Synthesis and Biological Evaluation of a New Family of Constrained Azabicyclic Homocholine Analogues

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General Experimental

Infrared absorption spectra were obtained using a Shimadzu FTIR-8400S (Fourier Transform Infrared Spectrometer). Compounds were prepared as a thin film between 0.5 cm sodium chloride plates seated on a custom made perch in the apparatus. Absorption maxima ($v_{\text{max}}$) are expressed in wavenumbers (cm$^{-1}$). $^1$H Nuclear magnetic resonance spectra were recorded using a Bruker Avance 200 (200.13 MHz), Bruker Avance 300 (300.13 MHz), Bruker DRX 400 (400.21 MHz) spectrometer or a Varian Gemini 300 and Varian Mercury 300 (300.06 MHz), and are recorded in parts per million (ppm) downfield shift from tetramethylsilane ($\delta_{\text{TMS}} = 0$), using residual chloroform solvent ($\delta$ 7.26) as internal reference. The data is reported as chemical shift ($\delta_{\text{H}}$), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, sext. = sextet, sept. = septet, m = multiplet), coupling constant ($J$ Hz) and assignment. $^{13}$C Nuclear magnetic resonance spectra were recorded using a Bruker Avance 300 (75.5 MHz), Bruker DRX 400 (100.6 MHz) or a Varian Gemini 300 and Varian Mercury 300 (75.5 MHz) spectrometer at ambient temperature with complete proton decoupling. Data is expressed in parts per million (ppm) downfield relative to tetramethylsilane ($\delta_{\text{TMS}} = 0$) using deuterated chloroform ($\delta$ 77.1) as an internal reference and is reported as chemical shift ($\delta_{\text{C}}$). Low resolution mass spectra were recorded using positive ion electrospray ionization (ESI+) on a Finnigan PolarisQ ion trap or Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer or by electron ionisation (EI) on a VG AutoSpec M series sector mass spectrometer. Major fragments are quoted in the form x (y), where x is the mass to charge ratio ($m/z$) and y is the percentage abundance relative to the base peak. High resolution mass spectra were recorded using positive ion electrospray ionization (ESI+) on Bruker Apex 4.7T FTICR-MS or by electron ionisation (EI) on a VG AutoSpec M series sector mass spectrometer. Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick aluminium-backed, pre-coated silica gel plates (Merck Kieselgel 60 F254). Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh ASTM), under a positive pressure of nitrogen. Solvent compositions were mixed v/v as specified.
8-Benzyl-8-azabicyclo[4.3.1]decan-10-one 6e

To a solution of $N,N$-bis(ethoxymethyl)benzylamine$^{[1,2]}$ 5 (R$^1$ = Bn) (2.68 g, 12.0 mmol) and chlorotrimethylsilane (2.57 g, 23.7 mmol) in acetonitrile (80 mL) was added cycloheptanone (0.897 g, 8.00 mmol) and the mixture was stirred at room temperature for 48 h. The reaction was quenched by the addition of ice water (20 mL) and partitioned between diethyl ether (40 mL) and water (30 mL). The organic layer was then extracted with hydrochloric acid (0.5 M, 4 × 8 mL) and the combined aqueous extracts washed with diethyl ether (40 mL), cooled to 0 °C and the pH brought to 9 by the addition of concentrated ammonia solution (~4 mL). The organic material was then extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to afford the title compound 6e (0.647 g, 2.66 mmol, 33%) as a yellow oil. $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2916, 2851, 2802, 2766 (C–H), 1713 (C=O); $^1$H NMR (300 MHz, CDCl$^3$) $\delta$ 7.36–7.26 (5H, m, NCH$_2$Ph), 3.52 (2H, s, NCH$_2$Ph), 2.85 (2H, d, $J$ 11.1, H7A, H9A), 2.62 (2H, m, H1, H6), 2.44 (2H, m, H7B, H9B), 2.06 (2H, m, H2A, H5A), 1.79 (2H, m, H3A, H4A), 1.59 (2H, m, H2B, H5B), 1.42 (2H, m, H3B, H4B); $^{13}$C NMR (50 MHz, CDCl$^3$) $\delta$C 212.5, 138.2, 128.6, 127.9, 126.8, 62.4, 59.3, 48.3, 31.0, 26.5; m/z (ESI+) 244 ([M+H]$^+$, 100); HRMS (ESI+) found 244.1697; C$_{16}$H$_{22}$NO ([M+H]$^+$) requires 244.1701.

General Procedure for Sodium Borohydride Reduction

Sodium borohydride (2 eq) was added to a stirred solution of ketone (1 eq) in ethanol/water (4:1) at 0 °C, and the reaction stirred for 2 h. Concentrated hydrochloric acid was added dropwise to quench the excess sodium borohydride and the mixture concentrated under reduced pressure to remove ethanol. The aqueous solution was made basic (pH 10) by the addition of aqueous sodium hydroxide (3 M) and the organic material extracted by diethyl ether (3 ×). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the crude alcohol. Purification by flash chromatography (ethyl acetate:hexane) then afforded the target compound.
The reaction was conducted according to the general procedure using 8-ethyl-8-azabicyclo[4.3.1]decan-10-one\cite{3} 6a (1.06 g, 5.85 mmol), sodium borohydride (0.441 g, 11.7 mmol) and ethanol/water (125 mL) to afford the title compound 7a (0.867 g, 4.73 mmol, 81%) as a colourless solid after flash chromatography (1:4, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 3393 (O$\text{–}$H), 2967, 2904, 2755 (C$\text{–}$H); $^1$H NMR (300 MHz, CD$_3$OD) $\delta$H 3.88 (1H, t, $J=5.4$, H10), 2.71 (2H, d, $J=10.9$, H7A, H9A), 2.25 (2H, q, $J=7.2$, NCH$_2$CH$_3$), 2.07–1.86 (8H, m, H1, H2A, H3A, H4A, H5A, H6, H7B, H9B), 1.68 (2H, m, H2B, H5B), 1.53 (2H, m, H3B, H4B), 1.04 (3H, t, $J=7.2$, NCH$_2$CH$_3$); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$C 76.2, 60.4, 52.4, 38.8, 31.7, 27.4, 13.0; m/z (ESI$^+$) 184 ([M+H]$^+$, 100). Found 184.1701, C$_{11}$H$_{22}$NO ([M+H]$^+$) requires 184.1693.

The reaction was conducted according to the general procedure using 8-isopropyl-8-azabicyclo[4.3.1]decan-10-one\cite{3} 6b (1.01 g, 5.17 mmol), sodium borohydride (0.391 g, 10.3 mmol) and ethanol/water (100 mL) to afford the title compound 7b (1.00 g, 5.07 mmol, 98%) as a colourless solid after flash chromatography (1:4, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 3261 (O$\text{–}$H), 2961, 2939, 2914, 2870, 2852 (C$\text{–}$H); $^1$H NMR (300 MHz, CD$_3$OD) $\delta$H 3.83 (1H, t, $J=5.4$, H10), 2.69 (1H, sept. $J=6.6$, NCH(CH$_3$)$_2$), 2.63 (2H, dd, $J=11.1$, 2.2, H7A, H9A), 2.31 (2H, dd, $J=11.3$, 2.8, H7B, H9B), 2.06 (2H, m, H1, H6), 1.97–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.68 (2H, m, H2B, H5B), 1.50 (2H, m, H3B, H4B), 0.98 (6H, d, $J=6.6$, NCH(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$C 76.8, 56.4, 55.4, 39.8, 32.7, 28.1, 18.3; m/z (ESI$^+$) 198 ([M+H]$^+$), 100. Found 198.1858, C$_{12}$H$_{24}$NO ([M+H]$^+$) requires 198.1852.

