Highly Enantio- and Diastereoselective Hetero-Diels–Alder Reactions
Catalyzed by New Chiral Tridentate Chromium Catalysts

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General

All $^1$H NMR and $^{13}$C NMR spectra were recorded using Bruker AM500 or AM400 FT spectrometers at ambient temperature unless otherwise noted. IR spectra were recorded as either KBr discs or thin film between NaCl plates on a Matteson FTIR 3000. Microanalyses were performed by Desert Analytics, Tuscon, Arizona. Optical rotations were measured using a Jasco DIP 370 digital polarimeter. Melting points were determined using a Koffler hot stage apparatus and are uncorrected. Solvents were purified and dried using standard methods: Tetrahydrofuran (THF), tert-butyl methyl ether (TBME), and diethyl ether were distilled from sodium/benzophenone ketyl; dichloromethane (CH$_2$Cl$_2$) was distilled from CaH$_2$; acetone was stirred with K$_2$CO$_3$ overnight and distilled onto 4Å molecular sieves. (2Z,4E)-3-Trialkylsilyl-2,4-hexadienes 4a-d and (3E)-triethylsilyloxy pentadiene 9 were prepared$^1$ by treatment of 4-hexen-3-one (Aldrich) or 3-penten-2-one$^2$, respectively, with triethylamine and the trialkylsilyl trifluoromethanesulfonate ester in diethyl ether at 0 °C and distilled prior to use. Dienes 4b and 9 were found to be 72% and 84% pure, respectively, by GC and were contaminated principally with bis(triethylsilyloxy) ether and other geometric isomers of the dienes. Benzylxoyacetalddehyde, (t-butyldimethylsilyloxy)acetalddehyde and 1-methoxybutadiene were used as supplied from Aldrich. Benzaldehyde, 2-furaldehyde, hydrocinnamaldehyde, and hexanal were distilled onto sieves prior to use. 6-Heptenal was prepared by NaIO$_4$ cleavage of the 7-octen-1,2-diol and t-butyl-N-(3’-propanal)carbamate was prepared by TPAP, NMO oxidation of the commercially available alcohol. Chromium(II) chloride and silver(I) hexafluoroantimonate were used as supplied from Strem. 4Å Molecular sieves were powdered and dried in a vacuum oven (130 °C) prior to use.

PART 1. Experimental Procedures and Analytical Data: Catalysts 3a and 3b.

3-(1-Adamantyl)-2-hydroxy-5-methylbenzaldehyde.

To a solution of 2-(1-adamantyl)-4-methylphenol (7, 6.55 g, 27 mmol) in dry toluene (60 mL) was added 2,6-lutidine (2.32 g, 22 mmol) under N$_2$ at ambient temperature. SnCl$_4$ (0.63 mL, 5.4 mmol) was added carefully to this solution, and the mixture was stirred 20 min.
Paraformaldehyde (2.43 g, 81 mmol) was added in one portion, and the mixture was stirred at ambient temperature for 1 h and then at 100 °C overnight. The resulting yellow mixture was cooled to room temperature, poured into water (200 mL) and acidified to pH 2 with 2 N hydrochloric acid. The mixture was filtered, and the residue was washed with ether (50 mL). The aqueous phase was extracted with ether (100 mL), and the combined ethereal extracts were washed with water (100 mL) and brine (50 mL) and dried (Na₂SO₄). The filtered solution was concentrated in vacuo and the residue recrystallized from hexanes to give the salicylaldehyde as an off-white solid (6.65 g, 91%), mp 151.5–152 °C. IR (KBr) 3200-2500, 1649, 1607, 1524, 1447, 1416, 1356, 1312, 1244, 1221, 1163, 1105, 1084, 1040, 963, 864 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.78 (s, 6H), 2.08 (s, 3H), 2.12 (s, 6H), 2.31 (s, 3H), 7.14 (d, J = 1.5 Hz, 1H), 7.26 (d, J = 1.5 Hz, 1H), 9.80 (s, 1H), 11.65 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 20.5, 28.9, 36.9, 36.9, 40.1, 120.3, 128.2, 131.2, 135.4, 138.1, 159.3, 197.1. Calculated for C₁₈H₂₂O₂: C, 79.96, H, 8.20. Found: C, 79.70; H, 8.16.

3-(1-Adamantyl)-2-hydroxy-5-methylbenzaldehyde-(1R,2S)-1-amino-2-indanol imine 8.

(1R,2S)-cis-1-Amino-2-indanol (470 mg, 3.15 mmol) was added in one portion to a stirring solution of 3-(1-adamantyl)-2-hydroxy-5-methylbenzaldehyde (811 mg, 3.00 mmol) in ethanol (15 mL). A yellow precipitate formed immediately, and the mixture was allowed to stir overnight. An additional portion of ethanol (15 mL) was added, and the mixture was heated to reflux to dissolve the precipitate. As this yellow solution cooled, imine 8 as a bright yellow solid (1.05 g, 87%). [α]²⁶⁰ +70.0° (c 1.00, THF). IR (KBr disk) 3584, 2905, 2849, 1624, 1597 cm⁻¹. ¹H NMR (500 MHz, d₆-DMSO) δ 1.69 (m, 6H), 1.99 (m, 3H), 2.05 (m, 6H), 2.23 (s, 3H), 2.95 (dd, J = 6.0, 15.5 Hz, 1H), 3.11 (dd, J = 6.1, 15.5 Hz, 1H), 4.54 (q, J = 5.7 Hz, 1H), 4.73 (d, J = 5.5 Hz, 1H), 5.23 (d, J = 4.9 Hz, 1H), 7.01 (s, 1H), 7.09 (s, 1H), 7.18–7.31 (m, 4H), 8.61 (s, 1H), 10.94 (s, 1H). ¹³C NMR (125.8 MHz, d₆-DMSO) δ 25.4, 33.5, 41.4, 41.7, 79.1, 123.4, 129.9, 130.2, 130.9, 131.9, 133.1, 134.8, 135.2, 141.6, 146.2, 147.2, 153.7. HRMS (m/z) (CI
NH$_3$) calc. for C$_{27}$H$_{35}$NO$_2$, 401.2355, found 401.2341 (M+NH$_4$)$^+$. Calculated for C$_{27}$H$_{35}$NO$_2$ (%): C, 80.76; H, 7.78; N 3.49; found(%): C, 80.51; H, 8.03, N 3.40.

