Enantioselective Rauhut-Currier Reactions Promoted By Protected Cysteine

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Supporting Information

General Procedures. Proton NMR spectra were recorded on a 500 or 400 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm) or with the solvent reference relative to TMS employed as the internal standard (CDCl_3 , δ 7.26 ppm; d_6 -DMSO, δ 2.50 ppm; CD_3OD , δ 3.31 ppm; D_2O , δ 4.79 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded at 125 or 100 MHz with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl_3 , δ 77.0 ppm). Infrared spectra were obtained on a Perkin-Elmer Spectrum 1000 spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with KMnO_4 or cerium ammonium molybdenate (CAM) solutions. Flash column chromatography was performed using Silica Gel 60 Å (32–63 μm).ⁱ Optical rotations were recorded on a Rudolf Research Analytical Autopol IV Automatic polarimeter at the sodium D line (path length 100 mm). High resolution mass spectra were obtained at the Mass Spectrometry Facility of either Boston College (Chestnut Hill, MA) or the University of Illinois (Urbana-Champaign, IL). The method of ionization is given in parentheses.

Analytical normal phase HPLC was performed on a Hewlett-Packard 1100 Series chromatograph equipped with a diode array detector (214 nm and 254 nm). All reactions were carried out under an argon or nitrogen atmosphere employing oven- and flame-dried glassware. All solvents were purified using a Seca Solvent Purification System by GlassContour. *t*-BuOK was freshly sublimed prior to use.

General Procedure A: Preparation of Intramolecular Rauhut-Currier Substrates (1a-d, 9, 11, 13).

(11). Cyclopentene (520 μ L, 5.9 mmol) was dissolved in CH_2Cl_2 (8.7 mL), cooled to -78°C , and ozone was bubbled through the reaction until the clear solution turned blue. Nitrogen was then bubbled through the solution until the blue color disappeared to remove excess ozone. Triphenylphosphine (2.3 g, 8.9 mmol) was added and the reaction was allowed to stir for 1 h at -78°C . Stabilized ylide¹¹ **19** (4.6 g, 12.4 mmol) was added at room temperature and the pale yellow solution was allowed to stir for 24 h and then concentrated. Flash chromatography of the crude material (hexanes-EtOAc, 5:1) gave **11** as a pale yellow oil (790 mg, 2.8 mmol, 47%). Compounds **1a-d**, **9**, and **13** were prepared by analogous methodology.

(11).

^1H NMR (CDCl_3 , 400 MHz) δ 7.63-7.62 (m, 2H), 7.27-7.24 (m, 2H), 7.15 (dt, $J = 15.4, 7.2$ Hz, 2H), 6.84 (d, $J = 15.6$ Hz, 2H), 6.56 (dd, $J = 3.5, 1.8$ Hz, 2H), 2.38 (q, $J = 6.8$ Hz, 4H), 1.78 (quintet, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 178.3, 153.7, 148.1, 146.9, 125.9, 118.0, 112.7, 32.4, 26.9; IR (film, cm^{-1}) 3124, 2933, 1664, 1620, 1564, 1465, 1392, 1297, 1010; TLC R_f 0.25 (2:1 hexanes-EtOAc); HRMS (ESI) m/z 285.1137 (285.1127 calcd for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$).

(1a).

^1H NMR (CDCl_3 , 500 MHz) δ 7.93 (dd, $J = 8.2, 1.2$ Hz, 4H), 7.55 (t, $J = 7.5$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 4H), 7.06 (dt, $J = 15.4, 6.9$ Hz, 2H), 6.92 (d, $J = 15.4$ Hz, 2H), 2.39 (q, $J = 6.8$ Hz, 4H), 1.83-1.75 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 190.6, 148.5, 137.8, 132.7, 128.5, 128.4, 126.4, 32.1, 26.7; IR (film, cm^{-1}) 3056, 2929, 2856, 1671, 1621, 1577, 1446, 1344, 1291, 1221,

1009, 968; TLC R_f 0.46 (3:1 hexanes-EtOAc); HRMS (ESI) m/z 305.1546 (305.1542 calcd for $C_{21}H_{21}O_2$ $[M+H]^+$).

(1b).

1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.7 Hz, 4H), 7.05 (dt, J = 15.2, 6.9 Hz, 2H), 6.97-6.90 (m, 6H), 3.88 (s, 6H), 2.39 (q, J = 7.1 Hz, 4H), 1.78 (quintet, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.8, 163.4, 147.5, 130.8, 130.7, 126.2, 113.8, 55.5, 32.1, 26.8; IR (film, cm^{-1}) 3010, 2930, 2835, 1662, 1621, 1594, 1570, 1506, 1302, 1259, 1235, 1167; TLC R_f 0.26 (2:1 hexanes-EtOAc); HRMS (ESI) m/z 365.1764 (365.1753 calcd for $C_{23}H_{25}O_4$ $[M+H]^+$).

(1c).

1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, J = 8.5 Hz, 4H), 7.61 (d, J = 8.5 Hz, 4H), 7.07 (dt, J = 15.1, 7.1 Hz, 2H), 6.82 (d, J = 15.1 Hz, 2H), 2.40 (q, J = 6.8 Hz, 4H), 1.78 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.3, 149.0, 136.5, 131.9, 130.0, 127.9, 126.0, 32.2, 26.6; IR (film, cm^{-1}) 2949, 2886, 2829, 2722, 1721, 1671, 1620, 1583, 1400, 1073, 1010; TLC R_f 0.42 (1:1 hexanes-Et₂O); HRMS (ESI) m/z 460.9771 (460.9752 calcd for $C_{21}H_{19}O_2Br_2$ $[M+H]^+$).

