Supporting Information

Enantioselective 1,3-Dipolar Cycloadditions of Diazoacetates with Electron-Deficient Olefins

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Characterization Data and Experimental Procedures:

α,β-unsaturated pyrazolidinone imides 1a-h, 5a-b, 7	S-2 to S-6
pyrazoline cycloadducts 3a-k, 6a-b, 8	S-6 to S-13
synthesis of manzacidin A	S-13 to S-15

General: Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Magnesium perchlorate and magnesium iodide were purchased from Aldrich. Magnesium triflimide was prepared according to literature procedure.¹ Cyclopropyl bisoxazoline ligand {3aR-[2(3'aS, 8'aR), 3aa, 8aa]}-2,2'-(cyclopropylidene)-bis{3a,8a-dihydro-8H-indeno[1,2d]-oxazole} (**4**) was prepared according to literature procedure.² Ethyl diazoacetate (**2a**) and *t*-butyl diazoacetate (**2b**) were purchased from Aldrich. Benzyl diazoacetate (**2c**) and phenyl diazoacetate (**2d**) were prepared according to literature procedure.³ Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCOTM CombiFlash Companion with AnaLogixTM RS-4 columns. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques. Molecular sieves were dried under vacuum prior to use.

¹ Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879-2882. Mg(NTf₂)₂ was prepared in similar manner as Zn(NTf₂)₂, except that Mg(OH)₂ instead of zinc powder. Ratio of bistrifluoromethanesulfonimide to Mg(OH)₂ was 2:1.

² Barnes, D. M.; Ji, Jianguo; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097-13105.

³ Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170-6171.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected. ^1H -NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual CDCl_3 (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C -NMR was recorded on Varian Unity/Inova-500 NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300 (75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl_3 (77.23) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower workstation. Rotations were recorded on a JASCO-DIP-370 instrument. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High Resolution Mass Spectra (HRMS) (ESI+) were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

General procedure for *N*(2)-acylation of pyrazolidinones (synthesis of α,β -unsaturated pyrazolidinone imides **1a-h, **5a-b**, **7**):**

To a solution of the appropriate α,β -unsaturated acid in a minimal volume of dichloromethane at 0°C , under nitrogen, was added oxalyl chloride (1.1 equiv) followed by one drop of DMF. After 10 minutes the solution was allowed to warm to room temperature and stir for two hours. The solvent and excess oxalyl chloride were removed *in vacuo* to give crude acid chloride, which was used without further purification.

In a separate flask, to a stirred solution of the appropriate pyrazolidinone in dry THF (0.3 M) at $-78\text{ }^{\circ}\text{C}$ was added 1.0 equiv of *n*-BuLi. After 30 minutes, 1.1 equiv of the appropriate acid chloride was added. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2-3 hours until the reaction was complete (TLC). The reaction was quenched with saturated aqueous ammonium chloride and THF was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. Crude products were purified by flash column chromatography or recrystallization. Average yields are 85-90%.

1-Benzyl-2-[(*E*)-2-butenoyl]-5,5-dimethyl-pyrazolidin-3-one (1a):

This compound has been previously prepared and characterized.⁴ mp $98-101\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz) δ 1.31 (s, 6H), 1.85 (dd, $J = 6.9, 1.5\text{ Hz}$, 3H), 2.56 (s, 2H), 4.08 (s, 2H), 6.83 (d, $J = 15.3\text{ Hz}$, 1H), 6.93-6.98 (m, 1H), 7.24-7.32 (m, 3H), 7.40-7.41 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 18.7, 26.4, 44.0, 57.2, 61.1, 123.0, 127.9, 128.6, 129.9, 137.3, 145.8, 163.5, 174.7; Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2$: C, 70.56; H, 7.40, N, 10.29. Found: C, 70.53; H, 7.24; N, 10.68.

2-Acryloyl-1-benzyl-5,5-dimethyl-pyrazolidin-3-one (1b):

The method of Ho and Mathre was employed.⁵ This compound has been previously prepared and characterized.⁶ White solid; mp $82-83\text{ }^{\circ}\text{C}$ (Hexane-Ethyl Acetate); ^1H NMR (CDCl_3 , 400 MHz) δ 1.26 (s, 6H), 2.54 (s, 2H), 4.04 (s, 2H), 5.65 (dd, $J = 10.4, 1.6\text{ Hz}$, 1H), 6.32 (dd, $J = 17.2, 1.6\text{ Hz}$, 1H), 7.05 (dd, $J = 17.2, 10.4$, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.3, 43.7, 57.2, 61.2, 127.8, 128.4, 128.6, 129.8, 130.9, 137.1, 163.2, 174.6; HRMS calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}^+$ 281.1260 found 281.1274.

