Formation and Isolation of Enantiomerically Pure Products in Quantity from Diels–Alder Reactions of 1,4-Benzoquinones

Thomas A. Engler,* Michael A. Letavic, Kenneth O. Lynch, Jr., and Fusao Takusagawa

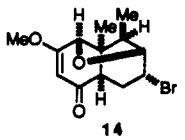
Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received November 10, 1993•

Diels–Alder reactions of 2-methoxy-6-methyl- and 2-methoxy-5-methyl-1,4-benzoquinones with various substituted dienes are promoted by a chiral complex prepared from $TiCl_4$, $Ti(O^iPr)_4$, and (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol. The products from several dienes are formed in moderate to good ee and are obtained enantiomerically pure after simple recrystallization steps.

The ultimate goal of the exploration of new asymmetric processes is the development of methods to prepare chiral molecules as single enantiomers, preferably in quantity and with a small number of synthetic and purification steps.[1] Enantioselective catalysis offers notable advantages over other conventional methods in that tedious and wasteful resolution procedures are not required, inefficient sequences involving attachment/detachment of chiral auxiliaries are not necessary, and the process is not limited to the availability of starting materials from the chiral pool with structures similar to the desired target and with proper absolute configuration. Recently, we reported a method to effect asymmetric quinone-based Diels–Alder reactions utilizing a chiral Ti(IV) complex as a promoter.[2] Because of the utility of quinone Diels–Alder adducts in syntheses of a large number of biologically and theoretically interesting molecules,[3] we scaled up some of these reactions and investigated methods for purification of the major enantiomers. Herein, we report the experimental details of several of these reactions that have been carried out on more than 10-mmol scale and the products obtained as single enantiomers in greater than 0.9-g amounts after simple purification steps.

Reactions of quinone **1** with dienes **2** at −78 °C were promoted by a complex formed *in situ* in toluene from diol (+)-**3**[4,5] and a solid prepared from a 5:1 mixture $TiCl_4$ and $Ti(O^iPr)_4$ (eqs 1 and 2 and Table 1). The products **4** were obtained in excellent yield and moderate to good ee following flash chromatography of the crude reaction mixtures to separate the adducts from the diol **3**, which could be reclaimed. In a similar manner, reaction of quinone **6** with piperylene (**2b**) gave **7** (eq 3). The enantiomeric excesses of **4a-e** and **7** were determined by 500-MHz ^1H NMR analysis in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent[6] and/or by HPLC (CHIRALPAK AS/CHIRALCEL OD). Products **4b/c** and **7** contained small amounts (≤5%) of a second diastereomer (by ^1H NMR) and in each case simple recrystallization from EtOAc/hexanes gave crystals that were diastereo- and enantiomerically homogeneous by 500-MHz ^1H NMR analysis.[2e] Compound **4a** was isolated as a single diastereomer and was obtained enantiomerically pure after recrystallization twice from EtOAc/hexanes.[2e] In the cases of **4d/e**, fractional recrystallization of the material obtained after chromatography gave crystals that were largely racemic. Concentration of the mother liquor followed by crystallization of the residue gave material that was enantiomerically pure. The overall yields and amounts of enantiomerically pure **4a-e/7** obtained after the chromatography and recrystallization steps were ≥32% and ≥0.93 g (Table 1). The structures and absolute configurations of **4/7** were determined by methods previously described.[2a,f,g] Comparison of the specific rotations of the products acquired from the initial



14

• Abstract published in *Advance ACS Abstracts*, February 15, 1994.

(1) For a few selected discussions, primarily on asymmetric synthesis in drug development, see: (a) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479. (b) Crossley, R. *Tetrahedron* **1992**, *48*, 8155. (c) Stinson, S. C. *Chem. Eng. News* **1992**, September 28, 46. (d) Stinson, S. C. *Ibid.* **1993**, September 27, 38. (e) Gross, M. *Ann. Rep. Med. Chem.* **1990**, *25*, 323. (f) Amato, I. *Science* **1992**, *256*, 964.

(2) (a) Engler, T. A.; Letavic, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1992**, *33*, 6731. For previous work in this area, see references cited in 2a and (b) Siegel, C.; Thornton, E. R. *Ibid* **1988**, *29*, 5225. For reviews, see: (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (d) Kagan, H. B.; Riant, O. *Ibid.* **1992**, *92*, 1007. (e) For a previous report of recrystallization of enantiomerically enriched quinone Diels–Alder products to improve enantiomeric purity, see: Dauben, W. G.; Bunce, R. A. *Tetrahedron Lett.* **1982**, *23*, 4875. (f) Single-crystal X-ray analysis of **14** was used to determine absolute configuration by the anomalous dispersion effect. Full experimental details for the preparation of **14** from **4b** are included in the supplementary material. The author has deposited the crystallographic data and atomic coordinates for **14** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. (g) Data from ^1H–^1H NOE experiments are included in the supplementary material.