(1d).

1H NMR ($CDCl_3$, 500 MHz) δ 8.32 (d, J = 8.8 Hz, 4H), 8.06 (d, J = 8.8 Hz, 4H), 7.13 (dt, J = 15.4, 6.9 Hz, 2H), 6.91 (d, J = 15.4 Hz, 2H), 2.45 (q, J = 6.9 Hz, 4H), 1.83 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.0, 150.6, 150.1, 142.6, 129.4, 126.1, 123.8, 32.3, 26.6; IR (film, cm^{-1}) 3109, 2934, 2856, 1671, 1617, 1601, 1524, 1344, 1213; TLC R_f 0.32 (2:1 hexanes-EtOAc); HRMS (ESI) m/z 395.1246 (395.1243 calcd for $C_{21}H_{19}N_2O_6$ $[M+H]^+$).

(9).

^1H NMR (CDCl_3 , 400 MHz) δ 6.78 (dt, $J = 15.9, 6.9$ Hz, 2H), 6.10 (d, $J = 16.0$ Hz, 2H), 2.31-2.24 (m, 10H), 2.39 (q, $J = 7.1$ Hz, 2H), 1.68 (quintet, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 198.5, 147.0, 131.8, 31.8, 27.0, 26.4; IR (film, cm^{-1}) 3001, 2933, 2856, 1697, 1673, 1620, 1427, 1359, 1254, 1182, 972; TLC R_f 0.29 (2:1 hexanes-EtOAc); HRMS (ESI) m/z 203.1054 (203.1048 calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2\text{Na} [\text{M}+\text{Na}]^+$).

(13).

^1H NMR (CDCl_3 , 500 MHz) δ 7.93 (d, $J = 7.0$ Hz, 2H), 7.56 (t, $J = 7.3$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.07-6.89 (m, 3H), 5.85 (dt, $J = 15.8, 1.5$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 2.36 (q, $J = 6.9$ Hz, 2H), 2.28 (q, $J = 6.9$ Hz, 2H), 1.72 (quintet, $J = 7.3$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 191.0, 166.9, 148.9, 148.4, 138.2, 133.1, 128.9, 128.9, 126.8, 122.4, 60.6, 32.4, 31.9, 26.9, 14.6; IR (film, cm^{-1}) 2980, 2936, 1715, 1672, 1652, 1616, 1442, 1264, 1178; TLC R_f 0.28 (3:1 hexanes-EtOAc); HRMS (ESI) m/z 295.1310 (295.1310 calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3\text{Na} [\text{M}+\text{Na}]^+$).

General Procedure B: Catalytic Intramolecular Rauhut-Currier Reactions.

Bisenone **1a** (30.0 mg, 0.10 mmol) was dissolved in acetonitrile (2.0 mL) and water (36 μL , 2.0 mmol) and cooled to -40°C . AcCysOMe (**5**) (17.6 mg, 0.10 mmol) and *t*-BuOK (67.0 mg, 0.59 mmol) were added sequentially and the reaction was allowed to stir for 24 h at -40°C . The reaction mixture was then filtered through a short plug of silica (hexanes-EtOAc, 1:1), concentrated, and purified by flash chromatography (hexanes-EtOAc, 5:1) to afford **2a** as a pale yellow oil (21 mg, 0.069 mmol, 70%). Compounds **2b-d**, **10**, **12**, and **14** were prepared by analogous methodology. NOTE: In order to ensure high efficiency and enantioselectivity, the

reaction concentration and equivalents of *t*-BuOK must be as described for each respective substrate. For runs employing less than 100 mol% catalyst, reaction parameters other than catalyst loading remain constant.

(2a).

2a

The characterization data for this compound matched that which has previously been reported.ⁱⁱⁱ $[\alpha]_D -38.6$ (*c* 0.76, CHCl₃, 95% ee); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 96:4 hexanes-isopropanol; Flow rate 0.75 mL/min; 15.1 min (major ent), 20.5 min (minor ent).

(2b).

2b

General procedure B was followed, except that bisenone **1b** (20.0 mg, 0.055 mmol) was employed as starting material with *t*-BuOK (43.2 mg, 0.39 mmol) in acetonitrile (5.5 mL). Yield: 73% (12.8 mg, 0.035 mmol); ¹H NMR (CDCl₃, 500 MHz) δ 8.05 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 6.96-9.92 (m, 4H), 6.53 (td, *J* = 3.9, 1.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.47-3.45 (m, 1H), 3.34 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.69 (dd, *J* = 14.4, 10.8 Hz, 1H), 2.38-2.29 (m, 1H), 2.23-2.15 (m, 1H), 1.81-1.57 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 198.7, 197.5, 163.8, 163.2, 142.7, 142.0, 132.1, 131.6, 131.2, 130.3, 114.1, 113.8, 55.9, 55.8, 42.8, 31.6, 27.0, 26.4, 18.8; IR (film, cm⁻¹) 2925, 2840, 1671, 1630, 1597, 1569, 1507, 1254, 1172, 1029; TLC *R_f* 0.36 (2:1 hexanes-EtOAc); $[\alpha]_D +7.0$ (*c* 0.77, CHCl₃, 90% ee); HRMS (ESI) *m/z* 365.1766 (365.1753 calcd for C₂₃H₂₅O₄ [M+H]⁺); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 80:20 hexanes-isopropanol; Flow rate 0.75 mL/min; 19.3 min (major ent), 28.0 min (minor ent).

