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Supporting Information

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Total Synthesis of (-)-Spirotryprostatin B

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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 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). Benzene was distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen. Triethylamine and pyridine were distilled from KOH. 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and quinoline were distilled prior to use. Butyl lithium (*n*BuLi) was titrated with *s*BuOH/phenanthroline. All other commercially available reagents were used without further purification. Diazomethane (CH_2N_2) and dimethyldioxirane (DMDO) were prepared according to literature procedures.[1]

Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F^{254} 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.[2] 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

[1] a) H. M. Fales, T. M. Jaouni, J. F. Babashak, *Analytical Chemistry* **1973**, *45*, 2302-2303; b) W. Adam, J. Bialas, L. Hadjiarapoglou, *Chemische Berichte* **1991**, *124*, 2377. Preparation of useful reagents and buffers, see last page.
[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

vacuum (0.01 Torr). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

NMR spectra were recorded either on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C acquisitions respectively or on a Bruker DRX500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C 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 ^{1}H, and chloroform (δ 77.0) and benzene (δ 128.0) for ^{13}C. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, 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 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 ml), and solvent.

Crystallographic structure determinations were performed on a Nonius CAD4 diffractometer, $Cu_{K\alpha}$ radiation (λ = 1.5418 Å). The structure was solved by direct methods[3] and refined by full-matrix least-squares analysis[4] 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.

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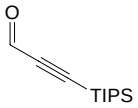
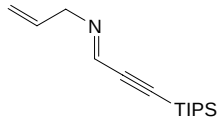
[3] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, J. Appl. Crystallogr., **1994**, *27*, 435.

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



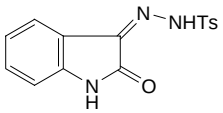
Triisopropylsilanyl-propynal

A solution of triisopropylsilanyl-acetylene (15.0 mL, 67.5 mmol, 1.00 equiv) in 100 mL THF was cooled to -78 °C. *n*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 °C for 0.5 h. A solution of ethyl formate (10.9 mL, 135 mmol, 2.00 equiv) in 100 mL THF was added dropwise. The reaction mixture was stirred for 45 min at -78 °C and then poured on 100 ml ice-water containing a trace of hydroquinone and 1 ml of acetic acid. The product was extracted with Et_2O (2 x 200 ml), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used for subsequent imine formation without further purification. R*f* = 0.89 (1:3 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 1.12-1.10 (m, 21H).



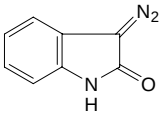
Ally-(3-triisopropylsilanyl-prop-2-ynylidene)-amine (10)

A solution of the crude triisopropylsilanyl-propynal (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 rt for 9 h. The reaction mixture turns slightly orange. The $MgSO_4$ was filtered off and the filter cake was washed with CH_2Cl_2 (3 x 20 mL). The solvent was evaporated in vacuo and the crude product was purified by distillation under reduced pressure (0.5 mbar, 90-95 °C) to afford the pure imine **10** as a colourless liquid: 13.42 g (80 % over two steps, *Z* and *E* isomer). R*f* = 0.50, 0.38 (1:50 EtOAc/hexanes); ^{1}H 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 Hz), 4.16 (dddd, 1H, *J* = 5.6, 1.9, 1.9, 1.3 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 calcd for $C_{15}H_{27}NSi$ $[M]^+$ 250.2; found, 249.2. Anal. Calcd for $C_{15}H_{27}NSi$: C, 72.22; H, 10.91; N, 5.61. Found: C, 72.25; H, 10.84; N, 5.57.



4-methyl-*N*'-[(3*Z*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]benzenesulfonohydrazide

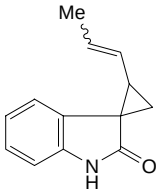
Isatin (9.44 g, 64.2 mmol, 1.00 equiv) was suspended in MeOH (300 mL). The suspension was heated to reflux whereupon a deep red solution was obtained. To this hot solution was added tosylhydrazine (12.1 g, 64.8 mmol, 1.02 equiv) in one portion. A yellow product starts precipitating from the hot mixture. The reaction mixture was allowed to cool to rt and the pure tosylhydrazone was filtered off: 18.2 g (90 %). R*f* = 0.12 (EtOAc); MP = 207 °C; ^{1}H 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 (8)

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 water-bath at 50 °C, then allowed to cool to rt. The reaction mixture was neutralized by addition of dry ice, whereupon the diazoketone precipitated: 5.36 g (88 %). The product was directly used in the subsequent reaction. R*f* = 0.54 (3:1 EtOAc/hexanes); MP = 168 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br, 1H,), 7.21-7.06 (m, 3H), 7.01-6.98 (m, 1H).

