Total Synthesis of (–)-Spirotryprostatin B — Synthesis and Related Studies

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SUPPORTING INFORMATION PARAGRAPH.

1. General methods

All non-aqueous reactions were carried out using oven-dried or flame-dried glassware under a positive pressure of dry nitrogen unless otherwise noted. Tetrahydrofuran, acetonitrile, toluene, diethyl ether and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, Karl-Fischer titration).¹ Benzene was distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen. Triethylamine and pyridine were distilled from KOH. Ethyl glyoxylate was freshly distilled from P_2O_5 , 1,1,1,3,3,3-hexamethyldisilazane (HMDS), *p*-tosylisocyanate and quinoline were distilled prior to use. Methyl iodide was filtered through silica gel prior to use. Potassium hydride (commercially available as a dispersion in mineral oil) was purified according to the procedure reported by Brown.² *n*-Butyl lithium was titrated with *s*BuOH/phenanthroline.³ All other commercially available reagents were used without further purification.

[¹] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

[²] Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913-3918.

[³] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-168.

Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F²⁵⁴ plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain.

Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230-400 mesh) using a forced flow of eluant at 0.3-0.5 bar.⁴ Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried for 12-72 h under high vacuum (0.01–0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Preparative thin layer chromatography was performed on pre coated plates silicat gel 60 F²⁵⁴ from E. Merck.

Kugelrohr distillations were performed with a Büchi Glass Oven B-580.

Radial chromatography was performed with a CycloGraph chromatodron using a 1mm CaSO₄-bound silica gel plate at a flow rate of 5-7 mL min⁻¹.

Melting points were measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 ml), and solvent.

NMR spectra were recorded on a Varian Gemini 200 spectrometer operating at 200 MHz for ¹H acquisitions, a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for ¹H and ¹³C acquisitions, respectively, or on a Bruker DRX500 spectrometer operating at 500 MHz and 125 MHz for ¹H and ¹³C acquisitions, respectively. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) and benzene (δ 7.15) for ¹H, and chloroform (δ 77.0) and benzene (δ 128.0) for ¹³C. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet; coupling constants in Hz. IR spectra were recorded on a Perkin Elmer Spectrum RXI FT-IR spectrophotometer. Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a

[⁴] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent.

IR spectra were recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm^{-1}).

Mass spectra were recorded by the MS service at ETH Zürich. EI-MS: VG-TRIBRID spectrometer; spectra were measured at 70 eV. FAB-MS: VG-ZAB2-SEQ spectrometer; spectra were determined in m-nitrobenzyl alcohol (3-NOBA) as matrix. MALDI-MS: IonSpec Ultima Fourier Transform Mass Spectrometer. Peaks are given in percent (m/z). Elemental analyses were performed at the Mikrolabor der ETH Zürich.

High-performance liquid chromatography was performed on a Merck Hitachi (Interface D-7000, UV-Detector L-7400, Pump L-7100, column: Säulentechnik 4 mm ID column packed with 5 μm spherisorb SW silica gel). The detector wavelength was fixed at $\lambda = 254 \text{ nm}$. A flow rate of 0.9 mL min^{-1} was used. All chromatograms were taken at ambient temperature.

Crystallographic structure determinations for **17** was performed on a Syntex P21 diffractometer, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The crystallographic structure determination for **18** was performed on a Picker-STOE diffractometer, $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). Crystallographic structure determinations for **46** and **59** were performed on a Nonius CAD4 diffractometer, $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). The structures were solved by direct methods⁵ and refined by full-matrix least-squares analysis⁶ including an isotropic extinction correction. All heavy atoms were refined anisotropically, H-atoms of the ordered part isotropically, whereby H-positions are based on stereochemical considerations.

[⁵] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, J. Appl. Crystallogr., **1994**, 27, 435.

[⁶] G.M. Sheldrick, 1997, SHELXL-97 Program for the Refinement of Crystal Structures. University of Goettingen, Germany.

2. Preparation of Useful Reagents and Buffers

LHMDS, 0.330 M in THF

To a solution of HMDS (1.00 mL, 4.73 mmol, 1.00 equiv), in THF (10 mL) at -78°C was added *n*BuLi (1.42 M in hexanes, 3.33 mL, 4.73 mmol, 1.00 equiv). The solution was allowed to stir at 0°C for 30 min.

CH_2N_2 , ≈ 0.4 M in Et_2O

A solution of KOH (500 mg, 8.77 mmol, 3.90 equiv) in H_2O (500 μL), was cooled to 0°C and Et_2O (5.6 mL) was added. To the biphasic mixture at 0°C was added *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine ($\approx 50\%$ in H_2O , 329 mg, 2.24 mmol, 1.00 equiv) in small portions. The yellow organic solution was decanted and used immediately.

BocProCl (45), 0.140 M in CH_2Cl_2

To a solution of DMF (103 μL , 1.38 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) at 0°C was added oxalyl chloride (121 μL , 1.38 mmol, 1.00 equiv). A white precipitate was formed. Pyridine (111 μL , 1.38 mmol, 1.00 equiv) was added dropwise to the reaction mixture; the precipitate dissolved and the solution turned yellow. *N*-Boc-L-proline (297 mg, 1.38 mmol, 1.00 equiv) was then added to the solution. The reaction mixture was stirred at 0°C for 30 min; this solution of *N*-Boc-L-proline chloride (**45**) solution was used for the subsequent peptide coupling.

$R_f = 0.73$ (EtOAc)

Dimethyl-dioxirane, ≈ 0.09 M in acetone

In a 2 L 2-neck flask (1 exit connected to 100 mL 2-neck receiving flask with dry ice condenser), a solution of NaHCO_3 (29 g) in acetone (96 mL) and H_2O (127 mL) was cooled to 5 – 10°C (ice-bath). Oxone (60 g) was added in 5 portions; in-between, the reaction mixture was stirred for 3 min. 3 min after the last addition, the condenser was filled with dry ice/acetone and the receiving flask was cooled with a -78°C cooling bath. The ice-bath was removed and the solution of DMDO in acetone distilled at reduced

pressure (80–100 Torr). About 60 mL of solution were obtained. The solution is dried (K_2CO_3) and stored over activated molecular sieves (3 Å) at $-4\text{ }^\circ\text{C}$.

pH 3.6 buffer

Solution of citric acid monohydrate (1.43 g) and $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ (2.31 g) in H_2O (98.5 mL).

3. Synthesis of (–)-Spirotryprostatin B

4-methyl-[1,3,2]dioxathiolane 2-oxide

1,2-Propane diol (10.0 g, 131 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (30 mL) and the solution was cooled to 0 °C. A solution of SOCl₂ (11.8 mL, 162 mmol, 1.24 equiv) in CH₂Cl₂ (20 mL) was added via addition funnel over 1 h. The reaction mixture was then heated to reflux for 1 h and allowed to cool to room temperature. H₂O (50 mL) was added to the reaction mixture, the layers were separated and the organic layer was washed with H₂O (2 × 50 mL) and brine (30 mL), dried (Na₂SO₄), filtered, then the solvent was evaporated in vacuo and a colorless liquid was obtained. The unpurified sulfite was used for the next step.

R_f = 0.48; ¹H NMR (CDCl₃, 200 MHz, [#] denotes major-, * minor diastereomer signals) δ 5.19-5.06 (m, 1[#]H), 4.73 (dd, 1H[#], J = 8.1, 5.8 Hz), 4.74-4.49 (m, 2H*), 4.32 (dd, 1H*, J = 9.1, 8.3 Hz), 3.90 (dd, 1H[#], J = 8.1, 7.1 Hz), 1.63 (d, 3H*, J = 6.2 Hz), 1.45 (d, 3H[#], J = 6.3 Hz).

4-methyl-[1,3,2]dioxathiolane 2,2-dioxide (13)

4-methyl-[1,3,2]dioxathiolane 2-oxide (8.00 g, 65.5 mmol, 1.00 equiv) was dissolved in CH₃CN/CCl₄ (1:1) (400 mL). The solution was cooled to 0 °C. Precooled H₂O (280 mL) was added to the mixture. Solid NaIO₄ (27.2 g, 131 mmol, 2.00 equiv) and RuCl₃·3H₂O (68.0 mg, 330 μ mol, 0.5 mol%) were added in one portion. The reaction mixture was vigorously stirred for 1 h. The phases were separated and the aqueous layer was extracted with Et₂O (300 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column chromatography (1:1 EtOAc/hexanes) afforded **13** (8.34 g, 92%) as colorless liquid.

$R_f = 0.32$; ^1H NMR (CDCl_3 , 200 MHz) δ 5.24-5.07 (m, 1H), 4.76 (dd, 1H, $J = 8.7, 5.8$ Hz), 4.34 (dd, 1H, $J = 8.7, 8.7$ Hz), 1.63 (d, 3H, $J = 6.2$ Hz).

1-benzyl isatin

To a solution of isatin (20.0 g, 136 mmol, 1.00 equiv) in DMF (250 mL) was cooled to 0 °C (ice bath). NaH (60% dispersion in mineral oil, 5.71 g, 143 mmol, 1.05 equiv) was added portionwise to the orange solution. The solution changed color to deep purple. When the gas evolution stopped, benzyl bromide (26.7 g, 156 mmol, 1.16 equiv) was added slowly, whereupon the mixture turned red-brown. After 15 min, H_2O (1.2 L) was introduced to precipitate the product. After filtration, the product was recrystallized from refluxing EtOH to afford 1-benzyl isatin (28.9 g, 90%) after drying.

mp = 130-132 °C; ^1H NMR (CDCl_3 , 200 MHz) δ 7.65 (dd, 1H, $J = 7.5, 1.3$ Hz), 7.50 (dt, 1H, $J = 7.9, 1.7$ Hz), 7.38-7.3 (m, 5H), 7.15-7.08 (m, 1H), 6.80 (d, 1H, $J = 7.9$ Hz), 4.96 (s, 2H).

1-benzyl-1,2-dihydro-indol-2-one

A solution of 1-benzyl isatin (26.1 g, 117 mmol) in hydrazine hydrate (125 mL) was heated to reflux till the gas evolution stopped (4 h). The color of the solution changed from orange via green to yellow during this time. The reaction mixture was allowed to cool to room temperature and the product was extracted with EtOAc (2×150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was evaporated in vacuo. The yellow product was recrystallized from refluxing Et₂O to afford 1-benzyl-1,2-dihydro-indol-2-one (17.0 g, 65%) after drying.

mp = 68 °C; ^1H NMR (CDCl_3 , 200 MHz) δ 7.34-7.14 (m, 7H), 7.05-6.97 (m, 1H), 6.73 (d, 1H, $J = 7.9$ Hz), 4.93 (s, 2H), 3.64 (s, 2H).

(±)-(1*S*,2*S*)-2-methyl-1'-(phenylmethyl)spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (15)

Cyclic sulfate **13** (68.1 mg, 490 μ mol, 1.10 equiv) was dissolved in DME (1.5 mL). NaH (95%, 54.0 mg, 1.34 mmol, 3.00 equiv) was added and to the resulting suspension, a solution of 1-benzyl-1,2-dihydro-indol-2-one (100 mg, 450 μ mol, 1.00 equiv) in DME (1 mL) was slowly added. The reaction mixture was stirred at room temperature for 16 h and was then quenched by addition of H₂O (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column chromatography (1:19 EtOAc/hexanes) afforded **15** (64.0 mg, 54%) as a colorless oil.

R_f = 0.49 (1:3 EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.33-7.25 (m, 5H), 7.12 (ddd, 1H, J = 7.8, 6.9, 2.2 Hz), 7.03-6.96 (m, 2H), 6.83-6.80 (m, 1H), 4.99 (s, 2H), 2.08-1.98 (m, 2H), 1.37 (d, 3H, J = 6.2 Hz), 1.37-1.33 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 177.3, 143.4, 136.3, 128.7, 128.4, 127.5, 127.4, 126.4, 121.5, 120.8, 109.0, 44.1, 32.0, 27.6, 26.0, 13.3; IR (KBr) ν 3055, 3004, 2984, 2924, 1705, 1613, 1487, 1466, 1453, 1431, 1396, 1386, 1370, 1352, 1186, 1103, 1034, 986, 870, 758, 735, 697; DEI-MS 263.2 (60 [M]⁺), 91.0 (100 [C₇H₇]⁺); Anal. calcd for C₁₈H₁₇NO: C 82.10, H 6.51, N 5.32, found: C 81.93, H 6.64, N 5.30.

(±)-(3*R*,5'*R*)-5'-methyl-1'-[(4-methylphenyl)sulfonyl]-1-(phenylmethyl)-2'*H*-spiro[indole-3,3'-pyrrolidine]-2,2'(1*H*)-dione (17)

(±)-(3*S*,5'*R*)-5'-methyl-1'-[(4-methylphenyl)sulfonyl]-1-(phenylmethyl)-2'*H*-spiro[indole-3,3'-pyrrolidine]-2,2'(1*H*)-dione (18)

A sealable tube was charged with spiro-cyclopropyl-oxindole **15** (885 mg, 340 μ mol, 1.00 equiv) and MgI₂ (23.0 mg, 84.0 μ mol, 25 mol%). *p*-Tosylisocyanate (56.3 μ L, 380

μmol , 1.10 equiv) was added followed by THF (0.3 mL). The tube was sealed and heated to 100 °C for 3 d. The reaction mixture was allowed to cool to room temperature and EtOAc (1 mL) was added, followed by H₂O (1 mL) as well as solid Na₂S₂O₃ (a crystal). The phases were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with H₂O and brine (20 mL each), dried (Na₂SO₄) and filtered. After removal of the solvent in vacuo, the product was purified by radial chromatography (3:17 EtOAc/hexanes) to afford the two diastereomers **17** and **18**, (combined yield: 74 mg (49%)) together with unreacted **15** (45.1 mg, 50%)

Minor diastereomer **17**: colorless crystals; yield: 31.0 mg (20%).

R_f = 0.25 (1:3 EtOAc/hexanes); mp = 162 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.98-7.93 (m, 2H), 7.35-6.99 (m, 10H), 6.68-6.64 (m, 1H), 4.83 (d, 1H, J = 15.7 Hz), 4.71 (d, 1H, J = 15.7 Hz), 2.88 (dd, 1H, J = 13.7, 7.5 Hz), 2.47-2.40 (m, 1H), 2.40 (s, 3H), 2.10 (dd, 2H, J = 13.0, 7.1 Hz), 1.80 (d, 3H, J = 6.2 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 173.7, 169.5, 145.3, 143.1, 135.6, 134.9, 129.7, 129.5, 129.2, 128.8, 128.3, 127.7, 127.0, 123.6, 123.4, 109.8, 58.5, 54.4, 44.1, 36.9, 22.8, 21.7; IR (KBr) ν 1739, 1704, 1609, 1487, 1467, 1365, 1328, 1211, 1176, 1119, 1077, 752, 704, 668, 577, 547; DEI-MS 460.1 (8.4 [M]⁺), 91.0 (100 [C₇H₇]⁺); Anal. calcd for C₁₈H₁₇NO: C 67.81, H 5.25, N 6.08, found: C 67.96, H 5.36, N 5.96.

