Syntheses of the Lower Portions of the Pamamycins from γ-(Silyloxy)allenes Using Stereoselective Cyclization, Reduction, and Aldehyde Addition Methodologies†

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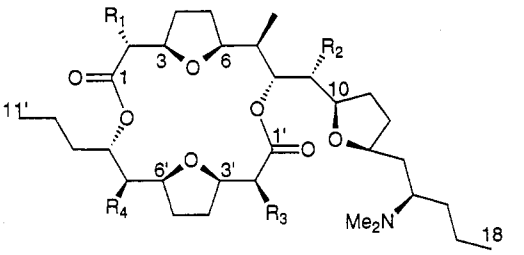
The pamamycins are a group of homologous macrodiolides produced by *Streptomyces alboniger* and *Streptomyces aurantiacus* JA 4570 which are remarkable for their autoregulatory, antifungal, antibacterial, and anion-transfering activities. The syntheses of the C_1–$C_{11'}$ ("lower") portions of pamamycin-607, pamamycin-649A, pamamycin-635A, pamamycin-649B, and pamamycin-635B as the methyl esters **8** and **10–12** are reported. The C_9–$C_{11'}$ portions of these esters were introduced by chelation-controlled allylations of $C_{8'}$ aldehyde intermediates derived from the $C_{8'}$ alcohols **9** (whose synthesis has been previously reported) and **13–15** using allyltrimethylsilane in the presence of titanium(IV) chloride. The alcohols **13–15** were synthesized via *cis* selective cyclizations of the trimethylsilyl ether derivatives of the nonracemic γ-hydroxy allenes **24**, **30**, and **31** using a one-pot oxymercuration/transpalladation/methoxycarbonylation reaction followed by a chelation-controlled conjugate reduction of the resulting acrylate intermediates. The γ-hydroxy allene **24** was synthesized via an enzymatic resolution of the γ-acetoxy allene **20**, and the γ-hydroxy allenes **30** and **31** were synthesized by asymmetric aldol reactions. During the syntheses of the products **14** and **15**, chemoselective hydrolyses and reduction reactions were employed in order to differentiate a $C_{8'}$ carboxyl group from the $C_{1'}$ carboxyl group. Starting from simple allenyl alcohol starting materials, overall yields from 2% (in 14 steps, for **10**) to 14% (in 9 steps, for **12**) were observed for the production of the C_1–$C_{11'}$ portions of the pamamycins.

The pamamycins are a class of homologous macrodiolides which were first isolated from *Streptomyces alboniger* by McCann and Pogell in 1979.[1] In 1987, Kondo *et al.* reported the elucidation of the structure of the pamamycin homolog having a molecular weight of 607, pamamycin-607 (**1**),[2] and in 1989 Natsume *et al.* reported a correlation study which established the absolute configuration of pamamycin-607 to be that indicated in structure **1**.[3] The mixture of pamamycins obtained from *S. alboniger* consists of at least eight difficult-to-separate homologs ranging in molecular weight from 593 to 691 (C_{34}–C_{41}, respectively).[4] The MW 621 and MW 635 homologs each exist as mixtures of three or more isomers. In 1991, Natsume *et al.* reported the structures of four new pamamycins, pamamycin-635A (**2**), -635B (**3**), -649A (**4**), and -649B (**5**).[5] Recent research by Grafe and coworkers has indicated that *Streptomyces aurantiacus* JA 4570 also produces pamamycins.[6]

The pamamycins are structurally unique natural products which are remarkable for possessing autoregulatory activity, antibiotic activity, and anionophoric activity. The autoregulatory activity of the pamamycins refers to their ability to affect aerial mycelium formation in *S. alboniger* in a structure-dependent manner. Pamamycin-607 (**1**),



	R_1	R_2	R_3	R_4	
1:	CH_3	CH_3	CH_3	H	(Pamamycin-607)
2:	CH_3	CH_2CH_3	CH_3	CH_3	(Pamamycin-635A)
3:	CH_3	CH_3	CH_2CH_3	CH_3	(Pamamycin-635B)
4:	CH_2CH_3	CH_2CH_3	CH_2CH_3	H	(Pamamycin-649A)
5:	CH_2CH_3	CH_2CH_3	CH_3	CH_3	(Pamamycin-649B)

when impregnated into an 8-mm paper disk, induces aerial mycelium formation in a growing agar culture of an aerial mycelium-negative *S. alboniger* mutant at a concentration of 0.1 μg per disk.[1,2,4] A pamamycin-621 homolog (structure not designated) exhibited activity similar to that of pamamycin-607.[4] Pamamycin-635B (**3**) was found to exhibit approximately one-third the mycelium-inducing activity of the lower homologs, while pamamycin-635A (**2**), -649A (**4**), and -649B (**5**) were observed to have no mycelium-inducing activity.[5] All of the pamamycins inhibited the growth of the aerial mycelium-negative *S. alboniger* when used at high concentrations (>30 μg per disk; >10 μg per disk for pamamycin-607).[4,5] The autoregulatory activity of the pamamycins compares with that of the structurally unrelated butanolide autoregulators of morphogenesis found in some other *Streptomyces* species, for example, A-factor from *Streptomyces griseus*, I-factor from *Streptomyces viridochromogenes*, and the virginiae butanolides from *Streptomyces virginiae*.[7] The discovery of binding proteins for A-factor and for the virginiae butanolides in their respective producing organisms and the identification of an A-factor-dependent promotor

† This paper is affectionately dedicated to Harry Ernst Walkup, M.D., and Mary Roe Groves Walkup, R.N., on the respective occasions of their 75th and 70th birthdays.

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(1) McCann, P. A.; Pogell, B. M. *J. Antibiot.* **1979**, *32*, 673–678.
(2) Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, H. *Tetrahedron Lett.* **1987**, *28*, 5861–5864.
(3) Natsume, M.; Kondo, S.; Marumo, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1911–1913.
(4) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot.* **1988**, *41*, 1196–1204.
(5) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett.* **1991**, *32*, 3087–3090.
(6) Stengel, C.; Reinhardt, G.; Grafe, U. *J. Basic Microbiol.* **1992**, *32*, 339–345.

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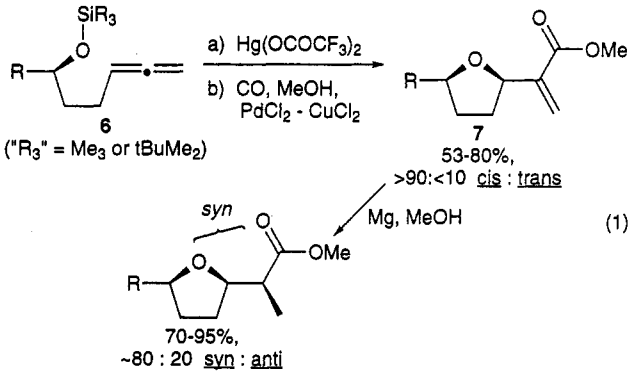
suggest that the butanolide autoregulators are bona fide prokaryotic hormones involved in the morphogenesis of the *Streptomyces* producing organisms.[7] The pamamycins in *S. alboniger* may have a similar hormonal function, but this remains to be proven.

In addition to their autoregulatory activity, the pamamycins are antibiotics. The mixture of pamamycin homologs isolated by McCann and Pogell was found to inhibit the growth of Gram-positive bacteria, the fungi *Neurospora crassa* and two species of *Mycobacteria*, but not Gram-negative bacteria.[1] Pamamycin-607 (1) was found to inhibit the growth of a variety of bacteria and fungi at minimum inhibitory concentrations (MIC) on the order of 3–41 μM; the greatest activity observed was against the fungi *Cochliobolus miyabeanus* and *Diaporthe citri* IFO 6443 (MIC 2.6 μM for each fungus) and against the bacteria *Bacillus subtilis* ATCC 6633 and *Bacillus cereus* (MIC 5.2 μM for each species).[4] Whether or not the subtle structural variations between the homologous pamamycins affect their antibiotic activity as much as they affect the autoregulatory activity remains to be determined.

Another property which the pamamycins (or, at least, pamamycins-607 and -621) possess is the ability to transfer lipophilic anions from acidic aqueous solutions to organic phases: pamamycin-607 will transport permanganate ion from a pH 5.0 aqueous phase to a toluene–butanol phase,[4] and a mixture of pamamycins-607 and -621 will transport methyl orange and, weakly, dichromate anions from a pH 5.0 aqueous phase to toluene.[6] Less lipophilic (i.e., less polarizable) anions such as citrate, pyruvate, chloride, and bromide are not transferred, and no transfer of any anion is observed at nonacidic pH. Pamamycin-607 was not observed to transport the cations Na^+, K^+, or Ca^{+2} in a two-phase partition system.[4] The anion-transfer ability of the pamamycins may be related to the observations by Chou and Pogell of the inhibition of phosphate and nucleoside transport in *Staphylococcus aureus* by a mixture of pamamycins, although these authors have speculated that this inhibition, a possible mechanism for the antibiotic action of the pamamycins, was due to the pamamycins binding to cell membranes and inhibiting an active transport process.[8] Grafe and co-workers screened 300 actinomycetes species for the presence of anion-transfer activity at pH 5 and found five positive strains, thus indicating that basic anion-transporting substances like the pamamycins may be relatively common in antibiotic producing microorganisms.[6]

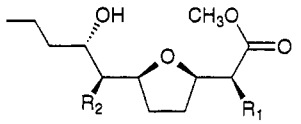
In view of the unique structures of the pamamycins, their various biological and chemical properties, the sensitivity of some of these properties to minor structural variations, and the difficulty in obtaining pure samples of each pamamycin homolog from *S. alboniger* cultures, the development of a synthetic route to these natural products is warranted. We have demonstrated that the *cis*-selective intramolecular oxymercuration reaction of γ-[(trialkylsilyl)oxy] allenes (6), followed, *in situ*, by the palladium(II)-mediated methoxycarbonylation of the intermediate vinylmercurial to form methyl 2-(tetrahydrofuran-2-yl)-2-propenoates 7, when followed by a chelation-controlled conjugate reduction using magnesium in methanol, as indicated in eq 1,[9] constitutes a viable synthetic route to



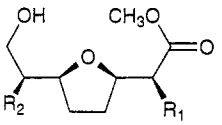
(1)

the "*cis,syn*" structural pattern which exists around two of the three tetrahydrofuran rings in the pamamycins.[10] Indeed, we have reported the stereoselective synthesis of the *racemic* methyl ester 8, which constitutes the C_1–$C_{11'}$ moiety of pamamycin-607, using this methodology,[11] and we have recently synthesized a nonracemic precursor, 9, to the C_1–$C_{11'}$ moiety of pamamycin-607 using like methodology applied to an enzymatically resolved allene precursor.[12] In addition, Mead and co-workers have developed powerful methodology for the stereoselective construction of the substituted tetrahydrofuranoid moieties of the pamamycins using unique 2-oxetanone ring-opening reactions.[13]

In this paper, we report the syntheses of the nonracemic methyl esters of the homologous C_1–$C_{11'}$ portions 8 and 10-12 of pamamycins-607, -649A, -635A/649B, and -635B, respectively, using our stereoselective allene cyclization/magnesium–methanol reduction methodology (eq 1), chelation-controlled organometallic additions to $C_{8'}$ aldehyde intermediates, and chemoselective carboxyl group transformations as key steps. The synthesis of the pamamycin subunit 8 utilizes the intermediate 9, whose synthesis via an enzymatically resolved γ-acetoxy allene has already been reported.[12] Pamamycin subunit 10 was synthesized by a similar chemoenzymatic route. The subunits 11 and 12 were prepared using an asymmetric aldol reaction to form the nonracemic allenol cyclization precursor.



