Exploration of Piperidine 3D Fragment Chemical Space: Synthesis and 3D Shape Analysis of Fragments Derived from 20 Regio- and Diastereoisomers of Methyl Substituted Pipecolinates

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1. Experimental Details

1.1. General

All non-aqueous reactions were carried out under oxygen free Ar or N₂ using flame-dried glassware. Et₂O and THF were freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against N-benzylbenzamide before use. Brine refers to a saturated solution. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F₂₅₄ aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in CDCl₃, chemical shifts are quoted in parts per million relative to CHCl₃ (δ_H 7.26) and CDCl₃ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (J) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.
1.2 General Procedures

**General Procedure A: Pyridine methyl ester formation**

Thionyl chloride (0.06-1.45 mL, 0.80-20.0 mmol, 1.1-3.0 eq.) was added dropwise over 5 min to a stirred solution of the carboxylic acid (0.73-10.0 mmol, 1.0 eq.) in MeOH (5-20 mL) at 0 °C under Ar. The resulting solution was stirred and heated at reflux for 1 h or 16 h. The mixture was then allowed to cool to rt and the solvent was evaporated under reduced pressure. And then the mixture was dissolved in CH₂Cl₂ (50 mL) and washed with saturated NaHCO₃(aq) (10 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

**General procedure B: Pyridine hydrogenation and neutralization**

PtO₂ (10-60 mg, 0.05-0.26 mmol, 10-30 mol%) or 10% Pd/C (70 mg, 0.07 mmol, 10 mol%) was added to a stirred solution of pyridine ester (0.45-2.64 mmol) in AcOH (1-5 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H₂ was charged and the reaction mixture was stirred vigorously under a balloon of H₂ for 24 h. The solids were removed by filtration through Celite and washed with MeOH (30 mL). The filtrate was evaporated under reduced pressure to give the crude product. The crude product was dissolved in CH₂Cl₂ (5 mL) and NH₄OH (aq) (2 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

**General Procedure C: Piperidine epimerisation via KOtBu**

\( N\text{-Benzyl}/N\text{-Boc} \) piperidine (50-173 mg, 0.20-0.70 mmol, 1.0 eq.) was added to a flask containing dry THF (3-5 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and the solution was cooled to \(-78 \, ^\circ\text{C}\). KOtBu (0.24-0.84 mL of a 1 M solution in THF, 0.24-0.84 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at \(-78 \, ^\circ\text{C}\) for 2 h. Then, water (1 mL) was added at \(-78 \, ^\circ\text{C}\) and the reaction mixture was allowed to warm to rt. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.
1.3 Experimental Procedures and Characterisation

**Methyl 2-methylpyridine-3-carboxylate 3a**

![Structure of 3a](image)

Using general procedure A, thionyl chloride (0.77 mL, 10.60 mmol, 3.0 eq.) and 2-methyl-nicotinic acid (485 mg, 3.54 mmol, 1.0 eq.) in MeOH (20 mL) gave pyridine 3a (443 mg, 82%) as an orange oil, IR (ATR) 1722 (C=O), 1571, 1433, 1278, 1084, 754 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.61 (dd, J = 5.0, 2.0 Hz, 1H, Ar), 8.19 (dd, J = 8.0, 2.0 Hz, 1H, Ar), 7.21 (dd, J = 8.0, 5.0 Hz, 1H, Ar), 3.92 (s, 3H, OMe), 2.83 (s, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 167.1 (C=O), 160.1 (ipso-Ar), 152.0 (Ar), 138.6 (Ar), 125.5 (ipso-Ar), 121.0 (Ar), 52.4 (OMe), 25.0 (Me); HRMS m/z calcd for C₈H₉NO₂ (M + H)+ 152.0706, found 152.0703 (+1.8 ppm error).

Lab Book – PJ-05-50

**Methyl (2R*,3R*)-2-methylpiperidine-3-carboxylate cis-4a and methyl (2R*,3S*)-2-methylpiperidine-3-carboxylate trans-4a**

![Structure of cis-4a and trans-4a](image)

Using general procedure B, PtO₂ (10 mg, 0.05 mmol, 10 mol%) and pyridine 3a (70 mg, 0.45 mmol, 1.0 eq.) in AcOH (5 mL) gave the crude product which contained a 90:10 mixture of piperidines cis-4a and trans-4a (65 mg, 93%) as a yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 3.68 (s, 3H, OMe), 3.10-3.03 (m, 1H, NCH), 2.96 (qd, J = 7.0, 3.5 Hz, 1H, CHMe), 2.66 (ddd, J = 13.5, 10.0, 3.5 Hz, 1H, NCH), 2.56-2.51 (m, 1H, CHCO₂), 2.02-1.94 (m, 1H, CH), 1.80-1.71 (m, 1H, CH), 1.71-1.60 (m, 2H, CH and NH), 1.42-1.33 (m, 1H, CH), 1.11 (d, J = 7.0 Hz, 2.7H, CHMe), 1.06 (d, J = 6.0 Hz, 0.3H); ¹³C NMR (100.6 MHz, CDCl₃) for cis-4a: δ 174.8 (C=O), 52.4 (CHMe), 51.3 (OMe), 45.3 (NCH₂), 44.1
(CHCO₂), 26.4 (CH₂), 22.8 (CH₂), 19.2 (CHMe). Spectroscopic data consistent with those reported in the literature.¹

The relative stereochemistry of cis-4a and trans-4a has been proven unambiguously in our previous work.²

Methyl (2R*,3R*)-1-benzyl-2-methylpiperidine-3-carboxylate cis-5a and methyl (2R*,3S*)-1-benzyl-2-methylpiperidine-3-carboxylate trans-5a

BnBr (0.14 mL, 1.20 mmol, 3 eq.) was added dropwise to a 90:10 solution of piperidine cis-4a and trans-4a (63 mg, 0.40 mmol, 1.0 eq.) in 1:1 CH₂Cl₂-sat. Na₂CO₃(aq) (4 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (4 × 10 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave N-benzyl piperidine cis-5a (63 mg, 64%) as a colourless oil, Rf (80:20 hexane-EtOAc) 0.13; IR (ATR) 2943, 1732 (C=O), 1138, 732, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 3.66 (d, J = 13.5 Hz, 1H, NCHPh), 3.65 (s, 3H, OMe), 3.54 (d, J = 13.5 Hz, 1H, NCHPh), 3.42 (qd, J = 6.5, 5.0 Hz, 1H, NCHMe), 2.84 (ddd, J = 12.5, 5.0, 5.0 Hz, 1H, CHCO₂), 2.48-2.37 (m, 2H, NCH), 1.82-1.73 (m, 1H, CH), 1.73-1.58 (m, 2H, CH), 1.56-1.45 (m, 1H, CH), 0.91 (d, J = 6.5 Hz, 3H, CHMe);¹³C NMR (100.6 MHz, CDCl₃) δ 174.7 (C=O), 139.8 (ipso-Ph), 128.6 (Ph), 128.4 (Ph), 126.9 (Ph), 59.3 (NCH₂Ph), 54.1 (NCHMe), 51.6 (OMe), 46.1 (CHCO₂), 44.6 (NCH₂), 24.5 (CH₃), 20.7 (CH₃), 6.2 (CHMe); HRMS m/z calcd for C₁₃H₂₁NO₂ (M + H)⁺ 248.1645, found 248.1652 (−2.0 ppm error).

Lab Book – PJ-05-51.
BnBr (0.23 mL, 1.91 mmol, 1.2 eq.) was added dropwise to a 90:10 solution of piperidine cis-4a and trans-4a (250 mg, 1.59 mmol, 1.0 eq.) in 1:1 CH₂Cl₂-sat Na₂CO₃(aq) (6 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (4 × 10 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave a 90:10 mixture N-benzyl piperidine cis-5a and N-benzyl piperidine trans-5a (274 mg, 70%) as a colourless oil.

Lab Book – PJ-06-18.

Using general procedure C, a 90:10 mixture of N-benzyl piperidine cis-5a and trans-5a (150 mg, 0.61 mmol, 1.0 eq.) and KOrBu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq.) in THF (5 mL) gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 80:20 mixture of N-benzyl piperidine cis-5a and trans-5a (61 mg, 41%) and N-benzyl piperidine trans-5a (84 mg, 56%) as a colourless oil, Rf (80:20 hexane-Et₂O) 0.19; IR (ATR) 2943, 2795, 1732 (C=O), 1434, 1138, 732, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 4H, Ph), 7.24-7.20 (m, 1H, Ph), 3.95 (d, J = 13.5 Hz, 1H, NCHPh), 3.67 (s, 3H, OMe), 3.25 (d, J = 13.5 Hz, 1H, NCHPh), 2.76-2.68 (m, 2H, NCHMe and NCH), 2.35 (ddd, J = 10.0, 9.0, 4.0 Hz, 1H, CHCO₂), 2.12-2.04 (m, 1H, NCH), 1.88-1.81 (m, 1H, CH), 1.65-1.56 (m, 2H, CH), 1.51-1.44 (m, 1H, CH), 1.15 (d, J = 6.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 175.7 (C=O), 139.5 (ipso-Ph), 129.0 (Ph), 128.3 (Ph), 126.9 (Ph), 57.6 (NCH₃Ph), 57.2 (CHMe), 51.7 (OMe), 51.2 (NCH₂), 49.5 (CHCO₂), 27.3 (CH₂), 24.0 (CH₂), 17.3 (CHMe); HRMS m/z calcd for C₁₅H₂₂NO₂ (M + H)+ 248.1645, found 248.1646 (-2.9 ppm error).

Lab Book PJ-06-22
PtO$_2$ (114 mg, 0.5 mmol, 10 mol%) was added to a stirred solution of methyl 2-chloro-6-methylpyridine-4-carboxylate 3b (928 mg, 5.0 mmol, 1.0 eq.) in glacial acetic acid (20 mL). The reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of hydrogen was added, and the reaction mixture was stirred vigorously at rt for 16 h. The mixture was filtered through Celite and washed with MeOH (20 mL) and the filtrate was evaporated under reduced pressure to give a >95:5 diastereomeric mixture of crude piperidine cis-4b·AcOH. cis-4b·AcOH was dissolved in CH$_2$Cl$_2$ (30 mL), Et$_3$N (3.48 ml, 25.0 mmol, 5.0 eq.) and Boc$_2$O (1.31 g, 6.0 mmol, 1.2 eq.) were added. The resulting mixture was stirred at rt for 16 h. Then, water (20 mL) and CH$_2$Cl$_2$ (20 mL) were added, and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 85:15 hexane-EtOAc as eluent gave piperidine cis-5b (1.16 g, 90%, >95:5 dr) as a clear oil, $R_f$ (8:2 hexane-EtOAc) 0.24; IR (ATR) 1732 (C=O, Ester), 1686 (C=O, Boc), 1409, 1363, 1198, 1170, 1072, 1051 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.25–4.08 (m, 1H, NCH), 3.83 (ddd, $J$ = 14.0, 6.0, 2.5 Hz, 1H, NCH), 3.70 (s, 3H, CO$_2$Me), 3.08 (ddd, $J$ = 14.0, 12.0, 4.0 Hz, 1H, NCH), 2.69–2.51 (m, 1H, CH), 2.04–1.85 (m, 3H, CH), 1.73 (ddd, $J$ = 13.5, 12.0, 6.0 Hz, 1H, CH), 1.45 (s, 9H, CMe$_3$), 1.07 (d, $J$ = 7.0 Hz, 3H, CHMe); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.8 (CO$_2$Me), 154.9 (CO$_2$CMe$_3$), 79.3 (CMe$_3$), 51.8 (CO$_2$Me), 46.8 (NCH), 35.7 (CH), 35.5 (NCH$_2$), 31.5 (CH$_2$), 28.5 (CMe$_3$), 25.6 (CH$_2$), 17.7 (CHMe); HRMS m/z calcd for C$_{13}$H$_{23}$NO$_4$ (M + Na)$^+$ 280.1519, found 280.1519 (0.0 ppm error). Spectroscopic data consistent with those reported in the literature.$^3$

