Synthesis of Bicyclic Ethers by a Palladium-Catalyzed
Oxidative Cyclization–Redox Relay–π-Allyl-Pd Cyclization Cascade

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A. Supplementary Figures and Tables

Additional figures and complete data on optimization of the bicyclization cascade reaction, from which selected entries are presented in Table 1 of the manuscript.

Figure S1. Synthesis of diene–diol substrates. aCrude A2 carried forward without further purification. bAryl bromides A3a–f prepared from corresponding phenols (not shown, see SECTION E below): SEMCl, i-Pr₂NEt, CH₂Cl₂; isolated yields: A3a: 98%, A3b: 95%, A3c: 89%, A3d: 100%, A3e: 92%, A3f: 81%. cCarbamate substrate A3e treated with NaH prior to lithiation. dIsolated yields: A4a: 82%, A4b: 65%, A4c: 60%, A4d: 69%, A4e: 47%, A4f: 71%. eIsolated yields: 8a: 85%, 8b: 88%, 8c: 63%, 8d: 98%, 8e: 38%, 8f: 63%. Abbreviations: Boc = t-butoxycarbonyl; SEM = (trimethylsilyl)ethoxymethyl; TBAF = tetra–butylammonium fluoride.

Figure S2. Mechanistic studies and proposed mechanism of cascade reaction. (a) Monocyclization reactions with mechanistic probes B1 (100% conversion) and B3 (10% conversion). Conditions: 9 mol% Pd(OTs)₂(MeCN)₂, 12 mol% 12, 3 equiv benzoquinone, 1 equiv Ca(OH)₂, 300 mg/mmol 3 Å MS, CPME, 80 °C, 16 h. (b) Proposed reaction mechanism leading to selective formation of cis-ring fusion product 9b. We propose that the complete diastereoselectivity for cis-ring fusion in the bicyclization cascade results not from the first, oxidative cyclization, but from the second, π-allyl-Pd cyclization. The diene–diol substrate 8b is deprotonated to form Pd-alkoxide intermediate B5, which undergoes reversible oxidative cyclization to form either diastereomeric intermediate B6 or B7. The oxypalladation reaction may be presumed to proceed via a syn-addition pathway, by analogy to related reactions, although anti-

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oxypalladation is also possible. Both intermediates B6 and B7 are competent to undergo processive β-hydride elimination–migratory insertion reactions in the redox-relay process to form π-allyl-Pd intermediates B8 and B9, respectively. However, only the syn diastereomer B9 proceeds to the cis-fused bicyclization product 9b, while conversion of the anti diastereomer B8 to the corresponding trans-fused product B10 is disfavored, presumably due to ring strain. Indeed, preliminary molecular mechanics studies (MacroModel) indicate that the cis-fused bicyclic ether products are much lower in energy than the corresponding trans-fused products, suggesting that the corresponding transition states may follow a similar trend (see Section M below). As a result, β-alkoxide elimination of intermediate B6 to reform Pd-alkoxide B5 becomes competitive with the forward reaction, resulting in an equilibrium between the two oxidative cyclization intermediates B6 and B7, eventually leading solely to the energetically favored cis-fused product 9b. Formation of a mixture of diastereomeric π-allyl-Pd complexes in B9 is expected, arising from mixtures of single-bond rotamers present during the redox-relay process. Cyclization of the soft alkoxide nucleophile is expected to proceed with inversion of configuration relative to Pd, leading to a mixture of α- and β-vinyl diastereomers in bicyclic ether 9b.

### Table S1. Attempted bicyclization cascades of 8a with PdX2-benzoquinone catalyst systems.

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd source</th>
<th>additive</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>8a</th>
<th>9a</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂</td>
<td>—</td>
<td>THF</td>
<td>65</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂</td>
<td>—</td>
<td>benzene</td>
<td>65</td>
<td>51</td>
<td>0</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂</td>
<td>—</td>
<td>DMF</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂</td>
<td>—</td>
<td>dioxane</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂</td>
<td>Cs₂CO₃b</td>
<td>dioxane</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>decomp</td>
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<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>—</td>
<td>THF</td>
<td>65</td>
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<tr>
<td>7</td>
<td>Pd(TFA)₂</td>
<td>—</td>
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<td>8</td>
<td>none</td>
<td>HClc</td>
<td>THF</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>100</td>
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</table>

*10 mol% PdX₂, 2 equiv benzoquinone; product ratios determined by ¹H-NMR analysis of crude reaction products. *2 equiv Cs₂CO₃. *0.4 equiv HCl.

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Table S2. Temperature effects in bicyclization cascade reaction of 8a with Pd(OTs)₂(MeCN)₂.

<table>
<thead>
<tr>
<th>entry</th>
<th>temp (°C)</th>
<th>8a</th>
<th>9a</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>100</td>
<td>0</td>
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<td>2</td>
<td>50</td>
<td>93</td>
<td>0</td>
<td>0</td>
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<td>3</td>
<td>60</td>
<td>52</td>
<td>33</td>
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<td>5</td>
<td>80</td>
<td>6</td>
<td>62</td>
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<td>5</td>
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</table>

*a* 8 mol% Pd(OTs)₂(MeCN)₂, 3 equiv benzoquinone, 10 mol% PyrOx ligand 12, 1 equiv Ca(OH)₂; product ratios determined by ¹H-NMR analysis of crude reaction products.

Table S3. Control experiments omitting reagents from bicyclization cascade reaction of 8a.

<table>
<thead>
<tr>
<th>entry</th>
<th>omitted reagent</th>
<th>8a</th>
<th>9a</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>6</td>
<td>62</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OTs)₂(MeCN)₂</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>benzoquinone</td>
<td>93</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ca(OH)₂</td>
<td>62</td>
<td>12</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>3 Å MS</td>
<td>27</td>
<td>48</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>78</td>
<td>0</td>
<td>14</td>
<td>9</td>
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</tbody>
</table>

*a* 8 mol% Pd(OTs)₂(MeCN)₂, 3 equiv benzoquinone, 10 mol% PyrOx ligand 12, 1 equiv Ca(OH)₂; product ratios determined by ¹H-NMR analysis of crude reaction products.
Table S4. Solvent effects in bicyclization cascade reaction of 8a.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
entry & solvent & 8a & 9a & 10 & 11 \\
\hline
1 & PhCF\textsubscript{3} & 6 & 62 & 27 & 5 \\
2 & toluene & 0 & 61 & 24 & 15 \\
3 & THF\textsuperscript{b} & & & & \\
4 & CPME & 0 & 85 & 10 & 5 \\
5 & dioxane & 0 & 83 & 3 & 14 \\
6 & CH\textsubscript{3}CN & decomp & & & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} 8 mol\% Pd(OTs)\textsubscript{2}(MeCN)\textsubscript{2}, 3 equiv benzoquinone, 10 mol\% PyrOx ligand 12, 1 equiv Ca(OH)\textsubscript{2}; product ratios determined by \textsuperscript{1}H-NMR analysis of crude reaction products. \textsuperscript{b}Sealed tube. CPME = cyclopentyl methyl ether.

Table S5. Ligand effects in bicyclization cascade reaction of 8a.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
entry & ligand & 8a & 9a & 10 & 11 \\
\hline
1 & 12 & 6 & 62 & 27 & 5 \\
2 & S-12 & 15 & 69 & 15 & 1 \\
3 & Bphen & 0 & 0 & 0 & 100 \\
4 & 2,2'-bipyridine & 0 & 0 & 0 & 100 \\
5 & & 40 & 45 & 13 & 2 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} 8 mol\% Pd(OTs)\textsubscript{2}(MeCN)\textsubscript{2}, 3 equiv benzoquinone, 10 mol\% ligand, 1 equiv Ca(OH)\textsubscript{2}; product ratios determined by \textsuperscript{1}H-NMR analysis of crude reaction products. Bphen = 4,7-diphenyl-1,10-phenanthroline.
Table S6. PyrOx ligand electronic effects in bicyclization cascade of 8a.\textsuperscript{a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{cccccc}
\hline
entry & ligand & 8a & 9a & 10 & 11 \\
\hline
1 & \includegraphics[width=0.1\textwidth]{ligand1.png} & 0 & 85 & 10 & 5 \\
2 & \includegraphics[width=0.1\textwidth]{ligand2.png} & 37 & 56 & 4 & 3 \\
3 & \includegraphics[width=0.1\textwidth]{ligand3.png} & 0 & 79 & 19 & 2 \\
4 & \includegraphics[width=0.1\textwidth]{ligand4.png} & 0 & 48 & 6 & 45 \\
5 & \includegraphics[width=0.1\textwidth]{ligand5.png} & 52 & 42 & 6 & 0 \\
\hline
\end{tabular}
\caption{PyrOx ligand electronic effects in bicyclization cascade of 8a.\textsuperscript{a}}
\end{table}

\textsuperscript{a}8 mol\% Pd(OTs)\textsubscript{2}(MeCN)\textsubscript{2}, 3 equiv benzoquinone, 10 mol\% ligand, 1 equiv Ca(OH)\textsubscript{2}; ratios determined by \textsuperscript{1}H-NMR analysis of crude product.
B. MATERIALS AND METHODS

Reagents

Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com), Acros Organics (www.fishersci.com), Alda Aesar (www.alfa.com), or TCI America (www.tcichemicals.com) and used without further purification unless otherwise indicated. Optima or HPLC grade solvents were obtained from Fisher Scientific (www.fishersci.com), degassed with Ar, and purified on a solvent drying system as described unless otherwise indicated.

Reactions

All reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred thru rubber septa via syringes flushed with Ar prior to use. Cold baths were generated as follows: 0 °C, wet ice/water; –40 °C and –78 °C, dry ice/acetone.

Chromatography

TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO₄), or cerium ammonium molybdenate (CAM). Silica flash chromatography was performed manually on E. Merck 230–400 mesh silica gel 60 or on an ISCO CombiFlash Rf+ instrument with RediSep silica gel normal phase columns or RediSep Gold silica gel normal phase columns with UV detection at 254 nm.

Analytical Instrumentation

Optical rotations were recorded on a JASCO model P-1020 digital polarimeter with P-103T temperature controller. IR spectra were recorded on a Bruker Optics Tensor 27 FTIR spectrometer with peaks reported in cm⁻¹. NMR spectra were recorded on a Bruker UltraShield Plus 500 MHz Avance III NMR or UltraShield Plus 600 MHz Avance III NMR with DCH CryoProbe at 24 °C in CDCl₃ unless otherwise indicated. Chemical shifts are expressed in ppm relative to TMS (¹H, 0 ppm) or solvent signals: CDCl₃ (¹³C, 77.0 ppm), C₆D₆ (¹H, 7.16 ppm; ¹³C, 128.0 ppm) or acetone-­d₆ (¹³C, 206.2 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Bruker TopSpin, Mieova (www.mestrelab.com/software/mnova-nmr), or nucleomatica iNMR (www.inmr.net) software. Mass spectra were obtained at the MSKCC Analytical Core Facility on a Waters Acuity SQD LC-MS or PE SCIEX API 100 by electrospray (ESI) ionization. High resolution mass spectra were obtained on a Waters Acuity Premier XE TOF LC-MS by electrospray ionization (ESI). X-ray crystallography analysis was carried out at the University of Toledo Instrumentation Center (http://www.utoledo.edu/nsm/ic/index.html) on a Bruker APEX Duo diffractometer using CuKα radiation (1.54178 Å) for absolute stereochemistry determination. Crystal structures were visualized using CCDC Mercury software (http://www.ccdc.cam.ac.uk/products/mercury/).

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**Molecular Modeling**

Molecular modeling was carried out using MacroModel and LigPrep (Schrödinger release 2017-4; [www.schrodinger.com](http://www.schrodinger.com)). Calculations were performed on an iMac (Retina 4K, 21.5 inch, 2017).

**Nomenclature**

Atom numbers shown in the figures herein may not correspond to IUPAC nomenclature, which was used solely to name each compound. Compounds not cited in the paper or Figures S1 and S2 are numbered herein from S1.
C. SYNTHESIS OF SUBSTITUTED PYROX LIGANDS (S3a–e)

Figure S3. Synthesis of substituted PyrOx ligands for reaction optimization. DAST = diethylamino-sulfur trifluoride; NMM = N-methylmorpholine.

General Procedure for PyrOx Ligand Synthesis (S3a–e)

Synthesis of PyrOx ligands was carried out by analogy to literature precedent for 12 (= S3a).6

In a roundbottom flask, the carboxylic acid S1 (1 equiv) was dissolved in CH2Cl2 (0.1 M substrate concentration). N-Methylmorpholine (1.15 equiv) was added and the solution cooled to 0 °C. Isobutylchloroformate (1.2 equiv) was added and the solution was stirred at 0 °C for 20 min. (−)-(R)-Phenylglycinol (or (+)-(S)-phenylglycinol for ent-S2a) (1.2 equiv) was added in a single portion, and the reaction was allowed to warm to rt with stirring over 16 h. The reaction was quenched with satd aq NH4Cl, and the aq phase was separated and extracted with CH2Cl2 (3x). The combined organic extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–80% EtOAc/hexanes) afforded the amide S2.

In a roundbottom flask, amide S2 was dissolved in CH2Cl2 (0.07 M). The solution was cooled to –78 °C, then DAST (1.4 equiv) was added. The solution was stirred for 1 h, then quenched with solid K2CO3 (2 equiv), then water. The aq phase was separated and extracted with CH2Cl2 (3x). The combined organic extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–100% EtOAc/hexanes with 1% Et3N) afforded the substituted PyrOx ligand S3.

(–)-(S)-N-(2-Hydroxy-1-phenylethyl)-5-(trifluoromethyl)picolinamide (ent-S2a). Prepared from (+)-(S)-phenylglycinol and 5-(trifluoromethyl)pyridine-2-carboxylic acid S1a as a clear sticky oil (210 mg, 65%). \([\alpha]_{18}^{18} – 4.5 \ (c \ 1.0, \ CH_2Cl_2)\). IR (ATR): 3374, 2961, 2877, 2364, 2356, 1672 (C=O), 1606, 1578, 1525, 1471, 1455, 1419, 1386, 1327, 1244, 1166, 1135, 1076, 1018, 981, 911, 869, 838, 758, 734, 700, 687, 674, 658, 640, 623, 616, 607. \(^1\)H-NMR (500 MHz, CDCl3) \(\delta 8.84 \ (dd, \ J = 1.9, 1.0 \ Hz, 1H), 8.68 \ (d, \ J = 7.6 \ Hz, 1H), 8.34 \ (dt, \ J = 8.2, 0.8 \ Hz, 1H), 8.11 \ (ddd, \ J = 8.2, 2.3, 0.7 \ Hz, 1H), 7.45 – 7.29 \ (m, 5H), 5.29 \ (ddd, \ J = 7.7, 5.6, 4.5 \ Hz, 1H), 4.04 \ (app. s, 2H), 2.36 \ (br s, \ OH)\). \(^1\)C-NMR (151 MHz, CDCl3) \(\delta 163.2, 152.4 \ (q, \ J = 1.5 \ Hz), 145.3 \ (q, \ J = 3.9 \ Hz), 138.5, 134.9 \ (q, \ J = 3.5 \ Hz), 129.0, 128.9, 128.1, 126.7, 122.2, 66.7, 56.2. \) HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_3\)F\(_3\) [M+H]\(^{+}\) 311.1007; found 311.1001.

(–)-(S)-2-(5-Fluoropyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (ent-12 = ent-S3a). Prepared from amide ent-S2a as a white solid (68 mg, 34%). \([\alpha]_{18}^{18} – 3.5 \ (c \ 1.0, \ CH_2Cl_2)\). IR (ATR): 3064, 3032, 2961, 2920, 1720, 1680, 1642 (C=N), 1604, 1574, 1520, 1493, 1455, 141, 1326, 1248, 1165, 1128, 1098, 1075, 1044, 1029, 1016, 871, 952, 903, 861, 786, 759, 734, 699, 679, 636, 620, 610. \(^1\)H-NMR (500 MHz, CDCl3) \(\delta 9.00 \ (d, \ J = 2.2 \ Hz, 1H), 8.31 \ (d, \ J = 8.2 \ Hz, 1H), 8.06 \ (dd, \ J = 8.4, 2.3 \ Hz, 1H), 7.43 – 7.28 \ (m, 5H), 5.58 – 5.43 \ (m, 1H), 4.95 \ (dd, \ J = 10.3, 8.6 \ Hz, 1H), 4.44 \ (t, \ J = 8.6 \ Hz, 1H). \) \(^1\)C-NMR (151 MHz, CDCl3) \(\delta 162.8, 149.7, 146.6 \ (q, \ J = 4.0 \ Hz), 141.3, 134.0 \ (q, \ J = 3.5 \ Hz), 128.9, 128.2 \ (q, \ J = 3.3 \ Hz), 127.9, 126.8, 124.0, 122.2, 75.6, 70.5. \) HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_3\)F\(_3\) [M+H]\(^{+}\) 293.0902; found 293.0890.

(+)-(R)-5-Fluoro-N-(2-hydroxy-1-phenylethyl)picolinamide (S2b). Prepared from (–)-(R)-phenylglycinol and 5-fluoropyridine-2-carboxylic acid S1b as a clear sticky oil (96 mg, 52%). \([\alpha]_{17}^{17} +1.3 \ (c \ 0.1, \ CH_2Cl_2)\). IR (ATR): 3386, 3063, 2935, 2358, 1666 (C=O), 1595, 1584, 1526,
1473, 1384, 1278, 1229, 1159, 1070, 911, 857, 789, 736, 700. **1H-NMR** (600 MHz, CDCl₃) δ 8.61 – 8.51 (m, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.24 (dd, J = 8.7, 4.5 Hz, 1H), 7.63 – 7.51 (m, 1H), 7.44 – 7.35 (m, 4H), 7.36 – 7.31 (m, 1H), 5.26 (ddd, J = 7.0, 5.1, 3.8 Hz, 1H), 4.06 – 3.98 (m, 2H), 2.60 (t, J = 6.1 Hz, O–H).

**13C-NMR** (151 MHz, CDCl₃) δ 163.7, 161.2 (d, J = 261.0 Hz), 145.8 (d, J = 3.9 Hz), 138.6, 136.7 (d, J = 25.3 Hz), 129.0, 128.0, 126.8, 124.2 (d, J = 5.6 Hz), 123.9 (d, J = 18.5 Hz), 66.9, 56.2. **HRMS** (ESI) m/z calcd for C₁₄H₁₄N₂O₂F [M+H]+ 251.1032; found 261.1039.

(+)-(R)-2-(5-Fluoropyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (S₃b). Prepared from amide S₂b as a white solid (68 mg, 76%). [α]¹⁷D +39.6 (c 1.0, CH₂Cl₂). **IR** (ATR): 3389, 3065, 2925, 2247, 1737, 1643 (C=O), 1584, 1485, 1455, 1399, 1358, 1318, 1277, 1233, 1096, 1023, 954, 910, 849, 760, 735, 700, 677. **1H-NMR** (600 MHz, CDCl₃) δ 8.58 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 8.7, 4.5 Hz, 1H), 7.57 – 7.46 (m, 1H), 7.41 – 7.28 (m, 5H), 5.46 (dd, J = 10.2, 8.6 Hz, 1H), 4.91 (dd, J = 10.3, 8.6 Hz, 1H), 4.40 (t, J = 8.5 Hz, 1H). **13C-NMR** (151 MHz, CDCl₃) δ 162.9, 160.6 (d, J = 262.1 Hz), 142.9, 141.6, 138.3 (d, J = 24.5 Hz), 128.8, 127.8, 126.8, 125.8 (d, J = 5.2 Hz), 123.5 (d, J = 18.7 Hz), 75.5, 70.4. **HRMS** (ESI) m/z calcd for C₁₄H₁₂N₂OF [M+H]+ 243.0934; found 243.0936.

(–)-(R)-5-Cyano-N-(2-hydroxy-1-phenylethyl)nicotinamide (S₂c). Prepared from (–)-(R)-phenylglycinol and 5-cyanopyridine-2-carboxylic acid S₁c as a clear sticky oil (132 mg, 73%). [α]¹⁸D -1.0 (c 0.1, CH₂Cl₂). **IR** (ATR): 3381, 3065, 3031, 2943, 2878, 2360, 2236, 1956, 1735, 1671 (C=O), 1593, 1564, 1519, 1470, 1375, 1292, 1239, 1191, 1156, 1070, 1024, 1003, 985, 911, 868, 839, 793, 733, 700, 648. **1H-NMR** (600 MHz, CDCl₃) δ 8.84 (dd, J = 2.1, 0.9 Hz, 1H), 8.64 (d, J = 7.7 Hz, 1H), 8.33 (dd, J = 8.1, 0.9 Hz, 1H), 8.15 (dd, J = 8.1, 2.1 Hz, 1H), 7.41 – 7.38 (m, 4H), 7.33 (ddt, J = 6.3, 4.6, 3.2 Hz, 1H), 5.28 (dt, J = 7.8, 5.0 Hz, 1H), 4.03 (dd, J = 6.3, 4.8 Hz, 2H), 2.39 (t, J = 6.1 Hz, O–H). **13C-NMR** (151 MHz, CDCl₃) δ 162.7, 152.1, 150.9, 141.0, 138.4, 129.0, 128.2, 126.7, 122.3, 116.0, 112.3, 66.4, 56.1. **HRMS** (ESI) m/z calcd for C₁₅H₁₂N₂O₂ [M-H]- 266.0940; found 266.0930.
(+)-(R)-6-(4-Phenyl-4,5-dihydrooxazol-2-yl)nicotinonitrile (S3c). Prepared from amide S2c as a off–white solid (106 mg, 89%). \([\alpha]^{18}_D +8.2\) (c 1.0, CH₂Cl₂). IR (ATR): 3401, 3062, 3031, 2904, 2362, 2235, 1639 (C=N), 1593, 1556, 1494, 1480, 1455, 1393, 1359, 1319, 1242, 1202, 1095, 1023, 951, 911, 859, 760, 734, 700, 676, 646. \(^1\)H-NMR (600 MHz, CDCl₃) δ 9.00 (dd, \(J = 2.1, 0.9\) Hz, 1H), 8.30 (dd, \(J = 8.3, 0.9\) Hz, 1H), 8.15 – 8.01 (m, 1H), 7.43 – 7.36 (m, 2H), 7.34 – 7.30 (m, 3H), 5.51 (dd, \(J = 10.3, 8.7\) Hz, 1H), 5.01 – 4.89 (m, 1H), 4.54 – 4.37 (m, 1H). \(^{13}\)C-NMR (151 MHz, CDCl₃) δ 162.5, 152.3, 149.4, 141.1, 140.0, 128.9, 128.0, 126.7, 124.0, 116.0, 111.7, 75.7, 70.5. HRMS (ESI) m/z calcd for C₁₅H₁₂N₃O \([M+H]^+\) 250.0980; found 250.0982.

