

Ring transformation of 2-(haloalkyl)azetidines into 3,4-disubstituted pyrrolidines and piperidines

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General experimental methods

¹H NMR spectra were recorded at 300 MHz with CDCl₃ as solvent and tetramethylsilane as internal standard. ¹³C NMR spectra were recorded at 75 MHz with CDCl₃ as solvent. Mass spectra were obtained with a mass spectrometer (70 eV) using a GC-MS coupling (20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or were recorded using a direct inlet system (70 eV). Diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. All other solvents were used as received from the supplier.

Synthesis of 4-(1-haloalkyl)azetidin-2-ones **1** and 4-(2-haloalkyl)azetidin-2-ones **10**

4-(1-Haloalkyl)azetidin-2-ones **1** and 4-(2-haloalkyl)azetidin-2-ones **10** were synthesised by [2+2]-cyclocondensation of the corresponding α -halogenated or β -halogenated imines

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and ketenes (formed *in situ* from the corresponding acid chlorides by treatment with triethylamine) in benzene.^{14,15}

Reduction of 4-(1-haloalkyl)azetidin-2-ones **1 and 4-(2-haloalkyl)azetidin-2-ones **10** with chloroalane (AlH_2Cl)**

As an example, the synthesis of 3-benzyloxy-1-*tert*-butyl-2-(1-chloro-1-methylethyl)azetidine **2a** is described. To a solution of aluminum(III) chloride (0.65g, 4.85 mmol) in 40 ml of dry ether was added lithium aluminum hydride (0.18g, 4.85 mmol) at 0°C. The reaction mixture was stirred for 30 minutes at room temperature. 3-Benzyloxy-1-*tert*-butyl-4-(1-chloro-1-methylethyl)azetidin-2-one **1a** (0.5g, 1.62 mmol) in 10 ml of dry ether was added dropwise at 0°C. After four hours at 0°C (18 hours in the synthesis of **3a** and **3b**) water was added carefully to neutralise the residual hydride. After decantation of the solvent, the residue was extracted three times with 20 ml of diethyl ether, and the combined organic fractions were dried (MgSO_4). After filtration and evaporation of the solvent 3-benzyloxy-1-*tert*-butyl-2-(1-chloro-1-methylethyl)azetidine **2a** was obtained in 63% yield. Further purification was performed by flash chromatography. For additional spectral data see also ref. 16.

3-Benzyloxy-2-(1-bromo-1-methylethyl)-1-*tert*-butylazetidine **2f**

White crystals, 61% yield, TLC Rf 0.3 (petroleum ether/ethyl acetate 9/1), Mp. 58°C ¹H NMR (300 MHz, CDCl_3): δ 1.08 (9H, s), 1.78 and 1.81 (6H, 2×s), 3.21 (1H, d×d, $J = 8.8$ Hz, $J = 7.2$ Hz), 3.29 (1H, d×d, $J = 8.8$ Hz, $J = 4.7$ Hz), 3.73 (1H, d, $J = 7.4$ Hz), 4.15

(1H, d×t, $J = 7.2$ Hz, $J = 4.7$ Hz), 4.40 (1H, d, $J = 11.8$ Hz), 4.48 (1H, d, $J = 11.8$ Hz), 7.22-7.35 (5H, m). **^{13}C NMR** (75 MHz, CDCl_3): δ 26.1, 29.6, 29.7, 51.7, 52.5, 72.4, 71.2, 71.5, 72.1, 127.4, 127.5, 128.3, 138.0. **IR** (NaCl , cm^{-1}): $\nu_{\text{max}} = 2970, 2935, 2871, 1497, 1456, 1364$. **MS** (70 eV) m/z (%): 296 (100); 260 ($\text{M}^+ - \text{Br}$, 65). Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{BrNO}$: C 60.00; H 7.70; N 4.12. Found: C 60.23; H 7.55; N 4.01.

