Asymmetric Total Synthesis of (+)-Milbemycin D

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Abstract: The enantioselective total synthesis of the potent antiparasitic agent milbemycin D (**1**) has been achieved. The spiroketal fragment is prepared through a novel spiroketalization of a hydroxy pyrone to set the anomeric stereocenter and establish functionality for the stereocontrolled attachment and subsequent extension of the connecting chain between the spiroketal and the hexahydrobenzofuran fragment. The hexahydrobenzofuran fragment is constructed through the exploitation of a sequential electrophilic cyclization−[2,3]-sigmatropic rearrangement to close the oxygen-containing ring and incorporate the C5 hydroxyl. A lithium bromide accelerated Wittig olefination joins the spiroketal-containing subunit and the hexahydrobenzofuran subunit at the C10,11 double bond in high yield. Subsequent oxidation of the C1 hydroxyl provides access to the seco acid, which smoothly undergoes macrolactonization. The sensitive C2 stereochemistry and the C3,4 double bond are incorporated without epimerization at C2 or migration of the C3,4 double bond.

The isolation and characterization of the first members of a structurally novel class of potent, broad-spectrum antiparasitic agents known as the milbemycins were reported in the 1970s.[1,2] The subsequent discovery of other members of the milbemycins[3] and the related avermectins[4] marked the beginning of an era of intense effort directed toward the total synthesis and synthetic modification of this group of remarkable anthelminthics.[5] The more recently isolated nemadectin family[6] has added new members to this general class. These macrocyclic compounds are among the most potent antiparasitic and insecticidal agents known. The milbemycins and avermectins now play an important role in the prevention and treatment of human and animal parasitic diseases because of their extraordinary potency and low toxicity.[7]

Synthetic studies on the avermectin class have included total syntheses of avermectin B_{1a} by Hanessian,[8] Ley,[9] and White[10] and a total synthesis of avermectin A_{1a} by Danishefsky.[11] The simpler milbemycins which lack the hexahydrobenzofuran unit, including β_3 and β_1, have been prepared by several groups,[12] but only milbemycin E[13] and α_1[14] of the more complex milbemycins have been synthesized previously.

The unusual molecular architecture of the milbemycins and avermectins centers around a 16-membered-ring lactone which contains a conjugated diene, a substituted 6,6-spiroketal moiety, and a highly sensitive hexahydrobenzofuran subunit. The major

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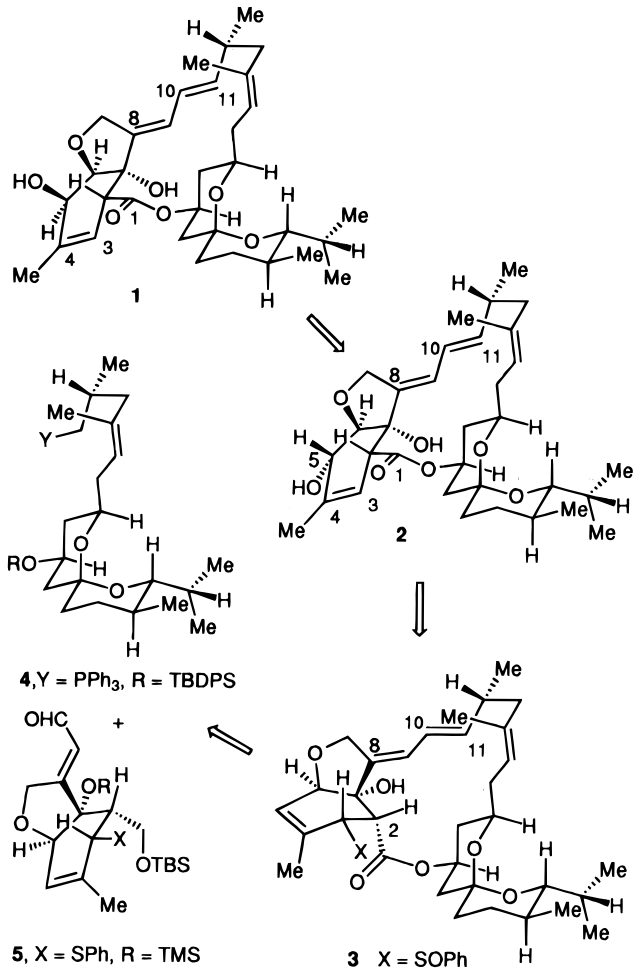
Scheme 1

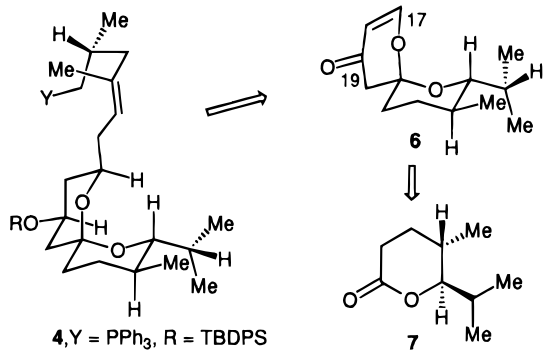


challenges to be overcome in a synthesis of this class are asymmetric stereocontrolled synthesis of the spiroketal, incorporation of the remote asymmetric center at C12, and stereocontrolled construction of the C1 to C8 hexahydrobenzofuran fragment while maintaining the C2 stereocenter and the positional integrity of the C3,4 double bond. Our initial efforts in this area, including the syntheses of the spiroketal fragment of the avermectin B_{1b}[15] and milbemycin D[16] as well as a preparation of the hexahydrobenzofuran subunit,[17] have been described. We report herein the culmination of this effort: the complete details of the first total asymmetric synthesis of milbemycin D (**1**).

Results and Discussion

Retrosynthesis. Our convergent synthesis hinged on the connection of a spiroketal moiety and a hexahydrobenzofuran unit through a Wittig olefination to form the C10−C11 double bond and construct the required (*E*,*E*)-diene prior to formation of the macrolactone. Our initial strategy was designed to address several problematic synthetic conversions. The hexahydrobenzofuran unit is particularly sensitive due to a propensity for the C3−C4 double bond to migrate to C2−C3, for epimerization to result at C2, or through aromatization from dehydration.[18] Since oxidation of a C1 hydroxyl cannot be accomplished if both C3 and C8 are sp^2-hybridized,[14] introduction of the C3,4 olefin was delayed until after C1 had been

Scheme 2



oxidized and the subsequent macrolactonization had been accomplished. Ultimately, a strategy involving rearrangement of the allylic sulfoxide **3** was designed as a method of avoiding these problems. Additionally, an improvement in the heretofore low yields of the fragment coupling between the spiroketal unit and the hexahydrobenzofuran which incorporates the conjugated diene was desired.[8,10,14] The spiroketal subunit **4** and the hexahydrobenzofuran precursor **5** were ultimately chosen for connection through an olefination reaction at C10−C11.

Preparation of the Spiroketal Subunit 4. Retrosynthetic Analysis. The plan for the synthesis of the spiroketal subunit **4** involved a stereocontrolled conjugate addition to enone **6** followed by any necessary extension or refunctionalization of the bridging chain. The spiroketal enone **6** would be derived from lactone **7** by utilizing a procedure developed specifically for the synthesis of the milbemycins and avermectins.[19]

Synthesis of Lactone 7. The synthesis of lactone **7** began with the Horner Emmons condensation of isobutyraldehyde with the sodium anion of ethyl diethylphosphonoacetate to produce the ester **8** (*E*:*Z* = 97:3) in 98% yield and is illustrated in Scheme 3. Reduction of the ester with diisobutylaluminum hydride ($LiAlH_4$ gave significant amounts of 1,4-reduction) provided 97% of the allylic alcohol **9**. The convergent synthesis required that both the spiroketal and the hexahydrobenzofuran subunits be prepared as a single enantiomer; thus, a Sharpless catalytic asymmetric epoxidation was carried out on allylic alcohol **9**[20] to generate the epoxy alcohol **10** in >95% ee (74% yield) as determined by preparation of Mosher's ester.[21] Treatment of epoxide **10** with lithium dimethylcuprate at 0 °C produced diol **11** accompanied by less than 10% of the 1,2-diol, which results from the regioisomeric epoxide opening. The minor isomer was readily removed by treating the crude product with sodium periodate to cleave the 1,2-diol. The major isomer was isolated in 90% yield after chromatography. While diol **11** had been previously converted to lactone **7** in seven high-yielding steps,[16] an improved procedure was developed. Selective tosylation of the primary alcohol followed by acetylation of the secondary alcohol gave the tosylate **12** in 75% overall yield. Displacement of the tosylate with sodium iodide in acetone produced 88% of the iodide **13**. Smooth intramolecular alkylation was accomplished when **13** added slowly to a solution of LDA in THF−HMPA at −78 °C, thus completing a reproducible preparation of multigram quantities of the required lactone **7**.

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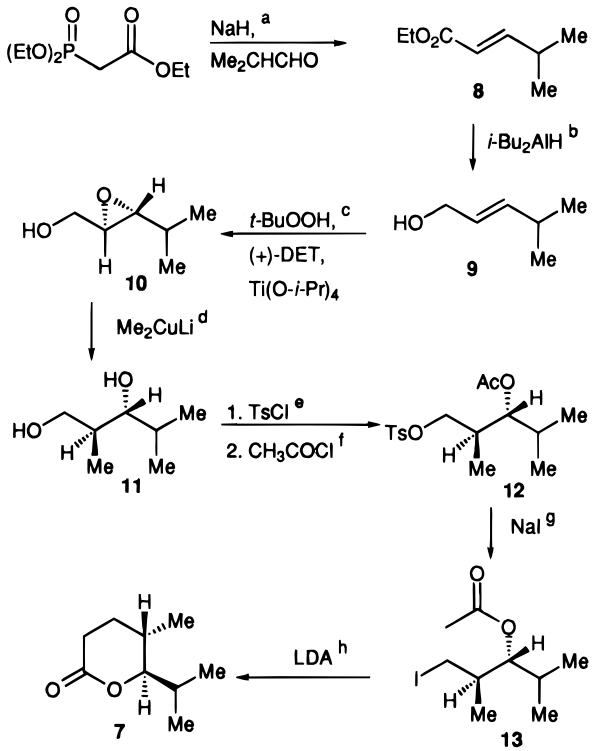
Scheme 3



[a] THF, 25 °C, 98%. [b] THF, −78 to 0 °C, 97%. [c] CH_2Cl_2, 4 Å molecular sieves, 20 °C, 74%. [d] 0 °C, Et_2O, then $NaIO_4$, THF, H_2O, 90%. [e] Et_3N, CH_2Cl_2. [f] CH_2Cl_2, Et_3N (75%, 2 steps). [g] Acetone, 60 °C, 88%. [h] THF, HMPA, −78 °C, 94%.

Preparation and Modification of the Spiroketal Enone 6. Synthesis of the spiroketal enone **6** from lactone **7** followed our previously reported procedure for the preparation of spiroketal enones.[19] Addition of the lactone to a solution of the lithium acetylide of 4-methoxy-3-buten-1-yne in THF at −78 °C resulted in ring opening of the lactone in high yield. The crude acetylenic ketone **14** was immediately treated with potassium carbonate in methanol to provide the crude acetal **15**. Exposure of acetal **15** to *p*-toluenesulfonic acid in 4:1 THF−water at 65 °C generated a 4:1 mixture of the desired spiroketal enone **6** and the pyrone **16**. Treatment of the crude mixture of enone **6** and pyrone **16** with trifluoroacetic acid in benzene converted the pyrone **16** to the spiroketal **6.** Lactone **7** was converted to spiroketal **6** in an overall four-step sequence in 75−80% yield, with purification only after the final step. The stereochemistry of the newly formed asymmetric center was controlled by the thermodynamic preference for diaxial oxygens in spiroketals due to the anomeric effect.[22]

With ready access to the spiroketal enone **6**, addition of the bridging chain at C17 was the next milestone to be achieved. The stereoselectivity of a 1,4-addition at C17 of the enone **6** was to be controlled by the C25 isopropyl group. The rigid conformation of spiroketal enone **6**, as approximated by the minimized structure in Figure 1, illustrates how the isopropyl group at C25 hinders attack from the axial face at C17. Although the enone-containing ring is planarized, the C25 substituent still effectively blocks axial attack. In any event, exposure of enone **6** to an excess of vinylmagnesium bromide in the presence of tetrakis[(tributylphosphine)copper] tetraiodide[23] at −45 °C resulted in a diastereoselectivity of 96:4 in

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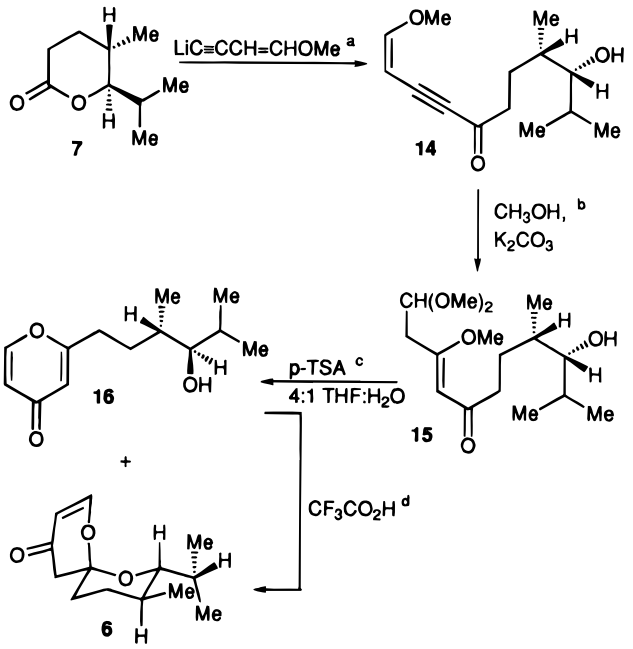
Scheme 4



[a] THF, −78 °C, 99%. [b] 88%. [c] 65 °C. [d] C_6H_6, 90%, 2 steps.

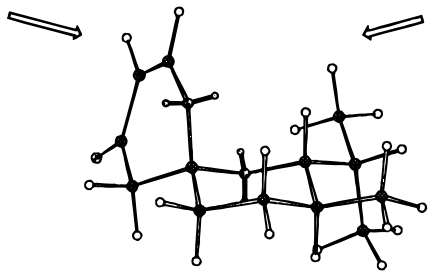


Figure 1.

preference for the equatorial product **18** (78% isolated yield after chromatography). The stereochemistry of the product was evident from the axial nature of both the C17 and C25 hydrogens (due to large vicinal coupling constants) and their close spacial relationship, as evidenced from NOESY experiments.

At this stage of the synthesis, only reduction of the C19 carbonyl remained to complete the stereoselective construction of the spiroketal subunit. While exposure of ketone **18** to sodium borohydride in dimethoxyethane produced a modest selectivity of (2−3):1 in favor of the equatorial alcohol **19b** over the axial isomer **19a**, the isomers were readily separated. The minor isomer **19a** was converted to the desired isomer **19b** through an oxidation−reduction sequence, resulting in the isolation of the equatorial alcohol **19b** in 90% yield after two recycles. The hydroxyl group of **19b** was initially protected as a *tert*-butyldimethylsilyl ether, but this protecting group proved to be too labile during later stages of the synthesis. The C19 hydroxyl was therefore protected as the more robust *tert*-butyldiphenylsilyl ether **20** in quantitative yield.

The spiroketal subunit was properly positioned for extension of the bridging chain to complete the C11-C31 fragment of milbemycin D. To begin the chain extension, exposure of **20** to borane−methyl sulfide to effect hydroboration of the C15−C16 olefin resulted in only a 74:26 selectivity for the primary alcohol. While the use of a bulkier borane reagent was anticipated to improve the regioselectivity, thexylborane gave only a 68:32 preference for the primary alcohol and attempts

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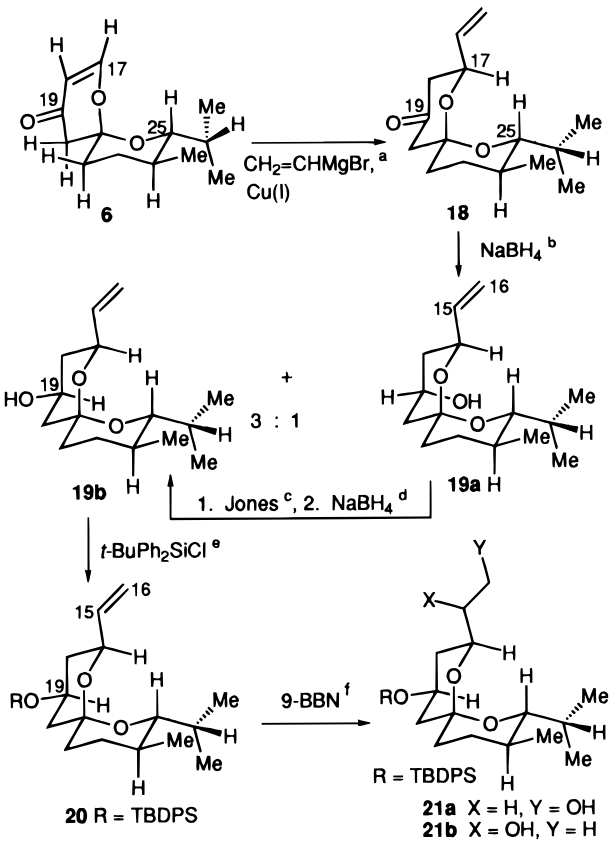
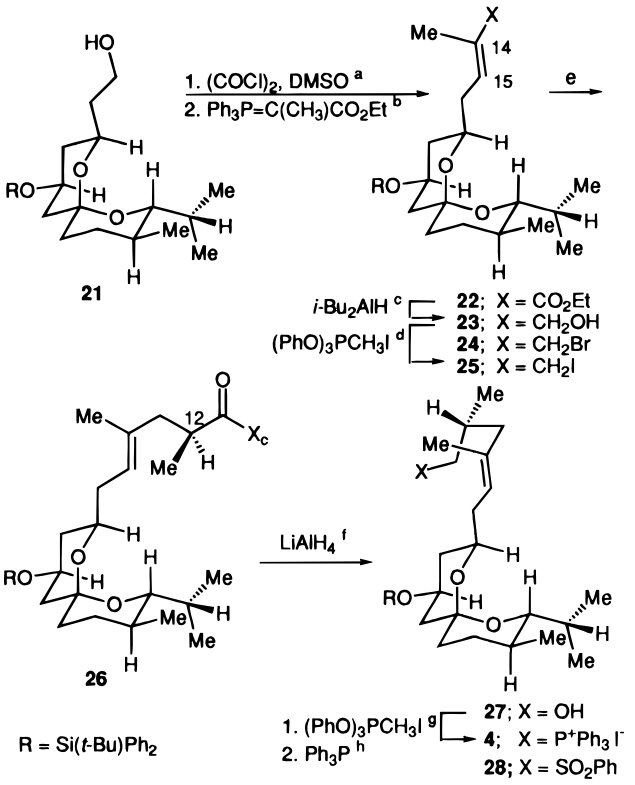
Scheme 5



[a] [(*n*-$Bu_3P)_3CuI]_4$, THF, −50 °C, 78%. [b] DME, 0 °C, 95%. [c] Acetone, 0 °C. [d] DME, 0 °C, 95%, 2 steps. [e] DMF, imidazole, 25 °C, 100%. [f] THF, ultrasound, 25 °C, 1 h, then H_2O_2, NaOH, 97%.