	R_1	R_2
8:	CH_3	H
10:	CH_2CH_3	H
11:	CH_3	CH_3
12:	CH_2CH_3	CH_3



	R_1	R_2
9:	CH_3	H
13:	CH_2CH_3	H
14:	CH_3	CH_3
15:	CH_2CH_3	CH_3

(7) (a) Horinuchi, S.; Beppu, T. *Crit. Rev. Biotechnol.* **1990**, *10*, 191–204. (b) Beppu, T. *Gene* **1992**, *115*, 159–165. (c) Horinuchi, S.; Beppu, T. *Ann. Rev. Microbiol.* **1992**, *46*, 377–398.

(8) (a) Chou, W.-G.; Pogell, B. M. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 344–350. (b) Chou, W.-G.; Pogell, B. M. *Antimicrob. Agents Chemother.* **1981**, *20*, 443–454.

(9) (a) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023–1026. (b) Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597–1603 (Correction: *J. Am. Chem. Soc.* **1990**, *112*, 5388).

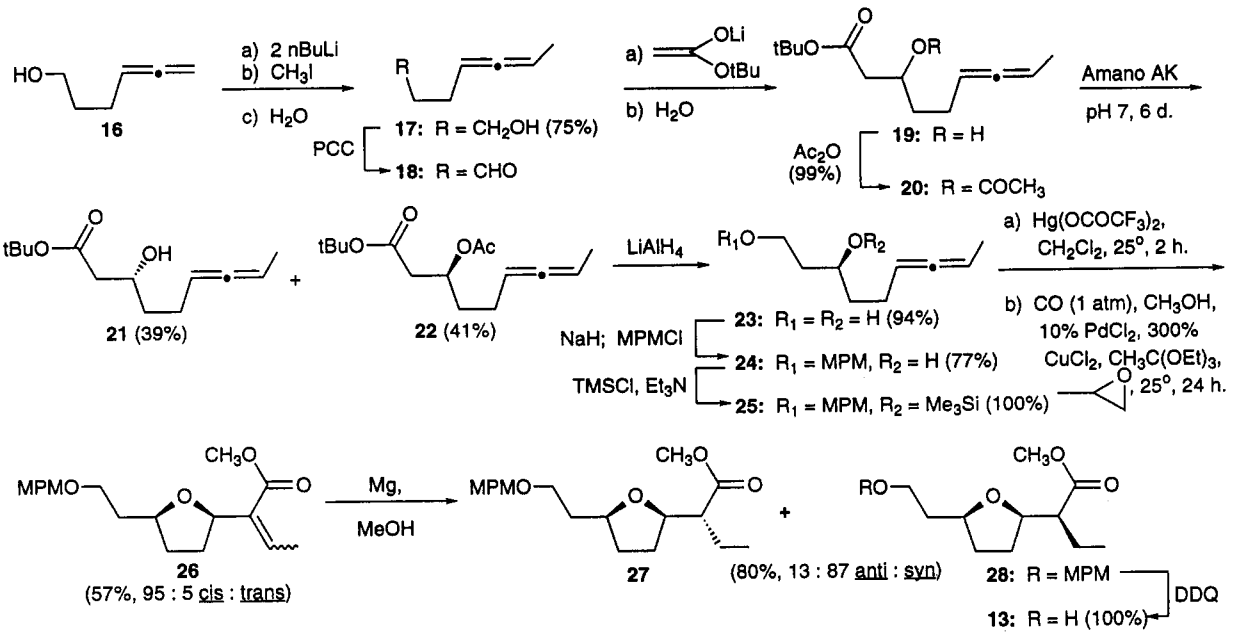
(10) An intermolecular palladium-mediated version of our cyclization methodology, the alkoxy addition/alkoxycarbonylation of allenes, was reported early on by Alper and co-workers: Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Chem. Soc., Chem. Commun.* **1984**, 905–906. In addition, Gallagher and co-workers have pioneered the related palladium-mediated aminocyclizations of allenes for applications to a variety of synthetic problems; see, e.g.: Fox, D. N. A.; Lathbury, D.;Mahon, M. F.; Molloy, K. D.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652–2656. Gallagher, T.; Davies, I. W.; Jones, S. W.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Shaw, R. W.; Vernon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 433–440 and references cited therein.

(11) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505–5508.

(12) Walkup, R. D.; Kim, S. W.; Wagy, S. D. *J. Org. Chem.* **1993**, *58*, 6486–6490.

(13) Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829–6832.

Scheme 1



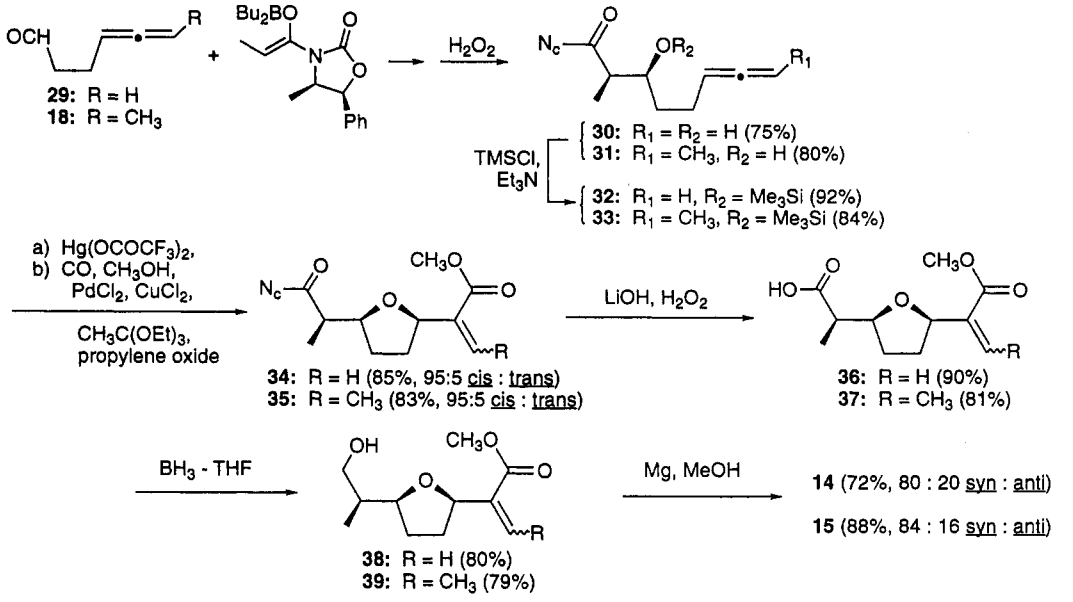
Results and Discussion

The key intermediates for the syntheses of the pamamycin subunits **8** and **10–12** were the hydroxy esters **9**[12] and **13–15**, constituting the C_1–$C_{8'}$ portions of the pamamycins. Intermediate **13**, the precursor to the C_1–$C_{11'}$ portion of pamamycin-649A, was prepared using the route indicated in Scheme 1, starting with 4,5-hexadien-1-ol (**16**).[12] Formation of the dianion of **16** followed by C-methylation afforded 4,5-heptadien-2-ol (**17**), which was oxidized to the aldehyde **18** and then reacted with the lithium enolate of *tert*-butyl acetate[14] to afford the β-hydroxy ester **19**. O-Acetylation of **19** afforded the β-acetoxy ester **20** which was then treated with Amano AK lipase to yield the easily separable (*R*)-alcohol **21** and (*S*)-diester **22** in good yields. The stereochemical purity of the two products was assessed using the chiral NMR shift reagent tris[3-(heptafluoropropyl)hydroxymethylene-(+)-camphorato]europium(III)[15] and authentic racemic materials as controls; as previously observed with the lower homolog,[12] enantiomeric excesses on the order of >95% were observed for both products **21** and **22**. (The presumed diastereomers of these compounds as well as **19**, **20**, and **23–25**, due to the chirality of the allene, could not be distinguished by NMR spectrometry or chromatography). Reduction of the diester **22** yielded the diol **23** whose primary alcohol group was protected as the (*p*-methoxyphenyl)methyl (MPM) ether **24**[16] and then O-silylated to yield the cyclization precursor **25**. Subjection of **25** to the previously described[9,11,12] cyclization/methoxycarbonylation protocol yielded the tetrahydrofuran **26** as a 95:5 *cis*/*trans* mixture with respect to the ring stereochemistry and as a ~50:50 *E*/*Z* mixture with respect to the alkene geometry. This intermediate was carried on as the mixture of diastereomers. Conjugate reduction of **26** using magnesium in methanol resulted in a 13:87 mixture of the diastereomeric alkoxyesters **27** and **28**, respectively. Oxidative removal of the MPM group from **28** yielded the pamamycin-649A subunit **13** in an overall yield of 5% for the 11 steps from 4,5-hexadien-1-ol.[17]

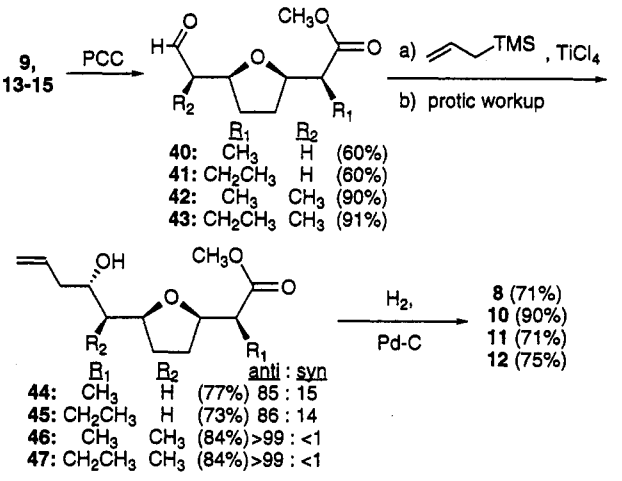
The hydroxy ester intermediates **14** and **15** for the C_1–$C_{11'}$ subunits **11** and **12** of pamamycin-635A/649B and -635B, respectively, were prepared as indicated in Scheme 2. Treatment of the known[12] aldehyde **29** with the dibutylboron enolate derived from (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one resulted in the *syn* aldol product **30**.[18] NMR analysis indicated the presence of less than 5% of the unwanted *anti* product. Similarly, treatment of the aldehyde **18** (cf. Scheme 1) produced the aldol product **31**. The products **30** and **31** were then O-silylated to produce the cyclization precursors **32** and **33**, respectively, which were subjected to the cyclization/methoxycarbonylation protocol to yield the tetrahydrofurans **34** and **35** in excellent yields and stereoselectivities. Selective hydrolyses of the *N*-acyloxazolidinone groups of **34** and **35** using conditions reported by Hruby[19] resulted in the monoesters **36** and **37**, which were then selectively reduced by borane[20] to yield the hydroxy acrylates **38** and **39**. The chemoselectivity observed in this hydrolysis/reduction sequence, where the $C_{8'}$ carboxyl group is differentiated from the $C_{1'}$ carboxyl group, is remarkable.[21] Subsequent magnesium–methanol reductions of **38** and **39** yielded 80:20 and 84:16 *syn*/*anti* mixtures of products, respectively, from which the *syn* hydroxy esters **14** and **15** were obtained. Thus, by using this six-step route, intermediate **14** was obtained in 23% overall yield from the aldehyde **29**, and **15** was obtained in 25% overall yield from **18**.

