Hypervalent Iodine Mediated Vicinal *syn*-Diazidation: Application to the Total Synthesis of (±)- Dibromophakellstatin

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Supporting Information

Experimental procedures and characterization data for compounds **1**, **6-10**,
14-16
(19 pages)

General experimental details. Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen (house nitrogen dried with Drierite[®] and KOH). Commercially available reagents and solvents were used as received from Aldrich Chemical Company, Inc., Fisher Scientific, Acros Organics, Mallinckrodt Baker, Inc., EM Science, Alfa Aesar, and Pharmco Products, Inc. Vacuum filtration was accomplished using a porcelain Buchner funnel fitted with Whatman filter paper of corresponding size or a glass Buchner funnel with medium frit and Celite[®] 454 filter agent. All reactions were magnetically stirred and monitored by thin-layer chromatography. Routine thin-layer chromatography was done using Si250F pre-coated silica gel plates from JT Baker or Silica Gel 60 F₂₅₄ pre-coated plates from EM Science. Unless otherwise stated, flash column chromatography was performed using the Isco CombiFlash system utilizing repackable columns loaded with 230-400 mesh Ultra Pure silica gel from SiliCycle or Isco RediSep[™] pre-packed columns. ¹H and ¹³C NMR spectra were obtained on Bruker Avance DPX-500 or DPX-400 spectrometers. Chemical shifts were reported with CDCl₃ (δ 7.26 ppm for ¹H and δ 77.23 ppm for ¹³C), DMSO-d₆ (δ 2.50 ppm for ¹H and δ 39.51 ppm for ¹³C), or MeOH-d₄ (δ 3.31 ppm for ¹H and δ 49.00 ppm for ¹³C) as internal references (Cambridge Isotope Labs, Inc.). Melting points were

taken on an Electrothermal[®] melting apparatus and are uncorrected. Infrared spectra were taken on a Midac Corporation M series FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlab (Norcross, GA) and mass spectrometry was conducted at the Mass Spectrometry Laboratory of the University of Illinois at Urbana-Champaign, School of Chemical Science. X-ray crystallographic analysis was provided by the Yale University Chemical Instrumentation Center X-ray crystallography facility.

(2-Hydroxymethyl-pyrrolidin-1-yl)-(1H-pyrrol-2-yl)-methanone (10). 2-

(trichloroacetyl)-pyrrole (**12**) (4.43 g, 20.9 mmol) was dissolved in dichloromethane (10 ml). While stirring, (s)-(+)-2-pyrrolidine-methanol (**11**) (2.3 ml, 2.4 g, 23.6 mmol) was added dropwise. The solution was stirred overnight at room temperature, then concentrated to a viscous, brown oily solid. The viscous, brown oily solid was adsorbed on silica gel and purified by flash column chromatography. The appropriate fractions were collected and concentrated to yield a white solid. The amorphous white solid was dissolved in a minimal amount of hot ethyl acetate and allowed to cool to rt overnight. This process was repeated twice to yield compound **10** as colorless to slightly yellow crystals (2.79 g, 69%). TLC (100% EtOAc, UV): R_f = 0.29. MP: 124-125°C. IR (film, cm^{-1}): 3262 (broad), 2956, 2876, 1582, 1442. ^1H NMR (CDCl_3): δ 10.10 (bs, 1H), 7.00-6.95 (m, 1 H), 6.67-6.64 (m, 1H), 6.30-6.26 (m, 1H), 4.94 (bs, 1H), 4.50-4.43 (m, 1H), 3.97-3.88 (m, 1H), 3.82-3.67 (m, 3H) 2.12-1.88 (m, 3H), 1.72-1.61 (m, 1H). ^{13}C (CDCl_3): δ 163.18, 125.64, 122.26, 113.73, 110.60, 67.95, 62.89, 49.85, 28.41, 25.42. Anal. calc (found) for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$: 61.84 (61.83), 7.27 (7.24), 14.42 (14.45), 16.47 (16.56). HRMS-EI (m/z) (M^+) calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$: 194.1055 Found: 194.1052.

