A Short, Enantioselective Total Synthesis of Okaramine N

Phil S. Baran, Carlos A. Guerrero and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138, USA

Supporting Information

General Techniques. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (ether) and methylene chloride (CH_2Cl_2) were obtained by drying over Na/benzophenone (THF, diethyl ether) or CaH_2 (toluene, CH_2Cl_2). Crystalline $\text{Pd}(\text{OAc})_2$ was freshly prepared from PdCl_2 following the published procedure.¹ Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an acidic mixture of phosphomolybdic acid/cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Photooxidations were carried out using 200 W sunlamp. Mass spectrometric data were collected by the Harvard University Department of Chemistry Mass Spectrometry Facility. High resolution ESI mass spectra were obtained by using a LCT mass spectrometer (Micromass Inc. (Beverly, MA)) using a mass resolution of 5000. ApCI mass spectra were obtained by using a Platform II mass spectrometer (Micromass Inc. (Beverly, MA)). NMR spectra were recorded on Varian Innova-600, Innova-500, or Mercury-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Nicolet Avatar 360 series FT-IR spectrometer. Low temperature experiments which were conducted for longer than 3 h used a Cryocool apparatus (Neslab Instruments, model CB80) with an isopropanol bath.

¹ Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. J. *Chem. Soc.* **1965**, 3632.

Tetracycle 4. To a solution of *l*-tryptophan methyl ester (218 mg, 1.0 mmol) in CH₂Cl₂ (2 mL) was added activated 4A molecular sieves (300 mg) followed by 2-methyl-3-butenal (96 μ L, 1.0 mmol). After 3 h at room temperature the resulting solution of imine was evaporated to dryness and the flask was charged with dry MeOH (4 mL). The suspension was cooled to 0 °C and NaBH₄ (46 mg, 1.2 mmol) was added. The ice bath was immediately removed and vigorous stirring continued for 30 min at which point the solvent was removed in vacuo and the amine **2**² could separated from the molecular sieves by trituration with CH₂Cl₂. The yield of amine **2** was essentially quantitative. A solution of this amine in CH₂Cl₂ (10 mL) was charged with tryptophan derivative **3** (494 mg, 1.0 mmol) and bis(2-oxo-3-oxazolidyl)phosphinic chloride (BOPCl; 305 mg, 1.2 mmol) and then cooled to 0 °C. Diisopropylethylamine (0.21 mL, 1.2 mmol) was then added slowly and the reaction was maintained at 0 °C until completion (3 h). The solution was then diluted with EtOAc (15 mL), and then sequentially with 1 *N* HCl (twice, 30 mL), water (twice, 30 mL), and brine (30 mL). The organic layer was dried (MgSO₄), the solvent removed in vacuo and the residue was purified by flash column chromatography (SiO₂, hexanes:EtOAc 6:1 to 2:1) to furnish 533 mg (70% yield) of tetracycle **4**: white powder; *R*_f = 0.24 (silica gel, hexanes/EtOAc 2:1), 0.13 (silica gel, hexanes/Et₂O 1:1); [α]_D = - 28 (c 0.45, CHCl₃); IR (neat) $\nu_{\max}$ 3313, 1716, 1662, 1456, 1234, 910, 737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 2:1 mixture of rotomers, data for both rotomers given) δ 7.77 (d, *J* = 7.5 Hz, 2.67 H), 7.68 (d, *J* = 7.5 Hz, 1.33 H), 7.58 (dd, *J* = 13, 6.5 Hz, 2.67 H), 7.52 (t, *J* = 8.0 Hz, 1.33 H), 7.40 (t, *J* = 7.5 Hz, 3 H), 7.33 – 7.27 (m, 5 H), 7.16 – 7.08 (m, 3 H), 6.21 (bs, 1 H, D₂O exchangeable), 6.12 (dd, *J* = 17.5, 11 Hz, 0.67 H), 6.06 (dd, *J* = 17.5, 11 Hz, 0.33 H), 5.91 (t, *J* = 6.0 Hz, 1 H), 5.51 (d, *J* = 9 Hz, 1 H), 5.22 (d, *J* = 11 Hz, 0.67 H), 5.16 (d, *J* = 17.5 Hz, 0.67 H), 5.15 (d, *J* = 11 Hz, 0.33 H), 5.12 (d, *J* = 17.5 Hz, 0.33 H), 4.97 (dd, *J* = 15, 8 Hz, 1 H), 4.52 – 4.33 (m, 7 H), 4.21 (dd, *J* = 12, 7 Hz, 1 H), 3.68 (s, 1 H), 3.49 (s, 2 H), 3.48 – 3.07 (m, 7 H), 1.73 (s, 6 H), 1.69 (s, 3 H), 1.68 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 171.2, 144.1, 143.8, 141.3, 135.9, 127.7 (2 C), 127.1 (3 C), 125.1 (2 C), 124.4, 123.3, 121.9, 120.8, 120.0 (3 C), 119.3, 119.1, 118.8, 118.3, 114.0, 113.7, 113.4, 111.3, 111.1, 108.5, 66.9, 59.4, 58.9, 52.1, 51.3, 47.1 (2 C), 46.5, 43.3, 41.1, 29.7, 29.3, 28.8, 27.9 (2 C), 25.3, 24.6, 17.4; MS (APCI+) 763.3 (M + H⁺); HRMS (ESI-MS) calcd. for C₄₈H₅₁N₄O₅⁺ [M + H⁺] 763.3859, found 763.3844.