Scheme 6



[a] Et_3N, CH_2Cl_2, −78 °C. [b] CH_2Cl_2, 40 °C, 89%, 2 steps. [c] −78 °C, THF. [d] DMF. [e] Sodium enolate of Evans (*S*)-propionylisopropyloxazolidinone. [f] Et_2O, 75%, 3 steps. [g] DMF. [h] $C_6H_5CH_3$, 110 °C, 90%, 2 steps.

at hydroboration of the alkene with 9-BBN at room temperature gave no reaction. The reaction of **20** with 9-borabicyclo[3.3.1]-nonane (9-BBN) in THF even at reflux temperatures was extraordinarily slow, requiring a large excess of borane and several days to proceed to near-completion. Eventually complete hydroboration was accomplished after only 1 h, through ultrasonic irradiation of a THF solution of equimolar quantities of **20** and 9-BBN.[24] Oxidation of the intermediate borane with hydrogen peroxide provided the primary alcohol **21a** as the only detectable isomer in 97% yield. Oxidation of alcohol **21a** under Swern conditions followed by immediate exposure of the resultant aldehyde to (carbethoxyethylidene)triphenylphosphorane in dichloromethane gave the unsaturated ester **22** as the only detectable isomer in 89% yield. Ester **22** was readily reduced to the allylic alcohol **23** with excess diisobutylaluminum hydride in 95% yield. Completion of the spiroketal subunit required the conversion of the allylic hydroxyl to a suitable leaving group and a subsequent asymmetric alkylation to introduce the C12 methyl group. Initial attempts to prepare the allylic halide through mesylation or tosylation followed by displacement with bromide or iodide caused scrambling of the C14−C15 alkene stereochemistry. However, exposure of alcohol **23** to carbon tetrabromide and triphenylphosphine in acetonitrile proved to be an effective method for the preparation of the allylic bromide **24**. Initial experiments using stoichiometric quantities of bromide **24** and the lithium enolate of the propionyl oxazolidinone derived from L-valinol[25] proved disappointing, and while the use of 10 equiv of the enolate improved the reaction, further improvement was needed because the sluggishness of the reaction caused decomposition of the enolate. An improved procedure involved exposure of alcohol **23** to methyltriphenoxyphosphonium iodide[26] in DMF to provide iodide **25**, which was used without purification in the alkylation with 3 equiv of the sodium enolate of the Evans L-valinol derived oxazolidinone (−78 °C)[25] to give high yields of the alkylated product **26**. The oxazolidinone was reduced with lithium aluminum hydride without purification, due to the difficulty of separating the alkylated material from the excess starting oxazolidinone. The resultant primary alcohol **27** was isolated as a single diastereomer in 75% yield from the ester **22** after flash chromatography (an average of 93% yield per step). Finally, the alcohol **27** needed to be converted into a suitable substrate for connection to the hexahydrobenzofuran unit. The coupling of the two fragments could be accomplished through the phosphonium salt, in anticipation of a Wittig olefination, or through the sulfone, to execute a Julia−Lythgoe coupling.[27] The sulfone **28** was easily obtained through tosylation of the primary alcohol **27** with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane followed by displacement with the sodium salt of thiophenol and subsequent oxidation of the sulfide with oxone. The corresponding phosphonium salt was available from the alcohol **27** in 90% overall yield by exposure to methyltriphenoxyphosphonium iodide in DMF as described previously, with subsequent displacement of the iodide by triphenylphosphine in acetonitrile at reflux.

Synthesis of the Hexahydrobenzofuran Subunit 5. Retrosynthetic Analysis. The hexahydrobenzofuran unit of the

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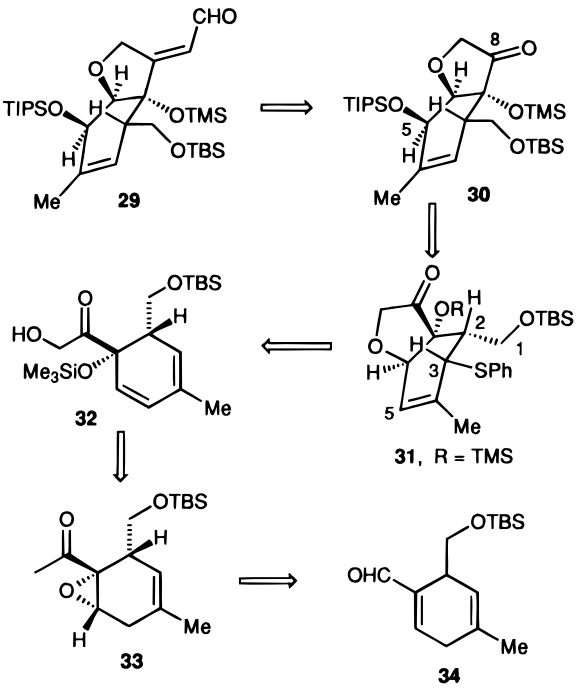
Scheme 7



milbemycins and avermectins contains an array of functionality which is particularly prone to functional reorganization, as mentioned earlier. Originally, a plan to prepare a fully functionalized C1 to C10 subunit, with the exception of C1, which would be incorporated as a primary alcohol and oxidized immediately prior to the macrolactonization, was considered. A strategy which involved masking the carbonyl at C1 to minimize the problem of conjugation of the C3−C4 double bond and epimerization at C2 was developed to synthesize the hexahydrobenzofuran **29**. The unsaturated aldehyde **29** was to be derived from olefination of the C8 ketone **30**, which in turn was to be derived from allylic sulfide **31** through an allylic rearrangement process which might require the inversion of the stereochemistry of the C5 hydroxyl.[28] Since C5 epi-milbemycin had been previously prepared from the natural material and converted to the natural product by an oxidation−reduction sequence,[29] the initial stereochemistry at C5 was deemed to be a point of flexibility. As a result, the stereochemistry of the sulfide was not considered critical, except for the possibility that a syn relationship between the C2 hydrogen and the C3 sulfide might result in elimination rather than the desired 2,3-sigmatropic rearrangement when the sulfide was converted to the sulfoxide. An electrophilic cyclization of diene **32** was anticipated to provide sulfide **31**. The diene **32** would be obtained from epoxy ketone **33**, which would be derived from the Diels−Alder adduct diene **34**.

Synthesis of Epoxy Ketone 33. The synthesis began with the reaction of methacrolein with (carbethoxymethylene)-triphenylphosphorane to give diene **35** (*E*:*Z* = >97:3), which provided silyl ether **37** after immediate reduction with lithium aluminum hydride at low temperature (−78 to 0 °C) and protection of the alcohol **36** as its *tert*-butyldimethylsilyl ether. Heating an equimolar solution of diene **37** and propargyl aldehyde in benzene at 120 °C for 15 h resulted in a near-quantitative yield of the single Diels−Alder adduct **34**. The racemic aldehyde **34** was thus readily available in large quantity from methacrolein in greater than 90% overall yield. While much of the early exploratory work on the construction of the hexahydrobenzofuran was conducted on racemic material for economy, the convergent nature of the synthesis required combination of two subunits of high optical purity. A resolution of the hexahydrobenzofuran fragment would be necessary at some point if it was to be derived from racemic aldehyde **34**. Because of the ready availability of of racemic **34**, it was decided to convert aldehyde **34** to the primary alcohol **38** and execute a Sharpless asymmetric epoxidation.[20] The epoxide effectively would be resolved, since two diastereomers of opposite absolute configuration at C2 were expected from the epoxidation. Reduction of aldehyde **34** with lithium aluminum hydride at −78 °C in ether produced the allylic alcohol **38** in 98% yield. Exposure of **38** to Sharpless catalytic asymmetric epoxidation conditions ((+)-diethyl tartrate, *t*-BuOOH, Ti(O-*i*-Pr)$_4$, 4 Å molecular sieves, CH_2Cl_2, −20 °C)[20] gave a 60:40 inseparable mixture of diastereomers **39**:**40**. Oxidation of the mixture under Swern conditions followed by addition of methylmagnesium chloride and a second Swern oxidation[30] generated the ketoepoxides **41** and **33**, again as a 60:40 mixture, which were readily separated by flash chromatography (73% overall yield for four steps from aldehyde **34**). The combination of methylmagnesium chloride with tetrahydrofuran in the second step was critical for complete conversion of the aldehyde to the secondary alcohol. Use of methyllithium as the nucleophile or ether as the solvent resulted in recovery of a substantial amount of unreacted aldehyde. Analysis of the individual diastereomers (NMR chiral shift study) revealed that **41** had been produced in 55% ee while the desired epoxide **33** was obtained in >95% ee. The high enantioselectivity in the production of epoxide **33** is a result of a matched epoxidation of **38*S*** and a mismatched epoxidation of **38*R***. Asymmetric epoxidation of **38*R*** apparently produces approximately a 3:1 mixture of **40** and the enantiomer of **39** because of an adverse steric effect of the adjacent CH_2-OTBS group. Ultimately epoxy ketone **33** was prepared in 26% overall yield (86% average yield for nine steps) in >95% ee.

Conversion of Epoxy Ketone 33 to the Hexahydrobenzofuran Subunit. As outlined in the retrosynthesis, the task of converting the epoxy ketone **33** to a suitable hexahydrobenzofuran subunit required rearrangement of the epoxide, hydroxylation of the methyl ketone to produce **32**, and electrophilic cyclization of the hydroxy ketone on the diene to provide **31** or a similar intermediate. Treatment of epoxide **33** with lithium diethylamide to effect epoxide rearrangement[31] met with significant decomposition through aromatization. Since the presence of the enolate anion might be adversely affecting the reaction, the methyl ketone was first converted to its *tert*-butyldimethylsilyl enol ether **42** with LDA and *tert*-butyldimethylsilyl chloride. Indeed, exposure of the enol ether **42** to lithium diethylamide at 0 °C caused elimination of the epoxide, albeit with concomitant silyl transfer of the TBS group to the tertiary alcohol in a significant portion of the material, producing **43** and **44** in 30% and 54% isolated yields, respectively. While either **43** or **44** was a useful intermediate, the inability to direct the reaction significantly in favor of one or the other was troublesome. However, the success of the epoxide elimination prompted an experiment where epoxy ketone **33** was treated with 3 equiv each of LDA and (TMS)Cl at −78 °C followed by warming to 25 °C. Silyl enol ether **45** was produced directly in one pot in quantitative yield. Presumably, the trimethylsilyl enol ether is formed at low temperature (−78 °C), followed by

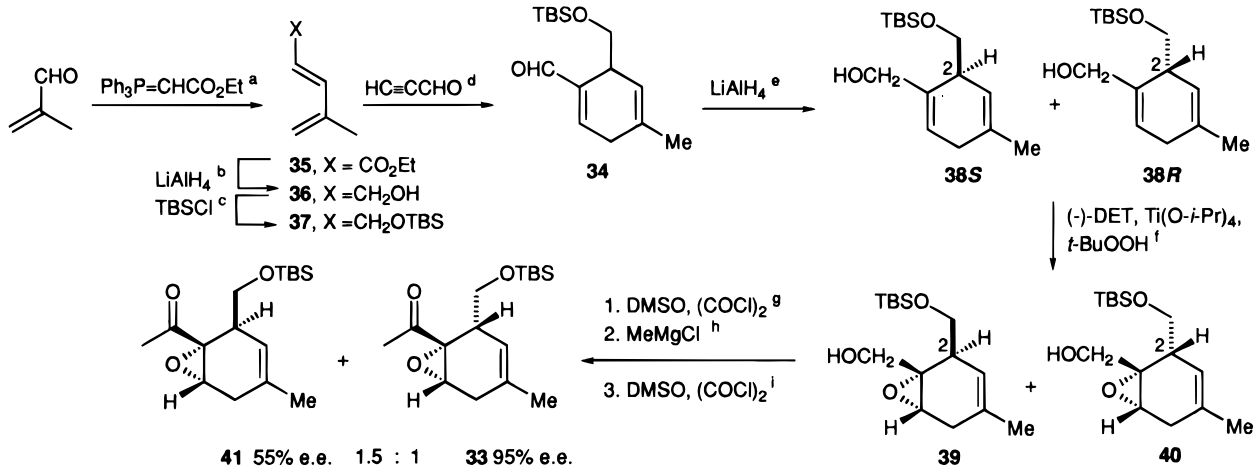
(28) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. For a similar selenide rearrangement see: Pearson, A. J.; Kole, S. L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060.

(29) Mishima, H.; Ono, M.; Muramatsu, S.; Ide, J. *J. Antibiot.* **1983**, *36*, 980.

(30) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(31) Nozaki, H.; Mori, T.; Noyori, R. *Tetrahedron* **1966**, *22*, 1207.

Scheme 8



[a] CH_2Cl_2, 40 °C, 98%. [b] Et_2O. [c] CH_2Cl_2, imidazole, 95%, 2 steps. [d] C_6H_6, 120 °C, 98%. [e] Et_2O, −78 to 0 °C, 98%. [f] CH_2Cl_2, 4 Å molecular sieves, −20 °C. [g] Et_3N, CH_2Cl_2, −78 °C. [h] Et_2O. [i] Et_3N, CH_2Cl_2, −78 °C, 78%, 3 steps.

epoxide elimination upon warming the mixture to 25 °C. The excess (TMS)Cl must silylate the tertiary alkoxide or the enolate oxygen (if silyl transfer occurred) immediately upon formation, preventing aromatization. The silyl enol ether **45** was immediately oxidized under Rubottom conditions,[32] which gave the hydroxy ketone **32** in 60% overall yield from **33** after slow chromatography on silica gel to cleave selectively the primary trimethylsilyl ether.

The next major goal in the synthesis was to accomplish an electrophilic cyclization on the diene **32** to close the five-membered ring and introduce an additional functional group at C3 or C5. Addition of phenylsulfenyl chloride to a solution of hydroxy ketone **32** in dichloromethane produced a single regio- and stereoisomer, sulfide **31**. The stereochemistry was determined by cleavage of the silyl ethers with 5% HF and formation of the benzylidene acetal **46** ($PhCH(OMe)_2$, *p*-TSA, CH_2Cl_2).[33] Examination of the vicinal coupling constants indicated a pseudoequatorial thiophenyl group, as shown in Figure 2. Exposure of the allylic sulfide **31** to *m*-chloroperbenzoic acid at −78 °C produced a sulfoxide which underwent [2,3]-sigmatropic rearrangement when heated at 65 °C in methanol and trimethyl phosphite to give the rearranged allylic alcohol **47**. Alternatively, treatment of the hydroxy ketone **32** with phenyl selenenyl chloride as the electrophile yielded selenide **48**. Immediate oxidation of the selenide with hydrogen peroxide resulted in spontaneous [2,3]-sigmatropic rearrangement to produce allylic alcohol **47** in 66% overall yield. Protection of the C5 hydroxyl as its *tert*-butyldimethylsilyl ether **49** and subsequent selective hydrolysis of the primary TBS and tertiary TMS silyl ethers gave the diol **50**.

At this point, it seemed prudent to establish the best conditions for the oxidation of C1 prior to coupling the hexahydrobenzofuran and spiroketal subunits. All attempts to oxidize the primary alcohol of diol **50** to the required carboxylic acid directly or stepwise through the aldehyde were completely unsuccessful. Likewise, experiments on the oxidation of similar molecules with a protected tertiary hydroxyl group or with different protecting groups on the C5 hydroxyl failed completely. The inability to oxidize C1 when both C8 and C3 are sp^2-hybridized has been previously noted by Hirama and prompted a reevaluation of the synthetic strategy.[14]

A potential solution to the C1 oxidation problem lay in postponing the [2,3]-sigmatropic rearrangement of the sulfoxide or selenoxide until a later stage of the synthesis, after the macrolactonization had been achieved. Successful oxidation of C1 would be possible, since C3 would be sp^3-hybridized. Additionally, the knowledge that the primary alcohol of bromide **53** could be oxidized with buffered pyridinium chlorochromate[17] improved the chances of this approach. Deprotection of the silyl ethers of **31** gave the diol **51**. While attempts to oxidize the primary alcohol of the diol under a variety of conditions were unsuccessful, initial protection of the tertiary alcohol as in **52** allowed the preparation of aldehyde **54** in excellent yield under standard Swern conditions[30] or by the Ley protocol with catalytic tetrapropylammonium perruthenate.[34] With the difficult problem of C1 oxidation overcome and a seemingly viable strategy for the complete functionalization of the hexahydrobenzofuran subunit in hand, attachment of two carbons at C8 and connection of the two major fragments remained.