**Chromium(III) complex (1R,2S) 3a.**

![Diagram of 3a]

Chromium(II) chloride (220 mg, 1.80 mmol) was added in one portion to a solution of Schiff base 8 (600 mg, 1.50 mmol) in dry THF (20 mL) in a dry box. The mixture was allowed to stir 5 h, and the flask was removed from the dry box. The green mixture was allowed to stir exposed air overnight. The flask was flushed with N$_2$, fitted with a septum, and 2,6-lutidine (0.420 mL 3.60 mmol) was added. This mixture was stirred at ambient temperature for 3 h, acquiring a brownish hue during this time. TBME (200 mL) was added and the mixture was washed with sat. NH$_4$Cl (aq) (3 × 50mL) and sat. NaCl (2 × 50 mL). The organic solution was dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. Traces of solvent were removed from the greenish-brown residue by high vacuum to give 3a as a brown solid (806 mg 99%) that was used without further purification. IR (KBr disk) 3531, 3317, 2969, 2899, 1618, 1537, 1229, 1081 cm$^{-1}$. LRMS (m/z) (FAB+ NBA) mass calc. for C$_{27}$H$_{35}$CrNO$_2$, (M-Cl)$^+$ 451 found 451; calc. for dimer 2[C$_{27}$H$_{35}$CrNO$_2$], (2M-2Cl)$^+$, 902; found 902; calc. for dimer 2[C$_{27}$H$_{35}$CrNO$_2$+H$_2$O], (2M-2Cl+H$_2$O)$^+$, 920; found 919; calc. for trimer 3[C$_{27}$H$_{35}$CrNO$_2$+H$_2$O], (3M-3Cl+H$_2$O)$^+$, 1371; found 1370; calc. for tetramer 4[C$_{27}$H$_{35}$CrNO$_2$+2H$_2$O], (4M-4Cl+2H$_2$O)$^+$, 1840; found 1840.

A sample of complex 3a was treated with TMSCl as described below to provide a sample for elemental analysis: Chlorotrimethylsilane (39.0 ul, 0.310 mmol) was added to solution of 3a (50.0 mg, 0.103 mmol) in dry TBME in a dry box. The mixture was stirred for 2h, and a green precipitate formed. The mixture was concentrated in vacuo, suspended in dry TBME (2mL), and filtered. The green residue was washed with dry TBME (2 mL) and the residue dried by high vacuum. Calculated for [C$_{27}$H$_{29}$ClCrNO$_2$+2HCl] (%) C, 57.92; H, 5.58; Cr, 9.29; N 2.50. Found(%): C, 57.49; H, 5.73; Cr, 9.00; N 2.48. The Cr/N was calculated found to be 0.98.
Chromium(III) complex (1R,2S) 3b.

Silver(I) hexafluoroantimonate (141 mg, 0.411 mg) was added in one portion to a stirring solution of (1R,2S)-3a (100 mg, 0.205 mmol) in dry TBME (30 mL) at ambient temperature under N₂. The flask was wrapped in aluminum foil, and the mixture was stirred for 3 h and filtered through a pad of diatomaceous earth. The filter cake was washed with TBME (30 mL), and the combined filtrates were concentrated in vacuo to give a brown residue that was dried by high vacuum (260 mg, 92%) and used without further purification. IR (KBr disk) 3378, 2973, 2905, 1615, 1538, 1229, 1069 cm⁻¹. LRMS (m/z) (FAB+ NBA matrix) mass calc. for C₂₇H₃₅CrNO₂, (M-Cl)⁺ 451 found 451; calc. for 2[C₂₇H₃₅NO₂]Cr, 854; found 854; calc. for dimer 2[C₂₇H₃₅CrNO₂], (2M-2Cl)⁺, 902; found 902; calc. for dimer 2[C₂₇H₃₅CrNO₂+H₂O], (2M-2Cl+H₂O)⁺, 920; found 921.
PART 2. Experimental Procedures and Analytical Data: Compounds 6a-h, 10, 12, 14-15.

(2R,3R,6R)-2-Phenyl-3,6-dimethyltetrahydropyran-4-one (6a, Table 1, entry 9).

\[
\begin{align*}
\text{OTES} & \quad + \quad \text{MeMeMeMe} \\
\text{4b} & \quad \text{H} \\
\rightarrow & \quad \text{6a}
\end{align*}
\]

