Asymmetric Hydrogenation Routes To Deoxypolyketide Chirons

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**General Experimental Conditions.** GC analysis of samples was preceded by filtering the samples through a small plug of silica, eluting with 2 ml of a 30% solution of ethyl acetate in hexanes. Freeze-thaw was performed by first cooling the sample to -78 °C under nitrogen, applying vacuum for 5 min, then warming to 25 °C under nitrogen. Ethyl tiglate, tiglic acid, *trans*-2-methyl-2-butenal, DMAP, methyl-2-bromopropionate, and triphenylphosphine were ordered from Sigma-Aldrich or TCI and used without further purification. Methoxymethyamine hydrochloride, oxalyl chloride, and (S)-2-methyl-1-butanol were purchased from Lancaster and used as received. Silver nitrate was purchased from Strem and used as received. Methoxycarbonylethylidene-triphenylphosphorane was generated using the known two-step procedure from methyl-2-bromopropionate, triphenylphosphine, and sodium hydroxide.\(^1\) Dichloromethane was distilled from calcium hydride prior to use. Other solvents and reagents were used as received. Details of the syntheses of the internal deoxypolyketide fragments were included in our previous publication.\(^2\) NMR spectra were recorded on a Varian Unity Plus 300 spectrometer (\(^1\)H at 300 MHz, and \(^{13}\)C at 75 MHz). Chemical shifts of \(^1\)H and \(^{13}\)C spectra were referenced to the NMR solvents. Flash chromatography was performed using silica gel (230–600 mesh). Thin layer chromatography was performed using glass plates coated with silica gel 60 F254 (E. Merck, Darmstadt, Germany). The hydrogenation results were analyzed using GC with a chiral column\(^3\) using two different conditions depending on the products: for hydrogenation products 2: {carrier gas: helium; temperature: 60 °C; flow rate: 2.0 ml/min; retention time varies by product (shown below)}/; for hydrogenation products 3: {carrier gas: helium; temperature: 90 °C; flow rate: 2.0 ml/min; retention time varies by product (shown below)}/. IR spectra were collected on a Perkin Elmer Spectrum One FT-IR instrument. HRMS data was collected on a PE SCIEX API QSTAR PULSAR instrument.
Synthesis of Monoenes and Dienes

Monoenes

**E-2-Methyl-2-butenol (2a).** E-2-methyl-2-butoenoic acid (3.15 g, 21.6 mmol, 1 eq.) was added slowly in 0.5 g portions to a slurry of 3.3 g (86 mmol, 4 eq.) lithium aluminum hydride in 50 ml dichloromethane cooled to 0-5 °C in an ice bath. This was allowed to warm to ambient temperature over 4 h, after which time it was cooled back to 0-5 °C, and 20 ml of methanol was added slowly, drop wise, to quench the excess hydride. After quenching, a solution of 150 ml of saturated sodium potassium tartrate was added and stirred for 2 h, after which time an additional 50 ml dichloromethane was added, and the layers separated. The aqueous layer was extracted an additional 3 times with 50 ml of dichloromethane, and the combined organic extracts dried over sodium sulfate. Concentration of the dichloromethane layers afforded 2.6 g of the title compound, a 96 % isolated yield of the title compound. \textsuperscript{1}H NMR matched the known alcohol. \textsuperscript{4,7} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ (ppm) = 5.52 (qt, \(J = 6.5, 1.3\) Hz, 1H), 4.03 (s, 2H), 1.69 (s, 3H), 1.40 (bs, 1H).

**E-3-methyl-4-(oxobenzyl)-2-butene (2b).** To 28 ml of tetrahydrofuran was added 1.0 g (12 mmol, 1 eq.) tiglic alcohol, then 560 mg (24 mmol, 2 eq.) sodium hydride (70% dispersion in mineral oil) was added after cooling to 0 °C. After stirring for 30 min, benzyl bromide (4 g, 23.2 mmol, 2 eq.) was added, and this was allowed to stir for 4 h. Concentration of the reaction mixture under reduced pressure followed by column chromatography with 1.5 % ethyl acetate in hexanes gave 530 mg, a 26 % isolated yield of the title compound as a slightly yellow oil. \textsuperscript{1}H NMR matched the known spectrum. \textsuperscript{8} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ (ppm) = 7.35 (m, 5H), 5.54 (qq, \(J = 6.8, 1.2\) Hz, 1H), 4.46 (s, 2H), 3.91 (s, 2H), 1.69 (s, 3H), 1.66 (dq, \(J = 6.7, 1.1\) Hz, 3H).

