Supporting information:

A novel asymmetric azaspirocyclisation using a Morita Baylis Hillman-type reaction

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Preparation of 4-oxooct-7-enoic acid 12a (n = 1)

4-Bromo-1-butene (1.0 ml, 8.4 mmol) in THF (10 ml) was added dropwise by cannula over 1 hour to a rapidly stirring suspension of magnesium (0.267 g, 11.0 mmol) in THF (10 ml) in a round-bottom flask equipped with a condenser. The solution of Grignard reagent formed was transferred dropwise by cannula to a solution of succinic anhydride (0.845 g, 8.44 mmol) in THF (20 ml), keeping the temperature below -5 °C. Once the addition was complete, the reaction was stirred at 0 °C and left to warm to room temperature overnight. The reaction was quenched with aqueous hydrochloric acid (1 M, 20 ml), and the THF removed by rotary evaporation. The organic residue was extracted into DCM (2 × 50 ml). The combined organic extracts were washed with NaOH (2 M, 2 × 50 ml). The aqueous layers were re-extracted into DCM (3 × 50 ml) after acidification with concentrated hydrochloric acid. The title compound was isolated crude as a colourless oil, and used directly in the following reaction. A sample was purified by column chromatography (eluting with 0.5:10:89.5% AcOH:EtOAc:Petroleum ether to give 223.7 mg, 1.49 mmol, 18%) for analysis: Rf 0.4 in 0.5:10:89.5% AcOH:EtOAc:Petroleum ether; 1H NMR (400 MHz, CDCl3) δ ppm 2.34 (2H, app. q, J=6.9 Hz, 6-CH2), 2.55 (2H, t, J=7.4 Hz, 5-CH2), 2.63 (2H, t, J=6.4 Hz, 2-CH2 or 3-CH2), 2.72 (2H, t, J=6.4 Hz, 2-CH2 or 3-CH2), 4.98 (1H, app. br. d, J=10.3 Hz, E-H of 8-CH2), 5.02 (1H, app. br. d, J=17.2 Hz, Z-H of 8-CH2), 5.73 - 5.86 (1H, ddt, J=17.0, 10.3, 6.5 Hz, 7-CH), 10.01 (1H, br. s., COOH); 13C NMR (101 MHz, CDCl3) δ ppm 27.64 (6-C), 36.82 (2-C), 37.74 (3-C), 41.68 (5-C), 115.34 (8-C), 136.84 (7-C), 178.55 (1-C), 207.92 (4-C).
Preparation of (3R,7aS)-7a-(but-3-enyl)-3-phenyltetrahydropyrrolo[2,1-b]oxazol-5(6H)-one 13a (n = 1)

Prepared by adaptation of the procedure of Vernon et al.9 A mixture of (R)-phenyl glycine (4.115 g, 30 mmol), pyridinium para-toluene sulfonate (1.5 g, 6 mmol) and the crude ketoacid 12a (prepared from 30 mmol succinic anhydride and purified by an acid/base cycle) in 500 ml toluene was heated to reflux in a Dean-Stark apparatus. After 18 h, the reaction mixture was allowed to cool and the resulting precipitate removed by filtration through celite. After solvent evaporation, the crude product was isolated as a yellow oil and was purified to a colourless oil (2.3502 g, 9.13 mmol, 30%) by column chromatography (50% EtOAc / petroleum ether). Rf 0.45 in 50% EtOAc / Petroleum ether; 1H NMR (400 MHz, CDCl₃) δ ppm 1.63 – 1.73 (1H, m, one of 1′-CH₂), 1.76 - 1.85 (1 H, m, one of 1′-CH₂), 2.12 - 2.24 (3H, m, one of 7-CH₂ and both of 2′-CH₂), 2.38 (1H, ddd, J=13.5, 9.8, 2.6 Hz, one of 7-CH₂), 2.60 (1H, ddd, J=17.3, 10.3, 2.6 Hz, one of 6-CH₂), 2.84 (1H, dt, J=17.3, 9.8 Hz, one of 6-CH₂), 4.08 (1H, dd, J=8.8, 7.2 Hz, one of 2-CH₂), 4.64 (1H, app. t, J=8.5 Hz, one of 2-CH₂), 4.93 (1H, dddd, J=10.1, 1.8, 1.2, 0.5 Hz, Z-H of 4′-CH₂), 4.99 (1H, dqq, J=17.1, 1.7, 0.5 Hz, E-H of 4′-CH₂), 5.19 (1H, app. t, J=7.7 Hz, 3-CH₂), 5.75 (1H, m, J=17.0, 10.3, 6.6, 6.6 Hz, 3′-CH₂), 7.21 - 7.30 (3 H, m, ArCH), 7.31 - 7.37 (2 H, m, ArCH); 13C NMR (101 MHz, CDCl₃) δ ppm 28.33 (2′-C), 30.89 (7-C), 33.18 (6-C), 35.50 (1′-C), 57.60 (3-C), 72.88 (2-C), 102.40 (7a-C), 115.06 (5′-C), 125.43 (2″ and 6″-C), 127.40 (4″-C), 128.67 (3″ and 5″-C), 137.29 (3′-C), 140.00 (1″-C), 179.31 (5-C).
Hoveyda-Grubbs second generation catalyst (155.9 mg, 248 µmol) was added to a stirring solution of (3R,7aS)-7a-(But-3-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one 13a (1.9 g, 7.38 mmol) and acrolein (2.47 ml, 36.9 mmol) in argon-degassed DCM (120 ml). The mixture was brought to reflux for 6 h, before cooling and transferring to a rotary evaporation flask charged with silica (3 g). The solvent was removed in vacuo and the resulting silica-adsorbed reaction mixture loaded on to a pre-prepared silica column. The title compound (1.2821 g, 4.49 mmol, 61%) was obtained as a dark brown oil by elution with a gradient of 60% → 80% EtOAc / Petroleum ether. (3R,7aS)-7a-(but-3-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one 9a was recovered as a brown oil (0.6476 g, 2.517 mmol, 34%). Both could be decolourised by stirring for 12 h with activated charcoal in DCM. Rf 0.2 in 50% EtOAc / Petroleum ether; IR ν\text{max} (neat) / cm\textsuperscript{-1} 2974 (C-H stretch), 1710 (conjugated aldehyde C=O stretch, obscuring lactam C=O stretch), 1641 (conjugated aldehyde C=C stretch), 763, 700 (phenyl ring stretch); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 1.77 (1H, ddd, J=13.9, 10.2, 5.8 Hz, one of 1'-CH\textsubscript{2}), 1.90 (1H, ddd, J=13.9, 9.6, 6.9 Hz, one of 1'-CH\textsubscript{2}), 2.25 (1H, dt, J=13.4, 10.2 Hz, one of 7-CH\textsubscript{2}), 2.33 - 2.38 (1H, m, one of 7-CH\textsubscript{2}), 2.38 - 2.48 (2H, m, 2'-CH\textsubscript{2}), 2.64 (1H, ddd, J=17.5, 10.2, 2.9 Hz, 6-CH\textsubscript{2}), 2.85 (1H, dt, J=17.5, 9.7, 0.5 Hz), 4.12 (1H, dd, J=8.8, 6.9 Hz, one of 2-CH\textsubscript{2}), 4.65 (1H, dd, J=8.8, 8.3 Hz, one of 2-CH\textsubscript{2}), 5.25 (1H, app. t, J=7.5 Hz, 3-CH\textsubscript{2}), 6.05 (1H, ddt, J=15.7, 7.8, 1.5 Hz, 4'-CH), 6.74 (1H, dt, J=15.7, 6.7 Hz, 3'-CH), 7.22 - 7.26 (2H, m, Ar-H), 7.28 - 7.32 (1H, m, Ar-H), 7.33 - 7.39 (2H, m, Ar-H), 9.46 (1 H, d, J=7.8 Hz, CHO). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 27.43 (7-C), 30.74 (2' or 6-C), 32.90 (2' or 6-C), 34.53 (1'-C), 57.59 (3-C), 72.65 (2-C), 101.83 (7a-C), 125.38 (4''-C), 127.60 (2" and 6"'-C), 128.79 (3" and 5"'-C), 133.16 (4'-C), 139.76 (1"'-C), 156.27 (3'-C), 179.16 (5-C), 193.53 (5'-C); HRMS (CI+) calculated for C\textsubscript{17}H\textsubscript{23}O\textsubscript{3}N\textsubscript{2} [M + NH\textsubscript{4}]\textsuperscript{+} 303.1703, found 303.1705.
