

A General Approach to Enantiomerically Pure Methylcarbinols. Asymmetric Synthesis of Antibiotic (-)-A26771B and the WCR Sex Pheromone

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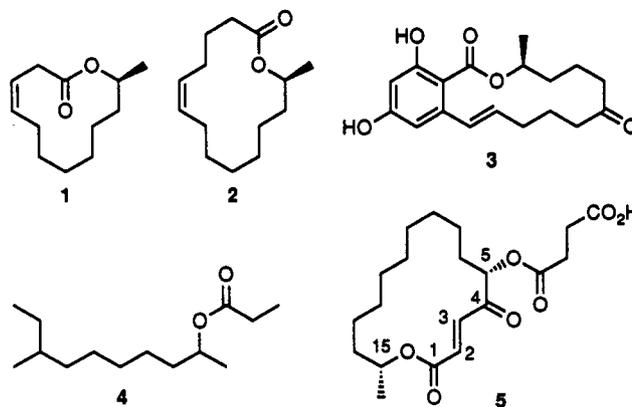
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Either (*R*) or (*S*) enantiomerically pure methylcarbinol groups are conveniently produced from monosubstituted alkenes via the Sharpless asymmetric dihydroxylation (AD) reaction. The initial AD product, 1,2-dihydroxyalkane, obtained with predictable absolute configuration and high enantiomeric purity, is converted into 2-acetoxy-1-bromoalkane and then subjected to reductive debromination. These conditions are compatible with a variety of functional groups, including acetal, ester, nitrile, ketone, and silyl ether. The advantages of this method are demonstrated by highly efficient, asymmetric syntheses of enantiomerically pure natural products. All four stereoisomers of the WCR sex pheromone **4** are prepared in six steps from nona-1,8-diene in 10–15% overall yield. Similarly, a highly efficient formal total synthesis of antibiotic (-)-A26771B (**5**) is accomplished via two alternative approaches. The first one transforms dodec-11-enal into enantiomerically pure **5** in 11 steps and 4.1% overall yield, while the second achieves the same transformation in 12 steps and 6.6% overall yield.

Introduction

The methylcarbinol group, CH₃CH(OH)C, appears ubiquitously in many biochemicals and pharmaceuticals, including naturally occurring macrocyclic lactones¹ and pheromones.² This stereogenic center, which represents the "starter unit" in polyketide natural products, is found in either (*R*) or (*S*) configuration.³ A reliable and widely used source of enantiomerically pure methylcarbinols for the synthesis of such target molecules is the "chiral pool" of natural products.⁴ An alternative, time-tested source for many chiral building blocks is asymmetric synthesis via enzyme catalysis.⁵ We have demonstrated the advantages of the latter approach by using *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH) to catalyze the reduction of a broad range of methyl ketones to the corresponding methylcarbinols with excellent enantioselectivity.⁶ We have also employed these alcohols in the

total synthesis of natural products containing methylcarbinol, including ferrulactone II (**1**)^{6a} (*S*)-(+)-(*Z*)-tetradec-5-en-13-olide (**2**)^{6d} (*S*)-(-)-zearealenone (**3**)^{6f} as well as all four isomers of 8-methyldec-2-yl propanoate (**4**), the sex pheromone emitted by the female western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte.^{6g}



WCR sex pheromone

Antibiotic A26771B

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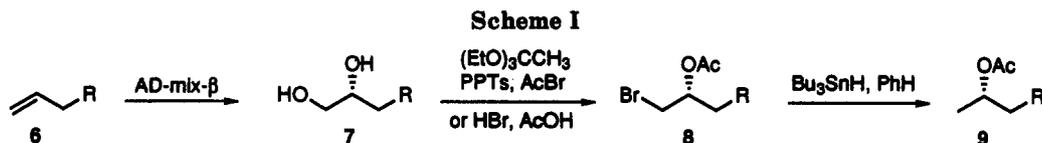
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Here we report on a very convenient, general, asymmetric synthesis of the methylcarbinol functionality from monosubstituted alkenes using the Sharpless asymmetric dihydroxylation (AD) reaction.⁷ We demonstrate the advantages of this method by the formal synthesis of all four stereoisomers of the WCR sex pheromone **4** and antibiotic (-)-A26771B (**5**) using achiral starting materials.

Results and Discussion

Our general approach to methylcarbinols is outlined in Scheme I. The AD reaction with monosubstituted alkenes

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**Table I**

R	7: yield (%), ee (%)	8: yield (%)	9: yield (%)
	93, 89 ^a	58	57
	96, 90 ^a	96	74
	94, 87 ^a	83	89
	99, 86 ^a	90	80
	92, 84	85	77

^a A single recrystallization of this diol from diethyl ether afforded a pure sample with enantiomeric excess greater than 97%.

6 is known to proceed with very high yields to give 1,2-dihydroxyalkanes 7, with predictable absolute configuration (AD-mix- α forms the 2*S* configuration while AD-mix- β produces the 2*R* stereochemistry) and high enantiomeric purity (80–98% ee).⁷ In many cases, such high levels of enantiomeric enrichment allow for essentially pure enantiomers to be achieved by a single recrystallization of the crude diol. Selective deoxygenation of the primary hydroxyl group in 7 could thus give rise to enantiomerically pure methylcarbinol (Scheme I).

The five representative examples shown in Table I illustrate the generality and chemoselectivity of the method with respect to variety of functional groups. Diol 7 was converted to 2-acetoxy-1-bromoalkane 8, by treatment with triethyl orthoacetate and catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) followed by addition of acetyl bromide.⁸ Alternatively, the same transformation was achieved using HBr in acetic acid.⁹ Reductive removal of the primary bromide in 8 was carried out under mild conditions using tributyltin hydride.¹⁰ For compounds having functional groups that are compatible with LiAlH₄, reduction with the latter reagent may proceed with higher yields to give the free alcohol of 9.¹¹ As shown in Table I, the method is compatible with variety of functional groups, including acetal, ester, nitrile, ketone, and silyl ether. In all cases, the AD reaction proceeded with very high yields (92–99%) and with high enantiomeric excess (84–90%). In four out of the five examples, a single recrystallization of the diol (7a–d) afforded an enantiomerically pure compound. Diol 7e was obtained as an oil. Conversion of 7 to 8 proceeded in satisfactory yields even with the acid-sensitive acetal substrate 7a that was converted to 8a in 58% yield. Similarly, the conditions for the debromination step with tin hydride were found

to be compatible with these representative functional groups. To confirm that no racemization occurred at the secondary carbinol center throughout these transformations, compound 9a (that was obtained from enantiomerically pure 7a) was hydrolyzed in KOH/methanol to the corresponding secondary alcohol, which was then converted to its Mosher ester. ¹H NMR analysis of the latter indicated that its enantiomeric purity was fully retained.

We have recently demonstrated the advantages of the AD reaction with disubstituted alkenes in the synthesis of enantiomerically pure polyoxygenated natural product.¹² Here we illustrate the usefulness of the above described method in the asymmetric synthesis of antibiotic (–)-A26771B (5) and the four isomers of the WCR sex pheromone 4, starting from achiral olefins.

Antibiotic A26771B. The sixteen-membered macrocyclic antibiotic A26771B (5) was isolated in 1977 from *Penicillium turbatum* and was found to be moderately active against Gram-positive bacteria, mycoplasma, and fungi.¹³ This polyketide secondary metabolite¹⁴ has attracted considerable synthetic efforts, yielding a number of alternative approaches to the racemic compound.¹⁵ Synthesis of 5 in its naturally occurring form was also achieved, starting from enantiomerically pure compounds, including D-glucose,¹⁶ D-glyceraldehyde,¹⁷ and (*R*)-(+)-methyloxirane.¹⁸ Here we present two alternative synthetic approaches to enantiomerically pure 5, starting with achiral polyalkene precursors and using the above described methodology (Schemes II and III). In both cases the stereogenic carbinol centers, 5*S* and 15*R*, are introduced in a single AD step.

