Rapid Generation of Molecular Complexity using "Hybrid" Multi-Component Reactions (MCRs): Application to the Synthesis of α-Amino Nitriles and 1,2-Diamines

Jason J. Shiers, Guy J. Clarkson, Michael Shipman,* and Jerome F. Hayes

Electronic Supporting Information

General Method A: Synthesis of 1,2-diamines using MCR. Copper(I) iodide (20 mol%) was heated under vacuum in a round-bottomed flask then purged with argon (3 cycles performed). Anhydrous THF (4 ml) was added and the mixture cooled to -30 °C whereupon the Grignard reagent (2 eq.) was added. After stirring for 10 min, the methyleneaziridine (1 eq.) in THF (1 ml) was added dropwise and the resulting mixture allowed to warm to room temperature. After stirring for 3 h, the mixture was cooled to 0 °C and the electrophile (1.89 mmol, 1.5 eq.) was added dropwise. The mixture was heated at 40 °C for 18 h, then cooled to 0 °C. In a separate flask, a solution of TMSCN (1.5 eq.) in THF (1 ml) at 0 °C was treated with glacial acetic acid (2.5 eq.). After stirring for 2 h at 0 °C, the resulting HCN solution (CAUTION) was added dropwise *via* cannula to the reaction mixture. The mixture was stirred at 0 °C for 2 h, then $LiAlH_4$ (3 or 8 eq) was added dropwise to the cooled mixture. After stirring for 10 min, the mixture was allowed to warm to room temperature and was stirred for 18 h. The mixture was then cooled to 0 °C and quenched (CAUTION) by dropwise

addition of water (2 ml), then $NaHCO_3$ (aq) (2 ml). After stirring for 10 min, the organic phase was separated and the residue washed with Et_2O (3 × 20 ml). The combined organic phases were washed with $NaHCO_3$ (aq) and brine, dried ($MgSO_4$) and evaporated to give the crude product which was purified by column chromatography.

***N*²-Benzyl-2-phenethylbutane-1,2-diamine, 3.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-Benzyl-2-methylene-aziridine (183 mg, 1.26 mmol), methylmagnesium chloride (2.95 M in THF, 854 μl, 2.52 mmol), benzyl chloride (218 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 10.1 ml, 10.1 mmol) were reacted together according to General method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **3** (162 mg, 46%) as a clear pale yellow oil. R_f 0.32 (1% c. NH_4OH, 5% MeOH, 94% CH_2Cl_2); IR (film) 3408, 3311, 2937, 1619, 1495, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.15 (10H, m, aryl), 3.65 (2H, s, NCH_2Ph), 2.62 (2H, s, CH_2NH_2), 2.61–2.57 (2H, m, $PhCH_2CH_2$), 1.68–1.63 (2H, m, $PhCH_2CH_2$), 1.48 (2H, qt, J = 7.5 Hz and 7.0 Hz CH_3CH_2), 1.23 (3H, br s, NH + NH_2), 0.90 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 142.9 (C, aryl), 141.3 (C, aryl), 128.5 (4 × CH, aryl), 128.29 (2 × CH, aryl), 128.28 (2 × CH, aryl), 126.9 (CH, aryl), 125.8 (CH, aryl), 58.1 (C), 45.7 (CH_2), 44.8 (CH_2), 35.3 (CH_2), 29.6 (CH_2), 26.0 (CH_2), 7.6 (CH_3); MS (ES^+) m/z 283 (100%, $[MH]^+$); HRMS (ES^+) found $[MH]^+$, 283.2169, $C_{19}H_{27}N_2$ requires 283.2169.

***N*²-Benzyl-2-phenethylpentane-1,2-diamine, 4.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), ethylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), benzyl chloride (218 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **4** (152 mg, 41%) as a clear pale yellow oil. R_f 0.58 (1% c. NH_4OH, 10% MeOH, 89% CH_2Cl_2); IR (film) 3308, 2930, 1602, 1495, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.42–7.15 (10H, m, aryl), 3.66 (2H, s, NCH_2Ph), 2.64 (2H, s, CH_2NH_2), 2.64–2.54 (2H, m, $PhCH_2CH_2$), 1.75–1.65 (2H, m, $PhCH_2CH_2$), 1.50–1.25 (7H, m, 2 × CH_2, NH and NH_2), 0.97 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 142.8 (C, aryl), 141.2 (C, aryl), 128.5 (4 × CH, aryl), 128.3 (2 × CH, aryl), 128.2 (2 × CH, aryl), 126.9 (CH, aryl), 125.8 (CH, aryl), 58.0 (C), 45.6 (CH_2), 45.3 (CH_2), 36.4 (CH_2), 35.9 (CH_2), 29.7 (CH_2), 16.5 (CH_2), 14.9 (CH_3); MS (ES^+) m/z 297 (100%, $[MH]^+$); HRMS (ES^+) found $[MH]^+$, 297.2328, $C_{20}H_{29}N_2$ requires 297.2325.

