Synthesis of 2-Substituted-5-halo-2,3-dihydro-4(*H*)-pyrimidin-4-ones and Their Derivatization Utilizing the Sonogashira Coupling Reaction in the Enantioselective Synthesis of α -Substituted β -Amino Acids

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General Methods. TLC, F₂₅₄ silica gel plates, detection by UV light or iodine vapor. Flash column chromatography: silica gel (230-400 mesh). All melting points are uncorrected. NMR spectra were recorded in DMSO-*d*₆ at 120 °C, in order to remove *cis/trans* issues around the amide bond. ¹H NMR: 400, 300, and 270 MHz spectrometers. ¹³C NMR: 100, 67.5, and 75 MHz spectrometers. IR spectra were obtained on a Perkin-Elmer Spectrum GX instrument. MS spectra were obtained at 20 eV. Optical rotations were measured using the sodium D-line (589 nm). Elemental analyses were obtained at the analytical laboratory of the Chemistry Department. HRMS were obtained in HPLC equipment coupled to MSD TOF at Instituto de Química, UNAM, México. Microwave heating was carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). Analytical HPLC was carried out using Waters 600 E and UV/Vis Waters 2487.

1-Benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxy-perhydropyrimidin-4-one, (2*S*,6*S*)-1a**.** The procedure described by Juaristi^{1a} was followed using L-asparagine and pivalaldehyde. Yield = 71 %, mp = 200-201 °C. [α]_D²⁵ = – 103.3 (c = 1, EtOH). [Lit.^{2a} mp = 202-203 °C. [α]_D²⁹ = – 107.0 (c = 1, EtOH)].

1-Benzoyl-2(*S*)-isopropyl-6(*S*)-carboxy-perhydropyrimidin-4-one, (2*S*,6*S*)-1b. The procedure described by Juaristi^{1a} was followed using L-asparagine and isobutyraldehyde. Yield = 68 %, mp = 173-174 °C. $[\alpha]_D^{25} = -149.8$ (c = 1, MeOH). [Lit.^{2b,3} mp = 175-177 °C. $[\alpha]_D^{25} = -156.0$ (c = 1, MeOH)].

1-Benzoyl-2(*S*)-phenyl-6(*S*)-carboxy-perhydropyrimidin-4-one, (2*S*,6*S*)-1c. The procedure described in the literature^{1a-b} was followed using L-asparagine and benzaldehyde. Yield = 15.3 %, mp = 181-183 °C. $[\alpha]_D^{25} = -10.1$ (c = 1, MeOH). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.38 (dd, 1H, *J* = 16.1 Hz, *J* = 9.9 Hz), 2.59 (dd, 1H, *J* = 16.1 Hz, *J* = 6.6 Hz), 4.80 (dd, 1H, *J* = 9.9 Hz, *J* = 6.6 Hz), 6.34 (s, 1H), 7.34-7.65 (m, 10H), 8.53 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 33.6 (CH₂), 54.4 (CH), 67.1 (CH), 127.1 (CH), 127.2 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 130.7 (CH), 135.9 (C), 140.6 (C), 168.9 (C), 171.3 (C), 171.5 (C). IR (KBr) ν (cm⁻¹): 3225, 3059, 1723, 1645, 1355. MS *m/z* (%): 324 (M⁺, 0.9), 306 (3.4), 298 (0.6), 263 (2.6), 219 (3.9), 194 (13.9), 174 (8.6), 158 (4.1), 147 (19), 122 (7.4), 105 (100), 77 (29.7), 51 (4.6). Anal. calcd for C₁₈H₁₆N₂O₄: C, 66.67; H, 4.97; N, 8.64. Found: C, 66.90; H, 5.06; N, 8.87.

General procedure for preparation of 5-iodoenones (*S*)-3a-c.