Crystal data for **17** at 293(2) K, M_r = 460.53, triclinic space group *P*-1, ρ_{calc} = 1.361 mg·cm⁻³, Z = 2, a = 9.750(10), b = 10.807(12), c = 12.172(10) Å, α = 103.37(8), β = 95.24(8), γ = 113.10(8)°, V = 1124(2) Å³. Final $R(F)$ = 0.0355, $wR(F^2)$ = 0.1044 for 301 parameters and 2279 reflections with $I > 2\sigma(I)$ and $1.76 < \theta < 20.04^\circ$.

CCDC 199469 (**17**) contains the supplementary crystallographic data for this structure. This data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Major diastereomer **18**: colorless crystals, yield: 43.0 mg (29%).

R_f = 0.23 (1:3 EtOAc/hexanes); mp = 171-173 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.99-7.95 (m, 2H), 7.35-6.95 (m, 10H), 6.67 (d, 1H, J = 7.9 Hz), 4.97 (d, 1H, J = 15.7 Hz), 4.83-4.72 (m, 1H), 4.79 (d, 1H, J = 15.7 Hz), 2.67 (dd, 1H, J = 13.3, 7.9 Hz), 2.42 (dd, 1H, J = 12.5, 5.0 Hz), 2.44 (s, 3H), 1.79 (d, 3H, J = 6.2 Hz); ¹³C NMR (CDCl₃,

75 MHz) δ 173.8, 169.6, 145.1, 143.6, 135.0, 129.5, 129.3, 128.9, 128.8, 127.7, 127.3, 127.0, 127.0, 123.6, 123.3, 109.6, 58.3, 54.7, 43.9, 37.8, 23.9, 21.7; IR (KBr) ν 1737, 1700, 1612, 1461, 1468, 1342, 1203, 1188, 1167, 1127, 1080, 755, 668, 576, 547; DEI-MS 460.1 (10.4 [M]⁺), 91.0 (100 [C₇H₇]⁺); Anal. calcd for C₁₈H₁₇NO: C 67.81, H 5.25, N 6.08, found: C 67.95, H 5.29, N 5.92.

Crystal data for **18** at 293(2) K, M_r = 460.53, triclinic space group *P*-1, ρ_{calc} = 1.295 mg·cm⁻³, Z = 4, a = 10.155(8), b = 14.690(14), c = 17.70(2) Å, α = 113.53(7), β = 101.53(7), γ = 90.01(7)°, V = 2362(4) Å³. Final $R(F)$ = 0.0386, $wR(F^2)$ = 0.0879 for 599 parameters and 3228 reflections with $I > 2\sigma(I)$ and $2.79 < \theta < 42.49^\circ$.

CCDC 199470 (**18**) contains the supplementary crystallographic data for this structure. This data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

1-benzyl-3-diazo-1,3-dihydro-indol-2-one (**25**)

1-Benzyl-isatin (1.00 g, 4.22 mmol, 1.00 equiv) was suspended in MeOH (20 mL). The suspension was heated to 60 °C, whereupon a deep-red solution was obtained. To this hot solution was added tosylhydrazine (793 mg, 4.26 mmol, 1.01 equiv) in one portion. A yellow product starts precipitating from the hot mixture. The reaction mixture was stirred at 60 °C for 18 h, and then allowed to reach room temperature. The intermediate tosylhydrazone (1.37 g, 80%) was collected by filtration and was used without further purification.

A solution of the tosylhydrazone (1.00 g, 2.47 mmol, 1.00 equiv) in THF (10 mL) was treated with a solution of NaOH (197 mg, 4.93 mmol, 2.00 equiv) in H₂O (25 mL). The reaction mixture was stirred for 3 h at room temperature. EtOAc (20 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was adjusted to pH 7 by addition of dry-ice, and extracted with EtOAc (30 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column

chromatography (3:17 EtOAc/hexanes) afforded **25** (451 mg, 73%) as deep-orange crystals.

R_f = 0.55 (1:3 EtOAc/hexanes); mp = 89 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.20 (m, 6H), 7.12-7.04 (m, 2H), 6.84-6.82 (m, 1H), 5.03 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 136.0, 133.7, 128.8, 127.7, 127.3, 125.5, 122.2, 118.3, 116.8, 109.6, 44.3; IR (thin film) ν 2130, 1668, 1610, 1589, 1481, 14.68, 1404, 1383, 1342, 1178, 1168, 1103, 740, 697, 681, 668, 636; DEI-MS 249.0 (13.5 $[\text{M}]^+$), 193.0 (35 $[\text{M}-\text{N}_2-\text{CO}]^+$), 91.0 (100 $[\text{C}_7\text{H}_7]^+$); Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}$: C 72.28, H 4.45, N 16.86, found: C 72.31, H 4.57, N 16.78.

2-methoxy-acrylic acid methyl ester

NaOMe (14.5 g, 231 mmol, 3.00 equiv) was dissolved in MeOH (120 mL) and the solution was cooled to 0 °C. To this solution, 2,3 dibromo-propionic acid ethyl ester was added slowly by addition funnel. The reaction mixture was allowed to stir at room temperature for 6 d. Then the mixture was quenched and adjusted to pH 7 by addition of dry-ice. The resulting white precipitate was removed by filtration; the filtrate was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (2×120 mL). The organic layer was dried over Na_2SO_4 , filtered, and the solvent was evaporated in vacuo. The remaining product was purified by distillation under reduced pressure (30 mbar) to give the ester (4.20 g, 36%) as a colorless liquid.

bp = 50 °C (30 mbar); ^1H NMR (300 MHz, CDCl_3) δ 5.38 (d, 1H, J = 2.9 Hz), 4.65 (d, 1H, J = 2.9 Hz), 3.84 (s, 3H), 3.68 (s, 3H).

methy 2-(methoxy)-2'-oxo-1'-(phenylmethyl)-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2-carboxylate (**19**)

In a 50 mL two-neck flask equipped with a reflux condenser and a CaCl_2 drying tube was placed $[\text{Rh}(\text{OAc})_2]_2$ (4.42 mg, 10.0 μmol , 2 mol%). Benzene (2 mL) and the 2-methoxy-

acrylic acid methyl ester (291 mg, 2.51 mmol, 5.00 equiv) were added and the mixture was heated to reflux. A solution of diazo-oxindole **25** (125 mg, 500 μ mol, 1.00 equiv) in benzene (2 mL) was added to the refluxing mixture by syringe pump over a period of 5 h. The reaction mixture was allowed to reach room temperature and was then filtered over Celite eluting with benzene. Evaporation of the solvent yielded an orange oil. The product was purified by column chromatography (1:4 EtOAc/hexanes) to afford **19** (two diastereomers) (150 mg, 89%).

Diastereomer 1: colorless oil, yield: 34.5 mg (20%).

R_f = 0.26 (1:3 EtOAc/hexanes); ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.23 (m, 5H), 7.20-7.11 (m, 2H), 7.00 (dt, 1H, J = 7.5, 0.9 Hz), 6.77 (d, 1H, J = 7.8 Hz), 4.99 (d, 1H, J = 15.9 Hz), 4.90 (d, 1H, J = 15.9 Hz), 3.84 (s, 3H), 3.47 (s, 3H), 2.59 (d, 2H, J = 6.2 Hz), 2.02 (d, 2H, J = 6.2 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 186.9, 164.1, 140.8, 133.6, 126.4, 125.3, 125.3, 124.9, 123.0, 120.1, 119.8, 106.7, 55.6, 50.1, 41.5, 35.7, 23.2, 11.7; IR (KBr) ν 2948, 1743, 1710, 1616, 1489, 1468, 1378, 1348, 1277, 1234, 1190, 1134, 1014, 750, 697; FAB-MS 338.0 (100 $[\text{M}]^+$).

Diastereomer 2: colorless solid, yield: 116 mg (69%).

R_f = 0.20 (1:3 EtOAc/hexanes); mp = 76 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.26 (m, 5H), 7.18-7.13 (m, 2H), 6.95 (dt, 1H, J = 7.6, 1.2 Hz), 6.77 (d, 1H, J = 7.9 Hz), 5.08 (d, 1H, J = 16.1 Hz), 4.90 (d, 1H, J = 16.1 Hz), 3.76 (s, 3H), 3.53 (s, 3H), 2.54 (d, 2H, J = 6.2 Hz), 2.51 (d, 2H, J = 6.2 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.0, 168.4, 143.6, 136.3, 129.0, 127.9, 127.8, 127.6, 125.5, 122.6, 122.1, 109.0, 58.8, 52.8, 44.4, 39.3, 25.4; IR (KBr) ν 1718, 1702, 1610, 1559, 1540, 1488, 1467, 1457, 1437, 1368, 1295, 1203, 1167, 1108, 1040, 751, 736; MS (MaldiTOF) 338.4 (100 $[\text{M}]^+$).

***meso*-diethyl 2'-oxo-1'-(phenylmethyl)-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2,3-dicarboxylate (**20**)**

A solution of diethyl fumarate (62.0 mg, 361 μ mol, 1.00 equiv) and diazo-oxindole **25** (108 mg, 433 μ mol, 1.20 equiv) in toluene (0.5 mL) was heated to reflux for 3 d. The

solvent was evaporated in vacuo and the residue was purified by column chromatography (1:4 EtOAc/hexanes) to afford **20** (118 mg, 83%) as a white solid.

R_f = 0.37; ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.26 (m, 6H), 7.22-7.16 (m, 1H), 7.00 (dt, 1H, J = 7.5, 0.9 Hz), 6.78 (d, 1H, J = 8.1 Hz), 5.06 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 15.6 Hz), 4.27-4.09 (m, 4H), 3.33 (s, 2H), 1.28-1.21 (m, 6H); HiResMALDI-MS calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_5$ $[\text{M}+\text{Na}]^+$ 416.1474, found, 416.1466.

2'-oxo-1'-(phenylmethyl)-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2-carbonitrile (21)

A mixture of diazo-oxindole **25** (108 mg, 660 μmol , 1.00 equiv) and $\text{Pd}(\text{OAc})_2$ (1.42 mg, 6.60 μmol , 1 mol%) in acrylonitrile (16.5 mL) was heated to reflux for 16 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography (1:4 EtOAc/hexanes) to afford the **21** (two diastereomers) (160 mg, 80%).

Diastereomer 1: 85.0 mg (47%).

R_f = 0.35; ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.24 (m, 6H), 7.25-7.19 (m, 1H), 7.17 (dt, 1H, J = 7.3, 0.9 Hz), 6.88 (d, 1H, J = 7.6 Hz), 5.01 (d, 1H, J = 15.3 Hz), 4.96 (d, 1H, J = 15.3 Hz), 2.52 (dd, 1H, J = 6.8, 5.0 Hz), 2.21 (dd, 1H, J = 6.8, 3.4 Hz), 1.94 (dd, 1H, J = 5.0, 3.4 Hz).

Diastereomer 2: 75.0 mg (41%).

R_f = 0.18; ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.25 (m, 5H), 7.23 (dt, 1H, J = 7.4, 0.9 Hz), 7.22 (dt, 1H, J = 7.3, 0.8 Hz), 6.86-6.80 (m, 2H), 5.07 (d, 1H, J = 15.8 Hz), 4.98 (d, 1H, J = 15.8 Hz), 2.35 (dd, 1H, J = 6.1, 5.0 Hz), 2.26 (dd, 1H, J = 5.0, 3.3 Hz), 2.02 (dd, 1H, J = 6.1, 3.3 Hz).

1-(tert-butyl-dimethyl-silanyloxy)-propane-1,2-diol

Allyl alcohol (1.00 mL, 15.0 mmol, 1.00 equiv) was dissolved in DMF (7 mL), and the solution was cooled to 0 $^\circ\text{C}$. Imidazole (1.30 g, 19.0 mmol, 1.30 equiv) was added

followed by TBSCl (2.88 g, 19.0 mmol, 1.30 equiv). The reaction mixture was allowed to stir for 15 min, and was quenched by addition of H₂O (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was carefully removed to afford TBS-protected allyl alcohol.

R_f = 0.73; (1:1 EtOAc/hexanes).

To a solution of K₂OsO₄ (17.3 mg, 47.0 μmol, 0.3 mol%) and NMO·H₂O (2.15 g, 15.9 mmol, 1.06 equiv) in a mixture of H₂O/acetone/*t*BuOH (6:15:2, 11.5 mL) was slowly added the protected allyl alcohol. The reaction mixture was stirred at room temperature for 16 h, then quenched by addition of 10% aq Na₂SO₄. The mixture is filtered through Celite (eluting with CH₂Cl₂) and the layers of the filtrate were separated. The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried (Na₂SO₄) and filtered. Column chromatography (EtOAc) afforded 1-(*tert*-butyl-dimethylsilanyloxy)-propane-1,2-diol (1.86 g, 60%).

R_f = 0.40; ¹H NMR (200 MHz, CDCl₃) δ 3.75-3.65 (m, 5H), 2.56 (d, 1H, *J* = 4.6 Hz), 2.10 (d, 1H, *J* = 5.0 Hz), 0.93-0.91 (m, 9H), 0.10-0.09 (m, 6H).

***tert*-butyl-(2,2-dioxo-2λ⁶-[1,3,2] dioxathiolan-4-ylmethoxy)-dimethyl-silane**

A solution of 1-(*tert*-butyl-dimethyl-silanyloxy)-propane-1,2-diol (1.86 g, 9.01 mmol, 1.00 equiv) and NEt₃ (4.99 mL, 36.0 mmol, 4.00 equiv) in CH₂Cl₂ (27 mL) was cooled to 0 °C. A solution of SOCl₂ (0.98 mL, 13.5 mmol, 1.50 equiv) in CH₂Cl₂ (2.25 mL) was added dropwise. The reaction mixture was then stirred at 0 °C for 1 h and diluted with Et₂O (50 mL). H₂O (50 mL) was added to the reaction mixture, and the layers were separated. The organic layer was washed with H₂O (2 × 50 mL) and brine (30 mL), dried (Na₂SO₄) and the solvent was evaporated in vacuo. The compound was filtered through a plug of silica gel eluting with 1:1 EtOAc/hexanes and a yellow oil was obtained.

A solution of the intermediate sulfite in CH₃CN/CCl₄ (1:1, 54 mL) was cooled to 0 °C. Precooled H₂O (40 mL) was added to the mixture. Solid NaIO₄ (3.85 g, 18.0 mmol, 2.00 equiv) and RuCl₃·3H₂O (9.30 mg, 45.0 μmol, 0.5 mol%) were added in one portion.

The reaction mixture was vigorously stirred for 1 h. The phases were separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic phases were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column chromatography (1:3 EtOAc/hexanes) afforded *tert*-butyl-(2,2-dioxo-2λ⁶-[1,3,2] dioxathiolan-4-ylmethoxy)-dimethyl-silane (1.38 g, 57%) as colorless liquid.

R_f = 0.46 (1:3 EtOAc/hexanes); ¹H NMR (CDCl₃, 200 MHz) δ 4.98-4.89 (m, 1H), 4.75-4.61 (m, 2H), 3.94-3.91 (m, 2H), 0.92-0.89 (m, 9H), 0.12-0.11 (m, 6H).