***N*²-Benzyl-2-(but-3-enyl)heptane-1,2-diamine, 5.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), butylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), allyl bromide (164 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **5** (144 mg, 42%) as a clear pale yellow

oil. R_f 0.42 (0.5% c. NH_4OH, 10% MeOH, 89.5% CH_2Cl_2); IR (film) 3315, 2929, 1640, 1603, 1495, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.20 (5H, m, aryl), 5.85 (1H, ddt, *J* = 17.1 Hz, 10.1 Hz, 6.5 Hz, =CH), 5.04 (1H, dd, *J* = 17.1 Hz and 1.8 Hz, =C*H*H), 4.95 (1H, dd, *J* = 10.1 Hz and 1.8 Hz, =CH*H*), 3.59 (2H, s, NCH_2Ph), 2.57 (2H, s, C*H*$_2$$NH_2$), 2.07–1.98 (2H, m, C*H*$_2$CH=CH_2), 1.52–1.10 (13H, m, 5 × CH_2, NH and NH_2), 0.90 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 141.3 (C, aryl), 139.0 (=CH), 128.4 (2 × CH, aryl), 128.2 (2 × CH, aryl), 126.9 (CH, aryl), 114.3 (=CH_2), 57.8 (C), 45.6 (CH_2), 45.3 (CH_2), 33.7 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 27.6 (CH_2), 22.74 (CH_2), 22.72 (CH_2), 14.1 (CH_3); MS (ES^+) m/z 275 (MH^+); HRMS (ES^+) found $[MH]^+$, 275.2479, $C_{18}H_{31}N_2$ requires 275.2482.

***N*^{2}-Benzyl-2-phenethylheptane-1,2-diamine, 6.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), butylmagnesium chloride (1.78 M in THF, 1.43 ml, 2.55 mmol), benzyl chloride (218 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **6** (199 mg, 49%) as a clear pale yellow oil. R_f 0.35 (1% c. NH_4OH, 5% MeOH, 94% CH_2Cl_2); IR (film) 3062, 3025, 2928, 1602, 1495, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.14 (10H, m, aryl), 3.64 (2H, s, NCH_2Ph), 2.68–2.52 (2H, m, PhC*H*$_2$$CH_2$), 2.63 (2H, s, C*H*$_2$$NH_2$), 1.70–1.63 (2H, m, $PhCH_2$C*H*$_2$), 1.48–1.25 (8H, m, 4 × CH_2), 1.12 (3H, br s, NH + NH_2), 0.92 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 142.9 (C, aryl), 141.3 (C, aryl), 128.5 (4 × CH,

aryl), 128.29 (2 × CH, aryl), 128.27 (2 × CH, aryl), 126.9 (CH, aryl), 125.8 (CH, aryl), 58.0 (C), 45.7 (CH_2), 45.4 (CH_2), 35.9 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3); MS (CI^+) m/z 325 (100%, $[MH]^+$), 294 (55%, $[M-CH_2NH_2]^+$); HRMS (ES^+) found $[MH]^+$, 325.2637, $C_{22}H_{33}N_2$ requires 325.2638.

***N*²-Benzyl-2-(4-(tetrahydropyran-2-yloxy)butyl)heptane-1,2-diamine, 7.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), butylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), 2-(3-bromopropoxy)-tetrahydropyran (421 mg, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **7** (160 mg, 34%) as a clear pale yellow oil. R_f 0.40 (0.5% c. NH_4OH, 10% MeOH, 89.5% CH_2Cl_2); IR (film) 3675, 3288, 2930, 1604, 1495, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.20 (5H, m, aryl), 4.58 (1H, t, *J* = 3.5 Hz O-CH-O), 3.94-3.85 (1H, m, OC*H*H), 3.82-3.75 (1H, m, OCH*H*), 3.58 (2H, s, NCH_2Ph), 3.55-3.45 (1H, m, OC*H*H), 3.44-3.37 (1H, m, OCH*H*), 2.56 (2H, s, CH_2NH_2), 1.88-1.77 (1H, m, C*H*H), 1.77-1.66 (1H, m, CH*H*), 1.66-1.10 (21H, m, 9 × CH_2, NH and NH_2), 0.90 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 141.3 (C, aryl), 128.4 (2 × CH, aryl), 128.3 (2 × CH, aryl), 126.8 (CH, aryl), 99.0 (O-CH-O), 67.3 (OCH_2), 62.5 (OCH_2), 57.9 (C), 45.6 (CH_2), 33.7 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 30.8 (CH_2), 30.34 (CH_2), 30.31 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 19.8 (CH_2), 19.74

