Enantioselective Total Synthesis of the Antitumor Macrolide Rhizoxin D

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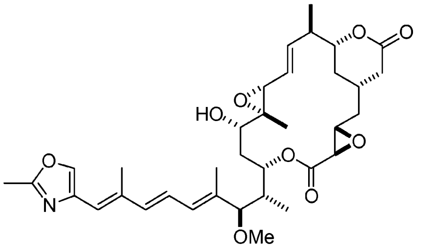
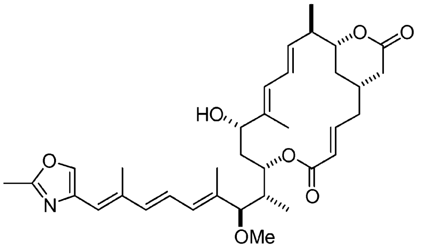
The convergent, highly enantioselective synthesis of rhizoxin D, a natural product possessing potent antitumor and antifungal bioactivity, is described. The C(1)−C(9) fragment of the molecule was synthesized utilizing a threefold pseudosymmetric intermediate ultimately derived from γ-butyrolactone. The central core of rhizoxin D was prepared via a chiral resolution/asymmetric aldol protocol. Several methods for the generation of the polyene fragment were explored, and the side-chain was ultimately prepared from serine in six steps. The unification of the left and right wings of the molecule was achieved using a one-step olefination protocol, and the macrocyclization was carried out using a Horner−Emmons olefination at the C(2)−C(3) olefin.

Introduction

In 1984, Iwasaki and co-workers reported the isolation of a novel family of macrolactones that possess potent biological activity.[2] Rhizoxin (**1**) represents the most extensively studied of these novel macrolides isolated from the fungus *Rhizopus chinensis*, the causal agent of rice seedling blight. In the original structure elucidation, rhizoxin was cited as possessing potent antifungal activity. Since this time, several studies have established that this alkaloid also exhibits other important medicinal properties; it has been shown to have profound antitumor activity, as well as antibiotic and antimicrobial activity.[3]



Rhizoxin (1)



Rhizoxin D (2)

FIGURE 1.

The discovery of rhizoxin was soon followed by the isolation of several close structural analogues,[4] including rhizoxin D (**2**, Figure 1), which is believed to be a biogenetic precursor of **1**. Studies have shown that this desepoxy homologue possesses bioactivity and antitumor activities equivalent to those of rhizoxin, demonstrating that the epoxide moieties are not needed for in vitro activity.[3b] It seems probable that in vivo hydrolysis of the epoxides may be responsible to some degree for the very short half-life of rhizoxin in the body, making compound **2** an intriguing potential therapeutic agent. In the years since rhizoxin was isolated, several workers have published progress toward its synthesis,[5,6] and Ohno and co-

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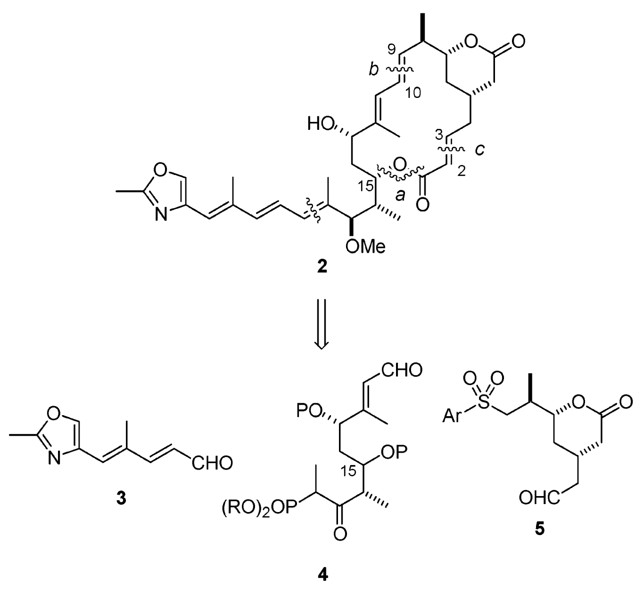
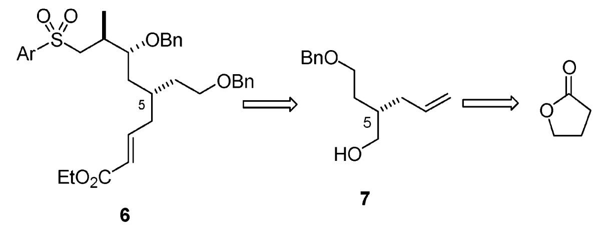
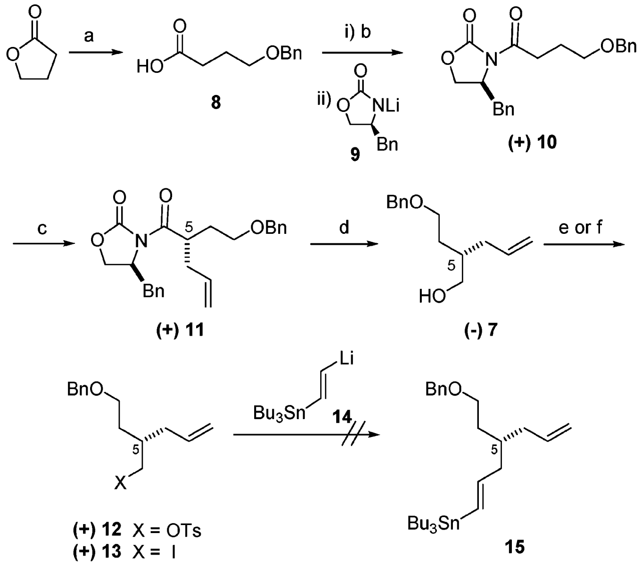
SCHEME 1



SCHEME 2



SCHEME 3[a]



[a] Reaction conditions: (a) KOH, BnBr (98%); (b) EtOCOCl, Et$_3$N (88%); (c) NaHMDS, allyl bromide (73%); (d) LiBH$_4$ (76%); (e) TsCl, Et$_3$N, DMAP (97%); (f) I$_2$, PPh$_3$, imidazole (70%).

workers have successfully completed the task.[7] In addition, six groups, including ours, have reported the successful synthesis of **2**.[8] In this work, we describe our enantioselective total synthesis of rhizoxin D.

Results and Discussion

Retrosynthetic Analysis. As we began our retrosynthetic analysis of rhizoxin D, we imagined a number of possible cyclization strategies that could give rise to the macrocycle, as shown in Scheme 1. We initially considered two complementary macrolactonization alternatives (disconnection *a*): a standard macrolactonization wherein activation of the carboxyl group would lead to retention of configuration at the eventual C15 position and a Mitsunobu macrolactonization.[9] The latter cyclization, which occurs via activation of the alcohol component and inversion of configuration at C15, would provide an opportunity to access the central portion of the molecule in a much more facile manner. Given the potential difficulties often associated with macrolactonizations, we considered two additional macrocyclization strategies. Specifically, both the C9−C10 and C2−C3 olefins (disconnections *b* and *c*, respectively) could potentially be formed while closing the macrocycle. These options seemed ideal since all were accessible without necessitating a complete redesign of the synthesis. Instead, simply rearranging the order in which the transformations would be conducted would allow us to redirect our efforts. In practice, this flexibility proved to be valuable, as we ultimately explored all of these options (vide infra).

Macrolactonization: Initial Synthetic Strategy. Because the macrolactonization strategy represented two distinctly different possibilities that would ideally require very little resynthesis of the intermediates, we chose to pursue this option at the outset. We thus embarked on a synthetic approach to the requisite building blocks.

Our route to the C1−C9 portion of rhizoxin D was based on a versatile synthetic intermediate, **7** (Scheme 2). The structural similarity in each of the three "arms" of **7** about C5 gives the synthesis a degree of flexibility, because any of the three arms could be converted into one particular carbon chain in the natural product. In this way, the intermediate can be mapped onto **6**, the appropriate intermediate for macrolactonization, in three different ways by simply rotating about the C5 stereocenter. Compound **7** would be prepared starting from γ-butyrolactone.

The synthesis of **6** began with the opening of γ-butyrolactone with potassium hydroxide in the presence of benzyl bromide to afford the corresponding benzyl ether **8** (Scheme 3).[10] The carboxylic acid was activated as the mixed anhydride and added to the anion of oxazolidinone

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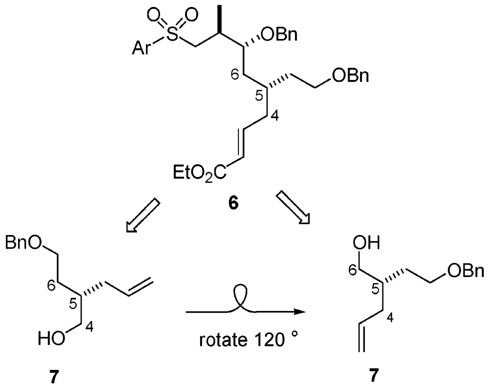
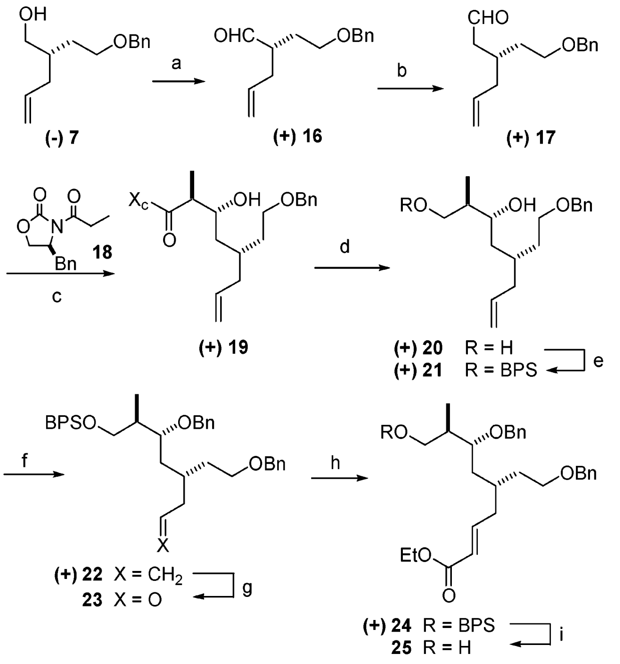
SCHEME 4



9. The ketoimide formed (**10**) was then alkylated diastereoselectively with allyl bromide, giving product **11**.[11] After removal of the chiral auxiliary to give alcohol **7**, we sought to extend the alcohol to give vinylstannane **15**, which could eventually serve as the α,β-unsaturated ester of our target. Alcohol **7** was therefore converted to the tosylate (**12**) or the iodide (**13**), and both of these compounds were explored as potential electrophiles. Unfortunately, neither the tosylate nor the iodide was displaced by the lithium anion of vinyl stannane **14**. A variety of cuprates derived from **14** were also prepared, but all suffered from a lack of reactivity toward our system.

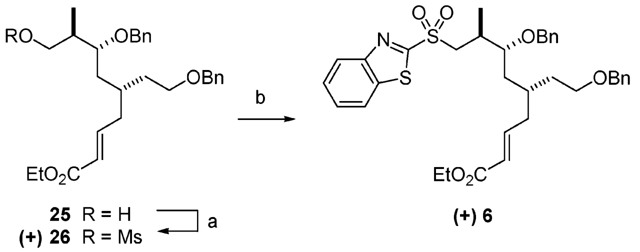
This setback was quickly addressed by re-examining our approach in light of our versatile intermediate, **7** (Scheme 4). We devised a modified retrosynthesis that was again based on this key intermediate; by remapping this alcohol onto the right wing we could elaborate the α-hydroxy carbon of **7** not as C4 of the natural product but as C6. The first requirement of this revised approach was the extension of the C6 arm of **7**. Thus, oxidation to the aldehyde (**16**),[12] followed by a Wittig olefination/acidic hydrolysis sequence, led to homologated aldehyde **17** (Scheme 5).[13] After screening a large number of acids to effect this hydrolysis of the methyl enol ether, we found that formic acid in ether and water gave consistently high yields of the desired aldehyde.[14] This compound was now employed in a *syn*-aldol reaction, which introduced the C7 and C8 chiral centers in a completely stereospecific manner.[15] Reductive removal of the chiral auxiliary with $LiBH_4$[11] gave a diol that could be selectively protected at the primary hydroxyl (**21**). Benzyl protection of the remaining alcohol was accomplished with the use of benzyl trichloroacetimidate[16] in the presence of catalytic triflic acid to provide the fully protected intermediate **22** in good yield.

SCHEME 5[a]



[a] Reaction conditions: (a) Dess−Martin oxidation (100%). (b) $Ph_3P{=}CHOMe$ (91%); HCO_2H (91%). (c) Bu_2BOTf, *i*-Pr_2EtN (80%). (d) $LiBH_4$ (99%). (e) BPSCl, imidazole, DMF (97%). (f) BnOC(NH)CCl_3, TfOH (79%). (g) OsO_4, NMO; $NaIO_4$ (100%). (h) $EtO_2CCH_2PO(OEt)_2$, DBU, LiCl (80%). (i) HF, CH_3CN (100%).

SCHEME 6[a]



[a] Reaction conditions: (a) MsCl, Et_3N, DMAP (96%). (b) NaSAr, DMF, 65 °C; Mo(VI), H_2O_2 (80%, two steps).

Oxidation of the terminal olefin to give aldehyde **23** was accomplished via a dihydroxylation/periodate cleavage sequence,[17] and a Horner−Emmons olefination[18] gave ester **24**. At this point, it remained only to convert the silyl-protected ether to a benzothiazole sulfone, which would be used for a Julia olefination later in the synthesis. Removal of the BPS protecting group proceeded smoothly, and the resulting alcohol was converted to the corresponding sulfone as shown in Scheme 6. We found the use of an ammonium molybdate-based oxidation,[19] in particular, was critical to providing the sulfone in good yield. This transformation marked the completion of the right wing (C1−C9) coupling partner of rhizoxin D, so we then turned our efforts to the left-hand portion (C10 to C26).

We felt from the outset that the best course of action would be to perform any macrocyclization on a fully

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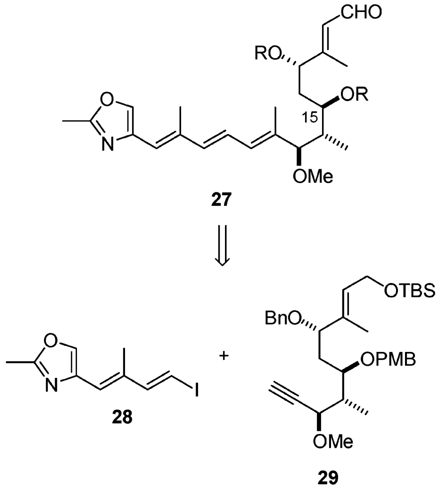
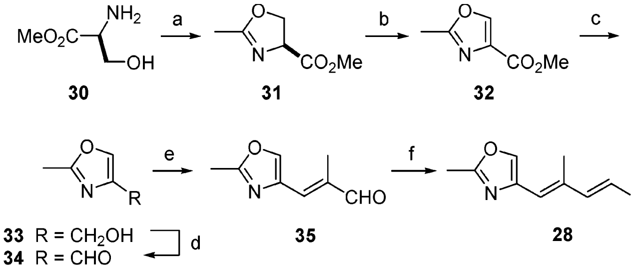
SCHEME 7



SCHEME 8[a]



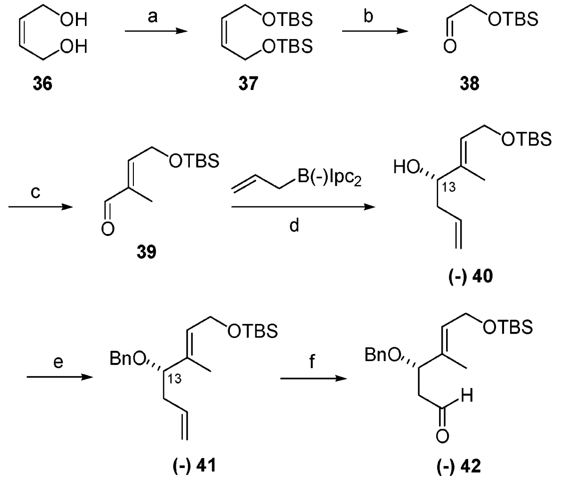
[a] Reaction conditions: (a) ethyl acetimidate HCl, Et$_3$N (80%); (b) CuBr$_2$, DBU, HMTA (85%); (c) LiAlH$_4$; (d) Swern oxidation (61%, two steps); (e) Ph$_3$P=C(CH$_3$)CHO (91%); (f) CHI$_3$, CrCl$_2$ (58%).

elaborated substrate in order to make the synthesis as convergent as possible. In that regard, we initially chose to construct the C10−C26 portion such that the triene portion would be made as late as possible, and we opted for a Negishi-type carbometalation[20] strategy in the hopes of avoiding undesired olefin isomers (Scheme 7). We also chose a synthetic route that would require inversion of the C15 stereocenter in the Mitsunobu macrocyclization step, as this would allow for facile access to the central core through the reliable and precedented syn aldol reaction (vide infra).

The synthesis of the oxazole side chain began from serine methyl ester, which was treated with ethyl acetimidate to cleanly afford the corresponding oxazoline (**31**, Scheme 8). Subsequent oxidation with cupric bromide[21] produced the oxazole in excellent yield. The methyl ester was then reduced to the aldehyde in a two-step protocol, and Wittig olefination gave the homologated aldehyde as a single isomer. Finally, a Takai[22] reaction on **35** produced our Negishi coupling partner, vinyl iodide **28**.

Turning to the synthesis of the central core, we began from *cis*-2-buten-1,4-diol (**36**, Scheme 9), which was bissilylated and then subjected to ozonolysis to afford 2 equiv of aldehyde **38**. Wittig olefination with 2-(triphenylphosphoranylidene)propionaldehyde gave the α,*β*-unsaturated aldehyde **39** as a single isomer. Using the chemistry of Brown,[23] **39** was allylated to yield the enantioenriched (88% ee) alcohol **40**, which was then benzylated to provide diene **41**. Selective ozonolysis of the terminal olefin was accomplished by the careful addition of 1 equiv of ozone to afford aldehyde **42**.

SCHEME 9[a]



[a] Reaction conditions: (a) TBSCl, Et$_3$N (100%). (b) O$_3$; PPh$_3$ (100%). (c) PPh$_3$=C(CH$_3$)CHO (84%). (d) NaOH, H$_2$O$_2$ (92%, 88% ee). (e) NaH, BnBr, Bu$_4$NI (96%). (f) O$_3$ (1.3 equiv); PPh$_3$ (57%).

Although this selective ozonolysis gave a reasonable recovery of the desired product, it was operationally difficult and gave mixtures of starting material, product, and over-oxidized material. While we investigated alternatives to this transformation, we were unable to adequately improve on these conditions. In addition, we had noticed that the Brown asymmetric allylation, which had reliably given **41** in high ees on a smaller scale, gave diminished enantioselectivity on the large scale required for our efforts. These two issues led us to explore alternative routes to aldehyde **42**. We believed that we could find a solution to both of these issues in the use of acetate aldol chemistry. Though we did explore asymmetric variants, the most selective methods required very low reaction temperatures (−115 °C) and were therefore not ideally suited for scale-up. Instead, we turned to the use of a kinetic resolution of an achiral aldol product. We were aware that such a route would have the obvious disadvantage that half of our material would be sacrificed, but we believed that this would be a reliable route to useful quantities of essentially enantiopure material, at a stage sufficiently early in the synthesis to be worth the compromise.