⁴ Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444.

⁵ Ho, G. J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

⁶ Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718.

(1c): Yellow solid; mp 127-130 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 1.32 (s, 6H), 1.46 (s, 9H), 2.59 (s, 2H), 3.97 (s, 2H), 6.39 (d, J = 16.0 Hz, 1H), 7.20-7.32 (m, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.2, 28.1, 43.1, 57.6, 61.7, 81.6, 128.1, 128.7, 130.6, 132.3, 134.2, 136.1, 162.6, 164.4, 174.1; IR (neat) 2977, 2932, 1751, 1716, 1683, 1313, 1229, 1152, 978 cm^{-1} ; HRMS calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4\text{Na}^+$ 381.1785 found 381.1781.

1-Benzyl-5,5-dimethyl-2-[(E)-2-penten-1-yl]-pyrazolidin-3-one

(1d): This compound has been previously prepared and characterized.⁶ White solid; yield; mp 81-83 °C (Hexane-Ethyl Acetate); ^1H NMR (CDCl_3 , 400 MHz) δ 1.01 (t, J = 6.8 Hz, 3H), 1.26 (s, 6H), 2.16 (m, 2H), 2.53 (s, 2H), 4.04 (s, 2H), 6.76 (d, J = 15.2 Hz, 1H), 6.97 (dt, J = 15.2, 6.4 Hz, 1H), 7.21-7.38 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 12.4, 25.9, 26.3, 43.9, 57.2, 61.1, 120.6, 127.8, 128.6, 129.8, 137.3, 152.0, 163.7, 174.6; HRMS calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}^+$ 309.1573 found 309.1559.

(1e): White solid; mp 83-85 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 1.00 (d, J = 6.8 Hz, 6H), 1.26 (s, 2H), 2.40 (dsept, J = 1.6, 6.8 Hz, 1H), 4.04 (s, 2H), 6.73 (d, J = 15.6 Hz, 1H), 6.91 (dd, J = 15.6, 6.8 Hz, 1H), 7.19-7.28 (m, 3H), 7.35-7.38 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.5, 26.3, 31.5, 43.9, 57.3, 61.1, 118.8, 127.7, 128.6, 129.8, 137.3, 156.8, 163.8, 174.5; IR (neat) 2966, 2930, 1746, 1679, 1372, 1228 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}^+$ 323.1735 found 323.1731.

(1f): White solid; mp 81-83 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 1.25 (s, 6H), 2.53 (s, 2H), 3.47 (d, J = 6.8 Hz, 2H), 4.03 (s, 2H), 6.82 (d, J = 15.2 Hz, 1H), 7.05 (dt, J = 15.2, 6.8 Hz, 1H), 7.11-7.14 (m, 2H), 7.18-7.35 (m, 8H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.3, 39.0, 43.9, 57.3, 61.2, 122.6, 126.8, 127.8, 128.6, 128.8, 129.0, 129.8, 137.2, 138.1, 148.3, 163.3, 174.5; IR (neat) 3027, 2973, 2931, 1742, 1683, 1635, 1373, 1233, 1029, 730 cm^{-1} ; HRMS calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}^+$ 371.1735 found 371.1735.

(1g): White solid; mp 66-67 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 0.80-1.20 (m, 5H), 1.24 (s, 6H), 1.29-1.68 (m, 6H), 2.03 (t, J = 7.2 Hz, 2H), 2.51 (s, 2H), 4.03 (s, 2H), 6.78 (d, J = 15.6 Hz, 1H), 6.93 (dt, J = 15.6, 7.2 Hz, 1H), 7.17-7.28 (m, 3H), 7.34-7.41 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.2, 26.3, 26.5, 33.3, 37.5, 40.6, 43.9, 57.1, 61.0, 122.3, 127.6, 128.5, 129.7, 137.3, 149.7, 163.3, 174.4; IR (neat) 2972, 2923, 2850, 1743, 1685, 1635, 1449, 1318, 1234, 1030, 432, 698 cm^{-1} ; HRMS calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}^+$ 377.2199 found 377.2206.

