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A Cyclopropane Fragmentation Approach to Heterocycle Assembly:
A Convergent Synthesis of Oxepanes.

Supporting Information

Materials and Methods. All reactions were magnetically stirred and monitored by thin layer chromatography with pre-coated silica gel plates (E. Merck); reactions were carried out under an argon atmosphere. Flash chromatography was performed with silica gel 60A (170-400 mesh) supplied by Fisher Scientific. Yields refer to chromatographically and spectroscopically pure compounds. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were used from Sigma-Aldrich and purified using a solvent purification system from Innovative Technology. All other reagents were used as received. Infrared (IR) spectra were obtained using a Nicolet-10DX FT-IR spectrometer with KBr or with NaCl plates for the neat IR; prominent and diagnostic peaks are reported in cm^{-1} . All NMR spectra (^1H and ^{13}C) were obtained using a Bruker ACE 400 MHz FT-NMR Spectrometer or a Bruker ACE 300 FT-NMR; chemical shifts are reported in ppm downfield from tetramethylsilane (δ 0.00) using CDCl_3 as the solvent. High resolution mass spectra were measured at the Nebraska Center for Mass Spectrometry.

Diol 10a: To a solution of THF (108 mL) and ethyl 3-hydroxy-4-methylpentanoate (3.34 g, 20.9 mmol) under Ar in a water bath (15-20 °C), $\text{Ti}(\text{O}i\text{-Pr})_4$ (5.71 g, 21.9 mmol) in THF (15 mL) was added *via* cannula (1 mL THF rinse). Ethyl magnesium bromide (3 M) in Et_2O (33.4 mL, 100 mmol) was then added drop-wise over 2 hr *via* syringe pump, keeping the temperature between 15-20 °C. The resultant solution was stirred for 2 hr. The reaction was cooled to 0 °C then quenched with the slow addition of saturated aqueous NH_4Cl (75 mL), vacuum filtered, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4 , vacuum filtered, and concentrated *in vacuo*. Flash chromatography (30:70 EtOAc/Hexanes) provided **10a** (1.5185 g, 51 % yield) as a yellow oil: IR (NaCl) 3362 (s, br), 3080 (m), 2962 (s), 2871 (s), 1466 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.83 (m, 1 H), 3.44 (br, 1 H), 2.47 (br, 1 H), 2.08 (dd, J = 4.3 Hz, 2H), 1.72 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.83 (s, 2H), 0.49 (m, 2H); ^{13}C NMR (400

MHz, CDCl₃) δ 56.1, 40.6, 34.0, 18.4, 17.6, 14.1, 12.5; high resolution mass spectrum (EI) m/z 145.1230 [(M + H)⁺; calcd for C₈H₁₇O₂ 145.1229].

Diol 10b: To a solution of THF (107 mL) and ethyl 3-hydroxyhexanoate (3.4 mL, 21 mmol) under Ar in a water bath (15-20 °C), Ti(Oi-Pr)₄ (5.50 g, 21.0 mmol) in THF (5.4 mL) was added *via* cannula (1 mL THF rinse). Ethyl magnesium bromide (3 M) in Et₂O (33.1 mL, 99.3 mmol) was then added drop-wise over 2 hr *via* syringe pump, keeping the temperature between 15-20 °C. The resultant solution was stirred for 2 hr. The reaction was cooled to 0 °C then quenched with the slow addition of saturated aqueous NH₄Cl (75 mL), vacuum filtered, and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (30:70 EtOAc/Hexanes) provided **10b** (1.5045 g, 51 % yield) as a yellow oil: IR (NaCl) 3354 (s, br), 3080 (m), 2957 (s), 2880 (s), 2728 (w), 1458 (s), 1278 (s), 1012 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.07 (m, 1H), 2.05 (m, 1H) 1.57 (m, 1H), 1.39 (m, 6H), 0.97 (t, J = 7.0 Hz, 3H), 0.83 (s, 2H), 0.51 (d, J = 10.6, 1H), 0.47 (d, J = 10.1, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 72.4, 55.9, 43.9, 40.0, 18.7, 14.0, 12.5; high resolution mass spectrum (EI) m/z 145.1226 [(M + H)⁺; calcd for C₈H₁₇O₂ 145.1229].