2-([[(1,1-dimethylethyl)(dimethyl)silyl]oxy]methyl)-1'-(phenylmethyl)spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (22)

The *tert*-butyl-(2,2-dioxo-2λ⁶-[1,3,2] dioxathiolan-4-ylmethoxy)-dimethyl-silane (1.38 g, 5.14 mmol, 1.00 equiv) was dissolved in DME (20 mL) and NaH (95%, 375 mg, 15.6 mmol, 3.00 equiv) was added. A solution of 1-benzyl-1,2-dihydro-indol-2-one (1.16 g, 5.21 mmol, 1.01 equiv) in DME (10 mL) was slowly added to the suspension. The reaction mixture was stirred at room temperature for 16 h and was then quenched by addition of MeOH (3 mL), followed by H₂O (30 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column chromatography (1:19 EtOAc/hexanes) afforded **22** (two diastereomers) (876 mg, 43%) along with unreacted oxindole (146 mg, 13%).

Diastereomer 1: colorless oil, yield: 35.0 mg (2%).

R_f = 0.50 (1:3 EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.33-7.24 (m, 5H), 7.13 (dt, 1H, *J* = 7.9, 1.6 Hz), 6.99 (dt, 1H, *J* = 6.1, 0.8 Hz), 6.83 (dd, 1H, *J* = 7.1, 0.8 Hz), 6.76 (d, 1H, *J* = 7.5 Hz), 5.06 (d, 1H, *J* = 15.8 Hz), 4.92 (d, 1H, *J* = 15.8 Hz), 4.16-4.13 (m, 2H), 2.25-2.18 (m, 1H), 1.86-1.76 (m, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

Diastereomer 2: colorless oil, yield: 841 mg (41%).

R_f = 0.42 (1:3 EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.32-7.24 (m, 5H), 7.19-7.11 (m, 1H), 7.07-6.94 (m, 2H), 6.79 (d, 1H, *J* = 7.9 Hz), 5.07 (d, 1H, *J* = 15.8 Hz),

4.92 (d, 1H, $J = 15.8$ Hz), 4.01 (dd, 1H, $J = 11.2, 5.4$ Hz), 3.88 (dd, 1H, $J = 11.2, 7.1$ Hz), 2.32-2.21 (m, 1H), 2.05-1.95 (m, 1H), 1.64-1.55 (m, 1H), 0.81 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).

2-(hydroxymethyl)-1'-(phenylmethyl)spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (23)

Spiro-cyclopropyl-oxindole **22** (diastereomer 2) (654 mg, 1.66 mmol, 1.00 equiv), was dissolved in THF (1 mL) and a solution of Bu₄NF (1 M in THF, 4.89 mL, 4.99 mmol, 3.00 equiv) was added. The reaction mixture was stirred for 30 min at room temperature, diluted with EtOAc (15 mL) and H₂O (5 mL) was added. The layers were separated and the organic layer was washed with brine (2 × 10 mL). The combined organic phases were dried (Na₂SO₄), filtered, and the solvent was evaporated in vacuo. Column chromatography (2:1 EtOAc/hexanes) afforded **23** (445 mg, 96%) as a colorless solid.

$R_f = 0.80$ (1:1 EtOAc/hexanes); mp = 119 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.33-7.27 (m, 5H), 7.25-7.14 (m, 1H), 7.09-6.96 (m, 2H), 6.85-6.82 (m, 1H), 5.04 (d, 1H, $J = 15.8$ Hz), 4.96 (d, 1H, $J = 15.8$ Hz), 4.15-4.06 (m, 1H), 3.87 (dd, 1H, $J = 12.5, 8.7$ Hz), 2.46-2.30 (m, 1H), 2.02 (dd, 1H, $J = 9.1, 4.6$ Hz), 1.58 (dd, 1H, $J = 7.5, 4.2$ Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 176.4, 143.3, 136.1, 128.8, 127.6, 127.3, 127.1, 122.1, 120.4, 109.4, 61.0, 44.2, 34.4, 31.0, 22.3; IR (KBr) ν 3407, 3026, 2916, 1687, 1612, 1490, 1467, 1451, 1432, 1391, 1356, 1305, 1193, 1152, 1124, 1102, 1054, 1032, 1017, 964, 757, 751, 736, 695, 668; DEI-MS 279.1 (43 [M]⁺), 235.1 (59 [M-CH₂=CHOH]⁺), 91.0 (100 [C₇H₇]⁺); Anal. calcd for C₁₈H₁₇NO₂: C 77.40, H 6.13, N 5.01, found: C 77.46, H 6.10, N 5.00.

1'-(phenylmethyl)-2-[1-prop-1-en-1-yl]spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (26)

In a 3-neck flask equipped with a reflux condenser and an addition funnel was placed $[\text{Rh}(\text{OAc})_2]_2$ (7.2 mg, 16 μmol , 5 mol%). Benzene (5 mL) and piperylene (**24**) (mixture of isomers, 162 μL , 1.62 mmol, 5.00 equiv) were added and the suspension was heated to reflux. A solution of **25** (81.0 mg, 325 μmol , 1.00 equiv) in benzene (5 mL) was added over 4 h by syringe pump. The reaction mixture was allowed to cool to room temperature and filtered over Celite. The filter cake was washed with benzene. The filtrate was concentrated in vacuo and purified by column chromatography (1:7 EtOAc/hexanes) to afford **26** (mixture of isomeric products) (85.0 mg, 90%).

Fraction 1: colorless oil, yield: 8.0 mg (8%).

R_f = 0.61 (1:3 EtOAc/hexanes); ^1H NMR (CDCl_3 , 300 MHz, two isomers, $^\#$ denotes major-, * minor isomer signals) δ 7.31-7.21 (m, 10H), 7.19-7.09 (m, 2H), 7.06-6.94 (m, 2H), 6.95-6.80 (m, 2H), 6.79-6.72 (m, 2H), 5.98-5.83 (m, 2H), 5.77-5.62 (m, 2H), 5.05-4.86 (m, 4H) 2.71 (dd, 1H * , J = 6.4, 6.4 Hz), 2.52 (dd, 1H $^\#$, J = 6.1, 6.1 Hz), 1.73 (d, 3H $^\#$, J = 5.2 Hz), 1.67 (d, 3H * , J = 5.3 Hz).

Fraction 2: colorless oil, yield: 77.0 mg (82%).

R_f = 0.52 (1:3 EtOAc/hexanes); ^1H NMR (CDCl_3 , 300 MHz, one isomer) δ 7.32-7.22 (m, 5H), 7.14 (dt, 1H, J = 1.6, 7.5 Hz), 7.02-6.90 (m, 2H), 6.80 (d, 1H, J = 7.8 Hz), 5.80 (ddd, 1H, J = 15.2, 6.5, 0.9 Hz), 5.53-5.45 (m, 1H) 5.02 (d, 1H, J = 15.9 Hz), 4.95 (d, 1H, J = 15.9 Hz), 2.70-2.62 (m, 1H), 2.09 (dd, 1H, J = 9.0, 4.7 Hz), 1.74-1.71 (m, 3H), 1.65 (dd, 1H, J = 7.6, 4.7 Hz).

1'-[(4-methylphenyl)sulfonyl]-2'-phenyl-1-(phenylmethyl)-5'-[1-prop-1-en-1-yl]spiro[indole-3,3'-pyrrolidin]-2(1H)-one (28)

A sealable tube with side inlet was charged with MgI_2 (2.0 mg, 7.3 μmol , 20 mol%), imine **27** (12.2 mg, 47.0 μmol , 1.30 equiv) and cyclopropane **26** (10.5 mg, 36.0 μmol , 1.00 equiv). THF (0.1 mL) was added by syringe. The tube was sealed, placed into an oil bath at 80 °C and heated for 14 h. The reaction mixture was allowed to reach room temperature. EtOAc (4 mL) and H_2O (5 mL) were added to the reaction mixture, followed by $\text{Na}_2\text{S}_2\text{O}_3$ (small crystal). This biphasic mixture was stirred for 1 h, then the phases were separated and the organic phase was washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The products could only be partially separated by column chromatography (3:17 EtOAc/hexanes) and one major fraction was obtained which could be identified as the desired product of the ring expansion **28** (mixture of isomers) (9.3mg, 47%).

R_f = 0.32 (1:3 EtOAc/hexanes); ^1H NMR (CDCl_3 , 300 MHz, mixture of isomers, only the major one is described) δ 7.62-6.87 (m, 16H), 6.62-6.48 (m, 2H), 5.84-5.64 (m, 2H), 5.22-5.14 (m, 1H), 5.06-4.70 (m, 1H), 4.71 (d, 1H, J = 11.2 Hz), 4.24 (d, 1H, J = 11.2 Hz), 2.42 (s, 3H), 2.33-2.20 (m, 2H), 1.72-1.69 (m, 3H).

allyl-(3-methyl-but-2-enylidene)-amine (29)

Allyl amine (1.56 mL, 20.9 mmol, 1.00 equiv) was cooled to 0 °C and prenal (2.00 mL, 20.9 mmol, 1.00 equiv) was slowly added. KOH (powdered, 200 mg) was added to the mixture. Stirring was continued for 2 h. The mixture was filtered, and the filtrate was Kugelrohr distilled (at 30 mbar) to give desired imine **29** (875mg, 34%) as colorless liquid.

^1H NMR (200 MHz, CDCl_3) δ 8.20 (dt, 1H, J = 9.6, 1.3 Hz), 6.09-5.92 (m, 2H), 5.24-5.09 (m, 2H), 4.12-4.09 (m, 2H), 1.94 (s, 3H), 1.90 (s, 3H).

allyl-(3-methoxy-3-methyl-butylidene)-amine (**30**)

A solution of oxalyl chloride (3.78 mL, 43.1 mmol, 1.10 equiv) in CH_2Cl_2 (100 mL) was cooled to $-60\text{ }^\circ\text{C}$. A solution of DMSO (6.10 mL, 86.0 mmol, 2.20 equiv) in CH_2Cl_2 (20 mL) was slowly added and stirring was continued till the gas evolution had stopped. A solution of 3-methoxy-3-methyl-butanol (5.00 mL, 39.1 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) was added and a white suspension formed. NEt_3 (27.0 mL, 196 mmol, 5.00 equiv) was added and the mixture was stirred for 15 min at $-60\text{ }^\circ\text{C}$ and was then allowed to reach room temperature. H_2O (150 mL) was introduced. The organic layer was separated, washed with 1 M aq HCl (200 mL), sat. aq NaHCO_3 (200 mL) and brine (200 mL), dried over Na_2SO_4 , filtered, concentrated in vacuo and distilled under reduced pressure (bp (10 mbar) = $55\text{ }^\circ\text{C}$) to yield the corresponding aldehyde (1.88 g, 41%).

To a solution of the intermediate aldehyde (520 mg, 4.48 mmol, 1.00 equiv) and allyl amine (335 μL , 4.48 mmol, 1.00 equiv) in CH_2Cl_2 (6 mL) was added MgSO_4 (20 mg). The reaction mixture was allowed to stir at room temperature for 12 h, filtration and evaporation of the solvent afforded imine **30** (612 mg, 88%) as colorless oil which was used without further purification.

^1H NMR (300 MHz, CDCl_3) δ 7.78-7.70 (m, 1H), 6.07-5.91 (m, 2H), 5.21-5.08 (m, 2H), 4.15-4.01 (m, 2H), 3.22 (s, 3H), 2.51-2.23 (m, 2H), 1.12 (s, 6H).

triisopropylsilanyl-propynal (**31**)

A solution of triisopropylsilanyl-acetylene (15.0 mL, 67.5 mmol, 1.00 equiv) in THF (100 mL) was cooled to $-78\text{ }^\circ\text{C}$. $n\text{BuLi}$ (1.60 M in hexanes, 42.2 mL, 67.5 mmol, 1.00 equiv) was added dropwise and the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 0.5 h. A solution of ethyl formate (10.9 mL, 135 mmol, 2.00 equiv) in THF (100 mL) was added

dropwise. The reaction mixture was stirred for 45 min at $-78\text{ }^{\circ}\text{C}$, then poured onto ice-water (100 mL) containing a trace of hydroquinone and acetic acid (1 mL). The product was extracted with Et_2O ($2 \times 200\text{ mL}$); the combined organic layers were dried (Na_2SO_4) filtered, and concentrated in vacuo. The unpurified aldehyde **31** was used for subsequent imine formation.

$R_f = 0.89$ (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 9.21 (s, 1H), 1.12-1.10 (m, 21H).

Ally-(3-triisopropylsilyl-prop-2-ynylidene)-amine (**32**)

A solution of triisopropylsilyl-propynal (**31**) (67.5 mmol, 1.00 equiv) in CH_2Cl_2 (100 mL) was treated with allyl amine (5.05 mL, 67.5 mmol, 1.00 equiv) and MgSO_4 (6 g) at room temperature for 9 h. The reaction mixture turned slightly orange. The MgSO_4 was filtered off and the filter cake was washed with CH_2Cl_2 ($3 \times 20\text{ mL}$). The solvent was evaporated in vacuo and the product was purified by distillation under reduced pressure (0.5 mbar, $90\text{--}95\text{ }^{\circ}\text{C}$) to afford imine **32** (*Z* and *E* isomer) (13.4 g, 80% over two steps) as a colorless liquid.

$R_f = 0.50, 0.38$ (1:50 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.58-7.57 (m, 2H), 6.07-5.94 (m, 2H), 5.25-5.11 (m, 4H), 5.25-5.11 (m, 4H), 4.33 (dddd, 1H, $J = 5.6, 1.87, 1.87, 1.87\text{ Hz}$), 4.16 (dddd, 1H, $J = 5.6, 1.9, 1.9, 1.3\text{ Hz}$) 1.10-1.09 (m, 42H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.7, 143.7, 134.9, 134.6, 116.9, 116.0, 103.4, 101.8, 98.3, 95.1, 64.2, 58.8, 18.6, 18.6, 11.2, 11.2; IR (thin film) ν 2945, 2867, 1644, 1612, 1593, 1464, 1384, 1366, 1072, 1027, 995, 919, 883, 678; EI-MS 249.2 ($1.2\text{ }[\text{M}]^+$), 206.1 (100 $[\text{NC-C}\equiv\text{C-TIPS}]$); Anal. calcd for $\text{C}_{15}\text{H}_{27}\text{NSi}$: C 72.22, H 10.91, N 5.61, found: C 72.25, H 10.84, N 5.57.

3-(tosyl-hydrazono)-1,3-dihydro-indol-2-one

Isatin (**34**) (9.44 g, 64.2 mmol, 1.00 equiv) was suspended in MeOH (300 mL). The suspension was heated to reflux, whereupon a deep-red solution was obtained. To this hot solution was added tosylhydrazine (12.1 g, 64.8 mmol, 1.02 equiv) in one portion. A yellow product starts precipitating from the hot mixture. The reaction mixture was allowed to cool to room temperature and the pure tosylhydrazone (18.2 g, 90%) was filtered off.

R_f = 0.12 (EtOAc); mp = 207 °C; ^1H NMR (300 MHz, CD_3OD) δ 7.97 (d, 2H, J = 8.09 Hz), 7.86 (d, 1H, J = 7.47 Hz), 7.41-7.35 (m, 3H), 7.11-7.06 (m, 1H), 6.91 (d, 1H, J = 7.47 Hz), 2.43 (s, 3H).