(2c).

General procedure B was followed, except that bisenone **1c** (30.0 mg, 0.065 mmol) was employed as starting material with *t*-BuOK (36.0 mg, 0.33 mmol) in acetonitrile (2.2 mL). Yield: 70% (21 mg, 0.045 mmol); ¹H NMR (CDCl₃, 500 MHz) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.62-7.53 (m, 6H), 6.62 (t, *J* = 3.6 Hz, 1H), 3.43-3.41 (m, 1H), 3.33 (dd, *J* = 14.8, 3.5 Hz, 1H), 2.80 (dd, *J* = 14.8, 10.2 Hz, 1H), 2.38-2.31 (m, 1H), 2.25-2.19 (m, 1H), 1.79-1.61 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 198.9, 197.2, 145.8, 141.6, 137.8, 135.8, 132.3, 131.8, 131.2, 130.4, 128.6, 126.9, 42.8, 30.7, 26.9, 26.5, 18.4; IR (film, cm⁻¹) 2932, 2861, 1679, 1640, 1585, 1393, 1263, 1067, 1008; TLC R_f 0.64 (3:1 hexanes-EtOAc); [α]_D +9.7 (*c* 1.0, CHCl₃, 93% ee); HRMS (ESI) *m/z* 460.9751 (460.9752 calcd for C₂₁H₁₉O₂Br₂ [M+H]⁺); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 96:4 hexanes-isopropanol; Flow rate 0.75 mL/min; 26.3 min (major ent), 32.8 min (minor ent).

(2d).

General procedure B was followed, except that bisenone **1d** (20.0 mg, 0.051 mmol) was employed as starting material with *t*-BuOK (11.4 mg, 0.10 mmol) in acetonitrile (5.1 mL) and the reaction was allowed to stir for 4 h. Yield: 71% (14.2 mg, 0.036 mmol); ¹H NMR (CDCl₃, 400 MHz) δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 6.69 (t, *J* = 3.6 Hz, 1H), 3.49-3.40 (m, 2H), 2.99 (dd, *J* = 15.0, 9.4 Hz, 1H), 2.45-2.37 (m, 1H), 2.33-2.23 (m, 1H), 1.81-1.69 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 197.9, 195.9, 150.3, 149.4, 148.1, 144.2, 141.1, 141.0, 129.9, 129.4, 123.9, 123.4, 42.8, 29.8, 26.5, 26.4, 17.8; IR (film, cm⁻¹) 2937, 2864, 1689, 1643, 1599, 1522, 1345, 1265; TLC R_f 0.32 (3:1 hexanes-EtOAc); [α]_D +15.0 (*c* 1.0, CHCl₃, 84% ee); HRMS (ESI) *m/z* 395.1259 (395.1243 calcd for C₂₁H₁₉N₂O₆ [M+H]⁺); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 80:20 hexanes-isopropanol; Flow rate 0.75 mL/min; 42.9 min (major ent), 39.0 min (minor ent).

(10).

10

General procedure B was followed, except that bisenone **9** (20.0 mg, 0.11 mmol) was employed as starting material with *t*-BuOK (37.0 mg, 0.33 mmol) in acetonitrile (5.5 mL) and the reaction was allowed to stir for 40 h. Yield: 55% (7.2 mg, 0.040 mmol); ^1H NMR (CDCl_3 , 500 MHz) δ 6.95 (t, $J = 3.9$ Hz, 1H), 3.20-3.15 (m, 1H), 2.60 (dd, $J = 15.6, 3.2$ Hz, 1H), 2.31-2.26 (m, 5H), 2.17 (s, 3H), 1.66-1.52 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz) δ ; 208.7, 199.2, 142.9, 142.5, 48.0, 30.1, 28.2, 26.6, 26.4, 25.9, 17.4; IR (film, cm^{-1}) 2923, 2854, 1717, 1660, 1635, 1351, 1233, 1160; TLC R_f 0.39 (2:1 hexanes-EtOAc); $[\alpha]_D -43$ (c 0.42, CHCl_3 , 90% ee); HRMS (ESI) m/z 203.1056 (203.1048 calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 97:3 hexanes-isopropanol; Flow rate 0.60 mL/min; 14.9 min (major ent), 16.0 min (minor ent).

(12).

