A Convenient Chiron for Substituted Cyclohexanones

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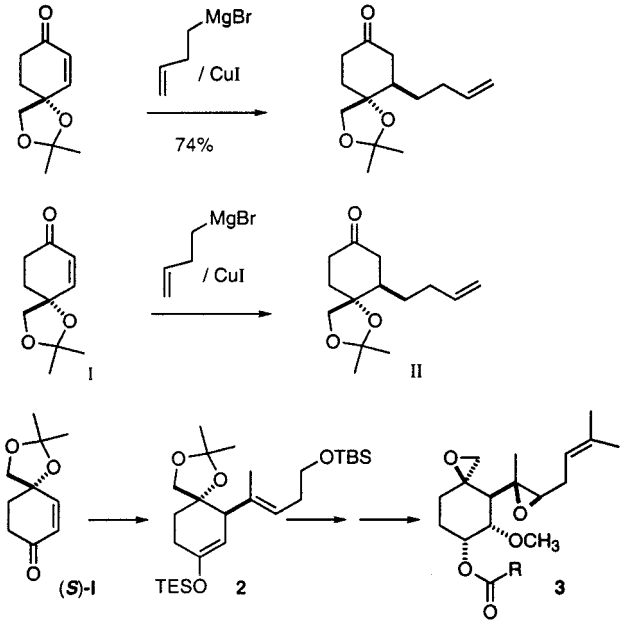
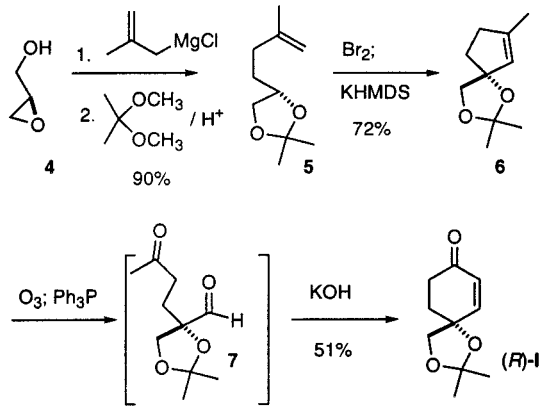
In the course of a recent synthesis of the antiangiogenic sesquiterpene fumagillin **3**,[2] we observed that conjugate addition to the enone (*S*)-**1** proceeded with high diastereoselectivity, to give predominantly **2**, the product from addition anti to the ketal oxygen. We have now found that this diastereoselective conjugate addition is a general phenomenon. We expect that the two enantiomers of cyclohexenone **1**, easily prepared in gram quantities from either (*S*)- or (*R*)-glycidol, will be useful chirons for the preparation of enantiomerically pure cyclohexane derivatives.[3]



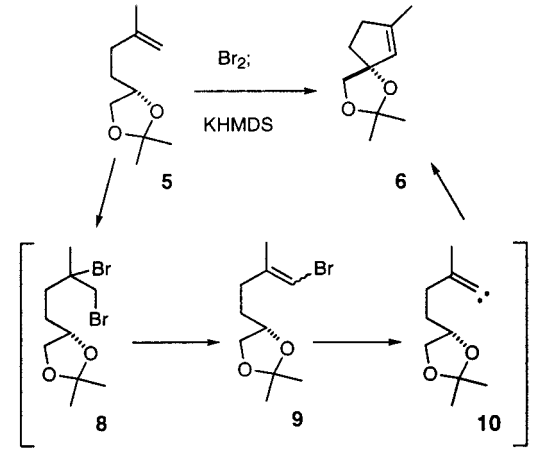
Preparation of Enone 1. The preparation of the cyclohexenone (*R*)-**1** (Scheme 1) began with the addition of the Grignard reagent prepared from 3-chloro-2-methylpropene to the commercially available (*S*)-glycidol **4**. Conversion of the resulting diol to the acetonide **5** then set the stage for the key reaction, the cyclization of **5** to **6**.