4-Benzoyloxy-1-*tert*-butyl-2,2-dimethylpyrrolidine 3a

Colourless oil, 63% yield, TLC Rf 0.05 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20/1). **^1H NMR** (300 MHz, CDCl_3): δ 1.03 (9H, s), 1.08 (6H, 2×s), 2.52-2.59 (2H, m), 2.67 (1H, d×d, $J = 9.5$ Hz, $J = 5.9$ Hz), 3.09 (1H, d×d, $J = 9.5$ Hz, $J = 6.2$ Hz), 3.55 (1H, t, $J = 5.9$ Hz), 4.49 (1H, d, $J = 12.1$ Hz), 4.57 (1H, d, $J = 12.1$ Hz), 7.24-7.38 (5H, m). **^{13}C NMR** (75 MHz, ref = CDCl_3): δ 22.1, 27.7, 25.9, 40.7, 50.9, 59.3, 72.0, 85.5, 127.4, 128.4, 139.1. **IR** (NaCl , cm^{-1}): $\nu_{\text{max}} = 2968, 2869, 1728, 1661, 1606, 1497, 1455, 1364$. **MS** (70 eV) m/z (%): 262 ($\text{M}^+ + 1$, 100). Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}$: C 78.11; H 10.41; N 5.36. Found: C 78.33; H 10.29; N 5.51.

1-Allyl-4-benzyloxy-2,2-dimethylpyrrolidine 3b

Colourless oil, 48% yield, TLC Rf 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20/1). **^1H NMR** (270 MHz, CDCl_3): δ 1.17 (6H, s), 2.76 (1H, d, $J = 10.6$ Hz), 2.95 (1H, d×d, $J = 12.0$ Hz, $J = 3.0$ Hz), 3.00 (1H, d, $J = 10.6$ Hz), 3.41-3.48 (2H, m), 3.51 (1H, d×d, $J = 12.0$ Hz, $J = 4.6$ Hz), 3.64-3.67 (1H, m), 4.34 (1H, d, $J = 11.9$ Hz), 4.73 (1H, d, $J = 11.9$ Hz), 5.28-5.37 (2H, m), 5.97-6.10 (1H, m), 7.26-7.34 (5H, m). **^{13}C NMR** (67.8 MHz, CDCl_3): δ 21.0, 26.3, 42.6, 56.9, 59.6, 64.0, 71.2, 121.7, 127.5, 128.4, 127.8, 130.6, 137.7). **IR** (NaCl ,

cm⁻¹): ν_{\max} = 3416, 2963, 2905, 2870, 2414, 2203, 1497, 1469, 1455, 1364. **MS** (70 eV) m/z (%): 246 ($M^+ + 1$, 100). Anal. Calcd for C₁₆H₂₃NO: C 78.32; H 9.45; N 5.71. Found: C 78.48; H 9.49; N 5.60.

Transformations of 2-(1-haloalkyl)azetidines **2 and 2-(2-haloalkyl)azetidines **10** towards pyrrolidines **4** and piperidines **12** and **13****

Pyrrolidines **4** and piperidines **12** and **13** were synthesised starting from the corresponding azetidines **2** and **10** (4 mmol) using reaction conditions as described in table 1. In the case of the use of sodium hydroxide (40 mmol), little amounts of water (1ml) have to be added to DMSO (30 ml) in order to dissolve sodium hydroxide. After the reaction, the solvent was evaporated in vacuo yielding crude **4a**, **4b** or **12** when acetonitrile was used as solvent. When DMSO was used as solvent, after addition of water, the reaction mixture was extracted three times with diethyl ether (20 ml) and the combined organic fractions were washed three times with water (20 ml). After drying (MgSO₄), filtration and evaporation of the solvent, the crude reaction mixture of **4c-e** or **13** was obtained. All crude reaction mixtures were purified by flash chromatography on silica gel.

1-Allyl-4-benzyloxy-3-chloro-2,2-dimethylpyrrolidine **4a**

Colourless oil, 46% yield, TLC R_f 0.15 (CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃): δ 1.07 and 1.15 (6H, 2×s), 2.53 (1H, d×d, J = 10.5 Hz, J = 4.1 Hz), 2.84 (1H, d×d, J = 13.2 Hz, J = 7.7 Hz), 3.35 (1H, d×d, J = 13.2 Hz, J = 5.2 Hz), 3.39 (1H, d×d, J = 10.5 Hz, J = 7.4 Hz), 3.87 (1H, d, J = 6.9 Hz), 4.02 (1H, d×t, J = 6.9 Hz, J = 3.9 Hz), 4.58 (1H, d, J = 12.1

Hz), 4.74 (1H, d, $J = 12.1$ Hz), 5.05-5.22 (2H, m), 5.72-5.86 (1H, m), 7.26-7.40 (5H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 15.0, 25.0, 52.1, 57.1, 63.0, 68.4, 72.6, 75.0, 116.7, 127.5, 127.7, 128.3, 136.4, 138.3. IR (NaCl, cm^{-1}): $\nu_{\text{max}} = 3066, 3030, 2971, 2928, 2869, 2814, 1721, 1643, 1497, 1454, 1383, 1365$. MS (70 eV) m/z (%): 380/2 ($M^+ + 1$, 100). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{ClNO}$: C 68.68; H 7.93; N 5.01. Found: C 68.82; H 7.82; N 5.16.