(CH_2), 19.68 (CH_2), 14.1 (CH_3); MS (ES^+) m/z 377 (100%, MH^+); HRMS (ES^+) found $[MH]^+$, 377.3163, $C_{23}H_{41}N_2O_2$ requires 377.3163.

***N*²-Benzyl-2-isopentylhex-5-ene-1,2-diamine, 8.** Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), iso-butylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), allyl bromide (164 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **8** (150 mg, 43%) as a clear pale yellow oil. R_f 0.40 (0.5% c. NH_4OH, 10% MeOH, 89.5% CH_2Cl_2); IR (film) 3323, 2928, 1639, 1603, 1495, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.22 (5H, m, aryl), 5.85 (1H, ddt, *J* = 17.2 Hz, 10.2 Hz, 6.5 Hz, =CH), 5.04 (1H, dd, *J* = 17.2 Hz and 1.8 Hz, =C*H*H), 4.96 (1H, dd, *J* = 10.0 Hz and 1.8 Hz, =CH*H*), 3.59 (2H, s, NCH_2Ph), 2.57 (2H, s, C*H*$_2NH_2$), 2.07–1.99 (2H, m, CH_2), 1.54 (1H, heptet, *J* = 6.5 Hz, CH), 1.48–1.40 (2H, m, CCH_2), 1.39–1.30 (2H, m, CCH_2), 1.30–1.00 (5H, m, CH_2, NH and NH_2), 0.92 (6H, d, *J* = 6.5 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 141.2 (C, aryl), 139.0 (=CH), 128.4 (2 × CH, aryl), 128.2 (2 × CH, aryl), 126.9 (CH, aryl), 114.3 (=CH_2), 57.8 (C), 45.6 (CH_2), 45.2 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 28.7 (CH), 27.5 (CH_2), 22.8 (2 × CH_3); MS (ES^+) m/z 275 (100%, $[MH]^+$); HRMS (ES^+) found $[MH]^+$, 275.2480, $C_{18}H_{31}N_2$ requires 275.2482.

2-(4-Methoxyphenethyl)-*N*²-Benzyl-5-methylhexane-1,2-diamine, 9. Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-

methyleneaziridine (183 mg, 1.26 mmol), iso-butylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), 4-methoxybenzyl chloride (256 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid (176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **9** (225 mg, 50%) as a clear pale yellow oil. R_f 0.41 (0.5% c. NH_4OH, 10% MeOH, 89.5% CH_2Cl_2); IR (film) 3333, 2930, 1611, 1584, 1511, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.20 (5H, m, aryl), 7.11 (2H, d, *J* = 8.6 Hz, aryl), 6.83 (2H, d, *J* = 8.6 Hz, aryl), 3.78 (3H, s, OCH_3), 3.64 (2H, s, NCH_2Ph), 2.62 (2H, m, CH_2NH_2), 2.59-2.50 (2H, m, $PhCH_2CH_2$), 1.68-1.60 (2H, m, $PhCH_2CH_2$), 1.54 (2H, heptet, *J* = 6.5 Hz, CH), 1.47-1.38 (2H, m, CH_2), 1.25-1.14 (5H, m, CH_2, NH and NH_2), 0.93 (6H, d, *J* = 6.5 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 157.8 (COMe, aryl), 141.2 (C, aryl), 134.8 (C, aryl), 129.1 (2 × CH, aryl), 128.5 (2 × CH, aryl), 128.3 (2 × CH, aryl), 126.9 (CH, aryl), 113.9 (2 × CH, aryl), 57.9 (C), 55.3 (OCH_3), 45.6 (CH_2), 45.2 (CH_2), 35.9 (CH_2), 32.2 (CH_2), 31.3 (CH_2), 28.71 (CH), 28.68 (CH_2), 22.8 (2 × CH_3); MS (ES^+) m/z 355 (100%, $[MH]^+$), 248 (35%, $[M-(PhCH_2NH)]^+$); HRMS (ES^+) found $[MH]^+$, 355.2746, $C_{23}H_{35}N_2O$ requires 355.2744.

