The double-Mannich annulation of cyclic ketones using *N,N*-bis(ethoxymethyl)alkylamine reagents

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Supporting Information

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General Procedure for Double Mannich Annulation

The appropriate *N,N*-bis(ethoxymethyl)alkylamine (1.2-1.5 eq) was added to a solution of chlorotrimethylsilane (3.0 eq) in dry acetonitrile (0.5 M), to which was added a solution of the appropriate cyclic ketone (1.0 eq, 4 mmol) in dry acetonitrile and the resultant mixture stirred under nitrogen for 48 h. The reaction was quenched by the addition of ice water (10 mL) and partitioned between diethyl ether (20 mL) and water (15 mL). The ether layer was then extracted with hydrochloric acid (0.5 M, 4 x 4 mL) and the combined aqueous extracts washed with ether (20 mL), cooled to 0 °C and the pH brought to 9 by the addition of concentrated ammonia solution (~2 mL). The organic material was then extracted with ether (3 x 50 mL) and the combined ether extracts washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to afford the *title compound* in pure form. The products displayed moderate instability to chromatography on silica gel resulting in low yields and reduced purity so they were used in subsequent reactions without further purification.

8-ethyl-8-aza-bicyclo[4.3.1]decan-10-one **7a**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)ethylamine **5a** (1.09 g, 6.77 mmol), chlorotrimethylsilane (1.89 g, 17.4 mmol), cycloheptanone **6** (0.637 g, 5.68 mmol) and acetonitrile (40 mL) to afford the *title compound 7a* (0.805 g, 78%) as a yellow oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2967, 2923, 2853, 2801, 2771 (C-H), 1712 (C=O); ¹H NMR (200 MHz, CDCl₃) δ_{H} 2.69 (2H, d, *J* 11.2, H7A, H9A), 2.43 (2H, m, H1, H6), 2.24 (2H, q, *J* 7.0, CH₂CH₃), 2.20 (2H, m, H7B, H9B), 1.91-1.37 (6H, m, H2, H3A, H4A, H5), 1.17 (2H, m, H3B, H4B), 0.92 (3H, t, *J* 7.1, CH₂CH₃); ¹³C NMR (50 MHz, CDCl₃) δ_{C} 213.8, 59.4, 51.6, 48.7, 31.6, 26.7, 12.8; *m/z* (EI) 182 (MH⁺, 100%), 180 (M-H⁺), 166 (M-Me⁺, 19), 72 (C₄H₁₀N⁺, 17), 58 (C₃H₈N⁺, 30). HRMS (EI) found 182.1537; C₁₁H₂₀NO (MH⁺) requires 182.1540.

8-isopropyl-8-aza-bicyclo[4.3.1]decan-10-one **7b**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)isopropylamine **5b** (0.587 g, 3.35 mmol) and chlorotrimethylsilane (0.728 g, 6.70 mmol) in acetonitrile (4 mL) and cycloheptanone **6** (0.250 g, 2.23 mmol) in acetonitrile (17 mL) to afford the *title compound 7b* (0.370 g, 85%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2962, 2918, 2853, 2799 (C-H), 1709 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 2.85 (1H, sept., *J* 6.6, CH(CH₃)₂), 2.77 (2H, dd, *J* 9.5, 1.6, H7A, H9A), 2.62-2.59 (2H, m, H1, H6), 2.60 (2H, d, *J* 9.5, H7B, H9B), 1.97 (2H, m, H3A, H4A), 1.79 (2H, m, H2A, H5A), 1.58 (2H, m, H2B, H5B), 1.36 (2H, m, H3B, H4B), 1.01 (6H, d, *J* 6.6, CH₂(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 214.9, 54.4, 53.6, 49.4, 31.9, 27.1, 18.5; *m/z* (ESI⁺) 196 (MH⁺, 100%). HRMS (ESI⁺) found 196.1696; C₁₂H₂₂NO (MH⁺) requires 196.1696.

