Supporting Information

Catalytic Asymmetric Synthesis of the Central Tryptophan Residue of Celogentin C

Steven L. Castle* and G. S. C. Srikanth

*Department of Chemistry and Biochemistry
Brigham Young University, Provo, Utah, 84602*

General Experimental Details

Methylene chloride, THF, and DMF were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina.¹ Propargyl bromide **7a**, iodide **7b**, chloride **7c**, and mesylate **7d** were synthesized by the methods of Jones,² Rigby,³ Marshall,⁴ and Magnus,⁵ respectively. Propargyl tosylate **7e** and diphenyl phosphate **7f** were both synthesized by the method of Cook.⁶ Flash chromatography was carried out using 60–230 mesh silica gel. ¹H NMR spectra were obtained on Varian 300 MHz or 500 MHz spectrometers with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ¹³C NMR spectra were obtained on Varian spectrometers operating at 75 MHz or 125 MHz with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR Spectrometer. Mass spectral data (EI, FAB) were obtained from the Brigham Young University mass

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

² Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937.

³ Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286.

⁴ Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796.

⁵ Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861.

⁶ Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.

spectrometry facility. Optical rotations were obtained on a Perkin–Elmer 241 Polarimeter.

(3-Bromo-1-propynyl)triethylsilane (7a): ^1H NMR (CDCl_3 , 300 MHz) δ 3.94 (s, 2H), 1.00 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 101.4, 90.3, 15.0, 7.6 (3C), 4.4 (3C); IR (film) ν_{max} 2952, 2881, 1198, 1041 cm^{-1} ; HRMS (EI) m/z 232.0291 (M^+ , $\text{C}_9\text{H}_{17}\text{BrSi}$ requires 232.0283).

(3-Iodo-1-propynyl)triethylsilane (7b): ^1H NMR (CDCl_3 , 300 MHz) δ 3.73 (s, 2H), 1.00 (t, J = 7.8 Hz, 9H), 0.61 (q, J = 7.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 103.3, 88.9, 7.6 (3C), 4.4 (3C), -17.8 ; IR (film) ν_{max} 2952, 2871, 1149, 1035 cm^{-1} ; HRMS (EI) m/z 280.0148 (M^+ , $\text{C}_9\text{H}_{17}\text{ISi}$ requires 280.0145).

(3-Chloro-1-propynyl)triethylsilane (7c): ^1H NMR (CDCl_3 , 300 MHz) δ 4.16 (s, 2H), 1.00 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 101.0, 89.7, 31.1, 7.5 (3C), 4.3 (3C); IR (film) ν_{max} 2952, 2914, 2871, 1464, 1421, 1247, 1231, 1030 cm^{-1} ; HRMS (EI) m/z 188.0789 (M^+ , $\text{C}_9\text{H}_{17}\text{ClSi}$ requires 188.0785).

3-Triethylsilyl-2-propynyl Methanesulfonate (7d): ^1H NMR (CDCl_3 , 300 MHz) δ 4.88 (s, 2H), 3.14 (s, 3H), 1.00 (t, J = 7.8 Hz, 9H), 0.64 (q, J = 7.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 98.0, 93.7, 58.6, 39.3, 7.5 (3C), 4.2 (3C); IR (film) ν_{max} 2957,

2871, 1367, 1171, 1014, 938 cm^{-1} ; HRMS (FAB) m/z 249.0976 (MH^+ , $\text{C}_{14}\text{H}_{20}\text{SSiH}$ requires 249.0981).

3-Triethylsilyl-2-propynyl *p*-Toluenesulfonate (7e): ^1H NMR (CDCl_3 , 300 MHz) δ 7.83 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 2H), 4.75 (s, 2H), 2.46 (s, 3H), 0.91 (t, $J = 7.8$ Hz, 9H), 0.52 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 145.2, 133.5, 130.0 (2C), 128.3 (2C), 97.5, 92.8, 58.7, 21.8, 7.4 (3C), 4.1 (3C); IR (film) ν_{max} 2952, 2876, 1372, 1176, 1024, 948 cm^{-1} ; HRMS (FAB) m/z 325.1283 (MH^+ , $\text{C}_{16}\text{H}_{24}\text{O}_3\text{SSiH}$ requires 325.1294).

