Biomimetic diversity-oriented synthesis of benzannulated medium rings via ring expansion

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I. SUPPLEMENTARY RESULTS

SUPPLEMENTARY FIGURES 1–15

Supplementary Figure 1. Medium rings are present in natural products but absent in current drugs. (a) Examples of benzannulated medium-ring natural products. (b) Frequency of aliphatic ring sizes in the top 200 brand name and top 200 generic drugs.

(1) McGrath, N.A., Brichacek, M. & Njardarson, J.T. A graphical journey of innovative organic architectures that have improved our lives. *J. Chem. Educ.* **87**, 1348–1349 (2010), see also: Njardarson Group – Top Pharmaceuticals Poster; http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster
Supplementary Figure 2. Results of PubChem substructure searches for core scaffolds of ODRE library. Substructure searches for scaffolds found in the PubChem database were carried out on Feb 25, 2011 using the substructure search function at http://pubchem.ncbi.nlm.nih.gov/. (Select “Chemical structure search”, followed by the “Substructure/Superstructure” tab). SMILES codes were entered for each scaffold to be searched and the results restricted to compounds in the MLSMR (Filters: Data source: From = MLSMR). Search results included non-medium ring structures, which were then excluded by manual inspection.
Supplementary Figure 3. Structures of 10 medium rings found in the MLSMR. PubChem Compound ID numbers are indicated.

Supplementary Figure 4. Modular synthesis of a tricyclic cyclohexadienone substrate via oxidative dearomatization. (i) TBSCI, NEt₃, CH₂Cl₂, 25 °C, 16 h, 99%; (ii) MeMgCl, THF, 25 °C, 12 h, 95%; (iii) allyltrimethylsilane, TiCl₄, CH₂Cl₂, −78 °C, 1 h, 95%; (iv) O₃, CH₂Cl₂/MeOH, −78 °C, 15 min; then NaBH₄, −78 °C → 25 °C, 1.5 h, 82%; (v) TBAF, THF, 0 °C, 15 min, 79%; (vi) Ph(OAc)₂, K₂CO₃, CF₃CH₂OH, 0 °C, 1 h, 84%. Ac, acetyl; TBAF, tetrabutylammonium fluoride; TBS, tert-butyldimethylsilyl.
Supplementary Figure 5. Attempted oxidative dearomatization of bicyclic phenol S1 having a C1-hydrogen substituent. Treatment with Phl(OAc)$_2$ results in complex mixture. Treatment with Phl(TFA)$_2$ results in benzylic oxidation to form spiroether S2.

Supplementary Figure 6. Ring expansion produces kinetic reaction products. Medium ring products 6 and 8 do not interconvert under ring expansion reaction conditions, although methyl ether 8 can undergo elimination to olefin 6 using a stronger Lewis acid, AlMeCl$_2$. Ring contraction of 6 and 8 is induced by TiCl$_4$ to afford the alternative tricycle 9.
Supplementary Figure 7. Proposed mechanism for the TiCl$_4$-mediated ring contraction of medium rings 8 and 6. Chlorotitanation of olefin 6 activates C1 for intramolecular Friedel–Crafts alkylation via intermediates 6-TiCl$_4$, 6-HCl, and 84a. In the proposed mechanism, 6-TiCl$_4$ can detitanate in the presence of a catalytic proton source and can subsequently expel chloride ion. The resulting carbocation 84a can either revert to starting material 6 to reinitiate the reaction sequence, or can undergo a transannular Friedel–Crafts reaction to generate 85a, which is poised to undergo a 1,2-alkyl shift to 86a and proton elimination to yield 9 irreversibly. This ring contraction reaction is proposed for methyl ether 8 through the initial kinetic elimination of MeOH to generate olefin 6 and subsequent organotitanation. Notably, treatment of 8 with AlMeCl$_2$ affords 6 and no ring contraction products, suggesting that the kinetically favored pathway of cation 84a is proton elimination and not necessarily Friedel–Crafts reaction.

(2) Demotie, A., Fairlamb, I.J.S. & Radford, S.K. On the selective reduction of the distal olefin in geraniol and farnesol derivatives. *Tetrahedron Lett.* **44**, 4539–4542 (2003).
Supplementary Figure 8. Molecular modeling of 6-, 7-, and 8-membered B-ring substrates for TsOH-induced ring expansion. For each structure, a conformational search was performed in SPARTAN using the MMFF force field to identify lowest energy conformations. Within each substrate series, as B-ring size increases, calculated ring strain energies (black) and overlap of the scissile bond (blue) with the cyclohexadienone π-system (green; angle measured using atoms 1-4-5) both increase. This increasing ring strain and stereoelectronic overlap is proposed to enable “MeOH-free” TsOH ring expansion of the 7- and 8-membered B-ring substrates directly via the corresponding proteo-oxocarbenium intermediates.
Supplementary Figure 9 (continued on next page). Structures of 25 cyclohexadienones and 47 benzannulated medium rings synthesized by ODRE and analyzed by PCA. All compounds were treated as racemates, except lactate-eleven-olefin-S.
Supplementary Figure 9 (continued).
Supplementary Figure 10. Structures of 20 benzannulated medium ring natural products selected for PCA.
Supplementary Figure 11. Structures of the top 40 brand-name small molecule drugs of 2006 selected for PCA. Structures are shown in no particular order.
Supplementary Figure 12 (continued on next two pages). Structures of 60 diverse natural products selected for PCA.
Supplementary Figure 12 (continued).
Supplementary Figure 12 (continued).
Supplementary Figure 13. Structures of 20 commercial drug-like library compounds in the MLSMR selected for PCA.  (a) Pyrazolecarboxamides from ChemBridge.  (b) Dihydrotriazolopyrimidines from ChemDiv. All compounds were treated as racemates as applicable. MLSMR = Molecular Libraries Small Molecule Repository. PubChem Compound ID numbers are indicated.
Supplementary Figure 14. Cheminformatic analysis of ODRE-derived library. Principal component analysis (PCA) of 47 benzannulated medium rings (MedRing Lib), 25 tricyclic cyclohexadienones (Cyclo Lib), 20 benzannulated medium ring natural products (MedRing NPs), and established reference sets of 40 top-selling brand-name drugs, 60 diverse natural products, and 20 ChemBridge and ChemDiv drug-like library members based on 20 physicochemical parameters. The hypothetical average structure for each series (-AVG) is also shown. (a) PCA plot of PC1 vs. PC2 with representative drug and natural product reference compounds labeled. (b) PCA plot of PC3 vs. PC2. (c) PCA plot of PC1 vs. PC3. The original 20-dimensional data set is projected onto three unitless, orthogonal axes that represent linear combinations of the original 20 parameters. Because several parameters are highly correlated, 74% of the total variation is represented in the first three principal components. High-profile synthetic drugs and related drug-like libraries cluster in a distinct region of the plot, while natural products, including the 20 benzannulated medium ring natural products, occupy a distinct, larger, and more dispersed area. The benzannulated medium ring scaffolds synthesized herein overlap with benzannulated medium ring natural products, and the corresponding polycyclic cyclohexadienones are even more distant from high-profile synthetic drugs and related drug-like libraries. See Supplementary Data Set 1 for complete data and Supplementary Methods for details on parameter and compound selection and data processing.
Supplementary Figure 15. Biplots and component loadings for PCA of OGRE library with benzannulated medium ring natural products and established reference sets. The biplots for (a) PC1 vs. PC2, (b) PC3 vs. PC2, and (c) PC1 vs. PC3, and (d) component loadings of the 20 original structural and physicochemical descriptors on the first three principal components indicate the influence of each structural and physicochemical descriptor upon the positioning of compounds in the PCA plots (Supplementary Fig. 14). The four most influential parameters on each principal component are highlighted (yellow). Overall, parameters associated with increasing molecular size shift molecules to the left along the x axis (PC1). Increased aromatic ring and nitrogen content shift molecules up along the y axis (PC2) while increased ring system size and complexity shift molecules downward. Increased hydrophobicity shifts molecules forward along the z axis (PC3) while increased aqueous solubility shifts molecules rearward. Stereochemical complexity shifts molecules left, downward, and rearward. See Supplementary Methods for details on data processing.
II. SUPPLEMENTARY NOTE 1

A. MATERIALS AND METHODS

Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) or Acros Organics (www.fishersci.com) and used without further purification. Optima 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. Triethylamine (Et$_3$N) and 2,6-lutidine were distilled from CaH under N$_2$. Reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring. Rubber septa and syringes were used for the transfer of liquid reagents and solutions. Cold baths were generated as follows: 0 °C, wet ice/water; –78 °C, dry ice/acetone.

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 (KMnO$_4$) or cerium ammonium molybdenate (CAM). Silica flash chromatography was performed on E. Merck 230–400 mesh silica gel 60.

Melting point determinations were performed on a Stanford Research Systems MPA100 OptiMelt Melting Point Apparatus and are uncorrected (benzoic acid, lit. 121.5 °C, found 117.6–119.9 °C). IR spectra were recorded on a Bruker Optics Tensor 27 FTIR spectrometer with peaks reported in cm$^{-1}$. NMR spectra were recorded on Bruker Avance II 500, Avance II 600, or DRX500 spectrometers at 24 °C in CDCl$_3$ unless otherwise indicated. Spectra were processed using Bruker TopSpin or nucleomatica iNMR (www.inmr.net) software, and chemical shifts are expressed in ppm relative to TMS ($^1$H, 0 ppm) or solvent signals: CDCl$_3$ ($^{13}$C, 77.0 ppm), C$_6$D$_6$ ($^1$H, 7.16 ppm; $^{13}$C, 128.0 ppm) or acetone-$d_6$ ($^{13}$C, 206.2 ppm); coupling constants are expressed in Hz. Mass spectra were obtained at the MSKCC Analytical Core Facility on a Waters 3100 mass spectrometer by electrospray (ESI) ionization.

Molecular modeling was carried out in Spartan’10 version 1.1.0 (http://www.wavefun.com/products/spartan.html). Molecular models were visualized using MacPyMOL (http://www.pymol.org).

(3) Pangborn, A.B., Giardello, M.A., Grubbs, R.H., Rosen, R.K. & Timmers, F.J. Safe and convenient procedure for solvent purification. Organometallics 15, 1518-1520 (1996).
B. FREQUENCY OF RING SIZES IN TOP SELLING DRUGS

Ring size data in Supplementary Fig. 1b was obtained by manual inspection of the chemical structures of top selling brand name and generic drugs with the aid of graphical drug posters available online from Njarðarson and coworkers (University of Arizona).\(^1\)

**Table 1. Frequency of ring sizes in top drugs by 2008 retail dollars.**\(^a\)

| Ring Size (atoms) | Frequency in Top 200 Brand Name Drugs | Frequency in Top 200 Generic Drugs |
|-------------------|---------------------------------------|-----------------------------------|
| 3                 | 16                                    | 2                                 |
| 4                 | 1                                     | 8                                 |
| 5 (Ar)            | 74                                    | 42                                |
| 5 (nonAr)         | 95                                    | 66                                |
| 6 (Ar)            | 271                                   | 243                               |
| 6 (nonAr)         | 207                                   | 177                               |
| 7                 | 7                                     | 15                                |
| 8                 | 0                                     | 0                                 |
| 9                 | 0                                     | 0                                 |
| 10                | 0                                     | 0                                 |
| 11                | 0                                     | 0                                 |
| ≥12               | 2                                     | 6                                 |

\(^a\) nonAr = non-aromatic; Ar = aromatic.
C. SYNTHESIS OF CYCLOHEXADIENONE 5 AND RING EXPANSION STUDIES

1. SYNTHESIS OF CYCLOHEXADIENONE 5

Supplementary Figure 16. Synthesis of cyclohexadienone 5.

6-(t-Butyldimethylsilyloxy)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (2). Tetralone S4 (6.47 g, 23.4 mmol) was dissolved in THF (115 mL) and cooled to 0 °C. A solution of MeMgCl (3 M in THF, 15.6 mL, 46.8 mmol, 2.00 equiv) was added by syringe. The reaction was allowed to warm to 25 °C and stirred for 12 h. The reaction was cooled to 0 °C and quenched slowly with satd aq NaHCO₃. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with satd aq NaHCO₃ and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc w/ 1% NEt₃) yielded benzylic alcohol 2 (6.50 g, 95%) as a yellow oil.

TLC: Rₓ 0.36 (4:1 hexanes/EtOAc). IR (NaCl, film): 3358 (O–H str), 2934, 2861, 1606, 1499, 1257, 840. ¹H-NMR (500 MHz): δ 7.42 (d, 1H, J = 8.5), 6.70 (d, 1H, J = 8.5), 6.54 (s, 1H), 2.78–2.65 (m, 2H), 2.38–2.22 (m, 1H), 1.92–1.86 (m, 3H), 1.80–1.76 (m, 1H), 1.51 (s, 3H), 1.03 (s, 9H), 0.24 (s, 6H). ¹³C-NMR (126 MHz): δ 154.4, 137.7, 135.9, 127.8, 119.2, 118.2, 70.2, 39.9, 31.0, 30.2, 25.7, 20.5, 18.2, −4.4. ESI-MS m/z (rel int): (pos) 275.2 ([M–OH]⁺, 100), 315.3 ([M+Na]⁺, 10).

(4) Hares, O., Hobbs-Mallyon, D. & Whiting, D.A. Synthetic studies on tricyclospirodielenones; model chemistry for novel mimics of steroid substrates. *J. Chem. Soc., Perkin Trans. 1*, 1481–1492 (1993).
(5- Allyl-5-methyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)(tert-butyl)dimethylsilane (3). Tertiary alcohol 2 (1.10 g, 3.76 mmol) and allyltrimethylsilane (3.0 mL, 18.8 mmol, 5.00 equiv) were dissolved in CH$_2$Cl$_2$ (38 mL) and cooled to −78 °C. A solution of TiCl$_4$ (1 M in toluene, 3.76 mL, 3.76 mmol, 1.00 equiv) was added by syringe over 3 min and the reaction was stirred for 1 h. The reaction was quenched slowly with satd aq NaHCO$_3$, warmed to 25 °C, and diluted with brine to solubilize titanium salts. The mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (100% hexanes) yielded 3 (1.13 g, 95%) as a clear oil.

TLC: $R_f$ 0.4 (hexanes). IR (NaCl, film): 2931, 2858, 1607, 1496, 1262, 840. $^1$H-NMR (500 MHz): δ 7.13 (d, 1H, $J$ = 8.5), 6.64 (d, 1H, $J$ = 8.5), 6.53 (s, 1H), 5.72–5.64 (m, 1H), 5.03 (d, 1H, $J$ = 8.9), 5.00 (s, 1H), 2.69 (t, 2H, $J$ = 6.2), 2.46 (dd, 1H, $J$ = 13.9, 6.8), 2.27 (dd, 1H, $J$ = 13.9, 7.9), 1.82–1.73 (m, 3H), 1.53–1.48 (m, 1H), 1.25 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H).

$^{13}$C-NMR (126 MHz): δ 152.9, 138.0, 137.3, 135.8, 127.7, 119.7, 117.6, 117.0, 48.0, 36.3, 35.6, 30.8, 29.9, 25.8, 19.5, 18.2, −4.3. ESI-MS $m/z$ (rel int): (pos) 317.3 ([M+H]$^+$, 100), 339.4 ([M+Na]$^+$, 20).

2-(6-[(tert-Butyldimethylsilyloxy)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (S5). Allylated intermediate 3 (2.37 g, 7.49 mmol) and K$_2$CO$_3$ (2.07 g, 2.00 equiv) were dissolved in CH$_2$Cl$_2$/MeOH (3:1, 38 mL) and cooled to −78 °C. Ozone was bubbled through the solution until TLC analysis indicated consumption of the starting material (10–30 min). The reaction was purged with N$_2$ for 15 minutes at −78 °C. NaBH$_4$ (1.42 g, 5.00 equiv) was added as a solid and the reaction was warmed to 25 °C. After stirring for 1.5 h, the reaction was cooled to 0 °C and was quenched slowly with satd aq NH$_4$Cl. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (4:1 hexanes/EtOAc) yielded primary alcohol S5 (1.96 g, 82%) as a brown oil.

TLC: $R_f$ 0.29 (4:1 hexanes/EtOAc). IR (NaCl, film): 3332 (O–H st), 2931, 2858, 1607 1496, 1295, 839. $^1$H-NMR (500 MHz): δ 7.12 (d, 1H, $J$ = 8.5), 6.62 (d, 1H, $J$ = 8.5), 6.50 (s, 1H), 3.67–3.60 (m, 1H), 3.58–3.51 (m, 1H), 2.66 (t, 2H, $J$ = 5.6), 2.01 (ddd, 1H, $J$ = 13.7, 9.1, 5.9), 1.85–1.74 (m, 4H), 1.58–1.55 (m, 1H), 1.26 (s, 3H), 1.08 (t, 1H, $J$ = 5.2), 0.98 (s, 9H), 0.19 (s, 6H). $^{13}$C-NMR (126 MHz): δ 153.0, 138.0, 136.6, 127.6, 119.9, 117.6, 117.0, 48.0, 36.3, 35.6, 30.8, 29.9, 25.8, 19.5, 18.2, −4.3.
31.1, 30.8, 25.7, 19.7, 18.2, –4.3. **ESI-MS** m/z (rel int): (pos) 343.0 ([M+Na]⁺, 100), 321.0 ([M+H]⁺, 5); (neg) 319.0 ([M–H]⁻, 100).

![Chemical structure](image)

**5-(2-Hydroxyethyl)-5-methyl-5,6,7,8-tetrahydrodronaphthalen-2-ol (4).** Alcohol **S5** (2.75 g, 8.59 mmol) was dissolved in THF (25 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 9.45 mL, 9.45 mmol, 1.1 equiv) was added by syringe and the reaction was stirred for 15 min. The reaction was warmed to 25 °C and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 CH₂Cl₂/MeOH w/ 1% AcOH) yielded diol **4** (1.4 g, 79%) as a colorless oil.

**TLC:** Rₚ 0.24 (6:4 hexanes/EtOAc). **IR** (NaCl, film): (O–H st), 3318, 2931, 1609, 1458, 1248, 1009, 731. **¹H-NMR** (500 MHz): δ 7.14 (d, 1H, J = 8.5), 6.60 (d, 1H, J = 8.5), 6.50 (s, 1H), 5.24 (s, 1H), 3.70–3.64 (m, 1H), 3.60–3.54 (m, 1H), 2.67 (t, 2H, J = 6.0), 2.04 (ddd, 1H, J = 14.1, 8.7, 5.7), 1.87–1.73 (m, 4H), 1.29 (br s, 1H), 1.26 (s, 3H).

**¹³C-NMR** (126 MHz): δ 153.2, 138.4, 136.0, 127.9, 115.3, 113.5, 50.8, 45.9, 36.2, 35.5, 31.1, 30.7, 19.6. **ESI-MS** m/z (rel int): (pos) 229.1 ([M+Na]⁺, 100), 244.9 ([M+K]⁺, 35); (neg) 205.0 ([M–H]⁻, 100).

**(3aR*,10aS*)-3a-Methyl-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (5).** Diol **4** (1.32 g, 6.41 mmol) and K₂CO₃ (1.77 g, 12.82 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (100 mL) and cooled to 0 °C. PhI(OAc)₂ (2.48 g, 7.69 mmol, 1.20 equiv) was added by syringe in 10 mL CH₂Cl₂ (adding PhI(OAc)₂ as a solid produced similar results). After 1 h the reaction was warmed to 25 °C and poured into H₂O (100 mL). The resulting mixture was extracted with Et₂O. The combined organic extracts were washed with H₂O (2×) and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (3:2 petroleum ether/Et₂O) yielded cyclohexadienone **5** (1.1 g, 84%) as a colorless oil.

**TLC:** Rₚ 0.35 (7:3 hexanes/EtOAc). **IR** (NaCl, film) 2937, 1670 (C=O st), 1634, 1012, 988, 919. **¹H-NMR** (500 MHz): δ 6.86 (d, 1H, J = 10.1), 6.20 (d, 1H, J = 10.2), 6.17 (s, 1H), 4.28 (q, 1H, J = 8.3), 4.20 (td, 1H, J = 11.5, 2.9), 2.61 (td, 1H, J = 11.4, 4.5), 2.27 (d, 1H, J = 12.3), 2.16 (dt, 1H, J = 12.5, 9.7), 1.95–1.86 (m, 2H), 1.79 (td, 1H, J = 13.6, 3.9), 1.61–1.51 (m, 1H), 1.47–1.42 (m, 1H), 0.96 (s, 3H). **¹³C-NMR** (126 MHz): δ 186.2, 160.3, 147.2, 128.3, 127.0, 81.7, 65.9, 50.8, 40.5, 35.9, 32.6, 25.9, 18.8. **ESI-MS** m/z (rel int): (pos) 205.2 ([M+H]⁺, 100), 227.2 ([M+Na]⁺, 50).
2. Complete Details for Rearrangements in Table 1 (6–11)

Supplementary Figure 17. Products obtained from tricycle 5. During screening of reaction conditions for the ring expansion of tricyclic cyclohexadienone 5, the desired medium rings 6–8 and alternative rearrangement products 9–11 were observed, with the reaction outcome dependent upon the reagent used.

(Z)-9-Methoxy-4-methyl-2,3,6,7-tetrahydrobenzo[b]oxonine (6) and 4,9-dimethoxy-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine (8). To a solution of tricyclic cyclohexadienone 5 (50 mg, 0.25 mmol) in MeOH/MeNO₂ (1:1, 2.5 mL) was added TsOH·H₂O (95 mg, 0.50 mmol, 2.0 equiv). After stirring at 25 °C for 12 h, the reaction was quenched with satd aq NaHCO₃ and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 → 90:10 hexanes/EtOAc) yielded elimination product 6 (35 mg, 64%) and solvent adduct 8 (14 mg, 22%) as yellow and colorless oils, respectively.

Alternatively, 6 and 8 were obtained using Cu(BF₄)₂·xH₂O: To a solution of tricyclic cyclohexadienone 5 (50 mg, 0.25 mmol) in MeOH (2.5 mL) was added Cu(BF₄)₂·xH₂O (12 mg, 0.05 mmol, 20 mol%) and TMOF (82 μL, 0.75 mmol, 3.0 equiv). The solution was warmed to 50 °C and stirred for 16 h. Once complete, the reaction was quenched with satd aq NH₄Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 → 90:10 hexanes/EtOAc) yielded elimination product 6 (36 mg, 66%) and solvent adduct 8 (14 mg, 22%) as yellow and clear oils, respectively.

6 (elimination product) TLC: R⁰ 0.49 (9:1 hexanes/EtOAc). IR (NaCl, film): 2928, 1499, 1457, 1215, 1045. ^1H-NMR (500 MHz): δ 6.94 (d, 1H, J = 8.8), 6.70 (dd, 1H, J = 8.8, 3.1), 6.59 (d, 1H, J = 3.1), 5.46 (t, 1H, J = 8.6), 4.17 (t, 2H, J = 5.2), 3.77 (s, 3H), 2.70 (t, 2H, J = 5.9), 2.36–2.32 (m, 2H), 2.15–2.11 (m, 2H), 1.71 (s, 3H). ^13C-NMR (126 MHz): δ 155.1, 151.7, 136.3, 133.3, 127.5, 121.0, 115.7, 112.2, 72.9, 55.5, 32.3, 32.0, 27.5, 23.4. ESI-MS m/z (rel int): (pos) 241.1 ([M+Na]^+), 100); 219.2 ([M+H]^+), 15. Olefin regiochemistry and (Z)-geometry were assigned by analogy to trflate 7.

8 (methanol adduct) TLC: R⁰ 0.27 (9:1 hexanes/EtOAc). IR (NaCl, film): 2934, 2360, 2341, 1500, 1203, 1045. ^1H-NMR (500 MHz): δ 6.94 (d, 1H, J = 8.8), 6.71 (dd, 1H, J = 8.8, 3.1), 6.61 (d, 1H, J = 3.1), 4.28–4.24 (m, 1H), 4.12–4.08 (m, 1H), 3.76 (s, 3H), 3.13 (s, 3H), 2.69–2.66 (m, 2H), 1.97–1.93 (m, 1H), 1.81–1.75 (m, 2H), 1.67–1.63 (m, 1H), 1.55–1.47 (m, 2H), 1.10 (s, 3H).
13C-NMR (126 MHz): δ 155.3, 150.5, 138.0, 120.6, 115.6, 112.3, 76.4, 69.5, 55.6, 48.7, 37.1, 35.1, 34.2, 23.3, 22.5.  
ESI-MS m/z (rel int): (pos) 272.9 ([M+Na]+, 100). The structure of 8 is consistent with the observation that treatment with AlMeCl₂ (2 equiv, CH₂Cl₂, −78 °C) results in elimination of MeOH to afford medium ring 6.

(Z)-4-Methyl-2,3,6,7-tetrahydrobenzo[b]oxonin-9-yl trifluoromethanesulfonate (7). Tricyclic cyclohexadienone 5 (50 mg, 0.25 mmol) and 2,6-di-tert-butyl-4-methylpyridine (77 mg, 0.375 mmol, 1.5 equiv) were dissolved in CH₂Cl₂ (2.5 mL) and cooled to 0 °C. A solution of triflic anhydride (1 M in CH₂Cl₂, 33 μL, 1.3 equiv) was added by syringe and the reaction was stirred for 1 h. The reaction was quenched at 0 °C with satd aq NaHCO₃, warmed to 25 °C, and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (100:0→95:5 hexanes/EtOAc) yielded a mixture of three olefin regioisomers of 7 (76 mg, 90%, 11.7:6.4:1.0 endocyclic-“down”/endocyclic-“up”/exocyclic) as a brown oil. The major isomer was isolated by preparative TLC (99:1 hexanes/EtOAc) for full characterization.

(major isomer) TLC: Rf 0.31 (95:5 hexanes/EtOAc). IR (NaCl, film): 2933, 1490, 1421, 1210, 1142. 1H-NMR (500 MHz): δ 7.06 (dd, 1H, J = 9.0, 2.6), 7.01 (d, 1H, J = 9.0), 6.94 (d, 1H, J = 2.6), 5.32 (t, 1H, J = 8.7), 4.25 (dd, 2H, J = 5.1, 4.9), 2.77 (t, 2H, J = 6.1), 2.43–2.39 (m, 2H), 2.22–2.17 (m, 2H), 1.67 (s, 3H). 13C-NMR (126 MHz): δ 158.5, 144.3, 137.1, 133.1, 127.2, 123.2, 121.3, 120.0, 117.5, 73.3, 32.3, 32.0, 26.8, 23.5. ESI-MS m/z (rel int): (pos) 359.1 ([M+Na]+, 20), 695.1 ([2M+Na]+, 80). Olefin regiochemistry was determined by 1H–1H COSY. (Z)-Olefin geometry was assigned by NOESY.

7-Methoxy-3a-methyl-2,3,3a,4,5,6-hexahydrobenzo[de]chromene (9). To a solution of tricycle 5 (50 mg, 0.25 mmol) in CH₂Cl₂ (1.2 mL) was added Proton-sponge® (Sigma-Aldrich) (107 mg, 0.50 mmol, 2.0 equiv) and Me₃OBF₄ (74 mg, 0.50 mmol, 2.0 equiv) sequentially. The reaction was warmed to reflux. After stirring for 2 h the reaction was cooled to 25 °C, quenched with satd aq NaHCO₃, and extracted with Et₂O (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20:1 hexanes/EtOAc) yielded tricycle 9 (33 mg, 60%) as a yellow oil.
TLC: $R_f$ 0.42 (9:1 hexanes/EtOAc). IR (NaCl, film): 2933, 1476, 1243, 1076. $^1$H-NMR (500 MHz): $\delta$ 6.61 (d, 1H, $J = 8.8$), 6.59 (d, 1H, $J = 8.8$), 4.44–4.38 (m, 1H), 4.31–4.27 (m, 1H), 3.76 (s, 3H), 2.81 (dd, 1H, $J = 18.3, 7.5$), 2.63–2.55 (m, 1H), 2.07–1.96 (m, 1H), 1.92–1.84 (m, 1H), 1.78 (dt, 1H, $J = 13.0, 6.0$), 1.73–1.66 (m, 2H), 1.44 (dt, 1H, $J = 13.3, 4.3$), 1.27 (s, 3H). $^{13}$C-NMR (126 MHz): $\delta$ 150.7, 146.6, 128.7, 124.3, 112.7, 108.7, 62.9, 55.7, 36.6, 36.1, 29.8, 22.7, 22.1, 17.3. ESI-MS m/z (rel int): (pos) 219.0 ([M+H]$,^+$, 95), 241.0 ([M+Na]$,^+$, 100).

3a-Methyl-2,3,3a,4,5,6-hexahydrobenzo[de]chromen-7-ol (10). To a solution of tricycle 5 (50 mg, 0.25 mmol) in CH$_2$Cl$_2$ (1.2 mL) was added Lewis acid by syringe (TiCl$_4$, 1 M in toluene, 300 μL, 1.2 equiv; OR AlMeCl$_2$, 1 M in hexanes, 300 μL, 1.2 equiv). After stirring for 2 h the reaction was quenched with satd aq NaHCO$_3$ and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2→6:4 petroleum ether/EtOAc) yielded tricycle 10 (from TiCl$_4$: 45 mg, 90%; from AlMeCl$_2$: 33 mg, 65%) as a yellow oil.

TLC: $R_f$ 0.36 (8:2 hexanes/EtOAc). IR (NaCl, film): 3389 (O–H st), 2930, 1455, 1248, 1073. $^1$H-NMR (500 MHz): $\delta$ 6.55 (d, 1H, $J = 8.6$), 6.52 (d, 1H, $J = 8.6$), 4.41 (ddd, 1H, $J = 13.0, 10.9, 4.1$), 4.3 (s, 1H), 4.32–4.28 (m, 1H), 2.78 (dd, 1H, $J = 17.4, 7.7$), 2.60 (ddd, 1H, $J = 17.4, 9.9, 8.1$), 2.10–2.02 (m, 1H), 1.96–1.90 (1H, m), 1.81–1.74 (m, 1H), 1.74–1.67 (m, 2H), 1.46 (td, 1H, $J = 13.4, 4.2$), 1.26 (s, 3H). $^{13}$C-NMR (126 MHz): $\delta$ 146.6, 146.5, 128.3, 121.6, 113.4, 113.3, 62.9, 36.5, 36.0, 29.8, 25.8, 21.9, 17.2. ESI-MS m/z (rel int): (pos) 227.1 ([M+Na]$,^+$, 70); (neg) 203.0 ([M–H]$^-$, 100). The structure was assigned by analogy to tricycle 9.

(5$R^*$,8$R^*$)-5-(2-Hydroxyethyl)-8-methoxy-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (11). To a vial containing neat tricycle 5 (50 mg, 0.25 mmol) was added a solution of NaOMe by syringe (0.5 M in MeOH, 1.5 mL, 0.75 mmol, 3.0 equiv). The vial was sealed with a Teflon-lined screw cap and heated in an oil bath at 80 °C. After stirring overnight the reaction was quenched with satd aq NH$_4$Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5→90:10 CH$_2$Cl$_2$/MeOH) yielded diol 11 (46 mg, 79%) as a colorless oil.
**TLC:** \( R_f 0.21 \) (4:6 hexanes/EtOAc). \( \text{IR (NaCl, film): 3332 (O–H st), 2934, 1457, 1069.} \) 1H-NMR (500 MHz): \( \delta 7.15 \) (d, 1H, \( J = 9.3 \)), 6.75–6.73 (m, 2H), 5.02 (s, 1H), 4.16 (t, 1H, \( J = 4.1 \)), 3.59–3.52 (m, 2H), 3.42 (s, 3H), 2.23–2.17 (m, 1H), 2.05–1.98 (m, 2H), 1.90–1.83 (m, 2H), 1.60 (br s, 1H), 1.42 (ddt, 1H, \( J = 13.5, 6.3, 3.2 \)), 1.24 (s, 3H). 13C-NMR (126 MHz): \( \delta 153.2, 137.0, 136.2, 128.4, 116.0, 115.9, 77.2 \) (peak identified by HSQC, buried under solvent peak), 60.1, 56.1, 45.7, 35.4, 31.4, 30.4, 24.0. ESI-MS \( m/z \) (rel int): (pos) 259.0 ([M+Na]+, 100); (neg) 235.1 ([M–H]–, 100). Diol \( 11 \) was peracetylated to form \( S6 \) in order to resolve peaks and to assign stereochemistry by NOESY (see below).

![Chemical Structure]

2-[[4R*,4R*]-6-Acetoxy-4-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl]ethyl acetate (S6). To a solution of diol \( 11 \) (5 mg, 0.021 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added NEt\(_3\) (15 µL, 0.105 mmol, 5.0 equiv), Ac\(_2\)O (1 M in CH\(_2\)Cl\(_2\), 63 µL, 3 equiv), and a crystal of DMAP. The reaction was stirred at 25 °C for 2 h and quenched with satd aq NaHCO\(_3\). The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded diacetate \( S6 \) (5 mg, 74%) as a clear film.

**TLC:** \( R_f 0.35 \) (7:3 hexanes/EtOAc). \( \text{IR (NaCl, film): 2360, 2341, 1760, 1737, 1237, 1205.} \) 1H-NMR (500 MHz): \( \delta 7.30 \) (d, 1H, \( J = 8.6 \)), 7.05 (d, 1H, \( J = 2.5 \)), 6.99 (dd, 1H, \( J = 8.6, 2.5 \)), 4.21 (t, 1H, \( J = 5.0 \)), 4.11 (td, 1H, \( J = 10.1, 5.6 \)), 3.96 (ddd, 1H, \( J = 10.7, 9.3, 6.1 \)), 3.40 (s, 3H), 2.29 (s, 3H), 2.11 (dddt, 2H, \( J = 13.8, 9.3, 4.5 \)), 1.98 (s, 3H), 1.98–1.89 (m, 3H), 1.48 (ddd, 1H, \( J = 13.5, 6.7, 3.8 \)), 1.26 (s, 3H). 13C-NMR (126 MHz): \( \delta 171.1, 169.6, 148.3, 141.6, 137.2, 127.8, 122.0, 121.3, 77.2 \) (methyl ether under solvent peak), 61.7, 56.1, 41.2, 35.7, 30.4, 30.2, 24.0, 21.2, 21.0. ESI-MS \( m/z \) (rel int): (pos) 343.1 ([M+Na]+, 100). Relative stereochemistry was assigned by NOESY.
D. MODULAR SYNTHESIS OF PHENOLS 12–30

1. SYNTHESIS OF PHENOL 12

![Synthesis of phenol 12](image)

5-(3-Hydroxypropyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (12). Allylated intermediate 3 (750 mg, 2.37 mmol) was dissolved in THF (10.5 mL) and cooled to 0 °C. A solution of 9-BBN in THF (0.5 M, 9.5 mL, 2.0 equiv) was added by syringe. The reaction was warmed to 25 °C and stirred overnight. After hydroboration was complete, the reaction was cooled to 0 °C and EtOH (6 mL) was added slowly, followed by NaOH (1 M aq, 12 mL) and H$_2$O$_2$ (30 wt% aq, 12 mL). The mixture was warmed to 50 °C and stirred for 4.5 h, during which time the t-butyldimethylsilyl group was cleaved. After cooling to 25 °C, the reaction was quenched with satd aq NH$_4$Cl and extracted into EtOAc (2×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexanes/EtOAc) yielded diol 12 (500 mg, 96%) as a colorless oil.

**TLC:** $R_f$ 0.23 (6:4 hexanes/EtOAc). **IR** (NaCl, film): 3332 (O–H st), 2934, 1499, 1242, 1052, 909, 733. **$^1$H-NMR** (500 MHz): $\delta$ 7.08 (d, 1H, $J = 8.5$), 6.60 (dd, 1H, $J = 8.5, 2.7$), 6.50 (d, 1H, $J = 2.7$), 5.51 (br s, 1H), 3.59 (t, 2H, $J = 6.5$), 2.66 (t, 2H, $J = 5.8$), 1.79–1.69 (m, 4H), 1.57–1.48 (m, 3H), 1.39–1.33 (m, 1H), 1.22 (s, 3H). **$^1$C-NMR** (126 MHz): $\delta$ 153.1, 138.4, 136.7, 127.9, 115.1, 113.3, 63.8, 39.4, 36.0, 35.5, 30.8, 30.6, 27.9, 19.5. **ESI-MS m/z** (rel int): (pos) 243.2 ([M+Na]$^+$, 60), 463.3 ([2M+Na]$^+$, 100); (neg) 219.0 ([M–H]$^-$, 75), 439.2 ([2M–H]$^-$, 100).
2. SYNTHESIS OF PHENOL 13

Supplementary Figure 19. Synthesis of phenol 13.

![Synthesis diagram]

([5-(2-Bromoallyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-yl]oxy)(-butyl)dimethylsilane (S7). Tertiary benzylic alcohol 2 (3.25 g, 11.1 mmol) and 2-bromoallyltrimethylsilane (90% technical grade, 11.9 g, 56 mmol, 5.0 equiv) were dissolved in CH₂Cl₂ (110 mL) and cooled to −78 °C. A solution of TiCl₄ (1 M in toluene, 12.2 mL, 12.2 mmol, 1.1 equiv) was added over 10 min by addition funnel and the reaction stirred for 1 h. The reaction was quenched slowly with satd aq NaHCO₃, warmed to 25 °C, and the resulting mixture was diluted with brine to solubilize the titanium salts. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (100% hexanes) yielded S7 (4.13 g, 94%) as a yellow oil.