3-diazo-1,3-dihydro-indol-2-one (**35**)

3-Tosylhydrazone-1,3-dihydro-indol-2-one (12.0 g, 38.1 mmol, 1.00 equiv) was treated with a solution of NaOH (3.04 g, 76.1 mmol, 2.00 equiv) in H_2O (375 mL). The reaction mixture was stirred for 15 h in a waterbath at 50 °C, and then allowed to cool to room temperature. The reaction mixture was neutralized by addition of dry ice, whereupon diazoketone **35** (5.36 g, 88%) precipitated. The product was directly used in the subsequent reaction.

R_f = 0.54 (3:1 EtOAc/hexanes); mp = 168 °C (decomp.); ^1H NMR (300 MHz, CDCl_3) δ 8.69 (br, 1H), 7.21-7.06 (m, 3H), 7.01-6.98 (m, 1H).

2-[1-prop-1-en-1-yl]spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (**36**)

In a 3-neck flask equipped with a reflux condenser and an addition funnel was placed $[\text{Rh}(\text{OAc})_2]_2$ (214 mg, 485 μmol , 1 mol%). Benzene (280 mL) and piperylene (mixture of isomers, 19.5 mL, 194 mmol, 4.00 equiv) were added and the suspension was heated to reflux. A solution of **35** (7.72 g, 48.5 mmol, 1.00 equiv) in CH_2Cl_2 (340 mL) was added over 3 h by syringe pump. The reaction mixture was allowed to cool to room temperature

and the solvent was partially removed (reduced to 1/10 of its volume). The remaining suspension was filtered over Celite and the filter cake was washed with acetone. The filtrate was concentrated in vacuo and purified by column chromatography (1:3 EtOAc/hexanes) to afford **36** (mixture of isomeric products) (69.1 g, 71%). The mixture was used without further purification in the upcoming ring-expansion step.

Ring expansion of **36** with **33**:

A sealable tube with side inlet was charged with MgI_2 (5.69 g, 20.5 mmol, 1.00 equiv). A solution of cyclopropane **36** (4.08 g, 20.5 mmol, 1.00 equiv) in THF (35 mL) was added via cannula, followed by imine **32** (6.12 g, 24.4 mmol, 1.20 equiv). The tube was sealed, placed into an oil bath at 75 °C and heated for 15 h. The reaction mixture was allowed to reach room temperature. EtOAc (250 mL) and H_2O (150 mL) were added to the reaction mixture, followed by $\text{Na}_2\text{S}_2\text{O}_3$ (500 mg). This biphasic mixture was stirred for 3 h, then the phases were separated and the organic phase was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo to give **37**. The following products were obtained by careful column chromatography purification (4:21 EtOAc/hexanes):

(±)-(2'R,3S,5'S)-1'-allyl-5'-[(1E)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro-[indole-3,3'-pyrrolidin]-2(1H)-one (38)

Pale yellow solid, 2.93 g (32%).

R_f = 0.59 (1:3 EtOAc/hexanes); mp = 121 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.84 (br, 1H), 7.50 (d, 1H, J = 7.5 Hz), 7.14 (ddd, 1H, J = 7.5, 7.5, 1.3 Hz), 7.00 (ddd, 1H, J = 7.5, 7.5, 1.3 Hz), 6.85 (d, 1H, J = 7.5 Hz), 6.04-5.91 (m, 1H), 5.74-5.60 (m, 1H),

5.46-5.37 (m, 1H), 5.24-5.20 (m, 2H), 3.83 (s, 1H), 3.59-3.37 (m, 3H), 2.50 (dd, 1H, $J = 13.1, 8.1$ Hz), 1.82 (dd, 1H, $J = 13.7, 8.1$ Hz), 1.58 (ddd, 3H, $J = 8.8, 6.2, 1.3$ Hz), 0.83-0.82 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.1, 140.4, 134.7, 132.5, 132.1, 129.1, 127.9, 125.6, 122.9, 119.6, 109.3, 103.1, 87.5, 63.1, 62.6, 56.0, 50.9, 42.2, 18.4, 17.8, 10.9; IR (thin film) ν 3207, 2942, 2864, 1712, 1618, 1471, 1337, 1234, 1171, 990, 912, 881, 749, 673; HiResMALDI-MS calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 449.2988, found, 449.2989; Anal. calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{SiO}$: C 74.95, H 8.98, N 6.24, found: C 74.95, H 8.89, N 6.01.

(±)-(2'*R*,3*R*,5'*R*)-1'-allyl-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro-[indole-3,3'-pyrrolidin]-2(1*H*)-one (39)

Pale yellow oil, 350 mg (3.8%).

$R_f = 0.65$ (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.65-7.57 (m, 3H), 7.22-7.16 (m, 1H), 7.04-6.98 (m, 1H), 6.81 (d, 1H, $J = 7.5$ Hz), 5.85-5.62 (m, 2H), 5.51-5.42 (m, 1H), 5.20 (d, 1H, $J = 18.1$), 5.00 (d, 1H, $J = 10.0$ Hz), 3.92 (s, 1H), 3.55-3.37 (m, 2H), 3.22 (dd, 1H, $J = 13.7, 8.1$ Hz), 2.70 (dd, 1H, $J = 13.1, 8.7$ Hz), 1.80 (dd, 1H, $J = 13.1, 6.9$ Hz), 1.70 (ddd, 3H, $J = 11.8, 6.2, 1.3$ Hz), 1.11 (s, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.1, 140.0, 136.3, 136.1, 132.5, 129.0, 127.8, 124.1, 122.3, 116.8, 109.0, 99.5, 90.6, 64.3, 62.5, 55.2, 50.7, 41.6, 18.7, 17.8, 11.3; IR (thin film) ν 3207, 3082, 2942, 2865, 2159, 1716, 1620, 1471, 1332, 1234, 1176, 995, 964, 917, 883, 750, 677; HiResMALDI-MS calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 449.2988, found, 449.2983.

Co-eluting fraction

2.90 g (32%) $R_f = 0.45$ (1:3 EtOAc/hexanes).

Allyl-deprotection of the co-eluting fraction:

To a solution of the co-eluting fraction (3.07 g, 6.85 mmol, 1.00 equiv) and NDMBA (3.42 g, 21.9 mmol, 3.20 equiv) in CH_2Cl_2 (150 mL) was added a solution of freshly prepared $\text{Pd}(\text{PPh}_3)_4$ (from $[\text{Pd}_2\text{dba}_3] \cdot \text{CHCl}_3$ (212 mg, 205 μmol , 6 mol% Pd) and PPh_3 (323 mg, 1.23 mmol, 18 mol%) in 20 mL CH_2Cl_2). The reaction mixture was stirred at 30 °C for 12 h. CH_2Cl_2 (350 mL) was added and the organic solution was washed with sat. aq Na_2CO_3 (2 $\times$ 175 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (1.5:8.5 $\rightarrow$ 1:4 EtOAc/hexanes) afforded:

($\pm$)-(2'*R*,3*S*,5'*R*)-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (40)

Pale yellow oil, 1.68 g (60%).

R_f = 0.71 (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.89 (br, 1H), 7.38 (d, 1H, J = 7.47 Hz), 7.23-7.18 (m, 1H), 7.06-7.01 (m, 1H), 6.87 (d, 1H, J = 7.5 Hz), 5.69-5.63 (m, 2H), 4.35 (s, 1H), 4.22 (ddd, 1H, J = 7.5, 7.5, 7.5 Hz), 2.25-2.21 (m, 2H), 1.71 (d, 3H, J = 5.0 Hz), 0.86-0.85 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 179.9, 140.4, 133.0, 131.5, 128.1, 126.9, 124.5, 122.5, 109.7, 103.7, 86.6, 60.4, 59.7, 58.7, 43.2, 18.4, 17.7, 10.9; IR (thin film) ν 3209, 2942, 2864, 1715, 1684, 1621, 1472, 883, 750, 679; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 409.2675, found, 409.2674; Anal. calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{SiO}$: C 73.48, H 8.88, N 6.85, found: C 73.29, H 8.97, N 6.66.

(±)-(2'*R*,3*S*,5'*R*)-5'-[(1*Z*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (41)

Pale yellow oil, 350 mg (13%).

R_f = 0.53 (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 8.08 (br, 1H), 7.45 (d, 1H, J = 7.5 Hz), 7.24-7.19 (m, 1H), 7.07-7.02 (m, 1H), 6.88 (d, 1H, J = 7.5 Hz), 5.68-5.55 (m, 2H), 4.62 (ddd, 1H J = 8.1, 8.1, 8.1 Hz), 4.37 (s, 1H), 2.34-2.12 (m, 2H), 1.71 (d, 3H, J = 5.0 Hz), 1.58 (br, 1H), 0.88-0.86 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.3, 132.7, 131.3, 128.2, 185.8, 124.7, 122.5, 109.5, 103.8, 86.7, 59.5, 58.9, 54.4, 43.4, 18.4, 13.4, 10.9; IR (thin film) ν 3199, 2943, 2865, 2170, 1714, 1621, 1471, 1337, 1236, 1110, 996, 919, 883, 750, 679; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 409.2675, found, 409.2676.

(±)-(2'*R*,3*R*,5'*S*)-5'-[1-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (42)

Pale yellow solid 510 mg (18%).

R_f = 0.73 (1:3 EtOAc/hexanes); mp = 63 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.35 (br, 1H), 7.23-7.17 (m, 2H), 7.05-7.00 (m, 1H), 6.90 (d, 1H, J = 7.5 Hz), 5.78-5.64 (m, 2H), 4.00-3.94 (m, 2H), 2.75 (br, 1 H) 2.44-2.31 (m, 1H), 2.21-2.08 (m, 1H), 1.73 (d, 3H, J = 5.6 Hz), 0.89 (s, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.7, 141.6, 131.0, 130.6, 128.2, 128.0, 122.3, 122.01, 109.7, 101.8, 85.8, 62.3, 62.1, 60.2, 43.3, 18.5, 17.9, 11.1; IR (thin film) ν 3186, 2942, 2865, 2175, 1706, 1621, 1472, 1439, 1345, 1109, 968, 883, 745, 678; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 409.2675, found, 409.2677.

Allyl-deprotection of **38**:

(±)-(2'*R*,3*S*,5'*S*)-5'-[(1*Z*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (43)

To a solution of **38** (1.63 g, 3.63 mmol, 1.00 equiv) and NDMBA (1.82 g, 11.6 mmol, 3.20 equiv) in CH_2Cl_2 (45 mL) was added a solution of freshly prepared $\text{Pd}(\text{PPh}_3)_4$ (from $[\text{Pd}_2\text{dba}_3]\cdot\text{CHCl}_3$ (75.0 mg, 72.0 μmol , 4 mol% Pd) and PPh_3 (114 mg, 436 μmol , 12 mol%) in 5 mL CH_2Cl_2). The reaction mixture was stirred at 30 °C for 12 h. CH_2Cl_2 (200 mL) was added to the reaction mixture and the organic solution was washed with sat. aq Na_2CO_3 (2 $\times$ 100 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (9:41 EtOAc/hexanes) afforded **43** (1.27 g, 86%) as a pale yellow solid.

R_f = 0.28 (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 8.37 (br, 1H), 7.35 (d, 1H, J = 7.5 Hz), 7.16 (dd, 1H, J = 7.5, 7.5 Hz), 7.00 (dd, 1H, J = 7.5, 7.5 Hz), 6.85 (d, 1H, J = 7.5 Hz), 5.79-5.51 (m, 2H), 4.21 (s, 1H), 3.95 (ddd, 1H, J = 8.1, 8.1, 8.1 Hz), 2.58

(dd, 1H, $J = 13.1, 8.1$ Hz), 2.18 (br, 1H), 1.88 (dd, 1H, $J = 13.1, 8.1$ Hz), 1.73-1.70 (m, 3H), 0.83-0.82 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.1, 140.4, 133.5, 131.7, 127.9, 127.8, 124.4, 122.5, 109.6, 103.0, 86.9, 60.5, 60.1, 58.9, 43.9, 18.4, 17.8, 10.9; IR (thin film) ν 3212, 2943, 2865, 2176, 1713, 1621, 1472, 1340, 1235, 1112, 965, 883, 748, 679; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{SiO}$ $[\text{M}+\text{H}]^+$ 409.2675, found, 409.2684.

3.1. Synthesis of Spirotryprostatin B from Intermediate 40

Coupling of **40** with *N*-Boc-L-proline chloride (**45**).

To a solution of **40** (141 mg, 345 μ mol, 1.00 equiv) and NEt_3 (48.0 μ L, 345 μ mol, 1.00 equiv) in CH_2Cl_2 (15 mL) at 0 $^\circ\text{C}$ was added *N*-Boc-L-proline chloride (**45**) (0.14 M in CH_2Cl_2 , 10.0 mL, 1.38 mmol, 4.00 equiv). The reaction mixture was allowed to warm slowly to room temperature and was stirred for 8 h. The reaction was quenched by addition of 10% aq NaHCO_3 (10 mL). The phases were separated; the organic layer was washed with sat. aq NaHCO_3 (10 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (1:3 EtOAc/hexanes) afforded:

tert-butyl (2S)-2-({(2'R,3S,5'R)-2-oxo-5'-[(1E)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'H-spiro[indole-3,3'-pyrrolidin]-1'-yl}carbonyl)pyrrolidine-1-carboxylate (46**)**

Colorless crystals, 94 mg (45%).

R_f = 0.63 (1:1 EtOAc/hexanes), $[\alpha]_D^{23}$ (c 0.250, CHCl_3) = +15.6; mp = 191 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 $^\#$ denotes major-, * minor rotamer signals) δ 7.94-7.78 (m, 2H), 7.25-7.15 (m, 4H), 7.06-7.01 (m, 2H), 6.90-6.83 (m, 2H), 5.76-5.50 (m, 4H), 5.35* (s, 1H), 5.20-5.18* (m, 1H), 2.26 $^\#$ (s, 1H), 4.98-4.74 (m, 3H), 3.67-3.63 $^\#$ (m, 1H), 3.59-3.54* (m, 1H), 3.52-3.38 (m, 2H), 2.88-2.00 (m, 10H), 1.88-1.71 (m, 5 H),

1.66-1.64* (m, 3H), 1.53* (s, 9H), 1.49-1.47[#] (m, 9H), 0.85-0.81 (m, 42H); ¹³C NMR (75 MHz, CDCl₃, * denotes minor rotamer signals) δ 179.3, 176.9*, 171.2, 170.5*, 154.5, 154.4*, 141.0, 140.6*, 133.6, 130.7*, 130.5, 128.8, 128.5*, 127.6, 127.4*, 125.6, 124.0*, 122.9*, 122.1, 110.3*, 109.9, 102.3*, 99.0, 92.0*, 87.3, 79.6, 79.2*, 60.4*, 59.6, 59.2*, 58.7*, 58.4, 58.1, 57.1, 56.6*, 46.5, 46.3*, 43.6, 39.8*, 30.1*, 29.1, 28.6*, 28.5, 23.1*, 22.8, 18.5*, 18.3, 17.8, 17.6*, 11.1, 10.9*; IR (thin film) ν 3212, 2942, 2865, 1729, 1689, 1472, 1397, 1366, 1299, 1254, 1164, 1126, 970, 919.3, 883, 750, 677; HiResMALDI-MS calcd for C₃₅H₅₁N₃SiO₄ [M+Na]⁺ 628.3546, found, 628.3491; Anal. calcd. for C₃₅H₅₁N₃SiO₄: C 69.38, H 8.48, N 6.94, found: C 69.40, H 8.36, N 6.92.