Lab Book – JDF_B_140

The relative stereochemistry of cis-5b was established through comparison to literature data.$^3$
1,4-Di-tert-butyl (2R*,4S*)-2-methylpiperidine-1,4-dicarboxylate trans-S1 and 1-tert-Butyl 4-methyl (2R*,4S*)-2-methylpiperidine-1,4-dicarboxylate trans-5b

Using general procedure C, N-Boc piperidine cis-5b (100 mg, 0.39 mmol, 1.0 eq.) and KOtBu (470 µL of a 1.0 M solution in THF, 0.47 mmol, 1.2 eq.) in THF (5 mL) gave a 40:60 mixture (by 1H NMR spectroscopy) of trans-S1 and trans-5b as single diastereomers. Purification by flash column chromatography on silica with 90:10 to 80:20 hexane-EtOAc as eluent gave tert-butyl ester trans-S1 (36 mg, 31%) as a clear oil, Rf (9:1 hexane-EtOAc) 0.24; IR (ATR) 1954, 1727 (C=O, ester), 1690 (C=O, Boc), 1412, 1392, 1365, 1335, 1152, 1072 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 4.46 (br s, 1H, NCH), 4.00 (br d, J = 10.5 Hz, 1H, NCH), 2.82 (br t, J = 13.0 Hz, 1H, NCH), 2.56–2.40 (m, 1H, CH), 1.85 (br d, J = 13.0 Hz, 1H, CH), 1.73–1.68 (m, 2H, CH), 1.52–1.45 (m, 1H, CH), 1.45 (s, 9H, CMe3), 1.43 (s, 9H, CMe3), 1.12 (d, J = 7.0 Hz, 3H, CHMe); 13C NMR (101 MHz, CDCl₃) δ 174.5 (CO₂CMe₃), 154.7 (CO₂N), 80.3 (CMe3), 79.3 (CMe3), 45.5 (br, NCH2), 37.6 (br, CH), 37.1 (CH), 32.7 (CH2), 28.4 (CMe3), 28.3 (CH2), 28.0 (CMe3), 15.9 (CHMe); HRMS m/z calcd for C₁₆H₂₉NO₄ (M + Na)⁺ 322.1989, found 322.1985 (+1.1 ppm error) and methyl ester trans-5b (53 mg, 53%) as a clear oil, Rf (9:1 hexane-EtOAc) 0.14; 1958, 1736 (C=O, ester), 1686 (C=O, Boc), 1411, 1365, 1328, 1162, 1125, 1072 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 4.47 (br s, 1H, NCH), 4.00 (br d, J = 10.5 Hz, 1H, NCH), 3.67 (s, 3H, CO₂Me), 2.23 (br t, J = 13.0 Hz, 1H, NCH), 2.70–2.51 (m, 1H, CH), 1.88 (d, J = 13.0 Hz, 1H, CH), 1.77–1.72 (m, 2H, CH), 1.57–1.46 (m, 1H, CH), 1.44 (s, 9H, CMe3), 1.12 (d, J = 7.0 Hz, 3H, CHMe); 13C NMR (101 MHz, CDCl₃) δ 175.5 (CO₂Me), 154.6 (CO₂N), 79.5 (CMe3), 51.8 (CO₂Me), 45.6 (br, NCH), 37.5 (NCH2), 36.2 (br, CH), 32.7 (CH2), 28.4 (CMe3), 28.1 (CH2), 15.8 (CHMe); HRMS m/z calcd for C₁₃H₂₃NO₄ (M + Na)⁺ 280.1519, found 280.1521 (−0.5 ppm error).

Lab Book – JDF_B_280
Methyl (3R*,6S*)-6-methylpiperidine-3-carboxylate cis-4c and methyl (3R*,6R*)-6-methylpiperidine-3-carboxylate trans-4c

Using general procedure B, PtO₂ (60 mg, 0.26 mmol, 10 mol%) and methyl-6-methylnicotinate (400 mg, 2.64 mmol, 1.0 eq.) in AcOH (4 mL) gave the crude product which contained an 85:15 mixture (by ¹H NMR spectroscopy) of piperidines cis-4c and trans-4c (386 mg, 93%) as a colourless oil, ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 2.55 H, OMe), 3.65 (s, 0.45 H, OMe), 3.41 (ddd, J = 13.0, 2.5, 2.5 Hz, 1H, NCH), 2.81 (dd, J = 13.0, 4.0 Hz, 1H, NCH), 2.64 (dqd, J = 13, 6.5, 3.0 Hz, 1H, NCHMe), 2.48-2.44 (m, 1H, CH), 2.20-2.12 (m, 1H, CH), 2.09 (br, 1H, NH), 1.71-1.61 (m, 1H, CH), 1.54 (ddd, J = 13.5, 7.0, 3.5 Hz, 1H, CH), 1.23-1.12 (m, 1H, CH), 1.07-1.02 (m, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 175.2 (C=O), 51.8 (OMe), 51.8 (CH), 47.4 (NCH₂), 39.1 (CH), 31.5 (CH₂), 26.1 (CH₂), 22.7 (Me). Spectroscopic data of cis-4c consistent with those reported in the literature.⁴

Methyl (3R*,6S*)-1-benzyl-6-methylpiperidine-3-carboxylate cis-5c and methyl (3R*,6R*)-1-benzyl-6-methylpiperidine-3-carboxylate trans-5c

BnBr (0.24 mL, 1.99 mmol, 1.2 eq.) was added dropwise to a stirred solution of an 85:15 mixture of piperidines cis-4c and trans-4c (260 mg, 1.66 mmol, 1.0 eq.) in saturated Na₂CO₃(aq) (2 mL) and CH₂Cl₂ (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were
dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave N-benzyl piperidine cis-5c (325 mg, 79%) as a colourless oil, $R_f$ (90:10 hexane-EtOAc) 0.1; IR (ATR) 2947, 1732 (C=O), 1434, 1192, 1149, 697 cm$^{-1}$, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34-7.27 (m, 4H, Ph), 7.22 (m, 1H, Ph), 3.78 (d, $J = 13.5$ Hz, 1H, NCHPh), 3.62 (s, 3H, OMe), 3.37 (d, $J = 13.5$ Hz, 1H, NCHPh), 2.83 (dd, $J = 11.5$, 7.5 Hz, 1H, NCH), 2.74-2.65 (m, 1H, NCHMe), 2.57-2.49 (m, 1H, CHCO$_2$), 2.44 (dd, $J = 11.5$, 4.0 Hz, 1H, NCH), 1.92-1.82 (m, 1H, CH), 1.74-1.63 (m, 2H, CH), 1.57 (m, 1H, CH), 1.06 (d, $J = 6.5$ Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 174.9 (C=O), 139.8 (ipso-Ph), 128.8 (Ph), 128.2 (Ph), 126.9 (Ph), 58.7 (NCH$_2$Ph), 53.9 (NCHMe), 51.5 (OMe), 50.1 (NCH$_2$), 41.3 (CHCO$_2$), 31.1 (CH$_2$), 23.4 (CH$_2$), 14.2 (CHMe); HRMS m/z calcd for C$_{15}$H$_{21}$NO$_2$ (M + H)$^+$ 248.1645, found 248.1636 (+4.1 ppm error).

Lab Book – PJ-06-23

Using general procedure C, N-benzyl piperidine cis-5c (150 mg, 0.61 mmol, 1.0 eq.) and KOTBu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq.) in THF (5 mL) gave a 75:25 mixture (by $^1$H NMR spectroscopy) of N-benzyl piperidines trans-5c and cis-5c. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 85:15 mixture of N-benzyl piperidine cis-5c and trans-5c (43 mg, 28%) as a colourless oil and N-benzyl piperidine trans-5c (80 mg, 53%) as a colourless oil, $R_f$ (80:20 hexane-EtOAc) 0.18; IR (ATR) 2947, 1732 (C=O), 1329, 1144, 697 cm$^{-1}$, $^1$H NMR (400 MHz, CDCl$_3$) δ 4.05 (d, $J = 13.5$ Hz, 1H, NCHPh), 3.58 (s, 3H, OMe), 3.16 (d, $J = 11.5$, 3.5 Hz, 1H, NCH), 2.49 (dd, $J = 11.5$, 3.5 Hz, 1H, NCH), 2.98 (dd, $J = 11.5$, 3.5 Hz, 1H, NCH), 2.49 (dd, $J = 11.5$, 3.5 Hz, 1H, NCH), 1.99-1.92 (m, 1H, CH), 1.74-1.68 (m, 1H, CH), 1.50-1.31 (m, 2H, CH), 1.18 (d, $J = 6.0$ Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 175.0 (C=O), 139.2 (ipso-Ph), 129.1 (Ph), 128.3 (Ph), 126.9 (Ph), 57.9 (NCH$_2$Ph), 56.4 (NCHMe), 54.1 (NCH$_2$), 51.6 (CHCO$_2$), 42.2 (OMe), 34.0 (CH$_2$), 27.7 (CH$_2$), 20.7 (CHMe); HRMS m/z calcd for C$_{15}$H$_{21}$NO$_2$ (M + H)$^+$ 248.1645, found 248.1638 (+2.3 ppm error).

Lab Book – PJ-06-25
Methyl (2R*,6R*)-6-methylpiperidine-2-carboxylate cis-4d

Using general procedure B, PtO$_2$ (30 mg, 0.13 mmol, 10 mol%) and methyl 6-methylpyridine-2-carboxylate (0.18 mL, 1.32 mmol, 1.0 eq.) in AcOH (4.9 mL) gave the crude product which contained (by $^1$H NMR spectroscopy) only piperidine cis-4d (200 mg, 97%) as a colourless oil. IR (ATR) 2929, 1737 (C=O), 1436, 1212, 1056, 735 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.68 (s, 3H, OMe), 3.34 (dd, $J = 11.0$, 3.0 Hz, 1H, NCH$_2$CO$_2$), 2.62 (dqd, $J = 12.5$, 6.5, 2.5 Hz, 1H, NCHMe), 1.99-1.92 (m, 1H, CH), 1.88-1.80 (m, 1H, CH), 1.62-1.54 (m, 1H, CH), 1.45-1.26 (m, 2H, CH), 1.08 (d, $J = 6.5$ Hz, 3H, CHMe), 1.06-0.96 (m, 1H, CH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 173.8 (C=O), 59.4 (NCH), 51.9 (NCHMe), 33.8 (CH$_2$), 29.0 (CH$_2$), 24.6 (CH$_2$), 22.9 (CHMe); HRMS m/z calcd for C$_{8}$H$_{15}$NO$_2$ (M + H)$^+$ 158.1176, found 158.1174 (+1.3 ppm error).

