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Supporting Information

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A Concise Asymmetric Synthesis of the Marine Hepatotoxin 7-epi-cylindrospermopsin**

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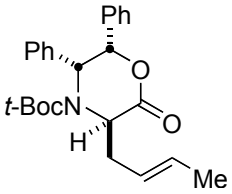
General Experimental procedures:

Dichloromethane and diisopropylamine were distilled from CaH_2 immediately prior to use. Tetrahydrofuran, toluene, and dimethylformamide were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed on Merk silica gel Kieselgel 60 (230-400 mesh) from EM science with the indicated solvent. $CHCl_3$ was distilled from $CaCl_2$ for optical rotations where indicated.

Instrumentation:

^1H and ^{13}C NMR were recorded on Varian 300 MHz or 400MHz spectrometers as indicated. Infrared spectra were obtained by sample deposition on NaCl plates and recorded on a Nicolet Avatar 320-FT IR spectrometer. Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec. Optical rotations were obtained with a 2 mL, 1 dm cell on a Rudolf Research Autopol III polarimeter operating at 589 nm. HPLC data was obtained on a Waters 600 HPLC system with indicated column and eluent conditions. Melting points are uncorrected.

3-(R)-But-2-enyl-2-oxo-5-(R),6-(S)-diphenyl-morpholine-4-carboxylic acid tert-butyl ester.

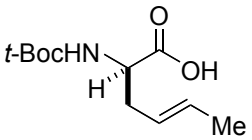


To a solution of NaI (6.00g, 40.0 mmol) in MeCN (30 mL) under an argon atmosphere was added TMSCl (5.08 mL, 40.0 mmol) dropwise over 10 min. H_2O (0.36 mL, 20.0 mmol) was then added followed by crotyl alcohol (3.40 mL, 40.0 mmol). After 30 min the reaction was diluted with H_2O (100 mL) and extracted 3 x 50 mL hexanes. The combined organics were washed with sat. $Na_2S_2O_3$, brine, and dried ($MgSO_4$). The organics were then concentrated under aspirator pressure to ~1/4 volume. To this solution, under an argon atmosphere, was added the oxazinone **1** (5.66 g, 16.0 mmol) and THF (100 mL). The mixture was cooled to -78°C and a 0.5 M solution of KHMDS in PhMe (32.0 mL, 16.0 mmol) was added dropwise over 10 min. After 0.5 h the reaction was quenched with sat. NH_4Cl and diluted with Et_2O. The organics were washed with sat. $Na_2S_2O_3$, brine, and dried (Na_2SO_4). Concentration afforded a white solid which was recrystallized from EtOH / H_2O. The while solid was dried at 60°C to constant mass giving the crotyloxazinone (5.97 g, 92%, m.p. 138-141°C). $[\alpha]^{25}_D$ = +13.2°(*c* 1.00, $CHCl_3$). Optical purity was determined by HPLC, Chiracel OD-H column eluting with 97:3 hexanes: *i*PrOH at 1 mL/min; (* indicates minor rotamer): 3(*S*), 5(*S*), 6(*R*) t_R = 5.78* min, 6.26 min; 3(*R*), 5(*R*), 6(*S*) t_R = 7.66* min, 9.35min.[1] ^{1}HNMR ($CDCl_3$, 400 MHz, 273 K): (mixture of rotamers, * indicates minor rotamer where discernable) δ 7.28-7.10 (m, 6H), 7.05 (t, *J* = 7 Hz, 2H), 6.94 (d, *J* = 7 Hz, 2H), 6.55 (t, *J*, = 8 Hz, 2 H), 6.00* (br d, *J* = 2 Hz, 1H), 5.92 (br d, *J* = 3 Hz, 1H), 5.7-5.5 (m, 2H), 5.19* (d, *J* = 2 Hz, 1H), 5.05 (app t, *J* = 7 Hz, 1H), 4.96 (d, *J* = 3 Hz, 1H), 4.88* (dd, *J* = 6, 8 Hz, 1H), 2.80 (br t, *J* = 6 Hz, 2H), 1.70 (overlapping d, *J*

[1] for examples of tertiary amide rotamer separation on chiral stationary phases see: Clayden, J.; Pink, J.H, *Angew. Chem. Int. Ed. Eng.***1998**, 1937-1939.

= 5 Hz, 3H), 1.43* (s, 9H), 1.08 (s, 9H). ^{13}CNMR ($CDCl_3$, 100 MHz, 273 K): (major rotamer) δ169.52, 153.87, 136.80, 134.68, 130.66, 128.71, 128.26, 127.88, 127.75, 127.67, 126.71, 125.16, 81.31, 79.07, 61.45, 57.21, 37.74, 28.02, 18.22. IR (Dep. $CDCl_3$): 2975(w), 1752, 1700 (both s), 1388, 1166, 700 (all m). HRMS (FAB+): Calc. for $C_{25}H_{29}NO_4$ [M+H]: 407.2097; Found 407.2094.

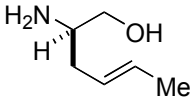
2-(R)-tert-Butoxycarbonylamino-hex-4-(E)-enoic acid (5).