2-(4-Methoxyphenethyl)-*N*^{2}-Benzyl-5-phenylbutane-1,2-diamine, 10. Copper(I) iodide (48 mg, 0.252 mmol), *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol), benzylmagnesium chloride (1.90 M in THF, 1.33 ml, 2.53 mmol), 4-methoxybenzyl chloride (256 μl, 1.89 mmol), TMSCN (251 μl, 1.88 mmol), glacial acetic acid

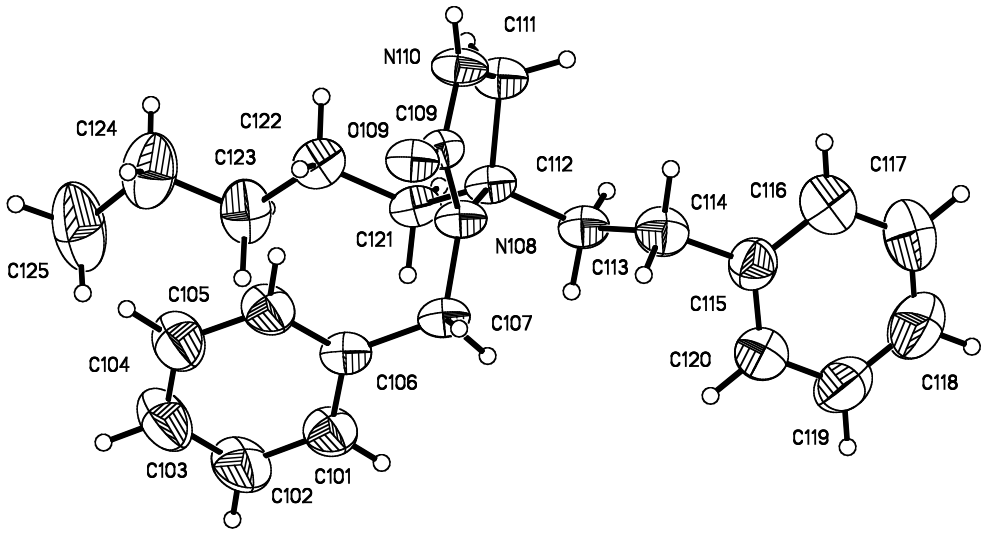
(176 μl, 3.08 mmol) and $LiAlH_4$ (1M in THF, 3.78 ml, 3.78 mmol) were reacted together according to General Method A. Column chromatography (5% MeOH in CH_2Cl_2) on SiO_2 pretreated with NH_4OH gave **10** (231 mg, 47%) as a clear pale yellow oil. R_f 0.41 (0.5% c. NH_4OH, 10% MeOH, 89.5% CH_2Cl_2); IR (film) 3248, 2933, 1609, 1583, 1510, 1495, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.42-7.15 (10H, m, aryl), 7.12 (2H, d, *J* = 8.6 Hz, aryl), 6.84 (2H, d, *J* = 8.6 Hz, aryl), 3.78 (3H, s, OCH_3), 3.70 (2H, s, NCH_2Ph), 2.70 (2H, s, CH_2NH_2), 2.68-2.55 (4H, m, 2 × $ArCH_2CH_2$), 1.80-1.72 (4H, m, 2 × $ArCH_2CH_2$), 1.21 (3H, br s, NH and NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 157.9 (COMe, aryl), 142.6 (C, aryl), 141.1 (C, aryl), 134.6 (C, aryl), 129.2 (2 × CH, aryl), 128.5 (2 × CH, aryl), 128.4 (2 × CH, aryl), 128.31 (2 × CH, aryl), 128.26 (2 × CH, aryl), 127.0 (CH, aryl), 125.9 (CH, aryl), 114.0 (2 × CH, aryl), 58.1 (C), 55.3 (OCH_3), 45.7 (CH_2), 45.3 (CH_2), 36.1 (CH_2), 35.9 (CH_2), 29.8 (CH_2), 28.9 (CH_2); MS (ES^+) m/z 389 (100%, $[MH]^+$), 282 (35%, $[M-(PhCH_2NH)]^+$); HRMS (ES^+) found $[MH]^+$, 389.2589, $C_{26}H_{33}N_2O$ requires 389.2587. Anal. calcd for $C_{26}H_{32}N_2O$: C, 80.37%; H, 8.30%; N, 7.21%. Found: C, 80.65%; H, 8.42%; N, 7.13%.