Diphenyl 3-Triethylsilyl-2-propynyl Phosphate (7f): ^1H NMR (CDCl_3 , 300 MHz) δ 7.38–7.32 (m, 4H), 7.27–7.18 (m, 6H), 4.89 (d, $J = 10.5$ Hz, 2H), 2.46 (s, 3H), 0.97 (t, $J = 7.8$ Hz, 9H), 0.60 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 150.6 (d, $J = 7.5$ Hz, 2C), 129.9 (4C), 125.6 (d, $J = 1.0$ Hz, 2C), 120.3 (d, $J = 5.0$ Hz, 4C), 99.3 (d, $J = 7.0$ Hz), 92.1, 57.3 (d, $J = 5.0$ Hz), 7.5 (3C), 4.2 (3C); IR (film) ν_{max} 3071, 2947, 2871, 1589, 1486, 1285, 1187 cm^{-1} ; HRMS (EI) m/z 403.1492 (MH^+ , $\text{C}_{21}\text{H}_{27}\text{O}_4\text{PSiH}$ requires 403.1495).

***tert*-Butyl (2*S*)-2-(Benzhydrylidene-amino)-5-triethylsilyl-4-pentynoate (8).** A solution of glycinate Schiff base **6** (253 mg, 0.856 mmol) and phase-transfer catalyst **5** (48.9 mg, 0.0871 mmol) in toluene–chloroform 7:3 (3.75 mL) was cooled to -20 $^{\circ}\text{C}$ and treated with propargyl bromide **7a** (490 mg, 2.10 mmol) followed by 50% aq KOH (1.25 mL). The resulting mixture was stirred at -20 $^{\circ}\text{C}$ under Ar for 7 h. It was then diluted

with Et₂O (100 mL) and washed with H₂O (2 × 25 mL). The organic layer was dried (MgSO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 3 × 16 cm, 5–9% Et₂O in hexanes gradient elution followed by 20% EtOAc in hexanes elution) afforded **8** (255 mg, 0.569 mmol, 66%, 75% based on recovered **6**) as a colorless oil, along with **6** (28.0 mg, 11% recovery) and **7a** (262 mg, 53% recovery). The phase-transfer catalyst **5** can also be recovered via the procedure of Corey.⁷ For **8**: $[\alpha]_D^{25} -74$ (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.66–7.63 (m, 2H), 7.46–7.43 (m, 3H), 7.40–7.28 (m, 5H), 4.19 (t, *J* = 6.8 Hz, 1H), 2.89 (d, *J* = 6.6 Hz, 2H), 1.45 (s, 9H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.53 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.6, 169.8, 140.1, 136.6, 130.4, 129.2 (2C), 128.8, 128.6 (2C), 128.5 (2C), 128.1 (2C), 105.2, 83.8, 81.6, 65.1, 28.2 (3C), 25.0, 7.6 (3C), 4.6 (3C); IR (film) ν_{max} 2955, 2874, 1734, 1625, 1447, 1153 cm⁻¹; HRMS (EI) *m/z* 447.2591 (M⁺, C₂₈H₃₇NO₂Si requires 447.2594).

8 was obtained in 94% ee as analyzed by HPLC (Chiralcel OD-H, 99.8:0.2 hexanes:*i*-PrOH, 1mL/min, R_T = 7.3 min (major enantiomer), 10.9 min). The absolute configuration of **8** was assigned based on previous reports that catalyst **5** affords (*S*)-amino acid derivatives.⁸ This assignment was reinforced by the observation that alkylations with BINOL-based catalyst **2**, which is known to provide (*R*)-amino acid derivatives,⁹ provided the slower-eluting enantiomer as the major product. The identities of the two enantiomers were confirmed by comparison with the HPLC chromatogram generated from a racemic sample of **8** (prepared with tetrabutylammonium bromide as catalyst).

⁷ Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

⁸ Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I.-Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.