**1-(E-2-methyl-2-butenyl)-tertbutyldimethylsilyl Ether (2c).** E-2-methyl-2-butenol (1 g, 11.6 mmol, 1 eq.) was added to 335 mg (13.9 mmol, 1.2 eq.) of previously hexane-
rinsed sodium hydride (from a 70 % dispersion in mineral oil) in 20 ml of diethyl ether at 0 °C. This was stirred 30 min, at the end of which time 2.1 g (13.9 mmol, 1.2 eq.) tertbutyldimethylsilyl chloride was added all at once, followed by stirring for 4 h. Concentration under reduced pressure followed by column chromatography with 7.5 % ethyl acetate in hexanes (Rf = 0.8 in 2% ethyl acetate in hexanes) gave the title compound as a clear oil, 1.15 g, 49 % isolated yield. ¹H NMR matched the known compound.⁹ ¹H NMR (CDCl₃, 300 MHz): d (ppm) = 5.50 (dt, J = 5.3, 1.5 Hz, 1H), 4.40 (s, 2H), 1.65 (q, J = 1.3, 1.1 Hz, 3H), 1.63 (s, 3H), 0.94 (s, 9H), 0.09 (s, 6H).

**Tetrabutylammonium 2-Methyl-2-butenoate (2e).** E-2-Butenoic acid (1 g, 10 mmol, 1 eq.) was added to 40 ml of water, and ammonium hydroxide was added until the solution had a slightly ammonal odour and was basic by litmus testing. After heating for 1 h at 70 °C to remove excess ammonia, silver nitrate (1.7 g, 10 mmol, 1 eq.) as a solution in 10 ml of water was added drop wise. Stirring for 20 min at 70 °C produced a solid which was filtered, then washed sequentially with water, ethanol, and ether, and dried 12 h under vacuum to produce 752 mg, 36 % isolated yield, of the silver salt as a white solid. This was then added along with tetrabutylammonium iodide (1.3 g, 3.6 mmol, 1 eq.) to 20 ml of methanol, and heated to 40 °C for 18 h. Filtration, and concentration of the filtrate under reduced pressure produced 1.2 g of the title compound as a hydroscopic white powder, 98 % isolated yield over the second step, or 35 % yield overall. IR: 3389, 2875, 2326, 1649, 1556 cm⁻¹ (which had absorbed some atmospheric moisture). ¹H NMR (CDCl₃, 300 MHz): d (ppm) = 6.67 (qt, J = 7.1, 1.5 Hz, 1H), 3.33 (t, J = 8.8 Hz, 12H), 1.83 (t, J = 1.1 Hz, 3H), 1.72 (d, J = 1.1 Hz, 3H), 1.70 (d, J = 1.1 Hz, 3H), 1.47 (sextet, J = 7.1, 7.1 Hz, 12H), 1.01 (t, J = 7.2 Hz, 14H). ¹³C{¹H} (CDCl₃, 100.4 MHz): d (ppm) = 131.2, 100.2, 59.1, 24.3, 20.0, 13.9 (incomplete carbon NMR was due to formation of some unidentified salts during the acquisition). MS (M/Z, positive and negative modes): calculated (tiglic anion): 99.04, found (in negative mode): 99.02; calculated (tetrabutylammonium cation): 242.28, found (in positive mode): 242.28.
Benzyl \textit{E}-2-Methyl-2-butenoate (2g). Tiglic acid (2 g, 20 mmol, 1 eq.) was added to 20 ml of tetrahydrofuran, followed by benzyl bromide (3.76 g, 22 mmol, 1.1 eq.) and triethylamine (4.4 ml, 30 mmol, 1.5 eq.). This was stirred at 0 °C for 2 h, then at ambient temperature for 18 h. Diethyl ether (30 ml) was then added, followed by 30 ml of sodium bicarbonate, which was then separated. The aqueous extracts were washed with an additional 20 ml of diethyl ether, and the combined organic layers washed with 30 ml of 1 M aqueous HCl solution, then dried over sodium sulfate. Concentration under reduced pressure followed by column chromatography with 2 % ethyl acetate in hexanes (Rf: 0.75) gave 800 mg of the product, 21 % isolated yield, as a viscous colorless oil. $^1$H NMR matched the known compound.$^9$ $^1$H NMR (CDCl$_3$, 300 MHz): d (ppm) = 7.4 (m, 5H), 6.95 (qq, $J$ = 7.1, 1.6 Hz, 1H), 5.22 (s, 2H), 1.90 (s, 3H), 1.83 (dq $J$ = 7.2, 1.1 Hz, 3H).