While the hindered nature of the carbonyl caused concern that a Wittig reaction of any type might be difficult at the C8 carbonyl of the hexahydrobenzofuran, the two adjacent oxygens might provide sufficient electronic activation to allow the reaction to succeed. Indeed, heating a solution of the ketone **31** and excess (carbethoxymethylene)triphenylphosphorane in toluene cleanly produced the unsaturated ester **55** as a single detectable geometric isomer. Reduction of the ester with lithium aluminum hydride gave the allylic alcohol **56**, which was immediately oxidized to the aldehyde **5** in 78% overall yield with either manganese dioxide or catalytic tetrapropylammonium perruthenate.[34]

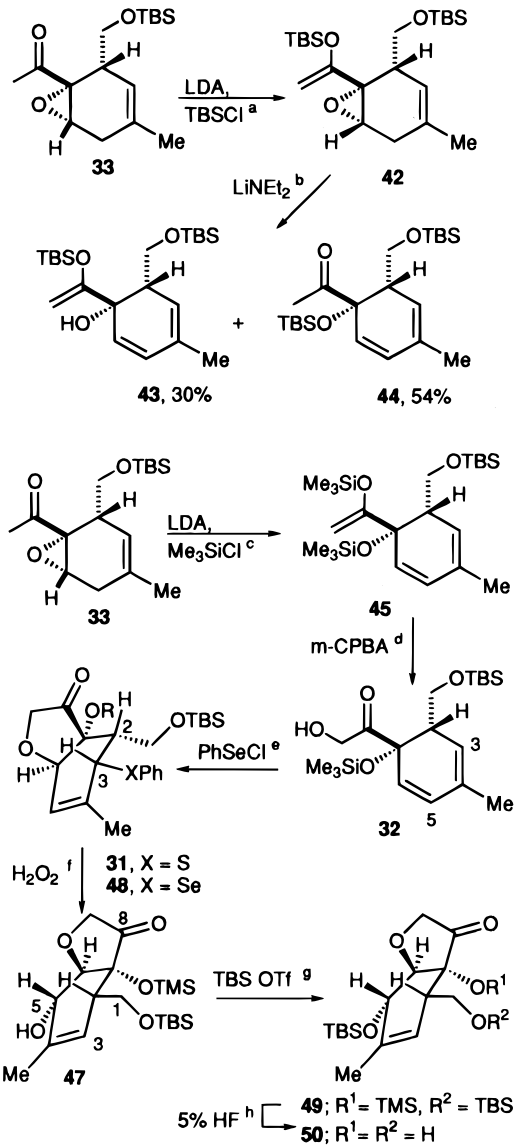
Coupling of the Spiroketal and Hexahydrobenzofuran Fragments. Having developed viable synthetic routes to both of the key fragments, we had reached a critical point in the synthesis. Most published reports on fragment coupling in this series using a Wittig olefination or Julia−Lythgoe coupling have resulted in modest overall yields for incorporating the diene and required the use of up to a 3-fold excess of one of the advanced intermediates.[8−10,14] Since high-yield, stoichiometric connection of the two subunits was critical to an efficient synthesis, a model study was undertaken to evaluate the best method for the coupling. Exposure of aldehyde **5** to the phosphorane derived from **4** prepared by the deprotonation of

(32) Rubottom, G. M.; Vazquez, M. A.; Pelegrinae, D. R. *Tetrahedron Lett.* **1974**, 4319. Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K., Jr.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4063.

(33) Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1564.

(34) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

Scheme 9



[a] THF, 100%. [b] THF. [c] −78 to 0 °C. [d] CH_2Cl_2, SiO_2 chromatography, 63%, 2 steps. [e] CH_2Cl_2, $NaHCO_3$, 78%. [f] CH_2Cl_2, X = S (100%), X = Se (66%). [g] 2,6-Lutidine, CH_2Cl_2, 100%. [h] CH_3CN, H_2O, 85%.

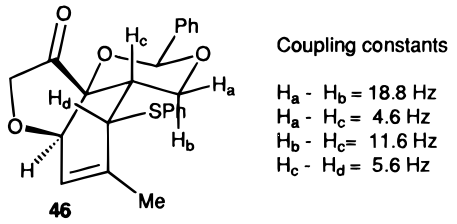
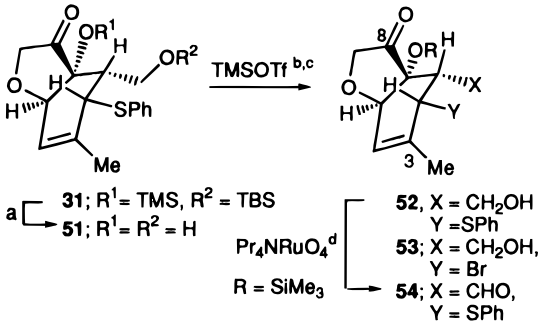


Figure 2.

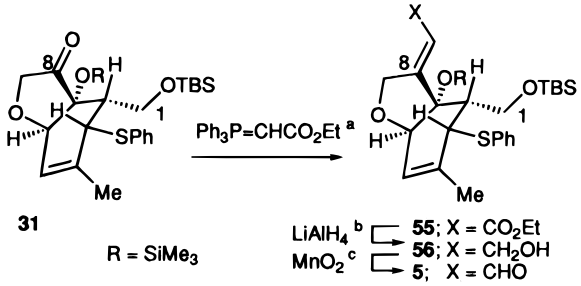
the phosphonium salt[35] with commercial *n*-butyllithium gave a 2:1 mixture of the *E* and *Z* isomers **57*E*** and **57*Z*** in 33% yield. A dramatic improvement in the yield was observed when the phosphorane was prepared from the phosphonium salt and methyllithium−lithium bromide complex. This procedure gave a 1:10 mixture of the *E*:*Z* isomers **57*E*** and **57*Z*** in 84% yield, even when a 1:1 ratio of the aldehyde and ylide was employed. Of equal importance was the determination that exposure of the mixture of olefin isomers to a trace amount of iodine in benzene quantitatively effected isomerization to the *E* isomer **57*E***.[37]

Scheme 10



[a] 5% HF, CH_3CN, 100%. [b] 2,6-Lutidine, CH_2Cl_2. [c] Silica gel chromatography. [d] NMO, CH_2Cl_2 or $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 91%.

Scheme 11



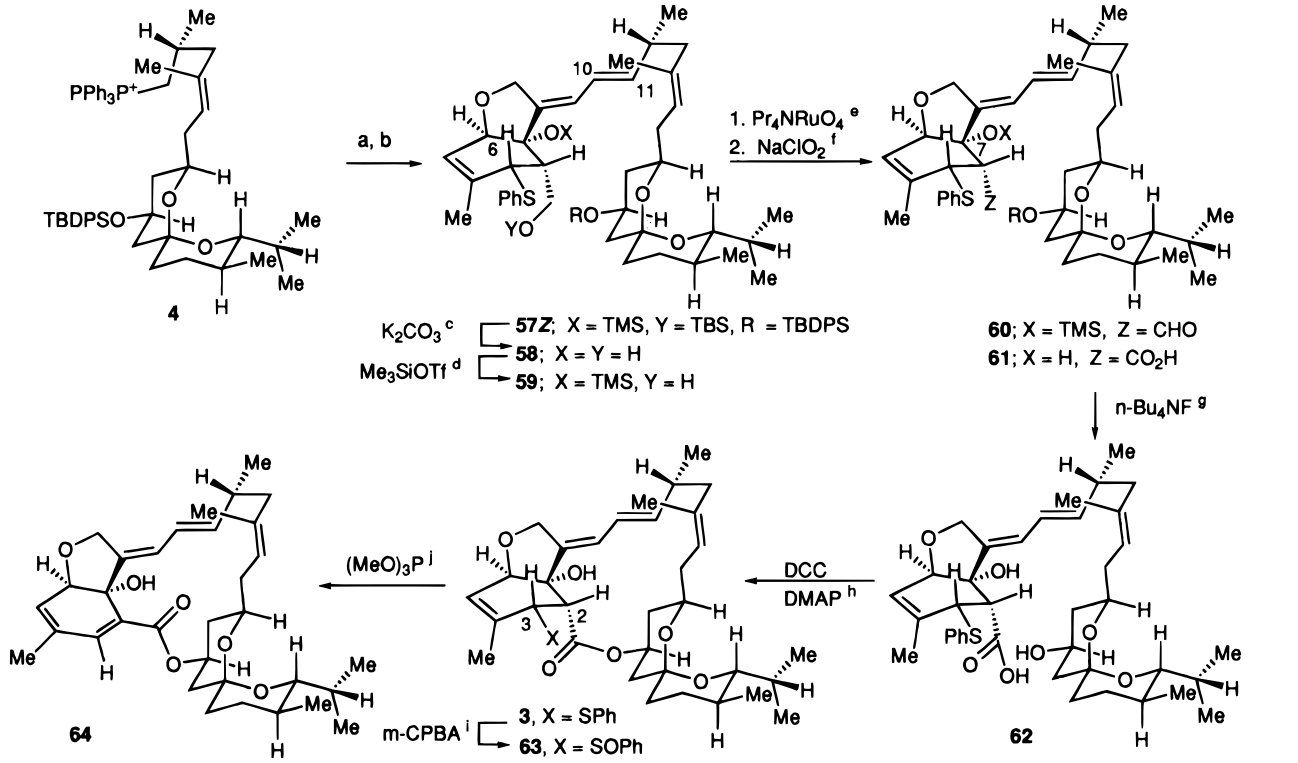
[a] $C_6H_5CH_3$, 110 °C, 82%. [b] Et_2O, −78 °C, 74%. [c] C_6H_6 or Pr_4NRuO_4, NMO, CH_2Cl_2, 95%.

With a significant improvement of the coupling in hand, the next key step called for the oxidation of the C1 hydroxyl followed by the formation of the 16-membered lactone. Deprotection of the C1 TBS and C7 TMS ethers was achieved in 87% yield by exposure of diene **57*E*** to potassium carbonate in methanol. Direct oxidation of the C1 hydroxyl of diol **58** failed, prompting the protection of the C7 hydroxyl. Silylation of both the C1 and C7 hydroxyls with trimethylsilyl triflate and subsequent selective cleavage of the primary TMS ether by exposure to slow silica gel chromatography gave alcohol **59**. Oxidation of alcohol **59** with tetrapropylammonium perruthenate[34] afforded aldehyde **60**, which upon further oxidation using sodium chlorite resulted in acid **61** in 43% overall yield from diene **57*E***. Cleavage of the C19 *tert*-butyldiphenylsilyl ether was accomplished in 83% yield by careful exposure of **61** to tetrabutylammonium fluoride in tetrahydrofuran to produce the seco acid **62**. After we evaluated several different macrolactonization procedures, Keck's macrolactonization[38] conditions were found to produce the best results, providing 57% of the lactone **3** after chromatography.

Attempted Sigmatropic Rearrangement of the C3 Sulfoxide. After we accomplished the connection of the two fragments and the closure of the macrolactone, the completion of the synthesis seemed imminent. Only rearrangement of the allylic sulfide via the sulfoxide and inversion of the resultant C5 hydroxyl remained to be done. Selective oxidation of the sulfide with *m*-chloroperbenzoic acid at −78 °C accomplished the conversion to the sulfoxide **63**. However, when the sulfoxide was treated with trimethyl phosphite in methanol,

(35) Kozikowski, A. P.; Chen, Y.-Y.; Wang, B. C.; Xu, Z.-B. *Tetrahedron* **1984**, *20*, 2345.
(36) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311.
(37) A similar transformation was recently reported: Karim, S.; Parmee, E. R.; Thomas, E. J. *Tetrahedron Lett.* **1991**, *32*, 2269−2272.
(38) Boden, E. P.; Keck, G. *J. Org. Chem.* **1985**, *50*, 2394−2395.

Scheme 12



[a] MeLi−LiBr, THF, −78 °C then aldehyde **5**, −78 °C, 3.5 h. [b] I_2, C_6H_6, 25 °C, 2 h, 84%, 2 steps. [c] MeOH, 92%. [d] 2,6-Lutidine, CH_2Cl_2, then silica gel chromatography, 87%. [e] NMO, CH_2Cl_2; 25 °C, 62%. [f] NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 25 °C, 74%. [g] THF, 83%. [h] DMAP−HCl, $CHCl_3$, 70 °C, 57%. [i] CH_2Cl_2, −78 °C, 90%. [j] MeOH, 65 °C.

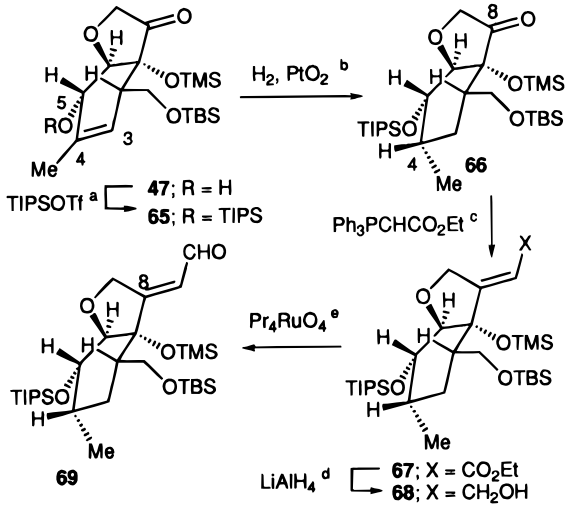
elimination of the sulfoxide to diene **64** rather than [2,3]-sigmatropic rearrangement was observed. The equatorial disposition of the sulfoxide and the fact that the macrolactone was closed apparently slowed the allylic rearrangement to the point that epimerization of either the C2 or C3 stereocenter was competitive with the [2,3]-sigmatropic rearrangement. Epimerization of C2 or C3 results in a syn relationship between the sulfoxide and the C2 hydrogen, allowing thermal elimination to occur. All attempts to circumvent this elimination have thus far been unsuccessful.

Reluctantly, an alternative, more secure strategy for the completion of the synthesis was pursued. If the double bond of alkene **47** were to be hydrogenated, the oxidation problems would be circumvented. The C3−C4 olefin could then be introduced at the end of the synthesis through selenylation and elimination on the C5 ketone.[9]

Completion of Milbemycin D. Experimentally, the C5 hydroxyl of ketone **47** was protected by exposure to triisopropylsilyl triflate and 2,6-lutidine in dichloromethane to give the silyl ether **65**. The alkene was quantitatively hydrogenated in the presence of platinum oxide and potassium carbonate in ethyl acetate to produce the single diastereomer **66**. While the stereochemistry of C4 was not rigorously proven, the similarity of the ^{1}H NMR data to those for an intermediate prepared by Ley[9] led to the tentative assignment shown. Since the stereocenter at C4 is ultimately destroyed, no further structural proof was carried out. Condensation of ketone **66** with (carbethoxymethylene)triphenylphosphorane in toluene at 120 °C provided 81% of the α,β-unsaturated ester **67**. Reduction of ester **67** to the corresponding allylic alcohol **68** with $LiAlH_4$ was followed by Ley oxidation[34] to generate the required labile aldehyde **69** in 78% overall yield.

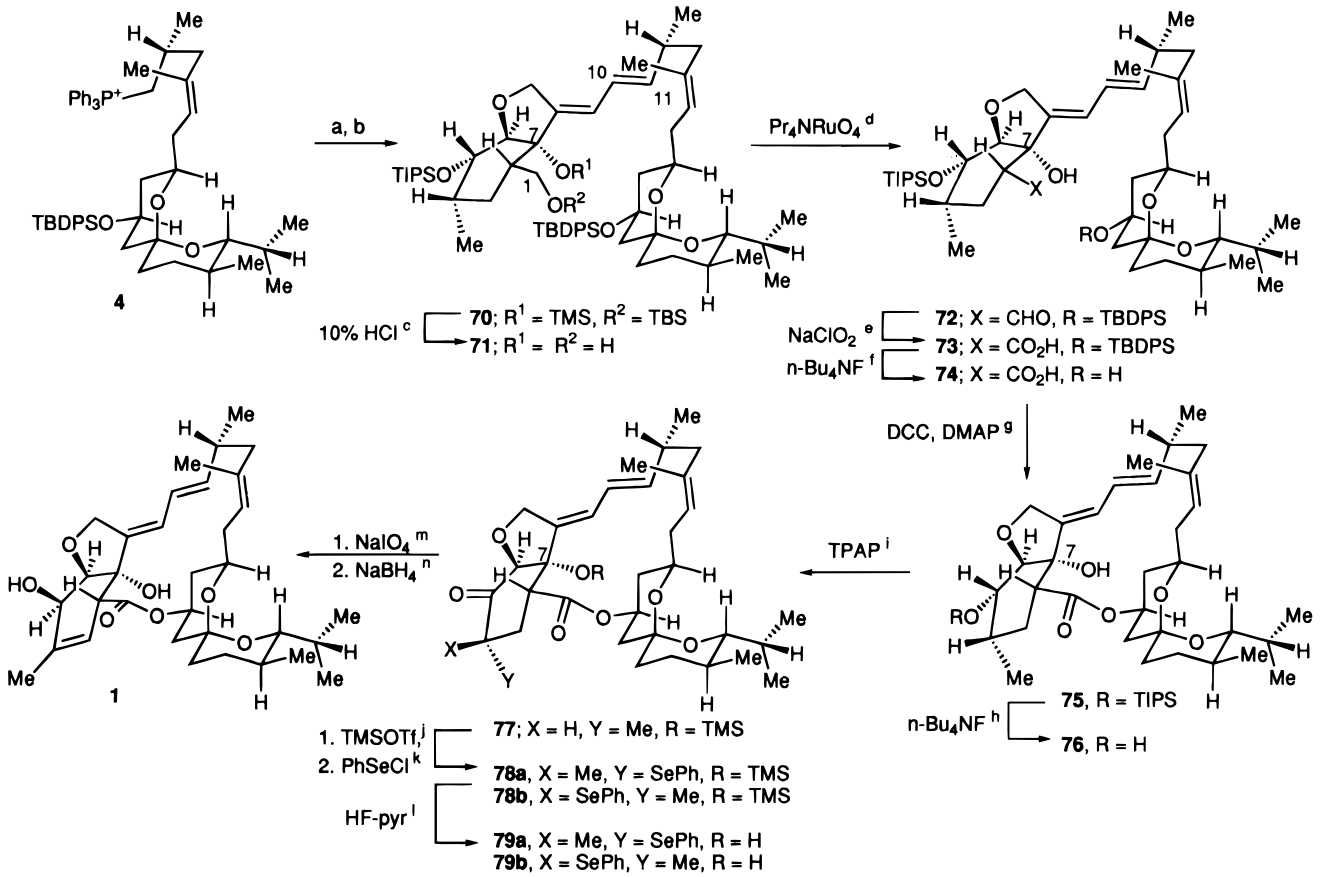
Deprotonation of the phosphonium salt **4** as described above followed by condensation with aldehyde **69** gave a 4.3:1 mixture of the *Z*:*E* dienes at the C10−C11 alkene. Isomerization of this mixture to the more stable (*E*,*E*)-diene **70** was accomplished in high yield by treatment with catalytic iodine in benzene.[37] Deprotection of the C1 and C7 silyl ethers was achieved in 87% yield by exposure of diene **70** to aqueous 10% HCl in THF. Oxidation of the C1 hydroxyl of diol **71** with tetrapropylammonium perruthenate[34] afforded aldehyde **72**, which upon further oxidation using sodium chlorite resulted in acid **73** in 43% overall yield for three steps. Simultaneous deprotection of the C5 and C19 silyl ethers could be accomplished via simple addition of excess *n*-Bu_4NF to acid **73**. Subjecting acid **73** to Keck's macrolactonization[16] conditions afforded a six-membered bridged bicyclic lactone incorporating the C5 oxygen instead of the desired macrolactone. Clearly, selective deprotection of

Scheme 13



[a] 2,6-Lutidine, CH_2Cl_2, 100%. [b] Li_2CO_3, EtOAc, 100%. [c] Toluene, 120 °C, 5 days, 81%. [d] THF, −78 to 25 °C, 1 h. [e] NMO, CH_2Cl_2, 78%, 2 steps.

