

Synthesis of 7-Substituted Benzolactam-V8s and their Selectivity for the Protein Kinase C Isozymes

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Supporting material

Experimental

2-(2'-Benzoxylethyl)-1,3-cyclohexanedione 4. To a solution of 1,3-cyclohexanedione (10.7 g, 92 mmol) in 50 mL of ethanol, 20 mL of dioxane and 10 mL of water was added potassium hydroxide (6.0 g, 88 mmol). The resulting solution was stirred for 10 min before 2-benzoxylethyl iodide (36.2 g, 138 mmol) was added. After the reaction mixture was heated at 90 °C overnight, it was concentrated. The residue was partitioned between ethyl acetate and 10% aqueous KOH. The organic layer was separated and the aqueous layer was extracted with 10% aqueous KOH for twice. The combined aqueous layers were acidified by adding 12 N HCl, and then extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residual oil was chromatographed (eluting with 1/1 ethyl acetate/hexane) to afford 13.76 g (64%) of **4** as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.29 (m, 4H), 5.35 (s, 1H), 4.60 (s, 2H), 4.00 (t, *J* = 4.6 Hz, 2H), 3.77 (t, *J* = 4.6 Hz, 2H), 2.46 (t, *J* = 6.3 Hz, 2H), 2.35 (t, *J* = 6.3 Hz, 2H), 1.98 (dt, *J* = 6.4 Hz, 2H); MS *m/z* 246 (M⁺), 203, 155, 140, 112, 105, 91, 65, 43; HRMS Calcd for C₁₅H₁₈O₃ (M⁺) 246.1256, found 246.1276; Anal. Calcd for C₁₅H₁₈O₃: C, 73.15, H, 7.37; found C, 72.88, H, 7.35.

Condensation of 4 with L-valine benzyl ester toluenesulfonic acid salt. A mixture of **4** (6.13 g, 24.9 mmol) and L-valine benzyl ester toluenesulfonic acid salt (10.39 g, 27.4 mmol) in 200 mL of toluene was refluxed with azeotropic removal of water until the starting material disappeared monitored by TLC. During the reaction pyridine (3.02 mL, 37.4 mmol) was added in 10 parts. The cooled solution was evaporated via rotavapor and the residual oil was partitioned between ethyl acetate and water. The aqueous layer was extracted and the combined organic layers were washed with brine. After the solution was dried over anhydrous Na₂SO₄, it was concentrated. Purification of the residual oil via chromatography (eluting with 1/2 ethyl acetate/hexane) afforded 8.77 g (81%) of **4**. [α]_D¹⁵ = +17.5 (*c* 5.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.29 (m, 4H), 7.27-7.21 (m, 4H), 6.50 (d, *J* = 9.2 Hz, 1H), 5.16 and 5.09 (ABq, *J* = 12.1 Hz, 2H), 4.46 and 4.40 (ABq, *J* = 12.0 Hz, 2H),

3.84 (dd, $J = 9.2, 6.4$ Hz, 1H), 3.59-3.48 (m, 2H), 2.70-2.59 (m, 2H), 2.38-2.24 (m, 3H), 2.12-1.96 (m, 2H), 1.93-1.78 (m, 2H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); MS m/z 435 (M^+), 344, 314, 192, 166, 91, 72, 55; Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45, H, 7.64, N, 3.22; found C, 74.08, H, 8.01, N, 3.38.

