Stereoselective Synthesis of 2,4,5-Trisubstituted Piperidines by Carbonyl Ene and Prins Cyclisations

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Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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General Procedure 1 for the Reduction of Amino Acids

The amino acid (182 mmol) was added in one portion to a suspension of sodium borohydride (436 mmol) in THF (480 mL). A solution of iodine (182 mmol) in THF (120 mL) was added dropwise over a 1 h period with considerable gas evolution. The resulting solution was heated at reflux for 18-20 h. After cooling to room temperature, MeOH (40 mL) was added dropwise with rapid stirring, resulting in vigorous gas evolution and dissolution of the white precipitate. Solvents were removed in vacuo to give a sticky white gum, which was dissolved in 20% (w/w) aqueous KOH (360 mL). The resulting solution was stirred overnight at room temperature. The solution was extracted with DCM (4 x 350 mL) and the combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo to give the crude amino alcohol.

(S)-Phenylalaninol, 2b

Amino alcohol 2b was prepared from (S)-phenylalanine (30.00 g, 182 mmol), sodium borohydride (16.49 g, 436 mmol) and iodine (46.09 g, 182 mmol) according to the general procedure 1. The crude product was recrystallised from toluene to afford 2b as white crystals (18.03 g, 66%).

[α]D²³ -21.7 (c 1.0 in CHCl₃) (lit. ³ [α]D²⁴ -25.8 (c 2.2 in CHCl₃)); mp 86-88 °C (from toluene) (lit.¹ mp 90-92 °C); IR (KBr) 3357, 3300, 3353, 3050, 2919, 2850, 1601, 1577, 1492, 1453, 1065, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.85 (3H, br s), 2.42 (1H, dd, J = 13.5, 8.6 Hz), 2.79 (1H, dd, J = 13.5, 5.1 Hz), 3.07-3.16 (1H, m), 3.38 (1H, dd, J = 10.7, 7.3 Hz), 3.63 (1H, dd, J = 10.7, 3.9 Hz), 7.20-7.33 (5H, stack); ¹³C NMR (75 MHz, CDCl₃) δ 40.8, 54.3, 66.3, 126.5, 128.7, 129.3, 138.8; MS (FAB)
m/z 152 (100%, [M+H]+), 120 (28, [M-CH2OH]+); HRMS (CI) Calcd for C9H14NO: 152.1075. Found: 152.1075.

(S)-tert-Leucinol, 2e

Amino alcohol 2e was prepared from (S)-tert-leucine (5.00 g, 38.2 mmol), sodium borohydride (3.47 g, 91.6 mmol) and iodine (9.69 g, 38.2 mmol) according to the general procedure 1. The crude product was purified by bulb-to-bulb distillation (oven temperature 100 °C/0.3 mmHg) to afford 2e as a white solid (3.73 g, 83%).

$[\alpha]_D^{26} +38.2$ (c 1.0 in CHCl₃) (lit.$^1$ +37 (c 1.0 in EtOH)); mp 31-33 °C (lit.$^1$ 30 °C); IR (KBr) 3369, 2959, 2862, 1586, 1478, 1367, 1045 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl₃) δ 0.89 (9H, s), 1.91 (3H, br s), 2.50 (1H, dd, J = 10.3, 4.1 Hz), 3.20 (1H, app t, J = 10.3 Hz), 3.70 (1H, dd, J = 10.3, 4.1 Hz); $^{13}$C NMR (75 MHz, CDCl₃) δ 26.4, 33.4, 61.9, 62.4; MS (EI) m/z 118.1 (1%, [M+H]+), 86.1 (50), 69.0 (13), 60.0 (100), 41.0 (23)

(S)-Phenylglycinol, 2f

Amino alcohol 2f was prepared from L-phenylglycine (10.05 g, 67 mmol), sodium borohydride (6.04 g, 160 mmol) and iodine (16.89 g, 67 mmol) according to the general procedure 1, with the exception that the amino acid was added after addition of the iodine was completed. The crude product was recrystallised from toluene to afford 2f as a white powder (6.37 g, 70%).

$[\alpha]_D^{27} +22.7$ (c 1.0 in CHCl₃) (lit.$^4$ +26.7 (c 1.0 in MeOH)); mp 71-73 °C (from toluene) (lit.$^1$ mp 69-71 °C); IR (KBr) 3330, 3274, 2910, 2837, 1607, 1496, 1453, 1050 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl₃) δ 2.17 (3H, br s), 3.49 (1H, dd, J = 10.6, 8.6 Hz), 3.67
(1H, dd, J = 10.6, 4.4 Hz), 3.95-4.01 (1H, m), 7.18-7.31 (5H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 57.5, 68.1, 126.6, 127.6, 128.8, 142.8; MS (FAB) m/z 138 (100%, [M+H]$^+$); HRMS (EI) Calcd for C$_8$H$_{12}$NO: 138.0919. Found: 138.0914; Anal. calcd for C$_8$H$_{11}$NO: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.08; H, 8.16; N, 10.03.

**General Procedure 2 for the Bistosylation of Amino Alcohols**

A solution of the amino alcohol (6.3 mmol) in DCM (6.5 mL) was added to a solution of TsCl (13.9 mmol) and pyridine (44.4 mmol) in DCM (7 mL) at 0 °C. The resulting solution was warmed to ambient temperature and stirred until the reaction was judged to be complete by TLC analysis (14-48 h). The reaction mixture was poured into a separating funnel containing cold aqueous HCl (1 M, 60 mL) and DCM (25 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (3 x 25 mL). The combined organic phases were washed with aqueous CuSO$_4$ (25 mL), brine (2 x 20 mL), dried over MgSO$_4$ and concentrated in vacuo to give the crude product as a solid.

**General Procedure 3 for the Nitrile Displacement**

A solution of the bistosylate (15 mmol) in DMF (63 mL) was added to a suspension of NaCN (46 mmol) in DMF (94 mL) at ambient temperature and stirring was continued until the reaction was judged to be complete by TLC analysis (16-48 h). The reaction mixture was diluted with water (100 mL) and extracted with Et$_2$O (4 x 80 mL). The combined organic phases were washed with water (2 x 100 mL), brine (100 mL), dried over MgSO$_4$ and concentrated in vacuo to give the crude product as a solid.
(3S)-(p-Toluenesulfonyl)amino-butyronitrile, 3a

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)alaninol was prepared from (S)-alaninol 2a (3.11 g, 41.4 mmol), TsCl (17.35 g, 91.1 mmol) and pyridine (23.4 mL, 289.8 mmol) according to the general procedure 2. Purification by flash column chromatography (EtOAc:petroleum ether, 1:2, \( R_f = 0.27 \)) afforded (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)alaninol as a white powder (13.53 g, 85%).

[\( \alpha \)]\(_D\)\(^{26} -41.7 \) (c 1.0 in CHCl\(_3\)) (lit.\(^5 \) [\( \alpha \)]\(_D\)\(^{23} -38.2 \) (c 1.02 in CHCl\(_3\))); mp 96-98 °C (from EtOAc:petroleum ether) (lit.\(^5 \) 104-105 °C from EtOAc:hexane); IR (KBr) 3339, 2987, 2926, 2876, 1598, 1494, 1360, 1181 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.07 (3H, d, \( J = 7.0 \) Hz), 2.42 (3H, s), 2.46 (3H, s), 3.49-3.57 (1H, m), 3.83 (1H, dd, \( J = 9.9, 4.8 \) Hz), 3.92 (1H, dd, \( J = 9.9, 4.1 \) Hz), 4.83 (1H, d, \( J = 8.1 \) Hz), 7.28 (2H, d, \( J = 8.1 \) Hz), 7.35 (2H, d, \( J = 8.5 \) Hz), 7.68-7.75 (4H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 18.1, 21.6, 21.8, 48.5, 72.6, 127.1, 128.1, 129.9, 130.1, 132.5, 137.6, 143.8, 145.4; MS (ES) \( m/z \) 406.2 (100%, [M+Na]\(^{+}\)), 234.1 (16); Anal. calcd for C\(_{17}\)H\(_{21}\)NO\(_5\)S\(_2\): C, 53.24; H, 5.52; N, 3.65. Found: C, 53.15; H, 5.48; N, 3.63.

Nitrile 3a was prepared from (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)alaninol (13.30 g, 34.7 mmol) and NaCN (5.10 g, 104.2 mmol) according to the general procedure 3. Work-up afforded 3a as a white powder (7.48 g, 90%).

(Toluene:Et\(_2\)O, 2:1, \( R_f = 0.25 \)); [\( \alpha \)]\(_D\)\(^{26} -64.4 \) (c 1.0 in CHCl\(_3\)); mp 91-93 °C (from Et\(_2\)O); IR (KBr) 3259, 2978, 2928, 2837, 2252, 1598, 1498, 1341, 1149 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.24 (3H, d, \( J = 7.0 \) Hz), 2.44 (3H, s), 2.55-2.59 (2H, m), 3.57-3.70 (1H, m), 4.80 (1H, d, \( J = 7.7 \) Hz), 7.34 (2H, d, \( J = 8.1 \) Hz), 7.77 (2H, d, \( J = 8.1 \) Hz);
\(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta 20.5, 21.7, 26.4, 46.3, 116.9, 127.1, 130.1, 137.2, 144.2;\) MS (ES) \(m/z 261.2\) (100%, [M+Na]\(^{+}\)); HRMS (ES) Calcd for C\(_{11}\)H\(_{14}\)N\(_2\)NaO\(_2\)S: 261.0674. Found: 261.0672; Anal. calcd for C\(_{11}\)H\(_{14}\)N\(_2\)O\(_2\)S: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.48; H, 6.12; N, 11.63.

**3(S)-(p-Toluenesulfonyl)amino-4-phenylbutyronitrile, 3b**

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)phenylalaninol was prepared from (S)-phenylalalalolin 2b (7.00 g, 46.36 mmol), TsCl (19.43 g, 101.99 mmol) and pyridine (26.2 mL, 324.50 mmol) according to the general procedure 2. Purification by flash column chromatography (EtOAc:petroleum ether, 1:2, \(R_f = 0.36\)) afforded (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)phenylalaninol as a white powder (15.93 g, 75%).

\([\alpha]\)\(_D\)^{23} -42.7 (c 1.0 in CHCl\(_3\)); mp 96-98 °C (from EtOAc:petroleum ether); IR (KBr) 3290, 3067, 2953, 2892, 1598, 1495, 1456, 1325, 1366, 1160 cm\(^{-1}\); \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta 2.40\) (3H, s), 2.46 (3H, s), 2.65 (1H, dd, \(J = 13.9, 7.2\) Hz), 2.80 (1H, dd, \(J = 13.9, 7.4\) Hz), 3.52-3.60 (1H, m), 3.84 (1H, dd, \(J = 10.1, 5.3\) Hz), 3.97 (1H, dd, \(J = 10.1, 3.5\) Hz), 4.71 (1H, d, \(J = 7.7\) Hz), 6.86 (2H, d, \(J = 7.2\) Hz), 7.11-7.18 (5H, m), 7.35 (2H, d, \(J = 8.5\) Hz), 7.51 (2H, d, \(J = 8.1\) Hz), 7.75 (2H, d, \(J = 8.1\) Hz); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta 21.6, 21.8, 37.7, 53.7, 70.3, 127.0, 128.1, 128.8, 129.2, 129.8, 130.1, 132.4, 135.8, 136.9, 143.6, 145.3; MS (ES) \(m/z 482.1\) (100%, [M+Na]\(^{+}\)), 310.1 (85); HRMS (ES) Calcd for C\(_{23}\)H\(_{25}\)NNaO\(_5\)S\(_2\): 482.1072. Found: 482.1060; Anal. calcd for C\(_{23}\)H\(_{25}\)NO\(_5\)S\(_2\): C, 60.11; H, 5.48; N, 3.05. Found: C, 60.19; H, 5.49; N, 2.99.
Nitrile 3b was prepared from (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)phenylalaninol (7.00 g, 15.25 mmol) and NaCN (2.24 g, 45.70 mmol) according to the general procedure 3. Work-up afforded 3b as colourless crystals (4.32 g, 90%).

(toluene:diethyl ether, 2:1, \( R_f = 0.38 \)); \([\alpha]_D^{23}\) -65.5 (c 1.0 in CHCl3) (lit. \( [\alpha]_D \) -58.6 (c 4.0 in CHCl3)); mp 82-84 °C (from toluene:diethyl ether) (lit.² oil); IR (KBr) 3350, 2920, 2850, 2246, 1597, 1380, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 2.42 (3H, s), 2.56 (1H, dd, \( J = 16.8, 3.9 \) Hz), 2.67 (1H, dd, \( J = 16.8, 6.3 \) Hz), 2.77 (1H, dd, \( J = 14.0, 7.7 \) Hz), 2.90 (1H, dd, \( J = 14.0, 7.0 \) Hz), 3.58-3.69 (1H, m), 4.85 (1H, d, \( J = 7.0 \) Hz), 6.99 (2H, m), 7.20-7.22 (5H, m), 7.55 (2H, d, \( J = 8.1 \) Hz); \(^13\)C NMR (75 MHz, CDCl3) \( \delta \) 21.6, 24.3, 39.9, 51.5, 116.9, 127.0, 127.4, 129.0, 129.1, 129.9, 135.3, 136.6, 143.8; MS (ES) \( m/z \) 337.1 (100%, [M+Na]⁺); HRMS (ES) Calcd for C\(_{17}\)H\(_{18}\)N\(_2\)NaO\(_2\)S: 337.0987. Found: 337.0993; Anal. calcd for C\(_{17}\)H\(_{18}\)N\(_2\)O\(_2\)S: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.79; H, 5.84; N, 8.81.

(3R)-(p-Toluenesulfonyl)amino-4-methylpentionitrile, 3c

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)valinol was prepared from (S)-valinol 2c (7.11 g, 69.1 mmol), TsCl (28.94 g, 151.9 mmol) and pyridine (39 mL, 483.4 mmol) according to the general procedure 2. Purification by flash column chromatography (EtOAc:petroleum ether, 1:3, \( R_f = 0.18 \)) afforded (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)valinol as a white powder (19.33 g, 68%).

\([\alpha]_D^{21}\) -53.5 (c 0.5 in CHCl3) (lit.⁶ \( [\alpha]_D^{20} \) -57.2 (in CHCl3)); mp 97-99 °C (from EtOAc:petroleum ether) (lit.⁶ 110-111 °C (from EtOH)); IR (KBr) 3275, 2970, 2931, 2882, 2877, 1600, 1497, 1361, 1323, 1180, 1159 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \)
Nitrile 3c was prepared from (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)valinol (8.56 g, 20.8 mmol) and NaCN (3.06 g, 62.5 mmol) according to the general procedure 3. Work-up afforded 3c as a white powder (4.58 g, 83%).

(toluene:Et₂O, 2:1, Rf = 0.32); [α]D²¹ -92.9 (c 0.5 in CHCl₃); mp 85-87 °C (from Et₂O); IR (KBr) 3251, 2964, 2927, 2874, 2252, 1598, 1498, 1447, 1368, 1328, 1187, 1154 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.81 (3H, d, J = 5.2 Hz), 0.84 (3H, d, J = 5.2 Hz), 1.85-1.97 (1H, m), 2.44 (3H, s), 2.59 (2H, d, J = 5.5 Hz), 3.17-3.26 (1H, m), 4.89 (1H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.3 Hz), 7.77 (2H, d, J = 8.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 17.6, 19.3, 21.7, 22.8, 31.0, 55.6, 117.1, 127.2, 130.0, 137.1, 144.1; MS (ES) m/z 289.0 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₃H₁₉N₂NaO₂S: 289.0987. Found: 289.0979; Anal. calcd for C₁₃H₁₉N₂O₂S: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.56; H, 6.76; N, 10.32.
(3R)-(p-Toluenesulfonyl)amino-4,4-dimethylpentanitrile, 3e

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)-tert-leucinol was prepared from (S)-tert-leucinol 2e (3.13 g, 26.74 mmol), TsCl (11.21 g, 58.82 mmol) and pyridine (15.1 mL, 187.16 mmol) according to the general procedure 2. Purification by flash column chromatography (EtOAc:petroleum ether, 2:1, \( R_f = 0.36 \)) afforded (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)-tert-leucinol as a white powder (8.63 g, 76%).

\[ \alpha_\text{D}^{26} +34.6 \text{ (c 1.0 in CHCl}_3\) \]; mp 99-101 °C (from EtOAc:petroleum ether); IR (KBr) 3282, 2969, 2932, 2873, 1599, 1498, 1446, 1400, 1359, 1340, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.86 (9H, s), 2.41 (3H, s), 2.46 (3H, s), 3.12-3.19 (1H, m), 3.79 (1H, dd, \( J = 10.3, 4.1 \) Hz), 4.00 (1H, dd, \( J = 10.3, 3.7 \) Hz), 4.73 (1H, d, \( J = 9.9 \) Hz), 7.25 (2H, d, \( J = 8.1 \) Hz), 7.33 (2H, d, \( J = 8.1 \) Hz), 7.66 (2H, d, \( J = 8.1 \) Hz), 7.70 (2H, d, \( J = 8.1 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 21.7, 21.8, 27.1, 34.7, 60.5, 69.1, 127.2, 128.1, 129.8, 130.0, 132.4, 137.9, 143.6, 145.2; MS (ES) \( m/z \) 448.1 (100%, [M+Na]+); HRMS (ES) Calcd for C\(_{20}\)H\(_{27}\)NaO\(_5\)S\(_2\): 448.1228. Found: 448.1231; Anal. calcd for C\(_{20}\)H\(_{27}\)NO\(_5\)S\(_2\): C, 56.45; H, 6.39; N, 3.29. Found: C, 56.48; H, 6.39; N, 3.11.

Nitrile 3e was prepared from (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)-tert-leucinol (8.43 g, 19.84 mmol) and NaCN (2.92 g, 59.51 mmol) according to the general procedure 3. Work-up afforded 3e as a white powder (4.54 g, 82%).

(Toluene:Et\(_2\)O, 2:1, \( R_f = 0.33 \)); \[ \alpha_\text{D}^{26} -72.5 \text{ (c 1.0 in CHCl}_3\) \]; mp 105-107 °C (from Et\(_2\)O); IR (KBr) 3316, 2960, 2876, 2250, 1597, 1480, 1449, 1377, 1352, 1329, 1244, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.91 (9H, s), 2.43 (3H, s), 2.48-2.51 (2H, m), 3.23-3.30 (1H, m), 5.01 (1H, d, \( J = 9.6 \) Hz), 7.33 (2H, d, \( J = 8.1 \) Hz), 7.80 (2H, d, \( J = 8.1 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 20.4, 21.7, 26.6, 35.4, 58.4, 117.8, 127.3,
130.0, 137.5, 144.0; MS (ES) m/z 303.1 (100%, [M+Na]+); HRMS (ES) Calcd for C_{14}H_{20}N_{2}NaO_{2}S: 303.1143. Found: 303.1137; Anal. calcd for C_{14}H_{20}N_{2}O_{2}S: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.68; H, 7.28; N, 9.74.

(3R)-Phenyl-3-(p-toluenesulfonyl)amino-propionitrile, 3f

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)phenylglycinol was prepared from (S)-phenylglycinol 2f (3.66 g, 26.7 mmol), TsCl (12.22 g, 64.1 mmol) and pyridine (14 mL, 173 mmol) according to the general procedure 2. Purification by flash column chromatography (EtOAc:petroleum ether, 1:2, \( R_f = 0.27 \)) afforded (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)phenylglycinol as a white powder (9.3 g, 78%). \([\alpha]_D^{27} +30.5 \) (c 1.0 in CHCl₃); mp 100-102 °C (from EtOAc:petroleum ether); IR (KBr) 3314, 2955, 2924, 1598, 1496, 1456, 1361, 1176 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 2.39 (3H, s), 2.44 (3H, s), 4.10 (1H, dd, \( J = 10.5, 5.5 \) Hz), 4.16 (1H, dd, \( J = 10.5, 6.3 \) Hz), 4.50-4.57 (1H, m), 5.25 (1H, d, \( J = 6.6 \) Hz), 7.00-7.04 (2H, m), 7.14-7.22 (5H, m), 7.29 (2H, d, \( J = 8.1 \) Hz), 7.58 (2H, d, \( J = 8.5 \) Hz), 7.63 (2H, d, \( J = 8.1 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 21.6, 21.8, 56.5, 71.3, 127.0, 127.2, 128.0, 128.4, 128.8, 129.6, 130.0, 132.3, 136.1, 137.0, 143.6, 145.2; MS (ES) m/z 468.0 (100%, [M+Na]+); HRMS (ES) Calcd for C_{22}H_{23}NNaO_{5}S_{2}: 468.0915. Found: 468.0912; Anal. calcd for C_{22}H_{23}NO_{5}S_{2}: C, 59.30; H, 5.20; N, 3.14. Found: C, 59.10; H, 5.47; N, 3.03.

Nitrile 3f was prepared from (2S)-O-(p-toluenesulfonyl)-N-(p-toluenesulfonyl)phenylglycinol (7.00 g, 15.25 mmol) and NaCN (2.24 g, 45.70 mmol) according to the general procedure 3. Purification by flash column chromatography (Et₂O:DCM, 1:20, \( R_f = 0.29 \)) afforded nitrile 3f as a white powder (4.35 g, 70%).
1-(p-Toluenesulfonyl)aminocyclohexane-1-methanol, 2d

After a slow addition of thionyl chloride (1.19 mL, 16.35 mmol) to MeOH (20 mL) at 0 °C, 1-aminocyclohexane carboxylic acid (2.34 g, 16.35 mmol) was added portionwise to the resulting solution. The reaction mixture was stirred at reflux for 2 days, after which the solvent was removed in vacuo. Aqueous NaHCO₃ (40 mL) was added to the residue and the aqueous phase was extracted with EtOAc (4 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo to afford methyl 1-aminocyclohexanecarboxylate as a colourless oil (2.00 g, 78%).

(MeOH, Rf = 0.75); IR (neat) 3376, 2934, 2857, 1728, 1450, 1166 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.32-1.62 (8H, stack), 1.84-1.91 (2H, stack), 3.67 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 21.7, 25.3, 35.2, 51.8, 57.1, 177.6; MS (EI) m/z 98 (100%, [M-COOME]⁺)
A solution of methyl 1-aminocyclohexanecarboxylate (0.40 g, 2.53 mmol) in DCM (7 mL) was added dropwise to a solution of TsCl (0.53 g, 2.79 mmol) and pyridine (614 µL, 7.60 mmol) in DCM (7 mL) at 0 °C. The resulting solution was warmed to ambient temperature and stirred for 36 h. The reaction mixture was poured into a separating funnel containing cold aqueous HCl (1 M, 10 mL) and DCM (20 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (4 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (hexane:EtOAc, 3:1, Rₜ = 0.11) afforded methyl 1-(p-toluenesulfonyl)amino-1-cyclohexanecarboxylate as a white solid (0.56 g, 71%).

mp 132-134 °C (lit.⁶ 143-144 °C); IR (film) 3291, 2949, 2867, 1741, 1598, 1496, 1320, 1167 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.20-1.46 (6H, stack), 1.75-1.88 (4H, stack), 2.40 (3H, s), 3.51 (3H, s), 4.95 (1H, d, J = 4.4 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.74 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 20.8, 21.2, 24.7, 33.1, 52.1, 61.5, 127.6, 129.7, 139.2, 143.6, 174.6; MS (ES) m/z 334.0 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₅H₂₁NNaO₄S: 334.1089. Found: 334.1086; Anal. calcd for C₁₅H₂₁NO₄S: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.83; H, 7.02; N, 4.41.

A solution of methyl 1-(p-toluenesulfonyl)amino-1-cyclohexanecarboxylate (100 mg, 0.32 mmol) in THF (5 mL) was cooled to 0 °C and LiAlH₄ (24 mg, 0.64 mmol) was added. The ice bath was removed and stirring continued for 3 h. After cooling to 0 °C, the reaction mixture was carefully acidified with 2 M aqueous HCl and the aqueous phase extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo to afford the alcohol 2d as a white solid (87 mg, 95%).
(hexane:EtOAc, 2:1, \( R_f = 0.15 \)); mp 112-114 °C (from hexane:EtOAc); IR (film) 3524, 3259, 2936, 2863, 1598, 1496, 1449, 1316, 1151, 1048 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.18-1.42 (8H, stack), 1.52-1.66 (2H, stack), 2.42 (3H, s), 2.54 (1H, br s), 3.59 (2H, s), 4.91 (1H, s), 7.29 (2H, d, \( J = 8.3 \) Hz), 7.81 (2H, d, \( J = 8.3 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 21.0, 21.2, 25.0, 32.6, 60.8, 67.3, 127.3, 130.0, 140.3, 143.7; MS (ES) \( m/z \) 306.1 (100%, [M+Na\(^+\])); HRMS (ES) Calcd for \( C_{14}H_{21}NNaO_3S \): 306.1140. Found: 306.1147.