Scheme 14



[a] MeLi−LiBr, THF, −78 °C then aldehyde **69**, −78 °C, 3.5 h. [b] I_2, C_6H_6, 25 °C, 2 h, 73%, 2 steps. [c] THF, 25 °C, 30 min, 87%. [d] NMO, CH_2Cl_2, 25 °C, 80%. [e] NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 25 °C, 61%. [f] THF, 68%. [g] DMAP−HCl, $CHCl_3$, 70 °C, 53%. [h] 3.0 equiv, THF, 95%. [i] NMO, CH_2Cl_2, 48%. [j] Et_3N, CH_2Cl_2, 0 °C. [k] CH_2Cl_2, −78 °C. [l] Pyridine, CH_3CN, 55%. [m] THF, H_2O. [n] $CeCl_3$, MeOH, 32%, 2 steps.

the C19 silyl ether over the hindered C5 was necessary prior to lactone formation. Carefully controlled addition of tetrabutylammonium fluoride to acid **73** yielded 68% of alcohol **74**, which upon exposure to the Keck macrolactonization conditions[38] resulted in a 53% yield of the desired 16-membered lactone **75**. Further treatment of macrolactone **75** with excess tetrabutylammonium fluoride provided 95% of diol **76**. Incorporation of the C3−C4 double bond via the oxidation/elimination of selenides **79a** and **79b** was next envisioned. Oxidation of alcohol **76** with tetrapropylammonium perruthenate[34] generated ketone **77**, which was converted to its silyl enol ether by treatment with trimethylsilyl triflate and triethylamine. Immediate exposure of the silyl enol ether to phenylselenenyl chloride gave a 1:1 mixture of the selenides **78a** and **78b**.

In accordance with Ley's observations,[9] the best endo:exo selectivity for the selenoxide elimination could be achieved if the α isomer **78a** was used and if the C7 silyl ether was converted to the free hydroxyl group prior to oxidative elimination of the selenide. Accordingly, selenide **78b** was subjected to HF−pyridine in acetonitrile to afford selenide **79b**, which **was** reduced to ketone **77** with tributyltin hydride in benzene at 80 °C. This recycle procedure provided selenide **78a** in 65% yield from ketone **77**. Exposure of selenide **78a** to HF−pyridine in acetonitrile afforded the tertiary C7 alcohol **79a** in 55% yield. Subsequent treatment of **79a** with sodium periodate followed by immediate reduction of the enone with sodium borohydride−cerium chloride in methanol[39] gave a 6:1 ratio of milbemycin D (**1**) to the exo olefin isomer.[2a] Final chromatographic purification provided milbemycin D in 32% isolated yield from selenide **79a**. The final product was identical with an authentic sample by TLC, ^{1}H NMR, ^{13}C NMR, and IR.

(39) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.

Experimental Section

General Considerations. Infrared (IR) spectra were obtained using a Mattson FT-IR 5000 Galaxy series infrared spectrometer. Proton, carbon, and phosphorus nuclear magnetic resonance (^{1}H, ^{13}C, and ^{31}P NMR) spectra were recorded on the following instruments: Bruker Model AC-200 (^{1}H at 200 MHz, ^{13}C at 50 MHz, ^{31}P at 81 MHz), Bruker Model WM-250 (^{1}H at 250 MHz), and Varian Model XL-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. High-resolution mass spectral analyses were performed at the North Carolina State University Mass Spectrometry Facility, Raleigh, NC.

2(*R*),3(*R*)-Epoxy-4-methyl-1-pentanol (10). To a suspension of 6.32 g of 4 Å molecular sieves in 215 mL of dry CH_2Cl_2 in a 1 L flask equipped with a mechanical stirrer were sequentially added, at −5 °C, 6.516 g (0.0316 mol) of (−)-diethyl tartrate as a solution in 15 mL of dry CH_2Cl_2 and 6.26 mL (0.0210 mol) of Ti(*i*-OPr)$_4$ via syringe. After it was stirred for 20 min at −5 °C, the reaction mixture was cooled to −20 °C. At this point 115.61 mL of a 4.1 M solution (0.474 mol) of anhydrous *t*-BuOOH in CH_2Cl_2 was added. The resulting solution was stirred at −20 °C for 10 min, and 31.606 g (0.3160 mol) of allylic alcohol **9** as a solution in 30 mL of dry CH_2Cl_2 was added dropwise with vigorous stirring. After the addition was complete and stirring had continued at −20 °C for 30 min, the reaction mixture and its cooling bath were placed in a −20 °C freezer for 20 h. The mixture was then warmed to room temperature and stirred for 30 min. Addition of 25 mL of 35% aqueous NaOH solution (saturated with NaCl) was effected, and the mixture was stirred for 30 min more. The mixture was filtered through a pad of Celite, dried over anhydrous Na_2SO_4, and concentrated to afford a liquid residue. Flash chromatography yielded 27.05 g

(0.2332 mol, 74%) of epoxy alcohol **10** as a colorless oil. $[\alpha]^{21}_D = +31.0°$ ($c = 4.47$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.00 (3H, d, $J = 6$ Hz), 1.08 (3H, d, $J = 6$ Hz), 1.64 (1H, m), 2.78 (1H, dd, $J = 6.6$, 3.6 Hz), 3.03 (1H, m), 3.39 (1H, broad s) 3.62 (2H, dd, $J = 12$, 5.6 Hz), 3.96 (2H, dd, $J = 12$, 2.8 Hz). IR (neat): 3440, 2970, 2935, 2875, 1470, 1380, 160 cm^{-1}. Anal. Calcd for $C_6H_{12}O_2$: C, 62.05; H, 10.41. Found: C, 62.16; H, 10.66.

2(*S*),4-Dimethyl-1,3(*R*)-pentanediol (11). To a rapidly stirred suspension of 144.41 g (0.578 mol) of CuI in 1 L of dry ether at 0 °C was added slowly 1.01 L of a 1.5 M solution (1.518 mol) of methyllithium in ether, and the resulting solution was stirred for 15 min at 0 °C. Epoxy alcohol **10** (29.32 g, 0.253 mol) in 50 mL of dry ether was then added dropwise. Once the addition was complete, the reaction mixture was stirred at 0 °C for 3.5 h. The reaction was quenched by the careful addition of saturated aqueous NH_4Cl. The mixture was filtered through a pad of Celite, and the salts were washed several times with ether. The ether solution was washed three times with aqueous NH_4OH and then with saturated NaCl. The aqueous layers were combined, saturated with NaCl, and extracted twice with 200 mL of ether. Concentration of the combined ether extracts provided 31.39 g (0.238 mol, 94%) of a yellow oil which was a 6:1 mixture of the regioisomeric diols.

This mixture was taken up in ether and stirred with 150 mL of water containing 26.736 g (0.125 mol) of $NaIO_4$ to cleave the 1,2-diol. The reaction was complete in 12−16 h. After the layers were separated, the aqueous layer was saturated with NaCl and extracted with 3 × 150 mL of ether. The combined extracts were dried and concentrated to give a crude liquid, which was subjected to flash chromatography, affording 24.718 g (0.187 mol, 74%) of diol **11**. $[\alpha]^{21}_D = +18.1°$ ($c = 0.02685$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.88 (6H, t, $J = 6$ Hz), 0.97 (3H, d, $J = 6.9$ Hz), 1.80 (1H, m), 3.33 (1H, m), 3.03 (1H, m), 3.67 (4H, m), 4.12 (1H, br s). IR (neat): 3380, 2965, 2935, 2925, 2875, 1470, 1390, 1370, 1345 cm^{-1}. Anal. Calcd for $C_7H_{16}O_2$: C, 63.60; H, 12.20. Found: C, 63.31; H, 12.29.

2(*S*),4-Dimethyl-1-[(*p*-tolylsulfonyl)oxy]-3(*R*)-acetoxypentane (12). A solution of 22.58 g (170 mmol) of diol **11**, 29 mL (359 mmol) of pyridine, and 500 mg of 4-(dimethylamino)pyridine in 300 mL of CH_2Cl_2 was cooled to 0 °C, whereupon a solution of 34.19 g (179 mmol) of *p*-TsCl in 200 mL of CH_2Cl_2 was added dropwise over 15 min. The mixture was warmed to room temperature for 24 h and then washed twice with 10% HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed (9:1 hexanes−EtOAc) to provide 40.12 g (82%) of tosylate as a colorless oil. $[\alpha]^{23}_D = -3.1°$ ($c = 2.360$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.83 (3H, d, $J = 7.5$ Hz), 0.94 (3H, d, $J = 7.5$ Hz), 0.95 (3H, d, $J = 7.5$ Hz), 1.65 (1H, d, $J = 6$ Hz), 1.67−1.98 (2H, m), 2.45 (3H, s), 3.23 (1H, m), 4.14 (2H, ddd, $J = 5$, 4, 9 Hz), 7.35 (2H, d, $J = 8$ Hz), 7.80 (2H, d, $J = 8$ Hz). IR (neat): 3560, 1600, 1475, 1355, 1180, 1175 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4S$: C, 58.72; H, 7.74. Found: C, 58.42; H, 7.82.

A solution of 43.974 g (153 mmol) of the primary tosylate from above, 21.4 mL (154 mmol) of Et_3N, 200 mg of 4-(dimethylamino)-pyridine, and 23.97 mL (254 mmol) of acetic anhydride was stirred at room temperature for 8 h. The reaction was quenched by the addition of solid and aqueous $NaHCO_3$ followed by extraction twice with 250 mL of ether. The ether extracts were dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (9:1 hexanes−EtOAc) gave 46.39 g (92%) of acetate **12**, a white crystalline solid. Mp: 43−44 °C. $[\alpha]^{23}_D = -13.19°$ ($c = 2.660$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.84 (3H, d, $J = 7.5$ Hz), 0.86 (3H, d, $J = 7.5$ Hz), 0.94 (3H, d, $J = 7.5$ Hz) 1.87 (1H, d, $J = 6$ Hz), 2.00 (3H, s), 2.12 (1H, m), 2.46 (3H, s), 3.80 (1H, dd, $J = 7.5$, 10.5 Hz), 4.06 (1H, dd, $J = 4.5$, 10.5 Hz), 4.67 (1H, dd, $J = 6$, 7.5 Hz), 7.35 (2H, d, $J = 9$ Hz), 7.78 (2H, d, $J = 8$ Hz). IR (neat): 1740, 1600, 1455, 1360, 1245, 1175 cm^{-1}.

2(*S*),4-Dimethyl-1-iodo-3(*R*)-acetoxypentane (13). A solution of 46.22 g (140 mmol) of tosylate **12** and 63.28 g (422 mmol) of sodium iodide in 500 mL of 2-butanone was heated to reflux for 4 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was partitioned between 500 mL of ether and 100 mL of water. The ether layer was washed with 10% sodium bisulfite, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed (19:1 hexanes−EtOAc) to provide 35.05 g (88%) of iodide **13**, which was used immediately in the next reaction. $[\alpha]^{22}_D = -6.61°$ ($c = 2.755$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.87 (3H, d, $J = 7.5$ Hz), 0.94 (3H, d, $J = 7.5$ Hz), 1.05 (3H, d, $J = 7.5$ Hz) 1.82−2.05 (2H, m), 2.09 (3H, s), 2.96 (1H, dd, $J = 9$, 10.5 Hz), 3.33 (1H, dd, $J = 3$, 10.5 Hz), 4.67 (1H, dd, $J = 5$, 7.5 Hz). IR (neat): 1745, 1370, 1235 cm^{-1}.

5(*S*)-Methyl-6(*R*)-isopropyltetrahydro-2(3*H*)-pyranone (7). A solution of 38.04 mL (27.46 g, 271 mmol) of diisopropylamine in 500 mL of dry THF was cooled to −78 °C. To this solution was added 170.4 mL (272 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes. After the mixture was stirred for 15 min at −78 °C, a solution of 35.05 g (123 mmol) of iodide **13** and 21.46 mL (22.10 g, 123 mmol) of hexamethylphosphoramide (HMPA) in 100 mL of dry THF was added dropwise over a 2 h period. The reaction was quenched with saturated ammonium chloride 5 min after the addition was complete. After it was warmed to room temperature, the mixture was diluted with 200 mL of ether and extracted three times with 100 mL of water and once with brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography provided 18.05 g (94%) of lactone **7** as a colorless liquid. $[\alpha]^{22}_D = +40.3$ ($c = 1.79$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.93 (3H, d, $J = 6.4$ Hz), 1.01 (3H, d, $J = 5.3$ Hz), 1.20 (3H, d, $J = 7.1$ Hz), 1.57 (1H, m), 1.77−2.07 (3H, band), 2.48 (1H, m), 2.64 (1H, m), 3.85 (1H, dd, $J = 10.1$, 3.0 Hz). IR (film): 2970, 2940, 2915, 2880, 1730, 1465, 1385, 1360, 1335 cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.31; H, 10.10.

1-Hydroxy-1(*R*)-isopropyl-9-methoxy-2(*S*)-methylnon-8-en-6-yn-5-one (14). To a solution of 1.331 g (0.0162 mol) of freshly distilled *cis*-methoxy-1-buten-3-yne in 100 mL of dry tetrahydrofuran at −78 °C was added via syringe 6.50 mL (0.0162 mol) of a 2.5 M solution of *n*-butyllithium in hexanes. After the mixture was stirred for 30 min, a solution of 2.533 g (0.0162 mol) of lactone **7** in 10 mL of dry THF was added dropwise. The reaction mixture was then stirred for 1 h and subsequently quenched at −78 °C with 25 mL of saturated ammonium chloride and warmed to room temperature. After addition of 50 mL of water and 100 mL of ether, the layers were separated and the aqueous layer was extracted with 2 × 50 mL of ether. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to provide 3.832 g (0.0161 mol, 99%) of crude, labile keto alcohol **14**, which was used without further purification. ^1H NMR (250 MHz, $CDCl_3$): δ 0.90 (3H, d, $J = 7.2$ Hz), 0.93 (3H, d, $J = 7.2$ Hz), 0.96 (3H, d, $J = 6.8$ Hz), 1.45−2.17 (4H, band), 2.66 (2H, m), 3.09 (1H, dd, $J = 5.7$, 5.7 Hz), 3.79 (1H, s), 3,88 (3H, s), 5.69 (1H, d, $J = 6.8$ Hz), 6.58 (1H, d, $J = 6.8$ Hz).

1-Hydroxy-1(*R*)-isopropyl-7,9,9-trimethoxy-2(*S*)-methylnon-6-en-5-one (15). A mixture of 3.832 g (0.0161 mol) of keto alcohol **14** and 2.245 g (0.0161 mol) of potassium carbonate in 100 mL of methanol was stirred for 16 h at room temperature. The majority of the solvent was removed, and 10 mL of water and 100 mL of ether were added. The ether layer was separated and dried over $MgSO_4$ to give 4.310 g (0.0143 mol, 88%) of the crude trimethoxy ketone **15**. This compound was relatively unstable and was used immediately in the next reaction. ^1H NMR (250 MHz, $CDCl_3$): δ 0.88 (3H, d, $J = 6.7$ Hz), 0.91 (3H, d, $J = 6.0$ Hz), 0.96 (3H, d, $J = 6.3$ Hz), 1.43−1.67 (2H, band), 1.76−2.05 (2H, band), 2.38−2.67 (2H, band) 3.08 (1H, m), 3.13 (1H, d, $J = 5.6$ Hz), 3.35 (6H, s), 3.69 (3H, s), 4.72 (1H, dd, $J = 5.6$, 5.6 Hz), 5.54 (1H, s). IR (film): 2965, 2935, 2875, 2170, 1730, 1660, 1620, 1465 cm^{-1}.

8(*R*)-Isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (6). A solution of 4.310 g (14.4 mmol) of the trimethoxy ketone **15** and 400 mg of *p*-toluenesulfonic acid in 400 mL of THF and 80 mL of water was heated at reflux for 15 h. The mixture was cooled to room temperature and neutralized by the addition of solid sodium bicarbonate. About half the THF was removed in vacuo, and the remaining solution was saturated with NaCl and diluted with 200 mL of ether. The aqueous layer was extracted three times with 100 mL of ether. The combined ether extracts were dried and concentrated. This crude product consisted of a 3:2 mixture of pyrone **16** to spiroketal **6**. Without purification, this crude material was dissolved in 300 mL of benzene and 1 mL of trifluoroacetic acid was added. The solution was stirred for 48 h at room temperature and then concentrated. The residue was chromatographed (9:1 hexanes−EtOAc) to provide 2.954

g (90%) of spiroketal **6** as a white crystalline solid. $[\alpha]^{22}_D = +326$ ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.79 (3H, d, $J = 6.4$ Hz), 0.84 (3H, d, $J = 7.2$ Hz), 0.87 (3H, d, $J = 7.1$ Hz), 1.50−1.70 (4H, band), 1.85 (1H, m), 2.00 (1H, m), 2.54 (1H, dd, $J = 16.7$, 1.2 Hz), 2.73 (1H, dd, $J = 16.7$, 1.0 Hz), 3.22 (1H, dd, $J = 2.3$, 9.8 Hz), 5.45 (1H, dd, $J = 1.2$, 6.0 Hz), 7.18 (1H, d, $J = 6.0$ Hz). IR (film): 3050, 2960, 2930, 2870, 1685, 1610, 1460, 1410 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.54; H, 8.83.