TLC: Rₜ0.30 (100% hexanes). IR (NaCl, film): 2931, 2858, 1607, 1497, 1254, 840. ¹H-NMR (500 MHz): δ 7.02 (d, 1H, J = 8.5), 6.53 (dd, 1H, J = 8.5, 2.2), 6.42 (d, 1H, J = 2.2), 5.40 (s, 1H), 5.26 (s, 1H), 2.79 (d, 1H, J = 15.0), 2.62–2.59 (m, 3H), 1.97–1.92 (m, 1H), 1.77–1.69 (m, 1H), 1.69–1.63 (m, 1H), 1.50–1.45 (m, 1H), 1.25 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H). ¹³C-NMR (126 MHz): δ 153.2, 137.9, 136.5, 130.1, 127.8, 120.5, 119.9, 117.8, 53.5, 37.4, 35.2, 30.7, 30.3, 25.8, 19.5, 18.2, −4.3. ESI-MS m/z (rel int): (pos) 417.2 ([M+Na]⁺, 100), 395.2 ([M+H]⁺, 25).
Methyl 2-([6-([t-butyldimethylsilyl]oxy]-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)acrylate (S8). To a solution of vinyl bromide S7 (600 mg, 1.52 mmol) in CH$_2$CN/MeOH (5:1, 15 mL) was added Pd(OAc)$_2$ (34 mg, 0.15 mmol, 10 mol%), PPh$_3$ (80 mg, 0.30 mmol, 20 mol%), and NEt$_3$ (423 μL, 3.00 mmol, 2.00 equiv). A balloon of carbon monoxide was attached and CO(g) was bubbled through the solution for 5 min. The reaction was then stirred under an atmosphere of CO(g) for 30 min at 25 °C. The balloon was removed, the reaction vessel was sealed, and the solution was heated to 70 °C. After 8 h, the reaction was diluted with satd aq NH$_4$Cl and extracted with EtOAc (2×). The organic layer was washed with more NH$_4$Cl and then with brine. The organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (97:3 hexanes/EtOAc) afforded S8 (416 mg, 73%) as a brown oil.

TLC: $R_f$ 0.33 (95:5 hexanes/EtOAc). IR (NaCl, film): 2932, 2858, 1725 (C=O st), 1497, 1260, 1157, 840. $^1$H-NMR (500 MHz): δ 7.13 (d, 1H, $J = 8.5$), 6.61 (dd, 1H, $J = 8.5, 2.5$), 6.51 (d, 1H, $J = 2.5$), 6.14 (s, 1H), 5.34 (s, 1H), 3.67 (s, 3H), 2.75 (d, 1H, 13.6), 2.68 (t, 2H, $J = 6.1$), 2.58 (d, 1H, $J = 13.6$), 1.85–1.81 (m, 1H), 1.76–1.70 (m, 1H), 1.52–1.48 (m, 1H), 1.21 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H). $^{13}$C-NMR (126 MHz): δ 168.7, 153.1, 138.3, 138.0, 136.7, 128.0, 127.6, 119.7, 117.5, 51.8, 43.5, 37.0, 35.6, 30.7, 29.4, 25.7, 19.3, 18.2, –4.3. ESI-MS m/z (rel int): (pos) 397.2 ([M+Na]$^+$, 100), 375.1 ([M+H]$^+$, 5).

5-(2-[Hydroxymethyl]allyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (13). Methyl ester S8 (143 mg, 0.382 mmol) was dissolved in CH$_2$Cl$_2$ (4 mL) and cooled to –78 °C. DIBAL (1.2 M in toluene, 955 μL, 1.15 mmol, 3.00 equiv) was added dropwise by syringe and the reaction was stirred for 1 h. The reaction was warmed to 25 °C and an aqueous solution of Rochelle’s salt (4 mL, 150 g/mL) was added. After stirring for 45 min, the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product, which was redissolved in THF (4 mL) and cooled to –78 °C. A solution of TBAF (1 M in THF, 495 μL, 0.495 mmol, 1.30 equiv) was added by syringe and the reaction was stirred for 20 min. The reaction was warmed to 25 °C and quenched with satd aq NH$_4$Cl. The mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexanes/EtOAc) yielded 13 (62 mg, 70%) as a colorless oil.
TLC: $R_f$ 0.35 (6:4 hexanes/EtOAc). IR (NaCl, film): 3340 (O–H st), 2928, 2865, 1498, 1457, 1241, 909. $^1$H-NMR (500 MHz): δ 7.20 (d, 1H, $J$ = 8.5), 6.62 (dd, 1H, $J$ = 8.5, 2.7), 6.50 (d, 1H, $J$ = 2.7), 5.11 (s, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 3.70–3.69 (m, 2H), 2.67 (t, 2H, $J$ = 6.4), 2.6 (d, 1H, $J$ = 13.9), 2.3 (d, 1H, $J$ = 13.9), 1.88–1.71 (m, 3H), 1.50 (ddd, 1H, $J$ = 13.0, 7.8, 2.9), 1.26 (s, 3H). $^{13}$C-NMR (126 MHz): δ 153.2, 146.7, 138.5, 136.4, 128.1, 115.2, 113.7, 113.2, 66.6, 46.8, 36.5, 35.6, 31.7, 30.9, 19.5.

ESI-MS m/z (rel int): (pos) 255.0 ([M+Na]$^+$, 100), 271.0 ([M+K]$^+$, 70); (neg) 231.1 ([M–H]$^-$, 100), 463.2 ([2M–H]$^-$, 45).

3. SYNTHESIS OF PHENOL 14

![Supplementary Figure 20. Synthesis of phenol 14.](image)

5-([t-Butyldimethylsilyl]oxy)-2,3-dihydro-1H-inden-1-one (S10).$^5$ Commercially available 5-hydroxyindanone S9 (95%, 2.00 g, 12.8 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL). Imidazole (1.92 g, 28.2 mmol, 2.20 equiv) and TBS-Cl (1.93 g, 12.8 mmol, 1.00 equiv) were added. The reaction was stirred for 5 h then quenched with satd aq NH$_4$Cl. The resulting mixture was extracted with Et$_2$O (2×). The combined organic extracts were washed with satd aq NH$_4$Cl and brine, dried (MgSO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 petroleum ether/Et$_2$O) yielded S10 (3.35 g, 99%) as a yellow oil.

TLC: $R_f$ 0.42 (8:2 hexanes/EtOAc). IR (NaCl, film): 2953, 2930, 2859, 1699 (C=O st), 1586, 1269, 782. $^1$H-NMR (500 MHz): δ 7.56 (d, 1H, $J$ = 8.7), 6.79 (d, 1H, $J$ = 1.5), 6.74 (dd, 1H, $J$ = 8.7, 1.5), 2.98 (t, 2H, $J$ = 5.9), 2.57–2.54 (m, 2H), 0.93 (s, 9H), 0.18 (s, 6H). $^{13}$C-NMR (126 MHz): δ 205.0, 161.8, 157.8, 130.9, 125.2, 120.1, 117.0, 36.4, 25.6 (2 peaks), 18.2, –4.4. ESI-MS m/z (rel int): (pos) 285.0 ([M+Na]$^+$, 100), 263.2 ([M+H]$^+$, 20).

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(5) Lee, J.H., Kim, W.H. & Danishefsky, S.J. Diels–Alder routes to angularly halogenated cis-fused bicyclic ketones: Readily accessible cyclynone intermediates. *Tetrahedron*, **51**, 4653–4654 (2010).
**5-[(t-Butyldimethylsilyloxy)-1-methyl-2,3-dihydro-1H-inden-1-ol (S11).** Indanone S10 (2.0 g, 7.6 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. A solution of MeMgCl (3 M in THF, 3.8 mL, 11.4 mmol, 1.5 equiv) was added by syringe. The reaction was allowed to warm to 25 °C and stirred for 12 h. The solution was cooled to 0 °C and quenched slowly with satd aq NaHCO₃. The resulting mixture was extracted with EtOAc (2 × ). The combined organic extracts were washed with satd aq NaHCO₃ and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc w/ 1% NEt₃) yielded benzyl alcohol S11 (1.78 g, 84%) as a yellow oil. This product was unstable and dehydrated over time to the corresponding styrene (e.g., after 6 days in benzene at −20 °C, 38% of S11 had dehydrated as determined by ¹H-NMR), and thus was carried on to the next step within 24 h of purification.

**TLC:** Rₓ 0.30 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 3356 (O–H st), 2928, 2856, 1488, 1266, 838. **¹H-NMR** (500 MHz): δ 7.19 (d, 1H, J = 8.0), 6.70 (d, 1H, J = 8.0), 6.69 (s, 1H), 3.00–2.94 (m, 1H), 2.79–2.73 (m, 1H), 2.24–2.14 (m, 2H), 1.91 (s, 1H), 1.56 (s, 3H), 0.99 (s, 9H), 0.22 (s, 6H).

**¹³C-NMR** (126 MHz): δ 156.0, 144.4, 141.2, 122.9, 118.7, 116.2, 80.8, 42.7, 29.3, 27.5, 25.7, 18.2, –4.3. **ESI-MS** m/z (rel int): (pos) 301.1 ([M+Na⁺], 100), 261.2 ([M–OH⁺], 20).

**Methyl 2-[(t-butyldimethylsilyloxy)-1-methyl-2,3-dihydro-1H-inden-1-yl)acetate (S12).** Tertiary benzylic alcohol S11 (1.00 g, 3.59 mmol) and 1-(t-butyldimethylsilyloxy)-1-methoxyethene (3.9 mL, 18.0 mmol, 5.0 equiv) were dissolved in CH₂Cl₂ (35 mL) and cooled to −78 °C. A solution of ZnCl₂ (0.5 M in THF, 7.9 mL, 1.1 equiv) was added slowly by syringe and the reaction stirred for 1 h at −78 °C. The reaction was quenched slowly with satd aq NaHCO₃ and was warmed to 25 °C. The resulting mixture was extracted with Et₂O (2 × ). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (97:5:2.5 hexanes/EtOAc) yielded methyl ester S12 (1.08 g, 90%) as a colorless oil.

**TLC:** Rₓ 0.30 (95:5 hexanes/EtOAc). **IR** (NaCl, film): 2955, 2858, 1739 (C=O st), 1488, 1264, 960, 840. **¹H-NMR** (500 MHz): δ 7.95 (d, 1H, J = 8.1), 6.66 (d, 1H, J = 1.8), 6.63 (dd, 1H, J = 8.1, 1.8), 3.61 (s, 3H), 2.82 (dt, 2H, J = 8.2, 4.6), 2.55 (d, 1H, J = 13.9), 2.45 (d, 1H, J = 13.9), 2.28–2.24 (m, 1H), 1.96–1.91 (m, 1H), 1.33 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H). **¹³C-NMR** (126 MHz): δ 172.5, 154.7, 144.2, 142.8, 122.8, 118.0, 116.1, 51.3, 45.6, 45.3, 39.2, 30.0, 26.5, 25.7, 18.2, −4.4. **ESI-MS** m/z (rel int): (pos) 357.1 ([M+Na⁺], 100), 691.4 ([2M+Na⁺], 20).
1-(2-Hydroxy-2-methylpropyl)-1-methyl-2,3-dihydro-1H-inden-5-ol (14). MeMgCl (3 M in THF, 600 µL, 3.0 equiv) was added by syringe to a solution of methyl ester S12 (200 mg, 0.60 mmol) in THF (6 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 12 h. The reaction was cooled to 0 °C and quenched with satd aq NH₄Cl. The crude tertiary alcohol was extracted with EtOAc. The combined organic extracts were washed with brine (2×), dried (Na₂SO₄), filtered, and concentrated to afford the crude intermediate with the TBS protecting group intact. This yellow oil was dissolved in THF (6 mL) and cooled to −78 °C. A solution of TBAF (1M in THF, 650 µL, 1.1 equiv) was added slowly by syringe. After 30 min the reaction was warmed to 25 °C, quenched with satd aq NH₄Cl, and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexanes/EtOAc) yielded 14 (105 mg, 79%) as a colorless oil.

TLC: Rf 0.22 (7:3 hexanes/EtOAc). IR (NaCl, film): 3332 (O–H st), 2965, 1608, 1491, 1466, 1259, 1097. ¹H-NMR (500 MHz): δ 7.01 (d, 1H, J = 8.1), 6.67 (d, 1H, J = 1.8), 6.63 (dd, 1H, J = 8.1, 1.8), 4.88–4.76 (br s, 1H), 2.92–2.83 (m, 2H), 2.33 (ddd, 1H, J = 12.6, 8.4, 6.8), 1.99 (d, 1H, J = 14.8), 1.95 (ddd, 1H, J = 12.6, 8.1, 6.0), 1.82 (d, 1H, J = 14.8), 1.32 (s, 3H), 1.29 (s, 1H), 1.26 (s, 3H), 1.23 (s, 3H). ¹³C-NMR (126 MHz): δ 154.5, 144.5, 144.4, 123.4, 113.3, 111.6, 72.4, 52.9, 46.6, 39.9, 32.5, 30.8, 30.4, 29.1. ESI-MS m/z (rel int): (pos) 243.2 ([M+Na]+, 100); (neg) 219.1 ([M–H]−, 100).

4. SYNTHESIS OF PHENOL 15

Supplementary Figure 21. Synthesis of phenol 15.

1-Bromo-5-(2-hydroxyethyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (14). Diol 4 (134 mg, 0.650 mmol) was dissolved in MeOH (10 mL) and cooled to −78 °C. Pyridinium
tribromide (95%, 262 mg, 0.780 mmol, 1.2 equiv) was added as a solid. After stirring the reaction at –78 °C for 40 min, the solution was warmed to 0 °C and stirred for 1 h. The reaction was then warmed to 25 °C and stirred for an additional 45 min. The reaction was quenched with 2 M aq Na₂S₂O₃ and stirred for 10 min. The resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexane/EtOAc) yielded 15 (171 mg, 92%) as a colorless oil.

TLC: Rₛ 0.24 (6:4 hexanes/EtOAc). IR (NaCl, film): 3334 (O–H st), 2936, 1478, 1295, 1011, 818. ¹H-NMR (500 MHz): δ 7.20 (d, 1H, J = 8.6), 6.88 (d, 1H, J = 8.6), 5.51 (s, 1H), 3.67–3.62 (m, 1H), 3.57–3.52 (m, 1H), 2.81–2.75 (m, 1H), 2.69–2.63 (m, 1H), 2.05–1.99 (m, 1H), 1.92–1.82 (m, 3H), 1.81–1.73 (m, 2H), 1.28 (s, 3H), 1.05 (t, 1H, J = 5.3).

5. SYNTHESIS OF PHENOL 16

6-[(t-Butyldimethylsilyl)oxy]-1-phenyl-1,2,3,4-tetrahydronaphthalen-1-ol (S13). Tetralone S4 (1.00 g, 3.62 mmol) was dissolved in THF (18 mL) and cooled to 0 °C. A solution of PhMgBr (1 M in THF, 7.24 mL, 7.24 mmol, 2.0 equiv) was added by syringe and the reaction was allowed to warm to 25 °C and stirred for 12 h. The reaction was quenched slowly with satd aq NaHCO₃. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc w/ 1% NEt₃) yielded benzylic alcohol S13 (1.10 g, 86%) as a brown oil.

TLC: Rₛ 0.55 (8:2 hexanes/EtOAc). IR (NaCl, film): 3450 (O–H st), 3027, 2927, 1606, 1252, 913. ¹H-NMR (500 MHz): δ 7.31–7.29 (m, 2H), 7.24 (t, 2H, J = 8.4), 7.19–7.16 (m, 1H), 6.85
(d, 1H, \( J = 8.5 \)), 6.60 (s, 1H), 6.57 (d, 1H, \( J = 8.5 \)), 2.78 (t, 2H, \( J = 6.2 \)), 2.23 (s, 1H), 2.09–2.00 (m, 2H), 1.97–1.92 (m, 1H), 1.73–1.69 (m, 1H), 0.98 (s, 9H), 0.19 (s, 6H).

\( ^{13}\text{C-NMR} \) (126 MHz): \( \delta \) 154.8, 149.4, 139.2, 135.2, 130.4, 128.4, 127.8, 126.6, 119.5, 118.5, 75.2, 41.8, 30.2, 25.8, 19.8, 18.3, −4.2.

**ESI-MS** \( m/z \) (rel int): (pos) 337.0 ([M–OH]\(^+\), 5), 377.0 ([M+Na]\(^+\), 20), 731.2 ([2M+Na]\(^+\), 100); (neg) 353.0 ([M–H]–, 100), 707.1 ([2M–H]–, 100).

**TBSO**

Ethyl 2-(6-[(t-Butyldimethylsilyloxy)-1-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (S14). Tertiary benzylic alcohol S13 (700 mg, 1.97 mmol) and 1,1-ethoxytrimethylsiloxethene\(^7\) (1.82 mL, 9.85 mmol, 5.00 equiv) were dissolved in \( \text{CH}_2\text{Cl}_2 \) (20 mL) and cooled to \(-78^\circ\text{C}\). A solution of TiCl\(_4\) (1 M in toluene, 2.16 mL, 2.16 mmol, 1.10 equiv) was added slowly by syringe and the reaction was stirred for 1 h. The reaction was quenched slowly with satd aq NaHCO\(_3\), warmed to 25 °C, and the resulting mixture was diluted with brine to dissolve the titanium salts. The mixture was extracted with EtOAc (3 ×). The combined organic extracts were washed with brine, dried (MgSO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 hexanes/EtOAc) yielded S14 (600 mg, 72%) as a yellow oil.

**TLC**: \( R_f \) 0.36 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2931, 2858, 1735 (C=O st), 1607, 1498, 1253, 1125, 841.

\( ^{1}H\text{-NMR} \) (500 MHz): \( \delta \) 7.24–7.19 (m, 2H), 7.15–7.12 (m, 1H), 7.01 (d, 2H, \( J = 8.5 \)), 6.95 (d, 1H, 7.8), 6.62 (d, 1H, \( J = 7.8 \)), 6.60 (s, 1H), 3.94–3.88 (m, 2H), 3.16 (d, 1H, \( J = 14.8 \)), 3.13 (d, 1H, \( J = 14.8 \)), 2.82–2.75 (m, 1H), 2.70–2.59 (m, 2H), 2.04–2.00 (m, 1H), 1.69–1.62 (m, 1H), 1.52–1.43 (m, 1H), 1.01 (t, 3H, \( J = 7.1 \)), 0.98 (s, 9H), 0.19 (s, 6H).

\( ^{13}\text{C-NMR} \) (126 MHz): \( \delta \) 171.5, 153.6, 150.2, 139.6, 132.9, 130.1, 127.8, 127.5, 125.8, 119.9, 117.7, 60.0, 46.4, 45.3, 37.8, 30.3, 25.8, 19.1, 18.3, 14.0, −4.3. **ESI-MS** \( m/z \) (rel int): (pos) 447.1 ([M+Na]\(^+\), 70), 871.4 ([2M+Na]\(^+\), 100); (neg) 459.1 ([M+Cl]–, 100).

**TBSO**

5-(2-Hydroxyethyl)-5-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (16). Ethyl ester S14 (600 mg, 1.41 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (7 mL) and cooled to \(-78^\circ\text{C}\). DIBAL (1.2 M in toluene, 3.5 mL, 4.23 mmol, 3.0 equiv) was added dropwise by syringe and the reaction was warmed to 0 °C and stirred for 30 min. The reaction was warmed to 25 °C and an aqueous solution of Rochelle’s salt (7 mL, 150 g/mL) was added. After stirring for 1 h, the mixture was

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\( ^{7} \) Oisaki, K., Suto, Y., Kanai, M. & Shibasaki, M. A new method for the catalytic aldol reaction to ketones. *J. Am. Chem. Soc.* **125**, 5644–5645 (2003).
extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated by rotary evaporation to afford the crude primary alcohol, which was redissolved in THF (7 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 1.55 mL, 1.55 mmol, 1.1 equiv) was added by syringe and the desilylation was stirred for 15 min. The reaction was warmed to 25 °C and quenched with satd aq NH₄Cl. The mixture was extracted with copious EtOAc (3×) due to poor solubility of the product in either the aqueous or organic layers. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude diol. Purification by silica flash chromatography (6:4 hexanes/EtOAc) yielded 16 (227 mg, 60%) as a white solid.

**TLC:** Rₖ 0.39 (1:1 hexanes/EtOAc). mp: 218 °C. IR (NaCl, film): 3332 (O–H st), 2926, 2867, 1473, 1289. ¹H-NMR (500 MHz, CD₃OD): δ 7.13 (t, 2H, J = 7.8), 7.03 (t, 1H, J = 7.8), 6.98 (d, 2H, J = 7.8), 6.82 (d, 1H, J = 8.5), 6.53 (dd, 1H, J = 8.5, 2.5), 6.50 (d, 1H, J = 2.5), 3.51–3.46 (m, 1H), 3.36–3.31 (m, 1H), 2.65–2.56 (m, 2H), 2.35–2.29 (m, 2H), 1.97–1.91 (m, 2H), 1.59–1.55 (m, 1H), 1.44–1.39 (m, 1H). ¹³C-NMR (126 MHz, CD₃OD): δ 156.4, 152.7, 140.7, 132.7, 131.1, 128.8, 128.5, 126.5, 116.0, 114.5, 60.5, 45.8, 45.1, 38.8, 31.4, 20.3.

ESI-MS m/z (rel int): (pos) 291.0 ([M+Na]⁺, 100); (neg) 267.0 ([M–H]⁻, 100).

### 6. Synthesis of Phenol 17

![Synthesis of Phenol 17](image)

Supplementary Figure 23. Synthesis of phenol 17.

2-((tert-Butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (S16).⁸ Benzosuberone S15 (755 mg, 4.28 mmol) was dissolved in CH₂Cl₂ (60 mL) and TBSCI (703 mg, 4.66 mmol, 1.09 equiv) was added followed by imidazole (635 mg, 9.33 mol, 2.18 equiv). The reaction was stirred at 25 °C for 12 h, then quenched with satd aq NH₄Cl. The

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⁸ Pinney, K. G.; Sriram, M.; George, C.; Tanpure, R. P. (Baylor University, USA). “Efficient method for preparing functionalized benzosuberenes useful as cytotoxic agents” PCT Int. Appl. WO 2012068284, 24 May 2012.

⁹ Negoro, N. *et al.* Discovery of TAK-875: A potent, selective, and orally bioavailable GPR40 agonist. *ACS Med. Chem. Lett.* 1, 290–294 (2010).
aqueous layer was extracted with CH₂Cl₂ (3×) and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10% EtOAc/hexanes) yielded S16¹⁰ (1.20 g, 96%) as a colorless oil.

**TLC:** Rₖ 0.4 (10% EtOAc/hexanes). **IR** (NaCl, film): 2934, 2860, 1673, 1597, 1490, 1270, 991, 844. **¹H-NMR** (600 MHz): δ 7.73 (d, 1H, J = 8.5), 6.76 (dd, 1H, J = 8.5, 2.4), 6.67 (d, 1H, J = 2.4), 2.90 (t, 2H, J = 6.3), 2.74–2.72 (m, 2H), 1.89 (quintet, 2H, J = 6.5), 1.82 (quintet, 2H, J = 6.5), 1.01 (s, 9H), 0.25 (s, 6H). **¹³C-NMR** (151 MHz): δ 204.6, 159.3, 144.1, 132.2, 131.1, 121.0, 118.0, 40.8, 32.7, 25.6, 25.1, 20.7, 18.2, 0.0, –4.3. **ESI-MS** m/z (rel int): (pos) 313.13 ([M+Na]+, 100), 291.13 ([M+H]+, 67).

2-((**tert**-Butyldimethylsilyl)oxy)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (S17). Ketone S16 (1.20 g, 4.13 mmol) was dissolved in THF and cooled to 0 °C. A solution of MeMgCl (3 M in THF, 2.8 mL, 8.3 mmol, 2.0 equiv) was added by syringe and the reaction was stirred at 0 °C to 25 °C for 15 h. The reaction was cooled to 0 °C and quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10% EtOAc/hexanes) yielded S17 (823 mg, 65%) as a colorless oil, in addition to unreacted ketone S16 (157 mg, 30%).

**TLC:** Rₖ 0.25 (10% EtOAc/hexanes). **IR** (NaCl, film): 3385, 2929, 2857, 1604, 1430, 1289, 1250, 1018, 840. **¹H-NMR** (600 MHz, C₆D₆): δ 7.61 (d, 1H, J = 8.4), 6.79 (dd, 1H, J = 8.5, 2.6), 6.76 (d, 1H, J = 2.6), 2.85–2.84 (m, 1H), 2.65–2.60 (m, 1H), 1.82–1.80 (m, 1H), 1.70–1.60 (m, 2H), 1.57–1.47 (m, 3H), 1.41–1.35 (m, 3H), 1.03 (s, 9H), 0.16 (s, 5H). **¹³C-NMR** (151 MHz, C₆D₆): δ 155.0, 141.2, 128.9, 128.57, 128.41, 128.25, 127.6, 123.2, 117.5, 75.2, 43.3, 37.5, 30.01, 28.9, 26.9, 26.3, 18.8, –3.9. **ESI-MS** m/z (rel int): (pos) 289.13 ([M–OH]+, 100), 329.08 ([M+Na]+, 66).

((**5**-**Allyl**-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl)oxy)(**tert**-butyl)dimethylsilane (S18). Alcohol S17 (108 mg, 0.351 mmol) was dissolved in CH₂Cl₂ (5 mL) and cooled to –78 °C. Allyltrimethylsilane (0.22 mL, 0.83 mmol, 5.1 equiv) was added followed by a solution of TiCl₄ (1 M in toluene, 0.39 mL, 0.39 mmol, 1.1 equiv) via syringe. The reaction was stirred at

¹⁰ Pinney, K.G., Sriram, M., George, C. & Tanpure, R.P. Efficient method for preparing functionalized benzosuberenes. *US 2012/0130129 A1* (2012).
–78 °C for 45 min. The reaction was quenched with satd aq NaHCO₃, diluted with CH₂Cl₂, allowed to warm to 25 °C and stirred for 30 min. The aqueous layer was extracted with CH₂Cl₂ (4×) and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (hexanes) yielded S18 (113 mg, 98%) as a colorless oil.

**TLC:** $R_f$ 0.31 (hexanes). **IR** (NaCl, film): 2929, 2858, 1604, 1994, 1294, 1252, 1023, 838. **¹H-NMR** (600 MHz): $\delta$ 7.12 (d, 1H, $J = 8.5$), 6.59 (dd, 1H, $J = 8.5, 2.8$), 6.56 (d, 1H, $J = 2.7$), 5.59 (td, 1H, $J = 17.2, 7.2$), 5.00–4.94 (m, 2H), 3.01 (td, 1H, $J = 13.0, 2.2$), 2.68 (ddd, 1H, $J = 14.8, 6.6, 2.3$), 2.55 (dd, 1H, $J = 13.6, 6.7$), 2.37 (dd, 1H, $J = 13.9, 7.4$), 1.88–1.79 (m, 3H), 1.77–1.73 (m, 1H), 1.59 (dd, 1H, $J = 13.9, 2.6$), 1.51–1.49 (m, 1H), 1.31 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H).

**¹³C-NMR** (151 MHz): $\delta$ 153.2, 143.3, 139.6, 135.9, 128.4, 122.6, 116.58, 116.45, 41.7, 39.8, 37.1, 29.8, 27.9, 25.7, 25.5, 18.2, –4.32 (one carbon unresolved). **ESI-MS** $m/z$ (rel int): (pos) 433.12 ([2(M–C₆H₁₄Si)+H]+, 85), 369.17 ([M+K]+, 50).

![Image of 2-(2-((tert-Butyldimethylsilyl)oxy)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-ethanol (S19).](image)

2-(2-((tert-Butyldimethylsilyl)oxy)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-ethanol (S19). Allylated intermediate S18 (62.5 mg, 0.189 mmol) was dissolved in CH₂Cl₂/MeOH (3:1, 4 mL) and cooled to –78 °C. Ozone was bubbled through the solution for 15 min then the solution was purged with N₂ for 15 min. NaBH₄ (35.8 mg, 0.956 mmol, 5.05 equiv) was added and the reaction was stirred at –78 °C for 10 min then gradually warmed to 0 °C and stirred for an additional 1.5 h. The reaction was quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes) yielded S19 (39.7 mg, 63%) as a colorless oil.

**TLC:** $R_f$ 0.19 (20% EtOAc/hexanes). **IR** (NaCl, film): 3322, 2929, 2858, 1604, 1493, 1293, 1254, 1022, 838, 780. **¹H-NMR** (600 MHz): $\delta$ 7.13 (d, 1H, $J = 8.5$), 6.59 (dd, 1H, $J = 8.5, 2.8$), 6.57 (d, 1H, $J = 2.7$), 3.60 (ddd, 1H, $J = 10.7, 8.6, 5.5$), 3.49–3.44 (m, 1H), 3.06 (td, 1H, $J = 13.5, 2.2$), 2.64 (ddd, 1H, $J = 14.7, 6.3, 2.3$), 2.34 (dt, 1H, $J = 14.0, 7.2$), 1.91–1.85 (m, 2H), 1.81 (dt, 1H, $J = 6.6, 3.5$), 1.73 (ddt, 2H, $J = 13.5, 8.7, 4.5$), 1.57 (td, 1H, $J = 12.5, 2.3$), 1.47–1.41 (m, 2H), 1.36 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H). **¹³C-NMR** (151 MHz): $\delta$ 153.5, 143.6, 138.8, 128.4, 128.1, 122.9, 116.7, 60.3, 41.6, 41.2, 40.8, 37.2, 30.4, 27.9, 25.7, 25.5, 18.2, –4.3. **ESI-MS** $m/z$ (rel int): (pos) 357.08 ([2(M+Na])+, 100), 691.32 ([2M+Na]+, 97).
5-(2-Hydroxyethyl)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-ol (17). Alcohol S18 (39.7 mg, 0.119 mmol) was dissolved in THF (2.5 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 0.13 mL, 0.13 mmol, 1.1 equiv) was added by syringe and the reaction was stirred for 45 min. The reaction was quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4 ×) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (50% EtOAc/hexanes) yielded 17 (24.1 mg, 92%) as a colorless oil.

TLC: Rf 0.18 (50% EtOAc/hexanes). IR (NaCl, film): 3385, 2921, 2851, 1633, 1608, 1454, 1256, 1039, 803. ¹H-NMR (500 MHz): δ 7.16 (d, 1H, J = 8.5), 6.59 (dd, 1H, J = 8.5, 2.9), 6.56 (d, 1H, J = 2.8), 3.61 (ddd, 1H, J = 10.6, 8.6, 5.5), 3.49 (ddd, 1H, J = 10.6, 8.4, 6.4), 3.07 (ddd, 1H, J = 14.6, 12.3, 2.3), 2.68–2.63 (m, 1H), 2.32 (ddd, 1H, J = 14.0, 8.2, 6.2), 1.91–1.80 (m, 3H), 1.79–1.73 (m, 3H), 1.57 (ddd, 1H, J = 13.5, 11.4, 2.2), 1.49–1.42 (m, 1H), 1.37 (s, 3H).

13C-NMR (151 MHz): δ 153.4, 143.9, 138.5, 128.5, 126.7, 118.3, 112.2, 60.2, 41.1, 40.7, 37.1, 30.4, 29.7, 25.4. ESI-MS m/z (rel int): (neg) 219.02 ([M–H]–, 35).

7. SYNTHESIS OF PHENOL 18

Supplementary Figure 24. Synthesis of phenol 18.

3-(2-((tert-Butyldimethylsilyl)oxy)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-propan-1-ol (S20). Allylated intermediate S18 (0.494 g, 1.49 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. A solution of 9-BBN (0.365 g, 2.99 mmol, 2.01 equiv) in THF (5 mL) was added via cannula and the reaction was stirred at 0 °C for 12 h. The reaction was cooled to 0 °C and phosphate buffer (7 mL, pH 7.2), aq H₂O₂ (30 wt%, 1.5 mL), and EtOH (1.5 mL) were added sequentially. The reaction was warmed to 25 °C and stirred for 7 h. The volatile solvents were removed by rotary evaporation and EtOAc was added. The aqueous layer was extracted with EtOAc (4x) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude
Partial purification by silica flash chromatography (10 → 20% EtOAc/hexanes) yielded S20 (0.528 g, 101%) containing ca. 10% of the 9-BBN byproduct as a colorless oil. The impurity did not have an adverse effect on subsequent reactions. An analytically pure sample was obtained by preparative TLC (CH₂Cl₂).

**TLC:** \( R_f \) 0.12 (10% EtOAc/hexanes). **IR** (NaCl, film): 3332, 2929, 2858, 1604, 1493, 1471, 1291, 985, 837. **¹H-NMR** (600 MHz): δ 7.10 (d, 1H, \( J = 8.5 \)), 6.58 (dd, 1H, \( J = 8.5, 2.8 \)), 6.54 (d, 1H, \( J = 2.7 \)), 3.55 (t, 2H, \( J = 6.6 \)), 3.02–2.97 (m, 1H), 2.66–2.62 (m, 1H), 1.90 (td, 1H, \( J = 12.7, 4.3 \)), 1.87–1.78 (m, 3H), 1.77–1.73 (m, 1H), 1.57 (tdd, 2H, \( J = 12.6, 5.9, 3.6 \)), 1.52–1.45 (m, 3H), 1.32 (s, 3H), 1.27–1.23 (m, 1H), 0.97 (s, 9H), 0.19 (s, 6H). **¹³C-NMR** (151 MHz): δ 153.4, 143.6, 139.7, 128.6, 122.9, 116.7, 64.0, 41.7, 40.5, 37.2, 35.8, 30.3, 28.2, 28.1, 26.0, 25.6, 18.4, −4.10. **ESI-MS** \( m/z \) (rel int): (pos) 371.19 ([M+Na]⁺, 100); (neg) 233.02 ([M–C₆H₁₅Si]⁻, 100).

5-(3-Hydroxypropyl)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-ol (18). Alcohol S20 (263 mg, 0.755 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 0.83 mL, 0.83 mmol, 1.1 equiv) was added by syringe and the reaction was stirred for 45 min. The reaction was quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4 ×) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes) yielded 18 (151 mg, 85% over 2 steps from S18) as a colorless oil.

**TLC:** \( R_f \) 0.15 (30% EtOAc/hexanes). **IR** (NaCl, film): 3331, 2925, 1608, 1582, 1497, 1445, 1289, 1253, 1053, 737. **¹H-NMR** (600 MHz): δ 7.13 (d, 1H, \( J = 8.5 \)), 6.58 (dd, 1H, \( J = 8.5, 2.9 \)), 6.55 (d, 1H, \( J = 2.9 \)), 4.89 (br s, 1H), 3.57 (t, 2H, \( J = 6.6 \)), 3.01 (ddd, 1H, \( J = 14.5, 12.2, 2.2 \)), 2.65 (ddd, 1H, \( J = 14.6, 6.3, 1.9 \)), 1.94–1.87 (m, 1H), 1.86–1.79 (m, 3H), 1.77–1.74 (m, 1H), 1.60–1.55 (m, 2H), 1.53–1.46 (m, 2H), 1.32 (s, 3H), 1.29–1.24 (m, 2H). **¹³C-NMR** (151 MHz): δ 153.2, 143.7, 139.0, 128.8, 118.0, 112.0, 77.2, 77.0, 76.8, 63.7, 41.5, 40.2, 37.0, 35.6, 30.0, 27.9, 27.8, 25.3. **ESI-MS** \( m/z \) (rel int): (pos) 257.10 ([M+Na]⁺, 100); (neg) 233.1 ([M–H]⁻, 100), 467.21 ([2M–H]⁻, 34).
8. SYNTHESIS OF PHENOL 19

2-Methoxy-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one (S22).\(^{11}\) 6-(3-Methoxyphenyl)hexanoic acid (S21)\(^{12}\) (1.348 g, 6.47 mmol) was dissolved in CH\(_2\)Cl\(_2\) (60 mL) and cooled to 0 °C. Oxalyl chloride (0.524 mL, 7.11 mmol, 1.10 equiv) was added followed by DMF (0.023 mL, 0.297 mmol, 0.0459 equiv). The solution was stirred at 0 °C to 25 °C for 3 h. Triflic acid (0.590 mL, 6.67 mmol) was dissolved in CH\(_2\)Cl\(_2\) (600 mL) and cooled to 0 °C. The solution of the acid chloride was added dropwise through an addition funnel to the triflic acid solution over a period of 2 h, while maintaining the temperature at 0 °C. After the addition was complete, the solution was stirred at 0 °C to 25 °C for 12 h. The reaction was quenched with 1 M aq NaOH and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3×). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes) afforded S22 (918 mg, 74%).

TLC: \(R_f\) 0.35 (20% EtOAc/hexanes). IR (NaCl, film): 2930, 1657, 1597, 1278, 1243, 1121. \(^1\)H-NMR (600 MHz): \(\delta\) 7.98 (d, 1H, \(J = 8.8\)), 6.82 (dd, 1H, \(J = 8.8, 2.6\)), 6.69 (d, 1H, \(J = 2.6\)), 3.85 (s, 3H), 3.14 (t, 2H, \(J = 6.9\)), 3.01 (t, 2H, \(J = 7.2\)), 1.86 (dt, 2H, \(J = 12.9, 6.7\)), 1.81 (dt, 2H, \(J = 13.0, 6.5\)) 1.46 (qd, 2H, \(J = 6.6, 4.8\)). \(^1\)C-NMR (151 MHz): \(\delta\) 203.1, 162.8, 143.2, 132.5,

\(^{11}\) Ghosh, A., Bhattacharya, S., Raychaudhuri, S.R., & Chatterjee, A. Indian J. Chem. Sec. B. 31B, 299–309 (1990).

\(^{12}\) (a) Prepared as described by Gapinski, D.M., Mallett, B.E., Froelich, L.L., & Jackson W.T. Benzophenone dicarboxylic acid antagonists of leukotriene B\(_4\). 2. Structure-activity relationships of the lipophilic side chain. J. Med. Chem. 33, 2807–2813 (1990). (b) See also: Askam, V., & Bailey, D. Ethyl 6-[2-(4-ethoxycarbonylbutyl)-5-methoxyphenyl]-hexanoate. J. Chem. Soc. 3872–3874 (1965).
131.6, 116.7, 111.5, 55.3, 42.9, 35.5, 27.7, 24.6, 23.2. **ESI-MS m/z (rel int):** (pos) 226.90 ([M+Na]⁺, 100), 431.13 ([2M+Na])⁺, 54.

**2-Hydroxy-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one (S23).** Methyl ether S22 (731 mg, 3.58 mmol) was dissolved in toluene (4 mL) and AlCl₃ (954 mg, 7.16 mmol, 2.00 equiv) was added. The solution was refluxed for 1 h, cooled to 25 °C and poured into H₂O. The aqueous layer was extracted with EtOAc (4×) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by recrystallization (EtOAc/hexanes) afforded S23 (144 mg, 81%) as a white solid.

