Syntheses of Enantiomerically Pure Tetrahydrofuran Building Blocks for Nactin and Pamamycin Antibiotics via an Enzymatically Resolved γ-Hydroxyallene

Robert D. Walkup,* Sang Woong Kim, and Stephen D. Wagy

Department of Chemistry and Biochemistry Texas Tech University Lubbock, Texas 79409-1061

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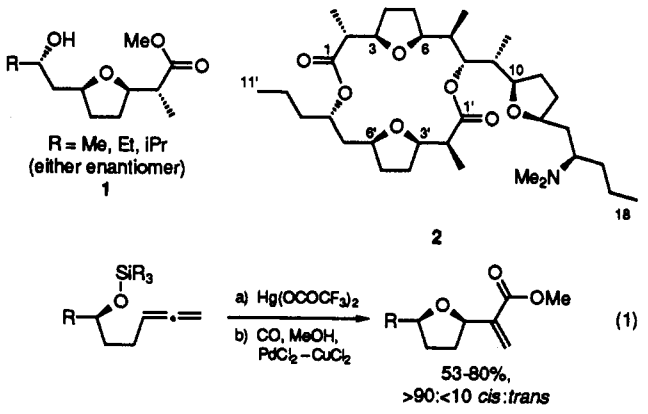
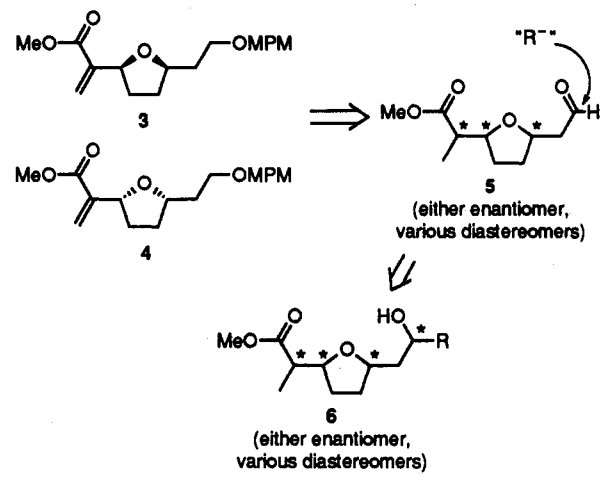
We have reported short synthetic routes to the racemic nonactic acid esters **1**[1] and to a racemic ester representing the C_1–$C_{11'}$ portion of pamamycin-607 **2**[2] using the stereoselective conversion of γ-(silyloxy)allenes to *cis* 5-substituted tetrahydrofuran-2-ylacrylates (eq 1), a one-pot process which proceeds via an intramolecular oxymercuration followed by a palladium(II)-mediated methoxycarbonylation.[1,3,4] In the interest of making this allene-based methodology more useful for the synthesis of such

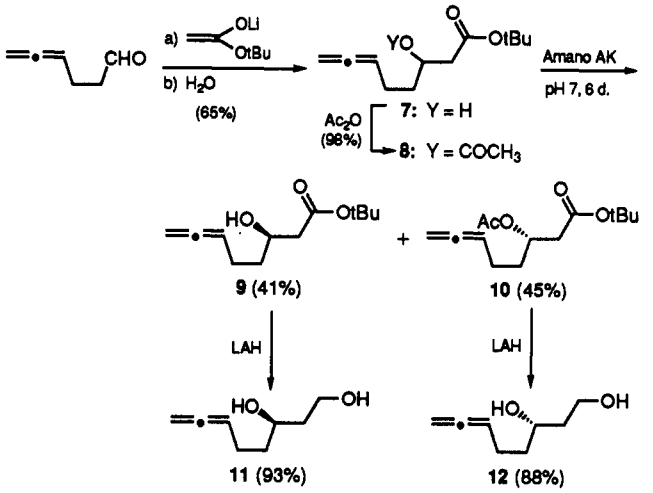


cis-tetrahydrofuran-containing antibiotics (or antibiotic subunits) as **1** and **2**, we directed our attention at using it to produce, as pure enantiomers, the tetrahydrofuranylacrylates **3** and **4** which, via the derived aldehydes **5** could be converted into any of a number of nonracemic nonactates or nonactate-like intermediates **6** using substrate-controlled nucleophilic additions like those developed by Ireland[5] and refined by Lygo[6] and Baldwin[7] for such β-(tetrahydrofuran-2-yl)propanal substrates **5**, as indicated in Scheme I. In this Note, we report the syntheses of the two enantiomeric tetrahydrofurans **3** and **4** by a common route which involves, as key steps, the lipase-catalyzed resolution of *tert*-butyl 3-acetoxy-6,7-octadienoate and the aforementioned *cis*-selective allene

Scheme I



Scheme II



cyclization. We also report the conversions of **3** and **4** into advanced intermediates for the syntheses of the nonactic acids and the pamamycins.[8,9]

Addition of the lithium enolate of *tert*-butyl acetate[10] to 4,5-hexadienal[11] proceeded cleanly to yield the racemic β-hydroxy ester **7**, as indicated in Scheme II. Acetylation of **7** afforded the β-acetoxy ester **8** in high yield. Attempted resolutions of **8** using porcine liver esterase or porcine

(1) Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597–1603; Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 5388.

