Supporting Information

A Stereodivergent Approach to Substituted 4-Hydroxypiperidines

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General information: All reactions in dry solvents were carried out under an inert atmosphere of dry nitrogen. Standard syringe techniques were applied for transfer of reagents and dry solvents. Infrared (IR) spectra were obtained from CHCl₃ solutions or neat using a Bruker IFS 28 spectrophotometer and absorptions are reported in cm⁻¹. Proton nuclear magnetic resonance (¹H-NMR) spectra were obtained from CDCl₃, unless stated otherwise, using a Bruker AC 200 (200 MHz) or a Bruker ARX 400 (400 MHz) spectrometer. Carbon nuclear magnetic resonance (¹³C-NMR) spectra were obtained from CDCl₃, unless stated otherwise, using a Bruker AC 200 (50 MHz) or a Bruker ARX 400 (100 MHz). Chemical shifts are reported on the δ scale in ppm and coupling constants (*J*) are reported in Hz. Mass spectra and accurate mass measurements were carried out using a JEOL JMS-SX/SX 102A Tandem Mass Spectrometer, a Varian NIAT 711 or a VG Micromass ZAB-HFQQ instrument. R_f values were obtained using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F₂₅₄) with the indicated solvent (mixture). Flash chromatography was performed with Acros Organics silica gel (0.035-0.070 mm). Melting points were determined with Büchi melting point B-545 apparatus.

Oxiranylacetic acid: Vinylacetic acid (5.00 g, 58.1 mmol) was added dropwise to a stirred suspension of Oxone® (35.7 g, 58.1 mmol) in 0.33M aqueous KOH solution (150 mL). The pH was maintained at 6 with 1M aqueous KOH solution using an automated buret. After the acid had been added, the white suspension was stirred until the pH remained constant. The reaction mixture was acidified to pH 3 with concentrated HCl and extracted with EtOAc (5×500 mL), the combined organic layers were dried with Na₂SO₄ and the solvent was evaporated under reduced pressure to yield the crude product as a yellow oil (6.0 g). The crude product was used in the next step. ¹H NMR (400 MHz): 3.32-3.27 (m, 1H), 2.87-2.85 (m, 1H), 2.69-2.55 (m, 3H).

4-Cyano-3-hydroxybutyric acid: MgSO₄·7H₂O (30 g, 0.12 mol) was added to a stirred solution of oxiranylacetic acid (6.0 g, 59 mmol) in 0.4M aqueous KOH solution (250 mL). After 30 min NaCN (2.9 g, 59 mmol) was added in one portion. After stirring for 20 h, the red-brown solution was acidified to pH 2 using concentrated HCl and extracted with EtOAc (5×500 mL). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was evaporated under reduced pressure to yield the product as a red-brown oil (4.1 g). The crude product was used directly in the next step. ¹H NMR (400 MHz, CD₃OD): 4.31-4.25 (m, 1H), 2.74 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.65 (dd, *J* = 16.9, 6.5 Hz, 1H), 2.61-2.51 (m, 2H).

4-Cyano-3-hydroxybutyric acid methyl ester (6): To a solution of SOCl_2 (150 μL , 2.0 mmol) in MeOH (30 mL), 4-cyano-3-hydroxybutyric acid (2.6 g, 20 mmol) in MeOH (10 mL) was added at 0 °C. The reaction was warmed to rt and stirred overnight. The solvent was removed *in vacuo* and the product was purified by flash chromatography (PE/EtOAc 1:3, R_f 0.34) to yield a pale yellow oil (2.7 g, 19 mmol, 51% from vinylacetic acid). ^1H NMR (400 MHz): 4.33-4.31 (m, 1H), 3.71 (s, 3H), 3.62 (d, $J = 3.8$ Hz, 1H), 2.66-2.57 (m, 4H). ^{13}C NMR (100 MHz): 171.8, 116.8, 64.0, 52.0, 39.7, 24.9. IR: 3423, 2066, 1742, 1640. HRMS (FAB) calculated for $\text{C}_6\text{H}_{10}\text{NO}_3$ (MH^+) 144.0661, found 144.0649.

4-Hydroxypiperidin-2-one (7): A solution of **2** (4.4 g, 31 mmol) in MeOH (25 mL) was hydrogenated with PtO₂ (0.35 mg, 1.5 mmol) under H₂ pressure (50 psi) for 24 h. The reaction mixture was filtrated over Celite and the solvent was evaporated under reduced pressure. Crystallization from hot MeOH afforded **3** as white crystals (2.9 g, 25 mmol, 81%), mp 170 °C. ¹H NMR (400 MHz, CD₃OD): 4.15-4.10 (m, 1H), 3.48-3.41 (m, 1H), 3.26-3.19 (m, 1H), 2.57 (dd, *J* = 17.6, 4.2 Hz, 1H), 2.26 (ddd, *J* = 17.6, 5.8, 1.0 Hz, 1H), 1.97-1.90 (m, 1H), 1.82-1.73 (m, 1H). ¹³C NMR (100 MHz): 173.7, 64.8, 40.6, 38.6, 30.4. HRMS (FAB) calculated for C₅H₁₀O₂N (MH⁺) 116.0712, found 116.0719.

