Supporting Information

A unified and straightforward total synthesis of (+)-porantheridine and (-)-6-epi-porantheridine

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General Information

All air and water sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF and was distilled from sodium-benzophenone, dichloromethane and N,N-dimethylformamide were distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60 F-254) that were analyzed by staining with Phosphomolybdic acid (100 mL of 95% EtOH, 10 g Phosphomolybdic acid), fluorescence upon 254 nm irradiation or by staining with Ninhydrin (100 mL Butanol of 1.5 g Ninhydrin and 3 mL of acetic acid) and Dinitrophenylhydrazine ( 80 mL H2O, 200 mL of 95% EtOH, 12 g Dinitrophenylhydrazine and 60 mL concentrated sulfuric acid). Silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. IR spectra were obtained using FT-IR Spectrometer. NMR spectra were recorded on a 400 (1H: 400 MHz, 13C: 100 MHz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets. High resolution mass spectra were obtained from a MALDI-TOF mass spectrometer.

Synthetic Procedures

(R,E)-N-(hex-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (8)

\[
\begin{align*}
\text{OH} & \quad \overset{1)}{(\text{COCl})_2 \cdot \text{DMSO} \cdot \text{Et}_3\text{N} \cdot \text{CH}_2\text{Cl}_2 \cdot -78^\circ\text{C}} \\
\text{CH}_2\text{Cl}_2 & \quad \overset{2)}{\text{PPTS} \cdot \text{MgSO}_4 \cdot \text{CH}_2\text{Cl}_2 \cdot \text{rt}} \\
\text{82\% over 2 steps} & \\
\text{H}_2\text{N} & \quad \overset{7)}{\text{O}} \\
\text{8} &
\end{align*}
\]

A solution of oxalyl chloride (12.7 mL, 149.76 mmol) in CH₂Cl₂ (180 mL) was stirred at -78 °C for 30 minutes, followed by the dropwise addition of dimethyl sulfoxide (21.3 mL, 299.52 mmol) in CH₂Cl₂ (80 mL) and the resulting mixture was allowed to stirred at the same temperature for another 30 minutes. 6 (10 g, 99.84 mmol) in CH₂Cl₂ (100 mL) was then introduced into the mixture and the latter was allowed to stirred for 30 minutes before triethylamine (80.4 mL, 577.08 mmol) in CH₂Cl₂ (140 mL) was added. After 1 h, the reaction mixture was then diluted with 1M HCl solution and washed with saturated NaHCO₃ (2 x 200 mL), followed by 1.0 M KHSO₄ (2 x 200 mL). The organic layer was further washed with NaHCO₃ (2 x 300 mL) before drying in Na₂SO₄ and evaporated in vacuo. Under nitrogen atmosphere, a suspension of the crude product (9.80 g, 99.84 mmol), (R)-(−)-tert-butylsulfinamide 7 (12.10 g, 99.84 mmol), PPTS (2.51 g, 9.98 mmol), and anhydrous MgSO₄ (48 g) in CH₂Cl₂ (192 mL) was stirred for 14 h at room temperature. The mixture was filtered through a pad of Celite and concentrated in vacuo. The residual oil was purified by flash chromatography on silica gel (EtOAc/hexane = 1:5) to produce the desired compound 8 as an oil (18.5 g, 82% yield): [α]₂⁵ = -257.308 (c 1.04, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.03-4.92 (m, 1H), 4.24-4.17 (m, 2H), 1.75-1.70 (m, 2H), 1.32 (q, J = 7.0 Hz, 2H), 0.92 (q, J = 7.4 Hz, 2H), 0.38 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 169.1, 137.4, 115.3,
Dienolate 9 (3.0 equiv) was added to a solution of 8 (0.5 g, 2.5 mmol) in CH₂Cl₂ (12 mL) and the solution was cooled to 0 °C under N₂. TMSOTf (0.54 mL, 3.0 mmol) was added dropwise. After being stirred for 2 h at the same temperature, the reaction was quenched by addition of a saturated aqueous NaHCO₃. The mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide an oily residue that was purified by flash chromatography on silica gel (EtOAc/hexane = 1:2) to gave the compounds 11 and 10 (364 mg, 49% yield, 92% brsm yield) as a oil in a 4.3:1. 11: [α]D° = -80.9 (c 1.68, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.86-6.78 (m, 1H), 5.77 (d, J = 15.7 Hz, 1H), 5.71-5.59 (m, 1H), 4.87 (dd, J = 20.2, 13.7 Hz, 2H), 3.61 (s, 3H), 3.33-3.27 (m, 1H), 3.07 (d, J = 6.0 Hz, 1H), 2.41-2.25 (m, 2H), 1.96 (q, J = 7.0 Hz, 2H), 1.51-1.30 (m, 4H), 1.09 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 145.1, 137.9, 123.5, 115.0, 77.5, 77.2, 76.8, 58.8, 58.6, 56.1, 54.8, 51.8, 33.7, 33.2, 33.1, 25.0, 24.3, 22.6; IR (neat) 2947, 2859, 1737, 1639, 1437, 1168, 1048, 910 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₈NO₃S [M+H]⁺ 302.1784, found 302.1784.

