

Supporting Information File 1
for
**Asymmetric synthesis of γ -chloro- α,β -diamino- and β,γ -aziridino-
 α -aminoacylpyrrolidines and -piperidines via stereoselective
Mannich-type additions of *N*-(diphenylmethylene)glycinamides
across α -chloro-*N*-sulfinylimines**

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**General experimental conditions, experimental procedures and data, copies
of ¹H NMR and ¹³C NMR spectra for compounds 3, *syn*-5, 8, and 10–13**

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I. General experimental methods

Flame-dried glassware was used for all nonaqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification, unless stated otherwise. Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere from sodium/benzophenone ketyl. Petroleum ether refers to the 40–60 °C boiling fraction. ¹H NMR (300 MHz), ¹³C NMR (75 MHz) spectra were recorded in deuterated solvents with tetramethylsilane (TMS, $\delta = 0$ ppm) as internal standard unless specified otherwise. Mass spectra were recorded by using a direct inlet system (ESI, 4000 V). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory. HRMS analysis was performed by using an HPLC coupled to a time-of-flight mass spectrometer equipped with an ESI/APCI-multimode source. Melting points of crystalline compounds were determined in open-end capillary tubes by using a hot stage apparatus and were not corrected. The purification of the reaction mixtures was performed by column chromatography with silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm). Thin-layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F₂₅₄, by using UV and KMnO₄ as a visualizing agent. (*S*_S)-*p*-Toluenesulfinamide is commercially available (>98% ee).

II. Experimental methods

Synthesis of (*S_S*)- α -chloro-*N*-*p*-toluenesulfinylaldimines (3). The synthesis of (*S_S*)-*N*-(2-chloro-2-ethylbutylidene)-*p*-toluenesulfinamide (**3b**) is representative. To a flame-dried round-bottomed flask, charged with 2-chloro-2-ethylbutanal (**1b**, 4.00 g, 29.72 mmol) in dry CH₂Cl₂ (100 mL), was added Ti(OEt)₄ (2 equiv, 13.60 g, 59.61 mmol) and (*S_S*)-*p*-toluenesulfinamide (**2**, 4.60 g, 29.64 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 18 h at rt. After completion, the reaction mixture was poured into H₂O:CH₂Cl₂ 1/1 (200 mL) while being rapidly stirred. The suspension was filtered over Celite[®] and the solids were washed with CH₂Cl₂ (2 $\times$ 50 mL). Subsequently, the combined organic phases were dried (MgSO₄), filtered and evaporated in vacuo. The crude product was purified by column chromatography to yield 5.27 g (19.39 mmol, 66%) of pure (*S_S*)-*N*-(2-chloro-2-ethylbutylidene)-*p*-toluenesulfinamide (**3b**).

(*S_S*)-*N*-(2-Chloro-2-ethylbutylidene)-*p*-toluenesulfinamide (3b). *R_f* 0.35 (petroleum ether:EtOAc 9/1). Yellow oil, yield 66% (5.27 g). [α]_D +264.4 (*c* 1.1, CHCl₃). IR (cm⁻¹): $\nu_{\max}$ 808, 1075, 1099, 1144, 1617. ¹H NMR (300 MHz, CDCl₃) δ 0.87 (3H, t, *J* = 7.15 Hz), 0.97 (3H, t, *J* = 7.15 Hz), 1.89-2.13 (4H, m), 2.40 (3H, s), 7.30 (2H, d, *J* = 8.26 Hz), 7.55 (2H, d, *J* = 8.26 Hz), 8.11 (1H, s). ¹³C NMR (75 MHz, CDCl₃) δ 8.7, 8.8, 21.5, 32.0, 32.1, 76.1, 124.7 (2C), 130.0 (2C), 141.3, 142.1, 166.2. MS (ESI⁺) *m/z* (%): 263 (100), 272/274 [M + H]⁺, 60). HRMS (ESI) calcd for C₁₃H₁₈ClNOS: 272.0870 MH⁺; found, 272.0864.

(*S_S*)-*N*-(1-Chlorocyclohexylmethylidene)-*p*-toluenesulfinamide (3c). *R_f* 0.31 (petroleum ether:EtOAc 9/1). Colourless oil, yield 30% (0.80 g). [α]_D +251.0 (*c* 1.2, CHCl₃). IR (cm⁻¹): $\nu_{\max}$ 809, 1075, 1098, 1144, 1618. ¹H NMR (300 MHz, CDCl₃) δ 1.18-1.35 (1H, m), 1.49-2.13 (9H, m), 2.41 (3H, s), 7.31 (2H, d, *J* = 8.26 Hz), 7.55 (2H, d, *J* = 8.26 Hz), 8.15 (1H, s).

^{13}C NMR (75 MHz, CDCl_3) δ 21.5, 22.0 (2C), 25.0, 36.6 (2C), 71.6, 124.8 (2C), 130.0 (2C), 141.3, 142.0, 166.0. MS (ESI^+) m/z (%): 177 (100), 284/286 [$\text{M} + \text{H}^+$, 40]. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{ClNOS}$: 284.0870 MH^+ ; found, 284.0861.

