JOC Article

Total Synthesis of Rhizoxin D, a Potent Antimitotic Agent from the Fungus *Rhizopus chinensis*

James D. White,* Paul R. Blakemore, Neal J. Green, E. Bryan Hauser, Mark A. Holoboski, Linda E. Keown, Christine S. Nylund Kolz,† and Barton W. Phillips

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@orst.edu

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Rhizoxin D (**2**) was synthesized from four subunits, A, B, C, and D representing C3−C9, C10−C13, C14−C19, and C20−C27, respectively. Subunit A was prepared by cyclization of iodo acetal **21**, which set the configuration at C5 of **2** through a stereoselective addition of the radical derived from dehalogenation of **21** at the β carbon of the (*Z*)-α,β-unsaturated ester. Aldehyde **29** was obtained from phenylthioacetal **24** and condensed with phosphorane **30**, representing subunit B, in a Wittig reaction that gave the (*E*,*E*)-dienoate **31**. This ester was converted to aldehyde **33** in preparation for coupling with subunit C. The latter in the form of methyl ketone **55** was obtained in six steps from propargyl alcohol. An aldol reaction of **33** with the enolate of **55** prepared with (+)-DIPCl gave the desired β-hydroxy ketone **56** bearing a (13*S*)-configuration in a 17−20:1 ratio with its (13*R*)-diastereomer. After reduction to anti diol **57** and selective protection as TIPS ether **58**, the C15 hydroxyl was esterified to give phosphonate **59**. An intramolecular Wadsworth−Emmons reaction of aldehyde **62**, derived from δ-lactone **60**, furnished macrolactone **63**, which was coupled in a Stille reaction with stannane **68** to give **2** after cleavage of the TIPS ether.

Introduction

In 1984, an unusual 16-membered macrolide was isolated by Okuda et al. from the fungus *Rhizopus chinensis* Rh-2 and was named rhizoxin (**1**).[1] Although interest in **1** was initially kindled by its role as a pathogen of rice seedling blight, its antifungal activity was found to be much less compelling than its remarkable antimitotic properties.[2] Subsequently, a second metabolite was discovered in *R. chinensis* that was identified as the didesepoxy derivative and probable biogenetic precursor of **1**.[3] Rhizoxin D (**2**) and rhizoxin (**1**) are now recognized as equipotent antimitotic agents with considerable promise as lead candidates for the treatment of human carcinomas,[4] especially those resistant to therapies involving the dimeric vinca alkaloids vincristine and vinblastine and adriamycin.[2b] Rhizoxin (**1**) has undergone extensive clinical trials,[5] but the less abundant rhizoxin D (**2**) has received only limited clinical evaluation[6] despite the conjecture that it may possess therapeutic properties superior to those of **1**.[7] Rhizoxin is believed to bind to tubulin β^s and to inhibit the assembly of microtubules in a manner similar to that of maytansine and ansamitocin P-3.[8] The stereostructure of rhizoxin, including its absolute configuration, was established by careful NMR studies and by a single-crystal X-ray determination in the course of the pioneering studies of the Tokyo group.[1]

Despite the intense synthetic interest focused on this pair of macrolides, only one total synthesis of rhizoxin (**1**) has been reported.[9] However, five completed syntheses of rhizoxin D (**2**) have been described,[10] and publications detailing the preparation of subunits for eventual as-

† Formerly Christine S. Nylund.

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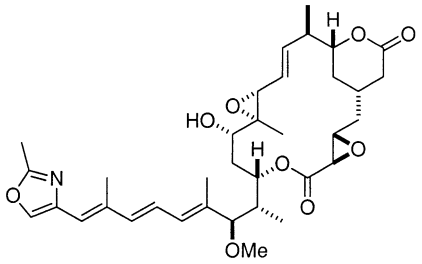
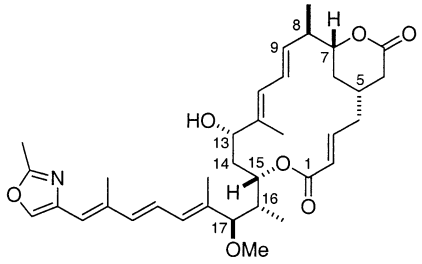


Rhizoxin (1)



Rhizoxin D (2)

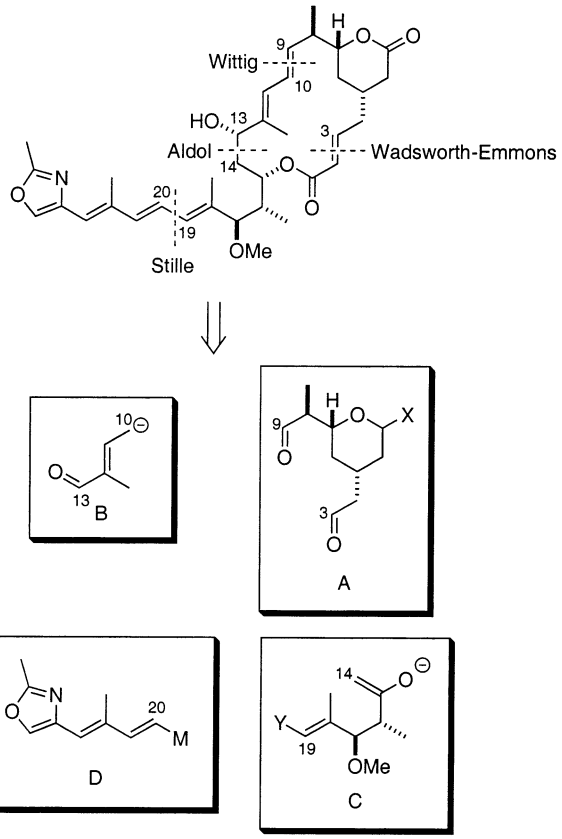
sembly into the rhizoxin macrocycle have appeared from several laboratories.[11] We now present a detailed account of our own efforts that have extended our earlier studies directed toward the rhizoxins[12] and have resulted in the total synthesis of **2**.

Our plan diagrammed in Scheme 1 envisioned the synthesis and assembly of subunits A−D for the construction of **2**, the coalescence of C with a subunit representing [A + B] being the most critical of the four projected fusions. After some initially unproductive efforts to establish the [AB] + C linkage, an aldol coupling was selected for this process in the hope that it would be possible to effect good stereocontrol at both C13 and C15 of **2** by this means. This strategy not only offers the advantage that it isolates the stereocenters of **2** to segments A and C where stereocontrol can be exercised independently but also allows for the incorporation of functional handles that facilitate subunit coupling via Wittig (A + B) and Stille (C + D) reactions. Closure of the 16-membered lactone was projected via an intramolecular Wadsworth−Emmons condensation, a feature of all five previous syntheses of **2**.[10]

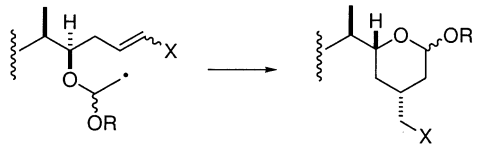
Synthesis of Subunits. Of the four rhizoxin segments identified in Scheme 1, subunit A was considered the most demanding in terms of stereocontrol. The principal stereochemical issue to be confronted in this fragment is setting the cis relationship of alkyl chains at C5 and C7 of the δ-lactone. This provided us with an opportunity to examine a protocol in which a 6-exo radical cyclization is programmed to set the C5 stereocenter of **2** in the required (*R*)-configuration. The concept is expressed in Scheme 2 where the product is a cyclic acetal bearing an appendage CH_2X attached to the carbon destined to become C5 of **2**. Rama Rao in his construction of the C1−C9 subunit of rhizoxin also employed a radical cyclization of the type shown in Scheme 2,[11c,d] but underlying stereochemical questions implicit in this reaction such as the import of (*E*)- vs (*Z*)-configurations of the double bond were not addressed.

The initial task of setting the syn relationship between C7 and C8 of **2** was first approached indirectly using the method of Keck in which anti homoallylic alcohol **3**, prepared in high diastereomeric excess by reacting (*R*)-3-benzyloxy-2-methylpropanal with allyltri-*n*-butylstannane in the presence of stannic chloride, is subjected to Mitsunobu inversion with *p*-nitrobenzoic acid to furnish **4** (Scheme 3).[13] Attempts to obtain the syn stereoisomer of **3** directly by reagent-controlled allylation of the same aldehyde with either the allyl boronate derived from

SCHEME 1



SCHEME 2



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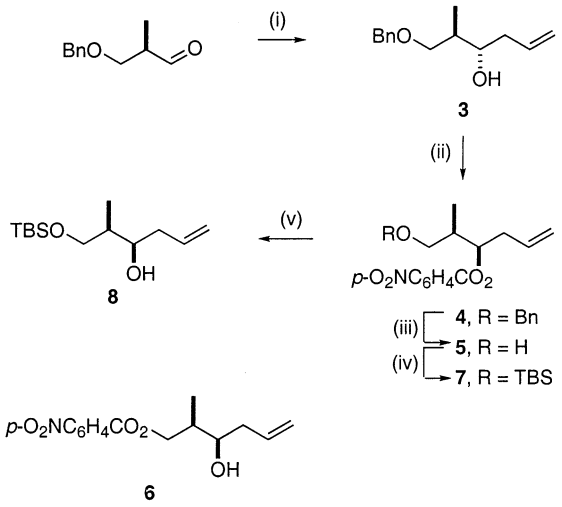
SCHEME 3[a]



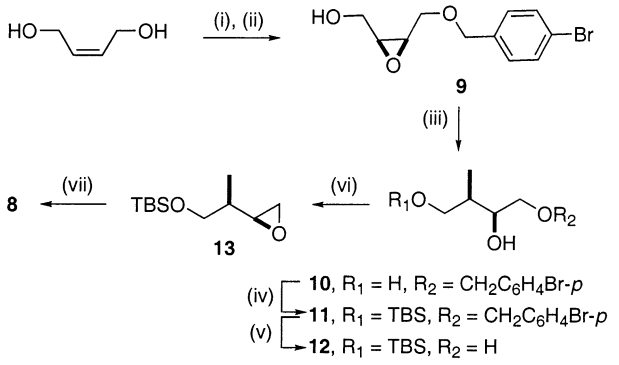
[a] Reaction conditions: (i) $Bu_3SnCH_2CH{=}CH_2$, $SnCl_4$, CH_2Cl_2, −90 °C, 92%; (ii) Ph_3P, $EtO_2CN{=}NCO_2Et$, *p*-$O_2NC_6H_4CO_2H$, THF, 65%; (iii) BCl_3, tol, −78 °C → 0 °C, 85%; (iv) TBSCl, imidazole, DMF, 83%; (v) NaOH, MeOH, 0 °C → rt, 86%.