A suspension of the carboxylic acid (1.0 mmol), DIB (644 mg, 2.0 mmol), and iodine (253 mg, 1.0 mmol) in CH₂Cl₂ (20 mL) was stirred at ambient temperature until TLC showed disappearance of the starting material (4-4.5 h). BF₃·OEt₂ (0.25 mL, 2 equiv.) was added and the resulting mixture was stirred for 1 h. Following addition of CH₂Cl₂ (20 mL), the reaction mixture was washed with four 15-mL portions of 5 % aqueous Na₂S₂O₃, two 10-mL portions of 3 % aqueous NaHCO₃, and two 10-mL portions of brine, dried over anhyd. Na₂SO₄, and evaporated to afford the desired iodoenone as a yellowish syrup that was purified by flash chromatography.

1-Benzoyl-2(*S*)-*tert*-butyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-3a. Yield = 55.5 %, mp = 115-117 °C.

mp = 255-258 °C. $[\alpha]_D^{25} = + 426.0$ (c = 1, CHCl₃). [Lit.⁴ mp = 258-260 °C. $[\alpha]_D^{25} = + 428.4$ (c = 1, CHCl₃)].

1-Benzoyl-2(S)-isopropyl-5-iodo-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-3b. Yield = 78 %, mp = 207-209 °C. $[\alpha]_D^{25} = + 377.3$ (c = 1, CHCl₃). [Lit.⁴ mp = 218-220 °C, $[\alpha]_D^{25} = + 389.27$ (c = 1, CHCl₃)].

1-Benzoyl-2(S)-phenyl-5-iodo-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-3c. Yield = 59.2 %, mp = 242-244 °C. $[\alpha]_D^{25} = + 258.7$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 270 MHz) δ 6.73 (d, 1H, *J* = 3.2 Hz), 7.30-7.41 (m, 5H), 7.49-7.62 (m, 6H), 8.69 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 67.5 MHz) δ 65.7 (CH), 75.0 (C), 125.9 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 131.7 (CH), 132.6 (C), 139.3 (C), 142.2 (CH), 159.3 (C), 167.3 (C). IR (KBr) ν (cm⁻¹): 3327, 3024, 1664, 1634, 1573. MS *m/z* (%): 405 (M⁺+1, 5), 404 (M⁺, 13), 327 (1), 300 (30), 299 (11), 277 (26), 210 (7), 172 (2), 105 (100), 77 (27). Anal. calcd for C₁₇H₁₃N₂O₂I: C 50.51, H 3.24, N 6.93; Found: C 50.68, H 3.35, N 7.25.

General procedure for preparation of compounds (S)-4a-c

A suspension of the carboxylic acid **1a-c** (1.0 mmol), DIB (644 mg, 2.0 mmol), and iodine (253 mg, 1.0 mmol) in CH₂Cl₂ (10 mL) was stirred at ambient temperature for 4-4.5 h. Acetonitrile (20 mL), NaI (300 mg, 2.0 mmol), and Me₃SiCl (0.254 mL, 217.3 mg, 2.0 mmol) were added and the resulting dark solution was stirred for 2.5-3 h at ambient temperature. The reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with four 20-mL portions of 5% aqueous Na₂S₂O₃, two 15-mL portions of 5% aqueous NaHCO₃, and two 15-mL portions of brine, dried over anhyd. Na₂SO₄, and evaporated to afford the desired enone as a yellowish syrup that was purified by flash chromatography.

1-Benzoyl-2(S)-tert-butyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-4a. Yield = 71 %, mp = 206-

207 °C. $[\alpha]_D^{25} = + 557.3$ (c = 1, CHCl₃). [Lit.^{2a} mp = 204-205 °C. $[\alpha]_D^{29} = + 564.5$ (c = 1, CHCl₃)].

1-Benzoyl-2(S)-isopropyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-4b. Yield = 72 %, mp = 154-155 °C. $[\alpha]_D^{25} = + 487.7$ (c = 1, CHCl₃). [Lit.⁵ mp = 155-156 °C. $[\alpha]_D^{25} = + 522.5$ (c = 1, CHCl₃)].