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

(3) Gallagher has developed similar methodology for the cyclizations of aminoallenes and derivatives, using palladium(II) to bring about the cyclization as well as the methoxy carbonylation. For leading references, see (a) 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. (b) Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697–4710.

(4) An early report described an intermolecular variant of this reaction, where the initial oxy-metalation is mediated by palladium(II): Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Chem. Soc., Chem. Commun.* **1984**, 905–906.

(5) Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, *59*, 572–583.

(6) Lygo, B.; O'Connor, N. *Tetrahedron Lett.* **1987**, *28*, 3597–3600.

(7) (a) Baldwin, S. W.; McIver, J. M. *J. Org. Chem.* **1987**, *52*, 320–322. (b) Baldwin, S. W.; McIver, J. M. *Tetrahedron Lett.* **1991**, *32*, 1937–1940.

(8) For reports of previous syntheses of methyl nonactate, see the literature cited in ref 1 and (a) Lygo, B.; O'Conner, N.; Wilson, P. R. *Tetrahedron* **1988**, *44*, 6881–6888. (b) Deschenaux, P.-F.; Jacot-Gillarmod, A. *Helv. Chem. Acta* **1990**, *73*, 1861–1864. (c) Iqbal, J.; Pandey, A.; Chauhan, B. P. S. *Tetrahedron* **1991**, *47*, 4143–4154. (d) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557–2560. (e) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1993**, *34*, 1609–1610. For previous syntheses of methyl homononactate, see ref 1 and (f) Schmidt, U.; Werner, J. *Synthesis* **1986**, 986–992. (g) Schmidt, U.; Werner, J. *J. Chem. Soc., Chem. Commun.* **1986**, 996–998.

(9) Leading reference on the occurence of pamamycin-607 and related antibiotics: (a) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett.* **1991**, *32*, 3087–3090. For a report of synthetic research related to the pamamycins, see (b) Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829–6832.

(10) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050–3051.

(11) Synthesized by pyridinium chlorochromate oxidation of 4,5-hexadien-1-ol, which in turn was synthesized by the "homologation" of 4-pentyn-1-ol using the method of Crabbe (Crabbe, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Syn.* **1984**, *63*, 203–205) or by the allenyllithium-based route of Gore (Arsiniyadis, S.; Gore, J.; Roumestant, M. L. *Tetrahedron* **1979**, *35*, 353–363). This aldehyde has been reported previously, synthesized by a different route (Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597–3607).

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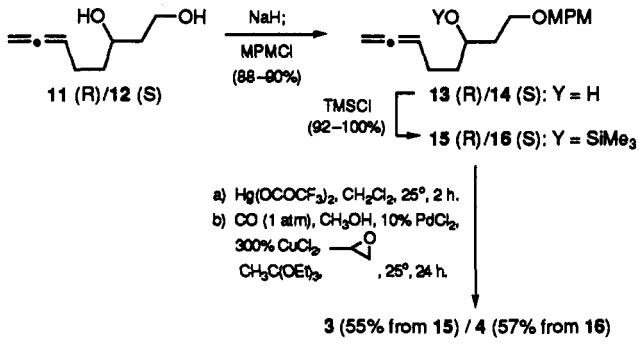
Scheme III



pancreatic lipase were unsuccessful,[12] but the resolution using the Amano AK lipase, as reported by Sih and coworkers for simpler *tert*-butyl β-acetoxy esters,[13] proceeded cleanly and efficiently to yield, upon chromatographic workup, the (*R*) alcohol **9** and the (*S*) diester **10**, each in high yield and in high enantiomeric excess, as discussed below. Reduction of the hydroxy ester **9** and the diester **10** using lithium aluminum hydride cleanly produced the (*R*) and the (*S*) enantiomers of 6,7-octadiene-1,3-diol, **11** and **12**, respectively.

Each of the enantiomeric diols **11** and **12** were subjected to the sequence indicated in Scheme III to form the tetrahydrofurans **3** and **4**. Sequential alkylation (to **13**, **14**)[14] and silylation of the two hydroxyl groups yielded the diethers **15** and **16**, which underwent cyclization–methoxycarbonylation to produce the desired products **3** and **4**, respectively, with stereospecificities of >95:<5 *cis*/*trans*, according to ^{1}H-NMR analyses of the crude reaction mixtures.[15] The minor *trans* diastereomers were not isolated, and the pure *cis*-tetrahydrofurans **3** and **4** were obtained in stereochemically pure form by flash chromatography.