**TLC:** Rₚ 0.16 (20% EtOAc/hexanes). **IR** (NaCl, film): 3318, 2927, 1639, 1594, 1445, 1309, 1240, 1116. **¹H-NMR** (600 MHz): δ 7.93 (d, 1H, J = 8.6), 6.75 (dd, 1H, J = 8.6, 2.6), 6.65 (d, 1H, J = 2.6), 5.35 (br s, 1H), 3.12 (t, 2H, J = 6.8), 3.00 (t, 2H, J = 7.2), 1.86 (dt, 2H, J = 12.9, 6.7), 1.80 (dt, 2H, J = 12.9, 6.5), 1.48–1.44 (m, 2H). **¹³C-NMR** (150 MHz): δ 203.3, 159.2, 143.7, 132.6, 131.9, 117.8, 113.5, 42.8, 35.3, 27.6, 24.5, 23.2. **ESI-MS m/z (rel int):** (pos) 231.00 ([M+Na]⁺, 100); (neg) 188.92 ([M–H])⁻, 100.

**2-((tert-Butyldimethylsilyloxy)-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one (S24).** Phenol S23 (596 mg, 3.13 mmol) was suspended in CH₂Cl₂ (60 mL). TBSCl (709 mg, 4.70 mmol, 1.5 equiv) was added followed by imidazole (640 mg, 9.40 mmol, 3.00 equiv). The reaction was stirred at 25 °C for 4 h, then quenched with satd aq NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ (3×) and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (5% → 10% EtOAc/hexanes) yielded S24 (954 mg, 100%).

**TLC:** Rₚ 0.30 (10% EtOAc/hexanes). **IR** (NaCl, film): 2930, 2857, 1663, 1595, 1486, 1256, 979, 841. **¹H-NMR** (600 MHz): δ 7.87 (d, 1H, J = 8.6), 6.75 (dd, 1H, J = 8.6, 2.5), 6.64 (d, 1H, J = 2.5), 3.09 (t, 2H, J = 6.8), 2.99 (t, 2H, J = 7.2), 1.85 (dt, 2H, J = 12.9, 6.7), 1.79 (dt, 2H, J = 12.9, 6.5), 1.48–1.44 (m, 2H), 0.99 (s, 9H), 0.23 (s, 6H). **¹³C-NMR** (150 MHz): δ 203.6, 159.4, 143.7, 132.6, 131.9, 117.8, 113.5, 42.8, 35.2, 27.6, 24.5, 23.4, 18.2, –4.3. **ESI-MS m/z (rel int):** (pos) 327.12 ([M+Na]⁺, 100), 305.15 ([M+H]⁺, 10).

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(14) Allinger, N.L. & Jones, E.S. Benzocyclanones *J. Org. Chem.* 27, 70–76 (1962).
2-((tert-Butyldimethylsilyl)oxy)-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-ol (S25). Ketone S24 (1.01 g, 3.32 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. A solution of MeMgCl (2.14 M in THF, 3.10 mL, 6.64 mmol, 2.00 equiv) was added and the reaction was stirred at 0 °C to 25 °C for 5 h. The reaction was cooled to 0 °C, quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4 ×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7.5% EtOAc/hexanes) afforded S25 (692 mg, 65%) as a colorless oil, in addition to unreacted ketone S24 (202 mg, 20%).

**TLC:** Rₓ 0.22 (7.5% EtOAc/hexanes). **IR** (NaCl, film): 3385, 2929, 2858, 1604, 1492, 1296, 1251, 981, 838, 780. **¹H-NMR** (600 MHz): δ 7.45 (d, 1H, J = 7.9), 6.65 (dd, 1H, J = 8.6, 2.7), 6.52 (d, 1H, J = 2.7), 3.22 (br s, 1H), 2.83 (br s, 1H), 2.15 (s, 1H), 1.99 (dd, 1H, J = 15.0, 5.2, 3.8), 1.73 (ddd, 1H, J = 11.6, 7.3, 4.2, 3.4), 1.68 (quintet, 2H, J = 6.5), 1.58–1.57 (m, 1H), 1.30 (br s, 1H), 1.10 (br s, 1H), 0.98 (s, 9H), 0.19 (s, 6H). **¹³C-NMR** (151 MHz): δ 154.5, 140.4, 139.3, 127.5, 122.3, 117.1, 75.5, 44.2, 34.4, 32.6, 30.1, 25.7, 23.0, 22.9, 18.2, −4.4 (2 peaks). **ESI-MS** m/z (rel int): (pos) 327.12 ([M–OH]⁺, 100), 343.19 ([M+Na]⁺, 24).

((5-Allyl-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-2-yl)oxy)(tert-butyl)dimethylsilane (S26). Tertiary alcohol S25 (299 mg, 0.934 mmol) was dissolved in CH₂Cl₂ (10 mL). Allyltrimethylsilane (0.59 mL, 4.7 mmol, 5.0 equiv) was added and the solution was cooled to −78 °C. A solution of TiCl₄ (1 M in toluene, 1.0 mL, 1.0 mmol, 1.1 equiv) was added by syringe and the solution was stirred at −78 °C for 25 min. The reaction was quenched with satd aq NaHCO₃ and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (4 ×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (1% EtOAc/hexanes) yielded S26 (305 mg, 95%) as a colorless oil.

**TLC:** Rₓ 0.17 (hexanes). **IR** (NaCl, film): 2930, 2858, 1605, 1492, 1297, 1251, 994, 863, 839, 780. **¹H-NMR** (600 MHz): δ 7.17 (d, 1H, J = 8.7), 6.52–5.51 (m, 1H), 4.93–4.89 (m, 2H), 3.29 (br s, 1H), 2.57 (br s, 2H), 2.25 (br s, 2H), 1.77–1.74 (m, 2H), 1.63–1.49 (m, 3H), 1.37 (s, 3H), 1.27–1.23 (m, 1H), 1.18–1.13 (m, 1H), 0.97 (s, 9H), 0.18 (s, 6H). **¹³C-NMR** (151 MHz): δ 153.3, 140.7, 139.8, 135.7, 128.9, 122.6, 117.0, 116.6, 42.0, 39.9, 35.0, 29.8, 28.9, 25.7, 25.1, 22.0, 18.2, 0.0, −4.4 (2 peaks), (one carbon unresolved). **ESI-MS** m/z (rel int): (pos) 367.12 ([M+Na]⁺, 100), 343.19 ([M+Na]⁺, 24).
2-(2-((tert-Butyldimethylsilyl)oxy)-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-yl)-ethanol (S27). Allylated intermediate S26 (166 mg, 0.482 mmol) was dissolved in CH$_2$Cl$_2$/MeOH (3:1, 12 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 10 min, then it purged with N$_2$ for 10 min. NaBH$_4$ (91.2 mg, 2.35 mmol, 4.87 equiv) was added and the mixture was stirred at −78 °C to 0 °C for 1.5 h. The reaction was quenched with satd aq NH$_4$Cl and diluted with CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (4×) and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes) yielded S27 (101 mg, 60%) as a colorless oil.

TLC: $R_f$ 0.41 (20% EtOAc/hexanes). IR (NaCl, film): 3332, 2930, 2858, 1605, 1492, 1297, 1252, 989, 840, 780. $^1$H-NMR (600 MHz): δ 7.21 (d, 1H, $J = 8.7$), 6.63 (dd, 1H, $J = 8.6, 2.8$), 6.47 (d, 1H, $J = 2.8$), 3.57–3.53 (m, 1H), 3.49–3.46 (m, 1H), 3.33 (br s, 2H), 2.60 (br s, 2H), 1.92–1.87 (m, 1H), 1.80–1.77 (m, 2H), 1.75–1.72 (m, 1H), 1.63–1.60 (m, 1H), 1.56–1.55 (m, 2H), 1.43 (s, 3H), 1.29–1.25 (m, 2H), 1.13–1.10 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H). $^{13}$C-NMR (151 MHz): δ 153.7, 140.9, 139.0, 128.8, 123.0, 117.3, 60.0, 49.70, 41.2, 40.8, 34.9, 30.17, 28.9, 25.7, 24.8, 22.0, 18.2, −4.4 (2 peaks). ESI-MS $m/z$ (rel int): (pos) 371.20 ([M+Na]$^+$, 100), 719.44 ([2M+Na]$^+$, 34).

5-(2-Hydroxyethyl)-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-2-ol (19). Alcohol S27 (101 mg, 0.290 mmol) was dissolved in THF (3 mL) and cooled to −78 °C. A solution of TBAF (1 M in THF, 0.32 mL, 0.32 mmol, 1.1 equiv) was added and the reaction was stirred at −78 °C for 25 min. The reaction was quenched with satd aq NH$_4$Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×). The combined organics were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (40% EtOAc/hexanes) yielded 19 (58.5 mg, 86%) as a colorless oil.

TLC: $R_f$ 0.10 (30% EtOAc/hexanes). IR (NaCl, film): 3332, 2919, 1606, 1456, 1240, 1038. $^1$H-NMR (500 MHz): δ 7.24 (d, 1H, $J = 8.7$), 6.63 (dd, 1H, $J = 8.6, 2.9$), 6.47 (d, 1H, $J = 2.9$), 4.66 (s, 1H), 3.60–3.55 (m, 1H), 3.53–3.48 (m, 1H), 3.37–3.31 (m, 1H), 2.65–2.60 (m, 2H), 1.93–1.88 (m, 1H), 1.84–1.74 (m, 3H), 1.66–1.64 (m, 1H), 1.61–1.59 (m, 2H), 1.44 (s, 3H), 1.32–1.28 (m, 1H), 1.18–1.12 (m, 1H), 0.90–0.87 (m, 1H). $^{13}$C-NMR (151 MHz): δ 153.6, 141.2, 138.5, 129.2, 118.2, 112.8, 59.9, 49.8, 41.2, 40.7, 34.9, 30.31, 30.3, 28.9, 24.8, 22.0.
ESI-MS m/z (rel int): (pos) 217.06 ([M–OH]+, 100) 257.01 ([M+Na]+, 69), 235.05 ([M+H]+, 65); (neg) 268.98 ([M+Cl]−, 100), 503.89 ([2M+Cl]−, 36).

9. SYNTHESIS OF PHENOL 20

![Synthesis of phenol 20](image)

Supplementary Figure 26. Synthesis of phenol 20.

5-(3-Hydroxypropyl)-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-2-ol (20). Allylated intermediate S26 (180 mg, 0.523 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. 9-BBN (128 mg, 1.05 mmol, 1.97 equiv) was dissolved in THF (2 mL) and added to the olefin solution via a cannula. The reaction was stirred at 0 °C to 25 °C for 14 h. The reaction was recooled to 0 °C, quenched with phosphate buffer (2 mL, pH 7.2) and H2O2 (30 wt%, 1 mL). EtOH (2 mL) was then added and the mixture was stirred at 0 °C to 25 °C for 6 h. The volatile solvents were removed by rotary evaporation and the aqueous mixture was extracted with EtOAc (4×). The combined organic layers were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Partial purification by silica flash chromatography (20% EtOAc/hexanes) afforded the alcohol (202 mg, 106%) with 5–10% 9-BBN byproducts that did not adversely effect subsequent reactions. The intermediate alcohol (103 mg, 0.284 mmol) was dissolved in THF (3 mL) and cooled to –78 °C. A solution of TBAF (1 M in THF, 0.31 mL, 0.31 mmol, 1.1 equiv) was added and the solution was stirred at –78 °C for 25 min. The reaction was quenched with satd aq NH4Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×). The combined organics were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by chromatography (40% EtOAc/hexanes) yield 20 (59.1 mg, 84% over two steps) as a colorless oil.

**TLC:** Rf 0.30 (40% EtOAc/hexanes). 
**IR** (NaCl, film): 3332, 2932, 1608, 1581, 1493, 1451, 1244, 1054, 816. 
**1H-NMR** (600 MHz): δ 7.20 (d, 1H, J = 8.6), 6.62 (dd, 1H, J = 8.6, 2.9), 6.45 (d, 1H, J = 2.9), 4.48 (s, 1H), 3.49 (q, 2H, J = 5.9), 3.33 (br s, 1H), 2.61–2.59 (br s, 2H), 1.81–1.73 (m, 2H), 1.67–1.63 (m, 2H), 1.60–1.57 (m, 2H), 1.49–1.44 (m, 2H), 1.39 (s, 3H), 1.31–1.26 (m, 2H), 1.19–1.14 (m, 1H). 
**13C-NMR** (151 MHz): δ 153.2, 141.3, 139.3, 129.4, 117.9, 112.5, 63.7, 43.7, 41.9, 40.0, 35.0, 30.0, 29.0, 27.8, 25.0, 22.0. 
**ESI-MS** m/z (rel int): (pos) 231.09 ([M–OH]+, 100), 271.04 ([M+Na]+, 73) 249.20 ([M+H]+, 67); (neg) 531.08 ([2M+Cl]−, 100), 283.08 ([M+Cl]−, 56).
10. SYNTHESIS OF PHENOL 21

Supplementary Figure 27. Synthesis of phenol 21.

3-(6-((tert-Butyldimethylsilyl)oxy)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propan-1-ol (S28). Allylated intermediate 3 (830 mg, 2.62 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. 9-BBN (640 mg, 5.24 mmol, 2.00 equiv) was dissolved in THF (8 mL) and added to the olefin solution via a cannula. The reaction was stirred at 0 °C to 25 °C for 12 h. The reaction was recooled to 0 °C, quenched with phosphate buffer (8 mL, pH 7.2) and H2O2 (30 wt%, 4.5 mL). EtOH (3 mL) was then added and the mixture was stirred at 0 °C to 25 °C for 5 h. The volatile solvents were removed by rotary evaporation and the aqueous mixture was extracted with EtOAc (4 × 1). The combined organic layers were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Partial purification by silica flash chromatography (10% EtOAc/hexanes) afforded alcohol S28 (883 mg, 101%) with 5–10% 9-BBN byproducts that did not adversely effect subsequent reactions.

TLC: Rf 0.15 (10% EtOAc/hexanes). IR (NaCl, film): 3345, 2929, 1607, 1496, 1256, 988, 956, 839, 780. 1H-NMR (600 MHz): δ 7.08 (d, 1H, J = 8.7), 6.61 (dd, 1H, J = 8.4, 2.5), 6.50 (d, 1H, J = 2.0), 3.58 (q, 2H, J = 6.0), 2.66 (t, 2H, J = 5.7), 1.78–1.69 (m, 4H), 1.54–1.51 (m, 3H), 1.38–1.33 (m, 1H), 1.23 (s, 3H), 1.17 (t, 3H, J = 5.4), 0.97 (s, 9H), 0.18 (s, 6H). 13C-NMR (151 MHz): δ 152.8, 138.0, 137.3, 127.5, 119.6, 117.6, 63.7, 39.4, 36.0, 35.4, 30.8, 30.5, 28.0, 25.7, 19.6, 18.1, −4.4 (2 peaks). ESI-MS m/z (rel int): (pos) 357.18 ([M+Na]+, 100), 691.52 ([2M+Na]+, 26).

3-(6-((tert-Butyldimethylsilyl)oxy)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanoic acid (S29). The alcohol S28 (409 mg, 1.22 mmol) was dissolved in acetone (10 mL) and cooled to 0 °C. A solution of Jones reagent, prepared by dissolving 670 mg CrO3 in 1.25 mL H2O followed by dropwise addition of 0.58 mL conc H2SO4,16 (0.75 mL) was added dropwise until an

(16) Eisenbraun, E.J. Cyclooctanone. Org. Synth. 45, 28 (1965).
orange color persisted. The solution was stirred for an additional 15 min, quenched with isopropanol and Celite (Fisher Scientific) was added. The mixture was stirred for 5 min, filtered through Celite and concentrated. In the event that water remained in the flask, the residue was redissolved in EtOAc and H$_2$O was added; the aqueous layer was extracted with EtOAc (4×) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes + 1% AcOH) yielded S28 (293 mg, 69%).

TLC: $R_f$ 0.20 (20% EtOAc/hexanes + 1% AcOH). IR (NaCl, film): 2930, 1706, 1607, 1497, 1459, 1253, 988, 952, 838, 780. $^1$H-NMR (600 MHz): $\delta$ 7.07 (d, 1H, $J = 8.5$), 6.62 (dd, 1H, $J = 8.5, 2.7$), 6.51 (d, 1H, $J = 2.6$), 2.66 (t, 2H, $J = 6.3$), 2.26 (ddd, 1H, $J = 16.1, 11.5, 4.8$), 2.13 (dt, 1H, $J = 11.0, 5.2$), 2.10–2.04 (m, 1H), 1.84 (ddd, 1H, $J = 13.8, 11.5, 5.0$), 1.80–1.74 (m, 1H), 1.68 (ddd, 1H, $J = 13.1, 9.6, 3.6$), 1.53 (ddd, 1H, $J = 13.0, 6.8, 3.1$), 1.24 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H).

$^{13}$C-NMR (151 MHz): $\delta$ 179.6, 153.0, 138.6, 135.6, 127.4, 119.8, 117.8, 37.6, 35.9, 35.3, 30.69, 30.54, 29.4, 25.7, 19.5, 18.1, -4.4 (2 peaks).

ESI-MS m/z (rel int): (pos) 371.19 ([M+Na]$^+$, 100); (neg) 347.12 ([M–H]$^-$, 100), 695.39 ([2M–H]$^-$, 40).

3-(2-Hydroxy-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)propanoic acid (21). Carboxylic acid intermediate S29 (293 mg, 0.840 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 1.7 mL, 1.7 mmol, 2.0 equiv) was added by syringe and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with satd aq NH$_4$Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes + 1% AcOH) yielded 21 (160 mg, 81%) as a white solid.

TLC: $R_f$ 0.17 (30% EtOAc/hexanes + 1% AcOH). IR (NaCl, film): 3314, 2933, 1701, 1610, 1583, 1499, 1457, 1237, 817, 735. $^1$H-NMR (600 MHz): $\delta$ 7.10 (d, 1H, $J = 8.5$), 6.63 (dd, 1H, $J = 8.5, 2.8$), 6.51 (d, 1H, $J = 2.8$), 2.68 (t, 2H, $J = 6.3$), 2.27 (ddd, 1H, $J = 16.1, 11.4, 4.9$), 2.14 (td, 1H, $J = 10.9, 5.2$), 2.11–2.04 (m, 2H), 1.85 (ddd, 1H, $J = 13.8, 11.4, 5.1$), 1.81–1.73 (m, 2H), 1.68 (td, 1H, $J = 11.4, 3.5$), 1.54 (ddd, 1H, $J = 13.0, 6.9, 3.1$), 1.25 (s, 3H). $^{13}$C-NMR (151 MHz): $\delta$ 179.6, 153.0, 138.6, 135.6, 127.8, 115.1, 113.4, 37.6, 36.0, 35.2, 30.67, 30.57, 29.6, 19.4. ESI-MS m/z (rel int): (pos) 257.08 ([M+Na]$^+$, 100); (neg) 233.08 ([M–H]$^-$, 100), 467.22 ([2M–H]$^-$, 66).
11. SYNTHESIS OF PHENOL 22

Supplementary Figure 28. Synthesis of phenol 22.

2-[(6-Hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]acrylic acid (22). A solution of methyl ester S8 (85 mg, 0.227 mmol) in THF (5 mL) was cooled to −78 °C. TBAF was added by syringe (1 M in THF, 250 μL, 0.250 mmol, 1.1 equiv). After 15 min the reaction was quenched with satd aq NH₄Cl and warmed to 25 °C. The product was extracted with EtOAc and washed with brine. The organic phase was dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. The crude methyl ester phenol was immediately dissolved in THF/H₂O (3:1, 5 mL) and LiOH·H₂O (48 mg 1.14 mmol, 5.0 equiv) was added. After stirring for 12 h at 25 °C, the reaction was warmed to 50 °C and stirred for an additional 12 h to consume unreacted methyl ester. The reaction was then cooled to 25 °C, diluted with EtOAc, and slowly quenched with HCl (1 N aq, 2 mL). The organic layer was separated and the aqueous layer was extracted with additional EtOAc (2×). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. The crude product was purified by silica flash chromatography (8:2→7:3 hexanes/EtOAc w/ 1% AcOH) to yield the free acid 22 (49 mg, 88%) as a colorless oil that solidified on standing.

TLC: Rf 0.28 (7:3 hexanes/EtOAc). IR (NaCl, film): 3286 (O–H st), 2933, 1692 (C=O st), 1619, 1499, 1440, 1239. ¹H-NMR (500 MHz, CD₃OD): δ 7.07 (d, 1H, J = 8.5), 6.50 (d, 1H, J = 8.5, 2.7), 6.07 (s, 1H), 5.30 (s, 1H), 2.65 (d, 1H, J = 13.5), 2.58 (t, 2H, J = 6.3), 2.50 (d, 1H, J = 13.5), 1.78–1.69 (m, 2H), 1.66–1.61 (m, 1H), 1.41 (ddd, 1H, J = 12.8, 9.7, 2.9), 1.16 (s, 3H). ¹³C-NMR (126 MHz, CD₃OD): δ 171.8, 155.8, 140.4, 139.1, 136.4, 129.3, 128.2, 115.9, 114.3, 44.3, 38.2, 36.8, 31.9, 30.1, 20.6. ESI-MS m/z (rel int): (pos) 269.0 ([M+Na]+, 100); (neg) 245.0 ([M–H]–, 100), 490.9 ([2M–H]–, 80).
12. SYNTHESIS OF PHENOL 23

Supplementary Figure 29. Synthesis of phenol 23.

3-(2-((tert-Butyldimethylsilyl)oxy)-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-propanoic acid (S30). Alcohol S20 (26.4 mg, 0.0789 mmol) was dissolved in CH2Cl2 (0.40 mL). Satd aq NaHCO3 (0.16 mL) was added followed by KBr (0.9 mg, 0.008 mmol, 0.1 equiv), N,N,N-trimethylbenzylammonium chloride (0.7 mg, 0.004 mmol, 0.05 equiv), and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (0.6 mg, 0.004 mmol, 0.05 equiv). The mixture was cooled to 0 °C and a solution of NaOCl (10–15% Cl, 0.062 mL, 2.51 mmol) was added by syringe. The reaction was stirred at 0 °C for 45 min, then quenched with 1 M aq HCl and diluted with CH2Cl2. The aqueous layer was extracted with CH2Cl2 (4×) and the combined organic layers were dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10% EtOAc/hexanes + 1% AcOH) yielded S30 (17.2 mg, 60%) as a colorless oil.

**TLC:** Rf 0.22 (10% EtOAc/hexanes + 1% AcOH). **IR** (NaCl, film): 2929, 2858, 1701, 1604, 1494, 1295, 1254, 986, 838, 780. **1H-NMR** (600 MHz): δ 7.08 (d, 1H, J = 8.7), 6.58 (dd, 1H, J = 8.5, 2.8), 6.55 (d, 1H, J = 2.7), 3.03–2.98 (m, 1H), 2.66–2.62 (m, 1H), 2.32–2.22 (m, 2H), 2.03–1.98 (m, 1H), 1.89–1.80 (m, 3H), 1.79–1.74 (m, 1H), 1.62–1.57 (m, 1H), 1.50–1.42 (m, 1H), 1.32 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H). **13C-NMR** (151 MHz): δ 177.4, 153.4, 143.5, 138.0, 128.4, 122.9, 116.6, 141.3, 40.2, 36.9, 29.7, 29.2, 27.8, 25.7, 25.3, 18.1, –4.4. **ESI-MS** m/z (rel int): (pos) 227.03 ([M–C7H14O2Si+Na]+, 100), 385.13 ([M+Na]+, 40); (neg) 361.19 ([M–H]–, 100).

3-(2-Hydroxy-5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)propanoic acid (23). Carboxylic acid S30 (57.3 mg, 0.158 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 0.32 mL, 0.32 mmol, 2.0 equiv) was added by syringe and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with satd aq NH4Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4x) and the combined organic extracts were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary
evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes + 1% AcOH) yielded 23 (31.9 mg, 81%) as a white solid.

**TLC:** \( R_f\ 0.20 \) (30% EtOAc/hexanes + 1% AcOH). **IR** (NaCl, film): 3314, 2926, 1701, 1609, 1583, 1497, 1457, 1251, 909, 732. **\(^1\)H-NMR** (600 MHz): \( \delta 7.11 \) (d, 1H, \( J = 8.5 \)), \( 6.59 \) (dd, 1H, \( J = 8.5, 2.8 \)), \( 6.56 \) (d, 1H, \( J = 2.8 \)), \( 3.05 \)–\( 3.00 \) (m, 1H), \( 2.67 \)–\( 2.64 \) (m, 1H), \( 2.33 \)–\( 2.27 \) (m, 1H), \( 2.27 \)–\( 2.22 \) (m, 1H), \( 1.90 \)–\( 1.75 \) (m, 5H), \( 1.62 \)–\( 1.57 \) (m, 1H), \( 1.50 \)–\( 1.44 \) (m, 1H), \( 1.32 \) (s, 3H). **\(^13\)C-NMR** (151 MHz): \( \delta 178.8, 153.3, 143.9, 137.7, 128.8, 118.2, 112.1, 41.3, 40.3, 36.9, 34.0, 29.7, 29.5, 27.7, 25.2.**

**ESI-MS** \( m/z \) (rel int): (pos) 271.0 ([M+Na]\(^+\), 100), 519.3 ([2M+Na]\(^+\), 23; (neg) 282.9 ([M+Cl]\(^−\), 100), 246.9 ([M+Cl]\(^−\), 71), 531.2 ([2M+Cl]\(^−\), 48).

13. **SYNTHESIS OF PHENOL 24**

![Supplementary Figure 30. Synthesis of phenol 24.](image)

3-(2-((tert-Butyldimethylsilyloxy)-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-yl)-propanoic acid (S31). Allylated intermediate S26 (180 mg, 0.523 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. 9-BBN (128 mg, 1.05 mmol, 1.97 equiv) was dissolved in THF (2 mL) and added to the olefin solution via a cannula. The reaction was stirred at 0 °C to 25 °C overnight. The reaction was recooled to 0 °C, quenched with phosphate buffer (2 mL, pH 7.2) and \( \text{H}_2\text{O}_2 \) (30 wt%, 1 mL). EtOH (2 mL) was then added and the mixture was stirred at 0 °C to 25 °C for 6 h. The volatile solvents were removed by rotary evaporation and the aqueous mixture was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)), filtered, and concentrated by rotary evaporation to afford the crude product. Partial purification by silica flash chromatography (20% EtOAc/hexanes) afforded the alcohol (202 mg, 106%) with 5–10% 9-BBN byproducts that did not adversely effect subsequent reactions. A sample of the intermediate alcohol (93.7 mg, 0.258 mmol) was dissolved in acetone (1.3 mL). The mixture was cooled to 0 °C and a solution of Jones reagent\(^16\) was added by pipette until an orange color persisted. The reaction was stirred at 0 °C for 45 min, then quenched with isopropanol and Celite (Fisher Scientific) was added. The mixture was stirred for 10 min then filtered through Celite and concentrated by rotary evaporation. The residue was dissolved in EtOAc and water and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried (\( \text{Na}_2\text{SO}_4 \)), filtered, and concentrated by rotary evaporation to afford the crude product.
product. Purification by silica flash chromatography (20% EtOAc/hexanes + 1% AcOH) yielded S31 (38.2 mg, 70% over 2 steps) as a colorless oil.

**TLC:** \( R_f \) 0.21 (20% EtOAc/hexanes + 1% AcOH). **IR** (NaCl, film): 2929, 1706, 1604, 1490, 1251, 992, 840, 780. 1H-NMR (600 MHz): \( \delta \) 7.15 (d, 1H, \( J = 8.7 \)), 6.62 (dd, 1H, \( J = 8.6, 2.8 \)), 6.46 (d, 1H, \( J = 2.8 \)), 3.28 (br s, 1H), 2.58 (br s, 2H), 2.20–2.15 (m, 1H), 2.09–2.04 (m, 1H), 1.90–1.83 (m, 2H), 1.81–1.73 (m, 2H), 1.66–1.61 (m, 1H), 1.60–1.55 (m, 1H), 1.52–1.48 (m, 1H), 1.40 (s, 3H), 1.30–1.26 (m, 2H), 1.16–1.08 (m, 1H), 0.98 (s, 9H), 0.19 (s, 6H). 13C-NMR (151 MHz): \( \delta \) 179.1, 153.7, 141.0, 138.3, 129.0, 122.9, 117.3, 41.7, 41.6, 40.1, 35.0, 29.7, 29.3, 29.1, 25.7, 24.9, 22.0, 18.2, –4.3 (2 peaks).**ESI-MS** m/z (rel int): (pos) 399.14 ([M+Na]+, 100); (neg) 375.14 ([M–H]–, 100), 283.08 ([M+Cl]–, 56).

3-(2-Hydroxy-5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-yl)propanoic acid (24). The carboxylic acid S31 (38.2 mg, 0.101 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 0.11 mL, 0.11 mmol, 1.1 equiv) was added by syringe and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4 ×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes + 1% AcOH) yielded 24 (25.8 mg, 98%) as a colorless oil.

**TLC:** \( R_f \) 0.20 (30% EtOAc/hexanes + 1% AcOH). **IR** (NaCl, film): 2930, 1703, 1608, 1580, 1492, 1449, 1241. 1H-NMR (600 MHz): \( \delta \) 7.18 (d, 1H, \( J = 8.6 \)), 6.61 (dd, 1H, \( J = 8.6, 2.9 \)), 6.45 (d, 1H, \( J = 2.9 \)), 3.30 (br s, 1H), 2.59 (br s, 2H), 2.22–2.16 (m, 1H), 2.09–2.04 (m, 1H), 1.89–1.83 (m, 2H), 1.82–1.73 (m, 2H), 1.66–1.62 (m, 1H), 1.62–1.53 (m, 1H), 1.53–1.46 (m, 1H), 1.40 (s, 3H), 1.31–1.25 (m, 1H), 1.17–1.12 (m, 1H). 13C-NMR (151 MHz): \( \delta \) 178.4, 153.5, 141.4, 137.8, 129.4, 118.0, 112.7, 41.7, 39.9, 34.9, 29.7, 29.2, 28.9, 24.9, 22.0, (one carbon unresolved). **ESI-MS** m/z (rel int): (pos) 285.07 ([M+Na]+, 100); (neg) 523.18 ([2M–H]–, 83).

### 14. Synthesis of Bisphenol 25

![Synthesis of bisphenol 25](image-url)
2-(3-[6-[[1-Butyldimethylsilyl]oxy]-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl]prop-1-en-2-yl)phenol (S32). To a solution of vinyl bromide S6 (8.13 g, 20.5 mmol) in toluene/EtOH (1:1, 100 mL) was added 2-hydroxyphenylboronic acid pinacol ester (5.42 g, 24.6 mmol, 1.20 equiv), Pd(PPh₃)₄ (1.2 g, 1.03 mmol, 5 mol%), and Na₂CO₃ (1 M aq, 62 mL, 3.0 equiv). The reaction was heated to 80 °C and stirred for 12 h. The reaction was then cooled to 25 °C and passed over a pad of Celite (Fisher Scientific). The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with H₂O (2×) and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10:0—9:1 hexanes/EtOAc) yielded S32 (7.62 g, 91%) as a yellow oil.

**TLC:** R, 0.42 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 3510 (O–H st), 2930, 2858, 1496, 1260, 839. **¹H-NMR** (500 MHz): δ 7.14–7.05 (m, 3H), 6.87–6.83 (m, 2H), 6.58 (dd, 1H, J = 8.5, 2.5), 6.50 (d, 1H, J = 2.5), 5.41 (s, 1H), 5.26 (s, 1H), 5.17 (s, 1H), 2.91 (d, 1H, J = 13.8), 2.75 (d, 1H, J = 13.8), 2.62–2.57 (m, 2H), 1.71–1.57 (m, 3H), 1.44–1.39 (m, 1H), 1.14 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H). **¹³C-NMR** (126 MHz): δ 153.0, 151.8, 143.8, 138.0, 136.7, 129.8, 128.1, 120.0, 119.8, 119.6, 117.6, 115.6, 50.5, 37.5, 35.4, 30.8 (2 peaks), 25.8, 19.5, 18.2, –4.3. **ESI-MS** m/z (rel int): (pos) 431.1 ([M+Na]+, 100); (neg) 407.2 ([M–H]–, 100).

5-(2-[[2-Hydroxyphenyl]allyl]-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (25). Phenol S32 (7.62 g, 18.6 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 20.5 mL, 20.5 mmol, 1.10 equiv) was added by syringe over 5 min and the reaction was stirred for an additional 10 min at 0 °C. The reaction was warmed to 25 °C, stirred an additional 20 min, and quenched with satd aq NH₄Cl. The crude product was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 CH₂Cl₂/MeOH) gave 25 (4.87 g, 89%) as a brown oil.

**TLC:** R, 0.27 (95:5 CH₂Cl₂/MeOH). **IR** (NaCl, film): 3384 (O–H st), 2929, 1608, 1498, 1447, 1232. **¹H-NMR** (500 MHz): δ 7.12–7.05 (m, 3H), 6.86–6.83 (m, 2H), 6.57 (dd, 1H, J = 8.4, 2.5), 6.47 (d, 1H, J = 2.5), 5.50–5.40 (br s, 1H), 5.26 (s, 1H), 5.16 (s, 1H), 5.10–4.95 (br s, 1H), 2.90 (d, 1H, J = 13.8), 2.73 (d, 1H, J = 13.8), 2.62–2.54 (m, 2H), 1.69–1.58 (m, 3H), 1.42–1.36
(m, 1H), 1.15 (s, 3H). $^{13}$C-NMR (126 MHz): $\delta$ 153.0, 151.6, 143.7, 138.5, 136.3, 129.7, 128.7, 128.5, 128.2, 120.8, 119.8, 115.6, 115.1, 113.2, 50.6, 37.5, 35.4, 30.9, 30.8, 19.4. ESI-MS m/z (rel int): (pos) 317.0 ([M+Na]$^+$, 100); (neg) 293.1 ([M–H]$^-$, 100).

15. SYNTHESIS OF PHENOL 26

$t$-Butyl-(5-(2,3-dimethoxyphenyl)allyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-yl]-oxy)dimethylsilane (S33). To a solution of vinyl bromide S6 (2.25 g, 5.7 mmol) in toluene/EtOH (1:1, 57 mL) was added 2,3-dimethoxyphenylboronic acid (1.35 g, 7.4 mmol, 1.30 equiv), Pd(PPh$_3$)$_4$ (329 mg, 0.285 mmol, 5 mol%), and Na$_2$CO$_3$ (1 M aq, 23 mL, 4 equiv). The reaction was heated to 80 °C and stirred for 6 h. The reaction was cooled to 25 °C and passed over a pad of Celite (Fisher Scientific). The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10:0→9:1 hexanes/EtOAc w/ 1% NEt$_3$) yielded S33 (2.4 g, 93%) as a brown oil.

TLC: $R_f$ 0.30 (95:5 hexanes/EtOAc). IR (NaCl, film): 2931, 1607, 1574, 1496, 1471, 1262, 1118, 840, 780. $^1$H-NMR (500 MHz): $\delta$ 7.14 (d, 1H, $J = 8.5$), 6.93 (t, 1H, $J = 7.9$), 6.80 (dd, 1H, $J = 8.5, 1.4$), 6.67 (dd, 1H, $J = 7.7, 1.4$), 6.55 (dd, 1H, $J = 8.5, 2.6$), 6.46 (d, 1H, $J = 2.5$), 5.10 (s, 1H), 5.07 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.03 (d, 1H, $J = 13.4$), 2.88 (d, 1H, $J = 13.9$), 2.63 (t, 2H, $J = 6.3$), 1.82 (dtt, 1H, $J = 13.4, 9.2, 4.4$), 1.79–1.75 (m, 1H), 1.65–1.60 (m, 1H), 1.44–1.39 (m, 1H), 1.12 (s, 3H), 1.00 (s, 3H), 0.21 (s, 6H). $^{13}$C-NMR (126 MHz): $\delta$ 152.7, 152.5, 146.2 (2 peaks), 138.9, 138.0, 137.6, 128.1, 123.8, 122.3, 119.4, 118.9, 117.4, 111.1, 60.6, 55.9, 48.9, 37.2, 35.3, 30.9, 30.4, 25.8, 19.5, 18.2, –4.3. ESI-MS m/z (rel int): (pos) 475.1 ([M+Na]$^+$, 100).
5-(2-[2,3-Dimethoxyphenyl]allyl)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (26). Tricycle S33 (2.4 g, 5.3 mmol) was dissolved in THF (25 mL) and cooled to –78 °C. A solution of TBAF (1 M in THF, 0.838 mL, 1.1 equiv) was added by syringe and the reaction was stirred for 20 min. The reaction was warmed to 25 °C and quenched with satd aq NH₄Cl. The crude product was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) gave 26 (1.61 g, 90%) as a brown oil.

**TLC**: Rf 0.38 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 3386 (O–H st), 2932, 1575, 1498, 1470, 1263, 1226, 1060, 1006, 909. **¹H-NMR** (500 MHz): δ 7.14 (d, 1H, J = 8.5), 6.93 (dd, 1H, J = 10.2, 5.7), 6.80 (dd, 1H, J = 8.2, 1.4), 6.65 (dd, 1H, J = 7.7, 1.4), 6.55 (dd, 1H, J = 8.5, 2.7), 6.54 (d, 1H, J = 2.6), 5.09 (s, 1H), 5.07 (s, 1H), 4.96–4.88 (br s, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.99 (d, 1H, J = 13.8), 2.88 (d, 1H, J = 13.8), 2.61 (t, 2H, J = 6.3), 1.83–1.78 (m, 1H), 1.77–1.70 (m, 1H), 1.65–1.58 (m, 1H), 1.39 (ddd, 1H, J = 13.1, 8.6, 2.8), 1.09 (s, 3H). **¹³C-NMR** (126 MHz): δ 152.9, 152.5, 146.2, 146.1, 138.8, 138.0, 137.6, 128.5, 123.9, 122.3, 119.0, 114.8, 113.0, 111.1, 60.7, 55.9, 48.9, 37.2, 35.2, 30.8, 30.3, 19.4. **ESI-MS** m/z (rel int): (pos) 361.0 ([M+Na]+, 85), 699.2 ([2M+Na]+, 100); (neg) 337.0 ([M–H]–, 100).

