Enantioselective Rare-Earth Catalyzed Quinone Diels-Alder Reactions

David A. Evans* and Jimmy Wu

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Supporting Information

General Information. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. THF, toluene, ether, and CH₂Cl₂ were purified by passage through a bed of activated alumina.¹ Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.² Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T\text{ }^\circ\text{C}}$ (c g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H NMR spectra were recorded on a Varian Inova-500 (500 MHz) or Varian Mercury-400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, brs=broad; integration; coupling constant(s) in Hz). Proton-decoupled ¹³C NMR spectra were recorded on Varian Inova-500 (125 MHz) or Varian Mercury-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers at the Harvard University Mass Spectrometry Laboratory. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series HPLC with a diode array detector using the indicated chiral column.

I. Preparation of Quinone Substrates. The corresponding hydroquinone precursor to quinone **2** was commercially available (Aldrich Co.) and was oxidized to quinone **2** according to the method described by Nakazaki and Naemura.³ Quinone **9** was prepared in 3 steps from commercially available methyl-1,4-benzoquinone (Aldrich Co.) as described in eq 5. A slight modification of the Nakazaki/Naemura³

oxidation method was used for the final oxidation to quinone **9**. Naphthoquinone **11** was synthesized by preparation of the corresponding methyl ester of 1,4-dihydroxy-2-naphthoic acid (Aldrich Co.). followed by oxidation as described by Nakazaki and Naemura.³

Preparation of 2,5-dihydroxy-4-methyl-benzoic acid methyl ester. A bomb was charged with 2-bromo-5-methyl-benzene-1,4-diol⁴ (1.50 g, 7.39 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (0.75 g, 0.92 mmol), DMF (13.5 mL), Bu₃N (2.74 mL, 14.8 mmol), and MeOH (6 mL) in that order. The vessel was purged with 3 x 300 psi CO

and then pressurized with CO (420 psi) and stirred at 110 °C for 30 h. The reaction was cooled to room temperature, diluted with CH₂Cl₂ (50 mL), washed with 2 x 35 mL of 1N HCl, 1 x 35 mL of 1:1 brine/water, and 1 x 35 of mL brine. The organic layers were combined and dried over MgSO₄ and concentrated under reduced pressure to afford a dark purple oil. The residue was purified by flash chromatography (5 – 10% EtOAc/hexanes) to afford the title compound (0.90 g, 67% yield) as a light brown solid that was homogeneous as judged by ¹H NMR spectroscopy. ¹H NMR (500 MHz, CDCl₃) δ 10.28 (brs, 1H), 7.19 (s, 1H), 6.77 (s, 1H), 3.91 (s, 3H), 2.25 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 155.9, 146.7, 135.0, 119.5, 114.2, 110.0, 52.4, 16.8.

Preparation of 4-methyl-3,6-dioxo-cyclohexa-1,4-dienecarboxylic acid methyl ester (9). To a 2-dram vial was added 2,5-dihydroxy-4-methyl-benzoic acid methyl ester (21.9 mg, 0.12 mmol), MgSO₄ (52.0 mg, 0.43 mmol), and toluene (0.8 mL).

The solution was warmed to 50 °C, charged with Ag₂O (Aldrich Co.) (83.4 mg, 0.36 mmol) in the dark, and then stirred for 30 min. The slurry was then filtered through a Pasteur pipette fitted with a small cotton plug and 0.5 cm of MgSO₄ and washed with 2 x 0.2 mL of toluene. The title compound was immediately used as a solution in toluene without further purification. The product is stable in solution at room temperature for at least 3 h without any noticeable decomposition as judged by ¹H NMR spectroscopy.

