Highly Diastereoselective Additions to Chiral α-Keto Acetals

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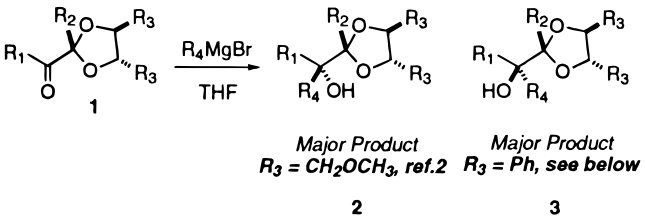
A general synthesis of (4*R**,5*R**)-2-acyl-4,5-diphenyl-1,3-dioxolanes and the addition of alkylmagnesium bromides to these compounds is described. The addition reactions occur with high diastereoselectivity (typical selectivity *ca*. 90:10). An example addition reaction carried out on an optically active acetal proves the sense of asymmetric induction for addition of organomagnesium reagents to these α-keto acetals. An explanation of the mechanism of asymmetric induction is given.

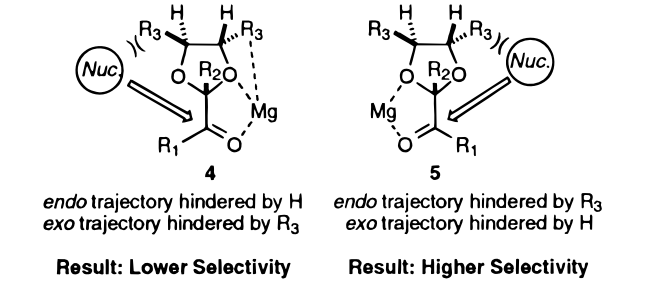
In this paper we describe highly diastereoselective addition reactions to chiral α-keto acetals. The use of C_2-symmetrical diols for the preparation of chiral acetals[1] has been investigated in several laboratories.[2] The diastereoselectivities for these reactions were variable. Using 1,4-dimethoxy-2,3-butanediol, derived from tartaric acid, as the diol precursor, the monoacetals of diketo compounds (Figure 1, $R_3 = CH_2OCH_3$) gave good diastereoselectivities in addition reactions with organomagnesium reagents, typically ranging from 4:1 to 9:1. However, for the acetals of keto aldehydes, (Figure 1, $R_2 = H$), the diastereoselectivities were poor, rarely exceeding 1.5:1.

We had two objectives at the outset of this research: (1) to elevate the diastereoselectivity of the addition by using a different chiral auxiliary, (2) to develop a chiral auxiliary that could be cleaved under mild, nonhydrolytic conditions.[3] To determine the best approach to elevate the diastereoselectivity of the addition reaction, we examined the trajectories available to the nucleophile for addition to the carbonyl. Chelation of the metal counterion by the carbonyl oxygen and one or the other of the acetal oxygens affords a bicyclo[3.3.0] structure. Addition reactions to the carbonyl should occur from the *exo* face of these intermediates. To maximize the selectivity of the addition reaction, steric hindrance along the trajectory for *endo* addition must be maximized, and hindrance for *exo* addition should be minimized. Previous workers had invoked a tridentate chelation of the oxygen atom of the carbonyl and one oxygen of the acetal and methoxy moieties (structure **4**, Figure 2) as the mechanism of asymmetric induction in the addition.[1] Examination of the trajectories of addition on **4** reveals that there are competing steric factors along the *endo* and *exo* trajectories of addition. In contrast, in chelated intermediate **5**, steric factors cooperate to hinder substantially the *endo* trajectory. On the basis of this analysis, we could conclude that large steric bulk and the absence of chelating heteroatom functionality in R_3 would afford the highest selectivity in the addition reaction. To examine



1 **2** **3**

Figure 1.



4 **5**

Figure 2.

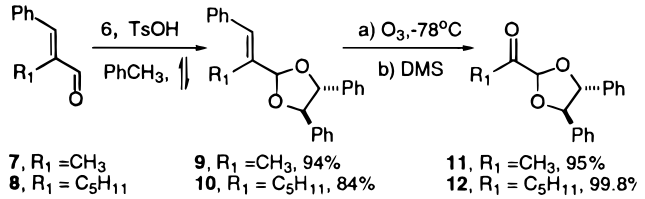


Figure 3.

this hypothesis, we examined that addition reaction of acetals synthesized from (1*R**, 2*R**)-1,2-diphenylethanediol (**6**).

The synthesis of α-keto acetals is facile from substituted cinnamaldehydes (Figure 3). Treatment of the 2-alkylcinnamaldehydes **7** or **8** with diol **6**[4,5] in toluene at reflux in the presence of catalytic *p*-toluenesulfonic acid led to clean formation of the acetals **9** or **10** in 94 and 85% yield, respectively. Ozonolysis of these compounds followed by reductive workup with dimethyl sulfide gave the desired ketoacetals **11** or **12**.