1-Benzyl-2-(3-phenyl-acryloyl)-5,5-dimethyl-pyrazolidin-3-one

(1h): This compound has been previously prepared and characterized.⁷ mp 105-107 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 1.33 (s, 6H), 2.60 (s, 2H), 4.10 (s, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.3 Hz, 2H), 7.34-7.43 (m, 6H), 7.50-7.51 (m, 2H), 7.62 (d, J = 15.8 Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.3, 44.0, 57.3, 61.3, 118.4, 128.0, 128.6, 128.7, 129.0, 130.0, 130.5, 135.1, 137.0, 145.3, 163.8, 174.7; Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.15; H, 6.79; N, 8.19.

1-Benzyl-5,5-dimethyl-(E-2-methylbut-2-enoyl)-pyrazolidin-3-one

(5a): This compound has been previously prepared and characterized.⁸ White solid; mp 90-92 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.31 (s, 6H), 1.67 (dd, J = 7.0, 1.0 Hz, 3H), 1.71 (t, J = 1.5 Hz, 3H), 2.59 (s, 2H), 4.07 (s, 2H), 5.98 (dq, J = 1.5 Hz, 7.0 Hz, 1H), 7.21-7.29 (m, 3H), 7.37 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.3, 14.1, 26.3, 43.5, 57.9, 61.6, 127.7, 128.4, 129.7, 132.8, 134.1, 137.1, 169.5, 174.0; HRMS Exact mass calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}^+$ 309.1573 found 309.1589.

⁷ Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, 3, 4181

⁸ Sibi, M. P.; Stanley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, 348, 2371-2374.

(5b): This compound has been previously prepared and characterized.⁸ White solid; mp 120-122 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.35 (s, 6H), 1.81 (quintet, *J* = 7.5 Hz, 2H), 2.35-2.44 (m, 4H), 2.58 (s, 2H), 4.02 (s, 2H), 6.36 (t, *J* = 2.0 Hz, 1H), 7.21-7.35 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 23.1, 26.4, 32.9, 33.6, 43.3, 58.2, 61.7, 127.9, 128.5, 130.4, 136.5, 138.8, 142.3, 165.2, 174.0; HRMS Exact mass calcd. for C₁₈H₂₂N₂O₂Na⁺ 321.1573 found 321.1587.

1-Benzyl-5,5-dimethyl-(2-methylpropenyl)-pyrazolidin-3-one (7):

This compound has been previously prepared and characterized.⁸ White solid; mp 103-105 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.30 (s, 6H), 1.86 (s, 3H), 2.58 (s, 2H), 4.07 (s, 2H), 5.23 (d, *J* = 4 Hz, 2H), 7.22-7.29 (m, 3H), 7.39 (d, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 19.3, 26.3, 43.3, 57.7, 61.6, 120.3, 127.8, 128.4, 129.7, 137.0, 140.7, 168.4, 174.0; HRMS Exact mass calcd. for C₁₆H₂₀N₂O₂Na⁺ 295.1417 found 295.1424.

General Procedure for Low-Temperature Enantioselective 1,3-Dipolar Cycloadditions of Diazoesters with α,β -Unsaturated Pyrazolidinone Imides (Table 1, Entries 1-12; Table 2, Entries 1-9, Scheme 2, 7→8, reactions run at –20 °C, 0 °C, or rt): A 6-dram vial containing 4 Å molecular sieves (100 mg), Lewis acid (0.020-0.060 mmol), ligand **6** (0.022-0.066 mmol), and the appropriate α,β -unsaturated pyrazolidinone imide **1a-g** or **7** (0.2 mmol) in CH₂Cl₂ (2 mL) was stirred for 30 minutes at room temperature under nitrogen. The flask was then cooled to the appropriate temperature and stirred for 5 minutes. Then diazoacetate **2a-d** (0.3 mmol) in CH₂Cl₂ (1 mL) was added to the reaction. The reaction was stirred at the appropriate temperature for 24-48 h until the

dipolarophile had been consumed (TLC). The reaction mixture was then filtered through a pad of celite and rinsed with CH₂Cl₂ (2 x 10 mL). Silica gel (2 g) was added to the diluted reaction mixture and the solvent was removed *in vacuo*. Cycloadducts were purified by flash column silica gel chromatography on an ISCO™ CombiFlash Companion with AnaLogix™ RS-4 columns.