10: ¹H NMR (400 MHz, CDCl₃) δ 5.89-5.71 (m, 2H), 5.31-5.16 (m, 2H), 4.96 (d, J = 22.0, 13.7 Hz, 2H), 3.67 (s, 3H), 3.47 (d, J = 10.7 Hz, 1H), 3.22-3.10 (m, 1H), 2.08-1.99 (m, 2H), 1.70-1.43 (m, 4H), 1.18 (t, J = 7.1 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 138.1, 133.3, 131.6, 120.4, 119.4, 114.8, 77.5, 77.2, 76.8, 58.8, 58.6, 56.1, 54.8, 51.8, 33.7, 33.2, 33.1, 25.0, 24.3, 22.6; IR (neat) 2947, 2859, 1737, 1639, 1437, 1168, 1048, 910 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₈NO₃S [M+H]⁺ 302.1784, found 302.1784.

(S)-methyl 5-((R)-1,1-dimethylethylsulfinamido)dec-9-enoate (12)²

To a solution of α,β-unsaturated ester 11 (9.15 g, 30.35 mmol), CuCl (6.01 mg, 6.71 mmol) and cyclohexene (24.6 mL, 242.83 mmol) in MeOH (202 mL) at 0 °C was added NaBH₄ (11.48 g, 303.54 mmol). The reaction was left at room temperature for 2 h, during which time it turned from green to brown. While still cold, the solvent was removed on the rotary evaporator. The products were partitioned between saturated aqueous NH₄Cl solution (100 mL) and CH₂Cl₂ (100 mL). The organic phase was separated and the aqueous layer was extracted with more CH₂Cl₂ (4 x 100 mL). The organic layers were combined, dried with Na₂SO₄, filtered and concentrated under reduced pressure to provide an oily residue that was deemed sufficiently purified by flash...
chromatography on silica gel (EtOAc/hexane = 1:2) to produce 12 the colourless oil (7.41 g, 81%): 
$[\alpha]_{D}^{25} = -34.73$ (c 2.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.80-5.70 (m, 1H), 4.94 (d, $J = 16.9, 15.0$ Hz, 2H), 3.63 (s, 3H), 3.21-3.18 (m, 1H), 3.04 (d, $J = 6.6$ Hz, 1H), 2.31 (t, $J = 7.0$ Hz, 2H), 2.04 (d, $J = 18.6$ Hz, 2H), 1.70-1.35 (m, 9H), 1.18 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.8, 138.25, 114.8, 77.5, 77.2, 76.8, 56.3, 55.8, 51.5, 34.9, 33.7, 33.5, 24.8, 22.6, 20.7; IR (neat) 2929, 2855, 1742, 1638, 1456, 1364, 1168, 1046, 906 cm$^{-1}$; HRMS (ESI) calcd for C$_{15}$H$_{29}$NO$_3$SNa [M+Na]$^+$ 326.1760, found 326.1754.

(S)-6-(pent-4-en-1-yl)piperidin-2-one (13)

To a stirred solution of 12 (8.15 g, 26.87 mmol) in MeOH (218 mL) was added a 4 M HCl solution in dioxane (67 mL, 268.7 mmol), under a nitrogen atmosphere at 0 °C. After 2 h of stirring at 0 °C, saturated NaHCO$_3$ solution was added and the MeOH was evaporated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was taken up in CH$_2$Cl$_2$ (290 mL), and TEA (37.4 mL, 268.7 mmol) was added. The solution was stirred 2 h, and water was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (MeOH/CH$_2$Cl$_2$ = 1:60) to produce the desired compound 13 as an oil (2.78 g, 62%): $[\alpha]_{D}^{25} = +7.16$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.64 (s, 1H), 5.77-5.67 (m, 1H), 4.93 (d, $J = 16.5, 14.9$ Hz, 2H), 3.30 (d, $J = 4.9$ Hz, 1H), 2.33 (d, $J = 12.8, 9.0$ Hz, 1H), 2.26-2.16 (m, 1H), 2.05-1.98 (m, 2H), 1.84 (d, $J = 9.3$ Hz, 2H), 1.66-1.56 (m, 1H), 1.51-1.26 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.6, 138.1, 115.0, 77.5, 77.2, 76.8, 53.0, 36.3, 33.5, 31.3, 28.2, 24.5, 19.7; IR (neat) 2931, 2853, 1730, 1653, 1404, 1183, 1081, 992, 910 cm$^{-1}$; HRMS (ESI) calcd for C$_{10}$H$_{18}$NO [M+H]$^+$ 168.1383, found 168.1383.

