

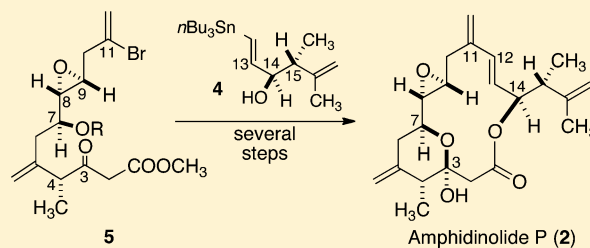
Studies for the Total Synthesis of Amphidinolide P[†]

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S Supporting Information

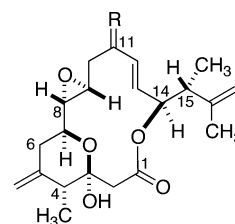
ABSTRACT: A convergent, enantiocontrolled total synthesis of the 15-membered macrolide, amphidinolide P, is described. The synthesis utilizes three nonracemic components for an efficient assembly of the macrolactone in 12 steps via the longest linear pathway. Key developments include studies of the Hosomi–Sakurai reaction for the formation of the C₆–C₇ bond, a “ligandless” palladium-mediated Stille cross-coupling of the vinylic stannane **4** and the alkenyl bromide **5** to produce a highly functionalized dienol, and a thermally induced, intramolecular lactonization via the late-stage formation of an intermediate α -acylketene.



INTRODUCTION

The amphidinolides are a structurally diverse family of approximately 40 representative substances that have been isolated from dinoflagellates of the genus *Amphidinium sp.*¹ Naturally occurring metabolites are produced by symbiotic dinoflagellates that live within the digestive tract of the Okinawan flatworm *Amphiscolops sp.* Additional examples of the family have also been produced by cultured, free-living dinoflagellates.² Many amphidinolides display potent antineoplastic activity against a variety of cancer cell lines and produce IC₅₀ values in the low micromolar range. In fact, caribenolide I³ and amphidinolide N,⁴ two closely related macrolide structures, exhibit subpicomolar activity against murine lymphoma L1210 and human epidermoid carcinoma KB. The exceedingly small quantities of isolated amphidinolides present a serious challenge for studies of structure determination, and for the assignments of relative and absolute stereochemistry. Because of the high biological activity and limited availability, these novel structures have been important targets for total synthesis.⁵ A number of studies have also documented the development of new methodology in the course of these investigations.⁶

Kobayashi and co-workers reported the isolation and structure determination of amphidinolides O (**1**) and P (**2**) in 1995.⁷ In 2000, we described a synthetic strategy that resulted in the first total synthesis of amphidinolide P (**2**).⁸ Subsequently, Chakraborty and co-workers completed a formal synthesis of **2** by the preparation of key intermediates, which correlated with our prior effort.⁹ More recently, Trost has described the development of a ruthenium-catalyzed alkene–alkyne coupling strategy for the total synthesis of **2**.¹⁰ Herein, we report, in full detail, our studies leading to the total synthesis of **2**, and we confirm the absolute configuration of natural amphidinolide P as the (+)-enantiomer.



1 Amphidinolide O (R = O)
2 Amphidinolide P (R = CH₂)

RESULTS AND DISCUSSION

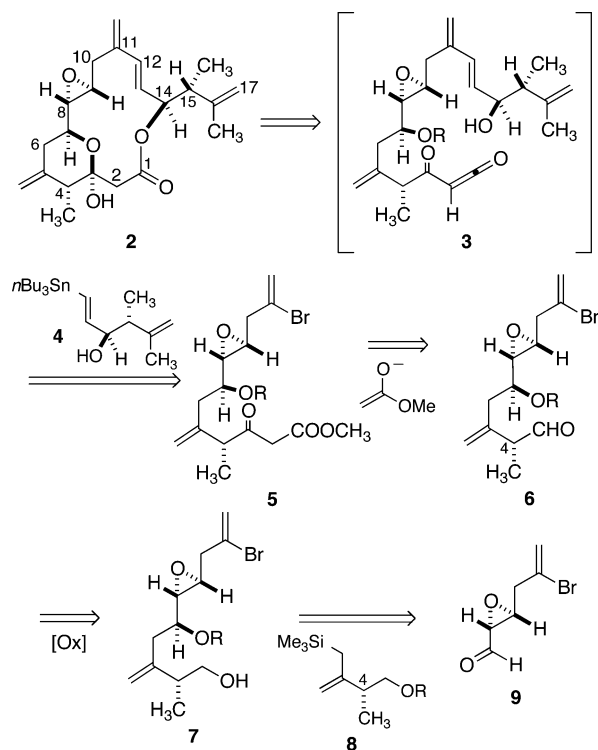
Our retrosynthetic analysis of **2**, as shown in Scheme 1, developed several postulates that were important elements for the success of the overall strategy. These primary considerations involved (a) macrolactonization via the internal capture of the acyl ketene intermediate **3** by the C₁₄ allylic alcohol, (b) cross-coupling of the *E*-alkenylstannane **4** with the functionalized bromide **5**, and (c) nucleophilic addition to the β,γ -unsaturated aldehyde of **6** with appropriate oxidations at C-3. The later transformations were cause for concern in our initial analysis because commonly used reaction conditions could jeopardize the integrity of the (*R*)-C₄ stereochemistry as incorporated from the nonracemic allylsilane **8** via the Hosomi–Sakurai reaction with chiral aldehyde **9**.

From the outset, our synthetic planning investigated a convergent pathway that promised to minimize the number of operations of significant potential for epimerization of the C₄ stereochemistry subsequent to the assembly of the carbon skeleton. On this basis, our efforts sought to circumvent the multistep sequence of enolate addition and oxidation chemistry suggested for the conversion of alcohol **7** into the ketoester **5** (Scheme 1). This premise led us to construct an elaborated nonracemic C₁–C₆ component. We began these studies with

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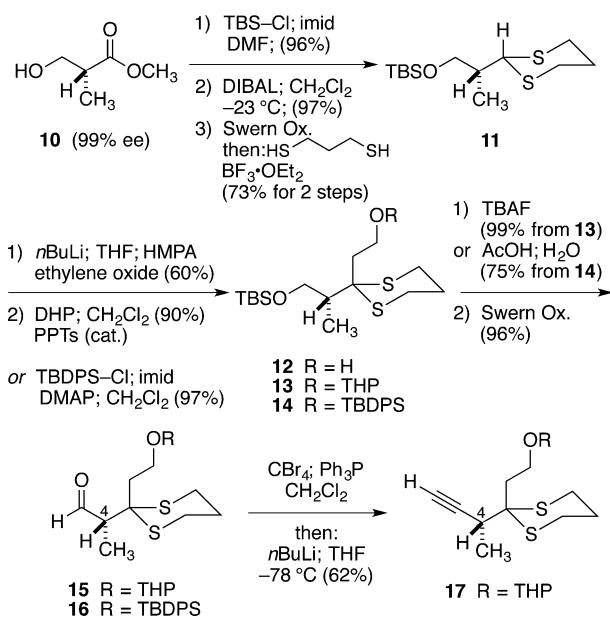
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Scheme 1. Retrosynthetic Analysis of Amphidinolide P (2)



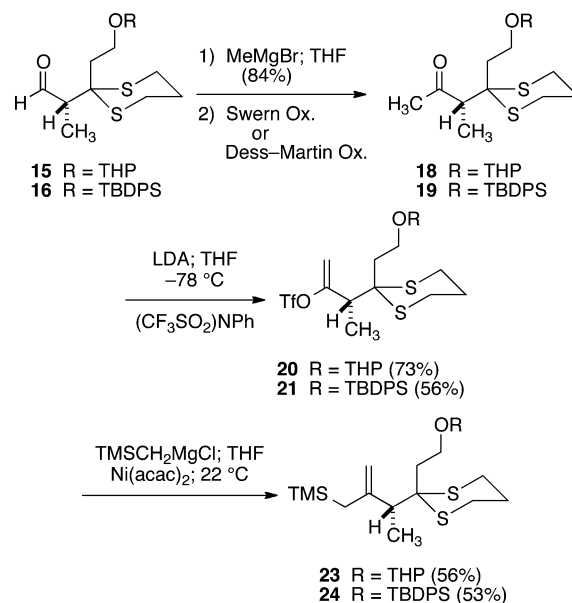
the commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (99% ee) via formation of the *tert*-butyldimethylsilyl (TBS) ether, followed by reduction, oxidation, and conversion to the known 1,3-dithiane **11** as summarized in Scheme 2.¹¹ The nonracemic, primary alcohol **12** (Scheme 2) was obtained in 60% yield by the deprotonation of dithiane **11** with *tert*-butyllithium in THF and HMPA followed by the addition of ethylene oxide.¹² A convenient purification of **12** was achieved by flash silica gel chromatography, which also led to the recovery of substantial amounts (20%) of recovered dithiane **11**. Thus, for these initial efforts, the starting dithiane

Scheme 2. Preparation of Nonracemic Alkyne 17



was recycled through the alkylation step on multigram scale without additional efforts on our part to optimize conditions for the deprotonation. Protections of **12** as the corresponding tetrahydropyranyl (THP) ether and the *tert*-butyldiphenylsilyl (TBDPS) ether provided quantities of **13** and **14** that were allocated for further explorations.

The cleavage of the TBS ether of **13** followed by Swern oxidation¹³ afforded the nonracemic aldehyde **15**, and the successful transformation of **15** into the terminal alkyne **17** was accomplished by application of the Corey–Fuchs protocol.¹⁴ Our studies planned to utilize the alkyne **17** for direct conversion into an allylic silane or stannane, which could effect an efficient S_E' reaction with the chiral aldehyde **9** of Scheme 1. Unfortunately, our attempts to achieve a regioselective cuprate addition to the internal (C_5) carbon of the alkyne moiety failed,^{15,16} and additional efforts to functionalize C_5 of **17** using hydroiodation techniques¹⁷ or a hydrostannylation¹⁸ also gave poor results. In both cases, starting **17** was consumed. However, hydroiodation led to cleavage of the THP ether, and hydrostannylation proceeded to give a mixture of regioisomeric stannanes. We were able to overcome these difficulties as illustrated in Scheme 3, starting with the chiral

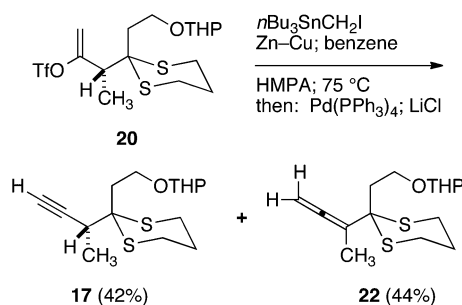
Scheme 3. Formation of the C_1 – C_6 Allylsilane Component

aldehydes **15** and **16**. Our concerns regarding C_4 epimerization in the course of the Swern oxidation¹³ of the precursor primary alcohols were initially addressed by carefully conducting these oxidations at low temperatures ($-78\text{ }^\circ\text{C}$) with subsequent warming to $-50\text{ }^\circ\text{C}$ for dropwise addition of freshly distilled triethylamine (2.2 equiv). The crude aldehyde **15** was evaluated by submitting a sample for DIBAL–H reduction at $-78\text{ }^\circ\text{C}$.

Proton NMR data of the recovered alcohol indicated a 1:1 mixture of OTHP diastereomers, which was identical to the starting alcohol. In the case of aldehyde **16**, DIBAL–H reduction was followed by the preparation of the corresponding Mosher esters. Once again, NMR analysis indicated that the extent of C_4 epimerization was less than 5%. Subsequently, we employed the Swern oxidation in scale-up reactions and used the Dess–Martin periodinane oxidation¹⁹ at ambient temperature with similar outcomes. This evidence alleviated our concerns regarding problems for C_4 epimerization in the

production of the corresponding methyl ketones. Thus, we pressed ahead with the conversion to ketones **18** and **19**, which allowed for kinetic, low-temperature deprotonation resulting in the formation of the stable vinyl triflates **20** and **21** as a reactive species for installation of the desired allylic silane or stannane. In fact, the cross-coupling reactions of alkenyl triflates with various organometallic species are well precedented.²⁰ However, initial attempts for a palladium-catalyzed coupling of the triflate **20** with an organocopper reagent, derived from tri-*n*-butylstannylmethyl iodide,^{21,22} led to approximately equal amounts of the previously prepared alkyne **17** (42%) and the allene **22** (44%) (Scheme 4). These products presumably arise via a facile β -hydride elimination of the vinyl palladium(II) intermediate, which is formed upon oxidative insertion.

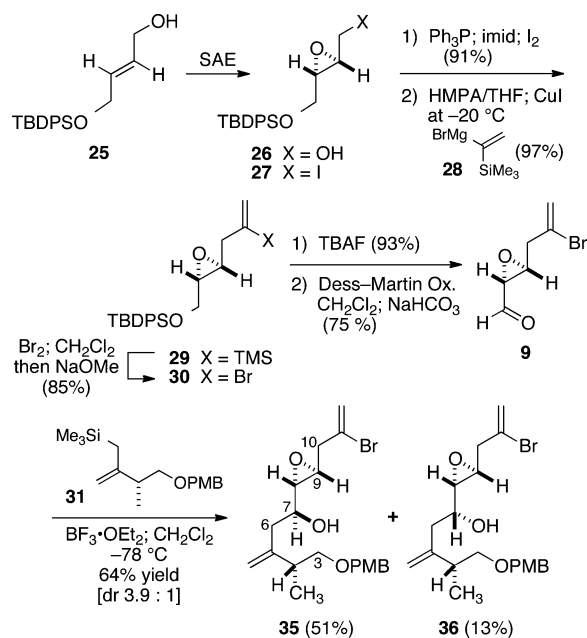
Scheme 4. Facile β -Hydride Eliminations of Triflate **20**



This side reaction was avoided by the use of Ni(acac)₂ as previously described by Kumada and co-workers for cross-coupling reactions of trimethylsilylmethylmagnesium chloride.²³ To our delight, the initial experiments produced allylsilanes **23** (56% yield) and **24** (53% yield) as confirmed by ¹H NMR data indicating the presence of the terminal alkene with characteristic hydrogen singlets at δ 4.88 and $\delta\delta$ 4.84 as well as the incorporation of the anticipated trimethylsilyl and methylene signals. A subsequent report has detailed the scope, limitations and ligand effects of nickel-catalyzed cross-couplings of vinylic triflates and Grignard reagents.²⁴ This study concluded that Ni(acac)₂ does not generally support cross-coupling reactions of alkyl (sp³) Grignard reagents with vinyl triflates, which may suggest unique behavior for trimethylsilylmethylmagnesium chloride in our examples.

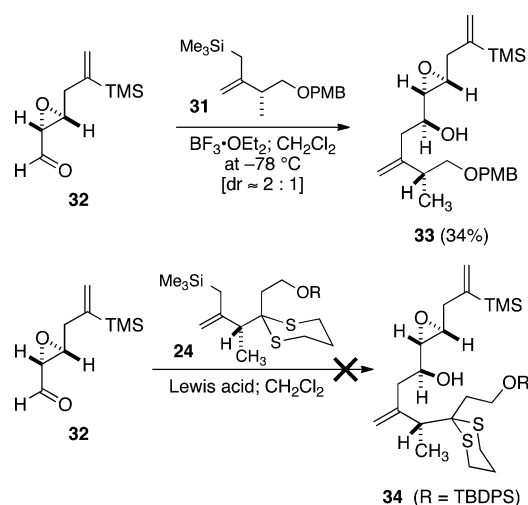
Construction of the C₁–C₁₁ Segment of Amphidinolide P. Our plan for a convergent, enantiocontrolled synthesis of amphidinolide P (**2**) relied on two crucial carbon–carbon bond forming reactions. These processes undertake a bidirectional extension of the carbon skeleton utilizing the central α,β -epoxyaldehyde **9** (Scheme 1). First, we envisioned a stereoselective S_E' reaction, which would afford a homoallylic alcohol via formation of the C₆–C₇ bond. A subsequent operation would then introduce the conjugated diene of **2** by sp²–sp² coupling for C₁₁–C₁₂ bonding. To this end, Scheme 5 illustrates an efficient preparation of the required aldehyde **9** (91% ee), starting with the known epoxyalcohol **26**, which was obtained by Sharpless asymmetric epoxidation of the corresponding allylic alcohol **25**.²⁵ The straightforward conversion to the epoxy iodide **27** led to a direct nucleophilic displacement resulting from a copper-catalyzed coupling with the Grignard reagent **28** to provide alkenylsilane **29** in excellent yield. This technique was previously described by Nicolaou and co-workers²⁶ and involves the addition of the vinylic Grignard species into a THF solution of iodide **27** containing anhydrous

Scheme 5. Synthesis of the C₃–C₁₁ Component **35**



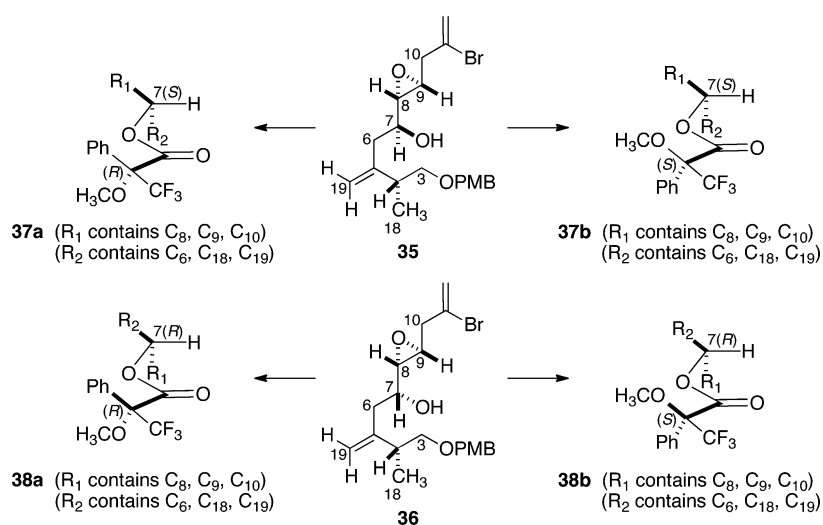
HMPA (4 equiv) and cuprous iodide. The application advantageously avoids side reactions that effect a reductive elimination, producing an allylic alcohol from **27** as well as base-induced isomerization of the desired product **29** to the corresponding conjugated diene. The electrophilic replacement of the trimethylsilyl substituent to yield the corresponding vinylic iodide from silane **29** was attempted under various conditions, but the apparent instability of the alkenyliodide product complicated our purification efforts. The conversion of **29** to the alkenylbromide **30** proceeded uneventfully with the low temperature addition of bromine followed by elimination upon treatment with sodium methoxide.²⁷ Our successful preparation of the nonracemic α,β -epoxyaldehyde **9** was concluded by fluoride-induced deprotection and an efficient Dess–Martin oxidation.¹⁹ However, the isolated yield (75%) of the aldehyde **9** was somewhat reduced because of the volatility of this material at reduced pressures.

