

**Highly Diastereoselective Desymmetrizations of Cyclo (Pro, Pro): An Enantioselective Strategy to Phakellin and Phakellstatin**

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**Supporting Information Available.** Selected experimental procedures and characterization data (including <sup>1</sup>H and <sup>13</sup>C NMR spectra) for compounds **6a-f** and **7-10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

**General.** Tetrahydrofuran (THF) was freshly distilled from sodium / benzophenone ketyl radical. Benzene, diisopropylamine and triethylamine were distilled from calcium hydride prior to use. DMF (99.99% anhydrous) was purchased from Acros and used as received. Ethyl acetate and hexanes were used without purification. Trisyl azide<sup>1</sup> and di-Boc thiourea<sup>2</sup> were prepared according to known procedures. Benzyl bromide, allyl bromide and methyl iodide were filtered through a short plug of basic alumina prior to use in order to eliminate traces of acid. Benzyl chloroformate was flushed with a stream of dry air and stored over sodium sulfate. Other chemicals were purchased from Aldrich or Acros and used without purification. Reactions were followed by thin layer chromatography (TLC) on silica Merck 60 F<sub>254</sub> (250 µm thick). TLC's were visualized with a UV lamp and stained using a solution of phosphomolybdic acid (80 g/L). Purifications of compounds were carried out by flash column chromatography using Whatman Silica (60 Å, 230-400 mesh). <sup>1</sup>H and <sup>13</sup>C NMR spectra were acquired using VARIAN spectrometers at the frequency indicated. Solvents are indicated for each compound. Chemical shifts are expressed in ppm referenced to TMS (in CDCl<sub>3</sub>) or to the solvent, as an internal standard. The multiplicity of signals are abbreviated as follows: app = apparent, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, br = broad signal. IR spectra were acquired using an Impact 910 Nicolet spectrometer in the solvent indicated. Vibration frequencies are expressed in cm<sup>-1</sup>. Optical rotations were measured with JASCO digital polarimeter DIP-360 (c indicates the concentration of the sample in g/100 mL) using a sodium lamp (589 nm). Gas chromatography was performed on a 2,3-di-*O*-acetyl-6-*O*-tert-butyl-dimethylsilyl-β-cyclodextrin column (30 m) at constant flow (3 mL/min) and constant temperature (indicated for each compound). Retention times are indicated in minutes.

**General procedure for azidation.** A solution of 0.500 g (2.57 mmol) of DKP **5** (azeotroped with anhydrous benzene) in 15 mL of THF was cooled to -78 °C and treated with 5.15 mL (2.57 mmol) of potassium bis-(trimethylsilyl)-amide (0.5°M in toluene). After 3 h at -78 °C, a pre-cooled solution of trisyl azide (3.1 mmol) in 10 mL THF was added to the enolate via cannula. After 2.5 h, the reaction was quenched with 1.16 g (11.84 mmol) of potassium acetate dissolved in 2 mL of distilled water. The cooling bath was removed and the mixture was allowed to stir overnight at 25 °C. The volatiles were

1 Leffler, J. E.°; Tsuno, Y. *J. Org. Chem.* **1963**, 28, 902.

2 Pons, J.-F.; Fauch re, J.-L.; Lamaty, F. Molla, A.; Lazaro, R. *Eur. J. Org. Chem.* **1998**, 5, 853-859.

removed *in vacuo* and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The organic layers were combined and dried (Na<sub>2</sub>SO<sub>4</sub>). Solvents were removed *in vacuo* and the residue was purified on a silica gel column (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 8:2) to provide 3-azido DKP **6a** (0.254 g, 42%) as a colorless oil and recovered DKP **5** (0.164 g, 33%).

**3-Azido DKP (6a):** R<sub>f</sub> 0.5 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> —127.9<sub>D</sub> (c5.12, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.36 (dd, *J* = 6.6, 8.7 Hz, 1H), 3.71 (ddd, *J* = 3.3, 8.4, 11.7 Hz, 1H), 3.52-3.62 (m, 3H), 2.33-2.55 (m, 3H), 1.92-2.21 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 167.4, 162.1, 82.5, 60.1, 45.6, 45.4, 38.8, 27.9, 22.9, 20.9; IR (CHCl<sub>3</sub>) 2105 (N<sub>3</sub>), 1675 (C=O); ESI HRMS calculated for C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub> 236.1147 [M+H]. Found 236.1139, 193.0977 [M-HN<sub>3</sub>].