(S)-tert-butyl 2-oxo-6-(pent-4-en-1-yl)piperidine-1-carboxylate (3)

DMAP (1.65 g, 13.52 mmol) was added to a solution of 13 (2.26 g, 13.52 mmol) in THF (65 mL) at room temperature, then cooled to 0 °C, di-tert-butyl dicarbonate (7.77 mL, 33.8 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature overnight and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (EtOAc/hexane = 1:8) provided N-protected product 3 as a yellow oil (3.41 g, 94%): $[\alpha]_{D}^{25} = +20.10$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.71-5.66 (m, 1H), 4.96-4.88 (m, 2H), 4.16-4.03 (m, 1H), 2.45-2.37 (m, 2H), 2.00 (dd, $J = 13.9, 7.0$ Hz, 2H), 1.91-1.53 (m, 6H),
1.45 (s, 9H), 1.40-1.24 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.5, 152.8, 138.1, 114.9, 82.6, 77.5, 77.2, 76.8, 55.5, 34.1, 33.4, 27.9, 25.6, 25.4, 17.0; IR (neat) 2926, 2853, 1715, 1457, 1364, 1286, 1151, 913 cm$^{-1}$; HRMS (EIS) calcd. for C$_{15}$H$_{25}$NO$_3$Na [M+Na]$^+$ 290.1727, found 290.1726.

(6S)-tert-butyl 2-hydroxy-6-(pent-4-en-1-yl)piperidine-1-carboxylate (14)

$$\begin{align*}
\text{O} \quad \text{N}^{\text{Boc}} \quad \text{CH}_{2}\text{Cl}_2 \quad \text{78°C} \\
\text{DIBAL'-H} \\
\text{3} \quad \text{14} \\
\text{87%}
\end{align*}$$

Piperidone 3 (0.7 g, 2.62 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (26 mL) under a N$_2$ atmosphere and cooled to -78 ºC. diisobutylaluminium hydrogen (4.4 mL, 6.60 mmol, 1.5 M in toluene) was added slowly and reaction mixture was stirred for 0.5 h. The reaction was quenched with MeOH (5 mL) and stirred at -78 ºC for 15 minutes. The quenched reaction was then treated with saturated solution sodium potassium tartrate (10 mL) and vigorously stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The title compound was obtained 14 as a clear oil (0.61 g, 87% yield) after SiO$_2$ flash chromatography (EtOAc/hexane $= 1:10$); $[\alpha]_{D}^{25} = +1.77$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.86-5.60 (m, 2H), 4.96 (dd, $J = 22.5$, 13.7 Hz, 2H), 4.04-3.83 (m, 1H), 2.05 (dd, $J = 14.1$, 7.1 Hz, 2H), 1.91-1.79 (m, 2H), 1.75-1.63 (m, 3H), 1.60-1.52 (m, 2H), 1.48-1.39 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.0, 114.6, 80.2, 77.5, 77.2, 76.8, 43.7, 34.2, 33.8, 30.8, 28.5, 27.1, 26.9, 13.3; IR (neat) 3442, 2935, 2859, 1690, 1376, 1174, 1098, 964, 874 cm$^{-1}$; HRMS (EIS) calcd. for C$_{15}$H$_{27}$NO$_3$Na [M+Na]$^+$ 292.1883, found 292.1883.

Piperidone 3 (0.7 g, 2.62 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (26 mL) under a N$_2$ atmosphere and cooled to -78 ºC. diisobutylaluminium hydrogen (4.4 mL, 6.60 mmol, 1.5 M in toluene) was added slowly and reaction mixture was stirred for 0.5 h. The reaction was quenched with MeOH (5 mL) and stirred at -78 ºC for 15 minutes. The quenched reaction was then treated with saturated solution sodium potassium tartrate (10 mL) and vigorously stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The title compound was obtained 14 as a clear oil (0.61 g, 87% yield) after SiO$_2$ flash chromatography (EtOAc/hexane $= 1:10$); $[\alpha]_{D}^{25} = +1.77$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.86-5.60 (m, 2H), 4.96 (dd, $J = 22.5$, 13.7 Hz, 2H), 4.04-3.83 (m, 1H), 2.05 (dd, $J = 14.1$, 7.1 Hz, 2H), 1.91-1.79 (m, 2H), 1.75-1.63 (m, 3H), 1.60-1.52 (m, 2H), 1.48-1.39 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.0, 114.6, 80.2, 77.5, 77.2, 76.8, 43.7, 34.2, 33.8, 30.8, 28.5, 27.1, 26.9, 13.3; IR (neat) 3442, 2935, 2859, 1690, 1376, 1174, 1098, 964, 874 cm$^{-1}$; HRMS (EIS) calcd. for C$_{15}$H$_{27}$NO$_3$Na [M+Na]$^+$ 292.1883, found 292.1883.