Cyclopropanation of piperylene with 8 (9)



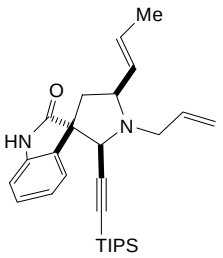
2-[prop-1-en-1-yl]spiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (9)

In a 3-neck flask equipped with a reflux condenser and an addition funnel was placed $[Rh(OAc)_2]_2$ (214 mg, 0.485 mmol, 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 **8** (7.72 g, 48.5 mmol, 1.00 equiv) in CH_2Cl_2 (340 mL) was added over 3 h. The reaction mixture was allowed to cool to RT 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 the crude material was purified by column chromatography (1:3 EtOAc/hexanes) to afford the pure product as a mixture of isomeric products **9** 69.1 g (71 %). The mixture was used without further purification in the upcoming ring-expansion step.

Ring expansion of 9 with 10 and allyl-deprotection (13)

A sealable tube with side inlet was charged with MgI_2 (5.69 g, 20.5 mmol, 1.00 equiv). A solution of cyclopropane **9** (4.08 g, 20.5 mmol, 1.00 equiv) in THF (35 mL) was added via cannula, followed by imine **10** (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 rt. EtOAc (250 mL) and H_2O (150 mL) were added to the reaction mixture, followed by $Na_2S_2O_3$ (1.5 g). 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. The following products were obtained by careful column chromatography purification (4:21 EtOAc/hexanes):



(±)-(2'*R*,3*S*,5'*S*)-1'-allyl-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (5'*S*-11)

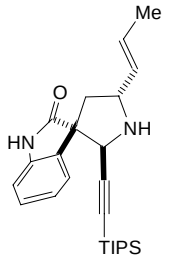
pale yellow solid, 2.93 g (32 %) R*f* = 0.59 (1:3 EtOAc/hexanes); MP = 121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (br, 1H), 7.50 (d, 1H, *J* = 7.5 Hz), 7.14 (ddd, 1H, *J* = 1.3, 7.5,

7.5 Hz), 7,00 (ddd, 1H, *J* = 1.3, 7.5, 7.5 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* = 8.1, 13.1 Hz), 1.82 (dd, 1H, *J* = 8.1, 13.7 Hz), 1.58 (ddd, 3H, *J* = 1.3, 6.2, 8.8 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 $C_{28}H_{40}N_2SiO$ $[M+H]^+$ 449.2988; found, 449.2989. Anal. Calcd for $C_{28}H_{40}N_2SiO$: C, 74.95; H, 8.98; N, 6.24. Found: C, 74.95; H, 8.89; N, 6.01.

N-allyl-spiro-pyrrolidine-oxindole **11**, mixture of isomers
2.90 g (32 %) R*f* = 0.45 (1:3 EtOAc/hexanes).

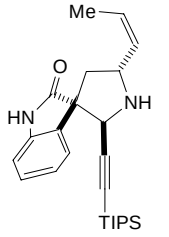
Allyl-deprotection of 11 (13)

To a solution of **11** (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 $Pd(PPh_3)_4$ (from 212 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.205 mmol, 6 mol% Pd) and 323 mg PPh_3 (1.232 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 x 175 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (1.5:8.5 → 1:4 EtOAc/hexanes) afforded:



(±)-(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 (13)

pale yellow oil 1.68 g (60 %). R*f* = 0.71 (1:3 EtOAc/hexanes); ^{1}H 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, 7.47 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 $C_{25}H_{36}N_2SiO$ $[M+H]^+$ 409.2675; found, 409.2674; Anal. Calcd for $C_{25}H_{36}N_2SiO$: C, 73.48; H, 8.88; N, 6.85. Found: C, 73.29; H, 8.97; N, 6.66.