A flame dried flask fitted with a CO_2 condenser was charged with flattened lithium metal (660 mg, 95.7 mmol) under argon. Ammonia (50 mL) was condensed into the flask at -78°C and the blue slurry stirred for 15min. A solution of the oxazinone (3.00 g, 7.36 mmol) in THF (10 mL) and EtOH (1.29 mL, 22.08 mmol) was added dropwise over 5 min. The cooling bath was removed and the mixture allowed to reflux at -33°C for 0.5 h. The reaction was quenched by the careful addition of NH_4Cl and the ammonia allowed to evaporate. The resulting residue was taken up in sat. $NaHCO_3$ (100 mL) and extracted 2 x Et_2O (50 mL). The aqueous layer was acidified to pH~2 with $NaHSO_4$ and extracted 3 x CH_2Cl_2 (50 mL). The combined organics were washed with brine and dried (Na_2SO_4). Concentration gave the acid as a light yellow oil (1.12 g, 67%) which was used without further purification. *Note*: smaller reaction scale (~1 mmol) resulted in increased ~80 % yields. $[\alpha]^{25}_D$ = –4.30° (*c* 1.0, $CHCl_3$). Optical purity can be determined by HPLC on the free amino acid after hydrolysis with conc. aq. HCl, Crownpak CR column eluting with aqueous $HClO_4$ (pH = 1) at 0.8 mL/min : 2(*R*) t_R = 3.95 min.; 2(*S*) t_R = 5.71 min. ^{1}HNMR ($CDCl_3$, 300MHz): δ 10.25 (br s, 1H), 5.60 (dq, *J* = 15.0, 6.3 Hz, 1H), 5.40-5.24 (m, 1H),

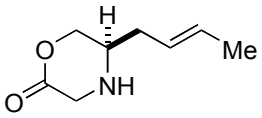
5.00 (d, J = 7.7 Hz, 1H), 4.34 (br m, 1H), 2.58-2.40 (m, 2H), 1.66 (dd, J = 6.3, 0.9 Hz, 3H), 1.44 (s, 9H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.22, 155.66, 130.48, 124.54, 80.45, 52.23, 35.44, 28.55, 18.27. IR (Dep. $CDCl_3$): 3330 (m, br); 2978 (m); 1716 (s, br); 1508 (m); 1165 (s). HRMS (FAB+): Calc. for $C_{11}H_{20}NO_4$ [M+H]: 230.1392; Found 230.1393.

2-(R,E)-aminohex-4-en-1-ol (6).



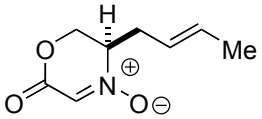
Acetyl chloride (1.39 mL, 19.5 mmol) was added dropwise to MeOH (40 mL) at 0 °C and the solution stirred for 15 min. A solution of the acid **5** (1.49g, 6.49 mmol) in MeOH (3 mL) was added and the mixture allowed to reach rt and stirred an additional 12h. The mixture was concentrated *in vacuuo* and further concentrated after the addition of Et_2O (2 x 20 mL) and PhMe (1 x 50 mL). The crude solid was slurried in THF (50 mL) and $LiAlH_4$ (500 mg, 13.2 mmol) added in portions over 0.5 h at 0 °C. After stirring at rt for an additional 3 h the reaction was quenched by the sequential addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (1.5 mL). The mixture was filtered through celite with THF and concentrated. The crude oil was purified by Kugelhror distillation, collecting material between 80-100 °C (0.5 mm Hg) to give the amino alcohol as a clear oil (487 mg, 65%). $[\alpha]^{22}_D$ = –14.3° (*c* 1.00, $CHCl_3$). ^{1}HNMR ($CDCl_3$, 300MHz): δ 5.45 (dq, J = 15, 6 Hz, 1H), 5.31 (dddq, J = 15, 6, 6, 1.5 Hz, 1H), 3.59 (dd, J = 11, 4 Hz, 1H), 3.24 (dd, J = 11, 8 Hz, 1H), 2.78 (dddd, J = 8, 6, 6, 4 Hz, 1H), 2.60 (br s, 3H), 2.06 (ddd, J = 13, 6, 6 Hz, 1H), 1.86 (ddd, J = 13, 6, 6 Hz, 1H), 1.61 (dd, J = 6, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.27, 127.39, 66.22, 52.64, 37.54, 18.17. IR (Dep. $CDCl_3$): 3335 (s), 1573, 1435, 1051, 968 (all m). HRMS (FAB+): Calc. for $C_6H_{13}NO$ [M+H]: 116.1075; Found 116.1080.

5-(R)-But-2-enyl-morpholin-2-one.



A solution of the amino alcohol **6** (395 mg, 3.43 mmol) and *i*Pr_2NEt (745 mg, 3.46 mmol, 1.01 eq) in MeCN (40 mL) was added dropwise over 1h to a solution of bromophenyl acetate in MeCN (131 mL, final conc. to be 0.02 M). The mixture was stirred for an additional 4h and concentrated. Purification on silica with a Na_2CO_3 pre-pad eluting with 5% *i*PrOH / EtOAc gave the morpholinone as a colourless oil (335 mg, 63%). $[\alpha]^{22}_D$ = –49.6° (*c* 1.00, $CHCl_3$). ^{1}HNMR (CD_3OD, 300 MHz): δ 5.58 (dq, *J* = 15.0, 6.3 Hz, 1H), 5.43 (ddd, *J* = 15.0, 6.6, 1.5 Hz, 1H), 4.38 (dd, *J* = 10.9, 3.7 Hz, 1H), 4.07 (dd, *J* = 10.9, 10.9 Hz, 1H), 3.62 (ABq, dd, *J* = 18.1, 18.1 Hz, 2H), 3.04 (m, 1H), 2.14 (dd, *J* = 6.6, 6.6 Hz, 2H), 1.68 (dd, *J* = 6.3, 1.2 Hz, 3H). ^{13}C NMR (CD_3OD, 75 MHz): δ 170.83, 130.12, 126.99, 75.02, 52.19, 48.24, 35.61, 18.28. IR (Dep. CD_3OD): 3400 (br s), 2964 (s), 1636, 1404 (both m), 1063 (vs). HRMS (FAB+): Calc. for $C_8H_{14}NO_2$ [M+H]: 156.1025; Found 156.1025.