dimethyl (2-oxopentyl)phosphonate (15)

$$\begin{align*}
\text{H}_3\text{CO}^+ \text{O} \quad \text{H}_3\text{CO}^- \\
\text{S1} \quad \text{S2} \\
\text{H}_3\text{CO}^+ \text{O} \quad \text{H}_3\text{CO}^- \\
\text{15} \\
\text{80%}
\end{align*}$$

To a stirred solution of diisopropylamine (2.0 equiv) in THF (120 mL) and cooled to 0 ºC, n-BuLi (2.0 equiv) was added slowly to the mixture at 0 ºC. The mixture was cooled to -78 ºC after stirred at 0 ºC for 0.5 h and the Dimethyl methylphosphonate S1 (10 g, 80.59 mmol, 8.8 mL) was added dropwise at -78 ºC. After 30 min, methyl butyrate S2 (27.5 mmol, 241.78 mmol, 3.0 equiv) was added and stirred at -78 ºC for 1 h. The mixture was warmed to room temperature and quenched with NH$_4$Cl. The product was then extracted with EtOAc (3 x 60 mL) and washed with water (2 x 200 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The title compound 15 was obtained as a clear oil (12.52 g, 80% yield) after SiO$_2$ flash chromatography (EtOAc/hexane $= 1:1$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.68 (d, $J = 11.2$ Hz, 6H), 2.98 (d, $J = 22.7$ Hz, 2H), 2.49 (t, $J = 7.2$ Hz, 2H), 1.55-1.42 (m, 2H), 0.81 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.2, 77.5, 77.2, 76.8, 52.3, 52.2, 45.2, 41.1, 39.9, 16.2, 12.8.

(S,Z)-tert-butyl (12-oxopentadeca-1,10-dien-6-yl)carbamate (16)$^4$

S5
To a flame-dried flask was added anhydrous THF (220 mL) and the flask was purged with N₂. Sodium hydride (0.88 g, 25 mmol, 2.0 equiv, 60% in mineral oil) was added to the flask followed by 15 (4.3 g, 22 mmol, 2.0 equiv) at 0 °C. The mixture was stirred for 1 h at room temperature. To this solution was added 14 (2.96 g, 10.99 mmol, 1.0 equiv) in THF (30 mL). The reaction was stirred for 2.5 h at room temperature and quenched with saturated NH₄Cl (40 mL). The product was then extracted with EtOAc (3 x 100 mL) and washed with brine (2 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The title compound 16 was obtained as a colourless oil (3.03 g, 82% yield) after SiO₂ flash chromatography (EtOAc/hexane = 1:9): [α]₂⁵D = +0.6 (c 2.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.75-6.64 (m, 1H), 5.98 (d, J = 15.9 Hz, 1H), 5.69-5.63 (m, 1H), 4.85 (dd, J = 21.9, 13.7 Hz, 2H), 4.41 (d, J = 9.2 Hz, 1H), 3.46 (s, 1H), 2.39 (t, J = 7.3 Hz, 2H), 2.18-2.03 (m, 2H), 1.99-1.88 (m, 2H), 1.57-1.45 (m, 2H), 1.38 -1.20 (m, 16H), 0.82 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.5, 155.7, 146.6, 138.4, 130.4, 114.5, 78.7, 77.5, 77.2, 76.8, 50.0, 41.9, 35.1, 34.9, 33.4, 32.1, 28.3, 25.1, 24.4, 17.6, 13.7; IR (neat) 293 2, 2856, 1695, 1362, 1247, 1171, 992, 907 cm⁻¹; HRMS (EIS) calcd. for C₂₀H₃₅NO₃Na [M+Na]+ 360.2509, found 360.2506.

