Ammonium-directed dihydroxylation: metal-free synthesis of the diastereoisomers of 3-amino-cyclohexane-1,2-diol

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Experimental

General Experimental

Reactions involving moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers. Water was purified by an Elix UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over MgSO₄. Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm), iodine, 1% aq KMnO₄, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

(1RS,2RS,3RS)-1-p-Toluenesulphonyloxy-2-acetoxy-3-N,N-dibenzylaminocyclohexane 10

Ac₂O (0.26 mL, 2.74 mmol) and DMAP (50 mg) were added sequentially to a stirred solution of 3 (851 mg, 1.83 mmol, >98% de) in DCM/pyridine (1:1, 40 mL). The resultant solution was stirred at rt for 24 h before being cooled to 0 °C. H₂O (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed sequentially with 10% aq. CuSO₄ (2 × 100 mL), 0.1 M aq. NaHCO₃ (2 × 100 mL) and brine (100 mL), dried, and concentrated in vacuo to give 10 as a colourless oil (928 mg, quant, >98% de);

ν_max (film) 2944 (C−H), 1746 (C=O);

δ_H (400 MHz, CDCl₃) 1.47-1.88 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂), 1.99 (3H, s, CO₂Me), 2.48 (3H, s, ArCH₃), 2.94-3.04 (1H, m, C(3)H), 3.64 (4H, AB system, N(C₄H₂Ph)₂), 4.60-4.65 (1H, br m, C(1)H), 5.05-5.09 (1H, br m, C(2)H), 7.13-7.51 (12H, m, Ar, Ph), 7.64 (2H, d, J 7.6, Ar); δ_C (400 MHz, CDCl₃) 19.5, 21.2, 21.8, 22.8, 26.2 (C(4), C(5), C(6), CO₂Me, ArCH₃), 53.6 (C(3)), 55.0 (N(CH₂Ph)₂), 71.1 (C(2)), 78.1 (C(1)), 126.8, 127.8, 128.2, 128.4, 129.8, 133.7, 140.2, 144.7 (Ar, Ph), 169.7 (C=O); m/z (ESI⁺) 508 ([M+H]⁺, 100%), 396 (50%); HRMS (ESI⁺) C₂₉H₃₄N₂O₅S⁺ ([M+H]⁺) requires 508.2152; found 508.2153.

(1RS,2SR,3SR)-3-N,N-dibenzylaminocyclohexane-1,2-diol 11

Method A: CaCO₃ (1.88 g, 18.8 mmol) was added to a stirred solution of 10 (9.93 g, 18.8 mmol, 90% de) in EtOH/H₂O (6:1, 236 mL) and the resultant suspension was heated at reflux for 48 h. The reaction mixture was concentrated in vacuo. H₂O (200 mL) was added to the residue and the mixture was extracted with DCM (3 × 200 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in MeOH (50 mL) and K₂CO₃ (200 mg) was added. The resulting suspension was stirred at rt for 16 h then concentrated in vacuo. H₂O (100 mL) was added and the mixture was extracted with DCM (3 × 200 mL). The combined organic extracts were washed sequentially with H₂O (2 × 250 mL) and brine (250 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 5%→100% EtOAc in 40-60 °C petrol) gave 14 as a pale yellow solid (215 mg, 4%, >98% de); mp 103-104 °C; ν_max (KBr) 3449 (O−H), 2936 (C−H); δ_H (400 MHz, CDCl₃) 1.22-1.47 (2H, m, C(4)H₆, C(6)H₆), 1.57-1.81 (2H, m, C(5)H₆), 1.88-2.09 (2H, m, C(4)H₆, C(6)H₆), 2.41 (2H, br s, 2 × OH), 2.91-3.05 (1H, m, C(3)H), 3.44 (2H, d, J 13.4, N(CH₃H₃Ph)₂), 3.52 (1H, dd, J 10.1, 3.0, C(2)H), 3.88 (2H, d, J 13.4, N(CH₃H₃Ph)₂), 4.14 (1H, q, J 3.0, C(1)H), 7.24-7.49 (10H, m, Ph); δ_C (100 MHz, CDCl₃) 19.5 (C(5)), 22.1
(C(4)), 29.6 (C(6)), 53.1, 53.6 (N(CH₂Ph)₂), 57.4 (C(3)), 68.3 (C(1)), 71.0 (C(2)), 128.2 (p-Ph), 128.5, 128.9 (o-, m-Ph), 139.3 (i-Ph); m/z (ESI⁺) 312 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₂⁺ ([M+H]⁺) requires 312.1958; found 312.1950. Further elution gave 11 as a pale yellow solid (3.48 g, 60%, >98% de); mp 62-63 °C; νmax (KBr) 3416 (O−H), 2936 (C−H); δH (400 MHz, CDCl₃) 1.07-1.22 (1H, m, C(5)Hₐ), 1.52-1.82 (5H, m, C(4)H₂, C(5)Hₐ, C(6)H₂), 2.55-2.64 (1H, m, C(3)H), 2.80 (2H, br s, 2 × OH), 3.42 (1H, ddd, J₁₁.₄, 5.₀, 2.₇, C(1)H), 3.81 (2H, d, J₁₆.₀, N(CH₂Ph)₂), 3.93 (2H, d, J₁₆.₀, N(CH₂Ph)₂), 4.25-4.29 (1H, m, C(2)H), 7.22-7.41 (10H, m, Ph); δC (100 MHz, CDCl₃) 22.0, 22.1 (C(4), C(5)), 28.4 (C(6)), 55.1 (N(CH₂Ph)₂), 60.6 (C(3)), 71.5, 71.8 (C(1), C(2)), 126.8 (p-Ph), 128.3, 128.4 (o-, m-Ph), 140.6 (i-Ph); m/z (ESI⁺) 312 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₂⁺ ([M+H]⁺) requires 312.1958; found 312.1956. Further elution gave 5 as a viscous, pale yellow oil (760 mg, 13%, >98% de).

