Electrophile induced ring expansions of β-lactams towards γ-lactams

Supporting Information:

General experimental methods

^{1}H NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ 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). CH_2Cl_2 was dried by distillation over calcium hydride. All other solvents were used as received from the supplier.

(3S*,4S*)-*Cis*-3-benzyloxy-4-(1-chloro-1-methylethyl)-1-*t*-butylazetidin-2-one 6b. 79% yield, TLC Rf 0.35 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 1.74 and 1.75 (6H, 2×s), 4.14 (1H, d, *J*=5.8 Hz), 4.52 (1H, d, *J*=5.8 Hz), 4.68 (1H, d, *J*=11.8 Hz), 4.90 (1H, d, *J*=11.8 Hz), 7.25-7.38 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 27.3, 29.8, 28.8, 54.8, 71.5, 68.3, 73.2, 79.4, 127.7, 127.9, 128.5, 137.0, 168.74. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$= 1737; ν_{max}= 2977, 1645, 1604, 1497, 1455. **MS** (70 eV) m/z (%): 312/10 (M^{+}+1, 100). Anal. Calcd for $C_{17}H_{24}ClNO_2$: C 65.90; H 7.81; N 4.52. Found: C 66.12; H 7.70; N 4.64.

(3S*,4S*)-*Cis*-1-benzyl-3-benzyloxy-4-(1-chloro-1-methylethyl)azetidin-2-one 6d. White crystals, 73% yield, Mp: 38°C, TLC Rf 0.35 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (300

MHz, $CDCl_3$): δ 1.65 and 1.73 (6H, 2×s), 3.90 (1H, d, *J*=5.3 Hz), 4.32 (1H, d, *J*=14.6 Hz), 4.58 (1H, d, *J*=5.3 Hz), 4.67 (1H, d, *J*=11.8 Hz), 4.88 (1H, d, *J*=14.6 Hz), 4.91 (1H, d, *J*=11.8 Hz), 7.22-7.37 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 27.8, 29.2, 44.8, 66.0, 71.6, 73.3, 81.5, 127.7, 128.5, 128.7, 135.6, 136.8, 168.3. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$= 1760, ν_{max}= 2936, 1497, 1455. **MS** (70 eV) m/z (%): 346/4 (M^++1, 100). Anal. Calcd for $C_{20}H_{22}ClNO_2$: C 69.86; H 6.45; N 4.07. Found: C 69.77; H 6.54; N 4.17.

(3S*,4R*)-*Cis*-1-cyclohexyl-4-isopropenyl-3-methoxyazetidin-2-one 7e. 77% yield, TLC Rf 0.15 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.11-1.97 (10H, m); 1.87 (3H, d, *J*=0.83 Hz); 3.35-3.44 (1H, m), 3.44 (3H, s), 4.25 (1H, d, *J*=4.8 Hz), 4.48 (1H, d, *J*= 4.8 Hz), 5.08-5.10 (2H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 19.1, 25.0, 25.1, 25.3, 30.3, 30.9, 52.6, 58.8, 62.3, 84.4, 116.2, 141.8, 166.9. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$= 1756; ν_{max}= 2933, 1451. **MS** (70 eV) m/z (%): 224 (M^++1; 100). Anal. Calcd for $C_{13}H_{21}NO_2$: C 69.92; H 9.48; N 6.27. Found: C 69.99; H 9.42; N 6.25.

(3S*,4R*)-*Cis*-3-benzyloxy-1-cyclohexyl-4-isopropenylazetidin-2-one 7f. White crystals, 82% yield, Mp: 77°C, TLC Rf 0.2 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.96-1.93 (10H, m), 1.87 (3H, d, *J*=1.1 Hz), 3.37-3.47 (1H, m), 4.23 (1H, d, *J*=4.95 Hz), 4.62 (1H, d, *J*=11.7 Hz), 4.65 (1H, d, *J*=5.0 Hz, OCH), 4.68 (1H, d, *J*=11.7 Hz), 5.08 (2H, d, *J*=1.1 Hz), 7.24-7.43 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 19.2, 25.0, 25.1, 25.3, 30.3, 30.9, 52.6, 62.5, 72.7, 82.0, 116.3, 127.9, 128.0, 128.4, 137.1, 141.9, 167.0. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$= 1746; ν_{max}= 2933, 1497, 1454. **MS** (70 eV) m/z (%): 300 (M^++1; 100). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22; H 8.42; N 4.68. Found: C 76.39; H 8.56; N 4.76.