Synthesis of ($S_S,2S,3S$)- N -[4-chloro-2-(diphenylmethyleamino)-3-(p -toluenesulfinyl-amino)alkanoyl]amines *syn*-5. The synthesis of ($S_S,2S,3S$)- N -[4-chloro-2-(diphenylmethyleamino)-4-methyl-3-(p -toluenesulfinylamino)pentanoyl]piperidine (*syn*-**5b**) is representative. A solution of N -[2-(diphenylmethyleamino)acetyl]piperidine (**4b**, 1.1 equiv, 0.91 mmol, 0.28 g) in THF (10 mL) was cooled to $-78\text{ }^\circ\text{C}$ under a nitrogen atmosphere. A 1.0 M solution of LiHMDS (1.1 equiv, 0.91 mL, 0.91 mmol) in THF was slowly added and the resulting solution was stirred for 1 h at $-78\text{ }^\circ\text{C}$. After deprotonation, a solution of (S_S)- α -chloro- N - p -toluenesulfinyl isobutyraldimine (**3a**, 1.0 equiv, 0.82 mmol, 0.20 g) in THF (5 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 15 min. To the reaction mixture was added a saturated solution of NH_4Cl (5 mL) while being stirred at $-78\text{ }^\circ\text{C}$ for 2 min. The reaction mixture was brought to rt followed by an extraction with EtOAc ($3 \times 20\text{ mL}$). The combined organic phases were dried (MgSO_4), filtered and evaporated in vacuo. The crude product was purified by recrystallization from diethyl ether to yield 0.32 g (0.58 mmol, 71%) of pure ($S_S,2S,3S$)- N -[4-chloro-2-(diphenylmethyleamino)-4-methyl-3-(p -toluenesulfinylamino)pentanoyl]-piperidine (*syn*-**5b**).

($S_S,2S,3S$)- N -[4-Chloro-2-(diphenylmethyleamino)-4-methyl-3-(p -toluenesulfinyl-amino)pentanoyl]pyrrolidine (*syn*-5a**).** White crystals, yield 57% (0.30 g). $[\alpha]_D^{25} +64.7$ (c 1.3, CHCl_3). Mp $132.3 \pm 2.0\text{ }^\circ\text{C}$. IR (cm^{-1}): ν_{max} 697, 703, 1069, 1096, 1277, 1424, 1444, 1635, 3291 (weak). ^1H NMR (300 MHz, CDCl_3) δ 1.45 (3H, s), 1.53-1.86 (4H, m), 1.77 (3H,

s), 2.25-2.35 (1H, m), 2.41 (3H, s), 3.26-3.40 (3H, m), 3.77 (1H, d, $J = 9.36$ Hz), 4.93 (1H, s), 6.16 (1H, d, $J = 9.36$ Hz), 7.12-7.19 (2H, m), 7.23-7.35 (4H, m), 7.35-7.50 (4H, m), 7.50-7.57 (2H, m), 8.07 (2H, d, $J = 8.26$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 21.4, 24.0, 26.0, 27.3, 32.4, 46.1, 46.2, 62.5, 66.6, 73.6, 126.1 (2C), 126.8 (2C), 128.1 (2C), 128.5 (2C), 128.6, 128.7 (2C), 129.6 (2C), 130.7, 137.8, 138.5, 141.2, 143.8, 169.5, 170.1. MS (ESI^+) m/z (%): 536/538 [$\text{M} + \text{H}^+$, 100]. HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{34}\text{ClN}_3\text{O}_2\text{S}$: 536.2133 MH^+ ; found, 536.2146.

($S_S, 2S, 3S$)-*N*-[4-Chloro-2-(diphenylmethyleamino)-4-methyl-3-(*p*-toluenesulfinyl-amino)pentanoyl]piperidine (*syn*-5b). White crystals, yield 71% (0.32 g). $[\alpha]_D +78.1$ (c 0.9, CHCl_3). Mp 125.4 ± 2.0 °C. IR (cm^{-1}): ν_{max} 700, 1070, 1098, 1222, 1442, 1640, 3355 (weak). ^1H NMR (300 MHz, CDCl_3) δ 0.90 (1H, m), 1.30-1.59 (5H, m), 1.47 (3H, s), 1.76 (3H, s), 2.41 (3H, s), 3.08-3.36 (3H, m), 3.52-3.64 (1H, m), 3.78 (1H, d, $J = 9.36$ Hz), 5.12 (1H, s), 6.04 (1H, d, $J = 9.36$ Hz), 7.12-7.18 (2H, m), 7.23-7.50 (8H, m), 7.53 (2H, d, $J = 8.26$ Hz), 7.95 (2H, d, $J = 8.26$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 21.4, 24.4, 25.4, 25.8, 27.5, 32.6, 43.3, 46.1, 61.3, 66.5, 73.7, 126.0 (2C), 127.1 (2C), 128.0 (2C), 128.57 (3C), 128.63 (2C), 129.6 (2C), 130.6, 137.4, 138.7, 141.3, 143.6, 169.2, 170.0. MS (ESI^+) m/z (%): 550/552 [$\text{M} + \text{H}^+$, 100]. HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{36}\text{ClN}_3\text{O}_2\text{S}$: 550.2290 MH^+ ; found, 550.2306.