4-(*tert*-Butyldiphenylsilyloxy)piperidin-2-one: To a solution of **7** (0.63 g, 5.5 mmol) in dry DMF (25 mL) was added imidazole (0.75 g, 11 mmol), DMAP (67 mg, 0.55 mmol) and TBDPSCl (1.6 mL, 6.0 mmol). The reaction was stirred at 80 °C for 16 h, cooled to rt, quenched with satd aqueous NH₄Cl (20 mL) and extracted with EtOAc (50 mL). The combined organic layers were washed with brine (3 × 20 mL), dried with MgSO₄, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc, R_f 0.15) afforded the product as a sticky oil (1.6 g, 4.5 mmol, 82%). ¹H NMR (200 MHz): 7.67-7.64 (m, 4H), 7.43-7.34 (m, 6H), 6.30 (bs, 1H), 4.17-4.12 (m, 1H), 3.54-3.48 (m, 1H), 3.13-3.07 (m, 1H), 2.41-2.96 (m, 2H), 1.74 (d, *J* = 5.4 Hz, 1H), 1.71 (d, *J* = 5.9 Hz, 1H), 1.07 (s, 9H). ¹³C NMR (50 MHz): 171.4, 135.4, 135.4, 133.5, 133.3, 129.6, 129.6, 127.5, 127.5, 65.7, 40.3, 37.4, 29.7, 26.7, 18.9, 18.8. IR: 3218, 3072, 2961, 2892, 2859, 1668. HRMS (FAB) calculated for C₂₁H₂₈NO₂Si (MH⁺) 354.1889, found 354.1902.

4-(*tert*-Butyldiphenylsilyloxy)-2-oxopiperidine-1-carboxylic acid methyl ester (8): To a solution of 4-(*tert*-butyldiphenylsilyloxy)piperidin-2-one (1.3 g, 3.8 mmol) in dry THF (20 mL) was added at -78°C *n*-BuLi (2.8 mL 1.6M in THF, 4.5 mmol). After 30 min methyl cyanoformate (0.60 mL, 7.6 mmol) was added. The reaction was monitored by TLC and after the starting material had reacted, the reaction was quenched with H_2O (10 mL), warmed to rt and extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine, dried with MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (EtOAc , R_f 0.20) afforded the product as a colorless oil (1.2 g, 2.9 mmol, 76%). ^1H NMR (200 MHz): 7.65-7.62 (m, 4H), 7.46-7.37 (m, 6H), 4.28 (p, $J = 4.6$ Hz, 1H), 3.96-3.91 (m, 1H), 3.86 (s, 3H), 3.66-3.61 (m, 1H), 2.59-2.57 (m, 2H), 1.85-1.80 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (50 MHz): 169.5, 154.9, 135.6, 133.5, 133.2, 130.0, 127.8, 65.7, 53.9, 43.9, 42.2, 30.9, 29.7, 26.9, 19.1. IR: 2955, 2932, 2857, 1779, 1719. HRMS (FAB) calculated for $\text{C}_{23}\text{H}_{30}\text{NO}_4\text{Si}$ (MH^+) 412.1944, found 412.1939.

4-(*tert*-Butyldiphenylsilyloxy)-2-ethoxypiperidine-1-carboxylic acid methyl ester (9):

To a solution of **8** (1.0 g, 2.4 mmol) in EtOH (50 mL), NaBH₄ (0.23 mg, 6.1 mmol) was added at -15 °C. The reaction was monitored by TLC and acidified to pH 2 with 2M H₂SO₄ in EtOH when the starting material had reacted completely. The reaction was warmed to rt and quenched with satd aqueous NH₄Cl (40 mL). The water layer was extracted with Et₂O (4 × 50 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification with flash chromatography (PE/EtOAc 3:1, R_f 0.43) afforded the product as a colorless oil (1.0 g, 2.3 mmol, 96%). ¹H NMR (200 MHz): 7.69-7.67 (m, 4H), 7.19-7.17 (m, 6H), 5.44 (bs, 1H), 4.32-4.24 (m, 1H), 3.85-3.81 (m, 1H), 3.45 (s, 3H), 3.23-3.12 (m, 2H), 2.76 (dt, *J* = 13.2, 2.8 Hz, 1H), 2.09-2.03 (m, 1H), 1.72-1.67 (m, 1H), 1.50-1.40 (m, 2H), 1.10 (s, 9H). ¹³C NMR (50 MHz): 155.7, 135.6, 134.4, 134.3, 129.5, 127.4, 81.4, 66.2, 62.1, 52.4, 39.6, 37.2, 34.7, 26.9, 19.0, 14.8. IR: 3072, 2957, 2892, 2859, 1708.