(*S*,*S*)-tartrate[14] or a chiral allylborane[15] resulted in lower diastereoselectivity and/or diminished yield. The benzyl ether of **4** was removed using boron trichloride,[16] but the expected product **5** was accompanied by ca. 10% of the secondary alcohol **6** in which migration of the *p*-nitrobenzoate had occurred. Alcohol **5** was silylated, and the resulting ether **7** was saponified to yield syn homoallyl alcohol **8**.

The tedious chromatographic separation required to remove the unwanted *p*-nitrobenzoate **6** from **5** prompted a search for an improved synthesis of **8**, and the epoxide **9**, obtained enantiopure after a single crystallization following Sharpless asymmetric epoxidation of the mono *p*-bromobenzyl ether of *cis*-buten-1,4-diol,[17] provided the starting point for a new approach as shown in Scheme 4. Exposure of **9** to methylmagnesium bromide and cuprous iodide afforded a 3:1 mixture of 1,3- and 1,2-diols, from which the undesired 1,2-diol was easily removed by oxidative cleavage with sodium periodate. The crystalline syn diol **10** was selectively protected as its primary silyl ether **11**, and the *p*-bromobenzyl ether was removed with sodium−ammonia to yield **12**. Conversion of **12** to its primary mesylate followed by exposure to base produced epoxide **13**, which underwent opening with vinylmagnesium bromide in the presence of cuprous iodide to furnish **8**.

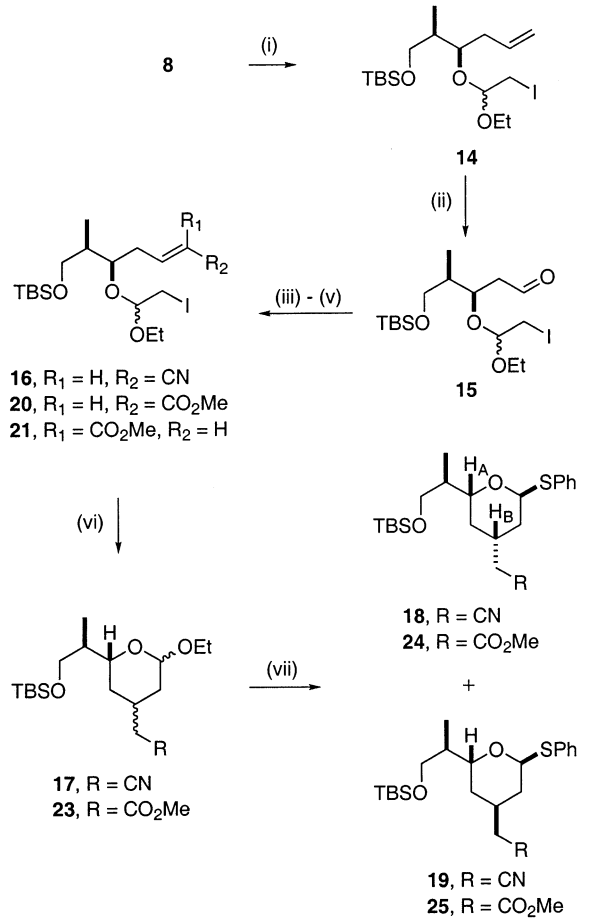
Alcohol **8** was advanced to iodoacetal **14** with the initial goal of effecting exo radical cyclization followed by entrapment of the resulting primary radical with *tert*-butylisocyanide (Scheme 5).[18] In the event, exposure of **14**, prepared from **8** with ethyl vinyl ether and *N*-iodosuccinimide, to tri-*n*-butylstannane, *tert*-butylisocyanide, and AIBN, produced only a low yield of an inseparable mixture of three stereoisomeric tetrahydropyrans in a ratio of 6:3:1. A complicating feature of this

SCHEME 4[a]



[a] Reaction conditions: (i) NaH, *p*-$BrC_6H_4CH_2Br$, Bu_4NI, THF, 0 °C → rt, 15 h, 88%; (ii) $Ti(O\textit{i}\text{-}Pr)_4$, *t*-BuOOH, L-DIPT, CH_2Cl_2, 4 Å mol sieves, −35 °C, 20 h, 72%; (iii) MeMgBr, CuI (10 mol %), Et_2O−THF, −40 °C, then $NaIO_4$, 62%; (iv) TBSCl, Et_3N, DMAP (cat), CH_2Cl_2, 89%; (v) Na, NH_3, *t*-BuOH−THF, −70 °C, 89%; (vi) MsCl, collidine, 0 °C, then K_2CO_3, MeOH, 93%; (vii) $CH_2{=}CHMgBr$, CuI (5 mol %), Et_2O−THF, −78 °C → −20 °C, 90%.

SCHEME 5[a]



[a] Reaction conditions: (i) NIS, $CH_2{=}CHOEt$, CH_2Cl_2, −20 °C → 0 °C, 92%; (ii) OsO_4 (cat), $NaIO_4$, THF−H_2O (1:1), 97%; (iii) Ph_3PCHCN, tol, 70 °C, 77% of **16**; (iv) Ph_3PCHCO_2Me, tol, 60 °C, 50% of **20**; (v) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, (**22**) KH, 18-crown-6, THF, −78 °C, 65% of **21**; (vi) *n*-Bu_3SnH, AIBN, tol, 80 °C; (vii) PhSH, $MgBr_2{\cdot}OEt_2$ (see Table 1).

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TABLE 1. Radical Cyclization of Iodoacetals 16, 20, and 21 and Subsequent Ketalization with Thiophenol

compound	products	yield (%)	ratio
16	**18** + **19**	80	1.7:1
20	**24** + **25**	92	1:1
21	**24** + **25**	93	15:1

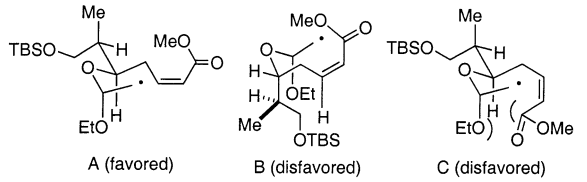


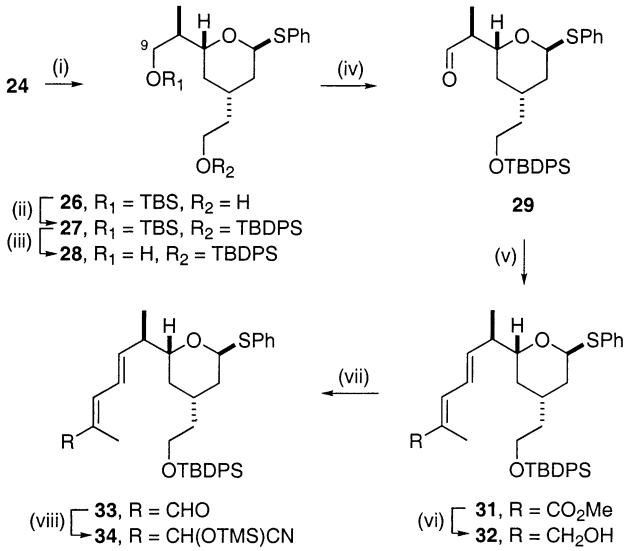
FIGURE 1. Three modes of radical cyclization of **21**: *si*-face attack (A) and *re*-face attack (B and C). Only the major pseudoaxial anomer is shown.

reaction was reduction of both the initial radical species from **14** and that produced after cyclization.

Precedent suggested that a more favorable entry to the tetrahydropyran nucleus of subunit A via a radical cyclization pathway would be found if an electron-withdrawing group were attached to the alkene terminus of **14**.[19] To this end, the vinyl group of **14** was cleaved oxidatively to aldehyde **15**, and the latter was subjected to a Wittig reaction with cyanotriphenylphosphorane to give (*E*)-α,*β*-unsaturated nitrile **16**. However, although **16** afforded an improved yield of cyclization product **17**, this material again proved to be an inseparable mixture of stereoisomers at both the anomeric carbon and the new stereocenter. The mixture was simplified after treatment of **17** with thiophenol and magnesium dibromide due to the formation of a single (presumably axial) phenylthio anomer, and this result permitted assessment of the stereoisomeric ratio of **18**:**19** as 1.7:1 by ^{13}C NMR. Assignment of configuration to the major isomer **18** was made on the basis of a 5.6% NOE between H_A and H_B in this compound; no NOE was observed in **19**.

For comparison with the radical cyclization of **16**, aldehyde **15** was converted to both (*E*)- and (*Z*)-α,*β*-unsaturated methyl esters **20** and **21**, the latter obtained using the Gennari−Still phosphonate **22** as shown in Scheme 5.[20] Not surprisingly, radical cyclization of (*E*)-ester **20** produced a stereoisomeric mixture of **23** little different from the ratio observed with nitrile **16** (see Table 1), a result that conflicts with that reported by Rama Rao,[11d] who obtained a single *δ*-lactone after hydrolysis of the acetal of **23** and oxidation. By contrast, cyclization of (*Z*)-ester **21** furnished **24** and **25** after ketal exchange of **23** with thiophenol as a 15:1 mixture in good yield, the major stereoisomer again corresponding closely with **18** according to ^1H NMR. An explanation for the higher stereoselectivity in the cyclization of (*Z*)-ester **21** can be found in a preference by the intermediate radical for conformation A in which the branched chain at C5 is pseudoequatorial and the *si*-face of the double bond is exposed to attack (see Figure 1). Alternative conformations such as B or C required for *re*-face attack would be disfavored by steric compression of pseudoaxial substituents (B) or a stereoelectronically poor alignment of the ester in an endo-like chair transition state (C). A similar steric argument cannot be made for **16** and **20** where the (*E*)-configuration of the double bond results in only a small difference in energy between *re*- and *si*-modes of radical attack.