12

General procedure B was followed, except that bisenone **11** (30.0 mg, 0.11 mmol) was employed as starting material with *t*-BuOK (74.0 mg, 0.66 mmol) in acetonitrile (2.2 mL) and the reaction was allowed to stir for 40 h. Yield: 54% (13.7 mg, 0.048 mmol); ^1H NMR (CDCl_3 , 500 MHz) δ 7.62 (dd, $J = 1.7, 0.7$ Hz, 1H), 7.57 (dd, $J = 1.7, 0.6$ Hz, 1H), 7.41 (d, $J = 3.7$ Hz, 1H), 7.11 (dd, $J = 3.6, 0.6$ Hz, 1H), 7.00 (td, $J = 3.9, 1.0$ Hz, 1H), 6.53-6.51 (m, 2H), 3.48-3.45 (m, 1H), 3.11 (dd, $J = 14.6, 3.2$ Hz, 1H), 2.66 (dd, $J = 14.6, 10.6$ Hz, 1H), 2.39-2.21 (m, 2H), 1.78-1.63 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.2, 183.7, 152.4, 152.3, 146.5, 146.4, 142.1, 140.9, 119.1, 118.2, 112.1, 111.7, 42.3, 30.6, 26.3, 26.1, 18.0; IR (film, cm^{-1}) 3130, 2934, 2860, 1673, 1628, 1564, 1463, 1390, 1285; TLC R_f 0.32 (2:1 hexanes-EtOAc); $[\alpha]_D +14$ (c 0.88, CHCl_3 , 92% ee); HRMS (ESI) m/z 285.1133 (285.1127 calcd for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 80:20 hexanes-isopropanol; Flow rate 0.75 mL/min; 10.2 min (major ent), 14.0 min (minor ent).

(14).

General procedure B was followed, except that bisenone **13** (20.0 mg, 0.073 mmol) was employed as starting material with *t*-BuOK (49.4 mg, 0.44 mmol) in acetonitrile (1.5 mL). Yield: 66% (13.4 mg, 0.049 mmol); ^1H NMR (CDCl_3 , 500 MHz) δ 7.67 (d, $J = 6.9$ Hz, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.4$ Hz, 2H), 6.54 (t, $J = 3.9$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.40-3.33 (m, 1H), 2.59 (dd, $J = 14.9, 4.4$ Hz, 1H), 2.40 (dd, $J = 15.1, 9.1$ Hz, 1H), 2.35-2.26 (m, 1H), 2.23-2.14 (m, 1H), 1.85-1.61 (m, 4H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 197.6, 172.4, 143.9, 141.2, 138.6, 131.6, 129.3, 128.0, 60.2, 38.1, 30.1, 27.1, 26.0, 18.3, 14.2; IR (film, cm^{-1}) 2927, 2851, 1728, 1641, 1593, 1443, 1368, 1265, 1249, 1173; TLC R_f 0.52 (3:1 hexanes-EtOAc); $[\alpha]_D -62$ (c 0.5, CHCl_3 , 67% ee); HRMS (ESI) m/z 295.1320 (295.1310 calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 96:4 hexanes-isopropanol; Flow rate 0.75 mL/min; 11.7 min (major ent), 14.6 min (minor ent).

^1H NMR (CDCl_3 , 500 MHz) δ 7.94 (dd, $J = 8.2, 1.2$ Hz, 2H), 7.78 (dd, $J = 8.2, 1.1$ Hz, 2H), 7.54 (t, $J = 7.25$ Hz, 1H), 7.51-7.42 (m, 3H), 7.35 (t, 7.8 Hz, 2H), 5.96-5.92 (m, 1H), 5.80-5.75 (m, 1H), 4.43 (bs, 1H), 3.06 (dd, $J = 17.0, 7.9$ Hz, 1H), 2.95 (dd, $J = 17.3, 6.0$ Hz, 1H), 2.85-2.78 (m, 1H), 2.20-2.07 (m, 3H), 1.80-1.72 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 201.3, 199.7, 137.2, 137.1, 133.1, 132.9, 129.9, 128.7, 128.5, 128.3, 127.9, 124.1, 45.8, 39.6, 31.9, 25.2, 23.6; IR (film, cm^{-1}) 3060, 3025, 2922, 1682, 1595, 1578, 1446, 1372, 1323, 1283, 1211, 999; TLC R_f 0.52 (3:1 hexanes-EtOAc); $[\alpha]_D +54.3$ (c 0.23, CHCl_3 , 84% ee); HRMS (ESI) m/z 305.1552 (305.1542 calcd for $\text{C}_{21}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$); Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 96:4 hexanes-isopropanol; Flow rate 0.75 mL/min; 26.1 min (major ent), 27.9 min (minor ent).

General Procedure C: Preparation of Rauhut-Currier Catalysts.

A white heterogeneous mixture of CysOMe·HCl (1.00 g, 5.82 mmol) in acetonitrile (58 mL) was cooled to 0 °C. N,N-Diisopropylethylamine (935 μ L, 5.24 mmol) and acetyl chloride (374 μ L, 5.24 mmol) were added and the reaction was allowed to stir for 20 minutes. NH₄Cl (50 mL) was added at 0 °C and the reaction mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with saturated NaHCO₃ (100 mL), and brine (100 mL), dried over Na₂SO₄, and concentrated. Flash chromatography of the crude material on silica gel (hexanes-EtOAc, 1:2) yielded **5** as a white fluffy solid (422 mg, 2.38 mmol, 41%). ¹H NMR (CDCl₃, 500 MHz) δ 6.41-6.33 (bs, 1H), 4.90 (dt, J = 7.9, 3.8 Hz, 1H), 3.80 (s, 3H), 3.07-2.98 (m, 2H), 2.08 (s, 3H), 1.34 (t, J = 8.9 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.0, 170.1, 53.9, 53.2, 27.2, 23.5; IR (film, cm⁻¹) 3276, 2952, 1748, 1652, 1532, 1437, 1369, 1213; TLC R_f 0.21 (1:2 hexanes-EtOAc); [α]_D +71 (c 1.0, CHCl₃); HRMS (ESI) m/z 200.0363 (200.0357 calcd for C₆H₁₁NO₃SNa [M+Na]⁺).