1-Allyl-3-chloro-4-methoxy-2,2-dimethylpyrrolidine 4b

Colourless oil, 44% yield, TLC Rf 0.22 (petrol ether/ethyl acetate 10/1). ^1H NMR (300 MHz, CDCl_3): δ 1.02 and 1.14 (6H, 2 \times s), 2.46 (1H, d \times d, $J = 10.5$ Hz, $J = 3.6$ Hz), 2.84 (1H, d \times d, $J = 13.2$ Hz, $J = 7.4$ Hz), 3.33 (1H, d \times d \times t, $J = 13.2$ Hz, $J = 5.2$ Hz, $J = 1.7$ Hz), 3.38 (1H, d \times d, $J = 10.5$ Hz, $J = 6.6$ Hz), 3.40 (3H, s), 3.81 (1H, d \times t, $J = 6.7$ Hz, $J = 3.9$ Hz), 3.86 (1H, d, $J = 6.7$ Hz), 5.06-5.23 (2H, m), 5.73-5.87 (1H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 15.1, 24.9, 52.1, 56.7, 58.6, 62.9, 68.1, 77.6, 116.7, 136.4. IR (NaCl, cm^{-1}): $\nu_{\text{max}} = 2973, 2929, 1643, 1462, 1383, 1365$. MS (70 eV) m/z (%): 204/6 ($M^+ + 1$, 100). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{ClNO}$: C 58.96; H 8.91; N 6.88. Found: C 59.14; H 8.78; N 6.98.

4-Benzyloxy1-tert-butyl-2,2-dimethylpyrrolidin-3-ol 4c

Colourless oil, 46% yield, TLC Rf 0.1 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20/1). ^1H NMR (300 MHz, CDCl_3): δ 0.94 and 1.08 (6H, 2 \times s), 2.53 (1H, d \times d, $J = 10.7$ Hz, $J = 3.9$ Hz), 2.88 (1H, d \times d, $J = 13.2$ Hz, $J = 7.2$ Hz), 3.23 (1H, d \times d, $J = 10.7$ Hz, $J = 7.7$ Hz), 3.24 (1H, d \times d, $J = 13.2$ Hz, $J = 5.8$ Hz), 3.68 (1H, d, $J = 5.8$ Hz), 4.03 (1H, d \times d \times d, $J = 7.2$, $J = 7.2$ Hz, $J = 3.9$ Hz), 4.48 (1H, d, $J = 11.6$ Hz), 4.58 (1H, d, $J = 11.6$ Hz), 5.05-5.22 (2H, m), 5.75-5.89 (1H, m), 7.26-7.39 (5H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 14.5, 23.9, 51.6, 56.1,

62.2, 72.3, 75.0, 78.3, 116.5, 127.7, 127.9, 128.5, 136.7, 137.7. **IR** (NaCl, cm^{-1}): $\nu_{\text{OH}}=3532$; $\nu_{\text{max}}=2965, 2926, 2870, 2807, 1642, 1455$. **MS** (70 eV) m/z (%): 262 (M^++1 , 100). Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_2$: C 73.61; H 9.81; N 5.05. Found: C 73.75; H 9.93; N 4.89.