1-Benzyl-5-pentyl-5-phenethylimidazolidin-2-one. Triphosgene (110 mg, 370 μmol) was added to a stirred solution of **6** (300 mg, 925 μmol) and triethylamine (309 μl, 2.22 mmol) in CH_2Cl_2 at 0 °C. The resulting solution was stirred at 0 °C for 18 h. The mixture was then quenched with NH_4Cl (2 ml) and diluted with CH_2Cl_2 (15 ml). The organic phase was separated and washed with $NaHCO_3$ (2 × 10 ml) then brine (10 ml), dried ($MgSO_4$) and evaporated. Purification of

the residue by column chromatography on SiO_2 (Et_2O) gave 1-benzyl-5-pentyl-5-phenethylimidazolidin-2-one (225 mg, 69%) as a white crystalline solid, m.p. 115-116 °C. R_f 0.20 (Et_2O); IR (film) 3216, 2924, 1676, 1496, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* = 7.0 Hz, aryl), 7.36-7.10 (6H, m, aryl), 6.85 (2H, d, *J* = 7.0 Hz, aryl), 4.60 (1H, s, NH), 4.41 (1H, d, *J* = 15.6 Hz, PhC*H*HN), 4.30 (1H, d, *J* = 15.6 Hz, PhCH*H*N), 3.36 (1H, d, *J* = 8.8 Hz, C*H*HNH), 3.32 (1H, d, *J* = 8.8 Hz, CH*H*NH), 2.55 (1H, td, *J* = 13.3 Hz and 5.0 Hz, PhC*H*HCH$_2$), 2.33 (1H, td, *J* = 13.3 Hz and 5.0 Hz, PhCH*H*CH$_2$), 1.78 (1H, td, *J* = 12.4 Hz and 4.8 Hz, PhCH$_2$CH*H*), 1.67 (1H, td, *J* = 12.4 Hz and 4.8 Hz, PhCH$_2$CH*H*), 1.56-1.38 (2H, m, CH_2), 1.30-0.95 (6H, m, 3 × CH_2), 0.82 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 162.6 (C=O), 141.6 (C, aryl), 139.7 (C, aryl), 128.50 (2 × CH, aryl), 128.49 (2 × CH, aryl), 128.4 (2 × CH, aryl), 128.2 (2 × CH, aryl), 127.2 (CH, aryl), 125.9 (CH, aryl), 63.9 (C), 47.1 (CH_2), 43.1 (CH_2), 41.0 (CH_2), 39.0 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); MS (ES^+) m/z 373 (30%, $[M+Na]^+$), 351 (100%, $[MH]^+$); HRMS (ES^+) found $[MH]^+$, 351.2433, $C_{23}H_{31}N_2O$ requires 351.2431. Anal. calcd for $C_{23}H_{30}N_2O$: C, 78.82%; H, 8.63%; N, 7.99%. Found: C, 78.97%; H, 8.58%; N, 8.04%.

X-Ray data for 1-benzyl-5-pentyl-5-phenethylimidazolidin-2-one. Crystal grown from petroleum ether/CH_2Cl_2 using vapour diffusion method. $C_{23}H_{30}N_2O$ colourless block, 0.60 x 0.50 x 0.18 mm, Monoclinic, P2(1)/c (No 14), alpha = 90 deg., beta = 101.470(13) deg., gamma = 90 deg., a = 27.33(2), b = 13.742(10), c = 11.347(8)Å, U = 4176(5)Å^3, Z 8, D(cal) = 1.115 gcm^{-3}, $2\theta_{max}$ 58.34, λ

= 0.71073 Å, 26328 reflections measured, 10240 unique [R(int) = 0.0747], R1[for 5389 reflections with I>2sigma(I)] = 0.0772, wR2 = 0.2203, T_{min} 0.8185, T_{max} 0.9879, $\mu(Mo_{K\alpha})$ = 0.068 mm^{-1}. Data / restraints / parameters 10240/ 0/ 477 refined against F^2 (SHELXTL: G. M. Sheldrick, *SHELXTL Ver 5.1*, Bruker Analytical X-ray Systems, **1997**). Largest difference Fourier peak and hole 0.326 and -0.225 e.$Å^{-3}$. CCDC 286809 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallograpic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



ORTEP view of 1-benzyl-5-pentyl-5-phenethylimidazolidin-2-one drawn at 50% probability level. The asymmetric unit contains two crystallographically independent, but chemically identical molecules, of which only one is shown.