1-Cyanomethyl-1-(\( \rho \)-toluenesulfonyl)aminocyclohexane, 3d

A solution of alcohol 2d (1.58 g, 5.58 mmol) in DCM (20 mL) was added to a solution of TsCl (1.91 g, 10.04 mmol) and pyridine (20.08 mmol, 1.62 mL) in DCM (20 mL) at 0 °C. The resulting solution was warmed to ambient temperature and stirred for 5 days. The reaction mixture was poured into a separating funnel containing cold aqueous HCl (1 M, 10 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (4 x 50 mL). The combined organic phases were washed with aqueous CuSO\(_4\) (50 mL), brine (50 mL), dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash column chromatography (hexane:EtOAc, 2:1, \( R_f = 0.32 \)) afforded O-(\( \rho \)-toluenesulfonyl)-1-(\( \rho \)-toluenesulfonyl)aminocyclohexane-1-methanol as a white solid (2.40 g, 98%).

mp 132-134 °C (from hexane:EtOAc); IR (film) 3288, 2938, 2864, 1598, 1495, 1450, 1332, 1176, 1094 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.09-1.43 (8H, stack), 1.59-1.75 (2H, stack), 2.38 (3H, s), 2.42 (3H, s), 3.94 (2H, s), 4.59 (1H, s), 7.22 (2H, d, \( J = 8.1 \) Hz), 7.32 (2H, d, \( J = 8.1 \) Hz), 7.68 (2H, d, \( J = 8.5 \) Hz), 7.71 (2H, d, \( J = 8.5 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 20.9, 21.6, 21.8, 25.0, 32.3, 58.4, 73.8, 127.0, 128.1, 129.7,
130.0, 132.7, 139.9, 143.3, 145.0; MS (ES) m/z 460.1 (100%, [M+Na]⁺); HRMS (ES) Calcd for C$_{21}$H$_{27}$NNaO$_5$S$_2$: 460.1228. Found: 460.1231; Anal. calcd for C$_{21}$H$_{27}$NO$_5$S$_2$: C, 57.64; H, 6.22; N, 3.20. Found: C, 57.41; H, 6.35; N, 3.10.

Nitrile 3d was prepared from O-(p-toluenesulfonyl)-1-(p-toluenesulfonyl)aminocyclohexane-1-methanol (2.27 g, 5.18 mmol) and NaCN (0.76 g, 15.55 mmol) according to the general procedure 3. After 16 h, work-up afforded 3d as a white powder (1.47 g, 97%).

(toluene:Et$_2$O, 2:1, $R_f = 0.39$); mp 146-148 °C (from Et$_2$O); IR (film) 3287, 2947, 2862, 2245, 1597, 1496, 1454, 1421, 1333, 1152 cm$^{-1}$; $^1$H NMR (300 MHz, CDC$_3$) $\delta$ 1.14-1.53 (8H, stack), 1.80-1.92 (2H, stack), 2.41 (3H, s), 2.82 (2H, s), 5.39 (1H, s), 7.30 (2H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz); $^{13}$C NMR (75 MHz, CDC$_3$) $\delta$ 21.2, 21.6, 24.8, 30.2, 35.4, 57.3, 117.3, 127.0, 129.8, 139.7, 143.6; MS (ES) m/z 315.2 (100%, [M+Na]⁺); HRMS (ES) Calcd for C$_{15}$H$_{20}$N$_2$NaO$_2$: 315.1143. Found: 315.1152.

**General Procedure 4 for the Hydrolysis of the Nitriles**

A mixture of the nitrile (3.2 mmol), glacial acetic acid (3.2 mL), water (3.2 mL) and concentrated sulfuric acid (3.2 mL) was stirred at 110 °C overnight under a reflux condenser. After cooling, the reaction mixture was diluted with water (30 mL) and the aqueous phase extracted with DCM (4 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the crude acid.
(3S)-(p-Toluenesulfonyl)amino-4-phenylbutyric acid, 4b

Acid 4b was prepared from nitrile 3b (1.01 g, 3.2 mmol), glacial acetic acid (3.2 mL), water (3.2 mL) and concentrated sulfuric acid (3.2 mL) according to the general procedure 4. Purification by flash column chromatography (petroleum ether:ethyl acetate, 1:1, Rf = 0.33) afforded 4b as a grey powder (0.87 g, 81%).

$\left[\alpha\right]_D^{20}$ -21.2 (c 1.0 in CHCl₃) (lit.⁹ $\left[\alpha\right]_D^{23}$ -14.6 (c 0.9 in CH₂Cl₂)); mp 63-65 °C (from petroleum ether:EtOAc) (lit.¹⁰ 85 °C (from petroleum ether:EtOAc)); IR (KBr) 3500, 3280, 2926, 2875, 1712, 1599, 1496, 1454, 1325, 1157 cm⁻¹;¹ H NMR (300 MHz, CDCl₃) δ 2.40 (3H, s), 2.54 (2H, d, J = 5.2 Hz), 2.78 (1H, dd, J = 13.6, 7.0 Hz), 2.87 (1H, dd, J = 13.6, 7.7 Hz), 3.70-3.81 (1H, m), 5.59 (1H, br d, J = 5.9 Hz), 7.01-7.03 (2H, m), 7.19-7.23 (5H, m), 7.62 (2H, d, J = 8.6 Hz);¹³ C NMR (75 MHz, CDCl₃) δ 21.7, 37.8, 40.7, 51.8, 127.0, 127.1, 128.9, 129.4, 129.8, 136.8, 137.4, 143.6, 175.9; MS (El) m/z 334 (9%, [M+H]⁺), 242 (52), 155 (38), 91 (100); HRMS (ES) Calcd for C₁₇H₂₀NO₄S: 334.1113. Found: 334.1110; Anal. calcd for C₁₇H₁₉NO₄S: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.16; H, 5.84; N, 4.01.

(3R)-(p-Toluenesulfonyl)amino-4-methylpentanoic acid, 4c

Acid 4c was prepared from nitrile 3c (0.15 g, 0.56 mmol), glacial acetic acid (0.6 mL), water (0.6 mL) and concentrated sulfuric acid (0.6 mL) according to the general procedure 4. Work-up afforded 4c, contaminated with a small amount of alkene, as a white powder (0.15 g, 95%).

(EtOAc:petroleum ether, 1:2, Rf = 0.14); $\left[\alpha\right]_D^{21}$ -40.5 (c 0.5 in CHCl₃); mp 120-122 °C (from DCM:hexane); IR (KBr) 3328, 2964, 2850, 1714, 1599, 1499, 1325, 1317, 1156
cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.82 (3H, d, J = 4.8 Hz), 0.84 (3H, d, J = 4.8 Hz), 1.79-1.90 (1H, m), 2.36-2.42 (4H, stack), 2.50 (1H, dd, J = 16.2, 4.8 Hz), 3.27-3.37 (1H, m), 5.26 (1H, d, J = 9.2 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.76 (2H, d, J = 8.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 18.7, 19.1, 21.7, 31.7, 36.3, 56.2, 127.2, 129.8, 137.9, 143.6, 176.1; MS (ES) m/z 308.2 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₃H₁₉NNaO₄S: 308.0932. Found: 308.0923; Anal. calcd for C₁₃H₁₉NO₄S: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.65; H, 6.92; N, 4.73.

(3R)-(p-Toluenesulfonyl)amino-4,4-dimethylpentanoic acid, 4e

Acid 4e was prepared from nitrile 3e (0.41 g, 1.45 mmol), glacial acetic acid (1.5 mL), water (1.5 mL) and concentrated sulfuric acid (1.5 mL) according to the general procedure 4. Work-up afforded 4e, contaminated with a small amount of alkene, as a cream powder (0.42 g, 97%).

(DCM:MeOH, 16:1, R₇ = 0.42); [α]D²¹ -27.4 (c 0.5 in CHCl₃); mp 87-89 °C (from DCM:hexane); IR (KBr) 3288, 2965, 1712, 1599, 1370, 1207, 1158 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.84 (9H, s), 2.34-2.37 (5H, stack), 3.41-3.48 (1H, m), 5.70 (1H, d, J = 9.6 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.7, 26.5, 35.5, 35.8, 59.2, 127.3, 129.7, 137.9, 143.5, 177.6; MS (ES) m/z 322 (100%, [M+Na]⁺), 240 (14); HRMS (ES) Calcd for C₁₄H₂₁NNaO₄S: 322.1089. Found: 322.1076.
General Procedure 5 for the Bis Alkylation of the N-tosyl β-Amino Acids

Cesium carbonate (7.8 mmol) was added to a solution of the acid (3.9 mmol) in acetonitrile (110 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (7.8 mmol) was added and stirring was continued until the reaction was judged to be complete by TLC analysis (3-20 h). The acetonitrile was removed in vacuo to give a white solid to which was added water (100 mL). The aqueous phase was extracted with Et₂O (4 x 100 mL). The combined organic phases were washed with water (2 x 100 mL), brine (100 mL), dried over MgSO₄ and concentrated in vacuo to give the crude bis alkylated product.

General Procedure 6 for the Reduction of the Esters into the Alcohols

A solution of the ester (0.72 mmol) in THF (1.6 mL) was cooled to 0 °C and ethereal LiAlH₄ (1.0 M, 0.60 mmol) was added dropwise. The ice bath was removed and stirring continued for 3 h. After cooling to 0 °C, the reaction mixture was carefully acidified with 2 M aqueous HCl and the aqueous phase extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo to afford the crude alcohol.

3-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]butanol, 6a

Acid 4a (1.00 g, 3.89 mmol) was reacted with cesium carbonate (2.54 g, 7.78 mmol) and 1-bromo-3-methylbut-2-ene (0.90 mL, 7.78 mmol) in acetonitrile according to the general procedure 5. Purification by flash column chromatography (EtOAc:hexane,
3:16, \( R_f = 0.29 \) afforded 3-methylbut-2-enyl 3-\([N-(3\text{-methylbut-2-enyl})-N-(p\text{-toluenesulfonyl})amino]\) butanoate as a colourless oil (1.27 g, 83%).

IR (neat) 2975, 2932, 1732, 1599, 1495, 1448, 1340, 1158 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.12 (3H, d, \( J = 6.6 \) Hz), 1.64 (3H, s), 1.66 (3H, s), 1.69 (3H, s), 1.75 (3H, s), 2.36-2.45 (4H, stack), 2.58 (1H, dd, \( J = 15.1, \) 5.9 Hz), 3.73 (1H, dd, \( J = 16.2, 7.4 \) Hz), 3.83 (1H, dd, \( J = 16.2 \) and 6.3 Hz), 4.29-4.41 (1H, m), 4.52 (2H, d, \( J = 7.0 \) Hz), 5.10 (1H, br t, \( J = 7.0 \) Hz), 5.29 (1H, dd, \( J = 7.4, 6.3 \) Hz), 7.25 (2H, d, \( J = 8.1 \) Hz), 7.69 (2H, d, \( J = 8.1 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 17.8, 18.1, 19.1, 21.5, 25.77, 25.81, 41.1, 42.3, 50.9, 61.6, 118.5, 121.9, 127.2, 129.5, 134.7, 138.5, 139.2, 142.9, 170.9; MS (ES) \( m/z \) 416.0 (100%, [M+Na]+), 348 (32), 258 (10); HRMS (ES) Calcd for C\(_{21}\)H\(_{31}\)NNaO\(_4\)S: 416.1872. Found: 416.1859; Anal. calcd for C\(_{21}\)H\(_{31}\)NNaO\(_4\)S: C, 64.09; H, 7.94; N, 3.56. Found: C, 64.11; H, 7.88; N, 3.51.

Alcohol 6a was prepared from 3-methylbut-2-enyl 3-\([N-(3\text{-methylbut-2-enyl})-N-(p\text{-toluenesulfonyl})amino]\) butanoate (5.48 g, 13.9 mmol) and LiAlH\(_4\) (1.0 M in Et\(_2\)O, 11 mL, 11 mmol) according to the general procedure 6. The 3-methylbut-2-en-1-ol side product was removed by bulb-to-bulb distillation (oven temperature 60 °C/0.3 mmHg) to leave the alcohol 6a as a colourless oil (4.09 g, 94%).

(EtOAc:hexane, 1:2, \( R_f = 0.21 \)); IR (neat) 3434, 2975, 2929, 1598, 1494, 1451, 1332, 1161, 1046 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.88 (3H, d, \( J = 6.6 \) Hz), 1.53-1.67 (8H, stack), 2.41 (3H, s), 2.57 (1H, br s), 3.54-3.61 (1H, m), 3.73-3.88 (3H, stack), 4.08-4.20 (1H, m), 5.11 (1H, br t, \( J = 5.9 \) Hz), 7.27 (2H, d, \( J = 8.5 \) Hz), 7.67 (2H, d, \( J = 8.5 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 17.9, 18.6, 21.6, 25.8, 38.2, 40.9, 50.0, 58.6, 121.9, 127.0, 129.7, 134.7, 138.3, 143.2; MS (ES) \( m/z \) 334.2 (100%, [M+Na]+);
HRMS (ES) Calcd for C_{16}H_{25}NNaO_{3}S: 334.1453. Found: 334.1447; Anal. calcd for C_{16}H_{25}NO_{3}S: C, 61.70; H, 8.09; N, 4.50. Found: C, 61.48; H, 7.81; N, 4.54.

*(3S)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutanoate, 6b*

3-Methylbut-2-enyl *(3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutanoate was prepared from acid 4b (0.87 g, 2.6 mmol), cesium carbonate (1.70 g, 5.2 mmol) and 1-bromo-3-methylbut-2-ene (0.60 mL, 5.2 mmol) in acetonitrile according to the general procedure 5. Purification by flash column chromatography (hexane:EtOAc, 5:1, R_{f} = 0.3) afforded 3-methylbut-2-enyl *(3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutanoate as a colourless oil (1.02 g, 83%).

[α]_{D}^{21} -6.7 (c 1.0 in CHCl_{3}); IR (film) 3028, 2971, 2929, 1731, 1675, 1600, 1496, 1453, 1338, 1155 cm^{-1}; ¹H NMR (300 MHz, CDCl_{3}) δ 1.64 (9H, s), 1.72 (3H, s), 2.38 (3H, s), 2.52 (1H, dd, J = 15.8, 6.6 Hz), 2.71 (1H, dd, J = 15.8, 7.7 Hz), 2.87 (1H, dd, J = 13.6, 8.1 Hz), 2.97 (1H, dd, J = 13.6, 6.6 Hz), 3.81 (2H, d, J = 6.8 Hz), 4.35-4.38 (1H, m), 4.41 (2H, d, J = 7.3 Hz), 5.08 (1H, t, J = 6.8 Hz), 5.24 (1H, t, J = 7.3 Hz), 7.12-7.27 (7H, m), 7.59 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl_{3}) δ 17.9, 18.1, 21.6, 25.8, 25.9, 38.4, 40.8, 44.0, 57.5, 61.7, 118.6, 121.5, 126.7, 127.5, 128.6, 129.41, 129.45, 135.4, 138.2, 138.5, 139.1, 142.9, 171.2; MS (ES) m/z 492.3 (100%, [M+Na]^+); HRMS (ES) Calcd for C_{27}H_{35}NNaO_{4}S: 492.2185. Found: 492.2169; Anal. calcd for C_{27}H_{35}NO_{4}S: C, 69.05; H, 7.51; N, 2.98. Found: C, 69.00; H, 7.44; N, 2.92.

Alcohol 6b was prepared from 3-methylbut-2-enyl *(3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutanoate (0.34 g, 0.72 mmol) and LiAlH₄ (1.0 M in
Et₂O, 0.59 mL, 0.59 mmol) according to the general procedure 6. Purification by flash column chromatography (petroleum ether:EtOAc, 2:1, Rᵣ = 0.32) afforded 6b as a colourless oil (0.22 g, 78%).

[α]₀^23 -43 (c 1.0 in CHCl₃); IR (neat) 3436, 2928, 1651, 1599, 1495, 1454, 1331, 1153, 1050 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.57 (1H, tt, J = 12.9, 3.3 Hz), 1.65-1.72 (7H, stack), 2.41 (3H, s), 2.50-2.63 (2H, m), 3.55 (1H, ddd, J = 11.7, 4.8, 3.3 Hz), 3.78 (1H, td, J = 11.7, 3.3 Hz), 3.83 (1H, dd, J = 16.2, 5.5 Hz), 3.94 (1H, dd, J = 16.2, 8.1 Hz), 4.14-4.24 (1H, m), 5.17 (1H, t, J = 6.5 Hz), 6.95-7.0 (2H, m), 7.18-7.23 (5H, m), 7.61 (2H, d, J = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 17.9, 21.5, 25.7, 34.6, 40.1, 41.6, 56.4, 58.4, 121.6, 126.5, 127.1, 128.6, 129.1, 129.6, 134.9, 137.9, 138.1, 143.2; MS (ES) m/z 410 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₂₂H₂₉NNaO₅S: 410.1766. Found: 410.1761; Anal. calcd for C₂₂H₂₉NO₅S: C, 68.18; H, 7.54; N, 3.61. Found: C, 68.19; H, 7.31; N, 3.62.

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-methylpentanol, 6c

Acid 4c (0.15 g, 0.52 mmol) was reacted with cesium carbonate (0.34 g, 1.05 mmol) and 1-bromo-3-methylbut-2-ene (121 µL, 1.05 mmol) in acetonitrile (15 mL) according to the general procedure 5. Purification by flash column chromatography (EtOAc:hexane, 3:16, Rᵣ = 0.33) afforded 3-methylbut-2-yl (3R)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-methylpentanoate as a colourless oil (0.16 g, 72%).

[α]₀^21 +14.2 (c 0.5 in CHCl₃); IR (neat) 2967, 2929, 1732, 1674, 1598, 1495, 1446, 1378, 1339, 1183, 1156 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.86 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.64 (6H, s), 1.68 (3H, s), 1.75-1.84 (4H, stack), 2.31 (1H,
dd, J = 15.8, 5.5 Hz), 2.39 (3H, s), 2.47 (1H, dd, J = 15.8, 7.4 Hz), 3.73 (2H, d, J = 6.6 Hz), 3.97-4.05 (1H, m), 7.22 (2H, d, J = 8.5 Hz), 7.71 (2H, d, J = 8.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.9, 18.1, 19.7, 20.8, 21.6, 25.8, 25.9, 32.7, 38.3, 43.0, 61.5, 61.7, 118.5, 121.7, 127.6, 129.4, 134.6, 138.6, 139.2, 142.8, 171.6; MS (ES) $m/z$ 444.2 (100%, [M+Na]$^+$); HRMS (ES) Calcd for C$_{23}$H$_{35}$NNaO$_4$S: 444.2185. Found: 444.2179; Anal. calcd for C$_{23}$H$_{35}$NO$_4$S: C, 65.52; H, 8.37; N, 3.32. Found: C, 65.66; H, 8.60; N, 3.25.

Alcohol 6c was prepared from 3-methylbut-2-enyl (3R)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-methylpentanoate (0.54 g, 1.28 mmol) and LiAlH$_4$ (1.0 M in Et$_2$O, 1.02 mL, 1.02 mmol) according to the general procedure 6. Purification by flash column chromatography (EtOAc:hexane, 1:2, $R_f$ = 0.28) afforded 6c as a colourless oil (0.42 g, 97%).

$[\alpha]_D^{21}$ +79.5 (c 1.0 in CHCl$_3$); IR (neat) 3532, 2963, 2850, 1670, 1598, 1494, 1448, 1378, 1330, 1157, 1050 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.46 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.39-1.50 (1H, m), 1.55-1.65 (7H, stack), 1.83-1.94 (1H, m), 2.40 (3H, s), 3.02 (1H, br s), 3.52-3.60 (2H, m), 3.74 (2H, d, J = 6.6 Hz), 3.78-3.82 (1H, m), 5.17 (1H, br t, J = 6.6 Hz), 7.25 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.5, 20.3, 20.9, 21.2, 25.5, 31.3, 33.7, 41.5, 58.6, 61.5, 122.2, 127.8, 129.7, 134.8, 139.0, 143.5; MS (ES) $m/z$ 362.3 (100%, [M+Na]$^+$); HRMS (ES) Calcd for C$_{18}$H$_{29}$NNaO$_3$S: 362.1766. Found: 362.1780; Anal. calcd for C$_{18}$H$_{29}$NO$_3$S: C, 63.68; H, 8.61; N, 4.13. Found: C, 63.56; H, 8.49; N, 3.98.
General Procedure 7 for the Swern Oxidation

Distilled DMSO (1.24 mmol) was added dropwise at a rapid rate to a solution of oxalyl chloride (0.62 mmol) in DCM (8 mL) at -60 °C. After 5 min a solution of the alcohol (0.52 mmol) in DCM (5 mL) was added dropwise. The mixture was stirred for another 20 min before dry Et₃N (2.59 mmol) was added dropwise and then the solution was stirred for a further 3 h at -60 °C. The mixture was allowed to warm to room temperature before addition of water (25 mL). The aqueous phase was separated and extracted with DCM (4 x 25 mL). The combined organic phases were washed with aqueous HCl (1 M, 50 mL), water (50 mL), brine (50 mL), dried over MgSO₄ and concentrated in vacuo to afford the crude aldehyde.

General Procedure 8 for the Alkylation of the Cyano N-Sulfonamides with 1-bromo-3-methylbut-2-ene

Cesium carbonate (0.70 mmol) was added to a solution of the sulfonamide (0.64 mmol) in CH₃CN (15 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (0.64 mmol) was added. The resulting mixture was stirred until the reaction was judged to be complete by TLC analysis (3-20 h), before removing the solvent in vacuo. Water (30 mL) was added to the resulting solid and the aqueous phase was extracted with Et₂O (4 x 30 mL). The combined organic phases were washed with water (2 x 50 mL), brine (50 mL), dried over MgSO₄ and concentrated in vacuo to afford the crude alkylated product.
General Procedure 9 for the Reduction of the Nitriles into the Aldehydes

A solution of DIBAL-H (1 M in toluene, 0.69 mmol) was added dropwise to a solution of the nitrile (0.58 mmol) in DCM (5 mL) at -78 °C. The mixture was stirred for 3 h, after which it was quenched by addition of MeOH (1 mL). The reaction mixture was allowed to warm to room temperature and then poured into ice-cold aqueous sulfuric acid (1 M, 2.5 mL) and stirred vigorously. The aqueous phase was separated and extracted with DCM (4 x 15 mL). The combined organic phases were washed with brine (15 mL), dried over MgSO₄ and concentrated in vacuo to afford the crude aldehyde.

3-[(N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]butanal, 1a

Aldehyde 1a was prepared from alcohol 6a (0.50 g, 1.62 mmol), oxalyl chloride (170 µL, 1.95 mmol), DMSO (275 µL, 3.88 mmol) and Et₃N (1.13 mL, 8.08 mmol) according to the general procedure 7. Purification by flash column chromatography (hexane:EtOAc, 3:1, Rf = 0.28) afforded 1a as a colourless oil (0.46 g, 92%).

IR (neat) 2975, 2925, 1724, 1645, 1598, 1494, 1451, 1336, 1305, 1156 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.08 (3H, d, J = 7.0 Hz), 1.65 (3H, s), 1.67 (3H, s), 2.41 (3H, s), 2.51 (1H, ddd, J = 16.9, 7.4, 1.5 Hz), 2.70 (1H, ddd, J = 16.9, 7.0, 1.8 Hz), 3.72 (1H, dd, J = 16.2, 7.7 Hz), 3.84 (1H, dd, J = 16.2, 5.9 Hz), 4.41-4.54 (1H, m), 5.10 (1H, br t, J = 6.3 Hz), 7.28 (2H, d, J = 8.1 Hz), 7.68 (2H, d, J = 8.1 Hz), 9.64 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 17.9, 19.1, 21.6, 25.8, 42.2, 48.8, 49.9, 121.6, 127.2, 129.7, 135.2, 138.2, 143.3, 200.3; MS (ES) m/z 332.2 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₆H₂₃NNaO₃S: 332.1296. Found: 332.1288.
(3S)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutanal, 1b

Swern oxidation:

Aldehyde 1b was prepared from alcohol 6b (0.20 g, 0.52 mmol), DMSO (88 µL, 1.24 mmol), oxalyl chloride (54 µL, 0.62 mmol) and Et₃N (362 µL, 2.59 mmol) according to the general procedure 7. Work-up afforded 1b as a colourless oil (0.20 g, 100%).

