A General Synthesis of Substituted Formylpyrroles from Ketones and 4-Formyloxazole

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General. Reagents and solvents were used as received from commercial sources. Reactions were conducted under an atmosphere of dry N₂. Reaction temperatures refer to internal temperatures unless noted otherwise. HPLC analyses were performed on a 4.6 mm x 10 cm column with particle size of 2 micron, wavelength 220 nm and 254 nm, at 25 °C. Mobile phases are A: water with 0.05% TFA, B: MeCN with 0.05% TFA. Gradient conditions are 90% A to 10% A in 15 min, hold 5 min, back to 90% A followed by a 3-min post run. ¹H and ¹³C NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer at 400 and 100 MHz, respectively. Melting points were measured using a Mel-Temp 3.0 melting point apparatus and are uncorrected. IR spectra were recorded neat using an Omnic IR spectrometer.

4-Formyloxazole (2). A solution of ethyl 4-oxazolecarboxylate (22.1 g, 156.6 mmol) in CH₂Cl₂ (300 mL) was treated at -70 °C with DIBALH (55.8 mL, 313.2 mmol) over 20 min. The reaction mixture was aged at -70 °C until HPLC analysis indicated consumption of starting ethyl ester (15-30 min). The reaction mixture was quenched with MeOH (50 mL), warmed to rt, and poured into 2 N aq. HCl. The layers were separated and the aqueous phase extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered through a short pad of SiO₂, and concentrated on a rotary evaporator at a bath temperature of 5-10 °C to give crude **2**. Recrystallization from CH₂Cl₂/hexanes gave 9.71 g of **2** as a white solid (64%). Mp (CH₂Cl₂/hexanes) 59-61 °C; IR 3133, 3080, 2843, 1691, 1561, 1519 cm⁻¹; ¹H NMR (CDCl₃) δ 9.96 (s, 1 H), 8.32 (d, 1 H, *J* = 0.9 Hz), 7.98 (s, 1 H); ¹³C NMR (CDCl₃) δ 184.1, 151.8, 144.1, 140.2.

Enone 3. To a suspension of NaH (680 mg, 17.0 mmol, 60 wt.%) in THF (50 mL) at 5 °C was added dropwise diethyl (2-oxo-2-phenylethyl)phosphonate (3.7 mL, 17.0 mmol). The reaction mixture was stirred at rt for 30 min. A solution of aldehyde **2** (1.50 g, 15.5 mmol) in THF (5 mL) was added dropwise at rt. The reaction mixture was stirred at rt for 30 min, quenched with 2N HCl, extracted with EtOAc, and the organic layer dried (MgSO₄), filtered and concentrated. Recrystallization of the crude red solid from CH₂Cl₂/hexanes gave 2.36 g of **3** as a tan solid (79%). Mp (CH₂Cl₂/hexanes) 78-81 °C; IR 3133, 3147, 1664, 1607, 1576, 1550 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.59 (s, 1 H), 8.56 (s, 1 H), 8.05-8.03 (m, 2 H), 7.74 (d, 1 H, *J* = 15.3 Hz), 7.70-7.66 (m, 1 H), 7.66 (d, 1 H, *J* = 15.5 Hz), 7.60-7.56 (m, 2 H);

^{13}C NMR (DMSO- d_6) δ 189.1, 153.1, 141.9, 137.3, 136.4, 133.2, 132.5, 128.9, 128.3, 122.7; HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{NO}_2$ $[\text{M}+\text{H}]$: 200.0706; found: 200.0705.

Pyrrole 4. A solution of enone **3** (350 mg, 1.76 mmol) in THF (6.0 mL) was treated at rt with aqueous 2N NaOH (6.0 mL). The reaction mixture was heated at 70 °C for 14 h, cooled to rt, diluted with brine, and extracted with EtOAc. The organic layer was concentrated and purified by chromatography on SiO_2 (90:10 hexanes/EtOAc) to give **4** as an orange solid (247 mg, 82%). Mp (CH_2Cl_2 /hexanes) 137-139 °C; IR 3289, 3054, 1638, 1606, 1566, 1469, 1426, 1261 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 12.41 (bs, 1 H), 9.49 (s, 1 H), 7.91-7.88 (m, 2 H), 7.44-7.40 (m, 2 H), 7.34-7.30 (m, 1 H), 7.08 (d, 1 H, $J = 3.9$ Hz), 6.79 (d, 1 H, $J = 3.9$ Hz); ^{13}C NMR (DMSO- d_6) δ 178.8, 139.5, 133.8, 130.8, 128.8, 128.0, 125.5, 121.9, 108.9; HRMS calcd for $\text{C}_{11}\text{H}_{10}\text{NO}$ $[\text{M}+\text{H}]$: 172.0756; found: 172.0761.

