376, base peak 110. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.77; H, 7.59.

(3aα,4β,6aα)-(±)-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((±)-2) [(±)-Isoavenaciolide]. To a solution of 15 mg (0.04 mmol) of bislactonic sulfide **23** in 0.5 mL of $CHCl_3$ at −20 °C was added a solution of 8.6 mg (0.04 mmol) of *m*-CPBA in 0.5 mL of $CHCl_3$. The reaction mixture was stirred at −20 °C for 40 min and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was washed once with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude sulfoxide was dissolved in 5 mL of $PhCH_3$. After the addition of 6.9 mg (0.05 mol) of solid K_2CO_3, the mixture was heated at reflux for 5 h. Concentration under reduced pressure followed by flash chromatography (elution with 3:1 hexanes–acetone) afforded 7.5 mg (71%) of (±)-isoavenaciolide ((±)-**2**) as a solid. Recrystallization from hexanes–ethyl acetate gave white needles, mp 101.0–102.0 °C (lit. mp 99–101,[1d] 99–99.5 °C[1c]), homogeneous by TLC and spectroscopic criteria: R_f 0.21 (4:1 ether–hexanes); IR ($CHCl_3$) 3022, 2960, 2932, 2860, 1785, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.6 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.12 (d, 1 H, J = 8.8 Hz), 4.76 (m, 1 H), 4.00 (m, 1 H), 1.60 (br m, 2 H), 1.25 (br s, 12 H)) 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.25, 167.92, 130.78, 128.93, 80.52, 74.87, 41.64, 32.25, 31.71, 29.28, 29.08, 26.01, 22.55, 14.00; MS (70 eV) parent peak +1 267, base peak 96. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.42; H, 8.50.

(3a*R*-(3aα,4β,6aα))-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((−)-2) [(−)-Isoavenaciolide]. The procedure for the conversion of **23** to (±)-**2** was followed. Concentration under reduced pressure followed by flash chromatography (elution with 3:1 hexanes–acetone) gave 13 mg (61%) of (−)-isoavenaciolide ((−)-**2**) as a solid. Recrystallization from hexanes–ethyl acetate afforded white needles, mp 128.0–129.0 °C (lit. mp 127.0–128.0,[1b] 129.0–130.0 °C[1a]), homogeneous by TLC and spectroscopic criteria: R_f 0.21 (3:1 hexanes–acetone); $[\alpha]_D^{22}$ −155.83° (*c* 0.50, EtOH) [lit. $[\alpha]_D^{20}$ −167.2° (*c* 1.2, EtOH),[1b] $[\alpha]_D^{27}$ −154° (*c* 1.1, EtOH)[1a]]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.6 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.12 (d, 1 H, J = 8.8 Hz), 4.76 (m, 1 H), 4.00 (m, 1 H), 1.61 (m, 2 H), 1.26 (br s, 12 H), 0.88 (t, 3 H, J = 6.6 Hz).

(3aα,4α,6aα)-(±)-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((±)-3) [(±)-Avenaciolide]. To a solution of 295 mg (0.77 mmol) of acid **19** in 4 mL of CH_2Cl_2 at 0 °C was added 0.47 mL (3.84 mmol) of $BF_3{\cdot}Et_2O$. The reaction mixture was stirred at 0 °C for 15 min and then warmed to 25 °C and stirred for 1.5 h. After concentration under reduced pressure, crude hydroxy acid **26** was dissolved in 35 mL of $PhCH_3$. A catalytic amount of camphorsulfonic acid was added, and the mixture was heated at reflux for 36 h. Concentration under reduced pressure followed by flash chromatography (elution with 4:1 hexanes–ethyl acetate) gave 102 mg (50%) of (±)-avenaciolide ((±)-**3**) as a solid. Recrystallization from pentane–ether afforded white needles, mp 56.0–57.0 °C (lit.[2e,i] mp 55–56 °C), homogeneous by TLC and spectroscopic criteria: R_f 0.33 (4:1 hexanes–ethyl acetate); IR ($CHCl_3$) 3025, 2960, 2933, 2862, 1790, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, 1 H, J = 2.5 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.06 (d, 1 H, J = 8.5 Hz), 4.42 (ddd, 1 H, J = 7.2, 6.0, 3.9 Hz), 3.56 (m, 1 H), 1.80 (m, 2 H), 1.45 (br m, 2 H), 1.28 (br s, 10 H), 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 169.77, 167.47, 134.64, 126.11, 85.19, 74.30, 44.11, 35.95, 31.69, 29.24, 29.04, 24.76, 22.52, 13.97; MS (15 eV) parent peak + 1 267, base peak 96. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.53; H, 8.55.

(3a*R*-(3aα,4α,6aα))-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((−)-3) [(−)-Avenaciolide]. The procedure for the conversion of **19** to (±)-**3** was followed. Concentration under reduced pressure followed by flash chromatography (elution with 4:1 hexanes–ethyl acetate) gave 123 mg (59%) of (−)-avenaciolide ((−)-**3**) as a solid. Recrystallization from pentane–ether gave white needles, mp 51.0–52.0 °C (lit. mp 49–50, 54–56;[2a] 50–51;[1b,2f] 54–56 °C[2g]), homogeneous by TLC and spectroscopic criteria: R_f 0.40 (4:1 Et_2O–hexanes); $[\alpha]_D^{24}$ −39.77° (*c* 1.28, EtOH) [lit. $[\alpha]_D^{26.5}$ −41.6° (*c* 1.2, EtOH),[2d] $[\alpha]_D^{29.5}$ −41.08° (*c* 0.274, EtOH),[1b,2f] $[\alpha]_D^{25}$ −41.6° (*c* 1.0, EtOH)[2g]]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, 1 H, J = 2.5 Hz), 5.88 (d, 1 H, J = 2.2 Hz), 5.05 (d, 1 H, J = 8.5 Hz), 4.42 (ddd, 1 H, J = 6.6, 6.5, 3.9 Hz), 3.56 (m, 1 H), 1.80 (m, 2 H), 1.27 (br s, 12 H), 0.88 (t, 3 H, J = 6.7 Hz).

Acknowledgment. We gratefully acknowledge the National Institutes of Health, the Alfred P. Sloan Foundation, and the National Science Foundation for generous financial support. Industrial matching funds for the NSF Presidential Young Investigator Award from Stuart Pharmaceuticals, Rohm and Haas Company, DuPont, Union Camp, SOHIO, and Hardwicke Chemicals are greatly appreciated. We are grateful to Professor Stuart Schreiber (then at Yale University, now Harvard) for providing spectra and a sample of (±)-avenaciolide for comparison.

Synthesis of the Lower Subunit of Rhizoxin

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Full details of a study leading to a synthesis of the optically active C13–C26 lower subunit of rhizoxin including the side-chain chromophore characteristic of the full class of antimitotic agents are described. A key element of the synthesis is the stereoselective introduction of the C18–C19 trisubstituted olefin through use of a Wadsworth–Horner–Emmons condensation of **3** with β-keto phosphonate **38** bearing resident functionality suitable for the diastereoselective introduction of C15–C17 employing a hydroxyl-directed reduction of the resultant β-hydroxy ketone.

Rhizoxin **1** (NSC-332598), a 16-membered macrolide isolated from *Rhizopus chinensis*, constitutes the most extensively examined member of a new class of agents that has been shown to possess antimicrobial activity, antifungal activity, potent in vitro cytotoxic activity, and confirmed in vivo antitumor activity including a pronounced efficacy against vincristine and adriamycin resistant tumor cell lines. The cytotoxic and antitumor activity of rhizoxin and its homologues[2] is believed to be

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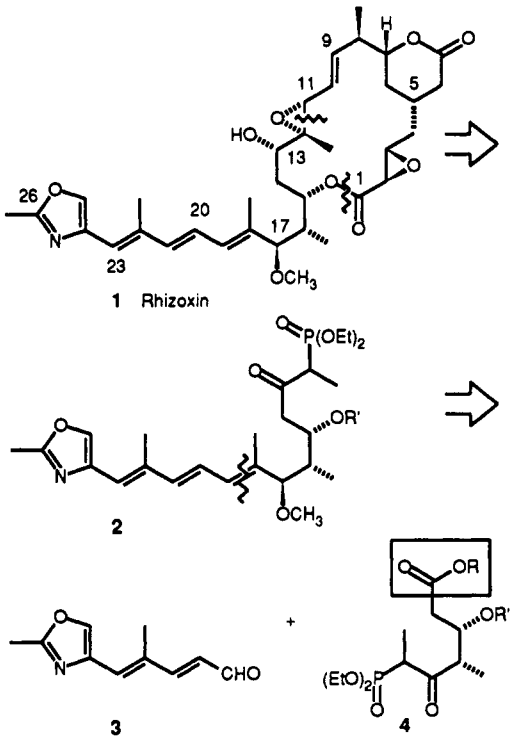
(1) (a) Iwasaki, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S.; Sato, Z.; Matsuda, I.; Noda, T. *J. Antibiot.* **1984**, *37*, 354. (b) Kiyoto, S.; Kawai, Y.; Kawakita, T.; Kino, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 762. (c) Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull.* **1986**, *34*, 1387.

0022-3263/92/1957-2235$03.00/0

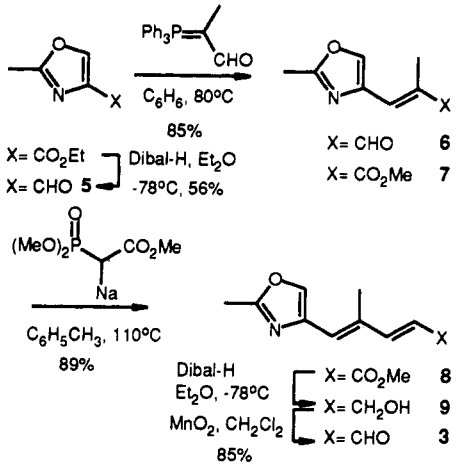
Scheme I



derived from their inhibition of microtubule polymerization and the resulting inhibition of cell mitosis. In these studies, rhizoxin has been shown to inhibit tubulin β^s cross-linking and enhance tubulin β^* cross-linking similar to maytansine and ansamitocin P-3.[3] Thus, rhizoxin and its homologues constitute a class of antitumor antibiotics that complement the existing, clinically effective mitotic inhibitors and that may prove especially useful in the treatment of resistant or refractory tumor cell lines.

Since the unambiguous structure determination of rhizoxin by single-crystal X-ray analysis[4] which established the relative and absolute configuration of its 11 stereocenters, synthetic efforts on the agents have been limited.[5] Herein, we detail studies conducted in the course of the synthesis of the optically active C13–C26 lower subunit of rhizoxin including the side-chain chromophore. Based on the analysis detailed in Scheme I, the C1–C11 subunit of rhizoxin is anticipated to be linked to the lower C12–C26 subunit through use of the Wadsworth–Horner–Emmons reagent **2**, which in turn was anticipated to be derived from condensation of β-keto phosphonate **4** with aldehyde **3** with well-precedented stereoselective introduction of the C18–C19 trisubstituted olefin. Consequently, our initial efforts on the synthesis of rhizoxin have focused on the preparation of **2** with control of the relative and absolute configuration of the three contiguous C15–C17 stereocenters.

Scheme II



Preparation of Aldehyde 3. Wittig reaction of (α-formylethylidene)triphenylphosphorane[6] with **5**, derived from direct diisobutylaluminum hydride reduction of ethyl 2-methyloxazole-4-carboxylate,[7] provided **6** with little or no detectable trace of the corresponding *Z* olefin (Scheme II). Subsequent condensation of **6** with trimethyl 2-sodiophosphonoacetate in refluxing toluene provided **8** with clean introduction of the *E* olefin. Diisobutylaluminum hydride reduction of **8** followed by subsequent manganese dioxide oxidation of the crude alcohol provided the desired aldehyde **3** in excellent overall conversion.