(–)-(R)-2-(4-Methoxypyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (S2d). Prepared from (–)-(R)-phenylglycinol and 4-methoxypyridine-2-carboxylic acid S1d as a clear sticky oil (52 mg, 59%). \([\alpha]^{17}_D -6.3\) (c 1.0, CH₂Cl₂). IR (ATR): 3372, 3030, 3011, 2943, 2901, 2340, 2212, 1665 (C=O), 1599, 1567, 1522, 1496, 1455, 1392, 1309, 1286, 1257, 1141, 1071, 1033, 994, 971, 911, 878, 806, 735, 701, 667, 616. \(^1\)H-NMR (600 MHz, CDCl₃) δ 8.71 (d, \(J = 7.4\) Hz, 1H), 8.35 (d, \(J = 5.6\) Hz, 1H), 7.74 (d, \(J = 2.6\) Hz, 1H), 7.50 – 7.29 (m, 5H), 7.00 – 6.87 (m, 1H), 5.25 (td, \(J = 6.8, 4.1\) Hz, 1H), 4.06 – 3.96 (m, 2H), 3.91 (s, 3H), 3.07 (m, 3H), 2.82 (dd, \(J = 7.3, 5.1\) Hz, OMe). \(^{13}\)C-NMR (151 MHz, CDCl₃) δ 167.0, 164.8, 151.5, 149.3, 138.7, 129.0, 128.0, 126.8, 113.2, 107.5, 67.0, 56.5, 55.6. HRMS (ESI) m/z calcd for C₁₅H₁₇N₂O₃ \([M+H]^+\) 273.1239; found 273.1242.

(–)-(R)-2-(4-Methoxypyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (S3d). Prepared from amide S2d as a clear sticky oil (27 mg, 55%). \([\alpha]^{17}_D +1.9\) (c 0.1, CH₂Cl₂). IR (ATR): 3063, 3028,
(+)-(R)-3,5-Difluoro-N-(2-hydroxy-1-phenylethyl)picolinamide (S2e). Prepared from (–)-(R)-phenylglycinol and 3,5-difluoropyridine-2-carboxylic acid S1e as a clear sticky oil (47 mg, 54%). \([\alpha]_{\text{D}}^{17} +10.6 (c 1.0, \text{CH}_2\text{Cl}_2)\). IR (ATR): 3386, 3068, 2932, 2884, 2250, 1673 (C=O), 1602, 1522, 1461, 1424, 1360, 1237, 1207, 1151, 1133, 1070, 1044, 999, 912, 885, 836, 737, 703, 648, 619. \(^1\text{H-NMR}\) (500 MHz, CDCl₃) \(\delta 8.49 (d, J = 2.3 \text{ Hz}, 1H), 7.47 – 7.27 (m, 6H), 5.53 (dd, J = 10.3, 8.5 \text{ Hz}, 1H), 4.87 (dd, J = 10.4, 8.5 \text{ Hz}, 1H), 4.36 (t, J = 8.5 \text{ Hz}, 1H).\) \(^{13}\text{C-NMR}\) (151 MHz, CDCl₃) \(\delta 160.5 (dd, J = 166.8, 6.0 \text{ Hz}), 159.8 (d, J = 9.3 \text{ Hz}), 158.7 (dd, J = 175.0, 6.0 \text{ Hz}), 141.4, 134.3 (dd, J = 23.4, 4.5 \text{ Hz}), 131.5 (dd, J = 9.2, 4.1 \text{ Hz}), 128.8, 127.8, 126.7, 113.0 (dd, J = 22.4, 21.1 \text{ Hz}), 74.5, 70.7. \ HRMS (ESI) \(m/z\) calcld for C₁₄H₁₃N₂O₂F₂ \([M+H]^+\) 279.0945; found 279.0941.

(+)-(R)-2-(3,5-Difluoropyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (S3e). Prepared from amide S2e as a white solid (33 mg, quantitative). \([\alpha]_{\text{D}}^{17} +4.3 (c 0.1, \text{CH}_2\text{Cl}_2)\). IR (ATR): 3409, 2926, 2356, 1708, 1648 (C=O), 1604, 1469, 1435, 1400, 1364, 1321, 1254, 1201, 1153, 1074, 941, 764, 703, 675. \(^1\text{H-NMR}\) (600 MHz, CDCl₃) \(\delta 8.49 (d, J = 2.3 \text{ Hz}, 1H), 7.47 – 7.27 (m, 6H), 5.53 (dd, J = 10.3, 8.5 \text{ Hz}, 1H), 4.87 (dd, J = 10.4, 8.5 \text{ Hz}, 1H), 4.36 (t, J = 8.5 \text{ Hz}, 1H).\) \(^{13}\text{C-NMR}\) (151 MHz, CDCl₃) \(\delta 160.5 (dd, J = 166.8, 6.0 \text{ Hz}), 159.8 (d, J = 9.3 \text{ Hz}), 158.7 (dd, J = 175.0, 6.0 \text{ Hz}), 141.4, 134.3 (dd, J = 23.4, 4.5 \text{ Hz}), 131.5 (dd, J = 9.2, 4.1 \text{ Hz}), 128.8, 127.8, 126.7, 113.0 (dd, J = 22.4, 21.1 \text{ Hz}), 74.5, 70.7. \ HRMS (ESI) \(m/z\) calcld for C₁₄H₁₁N₂OF₂ \([M+H]^+\) 261.0839; found 261.0837.
D. SYNTHESIS OF DIENE ALDEHYDE PRECURSORS (A2, S6, S8)

1. Synthesis of 1,5-Diene Aldehyde Precursor (A2)

(E)-2-Methylhepta-2,6-dienal (A2) was prepared as previously described.7

2. Synthesis of 1,4-Diene Aldehyde Precursor (S6)

(E)-2-Methylhexa-2,5-dien-1-ol (S5). In a 250-mL roundbottom flask, epoxide A1 (1 g, 11.88 mmol, 1 equiv) was dissolved in THF (50 mL). The mixture was cooled to –30 °C, and CuBr·SMe2 was added (120 mg, 0.59 mmol, 0.05 equiv). Vinylmagnesium bromide (1 M in THF, 24 mL, 24 mmol, 0.2 equiv) was added dropwise at –30 °C over 1 h. The solution was stirred at –30 °C for 2 h, then warmed to –20 °C. The reaction was quenched with satd aq NH4Cl and brine. The aq layer was separated and extracted with Et2O (3x 50 mL). The organic layer was dried (MgSO4) filtered, and concentrated by rotary evaporation to afford the crude alcohol S5 as a yellow oil (1.31 g, 98%), which was used without further purification. Alcohol S5 has been prepared via a different route but analytical data were not reported.8 Thus, a sample was purified by silica flash chromatography (0-25% hexanes/EtOAc) to afford alcohol S5 as a clear oil for characterization purposes. HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure.

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IR (ATR): 3318 (O-H stretch), 3079, 2977, 2916, 2861, 1638, 1432, 1414, 1384, 1229, 1012, 994, 908, 841, 776, 644. 

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.84 (ddt, $J = 16.8, 10.0, 6.2$ Hz, 1H), 5.49 (ddt, $J = 7.3, 5.9, 1.4$ Hz, 1H), 5.12 – 4.91 (m, 2H), 4.06 (d, $J = 4.8$ Hz, 2H), 2.84 (t, $J = 6.9$ Hz, 2H), 1.71 (s, 3H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 136.6, 136.0, 123.1, 114.7, 68.8, 31.9, 13.6.

(E)-2-Methylhexa-2,5-dien-1-ol (S6). In a 500-mL roundbottom flask, alcohol S5 (1.3 g, 12 mmol) was dissolved in CH$_2$Cl$_2$ (240 mL, 0.05 M substrate concentration). Celite (3 g) and PDC (13 g, 36 mmol) were added and the reaction was stirred at rt for 14 h. The mixture was filtered over a plug of Celite and the filtrate concentrated by rotary evaporation. Purification via silica flash chromatography (3% Et$_2$O/pentane) afforded the aldehyde S6 as a clear oil (520 mg, 40%). Analytical data matched those previously reported for aldehyde S6 prepared via a different route.$^9$

3. Synthesis of 1,6-Diene Aldehyde Precursor (S8)

Figure S6. Synthesis of 1,6-diene aldehyde precursor S8.

(E)-2-Methylocta-2,7-dien-1-ol (S7). In a 250-mL roundbottom flask, epoxide A1 (1 g, 11.88 mmol, 1 equiv) was dissolved in THF (50 mL). The solution was cooled to $-30$ °C, and CuBr·SMe$_2$ was added (120 mg, 0.59 mmol, 0.05 equiv). But-3-enylmagnesium bromide (0.5 M in THF, 48 mL, 24 mmol, 2 equiv) was added dropwise at $-30$ °C over 1 h. The mixture was stirred at $-30$ °C for 2 h, then warmed to $-20$ °C. The reaction was quenched with satd aq NH$_4$Cl and brine. The aq layer was separated and extracted with Et$_2$O (3x 50 mL). The combined organic extracts were dried (MgSO$_4$) filtered, and concentrated by rotary evaporation to afford the crude alcohol S7 as a yellow oil (1.6 g, quantitative), which was used without

further purification. Analytical data matched those previously reported for alcohol S7 prepared via a different route.\textsuperscript{10}

\(\text{O} \)

(E)-2-Methylocta-2,7-dienal (S8). In a 250-mL roundbottom flask, alcohol S7 (0.94 g, 7.4 mmol, 1 equiv) was dissolved in Et2O (100 mL). MnO\textsubscript{2} (26 g, 300 mmol, 40 equiv) was added and the suspension stirred at rt until the reaction was complete as judged by TLC analysis. Celite was added then the mixture was filtered over a pad of Celite. The solid materials were rinsed with Et2O (5x20 mL). The combined filtrates were concentrated by rotary evaporation to afford the crude aldehyde S8 as a light yellow oil (1.3 g, 78%), which was used without further purification. A sample of the crude material was purified by silica flash chromatography (0-20% hexanes/EtOAc) to afford aldehyde S8 as a clear oil for characterization purposes. HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure.

\textbf{IR (ATR):} 2954, 2927, 2858, 1686 (C=O stretch), 1525, 1445, 1361, 1237, 1042, 996, 913, 736.

\textbf{\textsuperscript{1}H-NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 9.34 (s, 1H), 6.46 – 6.31 (m, 1H), 5.74 (ddt, \(J = 16.9, 10.2, 6.7\) Hz, 1H), 5.10 – 4.78 (m, 2H), 2.30 (q, \(J = 7.5\) Hz, 2H), 2.12 – 1.99 (m, 2H), 1.74 – 1.65 (m, 3H), 1.55 (p, \(J = 7.5\) Hz, 2H).

\textbf{\textsuperscript{13}C-NMR} (151 MHz, CDCl\textsubscript{3}) \(\delta\) 195.4, 154.5, 139.6, 137.9, 115.3, 33.3, 28.3, 27.6, 9.3. \textbf{HRMS} (ESI) \(m/z\) calcd for C\textsubscript{9}H\textsubscript{15}O \([\text{M+H}]^{+}\) 139.1123; found 139.1117.

E. SYNTHESIS OF PROTECTED BROMOPHENOL PRECURSORS (A3a–f, S12)

1. Synthesis of 4-(Boc-amino)-2-bromophenol (S10e)

Figure S7. Synthesis of Boc-protected aminobromophenol precursor S10e. Boc = tert-butyloxy-carbonyl.

tert-Butyl (3-bromo-4-hydroxyphenyl)carbamate (S10e). In a 15-mL round-bottom flask, 4-aminophenol S9 (0.20 g, 1.0 mmol, Matrix Scientific, www.matrixscientific.com) was dissolved in THF (2.9 mL, 0.37 M). Di-tert-butyl dicarbonate (0.26 g, 1.2 mmol) was added and the reaction stirred at 25 °C for 16 h. Concentration by rotary evaporation afforded the crude carbamate S10e as a brown oil (302 mg, quantitative), which was used without further purification.

IR (ATR): 3334, 2982, 2935, 2255, 1698, 1597, 1515, 1456, 1411, 1395, 1370, 1276, 1246, 1162, 1062, 1043, 912, 865, 810, 740, 674, 650. 1H-NMR (600 MHz, CDCl3) δ 7.70 (s, 1H), 7.06 (dd, J = 8.8, 2.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 6.33 (s, 1H), 5.30 (s, 1H), 1.51 (s, 9H). 13C-NMR (151 MHz, CDCl3) δ 152.8, 148.3, 132.1, 122.4, 120.0, 115.9, 110.1, 80.7, 28.3. HRMS (ESI) m/z calcld for C11H13NO3Br [M-H] 286.0079; found 286.0093.

2. Synthesis of SEM-protected Bromophenols (A3a–f, S12)

Figure S8. SEM protection of bromophenol precursors (10a–f, S12). SEMCl = 2-(trimethylsilyl)-ethoxymethyl chloride.

General Procedure for SEM Protection of Bromophenols (A3a–f, S12)

In a roundbottom flask, the bromophenol S10 (or S11) (1 equiv) was dissolved in CH2Cl2 (1.0 M substrate concentration) and cooled to 0 °C. i-Pr2NEt (6 equiv) and SEMCl (1.1 equiv) were added sequentially. The mixture was allowed to warm to rt, then stirred until the reaction was complete as judged by TLC analysis. The reaction was quenched with satd aq NH4Cl. The aq layer was separated and extracted with Et2O. The combined organic extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation. Purification by silica flash
chromatography (0–10% EtOAc/hexanes) afforded the SEM-protected bromophenol A₃ (or S₁₂).

(2-((2-Bromo-4-((tert-butyl)phenoxy)methoxy)ethyl)trimethylsilane (A₃a). Prepared from 2-bromo-4-((tert-butyl)phenol, prepared as previously described,¹¹ as a clear oil (4.31 g, 98%). HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure. **IR** (ATR): 2690, 2903, 1759, 1604, 1501, 1365, 1261, 1250, 1151, 1099, 1045, 995, 918, 862, 838, 738, 694, 665, 611. **¹H-NMR** (600 MHz, CDCl₃) δ 7.53 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.6, 2.4 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 5.26 (s, 2H), 3.86 – 3.70 (m, 2H), 1.28 (s, 9H), 1.01 – 0.91 (m, 2H), 0.00 (s, 9H). **¹³C-NMR** (151 MHz, CDCl₃) δ 153.0, 147.6, 131.7, 126.7, 117.3, 113.9, 95.1, 78.6, 78.4, 78.2, 67.9, 35.7, 32.8, 19.4, 1.4.

(2-((2-Bromophenoxy)methoxy)ethyl)trimethylsilane (A₃b). Prepared from 2-bromophenol as a clear oil (8.3 g, 95%). Analytical data matched those reported previously for aryl bromide 1₀ᵇ prepared via a different route.¹² **IR** (ATR): 2954, 2899, 1591, 1478, 1444, 1410, 1381, 1249, 1234, 1153, 1124, 1048, 1031, 990, 916, 860, 836, 750, 694, 659. **¹H-NMR** (600 MHz, CDCl₃) δ 7.54 (dd, J = 7.9, 1.6 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.88 (td, J = 7.6, 1.5 Hz, 1H), 5.30 (s, 2H), 3.84 – 3.78 (m, 2H), 0.99 – 0.92 (m, 2H), 0.00 (s, 9H). **¹³C-NMR** (151 MHz, CDCl₃) δ 155.4, 134.7, 129.8, 124.3, 117.6, 114.2, 94.9, 68.1, 19.4, 1.4. **HRMS** (ESI) m/z calcd for C₁₂H₁₉O₂SiBrNa [M+Na]⁺ 325.0235; found 325.0230.

(2-((2-Bromo-4-fluorophenoxy)methoxy)ethyl)trimethylsilane (A₃c). Prepared from 2-bromo-4-fluorophenol as a clear oil (1.50 g, 89%). HRMS data could not be obtained because

the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure. 

**IR** (ATR): 3333, 2955, 2897, 2362, 1737, 1592, 1489, 1398, 1381, 1250, 1190, 1153, 1096, 1038, 990, 917, 880, 859, 836, 808, 737, 695, 671.  

**1H-NMR** (600 MHz, CDCl₃) δ 7.28 (dd, J = 7.8, 3.0 Hz, 1H), 7.13 (dd, J = 9.1, 4.9 Hz, 1H), 6.96 (ddd, J = 9.1, 7.8, 3.1 Hz, 1H), 5.23 (s, 2H), 3.86 – 3.71 (m, 2H), 1.01 – 0.85 (m, 2H), 0.00 (s, 9H).  

**13C-NMR** (151 MHz, CDCl₃) δ 158.7 (d, J = 244.1 Hz), 152.0 (d, J = 2.9 Hz), 121.6 (d, J = 25.7 Hz), 118.5 (d, J = 8.4 Hz), 116.3 (d, J = 22.5 Hz), 114.4 (d, J = 9.9 Hz), 95.5, 68.1, 19.4, 1.4.

**2-((2-Bromo-4-(trifluoromethyl)phenoxy)methoxy)ethyl)trimethylsilane (A3d).** Prepared from 2-bromo-4-(trifluoromethyl)phenol as a clear oil (0.38 g, quantitative). HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure. **IR** (ATR): 2958, 2914, 1762, 1612, 1505, 1403, 1384, 1327, 1269, 1251, 1176, 1129, 1105, 1083, 1048, 982, 941, 17, 894, 862, 838, 737, 697, 682, 652, 610.  

**1H-NMR** (600 MHz, CDCl₃) δ 7.81 (dd, J = 2.3, 0.8 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.25 (d, J = 9.5 Hz, 1H), 5.35 (s, 2H), 3.82 – 3.76 (m, 2H), 0.98 – 0.92 (m, 2H), 0.00 (s, 9H).  

**13C-NMR** (151 MHz, CDCl₃) δ 158.0, 132.0 (q, J = 3.8 Hz), 127.2 (q, J = 3.8 Hz), 126.3 (q, J = 33.4 Hz), 124.9 (q, J = 271.8 Hz), 116.7, 114.1, 94.8, 68.5, 19.4, 1.4.

**tert-Butyl (3-bromo-4-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)carbamate (A3e).** Prepared from phenol S10e as a clear oil (0.41 g, 92%). **IR** (ATR): 3329, 2954, 2897, 2359, 2253, 1729, 1703, 1588, 1498, 1455, 1393, 1368, 1249, 1216, 1161, 1096, 1055, 1042, 991, 914, 859, 836, 765, 734, 694, 670.  

**1H-NMR** (500 MHz, CDCl₃) δ 7.66 (s, 1H), 7.16 (dd, J = 8.9, 2.6 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.32 (s, 1H), 5.22 (s, 2H), 3.83 – 3.72 (m, 2H), 1.50 (s, 9H), 0.97 – 0.92 (m, 2H), 0.00 (s, 9H).  

**13C-NMR** (151 MHz, CDCl₃) δ 154.1, 151.3, 134.7, 125.0, 120.2, 118.2, 114.5, 95.4, 82.2, 68.0, 29.7, 19.4. **HRMS** (ESI) m/z calcd for C₁₇H₂₇NO₄SiBr [M-H]⁻ 416.0892; found 416.0898.
(2-((2-Bromo-4-methoxyphenoxy)methoxy)ethyl)trimethylsilane (A3f). Prepared from 2-bromo-4-methoxyphenol as a clear oil (1.3253, 81%). HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure. IR (ATR): 2953, 2898, 2836, 1604, 1574, 1493, 1464, 1661, 1406, 1381, 1249, 1213, 1183, 1152, 1094, 1036, 993, 916, 860, 836, 732, 695. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.09 (dd, J = 6.0, 3.0 Hz, 2H), 6.79 (dd, J = 9.0, 3.0 Hz, 1H), 5.20 (s, 2H), 3.83 – 3.77 (m, 2H), 3.75 (s, 3H), 0.98 – 0.92 (m, 2H), 0.00 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 156.3, 149.5, 119.8, 119.2, 115.3, 114.9, 95.8, 67.9, 57.3, 19.5, 1.4.

(2-((2-Bromo-3,5-dimethoxyphenoxy)methoxy)ethyl)trimethylsilane (S12). Prepared from 2-bromo-3,5-dimethoxyphenol, which was prepared as previously described,$^{13}$ as a clear oil (1.50 g, 67%). HRMS data could not be obtained because the compound did not ionize by ESI in positive or negative mode. However, the compound was carried on successfully to the next step, providing further corroboration of its assigned structure. IR (ATR): 3417, 2954, 2364, 1714, 1589, 1464, 1425, 1402, 1380, 1339, 1249, 1448, 1204, 1163, 1122, 1088, 1068, 1031, 1009, 910, 860, 836, 758, 694. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 6.44 (d, J = 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.27 (s, 2H), 3.86 (s, 3H), 3.82 – 3.79 (m, 2H), 3.79 (s, 3H), 1.01 – 0.91 (m, 2H), 0.00 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 161.6, 158.7, 157.0, 96.0, 95.1, 94.8, 94.6, 68.1, 57.7, 57.0, 19.4, 1.4.

