Supporting Information

for

Enantioselective synthesis of polyhydroxyindolizidinone
and quinolizidinone derivatives from a common precursor

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Experimental details and analytical data of all new compounds as well as their $^1$H and $^{13}$C NMR spectra

Content

Experimental procedures and characterization data for all new compounds S2–S15
Copies of NMR spectral data for all new compounds S16–S38
Experimental procedures and characterization data for all new compounds

Column chromatography was performed on silica gel, Merck grade (230-400 mesh). TLC plates were visualized with vaniline solution, in an iodine chamber or with UV, unless noted otherwise. Melting points were recorded in open capillaries and are uncorrected. Optical rotations were measured on a Rudolph Autopol-IV polarimeter purchased from a DST grant and IR spectra were recorded on a Perkin-Elmer Spectrum-1 instrument using KBr disks, chloroform solution or as neat. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 and 600, operating at 400, 600 MHz for $^1$H and 100 and 150 MHz for $^{13}$C NMR, respectively purchased from a DST-FIST grant. HRMS were performed in a JEOL-JNM mass spectrometer obtained from a paid source. Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF, toluene, benzene and ether were freshly distilled under argon from a purple solution of sodium and benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

(2S,4R,6R)-2-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-6-vinylpiperidin-4-ol (7).

A solution of oxazabicycle 6 (200 mg, 0.75 mmol) in acetic acid/water (v/v 80:20, 2.0 mL) was treated with activated zinc powder (245 mg, 3.75 mmol) portion wise at room temperature for 1 h. Water (2 mL) was then added, and the mixture was filtered. The filter cake was washed with water (5 mL) and the combined aqueous solution was neutralized with solid NaHCO$_3$. The aqueous mixture was then repeatedly extracted with EtOAc (3×10 mL) and the combined organic phase was washed with water (1×10 mL), brine solution (1×10 mL), and then dried over MgSO$_4$. The dried solution was then filtered, and the filtrate was concentrated under reduced pressure to leave a crude product which was purified by column chromatography over neutral alumina using ethyl acetate-hexane mixture (1:1) to give the piperidinol 7 as a colorless liquid (177 mg, 86%). $[\alpha]_D^2 +6.9$ (c 0.85, CHCl$_3$); IR (CHCl$_3$): 3392, 2936, 2858, 1645, 1449, 1367, 1281, 1163, 1100, 1040, 928 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 5.84$ (ddd, $J = 6.4$, 10.4, 16.8 Hz, 1 H), 5.18 (dd, $J = 1.2$, 16.8 Hz, 1 H), 5.05 (dd, $J = 0.8$, 10.0 Hz, 1 H), 4.09-4.04 (m, 1 H), 3.96 (d, $J = 6.4$ Hz, 2 H), 3.73 (dq, $J = 4.4$, 10.8 Hz, 1 H), 3.17-3.13 (m, 1 H), 2.90-2.86 (m, 1 H), 2.05-1.97 (m, 2 H), 1.77 (brm, 2 H),
1.62-1.58 (m, 8 H), 1.41-1.32 (m, 2 H), 1.17 (dd, J = 11.6, 22.8 Hz, 1 H), 1.00 (dd, J = 11.6, 22.8 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 140.4, 114.6, 109.5, 78.0, 69.0, 64.9, 57.2, 55.4, 41.5, 36.9, 36.0, 34.7, 25.1, 24.0, 23.8; HRMS (QTOF ES+) found m/z 268.1906 (M+H)$^+$; C$_{15}$H$_{26}$NO$_3$ requires 268.1913.

(2S,4R,6R)-4-(tert-Butyldimethylsilyloxy)-2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-6-vinylpiperidine (8).

DIEA (145 mg, 190 µl, 1.12 mmol) followed by TBS-OTf (295 mg, 260 µl, 1.12 mmol) was added drop wise to a stirred solution of the aminol 7 (200 mg, 0.75 mmol) in dry CH$_2$Cl$_2$ (5 mL) at −5 °C. The resulting mixture was stirred for 1 h at the same temperature before being quenched with dry methanol (1 mL). The reaction mixture was then diluted with CH$_2$Cl$_2$ (25 mL) and the combined organic solution was successively washed with water (1×25 mL), brine solution (1×25 mL) and then dried over MgSO$_4$. The dried solution was then filtered and the filtrate was concentrated in vacuo to leave a crude product, which was purified by flash chromatography over silica gel using 5% ethyl acetate in hexane to give the silyl ether 8 (260 mg, 91%) as a colorless oil. [α]$_D$ +5.9 (c 0.48, CHCl$_3$). IR (CHCl$_3$): 3436, 2936, 2857, 1645, 1463, 1448, 1362, 1252, 1163, 1099, 926, 837, 775 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 5.76 (ddd, $J = 6.8, 10.4, 17.2$ Hz, 1 H), 5.10 (dd, $J = 0.8, 17.2$ Hz, 1 H), 4.95 (dd, $J = 0.8, 10.8$ Hz, 1 H), 4.00-3.86 (m, 3 H), 3.60 (sep, $J = 4.4$ Hz, 1 H), 3.06-3.02 (m, 1 H), 2.83-2.79 (m, 1 H), 1.80-1.73 (m, 2 H), 1.55-1.51 (m, 10 H), 1.35-1.31 (m, 1 H), 1.14 (dd, $J = 11.6, 23.2$ Hz, 1 H), 0.94 (dd, $J = 11.6, 23.2$ Hz, 1 H), 0.82 (s, 9 H), -0.01 (s, 6 H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 140.9, 114.1, 109.2, 78.2, 69.8, 64.8, 57.2, 55.1, 42.2, 37.6, 36.0, 34.8, 25.8, 25.2, 23.9, 23.8, 18.1, -4.6; HRMS (QTOF ES+) found m/z 382.2774 (M+H)$^+$; C$_{21}$H$_{40}$NO$_3$Si requires 382.2777.
1-((2S,4R,6R)-4-(tert-Butyldimethylsilyloxy)-2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-6-vinylpiperidin-1-yl)prop-2-en-1-one (9).