DIBAL-H reduction:

(3S)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutyronitrile was prepared from sulfonamide 3b (0.20 g, 0.64 mmol), cesium carbonate (0.23 g, 0.70 mmol) and 1-bromo-3-methylbut-2-ene (74 µL, 0.64 mmol) according to the general procedure 8. Purification by flash column chromatography (hexane:EtOAc, 5:1, Rf = 0.24) afforded (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino]-4-phenylbutyronitrile as a yellow powder (0.20 g, 82%).

[α]D21 -24.6 (c 0.5 in CHCl₃); mp 65-67 °C (from hexane:EtOAc); IR (film) 3029, 2927, 2249, 1599, 1496, 1454, 1379, 1340, 1157, 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.67 (3H, s), 1.70 (3H, s), 2.41 (3H, s), 2.52 (1H, dd, J = 16.9, 5.5 Hz), 2.83 (1H, dd, J = 16.9, 8.5 Hz), 2.94-3.08 (2H, m), 3.85 (2H, br d, J = 6.8 Hz), 4.10-4.20 (1H, m), 5.10 (1H, br t, J = 6.8 Hz), 7.10-7.14 (2H, m), 7.23-7.30 (7H, m), 7.66 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 22.2, 25.9, 39.6, 43.8, 56.9, 117.8, 120.6, 127.3, 127.5, 129.0, 129.1, 129.8, 136.6, 136.9, 137.5, 143.7; MS (ES) m/z 405.4 (100%, [M+Na]+); HRMS (ES) Calcd for C₂₂H₂₆N₂NaO₂S: 405.1613. Found: 405.1611; Anal. calcd for C₂₂H₂₆N₂O₂S: C, 69.08; H, 6.85; N, 7.32. Found: C, 68.91; H, 6.80; N, 7.27.
Aldehyde 1b was prepared from (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutyronitrile (0.31 g, 0.80 mmol) and DIBAL-H (1.0 M in toluene, 960 µL, 0.96 mmol) according to the general procedure 9. Work-up afforded 1b as a colourless oil (0.31 g, 100%).

$[\alpha]_D^{10}$ -20 (c 0.5 in CHCl₃); IR (neat) 3028, 2965, 2925, 2863, 1724, 1599, 1495, 1454, 1337, 1156 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.69 (6H, s), 2.40 (3H, s), 2.52 (1H, dd, J = 17.1, 5.7 Hz), 2.71-2.80 (2H, stack), 2.89 (1H, dd, J = 13.6, 5.9 Hz), 3.84 (2H, d, J = 6.6 Hz), 4.43-4.53 (1H, m), 5.08 (1H, t, J = 6.6 Hz), 7.08-7.11 (2H, m), 7.12-7.29 (5H, m), 7.62 (2H, d, J = 8.5 Hz), 9.44 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 25.8, 40.6, 43.5, 46.7, 55.3, 121.2, 126.9, 127.3, 128.8, 129.3, 129.7, 135.8, 137.7, 138.1, 143.3, 200.2; MS (ES) m/z 408.0 (100%, [M+Na⁺]), 274.0 (17); HRMS (ES) Calcd for C₂₂H₂₇NNaO₃S: 408.1609]. Found: 408.1622.

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-methylpentanal, 1c

Aldehyde 1c was prepared from alcohol 6c (0.64 g, 1.89 mmol), DMSO (322 µL, 4.54 mmol), oxalyl chloride (198 µL, 2.27 mmol) and Et₃N (1.32 mL, 9.46 mmol) according to the general procedure 7. Purification by flash column chromatography (hexane:EtOAc, 3:1, Rₚ = 0.36) afforded 1c as a white solid (0.57 g, 89%).

$[\alpha]_D^{19}$ -12.2 (c 0.6 in CHCl₃); mp 42-44 ºC (from hexane:EtOAc); IR (film) 2964, 2927, 2872, 1720, 1645, 1598, 1494, 1452, 1338, 1304, 1154 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.83 (3H, d, J = 4.4 Hz), 0.85 (3H, d, J = 4.4 Hz), 1.63 (3H, s), 1.65 (3H, s), 1.72-1.85 (1H, m), 2.39-2.51 (4H, stack), 2.61 (1H, ddd, J = 16.9, 6.3, 1.5 Hz), 3.74 (2H, d, J = 6.7 Hz), 4.02 (1H, dt, J = 9.9, 6.3 Hz), 5.11 (1H, br t, J = 6.7 Hz), 7.25 (2H,
d, J = 8.5 Hz), 7.67 (2H, d, J = 8.5 Hz), 9.60 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 17.8, 20.1, 20.6, 21.5, 25.7, 32.2, 42.8, 47.1, 59.0, 121.4, 127.3, 129.5, 135.0, 138.2, 143.2, 200.2; MS (ES) m/z 360.0 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₈H₂₇NNaO₃S: 360.1609. Found: 360.1592.

1-(2-Oxoethyl)-1-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyle)amino]

cyclohexane, 1d

1-Cyanomethyl-1-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyle)amino] cyclohexane was prepared from nitrile 3d (1.47 g, 5.03 mmol), cesium carbonate (1.81 g, 5.54 mmol) and 1-bromo-3-methylbut-2-ene (755 µL, 6.54 mmol) according to the general procedure 8. After 16 h, work-up afforded 1-cyanomethyl-1-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyle)amino] cyclohexane as a white powder (1.76 g, 97%). (hexane:EtOAc, 2:1, Rₜ = 0.47); mp 92-94 °C (from Et₂O); IR (film) 2933, 2865, 2244, 1642, 1599, 1495, 1450, 1329, 1153 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.15-1.48 (6H, stack), 1.54 (3H, s), 1.66 (3H, s), 1.92-2.13 (4H, stack), 2.38 (3H, s), 3.25 (2H, s), 3.93 (2H, d, J = 5.9 Hz), 5.26-5.30 (1H, m), 7.25 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 17.8, 21.5, 22.7, 24.8, 25.7, 26.7, 34.7, 44.4, 63.1, 118.3, 123.3, 127.4, 129.5, 133.6, 139.3, 143.3; MS (ES) m/z 383.2 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₂₀H₂₈N₂NaO₂S: 383.1769. Found: 383.1783; Anal. calcd for C₂₀H₂₈N₂O₂S: C, 66.63; H, 7.83; N, 7.77. Found: C, 66.64; H, 8.03; N, 7.66.

Aldehyde 1d was prepared from 1-cyanomethyl-1-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyle)amino] cyclohexane (1.72 g, 4.77 mmol) and DIBAL-H (1.5 M in toluene, 4.70 mL, 7.05 mmol) according to the general procedure 9. Purification by
flash column chromatography (hexane:EtOAc, 4:1, \( R_f = 0.36 \)) afforded 1d as a colourless oil (1.14 g, 66%).

IR (neat) 2932, 2864, 2741, 1718, 1670, 1599, 1495, 1449, 1401, 1330, 1304, 1154 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.06-1.23 (1H, m), 1.27-1.41 (2H, stack), 1.46-1.57 (6H, stack), 1.64 (3H, s), 1.74-1.86 (2H, stack), 2.05-2.14 (2H, stack), 2.38 (3H, s), 3.04 (2H, \( J = 2.6 \) Hz), 3.97 (2H, \( d, J = 5.9 \) Hz), 5.19 (1H, br t, \( J = 5.9 \) Hz), 7.24 (2H, \( d, J = 8.3 \) Hz), 7.68 (2H, \( d, J = 8.3 \) Hz), 9.80 (1H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 17.6, 17.9, 20.2, 143.0, 202.4; MS (ES) \( m/z \) 386.2 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for C\(_{20}\)H\(_{29}\)NNaO\(_3\)S: 386.1766. Found: 386.1781.

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4,4-dimethylpentanal, 1e

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4,4-dimethylpentionitrile was prepared from nitrile 3e (0.50 g, 1.79 mmol), cesium carbonate (0.64 g, 1.96 mmol) and 1-bromo-3-methylbut-2-ene (206 \( \mu \)L, 1.79 mmol) according to the general procedure 8. Purification by flash column chromatography (hexane:EtOAc, 10:3, \( R_f = 0.37 \)) afforded (3R)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4,4-dimethylpentionitrile as a white solid (0.59 g, 95%).

\([\alpha]_D^{19} \) -21.3 (c 0.5 in CHCl\(_3\)); mp 66-68 °C (from hexane:EtOAc); IR (film) 2967, 2248, 1598, 1448, 1374, 1341, 1305, 1156, 1091 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.04 (9H, s), 1.57 (3H, s), 1.61 (3H, s), 2.30 (1H, dd, \( J = 16.8, 7.5 \) Hz), 2.41 (3H, s), 2.51 (1H, dd, \( J = 16.8, 4.4 \) Hz), 3.74 (2H, d, \( J = 6.3 \) Hz), 4.25 (1H, br s), 5.06 (1H, br s), 7.29 (2H, \( d, J = 8.1 \) Hz), 7.75-7.78 (2H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 17.6, 17.9,
21.6, 25.7, 27.9, 36.6, 43.1, 62.8, 118.5, 121.7, 128.1, 129.6, 134.2, 137.4, 143.7;
MS (ES) m/z 371.3 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₉H₂₈N₂NaO₂S: 371.1769. Found: 371.1782; Anal. calcd for C₁₉H₂₈N₂O₂S: C, 65.48; H, 8.10; N, 8.04.
Found: C, 65.65; H, 8.20; N, 8.00.

Aldehyde 1e was prepared from (3R)-[N-(3-methylbut-2-enyl)-N-(p-
toluenesulfonyl)amino]-4,4-dimethylpenti ontitrile (0.51 g, 1.47 mmol) and DIBAL-H (1.5 M in toluene, 1.17 mL, 1.76 mmol) according to the general procedure 9. Purification by flash column chromatography (hexane:EtOAc, 3:1, Rᵣ = 0.29) afforded 1e as a white solid (0.43 g, 84%).

[α]D¹⁹ -20.9 (c 1.0 in CHCl₃); mp 62-64 °C (from hexane:EtOAc); IR (film) 2962, 2722,
1723, 1598, 1447, 1399, 1367, 1339, 1304, 1158, 1090 cm⁻¹; ¹H NMR (300 MHz,
CDCl₃) δ 0.93 (9H, s), 1.57 (3H, s), 1.64 (3H, s), 2.14 (1H, br d, J = 16.9 Hz), 2.38
(3H, s), 2.59 (1H, dd, J = 16.9, 6.3 Hz), 3.54 (1H, dd, J = 16.9, 5.9 Hz), 3.73 (1H, dd,
J = 16.9, 5.2 Hz), 4.40 (1H, br s), 5.16 (1H, br s), 7.24 (2H, d, J = 8.1 Hz), 7.66 (2H,
d, J = 8.1 Hz), 9.51 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 17.9, 21.5, 25.6, 27.5, 36.1,
43.3, 43.9, 60.3, 122.5, 127.7, 129.4, 133.4, 137.3, 143.4, 200.0; MS (ES) m/z 374.3
(100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₉H₂₉NNaO₂S: 374.1766. Found: 374.1760.

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-tolu enesulfonyl)amino]-3-phenylpropan al, 1f

(3R)-[N-(3-Methylbut-2-enyl)-N-(p-tolu enesulfonyl)amino]-3-phenylpropionitrile was
prepared from nitrile 3f (0.50 g, 1.67 mmol), 1-bromo-3-methylbut-2-ene (192 µL,
1.67 mmol) and Cs₂CO₃ (0.60 g, 1.83 mmol) according to the general procedure 8.
Purification by flash column chromatography (EtOAc:hexane, 3:10, Rᵣ = 0.24)
afforded (3R)-{N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino}-3-phenylpropionitrile as a colourless oil (0.60 g, 98%).

\[\alpha\]^19 \, C = +40.4 \, \text{c} \, 1.0 \, \text{in CHCl}_3; \text{IR (neat) 3032, 2974, 2929, 2252, 1598, 1497, 1452, 1378, 1339, 1157 cm}^{-1}; ^1H \text{NMR (300 MHz, CDCl}_3) \delta 1.42 (3H, s), 1.63 (3H, s), 2.44 (3H, s), 3.14 (2H, d, J = 7.7 Hz), 3.47 (1H, dd, J = 16.0, 8.1 Hz), 3.82 (1H, dd, J = 16.0, 5.2 Hz), 4.91-4.96 (1H, m), 5.29-5.35 (1H, m), 7.08-7.12 (2H, m), 7.28-7.32 (5H, m), 7.70 (2H, d, J = 8.5 Hz); ^13C \text{NMR (75 MHz, CDCl}_3) \delta 17.9, 21.7, 22.1, 25.8, 43.3, 56.9, 117.4, 120.9, 127.5, 127.9, 128.8, 128.9, 129.8, 135.1, 136.3, 137.7, 143.8; \text{MS (ES) m/z 391.2 (100\%), [M+Na]^+}, 323.2 (15); \text{HRMS (ES) Calcd for C}_{21}H_{24}N_2NaO_2S: 391.1456. Found: 391.1463; \text{Anal. calcd for C}_{21}H_{24}N_2O_2S: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.48; H, 6.53; N, 7.40.

Aldehyde 1f was prepared from (3R)-{N-(3-methylbut-2-enyl)-N-(p-toluenesulfonfyl)amino}-3-phenylpropionitrile (0.52 g, 1.41 mmol) and DIBAL-H (1.5 M in toluene, 1.13 mL, 1.70 mmol) according to the general procedure 9. Purification by flash column chromatography (hexane:EtOAc, 3:1, \(R_f = 0.42\)) afforded 1f as a colourless oil (0.42 g, 80%).

\text{IR (neat) 2971, 2927, 1723, 1598, 1496, 1450, 1376, 1334, 1157 cm}^{-1}; ^1H \text{NMR (300 MHz, CDCl}_3) \delta 1.42 (3H, s), 1.58 (3H, s), 2.42 (3H, s), 3.00 (1H, ddd, J = 16.9, 6.3, 1.5 Hz), 3.19 (1H, ddd, J = 16.9, 8.6, 2.0 Hz), 3.51 (1H, dd, J = 16.2, 7.9 Hz), 3.80 (1H, dd, J = 16.2, 5.5 Hz), 4.87-4.92 (1H, m), 5.59-5.64 (1H, m), 7.06-7.09 (2H, m), 7.23-7.29 (5H, m), 7.66 (2H, d, J = 8.1 Hz), 9.71 (1H, s); ^13C \text{NMR (75 MHz, CDCl}_3) \delta 17.8, 21.6, 25.7, 43.0, 46.7, 55.1, 121.3, 127.3, 128.0, 128.2, 128.6, 129.7, 135.3, 137.3, 138.2, 143.4, 199.6; \text{MS (ES) m/z 394.2 (100\%), [M+Na]^+}; \text{HRMS (ES) Calcd for C}_{21}H_{25}NNaO_3S: 394.1453. Found: 394.1450.
General Procedure 10 for the Prins Cyclisation Catalysed by Aqueous HCl

Concentrated hydrochloric acid (37%, 85 µL, 0.99 mmol) was added to a solution of the aldehyde (0.33 mmol) in DCM (10 mL) at -78 °C. The solution was stirred at -78 °C overnight, after which it was quenched by addition of water (10 mL). The aqueous phase was then extracted with DCM (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford the crude piperidine.

General Procedure 11 for the Elimination of the Chloride

The piperidine chloride (0.06 mmol) in THF (5 mL) was stirred with an aqueous ammonia solution (5 mL) at ambient temperature. After careful addition of dilute HCl (2 M), the THF was removed in vacuo and the remaining aqueous phase was extracted with DCM (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford the 5-isopropenyl piperidine.

(2S', 4R', 5S')-4-Hydroxy-2-methyl-5-isopropenyl-1-(p-toluenesulfonyl) piperidine, 7a

Piperidine 7a was prepared from aldehyde 1a (102 mg, 0.33 mmol) and concentrated aqueous HCl (37%, 90 µL, 0.99 mmol) according to the general procedure 10. Purification by flash column chromatography (hexane:EtOAc, 3:2, Rf =
0.41) afforded 7a, contaminated with traces of cis chloride 11a, as a colourless oil (71 mg, 70%).

IR (neat) 3525, 2923, 1644, 1598, 1494, 1451, 1383, 1336, 1305, 1153, 1088 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, d, J = 7.0 Hz), 1.62-1.67 (2H, stack), 1.73 (3H, s), 1.79-1.83 (1H, m), 2.12 (1H, br d, J = 11.8 Hz), 2.40 (3H, s), 3.30 (1H, app t, J = 12.7 Hz), 3.62 (1H, dd, J = 13.2, 4.1 Hz), 3.99 (1H, app d, J = 2.6 Hz), 4.16-4.23 (1H, m), 4.69 (1H, s), 5.00 (1H, s), 7.27 (2H, d, J = 8.1 Hz), 7.69 (2H, d, J = 8.1 Hz);

¹³C NMR (75 MHz, CDCl₃) δ 18.9, 21.5, 22.8, 35.7, 37.6, 46.5, 47.4, 64.6, 112.3, 127.0, 129.7, 138.4, 143.0, 144.1; MS (ES) m/z 332.2 (100%, [M+Na]+); HRMS (ES) Calcd for C₁₆H₂₃NNaO₃S: 332.1296. Found: 332.1297.

**(2S, 4R, 5S)-2-Benzyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 7b**

Piperidine 7b was prepared from aldehyde 1b (197 mg, 0.51 mmol) and concentrated aqueous HCl (37%, 130 µL, 1.54 mmol) according to the general procedure 10. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.36) afforded 7b, contaminated with traces of cis chloride piperidine 11b, as a colourless thick oil (160 mg, 81%).

[α]D²⁷ -16.1 (c 0.18 in CHCl₃) (value obtained on a pure sample after elimination of the chloride 11b according to the general procedure 11); IR (neat) 3530, 3027, 2923, 1644, 1599, 1495, 1453, 1340, 1157, 1105 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.55-1.68 (2H, stack), 1.76 (3H, s), 1.93 (1H, dd, J = 14.3, 2.0 Hz), 2.23 (1H, br d, J = 11.8 Hz), 2.39 (3H, s), 2.87 (1H, dd, J = 13.0, 6.6 Hz), 3.19 (1H, dd, J = 13.0, 9.6 Hz), 3.43 (1H, dd, J = 13.6, 12.1 Hz), 3.64 (1H, dd, J = 13.6, 3.9 Hz), 4.04 (1H, app d, J =
2.0 Hz), 4.20-4.30 (1H, m), 4.74 (1H, s), 5.05 (1H, s), 7.17-7.29 (7H, m), 7.53 (2H, d, J = 8.1 Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 21.6, 22.9, 31.5, 38.3, 38.9, 46.2, 53.3, 64.8, 112.5, 126.3, 127.2, 128.5, 129.7, 129.8, 138.2, 139.4, 143.1, 144.2; MS (ES) m/z 408.1 (90%, [M+Na]\(^+\)), 386.1 (26, [M+H]\(^+\)), 368.1 (9), 286.0 (27), 274.0 (100); HRMS (ES) Calcd for C\(_{22}\)H\(_{27}\)NNaO\(_3\)S: 360.1609. Found: 360.1598.

\(\textbf{(2R, 4R, 5S)-4-Hydroxy-5-isopropenyl-2-isopropyl-1-(\rho\text{-toluenesulfonyl}) piperidine, 7c}\)

Piperidine 7c was prepared from aldehyde 1c (204 mg, 0.61 mmol) and aqueous HCl (37%, 160 \(\mu\)L, 1.82 mmol) according to the general procedure 10. Purification by flash column chromatography (EtOAc:hexane, 2:7, \(R_f\) = 0.31) afforded 7c, contaminated with traces of cis chloride 11c, as a white solid (152 mg, 75%). 

\([\alpha]_D^{15}\) -40 (c 1.1 in CHCl\(_3\)); mp 102-104 °C (from DCM) (values obtained on a pure sample after elimination of the chloride 11c according to the general procedure 11); IR (film) 3534, 2964, 2926, 2871, 1645, 1599, 1494, 1451, 1339, 1150, 1090, 1070 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.81 (3H, d, \(J = 7.0\) Hz), 0.94 (3H, d, \(J = 6.6\) Hz), 1.50 (1H, ddd, \(J = 14.7, 6.3, 2.9\) Hz), 1.60 (1H, d, \(J = 2.2\) Hz), 1.67 (3H, s), 1.95 (1H, br d, \(J = 12.5\) Hz), 2.13 (1H, dd, \(J = 14.7, 2.6\) Hz), 2.30-2.41 (4H, stack), 3.28 (1H, dd, \(J = 14.3, 12.5\) Hz), 3.49 (1H, dd, \(J = 11.0, 6.3\) Hz), 3.62 (1H, dd, \(J = 14.3, 4.0\) Hz), 3.90 (1H, app d, \(J = 2.6\) Hz), 4.64 (1H, s), 4.98 (1H, s), 7.27 (2H, d, \(J = 8.5\) Hz), 7.72 (2H, d, \(J = 8.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 20.6, 21.0, 21.6, 22.8, 29.5, 30.2, 38.7, 45.0, 58.7, 64.9, 112.4, 127.2, 129.7, 138.9, 143.1, 144.1; MS (ES) m/z 360.2 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for C\(_{19}\)H\(_{27}\)NNaO\(_3\)S: 360.1609. Found: 360.1606.
(3S\textsuperscript{,} 4R\textsuperscript{-})-3-Isopropenyl-1-(p-toluenesulfonyl)-1-aza-spirobicyclo[5.5]undecan-4-ol, 7d

Piperidine 7d was prepared from aldehyde 1d (206 mg, 0.57 mmol) and aqueous HCl (37\%, 150 \(\mu\)L, 1.75 mmol) according to the general procedure 10. Purification by flash column chromatography (hexane:EtOAc, 2:1, \(R_f = 0.34\)) afforded 7d as a white powder (140 mg, 68\%).

mp 115-117 °C (from hexane:EtOAc); IR (film) 3530, 2930, 2870, 1644, 1599, 1495, 1458, 1152, 1106 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 0.90-1.10\) (1H, m), 1.20-1.42 (3H, stack), 1.43-1.63 (5H, stack), 1.64-1.73 (1H, m), 1.79 (3H, s), 1.97 (1H, td, \(J = 12.9, 4.0\) Hz), 2.31-2.44 (4H, stack), 2.45-2.60 (2H, stack), 3.56 (1H, dd, \(J = 13.2, 12.5\) Hz), 4.01-4.12 (2H, stack), 4.73 (1H, s), 5.03 (1H, s), 7.24 (2H, d, \(J = 8.1\) Hz), 7.68 (2H, d, \(J = 8.1\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 21.6, 22.8, 22.9, 23.3, 25.6, 33.0, 36.9, 37.8, 40.7, 47.8, 61.7, 65.3, 112.6, 126.8, 129.5, 141.7, 142.6, 144.0

MS (ES) \(m/z\) 386.0 (100\%, [M+Na]\(^{+}\)); HRMS (ES) Calcd for C\(_{29}\)H\(_{28}\)NNaO\(_3\)S: 386.1766. Found: 386.1769.

(2R, 4R, 5S)-2-tert-Butyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)

piperidine, 7e

Piperidine 7e was prepared from aldehyde 1e (206 mg, 0.59 mmol) and aqueous HCl (37\%, 151 \(\mu\)L 1.76 mmol) according to the general procedure 10. Purification by flash column chromatography (hexane:EtOAc, 5:2, \(R_f = 0.28\)) afforded 7e as a white solid (76 mg, 37\%).
[α]D$^{15}$ -33 (c 1.0 in CHCl₃); mp 89-91 °C (from hexane:EtOAc); IR (film) 3529, 2966, 1644, 1598, 1446, 1400, 1364, 1334, 1226, 1158, 1098 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (9H, s), 1.47-1.71 (5H, stack), 1.82 (1H, dt, J = 12.1, 4.0 Hz), 2.08 (1H, ddd, J = 14.9, 4.6, 2.9 Hz), 2.41 (3H, s), 3.37 (1H, dd, J = 15.1, 12.1 Hz), 3.56 (1H, dd, J = 15.1, 4.4 Hz), 3.71-3.76 (1H, m), 3.89 (1H, dd, J = 8.8, 1.8 Hz), 4.60 (1H, s), 4.94 (1H, s), 7.28 (2H, d, J = 8.1 Hz), 7.74 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.6, 22.8, 28.6, 29.3, 36.4, 41.9, 43.8, 59.8, 63.6, 113.0, 127.5, 129.8, 138.5, 143.3, 143.9; MS (ES) m/z 374.2 (100%, [M+Na]+); HRMS (ES) Calcd for C₁⁹H₂₉NNaO₃S: 374.1766. Found: 374.1777.