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F. COUPLING OF DIENE ALDEHYDES AND PROTECTED BROMOPHENOLS
(A4a–f, S13, S14a–d, S15, (--)-A4b, (+)-A4b)

1. Synthesis of SEM-Protected Diol–1,5-Diene Substrates (A4a–f, S13)

Figure S9. Coupling of 1,5-diene aldehyde (A2) and protected bromophenols (A3, S12).

\[ n\text{-BuLi} \]

General Procedure for Aryl Bromide Lithiation and Addition to Aldehydes (A4a–f, S13)

In a round-bottom flask, the aryl bromide (1 equiv) was azeotroped using toluene (3 x 10 mL), then dissolved in THF (0.1 M substrate concentration; or 0.25 M for reactions >500 mg). The mixture was cooled to –40 °C, then \( n\text{-BuLi} \) (2.5 M in hexanes, 1 equiv) was added dropwise. The reaction was stirred at –40 °C for 30 min, then the aldehyde (1 equiv) was added dropwise. The reaction was stirred at –40 °C for 2 h, then quenched with satd aq NH\(_4\)Cl. The aq layer was separated and extracted with Et\(_2\)O. The combined organic extracts were dried (MgSO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (0–30% EtOAc/hexanes) afforded the SEM-protected diol–diene product.

(Protected diol–dienes A4e and S13 were prepared by modified procedures as detailed separately below.)

(±)-(E)-1-(5-(tert-Butyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylhepta-2,6-dien-1-ol (A4a). Prepared from diene aldehyde A2 and aryl bromide A3a as a yellow tinged oil (2.50 g, 82%). IR (ATR): 3444, 3076, 2956, 293, 2358, 1640, 1609, 1499, 1463, 1413, 1393, 1380, 1363, 1249, 1232, 1187, 1147, 1134, 1084, 1006, 912, 859, 835, 736, 694, 665. \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.32 (d, \( J = 2.5 \) Hz, 1H), 7.22 (dd, \( J = 8.6, 2.5 \) Hz, 1H), 7.04 (d, \( J = 8.6 \) Hz, 1H), 5.89 – 5.75 (m, 1H), 5.65 – 5.51 (m, 1H), 5.37 (d, \( J = 4.9 \) Hz, 1H), 5.26 – 5.14 (m, 2H), 5.07 – 4.90 (m, 2H), 3.79 – 3.65 (m, 2H), 2.64 – 2.53 (m, \( \text{OH} \)), 2.22 – 2.08 (m, 4H), 1.57 (d, \( J = 1.2 \) Hz, 3H), 1.29 (s, 9H), 0.99 – 0.93 (m, 2H), 0.00 (d, \( J = 0.5 \) Hz, 9H). \(^13\)C-NMR (151 MHz, CDCl\(_3\)) \( \delta \) 154.2, 145.8, 139.9, 137.5, 131.9, 126.5, 126.2, 116.0, 115.4, 94.7, 75.8, 67.7, 35.6,
35.1, 32.9, 28.6, 19.5, 14.6, 1.4. **HRMS** (ESI) \( m/z \) calcd for \( \text{C}_{24}\text{H}_{40}\text{O}_{3}\text{SiNa} [\text{M+Na}]^+ 427.2644; \) found 427.2629

(±)-(E)-2-Methyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hepta-2,6-dien-1-ol (A4b). Prepared from diene aldehyde A2 and aryl bromide A3\( \text{b} \) as a yellow tinged oil (0.75g, 65%). **IR** (ATR): 3437, 3075, 2953, 2920, 2337, 2247, 1640, 1601, 1588, 1488, 1454, 1413, 1381, 1280, 1249, 1224, 1150, 1086, 1047, 1003, 913, 859, 835, 754, 736, 694, 663, 649. **\( \text{H-NMR} \)** (600 MHz, CDCl\(_3\)) \( \delta \) 7.32 (dd, \( J = 7.6, 1.8 \) Hz, 1H), 7.23 (ddd, \( J = 8.3, 7.3, 1.8 \) Hz, 1H), 7.12 (dd, \( J = 8.2, 1.1 \) Hz, 1H), 7.00 (td, \( J = 7.4, 1.1 \) Hz, 1H), 5.61 (tt, \( J = 7.2, 1.4 \) Hz, 1H), 5.40 (d, \( J = 4.8 \) Hz, 1H), 5.29 – 5.16 (m, 2H), 5.10 – 4.91 (m, 2H), 3.74 (td, \( J = 8.2, 1.4 \) Hz, 2H), 2.48 (d, \( J = 4.9 \) Hz, OH), 2.22 – 2.08 (m, 4H), 1.57 (d, \( J = 1.3 \) Hz, 3H), 1.00 – 0.91 (m, 2H), 0.00 (s, 9H). **\( \text{13C-NMR} \)** (151 MHz, CDCl\(_3\)) \( \delta \) 156.4, 139.9, 137.5, 132.7, 129.9, 129.1, 126.6, 123.1, 116.1, 115.8, 94.5, 75.4, 67.8, 35.1, 28.6, 19.5, 14.6, 1.4. **HRMS** (ESI) \( m/z \) calcd for \( \text{C}_{20}\text{H}_{32}\text{O}_{3}\text{SiNa} [\text{M+Na}]^+ 371.2018; \) found 371.2034.

(±)-(E)-1-(5-Fluoro-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylhepta-2,6-dien-1-ol (A4c). Prepared from diene aldehyde A2 and aryl bromide A3\( \text{c} \) as a yellow tinged oil (0.66g, 60%). **IR** (ATR): 3441, 3077, 2953, 2362, 1640, 1600, 1492, 1429, 1381, 1249, 1186, 1142, 186, 1001, 913, 858, 835, 735, 710, 694, 648. **\( \text{H-NMR} \)** (600 MHz, CDCl\(_3\)) \( \delta \) 7.07 (ddd, \( J = 9.6, 6.1, 3.8 \) Hz, 2H), 6.95 – 6.83 (m, 1H), 5.88 – 5.76 (m, 1H), 5.61 (dq, \( J = 5.8, 2.8, 1.5 \) Hz, 1H), 5.37 (d, \( J = 4.3 \) Hz, 1H), 5.17 (ddd, \( J = 24.9, 6.9, 0.9 \) Hz, 2H), 5.09 – 4.90 (m, 2H), 3.81 – 3.65 (m, 2H), 2.41 – 2.30 (m, OH), 2.24 – 2.07 (m, 4H), 1.56 (s, 3H), 1.01 – 0.89 (m, 2H), 0.00 (s, 9H). **\( \text{13C-NMR} \)** (151 MHz, CDCl\(_3\)) \( \delta \) 159.3 (d, \( J = 239.9 \) Hz), 152.4 (d, \( J = 2.3 \) Hz), 139.7, 137.0, 134.8 (d, \( J = 6.4 \) Hz), 127.4, 117.2 (d, \( J = 8.0 \) Hz), 116.2, 115.8, 115.8 (d, \( J = 45.9 \) Hz), 95.1, 74.8, 67.8, 35.1, 28.5, 19.5, 14.4, 1.4. **HRMS** (ESI) \( m/z \) calcd for \( \text{C}_{20}\text{H}_{31}\text{O}_{3}\text{FSiNa} [\text{M+Na}]^+ 389.1924; \) found 389.1933.

(±)-(E)-2-Methyl-1-(5-(trifluoromethyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hepta-2,6-dien-1-ol (A4d). Prepared from diene aldehyde A2 and aryl bromide A3\( \text{d} \) as a yellow tinged
oil (0.37g, 69%). IR (ATR): 3421, 3080, 2957, 2925, 1762, 1643, 1618, 1505, 1434, 1384, 1333, 1252, 1163, 1124, 1094, 995, 915, 831, 838, 739, 696, 651. \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.66 (d, \(J = 2.3\) Hz, 1H), 7.55 – 7.45 (m, 1H), 7.19 (d, \(J = 8.6\) Hz, 1H), 5.82 (ddt, \(J = 16.5\), 10.2, 6.2 Hz, 1H), 5.61 (td, \(J = 5.8\), 2.9 Hz, 1H), 5.44 (d, \(J = 4.3\) Hz, 1H), 5.33 – 5.22 (m, 2H), 5.08 – 4.92 (m, 2H), 3.73 (ddd, \(J = 9.2\), 8.0, 1.9 Hz, 2H), 2.20 (d, \(J = 4.3\) Hz, OH), 2.20 – 2.11 (m, 4H), 1.56 (d, \(J = 2.0\) Hz, 3H), 0.99 – 0.89 (m, 2H), 0.00 (s, 9H).

\(^1\)C-NMR (151 MHz, CDCl\(_3\)) \(\delta\) 158.4, 139.6, 137.0, 133.1, 127.8, 127.1 (q, \(J = 3.8\) Hz), 126.7, 126.2 (q, \(J = 3.7\) Hz), 125.0 (q, \(J = 32.6\) Hz), 124.9, 116.3, 115.2, 94.2, 74.8, 68.1, 35.0, 28.5, 19.5, 14.2, 1.4. HRMS (ESI) \(m/z\) calcd for C\(_{21}\)H\(_{31}\)O\(_3\)F\(_3\)SiNa \([M+Na]^+\) 439.1892; found 439.1877.

\(\pm\)-(\(E\))-1-(5-Methoxy-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylhepta-2,6-dien-1-ol (A4f). Prepared from diene aldehyde A2 and aryl bromide A3f as a yellow tinged oil (1.32g, 71%). IR (ATR): 3476, 3077, 2955, 2922, 2361, 2250, 1642, 1611, 192, 1497, 1468, 1431, 1382, 126, 1251, 1206, 1151, 1087, 104, 1008, 915, 861, 838, 738, 7, 650, 612. \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.05 (d, \(J = 8.9\) Hz, 1H), 6.88 (d, \(J = 3.2\) Hz, 1H), 6.74 (dd, \(J = 8.9\), 3.2 Hz, 1H), 5.83 (ddt, \(J = 16.5\), 10.3, 6.2 Hz, 1H), 5.61 (tdd, \(J = 5.9\), 2.5, 1.3 Hz, 1H), 5.36 (d, \(J = 4.6\) Hz, 1H), 5.19 – 5.08 (m, 2H), 5.06 – 4.92 (m, 2H), 3.76 (s, 3H), 3.75 – 3.69 (m, 2H), 2.53 (app dd, \(J = 4.7\), 0.8 Hz, OH), 2.21 – 2.09 (m, 4H), 1.56 (d, \(J = 1.3\) Hz, 3H), 0.96 (dd, \(J = 9.1\), 7.7 Hz, 2H), 0.00 (s, 9H). \(^1\)C-NMR (151 MHz, CDCl\(_3\)) \(\delta\) 155.9, 150.6, 139.9, 137.3, 134.2, 126.7, 117.6, 116.1, 114.7, 114.5, 95.5, 75.2, 67.7, 57.0, 35.1, 28.6, 19.5, 14.1, 1.4. HRMS (ESI) \(m/z\) calcd for C\(_{21}\)H\(_{34}\)O\(_4\)SiNa \([M+Na]^+\) 401.2124; found 401.2121.

**Modified Procedure for Lithiation of Aryl Bromide A3e and Addition to Aldehyde A2 (A4e)**

\(\pm\)-tert-Butyl (\(E\))-(3-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)carbamate (A4e). In a 100-mL roundbottom flask, aryl bromide A3e (1.59 g, 3.8 mmol, 1 equiv) was azeotroped using toluene (3 x 10 mL), then dissolved in THF (38 mL, 0.1 M substrate concentration) and cooled to 0 °C. NaH (152 mg, 3.8 mmol) was added as one portion and the mixture stirred for 30 min at 0 °C. The mixture was cooled to –40 °C and \(n\)-BuLi (2.5 M in hexanes, 1.52 mL, 3.8 mmol, 1 equiv) was added dropwise. Aldehyde A2 (470 mg, 3.8 mmol, 1 equiv) was added dropwise and the reaction was stirred at –40 °C for 2 h. The reaction was quenched with satd aq NH\(_4\)Cl. The aq layer was separated and extracted with Et\(_2\)O. The combined organic extracts were dried (MgSO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (0–60%)
EtOAc/hexanes) afforded the SEM-protected diol–diene A4e as a clear yellow tinged oil (0.83 g, 47%).

**IR** (ATR): 3325, 3080, 2953, 2363, 2250, 1706, 1640, 1602, 1531, 1500, 1414, 1392, 1367, 1248, 1211, 1165, 1086, 1005, 912, 860, 836, 735, 695, 648, 613. 

**1H-NMR** (600 MHz, CDCl3) δ 7.36 (s, 1H), 7.15 (d, J = 2.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.34 (s, 1H), 5.91 – 5.77 (m, 2H), 5.59 (d, J = 7.2 Hz, 1H), 5.35 (d, J = 4.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 5.09 – 4.93 (m, 2H), 3.78 – 3.66 (m, 2H), 2.45 (d, J = 4.8 Hz, OH), 2.15 (q, J = 6.0, 5.4 Hz, 4H), 1.56 (s, 3H), 1.51 (s, 9H), 1.00 – 0.90 (m, 2H), 0.00 (s, 9H).

**13C-NMR** (151 MHz, CDCl3) δ 154.4, 152.3, 140.0, 139.9, 137.4, 133.8, 133.4, 126.8, 120.5, 119.9, 116.7, 116.0, 95.0, 81.7, 75.2, 67.7, 35.1, 29.8, 28.6, 19.5, 14.6, 1.4. 

**HRMS** (ESI) m/z calcd for C_{25}H_{41}O_{5}NSiNa [M+Na]^+ 486.2652; found 486.2659.

**Modified Procedure for Lithiation of Aryl Bromide S12 and Addition to Aldehyde A2 (S13)**

In a 25-mL roundbottom flask, aryl bromide S12 (320 mg, 0.89 mmol, 1 equiv) and LiCl (60 mg, 1.4 mmol, 1.6 equiv) were azeotroped using toluene (3 x 10 mL), then dissolved in Et2O (8.9 mL, 0.1 M substrate concentration). The mixture was cooled to –40 °C and n-BuLi (2.5 M in hexanes, 0.35 mL, 0.89 mmol, 1 equiv) was added dropwise. The reaction was stirred for 1 h, then freshly distilled aldehyde A2 (110 mg, 0.89 mmol, 1 equiv) was added dropwise, and the reaction was stirred for 2 h at –40 °C. The reaction was quenched at –40 °C with satd aq NH4Cl. The aq layer was separated and extracted with Et2O. The combined organic extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (0–40% hexanes/EtOAc) provided the SEM-protected diol–diene S13 as a yellow tinged oil (0.23 g, 63%).

**IR** (ATR): 3557, 3076, 2952, 2358, 1608, 153, 1493, 1456, 1407, 1380, 1323, 1249, 1202, 1149, 1117, 1074, 1010, 912, 859, 835, 736, 694, 634. 

**1H-NMR** (600 MHz, CDCl3) δ 6.40 (d, J = 2.3 Hz, 1H), 6.17 (d, J = 2.3 Hz, 1H), 5.86 – 5.74 (m, 1H), 5.44 (d, J = 11.5 Hz, 1H), 5.36 – 5.29 (m, 1H), 5.17 (d, J = 1.5 Hz, 2H), 5.04 – 4.86 (m, 2H), 3.86 (d, J = 11.5 Hz, OH), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 – 3.65 (m, 2H), 2.18 – 2.02 (m, 4H), 1.65 – 1.58 (m, 3H), 0.95 (d, J = 8.8, 7.7 Hz, 2H), 0.00 (s, 9H). 

**13C-NMR** (151 MHz, CDCl3) δ 154.4, 152.3, 140.0, 138.4, 123.6, 115.7, 113.2, 94.9, 94.7, 93.9, 72.5, 67.8, 57.0, 56.7, 35.2, 28.6, 19.4, 15.0, 1.4. 

**HRMS** (ESI) m/z calcd for C_{22}H_{36}O_{5}SiNa [M+Na]^+ 431.2230; found 431.2249.
2. Synthesis of SEM-Protected Diol–1,4-Diene Substrates (S14a–d)

SEM-protected diol–1,4-dienes S14a–d were synthesized using the general procedure above.

![Figure S10. Coupling of 1,4-diene aldehyde (S6) and protected bromophenols (A3).](image)

(SE)-1-(5-(tert-Butyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylhexa-2,5-dien-1-ol (S14a). Prepared from aryl bromide A3a and aldehyde S6 as a clear oil (190 mg, 43%). IR (ATR): 3456, 2954, 2902, 2359, 2341, 1738, 1638, 1609, 1498, 1462, 1410, 1379, 1363, 1249, 1230, 1133, 1083, 1004, 913, 859, 781, 741, 693, 665, 624, 608. \(^\text{1H-NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.33 (d, \(J = 2.5\) Hz, 1H), 7.22 (dd, \(J = 8.6, 2.6\) Hz, 1H), 7.04 (d, \(J = 8.6\) Hz, 1H), 5.83 (ddt, \(J = 16.5, 10.0, 6.2\) Hz, 1H), 5.64 (t, \(J = 7.4\) Hz, 1H), 5.39 (d, \(J = 5.0\) Hz, 1H), 5.21 (q, \(J = 6.8\) Hz, 2H), 5.10 – 4.88 (m, 2H), 3.73 (dd, \(J = 9.2, 7.5\) Hz, 2H), 2.83 (br s, 2H), 2.58 (d, \(J = 5.0\) Hz, 1H), 1.59 (s, 3H), 1.29 (s, 9H), 1.09 – 0.87 (m, 2H), 0.00 (s, 9H). \(^\text{13C-NMR}\) (151 MHz, CDCl\(_3\)) \(\delta\) 154.2, 145.8, 138.5, 138.2, 131.8, 132.5, 129.9, 124.3, 116.5, 10.0, 6.2 Hz, 1H), 7.22 (dd, \(J = 8.6\) Hz, 1H), 7.04 (d, \(J = 8.6\) Hz, 1H), 5.83 (ddt, \(J = 16.6, 10.0, 6.2\) Hz, 1H), 5.63 (tt, \(J = 7.3, 1.4\) Hz, 1H), 5.41 (d, \(J = 5.0\) Hz, 1H), 5.33 – 5.16 (m, 2H), 5.10 – 4.91 (m, 2H), 3.81 – 3.63 (m, 2H), 2.83 (t, \(J = 6.9\) Hz, 2H), 2.49 (d, \(J = 5.0\) Hz, 1H), 1.58 (d, \(J = 1.4\) Hz, 3H), 1.04 – 0.91 (m, 2H), 0.00 (s, 9H). \(^\text{HRMS}\) (ESI) m/z calcd for C\(_{23}\)H\(_{38}\)O\(_3\)NaSi ([M+Na]\(^+\)) 413.2488; found 413.3477.

(SE)-2-Methyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hexa-2,5-dien-1-ol (S14b). Prepared from aryl bromide A3b and aldehyde S6 as a clear oil (390 mg, 46%). IR (ATR): 3433, 2953, 2357, 1487, 1455, 1249, 1086, 1002, 914, 860, 836, 754, 691, 665, 624, 608. \(^\text{1H-NMR}\) (600 MHz, CDCl\(_3\)) \(\delta\) 7.33 (dd, \(J = 7.6, 1.7\) Hz, 1H), 7.25 – 7.19 (m, 1H), 7.12 (dd, \(J = 8.3, 1.1\) Hz, 1H), 7.01 (td, \(J = 7.5, 1.1\) Hz, 1H), 5.83 (ddt, \(J = 16.6, 10.1, 6.2\) Hz, 1H), 5.63 (tt, \(J = 7.3, 1.4\) Hz, 1H), 5.41 (d, \(J = 5.0\) Hz, 1H), 5.33 – 5.16 (m, 2H), 5.10 – 4.91 (m, 2H), 3.81 – 3.63 (m, 2H), 2.83 (t, \(J = 6.9\) Hz, 2H), 2.49 (d, \(J = 5.0\) Hz, 1H), 1.58 (d, \(J = 1.4\) Hz, 3H), 1.04 – 0.91 (m, 2H), 0.00 (s, 9H). \(^\text{13C-NMR}\) (151 MHz, CDCl\(_3\)) \(\delta\) 156.3, 138.5, 138.2, 132.5, 129.5, 129.1, 124.3,
123.1, 116.0, 115.8, 94.5, 75.4, 67.8, 33.4, 19.5, 14.5, 1.4. HRMS (ESI) m/z calcd for C_{19}H_{30}O_3NaSi ([M+Na]^+) 357.1862; found 357.1863.

$\text{ESI}} m/z$ calcd for C_{19}H_{30}O_3NaSi ([M+Na]^+) 357.1862; found 357.1863.

$\text{ESI}} m/z$ calcd for C_{20}H_{29}O_3F_3NaSi ([M+Na]^+) 425.1736; found 425.1727.

$\text{ESI}} m/z$ calcd for C_{20}H_{32}O_4NaSi ([M+Na]^+) 387.1968; found 387.1966.

3. Synthesis of SEM-Protected Diol–1,6-Diene Substrate (S15)

Figure S11. Coupling of 1,6-diene aldehyde (S8) and protected bromophenol (A3a).
(E)-1-(5-(tert-Butyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylocta-2,7-dien-1-ol (S15). Prepared from aryl bromide A3a and aldehyde S8 according to the general procedure above as a clear oil (1.5 g, 80%).

IR (ATR): 2955, 2359, 1497, 1363, 1249, 1135, 1083, 1004, 913, 695, 629, 617, 607. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.32 (d, $J = 2.5$ Hz, 1H), 7.22 (dd, $J = 8.6, 2.6$ Hz, 1H), 7.04 (d, $J = 8.6$ Hz, 1H), 5.81 (ddt, $J = 16.9, 10.2, 6.7$ Hz, 1H), 5.60 (app tt, $J = 7.3, 1.4$ Hz, 1H), 5.37 (s, 1H), 5.27 – 5.14 (m, 2H), 5.07 – 4.86 (m, 2H), 3.81 – 3.65 (m, 2H), 2.58 (s, 1H), 2.17 – 1.97 (m, 4H), 1.58 – 1.56 (m, 3H), 1.49 (p, $J = 7.5$ Hz, 2H), 1.29 (s, 9H), 0.99 – 0.93 (m, 2H), -0.00 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 154.23, 145.77, 140.21, 137.31, 131.93, 127.04, 126.47, 126.18, 115.88, 115.43, 94.72, 75.84, 67.74, 35.63, 34.80, 32.88, 30.25, 28.51, 19.46, 14.60, 0.00. HRMS (ESI) m/z calcd for C$_{25}$H$_{42}$O$_3$ ([M+Na$^+$]) 441.2801; found 441.2803.