Method B: KOAc (216 mg, 2.21 mmol) was added to a stirred solution of 10 (747 mg, 1.47 mmol, >98% de) in EtOH/H₂O (6:1, 40 mL) and the resultant suspension was heated at reflux for 48 h. The reaction mixture was then concentrated in vacuo. H₂O (100 mL) was added to the residue and the mixture was extracted with DCM (3 × 100 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in MeOH (10 mL) and K₂CO₃ (100 mg) was added. The resulting suspension was stirred at rt for 16 h then concentrated in vacuo. H₂O (50 mL) was added and the mixture was extracted with DCM (3 × 50 mL). The combined organic extracts were washed sequentially with H₂O (2 × 100 mL) and brine (100 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 5%→100% EtOAc in 40-60 °C petrol) gave 4 as a colourless oil (16 mg, 4%, >98% de). Further elution gave 11 as a pale yellow solid (337 mg, 74%, >98% de). Further elution gave 5 as a viscous, pale yellow oil (31 mg, 7%, >98% de).

(1RS,2RS,3RS)-1-Acetoxy-2-hydroxy-3-N,N-dibenzylaminocyclohexane 15

![Structure of 15](image_url)

A stirred solution of 4 (5.79 g, 19.8 mmol) in AcOH (15 mL) was heated at 50 °C for 24 h before being allowed to cool to rt. 0.1 M aq. NaHCO₃ (100 mL) was added and the mixture was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO₃ (5 × 100 mL), dried and concentrated in vacuo to give 15 as a yellow solid (6.98 g, quant, >98% de); mp 57-58 °C; νmax (KBr) 3456 (O−H), 2937 (C−H), 1717 (C=O); δH (400 MHz, CDCl₃) 1.42-1.86 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂), 1.92 (3H, s, COMe), 2.67 (1H, br s, OH), 2.88-2.94 (1H, m, C(3)H), 3.75 (2H, d, J 12.0, N(CH₂Ph₂), 3.84 (2H, d, J 12.0, N(CH₂Ph₂), 4.06 (1H, app t, J 3.2, C(2)H), 4.98-5.02 (1H, m, C(1)H), 7.19-7.44 (10H, m,
\[ \delta_C (100 \text{ MHz, CDCl}_3) 20.2, 23.0, 24.6 (C(4), C(5), C(6)), 21.1 (\text{COMe}), 54.8 (\text{N(CH}_2\text{Ph})_2), 57.5 (C(3)), 68.0 (C(2)), 72.5 (C(1)), 126.9 (p-\text{Ph}) 128.3, 128.6 (o-, m-\text{Ph}), 140.1 (i-\text{Ph}), 170.1 (\text{COMe}); m/z (\text{ESI}^+) 354 ([M+H]^+, 100\%); \text{HRMS (ESI}^+) \text{ C}_{22}\text{H}_{28}\text{NO}_3^+ ([M+H]^+) \text{ requires } 354.2064; \text{ found } 354.2059. \]