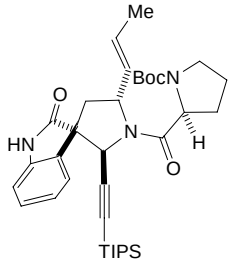


(±)-(2'*R*,3*S*,5'*R*)-5'-[(1*Z*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]spiro[indole-3,3'-pyrrolidin]-2(1*H*)-one (iso-13)

pale yellow oil 350 mg (13 %). R*f* = 0.53 (1:3 EtOAc/hexanes); ^{1}H 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 $C_{25}H_{36}N_2SiO$ $[M+H]^+$ 409.2675; found, 409.2676.

Coupling of 13 with Boc-L-ProCl[5] (14)

To a solution of **13** (141 mg, 0.345 mmol, 1.00 equiv) and NEt_3 (48.0 µL, 0.345 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added *N*-Boc-L-proline chloride (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 RT and stirred at RT 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:

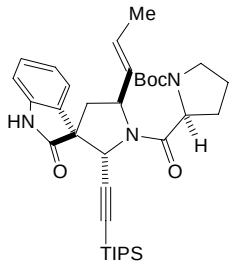


***tert*-butyl (2*S*)-2-({(2'*R*,3*S*,5'*R*)-2-oxo-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl}carbonyl)pyrrolidine-1-carboxylate (14)**

white crystals 94 mg (45 %). R*f* = 0.63 (1:1 EtOAc/hexanes), $[\alpha]_D^{23}$ (c 0.250 $CHCl_3$) = +15.6; MP = 191 °C; ^{1}H 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); ^{13}C NMR (75 MHz, $CDCl_3$, * 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 $C_{35}H_{51}N_3SiO_4$ $[M+Na]^+$ 628.3546; found, 628.3491; Anal. Calcd for $C_{35}H_{51}N_3SiO_4$: C, 69.38; H, 8.48; N, 6.94. Found: C, 69.40; H, 8.36; N, 6.92.

Crystal data for **14** at 223 K, M_r = 605.88, monoclinic space group *P2(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) Å^3. Final R(F) = 0.0564, wR(F^2) = 0.1601 for 464 parameters and 3015 reflections with $I > 2\sigma(I)$ and $\theta < 64.99°$. The *i*Pr$_3$Si groups in **14** are diordered. 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 (**14**) 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).



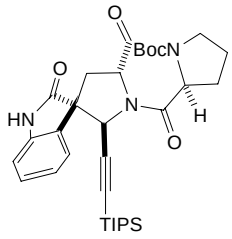
***tert*-butyl (2*S*)-2-({(2'*S*,3*R*,5'*S*)-2-oxo-5'-[(1*E*)-prop-1-en-1-yl]-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl}carbonyl)pyrrolidine-1-carboxylate (iso-14)**

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 °C; ^{1}H 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 Hz), 7.26-7.14 (m, 3H), 7.0-6.93 (m, 2H), 6.90-6.84 (m, 2H), 6.09* (ddd, 1H, J = 1.9,8.7, 15.6 Hz), 5.76-5.59 (m, 2H), 5.52$^{\#}$ (dd, 1H, J = 3.7, 8.7 Hz), 5.41* (ddd, 1H, J = 1.9, 7.5, 15.6 Hz), 5.17* (s, 1H),

[5] Preparation of useful reagents and buffers, see last page.

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* = 8.7, 13.7 Hz), 2.28-2.09 (m, 5H), 1.92-1.72 (m, 6 H), 1.76[#] (dd, 3H, *J* = 1.3, 6.2 Hz), 1.68* (dd, 3H, *J* = 1.3, 6.2 Hz), 1.47[#] (s, 9H), 1.42* (s, 9H), 0.96-0.95* (m, 21H), 0.83-0.82[#] (m, 21 H); ^{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 $C_{35}H_{51}N_3SiO_4$ $[M+Na]^+$ 628.3546; found, 628.3535.