4. Kinetic Resolution of SEM-Protected Diol–Diene Substrate A4b

Figure S12. Kinetic resolution of SEM-protected diol–diene A4b by Sharpless asymmetric epoxidation. DIPT = diisopropyl tartrate; DET = diethyl tartrate; TBHP = tert-butyl hydroperoxide.

(−)-(S,E)-2-Methyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hepta-2,6-dien-1-ol [(−)-A4b]. The kinetic resolution procedure was adapted from literature precedent.$^{14}$ In a 50-mL roundbottom flask, CH$_2$Cl$_2$ (12 mL, 0.1 M substrate concentration) was cooled to −20 °C. Titanium isopropoxide (340 mg, 1.2 mmol, 1.0 equiv), (+)-diisopropyl tartrate (340 mg, 1.4 mmol, 1.2 equiv), and SEM-protected diol–diene (±)-A4b (420 mg, 1.2 mmol, 1 equiv) were added. tert-Butyl hydroperoxide (110 µL, 5.5 M in decane, 0.5 equiv) was added dropwise. The reaction vessel was moved to a −20 °C freezer and allowed to stand for 16 h. The reaction was quenched by addition of an equivalent volume of acetone, then stirred until the mixture reached

rt. Satd aq NaHCO₃ was added and the aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–30% EtOAc/hexanes) separated the undesired epoxide S16 to afford the enantioenriched allylic alcohol (−)-A4b as a clear oil (150 mg, 336%). The enantiomeric excess was determined after deprotection in the next section. The absolute configuration was assigned by analogy to literature precedent.¹⁰

\([\alpha]_{17}^D –9.56 (c 0.1, CH₂Cl₂)\). All other analytical data matched that of (±)-A4b.

\(+\)-(R,E)-2-Methyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hepta-2,6-dien-1-ol [(+)-A4b]. Prepared as described above from allylic alcohol A4b, but using (−)-diethyl tartrate, as a clear oil (190 mg, 46%). The enantiomeric excess was determined after SEM deprotection in the next section. The absolute configuration was assigned by analogy to literature precedent. Error! Bookmark not defined.

\([\alpha]_{17}^D +9.44 (c 0.1, CH₂Cl₂)\). All other analytical data matched that of (±)-A4b.
G. Installation of R³ Terminal Olefin Substituents (S17, S18)

Figure S13. Installation of R³ terminal olefin substituents by olefin cross-metathesis.

(±)-(2E,6E)-2-Methyl-7-phenyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)hepta-2,6-dien-1-ol (S17). In a 10-mL roundbottom flask, alcohol A4a (73.4 mg, 0.18 mmol, 1 equiv) was dissolved in CH₂Cl₂ (1 mL, 0.2 M). Styrene (175 mg, 1.7 mmol, 9 equiv) was added in and the Grubbs II catalyst (8.5 mg, 0.01 mmol, 6 mol%) were added. The reaction was heated to 40 °C and stirred for 16 h. The crude reaction mixture was concentrated and purification by silica flash chromatography (EtOAc/hexanes) afforded the SEM-protected diol–diene S17 as a clear oil (47 mg, 53%).

IR (ATR): 3427, 3025, 2955, 2357, 2247, 1599, 1498, 1462, 1448, 1410, 1380, 1363, 1249, 1232, 1134, 1082, 1004, 965, 911, 859, 835, 738, 693, 665, 648. ¹H-NMR (600 MHz, CDCl₃) δ 7.36 – 7.27 (m, 6H), 7.26 – 7.17 (m, 2H), 7.04 (d, J = 8.6 Hz, 1H), 6.30 (d, J = 16.0 Hz, 1H), 6.24 (dt, J = 15.8, 6.5 Hz, 1H), 5.66 (ddd, J = 7.4, 4.6, 1.6 Hz, 1H), 5.39 (d, J = 4.8 Hz, 1H), 5.22 – 5.15 (m, 2H), 3.72 (ddd, J = 8.9, 7.9, 2.1 Hz, 2H), 2.59 (d, J = 5.0 Hz, OCH₂), 2.35 – 2.19 (m, 4H), 1.60 (d, J = 1.3 Hz), 1.29 (s, 9H), 1.01 – 0.91 (m, 2H), 0.00 (s, 9H). ¹³C-NMR (151 MHz, CDCl₃) δ 154.2, 145.8, 139.1, 137.8, 131.8, 131.8, 131.4, 129.9, 128.3, 127.3, 126.5, 126.3, 126.1, 115.5, 94.7, 75.9, 67.7, 35.6, 34.5, 32.9, 29.1, 19.5, 14.6, 1.4. HRMS (ESI) m/z calcd for C₃₀H₄₄O₃SiNa [M+Na]⁺ 503.2957; found 503.2967.

(±)-(2E,6E)-2,8,8-Trimethyl-1-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)nona-2,6-dien-1-ol (S18). In a 10-mL roundbottom flask, alcohol A4a (250 mg, 0.62 mmol, 1 equiv) was dissolved in 3,3-dimethylbut-1-ene (3.0 mL, 0.2 M substrate concentration). Grubbs II catalyst (26 mg, 0.03 mmol, 5 mol%) was added and the reaction was heated to 40 °C and stirred for
16 h. The mixture was concentrated by rotary evaporation. Purification by silica flash chromatography (0–30% EtOAc/hexanes) afforded the SEM-protected diol–diene alcohol **S18** as a clear oil (158 mg, 56%).

**IR** (ATR): 345, 2959, 2868, 2364, 344, 2250, 1656, 1610, 150, 1464, 1395, 1365, 1252, 1234, 1136, 185, 1009, 974, 913, 861, 838, 739, 695, 669, 651, 617.  

**1H-NMR** (600 MHz, CDCl₃) δ 7.33 (d, J = 2.5 Hz, 1H), 7.22 (dt, J = 8.6, 2.0 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 5.59 (t, J = 7.1 Hz, 1H), 5.45 (dt, J = 15.6, 1.1 Hz, 1H), 5.38 – 5.30 (m, 2H), 5.25 – 5.15 (m, 2H), 3.73 (td, J = 8.2, 1.6 Hz, 2H), 2.55 (d, J = 5.0 Hz, OH), 2.11 (p, J = 6.8 Hz, 2H), 2.07 – 2.01 (m, 2H), 1.57 (s, 3H), 1.29 (s, 9H), 1.01 – 0.92 (m, 9H), 0.00 (s, 9H).  

**13C-NMR** (151 MHz, CDCl₃) δ 154.2, 145.7, 143.2, 137.3, 131.9, 126.8, 126.4, 126.2, 125.5, 115.4, 94.7, 76.0, 67.7, 35.6, 34.1, 32.9, 31.2, 29.6, 19.5, 14.6, 1.4.  

**HRMS** (ESI) m/z calcd for C₂₈H₄₈O₃NaSi [M+Na]^+ 483.3270; found 483.3270.
H. DEPROTECTION OF LINEAR DIOL–DIENE SUBSTRATES (8a–f, S19–S21, 18a–d, 20)

1. Synthesis of Diol–1,5-Diene Substrates with Aryl Substituents (12a–f, S19)

![Figure S14. SEM deprotection to afford diol–1,5-diene substrates (8a–f, S19) for the cascade reaction. TBAF = tetrabutylammonium fluoride.](image)

**General Procedure for SEM Deprotection (8a–f, S19)**

In a roundbottom flask, the SEM-protected diol–diene (1 equiv) was azeotroped using toluene (3 x 10 mL), then TBAF (1.0 M in THF, 10 equiv) was added. The reaction was heated to 60 °C for 16 h. The reaction was quenched with satd aq NH₄Cl. The aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (0–40% EtOAc/hexanes) afforded the diol–diene product.

(±)-(E)-4-(tert-Butyl)-2-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)phenol (8a). Prepared from SEM-protected diol–diene A4a as a red-orange tinged oil (1.43g, 85%). **IR** (ATR): 3372, 3076, 2963, 2866, 1539, 1462, 1439, 1392, 1363, 1241, 1178, 1124, 1098, 997, 911, 825, 736, 347. **1H-NMR** (600 MHz, CDCl₃) δ 7.86 (s, OH), 7.19 (dd, J = 8.5, 2.5 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 5.82 (ddt, J = 16.6, 10.2, 6.2 Hz, 1H), 5.62 (t, J = 6.7 Hz, 1H), 5.53 (d, J = 2.9 Hz, 1H), 5.08–4.89 (m, 2H), 2.32 (d, J = 2.9 Hz, OH), 2.25–2.09 (m, 4H), 1.64 (d, J = 1.3 Hz, 3H), 1.26 (s, 9H). **13C-NMR** (151 MHz, CDCl₃) δ 153.6, 142.2, 138.0, 136.3, 127.6, 125.8, 124.8, 123.6, 116.6, 115.0, 81.3, 34.0, 33.4, 31.5, 27.0, 12.3. **HRMS** (ESI) m/z calcld for C₁₈H₂₅O₂ [M-H]⁻ 273.1855; found 273.1861.
(±)-(E)-2-(1-Hydroxy-2-methylhepta-2,6-dien-1-yl)phenol (8b). Prepared from SEM-protected diol–diene A4b as a red-orange tinged oil (0.198 g, 88%). IR (ATR): 3345, 3077, 2977, 2920, 2859, 2364, 2250, 1640, 1618, 1587, 1489, 1456, 1396, 1315, 1240, 1173, 1152, 1097, 995, 911, 851, 753, 650. ¹H-NMR (600 MHz, CDCl₃) δ 8.19 (s, OH), 7.18 (ddd, J = 8.4, 7.4, 1.7 Hz, 1H), 6.94 (dd, J = 7.7, 1.7 Hz, 1H), 6.87 (dd, J = 8.1, 1.2 Hz, 1H), 6.82 (td, J = 7.4, 1.2 Hz, 1H), 5.82 (ddt, J = 16.6, 10.1, 6.3 Hz, 1H), 5.66 – 5.55 (m, 1H), 5.36 (d, J = 2.8 Hz, 1H), 5.10 – 4.92 (m, 2H), 2.38 (d, J = 2.9 Hz, OH), 2.23 – 2.09 (m, 4H), 1.64 (d, J = 1.2 Hz, 3H). ¹³C-NMR (151 MHz, CDCl₃) δ 156.0, 138.0, 136.1, 129.0, 128.0, 128.0, 124.2, 119.5, 117.2, 115.0, 81.3, 33.4, 27.0, 12.1. HRMS (ESI) m/z calcd for C₁₄H₁₈O₂ [M-H]⁻ 217.1229; found 217.1233.

(–)-(S,E)-4-(tert-Butyl)-2-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)phenol [(–)-8b]. Prepared from enantioenriched SEM-protected diol–diene (–)-A4b as a red-orange tinged oil (84 mg, 99%). The enantiomeric excess was determined to be 94% by chiral HPLC analysis (tᵣ = 7.48 min, CHIRACEL OD-H 4.6 mm x 150 mm column, 95:5 hexanes/isopropanol isocratic, 1 mL/min) in comparison to racemic (±)-12b. [α]₁⁷D –72.0 (c 0.1, CH₂Cl₂). All other analytical data matched that of (±)-8b.

(+)-(R,E)-4-(tert-Butyl)-2-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)phenol [(+)-8b]. Prepared from enantioenriched SEM-protected diol–diene (+)-A4b as a red-orange tinged oil (108 mg, 96%). The enantiomeric excess was determined to be 94% as above (tᵣ = 5.86 min). [α]₁⁷D +67.8 (c 0.1, CH₂Cl₂). All other analytical data matched that of (±)-8b.
(±)-(E)-4-Fluoro-2-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)phenol (8c).
Prepared from SEM-protected diol–diene A4c as a red-orange tinged oil (0.081 g, 63%).
IR (ATR): 3349, 3079, 2980, 2921, 2362, 2343, 2250, 1642, 1602, 1497, 1442, 1384, 1248, 1189, 1141, 1088, 1001, 914, 863, 821, 773, 738, 672, 651, 620. \(^1\)H-NMR (600 MHz, CDCl₃) \(\delta\) 7.98 (s, OH), 6.86 (td, \(J = 8.4, 3.1\) Hz, 1H), 6.79 (dd, \(J = 8.9, 4.8\) Hz, 1H), 6.66 (dd, \(J = 9.2, 3.1\) Hz, 1H), 5.87 – 5.73 (m, 1H), 5.64 – 5.57 (m, 1H), 5.32 (d, \(J = 2.8\) Hz, 1H), 5.12 – 4.92 (m, 2H), 2.35 (d, \(J = 2.8\) Hz, OH), 2.25 – 2.11 (m, 4H), 1.63 (d, \(J = 1.3\) Hz, 3H). \(^13\)C-NMR (151 MHz, CDCl₃) \(\delta\) 156.2 (d, \(J = 236.9\) Hz), 151.9, 137.9, 135.8, 128.9, 125.2 (d, \(J = 6.4\) Hz), 118.1 (d, \(J = 7.9\) Hz), 115.3 (d, \(J = 22.9\) Hz), 115.2, 114.1 (d, \(J = 23.9\) Hz), 80.8, 33.3, 27.0, 11.9. HRMS (ESI) m/z calcld for C₁₄H₁₆O₂F [M-H]⁻ 235.1134; found 235.1141.

(±)-(E)-2-(1-Hydroxy-2-methylhepta-2,6-dien-1-yl)-4-(trifluoromethyl)phenol (8d).
Prepared from SEM-protected diol–diene A4d as a red-orange tinged oil (0.33 g, 98%).
IR (ATR): 3315, 3081, 2980, 2923, 2865, 1619, 1603, 1506, 1443, 1385, 1328, 1282, 1252, 1159, 1117, 1077, 996, 912, 861, 831, 759, 737, 684, 649, 625. \(^1\)H-NMR (600 MHz, CDCl₃) \(\delta\) 8.73 (s, OH), 7.42 (dd, \(J = 8.6, 2.3\) Hz, 1H), 7.17 (d, \(J = 2.3\) Hz, 1H), 6.96 – 6.88 (m, 1H), 5.80 (ddt, \(J = 16.6, 10.1, 6.3\) Hz, 1H), 5.64 (ddd, \(J = 7.0, 3.9, 1.4\) Hz, 1H), 5.41 (d, \(J = 2.6\) Hz, 1H), 5.10 – 4.91 (m, 2H), 2.41 (d, \(J = 2.7\) Hz, OH), 2.24 – 2.11 (m, 4H), 1.63 (d, \(J = 1.3\) Hz, 3H). \(^13\)C-NMR (151 MHz, CDCl₃) \(\delta\) 159.0, 137.7, 135.7, 129.4, 126.2 (q, \(J = 3.0\) Hz), 125.3 (q, \(J = 3.0\) Hz), 124.2, 123.5, 121.8 (q, \(J = 33.2\) Hz), 117.7, 115.3, 81.5, 33.3, 27.0, 11.8. HRMS (ESI) m/z calcld for C₁₅H₁₆O₂F₃ [M-H]⁻ 285.1102; found 285.1109.

(±)-tert-Butyl (E)-(4-hydroxy-3-(1-hydroxy-2-methylhepta-2,6-dien-1-yl)phenyl)carbamate (8e).
Prepared from SEM-protected diol–diene A4e, but with purification by silica flash chromatography (0–80% EtOAc/hexanes), as a clear yellow tinged oil (0.23 g, 38%).
IR (ATR): 3325, 2979, 2925, 2250, 1695, 164, 1534, 1505, 1435, 1392, 1368, 1239, 1162, 1105, 1059, 1031, 911, 814, 737, 649, 610. \(^1\)H-NMR (600 MHz, CDCl₃) \(\delta\) 7.94 (s, OH), 7.14 – 7.03 (m, 1H), 6.98 (s, 1H), 6.78 (d, \(J = 8.6\) Hz, 1H), 6.28 (s, 1H), 5.87 – 5.73 (m, 1H), 5.64 – 5.52 (m, 1H), 5.32 (d, \(J = 2.8\) Hz, 1H), 4.95 – 4.77 (m, 2H), 2.15 (d, \(J = 2.8\) Hz, OH), 2.06 – 1.95 (m, 4H), 1.63 (d, \(J = 1.7\) Hz, 3H). HRMS (ESI) m/z calcld for C₁₆H₁₇O₂N₂ [M-H]⁻ 295.1304; found 295.1300.
5.26 (s, 1H), 5.08 – 4.95 (m, 2H), 2.65 (app s, OH), 2.22 – 2.09 (m, 4H), 1.62 (d, J = 1.3 Hz, 3H), 1.49 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 153.2, 152.0, 138.1, 136.1, 130.2, 127.8, 120.4, 119.3, 117.5, 115.0, 80.8, 80.2, 33.4, 28.4, 27.0, 12.3. **HRMS** (ESI) m/z calcd for C$_{19}$H$_{27}$NO$_4$Na ([M+Na]$^+$) 356.1838; found 356.1830.

**HO**

![8f](image)

(±)-(E)-2-(1-Hydroxy-2-methylhepta-2,6-dien-1-yl)-4-methoxyphenol (8f). Prepared from SEM-protected diol–diene A4f as a red-orange tinged oil (0.081 g, 63%). **IR** (ATR): 3346, 3076, 2921, 2836, 1640, 1499, 1434, 1381, 1242, 1206, 1149, 1045, 912, 866, 818, 737, 648. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.65 (s, OH), 6.80 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.8, 3.0 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 5.82 (ddd, J = 16.9, 10.3, 6.3 Hz, 1H), 5.62 (tt, J = 7.0, 1.2 Hz, 1H), 5.31 (d, J = 2.8 Hz, 1H), 5.12 – 4.92 (m, 2H), 3.73 (s, 3H), 2.31 (d, J = 2.9 Hz, OH), 2.22 – 2.12 (m, 4H), 1.64 (m, 3H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 152.7, 149.8, 138.0, 136.1, 128.1, 125.1, 117.7, 115.1, 114.0, 113.5, 80.9, 55.7, 33.4, 27.0, 12.2. **HRMS** (ESI) m/z calcd for C$_{15}$H$_{19}$O$_3$ [M-H]$^-$ 247.1334; found 247.1331.

![MeO](image)

(±)-(E)-2-(1-Hydroxy-2-methylhepta-2,6-dien-1-yl)-3,5-dimethoxyphenol (S19). Prepared from SEM-protected diol–diene S13, but with purification by silica flash chromatography (0–60% EtOAc/hexanes), as a yellow tinged oil (0.47g, 73%). **IR** (ATR): 3318, 3076, 2938, 2841, 2360, 1626, 1594, 1508, 1457, 1439, 1364, 1212, 1147, 1101, 1053, 987, 911, 817, 735, 684, 637. $^1$H-NMR (600 MHz, CDCl$_3$) δ 8.44 (s, OH), 6.07 (d, J = 2.4 Hz, 1H), 6.00 (d, J = 2.4 Hz, 1H), 5.79 (dd, J = 16.9, 10.4 Hz, 1H), 5.65 (d, J = 2.3 Hz, 1H), 5.58 – 5.46 (m, 1H), 5.10 – 4.89 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.26 (d, J = 2.7 Hz, OH), 2.12 (m, 4H), 1.64 (d, J = 1.3 Hz, 3H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 160.7, 157.8, 138.2, 135.7, 126.1, 114.7, 105.9, 94.2, 90.8, 74.5, 55.5, 55.2, 33.5, 27.1, 12.6. **HRMS** (ESI) m/z calcd for C$_{16}$H$_{22}$O$_4$Na [M+Na]$^+$ 301.1416; found 301.1424.
2. Synthesis of Diol–1,5-Diene Substrates with Terminal Olefin Substituents (S20, S21)

Figure S15. SEM deprotection to afford diol–1,5-diene substrates with terminal olefin substituents (S20, S21) for the cascade reaction.

Diol–dienes S20 and S21 were synthesized using the general procedure above.

(±)-4-(tert-Butyl)-2-((2E,6E)-1-hydroxy-2-methyl-7-phenylhepta-2,6-dien-1-yl)phenol (S20).
Prepared from SEM-protected diol–diene S17 as a clear oil (40 mg, 77%). IR (ATR): 3340, 2972, 2360, 2341, 1706, 1610, 1520, 1450, 1390, 1375, 1279, 1247, 1163, 1143, 1104, 1052, 985, 966, 911, 856, 826, 781, 759, 738, 694, 676, 666, 648, 621. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.82 (s, OH), 7.33 – 7.26 (m, 4H), 7.23 – 7.16 (m, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.8, 6.6 Hz, 1H), 5.74 – 5.62 (m, 1H), 5.39 – 5.25 (m, 1H), 2.37 – 2.22 (m, 5H), 1.66 (app m, 3H), 1.25 (s, 9H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 153.5, 142.2, 137.6, 136.5, 130.4, 129.9, 128.5, 127.2, 126.9, 125.9, 124.8, 123.6, 116.7, 81.3, 34.0, 32.8, 31.5, 27.5, 12.4. HRMS (ESI) m/z calcd for C$_{24}$H$_{30}$O$_2$Na ([M+Na]$^+$) 373.2144; found 373.2147.