Preparation of 1-((R)-2-hydroxy-1-phenylethyl)-2-oxo-1-azaspiro[4.4]non-6-ene-6-carbaldehyde 10a (n = 1)

A stirring solution of (E)-6-((3R,7aS)-5-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazol-7a-yl)pent-2-enal 9a (59.4 mg, 208 µmol) in DCM (2 ml) was cooled to -78 °C. BF$_3$.OEt$_2$ (79 µl, 624 µmol) was added and the reaction stirred for 10 min. SMe$_2$ (46 µl, 624 µmol) was added and the reaction left to warm to room temperature over 18 h. Saturated sodium hydrogen carbonate (5 ml) was added and the mixture sonicated until the brown gum deposit was fully dissolved. DCM (40 ml) was added and the organic layer separated and dried by washing with saturated brine (50 ml). Drying was completed by addition of magnesium sulfate and filtration. The title compound was isolated as a fawn oil (46.2 mg, 162 µmol, 82:18 ratio of diastereomers, 78%) after solvent removal in vacuo. No further purification was necessary but column chromatography (3% → 5% MeOH / DCM) was used to isolate the major diastereomer for analysis: R$_f$ 0.3 (5% MeOH / DCM); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3285 (O-H stretch), 2943 (C-H stretch), 1675 (conjugated aldehyde C=O stretch), 1659 (lactam C=O stretch), 1617 (conjugated aldehyde C=C stretch), 732, 701 (phenyl ring stretch); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.86 (1H, ddd, $J$=14.1, 7.5, 6.5 Hz, one of 9-CH$_2$), 1.99 (1H, ddd, $J$=14.1, 7.5, 6.5 Hz, one of 9-CH$_2$), 2.08 (1H, ddd, $J$=13.2, 10.1, 7.1 Hz, one of 3-CH$_2$), 2.38 (1H, ddd, $J$=13.2, 10.1, 5.3 Hz, one of 3-CH$_2$), 2.45 (1H, ddd, $J$=7.5, 6.5, 2.8 Hz, one of 8-CH$_2$), 2.45 (1H, ddd, $J$=7.5, 6.5, 2.8 Hz, one of 8-CH$_2$), 2.54 (1H, ddd, $J$=17.0, 10.1, 5.3 Hz, 4-CH$_2$), 2.89 (1H, ddd, $J$=17.0, 10.1, 7.1, 0.5 Hz, 4-CH$_2$), 3.84 (1H, dd, $J$=11.7, 2.9 Hz, one of 2′-CH$_2$), 3.88 (1H, dd, $J$=6.5, 2.9 Hz, 1′-CH), 4.11 - 4.22 (1H, m, one of 2′-CH$_2$), 4.27 (1H, br. s., OH), 7.13 (1H, t, $J$=2.8 Hz, 7-CH), 7.21 - 7.26 (1H, m, ArCH), 7.28 - 7.34 (4H, m, ArCH), 9.82 (1H, s, CHO); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 30.49 (8-C), 30.80 (4-C), 32.27 (3-C), 36.89 (9-C), 61.13 (1′-C), 64.58 (2′-C), 75.82 (5-C), 127.09 (2″ and 6″-C), 127.30 (4″-C), 128.43 (3″ and 5″-C), 139.06 (1″-C), 146.62 (6-C), 157.22 (7-C), 177.13 (2-C), 188.79 (CHO); HRMS(CI+) calculated for C$_{17}$H$_{20}$NO$_3$ [M + H]$^+$ 286.1443, found 286.1436.