8(*R*)-Isopropyl-9(*S*)-methyl-2(*S*)-vinyl-1,7-dioxaspiro[5.5]undecan-4-one (18). To a suspension of 0.636 g (1.62 mmol) of tetrakis [(tributylphosphine)copper(I)] tetraiodide in 10 mL of dry ether at −45 °C was added via syringe 16.19 mL (162 mmol) of a 1.0 M solution of vinylmagnesium bromide in THF. The solution became deep red and then faded to a creamy pale yellow. Stirring was continued for 15 min at −45 °C, followed by the dropwise addition of a solution of 382 mg (1.62 mmol) of spiroenone **6** in 10 mL of dry ether. After 30 min at −45 °C, the reaction mixture was quenched with 50 mL of a 1:1 solution of 10% ammonium hydroxide and saturated ammonium chloride and warmed to room temperature. The ether layer was washed with 10% ammonium hydroxide until it was colorless and then washed with brine. The solution was dried over $MgSO_4$ and concentrated. The residue was flash-chromatographed to give 335 mg (1.27 mmol, 78%) of ketone **18** as a pale yellow oil. $[\alpha]^{21}_D = +67.0$ ($c = 4.04$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.79 (3H, d, $J = 6.4$ Hz), 0.82 (6H, d, $J = 6.4$ Hz), 0.94 (3H, d, $J = 7.9$ Hz), 1.40−1.70 (4H, band), 1.80−1.94 (2H, band), 2.31 (1H, dd, $J = 11.3$, 15.1 Hz), 2.42 (2H, s), 2.43 (1H, dd, $J = 15.1$, 3.8 Hz), 3.09 (1H, dd, $J = 2.3$, 9.8 Hz), 4.38 (1H, m), 5.27 (2H, m), 5.93 (1H, m). IR (film): 2960, 2930, 2875, 1730, 1455, 1380, 1360, 1305, 1200, 1170, 1005 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.89.

4(*S*)-Hydroxy-8(*R*)-isopropyl-9(*S*)-methyl-2(*S*)-vinyl-1,7-dioxaspiro-[5.5]undecane (19a). To a solution of 10.89 g (43.2 mmol) of ketone **18** in 500 mL of dry dimethoxyethane was added 3.33 g (88.0 mmol) of solid sodium borohydride. Gas evolution was observed, and after the mixture was stirred for 1 h, saturated ammonium chloride was added slowly. The mixture was extracted three times with 100 mL of ether, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude mixture of alcohols was separated by flash chromatography (9:1 hexanes−EtOAc to 4:1 hexanes−EtOAc) to give 8.12 g (74%) of the major, equatorial alcohol **19a** and 2.74 g (25%) of the minor, axial alcohol **19b**.

Oxidation of 19b. To a solution of 2.74 g of alcohol **19b** in 200 mL of acetone at 0 °C was added Jones reagent until a deep orange color persisted. After the mixture was stirred for 10 min, 2-propanol was added dropwise until the orange color had disappeared. The green chromium salts were removed by filtration through a pad of Celite. The solvent was evaporated to give 2.71 g (100%) of the crude ketone **18**, identical with that prepared above. This crude ketone was then immediately resubjected to the sodium borohydride reduction described above. After one additional recycle (three cycles total) a total of 10.40 g (95%) of the equatorial alcohol **19a** was obtained from ketone **18**. $[\alpha]^{21}_D = +76.2$ ($c = 2.25$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.79 (3H, d, $J = 6.4$ Hz), 0.82 (6H, d, $J = 6.8$ Hz), 0.97 (3H, d, $J = 6.8$ Hz), 1.26 (2H, m), 1.38−1.75 (6H, band), 1.87 (1H, m), 2.01 (2H, m), 3.07 (1H, dd, $J = 9.8$, 2.3 Hz), 4.02−4.26 (2H, band), 5.18 (2H, m), 5.88 (1H, m). IR (film): 3350, 2960, 2930, 2880, 1465, 1390 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.62; H, 10.25.

4(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-8(*R*)-isopropyl-9(*S*)-methyl-2(*S*)-vinyl-1,7-dioxaspiro[5.5]undecane (20). To a solution of 4.470 g (17.6 mmol) of alcohol **19a**, 2.64 g (38.7 mmol) of imidazole, and 220 mg (1.8 mmol) of 4-(dimethylamino)pyridine in 300 mL of dry dimethylformamide at 25 °C was added 4.83 g (17.6 mmol) of *t*-$BuPh_2$-SiCl, and the mixture was stirred for 60 h. To this solution was added 500 mL of pentane and 300 mL of water. The aqueous phase was extracted twice with 100 mL of pentane, and the organic extracts were combined and dried over Na_2SO_4. The extracts were concentrated and the residue was purified by flash chromatography to yield 8.67 g (100%) of silyl ether **20** as a clear viscous oil. $[\alpha]^{21}_D = +55.4$ ($c = 3.00$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.67 (3H, d, $J = 7.5$ Hz), 0.70 (6H, d, $J = 7.5$ Hz), 0.73 (3H, d, $J = 6.0$ Hz), 1.06 (9H, s), 1.23−1.88 (10H, band), 2.91 (1H, dd, $J = 10.1$, 1.9 Hz), 3.83 (1H, dd, $J = 6$, 11.9 Hz), 4.18 (1H, m), 5.12 (2H, m), 5.81 (1H, m), 7.37 (6H, m), 7.68 (4H, m). IR (film): 3075, 3015, 2960, 2930, 2860, 1460, 1430, 1385 cm^{-1}. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56; H, 9.00; Si, 5.70. Found: C, 75.30; H, 9.24; Si, 5.56.

4(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*R*)-(2-hydroxyethyl)-8(*R*)-isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]undecane (21a). To a solution of 8.09 g (16.4 mmol) of vinyl spiroketal **20** in 250 mL of dry THF was added 131.6 mL (65.8 mmol) of a 0.5 M solution of 9-BBN in THF. The resulting mixture was irradiated in an ultrasonic cleaner for 1 h, and 50 mL of water was added to quench the excess borane. After the mixture was stirred for 10 min, 78 mL of 3 N NaOH and 78 mL of 30% hydrogen peroxide were added cautiously. A vigorous evolution of gas occurred upon addition. The mixture was stirred for 3 h, and 39.2 g of potassium carbonate was added, followed by stirring for an additional 30 min. The mixture was diluted with 200 mL of ether, and 100 mL of water and the phases were separated. The aqueous layer was extracted twice with 50 mL of ether, and the combined ether extracts were dried and concentrated. Silica gel chromatography of the residue afforded 8.10 g (97%) of alcohol **21a** as a colorless oil. $[\alpha]^{24}_D = +45.3$ ($c = 2.04$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.69 (3H, d, $J = 6.0$ Hz), 0.72 (6H, d, $J = 7.0$ Hz), 0.75 (3H, d, $J = 6.5$ Hz), 1.06 (9H, s), 1.24−1.88 (12H, band), 2.83 (1H, m), 2.91 (1H, d, $J = 8.5$ Hz), 3.63 (1H, t, $J = 9.1$ Hz), 3.75 (2H, m), 4.15 (1H, m), 7.38 (6H, m), 7.67 (4H, m). IR (film): 3450, 3080, 3060, 2965, 2930, 2940, 2865, 1480, 1470, 1440, 1395, 1370 cm^{-1}. Anal. Calcd for $C_{31}H_{46}O_4$-Si: C, 72.90; H, 9.08; Si, 5.50. Found: C, 72.81; H, 9.28; Si, 5.66.

2(*R*)-(3-Methyl-4-ethoxy-4-oxo-2(*E*)-butenyl)-4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-8(*R*)-isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]-undecane (22). A solution of 0.80 mL (9.43 mmol) of oxalyl chloride in 200 mL of dry CH_2Cl_2 was cooled to −78 °C. A solution of 1.3 mL (18.85 mmol) of dry DMSO in 5 mL of dry CH_2Cl_2 was added dropwise at a rate to maintain the temperature below −65 °C. After 5 min of stirring at −78 °C after completion of the addition, a solution of 3.410 g (8.57 mmol) of alcohol **21a** in 20 mL of CH_2Cl_2 was added dropwise, maintaining the internal reaction temperature below −65 °C. The solution was stirred for an additional 15 min at −78 °C, and 6.0 mL (42.9 mmol) of triethylamine was added slowly, maintaining the internal temperature below −60 °C. After 5 min, the mixture was warmed to room temperature. After addition of 100 mL of water, the layers were separated and the CH_2Cl_2 layer was washed three times with 50 mL of water, dried over anhydrous $MgSO_4$, and concentrated. The crude aldehyde was obtained as a pale yellow oil (3.34 g, 98%) and was typically used without purification. $[\alpha]^{22}_D = +44.7$ ($c = 3.01$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.66 (3H, d, $J = 6.5$ Hz), 0.72 (6H, d, $J = 6.0$ Hz), 0.74 (3H, d, $J = 7.0$ Hz), 1.06 (9H, s), 1.25−1.94 (10H, band), 2.34 (1H, m), 2.56 (1H, m), 2.89 (1H, d, $J = 8.0$ Hz), 3.93 (1H, m), 4.18 (1H, m), 7.38 (6H, m), 7.66 (4H, m), 9.76 (1H, t, $J = 2.5$ Hz). IR (film): 3075, 3050, 2960, 2935, 2860, 2720, 1735, 1475, 1435, 1390, 1370 cm^{-1}. A solution of 3.34 g (8.43 mmol) of crude aldehyde from above and 3.36 g (9.30 mmol) of (carbethoxyethylidene)-triphenylphosphorane in 200 mL of CH_2Cl_2 was heated at reflux for 16 h. The solvent was removed in vacuo, and the residue was dissolved in a minimum of amount of CH_2Cl_2 and loaded onto a silica gel column. Elution of the column with 9:1 hexanes−EtOAc provided 4.42 g (89%) of unsaturated ester **22** as a viscous oil. $[\alpha]^{22}_D = +41.6$ ($c = 3.88$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.65 (3H, d, $J = 6.6$ Hz), 0.67 (6H, d, $J = 7.1$ Hz), 0.72 (3H, d, $J = 6.6$ Hz), 1.06 (9H, s), 1.23−1.87 (10H, band), 1.28 (3H, t, $J = 7.6$ Hz), 1.81 (3H, br s), 2.28 (2H, m), 2.87 (1H, d, $J = 10.1$ Hz), 3.41 (1H, m), 4.15 (1H, m), 4.18 (2H, q, $J = 7.5$ Hz), 6.78 (1H, t, $J = 7.1$ Hz), 7.38 (6H, m), 7.67 (4H, m). IR (film): 3070, 3050, 2960, 2930, 2860, 1720, 1465, 1435, 1390, 1370 cm^{-1}. Anal. Calcd for $C_{36}H_{52}O_5Si$: C, 72.93; H, 8.84; Si, 4.74. Found: C, 72.97; H, 8.64; Si, 5.06.

2(*R*)-[3-Methyl-4-hydroxy-2(*E*)-butenyl]-4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-8(*R*)-isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]undecane (23). A solution of 764 mg (1.29 mmol) of α,β-unsaturated ester **22** in 50 mL of dry THF was cooled to −78 °C, and 4.26 mL (4.26 mmol) of a 1.0 M solution of diisobutylaluminum hydride in THF was added dropwise. The resulting mixture was stirred at −78 °C for 40 min and then carefully quenched by the addition of 5 mL of methanol. After the mixture was warmed to 0 °C, 10% HCl was added carefully until the mixture was homogeneous. The mixture was diluted with 100 mL of ether, and the layers were separated. The organic layer

was washed with saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated. The residual oil was flash-chromatographed to give 648 mg (91%) of alcohol **23** as a viscous oil. $[\alpha]^{22}_D = +52.1$ ($c = 2.57$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.66 (3H, d, $J = 7.1$ Hz), 0.68 (6H, d, $J = 7.1$ Hz), 0.72 (3H, d, $J = 7.1$ Hz), 1.06 (9H, s), 1.16−1.87 (10H, band), 1.64 (3H, br s), 2.14 (2H, m), 2.18 (1H, s), 2.87 (1H, dd, $J =$ 1.5, 9.8 Hz), 3.33 (1H, m), 3.97 (1H, d, $J = 5.6$ Hz), 4.13 (1H, m), 5.39 (1H, t, $J = 6.8$ Hz), 7.38 (6H, m), 7.67 (4H, m). IR (film): 3400, 3080, 3060, 2970, 2940, 2870, 1600, 1480, 1470, 1435, 1395, 1370 1315 cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_4Si$: C, 74.13; H, 9.15; Si, 5.10. Found: C, 74.13; H, 9.06, Si, 5.32.

2(*R*)-[3,5(*R*)-Dimethyl-6-hydroxy-2(*E*)-hexenyl]-4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-8(*R*)-isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]-undecane (27). Methyltriphenoxyphosphonium iodide (1.48 g, 3.27 mmol) was added in one portion to a stirred solution of alcohol **23** (0.90 g, 1.63 mmol) in DMF (15 mL) at room temperature. The solution was stirred for 20 min at 25 °C. The reaction mixture was then diluted with pentane (20 mL), and washed twice with cold 10% NaOH (2 × 10 mL) and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude iodide **25**.

(*S*)-(+)-4-Isopropyl-3-propionyl-2-oxazolidinone (1.38 mL, 8.16 mmol) in THF (2 mL) was added to a solution of sodium hexamethyldisilazide (1.0 M in THF; 8.2 mL, 8.16 mmol) in THF (20 mL) at −78 °C. The solution was stirred for 1 h at −78 °C, and the freshly prepared crude iodide **25** in THF (5 mL) was added dropwise. The mixture was stirred for 3.5 h at −78 °C and warmed to 0 °C. The reaction was then quenched with a solution of saturated aqueous ammonium chloride (15 mL), and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude oxazolidinone **26** (1.04 g, 89%), which was used without further purification in the next step.

To a stirred suspension of $LiAlH_4$ (0.19 g, 4.9 mmol) in diethyl ether (20 mL) at −30 °C was added dropwise the crude oxazolidinone **26** (1.04 g, 4.9 mmol) in diethyl ether (2 mL), so as to maintain the temperature below −25 °C. After the addition was complete, the suspension was warmed to room temperature over 2 h and was quenched by cautious addition of 5% NaOH until only a flocculent white salt remained in suspension. The reaction mixture was filtered, and the salts were washed with more ether. The filtrate was washed with H_2O (10 mL) and brine and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5−10% EtOAc−hexanes) to afford alcohol **27** (0.676 g, 77%) as an oil. $[\alpha]^{22}_D = +49.6°$ ($c = 1.14$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.65 (d, 3 H, $J = 6.0$ Hz), 0.68 (d, 3 H, $J = 6.7$ Hz), 0.72 (d, 3 H, $J = 6$ Hz), 0.86 (d, 3 H, $J = 6.7$ Hz), 1.05 (s, 9 H), 2.29−1.23 (m, 13 H), 2.9 (bdd, 1 H, $J = 9$, 2.2 Hz), 3.32 (m, 1 H), 3.38 (dd, 1 H, $J = 10.5$, 5.2 Hz), 3.46 (dd, 1 H, $J = 10.5$, 5.2 Hz), 4.14 (m, 1 H), 5.17 (bt, 1 H, $J = 6.7$ Hz), 7.7−7.3 (m, 10 H). Anal. Calcd for $C_{37}H_{56}O_4Si$: C, 74.95; H, 9.52. Found: C, 75.32; H, 9.80.

2(*R*)-[3,5(*R*)-Dimethyl-6-(triphenylphosphonio)-2(*E*)-hexenyl]-4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-8(*R*)-isopropyl-9(*S*)-methyl-1,7-dioxaspiro[5.5]undecane Iodide (4). Methyltriphenoxyphosphonium iodide (0.54 g, 1.19 mmol) was added in one portion to a stirred solution of alcohol **27** (0.35 g, 0.59 mmol) in DMF (5 mL) at room temperature. The solution was stirred for 20 min at 25 °C. The reaction mixture was then diluted with pentane (20 mL) and washed twice with cold 10% NaOH (2 × 5 mL) and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude iodide. Purification by column chromatography (5% EtOAc−hexanes) gave the pure iodide (0.41 g, 98%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.65 (d, 3 H, $J = 5.6$ Hz), 0.66 (d, 3 H, $J = 5.6$ Hz), 0.71 (d, 3 H, $J = 6.5$ Hz), 0.91 (d, 3 H, $J = 6.5$ Hz), 1.04 (s, 9 H), 2.18−1.17 (m, 18 H), 2.89 (bdd, 1 H, $J = 9.3$, 1.8 Hz), 3.02 (dd, 1 H, $J = 9.3$, 5.6 Hz), 3.18 (dd, 1 H, $J = 9.3$, 4.6 Hz), 4.11 (m, 1 H), 3.31 (m, 1 H), 5.19 (bt, 1 H, $J = 6.5$ Hz), 7.7−7.3 (m, 10 H).

Triphenylphosphine (1.46 g, 5.56 mmol) was added in one portion to a stirred solution of the pure iodide (1.95 g, 2.78 mmol) in acetonitrile (5 mL). The solution was heated to reflux and stirred for 4 days. The mixture was cooled to room temperature and concentrated in vacuo. The crude residue was washed with hexanes to remove excess triphenylphosphine, thus leaving phosphonium salt **4** (2.68 g, 100%) as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.56 (d, 3 H, $J =$ 7.4 Hz), 0.77 (d, 3 H, $J = 6.5$ Hz), 0.83 (d, 3 H, $J = 5.6$ Hz), 0.87 (d, 3 H, $J = 6.5$ Hz), 0.96 (s, 9 H), 2.12−1.08 (m, 18 H), 2.72 (bd, 1 H, $J = 4$ Hz), 3.66−3.16 (m, 3 H), 4.03 (m, 1 H), 5.07 (bt, 1 H, $J = 7.4$ Hz), 7.8−7.2 (m, 25 H). ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.13.