(±)-4-(tert-Butyl)-2-((2E,6E)-1-hydroxy-2,8,8-trimethylnona-2,6-dien-1-yl)phenol (S21).
Prepared from SEM-protected diol–diene S18 as a clear oil (98 mg, 91%). IR (ATR): 3377, 2956, 2927, 2866, 2362, 2341, 1720, 1502, 145, 1376, 1298, 1245, 1164, 1144, 1104, 1052, 973, 911, 857, 828, 759, 739, 708, 670, 646, 631, 620, 610. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.84 (s, OH), 7.19 (dd, J = 8.5, 2.4 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.54 – 5.60 (m, 1H), 5.49 – 5.43 (m, 1H), 5.38 – 5.27 (m, 3H), 2.27 (d, J = 2.8 Hz, OH), 2.14 (dt, J = 7.7, 4.6 Hz, 2H), 2.11 – 2.03 (m, 2H), 1.63 (d, J = 1.3 Hz, 3H), 1.26 (s, 9H), 0.97 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 153.5, 142.2, 136.0, 127.8, 125.8, 124.8, 123.7, 123.6, 116.6,
81.4, 34.0, 32.8, 32.4, 31.5, 29.7, 28.0, 12.4. **HRMS (ESI) m/z calcd for C_{22}H_{33}O_{2} ([M-H]^{-}) 329.2481; found 329.2470.**

3. **Synthesis of Diol–1,4-Diene Substrates with Aryl Substituents (18a–d)**

![Figure S16. SEM deprotection to afford diol–1,4-diene substrates (18a–d) for the cascade reaction.](image)

Diol–dienes 18a–d were synthesized using the general procedure above.

(±)-(E)-4-(tert-Butyl)-2-(1-hydroxy-2-methylhexa-2,5-dien-1-yl)phenol (18a). Prepared from SEM-protected diol–diene S14a as a clear oil (120 mg, 71%). **IR** (ATR): 3339, 2965, 2899, 2878, 2360, 2339, 1725, 1591, 1502, 1462, 1365, 1235, 1124, 1095, 995, 913, 823, 765, 742. **^1H-NMR** (600 MHz, CDCl₃) δ 7.86 (s, 1H), 7.22 (dd, J = 8.5, 2.5 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 5.86 (ddt, J = 16.5, 10.1, 6.1 Hz, 1H), 5.69 (t, J = 7.4 Hz, 1H), 5.39 (d, J = 2.9 Hz, 1H), 5.20 – 4.93 (m, 2H), 2.94 – 2.79 (m, 2H), 2.37 (d, J = 3.0 Hz, 1H), 1.75 – 1.65 (m, 3H), 1.29 (s, 9H). **^13C-NMR** (151 MHz, CDCl₃) δ 153.6, 142.3, 137.1, 136.1, 125.9, 125.1, 124.9, 123.5, 116.7, 115.1, 81.2, 34.0, 31.8, 31.5, 12.3. **HRMS (ESI) m/z calcd for C_{17}H_{23}O_{2} ([M-H]^{-}) 259.1698; found 259.1705.**

(±)-(E)-2-(1-Hydroxy-2-methylhexa-2,5-dien-1-yl)phenol (18b). Prepared from SEM-protected diol–diene S14b as a clear oil (93 mg, 37%). **IR** (ATR): 3342, 2072, 2976, 2916, 1735, 1633, 1488, 1485, 1454, 1370, 1236, 1099, 1039, 1000, 906, 751. **^1H-NMR** (600 MHz, CDCl₃) δ 8.10 (s, 1H), 7.18 (ddd, J = 8.6, 7.4, 1.7 Hz, 1H), 6.94 (dd, J = 7.7, 1.7 Hz, 1H), 6.87 (dd, J = 8.2, 1.2 Hz, 1H), 6.85 – 6.79 (m, 1H), 5.82 (ddt, J = 17.1, 10.1, 6.2 Hz, 1H), 5.65 (dtt, J = 8.6, 7.3, 1.3 Hz, 1H), 5.38 (d, J = 2.8 Hz, 1H), 5.19 – 4.91 (m, 2H), 2.95 – 2.67 (m, 2H), 2.36 (d, J = 2.9 Hz, 1H), 1.65 (d, J = 1.2 Hz, 3H). **^13C-NMR** (151 MHz, CDCl₃) δ 156.0, 137.0,
136.0, 129.0, 128.0, 125.5, 124.2, 119.6, 117.3, 115.2, 81.2, 31.9, 12.2. **HRMS (ESI) m/z calcd for C_{13}H_{15}O_2 ([M-H]^-) 203.1072; found 203.1072.**

(±)-(E)-2-(1-Hydroxy-2-methylhexa-2,5-dien-1-yl)-4-(trifluoromethyl)phenol (18c). Prepared from SEM-protected diol–diene S_{14c} as a yellow oil (270 mg, 75%). **IR (ATR):** 3309, 3074, 2980, 2916, 1603, 1506, 1442, 1329, 1283, 1252, 1160, 1117, 1077, 995, 913, 832, 781, 762, 736, 685, 649, 625, 606. **^1H-NMR (600 MHz, CDCl₃) δ 8.72 (s, 1H), 7.45 (dd, J = 8.5, 2.3 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 5.85 (ddt, J = 16.5, 10.2, 6.2 Hz, 1H), 5.70 (ddt, J = 7.3, 6.1, 1.2 Hz, 1H), 5.51 – 5.40 (m, 1H), 5.16 – 4.98 (m, 2H), 2.89 (t, J = 6.9 Hz, 2H), 2.54 (d, J = 2.7 Hz, 1H), 1.68 (d, J = 1.4 Hz, 3H). **^13C-NMR (151 MHz, CDCl₃) δ 159.0, 136.4, 135.7, 126.9, 126.3 (q, J = 3.8 Hz), 125.3 (q, J = 3.9 Hz), 125.2, 124.2, 123.5, 121.9 (q, J = 32.7 Hz), 117.7, 115.4, 81.3, 31.9, 11.8. **HRMS (ESI) m/z calcd for C_{14}H_{14}O_2F₃ ([M-H]^-) 271.0946; found 271.0950.**

(±)-(E)-2-(1-Hydroxy-2-methylhexa-2,5-dien-1-yl)-4-methoxyphenol (18d). Prepared from SEM-protected diol–diene S_{14d} as a yellow oil (290 mg, 90%). **IR (ATR):** 3353, 3077, 2916, 2834, 2361, 2341, 1710, 1638, 1548, 1497, 1464, 1431, 1380, 1270, 1240, 1204, 1149, 116, 1039, 913, 872, 816, 754, 710, 650, 618, 610. **^1H-NMR (600 MHz, CDCl₃) δ 7.71 – 7.58 (m, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 3.1 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 5.85 (ddt, J = 17.2, 10.1, 6.2 Hz, 1H), 5.68 (tt, J = 7.2, 1.4 Hz, 1H), 5.36 (d, J = 2.7 Hz, 1H), 5.18 – 4.96 (m, 2H), 3.76 (s, 3H), 3.00 – 2.75 (m, 2H), 2.47 – 2.30 (m, 1H), 1.69 (d, J = 1.3 Hz, 3H). **^13C-NMR (151 MHz, CDCl₃) δ 152.7, 149.8, 136.9, 136.0, 125.7, 125.0, 117.8, 115.2, 114.1, 113.5, 80.9, 55.8, 31.9, 12.2. **HRMS (ESI) m/z calcd for C_{14}H_{17}O₃ ([M-H]^-) 233.1178; found 233.1181.**

4. Synthesis of Diol–1,6-Diene Substrate (20)

![Figure S17. SEM deprotection to afford diol–1,6-diene substrate (20) for the cascade reaction.](image)
(±)-(E)-4-(tert-Butyl)-2-(1-hydroxy-2-methylocta-2,7-dien-1-yl)phenol (20). Prepared from SEM-protected diol–diene S15 according to the general procedure above as a orange tinged oil (240 mg, 86%).

IR (ATR): 3326, 2963, 2361, 164, 1594, 1498, 1462, 1363, 1239, 1125, 995, 912, 825, 738, 629, 606. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 1.2$ Hz, 1H), 7.12 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 6.73 (dd, $J = 8.5, 0.8$ Hz, 1H), 5.73 (ddt, $J = 17.0, 10.2, 6.7$ Hz, 1H), 5.55 (tt, $J = 7.2, 1.3$ Hz, 1H), 5.26 (d, $J = 2.8$ Hz, 1H), 5.04 – 4.80 (m, 2H), 2.27 (dd, $J = 2.9, 1.0$ Hz, 1H), 2.11 – 1.92 (m, 4H), 1.56 (d, $J = 1.2$ Hz, 3H), 1.48 – 1.39 (m, 2H), 1.19 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 153.60, 142.20, 138.57, 136.09, 128.18, 125.81, 124.82, 123.60, 116.64, 114.70, 81.42, 33.99, 33.31, 31.52, 28.56, 27.05, 12.30. HRMS (ESI) m/z calcd for C$_{19}$H$_{27}$O ([M-H$_2$O]$^+$) 271.2062; found 271.2051.
I. INSTALLATION OF R² BRIDGEHEAD SUBSTITUENTS (S23, S24)

Figure S18. Synthesis of tertiary alcohol substrates (S23, S24) by oxidation–addition of diol–diene 12a.

(E)-1-(5-(tert-Butyl)-2-hydroxyphenyl)-2-methylhepta-2,6-dien-1-one (S22). In a 50-mL roundbottom flask, diol–diene 8a (520 mg, 1.9 mmol, 1 equiv) was dissolved in Et₂O (19 mL, 0.1 M substrate concentration). MnO₂ (9.88 g, 113.6 mmol, 60 equiv) was added as a single portion. The reaction was stirred at rt until complete as judged by TLC analysis. The mixture was filtered through Celite. The filtrate was concentrated by rotary evaporation to afford the crude ketone S22 as a yellow oil (0.36 g, 1.33 mmol, 70% crude yield), which was used without further purification. A sample of the crude material was purified by silica flash chromatography (10% hexanes/EtOAc) to afford ketone S22 as a yellow oil for characterization purposes.

IR (ATR): 3698, 3285, 3080, 2965, 2910, 2872, 2361, 2344, 2256, 1629, 1595, 1486, 1467, 1446, 1396, 1367, 1336, 1298, 1266, 1251, 1233, 1198, 1165, 1134, 1107, 1017, 914, 836, 822, 791, 738, 658, 627. ¹H-NMR (600 MHz, CDCl₃) δ 11.64 (s, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.51 (dd, J = 8.7, 2.5 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 6.18 – 5.99 (m, 1H), 5.96 – 5.74 (m, 1H), 5.17 – 4.85 (m, 2H), 2.40 (q, J = 7.3 Hz, 2H), 2.29 – 2.22 (m, 2H), 2.00 (s, 3H), 1.29 (s, 9H).

¹³C-NMR (151 MHz, CDCl₃) δ 203.6, 160.5, 141.3, 140.8, 137.3, 135.3, 133.2, 129.0, 118.2, 117.7, 115.6, 34.1, 32.6, 31.3, 28.0, 13.6. HRMS (ESI) m/z calcd for C₁₉H₂₃O₂ ([M-H]) 271.1698; found 271.1707

(±)-(E)-4-(tert-Butyl)-2-(2-hydroxy-3-methyl-octa-3,7-dien-2-yl)phenol (S23). In a 15-mL roundbottom flask, ketone S22 (156 mg, 0.57 mmol, 1 equiv) was azeotroped using toluene (3x5 mL), then dissolved in THF (5.7 mL, 0.1 M substrate concentration) and cooled to 0 °C. MeMgCl (3 M in THF, 763 uL, 2.29 mmol, 4 equiv) was added and the reaction was allowed to warm slowly to rt. The reaction was quenched with satd aq NH₄Cl. The aq layer was separated
and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered and concentrated using rotary evaporation. Purification by silica flash chromatography (0–40% EtOAc/hexanes) afforded the diene–diol **S23** as a yellow oil (89 mg, 54%).

**IR** (ATR): 3327, 3077, 2964, 2870, 2363, 2251, 1820, 1684, 1639, 1594, 1498, 1462, 1372, 1242, 1170, 1121, 1102, 1048, 994, 911, 825, 780, 737, 669, 648, 609. **¹H-NMR** (600 MHz, CDCl₃) δ 8.47 (s, O₇H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.84 (ddt, J = 16.7, 10.2, 6.2 Hz, 1H), 5.73 – 5.62 (m, 1H), 5.11 – 4.92 (m, 2H), 2.27 (s, O₈H), 2.24 – 2.11 (m, 4H), 1.74 (s, 3H), 1.59 (s, 3H), 1.25 (s, 9H).

**¹³C-NMR** (151 MHz, CDCl₃) δ 153.6, 141.8, 138.6, 138.1, 127.4, 125.6, 125.2, 123.8, 116.8, 114.9, 81.3, 34.0, 33.5, 31.5, 28.6, 27.3, 13.3. **HRMS** (ESI) m/z calcd for C₁₉H₂₈O₂Na ([M+Na]+) 311.1987; found 311.1982.

(±)-(E)-4-(tert-Butyl)-2-(1-hydroxy-2-methyl-1-phenylhepta-2,6-dien-1-yl)phenol (**S24**). In a 15-mL roundbottom flask, ketone **S22** (156 mg, 0.57 mmol, 1 equiv) was azeotroped using toluene (3 x 5 mL), then dissolved in THF (5.7 mL, 0.1 M substrate concentration) and cooled to -78 °C. PhLi (1.9 M in dibutyl ether, 1.544 mL, 2.93 mmol, 2.5 equiv) was added and the reaction stirred until completion as judged by TLC analysis. The reaction was quenched with satd aq NH₄Cl. The aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated using rotary evaporation. Purification by silica flash chromatography (0–40% EtOAc/hexanes with 1% Et₃N) afforded the diol–diene **S24** as a yellow oil (264 mg, 64%).

**IR** (ATR): 3365, 3061, 3028, 2960, 2869, 2250, 1640, 1593, 1495, 1462, 1446, 1413, 1379, 1363, 1240, 1164, 1124, 1099, 997, 910, 823, 756, 736, 701, 672. **¹H-NMR** (500 MHz, CDCl₃) δ 7.94 (s, O₇H), 7.37 – 7.11 (m, 5H), 6.98 – 6.68 (m, 3H), 5.78 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.15 (td, J = 7.1, 1.3 Hz, 1H), 5.06 – 4.91 (m, 2H), 3.13 (s, O₈H), 2.20 (p, J = 7.4 Hz, 2H), 2.14 – 2.04 (m, 2H), 1.73 (d, J = 1.2 Hz, 3H), 1.18 (s, 9H). **¹³C-NMR** (151 MHz, CDCl₃) δ 153.9, 143.4, 141.4, 138.0, 137.1, 130.2, 129.0, 128.2, 128.0, 127.7, 127.6, 126.7, 125.9, 125.3, 116.8, 115.0, 86.5, 33.9, 33.4, 31.4, 27.6, 14.4. **HRMS** (ESI) m/z calcd for C₂₄H₂₉O₂ [M-H]- 349.2168; found 349.2156.
**J. Pd-Catalyzed Cascade Reactions (9a–f, 13, 14a–b, 15a–b) and Further Functionalization (16–17)**

1. **Synthesis of 5,6-Bicycles with Aryl Substituents (9a–f, 13)**

![Figure S19. Cascade reactions of diol–1,5-diene substrates (8a–f, S19) to form fused bicyclic ethers (9a–f, 13). CPME = Cyclopentyl methyl ether.](image)

**General Procedure for Cascade Reaction**

In a 2-dram vial fitted with a PTFE-lined screw cap and stir bar was placed the diol–diene substrate (1 equiv). In a second 2-dram vial fitted with a PTFE-lined screw cap and stir bar benzoquinone (3 equiv), PyrOx ligand 12 (12 mol%) prepared as previously described,\(^{15}\) Pd(OTs)\(_2\)(MeCN)\(_2\) (9 mol%) prepared as previously described,\(^{16}\) Ca(OH)\(_2\) (1 equiv) and 3 Å MS (300 mg/mmol) were suspended in cyclopentyl methyl ether (0.1 M substrate concentration) and stirred for 10 min. The suspension was then transferred via pipette to the substrate vial. The mixture was heated to 80 °C for 16 h, then cooled to rt, diluted with MeOH, and filtered through Celite, eluting with MeOH. The filtrate was concentrated by rotary evaporation. The diastereomeric ratio at the vinyl substituent was determined by \(^1\)H-NMR analysis of the crude product. Purification by silica flash chromatography (dry load on Celite, 0–20% EtOAc/hexanes) afforded the bicyclization product.

\[(±)-(2S,4aS,9bS)-8-(tert-Butyl)-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]-benzofuran (\(\alpha\)-9a).\]

Prepared from diol–diene 8a as a clear oil (23 mg, 60%, average of two trials). A 4:1 mixture of diastereomers was observed by \(^1\)H-NMR analysis of the crude product. The major diastereomer \(\alpha\)-9a was isolated by silica flash chromatography and characterized.

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The minor diastereomer β-9a and side products 10 and 11, observed during reaction optimization, were also isolated by preparative TLC for characterization purposes below.

**Major Diastereomer (2S = α):** IR (ATR): 2961, 2872, 1729, 1620, 1489, 1464, 1364, 1265, 1239, 1185, 1108, 1084, 1066, 1000, 921, 898, 835, 796, 739, 702, 630. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.46 (d, $J = 2.2$ Hz, 1H), 7.27 (dd, $J = 8.4$, 2.2 Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 5.84 (ddd, $J = 17.1, 10.5, 6.3$ Hz, 1H), 5.23 (dt, $J = 17.3, 1.4$ Hz, 1H), 5.09 (dd, $J = 10.5, 0.6$ Hz, 1H), 4.59 (s, 1H), 3.92 (dddd, $J = 9.1, 7.7, 4.1, 2.4$ Hz, 1H), 2.33 (dt, $J = 14.6, 4.4$ Hz, 1H), 1.88 (ddd, $J = 14.6, 10.7, 5.9$ Hz, 1H), 1.71 – 1.63 (m, 2H), 1.30 (s, 9H), 1.23 (s, 3H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 157.5, 143.5, 138.8, 128.0, 127.4, 123.2, 115.7, 110.0, 84.3, 81.5, 75.3, 34.4, 31.7, 31.3, 26.8, 25.1. HRMS (ESI) m/z calcd for C$_{18}$H$_{25}$O$_2$ ([M+H]$^+$) 273.1855; found 273.1842.

![β-9a](image)

**Minor Diastereomer (2R = β):** (±)-(2R,4aS,9bS)-8-(tert-Butyl)-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyano[3,2-b]benzofuran (β-9a). IR (ATR): 2960, 2869, 2360, 2340, 1670, 1619, 1490, 1462, 1364, 1267, 1180, 1083, 166, 920, 834. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.38 (d, $J = 2.0$ Hz, 1H), 7.27 (dd, $J = 8.3$, 2.1 Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 5.89 (ddd, $J = 17.2, 10.5, 5.4$ Hz, 1H), 5.28 – 5.09 (m, 2H), 5.00 (s, 1H), 3.97 (dt, $J = 7.6$, 6.0 Hz, 1H), 2.06 – 1.80 (m, 3H), 1.53 – 1.46 (m, 1H), 1.43 (s, 3H), 1.30 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 157.4, 143.8, 138.9, 127.3, 125.3, 122.9, 115.1, 110.0, 84.3, 81.5, 75.3, 34.4, 31.7, 31.3, 26.8, 25.1. HRMS (ESI) m/z calcd for C$_{18}$H$_{25}$O$_2$ ([M+H]$^+$) 273.1855; found 273.1852.

![Minor Diastereomer](image)

**Side Product:** 2-(But-3-en-1-yl)-6-(tert-butyl)-3-methyl-2H-chromene (10). IR (ATR): 2960, 2929, 2870, 2359, 1733, 1641, 1496, 1462, 1363, 1272, 1238, 1207, 1160, 1124, 994, 914, 891, 821. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.07 (dd, $J = 8.4$, 2.5 Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.71 (dd, $J = 8.4$, 0.7 Hz, 1H), 6.21 – 6.10 (m, 1H), 5.90 – 5.71 (m, 1H), 5.13 – 4.86 (m, 2H), 4.62 (dd, $J = 9.6$, 2.8 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.25 – 2.16 (m, 1H), 1.88 – 1.78 (m, 4H), 1.60 (ddd, $J = 17.2, 9.8, 6.3$, 2.9 Hz, 1H), 1.28 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 148.9, 143.6, 138.1, 134.1, 124.9, 122.5, 122.0, 119.7, 115.1, 114.9, 78.0, 34.0, 31.5, 31.5, 29.5, 19.7. HRMS (ESI) m/z calcd for C$_{18}$H$_{22}$O ([M-H]$^-)$ 255.1749; found 255.1761.

![Side Product](image)
Side Product: (E)-1-(5-(tert-Butyl)-2-hydroxyphenyl)-2-methylhepta-2,6-dien-1-one (11). IR (ATR): 3698, 3285, 3080, 2965, 2927, 2361, 2344, 2256, 1629, 1595, 1486, 1467, 1446, 1396, 1367, 1336, 1298, 1266, 1251, 1233, 1198, 1165, 1134, 1107, 1017, 914, 836, 822, 791, 738, 658, 627. $^1$H-NMR (600 MHz, CDCl$_3$) δ 11.64 (s, 1H), 7.63 (d, $J = 2.5$ Hz, 1H), 7.51 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.18 – 5.99 (m, 1H), 5.96 – 5.74 (m, 1H), 5.17 – 4.85 (m, 2H), 2.40 (q, $J = 7.3$ Hz, 2H), 2.29 – 2.22 (m, 2H), 2.00 (s, 3H), 1.29 (s, 9H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) δ 203.6, 160.5, 141.3, 140.8, 137.3, 135.3, 133.2, 129.0, 118.2, 117.7, 115.6, 34.1, 32.6, 31.3, 28.0, 13.6. HRMS (ESI) m/z calcd for C$_{18}$H$_{23}$O$_2$ ([M-H]$^-$) 271.1698; found 271.1707.