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Oxathianes have also been investigated. See Eliel, E. L; Koskimies, J. K.; Lohri, B.; Frazee, W. J.; Morris-Natschke, S.; Lynch, J. E.; Soai, K. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Ed.; ACS Symposium Series 185; Americal Chemical Society: Washington, DC, 1982; pp 37−53.

(2) (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Heitz, M. P.; Gellibert,F.; Mioskowski, C. *Tetrahedron Lett.* **1986**, *27*, 3859. (c) Tamura, Y.; Ko, T.; Annoura, H.; Fuji, M.; Takeuchi, R.; Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 2117.

(3) Tamura, Y.; Annoura, H.; Fuji, M.; Yoshida, T.; Takeuchi, R.; Fujioka, H. *Chem. Pharm. Bull.* **1987**, *35*, 4736.

(4) Since, at this point, we were primarily interested in examining the diastereoselectivity of the addition reactions of organomagnesium reagents to chiral α-keto acetals, we chose to carry out this initial series of experiments with racemic **6**.

(5) (1*R**,2*R**)-1,2-Diphenylethane-1,2-diol is prepared from *trans*-stilbene by treatment with osmium tetraoxide and *N*-methylmorpholine *N*-oxide in acetone/H_2O.

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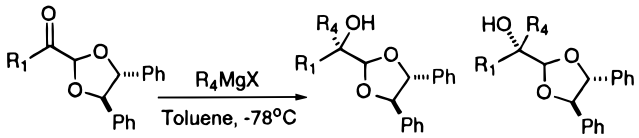
Table 1. Diastereoselective Additions to Chiral α-Keto Acetals



13, $R_1 = CH_3$ **14**, $R_1 = CH_3$
15, $R_1 = C_5H_{11}$ **16**, $R_1 = C_5H_{11}$

R_1	R_4	X	% yield	ratio	no.[a]
CH_3	phenyl	Cl	94	>**99:1**	**13a**
CH_3	allyl	Br	64	50:50	**13b**
CH_3	vinyl	Br	96	91:9	**13c**
CH_3	isopropyl	Cl	92	91:9	**13d**
CH_3	ethyl	Br	90	91:9	**13e**
$(CH_2)_4CH_3$	phenyl	Cl	81	>**99:1**	**15a**
$(CH_2)_4CH_3$	allyl	Br	94	60:40	**15b**
$(CH_2)_4CH_3$	vinyl	Br	85	>**99:1**	**15c**
$(CH_2)_4CH_3$	isopropyl	Cl	90	92:8	**15d**
$(CH_2)_4CH_3$	ethyl	Br	100	91:9	**15e**
$(CH_2)_4CH_3$	methyl	Br	63	80:20	**15f**

[a] Major product.

The results of addition reactions of alkyl-, aryl-, and vinylmagnesium halides to **11** and **12** are given in the Table 1 and show that the selectivity of addition is high for all of these reagents.[6] Typical reaction conditions required for maximum selectivity were the addition of a solution of excess organomagnesium reagent[7] to a precooled solution of α-keto acetal in toluene. Under these conditions, we found that the diastereoselectivities and yields were reproducibly high.[8] The exception to this trend was allylmagnesium bromide (Table 1, entries 2 and 7). The poor selectivity observed for this reagent stands in sharp contrast to the selectivities observed for all other examples.[9] Only one addition product was observed for the additions of phenylmagnesium bromide to **11** and **12** and the addition of vinylmagnesium bromide to **12**.

Having established the high diastereoselectivity of the addition reactions of organomagnesium reagents to the diphenyl acetals, we wished to determine the sense of asymmetric induction. To ascertain this we needed to synthesize optically active acetals. Diol **6** can be prepared in high enantiomeric excess from stilbene using Sharpless asymmetric dihydroxylation.[10] Treatment of optically active (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol with aldehyde **8** under the previously described conditions afforded optically active acetal **10′**.[11] Ozonolysis as before gave the desired α-keto acetal **12′**. Addition of methylmagnesium bromide to the carbonyl of **12′** furnished **15f′/16f′** with the same 80:20 diastereoselectivity as was observed for the racemic acetal **12** (see Table 1).

To prove the facial selectivity of the addition reaction, we converted the adducts **15f′/16f′** into the corresponding diols via reductive cleavage of the acetal and reduction of the aldehyde. The diphenyl acetal can be easily cleaved under hydrogenolytic conditions with Pearlman's catalyst[12] in ethanol to afford 2-hydroxyaldehyde **17** (Figure 4). Volatile aldehyde **17** could then be reduced ($NaBH_4$) to furnish diol **18**. To prove the sense of asymmetric induction, we synthesized **18** from 2-methyl-1-heptene by Sharpless asymmetric dihydroxylation with AD mix β.[13] After conversion to the MTPA esters,[14] the major diastereomeric esters were compared by ^{19}F NMR and found to be identical. Thus, addition of organomagnesium reagents to (4*R*,5*R*)-2-acyl-4,5-diphenyl-1,3-dioxolanes occurs from the *si* face of the carbonyl.

