Supporting Information

Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A

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Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained using Bruker 270MHz or 300MHz, or Varian 300MHz or 400MHz spectrometers. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual CHCl_3 at δ 7.27 ppm for proton spectra, and relative to CDCl_3 at δ 77.0 ppm for carbon spectra. IR spectra were recorded on a Perkin-Elmer 1600 FTIR as thin films from CH_2Cl_2 or CDCl_3 . Mass spectra were obtained using a Fisons VG Autospec spectrometer. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, AZ. Optical rotations were recorded on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm using a 1.0 decimeter cell of 1.0 mL total volume. Flash column chromatography was performed with silica gel grade 60 (230-400 mesh). Radial chromatography was performed with a Harrison Research Chromatotron model 7924 using Merck silica gel 60 PF₂₅₄ containing gypsum. One, two or four millimeter plates were used as needed. Preparative thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F₂₅₄ precoated glass plates (20 $\times$ 20 cm $\times$ 0.25 mm). Unless otherwise noted materials were obtained from commercially available sources and used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dichloromethane, triethylamine, pyridine, acetonitrile, toluene, benzene, and diisopropylamine were distilled from calcium hydride under a nitrogen atmosphere. DMF and HMPA were dried over activated 3 Å molecular sieves for 1 week prior to use. LiCl and AgBF_4 are hygroscopic and were handled rapidly. ZnCl was dried by heating to 210 °C for 4 h under vacuum in a flask.

***tert*-Butyl-(4-iodo-2-methyl-but-2-enyloxy)-dimethyl-silane (21).** To a stirred solution of 2-methyl-2-vinyl-oxirane (**20**) (4.70 g of 90% purity, 50.3 mmol, 1.0 eq) in CH_2Cl_2 (87.5 mL) at 0 °C were added MgSO_4 (3.0 g), *tert*-butyldimethylsilyl chloride (7.43 g, 49.3 mmol, 0.98 eq) and tetrabutylammonium iodide (22.25 g, 60.20 mmol, 1.2 eq). The reaction mixture was allowed to warm to room temperature and stirred for 27 h. The solvent was removed *in vacuo*, and hexane was added. The resulting suspension was filtered and the solid pad washed with hexane. The

filtrate was concentrated *in vacuo* and purified by Kugelrohr distillation collecting the fraction boiling at 80-90 °C at 0.1 mm Hg to afford the title compound (**21**) as a mixture of geometrical isomers (*E*:*Z* ~ 6.4:1) (9.33 g, 58%) as a colorless liquid.

Data for *E*:*Z* mixture: ¹H NMR (270 MHz, CDCl₃) δ : 0.05 (6 H, s), 0.89 (9 H, s), 1.65-1.82 (3 H, 3 δ s), 4.05 (2 H, s), 4.12-4.31 (2 H, m), 5.65-5.75 (1 H, m). ¹³C NMR (APT) (75 MHz, CDCl₃) δ : -5.2, 13.4, 13.4, 18.5, 21.3, 25.8, 26.0, 40.1, 40.5, 61.8, 67.4, 119.3, 121.9, 141.2, 141.6. IR (NaCl, neat): 2956, 2930, 2886, 2857, 1472, 1463, 1389, 1362, 1254, 1147, 1115, 1078, 1006, 837 cm⁻¹.

3-(Ethoxycarbonylmethyl-amino)-propionic acid ethyl ester. To a stirred solution of ethyl glycinate hydrochloride salt (100.5 g, 720 mmol, 1.0 eq) in 95% ethanol (1650 mL) at room temperature was added ethyl acrylate (79.3 g, 792 mmol, 1.1 eq) followed by triethylamine (73.3 g, 724 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 2 to 3 days until TLC showed that the reaction was complete, then it was concentrated and water added. The aqueous phase was extracted with EtOAc and the combined organic extracts washed with brine (3 times), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by vacuum distillation collecting the fraction boiling at 104-108 °C at 0.6-1.0 mm Hg (lit.⁴⁰ 84-90 °C at 0.4 mm Hg) to afford the title compound (111 g, 76%) as a colorless oil with spectral data identical to those previously reported.⁴¹

3-(*tert*-Butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionic acid ethyl ester (22**).** To a stirred solution of 3-(ethoxycarbonylmethyl-amino)-propionic acid ethyl ester (17.6 g, 86.8 mmol, 1.0 eq) in CHCl₃ (190 mL) at 0 °C was added (BOC)₂O (25.9 g, 119 mmol, 1.4 eq) followed by 5% aqueous NaOH (190 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 10 h then extracted with CHCl₃. The organic extract was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by vacuum distillation collecting the fraction boiling at 123-128 °C at 0.15 mm Hg to afford the title compound (**22**) (23.5 g, 90%) as a colorless oil with spectral data identical to those previously reported.^{23a}

3-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (23**).** A suspension of potassium *tert*-butoxide (24.48 g, 218.0 mmol, 1.5 eq) in toluene (580 mL) was cooled to 0 °C by means of an external ice-NaCl bath (-6 °C to -8 °C) and was stirred vigorously using a mechanical stirrer. A solution of **22** (44.8 g, 148 mmol, 1.0 eq) in toluene (80 mL) was added via cannula over 12 minutes. The reaction mixture was stirred at 0 °C for 85 minutes then quenched with acetic acid (16 mL, in one portion) followed by a cold solution of NaH₂PO₄·H₂O (80 g) in

H₂O (800 mL). The layers were separated and the aqueous layer extracted with CHCl₃ (500 mL + 300 mL). The combined organic extracts were washed with pH 7 phosphate buffer (2 × 150 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give an oil (36 g). Toluene (800 mL) was added to the oil and the resulting solution was washed with pH 10 sodium carbonate buffer (5 × 400 mL), followed by water (1 × 200 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford a reddish oil. The crude product was purified by Kugelrohr distillation collecting the fraction boiling at 125-145 °C at 2-3 mm Hg to afford the title compound (**23**) (14.0 g, 37%) as a colorless oil with spectral data identical to those previously reported.^{23a}

(2R, 3S)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (24).

To a 6 L Erlenmeyer flask immersed in a water bath were added in succession **23** (34.15 g, 0.133 mol), sucrose (513 g) and distilled water (2731 mL). The reaction mixture was stirred until the sucrose dissolved, after which dry baker's yeast (341 g, Red Star™) was added. The reaction mixture was stirred at 32-33 °C for 24 h then centrifuged. The aqueous layer was extracted with Et₂O (4 times) and the combined organic extracts dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica; 4:1 then 2:1 hexanes/EtOAc) to afford the title compound (**24**) (28.7 g, 84%) as a colorless oil with spectral data identical to those previously reported.^{23a} [α]_D²⁵ + 19.0 (c 1.21, CH₂Cl₂) (lit.^{23a} [α]_D²⁷ + 18.2 (c 1.45, CH₂Cl₂)). Both ¹H and ¹⁹F NMR spectra of the derived Mosher's ester of **24** indicated an enantiomeric excess of *ca.* 90%.

(2R, 3S)-2-[4-(tert-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (25). To a stirred solution of diisopropylamine (2.38 g, 23.5 mmol, 3.0 eq) in THF (7.5 mL) at 0 °C under N₂ was added CH₃Li (25.8 mL, 1.0 M in THF, 25.8 mmol, 3.3 eq) over 8 minutes. The resulting brown solution was stirred at 0 °C for 20 minutes and then cooled to -78 °C. A solution of **24** (2.02 g, 7.79 mmol, 1.0 eq) in THF (15 mL) was added via cannula over 7 minutes. The reaction mixture was stirred at -78 °C for an additional 3 minutes and at 0 °C for 50 minutes, then cooled back to -78 °C and stirred vigorously. A solution of **21** (4.56 g, 14.0 mmol, 1.8 eq) in HMPA (19.0 g, 106 mmol, 13.6 eq) was introduced in one portion then the reaction was allowed to proceed at 0 °C for a further 2 h before being quenched with EtOAc and saturated aqueous NH₄Cl. The mixture was extracted with EtOAc (3 times), and the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 4:1 hexanes/EtOAc) to afford the title compound (**25**) as a mixture of geometrical isomers (*E:Z* ~ 4.3:1) (2.08 g, 58%) as a colorless oil.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.01-0.02 (6 H, m), 0.85 (9 H, s), 1.17-1.26 (3 H, m), 1.32-1.41 (9 H, m), 1.37-1.70 (3 H, m), 1.89-1.98 (2 H, m), 2.50 (1 H, br s), 2.74-2.88 (2 H, m), 3.14-3.19 (1 H, m), 3.60-3.77 (1 H, m), 3.94 (2 H, s), 4.02-4.22 (3 H, m), 5.25-5.29 (1 H, m). ^{13}C NMR (75 MHz, CDCl_3) δ : -5.1, 14.0, 14.1, 14.3, 14.4, 18.5, 22.0, 26.0, 28.4, 28.5, 30.2, 30.4, 31.1, 31.4, 44.9, 45.4, 61.3, 68.1, 68.4, 71.2, 71.7, 76.5, 76.8, 79.6, 80.4, 117.7, 118.1, 138.2, 138.6, 153.8, 172.3. IR (NaCl, neat): 3449, 2977, 2955, 2928, 2857, 1739, 1703, 1391, 1367, 1251, 837, 774 cm^{-1} . Anal. calcd. for $\text{C}_{23}\text{H}_{43}\text{NO}_6\text{Si}$: C, 60.36; H, 9.47; N, 3.06. Found: C, 60.17; H, 9.30; N, 3.05.

(2*R*, 3*S*)-2-(4-Bromo-butyl)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (26). To a stirred solution of diisopropylamine (113 mg, 1.1 mmol, 2.8 eq) in THF (0.2 mL) at 0 °C under N_2 was added MeLi (1.32 mL, 1.0 M in THF, 1.32 mmol, 3.3 eq) over 3 minutes. After the solution had been stirred at 0 °C for 15 minutes then cooled to -50 °C, a solution of **24** (104 mg, 0.401 mmol, 1.0 eq) in THF (0.4 mL) was added via cannula over 3 minutes. The temperature of the reaction mixture was raised to -10 °C for 25 minutes and 0 °C for 5 minutes then lowered to between -35 °C and -40 °C. A solution of 1,4-dibromobutane (130 mg, 0.602 mmol, 1.5 eq) in HMPA (100 mg, 0.56 mmol, 1.4 eq) was added by syringe in one portion. After the reaction mixture had been stirred at 0 °C for 1 h and at room temperature for 19 h, it was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (4 $\times$ 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 1:1 hexanes/EtOAc) to afford the title compound (**26**) (54 mg, 49% based 16 mg of recovered **24**) as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ : 1.21-1.24 (3H, m), 1.28-1.40 (2H, m), 1.32-1.40, (9H, m), 1.83-2.40 (7 H, m), 2.62 (1 H, br s), 3.22-3.28 (1 H, m), 3.38 (1 H, t, $J = 6.5$ Hz), 3.65-3.75 (1 H, m), 4.06-4.22 (2 H, m), 4.24-4.30 (1 H, m). ^{13}C NMR (75 MHz, CDCl_3) δ : 14.4, 21.9, 22.1, 28.5, 30.6, 31.2, 32.4, 32.7, 32.9, 33.6, 34.0, 45.0, 45.5, 61.4, 71.0, 76.6, 76.8, 79.9, 80.5, 154.0, 172.3. IR (NaCl, neat): 3438, 2973, 2934, 2875, 1735, 1696, 1672, 1383, 1366, 1246, 1168, 772 cm^{-1} . $[\alpha]_D^{25}$ -22.8 (c 0.54, EtOAc). Anal. calcd. for $\text{C}_{16}\text{H}_{28}\text{BrNO}_5$: C, 48.74; H, 7.16; N, 3.55. Found: C, 48.90; H, 7.31; N, 3.60.

(2*R*, 3*S*)-2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methylsulfanyltio-carboxyoxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester. To a solution of **25** (92 mg, 0.20 mmol, 1.0 eq) in THF (3 mL) at 0 °C was added NaH (17 mg, 60% dispersion in oil, 0.43 mmol, 2.1 eq) under Ar. After 15 minutes, carbon disulfide (126 mg, 1.66 mmol, 8.2 eq) was added, producing a deep red solution. After a further 20 minutes, methyl iodide (454 mg,

3.20 mmol, 16 eq) was added in one portion. The resulting mixture was allowed to warm slowly to room temperature. After 8.5 h, it was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 $\times$ 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by radial chromatography (12:1 hexanes/EtOAc) to afford the title compound as a mixture of geometrical isomers (*E*:*Z* $\sim$ 3:1) (86 mg, 79%) as a colorless oil.

Data for *E*:*Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.05 (6 H, s), 0.89 (9 H, m), 1.25-1.35 (3 H, m), 1.40-1.50 (9 H, m), 1.60-1.75 (3 H, m), 2.00 (1 H, m), 2.30 (1 H, m), 2.50 (3 H, s), 2.75-2.90 (1 H, m), 3.30-3.42 (1 H, m), 3.68-3.90 (1 H, m), 4.00 (2 H, s), 4.05-4.25 (3 H, m), 5.05-5.35 (1 H, m), 5.85-5.95 (1 H, m). IR (NaCl, neat): 2979, 2958, 2931, 2851, 1744, 1701, 1390, 836, 775 cm^{-1} .

(2*S*)-2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-pyrrolidine-1,2-

dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (27). To a solution of AIBN (56 mg, 0.34 mmol, 0.9 eq) in toluene (20 mL) was added Bu_3SnH (892 mg, 3.06 mmol, 8.0 eq) via syringe under Ar, and the reaction mixture was heated to reflux. A solution of (2*R*, 3*S*)-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl] -3-methylsulfanylthiocarboxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (209 mg, 0.382 mmol, 1.0 eq) in toluene (10 mL) was added dropwise over 20 minutes. After 4.5 h, the solvent was removed *in vacuo* and the residue was purified by radial chromatography (silica, 12:1 hexanes/EtOAc) to afford the title compound (**27**) as a mixture of geometrical isomers (115 mg, 68%) as a colorless oil. Occasionally the *E* isomer could be obtained pure by radial chromatography.

Data for *E* isomer: ^1H NMR (300 MHz, CDCl_3) δ : 0.00-0.02 (6 H, m), 0.85-0.90 (9 H, m), 1.20-1.30 (3 H, m), 1.35-1.45 (9 H, m), 1.55-1.62 (3 H, m), 1.70-1.90 (2 H, m), 1.90-2.00 (2 H, m), 2.60-2.90 (2 H, m), 3.25-3.40 (1 H, m), 3.50-3.70 (1 H, m), 4.00 (2 H, s), 4.05-4.20 (2 H, m), 5.35 (1 H, m). IR (NaCl, neat): 2954, 2928, 2855, 1738, 1699, 1388, 1251, 1169, 836 cm^{-1} .