The reaction was conducted according to the general procedure using 8-tert-butyl-8-azabicyclo[4.3.1]decan-10-one\cite{3} 6c (1.01 g, 5.17 mmol), sodium borohydride (0.391 g, 10.3 mmol) and ethanol/water (100 mL) to afford the title compound 7c (1.00 g, 5.07 mmol, 98%) as a colourless solid after flash chromatography (1:4, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 3261 (O$\text{–}$H), 2961, 2939, 2914, 2870, 2852 (C$\text{–}$H); $^1$H NMR (300 MHz, CD$_3$OD) $\delta$H 3.83 (1H, t, $J=5.4$, H10), 2.69 (1H, sept. $J=6.6$, NCH(CH$_3$)$_2$), 2.63 (2H, dd, $J=11.1$, 2.2, H7A, H9A), 2.31 (2H, dd, $J=11.3$, 2.8, H7B, H9B), 2.06 (2H, m, H1, H6), 1.97–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.68 (2H, m, H2B, H5B), 1.50 (2H, m, H3B, H4B), 0.98 (6H, d, $J=6.6$, NCH(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$C 76.8, 56.4, 55.4, 39.8, 32.7, 28.1, 18.3; m/z (ESI$^+$) 198 ([M+H]$^+$), 100. Found 198.1858, C$_{12}$H$_{24}$NO ([M+H]$^+$) requires 198.1852.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-ol 7b

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-ol 7c
The reaction was conducted according to the general procedure using 8-tert-butyl-8-azabicyclo[4.3.1]decan-10-one\(^3\) 6c (1.00 g, 4.78 mmol), sodium borohydride (0.724 g, 19.2 mmol) and methanol/water (50 mL) to afford the *title compound* 7c (0.613 g, 2.90 mmol, 61%) as a colourless solid after flash chromatography (1:19, ethyl acetate:hexane). \(\nu_{\text{max}} (\text{NaCl})/\text{cm}^{-1} 3273 (\text{O}–\text{H}), 2961, 2910, 2851, 2795, 2739 (\text{C}–\text{H}); ^1\text{H} \text{NMR (300 MHz, CD}_3\text{OD}) \delta_H 3.83 (1H, t, \(J = 5.5\), H10), 2.88 (2H, dd, \(J = 8.6, 2.4\), H7A, H9A), 2.19 (2H, dd, \(J = 11.3, 2.6\), H7B, H9B), 2.06 (2H, m, H1, H6), 1.99–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.70 (2H, m, H2B, H5B), 1.50 (2H, m, H3B, H4B), 1.05 (9H, s, C(CH\(_3\))\(_3\)); ^13\text{C} \text{NMR (75 MHz, CD}_3\text{OD}) \delta_C 76.9, 53.8 (2C), 39.9, 32.6, 28.2, 26.7; \text{m/z (ESI+)} 212 ([M+H]\(^+\), 100), 156. Found 212.2009, C\(_{13}\)H\(_{26}\)NO ([M+H]\(^+\)) requires 212.2009.

(10s)-8-Propyl-8-azabicyclo[4.3.1]decan-10-ol 7d

The reaction was conducted according to the general procedure using 8-propyl-8-azabicyclo[4.3.1]decan-10-one\(^3\) 6d (0.225 g, 1.15 mmol), sodium borohydride (0.0870 g, 2.30 mmol) and ethanol/water (15 mL) to afford the *title compound* 7d (0.192 g, 0.973 mmol, 85%) as a colourless solid after flash chromatography (1:19, ethyl acetate:hexane). \(\nu_{\text{max}} (\text{NaCl})/\text{cm}^{-1} 3366 (\text{O}–\text{H}), 2964, 2935, 2878 (\text{C}–\text{H}); ^1\text{H} \text{NMR (300 MHz, CD}_3\text{OD}) \delta_H 3.89 (1H, t, \(J = 5.4\), H10), 2.71 (2H, d, \(J = 10.9\), H7A, H9A), 2.17 (2H, t, \(J = 7.0\), NC\(_2\text{H}_2\text{CH}_2\text{CH}_3\)), 2.08 (2H, m, H1, H6), 2.02 (2H, dd, \(J = 11.5, 3.0\), H7B, H9B), 2.06–1.88 (4H, m, H2A, H3A, H4A, H5A), 1.72 (2H, m, H2B, H5B), 1.58–1.45 (2H, m, H3B, H4B), 1.49 (2H, sext., \(J = 7.2\), NC\(_2\text{H}_2\text{CH}_2\text{CH}_3\)), 0.94 (3H, t, \(J = 7.4\), NC\(_2\text{H}_2\text{CH}_2\text{CH}_3\)); ^13\text{C} \text{NMR (75 MHz, CD}_3\text{OD}) \delta_C 76.3, 61.8, 61.6, 39.8, 32.6, 28.0, 21.5, 12.5; \text{m/z (ESI+)} 198 ([M+H]\(^+\), 100). Found 198.1854, C\(_{12}\)H\(_{24}\)NO ([M+H]\(^+\)) requires 198.1858.

(10s)-8-Benzyl-8-azabicyclo[4.3.1]decan-10-ol 7e

The reaction was conducted according to the general procedure using ketone 6e (0.470 g, 1.93 mmol), sodium borohydride (0.146 g, 3.87 mmol) and ethanol/water (40 mL) to afford the *title compound* 7e (0.455 g, 1.85 mmol, 96%) as a colourless solid after flash chromatography (1:9, ethyl...
acetate:hexane). \( \nu_{\text{max}} \) (NaCl)/cm\(^{-1}\) 3339 (O–H), 2945, 2907, 2870, 2853, 2806 (C–H); \(^1\)H NMR (200 MHz, CD\(_3\)OD) \( \delta \)H 7.31–7.20 (5H, m, NCH\(_2\)C\(_6\)H\(_6\)), 3.91 (1H, t, \( J \) 4.9, H10), 3.36 (2H, s, NCH\(_2\)C\(_6\)H\(_6\)), 2.67 (2H, d, \( J \) 10.6, H7A, H9A), 2.10–1.88 (8H, m, H1, H2A, H3A, H4A, H5A, H6, H7B, H9B), 1.75 (2H, m, H2B, H5B), 1.49 (2H, m, H3B, H4B); \(^{13}\)C NMR (50 MHz, CD\(_3\)OD) \( \delta \)C 168.7, 158.2, 157.3, 156.0, 104.3, 92.6, 89.6, 67.9, 60.5, 56.2; \( m/z \) (ESI+) 246 ([M+H]+, 100). Found 246.1851, \( C_{16}H_{24}NO \) ([M+H]+) requires 246.1858.

(11s)-9-Ethyl-9-azabicyclo[5.3.1]undecan-11-ol 7f

The reaction was conducted according to the general procedure using 9-ethyl-9-azabicyclo[5.3.1]undecan-11-one\(^3\) 6f (0.958 g, 4.90 mmol), sodium borohydride (0.371 g, 9.80 mmol) and ethanol/water (100 mL) to afford a mixture of epimers (1:4.2, 11r:11s) which was separated to give the title compound 7f (0.492 g, 2.49 mmol, 51%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). \( \nu_{\text{max}} \) (NaCl)/cm\(^{-1}\) 3369 (O–H), 2966, 2933, 2908, 2847, 2799, 2762 (C–H); \(^1\)H NMR (300 MHz, CD\(_3\)OD) \( \delta \)H 3.83 (1H, t, \( J \) 5.9, H11), 2.81 (2H, d, \( J \) 11.3, H8A, H10A), 2.31 (2H, q, \( J \) 7.2, NCH\(_2\)CH\(_3\)), 2.05 (2H, dd, \( J \) 11.7, 3.8, H8B, H10B), 1.95–1.88 (6H, m, H1, H2A, H3A, H5A, H6A, H7), 1.72–1.69 (5H, m, H2B, H3B, H4A, H5B, H6B), 1.34 (1H, m, H4B), 1.07 (3H, t, \( J \) 7.2, NCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (75 MHz, CD\(_3\)OD) \( \delta \)C 58.2, 53.3, 38.7, 33.5, 30.6, 25.6, 12.8, 6.7; \( m/z \) (ESI+) 198 ([M+H]+, 100). Found 198.1845, \( C_{12}H_{24}NO \) ([M+H]+) requires 198.1858.