(14) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050–3051.
(15) Sullivan, G. R. *Top. Stereochem.* **1977**, *10*, 287–329.
(16) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.
(17) In principle, the protection of the primary alcohol was not necessary; the free diol **23** could be bis-silylated and subjected to the cyclization to yield a hydroxy ester product (**26** with a free primary alcohol group). In practice, we found that the yields obtained using this protocol were much lower than observed when the primary alcohol group was masked as the MPM ether.
(18) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
(19) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733–4748.
(20) Yoon, N. M.; Park, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786–2792.
(21) Attempts to remove the oxazolidinone chiral auxiliary by transesterification or reduction reactions resulted in unwanted side reactions of the acrylate moiety.

Scheme 2



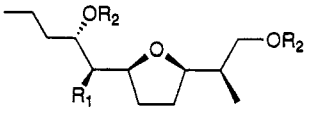
Scheme 3



With the key hydroxy ester intermediates **9** and **13–15** in hand, we completed the construction of the C_1–$C_{11'}$ moieties of the pamamycins by using a chelation-controlled allylation of the aldehydes **40–43** obtained by oxidation of the alcohols **9** and **13–15** (Scheme 3). Baldwin and McIver have reported that methyltrichlorotitanium(IV) added to aldehydes like **40–43** with high selectivity for the *anti* products,[22] and Danishefsky and co-workers,[23] following the results of Keck and his co-workers,[24] demonstrated efficient chelation-controlled allylations of carbohydrate-derived tetrahydrofuranyl aldehydes (α-alkoxy aldehyde substrates) using allyltrimethylsilane in the presence of titanium(IV) chloride. When the aldehydes **40–43** (β-alkoxy aldehyde substrates) were treated with allyltrimethylsilane and titanium(IV) chloride followed by a protic workup, the products **44–47** were obtained in good yield and with good to excellent diastereoselectivities, as indicated in Scheme 3. As expected, the added steric control due to having a methyl group at C_7, α to the aldehyde group (in **42** and **43**), resulted in complete stereocontrol of the allylation to yield **46** and **47** as >99:<1 *anti/syn* product mixtures. *Anti/syn* ratios on the order of 85:15 were observed for the less substituted aldehydes **42** and **43**. The absence of side products caused by Lewis acid mediated eliminative openings of the tetrahydrofuran rings in the substrates **40–43** is noteworthy.

Straightforward hydrogenation of the alkenes **44–47** yielded the C_1–$C_{11'}$ portions, **8** and **10–12**, of the pamamycin antibiotics. These products were produced in, at worst, 2% overall yield and 14 steps (for **10**) and, at best, 14% overall yield and 9 steps (for **12**) from simple allenyl alcohol starting materials.

To verify the stereochemical assignments and the stereochemical purities of the pamamycin subunits **8** and **10–12** synthesized as described above, the bis(*p*-bromobenzoate) **48**, obtained from **8** by lithium aluminum hydride reduction followed by acylation, was prepared and found to possess NMR signals identical with those observed by Natsume and co-workers for the same compound derived from pamamycin-607 and an optical rotation indicative of at least a 91% enantiomeric excess (see Experimental Section). Similarly, the diol **49**, obtained



by the reduction of **11**, exhibited NMR signals identical to those observed for the same diol derived from pamamycin-635A and an optical rotation indicative of at least a 96% enantiomeric excess (see Experimental Section). The enantiomer of **10**, synthesized from **21** (cf. Scheme 1) using the same route used to produce **10**, upon reduction and acylation yielded a bis(*p*-bromobenzoate) derivative which exhibited identical NMR signals and an optical rotation opposite to that of the same derivative derived from pamamycin-649A ($[\alpha]_D$ = −25.8° (chloroform, c = 0.03 g/mL) for the synthetic bis(*p*-bromobenzoate), $[\alpha]_D$ = +26.0° (chloroform, c = 1.0 g/mL) for the pamamycin-649A-derived bis(*p*-bromobenzoate)).[25] No chiroptical data are available for the C_1–$C_{11'}$ subunit of pamamycin-635B,

(22) Baldwin, S. W.; McIver, J. M. *Tetrahedron Lett.* **1991**, *32*, 1937–1940.
(23) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819.
(24) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265–268.

but the optical activities of 12 and its precursors are similar to those of the lower homologs 8, 10, and 11, suggesting a correlation between the stereochemistry of 12 and that of 8, 10, and 11.

With a viable route to the C_1–$C_{11'}$ subunits of the pamamycins available, studies of the efficiency of their coupling to alcohols to form macrolactone linkages can proceed. With that in mind, it bears noting that a change in the conditions for adding the C_9–$C_{11'}$ moiety to the $C_{8'}$ aldehyde (cf. 40–43 → 44–47, Scheme 3) to propylmagnesium chloride/zinc chloride results in selectivity for the *syn* alcohol,[22,25] thus allowing for ester coupling reactions which invert the $C_{8'}$ center, in case acylation-based methodologies do not work well.[26] In addition, we have recently synthesized a nonracemic C_1–C_{14} portion of pamamycin-607 and -635B using methodology similar to that employed in this work. Results from these studies will be reported in due course.

Experimental Section

General. Unless otherwise indicated, solvents and reagents were reagent grade and used without purification. The Amano AK lipase was purchased from Mitsubishi International Corp., Horsham, PA. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen immediately prior to use. Dichloromethane was distilled from calcium hydride immediately prior to use. Methanol was distilled from magnesium turnings and stored in a sealed container. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen in glassware that had been oven dried. The progress of reactions and chromatographic separations was followed using thin-layer chromatography (TLC) on silica gel plates with visualization using UV followed by a chromic acid spray reagent. Unless otherwise indicated, all reactions were worked up using an organic aqueous partition, followed by treatment of the organic phase with appropriate aqueous washes, a brine wash, drying over anhydrous magnesium sulfate, filtration, and concentration *in vacuo*. Flash chromatography was performed using 230–400-mesh silica gel (Aldrich). High-performance liquid chromatography (HPLC) was performed using a Dupont Zorbax-Sil column (5-μm silica gel packing, 25-cm × 4-mm i.d.), refractometry detection, and the isocratic hexane ethyl acetate eluents and flowrates indicated. Infrared spectra were recorded using neat films on sodium chloride plates and are reported in wavenumbers (cm^{-1}). ^1H (200 or 300 MHz) and ^{13}C (50 MHz) NMR were obtained from solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from a tetramethylsilane (TMS) internal standard. NMR data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, etc.), integration]. Low- and high-resolution mass spectra were obtained using electron ionization. Elemental analyses were done by Desert Analytics, Tuscon, AZ. For those compounds for which only high-resolution mass spectral data was obtained, copies of their ^1H- and ^{13}C-NMR spectra are provided as supplementary material. High-resolution mass spectra were measured by the Midwest Center for Mass Spectrometry, University of Nebraska—Lincoln, Lincoln, NB. Optical rotations were measured at the sodium D line (589 nm) using a Rudolph Autopol III polarimeter calibrated using a standard quartz control plate (Rudolph), using a 10-cm cell.

4,5-Heptadien-1-ol (17). To a solution of the alcohol **16** (1.00 g, 10.19 mmol) in dry THF (45 mL) at −78 °C under nitrogen was added a 2.0 M solution of n-BuLi in hexanes (11.21 mL, 22.42 mmol). The solution was stirred at −78 °C for 20 min, and then iodomethane (0.76 mL, 12.23 mmol) was added. After a further 50 min stirring at −78 °C, workup followed by chromatography (90:10 hexanes/ethyl acetate) yielded 0.857 g (75%) of **17**: ^1H NMR δ 5.05 (m, 2H), 3.68 (t, 2H, J = 6.4 Hz), 2.07 (m, 2H), 1.73–1.60 (m, 5H); ^{13}C NMR δ 204.73, 89.61, 86.01, 62.37, 31.88, 25.05, 14.52; IR 3354, 2931, 2884, 1960, 873 cm^{-1}; HRMS m/z 112.08842 ($C_7H_{12}O$, calcd 112.08881).

4,5-Heptadienal (18). To a stirring suspension of pyridinium chlorochromate (3.95 g, 18.3 mmol) in 40 mL of CH_2Cl_2 containing 0.5 g of $MgSO_4$ and 0.3 g of KOAc was added, dropwise, the alcohol **17** (3.46 g, 16.05 mmol) in 5 mL CH_2Cl_2. After 3 h at room temperature, the mixture was diluted with ether and filtered through a pad of Florisil, and the resulting colorless solution was concentrated down to a ~1 mL volume using a rotary evaporator (keeping the waterbath temperature <35 °C). NMR analysis indicated clean formation of the product **18**. Owing to the volatility of **18**, it was characterized in this crude form and used in the next step without further purification: ^1H NMR δ 9.75 (t, 1H, J = 1.5 Hz), 5.12 (m, 2H), 2.54 (m, 2H), 2.31 (m, 2H), 1.60 (m, 3H); ^{13}C NMR δ 204.73, 202.17, 88.79, 87.53, 42.28, 21.24, 14.36; IR 2955, 2931, 2861, 1725, 850 cm^{-1}.

(±)-*tert*-Butyl 3-Hydroxy-6,7-nonadienoate (19). To a 1.5 M solution of LDA in hexanes (9.8 mL, 14.7 mmol), stirring at −78 °C under nitrogen, was added *tert*-butyl acetate (1.8 mL, 13.4 mmol) in 2 mL of THF. After 1 h, 1.80 g (13.37 mmol) of the aldehyde **18** in 2 mL of THF was added. The solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature for 30 min. Workup and chromatography yielded **19** (2.39 g, 79%): HPLC retention time (90:10 hexanes:ethyl acetate at 1 mL/min) 11.6 min; ^1H NMR δ 5.05 (m, 2H), 3.99 (m, 1H), 2.40 (dd, 1H, J = 15.5, 3.6 Hz), 2.27 (dd, 1H, J = 15.5, 8.4 Hz), 2.07 (m, 2H), 1.67–1.44 (m, 5H), 1.44 (s, 9H); ^{13}C NMR δ 204.73, 172.51, 89.67, 86.08, 81.26, 67.54, 42.24, 35.53, 28.11, 24.74, 14.53; IR 3472, 2978, 2931, 1966, 1731, 1149, 873, 844, 761, 750 cm^{-1}; HRMS m/z 226.15591 ($C_{13}H_{22}O_3$, calcd 226.15688).

