Published in final edited form as:

J Org Chem. 2015 May 15; 80(10): 5252–5259. doi:10.1021/acs.joc.5b00671.

Regiodivergent Addition of Phenols to Allylic Oxides

David N. Vaccarello, Matthew J. Moschitto, and Chad A. Lewis*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853

Abstract

The regiodivergent addition of substituted phenols to allylic-oxides has been demonstrated using C₂-symmetric palladium complexes. Complex phenol donors tyrosine, estradiol, and griseofulvin follow the predictive model.

The Tsuji-Trost reaction is a powerful method to append both O- and C-donors to η^3 -allyl systems.¹ The η^3 -allyl progenitor structures include allylic esters, carbonates, halides, and oxides. Internal allylic oxides² remain one of the few systems that retain a marker of stereochemical induction with the newly liberated carbinol. The origin of the products can be traced to the diastereomeric η^3 -allyl intermediate and stereoisomer of oxide employed. We have recently identified³ a system capable of the conversion of racemic allylic oxides to distinct enantioenriched regioisomers using achiral phenol donors (Scheme 1). The allylic oxide regio-resolution (AORR) allowed the preparation of enantioenriched carbasugar natural products. We have now expanded this study to include a diverse array of achiral and chiral phenol donors.

The synthesis of aryl ether bonds were chosen for study due to their abundance within natural products, chiral catalyst scaffolds, and availability of phenol precursors. Prior to a full examination of chiral phenol structures with oxide **1**, a series of achiral phenol donors were studied using the developed predictive model.³ The absolute stereochemistry of addition was determined using *para*-methoxyphenol under oxidative cleavage conditions.^{3,4} The collected data was able to provide a working model for regiodivergence using ligand **4**⁵ with the donor phenols (Scheme 2). In parallel with Lloyd-Jones⁶ and Trost's^{1d} studies, a model was generated for oxide **1** that would be necessary for studying the AORR with complex phenol donors. It is predicted the (+)-**1** enantiomer with the (S,S)-**4** ligand will produce intermediate **5**, and is engaged by phenoxide to produce *syn*-1,2 product **2**. Similarly, the (–)-**1** enantiomer provides intermediate **6** that proceeded to *syn*-1,4 product **3**. The (R,R)-**4** ligand mirrors the regiodivergence of the (S,S)-**4** ligand with each enantiomer of oxide producing the alternative *syn*-addition products.

*Corresponding Author: chad.lewis@cornell.edu.

Supporting Information

¹H and ¹³C NMR spectra for all new compounds is provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

The utility of the AORR approach was advanced with numerous phenols. Native phenol provided useful enantioinduction (Table 1, entry 1, 98:2 er for 1,2-addition, 91:9 for 1,4-addition) in a combined yield of 58%. Allylic oxide **1** was not recovered and the mass balance is suspected to be due to competitive beta-hydride elimination. Alkyl substitution (entries 2,⁷ 3) proved similar in stereoinduction and the recovered allylic oxide was weakly enantiomerically enriched. One possible explanation for lack of resolution of recovered oxide **1** is each oxide enantiomer is forming the palladium-allyl at an identical rate. The newly formed allyl complexes are then steered toward each phenol addition product with high fidelity. Other phenol donors such as electron releasing substituents were similarly well tolerated (entries 4⁷ and 5) with the Boc-protected aniline providing lower conversion. 4-Nitrophenol provided the highest enantioinduction (97:3 and 98:2 for 1,2- and 1,4-addition respectively, entry 6) albeit with low yield and degradation upon standing. Sterically larger arenes, including *ortho*- and *meta*-substitution (entry 7 and 8 respectively) behaved similarly, and both 1- and 2-naphthol offered less selectivity overall (entries 9 and 10). Interestingly, sesamol provided high enantioinduction for both addition modes (entry 11). In all cases, the absence of palladium did not result in any conversion.

With these data in hand, the application of the AORR method upon chiral phenolic scaffolds was examined. The substrates were chosen for their biological activity and for the emergence of diastereomers by competitive 1,2- or 1,4-addition to the palladium-allyl. Estradiol, tyrosine, and griseofulvin were selected and regiodiverged into four distinct diastereomers under catalyst control.

Silyl protected estradiol⁸ was first examined to gauge the suitability of larger phenol substrates with remote stereochemical elements for the regiodivergence (Scheme 3a). Interestingly, the regiodivergence provided high stereoselectivity for the 1,2- and 1,4-addition products with no detectable diastereomers. Using (R,R)-**4**, the 1,2-adduct was obtained in 60% yield and the 1,4-adduct in 27%. The enhanced yield of the 1,2-product was surprising considering the achiral phenols were roughly equal in reactivity to produce 1,2- and 1,4-products. Switching to the (S,S)-**4** ligand, the 1,2-adduct was obtained in 44% with an increase to 41% for the 1,4-addition product as compared to the (R,R)-**4** ligand.

A more challenging regiodivergence was examined using tyrosine (Scheme 3b). The protected amino-acid, as compared to estradiol, was predicted to be prone to mixtures of diastereomers from carbamate chelation to palladium⁹ and/or populations of rotamers. Applying the AORR conditions resulted in the isolation of the 1,2- and 1,4-addition products in similar yield for each enantiomer of applied ligand. The additional constraints of the tyrosine moiety were reflected in the appearance of diastereomers for the 1,2-addition products: 4.37:1 for **13** and 4.20:1 for **15** in 45% and 51% yield respectively. The 1,4-adducts were isolated as single diastereomers in 40% yield for **14**, and 36% yield for **16**. The similarity in structure required the isolation of the 1,2- and 1,4-adducts as a co-mixture with ¹H NMR integration to determine yield of each isomer. The estradiol and tyrosine phenol substrates provided high-regiodivergence to the desired stereoisomers. Moving forward, the application of this method toward a multiply substituted hindered chiral phenol would demonstrate the robustness of the method with diverse phenolic substrates.

Polyketides continue to provide diverse functionality including spirocoumaranones such as griseofulvin,¹⁰ geodin,¹¹ and Sch202596.¹² The interesting biological properties of these phenolic spirocycles make them ideal substrates for analog generation using AORR.

The native structure of griseofulvin has recently been advanced as a cancer treatment¹³ and is readily available in large quantities. Cleavage of the C-4 methyl¹⁴ provided a chiral phenol donor that was then studied for the AORR (Scheme 3c).

In parallel with the estradiol and tyrosine studies, applying the (R,R)-**4** ligand resulted in two products. The 1,2-adduct **18** (60%) was dominant as compared to the 1,4-adduct **19** (31%) with the remaining mass balance attributed to recovered griseofulvin (**17**). Similar to the tyrosine studies, the complexity of the 1,2- and 1,4-adducts required isolation as a co-mixture and determination of yield by ¹H NMR integration. Crude reaction mixture analysis showed no starting material remained, with griseofulvin being regenerated from degradation of the 1,2- and 1,4-adducts during isolation.¹⁵ The (S,S)-**4** ligand proved similar in reactivity to provide 1,2-adduct **20** (54%) and 1,4-adduct **21** (25%) and recovered griseofulvin. The 1,2-addition products for both reactions was approximately double in yield as compared to the 1,4-products, a result we had observed previously with estradiol (Scheme 2a, **8**, (R,R)-**4** ligand), and appears to substrate dependent. The presence of diastereomers associated with off-catalyst addition modes was less than 2% when examining the ¹H-NMR of the product mixture for both ligands.

In conclusion, an asymmetric addition to an allylic-oxide has been applied to a series of achiral phenol donors resulting in an asymmetric regiodivergent reaction. The extension of the allylic-oxide regioresolution was then tested upon three complex natural products using the predicted model and efficiently generated the desired targets.