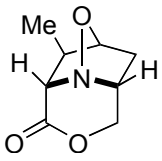
5-(R)-But-2-enyl-4-oxy-5,6-dihydro-[1,4]oxazin-2-one (7).



A solution of the oxazinone (260 mg, 1.67 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min to a solution of purified *m*CPBA (636 mg, 3.69 mmol) and Na_2HPO_4 (1.18g) in CH_2Cl_2 at –78°C. The reaction was allowed to proceed for 0.5h and quenched with sat. $Na_2S_2O_3$. The mixture was partitioned between H_2O and Et_2O and the organics further washed with 9% Na_2CO_3, brine, and dried (Na_2SO_4). The crude oil was purified on silica eluting with 1:1 hexanes : EtOAc to afford the nitrone as a colourless oil (236 mg, 84%). $[\alpha]^{25}_D$ = + 4.00° (*c* 4.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14 (s, 1H), 5.66 (dq, *J* = 15.0, 6.5 Hz, 1H), 5.46-5.30 (m,

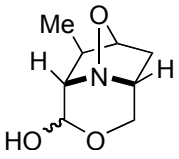
1H), 4.58 (dd, *J* = 12.3, 3.9 Hz, 1H), 4.43 (dd, *J* = 12.3, 3.9 Hz, 1H), 3.92 (dddd, *J* = 9.3, 3.9, 3.9, 3.9 Hz, 1H), 2.82-2.70 (m, 1H), 2.61-2.49 (m, 1H), 1.69 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.19, 132.27, 124.74, 123.25, 68.08, 65.62, 32.81, 18.27. IR (Dep. $CDCl_3$): 1715, 1556 (both s), 1209 (m), 1061, 968 (both w). HRMS (FAB+): Calc. for $C_8H_{12}NO_3$ [M+H]: 170.0818; Found 170.0817.

2-(S)-Methyl-5-(S),9-(R)-dioxa-8-(S)-aza-tricyclo[5.2.1.0^{3,8}]decan-4-one (8).



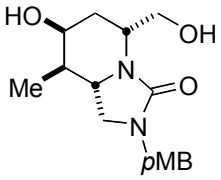
The nitrone **7** (60 mg, 0.35 mmol) was dissolved in dry toluene (7 mL) to be 0.05 M. This solution was heated in a sealed tube at 200 ℃ (sand bath temperature) for 2.5 h. The mixture was then cooled and the solvent removed *in vacuo*. The crude organics were purified on silica eluting with 1:1 hexanes: EtOAc to afford the tricyclic isoxazolidine (47 mg, 78%) as a colourless oil which solidified upon standing. An analytical sample was recrystallized from pet. ether / CH_2Cl_2 (m.p. 78-80 °C). $[\alpha]^{25}_D$ = +3.6° (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.56 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.45 (dd, *J* = 12.3, 1.2 Hz, 1H), 3.58 (burried m, 1H), 3.58 (d, *J* = 3.6 Hz, 1H), 2.30 (ddd, *J* = 11.7, 10.8, 5.4 Hz, 1H), 2.08 (qd, *J* = 6.9, 3.7, 1H), 1.56 (dd, *J* = 12.0, 6.0 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.92, 85.14, 70.37, 65.12, 57.70, 51.71, 34.69, 19.70. IR (Dep. $CDCl_3$): 2966 (w), 1746 (vs), 14548, 1404 (both w), 1227 (m), 1117 (w), 988 (m). HRMS (FAB+): Calc. for $C_8H_{12}NO_3$ [M+H]: 170.0817; Found 170.0812.

2-Methyl-5,9-dioxa-8-aza-tricyclo[5.2.1.0^{3,8}]decan-4-ol.



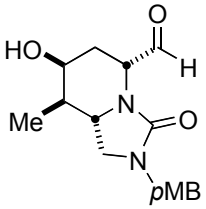
To a solution of the isoxazolidine **8** (167 mg, 0.99 mmol) in CH_2Cl_2 (20 mL) at –78 °C under argon was added DIBAL-H (1M / toluene, 0.99 mL, 0.99 mmol) over 0.5 h. The mixture was stirred for an additional 1 h, quenched with water (0.2 mL), allowed to warm to rt, and stirred for 2 h. The mixture was filtered through celite and concentrated. The resulting solid was recrystallized from $CHCl_3$ / pentane to give the lactol as white prisms (147 mg, 87 %). ^{1}HNMR ($CDCl_3$, 400MHz): [~2:1 mixture of anomers] δ 5.28 (s), 4.93 (d, *J* = 2.4 Hz), 4.39 (app d, *J* = 5.2 Hz), 4.34 (dd, *J* = 12.4, 2.0 Hz), 3.88 (dd, *J* = 12.8, 1.2 Hz), 3.69 (dd, *J* = 12.4, 1.2 Hz), 3.64 (dd, *J* = 12.4, 0.8 Hz), 3.35 (ddd, *J* = 10.8, 4.4, 2.0 Hz), 3.25 (ddd, *J* = 10.4, 4.4, 2.4 Hz), 3.04 (dd, *J* = 4.4, 2.4 Hz), 2.96 (d, *J* = 4.4 Hz), 2.14-2.01 (m), 1.99 (qd *J* = 6.8, 4.4 Hz), 1.79 (qd, *J* = 6.8, 4.4 Hz), 1.58 (dd, *J* = 11.2, 4.8 Hz), 1.51 9dd, *J* = 11.2, 4.8 Hz), 1.07 (d, *J* = 7.2 Hz), 1.05 (buried d, *J* = 7.2 Hz). ^{13}CNMR ($CDCl_3$ 100 MHz): [~2:1 mixture of anomers] δ92.24, 86.99, 86.88, 73.98, 73.09, 62.12, 59.90, 59.19, 58.17, 44.47, 40.30, 36.06, 35.88, 19.87, 19.01. IR (Dep. $CDCl_3$): 3406, 3131 (br, s), 2965, 2930 (both s), 1452, 1124, 1092, 985, 710 (all m). HRMS (FAB+): Calc. For $C_8H_{14}NO_3$ [M+H]: 172.0974; Found 172.0976.