1-Benzoyl-2(S)-phenyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-4c. Yield = 75.3 %, mp = 194-196 °C. $[\alpha]_D^{25} = + 368.0$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 5.18 (d, 1H, *J* = 8.0 Hz), 6.76 (s, 1H), 7.18 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 7.33-7.43 (m, 5H), 7.53-7.60 (m, 5H), 8.20 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 64.4 (CH), 104.7 (CH), 125.3 (CH), 127.3 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 130.7 (CH), 132.4 (C), 136.5 (CH), 139.2 (C), 161.9 (C), 167.5 (C). IR (KBr) ν (cm⁻¹): 3213, 1723, 1645, 1448, 1353. MS *m/z* (%): 279 (M⁺+1, 3), 278 (M⁺, 2), 201 (6), 174 (90), 173 (86), 146 (1), 145 (1), 105 (100), 77 (33). Anal. calcd. for C₁₇H₁₄N₂O₂: C, 73.37; H, 5.07. Found: C, 73.35; H 5.05.

General procedure for preparation of 5-bromoenones (S)-5a-c.

Pyridinium perbromide hydrobromide (638 mg, 2 equiv.) was added to a solution of the enone (1 mmol) in CH₂Cl₂ (20 mL). The solution was stirred for 30 min. at ambient temperature, diluted with CH₂Cl₂ (20 mL), washed with three 15-mL portions of saturated Na₂S₂O₃ solution, two 15-mL portions of 3 % aqueous NaHCO₃, and two 15-mL portions of brine, dried and evaporated to afford the desired bromoenone as a white solid that was purified by flash chromatography.

1-Benzoyl-2(S)-*tert*-butyl-5-bromo-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-5a. Yield = 69.1%, mp = 237-239 °C. $[\alpha]_D^{25} = + 510$ (c = 0.5, CHCl₃). ¹H NMR (DMSO-*d*₆, 270 MHz) δ 0.96 (s, 9H), 5.62 (dd, 1H, *J* = 5.2, *J* = 1.5 Hz), 7.45 (d, 1H, *J* = 1.7), 7.53-7.60 (m, 5H), 8.30 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 67.5 MHz) δ 26.3 (3CH₃), 40.3 (C), 71.0 (CH), 101.7 (C), 128.3 (CH), 129.4 (CH), 131.7 (CH), 133.8 (C), 138.0 (CH), 158.7 (C), 168.7 (C). IR (KBr) ν (cm⁻¹): 3446, 3320,

3203, 3098, 2953, 1681, 1669, 1605. MS m/z (%): 338 ($M^+ + 1$, 0.3), 337 (M^+ , 0.2), 282 (2), 281 (15.7), 279 (15.8), 105 (100), 77 (13.7). Anal. calcd for $C_{15}H_{17}BrN_2O_2$: C, 53.43; H, 5.08; N, 8.31. Found: C, 53.73; H, 5.11; N, 8.58.

1-Benzoyl-2(*S*)-isopropyl-5-bromo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-5b. Yield = 79.3 %, mp = 196-197 °C. $[\alpha]_D^{25} = +430.4$ ($c = 1$, $CHCl_3$). 1H NMR ($DMSO-d_6$, 400 MHz) δ 0.89 (d, 3H, $J = 6.6$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 2.19 (m, 1H), 5.42 (*broad*, 1H), 7.47 (s, 1H), 7.53-7.60 (m, 5H), 8.36 (*broad*, 1H). ^{13}C NMR ($DMSO-d_6$, 100 MHz) δ 18.1 (CH_3), 18.8 (CH_3), 33.4 (CH), 69.7 (CH), 100.8 (C), 128.4 (CH), 129.3 (CH), 131.9 (CH), 133.6 (C), 137.5 (CH), 158.7 (C), 168.1 (C). IR (KBr) ν (cm^{-1}): 3200, 3083, 2968, 1690, 1670, 1599. MS m/z (%): 324 ($M^+ + 1$, 1.1), 323 (M^+ , 0.5), 281 (21.4), 279 (20.9), 105 (100), 77 (16.4). Anal. calcd. for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 51.81; H, 4.71; N, 8.70.