Lab Book – PJ-05-88

The relative stereochemistry of cis-4d has been proven unambiguously in our previous work.$^2$

Methyl (2R*,6R*)-1-benzyl-6-methylpiperidine-2-carboxylate cis-5d

BnBr (0.23 mL, 1.91 mmol, 3.0 eq.) was added dropwise to a stirred solution of a >95:5 mixture of piperidines cis-4d and trans-4d (100 mg, 0.64 mmol, 1.0 eq.) in saturated Na$_2$CO$_3$(aq) (2 mL) and CH$_2$Cl$_2$ (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organics were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave N-benzyl piperidine cis-5d (139 mg, 88%) as a yellow oil, $R_f$ (95:5 hexane-EtOAc) 0.04; IR (ATR) 2932, 1747 (C=O), 1453, 1163, 729, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.27 (m, 4H, Ph), 7.24-7.19 (m, 1H, Ph), 3.84 (d, $J = 15.5$ Hz, 1H, NCHPh), 3.73 (d, $J = 15.5$ Hz, 1H, NCHPh), 3.60 (s, 3H,
OMe), 3.17 (dd, \(J = 10.5, 3.5 \text{ Hz}, 1\text{H, CHCO}_2\)), 2.41 (dq, \(J = 13.0, 6.0, 3.0 \text{ Hz}, 1\text{H, CHMe}\)), 1.85-1.78 (m, 1H, CH), 1.76-1.66 (m, 2H, CH), 1.64-1.56 (m, 1H, CH), 1.46-1.35 (m, 1H, CH), 1.29 (dddd, \(J = 13.0, 8.0, 2.0, 2.0 \text{ Hz}, 1\text{H, CHMe}\)), 1.14 (d, \(J = 6.0 \text{ Hz}, 3\text{H, CHMe}\)); \(^{13}\text{C} \text{ NMR (100.6 MHz, CDCl}_3\)) \(\delta 174.9 \) (C=O), 138.5 (ipso-Ph), 129.2 (Ph), 128.1 (Ph), 126.9 (Ph), 66.0 (NCHCO), 56.4 (CH2Ph), 55.7 (NCHMe), 51.8 (OMe), 34.2 (CH2), 30.3 (CH2), 23.2 (CH2), 21.4 (CHMe); HRMS \(m/z\) calcd for C\(_{15}\)H\(_{21}\)NO\(_2\) (M + H\(^+\)) 248.1645, found 248.1648 (−1.5 ppm error).

Lab Book - PJ-05-91

The stereochemistry of \(\text{cis-5d}\) was established through analysis of the coupling constants from the \(^1\text{H} \text{ NMR spectrum}. \) Proton at C-2 has \(^{3}J_{HH}\) coupling constant of 10.5 Hz and the proton at the C-6 has \(^{3}J_{HH}\) coupling constant of 13.0 Hz which suggests that the protons at the C-2 and C-6 position are axial and therefore confirms the \(\text{cis}\) relative stereochemistry.

\[
\text{cis-5d} \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO}_2\text{Me}
\end{array} \\ J = 13.0 \\
\text{Me} \\
\text{H} \\
\text{N} \\
\text{CO}_2\text{Me}
\] \(J = 10.5\)

\[\begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO}_2\text{Me}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO}_2\text{Me}
\end{array}
\]

\text{Methyl 5-methylpyridine-2-carboxylate 3e}

\[
\text{3e} \quad \begin{array}{c}
\text{N} \\
\text{CO}_2\text{Me}
\end{array}
\]

Using general procedure A, thionyl chloride (1.03 mL, 14.2 mmol, 2.0 eq.) and 5-methylpyridine-2-carboxylic acid (973 mg, 7.10 mmol, 1.0 eq.) in MeOH (20 mL) gave pyridine \(\text{3e}\) (771 mg, 72%) as a white solid; mp 56–57 °C (lit.,\(^5\) mp 54–55 °C); IR (ATR) 1725 (C=O), 1318, 1287, 1250, 1124, 779, 702, 644 cm\(^{-1}\); \(^1\text{H} \text{ NMR (400 MHz, CDCl}_3\)) \(\delta 8.55 \) (d, \(J = 1.5 \text{ Hz}, 1\text{H, Ar}\)), 8.03 (d, \(J = 8.0 \text{ Hz}, 1\text{H, Ar}\)), 7.63 (dd, \(J = 8.0, 1.5 \text{ Hz}, 1\text{H, Ar}\)), 3.98 (s, 3H, CO\(_2\)Me), 2.41 (s, 3H, ArMe); \(^{13}\text{C} \text{ NMR (101 MHz, CDCl}_3\)) \(\delta 165.8 \) (CO\(_2\)Me), 150.3 (Ar), 145.3 (ipso-Ar), 137.4 (ipso-Ar), 137.3 (Ar), 124.8 (Ar), 52.8 (CO\(_2\)Me), 18.6 (ArMe); HRMS \(m/z\) calcd for C\(_8\)H\(_9\)NO\(_2\) (M + H\(^+\)) 152.0706, found 152.0705 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.\(^5\)
Methyl (2\textit{R*},5\textit{R*})-1-benzyl-5-methylpiperidine-2-carboxylate \textit{cis}-5e and methyl (2\textit{R*},5\textit{S*})-1-benzyl-5-methylpiperidine-2-carboxylate \textit{trans}-5e

\[
\begin{align*}
\text{PtO}_2 \ (83 \text{ mg, 0.37 mmol, 10 mol\%}) & \text{ was added to a stirred solution of ester 3e (552 mg, 3.65 mmol, 1.0 eq.) in glacial acetic acid (10 mL). The reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of hydrogen was added, and the reaction mixture was stirred vigorously at rt for 16 h. The mixture was filtered through Celite and washed with MeOH (30 mL), and the filtrate was evaporated under reduced pressure to give a 75:25 mixture of crude diastereomeric piperidines 4e·AcOH (1.14 g). Crude 4e·AcOH was dissolved in CH}_2Cl_2 (10 mL) and sat. Na}_2CO_3 (aq.) (10 mL) and benzyl bromide (478 \mu L, 4.02 mmol, 1.1 eq.) were added. The resulting mixture was stirred at rt for 16 h. Then, water (30 mL) and CH}_2Cl_2 (30 mL) were added, and the two layers were separated. The aqueous layer was extracted with CH}_2Cl_2 (3 × 20 mL). The combined organic layers were dried (MgSO}_4), filtered and evaporated under reduced pressure to give a 75:25 mixture of crude products. Purification by flash column chromatography on silica with 9:1 to 8:2 hexane-Et}_2O as eluent gave piperidine \textit{cis}-5e (631 mg, 70\%) as a clear oil, \textit{R}_F (8:2 hexane-Et}_2O) 0.5; IR (ATR) 2927, 1735 (C=O), 1453, 1193, 1154, 1136, 1004, 735, 698 cm\textsuperscript{-1}; \text{^1H NMR (400 MHz, CDCl}_3) \delta 7.34–7.20 (m, 5H, Ph), 3.81 (d, \textit{J} = 14.0 Hz, 1H, CH}_2Ph), 3.75 (d, \textit{J} = 14.0 Hz, 1H, CH}_2Ph), 3.69 (s, 3H, OMe), 3.49 (dd, \textit{J} = 5.5, 3.0 Hz, 1H, NCH), 2.64 (dd, \textit{J} = 11.0, 11.0 Hz, 1H, NCH), 2.54 (dd, \textit{J} = 11.0, 4.0 Hz, 1H, NCH), 2.00 (ddd, \textit{J} = 13.0, 7.0, 3.5 Hz, 1H, CH), 1.83 (ddddd, \textit{J} = 13.0, 13.0, 5.5, 3.5 Hz, 1H, CH), 1.72–1.52 (m, 3H, CH), 1.12–0.98 (m, 1H, CH), 0.84 (d, \textit{J} = 6.5 Hz, 3H, CH}_Me); \text{^{13}C NMR (101 MHz, CDCl}_3) \delta 174.0 (CO}_2Me), 139.5 (ipso-Ph), 128.5 (Ar), 128.2 (Ar), 126.8 (Ar), 60.0 (NCH), 59.7 (CH}_2Ph), 54.8 (NCH}_2), 50.9 (CO}_2Me), 30.8 (CH), 29.2 (CH}_2), 28.2 (CH}_2), 19.3 (CH}_Me); \text{HRMS m/z calcd for C}_15H}_21NO}_2 (M + H\textsuperscript{+}) 248.1645, found 248.1637 (−3.1 ppm error) and piperidine \textit{trans}-5e (203 mg, 22\%) as a clear oil, \textit{R}_F (8:2 hexane-Et}_2O) 0.25; IR (ATR) 1747 (C=O), 1734, 1274, 1192, 1162, 1112, 738, 698 cm\textsuperscript{-1}; \text{^1H NMR (400 MHz, CDCl}_3) \delta 7.35–7.23 (m, 5H, Ph), 3.79–3.75 (m,}
4H, CO₂Me + CH₂Ph), 3.22 (d, J = 13.0 Hz, 1H, CH₂Ph), 2.91 (dd, J = 11.0, 3.0 Hz, 1H, NCH), 2.82 (ddd, J = 11.0, 3.0, 1.0 Hz, 1H), 1.91 (ddd, J = 12.5, 6.5, 3.0 Hz, 1H, CH), 1.82–1.60 (m, 3H, CH), 1.56 (dd, J = 11.0, 11.0 Hz, 1H, NCH), 0.98–0.84 (m, 1H, CH), 0.79 (d, J = 6.5 Hz, 1H, CHMe); ¹³C NMR (101 MHz, CDCl₃) δ 174.8 (CO₂Me), 137.2 (ipso-Ph), 129.5 (Ph), 128.1 (Ph), 127.1 (Ph), 66.2 (NCH), 60.8 (CH₂Ph), 59.1 (NCH₂), 51.9 (CO₂Me), 32.0 (CH₂), 30.3 (CH), 29.9 (CH₂), 19.4 (CHMe); HRMS m/z caled for C₁₅H₂₁NO₂ (M + H)⁺ 248.1645, found 248.1643 (–0.8 ppm error).

Lab Book – JDF_B_170 and JDF_B_174

The stereochemistry of trans-5e was established through analysis of the coupling constants from the ¹H NMR spectrum. Proton at C-2 has ²J_HH coupling constants of 11.0 and 3.0 Hz and the proton at the C-5 has ³J_HH coupling constant of 11.0 and 3.0 Hz which suggests that the protons at the C-2 and C-5 position are axial and therefore confirms the trans relative stereochemistry.

![Diagram of trans-5e and cis-5e](image)

Using general procedure C, N-benzyl piperidine cis-5e (50 mg, 0.20 mmol, 1.0 eq.) and KOrBu (0.24 mL of a 1 M solution in THF, 0.24 mmol, 1.2 eq.) in THF (3 mL) gave a 50:50 mixture (by ¹H NMR spectroscopy) of N-benzyl piperidines trans-5e and cis-5e. Purification by flash column chromatography on silica with 90:10 hexane-Et₂O as eluent gave N-benzyl piperidine cis-5e (23 mg, 48%) as a colourless oil and N-benzyl piperidine trans-5e (20 mg, 40%) as a colourless oil.

