8, –4.6, –4.8.

Subjection of the more polar pair of hydroxyphosphonamide diastereomers to refluxing toluene provided the C_{19}–C_{20} Z-olefin, data for which are provided below: ^1H NMR ($CDCl_3$, 500 MHz) 7.24 (d, J = 8.3, 2 H), 6.88 (d, J = 8.3, 2 H), 5.75–5.68 (m, 1 H), 5.39–5.36 (m, 1 H), 5.34–5.32 (m, 1 H) 5.07–5.00 (m, 2 H), 4.92 (br m, 1 H), 4.87 and 4.67 (rotamers, br s, 1 H), 4.58 (d, J = 10.8, 1 H), 4.25 (d, J = 10.8, 1 H), 4.19 (d, J = 3.4, 1 H), 4.02 and 3.78 (rotamers, br m, 1 H), 3.92 and 3.00 (rotamers, br m, 1 H), 3.90 (d, J = 5.0, 1 H), 3.82 (s, 3 H), 3.53 (m, 1 H), 3.47 (s, 3 H), 3.34 (s, 6 H), 3.29 (m, 1 H), 3.18 (m, 1 H), 2.96–2.92 (m, 1 H), 2.91–2.88 (m, 1 H), 2.85–2.83 (m, 1 H), 2.82–2.79 (m, 2 H), 2.42 (br m, 1 H), 2.20–2.10 (m, 4 H), 2.06–2.02 (m, 2 H), 1.95–1.85 (m, 4 H), 1.80–1.73 (m, 2 H), 1.67, 1.59, 1.58, and 1.50 (four broad singlets for the C_{19} and C_{27} methyl groups of each rotamer), 1.66–1.61 (m, 2 H), 1.56–1.54 (m, 1 H), 1.44 and 1.42 (rotamers, br s, 9 H), 1.38–1.32 (m, 2 H), 1.13 (d, J = 7.0, 3 H), 1.09–1.02 (m, 45 H), 0.92–0.88 (m, 12 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.8, 170.7, 159.9, 159.1, 155.5, 137.8, 137.6, 136.6, 136.2, 131.2, 130.8, 128.9, 127.0, 115.3, 113.7, 84.3, 81.5, 81.3, 80.4, 80.1, 79.6, 74.7, 73.6, 72.3, 70.1, 60.3, 60.2, 58.9, 57.3, 57.1, 55.2, 54.9, 54.8, 53.8, 42.0, 41.0, 39.3, 38.9, 38.5, 36.0, 35.8, 35.5, 35.0, 34.6, 34.2, 33.2, 31.3, 30.8, 30.4, 28.3, 28.2, 27.9, 27.0, 26.4, 26.0, 25.7, 25.0, 24.7, 23.5, 20.9, 20.6, 18.5, 18.4, 18.3, 18.1, 18.0, 13.3, 12.6, 12.4, 12.2, 11.8, 9.3, 9.1, –4.5, –4.7; HRMS calcd for $C_{82}H_{149}NO_{12}S_2Si_3$ (M + Na) 1510.9719, found 1510.9847.