(2*S*)-2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-pyrrolidine-2-carboxylic

acid ethyl ester. To a suspension of zinc bromide (53 mg, 0.24 mmol, 4.6 eq) in CH_2Cl_2 (1 mL) at room temperature was added a solution of **27** (as a mixture of *E* and *Z* isomers) (22.7 mg, 0.0514 mmol, 1.0 eq) in CH_2Cl_2 (1.6 mL) via cannula over 2 minutes. After 7 h, the reaction mixture was quenched with pH 10 sodium carbonate buffer and extracted with EtOAc (2 $\times$ 15 mL). The aqueous layer was filtered through a Celite pad, and the filtrate was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a mixture of geometrical isomers (17.5 mg, >99%) as a colorless oil that could be used without further

purification.

Data for *E* isomer: ^1H NMR (300 MHz, CDCl_3) δ : 0.01 (6 H, s), 0.86 (9 H, s), 1.20-1.40 (1 H, m), 1.22 (3 H, t, $J = 4.4$ Hz), 1.57 (3 H, s), 1.60-1.80 (3 H, m), 2.15 (1 H, m), 2.30 (1 H, dd, $J = 7.5$ Hz, $J = 14.4$ Hz), 2.55 (1 H, dd, $J = 7.5$ Hz, $J = 14.4$ Hz), 2.94 (2 H, t, $J = 6.6$ Hz), 3.96 (2 H, s), 4.10 (2 H, q, $J = 4.0$ Hz), 5.34 (1 H, m). IR (NaCl, neat): 2957, 2855, 1731, 1253, 1180, 835 cm^{-1} .

(2*S*)-1-Bromoacetyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-pyrrolidine-2-carboxylic acid ethyl ester (28**).** To a solution of (2*S*)-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-pyrrolidine-2-carboxylic acid ethyl ester (65 mg, 0.19 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at 0 °C was added 0.5 M aqueous K_2CO_3 (0.57 mL, 0.29 mmol, 1.5 eq) followed by bromoacetyl bromide (58 mg, 0.29 mmol, 1.5 eq). After 5 h, the reaction mixture was quenched with water and extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound (**28**) as a mixture of geometrical isomers (*E*:*Z* $\sim$ 3:1) (74 mg, 83%) as a colorless oil that could be used without further purification.

Data for *E* isomer: ^1H NMR (300 MHz, CDCl_3) δ : 0.01 (6H, s), 0.87 (9H, s), 1.23 (3H, t, $J = 7.2$ Hz), 1.58 (3H, s), 2.02 (4H, m), 2.70 (1H, dd, $J = 8.4$ Hz, $J = 15.0$ Hz), 3.13 (1H, dd, $J = 6.6$ Hz, $J = 15.0$ Hz), 3.50-3.60 (1H, m), 3.73 (1H, d, $J = 7.5$ Hz), 3.75 (1H, d, $J = 7.5$ Hz), 3.75 (1H, m), 3.97 (2H, s), 4.15 (2H, q, $J = 7.2$ Hz), 5.31 (1H, m). IR (NaCl, neat): 2951, 2853, 1738, 1654, 1439, 1412, 1209, 1108, 836 cm^{-1} .

(8*aS*)-8a-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione ((+)-29**).** A solution of **28** (35 mg, 0.076 mmol, 1.0 eq) in 2.59 M methanolic NH_3 (2.4 mL, 6.2 mmol, 82 eq) was stirred at room temperature for 28 h. The solvent and excess ammonia were removed *in vacuo*. EtOAc was added to the solid residue and the resulting suspension was filtered. The filtrate was concentrated *in vacuo* to afford the title compound ((+)-**29**) as a mixture of geometrical isomers (26 mg, 97%) as a colorless oil.

Data for *E* isomer: ^1H NMR (300 MHz, CDCl_3) δ : 0.05 (6 H, s), 0.85 (9 H, s), 1.56 (3 H, s), 1.98-2.00 (2 H, m), 2.13-2.18 (2 H, m), 2.47 (1 H, dd, $J = 8.4$ Hz, $J = 16.0$ Hz), 2.59 (1 H, dd, $J = 8.4$ Hz, $J = 16.0$ Hz), 3.45-3.55 (1 H, m), 3.73 (1 H, 1/2 ABq, $J = 16.8$ Hz), 3.70-3.82 (1 H, m), 3.95 (2 H, s), 4.12 (1 H, 1/2 ABq, $J = 16.8$ Hz), 5.50 (1 H, m), 6.00 (1 H, br s). IR (NaCl, neat): 3241, 2952, 2927, 2857, 2892, 1667, 1445, 1254, 1107 cm^{-1} . $[\alpha]_{\text{D}}^{25} = +51.4$ (c 0.36, EtOAc).

(8aR)-8a-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione ((-)-29). To a solution of (8aR)-4-(1,4-dioxo-hexahydro-pyrrolo[1,2-*a*]pyrazin-8a-yl)-2-methyl-but-2-enal (**30**)¹⁹ (142 mg, 0.601 mmol, 1.0 eq) in EtOH (1.2 mL) at 0 °C was added in portions sodium borohydride (46 mg, 1.2 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 20 minutes and at room temperature for 2 h, then cooled in an ice-bath. To it was added slowly water (0.5 mL) and 1 M aqueous HCl to pH 3. The volatiles were removed *in vacuo* and the solid residue washed with benzene (3 × 5 mL) and the filtrate discarded. The solid was dried *in vacuo* and then washed with 4:1 CH₂Cl₂/MeOH. The filtrate was concentrated *in vacuo* to afford (8aR)-8a-(4-hydroxy-3-methyl-but-2-enyl)-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione (143mg, >99%) as a colorless oil which could be used without further purification.

To a solution of (8aR)-8a-(4-hydroxy-3-methyl-but-2-enyl)-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione (130 mg, 0.546 mmol, 1.0 eq) in DMF (1.5 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (124 mg, 0.823 mmol, 1.5 eq) followed by Et₃N (84 mg, 0.82 mmol, 1.5 eq). After 3 h, saturated aqueous NH₄Cl was added and the reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 7:1 EtOAc/MeOH) to afford the title compound ((-)-29) (39 mg, 20%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ : 0.05 (6 H, s), 0.85 (9 H, s), 1.56 (3 H, s), 1.98-2.0 (2 H, m), 2.13-2.18 (2 H, m), 2.47 (1 H, dd, *J* = 8.4, *J* = 16.0 Hz), 2.59 (1 H, dd, *J* = 8.4, *J* = 16.0 Hz), 3.45-3.55 (1 H, m), 3.73 (1 H, 1/2 ABq, *J* = 16.8 Hz), 3.70-3.82 (1 H, m), 3.95 (2 H, s), 4.12 (1 H, 1/2 ABq, *J* = 16.8 Hz), 5.50 (1 H, m), 6.00 (1 H, br s). ¹³C NMR (75 MHz, CDCl₃) δ : 5.2, 13.7, 18.4, 20.4, 26.0, 34.8, 35.9, 45.2, 46.7, 67.8, 116.1, 116.1, 140.3, 163.5, 172.3. IR (NaCl, neat): 3241, 2952, 2857, 1667, 1445, 1254, 1107 cm⁻¹. [α]_D²⁵ = -62.5 (c 0.39, EtOAc).

(2R, 3S)-2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester. To a solution of **25** (9.00 g, 19.7 mmol, 1.0 eq) in CH₂Cl₂ (50 mL) at 0 °C was added diisopropylethylamine (13.08 g, 101.2 mmol, 5.1 eq) followed by methoxymethyl chloride (8.14 g, 101 mmol, 5.1 eq). The reaction mixture was allowed to warm to room temperature over 1 h and after 26 h at room temperature it was quenched with saturated aqueous NaHCO₃ (300 mL) and extracted with Et₂O. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 6:1 hexanes/EtOAc) to afford the title compound as a mixture of geometrical isomers (*E*:*Z* ~ 3.3:1) (9.00 g, 91%) as a colorless oil.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.04-0.11 (6 H, m), 0.90-0.91 (9 H, 3 δ s), 1.22-1.32 (3 H, m), 1.41, 1.44 and 1.45 (9 H, 3 δ s), 1.63, 1.67 and 1.77 (3 H, 3 δ s), 1.98-2.11 (2 H, m), 2.74-2.99 (2 H, m), 3.04-3.27 (1 H, m), 3.34 (3 H, 2 δ s), 3.68-3.91 (1 H, m), 4.02 (2 H, s), 4.04-4.32 (3 H, m), 4.59 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.62 (1 H, 1/2 ABq, $J = 6.9$ Hz), 5.07 (1/5 H, m), 5.24-5.34 (4/5 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.2, -5.1, 14.0, 14.5, 21.7, 28.4, 28.5, 28.9, 29.0, 29.5, 30.0, 31.1, 45.2, 45.7, 55.7, 61.0, 61.9, 62.0, 68.1, 68.5, 69.9, 70.1, 70.6, 81.1, 82.2, 82.6, 96.2, 96.4, 96.5, 117.6, 118.0, 120.0, 138.1, 138.5, 139.0, 153.7, 171.62, 171.6. IR (NaCl, neat): 2957, 2852, 1739, 1701, 1391 cm^{-1} . HRMS (FAB) $m/e = 502.3217$ ($\text{C}_{25}\text{H}_{48}\text{NO}_7\text{Si}$ requires 502.3200).

(2*R*, 3*S*)-2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-2-carboxylic acid ethyl ester (31). To a suspension of zinc bromide (11.0 g, 48.8 mmol, 2.7 eq) in CH_2Cl_2 (205 mL) at room temperature was added a solution of (2*R*, 3*S*)-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (9.00 g, 17.9 mmol, 1.0 eq) in CH_2Cl_2 (205 mL) via cannula under Ar. The reaction mixture was stirred at room temperature for 24 h, then poured into pH 10 sodium carbonate buffer (2 L). The aqueous solution was extracted with Et_2O (1300 mL + 800 mL + 700 mL). The combined ethereal extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound (**31**) as a mixture of geometrical isomers (*E:Z* ~ 3.5:1) (6.80 g, 94%) as a colorless oil that could be used in the next step without further purification.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.04-0.07 (6 H, 3 δ s), 0.87-0.94 (9 H, m), 1.27 (3 H, t, $J = 7.2$ Hz), 1.63 and 1.74 (3 H, 2 δ br s), 1.91-2.11 (2 H, m), 2.12-2.25 (1 H, m), 2.67 (1 H, dd, $J = 7.8$ Hz, $J = 14.4$ Hz), 2.74-3.14 (2 H, m), 3.24-3.43 (1 H, m), 3.35 (3 H, s), 4.00 (2 H, br s), 4.05-4.30 (3 H, m), 4.60 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.63 (1 H, 1/2 ABq, $J = 6.9$ Hz), 5.21 (2/7 H, m), 5.39 (5/7 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.2, -5.1, 14.0, 14.3, 18.5, 21.5, 26.1, 31.8, 35.0, 35.3, 44.5, 44.6, 55.7, 61.2, 61.3, 62.1, 68.7, 74.4, 83.5, 95.6, 100.1, 118.9, 120.3, 138.0, 138.4, 172.9. IR (NaCl, neat): 3360, 2953, 2891, 1739, 1250, 1182, 1040, 836 cm^{-1} . HRMS (FAB) $m/e = 402.2665$ ($\text{C}_{20}\text{H}_{40}\text{NO}_5\text{Si}$ requires 402.2675).

(2*R*, 3*S*)-1-Bromoacetyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-2-carboxylic acid ethyl ester. To a stirred solution of **31** (3.40 g, 8.47 mmol, 1.0 eq) in CH_2Cl_2 (155 mL) at 0 $^\circ\text{C}$ was added 0.5 M aqueous K_2CO_3 solution (43 mL, 22 mmol, 2.5 eq) followed by bromoacetyl bromide (3.48 g, 17.2 mmol, 2.0 eq). After 2.5 h, the reaction mixture was quenched with saturated aqueous NaHCO_3 (150 mL) and extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4

and concentrated *in vacuo* to afford the title compound as a mixture of geometrical isomers (*E:Z* ~ 3.5:1) (4.40 g, 99%) as a colorless oil that could be used in the next step without further purification.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.06 and 0.08 (6 H, 2 $\square$ br s), 0.91 (9 H, s), 1.27 and 1.28 (3 H, 2 $\square$ t, J = 7.2 Hz), 1.64 and 1.77 (3 H, 2 $\square$ s), 2.14-2.25 (2 H, m), 2.78-2.91 (1 H, m), 3.12-3.53 (2 H, m), 3.35 and 3.36 (3 H, 2 $\square$ s), 3.74 and 3.75 (1 H, 2 $\square$ 1/2 ABq, J = 10.8 Hz), 3.83 and 3.85 (1 H, 2 $\square$ 1/2 ABq, J = 10.8 Hz), 4.00 (2 H, br s), 4.07-4.27 (3 H, m), 4.64 (2 H, s), 5.05 (1/3 H, m), 5.26 (2/3 H, m). ^{13}C NMR (75 MHz, CDCl_3) δ : -5.0, 14.0, 14.2, 18.5, 21.8, 26.1, 27.3, 29.6, 29.9, 30.1, 55.8, 61.4, 61.9, 68.2, 71.6, 71.7, 80.7, 81.0, 96.4, 96.5, 117.0, 119.5, 138.9, 139.7, 164.7, 164.8, 170.1. IR (NaCl, neat): 2955, 2893, 1747, 1650, 1416, 1249, 839, 776 cm^{-1} . HRMS (FAB) m/e = 522.1727 ($\text{C}_{22}\text{H}_{41}\text{BrNO}_6\text{Si}$ requires 522.1709).

(2*R*, 3*S*)-1-Aminoacetyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-2-carboxylic acid ethyl ester (32). To a stirred solution of (2*R*, 3*S*)-1-bromoacetyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methoxymethoxy-pyrrolidine-2-carboxylic acid ethyl ester (6.66 g, 12.7 mmol, 1.0 eq) in MeOH (296 mL) at room temperature was added 5.76M methanolic NH_3 (165 mL, 950 mmol, 75 eq) over 1 minute. After 2 h, the solvent and excess ammonia were removed *in vacuo*. EtOAc (600 mL) was added to the residue followed by saturated aqueous NaHCO_3 (600 mL) and 1 M aqueous NaOH (60 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (2 $\square$ 200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound (**32**) as a mixture of geometrical isomers (*E:Z* ~ 3.5:1) (5.49 g, 94%) as a colorless oil that could be used in the next step without further purification.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.00-0.10 (6 H, m), 0.87 and 0.89 (9 H, 2 $\square$ s), 1.15-1.33 (3 H, m), 1.51-1.80 (3 H, m), 1.99-2.28 (2 H, m), 2.60-2.95 (1 H, m), 2.95-3.86 (8 H, m), 3.90-4.06 (2 H, m), 4.06-4.45 (3 H, m), 4.50-4.76 (2 H, m), 4.90-5.50 (1 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.2, -5.1, -3.4, 13.7, 14.0, 14.3, 18.4, 25.8, 26.0, 27.1, 30.0, 30.3, 34.6, 43.2, 45.1, 46.2, 48.2, 55.8, 56.0, 61.1, 61.3, 61.9, 67.6, 68.1, 71.9, 72.5, 72.8, 79.9, 80.5, 80.8, 96.1, 96.3, 96.4, 114.9, 116.8, 117.2, 138.5, 138.9, 139.2, 140.7, 162.5, 163.3, 168.6, 169.8, 170.2. IR (NaCl, neat): 3474, 3316, 3060, 2951, 2843, 1745, 1652, 1454, 1252, 1045, 838, 774 cm^{-1} . HRMS (FAB) m/e = 459.2908 ($\text{C}_{22}\text{H}_{43}\text{N}_2\text{O}_6\text{Si}$ requires 459.2890).