1-Allyl-4-benzyloxy-2,2-dimethyl-3-pyrrolidinecarbonitrile 4d

Colourless oil, 44% yield, TLC Rf 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1). **^1H NMR** (300 MHz, CDCl_3): δ 1.12 and 1.27 (6H, 2 \times s), 2.87 (1H, d \times d, $J=13.4$ Hz, $J=7.0$ Hz), 2.94-3.05 (2H, m), 3.15-3.24 (3H, m), 4.69 (2H, s), 5.11-5.25 (2H, m), 5.70-5.83 (1H, m), 7.27-7.40 (5H, m). **^{13}C NMR** (75 MHz, CDCl_3): δ 17.3, 23.9, 29.1, 45.3, 50.5, 52.9, 63.3, 65.4, 117.5, 119.4, 127.0, 127.7, 128.6, 135.1, 140.9. **IR** (NaCl, cm^{-1}): $\nu_{\text{C}\equiv\text{N}}=2246$; $\nu_{\text{max}}=2972, 2927, 2851, 1720, 1624, 1454$. **MS** (70 eV) m/z (%): 271 (M^++1 , 100). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$: C 75.52; H 8.20; N 10.36. Found: C 75.62; H 8.10; N 10.14.

1-Allyl-3-azido-4-benzyloxy-2,2-dimethylpyrrolidine 4e

Colourless oil, 52% yield, TLC Rf 0.25 (petroleum ether/ethyl acetate 4/1). **^1H NMR** (300 MHz, CDCl_3): δ 1.05 and 1.12 (6H, 2 \times s), 2.73 (1H, d \times d, $J=10.7$ Hz, $J=4.4$ Hz), 2.99 (1H, d \times d, $J=13.4$ Hz, $J=6.5$ Hz), 3.10 (1H, d \times d \times t, $J=13.4$ Hz, $J=6.1$ Hz, $J=1.4$ Hz), 3.14 (1H, d \times d, $J=10.7$ Hz, $J=7.7$ Hz), 3.32 (1H, d, $J=6.6$ Hz), 4.21 (1H, d \times d \times d, $J=7.7$, $J=6.6$ Hz, $J=4.4$ Hz), 4.54 (1H, d, $J=12.1$ Hz), 4.63 (1H, d, $J=12.1$ Hz), 5.04-5.22 (2H, m), 5.73-5.86 (1H, m), 7.25-7.38 (5H, m). **^{13}C NMR** (75 MHz, CDCl_3): δ 17.7, 23.1, 51.2, 56.5, 63.5, 70.1, 72.2, 75.9, 116.4, 127.6, 127.7, 128.4, 136.5, 137.9. **IR** (NaCl, cm^{-1}): $\nu_{\text{N}_3}=2105$; $\nu_{\text{max}}=2969, 2926, 2871, 2811, 1643, 1455$. **MS** (70 eV) m/z

(%): 287 ($M^+ + 1$, 100). Anal. Calcd for $C_{16}H_{22}N_4O$: C 67.11; H 7.74; N 19.56. Found: C 67.22; H 7.85; N 19.36.

Cis-5-benzyloxy-4-bromo-1-*t*-butyl-3,3-dimethylpiperidine 12a

Colourless oil, 98% yield. 1H NMR (300 MHz, $CDCl_3$): δ 1.03 and 1.13 (6H, 2xs), 2.18-2.25 (1H, m), 2.40-2.50 (1H, m), 2.45-2.80 (2H, m), 3.65-3.72 (1H, m), 4.27-4.32 (1H, m), 4.47 (1H, d, $J = 11.4$ Hz), 4.65 (1H, d, $J = 11.4$ Hz), 7.24-7.41 (5H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.4, 27.1, 36.3, 46.5, 46.5, 53.4, 67.8, 70.5, 74.8, 127.7, 127.9, 128.4, 128.6, 138.3. IR (NaCl, cm^{-1}): $\nu_{max} = 2974, 2892, 2812, 1477, 1454, 1390, 1370, 1359, 1339, 1256, 1226, 1200, 1138, 1104, 1025, 1011$. MS (70 eV): m/z (%) 354/6 ($M^+ + 1$, 100); 343 (12); 294 (9); 293 (50); 264 (18); 263 (87). Anal. Calcd for $C_{18}H_{28}BrNO$: C 61.02; H 7.97; N 3.95. Found: C 60.90; H 8.12; N 4.09.