[1(1*R*,3*R*,4*R*),1*E*,3(2*S*),3*S*,4*S*,5*S*,7*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*]-3-[*N*-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy]-15-[(*tert*-butyldimethylsilyl)oxy]-14,16-dimethoxy-7-[(4-methoxybenzyl)oxy]-1-[3-methoxy-4-[(triisopropylsilyl)oxy]cyclohex-1-yl)]-2,4,10,12,18-pentamethyl-8-(2-propen-1-yl)-5-[(triisopropylsilyl)oxy]-1,9-nonadecadien-19-al. To a solution of dithiane **65** (21.6 mg, 0.0145 mmol, dried azeotropically with 2 mL of xylene) in 0.9 mL of dichloromethane and 2.0 mL of methanol was added [bis(trifluoroacetoxy)iodo]benzene (9.5 mg, 0.022 mmol). The resulting solution was stirred at ambient temperature for 15 min, then diluted with dichloromethane, and quenched with aqueous $NaHCO_3$ and 5% aqueous $Na_2S_2O_3$. The organic layer was washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. Filtration and concentration provided a pale yellow oil which was purified via flash chromatography (7:13:0.8 to 10:10:1 dichloromethane/hexane/ether) to give the dimethyl acetal as a clear, colorless oil (17.5 mg, 0.0121 mmol, 84% yield). This material was dissolved in 4 mL of a solution prepared from 35 mL of dichloromethane, 5 mL of acetic acid, and 11.4 mg of glyoxylic acid hydrate. The mixture was stirred at ambient temperature for 19 h and then warmed to 35–40 °C for 2 h. The solution was diluted with dichloromethane, quenched with aqueous $NaHCO_3$, and then treated with sufficient solid $NaHCO_3$ to make the aqueous phase basic. The organic phase was washed with brine, dried over Na_2SO_4, then filtered, concentrated, and chromatographed (7:13:0.8 dichloromethane/hexane/ether) to provide the desired aldehyde as a clear, colorless oil (11.9 mg, 0.0085 mmol, 59% yield from the dithiane, 70% yield for the acetal hydrolysis): $[\alpha]^{23}_D$ –50.2° (c 0.63, $CHCl_3$); IR (thin film) 2943, 2867, 1742, 1730, 1699, 1514, 1464, 1250; ^1H NMR ($CDCl_3$, 500 MHz) 9.60 (s, 1 H), 7.26 (d, J = 8.5, 2 H), 6.89 (d, J = 8.5, 2 H), 5.73–5.66 (m, 1 H), 5.41–5.36 (m, 1 H), 5.35–5.29 (m, 1 H), 5.14 (d, J = 9.3, 1 H), 5.01–4.94 (m, 2 H), 4.88 and 4.68 (rotamers, br s, 1 H), 4.50 (d, J = 11.5, 1 H), 4.42 (d, J = 11.5, 1 H), 4.03 and 3.77 (rotamers, m, 1 H), 3.92 (dd, J = 5.6, 1.2, 1 H), 3.82 (s, 3 H), 3.76 and 2.98 (rotamers, m, 1 H), 3.56–3.51 (m, 1 H), 3.43 (s, 3 H), 3.35 (s, 3 H), 3.33–3.28 (m, 1 H), 3.19 (s, 3 H), 3.18–3.13 (m, 2 H) 2.98–2.92 (m, 2 H), 2.55–2.52 (m, 2 H), 2.36–2.29 (m, 1 H), 2.22–2.17 (m, 4 H), 2.07–2.03 (m, 2 H), 1.94–1.88 (m, 4 H), 1.74–1.69 (m, 2 H), 1.67–1.60 (m, 4 H), 1.58 (br s, 3 H), 1.54 (br s, 3 H), 1.53–1.50 (m, 2 H), 1.46 and 1.43 (rotamers, s, 9 H), 1.44–1.32 (m, 4 H), 1.11 (d, J = 7.0, 3 H), 1.09–1.01 (m, 45 H), 0.97–0.93 (m, 2 H), 0.92 (s, 9 H), 0.81 (d, J = 6.6, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 204.0, 172.2, 170.8, 159.1, 155.7, 155.2, 138.9, 138.7, 136.5, 136.2, 131.5, 131.2, 131.0, 129.1, 126.5, 126.3, 126.2, 124.8, 115.7, 113.8, 113.9, 84.4, 82.2, 82.0, 81.1, 78.8, 74.7, 74.3, 70.8, 70.4, 67.3, 61.0, 60.6, 58.5, 57.1, 56.8, 55.3, 53.9, 52.1, 47.4, 46.9, 43.2, 43.1, 42.6, 40.7, 38.5, 36.1, 35.7, 35.5, 35.3, 35.1, 34.2, 31.7, 30.5, 28.3, 27.1, 26.0, 25.3, 25.0, 20.8, 20.6, 19.9, 18.5, 18.3, 18.1, 18.0, 16.0, 13.3, 13.0, 12.6, 6.3, 5.7, 2.6, –4.5, –4.7; MS m/e (percent) 1421 (M + Na, 0.6), 768 (5.7), 767 (9.3), 579 (4.3), 423 (3.5), 329 (6.9), 316 (30.5), 307 (14.6), 289 (11.4), 288 (11.1), 257 (18.8), 256 (77.1), 226 (10.9), 212 (15.2) 201 (7.4); HRMS calcd for $C_{79}H_{143}NO_{13}Si_3$ (M + Na) 1420.9769, found 1420.9747.