(8*S*, 8*aR*)-8a-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-8-methoxymethoxy-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione (33). To a stirred solution of **32** (2.74 g, 5.97 mmol, 1.0 eq) in toluene (70 mL) at room temperature was added NaH (710 mg, 60% dispersion

in oil, 17.8 mmol, 3.0 eq) over 5 minutes followed by HMPA (5.5 mL). After 75 minutes, the reaction mixture was added dropwise to saturated aqueous NH_4Cl (300 mL). The mixture was extracted with EtOAc (300 mL + 200 mL + 100 mL). The combined organic extracts were washed with brine (3 $\times$ 260 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, EtOAc) to afford the title compound (**33**) as a mixture of geometrical isomers (*E:Z* $\sim$ 3:1) (2.06 g, 84%) as a colorless oil.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.03 and 0.04 (6 H, 2 $\times$ s), 0.88 (9 H, s), 1.56 and 1.74 (3 H, 2 $\times$ s), 2.02-2.32 (3 H, m), 2.60-2.76 (1 H, m), 3.34 and 3.35 (3 H, 2 $\times$ s), 3.51 (1 H, m), 3.72-3.85 (1 H, m), 3.89-4.07 (2 H, m), 3.96 (2 H, br s), 4.26-4.33 (1 H, m), 4.58 and 4.59 (1 H, 2 $\times$ 1/2 ABq, J = 7.2 Hz), 4.70 (1 H, 1/2 ABq, J = 7.2 Hz), 5.19 (1/3 H, m), 5.44 (2/3 H, m), 6.44-6.72 (1 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.1, -5.0, 13.9, 18.5, 21.8, 26.1, 27.2, 34.6, 34.7, 43.4, 46.3, 56.1, 61.6, 67.7, 72.9, 80.9, 96.2, 115.0, 117.5, 140.8, 141.8, 163.5, 168.9. IR (NaCl, neat) 3237, 2955, 2855, 1694, 1638, 1639, 1053, 1323, 1252, 1112, 1064, 835, 775 cm^{-1} . HRMS (FAB) m/e = 413.2475 ($\text{C}_{20}\text{H}_{37}\text{N}_2\text{O}_5\text{Si}$ requires 413.2471).

(8*S*, 8*aR*)-8a-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-8-methoxymethoxy-1,4-dioxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2,3-dicarboxylic acid dimethyl ester (34**).** To a stirred solution of **33** (5.02 g, 12.2 mmol, 1.0 eq) in THF (192 mL) at -78°C under Ar was added *n*BuLi (14.4 mL, 1.1 M in hexanes, 15.8 mmol, 1.3 eq) over 6 minutes. When the addition of *n*BuLi was almost over, the color of the reaction mixture changed to brown. The reaction was stirred for an additional 10 minutes at -78°C then methyl chloroformate (1.49 g, 15.8 mmol, 1.3 eq) was added over 3 minutes. After 40 minutes, the reaction was judged complete by TLC and was stirred for an additional 10 minutes -78°C . Further methyl chloroformate (4.60 g, 48.7 mmol, 4.0 eq) was then added over 2 minutes, followed by $\text{LiN}(\text{TMS})_2$ (60.8 mL, 1.0 M in THF, 60.8 mmol, 5.0 eq) over 8 minutes. After the reaction mixture had been stirred for 70 minutes, it was quenched with EtOAc (400 mL) and saturated aqueous NH_4Cl (800 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 $\times$ 400 mL). The combined organic extracts were washed with brine (3 $\times$ 500 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, EtOAc) to afford the title compound (**34**) as a mixture of geometrical isomers (6.0 g, 93%) as a colorless oil.

Data for *E:Z* mixture: ^1H NMR (300 MHz, CDCl_3) δ : 0.06 (6 H, s), 0.89 and 0.90 (9 H, 2 $\times$ s), 1.53, 1.58 and 1.75 (3 H, 3 $\times$ br s), 1.84-2.35 (2 H, m), 2.44-2.80 (2 H, m), 3.34 and 3.35 (3 H, 2 $\times$ s), 3.35-3.69 (2 H, m), 3.86 (3 H, s), 3.90 (3 H, s), 3.91-4.15 (3 H, m), 4.35 and 4.37 (1 H, 2 $\times$ br s), 4.57 and 4.58 (1 H, 2 $\times$ 1/2 ABq, J = 7.2 Hz), 4.65 (1 H, 1/2 ABq, J = 7.2 Hz), 5.23 (1/3 H, m), 5.43 (2/3 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.0, 18.5, 21.2, 21.9, 26.1, 27.0, 27.3, 34.6, 34.9, 44.2, 44.4, 54.0, 54.8, 56.2, 67.3, 67.3, 61.8, 63.2, 67.3, 68.3, 74.0, 74.1, 81.0,

81.7, 96.1, 96.2, 113.5, 116.0, 118.0, 139.8, 140.2, 158.42, 158.4, 165.8, 167.1. IR (NaCl, neat): 2955, 2857, 1793, 1749, 1680, 1434, 1375, 1222, 1035, 838, 779 cm^{-1} . HRMS (FAB) m/e = 529.2592 ($\text{C}_{24}\text{H}_{41}\text{N}_2\text{O}_9\text{Si}$ requires 529.2581).

6-Hydroxy-7-methoxy-1,3-dihydro-indol-2-one (43). To a mixture of nitrobenzenes **41** and **42**²⁷ (8.40 g, 37.0 mmol, 1.0 eq), NH_4Cl (23.75 g, 444 mmol, 12 eq) and iron powder (7.25 g, 130 mmol, 3.5 eq) was added water (350 mL). The reaction mixture was heated at reflux for 6.5 h then allowed to cool to room temperature, after which 1 M aqueous HCl was added to pH 2. The aqueous material (containing by-product **44**) was extracted with EtOAc (3 $\times$ 150 mL) and the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound (**43**) (4.9 g, 74%) as a white solid with spectral data identical to those previously reported.¹⁹

6-Hydroxy-7-(3-methyl-but-2-enyloxy)-1,3-dihydro-indol-2-one (46). To a solution of **45**¹⁹ (165 mg, 1.00 mmol, 1.0 eq) in DMF (2 mL) at 0 °C under Ar was added cesium carbonate (359 mg, 1.10 mmol, 1.1 eq) followed, dropwise, by prenyl bromide (155 mg, 1.04 mmol, 1.04 eq). The reaction mixture was stirred at 0 °C for 6.5 h then quenched by addition of saturated aqueous NH_4Cl . The aqueous material was extracted with EtOAc (4 times) and the combined organic extracts washed with 1 M aqueous NaOH (4 times). The combined basic extracts were neutralized by addition of 0.78 M aqueous H_2SO_4 and extracted with EtOAc (3 times). Finally, the combined EtOAc extracts from the neutralization were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 1:1 hexanes/EtOAc) to afford the title compound (**46**) (135 mg, 58%) as a reddish solid with spectral data identical to those previously reported.¹⁹

($\pm$)-3-Hydroxy-4,4-dimethyl-3,4,-dihydro-2H,10H-[1,4]dioxepino[2,3-g]indole (48). To a solution of **49**¹⁹ (2.90 g, 12.3 mmol, 1.0 eq) in THF (230 mL) at 0 °C was added DDQ (3.48 g, 15.3 mmol, 1.2 eq) over 2 to 3 minutes. After 20 minutes, the reaction mixture was concentrated. The residue was dissolved in EtOAc and washed with 1 M aqueous NaOH (200 mL), brine (2 $\times$ 150 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 1:1 hexanes/EtOAc) to afford the title compound (**48**) (2.60 g, 90%) as a white-purple solid with spectral data identical to those previously reported.¹⁹

($\pm$)-3-(tert-Butyl-dimethyl-silanyloxy)-4,4-dimethyl-3,4-dihydro-2H,10H-[1,4]dioxepino-[2,3-g]indole (51). A solution of **48**¹⁹ (2.68 g, 11.5 mmol, 1.0 eq), imidazole (5.13 g, 75.4 mmol, 6.6 eq) and TBSCl (4.88 g, 32.3 mmol, 2.8 eq) in DMF (22.6 mL) was heated at 44-45 °C for 24

h. The reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3 $\times$ 70 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:6 EtOAc/hexanes) to afford the title compound (**51**) (3.90 g, 98%) as a white solid with spectral data identical to those previously reported.¹⁹

(3*S*, 8*S*, 8*aR*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-octahydro-8-(methoxymethoxy)-1,4-dioxo-pyrrolo[1,2-*a*]pyrazine-3-carboxylic acid methyl ester (52**) and (3*R*, 8*S*, 8*aR*)-3-[[3-(*tert*-butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-octahydro-8-(methoxymethoxy)-1,4-dioxo-pyrrolo[1,2-*a*]pyrazine-3-carboxylic acid methyl ester (**53**).** To a flame-dried 1 L flask charged with diketopiperazine **34** (6.00 g, 11.3 mmol, 1.0 eq), gramine derivative **51**¹⁹ (5.04 g, 12.5 mmol, 1.1 eq) and molecular sieves (4 Å, 6.5 g) under Ar was added anhydrous MeCN (340 mL). The reaction mixture was stirred at room temperature for 10 minutes then Bu_3P (1.59 g, 7.86 mmol, 0.7 eq) was added in one portion. The reaction mixture was refluxed for 4 h then the volatiles removed *in vacuo*. The crude product was purified by flash chromatography (silica, 2.5:1 then 2:1 hexanes/EtOAc then EtOAc) to afford the 3*S* isomer (**52**) (high R_f) (5.0 g, 53%) as a white foam and the 3*R* isomer (**53**) (lower R_f) (1.6 g, 17%) as a white foam.

Data for **52** (mixture of four diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.03 and 0.04 (6 H, 2 $\times$ s), 0.12-0.19 (6 H, m), 0.88 and 0.91 (18 H, 2 $\times$ s), 1.11-1.17 (3 H, m), 1.46 and 1.48 (3 H, 2 $\times$ s), 1.55 and 1.68 (3 H, 2 $\times$ s), 1.82-2.19 (3 H, m), 2.20-2.36 (1 H, m), 2.46-2.63 (1 H, m), 3.22-3.60 (2 H, m), 3.23, 3.29, 3.31 and 3.75 (3 H, 4 $\times$ s), 3.71, 3.73, 3.74 and 3.32 (3 H, 4 $\times$ s), 3.79-4.28 (7 H, m), 4.41-4.50 (1 H, m), 4.53-4.62 (1 H, m), 5.11 (3/5 H, m), 5.34 (2/5 H, m), 6.11, 6.13 and 6.16 (1 H, 3 $\times$ s), 6.75 and 6.76 (1 H, 2 $\times$ d, J = 8.4 Hz), 6.97-7.02 (1 H, m), 7.06 (1 H, d, J = 8.4 Hz), 8.25 and 8.27 (1 H, 2 $\times$ br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.1, -4.6, -4.0, 13.7, 18.0, 18.5, 19.0, 19.6, 21.8, 25.8, 26.0, 27.1, 27.2, 28.1, 28.4, 33.8, 34.1, 43.9, 44.2, 53.6, 55.9, 61.6, 66.8, 66.9, 68.4, 71.6, 73.1, 76.2, 76.3, 80.5, 80.6, 80.9, 95.8, 95.9, 108.3, 113.15, 113.1, 116.5, 116.6, 117.8, 117.9, 123.7, 125.8, 125.9, 129.1, 129.2, 136.8, 137.0, 139.6, 140.3, 141.6, 141.9, 161.9, 166.9, 167.3, 169.6, 169.7. IR (NaCl, neat): 3310, 2954, 2857, 1742, 1676, 1438, 1251, 1091, 837, 776 cm^{-1} . HRMS (FAB) m/e = 829.4377 ($\text{C}_{42}\text{H}_{67}\text{N}_3\text{O}_{10}\text{Si}_2$ requires 829.4365). Anal. calcd. For $\text{C}_{42}\text{H}_{67}\text{N}_3\text{O}_{10}\text{Si}_2$: C, 60.76; H, 8.13; N, 5.06. Found: C, 60.58; H, 7.96; N, 5.13.

Data for **53** (mixture of four diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : -0.11-0.20 (12 H, m), 0.78-0.95 (18 H, m), 1.09 and 1.12 (3 H, 2 $\times$ s), 1.47 (3 H, s), 1.54-1.80 (3 H, m), 1.80-2.80 (4

H, m), 3.29 (3 H, s), 3.21-3.58 (2 H, m), 3.65-4.75 (11 H, m), 4.52 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.62 (1 H, 1/2 ABq, $J = 6.9$ Hz), 5.07-5.52 (1 H, m), 6.32-6.52 (1 H, m), 6.70-6.81 (1 H, m), 6.90-7.03 (1 H, m), 7.05-7.19 (1 H, m), 8.35, 8.39 and 8.46 (1 H, 3 $\square$ br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) $\square$: -5.3, -5.1, -4.6, -4.0, 13.8, 13.9, 18.0, 18.5, 19.1, 19.3, 25.8, 26.0, 27.4, 28.3, 28.4, 29.8, 33.6, 33.8, 35.0, 35.2, 43.8, 53.5, 55.8, 55.9, 61.7, 68.0, 71.6, 72.9, 72.9, 73.0, 73.1, 76.3, 80.2, 80.6, 95.6, 108.6, 113.8, 116.0, 116.1, 117.8, 124.5, 126.0, 129.0, 129.1, 136.8, 139.4, 139.6, 141.5, 141.6, 162.5, 166.4, 166.5, 168.7, 168.8. IR (NaCl, neat): 3285, 2950, 2855, 1751, 1678, 1662, 1442, 1254, 1091, 1044, 840, 777 cm^{-1} . HRMS (FAB) $m/e = 829.4360$ ($\text{C}_{42}\text{H}_{67}\text{N}_3\text{O}_{10}\text{Si}_2$ requires 829.4365).