General procedure C was followed, except that CysOMe·HCl (100 mg, 0.58 mmol) was used with isobutyryl chloride (55 μ L, 0.52 mmol) and N,N-diisopropylethylamine (94 μ L, 0.52 mmol) in acetonitrile (5.8 mL). Yield: 39% (47 mg, 0.23 mmol); ¹H NMR (CDCl₃, 500 MHz) δ 6.40-6.33 (bs, 1H), 4.89 (dt, J = 7.7, 3.7 Hz, 1H), 3.80 (s, 3H), 3.03 (dd, J = 8.8, 4.1 Hz, 2H), 2.47 (quintet, J = 6.9 Hz, 1H), 1.31 (t, J = 8.9 Hz, 1H), 1.20 (d, J = 4.1 Hz, 3H), 1.19 (d, J = 4.1 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 177.1, 171.2, 53.6, 53.2, 35.9, 27.3, 20.0, 19.7; IR (film, cm⁻¹) 3322, 2962, 2921, 1749, 1744, 1650, 1528, 1430, 1340, 1319, 1213; TLC R_f 0.64 (1:2 hexanes-EtOAc); [α]_D +59 (c 1.0, CHCl₃); HRMS (ESI) m/z 206.0858 (206.0851 calcd for C₈H₁₆NO₃S [M+H]⁺).

General procedure C was followed, except that CysOMe·HCl (200 mg, 1.2 mmol) was used with pivaloyl chloride (123 μ L, 1.0 mmol) and N,N-diisopropylethylamine (174 μ L, 1.0 mmol) in acetonitrile (11.6 mL). Yield: 42% (107 mg, 0.49 mmol); ¹H NMR (CDCl₃, 500 MHz) δ 6.58-6.48 (bs, 1H), 4.85 (dt, J = 7.9, 3.9 Hz, 1H), 3.80 (s, 3H), 3.03 (dd, J = 8.8, 4.1 Hz, 2H), 1.29 (t,

$J = 9.0$ Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 178.7, 171.3, 53.7, 53.2, 39.2, 27.8, 27.2; IR (film, cm^{-1}) 3349, 2953, 1747, 1653, 1648, 1513, 1438, 1207; TLC R_f 0.73 (1:2 hexanes-EtOAc); $[\alpha]_D +55$ (c 1.0, CHCl_3); HRMS (ESI) m/z 220.1004 (220.1007 calcd for $\text{C}_9\text{H}_{18}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$).

Determination of Absolute Configuration.

2,4-dinitrophenylhydrazine (5.4 mg, 0.022 mmol) and 0.5 N H_2SO_4 (22 μL , 0.011 mmol) were added to a solution of **2c** (10 mg, 0.022 mmol) in ethanol (100 μL). The red heterogeneous mixture was heated to reflux for 12 h, at which point excess 2,4-dinitrophenylhydrazine (10.8 mg, 0.044 mmol) was added and refluxed for an additional 12 h until starting material was consumed as indicated by TLC. The solid material was collected and purified by flash chromatography (hexanes-EtOAc, 10:1) to afford **18** as an orange solid (6.3 mg, 0.010 mmol, 45%). X-ray quality crystals were prepared by recrystallizing **18** from an ether-ethyl acetate solution affording bright orange plate crystals. ^1H NMR (CDCl_3 , 500 MHz) δ 11.6 (s, 1H), 9.17 (d, $J = 2.5$ Hz, 1H), 8.36 (dd, $J = 9.6, 2.5$ Hz, 1H), 8.08 (d, $J = 9.6$ Hz, 1H), 7.87 (d, $J = 8.6$ Hz, 2H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 6.69 (t, $J = 3.8$ Hz, 1H), 3.39-3.30 (m, 1H), 3.24 (dd, $J = 14.4, 5.6$ Hz, 1H), 2.79 (dd, $J = 14.4, 9.6$ Hz, 1H), 2.49-2.39 (m, 1H), 2.29-2.17 (m, 1H), 1.90-1.59 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 196.6, 154.5, 146.9, 145.4, 140.6, 138.8, 137.1, 135.6, 132.3, 131.9, 131.0, 130.6, 130.2, 129.1, 127.2, 125.1, 123.8, 117.3, 31.5, 31.2, 27.3, 26.6, 18.5; IR (film, cm^{-1}) 3317, 2927, 2856, 1645, 1617, 1586, 1514, 1502, 1486, 1331, 1307, 1263; TLC R_f 0.53 (3:1 hexanes-EtOAc); $[\alpha]_D + 50$ (c 0.45, CHCl_3); HRMS (ESI) m/z 641.0034 (641.0035 calcd for $\text{C}_{27}\text{H}_{23}\text{Br}_2\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$).

Crystallographic Data for Compound **18**.

Data Collection – Performed and solved by Dr. Christopher Incarvito.

An orange plate crystal of $\text{C}_{27}\text{H}_{22}\text{Br}_2\text{N}_4\text{O}_5$ having approximate dimensions of 0.20 x 0.20 x 0.10 mm^3 was mounted with epoxy cement on the tip of a fine glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo- $\text{K}\alpha$ radiation.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

$$\begin{array}{ll} a = 7.3503(15) \text{ \AA} & \alpha = 90^\circ \\ b = 11.878(2) \text{ \AA} & \beta = 90^\circ \end{array}$$

$$c = 33.132(7) \text{ \AA} \quad \gamma = 90^\circ$$

$$V = 2892.6(10) \text{ \AA}^3$$

For $Z = 4$ and F.W. = 642.31, the calculated density is 1.475 g/cm^3 . Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P2_12_12_1$ (#19).