4-Hydroxy-6-methoxypiperidin-2-one (10): A stirred solution of **7** (1.0 g, 8.7 mmol) and PhSO_3Na (0.73 g, 4.0 mmol) in MeOH (40 mL) was subjected to a potential of 3.0 V for 72 h at 10-15 °C. The methanol was evaporated and the product was purified using flash chromatography (EtOAc/MeOH 9:1) yielding **10** as a pale yellow oil (1.2 g, 8.3 mmol, 95%). R_f 0.35 (acetone). ^1H NMR (400 MHz): 4.69 (t, $J = 5.4$ Hz, 1H, *cis*), 4.62 (t, $J = 3.5$ Hz, 1H, *trans*), 4.27-4.20 (m, 1H, *trans*), 4.08-4.02 (m, 1H, *cis*), 3.37 (s, 3H, *cis*), 3.32 (s, 3H, *trans*), 2.67 (ddd, $J = 17.3, 5.5, 1.5$ Hz, 1H, *trans*), 2.58 (ddd, $J = 17.0, 4.9, 1.4$ Hz, 1H, *cis*), 2.34 (dd, $J = 21.1, 7.4$ Hz, 1H, *cis*), 2.23 (dd, $J = 17.4, 9.1$ Hz, 1H, *trans*), 2.18-2.13 (m, 1H, *trans* + *cis*), 1.87-1.73 (m, 1H, *trans* + *cis*). ^{13}C NMR (100 MHz): 174.2, 84.0 (*cis*), 83.0 (*trans*), 64.1 (*cis*), 62.3 (*trans*), 55.4, 41.7 (*trans*), 41.3 (*cis*), 37.2 (*trans*), 36.4 (*cis*). IR: 3310, 2937, 2834, 2373, 1652, 1072.

trans/cis 82:18

4-(*tert*-Butyldiphenylsilyloxy)-6-methoxypiperidin-2-one (11):

To a solution of **10** (1.2 g, 8.3 mmol) in dry MeCN (10 mL) was added imidazole (0.93 g, 14 mmol), DMAP (0.12 g, 1.0 mmol) and TBDPSCl (2.6 mL, 10 mmol). The reaction was stirred for 24 h after which the reaction was quenched with NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. After flash chromatography (EtOAc, R_f 0.38), the product was obtained as a colorless oil (2.4 g, 6.3 mmol, 76%). ¹H NMR (400 MHz): 7.67-7.58 (m, 4H), 7.46-7.35 (m, 6H), 7.22 (bs, 1H, *trans*), 6.99 (bs, 1H, *cis*), 4.57 (dd, *J* = 7.4, 3.8 Hz, 1H, *trans*), 4.46-4.42 (m, 1H, *cis*), 4.36-4.30 (m, 1H, *trans*), 3.98-3.91 (m, 1H, *cis*), 3.29 (s, 3H, *cis*), 3.14 (s, 3H, *trans*), 2.57 (ddd, *J* = 17.4, 5.2, 1.3 Hz, 1H, *trans*), 2.60-2.50 (m, 1H, *cis*), 2.46-2.36 (m, 1H, *cis*), 2.39 (dd, *J* = 17.4, 8.0 Hz, 1H, *trans*), 2.00-1.95 (m, 1H), 1.87-1.81 (m, 1H, *trans*), 1.87-1.73 (m, 1H, *cis*), 1.06 (s, 9H). ¹³C NMR (100 MHz): 172.2 (*trans*), 171.6 (*cis*), 135.4, 133.5, 133.3, 129.6, 127.5, 81.9 (*cis*), 81.5 (*trans*), 64.4 (*cis*), 63.3 (*trans*), 54.5 (*trans*), 54.4 (*cis*), 41.0 (*trans*), 40.9 (*cis*), 36.9 (*cis*), 36.0 (*trans*), 26.7 (*trans*), 26.6 (*cis*), 18.8. IR: 3220, 3071, 2932, 2858, 1668. HRMS (FAB) calculated for C₂₂H₃₀NO₃Si (MH⁺) 384.1995, found 384.1980.

General procedure for alkylation of carbamate **9:** To a stirred solution of **9** (100 mg, 0.23 mmol) and the nucleophile (1.4 mmol) in dry CH₂Cl₂ or dry MeCN (20 mL), BF₃·OEt₂ (0.12 mL, 0.95 mmol) or Sc(OTf)₃ (11 mg, 23 μmol) was added at –78 °C (CH₂Cl₂) or –50 °C (MeCN). The reaction was allowed to warm to rt and monitored by TLC. When the starting material had reacted, the reaction was quenched with H₂O (10 mL) and the water layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over MgSO₄ and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography.