The starting material for the first approach (Scheme II), methyl (*E,E*)-hexadeca-2,4,15-trienoate (10) was prepared via a Wittig reaction of dodec-11-enal and methyl-(diethylphosphono)crotonate under basic conditions (LDA, THF).¹⁹ Reaction of 10 with AD-mix- α and methanesulfonamide in a 1:1 mixture of *tert*-butyl alcohol/water followed by recrystallization from ethyl acetate afforded

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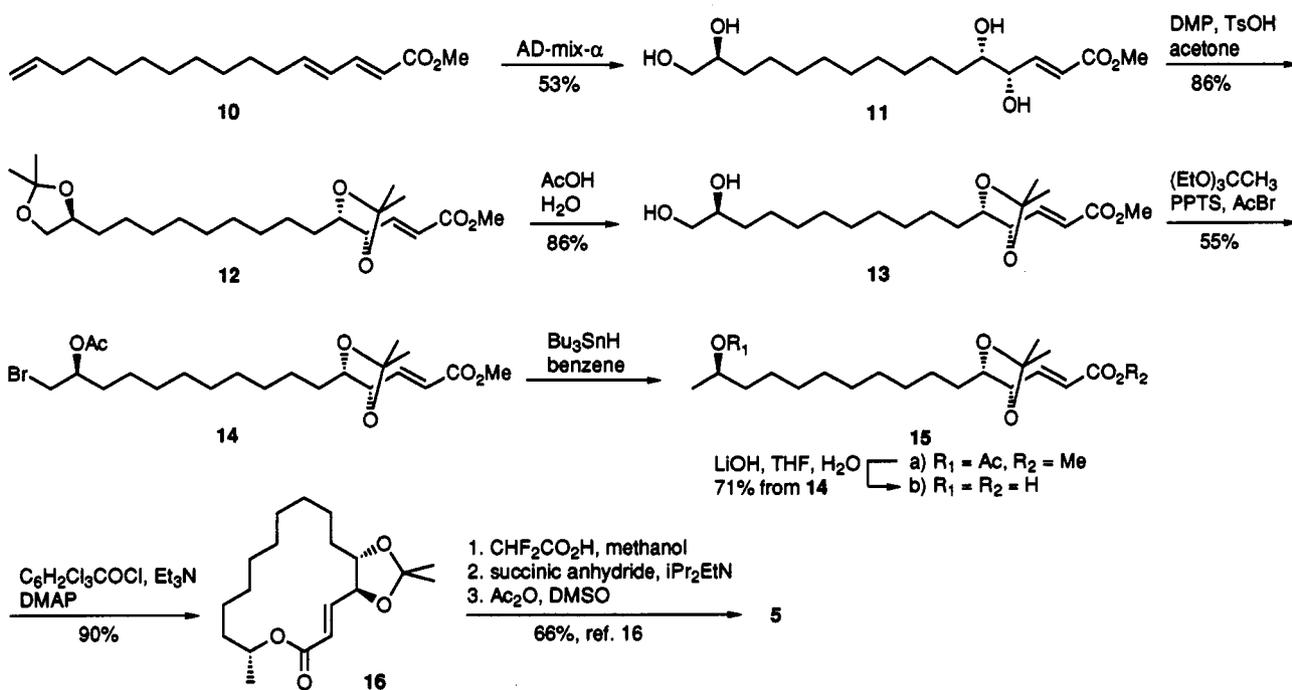
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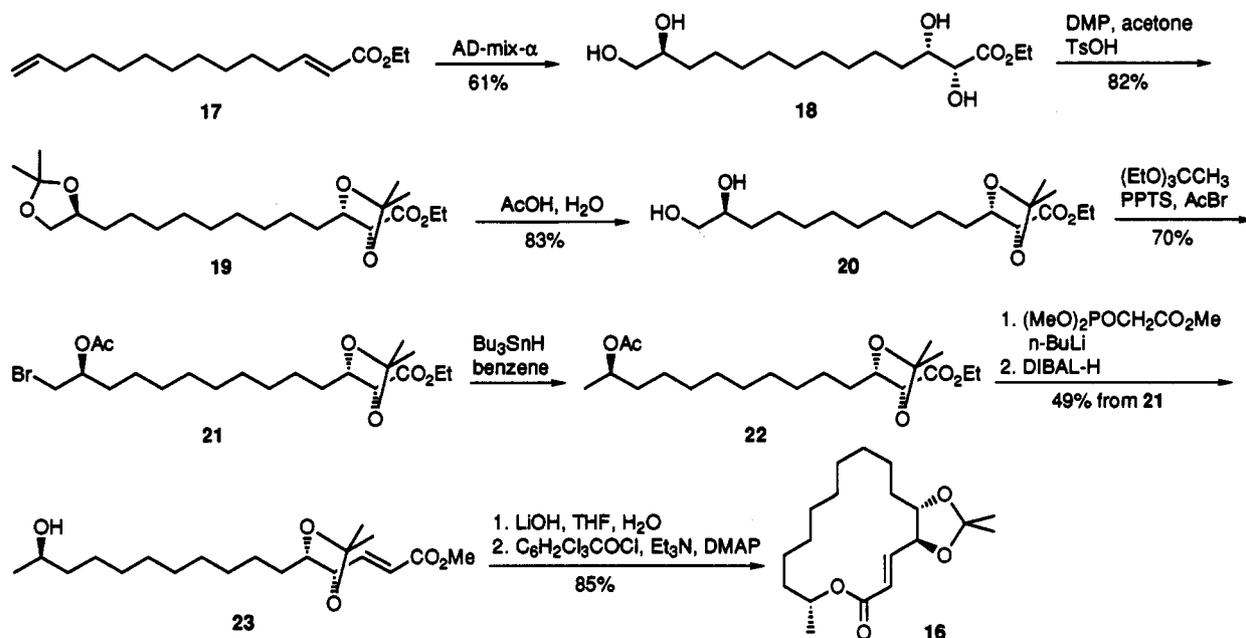
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Scheme II



Scheme III



methyl (4*S*,5*S*,15*S*)-4,5,15,16-tetrahydroxyhexadec-2-enoate (11) in 53% yield. This tetrol was converted to the bis-acetonide derivative 12 in 86% using dimethoxypropane in acidic acetone. Selective hydrolysis (acetic acid/water) of the less sterically hindered acetonide at positions 15,16 afforded the monoacetonide 13 in 86% yield. The free diol within 13 was converted to the corresponding bromoacetate 14 in 55% yield by treatment with triethyl orthoacetate and catalytic amounts of PPTS followed by acetyl bromide. Debromination with tributyltin hydride afforded the methylcarbinol derivative 15a. Hydrolysis of both esters within 15a using LiOH in aqueous THF produced (4*S*,5*S*,15*R*)-trihydroxyhexadec-2-enoic acid-4,5-acetonide (15b) in 71% combined yield for both steps. Yamaguchi lactonization²⁰ of this hydroxy acid using 2,4,6-trichlorobenzoyl chloride and triethylamine (to generate the mixed anhydride) followed by treatment with (di-

methylamino)pyridine, furnished the crystalline lactone 16 in 90% yield. Lactone 16 was found to be identical with the compound described by Tatsuta,¹⁶ who had already converted it in 66% yield to (–)-A26771B (5) via a three-step sequence, including acid-catalyzed hydrolysis of the acetonide, selective succinylation of the hydroxyl at position 5, and Swern oxidation of the remaining alcohol at position 4.

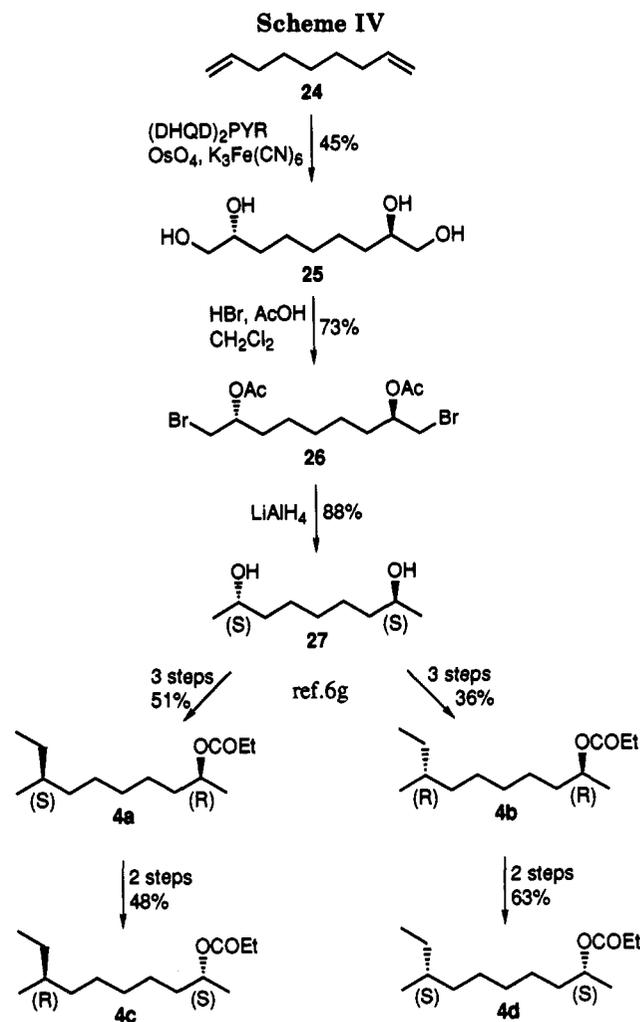
A key feature in the above-described synthesis is relatively low reactivity of the electron-deficient double bond at position 2 of triene 10 toward the AD reagent. This allowed for clean, regioselective formation of tetrol 11 from an achiral precursor having the entire 16-carbon skeleton of the target macrolide 5. Another characteristic