General Procedure for High-Temperature Enantioselective 1,3-Dipolar Cycloadditions of Ethyl Diazoacetate with α,β -Unsaturated Pyrazolidinone Imides (Table 2, Entry 10; Table 3, Entries 1-5, reactions run at 40 or 50 °C): A 15-mL heavy wall pressure vessel with threaded Teflon bushing containing 4 Å molecular sieves (100 mg), Lewis acid (0.060-0.20 mmol), ligand **6** (0.066-0.22 mmol), and the appropriate α,β -unsaturated pyrazolidinone imide **1h** or **5a-b** (0.2 mmol) in CH₂Cl₂ (2 mL) was stirred for 30 minutes at room temperature. Then ethyl diazoacetate **2a** (0.3 mmol) in CH₂Cl₂ (1 mL) was added to the reaction. The vessel was sealed and heated to the appropriate temperature for 24-48 h. The reaction mixture was allowed to cool to rt, then filtered through a pad of celite and rinsed with CH₂Cl₂ (2 x 10 mL). Silica gel (2 g) was added to the diluted reaction mixture and the solvent was removed *in vacuo*. Cycloadducts were purified by flash column silica gel chromatography on an ISCO™ CombiFlash Companion with AnaLogix™ RS-4 columns.

(3a): White foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) *t_R* 32.9 min (minor); *t_R* 44.9 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99%

ee. $[\alpha]_D^{25} = -212.8$ (*c* 0.50, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.26 (s, 3H), 1.31, (s, 3H), 1.35 (m, 6H), 2.59 (d, *J* = 17.5 Hz, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 3.39 (m, 1H),

3.98 (d, $J = 13.5$ Hz, 1H), 4.08 (d, $J = 13.5$ Hz, 1H), 4.29 (m, 2H), 4.56 (s, 1H), 6.64 (s, 1H), 7.22-7.29 (m, 3H), 7.37 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 17.2, 26.3, 26.4, 43.3, 43.5, 57.1, 61.3, 61.8, 70.9, 127.9, 128.6, 129.6, 136.8, 147.0, 162.1, 167.8, 175.3; IR (neat) 3349, 2979, 2933, 1748, 1700, 1588, 1453, 1369, 1327, 1093, 771 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_4\text{Na}^+$ 409.1846 found 409.1850.

(3b): White foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 16.6 min (major); t_R 19.8 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99%

ee. $[\alpha]_D^{25} = -149.3$ (c 0.53, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.24 (s, 3H), 1.28 (s, 3H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.51 (s, 9H), 2.55 (d, $J = 17.2$ Hz, 1H), 2.63 (d, $J = 17.2$ Hz, 1H), 3.37 (dq, $J = 5.2$ Hz, 7.2 Hz, 1H), 3.97 (d, $J = 13.2$ Hz, 1H), 4.06 (d, $J = 17.2$ Hz, 1H), 4.50 (br s, 1H), 6.54 (s, 1H), 7.18-7.28 (m, 3H), 7.34-7.37 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.2, 26.4, 28.2, 28.3, 43.4, 43.5, 57.0, 61.7, 70.9, 82.0, 127.9, 128.6, 129.5, 136.9, 148.5, 161.3, 167.8, 175.2; IR (neat) 3351, 2979, 2934, 1751, 1700, 1575, 1352, 1235, 1195, 736 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}^+$ 437.2159 found 437.2141.

(3c): White foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 20.7 min (minor); t_R 29.4 min (major) [Chiracel AS-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25} =$

-133.1 (c 0.52, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.24 (s, 3H), 1.28 (s, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 2.56 (d, $J = 17.2$ Hz, 1H), 2.65 (d, $J = 17.2$ Hz, 1H), 3.36 (dq, $J = 5.0$ Hz, 6.8 Hz, 1H), 3.93 (d, $J = 13.2$ Hz, 1H), 4.04 (d, $J = 13.2$ Hz, 1H), 4.48 (br s, 1H), 5.20 (d, $J = 12.4$ Hz, 1H), 5.27 (d, $J = 12.4$ Hz, 1H), 6.71 (br s, 1H), 7.11-7.24 (m, 3H), 7.27-7.39 (m, 7H); ^{13}C NMR (125 MHz, CDCl_3) δ 17.2, 26.2, 26.4, 43.2 (2C), 57.1, 61.9, 67.0, 70.9, 128.0, 128.5, 128.7 (2C), 128.8, 129.6, 135.6, 136.6, 146.3, 162.0, 168.0, 175.5; IR (neat) 3361, 3063, 3033, 2977, 2934, 1749, 1700, 1569, 1455, 1349, 1092, 734 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_4\text{Na}^+$ 471.2003 found 471.2011.