A second fraction afforded the (11r) isomer (31.3 mg, 0.159 mmol, 3%) which was not investigated further.

(11s)-9-tert-Butyl-9-azabicyclo[5.3.1]undecan-11-ol 7g

The reaction was conducted according to the general procedure using 9-tert-butyl-9-azabicyclo[5.3.1]undecan-11-one\(^3\) 6g (118 mg, 0.528 mmol), sodium borohydride (39.9 mg, 1.06 mmol) and ethanol/water (10 mL) to afford the title compound 7g (106 mg, 0.472 mmol, 89%) as a
colourless solid after flash chromatography (1:19, ethyl acetate:hexane). v_{\text{max}} (NaCl)/cm^{-1} 3339 (O–H), 2964, 2908, 2787 (C–H); \textsuperscript{1}H NMR (300 MHz, CD_{3}OD) \delta_{\text{H}} 3.83 (1H, m, H11), 2.98 (2H, d, J 11.1, H8A, H10A), 2.25 (2H, m, H8B, H10B), 2.01–1.61 (11H, m, H1, H2, H3, H4A, H5, H6, H7), 1.43 (1H, m, H4B), 1.09 (9H, s, NC(CH_{3})_{3}); \textsuperscript{13}C NMR (50 MHz, CD_{3}OD) \delta_{C} 76.1, 54.5, 51.4, 39.0, 33.4, 31.3, 26.6, 25.6; m/z (ESI+) 226 ([M+H]\textsuperscript{+}, 100), 170 (10). Found 226.2164, C_{14}H_{28}NO ([M+H]\textsuperscript{+}) requires 226.2171.

(9s)-3-Ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol 10a and (9r)-3-ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol 11a

The reaction was conducted according to the general procedure using 3-ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one\textsuperscript{31} 9a (501 mg, 2.56 mmol), sodium borohydride (194 mg, 5.13 mmol) and ethanol/water (50 mL) to afford the \textit{title compounds} as a mixture of epimers (1:2.2, 9r:9s) which was separated to give 10a (306 mg, 1.55 mmol, 60%) as a colourless solid after flash chromatography (1:9 ethyl acetate:hexane). v_{\text{max}} (NaCl)/cm^{-1} 3342 (O–H), 2966, 2945, 2922, 2870, 2800, 2770, 2748 (C–H); \textsuperscript{1}H NMR (400 MHz, CDCl_{3}) \delta_{\text{H}} 3.00 (1H, d, J 5.6, H9), 2.80–2.62 (1H, m, H7A), 2.73 (2H, dd, J 10.4, 1.3, H2A, H4A), 2.14 (2H, q, J 7.2, NCH_{2}CH_{3}), 1.80 (2H, d, J 10.4, H2B, H4B), 1.63–1.52 (3H, m, H6A, H7B, H8A), 1.41 (1H, bs, OH), 1.35 (2H, dd, J 13.8, 6.9, H6B, H8B), 1.01 (3H, t, J 7.2, NCH_{2}CH_{3}), 0.84 (6H, s, CCH_{3}); \textsuperscript{13}C NMR (50 MHz, CDCl_{3}) \delta_{C} 81.4, 66.3, 52.4, 36.2, 31.3, 25.5, 21.1, 13.0; m/z (ESI+) 198 ([M+H]\textsuperscript{+}, 100), 196 (32). Found 198.1853, C_{12}H_{24}NO ([M+H]\textsuperscript{+}) requires 198.185.

A second fraction afforded 11a (117 mg, 0.593 mmol, 23%) as a colourless oil. v_{\text{max}} (NaCl)/cm^{-1} 3441 (O–H), 2970, 2947, 2922, 2903, 2847, 2806 (C–H); \textsuperscript{1}H NMR (300 MHz, CD_{3}OD) \delta_{\text{H}} 3.02 (1H, s, H9), 2.80 (1H, m, H7A), 2.42 (2H, d, J 10.9, H2A, H4A), 2.23 (2H, q, J 7.2, NCH_{2}CH_{3}), 2.17 (2H, dd, J 11.0, 2.1, H2B, H4B), 1.65 (2H, ddd, J 13.6, 5.9, 0.8, H6A, H8A), 1.42–1.23 (3H, m, H6B, H7B, H8B), 1.04 (3H, t, J 7.2, NCH_{2}CH_{3}), 0.84 (6H, s, CCH_{3}); \textsuperscript{13}C NMR (75 MHz, CD_{3}OD) \delta_{C} 80.7, 59.5, 53.6, 41.3, 37.4, 25.7, 22.5, 13.0; m/z (ESI+) 198 ([M+H]\textsuperscript{+}, 100). Found 198.1858, C_{12}H_{24}NO ([M+H]\textsuperscript{+}) requires 198.185.
The reaction was conducted according to the general procedure using 3-isopropyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one[3] 9b (236 mg, 1.13 mmol), sodium borohydride (259 mg, 6.86 mmol) and ethanol/water (10 mL) to afford the title compounds as a mixture of epimers (1:1.7, 9r:9s) which was separated to give alcohol 10b (109 mg, 0.516 mmol, 46%) as a colourless solid after flash chromatography (1:9, ethyl acetate:hexane). ν_{max} (NaCl)/cm\(^{-1}\) 3354 (O–H), 2968, 2947, 2922, 2854, 2789 (C–H); \(^1\)H NMR (300 MHz, CD\(_3\)OD) δ 2.90 (1H, s, H9), 2.77 (1H, m, H7A), 2.66 (2H, dd, J \(10.3, 1.3\), H2A, H4A), 2.54 (1H, sept., J \(6.6\), CH(CH\(_3\))\(_2\)), 2.09 (2H, dd, J 11.6, 2.3, H2B, H4B), 1.63 (2H, tdd, J \(13.5, 6.5, 2.2\), H6A, H8A), 1.35–1.22 (3H, m, H6B, H7B, H8B), 0.96 (6H, d, J \(6.6\), CH(CH\(_3\))\(_2\)), 0.82 (6H, s, CCH\(_3\)); \(^{13}\)C NMR (75 MHz, CD\(_3\)OD) δ 82.0, 62.8, 54.9, 54.9, 41.6, 37.3, 25.8, 22.6, 18.4; m/z (ESI\(^{+}\)) 212 ([M+H]\(^{+}\), 100), 210 (M–H\(^+\), 20). Found [M+H]\(^+\) 212.2012, C\(_{13}\)H\(_{26}\)NO \([\text{M+H]}^{+}\) requires 212.20.