(2R,6S)-tert-butyl 2-(2-oxopentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (2)

To an oven dried flask equipped with magnetic stir bar was dissolved 16 (182 mg, 0.54 mmol) in dry dichloromethane (0.1 M) under argon atmosphere. The solution was kept at low the temperature (-20 °C) for 10 minutes before 0.4 mL of TfOH solution (CH₂Cl₂, 0.2 M, 1.0 equiv.) was added. The reaction mixture was stirred for 5 hours until TLC indicated the complete consumption of the starting material and 0.1 mL of triethylamine (1.0 equiv) was added in the reaction mixture before warming up to room temperature. The reaction mixture was then filtered through a pad of celite using diethyl ether to remove the catalyst. The resulting filtrate was condensed in vacuo to provide the crude residue. Purification using flash silica gel chromatography (EtOAc/hexane = 1:9) provided 141 mg (78% yield) of the intramolecular aza-Michael product 2. The ratio of diastereomers (cis/trans) was 14:86, based on the NMR integration. 2: [α]₂⁵D = +4.85 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.86-5.70 (m, 1H), 4.97-4.87 (m, 2H), 4.05 (dd, J = 8.7, 4.4 Hz, 1H), 3.83 (d, J = 30.0 Hz, 1H), 2.38-2.32 (m, 1H), 2.24-2.16 (m, 2H), 2.01 (dd, J = 14.1, 6.9 Hz, 2H), 1.77-1.33 (m, 23H), 0.90 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 209.3, 155.3, 138.8, 138.6, 114.5, 79.2, 77.5, 77.2, 76.8, 52.6, 47.6, 47.5, 44.90, 33.6, 32.8, 28.5, 26.2, 25.0, 17.2, 15.5, 13.8; IR (neat) 2935, 2867, 1687, 1363, 1171, 1062, 905, 731 cm⁻¹; HRMS (EIS) calcd. for C₂₀H₃₅NO₃Na [M+Na]+ 360.2509, found 360.2506.

2-((S)-2-hydroxypentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (1)
Sodium borohydride (0.57 g, 15.16 mmol) was added to a solution of 2 (1.42 g, 4.21 mmol) in methanol (21 mL) at 0 ºC, and the mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with saturated NH₄Cl (10 mL) and extracted with CH₂Cl₂. The combined extracts were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane = 1:20) to obtain 1 (1.116 g, 78% yield) as a colorless oil and 17 (0.254 g, 18% yield) as a oil.

1: [α]D²⁵ = +21.05 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.74-5.64 (m, 1H), 4.89 (dd, J = 21.7, 13.7 Hz, 2H), 3.84-3.82 (m, 1H), 3.60 (dd, J = 8.5, 4.3 Hz, 1H), 3.51-3.39 (m, 1H), 1.96 (dd, J = 14.0, 7.1 Hz, 2H), 1.76-1.49 (m, 9H), 1.42-1.22 (m, 16H), 0.83 (t, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 138.5, 114.4, 79.5, 77.5, 77.2, 76.8, 69.6, 51.9, 49.3, 43.6, 40.0, 33.7, 33.6, 28.4, 27.6, 26.4, 25.1, 23.7, 18.8, 14.0, 13.6; IR (neat) 3439, 2935, 2870, 1662, 1398, 1362, 1255, 1174, 1072, 907 cm⁻¹; HRMS (EIS) calcd. for C₂₀H₃₇NO₃Na [M+Na]⁺ 362.2666, found 362.2664.

17: [α]D²⁵ = +22.20 (c 2.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.83-5.73 (m, 1H), 5.03-4.88 (m, 2H), 4.16 (dd, J = 7.7, 3.6 Hz, 1H), 3.54 (dd, J = 9.1, 4.4 Hz, 1H), 3.52-3.42 (m, 1H), 2.04 (dd, J = 14.0, 7.0 Hz, 2H), 1.92-1.79 (m, 1H), 1.75-1.56 (m, 7H), 1.47 (d, J = 17.3 Hz, 12H), 1.40-1.30 (m, 5H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.14, 138.7, 114.8, 80.0, 77.5, 76.2, 76.8, 67.2, 52.3, 48.0, 43.8, 39.1, 34.0, 33.8, 28.6, 26.8, 26.2, 22.9, 19.3, 14.2, 13.8; IR (neat) 3450, 2935, 2870, 1659, 1457, 1398, 1364, 1174, 1107, 905, 776 cm⁻¹; HRMS (EIS) calcd. for C₂₀H₃₇NO₃Na [M+Na]⁺ 362.2666, found 362.2665.