Bromination of 5 with NBS: To a mixture of 5 (3.53 g, 8.1 mmol) and 40 mL of CCl_4 was added NBS (2.89 g, 16.2 mmol) at 0 °C. After the reaction solution was stirred at 0 °C overnight, it was passed a short column of silica gel to remove the resulting precipitate, and washed with 20 mL of CCl_4 . The elutant was dried over anhydrous Na_2SO_4 , and concentrated. The residue was dissolved in 60 mL of benzene before 1.36 g of $NaHCO_3$ was added. The resulting mixture was heated at 40 °C with stirring for 2 h. The cooled solution was partitioned between of ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. Chromatography of the residual oil eluting with 1/10 ethyl acetate/petroleum ether afforded 3.07 g (74%) of **8**, together with 387 mg (11%) of **9**. **8**: $[\alpha]_D^{15} = -21.9$ (c 2.9, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4H), 7.26-7.22 (m, 6H), 7.12 (d, $J = 8.8$ Hz, 1H), 6.08 (d, $J = 8.8$ Hz, 1H), 6.01 (s, OH), 5.12 and 5.08 (ABq, $J = 12.2$ Hz, 2H), 4.93 (br d, $J = 8.9$ Hz, NH), 4.49 and 4.42 (ABq, $J = 12.2$ Hz, 2H), 3.78 (d, $J = 5.2$ Hz, 1H), 3.74-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.05-2.88 (m, 2H), 2.02 (m, 1H), 1.01 (d, $J = 6.2$ Hz, 3H), 0.99 (d, $J = 6.5$ Hz, 3H); MS m/z 513 (M^+ , ^{81}Br), 511 (M^+ , ^{79}Br), 378, 376, 298, 270, 268, 91, 65. **9**: $[\alpha]_D^{13} = -7.6^\circ$ (c 1.66, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.79 (s, OH), 6.40 (d, $J = 8.1$ Hz, 1H), 6.21 (d, $J = 8.0$ Hz, 1H), 5.15 and 5.11 (ABq, $J = 12.3$ Hz, 2H), 4.51 (s, 2H), 4.27 (br d, $J = 9.1$, NH), 3.89 (dd, $J = 9.2, 5.9$ Hz, 1H), 3.73 (t, $J = 5.4$ Hz, 2H), 2.91 (m, 2H), 2.10 (m, $J = 6.6$ Hz, 1H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H); MS m/z 433 (M^+), 390, 298, 282, 190, 134, 91, 65; HRMS Calcd for $C_{27}H_{31}NO_4$ (M^+) 433.2253, found 433.2238; Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.80, H, 7.21, N, 3.23; found C, 74.58, H, 7.20, N, 3.33.

***N*-Methyl-*N*-[3-hydroxy-2-(2'-hydroxyethyl)]phenyl-(*S*)-valine 10:** A mixture of **8** and **9** (74/11 in mol, 3.28 g, 6.56 mmol) was dissolved in 20 mL of acetic acid.

To this stirring solution was added aqueous HCHO (38%, 5.4 mL, 71.9 mmol). After the resulting solution was stirred for 5 min, it was added NaBH₃CN (1.43 g, 21.6). The reaction mixture was stirred for 40 min before it was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residual oil was dissolved in 20 mL of ethanol. To this solution was added 60 mg of 10% Pd/C and NaHCO₃ (830 mg, 9.9 mmol). The resulting mixture was hydrogenated at 45 atm and 30 °C for 1 day. The solid was filtered off and the filtrate was diluted with ethyl acetate and acidified to pH = 3 using dilute HCl. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was chromatographed eluting with 3/1 ethyl acetate/petroleum ether to afford 1.59 g (91%) of **10**. $[\alpha]_D^{19} = +13.5$ (*c* 0.35, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 4.39 (t, *J* = 7.2 Hz, 2H), 3.26 (d, *J* = 9.1 Hz, 1H), 3.14 (dt, *J* = 7.2, 3.3, 2H), 2.76 (s, 3H), 2.21 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H); MS *m/z* 266 (M⁺ - H⁺), 252, 250, 222, 204, 160, 148, 133; HRMS Calcd for C₁₄H₂₁NO₄ (M⁺) 267.1471, found 267.1448; Anal. Calcd for C₁₄H₂₁NO₄: C, 62.90, H, 7.92, N, 5.24; found C, 62.69, H, 7.55, N, 5.02.

