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Asymmetric [4 + 3] Cycloadditions Between Benzofuranyldiazoacetates and Dienes: Formal Synthesis of (+)- Frondosin B

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Supporting Information

General: Reagents were purchased at the highest commercial quality and used without further purification unless stated otherwise. Analytical thin layer chromatography was performed on Whitman silica gel plates sing UV light unless stated otherwise. Flash column chromatography was performed on E. Merck silica 60. ¹H NMR spectra were recorded on Varian Nuclear Magnetic Resonance spectrometer at 300, 400, or 500 MHz. Daa is presented as follows: chemical shift (in ppm on the scale relative to H 7.26 for chloroform protons), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), coupling constant (J/Hz), and integration. ¹³C spectra were recorded at 74.45 or 125 MHz and all chemical shift values are reported in ppm on the scale, with an internal reference of C 77.0 for CDCl₃. Infrared spectra were obtained on a Nicolet Impact 420 FT-IR spectrometer. Mass spectra were recorded on a Hewlett-Packard GC-MS system using LC-MS (ESI). High-resolution mass spectra were obtained from the Mass Spectrometry Facility at the University of Buffalo, The Sate

University of New York. Elemental analyses were determined by Atlantic Microlab, Inc., Norcross, GA. Melting points are uncorrected and optical rotations were measured at the sodium D line (589 nm) and reported as follows: concentration (c in g/100 mL), and solvent (CHCl₃). Enantiomeric excess was determined by Varian ProStar high performance liquid chromatography (HPLC) using chiral analytical columns as stated. All moisture sensitive reactions were performed using glassware flame dried under vacuum, and under an argon atmosphere.

Methyl 2-(benzofuran-3-yl)diazoacetate (8): Methyl 2-(benzofuran-3-yl)acetate (2.23 g, 11.7 mmol), and para-acetamidobenzenesulfonyl azide (p-ABSA) (3.52 g, 14.7 mmol) were dissolved in acetonitrile (35 mL) and cooled to 0 °C. 1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) (3.56 g, 23.5 mmol) was added in one portion and the reaction was stirred at 0 °C for 1 h, the ice bath was removed and the reaction was stirred an additional 3 h at room temperature. The reaction was poured into saturated ammonium chloride and extracted into diethyl ether. The combined organic layers were washed with brine then dried over MgSO₄, filtered and concentrated to obtain the crude product. The crude material was purified by column chromatography (SiO₂, 90:10 petroleum ether/ diethyl ether) to obtain **8** as an orange solid in 67% yield (1.69 g). Mp: 83 °C; FTIR (neat): 2097, 1714, 1294, 1263 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.93 (s, 3H), 7.29 (t, 1H), 7.38 (t, 1H), 7.54 (m, 2H), 8.02 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 154.8, 141.5, 124.9, 124.3, 122.9, 118.5, 111.9, 103.7, 52.3; missing carbon attributed to C=N₂; Anal. Calcd. For C₁₁H₈N₂O₃: C, 61.11; H, 3.73, N, 12.96; Found: C, 61.22; H, 3.74; N, 12.62.

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Compound 9. Cyclopentadiene (459 mg, 6.94 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux ($110\text{ }^\circ\text{C}$) for one h, and allowed to cool to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess ($>94\%$) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **9** as a colorless oil in 83% yield (98 mg). $[\alpha]_{\text{D}}^{20} = -215.3^\circ$ (c 1.0, CHCl_3); HPLC analysis: ee $>98\%$ (OD-H column, 1% *i*-PrOH in hexanes, 1 mL/min, $\lambda = 254\text{ nm}$, $t_r = 6.13$, minor; 7.02, major); FTIR (neat): 2948, 1705, 1604, 1454, 1296, 1237 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.17 (d, 1H, $J = 11\text{ Hz}$), 2.26 (m, 1H), 3.37 (d, 1H, $J = 2.5\text{ Hz}$), 3.73 (d, 1H, $J = 1.5\text{ Hz}$), 3.85 (s, 3H), 5.32 (d, 1H, $J = 4.5\text{ Hz}$), 5.71 (m, 1H), 6.67 (m, 1H), 6.86 (d, 1H, $J = 8\text{ Hz}$), 6.93 (m, 1H), 7.27 (m, 1H), 8.24 (d, 1H, $J = 8\text{ Hz}$); The J coupling in the region of 4-6 Hz for the signal at δ 5.32 is indicative of an endo product.¹ ^{13}C NMR (75 MHz, CDCl_3) δ 166.1(qC), 163.2(qC), 145.9(CH), 145.2(qC), 131.7(CH), 131.1(qC), 128.2(CH), 127.3(CH), 124.9(qC), 121.2(CH), 110.5(CH), 83.0(CH), 51.5(CH_3), 44.1(CH), 41.9(CH_2), 41.9(CH); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3$: 254.0937, Found: 254.0941; Anal. Calcd. For $\text{C}_{16}\text{H}_{14}\text{O}_3$: C, 75.57; H, 5.55; Found: C, 75.17; H, 5.60.

