Electronic Supplementary Information for

Stereoselective Synthesis of Spirotryprostatin A

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General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated diethyl ether, tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated methanol, ethanol and acetonitrile were also purchased from Wako Pure Chemical Industries, Ltd. and stored over activated MS3A. All other reagents were commercially available and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F_{254}. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40-100 µm) purchased from Kanto Chemical Co., Inc. $^1$H and $^{13}$C NMR were recorded on a JEOL ECX-400 spectrometer. Preparative thin layer chromatography (PTLC) separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F_{254}. All $^1$H NMR spectra are reported in units, parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All $^{13}$C NMR spectra are reported in ppm relative to the central line of the triplet for CDCl$_3$ at 77.0 ppm or central line of the septet for DMSO-d$_6$ at 39.52 ppm. Infrared spectra (IR) were recorded on a FT/IR-4100 Fourier Transform Infrared Spectrophotometer, and are reported in wavenumbers (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus in positive electrospray ionization (ESI) method or direct analysis real time (DART) method using PEG as the internal standard. Optical rotations were measured on a JASCO P-2200 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.
To a stirred solution of \(N\)-Cbz-trans-4-hydroxy-L-proline (10, 60.7 g, 229 mmol) and L-proline methyl ester \(p\)-toluenesulfonate salt (9, 47.7 g, 158 mmol) in \(\text{CH}_2\text{Cl}_2\) (760 mL) were added EDCI·HCl (65.8 g, 343 mmol) and Et\(_3\)N (38.3 mL, 275 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h, then quenched with saturated \(\text{NH}_4\text{Cl}\) aq. (760 mL) and partitioned between \(\text{CH}_2\text{Cl}_2\) (240 mL) and water (240 mL). The organic phase was collected and the aqueous phase was extracted with \(\text{CH}_2\text{Cl}_2\) (300 mL) twice. The combined organic extract was washed with brine (150 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (\(n\)-hexane/EtOAc = 1/1 to MeOH/EtOAc = 1/10) to afford dipeptide S1 (53.4 g, 142 mmol, 90%) as a yellow oil. 

\[ \begin{align*}
\text{Rf} &= 0.31 \text{ (MeOH/EtOAc = 1/10, PMA); } [\alpha]_{25}^D \text{ –68 (c = 0.88, CHCl}_3) \text{; IR (neat) 3421, } 2952, 2361, 1744, 1558, 1541, 1421, 1359, 1199, 1174, 1123 \text{ cm}^{-1}; \text{^1H NMR (CDCl}_3, 400MHz): (1.4:1 mixture of two rotamers) (major) } \delta 7.34–7.26 \text{ (m, 5H), 5.15 (d, } J = 12.8 \text{ Hz, 1H), 5.07 (d, } J = 12.8 \text{ Hz, 1H), 4.71 (dd, } J = 7.8, 7.3 \text{ Hz, 1H), 4.62–4.58 (m, 1H), 3.89 (dd, } J = 7.3, 6.9 \text{ Hz, 1H), 3.78–3.31 (m, 4H), 3.72 (s, 3H), 2.29–2.14 (m, 2H), 2.09–1.76 (m, 2H), 1.67–1.25 (m, 2H); \text{^13C NMR (CDCl}_3, 100MHz): (major and minor) } \delta 172.7 \text{ (C), 172.4(C), 171.2(C), 170.9(C), 155.0(C), 154.3(C), 136.5(C), 136.3(C), 128.4(CH), 128.4(CH), 128.2(CH), 128.1(CH), 127.9(CH), 127.7(CH), 70.2(CH), 69.6(CH), 67.4(CH), 67.0(CH), 58.8(CH), 58.6(CH), 56.8(CH), 56.2(CH), 55.5(CH), 54.8(CH), 52.2(CH), 52.2(CH), 46.7(CH), 46.5(CH), 38.5(CH), 37.7(CH), 28.8(CH), 28.5(CH), 24.9(CH), 24.5(CH); \text{HRMS (ESI): caled for } \text{C}_{19}\text{H}_{29}\text{O}_{7}\text{N}_{2}\text{Na ([M+Na]}^+) \text{: 399.1532, found 399.1525.} \end{align*} \]

To a stirred solution of S1 (25.6 g, 68.0 mmol), TEMPO (1.00 g, 6.80 mmol) and KBr (809 mg, 6.80 mmol) in \(\text{CH}_2\text{Cl}_2\) (170 mL) and saturated \(\text{Na}_2\text{CO}_3\) aq. (170 mL) were added 3.5 M
NaOCl aq. (58 mL, 204 mmol) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 30 min, then quenched with saturated Na₂S₂O₃ aq. (170 mL) and partitioned between CH₂Cl₂ (350 mL) and water (170 mL). The organic phase was collected and the aqueous phase was extracted with CH₂Cl₂ (200 mL) twice. The combined organic extract was washed with brine (70 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/1 to 0/1) to afford 11 (23.0 g, 61.4 mmol, 90%) as yellow crystals.

Rf = 0.60 (EtOAc, Ce-PMA); M.p. 103.8–104.6 °C; [α]²⁵⁺D −26 (c = 1.32, CHCl₃); IR (neat) 2954, 1764, 1743, 1710, 1653, 1446, 1416, 1359, 1198, 1162 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) (2:1 mixture of two rotamers) (major) δ 7.35–7.26 (m, 5H), 5.26 (d, J = 11.9 Hz, 1H), 5.09 (d, J = 11.9 Hz, 1H), 4.96 (dd, J = 12.8, 8.2 Hz, 1H), 4.56 (dd, J = 8.7, 4.1 Hz, 1H), 4.13–3.90 (m, 3H), 3.71 (s, 3H), 3.71–3.63 (m, 1H), 2.87–2.77 (m, 1H), 2.64–2.60 (m, 1H), 2.29–2.20 (m, 1H), 2.10–1.97 (m, 3H) (minor) δ 7.35–7.26 (m, 5H), 5.26 (d, J = 11.9 Hz, 1H), 5.09 (d, J = 11.9 Hz, 1H), 5.03 (dd, J = 12.8, 11.5 Hz, 1H), 4.38–4.37 (m, 1H), 4.13–3.90 (m, 1H), 3.71–3.63 (m, 1H), 3.69 (s, 3H), 3.46–3.42 (m, 2H), 2.87–2.77 (m, 1H), 2.64–2.60 (m, 1H), 2.10–1.97 (m, 4H); (DMSO-d₆, 100 °C) δ 7.38–7.32 (m, 5H), 5.14 (d, J = 12.4 Hz, 1H), 5.05 (d, J = 12.4 Hz, 1H), 5.02 (d, J = 9.2 Hz, 1H), 4.34–4.26 (m, 1H), 3.90 (d, J = 18.1 Hz, 1H), 3.76 (d, J = 18.1 Hz, 1H), 3.60 (s, 3H), 3.60–3.49 (m, 2H), 3.09 (dd, J = 18.4, 9.2 Hz, 1H), 2.28 (d, J = 18.4 Hz, 1H), 2.17–2.01 (m, 1H), 1.96–1.76 (m, 3H); ¹³C NMR (CDCl₃, 100MHz) (major and minor) δ 207.5 (C), 207.0 (C), 171.6 (C), 171.4 (C), 170.0 (C), 169.9 (C), 154.4 (C), 153.4 (C), 135.5 (C), 135.4 (C), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.2 (CH), 67.1 (CH₂), 66.8 (CH₂), 58.2 (CH), 58.0 (CH), 54.2 (CH), 54.0 (CH), 52.6 (CH₂), 52.2 (CH₂), 51.6 (CH₃), 51.6 (CH₃), 46.3 (CH₂), 46.0 (CH₂), 40.1 (CH₂), 39.6 (CH₂), 28.3 (CH₂). 28.1 (CH₂), 24.3 (CH₂), 24.0 (CH₂); (DMSO-d₆, 100 °C) δ 207.5 (C), 171.3 (C), 169.7 (C), 153.6 (C), 136.0 (C), 127.8 (CH), 127.4 (CH), 127.1 (CH), 66.2 (CH₂), 58.0 (CH), 54.3 (CH), 52.4 (CH₂), 51.2 (CH₃), 45.9 (CH₂), 39.9 (CH₂), 27.9 (CH₂). 23.9 (CH₂); HRMS (ESI) calcd for C₁₅H₂₂O₆N₂Na ([M+Na⁺]⁺) 397.1376, found 397.1361.
(5aS,10aS)-hexahydrodipyrrrolo[1,2-a:1',2'-d]pyrazine-2,5,10(3H)-trione (6)