EXPERIMENTAL SECTION

Preparation and characterization of oxide **1**, as well as compounds **2b**, **3b**, **2d**, and **3d** have been reported previously.³

General Procedure A

Racemic epoxide **1** (43.0 mg, 0.279 mmol, 1.0 equiv.) was dissolved in 2.0 mL of toluene in a flame-dried vial outfitted with a septum followed by the addition of phenol (15.8 mg, 0.149 mmol, 0.6 equiv.). The resulting solution was degassed with argon and cooled to -40 °C. In a separate vial, Pd₂(dba)₃ (2.4 mg, 1.0 mol%) and (S,S)-**4**⁵ (6.6 mg, 3.0 mol%) were dissolved in 1.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 6 hours before additional phenol (16.4 mg (0.174 mmol, 0.6 equiv.) was added and the solution purged with argon. The reaction was stirred for an additional 12 hours at -40 °C before the reaction was quenched with an aqueous NH₄Cl solution, extracted with ether (2 × 1.5 mL), dried with MgSO₄, and concentrated under reduced pressure. The crude oil was purified by column chromatography (9:1 hexanes:EtOAc v/v) to give 1,2-product **2a** (21.5 mg, 31% yield, 98:2 e.r.) and 1,4-product **3a** (18.7 mg, 27% yield, 91:9 e.r.) as white solids.

Analytical standards used for the characterization of **2a** and **3a** were prepared from a separate trial giving enantiomeric ratios of 97:3 and 95:5 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(phenoxy)-cyclohex-1-enecarboxylate (2a)—

$[\alpha]_{\text{D}}^{20.0}$ –127.7 (*c* 1.00, CHCl₃); M.p. 63 – 66 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.25 (m, 2H), 7.20 – 7.15 (m, 2H), 7.15 – 7.12 (m, 1H), 7.02 – 6.91 (m, 1H), 5.28 (d, *J* = 3.7 Hz, 1H), 3.92 (dt, *J* = 11.5, 3.8 Hz, 1H), 3.61 (s, 3H), 2.54 (m, 1H), 2.39 – 2.26 (m, 1H), 2.10 – 1.93 (m, 1H), 1.93 – 1.82 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 159.6, 144.0, 129.5, 122.0, 117.3, 115.9, 73.2, 69.5, 51.8, 25.3, 25.3; IR (film, cm^{–1}) 3435, 2950, 2360, 1710, 1595, 1490, 1250, 1227, 750; TLC R_f = 0.37 (7:3 hexanes:EtOAc v/v); HPLC 97:3 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:methanol. Retention times: R_T = 8.0 min, 10.7 min; HRMS (EI⁺) *m/z* Calc'd for C₁₄H₁₆O₄ 248.1049, found 248.1047.

Methyl (3R, 6S)-3-hydroxy-6-O-(phenoxy)-cyclohex-1-enecarboxylate (3a)—

$[\alpha]_{\text{D}}^{20.0}$ –20.8 (*c* 0.50, CHCl₃); M.p. 36 – 39 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.25 (m, 2H), 7.12 (t, *J* = 1.8, 1.8 Hz, 1H), 7.04 – 6.95 (m, 3H), 5.14 (br s, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 3.75 (s, 3H), 2.24 – 2.14 (m, 1H), 2.05 – 1.96 (m, 1H), 1.91 – 1.77 (m, 1H), 1.61 (tt, *J* = 14.2, 3.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.3, 158.0, 145.8, 130.5, 129.6, 121.6, 116.9, 68.1, 67.8, 52.1, 26.5, 25.3; IR (film, cm^{–1}) 3403, 2950, 2358, 1718, 1490, 1250, 1226, 751; TLC R_f = 0.25 (7:3 hexanes:EtOAc v/v); HPLC 95:5 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T = 5.9 min, 6.6 min; HRMS (EI⁺) *m/z* Calc'd for C₁₄H₁₆O₄ 248.1049, found 248.1055.

1,2-product **2c** (21.9 mg, 28%, 96:4 e.r.) and 1,4-product **3c** (26.9 mg, 34%, 91:9 e.r.). Recovered epoxide **1** (9.5 mg, 24%, 52:48 e.r.).

Analytical standards used for the characterization of **2c** and **3c** were prepared from a separate trial giving enantiomeric ratios of 96:4 and 91:9 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-*tert*-butylphenoxy)-cyclohex-1-

enecarboxylate (2c)— $[\alpha]_{\text{D}}^{20.0}$ –92.4 (*c* 1.00, CHCl₃); M.p. 53 – 56 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.35 – 7.24 (m, 2H), 7.15 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.11 – 7.03 (m, 2H), 5.26 (d, *J* = 3.8 Hz, 1H), 3.90 (dt, *J* = 11.2, 3.7 Hz, 1H), 3.61 (s, 3H), 2.61 – 2.46 (m, 1H), 2.39 – 2.23 (m, 1H), 2.15 – 1.90 (m, 1H), 1.91 – 1.79 (m, 1H), 1.29 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.6, 157.2, 144.6, 143.9, 134.7, 129.4, 126.3, 116.7, 73.1, 69.5, 51.8, 34.2, 31.6, 25.4, 25.2; IR (film, cm^{–1}) 3435, 2953, 2358, 1716, 1509, 1220, 1043; TLC R_f = 0.42 (7:3 hexanes:EtOAc v/v); HPLC 96:4 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol. Retention times: R_T = 6.7 min, 7.2 min; HRMS (EI⁺) *m/z* Calc'd for C₁₈H₂₄O₄ 304.1675, found 304.1661.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-*tert*-butylphenoxy)-cyclohex-1-

enecarboxylate (3c)— $[\alpha]_{\text{D}}^{20.0}$ –10.1 (*c* 0.75, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 7.33 – 7.27 (m, 2H), 7.11 (br s, 1H), 6.96 – 6.91 (m, 2H), 5.11 (br s, 1H), 4.37 – 4.28 (m, 1H), 3.75 (s, 3H), 2.24 – 2.15 (m, 1H), 2.03 – 1.95 (m, 1H), 1.88 – 1.77 (m, 1H), 1.58 (tt, *J* = 14.2, 3.4 Hz, 1H), 1.29 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.4, 155.6, 145.7, 144.2,

130.6, 126.4, 116.3, 68.0, 67.8, 52.1*, 52.1*, 34.2, 31.6, 26.5, 25.3; IR (film, cm^{-1}) 3399, 2952, 2867, 2359, 1718, 1508, 1250, 1225, 1030, 757; TLC R_f = 0.29 (7:3 hexanes:EtOAc v/v); HPLC 91:9 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T = 4.6 min, 6.0 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{18}\text{H}_{24}\text{O}_4$ 304.1675, found 304.1673. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2e** (20.7 mg, 21%, 90:10 e.r.) and 1,4-product **3e** (22.3 mg, 23%, 84:16 e.r.). Recovered epoxide **1** (12.1 mg, 29%, 51:49 e.r.).

Analytical standards used for the characterization of **2e** and **3e** were prepared from a separate trial giving enantiomeric ratios of 94:6 and 89:11 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-N-Bocphenoxy)-cyclohex-1-enecarboxylate

(2e)— $[\alpha]_{\text{D}}^{20.0}$ –92.4 (*c* 0.50, CHCl_3); M.p. 134 – 136 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.27 – 7.23 (m, 2H), 7.15 (dd, J = 4.7, 3.0 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.35 (s, 1H), 5.15 (d, J = 3.6 Hz, 1H), 3.88 (ddt, J = 12.2, 8.5, 3.8 Hz, 1H), 3.61 (s, 3H), 2.58 – 2.47 (m, 1H), 2.37 – 2.24 (m, 1H), 2.03 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.5, 155.5, 153.1, 144.0, 132.7, 129.3, 120.3, 118.0, 80.4, 73.9, 69.5, 51.9, 28.5, 25.3, 25.3; IR (film, cm^{-1}) 3481, 3358, 2974, 2921, 1720, 1695, 1511, 1210, 1150; TLC R_f = 0.13 (7:3 hexanes:EtOAc v/v); HPLC 94:6 e.r., Chiral HPLC eluting at 1.00 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T = 33.1 min, 35.5 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{19}\text{H}_{25}\text{O}_6\text{N}$ 363.1682, found 363.1686.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-N-Bocphenoxy)-cyclohex-1-enecarboxylate

(3e)— $[\alpha]_{\text{D}}^{20.0}$ –19.8 (*c* 0.50, CHCl_3); M.p. 61 – 65 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.28 – 7.23 (m, 2H), 7.10 (dd, J = 1.9, 1.6 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.37 (s, 1H), 5.01 (t, J = 3.0 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.74 (s, 3H), 2.18 – 2.09 (m, 1H), 2.02 – 1.94 (m, 1H), 1.81 (tdd, J = 13.0, 10.4, 2.9 Hz, 1H), 1.58 (tt, J = 14.5, 3.0 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.3, 154.0, 153.2, 145.8, 132.4, 130.6, 120.6, 117.9, 80.4, 69.1*, 69.1*, 67.8, 52.2*, 52.1*, 28.5, 26.4, 25.3; IR (film, cm^{-1}) 3342, 2950, 1702, 1509, 1254, 1220, 1160; TLC R_f = 0.12 (7:3 hexanes:EtOAc v/v); HPLC 89:11 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T = 31.9 min, 34.0 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{19}\text{H}_{25}\text{O}_6\text{N}$ 363.1682, found 363.1688. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2f** (3.2 mg, 4%, 97:3 e.r.) and 1,4-product **3f** (2.9 mg, 4%, 98:2 e.r.). Recovered epoxide **1** (27.6 mg, 64%, 50:50 e.r.).