General procedure for aldol reactions: To THF (4 mL/mmol of ketone) at -70 °C was added LDA (1.1 eq relative to ketone, 1.5 M in cyclohexane). To the resultant solution of LDA was added dropwise a solution of ketone (1.0 eq) in a minimal amount of THF. The reaction mixture was stirred at -70 °C for 30 min. A solution of aldehyde **2** (1.1 eq) in a minimal amount of THF was added dropwise at -70 °C. The reaction mixture was stirred for 30 min at -70 °C, quenched with saturated aqueous NH_4Cl solution and allowed to warm to rt. The layers were cut, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (MgSO_4), filtered and concentrated. Where appropriate, diastereoselectivities were recorded from ^1H NMR of crude products prior to purification. Purification was effected by either crystallization or chromatography on SiO_2 using the indicated conditions. For the

synthesis of aldol **9**, 2.2 eq of LDA was used. For the synthesis of aldols **11** and **13**, 1.1 eq LHMDs (1.0 M in THF) was used in place of LDA.

General procedure for dehydration/oxazole hydrolysis/pyrrole formation: A solution of β -hydroxy- β -(4-oxazolyl)ketone in THF (4 mL/mmol of β -hydroxy- β -(4-oxazolyl)ketone) was treated at 0 °C with Et₃N (3.0 eq) followed by dropwise addition of MsCl (1.5 eq). The reaction mixture was stirred at 0 °C for 1 h to effect complete mesylation of starting material as monitored by HPLC. The reaction mixture was then treated with aqueous 2N NaOH (6 mL/mmol of β -hydroxy- β -(4-oxazolyl)ketone) and the reaction mixture was heated at 70 °C for 16 h (Note: In the conversion of **9** to **10**, the reaction mixture was heated at 70 °C for 48 h). After cooling to rt, the reaction mixture was diluted with saturated aqueous NaHCO₃ solution, extracted with EtOAc, and the organic layer dried (MgSO₄), filtered and concentrated. Purification was effected by either crystallization or chromatography on SiO₂ using the indicated conditions.

Aldol 6. Purified by crystallization from CH₂Cl₂/hexanes to give **6** as a white solid. Mp (CH₂Cl₂/hexanes) 76-78 °C; IR 3267, 3135, 1675, 1516, 1444, 1370, 1265, 1190 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.31 (d, 1 H, J = 0.7 Hz), 7.99-7.97 (m, 3 H), 7.67-7.62 (m, 1 H), 7.55-7.52 (m, 2 H), 5.49 (d, 1 H, J = 5.4 Hz), 5.17-5.13 (m, 1 H), 3.46 (dd, 1 H, J = 8.2, 16.1 Hz), 3.35 (dd, 1 H, J = 4.6, 16.1 Hz); ¹³C NMR (DMSO-d₆) δ 198.0, 151.9, 143.4, 137.0, 135.3, 133.1, 128.7, 128.1, 62.7, 45.0; HRMS calcd for C₁₂H₁₂NO₃ [M+H]: 218.0811; found: 218.0810.

Aldol 7. Purified by crystallization from hexanes/EtOAc to give **7** as a white solid. Mp (hexanes/EtOAc) 106-108 °C; IR 3280, 2899, 2852, 1700, 1511, 1058 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 8.31 (s, 1 H), 7.93 (d, 1 H, J = 0.8 Hz), 5.30 (d, 1 H, J = 5.5 Hz), 5.03-4.99 (m, 1 H), 2.99 (dd, 1 H, J = 8.2, 16.9 Hz), 2.79 (dd, 1 H, J = 4.5, 16.9 Hz), 2.03-1.99 (m, 3 H), 1.78-1.64 (m, 12 H); ^{13}C NMR (DMSO- d_6) δ 212.0, 151.7, 143.5, 135.1, 62.0, 45.6, 42.4, 37.2, 36.0, 27.3; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]$: 276.1594; found: 276.1596.