A second fraction afforded alcohol 11b (53 mg, 0.251 mmol, 22%) as a yellow oil. ν_{max} (NaCl)/cm\(^{-1}\) 3377, 3356 (O–H), 2962, 2928, 2870, 2851 (C–H); \(^1\)H NMR (300 MHz, CD\(_3\)OD) δ 3.02 (1H, s, H9), 2.86 (1H, m, H7A), 2.56 (1H, sept., J 6.6, CH(CH\(_3\))\(_2\)), 2.44 (2H, dd, J 10.9, 2.1, H2A, H4A), 2.32 (2H, d, J 10.7, H2B, H4B), 1.63 (2H, ddd, J 14.0, 6.3, 1.2, H6A, H8A), 1.45–1.19 (3H, m, H6B, H7B, H8B), 0.99 (6H, d, J 6.6, CH(CH\(_3\))\(_2\)), 0.84 (6H, s, CCH\(_3\)); \(^{13}\)C NMR (75 MHz, CD\(_3\)OD) δ 81.0, 55.3, 54.9, 41.6, 37.3, 25.8, 22.6, 18.7; m/z (ESI\(^{+}\)) 212 ([M+H]\(^{+}\), 25), 211 (40), 210 ([M–H]\(^+\), 100). Found [M–H]\(^+\) 210.1852, C\(_{13}\)H\(_{24}\)NO \([\text{M–H]}^{+}\) requires 210.1858.

The reaction was conducted according to the general procedure using tert-butyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one[3] 9c (82.7 mg, 0.37 mmol), sodium borohydride (28.0 mg, 0.74 mmol) and ethanol/water (6 mL) to afford the title compound as a mixture of epimers (1:1.7, 9r:9s) which was separated to give 10c (40.2 mg, 0.178 mmol, 48%) as a colourless solid. ν_{max} (NaCl)/cm\(^{-1}\) 3346 (O–H), 2968, 2949, 2907, 2868, 2851, 2791 (C–H); \(^1\)H NMR (300 MHz,
CD$_3$OD $\delta$H 2.89 (1H, s, H9), 2.84 (1H, m, H7A), 2.84 (2H, d, $J$ 11.4, H2A, H4A), 2.07 (2H, dd, $J$ 11.7, 2.1, H2B, H4B), 1.64 (2H, tdd, $J$ 13.2, 6.4, 2.0, H6A, H8A), 1.35–1.22 (3H, m, H6B, H7B, H8B), 1.02 (9H, s, (CD$_3$)$_3$C), 0.81 (6H, s, (CH$_3$)$_3$C); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$C 82.1, 59.9, 53.6, 36.9, 32.5, 26.6, 26.3, 22.1; $m/z$ (ESI+) 226 ([M+H]$^+$, 100), 170 (10). Found 226.2169, $C_{14}H_{28}$NO ([M+H]$^+$) requires 226.2171.

The minor isomer 11c was not isolated.

General Procedure for Acetylation

To a solution of alcohol (1 eq) and 4-(dimethylamino)pyridine (0.1 eq) in dichloromethane was added triethylamine (2 eq) and acetic anhydride (4 eq) under nitrogen. The reaction mixture was heated at reflux for 24 h at which time the reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (10 mL) and the organic material extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (ethyl acetate:hexane) to give the target compound.

(10s)-8-Ethyl-8-azabicyclo[4.3.1]decan-10-yl acetate 8a

The reaction was conducted according to the general procedure using alcohol 7a (67.0 mg, 0.366 mmol), 4-(dimethylamino)pyridine (5.0 mg, 0.0409 mmol), triethylamine (0.10 mL, 0.0728 g, 0.719 mmol), acetic anhydride (0.14 mL, 0.151 g, 1.48 mmol) and dichloromethane (2.5 mL) to afford the title compound 8a (0.0696 g, 0.309 mmol, 85%) as a clear colourless oil after flash chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2968, 2943, 2918, 2858, 2802, 2781, 2758 (C–H), 1740 (C=O); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$H 4.95 (1H, t, $J$ 5.7, H10), 2.69 (2H, dd, $J$ 11.1, 2.1, H7A, H9A), 2.31–2.20 (2H, m, H1, H6), 2.24 (2H, q, $J$ 7.2, NCH$_2$CH$_3$), 2.07 (3H, s, OCOCH$_3$), 2.08 (2H, dd, $J$ 11.1, 3.1, H7B, H9B), 1.91–1.77 (4H, m, H2A, H3A, H4A, H5A), 1.66–1.52 (4H, m, H2B, H3B, H4B, H5B), 1.02 (3H, s, NCH$_2$CH$_3$); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$C 170.9, 78.2, 60.2, 52.5, 36.0, 32.1, 27.1, 21.7, 13.0; $m/z$ (ESI+) 226 ([M+H]$^+$, 100), 224 (27). Found 226.1804, $C_{13}H_{24}$NO$_2$ ([M+H]$^+$) requires 226.1807.
The reaction was conducted according to the general procedure using alcohol 7b (0.100 g, 0.507 mmol), 4-(dimethylamino)pyridine (6.3 mg, 0.0516 mmol), triethylamine (0.14 mL, 0.103 g, 1.01 mmol), acetic anhydride (0.19 mL, 0.207 g, 2.02 mmol) and dichloromethane (5 mL) to afford the title compound 8b (0.113 g, 0.473 mmol, 93%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν<sub>max</sub> (NaCl)/cm<sup>–1</sup> 2962, 2941, 2916, 2860, 2799, 2785, 2746 (C–H), 1736 (C=O); ¹H NMR (200 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 4.89 (1H, t, J<sub>5.7</sub>, H<sub>10</sub>), 2.66 (1H, sept., J<sub>6.6</sub>, NC<sub>3</sub>CH<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>), 2.57 (2H, dd, J 11.3, 2.4, H<sub>7A</sub>, H<sub>9A</sub>), 2.34 (2H, dd, J 11.5, 3.1, H<sub>7B</sub>, H<sub>9B</sub>), 2.20 (2H, m, H1, H6), 2.03 (3H, s, OCOCH<sub>3</sub>), 1.86–1.74 (4H, m, H2A, H3A, H4A, H5A), 1.62–1.49 (4H, m, H2B, H3B, H4B, H5B), 0.93 (6H, d, J 6.6, NCH(C<sub>2</sub>H<sub>5</sub>))<sub>2</sub>; ¹³C NMR (50 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 170.8, 78.6, 53.3, 54.4, 36.0, 32.1, 27.2, 21.7, 18.3; m/z (ESI+) 240 ([M+H]<sup>+</sup>, 86), 238 (100). Found 240.1955, C<sub>14</sub>H<sub>26</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>) requires 240.1964.

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-yl acetate 8c<sup>[31]</sup>

The reaction was conducted according to the general procedure using alcohol 7c (0.112 g, 0.529 mmol), 4-(dimethylamino)pyridine (6.5 mg, 0.0532 mmol), triethylamine (0.15 mL, 0.109 g, 1.08 mmol), acetic anhydride (0.20 mL, 0.216 g, 2.12 mmol) and dichloromethane (2.5 mL) to afford the title compound 8c (0.129 g, 0.509 mmol, 96%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν<sub>max</sub> (NaCl)/cm<sup>–1</sup> 2968, 2943, 2914, 2874, 2860, 2789 (C–H), 1738 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 4.91 (1H, t, J 5.6, H10), 2.84 (2H, dd, J 8.5, 2.5, H7A, H9A), 2.27–2.20 (4H, m, H1, H6, H7B, H9B), 2.06 (3H, s, OCOCH<sub>3</sub>), 1.94–1.77 (4H, m, H2A, H3A, H4A, H5A), 1.64–1.51 (4H, m, H2B, H3B, H4B, H5B), 1.02 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>); ¹³C NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 170.9, 78.9, 53.3, 52.9, 36.3, 32.1, 27.3, 26.5, 21.8; m/z (ESI+) 254 ([M+H]<sup>+</sup>, 100), 252 (25), 198 (23). Found 254.2105, C<sub>15</sub>H<sub>28</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>) requires 254.2120.
(10s)-8-Propyl-8-azabicyclo[4.3.1]decan-10-yl acetate 8d

![Diagram of 8d]