**3-Azido 6-carbomethoxy DKP (9):** mp 130—132 °C (EtOAc/pentane); R<sub>f</sub> 0.44 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> —114.2<sub>D</sub> (c4.43, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.83 (s, 3H), 3.69-3.81 (m, 3H), 3.54-3.60 (m, 1H), 2.49-2.55 (m, 2H) and 2.42-2.46 (m, 1H), 2.32-2.39 (m, 1H) and 2.00-2.19 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.7, 164.3, 162.2, 82.2, 72.1, 54.0, 46.5, 46.3, 34.9, 34.5, 21.6, 21.1; IR (CH<sub>2</sub>Cl<sub>2</sub>) 2113 (N<sub>3</sub>), 1755 (C=O ester), 1677 (C=O lactam); ESI HRMS calculated for C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>O<sub>4</sub> 316.1022 [M+Na]. Found 316.1055.

**General method for alkylation and acylation of Cyclo (Pro, Pro) (5).** A solution of 201.2 mg (1.04 mmol) of DKP **5** (azeotroped with anhydrous xylenes) in 5 mL THF was cooled to —78 °C and treated with 2.1 mL (1.04 mmol) of potassium bis-(trimethylsilyl)-amide (0.5°M in toluene). After 3 h at —78 °C, 148 μL (1.243 mmol) of benzyl bromide was added to the enolate solution via syringe. After 3 h at —78 °C, the reaction was quenched with 10 mL of pH 7 buffer solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). Organic layers were combined and dried (Na<sub>2</sub>SO<sub>4</sub>). Solvents were removed *in vacuo* and the crude oil was purified on silica gel chromatography to afford 3-benzyl DKP **6f** (255.1 mg, 75%) as a white solid and recovered DKP **5** (12 mg, 6%).

**3-Methyl DKP (6d):** R<sub>f</sub> 0.23 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> —100.2<sub>D</sub> (c1.03, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.22 (dd, *J* = 6.9, 9 Hz, 1H), 3.53-3.61 (m, 4H), 2.21-2.41 (m, 2H) and 1.88-2.16 (m, 6H), 1.45 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.6, 166.2, 66.5, 60.1, 45.6, 45.1, 35.4, 28.6, 25.0, 23.2, 23.0; IR (CH<sub>2</sub>Cl<sub>2</sub>) 1665 (C=O). ESI HRMS calculated for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> 209.1290 [M+H]. Found 209.1294. The diastereomeric ratio was determined to be 27:1 by chiral GC (200 °C, 11psi) of an aliquot of the crude product passed through a short plug of SiO<sub>2</sub>; t<sub>(cis)</sub> = 6.62 min (major), t<sub>(trans)</sub> = 6.04 min (minor).

**3-Allyl DKP (6e):** R<sub>f</sub> 0.34 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 4:6); [α]<sub>D</sub><sup>25</sup> —62.3<sub>D</sub> (c0.88, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.79 (app ddd, *J* = 7.2, 9.3, 17.1 Hz, 1H), 5.14-5.21 (m, 2H),

4.25 (dd,  $J = 6, 9.6$  Hz, 1H), 3.70 (app dd,  $J = 8.1, 12.3$  Hz, 1H), 3.44-3.64 (m, 3H), 2.5 (app t,  $J = 6.6$  Hz, 2H), 1.88-2.37 (m, 8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4, 166.5, 131.8, 120.5, 69.7, 60.5, 45.6, 45.3, 41.5, 33.6, 28.9, 23.0, 21.3; IR ( $\text{CH}_2\text{Cl}_2$ ) 1660 ( $\text{C}=\text{O}$ ); ESI HRMS calculated for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2$  235.1446  $[\text{M}+\text{H}]$ . Found 235.1449. The diastereomeric ratio was determined to be 18:1 by chiral GC (200  $\mu\text{C}$ , 11 psi) of an aliquot of the crude product passed through a short plug of  $\text{SiO}_2$ ;  $t_{(\text{cis})} = 9.54$  min (major),  $t_{(\text{trans})} = 10.52$  min (minor).

**3-Benzyl DKP (6f):** mp 132—134  $\mu\text{C}$  ( $\text{CH}_2\text{Cl}_2$ /pentane);  $R_f$  0.17 ( $\text{CH}_2\text{Cl}_2$ /EtOAc, 1:1);  $[\alpha]_{\text{D}}^{25} -73.7$  (c 0.88, MeOH);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.29 (m, 3H), 7.11-7.14 (m, 2H), 3.81 (ddd,  $J = 8.7, 12, 17.1$  Hz, 1H), 3.45-3.57 (m, 2H) and 3.27-3.35 (m, 1H), 3.16 and 2.90 (AB,  $J = 13.5$  Hz, 2H), 2.17-2.35 (m, 3H), 1.83-2.07 (m, 4H) and 1.51-1.75 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.8, 166.6, 135.6, 130.4, 128.7, 127.8, 71.4, 59.6, 44.8, 44.8, 43.5, 35.5, 28.7, 22.3, 20.8; IR ( $\text{CH}_2\text{Cl}_2$ ) 1660 ( $\text{C}=\text{O}$ ); ESI HRMS calculated for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$  285.1603  $[\text{M}+\text{H}]$ . Found 285.1608. The diastereomeric ratio was determined to be 42:1 by chiral GC (220  $\mu\text{C}$ , 11psi) of an aliquot of the crude product passed through a short plug of  $\text{SiO}_2$ ;  $t_{(\text{cis})} = 16.89$  min (major),  $t_{(\text{trans})} = 12.65$  min (minor).