***N*-Methyl-*N*-[3-benzyloxy-2-(2'-hydroxyethyl)]phenyl-(*S*)-valine benzyl ester **11**:** A mixture of **10** (2.0 g, 7.5 mmol), anhydrous K₂CO₃ (5.2 g, 37.2 mmol), benzyl bromide (2.67 g, 22.5 mmol) in 30 mL of anhydrous acetone was heated at reflux until the starting material disappeared monitored by TLC. After removal of the solvent, the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was chromatographed eluting with 1/5 ethyl acetate/petroleum ether to afford 3.28 g (98%) of **11**. $[\alpha]_D^{18} = 5.3$ (*c* 3.85, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.34 (m, 6H), 7.30-7.25 (m, 2H), 7.17-7.15 (m, 2H), 7.02 (t, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.07 (s, 2H), 5.02 (s, 2H), 3.90-3.72 (m, 2H), 3.33 (d, *J* = 9.9 Hz, 1H), 3.21-3.16 (m, 1H), 3.04-2.98 (m, 1H), 2.80 (s, 3H), 2.57 (b, OH), 2.22 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); MS *m/z*

448 ($M^+ + H^+$), 430, 404, 312, 239, 178, 148, 91; Anal. Calcd for $C_{28}H_{33}NO_4$: C, 75.14, H, 7.43, N, 3.13; found C, 75.00, H, 7.14, N, 3.21.

***N*-Methyl-*N*-[3-benzoxy-2-(2'-oxo-ethyl)]phenyl-(*S*)-valine benzyl ester **12**:**

To a solution of **11** (1.72 g, 3.85 mmol) in 20 mL of methylene chloride was added Dess-Martin reagent (1.96 g, 4.62 mmol) at room temperature under argon atmosphere. The resulting solution was stirred for 30 min before it was passed a short column of silica gel. The elute was washed with saturated aqueous $Na_2S_2O_3$, and brine. After it was dried over Na_2SO_4 , the solution was concentrated and the residual oil was chromatographed eluting with 1/10 ethyl acetate/petroleum ether to afford 1.42 g (83%) of aldehyde **12**. $[\alpha]_D^{18} = -28.3$ (*c* 3.85, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 9.63 (t, $J = 1.4$ Hz, 1H), 7.42-7.33 (m, 6H), 7.30-7.28 (m, 3H), 7.18-7.14 (m, 2H), 7.10 (t, $J = 8.2$ Hz, 1H), 6.77 (d, $J = 7.9$ Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), 5.06 (s, 2H), 5.02 (s, 2H), 3.85 and 3.75 (ABq, $J = 17.3$ Hz, both doubled with $J = 1.4$ Hz, 2H), 3.18 (d, $J = 10.0$ Hz, 1H), 2.77 (s, 3H), 2.23 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); MS m/z 446 ($M^+ + H^+$), 445 (M^+), 417, 402, 326, 310, 282, 226, 176, 148, 91, 65; Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48, H, 7.01, N, 3.14; found C, 75.34, H, 6.96, N, 3.33.

Asymmetric Strecker reaction of **12.** To a solution of **12** (6.1 g, 13.7 mmol) in 25 mL of absolute methanol was added (*R*)-phenylglycinol at room temperature. The resulting solution was stirred for 10 min before it was heated to 40 oC. At this temperature trimethylsilyl cyanide (2.76 mL, 20.6 mmol) was added in a dropwise manner. After the reaction mixture was stirred for further 30 min, it was diluted with ethyl acetate and brine. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was chromatographed eluting with 1/3 ethyl acetate/petroleum ether to afford 5.6 g (69%) of **13**, together with 1.60 g (20%) of **14**. **13**: $[\alpha]_D^{18} = -77.8$ (*c* 2.37, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 5H), 7.19-7.10 (m, 5H), 7.05 (t, $J = 8.0$ Hz, 1H), 6.98-6.93 (m, 2H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 5.02 and 5.00 (ABq, $J = 12.3$ Hz, 2H), 4.93 and 4.90 (ABq, $J = 11.8$ Hz, 2H), 4.00 (dd, $J = 8.8, 4.0$ Hz, 1H), 3.71