² For a similar synthesis of amine **4** via the intermediate imine, see: Harrison, D. M.; Sharma, R. B. *Tetrahedron* **1993**, *49*, 3165 – 3184.

Pentacycle 5. A solution of $\text{Pd}(\text{OAc})_2$ (22.5 mg, 0.1 mmol) in dioxane (0.65 mL) was prepared by brief heating followed by slow cooling to room temperature. This dioxane solution was then added to intermediate **4** (76.2 mg, 0.1 mmol). After 1 min, acetic acid (0.17 mL) was added followed by dropwise addition water (0.17 mL). The reaction was stirred vigorously for 16 h under an atmosphere of oxygen at room temperature before being treated with saturated aqueous NaHCO_3 (5 mL). The crude mixture was then diluted with EtOAc (5 mL) washed with additional sat. aqueous NaHCO_3 (5 mL), water (5 mL), then brine (5 mL), dried (MgSO_4), and the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2 , hexanes:ether 2:1 to 1:1) furnished **5** (25.5 mg, 38% yield) and recovered tetracycle **4** (9.1 mg); white powder; R_f = 0.30 (silica gel, hexanes/ Et_2O 1:1); MS (APCI+) 760.2 (H^+); HRMS (ESI-MS) calcd. for $\text{C}_{48}\text{H}_{49}\text{N}_4\text{O}_5^+$ [$\text{M} + \text{H}^+$] 761.3703, found 761.3694. Since the ^1H NMR is a complex mixture of rotomers, full data of diketopiperazine **6** is given.

Diketopiperazine 6. To a solution of pentacycle **5** (67 mg, 0.1 mmol) in THF (10 mL) at 0 °C was added diethylamine (5 mL). The solution was allowed to warm to 23 °C over 2 h and the reaction was stirred for an additional 4 h after which the solution was concentrated in vacuo. The crude residue was passed through a silica gel plug to remove the non-polar byproducts to furnish diketopiperazine **6** (48 mg, 95% yield) as a white amorphous powder; R_f = 0.35 (silica gel, EtOAc); $[\alpha]_D = -52.5$ (c 0.2, MeOH); IR (neat) ν_{max} 3330, 1670, 1644, 1455, 1311, 1240, 925, 766 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.13 (s, 1 H, D_2O , exchangeable), 7.71 (dd, J = 8.0, 2.0 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.35 (dd, J = 6.0, 1.5 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.28 – 7.18 (m, 2 H), 7.04 (t, J = 8.0 Hz, 1 H), 6.97 (t, J = 8.0 Hz, 1 H), 6.03 (dd, J = 17.5, 10.5 Hz, 1 H), 5.88 (d, J = 8.0 Hz, 1 H), 5.86 (d, J = 8.0 Hz, 1 H), 5.85 (s, 1 H), 5.34 (brs, 1 H, D_2O exchangeable), 5.19 (d, J = 10.5 Hz, 1 H), 5.12 (d, J = 17.5 Hz, 1 H), 4.20 (d, J = 7.0 Hz, 1 H), 3.90 (d, J = 12.0 Hz, 1 H), 3.82 (d, J = 15 Hz, 1 H), 3.41 (dd, J = 14.5, 6.5 Hz, 1 H), 3.02 (dd, J = 14.0, 2.5 Hz, 1 H), 1.69 (s, 3 H), 1.68 (s, 3 H), 1.64 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (125 MHz, acetone- d_6) δ 165.8, 165.3, 144.6, 142.0, 141.6, 136.1, 135.5, 129.2, 128.9, 125.3, 122.6, 121.0, 120.5, 119.2, 118.7, 118.6, 118.4, 113.9, 112.9, 111.1, 107.7, 104.1, 58.9, 57.9,