(4-Nitrobenzyl) \textit{E}-2-Methylbutenoate (2h). To a solution of tiglic acid (1.0 g, 1.0 eq., 10 mmol) in 10 ml of acetonitrile was added 2.16 g (1.0 eq., 10 mmol) 4-nitrobenzylbromide. This was allowed to stir under reflux for 18 h, after which time the reaction mixture was washed with water then 10 ml of saturated sodium carbonate 3 times. The organic layer was then concentrated \textit{in vacuo} and 1.46 g of the title compound, 46% isolated yield, was isolated by filtration as it crystallized from solution as an off-white powder identical by $^1$H NMR to the known compound.$^1$ $^1$H NMR (CDCl$_3$, 300 MHz): d (ppm) = 8.27 (d, $J$ = 9.8 Hz, 2H), 7.60 (d, $J$ = 9.9 Hz, 2H), 6.95 (q, $J$ = 6.8 Hz, 1H), 5.30 (s, 2H), 2.10 (s, 3H), 1.95 (d, $J$ = 7.2 Hz, 3H).

\textit{N}-Methoxy-\textit{N},2-dimethyl-(2\textit{E})-2-butenamide (2i). \textit{E}-2-Methyl-2-butenoic acid (1 g, 10 mmol, 1 eq.) was dissolved in 20 ml of dichloromethane and cooled to 0 °C. Oxaly
chloride (5 ml, 50 mmol, 5 eq.) was added to this solution dropwise, and was stirred for 30 min at 0 °C followed by 30 min at ambient temperature. After concentrating under reduced pressure to remove excess oxalyl chloride, 20 ml of dichloromethane was added followed by cooling to 0 °C. Methoxymethylamine hydrochloride (1.46 g, 15 mmol, 1.5 eq.) and then dimethylaminopyridine (2.44 g, 20 mmol, 2 eq.) were added to the reaction (an older bottle of methoxymethylamine hydrochloride gave lower yield). This was allowed to warm to ambient temperature over 18 h. After concentrating to a slurry under reduced pressure, the material was subjected to column chromatography with 15 % methanol in dichloromethane (Rf: 0.9) to give 1.1 g of the title compound, 77% isolated yield. 1H NMR matched the known compound. 

\[ \text{1H NMR (CDCl}_3, 300 MHz): d (ppm) = 5.96 (qq, J = 7.0, 1.6 Hz, 1H), 3.62 (s, 3H), 3.22 (s, 3H), 1.86 (s, 3H), 1.73 (dq, J = 6.8, 1.2 Hz, 3H). \]

Dienes

\( \text{E,E-2,4-Dimethyl-2,4-hexadienol (3a).} \) Methyl-\( \text{E,E-2,4-dimethyl-2,4-hexanoate} \) (prepared below) (2.5 g, 16 mmol, 1 eq.) was added to 100 ml of dichloromethane and cooled to 0 °C. To this was added diisobutylaluminum hydride drop wise (43 mmol, 2.7 eq., 1 M in hexanes), and was stirred for 3 h, after which time it was quenched by slow addition of 50 ml of methanol (the addition was slow enough such that the temperature never rose above 10 °C). After quenching, 100 ml of a solution of saturated sodium potassium tartrate was added and stirred for 2 h, after which time 30 ml of diethyl ether was added, and the layers separated. The aqueous layer was extracted an additional 3 times with 30 ml of diethyl ether, and the combined organic extracts dried over anh. sodium sulfate. Concentration of the organic layers followed by column chromatography (20 % ethyl acetate in hexanes, Rf 0.3 when eluting with the same) afforded 1.54 g, a 75 % yield of the title compound. The 1H NMR matches the known compound. 