The data were collected at a temperature of 173(2) K to a maximum 2θ value of 58.22° . Three omega scans consisting of 108, 108, and 87 data frames, respectively, were collected with a frame width of 0.7° and a detector-to-crystal distance, D_x , of 43.0 mm. Each frame was exposed twice (for the purpose of de-zinging) for a total of 21 s. The data frames were processed and scaled using the DENZO software package.^{iv}

Data Reduction

A total of 7386 reflections were collected of which 7386 were unique and observed ($R_{\text{int}} = 0.000$, Friedel pairs not merged). The linear absorption coefficient, μ , for Mo-K α radiation is 28.44 cm^{-1} , and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods and expanded using Fourier techniques.^v The non-hydrogen atoms were refined anisotropically, and hydrogen atoms, with exceptions noted, were treated as idealized contributions. The final cycle of full-matrix least-squares refinement^{vi} on F was based on 7386 observed reflections ($I > 2.00\sigma(I)$) and 347 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.0521$$

$$R_w = \{ \sum [w (F_o^2 - F_c^2)^2] / \sum [w (F_o^2)^2] \}^{1/2} = 0.1252$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.990 and $-0.442 \text{ e}^-/\text{\AA}^3$ respectively.

Structural Description

The compound crystallized in the chiral orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit and four molecules in the unit cell.

H(2) was located from the residual electron difference map and freely refined with isotropic displacement parameters. No geometric restraints were applied to the N(2)-H(2) bond, which refined to a distance of $0.76(5) \text{ \AA}$. As illustrated in Figure 3, H(2) is hydrogen bonded to O(2) of the adjacent nitro-group. Interatomic distances are $2.03 \text{ \AA}$ for H(2)⋯O(2) and $2.60 \text{ \AA}$ for N(2)⋯O(2). The N(2)-H(2)⋯O angle is 131.3° .

Extensive π -stacking is present in the crystal lattice. As illustrated in Figures 4 and 5, the π -stacking is present between the dinitro-substituted phenyl ring, C(22-27) and one of the bromo-substituted phenyl rings, C(16-21). Interplane separations are approximately 3.6 Å and the stacking propagates along the crystallographic a-axis.

The absolute molecular configuration was unambiguously determined [Flack = -0.013(10)]. ORTEPs, packing diagrams and full crystallographic tables follow.

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{27} H_{22} Br_2 N_4 O_5$	
Formula weight	642.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.3503(15) Å	$\alpha = 90^\circ$.
	b = 11.878(2) Å	$\beta = 90^\circ$.
	c = 33.132(7) Å	$\gamma = 90^\circ$.
Volume	2892.6(10) Å ³	
Z	4	
Density (calculated)	1.475 g/cm ³	
Absorption coefficient	28.44 cm ⁻¹	
F(000)	1288	
Crystal size	0.20 x 0.20 x 0.10 mm ³	
Theta range for data collection	2.84 to 29.11°.	
Index ranges	-10 ≤ h ≤ 10, -16 ≤ k ≤ 16, -44 ≤ l ≤ 45	
Reflections collected	7386	
Independent reflections	7386 [R(int) = 0.0000]	
Completeness to theta = 29.11°	98.9 %	
Absorption correction	None	
Max. and min. transmission	0.7641 and 0.6001	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7386 / 0 / 347	
Goodness-of-fit on F ²	1.008	
Final R indices [I > 2sigma(I)]	R1 = 0.0521, wR2 = 0.1252	
R indices (all data)	R1 = 0.0891, wR2 = 0.1417	

Absolute structure parameter	-0.013(10)
Largest diff. peak and hole	0.990 and -0.442 e.Å ⁻³

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for miller_ca01. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	8864(1)	7359(1)	4467(1)	48(1)
Br(2)	8544(1)	9560(1)	8834(1)	45(1)
O(1)	8632(5)	8496(2)	6489(1)	35(1)
O(2)	6852(5)	13348(3)	6016(1)	43(1)
O(3)	6366(6)	14939(3)	5730(1)	51(1)
O(4)	5269(5)	18273(3)	7107(1)	41(1)
O(5)	4519(5)	18139(3)	6476(1)	43(1)
N(1)	7735(5)	12705(3)	7152(1)	25(1)
N(2)	7469(5)	13253(3)	6786(1)	27(1)
N(3)	6577(5)	14366(3)	6033(1)	34(1)
N(4)	5157(5)	17751(3)	6790(1)	31(1)
C(1)	9217(6)	9414(4)	5471(1)	33(1)
C(2)	9104(7)	9028(4)	5076(1)	41(1)
C(3)	8932(7)	7886(4)	5006(1)	36(1)
C(4)	8799(7)	7122(4)	5316(1)	36(1)
C(5)	8912(6)	7516(4)	5710(1)	29(1)
C(6)	9196(6)	8653(3)	5790(1)	25(1)
C(7)	9431(5)	9019(3)	6222(1)	26(1)
C(8)	10658(6)	9946(3)	6327(1)	25(1)
C(9)	12158(6)	10147(4)	6107(1)	30(1)
C(10)	13724(7)	10880(4)	6227(2)	42(1)
C(11)	13630(6)	11154(4)	6676(2)	36(1)
C(12)	11688(5)	11489(4)	6788(1)	29(1)
C(13)	10377(5)	10513(4)	6731(1)	24(1)
C(14)	8394(6)	10936(3)	6768(1)	25(1)
C(15)	8133(5)	11655(3)	7142(1)	24(1)
C(16)	8366(5)	11131(3)	7545(1)	24(1)
C(17)	8016(6)	9992(3)	7603(1)	30(1)