Preparation of 4-oxonon-8-enoic acid 12b (n = 2)

Prepared analogously to 4-oxooct-7-enoic acid 12a, with 5-Bromo-1-pentene (4.3 ml, 36.3 mmol) in THF (20 ml) added dropwise by cannula over 1 hour to a rapidly stirring suspension of magnesium (2.00 g, 82.2 mmol) in THF (20 ml) in a round-bottom flask equipped with a condenser. The solution of Grignard reagent formed was transferred dropwise by cannula to a solution of succinic anhydride (3.63 g, 36.3 mmol) in THF (40 ml), keeping the temperature below -5 °C. Once the addition was complete, the reaction was stirred at 0 °C and left to warm to room temperature overnight. The reaction was quenched with aqueous hydrochloric acid (1 M, 50 ml), and the THF removed by rotary evaporation. The organic residue was extracted into DCM (2 × 50 ml). The combined organic extracts were washed with NaOH (2 M, 2 × 50 ml). The aqueous layers were re-extracted into DCM (3 × 50 ml) after acidification with concentrated hydrochloric acid. The title compound was isolated crude as a colourless oil, and used directly in the following reaction. A sample was purified by column chromatography (eluting with 0.5:10:89.5% AcOH:EtOAc:Petroleum ether to give 3.588 g, 21.08 mmol, 58%) for analysis: Rf 0.4 in 0.5:10:89.5% AcOH:EtOAc:Petroleum ether; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.64 (2H, app. qui, 6-CH\(_2\)), 1.96 - 2.09 (2H, m, 7-CH\(_2\)), 2.39 (2H, t, \(J=7.4\) Hz, 5-CH\(_2\)), 2.54 - 2.66 (4H, m, 2-CH\(_2\) and 3-CH\(_2\)), 4.86 - 5.01 (2H, m, both of 9-CH\(_2\)), 5.69 (1H, ddt, \(J=17.1, 10.2, 6.7\) Hz, 8-CH), 10.43 (1H, br. s., COOH); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 22.64 (6-C), 27.74 (7-C), 32.94 (2-C), 36.76 (5-C), 41.69 (3-C), 115.24 (9-C), 137.81 (8-C), 178.83 (1-C), 208.75 (4-C).
Preparation of (3R,7aS)-7a-(Pent-4-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one 13b (n = 2)

Prepared by adaptation of the procedure of Vernon et al. 9 A mixture of (R)-phenyl glycinol (2.87 g, 20.9 mmol), pyridinium para-toluene sulfonate (1.05 g, 4.19 mmol) and the crude keto-acid 12b (prepared from 20.9 mmol succinic anhydride and purified by an acid/base cycle) in 250 ml toluene was heated to reflux in a Dean-Stark apparatus. After 18 h, the reaction mixture was allowed to cool and the resulting precipitate removed by filtration through celite. After solvent evaporation, the crude product was isolated as a yellow oil and was purified to a colourless oil (1.905 g, 7.02 mmol, 34%) by column chromatography (50% EtOAc / petroleum ether). Rf 0.4 in 50% EtOAc / Petroleum ether; IR νmax (neat) / cm⁻¹ 2941 (C-H stretch), 1709 (lactam C=O stretch), 1640 (C=C stretch), 1604 (phenyl ring stretch), 911 (olefinic C-H stretch), 760, 722 (phenyl ring stretch); ¹H NMR (400 MHz, CDCl₃) δ 1.44 - 1.59 (2H, m, 2'-CH₂), 1.59 - 1.73 (2H, m, 1'-CH₂), 2.01 (2H, app. qui d, J=7.6, 6.7 Hz, 3'-CH₂), 2.18 (1H, dt, J=13.4, 10.2 Hz, one of 7-CH₂), 2.37 (1H, ddd, J=13.4, 9.8, 2.5 Hz, one of 7-CH₂), 2.60 (1H, ddd, J=17.3, 10.2, 2.5 Hz, one of 6-CH₂), 2.84 (1H, ddd, J=17.3, 10.2, 9.8 Hz, one of 6-CH₂), 4.09 (1H, dd, J=8.7, 7.2 Hz, 2-CH₂β), 4.64 (1H, br. app. t, J=8.5 Hz, 2-CH₂α), 4.93 (1H, ddt, J=10.2, 2.0, 1.2 Hz, E-H of 5′-CH₂), 4.96 (1H, ddt, J=17.1, 2.0, 1.5 Hz, Z-H of 5′-CH₂), 5.19 (1H, br. app. t, J=7.7 Hz, 3-CH), 5.72 (1H, ddt, J=17.1, 10.2, 6.7 Hz, 4'-CH), 7.21 - 7.26 (2H, m, ArH), 7.28 - 7.39 (3H, m, Ar-H); ¹³C NMR (101 MHz, CDCl₃) δ 23.25 (2'-C), 30.95 (7-C), 33.29 (6-C or 3'-C), 33.45 (6-C or 3'-C), 35.65 (1'-C), 57.53 (3-C), 72.82 (2-C), 102.59 (7a-C), 115.09 (5'-C), 125.46 (2″ and 6″-C), 127.38 (4″-C), 128.65 (3″ and 5″-C), 137.93 (4′-C), 140.06 (1″-C), 179.31 (5-C); MS (Cl⁺) calculated for C₂₉H₁₉O₂S [M + H]⁺ 272.1645; found 272.1.
Preparation of (E)-6-((3R,7aS)-5-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazol-7a-yl)hex-2-enal 9b (n = 2)

Hoveyda-Grubbs second generation catalyst (105 mg, 211 µmol) was added to a stirring solution of (3R,7aS)-7a-(Pent-4-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one 13b (1.148 g, 4.23 mmol) and acrolein (1.4 ml, 21 mmol) in argon-degassed DCM (180 ml). The mixture was brought to reflux for 6 h, before cooling and transferring to a rotary evaporation flask charged with silica (2 g). The solvent was removed in vacuo and the resulting silica-adsorbed reaction mixture loaded on to a pre-prepared silica column. The title compound was obtained (0.8322 g, 2.77 mmol, 66%) as a dark brown oil by elution with a gradient of 60% → 80% EtOAc / Petroleum ether. This could be decolourised by stirring for 12 h with activated charcoal in DCM. Rf 0.2 in 50% EtOAc / Petroleum ether; IR ν\text{max} (neat) / cm$^{-1}$ 2948 (C-H stretch), 1707 (lactam C=O stretch), 1683 (aldehyde C=O stretch), 1637 (C=C stretch), 1605 (phenyl ring stretch), 975 (olefinic C-H stretch), 763, 727 (phenyl ring stretch)$^{1}$H NMR (400 MHz, CDCl$_3$) δ 1.49 - 1.74 (4H, m, 1′ and 2′-CH$_2$) 2.12 - 2.38 (4H, m, 7-CH$_2$ and 3′-CH$_2$) 2.59 (1H, ddd, $J$=17.4, 10.3, 2.7 Hz, one of 6-CH$_2$) 2.81 (1H, dt, $J$=17.4, 9.8 Hz, one of 6-CH$_2$) 4.09 (1H, app. t, $J$=7.1 Hz, 2-CH$_2$H$_\beta$) 4.60 (1H, app. t, $J$=8.5 Hz, 2-CH$_2$H$_\alpha$) 5.19 (1H, app. t, $J$=7.5 Hz, 3-CH) 6.02 (1H, ddt, $J$=15.6, 7.8, 1.4 Hz, 5′-CH) 6.66 (1H, dt, $J$=15.6, 6.8 Hz, 4′-CH) 7.18 - 7.26 (3H, m, Ar-H) 7.29 - 7.37 (2H, m, Ar-H) 9.40 (1H, d, $J$=7.8 Hz, 6′-CHO); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 22.33 (2′-C), 30.70 (7-C), 32.22 (6-C or 3′-C), 33.00 (6-C or 3′-C), 35.67 (1′-C), 57.35 (3-C), 72.45 (2-C), 102.14 (7a-C), 125.39 (2″ and 6″-C), 127.44 (4″-C), 128.64 (3″ and 5″-C), 133.28 (5′-C), 139.90 (1″-C), 157.09 (4″-C), 179.18 (5-C), 193.67 (6′-C); HRMS (Cl+) calculated for C$_{18}$H$_{25}$O$_3$N$_2$ [M + NH$_4$]$^+$ 317.1860, found 317.1862.