9'

Compound 9'. Cyclopentadiene (459 mg, 6.94 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux ($110\text{ }^\circ\text{C}$) for one h, then treated with HCl (2 mL) for 16 h. The reaction was cooled to room temperature poured into H_2O , extracted into diethyl ether, dried over MgSO_4 , and filtered. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/pentane) to obtain product **9'** as a white solid in 81% yield (95 mg). $[\alpha]_{\text{D}}^{20} = -48.6^\circ$ (c 0.6, CHCl_3); Mp = $53\text{ }^\circ\text{C}$ HPLC analysis: ee >94% (SS-WHELK column, 0.6% *i*-PrOH in hexanes, 0.6 mL/min, $\lambda = 254\text{ nm}$, tr = 29.76, minor; 32.80, major); FTIR (neat): 2952, 1740, 1448, 1178, 1023, 913, 745 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.11 (d, 1H, $J = 10\text{ Hz}$), 2.48 (m, 1H), 3.54 (m, 2H), 3.76 (s, 3H), 4.07 (d, 1H, $J = 6\text{ Hz}$), 5.81 (dd, 1H, $J = 5.6\text{ Hz}, 2.8\text{ Hz}$), 6.58 (dd, 1H, $J = 5.6\text{ Hz}, 2.8\text{ Hz}$), 7.19 (m, 2H), 7.36 (m, 1H), 7.43 (m, 1H); The J coupling in the region of 4-6 Hz for the signal at δ 4.07 is indicative of an endo product.¹ ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 159.7, 153.7, 141.5, 130.5, 128.7, 122.66, 119.2, 111.0, 105.2, 65.8, 51.8, 44.1, 42.8, 38.9, 15.2; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{12}\text{O}_3$: 254.0937, Found: 254.0939.

Compound 10. Furan (473 mg, 6.94 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **10** as a colorless oil in 92% yield (109 mg). $[\alpha]_D^{20} = -233.9^\circ$ (c 1.0, CHCl_3); HPLC analysis: ee 96% (OJ column, 0.3% i-PrOH in hexanes, 1 mL/min, $\lambda = 254\text{ nm}$, $t_r = 19.05$, major; 23.49, minor); FTIR (neat): 2951, 1711, 1605, 1471, 1324, 1273 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.84 (s, 3H), 5.22 (s, 1H), 5.39 (d, 1H, $J = 5.5\text{ Hz}$), 5.64 (dd, 1H, $J = 6\text{ Hz}$, 1.5 Hz), 5.84 (dd, 1H, $J = 6\text{ Hz}$, 1.5 Hz), 6.85 (m, 2H), 6.96 (t, 1H), 7.30 (m, 1H), 8.33 (d, 1H, $J = 7.5\text{ Hz}$); The J coupling in the region of 4-6 Hz for the signal at δ 5.39 is indicative of an endo product.¹ ^{13}C NMR (75 MHz, CDCl_3) δ 164.4(qC), 163.4(qC), 145.9(qC), 143.9(CH), 132.6(CH), 127.9(CH), 126.8(qC), 125.2(CH), 124.2(qC), 121.7(CH), 110.8(CH), 79.8(CH), 78.1(CH), 77.5(CH), 51.6(CH_3); HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_4$: 256.0730, Found: 256.0730.

Compound 10'. Furan (433 mg, 6.94 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux ($110\text{ }^\circ\text{C}$) then treated with HCl (2 mL) for 16 h. The reaction was poured into H_2O , extracted into diethyl ether, dried over MgSO_4 , and filtered. The solvent was then removed under reduced pressure and the diastereomeric excess ($>94\%$) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **10'** as a colorless oil in 91% yield (107 mg). $[\alpha]_{\text{D}}^{20} = 31.7^\circ$ (c 0.47, CHCl_3); HPLC analysis: ee 93% (OD-H column, 10% *i*-PrOH in hexanes, 1 mL/min, $\lambda = 254\text{ nm}$, $t_r = 18.61$, major; 15.95, minor); FTIR (neat): 1738, 1724, 1446, 1173, 1034 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.77 (s, 3H), 4.42 (d, 1H, $J = 6\text{ Hz}$), 5.43 (d, 1H, $J = 1.6\text{ Hz}$), 5.51 (dd, 1H, $J = 6\text{ Hz}$, 1.6 Hz), 6.05 (dd, 1H, $J = 6\text{ Hz}$, 1.6 Hz), 6.79 (dd, 1H, $J = 6\text{ Hz}$, 1.6 Hz), 7.22 (m, 2H), 7.45 (m, 2H); The J coupling in the region of 4-6 Hz for the signal at δ 4.42 is indicative of an endo product.¹ ^{13}C NMR (100 MHz, CDCl_3) δ 169.5(qC), 155.5 (qC), 153.8(qC), 139.6(CH), 128.0(CH), 127.7(CH), 123.4(CH), 122.9(CH), 119.9(CH), 111.3(CH), 105.2(qC), 79.8 (CH), 76.1(CH), 52.0 (CH₃), 42.7 (CH); HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_4$: 257.0808, Found: 257.0808.