In the development of the approach to **3**, alternatives to the five-step sequence detailed in Scheme II were examined which proved less successful or less direct. The reaction of **5** with 2-lithio-2-(trimethylsilyl)propionaldehyde *tert*-butylimine[8] provided **6** after imine hydrolysis (56%) albeit as a 5:1 mixture of *E*:*Z* olefin isomers. Similarly, the corresponding ester **7** could be derived from **5** by reaction with (α-carbomethoxyethylidene)triphenylphosphorane (85%, 14:1 *E*:*Z*) or methyl 2-sodio-2-(diethylphosphono)propionate (73%, >25:1 *E*:*Z*) and indirectly converted to **6** by sequential reduction (DIBAL-H) and oxidation (MnO_2). In addition, the direct conversion of **5** to **8** through Wittig reaction with (4-carbomethoxy-3-buten-2-ylidene)triphenylphosphorane[9] provided **8** albeit as a 1:1 mixture of *E*:*Z* olefin isomers and attempts to equilibrate the mixture to the more stable trisubstituted *E* olefin (cat. I_2, H_2SO_4, HCl, $BF_3{\cdot}OEt_2$, or C_6H_5SH) were not productive. Finally, attempts to prepare **3** directly from **6** through Wittig reaction with (α-formylmethylene)triphenylphosphorane[6] under thermal (C_6H_6, 80 °C; $C_6H_5CH_3$, 110 °C) or high-pressure reaction conditions[10] provided only trace conversions, and the reaction of **6** with 2-lithio-2-(trimethylsilyl)acetaldehyde *tert*-butylimine[8] provided **3** in modest yield (35%) after imine hydrolysis.

Studies on the Introduction of C14–C18. Prior to their implementation in efforts on the total synthesis of

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(3) (a) Sullivan, A. S.; Prasad, V.; Roach, M. C.; Takahashi, M.; Iwasaki, S.; Ludueña, R. F. *Cancer Res.* **1990**, *50*, 4277. (b) Takahaski, J.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y. *Biochem. Biophys. Acta* **1987**, *926*, 215. (c) Bai, R.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1990**, *265*, 17141. (d) Bai, R.; Pettit, G. R.; Hamel, E. *Biochem. Pharmacol.* **1990**, *39*, 1941. (e) Sawada, T.; Hashimoto, Y.; Li, Y.; Kobayashi, H.; Iwasaki, S. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 558.

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(9) Buchta, E.; Andree, F. *Chem. Ber.* **1959**, *92*, 3111. A modified preparation of the Wittig reagent was employed with use of high pressure reaction conditions (6.2 kbar, benzene–toluene (7:3), 25 °C, 46 h, 93%). See: Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293.

(10) Isaacs, N. S.; El-Din, G. N. *Tetrahedron Lett.* **1987**, *28*, 2191.

Scheme III

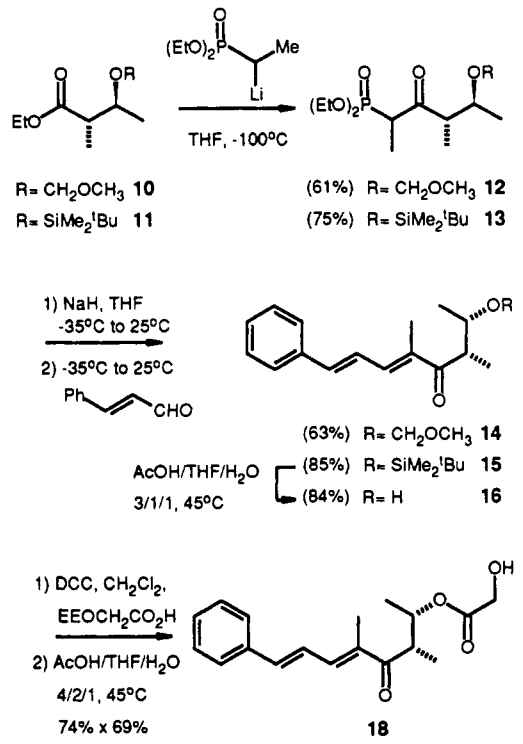

Table I. Reduction of 14

reducing agent (equiv)	solvent	temp (°C)	time (h)	19a:19b	yield (%)
DIBAL-H (1.8)	$PhCH_3$	-78	3	18:1	64
DIBAL-H (3)	THF	-78 to 0	10	15:1	63
$LiBH_4$ (0.55)	THF	0	3	9:1	55
$LiAlH_4$ (0.5)	Et_2O	0	5.5	4.5:1	38
$NaBH_4$ (1.15)	EtOH	0 to 25	19.5	5:1	40
L-Selectride (1.5)	THF	-78	2.25	4:1	44
$NaBH_4$ (1)–$CeCl_3$ (1)	DMSO	25	1	3:1	49
$Zn(BH_4)_2$ (2.5)	Et_2O	0	24	1:2	49

rhizoxin, we examined methods for introduction of C14–C18 with formation of the C18–C19 trisubstituted *E* olefin and control of the three C15–C17 contiguous stereocenters. In anticipation that the stereochemical control required for introduction of the olefin could be achieved through use of a Wadsworth–Horner–Emmons condensation of a β-keto phosphonate with aldehyde **3**, the studies focused on the identification of a viable phosphonate that contained the resident functionality for the diastereocontrolled introduction of C15–C17. The model phosphonates **12** and **13** incorporate two of the three stereocenters, and their use would require a single, subsequent diastereoselective ketone reduction to provide the desired anti 1,3-diol. Consequently, we examined the use of **12** and **13** in order to assess the potential accompanying problems of phosphonate β-elimination and/or epimerization and to subsequently address the key diastereoselective reduction with **14**–**18**.

Treatment of **10** and **11**[11] with diethyl (α-lithioethyl)-phosphonate[12] at −100 °C in tetrahydrofuran provided the β-keto phosphonates **12** and **13**, respectively (Scheme III). Sodium hydride deprotonation of **12** or **13** (−35 to 25 °C, THF) followed by their reaction with cinnamaldehyde (−35 to 25 °C) provided **14** or **15** (>25:1 *E*:*Z*, 63% and 85%, respectively) without detectable competitive β-elimination

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(12) (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5653. (b) Ford-Moore, A. H.; Williams, J. H. *J. Chem. Soc.* **1947**, 1465.

Scheme IV

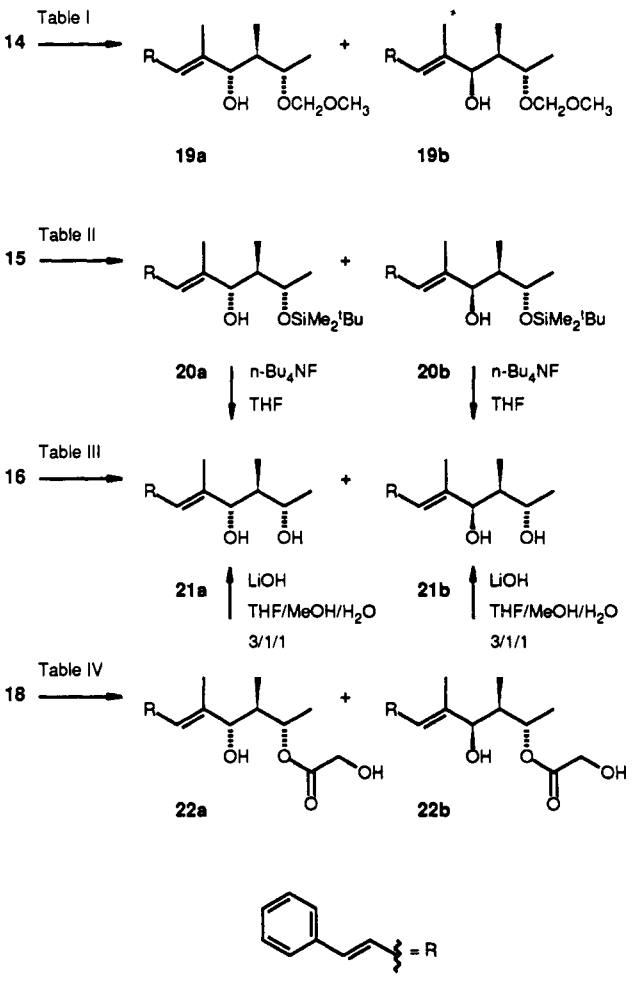


Table II. Reduction of 15

reducing agent (equiv)	solvent	temp (°C)	time (h)	20a:20b	yield (%)
DIBAL-H (2)	$PhCH_3$	-78	3	>25:1	86
$LiBH_4$ (0.75)	Et_2O	0 to 25	2.5	2.3:1	79
$Zn(BH_4)_2$ (1.6)	Et_2O	0 to 5	1.5	2.5:1	43
$LiAlH_4$ (0.65)	Et_2O	0 to 25	1.3	7.6:1	77
L-Selectride (2)	THF	-78	1	>25:1	38

Table III. Reduction of 16

reducing agent (equiv)	solvent	temp (°C)	time (h)	21a:21b	yield (%)
DIBAL-H (2.9)	$PhCH_3$	-78 to 25	10	1.9:1	66
$LiAlH_4$ (0.8)	Et_2O	0 to 25	9.5	1:2.1	69
$LiBH_4$ (2.6)	Et_2O	0 to 25	6	1:2.6	34
$Zn(BH_4)_2$ (1.3)	Et_2O	0	40	1:4.7	52
$Me_4NBH(OAc)_3$ (8)	CH_3CN–HOAc	-40 to 25	20	1:>25	73
Red-Al (1.1)	$PhCH_3$	-78	5.5	1:1.2	77

Table IV. Reduction of 18

reducing agent (equiv)	solvent	temp (°C)	time (h)	22a:22b	yield (%)
$Zn(BH_4)_2$ (2)	Et_2O	0	16	3.3:1	35
$Me_4NBH(OAc)_3$ (10)	CH_3CN–HOAc	-40 to 25	13	-	NR[a]
DIBAL-H (4)	$PhCH_3$	-78	1	12:1	66
Red-Al (1.2)	$PhCH_3$	-78	5	3:1	48

[a] NR = no reaction.

or α-epimerization and with superb control of the olefin stereochemistry. Cleavage of the *tert*-butyldimethylsilyl ether of **15** upon exposure to mild aqueous acid provided **16** and the subsequent dicyclohexylcarbodiimide-promoted

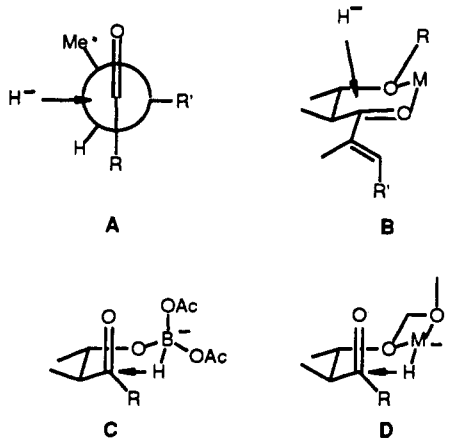
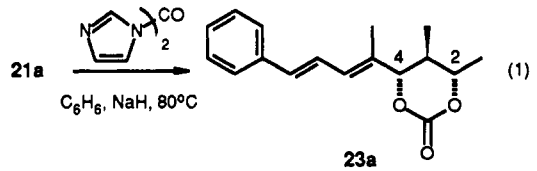
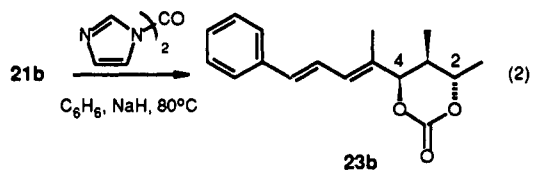


Figure 1.

coupling of 16 with *O*-(1-ethoxyethyl)glycolic acid[13] provided 17. Aqueous acid hydrolysis of the acetal of 17 provided 18.