**(1RS,2RS,3RS)-1-Acetoxy-2-methanesulphonyloxy-3-N,N-dibenzyldimino-cyclohexane 16**

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\begin{align*}
\text{Et}_3\text{N (96 µL, 0.69 mmol), DMAP (5 mg) and MsCl (27 µL, 0.34 mmol) were added sequentially to a stirred} \\
\text{solution of 15 (81 mg, 0.23 mmol) DCM (2 mL) at } -10^\circ\text{C. The reaction mixture was stirred at } -10^\circ\text{C for} \\
\text{48 h, after which time } \text{H}_2\text{O (1 mL) was added and the solution was allowed to warm to rt. The mixture was} \\
\text{extracted with DCM (3 x 10 mL). The combined organic extracts were washed sequentially with 10\% aq.} \\
\text{CuSO}_4 (3 x 30 mL), \text{H}_2\text{O (3 x 30 mL) and 0.1 M aq. NaHCO}_3 (3 x 30 mL), dried, and concentrated in vacuo} \\
to give 16 as a colourless oil (99 mg, quant, >98\% de); \nu_{\text{max}} (\text{film}) 3028, 2940 (C−H), 1740 (C=O); \delta_H (400 \\
\text{MHz, CDCl}_3); 1.44-1.95 (9H, m, C(4)H\textsubscript{2}, C(5)H\textsubscript{2}, C(6)H\textsubscript{2}, CO\textsubscript{Me}), 2.98-3.04 (1H, m, C(3)H), 3.07 (3H, s, \\
methyl), 3.73 (2H, d, J 14.2, N(CH\textsubscript{2}H\textsubscript{2}Ph\textsubscript{2})), 2.85-3.92 (2H, m, N(CH\textsubscript{2}H\textsubscript{2}Ph\textsubscript{2})), 4.94-4.99 (1H, br m, C(2)H), \\
5.06-5.12 (1H, br m, C(1)H), 7.14-7.49 (10H, m, Ph); \delta_C (100 MHz, CDCl\textsubscript{3}); 1.44-1.95 (9H, m, C(4)H\textsubscript{2}, C(5)H\textsubscript{2}, C(6)H\textsubscript{2}, COMe), 2.98-3.04 (1H, m, C(3)H), 3.07 (3H, s, \\
SMe), 3.73 (2H, d, J 14.2, N(CH\textsubscript{2}H\textsubscript{2}H\textsubscript{2}Ph\textsubscript{2})), 2.85-3.92 (2H, m, N(CH\textsubscript{2}H\textsubscript{2}H\textsubscript{2}Ph\textsubscript{2})), 4.94-4.99 (1H, br m, C(2)H), \\
5.06-5.12 (1H, br m, C(1)H), 7.14-7.49 (10H, m, Ph); \delta_C (100 MHz, CDCl\textsubscript{3}); 20.2, 22.3, 24.5 (C(4), C(5), \\
C(6)), 20.7 (COMe), 38.9 (SMe), 53.8 (C(3)), 54.7 (N(CH\textsubscript{2}Ph\textsubscript{2})), 70.1 (C(1)), 78.7 (C(2)), 126.9 (p-\text{Ph}), \\
128.2, 128.4 (o-, m-\text{Ph}), 140.1 (i-\text{Ph}), 169.5 (COMe); m/z (\text{ESI}^+) 432 ([M+H]^+, 100\%); \text{HRMS (ESI}^+) \\
\text{C}_{23}\text{H}_{30}\text{NO}_5^+ ([M+H]^+) \text{ requires } 432.1839; \text{ found } 432.1839. \]

**(1RS,2SR,3RS)-1,2-Epoxy-3-N,N-dibenzyldimino-cyclohexane 17**

\[
\begin{align*}
\text{K}_2\text{CO}_3 (100 mg) was added to a stirred solution of 16 (126 mg, 0.29 mmol) in MeOH (5 mL). The resultant} \\
suspension was stirred for 16 h at rt before being concentrated in vacuo. \text{H}_2\text{O (10 mL) was added and the} \\
mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were washed sequentially \\
with \text{H}_2\text{O (2 x 10 mL) and brine (10 mL), dried, and concentrated in vacuo. Purification via flash column} \\
chromatography (gradient elution, 0\%→100\%, \text{EtOAc in 40-60 °C petrol}) gave 17 as a white solid (39 mg, \\
46\%, >98\% de); mp 48-49 °C; \nu_{\text{max}} (\text{film}) 3061, 2937 (C−H); \delta_H (400 MHz, CDCl\textsubscript{3}) 1.16-1.36 (2H, m, \\
C(4)H\textsubscript{2}, C(5)H\textsubscript{2}), 1.39-1.53 (1H, m, C(5)H\textsubscript{2}), 1.57-1.73 (1H, m, C(6)H\textsubscript{2}), 1.73-1.86 (1H, m, C(4)H\textsubscript{2}), 2.05- \\
2.14 (1H, m, C(6)H\textsubscript{2}), 2.99-3.07 (1H, m, C(3)H), 3.21-3.25 (1H, m, C(1)H), 3.25-3.30 (1H, m, C(2)H), 3.75 \\
(4H, AB system, N(CH\textsubscript{2}Ph\textsubscript{2})), 7.23-7.49 (10H, m, Ph); \delta_C (100 MHz, CDCl\textsubscript{3}) 16.1 (C(5)), 22.2 (C(4)), 25.2 \\
\end{align*}
\]
(C(6)), 53.1 (C(3)), 53.5 (C(1)), 54.8 (N(CH₂Ph)₂), 55.6 (C(2)), 127.0 (p-Ph), 128.3, 128.4, (o-, m-,Ph), 139.9 (i-Ph); m/z (ESI⁺) 294 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO⁺ ([M+H]⁺) requires 294.1852; found 294.1849.