The high level of diastereoselectivity and the sense of asymmetric induction observed for the addition of organomagnesium reagents to these α-keto acetals is consistent with our hypothesis that chelation occurs and that elimination of heteroatom functionality and increased bulk in the diol will result in a reversal in and elevation of diastereoselectivity. In these models, the complexation of the magnesium ion with the carbonyl oxygen and one of the oxygens of the acetal results in the formation of a 2-magnesio-1,3,6-trioxabicyclo[3.3.0]oct-3-ene ring system. In structure **21**, the *endo* phenyl ring is placed two bonds away from the bridging C−O bond. In contrast, the *endo*-phenyl ring in structure **22** is in the sterically more encumbered position adjacent to the chelating magnesium ion and associated solvent ligands (Figure 5). Thus it is likely that **21** rather than **22** is the reactive chelate. Examination of the trajectories of addition of nucleophiles to the diastereotopic faces of the carbonyl in **21** shows that addition to the carbonyl from the *endo* side of the bicyclic system proceeds via a highly hindered trajectory. In contrast, addition from the *exo* face of **21** is free of steric hindrance.

These experiments show that, through analysis of the trajectories of addition of nucleophiles to carbonyls adjacent to acetals, the diastereoselectivity of addition can be significantly enhanced. In addition, the cleavage of the acetals of 1,2-diphenyl-1,2-ethanediol can be achieved easily under catalytic hydrogenation. We are currently extending this methodology to include other electrophilic systems and developing applications of this methodology in synthesis.

Experimental Section

General Experimental. All reactions involving moisture sensitive reagents were performed in oven-dried or flame-dried glassware under a positive pressure of argon. Benzene, toluene, and dichloromethane were distilled from CaH_2. Tetrahydrofuran and diethyl ether were distilled form sodium benzophenone ketyl. All reagents were obtained commercial sources and used as received. Nuclear magnetic resonance spectra were taken in $CDCl_3$ at 200, 360, or 400 MHz. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the $CHCl_3$. High resolution CI mass spectra were obtained by members of the UCLA Mass Spectrometry Facility. Melting points are uncorrected. Thin layer chromatograms were visualized using 254 nm ultraviolet light or by heating samples stained with vanillin solution. Chromatography was performed using 230−245 mesh silica gel and varying ratios of hexanes/ethyl acetate as eluent.

General Procedure for Acetal Formation. Unless otherwise stated, this protocol was used for synthesis of

(6) We also examined the impact of a variety of solvents and temperature combinations on the diastereoselectivity of the addition. The indicated conditions afforded the highest diastereoselectivities with the best reproducibility.

(7) See Experimental Section for details.

(8) The diastereomeric ratios were determined by integration of the ^1H NMR signals for the acetal protons of the diasteromers.

(9) This change in diastereoselectivity is likely due to a change in mechanism from inter- to intramolecular delivery of the nucleophile.

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(11) For compounds that were prepared in both racemic and optically active forms, a slanted prime following the number indicates that the compound is optically active.

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(14) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.

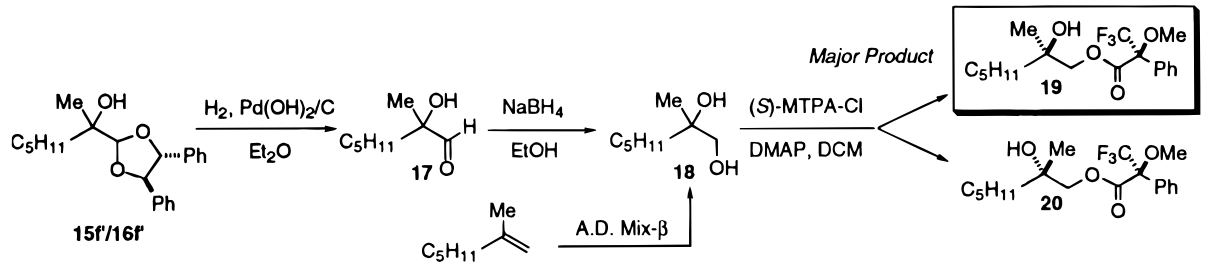

Figure 4.

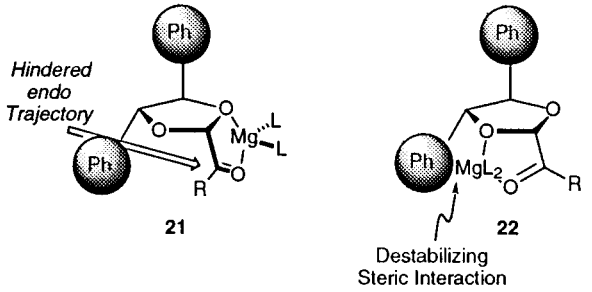

Figure 5.

acetals. To a stirred solution of an aldehyde (1 equiv, 0.1 M) in anhydrous benzene in the presence of *p*-toluenesulfonic acid (0.01 equiv) was added diol (1.2 equiv) at ambient temperature under argon. A Dean−Stark condenser was affixed to the flask and the resulting mixture heated at reflux overnight. The reaction mixture was allowed to cool to room temperature, quenched with a saturated solution of sodium bicarbonate, and extracted with diethyl ether (3×). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes:ethyl acetate (10:1) as eluent.