Benzaldehyde (100 ul, 1.00 mmol) was added to a mixture of chromium(III) complex 3b (21 mg, 0.03 mmol), acetone (200 ul), and 4Å molecular sieves (200 mg). The mixture was stirred 3 h under N₂ at ambient temperature and (2Z, 4E)-3-triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) was added. The mixture was stirred 40 h, diluted with THF (4 mL), and cooled to 0 °C. Acetic acid (114 ul, 2.00 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 1.5 mL, 1.50 mmol) were added, and the mixture was allowed to stir 30 min. The mixture was diluted with hexanes/diethyl ether (2:1, 60 mL) and washed with water (2 × 30 mL), sat. NaHCO₃ (30 mL) and sat. NaCl (30 mL). The pale yellow organic solution was dried (MgSO₄), filtered, and concentrated in vacuo. Purification by silica gel chromatography gave 6a as a colorless oil (147 mg, 72%) in 90% e.e. by chiral GC analysis (Cyclodex-B, 135 °C, isothermal \( t_R \) (minor) = 27.81 min, \( t_R \) (major) = 29.94 min). \( [\alpha]^{26}_D +28.9^\circ \) (c 1.02, CH₂Cl₂). \( R_f = 0.54 \) (1:1 hexanes/diethyl ether). IR (thin film) 2935, 2900, 1713, 1452, 1343, 1273, 1207, 1145, 1110 cm⁻¹. \( ^1H \) NMR (400 MHz, CDCl₃) \( \delta 1.45 \) (d, \( J = 6.0 \) Hz, 3H), 1.91 (d, \( J = 7.2 \) Hz, 3H), 2.23 (dd, \( J = 2.8, 14.6 \) Hz, 1H), 2.57 (dd, \( J = 11.5, 14.6 \) Hz, 1H), 2.66 (dd, \( J = 2.7, 7.2 \) Hz, 1H), 3.94 (dd\(^q\), \( J = 2.8, 6.0, 11.5 \) Hz, 1H), 4.82 (d, \( J = 2.7 \) Hz, 1H), 7.25–7.38 (m, 5H). \( ^13C \) NMR (100 MHz, CDCl₃) \( \delta 11.4, 22.2, 45.6, 50.8, 73.8, 86.0, 125.6, 127.4, 128.3, 128.7, 212.3. HRMS (m/z) (EI) calc. for C₁₃H₁₆O₂ (M)⁺ 204.1150, found 204.1147.

(2R,3R,6R)-2-(tert-Butyldimethylsilyloxy)methyl)-3,6-dimethyltetrahydropyran-4-one (6b, Table 1, entry 4).

\[
\begin{align*}
\text{OTES} & \quad + \quad \text{MeMeMeMe} \\
\text{4b} & \quad \text{H} \\
\rightarrow & \quad \text{6b}
\end{align*}
\]
(2Z, 4E)-3-Triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) was added to a stirring mixture of (t-butyldimethylsilyloxy)-acetaldehyde (200 ul, 1.00 mmol), chromium(III) complex 3a (15.0 mg, 0.03 mmol), and 4Å molecular sieves (200 mg) under N₂ at ambient temperature. The mixture was stirred for 16 hours. Work-up as above for 6a and purification by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 6b as a colorless oil (273 mg, 88%). The isolated material was determined to be 98% e.e. by chiral GC analysis (Cyclodex-B, 150 °C, isothermal tᵣ(minor) = 11.67 min tᵣ(major) = 12.19 min). [α]²⁶D –48.0° (c 1.00, CHCl₃) Rᵣ = 0.85 (3:1 hexanes/diethyl ether). IR (thin film) 2955, 2932, 2859, 1721, 1422, 1171, 1133, 1086 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 0.03 (s, 6H), 0.85 (s, 9H), 1.10 (d, J = 7.3 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 2.22 (dd, J = 2.6, 14.7 Hz, 1H), 2.39 (dd, J = 11.5, 14.7 Hz, 1H), 2.51 (dt, J = 2.8, 7.1 Hz, 1H), 3.59 (dd, J = 7.0, 9.9 Hz, 1H), 3.70 (dd, J = 2.8, 5.9, 7.0 Hz, 1H), 3.70–3.75 (m, 1H), 3.76 (dd, J = 5.9, 9.9 Hz, 1H). ¹³C NMR (125.8 MHz, CDCl₃) δ –5.5, –5.3, 10.6, 18.2, 22.0, 25.8, 46.0, 46.2, 62.1, 73.4, 78.8, 211.2. HRMS (m/z) (CI NH₃) mass calc. for C₁₄H₃₂NO₃Si (M+NH₄)⁺ 290.2151 found 290.2162.

(2R,3R,6R)-2-(Benzyloxymethyl)-3,6-dimethyltetrahydropyran-4-one (6c, Table 1, entry 11).

(2Z, 4E)-3-Triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) was added to a stirred mixture of benzyloxyacetaldehyde (155 ul, 1.00 mmol), chromium(III) complex 3b (21 mg, 0.030 mmol), 4Å sieves (200 mg) in acetone (200 ul) under N₂ at ambient temperature. The mixture was stirred 16 h. Work-up as above for 6a and purification by silica gel chromatography afforded 6c (221 mg, 89%) as a colorless oil. The isolated material was determined to be in 94% e.e. by chiral GC analysis (Cyclodex-B, 165 °C, isothermal tᵣ(minor) = 31.67 min tᵣ(major) = 32.55 min). [α]²⁶D –47.0° (c 0.500, CH₂Cl₂). IR (thin film) 2976, 2864, 1715, 1454, 1125, 1094 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, J = 7.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H), 2.26 (dd, J = 2.7, 14.7 Hz, 1H), 2.41 (dd, J = 11.5, 14.7 Hz, 1H), 2.48 (dq, J = 2.8, 7.1 Hz, 1H), 3.46 (dd, J = 5.5, 10.0 Hz, 1H), 3.65 (dd, J = 6.8, 10.0 Hz, 1H), 3.77 (ddq, J =
2.7, 6.1, 11.5 Hz, 1H), 3.89 (ddd, J = 2.8, 5.5, 6.8 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 7.27–7.37 (m, 5H). 13C NMR (125.8 MHz, CDCl3) δ 10.9, 22.1, 46.0, 46.6, 69.7, 73.5, 73.6, 76.8, 127.7, 128.4, 137.9, 142.6, 210.8. HRMS (m/z) (CI NH3) calc. for C15H24NO3 (M+NH4)+ 266.1756, found 266.1748.