(3d): White foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 22.1 min (minor); t_R 32.8 min (major) [Chiracel AS-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 1.0 mL/min] as 86%

ee. $[\alpha]_D^{25} = -184.8$ (*c* 0.54, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.31 (s, 3H), 1.35 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 2.64 (d, *J* = 17.5 Hz, 1H), 2.72 (d, *J* = 17.5 Hz, 1H), 3.52 (dq, *J* = 5.0, 7.0 Hz, 1H), 4.02 (d, *J* = 13.5 Hz, 1H), 4.12 (d, *J* = 13.5 Hz, 1H), 4.62 (br s, 1H), 6.86 (br s, 1H), 7.18-7.43 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 17.2, 26.2, 26.4, 43.1, 43.2, 57.2, 61.9, 71.0, 121.8, 126.1, 128.0, 128.7, 129.6, 129.7, 136.6, 145.6, 150.6, 160.6, 167.8, 175.5; IR (neat) 3364, 3062, 2978, 2934, 1749, 1716, 1592, 1351, 1194, 1061, 773 cm⁻¹; HRMS Exact mass calcd. for C₂₄H₂₆N₄O₄Na⁺ 457.1846 found 457.1852.

(3e): Colorless glassy solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 48.8 min (minor); t_R 58.9 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0

mL/min] as 97% ee. $[\alpha]_D^{25} = -110.3$ (*c* 0.52, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.29 (s, 3H), 1.31 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 2.59 (d, *J* = 17.5 Hz, 1H), 2.65 (d, *J* = 17.5 Hz, 1H), 3.20 (d, *J* = 10.0 Hz, 2H), 4.03 (d, *J* = 13.5 Hz, 1H), 4.10 (d, *J* = 13.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 5.01 (t, *J* = 10.0 Hz, 1H), 6.73 (s, 1H), 7.23-7.31 (m, 3H), 7.39 (d, *J* = 7.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.5, 26.2, 26.4, 35.0, 57.0, 61.4, 61.7, 63.6, 128.0, 128.6, 129.6, 136.8, 143.4, 162.2, 167.5, 175.2; IR (neat) 3356, 3062, 2982, 2937, 1756, 1716, 1576, 1351, 1060, 737 cm⁻¹; HRMS Exact mass calcd. for C₁₉H₂₄N₄O₄Na⁺ 395.1690 found 395.1688.

(3f): White foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 44.0 min (minor); t_R 47.8 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99%

ee. $[\alpha]_D^{25} = -202.2$ (*c* 1.02, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.31 (s, 3H), 1.32 (s,

3H), 1.36 (t, $J = 7.0$ Hz, 3H), 1.48 (s, 9H), 2.63 (app s, 2H), 4.09 (app s, 2H), 4.29-4.35 (m, 2H), 4.41 (d, $J = 4.5$ Hz, 1H), 5.25 (br s, 1H), 6.80 (br s, 1H), 7.24-7.32 (m, 3H), 7.41 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 26.1, 26.6, 28.1, 43.5, 53.3, 56.9, 61.4, 61.8, 68.3, 82.6, 128.0, 128.7, 129.6, 136.9, 140.8, 161.5, 165.4, 168.5, 175.3; IR (neat) 3350, 2979, 2933, 1760, 1716, 1567, 1392, 1234, 1158, 734 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_6\text{Na}^+$ 495.2214 found 495.2119.

(3g): Tan foam; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 36.9 min (minor); t_R 43.1 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99%

ee. $[\alpha]_D^{25} = -163.2$ (c 0.41, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 0.80 (t, $J = 7.6$ Hz, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.31 (app t, $J = 5.2$ Hz, 3H), 1.63-1.86 (m, 2H), 2.59 (d, $J = 17.2$ Hz, 1H), 2.66 (d, $J = 17.2$ Hz, 1H), 3.51 (app q, $J = 5.2$ Hz, 1H), 3.99 (d, $J = 13.6$ Hz, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 4.20-4.30 (m, 2H), 4.46 (br s, 1H), 6.62 (br s, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 10.3, 14.4, 26.3, 26.4, 43.4, 48.5, 57.4, 61.4, 61.0, 68.5, 128.2, 128.8, 129.8, 136.8, 145.2, 162.6, 168.3, 175.7; IR (neat) 3356, 2972, 2934, 1750, 1701, 1568, 1349, 1233, 1103, 733 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}^+$ 309.1573 found 309.1580.