Representative results from the subjection of **14–16** and 18 to reduction with a range of reagents are detailed in Tables I–IV and Scheme IV. The reduction product ratios were determined by ^{1}H NMR (300 MHz) integration of distinguishable signals. The relative stereochemical assignments were unambiguously established through chemical correlation with **21a** or **21b** and their independent conversion to the cyclic carbonates **23a** and **23b** for which the C2-H and C4-H coupling constants proved diagnostic, eqs 1–2. The chemical shift and coupling constants for

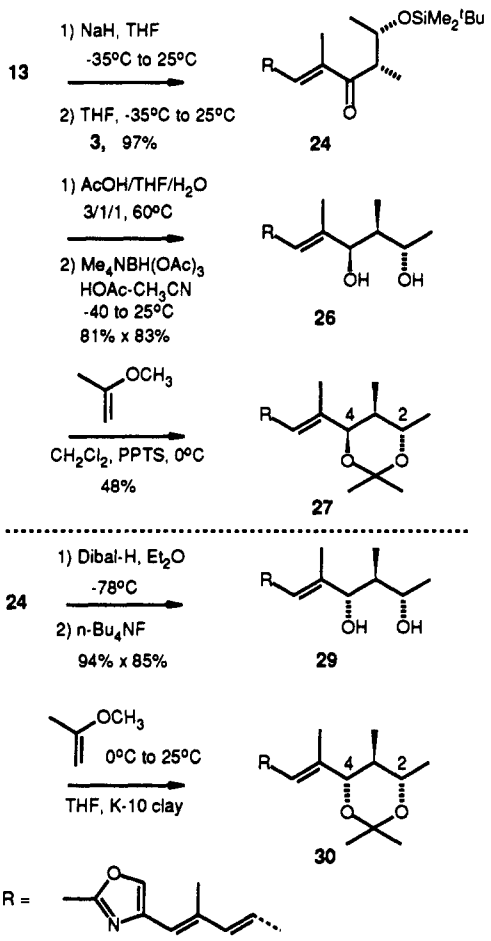




C2-H of **23a** and **23b** proved similar but the C4-H/C3-H coupling constant of **23a** was 10.7 Hz, characteristic of a C4-H axial proton, while that of **23b** was 3.3 Hz, characteristic of a C4-H equatorial proton. Consistent with this assignment, the chemical shift of the C4-H of **23a** was found at approximately 0.5 ppm higher field than that of **23b**. Good to superb diastereoselectivity (>25:1) for reduction to the undesired syn 1,3-diol derivative could be readily achieved with the agents in which the proximal β-hydroxyl group is protected (**14–15** and 18). Presumably this may be attributed to preferential reduction through a Felkin transition state (Figure 1, part A)[14a] or reagent bidentate chelation (Figure 1, part B) and axial hydride delivery.[14b] Efforts to alter the diastereoselectivity of the reduction to provide predominantly the anti 1,3-diol derivative through reagent chelation[14c] to the proximal β-substituent (Figure 1, part D) were not especially successful but did serve to increase the relative amount of anti to syn reduction product. Only the reduction of **14** with zinc borohydride[15] provided a modest 2:1 preference for generation of the desired anti versus syn 1,3-diol derivative. Initial attempts to exploit this diastereoselective reduction to the syn 1,3-diol derivatives through use of alcohol inversion at the newly generated hydroxyl center proved problematic. Attempts to directly displace the alcohol of **19a** and **20a** under a range of Mitsunobu reaction conditions[16] generally provided recovered starting materials and the conversion of the free alcohol to the corresponding mesylate or tosylate followed by an appropriate clean S_N2 displacement proved problematic.[17]

In contrast, reduction of the free alcohol **16** provided predominantly the desired anti 1,3-diol **21b**, and its near exclusive generation was observed under the reduction conditions exploited by Evans and co-workers (Table III).[18] Thus, treatment of **16** with tetramethylammonium triacetoxyborohydride under the tailored reaction conditions

Scheme V



(13) Prepared in three steps from glycolic acid by (1) Fischer esterification (MeOH, cat. H_2SO_4, 65 °C, 42 h, 64%), (2) reaction with ethyl vinyl ether and cat. pyridinium *p*-toluenesulfonate (CH_2Cl_2, 25 °C, 3 h, 82%), and (3) hydrolysis with LiOH (1 equiv) in THF–CH_3OH–H_2O (3:1:1) 25 °C, 0.5 h, 93%. This compound could be stored as its lithium salt which was carefully acidified prior to use.

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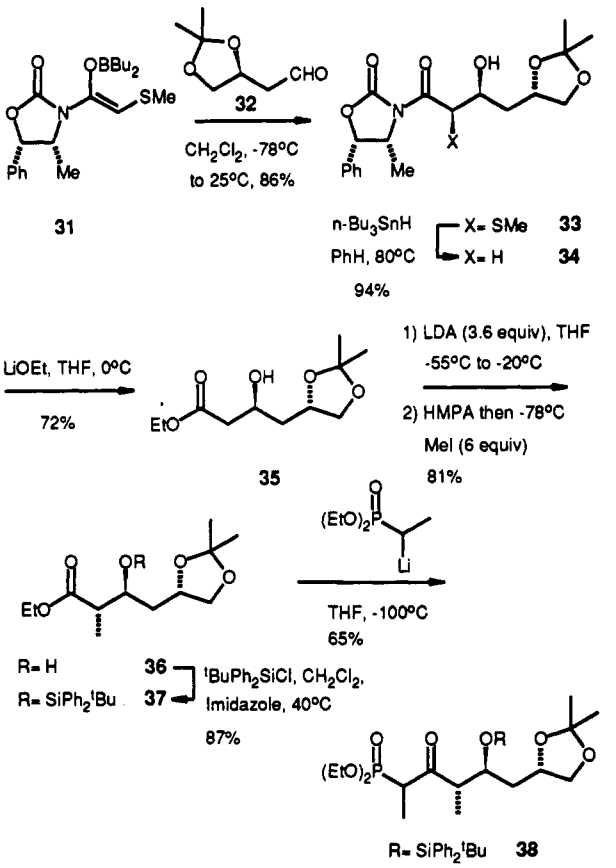
that ensure hydroxyl exchange with the triacetoxyborohydride and subsequent intramolecular hydride delivery to the proximal carbonyl (Figure 1, part C) provided the desired anti 1,3-diol **21b** (73%, >25:1 anti:syn).

The results of the extension of these observations to the rhizoxin aldehyde **3** are detailed in Scheme V. Condensation of the β-keto phosphonate **13** and **3** under the prescribed reaction conditions provided the triene **24** in excellent conversion (97%, >25:1 *E*:*Z*) without detectable β-elimination or epimerization. Acid-catalyzed deprotection of the *tert*-butyldimethylsilyl ether followed by reduction of the free alcohol **25** with tetramethylammonium triacetoxyborohydride provided exclusively the desired anti 1,3-diol **26** (83%, >25:1 anti:syn). Alternatively, direct diisobutylaluminum hydride reduction of **24** provided **28** in excellent yield and with exclusive generation of the undesired syn 1,3-diol derivative (94%, >25:1 syn:anti). Fluoride-induced deprotection of the *tert*-butyldimethylsilyl ether provided an authentic sample of the syn 1,3-diol **29** for comparative purposes. The stereochemistry of **26** and **29** was unambiguously established through conversion to their respective acetonides **27** and **30** and the comparative examination of the diagnostic C2-H and C4-H coupling constants. For **27** and **30**, the C2-H coupling constants and the chemical shifts were similar but the C4-H/C3-H coupling constant for **27** was 4.4 Hz, characteristic of a C4-H equatorial hydrogen, while that of **30** proved to be 10.3 Hz, characteristic of a C4-H axial hydrogen. Consistent with the assignment, the chemical shift of the C4-H of **27** was found 0.5 ppm downfield from that of **30**. The 2D ^1H–^1H NOESY NMR of **30** unambiguously established the stereochemical assignments on the six-membered 1,3-dioxane and the triene olefin geometry with diagnostic NOE crosspeaks being observed for C2-H/C3-Me, C4-H/C3-Me, C4-H/C2-H, C9-Me/C7-H, C9-Me/C5′-H, C7-H/C5-Me, and C6-H/C4-H.

Preparation of β-Keto Phosphonate 4. The application of these observations to the diastereoselective introduction of the authentic rhizoxin C15–C17 subunit requires the use of the functinoalized β-keto phosphonate **4** possessing a protected precursor to the terminal ester functionality and a preparation that would provide the material in optically active form. For this purpose, the acetonide derivative of a 1,2-diol was selected as the requisite functionality for oxidative 1,2-diol cleavage with liberation of the terminal carboxylate and permitted the selection of **38** as the key β-keto phosphonate.

A six-step synthesis of optically active **38** is detailed in Scheme VI and proved amenable to large scale preparation. Diastereoselective condensation of the boron *Z* enolate **31**[19] with (3*S*)-**32**[7b,20] provided the syn aldol adduct **33** (86% >25:1) in which the resident chirality of the auxilary leads to the introduction of the 2*R*,3*S* configuration. Tributyltin hydride treatment of **33** led to clean reductive desulfurization[21] and subsequent ethanolysis[22] of **34** provided **35**. Isolated **35** proved to be stereochemically pure as judged by capillary GC analysis (GB-20 M carbowax, 50 m × 0.25 mm, 170 °C, 36 mL/min, t_R = 31.4 min, >99:1 3*S*:3*R*). Dianion generation[23] followed by diastereoselective alkylation of the enolate with methyl iodide in THF–HMPA at low temperature (−78 °C) cleanly afforded **36** (81%, >15:1 2*S*:2*R*) under the conditions detailed by Seebach and Frater. The free alcohol was subsequently protected as a *tert*-butyldiphenylsilyl ether,[24] requiring somewhat vigorous conditions for reaction and the low-temperature addition of diethyl (α-lithioethyl)phosphonate[12] to **37** provided the key β-keto phosphonate **38**.

Scheme VI



Assemblage of the Rhizoxin C13–C26 Lower Subunit. Analogous to the results of the preliminary studies, condensation of the β-keto phosphonate **38** with **3** provided **39** in excellent yield with near complete control of the olefin stereochemistry (>44:1 *E*:*Z*) (Scheme VII). The terminal ester was unmasked in a sequence requiring three steps. Initial cleavage of the acetonide was accomplished with catalytic pyridinium *p*-toluenesulfonate in 4:1 methanol–ether at 50 °C to provide the internal ketal **40** (83%) as a single diastereomer possessing the indicated stereochemistry. This acetonide cleavage accompanied by mixed internal ketal formation proved to provide a stable intermediate as a single diastereomer amenable to simple isolation and purification. Subsequent room-temperature treatment of **40** with sodium periodate in aqueous dioxane provided aldehyde **41** and presumably proceeds by initial ketal cleavage to liberate the terminal 1,2-diol followed by oxidative cleavage of the glycol. Finally, further oxidation of **41** to the corresponding carboxylic acid **42** was accomplished with buffered aqueous sodium chlorite ($NaClO_2$–NaH_2PO_4)[25] with acetonitrile/*tert*-butyl alcohol as cosolvents and added 2-methyl-2-butene as a chlorine scavenger. Esterification of the crude carboxylic acid **42** with excess diazomethane provided the methyl ester **43** in