8-tert-butyl-8-aza-bicyclo[4.3.1]decan-10-one **7c**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)tert-butylamine **5c** (1.13 g, 5.71 mmol), chlorotrimethylsilane (1.81 g, 16.7 mmol), cycloheptanone **6** (0.476 g, 4.24 mmol) and acetonitrile (40 mL) to afford the *title compound 7c* (0.720 g, 81%) as a yellow oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2966, 2939, 2918, 2851, 2797, 2760 (C-H), 1705 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 3.03 (2H, d, *J* 10.7, H7A, H9A), 2.60 (2H, m, H1, H6), 2.51 (2H, dd, *J* 11.0, 2.6, H7B, H9B), 2.01 (2H, m, H2A, H5A), 1.80 (2H, m, H3A, H4A), 1.64-1.45 (2H, m, H2B, H5B), 1.42-1.31 (2H, m, H3B, H4B), 1.10 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 215.3, 53.6, 52.9, 49.5, 31.7, 27.2, 26.8; *m/z* (ESI⁺) 210 (MH⁺, 55), 194 (M-Me⁺, 100). HRMS (ESI⁺) found 210.1844; C₁₃H₂₄NO (MH⁺) requires 210.1853.

8-propyl-8-aza-bicyclo[4.3.1]decan-10-one **7d**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)propylamine **5d** (1.05 g, 6.03 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), cycloheptanone **6** (0.445 g, 3.97 mmol) and acetonitrile (40 mL) to afford the *title compound* **7d** (0.662 g, 85%) as a yellow oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2922, 2874, 2854, 2804, 2770, 2741 (C-H), 1709 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 2.84, (2H, d, *J* 11.3, H7A, H9A), 2.60 (2H, m, H1, H6), 2.37 (2H, dd, *J* 11.6, 3.6, H7B, H9B), 2.29 (2H, t, *J* 7.0, NCH₂CH₂CH₃), 1.99 (2H, m, H2A, H5A), 1.80 (2H, m, H3A, H4A), 1.60 (2H, m, H2B, H5B), 1.52 (2H, q, *J* 7.3, NCH₂CH₂CH₃), 1.38 (2H, m, H3B, H4B), 0.95 (3H, t, *J* 7.4, NCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 214.6, 60.3, 60.1, 49.1, 31.9, 27.1, 20.9, 12.4; *m/z* (ESI+) 208 (28), 197 (18), 196 (MH⁺, 100). HRMS (ESI+) found 196.1701; C₁₂H₂₂NO (MH⁺) requires 196.1696.

9-ethyl-9-aza-bicyclo[5.3.1]undecan-11-one **9a**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)ethylamine **5a** (0.967 g, 6.0 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), acetonitrile (32 mL), cyclooctanone **8** (0.504 g, 3.99 mmol) and acetonitrile (2 x 8 mL) to afford the *title compound* **9a** (0.749 g, 96%) as a viscous yellow oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2927, 2861, 2998 (C-H), 1712 (C=O); ¹H NMR (200 MHz, CDCl₃) δ_{H} 2.79 (2H, d, *J* 10.7, H8A, H10A), 2.42 (2H, q, *J* 7.1, CH₂CH₃), 2.35-2.13 (6H, m, H1, H2A, H3A, H5A, H6A, H7), 1.93-1.56 (5H, m, H2B, H4A, H5B, H8B, H10B), 1.29-1.41 (3H, m, H3B, H4B, H5B), 1.05 (3H, t, *J* 7.1, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 218.5, 58.5, 50.4, 49.5, 31.4, 30.6, 24.9, 12.9; *m/z* (EI+) 196 (MH⁺, 100), 180 (M-Me⁺, 20), 98 (16), 72 (C₄H₁₀N⁺, 15), 58 (C₃H₈N, 41). HRMS (ESI+) found 196.1703; C₁₂H₂₂NO (MH⁺) requires 196.1696.