The experimental conditions used for the cyclization–methoxycarbonylation reported here feature two improvements over the previously reported cyclizations of this type: (1) The *trimethylsilyl* ether group γ to the allene was used as the labile ether whose role is to guide the stereoselectivity, instead of the more expensive and less reliable *tert*-butyldimethylsilyl ether group used in previous applications of this transformation.[1,2,16] (2) The inclusion of propylene oxide, to scavenge the hydrochloric acid byproduct from the copper(II) chloride oxidation of palladium(0) to palladium(II) chloride, and triethyl orthoacetate, to scavenge water. The latter protocol, which was reported by Tamaru and co-workers for their reactions which utilized $PdCl_2$–$CuCl_2$–methanol conditions,[17] resulted in improved yields of the acid-sensitive acrylate products. The moderate yields of **3** and **4** observed (55%, 57%) are attributed to losses of material during silica gel chromatography.

The enantiomeric purity of each of the lipase-derived products **9** and **10** was assessed by ^{1}H-NMR spectrometry using the tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) (Eu(hfc)$_3$) chiral shift reagent.[18] The addition of 0.1 mol equiv of Eu(hfc)$_3$ to the racemic alcohol **7** resulted in a clean "splitting" of the singlet for the *tert*-butyl group (as well as other signals) into two singlets, thus allowing for the accurate integration of each. The resolved alcohol **9**, when treated in like manner, exhibited the two signals in a >97:<3 ratio, thus indicating, as a conservative estimate, a ~95% enantiomeric excess (ee) for **9**. Similarly, comparison of the Eu(hfc)$_3$-resolved spectra of the racemic diester **8** with that for the resolved diester **10**, again observing the signal for the *tert*-butyl group's protons, indicates a ~93% enantiomeric excess for **10**. These chemical shift experiments have been repeated at least five times, using different "batches" of resolved materials, and in each case the same results (with slight variations in chemical shifts and degree of splitting, attributable to variations in the amounts of added shift reagent for each experiment) were obtained. In addition, the specific rotations measured for **11** and **12** (+5.7° and −5.2°, respectively), for **13** and **14** (+13.1° and −12.8°, respectively), and for **3** and **4** (−26.1° and +24.9°, respectively) and the rotations observed for the compounds subsequently derived from **3** and **4** (see discussion below and Experimental Section) all agree with the conclusion that the lipase resolution produced **9** and **10** in comparably high enantiomeric excesses, with the hydroxy ester **9** being formed in slightly higher ee than the diester **10**.

In order to verify the assignments of the absolute configurations to the lipase-produced products **9** and **10**, which were initially assigned on the basis of Sih's precedent,[13] and to demonstrate the synthetic applicability of the tetrahydrofuran intermediates **3** and **4**, the latter were each converted to the enantiomeric hydroxy esters **17** and **18**, respectively, which are the synthetic intermediates reported by Ireland and Vevert for their carbohydrate-based syntheses of the two enantiomers of methyl nonactate.[5] As indicated in Scheme IV, removal of the MPM protecting group from **3** gave the hydroxy ester **19**.[14] Hydrogenation of **19** yielded the separable *anti* and *syn* diastereomers **17** and **20**, respectively, in approximately equal amounts. (Attempts to find reduction conditions which favor the formation of the *anti* diastereomer, necessary for the syntheses of nonactate esters, have been unsuccessful so far, as discussed in ref 1). For application to the synthesis of the C_1–$C_{11'}$ portion of pamamycin-607 (**2**), we desired the *syn* diastereomer **22** of this enantiomer. Therefore, a stereospecific reduction of **4** using magnesium

(12) Recent review: Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140.

(13) Scilimati, A.; Ngooi, T. K.; Sih, C. J. *Tetrahedron Lett.* **1988**, *29*, 4927–4930. For a relevant application of an Amano AK resolution of a β-acetoxy ester in a natural products synthesis, see Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 6449–6452.

(14) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.