Dihydroxylation and diol cleavage of 14 (15)



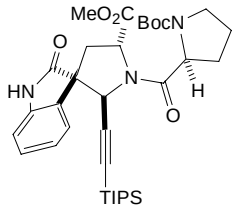
***tert*-butyl (2*S*)-2-({(2'*R*,3*S*,5'*R*)-5'-formyl-2-oxo-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydro-1'*H*-spiro[indole-3,3'-pyrrolidin]-1'-yl}carbonyl)pyrrolidine-1-carboxylate (15)**

A solution of **14** (405 mg, 0.668 mmol, 1.00 equiv) and NMO·H_2O (108 mg, 0.802 mmol, 1.20 equiv) in THF:*t*BuOH:H_2O 4:4:1 (20 mL) was stirred at RT 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 RT for 16 h, then quenched by addition of 2 M aq. $Na_2S_2O_3$ (25 mL) and EtOAc (25 mL). The biphasic mixture was stirred for 3h, the phases separated; the organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was used without further purification. R*f* = 0.67, 0.51 (3:1 EtOAc/hexanes).

To a solution of diols in EtOAc (20 mL) was added $Pb(OAc)_4$ (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 **15** as a white solid: 385 mg, (97%) R*f* = 0.83 (3:1 EtOAc/hexanes), MP = 90 °C; $[\alpha]_D^{26}$ (c 0.290 $CHCl_3$) = +50.8; ^{1}H 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 $C_{33}H_{47}N_3SiO_5$ $[M+Na]^+$ 616.3183; found, 616.3158; Anal. Calcd for $C_{33}H_{47}N_3SiO_5$: C, 66.75; H, 7.98; N, 7.08. Found: C, 66.91; H, 7.82; N, 6.87.

Oxidation and esterification of 15 (16)



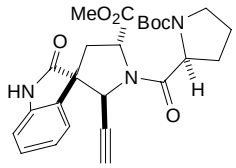
methyl (2'*R*,3*S*,5'*R*)-1'-{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2-oxo-2'-[(triisopropylsilyl)ethynyl]-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (16)

A solution of $NaClO_2$ (73 mg, 0.808 mmol, 10.0 equiv) in pH 3.6-buffer[6] (1.5 ml) was added to a solution of aldehyde **15** (48 mg, 810 μmol, 1.00 equiv) and 2-methyl-2-butene (1 mL) in *t*BuOH (3 mL). The reaction mixture was stirred at RT for 30 min, 2 M aq. HCl was added (10 mL), and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo; R*f*

[6] Preparation of useful reagents and buffers, see last page.

= 0.08 (3:1 EtOAc/hexanes). The crude product was dissolved in Et_2O (5 mL) and a solution of CH_2N_2 in Et_2O (≈ 0.4M in Et_2O)[7] was added till the yellow color of CH_2N_2 persisted. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (4:6 EtOAc/hexanes) to afford **16** as a white solid, 45 mg, (89 %); R*f* = 0.81 (3:1 EtOAc/hexanes), MP = 95 °C; $[\alpha]_D^{26}$ (c 1.525 $CHCl_3$) = +47.7; ^{1}H NMR (300 MHz, $CDCl_3$ # 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); ^{13}C NMR (75 MHz, $CDCl_3$, * 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 $C_{34}H_{49}N_3SiO_6$ $[M+Na]^+$ 646.3288; found, 646.3277; Anal. Calcd for $C_{34}H_{49}N_3SiO_6$: C, 65.46; H, 7.92; N, 6.74. Found: C, 65.72; H, 7.98; N, 6.57.

TIPS deprotection of 16 (17)



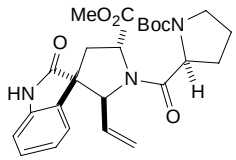
methyl (2'*S*,3*S*,5'*R*)-1'-{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-ethynyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (17)

To a solution of **16** (134 mg, 0.215 mmol, 1.00 equiv) in THF (5 mL), was added TBAF (1 M in THF, 260 μL, 0.258 mmol, 1.20 equiv). The reaction mixture was stirred at RT for 8 h, diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography

[7] Preparation of useful reagents and buffers, see last page.