The substrate to be resolved was prepared by treatment of aldehyde **39** with the sodium enolate of methyl acetate (Scheme 10), giving racemic alcohol **43** in good yield on a 50 g scale. This racemic aldol product was then treated with standard Sharpless asymmetric epoxidation conditions, but in the presence of only 0.6 equiv of the

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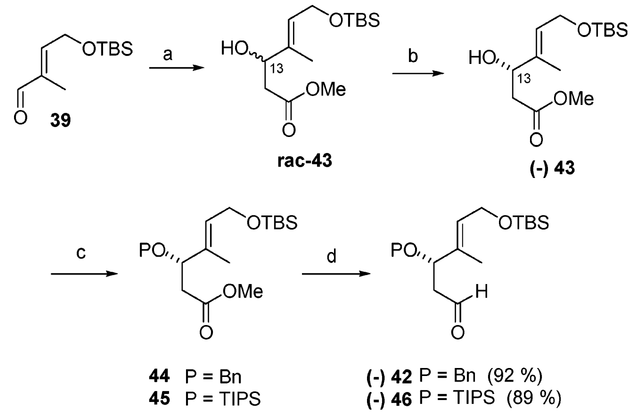
SCHEME 10[a]



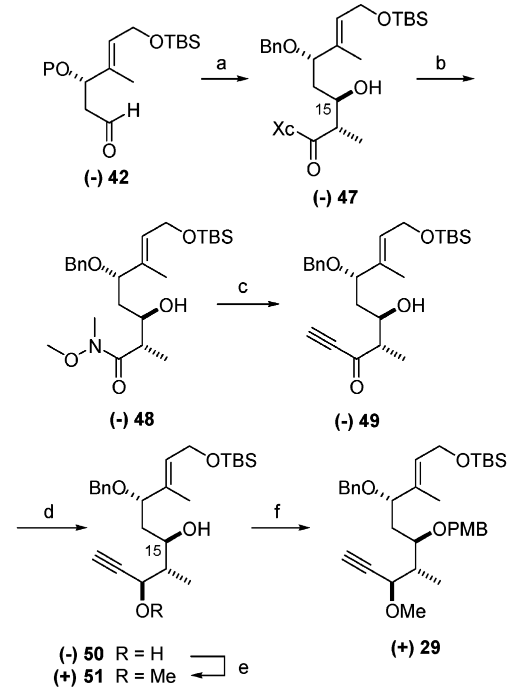
[a] Reaction conditions: (a) MeOAc, NaHMDS, THF, −78 °C (78%); (b) (−)-DIPT, Ti(OiPr)$_4$, TBHP (40%); (c) benzyl trichloroacetimidate, TfOH (76%) or TIPSOTf, 2,6-lutidine (99%); (d) DIBAL-H, 1 equiv.

stoichiometric oxidant, *tert*-butylhydroperoxide (TBHP).[24] The reaction was quenched when approximately 55% of the olefinic material had been consumed (as judged by ^{1}H NMR), and we were able to recover 40% of the desired homochiral **43**. Using both Mosher's ester analysis[25] and chiral shift reagents, we were unable to detect any undesired isomer. Importantly, this product was readily converted to aldehyde **42**, which allowed us to avoid the difficult ozonolysis. Ultimately, we found it necessary to modify our protecting group strategy (vide infra), and this was accomplished simply by silylation of the resolved alcohol to provide **46** in good overall yield.

With a facile route to the large-scale preparation of the desired aldehyde, we turned to the installation of the C15 and C16 chiral centers. To this end, a syn Evans aldol[15] reaction was performed on **42**, giving a product with the (desired) unnatural stereochemistry at C15 (Scheme 11). This hydroxyl would be inverted in the planned Mitsunobu macrocyclization. Oxazolidinone **47** was converted to the Weinreb amide,[26] and an acetylenic unit was introduced via the Grignard reagent. The resulting ketone was reduced to the *syn*-1,3-diol using diethylmethoxyborane.[27] We were pleased to find that selective methylation of the propargylic C17 hydroxyl was surprisingly facile in the presence of the free C15 hydroxyl. Protection of that remaining alcohol as the *p*-methoxybenzyl ether gave **29**, the substrate to be coupled to the oxazole side chain.

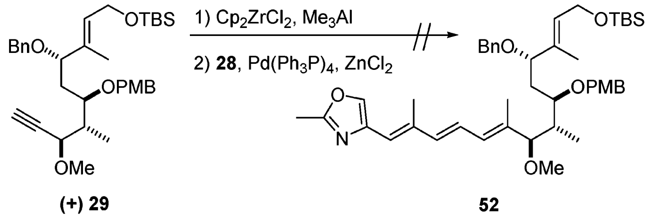
Unfortunately, we found that attempted carbometalation of the alkyne followed by treatment with the vinyl iodide side chain failed to produce triene **52**, even under forcing conditions (Scheme 12). Attempts to add various cuprates to the alkyne to form a vinyl cuprate were also unsuccessful. The difficulty in these reactions may be the result of the propargylic methoxy substituent present in **29**. Though there is precedent for carboaluminations on similar substrates,[28] propargylic substituents appear to make addition to the alkyne more difficult.[29]

SCHEME 11[a]



[a] Reaction conditions: (a) Bu$_2$BOTf, *i*-Pr$_2$NEt, **18** (89%); (b) MeO(Me)NH, Me$_3$Al (95%); (c) ethynylmagnesium bromide (66%); (d) Et$_2$BOMe, NaBH$_4$ (84%); (e) NaH, MeI (83%); (f) PMBOC(NH)CCl$_3$, TfOH (70%).

SCHEME 12



With the failure of the Negishi coupling, we redesigned our approach to the installation of the triene. While we investigated a series of alternatives for the generation of this sensitive region of the molecule, ultimately only one proved to be fruitful. In our revised approach, we planned to employ a Horner−Emmons olefination to unite the oxazole side chain **53** with a ketophosphonate central core (**54**, Scheme 13). A good portion of the chemistry we had already developed could be employed without the added risk of using Lewis acidic metals on highly functionalized intermediates.

The revised synthesis of oxazole fragment **53** was straightforward from previously prepared intermediate **35** (Scheme 14). Horner−Emmons olefination afforded ethyl ester **55**, which was reduced with DIBALH to the corresponding allylic alcohol **56**. This unstable alcohol

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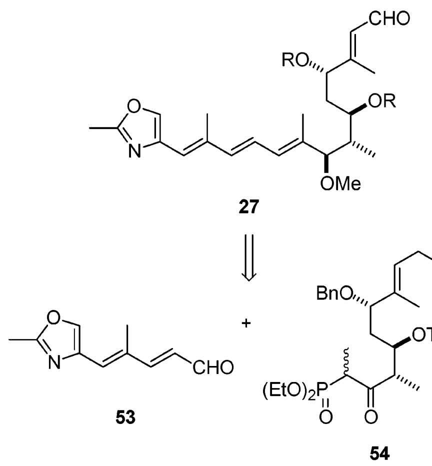
[26] Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

[27] Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

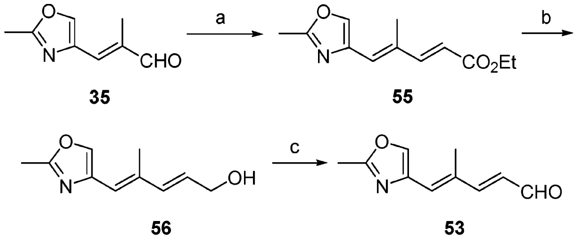
[28] (a) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639 (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

[29] (a) Normant, J. F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 1656. (b) Marfat, A.; McGuirk, P. R.; Helquist, P. *Tetrahedron Lett.* **1978**, *19*, 1363.

SCHEME 13



SCHEME 14[a]

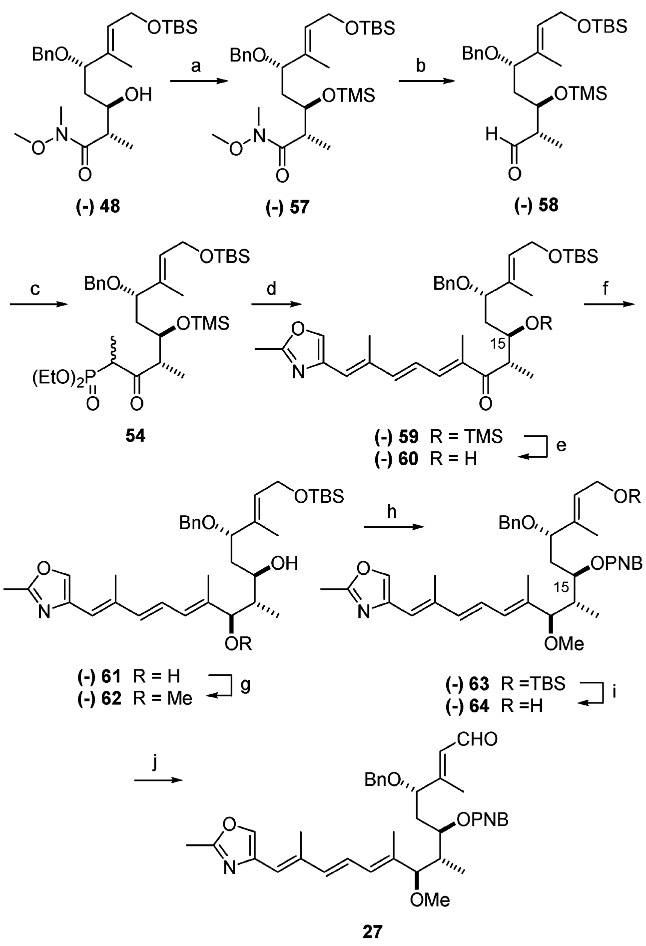


[a] Reaction conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN (93%); (b) DIBAL-H (97%); (c) Dess−Martin oxidation (75%).

was quickly carried into the following oxidation step to afford aldehyde **53**, which proved to be a stable, white, crystalline solid that could be stored for several months without significant decomposition.

With aldehyde **53** in hand, we turned to the synthesis of the revised central core fragment, starting from Weinreb amide **48** (Scheme 15). We were surprised to note that the anion of ethyl diethylphosphonate could not be added directly into **48** under any conditions. We postulated that the remaining alcohol functionality was interfering with the reactivity of the Weinreb amide. However, simple protection of the alcohol as a trimethylsilyl ether still did not allow for the addition to occur.[30] Thus, we were forced to prepare the more reactive aldehyde **58** as an intermediate, which underwent smooth addition of the phosphonate. Subsequent oxidation afforded the requisite diastereomeric mixture of *β*-ketophosphonates **54** in two steps.

SCHEME 15[a]



[a] Reaction conditions: (a) TMSCl, Et_3N (100%). (b) DIBAL-H (93%). (c) $(EtO)_2P(O)Et$, *t*-BuLi (89%); Dess−Martin oxidation (97%). (d) **53**, $Ba(OH)_2{\cdot}8H_2O$ (65%). (e) citric acid (89%). (f) Et_2BOMe, $NaBH_4$ (76%). (g) NaH, MeI (63%). (h) PNBCl, pyr. (82%). (i) TBAF (87%). (j) Dess−Martin oxidation (87%).

Efforts were next directed toward the Horner−Emmons olefination in order to introduce the oxazole side chain. Roush−Masamune[31] conditions failed to give **59**, but the use of barium hydroxide in aqueous THF worked well to install the triene.[32] Importantly, only the desired *trans*-olefin product was observed. With the triene securely in place, the trimethylsilyl group was readily removed with mild citric acid to reveal the C15 alcohol **60**. This alcohol was crucial for the introduction of the remaining stereocenter at C17. From the unnatural orientation at C15 in **60**, we required a chelation-controlled reduction of the ketone in order to generate the desired *syn*-1,3-diol **61**, which Prasad's method readily provided.[27] The allylic alcohol was then selectively methylated, and the remaining C15 alcohol was protected as the corresponding *p*-nitrobenzoate (PNB) ester **63**. Liberation of the TBS-protected alcohol with tetrabutylammonium fluoride was followed by Dess−Martin oxidation to give aldehyde **27**, which constitutes the entire C10−C26 fragment of rhizoxin, epimeric at only the macrolactonization center.

With the left and right wing coupling partners, **6** and **27**, respectively, in hand, we moved on to the installation of the C9−C10 olefin to unite the entire skeleton of our target. Early plans to employ a traditional Julia olefination[33] were redirected when yields of coupled products in model systems were consistently low. We instead

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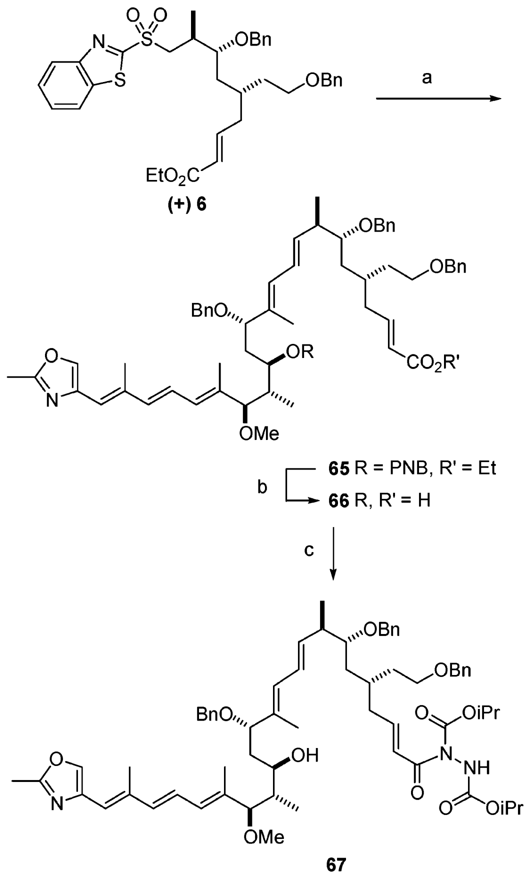
(30) Addition of the anion of methyl dimethylphosphonate to a Weinreb amide is known: Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron* **1990**, *46*, 2807. There are no reports of the use of ethyl diethylphosphonate in this context, however.

(31) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Rathke, M. W.; Nowak, M. J. *J. Org. Chem.* **1985**, *50*, 2624.

(32) Paterson, I.; Yeung, K.; Smaill, J. B. *Synlett* **1993**, 774.

(33) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. (b) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97.

SCHEME 16[a]

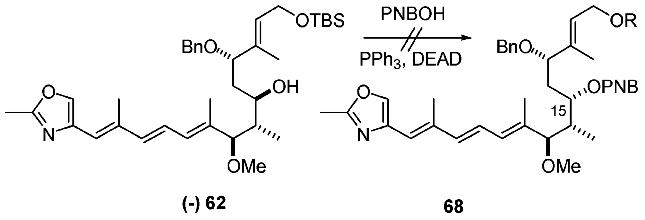


[a] Reaction conditions: (a) LiHMDS, **27** (50%); (b) TMSO$^-$K$^+$ (69%); (c) DIAD, PPh$_3$.

examined the use of a modified Julia olefination protocol, first introduced by Sylvestre Julia in 1991.[34] This procedure utilizes not a phenyl sulfone but a benzothiazole sulfone and represents a marked improvement over the traditional reaction because it requires only one synthetic operation to access the olefin, as opposed to three discrete steps. In addition, we found the modified olefination reaction to be milder and more tolerant of diverse functionality than the three-step protocol, as it was compatible with both the α,*β*-unsaturated ester of **6** and the sensitive triene moiety of **27**.

Treatment of a solution of sulfone **6** and aldehyde **27** with base led to the exclusive formation of **65** (Scheme 16). Compound **65** represents the complete (C1−C26) carbon skeleton of our target, and from this compound we could access the seco acid required for cyclization in one step. Traditional saponification protocols gave significant decomposition of our substrate, but we found that potassium trimethylsilanolate effectively cleaved both the ethyl ester and PNB ester in one step to afford **66**.[35] Attempts to close the ring through a Mitsunobu reaction were then undertaken. Unfortunately, our efforts were consistently plagued by amide formation, the result of azodicarboxylate addition into the phosphine-activated carboxylate of our substrate. This problem, most likely the result of steric hindrance at the hydroxyl center, can typically be avoided by changing the reaction conditions or by using a bulkier azodicarboxylate. Extensive efforts to optimize the cyclization were undertaken. The choice of solvent (benzene, toluene, THF), diazocarboxylate (DEAD, DIAD, ADDP), and order of addition of reagents was varied, but compounds such as **67** were the major products under all protocols examined.

SCHEME 17



There are other macrocyclization protocols that occur with inversion at the hydroxyl such as displacement of a mesylate with a cesium carboxylate salt. These methods, however, require activation of the alcohol prior to deprotection of the acid. Our approach, which released the alcohol and the acid in the same step, could not accommodate such procedures. It therefore seemed that macrocyclization with inversion of configuration was not a viable option in our case without significant revision of our efforts. However, we had initially anticipated this potential problem. We were cognizant that the C15 stereocenter could alternatively be controlled by the appropriate choice of protective conditions. Compound **62** would serve as the lynchpin for this plan. We had already demonstrated that standard esterification conditions led to the product with unnatural stereochemistry at C15 (as in Scheme 15). Similarly, we envisioned that protection under Mitsunobu conditions would yield the epimer with the natural configuration (**68**, Scheme 17). Much to our chagrin, treatment of **62** with *p*-nitrobenzoic acid under a variety of conditions failed to afford any of the desired product. In fact, only unreacted starting materials and a mixture of elimination products were returned. We also undertook efforts to invert the C15 stereocenter via an oxidation/reduction protocol. While a variety of methods were examined in this pursuit, no better than a 5:2 ratio of isomers favoring the desired product could be obtained. We were thus forced to install the desired stereochemistry at C15 at a much earlier juncture in our synthesis.

Macrolactonization: Revised Synthetic Strategy. With an efficient route to the C15 episeco acid already developed, it was our great desire to utilize as much of the work in place to complete our goal. We therefore set out to prepare the requisite Julia precursor with the natural (*S*)-stereochemistry at C15 (Scheme 18). We already had a tractable source of **53** in hand. We hoped that **70** could be generated by building on our previous success, the critical difference being that an efficient *anti*-aldol reaction was needed to install the natural stereochemistry.

A second-generation synthesis of the left wing, then, began from aldehyde **46**, which was studied extensively as the substrate for an *anti*-aldol reaction (Scheme 19). Our initial efforts met with little success, as the protocols of Paterson,[36] Heathcock,[37] Duthaler,[38] and Oppolzer[39] all failed to give the desired aldol adduct in good yield and/

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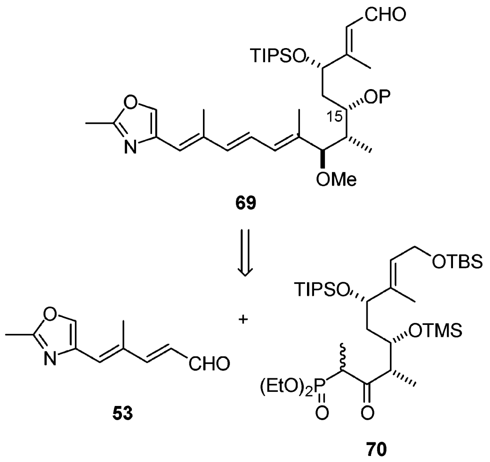
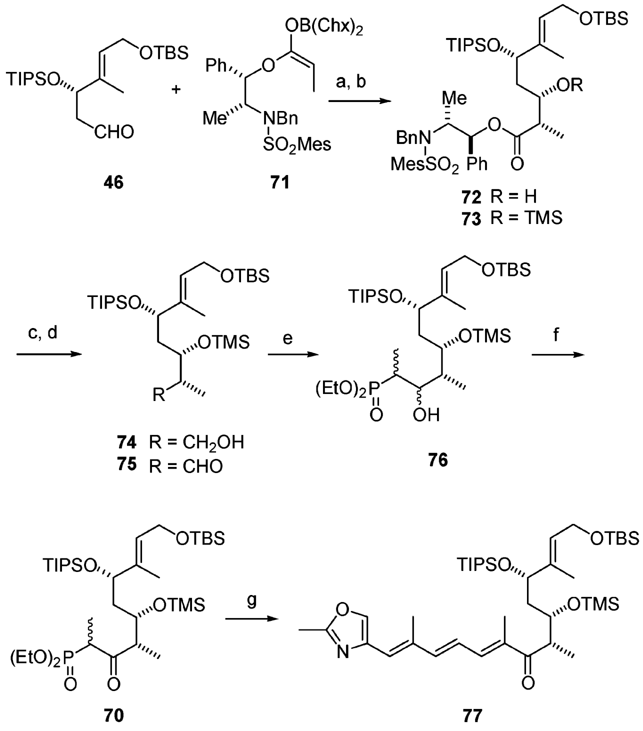
[34] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.