(±)-*tert*-Butyl 3-Acetoxy-6,7-nonadienoate (20). Acetic anhydride (5 mL) was added dropwise to a cooled (0 °C) solution of the alcohol **19** (2.48 g, 10.96 mmol) and DMAP (0.2 g) in 2.5 mL of triethylamine that was stirring under a $CaCl_2$ drying tube. The solution was allowed to warm to room temperature and stirred for 5 h, and then saturated $NaHCO_3$ (20 mL) and ether (50 mL) were added. Workup and chromatography (95:5 hexanes/ethyl acetate) yielded **20** (2.76 g, 94%): HPLC retention time (95:5 hexanes/ethyl acetate at 1 mL/min) 11.3 min; ^1H NMR δ 5.22 (p, 1H, J = 6.6 Hz), 5.04 (m, 2H), 2.59 (dd, 2H, J = 7.1, 0.7 Hz), 2.01 (s, 3H), 1.72 (m, 2H), 1.62 (m, 3H), 1.96 (m, 2H), 1.41 (s, 9H); ^{13}C NMR δ 204.69, 170.25, 169.54, 89.19, 86.32, 80.83, 70.23, 40.54, 33.16, 27.97, 24.52, 21.06, 14.45; IR 2978, 2943, 2872, 1964, 1732, 1713, 1682 cm^{-1}; HRMS m/z 212.1046 ($C_{11}H_{16}O_4$, $M^+ - C_4H_8$, calcd 212.10485), 152.0833 ($C_9H_{12}O_2$, $M^+ - C_6H_{12}O_2$, calcd 152.08372).

(*R*)-(−)-*tert*-Butyl 3-Hydroxy-6,7-nonadienoate (21) and (*S*)-(−)-*tert*-Butyl 3-Acetoxy-6,7-nonadienoate (22). To a solution of **20** (1.60 g, 5.96 mmol) in pH 7 phosphate buffer (40 mL) was added Amano lipase AK (2.5 g). The mixture was stirred at 25 °C for 6 days, dichloromethane (150 mL) was added, and stirring was continued for 12 h. The dichloromethane layer was then separated and successively washed with saturated $NaHCO_3$ (3 × 50 mL) and brine, dried over $MgSO_4$, concentrated, and chromatographed (95:5 hexanes/ethyl acetate) to yield **21** (0.53 g, 39%, NMR, IR, and HPLC retention time identical to those of **19**) [$[\alpha]^{25}_D$ −14.70° ($CHCl_3$, c = 0.015 g/mL)] and **22** (0.66 g, 41%, NMR, IR, and HPLC retention time identical to those of **20**): $[\alpha]^{25}_D$ −8.71° ($CHCl_3$, c = 0.014 g/mL).

(*S*)-(−)-6,7-Nonadien-1,3-diol (23). To a cooled (0 °C) stirring solution of **22** (0.78 g, 2.91 mmol) in ether (15 mL) under nitrogen was added lithium aluminum hydride (0.09 g, 2.4 mmol). The solution was stirred at 25 °C for 30 min and then cooled to 0 °C. Sodium hydroxide (1 N, 0.1 mL) and water (0.2 mL) were successively added, and then the mixture was dried, concentrated, and chromatographed (60:40 hexanes/ethyl acetate), yielding **23** (0.43 g, 94%): ^1H NMR δ 5.07 (m, 2H), 3.87 (m, 3H), 2.10 (m, 2H), 1.65 (m, 7H); ^{13}C NMR δ 204.65, 89.74, 86.09, 71.52, 61.58, 38.18, 36.75, 24.85, 14.50; IR 3331, 2931, 2871, 1960, 1055, 873, 844 cm^{-1}; HRMS m/z 155.10710 ($C_9H_{16}O_2$ − H, calcd 155.10720), 141.09155 ($C_9H_{16}O_2 - CH_3$, calcd 141.09155); $[\alpha]^{25}_D$ −6.18° ($CHCl_3$, c = 0.019 g/mL).

(25) Kim, S. W. Ph.D. Dissertation, Texas Tech University, 1993.

(26) In the similar nonactin systems, attempted DCC couplings resulted in poor yields, and S_N2 displacements at the alcohol center by a carboxylate were found to best afford the desired macrolide products. For a leading reference, see: Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304–5311.

(*S*)-(−)-1-[(4′-Methoxyphenyl)methoxy]-6,7-nonadien-3-ol (24). A solution of **23** (0.52 g, 3.33 mmol) in dry DMF (15 mL) was added to sodium hydride (0.16 g of a 60% mineral oil dispersion, washed three times with hexanes, ~3.4 mmol) under nitrogen at 0 °C. The mixture was allowed to stir at room temperature until gas evolution ceased (~1 h) and then it was cooled to 0 °C and 4-methoxybenzyl chloride (0.636 g, 4.06 mmol) was added. After 10 min the cooling bath was removed and stirring was continued for 5 h. Workup and chromatography (80:20 hexanes/ethyl acetate) yielded **24** (0.709 g, 77%): ^{1}H NMR δ 7.24 (m, 2H), 6.87 (m, 2H), 5.06 (m, 2H), 4.45 (s, 2H), 3.82 (m, 1H), 3.80 (s, 3H), 3.66 (m, 2H), 2.07 (m, 2H), 1.60 (m, 7H); ^{13}C NMR δ 204.63, 159.24, 129.99, 129.26, 113.80, 89.95, 85.90, 72.94, 70.89, 68.89, 55.24, 36.54, 36.25, 24.88, 14.54; IR (neat) 3460, 2931, 2861, 1960, 1614, 1514, 1173, 820, 750 cm^{-1}; HRMS *m/z* 276.17184 ($C_{17}H_{24}O_3$, calcd 276.37903); $[\alpha]^{25}_D$ −11.42° ($CHCl_3$, *c* = 0.012 g/mL).

(*S*)-1-[(4′-Methoxyphenyl)methoxy]-3-(trimethylsiloxy)-6,7-nonadiene (25). To a solution of **24** (0.6 g, 2.17 mmol) in dry THF (25 mL) was added triethylamine (1.5 mL) and chlorotrimethylsilane (0.8 mL, 6.3 mmol). The solution was stirred at room temperature under a $CaCl_2$ drying tube for 5 h. Workup and chromatography yielded **25** (0.76 g, 100%) which was cursorily characterized by NMR and IR spectrometry and then used without further characterization: ^{1}H NMR δ 7.24 (m, 2H), 6.85 (m, 2H), 5.04 (m, 2H), 4.40 (dd, 2H, *J* = 13.4, 11.6 Hz), 3.85 (m, 1H), 3.78 (s, 3H), 3.48 (t, 2H, *J* = 6.6 Hz), 2.01 (m, 2H), 1.60 (m, 7H), 0.09 (s, 9H); ^{13}C NMR δ 208.44, 159.10, 130.64, 129.26, 113.73, 90.07, 85.91, 72.61, 68.96, 66.81, 55.27, 37.34, 36.80, 24.73, 14.57, 0.40; IR 2953, 2857, 1956, 1728, 1613, 1514, 1249, 1094 cm^{-1}.

(3*R*,6*S*)-(+)-Methyl 2-Ethylidene-8-[(4′-methoxyphenyl)-methoxy]-3,6-epoxyoctanoate (26). To a solution of **25** (0.36 g, 1.03 mmol) in dry dichloromethane (10 mL) was added mercuric trifluoroacetate (0.5 g, 1.18 mmol) (CAUTION: TOXIC) under nitrogen. The solution was stirred at 25 °C for 2 h and then concentrated to a gum. The residue was immediately dissolved in methanol (10 mL), and then copper(II) chloride (0.5 g, 2.95 mmol), palladium(II) chloride (0.018 g, 0.1 mmol), propylene oxide (0.7 mL, 10 mmol), and triethyl orthoacetate (0.2 mL, 1 mmol) were added. The mixture was stirred at 25 °C under a balloon filled with carbon monoxide (CAUTION: USE HOOD) for 24 h. The resulting black mixture was concentrated, ethyl acetate was added, and the mixture was filtered through 25 g of Florisil. The filtrate was concentrated, and the residue was subjected to workup and chromatography (80:20 hexanes/ethyl acetate) to yield **26** (0.196 g, 57%). NMR and HPLC analysis of the crude reaction mixture indicated a 95:5 *cis*/*trans* ratio of isomers with respect to the newly formed tetrahydrofuran ring, and NMR analysis also indicated that a mixture of ~50:50 *E*/*Z* isomers with respect to the newly formed alkene were formed (based on closely spaced "doubling" of the alkene signals). The *cis* and *trans* isomers, but not the *E*/*Z* isomers, could be separated by HPLC. In practice, the mixture of isomers was carried on without separation of the diastereomers: HPLC retention times (90:10 hexanes/ethyl acetate at 1 mL/min) 20.9 min for *cis*, 42.3 min for *trans*. For *cis* isomer: ^{1}H NMR δ 7.24 (m, 2H), 6.85 (m, 2H), 6.33 (q, 1H, *J* = 7.3 Hz), 4.60 (m, 1H), 4.42 (s, 2H), 4.00 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.56 (m, 2H), 1.97 (d, 3H, *J* = 7.3 Hz), 1.86 (m, 4H), 1.59 (m, 2H); ^{13}C NMR δ 159.12, 135.40, 134.04, 130.64, 129.29, 129.19, 113.77, 78.28, 77.17, 72.67, 67.40, 55.25, 51.05, 32.95, 32.17, 30.98, 15.28. For *trans* isomer: ^{1}H NMR δ 7.24 (m, 2H), 6.85 (m, 2H), 6.33 (q, 1H, *J* = 7.3 Hz), 4.71 (m, 1H), 4.42 (s, 2H), 4.13 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.56 (m, 2H), 1.97 (d, 3H, *J* = 7.3 Hz), 1.86 (m, 4H), 1.59 (m, 2H) (^{13}C NMR of the *trans* isomer was not measured due to small amount of material obtained). For the purified mixture of diastereomers: IR 2955, 2861, 2355, 2332, 1725, 1713, 1614, 1514, 1437, 1249, 1085, 1038 cm^{-1}; HRMS *m/z* 333.4177 ($C_{19}H_{28}O_5$, calcd 334.4161); $[\alpha]^{25}_D$ +24.00° ($CHCl_3$, *c* = 0.015 g/mL).