To a stirred solution of 11 (12.5 g, 33.3 mmol) and TsOH·H₂O (3.16 g, 16.6 mmol) in MeOH (150 mL) were added CH(OMe)₃ (7.3 mL, 67 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 1 h before quenching with saturated Na₂CO₃ aq. (150 mL) and partitioned between EtOAc (300 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (200 mL) twice. The combined organic extract was washed with water (200 mL) and brine (60 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford the crude product which was used in the next reaction without further purification.

A mixture of the crude product and 10% Pd/C (M-type (wet, 50% water, Kawaken), 3.50 g, 1.66 mmol) was added MeOH (150 mL) under Argon atmosphere. The flask was charged with hydrogen gas (1 atm) at room temperature and the resulting suspension was vigorously stirred for 30 min. The reaction mixture was filtered through a Celite pad and the filtrate was stirred at 40 °C for 2 h. The reaction mixture was concentrated in vacuo to give a crude product, which was used for the next step without further purification.

To a stirred solution of the crude product in acetone (120 mL) were added 4 M HCl in 1,4-dioxane (15.0 mL) at 0 °C and the mixture was stirred at room temperature for 4 h. The white precipitates were collected in a Büchner funnel using suction filtration, washed with cold acetone (10 mL) twice and dried under vacuum to give the first crop of 6 (3.7 g, 17.8 mmol, 53%). Concentration of the mother liquor and recrystallization from acetone provided a second crop of 6 (0.64 g, 3.08 mmol, 9%). Concentrated mother liquor was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford another fraction of 6 (1.67 g, 8.03 mmol, 24%). The overall yield is 87% in three steps (6.01 g, 28.8 mmol).

Rf = 0.29 (MeOH/EtOAc = 1/10, Ce-PMA); M.p. 204.8–205.3 °C; [α]²⁷D −190 (c = 1.15, CHCl₃); IR (neat): 1764, 1660, 1437 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 4.68 (dd, J = 9.2, 8.7 Hz, 1H), 4.26 (dd, J = 8.3, 7.8 Hz, 1H), 4.14 (d, J = 19.7 Hz, 1H), 3.79 (d, J = 19.7 Hz, 1H), 3.61 (dd, J = 8.7, 5.2 Hz, 2H), 3.13 (dd, J = 19.2, 9.4 Hz, 1H), 2.93 (dd, J = 19.2, 8.7 Hz, 1H), 2.45–2.38 (m, 1H), 2.26–2.16 (m, 1H), 2.12–1.90 (m, 2H); ¹³C NMR (CDCl₃, 100MHz) δ 206.2 (C), 166.8 (C), 164.5 (C), 59.6 (CH), 57.4 (CH), 52.1 (CH₂), 45.7 (CH₂), 39.2 (CH₂), 27.8 (CH₂), 22.9 (CH₂); HRMS (DART) calcd for C₁₀H₁₃N₂O₃ ([M+H]+) 209.0926, found 209.0920.
(5aS,10aS)-7-((tert-butyldimethylsilyl)oxy)-1,2,3,5a,6,10a-hexahydopyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (14)

To a stirred solution of 6 (6.00 g, 28.8 mmol) in CH₂Cl₂ (280 mL) was added TBSOTf (7.90 mL, 34.6 mmol) and Et₃N (12.1 mL, 86.5 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 2.5 h. The reaction mixture was quenched with saturated Na₂CO₃ aq. (280 mL) and partitioned between EtOAc (500 mL) and water (220 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (250 mL) twice. The combined organic extract was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/1 to 0/1) to afford 14 (9.22 g, 28.6 mmol, 99%) as white crystals.

Rf = 0.64 (MeOH/EtOAc = 1/10, UV, Ce-PMA); M.p. 109.0–109.9 °C; [α]²⁷D +18 (c = 1.01, CHCl₃); IR (neat) 2930, 2359, 1677, 1640, 1436, 1255, 931, 839 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 6.18 (s, 1H), 4.61 (dd, J = 10.5, 9.6 Hz, 1H), 4.17 (dd, J = 8.3, 7.8 Hz, 1H), 3.60–3.56 (m, 2H), 3.30–3.28 (m, 1H), 2.75 (dd, J = 16.5, 11.0 Hz, 1H), 2.38–2.20 (m, 2H), 2.06–1.89 (m, 2H), 0.93 (s, 9H), 0.19 (s, 6H); ¹³C NMR (CDCl₃, 100MHz) δ 165.2 (C), 161.8 (C), 145.0 (C), 105.4 (CH), 60.0 (CH), 58.3 (CH), 45.5 (CH₂), 33.7 (CH₂), 27.8 (CH₂), 25.4 (CH₃), 23.3(CH₂), 18.0 (C), −4.8 (CH₃), −4.9 (CH₃); HRMS (ESI) calcd for C₁₆H₃₀N₂O₃SiNa ([M+Na]⁺) 345.1610, found 345.1598.
(5aS,10aS)-3-(2-((triisopropylsilyl)oxy)ethylidene)hexahydrodipyrrrolo[1,2-a:1',2'-d]pyrazine-2,5,10(3H)-trione (16)

To a stirred solution of 14 (8.13 g, 25.2 mmol) and aldehyde 15 (8.18 g, 37.8 mmol) in CH$_2$Cl$_2$ (200 mL) was added BF$_3$·OEt$_2$ (4.60 mL, 50.4 mmol) at -78 °C and the resulting mixture was stirred at -40 °C for 3 h. The reaction mixture was quenched with saturated NH$_4$Cl aq. (200 mL) and partitioned between CH$_2$Cl$_2$ (200 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with CH$_2$Cl$_2$ (300 mL) twice. The combined organic extract was washed with brine (80 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/1 to MeOH/EtOAc = 1/10) to afford 4:1 diastereomixtures of aldol (8.58 g, 20.2 mmol, 80%) as a clear viscous oil.