7(S)-Hydroxy-5(R)-hydroxymethyl-2(S)-(4-methoxy-benzyl)-8(S)-methyl-hexahydro-imidazo[1,5-a]pyridin-3-one (9).



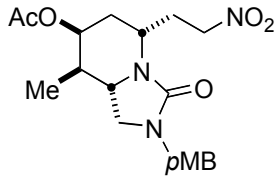
To a solution of the lactol (15 mg, 0.88 mmol) in EtOAc (3 mL) was added *p*-methoxybenzyl amine (17 mg, 0.12 mmol). The solution was degassed with argon and then 10% Pd/C (15 mg) was added. The solution was then purged with H_2 and stirred under a hydrogen atmosphere for 12 h. The mixture was filtered and concentrated. The crude oil was dissolved in MeCN (5 mL) and cooled to 0 ℃. A solution of *bis*-*p*-nitrophenyl carbonate (32 mg, 0.11 mmol) in MeCN (5 mL) was added dropwise over 15 min. After stirring an additional 0.5 h the mixture was concentrated, taken up in EtOAc (20 mL) and the organics washed 3 x 9% Na_2CO_3, 1 x brine and dried (Na_2SO_4). The crude material was purified on silica gel eluting with EtOAc / 5% *i*PrOH to give the urea as a clear oil (19 mg, 67 %). $[\alpha]^{25}_D$ = +37.7° (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.80 (dd, *J* = 9, 5 Hz, 1H), 4.4 (1/2 ABq, *J* = 15 Hz, 1H), 4.19 (1/2 ABq, *J* = 15 Hz, 1H), 3.94 (br dd, *J* = 2.4, 2.4 Hz, 1H), 3.90-3.72 (buried m, 3H), 3.80 (s, 3H), 3.51 (dddd, *J* = 9, 5, 3,3 Hz, 1H), 3.45 (ddd, *J* = 10, 9, 9 Hz, 1H), 3.28 (dd, *J* = 9, 9 Hz, 1H), 2.76 (dd, *J* = 9, 9, Hz, 1H), 1.82 (d, *J* = 3 Hz, 1H), 1.72 (ddd, *J* = 14, 3, 3 Hz, 1H), 1.62 (ddd, *J* = 12, 12, 2 Hz, 1H), 1.48 (ddd, *J* = 14, 6, 3 Hz, 1H), 0.89 (d, *J* = 6 Hz, 3H). ^{13}CNMR ($CDCl_3$ 75 MHz): δ 160.76, 158.96, 129.38, 114.04, 68.19, 64.77, 55.41, 54.37, 53.27, 47.96, 47.55, 39.99, 36.40. IR (Dep. $CDCl_3$): 3385, 2933 (both m), 1664, 1513, 1246 (all s). HRMS (FAB+): Calc. for $C_{17}H_{24}N_2O_4$ [M+H]: 322.1814; Found: 321.1811.

7(S)-Hydroxy-2(S)-(4-methoxy-benzyl)-8(S)-methyl-3-oxo-octahydro-imidazo[1,5-a]pyridine-5(R)-carbaldehyde (10).



To a solution of the diol (211 mg, 0.66 mmol) in $CDCl_3$ (3 mL) was added $PhI(OAc)_2$ (318 mg, 0.99 mmol) and TEMPO (41 mg, 0.26 mmol). Methane sulfonic acid (0.63 mg, 7 μmol, 1 mol%) was then added as a solution in $CDCl_3$. The mixture was stirred for 3h, diluted with EtOAc (30 mL) and the organics washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, brine, and dried (Na_2SO_4). The resulting oil was purified on silica gel eluting with EtOAc / 5% *i*PrOH) to give the aldehyde as a white foam (156 mg, 75%). $[\alpha]^{25}_D = +\ 84.8°$ (*c* 1.13, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.81 (d, *J* = 2.1 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.1, 2H), 4.36 (1/2 ABq, *J* = 15 Hz, 1H), 4.20 (1/2 ABq, *J* = 15 Hz, 1H), 4.00 (br s, 1H), 3.82 (buried m, 1H), 3.79 (s, 3H), 3.40 (ddd, *J* = 10.5, 9, 9 Hz, 1H), 3.28 (dd, *J* = 9, 9 Hz, 1H), 2.86 (dd, *J* = 9, 9 Hz, 1H), 1.90 (br d, *J* = 13.5 Hz, 1H), 1.64 (dd, *J* = 12, 12 Hz, 1H), 1.54 (br dd, *J* = 9, 9 Hz, 1H), 0.90 (d, *J* = 6.6 Hz). ^{13}CNMR ($CDCl_3$ 75 MHz): δ198.30, 160.43, 158.96, 129.39, 128.66, 114.02, 67.97, 57.36, 55.36, 53.31, 47.89, 47.28, 38.37, 32.89, 13.36. IR (Dep. $CDCl_3$): 3431, 2878 (both m), 1727, 1682, 1513, 1448, 1246 (all s). HRMS (FAB+): Calc. for $C_{17}H_{22}N_2O_4$ [M+H]: 319.1657; Found: 319.1664.

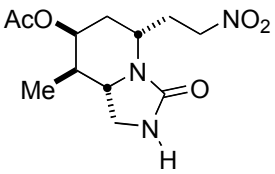
Acetic acid 2-(4-methoxy-benzyl)-8-methyl-5-(2-nitro-ethyl)-3-oxo-octahydro-imidazo[1,5-a]pyridin-7-yl ester (11).