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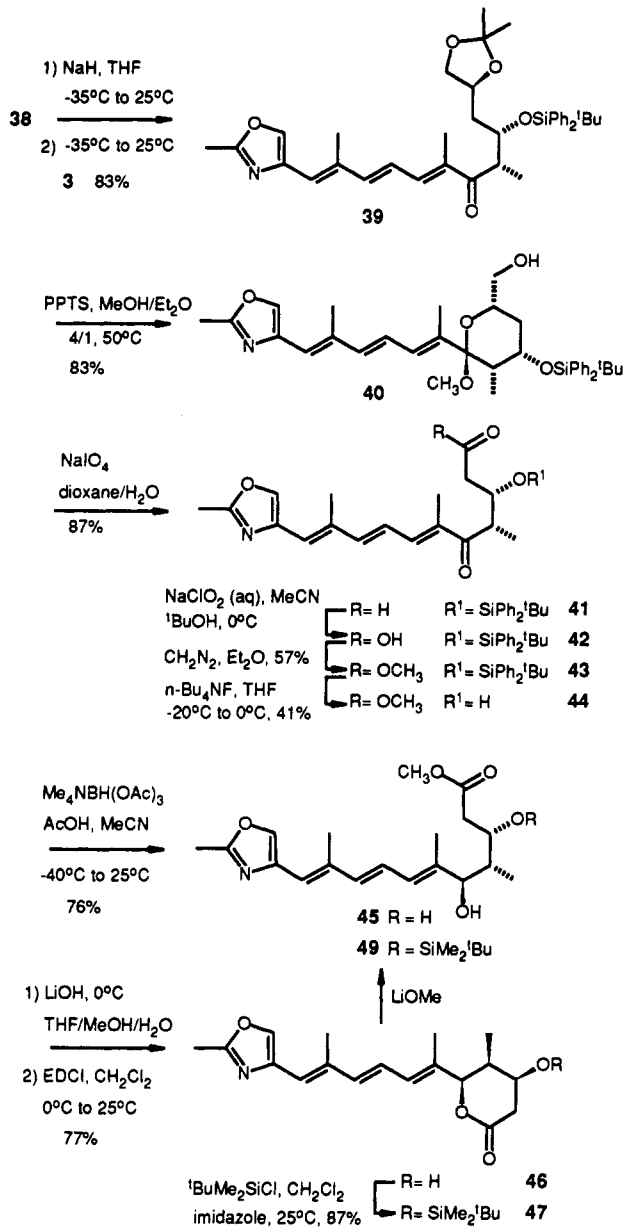
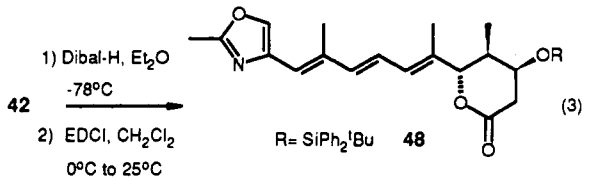
Scheme VII



57% overall yield from **41**. The completion of the preparation of the rhizoxin lower subunit required cleavage of the *tert*-butyldiphenylsilyl ether and subsequent diastereoselective reduction of the C17 ketone followed by effective differentiation of the two secondary alcohols. Treatment of **43** with tetra-*n*-butylammonium fluoride at −20 to 0 °C for a limited reaction time provided a mixture of **44** (41%) and recovered **43** (50%), and efforts to drive the reaction to completion have led to the observation of subsequent retroaldol products. Consequently, the deprotection reaction proved most efficient if recovered **43** is simply resubjected to the reaction conditions and in this manner effective conversions of 70–80% were realized. Hydroxyl-directed reduction of **44** with tetramethylammonium triacetoxyborohydride[18] at −40 to 25 °C provided the anti 1,3-diol **45** (76%) without significant detection of the corresponding diastereomer. Simple differentiation of the two secondary alcohols was conducted through formation of the δ-lactone **46** accomplished most effectively through deliberate methyl ester hydrolysis and subsequent EDCI-promoted lactonization. Protection of the remaining free hydroxyl group of **46** as a *tert*-butyldimethylsilyl ether provided **47** in which the stereochemistry was independently confirmed by 2D ^1H–^1H NOESY NMR. Methanolysis of the lactone provided the corresponding hydroxy ester **49** and a key intermediate for eventual conversion to **2**.

For comparison purposes, the agent **48** possessing the undesired syn 1,3-diol relationship was prepared in two steps from **42** (eq 3). Diastereoselective diisobutylaluminum hydride reduction of **42** at −78 °C which could be anticipated to cleanly provide the syn 1,3-diol derivative followed by EDCI-promoted lactonization of the crude hydroxy acid cleanly provided **48** constituting the C17 diastereomer of **47** and a useful agent for spectroscopic comparison. Thus, the C5-H/C4-H coupling constant of **47** (broad s) and **48** (J = 10.3 Hz) further supported the stereochemical assignments. Attempts to incorporate this latter sequence into the synthesis of the rhizoxin lower subunit thereby avoiding the C15 hydroxyl deprotection/reprotection steps by use of an intramolecular Mitsunobu reaction[16e] on the hydroxy acid derived from diisobutylaluminum hydride reduction of **42** failed to invert the C17 hydroxyl group upon lactonization and simply resulted in carboxylate activation[26] and subsequent lactonization to provide **48**.



Experimental Section[27]

2-Methyloxazole-4-carboxaldehyde (5). A solution of ethyl 2-methyloxazole-4-carboxylate[7] (520 mg, 3.4 mmol) and Et_2O (10 mL) was cooled to −78 °C and treated with diisobutylaluminum hydride (1 M in hexane, 7.1 mL, 7.1 mmol, 2.1 equiv) dropwise over 4 min. The mixture was stirred for 12.5 min at −78 °C and treated with 0.4 mL of CH_3OH. The reaction mixture was allowed to warm to 23 °C and was treated with 20 mL of aqueous 1 M potassium sodium tartrate. The aqueous phase was separated, saturated with NaCl, and further extracted with EtOAc (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), and evaporation of solvent under reduced pressure gave a yellow solid. Flash chromatography (10 × 3.5 cm SiO_2, 33% EtOAc–hexane) afforded **5** as a white solid (209 mg, 373 mg theoretical, 56%, typically 52–65%): mp 71–73 °C (white needles, Et_2O/hexanes, 1:1); ^1H NMR ($CDCl_3$, 300 MHz) 9.92 (s, 1 H), 8.19 (s, 1 H), 2.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 184.2, 163.7, 145.4, 141.2, 13.7; IR (KBr) ν_{max} 3129, 3084, 2854, 1684, 1597 cm^{-1}; EIMS m/e (relative intensity) 111 (M^+, 59), 82 (23), 70 (74), 54 (base); CIMS (isobutane) m/e (relative intensity) 112 ($M + H^+$, base); EIHRMS m/e 111.0315 ($C_5H_5NO_2$ requires 111.0320).

(1′*E*)-2-Methyl-4-(2′-methyl-3′-oxopropenyl)oxazole (6). A solution of **5** (526 mg, 4.7 mmol) and (α-formylethylidene)triphenylphosphorane[6a] (1.66 g, 5.2 mmol, 1.15 equiv) in C_6H_6 (29 mL) was warmed at 80 °C for 22 h. The mixture was allowed to cool to 23 °C and was treated with a solution of saturated

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(27) All high-pressure reactions were performed in a Leco hydraulic pressurized apparatus containing castor oil liquid media using Teflon reaction vessels sealed at both ends with brass screw clamps. Flash chromatography was performed on 230–400-mesh silica gel (SiO_2) or 150-mesh neutral alumina (Al_2O_3). Tetrahydrofuran (THF), diethyl ether (Et_2O), dioxane, benzene (C_6H_6) and toluene ($C_6H_5CH_3$) were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from P_2O_5. Methanol (CH_3OH) was distilled from magnesium turnings. Triethylamine (Et_3N), diisopropylethylamine (*i*-Pr_2NEt), and dimethylformamide (DMF) were distilled from CaH_2. All reactions requiring anhydrous conditions or an inert atmosphere were performed under a positive pressure of Ar or N_2.

aqueous NH_4Cl (25 mL). The aqueous phase was separated and further extracted with EtOAc (3 × 25 mL). The combined organic phase was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography (25 × 3.5 cm SiO_2, 33% EtOAc–hexane) afforded **6** as a white solid (609 mg, 716 mg theoretical, 85%): mp 80–82 °C (white needles, EtOAc/hexanes, 1:3); ^1H NMR ($CDCl_3$, 300 MHz) 9.55 (s, 1 H), 7.83 (s, 1 H), 7.08 (s, 1 H), 2.52 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 194.5, 162.1 140.0, 138.6, 138.0, 137.6, 13.9, 11.2; IR (KBr) ν_{max} 3129, 2839, 1689, 1664, 1634, 1598 cm^{-1}; EIMS *m/e* (relative intensity) 151 (M^+, 54), 123 (16), 122 (12), 109 (22), 82 (12), 81 (base), 53 (54); CIMS (isobutane) *m/e* (relative intensity) 152 (M + H^+, base); EIHRMS *m/e* 151.0632 ($C_8H_9NO_2$ requires 151.0633).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.50; H, 6.10; N, 9.67.

(1′*E*,3′*E*)-4-(4′-(Methoxycarbonyl)-2′-methyl-1′,3′-butadienyl)-2-methyloxazole (8). A solution of NaH (60% in oil, 93.4 mg, 2.3 mmol, 1.9 equiv) in dry toluene (4.3 mL) was treated dropwise with methyl (dimethylphosphono)acetate (421 mg, 2.3 mmol, 1.9 equiv) over 2 min. The mixture was warmed to 40 °C and stirred for 1.5 h. The solution was cooled to 23 °C and treated with a solution of **6** (183 mg, 1.21 mmol) in toluene (2.6 mL), and the mixture was warmed at 110 °C for 24 h. The mixture was allowed to cool to 23 °C and treated with a solution of saturated aqueous NH_4Cl (10 mL). The aqueous phase was separated and further extracted with EtOAc (3 × 25 mL). The combined organic phase was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography (12 × 3.5 cm SiO_2, 33% EtOAc–hexane) afforded **8** as a white solid (225 mg, 252 mg theoretical, 89%): mp 88–89 °C (white powder, EtOAc/hexanes, 1:3); ^1H NMR ($CDCl_3$, 300 MHz) 7.63 (s, 1 H), 7.44 (d, 1 H, *J* = 15.7 Hz), 6.56 (s, 1 H), 6.00 (d, 1 H, *J* = 15.7 Hz), 3.77 (s 3 H), 2.49 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 168.1, 161.8, 149.5, 138.6, 138.4, 135.0, 127.5, 117.6, 51.7, 14.0, 13.8; IR (KBr) ν_{max} 3125, 1686, 1636, 1615 cm^{-1}; EIMS *m/e* (relative intensity) 192 (11), 148 (base); CIMS (isobutane) *m/e* (relative intensity) 208 (M + H^+, base); EIHRMS *m/e* 207.0895 ($C_{11}H_{13}NO_3$ requires 207.0895).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.72; H, 6.29; N, 7.09.

(1′*E*,3′*E*)-4-(5′-Hydroxy-2′-methyl-1′,3′-pentadienyl)-2-methyloxazole (9). A solution of **8** (186 mg, 0.89 mmol) in anhydrous Et_2O (3 mL) cooled to −78 °C was treated dropwise with diisobutylaluminum hydride (1 M in hexanes, 2.7 mL, 2.7 mmol, 3 equiv) over 1 min. The resulting mixture was stirred for 1.5 h at −78 °C before it was treated with CH_3OH (0.5 mL). The mixture was allowed to warm to 23 °C and was treated with 1 M aqueous potassium sodium tartrate (10 mL). The aqueous phase was separated, saturated with NaCl and further extracted with EtOAc (3 × 25 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (8 × 2.5 cm SiO_2, 50% EtOAc–hexane) provided **9** as a yellow oil (144 mg, 161 mg theoretical, 89%). ^1H NMR ($CDCl_3$, 300 MHz) 7.52 (s, 1 H), 6.40 (d, 1 H, *J* = 15.7 Hz), 6.24 (s, 1 H), 5.94 (dt, 1 H, *J* = 15.7, 5.9 Hz), 4.27 (d, 2 H, *J* = 5.9 Hz), 2.46 (s, 3 H), 2.09 (s, 3 H); IR (neat) ν_{max} 3334, 2926, 2860, 1636, 1582, 1540 cm^{-1}; EIMS *m/e* (relative intensity) 179 (M^+, 19), 148 (base); CIMS (isobutane) *m/e* (relative intensity) 180 (M + H^+, base); EIHRMS *m/e* 179.0946 ($C_{10}H_{13}NO_2$ requires 179.0946).