(13:7 EtOAc/hexanes) to afford **17** as a white solid, 99 mg, (99 %); R*f* = 0.43 (3:1 EtOAc/hexanes), MP = 97 °C; $[\alpha]_D^{24}$ (c 1.340 $CHCl_3$) = +24.4; ^{1}H 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* = 5.0, 9.3 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 $C_{25}H_{29}N_3O_6$ $[M+Na]^+$ 490.1954; found, 490.1944; Anal. Calcd for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.18; H, 6.36; N, 8.90.

Hydrogenation of 17 (18)

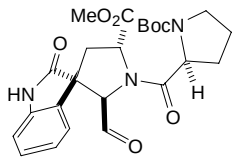


methyl (2'*S*,3*S*,5'*R*)-1'-{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2-oxo-2'-vinyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (18)

To a solution of **17** (20 mg, 430 μmol, 1.00 equiv) and quinoline (2.6 μL, 220 μmol, 0.50 equiv) in EtOH (2 mL), was added Pd/$BaSO_4$ (6.6 mg, 33 wt%). The reaction mixture was stirred at RT under H_2 atmosphere for 10 h. The solution was filtered over Celite and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (7:3 EtOAc/hexanes) to afford **18** as a white solid, 18 mg, (90 %); R*f* = 0.45 (3:1 EtOAc/hexanes), MP = 112 °C; $[\alpha]_D^{24}$ (c 1.590 $CHCl_3$) = -3.4; ^{1}H 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.

Dihydroxylation of 18 and diol cleavage (19)

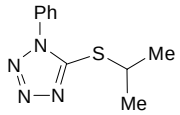


methyl (2'*R*,3*S*,5'*R*)-1'-{[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]carbonyl}-2'-formyl-2-oxo-1,2-dihydrospiro[indole-3,3'-pyrrolidine]-5'-carboxylate (19)

A solution of **18** (17 mg, 360 μmol, 1.00 equiv) and NMO·H_2O (6 mg, 430 μmol, 1.20 equiv) in THF:*t*BuOH:H_2O 4:4:1) (1 mL) was stirred at RT for 30 min before OsO_4 was added (4 wt%in H_2O, 230 μL, 360 μmol, 1 equiv). The reaction mixture was stirred at RT for 3 d. The reaction was quenched by addition of a 2 M aq. $Na_2S_2O_3$ (2 mL) and EtOAc (2 mL). The biphasic mixture was stirred for 6 h. The phases were separated; the organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (3:1 EtOAc/hexanes) afforded the diol as colourless oil: 16 mg (88 %). R*f* = 0.18 (3:1 EtOAc/hexanes), $[\alpha]_D^{26}$ (c 1.545 $CHCl_3$) = -1.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (br, 1H), 7.67 (d, 1H, *J* = 7.5 Hz), 7.20 (ddd, 1H, *J* = 1.3, 7.5, 7.5 Hz), 7.03 (ddd, 1H, *J* = 1.3, 7.5, 7.5 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* = 4.4, 8.1 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* = 10.0, 13.7 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); ^{13}C NMR (75 MHz, $CDCl_3$,) 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 $C_{25}H_{33}N_3O_8$ $[M+Na]^+$ 526.2165; found, 526.2155.

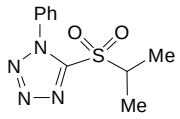
To a solution of the diol (88 mg, 0.175 mmol, 1.00 equiv) in EtOAc (5 mL) was added $Pb(OAc)_4$ (90 mg, 0.262 mmol, 1.50 equiv). A yellow suspension was obtained and after stirring for 10 min, the mixture was filtered through a plug of silica gel, eluting with EtOAc. Evaporation of the solvent and purification by column chromatography (3:1 EtOAc/hexanes) afforded **19** as a colourless oil: 72 mg, (87 %); R*f* = 0.51 (3:1 EtOAc/hexanes), $[\alpha]_D^{24}$ (c 0.760 $CHCl_3$) = +16.02; ^{1}H NMR (300 MHz, $CDCl_3$) 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* = 0.9, 7.5, 7.5 Hz), 7.02 (ddd, 1H, *J* = 0.9, 7.5, 7.5 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* = 4.1, 8.1 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); ^{13}C NMR (75 MHz, $CDCl_3$,) 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 $C_{24}H_{29}N_3O_7$ $[M+Na]^+$ 494.1903; found, 494.1907.