11

Compound 11. 2-Methyl Furan (1.14 g, 13.88 mmol) and $\text{Rh}_2(S\text{-DOSP})_4$ (17.4 mg, 0.009 mmol) were dissolved in toluene (10 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone

bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (200 mg, 0.93 mmol) was dissolved in toluene (6 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **11** as a white solid in 83% yield (208 mg). $[\alpha]_{\text{D}}^{20} = -291.2^\circ$ (c 1.0, CHCl_3); Mp = 72°C ; HPLC analysis: ee 94% (OD-H column, 1% i-PrOH in hexanes, 1 mL/min, $\lambda = 254\text{ nm}$, $t_r = 10.08$, major; 12.12, minor); FTIR (neat): 2978, 2951, 1716, 1616, 1455, 1268, 1241 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.83 (s, 3H), 3.86 (s, 3H), 5.09 (s, 1H), 5.25 (s, 1H), 5.69 (d, 1H, $J = 6\text{ Hz}$), 6.78 (dd, 1H, $J = 5\text{ Hz}$, 1.5 Hz), 6.89 (d, 1H, $J = 8.5\text{ Hz}$), 6.98 (t, 1H), 7.32 (m, 1H), 8.35 (d, 1H, $J = 7.5\text{ Hz}$); The J coupling in the region of 4-6 Hz for the signal at δ 5.69 is indicative of an endo product.¹ ^{13}C NMR (75 MHz, CDCl_3) δ 164.5(qC), 163.3(qC), 147.5(qC), 143.2(CH), 132.5(CH), 129.5(CH), 127.8(CH), 127.2(qC), 124.4(qC), 121.6(CH), 110.8(CH), 85.7(qC), 83.2(CH), 78.9(CH), 51.5(CH_3), 21.9(CH_3); HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_4$: 270.0887, Found: 270.0895.

11'

Compound 11'. 2-Methyl Furan (0.570 g, 6.94 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to -78°C in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux (110°C) then treated with HCl (2 mL) for 16 h. The reaction was poured into H_2O ,

extracted into diethyl ether, dried over MgSO_4 , and filtered. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **11'** as a colorless oil in 80% yield (100 mg). $[\alpha]_{\text{D}}^{20} = 32.5^\circ$ (c 0.66, CHCl_3); HPLC analysis: ee 88% (SS-WHELK, 10% i-PrOH in hexanes, 1 mL/min, $\lambda = 254$ nm, $t_r = 6.20$, major; 9.50, minor); FTIR (neat): 2952, 1740, 1447, 1380, 1288, 1258, 1200, 1193, 1129, 1003, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.80 (s, 3H), 3.77 (s, 3H), 4.42 (d, 1H, $J = 6$ Hz), 5.51 (dd, 1H, $J = 6$ Hz, 2 Hz), 5.97 (dd, 1H, $J = 5.6$ Hz, 2 Hz), 6.59 (d, 1H, $J = 6$ Hz), 7.21, (m, 2H), 7.45 (m, 2H); The J coupling in the region of 4-6 Hz for the signal at δ 4.42 is indicative of an endo product.¹ ^{13}C NMR (100 MHz, CDCl_3) δ 169.7, 157.5, 153.6, 143.3, 127.9 (2), 123.4, 122.9, 119.9, 111.4, 104.8, 82.9, 80.5, 52.0, 43.4, 16.7; HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{15}\text{O}_4$: 271.0965, Found: 271.0965.

Compound 12. (*E*)-1-(buta-1,3-dienyl)benzene (1.96 g, 14.9 mmol) and $\text{Rh}_2(R\text{-DOSPP})_4$ (18.7 mg, 0.009 mmol) were dissolved in toluene (20 mL) and cooled to -78°C in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (215 mg, 0.99 mmol) was dissolved in toluene (10 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **12** as a white solid in 62% yield (197 mg). $[\alpha]_{\text{D}}^{20} = 104.4^\circ$ (c 1.0, CHCl_3); Mp = 101°C ; HPLC