55.1, 37.1, 32.5, 32.4, 27.7 (2 C), 26.7, 26.4; MS (APCI+) 506.2 (M^+); HRMS (ESI-MS) calcd. for $C_{32}H_{35}N_4O_2^+$ [$M + H^+$] 507.2760, found 507.2772.

Okaramine N (1). To a solution of diketopiperazine **6** (4 mg, 0.0079 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C was added dropwise a solution of *N*-methyltriazolinedione (0.9 mg, 0.0079 mmol) over 10 min. With simple indoles, such as **10**, measuring the amount of MTAD was not necessary since the addition of this reagent stopped when the additive no longer lost its color (hot pink) in the reaction vessel. In this case, if a slight excess of MTAD was added, the *N*-*tert*-prenyl indole started to react. The solvent was then removed in vacuo and replaced with MeOH. A catalytic amount of methylene blue was added and oxygen bubbled through the solution. It was cooled to –28 °C using a Cryocool apparatus (isopropanol bath) and maintained at this temperature while being irradiated with a sunlamp (reaction mixture 13” from lamp) for 7.5 h at which point the sunlamp was turned off and 100 μ L of methyl sulfide were added. The solution was allowed to warm to –10 °C over 3 h after which the solvent was removed in vacuo. Finally, heating the residue without solvent at 110 °C for 30 min and purification by PTLC (silica gel, EtOAc or 10:1 CH_2Cl_2 :MeOH) furnished okaramine N (1.5 mg, 36% yield along with recovered **6**, 1.9 mg, 70% yield of **1** based on recovered **6**) which was spectroscopically identical to that reported by Hayashi and co-workers [α]_D = +273 (c 0.15, MeOH), lit +284 (c 0.15, MeOH); R_f = 0.44 (SiO₂, EtOAc); (500 MHz ¹H NMR (1+2D), IR, APCI, ESI-HRMS all identical to reported; see attached NMR spectra, Figures S1 and S2).

Indoline 8. To a solution of (S)-*N*-Boc-tryptophan methyl ester (1.84g, 5.78 mmol) in acetic acid (28 mL) at 0 °C was added NaBH₃CN (3.63g, 57.8 mmol). After addition, the reaction vessel was allowed to warm to room temperature. After 12 h, the crude material was diluted with water and CH_2Cl_2 (150 mL each). Using 1 *N* aq. NaOH, the pH of the mixture was brought to > 12. The organic layer of the resulting mixture was isolated and washed twice with water (200 mL) then once with brine (200 mL). The solution was dried (Na₂SO₄) and concentrated in vacuo. Purification by flash column chromatography (SiO₂, hexanes/EtOAc 6:1 to 1:1) yielded a 1:1

mixture (1.11g, 60% yield) of diastereomers whose spectral characteristics were identical to those reported in the literature.³