(2R, 4R, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 7f

Piperidine 7f was prepared from aldehyde 1f (176 mg, 0.47 mmol) and aqueous HCl (37%, 122 μL, 1.42 mmol) according to the general procedure 10. Purification by flash column chromatography (hexane:EtOAc, 5:2, Rf = 0.19) gave a colourless oil which was purified again by flash column chromatography (DCM:EtOAc, 100:1, Rf = 0.42) to afford cis piperidine 7f as a white solid (60 mg, 34%).
126.7, 127.0, 128.4, 129.8, 138.4, 140.3, 143.4, 143.7; MS (ES) m/z 394.0 (100%, [M+Na]+); HRMS (ES) Calcd for C_{21}H_{25}NNaO_{3}S: 394.1453. Found: 394.1456.

(2R, 4S, 5R)-4-Hydroxy-2-phenyl-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 9

Further elution afforded 9 as colourless crystals (7 mg, 4%).

(DCM:EtOAc, 100:1, R_f = 0.31); [α]_D^{15} -135 (c 0.5 in CHCl_3); mp 185-187 °C (from DCM:hexane); IR (film) 3514, 3028, 2966, 2910, 1648, 1598, 1494, 1454, 1374, 1339, 1166, 1089 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 1.57 (1H, br s), 1.83 (3H, s), 2.01 (1H, dt, \(J = 14.3, 3.7\) Hz), 2.20 (1H, ddd, \(J = 14.3, 11.0, 3.0\) Hz), 2.40 (3H, s), 2.59 (1H, br d, \(J = 11.8\) Hz), 3.11 (1H, t, \(J = 11.8\) Hz), 3.96 (1H, dd, \(J = 11.8, 3.7\) Hz), 4.02-4.05 (1H, m), 4.16 (1H, dd, \(J = 11.0, 3.3\) Hz), 4.74 (1H, s), 5.05 (1H, s), 7.14-7.23 (7H, m), 7.35 (2H, d, \(J = 8.1\) Hz); \(^{13}\)C NMR (75 MHz, CDCl_3) \(\delta\) 21.6, 23.1, 40.9, 45.6, 46.7, 57.8, 63.9, 112.7, 127.6, 127.9, 128.0, 128.7, 129.3, 135.3, 140.3, 143.2, 143.8; MS (ES) m/z 394.0 (100%, [M+Na]^+); HRMS (ES) Calcd for C_{21}H_{25}NNaO_{3}S: 394.1453. Found: 394.1450.

(2R, 4R, 5R)-4-Hydroxy-2-phenyl-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 10

Further elution afforded 10 as a colourless oil (4 mg, 2%).

(DCM:EtOAc, 100:1, R_f = 0.25); IR (neat) 3532, 3027, 2926, 1647, 1599, 1494, 1449, 1337, 1162, 1093 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 1.80 (3H, s), 1.94-2.04 (1H, m), 2.12 (1H, dt, \(J = 12.9, 4.4\) Hz), 2.37-2.48 (5H, stack), 2.70 (1H, dd, \(J = 12.1, 11.0\) Hz).
Hz), 3.65 (1H, td, J = 10.1, 4.4 Hz), 3.94 (1H, dd, J = 11.2, 3.3 Hz), 4.12 (1H, dd, J = 12.1, 3.7 Hz), 4.96 (1H, s), 4.98 (1H, t, J = 13.6, 11.8 Hz), 3.90 (1H, dd, J = 13.6, 3.3 Hz), 4.16-4.27 (1H, m), 4.36 (1H, br d, J = 2.2 Hz), 7.27 (2H, d, J = 8.5 °C, [M+Na]+); HRMS (ES) Calcd for C\textsubscript{21}H\textsubscript{25}NNaO\textsubscript{3}S: 394.1453. Found: 394.1442.

**General Procedure 12 for the Prins Cyclisation Catalysed by HCl Gas**

Anhydrous HCl gas was bubbled through a solution of the aldehyde (0.26 mmol) in DCM (10 mL) at -78 °C for 1 h. The reaction flask was fitted with a CaCl\textsubscript{2} drying tube and stirred for a further 4 h at -78 °C. The reaction mixture was allowed to warm up slowly to room temperature and stirred for a further 24 h, before being quenched by addition of water (10 mL). The aqueous phase was then extracted with DCM (4 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO\textsubscript{4} and concentrated *in vacuo* to afford the crude piperidine.

**\((2S^*, 4R^*, 5S^*)\)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-methyl-1-(p-toluene sulfonyl)piperidine, 11a**

Aldehyde 1a (115 mg, 0.37 mmol) was reacted with HCl gas according to the general procedure 12. Purification by flash column chromatography (hexane:EtOAc, 3:2, \(R_f = 0.30\)) afforded 11a as a white solid (71 mg, 55%).

mp 124-126 °C (from hexane:EtOAc); IR (film) 3517, 2979, 2926, 1598, 1457, 1084, 755 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.29 (3H, d, \(J = 7.4\) Hz), 1.56-1.71 (9H, stack), 2.00 (1H, br s), 2.40 (3H, s), 3.46 (1H, dd, \(J = 13.6, 11.8\) Hz), 3.90 (1H, dd, \(J = 13.6, 3.3\) Hz), 4.16-4.27 (1H, m), 4.36 (1H, br d, \(J = 2.2\) Hz), 7.27 (2H, d, \(J = 8.5\) Hz), 7.27 (2H, d, \(J = 8.5\) Hz).
Hz), 7.71 (2H, d, J = 8.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 19.7, 21.6, 31.1, 31.8, 36.4, 37.8, 47.4, 50.2, 66.2, 71.9, 127.0, 129.8, 138.4, 143.2; MS (ES) m/z 370.2 (4%, [M($^{37}$Cl)+Na$^+$]), 368.2 (22, [M($^{35}$Cl)+Na$^+$]), 333.2 (11), 332.1 (100); HRMS (ES) Calcd for C$_{16}$H$_{24}$ClINaO$_3$S: 368.1063. Found: 368.1051; Anal. calcd for C$_{16}$H$_{24}$ClNO$_3$S: C, 55.56; H, 6.99; N, 4.05. Found: C, 55.42; H, 7.08; N, 3.94.

(2S$^*$, 4S$^*$, 5S$^*$)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-methyl-1-(p-toluene sulfonyl)piperidine, 12a

Further elution afforded piperidine 12a as a colourless oil (14 mg, 11%). (hexane:EtOAc, 3:2, $R_f = 0.21$); IR (film) 3514, 2979, 2928, 1599, 1495, 1455, 1384, 1337, 1159, 1086, 733 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.09 (3H, d, J = 6.6 Hz), 1.58-1.79 (10H, stack), 2.42 (3H, s), 2.90 (1H, dd, J = 14.0, 11.8 Hz), 3.99-4.11 (2H, stack), 4.19-4.30 (1H, m), 7.30 (2H, d, J = 8.5 Hz), 7.71 (2H, d, J = 8.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 17.9, 21.7, 32.2, 32.3, 39.7, 40.5, 48.0, 53.5, 66.9, 72.3, 127.2, 129.9, 137.8, 143.5; MS (ES) m/z 370.2 (2%, [M($^{37}$Cl)+Na$^+$]), 368.2 (13, [M($^{35}$Cl)+Na$^+$]), 332.2 (100); HRMS (ES) Calcd for C$_{16}$H$_{24}$ClINaO$_3$S: 368.1063. Found: 368.1064.

(2S, 4R, 5S)-2-Benzyl-5-(1-chloro-1-methylethyl)-4-hydroxy-1-(p-toluene sulfonyl)piperidine, 11b

Piperidine 11b was prepared from aldehyde 1b (101 mg, 0.26 mmol) and HCl gas according to the general procedure 12. Purification by flash column chromatography (EtOAc:hexane, 1:2, $R_f = 0.36$) afforded 11b as colourless crystals (92 mg, 83%).
[α]D\(^{19}\) -26.6 (c 0.62 in CHCl₃); mp 126-128 °C (from EtOAc:hexane); IR (film) 3517, 2924, 1599, 1495, 1556, 1155, 751 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 1.53 (1H, ddd, \(J = 14.7, 6.4, 2.9\) Hz), 1.65-1.74 (7H, stack), 1.79 (1H, dd, \(J = 14.7, 2.6\) Hz), 2.28 (1H, br s), 2.39 (3H, s), 3.00 (1H, dd, \(J = 13.2, 7.4\) Hz), 3.20 (1H, dd, \(J = 13.2, 9.2\) Hz), 3.57 (1H, dd, \(J = 14.0, 11.4\) Hz), 3.87 (1H, dd, \(J = 14.0, 3.3\) Hz), 4.25-4.33 (1H, m), 4.40 (1H, br s), 7.16-7.28 (7H, m), 7.50 (2H, d, \(J = 8.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 21.6, 31.4, 31.9, 33.8, 37.1, 39.4, 49.6, 53.1, 66.5, 71.7, 126.3, 127.2, 128.5, 129.70, 129.73, 138.0, 139.3, 143.2; MS (ES) \(m/z\) 446.2 (5%, \([M^{(37)}\text{Cl}]+\text{Na}^+\)), 444.2 (32, \([M^{(35)}\text{Cl}]+\text{Na}^+\)), 409.2 (29), 408.1 (100); HRMS (ES) Calcd for C\(_{22}\)H\(_{28}\)ClN\(_3\)NaO\(_3\)S: 444.1376. Found: 444.1383; Anal. calcd for C\(_{22}\)H\(_{28}\)ClN\(_3\)NaO\(_3\)S: C, 62.62; H, 6.69; N, 3.32. Found: C, 62.79; H, 6.93; N, 3.11. 

(2S, 4S, 5S)-2-Benzyl-5-(1-chloro-1-methylethyl)-4-hydroxy-1-(\(p\)-toluene sulfonyl)piperidine, 12b

Further elution afforded piperidine 12b as a colourless oil (10 mg, 9%).

(EtOAc:hexane, 1:2, \(R_f = 0.23\)); [α]D\(^{19}\) -2.0 (c 0.6 in CHCl₃); IR (neat) 3504, 2930, 1598, 1495, 1454, 1316, 1154, 754 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 1.54-1.84 (10H, stack), 2.40 (3H, s), 2.69-2.83 (2H, m), 2.94 (1H, dd, \(J = 14.7, 11.8\) Hz), 4.00 (1H, dd, \(J = 14.7, 5.0\) Hz), 4.07-4.18 (1H, m), 4.29-4.37 (1H, m), 7.11-7.13 (2H, m), 7.21-7.29 (5H, m), 7.58 (2H, d, \(J = 8.1\) Hz); MS (ES) \(m/z\) 446.3 (12%, \([M^{(37)}\text{Cl}]+\text{Na}^+\)), 444.2 (51, \([M^{(35)}\text{Cl}]+\text{Na}^+\)), 409.3 (36), 408.2 (100); HRMS (ES) Calcd for C\(_{22}\)H\(_{28}\)ClN\(_3\)NaO\(_3\)S: 444.1376. Found: 444.1378.
(2R, 4R, 5S)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-isopropyl-1-(p-toluene sulfonyl)piperidine, 11c

Aldehyde 1c (77 mg, 0.23 mmol) was reacted with HCl gas according to the general procedure 12. Purification by flash column chromatography (EtOAc:hexane, 3:2, $R_f = 0.51$) afforded piperidine 11c as a white solid (58 mg, 68%).

$[\alpha]_D^{19}$ -17.9 (c 0.76 in CHCl$_3$); mp 130-132 °C (from EtOAc:hexane); IR (film) 3517, 2966, 1598, 1458, 1150, 759 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.87 (3H, d, $J = 6.6$ Hz), 0.94 (3H, d, $J = 6.6$ Hz), 1.37-1.49 (2H, stack), 1.58 (6H, s), 1.94-2.09 (1H, m), 2.32-2.50 (4H, stack), 3.40 (1H, dd, $J = 14.7$, 12.1 Hz), 3.51 (1H, dd, $J = 10.7$, 6.3 Hz), 3.86 (1H, dd, $J = 14.7$, 3.3 Hz), 4.27 (1H, br s), 7.26 (2H, d, $J = 8.1$ Hz), 7.72 (2H, d, $J = 8.1$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 20.6, 21.1, 21.6, 29.4, 31.1, 31.7, 32.4, 37.5, 48.5, 58.6, 66.6, 71.9, 127.2, 129.8, 138.6, 143.2; MS (ES) $m/z$ 398.2 (7%, [M$^{37}$Cl]+Na$^+$), 396.1 (31, [M$^{35}$Cl]+Na$^+$), 360.1 (100); HRMS (ES) Calcd for C$_{18}$H$_{26}$ClINaO$_3$S: 396.1376. Found: 396.1361; Anal. calcd for C$_{18}$H$_{26}$ClINaO$_3$S: C, 57.82; H, 7.55; N, 3.75. Found: C, 57.94; H, 7.61; N, 3.91.

(2R, 4S, 5S)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-isopropyl-1-(p-toluene sulfonyl)piperidine, 12c

Further elution afforded piperidine 12c as a white powder (4 mg, 5%).

(EtOAc:hexane, 3:2, $R_f = 0.36$); $[\alpha]_D^{19}$ +14.4 (c 0.72 in CHCl$_3$); mp 88-90 °C (from EtOAc:hexane); IR (film) 3514, 2966, 2932, 2873, 1598, 1494, 1454, 1336, 1157, 1091, 756 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.86 (3H, d, $J = 6.6$ Hz), 0.94 (3H, d, $J = 6.6$ Hz), 1.37-1.52 (2H, stack), 1.58 (1H, s), 1.61 (3H, s), 1.66 (3H, s), 1.80-1.88

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(1H, m), 1.97 (1H, dt, J = 13.6, 3.7 Hz), 2.43 (3H, s), 2.83 (1H, dd, J = 15.2, 11.9 Hz), 3.65-3.72 (1H, m), 3.97 (1H, dd, J = 9.2, 3.7 Hz), 4.05 (1H, dd, J = 15.2, 4.4 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 19.4, 20.1, 21.7, 28.5, 32.2, 32.3, 34.4, 41.5, 52.5, 58.8, 67.1, 72.4, 127.3, 129.9, 138.2, 143.5; MS (ES) m/z 398.2 (7%, [M($^{37}$Cl)+Na$^+$]), 396.3 (32%, [M($^{35}$Cl)+Na$^+$]), 374.3 (3, [M($^{35}$Cl)+H$^+$]), 360.2 (100); Anal. calcd for C$_{18}$H$_{26}$ClNO$_3$S: C, 57.82; H, 7.55; N, 3.75. Found: C, 57.64; H, 7.35; N, 3.56.

(3S, 4R)-3-(1-Chloro-1-methylethyl)-1-(p-toluenesulfonyl)-1-aza-spirobicyclo[5.5]undecan-4-ol, 11d

Aldehyde 1d (100 mg, 0.28 mmol) was reacted with HCl gas according to the general procedure 12. Purification by flash column chromatography (hexane:EtOAc, 3:1) afforded 11d as a white powder (72 mg, 65%).

mp 142-144 °C (from hexane:EtOAc); IR (film) 3514, 2931, 1599, 1495, 1459, 1310, 1152, 1090 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 0.94-1.13 (1H, m), 1.20-1.38 (3H, stack), 1.45 (1H, dd, J = 15.3, 3.1 Hz), 1.49-1.62 (3H, stack), 1.64-1.78 (7H, stack), 1.91 (1H, dt, J = 11.6, 2.9 Hz), 1.99 (1H, td, J = 12.9, 4.0 Hz), 2.17 (1H, br s), 2.33-2.46 (4H, stack), 2.57-2.67 (1H, m), 3.66 (1H, dd, J = 13.6, 11.4 Hz), 4.28 (1H, dd, J = 13.6, 2.2 Hz), 4.46 (1H, br s), 7.26 (2H, d, J = 8.5 Hz), 7.69 (2H, d, J = 8.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 21.6, 22.8, 23.4, 25.6, 31.5, 31.8, 33.3, 37.8, 39.1, 39.6, 51.5, 61.7, 67.3, 71.9, 126.9, 129.6, 141.5, 142.8; MS (ES) m/z 424.0 (14%, [M($^{37}$Cl)+Na$^+$]), 422.0 (63, [M($^{35}$Cl)+Na$^+$]), 386.0 (100); HRMS (ES) Calcd for C$_{20}$H$_{30}$ClINaO$_5$S: 422.1533. Found: 422.1515; Anal. calcd for C$_{20}$H$_{30}$ClINaO$_5$S: C, 60.06; H, 7.56; N, 3.50. Found: C, 60.09; H, 7.58; N, 3.69.
(3S', 4S')-3-(1-Chloro-1-methylethyl)-1-(p-toluenesulfonyl)-1-aza-spirobicyclo[5.5]undecan-4-ol, 12d

Further elution afforded piperidine 12d as a white solid (11 mg, 10%). (hexane:EtOAc, 3:1, \( R_f = 0.19 \)); mp 102-104 °C (from hexane:EtOAc); IR (film) 3508, 2929, 2868, 1599, 1495, 1153, 1087, 755 cm\(^{-1}\); \( ^1 \)H NMR (300 MHz, CDCl\(_3\) ) \( \delta \) 0.99-1.45 (3H, stack), 1.50-1.66 (6H, stack), 1.67-2.05 (8H, stack), 2.19 (1H, dd, \( J = 14.0, 4.4 \) Hz), 2.24 (1H, td, \( J = 12.9, 4.0 \) Hz), 2.36-2.47 (4H, stack), 3.15 (1H, dd, \( J = 14.0, 10.3 \) Hz), 3.99-4.17 (2H, stack), 7.27 (2H, d, \( J = 8.5 \) Hz), 7.71 (2H, d, \( J = 8.5 \) Hz); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\) ) \( \delta \) 21.6, 23.0, 23.2, 25.3, 31.4, 32.6, 33.8, 36.2, 40.0, 42.9, 54.9, 62.6, 67.3, 72.8, 127.2, 129.7, 140.5, 143.0; \( m/z \) (ES) 424.0 (2%, \([M^{37}\text{Cl}+\text{Na}]^+\) ), 422.2 (10, \([\text{M+Na}]^+\) ), 386.2 (100); HRMS (ES) Calcd for \( \text{C}_{20}\text{H}_{30}\text{ClNNaO}_5\text{S} \): 422.1533. Found: 422.1517; Anal. calcd for \( \text{C}_{20}\text{H}_{30}\text{ClNO}_5\text{S} \): C, 60.06; H, 7.56; N, 3.50. Found: C, 59.84; H, 7.71; N, 3.77.

(2R, 4R, 5S)-2-tert-Butyl-5-(1-chloro-1-methylethyl)-4-hydroxy-1-(p-toluene sulfonyl)piperidine, 11e

Aldehyde 11e (169 mg, 0.48 mmol) was reacted according to the general procedure 12. Purification by flash column chromatography (hexane:EtOAc, 3:1, \( R_f = 0.19 \)) afforded 11e as a white powder (53 mg, 28%). \([\alpha]_D^{19} +2.2 \) (c 1.0 in CHCl\(_3\) ); mp 108-110 °C (from hexane:EtOAc); IR (film) 3523, 2972, 1598, 1462, 1400, 1366, 1337, 1156, 1093, 757 cm\(^{-1}\); \( ^1 \)H NMR (500 MHz, CDCl\(_3\) ) \( \delta \) 1.07 (9H, s), 1.41 (1H, dt, \( J = 11.4, 3.3 \) Hz), 1.54-1.65 (8H, stack), 2.05-2.12
(1H, m), 2.42 (3H, s), 3.50 (1H, dd, $J = 15.1$, 11.8 Hz), 3.76 (1H, dd, $J = 15.1$, 3.3 Hz), 3.90 (1H, d, $J = 8.8$ Hz), 4.12-4.18 (1H, m), 7.28 (2H, d, $J = 8.1$ Hz), 7.75 (2H, d, $J = 8.1$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 21.7, 28.9, 31.3, 31.7, 31.8, 36.4, 40.1, 47.0, 59.3, 65.1, 72.1, 127.7, 129.8, 138.1, 143.5; MS (ES) $m/z$ 412.0 (8%, [M($^{37}$Cl)+Na$^+$]), 410.2 (38, [M($^{35}$Cl)+Na$^+$]), 374.1 (100); HRMS (ES) Calcd for C$_{19}$H$_{30}$ClINaO$_3$S: 410.1533. Found: 410.1534; Anal. calcd for C$_{19}$H$_{30}$ClNO$_3$S: C, 58.82; H, 7.79; N, 3.61. Found: C, 58.51; H, 7.98; N, 3.96.

(2R, 4S, 5S)-2-tert-Butyl-5-(1-chloro-1-methylethyl)-4-hydroxy-1-(p-toluene sulfonyl)piperidine, 12e

Further elution afforded piperidine 12e as white powder (68 mg, 36%).

(hexane:EtOAc, 3:1, $R_r = 0.09$); $[\alpha]_D^{23} +32.6$ (c 1.1 in CHCl$_3$); mp 106-108 °C (from hexane:EtOAc); IR (film) 3516, 2965, 2872, 1598, 1494, 1401, 1368, 1330, 1155, 1095, 757 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.93 (9H, s), 1.51 (3H, s), 1.62 (3H, s), 1.82-1.95 (4H, stack), 2.43 (3H, s), 3.00 (1H, dd, $J = 15.1$, 12.0 Hz), 3.73 (1H, dd, $J = 15.1$, 5.7 Hz), 4.02 (1H, t, $J = 7.4$ Hz), 4.09-4.16 (1H, m), 7.31 (2H, d, $J = 8.1$ Hz), 7.78 (2H, d, $J = 8.1$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.7, 27.8, 31.3, 31.6, 31.7, 36.7, 43.4, 51.7, 58.1, 67.1, 71.9, 127.8, 129.8, 137.1, 143.9; MS (ES) $m/z$ 412.0 (10%, [M($^{37}$Cl)+Na$^+$]), 410.2 (45, [M($^{35}$Cl)+Na$^+$]), 374.2 (100); HRMS (ES) Calcd for C$_{19}$H$_{30}$ClINaO$_3$S: 410.1533. Found: 410.1540; Anal. calcd for C$_{19}$H$_{30}$ClNO$_3$S: C, 58.82; H, 7.79; N, 3.61. Found: C, 58.88; H, 7.81; N, 3.80.
(2R, 4R, 5S)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-phenyl-1-(p-toluene sulfonyle) piperidine, 11f

Aldehyde 1f (197 mg, 0.53 mmol) was reacted according to the general procedure 12. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.26) afforded piperidine 11f as a white solid (91 mg, 42%). 

[α]D<sup>19</sup> +45.6 (c 1.0 in CHCl₃); mp 134-136 °C (from DCM:hexane); IR (film) 3524, 2929, 1599, 1495, 1448, 1332, 1158, 1094, 757 cm⁻¹; <sup>1</sup>H NMR (300 MHz, CDCl₃) δ 1.51 (3H, s), 1.56-1.63 (5H, stack), 1.86 (1H, ddd, J = 14.9, 6.6, 2.8 Hz), 2.43 (3H, s), 2.57 (1H, dd, J = 14.9, 2.4 Hz), 3.50 (1H, dd, J = 14.3, 12.1 Hz), 4.13 (1H, dd, J = 14.3, 3.3 Hz), 4.27 (1H, br s), 5.34 (1H, d, J = 6.6 Hz), 7.17-7.41 (7H, stack), 7.78 (2H, d, J = 8.1 Hz); <sup>13</sup>C NMR (75 MHz, CDCl₃) δ 21.7, 30.5, 31.4, 35.9, 38.0, 49.9, 52.6, 66.2, 72.1, 125.8, 127.1, 128.9, 130.0, 138.3, 140.1, 143.5; MS (ES) m/z 432.2 (11%, [M<sup>37</sup>Cl]+Na<sup>+</sup>), 430.2 (45, [M<sup>35</sup>Cl]+Na<sup>+</sup>), 394.1 (100); HRMS (ES) Calcd for C₂₁H₂₆ClINaNO₃S: 430.1220. Found: 430.1232.

(2R, 4S, 5S)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-phenyl-1-(p-toluene sulfonyle) piperidine, 12f

Further elution afforded piperidine 12f as a white solid (65 mg, 30%). 