(1′*E*,3′*E*)-2-Methyl-4-(2′-methyl-5′-oxo-1′,3′-pentadienyl)-oxazole (3). A solution of **9** (119 mg, 0.66 mmol) in CH_2Cl_2 (2.6 mL) was cooled to 0 °C and treated with MnO_2 (1.15 g, 10 wt. equiv), and the suspension was stirred vigorously for 20 h while being allowed to gradually warm to 23 °C. The suspension was filtered through a pad of Celite, and removal of the solvent under reduced pressure provided a yellow solid. Flash chromatography (5 × 2 cm SiO_2, 33% EtOAc–hexane) afforded **3** as a white solid (103 mg, 117 mg theoretical, 88%): mp 91–93 °C (white needles, EtOAc/hexanes, 1:3); ^1H NMR ($CDCl_3$, 300 MHz) 9.64 (d, 1 H, *J* = 7.5 Hz, CHO), 7.69 (s, 1 H, C5-H), 7.23 (d, 1 H, *J* = 15.1 Hz, C3′-H), 6.67 (s, 1 H, C1′-H), 6.26 (dd, 1 H, *J* = 15.1, 7.5 Hz, C4′-H), 2.51 (s, 3 H, C2-CH_3), 2.20 (s, 3 H, C2′-CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) 193.8, 161.6, 156.9, 138.7, 138.1, 134.9, 128.9, 128.4, 14.2, 13.9; IR (KBr) ν_{max} 3144, 2860, 1667, 1615, 1606, 1555 cm^{-1}; EIMS *m/e* (relative intensity) 177 (M^+, 18), 148 (base), 107 (21), 79 (60), 77 (68); CIMS (isobutane) *m/e* 178 (M + H^+, base); EIHRMS *m/e* 177.0790 ($C_{10}H_{11}NO_2$ requires 177.0790).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.25; N, 7.90. Found: C, 67.76; H, 6.41; N, 7.52.

(2′*R*,3′*S*,5′*S*,4*R*,5*S*)-3-(3′-Hydroxy-5′,6′-(isopropylidenedioxy)-2′-(methylthio)hexanoyl)-4-methyl-5-phenyl-2-oxazolidinone (33). A solution of (4*R*,5*S*)-4-methyl-3-(2′-(methylthio)acetyl)-5-phenyl-2-oxazolidinone[19] (4.06 g, 15.3 mmol, 1.1 equiv) in CH_2Cl_2 (32 mL) cooled to 0 °C was treated sequentially with freshly prepared *n*-Bu_2BOTf (4.74 g, 17.3 mmol, 1.2 equiv) and *i*-Pr_2NEt (3.3 mL, 245 mg, 24.1 mmol, 1.5 equiv), and the mixture was stirred for 70 min at −7 to 0 °C. The mixture was cooled to −70 °C, and a solution of (*S*)-3,4-dihydroxybutanal acetonide[7b,20] (**32**; 2.00 g, 13.9 mmol) in CH_2Cl_2 (10 mL) was added over 5 min. The mixture was stirred for 14 h while being allowed to gradually warm to 23 °C. An aqueous phosphate buffer solution (pH = 7, 50 mL) was added, and the mixture was stirred for 1.5 h. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (19 × 3.2 cm SiO_2, 20% EtOAc–hexanes) afforded **33** as a yellow oil (5.06 g, 5.70 g theoretical, 89%): $[\alpha]^{21}_D$ = +12.3 (*c* = 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) 7.48–7.29 (m, 5 H), 5.70 (d, 1 H, *J* = 7.5 Hz, C5-H), 4.84 (m, 1 H, C4-H), 4.70 (d, 1 H, *J* = 7.1 Hz, C*H*SCH$_3$), 4.38 (m, 1 H, C5′-H), 4.23 (m, 1 H, C3′-H), 4.14 (dd, 1 H, *J* = 8.2, 6.8 Hz, C6′-*H*H), 3.63 (dd, 1 H, *J* = 8.2, 6.5 Hz, C6′-H*H*), 3.18 (d, 1 H, *J* = 1.6 Hz, OH), 2.17 (s, 3 H, SCH_3), 1.84 (apparent t, 2 H, *J* = 6.2 Hz, C4′-H_2), 1.44 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 0.92 (d, 3 H, *J* = 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) 170.3, 152.8, 133.5, 129.4, 129.2, 126.1, 109.2, 79.1, 73.7, 70.0, 66.5, 54.8, 50.3, 38.6, 27.1, 25.8, 14.3, 13.0; IR (neat) ν_{max} 3482, 2985, 1773, 1701, 1687, 1654 cm^{-1}; EIMS *m/e* (relative intensity) 394 (13), 352 (14), 291 (21), 265 (base), 134 (69), 117 (31), 101 (42), 88 (64), 87 (81), 69 (52), 61 (32); CIMS (isobutane) *m/e* (relative intensity) 410 (M + H^+, 2), 352 (89), 266 (base); EIHRMS *m/e* 409.1555 ($C_{20}H_{27}NO_6S$ requires 409.1559).

Anal. Calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.92; H, 7.03; N, 3.44.

(3′*S*,5′*S*,4*R*,5*S*)-3-(3′-Hydroxy-5′,6′-(isopropylidenedioxy)hexanoyl)-4-methyl-5-phenyl-2-oxazolidinone (34). A solution of **33** (3.66 g, 8.9 mmol) in C_6H_6 (95 mL) was treated with *n*-Bu_3SnH (5 mL, 5.41 g, 18.6 mmol, 2.1 equiv) and AIBN (145 mg, 0.1 equiv), and the solution was warmed to 80 °C for 40 min. The mixture was allowed to cool to 23 °C, and the solvent was evaporated in vacuo. Flash chromatography (10 × 5 cm SiO_2, 27% EtOAc–hexanes) afforded **34** as a white crystalline solid (3.05 g, 3.23 g theoretical, 94%): mp 95–97 °C (white needles, Et_2O/hexane, 1:2); $[\alpha]^{22}_D$ = +42.9 (*c* = 0.37, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 7.45–7.26 (m, 5 H), 5.68 (d, 1 H, *J* = 7.3 Hz), 4.78 (m, 1 H), 4.45 (m, 2 H), 4.11 (dd, 1 H, *J* = 6.1, 8.0 Hz), 3.60 (apparent t, 1 H, *J* = 7.7 Hz), 3.23 (d, 1 H, *J* = 4.2 Hz), 3.16 (m, 2 H), 1.79 (apparent t, 2 H, *J* = 6.2 Hz), 1.55 (s, 3 H), 1.42 (s, 3 H), 0.91 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 172.8, 153.4, 133.5, 129.3, 129.2, 126.0, 109.1, 79.5, 73.5, 69.9, 65.7, 54.9, 43.2, 40.4, 27.1, 25.8, 14.6; IR (KBr) ν_{max} 3511, 2990, 2940, 2882, 1773, 1690 cm^{-1}; EIMS *m/e* (relative intensity) 348 (51), 178 (48), 134 (base), 107 (50), 72 (31), 69 (48); CIMS (isobutane) *m/e* (relative intensity) 364 (M + H^+, 28), 306 (base); EIHRMS *m/e* 363.1686 ($C_{19}H_{25}NO_6$ requires 363.1681).

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.89; H, 7.12; N, 4.13.

Ethyl (3*S*,5*S*)-3-Hydroxy-5,6-(isopropylidenedioxy)hexanoate (35). A solution of **34** (2.26 g, 6.22 mmol) in THF (22 mL) was cooled to 0 °C, treated with an ethanolic solution of LiOEt (1.1 M, 8.4 mL, 9.32 mmol, 1.5 equiv), and stirred for 70 min. The reaction mixture was treated with a solution of saturated aqueous NH_4Cl (20 mL). The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (12 × 3.5 cm SiO_2, 33% EtOAc–hexanes) afforded **35** as a colorless oil (1.03 g, 1.44 g theoretical, 72%): $[\alpha]^{22}_D$ = +14.2 (*c* = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 4.32 (m, 1 H), 4.22 (m, 1 H), 4.17 (q, 2 H, *J* = 7.2 Hz), 4.11 (dd, 1 H, *J* = 8.1, 6.1 Hz), 3.57 (apparent t, 1 H, *J* = 7.7 Hz), 3.23 (d, 1 H, *J* = 4.0 Hz), 2.54 (m, 2 H), 1.73 (apparent t, 2 H, *J* = 6.3 Hz), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 173.2, 109.1, 73.5, 69.8, 65.7, 60.9, 41.7,

40.0, 27.0, 25.8, 14.2; IR (neat) ν_{max} 3448, 2986, 1735, 1701, 1685, 1654, 1647 cm^{-1}; EIMS m/e (relative intensity) 217 (65), 175 (35), 157 (47), 129 (base), 111 (97), 87 (42), 83 (39), 72 (54), 71 (47), 69 (97), 59 (58); CIMS (isobutane) m/e (relative intensity) 233 (M + H$^+$, 20), 174 (base); EIHRMS m/e 232.1318 ($C_{11}H_{20}O_5$ requires 232.1310).

Ethyl (2*S*,3*S*,5*S*)-3-Hydroxy-5,6-(isopropylidenedioxy)-2-methylhexanoate (36). Lithium diisopropylamide (13.1 mmol, 3.65 equiv) in THF (4.7 mL) at −55 °C was treated with a solution of **35** (833 mg, 3.59 mmol) in THF (5.7 mL), and the solution was stirred at −55 °C to −30 °C (2 h), −30 °C to −20 °C (1 h). The mixture was recooled to −78 °C, HMPA (3 mL) was added, and (if necessary) the mixture was warmed to −40 °C to dissolve the HMPA. The mixture was recooled to −78 °C, CH_3I (1.5 mL, 3.42 g, 24 mmol, 6.7 equiv) was added, and the mixture was stirred at −78 °C to −55 °C for 35 h. Glacial HOAc (1.5 mL) was added followed by the addition of a solution of saturated aqueous $NaHCO_3$ (25 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (19 × 2.2 cm SiO_2, 20% EtOAc–hexanes) afforded **36** as a colorless oil (723 mg, 883 mg theoretical, 81%) as a mixture of diastereomers at C2 (>15:1, *S*:*R*) as determined by gas chromatography: GB-20M (carbowax) 50 m × 0.25 mm, 170 °C, flow rate 37.5 mL/min, t_R = 29.1 min (minor), t_R = 29.8 min (major). The structure of the minor product was verified by preparation of an authentic sample and co-injection.[28] For **36**: $[\alpha]^{22}_D$ = +2.9 (c = 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) 4.34 (m, 1 H), 4.17 (q, 2 H, J = 7.2 Hz), 4.11 (dd, 1 H, J = 8.2, 6.1 Hz, C6-*H*H), 3.91 (m, 1 H), 3.58 (dd, 1 H, J = 8.2, 7.2 Hz, C6-H*H*), 3.01 (d, 1 H, J = 6.4 Hz), 2.54 (m, 1 H), 1.82 (ddd, 1 H, J = 2.4, 7.5, 14 Hz, C4-*H*H), 1.64 (m, 1 H, C4-H*H*), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.28 (t, 3 H, J = 7.2 Hz), 1.22 (d, 3 H, J = 7.3 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) 176.3, 109.0, 73.8, 70.8, 69.9, 60.9, 45.7, 38.4, 27.1, 25.8, 14.2; IR (neat) ν_{max} 3448, 2985, 1734, 1718, 1701, 1696, 1685, 1654 cm^{-1}; EIMS m/e (relative intensity) 231 (27), 189 (10), 143 (base), 125 (37), 87 (43), 72 (40), 69 (64), 59 (32); CIMS (isobutane) m/e (relative intensity) 247 (M + H$^+$, 68), 189 (base); CIHRMS m/e 247.1549 ($C_{12}H_{22}O_5$ requires 247.1546).