(3*R*, 8*S*, 8*aR*, *E*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8*a*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-hexahydro-8-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine-1,4-dione (54*E*), (3*R*, 8*S*, 8*aR*, *Z*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8*a*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-hexahydro-8-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine-1,4-dione (54*Z*), (3*S*, 8*S*, 8*aR*, *E*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8*a*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-hexahydro-8-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine-1,4-dione (55*E*) and (3*S*, 8*S*, 8*aR*, *Z*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8*a*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-hexahydro-8-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine-1,4-dione (55*Z*). To a 50 mL flask charged with **52** (1.0 g, 1.2 mmol, 1.0 eq) and LiCl (260 mg, 6.13 mmol, 5.0 eq) under Ar was added a solution of water (32.5 mg, 1.80 mmol, 1.5 eq) in HMPA (9.32 mL). The reaction mixture was heated in an oil bath at 104-105 °C for 5 h then cooled to room temperature and poured into a 250 mL Erlenmeyer flask containing EtOAc (70 mL) and saturated aqueous NH_4Cl (60 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 $\square$ 40 mL). The combined organic extracts were washed with brine (6 $\square$ 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by radial chromatography (silica, 2:1 EtOAc/hexanes) to afford the *anti*-isomer (**54**) as a mixture of four diastereomers (280 mg, 30%) as a white foam and the *syn*-isomer (**55**) as a mixture of four diastereomers (545 mg, 59%) as a white foam. Analytical samples of **54E**, **54Z**, **55E** and **55Z** were obtained through careful separation of the products by flash chromatography (silica, 2:1 then 1:1 hexanes/EtOAc then EtOAc).

Data for **54E** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) $\square$: 0.01, 0.02, 0.15 and 0.16 (12 H, 4 $\square$ s), 0.87 (9 H, s), 0.91 (9 H, s), 1.14 (3 H, s), 1.49 (3 H, s), 1.53 and 1.54 (3

H, 2 □ s), 1.90-2.31 (4 H, m), 2.67 (1 H, br dd, $J = 8.4$ Hz, $J = 14.7$ Hz), 2.85 (1 H, dd, $J = 11.4$ Hz, $J = 14.7$ Hz), 3.12-3.77 (3 H, m), 3.37 (3 H, s), 3.81-4.10 (4 H, m), 4.18-4.38 (2 H, m), 4.60 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.72 (1 H, 1/2 ABq, $J = 6.9$ Hz), 5.40 (1 H, br t, $J = 6.9$ Hz), 5.70 (1 H, br s), 6.76 (1 H, d, $J = 8.4$ Hz), 7.02 and 7.03 (1 H, 2 □ br s), 7.09 (1 H, d, $J = 8.4$ Hz), 8.17 (1 H, br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) □: -5.2, -5.1, -4.6, -4.0, 13.7, 18.0, 18.4, 19.3, 19.4, 25.8, 26.0, 28.3, 28.4, 28.7, 28.8, 29.8, 34.5, 43.3, 54.4, 54.5, 56.0, 67.8, 67.9, 71.7, 73.5, 76.3, 80.8, 80.9, 96.1, 110.8, 110.9, 112.9, 113.0, 115.2, 115.4, 117.7, 117.8, 123.1, 125.03, 125.0, 129.7, 129.8, 137.1, 140.5, 141.9, 142.0, 165.5, 168.2. IR (NaCl, neat): 3366, 2955, 2929, 2894, 2857, 1681, 1445, 1251, 1107, 1043, 837, 776 cm^{-1} . HRMS (FAB) $m/e = 771.4286$ ($\text{C}_{40}\text{H}_{65}\text{N}_3\text{O}_8\text{Si}_2$ requires 771.4310). Anal. calcd. for $\text{C}_{40}\text{H}_{65}\text{N}_3\text{O}_8\text{Si}_2$: C, 62.22; H, 8.48; N, 5.44. Found: C, 62.40; H, 8.48; N, 5.34.

Data for **54Z** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) □: 0.03-0.17 (12 H, m), 0.88 (9 H, s), 0.92 (9 H, s), 1.14 and 1.16 (3 H, 2 □ s), 1.49 (3 H, s), 1.70 (3 H, s), 2.06-2.30 (4 H, m), 2.58-2.66 (1 H, m), 2.82 (1 H, dd, $J = 3.3$ Hz, $J = 11.4$ Hz), 3.37 (3 H, s), 3.41-3.59 (2 H, m), 3.69-3.75 (1 H, m), 3.86-4.06 (6 H, m), 4.61 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.73 (1 H, 1/2 ABq, $J = 6.9$ Hz), 5.16 (1 H, m), 5.67 (1 H, m), 6.77 (1 H, d, $J = 8.4$ Hz), 7.03 (1 H, s), 7.08 (1 H, d, $J = 8.4$ Hz), 8.16 (1 H, br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) □: -5.1, -4.6, -3.9, 13.8, 18.1, 18.5, 18.8, 19.3, 19.5, 21.7, 25.9, 26.0, 26.7, 27.5, 28.4, 28.6, 29.9, 34.5, 43.3, 44.1, 54.3, 54.4, 56.0, 61.6, 67.8, 67.7, 71.8, 73.5, 73.6, 76.3, 80.9, 81.0, 96.2, 96.3, 96.5, 110.8, 112.9, 115.3, 115.4, 117.8, 119.7, 124.8, 125.1, 125.7, 129.7, 129.9, 134.8, 137.2, 140.4, 140.5, 141.4, 141.5, 142.1, 165.6, 166.1, 168.3. IR (NaCl, neat): 3366, 2955, 2929, 2893, 2856, 1681, 1445, 1251, 1221, 1090, 1042, 837 cm^{-1} . HRMS (FAB) $m/e = 771.4286$ ($\text{C}_{40}\text{H}_{65}\text{N}_3\text{O}_8\text{Si}_2$ requires 771.4310).

Data for **55E** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) □: 0.01-0.18 (12 H, m), 0.85-0.95 (18 H, m), 1.13 and 1.14 (3 H, 2 □ s), 1.48 (3 H, s), 1.63 and 1.86 (3 H, 2 □ br s), 2.00-2.26 (3 H, m), 2.61-2.99 (2 H, m), 3.30 (3 H, s), 3.35-3.63 (2 H, m), 3.82-4.01 (2 H, m), 4.05-4.35 (6 H, m), 4.54 and 4.55 (1 H, 2 □ 1/2 ABq, $J = 6.9$ Hz), 4.61 and 4.62 (1 H, 2 □ 1/2 ABq, $J = 6.9$ Hz), 5.20-5.57 (1 H, m), 5.65-5.86 (1 H, m), 6.74-6.82 (1 H, m), 6.98-7.05 (1 H, m), 7.12-7.19 (1 H, m), 8.13-8.26 (1 H, m). IR (NaCl, neat): 3297, 2955, 2857, 1681, 1651, 1445, 1252, 1221, 1092, 1049, 837, 776 cm^{-1} . HRMS (FAB) $m/e = 771.4318$ ($\text{C}_{40}\text{H}_{65}\text{N}_3\text{O}_8\text{Si}_2$ requires 771.4310).

Data for **55Z** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) □: 0.10 (6 H, s), 0.15 and 0.17 (6 H, 2 □ s), 0.91 and 0.93 (9 H, 2 □ s), 1.14 (3 H, s), 1.49 (3 H, s), 1.87 (3 H, s), 2.07-2.28 (2 H, m), 2.70-2.88 (2 H, m), 3.30 (3 H, s), 3.37-3.47 (2 H, m), 3.55-3.63 (1 H, m), 3.85-4.00 (2 H, m), 4.16 (2 H, s), 4.20-4.30 (4 H, m), 4.54 (1 H, 1/2 ABq, $J = 7.2$ Hz), 4.62 (1 H, 1/2 ABq, $J = 7.2$ Hz), 5.28 (1 H, m), 5.74 (1 H, br s), 6.79 (1 H, d, $J = 8.4$ Hz), 7.01 (1 H, s), 7.16 (1

H, d, $J = 8.4$ Hz), 8.16 (1 H, br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) (mixture of **55E** and **55Z**) δ : -5.2, -5.1, -4.7, -4.0, 18.0, 18.5, 19.2, 21.9, 25.8, 26.0, 27.0, 28.3, 32.4, 33.5, 43.2, 55.8, 57.2, 57.3, 61.7, 68.0, 71.6, 73.0, 76.2, 80.7, 80.6, 95.4, 110.8, 110.9, 113.1, 116.0, 117.6, 117.7, 118.7, 123.3, 124.9, 129.6, 137.0, 139.9, 140.0, 141.8, 165.7, 166.5. IR (NaCl, neat): 3297, 2955, 2857, 1681, 1651, 1445, 1252, 1221, 1092, 1049, 837, 776 cm^{-1} . HRMS (FAB) $m/e = 771.4318$ ($\text{C}_{40}\text{H}_{65}\text{N}_3\text{O}_8\text{Si}_2$ requires 771.4310).

(3R, 8S, 8aR, E)-3-[[3-(tert-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-(tert-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-1-methoxy-8-(methoxymethoxy)-6,7,8,8a-tetrahydro-3H-pyrrolo[1,2-a]pyrazine-4-one (56E) and **(3R, 8S, 8aR, Z)-3-[[3-(tert-butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-(tert-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-1-methoxy-8-(methoxymethoxy)-6,7,8,8a-tetrahydro-3H-pyrrolo[1,2-a]pyrazine-4-one (56Z)**. To a flask charged with **54** (45.0 mg, 0.0583 mmol, 1.0 eq), Cs_2CO_3 (380 mg, 1.17 mmol, 20 eq) and Me_3OBF_4 (21.5 mg, 0.145 mmol, 2.5 eq) under Ar was added CH_2Cl_2 (1.93 mL). The reaction mixture was stirred at room temperature for 10 h then quenched with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 10:4:1 hexanes/EtOAc/MeOH) to afford **56E** (lower R_f) (21.3 mg, 46%) as a white foam and **56Z** (higher R_f) (8.3 mg, 18%) as a white foam.

Data for **56E** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.01-0.03 (6 H, 4 $\square$ s), 0.14 and 0.15 (6 H, 2 $\square$ s), 0.88, 0.89, 0.90 and 0.91 (18 H, 4 $\square$ s), 1.07 and 1.13 (3 H, 2 $\square$ s), 1.45 and 1.48 (3 H, 2 $\square$ s), 1.52 (3 H, s), 1.82-2.16 (3 H, m), 2.41 (1 H, m), 3.03 and 3.16 (3 H, 2 $\square$ s), 3.26-3.52 (3 H, m), 3.62 and 3.64 (3 H, 2 $\square$ s), 3.71-4.32 (10 H, m), 5.19-5.29 (1 H, m), 6.69 (1 H, d, $J = 8.4$ Hz), 6.99 and 7.03 (1 H, 2 $\square$ d, $J = 2.1$ Hz), 7.27 and 7.29 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 7.93 and 7.95 (1 H, 2 $\square$ br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -5.1, -4.5, -3.9, -3.8, 13.7, 18.1, 18.5, 18.7, 19.7, 25.9, 26.1, 27.7, 28.1, 28.7, 28.9, 29.1, 33.51, 33.5, 41.9, 42.0, 55.5, 55.6, 60.7, 61.0, 68.1, 68.2, 71.3, 71.4, 71.6, 71.7, 76.6, 79.5, 79.7, 80.2, 80.5, 94.9, 95.5, 113.5, 113.8, 114.5, 114.7, 115.9, 116.3, 116.4, 123.0, 123.1, 127.2, 127.6, 128.8, 136.6, 136.7, 139.9, 141.0, 141.4, 169.12, 169.1. IR (NaCl, neat): 3320, 2958, 2862, 1707, 1643, 1446, 1254, 1217, 1105, 1041, 839, 775 cm^{-1} . HRMS (FAB) $m/e = 785.4462$ ($\text{C}_{41}\text{H}_{67}\text{N}_3\text{O}_8\text{Si}_2$ requires 785.4466).

Data for **56Z** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.04 and 0.13-0.15 (12 H, 4 $\square$ s), 0.87-0.90 (18 H, s), 1.06 and 1.39 (3 H, 2 $\square$ s), 1.44 and 1.48 (3 H, 2 $\square$ s), 1.72 (3 H, s), 1.82-2.10 (3 H, m), 2.37-2.47 (1 H, m), 3.00 and 3.14 (3 H, 2 $\square$ s), 3.31-3.50 (3 H, m),

3.61 and 3.63 (3 H, 2 $\square$ s), 3.75-4.30 (10 H, m), 5.05 and 5.22 (1 H, 2 $\square$ m), 6.67 and 6.70 (1 H, 2 $\square$ s), 6.98 and 7.01 (1 H, 2 $\square$ d, $J = 5.1$ Hz), 7.24-7.29 (1 H, m), 7.94-7.95 (1 H, d, $J = 5.1$ Hz). IR (NaCl, neat): 3320, 2958, 2862, 1707, 1643, 1466, 1361, 1249, 1089, 837 cm^{-1} . HRMS (FAB) $m/e = 786.4507$ ($\text{C}_{41}\text{H}_{68}\text{N}_3\text{O}_8\text{Si}_2$ requires 786.4544).

(3*S*, 8*S*, 8*aR*)-3-[[3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl)methyl]-8*a*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-1-methoxy-8-(methoxymethoxy)-6,7,8,8*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4-one (57*E/Z*). To a flask charged with **55*E/Z*** (1.50 g, 1.94 mmol, 1.0 eq), Cs_2CO_3 (9.50 g, 29.2 mmol, 15 eq) and Me_3OBF_4 (863 mg, 5.83 mmol, 3 eq) under Ar was added CH_2Cl_2 (65 mL). The reaction mixture was stirred at room temperature for 11 h then quenched with water (120 mL) and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 1:1 EtOAc/hexanes) to afford **57*E/Z*** (877 mg, 57%, 86% based on 500 mg of a mixture of recovered starting material and product) as a foam.

Data for **57** (mixture of four diastereomers): ^1H NMR (300 MHz, CDCl_3) $\square$: 0.00-0.18 (12 H, m), 0.87, 0.88, 0.90 and 0.91 (18 H, 4 $\square$ s), 1.07 and 1.10 (3 H, 2 $\square$ s), 1.47 and 1.48 (6 H, 2 $\square$ s), 1.51-2.03 (4 H, m), 3.04-3.16 (1 H, m), 3.20-3.51 (2 H, m), 3.28 (3 H, s), 3.70 (3 H, br s), 3.74-3.86 (1 H, m), 3.90-4.23 (6 H, m), 4.37-4.47 (1 H, m), 4.53 (2 H, s), 5.15-5.29 (1 H, m), 6.72 (1 H, d, $J = 8.4$ Hz), 7.06-7.11 (1 H, m), 7.20 and 7.21 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 8.05 (1 H, br s). ^{13}C NMR (APT) (75 MHz, CDCl_3) $\square$: -5.2, -4.6, -3.9, 13.5, 18.0, 18.4, 18.8, 19.2, 21.8, 25.8, 26.0, 27.1, 28.3, 28.5, 31.6, 33.2, 33.6, 42.2, 52.7, 55.7, 61.6, 62.7, 62.8, 70.7, 70.8, 71.6, 79.5, 80.3, 80.4, 94.9, 113.6, 114.1, 114.2, 116.8, 119.3, 122.6, 126.4, 129.0, 128.9, 136.8, 138.3, 138.5, 139.3, 139.6, 141.4, 141.5, 158.5, 169.8. IR (NaCl, neat): 3327, 2956, 2855, 1694, 1644, 1448, 1252, 1087, 1042, 836 cm^{-1} . HRMS (FAB) $m/e = 786.4525$ ($\text{C}_{41}\text{H}_{68}\text{N}_3\text{O}_8\text{Si}_2$ requires 786.4544).