The cyclization of **5** to **6** (Scheme 2) involves initial bromination, to give the dibromide **8**, followed by elimination to give the bromoalkene **9**. Deprotonation of **9** followed by α-elimination gives the alkylidene carbene **10**, which inserts[4,5] (with retention of absolute configuration) into the methine H, to give **6**. Alkene **5** is particularly difficult to cyclize, because the ketal tends

Scheme 1



Scheme 2



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(5) Acetonide **6** was previously reported by Ohira: (a) Ohira, S.; Ishii, S.; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039. (b) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.

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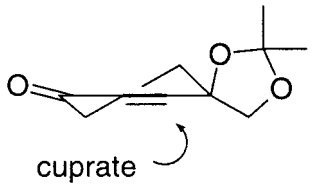
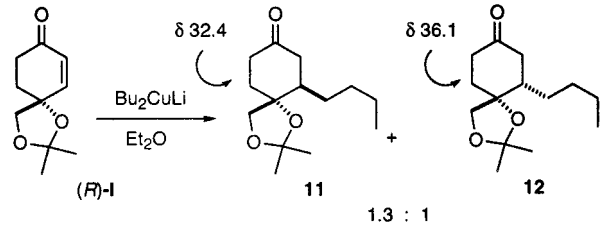
to participate in the bromination. An improved procedure for the cyclization of **5** to **6** is described in the Experimental Section. It is important to quickly add the KHMDS in toluene to the dibromide in ether at −78 °C, but not so quickly as to lead to a rise in the reaction temperature. We have developed an alternative general procedure for the cyclization of other 1,1-disubstituted alkenes that requires neither cryogenic temperatures nor such exacting conditions.[6]

Conjugate Addition to Enone 1. The diastereoselectivity that we had observed in the conversion of **1** to **2** (the structure of which was secured by X-ray crystallography of a derivative) was unusual. Typically, one would not expect that a quaternary center could be used to induce the absolute configuration of an adjacent ternary center as it formed. We had speculated, however, that the electronically favored conformation preferred by **1** would be as illustrated, with the oxygen of the ketal axial to maintain overlap with the enone. The expected axial addition of an organocuprate would then proceed primarily anti to the oxygen.[7]



Our initial attempts at conjugate addition were not encouraging. Addition of lithium di-*n*-butyl cuprate, prepared from *n*-butyllithium and CuI in ether, led to a 1.3:1 mixture of the diastereomers **11** and **12**. The structural assignment of **11** and **12** was based on the ^{13}C NMR spectra. The chemical shift for the ring methylene adjacent to the ketal for **11** was at δ 32.4, while the corrresponding chemical shift for **12** was at δ 36.1. This compares to δ 32.0 for the ketone derived from **2** following double desilylation. We have found this ^{13}C NMR pattern to be consistent through the series of conjugate addition products reported in this article. We expect that this difference is due to the differing electronic effect of the neighboring oxygen atom, which would be equatorial in **11**, and axial in **12**.



To our delight, the diastereoselectivity of the cuprate addition improved dramatically (Table 1) when chlorotrimethylsilane[8] was included in the reaction mixure. In this case, the crude reaction mixture was treated with tetrabutylammonium fluoride in THF to hydrolyze the initially formed silyl enol ether. Only traces of diastereomer **12** could be detected in the crude reaction product.

Table 1. Cu-Mediated Conjugate Addition to (*S*)-I Organometallic Ratio Major Diastereomer Isolated Yield, %

	Organometallic	Ratio	Major Diastereomer	Isolated Yield, %
1	Li	> 95:5	**11**	80
2	CH_3-Li	86:14	**13**	79
3	MgBr	86:14	**14**	73
4	MgBr	92:8	**15**	75
5	MgBr	93:7	**16**	74

The substantial diastereoselectivity observed for the chlorotrimethylsilane-promoted conjugate addition proved to be a general phenomenon (Table 1). Primary, secondary, and sp^2-hybridized organometallics added efficiently, to give the adducts **13**−**16**. The resulting diastereomers were readily separated by silica gel chromatography. The yields given are for the pure major diastereomer. In each case, the ring methylene adjacent to the ether oxygen for the major diasteromer resonated at higher field than the ring methylene adjacent to the ether oxygen for the minor diasteromer in the ^{13}C NMR.