(4*R,5*R**)-2-[1-Methyl-2-phenylethenyl]-4,5-diphenyl-1,3-dioxolane (9).** From α-methyl-*trans*-cinnamaldehyde (1.25 g, 8.5 mmol) and (1*R**, 2*R**)-1,2-diphenyl-1,2-ethanediol (2.00 g, 9.35 mmol) in benzene (190 mL). **9** was obtained (2.73 g, 94%) as colorless crystals (mp 112 °C). ^{1}H NMR ($CDCl_3$) δ 7.48−7.38 (m, 15H), 6.94 (s, 1H), 6.00 (s, 1H), 4.97 (AB_q, $\Delta\nu$ = 7.2 Hz, J_{ab} = 7.2, 2H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.06, 136.59, 136.28, 134.63, 130.62, 129.04, 128.50, 128.45, 128.11, 127.01, 126.32, 108.71, 86.74, 85.58, 12.11. IR (NaCl) 3032, 2883, 1495, 1452, 1348, 1248, 1093, 1076, 1016, 916, 868, 763, 698, 648 cm^{-1}. HRMS (CI) calculated for $C_{22}H_{24}O_2$ $(M - H)^+$ 341.1542, observed 341.1536.

(4*R,5*R**)-2-[1-Pentyl-2-phenylethenyl]-4,5-diphenyl-1,3-dioxolane (10).** From α-amylcinnamaldehyde (1.72 g, 8.5 mmol) and (1*R**, 2*R**)-(+)-1,2-diphenyl-1,2-ethanediol (2.00 g, 9.35 mmol) in benzene (190 mL). **10** was obtained (2.87 g, 84.8%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.44−7.28 (m, 15H), 6.87 (s, 1H), 6.14 (s, 1H), 4.89 (AB_q, $\Delta\nu$ = 9 Hz, J_{ab} = 7.2, 2H), 2.60−2.48 (m, 2H), 1.84−1.71 (m, 2H), 1.49−1.36 (m, 4H), 0.93 (t, J = 7.6, 3H). ^{13}C NMR ($CDCl_3$) δ 139.83, 138.94, 138.30, 136.78, 136.44, 130.76, 128.81, 128.56, 128.53, 128.25, 128.09, 127.89, 127.06, 126.91, 126.83, 126.44, 108.58, 86.88, 85.27, 79.08, 32.43, 28.99, 27.08, 22.36, 14.07. IR (NaCl) 3063, 3032, 2955, 2930, 2870, 1495, 1454, 1352, 1286, 1101, 1003, 761, 698 cm^{-1}. HRMS (CI) calculated for $C_{28}H_{31}O_2$ (M^+) 399.23241, observed 399.23247.

(4*R*,5*R*)-2-[1-Pentyl-2-phenylethenyl]-4,5-diphenyl-1,3-dioxolane (10′). An identical procedure was used starting from (1*R*,2*R*)-1,2-diphenylethane-1,2-diol to furnish **10′**. $[\alpha]^{22}_D$ +5.78 (c = 1.35, $CHCl_3$).

General Procedure for the Ozonolysis of Alkene Acetals. A solution of alkene (1 equiv, 0.1 M) in dichloromethane:methanol (10:1) containing sodium bicarbonate (0.10 equiv) was cooled to −78 °C in dry ice/acetone bath. The cooled solution was treated with a stream of ozone until a pale blue color was observed. The solution was then treated with 3 mL of dimethyl sulfide and allowed to stir overnight at room temperature. The solution was then diluted with water, and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes:ethyl acetate (10:1) as eluent.

(4*R,5*R**)-2-Acetyl-4,5-diphenyl-1,3-dioxolane (11).** Compound **11** was prepared by the ozonolysis protocol above starting from **9** (443 mg, 1.29 mmol) and sodium bicarbonate (11 mg, 0.129 mmol) in dichloromethane:methanol (15 mL). The chromatography provided **11** (330 mg, 95%) as a colorless oil. Although **11** could be handled for brief periods of time, we found it to be unstable. It can be stored overnight at a concentration of 0.1 M in a benzene matrix at −10 °C. ^{1}H NMR ($CDCl_3$) δ 7.51−7.24 (m, 10H), 5.57 (s, 1H), 4.85 (AB_q, $\Delta\nu$ = 14.4 Hz, J_{ab} = 7.2, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 203.29, 135.89, 135.07, 129.06, 128.70, 128.54, 128.49, 126.63, 126.43, 125.97, 102.51, 86.74, 85.50, 24.55. IR (NaCl) 3065, 3034, 2895, 1813, 1736, 1496, 1456, 1109, 1043, 914, 765, 698 cm^{-1}