[35] Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

SCHEME 18

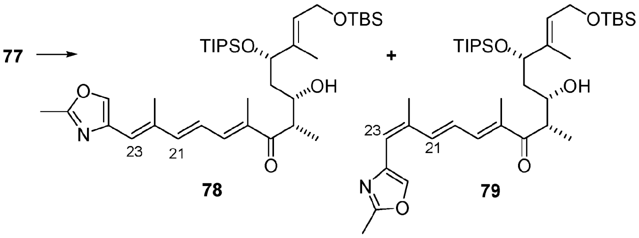


SCHEME 19[a]



[a] Reaction conditions: (a) Et_3N (81%); (b) TMSCl, imidazole (86%); (c) DIBAL-H (100%); (d) Dess–Martin oxidation (90%); (e) $(EtO)_2P(O)Et$, *t*-BuLi (100%); (f) Dess–Martin oxidation (96%); (g) **53**, $Ba(OH)_2\cdot H_2O$ (85%).

SCHEME 20



Conditions	**78** : **79**	Yield (%)[a]
Citric Acid, MeOH	6.5 : 1	80
K_2CO_3, MeOH	4.0 : 1	66
TBAF, THF	Loss of TIPS	---
CSA, MeOH	Decomp.	---
HF•pyridine, THF	4.3 : 1	80
H_2SiF_6, *t*-BuOH, rt	Loss of TBS	---
H_2SiF_6, *t*-amyl alcohol, 0 °C	3.8 : 1	90
H_2SiF_6, *i*-PrOH, -40 °C	15.7 : 1	90

[a] Combined yield of both isomers, after separation by chromatography.

or diastereoselectivity. In particular, we found that loss of the primary silyl protecting group or elimination of the protected hydroxyl β to the carbonyl were recurring problems.

Fortunately, during the course of our studies, Masamune and co-workers introduced novel aldol methodology that utilizes a norephedrine-derived auxiliary (**71**) to give *anti*-aldol products.[40] This new approach worked quite well on our substrate, allowing us to install the C15 and C16 stereocenters with excellent diastereoselectivity (90% de) and in good yield. Protection of the resultant free hydroxyl, followed by reductive removal of the chiral auxiliary afforded **74**. The alcohol was then oxidized to the corresponding aldehyde, which was converted in two steps to the β-ketophosphonate **70**. As before, a barium hydroxide-mediated Horner–Emmons olefination was used to unite the phosphonate with the oxazole side chain (**53**), giving rise to a single isomer at the newly formed olefin.

With all of the carbons again in place for the revised C10–C26 fragment, we were poised for what seemed to be the straightforward elaboration to **69** following the pathway previously developed with the epimer. However, the seemingly trivial differences between these two substrates created several difficult situations that needed to be addressed. Removal of the C15 TMS protecting group of **77** was the first example. Many of the typical deprotection conditions led to the formation of both **78** and an undesired side product (Scheme 20). This contaminant was shown by both one- and two-dimensional NOE studies to be **79**, the product of isomerization at the C22–C23 olefin. We found, however, that this isomerization could be minimized by employing fluorosilicic acid in isopropyl alcohol at reduced temperature to effect the deprotection.[41] Importantly, neither of the other silyl protecting groups were affected under these conditions, allowing access to **78** in high yield.

We were now in position to install the remaining stereocenter at C17. While we knew that it would be possible to effect a directed reduction in order to continue along our previously elaborated pathway, we were also aware of another unexpected consequence of the inversion at C15. As a result of our previous synthetic efforts, we were able to cull sufficient amounts of 1,3-*anti*-diol **80** from byproducts of our main route to perform model

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(36) Paterson, I; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.

(37) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.

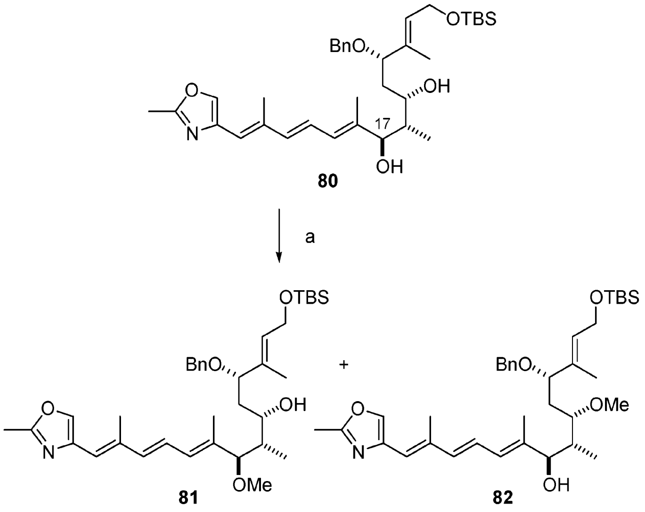
(38) Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Bold, G.; Rihs, G.; Rothe-Streit, P.; Wyss, B. *Inorg. Chim. Acta* **1994**, *222*, 95.

(39) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61.

(40) Abiko, A.; Liu, J.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

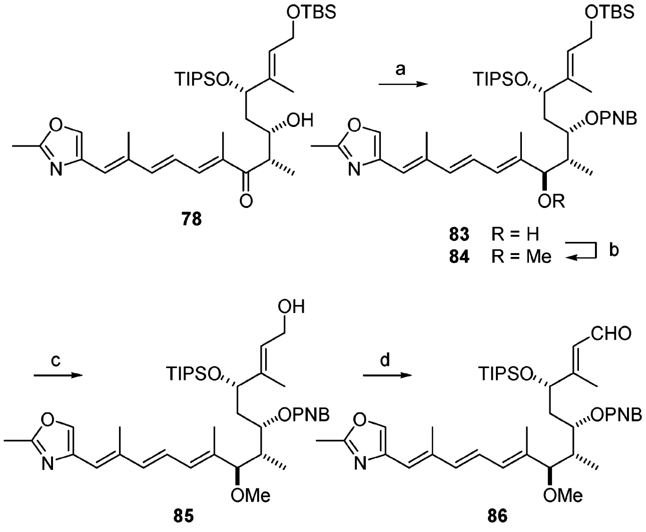
(41) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130.

SCHEME 21[a]



[a] Reaction conditions: (a) MeI, NaH.

SCHEME 22[a]

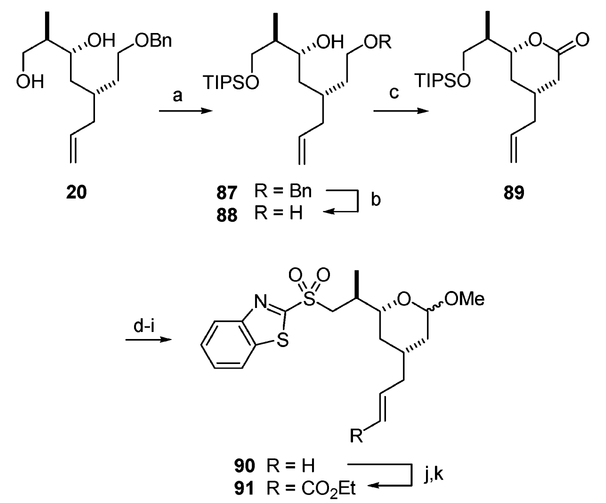


[a] Reaction conditions: (a) *p*-nitrobenzaldehyde, SmI_2 (83%); (b) MeI, Ag_2O, ultrasound (77%); (c) H_2SiF_6, 4:1 CH_3CN/*t*-BuOH (94%); (d) Dess−Martin oxidation (82%).

studies germane to our goal. Surprisingly, although the methylation of **61** had proceeded readily to give exclusively the desired product (Scheme 15), the natural isomer failed to undergo selective alkylation (Scheme 21). While we felt that this would bode well for the reactivity at C15 in terms of our eventual macrocyclization, we needed a way to distinguish between C15 and C17.

The intramolecular Tishchenko reaction proved to be a valuable transformation in our efforts. Treatment of **78** with *p*-nitrobenzaldehyde and samarium diiodide gave exclusively allylic alcohol **83** (Scheme 22).[42] Methylation under strongly basic conditions led to intramolecular scrambling of the ester, but we were able to introduce the methyl group by using methyl iodide and silver oxide.[43] While this reaction proceeded very slowly under the standard conditions, we found that the rate increased dramatically if the reaction mixture was sonicated.

SCHEME 23[a]



[a] Reaction conditions: (a) TIPSCl, imidazole, DMAP (95%). (b) Na/NH_3 (98%). (c) Ag_2CO_3/Celite (86%). (d) DIBAL (100%). (e) MeOH, Amberlyst 15 (87%). (f) TBAF (89%). (g) MsCl, NEt_3. (h) ArSNa (90%). (i) Mo(VI), H_2O_2 (91%). (j) OsO_4, NMO; $NaIO_4$ (83%). (k) $EtO_2CCH_2PO(OEt)_2$, LiCl, DBU (85%).

Selective removal of the TBS protecting group in the presence of the TIPS group proceeded smoothly with fluorosilicic acid, and oxidation to the α,β-unsaturated aldehyde **86** completed the synthesis of the C10−C26 portion of rhizoxin D.

At this point, we were poised to couple aldehyde **86** to the right wing of the molecule via the Julia olefination. Because the modified Julia reaction had proven to be tolerant of such diverse functionality, we decided to further explore the limits of the reaction by using a more advanced sulfone coupling partner, **91** (Scheme 23). In this new synthon, the six-membered ring is installed prior to coupling, allowing for a more convergent synthesis. In addition, the presence of the ring would remove some of the free rotation associated with our original macrocyclization precursor, more closely approximating the true seco acid of the natural product. The modified synthesis of the sulfone began from **20**, which was silylated and debenzylated to afford diol **88** in excellent yield. Fetizon oxidation[44] smoothly gave the corresponding δ-lactone **89**. Partial reduction of the lactone and acid-catalyzed addition of methanol gave the acetal as a mixture of unseparable diastereomers. The primary alcohol was then liberated and, following mesylation, converted into the requisite benzothiazolyl sulfone **90**. Oxidation of the olefin and Horner−Emmons olefination gave the pyran acetal analogue of **6**. To our delight, the Julia coupling of **86** and **91** was very successful, providing a good yield of material that once again contained all of the carbons necessary for the natural product. Saponification of both of the esters with potassium trimethylsilanolate as before gave the seco acid, now with the natural stereochemistry at the C15 position. Unfortu-

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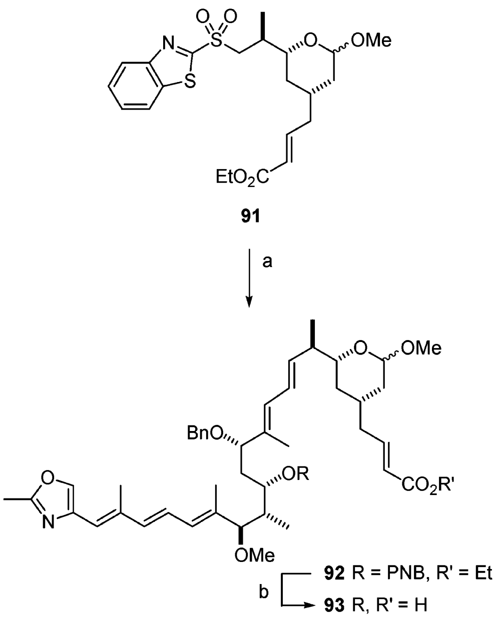
(42) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(43) Finch, N.; Fitt, J. J.; Hau, I. H. S. *J. Org. Chem.* **1975**, *40*, 206.

(44) (a) Girault, J. P.; Dana, G. *Tetrahedron Lett.* **1970**, 4135. (b) Fetizon, M.; Golfier, M. *C. R. Acad. Sc. Paris (C)* **1968**, *267*, 900. (c) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401.

SCHEME 24[a]



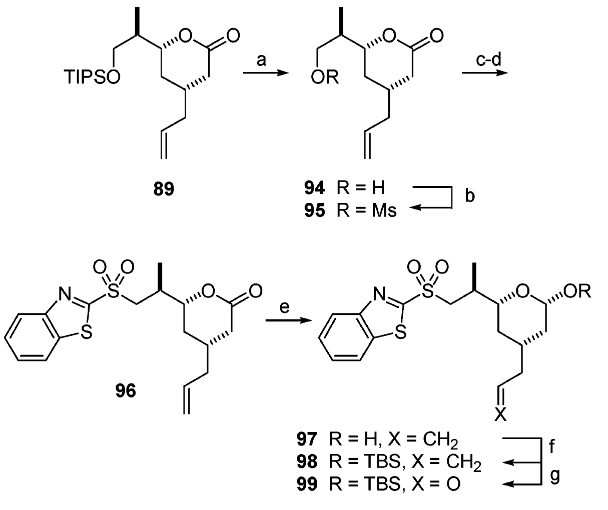
[a] Reaction conditions: (a) **86**, LiHMDS (81%); (b) $TMSO^-K^+$ (65%).

nately, all attempts to effect this macrolactonization were unsuccessful, leading to decomposition or recovered starting material. The triene portion of the molecule seemed particularly susceptible to decomposition when exposed to a variety of cyclization conditions. Fearing that steric hindrance at C15 and the sensitivity of the triene functionality made this approach untenable, we made the strategic decision to focus on other approaches to closing the macrocycle.

Macrocyclization via Olefination: Ring Closure at C9−C10. With the disappointing outcome of the first two cyclization strategies, we were forced to examine the alternative possibilities for closing the macrocycle. Of our remaining options, we were most intrigued by the possibility of closing the ring via a Julia olefination at C9−C10 (disconnection *b*, Scheme 1). This option represented a novel macrocyclization strategy that would occur at a site remote from our earlier failed efforts. Such a plan would also require minimal re-engineering of our earlier synthetic efforts. Since we were constantly striving to improve on our earlier work, we chose to explore methods that would remove the isomeric mixtures of acetals that had resulted from our cyclization of the δ-lactone. In that regard, desilylation of **89** followed by elaboration of the terminus to the aryl sulfone using the same protocol as before gave **96** (Scheme 25). Partial reduction again gave the hemiacetal, and we were pleased to see that silylation of this lactol gave **98** exclusively as the anomer in which the silyl group is the least sterically encumbered. Oxidative cleavage of the olefin then afforded aldehyde **99**.

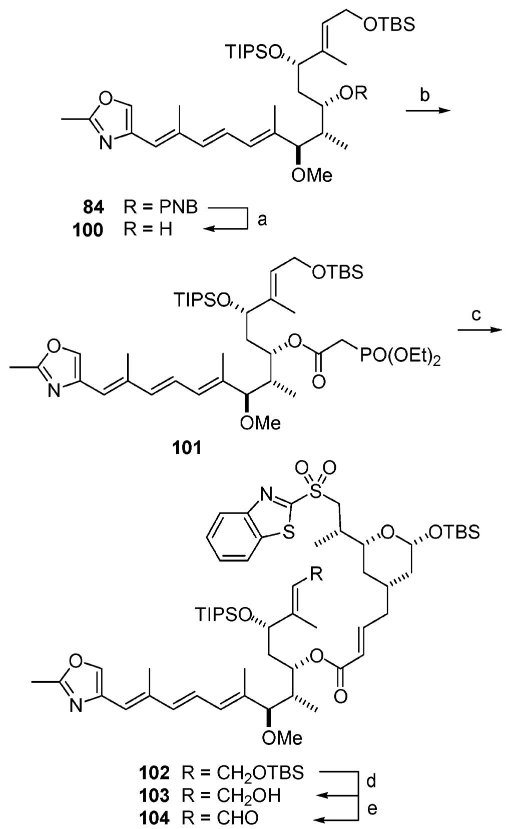
The other component of our Julia macrocyclization strategy also required some synthetic manipulation. The ester of **84** was reductively cleaved, and acylation with diethylphosphonoacetyl chloride[45] gave **101** (Scheme 26). With the two coupling partners in hand, we exposed **99** and **101** to standard Horner−Emmons olefination conditions, which gave **102** in good yield. The newly formed olefin was generated exclusively in the desired trans geometry.

SCHEME 25[a]



[a] Reaction conditions: (a) HF, MeCN (95%). (b) MsCl, NEt_3, DMAP (96%). (c) ArSNa (94%). (d) Mo(VI), H_2O_2 (91%). (e) DIBAL (80%). (f) TBSCl, imidazole (85%). (g) OsO_4, NMO; $NaIO_4$ (87%).

SCHEME 26[a]



[a] Reaction conditions: (a) DIBAL (77%); (b) $(EtO)_2POCH_2COCl$, pyr. (80%); (c) **99**, LiCl, DBU (83%); (d) H_2SiF_6, *tert*-amyl alcohol (88%); (e) Dess−Martin oxidation (72%).

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[45] (a) Cooke, M. P.; Biciunas, K. P. *Synthesis* **1981**, 283. (b) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850.

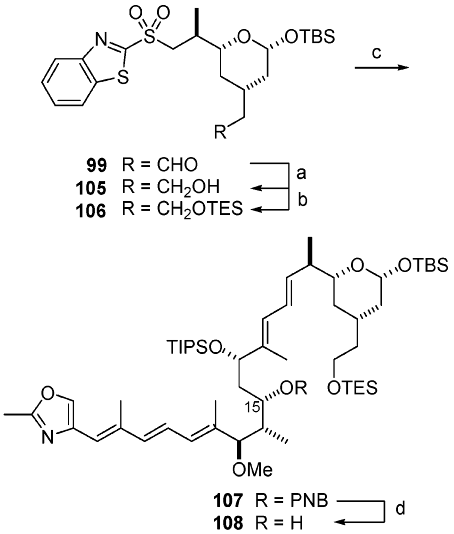
The next challenge involved conversion of the primary TBS ether of **102** to the α,*β*-unsaturated aldehyde required for the Julia olefination. This matter was complicated by the fact that the deprotection of the C10 hydroxyl had to be carried out in the presence of our TBS acetal. In fact, exposure of **102** to typical conditions such as HF·pyridine led to approximately equal amounts of the desired product (**103**) as well as the corresponding hemiacetal. Critically, no material that retained the primary silyl ether was obtained. Returning to conditions that had been successful on the central core synthesis, we found that the use of fluorosilicic acid in *t*-amyl alcohol gave excellent results. DeShong has studied the use of this acid for selective silyl deprotections[46] and has found that the best selectivity is obtained using bulky alcohols (such as *t*-BuOH) as the solvent. We found that *t*-amyl alcohol has the added advantage that it could be cooled to −15 °C, which, in our studies, conferred an additional degree of selectivity to the deprotection.

The final step prior to cyclization involved oxidation of the primary hydroxyl of **103** to the aldehyde required for the Julia. This reaction proceeded smoothly with the Dess Martin periodinane,[47] and we turned to the macrocyclization. Sulfone **104** was subjected to the standard reactions conditions used for the intermolecular Julia coupling, but the material isolated from this reaction was not the cyclized product. Along with significant decomposition, a compound that lacked the aldehyde moiety, but still possessed the sulfone, was recovered from the reaction. This compound, to which we were unable to assign a complete structure, had also undergone migration of the C2−C3 olefin, likely the result of deprotonation at C4. It was clear that treatment of **104** with base had not led to the desired results and had instead caused degradation of other functionality in our starting material.

Macrocyclization via Olefination: Coupling at C2−C3. With the failure of our Julia macrocyclization tactic, we were left with the one strategy we had yet to explore: cyclization via Horner−Emmons olefination at C2−C3 (disconnection *c*, Scheme 1). This plan would not require manipulation of aldehyde **86**, but we were once again faced with the prospect of tweaking our sulfone coupling partner (Scheme 27). To this end, we reduced **99** and protected the resultant alcohol as triethylsilyl ether **106**. We then turned to the Julia olefination with aldehyde **86**, which proceeded well to couple the right and left portions of our molecule in improved yields compared with previous substrates. As usual, only the desired *trans*-olefin geometry was observed. Subsequently, the lone ester was reductively cleaved to expose the C15 alcohol.