C(18)	8097(6)	9535(4)	7982(2)	35(1)
C(19)	8511(6)	10187(4)	8307(1)	30(1)
C(20)	8901(6)	11328(4)	8260(1)	31(1)
C(21)	8825(6)	11791(3)	7877(1)	28(1)
C(22)	6924(5)	14348(3)	6788(1)	22(1)
C(23)	6490(6)	14924(3)	6423(1)	27(1)
C(24)	5916(6)	16034(3)	6422(1)	27(1)
C(25)	5797(5)	16587(3)	6785(1)	26(1)
C(26)	6232(7)	16069(3)	7147(1)	28(1)
C(27)	6772(6)	14956(3)	7149(1)	26(1)

Table 3. Bond lengths [Å] and angles [°].

Br(1)-C(3)	1.895(4)	C(9)-C(10)	1.497(6)
Br(2)-C(19)	1.900(4)	C(10)-C(11)	1.524(7)
O(1)-C(7)	1.230(5)	C(11)-C(12)	1.528(6)
O(2)-N(3)	1.228(5)	C(12)-C(13)	1.520(6)
O(3)-N(3)	1.223(5)	C(13)-C(14)	1.546(6)
O(4)-N(4)	1.225(5)	C(14)-C(15)	1.516(6)
O(5)-N(4)	1.230(5)	C(15)-C(16)	1.482(6)
N(1)-C(15)	1.282(5)	C(16)-C(17)	1.391(6)
N(1)-N(2)	1.388(5)	C(16)-C(21)	1.393(6)
N(2)-H(2)	0.76(5)	C(17)-C(18)	1.367(6)
N(2)-C(22)	1.361(5)	C(18)-C(19)	1.360(7)
N(3)-C(23)	1.452(5)	C(19)-C(20)	1.394(6)
N(4)-C(25)	1.460(5)	C(20)-C(21)	1.383(6)
C(1)-C(2)	1.389(6)	C(22)-C(27)	1.402(6)
C(1)-C(6)	1.391(6)	C(22)-C(23)	1.426(6)
C(2)-C(3)	1.382(7)	C(23)-C(24)	1.385(6)
C(3)-C(4)	1.372(7)	C(24)-C(25)	1.372(6)
C(4)-C(5)	1.390(6)	C(25)-C(26)	1.386(6)
C(5)-C(6)	1.392(6)	C(26)-C(27)	1.381(6)
C(6)-C(7)	1.507(6)		
C(7)-C(8)	1.465(6)	C(15)-N(1)-N(2)	117.8(4)
C(8)-C(9)	1.344(6)	H(2)-N(2)-C(22)	119(4)
C(8)-C(13)	1.513(6)	H(2)-N(2)-N(1)	121(4)