***N*-Boc-*N'*-*tert*-prenyl-tryptophan Methyl Ester (9).** A solution of indoline **8** (742mg, 2.32 mmol) in THF (8 mL) was charged with CuCl (23mg, 0.23 mmol). The suspension was stirred for 5 min after which diisopropylethylamine (0.44 mL, 2.55 mmol) was added over 1 min. Again, the suspension was allowed to stir for 5 min after which 2-acetoxy-2-methyl-3-butyne (0.35 mL, 2.78 mmol) was added over 2 min. The suspension was heated at reflux for 8 h after which it was filtered through a pad of Celite. The crude material was purified by flash column chromatography (SiO₂, hexanes:EtOAc 6:1 to 4:1) to furnish 851 mg (95% yield) of the propargyl indoline. This intermediate (851 mg, 2.20 mmol) was dissolved in CH₂Cl₂ (11 mL) and cooled to 0 °C. DDQ (525 mg, 2.31 mmol) was then added in one portion and the reaction was allowed to stir for 20 min. The crude material was passed through a pad of Celite and diluted with EtOAc before being washed sequentially with 10% aq. NaHCO₃ (twice, 100 mL), water (twice, 50 mL), and brine (50 mL). The organic layer was dried (MgSO₄), the solvent removed in vacuo, and the residue dissolved in a solution of MeOH/quinoline (10:1, 8 mL total volume). A catalytic amount of 10% Pd/C was added and hydrogen bubbled through the solution until the reduction was complete (3 h). The crude material was passed through a pad of Celite and diluted with EtOAc (20 mL) before being washed sequentially 10% aq. H₂SO₄ (twice, 50 mL), water (twice, 50 mL), and brine (50 mL). The organic layer was dried (Mg₂SO₄), the solvent removed in vacuo, and the residue purified by flash column chromatography (SiO₂, hexanes/ether 3:1) to furnish 744 mg (87% yield from the propargyl indoline) of **9**: yellow viscous oil; *R*_f = 0.66 (silica gel, hexanes/EtOAc, 2:1); [α]_D = +93 (c 0.47, MeOH); IR (neat) ν_{max} 3371, 2977, 1743, 1711, 1499, 1456, 1365, 1242, 1200, 1163, 1017, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, *J* = 7.5 Hz, 2 H) 7.48 (d, *J* = 8 Hz, 1 H), 7.13 – 7.07 (m, 3 H), 6.13 (dd, *J* = 17.5, 11 Hz, 1 H), 5.21 (d, *J* = 11 Hz, 1 H), 5.16 (d, *J* = 17.5 Hz, 1 H), 5.05 (bd, *J* = 8.0 Hz, 1 H), 4.65 (bdd, *J* = 13, 5.5 Hz, 1 H), 3.68 (s, 3 H), 3.28 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.23 (dd, *J* = 14.5, 5.5 Hz, 1 H), 1.73 (s, 6 H), 1.43 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 155.2, 144.0 (2 C), 123.8, 120.8, 118.9, 118.8, 113.8 (2 C), 113.5 (2 C), 108.1, 58.9, 54.3, 52.1, 28.3 (3

³ Dinh, T. D.; Van Vranken, D. L. *J. Peptide Res.* **1999**, 53, 465-474.

C), 28.1, 27.9 (2 C); MS (APCI+) 329 ($M + H^+$); HRMS (ESI-MS) calcd. for $C_{21}H_{23}N_3O_2H^+$ [$M + H^+$] 387.2284, found 387.2292.