Ethyl (2*S*,3*S*,5*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5,6-(isopropylidenedioxy)-2-methylhexanoate (37). A solution of imidazole (335 mg, 4.9 mmol, 3 equiv) and DMAP (20 mg, 0.16 mmol, 0.1 equiv) in CH_2Cl_2 (1.7 mL) was treated with *t*-BuPh$_2$SiCl (0.58 mL, 0.55 g, 2.0 mmol, 1.2 equiv). The mixture was stirred for 15 min, and a solution of **36** (402 mg, 1.64 mmol) in CH_2Cl_2 (1.7 mL) was added. The flask was equipped with a reflux condenser, and the mixture was warmed at 40 °C for 40 h. The mixture was allowed to cool to 23 °C and poured into a solution of 2% aqueous HCl (35 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phase was washed with saturated aqueous NaCl (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (15.5 × 2.2 cm SiO_2, hexanes (200 mL) then 15:1 hexanes–EtOAc) afforded **37** as a colorless oil (696 mg, 793 mg theoretical, 87%): $[\alpha]^{22}_D$ = +22.1 (c = 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.61–7.66 (m, 4 H), 7.30–7.38 (m, 6 H), 4.38 (m, 1 H), 3.95 (m, 3 H), 3.75 (dd, 1 H, J = 6.0, 7.8 Hz, C6-*H*H), 3.20 (apparent t, 1 H, J = 7.7 Hz, C6-H*H*), 2.49 (m, 1 H), 1.54 (m, 2 H), 1.19 (s, 3 H), 1.10 (s, 3 H), 1.08–1.02 (m, 6 H), 0.99 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 174.2, 136.4, 135.2, 130.1, 130.0, 128.1, 128.0, 127.9, 108.9, 72.9, 72.0, 69.8, 60.4, 45.4, 37.5, 27.1, 27.0, 26.7, 25.8, 19.6, 10.3; IR (neat) ν_{max} 3072, 2984, 2958, 2933, 2893, 2858, 1735, 1718 cm^{-1}; EIMS m/e (relative intensity) 427 (12), 369 (37), 199 (base), 57 (28); CIMS (isobutane) m/e (relative intensity) 485 (M + H$^+$, 22), 427 (base); CIHRMS (isobutane) m/e 485.2703 ($C_{28}H_{40}O_5Si$ requires 485.2723).

(2*RS*,4*S*,5*S*,7*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2-(diethylphosphono)-7,8-(isopropylidenedioxy)-4-methyloctan-3-one (38). A solution of diethyl ethylphosphonate (745 mg, 4.48 mmol, 2.1 equiv) in THF (5.3 mL) was cooled to −78 °C and treated dropwise (4 min) with *n*-BuLi (2.05 M, 2.1 mL, 4.3 mmol, 2 equiv). The mixture was stirred for 10 min, cooled further to −100 °C, and treated dropwise (5 min) with a solution of **37** (1.03 g, 2.12 mmol) in THF (3.9 mL). The mixture was stirred for 20 min (−105 °C to −95 °C), treated sequentially with CH_3OH (anhydrous 2 mL) and a solution of saturated aqueous NH_4Cl (20 mL), and allowed to warm to 23 °C. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (12 × 3 cm SiO_2, 33% EtOAc–hexanes) provided **38** as a colorless oil (836 mg, 1.28 g theoretical, 65%): ^{1}H NMR ($CDCl_3$, 300 MHz) 7.78–7.49 (m, 4 H), 7.47–7.37 (m, 6 H), 4.25 (ddd, 1 H, J = 1.7, 2.8, 9.5 Hz), 4.17 (m, 1 H), 3.96 (m, 5 H), 3.32 (apparent t, 1 H, J = 7.8 Hz), 3.04 (dq, 1 H, J = 3.2, 7 Hz), 2.53 (dq, 1 H, J = 7, 24.5 Hz), 1.63 (m, 2 H), 1.29–1.11 (m, 15 H), 1.08 (s, 9 H), 1.00 (d, 3 H, J = 7.0 Hz); IR (neat) ν_{max} 3072, 2935, 2859, 1716, 1654, 1559 cm^{-1}; EIMS m/e (relative intensity) 549 (10), 548 (35), 547 (base), 489 (10), 273 (25); CIMS (isobutane) m/e (relative intensity) 605 (M + H$^+$, base); CIHRMS (isobutane) m/e 605.3051 ($C_{32}H_{49}O_7PSi$ requires 605.3063).

(2*S*,4*S*,5*S*,7*E*,9*E*,11*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1,2-(isopropylidenedioxy)-5,7,11-trimethyl-12-(2′-methyloxazol-4′-yl)-7,9,11-dodecatrien-6-one (39). A solution of NaH (41.6 mg, 50% in oil, 0.87 mmol, 1.26 equiv) in THF (1.2 mL) was cooled to −35 °C and treated dropwise with a solution of **38** (544 mg, 0.90 mmol, 1.3 equiv) in THF (1.9 mL). The mixture was stirred at −35 °C to −10 °C (30 min) at −10 °C to 0 °C (1 h), and at 22 °C (30 min). The mixture was recooled to −35 °C, and a solution of **3** (122 mg, 0.69 mmol) in THF (1.9 mL) was added. This was stirred while being allowed to gradually warm to 23 °C over 17 h. Following the addition of a solution of saturated aqueous NH_4Cl (6 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (7 × 3.5 cm SiO_2, 10% EtOAc–hexanes) afforded pure **39** as a yellow oil (302 mg, 432 mg theoretical, 70%) as well as a mixture (56 mg, 6.3:1 *E*:*Z*, 13%): $[\alpha]^{22}_D$ = −16.7 (c = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), 7.73–7.77 (m, 4 H), 7.53 (s, 1 H, C5′-H), 7.34–7.49 (m, 6 H), 6.53 (m, 2 H, C9-H and C8-H), 6.38 (s, 1 H, C12-H), 6.25 (d, 1 H, J = 13.2 Hz, C10-H), 4.46 (m, 1 H, H, C4-H), 4.13 (m, 1 H, C2-H), 3.88 (dd, 1 H, J = 6, 7.5 Hz, C1-*H*H), 3.43 (m, 1 H, C5-H), 3.34 (apparent t, 1 H, J = 7.7 Hz, C1-H*H*), 2.45 (s, 3 H, C2′-CH$_3$), 2.14 (s, 3 H, C11-CH$_3$), 1.78 (s, 3 H, C7-CH$_3$), 1.66 (ddd, 1 H, J = 3.6, 9.3, 14 Hz, C3-*H*H), 1.44 (ddd, 1 H, J = 2.5, 8.9, 14 Hz, C3-H*H*), 1.25 (s, 3 H, CH$_3$), 1.17 (s, 3 H, CH$_3$), 1.07 (s, 9 H, C(CH$_3$)$_3$), 0.95 (d, 3 H, J = 6.9 Hz, C*H*$_3$CH); ^{13}C NMR ($CDCl_3$, 50 MHz) 203.4, 161.7, 144.4, 138.9, 138.6, 137.2, 136.9, 136.5, 135.8, 134.9, 134.0, 130.3, 130.2, 128.1, 128.0, 124.7, 124.2, 108.8, 72.8, 71.6, 69.9, 45.5, 36.6, 27.1, 27.0, 25.8, 19.6, 14.3, 13.9, 12.1, 10.1; IR (neat) ν_{max} 3050, 2933, 2858, 1654, 1599 cm^{-1}; EIMS m/e (relative intensity) 570 (15), 267 (30), 216 (64), 199 (base), 101 (38); CIMS (isobutane) m/e (relative intensity) 628 (M + H$^+$, base); CIHRMS (isobutane) m/e 628.3443 ($C_{38}H_{49}NO_5Si$ requires 628.3458).

Anal. Calcd for $C_{38}H_{49}NO_5Si$: C, 72.69; H, 7.87; N, 2.23. Found: C, 72.46; H, 7.77; N, 2.39.

Methyl (1*R*(1′*E*,3′*E*,5′*E*),2*S*,3*S*,5*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1-(1′,5′-dimethyl-6′-(2-methyloxazol-4-yl)-1′,3′,5′-hexatrienyl)-2-methyl-2,4-dideoxymannopyranoside (40). A solution of **39** (490 mg, 0.78 mmol) in Et_2O (15.6 mL) and CH_3OH (63 mL) was treated with pyridinium *p*-toluenesulfonate (PPTS, 65 mg, 0.25 mmol, 0.33 equiv). The mixture was warmed at 50 °C (8 h), additional PPTS (64 mg, 0.25 mmol) was added, and the mixture was further warmed at 50 °C (6.5 h). The cooled mixture was treated with $NaHCO_3$ (1 g), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (10 × 3 cm SiO_2, 20% EtOAc–hexanes) afforded **40** as a yellow oil (390 mg, 469 mg theoretical, 83%): $[\alpha]^{21}_D$ = +34.4 (c = 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.67 (m, 4 H), 7.53 (s, 1 H,

(28) Ethyl (2*R*,3*S*,5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)-2-methylhexanoate was prepared by aldol reaction of the enolate generated from reaction of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone with Bu_2BOTf and *i*-Pr$_2$NEt, with (*S*)-3,4-dihydroxybutanal acetonide in CH_2Cl_2. Ethanolysis of the resulting product using LiOEt in THF at 0 °C provided a 12:1 (2*R*:2*S*) ratio by GC: ^{1}H NMR ($CDCl_3$, 300 MHz) 4.33 (m, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.10 (m, 2 H), 3.58 (apparent t, 1 H, J = 7.6 Hz), 2.93 (d, 1 H, J = 3.8 Hz), 2.55 (m, 1 H), 1.71–1.62 (m, 2 H), 1.40 (s, 3H), 1.36 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.20 (d, 3 H, J = 7.2 Hz); IR (neat) ν_{max} 3482, 2986, 2937, 1734, 1718, 1701, 1685, 1653 cm^{-1}; EIMS m/e (relative intensity) 231 (63), 143 (base); CIMS (isobutane) m/e (relative intensity) 247 (M + H$^+$, 22), 189 (base); EIHRMS m/e 246.1449 ($C_{12}H_{22}O_5$ requires 246.1467).

C5-H), 7.40 (m, 6 H), 6.53 (dd, 1 H, J = 10.9, 15 Hz, C3'-H), 6.43 (d, 1 H, J = 15 Hz, C4'-H), 6.36 (d, 1 H, J = 10.9 Hz, C2'-H), 6.27 (s, 1 H, C6'-H), 4.47 (dt, 1 H, J = 5, 6.6 Hz, C3-H), 3.54 (m, 3 H, C6-H_2 and C5-H), 2.84 (s, 3 H, OCH_3), 2.46 (s, 3 H, oxazole-CH_3), 2.13 (s, 3 H, C5'-CH_3), 1.99 (m, 1 H, C2-H), 1.63 (s, 3 H, C1'-CH_3), 1.56 (m, 1 H, C4-*H*H), 1.29 (m, 1 H, C4-H*H*), 1.06 (s, 9 H, C(CH_3)$_3$), 0.79 (d, 3 H, J = 7 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 50 MHz) 161.5, 139.3, 138.6, 137.5, 136.4, 136.3, 135.1, 134.8, 130.1, 128.5, 128.1, 124.9, 121.0, 104.5, 70.1, 68.2, 66.2, 48.7, 40.0, 30.5, 27.2, 19.4, 14.6, 14.0, 12.5, 8.4; IR (neat) ν_{max} 3050, 2928, 2856, 1734, 1718, 1700, 1684, 1654, 1636 cm^{-1}; CIMS (isobutane) m/e (relative intensity) 602 (M^+ + H, 19), 601 (M^+, 43), 345 (base).

Anal. Calcd for $C_{36}H_{47}NO_5Si$: C, 71.84; H, 7.87; N, 2.23. Found: C, 71.77; H, 8.17; N, 2.30.