SCHEME 6[a]



[a] Reaction conditions: (i) $NaBH_4$, $CaCl_2$, EtOH−THF, 0 °C, 92%; (ii) *t*-$BuPh_2SiCl$, Et_3N, DMAP, 76%; (iii) AcOH, THF, H_2O, 93%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 71%; (v) (*E*)-$Ph_3PCHCH{=}C(Me)CO_2Me$ (**30**), THF, Δ, 77%; (vi) DIBALH, Et_2O, −78 °C, 92%; (vii) MnO_2, Et_2O, 90%; (viii) TMSCN, ZnI_2, 92%.

Our remaining task in the construction of subunit A was the straightforward transformation of the protected C9 alcohol to an aldehyde so that segment B could be attached to produce the required (*E*,*E*)-diene moiety. For this purpose, ester **24** was first reduced with calcium borohydride to primary alcohol **26**, which was protected as its *tert*-butyldiphenylsilyl ether **27** (Scheme 6). After selective unmasking of the primary *tert*-butyldimethylsilyl ether, oxidation of **28** gave aldehyde **29**. Wittig reaction of **29** with phosphorane **30**[21] afforded a good yield of the (*E*,*E*)-diene **31**, which was advanced via alcohol **32** to aldehyde **33**.

Our initial plan was to employ the enolate of cyanohydrin derivative **34**, prepared in good yield from aldehyde **33** with trimethylsilyl cyanide in the presence of zinc iodide,[22] as a nucleophile for reaction with an alkylating agent representing C14−C19 of **2**. Attention was therefore turned toward an appropriate coupling partner for **34** with the goal of preparing a subunit that contained the three contiguous stereogenic centers at C15, C16, and C17. For this we chose the known (4*R*,5*R*)-lactone **35**[23] as our point of departure (Scheme 7). Substrate-directed α-hydroxylation of **35** with racemic 2-phenylsulfonyl-3-phenyloxaziridine gave both **36** and the epimeric alcohol, but asymmetric hydroxylation with (−)-

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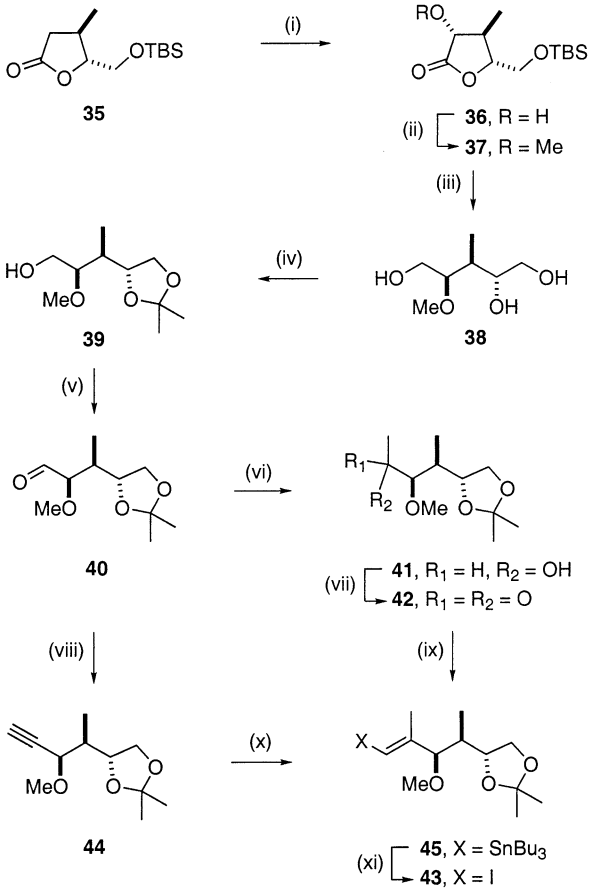
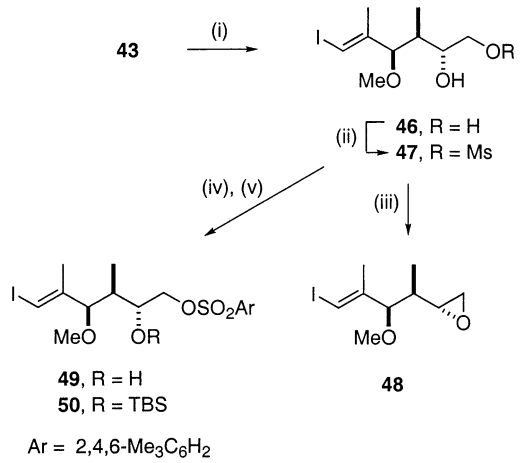
SCHEME 7[a]



[a] Reaction conditions: (i) NaHMDS, (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine, THF, 68%; (ii) CH_2N_2, BF_3·OEt_2, Et_2O, 90%; (iii) $LiAlH_4$, THF, then 10% HCl; (iv) Me_2CO, $CuSO_4$, *p*-TsOH, 84% from **37**; (v) Dess−Martin periodinane, CH_2Cl_2; (vi) MeMgBr, Et_2O, −78 °C, 83%; (vii) Dess−Martin periodinane, CH_2Cl_2, 91%; (viii) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C → rt, 87% from **39**; (ix) $CrCl_2$, CHI_3, THF, 45%; (x) $(Bu_3Sn)_2CuCNLi_2$, DMPU, MeI 79%; (xi) I_2, Et_2O, 67%.

camphorsulfonyloxaziridine resulted in **36** with excellent stereoselectivity.[24] This alcohol was converted to its methyl ether **37** with diazomethane in the presence of boron trifluoride etherate,[25] and the lactone was then reduced to triol **38** with lithium aluminum hydride. Protection of the 1,2-diol moiety as its acetonide **39** was followed by oxidation to aldehyde **40**. Two routes from **40** were examined for advancing this aldehyde toward an (*E*)-trisubstituted iodoalkene suitable for eventual linkage to segment D. The first approach employed a Grignard reaction of **40** with methylmagnesium bromide followed by oxidation of the resultant secondary alcohol **41** to give methyl ketone **42**. The latter was subjected to a Takai reaction[26] with chromous chloride and iodoform, but this gave a 2:1 mixture of (*E*)-iodoalkene **43** and its (*Z*) isomer from which pure **43** could be obtained in only modest yield. In an alternative approach to **43**, a route via alkyne **44**, prepared by treatment of **40** with Ohira's reagent,[27] was explored. Stannylcupration of **44** and

SCHEME 8[a]



[a] Reaction conditions: (i) MeOH, CSA, 77%; (ii) MsCl, collidine, CH_2Cl_2, 88%; (iii) K_2CO_3, MeOH, 90%; (iv) 2,4,6-$Me_3C_6H_2SO_2Cl$, DMAP, CH_2Cl_2, 84%; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91%.

subsequent methylation of the intermediate (*E*)-stannylvinylcopper species[28] afforded **45** as the sole isomer in good yield. Iodination of this substance then gave **43** free of its (*Z*)-isomer. Acidic methanolysis removed the acetonide from **43**, and diol **46** was converted to its primary mesylate **47** and then to epoxide **48** (Scheme 8). Unfortunately, **48** proved to be inert toward the enolate of **34**, and Lewis acid catalysts that could have facilitated opening of the epoxide led only to decomposition of **34**. The primary mesitylenesulfonate **49**, prepared from **46** and protected as silyl ether **50**, was also inert toward **34**, leading us to conclude that the carbanion from **34** was too highly delocalized to serve as a nucleophile for alkylation.

These disappointing results prompted us to consider an alternative scheme for coupling the [A + B] subunit with C in which the polarity of the carbon−carbon bond-forming process was reversed. Specifically, aldehyde **33** would now serve as an electrophile in an aldol coupling with a suitable methyl ketone enolate to forge the C13−C14 bond and generate the desired (*S*)-configuration at C13. In this revised plan, there remained the issue of the configuration at C15 since this new mode of coupling would allow inclusion of only two of three stereocenters in the C15−C17 triad. Our hope was that the (*S*)-stereocenter produced at C13 could induce the correct (*S*)-configuration at C15, and this indeed proved to be the case.

Subunit C now became a straightforward target for synthesis, which commenced from (*E*)-aldehyde **51** prepared by zirconation−methylation−iodination of propargyl alcohol followed by oxidation of the allylic alcohol[29] with manganese dioxide (Scheme 9). An asymmetric aldol coupling of **51** with the di-*n*-butylboron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one furnished syn product **52** in high yield,[30] and this was converted directly to

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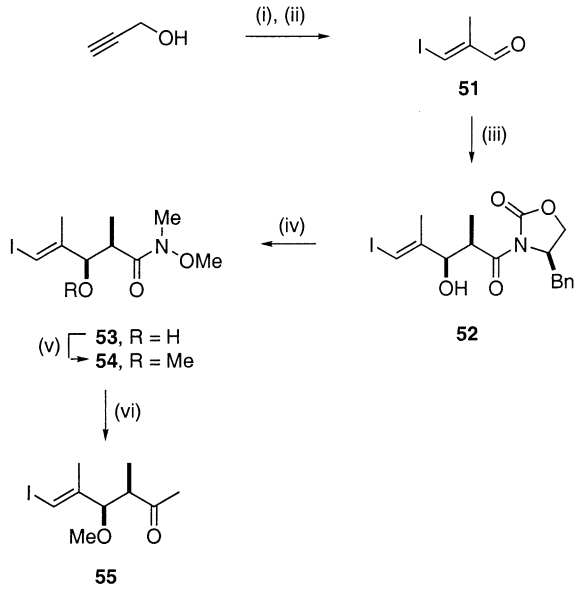
SCHEME 9[a]