9-isopropyl-9-aza-bicyclo[5.3.1]undecan-11-one **9b**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)isopropylamine **5b** (1.07 g, 6.12 mmol) and chlorotrimethylsilane (1.30 g, 12.0 mmol) in acetonitrile (8 mL) and cyclooctanone **8** (0.505 g, 4.00 mmol) in acetonitrile (32 mL) to afford the *title compound* **9b** (0.795 g, 95%) as a pale yellow oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2961, 2926, 2864, 2797 (C-H), 1703 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 2.88 (1H, sept., *J* 6.6, CH(CH₃)₂), 2.73 (2H, d, *J* 11.0, H8A, H10A), 2.58 (2H, dd, *J* 11.2, 2.2, H8B, H10B), 2.37-2.16 (4H, m, H1, H2A, H6A, H7), 1.92-1.72 (4H, m, H2B, H3A, H5A, H6B), 1.64 (1H, m, H4A), 1.29-1.14 (3H, m, H3B, H4B, H5B), 1.03 (6H, d, *J* 6.6, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 218.9, 77.6, 54.4, 54.1, 51.2, 31.6, 25.0, 18.7; *m/z* (ESI+) 210 (MH⁺, 100). HRMS (ESI+) found 210.1855; C₁₃H₂₄NO (MH⁺) requires 210.1853.

9-*tert*-butyl-9-aza-bicyclo[5.3.1]undecan-11-one **9c**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (1.14 g, 6.04 mmol) and chlorotrimethylsilane (1.30 g, 12.0 mmol) in acetonitrile (8 mL) and cyclooctanone **8** (0.505 g, 4.00 mmol) in acetonitrile (32 mL) to afford the *title compound* **9c** (0.692 g, 77%) as a white crystalline solid.

ν_{max} (NaCl)/cm⁻¹ 2968, 2924, 2866, 2847, 2797 (C-H), 1701 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 2.99 (2H, d, *J* 10.8, H8A, H10A), 2.46 (2H, dd, *J* 11.3, 2.6, H8B, H10B), 2.35-2.18 (4H, m, H1, H2A, H6A, H7), 1.90-1.63 (5H, m, H2B, H3A, H4A, H5A, H6B), 1.32-1.18 (3H, m, H3B, H4B, H5B), 1.10 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 219.2, 53.5, 51.9, 51.2, 31.7, 31.2, 27.1, 25.0; *m/z* (ESI+) 224 (MH⁺, 100), 168 (18). HRMS (ESI+) found 224.2000; C₁₄H₂₆NO (MH⁺) requires 224.2009.

9-propyl-9-aza-bicyclo[5.3.1]undecan-11-one **9d**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)propylamine **5d** (0.578 g, 3.30 mmol) and chlorotrimethylsilane (0.719 g, 6.62 mmol) in acetonitrile (4 mL) and cyclooctanone **8** (0.277 g, 2.20 mmol) in acetonitrile (16 mL) to afford the *title compound* **9d** (0.266 g, 74%) as a pale yellow oil.

ν_{max} (NaCl)/cm⁻¹ 2959, 2928, 2870, 2800, 2770 (C-H), 1701 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 2.80 (2H, d, *J* 10.0, H8A, H10A), 2.36-2.24 (8H, m, H1, H2A, H6A, H7, H8B, H10B, NCH₂CH₂CH₃), 1.90 (2H, m, H3A, H5A), 1.76 (2H, m, H2B, H6B), 1.62 (1H, m, H4A), 1.48 (2H, m, NCH₂CH₂CH₃), 1.30-1.18 (3H, m, H3B, H4B, H5B), 0.95 (3H, t, *J* 7.3, NCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 218.6, 59.6, 59.0, 50.8, 31.7, 31.5, 24.9, 20.9, 12.2; *m/z* (ESI+) 210 (MH⁺, 100). HRMS (ESI+) found 210.1847; C₁₃H₂₄NO (MH⁺) requires 210.1853.