(2R,6R)-tert-butyl2-((S)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-Carboxy-late (18)

A solution of compound 1 (0.85 g, 2.50 mmol) in a 10:1 DMF/H₂O mixture (55 mL) was treated with PdCl₂ (177 mg, 1.0 mmol) and CuCl (1.24 g, 12.5 mmol). The reaction mixture was then stirred under O₂ at room temperature for 24 h. The resulting mixture was filtered through Celite, then extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) afforded ketone 18 (0.74 g, 83%) : [α]D²⁵ = +21.20 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 3.91-3.88 (brs, 1H), 3.71-3.69 (brs, 1H), 3.58-3.56 (brs, 1H), 2.44-2.43 (m, 2H), 2.13 (s, 3H), 1.80-1.73 (m, 2H), 1.72-1.66 (m, 2H), 1.65-1.33 (m, 12H), 1.45 (s, 9H), 0.90 (t, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 208.1, 155.3, 79.1, 77.5, 77.2, 76.8, 69.0, 51.5, 48.9, 42.9, 39.7, 33.1, 29.4, 28.1, 24.7, 23.6, 20.8, 18.5, 13.7; IR (neat)
Trifluoroacetic acid (1.24 mL) was added to a solution of compound 18 (62 mg, 0.17 mmol) in CH$_2$Cl$_2$ (11 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated, and the residue was partitioned between aqueous NaHCO$_3$ and CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to afford the crude product which was purified by flash chromatography (MeOH/CH$_2$Cl$_2$ = 1:10) to give product (+)-porantheridine (35 mg, 85%) as a oil: [α]$^2$$_D$ = +25 (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 4.05-3.85 (m, 1H), 3.64-3.60 (m, 1H), 3.05-2.85 (m, 1H), 1.90-1.52 (m, 5H), 1.49-1.08 (m, 16H), 0.86 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 86.1, 77.5, 77.2, 76.8, 69.1, 49.3, 48.3, 40.0, 39.2, 34.2, 34.1, 30.8, 27.3, 23.7, 19.8, 19.4, 18.0, 14.3; IR (neat) 2929, 2864, 1628, 1440, 1376, 1255, 1126, 1050, 913, 787, 731 cm$^{-1}$; HRMS (EIS) calcd. for C$_{15}$H$_{28}$NO $[M+H]^+$ 238.2165, found 238.2164.

(6S)-tert-butyl 2-methoxy-6-(pent-4-en-1-yl)piperidine-1-carboxylate (19)

PPTS (0.33 g, 1.3 mmol) was added to the solution of 14 (1.75 g, 6.50 mmol) in MeOH (31 mL) at 0 ºC and then stirred for 0.5 h at the same temperature. The reaction was quenched with a saturated aqueous NaHCO$_3$ solution, and the mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford 19 (1.84 g, 80% yield) as a colorless oil.

(2S,6S)-tert-butyl 2-(2-oxopentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (5)

To a suspension of Sc(OTf)$_3$ (35 mg, 0.08 mmol) was added a mixture of 19 (0.1 g, 0.35 mmol) and silyl enolate 20 (3.0 equiv, 1.06 mmol) in CH$_3$CN (1.8 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h. Saturated aqueous sodium hydrogen carbonate was then added to quench the reaction,
and aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The product was isolated by silica gel column chromatography to afford product 5 (102 mg, 86% yield): $\lbrack \alpha \rbrack_{D}^{25} = +32.80$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.87-5.71 (m, 1H), 4.98 (dd, $J = 21.6, 13.7$ Hz, 2H), 4.62-4.54 (m, 1H), 4.13-4.01 (m, 1H), 2.72-2.61 (m, 1H), 2.54-2.45 (m, 1H), 2.45-2.37 (m, 2H), 2.07 (dd, $J = 13.2, 6.4$ Hz, 2H), 1.69-1.35 (m, 22H), 0.91 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 209.0, 155.1, 138.6, 114.6, 79.4, 77.5, 77.2, 76.8, 50.1, 47.4, 46.1, 44.7, 34.0, 38.6, 33.9, 33.4 (m), 28.4, 28.0, 27.3, 26.7, 17.1, 14.0, 13.7; IR (neat) 2932, 2864, 1659, 1401, 1252, 1171, 1098 cm$^{-1}$; HRMS (EIS) calcd. for C$_{20}$H$_{35}$NO$_3$Na $[M+Na]^+$ 360.2509, found 360.2511.

(2S,6S)-tert-butyl2-((R)-2-hydroxypentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxlate (4)

Sodium borohydride (0.51 g, 13.36 mmol) was added to a solution of 5 (1.25 g, 3.71 mmol) in methanol (21 mL) at 0 ºC, and the mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with saturated NH$_4$Cl (10 mL) and extracted with CH$_2$Cl$_2$. The combined extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane = 1:20) to obtain 4 (1.025 g, 82% yield) as a colorless oil and 21 (0.213 g, 17% yield) as an oil. 4: $\lbrack \alpha \rbrack_{D}^{25} = -23.17$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.71-5.54 (m, 1H), 4.82 (dd, $J = 22.0, 13.7$ Hz, 2H), 4.12-4.03 (m, 2H), 3.95-3.85 (m, 1H), 3.40-3.27 (m, 1H), 1.96-1.86 (m, 2H), 1.59 (d, $J = 9.2$ Hz, 1H), 1.51-1.20 (m, 24H), 0.77 (t, $J = 6.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.7, 138.3, 114.4, 79.3, 77.5, 77.2, 76.8, 69.4, 50.2, 47.5, 43.7, 39.9, 33.9, 33.4, 28.2, 27.4, 26.4, 18.7, 13.9; IR (neat) 3436, 2932, 2864, 1659, 1454, 1364, 1325, 1171, 1081, 910 cm$^{-1}$; HRMS (EIS) calcd. for C$_{20}$H$_{37}$NO$_3$Na $[M+Na]^+$ 362.2666, found 362.2665.