(EtOAc:hexane, 1:2, Rf = 0.17); [α]D<sup>19</sup> +33.4 (c 1.0 in CHCl₃); mp 118-120 °C (from hexane:EtOAc); IR (film) 3514, 2929, 1598, 1495, 1450, 1336, 1157, 757 cm⁻¹; <sup>1</sup>H NMR (300 MHz, CDCl₃) δ 1.56 (3H, s), 1.59 (3H, s), 1.73 (1H, ddd, J = 11.8, 6.6, 4.8 Hz), 1.91 (1H, ddd, J = 14.3, 7.9, 5.9 Hz), 2.01 (1H, br s), 2.29 (1H, ddd, J = 14.3, 6.3, 3.7 Hz), 2.40 (3H, s), 2.97 (1H, dd, J = 14.7, 11.8 Hz), 3.94-4.00 (1H, m), 4.13
(1H, dd, \(J = 14.7, 4.8\) Hz), 5.23 (1H, t, \(J = 5.9\) Hz), 7.22-7.27 (7H, stack), 7.65 (2H, d, \(J = 8.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 21.7, 31.5, 31.6, 37.9, 42.2, 53.5, 54.3, 67.2, 71.8, 126.3, 127.3, 127.4, 128.8, 129.8, 137.6, 140.1, 143.6; MS (ES) \(m/z\) 432.0 (9%, [M\(^{37}\)Cl]+Na\(^+\)), 430.0 (42, [M\(^{35}\)Cl]+Na\(^+\)), 394.0 (100); HRMS (ES) Calcd for C\(_{21}\)H\(_{26}\)CINaO\(_3\)S: 430.1220. Found: 430.1222.

**General Procedure 13 for the Carbonyl Ene Cyclisation Catalysed by MeAlCl\(_2\)**

Methyl aluminium dichloride (1 M solution in hexane, 0.48 mmol) was added to a solution of the aldehyde (0.48 mmol) in CHCl\(_3\) (20 mL). The solution was stirred overnight at reflux, after which it was quenched by addition of water (20 mL). The aqueous phase was then extracted with DCM (4 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO\(_4\) and concentrated in vacuo to afford the crude piperidine.

\((2S^*, 4S^*, 5S^*)\)-4-Hydroxy-2-methyl-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 8a

Piperidine 8a was prepared from aldehyde 1a (102 mg, 0.33 mmol) and MeAlCl\(_2\) (1.0 M in hexane, 330 \(\mu\)L, 0.33 mmol) according to the general procedure 13. Purification by flash column chromatography (hexane:EtOAc, 2:3, \(R_f = 0.20\)) afforded 8a as colourless crystals (70 mg, 69%).

mp 94-96 °C (from hexane:EtOAc); IR (film) 3514, 3076, 2978, 2927, 1645, 1599, 1495, 1453, 1383, 1336, 1160, 1086, 913 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.13 (3H, d, \(J = 7.0\) Hz), 1.48 (1H, td, \(J = 12.0, 5.5\) Hz), 1.72 (3H, s), 1.76 (1H, br s), 1.80-
1.96 (2H, stack), 2.41 (3H, s), 2.90 (1H, dd, J = 14.0, 12.1 Hz), 3.75-3.87 (2H, stack), 4.34-4.43 (1H, m), 4.85 (1H, s), 7.29 (2H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.5 Hz); 13C NMR (125 MHz, CDCl3) δ 17.0, 20.6, 21.6, 37.9, 43.0, 49.2, 52.3, 65.6, 114.5, 127.0, 129.9, 138.1, 142.6, 143.3; MS (ES) m/z 332.2 (100%, [M+Na]+); HRMS (ES) Calcd for C16H23NNaO3S: 332.1296. Found: 332.1306; Anal. calcd for C16H23NO3S: C, 62.11; H, 7.49; N, 4.53. Found: C, 62.14; H, 7.75; N, 4.34.

(2S, 4S, 5S)-2-Benzyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 8b

Piperidine 8b was prepared from aldehyde 1b (100 mg, 0.26 mmol) and MeAlCl2 (1.0 M in hexane, 260 µL, 0.26 mmol) according to the general procedure 13. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.19) afforded 8b as a colourless oil (73 mg, 73%).

[α]D27 -16.1 (c 0.18 in CHCl3); IR (film) 3498, 3058, 2925, 2855, 1644, 1599, 1495, 1454, 1378, 1337, 1155, 1087 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 1.30-1.40 (1H, m), 1.77 (3H, s), 1.88-2.02 (2H, stack), 2.08 (1H, br s), 2.40 (3H, s), 2.80-2.83 (2H, m), 2.99 (1H, dd, J = 14.3, 11.7 Hz), 3.82 (1H, dd, J = 14.3, 4.1 Hz), 3.95 (1H, td, J = 10.8, 4.4 Hz), 4.40-4.47 (1H, m), 4.90 (1H, s), 5.03 (1H, s), 7.14-7.31 (7H, m), 7.56 (2H, d, J = 8.5 Hz); 13C NMR (125 MHz, CDCl3) δ 20.3, 21.3, 34.1, 37.9, 44.2, 51.9, 55.2, 65.8, 114.9, 127.1, 127.4, 129.2, 129.6, 130.2, 138.4, 143.0, 143.8; MS (ES) m/z 408.1 (40%, [M+Na]+), 386.1 (100, [M+H]+), 376.1 (26), 368.1 (11), 270.1 (64), 226.1 (42); HRMS (ES) Calcd for C22H27NNaO3S: 408.1609. Found: 408.1601.
(2R, 4S, 5S)-4-Hydroxy-5-isopropenyl-2-isopropyl-1-(p-toluenesulfonyl) piperidine, 8c

Piperidine 8c was prepared from aldehyde 1c (102 mg, 0.30 mmol) and MeAlCl₂ (1.0 M in hexane, 305 µL, 0.30 mmol) according to the general procedure 13. Purification by flash column chromatography (hexane:EtOAc, 3:2, R₉ = 0.30) afforded 8c as a white solid (85 mg, 83%).

[α]D⁰ 27 -24.8 (c 0.29 in CHCl₃); mp 75-77 °C (from hexane:EtOAc); IR (film) 3515, 3068, 2966, 2932, 2868, 1644, 1599, 1494, 1454, 1337, 1157, 1085 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.93 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.10-1.21 (1H, m), 1.60-1.73 (5H, stack), 1.81-1.96 (1H, m), 2.03-2.09 (1H, m), 2.41 (3H, s), 2.83 (1H, dd, J = 14.9, 12.3 Hz), 3.67-3.84 (3H, stack), 4.75 (1H, s), 4.94 (1H, s), 7.29 (2H, d, J = 8.1 Hz), 7.72 (2H, d, J = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 20.2, 20.41, 20.43, 21.7, 27.8, 32.9, 43.9, 51.2, 60.4, 65.8, 114.3, 127.1, 129.9, 138.7, 142.6, 143.3; MS (ES) m/z 360.1 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₈H₂₇NNaO₃S: 360.1609. Found: 360.1618; Anal. calcd for C₁₈H₂₇NO₃S: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.66; H, 8.04; N, 4.28.

(3S, 4S’)-3-Isopropenyl-1-(p-toluenesulfonyl)-1-aza-spirobicyclo[5.5]undecan-4-ol, 8d

Piperidine 8d was prepared from aldehyde 1d (100 mg, 0.28 mmol) and MeAlCl₂ (1.0 M in hexane, 280 µL, 0.28 mmol) according to the general procedure 13. After 3 h at room temperature and work-up, purification by flash column chromatography (hexane:EtOAc, 2:1, R₉ = 0.28) afforded 8d as a white solid (77 mg, 76%).
mp 144-146 °C (from hexane:EtOAc); IR (film) 3484, 3074, 2931, 2870, 1645, 1599, 1495, 1460, 1328, 1087 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 1.01-1.15 (1H, m), 1.18-1.46 (3H, stack), 1.48-1.64 (5H, stack), 1.78 (3H, s), 1.84 (1H, s), 2.08-2.23 (3H, stack), 2.40 (1H, s), 2.53 (1H, dd, J = 13.2, 4.4 Hz), 3.11 (1H, dd, J = 14.0, 12.1 Hz), 3.79 (1H, td, J = 10.7, 4.4 Hz), 4.21 (1H, dd, J = 14.0, 4.4 Hz), 4.94 (1H, s), 5.02 (1H, s), 7.25 (2H, d, J = 8.1 Hz), 7.67 (2H, d, J = 8.1 Hz); ^13C NMR (75 MHz, CDCl₃) δ 20.7, 21.6, 22.7, 22.8, 25.4, 31.1, 37.0, 39.2, 45.1, 53.6, 63.1, 66.4, 114.4, 126.8, 129.6, 141.5, 142.8, 142.9; MS (ES) m/z 386.0 (100%, [M+Na]^+); HRMS (ES) Calcd for C₁₉H₂₉NNaO₃S: 386.1766. Found: 386.1778.

(2R, 4S, 5S)-2-tert-Butyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl) piperidine, 8e

Piperidine 8e was prepared from aldehyde 1e (168 mg, 0.48 mmol) and MeAlCl₂ (1.0 M in hexane, 480 μL, 0.48 mmol) according to the general procedure 13. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.22) afforded 8e as a colourless oil (147 mg, 87%). 

[α]D²⁰ -6.0 (c 0.3 in CHCl₃); IR (neat) 3498, 2964, 1646, 1598, 1401, 1367, 1336, 1157, 1084 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 1.05 (9H, s), 1.16-1.27 (1H, m), 1.30-1.39 (1H, m), 1.60 (3H, s), 1.71 (1H, s), 2.13 (1H, dd, J = 14.0, 4.4 Hz), 2.42 (3H, s), 3.04 (1H, dd, J = 15.4, 12.3 Hz), 3.79 (1H, dd, J = 15.4, 3.7 Hz), 3.91 (1H, td, J = 11.0, 4.4 Hz), 3.99 (1H, d, J = 8.1 Hz), 4.64 (1H, s), 4.89 (1H, s), 7.30 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz); ^13C NMR (100 MHz, CDCl₃) δ 20.3, 21.6, 29.5, 31.7, 36.9, 46.2, 49.9, 61.4, 66.5, 113.9, 127.2, 129.9, 138.4, 142.6, 143.4; MS (ES) m/z 374.1 (100%, [M+Na]^+); HRMS (ES) Calcd for C₁₉H₂₉NNaO₃S: 374.1766. Found:
374.1768; Anal. calcd for C_{19}H_{29}NO_{3}S: C, 64.92; H, 8.32; N, 3.98. Found: C, 64.83; H, 8.10; N, 3.79.

(2R, 4S, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 8f

Piperidine 8f was prepared from aldehyde 1f (104 mg, 0.28 mmol) and MeAlCl\textsubscript{2} (1.0 M in hexane, 280 \mu L, 0.28 mmol) according to the general procedure 13. Purification by flash column chromatography (EtOAc:hexane, 2:3, \textit{Rf} = 0.26) afforded piperidine 8f as a white solid (82 mg, 79%).

[\alpha]\textsubscript{D}\textsuperscript{19} = -4.3 (c 0.56 in CHCl\textsubscript{3}); mp 41-43 °C (from hexane:EtOAc); IR (film) 3480, 2926, 1646, 1598, 1495, 1449, 1338, 1156, 1086 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 1.56-1.63 (4H, stack), 1.79-1.87 (2H, stack), 2.45 (3H, s), 2.60 (1H, ddd, \textit{J} = 13.6, 4.0, 1.8 Hz), 2.83 (1H, dd, \textit{J} = 14.7, 12.1 Hz), 3.62 (1H, td, \textit{J} = 11.0, 4.0 Hz), 3.88 (1H, dd, \textit{J} = 14.7, 2.9 Hz), 4.70 (1H, s), 4.90 (1H, s), 5.45 (1H, d, \textit{J} = 5.5 Hz), 7.23-7.39 (7H, stack), 7.79 (2H, d, \textit{J} = 8.1 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 20.4, 21.7, 34.5, 44.5, 51.4, 55.7, 65.9, 114.4, 126.5, 127.0, 127.3, 128.9, 130.0, 138.27, 138.28, 142.3, 143.6; MS (ES) \textit{m/z} 394.0 (100%, [M+Na]\textsuperscript{+}); HRMS (ES) Calcd for C\textsubscript{21}H\textsubscript{25}NNaO\textsubscript{3}S: 394.1453. Found: 394.1454.

\textbf{O-tert-Butyldimethylsilyl-DL-homoserine methyl ester, 13}

DL-Homoserine (1.00 g, 8.40 mmol) was added in portions over 20 min to a solution of tert-butyldimethylsilyl chloride (4.40 g, 29.18 mmol) and DBU (4.18 mL, 27.95 mmol) in CH\textsubscript{3}CN (8 mL). The solvent was removed \textit{in vacuo}, and the residue was
dissolved into water (50 mL) and extracted into Et$_2$O (2 x 50 mL). The combined organic phases were washed with water (50 mL) and allowed to stand. A white precipitate formed and was filtered to give O-tert-butylidemethylsilyl-DL-homoserine (1.73 g, 88%).

Decomposes into a brown oil at 172 °C (from Et$_2$O); IR (film) 3409, 2957, 2857, 1623 cm$^{-1}$; $^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 0.12 (6H, s), 0.93 (9H, s), 1.90-2.01 (1H, m), 2.10-2.21 (1H, m), 3.65-3.70 (1H, m), 3.87 (2H, t, $J = 6.3$ Hz); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ -5.4, 19.1, 26.4, 34.5, 54.9, 62.1, 174.1; MS (ES) m/z 256.2 (100%, [M+Na]$^+$), 234.2 (71, [M+H]$^+$); HRMS (ES) Calcd for C$_{10}$H$_{23}$NNaO$_3$Si: 256.1345. Found: 256.1337.

Trimethylsilyldiazomethane (2.0 M in Et$_2$O, 2.7 mL, 5.4 mmol) was added to a solution of O-tert-butylidemethylsilyl-DL-homoserine (0.25 g, 1.07 mmol) in methanol (3 mL) and benzene (10 mL). The mixture was stirred at ambient temperature overnight. The solvents were removed in vacuo to give the methyl ester 13 as a yellow oil (0.26 g, 99%).

(ETOAc:MeOH, 9:1, $R_f = 0.58$); IR (neat) 3383, 2954, 2929, 2856, 1739 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.04 (6H, s), 0.87 (9H, s), 1.56 (2H, br s), 1.66-1.77 (1H, m), 1.90-2.02 (1H, m), 3.61 (1H, dd, $J = 7.7, 4.8$ Hz), 3.65-3.77 (5H, stack); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -5.3, 18.4, 26.0, 35.0, 37.4, 52.0, 60.0, 176.7; MS (ES) m/z 270.1 (100%, [M+Na]$^+$); HRMS (ES) Calcd for C$_{11}$H$_{25}$NNaO$_3$Si: 270.1501. Found: 270.1511.
O-tert-Butyldimethylsilyl-N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl) homoserine methyl ester, 14

A solution of 13 (0.14 g, 0.57 mmol) in DCM (1 mL) was added dropwise to a solution of TsCl (0.13 g, 0.69 mmol) and pyridine (92 µL, 1.14 mmol) in DCM (1 mL) at 0 °C. The resulting solution was warmed to ambient temperature and stirred for 36 h. The reaction mixture was poured into a separating funnel containing cold aqueous HCl (1 M, 2 mL) and DCM (20 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (4 x 20 mL). The combined organic phases were washed with aqueous CuSO₄ (20 mL), brine (20 mL), dried over MgSO₄ and concentrated in vacuo to afford O-tert-butyldimethylsilyl-N-(p-toluenesulfonyl)homoserine methyl ester as a white powder (0.18 g, 80%). (hexane:EtOAc, 2:1; Rₓ = 0.53); mp 51-53 °C (from DCM); IR (film) 3277, 2954, 2929, 2883, 2856, 1744, 1599, 1495, 1344, 1164 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.01 (6H, s), 0.86 (9H, s), 1.87-1.94 (2H, m), 2.40 (3H, s), 3.51 (3H, s), 3.59-3.72 (2H, m), 4.00-4.08 (1H, m), 5.56 (1H, d, J = 8.1 Hz), 7.27 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 8.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ -5.4, 18.3, 21.6, 26.0, 35.3, 52.5, 53.8, 59.3, 127.4, 129.7, 137.0, 143.6, 172.1; MS (ES) m/z 424.1 (100%, [M+Na]+); HRMS (ES) Calcd for C₁₈H₃₁NNaO₅SSi: 424.1590. Found: 424.1598; Anal. calcd for C₁₈H₃₁NO₅SSi: C, 53.83; H, 7.78; N, 3.49. Found: C, 53.65; H, 8.02; N, 3.48.

Cesium carbonate (44 mg, 0.14 mmol) was added to a solution of O-tert-butyldimethylsilyl-N-(p-toluenesulfonyl)homoserine methyl ester (50 mg, 0.12 mmol) in CH₃CN (1.5 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (15 µL, 0.12 mmol) was added. The resulting
mixture was stirred overnight before removing the solvent in vacuo. The resulting solid was dissolved into water (20 mL) and the aqueous phase was extracted with Et₂O (4 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄ and evaporated in vacuo to afford the alkylated product 14 as a colourless oil (58 mg, 100%).

(hexane:EtOAc, 2:1, Rf = 0.59); IR (neat) 2954, 2928, 2856, 1742, 1664, 1598, 1495, 1437, 1344, 1162, 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.03 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.58 (3H, s), 1.62 (3H, s), 1.74-1.86 (1H, m), 2.05-2.17 (1H, m), 2.39 (3H, s), 3.55 (3H, s), 3.62 (2H, t, J = 6.5 Hz), 3.82 (2H, br t, J = 5.7 Hz), 4.72 (1H, t, J = 7.2 Hz), 5.07 (1H, br t, J = 6.5 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ -5.3, -5.2, 17.9, 18.4, 21.6, 25.8, 26.0, 33.3, 43.8, 52.1, 56.1, 59.6, 121.0, 127.6, 129.4, 135.5, 137.9, 143.1, 171.9; MS (ES) m/z 492.1 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₂₃H₃₉NNaO₅S²Si: 492.2216. Found: 492.2221; Anal. calcd for C₂₃H₃₉NO₅S²Si: C, 58.81; H, 8.37; N, 2.98. Found: C, 58.66; H, 8.21; N, 2.97.

**Methyl 2-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-oxo butanoate, 1g**

The silyl ether 14 (0.63 g, 1.34 mmol) was dissolved in MeOH (7 mL) and PPTS (0.34 g, 1.34 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 24 h before removing the solvent in vacuo. Water (50 mL) was added to the residue and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO₄
and concentrated in vacuo to afford \(N\)-(3-methylbut-2-enyl)-\(N\)-(p-toluenesulfonyl)homoserine methyl ester as a colourless oil (0.48 g, 100%).

(hexane:EtOAc, 2:1, \(R_f = 0.15\)); IR (neat) 3532, 2952, 1740, 1598, 1495, 1437, 1337, 1157, 1059 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.59 (3H, s), 1.64 (3H, s), 1.77-1.89 (1H, m), 2.07-2.20 (1H, m), 2.42 (3H, s), 2.52 (1H, br s), 3.48 (3H, s), 3.66-3.94 (4H, stack), 4.75 (1H, dd, \(J = 10.9, 4.6\) Hz), 5.11 (1H, t, \(J = 6.4\) Hz), 7.28 (2H, d, \(J = 8.1\) Hz), 7.71 (2H, d, \(J = 8.1\) Hz); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 17.8, 21.7, 25.8, 32.7, 43.9, 52.2, 56.4, 58.2, 120.7, 127.6, 129.4, 135.9, 137.3, 143.5, 171.5; MS (ES) m/z 378.3 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for \(C_{17}H_{25}NNaO_5S\): 378.1351. Found: 378.1357.

Aldehyde \(1g\) was prepared from \(N\)-(3-methylbut-2-enyl)-\(N\)-(p-toluenesulfonyl)homoserine methyl ester (0.32 g, 0.91 mmol), DMSO (155 \(\mu\)L, 2.18 mmol), oxaly chloride (95 \(\mu\)L, 1.09 mmol) and Et\(_3\)N (635 \(\mu\)L, 4.54 mmol) according to the general procedure 7. Purification by flash column chromatography (EtOAc:hexane, 1:2, \(R_f = 0.29\)) afforded \(1g\) as a colourless oil (0.32 g, 99%).

IR (neat) 2953, 1740, 1674, 1598, 1495, 1438, 1341, 1158 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.59 (3H, s), 1.66 (3H, s), 2.42 (3H, s), 2.70 (1H, dd, \(J = 18.0, 5.2\) Hz), 3.30 (1H, dd, \(J = 18.0, 8.5\) Hz), 3.60 (3H, s), 3.79 (2H, d, \(J = 7.0\) Hz), 4.98 (1H, dd, \(J = 8.5, 5.2\) Hz), 5.01-5.07 (1H, m), 7.29 (2H, d, \(J = 8.3\) Hz), 7.72 (2H, d, \(J = 8.3\) Hz), 9.71 (1H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 17.8, 21.6, 25.8, 44.5, 44.7, 52.6, 53.9, 119.5, 127.6, 129.6, 137.1, 137.6, 143.6, 170.4, 198.2; MS (ES) m/z 376.1 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for \(C_{17}H_{23}NNaO_5S\): 376.1195. Found: 376.1192.
(1R, 4S, 5R)-4-Isopropenyl-2-(p-toluenesulfonyl)-2-aza-6-oxa-bicyclo[3.2.1]octan-7-one, 15

Lactone 15 was prepared from aldehyde 1g (74 mg, 0.21 mmol) and MeAlCl₂ (1.0 M in hexane, 210 µL, 0.21 mmol) at room temperature according to the general procedure 13. After 7 h, work-up and purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.28) afforded 1g as colourless crystals (53 mg, 79%). mp 128-130 °C (from DCM:hexane); IR (film) 2970, 2920, 2862, 1796, 1649, 1598, 1494, 1445, 1349, 1167 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.74 (3H, s), 2.14 (1H, d, J = 12.1 Hz), 2.37-2.46 (4H, stack), 2.60-2.72 (2H, stack), 3.88-4.00 (1H, m), 4.59 (1H, d, J = 5.0 Hz), 4.86 (1H, s), 4.88 (1H, s), 4.92 (1H, s), 7.33 (2H, d, J = 8.1 Hz), 7.74 (2H, d, J = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.8, 22.0, 37.9, 45.1, 46.0, 55.2, 79.3, 114.3, 128.1, 129.9, 134.2, 141.7, 144.5, 171.0; MS (ES) m/z 344.3 (100%, [M+Na]⁺); Anal. calcd for C₁₆H₁₅NO₄S: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.73; H, 6.02; N, 4.50.

(1R, 4S, 5R)-4-(1-Chloro-1-methylethyl)-2-(p-toluenesulfonyl)-2-aza-6-oxa-bicyclo[3.2.1]octan-7-one, 16

Aldehyde 1g (87 mg, 0.25 mmol) was reacted with HCl gas according to the general procedure 12. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.15) afforded a 1:1.3 mixture of piperidines 7g and 11g (68 mg, 74%). This fraction was further reacted with HCl gas. Purification by flash column chromatography (EtOAc:hexane, 1:2, Rf = 0.21) afforded 16 as a white powder (27 mg, 30%).

S53
mp 110-112 °C (from DCM:hexane); IR (film) 2873, 1797, 1598, 1494, 1456, 1350, 1167, 754 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.56 (6H, s), 2.09 (1H, d, \(J = 12.5\) Hz), 2.38-2.48 (5H, stack), 2.62 (1H, t, \(J = 11.8\) Hz), 4.07 (1H, dd, \(J = 11.8, 5.7\) Hz), 4.60 (1H, d, \(J = 4.4\) Hz), 5.17 (1H, d, \(J = 6.3\) Hz), 7.34 (2H, d, \(J = 8.1\) Hz), 7.74 (2H, d, \(J = 8.1\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 21.4, 29.6, 30.7, 37.7, 42.3, 51.3, 54.8, 70.0, 77.3, 128.4, 130.3, 134.6, 145.0, 171.3; MS (ES) \(m/z\) 382.0 (12%, [M\(^{37}\)Cl]+Na\(^+\)), 380.0 (70%, [M\(^{35}\)Cl]+Na\(^+\)), 344.0 (100); HRMS (ES) Calcd for C\(_{16}\)H\(_{20}\)ClNaO\(_4\)S: 380.0699. Found: 380.0707; Anal. calcd for C\(_{16}\)H\(_{20}\)ClNaO\(_4\)S: C, 53.70; H, 5.63; N, 3.91. Found: C, 53.44; H, 5.57; N, 3.70.