**3-Carbomethoxy DKP (6b):**  $R_f$  0.43 ( $\text{CH}_2\text{Cl}_2$ /EtOAc, 1:1);  $[\alpha]_{\text{D}}^{25} -28.4$  (c 1.68, MeOH);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.22 (dd,  $J = 7.5, 9$  Hz, 1H), 3.82 (s, 3H), 3.52-3.68 (m, 4H), 2.32-2.63 (m, 3H), 1.86-2.19 (m, 5H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.5, 162.2, 158.1, 68.3, 55.9, 49.1, 41.4, 40.9, 28.7, 23.5, 18.6, 17.3; IR ( $\text{CHCl}_3$ ) 1747 ( $\text{C}=\text{O}$ , ester), 1670 ( $\text{C}=\text{O}$ , lactam); ESI HRMS calculated for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$  253.1188  $[\text{M}+\text{H}]$ . Found 253.1200. The diastereomeric ratio was determined to be 11:1 by chiral GC (200  $\mu\text{C}$ , 11psi) of an aliquot of the crude product passed through a short plug of  $\text{SiO}_2$ ;  $t_{(\text{cis})} = 13.94$  min (major),  $t_{(\text{trans})} = 18.42$  min (minor).

**3-Carboxymethyl DKP (8):**  $R_f$  0.40 ( $\text{CH}_2\text{Cl}_2$ /EtOAc, 1:1);  $[\alpha]_{\text{D}}^{25} +14.3$  (c 2.32, MeOH);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.71 (app dt,  $J = 4.45, 11.5$  Hz, 1H), 4.08 (dd,  $J = 7, 9.5$  Hz, 1H), 3.64-3.72 (m, 2H), 3.51 (dddd,  $J = 7, 9.5, 12, 16.5$  Hz, 1H), 3.43 (dddd,  $J = 3.2, 8.5, 12, 14.5$  Hz, 1H), 2.53 (ddd,  $J = 8, 10.5, 13.5$  Hz, 1H), 2.44 (ddd,  $J = 4, 7, 13.5$  Hz, 1H), 2.28-2.33 (m, 1H), 1.81-2.14 (m, 7H), 1.63-1.71 (m, 3H), 1.41-1.46 (m, 2H), 0.95-1.06 (m, 2H), 0.88 (d,  $J = 7$  Hz, 3H), 0.85 (d,  $J = 7$  Hz, 3H), 0.67 (d,  $J = 7$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4, 167.0, 163.1, 73.0, 60.8, 46.9, 45.9, 45.7, 40.6, 34.2, 33.0, 31.6, 28.3, 26.5, 23.5, 23.4, 22.3, 22.1, 20.9, 16.3; IR ( $\text{CH}_2\text{Cl}_2$ ): 1737 ( $\text{C}=\text{O}$  ester), 1690 ( $\text{C}=\text{O}$  lactam). ESI MS calculated for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$  377  $[\text{M}+\text{H}]$ . Found 377. The diastereomeric excess was determined to be 97% by chiral GC (250  $\mu\text{C}$ , 11 psi) of an

aliquot of the crude product passed through a short plug of SiO<sub>2</sub>;  $t_{(L-cis)} = 12.78$  min (major),  $t_{(D-cis)} = 12.56$  min (minor).