CAUTION: The cyclohexenone (*S*)-**1** was shown to be >99% ee by chiral HPLC. After storage for 45 days at −20 °C, however, it had substantially racemized (49% ee).

The cyclohexenone (*R*)-**1** is easily prepared in gram quantities from the commercially available (*S*)-glycidol **4**. We anticipate that enones (*R*)-**1** and (*S*)-**1** will be generally useful chirons for the preparation of cyclohexanone derivatives of high enantiomeric purity.[3]

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian VXR-400S spectrometer at 400 and 100 MHz, respectively, unless otherwise noted. The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were obtained

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(7) For the origin of this analysis, see Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(8) For leading references to the use of R_3Si-Cl to promote Cu-mediated conjugate addition, see Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.

using FTMS at an ionizing potential of 70 eV. Optical rotations were determined at 20 °C with a 10 cm cell at a wavelength of 589 nm (Na^+ D-line). Substances for which C,H analysis are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. R_f values indicated refer to thin-layer chromatography on EM Science 5 × 10 cm, 250 um analytical plates coated with silica gel 60 F_{254} and developed in the solvent indicated. Materials were visualized using ceric molybdate in 50% aqueous methanol as stain. Column chromatography was performed on EM Science silica gel 60, 230−400 mesh. Solvent mixtures are volume/volume mixtures. All reactions were run under inert atmosphere (N_2), and all glassware was flame-dried immediately before use. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride under dry nitrogen. MTBE is methyl *tert*-butyl ether.

Alkene Acetonide (5). To a suspension of magnesium turnings (1.10 g, 45.2 mmol) and 1,2 dibromoethane (0.11 mL, 1.1 mmol) in dry diethyl ether (50 mL) chilled to 0 °C was added methallyl chloride (4.1 g, 45.2 mmol) over 20 min. This mixture was allowed to stir for 2 h at 0 °C and then at room temperature for 1 h. The reaction mixture was then chilled to −78 °C, and freshly distilled (*S*)-glycidol **4** (0.84 g, 11.31 mmol) in 10 mL of ether was added over 10 min. The reaction mixture was allowed to warm to room temperature over 30 min and then was stirred for an additional 1 h. The mixture was then partitioned between aqueous NH_4Cl and CH_2Cl_2, after which the aqueous phase was extracted with EtOAc. The organic fractions were combined and dried (Na_2SO_4) and then concentrated in vacuo, and the residue was carried on.

The crude diol (1.20 g, 9.23 mmol) was dissolved in 20 mL of 2,2-dimethoxypropane at room temperature, and TsOH (0.18 g, 0.92 mmol) was added. After 30 min at room temperature, the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled bulb to bulb ($bp_{0.5}$ (pot) = 50 °C-55 °C) to give 1.41 g (90% yield) of the acetonide **5** as a thin colorless oil (TLC R_f = 0.45, 5% EtOAc/hexane); $[\alpha]_D$ −7.0° (*c* 1.00, MeOH): ^{1}H NMR (300 MHz) δ 4.72 (d, *J* = 10 Hz, 2H), 4.10 (m, 2H), 3.55 (m, 1H), 2.21−2.01 (m, 2H), 1.85−1.60 (m, 2H), 1.65 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ C: 145.0, 108.6 CH: 75.4 CH_2: 110.1, 69.4, 33.8, 31.6 CH_3: 26.9, 25.7, 22.5; IR (neat) 2986, 1741, 1650, 1455, 1371 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_2$ 170.253221, found 170.254782.