EDC (200 mg, 1.05 mmol), acrylic acid (58 mg, 55 µL, 0.8 mmol), N-methylmorpholine (55 µL, 0.53 mmol) and HOBt (70 mg, 0.53 mmol) were sequentially added to a stirred solution of the amine 8 (200 mg, 0.53 mmol) in dry CH₂Cl₂ (5 mL) at 0 °C. The reaction mixture was then allowed to come to room temperature and stirred for 6 h. The reaction mixture was then extracted with CH₂Cl₂ (2×25 mL) and the combined extract was washed sequentially with 1 (N) HCl (1×20 mL), saturated aqueous NaHCO₃ solution (1×20 mL), water (1×20 mL) and brine (1×20 mL). The resulting solution was then dried over anhydrous MgSO₄, filtered, and the filtrate was concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using 1:8 ethyl acetate-hexane solution to give the amide 9 as a colourless oil (220 mg, 96%). [α]D = -4.3 (c 0.86, CHCl₃); IR (CHCl₃): 2935, 2858, 1649, 1613, 1420, 1366, 1254, 1163, 1011, 1067, 928, 910, 837, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 6.60-6.47 (m, 1 H), 6.24-6.07 (m, 2 H), 5.64-5.60 (m, 1 H), 5.34-4.84 (m, 3 H), 4.51-4.43 (m, 1 H), 3.97-3.62 (m, 4 H), 2.11 (br m, 1 H), 1.82-1.80 (m, 2 H), 1.65-1.45 (m, 9 H), 1.30–1.18 (m, 2 H), 0.81 (s, 9 H), -0.001 (s, 3 H), -0.02 (s, 3 H); ¹H NMR (DMSO-d₆, 400 MHz, 70 °C): δ = 6.71-6.62 (m, 1 H), 6.05 (br d, J = 16.4 Hz, 2 H), 5.63 (d, J = 10.0 Hz, 1 H), 5.00-4.97 (m, 2 H), 4.71-4.48 (m, 3 H), 4.03 (br s, 1 H), 3.71 (dd, J = 6.4, 8.0 Hz, 1 H), 3.65 (br m, 1 H), 2.0-1.92 (m, 1 H), 1.82-1.58 (m, 3 H), 1.48-1.36 (m, 8 H), 1.28-1.16 (m, 2 H), 0.80 (s, 9 H), -0.04 (s, 3 H), -0.05 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ = 167.5 (166.6), 140.7 (139.9), 128.9 (128.1), 116.9 (115.1), 109.8, 67.2, 65.8, 65.0, 54.3, 49.6 (48.8), 37.4, 36.4, 35.5, 34.6, 32.3, 31.3, 25.8, 25.2, 24.0, 23.9, 18.1, -4.9, -5.1; ¹³C NMR (DMSO-d₆, 100 MHz, 70 °C): δ = 166.4, 141.1, 129.2, 127.7, 114.8, 108.8, 76.7, 66.2, 64.6, 52.6, 48.8, 38.8, 36.4, 34.7, 31.1, 25.6, 24.6 (two signals), 23.7, 17.6, -5.2. HRMS (QTOF ES+) found m/z 436.2875 (M+H)+; C₂₄H₄₂NO₄Si requires 436.2883.
(5S,7R,8aR)-7-(tert-Butyldimethylsilyloxy)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-6,7,8,8a-tetrahydroindolizin-3(5H)-one (10).

Grubbs’ 2nd generation catalyst (31 mg, 8 mol %) was added to a stirred solution of the diene 9 (200 mg, 0.46 mmol) in dry degassed benzene (15 ml) under argon atmosphere and the homogeneous mixture was heated to reflux for 24 h. The reaction mixture was allowed to come to room temperature and then concentrated in vacuo to leave a crude product which on chromatography over silica gel using ethyl acetate–petroleum ether (2:8) provided the product 10 as a colorless solid (140 mg, 75%). Mp: 118-120 °C; [α]D −12.3 (c 0.89, CHCl3); IR (CHCl3): 2931, 2858, 1672, 1471, 1450, 1417, 1390, 1291, 1164, 1121, 1085, 935, 843, 775 cm−1; 1H NMR (CDCl3, 400 MHz): δ = 6.99 (dd, J = 1.2, 5.6 Hz, 1 H), 6.0 (d, J = 5.6 Hz, 1 H), 5.05 (ddd, J = 2.8, 6.0, 9.6 Hz, 1 H), 4.34 (dd, J = 6.0, 9.6 Hz, 1 H), 4.01 (dd, J = 3.2, 9.6 Hz, 1 H), 3.90-3.85 (m, 2 H), 3.21-3.16 (m, 1 H), 2.39-2.35 (m, 1 H), 2.23-2.20 (m, 1 H), 1.64-1.61 (m, 8 H), 1.42-1.41 (m, 2 H), 1.30 (dd, J = 11.6, 23.2 Hz, 1 H), 1.10 (dd, J = 11.6, 23.2 Hz, 1 H), 0.91 (s, 9 H), 0.1 (overlapped singlet, 6 H); 13C NMR (CDCl3, 100 MHz): δ = 168.7, 146.2, 128.1, 109.7, 74.9, 69.6, 69.0, 61.7, 58.3, 40.2, 39.0, 37.6, 34.2, 25.8, 25.2, 24.2, 23.7, 18.1, -4.6, -4.7. HRMS (QTOF ES+) found m/z 430.2391 (M+Na)+; C22H37NNaO4Si requires 430.2390.