***N*-Benzyl-2-ethylpiperidine-2-carbonitrile, 11.** Copper(I) iodide (48 mg, 0.252 mmol) was heated under vacuum in a round-bottomed

flask, and then purged with argon (3 cycles performed). Anhydrous THF (4 ml) was added and the mixture cooled to -30 °C, whereupon MeMgCl (2.95M in THF, 854 μl, 2.52 mmol) was added. After stirring for 10 min, *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol) in THF (1 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was added dropwise *via* cannula to a stirred solution of 1,3-diiodopropane (722 μl, 6.29 mmol) in THF (1 ml) at 0 °C. The mixture was then heated at 40 °C for 2 h. In a second flask, a solution of TMSCN (251 μl, 1.88 mmol) in THF (1 ml) at 0 °C was treated with glacial acetic acid (176 μl, 3.08 mmol) and this mixture was stirred for 2 h at 0 °C. The resulting HCN solution (CAUTION) was added dropwise *via* cannula to the first vessel. After 2 h at 0 °C, saturated $NaHCO_3$ (2 ml) was added slowly. The mixture was diluted with Et_2O (20 ml), the organic layer separated and washed with saturated $NaHCO_3$ (2 x 20 ml) then brine (20 ml). The organic phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the residue by column chromatography on SiO_2 (2% EtOAc/petrol) gave **11** (157 mg, 55%) as a clear colourless oil. R_f 0.31 (10% EtOAc in petrol); IR (film) 2940, 2217 (w), 1605, 1496, 1452, 1367 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) 7.30-7.21 (5H, m, aryl), 4.12 (1H, d, *J* = 13.8 Hz, C*H*HPh), 3.11 (1H, d, *J* = 13.8 Hz, CH*H*Ph), 2.75 (1H, pseudo dt, *J* = 12.3 Hz and 4.0 Hz, ring NC*H*H), 2.21 (1H, td, *J* = 12.3 Hz and 2.8 Hz, ring NCH*H*), 1.98-1.85 (3H, m, C*H*$_2$CH$_3$ and C*H*H), 1.78-1.52 (4H, m, 2 × CH_2), 1.47-1.32 (1H, m, CH*H*), 1.06 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 138.8 (C, aryl), 128.4 (2 × CH, aryl), 128.3 (2 ×

CH, aryl), 127.0 (CH, aryl), 119.3 (CN), 62.2 (*C*CN), 55.2 (CH_2Ph), 49.5 (CH_2), 33.9 (CH_2), 31.0 (CH_2), 25.1 (CH_2), 21.8 (CH_2), 7.5 (CH_3); MS (CI^+) m/z 229 (15%, MH^+), 202 (100%, $[M-CN]^+$); HRMS (CI^+) found MH^+, 229.1697, $C_{15}H_{21}N_2$ requires 229.1699. Anal. calcd for $C_{15}H_{20}N_2$: C, 78.90%; H, 8.83%; N, 12.27%. Found: C, 78.60%; H, 8.66%; N, 11.96%.

***N*-Benzyl-2-ethylpiperidine-2-carboxamide, 13.** *N*-Benzyl-2-ethylpiperidine-2-carbonitrile (370 mg, 1.62 mmol) was dissolved in TFA (2.25 ml) and conc. H_2SO_4 (2.25 ml) and heated at 50 °C for 18 h. The mixture was then cooled, poured onto crushed ice (*ca.* 50 g) and the resulting aqueous solution basified by addition of solid K_2CO_3. The mixture was then extracted with EtOAc (3 × 50 ml). The combined organic extracts were washed with $NaHCO_3$ (aq) (100 ml) then brine (100 ml), dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on SiO_2 (Et_2O) gave **13** (315 mg, 79%) as buff prisms, m.p. 134–136 °C. R_f 0.23 (Et_2O); IR (solid) 3414, 3171, 1682, 1577, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.22 (5H, m, aryl), 7.15 (1H, br s, NH), 5.35 (1H, br s, NH), 3.88 (1H, d, *J* = 14.0 Hz, C*H*HPh), 3.50 (1H, d, *J* = 14.0 Hz, CH*H*Ph), 2.75–2.67 (1H, m, ring NC*H*H), 2.54–2.47 (1H, m, ring NCH*H*), 1.96–1.89 (1H, m, C*H*H), 1.84–1.50 (6H, m, 3 × CH_2), 1.33–1.24 (1H, m, CH*H*), 1.04 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 178.8 (C=O), 139.7 (C, aryl), 128.2 (2 × CH, aryl), 127.8 (2 × CH, aryl), 126.7 (CH, aryl), 66.5 (*C*$CONH_2$), 52.1 (CH_2Ph), 46.0 (CH_2), 29.7 (CH_2), 25.8 (CH_2), 21.1 (CH_2), 9.1 (CH_3); MS (ES^+) m/z