(2*R*,3*R*,6*S*)-(−)-Methyl 2-Ethyl-8-[(4′-methoxyphenyl)-methoxy]-3,6-epoxyoctanoate (27) and (2*S*,3*R*,6*S*)-(+)-Methyl 2-Ethyl-8-[(4′-methoxyphenyl)methoxy]-3,6-epoxyoctanoate (28). To a solution of **26** (0.64 g, 1.91 mmol) in dry methanol (40 mL) was added magnesium turnings (1 g). The mixture was stirred at 0 °C under a $CaCl_2$ filled drying tube for 2 h and then at 25 °C for 6 h. Addition of 5% HCl (30 mL) follwed by workup and chromatography (90:10 hexanes/ethyl acetate) yielded pure product (0.51 g, 80%) as a 13:87 mixture of *anti* (**27**) and *syn* (**28**) isomers which were separated by preparative HPLC. Compound **27**: HPLC retention time (90:10 hexanes/ethyl acetate at 1 mL/min) 22.5 min; ^{1}H NMR δ 7.23 (m, 2H), 6.85 (m, 2H), 4.39 (s, 2H), 3.97 (m, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 3.49 (m, 2H), 2.30 (m, 1H), 1.95 (m, 2H), 1.75 (p, 2H, *J* = 7.2 Hz), 1.61–1.41 (m, 4H), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 174.85, 159.08, 130.69, 129.20, 113.73, 80.00, 76.99, 72.60, 67.41, 55.26, 53.94, 51.39, 36.16, 30.96, 29.23, 22.24, 11.90; IR 2955, 2872, 1731, 1614, 1514 cm^{-1}; HRMS *m/z* 336.19366 ($C_{19}H_{28}O_5$, calcd 336.19267); $[\alpha]^{25}_D$ −2.00° ($CHCl_3$, *c* = 0.005 g/mL). Compound **28**: HPLC retention time (90:10 hexanes/ethyl acetate at 1 mL/min) 11.2 min; ^{1}H NMR δ 7.23 (m, 2H), 6.85 (m, 2H), 4.40 (s, 2H), 3.94 (m, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.51 (t, 2H, *J* = 6.5 Hz), 2.38 (m, 1H), 1.99–1.54 (m, 8H), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 174.54, 159.09, 130.62, 129.18, 113.73, 79.34, 77.43, 72.60, 67.35, 55.24, 53.07, 51.31, 36.18, 30.95, 28.98, 22.92, 11.81; $[\alpha]^{25}_D$ +14.44° ($CHCl_3$, *c* = 0.01 g/mL). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 67.16; H, 8.10.

(2*S*,3*R*,6*S*)-(+)-Methyl 2-Ethyl-8-hydroxy-3,6-epoxyoctanoate (13). To a solution of **28** (0.32 g, 0.95 mmol) in dichoromethane (10 mL) and pH 7 buffer (2 mL) was added DDQ (0.23 g, 1.0 mmol). The solution was stirred at 25 °C for 20 min, water (20 mL) was added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$, dried, concentrated, and chromatographed (60:40 hexanes/ethyl acetate) to yield 0.21 g (100%) of **13**: ^{1}H NMR δ 3.97 (m, 2H), 3.69 (t, 2H, *J* = 6.0 Hz), 3.62 (s, 3H), 2.38 (m, 1H), 1.91 (m, 2H), 1.63 (m, 6H), 0.84 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 174.24, 79.77, 79.32, 61.23, 52.60, 51.36, 37.57, 30.98, 28.45, 22.66, 11.68; HRMS *m/z* 185.1172 ($C_{10}H_{17}O_3$, M$^+$ − OCH_3, calcd 185.11776), 171.1020 ($C_9H_{15}O_3$, M$^+$ − CH_2CH_2OH, calcd 171.10211); $[\alpha]^{25}_D$ +21.63° ($CHCl_3$, *c* = 0.011 g/mL).

(2′*R*,3′*S*,4*R*,5*S*)-(+)-3-(2′-Methyl-3′-hydroxy-6′,7′-octadienoyl)-4-methyl-5-phenyl-2-oxazolidinone (30). To a solution of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone (2.178 g, 9.34 mmol) in dichloromethane (50 mL) at 0 °C under nitrogen was added 1.0 M dibutylboron triflate in dichloromethane (10.27 mL, 10.27 mmol) and then *N*,*N*-diisopropylethylamine (1.95 mL, 11.21 mmol). After 30 min, the reaction mixture was cooled to −78 °C, and the aldehyde **29**[12] (1.07 g, 11.2 mmol) in 5 mL of dichloromethane was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and at room temperature for 1 h, and then pH 7 buffer (20 mL) was added, the layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined extracts were concentrated, the resulting yellow oil was dissolved in methanol (35 mL) and cooled in an ice/water bath, 30% aqueous hydrogen peroxide (12 mL) was added, and the solution was stirred at room temperature for 1 h. Water (60 mL) was added, the methanol was removed by rotary evaporation, and the aqueous suspension was extracted with dichloromethane (3 × 75 mL). The combined organic extracts were then washed with brine, dried, concentrated, and chromatographed (90:10 hexanes/ethyl acetate) to yield **30** (2.31 g, 75%): ^{1}H NMR δ 7.40 (m, 3H), 7.27 (m, 2H), 5.66 (d, 1H, *J* = 7.3 Hz), 5.15 (p, 1H, *J* = 6.7 Hz), 4.79 (p, 1H, *J* = 6.8 Hz), 4.66 (p, 2H, *J* = 3.3 Hz), 3.99 (ddd, 1H, *J* = 10.3, 4.2, 2.7 Hz), 3.75 (dq, 1H, *J* = 7.1, 2.7 Hz), 2.25 (m, 1H), 2.12 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.22 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 208.41, 177.17, 152.56, 133.04, 129.08, 128.78, 125.54, 89.43, 78.87, 75.23, 70.80, 54.89, 42.22, 32.99, 24.52, 14.31, 10.29; IR 4341, 4047, 3507, 3060, 3037, 2978, 2931, 2872, 2837, 1955, 1772, 1696, 1525 cm^{-1}; $[\alpha]^{25}_D$ + 20.83° ($CHCl_3$, *c* = 0.018 g/mL). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 69.28; H, 7.04. Found: C, 69.46; H, 7.03.

(2′*R*,3′*S*,4*R*,5*S*)-(+)-3-(2′-Methyl-3′-hydroxy-6′,7′-nonadienoyl)-4-methyl-5-phenyl-2-oxazolidinone (31). Following a procedure identical to that used for the preparation of **30**, crude aldehyde **18** (0.8 g, 7.26 mmol) was converted to **31** (1.99 g, 80%): ^{1}H NMR δ 7.40 (m, 3H), 7.27 (m, 2H), 5.66 (d, 1H, *J* = 7.2 Hz), 5.06 (m, 2H), 4.77 (p, 1H, *J* = 6.7 Hz), 3.99 (ddd, 1H, *J* = 10.3, 4.3, 2.7 Hz), 3.76 (dq, 1H, *J* = 7.1, 2.8 Hz), 2.11 (m, 2H), 1.59 (m, 5H), 1.22 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 204.70, 177.28, 152.58, 133.08, 128.81, 128.73, 125.58, 89.68, 86.10, 78.91, 70.88, 54.72, 42.20, 33.08, 25.20, 14.55, 14.34, 10.27; IR 3517, 3025, 2978, 2939, 1963, 1782, 1698, 1497, 1455, 1368, 1196,

1149, 1122 cm^{-1}; HRMS *m/z* 343.17834 ($C_{20}H_{25}NO_4$, calcd 343.17862); $[\alpha]_D$ +16.74° ($CHCl_3$, c = 0.016 g/mL).

(2′*R*,3′*S*,4*R*,5*S*)-3-[2′-Methyl-3′-(trimethylsiloxy)-6′,7′-octadienoyl]-4-methyl-5-phenyl-2-oxazolidinone (32). Following a procedure identical to that used for the preparation of **25**, the alcohol **30** (1.50 g, 4.73 mmol) was converted to **32** (1.75 g, 92%). This material was used for the next step as the crude product after NMR characterization: ^{1}H NMR δ 7.40 (m, 3H), 7.29 (m, 2H), 5,61 (d, 1H, *J* = 7.0 Hz), 5.11 (p, 1H, *J* = 6.7 Hz), 4.76 (p, 1H, *J* = 6.6 Hz), 4.67 (p, 2H, *J* = 3.4 Hz), 3.93 (m, 2H), 2.08 (m, 2H), 1.59 (m, 2H), 1.12 (d, 3H, *J* = 8.7 Hz), 0.88 (d, 3H, *J* = 6.5 Hz), 0.13 (s, 9H); ^{13}C NMR δ 208.37, 174.83, 152.62, 133.14, 128.59, 125.48 (two overlapping signals), 89.61, 78.70, 75.16, 73.05, 55.17, 43.31, 34.24, 24.09, 14.14, 12.21, 0.24.

(2′*R*,3′*S*,4*R*,5*S*)-3-[2′-Methyl-3′-(trimethylsiloxy)-6′,7′-nonadienoyl]-4-methyl-5-phenyl-2-oxazolidinone (33). Following a procedure identical to that used for the preparation of **25**, the alcohol **31** (1.12 g, 3.26 mmol) was converted to **33** (1.14 g, 84%). This material was used for the next step as the crude product after NMR characterization: ^{1}H NMR δ 7.39 (m, 3H), 7.28 (m, 2H), 5.60 (d, 1H, *J* = 7.0 Hz), 5.06 (m, 2H), 4.70 (m, 1H), 3.95 (m, 2H), 2.08 (m, 2H), 1.60 (m, 5H), 1.12 (d, 3H, *J* = 8.7 Hz), 0.87 (d, 3H, *J* = 6.6 Hz), 0.11 (s, 9H); ^{13}C NMR δ 204.66, 175.00, 152.74, 133.21, 128.69 (two overlapping signals), 125.56, 89.94, 86.06, 78.80, 73.19, 55.31, 43.38, 34.44, 34.29, 24.76, 14.25, 12.30, 0.32.

(2′*R*,3′*S*,6′*R*,4*R*,5*S*)-(+)-3-[7′-(Methoxycarbonyl)-2′-methyl-3′,6′-epoxy-7′-octenoyl]-4-methyl-5-phenyl-2-oxazolidinone (34). Following a procedure identical to that used for the preparation of **26**, intermediate **32** (1.75 g, 4.36 mmol) was converted to a 95:5 *cis/trans* mixture of product diastereomers (1.44 g, 85%). In practice, the mixture of isomers was carried on without separation of the diastereomers. For *cis* isomer **34**: ^{1}H NMR δ 7.43 (m, 3H), 7.30 (m, 2H), 6.23 (dd, 1H, *J* = 1.4, 1.3 Hz), 5.93 (dd, 1H, *J* = 1.6, 1.8 Hz), 5.68 (d, 1H, *J* = 7.2 Hz), 4.76 (p, 1H, *J* = 6.6 Hz), 4.65 (dd, 1H, *J* = 7.1, 1.5 Hz), 4.18 (m, 1H), 3.94 (m, 1H), 3.71 (s, 3H), 2.25 (m, 1H), 2.04 (m, 1H), 1.68 (m, 2H), 1.29 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 186.92, 175.55, 152.82, 141.46, 133.35, 128.70, 128.62, 125.62, 123.85, 81.68, 78.60, 76.92, 54.79, 51.62, 42.83, 31.79, 28.64, 14.47, 14.28. For *trans* isomer: ^{1}H NMR δ 7.43 (m, 3H), 7.30 (m, 2H), 6.14 (dd, 1H, *J* = 1.4, 1.3 Hz), 5.83 (dd, 1H, *J* = 1.6, 1.7 Hz), 5.68 (d, 1H, *J* = 7.2 Hz), 4.76 (p, 1H, *J* = 6.6 Hz), 4.65 (dd, 1H, *J* = 7.1, 1.5 Hz), 4.18 (m, 1H), 3.94 (m, 1H), 3.71 (s, 3H), 2.25 (m, 1H), 2.04 (m, 1H), 1.68 (m, 2H), 1.29 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.6 Hz) (^{13}C NMR of *trans* isomer not measured due to small amount of material obtained). For the purified mixture of diastereomers: IR 3542, 3060, 3037, 2978, 2955, 2884, 1778, 1708, 1631, 1455, 1437, 1296, 1196, 1120, 1073 cm^{-1}; $[\alpha]^{25}_D$ +28.66° ($CHCl_3$, *c* = 0.017 g/mL. Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50. Found: C, 64.71; H, 6.49.