Crystal data for **46** at 223 K, *M*_r = 605.88, monoclinic space group *P*2(1), *ρ*_{calc} = 1.116 g·cm⁻³, *Z* = 2, *a* = 12.642(2), *b* = 11.274(2), *c* = 13.052(4) Å, α = 90.00, β = 104.26(2), γ = 90.00°, *V* = 1802.9(7) Å³. Final *R*(*F*) = 0.0564, *wR*(*F*²) = 0.1601 for 464 parameters and 3015 reflections with *I* > 2σ(*I*) and θ < 64.99°. The *i*Pr₃Si groups in **46** are disordered. The disorder could be resolved for the atoms C(20), C(21), C(22), C(23), and C(25), i.e., two peaks were refined with population parameters of 0.6 and 0.4, respectively. (Only one population is displayed for clarity.)

CCDC 196803 contains the supplementary crystallographic data for **46**. This data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

tert-butyl (2*S*)-2-((2'*S*,3*R*,5'*S*)-2-oxo-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl)carbonylpyrrolidine-1-carboxylate (47**)**

White solid, 94 mg (45%).

$R_f = 0.50$ (1:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 0.745, CHCl_3) = -31.6 ; mp = $99\text{ }^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 # denotes major-, * minor rotamer signals) δ 7.69* (br, 1H), 7.58# (br, 1H), 7.47# (d, 1H, $J = 7.5\text{ Hz}$), 7.26-7.14 (m, 3H), 7.0-6.93 (m, 2H), 6.90-6.84 (m, 2H), 6.09* (ddd, 1H, $J = 15.6, 8.7, 1.9\text{ Hz}$), 5.76-5.59 (m, 2H), 5.52# (dd, 1H, $J = 8.7, 3.7\text{ Hz}$), 5.41* (ddd, 1H, $J = 15.6, 7.5, 1.9\text{ Hz}$), 5.17* (s, 1H), 4.97-4.86 (m, 2H), 4.86# (s, 1H), 4.55-4.48* (m, 1H), 3.65-3.36 (m, 4H), 2.69* (dd, 1H, $J = 13.7, 8.7\text{ Hz}$), 2.28-2.09 (m, 5H), 1.92-1.72 (m, 6H), 1.76# (dd, 3H, $J = 6.2, 1.3\text{ Hz}$), 1.68* (dd, 3H, $J = 6.2, 1.3\text{ Hz}$), 1.47# (s, 9H), 1.42* (s, 9H), 0.96-0.95* (m, 21H), 0.83-0.82# (m, 21H); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 179.0, 176.6*, 171.0, 154.3*, 154.2, 140.9, 140.4*, 133.5, 130.6, 130.4*, 128.7, 128.4*, 127.5, 127.3*, 125.5, 123.9*, 122.8*, 122.1, 110.2*, 109.8, 102.3, 99.0*, 92.0*, 87.3, 79.6, 79.2*, 59.7, 59.2, 58.7*, 58.5, 58.1*, 57.2*, 56.7, 46.6, 46.4*, 43.8, 39.9*, 30.3*, 29.2, 28.7*, 28.6, 23.2*, 22.9, 18.7*, 18.4, 17.9, 17.8*, 11.2, 11.0*; IR (thin film) ν 3214, 2943, 2866, 2175, 1728, 1702, 1676, 1622, 1472, 1401, 1366, 1241, 1164, 1126, 883, 750, 678; HiResMALDI-MS calcd for $\text{C}_{35}\text{H}_{51}\text{N}_3\text{SiO}_4$ $[\text{M}+\text{Na}]^+$ 628.3546, found, 628.3535.

***tert*-butyl (2*S*)-2-((2'*R*,3*S*,5'*R*)-5'-formyl-2-oxo-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl)carbonylpyrrolidine-1-carboxylate (330)**

A solution of **46** (405 mg, 668 μmol , 1.00 equiv) and $\text{NMO}\cdot\text{H}_2\text{O}$ (108 mg, 802 μmol , 1.20 equiv) in THF/*t*BuOH/ H_2O (4:4:1, 20 mL) was stirred at room temperature for 30 min before OsO_4 (4 wt% in H_2O , 170 μL , 270 μmol , 4 mol%) was added. The reaction mixture was stirred at room temperature for 16 h, then quenched by addition of 2 M aq $\text{Na}_2\text{S}_2\text{O}_3$ (25 mL) and EtOAc (25 mL). The biphasic mixture was stirred for 3 h, the phases separated; the organic layer was washed with brine (25 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The unpurified product (**48**) was used in the subsequent reaction.

$R_f = 0.67, 0.51$ (3:1 EtOAc/hexanes).

To a solution of diols **48** in EtOAc (20 mL) was added $\text{Pb}(\text{OAc})_4$ (344 mg, 1.00 mmol, 1.50 equiv). A yellow suspension was obtained and after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc. Purification by column chromatography (1:1 EtOAc/hexanes) afforded **49** (385 mg, 97%) as a white solid.

$R_f = 0.83$ (3:1 EtOAc/hexanes), mp = 90 °C; $[\alpha]_D^{26}$ (c 0.290, CHCl_3) = +50.8; ^1H NMR (300 MHz, CDCl_3 [#] denotes major-, * minor rotamer signals) δ 9.64* (d, 1H, $J = 2.8$ Hz), 9.52[#] (d, 1H, $J = 3.1$ Hz), 8.91 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.22 (m, 2H), 7.06-6.99 (m, 2H), 6.93-6.89 (m, 2H), 5.57[#] (s, 1H), 5.16* (s, 1H), 4.85-4.65 (m, 4H), 3.57-3.41 (m, 4H), 2.42-2.03 (m, 10H), 1.86-1.80 (m, 2H), 1.51* (s, 9H), 1.45[#] (s, 9H), 0.91-0.90 (m, 42H); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 198.7, 197.2*, 177.4*, 177.3, 174.1, 173.6*, 154.4, 153.4*, 140.6, 140.6*, 129.4*, 129.1, 128.1, 127.7*, 125.0*, 124.9, 122.5, 110.4, 101.6, 101.1*, 91.8*, 90.7, 80.49*, 79.8, 65.1, 64.8*, 60.4, 57.4, 56.5*, 47.2, 34.8*, 34.5, 31.9, 30.2, 29.7*, 28.5, 24.7, 23.2*, 18.5, 11.0; IR (thin film) ν 3243, 2944, 2866, 1730, 1687, 1655, 1623, 1472, 1403, 1367, 1299, 1257, 1164, 883, 752, 669; HiResMALDI-MS calcd for $\text{C}_{33}\text{H}_{47}\text{N}_3\text{SiO}_5$ $[\text{M}+\text{Na}]^+$ 616.3183, found, 616.3158; Anal. calcd for $\text{C}_{33}\text{H}_{47}\text{N}_3\text{SiO}_5$: C 66.75, H 7.98, N 7.08, found: C 66.91, H 7.82, N 6.87.

methyl (2'R,3S,5'R)-1'-{[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2-oxo-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (51**)**

A solution of NaClO_2 (73.0 mg, 808 μmol , 10.0 equiv) in pH 3.6 buffer (1.5 mL) was added to a solution of aldehyde **49** (48.0 mg, 810 μmol , 1.00 equiv) and 2-methyl-2-butene (1 mL) in $t\text{BuOH}$ (3 mL). The reaction mixture was stirred at room temperature for 30 min; 2 M aq HCl was added (10 mL), and the product was extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and

concentrated in vacuo; $R_f = 0.08$ (3:1 EtOAc/hexanes). The product **50** was dissolved in Et₂O (5 mL) and a solution of CH₂N₂ in Et₂O (≈ 0.4 M in Et₂O) was added until the yellow color of CH₂N₂ persisted. The solvent was evaporated in vacuo and the product was purified by column chromatography (4:6 EtOAc/hexanes) to afford **51** (45 mg, 89%) as a white solid.

$R_f = 0.81$ (3:1 EtOAc/hexanes), mp = 95 °C; $[\alpha]_D^{26}$ (c 1.525, CHCl₃) = +47.7; ¹H NMR (300 MHz, CDCl₃ # denotes major-, * minor rotamer signals) δ 8.59-8.42 (m, 2H), 7.28-7.23 (m, 2H), 7.21-7.10 (m, 2H), 7.06-6.98 (m, 2H), 6.94-6.87 (m, 2H), 5.46* (s, 1H), 5.24# (s, 1H), 5.19-5.16# (m, 1H), 5.08-5.05* (m, 1H), 4.90-4.74 (m, 2H), 3.78# (s, 3H), 3.72* (s, 3H) 3.67-3.35 (m, 4H), 2.6-2.48 (m, 2H), 2.34-2.26 (m, 2H), 2.22-2.02 (m, 4H), 1.98-1.91 (m, 2H), 1.84-1.77 (m, 2H), 1.58# (s, 9H), 1.47* (s, 9H), 0.83-0.82 (m, 42H); ¹³C NMR (75 MHz, CDCl₃, * denotes minor rotamer signals) δ 176.1*, 175.9, 174.6*, 174.2, 171.2, 153.9, 141.1, 130.6*, 130.4, 129.3, 123.9, 123.0, 110.9, 101.0*, 100.4, 91.9, 91.2*, 80.5, 79.4*, 61.2*, 60.6*, 60.4, 59.4, 57.5, 57.3*, 52.6, 52.4*, 47.2*, 47.1, 37.1, 36.8*, 32.4, 31.5*, 28.6*, 28.4, 24.3*, 23.4, 18.4, 11.0; IR (thin film) ν 3242, 3945, 2866, 2173, 1732, 1700, 1622, 1472, 1367, 1366, 1299, 1202, 1174, 1114, 884, 752, 679; HiResMALDI-MS calcd for C₃₄H₄₉N₃SiO₆ [M+Na]⁺ 646.3288, found, 646.3277; Anal. calcd for C₃₄H₄₉N₃SiO₆: C 65.46, H 7.92, N 6.74, found: C 65.72, H 7.98, N 6.57.

methyl (2'S,3S,5'R)-1'-{[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-ethynyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (52**)**

To a solution of **51** (134 mg, 215 μ mol, 1.00 equiv) in THF (5 mL), was added TBAF (1.0 M in THF, 260 μ L, 260 μ mol, 1.2 equiv). The reaction mixture was stirred at room temperature for 8 h, diluted with CH₂Cl₂, washed with sat. aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by column chromatography (13:7 EtOAc/hexanes) to afford **52** (99.0 mg, 99%) as a white solid.

$R_f = 0.43$ (3:1 EtOAc/hexanes), mp = 97 °C; $[\alpha]_D^{24}$ (c 1.340, CHCl_3) = +24.4; ^1H NMR (300 MHz, CDCl_3 $^\#$ denotes major-, * minor rotamer signals) δ 8.91-8.50 (m, 2H), 7.73-7.52 (m, 1H), 7.32-7.23 (m, 2H), 7.16-6.88 (m, 5H), 5.57* (dd, 1H, $J = 9.3, 5.0$ Hz), 5.36-5.36* (m, 1H), 5.15-5.14 $^\#$ (m, 1H), 4.99-4.91 (m, 2H), 4.84-4.74 $^\#$ (m, 1H), 4.36-4.27* (m, 1H), 3.77 $^\#$ (s, 3H), 3.73* (s, 3H) 3.70-3.36 (m, 3H), 2.93-2.70 (m, 2H), 2.60-2.51 (m, 2H), 2.39-1.78 (m, 10H), 1.58 $^\#$ (s, 9H), 1.46* (s, 9H); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 178.1*, 175.3, 173.6, 173.4*, 171.5*, 170.4, 154.4*, 153.5, 140.6*, 140.3, 129.7, 129.1, 129.0*, 128.9*, 126.2*, 123.9, 122.8, 122.4*, 110.3, 109.5*, 80.3, 79.9*, 79.4, 79.3*, 61.0*, 60.4, 58.8, 58.4*, 57.7*, 57.5, 56.1, 54.1*, 52.7*, 52.6, 47.2, 47.0*, 38.1*, 37.3, 32.5, 29.6*, 28.5*, 28.3, 24.8, 24.0*; IR (thin film) ν 3243, 2978, 1729, 1686, 1621, 1473, 1400, 1366, 1301, 1174, 752; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ 490.1954, found, 490.1944; Anal. calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_6$: C 64.23, H 6.25, N 8.99, found: C 64.18, H 6.36, N 8.90.

methyl (2'S,3S,5'R)-1'--[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl]-2-oxo-2'-vinyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (53**)**

To a solution of **52** (20.0 mg, 430 μmol , 1.00 equiv) and quinoline (2.6 μL , 22 μmol , 0.50 equiv) in EtOH (2 mL), was added Pd/BaSO₄ (6.6 mg, 33 wt%). The reaction mixture was stirred at room temperature under H₂ atmosphere for 10 h. The solution was filtered over Celite and the solvent was evaporated in vacuo. The product was purified by column chromatography (7:3 EtOAc/hexanes) to afford **53** (18.0 mg, 90%) as a white solid.

$R_f = 0.45$ (3:1 EtOAc/hexanes), mp = 112 °C; $[\alpha]_D^{24}$ (c 1.590, CHCl_3) = -3.4; ^1H NMR (300 MHz, CDCl_3 $^\#$ denotes major-, * minor rotamer signals) δ 8.56-8.40 (m, 2H), 7.70 $^\#$ (d, 1H, $J = 7.5$ Hz), 7.30-7.19 (m, 2H), 7.15-6.99 (m, 3H), 6.94-6.85 (m, 2H), 5.57-5.24 (m, 4H), 5.14-4.99 (m, 2H), 4.92-4.78 (m, 3H), 4.72-4.61 (m, 2H), 4.33-4.29 $^\#$ (m, 1H), 3.79 $^\#$ (s, 3H), 3.78* (s, 3H) 3.67-3.35 (m, 4H), 2.64-2.52 (m, 3H), 2.42-2.09 (m, 3H), 2.02-1.70 (m, 6H), 1.57* (s, 9H), 1.49 $^\#$ (s, 9H); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 178.7, 176.5*, 174.6*, 173.9, 172.5, 171.5*, 154.9*, 153.8,

141.0, 140.9*, 135.1, 134.7*, 129.2, 128.8*, 125.9, 123.7*, 122.9*, 122.7, 119.6*, 119.4, 114.6, 111.0*, 110.1, 80.4*, 79.8, 68.9*, 68.1, 61.1*, 59.8, 59.1*, 57.8, 57.1*, 56.4, 52.9, 52.6*, 47.3, 47.0*, 38.1, 37.0*, 32.2*, 29.6, 28.6, 28.5*, 24.9, 23.4*; IR (thin film) ν 3241, 2978, 1727, 1683, 1619, 1473, 1400, 1366, 1300, 1269, 1203, 1174, 1123, 753; HiResMALDI-MS calcd for $C_{25}H_{31}N_3O_6$ $[M+Na]^+$ 492.2110, found, 492.2100; Anal. calcd for $C_{25}H_{31}N_3O_6$: C 63.95, H 6.65, N 8.95, found: C 63.74, H 6.69, N 8.87.

methyl (2'R,3S,5'R)-1'-{[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-(1,2-dihydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (54)

A solution of **53** (17.0 mg, 36.0 μ mol, 1.00 equiv) and NMO $\cdot$ H₂O (6.0 mg, 43 μ mol, 1.2 equiv) in THF/*t*BuOH/H₂O (4:4:1, 1 mL) was stirred at room temperature for 30 min before OsO₄ (4 wt% in H₂O, 230 μ L, 36.0 μ mol, 1.00 equiv) was added. The reaction mixture was stirred at room temperature for 3 d. The reaction was quenched by addition of a 2 M aq Na₂S₂O₃ (2 mL) and EtOAc (2 mL) was added. The biphasic mixture was stirred for 6 h. The phases were separated; the organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by column chromatography (3:1 EtOAc/hexanes) afforded diol **54** (16.0 mg, 88%) as colorless oil.