A solution of nitromethane in THF (10 : 1, 20 mL) under argon was cooled to 0 °C. A 1.6 M solution of *n*BuLi (3.5 mL, 5.66 mmol) was added slowly (*caution!* highly exothermic) over 20 min. The mixture was stirred an additional 15 min and a solution of the aldehyde (180 mg, 0.57 mmol) in THF added. The reaction was allowed to proceed for 12 h, quenched with sat. NH_4Cl and extracted 3 x 10 mL EtOAc. The combined organics were washed brine and dried (Na_2SO_4). The crude oil was purified on silica eluting with 1 : 1 hexanes : EtOAc then EtOAc / 5% *i*PrOH to give the diastereomeric nitro alcohol (183 mg, 84%). To a solution of the nitroalcohol (41 mg, 0.11 mmol) and *N,N*-dimethylaminopyridine (3 mg, 0.025 mmol, 20 mol%) in CH_2Cl_2 under an argon atmosphere was added acetic anhydride (0.10 mL, 1.1 mmol). After stirring for 12 h the mixture was concentrated, taken up in EtOH (3 mL) and added dropwise to a slurry of $NaBH_4$ (101 mg, 2.67 mmol) in EtOH (5 mL). The mixture was stirred for 2 h and quenched by the addition of 50% AcOH / H_2O (0.4 mL). The mixture was concentrated under reduced pressure and partitioned between H_2O and EtOAc. The aqueous phase was extracted again with EtOAc and the combined organics washed with sat. $NaHCO_3$, brine, and dried (Na_2SO_4). The crude oil was purified on silical gel eluting with 1:1 hexanes : EtOAc to give the nitroalkane as a colourless oil (40 mg, 87%). $[\alpha]^{25}_D$ = +15.2° (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (d, *J* = 8 Hz, 2H), 6.87 (d, *J* = 8 Hz, 2H), 5.12 (br d, *J* = 6.8, 3 Hz, 1H), 4.72 (ddd, *J* = 13.6, 8.4, 5.6 1H), 4.61 (ddd, *J* = 13.6, 5.6, 5.6 Hz), 4.23 (s, 2H), 3.78 (s, 3H), 3.43 (dddd, *J* = 10.8, 10.8, 3, 3 Hz, 1H), 3.28 (ddd, *J* =

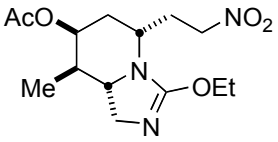
9, 8, 5.6 Hz, 1H), 3.18 (dd, *J* = 8, 8 Hz, 1H), 2.78 (dd, *J* = 8, 5 Hz, 1H), 2.41 (dd, *J* = 13.6, 8, 5, 5 Hz, 1H), 2.05 (s, 3H), 1.83 (ddd, *J* = 12, 3, 3 Hz, 1H), 1.70-1.60 (m, 2H), 0.78 (d, *J* =6.8 Hz, 3H). ^{13}CNMR ($CDCl_3$, 100 MHz) δ 170.36, 159.72, 159.07, 129.46, 128.99, 114.17, 73.68, 71.46, 56.06, 55.50, 48.81, 47.34, 46.45, 36.83, 36.40, 29.63, 21.34, 13.28. IR (Dep. $CDCl_3$): 2937 (m), 1737, 1693, 1550, 1513 (all s), 1442, 1374, 1351 (all m), 1242 (s). HRMS (FAB+): Calc. for $C_{20}H_{28}N_3O_6$ [M+H]: 406.1978; Found: 406.1969.

Acetic acid 8-methyl-5-(2-nitro-ethyl)-3-oxo-octahydro-imidazo[1,5-a]pyridin-7-yl ester.



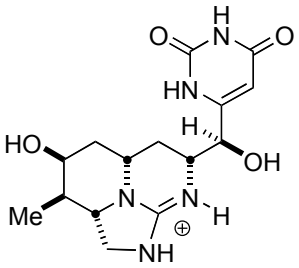
The protected urea (25 mg, 0.062 mmol) was dissolved in trifluoroacetic acid (1.5 mL). The mixture was refluxed for 1 h and concentrated under reduced pressure. The purple residue was taken up in EtOAc (10 mL) and washed 1 x H_2O, 1 x sat. $NaHCO_3$, 1 x brine, and dried (Na_2SO_4). The crude residue was purified on silica gel eluting with EtOAc / 5% *i*PrOH to give the urea (14 mg, 80%) as a white solid. $[\alpha]^{25}_D = +17.3°$ (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.14 (dd, *J* = 6, 3 Hz, 1H), 4.80 (br s, 1H), 4.76-4.54 (m, 2H), 3.52-3.38 (m, 3H), 3.1-2.9 (m, 2H), 2.37 (dddd, *J* = 15, 6, 6, 3 Hz, 1H), 2.09 (s, 3H), 1.86 (ddd *J* = 12, 3, 3 Hz, 1H), 1.84-1.78 (buried m, 1H), 1.66 (ddd, *J* = 12, 3, 3 Hz, 1H), 0.87 (d, *J* = 6 Hz, 3H). ^{13}CNMR ($CDCl_3$ 100 MHz): δ 170.53, 161.57, 73.61, 71.53, 58.84, 48.47, 42.52, 36.51, 36.61, 29.42, 21.24, 13.19. IR (Dep. $CDCl_3$): 3269, 2939 (both w), 1736, 1698, 1550 (all s), 1436, 1374 (both m), 1242 (s). HRMS (FAB+): Calc. for $C_{12}H_{20}N_3O_5$ [M+H]: 286.1403; Found: 286.1409.