Methyl (C_1,C_2-$^{13}C_2$)-[(2,4-dimethoxybenzyl)oxy]acetate (6*). A solution of 2,4-dimethoxybenzyl alcohol (0.741 g, 4.40 mmol) in 10 mL of THF was treated with NaH (0.352 g, 60%, 8.80 mmol) and heated to a gentle reflux for 2 h. After cooling to 0 °C, ($^{13}C_2$)-α-bromoacetic acid was added in 1 portion (Cambridge Isotope Labs, 0.315 g, 2.23 mmol). The resulting solution was warmed to ambient temperature over 45 min, heated to reflux for 2.5 h, and then stirred overnight at room temperature. The reaction was quenched by careful addition of H_2O and then partitioned between 50 mL of H_2O and 25 mL of CH_2Cl_2. The aqueous layer was extracted with 3 portions of CH_2Cl_2 to remove any unreacted dimethoxybenzyl alcohol, cooled to 0 °C, and carefully adjusted to pH 3.0 with 1 N HCl, monitoring with a pH meter. The resulting solution was extracted with four portions of Et_2O, and the combined organic extracts were treated with an ethereal solution of diazomethane. After drying over Na_2SO_4, the solution was filtered, concentrated, and then chromatographed to give 0.607 g of a clear, yellow oil. ^1H NMR showed the desired product contaminated with ca. 10% of methyl dimethoxybenzoate. Two more careful chromatographic cycles provided 364 mg of mixed fractions and 144 mg of pure product as a clear, pale yellow

oil: IR (thin film) (values in parentheses are the peaks in the IR of the unlabeled compound **6** which differed by more than 2 cm^{-1}) 2946, 1713 (1755), 1615, 1590, 1509, 1464, 1458, 1422, 1292, 1265, 1210, 1159, 1132, 1103 (1117), 1036; ^1H NMR ($CDCl_3$, 500 MHz) 7.28–7.26 (m, 1 H), 6.49–6.46 (m, 2 H), 4.61 (d, J_{COCH} = 4.4, 2 H), 4.11 (dd, J_{CH} = 178.5, J_{CCH} = 4.4, 2 H), 3.82 (s, 6 H), 3.76 (d, J_{CCH} = 6.2, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz, only the signals for the ^{13}C-labeled carbons are reported) 172.2 (d, J_{CC} = 62.9), 67.4 (d, J_{CC} = 62.9); MS *m/e* (percent) 243 (2, M + H), 242 (16, M^+), 241 (6, M + H − H_2), 167 (22), 151 (100). For comparison, MS for the unlabeled ester **6**: 241 (2, M + H), 240 (9, M^+), 239 (10, M + H − H_2), 167 (22), 151 (100).

(9*RS*,10*RS*,22*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-9-[(2,4-dimethoxybenzyl)oxy]-9,10,22-hexahydro-22-[(4-methoxybenzyl)oxy]-10-[(triethylsilyl)oxy]-24,32-bis[(triisopropylsilyl)oxy]-FK506 (67). A solution of diisopropylamine (45 μL, 0.32 mmol) in 10 mL of THF at 0 °C was treated with *n*-BuLi (168 μL of a 2.02 M solution, 0.338 mmol). After stirring for 10 min, the solution was cooled to −78 °C and treated with ester **6** (99.4 mg, 0.414 mmol). After 25 min at −78 °C, a precooled solution of the aldehyde derived from **65** (45.0 mg, 0.0322 mmol) in 5 mL of THF was added via cannula, rinsing with an additional 2 mL of THF. The resulting solution was stirred at −78 °C for 30 min and then quenched by the addition of 4 mL of 1 N LiOH. The reaction mixture was allowed to warm to ambient temperature and stirred for 2.5 h, at which point TLC analysis indicated complete hydrolysis of the methyl esters. The mixture was then extracted with 3 portions of EtOAc (this takes the desired carboxylate salt into the organic layer but leaves the reagent-derived carboxylate in the aqueous layer). The combined organic extracts were washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. Filtration and concentration provided a clear, yellow oil which was dried azeotropically with 2 mL of xylene. CH_2Cl_2 (8 mL) and 2,6-lutidine (75 μl, 0.64 mmol) were then added, and the resulting solution was cooled to −3 to 0 °C before being treated with triethylsilyl triflate (106 μL, 0.548 mmol). This solution was stirred at 0 °C for 1 h, then quenched with H_2O, and diluted with hexane. The organic phase was washed with 2 portions of H_2O and brine and then dried over Na_2SO_4. Filtration and concentration provided a residue which was applied to a column of silica gel packed with CH_2Cl_2 and aged for 70 min before eluting with 5:1 CH_2Cl_2/Et_2O, CH_2Cl_2, and then 2% to 5% to 10% MeOH in CH_2Cl_2. Concentration of the product-containing fractions provided 44.3 mg of the desired amino acid as a white foam, which was used immediately in the next reaction to avoid decomposition.