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of the AD reaction, i.e. the relatively low reactivity of *Z*-disubstituted alkenes, as compared with their *E*-isomers,²¹ allowed for the convenient use of a nonpurified 10 (a 9:1 mixture of 4*E*/4*Z* isomers) as a substrate for the production of enantiomerically pure 11. Nevertheless, we examined an alternative approach to 5 (Scheme III) that starts with diene 17 rather than triene 10, with the extra double bond being added on a later stage of the synthesis. Reaction of 17 (easily prepared in 82% yield by a Wittig olefination of dodec-11-enal) with AD-mix- α , followed by recrystallization from ethyl acetate, afforded enantiomerically pure methyl (2*R*,3*S*,13*S*)-2,3,13,14-tetrahydroxy-tetradec-2-enoate (18) in 61% yield. Partial protection of this tetrol at the 2,3 positions was carried out as described in the previous approach via formation of the bis-acetonide 19 in 82% yield, followed by selective hydrolysis to give the monoacetonide 20 in 83% yield. The free diol within 20 was converted to the corresponding bromoacetate 21 in 70% yield. Debromination with tributyltin hydride to give 22, followed by a one-pot, two-carbon homologation procedure, using a Horner–Emmons reagent and DIBAL-H,²² furnished the unsaturated ester 23 in 49% combined yield for both steps. The latter was obtained as a 92:8 mixture of the *E* and *Z* isomers. Ester hydrolysis with LiOH in aqueous THF followed by Yamaguchi lactonization, as described above, afforded lactone 16 (in 85% yield) possessing pure *E*-geometry.²³ This crude lactone was found (by ¹H NMR) to be contaminated with 1.5% of the 15*S* epimer,¹⁶ but a single recrystallization from acetone/ethanol/water produced enantiomerically pure 16.

WCR Sex Pheromones. The sex pheromone emitted by the female western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte, was isolated and identified as 8-methyldec-2-yl propanoate (4).²⁴ Although racemic 4 may be easily prepared,²⁵ the synthesis of any of the four stereoisomers 4a–d has been reported to involve many steps, including difficult separation procedures. As is usually the case with aliphatic carbon skeletons which contain essentially noninteracting asymmetric carbon atoms, synthesis of these isomers requires the preparation and cross-coupling of two different chiral building blocks, each containing an appropriate asymmetric center.²⁶

Starting with a symmetrical substrate, nona-1,8-diene (24) (Scheme IV), and dihydroxylating both double bonds with the same stereoselectivity, using (DHQD)₂-Pyr,^{7b} followed by recrystallization from acetone, generated enantiomerically pure (*R,R*)-1,2,8,9-tetrahydroxynonane (25) (in 45% yield). Bifunctional chiral intermediates having C₂ symmetry, such as 25, are very useful intermediates, as they do not require selective identification of either end of the molecule. Desymmetrization by modifying any one of the two ends produces a single diastereomer, that may be specifically manipulated. Thus, using the above-described method, tetrol 25 was converted to the bis(bromoacetate) 26 in 73% yield, without interrupting its C₂



symmetry. Finally, reduction of 26 with LiAlH₄ furnished (*S,S*)-2,8-dihydroxynonane (27) in 88% yield.

We have recently synthesized all four isomers of the WCR pheromones 4a–d using enzymic methods to produce the same C₂ (*S,S*) chiron 27 and then employing copper-mediated cross-coupling methods and alcohol inversion techniques to manipulate its asymmetric centers.^{6g} For example, isomers 4a or 4b are produced directly from the (*S,S*) chiron while isomers 4c and 4d are generated from the first two, respectively, by inversion of the carbinol center. Alternatively, isomers 4c and 4d may be prepared in a shorter route from the (*R,R*) enantiomer of 27, starting with nonadiene 24 and using AD-mix- α instead of the (DHQD)₂-Pyr/OsO₄/K₃Fe(CN)₆ mixture. This flexibility of choosing an appropriate catalyst with either enantioselectivity represents a major advantage of the AD methodology over the enzymic approach.

Conclusion

A very convenient, general, asymmetric synthesis of the methylcarbinol functionality from monosubstituted alkenes has been achieved, using the Sharpless asymmetric dihydroxylation reaction. The advantages of this method were demonstrated by highly efficient, asymmetric syntheses on enantiomerically pure natural products. All four stereoisomers of the WCR sex pheromone 4 are prepared in six steps from 1,8-nonadiene. For example, isomers 4a and 4b are synthesized in 14.7 and 10.4% overall yield, respectively. Similarly, a highly efficient synthesis of antibiotic (–)-A26771B (5) is described. The two alter-

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native approaches employ achiral starting materials, thus representing the first synthesis of this naturally occurring macrolide where the chiral centers have been generated by asymmetric induction. The first approach (Scheme II) transforms dodecenal into enantiomerically pure **5** in 11 steps and 4.1% overall yield, while the second one (Scheme III) achieves the same transformation in 12 steps and 6.6% overall yield. In comparison, the Tatsuta synthesis¹⁶ converts D-glucose into **5** in 21 steps (not counting the additional steps associated with the convergent nature of the synthetic scheme) and 4.4% overall yield. The Quinkert approach¹⁸ is also 21 steps long, starting from methoxymethyl phenyl ether, with 2.9% overall yield.

Experimental Section

General Methods: ¹H and ¹³C NMR spectra were measured in CDCl₃ at 400 and 100 MHz, respectively. Infrared spectra were measured neat. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured in a 1-dm (1 mL) cell using Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 70–230 mesh, Art. 9385) at atmospheric pressure. THF was dried by distillation over sodium benzophenone ketyl. (*R*)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetic acid (Mosher's acid) was purchased from Aldrich.

Preparation of Substrates: 2-(Dec-9-enyl)-1,3-dioxolane (**6a**) was prepared in 90% yield by mixing undec-10-enal with excess ethylene glycol and catalytic amounts of *p*-toluenesulfonic acid in benzene and refluxing overnight with continuous removal of water: ¹H NMR δ 5.81 (m, 1H), 4.99 (br d, J = 17.2 Hz, 1H), 4.93 (br d, J = 10.4 Hz, 1H), 4.84 (t, J = 4.8 Hz, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 2.02 (m, 2H), 1.64 (m, 2H), 1.45–1.20 (m, 12 H). Ethyl undec-10-enoate (**6b**) was purchased from Aldrich. Dodec-11-enenitrile (**6c**) was prepared in two steps from undec-10-en-1-ol in 85% yield: first formation of the tosylate ester with *p*-toluenesulfonyl chloride and pyridine and then treatment with KCN in DMSO at 100 °C for 1 h: ¹H NMR δ 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 2.33 (t, J = 7.1 Hz, 2H), 2.04 (m, 2H), 1.65 (m, 2H), 1.44 (m, 2H), 1.39 (m, 2H), 1.29 (br, 8H); HRMS (FAB) calcd for C₁₂H₂₂N (M + H)⁺ 180.1752, found 180.1745. Dodec-11-en-2-one (**6d**) was prepared in two steps from undec-10-enal in 80% yield: first treatment with methylmagnesium bromide and then oxidation with PCC in dichloromethane: ¹H NMR δ 5.77 (m, 1H), 4.97 (br d, J = 17.1 Hz, 1H), 4.90 (br d, J = 11.2 Hz, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.11 (s, 3H), 2.01 (br q, J = 6.9 Hz, 2H), 1.54 (m, 2H), 1.35 (m, 2H), 1.26 (br s, 8H); HRMS (FAB) calcd for C₁₂H₂₂O₂Na (M + Na)⁺ 205.1568, found 205.1560. Undec-10-enyl *tert*-butyldimethylsilyl ether (**6e**) was prepared in 92% yield from undec-10-enol by treatment with *tert*-butyldimethylchlorosilane and imidazole in DMF: ¹H NMR δ 5.80 (m, 1H), 4.98 (dq, J = 17.2, 1.8 Hz, 1H), 4.92 (dq, J = 10.2, 1.8 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 2.03 (br q, J = 7.7 Hz, 2H), 1.50 (m, 2H), 1.36 (m, 2H), 1.27 (br s, 10H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR δ 139.19, 114.06, 63.33, 33.80, 32.86, 29.56, 29.41, 29.11, 28.92, 25.96, 25.77, -5.29; IR (neat) 2927.3, 2855.5, 1641.2, 1466.8, 1255.0 cm⁻¹. Methyl (*E,E*)-hexadeca-2,4,15-trienoate (**10**) was prepared as follows: Compound **6c** (3.58 g, 20 mmol) was dissolved in dry toluene (40 mL). DIBAL-H (1 M in hexane, 24 mL, 24 mmol) was added dropwise at 0 °C, and the mixture was stirred at the same temperature for 3 h and then at 10 °C for 1 h and finally worked up with 3 N HCl and hexane. The organic layer was concentrated and purified on a silica gel column (using 40:1 hexane/ethyl acetate), affording dodec-11-enal (3.12 g, 86%): ¹H NMR δ 9.76 (t, J = 2.0 Hz, 1H), 5.79 (m, 1H), 4.98 (br d, J = 17.2 Hz, 1H), 4.92 (br d, J = 11.6 Hz, 1H), 2.41 (dt, J = 7.6, 2.0 Hz, 2H), 2.03 (q, J = 7.2 Hz, 2H), 1.62 (m, 2H), 1.37 (m, 2H), 1.28 (br s, 10 H). A solution of methyl(diethylphosphono)crotonate (1.18 g, 5 mmol) in dry THF (5 mL) was added