Lab Book – PJ-05-32.
Methyl (2R*,3S*)-3-methylpiperidine-2-carboxylate cis-4f and methyl (2R*,3R*)-3-methylpiperidine-2-carboxylate trans-4f

Using general procedure B, PtO$_2$ (20 mg, 0.10 mmol, 10 mol%) and methyl-3-methylpicolinate (0.13 mL, 0.99 mmol, 1.0 eq.) in AcOH (1.5 mL) gave the crude product which contained an 85:15 mixture (by $^1$H NMR spectroscopy) of piperidines cis-4f and trans-4f (150 mg, 97%) as a colourless oil, IR (ATR) 2929, 1741 (C=O), 1435, 1202, 1005, 758 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.72 (s, 0.45H, OMe), 3.71 (s, 2.55H, OMe), 3.52 (d, $J$ = 3.5 Hz, 0.85H, NCH$_2$CO$_2$), 3.16-3.08 (m, 1H, NCH), 2.96 (d, $J$ = 10.0 Hz, 0.15H, NCH$_2$CO$_2$), 2.65-2.57 (m, 1H, NCH), 2.24-2.13 (m, 1H, CH$_2$Me), 1.68-1.57 (m, 3H, CH), 1.39-1.32 (m, 1H, CH), 0.93 (d, $J$ = 7.0 Hz, 2.55H, CHMe), 0.87 (d, $J$ = 7.0 Hz, 0.45H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) for cis-4f: δ 173.6 (C=O), 62.2 (NCH$_2$CO$_2$), 51.8 (OMe), 46.1 (NCH$_2$), 30.9 (CH$_2$), 30.6 (CHMe), 21.2 (CH$_2$), 13.6 (CHMe); for trans-4f: 66.5 (NCH$_2$CO$_2$), 45.9 (CH$_2$), 34.9 (CH), 33.1 (CH$_2$), 26.7 (CH$_2$), 19.0 (CHMe); HRMS m/z calcd for C$_{18}$H$_{21}$NO$_2$ (M + H)$^+$ 158.1176, found 158.1177 (–1.3 ppm error).

Lab Book – PJ-04-37

The relative stereochemistry of cis-4f and trans-4f has been proven unambiguously in our previous work.$^2$

Methyl (2R*,3S*)-1-benzyl-3-methylpiperidine-2-carboxylate cis-5f and methyl (2R*,3R*)-1-benzyl-3-methylpiperidine-2-carboxylate trans-5f

PhCHO (0.36 mL, 3.5 mmol, 1.1 eq.) was added dropwise to a stirred solution of an 85:15 mixture of piperidines cis-4f and trans-4f (500 mg, 3.18 mmol, 1.0 eq.), NaBH(OAc)$_3$ (1.35 g, 6.37 mmol, 2.0 eq.) and AcOH (0.03 mL, 0.64 mmol, 0.2 eq.) in DCE (30 mL) at rt under Ar. The resulting mixture was
stirred at rt for 18 h. The reaction mixture was poured into sat NaHCO₃(aq) (100 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a green oil which contained a 90:10 mixture (by ¹H NMR spectroscopy) of piperidines cis-5f and trans-5f. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave N-benzyl piperidine cis-5f (626 mg, 80%) as a yellow oil, _R_f_ (95:5 hexane-EtOAc) 0.23; IR (ATR) 2928, 1728 (C=O), 1453, 1148, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.29 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 3.69 (s, 3H, OMe), 3.61 (d, _J_ = 13.5 Hz, 1H, NCHPh), 3.56 (d, _J_ = 13.5 Hz, 1H, NCHPh), 3.45 (d, _J_ = 5.0 Hz, 1H, NCHPh), 3.00-2.92 (m, 1H, NCHPh), 2.54-2.45 (m, 1H, NCH), 2.03-1.93 (m, 1H, CHMe), 1.71-1.64 (m, 1H, CH), 1.60-1.46 (m, 3H, CH), 0.90 (d, _J_ = 7.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 173.0 (C=O), 139.1 (ipso-Ph), 128.9 (Ph), 128.3 (Ph), 127.1 (Ph), 66.2 (NCHCO₂), 60.2 (NCH₂Ph), 50.5 (OMe), 47.0 (NCH₂), 33.2 (CHMe), 27.8 (CH₂), 25.2 (CH₂), 18.2 (CHMe); HRMS m/z calcd for C₁₅H₂₁NO₂ (M + H)+ 248.1645, found 248.1643 (–0.7 ppm error) and piperidine trans-5f (82 mg, 10%) as a yellow oil, _R_f_ (95:5 hexane-EtOAc) 0.1; IR (ATR) 2928, 1727 (C=O), 1453, 1147, 734, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.29 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 3.76 (s, 3H, OMe), 3.71 (d, _J_ = 13.5 Hz, 1H, NCHPh), 3.25 (d, _J_ = 13.5 Hz, 1H, NCHPh), 2.87 (ddd, _J_ = 11.0, 5.5, 5.5 Hz, 1H, NCH), 2.64 (d, _J_ = 9.0 Hz, 1H, NCHCO₂), 1.95-1.86 (m, 2H, CH), 1.76-1.68 (m, 1H, CH), 1.61-1.53 (m, 2H, CH), 1.05-0.94 (m, 1H, CH), 0.90 (d, _J_ = 7.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 174.3 (C=O), 137.7 (ipso-Ph), 129.6 (Ph), 128.3 (Ph), 127.2 (Ph), 73.7 (NCHCO₂), 61.2 (NCH₂Ph), 51.8 (OMe), 51.3 (NCH₂), 34.4 (CHMe), 32.0 (CH₂), 24.6 (CH₂), 18.9 (CHMe); MS (ESI) m/z 248 (M + H)+; HRMS m/z calcd for C₁₅H₂₁NO₂ (M + H)+ 248.1645, found 248.1641 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.⁶

Lab Book – PJ-02-45.

Using general procedure C, N-benzyl piperidine cis-5f (173 mg, 0.70 mmol, 1.0 eq.) and KOtBu (0.84 mL of a 1 M solution in THF, 0.84 mmol, 1.2 eq.) in THF (5 mL) gave a 70:30 mixture (by ¹H NMR spectroscopy) of _N_-benzyl piperidines trans-5f and cis-5f. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave _N_-benzyl piperidine cis-5f (40 mg, 23%) as a colourless oil and _N_-benzyl piperidine trans-5f (104 mg, 60%) as a colourless oil.

Lab Book – PJ-06-08.
Methyl 4-methylpyridine-2-carboxylate 3g

4-Methylpyridine-2-carbonitrile S2 (1.18 g, 10.0 mmol, 1.0 eq.) was suspended in 6M HCl(aq) (10 mL) and the resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. Then, MeCN (20 mL) was added to the residue and the resulting white solid was collected by filtration, washed with MeCN (30 mL) and dried under reduced pressure to give crude carboxylic acid S3·HCl (1.84 g) as a white solid containing ~5% S2. Using general procedure A, thionyl chloride (1.45 mL, 20.0 mmol, 2.0 eq.) and crude S3·HCl (1.84 g, 10.0 mmol max., 1.0 eq.) in MeOH (20 mL) gave pyridine 3g (980 mg, 65%) as a clear oil; 1H NMR (400 MHz, CDCl3) δ 8.57 (d, J = 5.0 Hz, 1H, Ar), 7.96 (s, 1H, Ar), 7.28 (d, J = 5.0 Hz, 1H, Ar), 3.98 (s, 3H, CO2Me), 2.42 (s, 3H, ArMe); 13C NMR (101 MHz, CDCl3) δ 165.9 (CO2Me), 149.5 (Ar), 148.5 (ipso-Ar), 147.7 (ipso-Ar), 127.7 (Ar), 126.0 (Ar), 52.82 (CO2Me), 21.0 (ArMe); HRMS m/z calcd for C8H9NO2 (M + H)+ 152.0706, found 152.0707 (~0.9 ppm error). Spectroscopic data consistent with those reported in the literature.7

Lab Book – JDF_B_143

1-tert-Butyl 2-methyl (2R*,4S*)-4-methylpiperidine-1,2-dicarboxylate cis-5g

PtO2 (68 mg, 0.2 mmol, 10 mol%) was added to a stirred solution of ester 3g (453 mg, 3.0 mmol, 1.0 eq.) in glacial acetic acid (10 mL). The reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of hydrogen was added, and the reaction
mixture was stirred vigorously at rt for 16 h. The mixture was filtered through Celite and washed with MeOH (20 mL) and the filtrate was evaporated under reduced pressure to give crude piperidine cis-4g·AcOH as a single diastereomer. cis-4g·AcOH was dissolved in CH₂Cl₂ (20 mL), Et₃N (2.09 ml, 15.0 mmol, 5.0 eq.) and Boc₂O (785 mg, 3.6 mmol, 1.2 eq.) were added. The resulting mixture was stirred at rt for 16 h. Then, water (20 mL) and CH₂Cl₂ (20 mL) were added, and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave piperidine cis-5g (657 mg, 85%) as a clear oil, Rf (9:1 hexane-EtOAc) 0.17; IR (ATR) 1745 (C=O, ester), 1695 (C=O, Boc), 1393, 1366, 1198, 1154, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.33 (br t, J = 6.0 Hz, 1H, NCH), 3.72 (s, 3H, CO₂Me), 3.53 (br s, 1H, NCH), 3.43–3.34 (br m, 1H, NCH), 2.01–1.92 (m, 1H, CH), 1.89–1.68 (m, 3H, CH), 1.44 (s, 9H, CMe₃), 1.37–1.27 (m, 1H, CH), 0.92 (d, J = 6.5 Hz, 3H, CHMe); ¹³C NMR (101 MHz, CDCl₃) δ 173.4 (CO₂Me), 80.1 (CMe₃), 54.2 (NCH), 52.0 (CO₂Me), 39.0 (NCH₂), 33.2 (CH₂), 30.9 (CH2), 28.3 (CMe₃), 26.1 (CH), 19.0 (CHMe); HRMS m/z calcd for C₁₃H₂₃NO₄ (M + Na)⁺ 280.1519, found 280.1520 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.⁸

Lab Book – JDF_B_146

The relative stereochemistry of cis-5g was established through comparison to literature data.⁸