1-methyl-3-*tert*-butyl-3-aza-bicyclo[3.3.1]nonan-9-one **17**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (1.14 g, 6.02 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), 2-methylcyclohexanone **10** (0.449 g, 4.00 mmol) and acetonitrile (40 mL) to afford the *title compound* **17** (0.790 g, 3.77 mmol, 94 %) as a clear colourless oil.

ν_{max} (NaCl)/cm⁻¹ 2972, 2924, 2854, 2793 (C-H), 1720 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 3.27 (1H, dt, *J* 10.9, 2.6, H2A), 3.11 (1H, dd, *J* 10.9, 2.9, H4A), 2.97 (1H, m, H7A), 2.64 (1H, m, H2B), 2.38-2.31 (2H, m, H4B, H5), 2.15-1.92 (3H, m, H6A, H6B, H8A), 1.72 (1H, m, H8B), 1.44 (1H, m, H7B), 1.07 (9H, s, NC(CH₃)₃), 0.89 (3H, s, CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 220.3, 60.5, 53.9, 53.5, 48.5, 47.6, 42.9, 35.1, 26.6, 21.7, 21.5; *m/z* (ESI+) 210 (MH⁺, 100), 154 (21). HRMS (ESI+) found 210.1854; C₁₃H₂₄NO (MH⁺) requires 210.1853.

3-ethyl-1,5-dimethyl-3-aza-bicyclo[3.3.1]nonan-9-one **18a**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)ethylamine **5a** (1.09 g, 6.8 mmol), chlorotrimethylsilane (1.89 g, 17.4 mmol), 2,6-dimethylcyclohexanone **11** (0.734 g, 5.82 mmol) and acetonitrile (10 mL) to afford the *title compound* **18a** (1.103 g, 97%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2970, 2926, 2754 (C-H), 1717 (C=O); ¹H NMR (200 MHz, CDCl₃) δ_{H} 3.08 (1H, m, H7A), 2.96 (2H, dd, *J* 11.7, 1.5, H2A, H4B), 2.20 (2H, q, *J* 7.1 CH₂CH₃), 2.11 (2H, dd, *J* 11.9, 2.0, H2B, H4B), 1.98 (2H, ddt, *J* 12.7, 6.1, 1.5, H6A, H8A), 1.64 (2H, dtt, *J* 12.7, 6.3, 1.9, H6B, H8B), 1.35 (1H, m, H7B), 1.01 (3H, t, *J* 7.1, CH₂CH₃), 0.85 (6H, s, CCH₃); ¹³C NMR (50 MHz, CDCl₃) δ_{C} 219.4, 67.4, 51.1, 47.3, 43.3, 21.6, 21.3, 13.1; *m/z* (ESI+) 219 (MNa⁺, 36), 196 (MH⁺, 100). HRMS (ESI+) found 218.1518; C₁₂H₂₁NONa (MNa⁺) requires 218.1515.

3-isopropyl-1,5-dimethyl-3-aza-bicyclo[3.3.1]nonan-9-one **18b**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)isopropylamine **5b** (1.08 g, 6.17 mmol) and chlorotrimethylsilane (1.34 g, 12.4 mmol) in acetonitrile (8 mL) and 2,6-dimethylcyclohexanone **11** (0.668 g, 4.12 mmol) in acetonitrile (32 mL) to afford the *title compound* **18b** (0.863 g, 97%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2966, 2926, 2903, 2845, 2795, 2768, 2741 (C-H), 1720 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 3.07 (1H, m, H7A), 2.90 (2H, d, *J* 11.5, H2A, H4B), 2.73 (1H, sept., *J* 6.6 CH(CH₃)₂), 2.38 (2H, dd, *J* 11.6, 1.9, H2B, H4B), 2.00 (2H, ddt, *J* 12.8, 6.2, 1.7, H6A, H8A), 1.68 (2H, dtt, *J* 12.8, 6.4, 2.0, H6B, H8B), 1.33 (1H, m, H7B), 0.97 (6H, d, *J* 6.6, CH(CH₃)₂), 0.89 (6H, s, CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 219.6, 62.8, 53.5, 47.3, 43.2, 21.6, 21.3, 18.4; *m/z* (ESI+) 210 (MH⁺, 100). HRMS (ESI+) found 210.1853; C₁₃H₂₄NO (MH⁺) requires 210.1851.