(3*R*, 8*S*, 8*aR*)-8-[[8*a*-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl)methyl]-3-[(*tert*-butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester. To a solution of **56*E/Z*** (300 mg, 0.382 mmol, 1.0 eq) in CH_2Cl_2 (3.74 mL) at 0 $^\circ\text{C}$ were added triethylamine (42.3 mg, 0.418 mmol, 1.1 eq), DMAP (46.6 mg, 0.381 mmol, 1.0 eq) and $(\text{BOC})_2\text{O}$ (250 mg, 1.15 mmol, 3.0 eq). The reaction mixture was stirred at 0 $^\circ\text{C}$ for 6 h then concentrated *in vacuo*. The crude product was purified by radial chromatography (silica, 3:1 hexanes/EtOAc) to afford the title compound as the (*E*) isomer (208 mg, 62%) as a white foam, and the title compound as a mixture of (*E*) and (*Z*) isomers (120 mg 35%) as a white foam.

Data for (*E*) isomer (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.01-0.02 (6 H, 4 $\square$ s), 0.14, 0.15 and 0.16 (6 H, 3 $\square$ s), 0.87, 0.88, 0.90 and 0.91 (18 H, 4 $\square$ s), 1.06 and 1.10 (3 H, 2 $\square$ s), 1.48 and 1.49 (3 H, 2 $\square$ s), 1.52 (3 H, br s), 1.60 (9 H, 2 $\square$ s), 1.76-1.95 (1 H, m), 1.97-2.13 (2 H, m), 2.35-2.48 (1 H, m), 3.02 and 3.15 (3 H, 2 $\square$ s), 3.18-3.48 (3 H, m), 3.55 and 3.61 (3 H, 2 $\square$ s), 3.70-4.06 (4 H, m), 3.93 (2 H, br s), 4.09-4.31 (4 H, m), 5.17-5.27 (1 H, m), (1 H, m), 6.85 (1 H, d, J = 8.4 Hz), 7.22-7.32 (2 H, m). ^{13}C NMR (75 MHz, CDCl_3) δ : -5.1, -4.6, -3.7, -3.6, 13.7, 18.2, 18.6, 18.7, 19.1, 26.0, 26.1, 27.7, 28.4, 28.6, 28.9, 33.5, 42.0, 52.7, 55.4, 55.6, 60.3, 60.7, 68.0, 68.1, 71.1, 71.2, 76.2, 79.0, 79.2, 80.3, 82.39, 82.44, 94.6, 114.9, 115.8, 116.7, 116.9, 119.1, 126.9, 127.0, 127.7, 131.1, 131.4, 139.9, 140.2, 140.3, 145.8, 145.9, 149.1, 158.0, 168.8, 169.2. IR (NaCl, neat): 2953, 2892, 1749, 1700, 1649, 1494, 1435, 1250, 1257, 1085 cm^{-1} . HRMS (FAB) m/e = 886.5069 ($\text{C}_{46}\text{H}_{76}\text{N}_3\text{O}_{10}\text{Si}_2$ requires 886.5069).

(3*R*, 8*S*, 8*aR*,)-8-[[8*a*-[4-Hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (58*E*). To a solution of the (*E*) isomer of the title compound from the previous reaction (190 mg, 0.214 mmol, 1.0 eq) in THF (2.6 mL) at room temperature was added TBAF (0.70 mL, 1.0 M in THF, 0.70 mmol, 3.3 eq). After 11 h, the reaction mixture was quenched with water (55 mL) and extracted with 1:1 EtOAc/Et₂O (3 times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by radial chromatography (1:2 hexanes/EtOAc) to afford **58*E*** (132 mg, 94%) as a white foam.

Data for **58*E*** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 1.19 and 1.21 (3 H, 2 $\square$ s), 1.55 and 1.57 (3 H, 2 $\square$ s), 1.59 (12 H, 2 $\square$ s), 1.77-1.97 (1 H, m), 1.98-2.16 (1 H, m), 2.44 (1 H, m), 3.01-3.12 (1 H, m), 3.04 and 3.15 (3 H, 2 $\square$ m), 3.20-3.44 (4 H, m), 3.49-3.67 (1 H, m), 3.52 and 3.61 (3 H, 2 $\square$ s), 3.75-4.38 (8 H, m), 3.95 (2 H, s), 5.22 (1 H, m), 6.88 (1 H, d, J = 8.4 Hz), 7.22-7.30 (2 H, m). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : 13.7, 23.4, 23.7, 25.5, 26.1, 27.5, 28.1, 28.4, 33.3, 33.4, 41.9, 52.5, 55.2, 55.4, 60.1, 60.5, 67.9, 70.7, 70.8, 71.1, 75.6, 78.7, 79.1, 79.8, 79.9, 82.4, 82.5, 94.4, 94.6, 115.2, 115.3, 116.4, 118.7, 126.8, 127.0, 127.8, 127.9, 131.1, 131.3, 140.5, 146.0, 148.8, 158.0, 168.9. IR (NaCl, neat): 3406, 2980, 2883, 1745, 1696, 1634, 1439, 1435, 1367, 1251, 1155, 1043, 966, 917 cm^{-1} . HRMS (FAB) m/e = 658.3328 ($\text{C}_{34}\text{H}_{48}\text{N}_3\text{O}_{10}$ requires 658.3339).

(3*S*, 8*S*, 8*aR*, *E*)-8-[[8*a*-[4-Hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (59*E*) and (3*S*, 8*S*, 8*aR*, *Z*)-8-[[8*a*-[4-hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-

8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl)methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (59Z**).** To a solution of **57E/Z** (877 mg, 1.12 mmol, 1.0 eq) in CH₂Cl₂ (8 mL) at 0 °C under Ar was added triethylamine (124 mg, 1.23 mmol, 1.1 eq), DMAP (136 mg, 1.11 mmol, 1.0 eq) and (BOC)₂O (730 mg, 3.34 mmol, 3.0 eq). After 4 h, the reaction mixture was concentrated *in vacuo*. THF (0.8 mL) and TBAF (2.84 mL, 1.0 M in THF, 2.84 mmol, 2.5 eq) were added to the residue at room temperature. After 16 h, additional TBAF (1.70 mL, 1.0 M in THF, 1.70 mmol, 1.5 eq) was added. The reaction mixture was stirred for 2 h, and then a third aliquot of TBAF (1.0 mL, 1.0 M in THF, 1.0 mmol, 0.9 eq) was added. The reaction was allowed to proceed for a further 10 h before being quenched with H₂O (400 mL) and extracted with 2:1 EtOAc/Et₂O (3 × 200 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by radial chromatography (1:2 hexanes/EtOAc) to afford **59E** (higher R_f) (536 mg, 73%) as a white foam and **59Z** (lower R_f) (198 mg, 27%) as a white foam.

Data for **59E** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ: 1.20 and 1.22 (3 H, 2 × s), 1.54-1.59 (6 H, m), 1.61 (9 H, s), 1.74-2.19 (4 H, m), 2.93-3.23 (2 H, m), 3.25-3.41 (2 H, m), 3.29 and 3.30 (3 H, 2 × s), 3.58 (1 H, br s), 3.70 (3 H, s), 3.80-3.95 (2 H, m), 4.00-4.17 (2 H, m), 4.23-4.35 (2 H, m), 4.42 (1 H, m), 4.54 and 4.55 (2 H, 2 × s), 4.71 and 5.03 (1 H, 2 × m), 6.91 and 6.92 (1 H, 2 × d, J = 8.4 Hz), 7.21 (1 H, d, J = 8.4 Hz), 7.35 and 7.39 (1 H, 2 × s). ¹³C NMR (APT) (75 MHz, CDCl₃) δ: 13.9, 14.3, 23.3, 23.6, 26.0, 26.4, 27.1, 28.2, 30.9, 33.8, 34.2, 42.3, 42.8, 52.7, 52.8, 61.8, 62.2, 68.3, 68.4, 70.9, 71.0, 75.8, 80.1, 80.2, 83.0, 94.8, 95.0, 115.1, 116.8, 117.1, 117.9, 118.2, 119.4, 119.5, 126.8, 126.9, 128.5, 130.4, 130.5, 138.8, 139.0, 141.0, 146.5, 146.6, 148.8, 158.4, 159.2, 169.3, 169.6. IR (NaCl, neat): 3416, 1750, 1693, 1636, 1493, 1368, 1157, 757 cm⁻¹. HRMS (FAB) m/e = 657.3263 (C₃₄H₄₇N₃O₁₀ requires 657.3261).

Data of **59Z** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ: 1.20 and 1.21 (3 H, 2 × s), 1.53 and 1.54 (3 H, 2 × s), 1.60 (9 H, s), 1.77 (3 H, s), 1.90-2.15 (3 H, m), 2.83-2.95 (2 H, m), 3.28 and 3.29 (3 H, 2 × s), 3.21-3.41 (3 H, m), 3.59 (1 H, br s), 3.67 and 3.68 (3 H, 2 × s), 3.83 and 3.97 (2 H, 2 × m), 4.01-4.15 (2 H, 2 × m), 4.27-4.28 (2 H, m), 4.37-4.42 (1 H, m), 4.53 and 4.54 (2 H, 2 × s), 5.05 (1 H, m), 6.91 (1 H, d, J = 8.4 Hz), 7.18 (1 H, d, J = 8.4 Hz), 7.37 and 7.39 (1 H, 2 × s). IR (NaCl, neat): 3420, 2977, 2945, 1750, 1699, 1635, 1368, 1154, 1037 cm⁻¹. HRMS (FAB) m/e = 657.3234 (C₃₄H₄₇N₃O₁₀ requires 657.3261).

(3*R*, 8*S*, 8*aR*, *E*)-8-[[8*a*-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl)methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (60E**).** To a solution of **58E** (55 mg, 0.084 mmol, 1.0 eq) in CH₂Cl₂ (1.5 mL) at 0 °C was added collidine (101

mg, 0.83 mmol, 10 eq) followed by dropwise addition of MsCl (151 μ L, 0.607 M MsCl in CH_2Cl_2 , 0.092 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 3.5 h and at 7 °C for 14 h until TLC showed that the starting material had disappeared and that the desired allylic mesylate and minor by-product bis-mesylate were formed. The reaction mixture was concentrated and CH_2Cl_2 (675 μ L) was added followed by HMPA (84.8 mg, 0.473 mmol, 5.7 eq). After the reaction mixture had been stirred at room temperature for 24 h, BnBu_3NCl (104 mg, 0.333 mmol, 4.0 eq) was added, and the mixture stirred at room temperature for an additional 6 h. The reaction mixture was concentrated and extracted with 2:1 EtOAc/Et₂O. The combined organic extracts were washed with 0.005 M aqueous HCl (5 $\times$ 35 mL), brine (once), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 25:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **60E** (43 mg, 76%) as a white foam.

Data for **60E** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl_3) δ : 1.18 and 1.21 (3 H, 2 $\times$ s), 1.53 and 1.56 (3 H, 2 $\times$ s), 1.58 and 1.59 (9 H, 2 $\times$ s), 1.67 (3 H, br s), 1.78-2.15 (4 H, m), 2.38-2.51 (1 H, m), 3.03-3.65 (4 H, m), 3.04-3.14 (3 H, m), 3.51 and 3.61 (3 H, 2 $\times$ s), 3.77-4.36 (7 H, m), 3.92 (2 H, s), 5.26-5.38 (1 H, m), 6.87 (1 H, d, *J* = 8.4 Hz), 7.21-7.29 (2 H, m). ¹³C NMR (APT) (75 MHz, CDCl_3) δ : 14.4, 23.2, 23.4, 26.0, 26.4, 27.5, 28.2, 28.4, 28.5, 33.8, 33.9, 42.0, 51.4, 52.6, 52.7, 55.3, 55.5, 60.0, 60.6, 70.8, 70.9, 71.0, 71.1, 75.8, 78.8, 79.2, 79.9, 80.0, 82.5, 82.6, 94.6, 94.7, 115.3, 115.4, 116.5, 116.7, 118.7, 118.9, 122.2, 126.9, 127.1, 128.0, 128.1, 131.1, 131.5, 137.1, 140.6, 140.7, 146.2, 148.9, 157.6, 157.7, 168.5. IR (NaCl, neat): 3419, 2978, 2894, 1745, 1698, 1645, 1436, 1158, 1037, 733 cm^{-1} . HRMS (FAB) *m/e* = 676.2992 ($\text{C}_{34}\text{H}_{47}\text{N}_3\text{O}_9\text{Cl} + \text{H}$ requires 676.2992).

(3*S*, 8*S*, 8*aR*, *E*)-8-[[8*a*-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (61E**)**. To a solution of **59E** (100 mg, 0.152 mmol, 1.0 eq) in CH_2Cl_2 (2.7 mL) at 0 °C was added collidine (183 mg, 1.52 mmol, 9.9 eq) followed by dropwise addition of MsCl (275 μ L, 0.607 M in CH_2Cl_2 , 0.167 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 2 h and at 7 °C for 17 h. The reaction mixture was concentrated and CH_2Cl_2 (1.35 mL) was added followed by HMPA (155 mg, 0.865 mmol, 5.7 eq). After the reaction mixture had been stirred at room temperature for 22 h, BnBu_3NCl (189 mg, 0.606 mmol, 4.0 eq) was added, and the mixture stirred at room temperature for an additional 5 h. The reaction mixture was concentrated and extracted with 2:1 EtOAc/Et₂O. The combined organic extracts were washed with 0.005 M aqueous HCl (4 $\times$ 70 mL + 15 mL), brine (once), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 18:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **61E** (90 mg, 88%, 90% based on recovery of 2 mg of **59E**) as a white foam.

Data for **61E** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 1.20 and 1.21 (3 H, 2 $\square$ s), 1.57 and 1.58 (3 H, 2 $\square$ s), 1.61 (9 H, s), 1.69 (3 H, br s), 1.78-1.95 (1 H, m), 1.96-2.11 (2 H, m), 2.12-2.33 (1 H, m), 2.84 (1 H, dt, $J = 9.3$ Hz, $J = 14.4$ Hz), 3.02-3.14 (1 H, m), 3.21-3.43 (2 H, m), 3.29 and 3.30 (3 H, 2 $\square$ s), 3.56-3.64 (1 H, m), 3.66 and 3.67 (3 H, 2 $\square$ s), 3.93 (2 H, s), 4.10-4.25 (2 H, m), 4.25-4.33 (2 H, m), 4.38 (1 H, m), 4.55 (2 H, m), 5.22 and 5.29 (1 H, 2 $\square$ br t, $J = 7.5$ Hz), 6.92 (1 H, d, $J = 8.4$ Hz), 7.19 and 7.27 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 7.42 and 7.43 (1 H, 2 $\square$ s). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : 14.4, 23.3, 23.4, 26.4, 27.0, 27.1, 28.2, 31.4, 31.5, 33.8, 33.9, 42.3, 51.5, 52.8, 55.8, 61.8, 70.7, 70.9, 75.7, 79.5, 79.6, 80.0, 80.1, 82.9, 94.8, 114.9, 116.8, 117.0, 119.4, 122.9, 123.0, 126.8, 128.4, 128.5, 130.3, 136.0, 136.1, 141.1, 146.6, 148.8, 157.8, 158.1, 169.5. IR (NaCl, neat): 3234, 2982, 2941, 1751, 1699, 1643, 1370, 1036 cm^{-1} . HRMS (FAB) $m/e = 675.2920$ ($\text{C}_{34}\text{H}_{46}\text{N}_3\text{O}_9\text{Cl}$ requires 675.2922). Anal. calcd. for $\text{C}_{34}\text{H}_{46}\text{N}_3\text{O}_9\text{Cl}$: C, 60.39; H, 6.85; N, 6.21. Found: C, 60.52; H, 6.74; N, 5.98.