(2′*R*,3′*S*,6′*R*,4*R*,5*S*)-(+)-3-[7′-(Methoxycarbonyl)-2′-methyl-3′,6′-epoxy-7′-nonenoyl]-4-methyl-5-phenyl-2-oxazolidinone (35). Following a procedure identical to that used for the preparation of **26**, intermediate **33** (0.75 g, 1.80 mmol) was converted to a 95:5 *cis/trans* mixture of product diastereomers which included indistinguishable *E/Z* alkene isomers (0.60 g, 83%). In practice, the mixture of isomers was carried on without separation of the diastereomers. For *cis* isomer **35**: ^{1}H NMR δ 7.34 (m, 3H), 7.21 (m, 2H), 6.34 (q, 1H, *J* = 7.4 Hz), 5.65 (d, 1H, *J* = 7.1 Hz), 4.71 (p, 1H, *J* = 6.6 Hz), 4.55 (m, 1H), 4.10 (m, 1H), 3.92 (p, 1H, *J* = 6.8 Hz), 3.69 (s, 3H), 2.10 (m, 2H), 1.95 (d, 3H, *J* = 7.3 Hz), 1.62 (m, 2H), 1.25 (d, 3H, *J* = 6.8 Hz), 0.83 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR δ 174.48, 167.07, 156.97, 152.54, 135.48, 133.11, 132.13, 128.52, 125.44, 83.65, 80.05, 78.60, 54.58, 50.97, 42.38, 31.75, 28.93, 15.17, 14.17, 13.75. For *trans* isomer: ^{1}H NMR δ 7.34 (m, 3H), 7.21 (m, 2H), 6.34 (q, 1H, *J* = 7.4 Hz), 5.65 (d, 1H, *J* = 7.1 Hz), 4.71 (p, 1H, *J* = 6.6 Hz), 4.67 (m, 1H), 4.25 (m, 1H), 3.92 (p, 1H, *J* = 6.8 Hz), 3.69 (s, 3H), 2.10 (m, 2H), 1.95 (d, 3H, *J* = 7.3 Hz), 1.62 (m, 2H), 1.25 (d, 3H, *J* = 6.8 Hz), 0.83 (d, 3H, *J* = 6.5 Hz) (^{13}C NMR of *trans* isomer not measured due to small amount of material obtained). For the purified mixture of diastereomers: IR 2966, 2943, 2884, 1784, 1702, 1455, 1343, 1232, 1196, 1067, 1026, 785, 767, 703 cm^{-1}; HRMS *m/z* 370.16479 ($C_{21}H_{24}NO_5$, M$^+$ − OCH_3, calcd 370.16543); $[\alpha]^{25}_D$ +17.80° ($CHCl_3$, *c* = 0.03 g/mL).

(2*R*,3*S*,6*R*)-(+)-7-(Methoxycarbonyl)-2-methyl-3,6-epoxy-2-octenoic Acid (36). To a solution of **34** (0.968 g, 2.50 mmol) in THF (35 mL) and water (18 mL) at 0 °C was added 30% hydrogen peroxide (0.74 mL, ~6.5 mmol) and lithium hydroxide monohydrate (0.136 g, 3.25 mmol). The solution was stirred for 30 min, and then sodium thiosulfate (1.3 g dissolved in 8 mL of water) and 25 mL of 0.5 N $NaHCO_3$ were added. The solution was concentrated, and the remaining aqueous phase was extracted with dichloromethane to recover the chiral oxazolidinone (0.443 g, 100%). The aqueous layer was then cooled to 0 °C, acidified by the dropwise addition of 6 N hydrochloric acid, and then extracted with ethyl acetate (4 × 50 mL), dried, concentrated, and chromatographed (80:20 hexanes/ethyl acetate) to yield **36** (0.57 g, 90%): ^{1}H NMR δ 6.20 (m, 1H), 5.91 (m, 1H), 4.67 (t, 1H, *J* = 7.0 Hz), 4.13 (q, 1H, *J* = 6.9 Hz), 3.74 (s, 3H), 2.65 (p, 1H, *J* = 7.0 Hz), 2.29 (m, 1H), 2.05 (m, 1H), 1.68 (m, 2H), 1.29 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 179.89, 166.02, 140.97, 123.56, 79.84, 76.10, 51.49, 44.28, 31.88, 28.70, 13.27; IR 3225 (broad), 2990, 2952, 2861, 1731, 1705, 1634, 1440, 1274, 1198, 1065 cm^{-1}; HRMS *m/z* 197.07615 ($C_{10}H_{13}O_4$, M$^+$ − CH_3O, calcd 197.08138), 155.07059 ($C_8H_{11}O_3$, M$^+$ − $C_3H_5O_2$, calcd 155.07081), 141.05477 ($C_7H_9O_3$, M$^+$ − $C_4H_7O_2$, calcd 141.05516); $[\alpha]^{25}_D$ +21.05° ($CHCl_3$, *c* = 0.02 g/mL).

(2*R*,3*S*,6*R*)-(+)-7-(Methoxycarbonyl)-2-methyl-3,6-epoxy-2-nonenoic Acid (37). Following a procedure identical to that used for the preparation of **36**, intermediate **35** (0.58 g, 1.44 mmol) was converted **37** (0.28 g, 81%): ^{1}H NMR δ 11.0 (broad, 1H), 6.34 (q, 1H, *J* = 7.3 Hz), 4.58 (t, 1H, *J* = 6.6 Hz), 4.05 (q, 1H, *J* = 6.8 Hz), 3.71 (s, 3H), 2.62 (p, 1H, *J* = 6.9 Hz), 2.19 (m, 2H), 1.96 (d, 3H, *J* = 7.3 Hz), 1.69 (m, 2H), 1.25 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 180.01, 167.20, 139.97, 136.05, 79.92, 78.91, 51.13, 44.42, 35.27, 28.93, 15.31, 13.51; IR 3660–3013 (broad), 2978, 2955, 1714, 1649, 1437, 1384, 1338, 1224, 1068, 1020 cm^{-1}; HRMS *m/z* 242.1153 ($C_{12}H_{18}O_5$, calcd 242.11541); $[\alpha]^{25}_D$ −4.80° ($CHCl_3$, *c* = 0.007 g/mL).

(3*R*,6*S*,7*S*)-(+)-Methyl 8-Hydroxy-7-methyl-2-methylidene-3,6-epoxyoctadienoate (38). To a solution of **36** (0.45 g, 1.97 mmol) in dry THF (5 mL) at 0 °C was added a 1.0 M solution of borane–tetrahydrofuran in THF (1.97 mL, 1.97 mmol) over 15 min. The clear reaction mixture was stirred for 5 h at 0 °C and then for 17 h at 25 °C, and then it was cooled to 0 °C and water (10 mL) and saturated sodium bicarbonate (10 mL) were added. Workup and chromatography (70:30 hexanes/ethyl acetate) yielded **38** (0.338 g, 80%): ^{1}H NMR δ 6.19 (dd, 1H, *J* = 1.1, 1.2 Hz), 5.88 (t, 1H, *J* = 1.5 Hz), 4.61 (t, 1H, *J* = 7.1 Hz), 3.73 (s, 3H), 3.69 (dd, 1H, *J* = 6.6, 10.8 Hz), 3.59 (dd, 1H, *J* = 4.8, 10.8 Hz), 2.25 (m, 2H), 1.65 (m, 2H), 0.97 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 166.30, 141.32, 123.78, 82.27, 76.90, 66.15, 51.73, 38.83, 32.06, 27.62, 12.09; IR 3445, 2956, 2884, 1716, 1633, 1436, 1198, 1155, 1071 cm^{-1}; HRMS *m/z* 182.09346 ($C_{10}H_{14}O_3$, M$^+$ − CH_3OH, calcd 182.09429), 155.06999 ($C_8H_{11}O_3$, M$^+$ − $C_3H_5O_2$, 155.070811); $[\alpha]^{25}_D$ +46.50° ($CHCl_3$, *c* = 0.02 g/mL).

(3*R*,6*S*,7*S*)-(+)-Methyl 2-(2′-Ethylidene)-7-methyl-8-hydroxy-3,6-epoxyoctadienoate (39). Following a procedure identical to that used for the preparation of **38**, intermediate **37** (0.27 g, 1.11 mmol) was converted to **39** (0.20 g, 79%): ^{1}H NMR δ 6.25 (q, 1H, *J* = 6.9 Hz), 4.43 (t, 1H, *J* = 6.5 Hz), 3.86 (q, 1H, *J* = 6.6 Hz), 3.66 (s, 3H), 3.51 (m, 2H), 2.04 (m, 1H), 1.93 (d, 3H, *J* = 7.2 Hz), 1.90 (m, 2H), 1.61 (m, 2H), 0.87 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 167.20, 135.73, 133.20, 81.89, 78.53, 65.64, 51.01, 38.74, 31.66, 27.41, 15.21, 12.15; IR 3442 (broad), 2955, 2884, 1714, 1649, 1438, 1336, 1255, 1223, 1155 cm^{-1}; HRMS *m/z* 213.11215 ($C_{11}H_{17}O_4$, M$^+$ − CH_3, calcd 213.11267); $[\alpha]^{25}_D$ +25.74° ($CHCl_3$, *c* = 0.06 g/mL).

(2*S*,3*R*,6*S*,7*S*)-(+)-Methyl 8-Hydroxy-2,7-dimethyl-3,6-epoxyoctadienoate (14). Following a procedure identical to that used for the preparation of **28**, intermediate **38** (0.25 g, 1.17 mmol) was reduced to a 80:20 *syn:anti* mixture of diastereomers (0.182 g, 72%) which were separated by preparative HPLC. *Syn* diastereomer **14**: ^{1}H NMR δ 3.94 (m, 2H), 3.65 (s, 3H), 3.63 (dd, 1H, *J* = 10.9, 6.7 Hz), 3.53 (dd, 1H, *J* = 10.9, 4.3 Hz), 2.56 (dq, 1H, *J* = 14.2, 7.1 Hz), 2.49 (m, 1H), 1.95 (m, 2H), 1.44 (m, 2H), 1.19 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 174.79, 82.68, 80.12, 66.02, 51.63, 44.29, 37.91, 28.52, 26.75, 13.90, 11.78; IR 3440, 2952, 2884, 1732, 1455, 1196, 1044 cm^{-1}; HRMS *m/z* 217.14285 ($C_{11}H_{21}O_4$, M$^+$ + H, calcd 217.14397), 185.11735 ($C_{10}H_{17}O_3$, M$^+$ − CH_3O, calcd 185.11776), 198.12467 ($C_{11}H_{18}O_3$, M$^+$ − H_2O, calcd 198.12559); $[\alpha]^{25}_D$ +25.36° ($CHCl_3$, *c* = 0.02

g/mL). *Anti* diastereomer: ^{1}H NMR δ 3.94 (m, 2H), 3.65 (s, 3H), 3.63 (dd, 1H, *J* = 6.6, 10.9 Hz), 3.49 (dd, 1H, *J* = 4.0, 10.9 Hz), 2.68 (m, 1H), 2.51 (dq, 1H, *J* = 7.0, 1.2 Hz), 1.93 (m, 2H), 1.61 (m, 2H), 1.09 (d, 3H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 175.20, 82.91, 80.64, 65.94, 51.66, 44.91, 37.84, 28.73, 26.59, 13.51, 11.85; HRMS *m/z* 198.1250 ($C_{11}H_{18}O_3$, M − H_2O, calcd 198.12559); $[\alpha]^{25}_D$ −20.08° ($CHCl_3$, *c* = 0.017 g/mL).