\[ \text{1H NMR (CDCl}_3, 300 MHz): d (ppm) = 5.92 (s, 1H), 5.46 (qt, J = 6.8 Hz, 1H), 4.07 (s, 2H), 1.84 (s, 3H), 1.78 (s, 3H), 1.72 (d, J = 7.0 Hz, 3H). \]
Methyl \(E,E\)-2,4-Dimethyl-2,4-hexadienoate (3b). The method developed by Patel and Pattendon was used.\(^{14,15}\) To a solution of methoxycarbonylethylidenetriphenylphosphorane (3.8 g, 11 mmol, 1.05 eq.) in dichloromethane (25 ml) was added \(E\)-2-methyl-2-butenal (860 mg, 10 mmol, 1 eq.). This solution was then heated at 40 °C for 18 h, at the end of which time it was concentrated \textit{in vacuo} onto silica gel and column chromatography was performed (0-2% ethyl acetate in hexanes, Rf = 0.55 in 2% ethyl acetate in hexanes). Concentration yielded 1.1 g of the title compound as a clear oil, 70% isolated yield. The \(^1\)H NMR matches the known compound. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(d\) (ppm) = 6.52 (s, 1H), 5.12 (q, \(J = 7.5\) Hz, 1H), 3.14 (s, 3H), 1.40 (s, 3H), 1.24 (s, 3H), 1.14 (d, \(J = 7.0\) Hz, 3H).

(S)-\(E\)-2,4-dimethyl-2-hexenol (3c). (S)-Methyl-\(E\)-2,4-dimethyl-2-hexenoate (prepared below) (200 mg, 1.3 mmol, 1 eq.) was added as a solution in 5 ml diethyl ether to a slurry of lithium aluminum hydride (150 mg, 3.8 mmol, 3 eq.) in 20 ml of diethyl ether at 0 °C. After stirring for 30 min, the reaction was quenched by slow addition of 5 ml of water (the addition was slow enough such that the temperature never rose above 10 °C). After quenching, the layers were separated, and the aqueous layer washed with 10 ml of diethyl ether 4 times. The combined organic extracts were dried over anh. sodium sulfate. Concentration of the ether layers \textit{in vacuo} afforded 142 mg, 85.4% yield of the title compound. The \(^1\)H NMR matches the known compound.\(^{16,17}\) \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(d\) (ppm) = 5.16 (quartet of quintets, \(J = 9.9, 1.2\) Hz, 1H), 3.98 (s, 2H), 2.3 -2.0 (m, 1H), 1.65 (d, 2H), 1.65 (bs, 1H), 1.40-1.15 (m, 2H), 0.93 (d, \(J = 6.6\) Hz, 3H), 0.85 (t, \(J = 7.4\) Hz, 3H) (some grease present).

Methyl (S)-\(E\)-2,4-Dimethyl-2-hexenoate (3d). (S)-2-Methyl butanol (3.4 g, 4.0 mmol, 1 eq.) was added to a slurry of 200 ml of dichloromethane, 4 Å molecular sieves (680 mg), and tetrapropylammonium perruthenate (80 mg, 0.40 mmol, 1 mol%). \(N\)-Methyl
morpholine N-oxide (10 g, 84 mmol, 2.1 eq.) was added to this solution all at once, and the resulting heterogeneous mixture was stirred for 6 h at 25 °C. The reaction mixture was filtered through a plug of silica, and the filter cake and silica plug were rinsed with more dichloromethane (200 ml). The combined dichloromethane filtrate was concentrated in vacuo to about half volume at 5 °C, and the resulting (S)-2-methylbutanal was used in the next step without further purification (1H NMR of the crude mixture matches the known compound: δ (ppm) = 9.65 (d, J = 2.0 Hz, 1H), 3.54 (m, 1H), 1.8-1.16 (m, 4H), 1.13 (d, J = 6.96 Hz, 3H)). A solution of methoxycarbonylethylidenetriphenylphosphorane (5.0 g, 160 mmol, 4.0 eq.) in dichloromethane (100 ml) was made and added to the (S)-2-Methylbutanal from the previous step. This solution was then heated to 40 °C for 18 h, at the end of which time it was concentrated in vacuo onto silica gel and column chromatography was performed (0-2% ethyl acetate in hexanes). Concentration yielded 4.44 g of the title compound, 71.1% isolated yield over both steps. The 1H NMR is indistinguishable from the enantiomer of the known compound18. 1H NMR (CDCl3, 300 MHz): δ (ppm) = 6.65 (dq, J = 10.3, 1.4 Hz, 1H), 3.74 (s, 3H), 2.40 (m, 1H), 1.85 (s, 3H), 1.75-1.10 (m, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.6 Hz, 3H).
Asymmetric Hydrogenation of Monoenes and Dienes