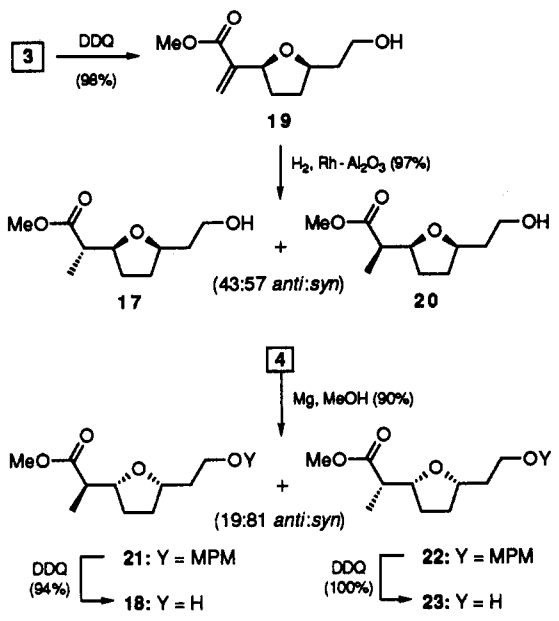
(15) As a "control" experiment, the cyclization–methoxycarbonylation reaction was performed using the racemic *alcohol* **13/14**, resulting in the formation of a ~50:50 mixture of *cis* and *trans* isomers of **3**/**4** (see Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023–1026); NMR analysis of the mixture indicated separate, integratable signals for several of the hydrogens in each of the two diastereomers. The ^{1}H-NMR spectrum indicates that the discernible chemical shifts for the signals for the hydrogens on the side chains (acrylate and MPMOCH$_2$CH$_2$) are consistently downfield for the *cis* diastereomer, relative to the *trans* diastereomer, and the signals for the ring methine hydrogens are consistently upfield for the *cis* diastereomer, relative to the trans diastereomer. This means of assigning *cis*/*trans* geometries, and of discerning *cis*/*trans* ratios to the product mixtures, has proven to be reliable, as evidenced by our earlier syntheses of the nonactate esters (ref 1).

(16) In fact, we found that the *tert*-butyldimethylsilyl ether counterpart to **15**/**16** did not cleanly undergo the cyclization–methoxycarbonylation, producing instead a complex mixture of acyclic unsaturated products along with small amounts of the desired product. This observation, which we have since made for other similar substrates, suggests that the trialkylsilyl ether employed as a stereodirecting group must possess some optimum steric bulk and/or lability in order for the mercury(II)-mediated cyclization to proceed.

(17) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, *56*, 1099–1105.

(18) Sullivan, G. R. *Top. Stereochem.* **1977**, *10*, 287–329.

Scheme IV



in methanol, as precedented by our earlier work with such reductions,[1,2] yielded the *anti* (**21**) and *syn* (**22**) esters in a 19:81 ratio. Removal of the MPM protecting group from **21** and **22** yielded **18** and **23**, respectively.[14] The assignments made to each diastereomer (*anti* vs *syn*) in the **17**/**20** and **18**/**23** series were based on the consistent trends in HPLC and ^{1}H-NMR behavior previously noted for diastereomers of this type.[1,2]

The specific rotations observed by us for the enantiomeric *anti* hydroxy esters **17** and **18** (+13.5° and −13.0°, respectively) were consistent with our earlier measurements (discussed above) and agreed with the *signs* of the rotations reported by Ireland and Vevert;[5] however, they differed in magnitude by a factor of 2 (Ireland and Vevert: +26.0° and −26.3° for their **17** and **18**, respectively).[19] The values obtained by us were reproducible for different "batches" of the products brought up separately, and ^{1}H-NMR experiments comparing the effects of the chiral shift reagent Eu(hfc)$_3$ upon racemic **17**/**18** versus **17**, observing, for example, the splitting of the peaks for the methyl ester group indicated, in agreement with the other NMR chiral shift experiments, that the products produced in the present work were of high (>90%) enantiomeric excess. The multiple measurements that we have made, all supporting a high enantiomeric excess for the intermediates reported here, support the contention that the specific rotations that we have measured may be more accurate than those previously reported.[20]

In conclusion, it has been demonstrated that enantiomeric building blocks **3** and **4** for the syntheses of tetrahydrofuranoid antibiotics can be obtained in high enantiomeric excess in five steps and each in ≥11% overall chemical yields from the same batch of 4,5-hexadienal starting material. The advanced intermediates for nonactate syntheses, **17** and **18**, can be obtained by our route in seven steps and 5% overall chemical yields from the same batch of 4,5-hexadienal (even counting the loss of half of the material due to the nonstereoselective hydrogenation step), as demonstrated by the synthesis of **17**. An advanced intermediate for the synthesis of pamamycin-607 (**2**), **23**, can be synthesized in seven steps and 8% overall yield from 4,5-hexadienal. By converting an unwanted enantiomer (**13** or **14**) to the desired enantiomer by a straightforward inversion reaction,[21] one could improve the overall yields of such intermediates. Thus an expeditious and experimentally facile route to nonactate-type products is indicated. This methodology is currently being utilized for the syntheses of the C_1–$C_{11'}$ portions of the antibiotics pamamycin-607 and pamamycin-649A.

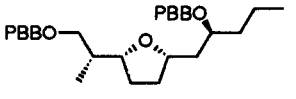
(19) The *syn* isomers **20** and **23** were also reported by Ireland and Vevert, but the specific rotations of these compounds were not reported (see Experimental Section).

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 and triethylamine were 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 and the indicated eluents. High-performance liquid chromatography (HPLC) was performed using a Dupont Zorbax-Sil column (5 μ silica gel packing, 25 cm × 4 mm ID), refractometry detection, and the isocratic hexane–ethyl acetate eluents and flow rates indicated. Infrared spectra were recorded using neat films on sodium chloride plates and are reported in wavenumbers (cm^{-1}). ^{1}H (200 or 300 MHz) and ^{13}C (50 or 75 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. 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 ^{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.