(3) For reviews and selected recent examples, see: (a) Desimoni, G.; Tacconi, G.; Barco, A.; Piero-Pollini, G. P. *National Product Synthesis Through Pericyclic Reactions*, ACS Monograph 180; American Chemical Society: Washington, DC 1983. (b) Finley, K. T. In *The Chemistry of Quinonoid Compounds*, Vol. 2, Part 2; Patai, S., Rappoport, Z., Eds.; Wiley–Interscience: New York, 1988; p 537. (c) Benchikh le-Hocine, M.; Do Khac, D.; Fétizon, M.; Guir, F.; Guo, Y.; Prangé, T. *Tetrahedron Lett.* **1992**, 1443. (d) Eaton, P. E.; Or, Y. S.; Branca, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 2134. (e) Mehta, G.; Reddy, A. V.; Murthy, A. N.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 540. (f) Engler, T. A.; Sampath, U.; Naganathan, S.; Vander Velde, D.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712. (g) Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 5859. (h) Wender, P. A.; Rawlins, D. B. *Tetrahedron* **1992**, *48*, 7033.

(4) For a recent compilation of previous uses of this and related diols in asymmetric reactions, see: (a) Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711.

(5) We mistakenly stated in our preliminary report[2a] that product **4g** was isolated enantiomercially pure by recrystallization. In fact, in our hands **4g** is an oil and was obtained in 92% ee. Although **4f**, **4g**, and products of **6** with **2c** and **2g** have not been isolated enantiomerically pure as yet, the full experimental details for their preparation and their spectral characteristics are included in the supplementary material.

(6) (a) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263. See also: (b) Weisman, G. R. In *Asymmetric Synthesis*; Morrison, T. D., Ed.; Academic Press: San Diego, 1983; p 153.

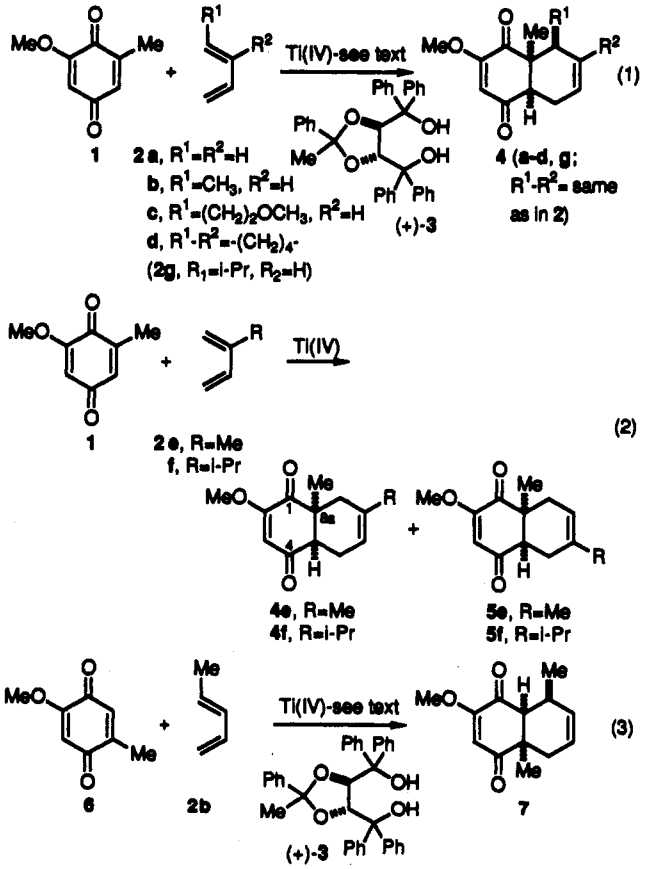
0022-3263/94/1959-1179$04.50/0

Table 1. Asymmetric Diels–Alder Reactions of 2-Methoxy-1,4-benzoquinones with Dienes

diene	quinone (mmol)	product (g)[a]	% yield	% ee[b]	g of enantiomerically pure product (% yield)[c]
2a	1 (14.6)	4a (2.6)	88	63	0.97 (32)
2b	1 (10.2)	4b (2.12)[d]	94	80[b]	1.22 (54)
2c	1 (10.1)	4c (2.27)[e]	85	61[b,f]	1.09 (41)
2d	1 (13.0)	4d (3.35)	97	67	1.88 (56)
2e	1 (12.9)	4e (2.83)[g]	99	58[b,h]	1.65 (59)
2b	6 (10.9)	7 (2.09)	88	54[h,i]	0.93 (51)

[a] After flash chromatography. [b] Of the major diastereomer. [c] Isolated after recrystallization steps. [d] As a 22:1 ratio of diastereomers. [e] As an 18:1 mixture of diastereomers. [f] A small-scale experiment (0.5 mmol of 1) gave 81% ee. [g] As a 7.8:1 mixture of regioisomers, see text. [h] Small-scale experiments gave 67–76% ee. On scale up, ee ranged from 58–67%. [i] On a small-scale (0.8 mmol 1), 66% ee was found.