R_f = 0.18 (3:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 1.545, CHCl₃) = -1.4 ; ¹H NMR (300 MHz, CDCl₃) δ 8.33 (br, 1H), 7.67 (d, 1H, J = 7.5 Hz), 7.20 (ddd, 1H, J = 7.5, 7.5, 1.3 Hz), 7.03 (ddd, 1H, J = 7.5, 7.5, 1.3 Hz), 6.81 (d, 1H, J = 7.5 Hz), 5.39 (d, 1H, J = 9.3 Hz), 5.27 (d, 1H, J = 10.6 Hz), 4.52 (s, 1H), 4.34 (dd, 1H, J = 8.1, 4.4 Hz), 4.07 (ddd, 1H, J = 8.7, 8.7, 8.7 Hz), 3.78 (s, 3H), 3.65-3.45 (m, 4H), 3.25-3.15 (m, 1H), 3.11 (dd, 1H, J = 13.7, 10.0 Hz), 2.68 (d, 1H, J = 14.9 Hz), 2.44-2.10 (m, 3H), 1.91-1.81 (m, 1H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 181.5, 175.7, 171.3, 155.7, 141.1, 128.8, 128.0, 127.7, 122.5, 109.8, 80.7, 71.7, 69.9, 62.1, 59.7, 58.6, 54.8, 52.8, 47.8, 38.1, 30.0, 28.5, 24.9; IR (thin film) ν 3449, 2977, 1722, 1660, 1474, 1412, 1368, 1328, 1206, 1165, 1131,

1030, 755; HiResMALDI-MS calcd for C₂₅H₃₃N₃O₈ [M+Na]⁺ 526.2165, found, 526.2155.

methyl (2'*R*,3*S*,5'*R*)-1'--1-((2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)carboxylate-2'-(1-hydroxy-2-methylpropyl)-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (55)

To a solution of diol **54** (88.0 mg, 0.175 mmol, 1.00 equiv) in EtOAc (5 mL) was added Pb(OAc)₄ (90.0 mg, 0.262 mmol, 1.50 equiv). A yellow suspension was obtained and after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc. Evaporation of the solvent and purification by column chromatography (3:1 EtOAc/hexanes) afforded **55** (72 mg, 87%) as a colorless oil.

R_f = 0.51 (3:1 EtOAc/hexanes), $[\alpha]_D^{24}$ (c 0.760, CHCl₃) = +16.0; ¹H NMR (300 MHz, CDCl₃) δ 9.05 (d, 1H, J = 4.7 Hz), 8.15 (br, 1H), 7.84 (d, 1H, J = 7.5 Hz), 7.23 (ddd, 1H, J = 7.5, 7.5, 0.9 Hz), 7.02 (ddd, 1H, J = 7.5, 7.5, 0.9 Hz), 6.87 (d, 1H, J = 7.5 Hz), 5.60 (dd, 1H, J = 8.4, 8.4 Hz), 4.53 (d, 1H, J = 4.7 Hz), 4.25 (dd, 1H, J = 8.1, 4.1 Hz), 3.82 (s, 3H), 3.55-3.38 (m, 2H), 2.78-2.61 (m, 2H), 2.34-1.96 (m, 3H), 1.92-1.80 (m, 1H), 1.49 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 195.0, 176.1, 173.9, 171.4, 154.5, 139.8, 129.3, 126.4, 125.4, 122.8, 110.4, 79.9, 70.3, 59.0, 56.9, 53.8, 52.9, 47.0, 40.4, 29.3, 28.4, 24.8; IR (thin film) ν 3250, 2979, 2251, 1732, 1681, 1652, 1651, 1474, 1404, 1367, 1272, 1210, 1165, 1131, 912, 732; HiResMALDI-MS calcd for C₂₄H₂₉N₃O₇ [M+Na]⁺ 494.1903, found, 494.1907.

methyl (2'*S*,3*S*,5'*R*)-1'--1-((2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)carboxylate-2'-(1-hydroxy-2-methylpropyl)-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (56)

A solution of aldehyde **55** (10.4 mg, 22.1 μmol , 1.00 equiv) in Et_2O (2 mL) was cooled to $-78\text{ }^\circ\text{C}$. $i\text{PrMgCl}$ (2.0 M in Et_2O , 16 μL , 33 μmol , 1.5 equiv) was added slowly and the reaction mixture was stirred for 2 h; then the mixture was allowed to reach room temperature slowly. After 14 h, Et_2O (5 mL) and sat. aq NH_4Cl (5 mL) were added, the layers were separated and the organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (1:1 EtOAc /hexanes) afforded **56** (11.1 mg, 97%) as colorless oil.

$R_f = 0.38$ (3:1 EtOAc /hexanes); ^1H NMR (300 MHz, CDCl_3) 8.25-7.85 (br, 1H), 7.61 (d, 1H, $J = 7.5$ Hz), 7.26-7.21 (m, 1H), 7.09-7.04 (m, 1H), 6.85 (d, 1H, $J = 7.8$ Hz), 5.28 (d, 1H, $J = 9.3$ Hz), 4.67 (s, 1H), 4.29-4.25 (m, 1H), 4.02 (d, 1H, $J = 12.1$ Hz), 3.76 (s, 3H), 3.54-3.43 (m, 2H), 3.31 (dd, 1H, $J = 13.1, 10.3$ Hz), 3.20-3.13 (m, 1H), 2.65 (d, 1H, $J = 13.1$ Hz), 2.47-2.38 (m, 1H), 2.27-2.09 (m, 2H), 1.92-1.49 (m, 3H), 1.28-1.23 (m, 9H), 0.87-0.83 (m, 6H); HiResMALDI-MS calcd for $\text{C}_{27}\text{H}_{37}\text{N}_3\text{O}_7$ $[\text{M}+\text{Na}]^+$ 538.2529, found, 538.2510.

(propane-2-sulfonyl)-benzene (**61**)

To a solution of sulfinate **60** (7.83 g, 47.7 mmol, 1.50 equiv) and Bu_4NI (750 mg) in H_2O /acetone (4:3, 17.5 mL) was added $i\text{PrI}$ (5.40 g, 31.8 mmol, 1.00 equiv) followed by benzene (7.5 mL). The reaction mixture was heated to reflux for 24 h, then cooled to room temperature and poured onto a mixture of H_2O (30 mL) and EtOAc (30 mL). The layers were separated and the organic layer was washed with 1 M aq $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL). The solvent was evaporated to afford a colorless oil. Purification by column chromatography (3:1 EtOAc /hexanes) afforded **61** (3.13 g, 36%) as colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.92-7.87 (m, 2H), 7.70-7.62 (m, 1H), 7.59-7.56 (m, 2H), 3.19 (quint, 1H, $J = 6.9$ Hz), 1.30 (d, 6H, $J = 6.9$ Hz).

5-(isopropylthio)-1-phenyl-1H-tetrazole (**66**)

To a mixture of *i*PrOH (79.0 μ l, 1.03 mmol, 1.00 equiv), triphenylphosphine (296 mg, 1.13 mmol, 1.10 equiv) and 2-phenyl-2*H*-tetrazole-5-thiol (**65**) (201 mg, 1.13 mmol, 1.10 equiv) in THF (12 ml) was added DEAD (178 μ l, 1.13 mmol, 1.10 equiv) dropwise over 10 min. The yellow solution was stirred at room temperature for 8 h and then concentrated under reduced pressure. A mixture of pentane and EtOAc (9:1, 20 ml) was added, the suspension was filtered over Celite and the filtrate concentrated under reduced pressure. Purification by flash chromatography (1:9 EtOAc/hexanes) provided 5-(isopropylsulfanyl)-1-phenyl-1*H*-tetrazole (**66**) (183 mg, 81% yield) as a colorless oil. R_f = 0.77 (1:3 EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.58-7.52 (m, 5H), 4.16 (quint, 1H, J = 6.5 Hz), 1.52 (d, 6H, J = 6.5 Hz).

5-(isopropylsulfonyl)-1-phenyl-1*H*-tetrazole (**67**)

To a solution of 5-(isopropylsulfanyl)-1-phenyl-1*H*-tetrazole (**66**) (183 mg, 0.831 mmol, 1.00 equiv) in methanol (8 mL) was added an aqueous solution (8 mL) of Oxone (1.53 g, 2.49 mmol, 3.00 equiv) at room temperature. After stirring at room temperature for 2 d, the mixture was diluted with Et_2O (20 mL), washed with H_2O (25 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography (1:4 EtOAc/hexanes) provided sulfone **67** (177 mg, 85% yield) as a white solid.

R_f = 0.38 (1:3 EtOAc/hexanes); mp = 67 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.69-7.56 (m, 5H), 4.03 (quint, 1H, J = 6.9 Hz), 1.52 (d, 6H, J = 6.9 Hz).

methyl (2'*S*,3*S*,5'*R*)-1'--{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-(2-methylprop-1-en-1-yl)-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (59**)**

To a solution of sulfone **67** (28.3 mg, 112 μmol , 2.30 equiv) in THF (0.7 mL) at -78°C was added dropwise LHMDs (0.330 M in THF, 340 μL , 120 μmol , 2.3 equiv). The yellow solution was stirred at -78°C for 30 min. This solution was added in one portion with a precooled syringe to a solution of aldehyde **55** (23.0 mg, 49.0 μmol , 1.00 equiv) in THF (0.7 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h; then the mixture was slowly warmed to room temperature and stirred for 8 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was purified by column chromatography (3:2 EtOAc/hexanes) to afford **59** (19 mg, 78%) as white crystals.

$R_f = 0.28$ (3:1 EtOAc/hexanes), $[\alpha]_D^{24}$ (c 0.985, CHCl_3) = +30.7; mp = 231°C ; ^1H NMR (300 MHz, CDCl_3 , # denotes major-, * minor rotamer signals) δ 7.92 (br, 2H), 7.51-7.45 (m, 1H*), 7.38-7.17 (m, 1H#), 7.12-6.96 (m, 4H), 6.89 (d, 1H#, $J = 7.5$ Hz), 6.81 (d, 1H*, $J = 7.5$ Hz), 5.50 (t, 1H*, $J = 7.8$ Hz), 5.50 (d, 1H*, $J = 9.7$ Hz), 5.22 (d, 1H*, $J = 9.7$ Hz), 4.98 (t, 1H*, $J = 9.0$ Hz), 4.84-4.70 (m, 2H#), 4.46 (dd, 1H#, $J = 8.7, 2.2$ Hz), 4.29 (dd, 1H*, $J = 8.1, 3.4$ Hz), 3.78 (s, 3H#), 3.73 (s, 3H*), 3.70-3.50 (m, 2H), 3.45-3.34 (m, 2H), 2.70-2.53 (m, 2H), 2.35-1.72 (m, 10H), 1.72 (s, 3H#), 1.59 (s, 9H#), 1.57 (s, 9H*), 1.53 (s, 3H#), 1.53 (s, 3H*), 1.51 (s, 3H*); ^{13}C NMR (75 MHz, CDCl_3) δ 176.0, 174.0, 171.2, 153.5, 139.9, 137.9, 129.5, 128.7, 123.7, 122.8, 121.4, 110.1, 80.2, 63.0, 60.7, 58.8, 57.2, 52.4, 46.8, 37.3, 32.2, 28.4, 25.9, 23.2, 18.3; IR (thin film) ν 3246, 2977, 2931, 1727, 1698, 1619, 1472, 1434, 1401, 1366, 1298, 1270, 1202, 1173, 1167, 752; HiResMALDI-MS calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ 520.2423, found, 520.2409.

Crystal data for **59** at 193 K, $M_r = 616.95$, orthorhombic space group $P2(1)2(1)2(1)$, $\rho_{\text{calc}} = 1.311 \text{ g}\cdot\text{cm}^{-3}$, $Z = 4$, $a = 8.9350(10)$, $b = 13.870(2)$, $c = 25.228(7) \text{ \AA}$, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00^\circ$, $V = 3126.5(10) \text{ \AA}^3$. Final $R(F) = 0.0608$, $wR(F^2) = 0.1778$ for 395 parameters and 2945 reflections with $I > 2\sigma(I)$ and $\theta < 69.98^\circ$.

CCDC 196804 (**59**) contains the supplementary crystallographic data for this structure. This data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

methyl (2'S,3S)-1'--{[(2S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-(2-methylprop-1-en-1-yl)-2-oxo-1,1',2,2'-tetrahydrospiro[indole-3,3'-pyrrole]-5'-carboxylate (68)

To a solution of **59** (9.0 mg, 180 μ mol, 1.0 equiv) in THF (1 mL) at 0 °C was added LHMDS (0.330 M in THF, 121 μ L, 400 μ mol, 2.20 equiv). The solution was kept at 0 °C for 30 min and a solution of phenylselenenyl chloride (7.6 mg, 400 μ mol, 2.2 equiv) in THF (1 mL) was added. The reaction mixture was stirred at 0 °C for 90 min, and quenched by addition of sat. aq NaHCO₃ (10 mL). The product was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The unpurified mixture was used without for the subsequent reaction.

R_f = 0.59, 0.51 (3:1 EtOAc/hexanes).

To a solution of the intermediate selenide in THF (0.5 mL) at 0 °C was added DMDO ($\approx$ 0.09 M in acetone, 80.0 μ L, 72.0 μ mol, 4.00 equiv). Stirring was continued for 3 h, the solvent was evaporated in vacuo. Column chromatography (11:9 EtOAc/hexanes) afforded **68** (6.9 mg, 74% over two steps) as a colorless oil.