**1-tert-Butyl 2-methyl (2R*,4R*)-4-methylpiperidine-1,2-dicarboxylate trans-5g**

\[ \text{trans-5g} \]

n-BuLi (155 µL of a 2.5 M solution in hexanes, 0.39 mmol, 2.0 eq.) was added dropwise to a stirred solution of diisopropylamine (55 µL, 0.39 mmol, 2.0 eq.) in THF (30 mL) at −78 °C under N₂. The resulting solution was stirred at −78 °C for 15 min, then warmed to 0 °C and stirred at 0 °C for 30 min. The solution was cooled to −78 °C and a solution of ester cis-5g (50 mg, 0.19 mmol, 1.0 eq.) in THF (2 mL) was added dropwise. The resulting solution was stirred at −78 °C for 2 h, then sat. NH₄Cl(aq) (5 mL) was added, and the resulting mixture warmed to rt. Water (5 mL) and EtOAc (10 mL) were added.
and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give a 80:20 mixture of trans-5g and cis-5g. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave piperidine trans-5g (33 mg, 65%) as a clear oil, \( R_F \) (9:1 hexane-EtOAc) 0.24; IR (ATR) 2929, 2873, 1972, 1745 (C=O, Ester), 1695 (C=O, Boc), 1393, 1365, 1198, 1178, 1158, 1142 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) \( \delta \) 4.92 (d, \( J = 5.0 \text{ Hz} \), 0.5H, NCH), 4.73 (d, \( J = 5.0 \text{ Hz} \), 0.5H, NCH), 4.03 (dd, \( J = 13.5, 3.0 \text{ Hz} \), 0.5H, NCH), 3.92 (dd, \( J = 13.5, 3.0 \text{ Hz} \), 0.5H, NCH), 3.72 (s, 1.5H, CO₂Me), 3.71 (s, 1.5H, CO₂Me), 2.98 (td, \( J = 13.5, 3.0 \text{ Hz} \), 0.5H, NCH), 2.87 (td, \( J = 13.5, 3.0 \text{ Hz} \), 0.5H, NCH), 2.20–2.10 (m, 1H, CH), 1.66–1.53 (m, 1H, CH), 1.46 (s, 4.5H, CMe₃), 1.42 (s, 4.5H, CMe₃), 1.40–1.24 (m, 2H, CH), 1.14–0.98 (m, 1H, CH), 0.91 (d, \( J = 6.0 \text{ Hz} \), 3H, CHMe); \(^{13}\)C NMR (101 MHz, CDCl₃) (mixture of rotamers) \( \delta \) 172.7 (CO₂Me), 172.4 (CO₂Me), 155.9 (CO₂CMe₃), 155.5 (CO₂CMe₃), 80.0 (CMe₃), 55.0 (NCH), 53.9 (NCH), 52.0 (CO₂Me), 41.9 (NCH₂), 41.1 (NCH₂), 34.9 (CH₂), 34.8 (CH₂), 33.4 (CH₂), 33.1 (CH₂), 28.4 (CMe₃), 28.3 (CMe₃), 27.5 (CH), 27.3 (CH), 21.9 (CHMe); HRMS m/z calcd for C₁₃H₂₅NO₄ (M + Na)+ 280.1519, found 280.1522 (0.8 ppm error). Spectroscopic data consistent with those reported in the literature.

Lab Book – JDF_B_157

**Methyl 3-methylpyridine-4-carboxylate 3h**

![3h](image)

Using general procedure A, thionyl chloride (0.23 mL, 3.16 mmol, 1.1 eq.) and 3-methyl-isonicotinic acid (393 mg, 2.87 mmol, 1.0 eq.) in MeOH (20 mL) gave pyridine 3h (345 mg, 80%) as an orange oil, \(^1\)H NMR (400 MHz, MeOH-\( d₄ \)) \( \delta \) 8.66-8.51 (m, 2H, Ar), 7.77 (d, \( J = 5.0 \text{ Hz} \), 1H, Ar), 3.94 (s, 3H, OMe), 2.56 (s, 3H, Me); \(^{13}\)C NMR (100.6 MHz, MeOH-\( d₄ \)) \( \delta \) 167.6 (C=O), 153.2 (Ar), 148.3 (Ar), 138.9 (ipso-Ar), 135.3 (ipso-Ar), 124.7 (Ar), 53.0 (OMe), 18.1 (Me). Spectroscopic data consistent with those reported in the literature.

Lab Book – PJ-04-79.
Methyl (3R*,4R*)-3-methylpiperidine-4-carboxylate cis-4h and methyl (3R*,4S*)-3-methylpiperidine-4-carboxylate trans-4h

Using general procedure B, PtO₂ (24 mg, 0.11 mmol, 10 mol%) and pyridine 3h (163 mg, 1.1 mmol, 1.0 eq.) in AcOH (2 mL) gave the crude product which contained an 85:15 mixture (by ¹H NMR spectroscopy) of piperidines cis-4h and trans-4h (147 mg, 89%) as a colourless oil, IR (ATR) 3319 (NH), 2951, 1726 (C=O), 1434, 1269, 1171 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H, OMe), 3.07 (ddd, J = 12.5, 4.5, 4.5 Hz, 1H, NCH), 2.89-2.76 (m, 2H, NCH, CHCO₂), 2.64-2.56 (m, 2H, NCH), 2.26-2.19 (m, 0.15H, CHMe), 2.14-2.06 (m, 0.85H, CHMe), 1.79 (ddddd, J = 14.5, 10.5, 10.5, 4.0 Hz, 1H, CH), 1.65-1.58 (m, 1H, CH), 1.53 (br s, 1H, NH), 0.94 (d, J = 7.0 Hz, 2.55H, CHMe), 0.82 (d, J = 7.5 Hz, 0.45H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 175.1 (C=O), 52.0 (NCH₂), 51.5 (OMe), 45.4 (NCH₂), 44.7 (CHCO₂), 31.3 (CHMe), 24.5 (CH₂), 13.8 (CHMe); HRMS m/z calcd for C₈H₁₅NO₂ (M + H)⁺ 158.1176, found 158.1178 (−1.3 ppm error).

Lab Book- PJ-05-09

The relative stereochemistry of cis-4h and trans-4h has been proven unambiguously in our previous work.²

1-tert-Butyl 4-methyl (3R*,4R*)-3-methylpiperidine-1,4-dicarboxylate cis-5h and 1-tert-butyl 4-methyl (3R*,4S*)-3-methylpiperidine-1,4-dicarboxylate trans-5h

Et₃N (0.16 mL, 1.16 mmol, 2.0 eq.) was added dropwise to a stirred solution of an 85:15 mixture of piperidines cis-4h and trans-4h (91 mg, 0.58 mmol, 1.0 eq.) and Boc₂O (252 mg, 1.16 mmol, 2.0 eq.)
in CH₂Cl₂ (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 99:1 CH₂Cl₂-acetone as eluent gave an 65:35 mixture (by ¹H NMR spectroscopy) of Boc piperidines cis-5h and trans-5h (20 mg, 14%) as a colourless oil and Boc piperidine cis-5h (73 mg, 49%) as a colourless oil, Rf (99:1 CH₂Cl₂-acetone) 0.14; IR (ATR) 2970, 1733 (C=O, CO₂Me), 1687 (C=O, Boc), 1425, 1161, 880 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 4.12-3.97 (m, 0.6H, NCH), 3.97-3.83 (m, 0.4H, NCH), 3.81-3.72 (m, 1H, NCH), 3.67 (s, 1.8H, OMe), 3.67 (s, 1.2H, OMe), 3.09-3.01 (m, 1H, NCH), 3.00-2.88 (m, 0.4H, NCH), 2.88-2.77 (m, 0.6H, NCH), 2.59 (ddd, J = 10.5, 6.5, 3.0 Hz, 1H, CHCO₂), 2.18 (br m, 1H, CHMe), 1.89-1.76 (m, 1H, CH), 1.75-1.59 (m, 1H, CH), 1.44 (s, 5.4H, CMe₃), 1.43 (s, 3.6H, CMe₃), 0.88 (d, J = 7.0 Hz, 1.8H, CHMe), 0.87 (d, J = 7.0 Hz, 1.2H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 174.4 (C=O, CO₂Me), 155.3 (C=O, Boc), 79.6 (CMe₃), 51.7 (OMe), 49.6 (NCH₂), 48.3 (NCH₂), 44.7 (CHCO₂), 43.0 (NCH₂), 42.3 (NCH₂), 31.3 (CHMe), 28.5 (CMe₃), 23.4 (CH₂), 22.9 (CH₂), 13.2 (CHMe); HRMS m/z calcd for C₁₃H₂₃NO₄ (M + Na)^+ 280.1519, found 280.1517 (+0.6 ppm error).

Lab Book – PJ-05-21

Et₃N (0.16 mL, 1.16 mmol, 2.0 eq.) was added dropwise to a stirred solution of an 85:15 mixture of piperidines cis-5h and trans-5h (91 mg, 0.58 mmol, 1.0 eq.) and Boc₂O (253 mg, 1.16 mmol, 2.0 eq.) in CH₂Cl₂ (5 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 90:10 hexane-Et₂O as eluent gave a 90:10 mixture (by ¹H NMR spectroscopy) of N-Boc piperidines cis-5h and trans-5h (117 mg, 78%) as a colourless oil.

Lab Book – PJ-04-100

Using general procedure C, a 90:10 mixture of N-Boc piperidines cis-5h and trans-5h (50 mg, 0.19 mmol, 1.0 eq.) and KOrBu (0.23 mL of a 1 M solution in THF, 0.23 mmol, 1.2 eq.) in THF (5 mL) gave a 90:10 mixture (by ¹H NMR spectroscopy) of Boc piperidine trans-5h and cis-5h (45 mg, 0.17 mmol, 90%) as a colourless oil, Rf (90:10 hexane-EtOAc) 0.14; IR (ATR) 2931, 1735 (C=O, CO₂Me), 1689 (C=O, Boc), 1420, 1158, 767 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) for trans-5h; δ 4.17-3.92 (m, 2H, NCH), 3.68 (s, 3H, OMe), 2.73-2.63 (m, 1H, NCH), 2.41-2.24 (m, 1H, NCH), 2.08 (ddd, J = 12.0,
11.0, 4.0 Hz, 1H, CHCO₂), 1.87-1.75 (m, 2H, CH and CHMe), 1.69-1.57 (dddd, J = 12.5, 12.5, 12.5, 4.5 Hz, 1H, CH), 1.45 (s, 9H, CMe₃), 0.87 (d, J = 6.5 Hz, 3H, CH₂), 1.69-1.57 (dddd, J = 12.5, 12.5, 12.5, 4.5 Hz, 1H, CH), 1.45 (s, 9H, CMe₃), 0.87 (d, J = 6.5 Hz, 3H, CH₂);

\( ^{13} \text{C NMR (100.6 MHz, CDCl}_3 \) for trans-5h: \( \delta 175.3 \ (\text{C} = \text{O, CO}_2 \text{Me}), 154.7 \ (\text{C} = \text{O, Boc}), 79.8 \ (\text{CMe}_3), 51.8 \ (\text{OMe}), 50.0 \ (\text{NCH}_2), 49.5 \ (\text{CHCO}_2), 43.2 \ (\text{NCH}_2), 33.1 \ (\text{CHMe}), 28.8 \ (\text{CH}_2), 28.6 \ (\text{CMe}_3), 17.1 \ (\text{CHMe}); \) HRMS m/z calcd for C₁₃H₂₃NO₄ (M + Na)\(^{+}\) 280.1519, found 280.1523 (–1.7 ppm error).