1-Benzoyl-2(*S*)-phenyl-5-bromo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-5c. Yield = 89.6 %, mp = 200-202 °C. $[\alpha]_D^{25} = +326.9$ ($c = 1$, $CHCl_3$). 1H NMR ($DMSO-d_6$, 270 MHz) δ 6.74 (d, 1H, $J = 3.2$ Hz), 7.30-7.43 (m, 5H), 7.49-7.63 (m, 6H), 8.76 (*broad*, 1H). ^{13}C NMR ($DMSO-d_6$, 67.5 MHz) δ 65.5 (CH), 100.3 (C), 125.9 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 131.8 (CH), 132.5 (C), 137.1 (CH), 139.1 (C), 158.5 (C), 167.6 (C). IR (KBr) ν (cm^{-1}): 3307, 1671, 1639, 1591. MS m/z (%): 358 ($M^+ + 1$, 1.1), 357 (M^+ , 0.3), 277 (4.7), 105 (100), 77 (7.4). Anal. calcd. for $C_{17}H_{13}BrN_2O_2$: C 57.16, H 3.67, N 7.84. Found: C 57.15, H 3.45, N 7.83.

Preparation of 5-alkynyl enones (*S*)-6a-d.

Typical procedure for Sonogashira coupling reaction. To an oven-dried round-bottom flask with a magnetic stirrer were added iodoenone (*S*)-**3a** (0.54 mmol), $PdCl_2$ (8 mol % based on iodoenone), CuI (8 mol % based on iodoenone) and PPh_3 (0.16 equiv). The flask was evacuated and backfilled with nitrogen (3x). Acetonitrile (6 mL) was added followed by triethylamine (3

equiv). The terminal alkyne was then added and the reaction mixture was stirred at room temperature until the reaction was completed (30 min to 1 h). The reaction mixture was evaporated to afford a dark syrup and the crude product was purified by flash chromatography.

1-Benzoyl-2(S)-isopropyl-5-phenylethynyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-6a.

Yield = 88 %, mp = 249-251 °C (dec). $[\alpha]_D^{25} = + 652.8$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.93 (d, 3H, *J* = 6.8 Hz), 1.0 (d, 3H, *J* = 6.7 Hz), 2.25 (m, 1H), 5.47 (*broad*, 1H), 7.33–7.42 (m, 5H), 7.49 (d, 1H, *J* = 1.5 Hz), 7.54-7.64 (m, 5H), 8.21 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 18.4 (CH₃), 19.1 (CH₃), 34.0 (CH), 69.8 (CH), 84.9 (C), 92.0 (C), 102.1 (C), 123.6(C), 128.8 (CH), 129.1 (CH), 129.3 (CH), 129.7 (CH), 132.0 (CH), 132.3 (CH), 133.8 (C), 141.3 (CH), 161.1 (C), 168.8 (C). IR (KBr) ν (cm⁻¹): 3336, 3055, 2962, 2217, 1674, 1635, 1592. MS *m/z* (%): 344 (M⁺, 26), 301 (96), 274 (14), 196 (6), 105 (100), 77 (21). Anal. calcd for C₂₂H₂₀N₂O₂: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.43; H, 5.83; N, 8.15.

1-Benzoyl-2(S)-isopropyl-5-hept-1-ynyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-6b. Yield = 75.5 %, mp = 157-158 °C. $[\alpha]_D^{25} = + 543.0$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 270 MHz) δ 0.86 (t, 3H, *J* = 7.4 Hz), 0.89 (d, 3H, *J* = 6.7 Hz), 0.96 (d, 3H, *J* = 6.9 Hz), 1.25–1.40 (m, 4H), 1.42–1.52 (m, 2H), 2.17 (m, 1H), 2.28 (t, 2H, *J* = 6.9 Hz), 5.42 (d, 1H, *J* = 4.7 Hz), 7.23 (d, 1H, *J* = 1.5), 7.50–7.62 (m, 5H), 8.04 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 67.5 MHz) δ 14.0 (CH₃), 18.(CH₃), 18.7 (CH₃), 19.4 (CH₂), 21.9 (CH₂), 28.3 (CH₂), 31.0 (CH₂), 33.7 (CH), 69.3 (CH), 75.0 (C), 93.0 (C), 102.7(C), 128.3 (CH), 129.3 (CH), 131.7(CH), 133.8 (C), 139.6 (CH), 161.0(C), 168.3 (C). IR (KBr) ν (cm⁻¹): 3446, 3295, 2227, 1673, 1639, 1604. MS *m/z* (%): 338 (M⁺, 6), 295 (58), 268 (14), 105 (100). Anal. calcd for C₂₁H₂₆N₂O₂: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.20; H, 7.85; N, 8.54.