247 (100%, MH^+); HRMS (ES^+) found MH^+, 247.1804, $C_{15}H_{23}N_2O$ requires 247.1805. Anal. calcd for $C_{15}H_{22}N_2O$: C, 73.13%; H, 9.00%; N, 11.37%. Found: C, 73.05%; H, 8.99%; N, 11.15%.

X-ray data for 13. Crystal grown by slow evaporation from diethyl ether. $C_{15}H_{22}N_2O$ colourless block, 0.60 x 0.40 x 0.18 mm, Monoclinic, P2(1)/n (No 14), alpha = 90 deg., beta = 100.508(8) deg., gamma = 90 deg., a = 11.149(6), b = 10.559(5), c = 11.588(6) Å, U = 1341.3(12) $Å^3$, Z 4, D(cal) = 1.220 gcm^{-3}, $2\theta_{max}$ 58.26, λ = 0.71073 Å, 8760 reflections measured, 3310 unique [R(int) = 0.0453], R1[for 5389 reflections with I>2sigma(I)] = 0.0772, wR2 = 0.2203, T_{min} 0.7642, T_{max} 0.9863, $\mu(Mo_{K\alpha})$ = 0.077 mm^{-1}. Data / restraints / parameters 3310/ 0/ 170 refined against F^2 (SHELXTL: G. M. Sheldrick, *SHELXTL Ver 5.1*, Bruker Analytical X-ray Systems, **1997**). Largest difference Fourier peak and hole 0.340 and -0.301 $e.Å^{-3}$. CCDC 286808 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallograpic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***N*-Benzyl-2-(3-methylbutyl)piperidine-2-carbonitrile, 12.** Copper(I) iodide (48 mg, 0.252 mmol) was heated under vacuum in a round-bottomed flask, then purged with nitrogen (3 cycles performed). Anhydrous THF (4 ml) was added and the mixture cooled to –30 °C, whereupon iso-BuMgCl (1.90M in THF, 1.33 ml, 2.52 mmol) was added. After stirring for 10 min, *N*-benzyl-2-methyleneaziridine (183 mg, 1.26 mmol) in THF (1 ml) was added dropwise. The mixture was

allowed to warm up to room temperature and was stirred for 3 h. The reaction mixture was cooled to 0 °C and 1,3-diiodopropane (361 μl, 3.14 mmol) was added dropwise. The reaction mixture was then heated at 40 °C for 18 h. In a second flask, a solution of TMSCN (251 μl, 1.88 mmol) in THF (1 ml) at 0 °C was treated with glacial acetic acid (176 μl, 3.08 mmol) and stirred for 2 h. The resulting HCN solution (CAUTION) was added dropwise *via* cannula to the first vessel. After 2 h at 0 °C, saturated $NaHCO_3$ (2 ml) was added slowly. After 5 min, the mixture was diluted with Et_2O (20 ml), the organic layer separated, and washed with saturated $NaHCO_3$ (2 x 20 ml) then brine (20 ml). The organic phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the residue by MPLC (2-5% EtOAc/petrol) gave **12** (182 mg, 53%) as a clear colourless oil. R_f 0.39 (10% EtOAc in petrol); IR (film) 2954, 2215 (w), 1605, 1496, 1453, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.20 (5H, m, aryl), 4.12 (1H, d, *J* = 13.8 Hz, C*H*HPh), 3.11 (1H, d, *J* = 13.8 Hz, CH*H*Ph), 2.75 (1H, m, ring NC*H*H), 2.20 (1H, td, *J* = 12.3 Hz and 2.8 Hz, ring NCH*H*), 1.98-1.82 (3H, m, CH_2 and CH), 1.80-1.30 (8H, m, 4 × CH_2), 0.91 (3H, d, *J* = 6.5 Hz, CH_3), 0.88 (3H, d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 138.8 (C, aryl), 128.42 (2 × CH, aryl), 128.38 (2 × CH, aryl), 127.0 (CH, aryl), 119.3 (CN), 61.9 (*C*CN), 55.3 (CH_2Ph), 49.5 (CH_2), 36.1 (CH_2), 34.5 (CH_2), 31.7 (CH_2), 28.3 (CH), 25.1 (CH_2), 22.6 (CH_3), 22.4 (CH_3), 21.9 (CH_2); MS (ES^+) m/z 271 (85%, MH^+), 244 (100%, $[M-CN]^+$); HRMS (ES^+) found MH^+, 271.2166, $C_{18}H_{27}N_2$ requires 271.2169. Anal. calcd for $C_{18}H_{26}N_2$: C, 79.95%; H, 9.69%; N, 10.36%. Found: C, 79.75%; H, 9.96%; N, 10.10%.