Cis-1-benzyl-5-benzyloxy-4-bromo-3,3-dimethylpiperidine 12b

Colourless oil, 97% yield. 1H NMR (300 MHz, $CDCl_3$): δ 1.12 and 1.16 (6H, 2xs), 2.05-2.45 (2H, m), 2.45-2.75 (2H, m), 3.44 (1H, d, $J = 13.5$ Hz), 3.54 (1H, d, $J = 13.5$ Hz), 3.71-3.81 (1H, m), 4.19-4.30 (1H, m), 4.43 (1H, d, $J = 11.8$ Hz), 4.60 (1H, d, $J = 11.8$ Hz), 7.19-7.37 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 27.8, 29.2, 36.7, 53.7, 60.5, 62.3, 67.1, 70.5, 74.8, 127.1, 127.8, 127.9, 128.4, 128.5, 128.8, 138.3, 138.9. IR (NaCl, cm^{-1}): $\nu_{max} = 2956, 2926, 2869, 2817, 1495, 1466, 1454, 1366, 1109, 1027$. MS (70 eV): m/z (%) 388/90 ($M^+ + 1$, 100); 387 (39); 312 (17); 311 (56). Anal. Calcd for $C_{21}H_{26}BrNO$: C 64.95; H 6.75; N 3.61. Found: C 65.12; H 6.63; N 3.53.

***Cis*-1-benzyl-4-bromo-5-methoxy-3,3-dimethylpiperidine 12c**

Colourless oil, 92% yield. **¹H NMR** (300 MHz, CDCl₃): δ 1.10 and 1.25 (6H, 2×s), 2.09-2.18 (1H, m), 2.30-2.40 (1H, m), 2.50-2.82 (2H, m), 3.35 (3H, s), 3.50 (1H, d, *J* = 13.4 Hz), 3.53-3.59 (1H, m); 3.59 (1H, d, *J* = 13.4 Hz), 4.21-4.32 (1H, m), 7.23-7.32 (5H, m). **¹³C NMR** (75 MHz, ref = CDCl₃): δ 26.9, 29.0, 36.5, 52.8, 56.3, 58.8, 62.3, 66.7, 75.4, 127.2, 128.4, 128.8, 138.6. **IR** (NaCl, cm⁻¹): ν_{max} = 2955, 2927, 2872, 2818, 2787, 1466, 1454, 1365, 1341, 1221, 1201, 1115, 1026. **MS** (70 eV): *m/z* (%) 312/4 (*M*⁺+1, 100); 296 (7); 232/234 (13). Anal. Calcd for C₁₅H₂₂BrNO: C 57.70; H 7.10; N 4.49. Found: C 57.52; H 7.21; N 4.63.

***Cis*-1-allyl-5-benzyloxy-4-bromo-3,3-dimethylpiperidine 12d**

Colourless oil, 95% yield. **¹H NMR** (300 MHz, CDCl₃): δ 1.13 and 1.16 (6H, 2×s), 2.05-2.40 (2H, m), 2.45-2.75 (2H, m), 2.94 (1H, d×d, *J* = 13.6 Hz, *J* = 6.5 Hz), 3.01 (1H, d×d, *J* = 13.6 Hz, *J* = 6.3 Hz), 3.70-3.74 (1H, m), 4.20-4.31 (1H, m), 4.48 (1H, d, *J* = 11.8 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 5.09-5.20 (2H, m), 5.72-5.86 (1H, m), 7.23-7.39 (5H, m). **¹³C NMR** (75 MHz, ref= CDCl₃): δ 27.1, 28.8, 36.5, 53.7, 59.8, 61.2, 67.0, 70.6, 73.4, 117.7, 127.4, 127.8, 127.9, 128.5, 135.4, 138.2. **IR** (NaCl, cm⁻¹): ν_{max} = 2958, 2928, 2906, 2870, 2806, 1455, 1366, 1109, 1028. **MS** (70 eV): *m/z* (%) 338/40 (*M*⁺+1, 67); 263 (10); 262 (23); 261 (100). Anal. Calcd for C₁₇H₂₄BrNO: C 60.36; H 7.15; N 4.14. Found: C 60.50; H 7.04; N 4.01.