The amino acid from the above sequence was dried azeotropically with 2 mL of xylene and treated with Et_3N (9.0 μL, 0.065 mmol). It was then added as a solution in 5.5 mL of CH_2Cl_2 (plus a 1.6-mL rinse) to a solution of *N*-methyl-2-chloropyridinium iodide (42.7 mg, 0.167 mmol) and Et_3N (45 μL, 0.32 mmol) in 32 mL of CH_2Cl_2 via syringe pump over a period of 95 min. The resulting solution was stirred at ambient temperature for 3 h, then quenched with H_2O, and diluted with CH_2Cl_2. The organic phase was washed with 3 portions of H_2O, brine, and then dried over Na_2SO_4. Filtration and concentration provided the desired lactam **67** as a mixture of four diastereomers, which was used immediately in the next reaction. On several earlier runs, the four isomers were separated by flash chromatography (33:1 to 20:1 to 15:1 hexane/ethyl acetate). Data for the major diastereomer are provided below: $[\alpha]^{23}_D$ −60.2° (*c* 0.90, CH_2Cl_2); IR (thin film) 2938, 2867, 1740, 1651, 1617, 1512, 1464, 1248, 1136, 1092, 884, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.80 (d, *J* = 8.1, 1 H), 7.48 (d, *J* = 8.6, 2 H), 6.97 (d, *J* = 8.6, 2 H), 6.54–6.50 (m, 2 H), 6.23–6.19 (m, 2 H), 5.97 (d, *J* = 8.7, 1 H), 5.82 (d, *J* = 5.1, 1 H), 5.44 (d, *J* = 8.9, 1 H), 5.34 (d, *J* = 17.1, 1 H), 5.21 (dd, *J* = 10.1, 1.6, 1 H), 4.99–4.95 (m, 2 H), 4.96 (d, *J* = 11.0, 1 H), 4.68 (d, *J* = 7.8, 1 H), 4.67–4.64 (m, 1 H), 4.58 (d, *J* = 11.0, 1 H), 4.29 (br m, 1 H), 4.08 (d, *J* = 8.5, 1 H), 3.98–3.94 (m, 1 H), 3.85–3.80 (m, 1 H), 3.81 (s, 3 H), 3.69–3.65 (m, 1 H), 3.61 (br s, 3 H), 3.48 (s, 3 H), 3.48–3.42 (m, 1 H), 3.44 (s, 3 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 3.07–3.04 (m, 1 H), 2.95–2.87 (m, 2 H), 2.72–2.68 (m, 1 H), 2.52–2.47 (m, 2 H), 2.41–2.38 (m, 2 H), 2.35–2.29 (m, 2 H), 2.28–2.23 (m, 2 H), 2.21–2.17 (m, 1 H), 2.12–2.08 (m, 1 H), 1.96 (br s, 3 H), 1.96–1.90 (m, 1 H), 1.82 (br s, 3 H), 1.82–1.76 (m, 2 H), 1.74–1.69 (m, 2 H), 1.55–1.48 (m, 4 H), 1.44 (d, *J* = 7.2, 3 H), 1.43–1.38 (m, 2 H), 1.34–1.20 (m, 70 H), 1.06–1.02 (m, 1 H), 0.89–0.80 (m, 6 H), 0.46 (br s, 6 H); ^{13}C NMR (C_6D_6, 125 MHz) (due to overlap, not all of the 91 carbons appeared as unique signals) 170.6, 160.8, 159.7, 159.6, 143.5, 138.9, 136.3, 133.7, 131.9, 129.3, 129.0, 119.2, 115.1, 114.1, 104.0, 98.8, 84.5, 83.1, 80.4, 79.6, 77.9, 77.2, 75.3, 74.8, 73.0, 70.3, 67.7, 60.6, 57.0, 56.5, 54.8 (br), 52.8, 45.6, 43.7 (br), 42.7, 41.4, 40.0, 39.6, 37.8, 37.1, 36.6, 36.1, 35.6, 35.2, 34.3, 33.9, 33.6, 31.4, 28.9, 27.1, 26.9, 26.6, 25.7, 23.7, 23.4, 21.5, 21.0, 19.0, 18.7, 18.6, 18.4, 16.2, 15.1, 13.9, 13.0, 12.5, 11.9, 9.4, 7.4, 5.6, −3.9, −4.1.