Investigations for C₆–C₇ bond formation using aldehyde **9** initially examined the Hosomi–Sakurai reaction²⁸ of chiral allylsilane **31**. The preparation of silane **31** followed a similar procedure as described by Forsyth and co-workers for the corresponding benzyl ether.²⁹ In this manner, the *para*-methoxybenzyl ether of methyl (2*S*)-3-hydroxy-2-methylpropionate (99% ee) was reacted with 3 equiv of trimethylsilylmethylmagnesium chloride in the presence of anhydrous CeCl₃ (3 equiv) to generally afford yields of **31** ranging from 50–60%. Preliminary model studies of reactions of the allylic silane **31** used aldehyde **32**, which was readily obtained by Parikh–Doering oxidation (SO₃·pyr) of the alcohol derived from TBAF deprotection of **29**. Using BF₃·OEt₂ at –78 °C, the Hosomi–Sakurai reaction of **31** provided for the facile formation of the C₆–C₇ bond and resulted in a mixture (2:1) of diastereomeric alcohols. The homoallylic alcohol **33** of Scheme 6 was purified and was identified as the major product (34% yield) by use of the Mosher ester analysis. On the basis of this positive outcome, we sought to extend these studies of the nonracemic aldehyde **32** for the Lewis acid-catalyzed Hosomi–Sakurai reaction of the fully elaborated (C₁–C₆) silane component **24** (from Scheme 3). Unfortunately, all attempts for the S_E'

Scheme 6. Hosomi–Sakurai Studies of Allyl Silanes **31** and **24**

allylation of aldehyde **32** with **24** did not result in any significant formation of the desired alcohol **34**. In these experiments, we observed substantial decomposition.

Destruction of starting **24** was rapid, whereas secondary decomposition of aldehyde **32** proceeded at a slower pace. These observations renewed some prior concerns about the inherent compatibility of the homoallylic dithiane moiety of silane **24**, as well as the stability of the epoxy aldehydes **9** and **32** in our planned condensation event. We rationalized that the destruction of silane **24** was due to the proximity of the thioketal functionality, which provided for facile solvolysis to yield a stabilized, nonclassical cyclopropylcarbinyl carbocation. Further rearrangements of this cation and the loss of the trimethylsilyl substituent would be anticipated. In fact, the decomposition of silane **24** gave numerous byproducts that lacked the TMS group. The instability of **24** may also contribute to the slow protodesilylation of **32**, which was identified as the major degradation pathway for the aldehyde. This negative outcome led us to examine the Sakurai process for the reaction of **9** with the allylic silane **31** (Scheme 5). Careful control of the reaction temperature led to a 65% yield of the desired homoallylic diastereomers **35** and **36** (dr 4:1). The purification by flash chromatography afforded **35** (51%) as the major product resulting from a Felkin–Anh addition to the α,β -epoxy-aldehyde. In addition, quantities of the purified minor adduct **36** (13% yield) were also obtained. This facilitated a full characterization of both isomers, and pertinent

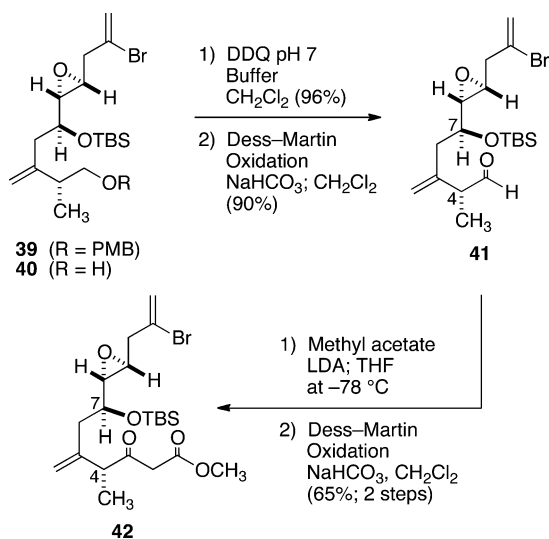
Table 1. Mosher Ester Analysis of Alcohols **35** and **36**

assignable hydrogens of C7 (S)-isomer 35	chemical shifts in δ S-MTPA 37b (ppm)	chemical shifts in δ R-MTPA 37a (ppm)	shift difference $\Delta\delta^{\text{SR}}$ ($\delta\text{S} - \delta\text{R}$) (ppm)
C ₇ -H	5.36	5.31	
C ₆ -H	2.43	2.52	-0.09
C ₁₈ -H	1.08	1.12	-0.04
C ₁₉ -H	4.86	4.98	-0.12
C ₈ -H	2.97	2.85	+0.12
C ₉ -H	3.17	3.06	+0.11
C ₁₀ -H	2.63	2.57	+0.06
assignable hydrogens of C7(R)-isomer 36	chemical shifts in δ S-MTPA 38a (ppm)	chemical shifts in δ R-MTPA 38b (ppm)	shift difference $\Delta\delta^{\text{SR}}$ ($\delta\text{S} - \delta\text{R}$) (ppm)
C ₇ -H	5.18	5.05	
C ₆ -H	2.50	2.44	+0.06
C ₁₈ -H	1.07	1.03	+0.04
C ₁₉ -H	4.97	4.89	+0.08
C ₈ -H	obscured	obscured	obscured
C ₉ -H	3.01	3.11	-0.10
C ₁₀ -H	2.57	2.62	-0.05

data from the Mosher ester analysis³⁰ is compiled in Table 1. The Mosher NMR-based technique allowed for the assignments of configuration of the stereogenic C-7 carbinols by conversion of the purified alcohols **35** and **36** into individual diastereomeric α -methoxy- α -trifluoromethyl phenylacetic acid (MTPA) esters. Thus, the preparation of *S*-MTPA and *R*-MTPA esters from **35** gave the pair of Mosher esters **37a** and **37b**, and likewise, alcohol **36** led to the Mosher esters **38a** and **38b**. Our ¹H NMR analysis of the *R*-MTPA ester **37a**, resulting from the (*S*)-C₇ alcohol **35**, shows signals for C₆H, C₁₈H and C₁₉H hydrogens, which are downfield relative to the corresponding chemical shifts of the (*S*)-Mosher ester **37b**. On the other hand, the chemical shifts of hydrogens at C₈, C₉ and C₁₀ of **37a** are shielded compared to the signals of **37b**. Conversely, the pair of (*R*)- and (*S*)-MTPA esters **38a** and **38b**, which are derived from the minor product **36**, showed the opposite trend of shielding effects as measured by the shift difference $\Delta\delta^{\text{SR}}$ ($\delta(\text{S-MTPA ester}) - \delta(\text{R-MTPA ester})$).³¹ Thus, our detailed analysis of the data correlates with Mosher's original conclusions. In this fashion, the C-7 stereochemistry of the chiral secondary alcohols **35** and **36** was assigned, and the major product, 7(*S*)-alcohol **35**, was utilized for further studies.

Because of the inability to perform the desired Sakurai reaction with silane **24**, we chose to functionalize the C₁–C₁₁ component using the enolate condensations as documented in our original retrosynthetic analysis (Scheme 1). This required our reassessment of potential problems arising from base-induced conjugation of the C₅-alkene, deprotonation at C₄, and epimerization of C₄ stereochemistry. These studies are examined in Scheme 7 by protection of **35** as the C₇ TBS

Scheme 7. Formation of β -Keto Ester **42**

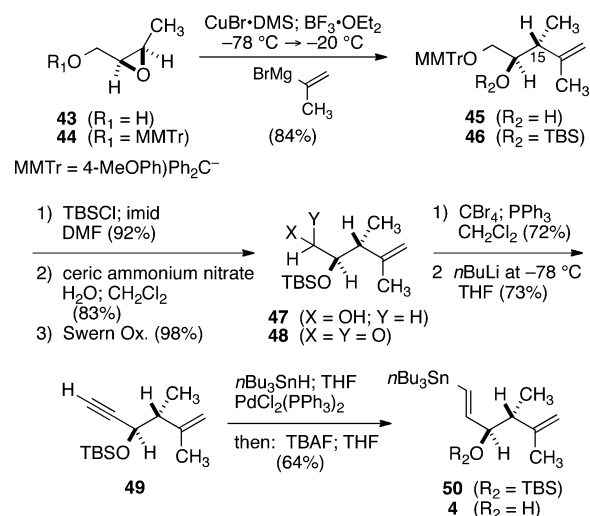


silyl ether **39**, and DDQ oxidation to provide the C₃ primary alcohol **40** in excellent yield. A buffered oxidation with Dess–Martin periodinane¹⁹ gave the sensitive aldehyde **41**, which was generated immediately prior to its use in subsequent reactions and was purified by flash silica gel chromatography. Our ¹H NMR analysis showed no evidence for migration of the β,γ -alkene into conjugation, and NMR spectra of **41** did not indicate the presence of diastereomers resulting from epimerization at C-4. With this crucial information in hand, a solution of aldehyde **41** was added into an excess of the lithium enolate generated from a kinetic deprotonation of methyl

acetate by treatment with lithium diisopropylamide (LDA) at $-78\text{ }^\circ\text{C}$.³² The resulting β -hydroxy esters (dr 2:1) were then directly oxidized using the buffered Dess–Martin protocol to provide the desired β -keto ester **42** in 65% overall yield for the two steps following flash chromatography. As in the case of aldehyde **41**, our ¹H NMR characterization of **42** showed no evidence of C-4 epimerization or C=C double bond conjugation.

Preparation of Nonracemic C₁₂–C₁₇ Segment of Amphidinolide P. The synthesis of the C₁₂–C₁₇ segment of amphidinolide P was designed to incorporate the asymmetry of the C₁₄ and C₁₅ stereocenters by utilizing a Stille cross coupling reaction of the C₁₁ alkenylbromide of **42** and the nonracemic (*E*)-organostannane **4** (Scheme 1). The nonracemic stannane **4** was prepared in eight steps from the optically active epoxide **43** as diagrammed in Scheme 8. The synthesis of the

Scheme 8. Preparation of the C₁₂–C₁₇ Stannane Component **4**



enantioenriched epoxide **44** was accomplished via the asymmetric Sharpless epoxidation of *cis*-2-butenol³³ followed by in situ protection of the primary alcohol as the *p*-methoxytrityl (MMTr) ether.³⁴ Thus, large quantities of nonracemic **44** were available in a one-pot operation, and the product was readily purified by flash silica gel chromatography (80% yield). The deprotection of a purified sample of **44** using DDQ in wet CH₂Cl₂ allowed for the Mosher ester derivatization and analysis of the Sharpless epoxyalcohol as its corresponding (*R*)- and (*S*)-MTPA esters.³⁰ The integration of ¹H NMR signals of the MTPA esters indicated 83% ee (91:9 er) for the asymmetric oxidation. A Lewis acid-promoted, regioselective opening of epoxide **44** was undertaken via the copper(I)-mediated addition of freshly prepared isopropenylmagnesium bromide. In the event, the 1,2-diol derivative **45** was obtained in 84% yield as the sole product arising from nucleophilic attack at the less hindered carbon of the starting oxirane. The role of the unusual MMTr protecting group is 2-fold in this reaction scheme. First, it provides the steric bulk necessary to direct nucleophilic opening to the β -carbon of **44** (labeled as C15 of alcohol **45**). Second, the MMTr ether is readily cleaved under pH 7 conditions with DDQ in wet CH₂Cl₂. This feature permitted the formation of the secondary TBS ether **46**, followed by the removal of the MMTr ether, without effecting O-migration of the silyl (TBS) group.

Migration of the TBS substituent to the less hindered primary alcohol is generally observed under the standard basic or acidic conditions employed to remove other protecting groups, and this behavior presented difficulties for the chromatographic purification of the desired alcohol. Small samples of the Grignard addition product **45** were submitted for the Mosher ester analysis protocol, and these results also confirmed the 83% ee (91:9 er) of the asymmetric Sharpless epoxidation.

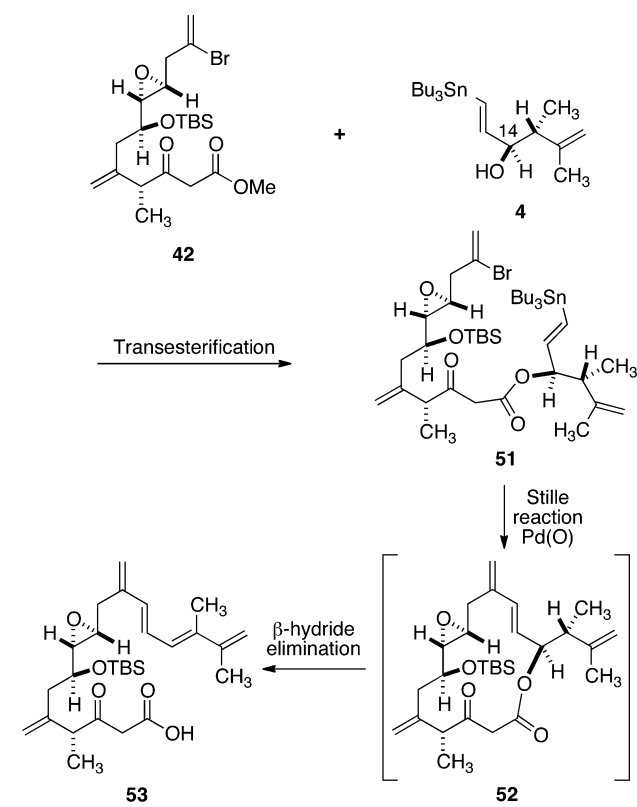
The use of *p*-anisylidiphenylcarbonyl as a protecting group is not common, and it is notable that ether cleavage is accomplished with a buffer at pH 7 using excess DDQ (5 equiv). After 18 h at ambient temperature, the primary alcohol **47** (Scheme 7) was reproducibly obtained in 73% yield along with small quantities (2–4%) of the corresponding unprotected diol and recovered starting material **46**. We could not observe the complete consumption of **46** by forcing these reactions to completion with longer reaction times or elevated temperatures without causing TBS ether migration and/or increasing the production of the undesired 1,2-diol. Support for an acid-catalyzed hydrolysis comes from the appearance of the bright red color of the reaction medium, which is indicative of the formation of the *p*-anisylidiphenylcarbonyl cation as well as the isolation of the *p*-methoxytrityl alcohol product. It is known that the hydration of DDQ provides an organic acid, which may promote the mild hydrolysis.³⁵ However, we could not duplicate these mild hydrolytic conditions for the removal of MMTr using aqueous acetic acid or by the addition of various phenols in wet CH₂Cl₂. Furthermore, the deprotection of **46** was achieved with ceric ammonium nitrate in a biphasic mixture of water and CH₂Cl₂ leading to an 83% yield of the alcohol **47**. Although there is no clear evidence of oxidative electron transfer in these processes, the latter reagent became the method of choice for scale-up reactions to provide **47** for Swern oxidation¹³ to give quantities of aldehyde **48**.

Subsequently, our application of the Corey–Fuchs reaction¹⁴ was utilized for conversion to give the terminal alkyne **49** (Scheme 8). Hydrostannylation³⁶ of **49** was successful using tri-*n*-butylstannane in the presence of a catalytic amount of PdCl₂(PPh₃)₂, and the crude *E*-alkenylstannane **50** was characterized by the large coupling constant ($J = 19.1$ Hz) observed for vinylic hydrogen signals at δ 6.02 (d, 1H) and δ 5.85 (dd, 1H) in the ¹H NMR spectrum. Immediate treatment of **50** with tetra-*n*-butylammonium fluoride resulted in pure samples of nonracemic stannane **4**, which was isolated in 64% yield from the starting alkyne **49**.

Formation of the C₁₁–C₁₂ Bond and Completion of the Total Synthesis. We recognized two possible pathways in our considerations for joining components **4** and **42** toward the completion of the synthesis of amphidinolide P. One route would join the C-14 alcohol **4** to **42** via transesterification to produce intermediate **51** for a subsequent intramolecular Stille macrocyclization (Scheme 9). This transformation was envisioned to be problematic because of competing opportunities leading to the formation of a π -allylpalladium species from the allylic ester **51**. Furthermore, the formation of a π -allylpalladium intermediate from product **52** could proceed to yield the stable tetraene **53** via a facile β -hydride elimination.