2,3-Dihydro-1H-dipyrrolo[1,2-a;1',2'-d]pyrazin-5-one (9). Compound **10** (961 mg, 4.95 mmol) was suspended in dry dichloromethane (20 ml). To the reaction mixture, Dess-Martin periodinane (2.2 g, 5.2 mmol) was added in one portion. The reaction was stirred for 2 hours after which it was quenched with a solution of sodium thiosulfate pentahydrate (6.42 g) in saturated sodium bicarbonate solution (75 ml). The resulting layers were separated and the aqueous layer was extracted with 3 portions of ethyl acetate. The combined organic portions were dried with anhydrous MgSO_4 and filtered.

Concentration of the filtrate yielded crude hydroxy-dipyrrolopyrazinone **13** as a mixture of inseparable diastereomers (1.24 g).

Crude hydroxy-dipyrrolopyrazinone **13** was taken up in dichloromethane (20 ml) and cooled to 0°C in an ice/water bath. While stirring, methanesulfonyl chloride (1.00 ml, 1.48 g, 12.9 mmol) was added dropwise followed by DBU (3.86 ml, 3.93 g, 25.8 mmol). The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction was then quenched with a saturated sodium bicarbonate solution. Resulting layers were separated and the aqueous portion was extracted 3 times with dichloromethane. Combined organics were dried with anhydrous MgSO₄ and filtered. Concentration of solution resulted in a brown solid. The solid was purified by flash chromatography (hexanes/EtOAc gradient), furnishing unsaturated compound **9** as a slightly yellow to white crystalline solid (67%, 2 steps). TLC (100% EtOAc, UV): R_f = 0.35. MP: 136-140°C (dec.). IR (film, cm⁻¹): 3118, 3104, 1627. ¹H NMR (MeOH-d₄): δ 7.26 (m, 2H), 6.97 (d, J = 4.0 Hz, 1H), 6.54 (dd, J = 4.0, 2.6 Hz, 1H), 3.97 (t, J = 7.0 Hz, 2 H), 2.97 (td, J = 7.5, 1.6 Hz, 2 H), 2.17 (p, J = 7.4 Hz, 2 H). ¹³C (MeOH-d₄): δ 157.57, 131.75, 124.77, 120.48, 113.78, 110.04, 105.41, 48.13, 29.22, 24.19. HRMS-EI (m/z) (M⁺) calcd for C₁₀H₁₀N₂O: 174.0793 Found: 174.0790.

10,10a-Diazido-2,3,10,10a-tetrahydro-1H-dipyrrolo[1,2-a;1',2'-d]pyrazin-5-one (syn-diazide) (8). Iodobenzene diacetate (1.41 g, 4.38 mmol) was suspended in anhydrous dichloromethane (10 ml) and cooled to -30°C. Azidotrimethylsilane (1.2 ml, 9.04 mmol) was added dropwise. The reaction developed a yellow color which dissipated upon stirring. After 30 minutes of stirring, triethylammonium iodide (1.17 g, 4.55 mmol) was then added in one portion. Immediate color change occurred. The reaction was allowed to warm to room temperature over a period of 10 minutes. The color changed to a deep reddish orange. Pyrazinone **9** (208 mg, 1.19 mmol) was added in one portion and stirred at room temperature overnight. Reaction was quenched with saturated sodium sulfite solution. Upon stirring, the color changed to yellow. Resulting layers were separated and the aqueous portion was extracted with 3 20-ml portions of dichloromethane. Organics were dried with anhydrous MgSO₄ and filtered. The solution was concentrated and the resulting yellow solid was purified by flash chromatography (hexanes/EtOAc gradient).