(9*RS*,22*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-9-[(2,4-dimethoxybenzyl)oxy]-22-[(4-methoxybenzyl)oxy]-9,22-tetrahydro-24,32-bis[(triisopropylsilyl)oxy]-FK506. The crude macrolactamization product obtained above (**67**, 44.3 mg) was dissolved in 10 mL of 20:1 THF/H_2O and treated with 0.50 mL of trifluoroacetic acid. After stirring for 9 h the mixture was diluted with H_2O and 1:1 hexane/ethyl acetate. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Filtration through a short plug of silica gel provided a clear, colorless oil, which was dried azeotropically with 2 mL of xylene, then dissolved in 8 mL of CH_2Cl_2, and treated with the Dess–Martin periodinane (41.2 mg, 0.0971 mmol). After stirring for 75 min at ambient temperature, the mixture was treated with 5% aqueous $Na_2S_2O_3$ and 5% aqueous $NaHCO_3$, then diluted with 1:1 hexane/ethyl acetate, washed with $NaHCO_3$ and brine, and dried over Na_2SO_4. Filtration and concentration provided the desired β-keto lactam as a mixture of two diastereomers (31.9 mg) which was used immediately in the next reaction. On several earlier runs the crude product was chromatographed (10:1 to 8:1 to 6:1 hexane/ethyl acetate) to provide a mixture of the two β-keto lactam diastereomers, data for which are provided below: IR (thin film) 2936, 2867, 1748 (br, C_1 ester and C_{10} ketone), 1653 and 1647 (C_8 amide rotamers), 1617, 1514, 1464, 1248, 1107, 884, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.30–7.24 (m, 3 H), 6.89–6.85 (m, 2 H), 6.46–6.43 (m, 2 H), 5.82–5.76 (m, 1 H), 5.50 (br s, 1 H), 5.25 (br d, 1 H), 5.18–5.12 (m, 2 H), 5.01 (d, *J* = 17.7, 1 H), 4.92–4.88 (m, 2 H), 4.77 (br s, 1 H), 4.71 (d, *J* = 11.3, 1 H), 4.64 (d, *J* = 11.0, 1 H), 4.61–4.55 (m, 1 H), 4.52 (d, *J* = 11.3, 1 H), 4.34 (d, *J* = 11.0, 1 H), 4.09–4.06 (m, 1 H), 3.85–3.78 (several singlets, 9 H), 3.67–3.64 (m, 1 H), 3.57–3.52 (m, 1 H), 3.45–3.40 (several singlets, 9 H), 3.08–2.96 (m, 2 H), 2.91–2.84 (m, 1 H), 2.42–2.36 (m), 2.35–2.22 (m), 2.10–1.84 (m), 1.64 (br s, 3 H), 1.61 (br s, 3 H), 1.70–1.58 (m), 1.44–1.32 (m), 1.26–1.22 (m), 1.09–1.04 (m, 2 × TIPS), 0.92 (br s, *t*-BuSi, 9 H), 0.90–0.82 (several Me doublets, 9 H), 0.08 and 0.06 ($SiMe_2$, 6 H).

A similar sequence using (C_8,C_9-$^{13}C_2$)-labeled **67** (**67***) provided the (C_8,C_9-$^{13}C_2$)-labeled β-keto lactam: IR (thin film) 2938, 2867, 1744 (br, C_1 ester and C_{10} ketone), 1613 ($^{13}C_8$ amide), 1512, 1464, 1248, 1210, 1134, 1107, 1090, 884, 835 cm^{-1}; ^{13}C NMR (C_6D_6, 125 MHz) C_8 (two diastereomers, each of which can exist as two rotamers) 167.4 (d, J_{CC} = 55.1 Hz), 167.3 (d, J_{CC} = 55.9 Hz), 165.1 (d, J_{CC} = 51.4); C_9 91.5 (d, J_{CC} = 51.7 Hz), 84.7 (d, J_{CC} = 56.9 Hz).