The reaction was conducted according to the general procedure using alcohol 7d (80.2 mg, 0.406 mmol), 4-(dimethylamino)pyridine (5.7 mg, 0.0548 mmol), triethylamine (0.115 mL, 0.168 g, 1.64 mmol) and acetic anhydride (0.155 mL, 0.168 g, 1.64 mmol) and dichloromethane (5 mL) to afford the title compound 8d (78.2 mg, 0.328 mmol, 81%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2941, 2918, 2874, 2860, 2804, 2779, 2752 (C–H), 1738 (C=O); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.94 (1H, t, J 5.7, H10), 2.63 (2H, dd, J 8.9, 2.2, H7A, H9A), 2.24–2.03 (4H, m, H1, H6, H7B, H9B), 2.13 (2H, q, J 7.2, NCH$_2$CH$_2$CH$_3$), 2.06 (3H, s, OCOCH$_3$), 1.89–1.78 (4H, m, H2A, H3A, H4A, H5A), 1.65–1.38 (4H, m, H2B, H3B, H4B, H5B), 1.44 (2H, sext., J 7.1, NCH$_2$CH$_2$CH$_3$), 0.90 (3H t, J 7.3, NCH$_2$CH$_2$CH$_3$); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$C 170.9, 78.9, 63.4, 60.2, 35.7, 31.6, 27.0, 21.5; m/z (ESI+) 240 ([M+H]$^+$, 29), 238 (100). Found 240.1951, C$_{14}$H$_{26}$NO$_2$ ([M+H]$^+$) requires 240.1964.

(10s)-8-Benzyl-8-azabicyclo[4.3.1]decan-10-yl acetate 8e

![Diagram of 8e]

The reaction was conducted according to the general procedure using alcohol 7e (198 mg, 8.07 mmol), 4-(dimethylamino)pyridine (9.8 mg, 0.080 mmol), triethylamine (0.22 mL, 163 mg, 1.61 mmol), acetic anhydride (0.30 mL, 0.329 g, 3.22 mmol) and dichloromethane (8 mL) to afford the title compound 8e (227 mg, 0.790 mmol, 98%) as a colourless oil after flash chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2915, 2858, 2801 (C–H), 1732 (C=O); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$H 7.33–7.23 (5H, m, NCH$_2$Ph), 4.98 (1H, t, J 5.5, H10), 3.39 (2H, s, NCH$_2$Ph), 2.46 (2H, d, J 10.9, H7A, H9A), 2.23–1.48 (12H, m, H1, H2, H3, H4, H5, H6, H7B, H9B), 2.07 (3H, s, OCOCH$_3$); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$C 170.7, 139.2, 129.0, 128.3, 127.0, 77.8, 63.4, 60.2, 35.7, 31.6, 27.0, 21.5; m/z (ESI+) 288 ([M+H]$^+$, 100). Found 288.1958, C$_{18}$H$_{26}$NO$_2$ ([M+H]$^+$) requires 288.1964.
(11s)-9-Ethyl-9-azabicyclo[5.3.1]undecan-11-yl acetate 8f

The reaction was conducted according to the general procedure using alcohol 7f (102 mg, 0.514 mmol), 4-(dimethylamino)pyridine (6.3 mg, 0.051 mmol), triethylamine (104 mg, 1.03 mmol), acetic anhydride (210 mg, 2.06 mmol) and dichloromethane (5 mL) to afford the title compound 8f (123 mg, 0.514 mmol, 99%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2966, 2914, 2795, 2764 (C–H), 1740 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 4.96 (1H, m, H11), 2.72 (2H, d, J 10.4, H8A, H10A), 2.30 (2H, q, J 6.7, NCH$_2$CH$_3$), 2.13–2.09 (4H, m, H1, H7, H8B, H10B), 2.09 (3H, m, OCOCH$_3$), 1.79–1.67 (10H, m, H2, H3, H4, H5, H6), 1.04 (3H, t, J 6.7, NCH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 170.6, 77.2, 57.4, 52.1, 35.0, 32.2, 30.9, 24.6, 21.6, 12.5; m/z (ESI+) 240 ([M+H]$^+$, 100). Found 240.1953, C$_{14}$H$_{26}$NO$_2$ ([M+H]$^+$) requires 240.1964.

(11s)-9-tert-Butyl-9-azabicyclo[5.3.1]undecan-11-yl acetate 8g

The reaction was conducted according to the general procedure using alcohol 7g (84.1 mg, 0.373 mmol), 4-(dimethylamino)pyridine (5.0 mg, 0.041 mmol), triethylamine (75.7 mg, 0.748 mmol), acetic anhydride (152 mg, 1.49 mmol) and dichloromethane (3.7 mL) to afford the title compound 8g (69.1 mg, 0.258 mmol, 69%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2966, 2916, 2868, 2795 (C–H), 1738 (C=O); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$H 4.97 (1H, t, J 5.4, H11), 2.87 (2H, d, J 11.3, H8A, H10A), 2.27 (2H, dd, J 11.5, 2.6, H8B, H10B), 2.07 (5H, m, H1, H7, OCOCH$_3$), 1.81–1.55 (10H, m, H2, H3, H4, H5, H6), 1.04 (9H, s, NC(CH$_3$)$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 170.7, 78.6, 53.5, 50.8, 35.6, 32.3, 31.2, 26.4, 24.5, 21.7; m/z (ESI+) 268 ([M+H]$^+$, 100), 212 (14). Found 268.2268, C$_{16}$H$_{30}$NO$_2$ ([M+H]$^+$) requires 268.2277.
The reaction was conducted according to the general procedure using alcohol 10a (97.9 mg, 0.496 mmol), 4-(dimethylamino)pyridine (6.8 mg, 0.056 mmol), triethylamine (102 mg, 1.0 mmol), acetic anhydride (206 mg, 2.0 mmol) and dichloromethane (2.0 mL) to afford the title compound 12a (110 mg, 0.460 mmol, 92%) as a colourless oil after flash chromatography (1:4, ethyl acetate:hexane).

\( \nu_{\text{max}} (\text{NaCl})/\text{cm}^{-1} \):

2967, 2929, 2755 (C–H), 1739 (C=O), 1241 (C–O);

\( {^1}H \text{ NMR (200 MHz, CDCl}_3 \)

\( \delta_H \): 4.53 (1H, s, H9), 2.81–2.64 (1H, m, H7A), 2.71 (2H, d, J 11.7, H2A, H4A), 2.14 (2H, q, J 6.4, \( \text{CH}_2\text{CH}_3 \)), 2.07 (3H, s, \( \text{OCCOCH}_3 \)), 1.89 (2H, dd, J 11.7, 2.2, H2B, H4B), 1.55 (2H, tdd, J 13.6, 6.5, 2.3, H6A, H8A), 1.40–1.22 (3H, m, H6B, H7B, H8B), 0.98 (3H, t, J 7.2, \( \text{CH}_2\text{CH}_3 \)), 0.69 (6H, s, \( \text{CCH}_3 \));

\( {^{13}}C \text{ NMR (75 MHz, CDCl}_3 \)

\( \delta_C \): 171.4, 81.9, 65.8, 52.2, 35.8, 32.2, 30.0, 25.2, 21.1, 13.0;

\( m/z \) (ESI+) 240 ([M+H]+, 100), 238 (89). Found 240.1958. \( \text{C}_{14}\text{H}_{26}\text{NO}_2 ([M+H]^+) \) requires 240.1964.

The reaction was conducted according to the general procedure using alcohol 10c (81.5 mg, 0.317 mmol), 4-(dimethylamino)pyridine (4.4 mg, 0.036 mmol), triethylamine (73.4 mg, 0.725 mmol), acetic anhydride (148 mg, 1.45 mmol) and dichloromethane (3.6 mL) to afford the title compound 12c (88.9 mg, 0.332 mmol, 92%) as a colourless oil after flash chromatography (1:9, ethyl acetate:hexane).