2-Pentyl-*N*-[(*S*)-1-phenylethyl]piperidine-2-carbonitrile, 15. Copper(I) iodide (48 mg, 0.252 mmol) was heated under vacuum in a round-bottomed flask, then purged with nitrogen (3 cycles performed). Anhydrous THF (4 ml) was added and the mixture cooled to –30 °C, whereupon BuMgCl (1.90M in THF, 1.33 ml, 2.53 mmol) was added. After stirring for 10 min, *N*-[(*S*)-1-phenylethyl]-2-methyleneaziridine (200 mg, 1.26 mmol) in THF (1 ml) was added dropwise. The mixture was allowed to warm up to room temperature and was stirred for 3 h. The reaction mixture was cooled to 0 °C and 1,3-diiodopropane (361 μl, 3.14 mmol) was added dropwise. The reaction mixture was then heated at 40 °C for 18 h. In a second flask, a solution of TMSCN (251 μl, 1.88 mmol) in THF (1 ml) at 0 °C was treated with glacial acetic acid (176 μl, 3.08 mmol) and stirred for 2 h. The resulting HCN solution (CAUTION) was added dropwise *via* cannula to the first vessel. After 2 h at 0 °C, saturated $NaHCO_3$ (2 ml) was added slowly. After 5 min, the mixture was diluted with Et_2O (20 ml), the organic layer separated, and washed with saturated $NaHCO_3$ (2 x 20 ml) then brine (20 ml). The organic phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Crude ^1H NMR analysis indicated that **15** had been produced as a 9:1 mixture of diastereomers. Purification on SiO_2 (2% EtOAc/petrol) gave **15** (145 mg, 41%) as a clear colourless oil. R_f 0.45 (10% EtOAc in petrol); IR (film) 2934, 2214 (w), 1602, 1494, 1445, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.47-7.37 (2H, m, aryl), 7.35-7.27 (2H, m, aryl), 7.25-7.15 (1H, m, aryl), 4.43 (0.9H, q, *J* = 6.9 Hz, C*H*CH_3Ph (major)), 4.29 (0.1H, q, *J* = 6.9 Hz, C*H*CH_3Ph (minor)), 3.14-3.08 (0.1H, m, ring NC*H*H

(minor)), 2.63-2.48 (1.8H, m, ring NCH_2 (major)), 2.41-2.30 (0.2H, m, ring NCH*H* and C*H*H (minor)), 2.05-1.20 (13.9H, m, 7 × CH_2), 1.51 (2.7H, d, *J* = 6.8 Hz, CHC*H*$_3$ (major)); 1.45 (0.3H, d, *J* = 7.3 Hz, CHC*H*$_3$ (minor)); 0.93 (0.3H, t, *J* = 7.0 Hz, CH_3 (minor)) , 0.87 (2.7H, t, *J* = 7.0 Hz, CH_3 (major)); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer: 144.3 (C, aryl), 128.1 (2 × CH, aryl), 127.1 (2 × CH, aryl), 126.5 (CH, aryl), 122.1 (CN), 59.9 (*C*CN), 53.5 (*C*HCH$_3$Ph), 42.8 (CH_2), 38.0 (CH_2), 36.3 (CH_2), 32.1 (CH_2), 25.5 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 14.0 (CH_3), 11.2 (CH_3); MS (CI^+) m/z 285 (5%, MH^+), 258 (100%, $[M-CN]^+$). Anal. calcd for $C_{19}H_{28}N_2$: C, 80.23%; H, 9.92%; N, 9.85%. Found: C, 79.93%; H, 9.95%; N, 9.63%.