Cis-5-benzyloxy-4-bromo-1-cyclohexyl-3,3-dimethylpiperidine 12e

Colourless oil, 95% yield. **¹H NMR** (300 MHz, CDCl₃): δ 1.12 and 1.14 (6H, 2xs), 1.57-1.76 (10H, m), 2.10 (1H, d, *J* = 11.3 Hz), 2.25-2.29 (1H, m), 2.55 (1H, d, *J* = 11.3 Hz), 2.55-2.80 (2H, m), 3.61-3.70 (1H, m), 4.19-4.28 (1H, m), 4.45 (1H, d, *J* = 11.8 Hz), 4.61 (1H, d, *J* = 11.8 Hz), 7.19-7.38 (5H, m). **¹³C NMR** (75 MHz, ref = CDCl₃): δ 26.0, 26.1, 26.6, 27.1, 28.1, 28.7, 29.2, 36.4, 50.1, 55.6, 63.4, 67.9, 70.4, 74.3, 127.6, 127.7, 128.4, 138.4. **IR** (NaCl, cm⁻¹): ν_{max} = 2928, 2854, 1453, 1382, 1364, 1343, 1210, 1109, 1028. **MS** (70 eV): *m/z* (%) 380/2 (*M*⁺+1, 100). Anal. Calcd for C₂₀H₃₀BrNO: C 63.15; H 7.95; N 3.68. Found: C 63.28; H 7.82; N 3.74.

Cis-1-allyl-5-benzyloxy-3,3-dimethylpiperidin-4-ol 14a

Colourless oil, 86% yield. **¹H NMR** (300 MHz, CDCl₃): δ 0.99 (6H, s), 2.13 (2H, s), 2.17-2.37 (1H, m), 2.67-2.76 (1H, m), 2.94 (1H, dxd, *J* = 13.6 Hz, *J* = 6.8 Hz), 3.01 (1H, dxd, *J* = 13.6 Hz, *J* = 6.1 Hz), 3.52 (1H, d, *J* = 2.8 Hz), 3.76-3.82 (1H, m), 4.55 (1H, d, *J* = 12.1 Hz), 4.59 (1H, d, *J* = 12.1 Hz), 5.09-5.19 (2H, m), 5.74-5.88 (1H, m), 7.24-7.37 (5H, m). **¹³C NMR** (75 MHz, CDCl₃): δ 24.1, 24.8, 35.3, 51.9, 59.2, 61.3, 70.7, 72.9, 74.8, 117.3, 127.6, 127.8, 128.4, 135.5, 138.1. **IR** (NaCl, cm⁻¹): ν_{OH} = 3561. **MS** (70 eV): *m/z* (%) 276 (100, *M*⁺+1). Anal. Calcd for C₁₇H₂₅NO₂: C 74.14; H 9.15; N 5.09. Found: C 74.01; H 9.29; N 4.94.

Cis-1-allyl-5-benzyloxy-3,3-dimethyl-4-piperidinecarbonitrile 14b

Colourless oil, 92% yield. **¹H NMR** (300 MHz, CDCl₃): δ 1.07 and 1.16 (6H, 2xs), 2.10-2.15 (1H, m), 2.20-2.38 (2H, m), 2.76 (1H, d, *J* = 3.3 Hz), 2.85-3.06 (3H, m), 3.79-3.83

(1H, m), 4.56-4.64 (2H, m), 5.12-5.20 (2H, m), 5.71-5.84 (1H, m), 7.26-7.36 (5H, m). **¹³C NMR** (75 MHz, CDCl₃): δ 26.1, 26.8, 34.0, 43.9, 54.5, 61.0, 71.0, 71.3, 117.9, 118.2, 127.6, 127.8, 128.5, 134.9, 137.7. **IR** (NaCl, cm⁻¹): ν_{CN} = 2239. **MS** (70 eV): m/z (%) 285 (M⁺+1, 100). Anal. Calcd for C₁₈H₂₄N₂O: C 76.02; H 8.51; N 9.85. Found: C 75.88; H 8.73; N 9.80.

***Cis*-1-allyl-4-azido-5-benzyloxy-3,3-dimethylpiperidine 14c**

Colourless oil, 72% yield. **¹H NMR** (300 MHz, CDCl₃): δ 0.97 and 1.03 (6H, 2×s), 1.94 (1H, d, *J* = 11.4 Hz), 2.12 (1H, d, *J* = 11.4 Hz), 2.21-2.30 (1H, m), 2.72-2.87 (1H, m), 2.91 (1H, d×d, *J* = 13.5 Hz, *J* = 6.8 Hz), 3.00 (1H, d×d, *J* = 13.5 Hz, *J* = 6.1 Hz), 3.42-3.45 (1H, m), 3.90-3.96 (1H, m), 4.60 (2H, s), 5.08-5.18 (2H, m), 5.71-5.84 (1H, m), 7.22-7.37 (5H, m). **¹³C NMR** (75 MHz, CDCl₃): δ 25.4, 25.7, 35.5, 52.5, 59.0, 61.1, 68.7, 71.0, 74.9, 117.4, 127.4, 127.6, 128.4, 135.3, 138.2. **IR** (NaCl, cm⁻¹): ν_{N3} = 2102. **MS** (70 eV): m/z (%) 301 (M⁺+1, 100); 246 (12). Anal. Calcd for C₁₇H₂₄N₄O: C 67.97; H 8.05; N 18.65. Found: C 67.90; H 8.19; N 18.49.