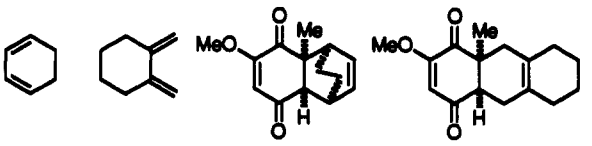
chromatography with those of enantiomerically pure samples of 4a-e/7 were in good agreement with the enantiomeric excesses measured by NMR. Thus, although the enantiomeric excesses of the products initially obtained upon separation from the diol are moderate, the process can still be used in many cases to access sizeable quantities of enantiomerically pure material.



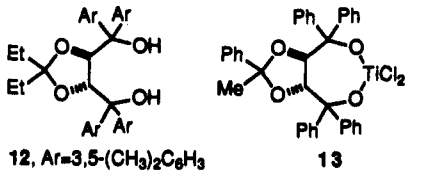
Reactions of 1 with dienes 2f and 2g and of 6 with 2g and 2c were also studied.[2a] Unfortunately, the products from the first three were oils[5] and the recrystallization of the adduct from 6 and 2c failed to improve the enantiomeric excess.

Reactions of 2-methoxy-1,4-benzoquinone with several of the dienes were examined briefly and preliminary studies indicated that products were formed with moderate levels of asymmetric induction. For example, reaction of 2-methoxy-1,4-benzoquinone with diene 2g gave an 8.4:1 mixture of isomeric products (presumably endo:exo) in 85% yield and the major isomer was formed in 53% ee by ^{1}H NMR. Unfortunately a severe, apparently allergic, reaction to this reaction mixture (probably due to small amounts of a hydroquinone tautomer) forced us to abandon further development of these reactions and prevented full structural characterization of the products.

Finally, reactions of cyclic dienes 8 and 9 with quinone 1 were studied as well. Although the yields of the products 10 and 11, respectively, were excellent (>95%), the ee values were poor; 10 was produced in 20–30% ee and 11 was racemic.



The formation of the Ti(IV) complex used in these studies requires some comment. Best results were obtained with an off-white solid produced upon addition of $TiCl_4$ to a solution of $Ti(O^iPr)_4$ in CH_2Cl_2 and stirring the mixture at room temperature. The solvent was removed from this "Ti(IV)-solid", the structure of which is unknown,[7] and the solid was combined in toluene with the diol 3 in a 1.5:1 ratio by weight. The quinone was then added as a solution in CH_2Cl_2 followed by the diene. The amount of quinone was varied from 0.5 to 1 equiv with respect to the diol. Full experimental details for each reaction are provided herein and in the supplementary material. Complexes prepared *in situ* from the dilithium salt of 3 (BuLi) and $TiCl_4$, the Ti(IV)-solid or 1:1 mixtures of $TiCl_4$:$Ti(O^iPr)_4$ were also examined as well as Ti(IV) complexes prepared from diols 3 and 12 via procedures reported by Narasaka[8] and Corey.[9] None of these complexes were as effective as that prepared from the Ti-(IV)-solid as described above. The use of other chiral ligands for the titanium were also examined including (*R*)-(−)-1,1′-bi-2-naphthol, (*R*,*R*)-(+)-hydrobenzoin,[10] (1*R*,2*R*)-(−)-ephedrine, and (1*R*,2*S*)-(−)-norephedrine. Again, in our hands, none of these other ligands were effective in providing products from the Diels–Alder reactions in high ee.



After our initial report appeared, Professor J. B. Hendrickson drew our attention to his previous studies

(7) The ^{1}H and ^{13}C NMR spectra of the "Ti(IV)-solid" [^{1}H (300 MHz, $CDCl_3$) δ 1.60 (d, J = 6 Hz, 6H), 5.15 (septet, J = 6 Hz, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 24.76, 95.55] are quite different than that of $TiCl_2(O^iPr)_2$ [^{1}H (300 MHz, $CDCl_3$) δ 1.42 (d, J = 6 Hz, 6H), 4.85 (septet, J = 6 Hz, 1H); ^{13}C δ 25.5, 88], formed as a white solid from a 1:1 mixture of $TiCl_4$ and $Ti(O^iPr)_4$ in hexane. NMR data for $TiCl_2(O^iPr)_2$ were taken from Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(8) (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340 and previous reports by this group cited therein. (b) We did successfully reproduce the Diels–Alder reaction between cyclopentadiene and *N*-crotyloxazolidinone (76% yield, 93% ee) exactly as described by Narasaka.

(9) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, 6289.