1-Benzoyl-2(S)-isopropyl-5-hex-1-ynyl-2,3-dihydro-4(H)-pyrimidin-4-one, (S)-6c. Yield =

81.8 %, mp = 129-131 °C. $[\alpha]_D^{25} = + 538.0$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 270 MHz) δ 0.86 (t, 3H, *J* = 7.6 Hz), 0.87 (d, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 1.29–1.49 (m, 4H), 2.14 (m, 1H), 2.27 (t, 2H, *J* = 6.6 Hz), 5.39 (t, 1H, *J* = 5.3), 7.21 (s, 1H), 7.48–7.69 (m, 5H), 8.03 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 67.5 MHz) δ 13.6 (CH₃), 18.0 (CH₃), 18.7 (CH₃), 19.0 (CH₂), 21.8 (CH₂), 30.8 (CH₂), 33.6 (CH), 69.3 (CH), 74.9 (C), 92.9 (C), 102.7 (C), 128.3 (CH), 129.3 (CH), 131.7 (CH), 133.8 (C), 139.6 (CH), 161.0 (C), 168.3 (C). IR (KBr) ν (cm⁻¹): 3301, 2958, 2227, 1674, 1640, 1604. MS *m/z* (%): 324 (M⁺, 6), 281 (63), 254 (14), 105 (100), 77 (7). Anal. calcd for C₂₀H₂₄N₂O₂: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.93; H, 7.87; N, 8.93.

1-Benzoyl-2(*S*)-isopropyl-5-(3-hydroxy-prop-1-ynyl)-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-

6d. Yield = 59 %, mp = 187-189 °C (dec). $[\alpha]_D^{25} = + 594.5$ (c = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 270 MHz) δ 0.88 (d, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 6.7 Hz), 2.16 (m, 1H), 4.16 (d, 2H, *J* = 5.4 Hz), 4.70 (t, 1H, *J* = 5.7 Hz), 5.42 (*broad*, 1H), 7.29 (d, 1H, *J* = 1.2 Hz), 7.51–7.60 (m, 5H), 8.07 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 67.5 MHz). δ 17.5 (CH₃), 18.2 (CH₃), 33.2 (CH), 49.8 (CH₂), 68.9 (CH), 78.0 (C), 91.6(C), 101.3 (C), 127.9 (CH), 128.9 (CH), 131.4 (CH), 133.2 (C), 140.3 (CH), 160.4 (C), 167.9 (C). IR (KBr) ν (cm⁻¹): 3202, 3098, 2960, 2231, 1676, 1605. MS *m/z* (%): 298 (M⁺, 4), 255 (39), 228 (7), 133 (53), 105 (100), 77 (19). Anal. calcd for C₁₇H₁₈N₂O₃: C, 68.44; H, 6.08. Found: C, 68.35; H, 6.38.

1-Benzoyl-2(*S*)-isopropyl-5-phenethyl-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-7. In a

hydrogenation flash was placed 263 mg (0.581 mmol) of acetylenic product (*S*)-**6a** and 26 mg of 10 % w/w Pd/C under a nitrogen atmosphere before the slow addition of 80 mL of MeOH. The resulting mixture was pressurized to 60 psi of hydrogen and mechanically stirred at ambient temperature for 22 h, filtered over Celite and the filtrate was concentrated in a rotary evaporator. The reaction product was purified by flash chromatography (eluent EtOAc-hexane, 4:6) to afford

214 mg (80 % yield) of (*S*)-**7**, as a white solid mp 131-133 °C, $[\alpha]_D^{25} = +249.8$ (*c* = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.79 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.7 Hz), 2.02 (m, 1H), 2.36 (m, 1H), 2.50–2.83 (m, 3H), 5.33 (*broad t*, 1H), 6.79 (s, 1H), 7.10–7.26 (m, 5H), 7.35–7.62 (m, 5H), 7.98 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 75 MHz). δ 18.6 (CH₃), 19.1 (CH₃), 29.3 (CH₂), 33.2 (CH), 35.0 (CH₂), 69.0 (CH), 116.9 (C), 126.5 (CH), 128.5 (CH), 129.0 (CH), 129.2 (CH), 129.5 (CH), 131.7 (CH), 133.3 (CH), 134.6 (C), 142.1 (C), 163.7 (C), 168.6 (C). IR (KBr) ν (cm⁻¹): 3249, 2975, 2882, 1678, 1640. MS *m/z* (%): 349 (*M*⁺+1, 0.3), 305 (90.8), 105 (100), 77 (9.6). Anal. calcd for C₂₂H₂₄N₂O₂: C, 75.84; H, 6.94; N, 8.04. Found: C, 76.14; H, 6.98; N 7.99.