Lab Book – PJ-05-17

**Methyl \((3R^*,4R^*)\)-4-methylpiperidine-3-carboxylate cis-4i and methyl \((3R^*,4S^*)\)-4-methylpiperidine-3-carboxylate trans-4i**

Using general procedure B, PtO₂ (45 mg, 0.20 mmol, 30 mol%) and methyl-4-methylnicotinate (100 mg, 0.66 mmol, 1.0 eq.) in AcOH (1 mL) gave the crude product which contained a 65:35 mixture (by \(^1\text{H NMR spectroscopy})\) of piperidines cis-4i and trans-4i (93 mg, 90%) as a yellow oil, IR (ATR) 3314 (NH), 2952, 1726 (C=O), 1435, 1197, 1139, 754 cm\(^{-1}\); \(^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta 3.66 \ (\text{s, 3H, OMe}), 3.20-3.10 \ (\text{m, 1H, NCH}), 3.07-2.96 \ (\text{m, 1H, NCH}), 2.86-2.79 \ (\text{m, 0.65H, NCH}), 2.69-2.57 \ (\text{m, 1.65H, CH}), 2.55-2.50 \ (\text{m, 0.65H, CH}), 2.15 \ (\text{br m, 1H, NH}), 2.12-2.04 \ (\text{m, 0.35H, CH}), 2.04-1.93 \ (\text{m, 0.65H, CH}), 1.83-1.72 \ (\text{m, 0.35H, CH}), 1.66 \ (\text{dddd, J = 7.0, 7.0, 5.0, 2.0, Hz, 0.35H, CH}), 1.59-1.46 \ (\text{m, 1H, CH}), 1.16-1.03 \ (\text{m, 0.35H, CH}), 0.94 \ (\text{d, J = 7.0 Hz, 1.95H, CHMe}), 0.90 \ (\text{d, J = 6.5 Hz, 1.05H, CHMe}); \(^{13} \text{C NMR (100.6 MHz, CDCl}_3 \) \( \delta 174.9 \ (\text{C}=\text{O}), 174.7 \ (\text{C}=\text{O}), 51.6 \ (\text{OMe}), 51.3 \ (\text{OMe}), 49.1 \ (\text{NCH}_2), 46.6 \ (\text{NCH}_2), 46.3 \ (\text{NCH}_2), 45.4 \ (\text{NCH}_2), 44.7 \ (\text{CHCO}_2), 34.4 \ (\text{CH}_2), 33.4 \ (\text{CHMe}), 31.5 \ (\text{CHMe}), 31.2 \ (\text{CH}_2), 20.6 \ (\text{CHMe}), 18.2 \ (\text{CHMe}); \) HRMS m/z calcd for C₈H₁₆NO₂ (M + H)\(^{+}\) 158.1176, found 158.1173 (+1.9 ppm error).

Lab Book – PJ-04-43
1-tert-Butyl 3-methyl 4-methylpiperidine-1,3-dicarboxylate cis-5i and trans-5i

Et₃N (0.14 mL, 0.98 mmol, 2.0 eq.) was added dropwise to a stirred solution of a 65:35 mixture of piperidines cis-4i and trans-4i (77 mg, 0.49 mmol, 1.0 eq.) and Boc₂O (214 mg, 0.98 mmol, 2.0 eq.) in CH₂Cl₂ (5 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave Boc piperidine trans-5i (28 mg, 22%) as a colourless oil, a 65:35 mixture of Boc piperidines cis-5i and trans-5i (22 mg, 18%) and a 90:10 mixture of Boc piperidines cis-5i and trans-5i (67 mg, 54%). The 65:35 and 90:10 mixtures of Boc piperidines cis-5i and trans-5i were combined and purified by flash column chromatography on silica with 98:2 CH₂Cl₂-acetone as eluent to give a 65:35 mixture (by ¹H NMR spectroscopy) of Boc piperidines cis-5i and trans-5i (18 mg, 14%) as a colourless oil and Boc piperidine cis-5i (59 mg, 47%) as a colourless oil, Rₚ (99:1 CH₂Cl₂-acetone) 0.18; IR (ATR) 2971, 1734 (C=O, CO₂Me), 1689 (C=O, Boc), 1422, 1365, 1163, 1138, 866 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.67 (br s, 3H, OMe), 3.61-3.55 (m, 2H, NCH), 3.47-3.40 (m, 1H, NCH), 3.40-3.32 (m, 1H, NCH), 2.60-2.53 (m, 1H, CHCO₂), 2.19-2.10 (m, 1H, CHMe), 1.72-1.64 (m, 1H, CH), 1.61-1.54 (m, 1H, CH), 1.45 (s, 9H, CMe₃), 0.97 (d, J = 7.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 173.2 (C=O, CO₂Me), 154.5 (C=O, Boc), 79.6 (CMe₃), 51.6 (OMe), 44.7 (CHCO₂), 42.9 (CH₂), 40.5 (CH₂), 30.5 (CHMe), 30.3 (CH₂), 28.5 (CMe₃), 15.6 (CHMe); HRMS m/z calcd for C₁₃H₂₃NO₄ (M + Na)+ 280.1519, found 280.1523 (−1.5 ppm error).

Lab Book – PJ-05-15

Et₃N (0.94 mL, 6.78 mmol, 2.0 eq.) was added dropwise to a stirred solution of a 65:35 mixture of piperidines cis-4i and trans-4i (533 mg, 3.39 mmol, 1.0 eq.) and Boc₂O (1.5 g, 6.78 mmol, 2.0 eq.) in CH₂Cl₂ (10 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash
column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 65:35 mixture of Boc piperidines cis-5i and trans-5i (740 mg, 84%) as a colourless oil.

Lab Book – PJ-04-71.

Using general procedure C, a 65:35 mixture of piperidines cis-5i and trans-5i (150 mg, 0.58 mmol, 1.0 eq.) and KOrBu (0.47 mL of a 1 M solution in THF, 0.47 mmol, 1.2 eq.) in THF (9 mL) gave the crude product as an orange oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave Boc piperidine trans-5i (68 mg, 68%) as a colourless oil, Rf (90:10 hexane-Et₂O) 0.19; IR (ATR) 2930, 1733 (C=O, CO₂Me), 1692 (C=O, Boc), 1419, 1241, 1145, 963 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.32-3.98 (m, 2H, NCH), 3.68 (s, 3H, OMe), 2.86-2.61 (m, 2H, NCH and CHCO₂), 2.14-2.05 (m, 1H, NCH), 1.86-1.73 (m, 1H, CHMe), 1.71-1.58 (m, 1H, CH), 1.44 (s, 9H, CMe₃), 1.20-1.05 (m, 1H, CH), 0.92 (d, J = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 174.1 (C=O, CO₂Me), 154.6 (C=O, Boc), 79.9 (CMe₃), 51.7 (OMe), 49.8 (CHCO₂), 46.2 (NCH₂), 44.0 (CH₂), 33.7 (CHMe), 33.0 (CH₂), 28.5 (CMe₃), 20.1 (CHMe); HRMS m/z calcld for C₁₃H₂₃NNaO₄ (M + Na)⁺ 280.1519, found 280.1519 (+0.3 ppm error).

Lab Book – PJ-05-26

The relative stereochemistry of cis-5i and trans-5i has been proven unambiguously in our previous work.

**Methyl 3-methylpyridine-5-carboxylate 3j**

Using general procedure A, thionyl chloride (60 µL, 0.80 mmol, 1.1 eq.) and methyl 3-methylpyridine-5-carboxylate (100 mg, 0.73 mmol, 1.0 eq.) in MeOH (5 mL) gave pyridine 3j (106 mg, 96%) as a white solid, mp 37-39 °C; IR (ATR) 2960, 1712 (C=O), 1574, 1293, 1108, 766 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.03 (d, J = 2.0 Hz, 1H, Ar), 8.61 (d, J = 2.0 Hz, 1H, Ar), 8.13-8.09 (m, 1H,
Supporting Information

Ar), 3.95 (s, 3H, OMe), 2.40 (s, 3H, Me); $^{13}$C NMR (100.6 MHz, MeOH-$d_4$) δ 166.9 (C=O), 154.3 (Ar), 148.2 (Ar), 139.1 (Ar), 135.7 (Ar), 127.5 (Ar), 52.9 (OMe), 18.2 (Me); HRMS m/z calcd for C$_8$H$_9$NO$_2$ (M + H)$^+$ 152.0706, found 152.0702 (+2.7 ppm error). Spectroscopic data consistent with those reported in the literature.$^{11}$

Lab Book – PJ-04-81

Methyl (3R*,5S*)-5-methylpiperidine-3-carboxylate *cis*-4j and methyl (3S*,5S*)-5-methylpiperidine-3-carboxylate *trans*-4j

Using general procedure B, PtO$_2$ (15 mg, 0.066 mmol, 10 mol%) and pyridine 3j (100 mg, 0.66 mmol, 1.0 eq.) in AcOH (5 mL), gave the crude product which contained a 60:40 mixture (by $^1$H NMR spectroscopy) of piperidines *trans*-4j and *cis*-4j (96 mg, 93%) as a colourless oil, IR (ATR) 2951, 1725 (C=O), 1435, 1198, 1177, 860 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.69 (s, 1.8H, OMe), 3.65 (s, 1.2H, OMe), 3.30-3.23 (m, 1H, NCH), 2.97-2.90 (m, 1H, NCH), 2.73 (dd, J = 13.0, 3.5 Hz, 0.6H, NCH), 2.59-2.54 (m, 1H, CHCO$_2$), 2.51-2.43 (m, 0.4H, NCH), 2.24 (dd, J = 13.0, 10.0 Hz, 0.6H, NCH), 2.15-2.04 (m, 1.2H, NCH, CH), 1.69-1.57 (m, 0.6H, CHMe), 1.57-1.47 (m, 0.4H, CHMe), 1.39-1.30 (m, 0.6H, NCH), 1.17 (m, 0.4H, CH), 0.86 (d, J = 6.6 Hz, 1.2H, CHMe), 0.84 (d, J = 6.7 Hz, 1.8H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 175.4 (C=O), 174.7 (C=O), 53.8 (NCH$_2$), 53.7 (NCH$_2$), 51.8 (OMe), 51.7 (OMe), 48.3 (CH$_2$), 47.4 (CH$_2$), 43.4 (CHCO$_2$), 39.7 (CHCO$_2$), 36.2 (CH$_2$), 34.5 (CH$_2$), 31.8 (CHMe), 28.8 (CHMe), 19.5 (CHMe), 19.1 (CHMe); HRMS m/z calcd for C$_8$H$_{13}$NO$_2$ (M + H)$^+$ 158.1176, found 158.1171 (−1.5 ppm error).