We were able to introduce the phosphonate ester at C15 using a procedure similar to the one previously optimized for **101** (Scheme 28). Now faced with the selective deprotection of compound **109**, we returned to the reagent that had given excellent results at other points in our synthesis. We found that, once again, fluorosilicic acid (this time in 2-propanol at −40 °C) cleaved our TES protecting group without any observed loss of the TBS group. Dess Martin oxidation of this primary alcohol led us to the familiar position of having a macrocyclization precursor. We began our cyclization studies by employing Roush−Masamune Horner−Emmons conditions. These conditions had worked well during our previous efforts to form the C2−C3 olefin, so we imagined that they would be compatible with this system. When we treated phosphonate **111** to standard reactions conditions, however, we found that we gratifyingly obtained cyclized material, but only in low yield. We therefore turned to a protocol that had previously proven to be successful for the installation of the triene: the use of barium hydroxide in aqueous THF. Running this reaction at high dilution and with 20 equiv of barium hydroxide, we found that this method reliably provided the desired macrocycle, **112**. Because this procedure employs hydroxide to effect the Horner−Emmons, a side product of the reaction resulted from saponification of the acyl phosphonate to give the free C15 hydroxyl. Thus, the closure of the ring proceeded in moderate yield, but we were nonetheless elated to have the macrocycle in hand.

SCHEME 27[a]



[a] Reaction conditions: (a) $NaBH_4$, MeOH (88%); (b) TESCl, Et_3N, DMAP, (96%); (c) **86**, LiHMDS (2.3 equiv) (79%); (d) DIBAL-H (90%).

We were finally within grasp of our target, rhizoxin D (**2**). We continued the synthesis through selective removal of the TBS acetal protecting group in the presence of a TIPS ether with a very concentrated solution of HF·pyridine. The Dess−Martin reaction that had been so reliable throughout the synthesis worked well to oxidize hemiacetal **113** on a very small scale, but on scale-up, the reaction gave only acetylation of the hemiacetal; this side reaction was the result of a slow oxidation and the presence of adventitious acetic acid in the reagent. The use of catalytic TPAP with NMO as the oxidant,[48] however, gave satisfactory results and afforded lactone **114** in reasonable yield.

The final transformation required to access **2** was removal of the TIPS protecting group at C13. We first employed standard HF·CH_3CN deprotection conditions

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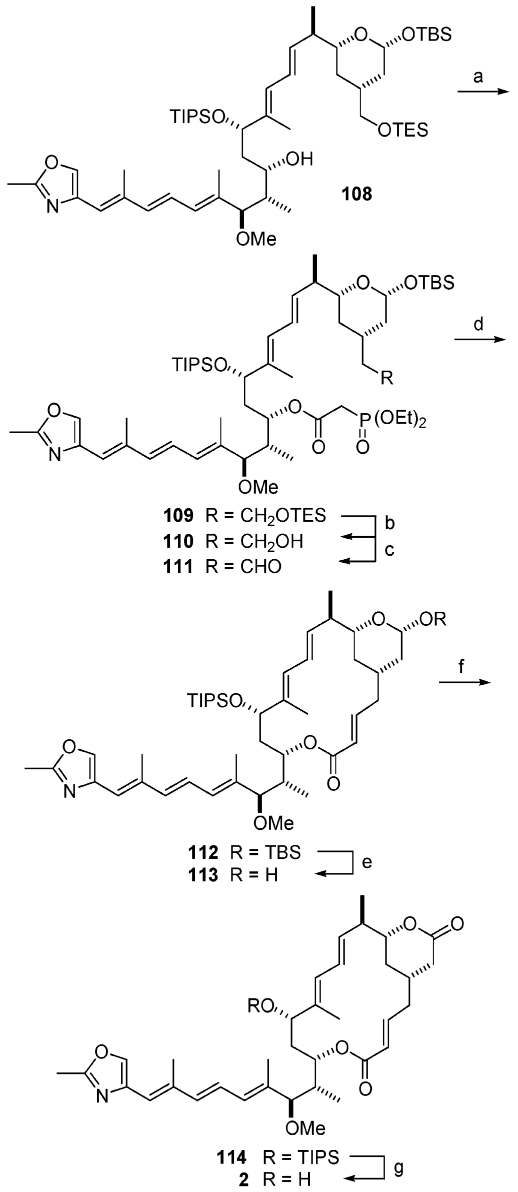
SCHEME 28[a]



[a] Reaction conditions: (a) $(EtO)_2POCH_2COCl$, pyr. (92%); (b) H_2SiF_6, 2-propanol, −40 °C (88%); (c) Dess−Martin oxidation (78%); (d) $Ba(OH)_2$, THF, H_2O (49%); (e) HF·pyridine (80%); (f) TPAP, NMO, 3 Å sieves (61%); (g) TBAF (73%).

to this end and were disappointed to find rapid and complete decomposition of our substrate. Using a much weaker solution of the same reagent did afford the desired product, but in only trace quantities and accompanied by two minor side products. Similar results were observed when the experiment was run in a polypropylene reaction vessel or when fluorosilicic acid was employed. As a final effort, we turned to TBAF, a reagent we were reluctant to try because its basicity had contributed to unsatisfactory results at earlier points in the synthesis. We were excited to find, though, that this reaction was extremely facile and much cleaner than the acidic methods we had tested. The protocol gave a 73% yield of **2**. The synthetic material compared favorably in all respects with data provided for the natural product.[4a]

Conclusions

Despite the many detours encountered in reaching our target, we believe that our strategy makes a positive contribution to the existing synthetic knowledge about this natural macrolide. Several aspects of our approach differ significantly from other published efforts and represent a nice complement to those endeavors. First, by introducing the oxazole side chain much earlier than in any of the other approaches, our synthesis provides insight regarding the compatibility of the triene with a wide variety of chemical transformations, while also making the synthesis more convergent. In addition, the problem of setting the four stereocenters of the C10−C19 portion of rhizoxin was successfully addressed in our approach, largely thanks to the use of *anti*-aldol methodology recently developed by Masamune. Finally, our synthesis benefits from a highly efficient method for the installation of the C9−C10 olefin: a modified, one-step Julia reaction allows us to assemble the framework of our target in high yield.

Experimental Section

(3*S*)-[2-(Benzyloxyethyl)]-5-hexenal (17). A suspension of (methoxymethyl)-triphenylphosphonium chloride (66.6 g, 194 mmol) in THF (300 mL) was cooled to −78 °C, and NaHMDS (1 M in THF, 188 mL, 188 mmol) was added to the mixture dropwise. The resulting orange solution was stirred for 1 h, and then aldehyde **16** (6.50 g, 29.0 mmol) in THF (100 mL) was added via syringe. After stirring for an additional 2 h at −78 °C, the mixture was allowed to warm to room temperature for 30 min, and then the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The material was extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. This crude material was then run through a plug of silica gel in order to separate nonpolar impurities, and the resulting mixture of two enol ethers ((*E*)- and (*Z*)-olefin isomers) was then carried directly into the following hydrolysis reaction.

The enol ethers from the above reaction (7.6 g, 29 mmol) were dissolved in 110 mL of Et_2O. To this solution were added 7.5 mL of water and 75 mL of formic acid, sequentially. The mixture was stirred at room temperature for 10 h, brought to neutral pH with 3 N NaOH, and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 5.9 g (82% from aldehyde **16**) of homologated aldehyde **17**: $[\alpha]^{23}_D$ +2.74 (*c* 0.4, $CHCl_3$); IR (thin film) 2919, 2859, 2760, 1728 cm^{-1}; ^1H NMR δ 1.49 (m, 1H), 1.61 (m, 1H), 1.94 (m, 1H), 2.06 (m, 1H), 2.18 (m, 1H), 2.29 (m, 2H), 3.40 (t, 2H, $J = 6.3$ Hz), 4.37 (s, 2H), 4.93 (m, 2H), 5.63 (m, 1H), 7.21 (m, 5H), 9.62 (t, 1H, $J = 1.9$ Hz); ^{13}C NMR δ 30.0, 33.8, 38.7, 47.9, 67.9, 72.9, 117.3, 127.58, 127.64, 128.4, 135.9, 138.3, 202.6. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.57; H, 8.74.

[4*S*,3(2*S*,3*R*,5*S*)]-4-Benzyl-3-(5-allyl-6-benzyloxy-3-hydroxy-2-methyl-1-heptanoyl)-2-oxazolidinone (19). (4*S*)-3-Propionyl-4-(benzyl)-2-oxazolidinone (5.13 g, 22.0 mmol) (**18**) was dissolved in CH_2Cl_2 (55 mL) and cooled to 0 °C. Bu_2BOTf (4.8 mL, 22.2 mmol) was then added via syringe, dropwise. After the mixture was stirred for 15 min, *i*-Pr_2EtN (4.22 mL, 24.2 mmol) was added to the solution, which was stirred for an additional 40 min. The mixture was then cooled to −78 °C, and aldehyde **17** (5.64 g, 24.2 mmol) in CH_2Cl_2 (70 mL) was added via cannula over 10 min. The resulting solution was stirred at −78 °C for 3 h, and the reaction was then quenched by the addition of 35 mL of pH 7 buffer and 45 mL of MeOH. The mixture was allowed to warm to room temperature, and an additional 50 mL of MeOH and 35 mL of 30% H_2O_2 were added. After stirring vigorously for 3 h, the mixture was allowed to stand overnight. The volatiles were then removed in vacuo, and the resulting paste was dissolved in saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography (30:1 hexanes/EtOAc) to afford 8.15 g (80%) of aldol adduct **19**, along with 1.07 g (19%) of recovered aldehyde **17**: $[\alpha]^{23}{}_{D}$ +49.2 (*c* 1.04, $CHCl_3$); IR (thin film) 3521, 2860, 1781, 1694 cm^{-1}; ^1H NMR δ 1.16 (d, 3H, J = 7.0 Hz), 1.28 (ddd, 1H, J = 3.6, 7.8, 11.5 Hz), 1.62 (m, 4H), 2.03 (m, 2H), 2.70 (dd, 1H, J = 9.4, 13.3 Hz), 2.82 (br s, 1H), 3.16 (dd, 1H, J = 3.3, 13.4 Hz), 3.45 (dt, 2H, J = 1.8, 6.7 Hz), 3.63 (dq, 1H, J = 3.0, 7.0 Hz), 4.00 (dt, 1H, J = 3.4, 9.1 Hz), 4.08 (m, 2H), 4.42 (s, 2H), 4.60 (m, 1H), 4.95 (m, 2H), 5.68 (m, 1H), 7.11−7.29 (m, 10H); ^{13}C NMR δ 10.6, 31.5, 33.6, 37.7, 37.8, 37.9, 42.6, 55.0, 66.0, 68.3, 69.4, 72.8, 116.6, 127.3, 127.4, 127.5, 128.2, 128.9, 129.3, 135.0, 136.4, 138.4, 152.9, 177.1. Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01. Found: C, 72.12; H, 7.53; N, 2.96.

(2*R*,3*R*,5*S*)-(*t*-Butyl)-[2-methyl-3-(benzyloxy)-5-[2-(benzyloxy)ethyl]-7-octenyl]oxy]diphenylsilane (22). Alcohol **21** (223 mg, 0.420 mmol) was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and cyclohexane (2.0 mL) and cooled to 0 °C. Benzyl trichloroacetimidate[33] (0.158 mL, 0.840 mmol) was then added dropwise, followed by triflic acid (3.7 μL, 40 μmol). The reaction mixture immediately became cloudy with precipitate upon addition of the acid, and stirring was continued at 0 °C for an additional 12 h. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude material was purified by column chromatography (petroleum ether to 99:1 petroleum ether/EtOAc) to afford 207 mg of benzyl ether **22** (79%): $[\alpha]^{23}{}_{D}$ +3.08 (*c* 1.04, $CHCl_3$); IR (thin film) 3068, 2929, 1427 cm^{-1}; ^1H NMR δ 0.96 (d, 3H, J = 6.9 Hz), 1.14 (s, 9H), 1.32−1.81 (m, 5H), 2.00 (ddd, 1H, J = 2.9, 6.8, 13.6 Hz), 2.14 (t, 2H, J = 5.9 Hz), 3.56 (t, 2H, J = 6.9 Hz), 3.64 (dd, 1H, J = 6.4, 9.9 Hz), 3.83 (m, 2H), 4.54 (d, 4H, J = 4.6 Hz), 5.05 (m, 2H), 5.68 (m, 1H), 7.29−7.50 (m, 16H), 7.71−7.75 (m, 4H); ^{13}C NMR δ 11.2, 19.2, 26.9, 31.6, 33.7, 35.7, 38.1, 39.1, 65.8, 68.4, 71.9, 72.8, 83.5, 116.4, 127.2, 127.4, 127.51, 127.52, 127.6, 128.2, 128.3, 129.5, 133.8, 135.6, 136.5, 138.6, 139.2. Anal. Calcd for $C_{41}H_{52}O_3Si$: C, 79.31; H, 8.44. Found: C, 79.50; H, 8.42.

(3*S*,5*R*,6*R*)-7-[[*t*-Butyldiphenylsilyl]oxy]-6-methyl-5-benzyloxy-3-[2-(benzyloxy)ethyl]-heptanal (23). Olefin **22** (207 mg, 0.334 mmol) was dissolved in a mixture of THF/water (3:1, 9.2 mL total) and cooled to 0 °C. To this solution were added *N*-methylmorpholine *N*-oxide (78.0 mg, 0.667 mmol) and OsO_4 (4 wt % in water, 0.105 mL, 0.017 mmol), sequentially. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched by the addition of solid sodium bisulfite (325 mg) to afford a dark red solution, which was then concentrated in vacuo to remove all volatiles. The resulting paste was partitioned between 1 N HCl and EtOAc and then extracted with Et_2O and EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over K_2CO_3, filtered, and concentrated. This crude diol was used directly in the oxidative cleavage step that follows.

The crude dihydroxylated material was dissolved in THF/water (3:1, 9.2 mL total), and $NaIO_4$ (142 mg, 0.667 mmol) was added to this solution in one portion. A white precipitate formed after several minutes, and after 8 h the reaction was judged to be complete by TLC analysis. The volatiles were removed in vacuo, and the resulting paste was dissolved in brine and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 212 mg of aldehyde **23** (100%): IR (thin film) 2931, 2861, 1718 cm^{-1}; ^1H NMR δ 0.89 (d, 3H, J = 6.9 Hz), 1.07 (s, 9H), 1.39 (m, 1H), 1.58−1.68 (m, 3H), 1.94 (ddd, 1H, J = 2.9, 6.8, 13.6 Hz), 2.23 (m, 1H), 2.33 (m, 2H), 3.44 (t, 2H, J = 6.4 Hz), 3.55 (dd, 1H, J = 6.4, 10.0 Hz), 3.68 (m, 1H), 3.73 (dd, 1H, J = 7.0, 10.0 Hz), 4.39 (d, a of ab quartet, 1H, J = 11.5 Hz), 4.41 (s, 2H), 4.46 (d, b of ab quartet, 1H, J = 11.4 Hz), 7.24−7.40 (m, 17H), 7.63 (m, 3H), 9.60 (s, 1H); ^{13}C NMR δ 11.5, 19.2, 26.9, 27.51, 27.55, 34.4, 36.2, 38.7, 48.4, 65.5, 68.0, 71.6, 72.6, 127.4, 127.5, 127.62, 127.66, 127.69, 128.2, 128.3, 129.6, 133.8, 135.6, 138.4, 138.9, 202.6. Anal. Calcd for $C_{40}H_{50}O_4Si$: C, 77.13; H, 8.09. Found: C, 76.77; H, 8.25.

Ethyl (2*E*,5*S*,7*R*,8*R*)-9-[[*t*-Butyldiphenylsilyl]oxy]-8-methyl-7-benzyloxy-5-[2-(benzyloxy)ethyl]-2-nonenoate (24). Triethylphosphonoacetate (99.7 μL, 0.500 mmol) was dissolved in CH_3CN (3.0 mL), and LiCl (16.9 mg, 0.399 mmol) and DBU (55.0 μL, 0.366 mmol) were added at room temperature, sequentially. This solution was stirred for 20 min, and then aldehyde **23** (207 mg, 0.333 mmol) in CH_3CN (0.3 mL) was added to the reaction mixture via syringe. After stirring at room temperature overnight, the solution had turned yellow-orange in color and contained some precipitate. The reaction was quenched with water and extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to a yellow-brown oil. This crude material was purified by column chromatography (49:1 hexanes/EtOAc) to give 177 mg (80%) of ester **24**: $[\alpha]^{23}{}_{D}$ +3.24 (*c* 1.45, benzene); IR (thin film) 2930, 2857, 2361, 1718, 1652 cm^{-1}; ^1H NMR δ 0.80 (d, 3H, J = 6.9 Hz), 0.98 (s, 9H), 1.21 (t, 3H, J = 7.1 Hz), 1.29 (m, 1H), 1.44−1.56 (m, 3H), 1.72 (m, 1H), 1.85 (ddd, 1H, J = 2.9, 6.8, 9.7 Hz), 2.10 (m, 2H), 3.46 (t, 2H, J = 6.8 Hz), 3.55 (dd, 1H, J = 6.5, 9.9 Hz), 1.73 (m, 2H), 4.18 (q, 2H, J = 7.1 Hz), 4.43 (m, 4H), 5.78 (d, 1H, J = 15.6 Hz), 6.86 (dt, 1H, J = 7.5, 15.6 Hz), 7.23−7.44 (m, 16H), 7.61−7.66 (m, 4H); ^{13}C NMR δ 11.3, 14.3, 19.3, 26.9, 31.5, 33.8, 35.6, 39.0, 60.2, 65.3, 68.1, 71.9, 73.0, 76.8, 123.1, 127.4, 127.5, 127.59, 127.62, 127.66, 128.3, 128.4, 129.6, 133.8, 135.6, 138.5, 139.0, 147.3, 166.4. Anal. Calcd for $C_{44}H_{56}O_5Si$: C, 76.26; H, 8.14. Found: C, 76.19; H, 7.91.

4-(4-Iodo-2-methyl-buta-1,3-dienyl)-2-methyl-oxazole (28). A solution of aldehyde **35** (0.542 g, 3.58 mmol) and iodoform (2.83 g, 7.57 mmol) in THF (15 mL) was added dropwise to a stirred suspension of chromium (II) chloride (2.66 g, 21.6 mmol) in THF (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 h and then poured onto water (75 mL). The aqueous layer was extracted with ether, and the organic layers were dried, filtered, and concentrated. The crude residue was purified by flash chromatography to give **28** (0.570 g, 58%) as a crystalline solid. IR (thin film) 2991, 2342, 1582, 1441 cm^{-1}; ^1H NMR δ 2.09 (s, 3 H), 2.46 (s, 3 H), 6.19 (s, 1 H), 6.41 (d, 1 H, J = 14.6 Hz), 7.16 (d, 1 H, J = 14.6 Hz), 7.55 (s, 1 H); ^{13}C NMR δ 13.7, 13.8, 76.1, 81.3, 121.0, 136.6, 137.9, 149.3, 161.1.

Alkyne 29. To a stirred solution of alcohol **51** (0.110 g, 0.247 mmol) and $PMBOC(NH)CCl_3$ (0.160 g, 0.567 mmol) in dry ether (3 mL) at room temperature was added triflic acid (0.1 μL, 0.001 mmol). The reaction mixture was stirred for 30 min and then partitioned between water (2 mL) and ether (20 mL). The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried, filtered, and concentrated. Purification by flash chromatography gave **29** (98.9 mg, 70%) as a colorless oil: $[\alpha]^{25}{}_{D}$ +0.7 (*c* 0.73); IR (thin film) 3295, 2952, 2857, 2359, 1613 cm^{-1}; ^1H NMR δ 0.089 (s, 6 H), 0.91 (s, 9 H), 1.03 (d, 3 H, J = 6.9 Hz), 1.62 (s, 3 H), 1.72 (dt, 1 H, J = 14.3, 6.0 Hz), 1.94 (m, 1 H), 2.02 (m, 1 H), 2.41 (d, 1 H, J = 1.5 Hz), 3.39 (S, 3 H), 3.79 (S, 3 H), 3.83 (M, 2 H), 4.02 (dd, 1 H, J = 1.7, 6.9 Hz), 4.30 (m, 3 H), 4.41 (d, 1 H, J = 7.1 Hz), 4.45 (d, 2 H, J = 8.2 Hz), 5.54 (t, 1 H, J = 5.9 Hz), 6.84 (d, 2 H, J = 8.4 Hz), 7.22 (d, 2 H, J = 8.4 Hz), 7.24 (m, 5 H); ^{13}C NMR δ −5.0, 10.1, 11.0, 18.4, 26.0, 35.7, 41.5, 55.3, 56.6, 59.9, 70.1, 71.3, 73.2, 74.5, 77.0, 81.9, 82.4, 113.7, 127.4, 127.9, 128.3, 129.2, 129.3, 131.2, 135.2, 138.7, 159.0. Anal. Calcd for $C_{34}H_{50}O_5Si$: C, 72.04; H, 8.89. Found: C, 72.34; H, 9.11.