(2R,3S,6R)-2-Pentyl-3,6-dimethyltetrahydropyran-4-one (6d, Table 1, entry 12).

(2Z, 4E)-3-Triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) was added to a stirred mixture of hexanal (120 ul, 1.00 mmol), chromium(III) complex 3b (21.0 mg, 0.03 mmol), and 4Å sieves (200 mg) under N2 at ambient temperature. The mixture was stirred 20 h. Work-up as above for 6a and purification by silica gel chromatography afforded 6d (157 mg, 81%) as a colorless oil. The isolated material was determined to be 98% e.e. by chiral GC analysis (Cyclodex-B, 130 °C, isothermal tR(minor) = 10.95 min, tR(major) = 12.19 min). [α]26D –65.4° (c 1.16, CH2Cl2). Rf = 0.62 (1:1 hexanes/diethyl ether). IR (thin film) 2956, 2934, 2862, 1715, 1459, 1413, 1377, 1351, 1322, 1094 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ 0.89 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.26–1.44 (m, 7H), 1.65–1.71 (m, 1H), 2.23 (dd, J = 2.7, 14.5 Hz, 1H), 2.32 (dt, J = 2.5, 7.2 Hz, 1H), 2.41 (dd, J = 11.5, 14.5 Hz, 1H), 3.56 (dt, J = 2.5, 7.7 Hz, 1H), 3.69 (ddt, J = 2.7, 6.1, 11.5 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ 10.6, 14.0, 22.1, 22.5, 25.4, 31.6, 31.6, 45.9, 48.6, 73.5, 79.0, 212.0. HRMS (m/z) (CI NH3) calc. for C12H26NO3 (M+NH4)+ 216.1964 found 216.1965.

(2R,3S,6R)-2-(5'-Hexenyl)-3,6-dimethyltetrahydropyran-4-one (6e, Table 1, entry 13).

(2Z, 4E)-3-Triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) was added to a stirred mixture of 6-heptenal (134 ul, 1.00 mmol), chromium(III) complex 3b (21 mg, 0.03
mmol), and 4Å sieves (200 mg) under N\textsubscript{2} at ambient temperature. The reaction was stirred 24 h. Work-up as above for 6a and purification by silica gel chromatography afforded 6e (163 mg, 78%) as a colorless oil. The isolated material was determined to be 98% e.e. by chiral GC analysis (Cyclodex-B, 135 °C, isothermal t\textsubscript{R}(minor) = 13.38 min, t\textsubscript{R}(major) = 14.74 min). [\alpha]\textsuperscript{26}\text{D} –73.0\text{o} (c 1.16, CH\textsubscript{2}Cl\textsubscript{2}). R\textsubscript{f} = 0.54 (1:1 hexanes/diethyl ether). IR (thin film) 2976, 2935, 2858, 1719, 1641, 1459, 1376, 1357, 1328, 1271, 1093 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.12 (d, J = 7.1 Hz, 3H), 1.27–1.35 (m, 1H), 1.33 (d, J = 6.8 Hz, 1H), 1.36–1.47 (m, 4H), 1.63–1.71 (m, 1H), 2.06 (q, J = 6.8 Hz, 1H), 2.20 (dd, J = 2.5, 14.4 Hz, 1H), 2.33 (q, J = 7.1 Hz, 1H), 2.40 (dd, J = 11.5, 14.4 Hz, 1H), 3.53–3.57 (m, 1H), 3.69 (ddq, J = 2.5, 6.1, 11.5 Hz, 1H). 13C NMR (100 MHz, CDCl\textsubscript{3}) δ 10.7, 22.2, 25.2, 28.8, 31.6, 33.6, 45.9, 48.7, 73.4, 79.0, 114.5, 138.7, 211.9. HRMS (m/z) (EI) calc. for C\textsubscript{13}H\textsubscript{22}O\textsubscript{2}M\textsuperscript{+} 210.1620, found 210.1619.

(2R,3S,6R)-2-(2'-Phenylethyl)-3,6-dimethyltetrahydropyran-4-one (6f, Table 1, entry 14).

Hydrocinnamaldehyde (264 ul, 2.00 mmol) was added to a mixture of chromium(III) complex 3b (21 mg, 0.03 mmol), acetone (200 ul), and 4Å sieves (200 mg). The mixture was stirred under N\textsubscript{2} at ambient temperature 3 h, and (2Z, 4E)-3-triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) added. The mixture was stirred 40 h. Work-up as above for 6a and purification by silica gel chromatography (5% ether/hexanes) afforded 6f as a colorless oil (180 mg, 78%). The isolated material was determined to be 98% e.e. by chiral GC analysis (Cyclodex-B, 150 °C, isothermal 15 min then 5°C/min t\textsubscript{R}(minor) = 23.32 min, t\textsubscript{R}(major) = 23.77 min). [\alpha]\textsuperscript{26}\text{D} –65.0\text{o} (c 1.30, CH\textsubscript{2}Cl\textsubscript{2}). R\textsubscript{f} = 0.55 (1:1 hexanes/diethyl ether). IR (thin film) 3062, 3027, 2974, 2939, 2859, 1712, 1496, 1455, 1412, 1376, 1351, 1327, 1271, 1101, 1087 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.14 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.58–1.68 (m, 1H), 1.98–2.07 (m, 1H), 2.23 (dd, J = 2.8, 14.6 Hz, 1H), 2.30 (dq, J = 2.4, 7.2 Hz, 1H), 2.40 (dd, J = 11.4, 14.6 Hz, 1H), 2.62–2.64 (m, 1H), 2.78–2.84 (m, 1H), 3.52–3.56 (m, 1H), 3.66 (ddq, J = 2.8, 6.1, 11.4 Hz, 1H), 7.13–7.30 (m, 5H). 13C NMR (100 MHz, CDCl\textsubscript{3}) δ 10.8, 22.1,
32.0, 33.4, 45.8, 48.8, 73.5, 77.8, 126.0, 128.4, 141.5, 211.5. HRMS (m/z) (E.I.) mass calc. for C_{15}H_{20}O_{2} (M)^{+} 232.1463 found 232.1463.