(3S*,4R*)-*Cis*-1-allyl-4-isopropenyl-3-methoxyazetidin-2-one 7g. 61% yield, TLC Rf 0.1 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (270 MHz, $CDCl_3$): δ 1.79 (3H, s), 3.47 (1H, d×d, *J*=15.2 Hz, *J*=7.3 Hz), 3.48 (3H, s), 4.14 (1H, d×d, *J*=15.2 Hz, *J*=5.3 Hz), 4.18 (1H, d, *J*=5.0 Hz), 4.59 (1H, d, *J*=5.0 Hz), 5.03 and 5.21 (2H, 2×d, *J*=0.7 Hz), 5.11-5.17 (2H, m), 5.66-5.81 (1H, m). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 19.3, 43.1, 58.9, 62.7, 85.3, 116.0, 118.9, 131.0, 140.1, 167.0. **IR** (NaCl, cm^{-1}): $\nu_{c=o}$=1763; ν_{max}= 3082, 2924, 2836, 1645, 1448, 1396, 1375, 1361. **MS** (70 eV) m/z (%): 182(M^++1, 45); 150(100); 122(15); 110(35); 109(12). Anal. Calcd for $C_{10}H_{15}NO_2$: C 66.27; H 8.34; N 7.73. Found: C 66.38; H 8.50; N 7.68.

(3S*,4R*)-*Cis*-1-allyl-3-benzyloxy-4-isopropenylazetidin-2-one 7h. 60% yield, TLC Rf 0.18 (petrol ether/ ethyl acetate 3/1). **^{1}H NMR** (270 MHz, $CDCl_3$): δ 1.82 (3H, s), 3.48 (1H, d×d, *J*=15.4 Hz, *J*=7.3 Hz), 4.1 (1H, d×d, *J*=15.4 Hz, *J*=5.3 Hz), 4.17 (1H, d, *J*=5.0 Hz), 4.65 (1H, d, *J*=11.5 Hz), 4.72 (1H, d, *J*=11.5 Hz), 4.75 (1H, d, J=5.0 Hz), 5.03 and 5.19 (2H, 2×s), 5.11-5.16 (2H, m), 5.65-5.80 (1H, m), 7.25-7.37 (5H, m). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 19.3, 43.1, 62.8, 72.7, 83.0, 116.2, 118.9, 127.9, 128.4, 131.0, 137.0, 140.2, 167.2. **IR** (NaCl, cm^{-1}): $\nu_{c=o}$=1760; ν_{max}= 3084, 2983, 2917, 1645, 1455, 1396, 1343. **MS** (70 eV) m/z (%): 258(M^++1, 55); 166(10); 91(100). Anal. Calcd for $C_{16}H_{19}NO_2$: C 74.68; H 7.44; N 5.44. Found: C 74.75; H 7.36; N 5.42.

(3S*,4R*,5S*)-3-Benzyloxy-5-bromo-4-(bromomethyl)-1-*t*-butyl-4-methylpyrrolidin-2-one 10b. Purity >95% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.28 (3H, s), 1.51 (9H, s), 3.43 (1H, d, *J*=10.3 Hz), 3.74 (1H, d, *J*=10.3 Hz), 3.99 (1H, s), 4.72 (1H, d, *J*=11.8 Hz), 5.15 (1H, d, *J*=11.8 Hz), 5.81 (1H, s), 7.27-7.41 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.3, 26.8, 40.5, 47.6, 56.3, 73.7, 78.7, 80.3, 128.1, 128.2, 128.5, 137.2, 174.1. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1685; ν_{max}= 2977, 1455, 1370.