1-((2S,4R,6R)-4-(tert-Butyldimethylsilyloxy)-2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-6-vinylpiperidin-1-yl)but-3-en-1-one (11).

EDC (300 mg, 1.58 mmol), vinyl acetic acid (86 µL, 1.02 mmol), N-methylmorpholine and HOBt (106 mg, 0.79 mmol) were sequentially added to a stirred solution of the amine 8 (300 mg, 0.79 mmol) in dry CH2Cl2 (8 mL) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 10 h. The resulting mixture was then extracted with CH2Cl2 (2×25 mL) and the combined extract was washed sequentially with 1 (N) HCl (1×20 mL),
saturated aqueous NaHCO₃ solution (1×20 mL), water (1×20 mL) and brine (1×20 mL). The residual solution was then dried over anhydrous MgSO₄, filtered, and the filtrate was concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using 1:9 ethyl acetate-hexane solution to give the amide 11 as colorless oil (318 mg, 90%). [α]D −19.1 (c 0.83, CHCl₃); IR (CHCl₃): 2938, 2856, 1652, 1611, 1422, 1254, 1160, 1101, 910, 834, 776 cm⁻¹; ¹H NMR (mixture of rotamers) (CDCl₃, 400 MHz): δ = 6.14-6.08 (m, 1 H), 5.94-5.86 (m, 1 H), 5.14-4.97 (m, 4 H), 4.81-4.78 (m, 1 H), 4.56-4.52 (m, 1 H), 4.36-4.35 (m, 1 H), 4.04-3.97 (m, 1 H), 3.84-3.63 (m, 2 H), 3.20-3.03 (m, 2 H), 2.12-2.03 (m, 1 H), 1.85-1.75 (m, 2 H), 1.66-1.41 (m, 9 H), 1.31-1.30 (m, 2 H), 0.83 (s, 9 H), 0.06 (-0.06) (m, 6 H); ¹H NMR (DMSO-d₆, 400 MHz, 70 °C): δ = 6.08-6.00 (m, 1 H), 5.89-5.78 (m, 1 H), 5.19-4.96 (m, 4 H), 4.67-4.48 (m, 3 H), 4.01 (d, J = 3.2 Hz, 1 H), 3.70 (d, J = 7.2 Hz, 1 H), 3.59-3.56 (m, 1 H), 3.05-2.93 (m, 2 H), 1.94 (d, J = 11.6 Hz, 1 H), 1.83-1.72 (m, 3 H), 1.46-1.39 (m, 8 H), 1.27-1.18 (m, 2 H), 0.8 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H).¹³C NMR (CDCl₃, 100 MHz): δ = 171.3 (170.8), 140.5 (139.9), 131.9 (131.7), 117.6 (117.4), 115.1, 110.2 (109.7), 77.5 (76.6), 67.1, 65.2 (64.9), 54.3 (53.9), 49.5 (48.5), 39.2 (39.1), 37.7 (37.2), 36.3, 35.5, 35.1 (34.7), 32.0 (31.4), 25.8, 25.2 (25.16), 23.94 (23.90), 18.0, -5.0, -5.1.¹³C NMR (DMSO-d₆, 100 MHz, 70 °C): δ = 171.2, 141.4, 133.4, 117.3, 115.4, 109.3, 77.2, 66.7, 65.1, 53.3, 49.1, 38.5, 36.8, 32.3, 35.3, 26.1 (two signals), 25.1, 24.1, 23.9, 18.1, -4.7. HRMS (QTOF ES+) found m/z 472.2853 (M + Na)⁺; C₂₅H₄₃NNaO₄Si requires 472.2859.

(2R,4S,9aR)-2-(tert-Butyldimethylsilyloxy)-4-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-3,4,7,9a-tetrahydro-1H-quinolinizin-6(2H)-one (12).

Grubbs’ 2nd generation catalyst (11 mg, 3 mol%) was added to a stirred solution of the diene 11 (200 mg, 0.45 mmol) in dry degassed benzene (15 mL) under an argon atmosphere and the homogeneous mixture was heated at 50 °C for 2 h. The reaction mixture was allowed to come to room temperature and then concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using ethyl acetate–hexane (2:8) to provide the product 12 as a colorless solid (178 mg, 95%). Mp: 136-138 °C; [α]D −75.0 (c 0.4, CHCl₃); IR (neat): 2938, 2891, 1642, 1471, 1319, 1162, 1075, 841, 775 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 5.66-5.58 (m, 2 H), 5.05 (ddd, J = 4.4, 6.4, 10.0 Hz, 1 H), 4.00 (dd, J
= 6.4, 8.8 Hz, 1 H), 3.79-3.72 (m, 2 H), 3.66 (d, J = 12.0 Hz, 1 H), 2.81 (d, J = 7.6 Hz, 2 H), 2.72-2.67 (m, 1 H), 2.24 (dd, J = 4.0, 12.4 Hz, 1 H), 1.97 (dd, J = 2.4, 12.8 Hz, 1 H), 1.54-1.41 (m, 9 H), 1.32 (brs, 2 H), 1.20 (dd, J = 12.0, 23.6 Hz, 1 H), 0.81 (s, 9 H), 0.01-(-0.01) (m, 6 H). 13C NMR (CDCl3, 100 MHz): δ = 167.6, 125.3, 121.9, 109.6, 76.0, 69.5, 67.2, 63.4, 58.4, 43.7, 38.0, 37.4, 34.4, 33.2, 25.7, 25.2, 24.1, 23.7, 18.0, -4.6, -4.7. HRMS (QTOF ES+) found m/z 444.2539 (M+Na)+, C23H39NNaO6Si requires 444.2546.