(±)-*tert*-Butyl 3-Hydroxy-6,7-octadienoate (7). To 15.0 mL of a 1.5 M solution of LDA in hexanes (22.4 mmol) and THF (40 mL) at −78 °C under nitrogen was added *tert*-butyl acetate (2.74 mL, 20.4 mmol) in THF (5 mL). After 1 h of stirring at −78 °C,

(20) As an additional indication of the accuracy of our results, we have recently (Walkup, R. D.; Kim, S. W., unpublished results) converted the hydroxy ester **23** to the bis(*p*-bromobenzoate) **i**, which exhibited an $[\alpha]_D$ of +24.7° (20 °C, c = 0.003 g/mL, $CHCl_3$), comparing well with the $[\alpha]_D$ of +27.2° (18°C, c = 0.001 g/mL, $CHCl_3$) found by Marumo and coworkers for the compound **i** derived from the natural product pamamycin-607 (**2**).



i

(PBB = *p*-bromobenzoate)

(21) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

a solution of 4,5-hexadienal (~20.4 mmol, obtained as a solution, due to its volatility, from 2.0 g of 4,5-hexadien-1-ol[11]) in THF (5 mL) was added. After stirring 1 h the cooling bath was removed and stirring continued for 30 min. The reaction was quenched by the addition of saturated ammonium chloride (10 mL) and then worked up in the usual manner. Chromatography (90:10 hexanes/ethyl acetate) yielded **7** (2.8 g, 65%): HPLC retention time (90:10 hexanes/ethyl acetate at 1 mL/min) 14.25 min; ^{1}H NMR δ 5.10 (p, J = 6.7 Hz, 1H), 4.64 (p, J = 3.3 Hz, 2H), 3.97 (m, 1H), 2.35 (m, 2H), 2.09 (m, 2H), 1.65 (m, 2H), 1.42 (s, 9H); ^{13}C NMR δ 208.5, 172.4, 89.5, 81.2, 75.2, 67.4, 42.2, 35.5, 28.1, 24.1; IR (neat) 3472, 2978, 2931, 1954, 1713, 850 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.50. Found: C, 67.50; H, 9.33.

(±)-*tert*-Butyl 3-Acetoxy-6,7-octadienoate (8). To a solution of *tert*-butyl 3-hydroxy-6,7-octadienoate (**7**) (2.8 g, 13.2 mmol), dry triethylamine (2.8 mL), and 4-(dimethylamino)-pyridine (0.24 g, 2.0 mmol) was added acetic anhydride (6.3 mL, 66.2 mmol) at 0 °C under nitrogen. The mixture was then allowed to stir at 25 °C for 5 h and then worked up in the usual manner following quenching with saturated sodium bicarbonate solution. Chromatography (95:5 hexanes/ethyl acetate) yielded 3.30 g (98%) of the pure product **8**: HPLC retention time (95:5 hexanes/ethyl acetate at 1 mL/min): 8.9 min; ^{1}H NMR δ 5.22 (p, J = 6.4 Hz, 1H), 5.08 (p, J = 6.6 Hz, 1H), 4.66 (p, J = 3.3 Hz, 2H), 2.46 (m, 2H), 2.00 (s, 3H), 1.96 (m, 2H), 1.73 (m, 2H), 1.41 (s, 9H); ^{13}C NMR: δ 208.4, 170.2, 169.4, 89.0, 80.9, 75.4, 70.2, 40.5, 33.2, 28.0, 23.9, 21.0; IR (neat) 2966, 2931, 1954, 1743, 1731, 849 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$; C, 66.12; H, 8.72. Found: C, 66.21,H, 8.82.

(*R*)-(−)-*tert*-Butyl 3-Hydroxy-6,7-octadienoate (9) and (*S*)-(−)-*tert*-Butyl 3-Acetoxy-6,7-octadienoate (10). To a solution of **8** (3.39 g, 13.3 mmol) in pH 7 phosphate buffer (80 mL) was added powdered Amano lipase AK (5.0 g). The mixture was stirred at 25 °C for 6 days, dichloromethane (300 mL) was added, and stirring was continued for 12 h. The dichloromethane layer was then separated and successively washed with saturated sodium bicarbonate (3 × 100 mL) and brine, dried over anhydrous $MgSO_4$, and then concentrated to a brown oil (3.22 g, 95%). Chromatography (95:5 hexanes/ethyl acetate) yielded 1.15 g (41%) of **9** (NMR, IR, and HPLC retention time identical to those of **7**): $[\alpha]^{26}_D$ −16.21° (CCl_4, c = 0.0174 g/mL) and 1.53 g (45%) of **10** (NMR, IR, and HPLC retention time identical to those of **8**): $[\alpha]^{26}_D$ −10.26° (CCl_4, c = 0.0175 g/mL)).