\((2R^*, 4R^*, 5S^*)\)-2-Carbomethoxy-5-(1-chloro-1-methylethyl)-4-hydroxy-1-(p-toluene sulfonyl)piperidine, 11g

Further elution afforded piperidine 11g as colourless crystals (26 mg, 27%). (EtOAc:hexane, 1:2, \(R_f = 0.08\)); mp 120-122 °C (from DCM:hexane); IR (film) 3514, 2950, 2924, 1744, 1598, 1494, 1441, 1343, 1186, 1103, 754 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.62 (3H, s), 1.63 (3H, s), 1.70-1.75 (1H, m), 1.85 (1H, ddd, \(J = 14.3, 6.6, 1.8\) Hz), 2.14 (1H, br s), 2.40-2.50 (4H, stack), 3.55-3.64 (4H, stack), 3.91 (1H, dd, \(J = 13.2, 3.7\) Hz), 4.37 (1H, br s), 4.73 (1H, d, \(J = 6.6\) Hz), 7.30 (2H, d, \(J = 8.1\) Hz), 7.73 (2H, d, \(J = 8.1\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 21.7, 31.2, 31.8, 35.7, 38.8, 50.5, 51.6, 52.5, 65.0, 71.6, 127.3, 129.7, 137.5, 143.5, 172.1; MS (ES) \(m/z\) 414.0 (22%, [M\(^{37}\)Cl]+Na\(^+\)), 412.0 (100, [M\(^{35}\)Cl]+Na\(^+\)), 376 (62); HRMS (ES) Calcd for C\(_{17}\)H\(_{24}\)ClNaO\(_5\)S: 412.0961. Found: 412.0955; Anal. calcd for C\(_{17}\)H\(_{24}\)ClNaO\(_5\)S: C, 52.37; H, 6.20; N, 3.59. Found: C, 52.55; H, 6.13; N, 3.65.
(2R*, 4R*, 5S*)-4-Hydroxy-2-hydroxymethyl-5-isopropenyl-1-(p-toluenesulfonyl) piperidine, 19

LiBH₄ (3 mg, 0.15 mmol) was added to a solution of 15 (49 mg, 0.15 mmol) in THF (5 mL) at 0 °C. After stirring the reaction mixture at 0 °C for 2 h, an aqueous solution of NaHCO₃ was added and the aqueous phase was extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo to afford 19 as a white solid (50 mg, 100%).

(hexane:EtOAc, 1:1, Rᵣ = 0.09); mp 110-112 °C (from EtOAc); IR (film) 3425, 2923, 1645, 1494, 1447, 1379, 1336, 1155, 1110, 1046 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.71 (3H, s) overlapping 1.70-1.79 (1H, m), 1.91-2.00 (2H, stack), 2.41 (3H, s), 2.63 (2H, br s), 3.46 (1H, dd, J = 13.6, 12.5 Hz), 3.62-3.72 (2H, stack), 3.79 (1H, dd, J = 11.8, 6.6 Hz), 3.93-3.96 (1H, m), 4.07-4.14 (1H, m), 4.66 (1H, s), 4.98 (1H, s), 7.28 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.6, 22.8, 32.1, 39.4, 45.4, 52.4, 63.4, 64.5, 112.6, 127.0, 129.9, 138.2, 143.5, 143.7; MS (ES) m/z 348.2 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₆H₂₃NNaO₄S: 348.1245. Found: 348.1259.

(2R*, 4R*, 5S*)-2-(tert-Butyl-diphenyl-silyloxy)methyl)-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)piperidine, 20

Imidazole (27 mg, 0.39 mmol) was added to a solution of 19 (51 mg, 0.16 mmol) in DCM (5 mL). TBDPSCI (41 µL, 0.16 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for a further 4 h at 0 °C. After warming up to room temperature, water was added (15 mL) and the aqueous phase was extracted with
DCM (4 x 20 mL). The combined organic phases were washed with brine (20 mL),
dried over MgSO₄ and concentrated \textit{in vacuo}. Purification by flash column
chromatography (hexane:EtOAc, 4:1, \(R_f = 0.27\)) afforded 20 as a white solid (77 mg,
87%).

mp 110-112 °C (from hexane:EtOAc); IR (film) 3480, 3070, 2930, 1639, 1599, 1496,
1452, 1340, 1159, 1091 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.05 (9H, s), 1.66-1.77
(4H, stack), 1.98 (1H, br d, \(J = 11.8\) Hz), 2.11 (1H, dd, \(J = 14.3, 2.2\) Hz), 2.19 (1H, s),
2.36 (3H, s), 3.19 (1H, dd, \(J = 14.0, 12.5\) Hz), 3.57 (1H, dd, \(J = 14.0, 3.8\) Hz), 3.74
(1H, dd, \(J = 10.3, 6.3\) Hz), 3.86 (1H, dd, \(J = 10.3, 6.6\) Hz), 3.95 (1H, br s), 4.19-4.26
(1H, m), 4.53 (1H, s), 4.92 (1H, s), 7.13 (2H, d, \(J = 8.1\) Hz), 7.34-7.46 (6H, m), 7.65
(6H, d, \(J = 8.1\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 19.3, 21.6, 22.7, 27.0, 31.7, 39.3,
45.4, 52.5, 64.2, 65.2, 112.1, 127.0, 127.8, 129.7, 129.8, 133.1, 133.3, 135.8, 138.5,
143.0, 144.1; MS (ES) \(m/z\) 586.2 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for
C\(_{32}\)H\(_{41}\)NNaO\(_4\)SSi: 586.2423. Found: 586.2402; Anal. calcd for C\(_{32}\)H\(_{41}\)NO\(_4\)SSi: C,
68.17; H, 7.33; N, 2.48. Found: C, 67.97; H, 7.32; N, 2.53.

\((2R^*, 4S^*, 5S^*)-2-(\text{tert-Butyl-diphenyl-silanyloxymethyl})-4-hydroxy-5-isopropenyl\)
-1-(\(\rho\)-toluenesulfonyl)piperidine, 21

MeAlCl\(_2\) (1.0 M in hexane, 100 \(\mu\)L, 0.10 mmol) was added to a solution of \textit{cis}
piperidine 20 (57 mg, 0.10 mmol) in CHCl\(_3\) (10 mL). The solution was stirred at reflux
for 1 h, after which it was quenched by addition of water (10 mL). The aqueous
phase was then extracted with DCM (4 x 20 mL). The combined organic phases were
washed with brine (20 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification
by flash column chromatography (hexane:EtOAc, 4:1, \( R_f = 0.15 \)) afforded trans piperidine 21 as a colourless oil (34 mg, 61%).

IR (neat) 3456, 3072, 2931, 2889, 2858, 1645, 1598, 1494, 1445, 1343, 1161, 1112 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.06 (9H, s), 1.19-1.35 (1H, m), 1.55 (3H, s), 1.59-1.78 (2H, stack), 2.19 (1H, dd, \( J = 13.2, 4.4 \) Hz), 2.40 (3H, s), 2.70 (1H, dd, \( J = 14.0, 12.1 \) Hz), 3.46 (1H, td, \( J = 11.0, 4.4 \) Hz), 3.59-3.74 (3H, stack), 4.28-4.35 (1H, m), 4.67 (1H, s), 4.90 (1H, s), 7.22 (2H, d, \( J = 8.1 \) Hz), 7.36-7.48 (6H, m), 7.58-7.72 (6H, m); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 19.3, 20.5, 21.6, 27.0, 32.2, 44.9, 51.3, 54.4, 63.1, 65.9, 114.3, 126.9, 127.9, 129.9, 130.0, 133.1, 133.2, 135.8, 138.3, 142.5, 143.3; MS (ES) \( m/z \) 586.2 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for C\(_{32}\)H\(_{41}\)NNaO\(_4\)S\(_3\)i: 586.2423. Found: 586.2426.

**General Procedure 14 for the Alkylation of the Cyano N-Sulfonamide with Crotyl Chloride**

Cesium carbonate (4.63 mmol) was added to a solution of the sulfonamide (4.21 mmol) in CH\(_3\)CN (50 mL). The reaction mixture was stirred at ambient temperature for 30 min before crotyl chloride (4.21 mmol) and NBu\(_4\)l (0.42 mmol) were added. The resulting mixture was stirred until the reaction was judged to be complete by TLC analysis (4-10 days), before removing the solvent \textit{in vacuo}. Water (50 mL) was added to the resulting solid and the aqueous phase was extracted with Et\(_2\)O (4 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford the crude alkylated product.
(3S)-[N-(But-2-enyl)-N-(p-toluenesulfonyl)amino]butyronitrile, 22a

Nitrile 3a (1.00 g, 4.21 mmol) was reacted with crotyl chloride (410 µL, 4.21 mmol), Cs$_2$CO$_3$ (1.51 g, 4.63 mmol) and NBu$_4$I (0.016 g, 0.42 mmol) according to the general procedure 14. Purification by flash column chromatography (EtOAc:hexane, 1:3, $R_f = 0.25$) afforded 22a as a colourless oil (0.88 g, 71%).

The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, only the signals resulting from the major trans stereoisomer are reported.

$[\alpha]_D^{19}$ +12.5 (c 0.5 in CHCl$_3$); IR (neat) 2978, 2938, 2857, 2252, 1672, 1598, 1494, 1453, 1339, 1158 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.26 (3H, d, $J = 7.0$ Hz), 1.67 (3H, d, $J = 5.5$ Hz), 2.42 (3H, s), 2.57 (1H, dd, $J = 16.7$, 8.2 Hz), 2.75 (1H, dd, $J = 16.7$, 6.4 Hz), 3.66 (1H, dd, $J = 15.8$, 7.4 Hz), 3.83-3.90 (1H, m), 4.10-4.22 (1H, m), 5.33-5.46 (1H, m), 5.54-5.71 (1H, m), 7.30 (2H, d, $J = 8.1$ Hz), 7.71 (2H, d, $J = 8.1$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.5, 17.8, 21.4, 24.6, 46.3, 50.5, 117.4, 127.0, 127.4, 129.6, 129.8, 137.3, 143.5; MS (ES) $m/z$ 315.1 (100%, [M+Na]$^+$); HRMS (ES) Calcd for C$_{15}$H$_{20}$N$_2$NaO$_2$S: 315.1143. Found: 315.1139; Anal. calcd for C$_{15}$H$_{20}$N$_2$O$_2$S: C, 61.61; H, 6.89; N, 9.58. Found: C, 61.58; H, 6.86; N, 9.69.

(3S)-[N-(But-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutyronitrile, 22b

Nitrile 3b (1.78 g, 5.68 mmol) was reacted crotyl chloride (555 µL, 5.68 mmol), Cs$_2$CO$_3$ (2.04 g, 6.25 mmol) and NBu$_4$I (0.21 g, 0.57 mmol) according to the general procedure 14. Purification by flash column chromatography (hexane:EtOAc, 3:1, $R_f = 0.18$) afforded 22b as a white solid (1.87 g, 89%).
The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, only the signals resulting from the major trans isomer are reported.

$\alpha_0^{15}$ -20 (c 1.0 in CHCl$_3$); mp 65-67 °C (from hexane:EtOAc); IR (film) 3027, 2923, 2249, 1671, 1598, 1496, 1454, 1380, 1339, 1304, 1157 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.66 (3H, d, J = 6.6 Hz), 2.38 (3H, s), 2.52 (1H, dd, J = 16.9, 5.5 Hz), 2.74-2.85 (1H, m), 2.96 (2H, d, J = 8.1 Hz), 3.71-3.94 (2H, m), 4.15-4.25 (1H, m), 5.34-5.45 (1H, m), 5.55-5.74 (1H, m), 7.08-7.11 (2H, m), 7.21-7.26 (5H, m), 7.64 (2H, d, J = 8.1 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.5, 21.3, 22.0, 39.0, 47.4, 56.6, 117.4, 126.9, 127.1, 127.7, 128.6, 128.8, 129.5, 130.1, 136.5, 137.2, 143.4; MS (ES) m/z 391.1 (100%, [M+Na]$^+$); HRMS (ES) Calcd for C$_{21}$H$_{24}$N$_2$NaO$_2$S: 391.1456. Found: 391.1461; Anal. calcd for C$_{21}$H$_{24}$N$_2$O$_2$S: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.20; H, 6.56; N, 7.55.

(3R)-[N-((But-2-ethyl)-N-(p-toluenesulfonyl)amino]-4,4-dimethylpentanitrile, 22e

Nitrile 3e (0.91 g, 3.26 mmol) was reacted with crotol chloride (317 μL, 3.26 mmol), Cs$_2$CO$_3$ (1.17 g, 3.58 mmol) and NBut$_4$I (0.12 g, 0.33 mmol) according to the general procedure 14. Purification by flash column chromatography (hexane:EtOAc, 4:1, $R_f = 0.24$) afforded 22e as a white solid (0.98 g, 90%).

The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, only the signals resulting from the major trans isomer are reported.

$\alpha_0^{20}$ -16.1 (c 1.0 in CHCl$_3$); mp 56-58 °C (from hexane:EtOAc); IR (film) 2967, 2249, 1660, 1598, 1449, 1404, 1371, 1330, 1157 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.99
(9H, s), 1.56 (3H, d, J = 6.6 Hz), 2.29-2.37 (4H, stack), 2.48 (1H, br d, J = 13.2 Hz), 3.39-3.75 (2H, m), 4.12-4.26 (1H, m), 5.23-5.39 (1H, m), 5.46-5.54 (1H, m), 7.26 (2H, d, J = 7.7 Hz), 7.66-7.81 (2H, m); ^13^C NMR (75 MHz, CDCl_3) δ 17.6, 17.7, 21.6, 27.9, 36.5, 46.9, 62.7, 118.4, 128.1, 128.2, 129.5, 129.7, 137.2, 143.7; MS (ES) m/z 357.1 (100%, [M+Na]^+); HRMS (ES) Calcd for C_{18}H_{26}N_2NaO_2S: 357.1613. Found: 357.1621; Anal. calcd for C_{18}H_{26}N_2O_2S: C, 64.64; H, 7.84; N, 8.38. Found: C, 64.47; H, 8.04; N, 8.33.

(3S)-[N-(But-2-enyl)-N-(p-toluenesulfonyl)amino]butanal, 23a

Aldehyde 23a was prepared from nitrile 22a (0.32 g, 1.09 mmol) and DIBAL-H (1.0 M in toluene, 1.31 mL, 1.31 mmol) according to the general procedure 9. Work-up afforded 23a as a yellow oil (0.31 g, 96%).

The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, only the signals resulting from the major trans stereoisomer are reported.

(DCM:MeOH, 100:1, R_f = 0.30); [α]_D^19 +23.8 (c 0.53 in CHCl_3); IR (neat) 2976, 2923, 2857, 1724, 1672, 1598, 1495, 1452, 1381, 1335, 1159 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 1.07 (3H, d, J = 7.0 Hz), 1.64 (3H, d, J = 6.3 Hz), 2.40 (3H, s), 2.52 (1H, ddd, J = 16.9, 7.4, 1.5 Hz), 2.71 (1H, ddd, J = 16.9, 6.6, 1.8 Hz), 3.64 (1H, dd, J = 15.8, 7.4 Hz), 3.82 (1H, dd, J = 15.8, 5.7 Hz), 4.39-4.51 (1H, m), 5.34-5.45 (1H, m), 5.48-5.67 (1H, m), 7.27 (2H, d, J = 8.1 Hz), 7.67 (2H, d, J = 8.1 Hz), 9.62 (1H, s); ^13^C NMR (75 MHz, CDCl_3) δ 17.6, 18.9, 21.4, 46.1, 48.8, 49.6, 127.0, 128.1, 129.2, 129.6, 137.9, 143.3, 200.2; MS (ES) m/z 318.1 (100%, [M+Na]^+); HRMS (ES) Calcd for C_{16}H_{21}NNaO_2S: 318.1140. Found: 318.1137.
(3S)-[N-(But-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanal, 23b

Aldehyde 23b was prepared from nitrile 22b (0.21 g, 0.56 mmol) and DIBAL-H (1.0 M in toluene, 680 µL, 0.68 mmol) according to the general procedure 9. Purification by flash column chromatography (DCM:MeOH, 50:1, Rf = 0.36) afforded 23b as a colourless oil (0.19 g, 90%). The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, only the signals resulting from the major trans stereoisomer are reported.

[α]D21 -22.1 (c 1.0 in CHCl3); IR (neat) 3028, 2926, 1725, 1599, 1496, 1454, 1338, 1156 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 1.68 (3H, d, J = 5.5 Hz), 2.39 (3H, s), 2.53 (1H, ddd, J = 16.9, 5.9, 0.9 Hz), 2.73-2.83 (2H, stack), 2.88 (1H, dd, J = 13.6, 5.9 Hz), 3.70-3.91 (2H, m), 4.44-4.53 (1H, m), 5.32-5.42 (1H, m), 5.55-5.72 (1H, m), 7.10 (2H, d, J = 7.7 Hz), 7.20-7.25 (5H, m), 7.61 (2H, d, J = 8.5 Hz), 9.42 (1H, s); ¹³C NMR (75 MHz, CDCl3) δ 17.7, 21.6, 40.4, 42.0, 46.7, 55.3, 126.9, 127.3, 127.8, 128.7, 129.2, 129.7, 129.9, 137.5, 137.9, 143.4, 200.1; MS (ES) m/z 394.0 (100%, [M+Na]+); HRMS (ES) Calcd for C21H26NNaO3S: 394.1453. Found: 394.1448.

(3R)-[N-(But-2-enyl)-N-(p-toluenesulfonyl)amino]-4,4-dimethylpentanal, 23e

Aldehyde 23e was prepared from nitrile 22e (0.30 g, 0.90 mmol) and DIBAL-H (1.0 M in toluene, 1.08 mL, 1.08 mmol) according to the general procedure 9. Work-up afforded 23e as a white powder (0.296 g, 98%).
The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, when it was possible, the cis isomer is referred to as “minor” and trans isomer as “major”.

(DCM:MeOH, 100:1, \(R_f = 0.46\)); \([\alpha]_D^{23} -16.3\) (c 1.0 in CHCl\(_3\)); mp 46-48 °C (from DCM); IR (film) 2963, 1724, 1668, 1598, 1494, 1444, 1399, 1367, 1340, 1305, 1159 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.91 (9H, s), 1.57 (3H from minor, d, \(J = 5.2\) Hz), 1.62 (3H from major, d, \(J = 5.2\) Hz), 2.13 (1H, br d, \(J = 16.0\) Hz), 2.37 (3H, s), 2.57 (1H, br dd, \(J = 16.0, 7.5\) Hz), 3.49 (1H, dd, \(J = 16.0, 5.7\) Hz), 3.65-3.81 (1H, m), 4.37 (1H, br s), 5.40-5.60 (2H, m), 7.23 (2H, d, \(J = 8.1\) Hz), 7.64 (2H, d, \(J = 8.1\) Hz), 9.48 (1H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 13.0, 17.7, 21.5, 27.4, 27.6, 36.1, 43.2, 47.5, 60.4, 127.7, 127.8, 129.4, 129.6, 137.1, 143.5, 199.7; MS (ES) \(m/z\) 360.0 (100%, [M+Na]+); HRMS (ES) Calcd for C\(_{18}\)H\(_{27}\)NNaO\(_3\)S: 360.1609. Found: 360.1613.

**General Procedure 15 for the Carbonyl Ene Cyclisation of the N-crotyl sulfonamide catalysed by MeAlCl\(_2\)**

Methyl aluminium dichloride (1 M in hexane, 1.03 mmol) was added to a solution of the aldehyde (0.34 mmol) in CH\(_2\)Cl\(_2\) (40 mL). The resulting solution was then stirred at room temperature for the specified time. After addition of Rochelle salt (40 mL), the resulting mixture was stirred vigorously for 15 min and the aqueous salt was then extracted with DCM (4 x 40 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO\(_4\) and concentrated *in vacuo* to afford the crude reaction mixture.
(2S, 4R, 5S)-4-Hydroxy-2-methyl-1-(p-toluenesulfonyl)-5-vinyl piperidine, 24a

Aldehyde 23a (100 mg, 0.34 mmol) was reacted with MeAlCl₂ (1.02 mL, 1.02 mmol) according to the general procedure 15. Purification by flash column chromatography (hexane:EtOAc, 3:2, Rₜ = 0.26) afforded piperidine 24a as a colourless oil (10 mg, 10%).

[α]D²⁵ -6.3 (c 0.58 in CHCl₃); IR (neat) 3528, 2923, 1641, 1598, 1494, 1454, 1383, 1336, 1305, 1154, 1092 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.23 (3H, d, J = 7.0 Hz), 1.53 (1H, br s), 1.74-1.80 (2H, m), 2.24-2.31 (1H, m), 2.41 (3H, s), 3.28 (1H, app t, J = 13.2 Hz), 3.64 (1H, dd, J = 13.2, 4.4 Hz), 3.96 (1H, br s), 4.14-4.23 (1H, m), 5.13 (1H, d, J = 17.7 Hz), 5.24 (1H, d, J = 11.0 Hz), 5.71-5.84 (1H, m), 7.27 (2H, d, J = 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 19.2, 21.6, 36.3, 38.3, 43.6, 47.4, 67.3, 117.9, 127.1, 129.8, 136.7, 138.5, 143.1; MS (ES) m/z 318.1 (100%, [M+Na]⁺); HRMS (ES) Calcd for C₁₅H₂₁NNaO₃S: 318.1140. Found: 318.1129; Anal. calcd for C₁₅H₂₁NO₃S: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.99; H, 7.47; N, 4.72.

(2S, 4S, 5R)-4-Hydroxy-2-methyl-1-(p-toluenesulfonyl)-5-vinyl piperidine, 26a

Further elution afforded a 77:23 (determined by analytical HPLC of the fraction) mixture of piperidines 26a and 25a as a colourless oil (40 mg, 40%).

Further purification by preparative HPLC (water-methanol gradient) allowed separation of the 2 diastereoisomers and afforded piperidine 26a as a colourless oil. Analytical HPLC was run at a flow rate of 1.0 mL/min using a water-methanol gradient; 100% water to 100% methanol over 40 minutes followed by 10 minutes at 100% methanol.
Preparative HPLC was run at a flow rate of 10.0 mL/min using a water-methanol gradient; 100% water to 100% methanol over 40 minutes followed by 10 minutes at 100% methanol.

(hexane:EtOAc, 3:2, \( R_f = 0.13 \)); Analytical HPLC (water-methanol gradient): \( t_r = 23.84 \text{ min} \); \([\alpha]_D^{25} +2.5 \text{ (c 0.55 in CHCl}_3\) \); IR (neat) 3469, 2979, 2931, 1640, 1598, 1495, 1452, 1382, 1324, 1165, 1086 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.02 (3H, d, \( J = 6.6 \text{ Hz} \)), 1.57-1.74 (2H, m), 1.80 (1H, br s), 2.40 (3H, s), 2.48-2.57 (1H, m), 3.23 (1H, dd, \( J = 13.1, 2.6 \text{ Hz} \)), 3.68 (1H, dd, \( J = 13.1, 2.6 \text{ Hz} \)), 3.87-3.96 (1H, m), 4.18-4.21 (1H, m), 5.18-5.28 (2H, stack), 5.79-5.92 (1H, m), 7.27 (2H, d, \( J = 8.1 \text{ Hz} \)), 7.66 (2H, d, \( J = 8.1 \text{ Hz} \)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 16.0, 21.6, 36.6, 43.7, 45.1, 49.4, 65.5, 120.2, 127.2, 129.7, 133.4, 137.7, 143.3; MS (ES) m/z 318.2 (100\%), [M+Na]\(^+\); HRMS (ES) Calcd for C\(_{15}\)H\(_{21}\)NNaO\(_3\)S: 318.1140. Found: 318.1149; Anal. calcd for C\(_{15}\)H\(_{21}\)NO\(_3\)S: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.71; H, 7.46; N, 4.72.

\((2\text{S, 4S, 5S)-4-Hydroxy-2-methyl-1-(p-toluenesulfonyl)-5-vinyl piperidine, 25a})\)

Further elution (preparative HPLC) afforded piperidine 25a as a colourless oil.