Aldehyde 34. To a solution of oxalyl chloride (0.460 mL, 5.15 mmol) in CH_2Cl_2 (15 mL) at −60 °C was added a solution of dimethyl sulfoxide (0.760 mL, 10.7 mmol) in CH_2Cl_2 (2 mL). The solution was stirred for 2 min followed by the addition of alcohol **33** (0.562 g, 4.97 mmol) in CH_2Cl_2 (7 mL) dropwise over 5 min. After 15 min, triethylamine (3.45 mL, 24.8 mmol) was added and the reaction mixture was stirred at −60 °C for 5 min, warmed to room temperature, and then stirred for 10 min. Water (25 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The crude residue was purified by flash chromatography (ether) to afford **34** (0.522 g, 94%) as a light yellow solid: IR (thin film) 3008, 2844, 1701 (s), 1599, 1564 cm^{-1}; ^{1}H NMR δ 2.54 (s, 3 H), 8.18 (s, 1 H), 9.91 (s, 1 H); ^{13}C NMR δ 13.7, 140.9, 144.5, 163.0, 183.7.

Enal 35. To a solution of aldehyde **34** (0.228 g, 2.05 mmol) in benzene (12 mL) was added 2-(triphenyl-phosphoranylidene)-propionaldehyde (0.797 g, 2.50 mmol) at room temperature. After 3 days, water (10 mL) was added and the mixture was extracted with ether. The combined organics were dried, filtered, and concentrated. Purification by flash chromatography yielded **35** (0.281 g, 91%): IR (thin film) 3003, 1688 (s), 1640, 1589 cm^{-1}; ^{1}H NMR δ 2.09 (s, 3 H), 2.52 (s, 3 H), 7.07 (s, 1 H), 7.83 (s, 1 H), 9.54 (s, 1 H); ^{13}C NMR δ 11.1, 13.8, 137.4, 137.8, 138.5, 139.7, 162.0, 194.4.

Aldehyde 38. A solution of **37** (21.3 g, 67.3 mmol) in dry CH_2Cl_2 (400 mL) was cooled to −78 °C, and ozone was bubbled through until the solution turned blue. Nitrogen was then bubbled through the solution until the reaction mixture turned colorless. Triphenylphosphine (20.7 g, 78.9 mmol) was added, and the mixture was warmed to room temperature and stirred under nitrogen for 1.5 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography to yield **38** (23.6 g, 100%) as a colorless oil: IR (thin film) 3458, 2952, 2858, 1740 (s) cm^{-1}; ^{1}H NMR δ 0.11 (s, 6 H), 0.93 (s, 9 H), 4.22 (d, 2 H, J = 0.7 Hz), 9.70 (t, 1 H, J = 0.7 Hz); ^{13}C NMR δ −5.4, 18.3, 25.7, 69.6, 202.3.

Enal 39. A solution of aldehyde **38** (3.43 g, 19.7 mmol) in dry benzene (100 mL) was cooled to 0 °C, and 2-(triphenyl-phosphoranylidene)-propionaldehyde (7.54 g, 23.7 mmol) was added. The suspension was warmed to room temperature and stirred for 2 days. Water (80 mL) was added, and the mixture was extracted with ether. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography provided **39** (3.57 g, 84%) as a colorless oil: IR (thin film) 2954, 2857, 1692 (s) cm^{-1}; ^{1}H NMR δ 0.062 (s, 6 H), 0.88 (s, 9 H), 1.68 (q, 3 H, J = 1.2 Hz), 4.46 (dq, 2 H, J = 5.3, 1.1 Hz), 6.48 (tq, 1 H, J = 5.3, 1.3 Hz), 9.39 (s, 1 H); ^{13}C NMR δ −5.4, 9.2, 18.2, 25.7, 60.4, 137.7, 152.9, 194.3. Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.35. Found: C, 61.50; H, 10.12.

Alcohol 40. A stirred solution of (−)-*B*-methoxy diisopinocampheylborane (5.06 g, 16.0 mmol) in dry ether (20 mL) was cooled to −78 °C, and allylmagnesium bromide (16.0 mL, 1.0 M in ether, 16.0 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min and then warmed to room temperature for 1 h. The solution was cooled to −78 °C, and a solution of aldehyde **39** (3.36 g, 15.7 mmol) in dry ether (10 mL) was added dropwise. The solution was stirred at −78 °C for 1 h and then warmed to room temperature for 1 h. Sodium hydroxide (12.0 mL, 3 M, 36.0 mmol) and hydrogen peroxide (30%, 8.0 mL) were added, and the resulting mixture was heated to reflux for 2 h. The organic layer was washed with water, dried, filtered, and concentrated. Purification by flash chromatography produced **40** (3.70 g, 92%) as a colorless oil: $[\alpha]^{25}{}_{D}$ −8.26 (*c* 1.00); IR (thin film) 3389 (b), 2930, 2857, 1669 cm^{-1}; ^{1}H NMR δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.63 (d, 3 H, J = 1.0 Hz), 2.02 (s, 1 H), 2.31 (m, 2 H), 4.06 (t, 1 H, J = 6.5 Hz), 4.23 (d, 2 H, J = 6.1 Hz), 5.11 (m 2 H), 5.56 (tt, 1 H, J = 1.2, 6.1 Hz), 5.77 (m, 1 H); ^{13}C NMR δ −5.2, 12, 18.3, 25.9, 39.6, 59.5, 75.9, 117.6, 126.1, 134.6, 137.6. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.37; H, 10.86.

Aldehyde 42. A solution of **41** (3.025 g, 8.73 mmol) in dry CH_2Cl_2 (20 mL) was cooled to −78 °C and a saturated solution of ozone (0.04 M in CH_2Cl_2, 290 mL, 11.6 mmol) at −78 °C was added rapidly via cannula. The reaction mixture was stirred for 10 min, and triphenylphosphine (2.87 g, 10.9 mmol) was added followed by warming to room temperature and stirring for 4 h. The reaction mixture was concentrated to give a crude white solid. Purification by flash chromatography gave the starting diene **41** (0.769 g, 2.22 mmol) and the desired aldehyde **42** (1.72 g, 57%, 76% BORSM) as a colorless oil: $[\alpha]^{25}{}_{D}$ −19.9 (*c* 1.17); IR (thin film) 2954, 2856, 1728 (s) cm^{-1}; ^{1}H NMR δ 0.086 (s, 3 H), 0.089 (s, 3 H), 0.92 (s, 9 H), 1.63 (d, 3 H, J = 1.0 Hz), 2.42 (ddd, 1 H, J = 2.0, 4.2, 16.1 Hz), 2.77 (ddd, 1 H, J = 2.7, 9.3, 16.1 Hz), 4.27 (m, 3 H), 4.29 (d, 1 H, J = 11.4 Hz), 4.50 (d, 1 H, J = 11.7 Hz), 5.64 (t, 1 H, J = 5.7 Hz), 7.30 (m, 5 H), 9.72 (t, 1 H, J = 2.3 Hz); ^{13}C NMR δ −5.1, 11.2, 18.3, 25.9, 47.7, 59.7, 70.0, 79.0, 127.7, 127.8, 128.4, 129.7, 133.7, 137.9, 200.9.

Methyl (4*E*)-6-[(*t*-Butyldimethylsilyl)oxy]-4-methyl-3-hydroxy-4-hexenoate (rac-43). A solution of diisopropylamine (6.96 mL, 49.7 mmol) in THF (36 mL) was cooled to −78 °C, and *n*-BuLi (2.5 M, 18.2 mL, 45.7 mmol) was added dropwise via syringe. The resulting solution was stirred for 15 min, after which a solution of methyl acetate (4.03 mL, 50.7 mmol) in THF (25 mL) was added dropwise. This mixture was stirred for 1 h, and aldehyde **39** (1.88 g, 9.90 mmol) in THF (10 mL) was then added to the enolate solution. After 5 min, all of the aldehyde had been consumed, and the reaction was quenched by the addition of saturated aqueous NH_4Cl; the mixture was then extracted with Et_2O. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified by column chromatography (hexanes to 9:1 hexanes/EtOAc) to provide 2.00 g (78%) of the racemic aldol product **43**: IR (thin film) 3479, 2952, 1731 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.87 (s, 9H), 1.61 (s, 3H), 2.48 (dd, 1H, J = 4.0, 15.5 Hz), 2.54 (dd, 1H, J = 9.0, 16.0 Hz), 2.90 (br s, 1H), 3.68 (s, 3H), 4.19 (d, 2H, J = 5.5 Hz), 4.41 (dd, 1H, J = 3.5, 8.5 Hz), 5.58 (t, 1H, J = 6.0 Hz); ^{13}C NMR δ −5.2, 12.1, 18.3, 25.9, 39.8, 51.7, 59.8, 72.7, 126.4, 136.3, 172.8. Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.06; H, 9.56.

Methyl (4*E*,3*S*)-6-[(*t*-Butyldimethylsilyl)oxy]-4-methyl-3-hydroxy-4-hexenoate ((−)-43). In a three-necked round-bottomed flask equipped with a thermometer, (−)-diisopropyl tartrate (DIPT) (62.5 mg, 0.260 mmol) and crushed 3 Å sieves (122 mg) were stirred in CH_2Cl_2 (6 mL) at −20 °C. This solution was treated with Ti(O*i*-Pr)$_4$ (52.5 μL, 0.178 mmol) and TBHP (predried over sieves, 4.0 M in CH_2Cl_2, 0.33 mL, 1.33 mmol) sequentially, and the resulting mixture was stirred for 30 min and then cooled to −30 °C. Racemic ester **43** (490 mg, 1.78 mmol) in 3 mL of CH_2Cl_2 was then added to the solution. This mixture was stirred at −20 °C for 20 h; at this time, NMR analysis of the crude reaction mixture revealed 55% conversion to the epoxide. The reaction was then quenched by the addition of $FeSO_4$/citric acid solution (2.5 g/0.85 g in 7.5 mL of water), and the mixture was diluted with Et_2O and extracted. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was then purified by column chromatography (19:1 hexanes/EtOAc) to afford 198 mg (40%) of olefin **43**: $[\alpha]^{23}{}_{D}$ −5.65 (*c* 0.92, $CHCl_3$).

(4*E*,3*S*)-6-[(*t*-Butyldimethylsilyl)oxy]-4-methyl-3-[(triisopropylsilyl)oxy]-4-hexenal (46). In a three-necked flask equipped with a thermometer, ester **45** (71.7 mg, 0.166 mmol) was dissolved in CH_2Cl_2 (1.66 mL) and cooled to −95 °C (N_2 (*l*)/EtOH). DIBAL-H (1.5 M in toluene, 0.143 mL, 0.215 mmol) was then added dropwise to this solution. The resulting mixture was stirred for 15 min, and then the reaction was quenched by the addition of MeOH. The solution was then warmed and diluted with aqueous Rochelle's salt solution and Et_2O and stirred vigorously for 2 h. The aqueous phase was then extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford a colorless oil. This crude material was then purified by column chromatography (19:1 hexanes/EtOAc) to give 59.2 mg (89%) of aldehyde **46**: $[\alpha]^{23}{}_{D}$ −2.04 (*c* 1.4, $CHCl_3$); IR (thin film) 2930, 2865, 1727 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 1.02 (s, 21H), 1.61 (s, 3H), 2.54 (ddd, 1H, $J = 2.7, 5.9, 15.6$ Hz), 2.61 (ddd, 1H, $J = 2.6, 5.9, 15.5$ Hz), 4.19 (d, 2H, $J = 5.6$ Hz), 4.62 (t, 1H, $J = 5.9$ Hz), 5.62 (t, 1H, $J = 5.3$ Hz), 9.74 (t, 1H, $J = 2.6$ Hz); ^{13}C NMR δ −5.3, 11.9, 12.2, 17.9, 18.0, 18.2, 25.8, 49.9, 59.7, 73.3, 126.6, 201.7.

Aldol Product 47. A solution of (4*S*)-3-propionyl-4-(benzyl)-2-oxazolidinone (2.69 g, 11.5 mmol) in CH_2Cl_2 (35 mL) was cooled to 0 °C, and dibutylboron triflate (2.88 mL, 11.5 mmol) was added dropwise. The reaction mixture was stirred for 10 min followed by the addition of diisopropylethylamine (2.00 mL, 11.5 mmol). The solution was stirred at 0 °C for 15 min and then cooled to −78 °C. A solution of **42** (2.68 g, 7.69 mmol) in CH_2Cl_2 (15 mL) was added dropwise followed by stirring for 3 h. The reaction was warmed to 0 °C, and 1 M sodium acetate in 9:1 MeOH/water (55 mL) and hydrogen peroxide (30%, 22 mL) were added. The cloudy mixture was stirred at 0 °C for 90 min and then concentrated. The crude residue was diluted with water (50 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography yielded **47** (3.97 g, 89%) as a colorless oil: $[\alpha]^{25}_D$ −22.7 (*c* 1.02); IR (thin film) 3505 (b), 2928, 2856, 1781 (s), 1695 (s) cm^{-1}; ^{1}H NMR δ 0.089 (s, 6 H), 0.92 (s, 9 H), 1.25 (d, 3 H, $J = 6.9$ Hz), 1.58 (m, 1 H), 1.63 (s, 3 H), 1.93 (dt, 1 H, $J = 14.2, 9.3$ Hz), 2.76 (dd, 1 H, $J = 9.5, 13.3$ Hz), 3.27 (dd, 1 H, $J = 3.4, 10.2$ Hz), 3.67 (d, 1 H, $J = 1.7$ Hz), 3.81 (m, 1 H), 4.01 (dd, 1 H, $J = 4.3, 9.8$ Hz), 4.09 (m, 1 H), 4.15 (m, 2 H), 4,26 (d, 1 H, $J = 11.4$ Hz), 4.27 (m, 2 H), 4.46 (d, 1 H, $J = 11.4$ Hz), 4.67 (m, 1 H), 5.61 (t, 1 H, $J = 5.7$ Hz), 7.26 (m, 10 H); ^{13}C NMR δ −5.1, 11.0, 11.5, 18.3, 25.9, 37.8, 37.9, 42.9, 55.3, 59.8, 66.0, 70.0, 71.3, 84.6, 127.3, 127.6, 127.9, 128.4, 128.9, 129.4, 129.6, 134.5, 135.2, 137.9, 153.1, 175.8. Anal. Calcd for $C_{33}H_{47}NO_6Si$: C, 68.12; H, 8.14; N, 2.41. Found: C, 67.88; H, 7.96; N, 2.34.

Weinreb Amide 48. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (0.777 g, 7.97 mmol) in dry THF (25 mL) at 0 °C was added dropwise trimethylaluminum (4.00 mL, 2.0 M in hexanes, 8.00 mmol). The resulting solution was stirred at 0 °C for 30 min followed by the addition of **47** (1.02 g, 1.75 mL) in THF (10 mL). The reaction mixture was warmed to room temperature and stirred for 12 h, cooled to 0 °C, and added via cannula to a cooled (0 °C) mixture of CH_2Cl_2 (50 mL) and 0.5 M HCl (40 mL). After stirring at 0 °C for 1 h, the mixture was extracted with CH_2Cl_2, dried over sodium sulfate, filtered, and concentrated. Flash chromatography afforded **48** (0.771 g, 95%) as a colorless oil: $[\alpha]^{25}_D$ −16.4 (*c* 1.09); IR (thin film) 3475 (b), 2930, 2857, 1739 (s), 1657 cm^{-1}; ^{1}H NMR δ 0.085 (s, 6 H), 0.91 (s, 9 H), 1.19 (d, 3 H, $J = 7.0$ Hz), 1.59 (m, 1 H), 1.61 (s, 3 H), 1.87 (dt, 1 H, $J = 14.1, 9.1$ Hz), 2.91 (bs, 1 H), 3.16 (s, 3 H), 3.65 (s, 3 H), 3.91 (m, 1 H), 3.99 (m, 1 H), 4.01 (s, 1 H), 4.26 (m, 2 H), 4.26 (d, 1 H, $J = 11.5$ Hz), 4.47 (d, 1 H, $J = 11.5$ Hz), 5.59 (t, 1 H, $J = 5.6$ Hz), 7.29 (m, 5 H); ^{13}C NMR δ −5.1, 11.0, 12.5, 18.3, 25.9, 31.9, 38.0, 40.3, 59.8, 61.4, 70.0, 71.4, 84.3, 127.6, 127.8, 128.4, 129.6, 134.5, 138.0, 151.2. Anal. Calcd for $C_{25}H_{43}NO_5Si$: C, 64.48; H, 9.31; N, 3.01. Found: C, 64.30; H, 9.08; N, 2.95.

Alkyne 49. To a solution of **48** (94.4 mg, 0.203 mmol) in THF (3 mL) at room temperature was added ethynylmagnesium bromide (4.0 mL, 0.5 M in THF, 2.0 mmol). The reaction mixture was stirred for 15 h and then filtered through a plug of silica gel, which was flushed with ethyl acetate. The filtrate was concentrated and the residue purified by flash chromatography to give **49** (57.9 mg, 66%): $[\alpha]^{25}_D$ −21.8 (*c* 0.92); IR (thin film) 3484 (b), 3261, 2359 (w), 2090, 1679 cm^{-1}; ^{1}H NMR δ 0.092 (s, 6 H), 0.92 (s, 9 H), 1.22 (d, 3 H, $J = 7.0$ Hz), 1.54 (m, 1 H), 1.63 (s, 3 H), 1.90 (dt, 1 H, $J = 14.3, 10.0$ Hz), 2.59 (m, 1 H), 3.26 (s, 1 H), 3.64 (s, 1 H), 4.01 (dd, 1 H, $J = 3.5, 10.0$ Hz), 4.26 (m, 3 H), 4.27 (d, 1 H, $J = 11.3$ Hz), 4.49 (d, 1 H, $J = 11.4$ Hz), 5.60 (t, 1 H, $J = 5.9$ Hz), 7.31 (m, 5 H); ^{13}C NMR δ −5.1, 10.0, 11.1, 18.3, 25.9, 38.4, 54.0, 59.8, 70.1, 71.1, 79.4, 81.0, 84.9, 127.8, 127.9, 128.5, 129.6, 134.4, 137.6, 189.6. Anal. Calcd for $C_{25}H_{38}O_4Si$: C, 69.72; H, 8.89. Found: C, 69.80; H, 8.81.

Diol 50. A stirred solution of **49** (0.323 g, 0.749 mmol) in THF (5 mL) was cooled to −78 °C under nitrogen, and diethylmethoxyborane (0.90 mL, 1.0 M in THF, 0.90 mmol) was added dropwise. The reaction mixture was stirred for 15 min followed by the addition of sodium borohydride (36.8 mg, 0.974 mmol). The solution was stirred at −78 °C for 3.5 h and then warmed to room temperature. Acetic acid (0.6 mL) and ethyl acetate (40 mL) were added, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. Purification by flash chromatography yielded **50** (0.272 g, 84%) as a colorless oil: $[\alpha]^{25}_D$ −40.6 (*c* 0.50); IR (thin film) 3428 (b), 3296 (b), 2856, 2360 cm^{-1}; ^{1}H NMR δ 0.089 (s, 3H), 0.092 (s, 3 H), 0.92 (s, 9 H), 1.09 (d, 3 H, $J = 7.0$ Hz), 1.47 (d, 1 H, $J = 14.6$ Hz), 1.64 (s, 3 H), 1.73 (m, 1 H), 2.01 (dt, 1 H, $J = 14.5, 10.2$ Hz), 2.43 (d, 1 H, $J = 2.1$ Hz), 3.52 (s, 1 H), 3.98 (dd, 1 H, $J = 2.9, 10.5$ Hz), 4.11 (d, 1 H, $J = 10.0$ Hz), 4.26 (d, 1 H, $J = 11.7$ Hz), 4.27 (m, 3 H), 4.49 (d, 1 H, $J = 11.4$ Hz), 4.65 (t, 1 H, $J = 3.2$ Hz), 5.59 (t, 1 H, $J = 5.8$ Hz), 7.31 (m, 5 H); ^{13}C NMR δ −5.1, 0.0, 7.1, 11.2, 18.3, 25.9, 38.6, 43.5, 59.8, 66.8, 70.1, 72.8, 75.3, 85.6, 127.9, 128.0, 128.6, 129.4, 134.6, 137.6. Anal. Calcd for $C_{25}H_{40}O_4Si$: C, 69.40; H, 9.32. Found: C, 69.19; H, 9.11.