Analytical standards used for the characterization of **2f** and **3f** were prepared from a separate trial giving enantiomeric ratios of 98:2 and 98:2 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-nitrophenoxy)-cyclohex-1-enecarboxylate

(2f)— $[\alpha]_{\text{D}}^{20.0}$ –108.2 (*c* 0.50, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 8.22 – 8.17 (m, 2H),

7.26 – 7.21 (m, 3H), 5.44 (d, $J = 3.7$ Hz, 1H), 3.96 (ddt, $J = 12.0, 8.0, 3.8$ Hz, 1H), 3.66 (s, 3H), 2.58 (dtd, $J = 20.3, 5.4, 2.3$ Hz, 1H), 2.45 – 2.32 (m, 1H), 2.05 – 1.87 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.1, 164.9, 145.1, 141.9, 128.2, 125.9, 116.6, 73.0, 69.8, 52.1*, 52.1*, 25.7, 25.2; IR (film, cm^{-1}) 3458, 2952, 1710, 1590, 1509, 1493, 1330, 1250; TLC $R_f = 0.12$ (7:3 hexanes:EtOAc v/v); HPLC 98:2 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: $R_T = 35.9$ min, 38.4 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{14}\text{H}_{15}\text{NO}_6$ 239.0899, found 239.0898. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-nitrophenoxy)-cyclohex-1-enecarboxylate

(3f)— $[\alpha]_{\text{D}}^{20.0} +37.5$ (c 0.50, CHCl_3) † ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.24 – 8.17 (m, 2H), 7.18 (dd, $J = 2.2, 1.4$ Hz, 1H), 7.06 – 7.00 (m, 2H), 5.28 (s, 1H), 4.38 (s, 1H), 3.74 (s, 3H), 2.21 – 2.13 (m, 1H), 2.10 – 2.02 (m, 1H), 1.88 – 1.69 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 165.9, 163.1, 146.6, 141.7, 129.4, 126.1, 115.8, 68.4, 67.5, 52.3, 26.4, 25.5; IR (film, cm^{-1}) 3391, 2950, 1708, 1438, 1255, 1041, 756; TLC $R_f = 0.09$ (7:3 hexanes:EtOAc v/v); HPLC 98:2 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: $R_T = 31.9$ min, 34.0 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{14}\text{H}_{15}\text{NO}_6$ 239.0899, found 239.0895. † Analytical standard was obtained as the enantiomer of **3f** from the (*R,R*)-**4**.

1,2-product **2g** (23.4 mg, 31%, 96:4 e.r.) and 1,4-product **3g** (25.8 mg, 34%, 84:16 e.r.). Recovered epoxide **1** (0.4 mg, 1%, 68:32 e.r.).

Analytical standards used for the characterization of **2g** and **3g** were prepared from a separate trial giving enantiomeric ratios of 85:15 and 90:10 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(2,4-dimethylphenoxy)-cyclohex-1-enecarboxylate (2g)

(2g)— $[\alpha]_{\text{D}}^{20.0} -106.6$ (c 0.75, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.19 – 7.11 (m, 2H), 7.00 – 6.89 (m, 2H), 5.20 (d, $J = 3.7$ Hz, 1H), 3.89 (ddt, $J = 12.0, 8.0, 3.7$ Hz, 1H), 3.57 (s, 3H), 2.62 – 2.47 (m, 1H), 2.41 – 2.31 (m, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 2.07 – 1.96 (m, 1H), 1.93 – 1.83 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.6, 155.5, 143.7, 131.5, 131.0, 129.8, 127.7, 127.3, 115.7, 73.5, 69.6, 51.8, 25.4, 25.4, 20.6, 16.5; IR (film, cm^{-1}) 3434, 2949, 1716, 1489, 1250, 1217, 1042; TLC $R_f = 0.50$ (7:3 hexanes:EtOAc v/v); HPLC 85:15 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: $R_T = 3.7$ min, 4.2 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ 276.1362, found 276.1357.

Methyl (3R, 6S)-3-hydroxy-6-O-(2,4-dimethylphenoxy)-cyclohex-1-enecarboxylate (3g)

(3g)— $[\alpha]_{\text{D}}^{20.0} -19.4$ (c 0.50, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.10 (dd, $J = 2.2, 1.3$ Hz, 1H), 7.03 – 6.92 (m, 3H), 5.09 (br s, 1H), 4.39 – 4.27 (m, 1H), 3.74 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H), 2.13 – 2.06 (m, 1H), 2.05 – 1.96 (m, 1H), 1.93 – 1.78 (m, 1H), 1.65 – 1.58 (dt, $J = 13.9, 3.3$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.4, 154.1, 145.3, 131.5, 130.8, 130.4, 128.0, 127.1, 114.3, 68.7, 67.7, 51.9, 26.6, 25.5, 20.5, 16.4; IR

(film, cm^{-1}) 3415, 2949, 1719, 1499, 1250, 1219, 1032; TLC R_f = 0.40 (7:3 hexanes:EtOAc v/v); HPLC 90:10 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:methanol. Retention times: R_T = 4.2 min, 5.0 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ 276.1362, found 276.1367.

1,2-product **2h** (21.5 mg, 31%, 90:10 e.r.) and 1,4-product **3h** (24.5 mg, 34%, 91:9 e.r.). Recovered epoxide **1** (9.2 mg, 23%, 52:48 e.r.).

Analytical standards used for the characterization of **2h** and **3h** were prepared from a separate trial giving enantiomeric ratios of 90:10 and 92:8 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(3,5-dimethylphenoxy)-cyclohex-1-

enecarboxylate (2h)— $[\alpha]_{\text{D}}^{20.0}$ -93.3 (c 1.00, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.15 (dd, J = 4.7, 3.0 Hz, 1H), 6.77 (s, 2H), 6.63 (s, 1H), 5.26 (d, J = 3.7 Hz, 1H), 3.90 (ddt, J = 12.3, 8.2, 3.7 Hz, 1H), 3.64 (s, 3H), 2.53 (dtd, J = 20.0, 5.2, 3.0 Hz, 1H), 2.33 (dddd, J = 9.7, 6.4, 3.1, 1.1 Hz, 1H), 2.28 (s, 6H), 2.02 – 1.92 (m, 1H), 1.90 – 1.82 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.5, 159.5, 143.9, 139.2, 129.4, 123.8, 114.8, 72.7, 69.5, 51.8*, 51.8*, 25.4, 25.2, 21.5; IR (film, cm^{-1}) 3434, 2949, 1714, 1590, 1293, 1246, 1150, 1039, 755; TLC R_f = 0.53 (7:3 hexanes:EtOAc v/v); HPLC 90:10 e.r., Chiral HPLC eluting at 1.25 mL/min with 97% hexanes:methanol. Retention times: R_T = 6.0 min, 6.4 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ 276.1362, found 276.1352. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(3,5-dimethylphenoxy)-cyclohex-1-

enecarboxylate (3h)— $[\alpha]_{\text{D}}^{20.0}$ -14.0 (c 0.75, CHCl_3); M.p. 93 – 95 C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.10 (dd, J = 2.2, 1.4 Hz, 1H), 6.63 (s, 3H), 5.11 (br s, 1H), 4.37 – 4.28 (m, 1H), 3.76 (s, 3H), 2.28 (s, 6H), 2.18 (ddt, J = 14.5, 4.0, 2.6 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.86 – 1.78 (m, 1H), 1.58 (dt, J = 14.0, 3.3 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.4, 157.9, 145.7, 139.3, 130.7, 123.4, 114.5, 67.9, 67.7, 52.1, 26.5, 25.3, 21.5; IR (film, cm^{-1}) 3408, 2949, 1717, 1590, 1292, 1252, 1150, 1031; TLC R_f = 0.29 (7:3 hexanes:EtOAc v/v); HPLC 92:8 e.r., Chiral HPLC eluting at 1.25 mL/min with 90% hexanes:isopropanol. Retention times: R_T = 3.6 min, 4.2 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ 276.1362, found 276.1370.