(1R,2R,5S,7R,8aR)-7-(tert-Butyldimethylsilyloxy)-1,2-dihydroxy-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)hexahydroindolizin-3(5H)-one (13).

NMO (115 mg, 0.98 mmol) was added in one portion to a solution of the olefin 10 (200 mg, 0.49 mmol) in a mixture of acetone / water (4:1) (5 mL) at room temperature, and then a solution of OsO4 in water (1 % by wt, 0.7 mL) was added drop wise over 5 minute. The resulting mixture was stirred for 12 h. before being quenched by addition of granular sodium bisulfite (20 mg). The inhomogeneous mixture was then filtered and the filtrate was concentrated in vacuo to leave a residue which was extracted with ethyl acetate (2 × 30 mL). The combined organic part was washed with water (2 × 30 mL), brine solution (1 × 30 mL) and then dried over MgSO4. The dried organic solution was then filtered and the filtrate was concentrated under reduced pressure to leave a crude mass which was purified over silica gel using 80 % ethyl acetate-hexane to give a colourless crystalline solid 13 (208 mg, 96 %). Mp: 222-224 °C. [α]D +9.2 (c 0.65, MeOH). IR (neat): 3436, 2934, 2859, 1706, 1686, 1671, 1447, 1374, 1254, 1164, 1124, 1093, 837, 770 cm-1. 1H NMR (CDCl3, 400 MHz): δ = 4.81 (ddd, J = 3.2, 6.0, 9.6 Hz, 1 H), 4.31 (br m, 1 H), 4.16 (dd, J = 7.0, 9.6 Hz, 2 H), 4.01 (d, J = 5.2 Hz, 1 H), 3.9 (dd, J = 3.2, 9.2 Hz, 1 H), 3.74-3.67 (m, 1 H), 3.26 (dd, J = 2.4, 13.2 Hz, 1 H), 2.99 (s, 1 H), 2.95-2.89 (m, 1 H), 2.23 (br d, J = 12.4 Hz, 1 H), 1.97 (br d, J = 12.0 Hz, 1 H), 1.62-1.50 (m, 8 H), 1.33 (brm, 2 H), 1.21-1.03 (m, 2 H), 0.80 (s, 9 H), -0.01 (s, 6 H). 13C NMR (CDCl3, 100 MHz): δ = 171.2, 110.0, 74.7, 70.7, 69.3, 69.1, 68.3, 62.9, 59.0, 38.9, 38.4, 37.5, 34.3, 25.7, 25.2, 24.1, 23.7, 18.0, -4.67, -4.7. HRMS (QTOF ES+) found m/z 464.2445 (M+Na)+; C22H39NNaO6Si requires 464.2444.
A solution of the diol 13 (100 mg, 0.23 mmol) in anhydrous THF (2 mL) was added dropwise to a stirred suspension of sodium hydride (28.0 mg, 0.64 mmol) in THF (3 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was then allowed to come to room temperature and stirred for 10 minutes. The resulting solution was cooled back to 0 °C and benzyl bromide (110 µL, 0.92 mmol) followed by n-tetrabutylammonium iodide (cat. 4 mg) were sequentially added. The reaction mixture was stirred for 6 h at room temperature, quenched with saturated NH₄Cl solution (2 ml) at 0 °C, and then extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed sequentially with water (1 × 20 mL), brine (1 × 20 mL), dried over anhydrous Na₂SO₄ and then filtered. The filtrate was concentrated under reduced pressure to leave a crude mass which was purified by column chromatography over silica gel using ethyl acetate in petroleum ether (1:9) to provide the compound 14 (98 mg, 70 %) as a colorless oil. [α]D +26.1 (c 0.88, CHCl₃); IR (CHCl₃): 2931, 2856, 1701, 1450, 1254, 1123, 1112, 837, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 7.31-7.19 (m, 10 H), 4.95 (ddd, J = 3.2, 6.0, 9.6 Hz, 1 H), 4.90 (d, J = 12.0 Hz, 1 H), 4.79 (d, J = 12.0 Hz, 1 H), 4.69 (d, J = 12 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.28 (dd, J = 6.0, 9.6 Hz, 1 H), 4.04 (dd, J = 3.2, 9.6 Hz, 1 H), 3.96 (d, J = 5.6 Hz, 1 H), 3.75 (dd, J = 2.4, 6.0 Hz, 1 H), 3.72-3.68 (m, 1 H), 3.37-3.34 (m, 1 H), 3.00-2.94 (m, 1 H), 2.28-2.24 (m, 1 H), 1.99-1.95 (m, 1 H), 1.66-1.57 (m, 8 H), 1.42-1.33 (m, 2 H), 1.22 (dd, J = 12.0, 24.0 Hz, 1 H), 1.05 (dd, J = 12.4, 23.2 Hz, 1 H), 0.88 (s, 9 H), 0.08-0.05 (m, 6 H); ¹³C NMR (CDCl₃, 100 MHz): δ = 169.5, 137.5, 137.4, 128.6, 128.5, 128.4, 128.2, 128.0, 127.0, 109.8, 76.3, 75.6, 74.8, 72.5, 72.2, 69.0, 68.6, 60.5, 58.9, 39.3, 38.3, 37.5, 34.2, 25.8, 25.2, 24.1, 23.7, 18.1, -4.6, -4.7. HRMS (QTOF ES+) found m/z 644.3394 (M + Na), C₃₆H₅₁NNaO₆Si requires 644.3383.
Acetic anhydride (120 mg, 1.15 mmol) was added to a stirred solution of the diol 13 (100 mg, 0.23 mmol) in anhydrous pyridine (2 mL) and the resulting reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then diluted with ethyl acetate (1 × 50 mL) and the organic extract was washed sequentially with HCl (1 N, 10 mL), water (1 × 20 mL) followed by brine solution (1 × 20 mL). The organic part was then dried over anhydrous Na$_2$SO$_4$, filtered and the filtrate was concentrated under reduced pressure to leave a crude mass which was purified over silica gel using ethyl acetate/petroleum ether (2:9) to provide the compound 15 (95 mg, 80 %) as a colorless solid. [α]$_D$ –7.6 (c 0.42, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 5.42 (d, $J$ = 6.0 Hz, 1 H), 5.23 (d, $J$ = 6.0 Hz, 1 H), 4.96 (ddd, $J$ = 2.8, 6.4, 9.6 Hz, 1 H), 4.28 (dd, $J$ = 6.0, 9.2 Hz, 1 H), 4.06 (ddd, $J$ = 2.8, 9.2 Hz, 1 H), 3.78 (dd, $J$ = 4.4, 10.4, 15.2 Hz, 1 H), 3.36 (dd, $J$ = 2.8, 13.2 Hz, 1 H), 3.00 (dt, $J$ = 2.4, 10.8 Hz, 1 H), 2.35-2.31 (m, 1 H), 2.22-2.18 (m, 1 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 1.64-1.58 (m, 8 H), 1.47-1.42 (m, 2 H), 1.35-1.30 (m, 2 H), 0.96 (s, 9 H), 0.01 (s, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 170.0 (s), 169.6 (s), 166.3 (s), 110.1 (s), 74.7 (d), 70.0 (d), 69.1 (d), 68.8 (d), 68.2 (t), 60.8 (d), 59.1 (d), 38.6 (t), 38.2 (t), 37.6 (t), 34.2 (t), 25.7 (q), 25.1 (t), 24.1 (t), 23.7 (t), 20.6 (q), 20.3 (q), 18.0 (s), -4.6 (q), -4.7 (q); HRMS (QTOF ES+) found m/z 548.2661 (M + Na)$^+$, C$_{26}$H$_{43}$NNaO$_8$Si requires 548.2656.