(5S,7S,8R,8aS)-3-ethoxy-8-methyl-5-(2-nitroethyl)-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-7-yl acetate (12).



To a solution of the urea (58 mg, 0.20 mmol) under argon in CH_2Cl_2 (10 mL) was added Cs_2CO_3 (650 mg, 2.0 mmol) and triethyloxonium tetrafluoroborate (386 mg, 2.0 mmol). The reaction was stirred at rt for 15 h and quenched by the addition of aq. 9% Na_2CO_3 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine and dried (Na_2SO_4). After concentration the crude mixture was purified on silica gel with 10% MeOH / CH_2Cl_2 to give the isourea as a clear oil (49 mg, 78 %). $[\alpha]^{25}_D$ = +6.2° (*c* 1.00, $CHCl_3$). ^{1}H NMR (CD_3OD, 400 MHz): δ 5.22 (app br dd, *J* = 8.0, 2.8 Hz, 1H), 4.61 (ddd, *J* = 7.6, 7.6, 2.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.59-3.46 (m, 2H), 3.55 (buried dd, *J* = 11.6, 4.0 Hz, 1H), 3.25 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.66 (dddd, *J* = 18, 8, 8, 8 Hz, 1H), 2.37 (dddd, *J* = 18, 8, 8, 6 Hz, 1H), 2.08 (s, 3H), 1.94-1.79 (m, 2H), 1.65 (ddd, *J* = 14, 12, 2 Hz, 1H), 1.32 (q, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}CNMR ($CDCl_3$,100 MHz): δ 170.57, 163.30, 72.99, 71.89, 65.43, 63.77, 52.48, 48.58, 36.16, 35.54, 30.33, 21.23, 14.63, 12.99. IR (Dep. $CDCl_3$): 2963 (m), 1735 (s), 1622, 1550, 1436, 1372, 1334 (all m), 1228 (s). HRMS (FAB+): Calc. for $C_{14}H_{24}N_3O_5$ [M+H]: 314.1715; Found: 314.1710.

7-epi-cylindrospermopsin diol (13).