1,2-product **2i** (25.8, 33%, 84:16 e.r.) and 1,4-product **3i** (25.7 mg, 33%, 84:16 e.r.). No recovered epoxide **1**.

Analytical standards used for the characterization of **2i** and **3i** were prepared from a separate trial giving enantiomeric ratios of 89:11 and 97:3 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(2-naphthoxy)-cyclohex-1-enecarboxylate (2i)—

$[\alpha]_{\text{D}}^{20.0}$ -124.3 (c 2.00, CHCl_3); M.p. 82 – 86 C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.78 – 7.74 (m, J = 8.4, 6.9 Hz, 3H), 7.57 (d, J = 2.5 Hz, 1H), 7.43 (ddd, J = 8.1, 6.8, 1.3, 1H), 7.34 (ddd, J = 8.2, 6.8, 1.2, 1H), 7.30 (dd, J = 8.9, 2.5 Hz, 1H), 7.19 (dd, J = 4.8, 3.0 Hz, 1H), 5.44 (d, J = 3.6 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.58 (s, 3H), 2.62 – 2.50 (m, 1H), 2.40 – 2.27

(m, 1H), 2.07 – 1.97 (m, 1H), 1.94 – 1.85 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.5, 157.4, 144.2, 134.5, 129.6, 129.4, 129.2, 127.6, 127.1, 126.3, 124.0, 119.6, 111.3, 73.2, 69.6, 51.8, 25.3, 25.3; IR (film, cm^{-1}) 3431, 3055, 2949, 1709, 1250, 1212, 1041, 747; TLC R_f = 0.29 (7:3 hexanes:EtOAc v/v); HPLC 89:11 e.r., Chiral HPLC eluting at 1.25 mL/min with 99% hexanes:isopropanol then a gradient of 1% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T = 26.2 min, 29.9 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_4$ 298.1205, found 298.1215.

Methyl (3R, 6S)-3-hydroxy-6-O-(2-naphthoxy)-cyclohex-1-enecarboxylate (3i)—

$[\alpha]_D^{20.0}$ –5.7 (c 0.50, CHCl_3); M.p. 63 – 66 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.79 – 7.71 (m, 3H), 7.44 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.34 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.31 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 8.9, 2.5 Hz, 1H), 7.16 (dd, J = 2.2, 1.4 Hz, 1H), 5.30 (t, J = 2.9 Hz, 1H), 4.36 (dddd, J = 10.5, 6.1, 2.2, 1.1 Hz, 1H), 3.75 (s, 3H), 2.32 – 2.25 (m, 1H), 2.07 – 1.98 (m, 1H), 1.94 – 1.81 (m, 1H), 1.67 (tt, J = 14.2, 3.2 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.4, 155.8, 146.0, 134.6, 130.4, 129.6, 129.4, 127.7, 126.9, 126.4, 123.9, 120.0, 109.9, 68.0*, 68.0*, 67.8, 52.2*, 52.2*, 26.6, 25.2; IR (film, cm^{-1}) 3420, 2949, 2359, 1717, 1250, 1214, 1031, 748; TLC R_f = 0.18 (7:3 hexanes:EtOAc v/v); HPLC 97:3 e.r., Chiral HPLC eluting at 1.25 mL/min with 99% hexanes:isopropanol then a gradient from 1% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T = 31.0 min, 31.5 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_4$ 298.1205, found 298.1194. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2j** (27.3 mg, 35%, 80:20 e.r.) and 1,4-product **3j** (29.8 mg, 38%, 88:12 e.r.). No recovered epoxide **1**.

Analytical standards used for the characterization of **2j** and **3j** were prepared from a separate trial giving enantiomeric ratios of 80:20 and 90:10 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(1-naphthoxy)-cyclohex-1-enecarboxylate (2j)—

$[\alpha]_D^{20.0}$ –123.2 (c 0.50, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 8.19 – 8.13 (m, 1H), 7.83 – 7.77 (m, 1H), 7.49 – 7.39 (m, 5H), 7.24 (dd, J = 4.9, 2.9 Hz, 1H), 5.52 (d, J = 3.7 Hz, 1H), 3.99 (ddt, J = 11.7, 9.8, 3.7 Hz, 1H), 3.44 (s, 3H), 2.69 – 2.58 (m, 1H), 2.47 – 2.33 (m, 1H), 2.21 – 2.09 (m, 1H), 2.01 – 1.93 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.5, 155.5, 144.2*, 144.2*, 134.7, 129.4, 127.8*, 127.7*, 126.6, 126.3*, 126.2*, 126.1*, 126.1*, 126.1*, 126.1*, 125.5*, 125.4*, 121.9*, 121.9*, 121.5*, 121.5*, 109.4, 73.9, 73.8, 69.7, 51.8*, 51.7*, 25.6, 25.5; IR (film, cm^{-1}) 3390, 2951, 1709, 1395, 1246, 1235, 1091, 1042, 770; TLC R_f = 0.28 (7:3 hexanes:EtOAc v/v); HPLC 80:20 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:methanol. Retention times: R_T = 10.7 min, 15.4 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_4$ 298.1205, found 298.1201. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(1-naphthoxy)-cyclohex-1-enecarboxylate (3j)—

$[\alpha]_D^{20.0}$ +67.0 (c 1.00, CHCl_3); M.p. 132 – 135 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 8.25 – 8.18 (m, 1H), 7.82 – 7.77 (m, 1H), 7.50 – 7.35 (m, 4H), 7.20 (dd, J = 2.2, 1.3 Hz, 1H), 7.08 (d, J = 7.4, 1H), 5.41 (t, J = 3.0 Hz, 1H), 4.42 – 4.35 (m, 1H), 3.70 (s, 3H), 2.30 – 2.22 (m,

1H), 2.07 – 1.87 (m, 2H), 1.68 (dt, $J = 14.0, 3.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.4, 153.8, 145.9, 134.7, 130.6, 127.5, 126.7, 126.4, 126.0, 125.3, 122.3, 120.9, 107.2, 68.2, 67.8, 52.2*, 52.2*, 26.9, 25.4; IR (film, cm^{-1}) 3244, 3052, 2950, 2359, 1717, 1256, 1234, 771; TLC $R_f = 0.19$ (7:3 hexanes:EtOAc v/v); HPLC 90:10 e.r., Chiral HPLC eluting at 1.0 mL/min with 98% hexanes:methanol. Retention times: $R_T = 7.9$ min, 11.6 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_4$ 298.1205, found 298.1207. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2k** (23.1 mg, 29%, 90:10 e.r.) and 1,4-product **3k** (18.5 mg, 23%, 95:5 e.r.). No recovered epoxide **1**.

Analytical standards used for the characterization of **2k** and **3k** were prepared from a separate trial giving enantiomeric ratios of 92:8 and 95:5 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(1,3-benzodioxol-5-yl)-cyclohex-1-

enecarboxylate (2k)— $[\alpha]_{\text{D}}^{20.0} +104.4$ (c 1.00, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.14 (dd, $J = 4.7, 3.0$ Hz, 1H), 6.74 (d, $J = 2.5$ Hz, 1H), 6.68 (d, $J = 8.4$ Hz, 1H), 6.60 (dd, $J = 8.5, 2.5$ Hz, 1H), 5.91 (s, 2H), 5.08 (d, $J = 3.7$ Hz, 1H), 3.87 (ddt, $J = 11.5, 9.2, 3.8$ Hz, 1H), 3.65 (s, 3H), 2.52 (dtd, $J = 20.1, 5.3, 2.8$ Hz, 1H), 2.37 – 2.25 (m, 1H), 2.02 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.5, 155.0, 148.1, 144.0, 142.6, 129.2, 109.8, 108.0, 101.3, 100.8, 74.8, 69.5, 51.9*, 51.9*, 25.3, 25.3; IR (film, cm^{-1}) 3446, 2950, 2360, 1710, 1480, 1242, 1175, 1035, 746; TLC $R_f = 0.20$ (7:3 hexanes:EtOAc v/v); HPLC 92:8 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol. Retention times: $R_T = 20.4$ min, 23.4 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{15}\text{H}_{16}\text{O}_6$ 292.0947, found 292.0952.