dropwise to a cold (-78 °C) solution of LDA (1.5 M in hexane, 3.35 mL, 5 mmol) in THF (10 mL) and the mixture was stirred for 10 min. A solution of dodec-11-enal (800 mg, 5 mmol) in THF (5 mL) was added dropwise and the mixture was stirred at same temperature for 1 h, allowed to warm to room temperature over 20 min, and then worked up with saturated aqueous ammonium chloride and ether. Purification over a silica gel column afforded compound **10** (580 mg, 44%) which was found to contain 8–10% (by NMR) of the (*2E,4Z*) isomer. This mixture was used in the AD reaction without further purification: ¹H NMR δ 7.26 (dd, J = 15.6, 10.0 Hz, 1H), 6.14 (m, 2H), 5.82 (m, 2H), 4.99 (dq, J = 17.2, 2.0 Hz, 1H), 4.92 (dq, J = 11.4, 1.1 Hz, 1H), 3.73 (s, 3H), 2.16 (br q, J = 7.2 Hz, 2H), 2.03 (br q, J = 8.0 Hz, 2H), 1.40 (m, 4H), 1.27 (br, 10 H); ¹³C NMR δ 167.68, 145.37, 144.91, 139.13, 128.20, 118.56, 114.06, 51.32, 33.76, 32.95, 29.44, 29.40, 29.35, 29.12, 29.07, 28.87, 28.63; HRMS (FAB) calcd for C₁₇H₂₈O₂ (M + H)⁺ 265.2168, found 265.2175.

Ethyl Tetradeca-2,13-dienoate, (17). A solution of triethyl phosphonoacetate (2.23 g, 10 mmol) in THF (5 mL) was added dropwise to a cold (0 °C) mixture of NaH (60% in mineral oil, 400 mg, 10 mmol) in dry THF (20 mL), and the mixture was stirred for 20 min at the same temperature. A solution of dodec-11-enal (960 mg, 6 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred at the same temperature for 20 min and then worked up with saturated aqueous ammonium chloride. The crude organic extract was purified on a short silica gel column (using 40:1 hexane/ethyl acetate) to give pure **17** in the form of a colorless oil (1.24 g, 82%): ¹H NMR δ 6.96 (dt, J = 15.6, 6.9 Hz, 1H), 5.81 (m, 2H), 4.99 (dq, J = 18.7, 1.6 Hz, 1H), 4.93 (dq, J = 10.1, 1.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.19 (qd, J = 7.0, 1.5 Hz, 2H), 2.04 (q, J = 6.8 Hz, 2H), 1.44 (m, 2H), 1.37 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.28 (br s, 10 H); ¹³C NMR 166.72, 149.40, 139.12, 121.14, 114.07, 60.04, 33.76, 32.15, 29.41, 29.32, 29.08, 29.87, 27.97, 14.23; HRMS (FAB) calcd for C₁₈H₂₈O₂ (M + H)⁺, 253.2168, found 253.2163.

General Method of Dihydroxylation. Monosubstituted alkenes **6** were dihydroxylated following the general procedure described by Sharpless.⁷ Enantiomeric purity was determined by conversion of the diol into a bis-Mosher's ester followed by HPLC analysis using a chiral Pirkle IA column (with 66:1 hexane/2-propanol).

2-[(*R*)-9,10-Dihydroxydecyl]-1,3-dioxolane (**7a**). Asymmetric dihydroxylation of **6a** (212 mg, 1 mmol) produced **7a** (230 mg, 93%, 89% ee) in the form of a white solid. Recrystallization from cold ether afforded enantiomerically pure **7a** (156 mg, 98% ee): mp 61–63 °C; ¹H NMR δ 4.84 (t, J = 4.8 Hz, 1H), 3.97 (m, 2H), 3.85 (m, 2H), 3.67 (m, 1H), 3.62 (dd, J = 11.1, 2.7 Hz, 1H), 3.41 (dd, J = 11.1, 7.7 Hz, 1H), 2.98 (br s, 2H), 1.65 (m, 2H), 1.41 (m, 4H), 1.29 (br s, 10 H); ¹³C NMR δ 104.63, 72.28, 66.71, 64.77, 33.86, 33.08, 29.57, 29.45, 29.40, 29.35, 25.51, 24.00; IR (KBr) 3374.3, 2917.4, 2850.9, 1470.6, 1407.6 cm⁻¹; HRMS (FAB) calcd for C₁₃H₂₆O₄Na (M + Na)⁺, 269.1729, found 269.1720.

Ethyl (*R*)-10,11-Dihydroxyundecanoate (7b**).** Asymmetric dihydroxylation of **6b** (217 mg, 1.02 mmol) produced **7b** (240 mg, 96%, 90% ee). Recrystallization from cold ether afforded enantiomerically pure **7b** (173 mg, >98% ee): mp 58–59 °C; ¹H NMR δ 4.12 (q, J = 7.1 Hz, 2H), 3.68 (m, 1H), 3.64 (br d, J = 11.0 Hz, 1H), 3.42 (dd, J = 11.0, 7.9 Hz, 1H), 2.92 (br s, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.42 (m, 2H), 1.30 (br s, 10H), 1.26 (t, J = 7.1 Hz, 3H). ¹³C NMR δ 174.00, 72.26, 66.74, 60.19, 34.32, 33.05, 29.50, 29.32, 29.11, 29.02, 25.48, 24.88, 14.20; IR (KBr) 3486.1, 3255.2, 2925.7, 2852.3, 1734.3, 1470.6 cm⁻¹; HRMS (FAB) calcd for C₁₃H₂₆O₄Na (M + Na)⁺ 269.1729, found 269.1733.

(*R*)-11,12-Dihydroxydodecanenitrile (7c**).** Asymmetric dihydroxylation of **6c** (179 mg, 1 mmol) produced **7c** (200 mg, 94%, 87% ee). Recrystallization from cold ether afforded enantiomerically pure **7c** (183 mg, 97% ee): mp 63–64 °C; ¹H NMR δ 3.63 (m, 2H), 3.40 (t, J = 9.0 Hz, 1H), 3.20 (br d, J = 9.3 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 1.65 (m, 2H), 1.43 (m, 4H), 1.30 (br s, 10 H); ¹³C NMR δ 119.87, 72.24, 66.77, 33.01, 29.55, 29.31, 29.16, 28.65, 28.56, 25.50, 25.26, 17.06; IR (KBr) 3478.0, 3239.2, 2920.8, 2851.2, 2247.0, 1467.9 cm⁻¹; HRMS (FAB) calcd for C₁₂H₂₂O₂NNa (M + Na)⁺, 236.1626, found 236.1624.

(*R*)-11-Oxododecane-1,2-diol (7d**).** Asymmetric dihydroxylation of **6d** (182 mg, 1 mmol) produced **7d** (215 mg, 99%, 86% ee). Recrystallization from cold ether afforded enantiomerically

pure **7d** (174 mg, 97% ee): mp 68–69 °C; $^1\text{H NMR}$ δ 3.71 (m, 1H), 3.66 (dd, $J = 11.0, 3.0$ Hz, 1H), 3.44 (dd, $J = 11.0, 7.6$ Hz, 1H), 2.42 (t, $J = 7.4$ Hz, 2H), 2.14 (s, 3H), 2.04 (br, 2H), 1.56 (m, 2H), 1.44 (br s, 3H), 1.29 (br s, 9H); $^{13}\text{C NMR}$ δ 72.24, 66.81, 43.75, 33.11, 29.86, 29.47, 29.24, 29.06, 25.44, 23.76; IR (KBr) 3378.2, 3281.5, 2929.7, 2849.4, 1707.9 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{12}\text{H}_{24}\text{O}_3\text{Na}$ ($M + \text{Na}$) $^+$ 239.1623, found 239.1633.