Preparation of 1-((R)-2-hydroxy-1-phenylethyl)-2-oxo-1-azaspiro[4.5]dec-6-ene-6-carbaldehyde 10b (n = 2)

A stirring solution of \((E)-6-((3\text{R},7\text{aS})-5\text{-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazol-7a-yl})\text{-hex-2-enal} 9\text{b}\) (0.5367 g, 1.793 mmol) in DCM (16 ml) was cooled to -78 °C. BF\(_3\).OEt\(_2\) (0.66 ml, 5.38 mmol) in DCM (2 ml) was added and the reaction stirred for 10 min. SMe\(_2\) (0.40 ml, 5.38 mmol) in DCM (2 ml) was added and the reaction left to warm to room temperature over 18 h. Saturated sodium hydrogen carbonate (25 ml) was added and the mixture sonicated until the brown gum deposit was fully dissolved. DCM (40 ml) was added and the organic layer separated and dried by washing with saturated brine (50 ml). Drying was completed by addition of magnesium sulfate and filtration. The title compound was isolated as a white foam (0.4343 mg, 1.45 mmol, 79:21 ratio of diastereomers, 81%) after solvent removal in vacuo. No further purification was necessary but column chromatography (3% → 5% MeOH / DCM) was used to isolate the major diastereomer for analysis: \(R_f 0.35\) (3% MeOH / DCM); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3313 (O-H stretch), 2941 (C-H stretch), 1684 (conjugated aldehyde C=O stretch), 1644 (lactam C=O stretch), 1631 (conjugated aldehyde C=C stretch), 767, 704 (phenyl ring stretch); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) ppm 1.26 (2H, s, 10-CH\(_2\)), 1.44 - 1.49 (1H, m, one of 9-CH\(_2\)), 1.71 (1H, s, one of 9-CH\(_2\)), 2.03 (1H, ddd, \(J=13.1, 10.7, 5.2\) Hz, one of 3-CH\(_2\)), 2.21 - 2.27 (1H, m, one of 8-CH\(_2\)), 2.27 (1H, ddd, \(J=13.1, 11.1, 7.0\) Hz, one of 3-CH\(_2\)), 2.39 (1 H, dt, \(J=20.5, 5.0\) Hz, one of 8-CH\(_2\)), 2.62 (1H, ddd, \(J=17.4, 10.7, 7.0\) Hz, one of 4-CH\(_2\)), 2.80 (1 H, ddd, \(J=17.4, 11.1, 5.2\) Hz, one of 4-CH\(_2\)), 3.94 (1 H, ddd, \(J=11.7, 3.7, 2.2\) Hz, one of 2′-CH\(_2\)), 3.95 (1H, dd, \(J=7.3, 2.2\) Hz, 1′-CH), 4.01 - 4.08 (1H, m, one of 2′-CH\(_2\)), 4.65 (1H, dd, \(J=9.8, 3.5\) Hz, 2′-CH\(_2\)OH), 7.08 (1H, dd, \(J=5.5, 1.5\) Hz, 7-CH), 7.23 - 7.26 (2H, m, ArCH), 7.28 - 7.34 (3H, m, ArCH), 9.46 (1H, s, CHO); \(^13\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) ppm 18.94 (9-C), 26.44 (8-C), 29.67 (10-C), 30.10 (4-C), 31.88 (3-C), 61.83 (1′-C), 64.84 (2′-C), 65.75 (5-C), 127.16 (2′, 4′ and 6′-C), 128.43 (3′ and 5′-C), 139.58 (1′′-C), 142.97 (6-C), 157.08 (7-C), 177.69 (2-C), 192.80 (CHO); HRMS (Cl+) calculated for C\(_{18}\)H\(_{22}\)NO\(_3\) [M + H]\(^+\) 300.1594; found 300.1593.