Synthesis of 3-bromopyrrolidines 7 from 2-(hydroxyethyl)aziridines 6

As a representative example, the synthesis of 1-allyl-4-benzyloxy-3-bromo-2,2-dimethylpyrrolidine **7a** is described. To a solution of 2-(1-allyl-3,3-dimethylaziridin-2-yl)-2-benzyloxyethanol **6a** (0.5g, 1.92 mmol) in 30 ml of THF was added *N*-bromosuccinimide (0.41g, 2.23 mmol) and triphenylphosphine (0.60 g, 2.23 mmol). After stirring at room temperature for 18 hours, 30 ml water was added, and the mixture was extracted three times with 30 ml of diethyl ether. The combined organic fractions were

dried (MgSO₄) and, after filtration and evaporation of the solvent, the crude reaction mixture was obtained. Purification was performed by flash chromatography on silica gel.

1-Allyl-4-benzyloxy-3-bromo-2,2-dimethylpyrrolidine 7a

Colourless oil, 68% yield, TLC R_f 0.15 (CH₂Cl₂/MeOH 99/1). **¹H NMR** (300 MHz, CDCl₃): δ 1.11 and 1.15 (6H, 2×s), 2.54 (1H, d×d, *J* = 10.5 Hz, *J* = 3.0 Hz), 2.85 (1H, d×d, *J* = 13.2 Hz, *J* = 7.7 Hz), 3.34-3.44 (2H, m), 3.96 (2H, m), 4.56 (1H, d, *J* = 12.1), 4.71 (1H, d, *J* = 12.1 Hz), 5.06-5.22 (2H, m), 5.72-5.86 (1H, m), 7.24-7.38 (5H, m). **¹³C NMR** (75 MHz, ref = CDCl₃): δ 16.4, 25.2, 52.6, 57.4, 62.1, 62.7, 72.6, 75.1, 116.8, 127.5, 127.6, 128.5, 136.6, 138.4. **IR** (NaCl, cm⁻¹): ν_{max} = 3066, 3030, 2971, 2927, 2869, 2814, 1721, 1643, 1497, 1455, 1383, 1365. **MS** (70 eV) *m/z* (%): 324/6 (M⁺+1, 100). Anal. Calcd for C₁₆H₂₂BrNO: C 59.27; H 6.84; N 4.32. Found: C 59.39; H 6.96; N 4.20.

1-Allyl-3-bromo-4-methoxy-2,2-dimethylpyrrolidine 7b

Colourless oil, 63% yield, TLC R_f 0.45 (CH₂Cl₂/MeOH 33/1). **¹H NMR** (270 MHz, CDCl₃): δ 1.06 and 1.14 (6H, 2×s), 2.48 (1H, d×d, *J* = 10.4 Hz, *J* = 3.8 Hz), 2.85 (1H, d×d, *J* = 13.2 Hz, *J* = 7.6 Hz), 3.33-3.43 (2H, m), 3.39 (3H, s), 3.76 (1H, d×t, *J* = 6.8 Hz, *J* = 4.0 Hz), 3.95 (1H, d, *J* = 6.8 Hz), 5.07-5.23 (2H, m), 5.73-5.88 (1H, m). **¹³C NMR** (75 MHz, ref = CDCl₃): δ 16.3, 24.9, 52.3, 56.7, 58.3, 61.6, 62.3, 77.3, 116.4, 136.4. **IR** (NaCl, cm⁻¹): ν_{max} = 3078, 2972, 2928, 2826, 1722, 1643, 1462, 1383, 1366. **MS** (70 eV) *m/z* (%): 248/50 (M⁺+1, 100). Anal. Calcd for C₁₀H₁₈BrNO: C 48.40; H 7.31; N 5.64. Found: C 48.65; H 7.42; N 5.47.