($S_S, 2S, 3S$)-*N*-[4-Chloro-2-(diphenylmethyleamino)-4-ethyl-3-(*p*-toluenesulfinylamino)-hexanoyl]pyrrolidine (*syn*-5c). White crystals, yield 41% (0.71 g). $[\alpha]_D +60.4$ (c 2.7, CHCl_3). Mp 143.3 ± 1.0 °C. IR (cm^{-1}): ν_{max} 699, 1073, 1103, 1294, 1422, 1442, 1636, 3348 (weak). ^1H NMR (300 MHz, CDCl_3) δ 0.93 (3H, t, $J = 7.43$ Hz), 1.12 (3H, t, $J = 7.15$ Hz), 1.51-2.20 (8H, m), 2.24-2.35 (1H, m), 2.41 (3H, s), 3.24-3.38 (3H, m), 4.00 (1H, d, $J = 9.36$ Hz), 4.91 (1H, s), 6.12 (1H, d, $J = 9.36$ Hz), 7.13-7.22 (2H, m), 7.23-7.35 (4H, m), 7.36-

7.58 (6H, m), 8.12 (2H, d, $J = 8.26$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 8.7, 8.9, 21.5, 24.0, 26.1, 29.4, 30.2, 46.2, 46.3, 62.2, 63.5, 83.0, 126.4 (2C), 126.9 (2C), 128.2 (2C), 128.7 (3C), 128.8 (2C), 129.7 (2C), 130.8, 137.9, 138.7, 141.2, 144.1, 169.7, 170.0. MS (ESI^+) m/z (%): 564/566 [$\text{M} + \text{H}^+$, 100]. HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{38}\text{ClN}_3\text{O}_2\text{S}$: 564.2446 MH^+ ; found, 564.2454.

($S_S, 2S, 3S$)- N -[4-Chloro-2-(diphenylmethyleamino)-4-ethyl-3-(p -toluenesulfinylamino)-hexanoyl]piperidine (*syn*-5d). White crystals, yield 65% (0.33 g). $[\alpha]_{\text{D}} +61.1$ (c 0.9, CHCl_3). Mp 138.5 ± 2.0 °C. IR (cm^{-1}): ν_{max} 701, 1074, 1111, 1252, 1439, 1634, 3332 (weak). ^1H NMR (300 MHz, CDCl_3) δ 0.83-1.04 (1H, m), 0.93 (3H, t, $J = 7.15$ Hz), 1.12 (3H, t, $J = 7.15$ Hz), 1.30-1.65 (5H, m), 1.72-2.16 (4H, m), 2.40 (3H, s), 2.98-3.09 (1H, m), 3.20-3.31 (1H, m), 3.39-3.47 (2H, m), 4.05 (1H, d, $J = 9.36$ Hz), 5.09 (1H, s), 5.95 (1H, d, $J = 9.36$ Hz), 7.12-7.17 (2H, m), 7.24-7.31 (4H, m), 7.35-7.49 (4H, m), 7.54 (2H, d, $J = 8.26$ Hz), 8.00 (2H, d, $J = 8.26$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 8.6, 8.9, 21.5, 24.5, 25.6, 26.1, 29.4, 30.3, 43.4, 46.1, 61.2, 63.1, 83.3, 126.2 (2C), 127.2 (2C), 128.1 (2C), 128.7 (5C), 129.7 (2C), 130.7, 137.5, 138.9, 141.3, 143.9, 169.7 (2C). MS (ESI^+) m/z (%): 578/580 [$\text{M} + \text{H}^+$, 100]. HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{40}\text{ClN}_3\text{O}_2\text{S}$: 578.2603 MH^+ ; found, 578.2609.

($S_S, 2S, 3S$)- N -[3-(1-Chlorocyclohexyl)-2-(diphenylmethyleamino)-3-(p -toluenesulfinylamino)propanoyl]pyrrolidine (*syn*-5e). White crystals, yield 59% (1.14 g). $[\alpha]_{\text{D}} +83.5$ (c 2.5, CHCl_3). Mp 138.8 ± 2.0 °C. IR (cm^{-1}): ν_{max} 696, 704, 1068, 1092, 1294, 1430, 1634, 3309 (weak). ^1H NMR (300 MHz, CDCl_3) δ 1.05-1.21 (1H, m), 1.48-1.94 (12H, m), 2.24-2.47 (2H, m), 2.41 (3H, s), 3.27-3.40 (3H, m), 3.74 (1H, d, $J = 9.36$ Hz), 5.01 (1H, s), 6.16 (1H, d, $J = 9.36$ Hz), 7.12-7.18 (2H, m), 7.24-7.35 (4H, m), 7.36-7.56 (6H, m), 8.10 (2H, d, $J = 8.26$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 21.5, 21.7, 22.1, 24.0, 24.8, 26.1, 33.7, 37.2, 46.2,

46.3, 62.3, 67.7, 80.1, 126.2 (2C), 126.9 (2C), 128.2 (2C), 128.6 (3C), 128.8 (2C), 129.7 (2C), 130.8, 137.9, 138.7, 141.3, 143.9, 169.7, 169.8. MS (ESI⁺) *m/z* (%): 576/578 [M + H⁺, 100]. HRMS (ESI) calcd for C₃₃H₃₈ClN₃O₂S: 576.2446 MH⁺; found, 576.2436.