Hydrogenation of Monoenes 2. The procedure for hydrogenation of ethyl tiglate is representative for substrates 2. To ethyl tiglate (129 mg, 1.0 mmol) was added 17.5 mg catalyst (10 µmol, 1 mol %), followed by 100 µl dichloromethane (10M in ethyl tiglate) in a small, 1 cm wide, test tube. This was immediately capped, and was degassed 3 times before placing into a cylindrical Parr bomb (internal dimensions of 5.1 by 15.2 cm). The Parr bomb was then flooded with a stream of hydrogen, to replace the atmosphere inside of it completely with hydrogen. The external vent was closed, and the pressure increased slowly to 20 atm. Stirring was then started at approximately 800 rpm. After 4 h, the stirring was stopped, the hydrogen pressure slowly vented and allowed to return to 1 atm, and the sample taken out in order to determine conversion and stereoselectivity (see determination of absolute stereochemistry below). Screening reactions were typically performed on 0.2 mmol of substrate, but up to 2 mmol of substrate could be fully reduced under these conditions; larger scales were not tested.

Hydrogenation of Dienes and Monoenes 3. Hydrogenation of both monoenes 3c and 3d was performed as described above. Dienes 3a and 3b were hydrogenated in the same manner, but 12 h and 50 atm was required for complete conversion. These samples were then filtered through a silica plug after diluting with 30 % ethyl acetate in hexanes to remove the catalyst, and then analyzed via GC and NMR.
Determination of Stereochemistry

**General.** GC analysis of compounds 2 were first performed and compared to racemic samples generated from reduction with 10% Pd/C under hydrogen to determine ee (in many cases, baseline resolution could be obtained, except as noted below). To determine absolute configuration, comparison with commercially available (S)-2-methylbutanol and racemic 2-methylbutanol via chiral GC analysis was performed. Compounds 2d, 2f, 2g, and 2h were chemically derived to form their alcohol counterparts by reduction with 3-5 eq. lithium aluminum hydride (noted below) followed by washing with sodium potassium tartrate solution (5-10 ml), extracting the organic phases with additional dichloromethane (10-20 ml), concentrating this sample, diluting with hexanes, filtering through a celite plug, and directly injecting onto chiral GC column. Compound 2b was hydrogenated using 10% Pd/C with H₂ and filtered to give the corresponding alcohol, and 2c was reacted with TBAF followed by extraction with 20 ml of dichloromethane and water to generate the alcohol. After the analysis of hydrogenated tiglic acid (2d), product 2e was acidified and compared to the now known retention time of (R)-2-methyl butanoic acid (2d) via GC analysis.
(S)-2-Methylbutanol (2a). After hydrogenating compound 1a, E-2-methyl-2-butenol (tiglic alcohol), the sample was directly analyzed by chiral GC and compared to the known compound’s retention time to reveal hydrogenation had given the title compound in 83 % ee.
(S)-1-(Oxobenzyl)-2-methylbutane (2b). After hydrogenating E-1-(oxobenzyl)-2-methyl-2-butene, the sample was reacted with 10 % palladium on carbon with a balloon of hydrogen for 6 h, filtered through celite then a silica plug with 30 % ethyl acetate in hexanes, and directly injected for analysis into chiral GC to show the known alcohol compound was formed in 59 % ee.