To a stirred solution of aldol (8.55 g, 20.1 mmol) and pyridine (6.50 mL, 80.5 mmol) in CH$_2$Cl$_2$ (200 mL) were added Tf$_2$O (4.10 mL, 24.2 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with saturated NH$_4$Cl aq. (200 mL) and partitioned between EtOAc (300 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (200 mL) twice. The combined organic extract was washed with brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/1 to 0/1) to afford inseparable diastereomixtures (6.6:1) of 16 (7.14 g, 17.6 mmol, 87%) as a yellow viscous oil.

R$_f$ = 0.52 (EtOAc, UV, Ce-PMA); IR (neat) 2943, 2866, 1742, 1676 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400MHz) (major) δ 6.30 (dd, $J$ = 6.9, 3.7 Hz, 1H), 4.82 (dd, $J$ = 17.9, 3.7 Hz, 1H), 4.70 (dd, $J$ = 9.2, 8.2 Hz, 1H), 4.38 (dd, $J$ = 17.9, 6.9 Hz, 1H), 4.34 (dd, $J$ = 8.2, 6.9 Hz, 1H), 3.64–3.61 (m, 2H), 3.12 (dd, $J$ = 19.7, 8.2 Hz, 1H), 2.93 (dd, $J$ = 19.7, 9.2 Hz, 1H), 2.42–2.22 (m, 2H), 2.11–1.90 (m, 2H), 1.16–1.05 (m, 21H); $^{13}$C NMR (CDCl$_3$, 100MHz) (major) δ 195.1 (C), 164.5 (C), 164.0 (C), 129.5 (C), 125.2 (CH), 62.1 (CH$_2$), 59.5 (CH), 57.3 (CH), 46.0 (CH$_2$), 37.0 (CH$_2$), 27.8 (CH$_2$), 22.9 (CH$_2$), 18.0 (CH$_3$), 11.9 (CH); HRMS (ESI) calcd for C$_{23}$H$_{35}$O$_4$N$_2$SiNa ([M+Na]$^+$) 429.2186, found 429.2197.
(35,5αS,10αS,E)-2-(2-bromoethylidene)-3-(2-((trisopropylsilyl)oxy)ethyl)octahydropyrrolo[1, 2-a:1',2'-d]pyrazine-5,10-dione (S3)

A mixture of 16 (7.14 g, 17.6 mmol) and 10% Pd/C (M-type (wt, 50% water, Kawaken), 3.70 g, 1.76 mmol) was added MeOH (150 mL) under Argon atmosphere. The flask was charged with hydrogen gas (1 atm) at room temperature and the resulting suspension was vigorously stirred for 30 min. The reaction mixture was filtered through a Celite pad and the filtrate was stirred at 40 °C for 2 h. The reaction mixture was concentrated in vacuo to give 17, which was used for the next step without further purification.

To a stirred solution of 17 in THF (85 mL) was added 1.0 M vinyl magnesium bromide solution in THF (35.1 mL, 35.1 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and quenched with saturated NH₄Cl aq. (85 mL). The resulting mixture was partitioned between EtOAc (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic extract was washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford the crude product which was used in the next reaction without further purification.

To a stirred solution of the crude product and pyridine (14.3 mL, 175 mmol) in CH₂Cl₂ (85 mL) was added SOBr₂ (6.70 mL, 52.7 mmol) in one portion at −20 °C and the resulting mixture was stirred at −20 °C for 20 min. The reaction mixture was quenched with saturated NH₄Cl aq. (85 mL) and partitioned between EtOAc (85 mL) and water (30 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic extract was washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/0 to 1/1) to afford S3 (5.86 g, 11.7 mmol, 67% in three steps) as a yellow viscous oil.

Rf = 0.62 (MeOH/EtOAc = 1/10, Ce-PMA); [α]D = 23 (c = 0.90, CHCl₃); IR (neat) 2942, 2865, 1671, 1460, 1711, 1101 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 5.84 (tm, J = 8.2 Hz, 1H), 4.67 (dm, J = 6.0 Hz, 1H), 4.25 (dd, J = 10.5, 7.3 Hz, 1H), 4.12 (dd, J = 8.2, 7.8 Hz, 1H), 4.00 (dd, J = 8.2 Hz, 2H), 3.75–3.66 (m, 2H), 3.58–3.54 (m, 2H), 3.04 (dd, J = 15.6, 7.3 Hz, 1H), 2.86 (ddm, J = 15.6, 10.5 Hz, 1H), 2.39–2.29 (m, 2H), 2.23–2.13 (m, 1H), 2.08–1.88 (m, 2H), 1.75–1.67 (m, 1H), 1.05–1.04 (m, 21H); ¹³C NMR (CDCl₃, 100MHz) δ 167.1 (C), 165.9 (C), 142.6 (C), 120.6 (CH), 60.7 (CH), 60.1 (CH), 59.2 (CH), 59.2 (CH), 45.0 (CH₂), 36.0 (CH₂), 27.9 (CH₂), 27.7 (CH₂), 23.3 (CH₂), 17.9 (CH₃), 11.8 (CH); HRMS (ESI) calcd for C₃₂H₃₀O₃N₂BrSiNa ([M+Na⁺]⁺) 521.1811, found 521.1816.
(3S,5aS,10aS,E)-2-ethylidene-3-(2-((triisopropylsilyl)oxy)ethyl)octahydrodipyrrlo[1,2-a:1',2'-d]
pyrazine-5,10-dione (18)

To a stirred solution of S3 (3.22 g, 6.45 mmol) in THF (64 mL) was added 1.0 M LiBHEt₃
solution in THF (12.9 mL, 12.9 mmol) at −20 °C. The resulting mixture was stirred at −20 °C for
30 min, then quenched with saturated NH₄Cl aq. (64 mL). The reaction mixture was partitioned
between EtOAc (100 mL) and water (30 mL). The organic phase was collected and the aqueous
phase was extracted with EtOAc (80 mL) twice. The combined organic extract was washed with
brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by
flash column chromatography on silica gel (n-hexane/EtOAc = 1/0 to 1/1) to afford 18 (2.50 g, 5.94
mmol, 92%) as a yellow oil.