$${\text{(2R,3S,6R)-2-(2'-\text{tert-Butoxycarbonylaminoethyl)-3,6-dimethyltetrahydropyran-4-one}} \quad (6g, \text{ Table 1, entry 15).}}$$

$t$-Butyl-$N$-(3-propanal)carbamate (344 ul, 2.00 mmol) was added to a mixture of chromium(III) complex 3b (21 mg, 0.03 mmol), acetone (200 ul), and 4Å sieves (200 mg). The mixture was stirred under N\textsubscript{2} at ambient temperature 3 h, and (2Z, 4E)-3-triethylsilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) added. The reaction was stirred 40 hours. Work-up as above for 6a and purification by silica gel chromatography (15% EtOAc/hexanes) afforded 6g as a colorless oil (76.8 mg, 28%). The isolated material was determined to be 96% e.e. by chiral GC analysis (Cyclodex-B, 160 °C, isothermal 32 min then 2°C/min\textsubscript{e}(major) = 43.04 min, \textit{t}\textsubscript{R}(minor) = 44.30 min). [\alpha]_{D}^{26} = -46.8° (c 0.490, CH\textsubscript{2}Cl\textsubscript{2}). \textit{R}_{f} = 0.43 (1:1 hexanes/diethyl ether). IR (thin film) 3363, 2977, 2934, 2876, 1712, 1518, 1367, 1271, 1252, 1172, 1092 cm\textsuperscript{-1}. \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \delta 1.12 (d, \textit{J} = 7.2 Hz, 3H), 1.32 (d, \textit{J} = 6.1 Hz, 3H), 1.44 (s, 9H), 1.53–1.59 (m, 1H), 1.78–1.87 (m, 1H), 2.25 (dd, \textit{J} = 2.9, 14.6 Hz, 1H), 2.31 (dq, \textit{J} = 2.3, 7.2 Hz, 1H), 2.39 (dd, \textit{J} = 11.5, 14.6 Hz, 1H), 3.19–3.25 (m, 1H), 3.29–3.36 (m, 1H), 3.66 (dt, \textit{J} = 2.9, 9.6 Hz, 1H), 3.72 (ddq, \textit{J} = 2.9, 6.1, 11.5 Hz, 1H), 4.86 (broad s, 1H). \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}) \delta 11.0, 22.2, 28.5, 28.3, 32.2, 38.3, 45.8, 49.1, 73.7, 79.3, 156.0, 211.2. HRMS (m/z) (CI NH\textsubscript{3}) calc. for C\textsubscript{14}H\textsubscript{29}N\textsubscript{2}O\textsubscript{4} (M+NH\textsubscript{4})\textsuperscript{+} 289.2137 found 289.2133.

$${\text{(2R, 3R, 6R)-2-(2'-furyl)-3,6-dimethyltetrahydropyran-4-one}} \quad (6h, \text{ Table 1, entry 16).}}$$

2-Furaldehyde (84.0 ul, 1.00 mmol) was added to a mixture of chromium(III) complex 3b (21 mg, 0.03 mmol), acetone (200 ul), and 4Å sieves (200 mg). The mixture was stirred under
N₂ at ambient temperature for 3 h, and (2Z, 4E)-3-triethoxysilyloxy-2,4-hexadiene 4b (72% pure, 342 ul, 1.38 mmol) added. The mixture was stirred 40 h. Work-up as above for 6a and purification by silica gel chromatography (5% ether/hexanes) afforded 6h as a colorless oil (150 mg, 72%). The isolated material was determined to be 95% e.e. by chiral GC analysis (Cyclodex-B, 115 °C, isothermal tᵣ(minor) = 25.39 min, tᵣ(major) = 27.83 min). [α]²⁶D -18.3° (c 1.01, CH₂Cl₂). Rᵣ = 0.51 (1:1 hexanes/diethyl ether). IR (thin film) 2978, 2902, 2877, 1717, 1456, 1383, 1339, 1195, 1113 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.08 (d, J = 7.2 Hz, 3H), 1.42 (d, J = 6.1 Hz, 3H), 2.34 (dd, J = 2.9, 14.9 Hz, 1H), 2.55 (dd, J = 11.4, 14.9 Hz, 1H), 2.75 (dq, J = 3.1, 7.2 Hz, 1H), 3.93 (ddq, J = 2.9, 6.1, 11.4 Hz, 1H), 4.84 (d, J = 3.1 Hz, 1H), 6.32–6.38 (m, 2H), 7.38–7.39 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 12.0, 22.2, 45.8, 48.7, 73.9, 75.8, 107.3, 110.3, 142.0, 151.8, 210.3. HRMS (m/z) (EI) calc. for C₁₁H₁₄O₃ (M)+ 194.0943, found 194.0944.

(2R,6R)-2-(tert-Butyldimethylsilyloxymethyl)-6-methyltetrahydropyran-4-one (10, Table 2, entry 1).