Acetonide-Protected Cyclopentene (6). The acetonide **5** (1.6 g, 9.4 mmol) in 200 mL of dry diethyl ether was chilled to −78 °C. Br_2 (1.50 g, 9.4 mmol) was then added over 2 min, and the reaction was allowed to stir for 5 min. A solution of KHMDS (0.5 M in toluene, 75.3 mL, 37.65 mmol) was added over 10 min while maintaining the temperature below −65 °C. The reaction mixture was maintained at −78 °C for 10 min and then allowed to come up slowly to −30 °C over 1.5 h. After an additional 10 h at −30 °C, the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled bulb to bulb ($bp_{0.5}$ (pot) = 60−65 °C) to give 1.13 g (72% yield) of the desired cyclopentene derivative **6** as a thick clear oil (TLC R_f = 0.50, 10% EtOAc/hexane): $[\alpha]_D$ −13.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 5.35 (s, 1H), 3.82 (s, 2H), 2.41 (m, 1H), 2.21−2.02 (m, 3H), 1.79 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ C: 146.2, 108.7, 93.0 CH: 127.0 CH_2: 73.2, 37.0, 35.0 CH_3: 26.8, 26.8, 16.9; IR (neat) 3048 (b), 2934 (s), 1660 (w), 1368 (s) cm^{-1}; HRMS calcd for $C_{10}H_{16}O_2$ 169.122855, found169.123422.

Cyclohexenone (*S*)-1. The cyclopentene derivative **6** (330 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 was chilled to −78 °C. Ozone was passed through the solution until the starting material was consumed (TLC),and then N_2 was passed through the solution for 5 min. Triphenylphospine (0.63 g, 2.4 mmol) was added, and the reaction was allowed to warm to room temperature and then was stirred for 1 h. The solution was concentrated, and the residue was chromatographed to give 320 mg (82% yield) of the keto aldehyde **7** as a thin clear oil (TLC R_f = 0.50, 50% EtOAc/hexane): $[\alpha]_D$ −19.2° (*c* 0.7, $CHCl_3$).

The keto aldehyde **7** (230 mg, 1.2 mmol) in 2.5 mL of CH_2Cl_2 and 2.5 mL of 5% aqueous potassium hydroxide were stirred at room temperature for 24 h. The mixture was partitioned between 5% aqueous potassium hydroxide and CH_2Cl_2, and the combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give 176 mg (51% yield from **6**) of the cyclohexenone derivative (*S*)-**1** as a thick colorless oil (TLC R_f = 0.47, 50% EtOAc/hexane): $[\alpha]_D$ −37.7° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 6.75 (d, *J* = 10.2 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.90 (d, *J* = 9.0 Hz, 1H), 2.65, (m, 1H), 2.40 (m, 1H), 2.21 (m, 2H), 1.55 (s, 3H), 1.46 (s, 3H), 1.44 (s, 1H); ^{13}C NMR δ C: 198.4, 110.5, 78.1 CH: 150.6, 130.0 CH_2: 71.7, 35.1, 33.3 CH_3: 27.1, 26.8; IR (neat) 3142 (m), 2908 (m), 1566 (s) cm^{-1}.

The cyclohexenone (*S*)-**1** was shown to be >99% ee by chiral HPLC on an analytical Chiralcel OD column. Eluting with 150:1 hexanes/2-propanol at 1.0 mL/min, the cyclohexenone (*S*)-**1** (18.8 min) and the *R* enantiomer (20.1 min) showed baseline resolution. Caution: after 45 days at −20 °C, the cyclohexenone (*S*)-**1** was substantially racemized (49% ee).

Addition of Di(*n*-butyl)cuprate to Enone (without TMSCl). To a 0 °C suspension of copper iodide (100 mg, 0.55 mmol) in ether (3 mL) was added *n*-butyllithium (0.44 mL, 2.5 M in hexane, 1.1 mmol). After 10 min, the reaction mixture was chilled to −78 °C and enone (*S*)-**1** (50 mg, 0.27 mmol) in ether (1 mL) was added. After 30 min, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extract was dried (Na_2SO_4) and then concentrated in vacuo. ^{1}H NMR indicated a 1.3: 1 mixture of diastereomers. These were separated by column chromatography.