Rf = 0.68 (MeOH/EtOAc = 1/10, Ce-PMA); [\(\alpha\)]D¹⁹ = –68 (ε = 1.69, CHCl₃); IR (neat) 2942,
2866, 1673, 1417 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 5.54–4.46 (m, 1H), 4.55–4.53 (m, 1H), 4.17
(dd, \(J = 11.0, 7.3 \) Hz, 1H), 4.10 (dd, \(J = 8.7, 7.8 \) Hz, 1H), 3.70–3.66 (m, 2H), 3.57–3.54 (m, 2H),
2.93 (dd, \(J = 15.6, 7.3 \) Hz, 1H), 2.71 (dd, \(J = 15.6, 11.0 \) Hz, 1H), 2.38–2.12 (m, 2H), 2.06–1.86 (m,
2H), 1.69 (d, \(J = 6.9 \) Hz, 3H), 1.69–1.62 (m, 1H), 1.07–1.04 (m, 2H); ¹³C NMR (CDCl₃, 100MHz)
δ 167.2 (C), 166.5 (C), 136.3 (C), 119.3 (CH), 61.0 (CH), 60.4 (CH), 59.6 (CH₂), 59.3 (CH), 45.0
(CH₂), 36.3 (CH₂), 27.9 (CH₂), 27.8 (CH₂), 23.4 (CH₂), 17.9 (CH₃), 14.3 (CH₃), 11.9 (CH); HRMS
(ESI) calcd for C₂₃H₄₀O₃SiNa ([M+Na⁺]) 443.2706, found 443.2714.
(35,5aS,10aS,E)-2-ethylidene-3-(2-hydroxyethyl)octahydrodipyrrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (19)

To a stirred solution of 18 (1.28 g, 3.04 mmol) in THF (30 mL) was added 30\% HF⋅pyridine (4.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and quenched with saturated NH₄Cl aq. (30 mL) The resulting mixture was partitioned between CH₂Cl₂ (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with 10\% MeOH in CH₂Cl₂ solution (60 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 19 (780 mg, 2.95 mmol, 97\%) as a yellow viscous oil.

\( \text{Rf} = 0.33 \) (MeOH/EtOAc = 1/10, Ce-PMA); [\( \alpha \)]\( ^{18} \)D = 133 (c = 0.72, CHCl₃); IR (neat) 3415, 2880, 1659, 1425 cm\(^{-1}\); \(^{1}\)H NMR (CDCl₃, 400MHz) \( \delta \) 5.51 (qm, \( J = 6.8 \) Hz, 1H), 4.58 (dd, \( J = 6.4 \), 6.4 Hz, 1H), 4.19 (dd, \( J = 11.0 \), 7.4 Hz, 1H), 4.14 (dd, \( J = 7.8 \), 7.8 Hz, 1H), 3.36–3.46 (m, 4H), 3.34 (brs, 1H), 2.94 (dd, \( J = 15.6 \), 7.4 Hz, 1H), 2.78–2.70 (m, 1H), 2.41–2.33 (m, 1H), 2.25–2.15 (m, 1H), 2.07–1.86 (m, 3H), 1.79–1.70 (m, 1H), 1.69 (dd, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 100MHz) \( \delta \) 169.2 (C), 166.4 (C), 137.3 (C), 119.1 (CH), 60.9 (CH), 60.8 (CH), 59.0 (CH₂), 58.6 (CH), 45.1 (CH₂), 39.9 (CH₂), 28.1 (CH₂), 27.1 (CH₂), 23.5 (CH₂), 14.3 (CH₃); HRMS (ESI) calcd for C₁₄H₂₀O₃N₂Na ([M+Na]\(^{+}\)) 287.1372, found 287.1366.

Electronic Supplementary Material (ESI) for Chemical Science
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2-((3S,5aS,10aS,E)-2-ethylidene-5,10-dioxodecahydrodipyrrrolo[1,2-α:1',2'-d]pyrazin-3-yl)acetaldehyde (20)

To a stirred solution of 19 (430 mg, 1.63 mmol) in CH₂Cl₂ (16 mL) was added Dess-Martin periodinane (1.00 g, 2.44 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 15 min. The reaction mixture was quenched with saturated Na₂S₂O₃ aq. (6 mL) and stirred for 10 min at 0 °C. The mixture was added saturated Na₂CO₃ aq. (10 mL) and partitioned between CH₂Cl₂ (30 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with CH₂Cl₂ (25 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 20 (361 mg, 1.38 mmol, 84%) as a yellow viscous oil.

Rf = 0.37 (MeOH/EtOAc = 1/10, Ce-PMA); [α]²⁵_D –23 (c = 0.66, CHCl₃); IR (neat) 2881, 2359, 1719, 1664, 1423 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 9.73 (dd, J = 1.8, 1.4 Hz, 1H), 5.61–5.55 (m, 1H), 4.83–4.81 (m, 1H), 4.25 (dd, J = 9.2, 9.2 Hz, 1H), 4.13 (dd, J = 8.7, 7.8 Hz, 1H), 3.64–3.52 (m, 2H), 3.04–2.95 (m, 2H), 2.87–2.75 (m, 2H), 2.38–2.30 (m, 1H), 2.19–1.89 (m, 3H), 1.69 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz) δ 198.9 (CH), 167.5 (C), 166.1 (C), 136.7 (C), 120.4 (CH), 60.6 (CH), 60.4 (CH), 56.5 (CH), 48.7 (CH₂), 45.2 (CH₂), 28.3 (CH₂), 27.9 (CH₂), 23.3 (CH₂), 14.5 (CH₃); HRMS (ESI) calcd for C₁₄H₁₈O₃N₂Na ([M+Na]⁺) 285.1215, found 285.1210.
(3S,5aS,10aS,E)-3-(2-(2-bromo-5-methoxyphenyl)-2-oxoethyl)-2-ethylideneoctahydrodipyrrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (22)

To a stirred solution of the 2-bromo-3-methoxy iodobenzene (1.50 g, 4.89 mmol) in THF (8 mL) was added 1.3 M i-PrMgBr-LiCl solution in THF (3.1 mL, 4.07 mmol) at −78 °C. The reaction mixture was stirred for 30 min at 20 °C to give the solution of 21. To a stirred solution of 20 (361 mg, 1.38 mmol) in THF (7.0 mL) was added 21 at −78 °C by cannulation and the resulting mixture was stirred at −78 °C for 45 min. The reaction mixture was quenched with saturated NH$_4$Cl aq. (7.0 mL) and partitioned between EtOAc (15 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (10 mL) twice. The combined organic extract was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was used in the next reaction without further purification.

To a stirred solution of the crude product in CH$_2$Cl$_2$ (14 mL) was added Dess-Martin periodinane (1.40 g, 3.26 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 30 min. The reaction mixture was quenched with saturated Na$_2$S$_2$O$_3$ aq. (6 mL) and stirred for 10 min at 0 °C. The resulting mixture was added saturated Na$_2$CO$_3$ aq. (8 mL) and partitioned between CH$_2$Cl$_2$ (20 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with CH$_2$Cl$_2$ (15 mL) twice. The combined organic extract was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1/1 to 0/1) to afford 22 (518 mg, 1.16 mmol, 84% in two steps) as a yellow viscous oil.