(10) Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396.

on reactions of quinone 1 with isoprene (2e).[11] When catalyzed by $TiCl_4$, mixtures of $TiCl_4$:$Ti(O^iPr)_4$, or $SnCl_4$ in CH_2Cl_2, these reactions produced the regioisomeric products 4e and 5e in ratios ranging from 2:1 to 1:2. However, as detailed above, promotion of the reaction with the chiral Ti(IV):diol 3 complex gave 7.6–9:1 ratios of 4e and 5e in 79–100% isolated yields and >60% ee (for several experiments). We also examined the $TiCl_4$-catalyzed reaction of 1 with 2e in toluene/CH_2Cl_2 at −78 °C and found a 2.6:1 ratio of 4e and 5e in 97% yield.[12] Similar results were found in reactions of 1 with diene 2f (R = ^{i}Pr). With $TiCl_4$ as promoter, a 2:1 mixture of 4f and 5f was produced in quantitative yield whereas with the chiral Ti(IV):diol 3 complex as promoter, 4f and 5f were obtained in an 8.9:1 ratio (97%) and the ee of the major isomer 4f was 82%. Professor Hendrickson also told us of their studies on reactions of 1 with 2e promoted by the Narasaka catalyst 13.[8] We examined reactions of quinone 1 with butadiene using the Narasaka catalyst (and others, *vide infra*) as well, although with little success.[2a,8b]

In conclusion, the method for preparation of the Ti(IV) reagent used to form the chiral Ti(IV) complex apparently has a dramatic influence on the regio- and enantioselectivity of the quinone Diels–Alder reactions and perhaps of other reactions as well. NMR studies show that the Ti(IV)-solid prepared as described above is undoubtedly different than the system described as $TiCl_2(O^iPr)_2$ and other simple mixtures of $TiCl_4$:$Ti(O^iPr)_4$ in $CDCl_3$.[7] We are pursuing studies to identify the complexes formed in these systems. At this time, however, it should be noted that in these asymmetric quinone Diels–Alder reactions, variations in experimental procedures can lead to vastly different results for reasons that have yet to be determined. Nevertheless, the results presently described demonstrate a simple and practical procedure for accessing enantiomerically pure products in gram quantities from Diels–Alder reactions of 2-methoxy-6-methyl-1,4-benzoquinone and 2-methoxy-5-methyl-1,4-benzoquinone.

Experimental Section[13]

Procedures for the preparation of 2c, 2d, 2f, and 2g[5] are included in the supplementary material. Since the Diels–Alder reactions producing 4a-g and 7 were conducted in a similar manner, one general experimental procedure is given. For the remaining examples, only the amounts of reagents used, yields, purification steps, and partial spectroscopic and physical data for the products are given. Full experimental descriptions and other spectroscopic data are given in the supplementary material. 2-Methoxy-6-methyl-1,4-benzoquinone,[14] 2-methoxy-5-methyl-1,4-benzoquinone,[14] 1,2-dimethylenecyclohexane (9),[15] and diol (+)-3[8a] were prepared by literature procedures.

General Procedure for the Diels–Alder Reactions. (4a*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-2-methoxy-8a-methyl-1,4-naphthalenedione (4a). To a solution of titanium(IV) isopropoxide (1.98 mL, 6.65 mmol) in dichloromethane (8.0 mL) at room temperature was added titanium(IV) chloride (3.66 mL, 33.4 mmol), and the mixture was stirred for 1 h at room temperature. The liquid was decanted from the solid that had formed. The solid was washed with dichloromethane (8.0 mL), dried under vacuum for ~15 min, and used immediately. To a solution of the Ti(IV)-solid (5.17 g) in toluene (38 mL) at −78 °C was added a solution of diol (+)-3 (7.55 g, 14.3 mmol) in toluene (25 mL). This mixture was allowed to warm to room temperature, stirred 0.5 h, and then recooled to −78 °C. A solution of 2-methoxy-6-methyl-1,4-benzoquinone (1, 2.22 g, 14.6 mmol) in dichloromethane (28 mL) was added, the mixture was stirred for 15 min and then butadiene (3.00 g, 55.5 mmol) was added dropwise, and the mixture was stirred for 4 h at −78 °C. Sodium bicarbonate (6.54 g) and 2-propanol (25 mL) were added to the mixture at −78 °C, which was then diluted with water, filtered through Celite, and extracted with dichloromethane (3 × 300 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave 4a (2.65 g, 88%) as a solid. The enantiomeric purity was estimated to be ~63% ee by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the signals for the angular methyl group and the methoxy group split into well-resolved pairs of singlets. Recrystallization (twice) from EtOAc/hexanes provided enantiomerically pure material (0.97 g, 32%): mp 115–116 °C; R_f (35% EtOAc/hexanes) 0.35; ^{1}H NMR (500 MHz) 1.34 (s, 3H), 1.77 (m, 1H), 2.15 (m, 1H), 2.51 (m, 1H), 2.66 (m, 1H), 2.79 (dd, J = 5, 5, 1H) 3.75 (s, 3H), 5.59 (m, 1H), 5.67 (m, 1H), 5.85 (s, 1H); ^{13}C NMR (125 MHz) 22.2, 23.0, 32.3, 47.1, 51.1, 56.3, 109.8, 123.5, 124.3, 160.0, 197.1, 198.3; ORD (10.3 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +46.4, $[\alpha]_{578}$ = +48.3, $[\alpha]_{546}$ = +53.3, $[\alpha]_{436}$ = +62.7, $[\alpha]_{365}$ = no transmittance; CD (0.76 mg/mL, $CHCl_3$) 255 ($\Delta\epsilon$ = +7.9), 289 (−7.1). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.25; H, 7.10.