(3S*,4R*,5S*)-5-Bromo-4-(bromomethyl)-1-isopropyl-3-methoxy-4-methylpyrrolidin-2-one 10c. Purity >91% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.24 (3H, s), 1.31 and 1.37 (6H, 2×d, *J*=6.9 Hz), 3.64 (1H, d, *J*= 10.2 Hz), 3.71 (3H, s), 3.85 (1H, s), 3.99 (1H, d, *J*=10.2 Hz), 4.14 (1H, septet, *J*=6.9 Hz), 5.67 (1H, s). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.1, 19.1, 19.4, 40.1, 46.7, 48.5, 60.7, 75.0, 82.9, 173.7. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1681.

(3S*,4R*,5S*)-1-Benzyl-3-benzyloxy-5-bromo-4-(bromomethyl)-4-methylpyrrolidin-2-one 10d. Purity >83% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.12 (3H, s), 3.44 (1H, d, *J*=10.2 Hz), 3.71 (1H, d, *J*=10.2 Hz), 3.84 (1H, d, *J*=14.9 Hz), 4.05 (1H, s), 4.78 (1H, d, *J*=11.9 Hz), 5.10 (1H, d, *J*=14.9 Hz), 5.19 (1H, d, *J*=11.8 Hz), 5.23 (1H, s); 7.19-7.38 (10H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.2, 40.1, 45.3, 47.0, 73.6, 76.9, 79.4, 128.2, 128.4, 128.6, 128.8, 128.9, 129.1, 133.9, 137.0, 172.8. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1689; ν_{max}= 2977, 1455.

(3S*,4R*,5S*)-5-Bromo-4-(bromomethyl)-1-cyclohexyl-3-methoxy-4-methylpyrrolidin-2-one 10e. Purity >81% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.23 (3H, s), 1.08-2.00 (10H, m), 3.64 (1H, d, *J*=10.18 Hz), 3.70 (3H, s), 3.70-3.82 (1H, m), 3.89 (1H, s), 3.98 (1H, d, *J*=10.2 Hz), 5.31 (1H, s). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.1, 25.2, 25.5, 29.4, 29.6, 40.4, 48.5, 54.0, 60.4, 76.3, 82.7, 173.1. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1681.

(3S*,4R*,5S*)-3-Benzyloxy-5-bromo-4-(bromomethyl)-1-cyclohexyl-3-methoxy-4-methylpyrrolidin-2-one 10f. Purity >78% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.26 (3H, s), 1.10-1.98 (10H, m), 3.42 (1H, d, *J*=10.2 Hz), 3.72 (1H, d, *J*=10.2 Hz), 3.70-3.77 (1H, m), 4.07 (1H, s); 4.71 (1H, d, *J*=11.8 Hz), 5.12 (1H, d, *J*=11.8 Hz), 5.64 (1H, s). **^{13}C NMR**

(75 MHz, $CDCl_3$): δ 17.4, 25.3, 25.5, 29.4, 29.7, 40.4, 48.3, 54.1, 73.7, 76.3, 79.9, 128.1, 128.6, 129.0, 137.2, 173.3. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1679.

1-Benzyl-3,5-dibromo-4-(bromomethyl)-4-methylpyrrolidin-2-one 16b. Purity >75% (^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.09 (3H, s), 3.72 (1H, d, *J*= 10.5 Hz), 3.90 (1H, d, *J*=14.6 Hz), 3.93 (1H, d, *J*= 10.5 Hz), 4.46 (1H, s), 5.08 (1H, d, *J*=14.6 Hz), 5.21 (1H, s), 7.25-7.40 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 16.7, 40.2, 45.7, 47.7, 74.1, 75.4, 128.8, 129.2, 129.8, 133.3, 175.1. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1698.