⁹ Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

***tert*-Butyl (2*S*)-2-Benzoyloxycarbonylamino-5-triethylsilyl-4-pentynoate (9).** A solution of Schiff base **8** (225 mg, 0.503 mmol) in THF (13.6 mL) at 0 °C was treated with HCl (1.0 N in H₂O, 1.7 mL, 1.7 mmol) and stirred at 0 °C for 50 min. Sat aq NaHCO₃ (2 mL) was added to the mixture, and it was extracted with EtOAc (3 × 12 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The resulting crude amine was dissolved in dioxane–water 10:1 (8.4 mL) at room temperature and treated with NaHCO₃ (106 mg, 1.26 mmol) followed by benzyl chloroformate (180 µL, 214 mg, 1.26 mmol). The resulting mixture was stirred at room temperature for 1.75 h. Sat aq NaHCO₃ (11 mL) was added to the mixture, and it was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 2 × 17 cm, 1:10 Et₂O:hexanes elution) afforded **9** (203 mg, 0.487 mmol, 97%) as a colorless oil: $[\alpha]_D^{25} +44$ (*c* 1.9, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.38–7.30 (m, 5H), 5.59 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 4.40 (dt, *J* = 4.2, 8.4 Hz, 1H), 2.80 (d, *J* = 4.2 Hz, 2H), 1.48 (s, 9H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.57 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.4, 155.8, 136.6, 128.7 (2C), 128.3, 128.2 (2C), 101.8, 85.8, 82.6, 67.1, 53.0, 28.1 (3C), 24.5, 7.6 (3C), 4.5 (3C); IR (film) $\nu_{\max}$ 2955, 1728, 1504, 1348, 1216, 1157 cm⁻¹; HRMS (FAB) *m/z* 440.2225 (MNa⁺, C₂₃H₃₅NO₄SiNa requires 440.2233).

5-Hydroxymethyl-2-iodo-nitrobenzene (11). To a solution of 4-iodo-3-nitrobenzoic acid (**10**)¹⁰ (480 mg, 1.64 mmol) in anhydrous THF (3 mL) at 0 °C was added BH₃·THF (1.0 M in THF, 3.4 mL, 3.4 mmol). The resulting red solution was stirred at room temperature under N₂ for 5 h. H₂O (5 mL) was added to the mixture, and it was saturated with K₂CO₃ (ca. 1 g). The mixture was then extracted with Et₂O (4 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 2 × 18 cm, 5% EtOAc in hexanes elution) afforded **11** (430 mg, 1.54 mmol, 94%) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 4.77 (s, 2H) 1.99 (br s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.3, 143.2, 142.2, 131.5, 123.6, 84.6, 63.6; IR (film) ν_{max} 3259, 1524, 1348, 1018, cm⁻¹; HRMS (EI) *m/z* 278.9401 (M⁺, C₇H₆O₃NI requires 278.9393).

5-(*tert*-Butyldimethylsilyloxymethyl)-2-iodo-nitrobenzene (12). To a solution of **11** (420 mg, 1.51 mmol) in anhydrous DMF (3 mL) was added imidazole (140 mg, 2.06 mmol) and TBS-Cl (300 mg, 1.99 mmol). The mixture was stirred at room temperature under N₂ for 16 h, then concentrated in vacuo. The residue was taken up in Et₂O (10 mL), washed with H₂O (5 mL) and brine (5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 2 × 5 cm, 0–2% EtOAc in hexanes gradient elution) afforded **12** (516 mg, 1.31 mmol, 87%) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 4.45 (s, 2H) 0.95 (s, 9H), 0.10 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.2, 144.1, 141.8,

¹⁰ Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, 38, 7963.

130.9, 123.0, 83.8, 63.5, 26.1 (3C), 18.6, -5.1 (2C); IR (film) $\nu_{\max}$ 2954, 1535, 1471, 1258, 1019 cm^{-1} ; HRMS (FAB) m/z 394.0341 (MH^+ , $\text{C}_{13}\text{H}_{20}\text{INO}_3\text{SiH}$ requires 394.0335).