(*R*)-(+)-6,7-Octadiene-1,3-diol (11). To a solution of **9** (0.92 g, 4.3 mmol) in dry ether (30 mL) at 0 °C was added lithium aluminum hydride (0.18 g, 4.7 mmol) with stirring under nitrogen. The solution was stirred at 25 °C for 30 min and then cooled to 0 °C. 1 N Sodium hydroxide (0.2 mL) and water (0.4 mL) were successively added and then the mixture was dried over $MgSO_4$, filtered, and concentrated. Chromatography (60:40 hexanes/ethyl acetate) yielded 0.57 g (93%) of **11**: ^{1}H NMR δ 5.11 (p, J = 6.6 Hz, 1H), 4.66 (p, J = 3.3 Hz, 2H), 3.86 (m, 3H), 2.09 (m, 2H), 1.73–1.58 (m, 4H); ^{13}C NMR δ 208.4, 89.5, 75.2, 71.5, 61.7, 38.2, 36.7, 24.2; IR (neat) 3385, 2937, 2857, 1952, 848 cm^{-1}; HRMS m/z 142.0976 ($C_8H_{14}O_2$, calcd 142.0994), $[\alpha]^{26}_D$ +5.73° (CCl_4, c = 0.024 g/mL).

(*S*)-(−)-6,7-Octadiene-1,3-diol (12). Following the same procedure used for the preparation of **11**, 1.20 g (4.7 mmol) of **10** was converted to 0.59 g (88%) of **12** (NMR and IR identical to those of **11**), $[\alpha]^{26}_D$ −5.16° (CCl_4, c = 0.019 g/mL)).

(*R*)-(+)-1-[(4′-Methoxyphenyl)methoxy]-6,7-octadien-3-ol (13). A solution of **11** (0.40 g, 2.8 mmol) in dry DMF (10 mL) was added to sodium hydride (0.1248 g of 60% mineral oil dispersion, washed three times with hexanes, ~3 mmol) under nitrogen. The mixture was stirred until gas evolution ceased (~1 h) and then it was cooled to 0 °C. 4-Methoxybenzyl chloride (0.49 g, 3.12 mmol) was added dropwise over 5 min. After 10 min the cooling bath was removed and stirring was continued for 5 h. Workup followed by chromatography (80:20 hexanes/ethyl acetate) yielded **13** (0.66 g, 90%): ^{1}H NMR δ 7.25 (m, 2H), 6.85 (m, 2H), 5.10 (p, J = 6.7 Hz, 1H), 4.64 (p, J = 3.3 Hz, 2H), 4.43 (s, 2H), 3.81 (m, 1H), 3.78 (s, 3H), 3.73–3.57 (m, 2H), 2.10 (m, 2H), 1.71 (m, 2H), 1.57 (m, 2H); ^{13}C NMR δ 208.5, 159.3, 130.0, 129.3, 113.9, 89.8, 75.0, 73.0, 70.8, 68.9, 55.3, 36.5, 36.3, 24.3; IR (neat) 3436, 2931, 2861, 1954, 1173, 844, 814, 756 cm^{-1}; $[\alpha]_D$ +13.05° ($CHCl_3$, c = 0.014 g/mL); HRMS: m/z 262.1565 ($C_{16}H_{22}O_3$, calcd 262.1569

(*S*)-(−)-1-[(4′-Methoxyphenyl)methoxy]-6,7-octadien-3-ol (14). Following the procedure used for the preparation of **13**, diol **12** (0.37 g, 2.60 mmol) was converted to **14** (0.60 g, 88%) (NMR) and IR identical to those of **13**, $[\alpha]_D$ −12.81° ($CHCl_3$, c = 0.015 g/mL).

(*R*)-1-[(4′-Methoxyphenyl)methoxy]-3-(trimethylsiloxy)-6,7-octadiene (15). To a solution of **13** (0.41 g, 1.5 mmol) in dry THF (20 mL) was added triethylamine (1.1 mL, 7.8 mmol) and chlorotrimethylsilane (0.6 mL, 4.7 mmol). The solution was stirred for 5 h and then worked up. Chromatography (95:5 hexanes/ethyl acetate) yielded **15** (0.52 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), 6.86 (m, 2H), 5.07 (p, J = 6.7 Hz, 1H), 4.64 (p, J = 3.3 Hz, 2H), 4.40 (dd, J = 13.6, 11.5 Hz, 2H), 3.85 (m, 1H), 3.78 (s, 3H), 3.48 (t, J = 6.7 Hz, 2H), 2.08–1.95 (m, 2H), 1.75 (m, 2H), 1.57 (m, 2H), 0.09 (s, 9H); ^{13}C NMR δ 208.5, 159.1, 130.6, 129.3, 113.7, 89.9, 75.1, 72.6, 69.0, 66.8, 55.3, 37.4, 36.8, 24.1, 0.4; IR (neat) 2955, 2861, 1954, 1614, 1514, 1249, 1173 cm^{-1}.