Product was isolated as a slightly yellow, crystalline solid (127 mg, 41%) along with 21.2 mg (7%) of anti-diazide **14**. TLC (100% EtOAc, UV): R_f = 0.63. MP: 102-104 °C. ^1H NMR (CDCl_3): δ 7.05 (m, 2H), 6.39 (dd, J = 2.9, 3.7 Hz, 1H), 5.24 (s, 1H), 3.99 (m, 1H), 3.71 (m, 1H), 2.50 (m, 1H), 2.20 (m, 3H). ^{13}C (CDCl_3): δ 157.00, 124.38, 121.72, 116.13, 112.32, 84.89, 76.05, 45.74, 37.27, 21.48. IR (film, cm^{-1}): 2959, 2892, 2112 (strong), 1655, 1548. Anal. calcd (found) for $\text{C}_{10}\text{H}_{10}\text{N}_8\text{O}$: C 46.51 (46.44), H 3.90 (3.86), N 43.39 (43.40), O 6.20 (6.19). HRMS-EI (m/z) (M^+) calcd for $\text{C}_{10}\text{H}_{10}\text{N}_8\text{O}$: 258.0978 Found: 258.0985.

10,10a-Diazido-2,3,10,10a-tetrahydro-1H-dipyrrolo[1,2-a;1',2'-d]pyrazin-5-one (anti-diazide) (14). Sodium azide (1.13 g, 17.4 mmol) was suspended in acetonitrile (6 ml) and cooled to $-15\text{ }^\circ\text{C}$. While stirring, a solution of ICl (826 mg, 5.09 mmol) in acetonitrile (6 ml) was added dropwise. The cooled reaction was allowed to stir for 5 minutes after which a solution of pyrazinone **9** (275 mg, 1.58 mmol) in acetonitrile (6 ml) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2.5 hours. The reaction was quenched with a solution of 5% sodium thiosulfate. Following vigorous bubbling and formation of two layers, and the layers were separated. The aqueous portion was extracted 3 times with EtOAc. The combined organic material was dried with MgSO_4 and filtered. The filtrate was then concentrated to reddish yellow oil, which was purified by flash chromatography (hexanes/EtOAc gradient). Product was isolated as a slightly yellow crystalline solid (255 mg, 62%). TLC (1:1 hexanes/EtOAc, UV): R_f = 0.52. MP: 100-102°C. IR (film, cm^{-1}): 2962, 2890, 2110 (strong), 1653, 1553. ^1H NMR (CDCl_3): δ 7.06 (dd, J = 3.8, 1.2, 1 H), 7.00 (dd, J = 1.4, 2.7, 1H), 6.39 (dd, J = 2.8, 3.8, 1H), 5.47 (s, 1H), 3.99-3.91 (m, 1H), 3.74-3.64 (m, 1H), 2.58-2.46 (m, 1H), 2.23-2.12 (m, 3H). ^{13}C (CDCl_3): δ 156.86, 124.40, 123.70, 116.06, 112.62, 84.48, 73.02, 45.76, 35.74, 21.72. HRMS-EI (m/z) (M^+) calcd for $\text{C}_{10}\text{H}_{10}\text{N}_8\text{O}$: 258.0978. Found: 258.0972.

1-Azido-2,3-dihydro-1H-dipyrrolo[1,2-a;1',2'-d]pyrazin-5-one (allyl azide) (15).

Iodobenzene diacetate (1.41 g, 4.38 mmol) was dissolved in dichloromethane (10 ml). The solution was cooled to $-30\text{ }^\circ\text{C}$ while stirring. Azidotrimethylsilane (1.2 ml, 9.04

mmol) was added dropwise to the stirring solution. The resulting suspension turned yellow then white. After stirring for 30 minutes, pyrazinone **9** was added in one portion. The reaction mixture was allowed to warm to room temperature. The reaction became exothermic and turned a deep burgundy red. After stirring at room temperature for 30 minutes, the reaction was quenched with saturated Na₂SO₃ solution. The aqueous layer was extracted with three 15-ml portions of dichloromethane. The combined organics were washed with brine, dried over anhydrous MgSO₄, and concentrated into a brown oil. Flash column chromatography provided allyl azide **15** as slightly brown crystals (50.6 mg, 26%). TLC (100% EtOAc, UV): R_f = 0.54. IR (film, cm⁻¹): 3125 (weak), 2105, 1681, 1625, 1387, 1242. ¹H NMR (CDCl₃): δ 7.21-7.11 (m, 3H), 6.59 (dd, *J* = 2.6, 4.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.21-4.12 (m, 1H), 4.08-3.98 (m, 1H), 2.46-2.34 (m, 1H), 2.27-2.16 (m, 1H). ¹³C (CDCl₃): δ 155.07, 128.21, 124.62, 119.48, 113.43, 110.41, 105.13, 61.56, 44.64, 30.77. HRMS-EI (*m/z*) (*M*⁺) calcd for C₁₀H₉N₅O: 215.0807 Found: 215.0812.