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

To a mixture of *i*PrOH (79 µl, 1.03 mmol, 1.00 equiv), triphenylphosphine (296 mg, 1.13 mmol, 1.10 equiv) and 2-phenyl-2*H*-tetrazole-5-thiol (201 mg, 1.13 mmol, 1.10 equiv) in THF (12 ml) was added DEAD (178 µl, 1.128 mmol, 1.10 equiv) dropwise over 10 min. The yellow solution was stirred at RT 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-(iso-

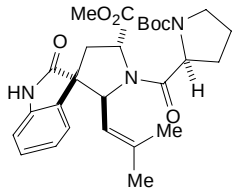
propylsulfanyl)-1-phenyl-1*H*-tetrazole (183 mg, 81 % yield) as colourless oil. R*f* = 0.77 (1:3 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.52 (m, 5H), 4.16 (quintuplet, 1H, *J* = 6.5 Hz), 1.52 (d, 6H, *J* = 6.5 Hz).



5-(isopropylsulfonyl)-1-phenyl-1*H*-tetrazole (20)

To a solution of 5-(iso-propylsulfanyl)-1-phenyl-1*H*-tetrazole (183 mg, 0.831 mmol, 1.00 equiv) in methanol (8 mL) was added an aq. solution (8 mL) of Oxone (1.53 g, 2.49 mmol, 3.00 equiv) at rt. After stirring at rt for 2 d, the mixture was diluted with Et_2O (20 mL), washed with H_2O (25 mL). The layers were separated and the aq. phase was extracted with Et_2O (3 x 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 **20** (177 mg, 85 % yield) as a white solid. R*f* = 0.38 (1:3 EtOAc/hexanes); MP = 67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.56 (m, 5H), 4.03 (quintuplet, 1H, *J* = 6.9 Hz), 1.52 (d, 6H, *J* = 6.9 Hz).

Julia Kociensky olefination of 19 (21)



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 (21)

To a solution of sulfone **20** (28.3 mg, 0.112 mmol, 2.30 equiv) in THF (0.7 mL) at -78°C was added dropwise LHMDS[8] (0.33M in THF, 340 µL, 0.112 mmol, 2.30 equiv). The yellow solution was stirred at -78°C for 30 min. This solution was added in one portion

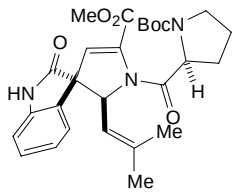
[8] Preparation of useful reagents and buffers, see last page.

with a precooled syringe to a solution of aldehyde **19** (23 mg, 0.049 mmol, 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 RT 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 crude product was purified by column chromatography (3:2 EtOAc/hexanes) to afford **21** as white crystals, 19 mg (78 %) R*f* = 0.28 (3:1 EtOAc/hexanes), $[\alpha]_D^{24}$ (c 0.985 $CHCl_3$) = +30.7; MP = 231 °C; ^{1}H 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* = 2.2, 8.7 Hz), 4.29* (dd, 1H, *J* = 3.4, 8.1 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 $C_{27}H_{35}N_3O_6$ $[M+Na]^+$ 520.2423; found, 520.2409.

Crystal data for **21** at 193 K, M_r = 616.95, orthorhombic space group *P2(1)2(1)2(1)*, ρ_{calc} = 1.311 g cm^3, Z = 4, a = 8.9350(10), b = 13.870(2), c = 25.228(7) Å, α = 90.00, β = 90.00, γ = 90.00°, V = 3126.5(10) Å^3. Final R(F) = 0.0608, wR(F^2) = 0.1778 for 395 parameters and 2945 reflections with $I > 2\sigma(I)$ and $\theta < 69.98°$.

CCDC 196804 (**21**) 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).