**16. SYNTHESIS OF PHENOL 27**

Supplementary Figure 33. Synthesis of phenol 27.
1-Allyl-6-(t-butylidemethylsilyloxy)-1,2,3,4-tetrahydronaphthalen-1-ol (S34). Tetralone S4 (600 mg, 2.17 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. A solution of allyl-MgBr (1 M in Et₂O, 4.3 mL, 4.3 mmol, 2.0 equiv) was added by syringe. The reaction was allowed to warm to 25 °C and stirred for 12 h. The reaction was quenched with satd aq NaHCO₃. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc w/ 1% NEt₃) yielded benzylic alcohol S34 (690 mg, 99%) as a clear oil.

TLC: R_f 0.29 (4:1 hexanes/EtOAc). IR (NaCl, film): 3396 (O–H str), 2932, 2859, 1639, 1497, 1257, 975, 840. ¹H-NMR (500 MHz): δ 7.37 (d, 1H, J = 8.5), 6.67 (d, 1H, J = 8.5), 6.52 (s, 1H), 5.81–5.72 (m, 1H), 5.10 (d, 1H, J = 6.8), 5.07 (s, 1H), 2.74–2.60 (m, 2H), 2.56 (d, 2H, J = 7.3), 1.96–1.94 (m, 1H), 1.91 (s, 1H), 1.83–1.74 (m, 3H), 0.96 (s, 9H), 0.17 (s, 6H).

¹³C-NMR (125 MHz): δ 154.5, 138.4, 134.7, 134.4, 127.6, 119.6, 118.4, 118.2, 71.7, 47.2, 36.3, 30.1, 25.7, 19.8, 18.2, –4.3. ESI-MS m/z (rel int): (pos) 341.1 ([M+Na]+, 100), 356.9 ([M+K]+, 5).

t-Butyl-(5,5-diallyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)dimethylsilane (S35). Tertiary benzylic alcohol S34 (570 mg, 1.79 mmol) and allyltrimethylsilane (1.43 mL, 8.95 mmol, 5.00 equiv) were dissolved in CH₂Cl₂ (18 mL) and cooled to –78 °C. A solution of TiCl₄ (1 M in toluene, 1.97 mL, 1.97 mmol, 1.10 equiv) was added slowly by syringe and the reaction stirred for 1 h at –78 °C. The reaction was quenched slowly with satd aq NaHCO₃, warmed to 25 °C, and the resulting mixture was diluted with brine to solubilize the titanium salts. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (hexanes) yielded S35 (574 mg, 94%) as a clear oil.

TLC: R_f 0.34 (hexanes). IR (NaCl, film): 2931, 2859, 1638, 1496, 1254, 978, 912, 840, 780. ¹H-NMR (500 MHz): δ 7.09 (d, 1H, J = 8.6), 6.62 (d, 1H, J = 8.6), 6.51 (s, 1H), 5.64–5.57 (m, 2H), 5.00–4.95 (m, 4H), 2.63 (t, 2H, J = 6.3), 2.48 (dd, 2H, J = 14.0, 6.5), 2.24 (dd, 2H, J = 14.0, 8.0), 1.75–1.72 (m, 2H), 1.67–1.65 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H). ¹³C-NMR (126 MHz): δ 153.0, 138.9, 136.3, 135.4, 135.2, 135.0, 128.1, 120.4, 117.2, 117.1, 46.7, 39.4, 30.7, 26.0, 25.9, 25.7, 19.4, 18.2, –4.4, –4.2. ESI-MS m/z (rel int): (pos) 343.0 ([M+H]+, 80), 365.1 ([M+Na]+, 100).
3,3′-(6-[(t-Butyldimethylsilyl)oxy]-1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(propan-1-ol) 
(S36). Diallyl intermediate S35 (300 mg, 0.88 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of 9-BBN in THF (0.5 M, 4.3 mL, 2.5 equiv) was added by syringe. The reaction was warmed to 25 °C and stirred overnight. The reaction was cooled to 0 °C again, and EtOH (3 mL) was added slowly. Phosphate buffer (10 mL, pH 7.2) and aq H₂O₂ (30 wt%, 1.8 mL) were added sequentially. The reaction was warmed to 25 °C and stirred for 8.5 h. The reaction was quenched with satd aq NH₄Cl and extracted into EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (4:6 hexanes/EtOAc) yielded diol S36 (267 mg, 81%) as a colorless oil.

TLC: Rₖ 0.21 (4:6 hexanes/EtOAc). IR (NaCl, film): 3334 (O–H st), 2933, 2859, 1607, 1496, 1257, 1059, 840, 781, 734. ¹H-NMR (500 MHz): δ 7.02 (d, 1H, J = 8.5), 6.59 (dd, 1H, J = 8.5, 2.6), 6.49 (d, 1H, J = 2.6), 3.51 (t, 4H, J = 6.5), 2.63 (t, 2H, J = 6.2), 1.88 (br s, 2H), 1.76–1.70 (m, 2H), 1.70–1.65 (m, 4H), 1.57–1.43 (m, 4H), 1.37–1.28 (m, 2H), 0.96 (s, 9H), 0.19 (s, 6H).

¹³C-NMR (126 MHz): δ 152.8, 138.9, 135.7, 127.7, 119.8, 117.6, 63.6, 38.7, 38.5, 32.2, 30.8, 27.8, 25.7, 19.8, 18.2, –4.3. ESI-MS m/z (rel int): (pos) 379.4 ([M+H]+, 20), 401.4 ([M+Na]+, 100); (neg) 377.3 ([M–H]–, 100).

3,3′-(6-Hydroxy-1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(propan-1-ol) (27). Diol S36 (205 mg, 0.54 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 600 μL, 0.60 mmol, 1.1 equiv) was added by syringe and the reaction was stirred for 15 min. The reaction was warmed to 25 °C and concentrated by rotary evaporation to afford the crude triol. Purification by silica flash chromatography (9:1 CH₂Cl₂/MeOH, 1% AcOH) yielded triol 27 (130 mg, 91%) as a yellow oil.

TLC: Rₖ 0.43 (100% EtOAc). IR (NaCl, film): 3319 (O–H st), 2939, 2869, 1610, 1498, 1454, 1240, 1056. ¹H-NMR (500 MHz, CD₃OD): δ 6.95 (d, 1H, 8.5), 6.47 (dd, 1H, J = 8.5, 2.7), 6.35 (d, 1H, J = 2.7), 3.35 (t, 4H, J = 6.6), 2.53 (t, 2H, J = 5.7), 1.68–1.56 (m, 6H), 1.47–1.32 (m, 4H), 1.25–1.16 (m, 2H). ¹³C-NMR (126 MHz, CD₃OD): δ 155.6, 140.2, 135.2, 129.1, 116.4, 115.4, 63.9, 50.3, 41.0, 40.2, 39.8, 30.0, 21.3. ESI-MS m/z (rel int): (neg) 263.3 ([M–H]–, 100), 527.3 ([2M–H]–, 50).
**17. SYNTHESIS OF PHENOL 28**

![Supplementary Figure 34. Synthesis of phenol 28.](image)

**3-(6-Hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propane-1,2-diol (28).** Allylated intermediate 3 (377 mg, 1.19 mmol) was dissolved in THF/H₂O (9:1, 10 mL). To this solution was added OsO₄ (4 wt% in H₂O, 378 μL, 56 μmol, 5 mol%), 4-methylmorpholine N-oxide (153 mg, 1.31 mmol, 1.10 equiv), and DABCO (~20 mg, catalytic). The resulting solution was stirred at 25 °C for 12 h. When the reaction was complete it was quenched with satd aq Na₂S₂O₃ and stirred for 15 min. The mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude diol, which was immediately redissolved in THF (10 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 1.3 mL, 1.3 mmol, 1.1 equiv) was added by syringe. After stirring for 15 min at 0 °C the reaction was warmed to 25 °C and concentrated by rotary evaporation to afford the crude triol. Purification by silica flash chromatography (95:5 EtOAc/MeOH w/ 1% AcOH) yielded 28 (245 mg, 88%, 1.2:1:0 dr) as a yellow oil.

**TLC:** Rₛ 0.19 (4:6 hexanes/EtOAc). **IR** (NaCl, film): 3334 (O–H st), 2932, 1611, 1501, 1446, 1240, 1067. **¹H-NMR** (500 MHz, 1:1 C₆D₆/CD₃OD): δ 7.10 (d, 1H-major, J = 8.5), 7.01 (d, 1H-minor, J = 8.5), 6.53 (d, 1H-major, 1H-minor, J = 8.5), 6.41 (s, 1H-minor), 6.40 (s, 1H-major), 3.68–3.63 (m, 1H-major), 3.50–3.46 (m, 1H-minor), 3.34–3.29 (m, 1H-major, 1H-minor), 3.22 (d, 1H-major, 1H-minor, J = 5.9), 2.64–2.57 (m, 2H-major, 2H-minor), 2.03 (ddd, 1H-minor, J = 13.4, 10.4, 3.2), 1.94–1.84 (m, 1H-major, 1H-minor), 1.83–1.76 (m, 1H-major), 1.77–1.62 (m, 3H-major, 3H-minor), 1.57–1.49 (m, 1H-major, 1H-minor), 1.22 (s, 3H-major, 3H-minor). **¹³C-NMR** (126 MHz): δ 155.7, 155.6, 139.5, 138.9, 137.2, 136.8, 116.5, 115.5, 114.9, 114.7, 114.2, 113.9, 71.6, 70.1, 70.5, 68.7, 48.0, 47.3, 37.3, 36.8, 32.6, 32.5, 31.8, 30.9, 21.8, 21.5, 20.9, 20.7. **ESI-MS m/z** (rel int): (pos) 259.2 ([M+Na]⁺, 90), 495.4 ([2M+Na]⁺, 100); (neg) 235.1 ([M–H]⁻, 100), 471.4 ([2M–H]⁻, 100). The ratio of diastereomers was determined based on the aromatic ¹H-NMR peaks meta to the phenol: δ 7.10 (d) major, 7.01 (d) minor.
18. **SYNTHESIS OF PHENOL 29**

![Chemical Structure](image)

**Supplementary Figure 35. Synthesis of phenol 29.** (a) Synthesis of phenol 29. (b) Intermediate S38 was acetylated in order to resolve $^1$H-NMR peaks for determination of stereochemistry by NOESY.

t-Butyldimethyl(5-methyl-7,8-dihyronaphthalen-2-ylxy)silane (S37). Tetralone S4 (600 mg, 2.17 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of MeMgCl (3 M in Et₂O, 1.45 mL, 4.35 mmol, 2.00 equiv) was added by syringe and the reaction was allowed to warm to 25 °C. After stirring for 12 h, the reaction was cooled to 0 °C and quenched with satd aq NH₄Cl. The resulting mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude tertiary alcohol product (2). This crude intermediate was dissolved in CH₂Cl₂ (10 mL), treated with catalytic PPTS (20 mg), and stirred for 1 h at 25 °C. The acid-catalyzed dehydration was quenched with satd aq NaHCO₃ and extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the desired styrene. Purification by silica flash chromatography (100% hexane) yielded S37 (507 mg, 85%, 11:1 exocyclic:endocyclic olefin) as a yellow oil.

**TLC:** R₁ 0.27 (hexanes). **IR** (NaCl, film): 3031, 2930, 2858, 1605, 1496, 1285, 1255, 963, 841, 780. **$^1$H-NMR** (500 MHz): δ 7.13 (d, 1H, J = 8.2), 6.70 (d, 1H, J = 8.2), 6.68 (s, 1H), 5.76 (t, 1H, J = 4.3), 2.75 (t, 2H, J = 8.1), 2.30–2.24 (m, 2H), 2.07 (s, 3H), 1.05 (s, 9H), 0.25 (s, 6H). **$^{13}$C-NMR** (126 MHz): δ 154.5, 138.0, 132.0, 129.6, 123.9, 123.1, 119.4, 117.3, 28.8, 25.8, 23.3, 19.5, 18.3, –4.3. **ESI-MS** m/z (rel int): (pos) 275.3 ([M+H]⁺).
(1R*,2R*)-1-Allly-6-([t-butyldimethylsilyloxy]-1-methyl-1,2,3,4-tetrahydronaphthalen-2-ol (S38). To a solution of S37 (200 mg, 0.73 mmol) in THF/H2O (9:1, 10 mL) was added OsO4 (230 μL, 4 wt% in H2O, 0.037 mmol, 0.05 equiv), NMO (94 mg, 0.80 mmol, 1.1 equiv), and DABCO (~10 mg, catalytic). The solution was stirred overnight, quenched with satd aq Na2S2O3 and stirred for an additional 30 min. The resulting mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (MgSO4), filtered, and concentrated by rotary evaporation to give a dark brown oil. This crude intermediate was dissolved in CH2Cl2 (7.4 mL) and allyltrimethylsilane (591 μL, 3.7 mmol, 5.0 equiv) was added. The solution was cooled to –78 °C. A solution of TiCl4 (1 M in toluene, 814 μL, 0.81 mmol, 1.1 equiv) was added slowly by syringe and the solution was stirred for 30 min. The reaction was quenched slowly at –78 °C with satd aq NaHCO3, warmed to 25 °C, and the resulting mixture was diluted with brine to solubilize the titanium salts. The resulting mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc) yielded S38 (181 mg, 75%, 7:1 dr) as a colorless oil.

TLC: Rf 0.36 (8:2 hexanes/EtOAc). IR (NaCl, film): 3396 (O–H st), 2931, 2858, 1608, 1497, 1252, 990, 840, 780. 1H-NMR (500 MHz): δ 7.14 (d, 1H, J = 8.6), 6.68 (dd, 1H, J = 8.6, 2.7), 6.59 (d, 1H, J = 2.7), 5.96 (ddt, 1H, J = 17.2, 9.9, 7.4), 5.15 (d, 1H, J = 17.2), 5.10 (d, 1H, J = 9.9), 3.85 (app q, 1H, J = 5.3), 2.98 (dt, 1H, J = 17.1, 7.2), 2.76 (dt, 1H, J = 17.1, 6.6), 2.55 (dt, 1H, J = 14.2, 7.2), 2.49 (dd, 1H, J = 13.9, 7.1), 2.04–1.98 (m, 2H), 1.91 (d, 1H, J = 5.3), 1.28 (s, 3H), 1.03 (s, 9H), 0.23 (s, 6H). 13C-NMR (126 MHz): δ 153.4, 136.4, 136.2, 135.5, 128.1, 119.6, 117.9, 117.3, 74.2, 42.6, 41.3, 26.9, 26.4, 26.3, 25.8, 18.2, –4.3. ESI-MS m/z (rel int): (pos) 355.2 ([M+Na]+, 100); (neg) 331.1 ([M–H]–, 100). The ratio of diastereomers was determined based on the internal olefinic 1H-NMR peak: δ 5.96 (ddt) major, 5.64 (m) minor.

The stereochemistry of allylsilane addition for the major product was determined by NOESY correlations of the acetylated derivative S41 (see below).

((5R*,6R*)-5-Allly-5-methyl-6-([triisopropylsilyloxy]-5,6,7,8-tetrahydronaphthalen-2-yl]-oxy)(t-butyldimethylsilane (S39). To a solution of secondary alcohol S38 (175 mg, 0.53 mmol) in CH2Cl2 (5 mL) was added 2,6-lutidine (153 μL, 1.32 mmol, 2.50 equiv) and TIPSOTf (179 μL, 0.67 mmol, 1.3 equiv). The reaction was warmed to reflux and stirred for 12 h. After cooling to 25 °C, the reaction was quenched with satd aq NaHCO3 and extracted with Et2O (2x). The combined organic extracts were washed with brine, dried (Na2SO4), filtered,
and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (100% hexanes) yielded S39 (200 mg, 77%) as a brown oil.

**TLC:** \(R_f\) 0.20 (100% hexanes). \textbf{IR} (NaCl, film): 2943, 2865, 1497, 1252, 1097, 842. \textbf{\(^1\)H-NMR} (500 MHz): \(\delta\) 7.10 (d, 1H, \(J = 8.6\)), 6.63 (dd, 1H, \(J = 8.6, 2.6\)), 6.53 (d, 1H, \(J = 2.6\)), 5.73–5.68 (m, 1H), 4.95–4.89 (m, 2H), 3.96 (dd, 1H, \(J = 11.8, 3.7\)), 2.82 (dd, 2H, \(J = 8.6, 4.0\)), 2.45 (dd, 1H, \(J = 13.5, 7.5\)), 2.34 (dd, 1H, \(J = 13.5, 7.5\)), 2.15–2.08 (m, 1H), 1.92–1.87 (m, 1H), 1.36 (s, 3H), 1.15–1.11 (m, 21H), 0.99 (s, 9H), 0.20 (s, 6H). \textbf{\(^{13}\)C-NMR} (126 MHz): \(\delta\) 153.3, 136.8, 136.1, 135.7, 128.8, 119.2, 117.2, 116.4, 42.7, 41.3, 28.8, 27.8, 25.7, 25.0, 18.4 (2 peaks), 18.2, 13.1, –4.3. \textbf{ESI-MS} \(m/z\) (rel int): (pos) 511.1 ([M+Na]\(^+\), 100).

2-([1R*,2R*]-6-([\(t\)-Butyldimethylsilyl]oxy)-1-methyl-2-((triisopropylsilyl]oxy)-1,2,3,4-tetrahydro-naphthalen-1-yl)ethanol (S40). Allylated intermediate S39 (200 mg, 0.41 mmol) and \(K_2CO_3\) (113 mg, 2.00 equiv) were suspended in \(CHCl_3/MeOH\) (3:1, 5 mL) and cooled to \(-78\) °C. Ozone was bubbled through until TLC analysis indicated consumption of the starting material (10–30 min). The reaction was purged with \(N_2\) for 15 minutes at \(-78\) °C. \(NaBH_4\) (77 mg, 5.0 equiv) was added as a solid and the reaction was warmed to 25 °C. After stirring for 1 h, the reaction was cooled to 0 °C and was quenched with satd aq \(NH_4Cl\). The resulting mixture was extracted with \(EtOAc\) (3×). The combined organic extracts were washed with brine, dried (\(Na_2SO_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc) yielded primary alcohol S40 (165 mg, 82%) as a yellow oil.

**TLC:** \(R_f\) 0.54 (8:2 hexanes/EtOAc). \textbf{IR} (NaCl, film): 3357 (O–Hst), 2945, 2865, 1497, 1253, 840. \textbf{\(^1\)H-NMR} (500 MHz): \(\delta\) 7.11 (d, 1H, \(J = 8.6\)), 6.63 (dd, 1H, \(J = 8.6, 2.6\)), 6.50 (s, 1H), 3.93 (dd, 1H, \(J = 12.1, 3.6\)), 3.74–3.69 (m, 1H), 3.56–3.53 (m, 1H), 3.20 (br s, 1H), 2.86–2.82 (m, 2H), 2.21–2.17 (m, 1H), 2.07 (dd, 1H, \(J = 14.6, 9.0, 5.3\)), 1.97–1.92 (m, 1H), 1.69 (dt, 1H, \(J = 14.9, 4.9\)), 1.46 (s, 3H), 1.13–1.10 (m, 21H), 0.99 (s, 9H), 0.19 (s, 6H). \textbf{\(^{13}\)C-NMR} (126 MHz): \(\delta\) 153.5, 137.6, 135.7, 127.5, 119.3, 117.9, 59.4, 42.8, 42.4, 28.9, 27.8, 25.7, 24.4, 18.3 (2 peaks), 18.2, 12.9, –4.3. \textbf{ESI-MS} \(m/z\) (rel int): (pos) 515.3 ([M+Na]\(^+\), 100).

2-([1R*,2R*]-6-([\(t\)-Butyldimethylsilyl]oxy)-1-methyl-2-((triisopropylsilyl]oxy)-1,2,3,4-tetrahydro-naphthalen-1-yl)ethanol (29). Alcohol S40 (165 mg, 0.33 mmol) was dissolved in THF (5 mL) and cooled to \(-78\) °C. A solution of TBAF (1 M in THF, 334 \(\mu\)L, 0.33 mmol, 1.0 equiv)
was added slowly by syringe and the reaction was stirred for 10 min. The reaction was quenched with satd aq NH₄Cl and warmed to 25 °C. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexanes/EtOAc) yielded diol 29 (95 mg, 76%) as a yellow oil.

**TLC:** R₀.30 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 3356 (O–H str), 2941, 2866, 1458, 1061, 882. **¹H-NMR** (500 MHz): δ 7.15 (d, 1H, J = 8.6), 6.65 (dd, 1H, J = 8.6, 2.6), 6.51 (d, 1H, J = 2.6), 2.89–2.84 (m, 2H), 2.2–2.17 (m, 1H), 1.98–1.94 (m, 1H), 1.68 (dt, 1H, J = 15.1, 5.3), 1.46 (s, 3H), 1.14–1.11 (m, 21H).

**¹³C-NMR** (126 MHz): δ 153.9, 136.9, 136.0, 127.8, 114.7, 114.7, 59.3, 42.8, 42.4, 28.9, 27.7, 24.3, 18.3 (2 peaks), 12.8. **ESI-MS m/z** (rel int): (pos) 401.1 (M+Na⁺, 100); (neg) 377.1 (M–H⁻, 100).

(1R*,2R*)-1-Allyl-6-[(t-butyldimethylsilyl)oxy]-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl acetate (S41). To a solution of alcohol S38 (10 mg, 0.030 mmol) in CH₂Cl₂ (1 mL) was added pyridine (7 μL, 0.09 mmol, 3 equiv), Ac₂O (1 M in CH₂Cl₂, 45 μL, 1.5 equiv), and a crystal of DMAP. The reaction was warmed to reflux. After 2 h, the reaction was quenched with satd aq NH₄Cl. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 hexanes/EtOAc) yielded acetate S41 (10 mg, 89%) as a brown oil.

**TLC:** R₀.63 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 2957, 1737 (C=O str), 1498, 1242, 840. **¹H-NMR** (500 MHz, C₆D₆): δ 7.01 (d, 1H, J = 8.6), 6.75 (dd, 1H, J = 8.6, 2.6), 6.66 (d, 1H, J = 2.6), 5.79 (ddd, 1H, J = 15.2, 11.9, 7.2), 5.09 (dd, 1H, J = 7.2, 2.5), 5.02–4.99 (m, 2H), 2.74–2.69 (m, 1H), 2.54 (dd, 1H, J = 13.8, 7.2), 2.49–2.42 (m, 2H), 1.99 (dd, 1H, J = 13.1, 7.3), 1.79–1.75 (m, 1H), 1.62 (s, 3H), 1.09 (s, 3H), 1.01 (s, 9H), 0.13 (s, 6H). **¹³C-NMR** (126 MHz, C₆D₆): δ 168.3, 152.5, 135.2, 134.3, 134.2, 126.9, 118.7, 116.7, 116.0, 74.3, 41.6, 38.8, 26.0, 24.9, 24.5, 22.2, 19.3, 17.0, –5.7. **ESI-MS m/z** (rel int): (pos) 397.2 ([M+Na⁺], 100), 413.2 ([M+K⁺], 10). The relative stereochemistry was determined by NOESY.

**19. SYNTHESIS OF PHENOL 30**

See Section G. ODRE cascade below.
E. SYNTHESIS OF CYCLOHEXADIENONES 31–50

1. SYNTHESIS OF CYCLOHEXADIENONE 31

Supplementary Figure 36. Synthesis of cyclohexadienone 31.

(4aR*,11aS*)-4a-Methyl-3,4,4a,5,6,7-hexahydrobenzo[i]chromen-9(2H)-one (31). Diol 12 (250 mg, 1.13 mmol) and K₂CO₃ (314 mg, 2.26 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (23 mL) and cooled to 0 °C. PhI(OAc)₂ (437 mg, 1.36 mmol, 1.20 equiv) was added by syringe in 2 mL CH₂Cl₂ (adding PhI(OAc) as a solid produced similar results). After 45 min the reaction was warmed to 25 °C and poured into H₂O (25 mL). The resulting mixture was extracted with Et₂O. The combined organic extracts were washed with H₂O (2x) and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 petroleum ether/Et₂O) yielded cyclohexadienone 31 (111 mg, 45%) as an orange oil.

TLC: Rₓ 0.36 (7:3 hexanes/EtOAc). IR (NaCl, film): 2928, 1670 (C=O st), 1279, 1080, 1028.
1H-NMR (500 MHz): δ 7.56 (d, 1H, J = 10.6), 6.33 (d, 1H, J = 10.6), 6.12 (s, 1H), 4.02–3.97 (m, 1H), 3.93–3.90 (m, 1H), 2.73–2.67 (m, 1H), 2.54–2.48 (m, 1H), 2.27–2.20 (m, 2H), 1.89–1.83 (m, 2H), 1.67–1.61 (m, 1H), 1.60–1.56 (m, 1H), 1.48–1.44 (m, 1H), 1.09–1.05 (m, 1H), 0.74 (s, 3H). 13C-NMR (126 MHz): δ 185.8, 162.0, 144.7, 130.2, 126.0, 74.4, 61.8, 43.8, 38.9, 32.7, 32.3, 24.1, 22.6, 21.0. ESI-MS m/z (rel int): (pos) 241.0 ([M+Na]⁺, 50), 219.1 ([M+H]⁺, 40), 459.3 ([2M+Na]⁺, 100); (neg) 217.0 ([M−H]⁻, 80).

2. SYNTHESIS OF CYCLOHEXADIENONE 32

Supplementary Figure 37. Synthesis of cyclohexadienone 32.
(4aR*,11aS*)-4a-Methyl-3-methylene-3,4,4a,5,6,7-hexahydrobenzo[i]chromen-9(2H)-one (S42). Diol 13 (159 mg, 0.684 mmol) and K₂CO₃ (189 mg, 1.37 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (14 mL) and cooled to 0 °C. PhI(OAc)₂ (264 mg, 0.82 mmol, 1.2 equiv) was added as a solid. After 1 h the reaction was warmed to 25 °C and poured into 15 mL H₂O. The resulting mixture was extracted with Et₂O and washed with H₂O (2×) followed by brine. The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 petroleum ether/Et₂O) yielded cyclohexadienone S42 (87 mg, 55%) as a colorless oil.

**TLC:** R, 0.48 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 2921, 1671 (C=O st), 1293, 1057, 895. **¹H-NMR** (500 MHz); δ 7.55 (d, 1H, J = 10.6), 6.37 (dd, 1H, J = 10.6, 2.0), 6.14 (s, 1H), 4.98 (s, 1H), 4.85 (s, 1H), 4.52 (d, 1H, J = 13.7), 4.23 (d, 1H, J = 13.7), 2.68 (td, 1H, J = 13.1, 6.8), 2.60 (d, 1H, J = 14.3), 2.30–2.21 (m, 2H), 2.04 (d, 1H, J = 14.3), 1.87–1.82 (m, 1H), 1.66–1.60 (m, 1H), 1.07–1.03 (m, 1H), 0.78 (s, 3H). **¹³C-NMR** (126 MHz); δ 185.7, 161.6, 143.8, 140.6, 130.7, 126.1, 111.7, 74.4, 66.7, 42.7, 41.1, 33.0, 32.3, 24.2, 21.7. **ESI-MS** m/z (rel int): (pos) 253.0 ([M+Na]+, 100), 231.0 ([M+H]+, 5).

(4aR*,11aR*)-3,4a-Dimethyl-4a,5,6,7-tetrahydrobenzo[i]chromen-9(2H)-one (32). In a 4-mL vial with a Teflon-lined screw cap, tricyclic cyclohexadienone S42 (45 mg, 0.195 mmol) was dissolved in CH₂Cl₂ (2 mL). TsOH·H₂O (37 mg, 0.195 mmol, 1.0 equiv) was added and the vial was sealed. The solution was warmed to 40 °C and stirred for 3.5 h. The reaction was quenched with satd aq NaHCO₃ and extracted with Et₂O (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to yield the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc) yielded cyclohexadienone 32 (45 mg, 100%) as a colorless oil.

**TLC:** R, 0.50 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 2922, 1671 (C=O st), 1450, 1293, 1075. **¹H-NMR** (500 MHz); δ 7.10 (d, 1H, J = 10.5), 6.29 (d, 1H, J = 10.5), 6.15 (s, 1H), 5.45 (s, 1H), 4.24 (d, 1H, J = 17.5), 4.17 (d, 1H, J = 17.5), 2.71–2.65 (m, 1H), 2.30–2.27 (m, 1H), 1.95–1.88 (m, 1H), 1.81–1.76 (m, 1H), 1.67 (s, 3H), 1.51–1.44 (m, 2H), 0.79 (s, 3H). **¹³C-NMR** (126 MHz); δ 186.1, 161.1, 146.4, 130.7, 130.1, 129.9, 126.4, 73.2, 66.0, 40.4, 36.9, 32.6, 23.4, 19.9, 18.2. **ESI-MS** m/z (rel int): (pos) 253.0 ([M+Na]+,100), 231.0 ([M+H]+, 5).
3. SYNTHESIS OF CYCLOHEXADIENONE 33

Supplementary Figure 38. Synthesis of cyclohexadienone 33.

(3aR*,9aS*)-2,2,3a-Trimethyl-3,3a,4,5-tetrahydroindeno[7a,1-b]furan-7(2H)-one (33). Diol 14 (116 mg, 0.523 mmol) and K₂CO₃ (218 mg, 1.58 mmol, 3.00 equiv) were suspended in CF₃CH₂OH (10 mL) and cooled to 0 °C. Phl(OAc)₂ (253 mg, 0.785 mmol, 1.5 equiv) was added as a solid. After 30 min the reaction was quenched with satd aq NaHCO₃. The resulting mixture was extracted with Et₂O (2 ×). The combined organic extracts were washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexane/EtOAc) yielded cyclohexadienone 33 (107 mg, 94%) as a brown oil.

TLC: Rf 0.24 (8:2 hexanes/EtOAc). IR (NaCl, film): 2969, 2871, 1673, 1646, 1183, 1323, 1010, 932. ¹H-NMR (500 MHz): δ 6.80 (d, 1H, J = 10.1), 6.10 (d, 1H, J = 10.1), 6.03 (s, 1H), 2.97–2.89 (m, 1H), 2.37 (ddd, 1H, J = 15.3, 9.0, 1.4), 2.23 (d, 1H, J = 13.1), 2.12–2.07 (m, 1H), 2.09 (d, 1H, J = 13.1), 1.77 (dt, 1H, J = 13.6, 9.3), 1.41 (s, 6H), 0.98 (s, 3H). ¹³C-NMR (126 MHz): δ 186.5, 165.9, 145.0, 128.9, 123.3, 87.1, 83.4, 54.7, 52.9, 39.2, 33.1, 29.4, 28.6, 24.4. ESI-MS m/z (rel int): (pos) 241.0 ([M+Na]⁺, 100); (neg) 217.2 ([M–H]⁻, 100).

4. SYNTHESIS OF CYCLOHEXADIENONES 34–36

Supplementary Figure 39. Synthesis of cyclohexadienones 34–36 by oxidative dearomatization and Pd-catalyzed couplings.
(3αR*,10αS*)-7-Bromo-3a-methyl-3α,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (34). Diol 15 (171 mg, 0.600 mmol) and K₂CO₃ (166 mg, 1.20 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (12 mL), cooled to 0 °C, and vigorously stirred. PhI(OAc)₂ (232 mg, 0.720 mmol, 1.2 equiv) was added as a solid and the reaction was stirred for 1 h. The solution was then warmed to 25 °C and stirred an additional 1 h. The reaction was poured into brine (50 mL) and extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexane/EtOAc) yielded cyclohexadienone 34 (125 mg, 74%) as a brown oil.

**TLC:** Rₛ 0.52 (6:4 hexanes/EtOAc). **IR** (NaCl, film): 3042, 1667 (C=O st), 1594, 988, 913. **¹H-NMR** (500 MHz): δ 6.88 (d, 1H, J = 10.1), 6.35 (d, 1H, J = 10.1), 4.32 (q, 1H, J = 8.7), 4.23–4.19 (m, 1H), 3.10 (dt, 1H, J = 13.0, 3.4), 2.56 (dt, 1H, J = 12.9, 4.4), 2.16 (dt, 1H, J = 12.6, 9.7), 1.99–1.90 (m, 2H), 1.81 (td, 1H, J = 13.3, 4.1), 1.62–1.55 (m, 1H), 1.49 (dt, 1H, J = 13.5, 3.5), 0.96 (s, 3H).

(3αR*,10αS*)-3α,7-Dimethyl-3α,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (35). To a solution of bromocyclohexadienone 34 (57 mg, 0.20 mmol) in DMF (5 mL) was added SnMe₄ (139 μL, 1.0 mmol, 5.0 equiv), CuBr (5.8 mg, 20 mol%), and Pd(PPh₃)₄ (46 mg, 20 mol%). The solution was heated at 80 °C for 12 h. The solution was cooled to 25 °C and passed over a pad of Celite (Fisher Scientific). The filtrate was diluted with Et₂O and washed with H₂O (4×) and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 petroleum ether/Et₂O) yielded cyclohexadienone 35 (39 mg, 89%) as a brown oil.

**TLC:** Rₛ 0.24 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 2934, 1667 (C=O st), 1594, 988, 913. **¹H-NMR** (500 MHz): δ 6.84 (d, 1H, J = 10.2), 6.23 (d, 1H, J = 10.2), 4.32 (q, 1H, J = 8.6), 4.18 (td, 1H, J = 9.5, 2.4), 2.67 (d, 1H, J = 13.0), 2.42–2.37 (m, 1H), 2.15 (dt, 1H, J = 12.3, 9.7), 1.93 (s, 3H), 1.93–1.86 (m, 2H), 1.78–1.75 (m, 1H), 1.49–1.42 (m, 2H), 0.93 (s, 3H). **¹³C-NMR** (126 MHz): δ 185.7, 153.2, 146.5, 131.8, 127.9, 81.9, 65.6, 50.5, 40.6, 36.3, 27.7, 25.1, 19.2, 10.9. **ESI-MS** m/z (rel int): (pos) 241.1 ([M+Na]⁺, 100), 459.2 ([2M+Na]⁺, 50).
(3aR*,10aS*)-7-(4-Methoxyphenyl)-3a-methyl-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]-furan-8(3H)-one (36). To a solution of bromocyclohexadienone 34 (150 mg, 0.530 mmol) in toluene/EtOH (1:1, 5 mL) was added 4-methoxyphenylboronic acid (97 mg, 0.636 mmol, 1.2 equiv), Pd(PPh₃)₄ (61 mg, 0.053 mmol, 10 mol%), and Na₂CO₃ (1 M aq, 2.12 mL, 4.0 equiv). The reaction was heated to 50 °C and stirred for 12 h. The reaction was cooled to 25 °C and passed over a pad of Celite (Fisher Scientific). The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with H₂O (2×) and brine (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded 36 (156 mg, 95%) as a yellow oil.

TLC: Rₜ 0.33 (7:3 hexanes/EtOAc). IR (NaCl, film): 2934, 1664 (C=O st), 1635, 1511, 1245, 1178, 941. ¹H-NMR (500 MHz): δ 7.03 (d, 2H, J = 8.0), 6.92 (d, 3H, J = 9.7), 6.32 (dd, 1H, 10.3, 0.9), 4.32 (q, 1H, J = 8.9), 4.26–4.22 (m, 1H), 3.82 (s, 3H), 2.41–2.34 (m, 2H), 2.21–2.18 (m, 1H), 1.95 (ddd, 1H, J = 12.4, 8.0, 2.7), 1.80–1.75 (m, 2H), 1.49–1.45 (m, 2H), 1.05 (s, 3H). ¹³C-NMR (126 MHz): δ 184.9, 158.8, 155.4, 146.3, 137.9, 130.8, 128.3, 127.4, 113.6, 82.0, 65.7, 55.2, 51.1, 40.6, 36.1, 28.8, 25.8, 19.2. ESI-MS m/z (rel int): (pos) 333.0 ([M+Na]⁺, 100), 311.1 ([M+H]⁺, 20), 643.3 ([2M+Na]⁺, 40).

5. SYNTHESIS OF CYCLOHEXADIENONE 37

Supplementary Figure 40. Synthesis of cyclohexadienone 37.

(3aS*,10aS*)-3a-Phenyl-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (37). Diol 16 (50 mg, 0.19 mmol) and K₂CO₃ (52 mg, 0.37 mmol, 2.0 equiv) were suspended in CF₃CH₂OH (20 mL) and cooled to 0 °C. Phl(OAc)₂ (73 mg, 0.23 mmol, 1.2 equiv) was added as a solid. Due to the low solubility of the starting material, vigorous stirring is required. The reaction was warmed to 25 °C, stirred for 30 min, and poured into 20 mL H₂O. The resulting mixture was
extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3 hexanes/EtOAc) yielded 37 (43 mg, 86%) as a white powder.

**TLC:** $R_f$ 0.30 (7:3 hexanes/EtOAc). **mp:** 172 °C. **IR** (NaCl, film): 2939, 2890, 1670 (C=O st), 1635, 1292, 1040, 702. **$^1$H-NMR** (500 MHz): $\delta$ 7.33–7.27 (m, 5H), 6.63 (d, 1H, $J$ = 10.2), 6.30 (t, 1H, $J$ = 1.8), 6.06 (d, 1H, $J$ = 10.2), 4.34 (q, 1H, $J$ = 8.6), 4.24 (td, 1H, $J$ = 9.3, 2.0), 2.77–2.67 (m, 2H), 2.54 (ddd, 1H, $J$ = 12.4, 7.8, 2.5), 2.49–2.45 (m, 1H), 2.05 (td, 1H, $J$ = 13.7, 3.8), 1.77–1.72 (m, 1H), 1.69–1.60 (m, 2H). **$^{13}$C-NMR** (126 MHz): $\delta$ 186.3, 160.7, 147.5, 142.6, 128.4, 128.2, 127.1, 127.0, 126.8, 79.1, 65.5, 39.3, 37.8, 32.5, 23.0.

**ESI-MS** m/z (rel int): (pos) 288.9 ([M+Na]$^+$, 100), 555.1 ([2M+Na]$^+$, 50).

**6. SYNTHESIS OF CYCLOHEXADIENONE 38**

**Supplementary Figure 41. Synthesis of cyclohexadienone 38.**

(3a$R^*$,11a$S^*$)-3a-Methyl-3,3a,4,5,6,7-hexahydrobenzo[1,7]cyclohepta[1,2-b]furan-9(2H)-one (38). Diol 17 (24.1 mg, 0.109 mmol) was dissolved in CF$_3$CH$_2$OH (2 mL) and K$_2$CO$_3$ (30.2 mg, 0.219 mmol, 2.01 equiv) was added. The mixture was cooled to 0 °C and Phl(OAc)$_2$ (42.0 mg, 0.130 mmol) was added in a single portion. The reaction was stirred at 0 °C for 45 min then quenched with H$_2$O and diluted with CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (4×) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes) yielded 38 (22.9 mg, 96%) as a colorless oil.