Preparation of the compounds (2*S*,5*S*)-**8** and (2*S*,5*R*)-**8**

1-Benzoyl-2(*S*)-isopropyl-5(*S*)-phenethyl-perhydropyrimidin-4-one, (2*S*,5*S*)-8**.** In a hydrogenation flask was placed 1.25 g (3.63 mmol) of acetylenic derivative (*S*)-**6a** and 60 mL of dry methanol under a nitrogen atmosphere before the addition of 4.6 g of Raney-Ni suspended in 60 mL of methanol and 1.2 mL of acetic acid. The resulting mixture was pressurized to 1750 psi of hydrogen and mechanically stirred at 80 °C for 24 h. The reaction mixture was filtered and the filtrate was concentrated in a rotary evaporator to afford the crude product consisting of a mixture of (*S*)-**7**, (2*S*,5*S*)-**8** and (2*S*,5*R*)-**8** in varying ratios. The major product was purified by flash chromatography (eluent EtOAc-hexane, 6:4) to give 0.51 g of (2*S*,5*S*)-**8** (40 % yield), mp 134-135 °C, $[\alpha]_D^{25} = +18.7$ (*c* = 1, CHCl₃). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.91 (d, 3H, *J* = 6.7 Hz), 1.0 (d, 3H, *J* = 6.6 Hz), 1.64 (m, 1H), 2.10 (m, 2H), 2.29 (m, 1H), 2.58 (m, 2H), 3.20 (dd, 1H, *J* = 11.6, *J* = 13.8 Hz), 4.01 (dd, 1H, *J* = 6.9, *J* = 13.6 Hz), 5.13 (d, 1H, *J* = 8.1 Hz), 7.07-7.25 (m, 5H), 7.35-7.39 (m, 2H), 7.44-7.53 (m, 3H), 7.78 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 18.9 (CH₃), 19.3 (CH₃), 30.8 (CH₂), 33.0 (CH₂), 34.6 (CH), 40.9 (CH), 43.5 (CH₂), 68.8 (CH), 126.5 (CH), 127.3 (CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 130.5 (CH), 136.6 (C), 142.3 (C),

170.5 (C), 171.4 (C). IR (KBr) ν (cm⁻¹): 3309, 3273, 2958, 2927, 2871, 1674, 1641, 1601. MS m/z (%): 350 (M⁺, 1.5), 307 (73.5), 244 (5.9), 105 (100), 77 (6). Anal. calcd for C₂₂H₂₆N₂O₂: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.76; H, 7.59; N 7.97.

1-Benzoyl-2(*S*)-isopropyl-5(*R*)-phenethyl-perhydropyrimidin-4-one, (2*S*,5*R*)-8. Flash column chromatography (eluent EtOAc-hexane, 6:4) from the crude product described above, gave 82 mg of the *trans* diastereomer (2*S*,5*R*)-**8** (6 % yield), mp 56-58 °C, $[\alpha]_D^{25} = +49.1$ (c = 1, CHCl₃, 1). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 0.89 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.5 Hz), 1.60 (m, 1H), 1.92 (m, 1H), 2.12 (m, 1H), 2.32 (m, 1H), 2.49 (m, 2H), 3.61 (dd, 1H, *J* = 5.7 Hz, *J* = 13.8 Hz), 3.88 (d, 1H, *J* = 11.8 Hz), 5.11 (*broad*, 1H), 7.06 (d, 2H, *J* = 7.3 Hz), 7.13 (t, 1H, *J* = 7.3 Hz), 7.23 (t, 2H, *J* = 7.3 Hz), 7.39-7.43 (m, 2H), 7.44-7.50 (m, 3H), 7.84 (*broad*, 1H). ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 18.8 (CH₃), 19.0 (CH₃), 32.6 (CH₂), 33.1 (CH₂), 34.1 (CH), 40.6 (CH), 42.7 (CH₂), 68.7 (CH), 126.3 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH), 129.1 (CH), 130.3 (CH), 136.3 (C), 141.9 (C), 170.5 (C), 171.4 (C). IR (KBr) ν (cm⁻¹): 3333, 2956, 2921, 2859, 1675, 1636. MS m/z (%): 350 (M⁺, 0.7), 307 (40.7), 244 (3.9), 105 (100), 77 (5.6). Anal. calcd for C₂₂H₂₆N₂O₂: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.35; H, 7.83; N 7.86.