(dd, $J = 8.5, 6.5$ Hz, 1H), 3.66 (dd, $J = 10.8, 4.0$ Hz, 1H), 3.42-3.35 (m, 2H), 3.30 (d, $J = 10.8$ Hz, 1H), 3.11 (dd, $J = 12.8, 6.4$ Hz, 1H), 2.61 (s, 3H), 2.22 (m, 1H), 1.18 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.5$ Hz, 3H); MS m/z 575 ($M^+ - OH + H^+$), 533, 428, 413, 336, 292, 278, 238, 201, 148, 91, 77; Anal. Calcd for $C_{37}H_{41}N_3O_4$: C, 75.10, H, 6.98, N, 7.10; found C, 74.75, H, 6.90, N, 6.80. $14 \square [\alpha]_D^{18} = -8.7$ (c 2.14, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 7.27-7.24 (m, 6H), 7.22-7.18 (m, 2H), 7.14-7.11 (m, 2H), 7.06 (t, $J = 8.2$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 5.00 (s, 2H), 4.98 (s, 2H), 4.07 (dd, $J = 8.0, 7.3$ Hz, 1H), 3.74 (dd, $J = 6.9, 4.5$ Hz, 1H), 3.55 (dd, $J = 11.0, 4.4$ Hz, 1H), 3.44 (dd, $J = 11.0, 7.0$ Hz, 1H), 3.25-3.17 (m, 3H), 2.74 (s, 3H), 2.24 (m, 1H), 1.22 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H); MS m/z 575 ($M^+ - OH + H^+$), 565, 534, 533, 456, 428, 413, 292, 278, 201, 148, 91, 65; Anal. Calcd for $C_{37}H_{41}N_3O_4$: C, 75.10, H, 6.98, N, 7.10; found C, 74.98, H, 6.90, N, 6.96.

Conversion of 14 to 13: A solution of **14** (1.23 g, 2.08 mmol) in 20 mL of absolute methanol was heated at 80 °C in a sealed tube for 3 h. The cooled solution was concentrated and the residual oil was chromatographed to afford 1.12 g (91%) of **13**.

Esterification of 13: A mixture of **13** (2.1 g, 3.55 mmol) in 20 mL of HCl-saturated methanol was stirred at 0 °C overnight. The reaction mixture was neutralized with cooled 1 N NaOH to pH = 8, and diluted with 50 mL of brine. The mixture was extracted with ethyl acetate for three times and the extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was chromatographed eluting with 1/3 ethyl acetate/petroleum ether to afford 2.11 (95%) of **15**. $[\alpha]_D^{17} = -49.8$ (c 2.8, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 8H), 7.17-7.11 (m, 5H), 7.06 (t, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 7.0$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 5.06 and 4.99 (ABq, $J = 12.2$ Hz, 2H), 4.89 and 4.76 (ABq, $J = 11.9$ Hz, 2H), 3.65 (s, 3H), 3.67-3.47 (m, 3H), 3.35-3.17 (m, 3H), 2.97 (dd, $J = 13.0, 4.7$ Hz, 1H), , 2.60 (s, 3H), 2.21 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H); MS m/z 625 ($M^+ + H^+$), 624 (M^+), 593, 565, 503, 457, 416, 352, 268, 238, 148, 91, 65; HRMS Calcd for $C_{37}H_{41}N_2O_5$ ($M^+ - CH_2OH$) 593.3016, found 593.2985.