(R)-10,11-Dihydroxyundecyl tert-Butyldimethylsilyl Ether (7e). Asymmetric dihydroxylation of **6e** (284 mg, 1 mmol) produced **7e** (294 mg, 92%, 84% ee) in the form of a colorless oil: $^1\text{H NMR}$ δ 3.66 (m, 2H), 3.60 (t, $J = 6.7$ Hz, 2H), 3.42 (dd, $J = 10.7, 7.6$ Hz, 1H), 2.58 (br, 1H), 1.50 (m, 2H), 1.43 (m, 3H), 1.28 (br, 12H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}\text{C NMR}$ δ 72.32, 66.77, 63.32, 33.12, 32.83, 29.61, 29.53, 29.47, 29.39, 25.96, 25.75, 25.50, -5.28; IR (neat) 3372.3, 2927.6, 2855.1, 1462.9, 1387.6, 1360.5, 1255.0; HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{38}\text{O}_3\text{SiCs}$ ($M + \text{Cs}$) $^+$ 451.1641, found 451.1643.

General Method of Bromoacetylation: Method A.⁹ Diol **7** (1 mmol) was dissolved in dichloromethane (2 mL) at 0 °C. Solution of HBr (30% in acetic acid, 3 mmol) was slowly added and the mixture was stirred at 0 °C for 3 h and then at room temperature for 15 min. Water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and dried over sodium sulfate, and solvent was removed under reduced pressure. Filtration over a short silica gel or alumina column produced **8**. The latter was found to be contaminated with approximately 3–4% of the isomeric bromoacetate.

Method B.⁸ A solution of **7** (1 mmol), triethyl orthoacetate (1.5 mmol), and PPTS (5 mg) in methylene chloride (5 mL) was stirred at 40 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in methylene chloride (2 mL) and cooled to 0 °C, triethylamine (10 μL) and acetyl bromide (1.5 mmol) were added sequentially, and the mixture was stirred at same temperature for 2 h. A saturated solution of sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvent under reduced pressure followed by filtration over a silica gel column afforded **8**. The latter was found to be contaminated with approximately 2–3% of the isomeric bromoacetate.

2-[(R)-9-Acetoxy-10-bromodecyl]-1,3-dioxolane (8a). Using method B, diol **7a** (97 mg, 0.39 mmol) was converted to **8a** (70 mg, 58%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 7.8^\circ$ ($c = 1.13, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.98 (m, 1H), 4.83 (t, $J = 4.8$ Hz, 1H), 3.97 (m, 2H), 3.84 (m, 2H), 3.50 (dd, $J = 10.8, 4.5$ Hz, 1H), 3.42 (dd, $J = 10.8, 5.4$ Hz, 1H), 2.08 (s, 3H), 1.64 (m, 4H), 1.40 (m, 2H), 1.28 (br s, 10H); $^{13}\text{C NMR}$ δ 170.40, 104.59, 72.39, 64.84, 34.22, 33.83, 32.44, 29.42, 29.33, 29.21, 24.97, 23.98, 20.99; IR (neat) 2926.6, 2855.8, 1742.0, 1372.0, 1235.0 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{27}\text{O}_4\text{BrCs}$ ($M + \text{Cs}$) $^+$ 483.0147, found 483.0141.

Ethyl (R)-10-Acetoxy-11-bromoundecanoate (8b). Using method A, diol **7b** (50 mg, 0.20 mmol) was converted to **8b** (66 mg, 92%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 7.49^\circ$ ($c = 1.95, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.99 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.51 (dd, $J = 10.8, 4.6$ Hz, 1H), 3.43 (dd, $J = 10.8, 5.5$ Hz, 1H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.09 (s, 3H), 1.64 (m, 4H), 1.29 (br s, 10H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ δ 173.77, 170.38, 72.36, 60.10, 34.27, 34.19, 32.41, 29.14, 29.05, 28.99, 24.95, 24.86, 20.98, 14.21; IR (neat) 2929.4, 2855.8, 1738.0, 1464.3, 1372.3 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{27}\text{O}_4\text{BrCs}$ ($M + \text{Cs}$) $^+$ 483.0147, found 483.0136.

(R)-11-Acetoxy-12-bromododecanenitrile (8c). Using method B, diol **7c** (72 mg, 0.34 mmol) was converted to **8c** (90 mg, 83%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 8.15^\circ$ ($c = 2.4, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.99 (m, 1H), 3.51 (dd, $J = 10.8, 4.6$ Hz, 1H), 3.39 (dd, $J = 10.8, 5.4$ Hz, 1H), 2.34 (t, $J = 7.1$ Hz, 2H), 2.09 (s, 3H), 1.67 (m, 4H), 1.44 (m, 2H), 1.30 (br, 10H); $^{13}\text{C NMR}$ δ 170.43, 119.82, 72.36, 34.22, 32.43, 29.19, 28.56, 25.33, 24.96, 21.00, 17.08; IR (neat) 2928.0, 2855.5, 2244.6, 1740.8, 1461.5, 1426.7, 1236.4 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{NBrCs}$ ($M + \text{Cs}$) $^+$ 450.0045, found, 450.0041.

(R)-12-Bromo-11-acetoxydodecan-2-one (8d). Using method A, diol **7d** (53 mg, 0.25 mmol) was converted to **8d** (71 mg, 90%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 7.77^\circ$ ($c = 2.57, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.99 (m, 1H), 3.51 (dd, $J = 10.8, 4.6$ Hz, 1H), 3.43 (dd, $J = 10.8, 5.5$ Hz, 1H), 2.39 (t, $J = 7.4$ Hz, 2H), 2.11 (s, 3H), 2.07 (s, 3H), 1.67 (m, 2H), 1.58 (m, 2H), 1.28 (br s, 10 H); $^{13}\text{C NMR}$

δ 209.26, 170.41, 72.40, 43.69, 34.20, 32.42, 29.18, 29.15, 29.03, 24.96, 23.72, 20.99; IR (neat) 2928.4, 2855.2, 1741.4, 1716.2, 1462.6, 1371.6, 1236.1 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{26}\text{O}_3\text{BrCs}$ ($M + \text{Cs}$) $^+$ 453.0041, found 453.0022.

(R)-10-Acetoxy-11-bromoundecyl tert-Butyldimethylsilyl Ether (8e). Using method B, diol **7e** (100 mg, 0.31 mmol) was converted to **8e** (113 mg, 85%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 6.85^\circ$ ($c = 3.76, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.99 (m, 1H), 3.59 (t, $J = 6.5$ Hz, 2H), 3.50 (dd, $J = 11.0, 4.4$ Hz, 1H), 3.42 (dd, $J = 11.0, 5.6$ Hz, 1H), 2.09 (s, 3H), 1.67 (m, 2H), 1.50 (m, 2H), 1.28 (br s, 12H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}\text{C NMR}$ δ 170.40, 72.41, 63.25, 34.20, 32.82, 32.46, 29.44, 29.34, 29.25, 25.95, 25.73, 25.01, 21.00, -5.27; IR 2927.3, 2855.4, 1744.7, 1471.1, 1371.8, 1234.1 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{39}\text{O}_3\text{BrSiCs}$ ($M + \text{Cs}$) $^+$ 555.0904, found 555.0911.

General Method of Debromination. To a solution of bromoacetate **8** (1 mmol) and AIBN (10 mg) in benzene (5 mL) was added tributyltin hydride (1.2 mmol) dropwise over 30 min, and the mixture was refluxed for an additional 1 h. Solvent was removed under reduced pressure, the residue was dissolved in methylene chloride (5 mL), iodine (3 mmol) was added, and the mixture was stirred at room temperature for 1 h and then washed with water. The organic layer was washed with 10% aqueous sodium thiosulfate, the solvent was removed, and the crude product was passed through a short bed of silica gel to give **9**.

2-[(S)-10-Acetoxydecyl]-1,3-dioxolane (9a). Debromination of **8a** (58 mg, 0.19 mmol) produced **9a** (27 mg, 57%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 1.52^\circ$ ($c = 0.79, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.90 (m, 1H), 4.84 (t, $J = 4.8$ Hz, 1H), 3.97 (m, 2H), 3.85 (m, 2H), 2.03 (s, 3H), 1.66 (m, 2H), 1.57 (m, 1H), 1.47 (m, 1H), 1.41 (m, 2H), 1.25 (br s, 10H), 1.20 (3H, d, $J = 6.3$ Hz); $^{13}\text{C NMR}$ δ 170.78, 104.65, 71.03, 64.79, 35.91, 33.86, 29.47, 29.38, 29.34, 25.34, 24.02, 21.36, 19.92; IR (neat) 2928.1, 2854.9, 1736.0, 1371.9, 1244.8 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4$ ($M + \text{H}$) $^+$ 273.2066, found 273.2068.

Ethyl (S)-10-Acetoxyundecanoate (9b). Debromination of **8b** (82 mg, 0.23 mmol) produced **9b** (47 mg, 74%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 1.02^\circ$ ($c = 2.34, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.88 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.28 (t, $J = 7.4$ Hz, 2H), 2.03 (s, 3H), 1.59 (m, 3H), 1.45 (m, 1H), 1.28 (br s, 10H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H); $^{13}\text{C NMR}$ δ 173.82, 170.73, 71.04, 60.09, 35.84, 34.26, 29.31, 29.25, 29.10, 29.03, 25.31, 24.88, 21.33, 19.90, 14.20; IR (neat) 2977.4, 2931.1, 2856.1, 1736.4, 1463.9, 1372.1 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4$ ($M + \text{H}$) $^+$ 273.2066, found 273.2066.