2-Methyl-5-[(*tert*-butyldimethylsilyl)oxy]-1,3-pentadiene (37). A solution of 118 g (0.78 mol) of *tert*-butyldimethylsilyl chloride, 4.4 g (36 mmol) of 4-(dimethylamino)pyridine, 119 mL (86.6 g, 0.86 mol) of triethylamine, and 70 g (0.71 mol) of 2-methyl-1,3-pentadien-5-ol in 500 mL of CH_2Cl_2 was stirred overnight at room temperature. The solution was washed with 200 mL of saturated sodium bicarbonate, 100 mL of water, and 100 mL of saturated ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was filtered through a short column of silica gel (9:1 hexanes−EtOAc), and the solvent was removed to give 155 g (100%) of diene **37** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 0.09 (6H, s), 0.92 (9H, s), 1.85 (3H, s), 4.25 (2H, d, $J = 5.6$ Hz), 4.94 (2H, br s), 5.72 (1H, dt, $J = 15.4$ Hz, 5.6 Hz), 6.32 (1H, d, $J = 15.4$ Hz). IR: 3095, 2965, 2935, 2895, 1623, 1471, 1383, 1370, 1260, 1135 cm^{-1}. Anal. Calcd for $C_{12}H_{24}OSi$: C, 67.86; H, 11.39; Si, 13.22. Found: C, 67.83; H, 11.31; Si, 13.46.

1-Formyl-6-[((*tert*-butyldimethylsilyl)oxy)methyl]-4-methyl-1,4-cyclohexadiene (34). A thick-walled glass tube equipped with a sealable Fisher−Porter valve was charged with 60.32 g (284 mmol) of diene **37**, 16.5 g (305 mmol) of propiolaldehyde, 500 mg of hydroquinone, and 200 mL of benzene. The tube was sealed and heated to 110−120 °C for 24 h. The mixture was cooled and filtered, and the solvent was removed in vacuo. The residue was taken up in ether, the solution was filtered, and the solvent was removed. This crude product (74.14 g, 98%) was found to be very sensitive to silica gel and was used without further purification. ^{1}H NMR ($CDCl_3$): δ 0.03 (6H, s), 0.86 (9H, s), 1.79 (3H, s), 2.86 (2H, m), 3.26 (1H, m), 3.66 (2H, 8-line AB of ABX), 5.56 (1H, br s), 6.90 (1H, t, $J = 4$ Hz), 9.49 (1H, s). IR: 2960, 2935, 2860, 2810, 2715, 1695, 1648, 1475, 1258, 1150 cm^{-1}.

4-(1-Oxoethyl)-4(*R*),5(*S*)-epoxy-3(*S*)-[((*tert*-butyldimethylsilyl)-oxy)methyl]-1-methyl-1-cyclohexene (33). A suspension of 1.63 g (43.0 mmol) of lithium aluminum hydride in 200 mL of dry ether was cooled to −78 °C. A solution of 22.00 g (83.0 mmol) of aldehyde **34** in 100 mL of dry ether was added dropwise. The reaction mixture was stirred for 5 min and carefully quenched by the slow addition of 10% NaOH until all the gray suspended solid had been converted to a granular white solid. The mixture was warmed to room temperature and filtered. The solids were washed several times with ether, and the combined ether washes were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue provided 21.7 g (98%) of the allylic alcohol **38**. ^{1}H NMR ($CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.66 (3H, s), 2.55 (2H, m), 2.90 (1H, m), 3.48 (1H, br s), 3.55 (2H, 8-line AB of ABX), 4.04 (2H, m), 5.29 (1H, br s), 5.74 (1H, t, $J = 3.6$ Hz).

A solution of 29.6 mL (99.3 mmol) of titanium isopropoxide in 150 mL of CH_2Cl_2 was cooled to −23 °C. A solution of 17 mL (99.3 mmol) of (+)-diethyl tartrate in 20 mL of CH_2Cl_2 was added slowly, and the mixture was stirred for 15 min at −20 °C. Then 26.7 g (99.3 mmol) of allylic alcohol **38** in 100 mL of CH_2Cl_2 was added dropwise, followed by the slow, dropwise addition of 26 mL (198.6 mmol) of 7.6 M *tert*-butyl hydroperoxide in CH_2Cl_2. The resulting yellow solution was stirred at −20 °C for 4 h and then placed in a −20 °C freezer overnight. The mixture was removed from the freezer and recooled to −23 °C, and 150 mL of a solution of 10% D-tartaric acid was added slowly. The mixture was kept at −23 °C for 30 min and then warmed to room temperature over 2 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was filtered through a short pad of silica gel with 19:1 hexanes−EtOAc to give 28.3 g (100%) of the epoxy alcohols **39** and **40** as an inseparable mixture. ^{1}H NMR ($CDCl_3$): δ 0.05 (3H, s), 0.07 (3H, s), 0.11 (6H, s), 0.89 (9H, s), 0.93 (6H, s), 1.65 (3H, s), 2.41 (2H, m), 2.79 (1H, m), 3.22−3.39 (1H, band), 3.41−4.05 (4H, band), 4.95−5.20 (1H, band). IR: 3450, 2930, 2885, 1478, 1420, 1365, 1255, 1098 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92; Si, 9.87. Found: C, 63.13; H, 9.90; Si, 9.66.

A solution of 60 mL (120 mmol) of a 2 M solution of oxalyl chloride in CH_2Cl_2 in an additional 200 mL of dry CH_2Cl_2 was cooled to −78 °C. A solution of 17 mL (239 mmol) of dry DMSO in 50 mL of dry CH_2Cl_2 was added dropwise at a rate to maintain the temperature below −65 °C. After 5 min of stirring at −78 °C after completion of the addition, a solution of 28.3 g (99.3 mmol) of alcohols **39** and **40** in 50 mL of CH_2Cl_2 was added dropwise, maintaining the internal reaction temperature below −65 °C. The solution was stirred for an additional 15 min at −78 °C, and 69.3 mL (437 mmol) of triethylamine was added slowly, maintaining the internal temperature below −60 °C. After 5 min, the mixture was warmed to room temperature. After addition of 100 mL of water, the layers were separated and the CH_2Cl_2 layer was washed three times with 50 mL of water, dried over anhydrous $MgSO_4$, and concentrated. The crude aldehyde was obtained as a pale yellow oil (29.0 g, 99%) and was used without purification. The crude aldehyde was dissolved in 100 mL of dry ether and added dropwise to a stirred solution of 40 mL (120 mmol) of 3 M methylmagnesium chloride in THF which had been diluted by an additional 100 mL of THF. After the addition was complete, the reaction mixture was stirred for 3 h and then quenched by the slow addition of 10% hydrochloric acid until all the salts had dissolved. The layers were separated, and the aqueous layer was extracted three times with 50 mL of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated to give 28.0 g (93.9 mmol) of the crude alcohols, which were oxidized without purification. A solution of 56.3 mL (112.6 mmol) of a 2 M solution of oxalyl chloride in CH_2Cl_2 in an additional 200 mL of dry CH_2Cl_2 was cooled to −78 °C. A solution of 16 mL (225 mmol) of dry DMSO in 50 mL of dry CH_2Cl_2 was added dropwise at a rate to maintain the temperature below −65 °C. After 5 min of stirring at −78 °C after completion of the addition, a solution of 28.0 g (93.8 mmol) of the crude alcohols from above in 50 mL of CH_2Cl_2 was added dropwise, maintaining the internal reaction temperature below −65 °C. The solution was stirred for an additional 15 min at −78 °C, and 65 mL (469 mmol) of triethylamine was added slowly, maintaining the internal temperature below −60 °C. After 5 min, the mixture was warmed to room temperature. After addition of 100 mL of water, the layers were separated and the CH_2Cl_2 layer was washed three times with 50 mL of water, dried over anhydrous $MgSO_4$, and concentrated to give a 1.5:1 mixture of ketoepoxides **41**:**33**. The diastereomers were separated by flash chromatography to give 12.80 g (47%) of ketoepoxide **41** (55% ee) and 8.54 g (31%) of ketoepoxide **33** (>95% ee). $[\alpha]^{22}_D = -52.0°$ (c = 5.01 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.05 (6H, s), 0.89 (9H, s), 1.66 (3H, s), 2.22 (3H, s), 2.44 (2H, AB), 3.31 (1H, m), 3.41−3.65 (3H, band), 5.08 (1H, br s). IR: (2965, 2935, 2890, 2865, 1740, 1475, 1415, 1362, 1255, 1098 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52; Si, 9.47. Found: C, 64.43; H, 9.36; Si, 9.37.

5(*S*)-(2-Hydroxy-1-oxoethyl)-5-[(trimethylsilyl)oxy]-6(*S*)-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-methyl-1,3-cyclohexadiene (32). To a stirred solution of 9.92 mL of diisopropylamine (70.78 mmol) in 60 mL of tetrahydrofuran at −78 °C under argon was added dropwise 44.97 mL (71.47 mmol) of butyllithium (1.6 M in hexanes). The solution was stirred for 5 min at −78 °C, and then 6.994 g (23.59 mmol) of epoxy ketone **33** in 20 mL of tetrahydrofuran was added dropwise. After the mixture was stirred for 35 min at −78 °C, 8.98 mL (70.78 mmol) of neat trimethylsilyl chloride was added slowly dropwise, so as to maintain a temperature below −65 °C. After the reaction mixture was stirred for 15 min at −78 °C, it was slowly warmed to room temperature by removing the cooling bath. The reaction mixture was then quenched by addition of saturated aqueous ammonium chloride solution (100 mL) and partitioned with ether. The organic layer was washed with water (100 mL) and brine and dried over Na_2SO_4. After filtration and concentration under vacuum, the residue was taken up in CH_2Cl_2 (100 mL). To the solution was added solid sodium bicarbonate (1.98 g, 23.59 mmol) in one portion, followed by 3-chloroperoxybenzoic acid (60%; 7.46 g, 25.95 mmol) in small batches over 30 min. The solution was stirred for 30 min and quenched by addition of a saturated aqueous sodium sulfite solution (100 mL). The organic layer was then washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed over 2 h (2−5% EtOAc−petroleum ether) to provide 5.72 g of diene **32** (63%) as an oil. R_f (25% EtOAc−hexanes): 0.54. $[\alpha]_D^{22}$ = +19.57° (c = 0.92, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (6 H, s), 0.06 (9 H, s), 0.84 (9 H, s), 1.81 (3 H, m), 3.03 (1 H, t, J = 4.84 Hz), 3.24 (1 H, m), 3.59 (1 H, dd, J = 9.69, 5.54 Hz), 3.80 (1H, dd, J = 10.38, 9.69 Hz), 4.45 (1 H, dd, J = 19.38, 4.84 Hz), 4.09 (1H, dd, J = 19.38, 4.84 Hz), 5.23 (1H, m), 5.55 (1H, d, J = 9.69 Hz), 6.05 (1H, d, J = 9.69 Hz). IR (film): 3500, 2960, 2935, 2860, 1738, 1675, 1610, 1476, 1409, 1365, 1195, 1150, 1118, 989, 931, 838, 790 cm^{-1}. IR: 3500, 2960, 2935, 2900, 2860, 1738, 1675, 1476, 1409, 1365, 1253, 1085 cm^{-1}. Anal. Calcd for $C_{19}H_{36}O_4Si_2$: C, 59.33; H, 9.43; Si, 14.60. Found: C, 59.54; H, 9.50; Si, 14.47.

Allylic Alcohol 47. A solution of 4.00 g (10.73 mmol) of hydroxy ketone **32** in 25 mL of dry CH_2Cl_2 was cooled to 0 °C. Solid sodium bicarbonate (1.8 g, 21.47 mmol) was added, followed by addition of 2.26 g (11.8 mmol) of solid phenyl selenium chloride in small portions. When the reaction was complete by TLC, the mixture was washed with saturated sodium bicarbonate and water. This CH_2Cl_2 solution of the crude selenide **48** was cooled to 0 °C, and 0.95 mL (11.8 mmol) of pyridine and 20 mL of 30% hydrogen peroxide solution were added. The heterogeneous mixture was stirred at 0 °C for 40 min, and the layers were separated. The aqueous layer was extracted twice with 10 mL of CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was chromatographed (85:15 hexanes−EtOAc) to provide 3.10 g (72%) of allylic alcohol **47** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.02 (3H, s), 0.04 (3H, s), 0.12 (9H, 2), 0.89 (9H, s), 1.84 (3H, br s), 2.48 (1H, m), 2.72 (1H, d, J = 9.6 Hz), 3.66 (2H, dd, J = 10.1, 3.4 Hz), 3.78 (1H, dd, J = 10.1, 5.8 Hz), 3.88 (1H, d, J = 9.6 Hz), 3.92 (1H, d, J = 18.3 Hz), 4.09 (1H, d, J = 18.3 Hz), 4.12 (1H, br s), 5.58 (1H, m). IR: 3410, 2910, 2935, 2885, 1755, 1465, 1442, 1410, 1364, 1258, 1066 cm^{-1}. Anal. Calcd for $C_{19}H_{36}O_5Si_2$: C, 59.96; H, 9.06; Si, 14.02. Found: C, 59.92; H, 8.97; Si, 13.83.

Aldehyde 5. To a stirred solution of 2.05 mL of oxalyl chloride (4.1 mmol, 2.0 M in CH_2Cl_2) in 15 mL of CH_2Cl_2 at −78 °C under argon was added 0.58 mL (8.2 mmol) of DMSO in 1 mL of CH_2Cl_2 dropwise, maintaining the temperature below −65 °C. The solution was stirred for 5 min and then 1.78 g (3.4 mmol) of alcohol **56** in 3 mL of CH_2Cl_2 was added dropwise. After the mixture was stirred for 35 min at −78 °C, 2.38 mL (17 mmol) of triethylamine was added slowly and dropwise so as to maintain a temperature below −65 °C. After the reaction mixture was stirred for 15 min at −78 °C, it was slowly warmed to room temperature by removing the cooling bath. The mixture was then extracted with water (10 mL), and the aqueous layer was back-extracted twice with fresh CH_2Cl_2 (2 × 10 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (5% EtOAc−petroleum ether) to provide 1.68 g (95%) of aldehyde **5** as an oil. R_f (25% EtOAc−hexanes): 0.4. ^{1}H NMR ($CDCl_3$): δ 0.01 (3H, s), 0.02 (3H, s), 0.16 (9H, s), 0.87 (9H, s), 1.83 (3H, br s), 2.28 (1H, m), 3.83 (1H, d, J = 5.0 Hz), 3.96 (1H, dd, J = 10.1, 4.0 Hz), 4.06 (1H, br d, J = 4.60 Hz), 4.36 (1H, dd, J = 9.9, 9.9 Hz), 4.91 (2H, m, 2 H), 5.54 (1H, br d, J = 3.5 Hz), 6.18 (1H, dt, J = 6.0, 2.6 Hz), 7.16−7.28 and 7.58−7.63 (5H, band), 9.80 (1H, d, J = 5.0 Hz). ^{13}C NMR ($CDCl_3$): δ 1.98, 17.96, 22.20, 25.65, 43.88, 50.62, 59.59, 68.24, 76.30, 79.88, 115.76, 121.61, 125.79, 128.40, 130.43, 140.23, 144.53, 167.17, 188.69.

Silyl Ether 65. To a solution of alcohol **47** (2.06 g, 5.14 mmol) in 70 mL of CH_2Cl_2 was added 2,6-lutidine (7.2 mL, 61.8 mmol) followed by triisopropylsilyl triflate (4.7 mL, 17.5 mmol). The resulting solution was stirred at room temperature for 2 days. The solution was quenched with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), and the mixture was vigorously stirred for an additional 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Column chromatography of the residue on silica gel (2% EtOAc/hexanes) afforded silyl ether **65** (2.86 g, 100%) as an oil. $[\alpha]^{22}_D = -10.6°$ (c = 0.97, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.012 (s, 3 H), 0.022 (s, 3 H), 0.088 (s, 9 H), 0.86 (s, 9 H), 1.25−1.05 (m, 21 H), 1.85−1.80 (bs, 3 H), 2.4−2.3 (m, 1 H), 3.62−3.55 (t, 1 H, J = 9.3 Hz), 3.87−3.81 (dd, 1 H, J = 9.9, 4.4 Hz), 4.0−3.94 (d, 1 H, J = 18 Hz), 4.12−4.05 (d, 1 H, J = 18 Hz), 4.15−4.10 (d, 1 H, J = 1.0 Hz), 4.25−4.2 (m, 1 H), 5.52−5.46 (m, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ

214.0, 135.5, 122.6, 88.7, 78.3, 72.3, 69.2, 62.4, 40.7, 26.0, 20.4, 18.3, 18.2, 12.7, 1.7, −5.3, −5.4. IR (film): 2920, 2860, 1760, 1440, 1380, 1250 cm^{-1}. Anal. Calcd for $C_{28}H_{56}O_5Si_3$: C, 60.38; H, 10.13. Found: C, 60.28; H, 10.13.

Ketone 66. A solution of silyl ether **65** (2.40 g, 4.31 mmol) in 90 mL of EtOAc was hydrogenated for 7 h under balloon pressure in the presence of Li_2CO_3 (0.35 g, 0.47 mmol) and 0.100 g of PtO_2. The solution was filtered through Celite and concentrated in vacuo. Purification by column chromatography on silica gel (2% EtOAc−hexanes) afforded reduced silyl ether **66** (2.41 g, 100%) as a solid. $[\alpha]^{25}_D = -1.6°$ (c = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ −0.01 (s, 3 H), 0.003 (s, 3 H), 0.092 (s, 9 H), 0.85 (s, 9 H), 1.1−1.0 (m, 24 H), 1.9−1.45 (m, 4 H), 3.34−3.26 (t, 1 H, J = 9.7 Hz), 3.79−3.74 (dd, 1 H, J = 10.2, 3.3 Hz), 3.87−3.86 (d, 1 H, J = 3.4 Hz), 3.93−3.86 (d, 1 H, J = 17.5 Hz), 4.03−4.01 (t, 1 H, J = 2.5 Hz), 4.28−4.21 (d, 1 H, J = 18 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 215.1, 85.2, 79.3, 71.3, 69.9, 62.7, 42.0, 33.0, 26.0, 25.6, 18.5, 18.4, 18.3, 13.0, 2.13, −5.3. IR (film): 2920, 2860, 1760, 1450, 1380, 1250 cm^{-1}. Anal. Calcd for $C_{28}H_{58}O_5Si_3$: C, 60.16; H, 10.46. Found: C, 59.99; H, 10.49.