5-(*tert*-Butyldimethylsilyloxymethyl)-2-iodoaniline (13). To a solution of **12** (300 mg, 0.763 mmol) in glacial acetic acid (5 mL) was added Fe (230 mg, 4.12 mmol). The mixture was heated at 100 °C under N_2 for 90 min and then allowed to cool to room temperature. The acetic acid was removed in vacuo, and the residue was partitioned between EtOAc (15 mL) and sat aq NaHCO_3 (5 mL). The aqueous layer was extracted with EtOAc (2×5 mL), and the combined organic layers were washed with brine (12 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2 , 4×15 cm, 0–2% EtOAc in hexanes gradient elution) afforded **13** (256 mg, 0.705 mmol, 92%) as a colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 7.57 (d, $J = 8.1$ Hz, 1H), 6.76 (d, $J = 1.8$ Hz, 1H), 6.44 (dd, $J = 1.8, 8.1$ Hz, 1H), 4.62 (s, 2H), 4.08 (br s, 2H), 0.95 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 146.8, 143.4, 138.9, 118.0, 112.5, 82.0, 64.5, 26.2 (3C), 18.6, -5.0 (2C); IR (film) $\nu_{\max}$ 3462, 3354, 2957, 2924, 2849, 1611, 1421, 1252, 1095 cm^{-1} ; HRMS (FAB) m/z 364.0600 (MH^+ , $\text{C}_{13}\text{H}_{22}\text{INOSiH}$ requires 364.0594).

***N*-Carbobenzyloxy-6-(*tert*-butyldimethylsilyloxymethyl)-2-triethylsilyl-L-tryptophan *tert*-Butyl Ester (14).** A solution of **9** (25.5 mg, 0.0611 mmol) and **13** (24.4 mg, 0.0672 mmol) in anhydrous DMF (765 μL) was treated with $\text{Pd}(\text{OAc})_2$ (0.8 mg, 0.003 mmol), LiCl (2.7 mg, 0.0637 mmol), and Na_2CO_3 (15.0 mg, 0.142 mmol). The resulting mixture was degassed with a stream of Ar for 10 min and stirred at 90 °C under

Ar for 23 h. The solvent was removed in vacuo, and the residue was dissolved in CH₂Cl₂ (5 mL), filtered through a pad of Celite (washed with 3 × 1 mL of CH₂Cl₂), and concentrated in vacuo. Flash chromatography (SiO₂, 1.5 × 10.5 cm, 10–20% EtOAc in hexanes gradient elution) afforded **14** (23.2 mg, 0.355 mmol, 58%) as a light brown oil: $[\alpha]_D^{25} +5.5$ (*c* 2.1, CH₃OH); ¹H NMR (CDCl₃, 500 MHz) δ 7.97 (br s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.34–7.25 (m, 5H), 7.02 (d, *J* = 8.5 Hz, 1H), 5.19 (d, *J* = 7.5 Hz, 1H), 5.01 (d, *J* = 13 Hz, 1H), 4.95 (d, *J* = 13 Hz, 1H), 4.86 (s, 2H), 4.54–4.50 (m, 1H), 3.31 (dd, *J* = 6.0, 15 Hz, 1H), 3.15 (dd, *J* = 9.0, 15 Hz, 1H), 1.35 (s, 9H), 1.03–0.91 (m, 24H), 0.14 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.9, 155.9, 138.9, 136.6, 136.3, 132.7, 128.6 (2C), 128.2, 128.1 (3C), 120.2, 118.9, 118.4, 108.5, 81.9, 66.8, 65.7, 56.2, 29.9, 28.1 (3C), 26.2 (3C), 18.7, 7.6 (3C), 3.9 (3C), –4.9 (2C); IR (film) ν_{max} 3348, 3175, 2952, 2930, 2876, 2860, 1714, 1253, 1160 cm^{–1}; HRMS (FAB) *m/z* 675.3622 (MNa⁺, C₃₆H₅₆N₂O₅Si₂Na requires 675.3625).

14 was obtained in 93% ee as analyzed by chiral HPLC (Chiralcel OD-H, 99:1 hexanes:*i*-PrOH, 1 mL/min, R_T = 13.7 min, 16.8 min (major enantiomer)), indicating that no racemization took place in the conversion of **8** to **14**. The identities of the two enantiomers were confirmed by comparison with the HPLC chromatogram generated from a racemic sample of **14** (prepared from a racemic sample of **8**).