On the basis of our risk analysis, we first elected to explore formation of the C₁₁–C₁₂ bond of amphidinolide P followed by macrolactonization. Using stannane **4** and the previously prepared alkenyl bromide **42**, we found that Pd(PPh₃)₄ in DMF at 110 °C provided 10–20% yields of the Stille cross-coupling product **54** along with varying amounts of the

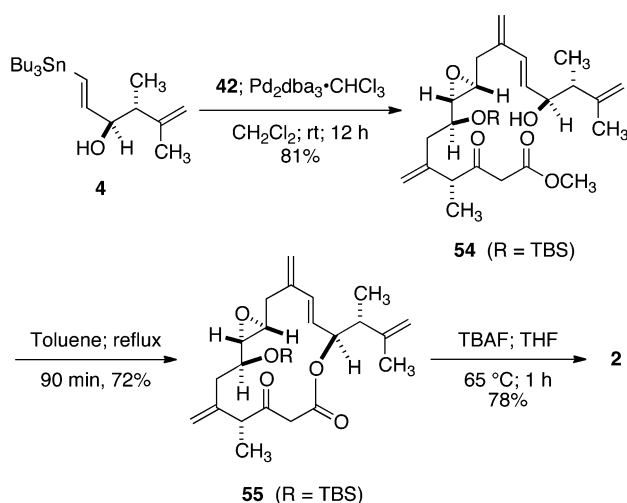
Scheme 9. Macrocyclization Considerations via the Stille Reaction



protodestannylated product of **4**. The addition of copper(I) salts facilitated the protodestannylation at lower temperatures. Our further studies showed that ligandless palladium conditions using Pd(OAc)₂ in toluene provided the expected diene at room temperature, whereas the addition of triphenylphosphine or other phosphines and polar solvents (DMF, NMP, THF) afforded little or none of the desired cross coupling.³⁷ Furthermore, the use of triphenylarsine in these reactions resulted in none of the desired product even after prolonged reaction times or elevated temperatures.³⁸ Our optimization of this Stille reaction, using Pd₂dba₃·CHCl₃ in methylene chloride³⁹ at room temperature overnight, resulted in the isolation of diene **54** in 81% yield (Scheme 10) along with small amounts (5–8%) of diastereomers arising from minor enantiomers of the starting chiral epoxides **26** and **44**. The subsequent macrolactonization of purified **54** was undertaken via a broadly applicable transesterification protocol for β -ketoesters as originally described by Bader and co-workers.⁴⁰ The mechanism of this reaction has been studied and suggests a concerted elimination of alcohol, which is consistent with a unimolecular process. Formation of an intermediate acylketene is followed by nucleophilic addition.⁴¹ In the event, the β -keto ester **54** was heated at 110 °C in refluxing toluene, and macrolactone **55** was produced as a single diastereoisomer in 72% yield (Scheme 10).

Final conversion to the natural product required deprotection of the C₇ TBS silyl ether and intramolecular hemiketal formation. This was cleanly accomplished in one step upon treatment of **55** with tetra-*n*-butyl ammonium fluoride in THF at 22 °C. Cleavage of the silyl ether led to spontaneous ring closure to yield a single hemiketal diastereomer, which proved to be synthetic (+)-amphidinolide P (**2**). The synthetic material

Scheme 10. Completion of the Total Synthesis of Amphidinolide P



was isolated as a white powder following flash silica gel chromatography: R_f 0.65 (15% EtOAc in hexanes); $[\alpha]_D^{23} +30.0^\circ$ (c 0.26, MeOH) ($[\alpha]_D^{25}$ lit. $+31^\circ$ (c 0.098, MeOH)).⁷ The optical rotation data is a correction of our previous studies,^{8b} which had led us to conclude that our route had erroneously produced (–)-amphidinolide P. In fact, we prepared three samples of synthetic **2** and can report that our specific rotations, at slightly different concentrations, ranged from $[\alpha]_D^{23} +27.5$ (c 0.40, MeOH) to $[\alpha]_D^{23} +30.0^\circ$ (c 0.26, MeOH). In all other respects, our synthetic sample is identical with the detailed spectroscopic data as reported for the natural product (Supporting Information contains comparison tables of proton and carbon NMR data and ^1H and ^{13}C NMR spectra). Thus, our synthesis effort has corrected our communication report and has shown that the absolute configuration of our synthetic (+)-amphidinolide P (**2**) is the same as the natural metabolite.

CONCLUSION

In summary, we have described an efficient, enantiocontrolled pathway to (+)-amphidinolide P in 12 steps (longest linear route) from readily available starting materials. Our studies have developed a pathway for the synthesis of functionalized, nonracemic allylsilanes incorporating the intact C_1 – C_6 segment of the natural product. Advantageously, this strategy is designed to directly incorporate the labile C_4 asymmetry of amphidinolide P from a chiral pool precursor. However, our studies of the subsequent Hosomi–Sakurai reaction failed because of the instability of these allylic silanes. We have concluded that allylsilanes that display homoallylic ketal and thioketal functionality are problematic and may result in facile formation of nonclassical cyclopropylcarbinylium cations, leading to further decomposition under the Lewis conditions of the reaction. This difficulty is circumvented by the stepwise assembly of the C_1 – C_6 region of the natural product. The process has utilized the Hosomi–Sakurai reaction of chiral silane **31** for Felkin–Anh addition with aldehyde **9**. A careful Mosher ester analysis of **35** and **36** provided the basis of the C_7 stereochemical assignment. Further oxidations and a condensation using an acetate aldol procedure avoided epimerization of the labile C_4 chirality. These studies have also examined the sp^2 – sp^2 cross coupling process required to assemble the functionalized diene of the

natural product. Concerns regarding this transformation involved the presence of the C_{15} alcohol and related derivatives, and is based on the proclivity for side reactions via the formation of π -allyl palladium species leading to β -hydride elimination. We have successfully demonstrated mild ligandless conditions for a Pd(0)-catalyzed Stille cross-coupling reaction, which successfully led to the desired, highly functionalized dienol. Finally, macrocyclization of the 15-membered lactone is achieved by an intramolecular transesterification via the formation and capture of an intermediate α -acylketene.

EXPERIMENTAL SECTION

General Methods. Flash chromatography was performed using silica gel 60 (230–400 mesh size). Preparative thin layer chromatography was performed on either 0.25 or 0.5 mm thick silica gel plates precoated with 60 F-254 on a 20 × 20 cm glass plate. Analytical thin layer chromatography (TLC) was performed on glass-backed 0.25 mm thick silica gel plates precoated with 60 F-254. Spots were visualized under UV light and/or with staining with ethanolic *p*-anisaldehyde or ceric ammonium molybdate. All silica products were commercially obtained. Optical rotations were obtained on a polarimeter at 589 nm (sodium D line) using a 10 cm path length and a 1.0 mL volume. Concentration (c) is reported in g per 100 mL of the solvent specified. Infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}).

Proton and carbon nuclear magnetic resonance (^1H NMR, ^{13}C NMR) spectra were measured on 400 and 500 MHz spectrometers. Proton NMR spectra were recorded in CDCl_3 or C_6D_6 solutions and are reported in parts per million (ppm) downfield (δ) from tetramethylsilane using residual chloroform (δ 7.26) or benzene (δ 7.20) as an internal reference. Proton NMR data are reported in the following form: δ (multiplicity, coupling constants, number of protons). Carbon NMR spectra were recorded in CDCl_3 or C_6D_6 solutions and are reported in parts per million (ppm) downfield (δ) from tetramethylsilane (TMS) using residual chloroform (CHCl_3 , δ 77.0) or benzene (δ 128.0) as an internal standard. Mass spectral data (MS, HRMS) were recorded on a magnetic sector mass spectrometer by use of chemical ionization (CI), electron impact (EI), or fast atom bombardment (FAB).

All reagents and solvents were commercial grade and were used as received unless noted otherwise. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled under N_2 from sodium benzophenone ketyl immediately before use. Acetonitrile (CH_3CN), benzene, *N,N*-diisopropylamine, *N,N*-diisopropylethylamine, methylene chloride (CH_2Cl_2), pyridine, toluene, and triethylamine (Et_3N) were distilled from calcium hydride. Dimethylsulfoxide (DMSO), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and hexamethylphosphoramide (HMPA) were distilled under argon from calcium hydride and stored over 4 Å molecular sieves under argon. Dimethylformamide (DMF) was distilled from anhydrous MgSO_4 and stored under an atmosphere of argon. 2-Methoxyethyl ether (diglyme) and ethylene glycol dimethyl ether (DME) were distilled from lithium aluminum hydride and were stored under an atmosphere of argon. Acetyl chloride and oxalyl chloride were distilled from calcium hydride. Boron trifluoride diethyl etherate ($\text{BF}_3\cdot\text{OEt}_2$) was freshly distilled from calcium hydride and Et_2O under an atmosphere of argon. Hexanes and ethyl acetate (EtOAc) were distilled prior to use in chromatography. 1-Lithiopropane was prepared from *n*-butyllithium (*n*-BuLi) and propyne gas on a calibrated Schlenk line; it was stored and handled in a glovebox under N_2 . Copper(I) bromide-dimethyl sulfide ($\text{CuBr}\cdot\text{DMS}$) was prepared from Cu_2Br_2 .²¹

All reactions were conducted in flame or oven-dried glassware under an atmosphere of argon unless otherwise noted. All nonvolatile samples were pumped to constant weight at ambient temperature (0.2–0.1 mmHg) following the removal of solvents in vacuo.

2-{2-[(1*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-methylethyl]-[1,3]dithian-2-yl}ethanol (**12**). *n*-Butyllithium (8.1 mL 2.5 M in hexanes) was added to a solution of dithiane **11**¹¹ (4.58 g, 15.7 mmol)

in THF (75 mL) at ambient temperature. The reaction stirred 5 min and was cooled to -78°C . Condensed ethylene oxide (2.3 mL, 47 mmol) was cannulated into the reaction mixture, and the reaction was warmed to ambient temperature over 3.5 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was transferred to a separatory funnel using Et_2O (50 mL) and water (10 mL). The aqueous layer was separated and washed with Et_2O (3×20 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (200 g SiO_2), using a gradient elution (hexanes to 25% EtOAc in hexanes) provided 3.00 g (60%) of **12** as a clear colorless oil: R_f 0.11 (20% EtOAc in hexanes); $[\alpha]_D^{26} +12.9$ (c 0.850, CHCl_3); IR (neat) 3395, 2955, 2857, 1422, 1254, 1044, 837, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.10 (dd, $J = 10.2$, 3.76 Hz, 1H), 3.87 (m, 2H), 3.56 (dd, $J = 10.2$, 8.1 Hz, 1H), 2.91 (m, 2H), 2.81 (m, 2H), 2.65 (s, OH), 2.34 (m, 1H), 2.26 (m, 2H), 2.08–1.84 (m, 2H), 1.17 (d, $J = 6.7$ Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 64.9, 59.7, 55.8, 42.1, 38.0, 26.0, 25.9, 25.8, 25.0, 18.3, 12.98, -5.3 ; MS (CI, NH_3) m/z (relative intensity) 336 (8), 291 (13), 279 (73), 261 (79), 249 (45), 231 (63), 191 (57), 187 (72), 175 (51), 165 (68), 149 (75), 105 (63), 89 (72), 75 (100), 73 (84); HRMS m/z calcd for $\text{C}_{15}\text{H}_{32}\text{O}_2\text{Si}_2$ (M^+) 336.1613, found 336.1607. Anal. Calcd for $\text{C}_{15}\text{H}_{32}\text{Si}_2$: C, 53.52; H, 9.58; Si, 19.05. Found: C, 53.83; H, 9.46; Si, 19.38.

2-[2-[(1R)-2-(tert-Butyldimethylsilyloxy)-1-methylethyl]-[1,3]dithian-2-yl]-1-(tetrahydropyran-2-yloxy)ethane (13). Alcohol **12** (3.12 g, 9.3 mmol) was stirred at room temperature with dihydropyran (0.45 mL, 4.97 mmol) and PPTS (104 mg, 0.41 mmol) in CH_2Cl_2 (21 mL) for 2 d. The reaction was quenched with saturated aqueous NaHCO_3 and diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4×40 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (325 g SiO_2 , 5% EtOAc in hexanes), which provided 3.51 g (90%) of a 1:1 mixture of tetrahydropyran diastereomers **13** as a colorless oil: R_f 0.64 (20% EtOAc in hexanes); $[\alpha]_D^{25} +25.7$ (c 1.50, CHCl_3); IR (neat) 2955, 2932, 2859, 1470, 1258, 1134, 1076, 1028, 839, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.59 (m, 1H), 4.14 (m, 0.5H), 4.12 (m, 0.5H), 3.96 (m, 1H), 3.88 (m, 1H), 3.63 (m, 1H), 3.53 (m, 2H), 2.92 (m, 2H), 2.76 (m, 2H), 2.32 (m, 2H), 2.10 (m, 1H), 1.90 (m, 3H), 1.71 (m, 1H), 1.54 (m, 4H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 99.2, 99.1, 64.9 (2), 65.5, 62.5, 62.4, 55.6, 42.4 (2), 35.4, 30.7 (2), 25.9 (3), 25.8, 25.7, 25.4, 25.1 (2), 19.7 (2), 18.3 (2), 12.6 (2), -5.3 (2) (Some carbon signals are coincident (overlapping) for these THP diastereomers and are not readily assignable); MS (CI, NH_3) m/z (relative intensity) 420 (2), 363 (4), 261 (32), 145 (81), 119 (24), 85 (100); HRMS m/z calcd for $\text{C}_{20}\text{H}_{40}\text{O}_3\text{Si}_2$ (M^+) 420.2188, found 420.2207.

(2R)-2-[2-[(2-Tetrahydropyran-2-yloxy)ethyl]-[1,3]dithian-2-yl]propionaldehyde (15). Tetrabutylammonium fluoride (TBAF) (15 mL, 1.0 M in THF, 14.9 mmol) was added to a solution of **13** (1.25 g, 2.98 mmol) and THF (5 mL). The reaction stirred 1 h at room temperature and was diluted with Et_2O (25 mL) and H_2O (25 mL). The organic layer was washed with H_2O (2×20 mL) and brine (25 mL). The aqueous layer was extracted with Et_2O (2×15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (45 g SiO_2 , 30% EtOAc in hexanes), which provided 0.91 g of (2R)-2-[2-[(2-tetrahydropyran-2-yloxy)ethyl]-[1,3]dithian-2-yl]propan-1-ol as a 1:1 mixture of tetrahydropyran diastereomers (99%) as a colorless oil: R_f 0.12 (20% EtOAc in hexanes); IR (neat) 3420, 2938, 2878, 2735, 2660, 1736, 1466, 139, 1422, 1088, 1032, 905, 870, 810, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.59 (m, 1H), 3.96 (m, 2H), 3.86 (m, 1H), 3.65 (m, 2H), 3.51 (m, 1H), 2.86 (m, 2H), 2.78 (m, 2H), 2.78 (m, 2H), 2.52 (m, 1H), 2.37 (m, 1H), 2.26 (m, 2H), 1.95 (m, 2H), 1.71 (m, 2H), 1.55 (m, 4H), 1.16 (d, $J = 7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 99.2, 99.1, 65.1, 64.4 (2), 62.5, 62.4, 55.4, 41.9, 35.2, 30.7, 25.9 (2), 25.4, 24.9, 19.7, 19.6, 13.1, 13.0 (Some carbon signals are coincident (overlapping) for these THP

diastereomers and are not readily assignable); MS (CI, NH_3) m/z (relative intensity) 306 (14), 247 (25), 181 (22), 142 (85), 100 (40), 85 (100); HRMS m/z calcd for $\text{C}_{14}\text{H}_{26}\text{O}_3\text{S}_2$ (M^+) 306.1323, found 306.1312.

Dimethylsulfoxide (0.77 mL, 10.9 mmol) was added to a -78°C solution of oxalyl chloride (0.47 mL, 5.44 mmol) and CH_2Cl_2 (18 mL). The reaction stirred 10 min, and a solution of the primary alcohol (1.51 g, 4.94 mmol) and CH_2Cl_2 (5 mL) was added dropwise via cannula. The reaction stirred 30 min, and Et_3N (3.4 mL, 24.7 mmol) was added dropwise. The reaction was stirred 15 min at -78°C , warmed to room temperature, diluted with hexanes (50 mL), and quenched with H_2O (5 mL). The aqueous layer was extracted with hexanes (3×15 mL). The combined organic layers were washed with brine (75 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. Aldehyde **15** was obtained in 98% yield as a 1:1 mixture of tetrahydropyran diastereomers, which was used in subsequent reactions without further purification. Characteristic data for aldehyde **15**: R_f 0.33 (20% EtOAc in hexanes); IR (neat) 2942, 2672, 1715, 1441, 1352, 1123, 1061, 1032, 905, 870 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.56 (m, 1H), 4.59 (m, 1H), 3.99 (m, 1H), 3.86 (m, 1H), 3.64 (m, 1H), 3.51 (m, 1H), 2.87 (m, 3H), 2.80 (m, 1H), 2.41 (m, 1H), 2.28 (m, 1H), 1.98 (m, 2H), 1.72–1.67 (m, 2H), 1.53 (m, 4H), 1.29 (m, 1H), 1.26 (d, $J = 6.8$ Hz, 3H).