Phosphonate 54. To a solution of ethyl diethylphosphonate (0.161 g, 0.966 mmol) at −78 °C in THF (5 mL) was added *tert*-butyllithium (0.570 mL, 1.7 M in pentane, 0.970 mmol) dropwise. After 45 min, a solution of aldehyde **58** (0.303 g, 0.633 mmol) in THF (2 mL) was added and the mixture was stirred for 15 min. Saturated aqueous NH_4Cl was added, and the mixture was extracted with ether. The combined organic extracts were dried, filtered, and concentrated. The crude oil was purified by flash chromatography to provide the product alcohols (0.363 g, 89%) as a mixture of diastereomers. See Supporting Information for the ^{1}H NMR spectrum: IR (thin film) 3427 (b), 2955, 2857 cm^{-1}.

Dess−Martin periodinane (0.253 g, 0.596 mmol) was added to a solution of the products from above (0.252 g, 0.391 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 20 min. Ether was added, and the organic layer was washed with 1 N sodium hydroxide and water, dried, filtered, and concentrated to give phosphonate **54** (0.244 g, 97%) as a colorless oil. The crude product, an expected mixture of diastereomers, was not purified further and was used directly in the next step. See Supporting Information for the ^{1}H NMR spectrum: IR (cm^{-1}) 2955, 2857, 1710 (s).

(1′*E*,3′*E*)-4-(4′-(Ethoxycarbonyl)-2′-methyl-1′,3′-butadienyl)-2-methyloxazole (55). Triethylphosphonoacetate (0.692 mL, 3.47 mmol) was dissolved in CH_3CN (20 mL), and LiCl (118 mg, 2.78 mmol) and DBU (380 mL, 2.54 mmol) were added at room temperature, sequentially. This solution was stirred for 20 min, and then aldehyde **35** (350 mg, 2.31 mmol) in CH_3CN (3 mL) was added to the reaction mixture via syringe. After stirring at room temperature for 3 days, the solution had turned yellow in color, and the reaction was judged to be complete by TLC analysis. The reaction was quenched with water and extracted with Et_2O (three times) and CH_2Cl_2 (one time), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to an oil. This crude material was purified by column chromatography (19:1 hexanes/EtOAc) to give 478 mg (93%) of ester **55** as a white solid: IR (thin film) 2360, 1670, 1610 cm^{-1}; ^{1}H NMR δ 1.29 (t, 3H, $J = 7.0$ Hz), 2.15 (s, 3H), 2.46 (s, 3H), 4.20 (q, 2H, $J = 7.0$ Hz), 5.97 (d, 1H, $J = 15.5$ Hz), 6.46 (s, 1H), 7.43 (d, 1H, $J = 15.5$ Hz), 7.62 (s, 1H); ^{13}C NMR δ 13.8, 14.0, 14.3, 60.3, 117.8, 126.9, 134.7, 137.7, 138.2, 148.8, 161.3, 167.2. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.32; H, 6.70; N, 6.42.

Aldehyde 58. To a solution of amide **57** (1.65 g, 3.06 mmol) in THF (30 mL) at −78 °C was added diisobutylaluminum hydride (2.90 mL, 1.5 M in toluene, 4.35 mmol). After the reaction was stirred for 45 min, a saturated aqueous solution of sodium potassium tartrate (100 mL) was added and the mixture was extracted with ether. The combined organic layers were dried, filtered, and concentrated. Purification by flash chromatography afforded alcohol **58** (1.37 g, 93%) as a colorless oil: $[\alpha]^{25}_{D}$ −2.2 (*c* 1.26); IR (thin film) 2955, 2857, 1732 (s) cm^{-1}; ^{1}H NMR δ 0.08 (s, 9 H), 0.091 (s, 3 H), 0.093 (s, 3 H), 0.92 (s, 9 H), 0.99 (d, 3 H, J = 7.0 Hz), 1.61 (s, 3 H), 1.67 (m, 1 H), 1.88 (m, 1 H), 2.24 (m, 1 H), 3.71 (dd, 1 H, J = 5.4, 8.1 Hz), 4.20 (d, 1 H, J = 11.9 Hz), 4.28 (m, 3 H), 4.48 (d, 1 H, J = 11.9 Hz), 5.56 (t, 1 H, J = 5.6 Hz), 7.30 (m, 5 H), 9.62 (d, 1 H, J = 0.7 Hz); ^{13}C NMR δ −5.1, 0.4, 7.5, 11.0, 18.3, 25.9, 38.7, 50.7, 59.8, 68.7, 69.6, 80.7, 127.5, 127.9, 128.3, 129.4, 134.7, 138.4, 204.6. Anal. Calcd for $C_{26}H_{46}O_4Si_2$: C, 65.22; H, 9.68. Found: C, 64.99; H, 9.49.

Triene 59. Barium hydroxide octahydrate (dried at 110 °C for 18 h, 0.730 g, 2.31 mmol) was added to a solution of phosphonate **54** (1.55 g, 2.41 mmol) in THF (10 mL), and the resulting suspension was stirred at ambient temperature for 30 min. A solution of aldehyde **53** (0.478 g, 2.70 mmol) in 40:1 THF/water (5 mL) was added, and the reaction mixture was stirred for 16.5 h. The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with saturated aqueous sodium bicarbonate and then dried, filtered, and concentrated. Purification by flash chromatography provided **59** (1.04 g, 65%) as a yellow oil: $[\alpha]^{25}_{D}$ −18.7 (*c* 0.61); IR (thin film) 2954, 2856, 1652 cm^{-1}; ^{1}H NMR δ 0.069 (s, 6 H), 0.092 (s, 9 H), 0.90 (s, 9 H), 1.10 (d, 3 H, J = 6.8 Hz), 1.53 (s, 3 H), 1.61 (dt, 1 H, J = 5.4 Hz), 1.80 (m, 1 H), 1.85 (s, 3 H), 2.14 (s, 3 H), 2.48 (s, 3 H), 3.49 (quint, 1 H, J = 7.2 Hz), 3.91 (t, 1 H, J = 6.5 Hz), 3.98 (m, 1 H), 4.25 (d, 1 H, J = 11.9 Hz), 4.26 (m, 2 H), 4.41 (d, 1 H, J = 11.9 Hz), 5.53 (t, 1 H, J = 6.2 Hz), 6.29 (s, 1 H), 6.54 (m, 2 H), 7.07 (d, 1 H, J = 10.3 Hz), 7.25 (m, 5 H), 7.59 (s, 1 H); ^{13}C NMR δ −5.1, 0.6, 10.9, 11.9, 13.8, 14.2, 15.4, 18.3, 25.9, 39.8, 45.1, 59.8, 69.5, 72.2, 81.1, 123.7, 124.5, 127.1, 127.5, 128.1, 129.3, 135.2, 135.3, 136.4, 136.8, 138.6, 138.6, 138.8, 144.1, 161.1, 204.5. Anal. Calcd for $C_{38}H_{59}NO_5Si_2$: C, 68.53; H, 8.93; N, 2.10. Found: C, 68.50; H, 9.13; N, 1.72.

Alcohol 60. To a solution of silyl ether **59** (0.433 g, 0.650 mmol) in THF (8 mL) at room temperature was added a solution of citric acid in methanol (11.0 mL, 1 M, 11.0 mmol). After 1 h, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ether. The combined organic layers were dried, filtered, and concentrated. Purification by flash chromatography afforded alcohol **60** (0.334 g, 89%): $[\alpha]^{25}_{D}$ −66.8 (*c* 1.16); IR (thin film) 3494 (b), 2953, 2856, 1646 (s) cm^{-1}; ^{1}H NMR δ 0.075 (s, 6 H), 0.90 (s, 9 H), 1.17 (d, 3 H, J = 7.0 Hz), 1.50 (dq, 1 H, J = 14.0, 2.3 Hz), 1.59 (s, 3 H), 1.79 (dt, 1 H, J = 14.2, 9.3 Hz), 1.94 (s, 3 H), 2.20 (s, 3 H), 2.48 (s, 3 H), 3.28 (quint, 1 H, J = 6.6 Hz), 3.86 (d, 1 H, J = 1.0 Hz), 3.98 (m, 2 H), 4.25 (m, 2 H), 4.26 (d, 1 H, J = 11.5 Hz), 4.47 (d, 1 H, J = 11.5 Hz), 5.58 (t, 1 H, J = 5.7 Hz), 6.42 (s, 1 H), 6.68 (m, 2 H), 7.15 (d, 1 H, J = 9.0 Hz), 7.29 (m, 5 H), 7.61 (s, 1 H); ^{13}C NMR δ −5.1, 11.0, 11.9, 13.82, 13.84, 14.2, 18.3, 25.9, 38.2, 44.3, 59.8, 70.0, 72.0, 84.3, 124.1, 124.3, 127.6, 127.9, 128.4, 129.6, 135.2, 136.3, 137.0, 137.9, 138.5, 139.3, 144.9, 161.2, 205.5. Anal. Calcd for $C_{35}H_{51}NO_5Si$: C, 70.79; H, 8.66; N, 2.36. Found: C, 71.17; H, 8.72; N, 1.98.

Diol 61. Diethylmethoxyborane (1.55 mL, 1.0 M in THF, 1.55 mmol) was added dropwise to a solution of hydroxy ketone **60** (0.668 g, 1.24 mmol) in THF (12 mL) and methanol (2 mL) at −78 °C. After 30 min, sodium borohydride (94.6 mg, 2.50 mmol) was added. After 3 h, the reaction was treated with acetic acid (2.0 mL) and ethyl acetate (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and then dried, filtered, and concentrated. The crude residue was dissolved in methanol and concentrated three times. Purification by flash chromatography gave **61** (0.561 g, 76%) as a yellow oil. The unstable diol was used directly in the next step: $[\alpha]^{25}_{D}$ −44.4 (*c* 0.93); IR (thin film) 3421 (b), 2931, 2856 cm^{-1}; ^{1}H NMR δ 0.075 (s, 3 H), 0.078 (s, 3 H), 0.82 (d, 3 H, J = 7.0 Hz), 0.90 (s, 9 H), 1.44 (d, 1 H, J = 14.2 Hz), 1.60 (m, 1 H), 1.63 (s, 3 H), 1.72 (s, 3 H), 1.98 (dt, 1 H, J = 14.4, 10.0 Hz), 2.11 (s, 3 H), 2.43 (s, 3 H), 3.71 (s, 1 H), 3.95 (s, 1 H), 3.99 (dd, 1 H, J = 2.9, 10.3 Hz), 4.06 (d, 1 H, J = 9.6 Hz), 4.25 (m, 2 H), 4,26 (d, 1 H, J = 11.5 Hz), 4.31 (s, 1 H), 4.49 (d, 1 H, J = 11.5 Hz), 5.57 (t, 1 H, J = 5.4 Hz), 6.21 (s, 1 H), 6.31 (d, 1 H, J = 11.1 Hz), 6.39 (d, 1 H, J = 15.0 Hz), 6.57 (dd, 1 H, J = 11.1, 15.0 Hz), 7.30 (m, 5 H), 7.49 (s, 1 H); ^{13}C NMR δ −5.1, 5.1, 11.2, 13.8, 14.4, 14.6, 18.3, 25.9, 39.2, 40.4, 59.8, 70.0, 76.1, 79.7, 85.4, 119.7, 124.5, 124.8, 127.8, 127.9, 128.5, 129.2, 134.7, 135.6, 136.5, 137.2, 137.6, 138.4, 138.8, 160.8.

Ester 72.[40] The norephedrine-based auxiliary **71** (260 mg, 0.543 mmol) and triethylamine (0.264 mL, 1.90 mmol) were dissolved in CH_2Cl_2 (4.0 mL), and the mixture was cooled to −78 °C. Dicyclohexylboron triflate (1 M in hexanes, 1.62 mL, 1.62 mmol) was then added to the solution via syringe, and the resulting mixture was stirred for 2 h at −78 °C. Aldehyde **46** (248 mg, 0.597 mmol) in CH_2Cl_2 (2.0 mL) was added to the solution dropwise via cannula, and the mixture was stirred at −78 °C for 1 h and then warmed to 0 °C for an additional 2 h. The reaction was then quenched by the addition of 1 M NaOAc in 9:1 MeOH/H_2O (10 mL) and 30% H_2O_2 (4 mL), and this mixture was stirred vigorously for 12 h. The volatiles were then removed in vacuo, and the resulting paste was partitioned between Et_2O and water and then extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil. The crude material was purified by column chromatography (hexanes to 40:1 hexanes/EtOAc) to afford 391 mg of aldol adduct **72** (81%): $[\alpha]^{23}_{D}$ −1.77 (*c* 0.6, $CDCl_3$); IR (thin film) 3452, 2930, 1730 cm^{-1}; ^{1}H NMR δ 0.06 (s, 6H), 0.89 (s, 9H), 1.04 (m, 23H), 1.08 (d, 3H, J = 7.5 Hz), 1.11 (d, 3H, J = 7.0 Hz), 1.52 (s, 3H), 1.63 (ddd, 1H, J = 4.5, 10.0, 14.5 Hz), 1.68 (ddd, 1H, J = 2.0, 5.5, 14.5 Hz), 2.45 (s, 3H), 2.50 (s, 8H), 3.38 (s, 1H), 3.91 (t, 1H, J = 8.0 Hz), 4.01 (m, 1H), 4.21 (m, 1H), 4.41 (t, 1H, J = 4.0 Hz), 4.60 (d, 1H, J = 16.5 Hz), 4.82 (d, 1H, J = 16.5 Hz), 5.67 (t, 1H, J = 6.0 Hz), 5.73 (d, 1H, J = 4.0 Hz), 6.79 (d, 2H, J = 7.0 Hz), 6.90 (s, 2H), 7.22 (m, 6H); ^{13}C NMR δ −5.29, −5.25, 12.2, 13.1, 13.2, 13.4, 17.98, 18.00, 18.2, 20.9, 22.9, 25.8, 38.5, 45.9, 48.2, 56.7, 59.7, 70.1, 75.7, 77.9, 125.7, 125.9, 127.0, 127.6, 127.7, 128.2, 128.3, 132.1, 133.5, 136.7, 138.4, 138.9, 140.3, 142.4, 173.7. Anal. Calcd for $C_{50}H_{79}NO_7SSi_2$: C, 67.14; H, 8.90; N, 1.57. Found: C, 67.15; H, 8.74; N, 1.47.

(2*E*,4*S*,6*S*,7*R*,8*RS*)-1-[(*t*-Butyldimethylsilyl)oxy]-9-(diethylphosphono)-3,7-dimethyl-4-[(triisopropylsilyl)oxy]-6-[(trimethylsilyl)oxy]-2-decaen-8-ol (76). Ethyl diethyl phosphonate (0.609 g, 9.17 mmol) was dissolved in THF (12.2 mL) and cooled to −78 °C, and *t*-BuLi (1.5 M in pentane, 6.11 mL, 9.17 mmol) was added dropwise. This solution was stirred for 45 min, and then a solution of aldehyde **75** (1.75 g, 3.21 mmol) in 12.2 mL of THF was added via syringe. After 10 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was diluted and extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (19:1 to 3:1 hexanes/EtOAc) to afford 2.28 g (100%) of hydroxy phosphonates **76** as a mixture of four isomers: IR (thin film) 3420, 2928 cm^{-1}. Anal. Calcd for $C_{34}H_{75}O_7PSi_3$: C, 57.42; H, 10.63. Found: C, 57.35; H, 10.46. See Supporting Information for the ^{1}H NMR spectrum.

(2*E*,4*S*,6*S*,7*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-9-(diethylphosphono)-3,7-dimethyl-4-[(triisopropylsilyl)oxy]-6-[(trimethylsilyl)oxy]-2-decaen-8-one (70). Hydroxy phosphonates **76** (125 mg, 0.175 mmol) were dissolved in CH_2Cl_2 (1.75 mL) and cooled to 0 °C. Dess−Martin periodinane (111 mg, 0.262 mmol) was added in one portion, and the resulting solution was stirred at 0 °C for 30 min. The reaction was then quenched with 1 N NaOH and then extracted with Et_2O. The organic extracts were combined and dried over $MgSO_4$, and the solution was filtered and concentrated in vacuo. The crude material was purified by column chromatography (14:1 to 6:1 hexanes/EtOAc) to afford 120 mg (96%) of ketophosphonate **70** as a mixture of two isomers: IR (thin film) 2941, 1717 cm^{-1}. Anal. Calcd for $C_{34}H_{73}O_7PSi_3$: C, 57.58; H, 10.38. Found: C, 57.39; H, 10.16. See Supporting Information for the ^{1}H NMR spectrum.

(2′-Methyloxazol-4′-yl)-4-[(triisopropylsilyl)oxy]-6-[(trimethylsilyl)oxy]-2,9,11,13-tetradecatetraen-8-one (77). Phosphonate **70** (880 mg, 1.28 mmol) and $Ba(OH)_2$ (dried at 110 °C for 24 h, 405 mg, 1.28 mmol) were stirred in THF (3.2 mL) at room temperature for 30 min. Aldehyde **53** (227 mg, 1.28 mmol) was then dissolved in a THF/H_2O mixture (40:1, 3.2 mL total) and added to the phosphonate via syringe. The resulting mixture was stirred for 48 h and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo, and the resulting crude oil was purified by column chromatography (hexanes to 19:1 hexanes/EtOAc) to afford 769 mg (85%) of triene **77** as one olefin isomer: $[\alpha]^{23}_{D}$ -5.75 (c 0.4, CH_2Cl_2); IR (thin film) 2945, 2864, 1655, 1599 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6H), 0.08 (s, 9H), 0.88 (s, 9H), 1.01 (m, 24H), 1.58 (s, 3H), 1.61 (m, 1H), 1.68 (m, 1H), 1.93 (s, 3H), 2.19 (s, 3H), 2.47 (s, 3H), 3.51 (m, 1H), 4.07 (m, 1H), 4.20 (m, 3H), 5.47 (t, 1H, $J = 5.0$ Hz), 6.41 (s, 1H), 6.67 (m, 2H), 7.17 (d, 1H, $J = 9.0$ Hz); 7.60 (s, 1H); ^{13}C NMR δ -5.30, -5.28, 0.6, 11.4, 12.2, 12.3, 12.6, 13.8, 14.2, 18.1, 18.2, 18.3, 25.9, 41.5, 46.0, 59.8, 72.1, 75.6, 123.7, 124.5, 126.0, 136.0, 136.4, 136.8, 138.5, 138.6, 138.9, 144.1, 161.1, 203.7. Anal. Calcd for $C_{40}H_{73}NO_5Si_3$: C, 65.61; H, 10.05; N, 1.91. Found: C, 65.33; H, 10.03; N, 1.99.