Pyrrole 8. Purified by crystallization from CH_2Cl_2 /hexanes (2 batches) to give **8** as a tan solid. Mp (CH_2Cl_2 /hexanes) 215-218 °C; IR 3279, 2902, 2849, 1640, 1478, 1244 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 11.72 (bs, 1 H), 9.35 (s, 1 H), 6.86 (dd, 1 H, J = 2.3, 3.7 Hz), 6.01 (dd, 1 H, J = 2.4, 3.8 Hz), 2.02-1.97 (m, 3 H), 1.92-1.89 (m, 6 H), 1.72-1.68 (m, 6 H); ^{13}C NMR (DMSO- d_6) δ 178.1, 151.7, 132.1, 121.3, 105.7, 41.1, 36.0, 33.4, 27.8; HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]$: 230.1539; found: 230.1539.

Aldol 9. Purified by chromatography on SiO_2 (60:40 EtOAc/hexanes $\rightarrow$ EtOAc) to give **9** as a tan solid. Mp (hexanes/EtOAc) 151-152 °C; IR 3125, 2932, 2869, 1665, 1619, 1517, 1445, 1065 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 11.94 (bs, 1 H), 8.30 (d, 2 H, J = 8.2 Hz), 8.22-8.20 (m, 1 H), 7.95 (s, 1 H), 7.47-7.45 (m, 1 H), 7.22-7.15 (m, 2 H), 5.41 (d, 1 H, J = 5.5 Hz), 5.17-5.15 (m, 1 H), 3.30 (dd, 1 H, J = 8.7, 15.2 Hz),

3.14 (dd, 1 H, $J = 4.4, 15.1$ Hz); ^{13}C NMR (DMSO- d_6) δ 192.8, 151.8, 143.8, 136.6, 135.1, 134.4, 125.4, 122.8, 121.7, 121.4, 117.0, 112.1, 63.2, 45.9; HRMS calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]$: 257.0920; found: 257.0925.

Pyrrole 10. Purified by chromatography on SiO_2 (40:60 $\rightarrow$ 80:20 EtOAc/hexanes) to give **10** as a brown solid. Mp (hexanes/EtOAc) 227-229 $^\circ\text{C}$; IR 3410, 3164, 1625, 1607, 1582, 1571, 1523, 1420, 1334, 1247 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 12.08 (bs, 1 H), 11.49 (bs, 1 H), 9.40 (s, 1 H), 8.08 (d, 1 H, $J = 2.1$ Hz), 7.89 (d, 1 H, $J = 7.8$ Hz), 7.45 (d, 1 H, $J = 7.8$ Hz), 7.20-7.10 (m, 3 H), 6.72 (dd, 1 H, $J = 2.2, 3.6$ Hz); ^{13}C NMR (DMSO- d_6) δ 177.3, 136.6, 136.4, 131.8, 124.6, 124.4, 123.3, 121.8, 120.0, 119.4, 112.0, 107.6, 106.9; HRMS calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}$ $[\text{M}+\text{H}]$: 211.0865; found: 211.0866.

Aldol 11. Purified by chromatography on SiO_2 (80:20 $\rightarrow$ 50:50 hexanes/EtOAc) to give **11** as a tan solid. Mp (hexanes/EtOAc) 109-111 $^\circ\text{C}$; IR 3220, 3133, 3090, 1653, 1519, 1413, 1310, 1230, 1056 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 8.30 (s, 1 H), 7.96 (s, 1 H), 7.82 (d, 1 H, $J = 4.0$ Hz), 7.40 (d, 1 H, $J = 4.0$ Hz), 5.57 (d, 1 H, $J = 5.5$ Hz), 5.10-5.05 (m, 1 H), 3.35 (dd, 1 H, $J = 8.5, 15.6$ Hz), 3.19 (dd, 1 H, $J = 4.4, 15.5$ Hz); ^{13}C NMR (DMSO- d_6) δ 190.2, 151.9, 146.0, 143.1, 135.3, 134.5, 132.4, 122.0, 62.9, 44.9; HRMS calcd for $\text{C}_{10}\text{H}_9\text{BrNO}_3\text{S}$ $[\text{M}+\text{H}]$: 301.9481; found: 301.9475.