3-*tert*-butyl-1,5-dimethyl-3-aza-bicyclo[3.3.1]nonan-9-one **18c**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (1.13 g, 5.99 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), 2,6-dimethylcyclohexanone **11** (0.644 g, 3.97 mmol) and acetonitrile (40 mL) to afford the *title compound* **18c** (0.759 g, 86%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2924, 2970, 2870, 2845, 2795, 2758, 2741 (C-H), 1720 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 3.12 (1H, m, H7A), 3.10 (2H, dd, *J* 9.7, 1.7, H2A, H4B), 2.33 (2H, dt, *J* 9.6, 1.9, H2B, H4B), 2.02 (2H, ddt, *J* 12.6, 6.4, 1.8, H6A, H8A), 1.70 (2H, dtt, *J* 12.6, 6.5, 2.0, H6B, H8B), 1.33 (1H, m, H7B), 1.11 (9H, s, C(CH₃)₃), 0.90 (6H, s, CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 220.1, 60.6, 53.4, 47.3, 43.1, 26.5, 21.6, 21.4; *m/z* (EI) 224 (MH⁺, 22), 208 (M-Me⁺, 100). HRMS (ESI+) found 224.2014; C₁₄H₂₆NO (MH⁺) requires 224.2009.

3-propyl-1,5-dimethyl-3-aza-bicyclo[3.3.1]nonan-9-one **18d**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)propylamine **5d** (1.06 g, 6.03 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), 2,6-dimethylcyclohexanone **11** (0.662 g, 4.08 mmol) and acetonitrile (40 mL) to afford the *title compound* **18d** (0.823 g, 96%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2964, 2926, 2874, 2847, 2802, 2772, 2758, 2739 (C-H), 1720 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 3.14 (1H, m, H7A), 2.99 (2H, dd, *J* 10.3, 1.5, H2A, H4B), 2.16 (2H, t, *J* 7.1, NCH₂CH₂CH₃), 2.12-1.98 (4H, m, NCH₂CH₂CH₃, H2B, H4B), 1.70 (2H, m, H6A, H8A), 1.57-1.32 (3H, m, H6B, H7B, H8B), 0.93 (3H, t, *J* 7.3, NCH₂CH₂CH₃), 0.91 (6H, s, CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 219.5, 67.8, 59.4, 47.4, 43.3, 21.5, 21.3, 20.8, 12.2; *m/z* (EI) 210 (MH⁺, 100). HRMS (ESI⁺) found 210.1857; C₁₃H₂₄NO (MH⁺) requires 210.1853.

1-allyl-3-*tert*-butyl-3-aza-bicyclo[3.3.1]nonan-9-one **19**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (0.568 g, 3.00 mmol), chlorotrimethylsilane (0.652 g, 6.00 mmol), 2-allylcyclohexanone **12** (0.276 g, 2.00 mmol) and acetonitrile (20 mL) to afford the *title compound* **19** (0.351 g, 1.49 mmol, 75 %) as a yellow liquid.