(1RS,2RS,3SR)-3-N,N-dibenzyaminocyclohexane-1,2-diol 18

Concentrated H₂SO₄ (0.24 mL) in H₂O (1.4 mL) was added to a stirred solution of 17 (266 mg, 0.91 mmol) in 1,4-dioxane (1 mL) and the resultant mixture was stirred at rt for 16 h before being concentrated in vacuo. 0.1 M aq. NaHCO₃ was added and the mixture was extracted with Et₂O (4 × 10 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO₃ (3 × 40 mL), dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0% → 100% EtOAc in 40-60 °C petrol) gave 18 as a pale yellow solid (124 mg, 44%, >98% de); mp 72-73 °C; νmax (KBr) 3417 (O−H), 3061, 3027, 2938 (C−H); δH (400 MHz, CDCl₃) 1.11-2.00 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂), 2.37-2.48 (1H, m, C(3)H), 3.02 (1H, br s, OH), 3.31-3.48 (3H, m, C(2)H, N(CH₃)₂), 3.69-3.98 (4H, br m, C(1)H, N(CH₃)₂, OH), 7.23-7.41 (10H, m, Ph); δC (100 MHz, CDCl₃) 21.6, 21.7, 31.5 (C(4), C(5), C(6)), 53.7 (N(CH₃)₂), 55.0 (C(1)), 61.2 (C(3)), 74.7 (C(2)), 127.3 (p-Ph), 128.4, 128.6 (o, m-Ph), 139.2 (i-Ph); m/z (ESI⁺) 312 ([M+H]⁺, 100%); HRMS C₂₀H₂₆NO₂⁺ ([M+H]⁺) requires 312.1958; found 312.1962.

(1RS,2RS,3SR)-1-p-Toluenesulphonyloxy-2-hydroxy-3-N,N-dibenzyaminocyclohexane 19

TsOH (800 mg, 4.21 mmol) was added to a stirred solution of 17 (273 mg, 0.93 mmol) in DCM (10 mL) and the reaction mixture was then stirred at rt for 16 h. 0.1 M aq. NaHCO₃ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO₃ (5 × 40 mL), dried and concentrated in vacuo to give 19 as a white solid (472 mg, quant, >98% de); mp 95-97 °C; νmax (KBr) 3442 (O−H), 2950 (C−H); δH (400 MHz, CDCl₃) 1.08-1.37 (2H, m, C(4)H₄, C(5)H₄), 1.41-1.54 (1H, app qd J 12.0, 4.0 C(6)H₂), 1.75-1.86 (1H, m, C(3)H), 1.87-1.96 (1H, m, C(4)H), 2.02-2.16 (1H, m, C(6)H₂), 2.38-2.47 (4H, m, C(3)H, ArMe), 3.36 (2H, d, J 13.3, N(CH₃)₂), 3.58 (2H, app t, J 9.6, C(2)H), 3.83 (2H, d, J 13.3, N(CH₃)₂), 4.34 (1H, ddd, J 11.6, 8.5, 4.8, C(1)H), 7.21-7.34 (12H, m, Ar, Ph), 7.82 (2H, d, J 8.0, Ar); δC (100 MHz, CDCl₃) 21.4, 21.6, 31.0 (C(4), C(5), C(6), ArMe), 53.6 (N(CH₃)₂), 61.8 (C(3)), 71.3 (C(2)), 84.9 (C(1)), 127.4, 127.8,
Cl₃CCO₂H (59 mg, 0.358 mmol) was added to a stirred solution of 17 (70 mg, 0.24 mmol) in DCM (2 mL) and the reaction mixture was stirred at rt for 16 h. 0.1 M aq. NaHCO₃ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO₃ (5 × 40 mL), dried and concentrated in vacuo to give an 80:20 mixture of 20:21 as a yellow oil (83 mg, 77%); ν<sub>max</sub> (film) 3419 (O−H), 2940 (C−H), 1762 (C=O); m/z (ESI<sup>+</sup>) 456 ([M+H]<sup>+</sup>, 100%), 313 (79%); HRMS (ESI<sup>+</sup>) C<sub>22</sub>H<sub>25</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>3</sub> requires 456.0895; found 456.0895.