Methyl (3R, 6S)-3-hydroxy-6-O-(1,3-benzodioxol-5-yl)-cyclohex-1-

enecarboxylate (3k)— $[\alpha]_{\text{D}}^{20.0} -16.7$ (c 0.75, CHCl_3); M.p. 70 – 73 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.09 (s, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 6.63 (d, $J = 2.4$ Hz, 1H), 6.48 (dd, $J = 8.5, 2.5$ Hz, 1H), 5.92 (q, $J = 1.43, 1.41$ Hz, 2H), 4.93 (t, $J = 2.8$ Hz, 1H), 4.35 – 4.29 (m, 1H), 3.78 (s, 3H), 2.21 – 2.10 (m, 1H), 2.04 – 1.97 (m, 1H), 1.91 – 1.76 (m, 1H), 1.54 (tt, $J = 14.4, 3.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.3, 153.3, 148.3, 145.7, 142.6, 130.5, 109.8, 108.1, 101.3, 100.9, 70.2, 67.8, 52.2*, 52.2*, 26.4, 25.2; IR (film, cm^{-1}) 3408, 2950, 1715, 1482, 1254, 1177, 1033; TLC $R_f = 0.14$ (7:3 hexanes:EtOAc v/v); HPLC 95:5 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: $R_T = 8.9$ min, 12.4 min; HRMS (EI^+) m/z Calc'd for $\text{C}_{15}\text{H}_{16}\text{O}_6$ 292.0947, found 292.0935. * denotes presumed rotamers in a 1:1 ratio.

Allylic-oxide Regio Resolution of Estradiol—17-O-*tert*butyldimethylsilylestradiol (**7**) was prepared according to literature procedures using a bis-TBS protection followed by selective removal of the phenolic silane.⁸ In addition to the discussed use of the (S,S)-**4**, (R,R)-**4** was also used and the results are included below. Products are a single diastereomer unless otherwise noted.

In a flame-dried flask outfitted with a septum, racemic epoxide **1** (68.0 mg, 0.44 mmol, 1.4 equiv) was dissolved in 6.5 mL of toluene followed by 17-O-*tert*butyldimethylsilylestradiol **7** (120.0 mg, 0.31 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to -40°C . In a separate flask, $\text{Pd}_2(\text{dba})_3$ (14.7 mg, 5.0 mol%) and (*R,R*)-**4** (36.7 mg, 15.0 mol%) were dissolved in 4.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40°C and added to the epoxide solution via syringe. After 96 hours at -40°C , the reaction was concentrated to a volume of 2.0 mL and then purified by flash chromatography (9:1, hexanes:EtOAc v/v) to yield **8** (101.5 mg, 60%) and **9** (46.9 mg, 27%), both as white solids and single diastereomers. The epoxide (**1**, 22%) was recovered in 93:7 enantiomeric ratio.

Methyl (5*R*, 6*S*)-5-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-

cyclohex-1-enecarboxylate (8)— $[\alpha]_{\text{D}}^{20.0} -97.3$ (*c* 1.00, CHCl_3); M.p. $38 - 42^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.19 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 4.6, 3.1 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 5.25 (d, *J* = 3.7 Hz, 1H), 3.91 (dt, *J* = 11.3, 3.7 Hz, 1H), 3.66 (s, 3H), 3.64 (t, *J* = 7.7 Hz, 1H), 2.88–2.77 (m, 1H), 2.57–2.48 (m, 1H), 2.37–2.22 (m, 2H), 2.21–2.11 (m, 1H), 2.11–1.79 (m, 6H), 1.66–1.63 (m, 1H), 1.55–1.03 (m, 7H), 0.89 (s, 9H), 0.73 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.5, 157.3, 143.8, 138.1, 134.1, 129.4, 126.4, 117.1, 114.1, 81.8, 72.7, 69.4, 51.8, 49.8, 44.2, 43.6, 38.9, 37.2, 31.0, 29.9, 27.4, 26.4, 25.9, 25.3, 25.1, 23.3, 18.2, 11.4, -4.3 , -4.6 ; IR (film, cm^{-1}) 3433, 2926, 2854, 1717, 1495, 1246, 1094, 834, 773; TLC R_f = 0.57 (7:3 hexanes:EtOAc v/v). HRMS (EI^+) *m/z* Calc'd for $\text{C}_{32}\text{H}_{48}\text{SiO}_5$ 540.3271, found 540.3263.

Methyl (3*S*, 6*R*)-3-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-

cyclohex-1-enecarboxylate (9)— $[\alpha]_{\text{D}}^{20.0} -25.6$ (*c* 1.00, CHCl_3); M.p. $43 - 47^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.20 (d, *J* = 8.1 Hz, 1H), 7.10 (dd, *J* = 2.2, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.09 (br s, 1H), 4.32 (dddd, *J* = 10.6, 6.1, 2.1, 1.0 Hz, 1H), 3.76 (s, 3H), 3.64 (t, *J* = 7.9 Hz, 1H), 2.89–2.78 (m, 1H), 2.34–2.10 (m, 3H), 2.04–1.76 (m, 5H), 1.71–1.03 (m, 10H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 155.7, 145.8, 138.2, 133.8, 130.6, 126.5, 117.0, 114.0, 81.8, 67.9*, 67.9*, 67.8, 52.1*, 52.1*, 49.8, 44.2, 43.7, 38.9, 37.2, 31.1, 29.9, 27.4, 26.5, 26.4, 26.0, 25.3, 23.4, 18.2, 11.4, -4.3 , -4.6 ; IR (film, cm^{-1}) 3389, 2926, 2853, 1719, 1496, 1247, 1094, 834, 773; TLC R_f = 0.43 (7:3 hexanes:EtOAc v/v). HRMS (EI^+) *m/z* Calc'd for $\text{C}_{32}\text{H}_{48}\text{SiO}_5$ 540.3271, found 540.3263. * denotes presumed rotamers in a 1:1 ratio.

In a flame-dried flask outfitted with a septum, racemic epoxide **1** (121.6 mg, 0.788 mmol, 1.4 equiv) was dissolved in 7.0 mL of toluene followed by 17-O-*tert*butyldimethylsilylestradiol **7** (208.1 mg, 0.539 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to -40°C . In a separate flask, $\text{Pd}_2(\text{dba})_3$ (26.2 mg, 5.0 mol%) and (*S,S*)-**4** (67.0 mg, 15.0 mol%) were dissolved in 4.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40°C and added to the epoxide solution via syringe. After 96 hours at -40°C , the reaction was concentrated to a volume of 2.0 mL

and then purified by flash chromatography (9:1, hexanes:EtOAc, (v/v) to yield **10** (127.9 mg, 44%) and **11** (119.2 mg, 41%) both as white solids and single diastereomers. The epoxide (**1**, 18%) was recovered in 66:34 enantiomeric ratio.

Methyl (5S, 6R)-5-hydroxy-6-O-(17-O-*tert*butyldimethylsilyl)estradiol)-

cyclohex-1-enecarboxylate (10)— $[\alpha]_D^{20.0}$ −28.0 (*c* 1.00, CHCl₃); M.p. 56 – 60 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 4.6, 3.1 Hz, 1H), 6.94 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 5.25 (d, *J* = 3.7 Hz, 1H), 3.91 (ddt, *J* = 11.3, 9.1, 3.7 Hz, 1H), 3.65 (s, 3H), 3.64 (t, *J* = 8.5 Hz, 1H), 2.86–2.79 (m, 1H), 2.58 – 2.47 (m, 1H), 2.37–2.23 (m, 2H), 2.20 – 2.11 (m, 1H), 2.06–1.80 (m, 6H), 1.71–1.59 (m, 1H), 1.54–1.07 (m, 7H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 157.3, 143.7, 138.0, 133.9, 129.3, 126.3, 116.9, 114.3, 81.8, 72.7, 69.4, 51.7*, 51.7*, 49.7, 44.2, 43.6, 38.8, 37.2, 31.0, 29.8, 27.3, 26.4, 25.9, 25.2*, 25.1*, 23.3, 18.1, 11.4, −4.3, −4.7; IR (film, cm^{−1}) 3435, 2928, 2855, 1719, 1496, 1246, 1095, 834, 774; TLC R_f = 0.57 (7:3 hexanes:EtOAc v/v). HRMS (EI⁺) *m/z* Calc'd for C₃₂H₄₈SiO₅ 540.3271, found 540.3264. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(17-O-*tert*butyldimethylsilyl)estradiol)-