(S)-11-Acetoxydodecanenitrile (9c). Debromination of **8c** (81 mg, 0.25 mmol) produced **9c** (54 mg, 89%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 0.78^\circ$ ($c = 2.57, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.89 (m, 1H), 2.34 (t, $J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.65 (m, 2H), 1.46 (m, 3H), 1.29 (br s, 11H), 1.22 (d, $J = 6.3$ Hz, 3H); $^{13}\text{C NMR}$ δ 170.78, 119.82, 70.97, 35.85, 29.31, 29.16, 28.69, 28.59, 25.32, 21.37, 19.93, 17.09; IR (neat) 2928.2, 2855.5, 2244.6, 1734.8, 1460.9, 1371.6, 1245.3 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{NCs}$ ($M + \text{Cs}$) $^+$ 372.0940, found 372.0932.

(S)-11-Acetoxydodecan-2-one (9d). Debromination of **8d** (50 mg, 0.15 mmol) produced **9d** (29 mg, 80%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 1.45^\circ$ ($c = 1.38, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.88 (m, 1H), 2.42 (t, $J = 7.5$ Hz, 2H), 2.14 (s, 3H), 2.03 (s, 3H), 1.56 (m, 3H), 1.42 (m, 1H), 1.28 (br s, 10H), 1.20 (d, $J = 6.3$ Hz, 3H); $^{13}\text{C NMR}$ δ 209.28, 170.74, 70.96, 43.72, 35.84, 29.30, 29.24, 29.06, 25.31, 23.75, 21.34, 19.90; IR (neat) 2929.7, 2855.2, 1735.1, 1712.8, 1371.3, 1244.7 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{27}\text{O}_3$ ($M + \text{H}$) $^+$ 243.1960, found 243.1953.

(S)-10-Acetoxyundecyl tert-Butyldimethylsilyl Ether (9e). Debromination of **8e** (109 mg, 0.26 mmol) produced **9e** (68 mg, 77%) in the form of a colorless oil: $[\alpha]_{\text{D}} + 1.00^\circ$ ($c = 3.40, \text{CHCl}_3$); $^1\text{H NMR}$ δ 4.88 (m, 1H), 3.60 (t, $J = 6.6$ Hz, 2H), 2.03 (s, 3H), 1.50 (m, 4H), 1.24 (br s, 12H), 1.20 (d, $J = 6.3$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}\text{C NMR}$ δ 170.75, 71.0, 63.28, 35.89, 32.86, 29.49, 29.43, 29.41, 29.37, 25.95, 25.74, 25.36, 21.36, 19.92, -5.29; IR (neat) 2928.6, 2856.1, 1739.4, 1463.1, 1371.6, 1245.2 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{41}\text{O}_3\text{Si}$ ($M + \text{H}$) $^+$ 345.2825 ($M + \text{H}$) $^+$, found 345.2833.

Methyl (4S,5S,15S)-4,5,15,16-Tetrahydroxyhexadec-2-enolate (11). A mixture of **10** (520 mg, 2 mmol), AD-mix- α (5.6 g), and methanesulfonamide (190 mg, 2 mmol) in *tert*-butyl alcohol/water (1:1, 80 mL) was stirred at 0 °C for 24 h. Sodium

metabisulfite (6 g) was slowly added and the mixture was extracted with ethyl acetate to give 11 in the form of white solid. This crude product was recrystallized from ethyl acetate (352 mg, 53%): mp 111–112 °C; $[\alpha]_D -20.3^\circ$ ($c = 2.0$, MeOH); $^1\text{H NMR}$ (CD_3OD) δ 7.02 (dd, $J = 15.7, 4.7$ Hz, 1H), 6.09 (dd, $J = 15.7, 1.7$ Hz, 1H), 4.16 (td, $J = 4.6, 1.7$ Hz, 1H), 3.72 (s, 3H), 3.54 (m, 2H), 3.46 (dd, $J = 11.1, 4.4$ Hz, 1H), 3.40 (dd, $J = 11.1, 6.6$ Hz, 1H), 1.47 (m, 4H), 1.31 (br s, 14H); $^{13}\text{C NMR}$ (CD_3OD) 168.56, 150.13, 121.76, 74.91, 74.88, 73.22, 67.35, 52.06, 34.40, 33.53, 30.82, 30.69, 30.66, 26.97, 26.67; HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{32}\text{O}_6\text{Cs}$ ($M + \text{Cs}$)⁺ 465.1253, found 465.1254.

Methyl (4*S*,5*S*,15*S*)-4,5,15,16-Tetrahydroxyhexadec-2-enoate Bis-Acetonide, (12). Tretol 11 (175 mg, 0.53 mmol) was dissolved in a mixture of dimethoxypropane (DMP) (5 mL) and acetone (5 mL) together with and *p*-toluenesulfonic acid (2 mg), and the mixture was stirred at 60 °C for 1 h. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted with CH_2Cl_2 . Removal of the solvent under reduced pressure afforded 12 (188 mg, 86%) in the form of a colorless oil: $[\alpha]_D -2.11^\circ$ ($c = 1.75$, CHCl_3); $^1\text{H NMR}$ δ 6.88 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.13 (dd, $J = 15.6, 1.2$ Hz, 1H), 4.15 (ddd, $J = 7.1, 5.7, 1.4$ Hz, 1H), 4.08 (m, 1H), 4.03 (t, $J = 5.9$ Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.50 (t, $J = 7.1$ Hz, 1H), 1.65 (m, 3H), 1.47 (m, 3H), 1.44 (s, 3H), 1.41 (s, 6H), 1.36 (s, 3H), 1.28 (br, 12H); $^{13}\text{C NMR}$ δ 166.43, 144.54, 122.07, 109.32, 108.52, 80.60, 80.16, 76.12, 69.49, 51.69, 33.56, 32.07, 29.58, 29.41, 29.38, 27.23, 26.92, 26.55, 25.93, 25.68; IR (neat) 2985.3, 2931.6, 2856.0, 1729.9, 1662.4 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{23}\text{H}_{40}\text{O}_8\text{Cs}$ ($M + \text{Cs}$)⁺ 545.1879; found 545.1887.

Methyl (4*S*,5*S*,15*S*)-4,5,15,16-Tetrahydroxyhexadec-2-enoate 4,5-Acetonide, (13). A solution of 12 (180 mg, 0.44 mmol) in acetic acid/water (1:1, 10 mL) was stirred at room temperature for 2 h. Solvents were removed under reduced pressure and the residue was purified by passing it through a short silica gel column using hexane/ethyl acetate (1:1) to give 13 (140 mg, 86%) in the form of a colorless oil: $[\alpha]_D -10.49^\circ$ ($c = 2.04$, CHCl_3); $^1\text{H NMR}$ δ 6.88 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.13 (dd, $J = 15.6, 1.4$ Hz, 1H), 4.15 (ddd, $J = 7.1, 5.7, 1.3$ Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.70 (m, 2H), 3.42 (dd, $J = 11.0, 7.6$ Hz, 1H), 2.73 (br s, 2H), 1.60 (m, 2H), 1.45 (m, 4H), 1.44 (s, 3H), 1.41 (s, 3H), 1.28 (br s, 12H); $^{13}\text{C NMR}$ δ 166.52, 144.59, 122.02, 109.34, 80.62, 80.15, 72.26, 66.74, 51.73, 33.10, 32.05, 29.55, 29.34, 27.25, 26.58, 25.88, 25.50; IR (neat) 3403.9, 2985.7, 2928.5, 2854.2, 1728.3, 1661.6 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{36}\text{O}_8\text{Cs}$ ($M + \text{Cs}$)⁺ 505.1566, found 505.1551.

Methyl (4*S*,5*S*,15*S*)-15-Acetoxy-16-bromo-4,5-dihydroxyhexadec-2-enoate 4,5-Acetonide (14). A solution of diol 13 (140 mg, 0.38 mmol), triethyl orthoacetate (107 μL , 0.56 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (2 mg) in CH_2Cl_2 (1 mL) was stirred at 45 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C, acetyl bromide (40 μL) was added, and the mixture was stirred at the same temperature for 2 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with CH_2Cl_2 . Removal of the solvent under reduced pressure followed by chromatographic purification (silica gel, hexane/ethyl acetate 9:1) afforded 14 (100 mg, 55%) in the form of colorless oil: $[\alpha]_D -17.09^\circ$ ($c = 1.75$, CHCl_3); $^1\text{H NMR}$ δ 6.88 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.13 (dd, $J = 15.6, 1.2$ Hz, 1H), 4.99 (m, 1H), 4.15 (ddd, $J = 7.1, 5.7, 1.3$ Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.59 (dd, $J = 10.9, 4.6$, Hz, 1H), 3.43 (dd, $J = 10.9, 7.6$ Hz, 1H), 2.09 (s, 3H), 1.67 (m, 2H), 1.59 (m, 2H), 1.47 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.29 (br s, 12H); $^{13}\text{C NMR}$ δ 170.40, 166.42, 144.53, 122.03, 109.31, 80.65, 80.09, 72.43, 51.72, 34.21, 32.44, 32.05, 29.55, 29.33, 29.21, 27.23, 26.59, 25.91, 24.99, 20.99; IR (neat) 2985.6, 2928.9, 2855.2, 1731.1, 1661.9 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{37}\text{O}_8\text{BrCs}$ ($M + \text{Cs}$)⁺ 609.0828, found 609.0828.