5-Azido-4-(bromomethyl)-1-isopropyl-3-methoxy-4-methylpyrrolidin-2-one 18b. Yield 65%, TLC Rf 0.1 (petrol ether/ ethyl acetate 4/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.16 (3H, d, *J*=0.6 Hz), 1.23 and 1.28 (6H, 2×d, *J*=6.9 Hz), 3.6 (1H, d, *J*= 10.2 Hz), 3.65 (3H, s), 3.72 (1H, s), 3.84 (1H, d×d, *J*=10.2 Hz, *J*=0.6 Hz), 4.29 (1H, septet, *J*=6.9 Hz), 4.66 (1H, s). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 16.9, 19.5, 21.0, 38.2, 43.5, 47.9, 60.3, 79.2, 82.3, 172.1. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$=1716; ν_{N3}=2108. **MS** (70 eV) m/z (%): 307/5 (M^++1, 100). Anal. Calcd for $C_{10}H_{17}BrN_4O_2$: C 39.36; H 5.61; N 18.36. Found: C 39.31; H 5.54; N 18.38.

5-Azido-3-benzyloxy-1-benzyl-4-(bromomethyl)-4-methylpyrrolidin-2-one 18c. Yield 48%, TLC Rf 0.2 (petrol ether/ ethyl acetate 8/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.11 (3H, s); 3.28 (1H, d, *J*=10.2 Hz), 3.52 (1H, d, *J*= 10.2 Hz), 3.89 (1H, s), 4.03 (1H, d, *J*=14.9 Hz), 4.39 (1H, s), 4.77 (1H, d, *J*=12.1 Hz), 5.03 (1H, d, *J*=14.9 Hz), 5.15 (1H, d, *J*=12.1 Hz), 7.26-7.42 (10H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.2, 37.9, 45.1, 46.6, 73.3, 78.8, 80.2, 128.2, 128.4, 128.6, 128.7, 129.2, 134.4, 137.2, 172.4. **IR** (NaCl, cm^{-1}): ν_{N3}=2109; $\nu_{C=O}$=1720; ν_{max}= 2928, 1455. **MS** (70 eV) m/z (%): 431/29 (M^++1, 100). Anal. Calcd for $C_{20}H_{21}BrN_4O_2$: C 55.95; H 4.93; N 18.61. Found: C 56.17; H 4.99; N 18.49.

5-Azido-4-(bromomethyl)-1-cyclohexyl-3-methoxy-4-methylpyrrolidin-2-one 18d. Yield 43%, TLC Rf 0.15 (petrol ether/ ethyl acetate 8/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.00 (3H, s), 0.93-1.83 (10H, m), 3.39 (1H, d, *J*=9.9 Hz), 3.50 (3H, s), 3.57 (1H, s), 3.68 (1H, d, *J*=9.9 Hz), 3.71-3.77 (1H, m), 4.51 (1H, s). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 16.9, 25.3, 25.4, 25.8, 30.1, 31.1, 38.3, 48.0, 51.4, 60.3, 79.5, 82.3, 172.1. **IR** (NaCl, cm^{-1}): ν_{N3}=2108; $\nu_{C=O}$=1713. **MS** (70 eV) m/z (%): 347/5 (M^++1, 100). Anal. Calcd for $C_{13}H_{21}BrN_4O_2$: C 45.23; H 6.13; N 16.23. Found: C 45.39; H 6.24; N 16.04.

5-Azido-3-benzyloxy-4-(bromomethyl)-1-cyclohexyl-4-methylpyrrolidin-2-one 18e. Yield 63%, TLC Rf 0.1 (petrol ether/ ethyl acetate 8/1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.20 (3H, s), 1.08-1.98 (10H, m), 3.34 (1H, d, *J*= 9.9 Hz), 3.57 (1H, d, *J*= 9.9 Hz), 3.88 (1H, s), 3.85-3.92 (1H, m), 4.65 (1H, s), 4.71 (1H, d, *J*=11.8 Hz), 5.11 (1H, d, *J*=11.8 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.2, 25.3, 25.4, 25.8, 30.1, 31.7, 38.2, 47.8, 51.5, 73.3, 79.0, 79.5, 128.2, 128.5, 137.4, 172.3. **IR** (NaCl, cm^{-1}): ν_{N3}=2108; $\nu_{C=O}$=1715. **MS** (70 eV) m/z (%): 423/1 (M^++1, 100). Anal. Calcd for $C_{19}H_{25}BrN_4O_2$: C 54.16; H 5.98; N 13.30. Found: C 54.27; H 6.07; N 13.39.