Preparation of 6-(hydroxymethyl)-1-(2-hydroxy-1-phenylethyl)-1-azaspiro[4.5]dec-6-en-2-one 14

Prepared according to the procedure of Lawrence et al. Sodium borohydride (17 mg, 450 µmol) was added to a solution of 1-((R)-2-hydroxy-1-phenylethyl)-2-oxo-1-azaspiro[4.5]dec-6-ene-6-carbaldehyde 10b (103.4 mg, 345 µmol) in freshly distilled MeOH (1 ml) at -30 °C. The reaction mixture was stirred at this temperature for 1 h, before pouring into a biphasic mixture of 1 M HCl (50 ml) and DCM (50 ml) in a separating funnel. Once effervescence had ceased, the aqueous layer was extracted with DCM (2 × 50 ml) and the combined DCM extracts washed with saturated brine (50 ml), then dried over MgSO₄. Solvent removal in vacuo gave a white foam which was purified by column chromatography (3% → 5% MeOH / DCM) to obtain a white foam (57.4 mg, 192 µmol, 56% yield). Rₚ 0.35 (3% MeOH / DCM); IR νmax (neat) / cm⁻¹ 3325 (O-H stretches), 2936 (C-H stretch), 1649 (lactam C=O stretch, obscuring C=C stretch), 814 (C=C-H out of plane), 726, 698 (phenyl ring stretch); ¹H NMR (500 MHz, CDCl₃) δ ppm 1.25 (1H, ddd, J=10.3, 4.8, 1.0 Hz, one of 10-CH₂), 1.34 - 1.53 (3H, m, one of 10-CH₂ and 9-CH₂), 1.73 - 1.91 (1H, m, 8-CH₂), 1.94 (2H, ddd, J=13.5, 9.4, 6.5 Hz, one of 3-CH₂), 2.15 (1H, ddd, J=13.5, 9.9, 8.0 Hz, one of 3-CH₂), 2.51 - 2.57 (1H, m, 4-CH₂), 3.41 (1H, br. s., 11-CH₂OH), 3.86 (1H, dt, J=11.9, 4.0 Hz, one of 2′-CH₂), 4.05 (2H, d, J=4.1 Hz, 11-CH₂), 4.19 (1H, dd, J=8.2, 4.0 Hz, 1′-CH), 4.33 (1H, dt, J=11.9, 4.0 Hz, one of 2′-CH₂), 4.66 (1 H, br. s., 2′-CH₂OH), 6.04 (1H, ddd, J=5.1, 2.6, 0.9 Hz, 7-CH), 7.12 - 7.31 (5 H, m, ArCH); ¹³C NMR (126 MHz, CDCl₃) δ ppm 19.78 (9-C), 24.90 (8-C), 30.37 (4-C), 32.13 (3-C), 35.98 (10-C), 61.28 (11-C), 62.10 (1′-C), 65.20 (2′-C), 68.65 (5-C), 127.16 (2″ and 4″-C), 127.29 (6″-C), 128.53 (3″ and 5″-C), 132.24 (7-C), 139.58 (6-C or 1″-C), 140.19 (6-C or 1″-C), 178.01 (2-C); HRMS (CI+) calculated for C₁₈H₂₄NO₃ [M + H]⁺ 302.1756; found 302.1762.