II. Preparation of Pybox Ligands and Metal-Pybox Complexes. During the course of this study, Ph-pybox and norephedrine-pybox were prepared exactly as described by Davies *et al.*⁵

III. Preparation of Metal-Pybox Complexes. Metal complexes **1a**-(Sm), **1a**-(Gd), and **1b**-(Gd) were prepared according to the following general procedure. An oven-dried, 2-dram vial was charged with either **1a** or **1b** (0.11 mmol) and either Sm(OTf)₃ or Gd(OTf)₃ (0.01 equiv) in an inert atmosphere (N₂) glove box. The vial was brought out of the glove box, charged with THF (1.0 mL), and the resulting solution was stirred at room temperature for 2 h. Aging for less than 2 h gave irreproducible results. The metal-ligand complexes were used as is without further purification.

IV. Lanthanide Survey and Solvent Optimization. A metal survey utilizing the derived Ph-pybox complexes was performed for the illustrated reaction between quinone **2** and diene **3** (Table 2). Due to the exceptional yields and the absence of side-products in the reaction catalyzed by **1a**-(Sm), this complex was chosen for further study in the subsequent solvent optimization (Table 3). A systematic survey of solvents using 10 mol% of complex **1a**-(Sm) revealed that enantioselectivity was highly dependent on the choice of solvent system. Of the solvents that were evaluated (DCM, THF, and mixtures of ether, THF, and toluene with DCM), the best results were obtained when the reaction was conducted in a 1:1 mixture of THF and toluene (entry 7). The desired product was produced in 97% ee and 87% isolated yield.

Table 2. Lanthanide Survey

Entry	Lanthanide	ee %
1	Sc(OTf) ₃	28
2	Sm(OTf) ₃	27
3	La(OTf) ₃	18
4	Yb(OTf) ₃	racemic
5	LuI ₃	racemic

Table 3. Solvent Effects

Entry	Solvent	ee %
1	CH ₂ Cl ₂	27
2	THF	87
3	CH ₂ Cl ₂ /ether (1:3)	racemic
4	CH ₂ Cl ₂ /toluene (1:1)	92
5	CH ₂ Cl ₂ /toluene (3:1)	51
6	CH ₂ Cl ₂ /toluene (1:3)	89
7	THF/toluene (1:1)	97

Experiments Executed.

General Procedure A: Diels-Alder Cycloaddition. To an oven-dried, 4-mL vial containing a magnetic stirring bar was added (*S,S*)-bis(phenyloxazoliny)pyridine (4.9 mg, 0.013 mmol) and Sm(OTf)₃ (6.9 mg, 0.012 mmol) in an inert atmosphere (N₂) glove box. For Table 1, entries 12 and 13, (*S,S,S,S*)-bis(norephedrineoxazoliny)pyridine (5.2 mg, 0.013 mmol) and Gd(OTf)₃ (6.9 mg, 0.012 mmol) was used instead. The vial was fitted with a serum cap, removed from the inert atmosphere box and charged with THF (1.0 mL). The resulting suspension was stirred at room temperature for 2 h to give a colorless, homogenous solution and then chilled to -78 °C. To this solution was added **2** (20.0 mg, 0.12 mmol), **9** (21.6 mg, 0.12 mmol), or **11** (25.9 mg, 0.12 mmol) as a solution in toluene (1.0 mL). The appropriate diene (0.60 mmol) was added after the reaction mixture was stirred at -78 °C for 5 min. The solution was stirred at -78 °C until the quinone was completely consumed (10 min – 3 h), as determined by TLC (30% EtOAc/hexanes). The reaction mixture was then filtered through a 0.3 x 2 cm plug of silica gel with Et₂O (50 mL). Concentration of the volatiles gave the unpurified cycloaddition products.