(4*R,5*R**)-2-Pentanoyl-4,5-diphenyl-1,3-dioxolane (12).** Compound **12** was prepared by the ozonolysis protocol above starting from **10** (751 mg, 1.89 mmol) and sodium bicarbonate (16 mg, 0.189 mmol) in dichloromethane:methanol (19 mL). The chromatography provided **12** (610 mg, 99.8%) as a colorless oil. Although **12** could be handled for brief periods of time, we found it to be unstable. It can be stored overnight at a concentration of 0.1 M in a benzene matrix at −10 °C. ^{1}H NMR ($CDCl_3$) δ 7.38−7.23 (m, 10H), 5.57 (s, 1H), 4.84 (AB_q, $\Delta\nu$ = 19.1 Hz, J_{ab} = 8.4, 2H), 2.78 (t, J = 6.8, 2H), 1.77−1.68 (m, 2H), 1.40−1.33 (m, 4H), 0.93 (t, J = 1.4, 3H). ^{13}C NMR ($CDCl_3$) δ 205.51, 136.03, 135.24, 128.67, 128.54, 128.50, 126.71, 126.47, 102.47, 86.77, 85.50, 37.11, 31.28, 22.54, 22.37, 13.84. IR (NaCl) 3065, 3034, 2957, 2932, 2872, 1732, 1496, 1456, 1113, 1022, 762, 698 cm^{-1}.

(4*R*,5*R*)-2-Pentanoyl-4,5-diphenyl-1,3-dioxolane (12′). An identical procedure was used starting from **10′** to furnish **12′**. $[\alpha]^{22}_D$ +40.6 (c = 2.42, $CHCl_3$).

General Procedure for the Addition of Alkylmagnesium Reagents to α-Keto acetals. A solution of α-keto acetals (0.1 M) in toluene was cooled to −78 °C in dry ice/acetone bath. Five equivalents of alkylmagnesium reagent was added dropwise to the solution via syringe. The resulting solution was stirred 10 min and quenched by the addition of saturated aqueous ammonium chloride solution, and the mixture was allowed to warm to room temperature. The mixture was extracted with diethyl ether (3×). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes:ethyl acetate (10:1) as eluent.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-phenylethyl]-4,5-diphenyl-1,3-dioxolane (13a) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-phenylethyl]-4,5-diphenyl-1,3-dioxolane (14a).** To a cooled (−78 °C) solution of **11** (24.7 mg, 0.092 mmol) in toluene (1.00 mL) was added phenylmagnesium chloride in THF (0.200 mL of 25% wt solution, 0.460 mmol) to obtain 30.0 mg (0.087 mmol, 94%) of the alcohols **13a**/**14a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.69−7.11 (m, 15H), 5.59 (s, 1H), 4.71 (AB_q, $\Delta\nu$ = 45.2 Hz, J_{ab} = 8.3, 2H), 2.53 (s, 1H), 1.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 143.12, 137.37, 135.73, 128.59, 128.49, 128.29,

128.03, 127.27, 126.82, 126.42, 125.98, 87.12, 58.56, 75.48, 24.19. IR (NaCl) 3402, 3063, 3032, 2887, 1604, 1496, 1456, 1373, 1338, 1101, 1026, 763, 698, 650 cm^{-1}.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-methyl-3-butenyl]-4,5-diphenyl-1,3-dioxolane (13b) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-methyl-3-butenyl]-4,5-diphenyl-1,3-dioxolane (14b).** To a cooled (−78 °C) solution of **11** (48.5 mg, 0.181 mmol) in toluene (1.80 mL) was added allylmagnesium bromide in diethyl ether (0.905 mL of 1.0 M solution, 0.905 mmol) to obtain 35.7 mg (0.115 mmol, 63.6%) of the alcohols **13b**/**14b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 10H), 6.07−5.96 (m, 1H), 5.33 (s, 1H), 5.22 (AB_q, $\Delta\nu$ = 4.0 Hz, J_{ab} = 1.4, 1H), 5.18 (d, J = 1.4, 1H), 4.79−4.75 (m, 2H), 2.56−2.40 (m, 2H), 2.16 (s, 1H), 1.36 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 137.72, 135.95, 128.66, 128.60, 128.54, 128.28, 126.83, 126.41, 118.67, 107.85, 107.74, 87.03, 85.47, 73.42, 41.93, 41.57, 21.72, 21.35. IR (NaCl) 3456, 3032, 2978, 2891, 1454, 1103, 1028, 914, 761, 698 cm^{-1}. HRMS (CI) calculated for $C_{20}H_{22}O_3$ (M + H)$^+$ 311.1647, observed 311.1645.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-methyl-2-propenyl]-4,5-diphenyl-1,3-dioxolane (13c) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-methyl-2-propenyl]-4,5-diphenyl-1,3-dioxolane (14c)**. To a cooled (−78 °C) solution of **11** (54.6 mg, 0.204 mmol) in toluene (2.00 mL) was added vinylmagnesium bromide in THF (1.018 mL of 1.0 M solution, 1.02 mmol) to obtain 58.1 mg (0.196 mmol, 96.4 %) of the alcohols **13c**/**14c** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (m, 10H), 6.24−6.12 (m, 1H), 5.34 (s, 1H), 5.42 (AB_q, $\Delta\nu$ = 72 Hz, J_{ab} = 17.4, 2H), 4.77 (AB_q, $\Delta\nu$ = 11.5 Hz, J_{ab} = 8.3, 2H), 2.31 (s, 1H), 1.47 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 140.18, 138.10, 136.55, 128.67, 128.56, 128.54, 128.35, 126.85, 126.48, 114.72, 107.88, 86.94, 85.76, 74.62, 22.46. IR (NaCl) 3460, 3032, 2982, 2883, 1496, 1456, 1101, 1039, 925, 761, 698 cm^{-1}. HRMS (CI) calculated for $C_{19}H_{20}O_3$ (M^+) 296.1412, observed 296.1416.