***Tert*-prenylated Indole 3.** To a solution of intermediate **9** (807 mg, 2.09 mmol) in MeOH (14 mL) was added $SOCl_2$ (0.23 mL, 3.13 mmol). The solution was immersed in a preheated oil bath (50 °C) for 2 h. The solution was then diluted with CH_2Cl_2 and water (30 mL each), and brought to pH > 12 with 1 *N* aq. NaOH. The organic layer was separated, washed with water and brine (30 mL each), dried ($MgSO_4$), and the solvent removed in vacuo. The residue was then dissolved in THF (104 mL). The solution was cooled to 0 °C before LiOH (750 mg, 31.3 mmol) in water (26 mL) was added over 3 min. When saponification was complete (2 h), CH_2Cl_2 (70 mL) and 10% aq. Na_2CO_3 (70 mL) were added followed by FmocCl (594 mg, 2.30 mmol). After 10 min, the crude reaction mixture was diluted with 100 mL EtOAc and acidified to pH < 5 using H_2SO_4 . The organic layer was isolated, washed twice with water (100 mL) and brine (100 mL), then dried ($MgSO_4$). The residue was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 3:1 to 1:1 then CH_2Cl_2 /MeOH 10:1) to furnish 837 mg (81% yield) of **3**: white powder; R_f = 0.57 (silica gel, CH_2Cl_2 /MeOH 10:1); $[\alpha]_D = -103$ (c 0.61, $CHCl_3$); IR (neat) ν_{max} 2977, 1720, 1450, 1286, 1244, 1197, 1108, 738 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7 Hz, 4 H), 7.55 – 7.45 (m, 3 H), 7.38 – 7.33 (m, 2 H), 7.27 – 7.21 (m, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.00 (t, J = 7.5 Hz, 1 H), 6.91 (s, 1 H), 6.05 (dd, J = 17.5, 11 Hz, 1 H), 5.44 (dd, J = 10, 5.0 Hz, 1 H), 5.14 (d, J = 11 Hz, 1 H), 5.10 (d, J = 17.5 Hz, 1 H), 4.41 (dd, J = 9.5, 7.0 Hz, 1 H), 4.19 (dd, J = 9.5, 7.0 Hz, 1 H), 4.03 (t, J = 7.0 Hz, 1 H), 4.43 (dd, J = 15, 5.0 Hz, 1 H), 3.14 (dd, J = 15, 10 Hz, 1 H), 1.65 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 152.9 (2 C), 144.0, 143.2 (2 C), 141.2 (2 C), 135.5 (2 C), 129.0, 127.8 (2 C), 127.2 (2 C), 125.0 (2 C), 120.9, 120.0, 119, 118.5, 133.8, 113.3, 108.6, 69.0, 58.8, 53.4, 46.5, 27.9, 25.2; MS (APCI+) 495.4 ($M + H^+$); HRMS (ESI-MS) calcd. for $C_{31}H_{31}N_2O_4^+$ [$M + H^+$] 495.2283, found 495.2271.

Figure S1. ^1H NMR of authentic okaramine N (spectra provided by H. Hayashi) (top) and of pure synthetic okaramine N [A = impurity from acetone solvent, B = water, C = acetone, D = grease (see, *J. Org. Chem.* **1997**, 62, 7513)].

Figure S2. Synthetic Okaramine N in CDCl₃ (top spectra) and HPLC analysis of the sample.

No.	Natural δ_{H} (Mult. J Hz)	Synthetic δ_{H} (Mult. J Hz)
2	4.43 (dd, 9.2, 6.4)	4.43 (dd, 9.0, 6.5)
3	2.43 (dd, 13.1, 9.2)	2.43 (dd, 13.1, 9.2)
	2.69 (dd, 13.1, 6.4)	2.69 (dd, 13.1, 6.4)
4	7.07 (dd, 7.3, 1.2)	7.07 (dd, 7.3, 1.2)
5	6.60 (td, 7.3, 1.2)	6.60 (t, 7.5)
6	6.88 (ddd, 8.6, 7.3, 1.2)	6.88 (ddd, 8.6, 7.3, 1.2)
7	6.49 (d, 8.6)	6.49 (d, 8.0)
8a	5.23 (s)	5.23 (s)
11	5.83 (dd, 17.7, 11.0)	5.83 (dd, 17.5, 10.5)
12	4.72 (dd, 11.0, 1.2)	4.72 (dd, 10.5, 1.2)
	4.82 (dd, 17.7, 1.2)	4.82 (dd, 17.5, 1.2)
13	1.11 (s)	1.11 (s)
14	1.04 (s)	1.04 (s)
1'	3.38 (dd, 15.0, 3.7)	3.38 (dd, 15.0, 4.0)
	3.56 (dd, 15.0, 3.7)	3.56 (dd, 15.0, 4.0)
2'	4.33 (t, 3.7)	4.33 (t, 4.0)
4'	5.93 (d, 8.6)	5.93 (d, 9.0)
5'	5.70 (d, 8.6)	5.70 (d, 9.0)
8'	7.15 (dd, 7.3, 1.2)	7.15 (d, 7.0)
9'	6.96 (ddd, 7.9, 7.3, 1.2)	6.96 (ddd, 8.0, 7.0, 1.2)
10'	6.93 (ddd, 7.9, 7.6, 1.2)	6.93 (ddd, 8.0, 7.0, 1.2)
11'	7.67 (dd, 7.6, 1.2)	7.67 (d, 7.0)
13'	1.12 (s)	1.12 (s)
14'	1.43 (s)	1.43 (s)
7'-NH	9.71 (bs)	9.71 (bs)
3a'-OH	4.61 (s)	4.61 (s)