Unsaturated Ester 67. A solution of silyl ether **66** (2.40 g, 4.29 mmol) in 10 mL of toluene was placed in a sealed tube followed by 10 g of (carbethoxymethylene)triphenylphosphorane. The mixture was heated in an oil bath at 120 °C, and an additional 1 g of (carbethoxymethylene)triphenylphosphorane was added every 2 days. Following a total of 8 days of heating, the solution was concentrated and filtered through a pad of silica using 50% EtOAc−CH_2Cl_2. The resulting brown residue was purified by column chromatography using 2−10% EtOAc−hexanes to give α,β-unsaturated ester **67** (2.18 g, 81%) as a white solid. $[\alpha]^{25}_D = -21.2°$ (c = 0.655, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.035 (s, 3 H), 0.04 (s, 3 H), 0.13 (s, 9 H), 0.89 (s, 9 H), 1.15−1.0 (m, 24 H), 1.32−1.26 (t, 3 H, J = 7.1 Hz), 1.85−1.4 (m, 4 H), 3.53−3.45 (t, 1 H, J = 9.5 Hz), 3.80−3.78 (d, 1 H, J = 3.3 Hz), 4.0−3.9 (m, 2 H), 4.3−4.1 (m, 2 H), 4.84−4.82 (t, 2 H, J = 2.5 Hz), 5.93−5.91 (t, 1 H, J = 2.5 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 165.9, 165.7, 112.6, 86.5, 81.9, 72.0, 69.6, 62.9, 60.3, 44.1, 32.8, 26.9, 26.0, 18.5, 18.4, 18.3, 17.8, 14.3, 13.1, 2.5, −5.3. IR (film): 2880, 1700, 1660, 1440, 1360, 1340 cm^{-1}. Anal. Calcd for $C_{32}H_{64}O_6Si_3$: C, 61.09; H, 10.25. Found: C, 60.85; H, 10.18.

Allylic Alcohol 68. Lithium aluminum hydride (8.8 mL, 8.8 mmol), as a 1.0 M solution in hexanes, was added dropwise to a −78 °C solution of ester **67** (2.4 g, 3.81 mmol) in 80 mL of THF. Following 45 min of stirring, the −78 °C bath was replaced by a wet ice bath. After an additional 45 min at 0 °C the reaction mixture was quenched slowly with 0.33 mL of H_2O, followed by 0.33 mL of 15% NaOH and again 0.99 mL of H_2O. The resulting granular mixture was filtered through Celite using warm EtOAc and concentrated in vacuo to yield crude alcohol **68** (2.24 g, 100%) as an oil. $[\alpha]^{25}_D = -31.3°$ (c = 0.85, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.029 (s, 3 H), 0.034 (s, 3 H), 0.099 (s, 9 H), 0.88 (s, 9 H), 1.1−0.95 (m, 24 H), 1.33−1.29 (t, 1 H, J = 5.5 Hz), 1.85−1.40 (m, 4 H), 3.56−3.48 (t, 1 H, J = 9.9 Hz), 3.78−3.77 (d, 1 H, J = 4 Hz), 3.86−3.83 (t, 1 H, J = 4.1 Hz), 3.99−3.93 (dd, 1 H, J = 9.9, 4.0 Hz), 4.15−4.05 (m, 2 H), 4.45−4.4 (bs, 2 H), 5.7−5.6 (m, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 145.3, 120.7, 87.6, 81.2, 72.6, 67.0, 63.3, 60.2, 43.6, 32.7, 27.1, 26.0, 18.4, 18.35, 17.5, 13.0, 2.5, −5.2. IR (film): 3360, 2840, 1430, 1360, 1240 cm^{-1}. HRMS: Calcd for $C_{30}H_{62}O_5Si_3$ 587.3983, found 587.3964.

Aldehyde 69. Tetrapropylammonium perruthenate (0.05 g, 0.142 mmol) and anhydrous *N*-methylmorpholine *N*-oxide (0.57 g, 4.87 mmol) were added to a solution of allylic alcohol **68** (2.24 g, 3.82 mmol) and 5.0 g of 4 Å powdered sieves in 80 mL of CH_2Cl_2. The black solution was stirred for 2 h at room temperature and filtered through a pad of silica gel using EtOAc and concentrated in vacuo. Column chromatography of the residue on silica gel (5% EtOAc−hexanes) provided labile aldehyde **69** (1.74 g, 78%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.0015 (s, 3 H), 0.009 (s, 3 H), 0.11 (s, 9 H), 0.85 (s, 9 H), 1.12−1.0 (m, 24 H), 1.85−1.4 (m, 4 H), 3.49−3.42 (t, 1 H, J = 9.5 Hz), 3.79−3.78 (d, 1 H, J = 3.0 Hz), 3.89−3.84 (dd, 1 H, J = 9.9, 4.0 Hz), 3.99−3.97 (t, 1 H, J = 3.3 Hz), 4.86−4.84 (t, 2 H, J = 2.5 Hz), 6.22−6.15 (m, 1 H), 9.73−9.71 (d, 1 H, J = 5 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 189.5, 168.4, 120.1, 86.3, 82.0, 71.8, 68.5, 62.8, 44.1, 32.8, 26.9, 26.0, 18.5, 18.4, 17.9, 13.2, 2.6, −5.3. IR (film): 2880, 1685, 1610, 1450, 1380, 1360, 1250 cm^{-1}.

Diene 70. A solution of methyllithium (0.16 mL, 0.24 mmol), as a complex with lithium bromide (1.5 M solution in diethyl ether), was added dropwise to a stirred solution of phosphonium salt **4** (0.20 g, 0.21 mmol) in 5.0 mL of THF at −78 °C. The solution was stirred for 1 h at −78 °C, and the freshly chromatographed aldehyde **69** (0.098 g, 0.17 mmol), in 2.0 mL of THF, was added to it dropwise via cannula. Following an additional 1 h at −78 °C the solution was warmed to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (silica gel, 5% EtOAc/hexanes) to afford a mixture of the cis,trans and trans,trans dienes (4.3:1.0; 0.16 g, 83%) as a white foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.016 (s, 3 H), 0.022 (s, 3 H), 0.08 (s, 6 H), 0.71−0.63 (m, 9 H), 2.2−0.8 (m, 69 H), 2.82−2.7 (m, 1 H), 2.89−2.85 (dd, 1 H, J = 9.7, 1.7 Hz), 3.35−3.2 (m, 1 H), 3.57−3.49 (t, 1 H, J = 10.0 Hz), 3.79−3.77 (t, 1 H, J = 3.3 Hz), 3.88−3.85 (t, 1 H, J = 3.7 Hz), 4.02−3.95 (dd, 1 H, J = 10.2, 4 Hz), 4.2−4.02 (m, 1 H), 4.48−4.47 (bd, 2 H, J = 2 Hz), 5.15−5.06 (bt, 1 H), 5.32−5.24 (t, 1 H, J = 10 Hz), 5.69−5.6 (t, 1 H, J = 11.5 Hz), 6.35−6.23 (m, 1 H), 7.7−7.25 (m, 10 H).

A light pink iodine solution was prepared with three crystals of iodine in 20 mL of dry benzene. To a benzene (10 mL) solution of the cis,-trans and trans,trans dienes (0.47 g, 0.41 mmol) was added enough of the iodine solution to acquire a light pink color. More of the iodine solution was added as needed while the progress of the reaction was monitored by ^{1}H-NMR. Upon completion, the reaction was quenched using aqueous 10% $Na_2S_2O_3$ (20 mL) and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue on silica gel (5% EtOAc−hexanes) yielded the trans,trans diene **70** (0.41 g, 87%) as a white foam. $[\alpha]^{25}_D = +2.2°$ (c = 0.90, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.02 (s, 6 H), 0.06 (s, 6H), 0.70−0.62 (m, 9 H), 2.4−0.85 (m, 70 H), 2.9−2.83 (bdd, 1 H, J = 9.9, 1.5 Hz), 3.35−3.2 (m, 1 H), 3.58−3.50 (t, 1 H, J = 9.9 Hz), 3.81−3.78 (t, 2 H, J = 4.6 Hz), 3.98−3.93 (dd, 1 H, J = 9.8, 4 Hz), 4.2−4.03 (m, 1 H), 4.5−4.45 (bs, 2 H), 5.15−5.06 (bt, 1 H), 5.66-5.57 (dd, 1 H, J = 15, 7 Hz), 5.82−5.72 (dd, 1 H, J = 15, 11 Hz), 6.02−5.93 (m, 1 H), 7.7−7.25 (m, 10 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 142.4, 142.1, 135.7, 134.7, 134.6, 134.5, 129.4, 127.5, 123.5, 122.9, 121.5, 97.2, 88.2, 81.3, 77.8, 72.9, 68.1, 67.7, 66.8, 63.6, 47.3, 45.3, 43.6, 41.0, 35.7, 35.0, 34.4, 32.7, 31.5, 28.2, 27.1, 27.0, 26.1, 20.6, 19.4, 19.2, 18.43, 18.37, 18.3, 18.2, 18.1, 18.0, 17.5, 17.4, 16.4, 14.0, 13.0, 12.74, 12.71, 2.4, 2.3, −5.2. IR (film): 2880, 1450, 1420, 1380, 1360, 1250 cm^{-1}. HRMS: Calcd for $C_{67}H_{114}O_7Si_4$ 1142.7642, found 1142.7656.

Diol 71. To a solution of **70** (0.41 g, 0.36 mmol) in 40 mL of THF was added aqueous 10% HCl (5.5 mL). The mixture was stirred at room temperature for 3 h and cooled to 0 °C. Solid $NaHCO_3$ was added carefully in small portions until all the bubbling subsided. The aqueous layer was extracted with ether (4 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5−10% EtOAc−hexanes) provided diol **71** (0.30 g, 87%) as a white foam. $[\alpha]^{25}_D = +23.5°$ (c = 1.1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.73−0.62 (m, 9 H), 0.91−0.88 (d, 3 H, J = 6.6 Hz), 1.09 (s, 24 H), 1.04 (s, 9 H), 2.4−1.1 (m, 22 H), 2.7−2.55 (bs, 1 H), 2.9−2.86 (bdd, 1 H, J = 9.9, 1.5 Hz), 3.13 (s, 1 H), 3.35−3.2 (m, 1 H), 3.65−3.5 (m, 2 H), 4.02−3.96 (dd, 1 H, J = 11.6, 4 Hz), 4.16−4.05 (m, 1 H), 4.19−4.18 (bd, 1 H, J = 2 Hz), 4.5−4.43 (dd, 1 H, J = 14, 3 Hz), 4.65−4.58 (dd, 1 H, J = 14, 2 Hz), 5.13−5.08 (bt, 1 H), 5.86−5.62 (m, 2 H), 6.05−5.95 (m, 1 H) 7.7−7.3 (m, 10 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 142.2, 140.9, 135.7, 134.6, 134.5, 134.4, 129.4, 127.4, 122.9, 120.4, 97.1, 83.1, 78.8, 77.7, 72.6, 68.0, 66.8, 63.1, 47.2, 45.3, 41.5, 41.0, 35.6, 34.8, 34.3, 32.5, 31.5, 28.1, 27.0, 26.2, 25.6, 20.6, 19.3, 19.1, 18.3, 17.3, 16.3, 13.9, 13.0. IR (film): 3380, 2840, 1420, 1360, 1240 cm^{-1}. Anal. Calcd for $C_{58}H_{92}O_7Si_2$: C, 72.75; H, 9.68. Found: C, 72.84; H, 9.63.

Aldehyde 72. Tetrapropylammonium perruthenate (0.050 g, 0.142 mmol) and anhydrous *N*-methylmorpholine *N*-oxide (0.23 g, 1.96 mmol)

were added to a solution of diol **71** (1.25 g, 1.31 mmol) and 2.5 g of 4 Å powdered sieves in 30 mL of CH_2Cl_2. The black mixture was stirred at room temperature for 3 h, filtered through a pad of silica gel using EtOAc, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5−10% EtOAc−hexanes) provided aldehyde **72** (1.0 g, 80%) as a white foam. $[\alpha]^{25}_D = +2.4°$ ($c = 0.88$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.71−0.63 (m, 9 H), 0.91−0.88 (d, 3 H, $J = 6.6$ Hz), 1.04 (s, 12 H), 1.09 (s, 21 H), 2.4−1.2 (m, 21 H), 2.5−2.46 (dd, 1 H, $J = 12$, 4 Hz), 2.9−2.86 (bdd, 1 H, $J = 9.8$, 1.8 Hz), 3.08 (s, 1 H), 3.35−3.25 (m, 1 H), 3.67−3.66 (d, 1 H, $J = 2.9$ Hz), 4.2−4.05 (m, 2 H), 4.63−4.56 (dd, 1 H, $J = 14$, 2 Hz), 4.72−4.66 (dd, 1 H, $J = 14$, 2 Hz), 5.14−5.09 (bt, 1 H, $J = 6.5$ Hz), 5.73−5.64 (dd, 1 H, $J = 15$, 6 Hz), 5.89−5.78 (dd, 1 H, $J = 15$, 10 Hz), 6.13−6.02 (m, 1 H), 7.7−7.3 (m, 10 H), 9.9 (s, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 203.6, 143.1, 140.2, 135.7, 134.7, 134.6, 134.4, 129.4, 127.5, 122.9, 122.7, 121.4, 97.2, 82.9, 77.7, 52.7, 47.2, 45.3, 41.0, 35.7, 34.8, 34.4, 31.5, 31.2, 28.2, 27.0, 22.9, 20.6, 19.2, 19.1, 18.3, 18.2, 18.1, 17.4, 16.3, 14.0, 12.9. IR (film): 3540, 2920, 2860, 1720, 1440, 1410, 1370 cm^{-1}.

Acid 74. *tert*-Butyl alcohol (26 mL) and H_2O (26 mL) were added to aldehyde **72** (0.826 g, 0.864 mmol), and the mixture was cooled to 0 °C. 2-Methyl-2-butene (26 mL), followed by $NaClO_2$ (0.637 g, 7.04 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.074 g, 7.78 mmol), were also added consecutively. After the mixture was warmed to room temperature and stirred vigorously for 4 h, it was quenched with a pH 4 buffer solution (20 mL). The aqueous layer was extracted with ether (5 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (10−240% EtOAc−hexanes) afforded acid **73** (0.517 g, 61%) as a white foam. $[\alpha]^{25}_D = +32.6°$ ($c = 1.45$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.72−0.64 (m, 9 H), 0.9−0.87 (d, 3 H, $J = 6.6$ Hz), 1.05 (s, 13 H), 1.11 (s, 20 H), 2.45−1.15 (m, 21 H), 2.71−2.65 (bdd, 1 H, $J = 12.4$, 3.6 Hz), 2.91−2.86 (dd, 1 H, $J = 9.5$, 1.8 Hz), 3.38−3.22 (m, 1 H), 3.74−3.73 (d, 1 H, $J = 2.9$ Hz), 4.25−4.0 (m, 3 H), 4.59−4.53 (dd, 1 H, $J = 14$, 2 Hz), 4.68−4.61 (dd, 1 H, $J = 14$, 2 Hz), 5.13−5.07 (bt, 1 H, $J = 6.5$ Hz), 5.85−5.6 (m, 2 H), 6.07−5.95 (m, 1 H), 7.7−7.3 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 143.2, 139.2, 135.7, 134.5, 134.4, 129.4, 127.5, 122.8, 122.6, 120.8, 97.1, 82.2, 77.7, 75.6, 71.9, 68.3, 68.1, 66.8, 47.6, 47.1, 45.2, 40.9, 35.6, 34.7, 34.3, 32.1, 31.5, 28.1, 27.0, 20.6, 19.1, 19.0, 18.2, 18.1, 17.8, 17.4, 16.2, 13.9, 12.9. IR (film): 3460, 3080, 2940, 2860, 1710, 1460, 1430, 1370 cm^{-1}.

Tetrabutylammonium fluoride (0.24 mL, 0.24 mmol), as a 1 M solution in THF, was added to a solution of acid **73** (0.24 g, 0.25 mmol) in 5.0 mL of THF. The resulting solution was stirred for 3 days at room temperature, and more TBAF (0.12 mL, 0.12 mmol) was added. Following an additional 1 day of stirring the solution was concentrated in vacuo and purified by column chromatography on silica gel (25−50% EtOAc−hexanes and then 10−30% MeOH−hexanes) to provide hydroxy acid **74** (0.123 g, 68%) as a white foam. $[\alpha]^{25}_D = +61.8°$ ($c = 0.677$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.77−0.75 (d, 3 H, $J = 5.9$ Hz), 0.98−0.93 (m, 6 H), 0.82−0.79 (d, 3 H, $J = 7.4$ Hz), 1.03−1.0 (d, 3 H, $J = 6.6$ Hz), 1.08 (s, 21 H), 2.5−1.2 (m, 23 H), 2.62−2.56 (bdd, 1 H, $J = 12.5$, 3.7 Hz), 3.04−2.99 (bdd, 1 H, $J = 9.5$, 1.5 Hz), 3.6−3.45 (m, 1 H), 3.71−3.7 (d, 1 H, $J = 2.2$ Hz), 4.25−4.05 (m, 2 H), 4.58 (s, 2 H), 4.97−4.92 (bt, 1 H, $J = 6.5$ Hz), 5.5−5.41 (dd, 1 H, $J = 15$, 8 Hz), 5.8−5.69 (dd, 1 H, $J = 15$, 11 Hz), 6.0−5.9 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 141.5, 140.6, 135.7, 124.1, 121.4, 120.4, 97.2, 82.8, 78.1, 75.5, 71.5, 68.1, 68.0, 65.8, 47.6, 47.2, 44.7, 38.9, 35.7, 35.0, 34.4, 32.4, 31.6, 28.2, 28.1, 26.6, 21.9, 20.8, 18.2, 17.9, 17.3, 16.1, 14.1, 13.0. IR (film): 3470, 2960, 2860, 1705, 1460, 1380 cm^{-1}. HRMS: calcd for $C_{42}H_{72}O_8Si$ 732.4996, found 732.5010.