analysis: ee 97% (OD-H column, 1% i-PrOH in hexanes, 0.6 mL/min, λ = 254 nm, tr = 13.14, major; 16.20, minor); FTIR (neat): 3026, 2949, 1711, 1603, 1462, 1453, 1263 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.45 (m, 2H), 3.86 (s, 3H), 4.01 (d, 1H, J = 4.5 Hz), 5.66 (m, 1H), 5.97 (m, 1H), 6.04 (d, 1H, J = 4.5 Hz), 6.62 (m, 2H), 7.00 (m, 5H), 7.18 (d, 1H, J = 6.5 Hz), 7.84 (d, 1H, J = 8 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 177.1 (qC), 167.5(qC), 164.9(qC), 149.5(qC), 136.2(Qc), 131.9(CH), 130.0(CH), 129.0(CH), 127.2(CH), 127.0(CH), 126.9 (CH), 126.6 (CH), 122.9(CH), 120.2(CH), 119.6(qC), 109.9(CH), 85.9(CH), 51.6(CH_3), 46.9(CH), 44.5(qC), 29.5(CH_2); HRMS (ESI) m/z calcd. for $\text{C}_{21}\text{H}_{18}\text{O}_3$: 318.1250, Found 318.1256.

12'

Compound 12'. (*E*)-1-(buta-1,3-dienyl)benzene (0.91 g, 6.96 mmol) and $\text{Rh}_2(R\text{-DOSPP})_4$ (8.7 mg, 0.005 mmol) were dissolved in toluene (7 mL) and cooled to -78°C in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.46 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux (110°C) then treated with HCl (2 mL) for 16 h, then allowed to cool to room temperature. The reaction was poured into H_2O , extracted into diethyl ether, dried over MgSO_4 , and filtered. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , diethyl ether/ pentane = 1:9) to obtain product **12'** as a colorless oil in 60% yield (89 mg). $[\alpha]_{\text{D}}^{20} = -35.0^\circ$ (c 0.15, CHCl_3); HPLC analysis: ee 95% (SS-WHELK column, 1% i-PrOH in hexanes, 1.0 mL/min, λ = 254 nm, tr = 14.06, major; 15.99, minor); FTIR (neat): 3026,

2949, 1732, 1454, 1252, 1197, 1029 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.67 (m, 1H), 2.98 (m, 1H), 3.68 (s, 3H), 4.10 (dd, 1H, $J = 5.6$ Hz, 4 Hz), 5.02 (t, 1H), 5.84 (m, 1H), 6.03 (m, 1H), 7.24 (m, 5H), 7.32 (m, 3H), 7.46 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.2, 153.5, 153.4, 141.8, 130.3, 129.4 (2), 128.5 (2), 127.9, 127.4, 126.7, 123.9, 122.4, 118.6, 114.3, 110.9, 52.0, 46.7, 39.5, 28.9; HRMS (ESI) m/z calcd. for $\text{C}_{21}\text{H}_{18}\text{O}_3$: 319.1329, Found 319.1331.

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Compound 13. (*E*)-penta-1,3-diene **5** (709 mg, 10.4 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (26.2 mg, 0.014 mmol) were dissolved in toluene (20 mL) and cooled to -78°C in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (300 mg, 1.39 mmol) was dissolved in toluene (10 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , diethyl ether/ pentane = 1:9) to obtain product **13** as a white solid in 62% yield (222 mg). $[\alpha]_{\text{D}}^{20} = -105.6^\circ$ (c 1.0, CHCl_3); Mp: 60°C ; HPLC analysis: ee >98% (OJ column, 1% *i*-PrOH in hexanes, 0.8 mL/min, $\lambda = 254$ nm, $t_r = 12.64$, major; 15.45, minor); FTIR (neat): 2969, 1709, 1601, 1462, 1260, 1217 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.86 (d, 3H, $J = 6.5$ Hz), 2.81 (d, 1H, $J = 4$ Hz), 3.29 (d, 2H, $J = 4.5$ Hz), 3.87 (s, 3H), 5.62 (m, 2H), 5.90 (d, 1H, $J = 4$ Hz), 6.92 (m, 2H), 7.30 (m, 1H), 8.16 (d, 1H, $J = 8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 167.8(qC), 165.4(qC), 148.7(qC), 132.3(CH) (2), 126.8(CH), 125.0(CH), 123.4(qC), 120.7(CH), 120.6(CH), 110.2(CH), 86.6(CH), 51.7(CH₃), 36.4(CH), 29.7(CH₂), 13.7(CH₃); HRMS (ESI) m/z calcd. for

C₁₆H₁₆O₃: 257.1172, Found: 257.1128; Anal. Calcd. For C₁₆H₁₆O₃: C, 74.98; H, 6.29, O, 18.73; Found: C, 74.94; H, 6.27; O, 18.59.