$R_f$ = 0.40 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{25}_D$ = −47 (c = 0.96, CHCl$_3$); IR (neat) 2937, 2339, 1665, 1422 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400MHz) δ 7.44 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 2.7 Hz, 1H), 6.82 (dd, J = 8.7, 2.7 Hz, 1H), 5.70–5.63 (m, 1H), 4.98–4.96 (m, 1H), 4.24 (dd, J = 10.3, 7.6 Hz, 1H), 4.13 (dd, J = 8.2, 7.8 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, J = 17.0, 3.2 Hz, 1H), 3.59–3.54 (m, 2H), 3.32 (dd, J = 17.0, 8.2 Hz, 1H), 2.97 (dd, J = 15.6, 7.6 Hz, 1H), 2.88–2–79 (m, 1H), 2.37–2.29 (m, 1H), 2.18–1.86 (m, 3H), 1.67 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 200.6 (C), 167.3 (C), 166.2 (C), 158.7 (C), 141.6 (C), 136.2 (C), 134.5 (CH), 120.8 (CH), 117.9 (CH), 114.1 (CH), 109.0 (C), 60.6 (CH), 60.4 (CH), 57.7 (CH), 55.6 (CH$_3$), 46.2 (CH$_2$), 45.1 (CH$_2$), 28.2 (CH$_2$), 27.8 (CH$_2$), 23.3 (CH$_2$), 14.5 (CH$_3$); HRMS (ESI) calcd for C$_{21}$H$_{25}$O$_6$N$_2$BrNa ([M+Na]$^+$) 469.0739, found 469.0750.
(6aS,8aS,13aS,14aS)-3-methoxy-14a-vinyl-6,6a,8a,9,10,11,14,14a-octahydrobenzo[e]pyrrolo[1',2':4,5]pyrazino[1,2-a]indole-5,8,13(13aH)-trione (23)

To a stirred solution of 22 (277 mg, 0.620 mmol), (o-tol)_3P (113 mg, 0.372 mmol) and Pd_2(dba)_3 (85.2 mg, 0.093 mmol) in toluene (6.2 mL) were added Et_3N (0.26 mL, 1.86 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl aq. (6 mL) and partitioned between CH_2Cl_2 (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (60 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 23 (219 mg, 0.597 mmol, 96%) as a yellow viscous oil. 

R_f = 0.33 (MeOH/EtOAc = 1/10, UV, Ce-PMA); [α]_D^22 +167 (c = 0.75, CHCl_3); IR (neat) 2952, 2360, 1667, 1607, 1494, 1416, 1287 cm\(^{-1}\); ^1H NMR (CDCl_3, 400MHz) δ 7.40 (d, J = 2.8 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 8.7, 2.8 Hz, 1H), 5.94 (dd, J = 17.4, 10.6 Hz, 1H), 5.34 (d, J = 10.6 Hz, 1H), 5.29 (d, J = 17.4 Hz, 1H), 4.55 (dd, J = 11.0, 5.5 Hz, 1H), 4.43 (dd, J = 9.6, 7.3 Hz, 1H), 4.15 (dd, J = 8.2, 7.8 Hz, 1H), 3.84 (s, 3H), 3.52–3.48 (m, 2H), 3.42 (dd, J = 15.6, 5.5 Hz, 1H), 2.77 (dd, J = 13.7, 7.3 Hz, 1H), 2.70 (dd, J = 13.7, 9.6 Hz, 1H), 2.62 (dd, J = 15.6, 11.0 Hz, 1H), 2.34–2.18 (m, 2H), 2.05–1.88 (m, 2H); ^13C NMR (CDCl_3, 100MHz) δ 194.6 (C), 166.9 (C), 166.1 (C), 158.8 (C), 142.2 (CH), 134.9 (C), 132.0 (C), 130.7 (CH), 122.5 (CH), 115.1 (CH_2), 108.6 (CH), 61.0 (CH), 60.6 (CH), 60.1 (CH), 55.5 (CH_3), 49.3 (C), 45.1 (CH_2), 40.0 (CH_2), 35.1 (CH_2), 27.3 (CH_2), 23.5 (CH_2); HRMS (ESI) caledd for C_{21}H_{22}O_4N_2Na ([M+Na]^+) 389.1477, found 389.1489.
To a stirred solution of 23 (211 mg, 0.575 mmol) in EtOH (5.8 mL) was added NH₂OH·HCl (120 mg, 1.73 mmol) and NaOAc (142 mg, 1.73 mmol) at room temperature and the resulting mixture was stirred at 50 °C for 20 min. The reaction was quenched with saturated NH₄Cl aq. (6 mL) and partitioned between CH₂Cl₂ (10 mL) and water (6 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH₂Cl₂ solution (6 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 24 (190 mg, 0.499 mmol, 87%) as a yellow viscous oil.

Rf = 0.44 (MeOH/EtOAc = 1/10, UV, Ce-PMA); [α]Dⁿ +112 (c = 0.92, CHCl₃); IR (neat) 3290, 3002, 2876, 1661, 1419 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 8.72 (brs, 1H), 7.28 (d, J = 2.8 Hz, 1H), 6.90 (dd, J = 8.8, 2.8 Hz, 1H), 5.83 (dd, J = 17.4, 10.5 Hz, 1H), 5.26 (d, J = 17.4 Hz, 1H), 5.23 (d, J = 10.5 Hz, 1H), 4.39 (dd, J = 11.4, 5.5 Hz, 1H), 4.38 (dd, J = 11.0, 6.9 Hz, 1H), 4.28 (dd, J = 14.2, 5.5 Hz, 1H), 4.18 (dd, J = 8.2, 7.8 Hz, 1H), 3.79 (s, 3H), 3.59–3.49 (m, 2H), 2.74 (dd, J = 13.7, 6.9 Hz, 1H), 2.52 (dd, J = 13.7, 11.0 Hz, 1H), 2.38–2.24 (m, 2H), 2.08–1.88 (m, 2H), 1.91 (dd, J = 14.2, 11.4 Hz, 1H); ¹³C NMR (CDCl₃, 100MHz) δ 167.4 (C), 166.5 (C), 158.3 (C), 151.5 (C), 142.9 (CH), 130.9 (C), 130.7 (C), 130.1 (C), 117.8 (CH), 113.9 (CH₂), 107.2 (CH), 60.7 (CH), 60.0 (CH), 59.9 (CH), 55.3 (CH₃), 49.3 (C), 45.2 (CH₂), 35.1 (CH₂), 27.4 (CH₂), 24.4 (CH₂), 23.6 (CH₂); HRMS (ESI) caled for C₂₁H₂₃O₄N₃Na ([M+Na]+) 404.1586, found 404.1599.
(6aS,8aS,13aS,14aS,E)-3-methoxy-5-(((methylsulfonyl)oxy)imino)-14a-vinyl-6,6a,8a,9,10,11,14,1

To a stirred solution of 24 (190 mg, 0.499 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added Et$_3$N (0.2
mL, 1.50 mmol) and MsCl (0.13 mL, 0.998 mmol) at room temperature. The resulting mixture was
stirred at room temperature for 30 min, then quenched with saturated NH$_4$Cl aq. (3 mL) and
partitioned between CH$_2$Cl$_2$ (3 mL) and water (2 mL). The organic phase was collected and the
aqueous phase was extracted with 10% MeOH in CH$_2$Cl$_2$ solution (3 mL) twice. The combined
organic extract was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified
by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 25 (188 mg,
0.409 mmol, 82%) as a yellow viscous oil.