(3S, 8S, 8aR, Z)-8-[[8a-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylic acid *tert*-butyl ester (61Z). To a solution of **59Z** (60 mg, 0.091 mmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) at 0 $^\circ\text{C}$ was added triethylamine (18.9 mg, 0.187 mmol, 2.0 eq) followed by dropwise addition of MsCl (150 μL , 0.607 M in CH_2Cl_2 , 0.091 mmol, 1.0 eq). The reaction mixture was stirred at 0 $^\circ\text{C}$ for 11 h and at room temperature for 3 h. The reaction mixture was concentrated and extracted with 2:1 EtOAc/Et₂O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 25:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **61Z** (29 mg, 47%, 75% based on recovery of 22.6 mg of **59Z**) as a white foam.

Data for **61Z** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 1.20-1.21 (3 H, 2 $\square$ s), 1.56-1.57 (3 H, 2 $\square$ s), 1.61 (9 H, s), 1.84 (3 H, s), 1.90-2.20 (3 H, m), 2.32-2.45 (1 H, m), 2.71-2.88 (1 H, m), 3.02-3.18 (1 H, m), 3.29-3.30 (3 H, s), 3.23-3.41 (2 H, m), 3.57-3.61 (1 H, m), 3.66-3.68 (3 H, s), 3.93-3.97 (2 H, m), 4.10-4.39 (5 H, m), 4.54-4.55 (2 H, s), 5.20 (1 H, m), 6.92 (1 H, d, $J = 8.4$ Hz), 7.18 (1 H, d, $J = 8.4$ Hz), 7.43 (1 H, s). IR (NaCl, neat): 3407, 2979, 2929, 1747, 1698, 1643, 1493, 1369, 1046 cm^{-1} . HRMS (FAB) $m/e = 676.2994$ ($\text{C}_{34}\text{H}_{47}\text{N}_3\text{O}_9\text{Cl}$ requires 676.2922).

(3R, 8S, 8aR, E)-8-[[8a-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-(*tert*-butyl-dimethylsilanyloxy)-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylic acid *tert*-butyl ester (62E). To a solution of **60E** (40.0 mg, 0.0592 mmol, 1.0 eq) and 2,6-lutidine

(12.7 mg, 0.119 mmol, 2.0 eq) in CH₂Cl₂ (1.18 mL) at 0 °C under Ar was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (23.4 mg, 0.0885 mmol, 1.5 eq). After 3.5 h, additional 2,6-lutidine (12.7 mg, 0.119 mmol, 2.0 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23.4 mg, 0.0885 mmol, 1.5 eq) were added, and the reaction was allowed to stir for a further 1 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 1:1 hexanes/EtOAc) to afford **62E** (41.5 mg, 89%) as a white foam.

Data for **62E** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.13, 0.14 and 0.15 (6 H, 3 $\square$ s), 0.89 and 0.90 (9 H, 2 $\square$ s), 1.05 and 1.10 (3 H, 2 $\square$ s), 1.47 and 1.48 (3 H, 2 $\square$ s), 1.59 (9 H, s), 1.65-1.69 (3 H, m), 1.81-1.93 (1 H, m), 1.96-2.11 (2 H, m), 2.37-2.49 (1 H, m), 3.00 and 3.13 (3 H, 2 $\square$ s), 3.18-3.40 (3 H, m), 3.53 and 3.60 (3 H, 2 $\square$ s), 3.73-4.26 (7 H, m), 3.92 (2 H, s), 4.27-4.35 (1 H, m), 5.28-5.36 (1 H, m), 6.84 (1 H, d, J = 6.3 Hz), 7.18-7.28 (2 H, m). ¹³C NMR (APT) (100 MHz, CDCl₃) δ : -4.7, -3.8, -3.7, 14.3, 14.4, 18.0, 18.5, 19.0, 21.2, 25.9, 27.5, 28.2, 28.4, 28.6, 28.7, 33.8, 33.9, 41.9, 42.0, 51.4, 52.7, 53.6, 55.3, 55.5, 60.1, 60.5, 60.6, 71.0, 71.1, 76.1, 76.2, 78.8, 79.0, 80.2, 82.4, 82.3, 94.6, 114.8, 114.9, 116.5, 116.6, 119.1, 122.2, 122.3, 126.9, 127.0, 127.6, 127.7, 131.0, 131.3, 137.1, 145.2, 145.9, 149.1, 157.7, 157.8, 168.8, 168.9, 171.3. IR (NaCl, neat): 2953, 2894, 1749, 1701, 1652, 1491, 1369, 1247, 1159 cm⁻¹. HRMS (FAB) m/e = 790.3854 (C₄₀H₆₁N₃O₉SiCl requires 790.3865).

(3S, 8S, 8aR, E)-8-[[8a-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-(tert-butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylic acid tert-butyl ester (63E). To a solution of **61E** (152 mg, 0.225 mmol, 1.0 eq) and 2,6-lutidine (48.2 mg, 0.450 mmol, 2.0 eq) in CH₂Cl₂ (4.4 mL) at 0 °C under Ar was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (88.6 mg, 0.335 mmol, 1.5 eq). After 4 h, additional 2,6-lutidine (48.2 mg, 0.450 mmol, 2.0 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (88.6 mg, 0.335 mmol, 2.0 eq) were added, and the reaction was allowed to stir for a further 2 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 1:1 hexanes/EtOAc) to afford **63E** (140 mg, 79%) as a white foam.

Data for **63E** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.14 and 0.15 (6 H, 2 $\square$ s), 0.89 (9 H, s), 1.07 and 1.09 (3 H, 2 $\square$ s), 1.48 (3 H, br s), 1.60 (9 H, s), 1.66 (3 H, s), 1.77-1.91 (1 H, m), 1.93-2.26 (3 H, m), 2.78-2.96 (1 H, m), 3.28 (3 H, s), 3.20-3.42 (2 H, m), 3.65 and 3.66 (3 H, 2 $\square$ s), 3.71-3.84 (1 H, m), 3.91-3.98 (1 H, m), 3.92 (2 H, br s), 4.08-4.23 (3

H, m), 4.35-4.41 (1 H, m), 4.50-4.57 (2 H, m), 5.20 and 5.29 (1 H, 2 $\square$ br t, $J = 7.5$ Hz), 6.89 (1 H, d, $J = 8.4$ Hz), 7.15 and 7.16 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 7.40 and 7.41 (1 H, 2 $\square$ s). ^{13}C NMR (APT) (100 MHz, CDCl_3) $\square$: -4.7, -3.9, 14.4, 18.0, 18.5, 18.6, 25.9, 27.1, 27.2, 28.2, 28.6, 28.7, 31.4, 31.5, 33.9, 34.0, 42.3, 51.4, 52.7, 55.7, 61.7, 61.8, 70.6, 70.7, 71.1, 76.0, 79.6, 80.3, 82.8, 94.8, 114.2, 116.9, 119.7, 122.9, 123.0, 126.7, 127.9, 130.1, 135.9, 136.1, 140.6, 146.2, 148.9, 149.0, 157.8, 158.1, 169.5. IR (NaCl, neat): 2955, 2855, 1749, 1699, 1644, 1433, 1368, 1252, 1157, 1087, 856, 835 cm^{-1} . HRMS (FAB) $m/e = 790.3853$ ($\text{C}_{40}\text{H}_{61}\text{N}_3\text{O}_9\text{SiCl}$ requires 790.3865).

(3*S*, 8*S*, 8*aR*, *Z*)-8-[[8*a*-[4-Chloro-3-methyl-2-butenyl]-3,4,6,7,8,8*a*-hexahydro-1-methoxy-8-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-(*tert*-butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (63Z**).** To a solution of **61Z** (17.5 mg, 0.0259 mmol, 1.0 eq) and 2,6-lutidine (5.5 mg, 0.0513 mmol, 2.0 eq) in CH_2Cl_2 (0.5 mL) at 0 $^\circ\text{C}$ under Ar was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.2 mg, 0.0386 mmol, 1.5 eq). After 2 h, additional 2,6-lutidine (5.5 mg, 0.0513 mmol, 2.0 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.2 mg, 0.0386 mmol, 1.5 eq) were added, and the reaction was allowed to stir for a further 2 h. The reaction mixture was quenched with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 2:1 hexanes/EtOAc) to afford **63Z** (15.4 mg, 75%) as a white foam. Data for **63Z** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) $\square$: 0.14 and 0.16 (6 H, 2 $\square$ s), 0.91 (9 H, s), 1.07 and 1.09 (3 H, 2 $\square$ s), 1.49-1.50 (3 H, s), 1.62-1.67 (9 H, s), 1.83 (3 H, s), 1.90-2.10 (3 H, m), 2.20-2.42 (1 H, m), 2.71-2.92 (1 H, m), 3.29-3.30 (3 H, s), 3.35-3.41 (2 H, m), 3.65-3.67 (3 H, s), 3.76-3.83 (1 H, m), 3.93-3.98 (3 H, m), 4.14-4.21 (3 H, m), 4.34-4.39 (1 H, m), 4.54 and 4.55 (2 H, 2 $\square$ s), 5.20 (1 H, m), 6.91-6.94 (1 H, d, $J = 8.4$ Hz), 7.16-7.19 (1 H, d, $J = 8.4$ Hz), 7.43 (1 H, s). IR (NaCl, neat): 2957, 2860, 1749, 1701, 1700, 1652, 1491, 1370, 1253, 1156, 1088, 1039 cm^{-1} . HRMS (FAB) $m/e = 789.3782$ ($\text{C}_{40}\text{H}_{60}\text{N}_3\text{O}_9\text{SiCl}$ requires 789.3782).

(3*S*, 8*S*, 8*aR*, 10*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4-dihydro-4,4-dimethyl-8-[[3,4,7,8-tetrahydro-1-methoxy-8-(methoxymethoxy)-10-(1-methylethenyl)-4-oxo-6*H*-3,8*a*-ethanopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid *tert*-butyl ester (64**).** To a suspension of NaH, washed by anhydrous ether, (79.0 mg, 3.29 mmol, 20 eq) in THF (9.6 mL) was added solid **63E** (128 mg, 0.162 mmol, 1.0 eq) under Ar. The reaction mixture was gently refluxed for 9.5 h then added dropwise to a flask containing water (100 mL) and EtOAc (35 mL). The layers were separated and the aqueous layer

was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give an oil which contained mostly the desired S_N2' product (**64**) and some minor S_N2' product with the N-*t*-BOC group removed. The above mixture was dissolved in CH₂Cl₂ (4 mL). Triethylamine (2.5 mg, 0.025 mmol, 0.16 eq), DMAP (2.8 mg, 0.023 mmol, 0.14 eq) and (BOC)₂O (15 mg, 0.069 mmol, 0.42 eq) were added to the above mixture solution at 0 °C under Ar. After 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by radial chromatography (1:2 then 1:1 EtOAc/hexanes) to afford **64** (107 mg, 87%) as a white foam.

Data for **64** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.15 and 0.16 (6 H, 2 $\times$ s), 0.90 (9 H, s), 1.09 and 1.10 (3 H, 2 $\times$ s), 1.39-1.49 (1 H, m), 1.49 (3 H, s), 1.61 (9 H, s), 1.64 (3 H, s), 1.98-2.06 (1 H, m), 2.08-2.24 (2 H, m), 2.44-2.54 (1 H, m), 3.02-3.12 (1 H, m), 3.33-3.42 (1 H, m), 3.42 and 3.43 (3 H, 2 $\times$ s), 3.52-3.72 (2 H, m), 3.69 and 3.61 (3 H, 2 $\times$ s), 3.75-3.87 (1 H, m), 3.93-4.00 (1 H, m), 4.15-4.24 (1 H, m), 4.29-4.36 (1 H, m), 4.62-4.91 (4 H, m), 6.85 and 6.86 (1 H, 2 $\times$ d, J = 8.4 Hz), 7.32 and 7.39 (1 H, 2 $\times$ d, J = 8.4 Hz), 7.47 and 7.56 (1 H, 2 $\times$ s). ¹³C NMR (APT) (100 MHz, CDCl₃) δ : -4.7, -3.7, 18.0, 18.7, 18.8, 19.7, 25.9, 26.8, 26.9, 28.2, 28.7, 31.4, 36.9, 41.5, 48.6, 48.9, 54.5, 54.6, 56.0, 66.0, 66.5, 66.6, 69.0, 69.3, 71.1, 71.6, 76.1, 79.0, 80.2, 82.4, 96.7, 115.8, 116.2, 116.3, 119.1, 127.6, 127.9, 131.5, 140.1, 140.2, 143.5, 143.8, 145.8, 149.1, 170.2, 171.2, 171.5. IR (NaCl, neat): 2950, 2892, 1749, 1677, 1633, 1474, 1368, 1248, 1156, 1089 cm⁻¹. HRMS (FAB) m/e = 754.4099 (C₄₀H₆₀N₃O₉Si requires 754.4094).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-17-methoxy-13-(methoxymethoxy)-4,4,15,15-tetramethyl-9-oxo-9*H*,11*H*-8a,13a-(nitrilomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester (65**).** To a flask charged with AgBF₄ (40.0 mg, 0.205 mmol, 3.1 eq) and PdCl₂ (55.0 mg, 0.310 mmol, 4.7 eq) was added MeCN (2.25 mL) at room temperature under Ar. After 6.5 h, propylene oxide (207 mg, 3.56 mmol, 54 eq) was added and the mixture was stirred for 15 minutes, then **64** (50.0 mg, 0.0663 mmol, 1.0 eq) was added in one portion as a solid. A deep red color was produced immediately. After the reaction mixture had been stirred at room temperature for 40 h and then cooled to 0 °C, absolute ethanol (1.68 mL) was added. NaBH₄ (30 mg, 0.79 mmol, 12 eq) was added portionwise over 45 minutes, yielding a black solid and a clear colorless solution. The mixture was stirred for an additional 40 minutes and filtered. The filtrate was concentrated, and EtOAc was added to the residue. The resulting solution was washed with 0.01 M aqueous HCl followed by brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.

The crude product was purified by preparative TLC (silica, 10:6:1 hexanes/EtOAc/MeOH) to afford **65** (32.8 mg, 66%) as a white foam.