(S_S,2S,3S)-N-[3-(1-Chlorocyclohexyl)-2-(diphenylmethyleamino)-3-(*p*-toluenesulfinyl-amino)propanoyl]piperidine (*syn*-5f). White crystals, yield 73% (1.20 g). [α]_D +86.9 (c 2.9, CHCl₃). Mp 132.2 ± 1.0 °C. IR (cm⁻¹): ν_{max} 701, 1073, 1104, 1221, 1441, 1638, 3320 (weak). ¹H NMR (300 MHz, CDCl₃) δ 0.82-0.98 (1H, m), 1.05-1.21 (1H, m), 1.31-1.81 (13H, m), 2.30-2.45 (1H, m), 2.41 (3H, s), 3.06-3.16 (1H, m), 3.18-3.38 (2H, m), 3.48-3.59 (1H, m), 3.76 (1H, d×d, *J* = 9.36 Hz, 1.10 Hz), 5.20 (1H, d, *J* = 1.10 Hz), 6.03 (1H, d, *J* = 9.36 Hz), 7.12-7.17 (2H, m), 7.24-7.56 (10H, m), 7.99 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 21.7, 22.1, 24.5, 24.8, 25.5, 25.9, 33.8, 37.4, 43.4, 46.2, 61.1, 67.8, 80.4, 126.1 (2C), 127.2 (2C), 128.1 (2C), 128.7 (5C), 129.7 (2C), 130.6, 137.5, 138.9, 141.4, 143.7, 169.5, 169.6. MS (ESI⁺) *m/z* (%): 590/592 [M + H⁺, 100]. HRMS (ESI) calcd for C₃₄H₄₀ClN₃O₂S: 590.2603 MH⁺; found, 590.2609.

Synthesis of (S_S,2S,2'S)-N-{2-amino-2-[1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}amines 8 and 11a. The synthesis of (S_S,2S,2'S)-N-{2-(diphenylmethyleamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}piperidine (**8b**) is representative. To a solution of (S_S,2S,3S)-N-[4-chloro-2-(diphenylmethyleamino)-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]-piperidine (*syn*-5b, 2.10 g, 3.82 mmol) in acetone (40 mL) was added K₂CO₃ (3.0 equiv, 11.45 mmol, 1.58 g) at rt. The reaction mixture was stirred for 24 h under reflux. After 24 h, the K₂CO₃ was filtered off and the solvent was evaporated in vacuo. The resulting oil was redissolved in EtOAc (40 mL) and washed with water (2 × 15 mL). The organic phase was dried (MgSO₄), filtered and evaporated in vacuo. The crude product was purified by

column chromatography to yield 1.75 g (3.41 mmol, 90%) of (*S_S,2*S*,2'*S**)-*N*-[2-(diphenylmethyleamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl]piperidine (**8b**).

(*S_S,2*S*,2'*S)-*N*-{2-(Diphenylmethyleamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetyl}pyrrolidine (8a).** *R_f* 0.09 (petroleum ether:EtOAc 1/1). Yellow oil, yield 59% (0.33 g). $[\alpha]_{\text{D}} +37.4$ (*c* 4.1, CHCl₃). IR (cm⁻¹): ν_{max} 697, 1072, 1093, 1278, 1444, 1638. ¹H NMR (300 MHz, CDCl₃) δ 1.15 (3H, s), 1.60-1.78 (4H, m), 1.69 (3H, s), 1.98 (3H, s), 2.80 (2H, t, *J* = 6.3 Hz), 3.34-3.51 (2H, m), 3.40 (1H, d, *J* = 8.81 Hz), 4.05 (1H, d, *J* = 8.26 Hz), 6.74 (2H, d, *J* = 7.71 Hz), 7.07-7.15 (2H, m), 7.28-7.49 (8H, m), 7.57 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 20.8, 21.5, 22.7, 23.8, 26.1, 46.0, 46.4, 48.0, 50.7, 64.7, 124.9 (2C), 127.9 (2C), 128.1 (2C), 129.05, 129.14 (2C), 129.4 (4C), 130.4, 135.1, 139.4, 141.8 (2C), 168.2, 169.6. MS (ESI⁺) *m/z* (%): 500 [*M* + H⁺, 100]. HRMS (ESI) calcd for C₃₀H₃₃N₃O₂S: 500.2366 MH⁺; found, 500.2375.

(*S_S,2*S*,2'*S)-*N*-{2-(Diphenylmethyleamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetyl}piperidine (8b).** *R_f* 0.10 (petroleum ether:EtOAc 1/1). Yellow oil, yield 90% (1.75 g). $[\alpha]_{\text{D}} +43.8$ (*c* 2.7, CHCl₃). IR (cm⁻¹): ν_{max} 696, 726, 1076, 1102, 1216, 1443, 1639. ¹H NMR (300 MHz, CDCl₃) δ 1.15 (3H, s), 1.17-1.31 (2H, m), 1.34-1.63 (4H, m), 1.70 (3H, s), 1.99 (3H, s), 2.83 (2H, br s), 3.19-3.31 (1H, m), 3.43 (1H, d, *J* = 8.26 Hz), 3.66-3.78 (1H, m), 4.15 (1H, d, *J* = 8.26 Hz), 6.74 (2H, d, *J* = 7.71 Hz), 7.11 (2H, d, *J* = 7.71 Hz), 7.25-7.49 (8H, m), 7.57 (2H, d, *J* = 7.71 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 20.7, 21.4, 22.4, 24.4, 25.6, 26.5, 43.4, 46.0, 47.7, 50.6, 63.0, 124.8 (2C), 127.7 (2C), 127.9 (2C), 129.0 (2C), 129.15, 129.21 (2C), 129.3 (2C), 130.3, 134.5, 139.4, 141.60, 141.64, 167.8, 169.3. MS

(ESI⁺) *m/z* (%): 514 [M + H⁺, 100]. Anal. calcd for C₃₁H₃₅N₃O₂S: 514.2523 MH⁺; found, 514.2513.