No resolution at this stage
1-((S)-2-Methyl-2-butenyl)-tert-butyldimethylsilyl Ether (2c). After hydrogenating 1-(E-2-methyl-2-butenyl)-tertbutyldimethylsilyl ether, the sample was mixed with tetrabutylammonium fluoride for 10 min, then filtered through a silica plug eluting with 30 % ethyl acetate in hexanes, then the sample was directly injected for analysis into chiral GC to give the known butanol compound in 49 % ee.


(R)-2-Methylbutanoic acid (2d). After hydrogenating E-2-methyl-2-butenoic acid (tiglic acid), the sample was reduced with lithium aluminum hydride as described above to give the corresponding alcohol compound in 55 % ee.
**Tetra-butylammonium (R)-2-Methylbutanoate (2e).** After hydrogenating tetrabutylammonium E-2-methyl-2-butenoate, the sample was acidified with 1 M HCl then extracted with dichloromethane for comparison with the known tiglic acid 2d by chiral GC to give the acid in 27 % ee.
Ethyl (R)-2-Methylbutanoate (2f). After hydrogenating ethyl E-2-methyl-2-butoenoate, the sample was reduced with lithium aluminum hydride as described above to reveal hydrogenation had produced the title compound in 67 % ee. The 10.75 min peak is an impurity from ethyl acetate.

(Solvent impurity at 10.75 min)
**Benzyl (R)-2-Methylbutanoate (2g).** After hydrogenating benzyl E-2-methyl-2-butenoate, the sample was reduced with lithium aluminum hydride as described above to give the alcohol compound in 72% ee.
(4-Nitrobenzyl) (R)-2-Methylbutanoate (2h). After hydrogenating (4-nitrobenzyl) E-2-methyl-2-butenoate, the sample was reduced with lithium aluminum hydride as described above, and GC analysis shows hydrogenation gave the corresponding alcohol in 42 % ee, but only 22 % overall conversion.
(R)-N,2-Dimethyl-N-methoxybutanamide (2i). After hydrogenating N-methoxy-N,2-dimethyl-(2E)-2-butenamide, the sample was reduced with lithium aluminum hydride as described above to give the alcohol compound in 46 % ee.
LAH
Determination of Absolute Configuration and ee For The Dyad Products

After hydrogenations, the aliphatic ester product 4a was reacted with 38 mg lithium aluminum hydride (0.6 mmol, 3 eq.) in 1 ml of diethyl ether at 0 °C for 10 min, this reaction mixture was quenched with 1 ml methanol at 0 °C followed by stirring with 5 ml water for 1 h, then allowed to warm to ambient temperature. The layers were separated, the aqueous washed twice with 5 ml of diethyl ether, and the combined organic phases dried over sodium sulfate and concentrated under reduced. Products 3a and 3c were analyzed by GC immediately after filtration, and product 3d was analyzed by comparison with the ester 3b and its known stereochemistry. These samples were all analyzed by chiral GC, comparing the retention times of compounds 3a, 3b, 3d, and the alcohol formed from 3b to the compounds of known stereochemistry generated by Myers’ methodology using pseudoephedrine as a chiral auxillary.¹⁹
(2S,4R)-2,4-Dimethylhexanol (3a). *E*,*E*-2,4-Dimethyl-2,4-hexadienol (32 mg, 0.2 mmol, 1 eq.) was hydrogenated as described above to give the title compound as a 11:1.0 mixture of diasteriomers, in 100 % yield, the major isomer having 97 % ee. The retention time on GC corresponded to the minor isomer generated from Myers’ enolate (generated in turn from (2R,4R)-pseudoephedrine).¹⁹
(2R,4R)-2,4-Dimethylhexanol (3b). Methyl-E,E-2,4-dimethyl-2,4-hexadienoate (32 mg, 0.2 mmol, 1 eq.) was hydrogenated as described above to give the ester 4a as a 2.9:1.0 mixture of diastereomers, in 100 % yield, the major isomer having 90 % ee. This was reduced with lithium aluminum hydride (38 mg, 0.60 mmol, 3 eq.) and washed with sodium potassium tartrate to generate the title compound in 85 % isolated yield (same d.r. and ee of the major diastereomers). The retention time on GC was analogous to the minor isomer generated from Myers’ enolate (generated in turn from (2S,4S)-pseudoephedrine).\textsuperscript{19}
(2S,4S)-2,4-Dimethylhexanol (3c). (S)-E-2,4-Dimethyl-2-hexenol (32 mg, 0.2 mmol, 1 eq.) was hydrogenated as described above to give the title compound as a 9.6:1.0 mixture of diastereomers, in 100 % yield, the major isomer having >98 % ee. The retention time on GC corresponded to the major isomer generated from Myers’ enolate (generated in turn from (2R,4R)-pseudoephedrine). Baseline resolution of this compound was not possible, thus the major peak may overlap with the minor for an inaccurate ee, but epimerization at C2 would only cause lower diastereoselectivity, ruling out a low ee.