***N*-Methyl-*N*-[3-benzyloxy-2-[(*S*)-2'-(*tert*-butyloxycarbonyl)amino-2'-methoxycarbonyl]ethyl]phenyl-(*S*)-valine benzyl ester **17**:** To a solution of **15** (230 mg, 0.37 mmol) in methylene chloride (2 mL) and methanol (2 mL) was added lead tetraacetate (196 mg, 0.44 mmol) at 0 °C. After the resultant mixture was stirred for 30 min., 5 mL of phosphate buffer (0.2 M, pH 7) was added to quench the reaction. The mixture was filtered through celite and washed with methylene chloride. The filtrate was mixed with 15 mL of 3 N HCl and 5 mL of ethanol. The resulting solution was stirred for 1 h before it was diluted with 40 mL of ether and petroleum ether (1/1). The organic layer was separated and the aqueous layer was extracted with a mixture of ether and petroleum ether (1/1). The aqueous phase was neutralized with saturated NaHCO₃ to pH = 8 before it was extracted with ethyl acetate. The extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was dissolved in 10 mL of dioxane before di-*tert*-butyl dicarbonate (130 mg, 0.6 mmol) was added. The reaction mixture was stirred for 2 h, and then concentrated. The residual oil was purified by chromatography eluting with 1/4 ethyl acetate/petroleum ether to afford 176 mg (79%) of **17**. $[\alpha]_D^{15} = -89.6$ (*c* 0.33, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.47-7.34 (m, 6H), 7.28-7.26 (m, 2H), 7.15-7.14 (m, 2H), 7.00 (t, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.54 (br d, *J* = 7.5 Hz, 1H), 5.07 (s, 2H), 5.01 (s, 2H), 4.46 (dd, *J* = 12.1, 8.4 Hz, 1H), 3.60 (s, 3H), 3.19-3.07 (m, 2H), 3.13 (d, *J* = 10.2 Hz, 1H), 2.83 (s, 3H), 2.25 (m, 1H), 1.32 (s, 9H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); MS *m/z* 604 (M⁺), 561, 531, 505, 469, 416, 413, 395, 369, 296, 190, 148, 91, 57; HRMS Calcd for C₃₂H₃₇N₂O₇ (M⁺ - Pr) 561.2601, found 561.2622.

Lactam **18:** A mixture of **17** (1.1 g, 1.82 mmol), 100 mg of 10% Pd/C and 20 mL of ethanol was hydrogenated at 50 atm and room temperature for 9 h. The Pd/C was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in 10 mL of anhydrous acetonitrile. After this solution was added SuOH (420 mg, 3.64 mmol), a solution of DCC (450 mg, 2.18 mmol) in 5 mL of acetonitrile was added dropwise at 0 °C. The resulting solution was stirred for 2 h before it was passed a

short column of silica gel. The elute was concentrated and the residual oil was chromatographed to give the corresponding activated ester.

The above ester was dissolved in 15 mL of methylene chloride. To this solution was added 2 mL of TFA at 0 °C. After the solution was stirred at the same temperature for 2 h, it was concentrated to dryness with maintaining the temperature below 30 °C. The residue was dissolved in 60 mL of ethyl acetate, and then 150 mg NaHCO₃ and 10 mL of saturated NaHCO₃ were added. The reaction mixture was stirred at reflux overnight. The organic layer was separated and washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by chromatography eluting with 1/1 ethyl acetate/petroleum ether to afford 473 mg (83% overall yield) of the lactam **18**. [α]_D²⁵ = -168.2 (c 0.55, MeOH); ¹H NMR (600 MHz, CDCl₃) δ 6.97 (t, *J* = 8.4 Hz, 1H), 6.79 (s, OH), 6.70 (d, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 5.4 Hz, NH), 6.35 (d, *J* = 8.4 Hz, 1H), 5.30 (br, s, 1H), 3.82 (s, 3H), 3.45 (m, 1H), 3.34 (m, 1H), 3.15 (m, 1H), 2.74 (s, 3H), 2.40 (d, *J* = 6.6 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ¹H NMR (300 MHz, (CD₃)₂CO) δ 7.01 (t, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 7.3 Hz, 1H), 4.97 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, *J* = 17.1, 3.2 Hz, 1H), 3.43 (d, *J* = 7.9 Hz, 1H), 3.09 (dd, *J* = 17.1, 8.7 Hz, 1H), 2.76 (s, 3H), 2.39 (dt, *J* = 6.9 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); MS *m/z* 306 (M⁺), 289, 263, 247, 235, 220, 190, 148, 57, 41; HRMS Calcd for C₁₆H₂₂N₂O₄ (M⁺) 306.1580, found 306.1560; Anal. Calcd for C₁₆H₂₂N₂O₄: C, 62.72, H, 7.24, N, 9.14; found C, 62.73, H, 7.26, N, 9.07.