(3h): White amorphous solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 46.0 min (minor); t_R 49.1 min (major) [Chiracel OD-H (1.0 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0

mL/min] as 96% ee. $[\alpha]_D^{25} = -203.8$ (c 0.21, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 0.75 (d, $J = 6.5$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H), 1.33 (s, 3H), 1.34-1.36 (m, 6H, $\text{CH}_3 + \text{CO}_2\text{CH}_2\text{CH}_3$), 2.43 (br s, 1H), 2.61 (d, $J = 17.5$ Hz, 1H), 2.69 (d, $J = 17.5$ Hz, 1H), 3.77 (s, 1H), 4.04 (d, $J = 13.5$ Hz, 1H), 4.13 (d, $J = 13.5$ Hz, 1H), 4.23-4.35 (m, 2H), 4.55 (br s, 1H), 6.77 (br s, 1H), 7.27-7.34 (m, 3H), 7.41 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 18.2, 19.9, 25.8, 26.8, 28.3, 43.4, 52.1, 57.2, 61.4, 62.0, 65.0, 128.2, 128.9, 129.8, 136.7, 144.3, 162.8, 167.5, 175.9; IR (neat) 3379, 2965, 2933, 1749, 1700,

1568, 1351, 1135, 1060, 773 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}^+$ 437.2159 found 437.2171.

(3i): White amorphous solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 52.6 min (major); t_R 58.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 95% ee. $[\alpha]_D^{25} = -203.2$ (c 0.51, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 1.21 (s, 3H), 1.24 (s, 3H), 1.33 (t, $J = 7.0$ Hz, 1H), 2.55 (m, 2H), 2.89 (dd, $J = 13.5, 8.0$ Hz, 1H), 3.28 (br d, $J = 10.5$ Hz, 1H), 3.98 (m, 3H), 4.22-4.32 (m, 2H), 4.69 (br s, 1H), 6.63 (br s, 1H), 7.16 (d, $J = 7.5$ Hz, 2H), 7.2 (t, $J = 7.5$ Hz, 1H), 7.25-7.34 (m, 7H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 26.2, 26.4, 37.2, 43.6, 48.3, 56.8, 61.3, 61.7, 68.2, 126.9, 128.0, 128.69, 128.72, 129.5, 129.6, 136.9, 137.9, 145.0, 162.4, 166.9, 175.5; IR (neat) 3372, 3059, 3029, 2982, 1749, 1705, 1570, 1465, 1349, 1265, 1223, 1198, 1123, 737, 702 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}^+$ 485.2159 found 485.2174.

(3j): Colorless glassy solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 24.6 min (minor); t_R 36.0 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 90% ee. $[\alpha]_D^{25} = -164.5$ (c 0.726, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 0.89-0.96 (m, 2H), 1.14-1.25 (m, 5H), 1.30-1.42 (m, 9H), 1.62-1.84 (m, 6H), 2.57 (d, $J = 17.5$ Hz, 1H), 2.65 (d, $J = 17.5$ Hz, 1H), 3.79 (m, 1H), 4.06 (d, $J = 14.0$ Hz, 1H), 4.12 (d, $J = 14.0$ Hz, 1H), 4.61 (br s, 1H), 6.77 (br s, 1H), 7.25-7.44 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 26.3, 26.4, 26.6, 32.8, 33.9, 35.3, 39.5, 43.5, 44.5, 56.9, 61.3, 61.8, 70.0, 128.0, 128.7, 129.7, 136.7, 146.5, 162.4, 167.1, 175.6; IR (neat) 3353, 2978, 2924, 2850, 1750, 1706, 1566, 1464, 1390, 1233, 1196, 1120, 735 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}^+$ 491.2629 found 491.2639.