Keto-oxepane 12: To a -10 °C suspension of CH₂Cl₂ (1 mL) and Na₂SO₄ (410 mg, 2.88 mmol) was added benzaldehyde (49.0 μ L, 0.480 mmol) under Ar. Al(OTf)₃ (45.5 mg, 0.096 mmol) was then added. In a separate flask, a solution of diol **8** (55.7 mg, 0.480 mmol) and CH₂Cl₂ (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH₂Cl₂ rinse). The resultant solution was stirred for 1 hr, then a solution of TiCl₄ in CH₂Cl₂ (1.0 M, 480 μ L, 0.480 mmol) was added. The resultant solution was stirred for 1.5 hr. The reaction was then diluted with CH₂Cl₂ (10 mL) and quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **12** (53.8 mg, 55 % yield) as a pale yellow oil: IR (NaCl) 3032 (m), 2932 (s), 1704 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35(s, 5H), 4.64 (d, J = 9.8 Hz, 1H), 4.16 (m, 1H), 2.21 (m, 1H), 2.06 (m, 1H), 1.97 (m, 2H), 1.38 (m, 1H), 1.28

(m, 1H), 0.62 (d, $J = 6.26$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 211.6, 143.3, 128.8, 127.9, 126.1, 84.8, 73.3, 53.9, 42.7, 34.5, 23.3; high resolution mass spectrum (EI) m/z 204.1149 [M^+ ; calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ 204.1150].

Keto-oxepane 18: To a -10 °C suspension of CH_2Cl_2 (1.5 mL) and Na_2SO_4 (430 mg, 3.02 mmol) was added 3-phenylpropionaldehyde (102 μL , 0.772 mmol) under Ar. $\text{Al}(\text{OTf})_3$ (73 mg, 0.154 mmol) was then added. In a separate flask, a solution of diol **8** (89.7 mg, 0.772 mmol) and CH_2Cl_2 (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH_2Cl_2 rinse). The resultant solution was stirred for 2 hr, then a solution of TiCl_4 in CH_2Cl_2 (1.0 M, 772 μL , 0.772 mmol) was added. The resultant solution was stirred for 0.5 hr. The reaction was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4 , vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **18** (91.8 mg, 51 % yield) as a pale yellow oil: IR (NaCl) 3084 (w), 3055 (w), 3020 (m), 2967 (s), 2915 (s), 2840 (m), 1695 (s), 1445 (m), 1328 (m), 1071 (m), 692 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28 (m, 5H), 3.92 (m, 1H), 3.49 (m, 1H), 3.0 - 2.5 (m, 6H), 1.9 - 1.6 (m, 4H), 1.31 (m, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 211.8, 142.4, 128.9, 126.2, 81.8, 73.0, 53.9, 42.6, 38.6, 32.6, 32.5, 23.0; high resolution mass spectrum (EI) m/z 232.1464 [M^+ ; calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ 232.1463].

Keto-oxepane 19: To a -10 °C suspension of CH_2Cl_2 (1.5 mL) and Na_2SO_4 (359 mg, 2.53 mmol) was added isobutyraldehyde (38 μL , 0.415 mmol) under Ar. $\text{Al}(\text{OTf})_3$ (61 mg, 0.129 mmol) was then added. In a separate flask, a solution of diol **8** (48.2 mg, 0.415 mmol) and CH_2Cl_2 (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH_2Cl_2 rinse). The resultant solution was stirred for 2 hr, then a solution of TiCl_4 in CH_2Cl_2 (1.0 M, 415 μL , 0.415 mmol) was added. The resultant solution was stirred for 2 hr. The reaction was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined

organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **19** (38.7 mg, 55 % yield) as a pale yellow oil: IR (NaCl) 2955 (s), 2920 (s), 2868 (s), 1695 (s), 1362 (m), 1089 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.90 (m, 1H), 3.20 (m, 1H), 2.8 - 2.5 (m, 4H), 1.86 (m, 1H), 1.8 – 1.6 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 212.3, 88.4, 73.4, 53.9, 42.6, 34.0, 29.6, 22.8, 19.6, 18.8; low resolution mass spectrum (EI) *m/z* 170.1305 [M⁺; calcd for C₁₀H₁₈O₂ 170.1307].