Data for 20: δ<sub>H</sub> (400 MHz, CDCl₃) 1.21-1.54 (2H, m, C(4)H<sub>A</sub>, C(6)H<sub>B</sub>), 1.79-1.98 (2H, m, C(5)H<sub>A</sub>), 1.98-2.06 (1H, m, C(4)H<sub>B</sub>), 2.06-2.15 (1H, m, C(6)H<sub>B</sub>), 2.48-2.59 (1H, m, C(3)H), 3.33-3.50 (2H, m, N(CH<sub>A</sub>H<sub>B</sub>Ph)<sub>2</sub>), 3.76 (1H, app t, J 9.6, C(2)H), 3.89-3.97 (2H, m, N(CH<sub>A</sub>H<sub>B</sub>Ph)<sub>2</sub>), 4.69 (1H, ddd, J 11.4, 9.1, 5.1, C(1)H), 7.21-7.39 (10H, m, Ph); δ<sub>C</sub> (100 MHz, CDCl₃) 21.3, 21.3 (C(4), C(5)), 28.7 (C(6)), 53.5 (N(CH<sub>2</sub>Ph)<sub>A</sub>), 55.3 (N(CH<sub>2</sub>Ph)<sub>B</sub>), 61.6 (C(3)), 71.0 (C(2)), 82.1 (C(1)), 90.0 (CCl<sub>3</sub>), 127.6 (p-Ph), 128.7, 129.0 (o-, m-Ph), 138.3 (i-Ph), 161.4 (COCCl<sub>3</sub>).

K<sub>2</sub>CO₃ (100 mg) was added to a stirred solution of an 80:20 mixture of 20:21 (83 mg, 0.18 mmol) in MeOH (10 mL) and the resultant suspension was stirred at rt for 16 h before being concentrated in vacuo. H<sub>2</sub>O (10 mL) was added and the mixture was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (40 mL), dried and concentrated in vacuo to give an 80:20 mixture of 18:5 as a colourless oil (57 mg, quant).

Cl₂CHCO₂H (0.07 mL, 0.86 mmol) was added to a stirred solution of 17 (50 mg, 0.17 mmol) in DCM (2 mL) and the reaction mixture was stirred at rt for 16 h. 0.1 M aq. NaHCO₃ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic
extracts were washed with 0.1 M aq. NaHCO$_3$ (5 × 40 mL), dried and concentrated in vacuo to give a 75:25 mixture of 22:23 (50 mg, 70%).

Data for 22: $\delta$$_H$ (400 MHz, CDCl$_3$) 1.12-2.17 (6H, m, C(4)H$_2$, C(5)H$_2$, C(6)H$_2$), 2.52-2.66 (1H, m, C(3)H), 3.43-3.57 (2H, d, J 13.3, N(CH$_A$H$_B$Ph)$_2$), 3.69-3.80 (1H, m, C(2)H), 3.95-4.05 (2H, d, J 13.3, N(CH$_A$H$_B$Ph)$_2$), 4.60-4.75 (1H, m, C(1)H), 5.98 (1H, s, C$_H$Cl$_2$), 7.22-7.57 (10H, m, Ph).

Data for 23: $\delta$$_H$ (400 MHz, CDCl$_3$) [selected peaks] 4.33-4.42 (1H, m, C(1)H) 5.46 -5.51 (1H, m, C(2)H), 5.95 (1H, s, C$_H$Cl$_2$).

K$_2$CO$_3$ (100 mg) was added to a stirred solution of a 75:25 mixture of 22:23 (50 mg, 0.12 mmol) in MeOH (10 mL) and the resultant suspension was stirred at rt for 16 h before being concentrated in vacuo. H$_2$O (10 mL) was added and the mixture was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO$_3$ (5 × 40 mL), dried and concentrated in vacuo to give an 81:19 mixture of 18:5 as a colourless oil (37 mg, quant).