(9*RS*,22*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-9,22-tetrahydro-24,32-bis[(triisopropylsilyl)oxy]-FK506. The crude β-keto lactam from the above sequence (31.9 mg) was dissolved in 4 mL of CH_2Cl_2 and treated with *tert*-butyl alcohol (480 μL), pH 7 buffer solution (480 μL), and DDQ (24 mg, 0.11 mmol). The resulting mixture was stirred vigorously. After 45 min, an additional portion of DDQ (12 mg, 0.053 mmol) was added. TLC analysis indicated complete deprotection after 2.5 h, at which time the reaction was quenched with aqueous $Na_2S_2O_3$ and aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The organic layer was washed twice with aqueous $NaHCO_3$ and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (10:10:0.8 dichloromethane/hexane/ether, then hexane, then 10:1 to 5:1 hexane/ethyl acetate) provided the desired diol as two separable diastereomers, the minor isomer (3.5 mg) at R_f 0.33 (6:1 hexane/ethyl acetate) and the major isomer (9.8 mg) at R_f 0.13, for a total of 13.3 mg (0.0108 mmol, 34% from the aldehyde derived from **65**). Data are provided for the major isomer only: IR (thin film) 3496 (br), 2936, 2867, 1736 (br, C_1 ester and C_{10} ketone), 1651 (C_8 amide), 1462, 1383, 1254, 1200, 1111, 1084, 1014, 883, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 5.75–5.68 (m, 1 H), 5.40–5.32 (m, 1 H), 5.28 (br d, *J* = 4.3, 1 H), 5.20 (br d, *J* = 9.2, 1 H), 5.02–4.92 (m, 2 H), 4.43–4.39 (m), 4.28–4.17 (m), 4.09–4.01 (m), 3.98–3.92 (m), 3.85–3.82 (br d, *J* = 5.7), 3.58–3.52 (m), 3.41 (s, 3 H), 3.38 (s, 3 H), 3.23–3.13 (m), 3.02 (br s, 3 H), 3.00–2.92 (m), 2.38–2.31 (m), 2.29–2.21 (m), 2.02–1.96 (m), 1.94–1.90 (m), 1.78–1.69 (m), 1.68–1.56 (m), 1.58–1.56 (several br singlets, 6 H), 1.53–1.50 (m), 1.39–1.34 (m), 1.17–1.12 (m), 1.09–1.06 (br m, 2 × TIPS), 0.97–0.86 (several Me doublets, 9 H), 0.90 (br s, *t*-BuSi, 9 H), 0.09 and 0.06 (s, Me_2Si).

The same sequence using the (C_8,C_9-$^{13}C_2$)-labeled β-keto lactam provided the analogous (C_8,C_9-$^{13}C_2$)-labeled diol: IR (thin film) 3500 (br), 2932, 2867, 1736 (br, C_1 ester and C_{10} ketone), 1611 ($^{13}C_8$ amide), 1464, 1383, 1252, 1200, 1107, 1011, 884, 837 cm^{-1}.

14-[(*tert*-Butyldimethylsilyl)oxy]-24,32-bis[(triisopropylsilyl)oxy]-FK506 (68). The two isomers from the above reaction (13.3 mg, 0.0108 mmol) were combined[70] and dried azeotropically with 2 mL of xylene, then dissolved in 4 mL of CH_2Cl_2, and treated with the Dess–Martin periodinane (28.1 mg, 0.0663 mmol). The reaction was allowed to stir for 15 h at ambient temperature and then quenched with 5% aqueous $Na_2S_2O_3$ and 5% aqueous $NaHCO_3$. After dilution with 1:1 hexane/ethyl acetate, the organic phase was washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. Flash chromatography (12:1 hexane/ethyl acetate) provided the desired triketone as a clear, pale yellow