Macrolactone 75. A solution of *N,N*-dicyclohexylcarbodiimide (DCC; 0.138 g, 0.67 mmol), 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), and DMAP·HCl (0.106 g, 0.67 mmol) in 350 mL of dry (ethanol-free) $CHCl_3$ was heated to reflux. Hydroxy acid **74** (0.240 g, 0.33 mmol) in 20 mL of dry (ethanol-free) $CHCl_3$ was added to the refluxing solution via a syringe pump over a period of 16 h. The long needle was inserted through the condenser and placed directly over the refluxing solution such that the refluxing chloroform washed the substrate droplets forming at its tip. Upon completion of the addition, the flask and syringe containing the substrate were washed by more chloroform (2 × 2 mL) and these solutions were delivered by syringe pump over a period of 1 h. The reaction mixture was cooled to room temperature, and excess DCC was consumed by adding MeOH (0.45 mL) and acetic acid (0.11 mL). The resulting solution was stirred at room temperature for 2 h, concentrated in vacuo, and purified by column chromatography on silica gel (0−10% EtOAc−hexanes) to afford macrolactone **75** (0.125 g, 53%) as a white foam. $[\alpha]^{25}_D = +90.8°$ ($c = 1.05$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78−0.76 (d, 3 H, $J = 5.8$ Hz), 0.83−0.81 (d, 3 H, $J = 6.6$ Hz), 1.03−0.95 (m, 9 H), 1.07 (s, 21 H), 2.47−1.15 (m, 21 H), 2.55−2.49 (dd, 1 H, $J = 12.8$, 2.9 Hz), 3.06−3.0 (bdd, 1 H, $J = 9.2$, 1.5 Hz), 3.62−3.5 (m, 1 H), 3.63 (s, 1 H), 3.71−3.7 (d, 1 H, $J = 2.2$ Hz), 4.15−4.10 (m, 1 H), 4.57 (s, 2 H), 4.98−4.92 (bt, 1 H, $J = 7.5$ Hz), 5.25−5.1 (m, 1 H), 5.36−5.27 (dd, 1 H, $J = 12$, 10 Hz), 5.85−5.65 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 142.0, 140.2, 137.0, 123.7, 121.0, 120.3, 97.5, 82.7, 78.2, 76.0, 71.5, 67.9, 67.8, 67.5, 48.5, 47.6, 41.6, 36.5, 36.0, 35.7, 34.6, 32.4, 31.6, 28.3, 28.1, 25.6, 22.4, 20.9, 18.2, 17.9, 17.4, 15.5, 14.1, 13.0. IR (film): 3480, 2960, 2880, 1710, 1460, 1380 cm^{-1}. HRMS: calcd for $C_{42}H_{70}O_7Si$ 714.4891, found 714.4846.

Alcohol 76. Tetrabutylammonium fluoride (0.23 mL, 0.23 mmol), as a 1 M solution in THF, was added to a solution of macrolactone **75** (0.054 g, 0.075 mmol) in 1.0 mL of THF. The resulting solution was stirred overnight at room temperature, concentrated in vacuo, and purified by column chromatography on silica gel (10−50% EtOAc−hexanes) to afford diol **76** (0.040 g, 95%) as a white foam. $[\alpha]^{25}_D = +154.5°$ ($c = 1.15$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.79−0.76 (d, 3 H, $J = 5.8$ Hz), 0.84−0.81 (d, 3 H, $J = 7$ Hz), 1.05−0.96 (m, 9 H), 1.95−1.2 (m, 17 H), 2.25−2.1 (m, 3 H), 2.45−2.3 (m, 1 H), 2.6−2.5 (m, 2 H), 3.07−3.03 (bdd, 1 H, $J = 9.5$, 1.8 Hz), 3.65−3.5 (m, 1 H), 3.75−3.74 (d, 1 H, $J = 2.6$ Hz), 3.90−3.80 (m, 1 H), 4.56 (s, 2 H), 4.93−4.87 (bt, 1 H, $J = 7.5$ Hz), 5.08 (s, 1 H), 5.45−5.25 (m, 2 H), 5.75−5.6 (m, 2 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.0, 142.6, 140.0, 136.8, 123.4, 120.8, 119.7, 97.4, 80.7, 78.4, 76.2, 70.2, 68.5, 68.0, 67.3, 48.5, 47.0, 41.1, 37.0, 36.0, 35.8, 34.8, 32.2, 31.6, 28.3, 28.1, 25.8, 22.3, 21.0, 17.4, 17.1, 15.5, 14.2. IR (film): 3460, 2960, 2940, 2860, 1710, 1460, 1380 cm^{-1}. HRMS: calcd for $C_{33}H_{50}O_7$ 559.3635, found 559.3546.

Ketone 77. Tetrapropylammonium perruthenate (0.002 g, 0.0057 mmol) and anhydrous *N*-methylmorpholine *N*-oxide (0.006 g, 0.0512 mmol) were added to a solution of diol **76** (0.016 g, 0.0268 mmol) and 0.20 g of 4 Å powdered sieves in 0.8 mL of CH_2Cl_2. The black mixture was stirred at room temperature for 4 h, filtered through a pad of Celite using CH_2Cl_2, and concentrated in vacuo. Purification of the black residue by column chromatography on silica gel (5−25% EtOAc−hexanes) afforded ketone **77** (0.011 g, 79%) as a white foam and recovered alcohol **76** (0.002 g). $[\alpha]^{25}_D = +138.9°$ ($c = 0.764$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.79−0.77 (d, 3 H, $J = 6.2$ Hz), 0.84−0.81 (d, 3 H, $J = 7$ Hz), 0.99−0.96 (d, 3 H, $J = 6.6$ Hz), 1.03−1.0 (d, 3 H, $J = 6.9$ Hz), 1.09−1.06 (d, 3 H, $J = 6.6$ Hz), 2.5−2.3 (m, 1 H), 2.25−1.2 (m, 19 H), 2.87−2.7 (m, 1 H), 3.08−2.95 (m, 2 H), 3.74 (s, 1 H), 3.65−3.5 (m, 1 H), 4.62 (s, 1 H), 4.66−4.59 (dd, 1 H, $J = 14$, 2 Hz), 4.78−4.71 (dd, 1 H, $J = 14$, 2 Hz), 4.95−4.89 (bt, 1 H, $J = 7.5$ Hz), 5.48−5.32 (m, 2 H), 5.8−5.6 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.7, 174.0, 143.5, 138.5, 136.8, 123.3, 120.7, 120.2, 97.4, 84.3, 82.4, 78.3, 69.7, 68.4, 67.3, 48.4, 46.6, 41.3, 41.1, 36.9, 36.0, 35.7, 34.7, 33.0, 31.6, 28.2, 28.0, 22.2, 20.9, 17.3, 15.5, 14.1, 13.8. IR (film): 3480, 2980, 2940, 2880, 1740, 1720, 1470, 1400 cm^{-1}. HRMS: calcd for $C_{33}H_{48}O_7$ 556.3400, found 556.3391.

Selenides 78a,b. To a solution of ketone **77** (0.037 g, 0.066 mmol) in 0.8 mL of CH_2Cl_2 at 0 °C was added triethylamine (0.40 mL, 2.86 mmol) followed by (TMS)OTf (0.22 mL, 1.13 mmol), and the resulting solution was stirred at 0 °C for 8 h. The reaction mixture was quenched slowly with saturated aqueous $NaHCO_3$ (1.0 mL) and stirred an additional 20 min at 0 °C. The aqueous layer was then extracted with CH_2Cl_2 (3 × 2 mL); the extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Without further purification, the crude silyl enol ether was dissolved in CH_2Cl_2 (2.0 mL) and the solution cooled to −78 °C. Phenylselenenyl chloride (0.019 g, 0.099 mmol) was added in small portions, and the solution was maintained at −78 °C for another 1 h. The reaction was quenched while at −78 °C with saturated aqueous $NaHCO_3$ (2.0 mL) and warmed to room temperature. The

aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the yellow residue by column chromatography on silica gel (0−25% EtOAc−hexanes) afforded β-selenide **78b** (0.026 g) and α-selenide **78a** (0.023 g; 94%) as white solids. Less polar β-selenide **78b**: $[\alpha]^{25}_D = +65.7°$ ($c = 0.35$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.025 (s, 9 H), 0.77 (d, 3 H, $J = 5.8$ Hz), 0.83 (d, 3 H, $J = 6.9$ Hz), 0.99 (d, 3 H, $J = 1.5$ Hz), 1.02 (d, 3 H, $J = 1.8$ Hz), 2.25−1.2 (m, 21 H), 2.42 (m, 1 H), 2.57 (dd, 1 H, $J = 15.4$, 13.2 Hz), 3.05 (bdd, 1 H, $J = 9.6$, 1.9 Hz), 3.32 (dd, 1 H, $J = 12.8$, 2.5 Hz), 3.8 (m, 1 H), 3.84 (s, 1 H), 4.63 (d, 1 H, $J = 14$ Hz), 4.81 (d, 1 H, $J = 14$ Hz), 4.95 (bt, 1 H, $J = 7.5$ Hz), 5.08 (m, 1 H), 5.38 (m, 1 H), 5.72 (m, 2 H), 7.55−7.25 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 169.6, 142.7, 138.4, 137.7, 136.9, 129.7, 128.9, 123.7, 122.3, 121.2, 97.5, 84.3, 84.0, 78.2, 69.0, 67.8, 67.5, 51.3, 48.6, 44.5, 41.8, 36.4, 36.3, 36.2, 35.8, 34.5, 31.6, 28.3, 28.1, 25.2, 22.4, 20.9, 17.4, 15.6, 14.1, 1.98; IR (film) 3060, 2960, 2860, 1740, 1700, 1580, 1450, 1380 cm^{-1}. Anal. Calcd for $C_{42}H_{60}O_7SeSi$: C, 64.35; H, 7.71. Found: C, 64.05; H, 7.78. More polar α-selenide **78a**: $[\alpha]^{25}_D = +81.0°$ ($c = 0.60$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.18 (s, 9 H), 0.77−0.75 (d, 3 H, $J = 5.8$ Hz), 0.84−0.81 (d, 3 H, $J = 7$ Hz), 1.03−0.98 (t, 6 H, $J = 6.2$ Hz), 2.05−1.15 (m, 18 H), 2.30−2.1 (m, 4 H), 2.5−2.35 (m, 1 H), 2.91−2.8 (t, 1 H, $J = 13.9$ Hz), 3.06−3.03 (bd, 1 H, $J = 9.1$ Hz), 3.65−3.5 (m, 1 H), 4.46−4.40 (d, 1 H, $J = 14$ Hz), 4.66−4.61 (d, 1 H, $J = 14$ Hz), 5.0−4.9 (m, 1 H), 5.01 (s, 1 H), 5.25−5.1 (m, 1 H), 5.46−5.37 (dd, 1 H, $J = 12$, 10 Hz), 5.85−5.65 (m, 2 H), 7.5−7.2 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 168.9, 143.5, 138.2, 137.7, 136.9, 129.6, 129.0, 127.1, 124.6, 123.8, 121.3, 97.5, 85.4, 84.5, 78.2, 68.7, 67.5, 67.4, 49.0, 48.3, 41.6, 36.4, 36.3, 36.0, 35.7, 34.4, 31.6, 28.3, 28.0, 25.1, 22.4, 20.9, 17.4, 15.4, 14.1, 2.1; IR (film) 3060, 2960, 2920, 2860, 1740, 1720, 1580, 1450, 1440 cm^{-1}. Anal. Calcd for $C_{42}H_{60}O_7SeSi$: C, 64.35; H, 7.71. Found: C, 64.13; H, 7.81.

Hydroxy Selenide 79b. To a solution of β-selenide **78b** (0.029 g, 0.037 mmol) in 5.0 mL of CH_3CN at 0 °C was added pyridine (0.5 mL), followed by 16 drops of 48 wt % HF/H_2O solution. The solution was slowly warmed and was stirred for 1 day at room temperature. It was carefully quenched with aqueous saturated $NaHCO_3$ (3 mL), and the mixture was extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5−10% EtOAc−hexanes) afforded alcohol **79b** (0.018 g, 70%) as a white solid. $[\alpha]^{25}_D = +71.3°$ ($c = 0.15$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.80−0.78 (d, 3 H, $J = 5.9$ Hz), 0.85−0.82 (d, 3 H, $J = 6.9$ Hz), 0.99−0.97 (d, 3 H, $J = 6.5$ Hz), 1.04−1.01 (d, 3 H, $J = 6.9$ Hz), 2.3−1.2 (m, 22 H), 2.46−2.35 (m, 1 H), 2.59−2.47 (dd, 1 H, $J = 14.9$, 13.2 Hz), 3.1−3.05 (dd, 1 H, $J = 8.4$, 1.8 Hz), 3.5−3.44 (dd, 1 H, $J = 12.8$, 2.5 Hz), 3.65−3.5 (m, 1 H), 3.81 (s, 1 H), 5.0−4.6 (m, 3 H), 5.55−5.3 (m, 2 H), 5.85−5.65 (m, 2 H), 7.6−7.25 (m, 5 H). IR (film): 3460, 2940, 2920, 2860, 1700, 1440, 1380 cm^{-1}. Anal. Calcd for $C_{39}H_{52}O_7Se$: C, 65.81; H, 7.36. Found: C, 65.52; H, 7.33.

Ketone 77. A 1 M solution of freshly distilled Bu_3SnH (0.54 mL, 2.0 mmol) and 5 crystals of AIBN in 2.0 mL of benzene was prepared, and 0.05 mL of this solution was added to β-selenide **78b** (0.004 g, 0.0056 mmol) in 0.5 mL of benzene. This mixture was heated at reflux for 45 min at 80 °C in an oil bath and then cooled to room temperature. The solution was concentrated in vacuo and purified by column chromatography on silica gel (5−25% EtOAc−hexanes) to afford ketone **77** (0.0027 g, 85%) as a white solid.

Alcohol 79a. A solution of HF−pyridine was prepared upon the addition of 8 drops of 48 wt % HF/H_2O solution to pyridine (0.25 mL) in CH_3CN (2.5 mL) at 0 °C. This solution was warmed to room temperature and was added (2.0 mL) to α-selenide **78a** (0.010 g, 0.013 mmol). This mixture was stirred for 1 day at room temperature and carefully quenched with aqueous saturated $NaHCO_3$ (2 mL), and the mixture was extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5−25% EtOAc−hexanes) afforded the deprotected silyl ether **79a** (0.003 g, 66%) and recovered α-selenide **78a** (0.005 g). $[\alpha]^{25}_D = +126.4°$ ($c = 0.14$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78−0.76 (d, 3 H, $J = 5.8$ Hz), 0.84−0.81 (d, 3 H, $J = 6.6$ Hz), 0.98−0.96 (d, 3 H, $J = 6.5$ Hz), 1.03−1.0 (d, 3 H, $J = 6.9$ Hz), 2.25−1.2 (m, 22 H), 2.45−2.3 (m, 1 H), 2.51−2.48 (dd, 1 H, $J = 13.1$, 3.3 Hz), 2.88−2.77 (t, 1 H, $J = 13.9$ Hz), 3.07−3.02 (bdd, 1 H, $J = 9.5$, 1.8 Hz), 4.45−4.35 (bs, 1 H), 3.65−3.5 (m, 1 H), 4.50−4.44 (dd, 1 H, $J = 14$, 2 Hz), 4.68−4.62 (dd, 1 H, $J = 14$, 2 Hz), 4.95−4.85 (m, 1 H), 4.84 (s, 1 H), 5.5−5.3 (m, 1 H), 5.75−5.65 (dd, 1 H, $J = 15$, 11 Hz), 5.9−5.8 (m, 1 H), 7.5−7.2 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.4, 173.3, 144.2, 139.6, 138.0, 137.1, 130.0, 129.3, 127.3, 124.0, 122.5, 121.1, 97.6, 84.2, 81.2, 78.6, 69.1, 68.9, 67.6, 49.2, 48.6, 46.2, 41.4, 37.2, 37.1, 37.0, 36.1, 35.9, 34.9, 31.9, 28.5, 28.2, 25.7, 22.4, 21.2, 17.6, 15.7, 14.4. IR (film): 3480, 2960, 2920, 2860, 1740, 1710, 1460, 1370 cm^{-1}.

Milbemycin D (1). Sodium periodate (0.020 g, 0.094 mmol) was added to a stirred solution of deprotected α-selenide **79a** (20 mg, 0.028 mmol) in THF/H_2O (4 mL/2 mL). Following 2 h at room temperature the reaction mixture was poured into a solution of $CeCl_3 \cdot 7H_2O$ in 5 mL of MeOH at 0 °C. The flask was rinsed with more MeOH (2 mL). Sodium borohydride (0.015 g, 0.40 mmol) was added in small portions, and the solution was stirred an additional 10 min at 0 °C. Saturated aqueous NH_4Cl (3.0 mL) was added and the mixture extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were washed with 10% $Na_2S_2O_3$ (3.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5−25% EtOAc−hexanes) afforded milbemycin D (**1**; 5 mg, 32%). $[\alpha]^{23}_D = +119.5°$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, 3 H, $J = 6.5$ Hz), 0.85 (d, 3 H, $J = 6.6$ Hz), 0.99 (d, 3 H, $J = 6.5$ Hz), 1.03 (d, 3 H, $J = 6.9$ Hz), 1.25−2.53 (m, 16 H), 1.51 (br s, 3H), 1.86 (br s, 3H), 3.07 (dd, 1 H, $J = 9.5$, 1.8 Hz), 3.26 (dd, 1H, $J = 3$, 2.5 Hz), 3.58 (m, 1H), 3.96 (d, $J = 6.25$ Hz), 4.29 (1H, d, $J = 6$ Hz), 4.68 (m, 2H), 4.95 (1H, t, $J = 7.25$ Hz), 5.3−5.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.17, 15.5, 17.32, 19.9, 20.93, 22.26, 28.05, 28.33, 31.6, 34.7, 35.73, 35.94, 36.7, 41.4, 45.76, 48.49, 67.39, 67.75, 68.51, 68.72, 78.36, 79.24, 80.24, 97.44, 118.2, 120.4, 121, 123.4, 136.9, 137.8, 139.5, 142.9, 173.6. IR (film): 3480, 2960, 2920, 2860, 1740, 1460, 1370 cm^{-1}.

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Supporting Information Available: Text giving experimental procedures for compounds **31**, **47**, and **51**−**64** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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