21: $\lbrack \alpha \rbrack_{D}^{25} = -12.25$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.80-5.68 (m, 1H), 4.98 (dd, $J = 21.6, 13.7$ Hz, 2H), 4.74-4.59 (m, 1H), 4.46-4.32 (m, 1H), 4.09-3.99 (m, 1H), 3.46-3.34(m, 1H), 2.02 (q, $J = 6.3, 5.5$ Hz, 2H), 1.82 (t, $J = 13.0$ Hz, 1H), 1.62-1.17 (m, 26H), 0.87 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.2, 138.4, 114.8, 80.2, 77.5, 77.2, 76.8, 67.3, 50.7, 46.3, 43.5, 38.9, 34.4, 33.7, 30.2, 28.5, 27.9, 27.0, 19.2, 14.7, 14.1; IR (neat) 3444, 2932, 2864, 1664,1406, 1171, 1101, 1073 cm$^{-1}$; HRMS (EIS) calcd. for C$_{20}$H$_{37}$NO$_3$Na $[M+Na]^+$ 362.2666, found 362.2665.

(2S,6R)-tert-butyl2-((R)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-carboxylate (22)

S9
A solution of compound 4 (135 mg, 0.40 mmol) in a 10:1 DMF/H₂O mixture (7.7 mL) was treated with PdCl₂ (29 mg, 0.16 mmol) and CuCl (198 mg, 2.0 mmol). The reaction mixture was then stirred under O₂ at room temperature for 24 h. The resulting mixture was filtered through Celite, then extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) afforded ketone 22 (121 mg, 85%): [α]²⁵<sub>D</sub> = -27.10 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CHCl₃) δ 4.20-4.08 (m, 1H), 4.05-3.86 (m, 1H), 3.52-3.33 (m, 1H), 2.46-2.34 (m, 2H), 2.07 (s, 3H), 1.61-1.30 (m, 25H), 0.86 (t, J = 5.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 208.5, 155.8, 79.7, 77.5, 77.2, 76.8, 69.7, 50.2, 47.7, 43.9, 43.3, 39.9, 34.0, 29.8, 29.6, 28.4, 27.5, 21.3, 18.9, 14.0; IR (neat) 3431, 2935, 2864, 1662, 1409, 1362, 1252, 1171, 1075 cm⁻¹; HRMS (EIS) calcd. for C₂₀H₃₇NO₄Na [M+Na]+ 378.2615, found 378.2617.

(-)-6-epi-porantheridine

Trifluoroacetic acid (1.2 mL) was added to a solution of compound 22 (58 mg, 0.16 mmol) in CH₂Cl₂ (8 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated, and the residue was partitioned between aqueous NaHCO₃ and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by flash chromatography (MeOH/CH₂Cl₂ = 1: 10) to give product (-)-6-epi-porantheridine (34 mg, 89%) as a oil: [α]²⁵<sub>D</sub> = +6.0 (c 0.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 3.80-3.70 (m, 1H), 2.56-2.39 (m, 1H), 2.15-2.06 (m, 1H), 1.65-1.15 (m, 25H), 0.87 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 86.2, 77.5, 77.2, 76.8, 67.6, 55.1, 51.7, 39.5, 39.1, 38.5, 34.3, 34.1, 33.7, 23.4, 20.7, 18.3, 14.0, 11.4; IR (neat) 2932, 2864, 1446, 1381, 1238, 1182, 1120, 1084, 731 cm⁻¹; HRMS (EIS) calcd. for C₁₅H₂₈NO [M+H]+ 238.2171, found 238.2165.