Diastereomer **11:** colorless oil, 28 mg (43% yield from (*S*)-**1**): TLC R_f = 0.49 (20% EtOAc/Hexane), $[\alpha]_D$ +29.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 3.91 (d, *J* = 8.6 Hz, 1H), 3.83 (d, *J* = 8.6 Hz,1H), 2.85 (m, 1H), 2.78−2.60 (m, 1H), 2.25 (m, 2H), 2.00 (m, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.35−1.00 (m, 6H), 0.88 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR δ C: 211.7, 109.5, 82.0 CH: 45.7 CH_2: 71.7, 42.0, 37.6, 32.4, 30.7, 29.6, 22.7 CH_3: 27.8, 26.8, 13.9; IR (neat) 2930, 2864, 1717, 1461, 1374 cm^{-1}; HRMS calc for $C_{14}H_{24}O_3$ 240.34486, found 240.34124.

Diastereomer **12:** colorless oil, 22 mg (34% yield from (*S*)-**1**), TLC R_f = 0.43 (20% EtOAc/hexane): $[\alpha]_D$ −27.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 4.03 (d, *J* = 8.6 Hz, 1H), 3.84 (d, *J* = 8.6 Hz, 1H), 2.74−2.62 (m, 1H), 2.40−2.30 (m, 3H), 2.21−2.15 (m, 1H), 1.95−1.65 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.40−1.05 (m, 6H), 0.89 (t, *J* = 5.5 Hz, 3H); ^{13}C NMR δ C: 211.0, 109.8, 81.2 CH: 44.0 CH_2: 72.1, 43.0, 37.9, 36.1, 29.7, 29.2 CH_3: 26.8, 26.6, 22.7, 14.0; IR (neat) 2929, 1716, 1250 cm-^{1}; HRMS calc for $C_{14}H_{24}O_3$ 240.34486, found 240.35021.

Addition of Dibutylcuprate to Enone (with TMSCl). To a 0 °C suspension of copper iodide (210 mg, 1.1 mmol) in ether (6 mL) was added *n*-butyllithium (0.88 mL, 2.5 M in hexane, 2.2 mmol). After 10 min, the reaction mixture was chilled to −78 °C and the enone (100 mg, 0.55 mmol) mixed with TMSCl (66 mg, 0.6 mmol) in ether (1 mL) was added. The reaction mixture was stirred for 30 min and then was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and then concentrated in vacuo. ^{1}H NMR of the crude residue indicated a single dominant diastereomer. Chromatography gave diastereomer **11** as a colorless oil, 105 mg (80% yield from **1**), data as above.

Addition of Lithium Dimethylcuprate to Enone 1 with TMSCl. To a 0 °C suspension of copper iodide (83.6 mg, 0.44 mmol) in ether (4 mL) was added methyllithium (0.58 mL, 1.5 M in ether, 0.88 mmol). After 10 min, the reaction mixture was chilled to −78 °C and TMSCl (85 μL, 0.66 mmol) was added, followed after 5 min by the enone **1** (40 mg, 0.22 mmol) in ether (0.5 mL). After 30 min, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **13** as a colorless oil, 34.6 mg (79% yield from **1**): TLC R_f = 0.32 (20% EtOAc/hexanes), $[\alpha]_D$ +16.26 (*c* 0.38, $CHCl_3$); ^{1}H NMR (250 MHz) δ 3.90 (d, *J* = 8.7 Hz, 1H), 3.80 (d, *J* = 8.7 Hz, 1H), 2.88 (m, 1H), 2.67 (m, 1H), 2.25 (m, 2H), 2.17 (m, 1H), 2.05 (m, 2H), 1.47 (s, 3H), 1.42 (s, 3H), 0.91 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR δ C: 211.4, 109.6, 81.8 CH: 40.1 CH_2: 71.4, 45.4, 37.8, 31.9 CH_3: 27.7, 26.8, 17.0; IR (neat) 2932, 2860, 1718, 1368 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_3$ 198.26277, found 198.26332.