$\nu_{\max}$ (NaCl)/cm⁻¹ 3074, 2974, 2922, 2853, 2793 (C-H), 1717 (C=O) 1639, 912 (C=C); ¹H NMR (300 MHz, CDCl₃) δ_{H} 5.81 (1H, m, H2'), 5.04 (1H, s, H3A'), 4.97 (1H, m, H3B'), 3.25 (1H, dt, *J* 10.9, 2.7, H2A), 3.14 (1H, dd, *J* 11.0, 2.8, H4A), 2.85 (1H, m, H7A), 2.65 (1H, dd, *J* 11.0, 2.6, H2B), 2.42-2.30 (2H, m, H4A, H5), 2.06 (4H, m, H6A, H8A, H1'), 1.72 (2H, m, H6B, H8B), 1.41 (1H, m, H7B), 1.08 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 219.5, 134.5, 117.6, 58.3, 53.7, 53.5, 49.5, 48.3, 39.6, 39.5, 34.6, 26.5, 21.4; *m/z* (ESI⁺) 236 (MH⁺, 100), 180 (58). HRMS (ESI⁺) found 236.2005; C₁₅H₂₆NO (MH⁺) requires 236.2009.

1-(benzyloxy)-3-*tert*-butyl-3-aza-bicyclo[3.3.1]nonan-9-one **20**

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (0.205 g, 1.01 mmol), chlorotrimethylsilane (0.325 g, 2.99 mmol), 2-benzyloxycyclohexanone **13** (0.288 g, 1.52 mmol) and acetonitrile (10 mL) to afford the *title compound* **20** (16.2 mg, 0.0537 mmol, 5 %) as a clear colourless liquid.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2970, 2926, 2853, 2795 (C-H), 1728 (C=O), 1130 (C-O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 7.28 (5H, m, PhCH₂O), 4.73 (1H, d, *J* 11.4, H1'A), 4.59 (1H, d, *J* 11.3, H1'B), 3.17 1H, dd, *J* 10.5, 2.6, H2A), 3.14 (1H, dt, *J* 11.0, 2.6, H4A), 2.79 (1H, m, H7A), 2.65 (2H, m, H2B, H4B), 2.48 (1H, m, H5), 2.18 (2H, m, H6A, H8A), 2.04-1.86 (2H, m, H6B, H8B), 1.51 (1H, m, H7B), 1.05 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 215.5, 139.5, 128.4, 127.8, 127.5, 81.9, 66.5, 58.7, 53.6, 53.3, 49.2, 39.0 33.6, 26.5, 21.9; *m/z* (ESI⁺) 324 (MNa⁺, 19), 302 (100), 246 (35), 236 (20). HRMS (ESI⁺) found 324.1931; C₁₉H₂₇NO₂ (MNa⁺) requires 324.1934.

7-oxa-3-*tert*butyl-3-aza-bicyclo[3.3.1]nonan-9-one 21

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)*tert*-butylamine **5c** (0.568 g, 3.00 mmol), chlorotrimethylsilane (0.652 g, 6.00 mmol), tetrahydro-4*H*-pyran-4-one **14** (0.200 g, 2.00 mmol) and acetonitrile (20 mL) to afford the *title compound 21* (351 mg, 01.49 mmol, 75 %) as a white solid.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2968, 2924, 2853 (C-H), 1738 (C=O), 1198 (C-O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 4.10 (2H, d, *J* 11.0, H2A, H4A), 3.83 (2H, dd, *J* 11.0, 4.0, H2B, H4B), 3.09 (2H, d, *J* 10.9, H6A, H8A), 2.94 (2H, dd, *J* 10.8, 5.9, H6B, H8B), 2.47 (2H, m, H1, H5), 1.00 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 213.0, 73.3, 53.7, 51.4, 49.8, 26.5; *m/z* (ESI+) 230 ([MH+MeOH]⁺, 100), 216 (15). HRMS (ESI+) found 230.1751; C₁₁H₂₀NO₂ ([MH+MeOH]⁺) requires 230.1751.

3-ethyl-1,5-diphenyl-3-aza-bicyclo[3.3.1]nonan-9-one 22

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)ethylamine **5a** (0.586 g, 3.63 mmol), chlorotrimethylsilane (0.986 g, 9.08 mmol), 2,6-diphenylcyclohexanone **15** (0.758 g, 3.03 mmol) and acetonitrile (11 mL) to afford the *title compound 22* (0.338 g, 35%) as a yellow liquid.