2-Allyl-4-(*tert*-butyldiphenylsilyloxy)piperidine-1-carboxylic acid methyl ester

(12a): Compound **12a** was obtained as a colorless oil (PE/EtOAc 4:1, R_f 0.37). ^1H

NMR (400 MHz): 7.75-7.65 (m, 4H), 7.46-7.36 (m, 6H), 5.82-5.73 (m, 1H, *cis*), 5.52-5.41 (m, 1H, *trans*), 5.81 (dd, $J = 14.3, 6.2$ Hz, 1H, *cis*), 5.76 (dd, $J = 7.0, 2.7$ Hz, 1H, *cis*), 4.89 (d, $J = 9.9$ Hz, 1H, *trans*), 4.80 (d, $J = 17.0$ Hz, 1H, *trans*), 4.31-4.19 (m, 1H), 4.15 (t, $J = 3.0$ Hz, 1H), 3.92-3.87 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.34 (dt, $J = 13.0, 3.2$ Hz, 1H), 2.90-2.84 (m, 1H), 2.67-2.55 (m, 1H), 1.97-1.89 (m, 1H), 1.79-1.61 (m, 1H), 1.60-1.51 (m, 1H), 1.46-1.30 (m, 1H), 1.11 (s, 9H), 1.07 (s, 3H). ^{13}C NMR (100 MHz): 156.2, 136.2, 135.8, 133.8, 129.7, 127.6, 116.5, 66.1, 52.4, 49.9, 37.7, 34.1, 33.9, 32.3, 27.0, 19.1. IR: 3071, 2953, 1701. HRMS (FAB) calculated for $\text{C}_{26}\text{H}_{35}\text{NO}_3\text{Si}$ (MH^+) 438.2464, found 438.2464.

COC(=O)N1CCCC(C1)C#N **4-(*tert*-Butyldiphenylsilyloxy)-2-cyanopiperidine-1-carboxylic acid methyl ester (12b)**: Nitrile **12b** was isolated as two separate diastereomers. *Trans*: white crystals, mp 165 °C (EtOAc/PE 1:9, R_f 0.20). ^1H NMR (400 MHz): 7.73-7.64 (m, 4H), 7.48-7.36 (m, 6H), 5.21 (bs, 1H), 4.08-4.00 (m, 2H), 3.73 (s, 3H), 2.92-2.85 (m, 1H), 1.96-1.92 (d, J = 13.0 Hz, 1H), 1.87-1.84 (d, J = 12.1 Hz, 1H), 1.73-1.66 (m, 1H), 1.58-1.47 (m, 1H), 1.07 (s, 9H). ^{13}C NMR: 135.6, 133.8, 129.9, 127.7, 116.8, 66.9, 53.4, 43.6, 40.6, 36.7, 34.1, 26.7, 19.1. IR: 2959, 2933, 2860, 2249, 1704. *Cis*: yellow oil, R_f 0.13 (PE/EtOAc 9:1). ^1H NMR (400 MHz): 7.73-7.70 (m, 4H), 7.48-7.37 (m, 6H), 5.26 (bs, 1H), 4.13 (t, J = 2.8 Hz, 1H), 3.90 (bs, 1H), 3.75 (s, 3H), 3.58-3.56 (bm, 1H), 3.57 (d, J = 5.6 Hz, 1H), 1.80-1.74 (m, 1H), 1.51-1.40 (m, 1H), 1.40-1.33 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (100 MHz): 135.8, 133.2, 129.8, 127.6, 118.6, 63.7, 53.2, 39.9, 35.7, 34.1, 31.4, 26.8, 19.0. IR: 2958, 2933, 2860, 2256, 1703. HRMS (FAB) calculated for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_3\text{Si}$ (MH^+) 423.2104, found 423.2126.

4-(*tert*-Butyldiphenylsilyloxy)-2-prop-2-ynylpiperidine-1-carboxylic acid methyl ester (12c**):** Acetylene **12c** was obtained as a colorless oil (PE:EtOAc 9:1, R_f 0.20). ^1H NMR (400 MHz): 7.71-7.64 (m, 4H), 7.46-7.35 (m, 6H), 4.34-4.32 (m, 1H), 4.13-4.11 (m, 1H), 3.91-3.87 (m, 1H), 3.69 (s, 3H), 3.33-3.26 (m, 1H), 3.06-2.99 (m, 1H), 2.74-2.68 (m, 1H), 2.14 (d, $J = 15.0$ Hz, 1H), 2.03-2.02 (m, 1H), 1.68-1.57 (m, 1H), 1.39-1.36 (m, 1H), 1.10 (s, 9H). ^{13}C NMR (100 MHz): 156.1, 135.9, 129.7, 127.7, 70.0, 66.2, 65.9, 52.5, 49.1, 34.0, 32.7, 31.9, 27.0, 22.8, 19.0. IR: 3308, 2252, 1686. HRMS (FAB) calculated for $\text{C}_{31}\text{H}_{38}\text{NO}_4\text{Si}$ (MH^+) 516.2570, found 516.2587.