(S_S,2S,2'S)-N-{2-(Diphenylmethyleamino)-2-[3,3-diethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetyl}pyrrolidine (8c). *R*_f 0.07 (petroleum ether:EtOAc 1/1). Yellow oil, yield 44% (0.12 g). [α]_D +71.6 (*c* 1.9, CHCl₃). IR (cm⁻¹): ν_{max} 696, 1076, 1102, 1277, 1427, 1444, 1644. ¹H NMR (300 MHz, CDCl₃) δ 0.79 (3H, t, *J* = 7.4 Hz), 1.04 (3H, t, *J* = 7.4 Hz), 1.08-1.22 (1H, m), 1.32-1.45 (1H, m), 1.53-1.70 (4H, m), 1.88 (3H, s), 1.90-2.10 (2H, m), 2.60-2.75 (2H, m), 3.24-3.42 (2H, m), 3.39 (1H, d, *J* = 8.26 Hz), 4.03 (1H, d, *J* = 8.26 Hz), 6.65 (2H, d, *J* = 7.71 Hz), 7.00-7.07 (2H, m), 7.19-7.45 (8H, m), 7.49 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 9.3, 10.6, 21.4, 23.8, 24.0, 24.4, 26.0, 45.8, 46.2, 51.1, 56.1, 64.0, 124.9 (2C), 127.7 (2C), 127.9 (2C), 129.0, 129.1 (2C), 129.2 (2C), 129.3 (2C), 130.3, 135.2, 139.3, 141.6, 141.8, 168.2, 169.4. MS (ESI⁺) *m/z* (%): 528 [M + H⁺, 100]. Anal. calcd for C₃₂H₃₇N₃O₂S: 528.2679 MH⁺; found, 528.2691.

(S_S,2S,2'S)-N-{2-(Diphenylmethyleamino)-2-[3,3-diethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetyl}piperidine (8d). *R*_f 0.08 (petroleum ether:EtOAc 1/1). Yellow oil, yield 50% (0.07 g). [α]_D +79.9 (*c* 2.8, CHCl₃). IR (cm⁻¹): ν_{max} 696, 1077, 1101, 1214, 1442, 1641. ¹H NMR (300 MHz, CDCl₃) δ 0.85 (3H, t, *J* = 7.4 Hz), 1.11 (3H, t, *J* = 7.4 Hz), 1.15-1.30 (3H, m), 1.37-1.60 (5H, m), 1.89-2.17 (2H, m), 1.96 (3H, s), 2.78-2.89 (2H, m), 3.18-3.31 (1H, m), 3.46 (1H, d, *J* = 8.26 Hz), 3.63-3.74 (1H, m), 4.19 (1H, d, *J* = 8.81 Hz), 6.73 (2H, d, *J* = 7.71 Hz), 7.12 (2H, d, *J* = 7.15 Hz), 7.27-7.45 (8H, m), 7.56 (2H, d, *J* = 7.15 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 9.4, 10.7, 21.5, 24.1, 24.3, 24.5, 25.7, 26.7, 43.5, 46.1, 51.1, 56.2, 62.6, 124.9 (2C), 127.8 (2C), 128.0 (2C), 129.1 (2C), 129.2, 129.3 (4C), 130.3, 134.8,

139.5, 141.7, 141.8, 167.9, 169.3. MS (ESI⁺) *m/z* (%): 542 [M + H⁺, 100]. HRMS (ESI) calcd for C₃₃H₃₉N₃O₂S: 542.2836 MH⁺; found, 542.2846.

(S_S,2S,2'S)-N-{2-(Diphenylmethyleamino)-2-[1-(*p*-toluenesulfinyl)-1-azaspiro[2.5]oct-2-yl]-acetyl}pyrrolidine (8e). *R*_f 0.21 (petroleum ether:EtOAc 2/1). Yellow oil, yield 36% (0.09 g). [α]_D +53.9 (*c* 2.5, CHCl₃). IR (cm⁻¹): ν_{max} 696, 751, 1075, 1096, 1260, 1431, 1444, 1638. ¹H NMR (300 MHz, CDCl₃) δ 1.14-1.77 (11H, m), 1.80-1.92 (1H, m), 1.94 (3H, s), 2.08 (2H, t, *J* = 6.05 Hz), 2.60-2.76 (2H, m), 3.32-3.50 (2H, m), 3.46 (1H, d, *J* = 8.81 Hz), 4.10 (1H, d, *J* = 8.26 Hz), 6.70 (2H, d, *J* = 7.71 Hz), 7.07-7.14 (2H, m), 7.28-7.50 (8H, m), 7.57 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 23.9, 24.8, 25.3, 25.7, 26.1, 32.0, 33.0, 45.8, 46.3, 51.0, 53.1, 63.9, 124.9 (2C), 127.8 (2C), 128.0 (2C), 129.0, 129.2 (2C), 129.3 (2C), 129.4 (2C), 130.3, 135.1, 139.4, 141.7, 141.8, 168.3, 169.4. MS (ESI⁺) *m/z* (%): 540 [M + H⁺, 100]. HRMS (ESI) calcd for C₃₃H₃₇N₃O₂S: 540.2679 MH⁺; found, 540.2681.