C8-C9 Olefination of 21 (22)



methyl (2'*S*,3*S*)-1'-{[(2*S*)-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 (22)

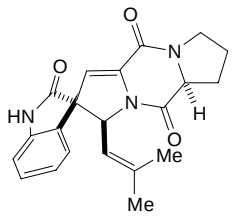
To a solution of **21** (9.0 mg, 180 μmol, 1.00 equiv) in THF (1 mL) at 0 °C was added LHMDS (0.33 M in THF, 121 μL, 400 μmol, 2.20 equiv). The solution was kept at 0 °C for 30 min and a solution of phenylselenyl chloride (7.6 mg, 400 μmol, 2.20 equiv) in THF (1 mL) was added. The reaction mixture was stirred at 0 °C for 90 min, then quenched by addition of sat. aq. $NaHCO_3$ (10 mL). The product was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was used without further purification. R*f* = 0.59, 0.51 (3:1 EtOAc/hexanes).

To a solution of the crude selenide in THF (0.5 mL) at 0 °C was added DMDO (≈ 0.09M in acetone, 80 μL, 0.072 mmol, 4.00 equiv)[9]. Stirring was continued for 3 h, the solvent was evaporated in vacuo. Column chromatography (11:9 EtOAc/hexanes) afforded **22** as a colourless oil, 6.9 mg (74 % over two steps) R*f* = 0.50 (3:1 EtOAc/hexanes), $[\alpha]_D^{25}$ (c 0.220 $CHCl_3$) = +42.0; ^{1}H NMR (300 MHz, $CDCl_3$, # 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); ^{13}C NMR (75 MHz, $CDCl_3$,) 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,

[9]Preparation of useful reagents and buffers, see last page.

1472, 1400, 1366, 1260, 1228, 1164, 1126, 753; HiResMALDI-MS calcd for $C_{27}H_{33}N_3O_6$ $[M+Na]^+$ 518.2267; found, 518.2276.

Preparation of spirotryprostatin B (2)



A solution of **22** (4.7mg, 0.010 mmol, 1.00 equiv) in 5:1 CH_2Cl_2/TFA (0.6 mL) was stirred at RT for 30 min. The solvent was evaporated in vacuo and the crude product was dissolved in CH_2Cl_2 (0.5 mL) and NEt_3 (5.2 μL, 0.038 mmol, 4.00 equiv) was added. The reaction mixture was stirred at RT for 4 h, then quenched by addition of sat. aq. $NaHCO_3$ (10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Column chromatography (75:20:8 CH_2Cl_2/EtOAc/*i*PrOH) afforded spirotryprostatin B as a white solid, 2.6 mg (74 % over two steps) R*f* = 0.23 (75:20:8 CH_2Cl_2/EtOAc/*i*-PrOH), MP = 136 °C; $[\alpha]_D^{26}$ (c 0.045 $CHCl_3$) = -148.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (br, 1H), 7.24 (ddd, 1H, *J* = 1.1, 7.6, 7.6 Hz), 7.07 (d, 1H, *J* = 7.6 Hz), 7.00 (ddd, 1H, *J* = 1.1, 7.6, 7.6 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* = 1.4, 8.9, 8.9 Hz), 4.34 (dd, 1H. *J* = 6.1, 10.7 Hz), 3.80 (ddd, 1H, *J* = 8.2, 12.2, 12.2 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); ^{13}C NMR (125 MHz, $CDCl_3$,) 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 $C_{21}H_{21}N_3O_3$ $[M+Na]^+$ 386.1481; found, 386.1478.

NMO = *N*-methylmorpholine-*N*-oxide, TBAF = tetrabutylammonium fluoride, LHMDS = lithium hexamethyldisilazide, DMDO = dimethyl-dioxirane, TFA = trifluoroacetic acid, NDMBA = *N*,*N*-dimethyl-barbituric acid.

Preparation of useful reagents and buffers:

LHMDS, 0.33M in THF

To a solution of HMDS (1 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, ≈ 0.4M 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 329 mg *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (≈ 50 % in H_2O, 2.24 mmol, 1.00 equiv) in small portions. The yellow organic solution was decanted and used immediately.

Boc-L-ProCl, 0.14 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 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 for 30 min; R*f* = 0.73 (EtOAc).

pH 3.6-buffer

Solution of citric acid monohydrate (1.43 g) and $Na_2HPO_4 \cdot 12\ H_2O$ (2.31 g) in H_2O (98.5 mL).

Dimethyl-dioxirane, ≈ 0.09M 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 DMDO/acetone solution was 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 °C.