(3E)-2-Triethylsilyloxy-1,3-pentadiene 9 (84% pure, 220 ul, 1.19 mmol) was added to a stirring mixture of (tert-butyldimethylsilyloxy)acetaldehyde (208 ul, 1.00 mmol), chromium(III) complex 3a (15 mg, 0.03 mmol), 4Å sieves (200 mg), and acetone (200 ul) under N₂ at ambient temperature. The mixture was stirred 16 h. Work-up as above for 6a and purification by silica gel chromatography (5% ether/hexanes) afforded 10 (169 mg, 78%) as a colorless oil. The isolated material was determined to be 98% e.e. by chiral GC analysis (Cyclodex-B, 110 °C, isothermal tᵣ(minor) = 65.15 min, tᵣ(major) = 65.53 min). [α]²⁶D +0.60° (c 0.685, CHCl₃). Rᵣ = 0.67 (10% diethyl ether, hexanes). IR (thin film) 2957, 2932, 2859, 1724, 1471, 1172, 1148 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.32 (d, J = 6.1 Hz, 3H), 2.22 (dd, J = 11.3, 14.4 Hz, 1H), 2.29–2.41 (m, 3H), 3.65–3.70 (m, 1H), 3.71–3.77 (m, 1H). ¹³C NMR
(125.8 MHz, CDCl$_3$) $\delta$ −5.2, 18.4, 22.0, 25.9, 44.0, 49.5, 66.0, 73.3, 77.4, 207.6. HRMS (m/z) (CI NH$_3$) calc. for C$_{13}$H$_{30}$NO$_3$Si (M+NH$_4$)$^+$ 276.1995, found 276.2002.

$\text{(2R,3R)-2-(tert-Butyldimethylsilyloxymethyl)-3-methyltetrahydropyran-4-one (12, Table 2, entry 2).}$

$\text{(3E)-3-Triethylsilyloxy-1,3-pentadiene 11 (73% pure, 200 ul, 1.38 mmol) was added to a}$
$\text{stirring mixture of (tert-butyldimethylsilyloxy)acetaldehyde (200 ul, 1.00 mmol), chromium(III)}$
$\text{complex 3a (15 mg, 0.03 mmol), 4Å sieves (160 mg) under N$_2$ at ambient temperature. The}$
$\text{mixture was stirred 26 h. Work-up as above for 6a and purification by silica gel chromatography}$
$\text{(10% ether/hexanes) afforded  After 16 h the reaction was quenched then aqueous work up and}$
$\text{isolation as above afforded 12 (128 mg, 50%) as a colorless oil. The isolated material was}$
$\text{determined to be 91% e.e. by chiral GC analysis (Cyclodex-B, 140 °C, isothermal $\tau_R$(minor) =}$
$\text{16.37 min, $\tau_R$(major) = 16.68 min). $[\alpha]^{26}_D$ −20.58° (c 0.982, CH$_2$Cl$_2$). R$_f$ = 0.385 (1:1 diethyl}$
$\text{ether / hexanes). IR (thin film) 2954, 2925, 2858, 1720, 1471, 1252, 1137, 1102 cm}^{-1}.^\text{1H NMR}$
$\text{(500 MHz, CDCl$_3$) $\delta$ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.13 (d, J = 7.0 Hz, 3H), 2.38 (‘dt’,}$
$\text{J = 4.9, 13.9 Hz, 1H), 2.58–2.67 (m, 2H), 3.73 (dd, J = 4.7, 10.7 Hz, 1H), 3.77–3.88 (m, 3H),}$
$\text{4.32 (‘q’, J = 6.0 Hz, 1H). ^13C NMR (125.8 MHz, CDCl$_3$) $\delta$ −5.2, −5.6, −5.6, 10.4, 18.2, 25.8, 39.7,}$
$\text{46.8, 63.0, 65.8, 79.8, 209.8. HRMS (m/z) (CI NH$_3$) calc. for C$_{13}$H$_{30}$NO$_3$Si (M+NH$_4$)$^+$}$
$\text{276.1995, found 276.1990.}$

$\text{(2S,6R)-6-(tert-Butyldimethylsilyloxymethyl)-2-methoxy-2,5-dihydropyran (14, Table 2,}$
$\text{entry 3).}$

$\text{1-Methoxybutadiene (13, 200 ul, 2.00 mmol) was added to a stirring mixture of (tert-}$
$\text{butyldimethylsilyloxy)acetaldehyde (416 ul, 2.00 mmol), chromium(III) complex 3a (15 mg,}$
$\text{...}
0.03 mmol), and 4Å molecular sieves (200 mg) under N₂ at ambient temperature. The mixture was stirred 16 h. Distillation of this mixture (Kügelrohr oven, 110 °C, 0.5 mmHg) afforded 14 (469 mg, 91%) as a colorless oil. GC analysis indicated the product to be 97% d.e. Further purification by flash column chromatography (5% ether/hexanes) gave 14 as a single diastereomer. [α]²⁶_D +55.3° (c 1.14, CDCl₃). R_f = 0.70 (1:1 ether/hexanes). IR (thin film) 2955, 2934, 2888, 2858, 1471, 1400, 1339, 1255, 1204, 1129, 1112, 1090, 1057 cm⁻¹. ^1H NMR (500 MHz, CDCl₃) δ 0.07 (s, 6H), 0.89 (s, 9H), 2.08 (m, 2H), 3.47 (s, 3H), 3.65 (dd, J = 6.5, 10.4 Hz, 1H), 3.76 (dd, J = 5.6, 10.4 Hz, 1H), 3.85 (‘q’, J = 6.3 Hz, 1H), 5.02 (m, 1H), 5.65 (‘dq’, J = 3.7, 10.2 Hz, 1H), 5.97 (‘dq’, J = 5.3, 10.2 Hz, 1H). ^13C NMR (125.8 MHz, CDCl₃) δ −5.2, −5.3, 18.4, 25.9, 26.8, 55.2, 65.5, 72.6, 97.7, 127.0, 128.5. HRMS (m/z) (CI NH₃) calc. for C₁₃H₃₀NO₃Si (M+NH₄⁺) 276.1995 found 276.2003.

(R)-6-(tert-Butyldimethylsilyloxymethyl)-5,6-dihydropyran-2-one (15).