4-(*tert*-Butyldiphenylsilyloxy)-2-(2-oxo-2-phenylethyl)piperidine-1-carboxylic acid methyl ester (12d): Ketone **12d** was obtained as a colorless oil, R_f 0.25

(PE/EtOAc 9:1). ^1H NMR (400 MHz) (*cis*): 7.94-7.25 (m, 15H), 4.86 (bs, 1H), 4.19-4.17 (m, 1H), 4.05 (dd, $J = 17.0, 8.9$ Hz, 1H), 3.95 (bs, 1H), 3.62 (s, 3H),

3.49-3.42 (m, 1H), 3.37 (dd, $J = 17.0, 4.6$ Hz, 1H), 2.01-1.97 (m, 1H), 1.78-1.64 (m, 1H), 1.57-1.40 (m, 2H), 0.98 (s, 9H). ^{13}C NMR (100 MHz): 198.4, 197.1, 155.7, 136.5, 135.5, 134.0, 132.9, 129.6, 128.4, 127.9, 127.5, 66.2, 52.4, 46.3, 41.4, 39.8, 38.9, 35.3, 33.7, 31.8, 26.9, 18.9. IR: 3012, 2958, 1696, 1675.

General procedure for alkylation of lactam **11:** To a solution of **11** (100 mg, 0.26 mmol) and the nucleophile (1.0 mmol) in dry CH₂Cl₂ or dry MeCN (5 mL), BF₃·OEt₂ (0.12 mL, 0.95 mmol) or Sc(OTf)₃ (11 mg, 23 μmol) was added at 0 °C. The reaction was allowed to warm to rt and was monitored by TLC. When the reaction was finished, satd aqueous NaHCO₃ (5 mL) was added and the water layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄ and concentrated *in vacuo*. Purification by flash chromatography afforded the products **13a-d**.

6-Allyl-4-(tert-butyldiphenylsilyloxy)piperidin-2-one (13a**):** Compound **13a** was obtained as a sticky oil (EtOAc, R_f 0.36). ¹H NMR (400 MHz): 7.70-7.62 (m, 4H), 7.46-7.36 (m, 6H), 6.54 (bs, 1H, *trans*), 6.41 (bs, 1H, *cis*), 5.75-5.62 (m, 1H), 5.16-5.09 (m, 2H), 4.27-4.26 (m, 1H, *trans*), 3.99-3.96 (m, 1H, *cis*), 3.87-3.80 (m, 1H, *trans*), 3.14-3.13 (m, 1H, *cis*), 2.59-2.53 (m, 2H, *cis*), 2.43-2.28 (m, 2H, *trans*), 2.26-2.08 (m, 2H), 2.00-1.96 (m, 1H, *cis*), 1.82-1.79 (m, 1H, *trans*), 1.36-1.30 (m, 1H), 1.06 (s, 9H). ¹³C NMR (100 MHz): 171.1, 135.6 (*cis*), 135.6 (*trans*), 133.6 (*trans*), 133.3 (*cis*), 133.1 (*trans*), 132.8 (*cis*), 129.8 (*trans*), 129.8 (*cis*), 127.7 (*trans*), 127.7 (*cis*), 119.2 (*cis*), 119.0 (*trans*), 66.3 (*cis*), 65.0 (*trans*), 48.8 (*cis*), 47.4 (*trans*), 41.0 (*cis*), 40.7 (*trans*), 40.6 (*trans*), 39.7 (*cis*), 37.9 (*cis*), 35.2 (*trans*), 26.8 (*trans*), 26.8 (*cis*), 19.1 (*trans*), 18.9 (*cis*). IR: 3205, 3072, 2931, 2858, 1667. HRMS (FAB) calculated for C₂₄H₃₂NO₂Si (MH⁺) 394.2202, found 394.2180.