(3*S*,4*S*,6*E*,8*E*,10*E*)-3-((*tert*-Butyldiphenylsilyl)oxy)-4,6,10-trimethyl-11-(2'-methyloxazol-4'-yl)-1-oxo-6,8,10-undecatrien-5-one (41). A solution of **40** (376 mg, 0.63 mmol) in dioxane (4 mL) and H_2O (3.3 mL) was treated with $NaIO_4$ (948 mg, 4.43 mmol, 7 equiv) in one portion and was stirred at 25 °C (10.5 h). The mixture was diluted with Et_2O (10 mL) and washed with H_2O (1 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (4 × 1.2 cm SiO_2, 10% EtOAc–hexanes) provided **41** as a yellow oil (304 mg, 347 mg theoretical, 87%): $[\alpha]^{22}_D$ = −21.6 (c = 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) 9.48 (dd, 1 H, J = 1.8, 2.8 Hz), 7.70–7.65 4 H), 7.63 (s, 1 H), 7.47–7.27 (m, 6 H), 6.75 (d, 1 H, J = 10.8 Hz), 6.52 (dd, 1 H, J = 10.8, 14.5 Hz), 6.38 (d, 1 H, J = 14.5 Hz), 6.35 (s, 1 H), 4.52 (m, 1 H,), 3.58 (m, 1 H), 2.45 (m, 2 H), 2.43 (s, 3 H), 2.10 (s, 3 H), 1.75 (s, 3 H), 1.00 (d, 3 H), 0.95 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 204.2, 202.8, 162.4, 145.8, 140.1, 139.6, 138.0, 137.6, 137.1, 136.9, 136.4, 134.7, 131.1, 131.0, 128.8, 125.3, 125.2, 71.0, 48.0, 45.3, 27.6, 20.0, 15.0, 14.6, 12.8, 12.7; IR (neat) ν_{max} 3050, 2931, 2857, 1719, 1654, 1597 cm^{-1}; EIMS m/e (relative intensity) 498 (18), 454 (16), 253 (69), 244 (27), 216 (base); CIMS (isobutane) m/e (relative intensity) 556 (M + H^+, base); CIHRMS (isobutane) m/e 556.2861 ($C_{34}H_{41}NO_4Si$ requires 556.2883).

Methyl (3*S*,4*S*,6*E*,8*E*,10*E*)-3-((*tert*-Butyldiphenylsilyl)oxy)-4,6,10-trimethyl-11-(2'-methyloxazol-4'-yl)-5-oxo-6,8,10-undecatrienoate (43). A solution of **41** (248 mg, 0.44 mmol) in CH_3CN (4.7 mL) and t-BuOH (4.7 mL) was cooled to 0 °C and treated with 2-methyl-2-butene (1.6 mL). A solution of $NaOCl_2$ (360 mg, 9 equiv) and NaH_2PO_4 (488 mg, 8 equiv) in H_2O (3 mL) was added dropwise (2 min), and the resulting mixture was vigorously stirred for 15 min at 0 °C. The aqueous phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with 1 M aqueous $NaHSO_3$ (2 × 10 mL) and saturated aqueous NaCl (1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. For **42**: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.60–7.64 (m, 4 H), 7.56 (s, 1 H), 7.40–7.20 (m, 6 H), 6.69 (d, 1 H, J = 10.7 Hz), 6.49 (dd, 1 H, J = 10.7, 14.7 Hz), 6.35 (s, 1 H), 6.34 (d, 1 H, J = 14.7 Hz), 4.47 (m, 1 H), 3.54 (m, 1 H), 2.46 (m, 2 H), 2.43 (s, 3 H), 2.09 (s, 3 H), 1.72 (s, 3 H), 0.99 (d, 3 H, J = 7 Hz), 0.96 (s, 9 H); IR (neat) ν_{max} 3300 (b), 3050, 2932, 2858, 1718, 1654, 1598 cm^{-1}; EIMS m/e (relative intensity) 200 (16), 199 (base); CIMS isobutane) m/e (relative intensity) 572 (M + H^+, base); EIHRMS (isobutane) m/e 571.2772 ($C_{34}H_{41}NO_5Si$ requires 571.2754).

The crude acid was treated with excess CH_2N_2 in Et_2O at 0 °C, and the mixture was allowed to stand overnight before the solvent was removed in vacuo. Flash chromatography (6 × 4 cm SiO_2, 10% EtOAc–hexanes) provided **43** as a yellow oil (147.6 mg, 260 mg theoretical, 57%): $[\alpha]^{20}_D$ = −44.9 (c = 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.69 (m, 4 H, aromatic), 7.63 (s, 1 H, C5'-H), 7.39 (m, 6 H, aromatic), 6.75 (d, 1 H, J = 10.6 Hz, C7-H), 6.55 (dd, 1 H, J = 10.6, 14.9 Hz, C8-H), 6.41 (s, 1 H, C11-H), 6.40 (d, 1 H, J = 14.9 Hz, C9-H), 4.56 (apparent q, 1 H, J = 5.3 Hz, C3-H), 3.64 (m, 1 H, C4-H), 3.47 (s, 3 H, OCH_3), 2.50 (s, 3 H, C2'-CH_3), 2.48 (m, 2 H, C2-H_2), 2.16 (s, 3 H, C10-CH_3), 1.80 (s, 3 H, C6-CH_3), 1.06 (d, 3 H, J = 6.8 Hz, CH_3CH), 1.02 (s, 9 H, (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 50 MHz) 203.5, 172.4, 161.7, 144.9, 139.2, 138.9, 137.3, 136.9, 136.5, 136.4, 135.9, 134.3, 134.0, 130.2, 130.1, 128.0, 127.9, 124.8, 124.4, 71.5, 51.5, 44.5, 38.3, 26.9, 19.4, 14.4, 13.9, 12.0, 11.6; IR (neat) ν_{max} 2932, 2858, 1735, 1718, 1701, 1696, 1685, 1676, 1654, 1647, 1636, 1598 cm^{-1}; EIMS m/e (relative intensity) 585 (M^+, 7), 529 (28), 528 (base), 199 (97); CIMS (isobutane) m/e (relative intensity) 586 (M + H^+, base); EIHRMS m/e (relative intensity) 585.2898 ($C_{35}H_{43}NO_5Si$ requires 585.2911).

Anal. Calcd for $C_{35}H_{43}NO_5Si$: C, 71.76; H, 7.40; N, 2.39. Found: C, 71.75; H, 7.74; N, 2.49.

Methyl (3*S*,4*S*,6*E*,8*E*,10*E*)-3-Hydroxy-4,6,10-trimethyl-11-(2'-methyloxazol-4'-yl)-5-oxo-6,8,10-undecatrienoate (44). A solution of **43** (195 mg, 0.33 mmol) in THF (2.7 mL) was cooled to −20 °C and treated dropwise with n-Bu_4NF (1.2 mL, 3.5 equiv, 1 M). The mixture was stirred at −20 °C to 0 °C (5 h) and at 0 °C (14 h). The mixture was treated with a solution of saturated aqueous NH_4Cl (4 mL), and the two phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phase was washed with saturated aqueous NaCl (1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (8.5 × 2 cm SiO_2, gradient elution, 20–33% EtOAc–hexanes) afforded **43** (97.7 mg recovered starting material, 50%) and **44** (47.9 mg, 115.8 mg theoretical, 41%). For **44**: $[\alpha]^{20}_D$ = −41.8 (c = 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.62 (s, 1 H), 7.24 (d, 1 H, J = 10.2 Hz), 6.69 (d, 1 H, J = 15.1 Hz), 6.68 (dd, 1 H, J = 10.2, 15.1 Hz), 6.44 (s, 1 H), 4.24 (m, 1 H), 3.71 (s, 3 H), 3.55 (d, 1 H, J = 4.4 Hz), 3.52 (m, 1 H), 2.56–2.45 (m, 2 H), 2.48 (s, 3 H), 2.20 (s, 3 H), 1.97 (s, 3 H), 1.19 (d, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 206.2, 173.1, 161.8, 145.8, 140.4, 138.9, 137.5, 136.8, 135.7, 124.9, 124.6, 71.0, 52.0, 43.1, 39.5, 15.5, 14.3, 13.9, 11.9; IR (neat) ν_{max} 3448, 2927, 1735, 1701, 1685, 1654, 1647, 1598 cm^{-1}; EIMS m/e (relative intensity) 347 (M^+, 6), 244 (32), 200 (17), 199 (base), 142 (32); CIMS (isobutane) m/e (relative intensity) 348 (M + H^+, base); EIHRMS m/e 347.1737 ($C_{19}H_{25}NO_5$ requires 347.1733).

Methyl (3*S*,4*S*,5*R*,6*E*,8*E*,10*E*)-3,5-Dihydroxy-4,6,10-trimethyl-11-(2'-methyloxazol-4'-yl)-6,8,10-undecatrienoate (45). A solution of $Me_4NBH(OAc)_3$ (616 mg, 2.3 mmol, 8 equiv) in CH_3CN (4.1 mL) was treated with anhydrous glacial HOAc (0.27 mL, 16 equiv), and the mixture was stirred at 23 °C for 1 h. The mixture was cooled to −40 °C and treated dropwise (2 min) with a solution of **44** (100 mg, 0.288 mmol) in CH_3CN (4.1 mL). The mixture was stirred for 19 h while being allowed to gradually warm to 23 °C and subsequently was treated with a solution of saturated aqueous NH_4Cl (6 mL). A 1 M aqueous solution of potassium sodium tartrate (12 mL) was added, and the two phases were separated. The aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (5.5 × 1.2 cm SiO_2, 33% EtOAc–hexanes) afforded **45** as a yellow oil (76.2 mg, 100.5 mg theoretical, 76%): $[\alpha]^{20}_D$ = −10.2 (c = 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.51 (s, 1 H, C5'-H), 6.56 (dd, 1 H, J = 15.0, 10.9 Hz, C8-H), 6.39 (d, 1 H, J = 15.0 Hz, C9-H), 6.29 (d, 1 H, J = 10.9 Hz, C7-H), 6.23 (s, 1 H, C11-H), 4.47 (broad s, 1 H, C5-H), 4.11 (apparent q, 1 H, J = 5.7 Hz, C3-H), 3.72 (s, 3 H, OCH_3), 3.70 (broad s, 1 H, OH), 3.06 (broad s, 1 H, OH), 2.60 (m, 2 H, C2-H_2), 2.45 (s, 3 H, C2'-CH_3), 2.10 (s, 3 H, C10-CH_3), 1.78 (m, 1 H, C4-H), 1.75 (s, 3 H, C6-CH_3), 0.87 (d, 3 H, J = 7.1 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 50 MHz) 174.0, 161.4, 139.3, 139.1, 137.6, 137.1, 136.1, 125.0, 124.9, 120.3, 75.0, 71.6, 52.1, 40.1, 39.5, 14.7, 14.5, 13.9, 10.2; IR (neat) ν_{max} 3568, 3448, 2927, 1740, 1735, 1730, 1718, 1701, 1654, 1437 cm^{-1}; EIMS m/e (relative intensity) 349 (M^+, 18), 190 (47) 148 (base); CIMS (isobutane) m/e (relative intensity) 350 (M + H^+, 59), 332 (base); CIHRMS (isobutane) m/e 350.1960 ($C_{19}H_{27}NO_5$ requires 350.1967).