cyclohex-1-enecarboxylate (11)— $[\alpha]_D^{20.0}$ +27.5 (*c* 0.50, CHCl₃); M.p. 64 – 69 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.10 (dd, *J* = 2.4, 1.3 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 5.09 (br s, 1H), 4.34 – 4.30 (m, 1H), 3.75 (s, 3H), 3.64 (t, *J* = 8.0 Hz, 1H), 2.88 – 2.77 (m, 1 H), 2.32 – 2.11 (m, 3H), 2.04 – 1.76 (m, 5H), 1.74 – 1.03 (m, 10H), 0.89 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 155.6, 146.0, 138.2, 133.8, 130.4, 126.4, 116.8, 114.3, 81.8, 67.9, 67.7, 52.1, 49.7, 44.2, 43.6, 38.9, 37.2, 31.0, 29.9, 27.3, 26.4, 26.3, 25.9, 25.2, 23.3, 18.2, 11.4, −4.3, −4.6; IR (film, cm^{−1}) 3410, 2928, 2855, 1720, 1496, 1247, 1095, 834, 773; TLC R_f = 0.43 (7:3 hexanes:EtOAc v/v). HRMS (EI⁺) *m/z* Calc'd for C₃₂H₄₈SiO₅ 540.3271, found 540.3268.

Allylic-oxide Regio Resolution of Tyrosine—In addition to the discussed use of (S,S)-**4**, (R,R)-**4** was also tested and the results are shown below. Products are shown to be a single diastereomer unless otherwise noted.

In flame dried flask outfitted with a septum, racemic epoxide **1** (264.7 mg, 1.71 mmol, 1.05 equiv.) was dissolved in 12.0 mL of toluene followed by the addition of Boc-L-Tyr-OMe **12** (482.5 mg, 1.63 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to −40 °C. In a separate flask, Pd₂(dba)₃ (12.4 mg, 1.0 mol%) and (R,R)-**4** (34.2 mg, 3.0 mol%) of was dissolved in 1.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to −40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 72 hours before being worked up as in general procedure A. The reaction was purified by flash chromatography (7:3 hexanes:EtOAc v/v) to yield 664.3 mg of an inseparable mixture of **13** (45% yield, 4.37:1 diastereomeric ratio), **14** (36% yield as a single diastereomer) and 0.8 mg of recovered oxide (59:41 e.r.). Analytical standards of

13 and **14** were purified by preparatory HPLC (90:10 to 1:99 water:acetonitrile v/v) and yields of **13** and **14** were determined by ^1H NMR analysis of the homogenous mixture.

Methyl (5S, 6R)-5-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate

(13)—Note: The following data are for the major diastereomer isolated (4.37:1).

^1H NMR (400 MHz, CDCl_3) δ 7.16 (dd, J = 4.7, 3.0 Hz, 1H), 7.08 – 7.00 (m, 4H), 5.23 (d, J = 3.7 Hz, 1H), 4.95 (br d, J = 8.1 Hz, 1H), 4.56 – 4.50 (m, 1H), 3.90 (dt, J = 11.2, 3.8 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.07 – 2.95 (m, 2H), 2.58 – 2.48 (m, 1H), 2.38 – 2.25 (m, 1H), 2.04 – 1.84 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 166.5, 158.8, 155.2, 144.1, 130.6, 130.4, 129.3, 117.5, 80.1, 73.3, 69.5, 54.6, 52.3, 51.8, 37.6, 28.4, 25.4, 23.5. Optical rotation, IR, and HRMS were not obtained due to mixture of diastereomers.

Methyl (3R, 6S)-3-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate

(14)— $[\alpha]_{\text{D}}^{20.0}$ +36.4 (c 1.00, CHCl_3); M.p. 38–42 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.11 (t, J = 1.6 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 6.94 – 6.88 (m, 2H), 5.07 (t, J = 2.8 Hz, 1H), 5.01 (d, J = 8.3 Hz, 1H), 4.53 (dt, J = 8.7, 6.0 Hz, 1H), 4.36 – 4.26 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.01 (tt, J = 14.1, 6.8 Hz, 2H), 2.17 – 2.09 (m, 1H), 2.00 – 1.92 (m, 1H), 1.80 (tdd, J = 12.9, 10.3, 2.7 Hz, 1H), 1.57 (tt, J = 14.3, 3.2 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 166.3, 157.1, 155.2, 145.8, 130.5, 128.9, 128.7, 117.0, 80.0, 68.2, 67.8, 54.6, 52.3*, 52.3*, 52.1*, 52.1*, 37.6, 28.4, 26.5, 25.3; IR (film, cm^{-1}) 3370, 2951, 1718, 1508, 1255, 1167, 1031; TLC R_f = 0.17 (7:3 hexanes:EtOAc v/v). HRMS (EI^+) m/z Calc'd for $\text{C}_{23}\text{H}_{31}\text{O}_8\text{N}$ 449.2049, found 449.2056. * denotes presumed rotamers in a 1:1 ratio.

In a flame-dried flask outfitted with a septum, racemic epoxide **1** (301.0 mg, 1.02 mmol, 1.0 equiv.) was dissolved in 12.0 mL of toluene followed by the addition of Boc-L-Tyr-OMe **12** (562.1 mg, 1.0 mmol, 0.98 equiv.). The resulting solution was degassed with argon and cooled to –40 °C. In a separate flask, $\text{Pd}_2(\text{dba})_3$ (14.5 mg, 1.0 mol%) and (*S,S*)-**4** (39.3 mg, 3.0 mol%) was dissolved in 6.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to –40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 72 hours before being worked up as in general procedure A. The reaction was purified by flash chromatography (7:3 hexanes:EtOAc v/v) to yield 712.0 mg of an inseparable mixture of **15** and **16** and 43.4 mg of recovered oxide (53:47 e.r.). Analytical standards of **15** and **16** were purified by preparatory HPLC (90:10 to 1:99 water:acetonitrile v/v) and yields of **15** (51% yield, 4.20 d.r. as determined by ^1H NMR) and **16** (40% yield as a single diastereomer) were determined by ^1H NMR analysis of the homogenous mixture.

Methyl (5R, 6S)-5-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate

(15)—Note: The following data are for the major diastereomer isolated (4.20:1).

^1H NMR (400 MHz, CDCl_3) δ 7.15 (dd, J = 4.7, 3.0 Hz, 1H), 7.08 – 6.99 (m, 4H), 5.22 (d, J = 3.6 Hz, 1H), 5.00 – 4.96 (m, 1H), 4.55 – 4.50 (m, 1H), 3.89 (dt, J = 11.4, 3.7 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.06 – 2.96 (m, 2H), 2.57 – 2.48 (m, 1H), 2.36 – 2.27 (m, 1H), 2.02 – 1.93 (m, 1H), 1.89 – 1.80 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 166.5, 158.8, 155.2, 144.1, 130.6, 130.4, 129.2, 117.5, 80.0, 73.3, 69.5, 54.6, 52.3,

51.8, 37.5, 28.4, 25.3, 25.3. Optical rotation, IR, and HRMS were not obtained due to mixture of diastereomers.

Methyl (3*S*, 6*R*)-3-hydroxy-6-*O*-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate

(16)— $[\alpha]_{\text{D}}^{20.0} +10.2$ (*c* 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.11 (t, *J* = 1.7 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.95 – 6.90 (m, 2H), 5.10 (t, *J* = 2.9 Hz, 1H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.54 (q, *J* = 6.7 Hz, 1H), 4.40 – 4.27 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.02 (qd, *J* = 14.0, 5.9 Hz, 2H), 2.19 – 2.13 (m, 1H), 2.04 – 1.96 (m, 1H), 1.87 – 1.73 (m, 1H), 1.59 (tt, *J* = 14.2, 3.2 Hz, 1H), 1.42 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 166.3, 157.1, 155.2, 146.1, 130.4, 130.2, 128.9, 117.0, 80.0, 68.2, 67.8, 54.6, 52.3*, 52.3*, 52.2*, 52.1*, 37.4, 28.4, 26.2, 25.2; IR (film, cm⁻¹) 3369, 2951, 1718, 1508, 1256, 1167, 1031; TLC R_f = 0.17 (7:3 hexanes:EtOAc v/v). HRMS (EI⁺) *m/z* Calc'd for C₂₃H₃₁O₈N 449.2049, found 449.2042. * denotes presumed rotamers in a 1:1 ratio.