References

NMR Spectra

Compound $8^{\text{1H}}$

Compound $8^{\text{13C}}$
Compound 11.\(^1\)H

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{S} \\
\text{O} & \quad \text{HN} \\
& \quad \text{O}
\end{align*}
\]

Compound 11.\(^{13}\)C

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{S} \\
\text{O} & \quad \text{HN} \\
& \quad \text{O}
\end{align*}
\]
Compound $^{13}_{-}^1$H

![NMR spectrum of Compound $^{13}_{-}^1$H]

Compound $^{13}_{-}^{13}$C

![NMR spectrum of Compound $^{13}_{-}^{13}$C]
Compound 3-\(^1\)H

\[
\text{Diagram of Compound 3-}\(^1\)H
\]

Compound 3-\(^{13}\)C

\[
\text{Diagram of Compound 3-}\(^{13}\)C
\]

S16
Compound 14$^{1}$H

Compound 14$^{13}$C

S17
Compound 2-\textsuperscript{13}C
Compound 1-$^1$H

Compound 1-$^{13}$C
Compound 18-\textsuperscript{1}H

\begin{center}
\includegraphics[width=\textwidth]{18-1H}
\end{center}

Compound 18-\textsuperscript{13}C

\begin{center}
\includegraphics[width=\textwidth]{18-13C}
\end{center}
Compound $^{\text{21}}\text{H}$

Compound $^{\text{21}}\text{C}$
Compound 22-$^1$H

![NMR spectrum of Compound 22-$^1$H](image1)

Compound 22-$^{13}$C

![NMR spectrum of Compound 22-$^{13}$C](image2)
(-)-6-epi-porantheridine-$^1$H

(-)-6-epi-porantheridine-$^{13}$C
STEREOCHEMICAL ASSIGNMENT OF 2,6-DISUBSTITUTED COMPOUND 2 AND COMPOUND 5

The relative position of the substituents in cis-piperidine 5 was established by means of a NOESY experiment which showed an interaction between H_a and H_b, indicating that both display a cis relationship. That interaction was not observed in the trans-piperidine 2.

![cis-piperidine 5](image)

NOESY experiment on cis-piperidine 5 (CDCl₃, 400 MHz)
NOESY experiment on trans-piperidine 2 (CDCl3, 400 MHz)
IR spectra

Compound 8

Compound 11

Compound 10
(+)-porantheridine

Compound 5

Compound 4
MS spectra:

**Compound 8:** HRMS (ESI) calcd for C\textsubscript{10}H\textsubscript{19}NOSNa [M+Na\textsuperscript{+}] 224.1080, found 224.1081.

**Compound 11:** HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{28}NO\textsubscript{3}S [M+H\textsuperscript{+}] 302.1784, found 302.1785.

**Compound 10:** HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{27}NO\textsubscript{3}SNa [M+H\textsuperscript{+}] 302.1784, found 302.1784.
Compound 12: HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{SNa} [\text{M+Na}]^+ \ 326.1760$, found 326.1754.

Compound 13: HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{18}\text{NO} [\text{M+H}]^+ \ 168.1383$, found 168.1383.

Compound 3: HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{SNa} [\text{M+Na}]^+ \ 290.1727$, found 290.1726.
Compound 14: HRMS (EIS) calcd. for C_{13}H_{27}NO_{3}Na [M+Na]^+ 292.1883, found 292.1883.

Compound 16: HRMS (EIS) calcd. for C_{20}H_{35}NO_{3}Na [M+Na]^+ 360.2509, found 360.2506.

Compound 2: HRMS (EIS) calcd. for C_{20}H_{35}NO_{3}Na [M+Na]^+ 360.2509, found 360.2510.
Compound 1: HRMS (EIS) calcd. for C$_{20}$H$_{37}$NO$_3$Na [M+Na]$^+$ 362.2666, found 362.2664.

Compound 17: HRMS (EIS) calcd. for C$_{20}$H$_{37}$NO$_3$Na [M+Na]$^+$ 362.2666, found 362.2665.

Compound 18: HRMS (EIS) calcd. for C$_{20}$H$_{37}$NO$_4$Na [M+Na]$^+$ 378.2615, found 378.2616.
(+)-porantheridine: HRMS (EIS) calcd. for C₁₅H₂₈NO [M+H]⁺ 238.2165, found 238.2164.

Compound 5: HRMS (EIS) calcd. for C₂₀H₃₅NO₃Na [M+Na]⁺ 360.2509, found 360.2511.

Compound 4: HRMS (EIS) calcd. for C₂₀H₃₇NO₃Na [M+Na]⁺ 362.2666, found 362.2665.
Compound 21: HRMS (EIS) calcd. for C_{20}H_{37}NO_3Na [M+Na]^+ 362.2666, found 362.2665.

Compound 22: HRMS (EIS) calcd. for C_{20}H_{37}NO_4Na [M+Na]^+ 378.2615, found 378.2617.

(-)-6-epi-porantheridine: HRMS (EIS) calcd. for C_{15}H_{28}NO [M+H]^+ 238.2165, found 238.2165.