HCl (10 %, 2 mL) was added drop wise to a stirred solution of the acetal derivative 14 (60 mg, 0.09 mmol) in THF (2 mL) at 0 °C. The resulting mixture was allowed to come to room temperature and stirred for 18 h. The homogeneous solution was then diluted with water (2
mL) and neutralized with solid NaHCO₃ before being extracted with ethyl acetate (2 × 10 mL). The combined organic extract was washed successively with water (1 × 5 mL), brine solution (1 × 5 mL), dried over MgSO₄ and then filtered. The filtrate was concentrated in vacuo to leave a crude viscous liquid which was purified by flash chromatography over silica gel using 20% methanol in ethyl acetate to provide 16 (36 mg, 89%) as a colorless gum. 

\[ \sigma_D^+ 5.1 \] (c 0.88, CHCl₃); IR (CHCl₃): 3438, 2935, 2862, 1706, 1684, 1671, 1374, 1258, 1161, 1124, 774 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz): δ = 7.41–7.11 (m, 10 H), 5.00 (brs, 1 H), 4.92 (d, J = 12.0 Hz, 1 H), 4.77 (d, J = 12.0 Hz, 1 H), 4.66 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.44 (brs, 1 H), 4.04 (d, J = 5.6 Hz, 1 H), 3.82 (brm, 1 H), 3.73 (dd, J = 2.8, 5.2 Hz, 1 H), 3.70–3.66 (m, 1 H), 3.59 (brm, 1 H), 3.50–3.47 (m, 1 H), 3.26 (d, J = 11.2 Hz, 1 H), 2.83 (brs, 1 H), 2.60 (brs, 1 H), 2.20–2.17 (m, 1 H), 1.97–1.93 (m, 1 H), 1.50 (dd, J = 11.2, 22.8 Hz, 1 H), 1.04 (dd, J = 12.0, 23.2 Hz, 1 H); \(^13\)C NMR (CDCl₃, 100 MHz): δ = 170.6, 137.3, 128.54, 128.5, 128.2, 128.1, 128.0, 127.7, 76.4, 75.9, 72.7, 72.2, 69.7, 67.5, 62.8, 61.1, 57.7, 33.7, 29.7. HRMS (QTOF ES+) found m/z 450.1892 (M + Na)⁺; C₂₄H₂₉NNaO₆ requires 450.1893.

\(1R,2R,5S,7S,8aR\)-1,2-Bis(benzyloxy)-7-hydroxy-5-(hydroxymethyl)hexahydroindolizin-3(5\(H\))-one (17).