Lab Book – PJ-05-28

Using general procedure B, 10% Pd/C (70 mg, 0.07 mmol, 10 mol%) and pyridine 3j (100 mg, 0.66 mmol, 1.0 eq.) in AcOH (5 mL), gave the crude product which contained a 70:30 mixture (by $^1$H NMR spectroscopy) of piperidines *trans*-4j and *cis*-4j (94 mg, 91%) as a colourless oil.
The relative stereochemistry of cis-4j and trans-4j has been proven unambiguously in our previous work.²

Methyl (3R*,5S*)-1-benzyl-5-methylpiperidine-3-carboxylate cis-5j and methyl (3R*,5R*)-1-benzyl-5-methylpiperidine-3-carboxylate trans-5j

BnBr (0.09 mL, 0.76 mmol, 1.2 eq.) was added dropwise to a 70:30 solution of piperidine trans-4j and cis-4j (100 mg, 0.63 mmol, 1.0 eq.) and Et₃N (0.11 mL, 0.79 mmol, 1.2 eq.) in CH₂Cl₂ (4 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (4 × 10 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave N-benzyl piperidine trans-5j (77 mg, 51%) as a colourless oil, Rₚ (90:10 hexane-EtOAc) 0.14; IR (ATR) 2949, 1732 (C=O), 1453, 1199, 1150, 697 cm⁻¹; ¹H NMR (400 MHz,CDCl₃) δ 7.31-7.28 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 3.67 (s, 3H, OMe), 3.56 (d, J = 13.5 Hz, 1H, NC₃H₇Ph), 3.39 (d, J = 13.5 Hz, 1H, NC₃H₇Ph), 2.96-2.88 (m, 1H, NCH), 2.69-2.63 (m, 1H, CHCO₂), 2.63-2.57 (m, 1H, NCH), 2.31-2.23 (m, 1H, NCH), 2.06-1.94 (m, 2H, CHMe and CH), 1.91-1.83 (m, 1H, NCH), 1.24-1.14 (m, 1H, CH), 0.92 (d, J = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 174.9 (C=O), 138.8 (ipso-Ph), 128.9 (Ph), 128.2 (Ph), 127.0 (Ph), 63.1 (CH₂Ph), 61.3 (NCH₂), 54.9 (NCH₂), 51.6 (OMe), 39.7 (CHCO₂), 33.4 (CH₂), 28.1 (CHMe), 19.2 (CHMe); HRMS m/z calcd for C₁₅H₂₁NO₂ (M + H)⁺ 248.1645, found 248.1646 (‒0.9 ppm error) and N-benzyl piperidine cis-5j (27 mg, 17%) as a colourless oil, Rₚ (90:10 hexane-EtOAc) 0.05; IR (ATR) 2951, 1732 (C=O), 1434, 1136, 1154, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.29 (m, 4H, Ph), 7.280-7.24 (m, 1H, Ph), 3.64 (s, 3H, OMe), 3.52 (s, 2H, NCH₂Ph), 3.12-3.06 (m, 1H, NCH), 2.84-2.79 (m, 1H, NCH), 2.64 (dddd, J = 12.0, 12.0, 4.0, 4.0 Hz, 1H, CHCO₂), 2.04-
1.98 (m, 1H, CH), 1.95 (dd, \( J = 12.0, 12.0 \) Hz, 1H, NCH), 1.78-1.66 (m, 1H, CHMe), 1.55 (d, \( J = 12.0 \) Hz, 1H, NCH), 1.02 (ddd, \( J = 12.0, 12.0, 12.0 \) Hz, 1H, CH), 0.87 (d, \( J = 6.5 \) Hz, 3H, CHMe); \(^{13}\)C NMR (100.6 MHz, CDCl:\(_3\) \( \delta \) 174.9 (C=O), 140.1 (ipso-Ph), 129.2 (Ph), 128.4 (Ph), 127.1 (Ph), 63.2 (CH\(_2\)Ph), 61.2 (NCH\(_2\)), 55.1 (NCH\(_2\)), 51.7 (OMe), 42.3 (CHCO\(_2\)), 35.9 (CH\(_2\)), 30.6 (CHMe), 19.5 (CHMe); HRMS \( m/z \) calcd for C\(_{15}\)H\(_{21}\)NO\(_2\) (M + H\(^+\)) 248.1645, found 248.1647 (1.1 ppm error).

Lab Book – PJ-06-36

Using general procedure C, piperidine trans-5j (150 mg, 0.61 mmol, 1.0 eq.) and KOrBu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq.) in THF (5 mL) gave a crude 85:15 mixture (by \(^1\)H NMR spectroscopy) of N-benzyl piperidines cis-5j and trans-5j (149 mg). Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave N-benzyl piperidine cis-5j (93 mg, 62%) as a yellow oil.

Lab Book – PJ-06-16

The stereochemistry of cis-5j was established through analysis of the coupling constants from the \(^1\)H NMR spectrum. Proton at C-4 has \( J_{HH} \) geminal coupling constants of 12.0 Hz and \( J_{HH} \) coupling constants of 12.0 Hz and 12.0 Hz which shows that the protons at the C-3 and C-5 position are axial and therefore confirms the cis relative stereochemistry.
**tert-Butyl 2-methylpiperidine-1-carboxylate 7a**

2-Methyl piperidine (5.0 mL, 42.5 mmol, 1.0 eq.) was added dropwise to a stirred solution of di-tert-butyl dicarbonate (10.2 g, 46.8 mmol, 1.1 eq.) in CH$_2$Cl$_2$ (200 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. H$_2$O (20 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 90:10 petrol-Et$_2$O as eluent gave N-Boc methyl piperidine 7a (7.6 g, 82%) as a colourless oil, $R_f$ (90:10 petrol-Et$_2$O) 0.3; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.41-4.30 (m, 1H, NCH), 3.90 (dd, $J$ = 13.5, 3.0 Hz, 1H, NCH), 2.79 (ddd, $J$ = 13.5, 13.5, 2.5 Hz, 1H, NCH), 1.68-1.45 (m, 5H CH), 1.44 (s, 9H, CMe$_3$), 1.40-1.32 (m, 1H, CH), 1.10 (d, $J$ = 7.0 Hz, 3H, Me); $^{13}$C NMR (101.6 MHz, CDCl$_3$) δ 155.0 (C=O), 79.0 (CMe$_3$), 46.0 (NCH), 38.6 (NCH$_2$), 30.1 (CH$_2$), 28.5 (CMe$_3$), 25.7 (CH$_2$), 18.7 (CH$_2$), 15.7 (Me). Spectroscopic data consistent with those reported in the literature.$^{12}$

**Lab Book – MCW/2/2**

**($2R^*,6S^*$)-1-(tert-Butoxycarbonyl)-6-methylpiperidine-2-carboxylic acid trans-8d**

$s$-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of N-Boc piperidine 7a (199 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq.) in Et$_2$O (7 mL) at −40 °C under Ar. The resulting yellow solution was stirred at −40 °C for 1.5 h. Then, CO$_2$ (excess) was bubbled through the reaction mixture at −40 °C for 10 min. H$_2$O (10 mL) was added. 1 M HCl$_{(aq)}$ (15 mL) was added, and the mixture extracted with Et$_2$O (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 90:10 CH$_2$Cl$_2$-Et$_2$O and 0.5% acetic acid and then
70:30 CH₂Cl₂-Et₂O and 0.5% acetic acid as eluent gave piperidine carboxylic acid trans-8d (199 mg, 82%) as a white solid, mp 82-84 °C; Rₚ (90:10 CH₂Cl₂-Et₂O) 0.2; IR (ATR) 2977, 2944, 1698 (C=O), 1445, 1380, 1227, 868, 779, 512 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.24-4.18 (m, 1H, NCH), 4.18 (dd, J = 7.0, 5.0 Hz, 1H, NCH), 2.09-1.80 (m, 3H, CH), 1.69-1.49 (m, 3H, CH), 1.45 (s, 9H, CMe₃), 1.18 (d, J = 7.0 Hz, 3H, Me); ¹³C NMR (101.6 MHz, CDCl₃) δ 178.3 (C=O, CO₂Me), 156.4 (C=O, Boc), 80.9 (CMe₃), 53.8 (NCH), 47.6 (NCH), 28.3 (CMe₂), 27.7 (CH₂), 25.6 (CH₂), 18.8 (Me), 15.0 (CH₂); HMRS (ESI) m/z calcd for C₁₂H₂₁NO₄ (M + Na)⁺ 266.1363, found 266.1355 (+2.9 ppm error).

Lab Book Reference: MCW/3/57/2

The relative stereochemistry of cis-8d has been proven unambiguously in our previous work.²

(2R*,6S*)-1-tert-Butyl 2-methyl 6-methylpiperidine-1,2-dicarboxylate trans-5d

Potassium carbonate (2.56 g, 18.5 mmol, 3.0 eq.) was added to a stirred solution of piperidine carboxylic acid trans-8d (1.50 g, 61.7 mmol, 1.0 eq.) in dimethylformamide (20 mL) at rt under Ar. The resulting suspension was stirred at rt for 30 min before the addition of methyl iodide (1.15 mL, 18.5 mmol, 3.0 eq.). The mixture was then stirred at rt for 18 h. The solvent was evaporated under reduced pressure and H₂O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 10% Na₂S₂O₃(aq) (15 mL) and the mixture extracted with EtOAc (20 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 80:20 hexane-Et₂O as eluent gave piperidine methyl ester trans-5d (1.55 g, 97%) as a yellow oil, Rₚ (80:20 hexane-Et₂O) 0.2; IR (ATR) 2972, 2950, 1746 (C=O, CO₂Me), 1692 (C=O, Boc), 1390, 1364, 1163, 1112, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.26-4.17 (m, 1H, NCH), 4.12 (dd, J = 7.0, 5.0 Hz, 1H, NCH), 3.72 (s, 3H, OMe), 2.04-1.92 (m, 1H, CH), 1.91-1.78 (m, 2H, CH), 1.67-1.48 (m, 3H, CH), 1.43 (s, 9H, CMe₃), 1.16 (d, J = 7.0 Hz, 3H, Me); ¹³C NMR (101.6 MHz, CDCl₃) δ 173.8 (C=O, CO₂Me), 156.0 (C=O, Boc), 80.1 (CMe₂), 54.1 (NCH), 52.0 (OMe), 47.5 (NCH), 28.3 (CMe₂),
28.0 (CH$_2$), 26.2 (CH$_2$), 18.8 (Me), 15.5 (CH$_2$); MS (ESI) m/z 280 [(M + Na)$^+$, 100], 258 [(M + H)$^+$, 15]; HMRS (ESI) m/z calcd for C$_{13}$H$_{23}$NO$_4$ (M + Na)$^+$ 280.1519, found 280.1507 (+4.2 ppm error).

Lab Book Reference: mcw/3/59/1

tert-Butyl 3-methylpiperidine-1-carboxylate 7b

A solution of Boc$_2$O (1.3 g, 6.0 mmol, 1.2 eq.) in CH$_2$Cl$_2$ (5 mL) was added dropwise to a stirred solution of piperidine (0.59 mL, 5.0 mmol, 1.0 eq.), and Et$_3$N (2.1 mL, 15.0 mmol, 3.0 eq.) in CH$_2$Cl$_2$ (15 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 99:1 hexane-EtOAc as eluent gave N-Boc piperidine 7b (975 mg, 98%) as a colourless oil, $R_F$ (99:1 hexane-EtOAc) 0.1; IR (ATR) 2959, 1690 (C=O), 1416, 1149, 1075, 969 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.07-3.74 (m, 2H, NCH), 2.68 (ddd, $J$ = 13.0, 11.5, 3.0 Hz, 1H, NCH), 2.49-2.21 (m, 1H, CH), 1.80-1.71 (m, 1H, CH), 1.68-1.50 (m, 2H, NCH and CHMe), 1.45 (s, 9H, CMe$_3$), 1.43-1.35 (m, 1H, CH), 1.09-0.97 (m, 1H, CH), 0.86 (d, $J$ = 6.5 Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.1 (C=O), 79.3 (CMe$_3$), 51.5 (NCH$_2$), 50.8 (NCH$_2$), 44.5 (NCH$_2$), 43.8 (NCH$_2$), 33.1 (CH$_2$), 31.1 (CHMe), 28.6 (CMe$_3$), 25.3 (CH$_2$), 19.1 (CHMe); HRMS m/z calcd for C$_{11}$H$_{21}$NO$_2$ (M + Na)$^+$ 222.1464, found 222.1471 (–3.8 ppm error).