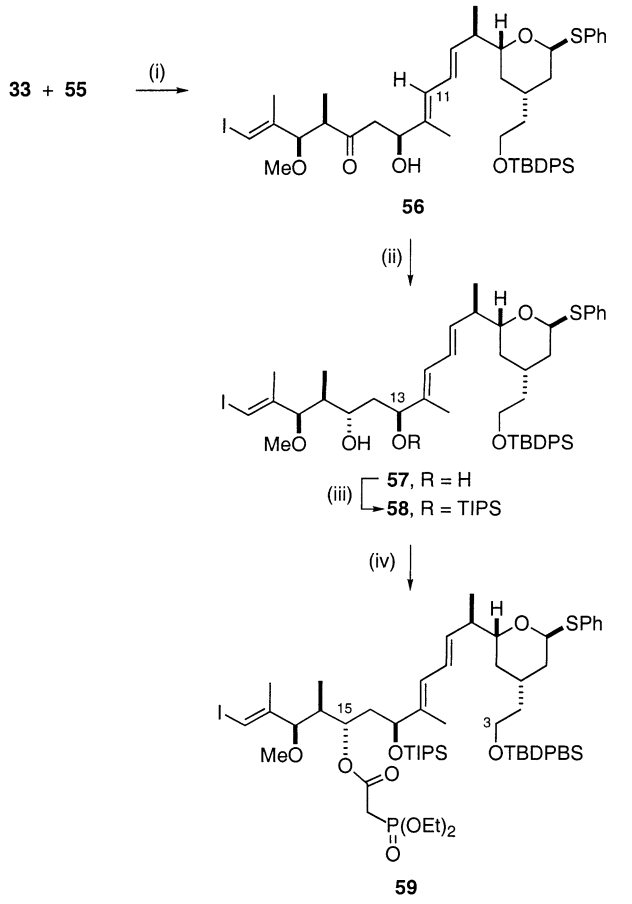


[a] Reaction conditions: (i) Cp_2ZrCl_2, Me_3Al, then I_2, Et_2O, −30 °C, 60%; (ii) MnO_2, Et_2O, 0 °C, 89%; (iii) (*R*)-4-benzyl-3-propionyloxazolidin-2-one, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 77%; (iv) MeNH(OMe)·HCl, Me_3Al, CH_2Cl_2, 0 °C, 85%; (v) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, tol, 70 °C, 91%; (vi) MeMgBr, THF, −20 °C → 0 °C, 91%.

Weinreb amide **53**.[31] Exposure of **53** to methyl triflate in base at elevated temperature gave methyl ether **54** in near quantitative yield, and a Grignard reaction of **54** with methylmagnesium bromide produced the desired ketone **55**.

Before investing **33** in an aldol reaction with **55**, a model study with tiglaldehyde and the enolate of methyl ketone **55** was carried out to ascertain conditions that would afford optimal stereoinduction of the resulting *β*-hydroxy ketone. Modest stereoselectivity (3:1 in favor of the (*S*)-alcohol) was observed when the di-*n*-butylboron enolate of **55** was used with tiglaldehyde, but this improved to 8:1 when the enolate of **55** prepared with (+)-chlorodiisopinocampheylborane (DIP−Cl)[32] was employed (Scheme 10). The enolate of **55** prepared with (−)-DIP−Cl gave a 1:1 mixture of stereoisomeric hydroxy ketones with tiglaldehyde, confirming that the enolate from (+)-DIP−Cl represents the "matched" case. Optimization of the reaction of the (+)-DIP enolate of **55** with aldehyde **33** necessitated careful adjustment of reaction conditions, and it was found that when the reaction was run at −20 °C for 6−10 h, the yield of **56** was consistently in the range 60−70%. The ratio of **56** to its (13*R*)-epimer was typically 17−20:1. The major hydroxy ketone was easily separated from its minor diastereomer by flash chromatography, and the configuration of the C13 stereocenter in **56** was ascertained by esterification of this alcohol with (*R*)- and (*S*)-*O*-methylmandelic acids. The Mosher model as applied to mandelates by Trost[33] predicts that the C11 proton of **56** will be shielded by the phenyl ring current in the ^1H NMR spectrum of the (*S*)-*O*-methylmandelate relative to the corresponding (*R*)-ester, and this was indeed the case ($\Delta\delta$ 0.25 ppm).

SCHEME 10[a]



[a] Reaction conditions: (i) **55**, (+)-DlPCl, Et_3N, Et_2O, 0 °C, 3 h, then **33**, −20 °C, 6 h, 65%; (ii) $Me_4NBH(OAc)_3$, AcOH−MeCN−THF, −25 °C → −10 °C, 74%; (iii) TIPSOTf (1 equiv), 2,6-lutidine, CH_2Cl_2, −8 °C, 92%; (iv) $(EtO)_2P(O)CH_2COCl$, pyr-CH_2Cl_2, rt, 36 h, 78%.

Reduction of ketone **56** with tetramethylammonium acetoxyborohydride required extensive experimentation in order to achieve good anti selectivity for the desired 1,3-diol, and when this reduction was conducted in a mixture of acetic acid, acetonitrile, and THF at −20 °C, **57** was obtained in excellent yield as shown in Scheme 10. The more sterically accessible hydroxyl group at C13 was selectively protected as its triisopropylsilyl ether **58**, and the remaining C15 alcohol was esterified with diethyl phosphonoacetyl chloride[34] to furnish **59**.

An issue that confronted us at this stage was the choice of a sequence that would modify both the appendage at C5 of the tetrahydropyran moiety of **58** and the thiophenyl substituent. To advance **59** toward a substrate suitable for the intramolecular Wadsworth−Emmons condensation projected for the macrolactonization step (Scheme 1), oxidation of the protected alcohol at C3 to the aldehyde level must take place. Because the sulfur atom of **59** could potentially interfere in that oxidation, it was decided to first transmute the phenylthioacetal moiety to the *δ*-lac-

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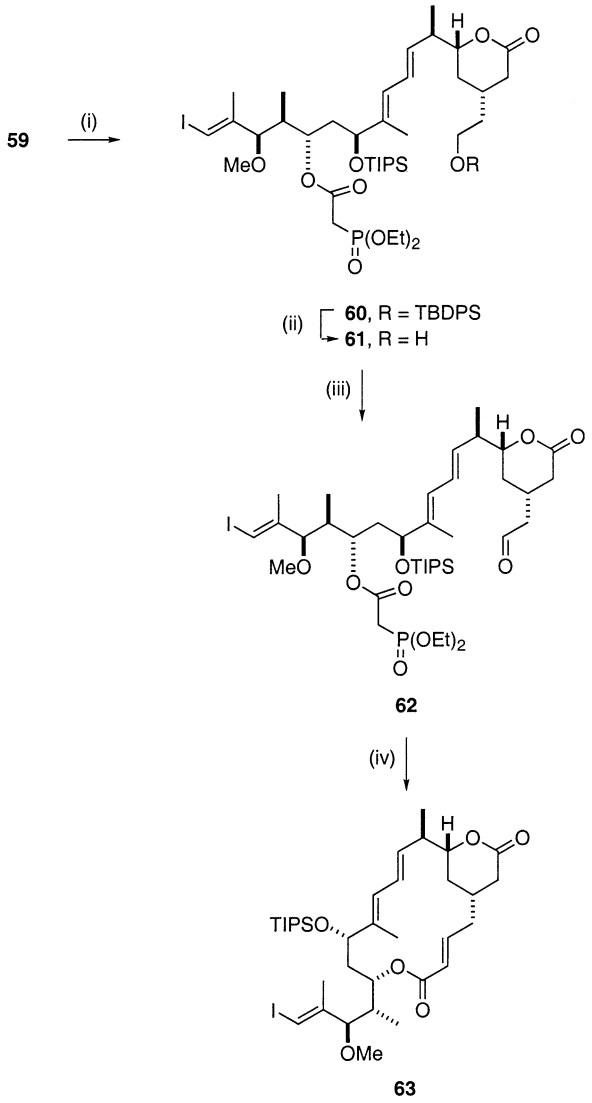
SCHEME 11[a]

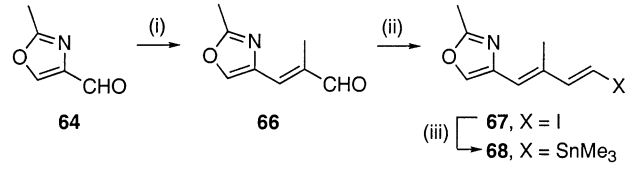


[a] Reaction conditions: (i) $AgNO_3$, 2,6-lutidine, THF−H_2O (5:1), rt, 15 min, then TPAP (cat), NMO, 4 Å mol sieves, CH_2Cl_2, 71%; (ii) TASF, DMF, 0 °C, 10 h, 70%; (iii) Dess−Martin periodinane, CH_2Cl_2, 100%; (iv) (*i*-Pr)$_2$NEt, LiCl, MeCN, 57%.

tone present in **2**. This was accomplished very efficiently by silver nitrate-catalyzed hydrolysis of **59** to a mixture (1.5:1) of stereoisomeric hemiacetals, which yielded a single *δ*-lactone **60** upon oxidation with the Ley reagent (Scheme 11).[35]

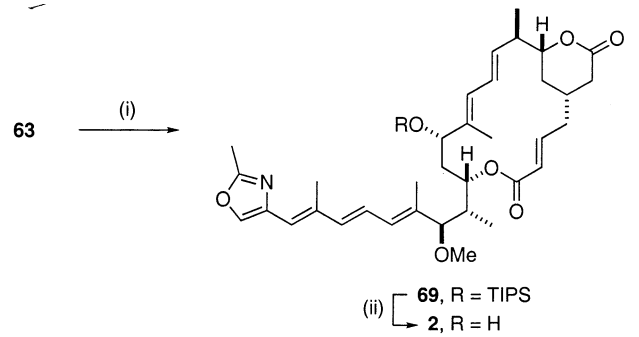
Selective unmasking of the *tert*-butyldiphenylsilyl ether of **60** in the presence of the triisopropylsilyl ether at C13 took advantage of the increased propensity of a silicon atom bearing aryl groups to undergo nucleophilic attack in comparison to those bearing only alkyl substituents. This distinction permitted selective deprotection of **60** with the mild fluoride source tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF)[36] and furnished alcohol **61** in good yield. An important prerequisite for success in this reaction was that it should be conducted in a

SCHEME 12[a]



[a] Reaction conditions: (i) $Ph_3P{=}C(Me_3)CHO$ (**65**), C_6H_6, Δ, 93%; (ii) $CrCl_2$, CHI_3, THF, 0 °C, 71%; (iii) $(Me_3Sn)_2$, $(Ph_3P)_2PdCl_2$, THF, 50 °C, 96%.