**TLC:** $R_f$ 0.15 (30% EtOAc/hexanes). **IR** (NaCl, film): 2938, 1667, 1630, 1462, 1383, 1284, 1073, 984. **$^1$H-NMR** (600 MHz): $\delta$ 6.85 (d, 1H, $J$ = 10.5), 6.14–6.12 (m, 3H), 4.23 (td, 1H, $J$ = 9.0, 7.5), 4.18 (td, 1H, $J$ = 9.1, 3.4), 2.77 (td, 1H, $J$ = 12.4, 7.2), 2.27 (dd, 1H, $J$ = 12.4, 6.5), 2.15 (dt, 1H, $J$ = 12.6, 9.4), 2.01 (ddd, 1H, $J$ = 12.6, 7.5, 3.4), 1.84 (dd, 1H, $J$ = 14.6, 10.4), 1.76–1.71 (m, 1H), 1.64–1.61 (m, 1H), 1.57 (ddd, $J$ = 12.5, 6.2, 4.2), 1.44–1.37 (m, 2H), 0.92 (s, 3H). **$^{13}$C-NMR** (151 MHz): $\delta$ 186.1, 163.0, 149.6, 128.5, 126.6, 85.4, 66.4, 49.8, 41.5, 37.9, 28.6, 26.1, 23.5, 20.3. **ESI-MS** m/z (rel int): (pos) 241.06 ([M+Na]$^+$, 100), 219.04 ([M+H]$^+$, 19).
7. SYNTHESIS OF CYCLOHEXADIENONE 39

Supplementary Figure 42. Synthesis of cyclohexadienone 39.

(4aR*,12aS*)-4a-Methyl-4,4a,5,6,7,8-hexahydro-2H-benzo[1,7]cyclohepta[1,2-b]pyran-10(3H)-one (39). Diol 18 (8.0 mg, 0.034 mmol) was dissolved in CF₃CH₂OH (0.75 mL) and K₂CO₃ (9.4 mg, 0.043 mmol, 2.0 equiv) was added. The mixture was cooled to 0 °C and PhI(OAc)₂ (14.0 mg, 0.043 mmol) was added in a single portion. The reaction was stirred at 0 °C for 45 min then quenched with H₂O and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (4×) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by Et₃N-doped silica flash chromatography (5% EtOAc/CH₂Cl₂) yielded 39 (3.1 mg, 39%) as a colorless oil.

TLC: Rₗ 0.16 (5% EtOAc/CH₂Cl₂). IR (NaCl, film): 2927, 2865, 1667, 1628, 1452, 1286, 1221, 1083, 1036. ¹H-NMR (600 MHz): δ 7.53 (d, 1H, J = 10.5), 6.28 (dd, 1H, J = 10.5, 2.0), 6.12 (d, 1H, J = 1.3), 3.99–3.93 (m, 2H), 2.96 (td, 1H, J = 12.2, 7.6), 2.47 (t, 1H, J = 13.3), 2.18–2.07 (m, 2H), 1.79 (td, 1H, J = 14.0, 4.4), 1.75–1.72 (m, 1H), 1.66–1.58 (m, 2H), 1.54–1.50 (m, 2H), 1.48–1.41 (m, 1H), 1.09 (dd, 1H, J = 14.6, 6.8), 0.66 (s, 3H). ¹³C-NMR (151 MHz): δ 185.7, 164.1, 145.0, 129.0, 128.6, 77.5, 61.3, 37.4, 36.3, 33.6, 27.9, 24.7, 24.0, 21.1, 19.4. ESI-MS m/z (rel int): (pos) 255.02 ([M+Na]⁺, 100), 487.21 ([2M+Na]⁺, 28).

8. SYNTHESIS OF CYCLOHEXADIENONE 40

Supplementary Figure 43. Synthesis of cyclohexadienone 40.
(3aR*,12aS*)-3a-Methyl-3a,4,5,6,7,8-hexahydro-2H-benzo[1,8]cycloocta[1,2-b]furan-10(3H)-one (40). Diol 19 (21.1 mg, 0.090 mmol) was dissolved in CF₂CH₂OH (1.5 mL) and cooled to 0 °C. K₂CO₃ (24.9 mg, 0.180 mmol, 2.00 equiv) was added followed by Phl(OAc)₂ (34.8 mg, 0.108 mmol). The solution was stirred at 0 °C for 20 min then quenched with H₂O and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (4×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (30% EtOAc/hexanes) yielded 40 (14.1 mg, 67%) as a colorless oil.

**TLC:** Rf 0.24 (30% EtOAc/hexanes). **IR** (NaCl, film): 2926, 1663, 1625, 1457, 1280, 1076. **¹H-NMR** (600 MHz): δ 6.85 (d, 1H, J = 10.1), 6.28 (t, 1H, J = 1.9), 6.15 (dd, 1H, J = 10.1, 2.0), 4.28–4.17 (m, 2H), 2.78 (d, 1H, J = 14.8, 12.7, 2.4), 2.36–2.33 (m, 1H), 2.19 (dt, 1H, J = 12.6, 10.3), 2.08 (dd, 1H, J = 11.4, 5.1), 2.05–2.01 (m, 1H), 1.81 (ddd, 1H, J = 12.7, 7.2, 2.1), 1.75–1.72 (m, 1H), 1.59–1.57 (m, 2H), 1.38–1.31 (m, 1H), 1.26–1.21 (m, 1H), 0.93 (s, 3H). **¹³C-NMR** (151 MHz): δ 185.4, 167.0, 150.8, 129.1, 127.0, 85.2, 66.4, 54.3, 43.7, 38.5, 30.0, 28.8, 28.5, 21.7, 21.6. **ESI-MS** m/z (rel int): (pos) 255.07 ([M+Na]⁺, 26); neg 231.06 ([M–H]⁺, 90).

9. **SYNTHESIS OF CYCLOHEXADIENONE 41**

(4aR*,13aS*)-4a-methyl-3,4,4a,5,6,7,8,9-octahydrobenzo[1,8]cycloocta[1,2-b]pyran-11(2H)-one (41). Diol 20 (37.7 mg, 0.152 mmol) was dissolved in CF₂CH₂OH (2 mL) and cooled to 0 °C. Potassium carbonate (0.0420 g, 0.304 mmol, 2.00 equiv) was added followed by Phl(OAc)₂ (53.8 mg, 0.167 mmol, 1.10 equiv). The solution was stirred at 0 °C for 20 min then quenched with H₂O and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (4×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes) afforded 41 (9.7 mg, 26%) as a colorless oil.
**10. SYNTHESIS OF CYCLOHEXADIENONE 42**

![Supplementary Figure 45. Synthesis of cyclohexadienone 42.](image)

**(4aR*,11aS*)-4a-Methyl-3,4,4a,5,6,7-hexahydrobenzo[i]chromene-2,9-dione (42).** Carboxylic acid 21 (160 mg, 0.682 mmol) was dissolved in CF₃CH₂OH (6.8 mL) and cooled to 0 °C. PhI(OAc)₂ (242 mg, 0.750 mmol, 1.10 equiv) was added and the reaction was stirred at 0 °C for 15 min. It was quenched with H₂O and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (4×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by flash silica chromatography yielded 42 (84.0 mg, 53%) as a colorless oil.

**TLC:** Rₜ 0.12 (30% EtOAc/hexanes + 1% AcOH). **IR** (NaCl, film): 2943, 1739, 1672, 1637, 1217, 1179, 1039, 998. **¹H-NMR** (500 MHz): δ 6.88 (d, 1H, J = 10.2), 6.33 (dd, 1H, J = 10.2, 1.8), 6.18 (s, 1H), 2.90–2.75 (m, 2H), 2.71–2.64 (m, 1H), 2.39–2.36 (m, 1H), 2.11 (dt, 1H, J = 14.6, 9.5), 2.02 (td, 1H, J = 13.6, 4.4), 1.95–1.91 (m, 1H), 1.80–1.70 (m, 2H), 1.35–1.32 (m, 1H), 0.94 (s, 3H). **¹³C-NMR** (126 MHz): δ 185.1, 169.9, 157.3, 144.1, 131.1, 126.6, 82.4, 38.4, 31.95, 31.83, 31.2, 26.2, 23.2, 21.4. **ESI-MS** m/z (rel int): (pos) 254.9 ([M+Na]⁺, 100), 487.1 ([2M+Na]⁺, 93), 233.2 ([M+H]⁺, 10).
11. SYNTHESIS OF CYCLOHEXADIENONE 43

Supplementary Figure 46. Synthesis of cyclohexadienone 43.

(4aR*,11aS*)-4a-Methyl-3-methylene-3,4,4a,5,6,7-hexahydrobenzo[i]chromene-2,9-dione (43). Acid 22 (191 mg, 0.775 mmol) and K₂CO₃ (214 mg, 1.55 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (16 mL) and cooled to 0 °C. Phl(OAc)₂ (300 mg, 0.93 mmol, 1.2 equiv) was added as a solid. After 30 min the reaction was warmed to 25 °C and poured into H₂O (15 mL). The resulting mixture was extracted with Et₂O. The combined organic extracts were washed with H₂O (2×) and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (7:3→6:4 hexanes/EtOAc) yielded cyclohexadienone 43 (178 mg, 94%) as a yellow oil.

TLC: Rf 0.29 (6:4 hexanes/EtOAc). IR (NaCl, film): 2941, 1726 (C=O st), 1672 (C=O st), 1298, 1184, 1000. ¹H-NMR (500 MHz): δ 6.86 (d, 1H, J = 10.2), 6.67–6.66 (m, 1H), 6.33 (dd, 1H, J = 10.2, 1.9), 6.18 (s, 1H), 5.73 (t, 1H, J = 1.3), 2.87 (dt, 1H, J = 17.3, 2.8), 2.72 (td, 1H, J = 13.5, 1.6), 2.49 (d, 1H, J = 17.3), 2.40–2.35 (m, 1H), 1.97–1.88 (m, 2H), 1.80–1.70 (m, 1H), 1.34–1.29 (m, 1H), 0.96 (s, 3H). ¹³C-NMR (126 MHz): δ 184.9, 164.2, 157.0, 143.6, 131.6, 131.0 (2 peaks), 126.3, 81.9, 39.5, 39.1, 32.6, 31.4, 23.1, 20.8. ESI-MS m/z (rel int): (pos) 511.1 ([2M+Na]+, 100), 267.0 ([M+Na]+, 30), 245.0 ([M+H]+, 10); (neg) 243.0 ([M−H]−, 100).

12. SYNTHESIS OF CYCLOHEXADIENONE 44

Supplementary Figure 47. Synthesis of cyclohexadienone 44.
(4aR*,12aS*)-4a-Methyl-4,4a,5,6,7,8-hexahydro-2H-benzo[1,7]cyclohepta[1,2-b]pyran-2,10(3H)-dione (44). Carboxylic acid 23 (31.9 mg, 0.128 mmol) was dissolved in CF$_3$CH$_2$OH (3 mL) and cooled to 0 °C. PhI(OAc)$_2$ (45.5 mg, 0.141 mmol, 1.10 equiv) was added and the reaction was stirred at 0 °C for 15 min. The reaction was quenched with H$_2$O and diluted with CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (4 ×) and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by flash silica chromatography (30% EtOAc/hexanes) yielded 44 (30.0 mg, 95%) as a colorless oil.

TLC: $R_f$ 0.10 (30% EtOAc/hexanes + 1% AcOH). IR (NaCl, film): 2940, 1742, 1667, 1213, 1040, 995, 731. $^1$H-NMR (500 MHz): δ 6.87 (d, 1H, $J = 10.2$), 6.28 (dd, 1H, $J = 10.2, 1.9$), 6.17 (t, 1H, $J = 0.9$), 2.91–2.73 (m, 3H), 2.41–2.36 (m, 1H), 2.12–2.04 (m, 2H), 1.84–1.79 (m, 1H), 1.78–1.68 (m, 3H), 1.57–1.50 (m, 1H), 1.37 (dd, 1H, $J = 14.7, 5.3$), 0.89–0.87 (m, 3H). $^{13}$C-NMR (151 MHz): δ 184.8, 169.4, 160.1, 146.5, 129.5, 128.9, 86.1, 37.5, 34.7, 33.8, 30.4, 26.2, 24.7, 22.3, 20.1. ESI-MS m/z (rel int): (pos) 269.04 ([M+Na]$^+$, 100), 515.18 ([2M+Na]$^+$, 9).

13. SYNTHESIS OF CYCLOHEXADIENONE 45

Supplementary Figure 48. Synthesis of cyclohexadienone 45.

(4aR*,13aS*)-4a-Methyl-3,4,4a,5,6,7,8,9-octahydrobenzo[1,8]cycloocta[1,2-b]pyran-2,11-dione (45). Carboxylic acid 24 (27.6 mg, 0.105 mmol) was dissolved in CF$_3$CH$_2$OH (5 mL) and cooled to 0 °C. PhI(OAc)$_2$ (37.3 mg, 0.116 mmol, 1.10 equiv) was added and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with H$_2$O and diluted with CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (4 ×) and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude
product. Purification by flash silica chromatography (30% EtOAc/hexanes + 1% AcOH → 50% EtOAc/hexanes + 1% AcOH) yielded 45 (11.5 mg, 42%) as a colorless oil.

**TLC:** $R_f$ 0.28 (50% EtOAc/hexanes). **IR** (NaCl, film): 2927, 1741, 1669, 1384, 1277, 1209, 1133, 1036, 991. **$^1$H-NMR** (600 MHz): δ 6.93 (d, 1H, $J = 9.9$), 6.27–6.25 (m, 1H), 2.8–2.65 (m, 3H), 2.50–2.46 (m, 1H), 2.23 (m, 1H), 2.16 (d, 1H, $J = 15.3$), 1.75 (tddd, 1H, $J = 15.1, 10.1, 3.7$), 1.63 (ddd, 1H, $J = 15.1, 10.1, 3.7$), 1.23 (m, 1H), 1.00 (m, 1H), 0.93 (m, 1H).

**13C-NMR** (151 MHz): δ 184.3, 169.2, 163.3, 148.0, 129.3, 128.7, 87.0, 40.2, 35.9, 34.6, 30.2, 28.9, 28.1, 26.1, 22.6, 21.7.

**ESI-MS** m/z (rel int): (pos) 283.05 ([M+Na]$^+$, 100), 261.06 ([M+H]$^+$, 13).

### 14. SYNTHESIS OF CYCLOHEXADIENONE 46

![Supplementary Figure 49. Synthesis of cyclohexadienone 46.](image)

(7aR*,14aS*)-7a-Methyl-9-methylene-5,6,7,7a,8,9-hexahydro-3H-benzo[b]naphtho[1,8a-f]-oxepin-3-one (S43). Bisphenol 25 (2.43 g, 8.25 mmol) and K$_2$CO$_3$ (2.28 g, 16.5 mmol, 2 equiv) were suspended in CF$_3$CH$_2$OH (80 mL) and cooled to 0 °C. Phl(OAc)$_2$ (2.93 g, 9.1 mmol, 1.10 equiv) was added in two portions over 5 min. After 30 min the reaction was warmed to 25 °C. The reaction was sonicated for 5 min to dissolve the remaining starting material, then stirred vigorously for an additional 2 h at 25 °C. The reaction was then poured into 100 mL H$_2$O. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with H$_2$O (2×) and brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 hexanes/EtOAc w/ 1% NEt$_3$) yielded tetracyclic cyclohexadienone S43 (1.37 g, 57%) as a yellow oil.

**TLC:** $R_f$ 0.45 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 2944, 1670 (C=O st), 1623, 1588, 1538, 1444, 1385, 1304, 1220, 1120, 1031, 996, 764. **$^1$H-NMR** (500 MHz): δ 7.29–7.26 (m, 1H), 7.18 (td, 1H, $J = 7.7, 1.8$), 7.09 (td, 1H, $J = 7.4, 1.2$), 6.85 (d, 1H, $J = 10.5$), 6.79 (dd, 1H, $J = 7.9, 1.1$), 6.23 (dd, 1H, $J = 10.5, 1.2$), 6.15 (s, 1H), 5.22 (s, 1H), 5.13 (s, 1H), 2.85 (td, 1H, $J = 13.3, 5.9, 1.7$), 2.70 (d, 1H, $J = 14.0$), 2.58 (td, 1H, $J = 13.9, 4.5$), 2.38–2.35 (m, 1H), 2.24 (d, 1H, $J = 14.0$), 1.95–1.89 (m, 1H), 1.74 (ddd, 1H, $J = 18.0, 13.5, 9.1, 4.5$), 1.22–1.18 (m, 1H), 0.84 (s, 3H). **$^{13}$C-NMR** (126 MHz): δ 185.9, 162.4,
153.3, 145.1, 145.0, 136.8, 131.0, 129.1, 128.7, 124.8, 124.4, 123.2, 118.5, 79.3, 46.3, 44.2, 32.6, 32.4, 23.0, 22.5. **ESI-MS** \( m/z \) (rel int): (pos) 315.0 ([M+Na]^+, 100), 293.0 ([M+H]^+, 5).

\( (7aR^*, 14aS^*)-7a\text{-Methyl-6,7,7a,8-tetrahydro-3H-benzo[}\text{b}]naphtho[1,8-af]\text{oxepine-3,9(5H)}\text{-dione (46).} \)

To a solution of cyclohexadienone \( S43 \) (1.37 g, 4.7 mmol) in \( \text{THF/H}_2\text{O} \) (3:1, 24 mL) was added OsO\(_4\) (4% in \( \text{H}_2\text{O} \), 1.5 mL, 0.235 mmol, 5 mol%), 4-methylmorpholine \( N\)-oxide (608 mg, 5.17 mmol, 1.1 equiv), and DABCO (26 mg, 0.235 mmol, 5 mol%). The reaction was warmed to 45 °C and stirred for 20 h. The reaction was cooled to 25 °C, quenched with \( \text{Na}_2\text{S}_2\text{O}_3 \) (2 M aq) and the resulting mixture was stirred for 30 min. The crude product was extracted into EtOAc. The combined organic extracts were washed with satd aq \( \text{NaHCO}_3 \), satd aq \( \text{NH}_4\text{Cl} \), and brine, dried (MgSO\(_4\)), filtered, and concentrated by rotary evaporation to afford a crude product.

This crude diol was immediately redissolved in EtOAc/CH\(_2\)Cl\(_2\) (1:1, 24 mL) and cooled to 0 °C. Lead tetraacetate (2.3 g, 5.17 mmol, 1.1 equiv) was added as a solid. The solution was stirred for 20 min then quenched with satd aq \( \text{NaHCO}_3 \) and warmed to 25 °C. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded tetracyclic diketone \( 46 \) (1.21 g, 88%) as a yellow oil.

**TLC:** \( R_f \) 0.35 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 2939, 1671 (C=O st), 1448, 1306, 1215, 773. **\(^1\text{H-NMR}\) (500 MHz):** \( \delta \) 7.56 (dd, 1H, \( J = 7.7, 1.5 \)), 7.44–7.40 (m, 1H), 7.18 (t, 1H, \( J = 7.5 \)), 7.02 (d, 1H, \( J = 10.4 \)), 6.93 (d, 1H, \( J = 8.1 \)), 6.33 (dd, 1H, \( J = 10.4, 1.8 \)), 6.20 (s, 1H), 3.10 (d, 1H, \( J = 14.3 \)), 2.92–2.87 (m, 1H), 2.70 (d, 1H, \( J = 14.3 \)), 2.44–2.41 (m, 1H), 2.19 (td, 1H, \( J = 13.5, 4.6 \)), 1.94–1.90 (m, 1H), 1.81–1.75 (m, 1H), 1.53 (d, 1H, \( J = 13.6 \)), 0.92 (s, 3H). **\(^{13}\text{C-NMR}\) (126 MHz):** \( \delta \) 201.0, 185.3, 160.8, 153.7, 143.1, 133.9 (2 peaks), 131.8, 129.1, 124.8, 124.5, 123.6, 80.6, 55.0, 43.4, 33.8, 31.8, 22.5, 20.1. **ESI-MS** \( m/z \) (rel int): (pos) 316.9 ([M+Na]^+, 100), 295.0 ([M+H]^+, 25); (neg) 293.1 ([M–H]^–, 100).

**15. Synthesis of cyclohexadienone 47**

Supplementary Figure 50. Synthesis of cyclohexadienone 47.
(4bS*,11aR*)-1,2-Dimethoxy-11a-methyl-13-methylene-9,10,11,11a,12,13-hexahydro-7H-benzo[d]phenanthren-7-one (47). Phenol 26 (1.61 g, 4.75 mmol) and K₂CO₃ (1.3 g, 9.5 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (50 mL) and cooled to 0 °C. PhI(OAc)₂ (1.84 g, 5.7 mmol, 1.2 equiv) was added as a solid. After 1 h the reaction was warmed to 25 °C and poured into H₂O (50 mL). The resulting mixture was extracted with Et₂O. The combined organic extracts were washed with H₂O (2 ×) and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded cyclohexadienone 47 (1.15 g, 72%) as a yellow oil.

TLC: Rₛ 0.40 (6:4 hexanes/EtOAc). IR (NaCl, film): 2935, 1662 (C=O st), 1475, 1264, 1061, 1003. ¹H-NMR (500 MHz): δ 7.06 (d, 1H, J = 10.1), 6.73 (d, 1H, J = 8.7), 6.58 (d, 1H, J = 8.7), 6.45 (s, 1H), 6.41 (s, 1H), 6.11 (dd, 1H, J = 10.1, 1.9), 5.38 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.94 (d, 1H, J = 14.8), 2.32 (d, 1H, J = 12.9), 2.16 (d, 1H, J = 14.8), 2.15–2.10 (m, 1H), 1.86 (td, 1H, J = 13.7, 4.6), 1.78–1.68 (m, 2H), 1.19 (d, 1H, J = 15.1), 0.92 (s, 3H). ¹³C-NMR (126 MHz): δ 187.2, 165.6, 154.0, 152.6, 148.2, 136.4, 128.7, 128.2, 127.9, 125.2, 123.7, 118.4, 112.2, 59.5, 55.9, 53.9, 45.6, 40.5, 34.1, 33.7, 24.2, 23.1. ESI-MS m/z (rel int): (pos) 359.2 ([M+Na]⁺, 100), 337.0 ([M+H]⁺, 400); (neg) 335.4 ([M–H]⁻, 100).

**16. SYNTHESIS OF CYCLOHEXADIENONE 48**

Supplementary Figure 51. Synthesis of cyclohexadienone 48.

(4aS*,11aS*)-4a-(3-Hydroxypropyl)-3,4,4a,5,6,7-hexahydrobenzo[i]chromen-9(2H)-one (48). Triol 27 (130 mg, 0.49 mmol) and K₂CO₃ (136 mg, 0.98 mmol, 2.0 equiv) were suspended in CF₃CH₂OH (10 mL) and cooled to 0 °C. PhI(OAc)₂ (206 mg, 0.59 mmol, 1.2 equiv) was added as a solid. The reaction was stirred for 1 h at 0 °C and poured into 10 mL H₂O. The resulting mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude
product. Purification by silica flash chromatography (95:5 CH₂Cl₂/MeOH) yielded cyclohexadienone 48 (71 mg, 55%) as a yellow oil.

**TLC**: Rₜ 0.43 (100% EtOAc). **IR** (NaCl, film): 3422 (O–H st), 2940, 1669 (C=O st), 1629, 1160, 1078. **¹H-NMR** (500 MHz): δ 7.56 (d, 1H, J = 10.6), 6.35 (d, 1H, J = 10.6), 6.12 (s, 1H), 4.01 (td, 1H, J = 12.8, 3.3), 3.94–3.90 (m, 1H), 3.56–3.51 (m, 2H), 2.72 (dt, 1H, J = 13.7, 5.2), 2.39 (dt, 1H, J = 12.8, 3.6), 2.28–2.24 (m, 1H), 2.24–2.14 (m, 1H), 1.84–1.79 (m, 1H), 1.76–1.62 (m, 3H), 1.60–1.48 (m, 2H), 1.43–1.30 (m, 4H), 0.96–0.91 (m, 1H). **¹³C-NMR** (126 MHz): δ 185.8, 161.8, 144.9, 130.6, 126.3, 74.6, 63.1, 61.8, 41.0, 32.8, 29.0, 28.9, 26.7, 25.5, 23.4, 20.7. **ESI-MS** m/z (rel int): (pos) 285.1 ([M+Na]⁺, 100); (neg) 261.2 ([M–H]⁻, 100).

17. **SYNTHESIS OF CYCLOHEXADIENONE 49**

![Supplementary Figure 52. Synthesis of cyclohexadienone 49.](image)

(3aR*,10aS*)-2-(Hydroxymethyl)-3a-methyl-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (49). Triol 28 (150 mg, 0.64 mmol) and K₂CO₃ (177 mg, 1.28 mmol, 2.00 equiv) were suspended in CF₃CH₂OH (10 mL) and cooled to 0 °C. PhI(OAc)₂ (247 mg, 0.77 mmol, 1.20 equiv) was added as a solid. The reaction was warmed to 25 °C and stirred overnight. The reaction solution was poured into 10 mL H₂O. The resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (3:7 hexanes/EtOAc) yielded cyclohexadienone 49 (107 mg, 71%, 1.2:1.0 dr) as a brown oil.

**TLC**: Rₜ 0.19 (4:6 hexanes/EtOAc). **IR** (NaCl, film): 3425 (O–H st), 2939, 1671, 1632, 1296, 1118, 1026. **¹H-NMR** (500 MHz): δ 6.97 (d, 1H-minor, J = 10.3), 6.92 (d, 1H-major, J = 10.3), 6.23 (d, 1H-minor, J = 10.3), 6.16 (s, 1H-minor), 6.12 (s, 1H-major), 6.11 (d, 1H-major, J = 10.3), 4.56 (dt, 1H-major, J = 9.7, 6.1, 3.5), 4.47–4.42 (m, 1H-minor), 3.88 (dd, 1H-minor, J = 11.6, 7.6), 3.83–3.73 (m, 1H-major, 1H-minor), 3.63 (dd, 1H-major, J = 11.6, 5.5), 2.63–2.53 (m, 1H-major, 1H-minor), 2.42 (br s, 1H-major, 1H-minor), 2.27–2.23 (m, 1H-major, 1H-minor), 2.18 (dd, 1H-minor, J = 12.9, 10.0), 2.04 (dd, 1H-major, J = 12.6, 10.2), 1.92–1.77 (m, 3H-major, 2H-minor), 1.74 (dt, 1H-major, J = 13.7, 7.2), 1.57–1.45 (m, 1H-major, 2H-minor),
1.41–1.37 (m, 1H-minor), 0.94 (s, 3H-major), 0.93 (s, 3H-minor). $^1$C-NMR (126 MHz): δ 186.3, 186.2, 160.2, 159.6, 149.3, 146.2, 128.8, 127.5, 127.2, 126.9, 82.3, 81.6, 79.6, 78.2, 66.0, 65.5, 51.2, 50.4, 43.0, 41.9, 37.5, 36.3, 32.8, 32.6, 25.9, 25.7, 19.7, 19.3. ESI-MS m/z (rel int): (pos) 235.1 ([M+H]$^+$, 10), 257.1 ([M+Na]$^+$, 40), 491.1 ([2M+Na]$^+$, 100); (neg) 233.1 ([M−H]$^−$, 100), 467.2 ([2M−H]$^−$, 50). The ratio of diastereomers was determined based on the olefinic $^1$H-NMR doublet α to the cyclohexadienone carbonyl: δ 6.92 (d) major, 6.97 (d) minor.

18. SYNTHESIS OF CYCLOHEXADIENONE 50

Supplementary Figure 53. Synthesis of cyclohexadienone 50.

(3a$S^*$,4$R^*$,10a$R^*$)-3a-Methyl-4-([triisopropylsilyl]oxy)-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (S44). Diol 29 (85 mg, 0.22 mmol) and K$_2$CO$_3$ (62 mg, 0.44 mmol, 2.0 equiv) were suspended in CF$_3$CH$_2$OH (15 mL) and cooled to 0 °C. PhI(OAc)$_2$ (87 mg, 0.27 mmol, 1.2 equiv) was added as a solid. The reaction was stirred for 15 min and poured into 15 mL H$_2$O. The resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 hexanes/EtOAc) yielded cyclohexadienone S44 (76 mg, 89%) as a yellow oil.

TLC: R$_f$ 0.38 (8:2 hexanes/EtOAc). IR (NaCl, film): 2943, 2866, 1671 (C=O st), 1462, 1113, 1067. $^1$H-NMR (500 MHz): δ 6.85 (d, 1H, J = 10.0), 6.15 (m, 2H), 4.18–4.12 (m, 2H), 3.51 (dd, 1H, J = 11.2, 3.6), 2.93–2.81 (m, 2H), 2.30 (dd, 1H, J = 16.1, 8.2), 1.99–1.94 (m, 1H), 1.81–1.75 (m, 2H), 1.10–1.04 (m, 21H), 0.99 (s, 3H). $^{13}$C-NMR (126 MHz): δ 185.7, 160.2, 146.8, 127.2, 126.7, 83.2, 75.8, 67.3, 56.0, 33.7, 29.5, 27.5, 22.6, 18.3, 18.2, 12.9. ESI-MS m/z (rel int): (pos) 399.2 ([M+Na]$^+$, 100), 377.2 ([M+H]$^+$, 20); (neg) 375.1 ([M−H]$^−$, 100).

(3a$S^*$,4$R^*$,10a$R^*$)-4-Hydroxy-3a-methyl-3a,4,5,6-tetrahydro-2H-naphtho[8a,1-b]furan-8(3H)-one (50). Cyclohexadienone S44 (50 mg, 0.13 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. A solution of TBAF (1 M in THF, 146 μL, 0.146 mmol, 1.10 equiv) was added by syringe and the reaction was warmed to 25 °C. After 1 h the reaction was quenched with satd
aq NH₄Cl. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (1:1 hexanes/EtOAc) yielded alcohol 50 (26 mg, 89%) as a yellow oil.

**TLC:** R, 0.19 (1:1 hexanes/EtOAc). **IR** (NaCl, film): 3443 (O–H st), 2961, 2882, 1667 (C=O st), 1627, 1125, 947, 892. **¹H-NMR** (500 MHz): δ 6.88 (d, 1H, J = 10.7), 6.23–6.21 (m, 2H), 4.24 (td, 1H, J = 8.8, 7.2), 4.15 (td, 1H, J = 9.5, 4.4), 3.51 (ddd, 1H, J = 9.0, 5.7, 3.2), 2.89 (ddddd, 1H, J = 14.3, 11.1, 5.6, 1.9), 2.66 (ddd, 1H, J = 12.9, 8.7, 4.4), 2.39 (d, 1H, J = 9.16), 2.29 (dt, 1H, J = 14.3, 5.0), 2.09–2.04 (m, 1H), 2.00 (ddd, 1H, J = 12.7, 10.1, 7.1), 1.87 (ddddd, 1H, J = 10.9, 8.2, 5.5, 2.9), 0.96 (s, 3H). **¹³C-NMR** (126 MHz): δ 185.7, 158.5, 145.6, 128.4, 127.6, 82.2, 74.9, 67.7, 54.9, 36.3, 31.8, 26.4, 20.0. **ESI-MS** m/z (rel int): (pos) 242.9 ([M+Na]+, 100), 463.1 ([2M+Na]+, 80); (neg) 219.0 ([M–H]–, 100).
F. RING EXPANSION REACTIONS OF 31–50

1. GENERAL PROCEDURES FOR RING EXPANSION

The following general procedures were used for the ring expansion of polycyclic cyclohexadienones as described in Tables 1 and 2 of the manuscript. All ring expansions were run on a scale of 30–60 mg, with the exception of 46→77 (TsOH and CuBF₄) and 47→78 (Tf₂O), which were run on gram scale.

TsOH-Mediated Ring Expansion (Conditions A): To a solution of cyclohexadienone in MeOH/MeNO₂ (1:1, 0.1 M) was added TsOH·H₂O (2.0 equiv). The solution was stirred at 25 °C for 5–20 h. Once complete, the reaction was quenched with satd aq NaHCO₃ and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

TsOH-Mediated Ring Expansion, MeOH-free (Conditions A’): To a solution of cyclohexadienone in MeNO₂ (0.1 M) was added TsOH·H₂O (2.0 equiv). The solution was stirred at 25 °C for 5–20 min. Once complete, the reaction was quenched with satd aq NaHCO₃ and extracted with CH₂Cl₂ (4×). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation. The product(s) were purified by silica gel chromatography (hexanes/EtOAc).

Cu(BF₄)₂-Mediated Ring Expansion (Conditions B): To a solution of cyclohexadienone in MeOH (0.1 M) was added Cu(BF₄)₂·xH₂O (20 mol%) and trimethyl orthoformate (3 equiv). The solution was warmed to 50 °C and stirred for 5–16 h. The reaction could be accelerated by adding more Cu(BF₄)₂ with no deterioration in yield (e.g., 50 or 100 mol% catalyst). Once complete, the reaction was quenched with satd aq NH₄Cl and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

Cu(BF₄)₂′-Mediated Ring Expansion, i-PrOH variant (Conditions B’): To a solution of cyclohexadienone in i-PrOH (0.1 M) was added Cu(BF₄)₂·xH₂O (20 mol%). The solution was stirred at 25 °C for 2 h. Once complete, the reaction was quenched with satd aq NH₄Cl and extracted with CH₂Cl₂ (4×). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

Tf₂O-Mediated Ring Expansion (Conditions C): To a solution of cyclohexadienone and 2,6-di-tert-butyl-4-methylpyridine (1.5 equiv) in CH₂Cl₂ (0.1 M) at 0 °C was added triflic anhydride (1M in CH₂Cl₂, 1.3 equiv). The reaction was allowed to stir for 0.25–6 h. An extra 0.5 equiv of triflic anhydride could be added to accelerate sluggish ring expansions. The reaction was quenched at 0 °C with satd aq NaHCO₃, warmed to 25 °C, and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).
2. Ring Expansion of 31

Supplementary Table 2. Ring Expansion of 31.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| ![Image of Starting Material](image1.png) | A<sup>a</sup> | 6 h | ![Image of Product](image2.png) 52 | 82% |
| ![Image of Starting Material](image3.png) | B<sup>b</sup> | 6 h | ![Image of Product](image4.png) 52 | 86% |
| ![Image of Starting Material](image5.png) | C<sup>c</sup> | 15 min | ![Image of Product](image6.png) 53 | 91% |

<sup>a</sup> Ring expansion gave a mixture of three olefin isomers and a methanol adduct. To simplify this mixture, once ring expansion was complete, the reaction was heated at 50 °C for an additional 5 h to isomerize all products to 52.

<sup>b</sup> Ring expansion gave a mixture of three olefin isomers and a methanol adduct. To simplify this mixture, the reaction was worked up and the crude material was redissolved in MeOH and stirred with TsOH (2 equiv) at 50 °C for an additional 5 h to isomerize all products to 52. Yield after treatment with TsOH is shown.

<sup>c</sup> Ring expansion gave a mixture of olefin isomers. To simplify this mixture, the isomers were equilibrated to the thermodynamic product 53 by stirring, after work up, in CH<sub>2</sub>Cl<sub>2</sub> with TsOH (4.0 equiv) for 12 h at 25 °C. Yield after treatment with TsOH is shown.

(Z)-10-Methoxy-5-methyl-3,6,7,8-tetrahydro-2H-benzo[b]oxecine (52). Olefin regiochemistry determined by <sup>1</sup>H–<sup>1</sup>H COSY; (Z)-olefin geometry assigned by NOESY. TLC: R<sub>f</sub> 0.70 (8:2 hexanes/EtOAc). IR (NaCl, film): 2923, 1498, 1211, 1046, 849, 799. <sup>1</sup>H-NMR (500 MHz): δ 6.97 (d, 1H, J = 8.7), 6.73 (d, 1H, J = 2.7), 6.72 (dd, 1H, J = 8.7, 2.7), 5.31 (t, 1H, J = 8.2), 4.17–4.15 (m, 2H), 3.77 (s, 3H), 2.64–2.67 (m, 2H), 2.09–2.01 (m, 2H), 1.87–1.79 (m, 4H), 1.72 (s, 3H). <sup>13</sup>C-NMR (126 MHz): δ 154.9, 149.7, 136.7, 135.3, 123.6, 118.5, 114.8, 112.3, 70.6, 55.6, 27.7, 27.4, 26.9, 24.1, 22.6. ESI-MS m/z (rel int): (pos) 265.1 ([M+Na]<sup>+</sup>, 100), 233.1 ([M+H]<sup>+</sup>, 75).

(Z)-5-Methyl-3,6,7,8-tetrahydro-2H-benzo[b]oxecin-10-yl trifluoromethanesulfonate (53). Olefin regiochemistry determined by <sup>1</sup>H–<sup>1</sup>H COSY; (Z)-olefin geometry assigned by analogy to
anisole 52. **TLC**: \( R_f 0.34 \) (95:5 hexanes/EtOAc). **IR** (NaCl, film): 2932, 1489, 1421, 1211, 1142, 927. **\(^{1}\text{H-NMR}** (500 MHz): \( \delta 7.09–7.04 \) (m, 3H), 5.29 (t, 1H, \( J = 8.0 \)), 4.25–4.21 (m, 2H), 2.70–2.63 (m, 2H), 2.12–2.05 (m, 2H), 1.86–1.78 (m, 4H), 1.69 (s, 3H). **\(^{13}\text{C-NMR}** (126 MHz): \( \delta 156.0, 144.3, 137.1, 136.9, 123.0, 122.6, 119.7, 118.6, 117.5, 70.6, 27.7 \) (2 peaks), 26.9, 24.4, 22.5. **ESI-MS** \( m/z \) (rel int): (pos) 389.3 ([M+K]\(^{+}\), 20), 241.0 ([M–SO\(_2\)CF\(_3\)+H+Na]\(^{+}\), 100).