(S_S,2S,2'S)-N-{2-(Diphenylmethyleamino)-2-[1-(*p*-toluenesulfinyl)-1-azaspiro[2.5]oct-2-yl]-acetyl}piperidine (8f). *R*_f 0.13 (petroleum ether:EtOAc 2/1). Yellow oil, yield 43% (0.10 g). [α]_D +49.1 (*c* 2.3, CHCl₃). IR (cm⁻¹): ν_{max} 696, 751, 1075, 1099, 1218, 1443, 1639. ¹H NMR (300 MHz, CDCl₃) δ 1.10-1.75 (13H, m), 1.80-1.92 (1H, m), 1.95 (3H, s), 2.08 (2H, t, *J* = 6.05 Hz), 2.70-2.86 (2H, m), 3.20-3.31 (1H, m), 3.45 (1H, d, *J* = 8.26 Hz), 3.67-3.77 (1H, m), 4.18 (1H, d, *J* = 8.26 Hz), 6.70 (2H, d, *J* = 8.26 Hz), 7.08-7.16 (2H, m), 7.28-7.47 (8H, m), 7.56 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.4, 24.4, 24.8, 25.2, 25.6 (2C), 26.6, 31.9, 32.7, 43.3, 46.0, 50.8, 53.1, 62.2, 124.8 (2C), 127.7 (2C), 127.9 (2C), 129.08 (2C), 129.14, 129.2 (4C), 130.2, 134.6, 139.4, 141.6, 141.7, 167.9, 169.1. MS (ESI⁺) *m/z* (%): 554 [M + H⁺, 100]. HRMS (ESI) calcd for C₃₄H₃₉N₃O₂S: 554.2836 MH⁺; found, 554.2836.

(S_S,2S,2'S)-N-[2-Amino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl]-piperidine (11b). *R*_f 0.10 (petroleum ether:EtOAc 1/1). Yellow oil, yield 86% (0.18 g). [α]_D +52.0 (*c* 2.1, CHCl₃). IR (cm⁻¹): ν_{max} 751, 813, 1065, 1088, 1221, 1444, 1631, 3272. ¹H NMR (300 MHz, CDCl₃) δ 1.07-1.36 (2H, m), 1.28 (3H, s), 1.40-1.71 (6H, m), 1.57 (3H, s), 2.42 (3H, s), 2.63 (1H, d, *J* = 8.26 Hz), 3.32 (1H, d, *J* = 8.26 Hz), 3.35-3.62 (4H, m), 7.34 (2H, d, *J* = 8.26 Hz), 7.72 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 20.9, 21.5, 22.0, 24.4, 25.5, 26.6, 43.1, 46.5, 49.9, 51.0, 51.3, 125.3 (2C), 129.7 (2C), 142.7, 142.8, 169.9. MS (ESI⁺) *m/z* (%): 350 [M + H⁺, 100]. HRMS (ESI) calcd for C₁₈H₂₇N₃O₂S: 350.1897 MH⁺; found, 350.1892.

Synthesis of (S_S,2S,3S)-N-[2-amino-4-chloro-3-(*p*-toluenesulfinylamino)alkanoyl]amines

10. The synthesis of (S_S,2S,3S)-N-[2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]piperidine (**10b**) is representative. To a solution of (S_S,2S,3S)-N-[4-chloro-2-(diphenylmethylenamino)-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]piperidine (**syn-5b**, 0.82 g, 1.49 mmol) in acetone/H₂O (2:1) (30 mL) was added dropwise trifluoroacetic acid (5 equiv, 7.45 mmol, 0.57 mL) at rt. The reaction mixture was stirred for 15 min at rt and subsequently quenched with NH₄OH in H₂O until pH 10 and concentrated in vacuo. The residue was redissolved in water (10 mL) and NH₄OH in H₂O was added until pH 10. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated in vacuo. The crude product was purified by crystallization from diethyl ether to yield 0.12 g (0.31 mmol, 21%) of pure (S_S,2S,3S)-N-[2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-piperidine (**10b**).

(S_S,2S,3S)-N-[2-Amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-

pyrrolidine (10a). White crystals, yield 70% (0.26 g). [α]_D +51.0 (*c* 2.9, CHCl₃). Mp 125.4 ±

2.0 °C. IR (cm⁻¹): $\nu_{\max}$ 892, 1062, 1083, 1343, 1451, 1599, 1629, 3230. ¹H NMR (300 MHz, CDCl₃) δ 1.55 (3H, s), 1.68 (3H, s), 1.77 (2H, br s), 1.84-2.13 (4H, m), 2.41 (3H, s), 3.44-3.59 (2H, m), 3.63 (2H, t, J = 6.6 Hz), 3.66 (1H, d $\times$ d, J = 9.6 Hz, 2.20 Hz), 4.24 (1H, d, J = 2.20 Hz), 4.89 (1H, d, J = 9.6 Hz), 7.32 (2H, d, J = 8.26 Hz), 7.83 (2H, d, J = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.4, 24.0, 26.3, 29.2, 31.9, 46.6, 46.8, 52.4, 65.0, 73.7, 125.7 (2C), 129.6 (2C), 141.6, 142.7, 171.7. MS (ESI⁺) m/z (%): 372/374 [M + H⁺, 100]. HRMS (ESI) calcd for C₁₇H₂₆ClN₃O₂S: 372.1507 MH⁺; found, 372.1513.