(4*R,5*R**)-2-[(1*S**-1-Hydroxy-1,2-dimethylpropyl]-4,5-diphenyl-1,3-dioxolane (13d) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1,2-dimethylpropyl]-4,5-diphenyl-1,3-dioxolane (14d)**. To a cooled (−78 °C) solution of **11** (48.5 mg, 0.181 mmol) in toluene (1.80 mL), isopropylmagnesium chloride in diethyl ether (0.452 mL of 2.0 M solution, 0.905 mmol) was added to obtain 51.7 mg (0.166 mmol, 91.7%) of the alcohols **13d**/**14d** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.22 (m, 10H), 5.44 (s, 1H), 4.79 (m, 2H), 2.12−2.04 (m, 2H), 1.27 (s, 3H), 1.07−1.00 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 137.98, 136.17, 128.61, 128.54, 128.23, 126.82, 126.82, 126.38, 106.87, 86.99, 85.26, 75.45, 33.86, 17.59, 16.78. IR (NaCl) 3491, 3032, 2968, 2885, 1454, 1122, 1009, 1026, 761, 698 cm^{-1}.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-methylpropyl]-4,5-diphenyl-1,3-dioxolane (13e) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-methylpropyl]-4,5-diphenyl-1,3-dioxolane (14e)**. To a cooled (−78 °C) solution of **11** (48.5 mg, 0.181 mmol) in toluene (1.80 mL) was added ethylmagnesium bromide in diethyl ether (0.302 mL of 3.0 M solution, 0.90 mmol) to obtain 51.2 mg (0.172 mmol, 95.0%) of the alcohols **13e**/**14e** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37−7.22 (m, 10H), 5.32 (s, 1H), 4.77 (AB_q, $\Delta\nu$ = 16.4 Hz, J_{ab} = 8.3, 2H), 2.05 (s, 1H), 1.83−1.65 (m, 2H), 1.34 (s, 3H), 1.05 (t, J = 7.5, 3H). ^{13}C NMR ($CDCl_3$) δ 137.78, 136.10, 129.21, 128.57, 128.53, 128.27, 126.79, 126.44, 126.06, 108.05, 86.99, 85.43, 73.89, 29.84, 20.54, 7.39. IR (NaCl) 3481, 3034, 2974, 2883, 1813, 1456, 1107, 1057, 1003, 762, 698 cm^{-1}. HRMS (CI) calculated for $C_{19}H_{22}O_3$ (M + H)$^+$ 299.1647, observed 299.1649.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-phenylhexyl]-4,5-diphenyl-1,3-dioxolane (15a) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-phenylhexyl]-4,5-diphenyl-1,3-dioxolane (16a).** To a cooled (−78 °C) solution of **12** (20.8 mg, 0.064 mmol) in toluene (0.650 mL) was added phenylmagnesium chloride in THF (0.175 mL of 25% wt solution, 0.321 mmol) to obtain 20.8 mg (0.052 mmol, 80.6%) of the alcohols **15a**/**16a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.64−7.04 (m, 15H), 5.59 (s, 1H), 4.68 (AB_q, $\Delta\nu$ = 54.7 Hz, J_{ab} = 8.2, 2H), 2.64 (s, 1H), 2.27−1.99 (m, 2H), 1.47−1.42 (m, 1H), 1.30−1.27 (m, 4H), 1.12−1.06 (m, 1H), 0.85 (t, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$) δ 141.60, 137.54, 135.84, 128.73, 128.59, 128.50, 128.48, 128.24, 127.98, 127.14, 126.99, 126.88, 126.38, 126.36, 108.45, 86.99, 85.49, 77.88, 36.55, 32.30, 22.54, 22.33, 14.03. IR (NaCl) 3491, 3063, 3032, 2953, 2930, ,2870, 1497, 1456, 1115, 1043, 762, 698 cm^{-1}. HRMS (CI) calculated for $C_{27}H_{30}O_3$ (M + H)$^+$ 401.2117, observed 401.2112.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-(2-propenyl)hexyl]-4,5-diphenyl-1,3-dioxolane (15b) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-(2-propenyl)hexyl]-4,5-diphenyl-1,3-dioxolane (16b)**. To a cooled (−78 °C) solution of **12** (24.7 mg, 0.076 mmol) in toluene (1.00 mL) was added allylmagnesium bromide in diethyl ether (0.381 mL of 1.0 M solution, 0.381 mmol) to obtain 26.2 mg (0.072 mmol, 93.9%) of the alcohols **15b**/**16b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.38−7.21 (m, 10H), 6.05−5.93 (m, 1H), 5.38 (s, 1H), 5.23−5.18 (m, 2H), 4.78 (AB_q, $\Delta\nu$ = 21.9 Hz, J_{ab} = 11.6, 2H), 2.59−2.47 (m, 2H), 1.98 (s, 1H), d 1.71 (t, J = 8.8, 2H), 1.55−1.49 (m, 2H), 1.44−1.32 (m, 4H), 0.91 (t, J = 6.9, 3H). ^{13}C NMR ($CDCl_3$) δ 138.00, 136.11, 128.60, 128.53, 128.21, 126.88, 126.83, 126.39, 126.31, 118.41, 107.02, 86.92, 85.28, 74.70, 39.52, 39.13, 35.13, 34.64, 32.53, 28.54, 22.61, 22.52, 14.06. IR (NaCl) 3500, 3067, 3034, 2955, 2928, 2872, 1497, 1456, 1171, 1116, 1026, 908, 762, 735, 698, 650 cm^{-1}. HRMS (CI) calculated for $C_{24}H_{30}O_3$ (M − H)$^+$ 365.2117, observed 365.2119.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-ethenylhexyl]-4,5-diphenyl-1,3-dioxolane (15c) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-ethenylhexyl]-4,5-diphenyl-1,3-dioxolane (16c)**. To a cooled (−78 °C) solution of **12** (20.8 mg, 0.064 mmol) in toluene (0.650 mL) was added vinylmagnesium bromide in THF (0.321 mL of 1.0 M solution, 0.321 mmol) to obtain 19.1 mg (0.054 mmol, 84.5%) of the alcohols **15c**/**16c** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35−7.19 (m, 10H), 6.10−6.02 (m, 1H), 5.45 (AB_q, $\Delta\nu$ = 47.6 Hz, J_{ab} = 17.5, 2H), 5.36 (s, 1H), 4.75 (AB_q, $\Delta\nu$ = 11.6 Hz, J_{ab} = 8.3, 2H), 2.24 (s, 1H), 1.79−1.75 (m, 2H), 1.48−1.26 (m, 6H), 0.90 (t, J = 6.8, 3H). ^{13}C NMR ($CDCl_3$) δ 138.96, 137.43, 135.88, 128.55, 126.91, 126.45, 115.39, 107.80, 86.84, 85.72, 35.26, 32.32, 22.63, 22.33, 14.07. IR (NaCl) 3486, 3032, 2953, 2928, 2870, 1456, 1167, 1120, 1026, 1001, 762, 698, 648 cm^{-1}. HRMS (CI) calculated for $C_{23}H_{28}O_3$ (M-H)$^+$ 351.1960, observed 351.1955.