2-[2-(Tetrahydropyran-2-yloxy)ethyl]-2-(1-methylprop-2-ynyl)-[1,3]dithiane (17). Carbon tetrabromide (2.16 g, 6.5 mmol) was added to a solution of triphenylphosphine (3.41 g, 13 mmol) dissolved in CH_2Cl_2 (10 mL) at 0°C . The yellow reaction was stirred 10 min and was cooled to -78°C . Anhydrous granular Na_2SO_4 was added to a solution of aldehyde **15** (~ 2.64 mmol) and CH_2Cl_2 (6 mL). The mixture stirred 15 min and was added via cannula to the solution containing carbon tetrabromide and triphenylphosphine using CH_2Cl_2 (3×1 mL). The reaction stirred 15 min at -78°C , was warmed to room temperature, and diluted with CH_2Cl_2 (10 mL) and H_2O (15 mL). The organic layer was separated and washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (250 g SiO_2 , 10% EtOAc in hexanes), which provided 645 mg (54% over 2 steps from alcohol **12**) of a 1:1 mixture of tetrahydropyran diastereomers 2-[(1R)-3,3-dibromo-1-methylallyl]-2-[(tetrahydropyran-2-yloxy)ethyl]-[1,3]dithiane as a colorless oil: R_f 0.38 (20% EtOAc in hexanes); IR (neat) 3023, 2944, 2733, 2658, 1736, 1638, 1439, 1371, 1103, 909, 787 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.67 (d, $J = 9.6$ Hz, 1H), 4.60 (m, 1H), 3.96 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 3.52 (m, 1H), 3.04 (m, 1H), 2.82 (m, 4H), 2.29 (m, 2H), 1.66–2.01 (m, 4H), 1.55 (m, 4H), 1.20 (d, $J = 6.9$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5, 99.1 (2), 88.8 (2), 64.4, 64.3, 62.4, 62.3, 55.1, 45.2, 35.6, 30.7, 26.0, 35.4, 24.8, 19.6, 19.5, 14.1 (2); MS (CI, NH_3) m/z (relative intensity) 460 (5), 377 (33), 359 (18), 247 (73), 147 (95), 146 (60), 145 (100), 85 (92); HRMS m/z calcd for $\text{C}_{15}\text{H}_{24}\text{Br}_2\text{O}_2\text{S}_2$ (M^+) 459.9565, found 459.9560.

The alkenyl dibromide prepared above (0.579 g, 1.26 mmol) was diluted with THF (6.3 mL) and cooled to -78°C . *n*-Butyllithium (1.11 mL, 2.5 M in hexanes) was added dropwise. The yellow reaction stirred 15 min and was quenched with saturated aqueous NH_4Cl . The mixture was diluted with Et_2O (10 mL) and H_2O (5 mL). The organic layer was washed with H_2O (2×10 mL) and brine (15 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography (15 g SiO_2 , 10% EtOAc in hexanes), which provided 229 mg (62%) of a 1:1 mixture of tetrahydropyran diastereomers of **17** as a white solid: mp 89.0–91.5 $^{\circ}\text{C}$; R_f 0.34 (20% EtOAc in hexanes); $[\alpha]_D^{25} +18.8$ (c 1.67, CHCl_3); IR (neat) 3306, 3001, 2945, 2875, 1121, 1074, 1028, 746 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.61 (m, 1H), 4.01 (m, 1H), 3.89 (m, 1H), 3.69 (m, 1H), 3.51 (m, 1H), 3.20 (m, 1H), 2.85 (m, 4H), 2.47 (m, 1H), 2.30 (m, 1H), 2.23 (d, $J = 2.6$, 1H), 1.94 (m, 2H), 1.81 (m, 1H), 1.71 (m, 1H), 1.54 (m, 4H), 1.44 (d, $J = 7.0$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 99.0, 98.9, 84.7, 77.2, 71.7, 64.2, 64.1, 62.4, 62.3, 54.9, 54.8, 35.8, 34.8, 30.7, 30.6, 26.1, 26.0, 25.4, 24.5, 19.6, 19.5, 16.9, 14.2 (Some carbon signals are coincident (overlapping) for these THP diastereomers and are not readily assignable); MS (CI, NH_3) m/z

(relative intensity) 300 (16), 247 (100), 171 (20), 147 (88), 85 (58); HRMS m/z calcd for $C_{15}H_{24}O_3S_2$ (M^+) 300.1218, found 300.1218.

(3R)-3-{2-[2-(Tetrahydropyran-2-yloxy)ethyl]-[1,3]dithian-2-yl}butan-2-one (18). Aldehyde **15** (4.94 mmol) was diluted in THF (25 mL) and was cooled to -78 °C. Methylmagnesium bromide (3.8 mL, 3 M in Et_2O) was added dropwise. After stirring 10 min, the reaction was warmed to 0 °C. After another 10 min, saturated aqueous NH_4Cl was added. The mixture was transferred to a separatory funnel using Et_2O (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (2×25 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (40 g SiO_2 , 15% $EtOAc$ in hexanes), which provided 1.33 g of a 1:1:1:1 mixture of diastereomeric alcohols as a colorless oil: R_f 0.34 (20% $EtOAc$ in hexanes); $[\alpha]_D^{23} -5.87$ (c 1.50, $CHCl_3$); IR (neat) 3489, 2940, 1452, 1422, 1352, 1273, 1119, 1059, 1032, 907, 812 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 4.68 (m, 1H), 4.58 (m, 1H), 3.81–3.92 (m, 2H), 3.47–3.57 (m, 2H), 2.92–3.02 (m, 2H), 2.64–2.72 (m, 2H), 2.52–2.61 (m, 1H), 2.41 (br s, 1H–OH), 2.33–2.41 (m, 1H), 2.04 (m, 1H), 1.75–1.90 (m, 3H), 1.69 (m, 1H), 1.49–1.58 (m, 4H), 1.15 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 7.1$ Hz, 1.5H), 1.11 (d, $J = 7.1$ Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.1, 99.0, 66.6, 64.4 (2), 62.4, 62.3, 57.1, 45.7, 35.7, 30.6, 25.9, 25.9, 25.8, 25.3, 25.1, 22.0, 22.0, 19.6, 19.5, 6.8 (2); MS (CI, CH_4) m/z (relative intensity) 320 (14), 247 (21), 192 (9), 147 (30), 85 (100); HRMS m/z calcd for $C_{15}H_{28}O_3S_2$ (M^+) 320.1480, found 320.1483.

Dess–Martin periodinane¹⁹ (0.8 g, 1.88 mmol) was added to a solution of the diastereomeric alcohols (0.50 g, 1.56 mmol), pyridine (0.76 mL, 9.39 mmol), and CH_2Cl_2 (8 mL). The reaction stirred 8 h at ambient temperature and was quenched by dilution with Et_2O (20 mL) and H_2O (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (15 g SiO_2 , 10% $EtOAc$ in hexanes), which provided 460 mg (92%) of a 1:1 mixture of tetrahydropyranyl isomers of **18** as a white solid: mp 57 – 59 °C, R_f 0.33 (30% $EtOAc$ in hexanes); $[\alpha]_D^{24} +40.1$ (c 2.08, $CHCl_3$); IR (neat) 2938, 1711, 1424, 1352, 1032, 934, 754 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 4.58 (m, 1H), 4.00 (m, 1H), 3.86 (m, 1H), 3.65 (m, 1H), 3.49 (m, 1H), 3.40 (q, $J = 7.1$ Hz, 1H), 2.86 (m, 1H), 2.84–2.65 (m, 3H), 2.42 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.02–1.62 (m, 5H), 1.52 (m, 3H), 1.27 (d, $J = 7.1$ Hz, 1.5 Hz), 1.26 (d, $J = 7.1$ Hz, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 99.0, 98.9, 64.3, 62.4, 62.3, 52.8, 52.1, 34.9, 31.5, 30.7, 26.4, 26.1, 26.0, 25.4, 24.5, 19.6, 19.5, 13.3 (Some carbon signals are coincident (overlapping) for these THP diastereomers and are not readily assignable); MS (CI, NH_3) m/z (relative intensity) 318 (20), 275 (44), 247 (17), 189 (17), 147 (49), 85 (100); HRMS m/z calcd for $C_{15}H_{26}O_3S_2$ (M^+) 318.1323, found 318.1327.

Trifluoromethanesulfonic acid (1R)-1-(1-[2-(tetrahydropyran-2-yloxy)ethyl]-[1,3]dithian-2-yl)ethyl vinyl ester (20). Lithium diisopropylamide (LDA) (1.2 mL, 0.5 M in THF) was added to a -78 °C solution of ketone **18** (150 mg) and THF (2.0 mL). The reaction stirred 50 min, and a solution of *N*-(5-chloro-2-pyridyl)trifluorimide⁴² and THF (0.5 mL) was added via cannula. The reaction warmed to -20 °C over 2 h and then was stirred for an additional 2 h. The reaction was concentrated via rotary evaporator. Purification by flash column chromatography (25 g SiO_2 , using 10% $EtOAc$ in hexanes) provided 155 mg (73%) of triflate **20** as a 1:1 mixture of tetrahydropyranyl diastereomers as a colorless oil: R_f 0.31 (20% $EtOAc$ in hexanes); $[\alpha]_D^{26} +31.6$ (c 0.995, $CHCl_3$); IR (neat) 2942, 2876, 1738, 1657, 1416, 1248, 1125, 1032, 934 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 5.33 (dt, $J = 4.1, 1.3$ Hz, 1H), 5.18 (d, $J = 3.9$ Hz, 1H), 4.60 (m, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 3.67 (m, 1H), 3.51 (m, 1H), 3.16 (m, 1H), 2.82 (m, 4H), 2.24 (m, 2H), 1.94 (m, 2H), 1.80 (m, 1H), 1.72 (m, 1H), 1.50–1.59 (m, 4H), 1.41 (dd, $J = 7.3, 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 107.0, 99.3, 99.2, 64.4, 62.5, 62.4, 45.9, 34.8, 30.6, 26.4, 26.3, 25.4, 24.3, 19.6, 15.0; MS (CI, NH_3) m/z (relative intensity) 367 (10), 317 (82), 233 (81), 215 (77), 163 (95), 147 (74), 145 (100), 133 (68), 85 (97); HRMS m/z calcd for $C_{11}H_{16}F_3O_3S_3$ ($M^+ - C_3H_9O_2$) 349.0214, found 349.0224.

2-[2-(Tetrahydropyran-2-yloxy)ethyl]-2-(1-methylpropa-1,2-dienyl)-[1,3]-dithiane (22). Tri-*n*-butylstannylmethyl iodide²² (0.82 g, 1.89 mmol) was dissolved in benzene (9 mL) and HMPA (0.66 mL). Zinc–copper couple (490 mg) was added, and the reaction was heated to 75 °C for 2 h and then refluxed for 30 min. Proton NMR and TLC indicated that none of the starting stannane remained. The reaction was cooled to ambient temperature, and triflate **20** (85 mg, 0.19 mmol), LiCl (32 mg, 0.76 mmol) and $Pd(PPh_3)_4$ (8.7 mg, 7.6 mmol) were added. The reaction stirred 14 h at ambient temperature and was heated to 57 °C for 4 h. After cooling to ambient temperature, saturated aqueous NH_4Cl was added (5 mL). The reaction was filtered through a pad of silica to remove the zinc salts using Et_2O . The filtrate was transferred to a separatory funnel using Et_2O . The organic layer was washed with H_2O (10 mL) and brine (15 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (20 g SiO_2 , 10% $EtOAc$ in hexanes), which provided 25 mg (44%) of allene **22** and 24 mg (42%) of alkyne **17** a colorless oil. Alkyne **17** was fully characterized as previously described. Data for **22**: R_f 0.54 (20% $EtOAc$ in hexanes); IR (neat) 2944, 2926, 1952, 1439, 1352, 1262, 1136, 1121, 1061, 1032, 907, 847 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 4.85 (q, $J = 2.9$ Hz, 2H), 4.58 (m, 1H), 3.86 (m, 2H), 3.67 (m, 2H), 2.91 (m, 2H), 2.70 (ddd, $J = 14.3, 6.3, 3.2$ Hz, 2H), 2.27 (t, $J = 7.3, 2H$), 1.99 (m, 1H), 1.93 (m, 1H), 1.83 (t, $J = 3.0, 3H$), 1.79 (m, 1H), 1.69 (m, 1H), 1.53 (m, 3H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 102.0, 99.0, 76.3, 63.5, 62.2, 53.0, 38.6, 30.6, 27.3, 25.4, 25.2, 19.5, 16.3; MS (CI, NH_3) m/z (relative intensity) 300 (57), 247 (13), 198 (74), 172 (62), 156 (60), 151 (53), 138 (69), 112 (44), 85 (100); HRMS m/z calcd for $C_{15}H_{24}O_2S_2$ (M^+) 300.1218, found 300.1223.

2-[2-(Tetrahydropyran-2-yloxy)ethyl]-2-[(1R)-1-methyl-2-(trimethylsilylamethyl)allyl]-[1,3]-dithiane (23). Trimethylsilylmethylmagnesium chloride (2.7 mL, 1 M in Et_2O) was added to a solution of vinyl triflate **20** (150 mg, 0.334 mmol), $Ni(acac)_2$ (2.0 mg, 6.7 mmol), and THF (2 mL). The reaction stirred 24 h, and additional Grignard reagent was added (2 mL, 1 M in Et_2O). After 24 h the reaction was quenched by the addition of saturated aqueous NH_4Cl . The mixture was diluted with Et_2O , and the organic layer was washed with saturated aqueous NH_4Cl (10 mL), H_2O (10 mL), and brine (15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (12 g SiO_2 , 10% $EtOAc$ in hexanes), which provided 97 mg (56%) of **23** as a colorless oil: R_f 0.49 (20% $EtOAc$ in hexanes); $[\alpha]_D^{25} +35.2$ (c 0.815, $CHCl_3$); IR (neat) 3081, 2944, 1626, 1452, 1422, 1248, 1123, 1030, 855 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.84 (s, 1H), 4.60 (m, 1H), 3.85–4.00 (m, 2H), 3.63 (m, 1H), 3.51 (m, 1H), 2.94 (m, 2H), 2.73 (m, 2H), 2.58 (m, 1H), 2.40 (m, 2H), 1.97 (m, 1H), 1.80–1.90 (m, 2H), 1.76 (d, 4.0 Hz, 2H), 1.71 (m, 1H), 1.53 (m, 4H), 1.29 (d, $J = 7.0$ Hz, 1.5H), 1.28 (d, $J = 7.0$ Hz, 1.5H), 0.04 (s, 9H); MS (CI, CH_4) m/z (relative intensity) 388 (1), 287 (3), 247 (52), 163 (13), 147 (79), 145 (100), 85 (80), 73 (66); HRMS m/z calcd for $C_{19}H_{36}O_2S_2Si$ (M^+) 388.1926, found 388.1910.

2-[2-[(1R)-2-(tert-Butyldimethylsilyloxy)-1-methylethyl]-[1,3]dithian-2-yl]-1-(tert-butyl)diphenylsilyloxy)ethane (14). Alcohol **12** (2.79 g, 8.31 mmol), *tert*-butyldiphenylsilyl chloride (2.2 mL, 8.31 mmol), dimethylaminopyridine (DMAP) (~50 mg), and imidazole (2.1 g, 31 mmol) were stirred in CH_2Cl_2 (15 mL) at ambient temperature 24 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with saturated aqueous NH_4Cl (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (160 g SiO_2 , 3% Et_2O in hexanes), which provided 4.63 g (97%) of **14** as a thick oil: R_f 0.62 (20% $EtOAc$ in hexanes); $[\alpha]_D^{24} +8.93$ (c 2.89, $CHCl_3$); IR (neat) 3071, 3050, 2955, 2859, 1589, 1472, 1427, 1254, 1113, 1067, 835, 777, 739, 702 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.40 (m, 6H), 4.06 (dd, $J = 9.9, 3.5$ Hz, 1H), 3.87 (t, $J = 7.5$ Hz, 2H), 3.49 (dd, $J = 9.8, 8.7$ Hz, 1H), 2.65 (m, 4H), 2.31 (m, 1H), 2.24 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H), 1.80 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 1.05 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9,

133.8, 129.6, 127.6, 64.8, 60.9, 55.0, 42.5, 38.0, 26.9, 25.9, 25.8, 25.6, 25.1, 19.1, 18.2, 12.4, -5.3; MS (CI, CH₄) *m/z* (relative intensity) 574 (3), 517 (62), 445 (42), 401 (60), 385 (64), 355 (40), 313 (47), 261 (63), 181 (80), 115 (100), 91 (77), 89 (96), 73 (84); HRMS *m/z* calcd for C₃₁H₅₀O₂S₂Si₂ (M⁺) 574.2791, found 574.2781.

(2R)-2-{2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-[1,3]-dithian-2-yl}propionaldehyde (16). A mixture of the silyl ether **14**, acetic acid (8 mL), THF (5 mL), and H₂O (5 mL) was heated to 42 °C for 22 h. The reaction was cooled to ambient temperature and diluted with Et₂O (20 mL). The organic layer was washed with NaOH (2 × 10 mL), saturated aqueous NaHCO₃ (2 × 10 mL), and brine (20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (28 g SiO₂, 20% EtOAc in hexanes), which provided 589 mg (75%) of the primary alcohol, resulting from selective cleavage of the TBS silyl ether, as a thick oil: *R_f* 0.20 (20% EtOAc in hexanes); IR (neat) 3407, 3071, 2930, 2888, 2857, 1589, 1472, 1427, 1103, 1030, 909, 824, 739, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (m, 4H), 7.41 (m, 6H), 3.89 (m, 2H), 3.86 (A of ABX, *J*_{AB} = 11.6 Hz, *J*_{AX} = 5.6 Hz, 1H), 3.66 (B of ABX, *J*_{AB} = 11.6 Hz, *J*_{BX} = 5.1 Hz, 1H), 2.77 (m, 2H), 2.65 (m, 2H), 2.32 (m, 1H), 2.21 (m, 1H), 2.13 (m, 1H), 1.68 (m, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 135.6, 133.7, 129.6, 127.7, 65.2, 60.8, 60.4, 55.2, 41.8, 37.9, 26.9, 25.8, 24.9, 19.1, 12.8; MS (CI, CH₄) *m/z* (relative intensity) 460 (1), 443 (1), 403 (36), 385 (23), 373 (35), 343 (39), 325 (58), 295 (51), 273 (30), 211 (69), 199 (100), 197 (63), 135 (78), 77 (51); HRMS *m/z* calcd for C₂₅H₃₆O₂S₂Si (M⁺) 460.1926, found 460.1942.