Pyridinium dichromate (1.04 g, 2.75 mmol) was added to a solution of acetal 14 (356 mg, 1.38 mmol) and acetic acid (3 mL) in CH₂Cl₂ (20 mL) at ambient temperature. The mixture was stirred overnight, diluted with 1:1 ether/hexanes (20 mL), and filtered through a pad of MgSO₄. The solid residue in the flask was washed thoroughly with 1:1 ether/hexanes (4 ´ 20 mL) and filtered. The combined filtrates were again filtered through a fresh pad of MgSO₄ and concentrated in vacuo. Kügelrohr distillation (210-220 °C, 10 mmHg) gave 15 as a colorless oil (267 mg, 57%). The isolated material was determined to be >99% e.e. by chiral GC analysis (Cyclodex-B, 135 °C, isothermal t_R(minor) = 49.23 min, t_R(major) = 50.23 min). [α]²⁶_D +79.0° (c 1.00, CDCl₃). R_f = 0.17 (10% diethyl ether/hexanes). IR (thin film) 2955, 2930, 2859, 1732, 1471, 1407, 1251, 1136, 1093, 1043 cm⁻¹. ^1H NMR (500 MHz, CDCl₃) δ 0.06 (s, 6H), 0.87 (s, 9H), 2.40 (‘dt’, J = 4.6, 18.6 Hz, 1H), 2.51 (ddd, J = 2.6, 11.1, 18.6 Hz, 1H), 3.78 (dd, J = 5.4, 10.9 Hz, 1H), 3.80 (dd, J = 4.4, 10.9 Hz, 1H), 4.45 (dddd, J = 4.4, 4.6, 5.4, 11.1 Hz, 1H), 5.99 (d, J = 9.7 Hz, 1H), 6.89 (ddd, J = 2.6, 5.8, 9.7 Hz, 1H). ^13C NMR (125.8 MHz, CDCl₃) δ -5.4, 18.3, 25.8, 64.2, 77.8, 121.1, 145.0, 163.9. HRMS (m/z) (Cl NH₃) calc. for C₁₂H₂₆NO₃Si (M+NH₄⁺) 260.1682, found 260.1679.
PART 3. Determination of Relative Stereochemistry.

Nuclear Overhauser experiments determined that compounds 6a, 6d, 6h, and 14 were of the all cis relative configuration as summarized graphically below. Compounds 6c, 6e-g, 10 and 12 were assigned the same all cis relative configuration by comparison of their $^1$H (coupling constants) and $^{13}$C NMR spectra to those of 6a, 6d and 6h.

Nuclear Overhauser enhancements observed for Compounds 6a, 6d, 6h, and 14.

Compound 6b was assigned the all cis relative configuration by this same analysis and confirmed by coupling constant and nOe analysis of its L-Selectride reduction product 16 (all cis, see below).

Nuclear Overhauser enhancements (left) and coupling constants (right) observed for Compound 16.

(2R,3R,4S,6R)-2-(tert-Butyldimethylsilyloxy)methyl)-3,6-dimethyltetrahydropyran-4-ol (16).
L-Selectride (1.0 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of ketone 6b (200 mg, 0.735 mmol) in dry THF (5 mL) under N₂ at –78 °C. The solution was stirred at –78 °C for 6 h and allowed to warm to ambient temperature overnight. The mixture was cooled to 0 °C and water (2 mL) was added (dropwise), followed by 2M NaOH (aq) (1 mL) and 50 vol H₂O₂ (1 mL). After 1 h the solution was diluted with ether (40 mL) and washed with 20% NaSO₃ (aq) (30 mL), water (20 mL) and sat. NaCl (20 mL). The organic solution was dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (2:1 hexanes/ether) to give alcohol 16 as a colorless oil (148 mg, 73%). \( [\alpha]^{26}_{D} \) –14.3° (c 1.02, CHCl₃). \( R_f = 0.28 \) (1:1 hexanes/diethyl ether). IR (thin film) 3473, 2954, 2932, 2883, 2858, 1642, 1493, 1253, 1132, 1087 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 0.05 (s, 6H), 0.85 (d, \( J = 6.9 \) Hz, 3H), 0.89 (s, 9H), 1.21 (d, \( J = 6.1 \) Hz, 3H), 1.38 (‘q’, \( J = 11.7 \) Hz, 1H), 1.52 (b, 1H), 1.65 (ddd, \( J = 4.0, 4.8, 11.7 \) Hz, 1H), 2.05 (‘qn’, \( J = 5.8 \) Hz, 1H), 3.42–3.51 (m, 2H), 3.54 (dd, \( J = 7.5, 10.0 \) Hz, 1H), 3.69 (dd, \( J = 6.1, 10.0 \) Hz, 1H), 3.89 (‘dt’, \( J = 4.8, 11.7 \) Hz, 1H). \(^1\)C NMR (125.8 MHz, CDCl₃) \( \delta \) –5.2, –5.4, 4.6, 18.3, 21.6, 25.9, 35.1, 37.3, 63.1, 70.9, 72.3, 78.9. HRMS (m/z) (CI NH₃) calc. for C₁₄H₃₄NO₃Si, 292.2308 (M+NH₄)⁺, found 292.2307.

Having established the relative configuration of compounds 6a-6h as above, the L-Selectride reduction product of 6b (compound 15 - all cis, see above) was used to establish the absolute configuration of these compounds, using the variable temperature $^1$H NMR method of Riguera. As described below, esterification of 16 with (S)-methoxy-phenylacetic acid afforded ester 17, and variable temperature $^1$H NMR analysis of this compound established the absolute configuration at the carbinol center to be (S), which in turn established the absolute configuration of 6b to be (2R,3R,6R). The major enantiomers of compounds 6a and 6c-6h were assigned the same sense of absolute configuration as they all displayed the same elution profile by chiral GC (Cyclodex B): In all cases, the minor enantiomer eluted first, the major enantiomer second.