(1RS,2RS,3SR)-1-Trifluoroacetoxy-2-hydroxy-3-N,N-dibenzylaminocyclohexane 24

F$_3$CCO$_2$H (39 µL, 0.53 mmol) was added to a stirred solution of 17 (31 mg, 0.106 mmol, >98% de) in DCM (2 mL) and the reaction mixture was stirred at rt for 16 h. 0.1 M aq. NaHCO$_3$ (10 mL) was then added, the organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with 0.1 M aq. NaHCO$_3$ (5 × 40 mL), dried and concentrated in vacuo to give a 22:4:55:17:2 mixture of 24:25:18:26:5 (57 mg).

Data for 24: $\delta$$_H$ (400 MHz, CDCl$_3$) [selected peaks] 3.63-3.77 (1H, m, C(2)H), 4.75 (1H, ddd, J 12.0, 8.0, 4.0, C(1)H).

Data for 25: $\delta$$_H$ (400 MHz, CDCl$_3$) [selected peaks] 2.73-2.83 (1H, m, C(3)H), 5.07-5.14 (1H, m, C(2)H).

Data for 26: $\delta$$_H$ (400 MHz, CDCl$_3$) [selected peaks] 4.00-4.10 (1H, m, C(2)H) 5.20-5.26 (1H, m, C(1)H).

K$_2$CO$_3$ (60 mg) was added to a stirred solution of a 22:4:55:17:2 mixture of 24:25:18:26:5 (57 mg) in MeOH (5 mL) and the resultant suspension was stirred at rt for 16 h before being concentrated in vacuo. H$_2$O (5 mL) was added and the mixture was extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (40 mL), dried and concentrated in vacuo to give an 81:19 mixture of 18:5 as a colourless oil (20 mg).
(1RS,2RS,3SR)-1-Acetoxy-2-hydroxy-3,N,N-dibenzylaminocyclohexane 28

A stirred solution 17 (50 g, 0.171 mmol, >98% de) in AcOH (1 mL) was heated at 50 ºC for 24 h before being allowed to cool to rt. 0.1 M aq. NaHCO₃ (10 mL) was then added and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were then washed with 0.1 M aq. NaHCO₃ (5 × 10 mL), dried and concentrated in vacuo to give a 44:36:11:9 mixture of 28:29:30:31 (53 mg) as a colourless oil.

Data for 28: δ_H (400 MHz, CDCl₃) [selected peaks] 2.43-2.52 (1H, m, C(2)H), 4.49-4.60 (1H, m, C(1)H).
Data for 29: δ_H (400 MHz, CDCl₃) [selected peaks] 3.09-3.16 (1H, m, C(1)H), 5.17-5.22 (1H, m, C(2)H).
Data for 30: δ_H (400 MHz, CDCl₃) [selected peaks] 5.05-5.10 (1H, m, C(1)H).
Data for 31: δ_H (400 MHz, CDCl₃) [selected peaks] 5.34-5.39 (1H, m, C(2)H).

K₂CO₃ (100 mg) was added to a stirred solution of a 44:36:11:9 mixture of 28:29:30:31 (53 mg) in MeOH (10 mL) and the resultant suspension was stirred at rt for 16 h before being concentrated in vacuo. H₂O (10 mL) was added and the mixture was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (40 mL), dried and concentrated in vacuo to give a 44:36:20 mixture of 18:5:14 as a colourless oil (23 mg).

(1RS,2SR,3RS)-3-N,N-dibenzylaminocyclohexane-1,2-diol 14

KOAc (23 mg, 0.24 mmol) was added to a stirred solution of 16 (99 mg, 0.23 mmol) in EtOH/H₂O (6:1, 5 mL) and the resultant suspension was heated at reflux for 48 h. The reaction mixture was allowed to cool to rt and concentrated in vacuo. H₂O (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in MeOH (10 mL) and K₂CO₃ (100 mg) were added. The resultant suspension was stirred for 16 h before being concentrated in vacuo. H₂O (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed sequentially with H₂O (2 × 30 mL) and brine (30 mL), dried, and concentrated in vacuo to give 14 as a pale yellow solid (31 mg, 43%, >98% de).
X-ray Crystal Structure Determination for 14

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²

X-ray crystal structure data for 14 [C₂₀H₂₅NO₂]: M = 311.42, monoclinic, space group P 1 2/a 1, a = 10.83920(10) Å, b = 28.0222(3) Å, c = 12.21180(10) Å, β = 110.5571(5)º, V = 3473.00(6) Å³, Z = 8, µ = 0.76 mm⁻¹, colourless plate, crystal dimensions = 0.1 × 0.3 × 0.4 mm³. A total of 7908 unique reflections were measured for 5 < θ < 27 and 4662 reflections were used in the refinement. The final parameters were wR₂ = 0.042 and R₁ = 0.040 [I>3.0σ(I)].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 681276. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(1RS,2RS,3SR)-1-p-Toluenesulphonyloxy-2-acetoxy-3-N,N-dibenzylaminocyclohexane 34