For the minor diastereomer: TLC R_f = 0.27 (20% EtOAc/hexane); ^{1}H NMR (250 MHz) δ 4.0 (d, J = 8.64 Hz, 1H), 3.81 (d, J = 8.64 Hz, 1H), 2.7 (m, 1H), 2.6 (m, 1H), 2.35−1.75 (m, 5H), 1.46 (s, 3H), 1.44 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H).

General Procedure for the Addition of Phenyl, 3-Butenyl, and Isopropyl Grignard to Enone 1 with TMSCl. Copper(I) bromide−dimethyl sulfide complex (103 mg, 0.5 mmol) and dry lithium chloride (21.2 mg, 0.5 mmol) were placed in a 10 mL flame-dried round-bottom flask. THF (3 mL) was injected, and the mixture was stirred for 5 min to give a yellow solution. The mixture was chilled to −78 °C, and the alkyl or arylmagnesium bromide solution (0.7 mL of 0.72 M in THF, 0.5 mmol) was added. After a few minutes, TMSCl (64 μL, 0.5 mmol) was added, followed immediately by the addition of the enone (45 mg, 0.25 mmol) in THF (0.5 mL). The reaction mixture was stirred for 15 min at − 78 °C and then warmed to −30 °C over 30 min. After stirring for 15 min at −30 °C the mixture was partitioned between saturated aqueous NH_4Cl (4 mL) and diethyl ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was taken up in THF (15 mL), and TBAF (0.2 mL of 1 M in THF) was added. After 30 min, the mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed, followed by bulb-to-bulb distillation before determinaton of $[\alpha]_D$.

Addition of Isopropyl Grignard to Enone 4 with TMSCl. Conjugate addition of isopropyl Grignard (0.7 mL of a 0.72 M solution in THF) to 36 mg of the enone proceeded to give an 86:14 ratio of the two adducts in 90% isolated yield. The major product **14** was isolated as a white solid, 45 mg (73% yield from **1**): TLC R_f = 0.49 (20% EtOAc/hexane), $[\alpha]_D$ +16.12 (c 0.8, $CHCl_3$); ^{1}H NMR (250 MHz) δ 3.96 (d, J = 8.7 HZ, 1H), 3.91 (d, J = 8.7 Hz, 1H), 2.81 (dd, J = 5.6, 16.0 Hz, 1H), 2.7−2.6 (m, 1H), 2.41−2.25 (m, 2H), 2.1−1.96 (m, 2H), 1.87 (m, 1H), 1.7−1.5 (m, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (73 MHz) δ C: 211.8, 108.5, 82.4 CH: 51.2, 28.5 CH_2: 71.7, 40.81, 37.35, 32.61 CH_3: 27.90, 26.50, 23.05, 20.01; IR (neat) 2983, 2960, 2874, 1711 cm^{-1}.

For the minor diasteroemer: TLC R_f = 0.45 (20% EtOAc/hexane); ^{1}H NMR δ 4.04 (d, J = 8.6 Hz, 1H), 3.81 (d, J = 8.6 Hz, 1H), 2.8−2.5 (m, 2H), 2.35−2,2 (m, 4H), 1.85−1.62 (m, 2H), 1.46 (s, 3H), 1.45 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 7 Hz, 3H).

Addition of Phenyl Grignard to Enone 4 with TMSCl. Conjugate addition of phenyl Grignard (0.5 mL of a 0.97 M solution in THF) to 38 mg of the enone proceeded to give a 92:8 ratio of the two adducts in 91% isolated yield. The major product **15** was isolated as a white solid, 41.7 mg (75% yield from **1**): TLC R_f = 0.32 (20% EtOAc/hexane), $[\alpha]_D$ −4.93° (c 0.73, $CHCl_3$); ^{1}H NMR (250 MHz) δ 7.35−7.25 (m, 3H), 7.15−7.11 (m, 2H), 4.04 (d, J = 8.9 Hz, 1H), 3.57 (d, J = 8.9 Hz, 1H), 3.44 (t, J = 5.05 Hz, 1H), 2.99 (m, 1H), 2.81 (m, 1H), 2.65−2.46 (m, 2H), 2.1 (m, 1H), 1.95 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR δ C: 211.1, 140.3, 109.8, 81.5 CH: 128.8, 128.4, 127.3, 50.2 CH_2: 70.3, 43.5, 37.8, 31.65 CH_3: 27.5, 26.6; IR (neat) 2982, 2959, 2870, 1702, 1452 cm^{-1}.