\( \nu_{\text{max}} (\text{NaCl})/\text{cm}^{-1} \):

2966, 2926, 2910, 2872, 2853 (C–H), 1738 (C=O);

\( {^1}H \text{ NMR (200 MHz, CDCl}_3 \)

\( \delta_H \): 4.52 (1H, s, H9), 2.91–2.76 (1H, m, H7A), 2.81 (2H, d, J 11.6, H2A, H4A), 2.16 (2H, dd, J 11.7, 1.9, H2B, H4B), 2.09 (3H, s, \( \text{COOCCH}_3 \)), 1.66–1.49 (2H, m, H6A, H8A), 1.41–1.25 (3H, m, H6B, H7B, H8B), 1.01 (9H, s, \( \text{NC(CH}_3)_3 \)), 0.70 (6H, s, \( \text{CCH}_3 \));

\( {^{13}}C \text{ NMR (75 MHz, CDCl}_3 \)

\( \delta_C \): 171.4, 82.3, 68.3, 53.0, 35.5, 32.3, 29.8, 26.0, 25.2, 21.2; \( m/z \) (ESI+) 268 ([M+H]+, 100), 212 (21). Found 268.2270. \( \text{C}_{16}\text{H}_{30}\text{NO}_2 ([M+H]^+) \) requires 268.2277.
General Procedure for Esterification

To a solution of alcohol (1 eq) and acid chloride (1.5 eq) in dichloromethane (0.25 M) at 0 °C was added triethylamine (2.1 eq) dropwise under nitrogen. The solution was warmed to room temperature and the reaction heated at reflux for 16 h at which time the reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (10 mL) and the organic material extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (ethyl acetate:hexane) to give the target compound.

(10S)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl cyclohexanecarboxylate 13

The reaction was conducted according to the general procedure using alcohol 7b (70.0 mg, 0.355 mmol), cyclohexanecarbonyl chloride (77.7 mg, 0.530 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the title compound 13 (100 mg, 0.326 mmol, 92%) as a colourless oil after chromatography (1:19, ethyl acetate:hexane). ν_{max} (NaCl)/cm$^{-1}$ 2961, 2930, 2854, 2799, 2787 (C–H), 1728 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) δH 4.93 (1H, t, J 5.6, H10), 2.69 (1H, sept., J 6.6, NCH(CH$_3$)$_2$), 2.60 (2H, d, J 11.3, H7A, H9A), 2.37 (2H, dd, J 11.5, 3.1, H7B, H9B), 2.31 (1H, m, H1'), 2.21 (2H, m, H1, H6), 1.94–1.22 (18H, m, H2, H3, H4, H5, H2', H3', H4', H5', H6'), 0.96 (6H, d, J 6.6, NCH(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) δC 175.7, 77.9, 55.3, 54.2, 43.8, 36.0, 32.0, 29.3, 27.1, 26.0, 25.7, 18.2; m/z (ESI+) 308 ([M+H]$^+$), 306 (100). Found 308.2576, C$_{19}$H$_{34}$NO$_2$ ([M+H]$^+$) requires 308.2590.

(10S)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl pivalate 14

The reaction was conducted according to the general procedure using alcohol 7b (70.1 mg, 0.355 mmol), pivaloyl chloride (64.6 mg, 0.536 mmol), triethylamine (76.4 mg, 0.755 mmol) and...
dichloromethane (1.5 mL) to afford the title compound 14 (99.0 mg, 0.352 mmol, 99%) as a colourless oil after chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2964, 2945, 2914, 2872, 2860, 2799, 2785 (C–H), 1726 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 4.92 (1H, t, J 5.7, H10), 2.69 (1H, sept., J 6.6, NCH(CH$_3$)$_2$), 2.60 (2H, d, J 11.2, H7A, H9A), 2.37 (2H, dd, J 11.6, 2.7, H7B, H9B), 2.20 (2H, m, H1, H6), 1.91–1.78 (4H, m, H2A, H3A, H4A, H5A), 1.66–1.52 (4H, m, H2B, H3B, H4B, H5B), 1.22 (9H, s, OCOC(CH$_3$)$_3$), 0.96 (6H, d, J 6.6, NCH(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 178.1, 78.0, 55.3, 54.2, 39.1, 36.0, 32.0, 27.5, 27.1, 18.2; m/z (ESI+) 282 ([M+H]$^+$, 38), 280 (100). Found 282.2421, C$_{17}$H$_{32}$NO$_2$ ([M+H]$^+$) requires 282.2433.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl 2-methoxybenzoate 15

![Structure of 15](image)

The reaction was conducted according to the general procedure using alcohol 7b (70.1 mg, 0.355 mmol), o-anisoyl chloride (90.5 mg, 0.531 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the title compound 15 (95.4 mg, 0.288 mmol, 81%) as a colourless solid after chromatography (1:19, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2962, 2914, 2858, 2799, 2785 (C–H), 1724 (C=O), 1600 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 7.85 (1H, dd, J 8.1, 1.8, H6'), 7.45 (1H, td, J 7.4, 1.1, H4'), 6.99–6.95 (2H, m, H3', H5'), 5.20 (1H, t, J 5.6, H10), 3.88 (3H, s, ArOCH$_3$), 2.71 (1H, sept., J 6.6, NCH(CH$_3$)$_2$), 2.64 (2H, d, J 11.1, H7A, H9A), 2.43 (2H, dd, J 11.6, 2.7, H7B, H9B), 2.36 (2H, m, H1, H6), 2.01–1.86 (4H, m, H2A, H3A, H4A, H5A), 1.80–1.69 (2H, m, H2B, H5B), 1.61–1.53 (2H, m, H3B, H4B), 0.98 (6H, d, J 6.6, NCH(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 165.7, 158.4, 133.4, 131.8, 120.8, 120.2, 112.0, 78.8, 55.8, 55.3, 54.2, 36.1, 32.0, 26.9, 18.1; m/z (ESI+) 685 (24), 354 (18), 332 ([M+H]$^+$, 100). Found 332.2214, C$_{20}$H$_{30}$NO$_3$ ([M+H]$^+$) requires 332.2226.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl cyclohexanecarboxylate 16

![Structure of 16](image)

The reaction was conducted according to the general procedure using alcohol 7e (100 mg, 0.473 mmol), cyclohexanecarbonyl chloride (106 mg, 0.721 mmol), triethylamine (98.3 mg, 0.971 mmol)
and dichloromethane (2.0 mL) to afford the **title compound 16** (105 mg, 0.327 mmol, 69%) as a clear colourless oil after chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2968, 2918, 2854, 2789, 2733, 2667 (C–H), 1728 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 4.92 (1H, t, $J$ 5.7, H10), 2.84 (2H, d, $J$ 11.1, H7A, H9A), 2.31 (1H, tt, $J$ 11.2, 3.6, H1'), 2.25 (2H, dd, $J$ 11.1, 3.8, H7B, H9B), 2.20 (2H, m, H1, H6), 1.99–1.92 (4H, m, H2A', H3A, H4A, H6A'), 1.84–1.74 (4H, m, H2A, H3A', H5A, H5A'), 1.68–1.59 (3H, m, H3B, H4A', H4B), 1.55–1.41 (4H, m, H2B, H2B', H5B, H6B') 1.34–1.21 (3H, m, H3B', H4B', H5B'), 1.02 (9H, s, NC(CH$_3$)$_3$);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 175.7, 78.1, 53.1, 52.7, 43.9, 36.2, 31.9, 27.1, 26.4, 26.0, 25.7; m/z (ESI+) 322 (M+H$^+$, 100), 266 (28). Found 322.2739, C$_{20}$H$_{36}$NO$_2$ ([M+H$^+$]) requires 322.2746.