(3*S*,4*S*,5*R*,6*E*,8*E*,10*E*)-3,5-Dihydroxy-4,6,10-trimethyl-11-(2'-methyloxazol-4'-yl)-6,8,10-undecatrienoic Acid 1,5-Lactone (46). A solution of **45** (80.0 mg, 0.229 mmol) in THF (4 mL) and CH_3OH (1.4 mL) was cooled to 0 °C and treated dropwise (1 min) with an aqueous solution of LiOH (1.4 mL, 12 mg/mL). The mixture was stirred at 0 °C for 20 min, treated sequentially with H_2O (3.9 mL) and glacial HOAc (1 mL), and poured into 30% 2-propanol–$CHCl_3$ (12 mL). The aqueous phase was separated and extracted with 30% 2-propanol–$CHCl_3$ (3 × 5 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Dry toluene was added (15 mL) and evaporated in vacuo to azeotropically remove trace amounts of HOAc. A solution of the crude carboxylic acid in CH_2Cl_2 (8 mL) at 0 °C was treated with EDCI (60 mg, 0.31 mmol, 1.4 equiv), and the mixture was stirred while being allowed to gradually warm to 23 °C over 15 h. The mixture was washed with half-saturated aqueous NaCl (2 × 4 mL), and the organic phase was dried

($MgSO_4$) and concentrated in vacuo. Flash chromatography (4.5 × 1.2 cm SiO_2, 50% EtOAc–hexanes) afforded **46** as a yellow oil (56.2 mg, 72.6 mg theoretical, 77%): $[\alpha]^{22}_D$ = −14.9 (*c* = 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 7.53 (s, 1 H), 6.54 (dd, 1 H, *J* = 10.7, 14.9 Hz), 6.41 (d, 1 H, *J* = 14.9 Hz), 6.34 (d, 1 H, *J* = 10.7 Hz), 6.25 (s, 1 H,), 4.69 (broad s, 1 H), 4.34 (m, 1 H), 2.91 (dd, 1 H, *J* = 6.9, 18.4 Hz), 2.53 (dd, 1 H, *J* = 10.6, 18.4 Hz), 2.45 (s, 3 H), 2.39 (m, 1 H), 2.13 (s, 3 H), 1.80 (s, 3 H), 0.83 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 170.4, 161.4, 139.1, 138.7, 137.3, 136.4, 131.8, 126.2, 124.1, 121.0, 82.6, 67.3, 36.3, 35.4, 14.4, 14.3, 13.9, 4.2; IR (neat) ν_{max} 3568, 3448, 2927, 1773, 1735, 1719, 1701, 1696, 1685, 1676, 1670, 1654, 1647, 1636, 1617 cm^{-1}; EIMS *m/e* (relative intensity) 317 (M^+, 5), 148 (36), 97 (37), 83 (62), 71 (54), 69 (65), 55 (base); CIMS (isobutane) *m/e* (relative intensity) 318 (M + H^+, 72), 178 (base); CIHRMS (isobutane) *m/e* 318.1699 ($C_{18}H_{23}NO_4$ requires 318.1705).

(3*S*,4*S*,5*R*,6*E*,8*E*,10*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-4,6,10-trimethyl-11-(2′-methyloxazol-4′-yl)-6,8,10-undecatrienoic Acid 1,5-Lactone (47). A solution of *t*-$BuMe_2SiCl$ (84 mg, 0.55 mmol, 3.5 equiv), imidazole (53.6 mg, 0.78 mmol, 5 equiv), and DMAP (22 mg, 0.18 mmol, 1.1 equiv) in CH_2Cl_2 (0.4 mL) was treated with a solution of **46** (50 mg, 0.157 mmol) in CH_2Cl_2 (1 mL), and the mixture was warmed at 40 °C for 36 h. The mixture was allowed to cool to 23 °C, diluted with CH_2Cl_2 (5 mL), and washed with 2% aqueous HCl (5 mL) and saturated aqueous NaCl (5 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5 × 1.2 cm SiO_2, 20% EtOAc–hexanes) afforded **47** as a yellow solid (57.5 mg, 67.9 mg theoretical, 85%): mp 154–155 °C (yellow needles, Et_2O/hexanes, 1:5); $[\alpha]^{22}_D$ = −20.8 (*c* = 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 7.53 (s, 1 H, C5′-H), 6.55 (dd, 1 H, *J* = 10.7, 15.0 Hz, C8-H), 6.43 (d, 1 H, *J* = 15.0 Hz, C9-H), 6.35 (d, 1 H, *J* = 10.7, C7-H), 6.26 (s, 1 H, C11-H), 4.68 (broad s, 1 H, C5-H), 4.21 (ddd, 1 H, *J* = 4.5, 6.8, 10.2 Hz, C3-H), 2.79 (dd, 1 H, *J* = 6.6, 18.4 Hz, C2-H_{eq}), 2.52 (dd, 1 H, *J* = 10.3, 18.4 Hz, C2-H_{ax}), 2.46 (s, 3 H, C2′-CH_3), 2.22 (m, 1 H, C4-H), 2.16 (s, 3 H, C10-CH_3), 1.81 (s, 3 H, C6-CH_3), 0.90 (s, 9 H, $(CH_3)_3C$), 0.81 (d, 3 H, *J* = 7.1 Hz, CH_3CH), 0.09 (s, 6 H, $(CH_3)_2Si$); 2D ^1H–^1H NOESY NMR (diagnostic NOE crosspeaks) C4-CH_3/C2-H_{ax}, C3-H/C5-H, C4-CH_3/C6-CH_3, C4-H/C3-$OSiMe_2$, C6-CH_3/C8-H, C10-CH_3/C8-H, C9-H/C11-H, C7-H/C9-H, C5′-H/C10-CH_3; ^{13}C NMR ($CDCl_3$, 125 MHz) 171.1, 160.8, 138.7, 138.2, 136.7, 136.0, 131.6, 125.7, 123.7, 120.6, 82.3, 67.7, 36.9, 36.2, 25.7, 18.0, 14.3, 13.9, 4.4, −4.6, −4.8; IR (KBr) ν_{max} 2927, 1719, 1685, 1654, 1648, 1637 cm^{-1}; EIMS *m/e* (relative intensity) 431 (14), 188 (34), 174 (28), 148 (80), 101 (base), 75 (99), 73 (98), 59 (60); CIMS (isobutane) *m/e* (relative intensity) 432 (M + H^+, base); EIHRMS *m/e* 431.2497 ($C_{24}H_{37}NO_4Si$ requires 431.2492).

Anal. Calcd for $C_{24}H_{37}NO_4Si$: C, 66.78; H, 8.64; N, 3.24. Found: C, 66.61; H, 8.91; N, 3.24.

(3*S*,4*S*,5*S*,6*E*,8*E*,10*E*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-hydroxy-4,6,10-trimethyl-11-(2′-methyloxazol-4′-yl)-6,8,10-undecatrienoic Acid 1,5-Lactone (48). A solution of **42** (18.6 mg, 32.5 μmol) in Et_2O (0.34 mL) was cooled to −78 °C and treated with diisobutylaluminum hydride (1 M in hexane, 0.13 mL, 4 equiv) and stirred for 6 h. CH_3OH (0.5 mL) was added followed by 1 M aqueous potassium sodium tartrate (1 mL), and the mixture was allowed to warm to 23 °C. The aqueous phase was separated, saturated with NaCl, and extracted with EtOAc (3 × 3 mL). The combined organic phase was washed with 1 M aqueous potassium sodium tartrate (1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude alcohol (10.8 mg, 18.6 mg theoretical, 58%) which was one detectable diastereomer (>25:1 at C-5 by ^1H NMR) was taken into the subsequent cyclization reaction without further purification. A solution of the crude alcohol (6.7 mg, 11.7 μmol) in CH_2Cl_2 (2.3 mL) was treated with EDCI (3.7 mg, 12.9 μmol, 1.1 equiv), and the mixture was stirred at 23 °C for 20 h. The mixture was diluted with CH_2Cl_2 (5 mL), washed with aqueous phosphate buffer (pH = 7, 1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (3 × 0.8 cm SiO_2, 20% EtOAc–hexanes) provided **48** as a yellow oil (3.3 mg, 6.5 mg theoretical, 51%): $[\alpha]^{20}_D$ = +30.0 (*c* = 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 7.65 (m, 4 H), 7.55 (s, 1 H), 7.44 (m, 6 H), 6.50 (dd, 1 H, *J* = 9.6, 15 Hz), 6.44 (d, 1 H, *J* = 15 Hz), 6.29 (s, 1 H), 6.19 (d, 1 H, *J* = 9.6 Hz,), 4.95 (d, 1 H, *J* = 10.3 Hz), 4.06 (m, 1 H), 2.58 (dd, 1 H, *J* = 2.8, 18 Hz), 2.47 (s, 3 H), 2.39 (dd, 1 H, *J* = 3.8, 18 Hz), 2.14 (s, 3 H), 1.86 (ddq, 1 H, *J* = 1.6, 6.8, 10.3 Hz), 1.76 (s, 3 H), 1.10 (s, 9 H), 0.86 (d, 3 H, *J* = 6.8 Hz); IR (neat) ν_{max} 2928, 1736, 1700, 1686, 1656, 1639, 1578 cm^{-1}; EIMS *m/e* (relative intensity) 556 (M + H^+, 17), 555 (M^+, 56), 225 (base), 199 (85), 183 (98), 145 (58), 135 (48); CIMS (isobutane) *m/e* (relative intensity) 556 (M + H^+, base); EIHRMS *m/e* 555.2816 ($C_{34}H_{41}NO_4Si$ requires 555.2835).

Methyl (3*S*,4*S*,5*R*,6*E*,8*E*,10*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-4,6,10-trimethyl-11-(2′-methyloxazol-4′-yl)-6,8,10-undecatrienoate (49). A solution of **47** (65 mg, 0.15 mmol) in THF (0.25 mL) and CH_3OH (2.35 mL) was treated with Li_2CO_3 (115 mg, 1.55 mmol, 10 equiv), and the mixture was stirred at 23 °C for 14 h. The mixture was diluted with Et_2O (10 mL), filtered through Celite, and concentrated in vacuo. Flash chromatography (6 × 1.2 cm SiO_2, 36% EtOAc–hexanes) provided **49** as a yellow oil (38.2 mg, 69.4 mg theoretical, 55%) and recovered starting material (13.5 mg, 21%). For **49**: $[\alpha]^{22}_D$ = +17.5 (*c* = 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) 7.51 (s, 1 H, C5′-H), 6.56 (dd, 1 H, *J* = 11, 15 Hz, C8-H), 6.40 (d, 1 H, *J* = 15 Hz, C9-H), 6.31 (d, 1 H, *J* = 11 Hz, C7-H), 6.22 (s, 1 H, C11-H), 4.44 (broad s, 1 H, C5-H), 4.27 (dt, 1 H, *J* = 2.7, 6.7 Hz, C3-H), 3.69 (s, 3 H, OCH_3), 3.31 (broad s, 1 H, OH), 2.73 (dd, 1 H, *J* = 7.1, 15.1 Hz, C2-H*H*), 2.66 (dd, 1 H, *J* = 6.3, 15.1 Hz, C2-*H*H), 2.45 (s, 3 H, C2′-CH_3), 2.13 (s, 3 H, C10-CH_3), 1.81 (m, 1 H, C4-H), 1.72 (s, 3 H, C6-CH_3), 0.90 (broad s, 12 H, CH_3CH and $(CH_3)_3C$), 0.13 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$, 50 MHz) 172.2, 161.3, 139.2, 138.5, 137.6, 137.0, 136.1, 125.0, 120.2, 74.8, 74.4, 51.8, 40.4, 39.2, 25.8, 18.0, 14.5, 13.9, 10.4, −4.8, −4.9; IR (neat) ν_{max} 3448, 2928, 2857, 1735, 1718, 1701, 1696, 1685, 1654, 1647, 1636, 1577 cm^{-1}; EIMS *m/e* (relative intensity) 463 (M^+, 12), 190 (28), 162 (30), 148 (base), 75 (65), 73 (73); CIMS (isobutane) *m/e* (relative intensity) 464 (M + H^+, 26), 432 (base); EIHRMS *m/e* 463.2745 ($C_{25}H_{41}NO_5Si$ requires 463.2754).

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Supplementary Material Available: Full experimental details for the preparation of **12–30** and ^1H NMR spectra for compounds **3**, **5–9**, **12–18**, **19a–b**, **20a**, **21a–b**, **23a–b**, **24–30**, and **33–49** including ^1H–^1H NOESY NMR spectra for **30**, **40**, and **47** (65 pages). Ordering information is given on any current masthead page.