![Diagram](attachment:OGLE\SIG10360.D)

![Diagram](attachment:OGLE\SIG10265.D)
(2R,4S)-2,4-Dimethylhexanol (3d). Methyl-\(E,E\)-2,4-dimethyl-2,4-hexadienoate (32 mg, 0.2 mmol, 1 eq.) was hydrogenated as described above to give the ester compound as a 5.0:1.0 mixture of diastereomers, in 100 % yield, the major isomer having >98 % \(ee\). Comparison of this product with the known diastereomeric methyl ester (identified from GC analysis of 3c above) confirmed the predicted \(anti\)-relationship of the stereocenters.
Description of Alternative Reaction Pathways Examined in Computational Study

Details of the computational approach used were identical to those reported in reference 18 of the text. All calculations were carried out in GAUSSIAN 03.

Favored Energy Pathway As Shown in Figure 3

The following mechanism was calculated and represents the lowest energy pathway found for hydrogenation the ester substrate on that enantioface.

![Diagram of reaction pathways](image)

**Figure S1.** Lowest energy pathway, presented in Figure 3 in the text.
Pathway Corresponding to Figure S1 With Hydrogenation On The Other Enantioface

The following pathway gives a higher energy transition state than any in Figure S1 or in Figure 4 in the manuscript (i.e. the hydrogenation pathway for stilbenes and styrenes), hence this can be excluded.\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_s2.png}
\caption{Mechanism corresponding to Figure S1 but with other enantioface of alkene coordinated.}
\end{figure}

Pathways With Alkene \textit{Trans}-to Carbene, Carbonyl \textit{Trans}-to Hydride

Steps with hydrogenations on both enantiofaces of the alkene each give transition state energies greater than calculated in Figure S1, hence they can be excluded.
Figure S3. Mechanisms with alkene coordinating trans-to the carbene ligand and carbonyl coordinating trans-to hydride give higher energy transitions states and can be excluded.

Pathways With Alkene Trans-to Carbene, Carbonyl Trans-to Oxazoline

In these mechanisms (for both enantiofaces) even the intermediates gave higher energies than transitions states in Figure S1, hence they can be excluded.

Figure S4. Mechanisms with alkene coordinating trans-to the carbene ligand and carbonyl coordinating trans-to oxazoline give higher energy intermediates and can be excluded.
Note On Hydrogenation of the Allylic Alcohols

Some mechanisms besides simple adaptation of that shown in Figure 4 have been examined but none so far give lower energy pathways. These investigations are in progress.