13'

Compound 13'. (*E*)-penta-1,3-diene **5** (945 mg, 13.9 mmol) and Rh₂(*R*-DOSP)₄ (17.4 mg, 0.009 mmol) were dissolved in toluene (14 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (200 mg, 0.93 mmol) was dissolved in toluene (6 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was then heated to reflux (110 °C) then treated with HCl (2 mL) for 16 h, then cooled to room temperature. The reaction was poured into H₂O, extracted into diethyl ether, dried over MgSO₄, and filtered. The solvent was then removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ¹H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO₂, 1:9 diethyl ether/ pentane) to obtain product **13'** as a colorless oil in 64% yield (152 mg). [α]_D²⁰ = -36.0° (c 0.18, CHCl₃); HPLC analysis: ee >98% (SS-WHELK column, 0.8% *i*-PrOH in hexanes, 0.8 mL/min, λ = 254 nm, tr = 17.87, major; 19.22, minor); FTIR (neat): 2950, 1731, 1455, 1195, 1168, 1099 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.50 (d, 3H, *J* = 7.2 Hz), 2.63 (m, 1H), 2.87 (dq, 1H), 3.67 (s, 3H), 3.84 (m, 1H), 4.00 (m, 1H), 5.65 (dq, 1H), 5.89 (m, 1H), 7.20 (m, 2H), 7.40 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 155.9, 153.1, 132.9, 129.6, 126.7, 123.5, 122.3, 118.6, 112.6, 110.7, 52.1, 39.7, 34.5, 28.9, 20.3; HRMS (ESI) *m/z* calcd. for C₁₆H₁₆O₃: 257.1170, Found: 257.1172.

14

Compound 14. (*Z*)-penta-1,3-diene (645 mg, 13.8 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (17.4 mg, 0.0093 mmol) were dissolved in toluene (9 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (200 mg, 0.93 mmol) was dissolved in toluene (6 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess of 73% was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:19 diethyl ether/ pentane) to obtain cyclopropane as a white solid in 43% yield (101 mg). Cyclopropane was dissolved in xylenes (8 mL) and heated to $140\text{ }^\circ\text{C}$ for 4 h, then allowed to cool to room temperature and concentrated to obtain product **14** as a colorless oil in 100% yield (101 mg). $[\alpha]_{\text{D}}^{20} = -31.2^\circ$ (c 0.25, CHCl_3); HPLC analysis: ee >93% (AS-H column, 1% i-PrOH in hexanes, 0.8 mL/min, $\lambda = 254\text{ nm}$, tr = 7.27, minor; 9.01, minor); FTIR (neat): 2951, 1711, 1601, 1462, 1265 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.30 (d, 3H, $J = 7\text{ Hz}$), 2.42 (m, 1H), 3.19 (m, 2H), 3.87 (s, 3H), 5.37(m, 1H), 5.49 (d, 1H, $J = 11\text{ Hz}$), 5.71 (m, 1H), 6.93 (m, 2H), 7.31 (t, 1H), 8.22 (d, 1H, $J = 8\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3) δ 167.7(qC), 164.5(qC), 149.9(qC), 133.1(CH), 132.3(CH), 127.5(CH), 124.9(CH), 122.5(qC), 122(qC), 120.8(CH), 110.7(CH), 88.8(CH), 51.7(CH_3), 36.6(CH), 28.7(CH_2), 19.6(CH_3); HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3$: 257.1172, Found: 257.1173.

14'

Compound 14'. (*Z*)-penta-1,3-diene (645 mg, 13.8 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (17.4 mg, 0.0093 mmol) were dissolved in toluene (9 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (200 mg, 0.93 mmol) was dissolved in toluene (6 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess of 73% was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:19 diethyl ether/ pentane) to obtain cyclopropane as a white solid in 43% yield (101 mg). Cyclopropane was dissolved in xylenes (8 mL) and heated to $140\text{ }^\circ\text{C}$ for 4 h, then treated with HCl (2 mL) for 16 h. The reaction was poured into H_2O , extracted into diethyl ether, dried over MgSO_4 then concentrated to obtain product **14'** as a colorless oil in 94% yield (95 mg). $[\alpha]_{\text{D}}^{20} = 32.0^\circ$ (c 0.30, CHCl_3); HPLC analysis: ee >97% (SS-WHELK column, 0.8% *i*-PrOH in hexanes, 0.8 mL/min, $\lambda = 254\text{ nm}$, $t_{\text{r}} = 17.84$, minor; 22.46, major); FTIR (neat): 2952, 1731, 1456, 1226, 1198, 1170, 905 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.48 (d, 3H, $J = 7.2\text{ Hz}$), 2.72 (m, 1H), 2.86 (m, 1H), 3.67 (s, 3H), 3.81 (t, 1H), 4.01 (t, 1H), 5.90 (m, 2H), 7.22 (m, 2H), 7.40 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 156.1, 152.9, 133.3, 129.6, 127.1, 123.5, 122.3, 118.9, 112.6, 110.6, 52.1, 40.4, 34.3, 28.9, 19.4; HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3$: 257.1171, Found: 257.1172.