Dimethylsulfoxide (0.12 mL, 1.74 mmol) was added dropwise to a solution of oxalyl chloride (0.45 mL, 0.52 mmol) and CH₂Cl₂ (2 mL) at -78 °C. After 15 min, a solution of the primary alcohol, prepared as described above, (200 mg, 0.434 mmol) and CH₂Cl₂ (1 mL) was added. The reaction stirred 30 min at -78 °C, and Et₃N (0.24 mL, 1.74 mmol) was added dropwise. The reaction was stirred 30 min at -78 °C, warmed to ambient temperature, and diluted with hexanes (10 mL) and H₂O (2 mL). The organic layer was washed with saturated aqueous NH₄Cl (2 × 5 mL), H₂O (2 mL), and brine (10 mL); dried over Na₂SO₄; filtered; and concentrated in vacuo to provide 191 mg (96%) of aldehyde **16** as a colorless oil, which was of sufficient purity for further use. Spectroscopic characterization data for **16**: *R_f* 0.50 (20% EtOAc in hexanes); IR (neat) 3069, 2955, 2932, 2859, 1717, 1466, 1427, 1389, 1109, 1078, 739, 704, 617 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.89 (d, *J* = 2.7 Hz, 1H), 7.69 (m, 4H), 7.42 (m, 6H), 3.89 (m, 2H), 2.76 (m, 3H), 2.67 (m, 2H), 2.35 (m, 1H), 2.21 (m, 1H), 1.89 (m, 2H), 1.14 (d, *J* = 7.3 Hz, 3H), 1.05 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 202.0, 135.6, 133.5, 129.7, 127.7, 60.6, 51.8, 51.4, 38.1, 26.8, 26.0, 25.4, 24.5, 19.1, 9.8; MS (CI, CH₄) *m/z* (relative intensity) 401 (85), 343 (24), 311 (17), 239 (45), 225 (40), 211 (57), 199 (100), 183 (71), 135 (80), 77 (50); HRMS *m/z* calcd for C₂₁H₂₅O₂S₂Si (M⁺ - C₄H₉) 401.1065, found 401.1071.

(3R)-3-{2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-[1,3]-dithian-2-yl}butan-2-one (19). Aldehyde **16** (188 mg, 0.410 mmol) was diluted in THF (2.8 mL) and was cooled to -78 °C. Methylmagnesium bromide (0.57 mL, 3 M in Et₂O) was added dropwise. After stirring 30 min, the reaction was warmed to ambient temperature and saturated aqueous NH₄Cl was added. The mixture was transferred to a separatory funnel using Et₂O (10 mL) and H₂O (3 mL). The organic layer was washed with H₂O (2 × 3 mL) and brine (3 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (8 g SiO₂, 20% EtOAc in hexanes), which provided 166 mg (85%) of a 1:1 mixture of alcohol diastereomers as a colorless oil: *R_f* 0.43 (20% EtOAc in hexanes); [*α*]_D²⁴ -4.46 (c 1.12, CHCl₃); IR (neat) 3464, 3071, 2928, 2857, 1589, 1460, 1427, 1271, 1109, 1069, 999, 689 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (m, 4H), 7.42 (m, 6H), 4.61 (qd, *J* = 6.5, 1.2 Hz, 1H), 3.81 (m, 2H), 2.88 (m, 1H), 2.66 (m, 2H), 2.52 (m, 2H), 2.35 (m, 1H), 1.99 (m, 2H), 1.80 (m, 2H), 1.70 (q, *J* = 7 Hz, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.6, 133.7, 129.7, 127.7, 66.7, 61.0, 45.6, 38.3, 26.8, 25.8 (2), 25.7, 25.2, 21.7, 19.1, 6.7; MS (CI, NH₃) *m/z*

(relative intensity) 417 (2), 373 (40), 343 (5), 295 (13), 199 (100), 169 (22), 119 (36); HRMS *m/z* calcd for C₂₂H₂₉O₂S₂Si (M⁺ - C₄H₉) 417.1378, found 417.1381.

Dimethylsulfoxide (0.39 mL, 5.51 mmol) was added dropwise to a solution of oxalyl chloride (0.14 mL, 1.65 mmol) and CH₂Cl₂ (6 mL) at -78 °C. After 15 min, a solution of the secondary alcohols, as prepared above, (654 mg, 1.38 mmol) and CH₂Cl₂ (1 mL) was added. The reaction stirred 30 min at -78 °C, and Et₃N (0.77 mL, 5.51 mmol) was added dropwise. The reaction was stirred 30 min at -78 °C, warmed to ambient temperature, and diluted with hexanes (30 mL) and H₂O (8 mL). The organic layer was washed with saturated aqueous NH₄Cl (2 × 10 mL), H₂O (10 mL), and brine (15 mL); dried over Na₂SO₄; filtered; and concentrated in vacuo. The residue was purified by flash column chromatography (40 g SiO₂, 8% EtOAc in hexanes), which provided 512 mg (78%) of ketone **19** as a waxy white solid: mp 70.5–76 °C; *R_f* 0.27 (20% EtOAc in hexanes); [*α*]_D²³ +18.7 (c 2.07, CHCl₃); IR (neat) 3071, 2957, 2932, 2857, 1713, 1460, 1427, 1352, 1107, 1072, 824, 741, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.69 (m, 4H), 7.40 (m, 6H), 3.94 (t, *J* = 7.4 Hz, 2H), 3.31 (q, *J* = 7.1 Hz, 1H), 2.85 (m, 1H), 2.66–2.77 (m, 2H), 2.62 (m, 1H), 2.40 (m, 1H), 2.25 (s, 3H), 2.19 (m, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.20 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 209.1, 135.6, 133.8 (2), 129.6, 128.3, 127.6, 60.8, 52.3, 52.1, 37.6, 31.5, 26.9, 26.2, 26.0, 24.4, 19.1, 13.1; MS (CI, NH₄) *m/z* (relative intensity) 415 (38), 343 (90), 309 (14), 199 (100), 146 (40), 135 (50), 106 (26); HRMS *m/z* calcd for C₂₂H₂₇O₂S₂Si (M⁺ - C₄H₉) 415.1221, found 415.1222.

Trifluoromethanesulfonic acid (1R)-1-(1-{2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-[1,3]-dithian-2-yl}ethyl)vinyl ester (21). Sodium bis(trimethylsilyl)amide (NaHMDS) (0.16 mL, 1.0 M in THF) was added to a -78 °C solution of ketone **19** (25 mg) and THF (0.5 mL). The reaction stirred 50 min, and DMPU (26 mL, 0.21 mmol) was added. After an additional 40 min at -78 °C, a solution of *N*-phenyltrifluoromethanesulfonimide (94 mg, 0.264 mmol) and THF (0.5 mL) was added via cannula. The reaction was stirred 1 h at -78 °C, warmed to ambient temperature, stirred 1 h, and concentrated via rotary evaporator. Purification by flash column chromatography (4 g SiO₂, using 5% EtOAc in hexanes) provided 16 mg (56%) of triflate **21** as a colorless oil: *R_f* 0.53 (20% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.26 (d, *J* = 4.0 Hz, 1H), 5.05 (d, *J* = 4.0 Hz, 1H), 3.93 (dt, *J* = 7.5, 1.9 Hz, 2H), 3.07 (q, *J* = 7.0 Hz, 1H), 2.75 (m, 1H), 2.70–2.63 (m, 3H), 2.18 (m, 3H), 1.85 (m, 2H), 1.33 (d, *J* = 7.3 Hz, 3H), 1.05 (s, 9H). Triflate **21** was not characterized further but was directly used for production of **24**.

2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-[(1R)-1-methyl-2-(trimethylsilylmethyl)allyl]-[1,3]-dithiane (24). Trimethylsilylmethylmagnesium chloride (0.83 mL, 1 M in Et₂O) was added to a solution of vinyl triflate **21** (45 mg, 0.083 mmol), Ni(acac)₂ (~2.0 mg), and THF (2 mL). The reaction stirred 16 h, and the reaction was quenched by the addition of pH 7 aqueous buffer. The mixture was diluted with Et₂O. The aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (5 g Et₃N washed SiO₂, hexanes), which provided 24 mg (53%) of **24** as a colorless oil: *R_f* 0.70 (20% EtOAc in hexanes); IR (neat) 3092, 2945, 1425, 1030, 855 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (m, 4H), 7.40 (m, 6H), 4.80 (s, 1H), 4.78 (s, 1H), 3.86 (m, 2H), 2.53–2.75 (m, 4H), 2.28–2.44 (m, 2H), 1.87 (m, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.56 (s, 2H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.05 (s, 9H), 0.00 (s, 9H); HRMS *m/z* calcd for C₃₀H₄₆OS₂Si₂ (M⁺) 542.2529, found 542.2531.

(2S,3S)-4-(*tert*-Butyldiphenylsilyloxy)-2,3-epoxy-1-iodobutane (27). Triphenylphosphine (2.62 g, 10.0 mmol) and imidazole (1.36 g, 20.0 mmol) were dissolved in CH₂Cl₂ (25 mL) at 0 °C. Iodine (2.54 g, 10.0 mmol) was added, and the resulting mixture stirred 30 min. Alcohol **26** ([*α*]_D²⁴ -13.0 (c 2.86, CHCl₃), 91% ee by Mosher Ester analysis)³⁰ (1.7 g, 5.0 mmol) was added, and the resulting mixture stirred 1 h. Aqueous sodium sulfite (10%, 20 mL) was added, and the organic layer was separated. The aqueous layer was extracted

with CH_2Cl_2 , and the combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (80 g SiO_2), using a gradient elution (hexanes to 5% EtOAc in hexanes) provided 2.1 g (91%) of **27** as a colorless oil: R_f 0.44 (5% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} +1.74$ (c 1.95, CHCl_3); IR (neat) 3071, 2959, 2930, 2859, 1472, 1427, 1113, 741, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.68 (m, 4H), 7.42 (m, 6H), 3.81 (A of ABX, $J_{\text{AB}} = 12.0$ Hz, $J_{\text{AX}} = 4.3$ Hz, 1H), 3.77 (B of ABX, $J_{\text{AB}} = 12.0$ Hz, $J_{\text{BX}} = 3.4$ Hz, 1H), 3.25 (A of ABX, $J_{\text{AB}} = 9.7$ Hz, $J_{\text{AX}} = 6.4$ Hz, 1H), 3.05 (B of ABX, $J_{\text{AB}} = 9.7$ Hz, $J_{\text{BX}} = 5.8$ Hz, 1H), 3.18 (ddd, $J = 6.4$, 5.8, 2.0 Hz, 1H), 3.02 (ddd, $J = 4.3$, 3.4, 2.0 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.6, 135.5, 129.8, 127.8, 63.0, 62.0, 55.7, 26.7, 19.2, 4.1; MS (CI, CH_4) m/z (relative intensity) 395 (50), 365 (80), 309 (100), 267 (40), 199 (70), 181 (50), 128 (92), 91 (65); HRMS m/z calcd for $\text{C}_{16}\text{H}_{16}\text{IO}_2\text{Si}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 394.9964, found 394.9979. Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{IO}_2\text{Si}$: C, 53.10; H, 5.57. Found: C, 53.04; H, 5.58.

(4S,5S)-6-(tert-Butyldiphenylsilyloxy)-4,5-epoxy-2-trimethylsilylhex-1-ene (29). 1,2-Dibromoethane (0.45 mL, 5.0 mmol) was added to magnesium turnings (1.7 g, 72 mmol) in THF (20 mL). 1-Bromovinyltrimethylsilane⁴³ (3.2 g, 18 mmol) in THF (5 mL) was added dropwise while maintaining reflux. The reaction was heated to reflux for 30 min and then cooled to ambient temperature. The Grignard reagent was cannulated into a mixture of iodide **27** (4.10 g, 9.0 mmol), copper(I) iodide (171 mg, 0.9 mmol), HMPA (6.3 mL, 36 mmol), and THF (8.0 mL) at -25 °C. The reaction was stirred 1 h, quenched with saturated aqueous NH_4Cl , and diluted with ether (150 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (80 g SiO_2), using a gradient elution (hexanes to 5% EtOAc in hexanes) provided 3.46 g (91%) of **29** as a clear colorless oil: R_f 0.51 (5% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} -7.85$ (c 1.35, CHCl_3); IR (neat) 3071, 3052, 2957, 2895, 2859, 1588, 1472, 1427, 1248, 1113, 839, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.69–7.67 (m, 4H), 7.43–7.36 (m, 6H), 5.71 (ddd, $J = 3.0$, 1.5, 1.5 Hz, 1H), 5.43 (d, $J = 3.0$ Hz, 1H) 3.80 (A of ABX, $J_{\text{AB}} = 11.9$ Hz, $J_{\text{AX}} = 4.4$ Hz, 1H), 3.76 (B of ABX, $J_{\text{AB}} = 11.9$ Hz, $J_{\text{BX}} = 3.6$ Hz, 1H), 2.97–2.90 (m, 2H), 2.44 (A of ABX, $J_{\text{AB}} = 15.2$ Hz, $J_{\text{AX}} = 5.8$ Hz, 1H), 2.27 (B of ABX, $J_{\text{AB}} = 15.2$ Hz, $J_{\text{BX}} = 5.8$ Hz, 1H), 1.05 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.8, 135.6, 133.3, 129.7, 127.7, 126.4, 63.9, 58.7, 55.6, 37.9, 26.7, 19.2, -1.8 ; MS (EI) m/z (relative intensity) 367 (15), 293 (12), 271 (65), 241 (35), 217 (50), 195 (65), 163 (55), 135 (62), 91 (70), 73 (100); HRMS m/z calcd for $\text{C}_{21}\text{H}_{27}\text{O}_2\text{Si}_2$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 367.1549, found 367.1557. Anal. Calcd for $\text{C}_{25}\text{H}_{36}\text{O}_2\text{Si}_2$: C, 70.70; H, 8.54. Found: C, 70.54; H, 8.51.

(4S,5S)-2-Bromo-6-(tert-butylidiphenylsilyloxy)-4,5-epoxyhex-1-ene (30). A solution of bromine (0.49 mL, 9.5 mmol) and CH_2Cl_2 (10 mL) was added to a solution of alkene **29** (3.1 g, 7.3 mmol) and CH_2Cl_2 (10 mL) at -78 °C. After 10 min, a solution of sodium sulfite (0.55 g, 4.4 mmol) and methanol (10 mL) was added. The resulting mixture stirred 10 min, and aqueous sodium sulfite (10%, 10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was dissolved in methanol (20 mL) and cooled to 0 °C. Sodium methoxide (11.7 mL, 1.0 M in methanol) was added. After 2 h, water (30 mL) and hexanes (30 mL) were added. The organic layer was separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (65 g SiO_2), using a gradient elution (hexanes to 5% EtOAc in hexanes) provided 2.65 g (85%) of **30** as a clear colorless oil: R_f 0.49 (5% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} -3.03$ (c 1.06, CHCl_3); IR (neat) 3071, 3050, 2930, 2855, 1632, 1472, 1427, 1111, 909 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.70–7.66 (m, 4H), 7.44–7.37 (m, 6H), 5.72 (s, 1H), 5.53 (d, $J = 1.9$ Hz, 1H), 3.84 (A of ABX, $J_{\text{AB}} = 11.8$ Hz, $J_{\text{AX}} = 4.5$ Hz, 1H), 3.78 (B of ABX, $J_{\text{AB}} = 11.8$ Hz, $J_{\text{BX}} = 3.4$ Hz, 1H), 3.08 (ddd, $J = 6.0$, 6.0, 2.1 Hz, 1H), 3.01 (ddd, $J = 4.5$, 3.6, 2.1 Hz, 1H), 2.75 (A of ABX, $J_{\text{AB}} = 15.2$ Hz, $J_{\text{AX}} = 6.0$ Hz, 1H), 2.58 (B of ABX, $J_{\text{AB}} = 15.2$ Hz,

$J_{\text{BX}} = 5.6$ Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.6, 133.3, 129.8, 128.4, 127.7, 118.9, 63.6, 58.3, 54.0, 43.8, 26.8, 19.2; MS (CI, CH_4) m/z (relative intensity) 373 (14), 293 (39), 263 (78), 253 (47), 241 (77), 225 (84), 199 (100), 183 (80), 163 (86), 139 (88), 115 (47), 91 (78); HRMS m/z calcd for $\text{C}_{18}\text{H}_{18}\text{BrO}_2\text{Si}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 373.0259, found 373.0260. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{BrO}_2\text{Si}$: C, 61.25; H, 6.31; Br 18.52. Found: C, 61.48; H, 6.31; Br 18.33.

(2R,3S)-5-Bromo-2,3-epoxyhex-5-ene (9). Tetra-*n*-butylammonium fluoride (0.83 mL, 1 M in THF) was added into a flask containing the silyl ether **30** (300 mg, 0.7 mmol), and the reaction stirred 1 h. The mixture was placed directly on a column of silica gel, and purification by flash chromatography using a solvent gradient elution (40% Et_2O in hexanes to 90% Et_2O in hexanes) provided 125 mg (93%) of the expected alcohol as a clear yellow oil: R_f 0.20 (20% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} +14.0$ (c 1.0, CHCl_3); IR (neat) 3404, 2998, 2920, 1632, 1415, 1150, 1010, 897 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.73 (d, $J = 1.1$ Hz, 1H), 5.55 (d, $J = 1.1$ Hz, 1H), 3.96 (A of ABX, $J_{\text{AB}} = 12.7$ Hz, $J_{\text{AX}} = 4.1$ Hz, 1H), 3.69 (B of ABX, $J_{\text{AB}} = 12.7$ Hz, $J_{\text{BX}} = 2.5$ Hz, 1H), 3.21 (m, 1H), 2.77 (A of ABX, $J_{\text{AB}} = 15.3$ Hz, $J_{\text{AX}} = 6.0$ Hz, 1H), 2.65 (B of ABX, $J_{\text{AB}} = 15.3$ Hz, $J_{\text{BX}} = 5.3$ Hz, 1H), 1.90 (br s, 1H–OH); ^{13}C NMR (100 MHz, CDCl_3) δ 128.1, 119.2, 61.2, 58.3, 53.7, 43.6; MS (CI, CH_4) m/z (relative intensity) 191 (1), 182 (3), 163 (50), 161 (35), 135 (10), 121 (10), 84 (100); HRMS m/z calcd for $\text{C}_6\text{H}_9\text{BrO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 214.9702, found 214.9734. Anal. Calcd for $\text{C}_9\text{H}_9\text{O}_2\text{Br}$: C, 37.33; H, 4.70; Br, 41.39. Found: C, 37.55; H, 4.90; Br, 41.10.