Preparation of 1,4-dimethyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (4a). The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (5% EtOAc/hexanes) as a colorless oil that was homogeneous as judged by ¹H NMR spectroscopy (87% yield): [α]_D +17.3 ° (*c* = 1.18, CHCl₃); IR (film) 2965, 2880, 2348, 1747, 1704, 1682, 1455,

1373, 1241, 1076 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.73 (d, 1H, *J* = 10.7 Hz), 6.68 (d, 1H, *J* = 10.3 Hz), 5.56 (s, 2H), 3.76 (s, 3H), 3.72 (d, 1H, *J* = 6.3 Hz), 2.89 – 2.84 (m, 1H), 2.50 – 2.44 (m, 1H), 1.10 (t, 6H, *J* = 7.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 198.8, 196.6, 171.5, 141.5, 141.2, 129.4, 129.2, 63.1, 53.4, 53.3, 34.7, 30.3, 18.3, 17.8; HRMS (ESI): Exact mass calcd for C₁₄H₁₇O₄ [M+H]⁺, requires *m/z*: 249.1127, found *m/z*: 249.1126; Enantiomeric excess determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; *t*_r (major) = 19.2, *t*_r (minor) = 21.0, 97% ee.

Preparation of 5-methyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (4b). The indicated compound was prepared according to General

Procedure A. The product was isolated as a colorless oil (96% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. Attempts to purify the title compound by silica gel chromatography resulted in isomerization to the thermodynamically more stable *trans* isomer. $[\alpha]_{\text{D}} -235.0^\circ$ ($c = 1.35$, CHCl_3); IR (film) 3030, 2958, 2341, 1748, 1702, 1682, 1607, 1435, 1256, 1230 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.76 (d, 1H, $J = 10.6$ Hz), 6.72 (d, 1H, $J = 10.2$ Hz), 5.68 – 5.56 (m, 2H), 3.77 (s, 3H), 3.73 (dd, 1H, $J = 4.0, 7.3$ Hz), 3.07 – 2.97 (m, 1H), 2.69 – 2.62 (m, 1H), 2.13 – 2.05 (m, 1H), 0.98 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 197.8, 196.8, 170.8, 140.4, 140.3, 130.6, 122.7, 63.2, 53.5, 48.3, 34.7, 22.2, 18.5; HRMS (ESI): Exact mass calcd for $\text{C}_{13}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 235.0970, found m/z : 235.0962; Enantiomeric excess determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; t_{r} (minor) = 27.3, t_{r} (major) = 30.0, 96% ee.

Preparation of 5,7-dimethyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (4c). The indicated compound was prepared according to General Procedure A. The product was isolated as a colorless oil (97% yield) after filtration and was analytically pure as determined by ^1H NMR spectroscopy. Attempts

to purify the title compound by silica gel chromatography resulted in isomerization to the thermodynamically more stable *trans* isomer. $[\alpha]_{\text{D}} -222.7^\circ$ ($c = 1.48$, CHCl_3); IR (film) 2946, 2898, 2349, 1748, 1686, 1606, 1435, 1382, 1255, 1229, 1079 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.74 (d, 1H, $J = 10.3$ Hz), 6.70 (d, 1H, $J = 10.3$ Hz), 5.36 – 5.35 (m, 1H), 3.77 (s, 3H), 3.75 (dd, 1H, $J = 4.4, 7.3$ Hz), 3.02 – 2.99 (m, 1H), 2.56 – 2.52 (m, 1H), 2.00 – 1.96 (m, 1H), 1.67 (s, 3H), 0.95 (d, 3H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 197.9, 197.0, 170.9, 140.4, 140.2, 130.1, 124.9, 63.0, 53.4, 48.8, 35.1, 26.8, 23.4, 18.9; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 249.1127, found m/z : 249.1126; Enantiomeric excess determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; t_{r} (minor) = 21.1, t_{r} (major) = 23.5, 91% ee.