Pyrrole 12. Purified by chromatography on SiO₂ (90:10→80:20 hexanes/EtOAc) to give **12** as a red solid. Mp (hexanes/EtOAc) 138-141 °C; IR 3246, 1634, 1578, 1561, 1523, 1480, 1268 cm⁻¹; ¹H NMR (DMSO-d₆) δ 12.56 (bs, 1 H), 9.47 (s, 1 H), 7.49 (s, 1 H), 7.24 (s, 1 H), 7.04 (s, 1 H), 6.54 (s, 1 H); ¹³C NMR (DMSO-d₆) δ 178.9, 135.6, 133.5, 132.8, 131.5, 125.4, 122.2, 111.1, 109.3; HRMS calcd for C₉H₇BrNOS [M+H]⁺: 255.9426; found: 255.9419.

Aldol 13. Purified by chromatography on SiO₂ (75:25→50:50 hexanes/EtOAc) to give **13** as a 1:1 mixture of diastereomers (white solid). Nonpolar diastereomer (white solid): Mp (hexanes/EtOAc) 127-128 °C; IR 3235, 3113, 1672, 1589, 1509, 1404, 1374 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.34 (s, 1 H), 8.05 (s, 1 H), 8.02-7.99 (m, 2 H), 7.63-7.60 (m, 2 H), 5.43 (d, 1 H, *J* = 4.8 Hz), 4.77-4.74 (m, 1 H), 4.01-3.94 (m, 1 H), 0.86 (d, 3 H, *J* = 6.8 Hz); ¹³C NMR (DMSO-d₆) δ 202.0, 152.0, 141.5, 137.9, 136.5, 136.0, 130.2, 128.7, 68.1, 45.3, 14.0; HRMS calcd for C₁₃H₁₃ClNO₃ [M+H]⁺: 266.0578; found: 266.0577. Polar diastereomer (white solid): Mp (hexanes/EtOAc) 104-106 °C; IR 3249, 3124, 1703, 1636, 1468, 1419 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.23 (s, 1 H), 7.94-7.92 (m, 2 H), 7.87 (s, 1 H), 7.61-7.58 (m, 2 H), 5.52 (d, 1 H, *J* = 5.9 Hz), 4.85 (t, 1 H, *J* = 6.0 Hz), 4.00-3.93 (m, 1 H), 1.09 (d, 3 H, *J* = 6.8 Hz); ¹³C NMR (DMSO-d₆, 500 MHz) δ 201.3, 152.1, 142.8, 138.2, 136.2, 135.4, 130.4, 129.2, 67.6, 46.0, 12.4; HRMS calcd for C₁₃H₁₃ClNO₃ [M+H]⁺: 266.0578; found: 266.0576.

Pyrrole 14. Purified by chromatography on SiO₂ (95:5→85:15 hexanes/EtOAc) to give **14** as a light orange solid. Mp (hexanes/EtOAc) 138-139 °C; IR 3254, 2829, 1647, 1422, 1284, 1257 cm⁻¹; ¹H NMR (CDCl₃) δ 9.44 (bs, 1 H), 9.38 (s, 1 H), 7.40-7.35 (m, 4 H), 6.79 (d, 1 H, *J* = 2.4 Hz), 2.19 (s, 3 H); ¹³C NMR (CDCl₃) δ 178.7, 135.8, 134.2, 131.6, 130.0, 129.2, 128.4, 123.7, 119.7, 12.5; HRMS calcd for C₁₂H₁₁ClNO [M+H]: 220.0523; found: 220.0520.