$\nu_{\max}$ (NaCl)/cm⁻¹ 3055, 2968, 2922, 2855, 2802 (C-H), 1719 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 7.37-7.16 (10H, m, ArH), 3.47 (1H, m, H7A), 3.39 (2H, m, H2A, H4A), 2.96 (2H, d, *J* 10.8, H6A, H8A), 2.68 (2H, dd, *J* 12.9, 6.0, H2B, H4B), 2.50-2.39 (2H, m, H6B, H8B), 2.45 (2H, q, *J* 6.9, CH₂CH₃), 1.82 (1H, m, H7B), 1.15 (3H, t, *J* 7.1, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 219.2, 141.8, 128.0, 127.7, 127.1, 67.2, 55.1, 52.0, 41.8, 21.8, 13.1; *m/z* (EI) 320 (MH⁺, 54), 319 (M⁺, 100). HRMS (EI) found 319.1933; C₂₂H₂₆NO (MH⁺) requires 319.1936.

10-propyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-12-one 23

The reaction was conducted according to the general procedure using *N,N*-bis(ethoxymethyl)propylamine **5d** (1.05 g, 6.00 mmol), chlorotrimethylsilane (1.30 g, 12.0 mmol), 2-indanone **16** (0.529 g, 4.00 mmol) and acetonitrile (40 mL) to afford the *title compound 23* (90.2 mg, 0.453 mmol, 11 %) as a brown oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2961, 2932, 2872, 2795 (C-H), 1769 (C=O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 7.16 (4H, m, H3, H4, H5, H6), 3.25 (2H, d, *J* 3.6, H1, H8), 3.06 (2H, dd, *J* 11.0, 3.8, H9A, H11A), 2.58 (2H, d, *J* 10.7, H9B, H11B), 2.20 (2H, t, *J* 7.2, NCH₂CH₂CH₃), 1.18 (2H, m, NCH₂CH₂CH₃), 0.53 (3H, t, *J* 7.3, NCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 214.9, 139.5, 127.5, 122.3, 59.0, 57.2, 53.1, 20.1, 11.3; *m/z* (ESI+) 248 ([MH+MeOH]⁺, 100), 216 (21). HRMS (ESI+) found 248.1640; C₁₄H₁₈NO ([MH+MeOH]⁺) requires 248.1645.

(10s)-8-tert-butyl-8-aza-bicyclo[4.3.1]decan-10-ol **24**

Sodium borohydride (0.724 g, 19.2 mmol) was added to a solution of **7c** (1.00 g, 4.78 mmol) in methanol/water (4:1, 50 mL) at 0 °C and the reaction stirred for 2h. The excess sodium borohydride was quenched by the drop-wise addition of conc. hydrochloric acid and the mixture concentrated *in vacuo* to remove methanol. The solution was then made basic with aqueous sodium hydroxide (3 M) to give pH 10. The organic material was extracted into diethyl ether (3 x 50 mL) and the combined ether extracts dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to give crude alcohol. Purification by flash chromatography (1:19, EtOAc:Hexane) afforded the *title compound* **24** (0.613 g, 2.90 mmol, 61%) as a white crystalline solid.

$\nu_{\max}$ (NaCl)/cm⁻¹ 3273 (O-H), 2961, 2910, 2851, 2795, 2739 (C-H); ¹H NMR (300 MHz, CD₃OD) δ_{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, 2.00-1.85 (4H, m, H2A, H3A, H4A, H5A), 1.73-1.67 (2H, m, H2B, H5B), 1.54-1.46 (2H, m, H3B, H4B), 1.05 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CD₃OD) δ_{C} 76.9, 53.8 (2C), 39.9, 32.6, 28.2, 26.7; *m/z* (ESI+) 212 (MH⁺, 100), 156 (17). HRMS (ESI+) found 212.2009; C₁₃H₂₆NO (MH⁺) requires 212.2009.