(±)-(2S,4aS,9bS)-4a-Methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran (9b). Prepared from diol–diene 8b as a clear oil (19 mg, 52%, average of two trials. A 5:1 mixture of diastereomers was observed by $^1$H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a) was isolated and characterized. IR (ATR): 3079, 3051, 3036, 315, 297, 2928, 288, 2846, 2378, 2641, 192, 1857, 1714, 1644, 1614, 1599, 1475, 1464, 1428, 1409, 1375, 1345, 1324, 1315, 1295, 1270, 1238, 1182, 115, 195, 1065, 1012, 998, 988, 921, 904, 875, 854, 840, 812, 789, 750, 675, 642, 616. $^1$H-NMR (600 MHz, CDCl$_3$) δ 7.51 – 7.38 (m, 1H), 7.24 (td, $J = 7.7, 1.4$ Hz, 1H), 6.91 (td, $J = 7.4$, 1.0 Hz, 1H), 6.85 (dd, $J = 8.1$, 0.9 Hz, 1H), 5.82 (ddd, $J = 17.3$, 10.5, 6.2 Hz, 1H), 5.22 (d, $J = 17.3$ Hz, 1H), 3.98 – 3.85 (m, 1H), 2.35 (dt, $J = 14.6$, 4.3 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.72 – 1.59 (m, 2H), 1.23 (s, 3H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 159.8, 138.7, 130.4, 128.6, 126.4, 120.6, 115.6, 110.8, 84.2, 81.0, 75.1, 31.2, 26.8, 24.9. HRMS (ESI) m/z calcd for C$_{14}$H$_{17}$O$_2$ [M+H]$^+$ 217.1229; found 217.1220.
Table S7. Effect of ligand enantiomer and substrate enantiomer on diastereoselectivity of cascade reaction at the vinyl side chain.\(^a\)

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<tr>
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<td>ent-12</td>
<td>(+)-8b</td>
<td>1.00 : 0.26</td>
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<td>3</td>
<td>ent-12</td>
<td>(-)-8b</td>
<td>1.00 : 0.24</td>
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<tr>
<td>4</td>
<td>12</td>
<td>(±)-8b</td>
<td>1.00 : 0.24</td>
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<tr>
<td>5</td>
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<td>12</td>
<td>(-)-8b</td>
<td>1.00 : 0.24</td>
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</tbody>
</table>

\(^a\)dr determined by \(^1\)H-NMR integration of diagnostic bridgehead protons in the crude reaction mixture (major: 4.61 ppm, minor: 5.02 ppm).

(±)-(2S,4aS,9bS)-8-Fluoro-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran (9c). Prepared from diol–diene 8c as a clear oil (17 mg, 40%, average of two trials). A 6:1 mixture of diastereomers was observed by \(^1\)H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a) was isolated and characterized. \(\text{IR (ATR)}: 3080, 2933, 1722, 1644, 1483, 1452, 1377, 1307, 1267, 1236, 1202, 1150, 1109, 1069, 1000, 921, 868, 843, 814, 757, 736, 652, 626. \(^1\)\text{H-NMR (600 MHz, major, CDCl}_3\text{)} \& \text{δ:} 7.13 (dd, \(J = 8.9, 2.8 \text{ Hz, 1H}), 6.93 (td, \(J = 8.9, 2.8 \text{ Hz, 1H}), 6.76 (dd, \(J = 8.7, 4.0 \text{ Hz, 1H}), 5.81 (ddd, \(J = 17.0, 10.5, 6.1 \text{ Hz, 1H}), 5.29 – 5.18 (m, 1H), 5.10 (dt, \(J = 10.5, 1.3 \text{ Hz, 1H}), 4.57 (s, 1H), 3.89 (dt, \(J = 7.2, 5.8 \text{ Hz, 1H}), 2.34 (dt, \(J = 14.7, 4.2 \text{ Hz, 1H}), 1.87 (ddd, \(J = 14.7, 9.3, 7.7 \text{ Hz, 1H}), 1.66 (ddddd, \(J = 7.4, 5.2, 4.1, 1.7 \text{ Hz, 2H}), 1.23 (s, 3H). \(^1\)\text{C-NMR (151 MHz, CDCl}_3\text{)} \& \text{δ:} 157.2 (d, \(J = 237.4 \text{ Hz}), 155.8, 138.4, 129.6 (d, \(J = 8.5 \text{ Hz}), 116.7 (d, \(J = 24.2 \text{ Hz}), 115.81, 113.3 (d, \(J = 24.3 \text{ Hz}), 111.1 (d, \(J = 8.3 \text{ Hz}), 84.9, 80.9, 75.2, 31.2, 26.6, 24.8. \text{HRMS (ESI)} m/z \text{calcd for C}_{14}\text{H}_{16}\text{O}_{2}\text{F} ([M+H]^+) 235.1134; found 235.1142.}

(±)-(2S,4aS,9bS)-4a-Methyl-8-(trifluoromethyl)-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran (9d). Prepared from diol–diene 8d as a clear oil (17 mg, 42%, average of two trials). A 3:1 mixture of diastereomers was observed by \(^1\)H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a) was isolated and characterized. \(\text{IR (ATR)}: 3801, 2975, 2935, 1730, 1626, 1498, 1448, 1379, 1325, 1276, 1245, 1163, 1119, 1071, 1056, 1000, 916, 884, 844, 829, 803, 736, 656. \(^1\)\text{H-NMR (600 MHz, CDCl}_3\text{)} \& \text{δ:} 7.76 – 7.62 (m, 1H), 7.52 (ddd, \(J = 8.5, 2.0, 0.8 \text{ Hz, 1H}), 6.91 (dd, \(J = 8.3, 0.8 \text{ Hz, 1H}), 5.86 – 5.71 (m, 1H),...
5.23 (d, $J = 17.2$ Hz, 1H), 5.11 (d, $J = 10.5$ Hz, 1H), 4.64 (s, 1H), 3.92 (dddd, $J = 9.8$, 4.8, 2.4, 1.2 Hz, 1H), 2.38 (dt, $J = 14.8$, 4.3 Hz, 1H), 1.91 (ddd, $J = 14.8$, 11.2, 5.8 Hz, 1H), 1.72 – 1.61 (m, 2H), 1.25 (s, 3H).  

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 162.4, 138.2, 129.3, 128.2 (q, $J = 3.8$ Hz), 124.0 (q, $J = 3.8$ Hz), 123.0 (q, $J = 32.5$ Hz), 116.0, 111.0, 85.8, 80.2, 75.1, 31.0, 26.5, 24.7.  

HRMS (ESI) $m/z$ calcd for C$_{15}$H$_{14}$O$_2$F$_3$ ([M-H]$^-$) 283.0946; found 283.0959.

(±)-(2S,4aS,9bS)-tert-Butyl-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran-8-yl)carbamate (9e). Prepared from diol–diene 8e as a clear oil (18 mg, 47%, average of two trials). A 3:1 mixture of diastereomers was observed by $^1$H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a above) was isolated and characterized.


$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.52 (s, 1H), 7.12 (dd, $J = 8.6$, 2.4 Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 6.34 (s, 1H), 5.81 (ddd, $J = 16.9$, 10.5, 6.1 Hz, 1H), 5.21 (dt, $J = 17.3$, 1.5 Hz, 1H), 5.08 (dt, $J = 10.5$, 1.3 Hz, 1H), 4.56 (s, 1H), 3.95 – 3.80 (m, 1H), 2.33 (dt, $J = 14.7$, 4.2 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.64 (dd, $J = 8.2$, 4.2 Hz, 2H), 1.50 (s, 9H), 1.21 (s, 3H).  

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 156.0, 153.3, 138.6, 131.2, 129.1, 122.2, 118.4, 115.7, 84.6, 81.1, 75.1, 31.3, 26.7, 24.9.  

HRMS (ESI) $m/z$ calcd for C$_{18}$H$_{25}$O$_2$ ([M+H]$^+$) 273.1855; found 273.1842.

(±)-(2S,4aS,9bS)-8-Methoxy-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran (9f). Prepared from diol–diene 8f as a clear oil (28 mg, 69%, average of two trials). A 4:1 mixture of diastereomers was observed by $^1$H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a above) was isolated and characterized.

IR (ATR): 3076, 2937, 2833, 1645, 1604, 1486, 1436, 1375, 1326, 1310, 1268, 1243, 1217, 1184, 1140, 1109, 1064, 1032, 1016, 999, 919, 842, 810, 736, 680, 654.  

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.01 (d, $J = 2.7$ Hz, 1H), 6.81 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.76 (d, $J = 8.7$ Hz, 1H), 5.83 (ddd, $J = 17.0$, 10.5, 6.3 Hz, 1H), 5.23 (d, $J = 17.3$ Hz, 1H), 5.09 (dt, $J = 10.5$, 1.3 Hz, 1H), 4.57 (s, 1H), 3.90 (ddddd, $J = 10.3$, 6.4, 3.1, 1.2 Hz, 1H), 3.76 (s, 3H), 2.33 (dt, $J = 14.7$, 4.2 Hz, 1H), 1.92 – 1.78 (m, 1H), 1.66 (ttt, $J = 9.4$, 5.3, 4.8, 1.9 Hz, 2H), 1.62 (s, 3H).  

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 154.0, 153.9, 138.6, 129.1, 116.3, 115.7, 111.6, 111.0, 84.2, 81.4, 75.3, 56.0, 31.3, 26.8, 25.0.  

HRMS (ESI) $m/z$ calcd for C$_{15}$H$_{19}$O$_3$ ([M+H]$^+$) 247.1334; found 247.1344.
(±)-(2S,4aS,9bS)-7,9-Dimethoxy-4a-methyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]-benzofuran (13). Prepared from diol–diene S19 as a clear oil (29 mg, 73%, average of two trials). A 3:1 mixture of diastereomers was observed by 1H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a above) was isolated and characterized. IR (ATR): 2932, 2842, 2366, 1714, 1610, 1502, 1464, 1454, 1439, 1428, 1363, 1328, 1306, 1272, 1216, 1199, 1171, 1144, 1091, 1061, 963, 940, 921, 897, 847, 810, 791, 754, 709, 693, 669, 637, 625, 616, 606. 1H-NMR (600 MHz, CDCl3) δ 6.07 (d, J = 1.9 Hz, 1H), 6.02 (d, J = 2.1 Hz, 1H), 5.87 – 5.79 (m, 1H), 5.20 (dt, J = 17.3, 1.5 Hz, 1H), 5.06 (dd, J = 10.6, 1.4 Hz, 1H), 4.72 (s, 1H), 3.96 – 3.86 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.31 (dt, J = 14.6, 4.4 Hz, 1H), 1.86 (dt, J = 14.6, 8.3 Hz, 1H), 1.67 – 1.62 (m, 2H), 1.24 (s, 3H). 13C-NMR (151 MHz, CDCl3) δ 163.2, 162.3, 158.0, 139.0, 115.2, 108.4, 91.7, 89.2, 85.6, 78.7, 74.6, 55.6, 31.3, 26.6, 25.0. HRMS (ESI) m/z calcd for C16H21O4 ([M+H]+) 277.1440; found 277.1452.

2. Synthesis of 5,6-Bicycles with Bridgehead Substituents (14a, 14b)

Figure S20. Cascade reactions of diol–1,5-diene substrates with tertiary alcohols (S23, S24) to form fused bicyclic ethers with bridghead substituents (14a, 14b).

(±)-(2S,4aS,9bS)-8-(tert-Butyl)-4a,9b-dimethyl-2-vinyl-3,4,4a,9b-tetrahydro-2H-pyrano-[3,2-b]benzofuran (14a). Prepared from diol–diene S23 according to the general procedure above as a clear oil (25 mg, 65%, average of two trials). A 3:1 mixture of diastereomers was observed by 1H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a above) was isolated and characterized. IR (ATR): 2962, 2869, 1645, 1616, 1488, 1463, 1444, 1379, 1363, 1312, 1290, 1264, 1246, 1202, 1164, 1117, 114, 1088, 1057, 1022, 1005, 947, 914, 883, 835, 817, 802, 735, 711, 688, 634, 612. 1H-NMR (600 MHz, CDCl3) δ 7.29 (d, J = 2.1 Hz, 1H), 7.27 – 7.19 (m, 1H), 6.76 (d, J = 8.3 Hz, 1H), 5.78 (ddd, J = 17.0, 10.4, 6.3 Hz,
1H), 5.17 (dt, \( J = 17.3, 1.4 \) Hz, 1H), 5.04 (dt, \( J = 10.4, 1.3 \) Hz, 1H), 4.00 – 3.93 (m, 1H), 2.35 – 2.22 (m, 1H), 1.91 – 1.67 (m, 2H), 1.62 (s, 3H), 1.59 – 1.54 (m, 1H), 1.30 (s, 9H), 1.15 (s, 3H). \( ^{13}\)C-NMR (151 MHz, CDCl\(_3\)) \( \delta \) 156.4, 143.3, 139.3, 132.7, 126.8, 120.3, 115.4, 109.8, 87.3, 82.0, 72.1, 34.4, 31.7, 31.0, 27.0, 24.4, 16.3. HRMS (ESI) \( m/z \) calcd for \( \text{C}_{19}\text{H}_{27}\text{O}_2 \) ([M+H]+) 287.2011; found 287.2022.

(\pm\)-(2S,4aS,9bS)-8-(tert-Butyl)-4a-methyl-9b-phenyl-2-vinyl-3,4,4a,9b-tetrahydro-2\( H \)-pyrano[3,2-\( b \)]benzofuran (14b). Prepared from diol–diene S24 according to the general procedure above, except that the reaction time was 48 h rather than 16 h, as a clear oil (25 mg, 49%, average of two trials). A 19:1 mixture of diastereomers was observed by \(^1\)H-NMR analysis of the crude product. The major diastereomer (assigned by analogy to 9a) was isolated and characterized. IR (ATR): 3060, 323, 2960, 2869, 2372, 2349, 2339, 2321, 2246, 1728, 1630, 1614, 1490, 1448, 1393, 1376, 1363, 1336, 1307, 1270, 1244, 1203, 1174, 1158, 1122, 1089, 1075, 1058, 1032, 991, 970, 909, 890, 839, 818, 758, 735, 709, 672, 651, 621, 609. \( ^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.35 – 7.20 (m, 6H), 7.10 (d, \( J = 2.2 \) Hz, 1H), 6.75 (d, \( J = 8.5 \) Hz, 1H), 5.60 (ddd, \( J = 17.1, 10.4, 6.7 \) Hz, 1H), 5.07 (d, \( J = 17.3 \) Hz, 1H), 4.89 (d, \( J = 10.4 \) Hz, 1H), 4.69 – 4.33 (m, 1H), 2.12 (dt, \( J = 13.7, 4.1 \) Hz, 1H), 1.96 – 1.84 (m, 1H), 1.82 – 1.68 (m, 2H), 1.25 (s, 9H), 0.99 (s, 3H). \( ^{13}\)C-NMR (151 MHz, CDCl\(_3\)) \( \delta \) 157.2, 143.6, 142.5, 140.4, 131.7, 127.6, 127.5, 127.1, 124.1, 114.8, 108.8, 89.4, 87.9, 75.1, 34.4, 31.9, 31.6, 26.0, 24.4. HRMS (ESI) \( m/z \) calcd for \( \text{C}_{24}\text{H}_{29}\text{O}_2 \) ([M+H]+) 349.2168; found 349.2171.

3. Synthesis of 5,6-Bicycles with Terminal Olefin Substituents (15a, 15b)

![Figure S21](image-url) Figure S21. Cascade reactions of diol–1,5-diene substrates with terminal olefin substituents (S20, S21) to form fused bicyclic ethers with terminal olefin substituents (15a, 15b).
(±)-(2RS,4aS,9bS)-8-(tert-Butyl)-4a-methyl-2-((E)-styril)-3,4,4a,9b-tetrahydro-2H-pyrano-[3,2-b]benzofuran (15a). Prepared from diol–diene S20 according to the general procedure above as a clear oil (24 mg, 60%, average of two trials). The two diastereomers were inseparable and were characterized as a 3:2 mixture (major diastereomer assigned by analogy to 9a). Peaks attributed solely to the minor diastereomer are indicated with *. IR (ATR): 2961, 2928, 2869, 2357, 1728, 1617, 1489, 1450, 1364, 1294, 1265, 1179, 1104, 1086, 1062, 114, 966, 910, 882, 831, 818, 795, 743, 694, 665, 648, 624, 614, 601.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.54 – 7.28 (m, 7H), 7.23 – 7.16 (m, 0H), 6.77 (dd, $J$ = 29.0, 8.4 Hz, 1H), 6.66 – 6.47 (m, 1H), 6.23 (ddd, $J$ = 36.9, 16.0, 6.4 Hz, 1H), 4.85 (s, 1H), 4.20 – 4.03 (m, 1H), 2.47 – 1.57 (m, 4H), 1.31 (d, $J$ = 8.7 Hz, 9H), 1.27 – 1.18 (m, 3H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 157.5*, 157.4, 143.9, 143.6*, 136.7, 136.7*, 130.8*, 130.3, 130.3, 130.1*, 128.5, 128.4*, 128.0*, 127.6, 127.6*, 127.5*, 127.5, 126.5*, 126.4, 125.3, 123.2*, 123.0, 110.0*, 109.6, 85.1, 84.3*, 81.4, 75.2*, 69.3, 34.4, 31.7, 31.4*, 28.9, 27.2*, 25.5, 25.1*, 25.0.

HRMS (ESI) $m/z$ calcd for C$_{24}$H$_{29}$O$_2$ ([M+H]$^+$) 349.2168; found 349.2163.

(±)-(2RS,4aS,9bS)-8-(tert-butyl)-2-((E)-3,3-dimethylbut-1-en-1-yl)-4a-methyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]benzofuran (15b). Prepared from diol–diene S21 according to the general procedure as a clear oil, (29.4 mg, 74%, average of two trials). The two diastereomers were inseparable and were characterized as a 2:1 mixture (major diastereomer assigned by analogy to 9a). Peaks attributed solely to the minor diastereomer are indicated with *.


$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (dd, $J$ = 36.1, 2.2 Hz, 1H), 7.27 (d, $J$ = 2.2 Hz, 1H), 6.74 (dd, $J$ = 25.4, 8.4 Hz, 1H), 5.63 (ddd, $J$ = 22.0, 15.8, 1 Hz, 1H), 5.40 (ddd, $J$ = 22.5, 15.8, 6.7 Hz, 1H), 4.79 (d, $J$ = 219.6 Hz, 1H), 3.89 (qd, $J$ = 7.3, 4.7 Hz, 1H), 2.45 – 1.66 (m, 3H), 1.53 – 1.45 (m, 1H), 1.43 (s, 2H), 1.30 (d, $J$ = 5.7 Hz, 9H), 1.22* (s, 1H), 0.99 (d, $J$ = 17.1 Hz, 9H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 157.51*, 157.4, 143.8*, 143.3, 143.0, 128.1, 127.9*, 127.4*, 127.2, 125.9, 125.5*, 125.3, 123.3*, 123.0, 110.0*, 109.5, 85.0, 84.4*, 81.5, 80.6*, 75.7*, 69.6, 34.4, 32.9*, 32.8, 31.7, 31.7*, 31.4*, 29.4, 29.3*, 29.0,
27.5*, 25.6, 25.1, 25.1*. HRMS (ESI) m/z calc’d for C_{22}H_{33}O_{2} ([M+H]^+) 329.2481; found 329.2482.

4. Functionalization and epimerization of bicycle 9a (16–17)

\[
\text{Figure S22. Synthesis and epimerization of bicycle 9a to ester 17.} \quad \text{The material used had a 5:1 ratio of } \alpha:\beta \text{ isomers and was equilibrated to a 20:1 ratio.}
\]

\[\text{O}_3; \text{NaClO}_2, \text{NaHSO}_3 \]

\[9a, 5:1 \text{ dr (isolated)} \quad \text{16 (R = H): crude, 7:1 dr} \quad \text{17 (R = Me): 85%, 20:1 dr}\]

\[(\pm)-\text{Methyl (2S,4aS,9bS)-8-(tert-butyl)-4a-methyl-3,4,4a,9b-tetrahydro-2H-pyrano[3,2-b]-benzofuran-2-carboxylate (17).} \quad \text{In a 50-mL roundbottom flask bicyclic ether 9a (19 mg, 0.070 mmol, 1 equiv, isolated as 5:1 mixture of diastereomers) was dissolved in 10:1 v/v acetonitrile/water (4.7 mL, 0.015 M). The solution was cooled to 0 °C then sparged with oxygen for 5 min. Ozone was sparged through the solution until disappearance of starting material as judged by TLC analysis. A solution of aq NaClO}_2 (1 mL, 25 mg/mL, 0.28 mmol, 4 equiv) was added to the reaction mixture. The solution was allowed to slowly warm from 0 °C to 25 °C and was allowed to stir for 16 hrs. A solution of NaHSO}\_3 (1 mL, 32 mg/mL, 0.31 mmol, 4.4 equiv) was added slowly, then the mixture allowed to stir for 1.5 h. A solution of 3 M aq HCl was added dropwise until the solution was adjusted to pH 2, then the aq layer was extracted with EtOAc. The combined organic extracts were dried (MgSO}_4), filtered, and concentrated by rotary evaporation. The crude carboxylic acid 16, was used without further purification.} \]

Crude carboxylic acid 16 (20 mg, 0.070 mmol, 1 equiv) was dissolved in THF (0.70 mL, 0.1 M). Solid K}_2CO}_3 (20 mg, 0.14 mmol, 2 equiv) was added in a single portion to the reaction mixture, followed by iodomethane (130 µL, 300 mg, 2.1 mmol, 30 equiv) in a single portion. The solution was capped and heated to 65 °C for 40 h. The reaction was quenched with satd aq NH}_4Cl. The aq layer was separated and extracted with Et\_2O. The combined organic extracts were dried (MgSO}_4), filtered, and concentrated by rotary evaporation. A 19:1 mixture of diastereomers was observed by \(^1\)H-NMR analysis of the crude product. Purification by silica flash chromatography (0–10% EtOAc in hexanes) afforded the major diastereomer methyl ester 17 as a clear oil (18 mg, 85%), whose stereochemical configuration was assigned by analogy to 9a based on the chemical shift of the diagnostic bridgehead proton (δ 4.67 major (α), 5.14 minor (β)).
IR (ATR): 2957, 1738, 1619, 1489, 1438, 1364, 1265, 1209, 1181, 1098, 1051, 1006, 923, 881, 835, 796. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 2.1$ Hz, 1H), 7.28 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 1H), 4.67 (s, 1H), 4.18 – 3.98 (m, 1H), 3.71 (s, 3H), 2.39 – 2.30 (m, 1H), 2.01 – 1.85 (m, 3H), 1.30 (s, 9H), 1.27 (s, 3H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 171.5, 157.7, 143.7, 127.9, 126.5, 123.5, 110.1, 84.3, 82.2, 72.8, 52.3, 34.4, 31.7, 31.0, 25.0, 23.7.