Preparation of 1-ethyl-8-hydroxy-4-methyl-5-oxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (4d). The indicated compound was prepared according to General Procedure A as an inseparable mixture of regioisomers (3.8:1). Purification by flash chromatography (5% EtOAc/hexanes) yielded the same mixture of

regioisomers as a colorless oil as judged by ^1H NMR spectroscopy (27.0 mg, 85% yield). In a 25 mL

round bottom flask was added the isolated mixture, MeOH (8.0 mL), and CeCl₃ (41.8 mg, 0.011 mmol), stirred at room temperature for 15 min, and then cooled to 0 °C.⁶ To the resulting reaction mixture was added NaBH₄ (3.9 mg, 0.01 mmol). After 5 min the reaction was diluted with water and extracted with 3 x 10 mL of CH₂Cl₂. The organic layers were combined, dried with MgSO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (6% EtOAc/hexanes) to afford the title compound as a single regioisomer (14.2 mg, 66% yield after correcting for using a 3.8:1 mixture of regioisomeric starting material) that was homogeneous as judged by ¹H NMR spectroscopy. [α]_D – 369.9 ° (*c* = 0.82, CHCl₃); IR (film) 3520, 3023, 2961, 1744, 1674, 1462, 1378, 1222 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.91 (dd, 1H, *J* = 5.5, 10.2 Hz), 6.13 (d, 1H, *J* = 10.2 Hz), 5.80 – 5.70 (m, 2H), 4.55 – 4.52 (m, 1H), 3.74 (s, 3H), 3.39 – 3.34 (m, 1H), 2.99 (t, 1H, *J* = 5.5 Hz), 2.35 (d, 1H, *J* = 3.7 Hz), 2.02 – 1.92 (m, 1H), 1.73 – 1.53 (m, 2H), 1.07 (d, 3H, *J* = 7.7 Hz), 1.03 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 198.3, 173.1, 146.7, 133.1, 129.9, 129.4, 63.1, 60.6, 53.3, 39.6, 36.6, 32.6, 24.6, 17.8, 12.5; HRMS (ESI): Exact mass calcd for C₁₅H₂₁O₄ [M+H]⁺, requires *m/z*: 265.1440, found *m/z*: 265.1436; Enantiomeric excess determined by HPLC with Chiracel AD column, 4% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; *t*_r (minor) = 24.2, *t*_r (major) = 27.6, 91% ee.

Preparation of 1-hydroxy-5-methyl-4-oxo-8-propyl-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (4e). The indicated compound was prepared

according to General Procedure A and isolated as an inseparable mixture of regioisomers (11:1). Purification by flash chromatography (4% EtOAc/hexanes) yielded a colorless oil (25.6 mg, 83% yield) that was enriched to a 15:1 mixture of regioisomers as determined by ¹H NMR spectroscopy. Luche reduction⁶ was performed according to the procedure in the preceding example to afford the title compound as a single regioisomer (16.6 mg, 64% yield after correcting for using a 15:1 mixture of regioisomeric starting material) that was homogeneous as judged by ¹H NMR spectroscopy after purification by flash chromatography (5% EtOAc/hexanes). [α]_D – 353.2 ° (*c* = 0.73, CHCl₃); IR (film) 3523, 2944, 2874, 2357, 1747, 1674, 1456, 1376, 1222 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.91 (dd, 1H, *J* = 5.5, 10.2 Hz), 6.13 (d, 1H, *J* = 9.9 Hz), 5.77 – 5.69 (m, 2H), 4.55 – 4.52 (m, 1H), 3.74 (s, 3H), 3.37 – 3.35 (m, 1H), 2.97 (t, 1H, *J* = 5.5 Hz), 2.37 (d, 1H, *J* = 4.4 Hz), 2.17 – 2.08 (m, 1H), 1.69 – 1.20 (m, 5H), 1.07 (d, 3H, *J* = 8.1 Hz), 0.95 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 198.4, 173.1, 146.7, 133.1, 129.9, 77.4, 63.2, 60.6, 53.2, 39.5, 34.3, 33.7, 32.5, 21.0, 17.8, 14.2; HRMS (ESI): Exact mass calcd for C₁₆H₂₃O₄ [M+H]⁺, requires *m/z*: 279.1596, found *m/z*: 279.1595; Enantiomeric

excess determined by HPLC with Chiracel AD column, 5% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; t_r (minor) = 18.3, t_r (major) = 20.7, 96% ee.