(S_S,2S,3S)-N-[2-Amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-piperidine (10b). White crystals, yield 21% (0.12 g). [α]_D +67.5 (c 2.4, CHCl₃). Mp 119.8 $\pm$ 2.0 °C. IR (cm⁻¹): $\nu_{\max}$ 821, 854, 1066, 1092, 1244, 1446, 1460, 1613, 3181. ¹H NMR (300 MHz, CDCl₃) δ 1.50-1.77 (6H, m), 1.56 (3H, s), 1.69 (3H, s), 1.81 (2H, br s), 2.41 (3H, s), 3.46-3.58 (2H, m), 3.61 (1H, d $\times$ d, J = 9.91 Hz, 1.65 Hz), 3.67-3.81 (2H, m), 4.49 (1H, d, J = 1.65 Hz), 4.93 (1H, d, J = 9.91 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.4, 24.6, 25.6, 26.3, 28.7, 32.3, 44.0, 46.4, 50.4, 65.6, 73.8, 125.8 (2C), 129.6 (2C), 141.5, 142.7, 171.5. MS (ESI⁺) m/z (%): 386/388 [M + H⁺, 100]. HRMS (ESI) calcd for C₁₈H₂₈ClN₃O₂S: 386.1664 MH⁺; found, 386.1676.

(S_S,2S,3S)-N-[2-Amino-4-chloro-4-ethyl-3-(*p*-toluenesulfinylamino)hexanoyl]pyrrolidine (10c). White crystals, yield 91% (0.16 g). [α]_D +49.4 (c 2.6, CHCl₃). Mp 127.3 $\pm$ 2.0 °C. IR (cm⁻¹): $\nu_{\max}$ 637, 811, 1056, 1086, 1324, 1440, 1612, 1630, 3282. ¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.15 Hz), 1.06 (3H, t, J = 7.15 Hz), 1.76 (2H, br s), 1.82-2.10 (8H, m), 2.41 (3H, s), 3.42-3.70 (4H, m), 3.90 (1H, d $\times$ d, J = 9.91 Hz, 1.65 Hz), 4.17 (1H, d, J = 1.65 Hz), 4.78 (1H, d, J = 9.91 Hz), 7.32 (2H, d, J = 8.26 Hz), 7.86 (2H, d, J = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 8.7, 8.8, 21.5, 24.1, 26.4, 29.7, 30.5, 46.7, 46.8, 52.7, 61.3,

83.0, 125.8 (2C), 129.7 (2C), 141.6, 143.0, 171.8. MS (ESI⁺) *m/z* (%): 400/402 [M + H⁺, 100]. HRMS (ESI) calcd for C₁₉H₃₀ClN₃O₂S: 400.1820 MH⁺; found, 400.1827.

(S_S,2S,3S)-N-[2-Amino-4-chloro-4-ethyl-3-(*p*-toluenesulfinylamino)hexanoyl]piperidine

(10d). Yellow oil, yield 59% (0.07 g). [α]_D +41.8 (*c* 2.3, CHCl₃). IR (cm⁻¹): $\nu_{\max}$ 751, 812, 1056, 1087, 1254, 1444, 1598, 1638, 3188. ¹H NMR (300 MHz, CDCl₃) δ 0.92 (3H, t, *J* = 7.15 Hz), 1.10 (3H, t, *J* = 7.15 Hz), 1.48-1.72 (6H, m), 1.76 (2H, br s), 1.85-2.12 (4H, m), 2.41 (3H, s), 3.36-3.53 (2H, m), 3.70-3.90 (2H, m), 3.85 (1H, d $\times$ d, *J* = 9.6 Hz, 1.65 Hz), 4.43 (1H, d, *J* = 1.65 Hz), 4.80 (1H, d, *J* = 9.6 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 8.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 8.7, 8.9, 21.5, 24.7, 25.7, 26.6, 29.6, 30.5, 44.0, 46.4, 50.6, 61.7, 83.0, 125.9 (2C), 129.7 (2C), 141.6, 142.9, 171.7. MS (ESI⁺) *m/z* (%): 414/416 [M + H⁺, 100]. HRMS (ESI) calcd for C₂₀H₃₂ClN₃O₂S: 414.1977 MH⁺; found, 414.1980.

(S_S,2S,3S)-N-[2-Amino-3-(1-chlorocyclohexyl)-3-(*p*-toluenesulfinylamino)propanoyl]-

piperidine (10f). Yellow crystals, yield 78% (0.28 g). [α]_D +73.2 (*c* 2.3, CHCl₃). Mp 95.7 $\pm$ 2.0 °C. IR (cm⁻¹): $\nu_{\max}$ 813, 853, 889, 1068, 1092, 1243, 1444, 1634, 3165. ¹H NMR (300 MHz, CDCl₃) δ 1.05-2.20 (18H, m), 2.41 (3H, s), 3.44-3.59 (2H, m), 3.62 (1H, d $\times$ d, *J* = 9.91 Hz, 1.65 Hz), 3.67-3.80 (3H, m), 4.50 (1H, d, *J* = 1.65 Hz), 4.91 (1H, d, *J* = 9.91 Hz), 7.32 (2H, d, *J* = 8.26 Hz), 7.82 (2H, d, *J* = 8.26 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 21.6, 22.1, 24.7, 24.8, 25.6, 26.4, 35.8, 37.4, 44.0, 46.4, 50.3, 66.5, 80.0, 125.9 (2C), 129.7 (2C), 141.6, 142.8, 171.6. MS (ESI⁺) *m/z* (%): 426/428 [M + H⁺, 100]. HRMS (ESI) calcd for C₂₁H₃₂ClN₃O₂S: 426.1977 MH⁺; found, 426.1972.