NaIO₄ (80 mg, 0.38 mmol) was added portion wise over 5 min to a solution of the diol 16 (80 mg, 0.19 mmol) in acetonitrile /water (v/v 3:1) (3 mL) at 5–10 °C and the resulting mixture was stirred for 30 min. The reaction mixture was allowed to come to room temperature and then filtered. The filtrate was diluted with dichloromethane (20 mL) and the combined organic solution was washed sequentially with water (1 × 10 mL), brine solution (1 × 10 mL) and then dried over MgSO₄. The organic part was filtered and the filtrate was concentrated in vacuo to leave the crude product which was used as such in the next step. The crude aldehyde, thus obtained, was dissolved in dry methanol (2 mL) and cooled to 0 °C. NaBH₄ (10 mg, 0.28 mmol) was then added in one portion and the resulting reaction mixture was allowed to come to room temperature over 30 min while stirring. The reaction mixture was then concentrated and the residue was extracted with ethyl acetate (2 × 10 mL). The combined organic extract was washed with water (5 mL), brine solution (5 mL), and dried.
over MgSO₄. The organic part was then filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified over silica gel using 50% ethyl acetate-hexane solution to give the product 17 as a viscous liquid (68 mg, 92% over two steps). [α]D +70.1 (c 1.5, CHCl₃); IR (CHCl₃): 3432, 2941, 2859, 1709, 1680, 1371, 1164, 1114, 1094, 774 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 7.42-7.27 (m, 10 H), 5.02 (br s, 1 H), 4.93 (d, J = 11.6 Hz, 1 H), 4.77 (d, J = 11.6 Hz, 1 H), 4.65 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 3.98 (d, J = 6.0 Hz, 1 H), 3.90-3.74 (m, 4 H), 3.68 (t, J = 5.6 Hz, 1 H), 3.50 (ddd, J = 3.2, 4.8, 8.0 Hz, 1 H), 3.23 (ddd, J = 2.8, 6.4, 9.2 Hz, 1 H), 2.28-2.24 (m, 1 H), 1.86-1.80 (m, 1 H), 1.02 (dd, J = 12.0, 23.2 Hz, 1 H), 0.89-0.84 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz): δ = 170.7, 137.2, 137.16, 128.56, 128.50, 128.4, 128.15, 128.09, 128.0, 75.0, 72.4, 72.1, 67.4, 63.1, 60.7, 58.1, 38.8, 36.9, 29.7. HRMS (QTOF ES+) found m/z 420.1790 (M+Na)⁺; C₂₃H₂₇NNaO₅ requires 420.1787.

(1R,2R,5S,7S,8aR)-1,2,7-Trihydroxy-5-(hydroxymethyl)hexahydroindolizin-3(5H)-one (18).

Pd(OH)₂-C (10%, 4 mg) was added to a solution of the benzyl ether 17 (25 mg, 0.06 mmol) in methanol (2 mL) and the resulting heterogeneous mixture was vigorously stirred under hydrogen atmosphere for 3 h. The reaction mixture was then filtered through celite, the filter cake was washed with methanol (10 mL), and the combined filtrate was concentrated in vacuo to leave a crude product which was purified by chromatography over neutral alumina using MeOH/EtOAc (1:4) to obtain the tetrahydroxyindolizidine derivative 18 (11 mg, 81%) as a colourless foam. [α]D +2.1 (c 0.47, MeOH); ¹H NMR (DMSO-d₆, 400 MHz): δ = 5.49 (br s, 1 H), 5.02 (s, 1 H), 4.91-4.88 (m, 1 H), 4.06 (s, 1 H), 3.79 (brm, 3 H), 3.64 (m, 1 H), 3.21-3.07 (m, 3 H), 1.99 (d, J = 10.4 Hz, 1 H), 1.79 (d, J = 10.8 Hz, 1 H), 1.09-0.96 (m, 2 H). ¹³C NMR (DMSO-d₆, 100 MHz): δ = 172.5, 71.2, 70.1, 67.0, 63.1, 62.2, 57.7, 38.4, 37.7; HRMS (QTOF ES+) found m/z 240.0849 (M+Na)⁺; C₉H₁₅NNaO₅ requires 240.0848.
(1R,2S,6S,8R,9aR)-8-(tert-Butyldimethylsilyloxy)-1,2-dihydroxy-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl)hexahydro-1H-quinolizin-4(6H)-one (19).