(3k): White amorphous solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 56.8 min (major); t_R 64.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0

mL/min] as 90% ee. $[\alpha]_D^{25} = -323.4$ (c 0.42, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 1.21-1.24 (m, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 2.59 (d, $J = 17.5$ Hz, 1H), 2.63 (d, $J = 17.5$ Hz, 1H), 4.09 (s, 2H), 4.13-4.25 (m, 2H), 4.78 (d, $J = 6.5$ Hz, 1H), 4.92 (br s, 1H), 6.80 (br s, 1H), 7.23-7.40 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.2, 25.6, 26.3, 43.6, 52.7, 57.0, 61.2, 61.8, 72.8, 127.7, 128.0, 128.2, 128.7, 129.0, 129.6, 136.9, 140.1, 145.7, 161.7, 166.2, 175.2; IR (neat) 3355, 3062, 3031, 2981, 2933, 1753, 1704, 1584, 1495, 1333, 1230, 1195, 1111, 736 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_4\text{Na}^+$ 471.2003 found 471.1975.

(6a): White amorphous solid. The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 20.5 min (minor); t_R 32.5 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0

mL/min] as 96% ee. $[\alpha]_D^{25} -18.2$ (c 0.69, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ ; 1.18 (d, $J = 7.2$ Hz, 3H), 1.23 (s, 3H), 1.25 (s, 3H), 1.32 (t, $J = 7.6$ Hz, 3H), 1.35 (s, 3H), 2.56 (d, $J = 16.8$ Hz, 1H), 2.71 (d, $J = 16.8$ Hz, 1H), 3.34 (q, $J = 7.2$ Hz, 1H), 3.96 (d, $J = 13.2$ Hz, 1H), 4.03 (d, $J = 13.2$ Hz, 1H), 4.25 (m, 2H), 7.18-7.42 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ ; 11.7, 14.4, 16.2, 25.9, 2.6, 44.0, 44.7, 57.1, 61.1, 61.6, 74.8, 127.8, 128.5, 129.6, 136.9, 146.1, 162.5, 171.9, 175.1. IR (KBr): 3360, 3140, 2985, 2940, 1720, 1700, 1571, 1340, 737 cm^{-1} . HRMS Exact mass calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_4\text{Na}^+$ 423.2008. found 423.1994.

(6b): White amorphous solid. The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 26.6 min (minor); t_R 31.8 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 1.0

mL/min] as 99% ee. $[\alpha]_D^{25} -10.3$ (c 0.76, benzene); ^1H NMR (CDCl_3 , 400 MHz) δ ; 1.22

(s, 3H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.32 (s, 3H), 1.45 (m, 1H), 1.64 (m, 1H), 1.90 (m, 1H), 2.18 (m, 1H), 2.48 (d, $J = 16.8$ Hz, 1H), 2.89 (d, $J = 16.8$ Hz, 1H), 3.78 (m, 1H), 3.85 (d, $J = 13.2$ Hz, 1H), 4.11 (d, $J = 13.2$ Hz, 1H), 4.27 (m, 2H), 7.13-7.31 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.5, 25.0, 25.5, 25.6, 27.3, 32.9, 41.2, 43.9, 54.8, 57.2, 60.9, 61.6, 82.4, 127.7, 128.5, 129.9, 365, 142.6, 162.6, 169.9, 175.2. IR (KBr): 3406, 3020, 2980, 2934, 1735, 1710, 1340, 735 cm^{-1} . HRMS Exact mass calcd. for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_4\text{Na}^+$ 435.2008 found 435.2019.

(8): White glassy solid; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 23.9 min (minor); t_R 28.6 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99%

ee. $[\alpha]_D^{25} = -114.2$ (c 0.50, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 1.29 (s, 3H), 1.35 (s, 3H), 1.36 (t, $J = 7.0$ Hz, 3H), 1.48 (s, 3H), 2.58 (d, $J = 17.0$ Hz, 1H), 2.76 (d, $J = 18.0$ Hz, 1H), 2.84 (d, $J = 17.0$ Hz, 1H), 3.13 (d, $J = 18.0$ Hz, 1H), 3.97 (d, $J = 13.0$ Hz, 1H), 4.13 (d, $J = 13.0$ Hz, 1H), 4.31 (q, $J = 7.0$ Hz, 2H), 7.19-7.29 (m, 3H), 7.38 (d, $J = 7.0$ Hz, 2H), 7.48 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.5, 23.1, 25.4, 27.0, 43.0, 44.0, 57.2, 61.2, 61.7, 72.9, 127.8, 128.4, 130.0, 136.5, 141.4, 162.5, 170.6, 175.1; IR (neat) 3385, 3061, 2979, 2933, 1739, 1701, 1570, 1412, 1246, 1122, 735 cm^{-1} ; HRMS Exact mass calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_4\text{Na}^+$ 409.1846 found 409.1836.