(4a*R*,8*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-8,8a-dimethyl-2-methoxy-1,4-naphthalenedione (4b). Following the general procedure described above, the Ti(IV):(+)-3 complex was prepared from the Ti(IV)-solid (3.59 g) and diol (+)-3 (5.23 g, 9.89 mmol) in toluene (73 mL). A solution of quinone 1 (1.55 g, 10.2 mmol) in CH_2Cl_2 (25 mL) was then added to the mixture at −78 °C followed by piperylene (4.5 mL, 45.2 mmol). The mixture was stirred 2 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave a 22:1 mixture of 4b and a second unidentified isomer (2.12 g, 94%). The major product 4b was estimated to be ~80% ee by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the OCH_3 signal split into two singlets. Recrystallization from EtOAc/hexanes gave enantiomerically pure material (1.22 g, 54%): mp 100.0–100.5 °C; R_f (35% EtOAc/hexanes) 0.34; ^{1}H NMR (500 MHz) 0.86 (d, J = 7, 3H), 1.41 (s, 3H), 2.05 (m, 1H),

(11) Hendrickson, J. B.; Haestier, A. M.; Stieglitz, S. G.; Foxman, B. M. *New J. Chem.* **1990**, *14*, 689.

(12) Isomers 4e and 5e are readily distinguished by high-field NMR.[11] In 4e, H-6 appears as a broad singlet at ~5.36 ppm and H-4a appears as a triplet (dd, J = 6, 6 Hz) at ~2.74 ppm. In 5e, the signals from H-7 and H-4a appear at ~5.28 and 2.81 ppm, respectively.

(13) **General.** All reactions were done in oven-dried glassware under an atmosphere of argon or nitrogen and with magnetic stirring unless otherwise stated. Proton nuclear magnetic resonance (^{1}H) spectra were obtained on a Varian FT-80A (80 MHz), a Varian XL-300 (300 MHz), or a Bruker AM-500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C) spectra were obtained on a Varian XL-300 at 75 MHz or a Bruker AM-500 spectrometer at 125 MHz. All NMR spectra were recorded in deuteriochloroform and chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane or residual chloroform. Abbreviations for NMR multiplets are as follows: s singlet, d doublet, t triplet, q quartet, m multiplet, dd doublet of doublets, dt doublet of triplets, and ddd doublet of doublet of doublets and coupling constants are in hertz (J). Some elemental analyses were performed by Galbraith Laboratores, Inc. Knoxville, TN. Melting points are uncorrected and were obtained on a Mel-Temp apparatus. Thin-layer chromatography (TLC) was done on precoated silica gel plates (Merck) containing a fluorescent indicator and developed in the indicated solvents. Compounds were visualized by staining with phosphomolybdic acid, *p*-anisaldehyde/H_2SO_4, or under a UV lamp. Chromatographic separations were done by flash chromatography with MN-Keiselgel 60 silica gel (0.04–0.063 mm mesh). Optical rotations were recorded in a 10-cm cell on a Perkin-Elmer Model 241 polarimeter at ambient temperature with sodium or mercury lamps tuned to the indicated wavelengths. Circular dichroism (CD) spectra were recorded on a Aviv spectrometer using a 0.1-cm cell at room temperature. Dichloromethane (CH_2Cl_2) and titanium(IV) chloride were distilled from calcium hydride under nitrogen. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Hexanes (bp 65–70 °C) were fractionally distilled and ethyl acetate was distilled from anhydrous potassium carbonate. 1,3-Cyclohexadiene, isoprene, piperylene, and titanium(IV) isopropoxide were purchased from Aldrich Chemical Co. and used without further purification. 1,3-Butadiene was purchased from Matheson and distilled into a cold trap (−78 °C) prior to use.

(14) Prepared from 3-methylguaiacol or 3-hydroxy-4-methoxytoluene (Ng, G. P.; Dawson, C. R. *J. Org. Chem.* **1978**, *43*, 3205) by Fremy's salt oxidation according to the procedure outlined in Hayakawa, K.; Ueyama, K.; Kanematsu, K. *Ibid.* **1985**, *50*, 1963.

(15) Block, E.; Aslam, M. *Org. Synth.* **1987**, *65*, 90.