SCHEME 13[a]



[a] Reaction conditions: (i) **68**, $PdCl_2$ $(MeCN)_2$, DMF, 84%; (ii) HF·pyr, THF, 0 °C → rt, 59%.

plastic vessel, since adventitious hydrofluoric acid formed from contact of TASF with glass contributed to cleavage of both silyl ethers of **60**. Dess−Martin oxidation of **61** gave aldehyde **62**, our putative macrolactonization precursor, and a variety of reaction conditions designed to effect intramolecular Wadsworth−Emmons condensation of **62** were investigated for this purpose. The most efficient of these employed Hunig's base and a large excess of lithium chloride in acetonitrile.[37] This protocol produced α,*β*-unsaturated macrolactone **63** as a single (*E*)-isomer in high yield, whereas other conditions (particularly the use of DBU as the base) resulted in a mixture of (*E*)- and (*Z*)-α,*β*-unsaturated lactones.

The final segment D (Scheme 1) required to complete the synthesis of **2** was prepared from 2-methyloxazole-4-carboxaldehyde (**64**) (Scheme 12).[38] A Wittig reaction of **64** with phosphorane **65**[39] gave (*E*)-α*β*-unsaturated aldehyde **66**, which was subjected to a Takai reaction[26] with chromium(II) chloride and iodoform to provide (*E*,*E*)-iododiene **67** in good yield. Halogen−metal exchange with hexamethylditin in the presence of bis(triphenylphosphine)palladium dichloride[40] furnished stannane **68** in virtually quantitative yield (Scheme 12). Stille coupling[41] of this stannane with iodolactone **63** in the presence of palladium(II) chloride bis(acetonitrile), as shown in Scheme 13, gave triisopropylsilylrhizoxin D (**69**), whose ^{1}H NMR spectrum exactly matched that of the same substance previously prepared by Leahy.[10c] Final depro-

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tection of this material with HF−pyridine complex afforded rhizoxin D (**2**) with ^{1}H and ^{13}C NMR spectra essentially identical to those of **2** synthesized by Williams (Scheme 13)[10b] and with a specific rotation in good agreement with that recorded in the literature.

In summary, a modular synthesis of **2** has been accomplished in which the longest linear sequence is 17 steps. An asymmetric aldol reaction was used as the key reaction to couple two principal segments and led to a synthesis of rhizoxin D that is 27 steps from **9**. The modular design of this route affords opportunities to incorporate additional structural features into the rhizoxin scaffold, including the two epoxide functions that characterize **1**.

Experimental Section

General. Solvents were dried by distillation immediately prior to use. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone under an argon atmosphere. Triethylamine, diisopropylethylamine, toluene, benzene, and dichloromethane were distilled from calcium hydride under argon. Acetone was distilled from calcium sulfate. Methanol and ethanol were distilled from magnesium turnings. Analytical thin-layer chromatography (TLC) was conducted using 1.5 × 5.0 cm precoated aluminum TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Flash chromatography was carried out using silica gel 60 (230−400 mesh ASTM). Melting points are uncorrected. Infrared (IR) spectra were recorded with a FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on either a 300 MHz or a 400 MHz spectrometer. Low resolution mass spectra (MS) were measured at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were recorded using either CI or FAB.

Iodo Acetal 14. To a stirred suspension of **8** (3.32 g, 0.013 mol) and *N*-iodosuccinimide (3.40 g, 0.015 mol) in dry CH_2Cl_2 (60 mL) at −23 °C was added freshly distilled ethyl vinyl ether (2.75 mL, 0.024 mmol) over a period of 10 min. The mixture was stirred at −23 °C for 4 h and at 0 °C for 11 h. A saturated solution of aqueous $NaHCO_3$ (55 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 45 mL). The combined extract was washed with 10% aqueous sodium thiosulfate and dried ($MgSO_4$). Removal of the solvent in vacuo and chromatography of the residue gave 5.30 g (92%) of **14** (mixture of two diastereomers) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (m, 6H), 0.85 (m, 12H), 1.22 (dt, J = 7, 2 Hz, 3H), 1.85−1.6 (m, 1H), 2.5−2.2 (m, 2H), 3.27−3.18 (m, 2H), 3.77−3.48 (m, 5H), 4.67−4.61 (m, 1H), 5.11−5.02 (m, 2H), 5.78 (m, 1H).

Aldehyde 15. To solution of **14** (4.10 g, 9.25 mmol) in THF (95 mL) and H_2O (80 mL) was added a solution of OsO_4 (125 mg) in H_2O (10 mL), followed by sodium periodate (1.97 g, 9.25 mmol). After 1 h, an additional quantity of sodium periodate (5.91 g, 27.8 mmol) was added, and the mixture was stirred for 13 h. The reaction was quenched with saturated aqueous sodium thiosulfate (50 mL), and the layers were separated. The aqueous layer was extracted with 25% hexanes in Et_2O (3 × 200 mL), and the combined extract was dried (Na_2SO_4) and filtered through a plug of silica. The filtrate was concentrated in vacuo to yield 4.01 g (97%) of **15**, which was used immediately in the next reaction.

α,β-Unsaturated Ester 21. To a solution of methyl bis-(2,2,2-trifluoroethoxy)phosphonyl acetate (1.88 mL, 8.90 mmol) and 18-crown-6 (1.07 g, 4.05 mmol) in THF (200 mL) at −78 °C was added KHMDS (0.5 M in toluene, 17.8 mL, 8.90 mmol) over a period of 10 min. The yellow solution was stirred for 30 min, and a solution of **15** prepared above (3.60 g, 8.11 mmol) in THF (1.0 mL) was added over a period of 10 min. After 45 min, the orange solution was diluted with saturated aqueous NH_4Cl, and the mixture was allowed to warm slowly to room termperature. The mixture was extracted with Et_2O (3 × 200 mL), and the combined extract was washed with brine and dried (Na_2SO_4). Removal of the solvent in vacuo and chromatography of the residue (hexanes to 5% EtOAc/hexane) gave 2.56 g (65%) of **21**: IR (film) 2951, 1720, 1642, 1435, 1251, 1175, 842, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, two diastereomers) δ −0.02−0.05 (m, 6H), 0.08−0.98 (m, 12H), 1.25−1.35 (m, 3H), 1.65−1.75 (m, 1H), 2.85−3.02 (m, 2H), 3.10−3.19 (m, 2H), 3.39−3.48 (m, 1H), 3.51−3.65 (m, 3H), 3.67−3.68 (s, 3H), 3.71−3.79 (m, 1H), 4.61−4.70 (m, 1H), 5.82−5.89 (m, 1H), 6.30−6.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 5.5, 5.9, 6.4, 10.6, 11.5, 15.1, 18.1, 25.8, 25.8, 30.8, 32.0, 39.4, 39.5, 50.9, 51.0, 62.1, 62.5, 64.4, 64.4, 76.0, 76.3, 100.3, 102.0, 120.1, 120.8, 146.1, 146.9, 166.4, 166.5; HRMS (CI) *m*/*z* found 485.1218, calcd for $C_{18}H_{34}IO_5Si$ *m*/*z* 485.1220.

Tetrahydropyran 23. To a deoxygenated solution of **21** (1.29 g, 2.58 mmol) and AIBN (42 mg, 0.26 mol) in toluene (130 mL) at 80 °C was added tri-*n*-butylstannane (1.04 mL, 3.87 mmol) in one portion. The mixture was stirred for 2 h at 80 °C, and the toluene was removed by distillation. The residue was taken up in CH_2Cl_2 (50 mL), and the solution was washed with 10% aqueous sodium thiosulfate (20 mL) and brine and dried ($MgSO_4$). Removal of the solvent in vacuo left 830 mg (86%) of **23** as a mixture of inseparable anomers: IR (film) 2955, 1733, 1475, 1260, 1056, 837, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, two diasteromers) δ 0.00 (s, 2H), 0.01 (s, 4H), 0.81−0.96 (m, 12H), 0.97−1.13 (m, 1H), 1.18 (t, J = 7 Hz, 2H), 1.20 (t, J = 7 Hz, 1H), 1.24−1.41 (m, 2H), 1.45−1.87 (m, 4H), 2.00−2.27 (m, 2H), 2.27−2.49 (m, 0.8H), 2.49−2.63 (m, 0.2H), 3.25−3.60 (m, 3.5H), 3.62−3.67 (m, 3H), 3.70 (dd, J = 6, 4H, 0.6H), 3.80 (ddd, J = 12, 5, 2 Hz, 0.5H), 3.84−3.98 (m, 0.5H), 4.38 (dd, J = 10, 2 Hz, 0.3H), 4.84 (d, J = 3 Hz, 0.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, 11.8, 11.9, 15.0, 15.2, 18.2, 25.8, 27.2, 31.4, 34.5, 34.8, 36.3, 37.6, 40.4, 40.5, 40.9, 41.4, 51.3, 51.4, 61.8, 64.0, 64.9, 64.9, 68.2, 74.8, 96.4, 101.3, 172.6; MS (EI) 373 (M − I), 329, 271, 243, 157; HRMS (EI) *m*/*z* found 373.2411, calcd for $C_{19}H_{37}O_5Si$ *m*/*z* 373.2410.

Thiophenyl Acetal 24. To a solution of **23** (7:1 mixture of stereoisomers, 53 mg, 0.14 mmol) and $MgBr_2{\cdot}OEt_2$ (36 mg, 0.14 mmol) in Et_2O (1.5 mL) at room temperature under argon was added thiophenol (17 μL, 0.16 mmol) via syringe. After 2 h, the mixture was diluted with Et_2O and washed with saturated $NaHCO_3$. The organic solution was dried ($MgSO_4$), and the solvent was removed in vacuo to leave an oily residue that ^{1}H NMR showed to be a 15:1 mixture of stereoisomers. This was purified by chromatography (5% EtOAc/hexanes) to give 54 mg (87%) of pure **24** as a colorless oil: $[\alpha]_D^{23}$ −19.9 (*c* 1.00, $CHCl_3$); IR (film) 3059, 2921, 1739, 1585, 1469, 1431, 1161, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.87 (s, 12H), 0.87−0.9 (m, 1H), 1.10−1.30 (m, 2H), 1.60−1.72 (m, 3H), 2.02−2.08 (m, 1H), 2.23 (d, J = 4 Hz, 1H), 2.25 (d, J = 2 Hz, 1H), 2.31−2.42 (m, 1H), 3.38 (dd, J = 10, 7 Hz, 1H), 3.49 (dd, J = 10, 6 Hz, 1H), 3.71 (s, 1H), 4.24 (ddd, J = 10, 5, 2 Hz, 1H), 5.69 (d, J = 5 Hz, 1H), 7.20−7.30 (m, 3H), 7.40−7.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, 11.9, 18.2, 25.9, 28.6, 35.2, 37.3, 40.5, 41.3, 51.6, 65.3, 69.9, 84.8, 126.5, 128.7, 130.8, 135.9, 172.4. There was also obtained 4 mg (6%) of **25**.