(hexane:EtOAc, 3:2, \( R_f = 0.13 \)); Analytical HPLC (water-methanol gradient): \( t_r = 24.34 \text{ min} \); \([\alpha]_D^{25} +34.5 \text{ (c 0.77 in CHCl}_3\) \); IR (neat) 3434, 2979, 2927, 1642, 1598, 1494, 1460, 1336, 1159, 1085 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.10 (3H, d, \( J = 7.0 \text{ Hz} \)), 1.49 (1H, td, \( J = 12.5, 5.4 \text{ Hz} \)), 1.81 (1H, ddd, \( J = 12.5, 4.3, 2.2 \text{ Hz} \)), 1.90-2.03 (1H, m), 2.41 (3H, s), 2.50 (1H, br s), 2.85 (1H, dd, \( J = 13.7, 11.4 \text{ Hz} \)), 3.62 (1H, td, \( J = 10.8, 4.0 \text{ Hz} \)), 3.80 (1H, dd, \( J = 13.7, 4.4 \text{ Hz} \)), 4.32-4.45 (1H, m), 5.22 (1H, d, \( J = 11.0 \text{ Hz} \)), 5.26 (1H, d, \( J = 2.6 \text{ Hz} \)), 5.50-5.63 (1H, m), 7.28 (2H, d, \( J = 8.1 \text{ Hz} \)), 7.69 (2H, d, \( J = 8.1 \text{ Hz} \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 16.8, 21.7, 37.8, 43.1, 49.2, 49.5,
67.3, 120.0, 127.1, 129.9, 135.7, 138.0, 143.4; MS (ES) m/z 318.1 (100%, [M+Na]+); HRMS (ES) Calcd for C_{15}H_{21}NNaO_3S: 318.1140. Found: 318.1141; Anal. calcd for C_{15}H_{21}NO_3S: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.95; H, 7.12; N, 4.85.

(2S, 4R, 5S)-2-Benzyl-4-hydroxy-1-(p-toluenesulfonyl)-5-vinyl piperidine, 24b

Aldehyde 23b (88 mg, 0.24 mmol) was reacted with MeAlCl_2 (720 μL, 0.72 mmol) according to the general procedure 15. Purification by flash column chromatography (hexane:EtOAc, 2:1, R_f = 0.30) afforded piperidine 24b as a white powder (15 mg, 18%).

[α]_D^{15} -51 (c 0.5 in CHCl_3); mp 70-72 °C (from hexane:EtOAc); IR (neat) 3526, 3062, 3026, 2923, 1639, 1598, 1494, 1453, 1333, 1153, 1092 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) δ 1.53-1.63 (1H, m), 1.84 (1H, dd, J = 14.5, 1.7 Hz), 2.38-2.43 (5H, stack), 2.89 (1H, dd, J = 13.2, 6.4 Hz), 3.18 (1H, dd, J = 13.2, 9.6 Hz), 3.38 (1H, dd, J = 13.6, 12.1 Hz), 3.67 (1H, dd, J = 13.6, 4.2 Hz), 3.99 (1H, m), 4.22-4.29 (1H, m), 5.15 (1H, d, J = 18.0 Hz), 5.27 (1H, d, J = 11.0 Hz), 5.74-5.85 (1H, m), 7.18-7.26 (7H, m), 7.54 (2H, d, J = 8.1 Hz); \(^{13}\)C NMR (75 MHz, CDCl_3) δ 21.6, 31.9, 38.7, 38.9, 43.2, 53.1, 67.3, 117.9, 126.3, 127.1, 128.5, 129.7, 129.8, 136.7, 138.2, 139.3, 143.1; MS (ES) m/z 394.3 (100%, [M+Na]+); HRMS (ES) Calcd for C_{21}H_{25}NNaO_3S: 394.1453. Found: 394.1445.
(2S, 4S, 5R)-2-Benzyl-4-hydroxy-1-(p-toluenesulfonyl)-5-vinyl piperidine 26b

Further elution afforded piperidines 26b and 25b in a 77:23 ratio as colourless crystals (53 mg, 60%).

The diastereomers were not separable by flash column chromatography so data were recorded on the mixture. In NMR assignments, piperidine 26b is referred to as “major” and piperidine 25b as “minor”.

(hexane:EtOAc, 2:1, \( R_t = 0.14 \)); IR (film) 3505, 3026, 2930, 1640, 1599, 1496, 1454, 1339, 1159, 1091 cm\(^{-1} \); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.30-1.45 (1H from major and 1H from minor, stack), 1.56 (1H from major and 1H from minor, br s), 1.65 (1H from major, dd, \( J = 13.2, 3.3 \text{ Hz} \)), 1.85-1.90 (1H from minor, m), 1.97-2.08 (1H from minor, m), 2.39 (3H from minor, s), 2.40 (3H from major, s), 2.58-2.64 (2H from major and 1H from minor, m), 2.74-2.82 (1H from major and 1H from minor, mr), 2.95 (1H from minor, dd, \( J = 14.3, 11.8 \text{ Hz} \)), 3.33 (1H from major, dd, \( J = 13.4, 2.8 \text{ Hz} \)), 3.69-3.80 (2H from minor, m), 3.88 (1H from major, d, \( J = 14.0 \text{ Hz} \)), 4.03-4.07 (1H from major, m), 4.31-4.34 (1H from major, m), 4.38-4.46 (1H from minor, m), 5.22-5.29 (2H from major and 2H from minor, m), 5.56-5.68 (1H from minor, m), 5.76-5.88 (1H from major, m), 7.09-7.28 (7H from major and 7H from minor, m), 7.55 (2H from minor, d, \( J = 8.1 \text{ Hz} \)), 7.69 (2H from major, d, \( J = 8.5 \text{ Hz} \)); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 21.6 (from major and minor), 31.1 (from major), 34.0 (from minor), 36.0 (from major), 37.3 (from minor), 43.8 (from minor), 44.3 (from major), 45.1 (from major), 49.1 (from minor), 55.2 (from minor), 55.6 (from major), 65.4 (from major), 67.4 (from minor), 119.9 (from minor), 120.6 (from major), 126.8 (from major and minor), 127.1 (from major and minor), 128.8 (from major and minor), 129.2 (from major and minor), 129.8
(from major and minor), 133.2 (from major), 135.7 (from minor), 137.9 (from major and minor), 143.4 (from major and minor), (1 Cq from major and 1 Cq from minor are not visible); MS (ES) m/z 394.1 (100%, [M+Na]+); HRMS (ES) Calcd for C21H25NNaO3S: 394.1453. Found: 394.1450.

(2R, 4R, 5S)-2-tert-Butyl-4-hydroxy-1-(p-toluenesulfonyl)-5-vinyl piperidine, 24e

Aldehyde 23e (101 mg, 0.30 mmol) was reacted with MeAlCl2 (1.0 M in hexane, 900 µL, 0.90 mmol) according to the general procedure 15. Purification by flash column chromatography (DCM:MeOH, 50:1, Rf = 0.18) gave a colourless oil which was recolumned (hexane:EtOAc, 2:1, Rf = 0.30) affording cis piperidine 24e as a colourless oil (7 mg, 7%).

IR (neat) 3520, 3061, 3025, 2963, 1642, 1598, 1496, 1452, 1397, 1365, 1335, 1156, 1095 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (9H, s), 1.44 (1H, dd, J = 18.0, 6.8 Hz), 1.57 (1H, br s), 1.72-1.80 (1H, m), 2.33-2.47 (4H, stack), 3.11 (1H, dd, J = 15.4, 10.7 Hz), 3.55-3.70 (2H, stack), 3.94 (1H, t, J = 7.5 Hz), 5.07 (1H, d, J = 17.3 Hz), 5.21 (1H, d, J = 10.5 Hz), 5.61 (1H, ddd, J = 17.3, 10.5, 8.1 Hz), 7.30 (2H, d, J = 8.2 Hz), 7.77 (2H, d, J = 8.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.7, 27.7, 29.1, 36.7, 42.3, 44.7, 61.2, 66.0, 119.7, 127.6, 129.8, 135.0, 138.2, 143.5; MS (ES) m/z 360.2 (100%, [M+Na]+); HRMS (ES) Calcd for C₁₈H₂₇NNaO₃S: 360.1609. Found: 360.1595.
N-But-2-enyl-p-toluenesulfonamide, 27

Aldehyde 23a (100 mg, 0.34 mmol) was reacted with HCl gas according to the general procedure 12. Purification by flash column chromatography (hexane:EtOAc, 2:1, \( R_f = 0.34 \)) afforded 27 as a colourless oil (33 mg, 43%).

The cis and trans isomers were not separable by flash column chromatography so data were recorded on the mixture. In the case of the NMR spectra, the trans stereoisomer is referred to as “major” and the cis stereoisomer as “minor”.

IR (neat) 3280, 2922, 1598, 1496, 1449, 1328, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\), δ 1.55 (3H from minor, d, \( J = 7.0 \) Hz), 1.60 (3H from major, dd, \( J = 6.6, 1.5 \) Hz), 2.43 (3H, s), 3.50 (2H from major, t, \( J = 6.3 \) Hz), 3.60 (2H from minor, t, \( J = 6.3 \) Hz), 4.39 (1H, br t, \( J = 5.5 \) Hz), 5.27-5.38 (1H, m), 5.50-5.63 (1H, m), 7.31 (2H, d, \( J = 8.3 \) Hz), 7.74 (2H, d, \( J = 8.3 \) Hz); \(^3\)C NMR (75 MHz, CDCl\(_3\)) δ 13.1 (from minor), 17.7 (from major), 21.7, 40.0 (from minor), 45.5 (from major), 124.8 (from minor), 125.8 (from major), 127.3, 128.9 (from minor), 129.8, 129.9 (from major), 137.2, 143.5; MS (ES) \( m/z \) 248.0 (100%, [M+Na]\(^+\)); HRMS (ES) Calcd for C\(_{11}\)H\(_{15}\)NNaO\(_2\)S: 248.0721. Found: 248.0729; Anal. calcd for C\(_{11}\)H\(_{15}\)NO\(_2\)S: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.47; H, 7.00; N, 6.05.

General Procedure 16 for the Removal of the Tosyl Group

A freshly prepared solution of sodium naphthalenide (1.0 M in THF, 1.43 mmol) was added to a solution of the \( N-(p\)-toluenesulfonyl)piperidine (0.31 mmol) in THF (1.5 mL) at -78 °C. After 5 min the reaction was quenched with MeOH (0.3 mL), warmed up to room temperature, diluted with water (5 mL) and acidified to pH 1 with aqueous
HCl (2 M). The aqueous phase was washed with Et<sub>2</sub>O (3 × 10 mL), basified to pH 9 with aqueous NaOH (2 M) and extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo to afford the demesylated piperidine.

(2S', 4R', 5S')-4-Hydroxy-2-methyl-5-isopropenyl piperidine, 35a

Piperidine 35a was prepared from piperidine 7a (100 mg, 0.32 mmol) and sodium naphthalenide (1.0 M in THF, 1.49 mL, 1.49 mmol) according to the general procedure 16. Work-up afforded piperidine 35a as a colourless oil (27 mg, 54%).

(DCM:MeOH:Et<sub>3</sub>N, 100:15:1, R<sub>r</sub> = 0.12); IR (neat) 3373, 3080, 2965, 2929, 1644, 1453, 1094 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.22 (3H, d, J = 6.6 Hz), 1.56 (1H, dt, J = 13.6, 7.7 Hz), 1.81-1.89 (4H, stack), 2.37-2.43 (1H, m), 2.72 (2H, br s), 2.78 (1H, dd, J = 12.9, 3.7 Hz), 2.90-2.97 (1H, m), 3.17 (1H, dd, J = 12.9, 5.9 Hz), 3.89-3.96 (1H, m), 4.91 (1H, s), 5.02 (1H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 21.5, 24.6, 38.2, 43.9, 46.4, 49.2, 68.4, 113.8, 144.6; MS (El) m/z 155 (18%, [M]+), 56 (100), 44 (74); HRMS (ES) Calcd for C<sub>9</sub>H<sub>17</sub>NO: 155.1310. Found: 155.1317.

(2S', 4S', 5S')-4-Hydroxy-2-methyl-5-isopropenyl piperidine, 36a

Piperidine 36a was prepared from piperidine 8a (103 mg, 0.33 mmol) and sodium naphthalenide (1.0 M in THF, 1.53 mL, 1.53 mmol) according to the general procedure 16. Purification by flash column chromatography (DCM:MeOH:Et<sub>3</sub>N, 100:15:1, R<sub>r</sub> = 0.09) afforded 36a as a colourless oil (27 mg, 52%).
IR (neat) 3286, 3076, 2967, 2926, 1643, 1455, 1377, 1087 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.18 (3H, d, J = 7.0 Hz), 1.58 (1H, ddd, J = 12.9, 9.9, 5.2 Hz), 1.75 (3H, s), 1.87 (1H, dt, J = 12.9, 3.7 Hz), 2.04 (1H, td, J = 9.2, 4.8 Hz), 2.64 (2H, br s), 2.83 (1H, dd, J = 13.2, 9.6 Hz), 2.91 (1H, dd, J = 13.2, 4.8 Hz), 3.36-3.42 (1H, m), 3.92 (1H, td, J = 9.2, 4.1 Hz), 4.89 (1H, s), 4.96 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 19.0, 21.0, 39.0, 43.3, 47.9, 53.7, 66.0, 113.4, 144.2; MS (EI) m/z 155 (10%, [M⁺]), 56 (100); Anal. calcd for C₉H₁₇NO: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.62; H, 10.80; N, 9.15.

(2S, 4R, 5S)-2-Benzyl-4-hydroxy-5-isopropenyl piperidine, 35b

Piperidine 35b was prepared from piperidine 7b (100 mg, 0.26 mmol) and sodium naphthalenide (1.0 M in THF, 1.19 mL, 1.19 mmol) according to the general procedure 16. Purification by flash column chromatography (EtOAc:MeOH:Et₃N, 100:15:1, Rf = 0.11) afforded 35b as a colourless oil (37 mg, 61%).

[α]D²³ -17 (c 0.82 in CHCl₃); IR (neat) 3330, 3085, 2919, 1643, 1604, 1496, 1454, 1374, 1095 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.65-1.75 (1H, m), 1.80-1.89 (4H, stack), 1.94 (2H, br s), 2.36-2.40 (1H, m), 2.69 (1H, dd, J = 12.3, 3.9 Hz), 2.81-2.86 (1H, m), 2.93-3.03 (2H, m), 3.19 (1H, dd, J = 12.3, 6.8 Hz), 3.91-3.96 (1H, m), 4.92 (1H, s), 5.01 (1H, s), 7.19-7.32 (5H, m); ¹³C NMR (75 MHz, CDCl₃) δ 24.5, 36.1, 41.6, 43.4, 47.1, 54.9, 68.1, 113.5, 126.3, 128.6, 129.4, 139.8, 145.1; MS (ES) m/z 232.0 (100%, [M+H]+); HRMS (ES) Calcd for C₁₅H₂₂NO: 232.1701. Found: 232.1709.
(2S, 4S, 5S)-2-Benzyl-4-hydroxy-5-isopropenyl piperidine, 36b

Piperidine 36b was prepared from piperidine 8b (99 mg, 0.26 mmol) and sodium naphthalenide (1.0 M in THF, 1.18 mL, 1.18 mmol) according to the general procedure 16. Work-up afforded 36b as a white powder (52 mg, 87%).

$[\alpha]_D^{23}$ -49 (c 0.98 in CHCl$_3$); mp 119-121 °C (from DCM:hexane); IR (film) 3306, 2917, 1641, 1602, 1493, 1455, 1090 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.63 (1H, ddd, $J = 12.9, 9.9, 5.1$ Hz), 1.79 (3H, s), 1.91 (1H, br s), 1.97 (1H, dt, $J = 12.9, 3.7$ Hz), 2.07-2.15 (1H, m), 2.72 (1H, dd, $J = 13.4, 6.4$ Hz), 2.86-2.94 (3H, stack), 3.32-3.41 (1H, m), 3.99 (1H, td, $J = 9.4, 4.1$ Hz), 4.94 (1H, s), 4.98 (1H, s), 7.16-7.33 (5H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.2, 37.0, 38.8, 43.7, 53.4, 54.4, 66.4, 113.3, 126.4, 128.7, 129.1, 139.6, 144.4; MS (ES) m/z 232.2 (65%, [M+H]$^+$), 214.1 (100); HRMS (ES) Calcd for C$_{15}$H$_{22}$NO: 232.1701. Found: 232.1700; Anal. calcd for C$_{15}$H$_{21}$NO: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.80; H, 9.22; N, 6.19.

(2R, 4S, 5S)-4-Hydroxy-5-isopropenyl-2-isopropyl piperidine, 36c

Piperidine 36c was prepared from piperidine 8c (105 mg, 0.31 mmol) and sodium naphthalenide (1.0 M in THF, 1.43 mL, 1.43 mmol) according to the general procedure 16. Work-up afforded 36c as a white powder (51 mg, 90%).

$[\alpha]_D^{23}$ -2 (c 1.0 in CHCl$_3$); mp 60-62 °C (from EtOAc); IR (film) 3358, 3080, 2960, 2875, 1644, 1454, 1078 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.91 (3H, d, $J = 6.6$ Hz), 0.92 (3H, d, $J = 6.3$ Hz), 1.45-1.60 (1H, m), 1.73 (3H, s), 1.78-1.92 (1H, m), 2.00-2.16 (2H, stack), 2.58-2.79 (2H, stack), 2.84-2.98 (3H, stack), 3.85 (1H, dt, $J = 9.0, 4.0$ Hz), 4.88 (1H, s), 4.93 (1H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 20.0, 20.1, 21.2, 27.9,
34.5, 43.7, 52.8, 59.0, 66.3, 113.3, 144.3; MS (ES) m/z 184.1 (100%, [M+H]+); HRMS (ES) Calcd for C_{11}H_{22}NO: 184.1701. Found: 184.1707.

(3S, 4S)-3-Isopropenyl-1-aza-spirobicyclo[5.5]undecan-4-ol, 36d

Piperidine **36d** was prepared from piperidine **8d** (101 mg, 0.28 mmol) and sodium naphthalenide (1.0 M in THF, 1.28 mL, 1.28 mmol) according to the general procedure 16. Work-up afforded **36d** as a white solid (50 mg, 86%). 

mp 75-77 °C (from EtOAc); IR (film) 3350, 2933, 2856, 1644, 1454, 1072 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.08 (1H, dd, \(J = 12.5, 11.8 \text{ Hz}\)), 1.32-1.61 (10H, stack), 1.72 (3H, s), 2.00 (1H, td, \(J = 11.0, 4.4 \text{ Hz}\)), 2.14 (1H, dd, \(J = 12.5, 4.4 \text{ Hz}\)), 2.51 (2H, br s), 2.71 (1H, dd, \(J = 13.2, 11.4 \text{ Hz}\)), 2.84 (1H, dd, \(J = 13.2, 4.4 \text{ Hz}\)), 3.78 (1H, td, \(J = 10.7, 4.4 \text{ Hz}\)), 4.87 (1H, s), 4.93 (1H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 20.5, 21.8, 21.9, 26.3, 31.9, 41.2, 43.7, 44.0, 53.6, 55.3, 66.5, 113.5, 144.2; MS (ES) m/z 210.1 (100%, [M+H]+); HRMS (ES) Calcd for C_{13}H_{24}NO: 210.1858. Found: 210.1849.

(2R, 4S, 5S)-2-tert-Butyl-4-hydroxy-5-isopropenyl piperidine, 36e

Piperidine **36e** was prepared from piperidine **8e** (108 mg, 0.31 mmol) and sodium naphthalenide (1.0 M in THF, 1.41 mL, 1.41 mmol) according to the general procedure 16. Work-up afforded **36e** as a pale yellow powder (60 mg, 99%). 

\([\alpha]_D^{15}\) +49 (c 1.0 in CHCl\(_3\)); mp 53-55 °C (from EtOAc); IR (film) 3350, 2955, 1642, 1451, 1394, 1366, 1244, 1098 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.88 (9H, s), 1.57-1.65 (2H, m), 1.78 (3H, s), 2.08 (1H, br s), 2.32 (2H, br s), 2.66 (1H, dd, \(J = 8.8, 5.9 \text{ Hz}\)), 3.10 (1H, dd, \(J = 13.2, 1.8 \text{ Hz}\)), 3.21 (1H, dd, \(J = 13.2, 4.4 \text{ Hz}\)), 4.18-4.26 (1H,
m), 4.95 (1H, s), 4.99 (1H, s); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.2, 26.6, 30.5, 33.5, 44.4, 46.9, 59.4, 67.7, 112.5, 144.9; MS (ES) m/z 198.2 (100%, [M+H]$^+$); HRMS (ES) Calcd for C$_{12}$H$_{24}$NO: 198.1858. Found: 198.1854.

(2R, 4S, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl piperidine, 36f

Piperidine 36f was prepared from piperidine 8f (104 mg, 0.28 mmol) and sodium naphthalenide (1.0 M in THF, 1.29 mL, 1.29 mmol) according to the general procedure 16. Purification by flash column chromatography (EtOAc:MeOH, 100:3, $R_f$ = 0.14) afforded 36f as a colourless oil (41 mg, 67%).

[$\alpha$]$_D^{15}$ -5 (c 1.3 in CHCl$_3$); IR (neat) 3328, 3085, 2925, 1643, 1603, 1494, 1450, 1377, 1066 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.66 (3H, s), 1.79 (1H, ddd, $J = 13.6$, 8.8, 4.8 Hz), 2.01-2.17 (3H, stack), 2.45 (1H, ddd, $J = 13.6$, 5.2, 3.7 Hz), 2.78 (1H, dd, $J = 13.1$, 8.3 Hz), 3.02 (1H, dd, $J = 13.1$, 4.1 Hz), 3.87 (1H, td, $J = 8.1$, 3.7 Hz), 4.29 (1H, dd, $J = 5.2$, 4.8 Hz), 4.91 (1H, s), 4.93 (1H, s), 7.22 (1H, d, $J = 8.5$ Hz), 7.28-7.34 (1H, m), 7.41 (1H, d, $J = 7.7$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.6, 37.5, 44.6, 52.4, 54.8, 66.8, 113.3, 126.7, 128.6, 142.9, 144.5; MS (ES) m/z 218.0 (100%, [M+H]$^+$); HRMS (ES) Calcd for C$_{14}$H$_{20}$NO: 218.1545. Found: 218.1538.

(2R', 4S', 5S')-2-(tert-Butyl-diphenyl-silanyloxymethyl)-4-hydroxy-5-isopropenyl piperidine, 37

A freshly prepared solution of sodium naphthalenide (1.0 M in THF, 370 $\mu$L, 0.37 mmol) was added to a solution of 21 (45 mg, 0.08 mmol) in THF (1 mL) at -78 °C. After 5 min the reaction was quenched with MeOH, warmed up to room temperature,
diluted with water (5 mL) and the aqueous phase was extracted with Et₂O (4 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (EtOAc:MeOH, 20:3, Rᵣ = 0.42) afforded 37 as a colourless oil (24 mg, 73%).