R$_f$ = 0.46 (MeOH/EtOAc = 1/10, UV, Ce-PMA); [$\alpha$]$^{19}_{D}$ +76 (c = 1.16, CHCl$_3$); IR (neat)
2971, 1668, 1495, 1416, 1366, 1296, 1239, 1182 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400MHz) $\delta$
7.40 (d, $J$ = 2.7 Hz, 1H), 7.23 (d, $J$ = 9.2 Hz, 1H), 7.05 (dd, $J$ = 9.2, 2.7 Hz, 1H), 5.89 (dd, $J$
= 17.4, 10.5 Hz, 1H), 5.32 (d, $J$ = 10.5 Hz, 1H), 5.26 (d, $J$ = 17.4 Hz, 1H), 4.39 (dd, $J$
= 10.1, 7.4 Hz, 1H), 4.34 (dd, $J$ = 10.5, 5.5 Hz, 1H), 4.14 (dd, $J$ = 8.2, 7.8 Hz, 1H), 4.01 (dd,
$J$ = 15.1, 5.5 Hz, 1H), 3.83 (s, 3H), 3.52–3.49 (m, 2H), 3.24 (s, 3H), 2.73 (dd, $J$ = 13.8, 7.4 Hz,
1H), 2.55 (dd, $J$ = 13.8, 10.1 Hz, 1H), 2.37 (dd, $J$
= 15.1, 10.5 Hz, 1H), 2.35–2.20 (m, 2H), 2.08–1.88 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100MHz) $\delta$
167.1 (C), 166.1 (C), 159.7 (C), 158.5 (C), 142.0 (CH), 132.4 (C), 130.7 (CH), 127.6 (C), 119.7 (C), 115.1
(CH$_2$), 108.6 (CH), 60.6 (CH), 59.9 (CH), 59.6 (CH), 55.5 (CH$_3$), 49.4 (C), 45.2 (CH$_2$), 36.7 (CH$_3$),
35.3 (CH$_2$), 27.3 (CH$_2$), 26.4 (CH$_2$), 23.5 (CH$_2$); HRMS (ESI) caled for C$_{22}$H$_{25}$O$_8$N$_3$SNa ([M+Na]$^{+}$)
482.1362, found 482.1349.
To a stirred red solution of 25 (114 mg, 0.247 mmol) in CH₂Cl₂ (2.5 mL) was added 1.0 M TiCl₄ solution in CH₂Cl₂ (1.0 mL, 0.98 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h, then quenched with saturated NH₄Cl aq. (3 mL) and partitioned between CH₂Cl₂ (3 mL) and water (2 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH₂Cl₂ solution (3 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 26 (80.9 mg, 0.212 mmol, 86%) as a yellow viscous oil. 

Rf = 0.16 (MeOH/EtOAc = 1/10, UV, Ce-PMA); M.p. 239.0–239.9 °C; [α]²³D +156° (c = 0.60, CHCl₃); IR (neat) 3234, 2984, 2360, 2338, 1671 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 7.38 (brs, 1H), 7.30 (d, J = 8.7 Hz, 1H), 6.71 (dd, J = 8.7, 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.07 (dd, J = 17.4, 10.5 Hz, 1H), 5.39 (d, J = 10.5 Hz, 1H), 5.22 (d, J = 17.4 Hz, 1H), 4.66 (dd, J = 4.6, 3.2 Hz, 1H), 4.22 (dd, J = 11.0, 6.8 Hz, 1H), 4.14 (dd, J = 8.2, 7.8 Hz, 1H), 3.80 (s, 3H), 3.64–3.57 (m, 2H), 3.52–3.46 (m, 1H), 3.12–2.98 (m, 2H), 2.56–2.53 (m, 1H), 2.38–2.22 (m, 3H), 1.97–1.85 (m 1H); ¹³C NMR (CDCl₃, 100MHz) δ 171.5 (C), 167.4 (C), 166.3 (C), 159.4 (C), 141.7 (CH), 137.4 (C), 131.0 (CH), 125.4 (C), 114.5 (CH₂), 110.7 (CH), 109.1 (CH), 65.4 (CH), 60.8 (CH), 58.1 (CH), 55.4 (CH₃), 52.6 (C), 45.2 (CH₂), 35.4 (CH₂), 34.4 (CH₂), 28.0 (CH₂), 23.4 (CH₂); HRMS (ESI) calcd for C₂₁H₂₃O₄N₃Na ([M+Na⁺) 404.1586, found 404.1583.
(7aS,9aS,14aS,15aS)-*tert*-butyl 3-methoxy-6,9,14-trioxo-15a-vinyl-6,7,9,9a,10,11,12,14,14a,15,15a-dodecahydro-5H-benzo[b]pyrrolo[1''',2''':4',5']pyrazino[1',2':1,5]pyrrolo[3,2-d]azepine-5-carboxylate (27)

![chemical structure](image)

To a stirred solution of 26 (80.9 mg, 0.212 mmol) in MeCN (1.0 mL) was added Boc₂O (69.4 mg, 0.318 mmol) and DMAP (2.6 mg, 0.021 mmol) at room temperature and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated NH₄Cl aq. (1 mL) and partitioned between CH₂Cl₂ (2 mL) and water (2 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH₂Cl₂ solution (3 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo.

The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford 27 (98.1 mg, 0.204 mmol, 96%) as a yellow viscous oil.