(2*E*,4*S*,6*S*,7*S*,9*E*,11*E*,13*E*)-1-[(*t*-Butyldimethylsilyl)oxy]-6-hydroxy-3,7,9,13-tetramethyl-14-(2′-methyl-4′-oxazolyl)-4-[(triisopropylsilyl)oxy]-2,9,11,13-tetradecatetraen-8-one (78). Triene **77** (769 mg, 1.05 mmol) was dissolved in 2-propanol (15 mL) and cooled to -40 °C (CH_3CN/dry ice bath), and fluorosilicic acid (25% in water, 0.25 mL) was added dropwise. The mixture was allowed to stir for 1 h, and the reaction was then quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by column chromatography (19:1 to 6:1 hexanes/EtOAc) to afford 584 mg of the desired product **78** (86%) along with an additional 37.2 mg (4%) of the isomerized material **79**: $[\alpha]^{23}_{D}$ -43.3 (c 0.6, CH_2Cl_2); IR (thin film) 3470, 2927, 1654 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 1.03 (m, 21H), 1.14 (d, 3H, $J = 4.5$ Hz), 1.56 (s, 3H), 1.64 (ddd, 1H, $J = 4.5$, 10.0, 14.5 Hz), 1.70 (ddd, 1H, $J = 2.5$, 6.0, 14.0 Hz), 1.94 (s, 3H), 2.19 (s, 3H), 2.47 (s, 3H), 3.37 (m, 1H,), 3.49 (d, 1H, $J = 5.0$ Hz), 3.95 (br s, 1H), 4.20 (m, 2H), 4.41 (t, 1H, $J = 5.0$ Hz), 5.62 (t, 1H, $J = 6.0$ Hz), 6.41 (s, 1H), 6.69 (m, 2H), 7.19 (d, 1H, $J = 10.5$ Hz), 7.60 (s, 1H); ^{13}C NMR δ -5.29, -5.26, 11.8, 12.3, 12.6, 13.8, 14.2, 14.8, 18.02, 18.04, 18.2, 25.8, 39.9, 44.2, 59.7, 70.8, 75.5, 124.3, 125.6, 135.5, 136.4, 136.9, 137.6, 1385, 139.3, 144.8, 161.2, 205.9. Anal. Calcd for $C_{37}H_{65}NO_5Si_2$: C, 67.32; H, 9.93; N, 2.12. Found: C, 66.97; H, 10.18; N, 2.28.

(2*E*,4*S*,6*S*,7*S*,8*R*,9*E*,11*E*,13*E*)-1-[(*t*-Butyldimethylsilyl)oxy]-3,7,9,13-tetramethyl-14-(2′-methyl-4′-oxazolyl)-6-(*p*-nitrobenzoate)-4-[(triisopropylsilyl)oxy]-2,9,11,13-tetradecatetraen-8-ol (83). In a flame-dried flask, diiodomethane (0.033 mL, 0.41 mmol) was dissolved in THF (3.0 mL), and this solution was added dropwise to samarium metal (73 mg, 0.48 mmol). The resulting mixture was cooled to 0 °C in the dark for 45 min to generate a 0.1 M solution of SmI_2. In a separate flask, ketone **78** (30.2 mg, 0.046 mmol) was dissolved in dry THF (0.15 mL) and cooled to -10 °C (MeOH/ice), and *p*-nitrobenzaldehyde (34.6 mg, 0.229 mmol) was added in one portion. The SmI_2 solution (0.136 mL, 13.5 mmol) was then added dropwise, and the mixture was stirred for 3.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by column chromatography (14:1 to 6:1 hexanes/EtOAc) to give 30.7 mg (83%) of product **83**. This compound was found to be extremely unstable and was used immediately in the following reaction: $[\alpha]^{23}_{D}$ $+38.0$ (c 1.8, CH_2Cl_2); IR (thin film) 3433, 2943, 2864, 1721 cm^{-1}; ^{1}H NMR δ 0.00 (s, 6H), 0.85 (s, 9H), 0.97 (m, 24H), 1.57 (s, 3H), 1.86 (s, 3H), 1.98 (m, 2H), 2.12 (s, 3H), 2.14 (m, 1H), 2.46 (s, 3H), 3.84 (dd, 1H, $J = 5.5$, 12.5 Hz), 4.00 (dd, 2H, $J = 6.5$, 13.5 Hz), 4.18 (dd, 1H, $J = 12.5$, 13.5 Hz), 5.13 (m, 1H), 5.39 (t, 1H, $J = 5.5$ Hz), 6.22 (m, 2H), 6.36 (d, 1H, $J = 15.0$ Hz), 6.55 (dd, 1H, $J = 11$, 15 Hz), 7.53 (s, 1H), 8.17 (d, 2H, $J = 9.0$ Hz), 8.29 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR δ -5.4, 9.7, 11.3, 12.4, 13.2, 13.8, 14.3, 18.0, 18.1, 18.2, 25.8, 37.0, 39.7, 59.5, 75.4, 76.0, 76.9, 120.3, 123.5, 124.3, 126.6, 130.6, 135.6, 135.8, 136.9, 137.4, 137.7, 137.9, 138.7, 150.5, 160.8, 164.5.

(2*E*,4*S*,6*S*,7*S*,8*R*,9*E*,11*E*,13*E*)-1-[(*t*-Butyldimethylsilyl)oxy]-3,7,9,13-tetramethyl-8-methoxy-14-(2′-methyl-4′-oxazolyl)-6-(*p*-nitrobenzoate)-4-[(triisopropylsilyl)oxy]-2,9,11,13-tetradecatetraene (84). In a flame-dried flask, crushed 3 Å sieves (110 mg) and Ag_2O (112 mg, 0.483 mmol) were stirred in dry benzene (0.1 mL) for 5 min. Methyl iodide (60.2 mL, 0.967 mmol) was added to the solution, which was stirred for another 10 min. Alcohol **83** (26.3 mg, 0.032 mmol) in benzene (0.1 mL) was added to the mixture, and the solution was sonicated for 12 h. The reaction mixture was then loaded directly onto a flash column and purified (hexanes to 6:1 hexanes/EtOAc) to afford 20.7 mg (77%) of the methylated material **84**: $[\alpha]^{23}_{D}$ $+22.2$ (c 2.44, $CDCl_3$); IR (thin film) 2930, 1723 cm^{-1}; ^{1}H NMR δ 0.22 (s, 6H), 0.84 (s, 9H), 0.95 (s, 21H), 1.03 (d, 3H, $J = 6.6$ Hz), 1.55 (s, 3H), 1.81 (ddd, 1H, $J = 1.5$, 7.0, 14.5 Hz), 1.91 (s, 3H), 1.94 (ddd, 1H, $J = 6.5$, 10.5, 14.5 Hz), 2.13 (s, 3H), 2.27 (ddd, 1H, $J = 1.0$, 4.0, 13.5 Hz), 2.47 (s, 3H), 3.18 (s, 3H), 3.27 (d, 1H, $J = 8.1$ Hz), 3.80 (ddd, 1H, $J = 0.5$, 5.4, 13.0 Hz), 3.97 (dd, 1H, $J = 6.6$, 13.0 Hz), 4.15 (t, 1H, $J = 6.6$ Hz), 5.06 (ddd, 1H, $J = 1.5$, 4.0, 10.5 Hz), 5.35 (t, 1H, $J = 5.5$ Hz), 6.09 (d, 1H, $J = 10.8$ Hz), 6.24 (s, 1H), 6.36 (d, 1H, $J = 15.3$ Hz), 6.58 (dd, 1H, $J = 10.5$, 15.0 Hz), 7.54 (s, 1H), 8.15 (d, 2H, $J = 9.0$ Hz), 8.27 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR δ -5.4, 1.0, 10.4, 11.2, 11.9, 12.4, 13.8, 14.3, 18.0, 18.1, 25.8, 35.3, 38.9, 56.2, 59.6, 74.4, 76.0, 88.9, 120.6, 123.5, 124.1, 126.6, 129.3, 130.4, 135.8, 135.9, 136.0, 136.8, 137.5, 136.8, 138.7, 150.4, 160.8, 163.7. Anal. Calcd for $C_{45}H_{72}N_2O_8Si_2$: C, 65.45; H, 8.79; N, 3.39. Found: C, 65.29; H, 9.02; N, 3.48.

(2*R*,3*R*,5*S*)-1-[(Triisopropylsilyl)oxy]-2-methyl-5-[(2-hydroxy)ethyl]-7-octene-3-ol (88). A three-necked flask was equipped with a mechanical stirrer and a dry ice/acetone condenser and cooled to -78 °C. Anhydrous NH_3 gas (ca. 200 mL) was then condensed into the flask, and 2.0 g (87 mmol) of sodium, broken into small pieces, was added to form a dark blue solution. Alcohol **87** (2.5 g, 5.7 mmol) was then dissolved in THF (50 mL) and added to the Na/NH_3 solution via syringe. The resulting mixture was stirred for 30 min at -78 °C, and the reaction was then quenched by the addition of solid NH_4Cl until the blue color dissipated. The reaction was allowed to warm to room temperature over several minutes, causing most of the ammonia to evolve and giving a thick white paste. This paste was dissolved in water, diluted with Et_2O, and extracted. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated in vacuo, and the resulting crude material was purified by column chromatography (9:1 to 2:1 hexanes/EtOAc). Diol **88** (2.0 g, 98%) was recovered as a colorless oil: $[\alpha]^{23}_{D}$ $+19.3$ (c 1.2, CH_2Cl_2); IR (thin film) 3340, 2941 cm^{-1}; ^{1}H NMR δ 0.89 (d, 3H, $J = 7.0$ Hz), 1.04 (m, 21H), 1.23 (m, 1H), 1.40 (m, 1H), 1.51 (ddd, 1H, $J = 4.5$, 10.0, 14.0 Hz), 1.68 (m, 2H), 2.07 (m, 1H), 3.23 (br s, 2H), 3.61 (m, 1H), 3.68 (ddd, 1H, $J = 5.5$, 8.0, 11.0 Hz), 3.73 (dd, 1H, $J = 3.5$, 10.0 Hz), 3.80 (dd, 1H, $J = 3.5$, 10.0 Hz), 3.87 (dt, 1H, $J = 3.0$, 10.5 Hz), 4.97 (m, 2H), 5.74 (m, 1H); ^{13}C NMR δ 10.6, 11.7, 17.86, 17.87, 31.0, 37.16, 37.23, 39.1, 39.6, 60.1, 68.6, 73.4, 116.3, 136.7. Anal. Calcd for $C_{20}H_{42}O_3Si$: C, 66.98; H, 11.80. Found: C, 67.01; H, 11.60.

[4*R*,6*R*,6(1*R*)]-4-Allyl-6-[1-methyl-2-((triisopropyl-silyl)oxy)ethyl]-4*H*-pyran-2-one (89). In a 500 mL round-bottomed flask equipped with a Dean–Stark trap and a condenser, diol **88** (2.0 g, 5.6 mmol) was dissolved in 250 mL of dry benzene. To this solution was added Ag_2CO_3 on Celite (approximately 1.0 mmol/0.57 g of Celite, 32 g), and the resulting slurry was protected from light with foil, stirred vigorously, and heated to 80 °C for 12 h. The reaction mixture, which had turned from green to black in color over the 12 h, was then cooled to room temperature and filtered through sintered glass to remove all solids. The solids were washed sequentially with benzene (two times) and CH_2Cl_2 (two times), and the combined yellow filtrate was concentrated to an oil in vacuo. This crude oil was purified by column chromatography (hexanes to 19:1 hexanes/EtOAc) to give 1.7 g (86%) of lactone **89** as a colorless oil: $[\alpha]^{23}_{D}$ −18.4 (*c* 0.64, CH_2Cl_2); IR (thin film) 2942, 1742 cm^{-1}; ^1H NMR δ 0.96 (d, 3H, J = 6.7 Hz), 1.03−1.08 (m, 21H), 1.36 (m, 1H), 1.81 (m, 1H), 1.91 (d, 1H, J = 14.3 Hz), 2.05−2.12 (m, 4H), 2.67 (ddd, 1H, J = 1.9, 5.3, 17.5 Hz), 3.65 (dd, 1H, J = 5.1, 9.7 Hz), 3.71 (dd, 1H, J = 7.2, 9.8 Hz), 4.47 (ddd, 1H, J = 2.9, 3.6, 12.1 Hz), 5.08 (m, 2H), 5.71 (m, 1H); ^{13}C NMR δ 11.0, 11.9, 17.6, 18.0, 31.5, 32.3, 36.0, 40.5, 40.6, 64.6, 80.4, 117.6, 134.6, 171.6. Anal. Calcd for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80. Found: C, 68.14; H, 10.99.

Sulfone 96. In a round-bottomed flask equipped with a condenser, 2-mercaptobenzothiazole (455 mg, 2.72 mmol) was dissolved in DMF (2.0 mL) and cooled to 0 °C. NaH (60% dispersion in oil, 108.8 mg, 2.72 mmol) then was added to the solution in one portion, and the resulting resulting dark yellow mixture was cooled to 0 °C and stirred for 20 min. Mesylate **95** (250 mg, 0.907 mmol) in 0.11 mL of DMF was then added to the anion via syringe, and the cloudy mixture was heated to 65 °C for 2 h. The reaction mixture was then passed directly through a column of silica gel (hexanes to 4:1 hexanes/EtOAc), affording 295 mg (94%) of the desired sulfide: $[\alpha]^{23}_{D}$ −58.8 (*c* 0.41, CH_2Cl_2); IR (thin film) 2917, 1733 cm^{-1}; ^1H NMR δ 1.13 (d, 3H, J = 7.0 Hz), 1.35 (m, 1H), 1.85 (dq, 1H, J = 1.5, 13.5 Hz), 2.06−2.11 (m, 4H), 2.21 (ddd, 1H, J = 3.0, 7.0, 14.0 Hz), 2.69 (ddd, 1H, J = 1.5, 5.0, 17.0 Hz), 3.43 (dd, a of ab quartet, 1H, J = 6.5, 13.5 Hz), 3.47 (dd, b of ab quartet, 1H, J = 6.5, 13.5 Hz), 4.54 (dt, 1H, J = 2.5, 12.0 Hz), 5.07 (m, 2H), 5.70 (m, 1H), 7.29 (ddd, 1H, J = 1.0, 7.5, 8.5 Hz), 7.04 (ddd, 1H, J = 1.0, 7.5, 8.5 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.84 (d, 1H, J = 8.0 Hz); ^{13}C NMR δ 13.4, 31.3, 32.0, 36.0, 36.4, 37.6, 40.3, 81.0, 117.8, 121.0, 121.5, 124.3, 126.0, 134.4, 135.2, 153.1, 166.4, 171.1. Anal. Calcd for $C_{18}H_{21}NO_2S_2$: C, 62.22; H, 6.09; N, 4.03. Found: C, 62.03; H, 5.95; N, 4.08.

Ammonium molybdate (272 mg, 0.204 mmol) was added to 30% H_2O_2 (0.340 mL, 3.36 mmol) at 0 °C to give a bright yellow solution. In a separate flask, the thioether from above (295 mg, 0.851 mmol) was dissolved in 5.1 mL of absolute EtOH and cooled to 0 °C. The molybdate solution was then added by syringe to the thioether, resulting in a cloudy yellow mixture that was stirred for 24 h. The solution was diluted with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O, and the combined organic extracts were then dried over $MgSO_4$, filtered, and concentrated. The resulting crude material was purified by column chromatography (19:1 to 2:1 hexane/EtOAc) to give 234 mg (91%) of sulfone **96**: $[\alpha]^{23}_{D}$ −20.0 (*c* 0.58, CH_2Cl_2); IR (thin film) 2918, 1731 cm^{-1}; ^1H NMR δ 1.11 (d, 3H, J = 7.0 Hz), 1.27 (m, 1H), 1.89 (d, 1H, J = 11.9 Hz), 2.09 (m, 4H), 2.66 (m, 2H), 3.50 (dd, 1H, J = 6.4, 14.5 Hz), 3.84 (dd, 1H, J = 6.1, 14.5 Hz), 4.60 (dt, 1H, J = 2.6, 11.9 Hz), 5.10 (m, 2H), 5.70 (m, 1H), 7.60 (dt, 1H, J = 1.4, 7.2 Hz), 7.65 (dt, 1H, J = 1.5, 7.2 Hz), 8.02 (m, 1H), 8.21 (m, 1H); ^{13}C NMR δ 13.6, 31.2, 31.5, 32.5, 35.8, 40.3, 57.4, 81.2, 118.0, 122.3, 125.5, 127.7, 128.1, 134.2, 136.5, 152.5, 166.0, 170.6. Anal. Calcd for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69. Found: C, 56.71; H, 5.75; N, 3.65.

Aldehyde 99. Olefin **98** (97.0 mg, 0.196 mmol) was dissolved in a mixture of THF/water (3:1, 5.6 mL total) and cooled to 0 °C. To this solution were added *N*-methylmorpholine *N*-oxide (46.1 mg, 0.393 mmol) and OsO_4 (4 wt % in water, 62.0 μL, 9.80 μmol) sequentially. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched by the addition of solid sodium bisulfite (325 mg) to afford a dark red solution that was then concentrated in vacuo to remove all volatiles. The resulting paste was partitioned between 1 N HCl and EtOAc and then extracted with Et_2O (two times) and EtOAc (two times). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over K_2CO_3, filtered, and concentrated. This crude diol was used directly in the oxidative cleavage step that follows.

The crude dihydroxylated material was dissolved in THF/water (3:1, 5.6 mL total), and $NaIO_4$ (84.2 mg, 0.393 mmol) was added to this solution in one portion. A white precipitate formed after several minutes, and after 1 h the reaction was judged to be complete by TLC analysis. The volatiles were removed in vacuo, and the resulting paste was dissolved in brine and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 84.6 mg of aldehyde **99** (87%): $[\alpha]^{23}_{D}$ +4.2 (*c* 0.5, CH_2Cl_2); IR (thin film) 2927, 1723 cm^{-1}; ^1H NMR δ 0.07 (s, 6H), 0.86 (s, 9H), 0.96 (m, 1H), 1.06 (m, 1H), 1.14 (d, 3H, J = 7.0 Hz), 1.51 (d, 1H, J = 11.0 Hz), 1.82 (d, 1H, J = 12.5 Hz), 2.20 (m, 1H), 2.38 (d, 2H, J = 7.0 Hz), 2.46 (m, 1H), 3.40 (dd, 1H, J = 7.0, 14.0 Hz), 3.62 (d, 1H, J = 11.5 Hz), 3.78 (dd, 1H, J = 5.0, 14.0 Hz), 4.74 (d, 1H, J = 9.0 Hz), 7.60 (t, 1H, J = 7.0 Hz), 7.64 (t, 1H, J = 7.5 Hz), 8.01 (d, 1H, J = 8.0 Hz), 8.21 (d, 1H, J = 8.0 Hz), 9.75 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ −5.1, −3.9, 14.6, 17.9, 25.7, 28.6, 32.7, 33.1, 40.1, 50.1, 57.9, 76.1, 96.5, 122.3, 125.4, 127.6, 128.0, 136.7, 152.7, 166.3, 201.0. Anal. Calcd for $C_{23}H_{35}NO_5S_2Si$: C, 55.50; H, 7.09; N, 2.81. Found: C, 55.77; H, 6.96; N, 2.98.

Alcohol 105. To a solution of aldehyde **99** (47.4 mg, 95.0 μmol) in 1 mL of MeOH at 0 °C was added sodium borohydride (7.2 mg, 0.19 mmol). The reaction was judged to be complete by TLC analysis after 5 min of stirring and then quenched by the addition of 0.5 M aqueous Rochelle's salt. The mixture was diluted with Et_2O, stirred for several min, and then extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 41.8 mg (88%) of the desired alcohol **105**: $[\alpha]^{23}_{D}$ +3.68 (*c* 1.44, CH_2Cl_2); IR (thin film) 3440, 2930, 1472 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.86 (s, 9H), 0.90−1.05 (m, 2H), 1.12 (d, 3H, J = 7.0 Hz), 1.50 (m, 4H), 1.77 (m, 2H), 2.45 (m, 1H), 3.40 (dd, 1H, J = 7.5, 14.5 Hz), 3.55 (d, 1H, J = 13.0 Hz), 3.67 (t, 2H, J = 6.5 Hz), 3.78 (dd, 1H, J = 5.5, 14.0 Hz), 4.70 (dd, 1H, J = 2.0, 9.0 Hz), 7.58 (dt, 1H, J = 1.0, 7.5 Hz), 7.63 (dt, 1H, J = 1.0, 7.5 Hz), 8.01 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 8.0 Hz); ^{13}C NMR δ −5.0, −3.9, 14.7, 17.9, 25.7, 30.6, 32.8, 33.3, 39.1, 40.3, 58.1, 60.4, 76.5, 96.9, 122.3, 125.4, 127.6, 128.0, 136.7, 152.6, 166.4. Anal. Calcd for $C_{23}H_{37}NO_5S_2Si$: C, 55.28; H, 7.46; N, 2.80. Found: C, 55.68; H, 7.29; N, 2.99.