Primary alcohol, prepared as described above, (1.5 g, 7.77 mmol) was dissolved in CH_2Cl_2 (28 mL). Sodium bicarbonate (6.5 g, 77.4 mmol) and Dess–Martin periodinane (6.55 g, 15.5 mmol) were added. The reaction mixture was stirred 1.5 h and then placed directly on a column of silica gel. Purification by flash column chromatography using a solvent gradient elution (5% EtOAc in hexanes to 15% EtOAc in hexanes) provided 1.1 g (75%) of aldehyde **9** as a light yellow oil: R_f 0.30 (30% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} +33.4$ (c 1.0, CHCl_3); IR (neat) 2999, 2917, 2836, 2733, 1730, 1632, 1415, 1146, 1018, 901 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.06 (d, $J = 6.2$ Hz, 1H), 5.77 (d, $J = 0.8$ Hz, 1H), 5.60 (d, $J = 1.9$ Hz, 1H), 3.49 (m, 1H), 3.28 (dd, $J = 6.2$, 1.6 Hz, 1H), 2.83 (A of ABX, $J_{\text{AB}} = 15.3$ Hz, $J_{\text{AX}} = 6.1$ Hz, 1H), 2.76 (B of ABX, $J_{\text{AB}} = 15.3$ Hz, $J_{\text{BX}} = 4.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.2, 126.7, 120.1, 58.6, 54.7, 43.0; MS (CI, CH_4) m/z (relative intensity) 161 (5), 151 (3), 135 (7), 121 (10), 88 (45), 86 (87), 84 (100), 83 (48); HRMS m/z calcd for $\text{C}_6\text{H}_7\text{BrO}_2$ (M^+) 189.9502, found 189.9506.

(R)-4-(4'-Methoxybenzyloxy)-3-methyl-2-(trimethylsilylmethyl)-1-butene (31). Cerium(III) chloride heptahydrate (17.2 g, 46.2 mmol) was stirred under 2 mmHg at 150 °C for 7 h. The dried cerium chloride was brought to ambient temperature, and anhydrous THF (46 mL) was added. The suspension was allowed to stir at ambient temperature for 12 h and then cooled to -78 °C. A solution of trimethylsilylmethylmagnesium chloride (46.2 mL, 1 M in Et_2O) was added. After stirring for 30 min, neat (*S*)-3-(4-methoxybenzyloxy)-2-methylpropionic acid methyl ester (2.75 g, 11.5 mmol) was added dropwise over 3 min. The reaction was warmed to ambient temperature and stirred for 4 h. The reaction was then cooled to 0 °C, diluted with ether, and quenched by the addition of saturated aqueous NH_4Cl . The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The residue was diluted with dichloromethane (100 mL) and silica gel (15 g). The suspension was stirred 3 d and filtered by rinsing the silica sequentially with ether, dichloromethane, ethyl acetate. The organic filtrate was concentrated, and the residue was purified by flash column chromatography on neutralized silica using hexanes to provide 1.68 g (50%) of allyl silane **31** as a colorless oil: R_f 0.44 (5% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25} +8.15$ (c 1, CHCl_3); IR (neat) 3077, 2957, 2857, 1615, 1514, 1248, 1036, 853 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.61 (s, 1H), 4.59 (s, 1H), 4.46 (A of AB, $J_{\text{AB}} = 11.6$ Hz, 1H), 4.43 (B of AB, $J_{\text{AB}} = 11.6$ Hz, 1H), 3.81 (s, 3H), 3.49 (A of ABX, $J_{\text{AB}} = 9.1$ Hz, $J_{\text{AX}} = 8.3$ Hz, 1H), 3.20 (B of ABX, $J_{\text{AB}} = 9.1$ Hz, $J_{\text{BX}} = 5.1$ Hz, 1H), 2.24 (m, 1H),

1.56 (A of AB, $J_{AB} = 13.8$ Hz, 1H), 1.51 (B of AB, $J_{AB} = 13.8$ Hz, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 149.8, 130.8, 129.1, 113.7, 106.5, 76.7, 74.8, 72.6, 55.2, 41.0, 26.6, 17.1, -1.3; HRMS m/z calcd for $\text{C}_{17}\text{H}_{28}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{H}$) 291.1780, found 291.1778.

(2R,3S)-2,3-Epoxy-5-trimethylsilylhexa-5-enal (32). Tetra-*n*-butylammonium fluoride (TBAF) (2.6 mL, 1.0 M in THF) was added to a solution of silyl ether **29** (1.00 g, 2.35 mmol) in THF (20 mL) at 0 °C. The reaction stirred 6 h at room and was diluted with Et_2O (10 mL) and H_2O (10 mL). The organic layer was washed with H_2O (2 \times 20 mL), saturated aqueous NH_4Cl (2 \times 15 mL), and brine (20 mL). The combined aqueous layers were extracted with Et_2O (2 \times 15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (28 g SiO_2 , 20% EtOAc in hexanes), which provided 0.440 g (quant.) of the desired primary alcohol as a colorless oil: R_f 0.13 (40% EtOAc in hexanes); $[\alpha]_D^{24} -29.3$ (c 4.88, CHCl_3); IR (neat) 3424, 3052, 2955, 2899, 1412, 1248, 1080, 1017, 930, 841, 758, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.71 (br s, 1H), 5.45 (br s, 1H), 3.93 (A of ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 4.0$ Hz, 1H), 3.65 (B of ABX, $J_{AB} = 12.6$ Hz, $J_{BX} = 2.4$ Hz, 1H), 3.05 (td, $J = 5.8, 2.3$ Hz, 1H), (2.95 (m, 1H), 2.45 (A of ABX, $J_{AB} = 15.3$ Hz, $J_{AX} = 5.9$ Hz, 1H), 2.34 (B of ABX, $J_{AB} = 15.3$ Hz, $J_{BX} = 5.6$ Hz, 1H), 1.63 (br s, 1H-OH), 0.11 (s, 9H); MS (CI, CH_4) m/z (relative intensity) 171 (4), 155 (53), 141 (36), 127 (67), 117 (42), 101 (43), 75 (100), 73 (87); HRMS m/z calcd for $\text{C}_8\text{H}_{15}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{CH}_3$) 171.0841, found 171.0839.

Sulfur trioxide pyridine complex (1.12 g, 7.05 mmol) was added into a solution of the alcohol, as prepared above, in DMSO (2 mL, 28.2 mmol), Et_3N (2 mL, 14.1 mmol), and CH_2Cl_2 (15 mL). After the reaction mixture was stirred for 17 h at ambient temperature, pentane (50 mL) and water (10 mL) were added. The organic layer was washed with NH_4Cl (3 \times 15 mL) and H_2O (2 \times 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (16 g SiO_2 , 20% Et_2O in hexanes), which provided 300 mg (69%) of aldehyde **32** as a colorless oil: R_f 0.57 (40% EtOAc in hexanes); $[\alpha]_D^{23} +91.3$ (c 3.14, CHCl_3); IR (neat) 3054, 2957, 2899, 2822, 2731, 1728, 1429, 1250, 934, 839, 727 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.04 (d, $J = 6.2$ Hz, 1H), 5.73 (d, $J = 1.9$ Hz, 1H), 5.50 (d, $J = 1.9$ Hz, 1H), 3.32 (td, $J = 5.5, 1.9$ Hz, 1H), 3.16 (dd, $J = 6.3, 2.0$ Hz, 1H), 2.47 (d, $J = 5.6$ Hz, 2H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.1, 146.8, 127.5, 59.1, 56.1, 37.3, -1.8; MS (CI, CH_4) m/z (relative intensity) 169 (5), 141 (17), 127 (17), 101 (16), 95 (13), 75 (62), 73 (100); HRMS m/z calcd for $\text{C}_8\text{H}_{13}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{CH}_3$) 169.0685, found 169.0687. Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_2\text{Si}$: C, 58.65; H, 8.75. Found: C, 58.36; H, 8.58.

(2R,5S,6S,7S)-6,7-Epoxy-1-(4-methoxybenzyloxy)-2-methyl-3-methylene-9-trimethylsilyldec-9-en-5-ol (33). Freshly distilled boron trifluoride diethyl etherate (9.6 mL, 0.076 mmol) was added to a -78 °C solution of allylsilane **31**, aldehyde **32**, and CH_2Cl_2 . After the reaction stirred 45 min, saturated aqueous NaHCO_3 was added. The mixture was transferred to separatory funnel using Et_2O (10 mL). The organic layer was washed with NaHCO_3 (5 mL), H_2O (5 mL), and brine (5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The proton NMR spectra of the crude material indicated a >2:1 mixture of C_7 diastereomeric alcohols. Purification of the crude residue was carried out by flash column chromatography (4 g SiO_2 , 10% EtOAc in hexanes), which provided 10.4 mg (34%) of alcohol **33** as a colorless oil. A second compound (R_f 0.18 (20% EtOAc in hexanes)) was also isolated. This minor 7*R*-diastereomer was not purified for further characterization. Partial characterization data for the alcohol diastereomer **33**: R_f 0.19 (20% EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.74 (dt, $J = 2.7, 1.5$ Hz, 1H), 5.45 (dt, $J = 2.7, 1.1$ Hz, 1H), 4.98 (s, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.74 (m, 1H), 3.42 (A of ABX, $J_{AB} = 9.1$ Hz, $J_{AX} = 7.3$ Hz, 1H), 3.34 (B of ABX, $J_{AB} = 9.1$ Hz, $J_{BX} = 6.4$ Hz, 1H), 3.08 (td, $J = 5.7, 2.2$ Hz, 1H), 2.77 (dd, $J = 4.6, 2.1$ Hz, 1H), 2.51 (m, 1H), 2.42 (A of ABX, $J_{AB} = 14.2$ Hz, $J_{AX} = 9.4$ Hz, 1H), 2.37 (d, $J =$

$J = 5.6$ Hz, 2H), 2.21 (B of ABX, $J_{AB} = 14.2$ Hz, $J_{BX} = 3.5$ Hz, 1H), 2.59 (s, 1H-OH), 1.06 (d, $J = 7.0$ Hz, 3H), 0.11 (s, 9H).

(2R,5S,6S,7S)-9-Bromo-6,7-epoxy-1-(4-methoxybenzyloxy)-2-methyl-3-methylene-dec-9-en-5-ol (35). Allylsilane **31** (2.02 g, 6.91 mmol) and aldehyde **9** (1.1 g, 5.76 mmol) were dissolved in CH_2Cl_2 (58 mL) and cooled to -78 °C. Boron trifluoride diethyl etherate (0.85 mL, 6.91 mmol) was added, and the reaction was stirred 2 h at -78 °C. Saturated aqueous Na_2CO_3 (50 mL) was then added, and the mixture was allowed to warm to ambient temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 \times 50 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (200 g silica gel), using a solvent gradient elution (5% EtOAc in hexanes to 30% EtOAc in hexanes) provided 1.2 g (51%) of alcohol **35** and 310 mg (13%) of alcohol **36** as colorless oils. Data for **35**: R_f 0.25 (30% EtOAc in hexanes); $[\alpha]_D^{23} -6.29$ (c 1.34, CHCl_3); IR (neat) 3449, 2961, 2932, 2907, 2859, 1632, 1613, 1512, 1246, 1034, 895, 820 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.74 (d, $J = 1.3$ Hz, 1H), 5.54 (d, $J = 1.6$ Hz, 1H), 4.98 (s, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.80 (m, 1H), 3.41 (A of ABX, $J_{AB} = 9.1$ Hz, $J_{AX} = 7.6$ Hz, 1H), 3.35 (B of ABX, $J_{AB} = 9.1$ Hz, $J_{BX} = 6.1$ Hz, 1H), 3.22 (td, $J = 5.6, 2.1$ Hz, 1H), 2.87 (dd, $J = 4.3, 2.1$ Hz, 1H), 2.72 (A of ABX, $J_{AB} = 15.6$ Hz, $J_{AX} = 6.0$ Hz, 1H), 2.66 (B of ABX, $J_{AB} = 15.6$ Hz, $J_{BX} = 5.0$ Hz, 1H), 2.58 (br s, 1H-OH), 2.52 (q, $J = 6.9$ Hz, 1H), 2.45 (A of ABX, $J_{AB} = 14.3$ Hz, $J_{AX} = 9.4$ Hz, 1H), 2.24 (B of ABX, $J_{AB} = 14.3$ Hz, $J_{BX} = 3.5$ Hz, 1H), 1.06 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.3, 148.3, 130.3, 129.3, 128.4, 118.9, 113.8, 112.7, 74.6, 72.8, 68.7, 60.5, 55.3, 53.9, 43.8, 40.1, 39.7, 17.2; MS (CI, CH_4) m/z (relative intensity) 410 (0.3), 203 (10), 137 (41), 122 (46), 121 (100), 82 (21); HRMS m/z calcd for $\text{C}_{20}\text{H}_{27}\text{BrO}_4$ (M^+) 410.1093, found 410.1087. Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{BrO}_4$: C, 58.40; H, 6.62; Br, 19.43. Found: C, 58.12; H, 6.59; Br, 19.41

Data for the minor product, 7(*R*)-diastereomer **36**: R_f 0.13 (30% EtOAc in hexanes); $[\alpha]_D^{24} +4.09$ (c 1.20, CHCl_3); IR (neat) 3441, 3075, 2938, 2870, 1613, 1512, 1460, 1240, 1030, 897 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, $J = 6.3$ Hz, 1H), 6.85 (d, $J = 6.3$ Hz, 1H), 5.71 (d, $J = 1.2$ Hz, 1H), 5.51 (d, $J = 1.2$ Hz, 1H), 4.97 (s, 1H), 4.96 (s, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.75 (ddd, $J = 4.5, 4.5, 3.3$ Hz, 1H), 3.41 (dd, $J = 6.9, 6.3$ Hz, 1H), 3.33 (dd, $J = 6.9, 4.5$ Hz, 1H), 3.16 (ddd, $J = 4.5, 4.5, 1.5$ Hz, 1H), 2.89 (dd, $J = 3.3, 1.5$ Hz, 1H), 2.73 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.60 (dd, $J = 14.4, 3.9$ Hz, 1H), 2.45 (m, 1H), 2.32 (d, $J = 4.8$ Hz, 2H), 1.01 (d, $J = 5.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.2, 147.7, 130.0, 129.3, 128.3, 119.0, 113.8, 112.9, 74.2, 72.7, 68.6, 61.0, 55.2, 54.1, 43.7, 40.3, 39.0, 17.4; MS (CI, CH_4) m/z (relative intensity) 410 (3), 331 (4), 273 (9), 203 (20), 137 (55); HRMS m/z calcd for $\text{C}_{20}\text{H}_{27}\text{BrO}_4$ (M^+) 410.1093, found 410.1095. Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{BrO}_4$: C, 58.40; H, 6.62; Br, 19.43. Found: C, 57.81; H, 6.63; Br, 19.35.

(2R,5S,6S,7S)-9-Bromo-5-(tert-butylidimethylsilyloxy)-6,7-epoxy-1-(4-methoxybenzyloxy)-2-methyl-3-methylene-dec-9-ene (39). *tert*-Butylidimethylsilyl trifluoromethanesulfonate (1.19 mL, 5.2 mmol) was added to a solution of alcohol **35** (1.07 g, 2.6 mmol), and *N,N*-diisopropylethylamine (2.27 mL, 13.0 mmol) in CH_2Cl_2 (11.6 mL). The reaction was stirred 2.5 h and diluted with CH_2Cl_2 (30 mL), and saturated aqueous NH_4Cl (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 \times 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (150 g SiO_2 using 5% EtOAc in hexanes) gave 0.98 g (74%) of compound **39** as a clear colorless oil: R_f 0.47 (20% EtOAc in hexanes); $[\alpha]_D^{23} -2.2$ (c 1.5, CHCl_3); IR (neat) 3079, 2955, 2930, 2857, 1632, 1613, 1512, 1248, 1103, 835, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.72 (d, $J = 1.6$ Hz, 1H), 5.52 (d, $J = 1.6$ Hz, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 4.44 (A of AB, $J_{AB} = 11.8$ Hz, 1H), 4.42 (B of AB, $J_{AB} = 11.8$ Hz, 1H), 3.82 (m, 1H), 3.80 (s, 3H), 3.46 (A of ABX, $J_{AB} = 9.1$ Hz, $J_{AX} = 7.9$ Hz, 1H), 3.26 (B of ABX, $J_{AB} = 9.1$ Hz, $J_{BX} = 5.6$ Hz, 1H), 3.15 (m, 1H), 2.81 (dd, $J = 4.0, 2.0$ Hz, 1H), 2.67 (A of ABX, $J_{AB} = 15.4$ Hz, $J_{AX} = 6.6$ Hz, 1H), 2.61 (B of ABX, $J_{AB} = 15.4$ Hz, $J_{BX} = 4.2$ Hz, 1H), 2.45 (q, $J = 6.7$ Hz, 1H), 2.36

(A of ABX, $J_{AB} = 14.2$ Hz, $J_{AX} = 6.6$ Hz, 1H), 2.29 (B of ABX, $J_{AB} = 14.2$ Hz, $J_{BX} = 5.5$ Hz, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 147.5, 130.7, 129.1, 128.7, 118.8, 113.8, 112.3, 74.5, 72.7, 69.5, 60.5, 55.3, 53.7, 43.9, 41.3, 39.4, 25.8, 18.1, 16.9, -4.4, -4.8; MS (CI, CH_4) m/z (relative intensity) 467 (1), 343 (2), 228 (7), 197 (21), 135 (18), 122 (61), 121 (100); HRMS m/z calcd for $\text{C}_{26}\text{H}_{42}\text{BrO}_4\text{Si}$ ($\text{M}^+ + 1$) 525.2054, found 525.2070. Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{BrO}_4\text{Si}$: C, 59.42; H, 7.86; Br, 15.20. Found: C, 59.67; H, 7.90; Br, 15.26.