Synthesis of (4'S,5'S)-N-[5-(2-chloro-2-propyl)-2,2-diphenylimidazolidin-4-yl]carbonyl-piperidine (12b). To a solution of (S_S,2S,3S)-N-[4-chloro-2-(diphenylmethyleamino)-4-

methyl-3-(*p*-toluenesulfinylamino)pentanoyl]piperidine (*syn*-**5b**, 0.40 g, 0.73 mmol) in EtOH (20 mL) was added dropwise trifluoroacetic acid (10 equiv, 7.26 mmol, 0.56 mL) at rt. The reaction mixture was stirred for 16 h at rt and subsequently quenched with NH₄OH in H₂O until pH 10 and concentrated in vacuo. The residue was redissolved in water (10 mL) and NH₄OH in H₂O was added until pH 10. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated in vacuo. The crude product was purified by crystallization in diethyl ether to yield 0.16 g (0.40 mmol, 55%) of pure (4'*S*,5'*S*)-*N*-[5-(2-chloro-2-propyl)-2,2-diphenyl-imidazolidin-4-yl]carbonylpiperidine (**12b**).

(4'*S*,5'*S*)-*N*-[5-(2-Chloro-2-propyl)-2,2-diphenylimidazolidin-4-yl]carbonylpiperidine

(12b). White crystals, yield 55% (0.16 g). [α]_D −33.4 (*c* 0.8, CHCl₃). Mp 132.7 ± 2.0 °C. IR (cm^{−1}): $\nu_{\max}$ 707, 752, 1025, 1216, 1260, 1452, 1642, 3315 (weak). ¹H NMR (300 MHz, CDCl₃) δ 1.49-1.89 (6H, m), 1.52 (3H, s), 1.73 (3H, s), 2.59-2.74 (2H, m), 3.32-3.43 (1H, m), 3.52-3.69 (2H, m), 3.76-3.98 (2H, m), 3.85 (1H, d, *J* = 7.43 Hz), 7.13-7.35 (6H, m), 7.57-7.65 (4H, m). ¹³C NMR (75 MHz, CDCl₃) δ 24.7, 25.5, 26.4, 31.3, 31.7, 43.5, 47.1, 60.4, 71.3, 73.3, 85.6, 125.7 (2C), 126.0 (2C), 127.1 (2C), 128.2 (2C), 128.4 (2C), 146.2, 146.7, 169.6. MS (ESI⁺) *m/z* (%): 412/414 [*M* + H⁺, 100]. HRMS (ESI) calcd for C₂₄H₃₀ClN₃O: 412.2150 MH⁺; found, 376.2376 (100%), 412.2144 (70%).

Synthesis of (2*S*,3*S*)-*N*-[2,3-diamino-4-chloro-4-methylpentanoyl]pyrrolidine dihydrochloride (13a). (*S*_S,2*S*,3*S*)-*N*-[4-Chloro-2-(diphenylmethyleneamino)-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]pyrrolidine (*syn*-**5a**, 0.19 g, 0.35 mmol) was dissolved in a mixture of 0.5 M (aq.) HCl/EtOAc (2:1) (12 mL) and the mixture was stirred for 30 min at rt. The organic phase was removed and the aqueous phase was washed with EtOAc (3 × 5 mL).

Subsequently, the aqueous phase was lyophilized to yield 0.09 g (0.29 mmol, 83%) of pure (2*S*,3*S*)-*N*-[2,3-diamino-4-chloro-4-methylpentanoyl]pyrrolidine dihydrochloride (**13a**).

(2*S*,3*S*)-*N*-[2,3-diamino-4-chloro-4-methylpentanoyl]pyrrolidine dihydrochloride (13a**).**

White crystals, yield 83% (0.09 g). $[\alpha]_{\text{D}} -3.1$ (*c* 2.4, MeOH). Mp 227.3 ± 2.0 °C. IR (cm^{-1}): ν_{max} 1123, 1166, 1404, 1453, 1514, 1543, 1636, 2973, 3399. ^1H NMR (300 MHz, D_2O) δ 1.79 (3H, s), 1.82-2.04 (4H, m), 1.86 (3H, s), 3.35-3.60 (3H, m), 3.62-3.77 (1H, m), 4.07 (1H, d, $J = 2.20$ Hz), 4.90 (1H, d, $J = 2.20$ Hz). ^{13}C NMR (75 MHz, D_2O) δ 23.8, 25.5, 29.0, 30.9, 47.3, 47.6, 49.8, 57.6, 67.8, 164.1. MS (ESI $^+$) m/z (%): 234/236 [$\text{M} + \text{H}^+ - 2 \times \text{HCl}$, 100]. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{20}\text{ClN}_3\text{O}$: 198.1601 [$\text{MH}^+ - 3 \times \text{HCl}$]; found, 198.1596.

II. Copies of ^1H NMR and ^{13}C NMR spectra of **3**, *syn*-**5**, **8** and **10–13**























































