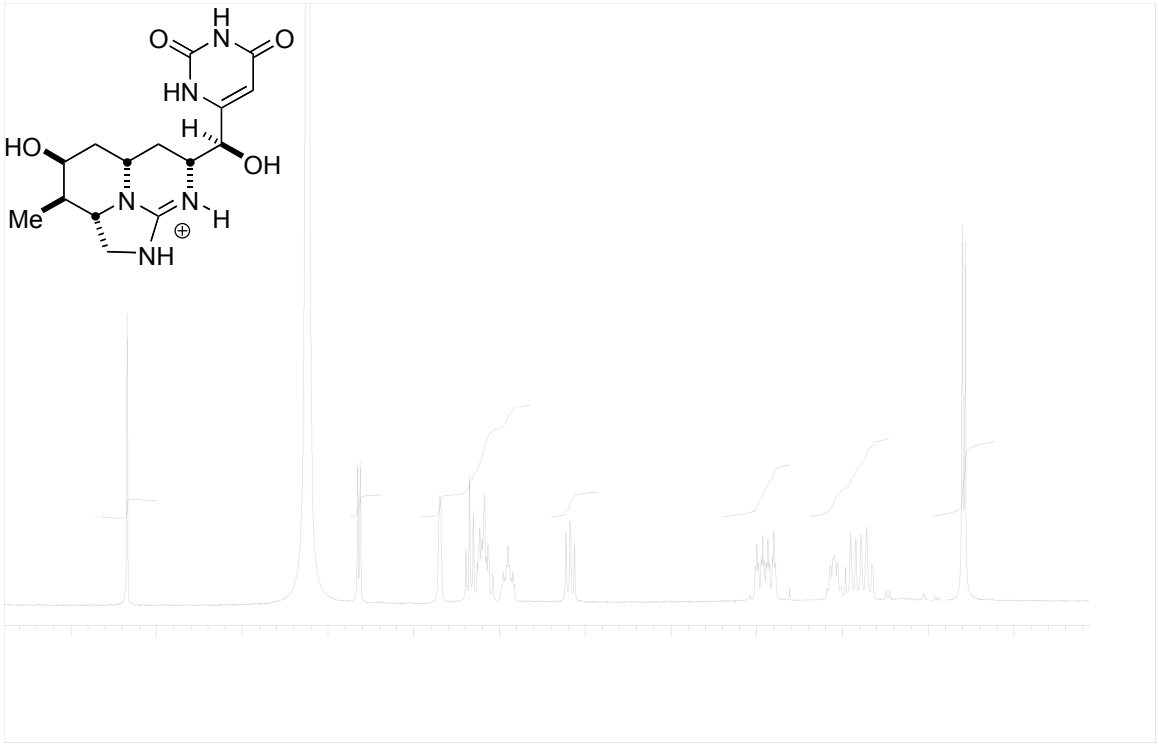


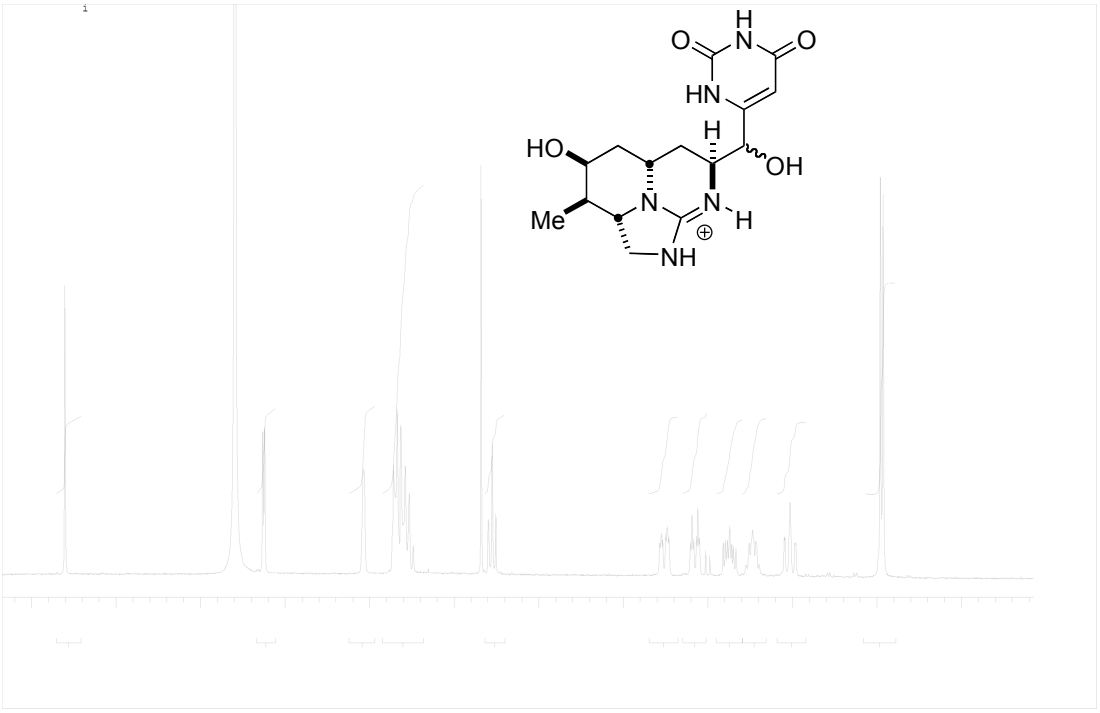
To a solution of the *O*-ethyl isourea **12** (8.0 mg, 26 μmol) and pyrimidine aldehyde (5.2 mg, 31 μmol) in THF at -15 °C was added a 1 M solution of tetra-*n*-butylammonium fluoride (51 μL, 51 μmol). The reaction was allowed to proceed for 0.5 h and quenched with 20% AcOH / THF (0.5 mL). The mixture was concentrated and the crude oil dissolved in 5% AcOH / MeOH (5.1 mL, to be 5 mM) and the solution purged with argon. 20% $Pd(OH)_2$ on carbon (32 mg) was added and the solution purged with hydrogen. After stirring for 12 h under an H_2 atmosphere the mixture was filtered through a 0.45μm Acrodisc® and concentrated. Purification (to remove 6-hydroxymethyl pyrimidine and TBAF) by PTLC eluting with 20% MeOH / CH_2Cl_2 with 1% HCO_2H afforded an inseparable mixture (1 : 0.8) of the two C-7 diastereomers after stripping the silica with 20% abs. EtOH / CH_2Cl_2. This mixture was then refluxed in conc. HCl for 8 h and concentrated. Purification of the uracils was achieved by HPLC using a Waters Symmetry® C-18 colum (4.6 x 250 mm) eluting with 4% MeOH / H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm to give 7-epi-cylindrospermopsin diol as a white solid (3.0 mg, 32%, t_R = 19.05 min) and the other C8 diastereomer also as a white crystalline solid (2.7 mg, 29 %, t_R = 23.53 min).

7-epi-cylindrospermopsin diol (13): ^1H and ^{13}C NMR agreed with those previously reported.[11a] $[\alpha]^{25}_D = -11.7°$ (*c* 0.06, H_2O); (lit $[\alpha]_D^{24} = -8.3°$ (*c* 0.06, H_2O))[12];

8-epi-cylindrospermopsin diol (14) : $[\alpha]_D^{24} = +70°$ (*c* 0.20, H_2O). ^1H NMR (D_2O, 400 MHz): δ 5.80 (s, 1H), 4.62 (d, *J* = 4.4 Hz, 1H), 4.04 (br s, 1H), 3.88-3.74 (m, 3H), 3.28 (app t, *J* = 8.4 Hz, 1H), 2.26 (ddd, *J* = 14, 4, 3 Hz, 1H), 2.07 (ddd, *J* = 14, 4, 4 Hz, 1H),

1.87 (ddd, J = 15, 10, 6 Hz, 1H), 1.78-1.68 (m, 1H), 1.52 (app t, J = 13 Hz, 1H), 0.97 (d, J = 7 Hz, 3H). HRMS (FAB+): Calc. for $C_{15}H_{22}N_5O_4$ [M+H]: 336.1672; Found: 336.1672.