6-Cyano-4-(*tert*-butyldiphenylsilyloxy)piperidin-2-one (13b): Nitrile **13b** was obtained as separate diastereoisomers, both pale yellow oils. First: (EtOAc, R_f 0.56)

^1H NMR (400 MHz): 7.64-7.60 (m, 4H), 7.49-7.38 (m, 6H), 6.71 (s, mH), 4.69-4.66 (m, 1H), 4.34-4.33 (m, 1H), 2.49-2.44 (m, 2H), 2.19-1.95 (m, 2H), 1.07 (s, 9H). ^{13}C

NMR (100 MHz): 170.1, 135.6, 132.8, 130.1, 129.9, 127.7, 11.5, 64.5, 60.3, 39.7, 39.5, 32.1, 26.7, 18.9. IR: 3340, 3072, 2933, 2933, 2859, 2360, 1669. Second: (EtOAc, R_f 0.37). HRMS (FAB) calculated for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2\text{Si}$ (MH^+) 379.1842, found 379.1844.

4-(*tert*-Butyldiphenylsilyloxy)-6-prop-2-ynylpiperidin-2-one (13c): Acetylene **13c** was obtained as a pale yellow oil (EtOAc, R_f 0.42). ^1H NMR (400 MHz) (*cis/trans* 1:1): 7.67-7.62 (m, 8H), 7.45-7.36 (m, 12H), 7.00 (bs, 1H), 6.94 (bs, 1H), 4.28-4.27 (m, 1H), 4.03-3.92 (m, 2H), 3.31-3.27 (m, 1H), 2.57-2.51 (m, 1H), 2.44-2.30 (m, 7H), 2.08-2.02 (m, 4H), 1.92-1.89 (m, 1H), 1.46-1.40 (m, 1H), 1.07 (s, 18H). ^{13}C NMR (100 MHz) (*cis/trans* 1:1): 171.4, 171.2, 135.6, 133.5, 133.4, 133.2, 129.9, 129.8, 129.8, 127.7, 127.7, 79.3, 79.2, 66.0, 64.8, 48.6, 47.3, 47.2, 40.8, 39.8, 39.6, 36.8, 34.8, 26.8, 26.8, 26.3, 26.0, 21.0, 19.0, 18.9. IR: 3305, 3217, 3071, 2958, 2931, 2858, 1667. HRMS (FAB) calculated for $\text{C}_{24}\text{H}_{30}\text{NO}_2\text{Si}$ (MH^+) 392.2046, found 392.2035.

4-(*tert*-Butyldiphenylsilyloxy)-6-(2-oxo-2-phenylethyl)piperidin-2-one

(13d): Ketone 13d was obtained as separate diastereoisomers, both pale yellow oils. *Cis*: R_f 0.29 (PE/EtOAc 1:4). ^1H NMR (400 MHz): 8.02-7.28 (m, 15H), 6.53 (s, 1H), 4.15-4.08 (m, 1H), 3.89-3.83 (m, 1H), 3.28-3.15 (m, 1H),

2.57 (ddd, $J = 17.2, 5.2, 1.6$ Hz, 1H), 2.41 (dd, $J = 17.2, 8.6$ Hz, 1H), 2.05-2.02 (m, 1H), 1.71-1.63 (m, 1H), 1.08 (s, 9H). ^{13}C NMR: 199.1, 170.5, 135.5, 133.5, 133.1, 129.9, 129.8, 127.7, 127.7, 66.1, 45.6, 45.5, 40.9, 36.9, 26.7, 19.0. IR: 3390, 3069, 2957, 2930, 2892, 2857, 1661. *Trans*: R_f 0.19 (PE/EtOAc 1:4). ^1H NMR (400 MHz): 7.89-7.35 (m, 15H), 6.59 (s, 1H), 4.38-4.33 (m, 1H), 4.21-4.25 (m, 1H), 3.01 (dd, $J = 17.9, 3.9$ Hz, 1H), 2.94 (dd, $J = 17.9, 9.1$ Hz, 1H), 2.49-2.38 (m, 2H), 1.93-1.87 (m, 1H), 1.50-1.45 (m, 1H), 1.08 (s, 9H). ^{13}C NMR (100 MHz): 197.8, 170.4, 136.2, 135.6, 133.6, 133.2, 128.6, 127.8, 127.7, 127.7, 64.7, 44.8, 44.6, 40.0, 35.5, 26.8, 19.0. HRMS (FAB) calculated for $\text{C}_{29}\text{H}_{34}\text{NO}_3\text{Si}$ (MH^+) 472.2308, found 472.2281.