Addition of 3-Butenyl Grignard to Enone 4 with TMSCl. Conjugate addition of 3-butenyl Grignard (0.7 mL of a 0.73 M solution in THF) to 38 mg of the enone **1** proceeded to give a 93:7 ratio of the two adducts in 92% isolated yield. The major product **16** was isolated as an oil, 35.7 mg (74% yield from **1**): TLC R_f = 0.43 (20% EtOAc/hexane), $[\alpha]_D$ +34.5 (c 0.95, CHCl3), ^{1}H NMR (250 MHz) δ 5.71 (m, 1H), 4.97 (m, 2H), 3.89 (d, J = 8.6 Hz, 1H), 3.82 (d, J = 8.6 Hz, 1H), 2.84 (dd, J = 5.3, 14.4 Hz, 1H), 2.75−2.6 (m, 1H), 2.3−2.15 (m, 3H), 2.1−1.9 (m, 4H), 1.46 (s, 3H), 1.40 (s, 3H), 1.38−1.1 (m, 2H); ^{13}C NMR δ C: 211.4, 109.5, 81.8 CH: 137.5, 44.8 CH_2: 115.5, 71.6, 41.8, 37.5, 32.4, 31.2, 30.0 CH_3: 27.7, 26.7; IR (neat) 3075, 2983, 2932, 2865, 1718, 1640 cm^{-1}.

To check the enantiomeric purity, **16** (28.3 mg, 0.1 mmol) was dissolved in 2 mL of a mixture of acetone and water (acetone: water/3:1). PPTS (12.0 mg, 0.05 mmol) was added, and the reaction mixture was heated to reflux for 5 h and then diluted with EtOAc. Acetone was removed under vacuum, and the reaction mixture was partitioned between EtOAc and saturated brine. The combined organic extract was dried (Na_2SO_4) and then concentrated, and the residue was carried on.

The crude diol (15.0 mg, 0.08 mmol) was dissolved in 0.5 mL of dichloromethane. Triethylamine (17.0 mg, 0.2 mmol), 4-DMAP (2.0 mg, 0.02 mmol), and benzoyl chloride (22.4 mg, 0.2 mmol) were added sequentially. After stirring at room temperature for 1 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl at 0 °C. The mixture was then partitioned between dichloromethane and sequentially, 5% aqueous NaOH, 5% HCl, and saturated brine, and the combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the primary benzoate as pale yellow oil (18.3 mg, 50% yield based on **16**). TLC R_f = 0.32 (50% EtOAc/petroleum ether). ^{1}H NMR δ 1.19 (m, 2H), 1.60 (m, 1H), 1.96 (m, 3H), 2.24 (m, 4H), 2.69 (m, 1H), 2.89 (dd, J = 5.2 and 14.2 Hz, 1H), 4.41 (dd, J = 11.8 and 37.4 Hz, 2H), 5.94 (m, 2H), 5.67 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.57 (m, 1H), 8.00 (m, 2H); ^{13}C NMR δ d 43.3, 128.8, 129.9, 133.7, 137.6; u 29.2, 31.3, 31.4, 36.9, 40.6, 69.4, 72.7, 115.9, 129.6, 167.0, 211.5; IR 3435, 2938, 1722, 1714, 1451 cm^{-1}. The benzoate was shown to be 86% ee by chiral HPLC on an analytical Chiralcel OD column. Eluting with 100:20 hexanes/2-propanol at 1.0 mL/min, the benzoate (8.9 min) and the *ent*-benzoate (7.0 min) showed baseline resolution.

As all of the conjugate additions described above were carried out within a week of each other, we expect that each of the products had about this same ee.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **5**, **6**, **11**, **12**, **13**, **14**, **15**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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