2.14 (m, 1H), 2.80 (dd, J = 2, 7, 1H) 2.87 (m, 1H), 3.75 (s, 3H), 5.56 (m, 1H), 5.58 (m, 1H), 5.97 (s, 1H); ^{13}C NMR (125 MHz) 19.1, 20.9, 23.8, 39.4, 49.6, 49.9, 56.3, 112.0, 122.6, 130.0, 161.8, 197.8, 198.3; ORD (10.2 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +328, $[\alpha]_{578}$ = +343, $[\alpha]_{546}$ = +394, $[\alpha]_{436}$ = +699, $[\alpha]_{365}$ = no transmittance; CD (0.31 mg/mL, $CHCl_3$) 267 ($\Delta\epsilon$ = +40.6), 289 (−0.49). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.10; H, 7.30.

(4a*R*,8*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-2-methoxy-8-(2-methoxyethyl)-8a-methyl-1,4-naphthalenedione (4c). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (7.23 g) and diol (+)-**3** (10.7 g, 20.2 mmol) in toluene (75 mL). A solution of quinone **1** (1.53 g, 10.1 mmol) in CH_2Cl_2 (15 mL) was then added to the mixture followed by 6-methoxy-1,3-hexadiene (1.68 g, 15.0 mmol). The mixture was stirred 3 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave an 18:1 mixture of **4c** and an unidentified isomer (2.27 g, 85%). The major product was estimated to be ~61% ee by ^{1}H NMR the analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the signal for the angular methyl group split into well-resolved singlets. Recrystallization from EtOAc/hexanes gave enantiomerically pure material (1.09 g, 41%): mp 111.1–111.7 °C; R_f (35% EtOAc/hexanes) 0.22; ^{1}H NMR (500 MHz) 1.39 (s, 3H), 1.45 (m, 1H), 1.59 (m, 1H), 2.08 (m, 1H), 2.15 (m, 1H), 2.74 (m, 1H), 2.80 (dd, J = 4, 7, 1H), 3.20 (s, 3H), 3.27 (m, 2H), 3.72 (s, 3H), 5.60 (m, 1H), 5.64 (m, 1H), 5.89 (s, 1H); ^{13}C NMR (125 MHz) 22.2, 24.1, 32.8, 40.9, 49.9, 50.8, 56.3, 58.4, 70.3, 111.1, 123.6, 127.5, 161.5, 197.6, 198.1; ORD (9.91 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +198, $[\alpha]_{578}$ = +208, $[\alpha]_{546}$ = +239, $[\alpha]_{436}$ = +406, $[\alpha]_{365}$ = no transmittance; CD (0.25 mg/mL, $CHCl_3$) 269 ($\Delta\epsilon$ = +30.3), 345 (+2.4). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.39; H, 8.00.

(4a*R*,8*S*,8a*S*)-1,4,4a,4b,5,6,7,8,10,10a-Decahydro-3-methoxy-4a-methyl-1,4-phenanthrenedione (4d). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (4.75g) and diol (+)-**3** (6.95 g, 13.2 mmol) in toluene (65 mL). A solution of quinone **1** (1.97 g, 13.0 mmol) in CH_2Cl_2 (24 mL) was then added to the mixture at −78 °C followed by 1-vinylcyclohexene (2.12 g, 19.6 mmol). The mixture was stirred for 2 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave **4d** (3.35 g, 99%). The enantiomeric purity was estimated at ~67% ee by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the OCH_3 signal split into two singlets. Fractional recrystallization from THF/pentanes gave crystals (0.95 g) that were largely racemic. Concentration of the mother liquor followed by crystallization of the residue from EOAc/hexanes provided enantiomerically pure **4d** (1.88 g, 56%): mp 89.5–91 °C; R_f (35% EtOAc/hexanes) 0.34; ^{1}H NMR (500 MHz) 1.01 (ddd, J = 24, 12, 3, 1H), 1.18 (m, 2H), 1.33 (m, 1H), 1.36 (s, 3H), 1.64 (m, 2H), 1.86 (m, 2H), 1.98 (m, 1H), 2.15 (m, 1H), 2.72 (d, J = 7, 1H), 2.86 (dd, J = 5, 18, 1H), 3.72 (s, 3H), 5.32 (m, 1H), 5.95 (s, 1H); ^{13}C NMR (125 MHz) 19.8, 23.5, 27.4, 28.7, 33.8, 37.0, 48.2, 48.9, 50.1, 56.2, 112.5, 114.9, 138.4, 161.9, 197.3, 198.7; ORD (11.2 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +388, $[\alpha]_{578}$ = +409, $[\alpha]_{546}$ = +476, $[\alpha]_{436}$ = +919, $[\alpha]_{365}$ = no transmittance; CD (0.29 mg/mL, $CHCl_3$) 270 ($\Delta\epsilon$ = +43.9), 345 (+3.1). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.42; H, 7.79.