(2R,5S,6S,7S)-9-Bromo-5-(tert-butylidimethylsilyloxy)-6,7-epoxy-2-methyl-3-methylene-dec-9-en-1-ol (40). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (807 mg, 3.56 mmol) was added to a solution of the PMB ether **39** (890 mg, 1.69 mmol), aqueous pH 7 buffer (5.9 mL), *tert*-butyl alcohol (5.9 mL), and CH_2Cl_2 (29.6 mL). After the red reaction stirred for 1.5 h at room temperature, it was diluted with CH_2Cl_2 (40 mL), and saturated aqueous NaHCO_3 (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with saturated NaHCO_3 (25 mL), H_2O (25 mL), and brine (30 mL), dried over Na_2SO_4 , and then filtered and concentrated in vacuo. Purification of the residual oil by flash column chromatography (75 g SiO_2), using a solvent gradient elution (10% EtOAc in hexanes to 50% EtOAc in hexanes) gave 622 mg (95%) of primary alcohol **40** as a clear colorless oil: R_f 0.23 (20% EtOAc in hexanes); $[\alpha]_D^{23} +18.2$ (c 1.0, CHCl_3); IR (neat) 3451, 2955, 2930, 2857, 1632, 1472, 1254, 1107, 837, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.72 (d, $J = 1.8$ Hz, 1H), 5.53 (d, $J = 1.9$ Hz, 1H), 5.05 (d, $J = 1.1$ Hz, 1H), 4.99 (s, 1H), 3.73 (dt, $J = 6.2$, 5.2 Hz, 1H), 3.56 (m, 2H), 3.13 (m, 1H), 2.84 (dd, $J = 5.2$, 2.1 Hz, 1H), 2.68 (A of ABX, $J_{AB} = 15.4$ Hz, $J_{AX} = 6.4$ Hz, 1H), 2.64 (B of ABX, $J_{AB} = 15.4$ Hz, $J_{BX} = 4.5$ Hz, 1H), 2.40 (A of ABX, $J_{AB} = 14.1$ Hz, $J_{AX} = 6.3$ Hz, 1H), 2.37 (m, 1H), 2.34 (B of ABX, $J_{AB} = 14.1$ Hz, $J_{BX} = 6.1$ Hz, 1H), 1.84 (s, 1H-OH), 1.06 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.8, 128.4, 119.0, 113.4, 70.3, 66.2, 60.6, 54.6, 43.8, 41.9, 41.8, 25.8, 18.1, 16.5, -4.4, -4.7; MS (CI, CH_4) m/z (relative intensity) 389 (1), 330 (4), 305 (40), 249 (30), 225 (60), 197 (40), 157 (50), 115 (77), 75 (100); HRMS m/z calcd for $\text{C}_{18}\text{H}_{33}\text{BrO}_3\text{SiNa}$ ($\text{M}^+ + \text{Na}$) 427.1281, found 427.1288.

(2R,5S,6S,7S)-9-Bromo-5-(tert-butylidimethylsilyloxy)-6,7-epoxy-2-methyl-3-methylene-dec-9-enal (41). Alcohol **40** (310 mg, 0.76 mmol) was dissolved in CH_2Cl_2 (38 mL). Sodium bicarbonate (642 mg, 7.6 mmol) and Dess–Martin periodinane (648 mg, 1.53 mmol) were then added. The reaction mixture was stirred for 1.5 h, and the mixture was placed directly on a column of silica gel (100 g). Purification by flash column chromatography using 15% EtOAc in hexanes provided 277 mg (90%) of aldehyde **41** as a colorless oil: R_f 0.48 (20% EtOAc in hexanes); $[\alpha]_D^{23} +24.5$ (c 1.0, CHCl_3); IR (neat) 2930, 2857, 1723, 1632, 1462, 1254, 1096, 837, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.48 (d, $J = 1.9$ Hz, 1H), 5.72 (d, $J = 1.0$ Hz, 1H), 5.53 (d, $J = 1.6$ Hz, 1H), 5.18 (s, 1H), 5.02 (s, 1H), 3.77 (q, $J = 5.4$ Hz, 1H), 3.13 (m, 2H), 2.81 (dd, $J = 4.6$, 2.2 Hz, 1H), 2.69 (A of ABX, $J_{AB} = 15.5$ Hz, $J_{AX} = 6.9$ Hz, 1H), 2.63 (B of ABX, $J_{AB} = 15.5$ Hz, $J_{BX} = 4.3$ Hz, 1H), 2.38 (m, 2H), 1.24 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 141.7, 128.3, 119.0, 116.4, 69.8, 60.1, 54.3, 52.6, 43.8, 41.6, 25.8, 18.1, 12.8, -4.4, -4.9; MS (CI, CH_4) m/z (relative intensity) 401 (9), 347 (12), 305 (40), 249 (35), 225 (58), 197 (53), 155 (63), 105 (100), 75 (95) HRMS m/z calcd for $\text{C}_{18}\text{H}_{31}\text{BrO}_3\text{Si}$ (M^+) 402.1226, found 402.1230.

(4R,7S,8S,9S)-11-Bromo-7-(tert-butylidimethylsilyloxy)-8,9-epoxy-4-methyl-5-methylene-3-oxo-dodec-11-enoic acid methyl ester (42). *n*-Butyllithium (0.54 mL, 2.5 M in hexanes) was added to diisopropylamine (0.20 mL, 1.43 mmol) in THF (2.6 mL) at -78°C . After 10 min, distilled methyl acetate (0.5 M in THF, 2.4 mL, 1.2 mmol) was added. The resulting reaction mixture was stirred for 15 min, and aldehyde **41** (160 mg, 0.397 mmol) was then added dropwise. After an additional 20 min at -78°C , the reaction was quenched by the addition of saturated aqueous NH_4Cl and was diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried

over NaSO_4 , filtered, and concentrated in vacuo, which provided 188 mg (99%) of a mixture of β -hydroxy esters as a clear colorless oil: R_f 0.11 (20% EtOAc in hexanes).

The mixture of alcohols (188 mg, 0.394 mmol), prepared as described above, was dissolved in CH_2Cl_2 (12.6 mL). Sodium bicarbonate (440 mg, 5.25 mmol) and Dess–Martin periodinane (334 mg, 0.787 mmol) were added. After stirring at room temperature for 1 h, the mixture was placed directly on a column of silica gel (70 g). Purification by flash column chromatography using 15% EtOAc in hexanes provided 121 mg (65%, 2 steps) of the β -ketoester **42** as a light yellow oil: R_f 0.34 (15% EtOAc in hexanes); $[\alpha]_D^{23} -19.5$ (c 1.42, CHCl_3); IR (neat) 2857, 1750, 1715, 1634, 1468, 1254, 1119, 837, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.71 (s, 1H), 5.52 (d, $J = 1.7$ Hz, 1H), 5.13 (s, 1H), 5.03 (s, 1H), 3.77 (m, 1H), 3.71 (s, 3H), 3.52 (A of AB, $J_{AB} = 15.8$ Hz, 1H), 3.50 (B of AB, $J_{AB} = 15.8$ Hz, 1H), 3.37 (q, $J = 6.9$ Hz, 1H), 3.13 (m, 1H), 2.80 (dd, $J = 4.8$, 1.9 Hz, 1H), 2.68 (A of ABX, $J_{AB} = 15.4$ Hz, $J_{AX} = 6.5$ Hz, 1H), 2.62 (B of ABX, $J_{AB} = 15.4$ Hz, $J_{BX} = 4.0$ Hz, 1H), 2.34 (d, $J = 5.7$ Hz, 2H), 1.25 (d, $J = 6.9$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.0, 167.7, 143.1, 128.4, 119.0, 116.2, 69.7, 60.2, 54.3, 53.3, 52.3, 46.3, 43.8, 41.1, 25.7, 18.1, 15.1, -4.4, -4.8; MS (CI, CH_4) m/z (relative intensity) 419 (6), 417 (5), 305 (8), 269 (5), 225 (13), 101 (26), 75 (100); HRMS m/z calcd for $\text{C}_{21}\text{H}_{36}\text{BrO}_5\text{Si}$ ($\text{M}^+ + 1$) 475.1533, found 475.1551. Anal. Calcd for $\text{C}_{21}\text{H}_{35}\text{O}_5\text{BrSi}$: C, 53.05; H, 7.42; Br, 16.80. Found: C, 53.33; H, 7.45; Br, 16.89.

(2S,3R)-2,3-Epoxy-1-[(4-methoxyphenyl)diphenylmethoxy]butane (44). Titanium(IV) isopropoxide (1.2 mL, 4.2 mmol) was added to a solution of crushed, flame-dried 4 Å molecular sieves (3 g), (+)-diethyl tartrate (0.86 mL, 5.0 mmol), and CH_2Cl_2 (200 mL) at -20°C . The reaction was stirred 10 min, and a solution of *cis*-but-2-en-1-ol (6.0 g, 83 mmol) and CH_2Cl_2 (5 mL) was added dropwise. After stirring the reaction for 30 min at -20°C , *tert*-butyl hydroperoxide (33 mL, 3.77 M in toluene) was added dropwise. The reaction was stirred for 1 h, sealed with parafilm, and placed in a -20°C freezer. After 25 h, the reaction was placed in a -20°C bath under argon, and trimethylphosphite (4.9 mL, 42 mmol) was added to the reaction over 1.6 h. The reaction stirred 15 min. Triethylamine (23 mL, 170 mmol), dimethylaminopyridine (DMAP) (0.5 g), and 4-methoxytrityl chloride (MMTrCl) (28 g, 92 mmol) were added. The reaction was warmed to 0°C , stirred 6 h, and placed in a 0°C freezer overnight. Thin layer chromatography indicated the reaction was not complete, and additional MMTrCl (2 g, 6.6 mmol) was then added. After stirring 3 h at 0°C , MeOH (10 mL) was added. The reaction mixture was then filtered through a silica (40 g) and Celite (25 g) pad using CH_2Cl_2 . The filtrate was concentrated in vacuo. Hexanes (400 mL) were added to the resulting thick paste, which was transferred to a fritted funnel. The filtrate was again concentrated in vacuo. Purification by flash column chromatography (800 g SiO_2), using a solvent gradient elution (hexanes to 30% EtOAc in hexanes) provided 24 g (80%) of **44** as a thick oil: R_f 0.48 (40% EtOAc in hexanes); $[\alpha]_D^{23} +16.0$ (c 3.95, CHCl_3); IR (neat) 3032, 2928, 1607, 1501, 1447, 1250, 1179, 1034 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (m, 4H), 7.21–7.36 (m, 8H), 6.83 (m, 2H), 3.80 (s, 3H), 3.30 (A of ABX, $J_{AB} = 9.94$ Hz, $J_{AX} = 5.37$ Hz, 1H), 3.18 (m, 1H), 3.12 (B of ABX, $J_{AB} = 9.8$ Hz, $J_{BX} = 4.8$ Hz, 1H), 3.09 (m, 1H), 1.14 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.5, 144.4, 144.2, 135.5, 130.3, 128.3, 127.8, 126.9, 113.1, 86.5, 61.9, 55.3, 55.2, 52.1, 13.4; MS (EI) m/z (relative intensity) 360 (20), 273 (100), 213 (25), 165 (20), 135 (18), 105 (37); HRMS m/z calcd for $\text{C}_{24}\text{H}_{24}\text{O}_3$ (M^+) 360.1725, found 360.1734.

(2R,3R)-1-[(4-Methoxyphenyl)diphenylmethoxy]-3,4-dimethylpent-4-en-2-ol (45). 1,2-Dibromoethane (3 drops) was added to a solution of 2-bromopropene (10 drops), flame-dried Mg turnings (3.1 g), and THF (30 mL). 2-Bromopropene (5.7 mL, 64.6 mmol) and THF (60 mL) were then simultaneously added via separate syringes maintaining a steady reflux. The reaction was stirred 1.5 h and cannulated into a -78°C slurry of $\text{CuBr}\cdot\text{DMS}$ (6.6 g, 32.3 mmol) and THF (20 mL). The deep orange reaction stirred 15 min, and a solution of epoxide **44** (7.76 g, 21.5 mmol) and THF (80 mL) was added. After 15 min, $\text{BF}_3\cdot\text{OEt}_2$ (2.5 mL, 14.4 mmol) was added dropwise. The reaction was warmed slowly to -20°C over 2 h, at

which time it turned black. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was transferred to a separatory funnel with Et_2O . The organic layer was washed with H_2O (2×100 mL) and brine (150 mL). The aqueous layers were extracted with Et_2O (50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (400 g SiO_2), using a solvent gradient elution (hexanes to 10% Et_2O in hexanes) provided 7.15 g (84%) of alcohol **45** as a thick clear colorless oil, which crystallized upon storage in a -20 °C freezer. Mosher ester analysis indicated 83% ee by ^1H NMR integration of selected signals. Characterization data for **45**: mp 94 – 97 °C; R_f 0.40 (20% Et_2O in hexanes); $[\alpha]_D^{23}$ -4.03 (c 1.49, CHCl_3); IR (neat) 3584, 3061, 2965, 2930, 1607, 1510, 1447, 1250, 1090, 1036, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (m, 4H), 7.21–7.36 (m, 8H), 6.84 (m, 2H), 4.82 (s, 1H), 4.79 (s, 1H), 3.80 (s, 3H), 3.60 (m, 1H), 3.32 (A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 6.5$ Hz, 1H), 3.05 (B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 3.0$ Hz, 1H), 2.40 (dq, $J = 8.5, 6.8$ Hz, 1H), 2.27 (d, $J = 3.4$ Hz, 1H), 1.68 (s, 3H), 0.83 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.5, 147.5, 144.5, 144.4, 135.6, 130.3, 128.4, 127.8, 126.9, 113.1, 86.3, 72.5, 65.5, 55.2, 44.4, 19.1, 15.6; MS (CI, CH_4) m/z (relative intensity) 402 (8), 325 (3), 273 (100), 213 (9), 143 (8); HRMS m/z calcd for $\text{C}_{27}\text{H}_{30}\text{O}_3$ (M^+) 402.2195, found 402.2197.

(2R,3R)-2-(tert-Butyldimethylsilyloxy)-1-[(4-methoxyphenyl)diphenylmethoxy]-3,4-dimethylpent-4-ene (46). Alcohol **45** (3.55 g, 8.82 mmol), *tert*-butyldimethylsilyl chloride (1.6 g, 11 mmol), dimethylaminopyridine (DMAP) (54 mg, 0.44 mmol), and imidazole (1.2 g, 18 mmol) were stirred in DMF (15 mL) at ambient temperature 4 days. The reaction mixture was diluted with hexanes (50 mL) and extracted with saturated aqueous NH_4Cl (3×10 mL), H_2O (10 mL), and brine (15 mL). The combined aqueous layers were extracted with hexanes (3×15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (150 g SiO_2 , 5% EtOAc in hexanes), which provided 4.1 g (92%) of **46** as a thick oil: R_f 0.60 (20% EtOAc in hexanes); $[\alpha]_D^{24}$ $+4.74$ (c 1.02, CHCl_3); IR (neat) 3063, 2955, 2857, 1609, 1510, 1252, 1179, 1067, 1038, 833, 774, 704 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (m, 4H), 7.35 (m, 2H), 7.29 (m, 4H), 7.23 (m, 2H), 6.84 (m, 2H), 4.69 (s, 2H), 3.82 (s, 3H), 3.78 (m, 1H), 3.05 (d, $J = 6.3$ Hz, 2H), 2.57 (dq, $J = 7.3, 4.0$ Hz, 1H), 1.67 (s, 3H), 1.01 (d, $J = 7.3$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.4, 146.8, 144.8, 136.1, 130.4, 128.5, 127.6, 112.9, 111.9, 86.3, 74.6, 65.6, 55.2, 44.1, 25.9, 21.5, 18.0, 15.4, -4.3 , -5.0 ; MS (CI, CH_4) m/z (relative intensity) 273 (100), 265 (50), 229 (10), 213 (30), 197 (30); HRMS (FAB, Na) m/z calcd for $\text{C}_{33}\text{H}_{44}\text{O}_3\text{SiNa}$ (M^+Na^+) 539.2958, found 539.2956. Anal. Calcd for $\text{C}_{33}\text{H}_{44}\text{O}_3\text{Si}$: C, 76.70; H, 8.58. Found: C, 76.98; H, 8.63.