Allylic-oxide Regio Resolution of Griseofulvin—4-des-methyl-griseofulvin **17** was prepared by the demethylation of griseofulvin following a literature procedure.¹⁴ In addition to the discussed use of (*S,S*)-DPEN-ligand **4**, (*R,R*)-DPEN-ligand **4** was also tested and the results are shown below. Products are shown to be a single diastereomer unless otherwise noted.

In flame-dried flask outfitted with a septum, racemic epoxide **1** (81.2 mg, 0.527 mmol, 1.8 equiv.) was dissolved in 1.3 mL of toluene followed by the addition of 4-des-methyl-griseofulvin **17** (99.5 mg, 0.294 mmol, 1.0 equiv.). The resulting solution was thoroughly degassed with argon and cooled to –40 °C. In a separate flask, Pd₂(dba)₃ (17.1 mg, 5.0 mol %) and (*R,R*)-**4** (39.9 mg, 15.0 mol%) was dissolved in 0.6 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to –40 °C and added to the epoxide solution via syringe. The reaction was continued at –40 °C and monitored by ¹H NMR until total consumption of the starting phenol was observed (approx. 18 hours). The reaction was then concentrated to dryness and was purified by flash chromatography (100% DCM, then 95:5 DCM:MeOH v/v) using Florisil as the stationary phase to yield 132.4 mg of a mixture containing **18** (60% yield), **19** (31% yield), and 9.0 mg of recovered phenol **17** (9%). Degradation of the products on Florisil is suspected to regenerate griseofulvin **17**. Similar degradation, but to a much greater extent, was observed when using silica as the stationary phase. Analytical standards of **18** and **19** could be separated from one another and purified by a silica column (5:1 toluene/acetone v/v) then preparatory HPLC (80:20 to 35:65 water:acetonitrile v/v over 35 minutes) to remove **17**. Both products were isolated as white solids.

Methyl (5*R*, 6*S*)-5-hydroxy-6-*O*-(4-des-methyl-griseofulvin)-cyclohex-1-

enecarboxylate (18)— $[\alpha]_{\text{D}}^{20.0} +366.6$ (*c* 1.00, CHCl₃); M.p. 90 – 92 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (dd, *J* = 4.9, 2.7 Hz, 1H), 7.18 (s, 1H), 5.55 (s, 1H), 5.24 (d, *J* = 3.4 Hz, 1H), 4.05 (s, 3H), 3.79 (dt, *J* = 12.0, 3.8 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.93 (dd, *J* = 16.2, 13.3 Hz, 1H), 2.82 (ddd, *J* = 13.4, 6.7, 4.3 Hz, 1H), 2.59 (dt, *J* = 20.4, 5.3 Hz, 1H), 2.48 – 2.30 (m, 2H), 2.24 – 2.09 (m, 1H), 2.00 – 1.89 (m, 1H), 0.95 (d, *J* = 6.6 Hz,

3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.8, 194.1, 170.8, 169.0, 166.7, 165.2, 158.6, 146.8, 127.9, 106.8, 105.1, 98.4, 97.1, 91.1, 77.3, 69.3, 57.4, 56.8, 52.2, 40.2, 36.6, 25.8, 24.6, 14.4; IR (film, cm^{-1}) 3457, 2949, 1709, 1611, 1584, 1224, 1210, 753; TLC R_f = 0.28 (1:4 acetone:toluene v/v); HRMS (DART) m/z Calc'd for $\text{C}_{24}\text{H}_{26}\text{ClO}_9$ ($\text{M}+\text{H}$) $^+$: 493.1260, found 493.1269.

Methyl (3S, 6R)-3-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-

enecarboxylate (19)— $[\alpha]_{\text{D}}^{20.0}$ +298.9 (c 1.00, CHCl_3); M.p. 126 – 128 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.18 (d, J = 1.3 Hz, 1H), 6.55 (s, 1H), 5.52 (s, 1H), 5.35 (br s, 1H), 4.33 (ddd, J = 9.2, 6.2, 2.0 Hz, 1H), 4.02 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 2.95 (dd, J = 16.5, 13.4 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.60 (br s, 1H), 2.39 (dd, J = 16.6, 4.6 Hz, 1H), 2.18 – 1.92 (m, 3H), 1.71 (tt, J = 13.7, 3.5 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.0, 192.2, 171.0, 169.3, 166.2, 164.6, 156.7, 147.6, 128.9, 106.5, 104.9, 97.8, 93.9, 90.7, 70.8, 67.4, 57.2, 56.8, 52.1, 40.0, 36.7, 27.0, 26.4, 14.3; IR (film, cm^{-1}) 3399, 2950, 1711, 1611, 1585, 1357, 1224, 751; TLC R_f = 0.17 (1:4 acetone:toluene v/v); HRMS (DART) m/z Calc'd for $\text{C}_{24}\text{H}_{26}\text{ClO}_9$ ($\text{M}+\text{H}$) $^+$: 493.1260, found 493.1268.

In flame dried flask outfitted with a septum, racemic epoxide **1** (81.2 mg, 0.527 mmol, 1.8 equiv.) was dissolved in 1.3 mL of toluene followed by the addition of 4-des-methyl-griseofulvin **17** (99.5 mg, 0.294 mmol, 1.0 equiv.). The resulting solution was thoroughly degassed with argon and cooled to –40 °C. In a separate flask, $\text{Pd}_2(\text{dba})_3$ (16.7 mg, 5.0 mol %) of and (*S,S*)-**4** (38.9 mg, 15.0 mol%) was dissolved in 0.6 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to –40 °C and added to the epoxide solution via syringe. The reaction was continued at –40 °C and monitored by ^1H NMR until total consumption of the starting phenol was observed (approx. 18 hours). The reaction was then concentrated to dryness and purified by flash chromatography (100% DCM, then 95:5 DCM:MeOH v/v) using Florisil as the stationary phase to yield 132.4 mg of a mixture containing **20** (54% yield), **21** (25% yield), and 6.2 mg of recovered phenol **17** (6%). Degradation of the products on Florisil is suspected to regenerate griseofulvin **17**. Similar degradation, but to a much greater extent, was observed when using silica as the stationary phase. Analytical standards of **20** and **21** could be separated from one another and purified by a silica column (5:1 toluene/acetone v/v) then preparatory HPLC (80:20 to 35:65 water:acetonitrile v/v over 35 minutes) to remove **17**. Both products were isolated as white solids.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-

enecarboxylate (20)— $[\alpha]_{\text{D}}^{20.0}$ +61.0 (c 1.00, CHCl_3); M.p. 196 – 198 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 7.32 – 7.27 (m, 1H), 7.20 (s, 1H), 5.53 (s, 1H), 5.23 (d, J = 3.8 Hz, 1H), 4.05 (s, 3H), 3.81 (dt, J = 11.7, 3.9 Hz, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 3.05 (dd, J = 16.5, 13.5 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.64 – 2.52 (m, 1H), 2.50 – 2.28 (m, 2H), 2.23 – 2.09 (m, 1H), 2.04 – 1.91 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.9, 194.7, 170.6, 169.1, 166.7, 165.3, 158.7, 146.8, 127.9, 107.2, 104.9, 98.6, 97.8, 90.8, 77.7, 69.2, 57.4, 56.8, 52.2, 40.2, 36.5, 25.8, 24.6, 14.3; IR (film, cm^{-1}) 3468, 2949, 1709,

1611, 1224, 1046, 753; TLC R_f = 0.26 (1:4 acetone:toluene v/v); HRMS (DART) m/z Calc'd for $C_{24}H_{26}ClO_9$ (M+H)⁺: 493.1260, found 493.1268.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-enecarboxylate (21)— $[\alpha]_D^{20.0} +96.9$ (c 1.00, $CHCl_3$); M.p. 102 – 104 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 7.15 (dd, J = 2.4, 1.2 Hz, 1H), 6.53 (s, 1H), 5.51 (s, 1H), 5.34 (d, J = 3.2 Hz, 1H), 4.33 (ddd, J = 10.3, 6.2, 2.6 Hz, 1H), 4.01 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 3.04 – 2.93 (m, 1H), 2.87 – 2.78 (m, 1H), 2.47 – 2.35 (m, 2H), 2.20 – 1.94 (m, 2H), 1.73 (tt, J = 13.9, 3.6 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0, 192.2, 171.0, 169.3, 166.2, 164.5, 156.6, 147.5, 129.0, 106.7, 104.8, 97.8, 94.1, 90.6, 70.9, 67.5, 57.2, 56.7, 52.2, 40.1, 36.5, 27.0, 26.4, 14.4; IR (film, cm^{-1}) 3400, 2940, 1712, 1612, 1357, 1177, 750; TLC R_f = 0.17 (1:4 acetone:toluene v/v); HRMS (DART) m/z Calc'd for $C_{24}H_{26}ClO_9$ (M+H)⁺: 493.1260, found 493.1272.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The project described was supported by Award Number T32GM008500 from the National Institute of General Medical Sciences and generously supported by Cornell University. We thank Emil Lobkovsky for x-ray analysis, Anthony Condo for mass spectra collection, and Ivan Keresztes for NMR assistance.