R_f = 0.50 (3:1 EtOAc/hexanes), $[\alpha]_D^{25}$ (c 0.220, CHCl₃) = +42.0; ¹H NMR (300 MHz, CDCl₃, [#] denotes major-, * minor rotamer signals) δ 7.97-7.60 (br, 2H), 7.26-7.19 (m, 2H), 7.14-7.10 (m, 2H), 7.07-6.97 (m, 2H), 6.85 (d, 2H, J = 7.5 Hz), 5.71-5.67 (m, 2H*), 5.49-5.44 (m, 2H[#]), 5.31-5.23 (m, 2H), 4.52-4.48 (m, 1H*), 4.37-4.35 (m, 1H[#]), 3.85 (s, 3H[#]), 3.84 (s, 3H*), 3.68-3.55 (m, 2H), 3.47-3.29 (m, 2H), 2.18-1.65 (m, 8H), 1.58 (s, 6H), 1.50 (s, 9H[#]), 1.45 (s, 9H*), 1.42 (s, 3H*), 1.25 (s, 3H[#]); ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 171.7, 162.1, 153.6, 140.3, 140.0, 137.6, 129.1, 128.9, 127.5, 126.8, 122.3, 122.0, 109.8, 80.2, 65.5, 58.2, 52.6, 46.8, 31.5, 28.6, 25.4, 23.4, 18.3, 17.8; IR (thin film) ν 3248, 2977, 2932, 1732, 1694, 1619, 1472, 1400, 1366, 1260, 1228, 1164, 1126, 753; HiResMALDI-MS calcd for C₂₇H₃₃N₃O₆ [M+Na]⁺ 518.2267, found, 518.2276.

spirotryprostatin B (**1**)

A solution of **68** (4.7 mg, 10 mmol, 1.0 equiv) in CH₂Cl₂/TFA (5:1, 0.6 mL) was stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the product was dissolved in CH₂Cl₂ (0.5 mL), and NEt₃ (5.2 μL, 38 μmol, 4.0 equiv) was added. The reaction mixture was stirred at room temperature for 4 h, and quenched by addition of sat. aq NaHCO₃ (10 mL). The product was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. Column chromatography (75:20:8 CH₂Cl₂/EtOAc/*i*PrOH) afforded spirotryprostatin B (**1**) (2.6 mg, 74% over two steps) as a white solid.

R_f = 0.23 (75:20:8 CH₂Cl₂/EtOAc/*i*-PrOH), mp = 136 °C; $[\alpha]_D^{26}$ (*c* 0.045, CHCl₃) = -148.8; ¹H NMR (500 MHz, CDCl₃) δ 7.53 (br, 1H), 7.24 (ddd, 1H, *J* = 7.6, 7.6, 1.1 Hz), 7.07 (d, 1H, *J* = 7.6 Hz), 7.00 (ddd, 1H, *J* = 7.6, 7.6, 1.1 Hz), 6.85 (d, 1H, *J* = 7.6 Hz), 5.78 (s, 1H), 5.43 (d, 1H, *J* = 8.9 Hz), 5.21 (ddd, 1H, *J* = 8.9, 8.9, 1.4 Hz), 4.34 (dd, 1H, *J* = 10.7, 6.1 Hz), 3.80 (ddd, 1H, *J* = 12.2, 12.2, 8.2 Hz), 3.57 (m, 1H), 2.51-2.47 (m, 1H), 2.13-2.09 (m, 1H), 2.04-1.93 (m, 2H), 1.57 (s, 3H), 1.28 (d, 3H, *J* = 1.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 177.8, 162.6, 155.1, 140.3, 138.4, 138.3, 129.1, 127.9, 127.3, 122.3, 120.5, 116.3, 109.8, 64.2, 61.8, 61.6, 44.9, 29.3, 25.5, 22.1, 18.3; IR (thin film) ν 3212, 2926, 1855, 1725, 1682, 1644, 1471, 1434, 1326, 1293, 1215, 1157, 1105, 753; HiResMALDI-MS calcd for C₂₁H₂₁N₃O₃ [M+Na]⁺ 386.1481, found, 386.1478.

3.2. Synthesis of Spirotryprostatin B from Intermediate 41

Coupling of **41** with *N*-Boc-L-proline chloride.

To a solution of **41** (150 mg, 367 μ mol, 1.00 equiv) and NEt_3 (51.0 μ L, 367 μ mol, 1.00 equiv) in CH_2Cl_2 (13 mL) at 0 $^\circ\text{C}$ was added *N*-Boc-L-proline chloride (**45**) (0.140 M in CH_2Cl_2 , 6.70 mL, 918 μ mol, 2.50 equiv). The reaction mixture was allowed to warm slowly to room temperature and stirred for 8 h. The reaction was quenched by addition of 10% aq NaHCO_3 (10 mL). The phases were separated; the organic layer was washed with sat. aq NaHCO_3 (10 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (1:3 EtOAc/hexanes) afforded:

tert-butyl (2S)-2-((2'R,3S,5'R)-2-oxo-5'-[(1Z)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'H-spiro[indole-3,3'-pyrrolidin]-1'-yl)carboxylate (69)

White solid, 89 mg (40%).

R_f = 0.59 (1:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 0.425, CHCl_3) = -4.03 ; mp = 86-87 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 $^\#$ denotes major-, * minor rotamer signals) δ 8.47 (br, 1H*), 8.34 (br, 1H $^\#$), 7.37-7.13 (m, 4H), 7.10-6.99 (m, 2H), 6.94-6.84 (m, 2H), 5.66-5.41 (m, 4H), 5.41 (s, 1H*), 5.25-5.13 (m, 2H), 5.14 (s, 1H $^\#$), 4.95-4.68 (m, 2H), 3.69-3.34 (m, 4H), 2.39-1.96 (m, 8H), 1.85-1.64 (m, 10H), 1.55 (s, 9H $^\#$), 1.45 (s, 9H*), 0.82 (s,

42H); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 176.3*, 176.2, 173.3*, 172.9, 154.1*, 153.5, 140.1, 131.6*, 130.7, 128.7, 128.4*, 127.8, 127.1*, 124.8, 124.4*, 124.2, 123.7*, 122.9, 122.8*, 110.1*, 109.9, 102.0*, 101.1, 90.8, 89.5*, 79.9, 79.2*, 58.7, 57.9*, 57.7, 56.7, 56.5*, 56.1*, 54.5*, 47.3, 40.2, 40.0*, 32.2, 30.4*, 29.8*, 29.3, 28.8, 28.5*, 24.7, 23.5*, 18.5, 13.2, 13.1*, 11.0; IR (thin film) ν 3206, 2942, 2865, 2171, 1728, 1688, 1471, 1397, 1297, 1166, 1121, 883, 768, 752, 676; HiResMALDI-MS calcd for $\text{C}_{35}\text{H}_{51}\text{N}_3\text{SiO}_4$ $[\text{M}+\text{Na}]^+$ 628.3546, found, 628.3535.

***tert*-butyl (2*S*)-2-((2*S*,3*R*,5*S*)-2-oxo-5'-[(1*Z*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl}carbonyl)pyrrolidine-1-carboxylate (70)**

White solid, 87mg (39%).

R_f = 0.42 (1:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 0.450, CHCl_3) = -9.87; mp = 96 °C; ^1H NMR (300 MHz, CDCl_3 # denotes major-, * minor rotamer signals) δ 8.71 (br, 1H*), 8.57 (br, 1H#), 7.48 (d, 1H#, J = 7.5 Hz), 7.25-7.19 (m, 3H), 7.04-6.88 (m, 4H), 6.12-6.05 (m, 1H*), 5.71-5.45 (m, 3H), 5.29-5.15 (m, 2H), 5.19 (s, 1H*), 4.68-4.87 (m, 1H), 4.90 (s, 1H#), 3.68-3.36 (m, 4H), 2.70 (dd, 1H#, J = 13.1, 8.1 Hz), 2.32-2.10 (m, 5H), 2.00-1.77 (m, 7H), 1.73-1.67 (m, 6H), 1.48 (s, 9H#), 1.43 (s, 9H*), 0.96-0.95 (m, 21H*), 0.85-0.82 (m, 21 H#); ^{13}C NMR (75 MHz, CDCl_3 , * denotes minor rotamer signals) δ 178.6, 176.3*, 170.7, 170.3*, 154.2*, 154.1, 140.7, 140.3*, 133.2, 132.2*, 131.1, 130.5*, 128.7, 128.4*, 125.5, 125.5*, 124.8, 124.0*, 122.9*, 122.1, 110.1, 109.7*, 102.0, 99.0*, 91.9*, 87.3, 79.7, 79.1*, 59.1, 58.6*, 58.1, 57.0*, 56.4, 55.7*, 53.7*, 53.5, 46.5, 46.4*, 43.1, 39.3*, 30.2*, 29.7, 28.6, 28.5*, 23.3*, 22.9, 18.6, 18.4*, 13.3*, 13.0, 11.2, 11.0*; IR (thin film) ν 3208, 2942, 2865, 2171, 1728, 1704, 1676, 1621, 1472, 1399, 1366, 1265, 1166, 1125, 883, 749, 678; HiResMALDI-MS calcd for $\text{C}_{35}\text{H}_{51}\text{N}_3\text{SiO}_4$ $[\text{M}+\text{Na}]^+$ 628.3546, found, 628.3536.

***tert*-butyl (2*S*)-2-((2'*R*,3*S*,5'*R*)-5'-formyl-2-oxo-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl)carbonylpyrrolidine-1-carboxylate (49)**

A solution of **69** (21.6 mg, 35.7 μ mol, 1.00 equiv) and NMO $\cdot$ H₂O (5.0 mg, 43 μ mol, 1.2 equiv) in THF/*t*BuOH/H₂O (4:4:1, 1 mL) was stirred at room temperature for 30 min before OsO₄ (4 wt% in H₂O, 9.0 μ L, 1.4 μ mol, 4 mol%) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of 2 M aq Na₂S₂O₃ (2 mL) and EtOAc (5 mL) was added. The biphasic mixture was stirred for 3 h. The phases were separated; the organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The mixture of isomeric products **71** was used without further purification.

R_f = 0.16 (3:1 EtOAc/hexanes).

To a solution of diols **71** in EtOAc (1.5 mL) was added Pb(OAc)₄ (18.3 mg, 53.6 μ mol, 1.50 equiv). A yellow suspension was obtained and after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc. Purification by column chromatography (1:1 EtOAc/hexanes) afforded **49** (18 mg, 85%) as a white solid.

3.3. Synthesis of Spirotryprostatin B from Intermediate 43

Coupling of **43** with *N*-Boc-L-proline chloride.

To a solution of **43** (150 mg, 367 μmol , 1.00 equiv) and NEt_3 (51.0 μL , 367 μmol , 1.00 equiv) in CH_2Cl_2 (10 mL) at 0 $^\circ\text{C}$ was added *N*-Boc-L-proline chloride (0.140 M in CH_2Cl_2 , 7.00 mL, 929 μmol , 2.50 equiv). The reaction mixture was allowed to warm slowly to room temperature and stirred at room temperature for 8 h. The reaction was quenched by addition of 10% aq NaHCO_3 (10 mL). The phases were separated; the organic layer was washed with sat. aq NaHCO_3 (10 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (11:9 EtOAc/hexanes) afforded the product as a mixture of isomers **72/73** (182 mg, 82%), which were used for the following steps without further separation. R_f = 0.15 (1:1 EtOAc/hexanes).

Transformation to **74/75**

Dihydroxylation and diol cleavage:

A solution of **72/73** (122 mg, 202 μmol , 1.00 equiv) and $\text{NMO}\cdot\text{H}_2\text{O}$ (33.0 mg, 242 μmol , 1.20 equiv) in $\text{THF}/t\text{BuOH}/\text{H}_2\text{O}$ (4:4:1, 5 mL) was stirred at room temperature for 30 min before OsO_4 (4 wt% in H_2O , 52.0 μL , 81.0 μmol , 4 mol%) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of 2 M aq $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and EtOAc (5 mL). The biphasic mixture was stirred for 3 h. The phases were separated; the organic layer was washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The mixture of isomeric products was used without further purification.

$R_f = 0.27$ (3:1 $\text{EtOAc}/\text{hexanes}$).

To a solution of diols in EtOAc (10 mL) was added $\text{Pb}(\text{OAc})_4$ (104 mg, 303 μmol , 1.50 equiv). A yellow suspension was obtained and after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc . The mixture of isomeric products was used without further purification.

$R_f = 0.32$ (3:1 $\text{EtOAc}/\text{hexanes}$).

Oxidation and ester formation:

A solution of NaClO_2 (182 mg, 2.01 mmol, 10.0 equiv) in pH 3.6 buffer (3.5 mL) was added to a solution of the aldehydes and 2-methyl-2-butene (2.1 mL) in $t\text{BuOH}$ (7 mL). The reaction mixture was stirred at room temperature for 30 min, 2 M aq HCl was added (5 mL), and the product was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo.

$R_f = 0.06$ (3:1 $\text{EtOAc}/\text{hexanes}$).

The products were dissolved in Et_2O (4 mL) and a solution of CH_2N_2 in Et_2O (≈ 0.4 M in Et_2O) was added until the yellow color of CH_2N_2 persisted. The solvent was evaporated in vacuo and the unpurified products were used for the next reaction.

$R_f = 0.44$ (3:1 $\text{EtOAc}/\text{hexanes}$).

TIPS deprotection:

To a solution of the esters in THF (6 mL), was added TBAF (1.0 M in THF, 240 μ L, 240 μ mol, 1.2 equiv). The reaction mixture was stirred at room temperature for 8 h, and diluted with CH₂Cl₂. The organic solution was washed with sat. aq NaHCO₃, and dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by column chromatography (13:7 EtOAc/hexanes) to afford the two isomers **74** and **75** in combined yield of 72 mg (75%).

methyl (2'*R*,3*R*,5'*R*)-1'-{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-ethynyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (74**)**

Colorless solid, 46 mg (49%).

R_f = 0.22 (3:1 EtOAc/hexanes); mp = 142-144 °C $[\alpha]_D^{26}$ (c 1.00, CHCl₃) = +31.5; ¹H NMR (300 MHz, mixture of rotamers, only the major rotamer is described) δ 8.30 (br, 1H), 7.62 (d, 1H, J = 7.1 Hz), 7.31 (dt, 1H, J = 7.8, 1.2 Hz), 7.11-7.06 (m, 1H), 6.92 (d, 1H, J = 7.5 Hz), 4.88 (dd, 1H, J = 8.1, 9.7 Hz), 4.69 (d, 1H, J = 2.2 Hz), 4.58 (dd, 1H, J = 8.4, 2.2 Hz), 3.78 (s, 3H), 3.69-3.58 (m, 1H), 3.56-3.36 (m, 1H), 2.67 (d, 1H, J = 2.2 Hz), 2.57-2.46 (m, 3H), 2.19-1.71 (m, 3H), 1.49 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, mixture of rotamers, the two major ones are described) δ 179.4, 178.8, 171.8, 171.6, 171.4, 171.2, 154.2, 154.0, 141.7, 141.6, 132.1, 132.0, 129.5, 129.1, 128.6, 128.4, 125.9, 125.8, 125.4, 124.9, 122.1, 122.0, 110.3, 110.1, 80.3, 80.1, 79.7, 79.5, 78.7, 78.5, 58.4, 58.3, 57.6, 55.2, 55.1, 53.8, 53.0, 52.4, 46.9, 46.8, 40.7, 36.6, 30.0, 29.4, 28.5, 28.4, 23.4, 23.1, 14.3, 12.9; IR (thin film) ν 3233, 2977, 1716, 1621, 1473, 1403, 1364, 1331, 1262, 1240, 1168, 1128, 754; HiResMALDI-MS calcd for C₂₅H₂₉N₃O₆ [M+Na]⁺ 490.1954, found, 490.1945.

methyl (2'*S*,3*S*,5'*S*)-1'--{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-ethynyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (75)

Colorless oil, 25 mg (26%).