Preparation of 2,5,8-trimethyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (10a). The indicated compound was prepared

according to General Procedure A. The product was isolated as a colorless oil (91% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. $[\alpha]_D -193.5^\circ$ ($c = 0.17$, CHCl_3); IR (film) 2950, 2359, 1742, 1709, 1666, 1622, 1444, 1375, 1260, 1227, 1173, 1103, 1024, 745 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.55 – 6.54 (m, 1H), 5.54 (s, 2H), 3.74 (s, 3H), 3.70 (d, 1H, $J = 6.2$ Hz), 2.97 – 2.91 (m, 1H), 2.42 – 2.35 (m, 1H), 1.98 (d, 3H, $J = 1.5$ Hz), 1.13 (d, 3H, $J = 7.7$ Hz), 1.01 (d, 3H, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 199.2, 196.6, 171.5, 152.3, 137.2, 129.4, 129.3, 63.8, 53.4, 52.9, 34.4, 30.2, 18.1, 18.0, 16.4; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 263.1283, found m/z : 263.1284; Enantiomeric excess determined by HPLC with Chiracel ODH column, 2% *i*-PrOH/hexanes, 0.8 mL/min, 225 nm; t_r (major) = 16.4, t_r (minor) = 18.3, >99% ee.

Preparation of 2,5-dimethyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (10b). The indicated compound was prepared according

to General Procedure A. The product was isolated as a colorless oil (88% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. $[\alpha]_D -452.3^\circ$ ($c = 0.80$, CHCl_3); IR (film) 3030, 2961, 1749, 1698, 1673, 1622, 1433, 1372, 1256, 1222, 1122, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.58 – 6.51 (m, 1H), 5.68 – 5.56 (m, 2H), 3.76 (s, 3H), 3.74 (dd, 1H, $J = 2.9, 7.3$ Hz), 3.09 – 3.04 (m, 1H), 2.78 – 2.71 (m, 1H), 2.07 – 1.99 (m, 1H), 2.03 (d, 3H, $J = 1.5$ Hz), 0.89 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 198.3, 196.7, 170.9, 151.1, 136.9, 130.6, 122.9, 63.4, 53.4, 47.6, 34.5, 21.8, 18.7, 16.7; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 249.1127, found m/z : 249.1129; Enantiomeric excess determined by HPLC with Chiracel ODH column, 3% *i*-PrOH/hexanes, 0.8 mL/min, 225 nm; t_r (minor) = 21.8, t_r (major) = 23.9, 95% ee.

Preparation of 2,5,7-trimethyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (10c).

The indicated compound was prepared according to General Procedure A. The product was isolated as a colorless oil (84% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. $[\alpha]_{\text{D}} -357.6^\circ$ ($c = 1.33$, CHCl_3); IR (film) 2964, 1749, 1698, 1673, 1626, 1435, 1378, 1250, 1225, 1130, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.56 – 6.55 (m, 1H), 5.35 – 5.34 (m, 1H), 3.75 (s, 3H), 3.74 (dd, 1H, $J = 3.3, 7.0$ Hz), 3.06 – 3.03 (m, 1H), 2.63 – 2.58 (m, 1H), 2.02 (d, 3H, $J = 1.8$ Hz), 1.97 – 1.90 (m, 1H), 1.67 (s, 3H), 0.86 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 198.4, 196.9, 170.9, 150.9, 137.0, 130.2, 124.9, 63.2, 53.3, 48.2, 34.9, 26.4, 23.4, 19.0, 16.7; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 263.1283, found m/z : 263.1290; Enantiomeric excess determined by HPLC with Chiracel ODH column, 2% *i*-PrOH/hexanes, 0.8 mL/min, 225 nm; t_{r} (minor) = 22.3, t_{r} (major) = 23.7, 98% ee.

Preparation of 1,4-dimethyl-9,10-dioxo-1,9,9a,10-tetrahydro-4H-anthracene-4a-carboxylic acid methyl ester (12a).