### 3. RING EXPANSION OF 32

**Supplementary Table 3. Ring Expansion of 32.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| ![32](image)      | A          | 5 h  | ![54](image) | 90%   |
| ![32](image)      | B          | 14 h | ![54](image) | 49%   |
| ![32](image)      | C          | 2 h  | complex mixture | --    |

(Z)-3,10-Dimethoxy-3,5-dimethyl-3,6,7,8-tetrahydro-2H-benzo[b]oxecine (54). Olefin regiochemistry determined based on the olefin proton observed at \( \delta 5.01 \) (coupled to carbon at \( \delta 125.9 \) in HSQC) being a singlet and by \(^{1}\text{H–}^{1}\text{H COSY}; \) (Z)-olefin geometry assigned by NOESY. **TLC**: \( R_f 0.31 \) (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2926, 1499, 1211, 1052. **\(^{1}\text{H-NMR}** (500 MHz): \( \delta 6.87 \) (d, 1H, \( J = 8.5 \)), 6.67 (dd, 1H, \( J = 8.5, 2.8 \)), 6.66 (s, 1H), 5.01 (s, 1H), 4.40 (d, 1H, 11.4), 3.87 (d, 1H, \( J = 11.4 \)), 3.76 (s, 3H), 3.15 (s, 3H), 2.74–2.67 (m, 1H), 2.62–2.54 (m, 2H), 1.87–1.79 (m, 2H), 1.74 (s, 3H), 1.73–1.67 (m, 1H), 1.21 (s, 3H). **\(^{13}\text{C-NMR}** (126 MHz): \( \delta 154.0, 152.3, 133.4, 125.9, 117.2, 115.8, 114.8, 111.6, 79.4, 75.1, 55.6, 50.9, 29.7, 28.7, 27.5, 27.3, 24.0 \). **ESI-MS** \( m/z \) (rel int): (pos) 245.1 ([M–OMe]\(^{+}\), 100), 299.1 ([M+Na]\(^{+}\), 30), 277.1 ([M+H]\(^{+}\), 20).
4. Ring Expansion of 33

**Supplementary Table 4. Ring Expansion of 33.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A                 |            | 16 h | [S45]      | <25%  |
| B                 |            | 48 h | [S45]      | <25%  |
| C                 | 30 min     |      | [55]       | 75%   |

*The structure of S45 was assigned based on the following diagnostic ¹H-NMR peaks: δ 3.76 (s, 3H), 3.21 (s, 3H).*

2,2-Dimethyl-4-methylene-3,4,5,6-tetrahydro-2H-benzo[b]oxocin-8-yl trifluoromethanesulfonate (55). Obtained as an inseparable mixture of 5.5:1.0 exocyclic:endo cyclic olefins. Ratio of olefin regioisomers determined based on olefinic ¹H-NMR peaks: δ 4.91 major, 5.14 minor. The structure of the major isomer is consistent with ¹H and ¹³C-NMR data (e.g., singlets at δ 4.91, 4.74 for geminal protons attached to a carbon resonating at δ 115.4 [HSQC]; geminally coupled allylic protons at δ 2.38, 2.29 [J = 13.7 Hz] attached to a carbon resonating at δ 47.5 [HSQC]). **TLC:** Rf 0.53 (95:5 hexanes/EtOAc). **IR** (NaCl, film): 2934, 1488, 1421, 1250, 1210, 1142. ¹H-NMR (500 MHz): δ 6.99–6.96 (m, 2H), 6.79–6.77 (m, 1H), 4.91 (s, 1H), 4.74 (s, 1H), 2.81 (q, 2H, J = 7.2), 2.38 (d, 1H, J = 13.7), 2.29 (d, 1H, J = 13.7), 1.87 (dt, 1H, J = 13.9, 7.0), 1.82 (s, 3H), 1.81–1.75 (m, 1H), 1.29 (s, 3H). ¹³C-NMR (126 MHz): δ 153.4, 142.2, 141.8, 122.5, 121.9, 120.2, 118.5, 118.2, 115.4, 47.5, 30.8, 24.4, 24.2, 22.3. **ESI-MS** m/z (rel int): (pos) 351.0 ([M+H]+, 100), 217.1 ([M–SO₂CF₃]+, 75).
5. **RING EXPANSION OF 34**

**Supplementary Table 5. Ring Expansion of 34.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A                 | (50 °C)   | 24 h | ![Structure A](image1.png) | 50%   |
| B                 | (80 °C)   | 24 h | ![Structure B](image2.png) 56 | 85%   |
| C                 | (25 °C)   | 6 h  | ![Structure C](image3.png) 57 | 96%   |

(Z)-**8-Bromo-9-methoxy-4-methyl-2,3,6,7-tetrahydrobenzo[b]oxonine** (56). Structure assigned by analogy to parent olefins 6 and 7. **TLC:** $R_f$ 0.58 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 2929, 1473, 1263, 1226, 1073, 1018. **$^1$H-NMR** (500 MHz): δ 6.99 (d, 1H, $J = 8.8$), 6.75 (d, 1H, $J = 8.8$), 5.5 (t, 1H, $J = 8.4$), 4.20–4.19 (m, 2H), 3.87 (s, 3H), 3.02–2.98 (m, 2H), 2.31–2.26 (m, 2H), 2.09–2.06 (m, 2H), 1.71 (s, 3H). **$^{13}$C-NMR** (126 MHz): δ 152.2, 151.7, 138.1, 133.9, 127.4, 119.4, 114.1, 109.7, 73.4, 56.6, 32.2, 30.8, 25.8, 23.2. **ESI-MS** $m/z$ (rel int): (neg) 282.9 ([M−CH$_3$]$^-$, 100), 295.0 ([M−H]$^-$, 5); (pos) 301.0 ([M−CH$_3$+H$_2$O]$^+$, 100).

**8-Bromo-4,9-dimethoxy-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine** (S46). Structure assigned by analogy to parent methyl ether 8. **TLC:** $R_f$ 0.37 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 2936, 1474, 1257, 1076, 806. **$^1$H-NMR** (500 MHz): δ 6.95 (d, 1H, $J = 8.8$), 6.74 (d, 1H, $J = 8.8$), 4.23 (dd, 1H, $J = 12.4, 7.9$), 4.11 (dd, 1H, $J = 12.4, 7.9$), 3.86 (s, 3H), 3.11 (s, 3H), 3.00 (t, 2H, $J = 6.0$), 1.85–1.79 (m, 1H), 1.75 (td, 2H, $J = 15.2, 8.2$), 1.61 (td, 2H, $J = 16.8, 9.7$), 1.59–1.54 (m, 1H), 1.10 (s, 3H). **$^{13}$C-NMR** (126 MHz): δ 152.2, 151.9, 138.0, 119.3, 113.9, 109.9, 76.1, 70.3, 56.6, 48.7, 36.7, 35.9, 31.7, 23.4, 20.7. **ESI-MS** $m/z$ (rel int): (pos) 351.0 ([M+Na]$^+$, 100).
(Z)-8-Bromo-4-methyl-2,3,6,7-tetrahydrobenzo[b]oxonin-9-yl trifluoromethanesulfonate (57). Obtained as an inseparable mixture of 11.7:6.4:1.0 endocyclic-“down”/endocyclic-“up”/exocyclic olefins. The major isomer was isolated by preparative TLC for characterization; the two minor isomers were not separable from each other. Structure of major isomer assigned by analogy to parent olefins 6 and 7. **Major isomer: TLC:** $R_f$ 0.31 (95:5 hexanes/EtOAc). **IR** (NaCl, film): 2935, 1453, 1427, 1215, 1140, 1018, 947, 839. **$^1$H-NMR** (500 MHz): $\delta$ 7.17 (d, 1H, $J$ = 8.9), 7.01 (d, 1H, $J$ = 8.9), 5.61 (t, 1H, $J$ = 7.4), 4.52–4.42 (m, 2H), 2.93–2.88 (m, 2H), 1.97–1.91 (m, 2H), 1.90–1.85 (m, 2H), 1.75 (s, 3H). **$^{13}$C-NMR** (126 MHz): $\delta$ 159.1, 146.2, 143.2, 138.5, 121.6, 121.2, 120.8, 118.5, 117.4, 71.0, 30.9, 28.5, 24.7, 22.8. **ESI-MS** $m/z$ (rel int): (pos) 453.0 ([M+K]$^+$, 100); (neg) 412.9 ([M–H]$^-$, 100).

### 6. RING EXPANSION OF 35

**Supplementary Table 6. Ring Expansion of 35.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| ![35](image) | A | 16 h | ![58](image) $^{(3:1)}$ S47 | 85% |
| ![35](image) | B | 16 h | ![58](image) $^{(3:1)}$ S47 | 84% |
| ![35](image) | C | 30 min | ![59](image) $^{(10:3:2:1)}$ | 92% |

(Z)-9-Methoxy-4,8-dimethyl-2,3,6,7-tetrahydrobenzo[b]oxonine (58). Structure assigned by analogy to parent olefins 6 and 7. **TLC:** $R_f$ 0.49 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2940,
1653, 1559, 1541, 1507, 1479, 1258, 1059.  

**1H-NMR** (500 MHz): δ 6.88 (d, 1H, J = 8.8), 6.69 (d, 1H, J = 8.8), 5.56 (t, 1H, J = 8.4), 4.18 (t, 2H, J = 4.7), 3.79 (s, 3H), 2.74 (t, 2H, J = 5.8), 2.26–2.16 (m, 2H), 2.16 (s, 3H), 2.06–2.00 (m, 2H), 1.74 (s, 3H).  

**13C-NMR** (126 MHz): δ 153.6, 150.8, 136.7, 134.0, 127.6, 124.8, 108.7, 73.0, 55.9, 32.0, 26.8, 26.4, 23.3, 10.1.  

**ESI-MS** m/z (rel int): (pos) 255.1 ([M+Na]+, 100); (neg) 325.1 ([M+Cl+NaCl]-, 100).  

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4,9-Dimethoxy-4,8-dimethyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine (S47). Structure assigned by analogy to parent methyl ether 8.  

**TLC:** Rf 0.28 (9:1 hexanes/EtOAc).  

**IR** (NaCl, film): 2934, 1480, 1253, 1104, 805.  

**1H-NMR** (500 MHz): δ 6.88 (d, 1H, J = 8.8), 6.69 (d, 1H, J = 8.8), 5.56 (t, 1H, J = 8.4), 4.18 (t, 2H, J = 4.7), 3.79 (s, 3H), 2.74 (t, 2H, J = 5.8), 2.26–2.16 (m, 2H), 2.16 (s, 3H), 2.06–2.00 (m, 2H), 1.74 (s, 3H).  

**13C-NMR** (126 MHz): δ 153.6, 150.8, 136.7, 134.0, 127.6, 124.8, 108.7, 73.0, 55.9, 48.6, 36.4, 36.3, 27.9, 23.4, 21.3, 11.8.  

**ESI-MS** m/z (rel int): (pos) 287.0 ([M+Na]+, 100).  

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(Z)-4,8-Dimethyl-2,3,6,7-tetrahydrobenzo[b]oxonin-9-yl trifluoromethanesulfonate (59). Obtained as an inseparable mixture of 10:3:2:1.0 endocyclic-“down”/endocyclic-“up”/exocyclic olefins. Ratio of regioisomers determined based on olefinic 1H-NMR peaks: δ 5.65 endocyclic-“down”, 5.45 endocyclic-“up”, 5.09/4.99 exocyclic. The structure of the major isomer was assigned by analogy to parent olefins 6 and 7.  

**TLC:** Rf 0.35 (95:5 hexanes/EtOAc).  

**IR** (NaCl, film): 2921, 1458, 1419, 1209, 1141, 919.  

**1H-NMR** (500 MHz): δ (major, 30a) d 7.08 (d, 1H, J = 8.8), 6.90 (d, 1H, J = 8.8), 5.65 (t, 1H, J = 7.25), 4.44–4.41 (m, 2H), 2.79–2.72 (m, 2H), 2.32 (s, 3H), 2.31–2.26 (m, 2H), 1.92 (t, 2H, J = 5.8), 1.77 (s, 3H).  

**13C-NMR** (126 MHz): (mixture of all 3 isomers) δ 158.8, 158.5, 157.0, 145.9, 145.5, 144.4, 144.0, 137.6, 136.5, 135.7, 133.9, 130.4, 130.2, 129.7, 127.2, 121.8, 121.7, 120.2, 119.9 (2 peaks), 119.7, 119.6 (2 peaks), 118.7, 117.9, 117.6, 113.3, 73.1, 72.7, 70.6, 37.6, 32.2, 30.7, 29.2, 27.7, 26.8, 26.0, 25.4, 24.5, 23.3, 23.1, 22.8, 13.5, 12.93, 12.75.  

**ESI-MS** m/z (rel int): (pos) 389.2 ([M+K]+, 100), 373.0 ([M+Na]+, 25); (neg) 349.0 ([M–H]+, 100).
7. Ring Expansion of 36

Supplementary Table 7. Ring Expansion of 36.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
|                   | A          | 20 h | 60 (3:1)  | S48   | 89%   |
|                   | B          | 16 h | 60 (3:1)  | S48   | 85%   |
|                   | C          | 30 min |       |       | 83%   |

(Z)-9-Methoxy-8-(4-methoxyphenyl)-4-methyl-2,3,6,7-tetrahydrobenzo[b]oxonine (60).
Structure assigned by analogy to parent olefins 6 and 7. TLC: Rf 0.48 (8:2 hexanes/EtOAc). IR (NaCl, film): 2933, 1515, 1475, 1244, 1073, 831. $^1$H-NMR (500 MHz): $\delta$ 7.10 (d, 2H, $J = 8.7$), 7.03 (d, 1H, $J = 8.8$), 6.96 (d, 2H, $J = 8.7$), 6.78 (d, 1H, $J = 8.8$), 5.46 (t, 1H, $J = 8.4$), 4.24 (t, 2H, $J = 5.1$), 3.85 (s, 3H), 3.67 (s, 3H), 2.46 (t, 2H, $J = 5.9$), 2.14–2.07 (m, 4H), 1.74 (s, 3H). $^{13}$C-NMR (126 MHz): $\delta$ 158.3, 153.0, 151.5, 133.4, 131.1, 131.0, 130.9, 130.0, 127.7, 119.2, 113.4, 109.2, 72.7, 56.1, 55.2, 32.1, 30.3, 27.5, 23.3. ESI-MS m/z (rel int): (pos) 347.1 ([M+Na]$^+$, 100), 671.3 ([2M+Na]$^+$, 50).
4,9-Dimethoxy-8-(4-methoxyphenyl)-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine (S48). Structure assigned by analogy to parent methyl ether 8. TLC: $R_f$ 0.28 (8:2 hexanes/EtOAc). IR (NaCl, film): 2921, 1515, 1475, 1253, 1076. $^1$H-NMR (500 MHz): $\delta$ 7.13-7.08 (m, 2H), 6.99 (d, 1H, $J$ = 8.8), 4.16 (dd, 1H, $J$ = 12.1, 7.9), 3.86 (s, 3H), 3.67 (s, 3H), 3.13 (s, 3H), 2.48–2.46 (m, 2H), 1.92–1.88 (m, 1H), 1.76–1.71 (m, 2H), 1.51–1.57 (m, 2H), 1.37–1.33 (m, 1H), 1.11 (s, 3H). $^{13}$C-NMR (126 MHz): $\delta$ 158.3, 153.0, 131.3, 130.9, 129.7, 118.7, 113.4, 113.3, 109.3, 76.3, 69.5, 56.2, 55.2, 48.7, 37.2, 30.3, 29.4, 23.3, 22.2. ESI-MS $m/z$ (rel int): (pos) 379.1 ([M+Na]$^+$, 100), 735.4 ([2M+Na]$^+$, 40); (neg) 355.1 ([M–H]$^-$, 100).

(Z)-8-(4-Methoxyphenyl)-4-methyl-2,3,6,7-tetrahydrobenzo[b]oxoxin-9-yl trifluoromethanesulfonate (61). Obtained as an inseparable mixture of 8.6:4.3:1.0 endocyclic-“down”/endocyclic-“up”/exocyclic olefins. Ratio of regioisomers determined based on olefinic $^1$H-NMR peaks: $\delta$ 5.59 endocyclic-“down”, 5.35 endocyclic-“up”, 5.01/4.89 exocyclic. Structure of major isomer assigned by analogy to parent olefins 6 and 7. TLC: $R_f$ 0.26 (95:5 hexanes/EtOAc). IR (NaCl, film): 2936, 1516, 1458, 1420, 1249, 1209, 1142, 838. $^1$H-NMR (500 MHz): $\delta$ (major) 7.16–7.13 (m, 3H, $J$ = 8.8), 6.96–6.95 (m, 3H, $J$ = 8.7), 5.59 (t, 1H, $J$ = 7.3), 4.51–4.49 (m, 2H), 3.86 (s, 3H), 2.59–2.54 (m, 2H), 2.19–2.16 (m, 2H), 1.92 (t, 2H, $J$ = 5.8), 1.71 (s, 3H). $^{13}$C-NMR (126 MHz): (mixture of all 3 isomers) $\delta$ 159.3 (2 peaks), 158.7, 145.8, 143.3, 142.9, 137.1, 136.3, 135.9, 133.3, 131.1 (2 peaks), 131.0, 127.4, 126.7, 126.1, 121.3, 121.2, 119.2, 119.8, 119.5, 119.4, 117.3, 113.7, 113.6 (3 peaks), 73.0, 72.7, 70.4, 55.3 (2 peaks), 37.2, 32.3, 30.9, 29.9, 28.5, 27.7, 26.0, 25.0, 23.4, 22.8. ESI-MS $m/z$ (rel int): (pos) 443.1 ([M+H]$^+$, 40), 465.0 ([M+Na]$^+$, 100).
8. Ring Expansion of 37

Supplementary Table 8. Ring Expansion of 37.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A                 | A          | 14 h | 62 (R = H) + S49a (R = Me) (3:1) | 57%   |
|                   | A'         | 10 min | 62 (3:1) | 54%   |
|                   | TsOH (2 equiv) CH₂Cl₂, 25 °C | 12 h | 62 | 67%   |
|                   | B          | 14 h | 62 + S49a + S49b (2.3:1:4:1) | 77%   |
|                   | C          | 30 min | S50b (1:1) | N.D. |

* The structure of 62' was assigned by 1H–1H COSY and NOESY (*vide infra*).

* The structures of S50 were assigned based on the following diagnostic 1H-NMR peaks: (1:1 mixture of olefins) δ 5.92 (t, 1H, J = 7.1), 5.58 (t, 1H, J = 9.0), 4.71–4.69 (m, 1H), 4.26–4.24 (m, 2H).

* N.D. = not determined.

(E)-4-Phenyl-2,3,6,7-tetrahydrobenzo[b]oxonin-9-ol (62). Structure assigned by analogy to methyl-substituted olefins 6 and 7. TLC: Rf 0.43 (7:3 hexanes/EtOAc). IR (NaCl, film): 3370 (O–H st), 2919, 1496, 1445, 1197, 1022. 1H-NMR (500 MHz): δ 7.26–7.18 (m, 3H), 7.11 (d, 2H, J = 7.6), 6.83 (d, 1H, J = 8.7), 6.62 (dd, 1H, J = 8.7, 3.1), 6.55 (d, 1H, J = 3.1), 5.77 (t, 1H, J = 8.7), 4.46 (br s, 1H), 4.20–4.15 (m, 2H), 2.86 (t, 2H, J = 6.6), 2.73–2.64 (m, 4H). 13C-NMR
(126 MHz): δ 150.8, 143.2, 137.8, 130.8, 128.2, 127.8, 127.6, 123.7 (2 peaks), 121.0, 117.1, 113.9, 73.4, 31.8, 31.2, 27.5. **ESI-MS** m/z (rel int): (pos) 289.1 ([M+Na]^+, 100), 267.01 ([M+H]^+, 30); (neg) 265.0 ([M–H]^−, 100).

(E)-9-Methoxy-4-phenyl-2,3,6,7-tetrahydrobenzo[b]oxonine (S49a). **TLC**: Rf 0.16 (10% EtOAc/hexanes). **1H-NMR** (500 MHz): δ 7.25 (d, 2H, J = 7.6), 7.21 (d, 1H, J = 7.0), 7.14–7.12 (m, 2H), 6.89 (d, 1H, J = 8.8), 6.70 (dd, 1H, J = 8.8, 3.1), 6.63 (d, 1H, J = 3.0), 5.80 (t, 1H, J = 8.9), 4.19 (t, 2H, J = 5.0), 3.79 (s, 3H), 2.90 (t, 2H, J = 6.1), 2.70 (s, 4H). **13C-NMR** (151 MHz): δ 155.0, 143.1, 137.6, 130.8, 128.3, 127.1, 126.7, 126.6, 120.8, 115.8, 112.3, 73.5, 55.6, 32.0, 31.1, 27.6 (one carbon unresolved). **ESI-MS** m/z (rel int): (pos) 303.15 ([M+Na]^+, 100), 281.19 ([M+H]^+, 30).

4,9-Dimethoxy-phenyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine (S49b). **TLC**: Rf 0.20 (20% EtOAc/hexanes). **1H-NMR** (500 MHz): δ 7.40–7.39 (m, 2H), 7.35 (t, 2H, J = 7.6), 6.95 (d, 1H, J = 8.6), 6.74 (dd, 1H, J = 8.7, 3.1), 6.64 (s, 1H), 4.18 (br s, 1H), 3.97 (br s, 1H), 3.79 (s, 3H), 2.89 (s, 3H), 2.75–2.73 (m, 2H), 2.41 (br s, 2H), 2.05–2.00 (m, 1H), 1.72–1.69 (m, 2H). **13C-NMR** (151 MHz): 155.3, 150.1, 144.2, 138.3, 128.2, 127.1, 126.9, 120.8, 115.8, 112.5, 80.7, 69.1, 55.5, 49.7, 34.6, 26.4, 21.4 (one carbon unresolved). **ESI-MS** m/z (rel int): (pos) 335.16 ([M+Na]^+, 100), 281.19 ([M–CH3O]^+, 31).

(E)-4-Phenyl-2,5,6,7-tetrahydrobenzo[b]oxonin-9-ol (62'). Ratio of regioisomers determined based on olefinic **1H-NMR** peaks: δ 5.77 endocyclic-“up”, 6.10 endocyclic-“down” olefin. Olefin regiochemistry determined by **1H–1H COSY**; (E)-olefin geometry assigned by NOESY. **TLC**: Rf 0.38 (30% EtOAc/hexanes). **1H-NMR** (600 MHz): δ 7.31–7.27 (m, 3H), 7.25 (s, 1H), 7.19–7.17 (m, 2H), 6.53–6.50 (m, 2H), 6.10 (t, 1H, J = 6.7), 4.37 (s, 1H), 4.32 (s, 1H), 3.65 (d, 2H, J = 6.6), 3.08–3.03 (m, 2H), 2.61–2.59 (m, 2H), 1.84–1.82 (m, 2H). **ESI-MS** m/z (rel int): (pos) 287.17 ([M+Na]^+, 36).
9. Ring Expansion of 38

Supplementary Table 9. Ring Expansion of 38.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A                 | 15 min     |      | 63         | 95%   |
|                   |            |      | (3:1) S51a |       |
| A’                | 5 min      |      |            | 98%   |
|                   |            |      |            |       |
| B                 | 12 h       |      | complex mixture | --   |
|                   |            |      |            |       |
| Cb                | 25 min     |      | 64         | 57%   |

\(^a\) The structure of S51 was assigned based on the following diagnostic \(^1\)H NMR peaks: \(\delta 4.28\) (s, 1H), \(3.20\) (s, 3H).

\(^b\) Ring expansion gave a mixture of olefin isomers. To simplify this mixture, the isomers were equilibrated to the thermodynamic product 64 by stirring, after work up, in \(\text{CH}_3\text{NO}_2\) with TsOH (4.0 equiv) for 12 h at 25 °C. Yield after treatment with TsOH is shown.

\((Z)-4\)-Methyl-3,6,7,8-tetrahydro-2\(H\)-benzo[b]oxecin-10-ol (63). TLC: \(R_f 0.22\) (20% EtOAc/hexanes). IR (NaCl, film): 3384, 2966, 2912, 2854, 1493, 1449, 1207, 1192, 1052, 1024, 882. \(^1\)H-NMR (600 MHz): \(\delta 6.93\) (d, 1H, \(J = 8.3\)), 6.65–6.62 (m, 2H), 5.20 (t, 1H, \(J = 8.1\)), 4.42 (s, 1H), 4.26 (t, 2H, \(J = 5.3\)), 2.80–2.42 (br s, 2H), 2.26–2.20 (br s, 2H), 1.80 (s, 3H), 1.77–1.76 (m, 2H), 1.70 (dd, 2H, \(J = 7.8, 4.1\)). \(^13\)C-NMR (151 MHz): \(\delta 150.6, 149.8, 135.4, 132.5, 127.6, 118.2, 116.1, 113.6, 67.8, 30.8, 29.5, 24.6, 24.2, 22.6\). ESI-MS \(m/z\) (rel int): (neg) \(216.96 ([\text{M+H}]^+, 100)\), 435.21 ([2M–H]–, 20).
4-Methoxy-4-methyl-3,4,5,6,7,8-hexahydro-2H-benzo[b]oxecin-10-ol (S51). TLC: \( R_f 0.18 \) (10% EtOAc/hexanes). \(^1\)H-NMR (500 MHz): \( \delta 6.65–6.57 \) (m, 3H), 4.28 (s, 1H), 4.01–3.96 (m, 1H), 3.85–3.81 (m, 1H), 3.20 (s, 3H), 2.87–2.80 (m, 1H), 2.53–2.47 (m, 1H), 2.03–1.96 (m, 2H), 1.88–1.82 (m, 1H), 1.67–1.63 (m, 3H), 1.10 (s, 3H). ESI-MS \( m/z \) (rel int): (pos) 273.17 ([M+Na]\(^+\), 100), (neg) 248.91 ([M–H]\(^-\), 100).

(Z)-4-Methyl-3,6,7,8-tetrahydro-2H-benzo[b]oxecin-10-yl trifluoromethanesulfonate (64). TLC: \( R_f 0.17 \) (3% EtOAc/hexanes). IR (NaCl, film): 2918, 1489, 1420, 1209, 1141, 948. \(^1\)H-NMR (600 MHz): \( \delta 7.09–7.05 \) (m, 3H), 5.20 (t, 1H, \( J = 7.5 \)), 4.33 (t, 2H, \( J = 5.3 \)), 2.92–2.56 (br s, 2H), 2.31–1.97 (br s, 2H), 1.79 (s, 3H), 1.76–1.71 (m, 4H). \(^{13}\)C-NMR (151 MHz): \( \delta 155.9, 144.3, 136.6, 132.0, 127.9, 122.6, 119.5, 118.8 \) (q, \( J_{C,F} = 273 \)), 117.9, 67.7, 31.1, 29.6, 24.65, 24.64, 22.7. ESI-MS \( m/z \) (rel int): 373.0 ([M+Na]\(^+\), 100), 389.1 ([M+K]\(^+\), 10).
10. RING EXPANSION OF 39

Supplementary Table 10. Ring Expansion of 39.

| Starting Material | Conditions | Time | Product(s)                  | Yield |
|-------------------|------------|------|-----------------------------|-------|
| A'                | 10 min     |      | 65 (7.9:4.5:1)              | 63%   |
| B                 | 14 h       |      | S52 (2.5:1.6:1:2:1)         | 61%   |
| C                 | 2 h        |      | 66 (8.1:4:9:1)              | 52%   |

The structures of S52 were assigned based on the following diagnostic 1H-NMR peaks: (endo-down E-olefin) δ 5.11 (t, 1H, J = 8.2), 4.32 (s, 1H), 4.04 (t, 2H, J = 4.9), 2.22–2.20 (m, 2H), 2.02 (dd, 2H, J = 12.5, 7.4), 1.95–1.91 (m, 2H); (MeOH adduct) δ 4.28 (s, 1H), 3.20 (3H); (endo-down Z-olefin) δ 5.02 (t, 1H, J = 7.2), 4.28 (s, 1H), 3.97 (t, 2H, J = 5.0); (endo-up Z-olefin) δ 5.34 (t, 1H, J = 8.2), 4.26 (s, 1H), 3.86 (t, 2H, J = 4.5). Olefin regiochemistry was determined by 1H–1H COSY. (E)-Olefin geometry was determined by NOESY (vide infra).

(Z)-5-Methyl-2,3,6,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-ol (65). Obtained as an inseparable mixture of 7.9:4.5:1 Z-endocyclic-“up” (major) / endocyclic-“down” (minor) / E-endocyclic-“up” (trace) olefins. Ratio of regioisomers determined based on olefinic 1H-NMR peaks: δ 5.33 Z-endocyclic-“up”, 5.02 endocyclic-“down”, 5.18 E-endocyclic-“up”. Olefin regiochemistry determined by 1H–1H COSY; (Z)-olefin geometry assigned by NOESY. TLC: Rf 0.20 (10% EtOAc/hexanes). IR (NaCl, film): 3356, 2924, 1596, 1501, 1443, 1219. 1H-NMR (600 MHz): δ 6.64–6.53 (m, 6H), 5.35–5.32 (m, 1H, major), 5.15 (m, 0.13H, trace), 5.03–5.01 (m, 0.6 H, minor), 4.30 (s, 0.6H, minor), 4.26 (s, 1H, major), 3.97 (t, 1.2H, J = 5.0, minor), 3.85–3.84 (m, 2H, major), 2.60–2.59 (m, 2H), 2.54–2.53 (m, 1.4 H), 2.42–2.40 (m, 2H), 2.36–2.32 (m, 2H), 2.18–2.16 (m, 1.2 H), 2.00–1.97 (m, 1.4H), 1.91 (dd, 1.2H, J = 10.8, 5.4), 1.78 (d, 1.4H, J = 1.2), 1.71–1.67 (m, 1.4 H), 1.64 (s, 2H, minor), 1.56 (s, 3H, major), 1.54–1.50 (m, 2H), 1.44–
1.40 (m, 2.4H). $^{13}$C-NMR (151 MHz): (mixture of isomers) δ 152.0, 151.6, 149.0, 148.5, 140.5, 136.1, 133.4, 133.0, 126.5, 121.7, 117.8, 117.1, 112.7, 112.4, 111.4, 110.1, 70.9, 67.7, 32.0, 30.8, 29.7, 28.9, 28.6, 28.0, 27.5, 26.9, 26.3, 25.7, 25.3, 23.8, 23.0. ESI-MS m/z (rel int): (pos) 231.06 ([M+H]$^+$, 100), 463.27 ([2M+H]$^+$, 48).

(E)-5-methyl-2,3,4,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-ol (S52). Components of the mixture were assigned based on diagnostic $^1$H NMR (600 MHz) peaks: δ (endo-down E-olefin, major) 5.11 (t, 1H, $J = 8.2$), 4.32 (s, 1H), 4.04 (t, 2H, $J = 4.9$), 2.22–2.20 (m, 2H), 2.02 (dd, 2H, $J = 12.5, 7.4$), 1.95–1.91 (m, 2H); (MeOH adduct) δ 4.28 (s, 1H), 3.20 (s, 3H); (endo-down Z-olefin) δ 5.02 (t, 1H, $J = 7.2$), 4.28 (s, 1H), 3.97 (t, 2H, $J = 5.0$); (endo-up Z-olefin) δ 5.34 (t, 1H, $J = 8.2$), 4.26 (s, 1H), 3.86 (t, 2H, $J = 4.5$). Ratio of products was based on olefin and methyl ether $^1$H-NMR peaks: δ 5.11 (endo-down E-olefin), 4.28 (MeOH adduct), 5.02 (endo-down Z-olefin), 5.34 (endo-up Z-olefin). Olefin regiochemistry was determined by $^1$H–$^1$H COSY. (E)-Olefin geometry was determined by NOESY.

(Z)-5-Methyl-2,3,6,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-yl trifluoromethanesulfonate (66). Obtained as an inseparable mixture of 8:1:4.9:1 endocyclic-“up”/endocyclic-“down”/exocyclic olefins. Ratio of regioisomers determined based on olefinic $^1$H-NMR peaks: δ 6.67 Z-endocyclic-“up”, 5.08 E-endocyclic-“down”, 4.72 and 4.66 exocyclic olefin. Structures assigned by analogy to 65. TLC: R$_f$ 0.18 (3% EtOAc/hexanes). IR (NaCl, film): 2932, 1494, 1421, 1249, 1210, 1142, 1041, 953, 884, 847. $^1$H-NMR (600 MHz): δ 7.03–6.98 (m, 3.6H), 6.77 (d, 0.6H, $J = 8.7$, endocyclic-down), 6.73 (d, 1H, $J = 8.8$, major), 6.67 (d, 1H, $J = 8.7$, major), 5.34 (t, 1H, $J = 8.3$, major), 5.08 (td, 0.6H, $J = 7.7$, 1.0, endocyclic-down), 4.72 (s, 0.1H, exocyclic), 4.66 (s, 0.1H, exocyclic), 4.14 (t, 0.6H, $J = 5.0$, major), 3.97 (t, 0.1H, $J = 4.8$, exocyclic), 3.90 (d, 2H, $J = 0.7$, major), 2.65–2.63 (m, 2H), 2.53 (t, 1H, $J = 6.2$), 2.47 (br s, 2H), 2.35 (t, 2H, $J = 7.6$), 2.31 (t, 1H, $J = 5.6$), 2.25–2.23 (m, 1H), 2.02 (q, 1H, $J = 6.4$), 1.96 (dt, 2H, $J = 10.2, 5.7$), 1.77 (d, 0.1H, $J = 1.3$, exocyclic), 1.72–1.70 (m, 2H), 1.65 (s, 3H, major), 1.62 (s, 1.8H, endocyclic-down), 1.53–1.50 (m, 2H), 1.45–1.41 (m, 2H). $^{13}$C-NMR (151 MHz): (mixture of three isomers) δ 156.6, 155.2, 142.7, 142.3, 140.7, 135.87, 135.73, 134.1, 126.2, 124.9, 122.9, 122.7, 122.4, 121.4, 119.8 (2 peaks), 119.3, 118.8, 117.7 (2 peaks), 112.6, 111.1, 110.5, 110.3, 110.1, 70.9, 69.3, 67.9, 40.3, 34.9, 31.3, 30.6, 29.3, 28.61, 28.60, 27.7, 27.50, 27.30, 27.20, 26.7,
25.5, 25.3, 24.9, 24.5, 23.0, 15.8. **ESI-MS** \(m/z\) (rel int): (pos) 419.03 ([M+MeOH+Na]^+, 100), 363.08 ([M+H]^+, 32).

**11. Ring Expansion of 40**

**Supplementary Table 11. Ring Expansion of 40.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A'                | 5 min      |      | 67         | 82%   |
|                   |            |      | (4:2:1)    |       |
| B                 | 14 h       |      | 67         | 74%   |
|                   |            |      | (3:1)      | S53\(^a\) |
| B'                | 2 h        |      | 67         | 75%   |
| C                 | 20 min     |      | 68         | 87%   |
|                   |            |      | (2:1.7:1.4:1) |       |

\(^a\) The structure of S53 was assigned based on the following diagnostic \(^1\)H-NMR peaks: \(\delta\) 4.27 (s, 1H), 3.20 (s, 3H).

(E)-4-Methyl-2,3,6,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-ol (67). Olefin regiochemistry determined by \(^1\)H–\(^1\)H COSY; (E)-olefin geometry assigned by NOESY. **TLC:** \(R_f\) 0.42 (30% EtOAc/hexanes). **IR** (NaCl, film): 3385, 2926, 2856, 1498, 1449, 1206, 1043, 877, 809. **\(^1\)H-NMR** (600 MHz): \(\delta\) 6.77–6.76 (m, 1H), 6.59–6.57 (m, 2H), 5.12 (t, \(1H, J = 7.7\)), 4.35 (s, 1H), 4.14 (t, 2H, \(J = 5.5\)), 2.61 (t, 2H, \(J = 7.5\)), 2.33 (t, 2H, \(J = 5.5\)), 2.07 (q, 2H, \(J = 6.2\)), 1.60 (s, 1H).
2H), 1.55–1.53 (m, 2H), 1.49–1.45 (m, 2H). $^{13}$C-NMR (151 MHz): δ 151.3, 149.3, 134.3, 130.2, 129.3, 116.0, 115.9, 112.6, 67.5, 40.2, 28.30, 28.15, 28.02, 25.6, 15.2. **ESI-MS m/z** (rel int): (pos) 255.1 ([M+Na]$^+$, 100), 487.2 ([2M+Na]$^+$, 95).

4-Methoxy-4-methyl-2,3,4,5,6,7,8,9-octahydrobenzo[b][1]oxacycloundecin-11-ol (S53). **TLC:** $R_f$ 0.15 (30% EtOAc/hexanes). $^1$H-NMR (500 MHz): δ 6.78–6.76 (m, 1H), 6.60–6.58 (m, 2H), 4.32 (s, 1H), 3.99–3.95 (m, 1H), 3.92–3.88 (m, 2H), 3.20 (s, 3H), 2.63–2.60 (m, 2H), 2.37–2.33 (m, 2H), 2.09–2.06 (m, 1H), 1.95–1.91 (m, 1H), 1.85–1.81 (m, 3H), 1.49–1.47 (m, 1H), 1.42–1.38 (m, 2H), 1.18 (s, 3H). **ESI-MS m/z** (rel int): (pos) 287.17 ([M+Na]$^+$, 70), 303.12 ([M+K]$^+$, 100).