HRMS (ESI) m/z calcd for C$_{18}$H$_{25}$O$_4$ ([M+H]$^+$) 305.1753; found 305.1761.

5. Synthesis of 5,5-Bicycles with Aryl Substituents (19a–d)

Bicycles 19a–d were synthesized using the general procedure above.

Figure S23. Cascade reactions of diol–1,4-diene substrates (18a–d) to form fused [5,5]-bicyclic ethers (19a–d).

Bicycles 19a–d were synthesized using the general procedure above.

(±)-(2R,3aS,8bS)-7-(tert-Butyl)-3a-methyl-2-vinyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran and (±)-(2S,3aS,8bS)-7-(tert-Butyl)-3a-methyl-2-vinyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran (19a). Prepared from diol–diene 18a as a clear oil (39 mg, 96%, average of two trials). A 2:1 mixture of diastereomers was observed by $^1$H-NMR analysis of the crude product. The two diastereomers were separated for characterization.

Major diastereomer ($2R = \beta$): IR (ATR): 3697, 3680, 2965, 2867, 1735, 1617, 1489, 1463, 1377, 1363, 1295, 1268, 1229, 1182, 1104, 1084, 1032, 926, 889, 848, 808, 735, 697, 686, 606. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J = 2.2$ Hz, 1H), 7.32 (dd, $J = 10.4, 6.8$ Hz, 1H), 5.89 (ddd, $J = 17.2, 10.4, 6.8$ Hz, 1H), 5.30 (dt, $J = 17.2, 1.3$ Hz, 1H), 5.26 (s, 1H), 5.19 (dt, $J = 10.5, 1.2$ Hz, 1H), 4.29 (dddt, $J = 11.1, 6.6, 4.5, 1.0$ Hz, 1H), 2.46 (dd, $J = 13.2, 4.5$ Hz, 1H), 1.85 (dd, $J = 13.2, 10.0$ Hz, 1H), 1.61 (s, 3H), 1.33 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$ 158.3, 144.0, 136.7, 127.8, 125.0, 123.5, 117.4, 109.0, 95.5, 88.1, 78.8, 46.4, 34.4, 31.7, 23.3. HRMS (ESI) m/z calcd for C$_{17}$H$_{23}$O$_2$ ([M+H]$^+$) 259.1698; found 259.1686.

Minor diastereomer ($2S = \alpha$): IR (ATR): 2963, 2903, 2871, 2360, 2339, 1728, 1618, 1489, 1464, 1364, 1295, 1269, 1243, 1213, 1183, 1124, 1081, 1035, 986, 925, 818, 757, 737, 668, 634, 620. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J = 2.2$ Hz, 1H), 7.33 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.75 (d, $J = 8.5$ Hz, 1H), 5.82 (ddd, $J = 17.3, 10.3, 7.1$ Hz, 1H), 5.23 (dt, $J = 17.1, 1.3$ Hz, 1H), 5.13 – 5.08 (m, 1H), 4.47 (dddt, $J = 8.5, 7.1, 5.9, 0.9$ Hz, 1H), 2.38 (dd, $J = 13.1, 5.9$ Hz, 1H), 2.26 (dd,
J = 13.1, 8.6 Hz, 1H), 1.58 (s, 4H), 1.33 (s, 9H). $^{13}$C-NMR (151 MHz, CDCl$_3$) δ 157.5, 143.8, 137.5, 127.9, 125.7, 123.1, 117.2, 109.7, 95.8, 88.7, 80.6, 46.7, 34.4, 31.7, 23.8. HRMS (ESI) m/z calcd for C$_{17}$H$_{23}$O$_2$ ([M+H]+) 259.1698; found 259.1691.

(±)-(2RS,3aS,8bS)-3a-Methyl-2-vinyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran (19b). Prepared from 18b as a yellow tinged oil (33 mg, 93%, average of two trials). The two diastereomers were inseparable and are characterized as a 2:1 mixture (major diastereomer assigned by analogy to 19a). IR (ATR): 3085, 2974, 2931, 2871, 2362, 2334, 1725, 1693, 1598, 1478, 1465, 1429, 1378, 1254, 1259, 1184, 1150, 1091, 1031, 988, 932, 905, 885, 854, 829, 752, 657, 630, 614. $^1$H-NMR (600 MHz, Methanol-d$_4$) Major diastereomer (2R = β): δ 7.40 – 7.29 (m, 1H), 7.29 – 7.18 (m, 1H), 6.94 – 6.85 (m, 2H), 6.79 – 6.69 (m, 1H), 5.86 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.24 (dt, J = 17.2, 1.4 Hz, 1H), 5.15 (d, J = 17.2 Hz, 0H), 4.15 (dddt, J = 11.2, 6.7, 4.5, 1.0 Hz, 1H), 2.40 (ddd, J = 13.2, 7.9, 5.4 Hz, 1H), 1.85 (dd, J = 13.2, 11.0 Hz, 1H), 1.54 (s, 3H). Minor diastereomer (2S = α): δ 7.39 – 7.35 (m, 1H), 7.27 – 7.25 (m, 1H), 6.89 – 6.86 (m, 1H), 6.75 – 6.71 (m, 1H), 5.73 (ddd, J = 17.2, 10.4, 6.9 Hz, 1H), 5.15 (d, J = 17.2 Hz, 1H), 5.04 (s, 1H), 4.99 (dt, J = 10.4, 1.3 Hz, 1H), 4.55 – 4.38 (m, 1H), 2.45 – 2.40 (m, 1H), 2.15 (dd, J = 13.2, 8.0 Hz, 1H), 1.51 (s, 3H). $^{13}$C-NMR (151 MHz, Methanol-d$_4$) Major diastereomer (2R = β): δ 162.1, 138.1, 131.8, 127.8, 121.9, 117.6, 110.7, 96.6, 89.0, 80.4, 47.4, 23.3. Minor diastereomer (2S = α): δ 161.2, 139.1, 127.5, 126.8, 121.7, 116.9, 111.4, 97.0, 89.6, 81.9, 47.5, 23.7. HRMS (ESI) m/z calcd for C$_{13}$H$_{15}$O$_2$ ([M+H]+) 203.1065; found 203.1072.

(±)-(2RS,3aS,8bS)-3a-Methyl-7-(trifluoromethyl)-2-vinyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran (19c). Prepared from 18c as a yellow oil (27 mg, 71%, average of two trials). The two diastereomers were inseparable and were characterized as a 2:1 mixture (major diastereomer assigned by analogy to 19a). IR (ATR): 2980, 2938, 2360, 2341, 1624, 1498, 1444, 1383, 1332, 1293, 1277, 1161, 1119, 1058, 936, 893, 832, 742, 655, 613. $^1$H-NMR (600 MHz, CDCl$_3$) Major diastereomer (2R = β): δ 7.67 – 7.60 (m, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 5.85 (ddd, J = 17.1, 10.4, 6.7 Hz, 1H), 5.28 (d, J = 18.7 Hz, 2H), 5.22 – 5.15 (m, 1H), 4.28 – 4.16 (m, 1H), 2.48 (dd, J = 13.3, 4.4 Hz, 1H), 1.86 (dd, J = 13.3, 11.1 Hz, 1H), 1.62 (s, 3H). Minor diastereomer (2S = α): δ 7.68 (s, 1H), 7.54 (d, J = 2.1 Hz, 1H), 6.84 (m, 1H), 5.74 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.20 (d, J = 1.4 Hz, 1H), 5.11 – 4.97 (m, 2H), 4.50 (q, J = 7.2 Hz, 1H), 2.40 (dd, J = 13.3, 6.2 Hz, 1H), 2.27 (dd, J = 13.3, 8.0 Hz, 1H), 1.58 (s, 3H). $^{13}$C-NMR (151 MHz, CDCl$_3$) Major diastereomer (2R = β): δ 162.9, 136.0, 128.4 (q, J = 3.7 Hz), 126.3, 124.5 (q, J = 3.8 Hz), 123.4 (q, J = 32.6 Hz), 117.8, 110.0, 97.1, 86.75, 79.0, 46.1, 23.0. Minor diastereomer (2S = α): δ 162.1, 137.0, 128.5 (q, J = 3.0 Hz), 127.1, 124.1 (q, J = 3.8 Hz), 123.4 (q, J = 31.7 Hz), 117.2, 110.7, 97.4, 87.3, 80.6, 46.1, 23.5.
(±)-(2RS,3aS,8bS)-7-Methoxy-3a-methyl-2-vinyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran (19d). Prepared from 18d as a clear oil (33 mg, 68%, average of two trials). The two diastereomers were inseparable and were characterized as a 2:1 mixture (major diastereomer assigned by analogy to 19a). IR (ATR): 382, 2971, 2932, 2878, 2833, 2357, 2329, 1651, 169, 1487, 1434, 1378, 1307, 1269, 1243, 1186, 1149, 1116, 1097, 1031, 989, 931, 902, 844, 828, 762, 725, 668, 613. ¹H-NMR (600 MHz, CDCl₃) Major diastereomer (2R = β): δ 6.95 (d, J = 2.7 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.71 (d, J = 8.7 Hz, 1H), 5.86 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.27 (dt, J = 17.3, 1.3 Hz, 1H), 5.22 (s, 1H), 5.19 – 5.13 (m, 1H), 4.30 – 4.21 (m, 1H), 3.77 (d, J = 1.3 Hz, 5H), 2.43 (dd, J = 13.2, 4.4 Hz, 1H), 1.82 (dd, J = 13.2, 11.1 Hz, 1H), 1.58 (s, 3H). Minor diastereomer (2S = α): δ 6.97 (d, J = 2.7 Hz, 1H), 6.84 (d, J = 2.7 Hz, 1H), 6.71 – 6.69 (m, 1H), 5.77 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H), 5.20 (d, J = 1.3 Hz, 1H), 5.05 (dd, J = 10.5, 1.3 Hz, 1H), 5.03 (s, 1H), 4.52 – 4.41 (m, 1H), 3.77 (s, 3H), 2.35 (dd, J = 13.1, 6.1 Hz, 1H), 2.23 (dd, J = 13.1, 8.1 Hz, 1H), 1.55 (s, 3H). ¹³C-NMR (151 MHz, CDCl₃) Major diastereomer (2R = β): δ 154.6, 154.3, 136.4, 125.9, 117.5, 117.2, 111.1, 110.0, 95.6, 88.2, 79.0, 56.0, 46.4, 23.2. Minor diastereomer (2S = α): δ 154.1, 153.7, 137.5, 126.8, 117.2, 117.0, 110.9, 110.8, 95.8, 88.7, 80.7, 56.0, 46.6, 23.7. HRMS (ESI) m/z calcd for C₁₄H₁₇O₃ ([M+H]⁺) 233.1178; found 233.1183.
**K. SYNTHESIS AND REACTIONS OF MECHANISTIC PROBES (B1–B4)**

1. **Synthesis and Monocyclization of Truncated Substrate B1 (B2)**

![Figure S24. Synthesis and reaction of truncated substrate B2.](image)

**Figure S24.** Synthesis and reaction of truncated substrate B2.

**SEMO Br**

2-methyl-2-butenal

n-BuLi

THF

-40 oC

63%

**SEMO OH**

**A3a**

**S25**

**Pd(OTs)2(MeCN)2** (9 mol%)

benzoquinone 3 equiv.

Ca(OH)2 1 equiv.

MS3Å, 80 oC

CPME

**B2, 2.5:1 dr**

**(E)-1-(5-(tert-Butyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-2-methylbut-2-en-1-ol (S25).** In a 25-mL roundbottom flask, aryl bromide A3a (260 mg, 0.72 mmol, 1 equiv) was azeotroped using toluene (3 x 10 mL), then dissolved in THF (7.2 mL, 0.1 M substrate concentration) and cooled to –40 °C. n-BuLi was added dropwise (2.5 M in hexanes, 0.29 mL, 0.72 mmol, 1 equiv) and the reaction was stirred at –40 °C for 30 min. 2-Methyl-2-butenal (70 µL, 0.72 mmol, 1 equiv) was added and the reaction was stirred at –40 °C for 2 h. The reaction was quenched with satd aq NH4Cl. The aq layer was separated and extracted with Et2O. The combined organic extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–30% EtOAc/hexanes) afforded the SEM-protected diol S25 as a clear oil (165 mg, 63%).

**IR** (ATR): 3434, 2956, 1608, 1499, 1380, 1363, 1249, 1134, 1082, 1006, 917, 859, 835, 694.  **1H-NMR** (600 MHz, CDCl3) δ 7.34 (d, J = 2.5 Hz, 1H), 7.22 (dd, J = 8.6, 2.6 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 5.62 (tdd, J = 7.0, 5.6, 1.4 Hz, 1H), 5.36 (d, J = 4.8 Hz, 1H), 5.24 – 5.15 (m, 2H), 3.78 – 3.66 (m, 2H), 2.58 (d, J = 5.1 Hz, OH), 1.68 – 1.61 (m, 3H), 1.59 (d, J = 1.7 Hz, 3H), 1.29 (s, 9H), 0.99 – 0.93 (m, 2H), -0.00 (s, 9H).  **13C-NMR** (151 MHz, CDCl3) δ 154.0, 145.7, 138.0, 131.9, 126.4, 126.2, 121.6, 115.3, 94.5, 76.3, 67.7, 35.6, 32.9, 19.5, 14.7, 14.2, 0.00.  **HRMS** (ESI) m/z calcd for C21H36O3SiNa [M+Na]+ 387.2331; found 387.2320
**E**-4-(*tert*-Butyl)-2-(1-hydroxy-2-methylbut-2-en-1-yl)phenol (B1). In a 25-mL roundbottom flask, SEM-protected diol S25 (165 mg, 0.53 mmol, 1 equiv) was azeotroped using toluene (3 x 10 mL), then TBAF (1.0 M in THF, 5.3 mL, 5.3 mmol, 10 equiv) was added. The reaction was stirred at 60 °C for 16 h. The reaction was quenched with satd aq NH₄Cl. The aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–40% EtOAc/hexanes) afforded the diol B1 as a clear oil (92.5 mg, 97%).

**IR** (ATR): 3366, 2963, 2867, 1596, 1502, 1463, 1380, 1363, 1241, 1203, 1177, 1124, 1101, 1000, 910, 824, 736, 708, 657. **¹H-NMR** (600 MHz, CDCl₃) δ 7.88 (s, OH), 7.22 (dd, J = 8.5, 2.5 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 5.71 (ddd, J = 8.3, 6.8, 5.4 Hz, 1H), 5.35 (d, J = 2.8 Hz, 1H), 2.32 (d, J = 2.9 Hz, OH), 1.71 (dd, J = 6.7, 1.1 Hz, 3H), 1.67 (app t, 3H), 1.29 (s, 9H).

**¹³C-NMR** (151 MHz, CDCl₃) δ 153.5, 142.2, 136.6, 125.8, 124.9, 123.7, 122.5, 116.6, 81.4, 34.0, 31.5, 13.3, 12.2. **HRMS** (ESI) m/z calcd for C₁₅H₂₁O₂ [M-H]⁻ 233.1542; found 233.1547.

**5-(*tert*-Butyl)-2-methyl-2-vinyl-2,3-dihydrobenzofuran-3-ol (B2).** Prepared from diol B1 by treatment according to the general procedure for the cascade reaction above. The two diastereomers of monocyclization product B2 were inseparable and were characterized by **¹H-NMR** analysis of the crude product as a 2.5:1 mixture (major diastereomer assigned by analogy to related literature compounds¹⁷). Peaks attributed solely to the minor diastereomer are indicated with *.

**¹H-NMR** (500 MHz, CDCl₃) δ 7.41 (dd, J = 11.1, 2.2 Hz, 1.4 H), 7.30 (ddd, J = 7.7, 5.4, 2.2 Hz, 1.4 H), 6.79 (dd, J = 8.5, 6.5 Hz, 1.4 H), 6.09 (dd, J = 17.4, 11.0 Hz, 1H), 5.90* (dd, J = 17.2, 10.8 Hz, 0.4 H), 5.52 (dd, J = 17.4, 1.5 Hz, 1H), 5.34 (dd, J = 11.0, 1.6 Hz, 1H), 5.31 – 5.27* (m, 0.4H), 5.07* (dd, J = 10.7, 1.0 Hz, 0.4H), 4.86 (dd, J = 12.8, 8.8 Hz, 1.4H), 1.89* (d, J = 8.8 Hz, 0.4H), 1.81 (d, J = 9.1 Hz, 1H), 1.45 (s, 3H), 1.31 (s, 10H).

2. Synthesis and Monocyclization of Methyl Ether-Protected Substrate B3 (B4)

(E)-4-(tert-Butyl)-2-(1-methoxy-2-methylhepta-2,6-dien-1-yl)phenol (B3). In a 25-mL roundbottom flask, the SEM-protected diol A4a (210 mg, 0.52 mmol, 1 equiv), was dissolved in THF (5.2 mL, 0.1 M substrate concentration), and the solution cooled to 0 °C. Sodium hydride (48 mg, 1.2 mmol, 2.3 equiv) was added in a single portion, and the reaction was stirred at 0 °C for 30 min. Mel (0.97 mL, 16 mmol, 30 equiv) was added in a single portion. The solution was allowed to warm to 25 °C and stirred for 12 h. The solution was quenched with satd aq NH₄Cl. The aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation to afford the crude SEM-protected methyl ether S26 (213 mg, 98%), which was used without further purification.

In a 25-mL roundbottom flask, to crude SEM-protected methyl ether S26 (213 mg, 0.51 mmol, 1 equiv) was added TBAF (1.0 M in THF, 5.1 mL, 10 equiv). The solution was heated to 60 °C and stirred for 12 h. The solution was quenched with satd aq NH₄Cl. The aq layer was separated and extracted with Et₂O. The combined organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation to afford the monomethyl ether B3 as a clear oil (109 mg, 74% over two steps).

IR (ATR): 3366, 375, 2962, 2868, 2827, 2362, 164, 1619, 1592, 1502, 1464, 146, 1362, 1332, 1270, 1237, 1203, 1170, 1123, 1070, 992, 965, 911, 860, 826, 736, 648, 622. ¹H-NMR (600 MHz, CDCl₃) δ 8.25 (s, OH), 7.17 (dd, J = 8.5, 2.5 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.82 (ddt, J = 17.0, 10.3, 6.5 Hz, 1H), 5.60 – 5.52 (m, 1H), 5.06 – 4.94 (m, 2H), 4.78 (s, 1H), 3.39 (s, 3H), 2.24 – 2.11 (m, 4H), 1.57 (d, J = 1.3 Hz, 3H), 1.25 (s, 9H). ¹³C-NMR (151 MHz, CDCl₃) δ 153.6, 141.9, 138.1, 134.0, 129.5, 125.6, 124.9, 122.3, 116.4, 114.9, 91.2,
56.3, 33.9, 33.5, 31.5, 27.1, 11.7. **HRMS** (ESI) m/z calcd for C_{19}H_{27}O_{2} [M-H]^− 287.2011; found 287.2010.

(E)-5-(tert-Butyl)-3-methoxy-2-methyl-2-(penta-1,4-dien-1-yl)-2,3-dihydrobenzofuran (B4). Prepared from monomethyl ether B3 by treatment according to the general procedure for the cascade reaction above. The two diastereomers of monocyclization product B4 were inseparable and were characterized by \(^1\)H-NMR analysis of the crude product as a 1:1 mixture. Diagnostic peaks attributed solely to the minor diastereomer are indicated with *.

**Diagnostic peaks:** \(^1\)H-NMR (500 MHz, CDCl\(_3\)) δ 4.50 (s, 1H), 4.46* (s, 1H), 3.45* (s, 3H), 3.35 (s, 3H), 2.93 – 2.84 (m, 2H), 2.74* (td, \(J = 6.4, 1.5\) Hz, 2H).
Figure S26. Synthesis and X-ray crystallographic analysis of phenyl-substituted bicycle derivative S27. The crystal selected for analysis had the \((R,R,R)\) configuration, which is enantio-meric to the arbitrary stereochemistry depicted for racemic materials throughout the manuscript and Supporting Information.

\((\pm)-(2R,4aR,9bR)-4a-Methyl-2-((E)-styryl)-3,4,4a,9b-tetrahydro-2H-pyran[3,2-b]benzo-furan (rac-α-S27)\). In a 20-mL vial fitted with a PTFE-lined screw cap and a stir bar were placed bicyclic ether \(\text{rac-}α-9b\) (95 mg, 0.44 mmol, 1 equiv), and phenylboronic acid (160 mg, 1.32 mmol, 3 equiv). In a second 20-mL vial fitted with a PTFE-lined screw cap and a stir bar, \(\text{Pd(OTs)}_2(\text{MeCN})_2\) (14 mg, 0.026 mmol, 6.0 mol%), \(\text{Cu(OTf)}_2\) (9.5 mg, 0.026 mmol, 6.0 mol%), \(\text{PyrOx ligand 12}\) (17 mg, 0.057 mmol, 13 mol%), and 3 Å MS (66 mg, 150 mg/mmol) were suspended in DMF (8.8 mL, 0.5 M substrate concentration). The mixture was sparged with \(O_2\), capped, and stirred for 10 min. This solution was then pipetted into the substrate vial prepared above. The solution was stirred under \(O_2\) atmosphere at 25 °C for 16 h. The solution was diluted with \(Et_2O\), and water was added. The aq layer was separated and extracted with \(Et_2O\) (3x10 mL). The combined organic extracts were washed with water (2x10 mL) and brine (2x10 mL), dried (\(\text{MgSO}_4\)), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (0–15% \(EtOAc/hexanes\)) afforded styrene-substituted bicyclic ether \(α-S27\) as a white foam (54 mg, 42%).