Synthesis of 2,5-dihydro-1*H*-pyrroles **8**

As a representative example, the synthesis of 1-allyl-4-benzyloxy-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole **8a** is described. Sodium hydride (0.074g, 3.0 mmol) was added to 30 ml of DMSO. After all of the sodium hydride was reacted, 1-allyl-4-benzyloxy-3-bromo-2,2-dimethylpyrrolidine **7a** (0.5g, 1.5mmol) was added and the reaction mixture was stirred for 2 hours at 130°C. After two hours, the reaction mixture was cooled to room temperature and 30 ml of water was added. The resulting suspension was extracted three times with 30 ml of diethyl ether, and the combined organic fractions were dried (MgSO₄). After filtration and evaporation of the solvent 1-allyl-4-benzyloxy-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole **8a** was obtained.

1-Allyl-4-benzyloxy-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole **8a**

Colourless oil, 88% yield. ¹H NMR (300 MHz, CDCl₃): δ 1.14 (6H, s), 3.15 (2H, d×t, *J* = 6.3 Hz, *J* = 1.2 Hz), 3.45 (2H, d, *J* = 1.4 Hz), 4.58 (1H, t, *J* = 1.2 Hz), 4.76 (2H, s), 5.04-5.24 (1H, m), 5.82-5.99 (1H, m), 7.27-7.46 (5H, m). ¹³C NMR (75 MHz, CDCl₃): δ 24.8, 51.5, 56.5, 64.8, 71.2, 104.3, 116.3, 127.7, 128.0, 128.5, 136.7, 137.3, 154.9. IR (NaCl, cm⁻¹): ν_{max} = 2958, 2924, 1656, 1456, 1360. MS (70 eV) *m/z* (%): 244(M⁺+1, 100). Anal. Calcd for C₁₆H₂₁NO: C 78.97; H 8.70; N 5.76. Found: C 78.79; H 8.90; N 5.87.

1-Allyl-4-methoxy-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole **8b**

Colourless oil, 86% yield. ¹H NMR (300 MHz, CDCl₃): δ 1.12 (6H, s), 3.15 (2H, d×t, *J* = 6.5 Hz, *J* = 1.4 Hz), 3.37 (2H, d, *J* = 1.7 Hz), 3.58 (3H, s), 4.48 (1H, t, *J* = 1.4 Hz), 5.05-5.25 (1H, m), 5.82-5.95 (1H, m). ¹³C NMR (75 MHz, CDCl₃): δ 24.9, 51.5, 56.3, 56.4,

64.8, 103.2, 116.3, 137.4, 156.0. **IR** (NaCl, cm^{-1}): ν_{max} = 2924, 1664, 1459, 1377. **MS** (70 eV) m/z (%): 168($M^+ + 1$, 80); 136(100). Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}$: C 71.81; H 10.25; N 8.37. Found: C 71.65; H 10.39; N 8.49.

Synthesis of 1-allyl-5,5-dimethyl-3-pyrrolidinone **9**

1-Allyl-4-methoxy-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole **8b** was dissolved in 30 ml of 2N HCl and stirred at room temperature for 18 hours. After the reaction, 1N NaOH was added until the reaction mixture was basic. After extraction of this mixture with three times 30 ml of dichloromethane, drying (MgSO_4) of the combined organic fractions, filtration and evaporation of the solvent, 1-allyl-5,5-dimethyl-3-pyrrolidinone **9** was obtained in 89% yield.

1-Allyl-5,5-dimethyl-3-pyrrolidinone **9**

Colourless oil, 89% yield. **^1H NMR** (300 MHz, CDCl_3): δ 1.18 (6H, s), 2.31 (2H, s), 3.11 (2H, s), 3.14 (2H, d, $J = 6.3$ Hz, $J = 0.8$ Hz), 5.09-5.25 (2H, m), 5.77-5.90 (1H, m). **^{13}C NMR** (75 MHz, CDCl_3): δ 22.5, 51.2, 53.4, 59.0, 59.1, 116.9, 136.1, 214.1. **IR** (NaCl, cm^{-1}): ν_{max} = 2969, 2930, 2872, 2807, 1758, 1693, 1367. **MS** (70 eV) m/z (%): 154($M^+ + 1$, 100). Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NO}$: C 70.55; H 9.87; N 9.14. Found: C 70.69; H 9.97; N 9.02.