Diene Ester 31. To a solution of **29** (60 mg, 0.113 mmol) in THF (6 mL) was added **30** (126 mg, 0.336 mmol), and the yellow solution was heated at reflux for 16 h. After cooling to room temperature, the mixture was filtered through a plug of silica, and the filtrate was concentrated to leave an orange oil. This was purified by chromatography (hexanes to 5% EtOAc/hexanes) to give 50 mg (77%) of **31** as an off-white semisolid: IR (film) 2954, 1708, 1637, 1428, 1250, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 7 Hz, 3H), 1.01−1.10 (s, 9H), 1.45−1.5 (m, 2H), 1.57−1.69 (m, 3H), 1.88−1.96 (m, 3H), 1.95−2.10 (m, 2H), 2.31 (quint, J = 7 Hz, 1H), 3.70 (t, J = 8 Hz, 2H), 3.77 (s, 3H), 4.06 (ddd, J = 11, 6, 2 Hz, 1H), 5.95 (dd, J = 15, 8 Hz, 1H), 6.33 (dd, J = 14, 11 Hz, 1H), 7.14 (d, J = 11 Hz, 1H), 7.17−7.80 (m, 15H); ^{13}C NMR δ 12.7, 15.7, 19.2, 26.9, 28.0, 35.8, 37.6, 39.4, 42.4, 51.8, 61.0, 73.3, 85.5,

125.3, 125.6, 126.5, 127.7, 128.8, 129.6, 130.5, 130.9, 133.9, 135.6, 136.0, 138.9, 145.0, 169.0; MS (Cl) *m/z* 627, 571, 519, 197, 183, 135; HRMS (CI) *m/z* found 627.2962 (M − 1), calcd for $C_{38}H_{47}O_4SSi$ *m/z* 627.2964.

3-[(*E*)-(2*R*,3*R*)-2,4-Dimethyl-5-iodo-3-hydroxypent-4-enoyl]-(*R*)-4-benzyloxazolidin-2-one (52). To a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (3.03 g, 13.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise di-*n*-butylboron triflate (15 mL, 15 mmol) during 10 min. To this solution was slowly added Et_3N (2.35 mL, 17.0 mmol), and the resulting yellow mixture was cooled to −78 °C. A solution of **51** (3.80 g, 19.6 mmol) in CH_2Cl_2 (30 mL) was added, and the mixture was stirred for 30 min at −78 °C and for 1 h at 0 °C. The reaction was quenched by the addition of pH 7 phosphate buffer (15 mL) followed by MeOH (45 mL), and a precooled solution of 30% H_2O in MeOH (45 mL) was added slowly. This mixture was stirred for 1 h at 0 °C, and the solvent was removed under vacuum to leave a slurry that was extracted with Et_2O (3 × 75 mL). The combined extract was washed with saturated sodium thiosulfate and brine and dried ($MgSO_4$). Removal of the solvent in vacuo and chromatography of the residue (20% EtOAc/hexanes) gave 4.30 g (77%) of **52**: $[\alpha]_D^{23}$ −30.0 (*c* 0.16, $CHCl_3$); IR (neat) 3496, 2919, 1779, 1694, 1456, 1382, 1212, 1106, 1003, 971, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7 Hz, 3H), 1.82 (d, J = 1 Hz, 3H), 2.81 (dd, J = 13, 9 Hz, 1H), 3.16 (d, J = 3 Hz, 1H), 3.27 (dd, J = 13, 3 Hz, 1H), 4.01 (qd, J = 7, 3 Hz, 1H), 4.22 (dd, J = 9, 3 Hz, 1H), 4.27 (dd, J = 9, 7 Hz, 1H), 4.50−4.54 (m, 1H), 4.71 (ddt, J = 9, 7, 3 Hz, 1H), 6.45 (quintet, J = 1 Hz, 1H), 7.19−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 21.8, 38.0, 40.2, 55.4, 66.5, 75.3, 79.5, 127.7, 129.2 (2C), 129.6 (2C), 135.1, 145.8, 153.1, 176.9; MS (FAB) *m/z* 412 (M − 17), 282, 235, 178; HRMS (FAB) *m/z* found 412.0418, calcd for $C_{17}H_{19}INO_3$ *m/z* 412.0410.

(2*R*,3*R*)-*N*-Methoxy-*N*-methyl (*E*)-2,4-Dimethyl-5-iodo-3-hydroxypent-4-enamide (53). *N*,*O*-Dimethylhydroxylamine (377 mg, 3.86 mmol) in THF (2 mL) was cooled to 0 °C, and a solution of trimethylaluminum in toluene (2.0M, 1.93 mL, 3.86 mmol) was added. The homogeneous solution was stirred at room temperature for 30 min and then cooled to 0 °C, and a precooled solution of **52** (415 mg, 0.966 mmol) in THF (1 mL) was added via cannula. The mixture was stirred for 2 h and transferred into a mixture of EtOAc (90 mL) and sodium potassium tartrate (90 mL). The mixture was stirred vigorously for 30 min; the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an amorphous solid that was purified by chromatography (50% CH_2Cl_2/hexanes) to give 256 mg (85%) of **53** as an amorphous white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, J = 7 Hz, 3H), 1.80 (s, 3H), 3.10 (m, 1H), 3.22 (s, 3H), 3.74 (s, 3H), 4.4 (m, 1H), 6.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 32.0, 39.4, 61.6, 75.3, 79.3, 106.1, 145.3, 177.2.

(2*R*,3*R*)-*N*-Methoxy-*N*-methyl-(*E*)-2,4-dimethyl-5-iodo-3-methoxypent-4-enamide (54). To a solution of **53** (100 mg, 0.319 mmol) in toluene (2 mL) was added 4-methyl-2,6-di-*tert*-butylpyridine (656 mg, 3.20 mmol) and methyl triflate (181 mL, 1.60 mmol), and the mixture was stirred at 70 °C for 26 h. After the mixture had cooled to room temperature, the reaction was quenched with MeOH that was saturated with NH_3. The mixture was diluted with Et_2O (20 mL), and the solution was washed with water (10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by chromatography (10% EtOAc in hexanes) to give 95 mg (91%) of **54** as a colorless oil: IR (film) 2978, 2879, 1660, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 7 Hz, 3H), 1.73 (s, 3H), 3.10 (s, 3H), 3.13−3.17 (m, 1H), 3.20 (s, 3H), 3.62 (s, 3H) 3.79 (d, J = 10 Hz, 1H), 6.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.0, 31.5, 61.6, 76.6, 80.7, 87.1, 106.1, 146.2, 175.1; MS (FAB) *m/z* 328 (M + 1), 296, 211, 154; HRMS (FAB) *m/z* found 328.0407, calcd for $C_{10}H_{19}INO_3$ *m/z* 328.0409.

(3*R*,4*R*)-(*E*)-3,5-Dimethyl-6-iodohex-5-en-2-one (55). A solution of methylmagnesium bromide in Et_2O (3.0 M, 0.60 mL, 1.8 mmol) was diluted with THF (1.5 mL) and cooled to −20 °C, and a solution of **54** (165 mg, 0.505 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm slowly to 0 °C, and after 1 h the reaction was quenched with saturated NH_4Cl. The mixture was diluted with Et_2O (20 mL); the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined extract was washed with aqueous citric acid and brine and dried (Na_2SO_4). The solvent was removed in vacuo to give 130 mg (91%) of pure **55** as a colorless oil: $[\alpha]_D^{23}$ +32.2 (*c* 0.36, $CHCl_3$); IR (film) 3052, 2976, 2875, 1701, 1355, 1258, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J = 7 Hz, 3H), 1.75 (s, 3H), 2.12 (s, 3H), 2.73 (m, 1H), 3.21 (s, 3H), 3.86 (d, J = 8 Hz, 1H), 6.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 20.0, 50.1, 57.0, 80.3, 86.3, 106.0, 145.3, 210.0; MS (CI) *m/z* 283 (M + 1), 211, 155; HRMS (CI) *m/z* found 283.0173, calcd for $C_9H_{16}IO_2$ *m/z* 283.0195.