10,10a-Diamino-2,3,10,10a-tetrahydro-1H-dipyrrolo[1,2-a;1',2'-d]pyrazin-5-one (syn-diamine) (7). Syn-diazide **8** (99.0 mg, 0.383 mmol) was dissolved in MeOH (2 ml) and 10% Pd/C (catalytic amount) was added. Air was evacuated from reaction flask and the mixture was stirred overnight at room temperature under hydrogen delivered by a gas expansion balloon (Aldrich Co.). The resulting reaction was then filtered over a pad of Celite[®] 545 filtering agent. The filtrate was concentrated and purified by traditional flash chromatography with 3:10 MeOH/EtOAc as eluent. Desired product was isolated as a white solid (58.9 mg, 75%). MP: 124-125°C (dec.). TLC (3:10 MeOH/EtOAc, UV): R_f = 0.34. IR (film, cm⁻¹): 3369, 3305, 2975, 2884, 1628, 1547. ¹H NMR (MeOH-d₄): δ 7.26 (m, 1H), 6.84 (dd, *J* = 5.3, 1.6 Hz, 1H), 6.24 (dd, *J* = 1.6, 3.7 Hz, 1H), 4.88 (s, 1H), 3.79 (m, 1H), 3.61 (m, 1H), 2.15 (m, 4H). ¹³C (MeOH-d₄): δ 160.06, 125.05, 123.20, 115.32, 110.94, 79.87, 73.16, 45.90, 38.52, 22.63. HRMS-EI (*m/z*) (*M*⁺) calcd for C₁₀H₁₄N₄O: 206.1168 Found: 206.1165.

(±)-Thiophakellstatin (16). 33.2 mg (0.134 mmol) syn-diamine **7** was dissolved in acetonitrile (3 ml) in a 15-ml round bottom. 87 µL of 0.11 M imidazole in acetonitrile (9.57 µmol, 7 mol%) was added to the solution followed by 25.0 mg (0.140 mmol) 1,1'-

thiocarbonyldiimidazole. A reaction flask was then fitted with a Vigreux column capped with a drying tube containing Drierite[®]. The resulting yellow solution was stirred at 50°C until no starting material was observed by TLC. Desired product precipitated from solution. The product was filtered and allowed to air-dry and desired compound was isolated as a peach-colored powder (22.9 mg, 69%). Thiophakellstatin was used with no further purification. MP: 248-250°C (dec.). TLC (3:10 MeOH/EtOAc, UV): R_f = 0.67. IR (KBr, cm^{-1}): 3392, 3117, 2883, 1618, 1555, 1518, 1441, 1425, 1171. ^1H NMR (DMSO-d_6): δ 9.69 (br s, 1H), 9.65 (br s, 1H), 7.14 (dd, J = 1.6, 2.6 Hz, 1 H), 6.69 (dd, J = 1.6, 3.7 Hz, 1 H), 6.31 (dd, J = 2.7, 3.7 Hz, 1H), 5.90 (s, 1H), 3.61-3.52 (m, 1H), 3.52-3.41 (m, 1H), 2.32-2.22 (m, 1H), 2.21-2.04 (m, 2H), 2.03-1.92 (m, 1H). ^{13}C (DMSO-d_6): δ 181.42, 155.76, 123.56, 122.44, 111.86, 111.56, 83.03, 69.32, 44.92, 38.56, 19.70. HRMS-EI (m/z) (M^+) calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{OS}$: 248.0732 Found: 248.0747.