(2R,3R)-2-(tert-Butyldimethylsilyloxy)-3,4-dimethylpent-4-en-1-ol (47). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.8 g, 7.7 mmol) was added to a solution of MMTr ether **46** (1.02 g, 1.94 mmol), *tert*-butyl alcohol (6 mL), aqueous pH 7 buffer (6 mL), and CH_2Cl_2 (30 mL). The red reaction was stirred 18 h, quenched with saturated aqueous NaHCO_3 (10 mL), and transferred to a separatory funnel using CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (15 mL), H_2O (15 mL), and brine (20 mL); dried over MgSO_4 ; filtered; and concentrated in vacuo. The residue was taken up in hexanes (20 mL). The organic layer was washed with NaHCO_3 (10 mL), H_2O (10 mL), and brine (15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo to provide an orange oil. Purification by flash column chromatography (50 g SiO_2), using a solvent gradient elution (hexanes to 10% EtOAc in hexanes) provided 373 mg (73%) of alcohol **47** as a clear colorless oil, which could be further purified by Kugelrohr distillation (90 °C, 0.2 mmHg). Chromatography led to the recovery of starting ether **46** (20% yield), which was recycled. Data for **47**: R_f 0.55 (20% EtOAc in hexanes); $[\alpha]_D^{23}$ $+2.93$ (c 2.00, CHCl_3); IR (neat) 3426, 3073, 2957, 2930, 2859, 1642, 1462, 1256, 1065, 812, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.80 (s, 1H), 4.77 (s, 1H), 3.77 (m, 1H), 3.54 (d, $J =$

4.8 Hz, 2H), 2.42 (dq, $J = 6.9, 6.7$ Hz, 1H), 1.65 (s, 3H), 1.70 (br s, 1H–OH), 1.04 (d, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.1, 111.7, 74.7, 64.0, 44.0, 25.8, 23.3, 21.4, 14.4, -4.5 , -4.7 ; MS (CI, CH_4) m/z (relative intensity) 227 (1), 213 (4), 175 (11), 159 (8), 137 (7), 115 (10), 95 (11), 87 (37), 85 (80), 83 (100); HRMS m/z calcd for $\text{C}_{13}\text{H}_{28}\text{O}_2\text{Si}$ (M^+) 244.1831, found 244.1829. Anal. Calcd for $\text{C}_{13}\text{H}_{28}\text{O}_2\text{Si}$: C, 63.87; H, 11.55. Found: C, 63.57; H, 11.48.

An alternate procedure for the preparation of alcohol **47** was carried as follows: ceric ammonium nitrate ($\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$) (1.00 g, 1.82 mmol) was added to a solution of **46** (510 mg, 0.987 mmol), CH_2Cl_2 (12 mL), and H_2O (0.5 mL). The reaction stirred 2.5 h, and additional ($\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$) (0.25 g) and water (1.0 mL) were then added. After 4 h, the reaction mixture was slowly quenched with saturated aqueous NaHCO_3 . The mixture was diluted with CH_2Cl_2 , and the organic layer was separated, washed with saturated aqueous NaHCO_3 (10 mL), H_2O (10 mL), and then brine (15 mL). It was then dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (40 g SiO_2 , 10% EtOAc in Hexanes) provided 200 mg (83%) of alcohol **47** as a clear colorless oil. This material was identical to the sample prepared above.

(2R,3R)-2-(tert-Butyldimethylsilyloxy)-3,4-dimethylpent-4-enal (48). Dimethylsulfoxide (0.46 mL, 6.55 mmol) was added dropwise to a solution of oxalyl chloride (0.29 mL, 3.3 mmol) and CH_2Cl_2 (8 mL) at -78 °C. After 20 min, a solution of alcohol **47** (400 mg, 1.6 mmol) and CH_2Cl_2 (4 mL) was added. The reaction stirred 30 min at -78 °C, and Et_3N (1.8 mL, 13 mmol) was added dropwise. The reaction was stirred 30 min at -78 °C, warmed to ambient temperature, and diluted with pentane (30 mL) and H_2O (10 mL). The organic layer was washed with H_2O (15 mL), saturated aqueous NH_4Cl (3×15 mL), and brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. Proton NMR and TLC indicated that alcohol **47** was cleanly converted to aldehyde **48**, and this material was used directly in the subsequent reactions without further purification. Data for **48**: R_f 0.60 (20% EtOAc in hexanes); IR (neat) 3075, 2957, 2932, 2897, 2859, 1736, 1462, 1256, 1080, 839, 779 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.53 (d, $J = 2.2$ Hz, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 3.9 (dd, $J = 5.5, 2.2$ Hz, 1H), 2.59 (dq, $J = 7.0, 5.5$ Hz, 1H), 1.74 s (3H), 1.09 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.054 (s, 3H), 0.047 (s, 3H); MS (CI, CH_4) m/z (relative intensity) 241 (3), 213 (32), 185 (100), 155 (13), 115 (9), 83 (40), 73 (45), 75 (45); HRMS m/z calcd for $\text{C}_{13}\text{H}_{26}\text{O}_2\text{Si}$ (M^+) 242.1667, found 242.1671.

(3R,4R)-4-(tert-Butyldimethylsilyloxy)-2,3-dimethylhex-1-en-5-yne (49). Triphenylphosphine (2.6 g, 9.8 mmol) was added to a 0 °C solution of CBr_4 (1.6 g, 4.9 mmol), and CH_2Cl_2 (15 mL). The reaction stirred 10 min and was cooled to -78 °C. A solution of aldehyde **48** (398 mg, 1.64 mmol) in CH_2Cl_2 (5 mL) was added. After the reaction stirred 2 h at -78 °C, it was diluted with hexanes (30 mL) and water (5 mL). The organic layer was washed with H_2O (10 mL), saturated aqueous NH_4Cl (15 mL), and brine (20 mL), dried over MgSO_4 , filtered through a plug of silica, and concentrated in vacuo. Purification by flash column chromatography (16 g SiO_2), using a solvent gradient elution (hexanes to 5% EtOAc in hexanes) provided 470 mg of (3R,4R)-1,1-dibromo-3-(*tert*-butyldimethylsilyloxy)-4,5-dimethylhexa-1,5-diene (72%, 2 steps from **47**) as a clear colorless oil: R_f 0.73 (20% EtOAc in hexanes); $[\alpha]_D^{23}$ -16.8 (c 1.64, CHCl_3); IR (neat) 3075, 2957, 2930, 2859, 1649, 1616, 1462, 1375, 1254, 1074, 839, 775 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.34 (d, $J = 8.6$ Hz, 1H), 4.79 (t, $J = 1.6$ Hz, 1H), 4.74 (s, 1H), 4.23 (dd, $J = 8.6, 6.7$ Hz, 1H), 2.3 (dq, $J = 7.0, 6.7$ Hz, 1H), 1.73 (s, 3H), 1.03 (d, $J = 7.1$ Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.2, 140.9, 112.4, 88.9, 76.1, 47.0, 25.7, 20.6, 18.0, 15.2, -4.4 , -5.2 ; HRMS m/z calcd for $\text{C}_{14}\text{H}_{26}\text{Br}_2\text{OSi}$ (M^+) 398.0195, found 398.0186.

n-Butyllithium (0.35 mL, 2.5 M in hexanes) was added to a -78 °C solution of the dibromide prepared above (150 mg, 0.377 mmol) and THF (2.5 mL). The reaction stirred for 1.5 h while warming to -50 °C. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was transferred to a separatory funnel using Et_2O (10 mL). The organic layer was washed with water (5 mL) and brine (10 mL), dried over

MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (8 g SiO₂, pentane) provided 65.5 mg (73%) of the alkyne **49** as a clear colorless oil: *R*_f 0.55 (hexanes); [α]_D²³ +46.2 (c 1.8, CHCl₃); IR (neat) 3312, 3077, 2957, 2932, 2859, 1649, 1462, 1252, 1098, 837, 777, 629 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.82 (s, 1H), 4.81 (s, 1H), 4.31 (dd, *J* = 6.7, 2.1 Hz, 1H), 2.39 (m, 2H), 1.73 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.1, 112.1, 84.4, 73.1, 66.1, 47.7, 25.7, 20.7, 18.2, 14.8, -4.5, -5.3; MS (CI, CH₄) *m/z* (relative intensity) 238 (5), 223 (47), 181 (82), 169 (70), 139 (49), 113 (49), 85 (100), 75 (70); HRMS *m/z* calcd for C₁₄H₂₆O₂Si (M⁺) 238.1753, found 238.1748.

(1E,3R,4R)-4,5-Dimethyl-1-(tributylstannyl)hexa-1,5-dien-3-ol (4). Tri-*n*-butylstannane (0.37 mL, 1.36 mmol) was added to a solution of alkyne **49** (290 mg, 1.21 mmol) and PdCl₂(PPh₃)₂ (17.1 mg, 0.024 mmol) in THF (6.1 mL). After 15 min, the reaction was concentrated in vacuo. Purification by flash column chromatography (40 g silica gel, hexanes) gave the alkenyl stannane **50** as a colorless oil: *R*_f 0.57 (hexanes); [α]_D²⁶ +14.0 (c 0.865, CHCl₃); IR (neat) 2957, 2928, 2857, 1462, 1375, 1254, 1096, 1061, 835, 775 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.02 (d, *J* = 19.1 Hz, 1H), 5.85 (dd, *J* = 19.1, 6.3 Hz, 1H), 4.75 (s, 1H), 4.70 (s, 1H), 3.98 (apparent t, *J* = 6.3 Hz, 1H), 2.42 (apparent q, *J* = 6.8 Hz, 1H), 1.72 (s, 3H), 1.50 (m, 6H), 1.30 (m, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.89 (m, 15H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

Tetrabutylammonium fluoride (5 mL, 1.0 M in THF) was added to the vinyl stannane **50**, and the mixture was stirred for 36 h. Saturated aqueous NH₄Cl (0.4 mL) was added, and the mixture was placed directly on a column of silica gel (40 g). Purification by flash column chromatography using 5% EtOAc hexanes provided 325 mg of **4** (64%, for 2 steps from alkyne **49**) as a clear yellow oil: *R*_f 0.62 (20% EtOAc in hexanes); [α]_D²³ +15.8 (c 1.39, CHCl₃); IR (neat) 3443, 2959, 2926, 2872, 2855, 1645, 1456, 1375, 1094, 990, 889 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.20 (d, *J* = 18.8 Hz, 1H), 5.92 (dd, *J* = 19.0, 6.4 Hz, 1H), 4.91 (s, 1H), 4.86 (s, 1H), 3.84 (m, 1H), 2.24 (dq, *J* = 8.9, 7.0 Hz, 1H), 1.88 (s, 1H-OH), 1.73 (s, 3H), 1.49 (m, 6H), 1.31 (m, 6H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 15H); ¹³C NMR (100 MHz, CDCl₃) δ 148.7, 147.2, 130.7, 113.0, 77.5, 47.6, 29.1, 27.2, 19.1, 15.6, 13.7, 9.5; HRMS *m/z* calcd for C₂₀H₃₉O₂Sn (M⁺ - H) 415.2017, found 415.2013. Anal. Calcd for C₂₀H₄₀O₂Sn: C, 57.85, H, 9.71. Found: C, 58.20; H, 9.77.

(4R,7S,8S,9S,12E,14S,15R)-7-(tert-Butyldimethylsilyloxy)-5,11-dimethylheptadeca-8,9-epoxy-14-hydroxy-3-oxo-4,15,16-trimethylheptadeca-12,16-diene (54). Alkenyl bromide **42** (38 mg, 0.080 mmol), vinylic stannane **4** (31 mg, 0.080 mmol), and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (9.0 mg, 0.017 mmol) were combined in CH₂Cl₂ (1.0 mL) under argon atmosphere, and the mixture was stirred for 20 h at ambient temperature. The mixture was placed directly on a silica gel column (10 g). Purification by flash column chromatography using a solvent gradient elution (5% EtOAc in hexanes to 30% EtOAc in hexanes) provided 31 mg (81%) of diene **54** as a thick clear colorless oil: *R*_f 0.40 (30% EtOAc in hexanes); [α]_D²³ -25.0 (c 0.34, CHCl₃); IR (neat) 3505, 3077, 2955, 2857, 1748, 1715, 1645, 1456, 1255, 1086, 837 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.34 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8, 7.3 Hz, 1H), 5.14 (s, 2H), 5.13 (s, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.88 (s, 1H), 3.94 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 3.73 (m, 1H), 3.72 (s, 3H), 3.53 (A of AB, *J*_{AB} = 15.8 Hz, 1H), 3.51 (B of AB, *J*_{AB} = 15.8 Hz, 1H), 3.37 (q, *J* = 6.8 Hz, 1H), 3.04 (m, 1H), 2.73 (dd, *J* = 5.0, 2.0 Hz, 1H), 2.48 (A of ABX, *J*_{AB} = 15.4 Hz, *J*_{AX} = 6.9 Hz, 1H), 2.40 (B of ABX, *J*_{AB} = 15.4 Hz, *J*_{BX} = 4.2 Hz, 1H), 2.32 (m, 2H), 2.27 (m, 1H), 1.96 (d, *J* = 2.2 Hz, 1H-OH), 1.74 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.3 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.1, 167.8, 146.9, 143.2, 141.4, 134.0, 130.5, 117.6, 116.1, 113.5, 74.4, 70.1, 60.5, 55.3, 53.3, 52.3, 48.2, 46.3, 41.2, 34.5, 25.8, 18.8, 18.1, 15.7, 15.1, -4.4, -4.8; HRMS *m/z* calcd for C₂₉H₄₈O₆SiNa (M⁺ + Na) 543.3118, found 543.3119.

(5R,8S,9S,10S,13E,15S)-8-(tert-Butyldimethylsilyloxy)-[(1R)-1,2-dimethylallyl]-9,10-epoxy-5-methyl-6,12-dimethyl-

lene-4-oxacyclopentadec-13-ene-2,4-dione (55). Methyl ester **54** (43 mg, 0.081 mmol) was dissolved in toluene (40 mL) and heated to reflux (oil bath temperature, 120–130 °C) in a culture tube sealed with a Teflon coated cap for 3 h. The reaction was concentrated in vacuo and purified by flash column chromatography (5% EtOAc in hexanes) to give the macrolide **55** (23 mg, 72%) as a colorless oil: *R*_f 0.41 (15% EtOAc in hexanes); [α]_D²³ -42.0 (c 0.27, CHCl₃); IR (neat) 3082, 2953, 2857, 1746, 1715, 1462, 1250, 1126, 965, 837 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.36 (d, *J* = 15.9 Hz, 1H), 5.51 (dd, *J* = 15.8, 9.1 Hz, 1H), 5.22 (dd, *J* = 15.4, 9.1 Hz, 1H), 5.20 (s, 2H), 5.11 (s, 1H), 5.08 (s, 1H), 4.78 (s, 1H), 4.75 (s, 1H), 4.00 (td, *J* = 5.6, 2.2 Hz, 1H), 3.51 (A of AB, *J*_{AB} = 14.1 Hz, 1H), 3.32 (B of AB, *J*_{AB} = 14.1 Hz, 1H), 3.32 (m, 1H), 2.85 (s, 1H), 2.85 (m, 1H), 2.79 (s, 1H), 2.50 (dq, *J* = 15.4, 6.9 Hz, 1H), 2.20 (m, 1H), 2.06 (d, *J* = 5.5 Hz, 2H), 1.69 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.4, 165.1, 145.6, 143.2, 140.4, 137.3, 125.7, 121.1, 115.5, 112.7, 78.7, 68.2, 62.7, 54.6, 53.4, 46.7, 44.7, 40.1, 34.7, 25.7, 19.6, 18.2, 15.4, 14.9, -4.7, -4.9; MS (EI) *m/z* (relative intensity) 488 (20), 431 (67), 387 (30), 339 (25), 283 (100), 239 (60), 197 (75), 133 (40), 91 (40); HRMS *m/z* calcd for C₂₈H₄₄O₅Si (M⁺) 488.2958, found 488.2950.

(+)-Amphidinolide P (2). Tetrabutylammonium fluoride (1.80 mL, 0.62 M in THF) was added to the ketoester **55** (17.0 mg, 0.035 mmol). The reaction mixture was stirred for 20 h at ambient temperature, and the mixture was placed directly on a column of silica gel (5 g). Purification by flash column chromatography (5% EtOAc in hexanes) gave synthetic amphidinolide P (**2**) (9.0 mg, 70%) as a white solid: *R*_f (15% EtOAc in hexanes); [α]_D²³ +30.0 (c 0.4, MeOH); IR (neat) 3488, 3081, 2930, 1713, 1643, 1439, 1188, 972, 897 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.24 (d, *J* = 16.3 Hz, 1H), 5.64 (dd, *J* = 16.2, 7.6 Hz, 1H), 5.34 (dd, *J* = 9.0, 7.8 Hz, 1H), 4.98 (br s, 1H), 4.94 (br s, 1H), 4.92 (br s, 1H), 4.86 (br s, 1H), 4.85 (br s, 1H), 4.81 (br s, 1H), 4.27 (d, *J* = 2.0 Hz, 1H), 3.51 (ddd, *J* = 11.6, 8.4, 2.6 Hz, 1H), 2.72 (d, *J* = 13.8 Hz, 1H), 2.66 (dd, *J* = 8.4, 1.8 Hz, 1H), 2.56 (dd, *J* = 12.8, 2.6 Hz, 1H), 2.52 (br d, *J* = 9.5 Hz, 1H), 2.47 (dq, *J* = 9.2, 7.1 Hz, 1H), 2.41 (d, *J* = 11.9 Hz, 1H), 2.31 (d, *J* = 12.1 Hz, 1H), 2.21 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.15 (t, *J* = 12.6, 11.8 Hz, 1H), 1.99 (br q, *J* = 6.5 Hz, 1H), 1.71 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 172.4, 146.5, 143.7, 142.2, 133.6, 129.1, 118.2, 112.3, 110.0, 99.2, 78.5, 73.5, 62.8, 58.3, 45.2, 45.02, 45.01, 39.4, 36.3, 19.5, 16.1, 11.8; HRMS *m/z* calcd for C₂₂H₃₀O₅Na (M⁺ + Na) 397.1991, found 397.1980. Our synthetic amphidinolide P was studied by COSY-NMR experiments and by comparisons to the ¹H NMR and ¹³C NMR data recorded for the natural product. NMR spectra and these data are tabulated in Supporting Information.

■ ASSOCIATED CONTENT

📄 Supporting Information

Tables S1 and S2 of tabulated comparisons of proton and carbon NMR data for natural and synthetic amphidinolide P. Proton NMR spectra of synthetic amphidinolide P (**2**) and intermediate compounds **4**, **9**, **12–19**, alcohol precursor of **15**, alcohol precursor of **16**, **24**, **27**, **29**, alcohol precursor of **30**, **30–32**, **35**, **36**, **39–42**, **44–50**, dibromide precursor to **49**, **54** and **55** are also included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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DEDICATION

†Dedicated to the memory of Robert E. Ireland.

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