Ac₂O (0.13 mL, 1.4 mmol) and DMAP (50 mg) were added sequentially to a stirred solution of 19 (472 mg, 0.93 mmol) in DCM/pyridine (1:1, 20 mL). The resultant solution was stirred at rt for 24 h before being cooled to 0 °C. H₂O (20 mL) was added, the organic layer was separated and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic extracts were washed sequentially with 10% aq. CuSO₄ (2 × 50 mL), 0.1 M aq. NaHCO₃ (2 × 50 mL) and brine (50 mL), dried, and concentrated in vacuo to give 34 as a white solid (373 mg, 72%, >98% de); mp 105-106 °C; νmax (KBr) 2942, 2867 (C−H), 1741 (C=O); δH (400 MHz, CDCl₃) 1.06-1.20 (1H, m, C(5)H₆), 1.29-1.43 (1H, m, C(4)H₆), 1.43-1.56 (1H, m, C(6)H₆), 1.73-1.82 (1H, m, C(5)H₆), 1.94-2.02 (4H, m, C(4)H₆, COMe), 2.03-2.12 (1H, m, C(6)H₆), 2.44 (3H, s, ArMe), 2.67 (1H, app td J 12.0, 4.0, C(3)H), 3.43 (2H, d, J 13.5, N(CH₂ArMe₆)₂), 3.78 (2H, d, J 13.5, N(CH₂ArMe₆)₂), 4.45 (1H, ddd, J 12.0, 8.0, 4.0, C(1)H), 5.18 (1H, app t, J 9.9 C(2)H), 7.17-7.35 (12H, m, Ph, Ar), 7.74 (2H, d, J 8.1, Ar); δC (400 MHz, CDCl₃) 20.9, 23.7, 31.5 (C(4), C(5), C(6)), 21.1, 21.6 (COMe, ArMe), 53.6 (N(CH₂Ph)₂), 59.5 (C(3)), 72.4 (C(2)), 82.4 (C(1)), 126.9, 127.5, 128.2, 128.7, 129.7, 139.6 (Ar,

Ph), 170.2 (COMe); m/z (ESI⁺) 508 ([M+H]⁺, 100%); HRMS (ESI⁺) C_{29}H_{34}NO_{5}S⁺ ([M+H]⁺) requires 508.2152; found 508.2152.

(1RS,2SR,3RS)-3-N,N-dibenzylaminocyclohexane-1,2-diol 14 from 34

KOAc (73 mg, 0.74 mmol) was added to a stirred solution of 34 (373 mg, 0.74 mmol) in EtOH/H_{2}O (6:1, 20 mL) and the resultant suspension was heated at reflux for 72 h. The reaction mixture was allowed to cool to rt and concentrated in vacuo. H_{2}O (20 mL) was added and mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in MeOH (10 mL) and K_{2}CO_{3} (100 mg) were added. The resultant suspension was stirred for 16 h at rt before being concentrated in vacuo. H_{2}O (20 mL) was added and mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were washed sequentially with H_{2}O (2 × 50 mL) and brine (50 mL), dried, and concentrated in vacuo to give 14 as a white solid (130 mg, 57%, >98% de).

(1RS,2RS,3RS)-3-Aminocyclohexane-1,2-diol 6

Pd(OH)_{2}/C (78 mg) was added to a vigorously stirred solution of 5 (157 mg, 0.50 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_{2} (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated in vacuo to give 6 as a pale yellow solid (53 mg, 80%, >98% de); mp 115-116 °C; ν_{max} (KBr) 3355 (O−H), 2936, 2867 (C−H); δ_{H} (400 MHz, d_{4}-MeOH) 1.34-1.46 (1H, m, C(6)H_{A}), 1.47-1.66 (4H, m, C(4)H_{2}, C(5)H_{2}), 1.74-1.87 (1H, m, C(6)H_{B}), 3.02-3.12 (1H, m, C(3)H), 3.52 (1H, dd, J 5.3, 3.3, C(2)H), 3.74-3.82 (1H, m, C(1)H); δ_{C} (100 MHz, d_{4}-MeOH) 18.6, 29.2 (C(4), C(5)), 47.4 (C(6)), 49.9 (C(3)), 70.0 (C(1)), 74.2 (C(2)); m/z (ESI⁺) 132 ([M+H]⁺, 100%); HRMS (ESI⁺) C_{6}H_{14}NO_{2}⁺ ([M+H]⁺) requires 132.1019; found 132.1022.