(2*S*,3*R*,6*S*,7*S*)-(+)-Methyl 2-Ethyl-7-methyl-8-hydroxy-3,6-epoxyoctadienoate (15). Following a procedure identical to that used for the preparation of **28**, intermediate **39** (0.11 g, 0.48 mmol) was reduced to a 84:16 *syn*:*anti* mixture of diastereomers (0.097 g, 88%) which were separated by preparative HPLC. *Syn* diastereomer **15**: ^{1}H NMR δ 3.90 (m, 2H), 3.61 (s, 3H), 3.50 (m, 2H), 2.42 (m, 1H), 1.91 (m, 3H), 1.65 (m, 4H), 0.83 (t, 3H, *J* = 7.3 Hz), 0.82 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 174.21, 82.30, 79.23, 65.82, 52.64, 51.33, 38.09, 28.40, 26.81, 22.66, 11.70 (two signals); IR 3442, 2964, 2931, 2878, 1737, 1461, 1437, 1383, 1270, 1199, 1166 cm^{-1}; HRMS *m/z* 199.13374 ($C_{11}H_{19}O_3$, M$^+$ − CH_3O, calcd 199.13341); $[\alpha]^{25}_D$ +14.15° ($CHCl_3$, *c* = 0.008 g/mL). *Anti* diastereomer: ^{1}H NMR δ 3.95 (m, 2H), 3.67 (s, 3H), 3.55 (m, 2H), 2.32 (m, 1H), 1.98 (m, 2H), 1.84 (m, 1H), 1.59 (m, 4H), 0.88 (t, 3H, *J* = 7.6 Hz), 0.84 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 174.72, 82.75, 80.12, 65.87, 53.87, 53.30, 51.48, 27.78, 29.37, 26.45, 22.36, 11.88 (two overlapping signals); HRMS *m/z* 199.13294 ($C_{11}H_{19}O_3$, M$^+$ − OCH_3, calcd 199.13341); $[\alpha]^{25}_D$ −11.38° ($CHCl_3$, *c* = 0.006 g/mL).

(2*S*,3*R*,6*S*)-Methyl 8-Oxo-2-methyl-3,6-epoxyoctanoate (40). To a stirring suspension of pyridinium chlorochromate (0.135 g, 0.63 mmol) in 10 mL of CH_2Cl_2 containing 0.1 g of $MgSO_4$ and 0.1 g of KOAc was added, dropwise, the alcohol **9**[12] (3.46 g, 16.05 mmol) in 5 mL of CH_2Cl_2. After 2 h at room temperature, the mixture was diluted with ether and filtered through a pad of Florisil, and the resulting colorless solution was concentrated to yield **40** (0.09 g, 70%). NMR spectrometry indicated clean formation of the product, and it was used without further characterization in order to avoid epimerization and decomposition: ^{1}H NMR δ 9.72 (t, 1H, *J* = 2.1 Hz), 4.28 (p, 1H, *J* = 6.8 Hz), 3.97 (q, 1H, *J* = 6.9 Hz), 3.62 (s, 3H), 2.59–2.46 (m, 3H), 2.08–1.92 (m, 2H), 1.73–1.50 (m, 2H), 1.13 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR δ 201.06, 175.75, 80.42, 74.13, 51.58, 49.50, 44.63, 31.01, 28.69, 13.68.

(2*S*,3*R*,6*S*)-Methyl 2-Ethyl-8-oxo-3,6-epoxyoctanoate (41). Following a procedure identical to that used for the preparation of **40**, alcohol **13** (0.05 g, 0.23 mmol) was oxidized to **41** (29.6 mg, 60%). NMR spectrometry indicated clean formation of the product, and it was used without further characterization in order to avoid epimerization and decomposition: ^{1}H NMR δ 9.73 (t, 1H, *J* = 2.1 Hz), 4.26 (p, 1H, *J* = 6.7 Hz), 3.97 (q, 1H, *J* = 7.0 Hz), 3.63 (s, 3H), 2.52 (m, 3H), 1.99 (m, 2H), 1.64 (m, 4H), 0.85 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 200.98, 174.75, 79.70, 74.02, 52.57, 51.37, 49.59, 30.87, 28.62, 22.74, 11.69.

(2*S*,3*R*,6*S*,7*R*)-Methyl 2,7-Dimethyl-8-oxo-3,6-epoxyoctanoate (42). Following a procedure identical to that used for the preparation of **40**, the alcohol **14** (0.05 g, 0.23 mmol) was oxidized to **42** (0.044 g, 90%). NMR spectrometry indicated clean formation of the product, and it was used without further characterization in order to avoid epimerization and decomposition: ^{1}H NMR δ 9.70 (d, 1H, *J* = 1.2 Hz), 4.10 (m, 1H), 3.94 (m, 1H), 3.63 (s, 3H), 2.50 (m, 2H), 1.96 (m, 2H), 1.66 (m, 2H), 1.18 (d, 3H, *J* = 6.7 Hz), 1.06 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR δ 203.94, 174.76, 80.03, 78.70, 51.53, 50.37, 44.42, 28.80, 28.21, 13.83, 9.19.

(2*S*,3*R*,6*S*,7*R*)-Methyl 2-Ethyl-7-methyl-8-oxo-3,6-epoxyoctanoate (43). Following a procedure identical to that used for the preparation of **40**, the alcohol **15** (0.06 g, 0.26 mmol) was oxidized to **43** (0.05 g, 91%). NMR spectrometry indicated clean formation of the product, and it was used without further characterization in order to avoid epimerization and decomposition: ^{1}H NMR δ 9.65 (s, 1H), 4.02 (m, 1H), 3.89 (m, 1H), 3.60 (s, 3H), 2.50 (m, 1H), 2.37 (m, 1H), 1.89 (m, 2H), 1.78 (m, 4H), 1.02 (d, 3H, *J* = 7.0 Hz), 0.82 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 203.86, 174.17, 79.29, 78.56, 52.26, 51.29, 50.35, 28.72, 28.07, 22.73, 11.63, 9.06.

(2*S*,3*R*,6*S*,8*S*)-Methyl 8-Hydroxy-2-methyl-3,6-epoxy-10-undecenoate (44). To a stirring solution of **40** (55 mg, 0.275 mmol) in dry dichlomethane (10 mL) at −78 °C under nitrogen was added $TiCl_4$ (0.55 mL of a 1 M solution in CH_2Cl_2, 0.55 mmol). After 15 min, allyltrimethylsilane (0.07 mL, 0.413 mmol) was added, and the resulting solution was stirred for 30 min at −78 °C. Saturated $NaHCO_3$ was added, and workup and chromatography (70:30 hexanes/ethyl acetate) yielded the product as a 15:85 *syn*/*anti* mixture (0.15 mg, 77%). The two diastereomers were separated by preparative HPLC and characterized by NMR spectrometry, and the *anti* isomer was carried on to the next step without further characterization. *Anti* diastereomer **44**: HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 42.2 min; ^{1}H NMR δ 5.79 (m, 1H), 5.10 (m, 2H), 4.11 (m, 1H), 3.89 (m, 2H), 3.65 (s, 3H), 2.57 (p, 1H, *J* = 7.0 Hz), 2.24 (m, 2H), 2.00–1.89 (m, 2H), 1.80–1.53 (m, 4H), 1.19 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 174.86, 135.00, 117.51, 80.47, 77.11, 68.30, 51.63, 44.75, 41.87, 40.75, 30.81, 28.83, 13.93; IR 3519, 3072, 2943, 2882, 1731, 1637 cm^{-1}. *Syn* diastereomer: HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 27.5 min; ^{1}H NMR δ 5.82 (m, 1H), 5.09 (m, 2H), 4.02 (m, 2H), 3.85 (m, 1H), 3.65 (s, 3H), 2.55 (p, 1H, *J* = 7.2 Hz), 2.15 (m, 2H), 2.12–1.98 (m, 2H), 1.80–1.35 (m, 4H), 1.19 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 174.79, 134.97, 117.20, 80.95, 80.12, 71.14, 51.67, 44.81, 41.92, 39.72, 31.85, 28.54, 13.90.

(2*S*,3*R*,6*S*,8*S*)-Methyl 2-Ethyl-8-hydroxy-3,6-epoxy-10-undecenoate (45). Following a procedure identical to that used for the preparation of **44**, intermediate **41** (0.02 g, 0.093 mmol) was converted to a 14:86 *syn*:*anti* mixture of products (0.0174 g, 73%). The two diastereomers were separated by preparative HPLC and characterized by NMR spectrometry, and the *anti* isomer was carried on to the next step without further characterization. *Anti* diastereomer **45**: HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 13.5 min; ^{1}H NMR δ 5.80 (m, 1H), 5.07 (m, 2H), 4.09 (m, 1H), 3.92 (m, 2H), 3.64 (s, 3H), 2.46 (m, 1H), 2.23 (t, 2H, *J* = 6.3 Hz), 1.97 (m, 2H), 1.61 (m, 6H), 0.88 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 174.31, 134.98, 117.48, 79.71, 77.01, 68.30, 52.65, 51.41, 41.83, 40.79, 30.64, 28.76, 22.83, 11.78. *Syn* diastereomer: HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 9.4 min; ^{1}H NMR δ 5.80 (m, 1H), 5.10 (m, 2H), 4.08 (m, 2H), 3.87 (m, 1H), 2.41 (m, 1H), 2.24 (m, 2H), 1.99 (m, 2H), 1.66 (m, 6H), 0.86 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 174.25, 134.96, 117.19, 80.09, 79.32, 71.32, 52.67, 51.46, 41.91, 41.54, 31.70, 28.52, 22.83, 11.65.

(2*S*,3*R*,6*S*,7*S*,8*S*)-Methyl 8-Hydroxy-2,7-dimethyl-3,6-epoxy-10-undecenoate (46). Following a procedure identical to that used for the preparation of **44**, intermediate **42** (0.04 g, 0.187 mmol) was converted to **46** (0.04 g, 84%). HPLC and NMR analysis indicated <1% of the *syn* diastereomer. The product was characterized by NMR spectrometry and carried on to the next step without further characterization: ^{1}H NMR δ 5.87 (m, 1H), 5.08 (m, 2H), 4.06 (m, 1H), 3.91 (q, 1H, *J* = 6.8 Hz), 3.64 (s, 3H), 3.32 (m, 1H), 2.57 (p, 1H, *J* = 7.1 Hz), 2.23 (m, 3H), 1.91 (m, 2H), 1.66 (m, 2H), 1.19 (d, 3H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 174.72, 135.36, 116.99, 81.19, 80.27, 73.12, 51.63, 44.32, 39.57, 29.66, 28.66, 26.82, 14.07, 11.72.