**3-Carbobenzyloxy DKP (6c).** A solution of 15.36 g (79.08 mmol) of DKP **5** (azeotroped with anhydrous benzene) in 100 mL of THF was added to a pre-cooled solution of 174 mL (86.99 mmol) of potassium bis-(trimethylsilyl) amide (0.5 M in toluene) in 300 mL of THF. After 2.5 h at  $-78^{\circ}\text{C}$ , the enolate solution was added via cannula to a pre-cooled solution of 13.5 mL (94.89 mmol) of benzyl chloroformate in 200 mL of THF. After 5 h at  $-78^{\circ}\text{C}$ , the reaction was quenched with 100 mL of pH 4 buffer. The layers were separated and the aqueous layer was extracted with EtOAc (2x100 mL). The organic layers were combined and dried (Na<sub>2</sub>SO<sub>4</sub>). After filtration, solvents were removed *in vacuo* and the residue was purified on a silica gel column (hexanes/EtOAc, 1:1) to provide 3-carbobenzyloxy DKP **6c** (18.14 g, 70%) as a white solid:  $R_f$  0.33 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1);  $[\alpha]_D^{25} -34.0$  (c 4.99, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.37 (m, 5H), 5.23 (d,  $J = 2.1$  Hz, 2H), 4.03 (dd,  $J = 6.9, 9$  Hz, 1H), 3.46-3.64 (m, 4H), 2.44-2.60 (m, 2H) and 2.18-2.34 (m, 1H), 1.71-2.12 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.6, 167.0, 162.8, 135.2, 128.8, 128.8, 128.2, 73.1, 68.3, 60.7, 46.0, 45.7, 33.2, 28.3, 23.3, 22.2; IR (CH<sub>2</sub>Cl<sub>2</sub>): 1744 (C=O ester), 1675 (C=O lactam). FAB HRMS calculated for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> 329.1501 [M+H]. Found 329.1513. The diastereomeric ratio was determined to be 12:1 by chiral GC (220  $^{\circ}\text{C}$ , 11 psi) of an aliquot of the crude product passed through a short plug of SiO<sub>2</sub>;  $t_{(cis)} = 43.09$  min (major),  $t_{(trans)} = 31.92$  min (minor).

**di-Boc-Guanidine DKP (7).** To a solution of azido DKP **6a** (85.9 mg, 0.365 mmol) in 5 mL absolute ethanol was added catalytic amount of 10% Pd/C. The reaction flask was purged with H<sub>2</sub> by repeated aspirator vacuum/H<sub>2</sub> purge cycles. A H<sub>2</sub> balloon was connected to the flask. After 30 minutes under H<sub>2</sub>, the mixture was filtered over Celite and ethanol was removed *in vacuo*. To the free amine was added successively mercuric chloride (109.0 mg, 0.401 mmol), di-Boc thiourea (111.0 g, 0.401 mmol) and 1 mL anhydrous DMF. Upon addition of triethylamine (170  $\mu\text{L}$ , 1.20 mmol) the reaction mixture turned black. After 16 h at 25  $^{\circ}\text{C}$ , the mixture was filtered over Celite. Once the solvents were removed *in vacuo*, the crude was purified on silica gel chromatography (hexanes/EtOAc, 1:1) to afford di-Boc-guanidine **7** (90.0 mg, 55%) as a white solid:  $R_f$  0.44 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1);  $[\alpha]_D^{25} -138.5$  (c 4.78, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  11.14 (s, 1H), 8.85 (s, 1H), 5.14 (dd,  $J = 6, 10.5$  Hz, 1H), 3.92-3.98 (m, 1H), 3.57-3.60 (m, 2H), 3.41-3.46 (m, 1H), 2.35-2.47 (m, 2H) and 1.87-2.18 (m, 6H), 1.49 (s, 9H) and 1.42 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.3 (C=N), 164.2, 162.2 (C=O lactam), 154.3, 153.2 (C=O carbamate), 84.1, 79.5, 76.5, 61.2, 45.0, 43.7, 38.4, 28.4, 28.2, 22.3,

20.2; IR (CH<sub>2</sub>Cl<sub>2</sub>) 1731, 1685, 1650, 1624; FAB HRMS calculated for C<sub>21</sub>H<sub>33</sub>N<sub>5</sub>O<sub>6</sub> 452.2509 [M+H]. Found 452.2510.

**Tetracyclic tris-lactam (10).** To the azido carbomethoxy DKP **9** (458.5 mg, 1.563 mmol) in 5 mL absolute ethanol was added 46 mg of 10% Pd/C. The reaction flask was purged with H<sub>2</sub> by repeated aspirator vacuum/H<sub>2</sub> purge cycles. A H<sub>2</sub> balloon was connected to the flask. After 30 minutes under H<sub>2</sub>, the mixture was filtered over Celite and ethanol was removed *in vacuo*. The crude amine was partially dissolved in 20 mL freshly distilled benzene and refluxed for 3 h. After removal of solvent *in vacuo* the crude oil was purified on silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1) to provide the tetracyclic tris-lactam **10** (20.2 mg, 68%) as a white crystalline solid: mp 110—113 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane); R<sub>f</sub> 0.31 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 1:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.33 (br s, 1H), 3.53-3.57 (m, 2H) and 3.45 (app dd, *J* = 6.9 Hz, 2H), 2.89-2.97 (m, 1H), 2.45-2.61 (m, 2H), 2.00-2.27 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.2, 165.7, 164.5, 78.6, 75.0, 44.1, 44.0, 27.7, 25.4, 24.6, 22.5; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3550 (broad) 1747, 1711; ESI HRMS calculated for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub> 258.0855 [M+Na]. Found 258.1001.

