(S)-MPA ester 17.

![Chemical Structure](image)

DMAP (10 mg) was added to a solution of alcohol 16 (50.0 mg, 0.182 mmol), (S)-methoxyphenylacetic acid (33.1 mg, 0.201 mmol), and DCC (44.5 mg, 0.201 mmol) in dry CH$_2$Cl$_2$ (5 mL). The mixture was stirred for 6 h (low conversion by TLC analysis) and heated at reflux for 6 h. The mixture was concentrated in vacuo, resuspended in hexanes (30 mL) and filtered through MgSO$_4$. The filtrate was diluted with hexane (40 mL), washed with 1M HCl (2 x 30 mL), sat. NaHCO$_3$ (2 x 30 mL), and brine (30 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The white solid residue was purified by silica gel chromatography (10% ether/hexanes) to give 17 as a colorless oil. $\alpha^26_D$ +36.1$^\circ$ (c 0.255, CH$_2$Cl$_2$). R$_f$ = 0.53 (1:1 hexanes/diethyl ether). IR (thin film) 2987, 2960, 2934, 2836, 1730, 1460, 1368, 1237, 1079 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.01 (s, 6H), 0.57 (d, $J$ = 6.9 Hz, 3H), 0.84-0.87 (m, 9H), 1.19 (d, $J$ = 6.2 Hz, 3H), 1.49 ('q', $J$ = 12.0 Hz, 1H), 1.69 (ddd, $J$ = 2.7, 4.7, 12.0 Hz, 1H), 1.98 ('qn', $J$ = 5.9 Hz, 1H), 3.41-3.46 (m, 5H), 3.47-3.53 (m, 1H), 3.62 (dd, $J$ = 9.4, 13.8 Hz, 1H), 4.75 (s, 1H), 5.01 ('dt', $J$ = 4.8, 12.0 Hz, 1H), 7.31-7.44 (m, 5H). $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ −5.4, −5.1, 5.1, 18.3, 21.5, 25.9, 32.3, 33.8, 57.4, 63.0, 72.2, 74.1, 78.6, 82.7, 127.3,
HRMS (m/z) (FAB NBA+NaI) calc. for C_{23}H_{38}NO_{5}SiNa (M+Na)^+ 445.2387, found 445.2386.

The absolute configuration of 10 was determined to be (2R,6R) by Saegusa oxidation (see below) of the triethylsilylenol ether formed in the asymmetric hetero-Diels–Alder reaction of diene 9 and aldehyde 5b and subsequent removal of the TBS group to yield the natural product erinapyrone B. Comparison of the sign of the specific rotation of the synthetic material to that reported for the natural product established the former to be of the (6R) configuration, which in turn established the absolute configuration of 10 to be (2R,6R).

Similarly, the absolute configuration of 15 was established by removal of the TBS group and comparison of the sign of the specific rotation of the purified material to that reported for the same compound. In this manner, 15 was found to be of the (R) configuration.

(-)-Erinapyrone B 18.

(3E)-2-Triethylsilyloxy-1,3-pentadiene (84% pure, 56.0 ul, 0.250 mmol) was added to a stirring mixture of (tert-butylidimethylsilyloxy)acetaldehyde 6b (47.0 ul, 0.250 mmol), chromium(III) complex 3a (3.70 mg, 0.0075 mmol), and 4Å molecular sieves (50 mg) under N\textsubscript{2} at ambient temperature. After 16 hours the mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (4 mL) and filtered through a short plug of silica gel, eluting with an additional portion CH\textsubscript{2}Cl\textsubscript{2} (4 mL). The the combined filtrates were concentrated in vacuo and the crude triethylsilylenol ether product was dissolved in CH\textsubscript{3}CN (2 mL). Pd(OAc)\textsubscript{2} (112 mg, 0.500 mmol) was added, and the black mixture was allowed to stir 2 h, diluted with 2:1 hexanes/ether (5 mL), and filtered through a plug of silica gel. The plug was washed with 2:1 hexanes/ether (10 mL) and the combined filtrates concentrated in vacuo and the yellow oil purified by silica gel chromatography (35.0 mg, 55%). The enone product (25.0 mg, 0.039 mmol) was dissolved in THF (400 ul), cooled to 0 °C, and
treated with TBAF (1.0 M in THF, 43.0 ul, 0.0430 mmol). The mixture was stirred 5 min, diluted with 2:1 hexanes/ether (20 mL), and filtered through a plug of silica, eluting with EtOAc (10 mL). The combined filtrates were concentrated in vacuo, and purification of the residue by silica gel chromatography (50%-100% EtOAc/hexanes) gave erinapyrone B (18) as a white solid (9.10 mg, 68%). \([\alpha]^{26}_D -198^\circ (c 1.77, \text{CHCl}_3)\); lit.\(^4\) –210\(^\circ\) (c 1.71 CHCl\(_3\)).

(R)-6-(Hydroxymethyl)-5,6-dihydro-2\(H\)-pyranone-2-one 18.

\[
\begin{align*}
\text{Lactone 15 (33.0 mg, 0.136 mmol) was dissolved in THF (1.5 mL), cooled to 0 ^\circ C, and treated with TBAF (1.0 M in THF, 15.0 ul, 0.150 mmol). The solution was stirred 10 min, diluted with 2:1 hexanes/ether (20 mL), and filtered through a plug of silica, eluting with EtOAc (10 mL). The combined filtrates were concentrated in vacuo and purification of the residue by silica gel chromatography (50%-100% EtOAc/hexanes) afforded 19 as a yellow oil (7.40 mg, 42%). [\alpha]^{26}_D +159^\circ (c 0.37, \text{CHCl}_3); \text{lit.}^5 +160^\circ (c 0.850 \text{CHCl}_3).}
\end{align*}
\]