Methyl (4*S*,5*S*,15*R*)-15-Acetoxy-4,5-dihydroxyhexadec-2-enoate 4,5-Acetonide (15a). A solution of 14 (69 mg, 0.14 mmol), tributyltin hydride (0.046 mL, 0.17 mmol), and AIBN (5 mg) in benzene (1 mL) was refluxed for 1 h. Filtration of the reaction mixture over silica gel (hexane/ethyl acetate, 9:1) afforded crude 15a (75 mg, contaminated with traces of organotin compounds), which was taken to the next step without further purification. An analytical sample was prepared by treatment of the crude compound with iodine in CH_2Cl_2 and then with a mixture of DMP, acetone, and catalytic amounts of TsOH: $[\alpha]_D -10.97^\circ$ (c

$= 1.75$, CHCl_3). The $^1\text{H NMR}$ spectrum of 15a was found to be identical to the reported spectrum of the corresponding mixture of epimers at position 15.¹⁶ HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{36}\text{O}_8\text{Cs}$ ($M + \text{Cs}$)⁺ 531.1723, found 531.1736.

(4*S*,5*S*,15*R*)-15-Acetoxy-4,5-Dihydroxyhexadec-2-enoic Acid 4,5-Acetonide (15b). The crude 15a (75 mg) was treated with a mixture of aqueous LiOH (0.2 M, 1 mL) and THF/ H_2O (3:2, 4 mL) for 2 days, acidified with oxalic acid, and filtered over silica gel (hexane/acetone, 3:2) to give 15b (34 mg, 71% from 14): $^1\text{H NMR}$ δ 6.96 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.14 (dd, $J = 15.6, 1.6$ Hz, 1H), 6.0 (br, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 1.62 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.50–1.20 (m, 17H), 1.19 (d, $J = 6.4$ Hz, 3H).

(4*S*,5*S*,15*R*)-4,5-Dihydroxyhexadec-2-en-15-olide 4,5-Acetonide (16). A solution of acid 15b (34 mg, 0.1 mmol), triethylamine (0.032 mL, 0.23 mmol), and 2,4,6-trichlorobenzoyl chloride (50 mg, 0.2 mmol) in dry THF (1 mL) was stirred at room temperature for 1 h. The mixture was diluted with toluene (20 mL), filtered under argon, and added dropwise (over 6 h) to a hot (90 °C) solution of 4-(*N,N*-dimethylamino)pyridine (78 mg, 0.64 mmol) in toluene (10 mL). The mixture was stirred for an additional 1 h, filtered, concentrated, and passed through a short silica gel column with hexane/ethyl acetate, 19:1, affording 16 (29 mg, 90%) in the form of white, fine needles: mp 70–71 °C (lit.²² 74–75 °C); $[\alpha]_D +6.82^\circ$ ($c = 1.05$, CHCl_3), (lit.²² +7.0°, $c = 1.0$, CHCl_3); $^1\text{H NMR}$ δ 6.89 (dd, $J = 15.6, 6.8$ Hz, 1H), 6.13 (dd, $J = 15.6, 1.2$ Hz, 1H), 5.03 (m, 1H), 4.13 (ddd, $J = 8.2, 6.8, 1.0$ Hz, 1H), 3.76 (td, $J = 8.2, 5.3$ Hz, 1H), 1.81 (m, 1H), 1.62 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.50–1.15 (br m, 14H), 1.26 (d, $J = 6.3$ Hz, 3H); $^{13}\text{C NMR}$ δ 165.52, 144.32, 123.66, 109.25, 80.86, 80.10, 71.21, 35.31, 31.05, 27.85, 27.27, 27.20, 26.96, 26.59, 26.48, 24.82, 23.33, 20.51.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-tetrahydroxytetradecanoate (18). A solution of 17 (1.14 g, 4.5 mmol), AD-mix- α (12.8 g), and methanesulfonamide (855 mg) in *tert*-butyl alcohol/water (1:1, 134 mL) was stirred at 0 °C for 24 h. Sodium metabisulfite (13.5 g) was added slowly and the mixture was extracted with ethyl acetate. Removal of the solvent under reduced pressure afforded 18 (1.12 g, 77%) in the form of a white solid. The latter was recrystallized from ethyl acetate (880 mg, 61%): mp 95–96 °C; $[\alpha]_D -11.13^\circ$ ($c = 2.75$, MeOH); $^1\text{H NMR}$ (CD_3OD) δ 4.21 (qd, $J = 7.2, 1.7$ Hz, 2H), 4.04 (d, $J = 2.8$ Hz, 1H), 3.82 (td, $J = 6.7, 2.8$ Hz, 1H), 3.56 (m, 1H), 3.46 (dd, $J = 11.1, 4.5$ Hz, 1H), 3.40 (dd, $J = 11.1, 6.6$ Hz, 1H), 1.55 (m, 2H), 1.47 (m, 3H), 1.32 (br s, 13H), 1.28 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (CD_3OD) δ 174.73, 74.85, 73.69, 73.25, 67.39, 62.16, 34.43, 34.21, 30.83, 30.67, 26.91, 26.69, 14.51; HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{32}\text{O}_8\text{Na}$ ($M + \text{Na}$)⁺, 343.2097, found 343.2100.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-Tetrahydroxytetradecanoate Bisacetonide (19). Tretol 18 (640 mg, 2 mmol) and *p*-toluenesulfonic acid (10 mg) were dissolved in a 1:1 mixture (20 mL) of 2,2-dimethoxypropane and acetone and stirred at 60 °C for 1 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvent under reduced pressure afforded 19 (650 mg, 82%) in the form of a colorless oil: $[\alpha]_D -2.64^\circ$ ($c = 4.63$, CHCl_3); $^1\text{H NMR}$ δ 4.24 (qd, $J = 7.2, 2.0$ Hz, 2H), 4.14–4.01 (m, 4H), 3.50 (t, $J = 7.2$ Hz, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.50–1.20 (m, 15H), 1.47 (br s, 3H), 1.44 (br s, 3H), 1.41 (br s, 3H), 1.35 (br s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ δ 170.95, 110.64, 108.49, 79.15, 76.09, 69.46, 61.21, 33.54, 33.47, 29.58, 29.41, 29.37, 27.13, 26.90, 25.70, 25.60, 25.56, 14.12; IR (neat) 2984.4, 2928.4, 2854.7, 1758.2, 1730.7, 1454.1, 1368.7 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{40}\text{O}_8$, C, 65.97; H, 10.07. Found: C, 65.80; H, 9.81.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-Tetrahydroxytetradecanoate 2,3-Acetonide (20). Compound 19 (400 mg, 1 mmol) was dissolved in a 1:1 mixture (10 mL) of acetic acid and water and stirred at room temperature for 2 h. Solvents were removed under reduced pressure, and the residue was passed through a short silica gel column using 1:1 hexane/ethyl acetate to give 20 (300 mg, 83%) in the form of a colorless oil: $[\alpha]_D -12.66^\circ$ ($c = 1.39$, CHCl_3); $^1\text{H NMR}$ δ 4.24 (qd, $J = 7.1, 2.2$ Hz, 2H), 4.11 (m, 2H), 3.70 (m, 1H), 3.65 (dd, $J = 11.0, 3.0$ Hz, 1H), 3.43 (dd, $J = 11.0, 7.6$ Hz, 1H), 2.05 (br s, 2H), 1.70 (m, 2H), 1.50–1.20 (m, 16H), 1.47 (s, 3H), 1.44 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ δ 171.01, 110.65, 79.02, 72.23, 66.63, 61.26, 33.44, 33.01, 29.60,

29.47, 29.42, 29.38, 27.10, 25.55, 14.09; IR (neat) 3391.4, 2984.9, 2926.0, 2853.1, 1753.3, 1732.9, 1455.9 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{36}\text{O}_6\text{Na}$ ($M + \text{Na}$)⁺ 383.2410, found 383.2408.