(10s)-8-tert-butyl-8-aza-bicyclo[4.3.1]decan-10-yl acetate **25**

A solution of acetic anhydride (0.20 mL, 0.216 g, 2.12 mmol), triethylamine (0.15 mL, 0.109 g, 1.08 mmol) and 4-dimethylaminopyridine (DMAP, 0.0065 g, 0.0532 mmol) in dichloromethane (2.5 mL) was added to a solution of alcohol **24** (0.112 g, 0.529 mmol) in dichloromethane (2.5 mL). The mixture was stirred at reflux (50 °C), under N₂ for 27 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 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to give crude acetate. Purification by flash chromatography (1:19, EtOAc:Hexane) afforded the *title compound* **25** (0.129 g, 0.509 mmol, 96%) as a clear colourless oil.

$\nu_{\max}$ (NaCl)/cm⁻¹ 2968, 2943, 2914, 2874, 2860, 2789 (C-H), 1738 (C=O), 1242 (C-O); ¹H NMR (300 MHz, CDCl₃) δ_{H} 4.91 (1H, t, *J* 5.6, H10), 2.84 (2H, dd, *J* 8.5, 2.5, H7A, H9A), 2.28-2.06 (4H, m, H1, H6, H7B, H9B), 1.94 (3H, s, OCOCH₃), 1.91-1.78 (4H, m, H2A, H3A, H4A, H5A), 1.64-1.52 (4H, m, H2B, H3B, H4B, H5B), 1.02 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 170.9, 78.9, 53.3, 52.9, 36.3, 32.1, 27.3, 26.5, 21.8; *m/z* (ESI+) 255 (17), 254 (MH⁺, 100), 252 (25), 198 (23). HRMS (ESI+) found 254.2105; C₁₅H₂₈NO₂ (MH⁺) requires 254.2115.

7a 200.1 MHz, ^1H , CDCl_3

7a 50.3 MHz, ^{13}C , CDCl_3

7b 300.1 MHz, ^1H , CDCl_3

7b 75.5 MHz, ^{13}C , CDCl_3

7c 300.1 MHz, ^1H , CDCl_3

7c 75.5 MHz, ^{13}C , CDCl_3

7d 300.1 MHz, ^1H , CDCl_3

7d 75.5 MHz, ^{13}C , CDCl_3

9a 300.1 MHz, ^1H , CDCl_3

9a 75.5 MHz, ^{13}C , CDCl_3

9b 300.1 MHz, ^1H , CDCl_3

S19

9b 75.5 MHz, ^{13}C , CDCl_3

9c 300.1 MHz, ^1H , CDCl_3

9c 75.5 MHz, ^{13}C , CDCl_3

9d 300.1 MHz, ^1H , CDCl_3

9d 75.5 MHz, ^{13}C , CDCl_3

17 300.1 MHz, ^1H , CDCl_3

18a 200.1 MHz, ^1H , CDCl_3

18a 50.3 MHz, ^{13}C , CDCl_3

18b 300.1 MHz, ^1H , CDCl_3

18b 75.5 MHz, ^{13}C , CDCl_3

18c 300.1 MHz, ^1H , CDCl_3

18c 75.5 MHz, ^{13}C , CDCl_3

18d 300.1 MHz, ^1H , CDCl_3

18d 75.5 MHz, ^{13}C , CDCl_3

19 200.1 MHz, ^1H , CDCl_3

19 75.5 MHz, ^{13}C , CDCl_3

20 300.1 MHz, ^1H , CDCl_3

20 75.5 MHz, ¹³C, CDCl₃

S38

22 300.1 MHz, ^1H , CDCl_3

22 75.5 MHz, ^{13}C , CDCl_3

24 300.1 MHz, ^1H , CD_3OD

24 75.5 MHz, ^{13}C , CD_3OD

25 300.1 MHz, ^1H , CDCl_3

25 75.5 MHz, ^{13}C , CDCl_3