C(22)-N(2)-N(1)	119.0(4)	C(21)-C(16)-C(15)	120.2(4)
O(3)-N(3)-O(2)	122.0(4)	C(18)-C(17)-C(16)	120.4(4)
O(3)-N(3)-C(23)	118.1(4)	C(19)-C(18)-C(17)	120.7(4)
O(2)-N(3)-C(23)	119.8(4)	C(18)-C(19)-C(20)	120.7(4)
O(4)-N(4)-O(5)	124.2(4)	C(18)-C(19)-Br(2)	120.5(3)
O(4)-N(4)-C(25)	117.9(4)	C(20)-C(19)-Br(2)	118.8(3)
O(5)-N(4)-C(25)	117.9(4)	C(21)-C(20)-C(19)	118.7(4)
C(2)-C(1)-C(6)	120.1(4)	C(20)-C(21)-C(16)	120.7(4)
C(3)-C(2)-C(1)	119.1(5)	N(2)-C(22)-C(27)	121.3(4)
C(4)-C(3)-C(2)	122.0(4)	N(2)-C(22)-C(23)	121.4(4)
C(4)-C(3)-Br(1)	119.0(3)	C(27)-C(22)-C(23)	117.3(4)
C(2)-C(3)-Br(1)	118.9(4)	C(24)-C(23)-C(22)	121.8(4)
C(3)-C(4)-C(5)	118.4(4)	C(24)-C(23)-N(3)	116.4(4)
C(4)-C(5)-C(6)	120.9(4)	C(22)-C(23)-N(3)	121.7(4)
C(5)-C(6)-C(1)	119.2(4)	C(25)-C(24)-C(23)	118.2(4)
C(5)-C(6)-C(7)	118.5(4)	C(24)-C(25)-C(26)	122.1(4)
C(1)-C(6)-C(7)	122.2(4)	C(24)-C(25)-N(4)	118.9(4)
O(1)-C(7)-C(8)	120.2(4)	C(26)-C(25)-N(4)	119.0(4)
O(1)-C(7)-C(6)	118.8(4)	C(27)-C(26)-C(25)	119.8(4)
C(8)-C(7)-C(6)	120.9(4)	C(26)-C(27)-C(22)	120.8(4)
C(9)-C(8)-C(7)	120.7(4)		
C(9)-C(8)-C(13)	120.9(4)		
C(7)-C(8)-C(13)	117.4(4)		
C(8)-C(9)-C(10)	126.2(4)		
C(9)-C(10)-C(11)	110.4(4)		
C(10)-C(11)-C(12)	109.7(4)		
C(13)-C(12)-C(11)	111.3(3)		
C(8)-C(13)-C(12)	111.3(3)		
C(8)-C(13)-C(14)	110.1(3)		
C(12)-C(13)-C(14)	109.9(3)		
C(15)-C(14)-C(13)	111.5(3)		
N(1)-C(15)-C(16)	114.3(4)		
N(1)-C(15)-C(14)	126.7(4)		
C(16)-C(15)-C(14)	118.9(3)		
C(17)-C(16)-C(21)	118.8(4)		
C(17)-C(16)-C(15)	120.9(4)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
<hr/>						
Br(1)	48(1)	67(1)	31(1)	-16(1)	5(1)	-21(1)
Br(2)	52(1)	47(1)	35(1)	13(1)	0(1)	7(1)
O(1)	49(2)	28(2)	29(2)	0(1)	7(2)	-6(2)
O(2)	68(3)	29(2)	33(2)	-4(1)	-2(2)	6(2)
O(3)	86(3)	41(2)	25(2)	3(1)	-1(2)	14(2)
O(4)	55(2)	24(2)	45(2)	-9(2)	1(2)	3(2)
O(5)	55(2)	28(2)	45(2)	5(2)	-10(2)	12(2)
N(1)	29(2)	20(2)	27(2)	2(2)	-2(1)	2(2)
N(2)	38(2)	21(2)	22(2)	-1(2)	2(2)	2(2)
N(3)	38(2)	37(2)	26(2)	2(2)	1(2)	5(2)
N(4)	32(2)	20(2)	42(2)	-1(2)	3(2)	-1(2)
C(1)	43(2)	25(2)	30(2)	-3(2)	-3(2)	-2(2)
C(2)	49(3)	45(3)	30(2)	2(2)	0(2)	-6(2)
C(3)	38(3)	41(3)	29(2)	-12(2)	2(2)	-7(2)
C(4)	41(3)	32(2)	36(2)	-10(2)	-1(2)	-10(2)
C(5)	25(2)	27(2)	34(2)	-5(2)	3(2)	-4(2)
C(6)	27(2)	25(2)	23(2)	-6(2)	-1(2)	-2(2)
C(7)	26(2)	22(2)	31(2)	-2(2)	3(2)	2(2)
C(8)	27(2)	20(2)	27(2)	2(2)	-1(2)	4(2)
C(9)	30(2)	25(2)	34(3)	-4(2)	6(2)	-4(2)
C(10)	32(2)	48(3)	45(3)	-14(2)	10(2)	-9(2)
C(11)	24(2)	43(3)	43(3)	-9(2)	0(2)	-3(2)
C(12)	22(2)	29(2)	37(2)	-6(2)	0(2)	3(2)
C(13)	24(2)	23(2)	26(2)	-3(2)	-1(2)	4(2)
C(14)	26(2)	22(2)	26(2)	-6(2)	-3(2)	2(2)
C(15)	19(2)	26(2)	29(2)	1(2)	0(2)	-4(2)
C(16)	19(2)	22(2)	31(2)	-3(2)	-2(2)	3(2)
C(17)	32(2)	20(2)	39(3)	-2(2)	-4(2)	1(2)
C(18)	38(2)	22(2)	45(3)	4(2)	0(2)	5(2)

C(19)	27(2)	34(2)	29(2)	7(2)	-2(2)	8(2)
C(20)	34(2)	30(2)	30(2)	-3(2)	0(2)	0(2)
C(21)	30(2)	22(2)	31(2)	-1(2)	-3(2)	-1(2)
C(22)	22(2)	21(2)	24(2)	2(2)	1(2)	-1(2)
C(23)	29(2)	26(2)	27(2)	-2(2)	3(2)	-3(2)
C(24)	30(2)	25(2)	25(2)	4(2)	2(2)	1(2)
C(25)	21(2)	24(2)	32(2)	1(2)	0(2)	2(2)
C(26)	34(2)	24(2)	26(2)	-3(2)	2(2)	-3(2)
C(27)	34(2)	23(2)	21(2)	1(2)	-3(2)	3(2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$).

	x	y	z	U(eq)
H(2)	7640(70)	12960(40)	6587(15)	30(14)
H(1A)	9309	10198	5523	39
H(2A)	9146	9542	4857	50
H(4A)	8633	6344	5262	44
H(5A)	8794	7001	5928	35
H(9A)	12230	9791	5851	36
H(10A)	13693	11587	6068	50
H(10B)	14882	10489	6167	50
H(11A)	14474	11779	6739	44
H(11B)	14004	10488	6835	44
H(12A)	11658	11737	7074	35
H(12B)	11298	12130	6618	35
H(13A)	10603	9948	6949	29
H(14A)	8077	11382	6526	30
H(14B)	7562	10281	6781	30
H(17A)	7720	9528	7379	36
H(18A)	7861	8756	8018	42
H(20A)	9213	11779	8486	37
H(21A)	9088	12567	7840	33
H(24A)	5613	16403	6177	32
H(26A)	6159	16479	7392	34

Figure 1. X-ray crystal structure for compound **18**.

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