2-Allyl-4-(tert-butyldiphenylsilyloxy)-6-oxopiperidine-1-carboxylic acid

methyl ester: To a stirred solution of **13a** (100 mg, 0.25 mmol) in THF (2 mL) was added *n*-BuLi (0.24 mL 1.6M in THF, 0.38 mmol) at -78°C . After 30 min methyl cyanoformate (40 μL , 0.51 mmol) was added and the reaction was stirred at -78°C for 8 h. Satd aqueous NH_4Cl (2 mL) was added and the water layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. After purification by flash chromatography (PE/EtOAc 2:1, R_f 0.41), the product was obtained as a colorless oil (110 mg, 0.24 mmol, 96%). ^1H NMR (400 MHz): 7.66-7.62 (m, 4H), 7.47-7.37 (m, 6H), 5.79-5.68 (m, 1H, *cis*), 5.46-5.36 (m, 1H, *trans*), 5.14-5.10 (m, 1H, *cis*), 4.93-4.82 (m, 1H, *trans*), 4.82-4.78 (m, 1H, *trans*), 4.31-4.25 (m, 1H), 4.23-4.17 (m, 1H), 3.85 (s, 3H, *trans*), 3.82 (s, 3H, *cis*), 2.72 (ddd, $J = 17.1, 5.5, 1.2$ Hz, 1H), 2.59 (dd, $J = 17.1, 7.7$ Hz, 1H), 2.31-2.25 (m, 1H), 1.96-1.80 (m, 3H), 1.07 (s, 9H, *cis*), 1.05 (s, 9H, *trans*). ^{13}C NMR (100 MHz): 169.8, 154.8, 135.7 (*cis*), 133.5 (*trans*), 133.2, 132.9, 130.0, 127.8, 118.7 (*cis*), 118.5 (*trans*), 65.7, 63.6, 54.0 (*cis*), 53.9 (*trans*), 53.3, 44.0 (*trans*), 43.8 (*cis*), 39.5 (*cis*), 38.8 (*trans*), 34.7 (*cis*), 34.5 (*trans*), 26.9 (*cis*), 26.8 (*trans*), 19.0. IR: 3070, 29.54, 2931, 2857, 1774, 1719. HRMS (FAB) calculated for $\text{C}_{26}\text{H}_{34}\text{NO}_4\text{Si}$ (MH^+) 452.2257, found 452.2262.

(rel-1R,4S)-2-Allyl-4-(tert-butyldiphenylsilyloxy)piperidine-1-carboxylic acid

methyl ester (12a): To a solution of 2-allyl-4-(tert-butyldiphenylsilyloxy)-6-oxopiperidine-1-carboxylic acid methyl ester (100 mg, 221 μmol) in THF (1 mL) was added DIBAL (663 μL , 663 μmol) at -78°C . After 6 h, the reaction was quenched with EtOAc (2 mL) and satd aqueous Na_2SO_4 (0.5 mL). The mixture was allowed to warm to room

temperature and, after addition of solid Na₂SO₄, filtered and concentrated *in vacuo* to afford 2-allyl-4-(*tert*-butyldiphenylsilanyloxy)-6-hydroxypiperidine-1-carboxylic acid methyl ester as a yellow oil (66 mg). The crude product was used directly in the next reaction.

To a solution of 2-allyl-4-(*tert*-butyldiphenylsilanyloxy)-6-hydroxypiperidine-1-carboxylic acid methyl ester (45 mg, 99 μ mol) in CH₂Cl₂ (5 mL) was added at 0 °C Et₃SiH (95 μ L, 594 μ mol), TFAA (42 μ L, 297 μ mol) and TFA (23 μ L, 297 μ mol). After 6 h, the reaction was quenched with satd aqueous NaHCO₃ (10 mL) and the mixture was allowed to warm to room temperature. The water layer was extracted with CH₂Cl₂ (3 $\times$ 10 mL) after which the combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification with flash chromatography (PE/EtOAc 3:1, R_f 0.46) afforded the product as a colorless oil (16 mg, 37 μ mol, 16%). ¹H NMR (400 MHz): 7.86-7.63 (m, 4H), 7.45-7.29 (m, 6H), 5.53-5.43 (m, 1H), 4.90-4.77 (m, 2H), 4.27 (bs, 1H), 4.00-3.98 (bm, 1H), 3.94-3.86 (m, 1H), 3.65 (s, 3H), 2.71-2.63 (m, 1H), 2.08-2.01 (m, 1H), 1.93-1.86 (m, 1H), 1.80-1.71 (m, 2H), 1.58-1.41 (m, 2H), 1.04 (s, 9H). ¹³C NMR (100 MHz): 156.0, 135.8, 134.8, 134.2, 129.7, 127.7, 117.0, 66.4, 52.5, 51.0, 38.0, 36.9, 35.3, 35.1, 26.9, 19.0. IR: 3071, 2931, 2857, 1701, 1678.

General procedure for the enzyme-catalyzed hydrolysis of nitriles: The *Rhodococcus erythropolis* NCIMB 11540 whole cells were incubated with the substrate in 100 mM potassium or sodium phosphate buffer (pH 7) at 30 °C. The reaction was quenched by adding 2 M HCl until the reaction mixture reached a pH of 1. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over MgSO₄ and evaporated *in vacuo*.