Aldol 15. Purified by crystallization from hexanes/EtOAc to give the major (nonpolar) diastereomer of **15** as a white solid. Mp (hexanes/EtOAc) 106-108 °C; IR 3316, 3132, 3101, 2968, 1633, 1600, 1507, 1173 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.32 (s, 1 H), 7.99 (s, 1 H), 7.70 (m, 2 H), 7.48 (d, 1 H, *J* = 16.1 Hz), 7.43-7.41 (m, 3 H), 6.99 (d, 1 H, *J* = 16.1 Hz), 5.32 (d, 1 H, *J* = 5.5 Hz), 4.96 (dd, 1 H, *J* = 5.6, 8.1 Hz), 3.25 (dd, 1 H, *J* = 6.3, 8.5 Hz), 1.80 (m, 1 H), 0.90 (d, 3 H, *J* = 6.9 Hz), 0.81 (d, 3 H, *J* = 6.8 Hz); ¹³C NMR (DMSO-d₆) δ 201.2, 151.9, 142.3, 140.8, 136.0, 134.5, 130.3, 128.9, 128.4, 128.0, 65.4, 59.8, 27.2, 21.2, 18.6; HRMS calcd for C₁₇H₂₀NO₃ [M+H]: 286.1437; found: 286.1439.

Pyrrole 16. Purified by chromatography on SiO₂ (97:3→90:10 hexanes/EtOAc) to give **16** as a tan solid. Mp (hexanes/EtOAc) 110-113 °C; IR 3279, 2961, 1636, 1471, 1427, 1267, 1147 cm⁻¹; ¹H NMR (DMSO-d₆) δ 12.01 (bs, 1 H), 9.41 (s, 1 H), 7.57-7.55 (m, 2 H), 7.44-7.36 (m, 3 H), 7.28-7.25 (m, 1 H), 7.14 (d, 1 H, *J* = 16.5 Hz), 6.92 (d, 1 H, *J* = 1.6 Hz), 3.17-3.10 (m, 1 H), 1.18 (d, 6 H, *J* = 6.8 Hz); ¹³C NMR (DMSO-d₆) δ 178.3, 137.0, 133.9, 133.5, 132.4, 128.8, 128.7, 127.7, 126.3, 118.3, 115.9, 24.1; HRMS calcd for C₁₆H₁₈NO [M+H]: 240.1382; found: 240.1381.

Aldol 17. Purified by chromatography on SiO₂ (60:40→30:70 hexanes/EtOAc) to give **17** as a 1.4:1 (nonpolar:polar) mixture of diastereomers (white solid). Major (nonpolar) diastereomer (white solid): Mp (hexanes/EtOAc) 110-112 °C; IR 3281, 2947, 2890, 2841, 1674, 1599, 1493, 1247 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.32 (s, 1 H), 7.90 (s, 1 H), 7.87 (d, 1 H, *J* = 8.7 Hz), 6.90 (dd, 1 H, *J* = 2.5, 8.7 Hz), 6.84 (d, 1 H, *J* = 2.4 Hz), 5.49-5.47 (m, 1 H), 5.44-5.43 (m, 1 H), 3.82 (s, 3 H), 2.94-2.85 (m, 2 H), 2.83-2.78 (m, 1 H), 2.04-1.94 (m, 1 H), 1.81-1.74 (m, 1 H); ¹³C NMR (DMSO-d₆) δ 195.7, 163.1, 152.0, 147.1, 143.2, 136.1, 129.0, 126.1, 113.3, 112.4, 64.9, 55.5, 51.1, 28.2, 21.4; HRMS calcd for C₁₅H₁₆NO₄ [M+H]: 274.1073; found: 274.1071. Minor (polar) diastereomer (white solid): Mp (hexanes/EtOAc) 123-124 °C; IR 3283, 2921, 2851, 1664, 1597, 1505, 1256 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.19 (s, 1 H), 7.87 (s, 1 H), 7.81 (d, 1 H, *J* = 8.7 Hz), 6.88 (dd, 1 H, *J* = 2.5, 8.7 Hz), 6.82 (d, 1 H, *J* = 2.4 Hz), 5.44 (d, 1 H, *J* = 5.2 Hz), 5.30-5.28 (m, 1 H), 3.81 (s, 3 H), 2.92-2.83 (m, 3 H), 2.14-2.07 (m, 1 H), 1.72-1.62 (m, 1 H); ¹³C NMR (DMSO-d₆) δ 195.6, 162.9, 151.5, 146.6, 141.8, 136.1, 129.0, 126.0, 113.3, 112.3, 65.7, 55.4, 52.4, 27.9, 23.5; HRMS calcd for C₁₅H₁₆NO₄ [M+H]: 274.1073; found: 274.1074.