$(E)$-4-Methyl-2,3,6,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-yl trifluoromethanesulfonate (68). Structure was assigned by analogy to 67. **TLC:** $R_f$ 0.15 (3% EtOAc/hexanes). **IR** (NaCl, film): 2932, 1492, 1421, 1248, 1210, 1142, 936, 888, 845. $^1$H-NMR (600 MHz): δ 7.02 (dd, 1H, $J$ = 8.9, 3.1), 6.98 (d, 1H, $J$ = 3.1), 6.88 (d, 1H, $J$ = 8.9), 5.05 (t, 1H, $J$ = 7.7), 4.19 (t, 2H, $J$ = 5.6), 2.65 (t, 2H, $J$ = 7.6), 2.37 (t, 2H, $J$ = 5.6), 2.08–2.05 (m, 2H), 1.61 (s, 3H), 1.54–1.52 (m, 1H), 1.47–1.43 (m, 2H). $^{13}$C-NMR (151 MHz): δ 156.6, 143.1, 135.3, 129.9, 129.6, 121.8, 119.0, 118.7 (q, $J_{C,F}$ = 319), 115.3, 66.9, 39.8, 28.6, 28.2, 27.7, 25.4, 15.1. **ESI-MS m/z** (rel int): (neg) 363.02 ([M–H]$^-$, 100).
12. **RING EXPANSION OF 41**

Supplementary Table 12. Ring Expansion of 41.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
|                  | A’         | 10 min | ![69 (4:1)](image) | 90%   |
| ![41](image)      | B          | 1 h   | ![69 (5:1)](image) | 88%   |
|                  | C          | 2 h   | ![70 (10:1 regioisomic ratio of olefins)](image) | 59%   |

**(E)-5-Methyl-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxacyclododecin-12-ol** (69). Ratio of regioisomers determined based on phenoxymethylene $^1$H-NMR peaks: δ 3.93 $E$-endocyclic-“down”, 4.10 Z-endocyclic-“up” olefin. Olefin regiochemistry determined by $^1$H–$^1$H COSY; ($E$)-olefin geometry assigned by NOESY. **TLC**: $R_f$ 0.19 (10% EtOAc/hexanes). **IR** (NaCl, film): 3357, 2920, 2852, 1497, 1209. **$^1$H-NMR** (600 MHz): (major isomer) δ 6.75 (d, 1H, $J = 8.6$), 6.61–6.56 (m, 2H), 5.13 (td, 1H, $J = 7.3, 1.1$), 4.30 (s, 1H), 3.93 (t, 2H, $J = 4.9$), 2.38–2.36 (m, 2H), 2.27 (t, 2H, $J = 5.8$), 2.19 (q, 2H, $J = 6.6$), 1.99–1.95 (m, 2H), 1.76 (d, 3H, $J = 0.5$), 1.53–1.51 (m, 2H), 1.50–1.46 (m, 2H). **$^{13}$C-NMR** (151 MHz): (major isomer) δ 151.2, 149.4, 135.1, 135.0, 124.0, 116.8, 115.1, 112.6, 71.3, 39.9, 30.0, 28.1, 26.6, 25.9, 25.3, 15.6. **ESI-MS m/z** (rel int): (pos) 269.1 ([M+Na]$^+$, 100), 515.3 ([2M+Na]$^+$, 42).
(E)-5-Methyl-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxacyclododecin-12-yl trifluoromethanesulfonate (70). Structures assigned by analogy to 69. TLC: R\text{f} 0.16 (3% EtOAc/hexanes). IR (NaCl, film): 2924, 1492, 1424, 1211, 934, 846. \textsuperscript{1}H-NMR (600 MHz): δ 7.01–7.00 (m, 2H), 6.82 (d, 2H, J = 9.8), 5.11 (t, 1H, J = 7.1), 4.03 (t, 2H, J = 5.0), 2.42 (t, 2H, J = 7.7), 2.29 (t, 2H, J = 5.6), 2.18 (d, 2H, J = 6.3), 2.01–1.98 (m, 2H), 1.75 (s, 3H), 1.52–1.49 (m, 4H). \textsuperscript{13}C-NMR (151 MHz): δ 156.5, 142.8, 135.2, 135.0, 123.9, 123.0, 118.7 (q, J\textsubscript{C-F} = 319), 112.7, 70.5, 39.6, 27.5, 25.0, 15.8. ESI-MS m/z (rel int): (pos) 401.0 ([M+Na]+), 100.

13. Ring Expansion of 42

Supplementary Table 13. Ring Expansion of 42.

| Starting Material | Conditions | Time  | Product(s)          | Yield |
|-------------------|------------|-------|---------------------|-------|
| A                 | A          | 14 h  | complex mixture     | --    |
| A'                | A'         | 14 h  | complex mixture     | --    |
| B                 | B          | 12 h  | S54\textsuperscript{a} (3:1) | <30%  |
| C                 | C          | 2 h   | 71 (3.2:1.5:1)      | 64%   |

\textsuperscript{a}The structures of S54 were assigned based on the following diagnostic \textsuperscript{1}H-NMR peaks: (olefin) δ 5.15 (t, 1H, J = 7.1), 3.67 (s, 3H), 3.13 (s, 3H); (MeOH adduct) δ 3.68 (s, 3H), 3.13 (s, 3H).
(E)-5-Methyl-2-oxo-3,4,7,8-tetrahydro-2H-benzo[b]oxecin-10-yl trifluoromethanesulfonate (71). Ratio of regioisomers determined by the olefin $^1$H-NMR peaks: δ 5.50 endocyclic-“up”, 5.14 endocyclic-“down” and exocyclic, 5.06 exocyclic olefin. Olefin regiochemistry determined by $^1$H–$^1$H COSY; (E)-olefin geometry assigned by NOESY. TLC: R$_f$ 0.24 (10% EtOAc/hexanes). IR (NaCl, film): 2933, 1761, 1488, 1422, 1212, 1171, 1142, 969, 914, 847. $^1$H-NMR (600 MHz): δ (mixture) 7.29 (d, 1H, $J = 8.7$), 7.27–7.23 (m, 0.8H, $J = 8.6$), 7.16–7.13 (m, 3.2H), 5.51–5.48 (m, 0.3H) 5.17–5.14 (m, 1.4H), 5.06 (d, 0.4H, $J = 1.0$), 3.16 (d, 0.3H, $J = 6.2$), 2.95 (td, 1H, $J = 12.8, 3.5$), 2.75–2.72 (m, 0.4H), 2.70 (t, 1H, $J = 6.5$), 2.65 (t, 1.4H, $J = 6.6$), 2.64–2.61 (m, 0.6H), 2.59 (t, 0.3H, $J = 3.7$), 2.58 (t, 1H, $J = 3.7$), 2.55–2.50 (m, 2H), 2.44 (t, 1H, $J = 6.5$), 2.42–2.37 (m, 1.3H), 2.34–2.31 (m, 1H), 2.08–2.05 (m, 0.3H), 2.01 (dd, 1.4H, $J = 7.5, 4.8$), 1.99–1.96 (m, 0.4H), 1.83 (s, 3H), 1.77 (t, 0.9H $J = 1.9$). $^{13}$C-NMR (151 MHz): δ (mixture) 172.5, 171.5, 148.7, 148.3, 146.6, 146.4, 145.7, 137.3, 135.9 (2 peaks), 125.9, 124.6 (2 peaks), 124.5, 124.3 (2 peaks), 123.4, 119.8, 119.5, 119.3, 117.6, 113.7, 37.0, 36.9, 35.0, 34.5, 34.3, 34.1, 32.1, 31.9, 29.6, 28.6, 27.5, 26.8, 26.7, 25.9, 25.7, 23.7, 23.0, 16.0. ESI-MS m/z (rel int): (pos) 387.02 ([M+Na]$^+$, 100).

14. RING EXPANSION OF 43

**Supplementary Table 14. Ring Expansion of 43.**

| Starting Material | Conditions | Time | Product(s)          | Yield |
|-------------------|------------|------|---------------------|-------|
| A                 |            | 8 h  | complex mixture     |       |
| B                 |            | 8 h  | complex mixture     |       |
| C (25 °C)         |            | 1 h  | TIO                  | 78%   |
(Z)-5-Methyl-3-methylene-2-oxo-3,6,7,8-tetrahydro-2H-benzo[b]oxecin-10-yl trifluoromethanesulfonate (72). Olefin regiochemistry determined by $^1$H–$^1$H COSY; (Z)-olefin geometry assigned by NOESY. TLC: $R_f$ 0.25 (95:5 hexanes/EtOAc). IR (NaCl, film): 2920, 1748 (C=O st), 1489, 1421, 1210, 1141, 925. $^1$H-NMR (500 MHz): δ 7.59 (d, 1H, $J$ = 8.8), 7.17 (d, 1H, $J$ = 8.8), 6.18 (s, 1H), 5.93 (s, 1H), 5.51 (s, 1H), 2.72–2.66 (m, 2H), 2.06–2.01 (m, 2H), 1.92–1.85 (m, 1H), 1.88 (s, 3H), 1.54–1.52 (m, 1H). $^{13}$C-NMR (126 MHz): δ 166.7, 148.4, 146.5, 140.9, 138.5, 137.7, 125.0, 124.4, 123.6, 123.5, 119.6, 117.7, 31.3, 27.7, 27.2, 23.1. ESI-MS $m/z$ (rel int): (pos) 398.8 ([M+Na]$^+$, 100).

15. Ring Expansion of 44

Supplementary Table 15. Ring Expansion of 44.

| Starting Material | Conditions | Time | Product(s) | Yield |
|------------------|------------|------|------------|-------|
| A                | 14 h       |      | complex mixture | --    |
| A'               | 10 min     |      | ![Image](image1.png) 73 (2:1) | 56%   |
| B                | 18 h       |      | ![Image](image2.png) S55 (5:1:7:1) | <30%  |
| C                | 1 h        |      | ![Image](image3.png) 74 (4:8:2:5:1) | 56%   |

$^a$The structures of S55 were assigned based on the following diagnostic $^1$H-NMR peaks: (anisole-olefin) δ 5.16 (t, 1H, $J$ = 7.6), 3.68 (s, 3H); (anisole-MeOH adduct) δ 3.71 (s, 3H), 3.14 (s, 3H); (phenol-olefin 73) δ 5.10 (t, 1H, $J$ = 8.4), 4.61 (s, 1H).
(Z)-11-Hydroxy-5-methyl-3,4,8,9-tetrahydrobenzo[b][1]oxacycloundecin-2(7H)-one (73). Olefin regiochemistry determined by $^1$H–$^1$H COSY; (Z)-olefin geometry assigned by NOESY. 

TLC: R$_f$ 0.21 (3% EtOAc/hexanes). IR (NaCl, film): 3424, 2921, 1726, 1493, 1444, 1249, 1188. 

$^1$H-NMR (600 MHz): δ 6.84 (d, 1H, $J = 8.4$), 6.68–6.63 (m, 2H), 5.10 (t, 1H, $J = 7.4$), 4.61 (s, 1H), 2.72–2.70 (m, 2H), 2.42–2.40 (m, 3H), 2.38–2.14 (m, 3H), 1.80 (s, 3H), 1.69 (br s, 2H).

$^{13}$C-NMR (151 MHz): δ 171.2, 153.5, 142.6, 137.2, 134.4, 128.4, 122.9, 118.3, 113.9, 32.2, 30.2, 28.0, 27.4, 26.1, 23.2. ESI-MS m/z (rel int): (pos) 269.17 ([M+Na]$^+$, 100), 247.19, ([M+H]$^+$, 15), (neg) 244.92 ([M–H]$^-$, 100), 491.36 ([2M–H]$^-$, 23).

(Z)-5-methyl-2-oxo-2,3,6,7,8,9-hexahydrobenzo[b][1]oxacycloundecin-11-yl trifluoromethanesulfonate (74). Olefin regiochemistry determined by $^1$H–$^1$H COSY; (Z)-olefin geometry assigned by NOESY. TLC: R$_f$ 0.21 (3% EtOAc/hexanes). IR (NaCl, film): 2938, 1758, 1486, 1421, 1210, 1174, 1141, 958, 917, 855. 

$^1$H-NMR (600 MHz): δ 7.32 (d, 1H, $J = 7.9$), 7.13–7.11 (m, 2H), 5.52 (t, 1H, $J = 8.0$), 3.26 (d, 2H, $J = 8.1$), 2.64 (br s, 2H), 2.33 (br s, 2H), 1.74 (s, 3H), 1.52 (br s, 4H). 

$^{13}$C-NMR (151 MHz): δ 170.0, 148.9, 146.4, 142.2, 137.4, 123.7, 123.1, 119.6, 118.7 (q, $J_{C–F} = 319$), 116.4, 33.5, 29.3, 29.1, 27.9, 24.1, 22.7. ESI-MS m/z (rel int): (pos) 401.03 ([M+Na]$^+$, 100).
16. **RING EXPANSION OF 45**

**Supplementary Table 16. Ring Expansion of 45.**

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
|                   | A          | 14 h | complex mixture | --    |
|                   | A'         | 20 min | ![Image](image1.png) | 51%   |
|                   | B          | 14 h | complex mixture | --    |
|                   | C          | 1 h  | ![Image](image2.png) | 68%   |

(E)-12-Hydroxy-5-methyl-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxacyclododecin-2-one (75). TLC: *R*$_f$ 0.25 (20% EtOAc/hexanes). IR (NaCl, film): 3417, 2922, 2853, 1725, 1591, 1493, 1444, 1343, 1183, 1132. $^1$H-NMR (600 MHz): δ 6.79 (d, 1H, *J* = 8.6), 6.66 (d, 1H, *J* = 3.0), 6.62 (dd, 1H, *J* = 8.6, 3.0), 5.21 (t, 1H, *J* = 6.7), 4.62 (s, 1H), 2.72–2.70 (m, 2H), 2.50 (t, 2H, *J* = 6.6), 2.28–2.25 (m, 2H), 2.18 (q, 2H, *J* = 6.5), 1.81 (s, 3H), 1.59–1.56 (m, 2H), 1.46–1.39 (m, 2H). $^{13}$C-NMR (151 MHz): δ 173.0, 153.2, 142.5, 136.9, 132.7, 126.5, 123.5, 117.0, 113.6, 37.2, 33.3, 29.3, 28.7, 25.4, 24.9, 15.0. ESI-MS *m/z* (rel int): (pos) 283.06 ([M+Na]$^+$, 100), 261.10 ([M+H]$^+$, 22), (neg) 259.12 ([M−H]$^-$, 100).
(E)-5-Methyl-2-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxacyclododecin-12-yl trifluoromethanesulfonate (76). Structure assigned by analogy to 75. TLC: \( R_f \) 0.15 (3% EtOAc/hexanes). IR (NaCl, film): 2922, 1758, 1488, 1421, 1210, 1171, 1120, 937. \(^1\)H-NMR (600 MHz): \( \delta \) 7.12 (d, 1H, \( J = 2.8 \)), 7.09 (dd, 1H, \( J = 8.6, 3.0 \)), 7.00 (d, 1H, \( J = 8.8 \)), 5.21 (t, 1H, \( J = 7.0 \)), 2.74 (t, 2H, \( J = 6.5 \)), 2.51 (t, 2H, \( J = 6.5 \)), 2.37–2.34 (m, 2H), 2.21–2.18 (m, 2H), 1.82 (s, 3H), 1.61–1.57 (m, 2H), 1.45–1.40 (m, 2H). \(^1\)C-NMR (151 MHz): \( \delta \) 172.2, 148.3, 146.8, 138.5, 132.7, 126.5, 124.5, 123.3, 119.6, 37.2, 33.3, 29.3, 28.6, 25.2, 24.8, 15.0 (CF\(_3\) carbon unresolved). ESI-MS \( m/z \) (rel int): (pos) 415.09 ([M+Na]\(^+\), 100).

17. RING EXPANSION OF 46

Supplementary Table 17. Ring Expansion of 46.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| 46                | A          | 20 h | \( \text{Product 77} \) | 89%   |
| 46                | B          | 16 h | \( \text{Product 77} \) | 74%   |
|                   | C          | 1 h  | complex mixture | --    |

(E)-12-Methoxy-7-methyl-9,10-dihydrodibenzo[b,j][1]oxacycloundecin-5(8H)-one (77). Olefin regiochemistry determined by \(^1\)H–\(^1\)H COSY; (E)-olefin geometry assigned by NOESY. TLC: \( R_f \) 0.19 (9:1 hexanes/EtOAc). IR (NaCl, film): 2926, 2855, 1666 (C=O st), 1496, 1450, 1212, 792. \(^1\)H-NMR (500 MHz): \( \delta \) 7.73 (dd, 1H, 7.7, 1.7), 7.59-7.56 (m, 1H), 7.32 (t, 1H, \( J = 8.8 \)), 7.12 (d, 1H, \( J = 2.8 \)), 6.75 (d, 1H, \( J = 7.7 \)).
7.5), 7.24 (d, 1H, J = 7.9), 6.81 (d, 1H, 3.1), 6.66 (s, 1H), 6.44 (dd, 1H, J = 9.0, 3.1), 6.09 (d, 1H, J = 9.0), 3.72 (s, 3H), 2.86–2.78 (m, 2H), 2.23 (t, 2H, J = 6.3), 2.17–2.12 (m, 2H), 1.49 (s, 3H).

\[ ^{13}\text{C-NMR} \ (126 \text{ MHz}): \delta 192.2, 155.3, 154.5, 152.4, 151.7, 134.1, 133.3, 132.3, 131.3, 128.8, 125.5, 124.2, 116.3, 114.3, 111.1, 55.7, 40.9, 27.9, 25.5, 16.6. \]

**ESI-MS m/z** (rel int): (pos) 331.0 ([M+Na]\(^+\), 100), 309.0 ([M+H]\(^+\), 50).

### 18. Ring Expansion of 47

**Supplementary Table 18. Ring Expansion of 47.**

| Starting Material | Conditions | Time | Product(s)      | Yield |
|-------------------|------------|------|-----------------|-------|
|                   | A          | 8 h  | complex mixture | --    |
|                   | B          | 8 h  | complex mixture | --    |
|                   | C          | 1 h  | 84%             |       |

\( ^{1}H\)-\( ^{1}H \) COSY; \( ^{13}C\)-\( ^{13}C \) NMR; IR; TLC; ESI-MS; ESI-MS m/z (rel int): (pos) 491.0 ([M+Na]\(^+\), 100), 469.1 ([M+H]\(^+\), 10).

\((E)-11,12\)-Dimethoxy-8-methyl-10-methylene-5,6,9,10-tetrahydrodibenzo[\(a,c\)][10]annulen-3-yl trifluoromethanesulfonate (78). Olefin regiochemistry determined by \(^{1}H\)-\(^{1}H\) COSY; (E)-olefin geometry and crown-like conformation assigned by NOESY.

**TLC:** R\(_f\) 0.53 (8:2 hexanes/EtOAc). IR (NaCl, film): 2933, 1473, 1423, 1211, 1142, 918. **\(^{1}H\)-NMR (500 MHz):** \(\delta\) 7.14 (d, 1H, J = 2.7), 7.12 (d, 1H, J = 8.5), 7.04 (dd, 1H, J = 8.5, 2.7), 6.86 (d, 1H, J = 8.4), 6.71 (d, 1H, J = 8.4), 5.22 (s, 1H), 4.94 (d, 1H, J = 1.9), 4.40–4.36 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.84 (d, 1H, J = 11.9), 2.69–2.63 (m, 3H), 2.18–2.11 (m, 1H), 2.09–2.03 (m, 1H), 0.62 (s, 3H).

**\(^{13}C\)-NMR (126 MHz):** \(\delta\) 152.0, 148.6, 146.5, 143.2, 142.7, 142.1, 136.8, 134.3, 133.9, 131.9, 125.6, 123.5, 123.2, 120.2, 117.3, 116.6, 110.3, 61.6, 55.9, 50.4, 33.7, 30.6, 14.1.

**ESI-MS m/z** (rel int): (pos) 491.0 ([M+Na]\(^+\), 100), 469.1 ([M+H]\(^+\), 10).
## 19. Ring Expansion of 48

### Supplementary Table 19. Ring Expansion of 48.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
| A                 | 12 h       | ![48](image1.png) | MeO          | 71%   |
| B                 | 12 h       | ![48](image2.png) | MeO          | 74%   |
| C                 | N/A        | N/A  | N/A        | N/A   |

10-Methoxy-2,3,4,4’,5’,6,7,8-octahydro-3’H-spiro[benzo[b]oxecine-5,2’-furan] (79).

Structure assigned by analogy to methyl ether 8. **TLC:** $R_r 0.33$ (8:2 hexanes/EtOAc); $R_r 0.15$ (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2922, 1499, 1466, 1228, 1154, 1045. **¹H-NMR** (500 MHz): $\delta$ 6.94 (d, 1H, $J = 8.7$), 6.72–6.67 (m, 2H), 4.16–4.13 (m, 1H), 4.09–4.05 (m, 1H), 3.82–3.75 (m, 2H), 3.78 (s, 3H), 2.87–2.80 (m, 2H), 2.00–1.92 (m, 2H), 1.92–1.85 (m, 2H), 1.77–1.69 (m, 2H), 1.61 (t, 2H, $J = 7.5$), 1.63–1.57 (m, 1H), 1.53–1.49 (m, 1H), 1.45–1.39 (m, 1H), 1.36–1.28 (m, 1H). **¹³C-NMR** (126 MHz): $\delta$ 154.8, 150.3, 135.2, 118.8, 115.0, 112.1, 85.9, 71.9, 66.6, 55.6, 36.7, 33.3, 32.2, 29.7, 27.6, 25.7, 22.9. **ESI-MS** $m/z$ (rel int): (pos) 299.0 ([M+Na]$^+$, 100), 277.1 ([M+H]$^+$, 10); (neg) 311.1 ([M+Cl]$^-$, 100).
20. RING EXPANSION OF 49

Supplementary Table 20. Ring Expansion of 49.

| Starting Material | Conditions | Time | Product(s) | Yield |
|-------------------|------------|------|------------|-------|
|                   | A         | 6 h  | ![Image](image1.png) | 73%   |
|                   | B         | 6 h  | ![Image](image2.png) | 44%   |
|                   | C, then   | 2 h  | ![Image](image3.png) | N.D.  |

*Ring Expansion of 49.*

\(^{a}\) Required 2.5 equiv of Tf\(_2\)O. Quenched with AcSK to exchange the labile primary triflate generated during the reaction with a more stable thioacetate.

\(^{b}\) N.D. = not determined; these conditions produced an inseparable mixture of three medium ring isomers in <40% yield (not characterized).

\(^{c}\) The structure of S56 was assigned based on the following diagnostic \(^{1}\)H-NMR peaks: δ 5.44–5.42 (m, 1H), 4.28–4.26 (m, 2H), 3.44 (dd, 1H, \(J = 14.0, 6.5\)), 3.32 (dd, 1H, \(J = 13.9, 6.7\)), 2.43 (s, 3H).

\((Z)-(9\text{-Methoxy-4-methyl-2,3,6,7-tetrahydrobenzo}\{b\}\text{oxonin-2-yl})\text{methanol (80).}\) Ratio of olefin regioisomers determined based on olefinic \(^{1}\)H-NMR peaks: δ 5.09–5.06 (m) major, 4.91 (s) minor. Olefin regiochemistry of major isomer determined by \(^{1}\)H–\(^{1}\)H COSY; (Z)-olefin geometry assigned by NOESY. **TLC:** \(R_f\) 0.32 (7:3 hexanes/\(\text{EtOAc}\)). **IR** (NaCl, film): 3423 (O–H st), 2918, 1499, 1455, 1214, 1047, 867. **\(^{1}\)H-NMR** (500 MHz): δ 6.93 (d, 1H, \(J = 8.8\)), 6.65 (dd, 1H, \(J = 8.8, 3.1\)), 6.51 (d, 1H, \(J = 3.1\)), 5.09–5.06 (m, 1H), 4.08 (ddddd, 1H, \(J = 10.4, 8.4, 3.8, 1.9\)), 3.80–3.71 (m, 5H), 3.14–3.05 (m, 2H), 2.72 (dd, 1H, \(J = 14.0, 10.9\)), 2.66–2.61 (m, 1H), 2.21 (dd, 1H, \(J = 5.0, 4.1\)), 1.70 (dd, 1H, \(J = 10.6, 1.8\)), 1.56 (s, 3H). **\(^{13}\)C-NMR** (126 MHz): δ 154.8, 153.8, 133.2, 131.6, 126.8, 120.3, 116.3, 111.9, 84.9, 66.4, 55.5, 34.2, 32.4, 26.2, 24.7. **ESI-MS** m/z (rel int): (pos) 271.3 ([M+Na]\(^{+}\), 100); (neg) 247.4 ([M–H]\(^{-}\), 100).
21. Ring Expansion of 50

Supplementary Table 21. Ring Expansion of 50.

| Starting Material | Conditions | Time | Product(s)       | Yield |
|-------------------|------------|------|------------------|-------|
| A                 |            | 8 h  | complex mixture  | --    |
| B                 |            | 5 h  |                  | 80%   |
| C                 |            | 1 h  | complex mixture  | --    |

9-Methoxy-4-methyl-3,4,6,7-tetrahydrobenzo[b]oxonin-5(2H)-one (81). Structure assigned based on methyl 1H-NMR doublet at δ 1.12 and ketone 13C-NMR signal at δ 214.8. 1H–1H COSY also consistent with this structure. TLC: Rf 0.39 (7:3 hexanes/EtOAc). IR (NaCl, film): 2918, 1704 (C=O st), 1501, 1230, 1046. 1H-NMR (500 MHz): δ 6.86 (d, 1H, J = 8.8), 6.72 (dd, 1H, J = 8.8, 3.0), 6.68 (d, 1H, J = 3.0), 4.31 (ddd, 1H, J = 10.7, 5.0, 3.6), 3.95 (td, 1H, J = 10.1, 2.4), 3.76 (s, 3H), 3.08–3.03 (m, 1H), 2.86–2.81 (m, 1H), 2.67–2.60 (m, 1H), 2.54 (ddd, 1H, J = 13.5, 9.6, 1.3), 2.46 (ddd, 1H, J = 13.5, 9.6, 1.3), 2.09–2.01 (m, 1H), 1.96–1.91 (m, 1H), 1.12 (d, 3H, J = 6.8). 13C-NMR (126 MHz): δ 214.8, 154.4, 151.7, 134.4, 117.4, 115.7, 112.4, 70.4, 55.6, 45.9, 40.2, 35.8, 30.3, 16.1. ESI-MS m/z (rel int): (pos) 257.0 ([M+Na]^+, 100), 491.1 ([2M+Na]^+, 25).
G. ODRE CASCADE OF PHENOL 30

Supplementary Figure 54. Synthesis and oxidative dearomatization of bicyclic phenol 30. Triol 30 was generated from silyl protected S57 and used immediately as a crude material due to its instability. Oxidative dearomatization of 30 led directly to ring expansion product 82 via putative tricyclic cyclohexadienone intermediate 51.

6-([t-Butyldimethylsilyl]oxy)-1-(3-[(triisopropylsilyl)oxy]propyl)-1,2,3,4-tetrahydronaphthalen-1-ol (S57). To a solution of (3-iodoproxy)triisopropylsilane (161 mg, 0.471 mmol, 1.3 equiv) in Et2O (3 mL) at –78 °C was added t-BuLi (1.7 M in pentane, 500 μL, 0.851 mmol, 2.35 equiv) by syringe. The lithium halogen exchange reaction was stirred at –78 °C for 30 min then warmed to 25 °C and stirred for an additional 45 min. The reaction was cooled back to –78 °C and tetralone S4 (100 mg, 0.362 mmol) was added slowly in Et2O (2 mL). The reaction was warmed to 25 °C and stirred for 4 h. The reaction was quenched with satd aq NH4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na2SO4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (95:5 hexanes/EtOAc) yielded tertiary alcohol S57 (141 mg, 79%) as a yellow oil.

**TLC**: Rf 0.57 (8:2 hexanes/EtOAc). **IR** (NaCl, film): 3408 (O–H str), 2943, 2867, 1498, 1257, 1103, 841, 783. **1H-NMR** (500 MHz): δ 7.39 (d, 1H, J = 8.5), 6.67 (dd, 1H, J = 8.5, 2.6), 6.52 (d, 1H, J = 2.5), 3.71 (t, 2H, J = 6.2), 2.76–2.63 (m, 2H), 2.44 (s, 1H), 2.00–1.93 (m, 2H), 1.91–1.74 (m, 4H), 1.65 (ddq, 1H, J = 13.2, 9.9, 6.5), 1.54–1.47 (m, 1H), 1.13–1.02 (m, 21H), 0.98 (s, 9H), 0.17 (s, 6H). **13C-NMR** (126 MHz): δ 154.3, 138.2, 135.4, 127.5, 119.5, 118.2, 71.8, 63.9, 39.5, 36.1, 30.1, 27.9, 25.7, 19.9, 18.2, 18.1, 12.0, –4.4. **ESI-MS m/z** (rel int): (pos) 475.5 ([M–OH]+, 50), 515.5 ([M+Na]+, 100); (neg) 491.5 ([M–H]−, 100).
 Spiroketal 82 was obtained from desilylation and subsequent oxidative dearomatization of S57. Tertiary alcohol S57 (200 mg, 0.400 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. TBAF was added by syringe (1 M in THF, 880 μL, 0.88 mmol, 2.2 equiv) and the solution was stirred for 10 min. The reaction was warmed to 25 °C and stirred for 12 h. The solution was concentrated by rotary evaporation and the crude oil was immediately dissolved in CH₂Cl₂. The solution was cooled to 0 °C and PhI(OAc)₂ (194 mg, 0.60 mmol, 1.5 equiv) was added as a solid. The reaction was stirred for 1 h at 0 °C, then warmed to 25 °C and stirred overnight. The reaction was quenched by pouring into H₂O (10 mL). The product was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded spiroketal 82 (37 mg, 42%) as clear oil.

**TLC**: Rₗ 0.30 (7:3 hexanes/EtOAc). **IR** (NaCl, film): 3356 (O–H st), 2938, 2360, 2341, 1496, 1190, 908. **¹H-NMR** (500 MHz): δ 6.76 (d, 1H, J = 8.3), 6.58–6.54 (m, 2H), 4.50 (s, 1H), 4.02 (dt, 1H, J = 8.4, 4.3), 3.93 (td, 1H, J = 8.1, 6.8), 2.82–2.78 (m, 1H), 2.63 (ddd, 1H, J = 14.1, 6.9, 3.0), 2.25–2.20 (m, 2H), 2.08–1.96 (m, 3H), 1.82–1.71 (m, 3H). **¹³C-NMR** (126 MHz): δ 151.4, 147.4, 137.1, 123.4, 116.5, 113.2, 109.9, 68.4, 39.0, 37.5, 33.5, 23.7, 22.1. **ESI-MS m/z** (rel int): (pos) 243.2 ([M+Na]+, 100), 221.2 ([M+H]+, 20); (neg) 219.2 ([M–H]–, 100).
H. Molecular Modeling Analysis of Ring Size Effects

Molecular modeling in Supplementary Figure 8 was done in Spartan’10 version 1.1.0. For each cyclohexadienone, a conformational search was done using the Set Torsion option for each ring atom outside the cyclohexadienone ring by changing the Fold value from 0 to 3. In the Calculations menu, the Equilibrium Conformer at the Ground state using Molecular Mechanics (MMFF) was selected and the calculation was submitted. Energy values were obtained from the Spartan output. The minimized structures were saved as SDF files and the models were visualized using MacPyMOL. Bond angles were obtained using the Measurement Wizard of MacPyMOL by selecting the Measurement Mode: Angles and selecting atoms 1, 4, and 5.
I. **Downstream Modifications of Odre Scaffolds**

1. **Cyclopropanation of diaryl ether 77**

![Supplementary Figure 55. Cyclopropanation of diaryl ether 77 to form cyclopropane 88.](image)

(12aR*,13aR*)-8-Methoxy-12a-methyl-12,12a,13,13a-tetrahydro-10H-dibenzo[b,j]cyclopropa[e][1]oxacycloundecin-14(11H)-one (88). Trimethylsulfoxonium iodide (1.3 mg, 59 μmol, 1.01 equiv) was dissolved in DMSO (0.75 mL). NaH (2.4 mg, 100 μmol, 1.7 equiv) was added and the solution was stirred at 25 °C for 1 h. Enone 77 (108 mg, 58.4 μmol) was dissolved in THF (0.75 mL) and added to the ylide solution via syringe. The reaction solution was stirred at 25 °C for 20 h, then quenched with satd aq NH₄Cl and diluted with Et₂O. The aqueous layer was extracted with Et₂O (4×) and the combined organic extracts were washed with water (2×), brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10% EtOAc/hexanes) yielded 88 (9.0 mg, 80%) as a colorless oil.

**TLC:** Rf 0.23 (10% EtOAc/hexanes). **IR** (NaCl, film): 2925, 1664, 1598, 1496, 1475, 1223, 1201, 1041, 783. **1H-NMR** (600 MHz): δ 7.57 (d, 1H, J = 7.7, 1.6), 7.46–7.43 (m, 1H), 7.16 (t, 2H, J = 7.2), 6.78 (d, 1H, J = 3.1), 6.60 (d, 1H, J = 9.4), 6.52 (dd, 1H, J = 8.9, 3.1), 3.69 (s, 3H), 3.03 (t, 1H, J = 11.7), 2.68–2.66 (m, 1H), 2.35 (t, 1H, J = 6.5), 1.99–1.83 (m, 3H), 1.23 (dd, 1H, J = 5.5, 3.6), 0.94 (s, 3H), 0.74 (td, 2H, J = 13.6, 2.7), 0.61 (dd, 1H, J = 7.7, 3.6). **13C-NMR** (151 MHz): δ 200.9, 155.1, 154.5, 149.8, 134.7, 132.81, 132.71, 130.7, 124.8, 122.5, 116.3, 114.7, 111.4, 55.9, 38.2, 30.4, 30.0, 27.4, 25.2, 23.9, 14.6. **ESI-MS** m/z (rel int): (pos) 323.14 ([M+H]+, 100), 345.10 ([M+Na]+, 50).
2. Epoxidation of diaryl ether 77

Supplementary Figure 56. Epoxidation of diaryl ether 77 to form epoxide 89.

(12aS*,13aR*)-8-Methoxy-12a-methyl-10,11,12,12a-tetrahydrodibenzo[b,j]oxireno[2,3-e]-[1]oxacycloundecin-14(13aH)-one (89). Enone 77 (13.3 mg, 43.1 µmol) was dissolved in CH₂Cl₂ (1 mL) and cooled to 0 °C. m-CPBA (recrystallized, 8.5 mg, 49 µmol, 1.1 equiv) was added and the reaction was stirred at 0 °C to 25 °C for 14 h. The reaction was quenched with satd aq Na₂S₂O₃, diluted with CH₂Cl₂ and stirred for 15 min. The aqueous layer was extracted with CH₂Cl₂ (4×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (10% EtOAc/hexanes) yielded 89 (8.5 mg, 61%) as a colorless oil.

TLC: R₀ 0.10 (10% EtOAc/hexanes). IR (NaCl, film): 2938, 1674, 1597, 1476, 1447, 1282, 1226, 1041, 970, 760, 734. ¹H-NMR (600 MHz): δ 7.94 (dd, 1H, J = 7.8, 1.7), 7.62 (t, 1H, J = 7.7), 7.32 (t, 1H, J = 7.6), 7.27–7.25 (m, 1H), 6.85 (d, 1H, J = 3.0), 6.68 (d, 1H, J = 7.8), 6.63 (dd, 1H, J = 8.9, 3.0), 3.88 (s, 1H), 3.78 (s, 3H), 3.11 (dt, 1H, J = 14.3, 7.4), 2.76–2.73 (m, 1H), 2.11 (dt, 1H, J = 14.4, 4.0), 2.03–1.98 (m, 2H), 1.20–1.16 (m, 4H). ¹³C-NMR (151 MHz): δ 195.0, 155.5, 155.0, 149.0, 134.7, 131.7, 131.4, 130.40, 125.1, 121.8, 116.8, 113.7, 111.9, 69.7, 64.7, 55.9, 36.3, 26.9, 25.4, 14.9. ESI-MS m/z (rel int): (pos) 347.13 ([M+Na]⁺, 100), 671.30 ([2M+Na]⁺, 35), 325.14 ([M+H]⁺, 31).

3. Dihydroxylation of diaryl ether 77

Supplementary Figure 57. Dihydroxylation of diaryl ether 77 to form 1,2-diol 90.
(6R*,7S*)-6,7-dihydroxy-12-methoxy-7-methyl-7,8,9,10-tetrahydrodibenzo-[b,j][1]oxacycloundecin-5(6H)-one (90). Enone 77 (5 mg, 16 µmol) was dissolved in acetone/H₂O (3:1, 1 mL) and cooled to 0 °C. OsO₄ (0.04 mg, 0.16 µmol, 1 mol%) was added in 100 µL H₂O. NMO (3.7 mg, 0.032 mmol, 2 equiv) was added as a solid. The reaction was stirred for 15 min at which point TLC indicated complete consumption of the starting material. Sat aq Na₂SO₃ (1 mL) was added and the quenched reaction was stirred for 30 min. The resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (8:2 hexanes/EtOAc) yielded diol 90 (4.5 mg, 82%) as a clear film.

TLC: Rₚ 0.15 (4:1 hexanes/EtOAc). IR (NaCl, film): 3448 (O–H st), 2964, 1655 (C=O st), 1597, 1494, 1476, 1449, 1225. ¹H-NMR (500 MHz): δ 7.80 (d, 1H, J = 6.2), 7.38 (t, 1H, J = 8.4), 7.09–7.04 (m, 1H), 7.01 (d, 1H, J = 8.6), 6.81 (dd, 1H, J = 11.7, 3.0), 6.78 (d, 1H, J = 3.0), 6.55 (d, 1H, J = 8.4), 5.69 (d, 1H, J = 6.8), 4.31 (d, 1H, J = 6.62), 3.83 (s, 3H), 3.08 (br s, 1H), 2.77–2.71 (m, 1H), 2.22 (dt, 1H, J = 15.3, 3.9), 2.15–2.03 (m, 2H), 1.93–1.88 (m, 1H), 1.41 (dd, 1H, J = 13.3, 9.1), 0.91 (s, 3H). ¹³C-NMR (126 MHz): δ 201.3, 158.1, 157.2, 144.4, 138.0, 135.2, 131.4, 125.5, 124.1, 121.8, 116.8, 113.0, 112.4, 79.1, 55.6, 40.0, 33.6, 24.3 (2 peaks), 23.2. ESI-MS m/z (rel int): (pos) 365.3 ([M+Na]+, 100); 341.1 ([M–H]−, 100).

4. LUCHE REDUCTION OF DIARYL ETHER 77

Supplementary Figure 58. Luche reduction of diaryl ether 77 to form allylic alcohol 91.