(4a*R*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-7,8a-dimethyl-2-methoxy-1,4-naphthalenedione (4e). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (5.07 g) and diol (+)-**3** (7.65 g, 14.5 mmol) in toluene (70 mL). A solution of quinone **1** (1.97 g, 12.9 mmol) in CH_2Cl_2 (25 mL) was then added to the mixture at −78 °C followed by isoprene (2.60 mL, 25.8 mmol). The mixture was stirred for 1 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 10% and then 35% ethyl acetate/hexanes as eluents gave a 7.8:1 mixture (by ^{1}H NMR) of **4e** and **5e** (2.83 g, 99%). The major product was identified as **4e** and was estimated to be 65% enantiomerically pure by HPLC (CHIRALPAK AS and CHIRALCEL OD columns in tandem, 97:2:1 hexanes/*i*-PrOH/EtOH; t_R for the minor enantiomer = 73.9 min, t_R for the major enantiomer = 84 min). Recrystallization from EtOAc/hexanes gave crystals (0.69 g) that were largely racemic. Concentration of the mother liquor and crystallization of the residue from EtOAc/hexanes gave enantiomerically pure **4e** (1.65 g for 5 crops, 59%): mp 78–79 °C; R_f (35% EtOAc/hexanes) 0.27; ^{1}H NMR (500 MHz) 1.33 (s, 3H), 1.61 (d, J = 1, 3H), 1.66 (d, J = 18, 1H), 2.15 (m, 1H), 2.44 (d, J = 18, 1H), 2.62 (m, 1H), 2.74 (dd, J = 6, 6, 1H), 3.76 (s, 3H), 5.36 (m, 1H), 5.85 (s, 1H); ^{13}C NMR (125 MHz) 22.5, 23.4, 23.7, 37.0, 47.7, 51.1, 56.2, 109.8, 118.1, 130.8, 160.0, 197.1, 198.7; ORD $[\alpha]_{589}$ = +35 (54.4 mg/10 mL, $CHCl_3$); CD (0.78 mg/mL, $CHCl_3$, this sample was 67% ee) 258 ($\Delta\epsilon$ +8.0), 293 (−3.0). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.80; H, 7.68.

(4a*R*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-2-methoxy-8a-methyl-7-(1-methylethyl)-1,4-naphthalenedione (4f). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (0.451 g) and diol (+)-**3** (0.662 g, 1.25 mmol) in toluene (7 mL). A solution of quinone **1** (0.190 g, 1.25 mmol) in CH_2Cl_2 (3 mL) was then added to the mixture at −78 °C followed by 2-isopropyl-1,3-butadiene (**2f**, 0.167 g, 1.74 mmol). The mixture was stirred 3 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave an 8.9:1 mixture of **4f** and a second isomer, tentatively identified as **5f**, as a clear oil (0.301 g, 97%). The major isomer was ~82% enantiomerically pure by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the signal for the angular methyl group split into two well-resolved singlets. Physical and spectral characteristics for **4f**: R_f (35% EtOAc/hexanes) 0.34; ^{1}H NMR (500 MHz) 0.94 (d, J = 7, 3H), 1.32 (s, 3H), 1.70 (d, J = 17, 1H), 2.11–2.21 (m, 2H), 2.45 (dd, J = 17, 2, 1H), 2.60–2.65 (m, 1H), 2.76 (dd, J = 6, 6, 1H), 5.36 (m, 1H), 5.85 (s, 1H); ^{13}C NMR (125 MHz) 20.9, 21.0, 23.9, 33.4, 34.8, 47.6, 51.5, 56.2, 109.8, 115.4, 140.4, 159.9, 197.3, 198.8; HRMS m/z 248.1408 (calcd for $C_{15}H_{20}O_3$ 248.1412); ORD (12.0 mg/mL, $CHCl_3$) α_{589} = +0°; CD (0.48 mg/mL, $CHCl_3$) 258 ($\Delta\epsilon$ = +7.6), 293 (−4.1). Attempts to induce crystallization of the mixture of **4f**/**5f** were not successful.

(4a*R*,8*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-4a,8-dimethyl-2-methoxy-1,4-naphthalenedione (7). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (3.93 g) and diol (+)-**3** (5.78 g, 10.9 mmol) in toluene (40 mL). A solution of quinone **6** (1.66 g, 10.9 mmol) in CH_2Cl_2 (15 mL) was then added to the mixture at −78 °C followed by piperylene (4.9 mL). The mixture was stirred 3 h at −78 °C and worked up as described above. Chromatography of the resulting oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave **7** (2.09 g, 89%) as an oil. The product was estimated to be 54% ee by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ in which the angular methyl group split into well-resolved singlets at 1.19 and 1.16 ppm. Recrystallization of 1.84 g of this material from EtOAc/hexanes gave enantiomerically pure **7** (0.93 g, 51%): mp 90–91 °C; R_f (35% EtOAc/hexanes) 0.35; ^{1}H NMR[16] (500 MHz) 1.07 (d, J = 7, 3H) 1.31 (s, 3H), 1.77 (m, 1H), 2.59 (m, 1H), 2.61 (m, 1H), 2.98 (d, J = 6, 1H), 3.74 (s, 3H), 5.55 (m, 1H), 5.61 (m, 1H), 5.80 (s, 1H); ^{13}C NMR (125 MHz) 18.1, 25.5, 30.5, 32.2, 47.9, 56.3, 56.5, 109.0, 123.0, 130.2, 162.0, 195.6, 201.4; ORD (4.0 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +81. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.69; H, 7.30.