Lab Book - PJ-05-79
(2R*,5S*)-1-[(tert-Butoxy)carbonyl]-5-methylpiperidine-2-carboxylic acid trans-8e and (2R*,5R*)-1-[(tert-butoxy)carbonyl]-5-methylpiperidine-2-carboxylic acid cis-8e

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added drop wise to a stirred solution of N-Boc piperidine 7b (199 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq.) in Et₂O (4 mL) at −60 °C under Ar. The resulting solution was stirred at −60 °C for 3 h. Then, CO₂ (excess) was bubbled through the reaction mixture at −60 °C for 10 min. 1 M HCl\textsubscript{(aq)} (10 mL) was added, and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 99:1 to 98:2 CH₂Cl₂-acetic acid as eluent gave a 90:10 mixture of piperidine carboxylic acid trans-8e and cis-8e (140 mg, 57 %) as a white solid, m.p 99-101 °C; \( R_f \) (95:5 CH₂Cl₂-AcOH) 0.22; IR (ATR) 2936, 1725 (C=O, CO₂H), 1622 (C=O, Boc), 1438, 1365, 1151, 850 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃) trans-8e: \( \delta \) 11.56-10.82 (m, 1H, CO₂H), 4.97-4.51 (m, 1H, NCHCO₂), 3.69-3.45 (m, 1H, NCH), 3.18 (dd, \( J = 13.0, 3.0 \) Hz, 1H, NCH), 1.97-1.93 (m, 2H, CH₂), 1.92-1.82 (m, 1H, CHMe), 1.68-1.54 (m, 1H, CH), 1.53-1.34 (m, 10H, CMe₃ and CH), 0.97 (d, \( J = 7.0 \) Hz, 2H, CHMe); \(^{13}\)C NMR (100.6 MHz, CDCl₃) \( \delta \) 178.0 (C=O, CO₂H), 156.5 (C=O, Boc), 80.5 (CMe₃), 53.9 (NCHCO₂), 47.5 (NCH₂), 28.4 (CMe₃), 27.1 (CHMe), 27.0 (CH₂), 21.6 (CH₂), 16.7 (CHMe); HRMS \( m/z \) calcd for C₁₂H₂₁NO₄ (M + Na)⁺ 266.1363, found 266.1367 (−3.8 ppm error). Spectroscopic data consistent with those reported in the literature.\(^{13}\)

Lab Book - PJ-05-90

The relative stereochemistry of trans-8e was established through comparison to literature data.\(^{13}\)
1-tert-Butyl 2-methyl (2$R^*$,5$S^*$)-5-methylpiperidine-1,2-dicarboxylate dicarboxylate trans-S4 and 1-tert-Butyl 2-methyl (2$R^*$,5$R^*$)-5-methylpiperidine-1,2-dicarboxylate cis-S4

Potassium carbonate (86 mg, 0.62 mmol, 3.0 eq.) was added to a stirred solution of piperidine carboxylic acid trans-8e (50 mg, 0.21 mmol, 1.0 eq.) in dimethylformamide (3 mL) at rt. The resulting suspension was stirred at rt for 30 min before the addition of methyl iodide (0.038 mL, 0.62 mmol, 3.0 eq.). The mixture was then stirred at rt for 18 h. The reaction mixture was taken up into water (3 mL) and extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (4 × 5 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 90:10 hexane-EtOH as eluent gave a 90:10 mixture of piperidine ester trans-S4 and cis-S4 (47 mg, 87%) as a yellow oil, $R_f$ (90:10, hexane-EtOH) 0.17; IR (ATR) 2940, 1743 (C=O, CO$_2$Me), 1690 (C=O, Boc), 1363, 1147, 864 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.86-4.59 (m, 1H, NCHCO$_2$Me), 3.72 (s, 3H, OMe), 3.64-3.55 (m, 1H, NCH), 3.20-3.11 (m, 1H, NCH), 1.97-1.90 (m, 2H, CH), 1.90-1.83 (m, 1H, CHMe), 1.59-1.50 (m, 1H, CH), 1.44 (s, 9H, CMe$_3$), 1.41-1.32 (m, 1H), 0.98 (d, $J = 7.0$ Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 172.7 (C=O, CO$_2$Me), 156.3 (C=O, Boc), 80.1 (CMe$_3$), 54.5 (NCHCO$_2$), 52.2 (OME), 47.3 (NCH$_2$), 28.4 (CMe$_3$), 27.2 (CHMe), 27.1 (CH$_2$), 21.8 (CH$_2$), 16.7 (CHMe); HRMS $m/z$ calcd for C$_{13}$H$_{23}$NNaO$_4$ (M + Na)$^+$ 280.1519, found 280.1525 (−2.0 ppm error).

Lab Book – PJ-05-95
Methyl (2\textsuperscript{R*},5\textsuperscript{R*})-1-benzyl-5-methylpiperidine-2-carboxylate \textit{cis}-5\text{e} and methyl (2\textsuperscript{R*},5\textsuperscript{S*})-1-benzyl-5-methylpiperidine-2-carboxylate \textit{trans}-5\text{e}

TFA (1 mL) was added to a stirred solution of a 90:10 mixture of piperidine ester \textit{trans}-S\text{4} and \textit{cis}-S\text{4} (47 mg, 0.18 mmol, 1.0 eq.) in \text{CH}_2\text{Cl}_2 (5 mL) at 0 °C under Ar. The resulting solution was warmed to rt and stirred for 3 h at rt, then evaporated under reduced pressure. The residue was dissolved in \text{CH}_2\text{Cl}_2 (2 mL) and sat \text{Na}_2\text{CO}_3(\text{aq}) (2 mL) and benzyl bromide (0.06 mL, 0.54 mmol, 3.0 eq.) were added. The resulting mixture was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with \text{CH}_2\text{Cl}_2 (3 \times 5 \text{ mL}). The combined organics were dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave N-benzyl piperidine \textit{cis}-5\text{e} (4 mg, 7%) as a colourless oil and N-benzyl piperidine \textit{trans}-5\text{e} (38 mg, 85%) as a colourless oil.

Lab Book – PJ-05-98.
2. Isomers of dimethyl pyridine 1 and dimethyl NH piperidine 2

Figure S1. Isomers of dimethyl pyridine 1 and dimethyl NH piperidine 2.
3. Virtual Library Analysis

3.1. Principle Moments of Inertia and Molecular Properties

**Shape analysis**

3-Dimensional structures of piperidines 6a-6d were generated Pipeline Pilot 16.5.0.143, 2016, Accelrys Software Inc. Prior to conformer generation a wash step was performed, which involved stripping salts and ionising the molecule at pH 7.4. SMILES strings were converted to their canonical representation and the original stereochemistry at each chiral centre was recorded. Any stereocentre created during the ionisation would have undefined stereochemistry. A SMILES files was written that contained all possible stereoisomers of the molecule. Conformers were generated using Catalyst with the BEST conformational analysis method and relative stereochemistry. Catalyst was run directly on the server and not through the built-in Conformation Generator component. The maximum relative energy threshold was left at the default 20 kcal mol⁻¹ and a maximum of 255 conformers were generated for each compound. The aim of this was to give the best possible coverage of conformational space. The resulting conformations from Catalyst were read and only those where the stereochemistry matched the original molecule or its enantiomer were kept. These were then all standardised to the original stereochemistry by mirroring the coordinates of the enantiomers. Duplicate conformations were filtered with a RMSD threshold of 0.1. Each conformation was minimised using 200 steps of Conjugate Gradient minimisation with an RMS gradient tolerance of 0.1. This was performed using the CHARMm forcefield with Momany-Rone partial charge estimation and a Generalised Born implicit solvent model. After minimisation, duplicates were filtered again with a RMSD threshold of 0.1. The lowest energy conformer of each molecule was selected and the generated conformations were used to generate the three Principal Moments of Inertia (I₁, I₂ and I₃) which were then normalised by dividing the two lower values by the largest (I₁/I₃ and I₂/I₃) using Pipeline Pilot built-in components.

3-Dimensional structures of pyridines 3 were generated using RDKIT v4.5 in KNIME v4.4.1. A maximum of 50 conformers were generated for each molecule and the geometry of each was optimised using MMFF94 force field with 1000 iterations. Prior to calculation, salts were stripped and explicit hydrogens added. The lowest energy conformer of each molecule was selected and the three Principal Moments of Inertia calculated using Vernalis PMI KNIME nodes.

Principal moments of inertia (PMI) about the principal axes of a molecule were calculated according to the following rules:
1. The moments of inertia are computed for a series of straight lines through the centre of mass.

2. Distances are established along each line proportional to the reciprocal of the square root of I on either side of the centre of mass. The locus of these distances forms an ellipsoidal surface. The principal moments are associated with the principal axes of the ellipsoid.

**Molecular properties**

Heavy atom count (HAC) was calculated using RDKit v3.4 in KNIME v3.5.2. Prior to calculation, salts were stripped. ClogP values were calculated using Daylight/BioByte ClogP v4.3.

**3.2 Virtual Library Enumeration and Lead-Likeness Analysis**

To assess the suitability of our piperidines for the generation of lead-like compounds we used the open access tool LLAMA.\textsuperscript{14,15} Using our deprotected piperidines (as amino acids) as scaffolds, LLAMA computationally decorated (once or twice) the amine and acid functionalities and analysed the resulting virtual molecules for their lead-likeness (for leading examples of lead-oriented synthesis see\textsuperscript{16–19}). LLAMA generated 1599 virtual compounds from our 20 deprotected piperidines. The default set of capping groups was used, and of the standard decoration reactions, “Secondary amide alkylation” and “Secondary amide arylation” were disabled to prevent two diversification events occurring at the same diversification point of the scaffolds.

Of the 1599 virtual compounds, 78% fell within lead-like space (defined as molecular weight between 200 and 350, and AlogP between -1 and 3)\textsuperscript{14} (Figure S2). For comparison, only 23% of the ZINC database of commercially available screening compounds fall within lead-like space.\textsuperscript{14,17} LLAMA also generates a lead-likeness penalty (LLP) score for each molecule (the lower the better), considering the number of aromatic rings and the presence of unwanted structural features as well as molecular weight and AlogP. Our virtual library had a mean LLP of 1.02 (\textit{cf}. 4.17 for ZINC) indicating that compounds derived from di-substituted piperidines 5 would be highly lead-like. Furthermore, analysis of the degree of saturation of the virtual library showed that it had a mean Fsp\textsuperscript{3} of 0.62, whereas the mean value for the Zinc library is only 0.33.
Figure S2. Molecular properties of the virtual lead-like library (coloured per lead likeness penalty: 0, green; 3, orange; 6+ red).
4. $^1$H and $^{13}$C NMR Spectra

400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
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400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
Supporting Information

400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; MeOH-$d_4$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
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400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; CDCl$_3$ 100.6 MHz $^{13}$C NMR spectrum; MeOH-$d_4$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
400 MHz $^1\text{H}$ NMR spectrum; 100.6 MHz $^{13}\text{C}$ NMR spectrum; CDCl$_3$
400 MHz $^1$H NMR spectrum; 100.6 MHz $^{13}$C NMR spectrum; CDCl$_3$
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