oil (10.9 mg, 0.00885 mmol, 82% yield): IR (thin film) 2937, 2867, 1738 (C_1 ester), 1713 (C_9, C_{10}, C_{22} ketones), 1655 (C_8 amide), 1462, 1383, 1252, 1140, 1109, 884, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 5.73-5.66 (m, 1 H), 5.36 (d, J = 8.7, 1 H), 5.24 (d, J = 10.1, 1 H), 5.21-5.18 (m, 1 H), 5.05-4.97 (m, 2 H), 4.87 (d, J = 10.4, 1 H), 4.34 (dd, J = 10.2, 3.3, 1 H), 4.28-4.25 (m, 1 H), 3.76-3.72 (br, t, 1 H), 3.57-3.52 (m, 1 H), 3.44-3.40 (m, 1 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 3.28-3.21 (m, 1 H), 3.19 (s, 3 H), 3.04-2.98 (m, 1 H), 2.98-2.92 (m, 1 H), 2.48-2.42 (m), 2.38-2.31 (m), 2.30-2.17 (m), 2.05-2.00 (m), 1.98-1.88 (m), 1.80-1.50 (m), 1.76 (br s, 3 H), 1.51 (br s, 3 H), 1.18 (d, J = 6.8, 3 H), 1.10-1.05 (br s, 2 × TIPS), 0.92 (br s, t-BuSi), 0.90-0.80 (several Me doublets, 6 H), 0.12-0.08 (m, Me_2Si).

The same sequence using the (C_8,C_9-$^{13}C_2$)-labeled diols provided the analogous (C_8,C_9-$^{13}C_2$)-labeled triketone **68***: IR (thin film) 2937, 2867, 1734 (C_1 ester), 1713 (C_{10}, C_{22} ketones), 1676 ($^{13}C_9$ ketone), 1617 ($^{13}C_8$ amide), 1458, 1252, 1140, 1107, 884, 837 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125 MHz) C_8 (two rotamers) 166.5 (d, J_{CC} = 64.2 Hz, major), 166.0 (d, J_{CC} = 60.3 Hz, minor); C_9 188.4 (d, J_{CC} = 64.6 Hz, minor), 186.6 (d, J_{CC} = 64.6 Hz, major).

FK506 (1). Triketone **68** (10.9 mg, 0.00885 mmol) was treated with 1.5 mL of a 3.0 N aqueous HF/CH_3CN solution (prepared by diluting 11 mL of 48% aqueous HF with CH_3CN to a total volume of 100 mL) in a polypropylene (Eppendorf-like) tube. The resulting solution was stirred at ambient temperature for 18 h, then neutralized with aqueous $NaHCO_3$, and extracted with several portions of CH_2Cl_2. The combined organic extracts were washed with 2 portions of aqueous $NaHCO_3$ and dried over Na_2SO_4. Filtration, concentration, and flash chromatography (1:1 to 2:3 hexane/ethyl acetate) provided FK506 (**1**) as a white powder (5.2 mg, 0.0065 mmol, 73% yield). ^1H NMR, IR, and TLC behavior of synthetic **1** in several solvent systems (2:1 CH_2Cl_2/CH_3CN, 1:1 THF/hexane, 100% EtOAc, 5:2 benzene/acetone, 10:1 CH_2Cl_2/MeOH) were indistinguishable from a sample of the natural material: $[\alpha]^{23}_D$ -85° (*c* 0.20, $CHCl_3$); lit. $[\alpha]^{23}_D$ -84.4° (*c* 1.02, $CHCl_3$);[2b] IR (thin film) 3494 (br), 2937, 2874, 2826, 1744 (C_1 ester), 1717 (C_9 ketone), 1705 (C_{22} ketone), 1651 (C_8 amide), 1451, 1381, 1350, 1327, 1285, 1196, 1173, 1102, 1036, 990, 914, 733 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125 MHz) (The signal for the C_{22} ketone at 212.7 ppm in the spectrum of natural FK506 was not observed in the spectrum of our synthetic FK506 due to the inadvertent use of a sweep width that did not collect data above 200 ppm. The spectra were identical in all other respects, however.) 196.1, 169.0, 164.6, 139.0, 135.6, 135.4, 132.4, 131.8, 129.7, 122.5, 116.7, 98.7, 97.0, 84.2, 77.9, 75.2, 73.7, 72.8, 72.2, 70.0, 68.9, 57.6, 57.0, 56.6, 56.3, 56.1, 52.8, 48.6, 43.9, 40.5, 39.4, 39.3, 35.6, 35.1, 34.9, 34.8, 34.7, 34.6, 33.6, 32.9, 32.7, 31.2, 30.6, 27.7, 26.3, 24.6, 24.5, 21.1, 20.9, 20.4, 19.4, 16.3, 16.0, 15.8, 14.3, 14.1, 9.8, 9.5; ^1H NMR ($CDCl_3$, 500 MHz) 5.76-5.67 (m, 1 H), 5.33 and 5.20 (rotamers, d, J = 2.1, 1 H), 5.10 (br d, J = 9.0, 1 H), 5.05 (br d, J = 12.3, 1 H), 5.01 (br d, J = 10.1, 1 H), 4.88 and 4.26 (rotamers, br s, 1 H), 4.63 (br d, J = 5.2, 1 H), 4.44 and 3.72 (rotamers, m, 1 H), 3.97-3.90 (m, 1 H), 3.89 and 3.70 (rotamers, m, 1 H), 3.61-3.58 (m, 1 H), 3.49-3.40 (m, 3 H), 3.419, 3.417, 3.399, 3.390, 3.347, and 3.309 (rotamers of 3 methoxyls, s, total of 9 H), 3.05-3.00 (m, 3 H), 2.81 and 2.74 (rotamers, dd, J = 16.1, 2.8, 1 H), 2.52-2.44 (m, 1 H), 2.38-2.26 (m, 3 H), 2.23-2.14 (m, 3 H), 2.12-1.99 (m, 4 H), 1.94-1.88 (m, 2 H), 1.83-1.72 (m, 4 H), 1.65-1.30 (m, 10 H), 1.67 and 1.65 (rotamers, br s, 3 H) 1.65 and 1.61 (rotamers, br s, 3 H), 1.10-1.03 (m, 2 H), 1.01, 0.97, 0.94, 0.93, 0.88, 0.83 (rotamers of 3 methyls, d, J = 6.4, 6.6, 6.5, 7.2, 7.1, 6.5, total of 9 H).