(E)-12-Methoxy-7-methyl-5,8,9,10-tetrahydrodibenzo[b,j][1]oxacycloundecin-5-ol (91). Enone 77 (6.7 mg, 22 µmol) and CeCl₃·7H₂O (16.9 mg, 44.6 µmol, 2.0 equiv) were dissolved in
MeOH (1 mL) and cooled to –78 °C. NaBH₄ (ca. 1.6 mg, 42 µmol, 1.8 equiv) was added and the reaction was stirred at –78 to 15 °C for 3 h. The reaction was quenched with satd aq NH₄Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (20% EtOAc/hexanes) yielded 91 (5.3 mg, 77%).

**TLC:** Rₜ 0.17 (20% EtOAc/hexanes). **IR** (NaCl, film): 3418, 2930, 1495, 1448, 1218, 1038, 791. **¹H-NMR** (600 MHz): δ 7.79 (d, 1H, J = 7.6), 7.29–7.28 (m, 1H), 7.24 (t, 1H, J = 7.5), 6.97 (dd, 1H, J = 7.9, 1.1), 6.82 (d, 1H, J = 3.1), 6.58 (dd, 1H, J = 8.8, 3.1), 6.41 (d, 1H, J = 8.8), 5.54 (d, 1H, J = 9.5), 5.05–5.04 (m, 1H), 3.79 (s, 3H), 2.70–2.66 (m, 1H), 2.51–2.48 (m, 1H), 2.22 (d, 1H, J = 11.8), 2.14–2.10 (m, 1H), 2.06 (dd, 1H, J = 12.4, 4.6), 1.88–1.84 (m, 1H), 1.60 (s, 3H).

**¹³C-NMR** (151 MHz): δ 155.2, 152.6, 148.8, 135.2, 133.5, 128.5, 128.1, 127.3, 124.3, 121.2, 116.9, 116.6, 111.9, 111.4, 66.8, 55.9, 40.2, 28.9, 26.1, 15.4.

**ESI-MS** m/z (rel int): (pos) 333.11 ([M+Na]⁺, 100).

### 5. Demethylation of Diaryl Ether 77

Supplementary Figure 59. Demethylation of diaryl ether 77 to form phenol 92.

(E)-12-Hydroxy-7-methyl-9,10-dihydrodibenzo[بذ][1]oxacycloundecin-5(8H)-one (92).

Methyl ether 77 (5.0 mg, 16 µmol) was dissolved in CH₂Cl₂ (500 µL) and cooled to 0 °C. A solution of BBr₃ in CH₂Cl₂ (1 M, 32 µL, 32 µmol, 2 equiv) was added by syringe. The reaction was allowed to warm to 25 °C, stirred for 2 h, and quenched with satd aq NaHCO₃. The resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (9:1 → 8:2 hexanes/EtOAc) yielded phenol 92 (4 mg, 85%) as a clear film.

**TLC:** Rₜ 0.15 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3317 (O–H st), 1654 (C=O st), 1598, 1494, 1473, 1450, 1027. **¹H-NMR** (500 MHz): δ 7.72 (d, 1H, J = 7.6), 7.57 (t, 1H, J = 7.7), 7.31 (t, 1H, J = 7.7), 7.24 (d, 1H, J = 8.2), 6.75 (d, 1H, J = 3.4), 6.67 (s, 1H), 6.35 (dd, 1H, J = 8.1, 3.2), 6.03 (d, 1H, J = 8.5), 4.49 (s, 1H), 2.85–2.75 (m, 2H), 2.26–2.22 (m, 2H), 2.16–2.10 (m, 2H),...
1.52 (s, 3H).  \(^{13}\text{C-NMR}\) (126 MHz): δ 192.3, 155.3, 152.7, 151.6, 150.3, 134.0, 133.3, 132.6, 131.2, 128.8, 125.5, 124.2, 117.0, 114.6, 113.2, 40.9, 27.9, 25.5, 16.7.  \(\text{ESI-MS}\) \(m/z\) (rel int): (pos) 295.2 ([M+H]\(^{+}\), 60), 317.3 ([M+Na]\(^{+}\), 100); 329.1 ([M+Cl]\(^{+}\), 100), 294.0 ([M–H]\(^{−}\), 35).

6. Mitsunobu Alkylation of Phenol 92

Supplementary Figure 60. Mitsunobu alkylation of phenol 92 to form lactate derivative 93.

(S,E)-Methyl 2-((8-methyl-10-oxo-5,6,7,10-tetrahydrodibenz[b,j][1]oxacycloundecin-3-yl)-oxy)propanoate (93). PPh\(_3\) (5.5 mg, 21 µmol, 2.0 equiv) was dissolved in THF (0.1 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (0.004 mL, 20 µmol, 2 equiv) was added by syringe and a precipitate formed within several minutes. The slurry was stirred at 0 °C to 25 °C for 1 h, then recooled to 0 °C. Phenol 92 (3.1 mg, 11 µmol) was dissolved in THF (0.1 mL) and the solution was added via syringe to the PPh\(_3\)/DIAD solution at 0 °C. The precipitate vanished and methyl \((R)\)-lactate (0.002 mL, 0.02 mmol, 2 equiv) was added by syringe. The reaction was stirred at 0 °C to 25 °C for 12 h. The mixture was concentrated by rotary evaporation. Purification by silica flash chromatography (10% EtOAc/hexanes) yielded 93 (3.4 mg, 84%) as a colorless oil.

\(\text{TLC}: R_f\) 0.11 (10% EtOAc/hexanes).  \(\text{IR}\) (NaCl, film): 3334, 2987, 2975, 1755, 1737, 1665, 1621, 1349, 1452, 1279, 1213, 136, 1104, 762.  \(^{1}\text{H-NMR}\) (600 MHz): δ 7.73 (dd, 1H, \(J = 7.6, 1.8\)), 7.59–7.56 (m, 1H), 7.33 (t, 1H, \(J = 7.5\)), 7.24 (d, 1H, \(J = 8.2\)), 6.86 (d, 1H, \(J = 3.0\)), 6.66 (s, 1H), 6.42 (dd, 1H, \(J = 9.0, 3.1\)), 6.07 (d, 1H, \(J = 9.0\)), 4.64 (q, 1H, \(J = 6.8\)), 3.72 (s, 3H), 2.82–2.81 (m, 2H), 2.23 (t, 2H, \(J = 6.3\)), 2.16–2.11 (m, 2H), 1.57 (d, 3H, \(J = 6.8\)), 1.48 (s, 3H).  \(^{13}\text{C-NMR}\) (151 MHz): δ 192.1, 172.8, 155.2, 152.4, 152.3, 134.0, 133.3, 132.6, 131.3, 128.9, 125.6, 124.1, 118.2, 114.4, 112.9, 73.3, 52.3, 40.9, 27.9, 25.5, 18.6, 16.5.  \(\text{ESI-MS}\) \(m/z\) (rel int): (pos) 403.11 ([M+Na]\(^{+}\), 100), 381.12 ([M+H]\(^{+}\), 41).
7. Dihydroxylation of Other ODRE scaffolds

General procedure for dihydroxylation:
The olefin was dissolved in acetone/H\textsubscript{2}O (3:1, 0.02 M) and cooled to 0 °C. OsO\textsubscript{4} (4 wt % in H\textsubscript{2}O, 5 mol%) was added to the solution followed by NMO (1.1 equiv). The reaction was stirred at 0 °C to 25 °C for 1–14 h and monitored by TLC. Upon completion, the reaction was quenched with satd aq Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} or Na\textsubscript{2}SO\textsubscript{3} and stirred for 20 min. The resulting mixture was diluted with EtOAc and the aqueous layer was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (EtOAc/hexanes) yielded the diol.

\[(7S^*,8S^*)-7,8-Dihydroxy-11,12-dimethoxy-8-methyl-10-methylene-5,6,7,8,9,10-hexahydroidenzo[a,c][10]annulen-3-yl trifluoromethanesulfonate (94).\]

TLC: \(R_f 0.20\) (6:4 hexanes/EtOAc). \textbf{IR} (NaCl, film): 3475 (O–H), 2938, 1474, 1423, 1142. \textbf{\textsuperscript{1}H-NMR} (500 MHz): \(\delta 7.14\) (d, 1H, \(J = 9.1\)), 7.10–7.08 (m, 2H), 6.93 (d, 1H, \(J = 8.4\)), 6.89 (d, 1H, \(J = 8.4\)), 5.30 (s, 1H), 5.04 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.01 (s, 1H), 2.84 (d, 1H, \(J = 6.2\)), 2.74 (dd, 1H, \(J = 13.8, 8.4\)), 2.57 (t, 1H, \(J = 12.3\)), 2.36 (s, 1H), 2.18 (d, 1H, \(J = 15.6\)), 1.87 (dd, 1H, \(J = 15.6, 8.4\)), 1.60 (d, 1H, \(J = 15.6\)), 1.44–1.38 (m, 1H), 0.95 (s, 3H). \textbf{\textsuperscript{13}C-NMR} (126 MHz): \(\delta 153.1, 149.2, 145.5, 144.7, 140.0, 139.4, 137.3, 131.7, 131.0, 124.9, 122.7, 121.9, 118.4, 111.0, 74.7, 62.4, 55.8, 45.4, 35.1, 33.3, 29.7, 20.8. ESI-MS \textit{m/z} (rel int): (pos) 525.0 ([M+Na]\textsuperscript{+}, 100); 501.2 ([M–H]\textsuperscript{+}, 60), 537.1 ([M+Cl]\textsuperscript{+}, 100).

\[(4R^*,5S^*)-9-Methoxy-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine-4,5-diol (96).\]

TLC: \(R_f 0.20\) (50% EtOAc/hexanes). \textbf{IR} (NaCl, film): 3424, 2923, 2851, 1501, 1461, 1203, 1042. \textbf{\textsuperscript{1}H-NMR} (600 MHz): \(\delta 6.95\) (d, 1H, \(J = 8.8\)), 6.77 (dd, 1H, \(J = 8.8, 3.1\)), 6.66 (d, 1H, \(J = 3.1\)),
4.37 (t, 1H, J = 11.5), 4.10 (dd, 1H, J = 12.7, 6.3), 3.81 (d, 1H, J = 8.6), 3.79 (s, 3H), 3.04 (t, 1H, J = 12.7), 2.59 (t, 1H, J = 12.4), 2.36–2.30 (m, 1H), 1.66–1.63 (m, 3H), 1.21 (s, 3H). 13C-NMR (151 MHz): δ 155.8, 148.9, 137.1, 120.7, 116.3, 113.3, 73.3, 69.7, 55.8, 36.0, 30.0, 27.1, 24.9. 

**ESI-MS m/z (rel int):** (pos) 275.09 ([M+Na]+, 100).

(4R*,5S*)-4-Phenyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine-4,5,9-triol (97). 

**TLC:** Rf 0.22 (50% EtOAc/hexanes). **IR** (NaCl, film): 3385, 2926, 2853, 1499, 1446, 1198, 1027. 1H-NMR (600 MHz): δ 7.63 (d, 1H, J = 7.8), 7.43 (t, 2H, J = 7.8), 7.33 (t, 2H, J = 7.4), 6.93 (d, 1H, J = 8.6), 6.72 (dd, 1H, J = 8.6, 3.1), 6.64 (d, 1H, J = 3.1), 4.66 (br s, 1H), 4.18 (br s, 1H), 4.10 (t, 1H, J = 11.1), 2.88 (br s, 2H), 2.26–2.20 (m, 2H), 2.03–1.98 (m, 1H), 1.90–1.85 (m, 1H). 13C-NMR (151 MHz): δ 151.4, 149.9, 145.3, 137.6, 129.0, 127.7, 126.5, 126.4, 121.0, 117.6, 78.0, 69.6, 32.2, 23.0, 14.4. **ESI-MS m/z (rel int):** (pos) 323.12 ([M+Na]+, 100); (neg) 298.98 ([M–H–], 100).

(4R*,5S*)-8-Bromo-9-methoxy-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine-4,5-diol (98). 

**TLC:** Rf 0.18 (50% EtOAc/hexanes). **IR** (NaCl, film): 3332, 2971, 1474, 1438, 1257, 1054. 1H-NMR (600 MHz): δ 6.98 (d, 1H, J = 8.9), 6.81 (d, 1H, J = 9.0), 4.40 (t, 1H, J = 11.0), 4.12–4.09 (m, 1H), 3.90 (s, 1H), 3.81–3.78 (m, 1H), 3.33 (br s, 1H), 3.17 (t, 1H, J = 13.1), 3.09–3.05 (m, 1H), 2.34–2.28 (m, 1H), 1.66 (dd, 2H, J = 15.3, 11.4), 1.51–1.45 (m, 1H), 1.22 (s, 3H). 13C-NMR (151 MHz): δ 152.8, 150.1, 137.9, 118.9, 114.8, 110.7, 77.1 (HSQC), 73.2, 70.4, 56.9, 36.5, 28.5, 25.8. **ESI-MS m/z (rel int):** (pos) 315.0 ([M–OH]+, 30).
(4R*,5S*)-9-Methoxy-8-(4-methoxyphenyl)-4-methyl-2,3,4,5,6,7-hexahydrobenzo[b]oxonine-4,5-diol (100). TLC: Rf 0.18 (50% EtOAc/hexanes). IR (NaCl, film): 3424, 2935, 1515, 1476, 1253, 1052, 730. 1H-NMR (600 MHz): δ 7.11 (t, 2H, J = 8.9), 7.01 (d, 1H, J = 8.9), 6.98 (d, 2H, J = 8.6), 6.83 (d, 1H, J = 8.9), 4.42 (dd, 1H, J = 12.2, 10.5), 4.18–4.13 (m, 1H), 3.87 (s, 3H), 3.77 (d, 1H, J = 8.6), 3.70 (s, 3H), 2.70 (dd, 1H, J = 14.7, 10.4), 2.43 (dd, 1H, J = 14.9, 9.5), 2.17–2.11 (m, 1H), 1.68–1.63 (m, 2H), 1.50 (dd, 1H, J = 15.3, 10.7), 1.24 (s, 3H).

13C-NMR (151 MHz): δ 158.5, 153.4, 149.3, 136.4, 131.4, 131.3, 131.0, 129.3, 118.5, 113.6 (2 peaks), 109.8, 73.1, 69.5, 56.1, 55.2, 36.1, 26.8, 14.3 (two carbons unresolved). ESI-MS m/z (rel int): (pos) 341.3 ([M–OH]+, 100), 381.3 ([M+Na]+, 8).

(Z)-3-Hydroxy-3-(hydroxymethyl)-5-methyl-2-oxo-3,6,7,8-tetrahydro-2H-benzo[b]oxecin-10-yl trifluoromethanesulfonate (101). TLC: Rf 0.25 (50% EtOAc/hexanes). IR (NaCl, film): 3424, 2925, 2854, 1763, 1490, 1422, 1211, 1141, 927, 860. 1H-NMR (600 MHz): δ 7.35 (d, 1H, J = 8.8), 7.20 (dd, 1H, J = 8.8, 3.0), 7.18 (d, 1H, J = 2.9), 5.49 (s, 1H), 4.08 (d, 1H, J = 11.4), 3.80 (d, 1H, J = 11.4), 3.53 (br s, 1H), 2.77 (t, 1H, J = 12.9), 2.52–2.48 (m, 1H), 2.17–2.12 (m, 1H), 2.06 (s, 1H), 1.92 (d, 1H, J = 13.2), 1.56–1.54 (m, 1H), 1.84 (s, 3H). 13C-NMR (151 MHz): δ 174.0, 148.0, 147.4, 141.0, 137.8, 125.4, 125.2, 124.2, 120.2, 118.95 (q, JCF = 319), 76.6, 68.6, 29.8, 27.4 (2 peaks), 24.0. ESI-MS m/z (rel int): (pos) 433.08 ([M+Na]+, 100).

8. Detriflation of biaryl triflate 94

Supplementary Figure 61. Detriflation of biaryl triflate 94 to form phenol 95.
(7S*,8S*)-11,12-Dimethoxy-8-methyl-10-methylene-5,6,7,8,9,10-hexahydrodibenzo[ac]-[10]annulene-3,7,8-triol (95). Triflate 94 (20 mg, 40 µmol) was dissolved in MeOH (1 mL) and cooled to 0 °C. LiOH (4.8 mg, 200 µmol, 5 equiv) was added as a solid. The reaction was warmed to 25 °C and stirred for 30 min. Sat aq NH₄Cl (2 mL) was added and the resulting mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (6:4 hexanes/EtOAc) yielded phenol 95 (15 mg, 100%) as a yellow oil.

**TLC:** Rₚ 0.13 (6:4 hexanes/EtOAc).  
**IR** (NaCl, film): 3385 (O–H st), 2922, 1596, 1474, 1293, 1257, 1078.  
**¹H-NMR** (500 MHz): δ 6.92 (d, 1H, J = 8.8), 6.90–6.89 (m, 2H), 6.66–6.63 (m, 2H), 5.27 (t, 1H, J = 2.0), 5.01 (t, 1H, J = 2.0), 4.73 (s, 1H), 3.93 (s, 6H), 3.04 (s, 1H), 2.83 (d, 1H, J = 6.4), 2.63 (dd, 1H, J = 13.6, 8.4), 2.49 (t, 1H, J = 12.5), 2.37 (s, 1H), 2.16 (d, 1H, J = 15.4), 1.83–1.76 (m, 2H), 1.45–1.39 (m, 1H), 0.96 (s, 3H).  
**¹³C-NMR** (126 MHz): δ 155.3, 152.6, 144.5, 144.1, 140.1, 137.8, 132.6, 132.2, 131.1, 125.6, 121.9, 115.8, 112.6, 110.7, 74.8, 62.4, 55.7, 45.4, 35.2, 33.3, 20.9.  
**ESI-MS** m/z (rel int): (pos) 393.3 ([M+Na]⁺, 100); 369.1 ([M–H]⁻, 100).
III. SUPPLEMENTARY NOTE 2

PRINCIPAL COMPONENT ANALYSIS

1. PCA COMPOUND SELECTION

To generate the plots shown in Supplementary Figs. 14, 15, a total of 212 compounds (Supplementary Table 23) were compared by principal component analysis (PCA).\textsuperscript{14,15,16,17}

The compounds analyzed by PCA included the following:

- 40 top selling brand-name, small-molecule drugs by revenue in 2006 (Supp. Fig. 11)\textsuperscript{1}
- 60 natural products with diverse structures and biological activities (Supp. Fig. 12)
- 10 drug-like pyrazolecarboxamides in the MLSMR from ChemBridge (Supp. Fig. 13a)
- 10 drug-like dihydrotiazolopyrimidines in the MLSMR from ChemDiv (Supp. Fig. 13b)
- 20 benzannulated medium ring natural products (Supp. Fig. 10)
- 47 synthetic benzannulated medium ring scaffolds derived from ODRE (Supp. Fig. 9)
- 25 synthetic cyclohexadienones derived as intermediates from ODRE (Supp. Fig. 9)

The drug reference set was selected to illustrate the structural bias in high-profile synthetic drugs currently targeted by the pharmaceutical industry. The broad natural product reference set represents a diverse range of biological activities and biosynthetic origins; this set includes all 24 natural products that have advanced to an approved drug in 1981–2006,\textsuperscript{18} as well as 13 other clinically used drugs. The drug-like library reference set is comprised of two scaffold classes from ChemBridge and ChemDiv, two major commercial library suppliers, and all of these compounds are present in the NIH Molecular Libraries Small Molecule Repository. The benzannulated medium ring natural products have diverse ring linkages and were included for comparison to the 50 benzannulated medium ring scaffolds synthesized herein, as well as the 25 corresponding polycyclic cyclohexadienone precursors.

2. PCA DESCRIPTOR SELECTION\textsuperscript{16,17}

A set of 20 physicochemical properties (Supplementary Table 22) for all 212 compounds was obtained from PubChem and/or calculated using free online cheminformatics tools (Molinspiration,\textsuperscript{19} VCCLab\textsuperscript{20,21}), ChemDraw, JChem for Excel, and manual inspection.\textsuperscript{16} These

\textsuperscript{14} Moura-Letts, G., DiBlasi, C.M., Bauer, R.A. & Tan, D.S. Solid-phase synthesis and chemical space analysis of a 190-membered alkaloid/terpenoid-like library. Proc. Natl. Acad. Sci. U.S.A. 108, 6745–6750 (2011).
\textsuperscript{15} Bauer, R.A., DiBlasi, C.M. & Tan, D.S. The tert-butylsulfamamide lynchpin in transition-metal-mediated multiscaffold library synthesis. Org. Lett. 12, 2084–2087 (2010).
\textsuperscript{16} Bauer, R.A., Wurst, J.M. & Tan, D.S. Expanding the range of ‘druggable’ targets with natural product-based libraries: An academic perspective. Curr. Opin. Chem. Biol. 14, 308–314 (2010).
\textsuperscript{17} Kopp, F., Stratton, C.F., Akella, L. B. & Tan, D. S. A diversity-oriented synthesis approach to macrocycles via oxidative ring expansion. Nat. Chem. Biol. 8, 358–365 (2012).
\textsuperscript{18} Ganesan. The impact of natural products upon modern drug discovery. Curr. Opin. Chem. Biol. 12, 306–317 (2008).
\textsuperscript{19} MolInspiration – free on-line cheminformatics tool; http://www.molinspiration.com/cgi-bin/properties
\textsuperscript{20} Tetko, I.V., Virtual Computational Chemistry Laboratory; http://www.vcclab.org/lab/alogps/
\textsuperscript{21} Tetko, I.V., Tanchuk, V.Y., Kasheva, T.N. & Villa, A.E.P. Internet software for the calculation of the lipophilicity and aqueous solubility of chemical compounds. J. Chem. Inf. Comput. Sci. 41, 246–252 (2001).
properties were selected based on several criteria. First, Lipinski parameters\(^{22}\) (MW \(\leq 500\), logP \(\leq 5\), HBA \(\leq 10\), HBD \(\leq 5\)) and Veber parameters\(^{23}\) (RotB \(\leq 10\), tPSA \(\leq 140 \, \text{Å}^2\)) have been correlated with oral bioavailability. While oral bioavailability is not an immediate goal of most academic screening campaigns, some attention to these parameters is useful to the extent that they correlate partially to cell permeability,\(^{25}\) which is relevant to the utility of new chemical probes discovered from library screening. Second, Tetko’s calculated logS aqueous solubility (ALOGpS)\(^{24}\) was included since compound solubility is critical in screening and is often problematic for commercial drug-like libraries. Third, several stereochemical parameters (nStereo, R, S, nStMW, RSdelta) were included as a first-order approximation of three-dimensional complexity, and to enable the differentiation of enantiomeric structures. Indeed, the number of stereogenic centers is a key distinguishing factor between synthetic drugs and natural products,\(^{25}\) and has recently been shown to impact protein binding selectivity and frequency.\(^{26}\) Racemic compounds were treated as having the same number of R and S stereocenters equal to \(n_{\text{Stereo}} \div 2\), such that RSdelta = 0. Fourth, several additional parameters found previously to differentiate synthetic drugs and natural products were included.\(^{16}\) Synthetic drugs tend to have higher nitrogen content, while natural products tend to have higher oxygen content (N,O). Natural products also tend to have fewer aromatic rings and more complex, fused ring systems (Rings, RngAr, RngSys, RngLg, RRSys). While analyses using larger compound datasets and parameter lists are possible, we believe that there is limited additional value to such an analysis in the context of library planning.

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(22) Lipinski, C.A., Lombardo, F., Dominy, B.W. & Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **23**, 3–25 (1997).

(23) Veber, D.F. *et al.* Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **45**, 2615–2623 (2002).

(24) Tetko, I.V., Tanchuk, V.Y., Kasheva, T.N. & Villa, A.E.P. Estimation of aqueous solubility of chemical compounds using E-state indices. *J. Chem. Inf. Comput. Sci.* **41**, 1488–1493 (2001).

(25) Feher, M. & Schmidt, J.M. Property distributions: Differences between drugs, natural products, and molecules from combinatorial chemistry. *J. Chem. Inf. Comput. Sci.* **43**, 218–227 (2003).

(26) Clemons, P.A. *et al.* Small molecules of different origins have distinct distributions of structural complexity that correlate with protein-binding profiles. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 18787–18792 (2010).
**Supplementary Table 22. Structural and physicochemical parameters used in PCA.**

| Parameter | Description                              | Method of Determination                      |
|-----------|------------------------------------------|----------------------------------------------|
| MW        | molecular weight                         | ChemDraw Analysis Window                     |
| N         | number of nitrogens                      | ChemDraw Analysis Window                     |
| O         | number of oxygens                        | ChemDraw Analysis Window                     |
| XlogP     | calc n-octanol/water partition coefficient| http://www.vcclab.org                         |
| HBD       | number of hydrogen bond donors           | http://www.molinspiration.com                |
| HBA       | number of hydrogen bond acceptors        | http://www.molinspiration.com                |
| RotB      | number of rotatable bonds                | http://www.molinspiration.com                |
| tPSA      | topological polar surface area           | http://www.molinspiration.com                |
| ALOGPs    | calc n-octanol/water partition coeff (alt)| http://www.vcclab.org                       |
| ALOGpS    | calculated aqueous solubility            | http://www.vcclab.org                        |
| nStereo   | number of stereocenters                  | http://www.molinspiration.com                |
| R         | number of R stereocenters                | ChemDraw Show Stereochemistry                |
| S         | number of S stereocenters                | ChemDraw Show Stereochemistry                |
| RSdelta   | $R - S$                                   | Microsoft Excel                              |
| nStMW     | $nStereo \div MW$ (stereochemical density)| Microsoft Excel                              |
| Rings     | number of rings                          | Manual inspection                            |
| RngAr     | number of aromatic rings                 | Manual inspection                            |
| RngSys    | number of ring systems                   | Manual inspection                            |
| RngLg     | number of atoms in largest ring outline  | Manual inspection                            |
| RRSys     | $Rings \div RngSys$ (ring complexity)    | Microsoft Excel                              |

These PCA descriptor values were assembled in a Microsoft Excel spreadsheet (Supplementary Data Set 1) and average values for each parameter were calculated within each compound series. This hypothetical average molecule for each compound series was also included in the PCA analysis (Supplementary Table 24).
Supplementary Table 23. Compounds used in principal component analysis.

| Series                        | Compounds                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| **Best-Selling Brand Name Drugs** (40 entries) | Lipitor | Lexapro | Topamax | Coreg |
|                               | Nexium | Seroquel | Toprol  | Valtrex |
|                               | Prevacid | Protonix | Zetia  | Adderall |
|                               | Fionase | Ambien   | Fosamax | Aciphex |
|                               | Serevent | Actos   | Ability | Cymbalta |
|                               | Singulair | Zoloft  | Levaquin | Crestor |
|                               | Effexor | Wellbutrin | Lamictal | Diovan |
|                               | Plavix | Avandia | Celebrex | Tricor |
|                               | Zocor | Risperdal | Benazepril | Concerta |
|                               | Norvasc | Zyprexa | Zytec  | Lmitrex |
| **ChemBridge Library** (10 entries) | PubChem compound CIDs: 5771429 5771374 5309772 5309762 5309246 | Norvasc | Zyprexa | Zytec  | Lmitrex |
| **ChemDiv Library** (10 entries) | PubChem compound CIDs: 2529482 2529498 2474145 2474174 2490059 1340935 2490068 1342784 | Norvasc | Zyprexa | Zytec  | Lmitrex |
| **Natural Products** (60 entries) | cephamycin C | mizoridine | coformycin | compactin |
|                               | spergulin | SQ26180 | arglabin | artemisinin |
|                               | forskolin | thi amycin | bestatin | plau notol |
|                               | daptomycin | valid amycin | midecamycin A1 | rapamycin |
| echinocandin B | avermectin B1a | cyclosporin A | taxol | FK506 |
| calicheamycin γ1 | geldanamycin | trapoxin B | pseudomonic acid A | lipstatin |
| actinonin | vincristine | vircrinine | talaromycin B | bleomycin |
| discodermolide | colchicine | trichostatin | spongistatin 1 | brefeldin A |
| monensin | calyculin A | fumagilllin | radicicol | cytochalasin B |
| calyculin A | amphoterin B | staurosporine | salicylihalamide A | epothilone A |
| adriamycin | erythromycin A | streptomyycin | brevetoxin B | apotolidin |
| ginkgolide B | penicillin G | telomestatin | rifamycin B | lactacycin |
| phorbol myristoyl acetate |  |  |  | duocarmycin A |
| **Benzannulated Medium Ring Natural Products** (20 entries) | xestodecalactone A | xestodecalactone B | cri powellin aglycon | stagana cin |
|                               | aspercycle A | citreofuran | sporostatin | puerol A |
| heliannuol A | rhamzinlam | brasilone | apicularen A | clavilactone C |
| clavilactone A | brasilone | brasilone | kadsulignan E | vermo xicon A |
| coleophomone B | brasilone | brasilone | pterocaryanin C | kurzichalcolactone A |
| **Benzannulated Medium Ring Library** (50 entries) | 6 | 57 | 64 | 71 | 78 | 90 | 97 |
|                               | 7 | 58 | 65 | 72 | 79 | 91 | 98 |
|                               | 52 | 59 | 66 | 73 | 80 | 92 | 99 |
|                               | 53 | 60 | 67 | 74 | 81 | 93 | 100 |
|                               | 54 | 61 | 68 | 75 | 82 | 94 | 101 |
|                               | 55 | 62 | 69 | 76 | 88 | 95 | 101 |
|                               | 56 | 63 | 70 | 77 | 89 | 96 | 101 |
| **Cyclohexadienone Library** (25 entries) | 5 | 34 | 38 | 42 | 46 | (2R)-49 | S43 |
|                               | 31 | 35 | 39 | 43 | 47 | 50 | 51 |
|                               | 32 | 36 | 40 | 44 | 48 | 51 | 52 |
|                               | 33 | 37 | 41 | 45 | (2S)-49 | S42 | 53 |
Supplementary Table 24. Average structural and physicochemical parameters by compound series.

|        | Drugs | NPs  | ChBr | ChDv | Med Ring NPs | Med Ring Lib | Cyclohexa-dienone Lib |
|--------|-------|------|------|------|--------------|--------------|------------------------|
| MW     | 361.0 | 629.0| 381.5| 446.4| 385.7        | 319.6        | 247.5                  |
| N      | 2.2   | 2.6  | 4.3  | 4.7  | 0.2          | 0.0          | 0.0                    |
| O      | 2.9   | 9.7  | 3.1  | 3.4  | 6.8          | 3.7          | 2.5                    |
| XLogP  | 2.7   | 1.5  | 2.9  | 1.8  | 2.2          | 3.8          | 1.9                    |
| HBD    | 1.5   | 4.9  | 1.1  | 1.9  | 2.7          | 0.7          | 0.2                    |
| HBA    | 5.4   | 10.8 | 5.9  | 7.7  | 6.8          | 4.7          | 2.5                    |
| RotB   | 6.3   | 9.7  | 5.3  | 6.1  | 2.7          | 1.9          | 0.5                    |
| tPSA   | 68.9  | 183.2| 102.9| 93.6 | 106.7        | 49.9         | 34.6                   |
| ALOGPs | 2.8   | 2.1  | 3.3  | 2.7  | 2.7          | 4.0          | 2.5                    |
| ALOGpS | -3.9  | -3.8 | -4.0 | -3.8 | -3.5         | -4.3         | -3.5                   |
| nStereo| 1.4   | 9.1  | 0.0  | 1.0  | 2.3          | 0.6          | 2.1                    |
| R      | 0.6   | 4.1  | 0.0  | 0.5  | 1.2          | 0.3          | 1.1                    |
| S      | 0.8   | 5.0  | 0.0  | 0.5  | 1.1          | 0.3          | 1.1                    |
| nStMW †| 3.7   | 13.9 | 0.0  | 2.2  | 5.8          | 1.6          | 8.7                    |
| RSdelta| -0.2  | -0.9 | 0.0  | 0.0  | 0.1          | 0.0          | 0.0                    |
| Rings  | 2.9   | 3.8  | 3.2  | 4.2  | 3.6          | 2.4          | 3.2                    |
| RngAr  | 2.1   | 1.0  | 2.9  | 2.9  | 1.8          | 1.3          | 0.2                    |
| RngSys | 2.1   | 2.0  | 3.1  | 3.1  | 1.5          | 1.1          | 1.1                    |
| RngLg  | 8.4   | 15.8 | 6.3  | 9.4  | 16.6         | 15.1         | 14.3                   |
| RRSys  | 1.4   | 2.3  | 1.0  | 1.4  | 2.9          | 2.2          | 3.0                    |

† = nStMW x 1000 for clarity
3. PCA COMPUTATIONAL PROTOCOL

To provide a visual representation of the position of each compound in chemical space, we then carried out principal component analysis with the “R” open source statistical computing package to reduce the 20-dimensional vector corresponding to each compound to a 2-dimensional vector, with minimal loss of information. The detailed protocol is as follows:

1) In MS Excel, a “Raw” worksheet was created with compounds in rows and physicochemical descriptors in columns. Note that compound names must not have spaces or other punctuation.

2) Mean values were calculated for individual compound categories (e.g., for “Drugs”, “Natural Products”, etc.). In addition, mean and standard deviation values were calculated for each column.

3) A “Norm” worksheet was created and mean-centered, standardized values were generated for each column using the equation:

\[
\text{normval} = \frac{\text{val} - \text{Column Mean}}{\text{Column Standard Deviation}}
\]

4) With the upper left cell blank (R requires this to recognize a header row), the Number format was designated for all data columns to 4 decimal places.

5) The Excel workbook was saved.

6) The “Norm” worksheet was saved as “Data.txt” (Text–Tab Delimited) on the Desktop (Mac).

7) The Excel workbook was closed and the changes discarded.

8) The “R” open source computing package was opened and the following commands were entered:

9) \text{R> read.table("~/Desktop/Data.txt") -> a} \quad \# \text{read data into dataframe a}

10) \text{R> prcomp(a) -> b} \quad \# \text{PCA of dataframe a, results to b}

11) \text{R> summary(b)} \quad \# \text{prints summary of %contributions}

12) \text{R> b} \quad \# \text{prints the rotation (loading) matrix}

13) \text{R> biplot(b, choices = c(1,2), col = c("gray", "red"))} \quad \# \text{Biplot of scores and eigenvectors for PC1 vs PC2}

14) \text{R> biplot(b, choices = c(1,3), col = c("gray", "red"))} \quad \# \text{Biplot of scores and eigenvectors for PC1 vs PC3}

15) \text{R> biplot(b, choices = c(3,2), col = c("gray", "red"))} \quad \# \text{Biplot of scores and eigenvectors for PC3 vs PC2}

16) \text{R> b$x} \quad \# \text{prints the rotated data (scores)}

17) This final command prints the rotated data (scores) and the first section of the data was selected and copied (PC1–PC10, without top headers).

18) These results were pasted into a MS Word text file and the font changed to Courier 5 pt.

19) This MS Word file was Saved as... “Scores.txt” (Text Only with Line Breaks)

20) Excel was opened again and the scores were imported by selecting “Get External Data” in the Data menu, then “Import from Text file”.

21) The “Fixed” width button was left checked and dividers were adjusted, making sure to include minus signs in the second column (PC1) rather than the first (compound names).

22) This data file was imported into a new Excel worksheet “Scores”.

23) The first four columns (compound names, PC1, PC2, and PC3) where copied into a new worksheet “PCA”, and the Number format was designated to 3 decimal places.

24) Each group of compounds was then sorted in order of ascending PC1 to facilitate its location on the PCA plot.

25) With the PC1 and PC2 columns selected, the Scatter XY plot was selected in the Chart Wizard.

26) Series information for each set of compounds, e.g. Drugs, AVG Drug, etc., was entered and the chart formatted as desired.

27) Steps 25) and 26) were repeated to generate plots of PC1 vs PC3 and PC3 vs PC2.

(30) The R Project for Statistical Computing; http://www.r-project.org/
4. PCA PLOT GENERATION

Following PCA, all 215 molecules were plotted on newly generated, unitless, orthogonal axes (principal components) that are based on linear combinations of the original 20 parameters (Supplementary Fig. 14, and Supplementary Data Set 1). Summary information from R is shown in Supplementary Table 25 and Supplementary Fig. 62.

Supplementary Table 25. Standard deviation and percent contribution for each principal component in PCA plot (R Summary).

|                | PC1     | PC2     | PC3     | PC4     | PC5     | PC6     | PC7     | PC8     | PC9     | PC10    |
|----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Standard deviation | 2.949   | 1.760   | 1.743   | 1.321   | 1.049   | 0.874   | 0.667   | 0.549   | 0.438   | 0.414   |
| Proportion of Variance | 0.435   | 0.155   | 0.152   | 0.087   | 0.055   | 0.038   | 0.022   | 0.015   | 0.010   | 0.009   |
| Cumulative Proportion | 0.435   | 0.590   | 0.742   | 0.829   | 0.884   | 0.922   | 0.944   | 0.959   | 0.969   | 0.977   |

Supplementary Figure 62. Plot of percent contributions for principal components 1–10 of PCA plot. >90% of the variance in the complete 20-dimensional dataset is accounted for by the first six principal components (PC1–PC6).

These data indicate that >90% of the variance in the complete 20-dimensional dataset is accounted for by the first six principal components (PC1–PC6), due to correlations between some of the original 20 parameters. For visualization purposes, the first three principal components (PC1, PC2, PC3) were used to generate the plots shown in Supplementary Fig. 14. Together, these three principal components account for 74.2% of the variance in the complete dataset, with individual contributions of 43.5%, 15.5%, and 15.2%, respectively (Supplementary Table 25).

The component loadings of the original 20 parameters were obtained from R (step 12 in protocol above; Supplementary Fig. 15d) and the Biplot() function (steps 13–15 in protocol above) was used to display the loadings on 2-dimensional principal component plots in Supplementary Fig. 15a–c. These data indicate that O, MW, HBA, tPSA have the largest loadings on PC1 and shift compounds to the left in the PC1 vs. PC2 and PC1 vs. PC3 plots. The descriptors with the largest loadings on PC2 are RngAr and N, which shift compounds to the top of the PC1 vs. PC2 and PC3 vs. PC2 plots, as well as RngLg and RRSys, which shift compounds to the bottom of
the PC1 vs. PC2 and PC3 vs. PC2 plots. The descriptors with the largest loading on PC3 are XlogP, ALOGPs, and RngAr, which shift compounds in the positive direction along PC3, as well as ALOGpS, which shifts compounds in the negative direction along PC3.
### IV. Supplementary Note 3

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18

HO

HO

Me
three olefin regioisomers
three olefin regioisomers
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