Data for **65** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.11 and 0.14 (6 H, 2 $\square$ s), 0.90 and 0.91 (9 H, 2 $\square$ s), 1.10 and 1.20 (3 H, 2 $\square$ s), 1.23 and 1.26 (3 H, 2 $\square$ s), 1.33-1.35 (3 H, 2 $\square$ s), 1.47 and 1.49 (3 H, 2 $\square$ s), 1.58 and 1.60 (9 H, 2 $\square$ s), 1.73 (1 H, dd, J = 4.2 Hz, J = 12.9 Hz), 1.94-2.07 (1 H, m), 2.11-2.32 (3 H, m), 3.00-3.10 (1 H, m), 3.34-3.76 (3 H, m), 3.47 (3 H, s), 3.83 (3 H, s), 3.83-3.96 (2 H, m), 4.04-4.19 (1 H, m), 4.43 (1 H, m), 4.75 (1 H, d, J = 7.2 Hz), 4.86 (1 H, d, J = 7.2 Hz), 6.80 and 6.81 (1 H, 2 $\square$ d, J = 8.1 Hz), 7.06-7.07 (1 H, d, J = 8.1 Hz). ^{13}C NMR (APT) (75 MHz, CDCl_3) δ : -4.8, -4.7, -4.0, -3.9, 18.0, 19.1, 19.5, 20.4, 20.5, 26.9, 27.3, 27.5, 28.0, 28.6, 28.8, 31.6, 32.0, 37.0, 40.5, 41.6, 49.0, 49.1, 54.6, 56.0, 65.3, 67.0, 71.4, 72.1, 76.3, 79.1, 79.1, 80.2, 80.7, 84.2, 84.4, 96.8, 110.8, 113.0, 113.1, 118.1, 118.7, 125.6, 125.7, 129.2, 129.3, 138.1, 138.6, 139.3, 139.5, 143.3, 143.4, 153.6, 170.7, 171.7. IR (NaCl, neat): 2975, 2956, 2897, 1745, 1682, 1633, 1369, 1047, 837 cm^{-1} . HRMS (FAB) m/e = 753.4034 ($\text{C}_{40}\text{H}_{59}\text{N}_3\text{O}_9\text{Si}$ requires 753.4020).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-8a-Amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3,4,8a,9,12,13,14a*S*,15-octahydro-13-(methoxymethoxy)-4,4,15,15-tetramethyl-9-oxo-2*H*,8*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-13a,16(11*H*,14*H*)-dicarboxylic acid 16-*tert*-butyl 13a-methyl ester (66**). To a solution of crude **65** (a product from the $\text{PdCl}_2/\text{AgBF}_4$ mediated cyclization reaction, 201 mg, 0.267 mmol scale) in THF (25 mL) at 0 $^\circ\text{C}$ was added 0.1 M aqueous HCl (2 mL). The reaction mixture was stirred at room temperature for 1 h then cooled to 0 $^\circ\text{C}$, quenched with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (silica, 20:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **66** (155.2 mg, 75% over two steps) as a white foam.**

Data for **66** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.11, 0.12 and 0.13 (6 H, 3 $\square$ s), 0.89 and 0.91 (9 H, 2 $\square$ s), 1.08 and 1.17 (3 H, 2 $\square$ s), 1.47 and 1.48 (3 H, 2 $\square$ s), 1.54 and 1.55 (3 H, 2 $\square$ s), 1.62 and 1.64 (9 H, 2 $\square$ s), 1.77 and 1.78 (3 H, 2 $\square$ s), 1.88-2.15 (3 H, m), 2.24-2.41 (1 H, m), 2.78 (1 H, d, J = 16.8 Hz), 2.86 (1 H, dd, J = 2.1 Hz, J = 16.8 Hz), 3.16 (1 H, br d, J = 13.8 Hz), 3.35 (3 H, s), 3.63-3.96 (5 H, m), 3.83 (3 H, s), 4.13 (1 H, m), 4.64 (2 H, m), 6.78 and 6.79 (1 H, 2 $\square$ d, J = 8.4 Hz), 6.88 (1 H, d, J = 8.4 Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : -4.8, -4.7, -4.0, -3.9, 18.1, 19.2, 19.4, 25.9, 26.0, 27.0, 27.2, 27.6, 28.6, 28.9, 30.5, 30.7, 31.2, 33.6, 33.7, 36.0, 43.8, 50.1, 50.2, 52.9, 56.0, 57.8, 69.6, 69.7, 71.5, 72.0, 76.2, 76.3, 80.4, 80.8, 83.5, 84.7, 84.9, 96.3, 107.17, 107.21, 112.4, 118.3, 118.8, 125.6, 125.7, 129.0, 129.1, 138.1, 138.6, 138.9, 139.0, 143.4, 153.4, 171.2, 171.2, 175.0. IR (NaCl, neat): 2954, 2930, 2891,

2861, 1743, 1644, 1496, 1438, 1368, 1251, 1232, 1155, 1115, 1091, 1050, 838, 776 cm^{-1} . HRMS (FAB) $m/e = 772.4222$ ($\text{C}_{40}\text{H}_{62}\text{N}_3\text{O}_{10}\text{Si}$ requires 772.4204).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-13-(methoxymethoxy)-4,4,15,15-tetramethyl-9,17-dioxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester (67**).** To a solution of **66** (155.2 mg, 0.201 mmol, 1.0 eq) in toluene (6.7 mL) was added 2-hydroxypyridine (20.8 mg, 0.219 mmol, 1.1 eq). The reaction mixture was heated at 120 °C for 2 h then concentrated *in vacuo*. The residue was purified by preparative TLC (silica, 5:10:1 hexanes/EtOAc/MeOH) to afford **67** (124.0 mg, 83%) as a white foam.

Data for **67** (mixture of two diastereomers); ^1H NMR (300 MHz, CDCl_3) δ : 0.11 and 0.14 (6 H, 2 $\times$ s), 0.90 and 0.91 (9 H, 2 $\times$ s), 1.10 and 1.21 (3 H, 2 $\times$ s), 1.25 and 1.27 (3 H, 2 $\times$ s), 1.36 and 1.37 (3 H, 2 $\times$ s), 1.47 and 1.49 (3 H, 2 $\times$ s), 1.59 and 1.61 (9 H, 2 $\times$ s), 1.89 (1 H, dd, $J = 4.8$ Hz, $J = 13.2$ Hz), 2.14-2.29 (2 H, m), 2.34 (1 H, dd, $J = 10.2$ Hz, $J = 13.2$ Hz), 2.52-2.65 (2 H, m), 3.48 (3 H, s), 3.58-4.17 (5 H, m), 4.05-4.21 (1 H, m), 4.44 (1 H, m), 4.78 (1 H, 1/2 ABq, $J = 7.2$ Hz), 5.00 (1 H, 1/2 ABq, $J = 7.2$ Hz), 5.94 (1 H, br s), 6.81 and 6.83 (1 H, 2 $\times$ d, $J = 8.4$ Hz), 7.00 and 7.01 (1 H, 2 $\times$ d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : -4.8, -4.6, -4.0, -3.9, 18.1, 18.2, 19.1, 19.7, 20.0, 20.2, 25.1, 25.9, 26.0, 26.7, 27.0, 27.6, 28.7, 28.9, 31.2, 31.5, 36.7, 42.5, 51.1, 51.2, 56.1, 59.7, 68.4, 68.5, 71.5, 72.4, 76.3, 79.2, 80.4, 81.0, 84.6, 84.8, 97.4, 108.5, 112.5, 112.7, 118.3, 119.0, 124.9, 125.1, 129.1, 129.3, 138.0, 138.7, 139.3, 139.5, 143.4, 143.6, 153.2, 153.3, 168.2, 172.2. IR (NaCl, neat): 2954, 2930, 2891, 2861, 1743, 1644, 1496, 1438, 1368 cm^{-1} . HRMS (FAB) $m/e = 739.3848$ ($\text{C}_{39}\text{H}_{57}\text{N}_3\text{O}_9\text{Si}$ requires 739.3864).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-13-(methoxymethoxy)-4,4,15,15-tetramethyl-17-oxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester (68**).** To a solution of **67** (32.8 mg, 0.0443 mmol, 1.0 eq) in CH_2Cl_2 (2.2 mL) at 0 °C was added DIBAL-H (0.22 mL, 1.0 M in toluene, 0.22 mmol, 5.0 eq). After the reaction mixture had been stirred at 0 °C for 1 h and at room temperature for 1 h, additional DIBAL-H (0.14 mL, 1.0 M in toluene, 0.14 mmol, 3.2 eq) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h then cooled to 0 °C and quenched with saturated aqueous NH_4Cl . The aqueous material was extracted with EtOAc and the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, eluted twice with 10:6:1 hexanes/EtOAc/MeOH) to afford **68** (23.3 mg, 72%) as a white foam.

Data for **68** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.12-0.14 (6 H, 3 $\square$ s), 0.90 and 0.91 (9 H, 2 $\square$ s), 1.14 and 1.18 (3 H, 2 $\square$ s), 1.40 and 1.41 (3 H, 2 $\square$ s), 1.48 (3 H, s), 1.56 (3 H, s), 1.62 and 1.64 (9 H, 2 $\square$ s), 1.84 (1 H, dd, $J = 4.2$ Hz, $J = 13.2$ Hz), 2.10-2.52 (6 H, m), 2.73 (1 H, 1/2 ABq, $J = 15.6$ Hz), 2.82 (1 H, 1/2 ABq, $J = 15.6$ Hz), 3.19 (1 H, td, $J = 5.4$ Hz, $J = 8.7$ Hz), 3.44-3.50 (1 H, m), 3.45 (3 H, s), 3.74-3.97 (2 H, m), 4.03 (1 H, t, $J = 9.0$ Hz), 4.16 (1 H, td, $J = 3.3$ Hz, $J = 11.7$ Hz), 4.79 (2 H, s), 5.95 (1 H, br s), 6.81 and 6.82 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 6.92 (1 H, d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : -4.7, -4.6, -4.0, -3.8, 18.2, 19.5, 19.7, 22.0, 22.1, 26.0, 27.7, 28.5, 28.6, 28.7, 28.93, 29.04, 30.1, 30.4, 35.7, 35.8, 47.9, 52.8, 55.7, 56.3, 59.9, 64.3, 71.7, 72.3, 76.3, 76.4, 80.7, 81.0, 81.4, 84.9, 85.0, 96.9, 108.0, 108.1, 112.0, 112.1, 118.5, 118.9, 125.0, 125.1, 129.4, 138.3, 138.7, 141.2, 141.3, 143.5, 153.3, 153.4, 172.2. IR (NaCl, neat): 2937, 2932, 2902, 2855, 1748, 1693, 1682, 1496, 1446, 1369, 1308, 1253, 1234, 1155, 1111, 1092, 1052, 992, 914, 838, 776, 732 cm^{-1} . HRMS (FAB) $m/e = 726.4168$ ($\text{C}_{39}\text{H}_{60}\text{N}_3\text{O}_8\text{Si}$ requires 726.4150).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-13-(methoxymethoxy)-4,4,15,15,18-pentamethyl-17-oxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester.

To a solution of **68** (37.8 mg, 0.0521 mmol, 1.0 eq) in DMF (1.7 mL) at 0 °C was added NaH (43.1 mg, 60% dispersion in oil, 1.08 mmol, 21 eq). After 15 minutes MeI (159 mg, 1.12 mmol, 22 eq) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 5:10:1 hexanes/EtOAc/MeOH) to afford the title compound (36.9 mg, 96%) as an amorphous solid.

Data for title compound (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) δ : 0.12 and 0.14 (6 H, 2 $\square$ s), 0.90 and 0.91 (9 H, 2 $\square$ s), 1.16 and 1.19 (3 H, 2 $\square$ s), 1.40 and 1.41 (3 H, 2 $\square$ s), 1.49 (3 H, s), 1.58 and 1.60 (3 H, 2 $\square$ s), 1.62 and 1.64 (9 H, 2 $\square$ s), 1.78-1.88 (1 H, m), 2.05-2.44 (6 H, m), 2.73-2.82 (1 H, m), 3.07 (3 H, s), 3.12-3.24 (2 H, m), 3.34-3.42 (1 H, m), 3.45 (3 H, s), 3.76-4.04 (3 H, m), 4.09-4.20 (1 H, m), 4.77 (1 H, 1/2 ABq, $J = 6.9$ Hz), 4.80 (1 H, 1/2 ABq, $J = 6.9$ Hz), 6.82 and 6.83 (1 H, 2 $\square$ d, $J = 8.4$ Hz), 6.96 (1 H, d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : -4.7, -4.6, -4.0, -3.8, 18.1, 19.5, 19.6, 22.5, 22.6, 24.7, 25.9, 27.7, 28.2, 28.3, 28.7, 28.8, 29.0, 29.8, 36.1, 36.2, 46.9, 47.0, 53.1, 55.6, 58.4, 60.0, 63.4, 71.8, 72.2, 76.3, 76.4, 80.7, 81.0, 81.7, 81.7, 84.8, 84.9, 96.8, 108.2, 108.4, 111.9, 118.4, 118.8, 125.1, 125.3, 129.5, 129.7, 138.3, 138.7, 140.8, 141.0, 143.5, 153.3, 172.1. IR (NaCl, neat): 2955, 2932, 2896, 2857, 1747, 1677, 1496, 1368, 1252, 1233, 1154, 1116, 1091, 1052, 838 cm^{-1} . HRMS (FAB) $m/e = 740.4391$ ($\text{C}_{40}\text{H}_{62}\text{N}_3\text{O}_8\text{Si}$ requires 740.4306).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-13-hydroxy-4,4,15,15,18-pentamethyl-17-oxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester (69**).** To a solution of the title compound from the previous reaction (36.9 mg, 0.0499 mmol, 1.0 eq) in CH₂Cl₂ (2.5 mL) at 0 °C was added bromocatecholborane (1.5 mL, 0.2 M in CH₂Cl₂, 0.30 mmol, 6.0 eq). The reaction mixture was stirred at room temperature for 0.5 h, then quenched with 10% aqueous NaOH (3 mL), and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 10:6:1 hexanes/EtOAc/MeOH) to afford **69** (31.5 mg, 91%) as an amorphous solid.