1-Benzoyl-2(*S*)-isopropyl-5(*S*)-phenethyl-perhydropyrimidin-4-one, (2*S*,5*S*)-8. In a hydrogenation flask was placed 1.086 g (3.12 mmol) of compound (*S*)-**7** and 60 mL of dry methanol under a nitrogen atmosphere before the addition of 3.9 g of Raney-Ni suspended in 60 mL of methanol and 1.2 mL of acetic acid. The resulting mixture was pressurized to 1900 psi of hydrogen and mechanically stirred at 80 °C for 22 h. The reaction mixture was filtered and the filtrate was concentrated in a rotary evaporator to afford the crude product consisting of a mixture of (*S*)-**7**, (2*S*,5*S*)-**8** y (2*S*,5*R*)-**8** in varying ratios. The major product was purified by flash chromatography (eluent EtOAc-hexane, 6:4) to give 0.53 g of (2*S*,5*S*)-**8** (49 % yield).

1-Benzoyl-2(*S*)-isopropyl-5(*R*)-phenethyl-perhydropyrimidin-4-one, (2*S*,5*R*)-8. Flash

column chromatography (eluent EtOAc-hexane, 6:4) from the crude product described above, gave 126 mg of the *trans* diastereomer (2*S*,5*R*)-**8** (12 % yield).

(S)-2-(Aminomethyl)-4-phenylbutanoic acid, (S)-9. In a 25-mL round-bottom flask was placed 150 mg (0.43 mmol) of pyrimidinone (2*S*,5*S*)-**8** and 20 mL of a 4N HCl solution. The resulting mixture was set on a microwave (MW) apparatus, adapted with a condenser and subjected to 200 W MW irradiation during 6 h at a temperature of 98 °C with a flow of air. The reaction mixture was allowed to cool to room temperature and was then extracted with three 20-mL portions of CH₂Cl₂. The aqueous phase was concentrated at reduced pressure and the residue was purified by silica gel chromatography, eluent isopropanol/MeOH/NH₃OH (5:1:1)⁶ to give 55 mg (66 % yield) of a white powder, mp 220-221 °C, $[\alpha]_D^{25} = -24.4$ (c = 0.6, 1M HCl). [Lit.⁷ mp = 228-230 °C, $[\alpha]_D^{25} = -26.4$ (c = 0.6, 1M HCl)].

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X-Ray crystallographic structures of compounds (S)-4c, (S)-5b and (S)-6a