Synthesis of Internal Deoxypolyketide Fragments

To a solution of the $\alpha,\beta$-unsaturated ester (4.26 g, 10.7 mmol) in THF (50 ml) at 0 °C was added a solution of TBAF (1 M in THF, 98 ml, 98 mmol) drop wise. The reaction temperature was raised to 25 °C and continued to stir for 1 h. Saturated NH$_4$Cl aqueous solution (30 ml) was then added followed by Et$_2$O (30 ml). The layers were separated and the aqueous layer was extracted with Et$_2$O (3 × 15 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 30% ethyl acetate in hexanes gave the homoallylic alcohol as a colorless oil (1.65 g, 97%). GC analysis gave > 99% ee of this material. (The racemic homoallylic alcohol was synthesized according to Scheme S1, $t_{R(S)} = 40.86$ min, $t_{R(R)} = 41.32$ min). $\alpha$/$\beta$ +23.3 (c 1.68, CHCl$_3$); IR (neat) 3447(br), 2954, 2874, 1709, 1648, 1435, 1289 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) d 6.57 (dq, $J = 9.0$, 1.2 Hz, 1H), 3.69 (s, 3H), 3.62 (dd, $J = 5.9$, 10.6 Hz, 1H), 3.54 (dd, $J = 7.2$, 10.6 Hz, 1H), 2.85-2.71 (m, 1H), 2.20 (br, s, 1H), 1.84 (d, $J = 1.2$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) d 168.6, 144.4, 128.6, 66.9, 51.8, 36.1, 15.9, 12.6. HRMS (ESI): Exact mass calculated for C$_8$H$_{15}$O$_3$ [M+H$^+$] 159.1021. Found 159.1023.
Hydrogenation of the homoallylic alcohol (1.73 g, 10.9 mmol) was carried out according to the general procedure using D-1 (0.2 mol%, 36 mg, 0.02 mmol) in CH₂Cl₂ (2 ml). NMR of the crude product showed 100% conversion and partial lactonization. Thus without isolation, the reaction mixture was diluted with CH₂Cl₂ (10 ml) then p-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol) was added. After 1 h, saturated aqueous NaHCO₃ solution (5 ml) was added and the layers were separated. The aqueous layer was extracted with 3 portions of dichloromethane (5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. GC analysis of this material gave a cis:trans lactone in a ratio of 15:1.0 (t<sub>r</sub>(cis) = 46.83 min, t<sub>r</sub>(trans) = 48.10 min; for small scale reaction 1 mol% D-1 gave the same diastereoselectivity). Recrystallization from diethyl ether gave cis-lactone as white crystals (1.06 g, 76%; cis:trans = 146:1.00 by GC analysis). mp 47-48 °C (lit<sup>21</sup>, mp 46-47 °C), [α]<sup>23</sup>D +42.3 (c 2.32, CHCl₃); <sup>1</sup>H NMR (300 MHz, CDCl₃) δ 4.28 (ddd, J = 11.2, 4.9, 2.4 Hz, 1H), 3.86 (dd, J = 8.8, 10.7 Hz, 1H), 2.57-2.44 (m, 1H), 2.18-1.99 (m, 2H), 1.28-1.16 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H).

(i) TBDPSCI, Imid. CH₂Cl₂, 92%
(ii) BH₃·DMS, NaOH, H₂O₂, 88%

(i) PCC, CH₂Cl₂, 25 °C
(ii) Ph₃P=O, toluene, 80 °C, 89% (2 steps)

(i) TBAF, THF, 25 °C, 97%
Scheme S1. Synthesis of racemic substrates for determinations of ee.

Table S1. Asymmetric Hydrogenation of Alkenes Not Shown in the Text

<table>
<thead>
<tr>
<th>alkene substrates</th>
<th>diastereoselectivities of catalytic hydrogenations (Ir* 1mol%, 50 atm H₂, CH₂Cl₂, 25 °C); ratios determined by GC analysis</th>
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<tbody>
<tr>
<td><img src="image1" alt="alkene substrate" /></td>
<td><img src="image2" alt="alkene substrate" /></td>
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<tr>
<td><img src="image3" alt="alkene substrate" /></td>
<td><img src="image4" alt="alkene substrate" /></td>
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</tbody>
</table>

BnO
Me
Me
OMe

Ir*(L) syn:anti 1.0 : 3.9
Ir*(D) 3.9 : 1.0

BnO
Me
Me
OH

Ir*(L) syn:anti 3.1 : 1.0
Ir*(D) 1.0 : 4.9
syn,syn : anti, syn : syn, anti : anti, anti

Ir*(L) 4.3 : 2.7 : 12.9 : 1.0
Ir*(D) 6.7 : 1.0 : 5.0 : 2.1

syn,syn : anti, syn : syn, anti : anti, anti

Ir*(L) 1.0 : 3.4 : 5.5 : 1.3
Ir*(D) 1.0 : 3.1 : 1.7 : 4.7

syn:anti

Ir*(L) 1.3 : 1.0
Ir*(D) 1.0 : 2.8
References