Oxazole 107. A solution of sulfone **106** (90.0 mg, 0.146 mmol) and aldehyde **86** (104 mg, 0.146 mmol) in 5.7 mL of THF was cooled to −78 °C, and LiHMDS (1.0 M in THF, 0.337 mL) was added dropwise. The resulting dark yellow mixture was stirred for 2 h at −78 °C, during which time it became progressively darker in color. The solution was then allowed to warm to room temperature and was stirred for 10 min after reaching ambient temperature. The reaction was judged to be complete by TLC analysis and was quenched by the addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was then purified by column chromatography (hexanes to 14:1 hexanes/EtOAc) to afford 128 mg (79%) of the coupled product (**107**) as a yellow foam: $[\alpha]^{23}_{D}$ +41.2 (*c* 0.17, CH_2Cl_2); IR (thin film) 2954, 2866, 1724, 1530 cm^{-1}; ^1H NMR δ 0.09 (s, 3H), 0.11 (s, 3H), 0.58 (q, 6H, J = 7.9 Hz), 0.88 (s, 9H), 0.89 (m, 9H), 0.95 (m, 21H), 1.03 (d, 3H, J = 6.9 Hz), 1.04 (m, 3H), 1.26−

1.29 (m, 3H), 1.43−1.52 (m, 3H), 1.66 (s, 3H), 1.71 (m, 2H), 1.79 (m, 2H), 1.88 (s, 3H), 1.96 (m, 1H), 2.14 (s, 3H), 2.22 (m, 1H), 2.47 (s, 3H), 3.04 (dd, 1H, $J = 8.1$, 9.2 Hz), 3.17 (s, 3H), 3.28 (d, 1H, $J = 8.3$ Hz), 3.64 (t, 2H, $J = 6.4$ Hz), 4.63 (dd, 1H, $J = 1.4$, 9.0 Hz), 5.08 (dd, 1H, $J = 2.7$, 9.9 Hz), 5.47 (dd, 1H, $J = 7.6$, 15.0 Hz), 5.79 (d, 1H, $J = 10.9$ Hz), 5.88 (dd, 1H, $J = 10.2$, 15.0 Hz), 6.10 (d, 1H, $J = 10.7$ Hz), 6.26 (s, 1H), 6.36 (d, 1H, $J = 15.1$ Hz), 6.60 (dd, 1H, $J = 11.1$, 15.3 Hz), 7.55 (s, 1H), 8.11 (d, 2H, $J = 8.6$ Hz), 8.25 (d, 2H, $J = 8.6$ Hz); ^{13}C NMR δ −5.2, −4.0, 4.4, 6.8, 10.5, 11.7, 12.0, 12.4, 13.8, 14.4, 16.2, 18.0, 18.1, 25.8, 30.7, 34.7, 35.1, 35.6, 39.1, 39.5, 40.4, 42.0, 56.2, 60.0, 74.4, 76.4, 79.0, 89.0, 97.1, 120.6, 123.4, 124.2, 125.3, 125.9, 129.3, 130.5, 135.9, 136.0, 136.2, 136.7, 136.9, 137.56, 137.65, 138.7, 150.3, 160.9, 163.8; HRMS (FAB) *m/z* calcd for $C_{61}H_{102}N_2O_{10}Si_3$ (M^+) 1106.6842, found 1106.6849.

Phosphonate 109. To a solution of diethyl phosphonoacetic acid (100 mg, 0.509 mmol) in benzene (2 mL) was added oxalyl chloride (133 μL, 1.52 mmol) dropwise, followed by DMF (8 μL). The visible evolution of gas ceased after ca. 10 min, and the clear solution was stirred for an additional 40 min. The mixture was then concentrated in vacuo to remove all volatiles, leaving a pale yellow oil, which was dissolved in 1 mL of THF to give a 0.5 M solution of diethylphosphonoacetyl chloride.[45b]

In a separate flask, alcohol **108** (91.8 mg, 95.9 μmol) was dissolved in THF (1 mL) and cooled to 0 °C, and pyridine (46.6 μL, 57.5 μmol) was added. A portion of the acid chloride solution (0.85 mL) was then added to the mixture dropwise. The resulting cloudy solution was stirred for 10 min, and the reaction was then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude material by column chromatography (9:1 to 3:1 hexanes/EtOAc) afforded phosphonate **109** (102 mg, 92%): $[\alpha]^{23}_D$ +37.3 (*c* 0.55, CH_2Cl_2); IR (thin film) 2932, 2865, 1733 cm^{-1}; ^{1}H NMR δ 0.09 (s, 3H), 0.11 (s, 3H), 0.57 (q, 6H, $J = 7.9$ Hz), 0.89 (s, 9H), 0.96 (m, 30H), 1.00 (m, 1H), 1.08 (d, 3H, $J = 6.7$ Hz), 1.25 (m, 2H), 1.31 (dt, 6H, $J_{H-H} = 7.1$ Hz, $J_{P-H} = 1.8$ Hz), 1.42−1.51 (m, 3H), 1.65−1.79 (m, 6H), 1.69 (s, 3H), 1.82 (s, 3H), 2.12 (s, 3H), 2.13 (m, 1H), 2.30 (m, 1H), 2.46 (s, 3H), 2.72 (dd, 1H, $J_{H-H} = 14.2$ Hz, $J_{P-H} = 21.7$ Hz), 2.83 (dd, 1H, $J_{H-H} = 14.2$ Hz, $J_{P-H} = 21.7$ Hz), 3.10 (m, 1H), 3.16 (s, 3H), 3.22 (d, 1H, $J = 8.3$ Hz), 3.62 (t, 2H, $J = 6.5$ Hz), 4.08 (t, 1H, $J = 6.5$ Hz), 4.13 (m, 4H), 4.64 (dd, 1H, $J = 2.0$, 9.0 Hz), 4.80 (dd, 1H, $J = 2.5$, 9.5 Hz), 5.54 (dd, 1H, $J = 7.8$, 15.2 Hz), 5.71 (d, 1H, $J = 11.2$ Hz), 6.06 (d, 1H, $J = 10.3$ Hz), 6.14 (dd, 1H, $J = 10.9$, 15.0 Hz), 6.23 (s, 1H), 6.34 (d, 1H, $J = 15.2$ Hz), 6.55 (dd, 1H, $J = 10.8$, 15.5 Hz), 7.53 (s, 1H); ^{13}C NMR δ −5.3, −4.0, 4.3, 6.7, 10.0, 11.7, 11.9, 12.3, 12.4, 13.8, 14.3, 16.29 (d, $J_{C-P} = 6.0$ Hz), 16.32 (d, $J_{C-P} = 6.0$ Hz), 16.6, 18.00, 18.05, 18.1, 25.8, 30.7, 34.5 (d, $J_{C-P} = 134.0$ Hz), 35.28, 35.30, 38.6, 39.4, 40.3, 42.2, 56.1, 60.0, 62.39 (d, $J_{C-P} = 6.3$ Hz), 62.43 (d, $J_{C-P} = 6.3$ Hz), 73.9, 76.2, 79.0, 88.8, 97.1, 120.3, 124.3, 125.5 (d, $J_{C-P} = 3.8$ Hz), 129.0, 135.7, 136.2, 136.7, 136.9, 137.3, 138.2, 138.7, 160.8, 164.8.

Ester 112. To a solution of aldehyde **111** (74.1 mg, 71.5 μmol) in THF (143 mL) and water (1.8 mL) was added $Ba(OH)_2$ (dried at 110 °C, 452 mg, 1.43 mmol). The cloudy reaction mixture was then allowed to stir at room temperature for 4 days, after which TLC analysis revealed the consumption of all starting material. Solid $NaHCO_3$ was added to the mixture, which was then concentrated to remove most of the THF. The resulting white residue was taken up in water and extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude material by column chromatography (hexanes to 14:1 hexanes/EtOAc) afforded 30.9 mg (49%) of macrocycle **112**: $[\alpha]^{23}_D$ +118.4 (*c* 1.03, CH_2Cl_2); IR (thin film) 2957, 2863, 1715; ^{1}H NMR 0.10 (s, 3H), 0.12 (s, 3H), 0.28 (m, 1H), 0.90 (s, 9H), 1.01 (m, 24H), 1.07 (d, 3H, $J = 6.3$ Hz), 1.08 (m, 1H), 1.26 (m, 1H), 1.42 (m, 1H), 1.64 (m, 2H), 1.73 (s, 3H), 1.69−1.77 (m, 2H), 1.90 (s, 3H), 2.14 (s, 3H), 2.13−2.27 (m, 2H), 2.36 (d, 1H, $J = 11.7$ Hz), 2.46 (s, 3H), 2.79 (dd, 1H, $J = 9.7$, 10.3 Hz), 3.15 (s, 3H), 3.20 (m, 1H), 3.99 (dd, 1H, $J = 2.8$, 10.7 Hz), 4.44 (dd, 1H, $J = 2.8$, 10.7 Hz), 4.62 (d, 1H, $J = 7.9$ Hz), 5.06 (dd, 1H, $J = 10.1$, 15.1 Hz), 5.53 (d, 1H, $J = 15.6$ Hz), 5.67 (d, 1H, $J = 11.0$ Hz), 6.04 (d, 1H, $J = 11.0$ Hz), 6.13 (dd, 1H, $J = 10.9$, 15.0 Hz), 6.24 (s, 1H), 6.33 (d, 1H, $J = 15.2$ Hz), 6.61 (dd, 1H, $J = 10.8$, 15.2 Hz), 6.75 (ddd, 1H, $J = 4.6$, 11.5, 15.9 Hz), 7.55 (s, 1H); ^{13}C NMR δ −5.3, −4.0, 10.1, 11.1, 11.6, 12.4, 13.8, 14.4, 17.3, 18.0, 18.1, 18.2, 25.8, 31.9, 34.2, 37.6, 38.8, 40.7, 44.9, 56.0, 73.6, 78.2, 78.6, 89.9, 97.0, 120.4, 123.3, 124.3, 125.0, 128.9, 129.3, 134.8, 135.8, 137.05, 137.11, 137.4, 138.7, 139.0, 147.4, 154.9, 166.2; HRMS (FAB) *m/z* calcd for $C_{50}H_{83}NO_7Si_2$ (M^+) 865.5708, found 865.5715.

Hemiacetal 113. To a solution of silyl ether **112** (34.0 mg, 0.390 mmol) in THF (0.5 mL) was added 400 μL of a mixture of HF (49%) and pyridine (1:1 v/v) at room temperature. The resulting solution was stirred for 9 h and then diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated, and the resulting crude material was purified by column chromatography (hexanes to 3:1 hexanes/EtOAc). Product **113** (23.3 mg, 80%) was obtained as a mixture (~1:1) of isomers at the acetal position. Data for the mixture of isomers: $[\alpha]^{23}_D$ +144.7 (*c* 0.30, CH_2Cl_2); IR (thin film) 3418, 2927, 2862, 1716 cm^{-1}; ^{1}H NMR δ 0.29 (m, 2H), 1.01 (m, 48H), 1.07 (d, 3H, $J = 6.4$ Hz), 1.11 (d, 3H, $J = 6.4$ Hz), 1.26 (m, 4H), 1.57−1.70 (m, 8H), 1.74 (s, 6H), 1.91 (s, 6H), 2.04 (s, 6H), 2.22−2.28 (m, 4H), 2.40 (m, 2H), 2.45 (s, 6H), 2.87 (dd, 1H, $J = 9.6$, 9.8 Hz), 2.91 (br s, 1H), 3.16 (s, 6H), 3.20 (d, 2H, $J = 9.4$ Hz), 3.33 (d, 1H, $J = 9.2$, 10.1 Hz), 3.98 (dt, 2H, $J = 2.8$, 10.7 Hz), 4.27 (m, 1H), 4.54 (d, 2H, $J = 10.7$ Hz), 4.69 (d, 1H, $J = 7.9$ Hz, O−C*H*−OH), 5.06 (dd, 2H, $J = 9.8$, 15.0 Hz), 5.36 (s, 1H, O−C*H*−OH), 5.51 (d, 2H, $J = 15.7$ Hz), 5.56 (d, 2H, $J = 15.7$ Hz), 5.66 (d, 2H, $J = 10.3$ Hz), 5.69 (d, 2H, $J = 10.8$ Hz), 6.04 (d, 2H, $J = 11.8$ Hz), 6.11 (dd, 2H, $J = 11.4$, 14.7 Hz), 6.14 (dd, 2H, $J = 11.4$, 14.7 Hz), 6.24 (s, 2H), 6.33 (d, 2H, $J = 15.2$ Hz), 6.61 (dd, 2H, $J = 11.1$, 14.8 Hz), 6.75 (ddd, 2H, $J = 4.6$, 10.7, 15.7 Hz), 7.55 (s, 2H).

Lactone 114. To a solution of hemiacetal **113** (12.3 mg, 16.3 μmol) in CH_2Cl_2 (0.3 mL) were added 3 Å sieves (15 mg) and tetrapropylammonium perruthenate (TPAP) (2.0 mg, 5.9 μmol) at room temperature. After stirring for 10 min, the solution was cooled to 0 °C, and *N*-methylmorpholine *N*-oxide (2.0 mg, 17 μmol) was added to the reaction mixture, which quickly turned from pale to dark green. The mixture was stirred for 5 min and was then loaded directly onto a silica gel flash column. The column was flushed with 3:1 hexanes/EtOAc to afford 7.5 mg (61%) of the oxidized product **114**: $[\alpha]^{23}_D$ +156.9 (*c* 0.36, $CDCl_3$); ^{1}H NMR δ 0.67 (ddd, 1H, $J = 11.8$, 12.0, 14.1 Hz), 1.01 (m, 24H), 1.19 (d, 3H, $J = 6.4$ Hz), 1.66 (dd, 1H, $J = 2.7$, 14.4 Hz), 1.72 (m, 1H), 1.76 (s, 3H), 1.76 (m, 1H), 1.90 (s, 3H), 2.00 (m, 1H), 2.12 (m, 1H), 2.14 (s, 3H), 2.15 (m, 1H), 2.27 (m, 2H), 2.47 (s, 3H), 2.52 (m, 1H), 2.76 (ddd, 1H, $J = 2.1$, 4.9, 17.8 Hz), 3.16 (s, 3H), 3.21 (d, 1H, $J = 9.3$ Hz), 3.67 (ddd, 1H, $J = 2.6$, 9.4, 9.5 Hz), 3.91 (dd, 1H, $J = 2.8$, 10.8 Hz), 4.54 (dd, 1H, $J = 2.9$, 11.2 Hz), 5.09 (dd, 1H, $J = 9.4$, 15.2 Hz), 5.61 (d, 1H, $J = 16.1$ Hz), 5.69 (d, 1H, $J = 10.1$ Hz), 6.04 (d, 1H, $J = 10.0$ Hz), 6.21 (dd, 1H, $J = 10.8$, 14.8 Hz), 6.25 (s, 1H), 6.33 (d, 1H, $J = 15.2$ Hz), 6.62 (dd, 1H, $J = 10.8$, 15.1 Hz), 6.75 (ddd, 1H, $J = 4.9$, 11.0, 15.5 Hz), 7.55 (s, 1H); ^{13}C NMR δ 10.0, 11.0, 11.5, 12.3, 13.7, 14.1, 16.6, 18.0, 18.2, 29.7, 34.2, 34.6, 36.8, 38.1, 38.7, 45.3, 56.1, 73.8, 78.5, 89.7, 120.0, 123.2, 124.4, 124.5, 124.6, 129.2, 130.0, 133.2, 135.8, 137.2, 137.3, 137.4, 138.2, 140.1, 145.8, 161.2, 165.6, 170.4.

Rhizoxin D (2). A solution of lactone **114** (3.8 mg, 5.06 μmol) in THF (0.3 mL) was cooled to −78 °C. In a separate flask, a dilute solution of TBAF was prepared (0.20 mL of 1.0 M TBAF in THF dissolved in an additional 10.0 mL of THF), and 280 μL (5.6 μmol) of this solution was added to the lactone. The reaction mixture was gradually warmed to room temperature over 2.5 h and then allowed to stir at room temperature for 14.5 h. The solution then was diluted with Et_2O, and the reaction was quenched by the addition of pH 7 buffer. The aqueous phase was extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was then purified by column chromatography (hexanes to 1:1 hexanes/EtOAc) to afford 2.2 mg (73%) of didesepoxyrhizoxin as a white solid, which compared favorably with the natural product in all respects.

Data for synthetic rhizoxin D: $[\alpha]^{23}_{D}$ +285 (*c* 0.16, MeOH); ^{1}H NMR δ 0.68 (ddd, 1H, J = 12.0, 12.0, 14.5 Hz), 1.00 (d, 3H, J = 7.0 Hz), 1.19 (d, 3H, J = 6.5 Hz), 1.70 (m, 1H), 1.74 (m, 1H), 1.75 (m, 1H), 1.79 (s, 3H), 1.89 (s, 3H), 1.98 (ddd, 1H, J = 2.0, 2.0, 14.2 Hz), 2.08 (dd, 1H, J = 11.0, 17.9 Hz), 2.14 (m, 1H), 2.15 (s, 3H), 2.27 (m, 2H), 2.46 (s, 3H), 2.53 (m, 1H), 2.76 (ddd, 1H, J = 2.5, 5.5, 18.0 Hz), 3.17 (s, 3H), 3.26 (d, 1H, J = 9.2 Hz), 3.67 (ddd, 1H, J = 2.7, 9.3, 11.8 Hz), 3.91 (dd, 1H, J = 2.8, 10.8 Hz), 4.58 (dd, 1H, J = 3.0, 10.8 Hz), 5.15 (dd, 1H, J = 9.7, 15.4 Hz), 5.61 (d, 1H, J = 16.2 Hz), 5.81 (d, 1H, J = 11.0 Hz), 6.12 (d, 1H, J = 10.8 Hz), 6.23 (dd, 1H, J = 10.9, 15.3 Hz), 6.27 (s, 1H), 6.41 (d, 1H, J = 15.3 Hz), 6.63 (dd, 1H, J = 10.9, 15.2 Hz), 6.77 (ddd, 1H, J = 4.8, 11.1, 15.9 Hz), 7.55 (s, 1H). HRMS (FAB) *m/z* calcd for $C_{35}H_{48}NO_7$ ($[M + H]^+$): 594.3431. Found: 594.3432.

Data for natural rhizoxin D:[4a,49] $[\alpha]^{24}_{D}$ +287.1 (*c* 0.48, MeOH); ^{1}H NMR δ 0.68 (ddd, 1H, J = 12.0, 12.0, 14.4 Hz), 1.00 (d, 3H, J = 7.0 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.70 (m, 1H), 1.74 (m, 1H), 1.75 (m, 1H), 1.79 (s, 3H), 1.89 (s, 3H), 1.98 (dddd, 1H, J = 2.4, 2.4, 2.8, 14.4 Hz), 2.08 (dd, 1H, J = 11.6, 18.0 Hz), 2.14 (m, 1H), 2.15 (s, 3H), 2.27 (m, 2H), 2.46 (s, 3H), 2.53 (m, 1H), 2.76 (ddd, 1H, J = 2.4, 5.4, 18.0 Hz), 3.17 (s, 3H), 3.26 (d, 1H, J = 9.2 Hz), 3.67 (ddd, 1H, J = 2.8, 9.6, 12.0 Hz), 3.90 (dd, 1H, J = 3.0, 11.0 Hz), 4.58 (dd, 1H, J = 3.0, 10.8 Hz), 5.15 (dd, 1H, J = 9.6, 15.2 Hz), 5.61 (d, 1H, J = 16.0 Hz), 5.81 (d, 1H, J = 11.0 Hz), 6.12 (d, 1H, J = 10.8 Hz), 6.23 (dd, 1H, J = 11.0, 15.2 Hz), 6.27 (s, 1H), 6.41 (d, 1H, J = 15.2 Hz), 6.63 (dd, 1H, J = 10.8, 15.2 Hz), 6.75 (ddd, 1H, J = 5.0, 11.0, 16.0 Hz), 7.55 (s, 1H); HRMS (EI) *m/z* calcd for $C_{35}H_{47}NO_7$ ($[M]^+$) 593.3414, found 593.3382.

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Supporting Information Available: Complete experimental descriptions of transformations not included in the Experimental Section and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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