(*S*)-1-[(4′-Methoxyphenyl)methoxy]-3-(trimethylsiloxy)-6,7-octadiene (16). Following the procedure used for the preparation of **15**, the alcohol **14** (0.5 g, 1.9 mmol) was converted to **16** (0.59 g, 92%) (NMR and IR identical to those of **15**).

(3*S*,6*R*)-(−)-Methyl 8-[(4′-Methoxyphenyl)methoxy]-2-methylidene-3,6-epoxyoctanoate (3). To a solution of **15** (0.66 g, 1.97 mmol) in dry dichloromethane (20 mL) was added mercuric trifluoroacetate (1.01 g, 2.36 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 (15 mL), and then copper(II) chloride (1.01 g, 5.91 mmol), palladium(II) chloride (0.035 g, 0.20 mmol), propylene oxide (1.4 mL, 20 mmol), and triethyl orthoacetate (0.4 mL, 2 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 solution was concentrated, ethyl acetate was added, and the resulting mixture was filtered through Florisil (50 g). The filtrate was concentrated and the residue was subjected to an ether-water workup. Chromatography (80:20 hexane/ethyl acetate) yielded **3** (0.35 g, 55%). NMR and HPLC analysis of the crude reaction mixture indicated 96:4 *cis*/*trans* ratio: HPLC retention time (90:10 hexanes/ethyl acetate at 1 mL/min) 22.1 min (43.0 min for the *trans* isomer); ^{1}H NMR δ 7.26 (m, 2H), 6.85 (m, 2 H), 6.18 (dd, J = 1.5, 1..4 Hz, 1H), 5.89 (dd, J = 1.7, 1.8 Hz, 1H), 4.68 (t, J = 6.7 Hz, 1H), 4.42 (s, 2H), 4.06 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.54 (t, 2H, J = 6.5 Hz), 2.00–1.82 (m, 4H), 1.66–1.45 (m, 2H); ^{13}C NMR δ 166.4, 159.1, 142.2, 130.5, 129.2, 123.5, 113.7, 77.3, 76.7, 72.6, 67.4, 55.2, 51.6, 35.9, 32.2, 30.8; IR (neat) 2943, 2861, 1713, 1508, 1243, 1091 cm^{-1}; $[\alpha]_D$ −26.10° ($CHCl_3$, c = 0.015 g/mL); HRMS m/z 320.1620 ($C_{18}H_{24}O_5$, calcd 320.1624) .

(3*R*, 6*S*)-(+)-Methyl 8-[(4′-Methoxyphenyl)methoxy]-2-methylidene-3,6-epoxyoctanoate (4). Following the procedure used for the preparation of **3**, **16** (0.41 g, 1.23 mmol) was converted to **4** (0.22 g, 57%) (NMR and IR identical to **3**): $[\alpha]_D$ +24.90° ($CHCl_3$, c = 0.0145 g/mL).

(3*S*,6*R*)-(−)-Methyl 8-Hydroxy-2-methylidene-3,6-epoxyoctanoate (19). To a solution of **3** (0.27 g, 0.85 mmol) in dichloromethane (10 mL) and pH 7 buffer (2 mL) was added DDQ (0.23 g, 1.02 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 sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated. Chromatography (60:40 hexanes/ethyl acetate) yielded 0.167 g (98%) of **19**: ^{1}H NMR δ 6.20 (dd, J = 1.2, 1.0 Hz, 1H), 5.87 (dd, J = 1.5, 1.4 Hz, 1H), 4.70 (m, 1H), 4.04 (m, 1H), 3.79 (t, J = 5.7 Hz, 2H), 3.73 (s, 3H), 2.29–2.19 (m, 2H), 1.84 (q, J = 5.6 Hz, 2H), 1.67–1.51 (m, 2H); ^{13}C NMR δ 166.1, 141.5, 123.6, 79.3, 76.8, 61.1, 51.5, 37.5, 31.6, 30.8; IR (neat) 3425, 2955, 2884, 1719, 1631, 1437, 1196, 1073, 955, 820 cm^{-1}; $[\alpha]_D$ −48.10° ($CHCl_3$, c = 0.013 g/mL). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.05. Found: C, 59.82; H, 8.04.