To a stirred suspension of NaBH_4 (80 mg, 2.1 mmol) in THF (5 mL) at -78 °C, was added a solution of **8** (204 mg, 0.53 mmol) in THF (3 mL) dropwise. The reaction was allowed to stir at -78 °C for 30 min, then slowly allowed to warm to rt. After the temperature of the reaction had reached rt, the reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was eluted through a short column of silica gel (hexane/ethyl acetate 1:4) to yield a mixture of

the desired amino alcohol and pyrazolidinone auxiliary. To this mixture was added methyl orthoformate (4.0 mL) and a catalytic amount of pyridinium *p*-toluenesulfonate (0.008 g, 0.032 mmol). After 2h the reaction was quenched with aqueous NaHCO₃ and extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column silica gel chromatography to give **9** as a colorless oil (0.723 g, 0.317 mmol, 60% yield).

(9): This compound has been previously prepared and characterized.⁹ Colorless oil; $[\alpha]_D^{25} = -530.2$ (*c* 1.12, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.35 (t, *J* = 7.0 Hz, 3H), 1.58 (s, 3H), 2.90 (d, *J* = 18.0 Hz, 1H), 3.17 (d, *J* = 18.0 Hz, 1H), 3.43 (s, 3H), 3.80 (d, *J* = 8.5 Hz, 1H), 3.93 (d, *J* = 8.5 Hz, 1H), 4.32 (m, 2H), 5.95 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 26.0, 45.6, 53.9, 62.0, 70.1, 76.7, 113.1, 148.6, 161.8; HRMS Exact mass calcd. for C₁₀H₁₆N₂O₄Na⁺ 251.1002 found 251.0993.

Manzacin A was prepared according to a modified literature procedures.^{9,10} To a solution of **9** (41 mg, 0.18 mmol) in isopropanol/H₂O (1.5 mL/0.5 mL) was added Raney 2400 nickel (57 mg, purchased from Aldrich). *Note: It was imperative for us to wash the Raney nickel 4-6 times with isopropanol for reduction of the desired imine functionality and N-N bond cleavage to proceed.* A hydrogen balloon was then added to the flask and the mixture heated to 80 °C. The reaction was heated overnight at the given temperature, then filtered through celite, and washed with methanol (*Caution: avoid allowing the celite pad to dry out as the Raney nickel is sufficiently active to catch fire*). After concentration the residue was eluted through a column of Dowex 50 x 8 (100-200 mesh, H⁺ form) with H₂O, then 1N aqueous NH₃, providing the crude intermediate

⁹ Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174-2175.

¹⁰ Namba, K.; Shinada, T.; Teramoto, T.; Ohfuné, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708-10709.

tetrahydropyrimidine, which was used without further purification.

To the intermediate tetrahydropyrimidine in DMF (5 mL) was added NaH (60% dispersion in mineral oil, 14.4 mg, 0.36 mmol) at room temperature. After 15 minutes 4-Br-2-trichloroacetylpyrrole (126 mg, 0.43 mmol) was added to the reaction. The mixture was stirred at rt for 4 h, quenched with 2N HCl, and extracted with EtOAc. The aqueous layer was concentrated and purified by reverse-phase silica gel flash column chromatography on an ISCOTM CombiFlash Companion with an AnaLogixTM Septra C-18 column to provide 34.1 mg (0.099 mmol) an 85:15 mixture of **10**:**11**. A sample of manzaccin A was isolated by reverse phase HPLC (cosmosil 5C-18-AR-II, H₂O/MeCN/TFA, 75:25:0.1).

(10): This compound has been previously prepared and characterized.^{9,10,11} $[\alpha]_D^{25} = -26.3$ (*c* 0.30, MeOH); ¹H NMR (CDCl₃, 500 MHz) δ 1.47 (s, 3H), 2.23 (dd, *J* = 14.0, 10.0

Hz, 1H), 2.38 (dd, *J* = 14.0, 5.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.48 (dd, *J* = 10.0, 5.0 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 8.07 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 24.3, 31.1, 54.1, 69.1, 98.3, 118.7, 123.5, 125.4, 151.7, 160.8, 173.7; HRMS Exact mass calcd. for C₁₂H₁₄BrN₃O₄Na⁺ 366.0060 found 366.0041.

¹¹ (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3929. (b) When, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950-12951.