The structures were solved and refined using SHELX-97, Sheldrick, G. M. (1997) Programs for Crystal Structure Analysis, University of Göttingen, Germany. Within WinGX program version 1.64.05.28, Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837-838. Crystal data for (S)-**4c**: $C_{17}H_{14}N_2O_2$, Mol. Weight = 278.30, Orthorhombic P 21 21 21, $a = 7.9953(2)$ Å, $b = 11.2264(3)$ Å, $c = 31.0421(11)$ Å, $\alpha = 90.0^\circ$, $\beta = 90.0^\circ$, $\gamma = 90.0^\circ$, $V = 2786.29(14)$ Å³, crystal size: $0.20 \times 0.20 \times 0.30$ mm³, $R1 = 0.0444$ ($wR2 = 0.0661$). Crystal data for (S)-**5b**: $C_{14}H_{15}BrN_2O_2$, Mol. Weight = 323.29, Monoclinic C 2, $a = 14.4454(4)$ Å, $b = 7.2110(2)$ Å, $c = 14.2431(5)$ Å, $\alpha = 90.0^\circ$, $\beta = 105.9920(10)^\circ$, $\gamma = 90.0^\circ$, $V = 1426.23(8)$ Å³, crystal size: $0.17 \times 0.25 \times 0.37$ mm³, $R1 = 0.0405$ ($wR2 = 0.0987$). Crystal data for (S)-**6a**: $C_{22}H_{20}N_2O_2$, Mol. Weight = 344.40, Monoclinic P 21, $a = 10.130(3)$ Å, $b = 26.145(7)$ Å, $c = 11.359(3)$ Å, $\alpha = 90.0^\circ$, $\beta = 110.1010(10)^\circ$, $\gamma = 90.0^\circ$, $V = 2825.2(13)$ Å³, crystal size: $0.10 \times 0.20 \times 0.40$ mm³, $R1 = 0.0474$ ($wR2 = 0.0949$). Atomic coordinates for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, U.K. (Fax: (+44) 1223-336-036. e-mail: deposit@ccdc.cam.ac.uk; Deposition number: CCDC 260242, CCDC 260243 and CCDC 260244

Figure 2. (a) X-ray crystallographic structure and solid-state conformation of (*S*)-**4c**. (b) Simplified view of the heterocyclic six-membered ring of enone (*S*)-**4c** highlighting its envelope conformation.⁸

Figure 3. (a) X-ray crystallographic structure and solid-state conformation of compound (*S*)-**5b**. (b) Simplified view of the heterocyclic six-membered ring of bromoenone (*S*)-**5b** highlighting its envelope conformation.⁸

Figure 4. (a) X-ray crystallographic structure and solid-state conformation of alkyne (*S*)-**6a**. (b) Simplified view of the heterocyclic six-membered ring of compound (*S*)-**6a** highlighting its envelope conformation.⁸

NMR spectra. All NMR spectra were recorded at 120 °C in DMSO-*d*₆ in order to remove *cis/trans* issues around the amide bond.

Selected HPLC chromatograms

Millennium Sample Information

heran
 Sample Name: rac-BD-aa Acq Meth Set: Aminoacid
 Operator: Roberto Melgar 4 Unknown Flujo: 1.0 ml/min
 Injection: 1 Volume: 20 Microlitros 10.00
 Date Acquired: 10/31/06 04:28:36 PM Run Time: 30.0 min
 Channel: UV 210nm 486
 Phase: MeOH/H2O 80:20 1.00000 Mannich/organocatalizador 10/31/06 04:54:
 Column: Chirobiotic T 1.00000

Processing Method: impresion

Peak Results

#	Name	Ret Time (min)	Area (uV*sec)	Height (uV)	% Area	% Ht	Start Time (min)	End Time (min)
1		2.117	1438189	90805	12.41	22.22	1.617	2.917
2		3.300	1069097	20295	9.23	4.97	2.917	7.200
3		8.667	3959103	139435	34.18	34.11	7.200	9.633
4		10.200	5118401	158210	44.18	38.71	9.633	11.733

Millennium Sample Information

heran
 Sample Name: Hidro-118-P Acq Meth Set: Aminoacid
 Operator: Roberto Melgar 5 Unknown Flujo: 1.0 ml/min
 Injection: 1 Volume: 20 Microlitros 10.00
 Date Acquired: 10/31/06 04:51:28 PM Run Time: 20.0 min
 Channel: UV 210nm 486 Mannich/organocatalizador 10/31/06 05:08:41 PM
 Phase: MeOH/H2O 80:20 1.00000
 Column: Chirobiotic T 1.00000

Processing Method: impresion

Peak Results

#	Name	Ret Time (min)	Area (uV*sec)	Height (uV)	% Area	% Ht	Start Time (min)	End Time (min)
1		3.700	630802	24778	2.53	3.45	2.883	4.533
2		8.700	476601	19222	1.91	2.68	8.117	9.283
3		9.967	23872533	673435	95.57	93.87	9.283	11.700

2% = 796%
 98% e.e.