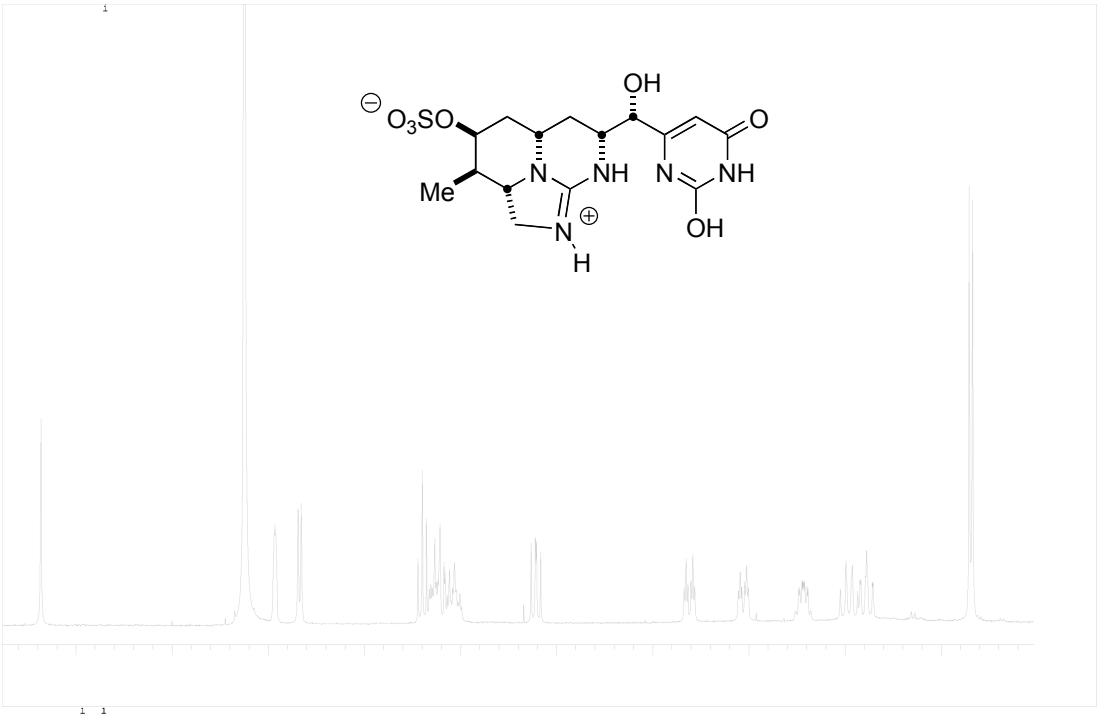


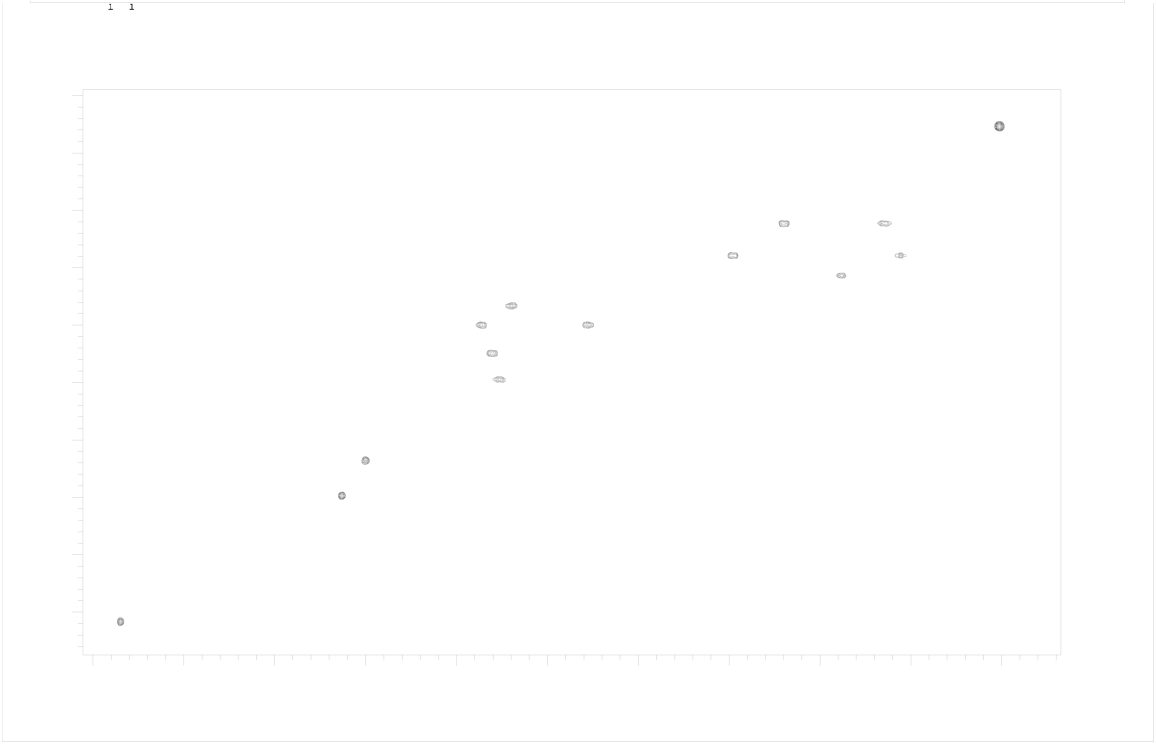


7-epi-cylindrospermopsin (2):

7-epi-cyclindrospermopsin diol (2.6 mg, 7.0 μmol) was co-concentrated with MeCN (2 x 5 mL) and PhMe (2 x 5 mL). The resulting solid was dried under vacuum for 0.5 h and placed under argon. DMF (0.4 mL) and activated, powdered 3Å molecular sieves (6 mg) were added and the mixture stirred for 15 min. To this solution was added solid SO_3^-pyr (11 mg, 70 μmol) and the mixture stirred for 1 h. MeOH (0.1 mL) was added and the solvents removed *in vacuuo*. The mixture was taken up in MeOH and filtered through a 0.45μm Acrodisc®. Purificataion by HPLC on a Waters Symmetry® C-18 colum (4.6 x 250 mm) eluting with 2% MeOH / H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm gave 7-epi-cylindrospermopsin (t_R = 9.22 min) as a white solid after lyophilization (1.7 mg, 59 %). This was preceded by its bis sulfate (t_R = 6.54 min) as a ~2:1 mixture.

$[\alpha]^{25}_D$ = –12.5°(*c* 0.04, H_2O); (lit $[\alpha]_D^{24}$ = –20.5°(*c* 0.04, H_2O)[3], ^1H and ^{13}C NMR spectra agree with those reported. HRMS (FAB+): Calc. for $C_{15}H_{22}N_5O_7S$ [M+H]: 416.1240; Found: 416.1247





RELIV278-gCHSQC (500 MHz): 7-epi-cylindrospermopsin gCHSQC.