Pyrrole 18. Purified by chromatography on SiO₂ (85:15→75:25 hexanes/EtOAc) to give **18** as a gray solid. Mp (hexanes/EtOAc) 172-175 °C; IR 3231, 2826, 1630, 1546, 1465, 1410, 1288, 1251 cm⁻¹; ¹H NMR (DMSO-d₆) δ 12.26 (s, 1 H), 9.36 (s, 1 H), 7.82 (d, 1 H, *J* = 8.4 Hz), 6.88-6.83 (m, 3 H), 3.77 (s, 3 H), 2.88-2.84 (m, 2 H), 2.69-2.65 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 177.6, 158.9, 138.6, 135.9, 132.1,

123.6, 120.6, 120.3, 120.2, 114.1, 112.0, 55.1, 29.4, 20.8; HRMS calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019; found: 228.1019.

Aldol 19. Purified by crystallization from hexanes/EtOAc to give the major (nonpolar) diastereomer of **19** as a white solid. Mp (hexanes/EtOAc) 58-61 °C; IR 3300, 3107, 2933, 1703, 1510 cm^{-1} ; 1H NMR (DMSO- d_6) δ 8.26 (s, 1 H), 7.90 (s, 1 H), 4.96 (d, 1 H, $J = 5.2$ Hz), 4.84-4.81 (m, 1 H), 3.07-3.01 (m, 1 H), 1.83-1.64 (m, 3 H), 1.58-1.50 (m, 1 H), 1.47-1.39 (m, 1 H), 1.25-1.12 (m, 1 H), 1.16 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (DMSO- d_6) δ 214.3, 151.6, 141.7, 135.6, 64.5, 51.1, 45.2, 41.2, 30.2, 25.3, 24.3, 20.6; HRMS calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$: 224.1281; found: 224.1283.

Pyrrole 20. Purified by chromatography on SiO_2 (95:5→90:10 hexanes/EtOAc) to give **20** as a light orange solid. Mp (hexanes/EtOAc) 105-109 °C; IR 3271, 2928, 2858, 1639, 1420, 1285, 1134 cm^{-1} ; 1H NMR (CD_2Cl_2) δ 9.48 (bs, 1 H), 9.36 (s, 1 H), 6.70 (d, 1 H, $J = 2.3$ Hz), 2.53 (t, 2 H, $J = 6.2$ Hz), 1.84-1.74 (m, 2 H), 1.69-1.66 (m, 2 H), 1.31 (s, 6 H); ^{13}C NMR (CD_2Cl_2) δ 178.3, 146.1, 131.8, 120.6, 120.4, 39.2, 32.1, 29.2, 23.5, 20.7; HRMS calcd for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1226; found: 178.1232.

Aldol 21. Purified by crystallization from hexanes/EtOAc (2 batches) to give the major (nonpolar) diastereomer of **21** as a white solid. Mp (hexanes/EtOAc) 121-122 °C; IR 3211, 3118, 2923, 1684, 1518,

1112, 1064 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 8.24 (s, 1 H), 7.89 (s, 1 H), 5.42 (d, 1 H, $J = 6.2$ Hz), 4.56 (dd, 1 H, $J = 6.3, 8.2$ Hz), 3.12-3.06 (m, 1 H), 2.27-2.06 (m, 3 H), 2.05-1.91 (m, 1 H), 1.73-1.27 (m, 7 H), 1.19-1.10 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 217.8, 151.6, 142.3, 135.8, 67.1, 54.3, 43.3, 29.8, 27.6, 24.9, 24.6, 23.3; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]$: 224.1281; found: 224.1281.

Pyrrole 22. Purified by crystallization from CH_2Cl_2 /hexanes (2 batches) to give **22** as an off-white solid. Mp (CH_2Cl_2 /hexanes) 128-130 $^\circ\text{C}$; IR 3231, 2928, 2853, 1630, 1509, 1437, 1349, 1121 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 11.68 (bs, 1 H), 9.23 (s, 1 H), 6.69 (s, 1 H), 2.69-2.66 (m, 2 H), 2.52-2.49 (m, 2 H), 1.62-1.48 (m, 4 H), 1.39-1.28 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 177.0, 140.4, 130.2, 122.7, 121.7, 30.7, 29.1, 25.2, 25.0, 24.3, 24.0; HRMS calcd for $\text{C}_{11}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]$: 178.1226; found: 178.1228.