In a one-necked round bottomed flask equipped with a magnetic stirring bar, olefin 12 (200 mg, 0.49 mmol) was taken in acetone / water (4:1) (5 mL) at room temperature. Solid N-methylmorpholine-N-oxide (115 mg, 0.98 mmol) followed by an aqueous solution of OsO₄ (1% by w/v, 0.4 mL) were then sequentially added to the reaction mixture which was stirred for 6 h before being quenched with granular sodium bisulfite (200 mg). The reaction mixture was then filtered, the filtrate was concentrated in vacuo, and the resulting residue was diluted with ethyl acetate (2 × 30 mL). The combined organic part was washed sequentially with water (2×20 mL) and brine solution (1×20 mL), and then dried over MgSO₄. The organic extract was then filtered and the filtrate was concentrated under reduced pressure to leave a crude product which was purified by column chromatography over silica gel using 80 % ethyl acetate-hexane to give compound 19 as a colourless crystalline solid (205 mg, 95 %). Mp: 208 °C; [α]D +5.1 (c 0.6, MeOH); IR (neat): 3466, 3350, 2887, 2859, 1649, 1619, 1123, 1084, 838, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 4.91 (ddd, J = 4.4, 6.0, 10.0 Hz, 1 H), 4.04-4.02 (br m, 1 H), 3.94 (dd, J = 6.0, 8.0 Hz, 1 H), 3.81-3.72 (m, 3 H), 3.29-3.26 (m, 1 H), 3.11 (d, J = 3.2 Hz, 1 H), 3.00 (d, J = 5.2 Hz, 1 H), 2.80 (t, J = 9.2 Hz, 1 H), 2.54 (dd, J = 9.6 Hz, 16.4 Hz, 1 H), 2.42 (dd, J = 5.6, 16.4 Hz, 1 H), 2.18 (dd, J = 4.4, 12.4 Hz, 1 H), 1.97 (dd, J = 4.8, 12.4 Hz, 1 H), 1.52-1.39 (m, 9 H), 1.37-1.30 (m, 2 H), 1.23-1.14 (m, 1 H), 0.8 (s, 9 H), -0.001 (s, 3 H), -0.01 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ = 168.1 (s), 109.8 (s), 76.1 (d), 70.9 (d), 69.0 (d), 67.0 (t), 65.0 (d), 62.3 (d), 60.4 (d), 40.5 (t), 37.6 (t), 37.4 (t), 37.3 (t), 34.4 (t), 25.7 (q), 25.2 (t), 24.1 (t), 23.7 (t), 18.0 (t), -4.6 (q), -4.7 (q). HRMS (QTOF ES+) found m/z 478.2612 (M + Na)⁺ C₂₃H₄₁NNaO₆Si requires 478.2601.
Compound 20 was prepared following the procedure described for 14. Yield: 114 mg, 82%. [α]D + 71.0 (c 0.53, CHCl3); IR (CHCl3): 2931, 2856, 1701, 1450, 1254, 1123, 1112, 837, 776 cm⁻¹; ¹H NMR (CDCl3, 400 MHz): δ = 7.31-7.23 (m, 10 H), 4.96 (ddd, J = 4.4, 6.0, 10.0 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.54-4.5 (m, 2 H), 4.46 (d, J = 12.0 Hz, 1 H), 3.99 (dd, J = 6.4, 8.8 Hz, 1 H), 3.82 (ddd, J = 2.4, 4.8, 7.2 Hz, 1 H), 3.75 (dd, J = 4.4, 9.2 Hz, 1 H), 3.70 (dd, J = 5.2, 10.0 Hz, 1 H), 3.53 (m, 1 H), 3.29-3.26 (m, 1 H), 2.80-2.68 (m, 2 H), 2.41 (dd, J = 4.8, 16.4 Hz, 1 H), 2.19 (dd, J = 4.8, 12.4 Hz, 1 H), 1.87 (dd, J = 4.8, 12.4 Hz, 1 H), 1.55-1.51 (m, 10 H), 1.42-1.35 (m, 1 H), 1.14-1.05 (m, 1 H), 0.81 (s, 3 H), -0.001 (s, 3 H), -0.01 (s, 3 H); ¹³C NMR (CDCl3, 100 MHz): δ = 167.4, 138.1, 137.8, 128.5, 127.9, 127.8, 127.6, 109.5, 76.6, 76.0, 72.3, 71.1, 71.0, 69.2, 67.4, 62.7, 58.9, 41.0, 37.9, 37.2, 35.5, 34.4, 25.8, 25.3, 24.1, 23.8, 18.0, -4.6, -4.7. HRMS (QTOF ES⁺) found m/z 658.3530 (M + Na)⁺, C₃₇H₅₃NNaO₆Si requires 658.3540.

Compound 21 was prepared following the procedure described for 16 but using 12 h instead of 18 h. Yield: 33 mg, 80%. [α]D + 16.6 (c 1.1, CHCl3); IR (CHCl3): 3438, 2933, 2860, 1706, 1679, 1374, 1256, 1167, 1121, 776 cm⁻¹; ¹H NMR (CDCl3, 400 MHz): δ = 7.38-7.29 (m, 10 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.64 (d, J = 11.6 Hz, 1 H), 4.56 (d, J = 11.6 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.11-4.03 (m, 2 H), 3.97 (br s, 1 H), 3.70 (d, J = 4.4 Hz, 1 H), 3.65-3.49 (m, 3 H), 3.47 (ddd, J = 1.6, 7.2 Hz, 1 H), 2.84 (dd, J = 5.2, 17.2 Hz, 1 H), 2.55-2.48 (m, 2 H), 2.09-2.03 (m, 1 H), 1.93-1.86 (m, 2 H), 1.42-1.30 (m, 1 H), 0.89-0.83 (m, 2 H); ¹³C NMR (CDCl3, 100 MHz): δ = 169.0, 137.8, 137.6, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8, 77.6, 77.3, 72.1, 71.6, 71.3, 69.8, 65.1, 63.3, 37.0, 36.1, 32.1, 29.7. HRMS (QTOF ES⁺) found m/z 464.2046 (M + Na)⁺, C₂₅H₃₁NNaO₆ requires 464.2049.
(1R,2S,6S,8S,9aR)-1,2-Bis(benzyloxy)-8-hydroxy-6-(hydroxymethyl)hexahydro-1H-quinolizin-4(6H)-one (22).

Compound 22 was prepared following the procedure described for 17. Yield: 67 mg, 90%. 

[α]D = –68.0 (c 3.0, CHCl3; IR (CHCl3): 3468, 3348, 2889, 2859, 1644, 1619, 1123, 1082, 846, 776 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ = 7.38-7.28 (m, 10 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.03-3.89 (m, 3 H), 3.68 (dd, J = 4.8, 12.4 Hz, 1 H), 3.53-3.45 (m, 2 H), 3.41-3.38 (m, 1 H), 2.87 (dd, J = 7.2, 17.2 Hz, 1 H), 2.52 (dd, J = 4.4, 17.2 Hz, 1 H), 2.36 (dd, J = 6.8, 12.4 Hz, 1 H), 2.00 (dt, J = 4.0, 14.0 Hz, 2 H), 1.70 (dt, J = 8.0, 13.6 Hz, 1 H), 1.37-1.20 (m, 2 H). ¹³C NMR (CDCl3, 100 MHz): δ = 168.3, 137.8, 137.6, 128.5, 128.0, 127.9, 127.7, 72.1, 71.2, 70.0, 66.1, 63.4, 58.9, 56.1, 38.5, 35.8, 35.7, 29.7. HRMS (QTOF ES⁺) found m/z 434.1952 (M + Na)⁺, C₂₄H₂₉NNaO₅ requires 434.1943.