Compound 15. 4-Methylpenta-1,3-diene (1.14 g, 13.9 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (17.5 mg, 0.0093 mmol) were dissolved in toluene (14 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (200 mg, 0.93 mmol) was dissolved in toluene (6 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was heated to reflux ($110\text{ }^\circ\text{C}$) for 20 h, then allowed to cool to room temperature. The solvent was then removed under reduced pressure and the diastereomeric excess ($>94\%$) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:19 diethyl ether/ pentane) to obtain product **15** as a colorless oil in 79% yield. $[\alpha]_{\text{D}}^{20} = 68.6^\circ$ (c 1.19, CHCl_3); HPLC analysis: 91% (AS-H column, 1% *i*-PrOH in hexanes, 0.8 mL/min, $\lambda = 254\text{ nm}$, $t_r = 6.31$, major; 7.42, minor); FTIR (neat): 2962, 1712, 1602, 1463, 1434, 1262, 1198, 1150 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.79 (s, 3H), 1.27 (s, 3H), 3.18 (m, 2H), 3.84 (s, 3H), 5.27 (dd, 1H, $J = 11.75\text{ Hz}$, 2 Hz), 5.56 (m, 2H), 6.90 (m, 2H) 7.30 (t, 1H), 8.14 (d, 1H, $J = 8\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3) δ 167.6(qC), 165.4(qC), 149.1(qC), 138.4(CH), 132.2(CH), 126.8(CH), 123.2(qC), 122.5(CH), 121.9(qC), 120.6(CH), 110.1 (CH) 90.6(CH), 51.6(CH_3), 38.9(qC), 28.8(CH_2), 28.2(CH_3), 21.4(CH_3) ; HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_3$: 270.1250, Found: 270.1244.

Compound 15'. 4-Methylpenta-1,3-diene (569 mg, 6.94 mmol) and $\text{Rh}_2(R\text{-DOSP})_4$ (8.73 mg, 0.0046 mmol) were dissolved in toluene (7 mL) and cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. Methyl 2-(benzofuran-3-yl)diazoacetate **8** (100 mg, 0.463 mmol) was dissolved in toluene (3 mL) and added via syringe pump over 1 h. The reaction was stirred for 16 h while being allowed to warm slowly to room temperature. The reaction was heated to reflux ($110\text{ }^\circ\text{C}$) for 20 h, then treated with HCl (2 mL) for 16 h and allowed to cool to room temperature. The reaction was poured into H_2O , extracted into diethyl ether, dried over MgSO_4 , then filtered. The solvent was then removed under reduced pressure and the diastereomeric excess ($>94\%$) was obtained (determined by ^1H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO_2 , 1:19 diethyl ether/ pentane = 1:19) to obtain product **15'** as a white solid in 79% yield. $[\alpha]_{\text{D}}^{20} = 46.0^\circ$ (c 0.18, CHCl_3); Mp = $64\text{ }^\circ\text{C}$; HPLC analysis: ee $>96\%$ (SS-WHELK, 0.8% *i*-PrOH in hexanes, 0.8 mL/min, $\lambda = 254\text{ nm}$, tr = 13.64, major; 14.99, minor); FTIR (neat): 2963, 2951, 1718, 1219, 1183, 1108, 922 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.48 (d, 6H), 2.63 (m, 1H), 2.82 (m, 1H), 3.65 (s, 3H), 4.03 (t, 1H), 5.53 (dd, 1H, $J = 11.6\text{ Hz}$, 2.4 Hz), 5.80 (m, 1H), 7.22 (m, 2H), 7.41 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 158.5, 152.9, 138.5, 129.6, 124.3, 123.5, 122.1, 118.6, 111.7, 110.6, 51.9, 39.9, 39.6, 29.9, 28.6, 28.5; HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_3$: 271.1329, Found: 271.1326.

5-Methoxybenzofuran-3(2H)-one. Compound **20** was synthesized via a modified literature procedure.² To an ice cold solution of boron trichloride (1M in methylene chloride, 90 mL) was added a solution of 4-methoxyphenol **19** (9.0 g, 72.5 mmol) in 1,2-dichloroethane (36 mL) dropwise over 1 h. To the resulting mixture was added chloroacetonitrile (5.51 mL, 87.0 mmol) dropwise over 10 min and solid aluminum

chloride (4.84 g, 36.3 mmol) was added portionwise over 30 min. The reaction was stirred for 2.5 h, then poured into a mixture of ice and 2N HCl (90 mL/ 100 mL). The aqueous layer was extracted with dichloromethane, washed with brine and dried over MgSO_4 . The reaction was filtered and concentrated to get the crude α -chloro-2-hydroxy-5-methoxyacetophenone. This material was dissolved in methanol (72 mL) and treated with sodium acetate (19.8 g, 219 mmol), then heated to reflux (65°C). The reaction was stirred for 1.5 h, cooled to room temperature and poured into H_2O (100 mL). The reaction was extracted with diethyl ether, washed with brine and dried over MgSO_4 . The reaction was filtered, concentrated and the residue was purified by recrystallization in petroleum ether to obtain product **20** as a red solid in 68% yield (8.10 g). ^1H NMR (500 MHz, CDCl_3) δ 3.82 (s, 3H), 4.63 (s, 2H), 7.05 (d, 2H, $J = 2$ Hz), 7.28 (dd, 1H, $J = 8$ Hz, 2 Hz). Matches previously reported data.