Ethyl (2*R*,3*S*,13*S*)-13-Acetoxy-14-bromo-2,3-dihydroxytetradecanoate 2,3-Acetonide (21). Compound 20 (262 mg, 0.81 mmol), triethylorthoacetate (314 mg, 1.94 mmol), and PPTS (10 mg) were dissolved in methylene chloride (1 mL) and stirred at 45 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in methylene chloride (1 mL) and cooled to 0 °C, acetyl bromide (0.10 mL) was added, and the mixture was stirred at the same temperature for 2 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvents under reduced pressure and purification over a silica gel column, using 9:1 hexane/ethyl acetate, afforded 21 (294 mg, 79%): $[\alpha]_{\text{D}} -17.62^\circ$ ($c = 2.02$, CHCl_3); $^1\text{H NMR}$ δ 4.99 (m, 1H), 4.24 (qd, $J = 7.2$, 2.0 Hz, 2H), 4.11 (m, 2H), 3.51 (dd, $J = 10.8$, 4.4 Hz, 1H), 3.43 (dd, $J = 10.8$, 5.6 Hz, 1H), 2.09 (s, 3H), 1.67 (m, 4H), 1.50–1.20 (m, 14H), 1.46 (s, 3H), 1.44 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ δ 170.96, 170.38, 110.64, 79.16, 79.09, 72.42, 61.23, 34.19, 33.47, 32.44, 29.41, 29.33, 29.21, 27.14, 25.62, 24.98, 20.98, 14.14; IR (neat) 2984.3, 2927.0, 2853.5, 1742.7, 1459.9, 1370.5 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{37}\text{O}_6\text{BrCs}$ ($M + \text{Cs}$)⁺ 597.0825, found 597.0816.

Ethyl (2*R*,3*S*,13*R*)-13-Acetoxy-2,3-dihydroxytetradecanoate Acetonide (22). Compound 21 (294 mg, 0.63 mmol) and AIBN (10 mg) were dissolved in benzene (5 mL). A solution of tributyltin hydride (0.20 mL, 0.76 mmol) in benzene (1 mL) was added slowly over 10 min, and the mixture was refluxed for 60 min and then passed through a short silica gel column (with hexane/ethyl acetate, 9:1) to give crude 22 (210 mg, contaminated with traces of organotin compounds), which was taken to next step without further purification. An analytical sample of 22 was prepared as described above for compound 15a: $[\alpha]_{\text{D}} -11.63^\circ$ ($c = 1.69$, CHCl_3); $^1\text{H NMR}$ δ 4.89 (m, 1H), 4.25 (qd, $J = 7.1$, 2.2 Hz, 2H), 4.11 (m, 2H), 2.03 (s, 3H), 1.75–1.20 (m, 18H), 1.47 (br s, 3H), 1.44 (br s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.20 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C NMR}$ δ 170.97, 170.74, 110.65, 79.09, 70.99, 61.24, 35.86, 33.48, 29.44, 29.39, 27.14, 25.61, 25.31, 19.91, 14.13; HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{38}\text{O}_6\text{Na}$ ($M + \text{Na}$)⁺ 409.2566, found 409.2564.

Methyl (4*S*,5*S*,15*R*)-4,5,15-Trihydroxyhexadec-2-enoate 4,5-Acetonide (23). *n*-BuLi (2.5 M in hexane, 1.17 mL, 2.92 mmol) was added dropwise to a cold (–78 °C) solution of trimethyl phosphonoacetate (531 mg, 2.92 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred at the same temperature for 0.5 h. Solution of compound 22 (210 mg, crude) in CH_2Cl_2 (1 mL) was added slowly, the mixture was stirred for 1 h, and then DIBAL-H (1 M in hexane, 3 mL, 3 mmol) was added dropwise over 2 h. The mixture was stirred for 16 h, allowing it to warm up to room temperature, and then refluxed for 1 h and finally quenched with saturated aqueous NH_4Cl . It was then extracted with ether, filtered over Celite, and purified over a silica gel column (hexane/ethyl acetate, 4:1) to give 23 (110 mg, 49% from 21). This product, which was found (by NMR) to be a 92:8 mixture of *E/Z* isomers, was taken to the next step without further purification: $^1\text{H NMR}$ δ 6.88 (dd, $J = 15.6$, 5.7 Hz, 1H), 6.13 (dd, $J = 15.6$, 1.4 Hz, 1H), 4.15 (ddd, $J = 7.2$, 5.7, 1.4 Hz, 1H), 3.78 (m, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 1.58 (m, 5H), 1.44 (s, 3H), 1.41 (s, 3H), 1.50–1.25 (br m, 14 H), 1.19 (d, $J = 6.2$ Hz, 3H); $^{13}\text{C NMR}$ δ 166.48, 144.58,

122.12, 109.34, 80.62, 80.18, 68.10, 51.72, 39.33, 32.08, 29.58, 29.51, 29.41, 29.38, 27.24, 26.60, 25.91, 25.73, 23.46 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{36}\text{O}_5\text{Cs}$ ($M + \text{Cs}$)⁺ 489.1614, found 489.1623.

Conversion of 23 to 16. Compound 23 (110 mg, 0.31 mmol) was hydrolyzed to 15b using LiOH in aqueous THF, as described above for compound 15a. Following the above-described Yamaguchi lactonization procedure, the resultant hydroxy acid 15b was converted to crystalline 16 (85 mg, 85% combined yield for both steps).

(*R,R*)-1,2,8,9-Tetrahydroxynonane (25). Sodium ferricyanide (9.88 g), K_2CO_3 (4.15 g), $(\text{DHQD})_2\text{-PYR}^{\text{b}}$ (80 mg) and OsO_4 (0.2 M in toluene, 0.1 mL) were mixed in *tert*-butyl alcohol/water (1:1, 200 mL), at 0 °C. Nona-1,8-diene (620 mg, 5 mmol) was added, and the mixture was stirred at 0 °C for 24 h and then quenched with sodium metabisulfite (15 g). The mixture was saturated with sodium chloride, extracted with 2-propanol, and dried over K_2CO_3 . Removal of the solvent under reduced pressure and recrystallization from acetone afforded 25 (434 mg, 45%): mp 74–76 °C; $[\alpha]_{\text{D}} +19.08^\circ$ ($c = 2.10$, MeOH); $^1\text{H NMR}$ (CD_3OD) δ 3.56 (m, 2H), 3.46 (dd, $J = 11.1$, 4.4 Hz, 2H), 3.40 (dd, $J = 11.1$, 6.6 Hz, 2H), 1.50 (m, 4H), 1.36 (br s, 6H); $^{13}\text{C NMR}$ δ 73.21, 67.36, 34.36, 30.87, 26.63; IR (KBr) 3485.6, 3385.8, 2928.3, 2853.6, 1473.4 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_9\text{H}_{20}\text{O}_4\text{Na}$ 215.1259, found 215.1259.

(*R,R*)-2,8-Diacetoxy-1,9-dibromononane (26). Compound 25 (460 mg, 2.4 mmol) was dissolved in methylene chloride (5 mL). A solution of HBr (30% in AcOH, 4.5 mL) was added dropwise at 0 °C and the mixture was stirred at same temperature for 1 h. Water was added and the mixture was extracted with ether, washed with brine, and dried over sodium sulfate. Solvent was removed under reduced pressure and the residue was passed through a silica gel or alumina columns, using hexane/ethyl acetate (19:1), affording 26 (704 mg, 73%). The latter was found to be contaminated with 3–4% of isomeric products: $^1\text{H NMR}$ δ 5.00 (m, 2H), 3.50 (dd, $J = 10.8$, 4.6 Hz, 2H), 3.43 (dd, $J = 10.8$, 5.4 Hz, 2H), 2.10 (s, 6H), 1.68 (br q, $J = 6.8$ Hz, 4H), 1.33 (br s, 6H); $^{13}\text{C NMR}$ δ 170.42, 72.23, 34.12, 32.31, 28.93, 24.82, 21.00; IR (neat) 2937.3, 2859.9, 1739.7, 1372.2, 1233.6 cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4\text{Br}_2\text{Cs}$ ($M + \text{Cs}$)⁺ 532.8939, found 532.8916.

(*S,S*)-2,8-Dihydroxynonane (27). Compound 26 (200 mg, 0.5 mmol) was dissolved in ether/THF (1:1, 5 mL). LiAlH_4 (114 mg, 3 mmol) was added slowly at 0 °C and the mixture was stirred at 0 °C for 2 h, and then refluxed for 16 h. The mixture was cooled to room temperature, quenched with wet ether, dried over sodium sulfate, filtered, and washed with ethyl acetate. Removal of solvents under reduced pressure followed by purification over a silica gel column, using 1:1 hexane/ethyl acetate, afforded 27 (70 mg, 88%). The latter was found to be contaminated with 3–4% of isomeric products. This compound was found to be identical (by $[\alpha]_{\text{D}}$, $^1\text{H NMR}$, $^{13}\text{C NMR}$, IR, and HRMS) to an authentic sample obtained from TBADH-catalyzed reduction of nonane-2,8-dione.^{6c}

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of 7a–e, 8a–e, 9a–e, 11–14, 16, and 18–22 (50 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.