Data for **69** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.12 and 0.14 (6 H, 2 $\square$ s), 0.90 and 0.91 (9 H, 2 $\square$ s), 1.15 and 1.19 (3 H, 2 $\square$ s), 1.41 and 1.49 (3 H, 2 $\square$ s), 1.58 (3 H, s), 1.62 and 1.64 (9 H, 2 $\square$ s), 1.82-2.06 (2 H, m), 2.13-2.45 (5 H, m), 2.79 (1 H, dd, *J* = 5.6 Hz, *J* = 11.8 Hz), 3.09 (3 H, s), 3.10-3.15 (1 H, m), 3.20 (1 H, d, *J* = 15.6 Hz), 3.43 (1 H, d, *J* = 9.9 Hz), 3.73- 3.97 (2 H, m), 4.04-4.23 (2 H, m), 5.40 and 5.41 (1 H, 2 $\square$ d, *J* = 11.4 Hz), 6.83 and 6.84 (1 H, 2 $\square$ d, *J* = 8.4 Hz), 6.96 (1 H, d, *J* = 8.4 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : -4.7, -4.6, -4.0, -3.8, 18.2, 19.6, 22.7, 22.8, 24.7, 26.0, 27.7, 27.9, 28.7, 28.8, 28.9, 29.0, 29.7, 32.5, 36.2, 36.3, 47.2, 47.3, 53.3, 58.7, 60.2, 62.0, 71.8, 72.3, 76.3, 76.4, 77.3, 80.8, 81.1, 85.0, 85.1, 107.8, 108.0, 111.9, 118.5, 118.9, 125.1, 125.2, 129.6, 129.7, 138.4, 138.7, 140.7, 140.8, 143.6, 153.3, 153.4, 175.8. IR (NaCl, neat): 3407, 2954, 2932, 2858, 1747, 1644, 1496, 1445, 1390, 1369, 1253, 1233, 1155, 1108, 1089, 838, 733 cm⁻¹. HRMS (FAB) *m/e* = 696.4032 (C₃₈H₅₈N₃O₇Si requires 696.4044).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-3,4,8,12,13,14,14a,15-octahydro-13-hydroxy-4,4,15,15,18-pentamethyl-13,17-dioxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylic acid *tert*-butyl ester. To a stirred solution of **69** (13.2 mg, 0.0190 mmol, 1.0 eq) in CH₂Cl₂ (1.9 mL) at room temperature was added Dess-Martin periodinane (40.7 mg, 0.0960 mmol, 5.1 eq). After 0.5 h, the reaction mixture was quenched with a solution of 0.5 M Na₂S₂O₃ in 1 M aqueous NaHCO₃ (0.8 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 10:6:1 hexanes/EtOAc/MeOH) to afford the title compound (11.2 mg, 85%) as an amorphous solid.

Data for title compound (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.12 and 0.14 (3 H, 2 $\square$ s), 0.90 and 0.91 (9 H, 2 $\square$ s), 1.16 and 1.20 (3 H, 2 $\square$ s), 1.39 and 1.40 (3 H, 2

□ s), 1.49 (3 H, s), 1.58 (3 H, s), 1.62 and 1.64 (9 H, 2 □ s), 1.90-2.02 (1 H, m), 2.14-2.28 (2 H, m), 2.32 (1 H, d, $J = 10.5$ Hz), 2.42-2.71 (5 H, m), 2.82 and 2.83 (1 H, 2 □ d, $J = 15.3$ Hz), 3.08 (3 H, d, $J = 10.5$ Hz), 3.19 (1 H, d, $J = 15.3$ Hz), 3.75-3.98 (2 H, m), 4.11-4.24 (1 H, m), 6.84 and 6.85 (1 H, 2 □ d, $J = 8.4$ Hz), 6.96 (1 H, d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) □: -4.7, -4.6, -4.0, -3.8, 18.1, 19.6, 22.6, 22.8, 25.0, 26.0, 26.9, 27.7, 27.8, 28.6, 28.8, 29.0, 36.3, 36.4, 36.9, 47.0, 47.1, 50.6, 57.9, 60.5, 67.6, 71.8, 72.4, 76.3, 76.4, 80.8, 81.1, 85.0, 85.1, 107.8, 111.9, 118.6, 118.9, 125.0, 125.1, 129.6, 129.7, 138.3, 138.7, 140.6, 140.8, 143.6, 153.2, 153.3, 169.9, 209.8. IR (NaCl, neat): 2956, 2930, 2855, 1760, 1748, 1670, 1496, 1252, 1233, 1157, 1139, 1112, 1092, 837 cm^{-1} . HRMS (FAB) $m/e = 694.3870$ ($\text{C}_{38}\text{H}_{56}\text{N}_3\text{O}_7\text{Si}$ requires 694.3888).

(8a*S*, 13*S*, 13a*R*, 14a*S*)-3-Hydroxy-3,4,8,12,13,14,14a,15-octahydro-13-hydroxy-4,4,15,15,18-pentamethyl-13,17-dioxo-9*H*,11*H*-8a,13a-(iminomethano)-2*H*,16*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole (70). To a solution of the title compound from the previous reaction (26.2 mg, 0.0378 mmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (2.22 g, 19.5 mmol, 517 eq). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 3 h, then it was quenched with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 5:25:1 hexanes/EtOAc/MeOH) to afford **70** (17.5 mg, 97%) as an amorphous solid.

Data for **70** (mixture of two diastereomers): ^1H NMR (300 MHz, CDCl_3) □: 1.24 and 1.26 (3 H, 2 □ s), 1.33 and 1.36 (3 H, 2 □ s), 1.41 and 1.44 (3 H, 2 □ s), 1.57 and 1.58 (3 H, 2 □ s), 1.88-2.00 (1 H, m), 2.16-2.28 (2 H, m), 2.35 (1 H, d, $J = 10.2$ Hz), 2.40-2.72 (3 H, m), 2.87 and 2.88 (1 H, 2 □ d, $J = 15.0$ Hz), 3.03-3.08 (1 H, m), 3.10 (3 H, s), 3.22 and 3.24 (1 H, 2 □ d, $J = 15.0$ Hz), 3.29-3.39 (1 H, m), 3.55 and 3.58 (1 H, 2 □ d, $J = 10.2$ Hz), 3.66 (1 H, dt, $J = 3.0$ Hz, $J = 11.4$ Hz), 4.22 (1 H, dd, $J = 4.2$ Hz, $J = 11.7$ Hz), 4.35 (1 H, dd, $J = 3.9$ Hz, $J = 11.7$ Hz), 6.79 and 6.80 (1 H, 2 □ d, $J = 8.4$ Hz), 7.04 (1 H, d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) □: 23.7, 23.8, 24.9, 25.1, 25.2, 26.1, 26.3, 26.7, 27.9, 30.8, 30.9, 34.8, 34.9, 45.2, 45.3, 50.8, 58.3, 58.4, 61.3, 67.5, 71.3, 76.0, 79.9, 104.9, 112.8, 116.8, 116.9, 125.2, 129.6, 137.6, 140.2, 142.2, 142.3, 169.9, 209.9. IR (NaCl, neat): 3374, 2970, 2932, 1759, 1654, 1507, 1474, 1397, 1364, 1232, 1136, 1096, 1065, 1048, 1025 cm^{-1} . HRMS (FAB) $m/e = 480.2478$ ($\text{C}_{27}\text{H}_{34}\text{N}_3\text{O}_5$ requires 480.2498).

(5a*S*, 7*R*, 8*aS*, 9a*R*)-2,2,3,3,8,9-Hexahydro-3-hydroxy-4,4,8,8,11-pentamethylspiro[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7[8*H*]-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]-cyclopent[*f*]indolizine]-1,9,10-trione (73). To a solution of **70** (9.8 mg, 0.0204 mmol, 1.0 eq) in pyridine (0.4 mL) at -15 °C was added *t*BuOCl (0.31 mL, 0.1 M in CH_2Cl_2 , 0.031

mmol, 1.5 eq). After 2 h, the reaction mixture was concentrated *in vacuo*, and the trace amount of pyridine was removed azeotropically with benzene. The residue was dissolved in THF (1.8 mL) and H₂O (0.2 mL) and to it was added TsOH·H₂O (18.4 mg, 0.104 mmol, 5.1 eq). The reaction mixture was refluxed for 0.5 h then cooled to room temperature and quenched with a mixture of EtOAc and 0.5 M aqueous K₂CO₃. The layers were separated and the aqueous layer extracted with further EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, eluted three times with 20:1 CH₂Cl₂/MeOH) to afford **73** (5.5 mg, 54%).

Data for **73** (mixture of two diastereomers): ¹H NMR (300 MHz, CDCl₃) δ : 0.84 and 0.86 (3 H, 2 $\square$ s), 1.08 and 1.09 (3 H, 2 $\square$ s), 1.26 and 1.29 (3 H, 2 $\square$ s), 1.53 and 1.55 (3 H, 2 $\square$ s), 1.56-1.64 (1 H, m), 1.81 and 1.90 (1 H, 2 $\square$ d, J = 15.3 Hz), 2.21 (1 H, t, J = 11.4 Hz), 2.37-2.76 (5 H, m), 2.98-3.46 (3 H, m), 3.09 and 3.10 (3 H, 2 $\square$ s), 3.62-3.78 (2 H, m), 4.08-4.30 (2 H, m), 6.62 and 6.66 (1 H, 2 $\square$ d, J = 8.1 Hz), 6.78 and 6.81 (1 H, 2 $\square$ d, J = 8.1 Hz), 7.72 and 7.94 (1 H, 2 $\square$ br s). ¹³C NMR (75 MHz, CDCl₃) δ : 20.7, 23.9, 24.3, 24.6, 25.6, 25.9, 26.1, 29.9, 36.7, 36.9, 37.2, 46.2, 46.4, 50.0, 52.4, 52.5, 60.1, 63.3, 66.3, 70.3, 71.3, 71.5, 75.6, 77.4, 80.9, 81.1, 116.8, 117.3, 121.1, 125.6, 133.6, 133.7, 136.2, 136.4, 148.1, 148.4, 168.7, 182.3, 182.5, 208.4. IR (NaCl, neat): 3421, 2975, 2936, 1762, 1705, 1653, 1498, 1464, 1418, 1390, 1330, 1212, 1194, 1149, 1112, 1065 cm⁻¹. HRMS (FAB) m/e = 496.2447 (C₂₇H₃₄N₃O₆ requires 496.2448).

(5a*S*, 7*R*, 8*aS*, 9a*R*)-2,3,8,9-tetrahydro-4,4,8,8,11-pentamethyl-spiro[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7[8*H*]-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]-cyclopent[*f*]indolizine]-1[9,10[10*H*]-trione (14**). To a solution of **73** (6.6 mg, 0.0133 mmol, 1.0 eq) in DMPU (0.27 mL) at room temperature was added methyltriposponium iodide (30.3 mg, 0.0670 mmol, 5.0 eq). The reaction mixture was stirred for 21 h then quenched with 1 M aqueous KOH and stirred for 10 minutes. 1 M aqueous HCl was added and the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, 10:1 CH₂Cl₂/MeOH) to afford **14** (3.6 mg, 57%).**

Data for **14**: ¹H NMR (300 MHz, CDCl₃) δ : 0.88 (3 H, s), 1.11 (3 H, s), 1.15 (3 H, s), 1.47 (3 H, s), 1.63 (1 H, m), 1.91 (1 H, d, J = 15.3 Hz), 2.22 (1 H, dd, J = 11.1 Hz, J = 12.6 Hz), 2.42-2.76 (5 H, m), 3.09 (3 H, s), 3.15 (1 H, t, J = 10.5 Hz), 3.35 (1 H, t, J = 8.1 Hz), 3.76 (1 H, d, J = 11.4 Hz), 4.91 (1 H, d, J = 7.8 Hz), 6.32 (1 H, d, J = 7.8 Hz), 6.70 (1 H, d, J = 8.4 Hz), 6.83 (1 H, d, J = 8.4 Hz), 7.31 (1 H, br s). ¹³C NMR (100 MHz, CDCl₃) δ : 20.7, 23.9, 24.6, 26.0, 29.9, 30.0, 30.1, 36.7, 37.0, 46.3, 49.9, 52.5, 60.0, 63.2, 66.3, 70.3, 80.0, 115.2, 117.6, 120.5, 125.0, 132.5, 135.5, 139.1, 146.3, 168.7, 182.4, 208.3. IR (NaCl, neat): 3226, 2927, 2853, 1762, 1702,

1654, 1502, 1466, 1387, 1328, 1190, 1112, 1047 cm^{-1} . HRMS (FAB) $m/e = 478.2336$ ($\text{C}_{27}\text{H}_{32}\text{N}_3\text{O}_5$ requires 478.2342).

(-)-Paraherquamide A (1). To a solution of **14** (5.3 mg, 0.011 mmol, 1.0eq) in THF at $-30\text{ }^{\circ}\text{C}$ was added MeMgBr (35 μL , 3 M in ether, 0.11 mmol, 9.5 eq). After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (silica, eluted five times with 5:25:1 hexanes/EtOAc/MeOH) to afford (-)-paraherquamide A (**1**) (2.0 mg, 42% based on recovery of 0.7 mg of **14**) as an amorphous solid.

Data for (-)-paraherquamide A (**1**): ^1H NMR (400 MHz, CDCl_3) δ 0.85 (3 H, s), 1.09 (3 H, s), 1.43 (3 H, s), 1.45 (3 H, s), 1.65 (3 H, s), 1.75-1.91 (4 H, m), 2.19-2.25 (1 H, m), 2.30-2.37 (1 H, m), 2.56 (1 H, d, $J = 11.6\text{ Hz}$), 2.64 (1 H, s), 2.69 (1 H, d, $J = 15.2\text{ Hz}$), 2.99-3.01 (1 H, m), 3.05 (3 H, s), 3.20 (1 H, m), 3.60 (1 H, d, $J = 11.2\text{ Hz}$), 4.88 (1 H, d, $J = 8.0\text{ Hz}$), 6.30 (1 H, d, $J = 8.0\text{ Hz}$), 6.68 (1 H, d, $J = 8.0\text{ Hz}$), 6.80 (1 H, d, $J = 8.0\text{ Hz}$), 7.41 (1 H, s, br). ^{13}C NMR (100 MHz, CDCl_3) δ 19.3, 20.7, 22.4, 24.0, 26.1, 30.0, 30.2, 37.4, 38.3, 46.6, 51.6, 52.1, 59.4, 63.2, 65.5, 71.5, 78.3, 80.0, 115.3, 117.5, 120.6, 125.3, 132.5, 135.4, 139.2, 146.3, 171.7, 182.5. IR (NaCl, neat): 3409, 3212, 2972, 2934, 1703, 1654, 1328, 1193, 1047 cm^{-1} . HRMS (FAB) $m/e = 494.2653$ ($\text{C}_{28}\text{H}_{36}\text{N}_3\text{O}_5$ requires 494.2654). The synthetic sample recrystallized from ether has m.p. $250\text{ }^{\circ}\text{C}$ (decomp.) and $[\alpha]_{\text{D}}^{25} = -22$ ($c = 0.2\text{ MeOH}$). A sample of natural paraherquamide A recrystallized from ether under the same conditions rendered a sample with m.p. $250\text{ }^{\circ}\text{C}$ (decomp.) and $[\alpha]_{\text{D}}^{25} = -21$ ($c = 0.2\text{ MeOH}$).

Additional References for Supporting Information

41. Sibi, M.P.; Christensen, J.W. *J. Org. Chem.* **1999**, *64*, 6434-6442.

^1H nmr (400 Mhz, CDCl_3) spectrum of synthetic paraherquamide A (top) and natural paraherquamide A (bottom).

1, (-)-paraherquamide A

^{13}C nmr (100 Mhz, CDCl_3) spectrum of synthetic paraherquamide