**IR** (ATR): 3025, 2968, 2927, 2360, 2341, 1734, 1690, 1653, 1599, 1538, 1494, 1476, 1464, 1449, 1374, 1347, 1314, 1296, 1278, 1238, 1178, 1137, 1094, 1063, 1012, 967, 923, 909, 878, 859, 828, 789, 694, 668, 643, 623. \(^1\text{H-NMR}\) (600 MHz, CDCl\(_3\)) \(δ\) 7.46 (dd, \(J = 7.4, 1.3\) Hz, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.25 (m, 3H), 7.23 – 7.14 (m, 1H), 6.92 (td, \(J = 7.4, 0.9\) Hz, 1H), 6.88 (d, \(J = 8.1\) Hz, 1H), 6.56 (d, \(J = 15.9\) Hz, 1H), 6.18 (dd, \(J = 16.0, 6.6\) Hz, 1H), 4.66 (s, 1H), 4.14 – 3.99 (m, 1H), 2.40 (dt, \(J = 14.6, 4.2\) Hz, 1H), 1.94 (ddd, \(J = 14.6, 11.3, 5.5\) Hz, 1H), 1.84 – 1.68 (m, 2H), 1.26 (s, 3H). \(^{13}\text{C-NMR}\) (151 MHz, CDCl\(_3\)) \(δ\) 159.81, 136.67, 130.75, 130.44, 129.98, 128.60, 128.43, 127.55, 126.46, 126.36, 120.68, 110.89, 84.22, 81.08, 75.04, 31.32, 27.20, 24.94. **HRMS** (ESI) \(m/z\) calcd for \(C_{20}H_{21}O_2\) \([M+H]^+\) 293.1542; found 293.1529.
**Crystallization of (2R,4aR,9bR)-4a-methyl-2-((E)-styryl)-3,4,4a,9b-tetrahydro-2H-pyran-3,2-b]benzofuran.** In a 4 mL vial, to racemic bicycle α-S27 was added 2 mL MeOH. CH₂Cl₂ was added dropwise until the solid was completely dissolved. The solution was allowed to stand at rt, open to air, for 3 days, resulting in formation of long, needle-like crystals. The crystal selected for X-ray crystallographic analysis was determined below to have the all-R absolute configuration and is enantiomeric to the structures drawn in the manuscript for racemic material.

A specimen of C₂₀H₂₀O₂ was used for X-ray crystallographic analysis at the University of Toledo Instrumentation Center at 200 K on a Bruker APEX Duo diffractometer using CuKα radiation (1.54178 Å) for absolute stereochemistry determination. The X-ray intensity data were measured. The total exposure time was 59.04 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 29320 reflections to a maximum θ angle of 70.94° (0.82 Å resolution), of which 3045 were independent (average redundancy 9.629, completeness = 99.7%, Rₚ同盟 = 3.64%, Rₛₚ同盟 = 1.71%) and 2948 (96.81%) were greater than 2σ(F²). The final cell constants of a = 16.7276(7) Å, b = 5.4692(2) Å, c = 17.8067(8) Å, β = 103.573(2)°, volume = 1583.58(11) Å³, are based upon the refinement of the XYZ-centroids of 9409 reflections above 20σ(I) with 5.105° < 2θ < 141.8°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.802.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group C2, with Z = 4 for the formula unit, C₂₀H₂₀O₂. The final anisotropic full-matrix least-squares refinement on F² with 279 variables converged at R₁ = 3.25%, for the observed data and wR2 = 8.88% for all data. The goodness-of-fit was 1.067. The largest peak in the final difference electron density synthesis was 0.189 e/Å³ and the largest hole was -0.106 e/Å³ with an RMS deviation of 0.024 e/Å³. On the basis of the final model, the calculated density was 1.226 g/cm³ and F(000), 624 e⁻. The Flack parameter is 0.1(2) from 1273 selected quotients (Parsons' method).

CCDC 1853052 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
Table S8. Sample and crystal data for \((R,R,R)\)-S27

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M. Molecular Modeling Studies of cis- and trans-Fused Bicycles (9a, S28)

Figure S27. Molecular modeling studies of the cis-and trans-fused bicycles with α- or β-diastereomers at the allylic position. The observed products of the bicyclization cascade reaction of diol–diene 8a are bicycles α-9a (major) and β-9a (minor).

Potential energies of the α- and β-vinyl diastereomers of cis-fused bicycles 9a and trans-fused bicycles S28 were calculated using MacroModel (Schrödinger Release 2017-4: MacroModel, Schrödinger, LLC, New York, NY 2018). Briefly, the structures were first converted from a 2D structure (sdf) into a 3D structure using LigPrep with default settings (Schrödinger Release 2017-4: LigPrep, Schrödinger, LLC, New York, NY 2018). All specified chiralities were retained. A conformational search was performed using Macromodel’s Conformational Search function to generate the lowest-energy conformers of each structure. The lowest-energy conformers were minimized with MacroModel's Minimization function, and the potential energy was calculated using MacroModel’s Current Energy calculation. Conformational search, minimization and potential energy calculations were done in gas phase (no solvent) using the OPLS3 force field and a constant (ε=1) dielectric electrostatic treatment, with otherwise default settings. Calculations were performed on an Apple iMac (Retina 4K, 21.5-inch, 2017).

For the α-vinyl diastereomers, the cis-fused bicycle α-9a ($U^\circ = -3.08$ kcal/mol) was lower in energy compared to the trans-fused bicycle α-S28 ($U^\circ = +9.55$ kcal/mol) by 12.63 kcal/mol. For the β-vinyl diastereomers, the cis-fused bicycle β-9a ($U^\circ = -1.53$ kcal/mol) was lower in energy compared to the trans-fused bicycle β-S28 ($U^\circ = +11.77$ kcal/mol) by 13.30 kcal/mol. This is consistent with the observed complete diastereoselectivity for cis-fused bicycles 9a.

Further, between the cis-fused bicycles, the major diastereomer α-9a was lower in energy than the minor diastereomer β-9a by 1.55 kcal/mol, which is generally consistent with the observed 4:1 diastereomeric ratio at the allylic position.
Access to the Schrödinger Small-Molecule Drug Discovery Suite (MacroModel) was generously provided by the Sanders Innovation & Education Initiative of the Tri-Institutional Therapeutics Discovery Institute.
N. $^1$H-NMR AND $^{13}$C-NMR SPECTRA

1. Synthesis of Substituted Pyrox Ligands (S2a–e, S3a–e) 
   S63

2. Synthesis of Diene Aldehyde Precursors (A2, S6, S8)
   - Synthesis of 1,4-Diene Aldehyde Precursor (S6) 
   - Synthesis of 1,6-Diene Aldehyde Precursor (S8) 
   S73

3. Synthesis of Protected Bromophenol Precursors (S10e, A3a–f, S12)
   - Synthesis of 4-(Boc-amino)-2-bromophenol (S10e) 
   - Synthesis of SEM-protected Bromophenols (A3a–f, S12) 
   S76

4. Coupling of Diene Aldehydes and Protected Bromophenols
   (A4a–f, S13, S14a–d, S15)
   - Synthesis of SEM-Protected Diol–1,5–Diene Substrates (A4a–f, S13) 
   - Synthesis of SEM-Protected Diol–1,4–Diene Substrates (S14a–d) 
   - Synthesis of SEM-Protected Diol–1,6–Diene Substrate (S15) 
   S84

5. Installation of R$^3$ Terminal Olefin Substituents (S17, S18) 
   S96

6. Deprotection of Linear Diol–Diene Substrates (8a–f, S19–S21, 18a–d, 20)
   - Synthesis of Diol–1,5–Diene Substrates with Aryl Substituents (8a–f, S19) 
   - Synthesis of Diol–1,5–Diene Substrates with Terminal Olefin Substituents (S20, S21) 
   - Synthesis of Diol–1,4–Diene Substrates with Aryl Substituents (18a–d) 
   - Synthesis of Diol–1,6–Diene Substrate (20) 
   S98

7. Installation of R$^2$ Bridgehead Substituents (S23, S24) 
   S112

8. Pd-Catalyzed Cascade Reactions (9a–f, 13, 14a–b, 15a–b, 16–17)
   - Synthesis of 5,6-Bicycles with Aryl Substituents (9a–f, 13) 
   - Synthesis of 5,6-Bicycles with Bridgehead Substituents (14a–b) 
   - Synthesis of 5,6-Bicycles with Terminal Olefin Substituents (15a–b) 
   - Synthesis and epimerization of a 5,6-Bicycle (16,17) 
   - Synthesis of 5,5 Bicycles with Aryl Substituents (19a–d) 
   S114

9. Synthesis and Reactions of Mechanistic Probes (B1-B4)
   - Synthesis and Monocyclization of Truncated Substrate B1 ($\rightarrow$ B2) 
   - Synthesis and Monocyclization of Methyl Ether-Protected Substrate B3 ($\rightarrow$ B4) 
   S156

10. Synthesis and X-ray Crystallographic Analysis of Bicycle S27 
    S161
ent-S2a

**1H NMR (500 MHz, Chloroform-d)**: δ 152.41 (s), 145.26 (s), 134.86 (s), 134.45 (s), 134.55 (s), 134.98 (s), 134.62 (s), 129.02 (s), 128.87 (s), 128.73 (s), 122.44 (s), 66.66 (s), 56.16 (s).

**13C NMR (151 MHz, CDCl3)**: δ 163.19, 152.42, 152.41, 152.40, 145.29, 145.26, 145.23, 138.45, 134.89, 134.87, 134.85, 134.82, 129.02, 128.87, 128.73, 122.44, 66.66, 56.16.
ent-12 (ent-S3a)

$^{13}$C NMR (15 MHz, CDCl$_3$): δ 162.82, 149.73, 146.68, 146.66, 146.63, 146.60, 141.28, 134.08, 134.06, 134.03, 134.01, 128.89, 128.59, 128.37, 128.15, 128.03, 127.95, 127.94, 126.76, 124.00, 122.19, 75.58, 70.46.
H2O

S2b

13C NMR (151 MHz, Chloroform-d) δ 161.21 (d, J = 261.0 Hz), 145.81 (d, J = 3.9 Hz), 136.72 (d, J = 25.3 Hz), 124.26 (d, J = 5.6 Hz), 123.92 (d, J = 18.5 Hz).
$^1$H NMR (600 MHz, Chloroform-d) δ 8.58 (d, J = 2.8 Hz, 2H), 8.21 (dd, J = 8.7, 4.5 Hz, 2H), 7.57 – 7.46 (m, 3H), 7.41 – 7.28 (m, 2H), 5.46 (dd, J = 10.2, 8.6 Hz, 2H), 4.91 (dd, J = 10.2, 8.6 Hz, 2H), 4.40 (t, J = 8.5 Hz, 2H).
H NMR (600 MHz, Chloroform-d) δ 8.84 (dd, J = 2.1, 0.9 Hz, 1H), 8.64 (dd, J = 7.7 Hz, 1H), 8.33 (dd, J = 8.1, 0.9 Hz, 1H), 8.15 (dd, J = 8.1, 2.1 Hz, 1H), 7.41 – 7.38 (m, 4H), 7.33 (dd, J = 6.3, 4.6, 3.2 Hz, 1H), 5.28 (dt, J = 7.8, 5.8 Hz, 1H), 4.03 (dd, J = 6.3, 4.8 Hz, 2H), 2.39 (t, J = 6.1 Hz, 2H).

C NMR (151 MHz, CDCl3) δ 162.65, 152.96, 150.85, 141.01, 138.35, 129.02, 128.15, 126.73, 122.31, 115.99, 112.34, 66.44, 56.08.

Supporting Information
**Supporting Information**

1H NMR (600 MHz, Chloroform-d): δ 9.00 (dd, J = 2.1, 0.9 Hz, 1H), 8.30 (dd, J = 8.3, 6.9 Hz, 1H), 8.15 – 8.00 (m, 1H), 7.43 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 5.51 (dd, J = 10.3, 8.7 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.54 – 4.37 (m, 1H).

**S3c**

**H₂O**

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13C NMR (151 MHz, CDCl₃): δ 162.52, 152.28, 149.49, 141.05, 140.04, 128.92, 128.01, 126.74, 124.01, 116.64, 111.68, 75.65, 70.54.
**Supporting Information**

**Supporting Information**

*H NMR (600 MHz, Chloroform-d) δ 8.71 (d, J = 7.4 Hz, 1H), 8.35 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 2.6 Hz, 1H), 7.50 – 7.29 (m, 5H), 7.00 – 6.87 (m, 1H), 5.25 (dd, J = 6.8, 4.1 Hz, 1H), 4.00 – 3.96 (m, 2H), 3.91 (s, 3H), 2.82 (dd, J = 7.3, 5.1 Hz, 1H).

**13C NMR (151 MHz, CDCl₃) δ 166.97, 164.78, 151.49, 149.27, 138.72, 128.85, 127.97, 126.83, 113.16, 107.54, 66.99, 56.45, 55.56.
1H NMR (600 MHz, Chloroform-d) δ 8.53 (s, J = 5.7 Hz, H1), 7.71 (d, J = 2.6 Hz, H3), 7.39 – 7.28 (m, 5H), 6.94 (dd, J = 5.7, 2.6 Hz, H1), 5.45 (dd, J = 10.2, 8.6 Hz, H1), 4.90 (dd, J = 10.2, 8.6 Hz, H1), 4.39 (t, J = 8.6 Hz, H1), 3.90 (s, 3H).

13C NMR (151 MHz, CDCl3) δ 166.12, 163.98, 150.81, 148.25, 141.73, 128.81, 127.78, 126.84, 112.71, 109.51, 78.38, 70.32, 55.53.
\[ \text{S3e} \]

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{N} & \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{N}
\end{align*}
\]

\[ \text{H} \text{NMR (600 MHz, Chloroform-}d) \text{: 8.49 (d, J = 2.3 Hz, 1H), 7.47 - 7.27 (m, 6H), 5.53 (dd, J = 10.3, 8.5 Hz, 1H), 4.87 (dd, J = 10.4, 8.5 Hz, 1H), 4.56 (s, J = 8.5 Hz, 1H).} \]

\[ \text{C} \text{NMR (151 MHz, CDCl}_3\text{) : 161.03, 160.99, 159.93, 159.89, 159.80, 159.74, 159.26, 159.22, 158.10, 158.06, 141.44, 134.43, 134.40, 134.28, 134.23, 131.58, 131.56, 131.52, 131.50, 128.80, 127.81, 126.74, 126.13, 122.98, 112.97, 112.83, 74.53, 70.73.} \]

\[ \text{C} \text{NMR (151 MHz, Chloroform-}d\text{) : 160.46 (dd, J = 166.8, 6.0 Hz), 159.77 (dd, J = 9.3 Hz), 158.66 (dd, J = 175.0, 6.0 Hz), 134.54 (dd, J = 23.4, 4.5 Hz), 131.54 (dd, J = 9.2, 4.1 Hz), 112.97 (dd, J = 22.4, 21.1 Hz).} \]
H2O

SEMO

A3a

H2O

MCL-2017-038-char.10.fld
Group Derek Tan
* luxm MCL-2017-038-char (10 1) CDDC3
24.06.2017 16:00:59 Bruker AVIII 600 MHz DCH cryo ZRC 2134: ppm = 1H 8.17 ppm *
:Proton CDC3 /opt/users/luxm luxm 49

MCL-2017-038-char.11.fld
Group Derek Tan
* luxm MCL-2017-038-char (11 1) CDDC3
24.06.2017 16:07:46 Bruker AVIII 600 MHz DCH cryo ZRC 2134: ppm = 13C 130.000 ppm; 1H 4.000
:Carbon CDC3 /opt/users/luxm luxm 49
^H NMR (600 MHz, Chloroform-d) δ 7.28 (dd, J = 7.8, 3.0 Hz, 2H), 7.13 (dd, J = 9.1, 4.9 Hz, 2H), 6.96 (ddd, J = 9.1, 7.8, 3.1 Hz, 3H), 5.23 (s, 2H), 3.86 – 3.71 (m, 2H), 1.01 – 0.85 (m, 2H), 0.00 (s, 6H).

^13C NMR (151 MHz, CDCl3) δ 159.51, 157.90, 151.96, 151.94, 121.73, 121.56, 118.48, 118.42, 116.34, 116.19, 114.43, 114.37, 95.53, 68.10, 19.44, 14.33.

^13C NMR (151 MHz, Chloroform-d) δ 151.95 (d, J = 2.9 Hz), 121.64 (d, J = 25.7 Hz), 118.45 (d, J = 8.4 Hz), 116.26 (d, J = 22.5 Hz), 114.40 (d, J = 9.9 Hz).
**Supporting Information**

Lux et al.

SEMO

OMe

A3f

H2O

MCL-2017-081.10.fid

Group Derek Tan

* luxm MCL-2017-081 (10) CDC3 24.0C February 30, 2017 20:30:40 Bruker AVIII 600MHz DCHA cryo ZRC 2134: zg30: 1H 8.175 ppm

Proton CDC3 . /opt/users/luxm luxm S3

\[^{13}C\] NMR (151 MHz, CDCl₃) δ 156.34, 149.52, 119.83, 119.23, 115.34, 114.89, 95.83, 67.90, 57.55, 19.45, 1.42.
SEMO

A4a

$^1$C NMR (151 MHz, CDCl₃) δ 154.23, 145.78, 139.89, 137.52, 131.88, 126.53, 126.19, 116.02, 115.44, 94.73, 75.81, 67.74, 35.64, 35.13, 32.88, 28.57, 19.47, 14.64, 1.42.
Supporting Information

A4b

SEMO OH

Proton CDC3 (opt)/users/luxm luxm 73

C NMR (151 MHz, CDCl3): 156.38, 139.88, 137.47, 132.66, 129.88, 129.08, 126.58, 123.11, 116.05, 115.79, 94.52, 75.37, 67.83, 35.14, 28.57, 19.47, 14.62, 1.42.

*luxm MCL-2017-091 (111) CDC3. 24.02 February 16, 2017. Bruker AVIII 600MHz DCI. FID 2134: zgpg30: 131 131 000 ppm, TH 4 000 ppm

Proton CDC3 (opt)/users/luxm luxm 73

MCL-2017-091.10.fid
Group Derek Tan

*luxm MCL-2017-091 (101) CDC3. 24.02 February 16, 2017. Bruker AVIII 600MHz DCI. FID 2134: zgpg30: 131 131 000 ppm, TH 4 000 ppm

Proton CDC3 (opt)/users/luxm luxm 73
A4d

SEMO
OH
CF₃

$^1$H NMR (600 MHz, Chloroform-d) δ 7.66 (d, J = 2.3 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.19 (d, J = 8.6 Hz, 1H), 5.82 (dd, J = 16.5, 10.2, 6.2 Hz, 1H), 5.61 (dd, J = 5.8, 2.9 Hz, 1H), 5.44 (d, J = 4.3 Hz, 1H), 5.33 - 5.22 (m, 2H), 5.08 - 4.95 (m, 2H), 3.73 (dd, J = 9.2, 8.0, 1.9 Hz, 2H), 2.20 (d, J = 4.3 Hz, 1H), 2.20 - 1.11 (m, 4H), 1.56 (d, J = 2.9 Hz, 3H), 0.99 - 0.89 (m, 2H), 0.00 (s, 9H).
SEMO

S14b

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 156.34, 138.46, 138.20, 132.54, 129.92, 129.07, 124.25, 123.12, 116.00, 115.78, 84.51, 75.42, 67.34, 33.37, 19.45, 14.59, 1.41.
SEMOC \( \text{OH} \)

CF\( _3 \)

\[ S_{14c} \]
α-9a
Figure S28. COSY NMR experiment for the major diastereomer of the bicyclic product.
Figure S29. HSQC spectrum of the major diastereomer.
Key correlations for HMBC

Figure S30. HMBC spectrum of the major diastereomer.
nOe difference experiments:

Irradiation of proton G:

Figure S31. Irradiation of proton G promoted positive NOE signals with both proton H and proton M.
Figure S32. Irradiation of proton H promoted a positive NOE signal with proton G.
Figure S33. Irradiation of proton M promoted positive NOE signals with proton H and proton G.

Figure S34. Important NOE signals supporting the stereochemistry of the major diastereomer. This was also confirmed using X-ray crystallography and a derivatized substrate.
$\beta$-9a
Figure S35. COSY spectrum of the minor diastereomer of the bicyclization.
Figure S36. HSQC spectrum of the minor diastereomer of the bicyclization.
Figure S37. HMBC spectrum of the minor diastereomer of the bicyclization.
**nOe difference experiments:**

Figure S38. Irradiation of proton L, caused positive NOE signal for proton G
Figure S39. Irradiation of proton H did not elicit a positive NOE signal for either protons G or L.
Figure S40. Irradiation of proton G caused a positive NOE signal for proton L.
Figure S41. A) Important NOE correlations supporting the assignment of the minor diastereomer. B) NOESY spectrum to further corroborate the NOE results.
Figure S42. COSY spectrum of the chromene product.
Figure S43. HSQC of the chromene product.
Figure S44. HMBC spectrum of the chromene product.
Figure S45. COSY spectrum of the benzylic oxidation product.
Figure S46. HSQC spectrum of the benzylic oxidation product.
H2O

15b - major

15b - minor

H2O
Figure S47. Irradiation of the allylic proton did not elicit a NOE signal with either the bridgehead proton or the bridgehead methyl protons.
Figure S48. Irradiation of the bridgehead methyl protons elicited a positive NOE signal with the bridgehead proton.

Figure S49. Illustration of the key NOE interactions.
Figure S50. Irradiation of the allylic proton elicited a positive NOE signal for the bridgehead proton.
Figure S51. Irradiation of the bridgehead methyl has elicited a positive NOE signal for both the bridgehead proton and the allylic proton.

Figure S52. Key NOE interactions for determining the stereochemistry of the minor bicyclization product.