(1R,2S,6S,8S,9aR)-1,2,8-Trihydroxy-6-(hydroxymethyl)hexahydro-1H-quinolizin-4(6H)-one (23).

Compound 23 was prepared following the procedure described for 18 but using a time of 6 h. Yield: 11 mg, 80%. [α]D = –31.0 (c 0.95, MeOH). ¹H NMR (DMSO-d₆, 400 MHz): δ = 5.07 (d, J = 5.2 Hz, 1 H), 4.94 (d, J = 3.6 Hz, 1 H), 4.91 (d, J = 4.0 Hz, 1 H), 4.79 (t, J = 6.0 Hz, 1 H), 3.8 (br m, 3 H), 3.72-3.66 (m, 2 H), 3.22 (dd, J = 7.6, 12.4 Hz, 1 H), 3.16 (d, J = 4.8 Hz, 1 H), 2.39 (dd, J = 4.0, 16.8 Hz, 1 H), 2.31 (dd, J = 6.4, 16.8 Hz, 1 H), 2.21 (dd, J = 6.4, 12.8 Hz, 1 H), 1.98-1.86 (m, 1 H), 1.56-1.51 (m, 1 H), 1.16-1.10 (m, 1 H). ¹H NMR (D₂O, 600 MHz): δ = 4.20-4.18 (m, 1 H), 4.13-4.10 (m, 1 H), 3.92 (dd, J = 5.4, 12.0 Hz, 1 H), 3.87 (dd, J = 5.4, 12.0 Hz, 1 H), 3.84 (dd, J = 1.8, 5.4 Hz, 1 H), 3.56-3.54 (m, 1 H), 3.48 (dd, J = 4.2, 12.0 Hz, 1 H), 2.68 (dd, J = 4.8, 17.4 Hz, 1 H), 2.59 (dd, J = 6.6, 17.4 Hz, 1 H), 2.38 (q, J = 6.0 Hz, 1 H), 2.09-2.07 (m, 1 H), 1.68 (dt, J = 7.8, 13.8 Hz, 1 H), 1.38 (dd, J = 12.0, 22.2 Hz, 1 H). ¹³C NMR (DMSO-d₆, 100 MHz): δ = 168.3, 71.0, 65.6, 65.4, 63.1, 58.1, 56.9, 38.9, 38.7, 35.1. HRMS (QTOF ES⁺) found m/z 254.1008 (M + Na)⁺, C₁₉H₁₇NNaO₅ requires 254.1004.
(1R,2S,6S,8S,9aR)-6-((S)-1,2-Dihydroxyethyl)-1,2,8-tri hydroxyhexahydro-1H-quinolizin-4(6H)-one (24).

Compound 24 was prepared following the procedure described for 18 but using a time of 6 h. Yield: 25 mg (from 51 mg, 85 %). [α]D − 76.0 (c 0.6, MeOH). ¹H NMR (D₂O, 400 MHz): δ = 4.22-4.18 (m, 1 H), 4.12-4.09 (m, 1 H), 3.96-3.93 (m, 1 H), 3.78-3.77 (m, 1 H), 3.48 (dd, J = 4.8, 12.0 Hz, 1 H), 3.45-3.40 (m, 2 H), 3.22-3.20 (m, 1 H), 2.53-2.48 (m, 2 H), 2.19 (dd, J = 6.0, 12.4 Hz, 1 H), 2.03-1.99 (m, 1 H), 1.46 (dt, J = 9.2, 13.2 Hz, 1 H), 1.29-1.20 (m, 1 H). ¹³C NMR (D₂O, 100 MHz): δ = 170.9, 70.8, 69.7, 66.7, 64.4, 62.8, 59.6, 59.4, 37.7, 36.5, 32.6. HRMS (QTOF ES+) found m/z 284.1104 (M + Na)⁺, C₁₁H₁₉NNaO₆ requires 284.1110.
Copies of NMR spectral data for all new compounds
$^1$H NMR spectrum of compound 8

$^{13}$C NMR spectrum of compound 8
1H NMR spectrum of compound 9
in DMSO-d6 at 70 °C

13C NMR spectrum of compound 9
in DMSO-d6 at 70 °C
1H NMR spectrum of compound 10

13C NMR spectrum of compound 10
1H NMR spectrum of compound 11 in DMSO-d6 at 70°C

13C NMR spectrum of compound 11 in DMSO-d6 at 70°C
$^1$H NMR spectrum of compound 12

$^{13}$C NMR spectrum of compound 12
1H NMR spectrum of compound 13

13C NMR spectrum of compound 13
1H NMR spectrum of compound 14

13C NMR spectrum of compound 14
$^1$H NMR spectrum of compound 15

$^{13}$C NMR spectrum of compound 15
$^1$H NMR spectrum of compound 18

$^{13}$C NMR spectrum of compound 17
$^{13}$C NMR spectrum of compound 18

PK2-N9-6-5-SKS
PK2-N9-6-5 19 (0.365) Sm (Mn, 100S 00), Cm (119)

HRMS spectrum of compound 18
1H NMR spectrum of compound 21

13C NMR spectrum of compound 21
1H-NMR in D2O

1H NMR spectrum of compound 23
in D2O, 400 MHz