Keto-oxepane 20: To a –10 °C suspension of CH₂Cl₂ (1.5 mL) and Na₂SO₄ (325 mg, 2.27 mmol) was added benzaldehyde (46 μL, 0.454 mmol) under Ar. Al(OTf)₃ (55 mg, 0.114 mmol) was then added. In a separate flask, a solution of diol **10a** (54.5 mg, 0.378 mmol) and CH₂Cl₂ (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH₂Cl₂ rinse). The resultant solution was stirred for 1 hr, then a solution of TiCl₄ in CH₂Cl₂ (1.0 M, 340 μL, 0.340 mmol) was added. The resultant solution was stirred for 1.5 hr. The reaction was then diluted with CH₂Cl₂ (10 mL) and quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **20** (60.2 mg, 69 % yield) as a pale yellow oil: IR (NaCl) 2962 (s), 2872 (s), 1703 (s), 1446 (m), 1095 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (m, 5H), 4.63 (d, *J* = 1.17 Hz, 1H), 3.74 (m, 1H), 2.94 (t, *J* = 13.11 Hz, 1H), 2.9 – 2.6 (m, 3H), 2.16 (m, 1H), 1.95 (m, 1H), 1.80 (m, 1H), 0.98 (t, *J* = 6.60 Hz, 6H); ¹³C NMR (400 MHz, CDCl₃) δ 211.8, 142.9, 128.3, 127.3, 125.6, 84.7, 81.7, 49.4, 42.0, 34.8, 33.9, 18.8, 18.0; high resolution mass spectrum (EI) *m/z* 232.1462 [M⁺; calcd for C₁₅H₂₀O₂ 232.1463].

Keto-oxepane 21: To a –10 °C suspension of CH₂Cl₂ (1.5 mL) and Na₂SO₄ (300 mg, 2.09 mmol) was added 3-phenylpropionaldehyde (46 μL, 0.349 mmol) under Ar. Al(OTf)₃ (50 mg, 0.105 mmol) was then added. In a separate flask, a solution of diol **10a** (50.2 mg, 0.349 mmol) and CH₂Cl₂ (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH₂Cl₂ rinse). The resultant solution was stirred for 2.5

hr, then a solution of TiCl_4 in CH_2Cl_2 (1.0 M, 350 μL , 0.350 mmol) was added. The resultant solution was stirred for 1 hr. The reaction was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4 , vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **21** (56.5 mg, 62 % yield) as a pale yellow oil: IR (NaCl) 3080 (m), 2953 (s), 2868 (s), 1699 (s), 1082 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (m, 5H), 3.0 – 2.5 (m, 2H), 2.71 (m, 6H), 2.0 – 1.6 (m, 5H), 1.01 (dd, J = 15.8, 7.1 Hz, 6H); ^{13}C NMR (400 MHz, CDCl_3) δ 212.1, 142.2, 128.4, 128.3, 125.8, 82.2, 81.1, 49.5, 41.8, 38.6, 34.0, 32.6, 32.4, 19.1, 18.1; high resolution mass spectrum (EI) m/z 260.1787 [M^+ ; calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2$ 260.1776].

Keto-oxepane 22: To a $-10\text{ }^\circ\text{C}$ suspension of CH_2Cl_2 (1.5 mL) and Na_2SO_4 (314 mg, 2.21 mmol) was added isobutyraldehyde (34 μL , 0.368 mmol) under Ar. $\text{Al}(\text{OTf})_3$ (52 mg, 0.110 mmol) was then added. In a separate flask, a solution of diol **10a** (53.0 mg, 0.368 mmol) and CH_2Cl_2 (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH_2Cl_2 rinse). The resultant solution was stirred for 1 hr, then a solution of TiCl_4 in CH_2Cl_2 (1.0 M, 370 μL , 0.370 mmol) was added. The resultant solution was stirred for 1 hr. The reaction was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4 , vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **22** (50.6 mg, 70 % yield) as a pale yellow oil: IR (NaCl) 2956 (s), 2868 (m), 1707 (s), 1462 (m), 1380 (m), 1077 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.51 (m, 1H), 3.23 (m, 1H), 2.8 – 2.5 (m, 4H), 1.88 (m, 2H), 1.8 – 1.6 (m, 4H), 0.97 (m, 12H); ^{13}C NMR (400 MHz, CDCl_3) δ 212.7, 87.8, 81.2, 49.5, 41.9, 34.0, 33.9, 29.5, 19.5, 19.1, 18.4, 17.8; low resolution mass spectrum (EI) m/z 198 [M^+ ; calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2$ 198].

