

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

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## General experimental methods

<sup>1</sup>H NMR spectra were recorded at 300 MHz with CDCl<sub>3</sub> as solvent and tetramethylsilane as internal standard. <sup>13</sup>C NMR spectra were recorded at 75 MHz with CDCl<sub>3</sub> 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  $\alpha$ -halogenated or  $\beta$ -halogenated imines

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and ketenes (formed *in situ* from the corresponding acid chlorides by treatment with triethylamine) in benzene.<sup>14,15</sup>

### **Reduction of 4-(1-haloalkyl)azetidin-2-ones 1 and 4-(2-haloalkyl)azetidin-2-ones 10 with chloroalane (AlH<sub>2</sub>Cl)**

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-Benzyl-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<sub>4</sub>). 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-Benzyl-2-(1-bromo-1-methylethyl)-1-*tert*-butylazetidine **2f****

White crystals, 61% yield, TLC R<sub>f</sub> 0.3 (petroleum ether/ethyl acetate 9/1), Mp. 58°C <sup>1</sup>**H** NMR (300 MHz, CDCl<sub>3</sub>): 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 $\times$ 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). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  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<sup>-1</sup>):  $\nu_{\text{max}} = 2970, 2935, 2871, 1497, 1456, 1364$ . **MS** (70 eV) m/z (%): 296 (100); 260 (M<sup>+</sup>-Br, 65). Anal. Calcd for C<sub>17</sub>H<sub>26</sub>BrNO: C 60.00; H 7.70; N 4.12. Found: C 60.23; H 7.55; N 4.01.

#### **4-Benzyl-1-*tert*-butyl-2,2-dimethylpyrrolidine 3a**

Colourless oil, 63% yield, TLC Rf 0.05 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20/1). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.03 (9H, s), 1.08 (6H, 2 $\times$ s), 2.52-2.59 (2H, m), 2.67 (1H, d $\times$ d,  $J$  = 9.5 Hz,  $J$  = 5.9 Hz), 3.09 (1H, d $\times$ 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). **<sup>13</sup>C NMR** (75 MHz, ref = CDCl<sub>3</sub>):  $\delta$  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<sup>-1</sup>):  $\nu_{\text{max}} = 2968, 2869, 1728, 1661, 1606, 1497, 1455, 1364$ . **MS** (70 eV) m/z (%): 262 (M<sup>+</sup>+1, 100). Anal. Calcd for C<sub>17</sub>H<sub>27</sub>NO: C 78.11; H 10.41; N 5.36. Found: C 78.33; H 10.29; N 5.51.

#### **1-Allyl-4-benzyl-2,2-dimethylpyrrolidine 3b**

Colourless oil, 48% yield, TLC Rf 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20/1). **<sup>1</sup>H NMR** (270 MHz, CDCl<sub>3</sub>):  $\delta$  1.17 (6H, s), 2.76 (1H, d,  $J$  = 10.6 Hz), 2.95 (1H, d $\times$ 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 $\times$ 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). **<sup>13</sup>C NMR** (67.8 MHz, CDCl<sub>3</sub>):  $\delta$  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,

$\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 3416, 2963, 2905, 2870, 2414, 2203, 1497, 1469, 1455, 1364$ . **MS** (70 eV) m/z (%): 246 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{16}H_{23}NO$ : 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 ( $\text{MgSO}_4$ ), 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 ( $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.07 and 1.15 (6H, 2 $\times$ s), 2.53 (1H, d $\times$ d,  $J = 10.5$  Hz,  $J = 4.1$  Hz), 2.84 (1H, d $\times$ d,  $J = 13.2$  Hz,  $J = 7.7$  Hz), 3.35 (1H, d $\times$ d,  $J = 13.2$  Hz,  $J = 5.2$  Hz), 3.39 (1H, d $\times$ d,  $J = 10.5$  Hz,  $J = 7.4$  Hz), 3.87 (1H, d,  $J = 6.9$  Hz), 4.02 (1H, d $\times$ 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).