(1RS,2SR,3SR)-3-Aminocyclohexane-1,2-diol 7

Pd(OH)_{2}/C (121 mg) was added to a vigorously stirred solution of 11 (243 mg, 0.78 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_{2} (1 atm) for 24 h. The suspension was
then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated in vacuo to give 7 as a colourless oil (103 mg, quant, >98% de); \(\nu_{\text{max}}\) (film) 3385 (O\(^{-}\)H), 2941, 2867 (C\(-\)H); \(\delta_H\) (400 MHz, \(d_4\)-MeOH) 1.11-1.76 (6H, m, C(4)H\(_2\), C(5)H\(_2\), C(6)H\(_2\)), 2.59-2.74 (1H, m, C(3)H), 3.46-3.59 (1H, m, C(1)H), 3.75-3.81 (1H, m, C(2)H); \(\delta_C\) (100 MHz, \(d_4\)-MeOH) 21.0, 27.6, 28.2 (C(4), C(5), C(6)), 52.2 (C(3)), 71.8 (C(1)), 73.2 (C(2)); \(m/z\) (ESI\(^+\)) 132 ([M+H]\(^+\), 100%); HRMS (ESI\(^+\)) \(C_6H_{14}NO_2^+\) ([M+H]\(^+\)) requires 132.1019; found 132.1020.

\((1RS,2SR,3RS)-3\)-Aminocyclohexane-1,2-diol 8

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\text{Pd(OH)}_2/C (25 mg) was added to a vigorously stirred solution of 14 (54 mg, 0.17 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H\(_2\) (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated in vacuo to give 8 as a white solid (14 mg, 64%, >98%); mp 134-135 °C; \(\nu_{\text{max}}\) (KBr) 3384 (O\(^{-}\)H), 2940, 2871 (C\(-\)H); \(\delta_H\) (400 MHz, \(d_4\)-MeOH) 1.14-1.27 (1H, m, C(4)H\(_A\)), 1.44-1.57 (2H, m, C(5)H\(_A\), C(6)H\(_A\)), 1.63-1.78 (1H, m, C(5)H\(_B\)), 1.79-1.97 (2H, m, C(4)H\(_B\), C(6)H\(_B\)), 2.92-3.03 (1H, m, C(3)H), 3.21 (1H, dd, J 9.6, 3.1, C(2)H), 4.00 (1H, app q, J 3.0, C(1)H); \(\delta_C\) (100 MHz, \(d_4\)-MeOH) 18.7 (C(5)), 31.4 (C(6)), 32.2 (C(4)), 50.4 (C(3)), 67.0 (C(1)), 77.3 (C(2)); \(m/z\) (ESI\(^+\)) 132 ([M+H]\(^+\), 55%); HRMS (ESI\(^+\)) \(C_6H_{14}NO_2^+\) ([M+H]\(^+\)) requires 132.1019; found 132.1022.

\((1RS,2RS,3SR)-3\)-Aminocyclohexane-1,2-diol 9

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\text{Pd(OH)}_2/C (55 mg) was added to a vigorously stirred solution of 18 (110 mg, 0.35 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H\(_2\) (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated in vacuo to give 9 as a white solid (47 mg, quant, >98% de); mp 45-46 °C; \(\nu_{\text{max}}\) (KBr) 3356 (O\(^{-}\)H), 2934, 2868 (C\(-\)H); \(\delta_H\) (400 MHz, \(d_4\)-MeOH) 1.25-1.46 (3H, m, C(4)H\(_A\), C(5)H\(_A\), C(6)H\(_A\)), 1.71-1.81 (1H, m, C(5)H\(_B\)), 1.88-2.02 (2H, m, C(4)H\(_B\), C(6)H\(_B\)), 2.75 (1H, app td, J 10.3, 3.7, C(3)H), 3.12 (1H, app t, J 9.2, C(2)H), 3.30-3.43 (1H, m, C(1)H); \(\delta_C\) (100 MHz, \(d_4\)-MeOH) 21.3 (C(5)), 30.5, 32.9 (C(4), C(6)), 54.6 (C(3)), 73.6 (C(1)), 78.6 (C(2)); \(m/z\) (ESI\(^+\)) 132 ([M+H]\(^+\), 100%); HRMS (ESI\(^+\)) \(C_6H_{14}NO_2^+\) ([M+H]\(^+\)) requires 132.1019; found 132.1022.