(4a*R*,5*S*,8*R*,8a*S*)-1,4,4a,8,8a-Hexahydro-5,8-ethano-2-methoxy-8a-methyl-1,4-naphthalenedione (10). Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (0.723 g) and the diol (+)-**3** (1.09 g, 2.00 mmol) in toluene (10 mL). A solution of the quinone **1** (0.154 g, 1.00 mmol) in CH_2Cl_2 (2mL) was then added to the mixture at −78 °C followed by 1,3-cyclohexadiene (0.23 g, 2.0 mmol). The mixture was stirred 1 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave **10** (0.235 g, 96%) as a solid. The % ee was estimated at ~30% by HPLC (CHIRALPAK AS and CHIRALCEL OD in tandem, 97:2:1 hexanes/*i*-PrOH/EtOH; t_R = 87 and 109 min) and by ^{1}H NMR analysis in the presence of 5 equiv of (*R*)-(−)-2,2,2-trifluoro-1-

(16) Bohlmann, F.; Mathar, W.; Schwarz, H. *Chem. Ber.* **1977**, *110*, 2028.

(9-anthryl)ethanol in $CDCl_3$ in which the signal at 2.51 ppm split into two broad singlets: R_f (35% EtOAc/hexanes) 0.19; ^1H NMR (500 MHz) 1.24 (m, 1H), 1.35 (m, 1H), 1.36 (s, 3H), 1.74 (m, 1H), 1.88 (m, 1H), 2.51 (d, J = 1, 1H), 2.98 (m, 1H), 3.08 (m, 1H), 3.74 (s, 3H), 5.94 (s, 1H), 6.15 (dd, J = 7, 8, 1H), 6.29 (dd, J = 7, 7, 1H); ^{13}C NMR (125 MHz) 18.4, 25.5, 25.9, 36.3, 38.9, 50.2, 55.8, 58.0, 112.7, 132.3, 135.3, 161.5, 197.2, 198.3; ORD (22.2 mg/mL, $CHCl_3$) α_{589} = −31. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.49; H, 6.98.

rel-(4a*R*,8a*S*)-**1,4,4a,5,6,7,8,9,9a,10-Decahydro-2-methoxy-10a-methyl-1,4-anthracenedione (11).** Following the general procedure described above, the Ti(IV):(+)-**3** complex was prepared from the Ti(IV)-solid (0.756 g) and the diol (+)-**3** (1.06 g, 2.00 mmol) in toluene (10 mL). A solution of the quinone **1** (0.154 g, 1.00 mmol) in CH_2Cl_2 (2mL) was then added to the mixture at −78 °C followed by 1,2-dimethylenecyclohexane (0.217 g, 2.00 mmol). The mixture was stirred 1 h at −78 °C and worked up as described above. Chromatography of the resultant oil on flash silica gel with 20% ethyl acetate/hexanes as eluent gave **11** (0.256 g, 97%) as a solid. The product was racemic by ^1H NMR analysis in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol in $CDCl_3$ in which the vinyl signal split into two well-resolved singlets and by HPLC (CHIRALPAK AS and CHIRALCEL OD in tandem, 97:2:1 hexanes/*i*-PrOH/EtOH; t_R = 79.8 and 89.3 min): mp 95.0–96.5 °C (EtOAc/hexanes); R_f (35% EtOAc/hexanes) 0.34; ^1H NMR (500 MHz) 1.31 (s, 3H), 1.50–1.62 (m, 5H), 1.73–1.83 (m, 4H), 2.04 (m, 1H), 2.43 (m, 2H), 2.76 (dd, J = 6, 6, 1H), 3.75 (s, 3H), 5.83 (s, 1H); ^{13}C NMR (125 MHz) 22.8 (3 C), 28.7, 29.5, 29.9, 37.4, 47.7, 52.0, 56.2, 109.8, 124.8, 125.2, 160.0, 197.3, 198.6. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.69; H, 7.99.

Acknowledgment. This research was supported financially by the National Institutes of Health (GM 39820 and 07775) and the National Science Foundation (CHE-9116576). T.A.E. acknowledges a fellowship from the Alfred P. Sloan Foundation and a granteeship from Eli Lilly and Company and M.A.L. acknowledges a NIH predoctoral fellowship. We thank Professor J. B. Hendrickson for drawing our attention to his previous work.

Supplementary Material Available: Experimental details for the preparation of dienes **2c**, **2d**, **2f**, and **2g**; full experimental procedures for Diels–Alder reactions of all dienes and for preparation of **14**; summary of data from ^1H–^1H NOE experiments; ^1H and/or ^{13}C NMR spectra of **2c**, **2f**, **2g**, **4f/g**, and the Diels–Alder products of **6** and **2c** and **2g**; IR, UV, and mass spectral data for all Diels–Alder adducts; and ORTEP drawing of **14** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.