Enzymatic hydrolysis of 3-hydroxypentanedinitrile: According to the general procedure of the enzyme-catalyzed hydrolysis of nitriles, 3-hydroxypentanedinitrile (100 mg, 0.91 mmol) was incubated with *Rhodococcus erythropolis* NCIMB 11540 whole cells (50 mg) in a potassium phosphate buffer (20 mL) for 72 h. The crude product was immediately methylated with diazomethane and the hydroxy function was benzoyl-protected for HPLC analysis. After purification by flash chromatography (petroleum ether/EtOAc 3:1, R_f 0.16), (*S*)-benzoic acid 2-cyano-1-methoxycarbonylmethylethyl ester (**17c**) (63.0 mg, 0.27 mmol, 30% over three steps) was obtained as a red-brown oil. [α]_D = +5.9 (CHCl₃, *c* = 1.0), ee = 13% (heptane/isopropanol 9:1, flow: 1 mL min⁻¹, rt (*R*) = 15.1 min, rt (*S*) = 20.2 min). ¹H-NMR (200 MHz): 8.04-7.41 (5 H, m), 5.56 (quint., *J* = 5.8, 1H), 3.71 (s, 3 H), 3.05-2.83 (m, 4 H). ¹³C-NMR (50 MHz, CD₃OD): 169.5, 165.2, 133.6, 130.0, 129.71, 128.9, 128.4, 128.3, 115.8, 65.7, 52.1, 37.2, 22.6. IR: 3683, 3620, 3443, 3020, 2976, 2895, 2400, 2252, 1732.

Enzyme-catalyzed hydrolysis of 3-benzyloxypentanedinitrile: According to the general procedure of the enzyme-catalyzed hydrolysis of nitriles, 3-benzyloxypentanedinitrile (1.0 g, 5.0 mmol) was incubated with *Rhodococcus erythropolis* NCIMB 11540 whole cells (2.0 g) in a sodium phosphate buffer (400 mL) for 24 h. The crude product was immediately methylated with diazomethane and after purification by flash chromatography (petroleum ether/EtOAc 2:1, R_f 0.26), (*S*)-3-benzyloxy-4-cyanobutyric acid methyl ester (**17b**) (766 mg, 2.8 mmol, 70% over two steps) was obtained as a red-brown oil. $[\alpha]_D = +12.1$ (CHCl_3 , $c = 1.0$). $ee = 96\%$ (heptane/isopropanol 9:1, flow: 1 mL min^{-1} , rt (*R*) = 17.2 min, rt (*S*) = 23.4 min). $^1\text{H-NMR}$ (200 MHz): 7.37-7.28 (m, 5 H), 4.63 (d, $J = 11.5$, 1 H), 4.59 (d, $J = 11.5$, 1 H), 4.11 (quint, $J = 5.9$, 1 H), 3.68 (s, 3 H), 2.77-2.59 (m, 4 H). $^{13}\text{C-NMR}$ (50 MHz): 170.3, 137.0, 128.3, 127.8, 127.6, 116.8, 72.0, 71.0, 51.7, 38.5, 22.8. IR: 3546, 3024, 3012, 2952, 2254, 1735.

Enzyme-catalyzed hydrolysis of benzoic acid 2-cyano-1-cyanomethylethyl ester: According to the general procedure of the enzyme-catalyzed hydrolysis of nitriles, benzoic acid 2-cyano-1-cyanomethylethyl ester (50 mg, 0.25 mmol) was incubated with *Rhodococcus erythropolis* NCIMB 11540 whole cells (50 mg) in a potassium phosphate buffer (20 mL) for 50 h. The crude product was immediately methylated with diazomethane and the hydroxy function (due to hydrolysis of the benzoyl ester) was benzoyl-protected for HPLC analysis. After purification by flash chromatography (petroleum ether/EtOAc 3:1, R_f 0.61), (*S*)-benzoic acid 2-cyano-1-methoxycarbonylmethylethyl ester (**17c**) (12 mg, 0.052 mmol, 21% over two steps) was obtained as a red-brown oil. $[\alpha]_D = +26.7$ (CHCl_3 , $c = 0.39$), $ee = 63\%$ (heptane/isopropanol 9:1, flow: 1 mL min^{-1} , rt (*R*) = 15.0 min, rt (*S*) = 19.1 min). $^1\text{H-NMR}$ (200 MHz): 8.04-7.41 (m, 5 H), 5.56 (quint, $J = 5.8$, 1H), 3.71 (s, 3H), 3.05-2.83 (m, 4 H). $^{13}\text{C-NMR}$ (50 MHz): 169.5, 165.2, 133.6, 130.0, 129.7, 128.9, 128.4, 128.3, 115.8, 65.7, 52.1, 37.2, 22.6. IR: 3683, 3620, 3443, 3020, 2976, 2895, 2400, 2252, 1732.