**Specifications**

- **Rf** = 0.37 (MeOH/EtOAc = 1/10, UV, Ce-PMA);
- [α]$_D^{24}$ +103 ($c$ = 0.62, CHCl₃);
- IR (neat) 1772, 1730, 1671, 1611, 1413, 1288, 1243, 1148 cm⁻¹;
- $^1$H NMR (CDCl₃, 400MHz) (10:1 mixture of two rotamers) (major) δ 7.31 (d, $J$ = 9.2 Hz, 1H), 6.81 (dd, $J$ = 9.2, 2.3 Hz, 1H), 6.73 (d, $J$ = 2.3 Hz, 1H), 6.14 (dd, $J$ = 17.4, 11.0 Hz, 1H), 5.49 (d, $J$ = 11.0 Hz, 1H), 5.29 (d, $J$ = 17.4 Hz, 1H), 4.59 (dd, $J$ = 3.7, 3.7 Hz, 1H), 4.22 (dd, $J$ = 11.0, 7.3 Hz, 1H), 4.12 (dd, $J$ = 8.2, 7.4 Hz, 1H), 3.80 (s, 3H), 3.69–3.62 (m, 1H), 3.51–3.45 (m, 1H), 3.22 (dd, $J$ = 12.8, 3.7 Hz, 1H), 3.03 (dd, $J$ = 14.2, 11.0 Hz, 1H), 2.37–2.25 (m, 2H), 2.31 (dd, $J$ = 12.8, 3.7 Hz, 1H), 2.30 (dd, $J$ = 14.2, 7.3 Hz, 1H), 2.10–2.00 (m, 1H), 1.95–1.84 (m, 1H), 1.52 (s, 9H); $^{13}$C NMR (CDCl₃, 100MHz) (major) δ 168.3 (C), 167.7 (C), 165.9 (C), 159.3 (C), 151.0 (C), 141.2 (CH), 138.9 (C), 130.1 (CH), 127.5 (CH), 115.0 (CH₂), 113.7 (CH), 112.7 (CH). 84.5 (C), 65.1 (CH), 60.7 (CH), 58.5 (CH), 55.5 (CH₃), 51.9 (C), 45.2 (CH₂), 36.5 (CH₂), 33.9 (CH₂), 28.2 (CH₂), 27.7 (CH₃), 23.3 (CH₂); HRMS (ESI) calcd for C$_{26}$H$_{31}$O$_6$N$_3$Na ([M+Na]$^+$) 504.2111, found 504.2130.
To a stirred solution of 27 (27.0 mg, 0.056 mmol) in THF (0.5 mL) was added 1.11 M MeLi solution in Et₂O (0.11 mL, 0.118 mmol) at -78 °C and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated NH₄Cl aq. (1.0 mL) and partitioned between 17% MeOH in CH₂Cl₂ (1.0 mL) and water (0.5 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH₂Cl₂ (1.5 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by PTLC (n-hexane/EtOAc/MeOH = 5/4/1) to afford 28 (17.0 mg, 0.033 mmol, 59%) as a pale yellow oil.

Rf = 0.38 (MeOH/EtOAc = 1/10, UV, Ce-PMA); [α]_{22}^{20} = -142 (c = 0.73, CHCl₃); IR (neat) 3402, 2974, 1731, 1680, 1654, 1522, 1465, 1418, 1233, 1156, 1042, 1026 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 7.48 (d, J = 2.8 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.72 (brs, 1H), 6.66 (dd, J = 8.7, 2.8 Hz, 1H), 5.94 (dd, J = 17.9, 10.5 Hz, 1H), 5.39 (d, J = 10.5 Hz, 1H), 5.28 (d, J = 17.9 Hz, 1H), 4.86 (dd, J = 8.2, 2.7 Hz, 1H), 4.22-4.16 (m, 1H), 4.19 (dd, J = 11.4, 11.4 Hz, 1H), 4.02 (brs, 1H), 3.82 (s, 3H), 3.62–3.49 (m, 2H), 2.86 (dd, J = 11.4, 11.4 Hz, 1H), 2.35–2.21 (m, 3H), 2.05–1.89 (m, 2H), 1.49 (s, 9H), 1.22–1.13 (m, 2H), 1.20 (s, 3H), 0.94 (s, 3H); ¹³C NMR (CDCl₃, 100MHz) δ 170.1 (C), 166.5 (C), 159.8 (C), 152.3 (C), 141.7 (CH), 137.2 (C), 128.2 (CH), 121.3 (C), 115.2 (CH₂), 109.8 (C), 108.4 (C), 80.8 (C), 67.8 (C), 61.2 (CH), 58.1 (CH), 55.9 (CH), 55.3 (CH₃), 54.9 (C), 46.0 (CH₂), 45.0 (CH₂), 34.1 (CH₂), 30.7 (CH₃), 28.3 (CH₃), 28.0 (CH₃), 27.5 (CH₂), 23.7 (CH₂); HRMS (ESI) caled for C₂₆H₃₉O₆N₃Na ([M+Na]⁺) 536.2737, found 536.2722.
To a stirred solution of 28 (9.4 mg, 0.018 mmol) in CH₂Cl₂ (1 mL) and MeOH (1 mL) was cooled to −78 °C and ozone was passed through the solution for 2 min until complete consumption of the starting material was observed on TLC analysis. The reaction flask was purged with argon, and Me₂S (0.1 mL, 1.34 mmol) was added and the reaction mixture was warmed to room temperature. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure and the crude product was used in the next reaction without further purification.

To a stirred solution of the crude product in acetone (0.6 mL) were added 2.7 M Jones reagent (17 µL, 0.045 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and the reaction was quenched with 2-propanol (50 µL). Cold 1 M HCl aq. (0.1 mL) was added to dissolve the chromium waste and the mixture was partitioned between 17% MeOH in CH₂Cl₂ (1 mL) and water (1 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH₂Cl₂ (2 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by PTLC (MeOH/EtOAc = 1/20) to afford 29 (6.5 mg, 0.013 mmol, 70% in two steps) as a clear oil.

RF = 0.46 (MeOH/ EtOAc = 1/10, UV, Ce-PMA); [α]₂²²⁰D −107 (c = 0.27, CHCl₃); IR (neat) 3384, 2973, 1792, 1763, 1734, 1671, 1654, 1149 cm⁻¹; ¹H NMR (CDCl₃, 400MHz) δ 7.54 (d, J = 2.3 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 6.72 (dd, J = 8.7, 2.3 Hz, 1H), 4.92 (dd, J = 9.2, 7.4 Hz, 1H), 4.38 (dd, J = 5.0, 4.6 Hz, 1H), 4.37 (brs, 1H), 4.29 (dd, J = 8.2, 7.8 Hz, 1H), 3.84 (s, 3H), 3.61–3.58 (m, 2H), 2.65 (dd, J = 13.7, 9.2 Hz, 1H), 2.48 (dd, J = 13.7, 7.4 Hz, 1H), 2.41–2.33 (m, 1H), 2.29–2.19 (m, 1H), 2.11–1.94 (m, 2H), 1.85–1.84 (m, 2H), 1.64 (s, 9H), 1.10 (s, 3H), 0.55 (s, 3H); ¹³C NMR (CDCl₃, 100MHz) δ 177.1 (C), 168.5 (C), 166.1 (C), 160.7 (C), 148.8 (C), 141.2 (C), 125.6 (CH), 117.4 (C), 110.0 (CH), 102.0 (CH), 85.0 (C), 68.6 (C), 61.0 (CH), 59.6 (CH), 59.0 (CH), 55.6 (CH), 55.4 (C), 45.2 (CH₂), 43.5 (CH₂), 34.3 (CH₂), 31.4 (CH₃), 28.1 (CH₃), 27.6 (CH₂), 26.9 (CH₃), 23.6 (CH₂); HRMS (ESI) calcd for C₂₇H₃₅O₇N₃Na ([M+Na]+) 536.2373, found 536.2386.
Spirotryprostatin A (1)

To a stirred solution of 29 (5.3 mg, 0.010 mmol) and Na₂SO₄ (5.0 mg) in toluene (1.0 mL) was added TsOH·H₂O (5.9 mg, 0.030 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 19 h. The reaction mixture was quenched with saturated NaHCO₃ aq. (0.5 mL) and partitioned between 17% MeOH in CH₂Cl₂ (0.5 mL) and water (0.5 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH₂Cl₂ solution (1 mL) twice. The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by PTLC (n-hexane/EtOAc/MeOH = 5/4/1) to afford spirotryprostatin A (1) (3.6 mg, 0.0091 mmol, 91%) as a clear oil.