7-Decynyl-benzolactam-V8 3a: To a solution of **18** (62 mg, 0.2 mmol) and triethylamine (71 μ L, 0.5 mmol) in 10 mL of anhydrous methylene chloride was added trifluoromethanesulfonic anhydride (41 μ L, 0.24 mmol) at -78 °C. After the resulting solution was stirred for 40 min at the same temperature, 1 mL of saturated NaHCO₃ was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated NaHCO₃, and brine. After the solution was dried over Na₂SO₄, it was concentrated to dryness. The residue was dissolved in 10 mL of DMF. To this solution were added Pd(PPh₃)₂Cl₂ (20 mg), CuI (15 mg), 2 mL of

triethylamine, 1-decyne (134 μ L, 0.7 mmol). The resultant mixture was heated at 40 $^{\circ}$ C for 4 h before it was passed a short column of silica gel. The elute was diluted with ethyl acetate, washed with water and brine. After the solution was dried over Na_2SO_4 , it was concentrated. The residue was dissolved in 2 mL of THF, and then LiBH_4 (4 mg, 0.18 mmol) was added. After the mixture was stirred for 40 min, it was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The residue was chromatographed eluting with 1/1 ethyl acetate/petroleum ether to afford 60 mg (76% overall yield) of **3a**. $[\alpha]_{\text{D}}^{13} = -270.9$ (*c* 0.95, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.06 (t, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.90 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.68 (br s, NH), 3.79 (m, 1H), 3.70 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.55 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.38 (d, *J* = 17.9 Hz, 1H), 2.98 (dd, *J* = 17.8, 7.5 Hz, 1H), 2.88 (s, 3H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.47-2.36 (m, 1H), 1.60-1.53 (m, 2H), 1.45-1.38 (m, 2H), 1.27-1.21 (m, 8H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 3.8 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); MS *m/z* 398 (M^+), 383, 367, 355, 339, 327, 312, 296, 282, 268, 257, 226, 210, 182, 168, 144, 114, 86, 41; HRMS Calcd for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_2$ (M^+) 398.2933, found 398.2884.

7-Decyl-benzolactam-V8 3b: A mixture of **3a** (8 mg, 0.02 mmol) and 5 mg of 10% Pd/C in 2 mL of ethanol was hydrogenated at ordinary pressure and temperature for 10 h. After the Pd/C was filtered off, the filtrate was concentrated. The residue was chromatographed eluting with 1/1 ethyl acetate/petroleum ether to afford 8 mg (98%) of **3b**. $[\alpha]_{\text{D}}^{19} = -168.4$ (*c* 0.50, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.12 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.80 (br s, NH), 4.12 (m, 1H), 3.74-3.71 (m, 1H), 3.62-3.56 (m, 1H), 3.45 (d, *J* = 8.4 Hz, 1H), 3.07-2.99 (m, 1H), 2.96-2.91 (m, 1H), 2.80 (s, 3H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.44 (m, 1H), 1.69 (m, 2H), 1.53 (m, 2H), 1.29 (m, 12H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.93-0.88 (m, 6H); MS *m/z* 402 (M^+), 359, 343, 331, 316, 300, 284, 272, 261, 144, 132, 114, 57, 43; HRMS Calcd for $\text{C}_{25}\text{H}_{42}\text{N}_2\text{O}_2$ (M^+) 402.3246, found 402.3210.