Aldol 23. Purified by chromatography on SiO_2 (80:20 $\rightarrow$ 60:40 hexanes/EtOAc) to give **23** as a 1.2:1 (nonpolar:polar) mixture of diastereomers (white solid). Major (nonpolar) diastereomer (white solid): Mp (hexanes/EtOAc) 119-121 $^\circ\text{C}$; IR 3209, 3118, 2924, 2856, 1684, 1517, 1466 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 8.25 (s, 1 H), 7.88 (s, 1 H), 5.41 (d, 1 H, $J = 6.2$ Hz), 4.70 (dd, 1 H, $J = 6.5, 7.8$ Hz), 3.04-2.99 (m, 1 H), 2.63-2.56 (m, 1 H), 2.39-2.31 (m, 1 H), 1.88-1.76 (m, 1 H), 1.68-1.59 (m, 1 H), 1.58-1.49 (m, 2 H), 1.35-1.06 (m, 14 H); ^{13}C NMR (DMSO-d_6) δ 211.6, 151.6, 142.5, 135.7, 65.0, 56.6, 37.8, 25.6, 25.3, 24.7, 23.6, 23.3, 23.1, 21.83, 21.76, 21.4; HRMS calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]$: 280.1907; found: 280.1903. Minor (polar) diastereomer (white solid): Mp (hexanes/EtOAc) 107-108 $^\circ\text{C}$; IR 3238,

3128, 2930, 2864, 1707, 1517, 1469 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 8.31 (s, 1 H), 8.01 (s, 1 H), 5.40 (d, 1 H, $J = 5.2$ Hz), 4.66 (dd, 1 H, $J = 5.2, 9.7$ Hz), 2.93-2.88 (m, 1 H), 2.75-2.67 (m, 1 H), 2.56-2.50 (m, 1 H), 1.80-1.69 (m, 1 H), 1.59-1.44 (m, 2 H), 1.36-0.98 (m, 15 H); ^{13}C NMR (DMSO-d_6) δ 212.2, 152.0, 141.7, 136.2, 66.3, 57.4, 37.1, 26.2, 25.8, 25.5, 23.7, 23.2, 23.0, 22.6, 21.8, 21.2; HRMS calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]$: 280.1907; found: 280.1905.

Pyrrole 24. Purified by crystallization from CH_2Cl_2 /hexanes to give **24** as an off-white solid. Mp (CH_2Cl_2 /hexanes) 142-143 $^\circ\text{C}$; IR 3221, 2931, 2862, 1637, 1469, 1419 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 11.61 (bs, 1 H), 9.27 (s, 1 H), 6.76 (d, 1 H, $J = 2.4$ Hz), 2.55 (t, 2 H, $J = 6.8$ Hz), 2.37 (t, 2 H, $J = 6.8$ Hz), 1.73-1.67 (m, 2 H), 1.63-1.56 (m, 2 H), 1.42-1.11 (m, 12 H); ^{13}C NMR (DMSO-d_6) δ 177.5, 139.7, 131.4, 123.4, 121.0, 28.7, 27.0, 24.6, 24.3, 24.1, 24.0, 22.1, 21.8, 21.6 ; HRMS calcd for $\text{C}_{15}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]$: 234.1852; found: 234.1849.

Enone 26. To a suspension of NaH (1.06 g, 26.6 mmol, 60 wt.%) in THF (75 mL) at 5 $^\circ\text{C}$ was added dropwise diethyl (2-oxo-2-phenylethyl)phosphonate (5.77 mL, 26.6 mmol). The reaction mixture was stirred at rt for 30 min. A solution of aldehyde **25** (2.00 g, 17.7 mmol) in THF (15 mL) was added dropwise at rt. The reaction mixture was stirred at rt for 1 h, quenched with 2N HCl, extracted with EtOAc, and the organic layer dried (MgSO_4), filtered and concentrated. The crude product was purified by chromatography on SiO_2 (90:10 hexanes/EtOAc) to give **26** as a yellow solid (3.35 g, 88%). Mp