Rf = 0.45 (MeOH/CHCl₃ = 1/20, UV, PMA); [α]_D^{24} = -109 (c = 0.18, CHCl₃); IR (neat) 2923, 1718, 1671, 1632, 1460 cm⁻¹; ^1H NMR (CDCl₃, 400MHz) δ 7.62 (brs, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.50 (dd, J = 8.4, 2.3 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 5.03 (dm, J = 10.0 Hz, 1H), 5.00 (dd, J = 10.5, 6.8 Hz, 1H), 4.78 (d, J = 10.0 Hz, 1H), 4.28 (dd, J = 7.8, 7.8 Hz, 1H), 3.80 (s, 3H), 3.64–3.54 (m, 2H), 2.61 (dd, J = 13.3, 10.5 Hz, 1H), 2.39 (dd, J = 13.3, 6.8 Hz, 1H), 2.37–2.25 (m, 2H), 2.08–1.91 (m, 2H), 1.65 (s, 3H), 1.17 (s, 3H); ^13C NMR (CDCl₃, 100MHz) δ 180.8 (C), 167.1 (C), 166.9 (C), 160.4 (C), 141.6 (C), 138.4 (C), 127.3 (CH), 121.3 (CH), 118.7 (C), 106.7 (CH), 96.6 (CH), 61.0 (CH), 60.2 (CH), 60.2(C), 58.5 (CH), 55.5 (CH₃), 45.2 (CH₂), 34.3 (CH₂), 27.4 (CH₂), 25.5 (CH₃), 23.7 (CH₂), 18.0 (CH₃); HRMS (ESI) calcd for C_{22}H_{25}O₄N₃Na ([M+Na]^+) 418.1743, found 418.1758.
S1

$^{1}$H NMR (400 MHz) in CDCl$_3$
**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

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**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

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**spirotryprostatin A (1)**

**HN**

**MeO**

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**spirotryprostatin A (1)**

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**MeO**

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**spirotryprostatin A (1)**

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**MeO**

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**H**

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**spirotryprostatin A (1)**

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**MeO**

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**spirotryprostatin A (1)**

**HN**

**MeO**

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**H**

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**spirotryprostatin A (1)**

**HN**

**MeO**

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**spirotryprostatin A (1)**

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**MeO**

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**MeO**

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**MeO**

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**H**

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**spirotryprostatin A (1)**

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**MeO**

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**spirotryprostatin A (1)**

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**MeO**

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**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**

**HN**

**MeO**

**O**

**N**

**N**

**H**

**H**

**O**

**O**

**spirotryprostatin A (1)**
HN
MeO
O
N
N
H
H
O
O
spirotryprostatin A (1)
BocN
MeO
O
N
N
H
H
O
O
OH

H NMR (400 MHz) in CDCl3

13C NMR (100 MHz) in CDCl3

13C NMR (100 MHz) in DMSO-d6

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HN
MeO
O
N
N
H
H
O
O
spirotryprostatin A (1)

NHBoc
MeO
O
N
N
H
H
O
O
OH
28
BocN
MeO
O
N
N
H
H
O
O
OH
29

H NMR (400 MHz) in CDCl$_3$

S1
N
O
CO
Me
N
Cbz
H
HO
6
N
N
H
H
O
O
O
O
S3
OTIPS
OTIPS
Br

13C NMR (100 MHz) in CDCl$_3$

13C NMR (100 MHz) in DMSO-d$_6$

13C NMR (100 MHz) in CDCl$_3$

13C NMR (100 MHz) in CDCl$_3$

13C NMR (100 MHz) in CDCl$_3$

13C NMR (100 MHz) in CDCl$_3$

13C NMR (100 MHz) in CDCl$_3$
$^1$H NMR (400 MHz) in CDCl$_3$
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$^{1}$H NMR (400 MHz) in CDCl$_3$
$^{13}$C NMR (100 MHz) in CDCl$_3$
N
H
O
MeO
H
O
23
S1
N
O
CO
2
Me
Cbz
H
HO
6
N
N
H
H
O
O
O
O
N
N
H
H
O
O
TBSO
14
N
N
H
H
O
O
OTIPS
16
OTIPS
Br
OMe
22
N
N
H
H
O
O
CHO
20
N
N
H
H
O
O
MeO
H
N
OMs
25
N
N
H
H
O
O
H
N
MeO
Boc
27
N
N
H
H
O
O
Br
OMe
24
N
N
H
H
O
O
H
N
MeO
26
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\(^1\)H NMR (400 MHz) in CDCl\(_3\)
$^{13}$C NMR (100 MHz) in CDCl$_3$
$\text{Br}$  S3  OTIPS

$^1\text{H NMR (400 MHz) in CDCl}_3$
$^{1}$H NMR (400 MHz) in CDCl$_3$
$\text{^1H NMR (400 MHz) in CDCl}_3$
$\text{H NMR (400 MHz) in CDCl}_3$
$^1$H NMR (400 MHz) in CDCl$_3$
$^1$H NMR (400 MHz) in CDCl$_3$
$^{13}$C NMR (100 MHz) in CDCl$_3$
$^1$H NMR (400 MHz) in CDCl$_3$
$^{13}$C NMR (100 MHz) in CDCl$_3$
$^{1}H$ NMR (400 MHz) in CDCl$_3$
$^{13}$C NMR (100 MHz) in CDCl$_3$
Electronic Supplementary Material (ESI) for Chemical Science
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HN
MeO
O
N
N
H
O
spirotryprostatin A (1)
NHBoc
MeO
O
N
N
H
O
OH
spirotryprostatin A (1)
H NMR (400 MHz) in CDCl₃

1H NMR (400 MHz) in CDCl₃

C NMR (100 MHz) in CDCl₃

C NMR (100 MHz) in CDCl₃

C NMR (100 MHz) in DMSO-d₆

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Electronic Supplementary Material (ESI) for Chemical Science
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spirotryprostatin A (1)

$^1$H NMR (400 MHz) in CDCl$_3$