The same sequence using **68*** provided (C_8,C_9-$^{13}C_2$)-labeled FK506 (**2**): IR (thin film) 3484 (br), 2932, 2869, 1744 (C_1 ester), 1705 (C_{22} ketone), 1684 ($^{13}C_9$ ketone), 1611 ($^{13}C_8$ amide), 1451, 1379, 1196, 1171, 1103, 1053, 1036, 988, 912 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125 MHz) C_9 major rotamer 196.1 (d, J_{CC} = 62.9), minor rotamer 192.6 (d, J_{CC} = 60.8); C_8 minor rotamer 165.8 (d, J_{CC} = 62.4), major rotamer 164.6 (d, J_{CC} = 63.0).

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Sequential Radical Cyclization Approach to Propellane Triquinanes. Total Synthesis of (±)-Modhephene

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Abstract: Modhephene (**1**) was synthesized in >21% yield from the α,β-unsaturated β-stannyl enoate **24**. The key steps were the radical addition-fragmentation reaction of vinylstannane **25**, which was endo stereoselective and occurred in 90% yield, and the radical cyclization of the iodovinyl ketone **52**, which occurred in 88% yield. The high stereoselectivity in the cyclization of **25** is due in part to the Me_3Sn substituent; the destannylated analogue **29** cyclized to give a 3:1 endo/exo mixture. The radical cyclization of bromoalkene **16** gave desmethylmodhephene (**19**), while the cyclization of bromoalkene **36** gave propellane **37**, which was nonselectively converted to modhephene (**1**) and isomodhephene (**39**) by Reetz dimethylation. The radical cyclization of cyclopentenyl bromide **8** gave a 5:1 mixture of stereoisomers **10** but only a 3:1 mixture of cyclized (**10**)/uncyclized (**11**) isomers. A new retrosynthetic notation for use in synthetic planning with radical reactions is also described.

We have previously demonstrated the efficiency of using sequential radical cyclizations for the synthesis of linear (hirsutene,[2] capnellene,[3] hypnophilin,[4] and coriolin[4]) and angular (silphiperfolene[5]) triquinanes.[6] Modhephene (**1**), 13-acetoxymodhephene (**2**), and modhephene epoxide (**3**) are members of a very small class of triquinane sesquiterpenes, the propellanes, that have been isolated from a variety of natural sources (Figure 1).[7-9] Modhephene's unusual [3.3.3]propellane structure has

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