(±)-Phakellstatin (6). 6.24 mg (0.025 mmol) thiophakellstatin (**16**) was dissolved in N,N -dimethylformamide (1 ml). 40 μL of 7 N ammonia in MeOH was added to the reaction followed by 0.3 ml 30% hydrogen peroxide solution. The reaction was stirred at room temperature for 4 hours open to air. The solvent was evaporated over a stream of nitrogen and resulting solid was triturated in MeOH and filtered. Desired product was isolated as a white powder (5.28 mg, 91%). IR (KBr, cm^{-1}): 3265 (br), 1736, 1709, 1621, 1549, 1440, 1114. ^1H NMR (DMSO-d_6): δ 8.14 (br s, 1H), 7.80 (br s, 1H), 7.12 (dd, J = 1.7, 2.5 Hz, 1H), 6.66 (dd, J = 1.6, 3.7 Hz, 1H), 6.27 (dd, J = 2.8, 3.6 Hz, 1H), 5.75 (s, 1H), 3.55-3.47 (m, 1H), 3.46-3.37 (m, 1H), 2.26-2.18 (m, 1H), 2.17-2.03 (m, 2H), 2.02-1.92 (m, 1H). ^{13}C (DMSO-d_6): δ 159.12, 156.01, 123.57, 122.17, 111.61, 111.09, 79.01, 67.98, 44.71, 38.94, 19.77. HRMS-EI (m/z) (M^+) calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2$: 232.0960 Found: 232.0958.

(±)-Dibromophakellstatin (1). 6.0 mg (0.026 mmol) phakellstatin was suspended in dry THF (1 ml) in a vial. While stirring, a solution of 12.3 mg (0.069 mmol) N -bromosuccinimide in 0.5 ml THF was added dropwise. Reaction was stirred overnight, capped. The solvent was then evaporated and purification of crude, orange material was accomplished by flash chromatography using 9:1 $\text{CH}_2\text{Cl}_2/\text{EtOH}$ to yield desired product

as a white solid (3.0 mg, 30%). TLC (9:1 CH₂Cl₂/EtOH, UV): R_f = 0.32. IR (KBr, cm⁻¹): 3229 (br), 1722, 1646, 1549, 1451. ¹H NMR (DMSO-d₆): δ 8.27 (br s, 1H), 7.97 (br s, 1H), 6.91 (d, J = 0.7 Hz, 1H), 5.99 (d, J = 2.1 Hz, 1H), 3.60-3.51 (m, 1H), 3.47-3.37 (m, 1H), 2.36-2.25 (m, 1H), 2.19-2.04 (m, 2H), 2.03-1.92 (m, 1H). ¹³C (DMSO-d₆): δ 157.84, 154.00, 154.43, 125.31, 113.72, 105.58, 101.09, 78.94, 68.55, 44.07, 18.78. C-11 hidden by DMSO peak. ¹HRMS-EI (m/z) (M⁺) calcd for C₁₁H₁₀N₄O₂Br₂: 387.9170 Found: 387.9180.

Figure S1. ORTEP diagram of *syn*-diamine **7**.

Figure S2. ORTEP diagram of *syn*-diazide **8**.

Figure S3. ORTEP diagram of *anti*-diazide **14**. **Figure S4.** ORTEP diagram of allyl azide **15**.

References

1. Pettit, G.R.; McNulty, J.; Herald, D.L.; Doubek, D.L.; Chapuis, J.-C.; Schmidt, J.M.; Tackett, L.P.; Boyd, M.R. *J. Nat. Prod.* **1997**, *60*, 180-183.

Current Data Parameters
NAME May07-2003-chu
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030507
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FIDRES 0.126314 Hz
AQ 3.9584243 sec
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DE 6.00 usec
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F2 - Processing parameters
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F2P -1.000 ppm
F2 -399.98 Hz
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HZCM 239.98801 Hz/cm

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dibromophakellstatin