(4*R,5*R**)-2-[(1*S**)-1-Hydroxy-1-isopropylhexyl]-4,5-diphenyl-1,3-dioxolane (15d) and (4*R**,5*R**)-2-[(1*R**)-1-Hydroxy-1-isopropylhexyl]-4,5-diphenyl-1,3-dioxolane (16d)**. To a cooled (−78 °C) solution of **12** (49.4 mg, 0.150 mmol) in toluene (1.50 mL) was added isopropylmagnesium chloride in diethyl ether (0.381 mL of 2.0 M solution, 0.762 mmol) to obtain 50.5 mg (0.137 mmol, 90%) of the alcohols **15d**/**16d** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 10H), 5.47 (s, 1H), 4.74 (AB_q, $\Delta\nu$ = 23.6 Hz, J_{ab} = 8.2, 2H), 2.20 (s, 1H), 2.15−2.12 (m, 1H), 1.81−1.64 (m, 2H), 1.38−1.31 (m, 4H), 1.08 (t, J = 4.4, 6H), 0.91 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$) δ 138.17, 136.28, 128.57, 128.53, 128.19, 126.74, 126.37, 106.84, 86.98, 84.86, 76.33, 32.98, 32.88, 32.44, 22.69, 17.39, 17.20, 14.11. IR (NaCl) 3501, 3034, 2957, 2928, 1732, 1497, 1456, 1116, 1016, 910, 762, 735, 698, 650 cm^{-1}. MS (CI) calculated for $C_{24}H_{32}O_3$ (M^+) 369.24, observed 369.24.