Methyl 2-(5-methoxybenzofuran-3-yl)acetate (21). Compound **21** was prepared via a literature procedure.³ 5-methoxybenzofuran-3(2H)-one **20** (0.98 g, 5.97 mmol), and methyl (triphenyl phosphoranylidene)acetate (3.0 g, 8.95 mmol) were dissolved in xylenes (20 mL) and heated to reflux (140 °C). The reaction was stirred at reflux for 60 h, cooled to room temperature, and filtered through a plug of silica. The filtrate was concentrated and the residue was purified by column chromatography (SiO_2 , 1:9 diethyl ether/ pentane) to obtain product **21** as a yellow oil in 61% yield (0.79 g). ^1H NMR (500 MHz, CDCl_3) δ 3.71 (s, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 6.93 (dd, 1H, $J = 2, 9$ Hz), 7.02 (d, 1H, $J = 2$ Hz), 7.38 (d, 1H, $J = 9$ Hz), 7.62 (s, 1H). Matches previously reported data.

Methyl 2-diazo-2-(5-methoxybenzofuran-3-yl)acetate (4). Methyl 2-(5-methoxybenzofuran-3-yl)acetate **21** (0.79 g, 3.6 mmol) and para-acetamidobenzenesulfonyl azide (p-ABSA) (1.09 g, 4.53 mmol) were dissolved in acetonitrile (15 mL) and cooled to 0 °C. 1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) (1.09 g, 7.2 mmol) was added in one portion and the reaction was stirred at 0 °C for 1 h, then 3 additional h at room temperature. The reaction was poured into saturated ammonium chloride and extracted into diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated to obtain the crude product. The crude material was purified by column chromatography (SiO₂, 9:1 petroleum ether/ diethyl ether) to obtain product **4** as an orange solid in 81% yield (0.72 g). Mp = 81 °C; FTIR (neat): 2092, 1697, 1479, 1434, 1256, 1213 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.84 (s, 3H), 3.90 (s, 3H), 6.94 (m, 2H), 7.41 (d, 1H, *J* = 8.5 Hz), 7.93 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 149.9, 142.8, 125.1, 113.5, 112.4 (2), 103.7, 101.5, 55.9, 52.4; missing carbon attributed to C=N₂; Anal. Calcd. For C₁₁H₈N₂O₃: C, 58.54; H, 4.09, N, 11.38; Found: C, 58.69; H, 4.11; N, 11.28.

(6R,10S)-Methyl 2-methoxy-6-methyl-7,8,9,10-tetrahydro-6H-benzo[b]cyclohepta[d]furan-10-carboxylate. (E)-penta-1,3-diene **5** (2.21 g, 32.5 mmol) and Rh₂(R-DOSP)₄ (30.5 mg, 0.016 mmol) were dissolved in toluene (25 mL) and cooled to -78 °C in a dry

ice/acetone bath. Methyl 2-(5-methoxybenzofuran-3-yl)acetate **4** (400 mg, 1.62 mmol) was dissolved in toluene (15 mL) and added via syringe pump over 1 h. The reaction was stirred for 4 h while being allowed to warm slowly to room temperature. The reaction was then heated to 80 °C for 30 minutes, cooled to room temperature and concentrated. A solution of the crude product and 5% Pd/C (400 mg) in ethanol (30 mL) was shaken at 42 psi H₂ for 4 h. The crude mixture was filtered through celite, washed with diethyl ether and the solvent was removed under reduced pressure and the diastereomeric excess (>94%) was obtained (determined by ¹H NMR of crude reaction mixture). The residue was purified by column chromatography (SiO₂, Diethyl ether/ Pentane = 1:9) to obtain **22** as a colorless oil in 57% yield (268 mg). [α]_D²⁰ = 24.5° (c 0.95, CHCl₃); HPLC analysis: ee >97% (OD-H column, 0.8% *i*-PrOH in hexanes, 1 mL/min, λ = 254 nm, tr = 7.89, major; 10.34, minor); FTIR (neat): 2931, 1736, 1477, 1208 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.35 (d, 3H, *J* = 7.5 Hz), 1.85 (m, 4H), 2.10 (m, 1H), 2.48 (m, 1H), 3.24 (m, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 3.96 (t, 1H), 6.83 (m, 2H), 7.28 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 161.6, 155.8, 148.2, 130.7, 112.1, 111.5, 111.0, 101.7, 56.0, 51.9, 39.6, 33.5, 33.2, 30.9, 21.4, 19.1; HRMS (ESI) *m/z* calcd. for C₁₇H₂₀O₄: 288.1356, Found: 288.1358.