Keto-oxepane 23: To a $-10\text{ }^\circ\text{C}$ suspension of CH_2Cl_2 (1 mL) and Na_2SO_4 (142 mg, 3.39 mmol) was added benzaldehyde (57 μL , 0.565 mmol) under Ar. $\text{Al}(\text{OTf})_3$ (54 mg, 0.113 mmol) was then added. In a

separate flask, a solution of diol **10b** (81.4 mg, 0.565 mmol) and CH₂Cl₂ (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH₂Cl₂ rinse). The resultant solution was stirred for 2 hr, then a solution of TiCl₄ in CH₂Cl₂ (1.0 M, 452 μ L, 0.452 mmol) was added. The resultant solution was stirred for 0.5 hr. The reaction was then diluted with CH₂Cl₂ (10 mL) and quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **23** (88.3 mg, 66 % yield) as a pale yellow oil: IR (NaCl) 3084 (m), 3061 (m), 3020 (m), 2956 (s), 2929 (s), 2868 (s), 1695 (s), 1450 (s), 1324 (s), 1091 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (s, 5H) 4.63 (d, *J* = 10.2 Hz, 1H), 4.00 (m, 1H), 2.95 (m, 1H), 2.71 (m, 3H), 2.14 (m, 1H), 2.00 (m, 1H), 1.45 (m, 4H), 0.93 (t, *J* = 3.0 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 211.5, 142.8, 128.4, 127.4, 125.8, 84.6, 76.6, 52.1, 42.2, 38.8, 34.3, 19.0, 13.9; high resolution mass spectrum (EI) *m/z* 232.1458 [M⁺; calcd for C₁₅H₂₀O₂ 232.1463].

Keto-oxepane 24: To a -10 °C suspension of CH₂Cl₂ (1.5 mL) and Na₂SO₄ (282 mg, 1.99 mmol) was added 3-phenylpropionaldehyde (44 μ L, 0.329 mmol) under Ar. Al(OTf)₃ (33 mg, 0.070 mmol) was then added. In a separate flask, a solution of diol **10b** (47.4 mg, 0.329 mmol) and CH₂Cl₂ (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH₂Cl₂ rinse). The resultant solution was stirred for 2 hr, then a solution of TiCl₄ in CH₂Cl₂ (1.0 M, 330 μ L, 0.330 mmol) was added. The resultant solution was stirred for 1 hr. The reaction was then diluted with CH₂Cl₂ (10 mL) and quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na₂SO₄, vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **24** (60.6 mg, 71 % yield) as a white solid: IR (NaCl) 3085 (w), 3056 (w), 3019 (w), 2950 (m), 2933 (m), 2901 (m), 2835 (m), 1708 (s), 1450 (m), 1082 (m), 698 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (s, 5H), 3.76 (m, 1H), 3.52 (m, 1H), 2.9 - 2.6 (m, 6H), 1.9 - 1.4 (m, 8H), 0.97 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 211.7, 142.1, 128.43, 128.41, 125.9, 82.0, 76.0, 52.3, 42.0, 39.0, 38.6, 32.5, 32.4, 19.2, 14.0; high resolution mass spectrum (EI) *m/z* 260.1778 [M⁺; calcd for C₁₇H₂₄O₂ 260.1776].

Keto-oxepane 25: To a $-10\text{ }^{\circ}\text{C}$ suspension of CH_2Cl_2 (60 mL) and Na_2SO_4 (5.93 g, 41.7 mmol) was added isobutyraldehyde (695 μL , 7.65 mmol) under Ar. $\text{Al}(\text{OTf})_3$ (660 mg, 1.39 mmol) was then added. In a separate flask, a solution of diol **10b** (1.001 g, 6.96 mmol) and CH_2Cl_2 (1 mL) was prepared and added to the reaction flask *via* cannula (1mL CH_2Cl_2 rinse). The resultant solution was stirred for 2 hr, then a solution of TiCl_4 in CH_2Cl_2 (1.0 M, 6.96 mL, 6.96 mmol) was added. The resultant solution was stirred for 1 hr. The reaction was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4 , vacuum filtered, and concentrated *in vacuo*. Flash chromatography (15:85 EtOAc/Hexanes) provided **25** (0.979 g, 71 % yield) as a clear oil: IR (NaCl) 2958 (s), 2868 (s), 1699 (s), 1454 (m), 1082 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.74 (m, 1H), 3.21 (m, 1H), 2.8 – 2.5 (m, 4H), 1.9 – 1.4 (m, 7H), 0.97 (m, 9H); ^{13}C NMR (400 MHz, CDCl_3) δ 212.2, 88.0, 76.3, 52.3, 42.1, 39.0, 34.0, 29.4, 19.5, 19.1, 18.4, 13.9; high resolution mass spectrum (EI) m/z 198.1619 [M^+ ; calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2$ 198.1620].

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