(hexanes/EtOAc) 78-82 °C; IR 3105, 1656, 1600, 1574, 1477, 1446, 1276, 1203 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.88 (s, 1 H), 8.10-8.08 (m, 2 H), 7.97 (d, 1 H, $J = 15.2$ Hz), 7.81 (d, 1 H, $J = 15.1$ Hz), 7.62-7.57 (m, 2 H), 7.52-7.48 (m, 2 H); ^{13}C NMR (CDCl_3) δ 190.4, 153.8, 153.1, 137.9, 135.5, 133.0, 128.65, 128.63, 124.2, 122.3; HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{NOS}$ [$\text{M}+\text{H}$]: 216.0477; found: 216.0475.

Thiazolium bromide 27. A solution of thiazole **26** (2.10 g, 9.76 mmol), benzyl bromide (8.12 mL, 68.3 mmol) and acetonitrile (8.1 mL) was heated at 85 °C for 96 h, cooled to rt, and concentrated to remove acetonitrile. The residue was triturated with hexanes and the resulting solid was washed with hexanes and dried under vacuum. Recrystallization from MeOH/EtOAc gave **27** as a tan solid (2.68 g, 71%). Mp (MeOH/EtOAc) 173-174 °C; IR 3039, 1664, 1606, 1594, 1580, 1449, 1298, 1225 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 10.50 (d, 1 H, $J = 2.3$ Hz), 9.18 (d, 1 H, $J = 2.3$ Hz), 8.22 (d, 1 H, $J = 15.5$ Hz), 8.12-8.10 (m, 2 H), 7.71-7.56 (m, 4 H), 7.43-7.33 (m, 5 H), 6.09 (s, 2 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 188.1, 161.8, 143.7, 136.3, 134.0, 133.3, 129.8, 129.2, 129.0, 128.8, 127.7, 126.8, 126.7, 55.7; HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{NOS}$ [$\text{M}-\text{Br}$]: 306.0947; found: 306.0949.

N-Benzyl pyrrole 28. A solution of salt **27** (230 mg, 0.595 mmol) in *n*-BuOH (6.0 mL) and water (1.0 mL) was treated at rt with 2N aqueous NaOH solution (0.89 mL, 1.78 mmol) followed by MeI (0.30 mL, 0.60 mmol, 2M in MTBE). The reaction mixture was stirred at rt for 30 min, at which time LC-MS analysis indicated complete consumption of **27**. 6N aqueous NaOH solution (4.0 mL) was added and the reaction mixture was heated at 120 °C for 17 h. After cooling to rt, the reaction mixture was diluted with

saturated aqueous NaHCO_3 solution, extracted with EtOAc and the organic phase dried over MgSO_4 , filtered and concentrated. The crude product was purified by chromatography on SiO_2 (90:10 hexanes/EtOAc) to give **28** as a tan solid (99 mg, 64%). Mp (hexanes/EtOAc) 69-71 °C; IR 3027, 2953, 2841, 1656, 1451, 1437, 1247, 1034 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.48 (s, 1 H), 7.32-7.28 (m, 3 H), 7.27-7.23 (m, 2 H), 7.18-7.09 (m, 3 H), 7.00 (d, 1 H, $J = 4.0$ Hz), 6.82-6.80 (m, 2 H), 6.31 (d, 1 H, $J = 4.0$ Hz), 5.55 (s, 2 H); ^{13}C NMR (CDCl_3) δ 179.2, 144.6, 138.6, 132.5, 131.1, 129.3, 128.8, 128.7, 128.5, 127.1, 126.0, 125.1, 111.4, 49.2; HRMS calcd for $\text{C}_{18}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]$: 262.1226; found: 262.1230.

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8028-065
NMR_1H_32_scans DMSO opt/xwinnmr guest 5

8028-169

8301-004
NMR_1H_16_scans /DMSO opt/xwinmr guest 89

8028-095

8028-099

8028-085

8028-091

7646-039-1
isolated product

8028-157

8189-035c

8189-035b

8189-035b

8028-151
NMR_1H_32_scans CDCl3 opt/xwinnmr guest 45

8028-167NP

8028-175

8028-129NP

8028-129P

8028-101

8028-107

8028-105NP

8028-113

8028-097NP

8028-097P

8028-103

8301-034

8301-051

8301-058