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-yl 2-methoxybenzoate 17

![Image of compound 17](image)

The reaction was conducted according to the general procedure using alcohol 7c (74.9 mg, 0.354 mmol), o-anisoyl chloride (90.5 mg, 0.531 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the **title compound 17** (98.6 mg, 0.285 mmol, 81%) as a colourless solid after chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2968, 2943, 2912, 2856, 2787, 2733 (C–H), 1724 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 7.85 (1H, d, $J$ 7.2, H6'), 7.46 (1H, t, $J$ 7.6, H4'), 7.00–6.96 (2H, m, H3', H5'), 5.19 (1H, t, $J$ 4.9, H10), 3.89 (3H, s, ArOCH$_3$), 2.89 (2H, d, $J$ 10.4, H7A, H9A), 2.35–2.31 (4H, m, H1, H6, H7B, H9B), 1.99–1.93 (4H, m, H2A, H3A, H4A, H5A), 1.77–1.68 (2H, m, H2B, H5B), 1.62–1.53 (2H, m, H3B, H4B), 1.05 (9H, s, NC(CH$_3$)$_3$);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 165.8, 159.5, 153.4, 131.9, 120.8, 120.2, 112.1, 79.1, 55.9, 53.1, 52.8, 36.3, 31.9, 27.0, 26.4; m/z (ESI+) 713 (48), 368 (25), 346 ([M+H$^+$], 100), 290 (39). Found 346.2369, C$_{21}$H$_{32}$NO$_3$ ([M+H$^+$]) requires 346.2382.

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-yl 4-methoxybenzoate 18

![Image of compound 18](image)

The reaction was conducted according to the general procedure using alcohol 7c (75.0 mg, 0.355 mmol), p-anisoyl chloride (90.4 mg, 0.530 mmol), triethylamine (76.4 mg, 0.755 mmol) and
dichloromethane (1.5 mL) to afford the title compound 18 (119 mg, 0.344 mmol, 97%) as a colourless solid after chromatography (1:9, ethyl acetate:hexane). $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 2968, 2947, 2918, 2854, 2799, 2787 (C–H), 1709 (C=O), 1606, 1510 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 8.03 (2H, d, J 8.8, H$_2$', H$_6$'), 6.93 (2H, d, J 8.8, H$_3$', H$_5$'), 5.17 (1H, t, J 5.4, H10), 3.86 (3H, s, ArOCH$_3$), 2.90 (2H, d, J 11.2, H7A, H9A), 2.34 (4H, m, H1, H6, H7B, H9B), 2.08–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.78–1.55 (4H, m, H2B, H3B, H4B, H5B), 1.05 (9H, s, NC(CH$_3$)$_3$); 13C NMR (75 MHz, CDCl$_3$) δ$_C$ 165.9, 163.4, 131.7, 123.6, 113.8, 78.9, 55.6, 53.2, 52.8, 36.4, 32.0, 27.3, 26.4; m/z (ESI+) 346 ([M+H]$^+$, 100), 290 (33). Found 346.2369, C$_{21}$H$_{32}$NO$_3$ ([M+H]$^+$) requires 346.2382.

(10s)-10-Acetoxy-8-azoniabicyclo[4.3.1]decane formate 19

Ammonium formate (87.8 mg, 1.39 mmol) was added to a solution of N-benzylamine 8e (80.0 mg, 0.278 mmol) and an equal weight of palladium on charcoal (10% wt) in dry methanol (20 mL). The mixture was heated at reflux for 12 min under nitrogen. The mixture was allowed to cool to room temperature and filtered through a pad of celite, washing with methanol and dichloromethane. The volatile solvent was removed under reduced pressure to afford the title compound 19 (48.7 mg, 0.200 mmol, 72%) as a colourless solid. $\nu_{\text{max}}$ (NaCl)/cm$^{-1}$ 3354 (N–H), 2914, 2858, 2802, 2729 (C–H), 1734 (C=O); $^1$H NMR (300 MHz, CD$_3$OD) δ$_H$ 8.54 (1H, s, OC=H), 5.10 (1H, t, J 5.5, H10), 2.96–2.84 (4H, m, H7, H9), 2.21 (2H, m, H1, H6), 2.07 (3H, m, OOC=CH$_3$), 1.97–1.74 (6H, m, H2, H3A, H4A, H5), 1.62–1.55 (2H, m, H3B, H4B); 13C NMR (75 MHz, CD$_3$OD) δ$_C$ 172.0, 170.4, 78.4, 52.9, 36.4, 31.8, 28.1, 21.2; m/z (ESI+) 198 ([M–OCHO]$^+$, 100). Found 198.1481, C$_{11}$H$_{20}$NO$_2$ ([M–OCHO]$^+$) requires 198.1489.

(10s)-8-(4-Chlorobenzyl)-8-azabicyclo[4.3.1]dec-10-yl acetate 20

Sodium triacetoxyborohydride (73.9 mg, 0.348 mmol) was added to a solution of amine 19 (60.6 mg, 0.249 mmol) and p-chlorobenzaldehyde (35.0 mg, 0.249 mmol) in dichloroethane (2.5 mL) and the mixture stirred under nitrogen at room temperature for 30 h. The reaction was quenched by the addition of sodium bicarbonate (sat. 10 mL) and the organic material extracted into
dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (1:19, ethyl acetate:hexane) to give the title compound 20 (67.0 mg, 0.208 mmol, 84%) as a colourless oil. ν<sub>max</sub> (NaCl)/cm<sup>–1</sup> 2917, 2858, 2797 (C–H), 1736 (C=O); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.27 (4H, s, ArH), 4.98 (1H, t, J 5.7, H10), 3.34 (2H, s, NCH<sub>2</sub>Ar), 2.64 (2H, d, J 11.1, H7A, H9A), 2.23 (2H, m, H1, H6), 2.15 (2H, dd, J 11.4, 3.0, H7B, H9B), 2.08 (3H, s, OCOCH<sub>3</sub>), 1.98–1.47 (8H, m, H2, H3, H4, H5); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 170.7, 137.7, 132.6, 130.3, 128.4, 77.6, 62.6, 60.1, 35.6, 31.6, 26.9, 21.5; m/z (ESI<sup>+</sup>) 324 (35), 322 ([M+H]<sup>+</sup>, 100), 138 (30), 125 (32). Found 324.1556, C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>37Cl ([M+H]<sup>+</sup>) requires 324.1544; Found 322.1579, C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>35Cl ([M+H]<sup>+</sup>) requires 322.1574.