(2*S*,3*S*,6*R*)-(+)-Methyl 8-Hydroxy-2-methyl-3,6-epoxyoctanoate (17) and (2*R*,3*S*,6*R*)-(−)-Methyl 8-Hydroxy-2-methyl-3,6-epoxyoctanoate (20). To a solution of **19** (0.162 g, 0.81 mmol) in methanol (20 mL) in a hydrogenation bottle was added rhodium on alumina (0.02 g, 0.08 mmol). The hydrogen bottle was shaken using a Parr apparatus under 50 psi of hydrogen gas for 40 h. The

solution was then diluted with ethyl acetate, filtered through Celite, and then concentrated. Chromatography (60:40 hexanes/ethyl acetate) yielded a 43:57 mixture of the *anti* (**17**) and *syn* (**20**) products (0.159 g, 97%) which were separated using preparative HPLC. Compound **17** exhibited spectroscopic data identical to that reported by Ireland and Vevert[5] for the same compound; HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 43.5 min; $[\alpha]^{28}_D$ +13.47° ($CHCl_3$, c = 0.0193 g/mL). Compound **20** exhibited spectroscopic data identical to that reported by Ireland and Vevert[5] for the same compound: HPLC retention time (70:30 hexanes/ethyl acetate at 1 mL/min) 30.0 min; $[\alpha]^{25}_D$ −20.40° ($CHCl_3$, c = 0.015 g/mL).

(2*R*,3*R*,6*S*)-(−)-Methyl 8-[(4′-Methoxyphenyl)methoxy]-2-methyl-3,6-epoxyoctanoate (21) and (2*S*,3*R*,6*S*)-(+)-Methyl 8-[(4′-methoxyphenyl)methoxy]-2-methyl-3,6-epoxyoctanoate (22). To a solution of **4** (0.23 g, 0.72 mmol) in dry methanol (40 mL) was added magnesium turnings (0.53 g). The mixture was stirred at 0 °C under a $CaCl_2$ drying tube for 2 h and then at 25 °C for 6 h. The reaction was quenched by addition of 5% HCl (30 mL) and then worked up. Chromatography (90:10 hexanes/ethyl acetate) yielded pure product (0.208 g, 90%) as a 19:81 mixture of *anti* (**21**) and *syn* (**22**) isomers which were separated by preparative HPLC. Compound **21**: HPLC retention time (80:20 hexanes/ethyl acetate at 1 mL/min) 8.50 min; ^{1}H NMR δ 7.23 (m, 2H), 6.85 (m, 2H), 4.40 (2, 2H), 4.02–3.87 (m, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 3.50 (t, J = 6.8 Hz, 2H), 2.50 (p, J = 7.1 Hz, 1H), 1.98–1.58 (m, 6H), 1.09 (d, J = 7.0 Hz, 3H; ^{13}C NMR δ 175.1, 159.1, 130.7, 129.2, 113.7, 80.3, 76.9, 72.6, 67.4, 55.3, 51.6, 45.4, 36.1, 31.1, 28.5, 13.3; $[\alpha]_D$ −2.20° ($CHCl_3$, c = 0.03 g/mL); HRMS m/z 322.1794 ($C_{18}H_{26}O_5$, calcd 322.1780). Compound **22**: HPLC retention time (80:20 hexanes/ethyl acetate at 1 mL/min) 7.25 min; ^{1}H NMR; δ 7.22 (m, 2H), 6.85 (m, 2H), 4.41 (s, 2H), 4.00–3.89 (m, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.51 (t, J = 6.6 Hz, 2H), 2.50 (p, J = 7.1 Hz, 1H), 1.98–1.58 (m, 6H), 1.19 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 175.1, 159.1, 130.6, 129.2, 113.7, 80.1, 76.9, 72.6, 67.4, 55.3, 51.5, 45.1, 36.1, 31.1, 29.1, 134.0; IR (neat) 2931, 2861, 1737, 1614, 1514, cm^{-1}; $[\alpha]_D$ +14.7° ($CHCl_3$, c = 0.011 g/mL); HRMS m/z 322.1764 ($C_{18}H_{26}O_5$, calcd 322.1780).

(2*R*,3*R*,6*S*)-(−)-Methyl 8-Hydroxy-2-methyl-3,6-epoxyoctanoate (18). Following the procedure used for the preparation of **19** (and chromatography conditions identical to those reported above for **17**/**20**), the ester **21** (0.05 g, 0.16 mmol) was converted to **18** (0.03 g, 94%), having spectroscopic properties identical to those reported by Ireland and Vevert[5] for the same compound and an HPLC retention time identical to that reported above for **17**. $[\alpha]^{25}_D$ −12.95° ($CHCl_3$, c = 0.017 g/mL).

(2*S*,3*R*,6*S*)-(+)-Methyl 8-Hydroxy-2-methyl-3,6-epoxyoctanoate (23). Following the procedure used for the preparation of **19** (and chromatography conditions identical to those reported above for **17**/**20**), the ester **22** (0.17 g, 0.52 mmol) was converted to **23** (0.10 g, 100%), having spectroscopic properties identical to those reported by Ireland and Vevert[5] for the same compound and an HPLC retention time identical to that reported above for **20**: $[\alpha]^{25}_D$ +20.43° ($CHCl_3$, c = 0.015 g/mL).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**, and **7**-**23** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.