Aldol Condensation of 33 and 55. Hydroxy Ketone 56. To a solution of (+)-DIP−Cl (205.6 mg, 0.641 mmol) in Et_2O (0.25 mL) at 0 °C was added Et_3N (90.0 μL, 0.641 mmol), followed by a solution of **55** (113 mg, 0.400 mmol) in Et_2O (0.5 mL). The mixture was stirred at 0 °C for 3 h and then cooled to −40 °C. A solution of **33** (236 mg, 0.395 mmol) in Et_2O (0.5 mL) was added, and the mixture was allowed to warm slowly to −10 °C and stirred at this temperature for 3 h. The reaction was quenched with MeOH (7.5 mL) and pH 7.0 buffer (3 mL), after which the solution was cooled to 0 °C, 30% H_2O_2 (0.75 mL) was added, and the mixture was stirred for 10 min at 0 °C and at room temperature for 1 h. The mixture was poured into H_2O (20 mL) and extracted with EtOAc−hexanes (1:1, 5 × 30 mL), and the combined extract was washed with H_2O and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by chromatography (5% EtOAc in hexanes) to give 226 mg (65%) of pure **56**: $[\alpha]_D^{23}$ −84.3 (*c* 0.82, CH_2Cl_2); IR (film) 3394, 2929, 2856, 1715, 1458, 1427, 1111, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 7 Hz, 3H), 1.06 (s, 9H), 1.13 (d, J = 7 Hz, 3H), 2.53 (dd, J = 17, 3 Hz, 1H), 2.67 (dd, J = 17, 9 Hz, 1H), 2.76 (sextet, J = 7 Hz, 1H), 3.20 (s, 3H), 3.70 (t, J = 6 Hz, 2H), 3.85 (d, J = 7 Hz, 1H), 4.00 (ddd, J = 11, 7, 2 Hz, 1H), 4.45 (bd, J = 9 Hz, 1H), 5.59 (dd, J = 15, 8 Hz, 1H), 5.71 (d, J = 5 Hz, 1H), 6.06 (bd, J = 11 Hz, 1H), 6.22 (s, 1H), 6.23 (ddd, J = 15, 11, 1 Hz, 1H), 7.18−7.20 (m, 1H), 7.25−7.30 (m, 1H), 7.38−7.44 (m, 6H), 7.46−7.50 (m, 3H), 7.66−7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 13.0, 19.2, 19.9, 26.9, 28.0, 36.0, 37.6, 39.5, 42.3, 47.6, 50.1, 57.0, 61.1, 72.2, 72.8, 80.6, 85.6, 86.3, 125.5, 125.6, 126.4, 127.7, 128.7, 129.6, 130.7, 133.9, 135.6, 135.8, 136.3, 137.4, 145.3, 212.8; MS (FAB) *m/z* 863 (M − 17), 753, 611, 475, 211; HRMS (FAB) *m/z* found 863.3034, calcd for $C_{46}H_{60}IO_4SSi$ *m/z* 863.3026.

Phosphonate 59. To diethylphosphonoacetic acid (0.20 mL, 1.24 mmol) was added benzene (5 mL), and after dissolution was complete the mixture was concentrated in vacuo and the residue taken up in anhydrous CH_2Cl_2 (4 mL). To the solution were added anhydrous DMF (2 drops) and activated 4 Å molecular sieves (100 mg), and the mixture was stirred at room temperature for 25 min. The supernatant was transferred to a flame-dried flask, and the solution was cooled to 0 °C. Freshly distilled oxalyl chloride (0.540 mL, 6.22 mmol) was added, and the solution was allowed to warm to room temperature over a period of 1 h. The solvent was removed under vacuum; the residue was taken up into benzene (5 mL), and the solvent was again removed under vacuum. The resulting brown residue was dissolved in anhydrous CH_2Cl_2 (3 mL) to yield a ca. 0.4 M solution of diethylphosphonoacetyl chloride.

To a solution of **58** (6.5 mg, 6.3 μmol) and anhydrous pyridine (25 μL, 0.32 mmol) in anhydrous CH_2Cl_2 (1 mL) at room temperature was added a solution of diethylphosphonoacetyl chloride prepared above (0.11 mL, 0.40 M in CH_2Cl_2, 44 μmol), and the mixture was stirred for 4 h, during which

time most of the CH_2Cl_2 was allowed to evaporate. To the residue was added EtOAc (5 mL) and pH 7 phosphate buffer (5 mL, 1 M); the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (5 mL). The combined extract was dried (Na_2SO_4); the solvent was removed in vacuo, and the residue was purified by chromatography (33% EtOAc in hexanes) to yield 6.1 mg (78%) of **59** as a colorless oil: $[\alpha]_D^{23}$ − 63.6 (*c* 0.36, CH_2Cl_2); IR (film) 2930, 2864, 1735, 1462, 1389, 1263, 1111, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 0.98−1.06 (m, 23H), 1.08 (s, 9H), 1.20−1.85 (m, 5H), 1.31 (td, J = 7, 4 Hz, 6H), 1.70 (bs, 3H), 1.82 (bs, 3H), 2.00−2.07 (m, 2H), 2.26 (sextet, J = 7 Hz, 1H), 2.76 (dd, J = 22, 14 Hz, 1H), 2.86 (dd, J = 22, 14 Hz, 1H), 3.18 (s, 3H), 3.44 (d, J = 7 Hz, 1H), 3.70 (t, J = 6 Hz, 2H), 4.01 (ddd, J = 11, 7, 2 Hz, 1H), 4.06−4.18 (m, 6H), 4.79 (ddd, J = 10, 4, 1 Hz, 1H), 5.56 (dd, J = 15, 8 Hz, 1H), 5.71 (d, J = 5 Hz, 1H), 5.83 (bd, J = 11 Hz, 1H), 6.16 (dd, J = 15, 10 Hz, 1H), 6.17 (bs, 1H), 7.17−7.23 (m, 1H), 7.25−7.32 (m, 2H), 7.36−7.45 (m, 6H), 7.46−7.52 (m, 2H), 7.65−7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, one signal obscured by $CHCl_3$ resonance) δ 9.9, 11.8, 12.7 (3C), 14.4, 16.6 (2C), 16.7, 18.3 (3C), 18.4 (3C), 19.4, 27.1 (3C), 28.1, 34.8 (d, J = 133 Hz), 35.9, 36.1, 37.8, 39.1, 39.8, 42.2, 56.9, 60.6, 62.7 (2C), 73.1, 74.1, 79.2, 85.8, 87.3, 125.8, 126.0, 126.6, 127.8 (4C), 128.9 (2C), 129.8 (2C), 130.9 (2C), 134.1 (2C), 135.8 (4C), 136.5, 136.8, 138.1, 146.6, 165.0 (d, J = 6 Hz); MS (FAB) *m*/*z* 1159 (M − 57), 933, 645, 475, 309; HRMS (FAB) *m*/*z* found 1159.3283, calcd for $C_{58}H_{73}IO_9PSSi_2$ *m*/*z* 1159.3263.

δ-Lactone 60. To a solution of **59** (6.0 mg, 4.9 μmol) and 2,6-lutidine (20 μL, 0.17 mmol) in THF−H_2O (5:1, 1.2 mL) at room temperature was added silver(I) nitrate (17 mg, 0.10 mmol), and the mixture was stirred for 15 min. The mixture was partitioned between EtOAc (10 mL) and H_2O (10 mL); the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined extract was washed with brine (5 mL) and dried (Na_2SO_4); the solvent was removed in vacuo, and the crude lactol (5.3 mg) was taken up in anhydrous CH_2Cl_2 (1 mL). To this solution were added *N*-methylmorpholine *N*-oxide (3.4 mg, 29 μmol) and activated 4 Å molecular sieves (10 mg), and the suspension was stirred for 10 min. Tetra-*n*-propylammonium perruthenate (0.4 mg, 1.1 μmol) was added, and the suspension was stirred for an additional 1 h. The mixture was diluted with CH_2Cl_2 (1 mL), and the solution was filtered through a pad of silica. The pad was washed successively with CH_2Cl_2 (3 × 2 mL) and Et_2O (2 × 2 mL); the combined filtrate was concentrated in vacuo, and the residue was purified by chromatography (50% EtOAc in hexanes) to yield 3.9 mg (71%) of **60** as a colorless oil: $[\alpha]_D^{23}$ +18.1 (*c* 0.31, CH_2Cl_2); IR (film) 2932, 2864, 1735, 1462, 1389, 1263, 1111, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 0.99−1.05 (m, 23H), 1.06 (s, 9H), 1.11 (d, J = 7 Hz, 3H), 1.32 (td, J = 7, 2 Hz, 6H), 1.45−1.90 (m, 3H), 1.72 (s, 3H), 1.82 (s, 3H), 1.97−2.15 (m, 4H), 2.50 (sextet, J = 7 Hz, 1H), 2.66 (dd, J = 17, 5 Hz, 1H), 2.76 (dd, J = 22, 14 Hz, 1H), 2.86 (dd, J = 22, 14 Hz, 1H), 3.18 (s, 3H), 3.44 (d, J = 7 Hz, 1H), 3.71 (t, J = 6 Hz, 2H), 4.07−4.20 (m, 6H), 4.79 (ddd, J = 10, 4, 2 Hz, 1H), 5.59 (dd, J = 15, 8 Hz, 1H), 5.87 (bd, J = 10 Hz, 1H), 6.18 (s, 1H), 6.24 (dd, J = 15, 11 Hz, 1H), 7.36−7.48 (m, 6H), 7.63−7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 11.9, 12.6 (3C), 14.3, 16.5 (3C), 18.3 (3C), 18.4 (3C), 19.4, 27.1 (3C), 28.6, 32.2, 34.7 (d, J = 133 Hz), 36.1, 36.6, 39.1 (2C), 41.9, 56.9, 61.0, 62.9 (2C), 74.0, 76.7, 79.2, 83.9, 87.3, 125.7, 127.1, 127.9 (4C), 130.0 (2C), 133.7, 134.2, 135.7 (5C), 139.3, 146.6, 165.0 (d, J = 6 Hz), 171.5; MS (FAB) *m*/*z* 1123 (M + 1), 1067, 911, 309, 211; HRMS (FAB) *m*/*z* found 1067.4207, calcd for $C_{51}H_{81}IO_{10}PSi_2$ *m*/*z* 1067.4151.