(R)-2-methoxy-6-methyl-10-methylene-7,8,9,10-tetrahydro-6H-benzo[b]cyclohepta[d]furan. A solution of compound **22** (0.260 g, 0.902 mmol) in tetrahydrofuran (10 mL) was cooled to -78 °C and treated with LiAlH₄, (2.4M in THF, 0.47 mL, 1.13 mmol). After being stirred at -78 °C for 15 min, the solution was warmed to 0 °C and stirred for 1.5 h. The reaction mixture was then quenched with sodium sulfate decahydrate. The material was then filtered through celite, washed with diethyl ether, and the filtrate was

concentrated under reduced pressure to obtain the crude alcohol. A solution of the crude alcohol was dissolved in dichloromethane (10 mL) and treated with toluenesulfonyl chloride (0.258 g, 1.41 mmol) and triethylamine (0.365 g, 3.61 mmol). The reaction was stirred for 4 h, then poured into H₂O (10 mL), and extracted into dichloromethane. The combined organics were washed with H₂O and brine, dried (MgSO₄), filtered and concentrated to obtain the crude tosylate. The crude tosylate was dissolved in dimethylformaldehyde (3 mL), treated with DBU (0.411 g, 2.71 mmol) and heated to 130 °C for 2 h. The reaction was cooled to room temperature and purified by column chromatography (SiO₂, pentane) to obtain product **23** as a colorless oil in 80% yield (176 mg). $[\alpha]_D^{20} = 20.7^\circ$ (c 0.10, CHCl₃); FTIR (neat): 2930, 1631, 1475, 1268, 1204 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.35 (d, 3H, *J* = 7 Hz), 1.75 (m, 1H), 1.84 (m, 1H), 1.97(m, 2H), 2.10 (m, 1H), 2.53 (m, 2H), 3.16 (m, 1H), 3.84 (s, 3H), 5.23 (s, 1H), 5.29 (d, 1H, *J* = 1.5 Hz), 6.82 (dd, 1H, *J* = 9 Hz, 2.5 Hz), 7.28 (d, 1H, *J* = 8.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 160.6(qC), 155.9(qC), 148.7(qC), 128.9(qC), 116.7(qC), 113.0(CH₂), 111.6(CH), 111.1(CH), 110.8(qC), 103.2(CH), 56.0(CH₃), 38.4 (CH₂), 34.1 (CH), 33.4(CH₂), 25.8 (CH₂), 18.9(CH₃); HRMS (ESI) *m/z* calcd. for C₁₆H₁₈O₂: 242.1301, Found: 242.1298.

(R)-2-methoxy-6-methyl-8,9-dihydro-6H-benzo[b]cyclohepta[d]furan-10(7H)-one. A solution of compound **23** (68.0 mg, 0.28 mmol), and RuCl₃·(H₂O)₂ (2.03 mg, 0.0098 mmol) were dissolved in acetonitrile (3 mL) and H₂O (2 mL) and stirred for 5 min. A mixture of Oxone (432 mg, 0.701 mmol) and NaHCO₃ (183 mg, 2.18 mmol) was added portionwise over 10 min, and the reaction was stirred for 16 h. The reaction was poured

into a solution of sat. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), and extracted into dichloromethane (3 X 8 mL). The combined organics were washed with H_2O and brine, dried (MgSO_4), filtered and concentrated to obtain the crude product. The crude product was purified by column chromatography (SiO_2 , 1:5 ethyl acetate/ hexanes) to obtain product **2** as a colorless oil in 73% yield (49.9 mg). $[\alpha]_{\text{D}}^{20} = 16.4^\circ$ (c 0.085, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.47 (d, 3H, $J = 7$ Hz), 1.79 (m, 1H), 1.89 (m, 1H), 2.03 (m, 1H), 2.21 (m, 1H), 2.81 (m, 2H), 3.34 (m, 1H), 3.88 (s, 3H), 6.89 (dd, 1H, $J = 8.75$ Hz, 2 Hz), 7.29 (d, 1H, $J = 9$ Hz), 7.77 (d, 1H, $J = 3$ Hz); HPLC analysis: ee 95% (OD column, 1% *i*-PrOH in hexanes, 2 mL/min, $\lambda = 254$ nm, $t_r = 6.36$, major; 7.71, minor). The spectral data matches the previously reported data.⁴

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