(4*R,5*R**)-2-[(1*R**)-1-Hydroxy-1-ethylhexyl]-4,5-diphenyl-1,3-dioxolane (15e) and (4*R**,5*R**)-2-[(1*S**)-1-Hydroxy-1-ethylhexyl]-4,5-diphenyl-1,3-dioxolane (16e)**. To a cooled (−78 °C) solution of **12** (20.8 mg, 0.064 mmol) in toluene (0.650 mL) was added ethylmagnesium bromide in diethyl ether (0.107 mL of 3.0 M solution, 0.321 mmol) to obtain 22.7 mg (0.064 mmol, 100%) of the alcohols **15e**/**16e** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37−7.21 (m, 10H), 5.38 (s, 1H), 4.78 (AB_q, $\Delta\nu$ = 9.9 Hz, J_{ab} = 8.3, 2H), 2.01 (s, 1H), 1.80−1.68 (m, 4H), 1.47−1.43 (m, 2H), 1.39−1.31 (m, 4H), 1.02 (t, J = 7.5, 3H), 0.91 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$) δ 138.03, 136.20, 128.59, 128.53, 128.20, 126.85, 126.38, 107.26, 86.87, 85.26, 75.12, 33.80, 32.62, 27.30, 22.69, 22.65, 14.07, 7.58. IR (NaCl) 3463, 3032, 2932, 1497, 1454, 1117, 1018, 762, 698 cm^{-1}.

(4*R,5*R**)-2-[(1*R**)-1-Hydroxy-1-methylhexyl]-4,5-diphenyl-1,3-dioxolane (15f) and (4*R**,5*R**)-2-[(1*S**)-1-Hydroxy-1-methylhexyl]-4,5-diphenyl-1,3-dioxolane (16f)**. To a cooled (−78 °C) solution of **12** (244 mg, 0.750 mmol) in toluene (7.50 mL) was added methylmagnesium bromide in diethyl ether (1.25 mL of 3.0 M solution, 3.76 mmol) to obtain 160 mg (0.471 mmol, 62.6%) of the alcohols **15f**/**16f** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.45−7.21 (m, 10H), 5.30 (s, 1H), 4.78 (AB_q, $\Delta\nu$ = 10 Hz, J_{ab} = 1.8, 2H), 2.02 (s, 1H), 1.71−1.65 (m, 2H),

1.59−1.47 (m, 2H), 1.41−1.31 (m, 6H), 0.92 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$) δ 137.80, 136.07, 129.22, 128.60, 128.54, 128.25, 126.85, 126.42, 126.06, 108.22, 86.94, 85.43, 73.76, 36.96, 32.54, 22.72, 22.67, 21.39, 14.07. IR (NaCl) 3460, 3032, 2932, 2870, 1815, 1496, 1454, 1373, 1115, 1028, 762, 698 cm^{-1}. HRMS (CI) calculated for $C_{22}H_{28}O_3$ (M − H)$^+$ 339.1960, observed 339.1955.

(4*R*,5*R*)-2-[(1*R*-1-Hydroxy-1-methylhexyl]-4,5-diphenyl-1,3-dioxolane (15f′) and (4*R*,5*R*)-2-[(1*S*)-1-Hydroxy-1-methylhexyl]-4,5-diphenyl-1,3-dioxolane (16f′). An identical procedure was used to furnish compounds **15f′** and **16f′**. $[\alpha]^{22}_D$ +36.6 (c = 3.11, $CHCl_3$).

2-Methyl-1,2-heptanediol (18). To a solution of **15f′** and **16f′** (80 mg, 0.231 mmol) in ether (2 mL) was added $Pd(OH)_2$ (80 mg). The reaction flask was then evacuated and back filled 2× with hydrogen gas. One atmosphere of H_2 was maintained for 18 h over the stirred reaction mixture with a rubber balloon. The solution was then filtered over Celite and carefully concentrated under vacuum to avoid loss of the volatile aldehyde **17**. The resulting oil was then dissolved in ethanol (2 mL), and $NaBH_4$ (10 mg, 0.27 mmol) was added. The mixture was stirred for 1 h at room temperature. The solution was then quenched with saturated NH_4Cl (5 mL), diluted with methylene chloride, and extracted (2×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes:ethyl acetate (5:1) as eluent. All spectral data were consistent with those obtained by Sharpless and coworkers for **18** (see reference 13).

(*R*)-2-Methyl-1,2-heptanediol (*S*)-α-Methoxy-α-(trifluromethyl)phenylacetate [MTPA] (19/20). Oxalyl chloride (22.4 μL, 0.254 mmol) was added to a solution of (*S*)-(−)MTPA (25 mg, 0.107 mmol) and DMF (8.5 μL, 0.107 mmol) in hexanes (4.45 mL) at room temperature. A white precipitate formed immediately. After stirring for 1 h, the mixture was filtered and the filtrate concentrated. A solution of **18** (6.5 mg, 0.045 mmol), Et_3N (17.8 μL, 0.134 mmol), and DMAP (*ca.* 5 mg) in $CDCl_3$ (500 μL) was added to the residue. After stirring for 2 h at room temperature, the mixture was analyzed by ^{19}F NMR. Compound **18** was also synthesized from 2-methyl-1-heptene by Sharpless asymmetric dihydroxylation with AD mix β (see reference 13). After conversion of this material to its MTPA esters, the major diastereomeric esters were compared by ^{19}F NMR and found to be identical. ^{19}F NMR ($CDCl_3$) δ (referenced to freon 113) −71.993, −72.029.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra, IR spectra, and where available mass spectra for compounds **9**−**15f** (85 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.

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