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 3066, 3030, 2971, 2928, 2869, 2814, 1721, 1643, 1497, 1454, 1383, 1365$ . **MS** (70 eV) m/z (%): 380/2 ( $\text{M}^+ + 1$ , 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).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.1, 24.9, 52.1, 56.7, 58.6, 62.9, 68.1, 77.6, 116.7, 136.4. **IR** (NaCl,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 2973, 2929, 1643, 1462, 1383, 1365$ . **MS** (70 eV) m/z (%): 204/6 ( $\text{M}^+ + 1$ , 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-Benzyl-1-*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).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\nu_{\text{OH}} = 3532$ ;  $\nu_{\text{max}} = 2965, 2926, 2870, 2807, 1642, 1455$ . **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,  $\text{CDCl}_3$ ):  $\delta$  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). **13C NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\nu_{\text{C}\equiv\text{N}} = 2246$ ;  $\nu_{\text{max}} = 2972, 2927, 2851, 1720, 1624, 1454$ . **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,  $\text{CDCl}_3$ ):  $\delta$  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). **13C NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\nu_{\text{N}_3} = 2105$ ;  $\nu_{\text{max}} = 2969, 2926, 2871, 2811, 1643, 1455$ . **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,  $CDCl_3$ ):  $\delta$  1.03 and 1.13 (6H, 2 $\times$ s), 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 =  $CDCl_3$ ):  $\delta$  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,  $CDCl_3$ ):  $\delta$  1.12 and 1.16 (6H, 2 $\times$ s), 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 =  $CDCl_3$ ):  $\delta$  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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): 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). **<sup>13</sup>C NMR** (75 MHz, ref = CDCl<sub>3</sub>): 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<sup>-1</sup>):  $\nu_{\text{max}} = 2955, 2927, 2872, 2818, 2787, 1466, 1454, 1365, 1341, 1221, 1201, 1115, 1026$ . **MS** (70 eV): m/z (%) 312/4 (M<sup>+</sup>+1, 100); 296 (7); 232/234 (13). Anal. Calcd for C<sub>15</sub>H<sub>22</sub>BrNO: 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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): 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). **<sup>13</sup>C NMR** (75 MHz, ref= CDCl<sub>3</sub>): 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<sup>-1</sup>):  $\nu_{\text{max}} = 2958, 2928, 2906, 2870, 2806, 1455, 1366, 1109, 1028$ . **MS** (70 eV): m/z (%) 338/40 (M<sup>+</sup>+1, 67); 263 (10); 262 (23); 261 (100). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>BrNO: 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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ 1.12 and 1.14 (6H, 2×s), 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). **<sup>13</sup>C NMR** (75 MHz, ref = CDCl<sub>3</sub>): 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<sup>-1</sup>):  $\nu_{\text{max}} = 2928, 2854, 1453, 1382, 1364, 1343, 1210, 1109, 1028$ . **MS** (70 eV): m/z (%) 380/2 (M<sup>+</sup>+1, 100). Anal. Calcd for C<sub>20</sub>H<sub>30</sub>BrNO: 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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ 0.99 (6H, s), 2.13 (2H, s), 2.17-2.37 (1H, m), 2.67-2.76 (1H, m), 2.94 (1H, d×d, *J* = 13.6 Hz, *J* = 6.8 Hz), 3.01 (1H, d×d, *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). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): 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<sup>-1</sup>):  $\nu_{\text{OH}} = 3561$ . **MS** (70 eV): m/z (%) 276 (100, M<sup>+</sup>+1). Anal. Calcd for C<sub>17</sub>H<sub>25</sub>NO<sub>2</sub>: 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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ 1.07 and 1.16 (6H, 2×s), 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).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  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<sup>-1</sup>):  $\nu_{CN}$  = 2239. **MS** (70 eV): m/z (%) 285 (M<sup>+</sup>+1, 100). Anal. Calcd for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O: 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. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.97 and 1.03 (6H, 2 $\times$ 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 $\times$ d,  $J$  = 13.5 Hz,  $J$  = 6.8 Hz), 3.00 (1H, d $\times$ 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). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  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<sup>-1</sup>):  $\nu_{N_3}$  = 2102. **MS** (70 eV): m/z (%) 301 (M<sup>+</sup>+1, 100); 246 (12). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>N<sub>4</sub>O: 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 ( $\text{MgSO}_4$ ) 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 Rf 0.15 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  99/1).  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.11 and 1.15 (6H, 2 $\times$ s), 2.54 (1H, d $\times$ d,  $J$  = 10.5 Hz,  $J$  = 3.0 Hz), 2.85 (1H, d $\times$ 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).  **$^{13}\text{C NMR}$**  (75 MHz, ref =  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 3066, 3030, 2971, 2927, 2869, 2814, 1721, 1643, 1497, 1455, 1383, 1365$ . **MS** (70 eV) m/z (%): 324/6 ( $\text{M}^++1$ , 100). Anal. Calcd for  $\text{C}_{16}\text{H}_{22}\text{BrNO}$ : 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 Rf 0.45 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  33/1).  **$^1\text{H NMR}$**  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.06 and 1.14 (6H, 2 $\times$ s), 2.48 (1H, d $\times$ d,  $J$  = 10.4 Hz,  $J$  = 3.8 Hz), 2.85 (1H, d $\times$ d,  $J$  = 13.2 Hz,  $J$  = 7.6 Hz), 3.33-3.43 (2H, m), 3.39 (3H, s), 3.76 (1H, d $\times$ 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).  **$^{13}\text{C NMR}$**  (75 MHz, ref =  $\text{CDCl}_3$ ):  $\delta$  16.3, 24.9, 52.3, 56.7, 58.3, 61.6, 62.3, 77.3, 116.4, 136.4. **IR** (NaCl,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 3078, 2972, 2928, 2826, 1722, 1643, 1462, 1383, 1366$ . **MS** (70 eV) m/z (%): 248/50 ( $\text{M}^++1$ , 100). Anal. Calcd for  $\text{C}_{10}\text{H}_{18}\text{BrNO}$ : 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 ( $\text{MgSO}_4$ ). 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. **<sup>1</sup>H NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.14 (6H, s), 3.15 (2H, d $\times$ 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). **<sup>13</sup>C NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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** ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}=2958, 2924, 1656, 1456, 1360$ . **MS** (70 eV)  $m/z$  (%): 244( $\text{M}^++1$ , 100). Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}$ : 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. **<sup>1</sup>H NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.12 (6H, s), 3.15 (2H, d $\times$ 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). **<sup>13</sup>C NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.9, 51.5, 56.3, 56.4,

64.8, 103.2, 116.3, 137.4, 156.0. **IR** (NaCl,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 2924, 1664, 1459, 1377$ . **MS** (70 eV) m/z (%): 168( $\text{M}^++1$ , 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 ( $\text{MgSO}_4$ ) 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. **<sup>1</sup>H NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.18 (6H, s), 2.31 (2H, s), 3.11 (2H, s), 3.14 (2H, d×d,  $J = 6.3$  Hz,  $J = 0.8$  Hz), 5.09-5.25 (2H, m), 5.77-5.90 (1H, m). **<sup>13</sup>C NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.5, 51.2, 53.4, 59.0, 59.1, 116.9, 136.1, 214.1. **IR** (NaCl,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}} = 2969, 2930, 2872, 2807, 1758, 1693, 1367$ . **MS** (70 eV) m/z (%): 154( $\text{M}^++1$ , 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.