R_f = 0.37 (3:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 0.240, CHCl_3) = -8.7 ; ^1H NMR (300 MHz, CDCl_3 , mixture of 4 rotamers, relative integration is given) δ 8.53-8.51 (m, 0.8H), 8.42 (s, 0.07H), 8.39 (s, 0.13H), 7.64-7.54 (m, 1H), 7.34-7.20 (m, 1H), 7.13-7.01 (m, 1H), 6.93-6.88 (m, 1H), 5.50 (d, 0.08H, J = 2.3 Hz), 5.46 (d, 0.31H, J = 2.3 Hz), 5.29 (m, 0.15H), 5.15-5.03 (m, 0.8H), 4.87 (d, 0.46H, J = 2.3 Hz), 4.85-4.82 (m, 0.2H), 4.68-4.65 (m, 0.4H), 4.58-4.54 (m, 0.46H), 4.26-4.22 (m, 0.14H), 3.86 (s, 0.16H), 3.77-3.77 (m, 0.84H), 3.67-3.39 (m, 2H), 2.73 (d, 0.08H, J = 2.3 Hz), 2.70 (d, 0.46H, J = 2.3 Hz), 2.66 (d, 0.31H, J = 2.3 Hz), 2.58-2.41 (m, 1.15H), 2.39-2.06 (m, 3H), 1.98-1.74 (m, 2H), 1.52-1.28 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers) δ 178.7, 178.6, 172.3, 171.6, 171.5, 154.3, 153.7, 141.4, 141.3, 129.5, 126.2, 126.0, 125.7, 125.6, 125.4, 124.9, 122.2, 122.0, 110.2, 80.2, 80.0, 79.6, 79.5, 58.6, 58.2, 57.6, 56.0, 55.5, 54.5, 53.1, 53.0, 52.5, 52.4, 47.1, 36.5, 31.5, 30.2, 28.6, 28.5, 24.3, 22.0; IR (thin film) ν 3246, 2977, 2116, 1721, 1687, 1673, 1620, 1473, 1402, 1366, 1261, 1241, 1166; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ 490.1954, found, 490.1945.

(2*R*,3*R*,5*aS*,10*aR*)-3-ethynyl-5*a*,6,7,8-tetrahydro-1*H*,5*H*-spiro[dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,3'-indole]-2',5,10(1'*H*,10*aH*)-trione (76)

A solution of **74** (15.3 mg, 41.6 μmol , 1.00 equiv) in $\text{CH}_2\text{Cl}_2/\text{TFA}$ (5:1, 2 mL) was stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the product was dissolved in CH_2Cl_2 (1 mL), and NEt_3 (22.8 μL , 166 μmol , 4.00 equiv) was added. The reaction mixture was stirred at room temperature for 4 h, and quenched by addition of sat. aq NaHCO_3 (10 mL). The product was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The

combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. Column chromatography (75:20:8 CH₂Cl₂/EtOAc/*i*PrOH) afforded **76** (6.0 mg, 43% over two steps) as a colorless oil.

R_f = 0.24 (75:20:8 CH₂Cl₂/EtOAc/*i*PrOH), $[\alpha]_D^{23}$ (*c* 0.250, CHCl₃) = -74.1; ¹H NMR (300 MHz, CDCl₃) δ 8.14 (br, 1H), 7.45 (d, 1H, *J* = 7.6 Hz), 7.29 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.08 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 6.91 (d, 1H, *J* = 7.6 Hz), 5.12 (ddd, 1H, *J* = 11.8, 8.1, 5.6 Hz), 4.91 (d, 1H, *J* = 2.5 Hz), 4.22 (ddd, 1H, *J* = 11.8, 68.1, 2 Hz), 4.06 (ddd, 1H, *J* = 15.6, 9.3, 6.8 Hz), 3.30 (ddd, 1H, *J* = 12.5, 10.0, 5.0 Hz), 2.66 (dd, 1H, *J* = 13.1, 5.6 Hz), 2.58 (d, 1H, *J* = 2.5 Hz), 2.57-2.38 (m, 1H), 2.18-1.79 (m, 4H); ¹³C NMR (125 MHz, CDCl₃,) δ 179.6, 165.0, 164.4, 140.7, 129.4, 126.6, 122.7, 110.0, 109.7, 78.1, 62.7, 58.0, 54.2, 53.3, 44.5, 38.6, 28.5, 22.1, 20.6; IR (thin film) ν 3262, 2925, 2125, 1715, 1660, 1619, 1472, 1445, 1311, 1189, 755; HiResMALDI-MS calcd for C₁₉H₁₇N₃O₃ [M+Na]⁺ 336.1343, found, 336.1350.

methyl (2'S,3S,5'R)-1'--[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl]-2-oxo-2'-vinyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (77)

To a solution of **75** (170 mg, 364 μ mol, 1.00 equiv) and quinoline (22.0 μ L, 182 μ mol, 0.50 equiv) in EtOH (4 mL) was added Pd/BaSO₄ (50 mg, 33 wt%). The reaction mixture was stirred at room temperature under H₂ atmosphere for 24 h. The solution was filtered over Celite to remove the catalyst and the solvent was evaporated in vacuo. The product was purified by column chromatography (57:43 EtOAc/hexanes) to afford **77** (167 mg, 98%) as a colorless oil.

R_f = 0.32 (3:1 EtOAc/hexanes), $[\alpha]_D^{22}$ (*c* 0.735, CHCl₃) = -9.6; ¹H NMR (300 MHz, CDCl₃ mixture of 4 rotamers, relative integration is given) δ 8.85-8.77 (m, 0.55H), 8.65 (s, 0.38H), 8.58 (s, 0.07H), 7.57 (d, 0.26H, *J* = 8.1 Hz), 7.32-7.12 (m, 1.74H), 7.09-6.85 (m, 2H), 5.99-5.84 (m, 0.68H), 5.77-5.29 (m, 2H), 5.22-5.20 (m, 0.32H), 5.14-5.03 (m, 1H), 4.95-4.83 (m, 0.55H), 4.68-4.64 (m, 0.45H), 4.58-4.55 (m, 0.15H), 4.43-4.36 (m, 0.69H), 4.29-4.22 (m, 0.16H), 3.86-3.85 (m, 0.25H), 3.87-3.86 (m, 2.57H), 3.67-3.33

(m, 2H), 2.70-2.18 (m, 2.85H), 2.11-1.74 (m, 3.15H), 1.48-1.40 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3 , mixture of 4 rotamers) δ 180.5, 179.7, 179.6, 178.7, 178.5, 173.5, 173.2, 172.4, 172.3, 171.8, 171.6, 171.4, 154.3, 154.2, 153.7, 153.6, 141.5, 141.4, 136.0, 135.9, 129.4, 129.3, 129.0, 128.9, 126.2, 126.2, 126.0, 122.0, 121.8, 121.7, 119.5, 119.1, 110.3, 110.2, 80.0, 79.6, 79.4, 79.3, 65.0, 64.0, 58.6, 58.5, 58.2, 57.9, 57.6, 57.4, 57.2, 56.9, 56.2, 55.9, 55.5, 54.5, 54.0, 52.9, 52.4, 52.4, 52.3, 47.2, 47.1, 36.4, 35.9, 35.8, 32.0, 31.5, 30.7, 30.2, 29.7, 29.1, 28.5, 24.3, 23.0; IR (thin film) ν 3242, 2977, 1721, 1687, 1473, 1403, 1366, 1257, 1242, 1202, 1167, 1125, 754, 668; HiResMALDI-MS calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ 492.2110, found, 492.2105.

methyl (2'R,3S,5'R)-1'--{[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-formyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (78)

A solution of **77** (60.0 mg, 128 μmol , 1.00 equiv) and $\text{NMO}\cdot\text{H}_2\text{O}$ (21.0 mg, 154 μmol , 1.20 equiv) in THF/*t*BuOH/ H_2O (4:4:1, 5 mL) was stirred at room temperature for 30 min before OsO_4 (4 wt% in H_2O , 813 μL , 128 μmol , 1.00 equiv) was added. The reaction mixture was stirred at room temperature for 2 d. The reaction was quenched by addition of 2 M aq $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and EtOAc (5 mL). The biphasic mixture was stirred for 6 h. The phases were separated; the organic layer was washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by column chromatography (3:2 EtOAc/hexanes) afforded the diol as colorless oil.

R_f = 0.10 (3:1 EtOAc/hexanes).

To a solution of the unpurified diol in EtOAc (5 mL) was added $\text{Pb}(\text{OAc})_4$ (43.0 mg, 125 μmol , 1.00 equiv). A yellow suspension was obtained, and, after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc. Evaporation of the solvent and purification by column chromatography (7:3 EtOAc/hexanes) afforded **78** (38 mg, 63%) as a colorless oil.

R_f = 0.49 (3:1 EtOAc/hexanes), $[\alpha]_D^{24}$ (*c* 1.650, CHCl_3) = -0.2 ; ^1H NMR (300 MHz, CDCl_3 , mixture of 4 rotamers, relative integration is given) δ 9.82-9.76 (m, 0.62H), 9.62

(d, 0.38H, $J = 2.8$ Hz), 9.04-8.95 (m, 0.52H), 8.83-8.69 (m, 0.48H), 7.29-7.20 (m, 1H), 7.12-6.87 (m, 3H), 5.24-4.87 (m, 1.48H), 4.83 (d, 0.18H, $J = 2.8$ Hz), 4.76-4.63 (m, 0.24H), 4.57-4.52 (m, 0.28H), 4.48-4.48 (m, 0.10H), 4.41-4.37 (m, 0.25H), 4.22-4.15 (m, 0.47H), 3.90 (s, 0.63H), 3.87 (s, 0.66H), 3.82-3.78 (m, 1.71H), 3.67-3.35 (m, 2H), 2.92-2.77 (m, 0.27H), 2.74-2.54 (m, 0.79H), 2.45-2.25 (m, 1.11H), 2.21-1.75 (m, 3.83H), 1.47-1.39 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3 , mixture of 4 rotamers) δ 197.3, 197.2, 178.2, 177.8, 173.0, 172.6, 172.0, 171.5, 154.1, 153.6, 141.0, (132.0), (131.9), 129.8, 129.5, (128.5), (128.3), 126.3, 125.5, 125.3, 124.8, 123.1, 122.7, 122.2, 110.7, 110.2, 80.4, 80.3, 79.8, 79.3, 70.2, 69.8, 69.3, 67.3, 60.0, 59.4, 58.3, 57.4, 56.4, 53.3, 53.1, 52.7, 47.0, 46.8, 40.4, 37.3, 31.2, 30.0, 29.7, 29.2, 28.5, 28.5, 24.5, 24.0, 23.3, 23.2; HiResMALDI-MS calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_7$ $[\text{M}+\text{Na}]^+$ 494.1903, found, 494.1894.

methyl (2'*S*,3*S*,5'*R*)-1'--[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-(2-methylprop-1-en-1-yl)-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (79)

To a solution of sulfone **67** (10.6 mg, 41.9 μmol , 2.50 equiv) in THF (0.5 mL) at -78°C was added dropwise LHMDS (0.330 M in THF, 123 μL , 41.9 μmol , 2.50 equiv). The yellow solution was stirred at -78°C for 30 min. This solution was added in one portion with a precooled syringe to a solution of aldehyde **78** (7.9 mg, 17 μmol , 1.0 equiv) in THF (0.5 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h; then the mixture was slowly warmed to room temperature and stirred for 8 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was purified by column chromatography (11:9 EtOAc/hexanes) to afford **79** (5.7 mg, 68%) as a colorless oil,

$R_f = 0.33$ (3:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 0.135, CHCl_3) = -0.0 ; ^1H NMR (500 MHz, CDCl_3 , mixture of 4 rotamers, relative integration is given) δ 7.82 (br, 1H), 7.24-7.17 (m, 1H), 7.14-7.05 (m, 1H), 7.03-6.93 (m, 1H), 6.89-6.84 (m, 1H), 5.56-5.51 (m, 0.82H),

5.44-5.34 (m, 0.32H), 5.22 (d, 0.16H, $J = 9.7$ Hz), 5.17 (d, 0.18H, $J = 9.2$ Hz), 5.11-5.06 (m, 0.82H), 4.89-4.86 (m, 0.18H), 4.81 (d, 0.52H, $J = 9.3$ Hz), 4.46-4.36 (m, 0.42H), 4.27-4.25 (m, 0.46H), 4.20-4.18 (m, 0.12H), 3.86 (s, 0.40H), 3.79-3.74 (m, 2.60H), 3.64-3.59 (m, 0.68H), 3.57-3.52 (m, 0.32H), 3.49-3.34 (m, 1H), 2.63-2.77 (m, 0.32H), 2.57-2.50 (m, 0.68H), 2.45-2.21 (m, 1.19H), 2.12-1.91 (m, 2.51H), 1.80-1.71 (m, 1.30H), 1.70 (s, 1.30H), 1.70 (s, 2.06H), 1.44-1.43 (m, 9H), 1.70 (s, 0.94H), 1.70 (s, 1.03 H), 1.70 (d, 1.20H, $J = 1.0$ Hz), 1.70 (s, 0.77H); ^{13}C NMR (125 MHz, CDCl_3 , mixture of 4 rotamers) δ 179.3, 172.9, 172.3, 153.8, 140.7, 137.1, 132.2, 132.0, 128.8, 128.5, 127.0, 126.4, 123.3, 122.8, 122.0, 121.6, 120.6, 109.4, 109.3, 79.9, 79.8, 61.7, 61.6, 58.9, 58.6, 58.5, 57.8, 57.6, 52.4, 52.3, 46.9, 36.0, 35.8, 31.3, 29.9, 29.7, 28.5, 28.5, 28.3, 25.5, 25.3, 24.1, 23.0, 17.8, 17.7; IR (thin film) ν 3227, 2976, 1724, 1695, 1624, 1468, 1401, 1366, 1260, 1242, 1202, 1167, 1118, 755; HiResMALDI-MS calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ 520.2423, found, 520.2413.

methoxy (2'S,3S)-1'-{[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-(2-methylprop-1-en-1-yl)-2-oxo-1,1',2,2'-tetrahydrospiro[indole-3,3'-pyrrole]-5'-carboxylate (68)

To a solution of **79** (3.3 mg, 6.6 μmol , 1.0 equiv) in THF (1 mL) at 0 °C was added LHMDS (0.330 M in THF, 76.0 μL , 25.2 μmol , 3.80 equiv). The solution was kept at 0 °C for 30 min and a solution of phenylselenenyl chloride (4.8 mg, 25 μmol , 3.8 equiv) in THF (1 mL) was added. The reaction mixture was stirred at 0 °C for 90 min; and then quenched by addition of sat. aq NaHCO_3 (6 mL). The product was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The mixture of isomeric products was used for elimination without further purification.

$R_f = 0.59, 0.51$ (3:1 EtOAc/hexanes).

To a solution of the selenide in THF (1 mL) at 0 °C was added DMDO (≈ 0.09 M in acetone, 300 μL , 265 μmol , 4.00 equiv). After stirring for 3 h, the solvent was evaporated

in vacuo. Preparative TLC (3:1 EtOAc/hexanes) afforded **68** (1.3 mg, 40% over two steps) as a colorless oil.