Alcohol 61. To a stirred solution of **60** (44.7 mg, 2.3 μmol) in anhydrous DMF 3.3 mL) at 0 °C was added a solution of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF, 376 μL, 0.11 M in DMF, 39.8 μmol). After 10 h, the mixture was diluted with EtOAc (10 mL) and pH 7 phosphate buffer (10 mL, 1M) and stirred vigorously for 5 min. The layers were separated; the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined extract was washed with H_2O (3 × 5 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by chromatography (1−5% MeOH/CH_2Cl_2) to yield 19.0 mg (54%) of **61** and 16.2 mg (36%) of **60**. The recovered starting material was resubjected to the above reactions conditions (twice), and the combined product from all runs was purified by column chromatography (1−5% MeOH/CH_2Cl_2) to yield 24.0 mg (68%) of **61** as a colorless oil: $[\alpha]_D^{23}$ +24.3 (*c* 0.07, $CHCl_3$); IR (film) 3421, 2918, 2866, 1731, 1461, 1383, 1254, 1087, 1054, 1024, 969, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 7 Hz, 3H), 1.00−1.06 (m, 23H), 1.16 (d, J = 7 Hz, 3H), 1.34 (q, J = 7 Hz, 6H), 1.45−1.70 (m, 3H), 1.71 (s, 3H), 1.82 (s, 3H), 1.95−2.20 (m, 5H), 2.31−2.48 (m, 1H), 2.72 (dd, J = 22, 14 Hz, 1H), 2.81 (dd, J = 22, 14 Hz, 1H), 3.18 (s, 3H), 3.41 (d, J = 7 Hz, 1H), 3.70 (t, J = 6 Hz, 2H), 4.03−4.20 (m, 6H), 4.72 (ddd, J = 10, 4, 2 Hz, 1H), 5.49 (dd, J = 15, 9 Hz, 1H), 5.81 (d, J = 11 Hz, 1H), 6.18 (s, 1H), 6.23 (dd, J = 15, 11 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, one signal obscured by $CHCl_3$ resonance) δ 10.0, 11.5, 12.6 (3C), 16.5 (2C), 17.0, 18.2 (3C), 18.3 (3C), 19.8, 28.5, 33.2, 34.7 (d, J = 133 Hz), 35.7, 36.5, 39.1, 39.4, 43.3, 56.9, 59.7, 62.9 (br, 2C), 73.9, 79.3, 83.6, 87.4, 125.7, 127.2, 134.6, 139.1, 146.7, 164.8, 171.7; MS (FAB) *m*/*z* 885 (M + 1), 750, 649, 423, 309; HRMS (FAB) *m*/*z* found 869.3288 $(M - CH_3)^+$, calcd for $C_{38}H_{67}IO_{10}PSi$ *m*/*z* 869.3286.

Aldehyde 62. To a solution of **61** (1.6 mg, 1.8 μmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature was added Dess−Martin periodinane (3 mg, 7.1 μmol), and the mixture was stirred for 10 min. The solution was diluted with CH_2Cl_2 (2 mL); a mixture of saturated sodium thiosulfate and $NaHCO_3$ (2 mL) was added, and the solution was stirred vigorously for 10 min. To this mixture were added H_2O (5 mL) and CH_2Cl_2 (5 mL); the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined extract was washed with saturated $NaHCO_3$ (5 mL) and dried (Na_2SO_4); the solvent was removed in vacuo, and the residue was purified by chromatography (5% MeOH/CH_2Cl_2) to yield 1.6 mg (100%) of **62** as a colorless oil: $[\alpha]_D^{23}$ +22.9 (*c* 0.07, $CHCl_3$); IR (film) 2930, 2858, 1736, 1463, 1377, 1255, 1086, 1050, 1021, 971, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 1.01−1.06 (m, 22H), 1.14 (d, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 3H), 1.34 (t, J = 7 Hz, 3H), 1.68−1.88 (m, 2H), 1.71 (s, 3H), 1.82 (s, 3H), 1.96−2.07 (m, 3H), 2.13 (dd, J = 17 Hz, 1H), 2.47−2.59 (m, 3H), 2.74 (dd, J = 22, 14 Hz, 1H), 2.79 (dd, J = 17, 2 Hz, 1H), 2.84 (dd, J = 22, 14 Hz, 1H), 3.19 (s, 3H), 3.43 (d, J = 7 Hz, 1H), 4.08−4.21 (m, 6H), 4.75 (ddd, J = 10, 4, 2 Hz, 1H), 5.54 (dd, J = 15, 8 Hz, 1H), 5.85 (d, J = 11 Hz, 1H), 6.17 (s, 1H), 6.24 (dd, J = 15, 11 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, one signal obscured by $CHCl_3$ resonance) δ 9.9, 11.8, 12.6 (3C), 16.2, 16.6 (2C), 18.3 (3C), 18.4 (3C), 19.9, 26.1, 32.1, 34.7 (d, J = 133 Hz), 36.1 (2C), 39.1, 42.2, 50.0, 56.9, 62.8 (2C), 74.0, 79.3, 83.5, 87.3, 125.6, 127.4, 133.9, 139.4, 146.7, 164.9, 170.6, 199.9; MS (FAB) *m*/*z* 883 (M + 1), 613, 309, 219, 210; HRMS (FAB) *m*/*z* found 883.3406, calcd for $C_{39}H_{69}IO_{10}PSi$ *m*/*z* 883.3442.

α,β-Unsaturated Lactone 63. To a stirred suspension of anhydrous LiCl (7.0 mg, 0.16 mmol) in anhydrous MeCN (8 mL) was added a solution of **62** (2.6 mg, 2.9 μmol) in anhydrous MeCN (2 mL). After 15 min, diisopropylethylamine (10 μL, 58 μmol) was added, the mixture stirred for 24 h, and the reaction quenched with saturated NH_4Cl (5 mL). The mixture was partitioned between brine (10 mL) and Et_2O (10 mL); the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined extract was washed with brine (10 mL) and dried (Na_2SO_4); the solvent was removed in vacuo, and the residue was purified by chromatography (70−100% Et_2O in hexanes) to yield 1.2 mg (57%) of **63** as a colorless oil: $[\alpha]_D^{23}$ +4.3 (*c* 0.14, CH_2Cl_2); IR (film) 2928, 2867, 1729, 1711, 1467, 1377, 1319, 1255, 1223, 1162, 1072, 1050, 978, 878, 803, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (dt, J = 14, 12 Hz, 1H), 0.98 (d, J = 7 Hz, 3H), 1.02−1.17 (m,

21H), 1.23 (d, $J = 6$ Hz, 3H), 1.61 (dd, $J = 15$, 3 Hz, 1H), 1.71−1.77 (m, 1H), 1.78 (bs, 3H), 1.81−1.87 (m, 1H), 1.92 (bs, 3H), 2.02 (dq, $J = 14$, 2 Hz, 1H), 2.10 (dd, $J = 18$, 12 Hz, 1H), 2.16 (dt, $J = 15$, 11 Hz, 1H), 2.22−2.32 (m, 2H), 2.51−2.56 (m, 1H), 2.78 (ddd, $J = 18$, 5, 2 Hz, 1H), 3.18 (s, 3H), 3.36 (d, $J = 9$ Hz, 1H), 3.70 (ddd, $J = 12$, 9, 3 Hz, 1H), 4.03 (dd, $J = 11$, 3 Hz, 1H), 4.47 (dd, $J = 11$, 3 Hz, 1H), 5.16 (dd, $J = 15$, 10 Hz, 1H), 5.62 (d, $J = 16$ Hz, 1H), 5.75 (bd, $J = 11$ Hz, 1H), 6.17 (bs, 1H), 6.24 (dd, $J = 15$, 11 Hz, 1H), 6.77 (ddd, $J = 16$, 11, 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 11.4, 12.6 (3C), 16.9, 18.3 (3C), 18.4 (3C), 19.1, 30.0, 34.5, 34.8, 37.1, 38.4, 38.9, 45.5, 56.7, 73.8, 78.8, 79.5, 83.6, 88.7, 124.8, 124.9, 130.2, 133.7, 140.1, 146.2, 147.4, 165.8, 170.6; MS (FAB) *m*/*z* 729 (M+1), 697, 601, 569, 463; HRMS (FAB) *m*/*z* found 729.3062, calcd for $C_{35}H_{58}IO_6Si$ *m*/*z* 729.3048.

***O*-Triisopropylsilylrhizoxin D (69).** To a solution of **68** (6.6 mg, 20.3 μmol) and **63** (7.4 mg, 10.1 μmol) in DMF (0.6 mL) was added a solution of bis(acetonitrile)palladium(II) dichloride (260 μL, 1.96 μmol/mL in DMF, 0.508 μmol, 5 mol %), and the mixture was stirred at room temperature for 14 h in the dark. The solution was diluted with Et_2O (10 mL); saturated $NaHCO_3$ (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (10 mL), and the extract was washed with H_2O (5 × 2 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by chromatography (from 50% CH_2Cl_2/hexanes to 2% MeOH/CH_2Cl_2) to yield 6.4 mg (84%) of **69** as a pale yellow oil: $[\alpha]_D^{23}$ +97.1 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65−0.75 (m, 1H), 1.00 (d, $J = 7$ Hz, 3H), 1.02−1.06 (m, 21H), 1.21 (d, $J = 6$ Hz, 3H), 1.40−1.75 (m, 2H), 1.77 (s, 3H), 1.91 (s, 3H), 1.96−2.13 (m, 3H), 2.14 (s, 3H), 2.18−2.40 (m, 3H), 2.48 (s, 3H), 2.50−2.56 (m, 1H), 2.77 (ddd, $J = 18$, 5, 2 Hz, 1H), 3.17 (s, 3H), 3.22 (d, $J = 9$ Hz, 1H), 3.67 (ddd, $J = 12$, 9, 3 Hz, 1H), 4.01 (dd, $J = 11$, 3 Hz, 1H), 4.56 (dd, $J = 11$, 3 Hz, 1H), 5.10 (dd, $J = 15$, 10 Hz, 1H), 5.62 (d, $J = 16$ Hz, 1H), 5.71 (bd, $J = 11$ Hz, 1H), 6.07 (bd, $J = 11$ Hz, 1H), 6.22 (dd, $J = 15$, 11 Hz, 1H), 6.26 (s, 1H), 6.35 (d, $J = 15$ Hz, 1H), 6.63 (dd, $J = 15$, 11 Hz, 1H), 6.76 (ddd, $J = 16$, 11, 5 Hz, 1H), 7.55 (s, 1H); MS (FAB) *m*/*z* 750 (M + 1), 551, 463, 282, 232; HRMS (FAB) *m*/*z* found 750.4784, calcd for $C_{44}H_{68}NO_7Si$ *m*/*z* 750.4765.

Rhizoxin D (2). To a stirred solution of **69** (5.9 mg, 7.86 mmol) in anhydrous THF (0.6 mL) in a polyethylene container was added pyridine (0.6 mL), and the mixture was cooled to 0 °C. To this solution was added HF·pyridine (0.3 mL), and the mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and stirred vigorously for 5 min. The layers were separated, and the organic phase was washed with saturated aqueous $CuSO_4$ (5 mL), saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL) and then dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by chromatography (3% MeOH/CH_2Cl_2) to yield 3.0 mg (59%) of **2**: $[\alpha]_D^{23}$ +174.1 (*c* 0.27, MeOH), with ^{1}H and ^{13}C NMR spectra identical to those of an authentic sample.

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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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