The indicated compound was prepared according to General Procedure A. The product was isolated as a colorless oil (99% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. $[\alpha]_{\text{D}} -30.0^\circ$ ($c = 1.72$, CHCl_3); IR (film) 3023, 2963, 2341, 1748, 1705, 1594, 1456, 1248 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.01 – 7.94 (m, 2H), 7.74 – 7.70 (m, 2H), 5.64 – 5.58 (m, 2H), 3.86 (d, 1H, $J = 6.2$ Hz), 3.66 (s, 3H), 3.0 – 2.94 (m, 1H), 2.57 – 2.53 (m, 1H), 1.03 (d, 3H, $J = 7.7$ Hz), 1.02 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 197.2, 195.2, 171.7, 136.4, 136.1, 134.5, 134.4, 129.6, 129.4, 126.9, 126.5, 63.4, 53.7, 53.3, 35.0, 30.6, 18.3, 17.7; HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 299.1283, found m/z : 299.1279; Enantiomeric excess determined by HPLC with Chiracel AD column, 1% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; t_{r} (minor) = 25.3, t_{r} (major) = 27.4, 91% ee.

Preparation 4-methyl-9,10-dioxo-1,9,9a,10-tetrahydro-4H-anthracene-4a-carboxylic acid methyl ester (12b).

The indicated compound was prepared according to General Procedure A. The product was isolated as a colorless oil (91% yield) after filtration and was analytically pure without further purification as determined by ^1H NMR spectroscopy. $[\alpha]_{\text{D}} +144.0^\circ$ ($c = 1.55$, CHCl_3); IR (film) 3029, 2956, 2884, 2359, 1748, 1702,

1594, 1434, 1254 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.09 – 7.99 (m, 2H), 7.77 – 7.73 (m, 2H), 5.72 – 5.62 (m, 2H), 3.88 (q, 1H, $J = 4.4, 7.0$ Hz), 3.13 – 3.08 (m, 1H), 2.78 – 2.71 (m, 1H), 2.19 – 2.11 (m, 1H), 0.88 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 196.4, 195.0, 171.2, 135.1, 134.8, 134.7, 134.6, 130.9, 127.3, 126.7, 122.9, 63.3, 53.3, 48.6, 34.9, 22.7, 18.1; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$, requires m/z : 285.1127, found m/z : 285.1127; Enantiomeric excess determined by HPLC with Chiracel AD column, 1% *i*-PrOH/hexanes, 0.6 mL/min, 225 nm; t_r (minor) = 35.9, t_r (major) = 40.7, 91% ee.

VI. Stereochemical Assignments. Various methods were employed for the determination of the relative stereochemical assignments of the products obtained (endo with respect to the quinone ring, Table 4). The absolute stereochemistries of compounds **4b** and **12b** were determined by the diastereo- and regioselective Luche reduction⁶ of the less sterically hindered ketone followed by Mosher Ester analysis.⁷ Formation of the diastereomer corresponding to hydride approach from the convex face of **4b** and **12b** was confirmed via NOE analysis prior to Mosher ester analysis. Determination of the absolute stereochemical assignments for the remaining products were made via analogy.

Table 4. Methods Used for the Determination of Endo Relative Stereochemistry

Compound	Method
4a	NOE Analysis
4b	Luche reduction followed by NOE analysis and single crystal X-ray analysis of the corresponding <i>trans</i> isomer
4c	analogy
4d	Luche reduction followed by NOE analysis
4e	Luche reduction followed by NOE analysis
10a	analogy
10b	single crystal X-ray analysis
10c	analogy
12a	Luche reduction followed by NOE analysis
12b	analogy

Mosher Ester Analysis of 4b. Mosher ester analysis was performed on the corresponding alcohol following Luche reduction of **4b** as described above. Formation of the diastereomer corresponding to hydride approach from the convex face of **4b** was confirmed via NOE analysis prior to Mosher ester analysis. ^1H NMR

(500 MHz, CDCl₃) δ 7.536 – 7.520 (m, 2H), 7.449 – 7.410 (m, 3H), 6.440 (td, 1H, J = 1.95, 10.25 Hz), 6.073 (dd, 1H, J = 2.44, 10.25 Hz), 6.016 – 5.998 (m, 1H), 5.566 – 5.537 (m, 1H), 5.455 – 5.415 (m, 1H), 3.810 (s, 3H), 3.570 (s, 3H), 3.264 – 3.214 (m, 1H), 2.674 – 2.656 (m, 1H), 2.009 – 1.965 (m, 2H), 1.307 (d, 3H, J = 7.81 Hz).