IR (neat) 3350, 3072, 2931, 2858, 1644, 1595, 1362, 1218, 1113 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.06 (9H, s), 1.25 (1H, br s), 1.59-1.69 (4H, stack), 1.95 (1H, dt, J = 13.6, 4.0 Hz), 2.17 (1H, td, J = 9.0, 4.0 Hz), 2.62 (1H, dd, J = 12.5, 9.6 Hz), 2.89 (1H, dd, J = 12.5, 4.0 Hz), 3.15 (1H, br s), 3.33-3.41 (1H, m), 3.58-3.67 (2H, stack), 3.74 (1H, dd, J = 10.3, 8.1 Hz), 4.84 (1H, s), 4.94 (1H, s), 7.35-7.47 (6H, m), 7.63-7.67 (4H, m); ¹³C NMR (75 MHz, CDCl₃) δ 19.4, 21.0, 27.1, 33.0, 43.1, 51.7, 53.7, 63.2, 66.2, 113.7, 127.9, 130.0, 133.2, 133.3, 135.7, 143.7; MS (ES) m/z 410.3 (100%, [M+H]⁺); HRMS (ES) Calcd for C₂₅H₃₆NO₂Si: 410.2515. Found: 410.2508.
$^{1}H$ NMR Spectrum (CDCl$_3$, 300 MHz)

(25)-O-(p-Toluene sulphonyl)-N-(p-toluene sulphonyl) alanine

[Chemical structure image]

Calcd - C$_{23}$H$_{27}$O$_4$N$_2$S

Calcd: C 53.12

Found: C 53.13
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(3S,4S)-P-Toluene sulfonyl t-amino-butyronitrile, 3a

Claire Carlow
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

3-Methylbut-2-enyl 3-[N-(3-methylbut-2-enyl)-N-p-toluenesulfonyl]amine [butionate]
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene

3-Methylbutyl-2-enyl 3-N-(3-methylbutyl-2-enyl)-N-(p-)

[Diagram of molecular structure]
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

3-[N-(3-Methylbutyl-2-ethyl)-N-(p-toluene sulfonyl)]amino[butan-1-ol] 6a
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

3-[[N-(3-Methylbutyl-2-eny)-N-(p-toluene sulfonyl)amino]butanoyl] 6a

$^{13}$C peformance, $^{1}$H decoupled

Hire Gentry, DDG 417C, AV300
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

3-[[N-3-Methylbut-2-eny1]-N-(p-toluene sulfonfyl) amine]buten, 1a

clc - claire carnou
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

3-[(3-Methylbut-2-enyl)N-(p-toluenesulfonyl)amino]butenal, 1a
H NMR Spectrum (CDCl₃, 300 MHz)

Toluenesulfonyl(N)-pyridine·8a

(2S, 4S, 5S)-4-hydroxy-2-methyl-5-isopropanyl-1-pyridone·8a
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

toluene sulfonyl (piperidine, Tfa)

(2S, 4R, 5S)-5-(1-chloro-1-methylethyl)-4-hydroxy-2-methyl-1-piperidine
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

Toluene sulfonyl(piperidine) 12a

(2S, 4S, 5S, 6S)-6-(1-Chloro-1-methyl-1-oxyl-4-hydroxy-2-methyl-1-)-p-
1H NMR Spectrum (CDCl₃, 75 MHz)

Toluene sulphonyl(piperidine, 12a)

(2S',4S',5S')-5-(1-Chloro-1-methylpropyl)-4-hydroxy-2-methyl-1-(p-)

\[ \text{Chemical Shifts:} \]
- 7.12 (s)
- 7.22 (s)
- 7.60 (d)
- 8.01 (d)
- 9.54 (s)
- 10.54 (s)
- 12.98 (s)
- 13.77 (s)
- 14.35 (s)
$^{1}H$ NMR Spectrum (CDCl$_3$, 300 MHz)

Chemical shifts and integrals are indicated on the spectrum. The structure shows a 6-membered ring with hydroxy and isopropyl groups. The notation (2S, 4R, 5S)-4-hydroxy-2-methyl-5-isopropylpiperidine, 35g, indicates the configuration and compound identity. The spectrum was recorded in CDCl$_3$ with proton ppm values.
$^{1}H$ NMR Spectrum (CDCl$_3$, 300 MHz)

(2S', 4S', 5S)-4-Hydroxy-2-methyl-5-isopropenylpiperidine, 36a

CIC - CLINE CARNOU
\(13^C\) NMR Spectrum (CDCl\textsubscript{3}, 75 MHz)

(2S,4S,5S)-4-Hydroxy-2-methyl-5-isopropenylpipecoline, 36a
(3S)-N-(But-2-enyl)-N-(p-toluenesulfonyl)amino[butane].

1H NMR Spectrum (CDCl₃, 300 MHz)

3.65 ppm
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(3S)-N-(but-2-enyl)-N'-p-toluene sulfonyl)(amino)butanenal, 234
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(2S, 4R, 5S)-4-Hydroxy-2-methyly-1-((p-toluene)sulfonyl) -5-vinyldipentene
$^{1}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

$\text{(2S, 4R, 5S)-4-Hydroxy-2-methyl-1-(p-toluenesulfonyl)-5-vinyl piperidine}^{\text{TS}}$
13C NMR spectrum (CDCl₃, 125 MHz)
dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled

dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled
dt5000: 13C, t-H–decoupled

(2S, 4R, 5S)-4-Hydroxy-2-methyl-1-[(p-toluenesulfonyl)-5-vinyl piperazine]
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)phenylalanine

Barcode: Label 2560
1H-Deuterated 13C-PENDANT, H-decoupled
Carbon Chemical: CDCl$_3$, +77C, AV000
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(3S)-p-Toluene sulfonylamino-4-phenylbutyronitrile, 3b
$^{1}H$ NMR Spectrum (CDCl$_3$, 300 MHz)

(3S)-(p-Toluene sulfonyl)amino-4-phenylbutyric acid, 4b
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

toluene sulfonyl(aminoo)4-phenylbutanate

3-Methylybut-2-ynyl (3S)-N-[3-methylybut-2-ynyl]-N-(p-)

ocl - claire carion
\textbf{\textit{13C NMR Spectrum (CDCl3, 75 MHz)}}

\begin{center}
\begin{tabular}{c}
\textbf{18.0186} \\
\textbf{21.6973} \\
\textbf{41.7161} \\
\textbf{50.5204} \\
\textbf{56.5784} \\
\textbf{66.7716} \\
\textbf{77.1760} \\
\end{tabular}
\end{center}

\textbf{Phenylobutanol, 6b}

\textbf{(35)-N-3-Methylbutyl-Z-ery(N)-p-toluenesulfonamide-4-}
H NMR Spectrum (CDCl₃, 300 MHz)

1H NMR Spectruim

phenylbutyronitrile

(3S)-N-[3-methylbut-2-eny1]-N-(p-toluenesulfonfyl)amino]-4-

H NMR Spectrum (CDCl₃, 300 MHz)
$^1$H NMR Spectrum (CDCl₃, 300 MHz)

Phenyllbutenial, 1b

$^{35}$-N-(3-Methylbut-2-enoil)-N-p-toluene sulphonylamino-4
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluenesulfonyl(piperidine) Tp

(2S, 4R, 5S)-2-Benzyl-4-hydroxy-5-isopropenyl-1-(p-)

$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene sulfonyl)piperidine, $gb$

(2S, 4S, 5S)-2-Benzy1-4-hydroxy-5-isopropenyl-1-(p-
$^1$H NMR spectrum (CDCl$_3$, 300 MHz)

Sulfonyl-piperdidine, 12b

$\text{(2S,4S,5S)-2-Benzyl-5-(1-chloro-1-methyl-ethy1)-4-hydroxy-1-p-toluen}$

dc 1435 proton hertz
(ppm)

$\text{H NMR Spectrum (CDCl}_3, 300 MHz}$

(2S, 4R, 5S)-2-Benzyly-4-hydroxy-5-isopropanyl piperidine, 35b

$\text{CIC: Claire Cauvou}$

[Chemical Structure Image]

$\text{Clc 1736 p dolor hertz}$
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2S, 4R, 5S)-2-Benzyi-4-hydroxy-5-isopropenyl piperidine, 356

C13: 173.5 ppm Carbon
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

(3S)-N-(but-2-eny1)-N-(p-toluenesulfonyl)amino-4-phenylbutyronitrile

22b
$^1H$ NMR Spectrum (CDCl$_3$, 300 MHz)

35|N-[(E)-(1-phenylethyl)-N-(p-toluenesulfonyl)amino]-4-phénylpentanal, Z3b
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

(3S)-N-(But-2-eny1)-N'-N-p-Toluene sulphonylamino)-4-phenylbutanal, 23b

de 509b carbon
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2S, 4R, 6S)-2-Benzyl-4-hydroxy-1-(p-toluene sulfonyl)-5-vinyl piperidine,
$^{1}H$ NMR Spectrum (CDCl₃, 300 MHz)

(2S, 4S, 5S)-2-benzyl-4-hydroxy-1-(p-toluene sulfonyl)-5-vinyl pyridine

(2S, 4S, 5R)-2-benzyl-4-hydroxy-1-(p-toluene sulfonyl)-5-vinyl pyridine
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

(2S, 4S, 5S)-2-Benzyl-4-hydroxy-1-(p-toluenesulfonyl)-5-vinyl piperidine

(2S, 4S, 5R)-2-Benzyl-4-hydroxy-1-(p-toluenesulfonyl)-5-vinyl piperidine
$^1$H NMR Spectra (CDCl$_3$, 300 MHz)
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2S)-O-(p-Toluene sulfonyl)-N-(p-toluene sulfonyl)valinol

$\text{OTs}$

$\text{NHTs}$

$\text{NH}_{\text{T}}$
\( ^1H \) NMR Spectrum (CDCl₃, 300 MHz)

(3R)-p-Toluenesulfonyl L-amino-4-methylpentenitrile, 3c

Integral

2.1641
2.1105
1.0000
1.0573
2.0624
3.2316
1.0837
6.7863

978.45
972.93
970.36
966.31
961.17
958.22
952.71

977.93
974.02
731.73

589.07
582.45
575.47
568.85
561.86
555.25

253.38
248.23
246.76
241.61

S142
$^{13}$C NMR Spectrum (CDCl₃, 75 MHz)

$^{22.7660}$

$^{33.6312}$

$^{27.5863}$

$^{17.6189}$

$^{27.1060}$

$^{23.3233}$

$^{3R}$-$(p$-Toluenesulfonyl)aminoo$-$4-methylpentan-2-one, 3c
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene sulfonyl (amino)-4-methylpentanoate

3-Methylbut-2-ynyl (3R)-N-(3-methylbut-2-ynyl)-N-(p-
$^1$H NMR spectrum (CDCl$_3$, 300 MHz)

Methyldiphenyl, 6c.

(3R)-N-(3-Methyldiphenyl-2-eny)-N-(p-toluene sulfonfonyl) amino]-4-
$^{13}$C NMR spectrum (CDCl$_3$, 75 MHz)

Methylpentanol, 6c

(3R)-N-(3-Methylbut-2-enyl)-N-(p-toluenesulphonyl)amino]4-
$^{1}H$ NMR Spectrum (CDCl₃, 300 MHz)

methylpentenal, Tc

(3R)-N-(3-methylbut-2-enyl)-N-(p-toluene-sulfonyl)amino]4-
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Metaphenylenedi, 1c

(3R)-1N-(3-Methylbut-2-enyl)-N-(p-toluenesulfonyl)aminoi-4-
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

pipeline, TC

$^{2R, 4R, 5S}$-4-Hydroxy-5-isopropenyl-2-isopropyl-1-(p-toluenesulfonyl)
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2R, 4S, 5S)-4-Hydroxy-6-isopropanyl-2-isopropanyl-1-(p-toluene)sulfonyl)
\[ \text{S154} \]

\[ \text{H NMR Spectrum (CDCl}_3, 300 MHz) \]

\[ \text{toluene sulfonyl (piperidine, Tc)} \]

\[ (2R, 4R, 5S)-1\text{-chloro-1-methylhexyl}-4\text{-hydroxy-2-Isopropyl-1-(p-} \]

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{OH} \]
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene sulfonyl)phenyl-piperidine, Tlc

(2R, 4R, 5S)-5-(1-Chloro-1-methyl-1-ethyli)-4-hydroxy-2-isopropyl-1-(p-Cl)
H NMR Spectrum (CDCl₃, 300 MHz)

Toluene sulphonyl(piperdine, 12c)

(2R, 4S, 5S)-5-(1-Chloro-1-methyl-1-propyl)-4-hydroxy-2-isopropyl-1-piperdine
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(2R, 4S, 5S)-5-(1-Chloro-1-methylethyl)-4-hydroxy-2-isopropyl-1-(p-toluenesulfonyl)piperidine, 12c
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

$\text{(2R,4S,5S)}$-4-Hydroxy-5-isopropenyl-2-isopropylpipеридине, 36e

dc 1870 Hertz
$^{1}H$ NMR Spectrum (CDCl$_3$, 300 MHz)

![Chemical Structure]

O-(p-Toluenesulfonyl)-1-(p-toluenesulfonyl)aminoacyclohexane-1-

methanol

CCl - Claire Czajka

2199.48, 2140.86, 2100.82, 2099.04, 2070.04, 2069.46, 2068.04
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

1-Cyanoacetethyl-$l$-(p-toluenesulfonyl)amino)cyclohexanone, 3d
SI71

1C NMR Spectrum (CDCl3, 75 MHz)

Cyclohexene

1-Cyanomethyl-1-[N-(3-methylbut-2-enyl)-N-(p-toluene sulfonyl)amino]
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

cyclohexane, l.d.

1-(2-Oxazolinyl)-1-[N-(3-methylbut-2-eny])-N-(p-toluenesulfonyl)amine
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

**Chemical Structure**

![Chemical Structure Image]

**Formula:** (3S, 4R)-2-Isopropenyl-1-(p-toluenesulfonyl)-1-aza-spirobicyclo[5.5.1]undecan-4-ol, 7d

**Additional Notes:**
- UV: 608b Hertz
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Spirobrolo[5.5]undecan-4-one, Td

(3S, 4R)-3-(1-isopropenyloxy)-1-(p-toluene)sulfonyl)-1-aza-

cis 60:40 carbon
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

[Chemical structure diagram]

spirobicyclo[5.5]undecan-4-ol, 8d

(3S,4S)-4-[3-isopropenyl-1-(p-toluenesulfonyl)-1-aza-8]-

110.89 11.13
76.41 14.12
42
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

spirobicyclo[6.5]undecan-4-ol, 8d

35', 4S', 4S'-Isopropenyl-3-(p-toluenesulfonyl)-1,4-aza-

[Image of a molecule structure]
$^{13}$C NMR Spectra (CDCl₃, 75 MHz)

Spirobicyclo[6.5.6]undecan-4-ol, 1td

(3S,4R)-3-(1-Chloro-1-methyl-1-phenylethyl)-1-(p-toluene sulfonyl)-1-aza-
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Spirobicyclo[6.5][undecan-4-ol, 12d]

(3S,4S)-3-(1-Chloro-1-methylethyli)-1-(p-toluenesulfonyl)-1-aza-

CIC 609C carbon
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(3S, 4S)-3-O-isopropenyl-1-aza-spirobicyclo[5.5]undecan-4-ol, 36d
$^{13}$C NMR Spectrum (CDCl$_3$, 76 MHz)

(3S, 4S)-3-isopropenyl-1-aza-spiro[5.5]undecan-4-ol, 36d

cr 556 carbon
H NMR Spectrum (CDCl₃, 300 MHz)

(2S)-O-p-Toluenesulfonyl)-N-(p-toluenesulfonyl)-L-tert-Leucinal
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(3R)-p-Toluenesulfonylamino-4,4-dimethylpentanolic acid, 4e

[Diagram of the molecular structure]
H NMR Spectrum (CDCl₃, 300 MHz)

Toluenesulfonyl(aminomethyl) 4,4-dimethylpentane

3-Methylbut-2-ynyl (3R)-N-(3-methylbut-2-ynyl)-N-(p-)

S190
1H NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene sulfonfonyl (amino) 4,4'-dimethylpentanate

3-Methylbut-2-enyl (3R, 1-N-1-N-(3-methylbut-2-enyl)-N-(p-)

- 172.8892
- 128.3089
- 133.8436
- 176.1648
- 118.8975
- 128.3089
- 133.8436
- 176.1648
$\text{H NMR Spectrum (CDCl}_3, \text{ 300 MHz)}$

**Piperidine, \text{be}**

![Chemical Structure](image)

(2R, 4S, 5S)-2-tert-Butyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)
13C NMR Spectrum (CDCl₃, 75 MHz)

Toluene sulfonyl)phenylhydrazone, The

(2R, 4R, 5S)-2-tert-BuO-5-(1-chloro-1-methyl-1-ethylyl)-4-hydroxy-1-(p-
$^1H$ NMR Spectrum (CDCl$_3$, 300 MHz)

Toluene sulfonyl]-piperidine, 12e

(2R, 4S, 5S)-2-tert-Butyl-5-(1-chloro-1-methyl-1-ethoxy)-1-hydroxy-1-p-
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene sulfonyl(Diphendine, 12e)

(2R, 4S, 5S)-2-tert-Butyl-5-(1-chloro-1-methyl-ethyl)-4-hydroxy-1-Phenyl
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(2R, 4S, 5S)-2-tert-Butyl-4-hydroxy-5-isopropenyl pyrrolidine, 36e

HPLC 5400 H ppm
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(3R)-N-(4-Bu-2-Enyl)-N-(p-toluenesulfonyl)amino]-4'-4-
dimethylpentanitrile 222
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

(dimethyl)dimethylsilane, 22e

(3R)-$N$-$N$-[N-(4-tert-butyl-2-enyl)(toluenesulfonyl)amino]-4,4-

21.5718 129.5451 137.3110 143.3794

21.5718 129.5451 137.3110 143.3794
$\text{H NMR Spectrum (CDCl}_3, 300 MHz)$

(3R)-[N-(but-2-eny)-N-[p-toluene sulfonyl]amino]-4,4-dimethylpentane

$236$
$^1{^3}C \text{ NMR spectrum (CDCl}_3, 75 MHz}$

(R)-N-(But-2-enyl)-N-(p-toluenesulfonyl)amino-4,4-dimethylpentenal,
H NMR Spectrum (CDCl₃, 300 MHz)

(2R, 4R, SS)-2-Fer-Bu₄I-4-hydroxy-1-p-toluene-sulfonyl-5-viny1 piperdine 246
(2R, 4R, 5S)-2-tert-Butyl-4-hydroxy-1-(p-toluenesulfonfyl)-5-vinyl piperidine, 24e

$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

- 66.0089
- 61.1727
- 44.6783
- 42.2547
- 36.6944
- 29.0951
- 27.7460
- 21.6903
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(2S)-O-(p-Toluenesulfonyl)-N-(p-toluenesulfonyl)phenylglycineol

OTs

NHS

OTs
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

$$\text{(3R,5R)-PhenyI-3-(p-toluene)sulfonyl)amino-propionitrile, 3F}$$

\[\text{CN} \quad \text{NHMe} \quad \text{Ph} \]

- 2.22 ppm
- 3.00 ppm
- 4.95 ppm
- 7.25 ppm
- 8.50 ppm

Chemical shifts and integrals for specific peaks.
^1H NMR Spectrum (CDCl3, 300 MHz)

\[
\text{Phenypropenal, Tf}
\]

\[
3R)-N-(3-Methylbutyl-2-eny)-N-(p-toluenesulfonyl)amino]-3-
\]
$\text{H NMR Spectrum (CDCl}_3, 300 MHz)$

(2R, 4R, 5S)-4-Hydroxy-2-phenyl-5-isopropyl-1-(p-toluenesulfonfyl)-1-(p-toluenesulfonfyl)pyrrolidine, $\text{Tt}$
(2R, 4R, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl-1-(p-toluene sulfonfonyl)piperidine, 7f

$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)
H NMR Spectrum (CDCl3, 300 MHz)

Toluene-4-sulfonyl(piperidine)Cl

(2R, 4S, 5S)-4-Hydroxy-2-phenyl-5-isopropyl-1-propylenyl-1-p-
S223

$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Toluene-sulfonyl(piperidine, BF)

(2R, 4S, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl-1-p-
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

Toluenesulfonyl)pyrrolidine, 9

(2R, 4S, 5R)-4-Hydroxy-2-Pheny1-5-isopropeny1-1-pyrrolidine-1-p
$^1$H NMR spectrum (CDCl$_3$, 300 MHz)

Sulfonyl(piperidine, $^{11}$F

(2R, 4R, 5S)-5-(1-Chloro-1-methy(l)ethyl)-4-hydroxy-2-phenyl-1-p-toluene
H NMR Spectrum (CDCl₃, 300 MHz)

'Sulfonyl)Piperidine, 12T

(2R, 4S, 5S)-1-Chloro-1-methyl(4-hydroxy-2-phenyl-1-p-toluen e)
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Sulfonyl(piperidine-12R, 4S, 5S)-1-Chloro-1-methylthio(1-4-naryoxy-7-pentynyl-1-4-piperidine

13C Carbon 144
$^{13}C$ NMR spectrum (CDCl$_3$, 75 MHz)

(2R, 4S, 5S)-4-Hydroxy-2-phenyl-5-isopropenyl piperidine, 29t
1H NMR Spectrum (CDCl₃, 300 MHz)

O-tert-Butyldimethylsilyl-N-[(p-toluene)sulfonyl]homoserine methyl ester

- 2316.03 → 2307.57
- 2184.77 → 2176.68
- 1672.96 → 1664.87
- 1222.55
- 1216.66
- 1214.46
- 1211.15
- 1208.37
- 1203.06
- 1116.29
- 1111.87
- 1107.09
- 1102.31
- 1096.06
- 1090.92
- 1086.50
- 1080.25
- 1032.31

- 718.82
- 580.94
- 577.63
- 575.43
- 572.12
- 569.54
- 566.60
- 560.72

- 258.48
- 4.42
$^{13}$C NMR spectrum (CDCl$_3$, 75 MHz)

O-tert-Butyldimethylsilylethyl-N-(p-toluenesulfonfonyl)homoserine methyl ester

[Structural formula and chemical shifts]

OTBDMS

O

NHTS

C 41.4C carbon
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

homoserine methyl ester, 14

O-tert-Butyl(dimethyl)silyl-N-(3-methylbut-2-eny1)-N-(p-toluenesulfonfyl)

TBDSMO
H NMR Spectrum (CDCl₃, 300 MHz)

![Chemical Structure Image]

Bulanoate, 19

Methyli-2-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-oxo-
**$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)**

![Chemical Structure](image)

**Butanoate, 1g**

**Methyl 2-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-oxo**
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

(p-toluene-sulfonyl)piperidine, $^{19}$Tg

$^{2R, 4R, 6S}$-2-Carbomethoxy-5-(1-chloro-1-methylethyl)-4-hydroxy-1-
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

Bicyclo[3.2.1]octan-7-one, 15

(1R, 4S, 6R)-4-isopropenyl-2-(p-toluene sulfonyl)-2-aza-6-oxa-
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

oxa-bicyclo[3.2.1]octan-7-one, 16

(1R, 4S, 5R)-4-(1-Chloro-1-methyllethy1)-2-(p-toluenesulfonyl)-2-aza-6-

TSN
1H NMR Spectrum (CDCl₃, 7.5 MHz)
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

Toluene-sulfonfonyl (piperidine, 19)

(2R, 4R, 5R)-4-Hydroxy-2-hydroxymethyl-5-isopropenyl-1-piperidine
$^{13}$C NMR spectrum (CDCl$_3$, 75 MHz)

toluene-sulfonyl (piperidine, 19)

(2R, 4R, 5S, 5S)-4-hydroxy-2-hydroxymethyl-5-isopropenyl-1-p-
$^1$H NMR Spectrum (CDCl$_3$, 300 MHz)

Isopropenyl-1-(p-toluenesulfonyl)pyrrolidine, 20

(2R,4R',4S)-N-(tert-butyl-diphenyl-silyloxy)methyl-4-hydroxy-c-
$^{13}$C NMR Spectrum (CDCl$_3$, 75 MHz)

Isopropenyli-p-toluensulfonyl(pipердине, 20)

2R, 4R', 5S)-2-(tert-Butyl-diphenyl-silyloxy)methyl-4-hydroxy-5-

TBDDS
(ppm)

\[ 1H \text{ NMR Spectrum (CDCl}_3, 300 MHz) \]

![H NMR spectrum](image)

Isopropenyl 1-(p-toluene sulfonyl) piperidine, 21

(2R, 4S, 5S, 7S)-2-(tert-Butyl) diphenyl silyl oxyloxymethyl)-4-hydroxy-5-

TBDPSO

TS
$^{13}C$ NMR Spectrum (CDCl$_3$, 75 MHz)

Isopropanoyl-1-(p-toluenesulfonyl)pyrrolidine, 21

(2R, 4S, 5S, 2R-tert-Butyldiphenyl-silyloxymenthyi)-4-hydroxy-5-

DC 456c carbon
H NMR Spectrum (CDCl₃, 300 MHz)

\[
\text{Isopropanyl Piperidine, 37}
\]

\[
\text{(2R', 4S', 5S')-2-(ter-BuPhyl-diphenyl-silyloxy)methyl-4-hydroxy-5-}
\]

\[
\text{TBDDS}
\]

\[
\text{HO}
\]

alyGly2-1
{\text{13C NMR spectrum (CDCl$_3$, 75 MHz)}}

\begin{center}
\includegraphics[width=0.5\textwidth]{13C_NMR_spectrum.png}
\end{center}

\text{Isopropenyl piperidine, 37}

\text{(2R, 4S, 5S)-2-(tert-Butyldiphenylsilyl)oxy(benzyl)4-hydroxy-5-}
Figure S1  ORTEP plot of 7c; ellipsoids at 30% probability level.
Figure S2  ORTEP plot of 8a; ellipsoids at 30% probability level.
Figure S3 ORTEP plot of 9; ellipsoids at 30% probability level.
Figure S4  ORTEP plot of 15; ellipsoids at 30% probability level.
Figure S5  ORTEP plot of 11g (the Cl and CH$_3$ are disordered over the two sites, with 70:30 occupancy); ellipsoids at 30% probability level.
Figure S6 ORTEP plot of 26b; ellipsoids at 30% probability level.