Preparation of 6-(hydroxymethyl)-1-azaspiro[4.5]dec-6-en-2-one

Prepared according to the procedure of Bosch. Liquid ammonia (20 ml) was condensed into a Schlenk flask cooled to -78 °C under argon. Sodium metal was added such that the solution turned deep blue in colour, and ammonia (5 ml) distilled into a second Schlenk flask at -78 °C. 6-(hydroxymethyl)-1-(2-hydroxy-1-phenylethyl)-1-azaspiro[4.5]dec-6-en-2-one (31.2 mg, 104 µmol) in anhydrous THF (1 ml) was added slowly to the distilled ammonia. Sodium (20 mg, 460 mmol) was added and stirred until complete dissolution (blue colour). 1 min 30 seconds after the colour change, ammonium chloride was added until the solution decolourised. The reaction was allowed to warm to room temperature with a purge of argon through the Schlenk into a cooled Dreschel flask filled with dilute sulfuric acid. The ammonia solution of sodium remaining from the redistillation was quenched and purged similarly. Once all ammonia had been purged, a DCM slurry was formed of the residual solid. Filtration through celite and solvent evaporation gave a colourless oil which was purified by column chromatography (4% → 7% EtOH / DCM) to yield the title compound (10.3 mg, 63 µmol, 61%) as a colourless oil. R_f 0.2 (7% EtOH / DCM); IR ν_{max} (neat) / cm⁻¹ 3248 (O-H stretch), 2926, 2856 (C-H stretches), 1655 (lactam C=O stretch, obscuring C=C stretch); ^1H NMR (500 MHz, CDCl₃) δ ppm 1.66 - 1.76 (3H, m, 9-CH₂ and one of 10-CH₂), 1.80 - 1.86 (1H, m, one of 10-CH₂), 1.97 - 2.04 (1H, m, one of 3-CH₂), 2.07 - 2.16 (2H, m, 8-CH₂), 2.23 (1H, dt, J=13.4, 9.1 Hz, one of 3-CH₂), 2.45 (1H, dd, J=9.5, 3.6 Hz, one of 4-CH₂), 2.43 (1H, dd, J=9.1, 0.9 Hz, one of 4-CH₂), 4.11 (1 H, d, J=12.9 Hz, one of 11-CH₂), 4.15 (1 H, d, J=12.8 Hz, one of 11-CH₂), 5.91 (1 H, t, J=3.7 Hz, 7-CH), 6.22 (1 H, br. s., either NH or OH); ^13C NMR (126 MHz, CDCl₃) δ ppm 19.69 (9-C), 24.84 (8-C), 29.87 (4-C), 32.41 (3-C), 37.29 (10-C), 59.80 (5-C), 63.15 (11-C), 129.42 (7-C), 139.69 (6-C), 177.82 (2-C); HRMS (CI+) calculated for C_{18}H_{16}NO₂ [M + H]^+ 182.1181; found 182.1180; [α]_{D}^{20} +18 (c 0.33, CHCl₃).
NMR spectra of (E)-5-((3R,7aS)-5-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazol-7a-yl)pent-2-enal 9a
NMR spectra of 1-((R)-2-hydroxy-1-phenylethyl)-2-oxo-1-azaspiro[4.4]non-6-ene-6-carbaldehyde 10a
NMR spectra of (E)-6-((3R,7aS)-5-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazol-7a-yl)hex-2-enal 9b
NMR spectra of 1-((R)-2-hydroxy-1-phenylethyl)-2-oxo-1-azaspiro[4.5]dec-6-ene-6-carbaldehyde 10b
NMR spectra of 6-(hydroxymethyl)-1-(2-hydroxy-1-phenylethyl)-1-azaspiro[4.5]dec-6-en-2-one 14
NMR spectra of 6-(hydroxymethyl)-1-azaspiro[4.5]dec-6-en-2-one 15