Mosher Ester Analysis of 4b. Mosher ester analysis was performed on the corresponding alcohol following Luche reduction of **4b** as described above. Formation of the diastereomer corresponding to hydride approach from the convex face of **4b** was confirmed via NOE analysis prior to Mosher ester analysis. ¹H NMR (500 MHz, CDCl₃) δ 7.519 – 7.503 (m, 2H), 7.458 – 7.411 (m, 3H), 6.357 (td, 1H, J = 1.95, 10.25 Hz), 6.044 (dd, 1H, J = 2.44, 10.25 Hz), 6.017 – 6.003 (m, 1H), 5.586 – 5.563 (m, 1H), 5.512 – 5.472 (m, 1H), 3.811 (s, 3H), 3.533 (s, 3H), 3.296 – 3.246 (m, 1H), 2.686 – 2.677 (m, 1H), 2.224 – 2.156 (m, 1H), 2.078 – 2.000 (m, 1H), 1.314 (d, 3H, J = 7.8 Hz).

Mosher Ester Analysis of 12b. Mosher ester analysis was performed on the corresponding alcohol following Luche reduction of **12b** as described above. Formation of the diastereomer corresponding to hydride approach from the convex face of **12b** was confirmed via NOE analysis prior to Mosher ester analysis. ¹H NMR (500 MHz, CDCl₃) δ 8.002 (dd, 1H, J = 1.47, 7.81 Hz), 7.617 – 7.598 (m, 2H), 7.521 – 7.398 (m, 5H), 7.138 (d, 1H, J = 7.81 Hz), 6.516 (d, 1H, J = 4.88 Hz), 5.619 – 5.586 (m, 1H), 5.415 – 5.375 (m, 1H), 3.737 (s, 3H), 3.617 (s, 3H), 3.364 – 3.319 (m, 1H), 2.849 – 2.810 (m, 1H), 1.928 – 1.863 (m, 1H), 1.789 – 1.715 (m, 1H), 1.408 (s, 3H, J = 7.81 Hz).

Mosher Ester Analysis of 12b. Mosher ester analysis was performed on the corresponding alcohol following Luche reduction of **12b** as described above. Formation of the diastereomer corresponding to hydride approach from the convex face of **12b** was confirmed via NOE analysis prior to Mosher ester analysis. ¹H NMR (500 MHz, CDCl₃) δ 7.984 (dd, 1H, J = 1.47, 7.32 Hz), 7.620 – 7.601 (m, 2H), 7.482 – 7.454 (m, 3H), 7.447 – 7.367 (m, 2H), 6.917 (d, 1H, J = 7.81 Hz), 6.532 (d,

1H, $J = 4.40$ Hz), 5.652 – 5.620 (m, 1H), 5.485 – 5.445 (m, 1H), 3.741 (s, 3H), 3.598 (s, 3H), 3.386 – 3.341 (m, 1H), 2.859 – 2.820 (m, 1H), 2.126 – 2.056 (m, 1H), 1.889 – 1.810 (m, 1H), 1.418 (d, 3H, $J = 7.81$ Hz).

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

² Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.

³ Nakazaki, M.; Naemura, K. *J. Org. Chem.* **1981**, *46*, 106-111.

⁴ Miller, L. L.; Stewart, R. F. *J. Org. Chem.* **1978**, *43*, 3078-3079.

⁵ Davies, I. W.; Gerena, L.; Nu, L.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629-9630.

⁶ White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404-2419.

⁷ Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.