(10s)-8-(4-Hydroxybenzyl)-8-azabicyclo[4.3.1]dec-10-yl acetate 21

Sodium triacetoxyborohydride (70.3 mg, 0.332 mmol) was added to a solution of ammonium salt 19 (57.9 mg, 0.238 mmol) and p-methoxybenzaldehyde (29.1 mg, 0.238 mmol) in dichloroethane (2.5 mL) and the mixture stirred under nitrogen at room temperature for 30 h. The reaction was quenched by the addition of sodium bicarbonate (sat. 10 mL) and the organic material extracted into dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (1:4, ethyl acetate:hexane) to give the title compound 21 (71.3 mg, 0.235 mmol, 99%) as a colourless oil. ν<sub>max</sub> (NaCl)/cm<sup>–1</sup> 3401 (O–H), 2916, 2800 (C–H), 1735, 1708 (C=O); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.16 (2H, d, J 8.4, H2', H6'), 6.79 (2H, d, J 8.5, H3', H5'), 5.81 (1H, bs, OH), 5.00 (1H, t, J 5.7, H10), 3.30 (2H, s, NCH<sub>2</sub>Ar), 2.65 (2H, d, J 11.2, H7A, H9A), 2.22 (2H, m, H1, H6), 2.11 (2H, m, H7B, H9B), 2.08 (3H, s, OCOH<sub>3</sub>), 2.08–1.45 (8H, m, H2, H3, H4, H5); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD) δ<sub>C</sub> 171.2, 154.8, 131.1, 130.3, 115.1, 78.2, 62.6, 60.0, 35.7, 31.6, 26.9, 21.5; m/z (EI) 303 (M<sup>++</sup>, 30), 244 (51), 228 (34), 196 (32), 138 (48), 107 (100), 91 (45), 43 (37). Found 303.1834, C<sub>18</sub>H<sub>25</sub>NO<sub>3</sub>(M<sup>++</sup>) requires 303.1834.
Inhibitory Concentration (IC\textsubscript{50}) Response Curves \textsuperscript{[4]}

The two-electrode voltage-clamp electrophysiology functional assay was conducted on esters 8c, 8e, 8g, 12c, 17 and 18 according to previously reported procedures\textsuperscript{[4]} with the following minor modifications. Oocytes were stored at 18 °C in frog ringer solution containing gentamycin (50 µM/mL), or calcium free frog ringer solution containing BaCl\textsubscript{2} (1.8 mM) and kanamycin (4 mg/L) for cells injected with α7 mRNA. Oocytes were continually superfused by frog ringer solution or calcium free frog ringer solution containing BaCl\textsubscript{2} (1.8 mM) and atropine (1 µM) for cells expressing α7 nAChR. Test compounds were applied to oocytes at intervals of 8–9 min. The amplitude of the current (I) recorded in response to each drug was normalised to the amplitude (I\textsubscript{m}) of the current response to acetylcholine (α3β4, 150 µM; α4β2, 150 µM; α7, 300 µM).

Inhibitory concentration (IC\textsubscript{50}) response curves at rat α3β4 receptor expressed in \textit{Xenopus} oocytes of 8c, 8e, 8g, 12c, 17 and 18 in the presence of and normalized to the current response by acetylcholine (150 µM). Data are the mean±SEM (n >3 oocytes).
Inhibitory concentration (IC$_{50}$) response curves at rat α4β2 receptor expressed in *Xenopus* oocytes of 8c, 8e, 8g, 17 and 18 in the presence of and normalized to the current response by acetylcholine (100 µM). Data are the mean±SEM (n >3 oocytes). Data for ester 12c did not provide a good fit to the model and so was not reported.

Inhibitory concentration (IC$_{50}$) response curves at rat α7 receptor expressed in *Xenopus* oocytes of 8c, 8g, 12c, 17 and 18 in the presence of and normalized to the current response by acetylcholine (300 µM). Data are the mean±SEM (n >3 oocytes). The IC$_{50}$ inhibitory concentration response curve for ester 8e was not completed.
References:


300 MHz, $^1\text{H}$, CDCl$_3$
50 MHz, $^{13}$C, CDCl$_3$
$7a$

300.1 MHz, $^1$H, CD$_3$OD
7a

75.5 MHz, $^{13}$C, CD$_3$OD
$\text{HO-} \begin{array}{c}
\text{atom1} \\
\text{atom2} \\
\text{atom3} \\
\text{atom4}
\end{array}$

$7b$

300.1 MHz, $^1\text{H}$, CD$_3$OD
75.5 MHz, $^{13}$C, CD$_3$OD
300.1 MHz, $^1$H, CD$_3$OD
$7c$

75.5 MHz, $^{13}$C, CD$_3$OD
300.1 MHz, $^1$H, CD$_3$OD
75.5 MHz, $^{13}$C, CD$_3$OD
$^{7f}$

300.1 MHz, $^1$H, CDCl$_3$
$7f$

75.5 MHz, $^{13}$C, CDCl$_3$
7g

300.1 MHz, $^1$H, CDCl$_3$
50.3 MHz, $^{13}$C, CD$_3$OD
10a
400.1 MHz, $^1$H, CDCl$_3$
$^{13}$C NMR, CDCl$_3$
11a

300.1 MHz, $^1$H, CD$_3$OD
$\text{11a}$

75.5 MHz, $^{13}$C, CD$_3$OD
10b

300.1 MHz, $^1$H, CD$_3$OD
75.5 MHz, $^{13}$C, CD$_3$OD
$\text{OH} \ 11b$

300.1 MHz, $^1H$, CD$_3$OD
11b

75.5 MHz, $^{13}$C, CD$_3$OD
HO
10c
300.1 MHz, $^1$H, CD$_3$OD
$^{13}$C, CD$_3$OD

75.5 MHz
200.1 MHz, $^1$H, CDCl$_3$
$50.3\text{ MHz, }^{13}\text{C, CDCl}_3$
$\text{O}$

200.1 MHz, $^1$H, CDCl$_3$
50.3 MHz, $^{13}$C, CDCl$_3$
$\text{O} \quad 8c$

$75.5 \text{ MHz, } ^{13}\text{C, CDCl}_3$
$^{8d}$

200.1 MHz, $^1$H, CDCl$_3$
50.3 MHz, $^{13}$C, CDCl$_3$
AcO
\[ \text{N} \]
\[ \text{8e} \]

50 MHz, $^{13}$C, CDCl$_3$
$^{1}H$, CDCl$_3$
$\text{AcO}$

$8f$

75.5 MHz, $^{13}\text{C}$, CDCl$_3$
AcO

200 MHz, $^1$H, CDCl$_3$
$8g$

$100 \text{ MHz, } ^{13}\text{C, CDCl}_3$
AcO

12a

300 MHz, $^1$H, CDCl$_3$
AcO

12a

75 MHz, $^{13}$C, CDCl$_3$
AcO-\text{R}-\text{N}

12c

200 MHz, $^1$H, CDCl$_3$
12c

75 MHz, $^{13}$C, CDCl$_3$
$\text{300.1 MHz, } ^1\text{H, CDCl}_3$
$^{13}$C NMR spectrum was recorded at 75.5 MHz in CDCl$_3$. The spectrum shows characteristic signals for the carbonyl group and the aromatic ring.
300.1 MHz, $^1$H, CDCl$_3$
$^{13}$C NMR spectrum of compound 14 in CDCl$_3$.

Chemical shift range: 0 - 220 ppm. Narrow peaks at around 20, 40, 60, and 80 ppm.
300.1 MHz, $^1$H, CDCl$_3$
75.5 MHz, $^{13}$C, CDCl$_3$
75.5 MHz, $^{13}$C, CDCl$_3$
$\text{OMe}$

$\text{O}$

$\text{N}^\text{Bu}$

300.1 MHz, $^1\text{H}$, CDCl$_3$
75.5 MHz, $^{13}$C, CDCl$_3$
MeO-\text{O}-\text{N}^\text{-}{^\text{t}}\text{Bu}\hspace{1cm}18

300.1\text{ MHz,}^1\text{H, CDCl}_3
MeO-\[\begin{array}{c}
\text{O} \\
\text{O} \\
\end{array}\] - N-Bu

18

75 MHz, $^{13}$C, CDCl$_3$
75 MHz, $^{13}$C, CD$_3$OD
$^{300}$ MHz, $^1$H, CDCl$_3$
AcO-N

75 MHz, \textsuperscript{13}C, CDCl\textsubscript{3}

20

ppm
AcO-\text{N-}\text{phenyl}OH

21

200 MHz, $^1$H, CDCl$_3$
AcO

21

75 MHz, $^{13}$C, CDCl$_3$