(2*S*,3*R*,6*S*,7*S*,8*S*)-Methyl 2-Ethyl-8-hydroxy-7-methyl-3,6-epoxy-10-undecenoate (47). Following a procedure identical to that used for the preparation of **44**, intermediate **43** (0.05 g, 0.22 mmol) was converted to **47** (0.05 g, 84%). HPLC and NMR analysis indicated <1% of the *syn* diastereomer. The product was characterized by NMR spectrometry and carried on to the next step without further characterization: ^{1}H NMR δ 5.85 (m, 1H), 5.06 (m, 2H), 4.05 (m, 1H), 3.86 (m, 1H), 3.63 (s, 3H), 3.55 (m, 1H), 2.40 (m, 1H), 2.21 (m, 2H), 1.86 (m, 3H), 1.64 (m, 4H), 0.83 (t, 3H, *J* = 7.2 Hz), 0.82 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 174.13, 135.38, 117.04, 81.12, 79.52, 73.22, 52.17, 51.47, 39.55 (two overlapping signals), 28.67, 26.75, 22.89, 11.74 (2 overlapping signals).

(2*S*,3*R*,6*S*,8*S*)-(+)-Methyl 8-Hydroxy-2-methyl-3,6-epoxy-10-undecanoate (8). A solution of **44** (50 mg, 0.21 mmol) and 0.045 g of palladium on activated carbon in absolute ethanol (10 mL) was stirred at 25 °C under 1 atm of hydrogen gas for 4 h. The mixture was then filtered through Celite, concentrated, and chromatographed (silica gel, 70:30 hexanes/ethyl acetate) to yield **8** (36 mg, 71%): HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 21.5 min; ^{1}H NMR δ 4.14 (m, 1H), 3.99 (q, 1H, *J* = 7.1 Hz), 3.83 (m, 1H), 3.68 (s, 3H), 2.58 (p, 1H, *J* = 7.1 Hz), 1.97 (m, 2H), 1.69–1.39 (m, 8H), 1.23 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR δ 174.58, 80.22, 76.10, 68.51, 51.35, 44.46, 40.83, 39.20, 30.46, 28.55, 18.68, 13.83, 13.68; HRMS

m/z 245.17527 ($C_{13}H_{25}O_4$, M + H, calcd 245.17638); $[\alpha]^{25}_D$ +20.30° ($CHCl_3$, *c* = 0.012 g/mL).

(2*S*,3*R*,6*S*,8*S*)-(+)-Methyl 2-Ethyl-8-hydroxy-3,6-epoxy-10-undecanoate (10). Following a procedure identical to that used for the preparation of **8**, intermediate **45** (0.012 g, 0.047 mmol) was converted to **10** (0.0109 g, 90%): ^{1}H NMR δ 4.10 (m, 1H), 3.94 (q, 1H, *J* = 8.1 Hz), 3.81 (m, 1H), 3.66 (s, 3H), 2.45 (dt, 1H, *J* = 8.5 Hz, J = 5.4 Hz), 1.92 (m, 2H), 1.63 (m, 6H), 1.42 (m, 4H), 0.90 (t, 3H, *J* = 6.8 Hz), 0.88 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR δ 174.31, 79.75, 77.21, 68.82, 52.63, 51.46, 41.03, 39.43, 30.57, 28.76, 22.87, 18.99, 14.12, 11.81; IR 3519, 2959, 2931, 2873, 1735, 1460, 1437, 1266, 1196, 1072 cm^{-1}; HRMS *m/z* 215.1281 ($C_{11}H_{19}O_4$, $M^+ - C_3H_7$, calcd 215.1283), 197.1165 ($C_{11}H_{17}O_3$, $M^+ - C_3H_7 - H_2O$, calcd 197.1178), 113.05919 ($C_6H_9O_2$, $M^+ - C_3H_7 - C_5H_{10}O_2$ (McLafferty), calcd 113.06025); $[\alpha]^{25}_D$ +18.50° ($CHCl_3$, *c* = 0.002 g/mL).

(2*S*,3*R*,6*S*,7*S*,8*S*)-(+)-Methyl 8-Hydroxy-2,7-dimethyl-3,6-epoxyundecanoate (11). Following a procedure identical to that used for the preparation of **8**, intermediate **46** (0.04 g, 0.156 mmol was converted to **11** (0.029 g, 71%): ^{1}H NMR δ 4.06 (m, 1H), 3.90 (m, 1H), 3.64 (s, 3H), 3.53 (m, 1H), 2.57 (q, 1H, *J* = 7.1 Hz), 2.22 (m, 1H), 2.03–1.61 (m, 5H), 1.49–1.31 (m, 3H), 1.19 (d, 3H, *J* = 6.9 Hz), 0.88 (m, 6H); ^{13}C NMR δ 174.71, 81.37, 80.29, 73.67, 51.61, 44.29, 39.95, 37.95, 37.46, 28.59, 26.72, 18.75, 14.18, 14.07, 12.05; IR 3500, 2957, 2872, 1732, 1462, 1377, 1336, 1258, 1199, 1167, 1057 cm^{-1}; HRMS *m/z* 259.19092 ($C_{14}H_{27}O_4$, M + H, calcd 259.19099); $[\alpha]^{25}_D$ +8.00° ($CHCl_3$, *c* = 0.06 g/mL).

(2*S*,3*R*,6*S*,7*S*,8*S*)-(−)-Methyl 8-Hydroxy-2-ethyl-7-methyl-3,6-epoxyundecanoate (12). Following a procedure identical to that used for the preparation of **8**, intermediate **47** (10.0 mg, 0.037 mmol) was converted to **12** (7.6 mg, 75%): ^{1}H NMR δ 4.08 (m, 1H), 3.90 (q, 1H, *J* = 7.1 Hz), 3.70 (s, 3H), 3.56 (m, 1H), 2.46 (m, 2H), 1.82 (m, 6H), 1.39 (m, 4H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.85 (t, 6H, *J* = 7.4 Hz); ^{13}C NMR δ 174.21, 81.29, 79.53, 73.78, 52.12, 51.47, 39.96, 37.54, 28.62, 26.69, 22.89, 18.82, 14.23, 12.06, 11.74; IR 3460, 2962, 2919, 2875, 1737, 1462, 1266, 1233, 1058 cm^{-1}; HRMS *m/z* 273.20798 ($C_{15}H_{29}O_4$, M + H, calcd 273.20657), 254.1879 ($C_{15}H_{26}O_3$, $M - H_2O$, calcd 254.1882), 241.1806 ($C_{14}H_{25}O_3$, $M - OCH_3$, calcd 241.1804); $[\alpha]^{25}_D$ −6.33° ($CHCl_3$, *c* = 0.002 g/mL).

(2*R*,3*R*,6*S*,8*S*)-(+)-1,8-Bis[(4′-bromobenzoyl)oxy]-2-methyl-3,6-epoxyundecane (48). To a stirring, cooled (0 °C) solution of **8** (0.02 g, 0.08 mmol) in dry ether (15 mL) was added lithium aluminum hydride (0.003 g, 0.08 mmol) under nitrogen. The solution was stirred at room temperature for 30 min and then cooled to 0 °C, and 1 N NaOH (0.1 mL) and water (0.2 mL) were successively added. The resulting mixture was dried, concentrated, and chromatographed (60:40 hexanes/ethyl acetate) to yield **(2*S*,3*R*,6*S*,8*S*)-2-methyl-3,6-epoxyundecane-1,8-diol** (0.013 g, 75%): ^{1}H NMR δ 4.09 (m, 1H), 3.96 (m, 1H), 3.80 (m, 1H), 3.67 (dd, 1H, *J* = 10.8 Hz, 6.8 Hz), 3.55 (dd, 1H, *J* = 10.8, 4.8 Hz), 1.78–1.29 (m, 8H), 1.94 (m, 2H), 0.93 (t, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 82.23, 76.74, 68.86, 65.95, 41.54, 39.75, 33.53, 31.05, 27.30, 18.89, 14.08, 12.10; IR 3378, 2955, 2931, 2872, 1460, 1044 cm^{-1}. A solution of this diol (0.013 g, 0.06 mmol), triethylamine (0.04 mL, 0.3 mmol), 4(*N*,*N*-dimethylamino)-pyridine (0.0007 g, 0.006 mmol), and 4-bromobenzoyl chloride (0.053 g, 0.24 mmol) in dichloromethane (10 mL) was stirred for 12 h at 25 °C. Workup and chromatography (95:5 hexanes/ethyl acetate) yielded **48** (0.017 g, 50%): HPLC retention time (95:5 hexanes/ethyl acetate at 1 mL/min) 13.3 min; ^{1}H NMR δ 7.90 (d, 2H, *J* = 8.6 Hz), 7.89 (d, 2H, *J* = 8.6 Hz), 7.58 (d, 2H, *J* = 8.6 Hz), 7.57 (d, 2H, *J* = 8.6 Hz), 5.27 (tt, 1H, *J* = 6.5, 5.5 Hz), 4.26 (dd, 1H, *J* = 10.9, 5.9 Hz), 4.16 (dd, 1H, *J* = 10.9, 6.6 Hz), 4.18 (dd, 1H, *J* = 10.9, 6.6 Hz), 3.91 (p, 1H, *J* = 6.5 Hz), 3.81 (q, 1H, *J* = 6.2 Hz), 2.10–1.92 (m, 4H), 1.50–1.30 (m, 8H), 1.04 (d, 3H, *J* = 6.8 Hz), 0.93 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.84, 165.41, 131.71, 131.64, 131.09 (two overlapping signals), 129.64, 129.27, 127.98, 127.82, 80.11, 76.04, 73.32, 67.66, 40.49, 37.61, 36.93, 31.79, 28.65, 18.43, 13.98, 13.02; IR 2966, 2931, 2872, 2367, 2249, 1725, 1713, 1590, 1484, 1396, 1279, 1114 cm^{-1}; $[\alpha]^{25}_D$ + 24.7° ($CHCl_3$, *c* = 0.003 g/mL) [lit.[5] $[\alpha]^{25}_D$ +27.2° ($CHCl_3$)].

(2S,3R,6S,8S)-(−)-2,7-Dimethyl-3,6-epoxyundecane-1,8-diol (49). Following a procedure identical to that used for the first step in the preparation of **48**, the hydroxy ester **11** (0.03 g, 0.116 mmol) was reduced to the diol **49** (0.024 g, 91%): ^{1}H NMR δ 4.02 (m, 1H), 3.86 (m, 1H), 3.54 (m, 3H), 1.86 (m, 4H), 1.66 (m, 2H), 1.43 (m, 4H), 0.89 (m, 4H); ^{13}C NMR δ 81.62, 80.91, 73.61, 65.82, 40.48, 38.88, 37.29, 27.61, 27.04, 18.72, 14.19, 12.16, 11.90; $[]^{25}_D$ −19.10° (benzene, *c* = 0.06 g/mL) [Lit.[5] $[\alpha]^{25}_D$ −20° (benzene, *c* = 1.0)].

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds **8**, **10–15**, **17–20**, **23–27**, **31–33**, and **35–49** (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.