References

1. (a) Tsuji J, Kataoka H, Kobayashi Y. *Tetrahedron Lett.* 1981; 22:2575–2578. (b) Trost BM, Molander GA. *J Am Chem Soc.* 1981; 103:5969–5972. (c) Trost BM, Van Vranken DL. *Chem Rev.* 1996; 96:395–422. [PubMed: 11848758] (d) Trost BM, Crawley ML. *Chem Rev.* 2003; 103:2921–2943. [PubMed: 12914486]
2. For examples of allylic oxides by Trost and coworkers, see: (a) Trost BM, Bunt RC, Lemoine RC, Calkins TL. *J Am Chem Soc.* 2000; 122:5968–5976. (b) Trost BM, Jiang C. *J Am Chem Soc.* 2001; 123:12907–12908. [PubMed: 11749552]
3. Moschitto MJ, Vaccarello DN, Lewis CA. *Angew Chem Int Ed.* 2015; 54:2142–2145.
4. Fabris F, Collins J, Sullivan B, Leisch H, Hudlicky T. *Org Biomol Chem.* 2009; 7:2619. [PubMed: 19503938]
5. Trost BM, Van Vranken DL, Bingel C. *J Am Chem Soc.* 1992; 114:9327–9343.
6. (a) Butts CP, Fiali E, Lloyd-Jones GC, Norrby P, Sale DA, Schramm Y. *J Am Chem Soc.* 2009; 131:9945–9957. [PubMed: 19435358] (b) Lloyd-Jones GC, Stephen SC, Fairlamb IJS, Martorell A, Dominguez B, Tomlin PM, Murray M, Fernandez JC, Riis-Johannessen T, Guertziz T. *Pure Appl Chem.* 2004; 76:589–601.
7. These data have been reported previously and included to complete Table 1, see reference 3.
8. Jadhav VH, Lee SB, Jeong H-J, Lim ST, Sohn M-H, Kim DW. *Tetrahedron Lett.* 2012; 53:2051.
9. The directing capability of carbamates for palladium mediated Heck reactions was observed by Rawal and coworkers, see: (a) Rawal VH, Michoud C. *J Org Chem.* 1993; 58:5583–5584. A Boc-directed C-H activation has been established: (b) Wang D-H, Hao X-S, Wu D-F, Yu J-Q. *Org Lett.* 2006; 8:3387–3390. [PubMed: 16836412] The use of carbamates to direct palladium catalyzed arene-arene couplings has recently been reported: (c) Zhao X, Yeung CS, Dong VM. *J Am Chem Soc.* 2010; 132:5837–5844. [PubMed: 20359220]
10. Griseofulvin isolation: (a) Oxford AE, Raistrick H, Simonart P. *Biochem J.* 1939; 33:240–248. [PubMed: 16746904] Structure determination: (b) Grove JF, MacMillan J, Mulholland TPC,

- Rogers MAT. J Chem Soc. 1952:3977–3987. For a review of the chemistry of griseofulvin, see: (c) Petersen AB, Rønneest MH, Larsen TO, Clausen MH. Chem Rev. 2014; 114:12088–12107. [PubMed: 25476923]
11. Geodin isolation: (a) Raistrick H, Smith G. Biochem J. 1936; 30:1315–1322. [PubMed: 16746160] Structure determination: (b) Barton DHR, Scott AI. J Chem Soc. 1958:1767–1772. Crystal structure: (c) Rønneest MH, Nielsen MT, Leber B, Mortensen UH, Krämer A, Clausen MH, Larsen TO, Harris P. Acta Cryst. 2011; C67:o125–o128.
12. Sch202596 isolation: Chu M, Mierzwa R, Truumes I, King A, Sapidou E, Barrabee E, Terracciano J, Patel MG, Gullo VP, Burrier R, Das PR, Mittelman S, Puar MS. Tetrahedron Lett. 1997; 38:6111–6114.
13. (a) Ho YS, Duh JS, Jeng JH, Wang YJ, Liang YC, Lin CH, Tseng CJ, Yu CF, Chen RJ, Lin JK. Int J Cancer. 2001; 91:393–401. [PubMed: 11169965] (b) Rathinamy K, Jindal B, Asthana J, Singh P, Balaji PV, Panda D. BMC Cancer. 2010; 10:213. [PubMed: 20482847] (c) Panda D, Rathinasamy K, Santra MK, Wilson L. Proc Nat Acad Sci USA. 2005; 102:9878–9883. [PubMed: 15985553]
14. Rønneest MH, Harris P, Gotfredsen CH, Larsen TO, Clausen MH. Tetrahedron Lett. 2010; 51:5881.
15. The use of Florisil greatly diminished the degradation as compared to silica gel.

Scheme 1.
Allylic-oxide regio-resolution (AORR)

Scheme 2.
Allylic-oxide regio-resolution model

Scheme 3. Applying the AORR method with estradiol, tyrosine, and griseofulvin

^aReagents and conditions: (a) 5.0 mol% Pd₂(dba)₃, 15.0 mol% (R,R)-**4**, toluene, **1** (1.4 equiv.), -40 °C, 96 h; (b) 5.0 mol% Pd₂(dba)₃, 15.0 mol% (S,S)-**4**, **1** (1.4 equiv.), toluene, -40 °C, 96 h; (c) 1.0 mol% Pd₂(dba)₃, 3.0 mol% (R,R)-**4**, **1** (1.0 equiv.), toluene, -40 °C, 72 h; (d) 1.0 mol% Pd₂(dba)₃, 3.0 mol% (S,S)-**4**, **1** (1.1 equiv.), toluene, -40 °C, 72 h; (e) 5.0 mol% Pd₂(dba)₃, 15.0 mol% (R,R)-**5**, toluene, **1** (1.8 equiv.), -40 °C, 18 h; (f) 5.0 mol% Pd₂(dba)₃, 15.0 mol% (S,S)-**4**, toluene, **1** (1.8 equiv.), -40 °C, 18 h.

Table 1

Scope of regiodivergence

entry	phenol	1 er ^a	Product	2 er ^b	Product	3 er ^b	% yield ^c (1:2:3)
1	R = H	-	2a	98:2	3a	91:9	0:31:27
2	R = 4-Me	57:43	2b	96:4	3b	93:7	2:39:34
3	R = 4- <i>t</i> Bu	52:48	2c	96:4	3c	91:9	24:28:34
4	R = 4-OMe	56:44	2d	85:15	3d	95:5	1:48:35
5	R = 4-NHBoc	51:49	2e	90:10	3e	84:16	29:21:23
6	R = 4-NO ₂	50:50	2f	97:3	3f	98:2	64:4:4
7	R = 2,4-dimethyl	68:32	2g	94:6	3g	84:16	8:31:34
8	R = 3,5-dimethyl	52:48	2h	90:10	3h	91:9	23:31:34
9	R = 2-nap	-	2i	84:16	3i	84:16	0:33:33
10	R = 1-nap	-	2j	80:20	3j	88:12	0:35:38
11		-	2k	90:10	3k	95:5	0:29:23

^a Enantiomeric ratio of recovered epoxide was determined by GC analysis.^b Enantiomeric ratios were determined by LC analysis against prepared racemic standards.^c Yield refers to Isolated yields following silica gel chromatography.